SYNTHETIC APPROACHES TOWARDS A-RING FUNCTIONALISED NORDITERPENE DILACTONES

A Thesis presented by

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To my parents...

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Finally I am greatful to my friends and colleages at the department, especially [redacted] with whom I shared many memorable moments.

ABSTRACT

The literature on norditerpene dilactones has been examined with particular emphasis on reviewing comprehensively their previous synthetic approaches. Section A also includes our proposal for a new synthetic strategy, the success of which depends largely on an efficient Diels-Alder cycloaddition reaction. Introductory discussion of cycloaddition reactions is given with a detailed report of the Lewis acid catalysed cycloadditions.

Section B covers all the material on the intermediate compounds of the synthetic route prior to the cycloaddition reaction. An efficient and convenient method for large scale preparation of 3-methyl-2-buteneoic acid and 3-methyl-2-pyrone has been developed.

The final section has been devoted to examination of cycloaddition reactions of 3-methyl-2-pyrone. Ten new adducts have been synthesised and their stereostructures discussed. Influence of heat, high pressure, aqueous medium, and Lewis acids on the Diels-Alder cycloaddition reactions under study have been examined. Novel products from reaction of nitrosobenzene with 3-methyl-2-pyrone and 3-methyl-2-thiopyrone have been isolated and identified. A chemical method for opening the lactone bridge in the pyrone-xyloquinone adduct has proved successful and thus

optimisation of the developed chemical steps should allow access to A-ring functionalised norditerpene dilactones.

Isolation and characterisation of the products have been achieved by modern chromatographic and spectroscopic methods. Analytical and preparative high performance liquid chromatography (HPLC) proved invaluable in resolving, identifying, and separating complex mixtures into their components. Examples of structural characterisation using high resolution nuclear magnetic resonance spectroscopy (NMR) aided by nuclear overhauser enhancement difference spectroscopy (NOEDS) and hydrogen decoupling spectroscopy are given.

SECTION A

LITERATURE SURVEY OF AND A SYNTHETIC STRATEGY FOR NORDITERPENE DILACTONES

Chapter 1: Review of norditerpene dilactones.

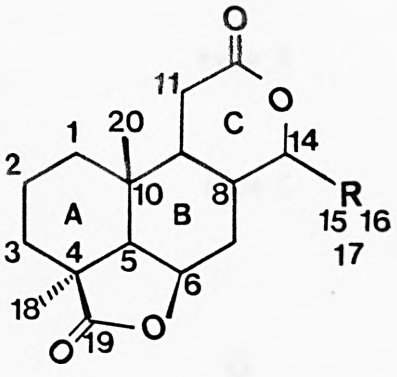
1.1 Introduction

As the search for new and biologically active compounds continues all over the world, a series of norditerpene dilactones have attracted attention. Since 1968, over fifty different norditerpene dilactones have been isolated from plant tissues, and have been characterised, their biological activities studied and synthetic routes sought.

Norditerpenes are a class of compounds isolated from Podocarpaceae, a genus of eighty species belonging to the division Gymnospermae. These are plants which are distributed throughout tropical and sub-tropical areas of Eastern Asia and the southern hemisphere. Work mainly carried out in Australia, Brazil, Chile, Japan and New Zealand has shown the presence of various types of compounds in roots, bark, seeds, leaves, and timber of these plants; eg. lignans, steroids, terpenoids, and diterpenoids (podocarpane, isopimarane, friedo-isopimarane, abiatane, totarane, 13α— and 13β— kaurane and dilactones). Norditerpene dilactones have shown many interesting biological properties including antitumor, plant growth regulation, termiticidal, and insect toxicity activities.

1.2 Structure

All of the fifty three known lactones have the basic ring system shown. The common structural features of the whole group are that they have:



a) Degraded ring C of totarane (7) carbon skeleton, to form an unsaturated δ-lactone.

b) a γ-lactone between the C-19 and the β-orientated hydroxyl group at C6.

c) Two tertiary methyl groups : a methyl at C-4 and β-methyl at C-10.

d) There are often extensively oxidised carbocyclic rings A and B with hydroxyl, epoxy, olefinic groups.

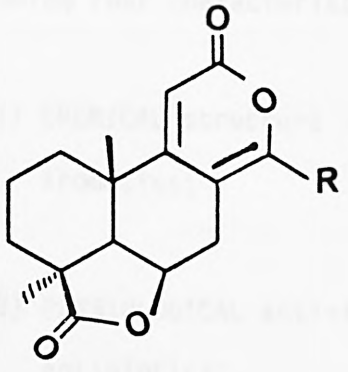
e) In the simplest cases R is an isopropyl group, but this can be extensively modified.

All of the dilactones have 20 carbon atoms at the most and up to nine oxygen atoms in the molecule. The dilactones are structurally classified into three major sub-groups[2] ,

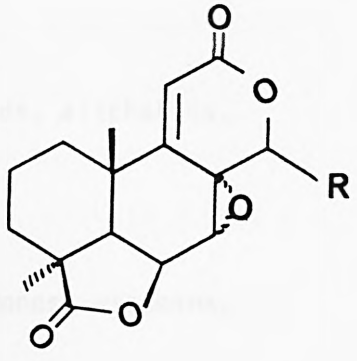
I. a-pyrone [8(14), 9(11)-dieneolide] : type A

II. 7α,8α-epoxy-9(11)-enolide : type B

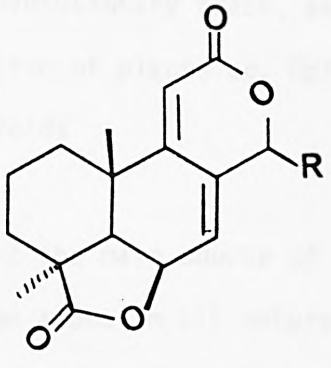
III. 7(8),9(11)-dieneolide : type C



TYPE A



TYPE B



TYPE C

Structures of 54 characterised dilactones are illustrated at the end of this chapter and include the very recent structures identified in our laboratories.[1]

1.3. Classification.

A brief review of the classification of natural products will establish the position of norditerpene dilactones in relation to all the other natural products.

Natural products include almost all types of organic molecules and can be classified according to one of the following four characteristics :

1) CHEMICAL structure : eg. benzenoids, aliphatics, aromatics;

2) PHYSIOLOGICAL activity : eg. hormones, vitamins, antibiotics;

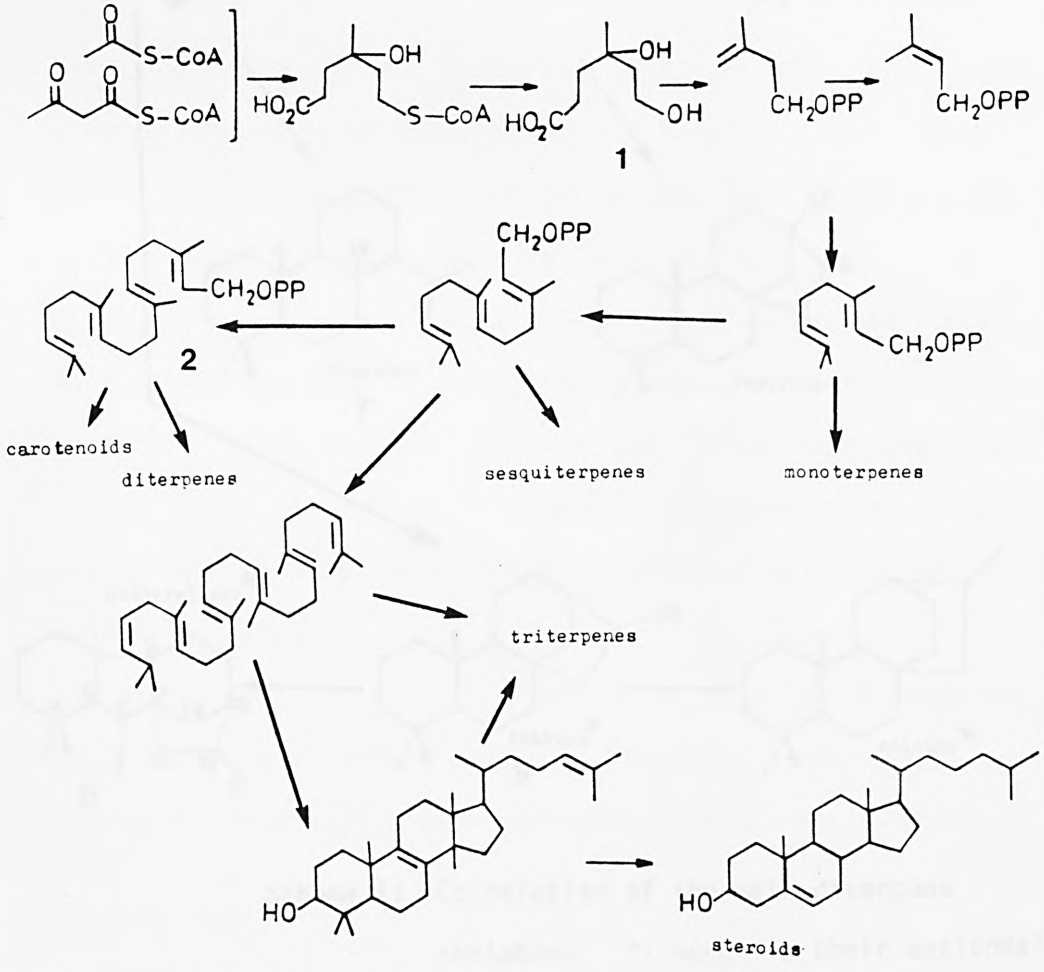
3) CHEMOSYSTEMATIC or CHEMOTAXONOMIC : this system attempts to review plant constituents as markers for taxa, evolutionary track, and for the classification of plants eg. Opium alkaloids, ergot alkaloids

4) BIOGENETIC : the main source of carbon and nitrogen atoms in all natural products are largely confined to five types of precursors:
   a) acetyl-Co-A (acetogeninoids) [CH3-CO$\frac{}{}$]
   b) shikimic acid (phenyl propanoids)
   c) mevalonic acid (isoprenoids) [CH2=C(CH3)$\sim\!\!\sim$]
   d) amino acid (alkaloids)

e) S-5-deoxy-adenyl methionine(C1 units)

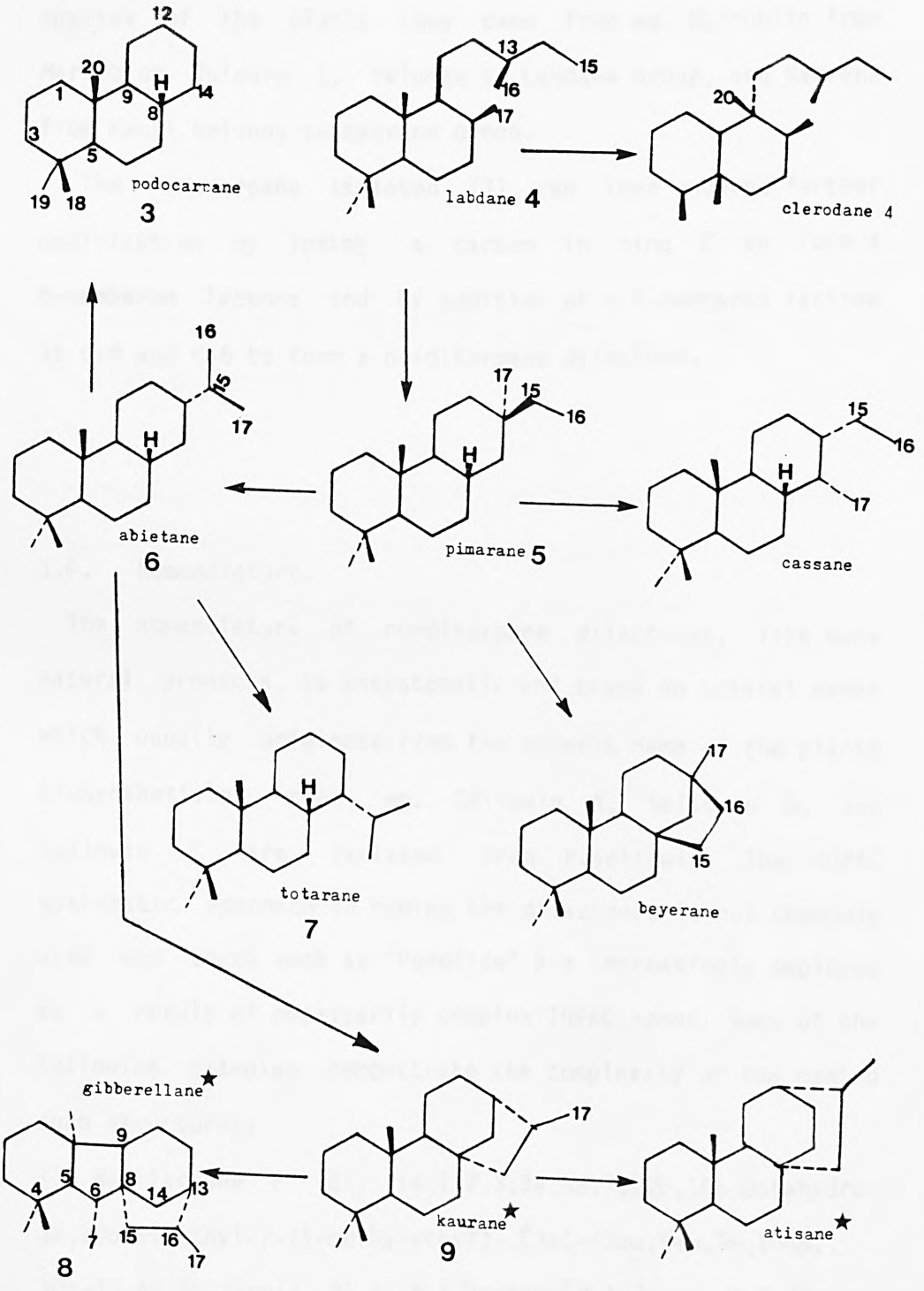
some compounds are formed from combination of these units.

The isoprenoid class of biogenetic classification is concerned with the biosynthesis of mevalonic acid (1), and its subsequent conversion to terpenes and related compounds such as steroids (Scheme I). Diterpenoids belong to this class and are subject to further discussion here as they are precursors to norditerpene dilactones. Diterpenes are a group of C20 compounds derived from geranylgeranyl pyrophosphate (2), in turn derived from mevalonic acid (1). They are of immense variety and mainly occur in plants and fungi.



Scheme I Biosynthesis of terpenes and steroids

Rowe proposed a further classification of diterpenoids according to the main skeleton, which is now widely recognised .



Scheme II Correlation of the main diterpene skeletons *: occur in their antipodal form in nature.

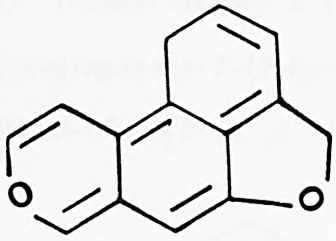
As one can see the names of the carbon skeletal systems are loosely derived from the first plant origin and compounds first isolated are labelled after their genus and species of the plants they came from eg. Marrubiin from Marrubium Vulgare L. belongs to Labdane Group, and Kaurene from Kauri belongs to Kaurane group.

The Podocarpane skeleton (3) can then undergo further modification by losing a carbon in ring C to form a 6-membered lactone and by addition of a 5-membered lactone at C-4 and C-6 to form a norditerpene dilactone.

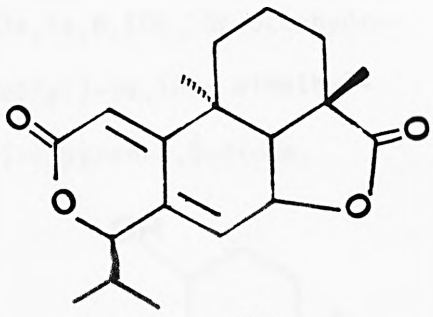
1.4. Nomenclature.

The nomenclature of norditerpene dilactones, like many natural products, is unsystematic and based on trivial names which usually originate from the generic name of the plants biosynthesising them eg. Sellowin A, Sellowin B, and Sellowin C are isolated from P.sellowii. The IUPAC systematic approach to naming the dilactones is not commonly used and terms such as "Podolide" are increasingly employed as a result of necessarily complex IUPAC names. Some of the following examples demonstrate the complexity of the naming such structures;

1) Nagilactone F (67) is 1,2,3,3a,5a,7,10b,10c-Octahydro-3a,10b-dimethyl-7-(1-methylethyl)-,[3aS-(3aα,5aα,7α,10bβ, 10cα)],4H,9H-furo[2',3',4':4,5]naphtho[2,1c]pyran-4,9-dione.



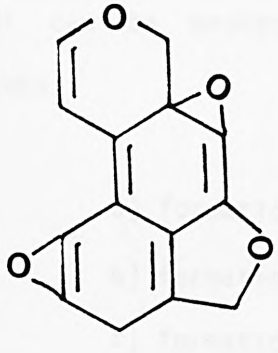
67a



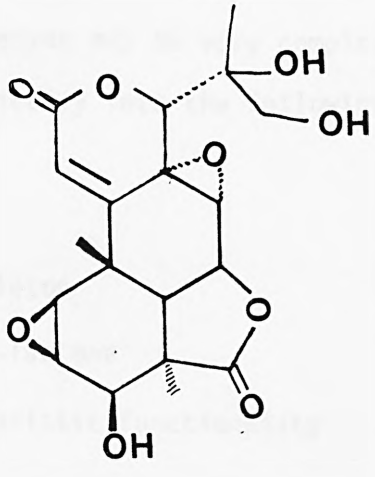
67

1H,4H-Furo[2',3',4':4,5]naphtho[2,1c]pyran (67a) is the chosen parent molecule.

2) Podolactone B (61) is [1aR-(1aα,1bβ,3aβ,3bβ,4α,4aα,5aα, 5bα, 9β,9aR)]-9-(1,2-dihydroxy-1-methylethyl)-1a,1b,3a,3b, 4,4a,5a,5b,9,9a-octahydro-4-hydroxy-3a,5b-dimethyl-3H,7H-oxireno[i]oxireno[5,6]isobenzofuro[7,1-fg][2]benzopyran-3,7-dione.



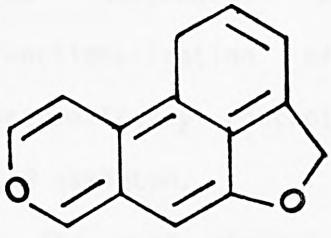
61a



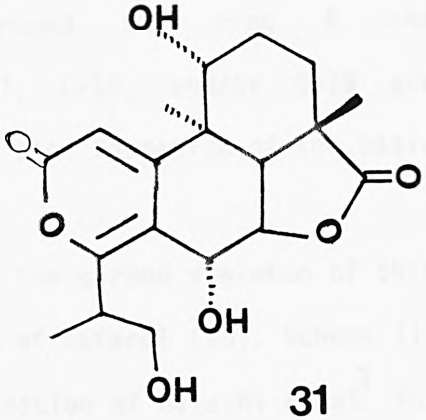
61

3H,9H-Oxireno[i]oxireno[5,6]iso-benzofuro[7,1-fg][2] benzopyran (61a) is the chosen parent molecule.

3) Inumakilactone E (31) is 1,2,3,3a,5a,6,10b,10c-octahydro-1,6-dihydroxy-7-(2-hydroxy-1-methylethyl)-3a,10b- dimethyl-4H,9H- furo[2',3',4':4,5]naphtho[2,1-c]pyran-4,9-dione.



31a



31

1H,4H-furo[2',3',4':4,5]naphtho[2,1c]pyran (31a) is the parent structure.

1.5. Biogenesis.

The question of how norditerpene dilactones are synthesised by natural processes in living tissues is far from being understood. These processes may be very complex but can be broken down hypothetically into the following steps;

a) formation of the C19-skeleton

b) formation of the C4-C6 ɣ-lactone

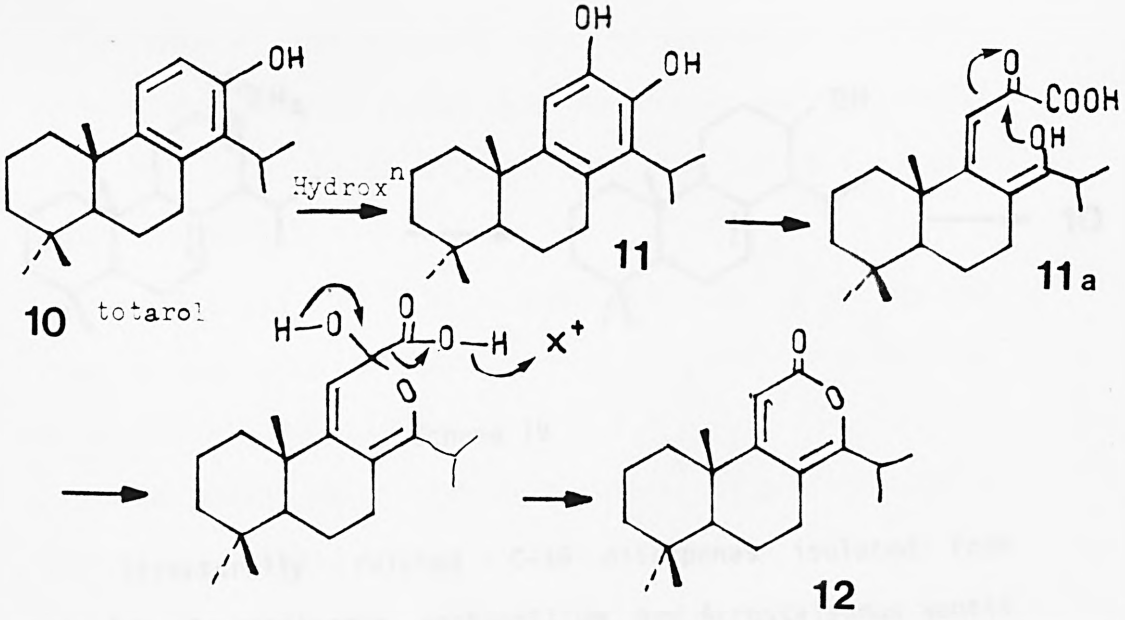
c) formation of the characteristic functionality around ring A or B

d) functionalization of the C-17, C-18, or C-19.

Presently the sequence in which the above processes occur

is purely speculative, For example it is not known whether δ-lactone is formed before or after the formation of the C19 skeleton. On the other hand it is tempting to suggest that the oxygenation patterns around the ring A and functionalization of the C-17, C-18, and/or C-19 are enzymatically controlled after the formation of the basic C19 skeleton.

The most obvious route to the carbon skeleton of this type is through transformation of totarol (10). Scheme III demonstrates the tentative suggestion of Hayashi et al.[3] for the biosynthetic route through which the totarol skeleton is transformed into (12).

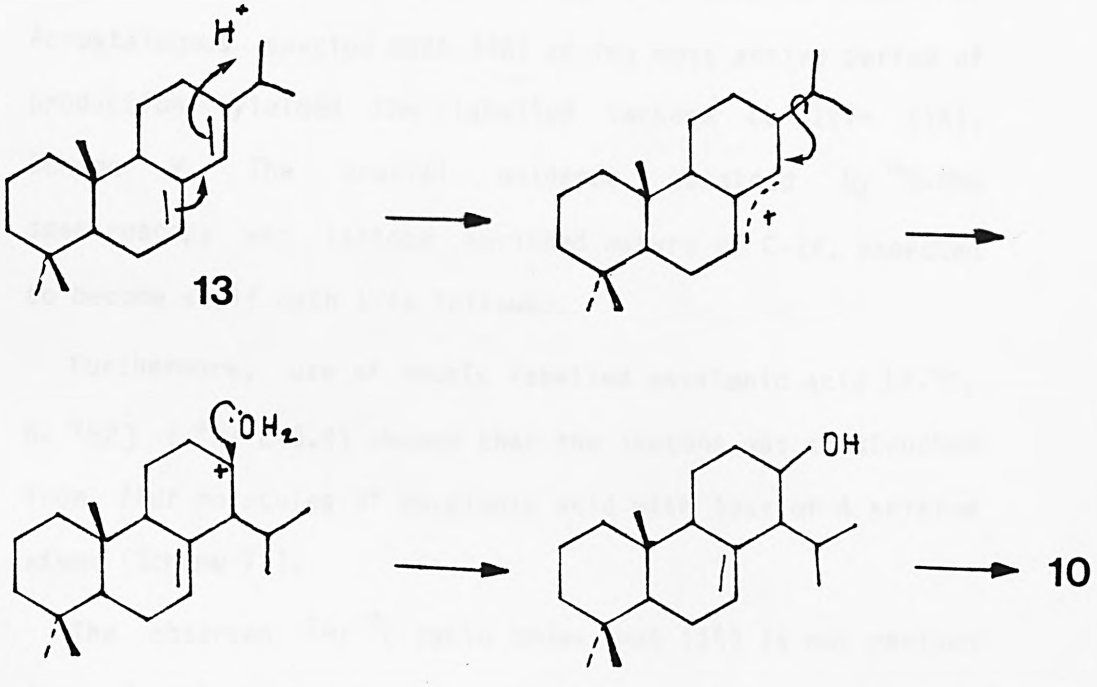


Scheme III

The catechol oxidative cleavage of hydroxy totarol (11) yields (11a) which is converted to 2-pyrone derivatives by

meta-pyrocatechase type fission. This route explains the loss of one carbon atom and the position of the isopropyl side group at C-14 .

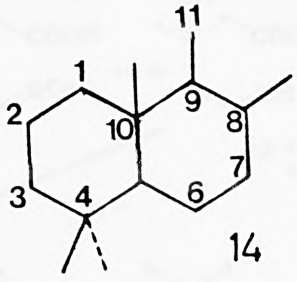
However the literature does not hold a proven biosynthetic route to totarol. Prazeres[4] has suggested a Wagner-Meerwein rearrangement of an allylic carbonium ion resulting from protonation of an abietane type skeleton (13), followed by quenching with water to construct the totarol skeleton (10)(Scheme IV).



Scheme IV

Structurally related C-16 diterpenes isolated from moulds Acrostalagmus verticillium and Acrostalagmus wentii are of interest in connection with the biogenesis of nor-diterpene dilactones. The lack of a C-14 isopropyl unit in the mould diterpenes, as compared to plant diterpenes raises interesting biogenetic questions. A possible origin

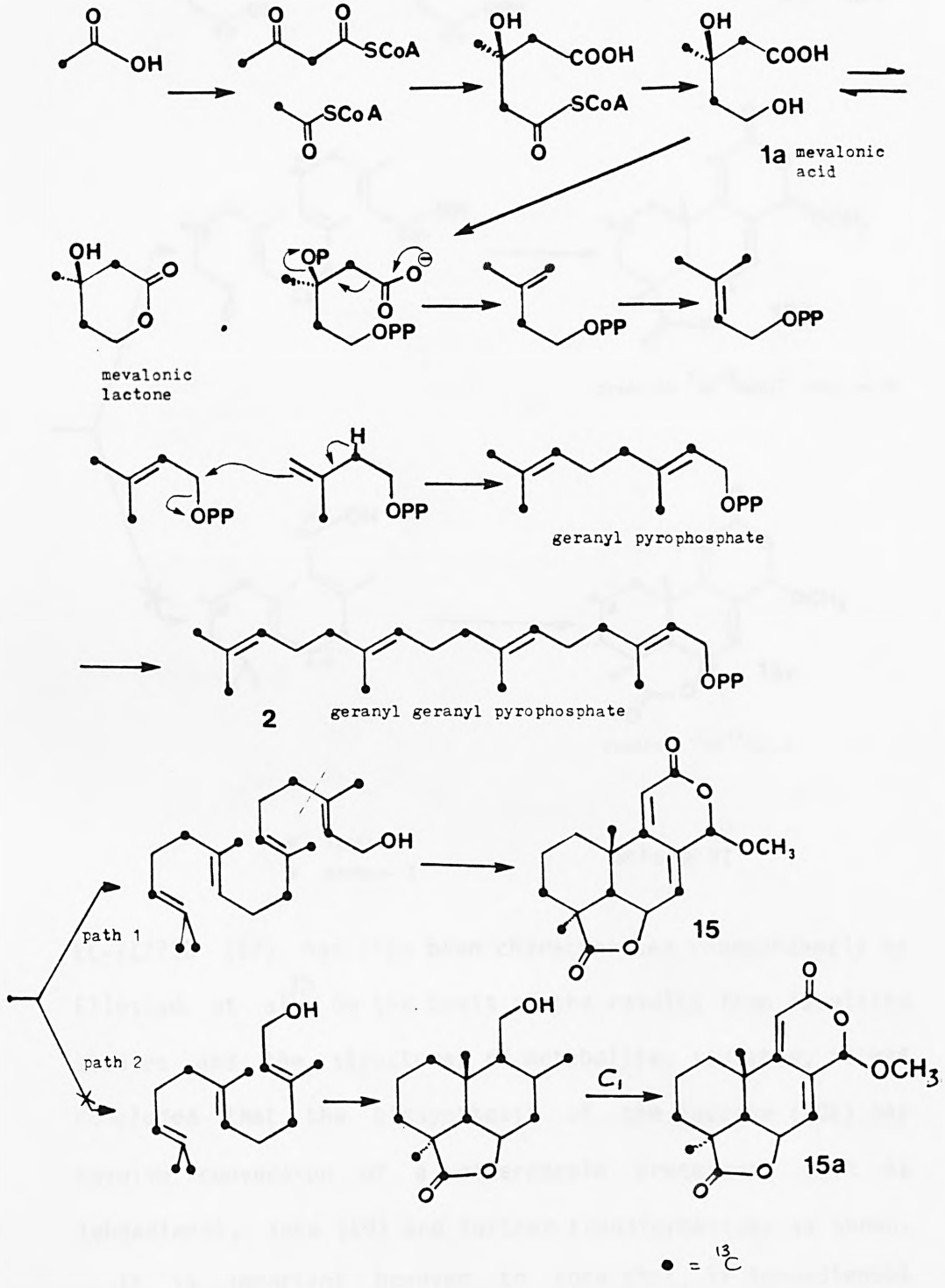
from a C20 precursor by microbiological degradation is plausible although one might also consider derivation from a C15 precursor (14) by the addition of a C1 unit to C11[5]. An isotope labelling experiment by Kakisawa et al.[6] established the biosynthetic route in 1973. They reported that isotope-enriched acetic acid or mevalonic acid added to the culture medium of Acrostalagmus species NRRL-3481 at its most active period of production yielded the labelled lactone LL-Z127∝ (15), Scheme V. The crucial evidence obtained by ^{13}C-NMR spectroscopy was isotope enriched nature of C-12, expected to become so if path 1 is followed.



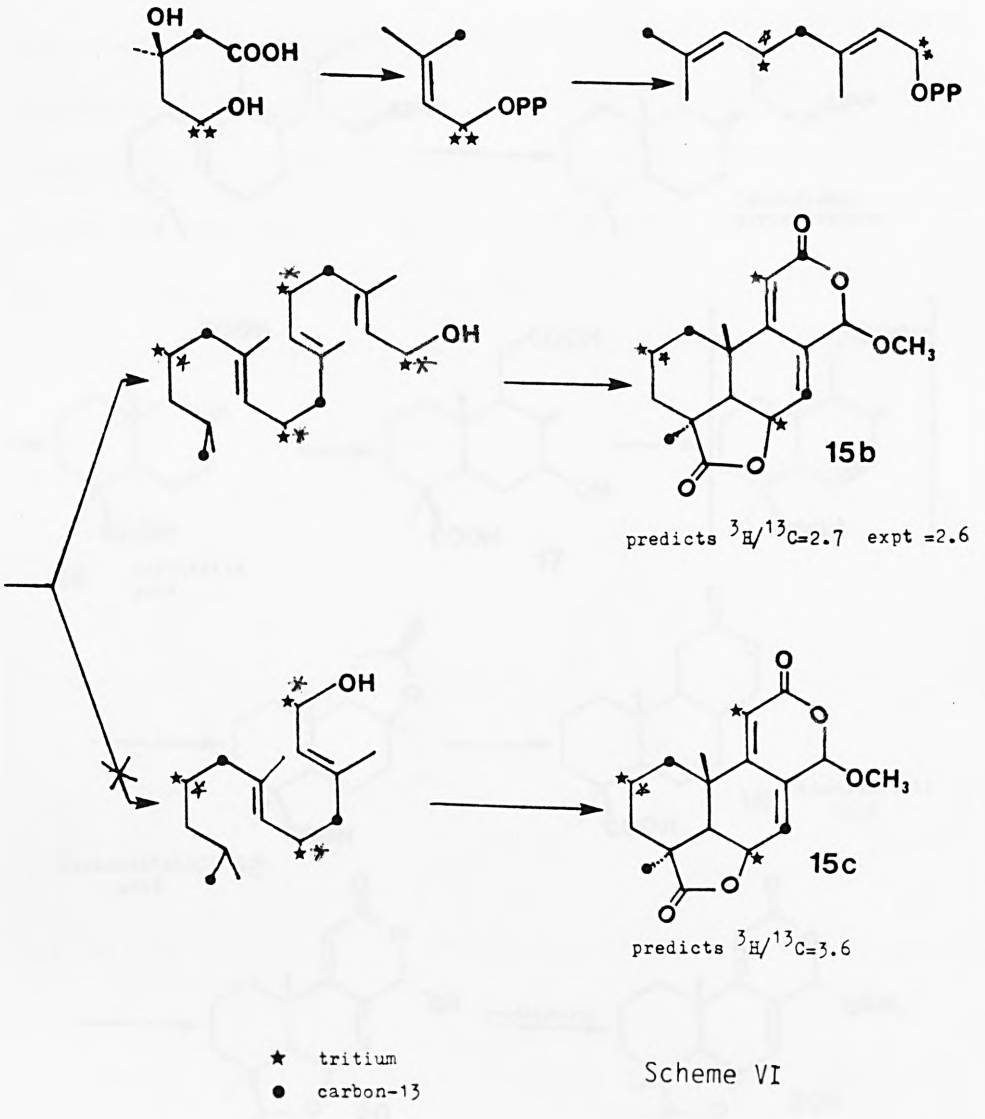
Furthermore, use of doubly labelled mevalonic acid [2-^{13}C, 5-$^{3}H2$] ($^{3}H/^{13}C$=5.4) showed that the lactone was constructed from four molecules of mevalonic acid with loss of 4 tritium atoms (Scheme VI).

The observed $^{3}H/^{13}C$ ratio shows that (15) is not derived from 3 molecules of mevalonic acid (which required an expected $^{3}H/^{13}C$ ratio of 3.6)

Three years later Sato and Kakisawa[7a] in continuation of their biosynthetic investigations, isolated three new C16 terpenoids from the culture fluid of NRRL-3481. These metabolites, designated as acrostalic acid (16), isoacrostalidic acid (18) and acrostalidic acid (19) may be on the biosynthetic pathway for the antifungal metabolite LL-Z1271∝ (20) Scheme VII


SCoA
SCoA
COOH
SCoA
COOH
OH
1a mevalonic acid
mevalonic lactone
OPP
OPP
OPP
OPP
OPP
OPP
geranyl pyrophosphate
2
geranyl geranyl pyrophosphate
OH
OCH3
15
path 1
path 2
OH
OH
C1
OCH3
15a
● = 13C

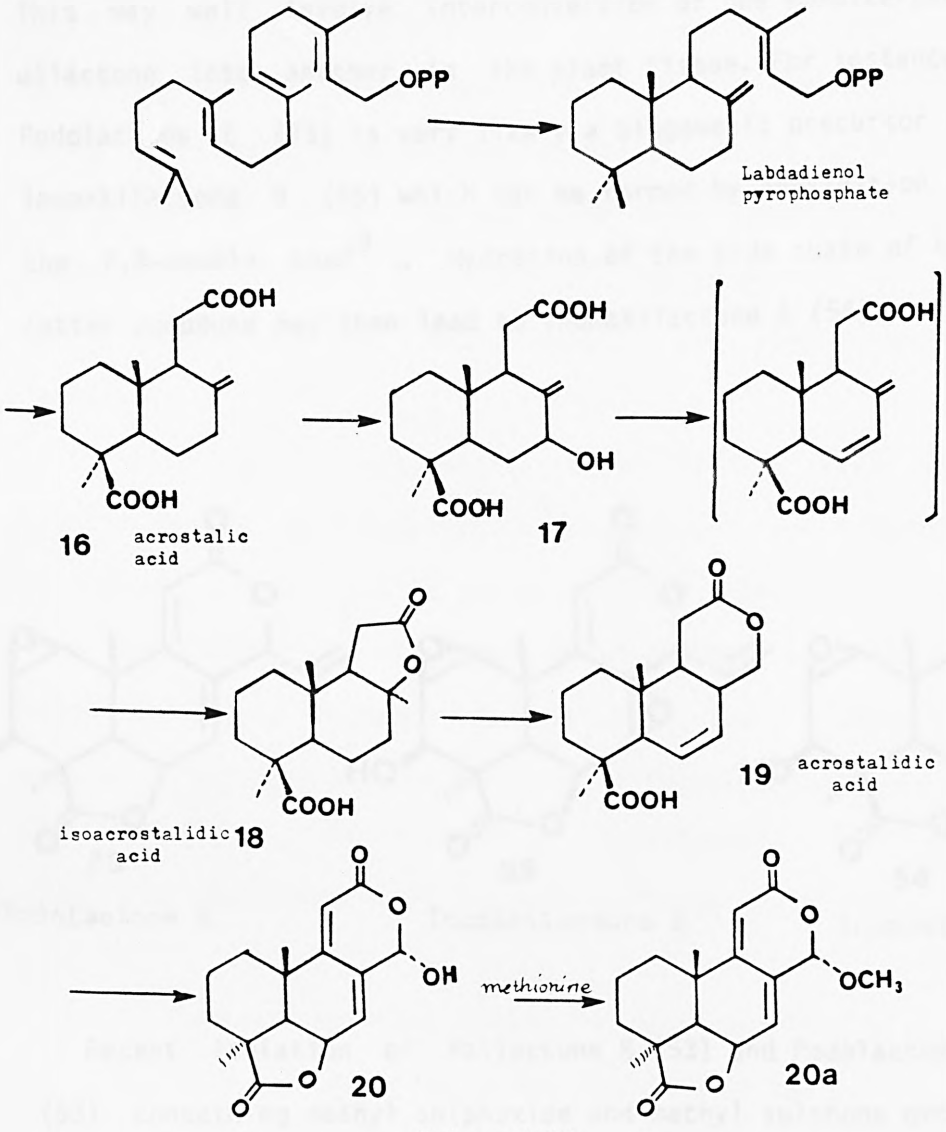
Scheme V



Scheme VI

LL-Z1271B (17) has also been characterised independently by Ellestad et al.[7b]. On the basis of the results from labelling studies and the structures of metabolites isolated, it was concluded that the biosynthesis of the lactone (20a) may involve conversion of a diterpenoid precursor, such as labdadienol, into (19) and further transformations as shown.

It is important however to note that, if labdadieneol pyrophosphate is one of the precursors, then based on evidence so far obtained a C4-pyrophosphate fragmentation probably occurs (to produce an acrostalic acid (16) type



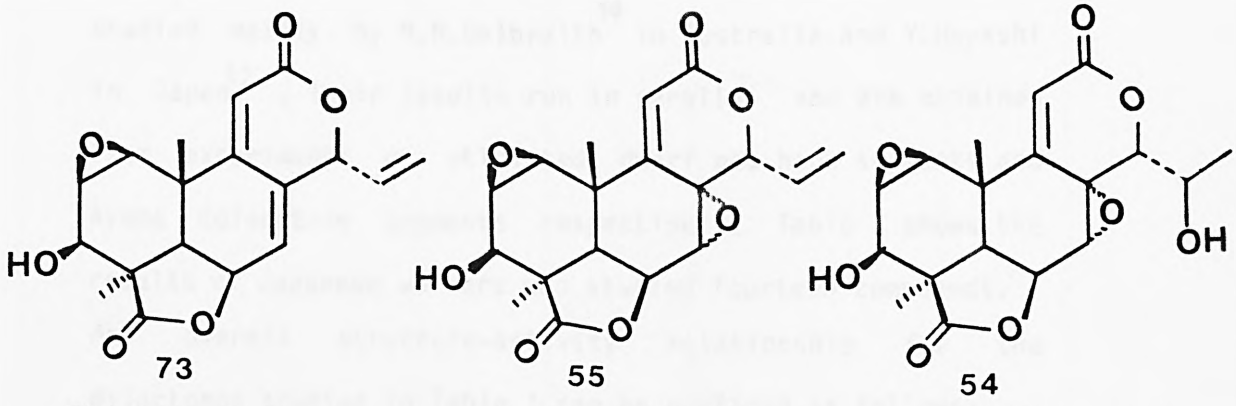
Scheme VII

intermediate), with the introduction of the isopropyl unit on C14 at a later stage of the biosynthesis.

In 1974 Brown et al.[8] proposed, based on the observation that fungi assigned to the geni verticillium and wentii are usually isolated from soil commonly associated with the plant roots, that some dilactones may be plant-altered mycorrhizal fungal metabolites.

The diversity of the detail structures of dilactones suggests subtle variations in their biosynthetic routes.

This may well involve interconversion of one norditerpene dilactone into another in the plant tissue. For instance, Podolactone E (73) is very likely a biogenetic precursor of Inumakilactone B (55) which can be formed by epoxidation of the 7,8-double bond[9]. Hydration of the side chain of the latter compound may then lead to Inumakilactone A (54).



73 Podolactone E

55 Inumakilactone B

54 Inumakilactone A

Recent isolation of Hallactone B (53) and Podolactone D (63) containing methyl sulphoxide and methyl sulphone groups in the side chain is the first indication of occurance of unusual sulphur-containing diterpenes in this group. Methylation and oxidation of the corresponding 16-thiols is their possible biogenetic origin.

1.6. Biological Activity.

The remarkable biological activities of nor-diterpene dilactones are well recognised and the dilactone members in each of the three structural types show fine differences in

their biological properties. A complete map of structure-activity relationship has not yet been obtained owing to limited availability of the dilactones to perform the biological tests. A recent paper also reported revised geometrical structures for some of the compounds.[20] All the structures given in this report are the corrected structures.

As plant growth regulators, their effects have been studied mainly by M.N.Galbraith[10] in Australia and Y.Hayashi in Japan[12] . Their results run in parallel and are obtained from experiments on etiolated dwarf pea hook segments and Avena Coleoptile segments respectively. Table 1 shows the results of Japanese workers who studied fourteen compounds. An overall structure-activity relationship for the dilactones studied in Table 1 can be outlined as follows:

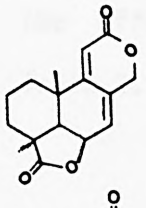
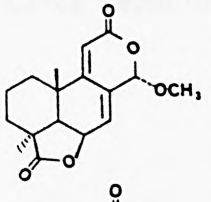
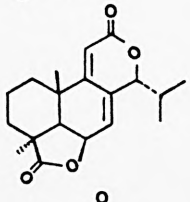
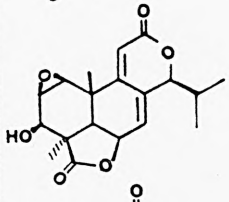
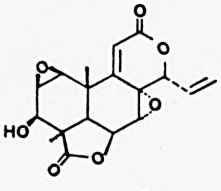
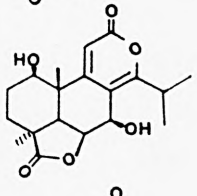
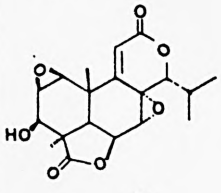
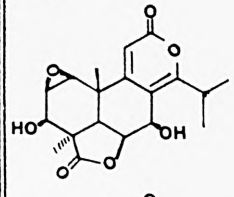
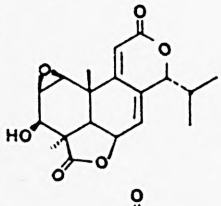
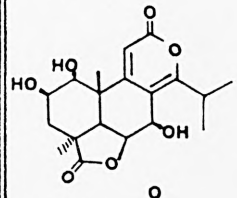
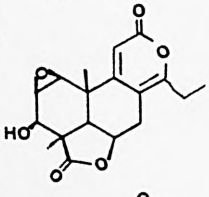
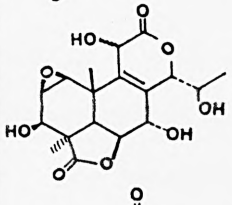
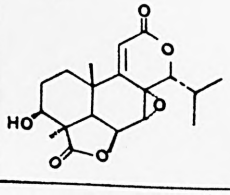
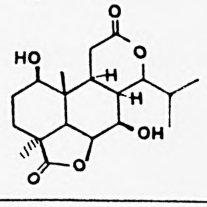
A) The most important factor for development of inhibitory activity is the presence of the conjugated dienolide or γ,δ-epoxy-α,β-enolide system over rings B and C.

B) Lactones which have 2-pyrone partial structure show dual activity (inhibitory or promotive) depending upon their concentrations.

C) A smaller number of polar substituents in the molecule seems to result in stronger activity in the inhibitors

Table 1 The concentration ($x10^{-7}$ mol/l, IC_{50}) of the lactones for 50% inhibition of straight growth on Avena coleoptile sections[1]

* growth promotive effect at lower conc.

STRUCTURE	cpd No	IC_{50}	STRUCTURE	cpd No	IC_{50}
	70	1		20a	100
	67	1		75	500
	55	20		21	500★
	54	30		23	600★
	74	30		22	700★
	24	30★		56	inactive
	35	50		76	inactive

D) Converting the α-isopropyl to β-isopropyl reduces the activity by 18-fold.

However, Galbraith et al.[11] observed that the C1-C2 epoxide is important to the biological activities. This was supported by the findings of J.W.Dorner et al.[13] who investigated the activity of Wentilactone A (70) and B (71). The effect of removing the C1-C2 epoxide is depicted in Table 2.

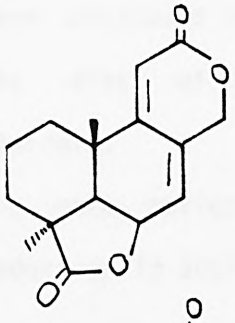
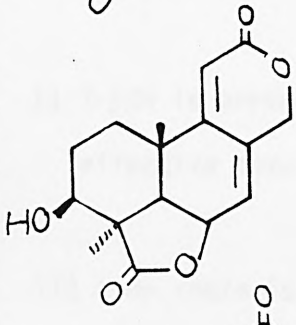
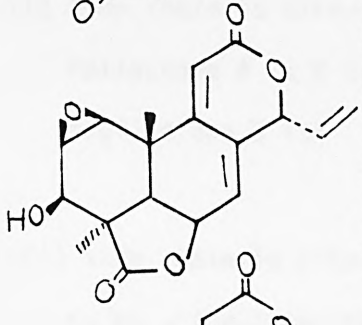
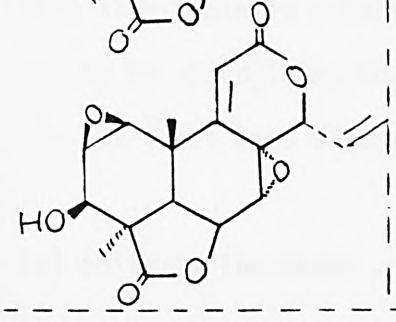
STRUCTURE	NO.	CONCENTRATION			
		10^{-3} M	10^{-4} M	10^{-5} M	10^{-6} M
	70	81	81	48	0
	71	100	81	0	0
	73	82	64	55	0
	55	96	82	62	0

Table 2. Growth inhibiting activity of Wentilactone A,B, Podolactone E and Inumakilactone B in wheat coleoptile bioassay expressed as % inhibition compared to controls.

Australian workers who were the first to observe insecticidal activities of norditerpene dilactones published a series of papers examining the relationship between lactone structure and toxicity to housefly[14] . Table 3 summarises the results of their findings when the lactones were dissloved in ethanol and the solution incorporated into the diet of the housefly larvae and checked against controls.

The more obvious comparisons of the LD50 values suggest reduction in activity when:

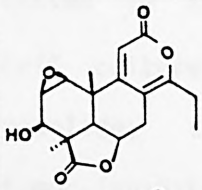
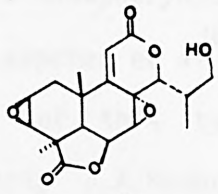
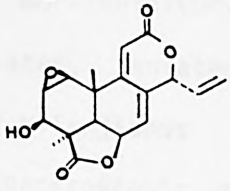
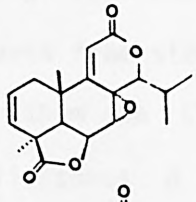
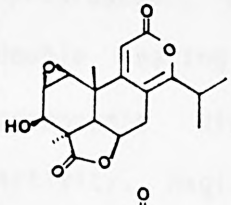
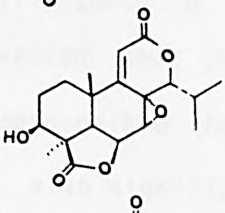
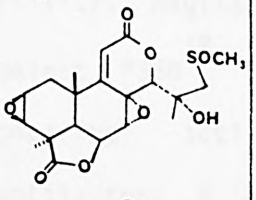
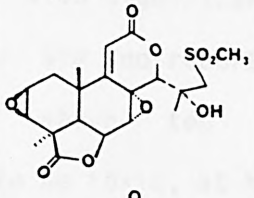
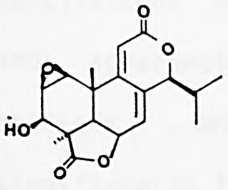
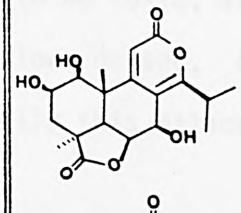
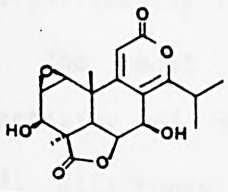
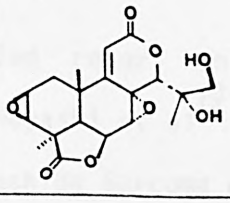
i) 7-βOH is present (ie. Nagilactone C is 3.5 times less effective than Hallactone A is)

ii) side chain is altered from R=Et to R=isopropyl (ie. Hallactone A is 5 times less effective than Nagilactone D is)

iii) side chain is altered from R= $-C(CH_3)(OH)(SOCH_3)$ to R= $-C(CH_3)(OH)(SO_2CH_3)$ (ie. Hallactone B is 5.9 times less effective than Podolactone C is).

iv) polarity increases .

Table 3 Toxicity of diterpene lactones to housefly expressed as dose required to give 50% total mortality—larvae to adults.[13]

STRUCTURE	cpd No	LD_{50} ppm	STRUCTURE	cpd No	LD_{50} ppm
	24	0.7		58	13.3
	73	<1.3+		51	33.9
	33	3.5		35	40.8
	62	8.2		53	48.2
	75	9.7		22	135.0
	23	12.0		60	<250 +

Japanese workers[15], via termite tests, isolated Inumakilactone A, which has comparable structural features to those dilactones showing insecticidal activity reported by the Australians. Insecticidal and termicidal activities suggest that these lactones may be important in the chemical ecology of Podocarpus species, representing potent lines of defence against insect attack.

Activity-directed fractionation of twigs and leaves of P.Gracilior, using tests against P388 lymphocytic leukemia system in the mouse and Eagles 9KB nasopharyngeal carcinoma cell culture system, enabled S.M.Kupchan et al.[16] to isolate podolide, the first compound of this type to show tumor-inhibitory activity. Similarly J.A.Hembree et al[17] later, isolated four active components from stem and bark of P.Milanjianus and characterised them on the basis of spectroscopic evidence as Milanjilactones A and B, This double testing of fractions revealed that the cyctotoxic components differ from those responsible for the P388 activity. Nagilactones A-E have also significant activity against P388[18]. However, there are no reports directly comparing activities of the above ten compounds. Wentilactone B has been shown to be toxic, at high dosage and, apparently, non-toxic at low dosage, to 1-day-old chickens. When administered orally this dilactone appeared significantly less toxic (2 fold).

The most extensively studied report on biological activity of dilactones was by Y.Hayashi et al[19] who studied 31 dilactones against cultured Yoshida Sarcoma cells. Table 4 enables one to compare the structure/activity relationships.

Table 4 Cytotoxicity against Yoshida sarcoma cells in vivo[9]

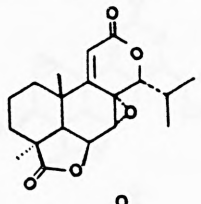
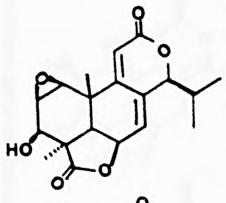
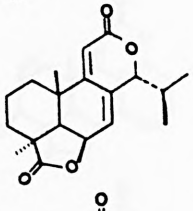
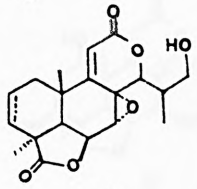
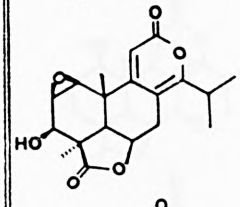
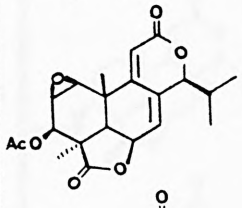
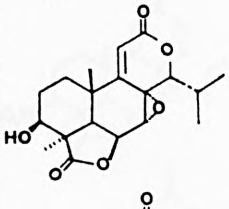
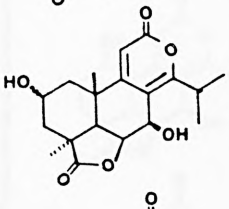
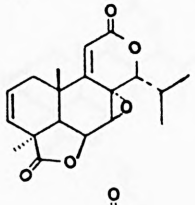
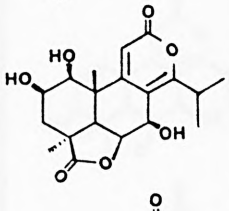
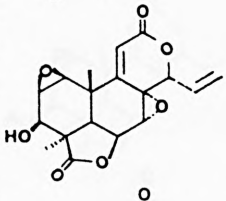
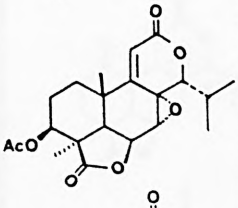
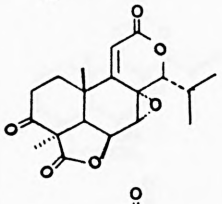
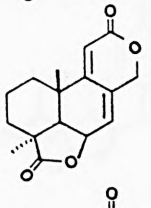
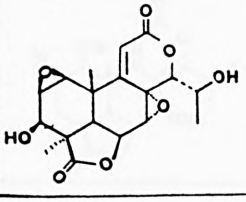
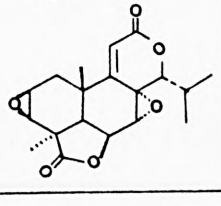
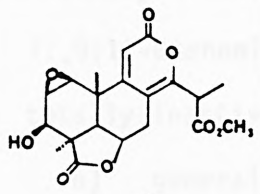
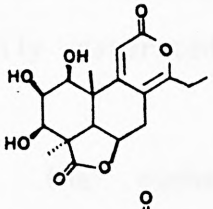
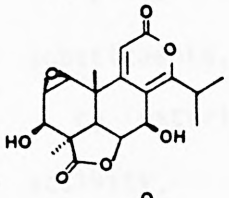
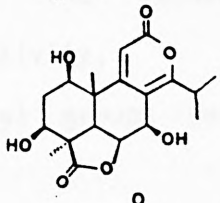
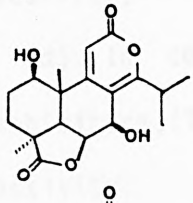
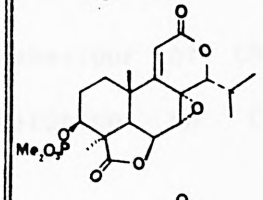
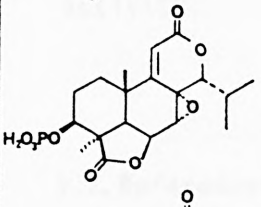
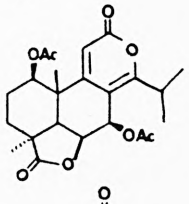
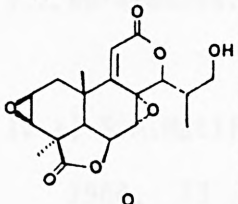
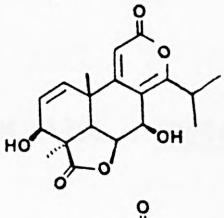
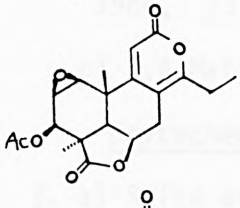
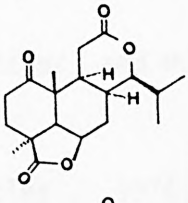
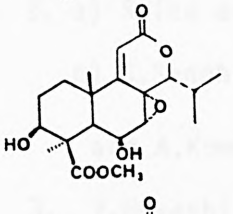
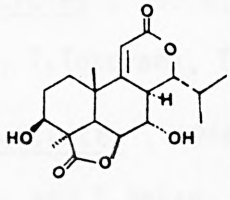
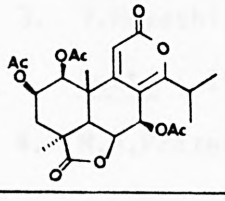
STRUCTURE	cpd No	IC_{50}	STRUCTURE	cpd No	IC_{50}
	36	1.48		75	12.20
	67	1.70		42 & 45 1 : 1	14.80
	33	3.32		75a	16.10
	35	3.36		28	16.40
	51	3.72		22	17.20
	55	4.11		35a	18.30
	77	4.19		70	18.90
	54	10.40		52	20.60

Table 4 .....continued. Cytotoxicity against Yoshida sarcoma cells in vivo

STRUCTURE	cpd No	IC_{50}	STRUCTURE	cpd No	IC_{50}
	25	21.50		30	305.0
	23	22.50		26	487.0
	21	32.00		35c	607.0
	35b	87.00		21a	1000
	58	110		79	1460
	24a	119		80	inactive
	78	130		81	inactive
	22a	138			

Based on the results of Table 4, the following points can be deduced.

a) the most fundumental structural requirments for the activity are 2-pyrone, 7,8-epoxy-9:11-enolide or 7:,9:11-dieneolide since a fully saturated compound is totally inactive,

b) generally the smaller the number of polar substituents, the stronger the activity,

c) esterification of hydroxyl groups generally lowers activity,

d) In contrast to the behaviour of the plant growth inhibitors,(Table 1), substitution on C-14 increases activity.

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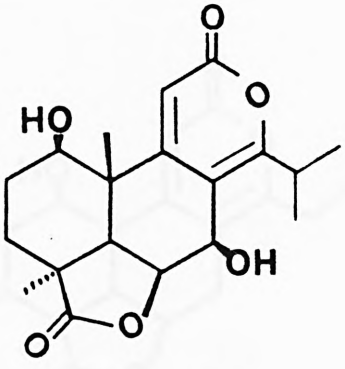
TYPE A



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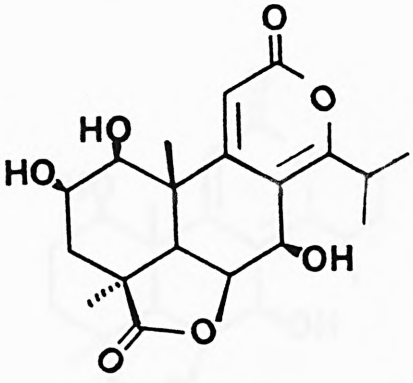

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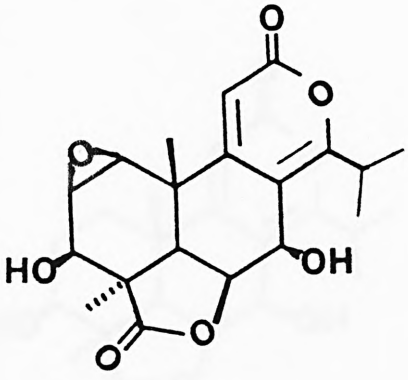

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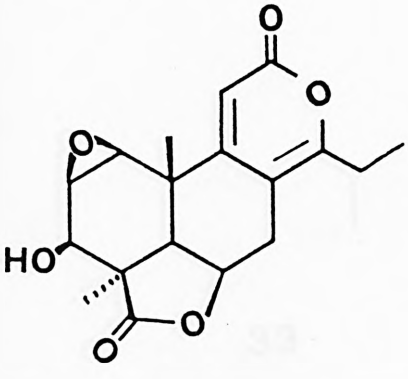

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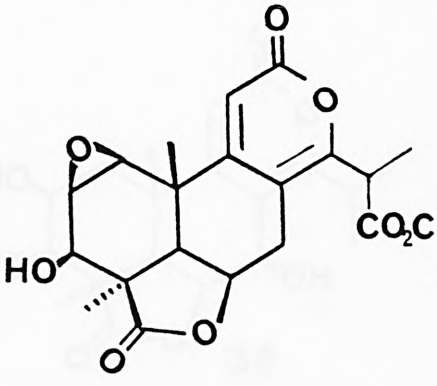

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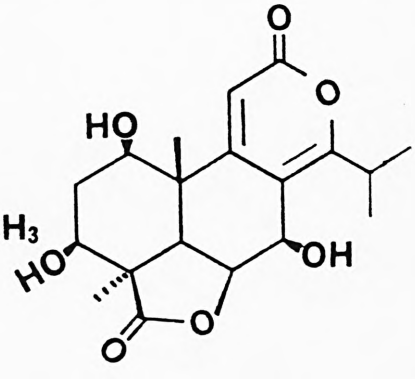

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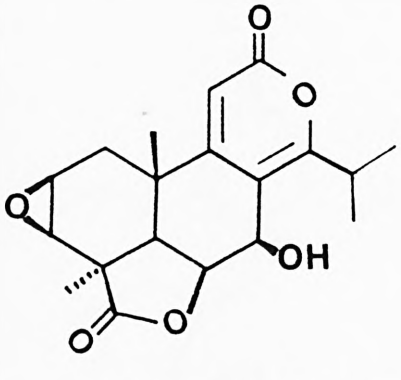

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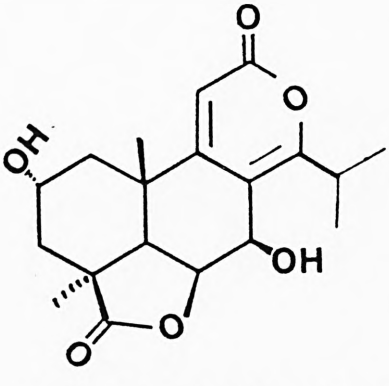

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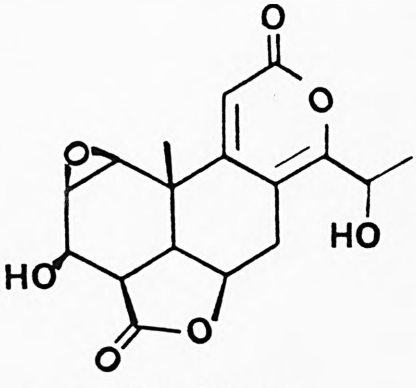

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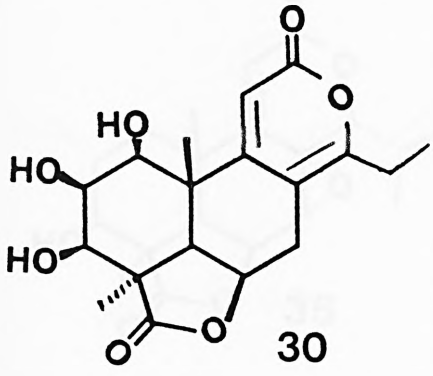

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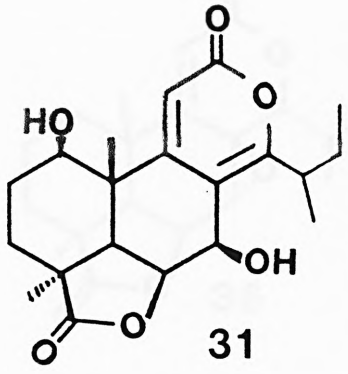

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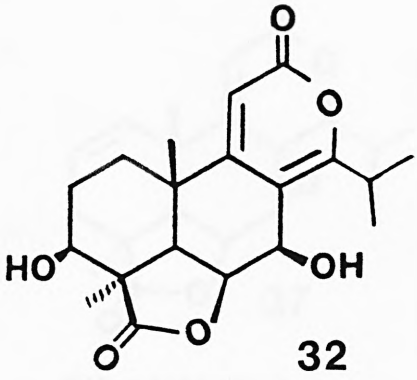

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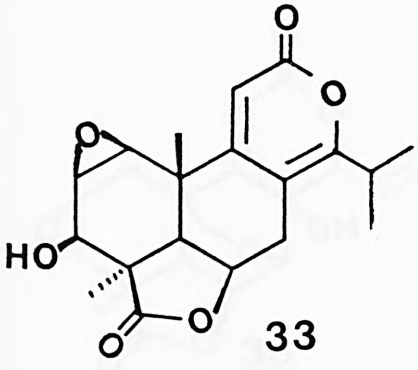

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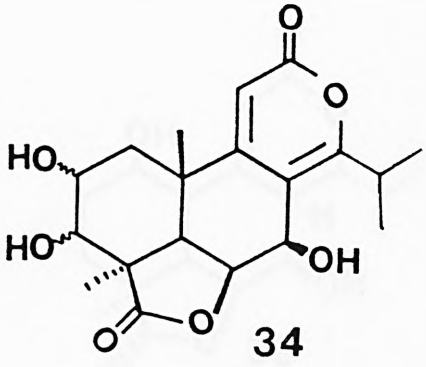

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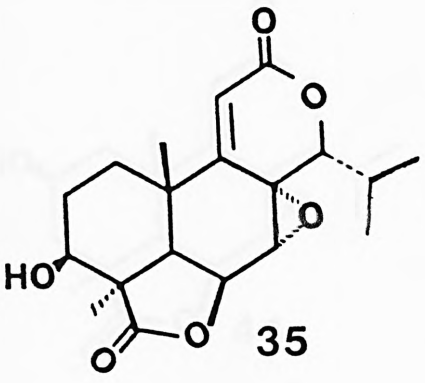

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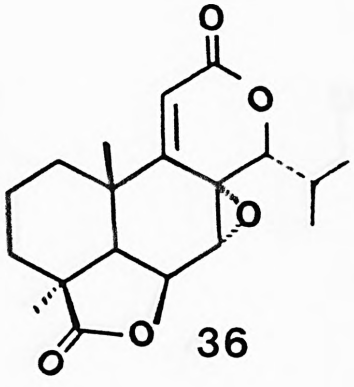

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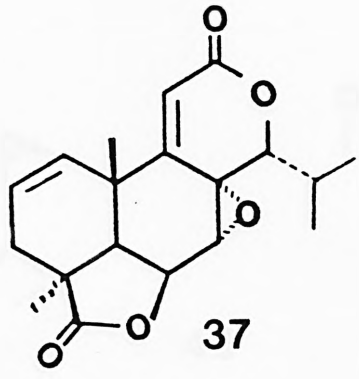

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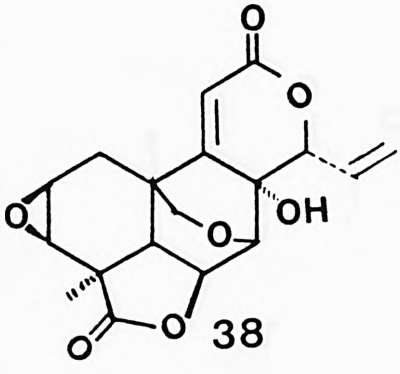

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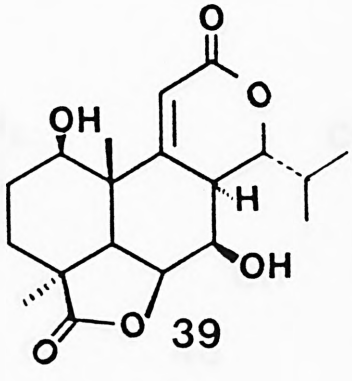

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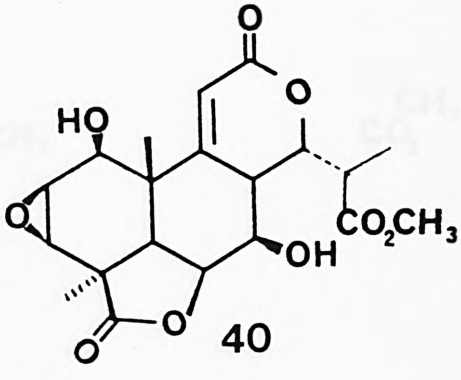

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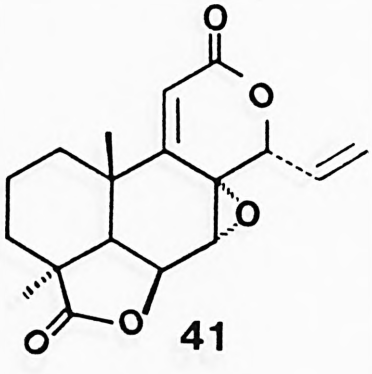

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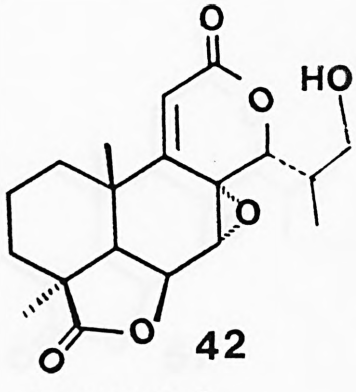

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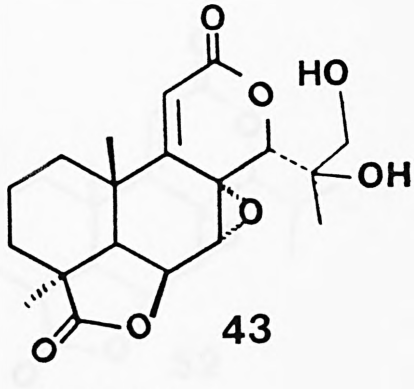

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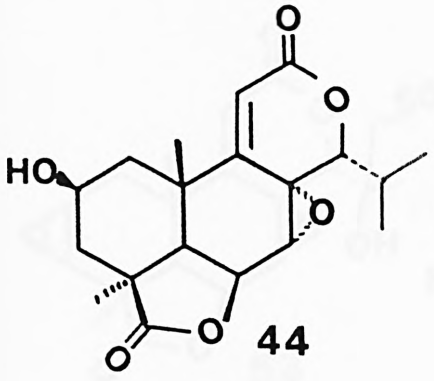

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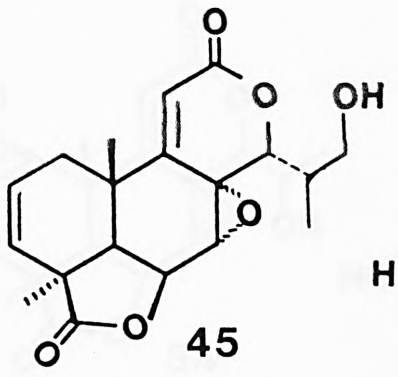

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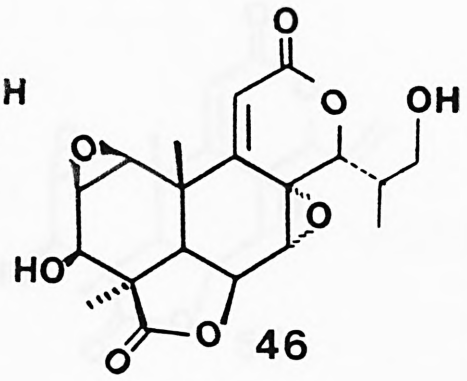

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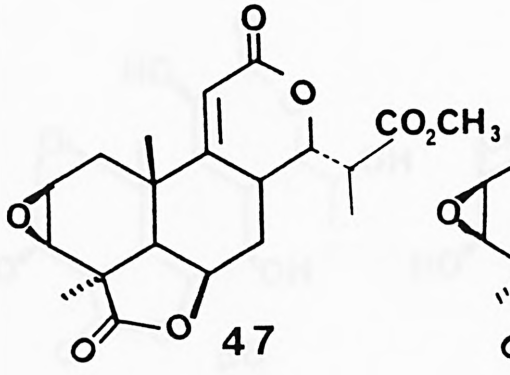

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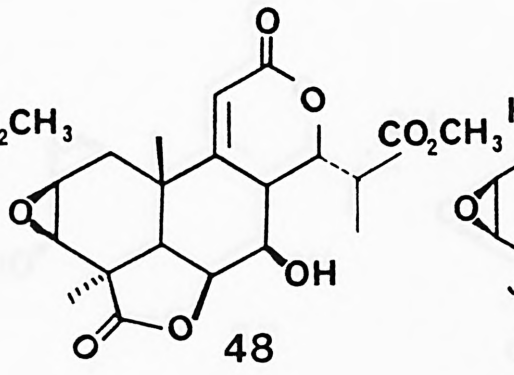

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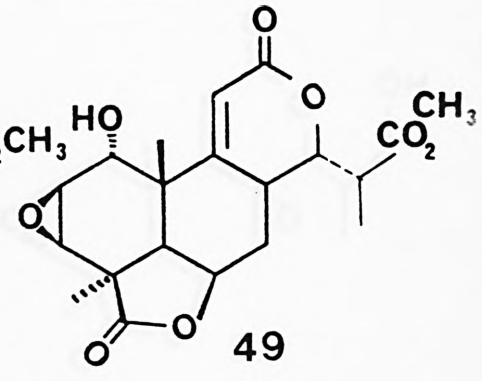

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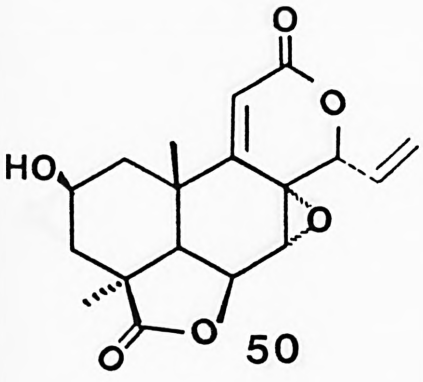

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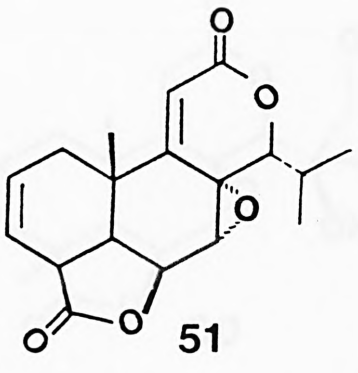

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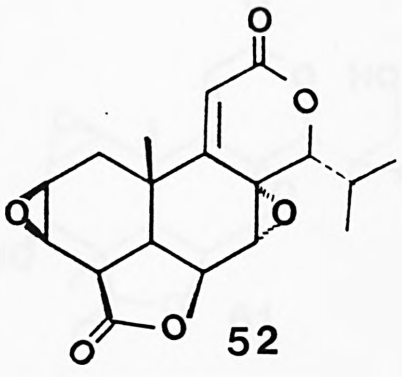

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2α,3α-epoxy
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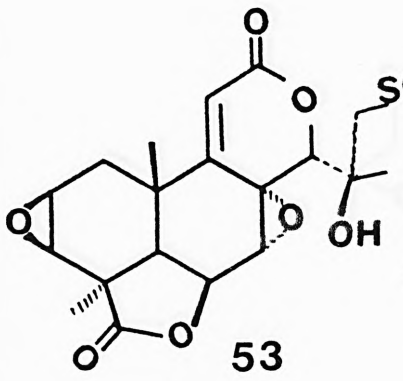

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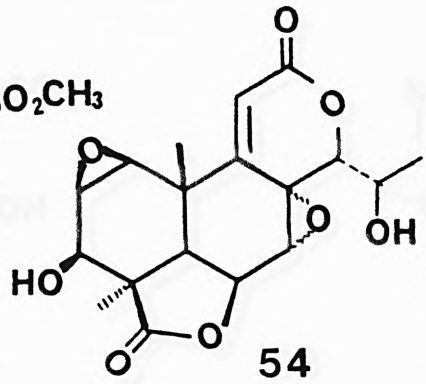

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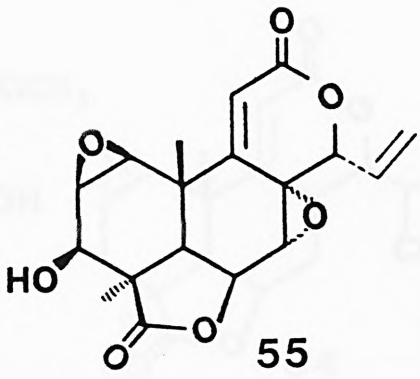

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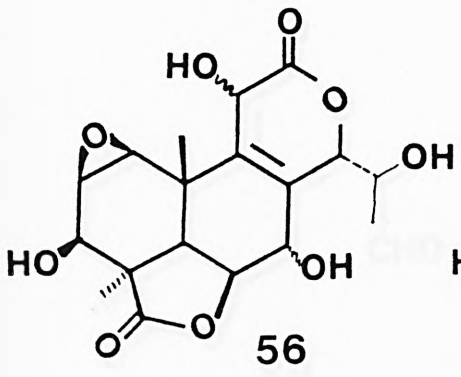
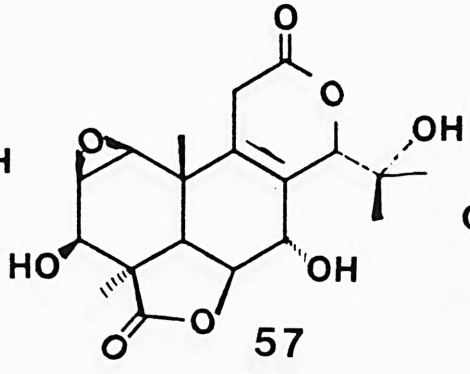


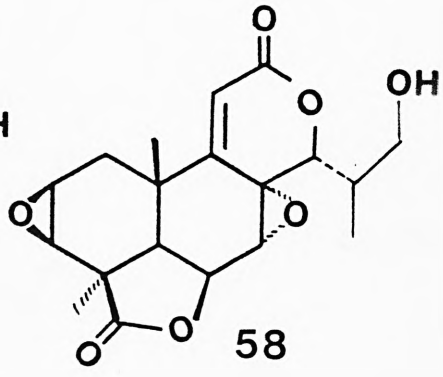
56

Inumakilactone C



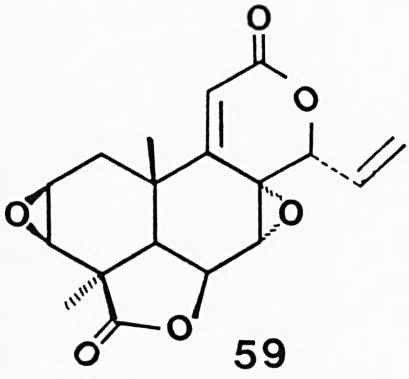
57

Inumakilactone D



58

Sellowin A



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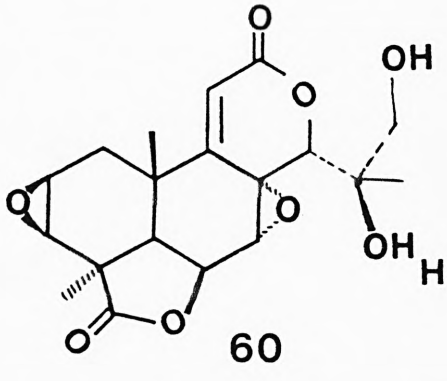
Sellowin B



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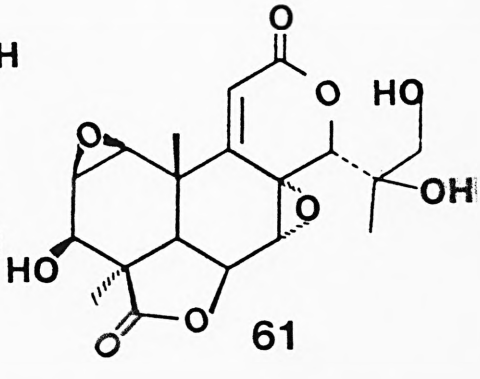
Podolactone A



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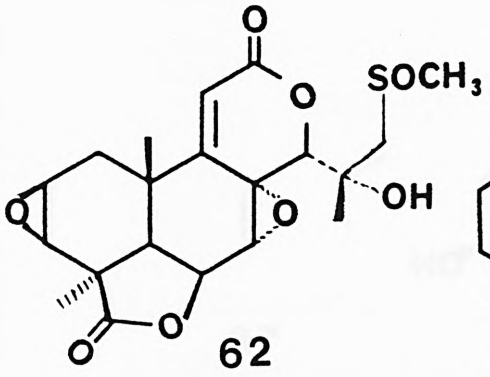
Podolactone B



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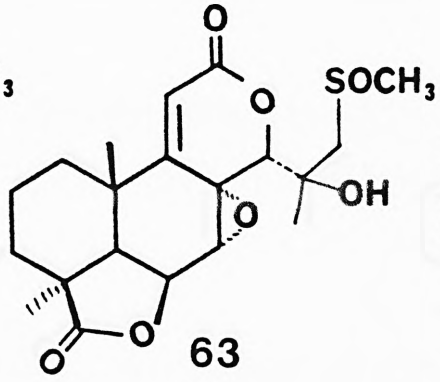
Podolactone C



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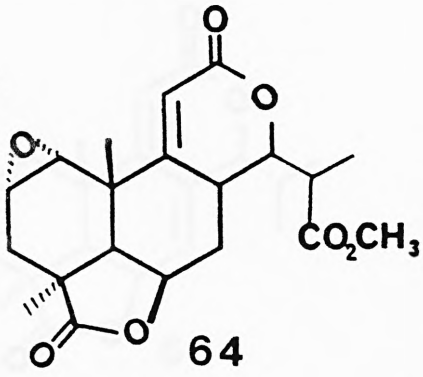
Podolactone D



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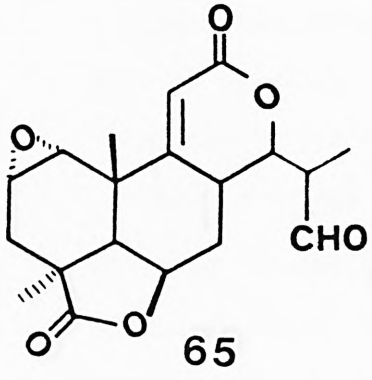
Lactone A



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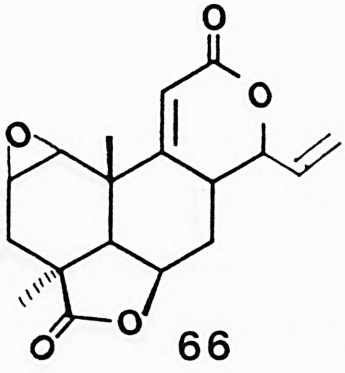
Lactone B



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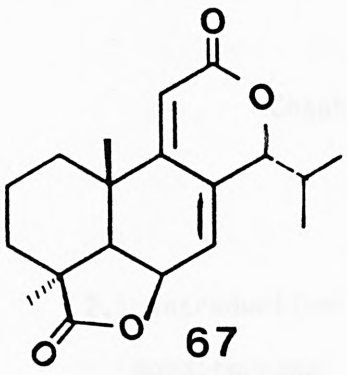
Lactone C

TYPE C



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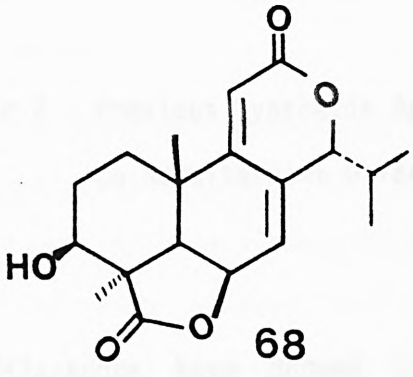
Nagilactone F



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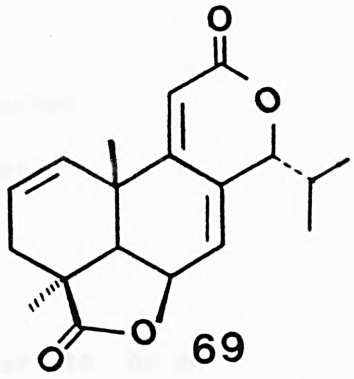
3β-hydroxy Nagilactone F



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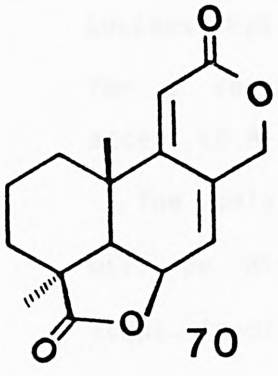
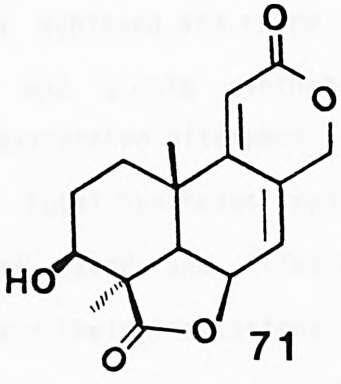
Milanjilactone B



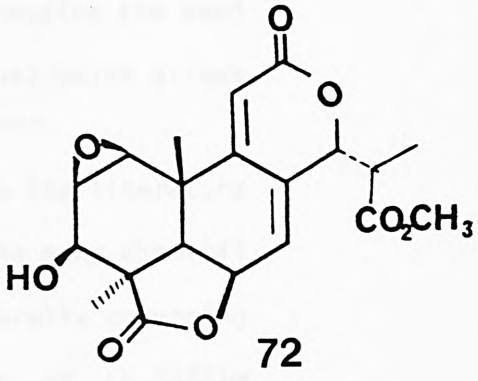
70

Wentilactone A



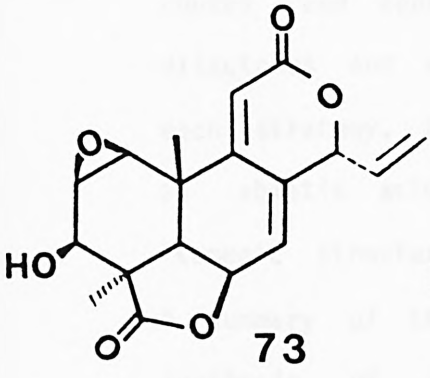
71

Wentilactone B



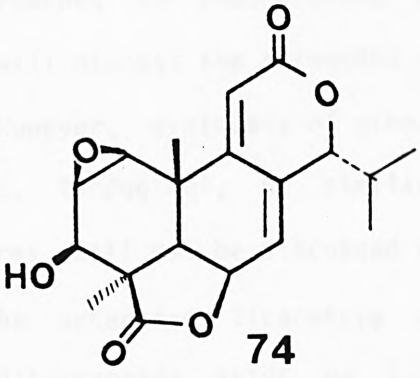
72

Nubilactone



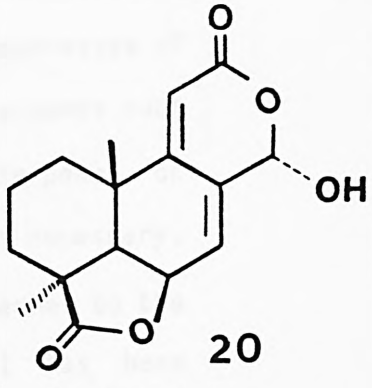
73

Podolactone E



74

Ponalactone A



20

LL-Z1271∝

Chapter 2 : Previous Synthetic Approaches to Norditerpene Dilactones.

2.1 Introduction

Norditerpene dilactones have proved so far to be an unyielding group of compounds to synthetic chemists. Ever since they were first identified in the early 1960's their synthesis has been a target for several groups wishing to carry out biological activity tests. So far, very limited success has been achieved and there still remains the need for a versatile and simple synthetic route which allows access to A-ring oxygenated diterpene dilactones.

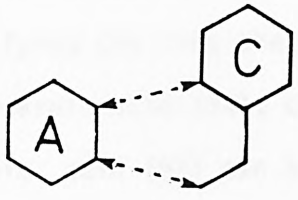
The only two total syntheses reported in the literature will be discussed later and illustrate the many chemical steps involved and their limitations. A naturally occurring precursor has been used to aid synthesis of LL-Z1271α norditerpene dilactone.

This chapter will specifically deal with the synthetic routes and approaches to podocarpanes and norditerpene dilactones and will discuss the strengths and weaknesses of each strategy. However, synthesis of other diterpenes such as abietic acid, ferruginol, or similar diterpenes of isomeric structures will not be discussed unless necessary. A summary of the extensive literature approaches to the synthesis of diterpenoids acids up to 1961 has been published by Rogers et al[1] .

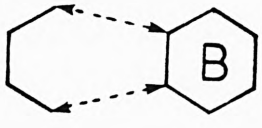
2.2 Synthetic Strategies

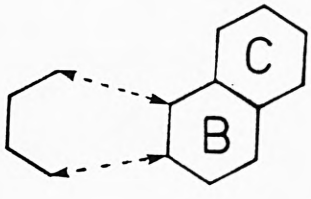
There have been numerous synthetic approaches to a variety of polycyclic diterpenoids of which diterpenoid resin acids and dilactones constitute just a part. Construction of the ring systems has employed various permutations of the order in which the three rings A, B, C or fragments are assembled. These are

1) type I

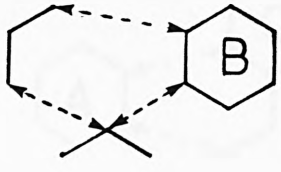


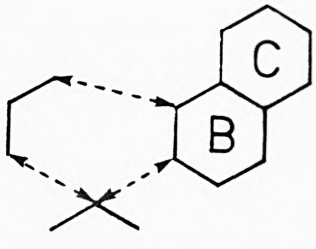
2) type II

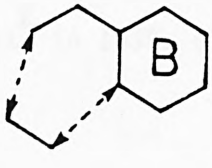


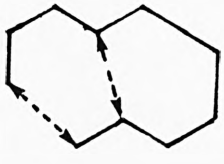


3) type III









The above also represents the way in which the survey is presented in this chapter. The synthesis must be designed so that the following features are met:

a) The angular methyl at C-10 is present

b) The stereochemistry of the methyl and COOH groups at the C-4 position is correct ie. 4-COOH cis to C-10 (methyl).

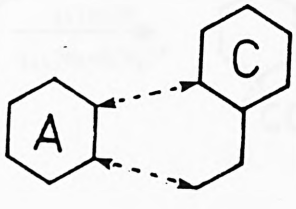
c) The configuration about C10-C5 bond is trans.

d) Ring A is functionalised.

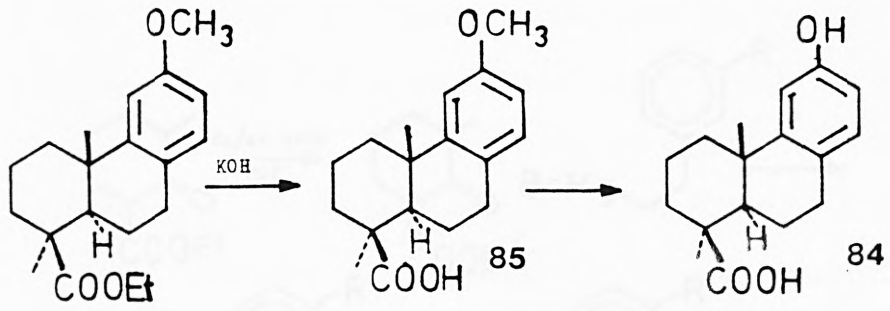
These features can be achieved either by choosing proper starting materials or by modifying the ring skeleton after it has been put together. Podocarpic acid (84), callitrisic acid (83), and desoxypodocarpic acid (82) can be and have been used as precursors to norditerpene dilactones. Their C-ring can be transformed into a pyrone and a γ-lactone formed at C4-C6.

2.3 Literature Survey of Synthetic Methods.

2.3.1 Type 1

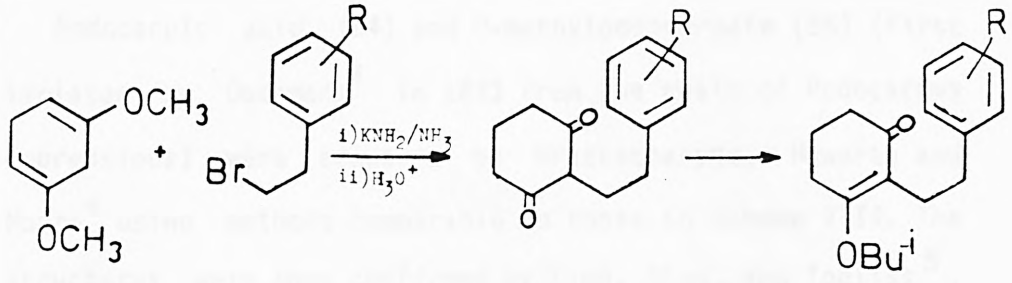


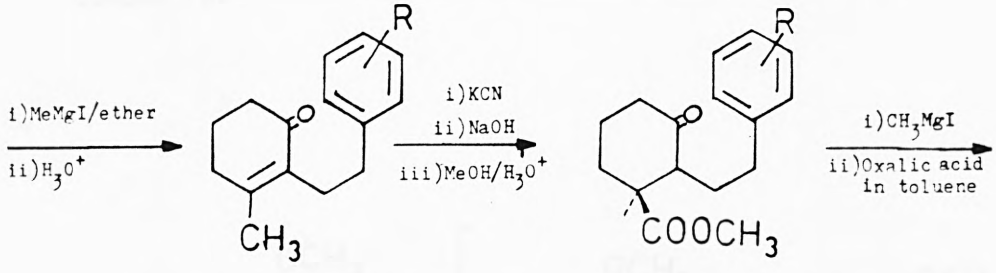
The strategy depicted in this category includes the first synthesis of desoxypodocarpic acid (82) and callitrisic acid (83) by Haworth et al.[2] in 1939. (Scheme VIII).

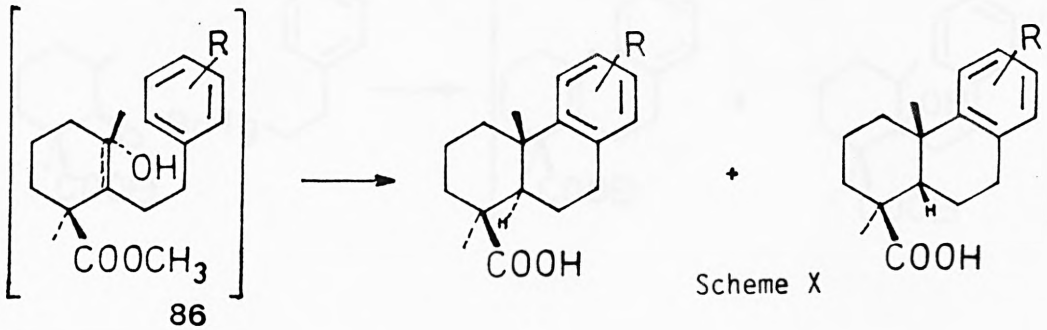


Scheme IX

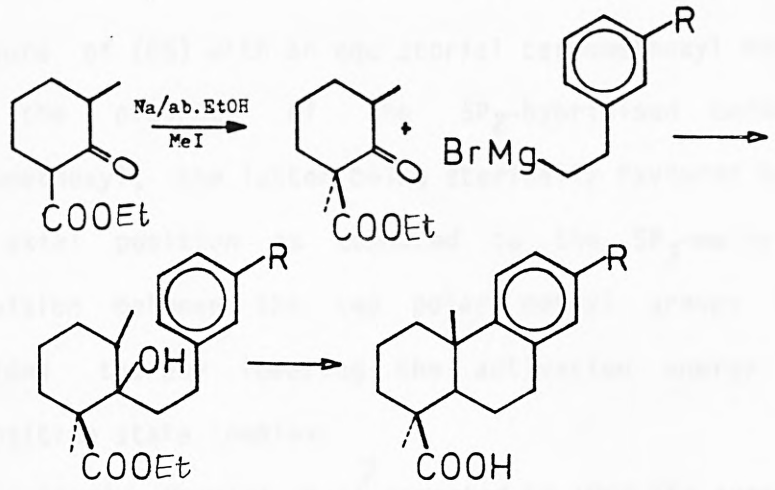
Ranjanghatak et al.[6] also reported preparation of desoxypodocarpic acid (82) ,which involved in turn construction of the correct stereochemistry of substituents on C-4, introduction of C-10, and B-ring cyclisation to effect the correct orientation of the C-10 methyl group about the trans A-B ring junction (Scheme X).







Scheme X

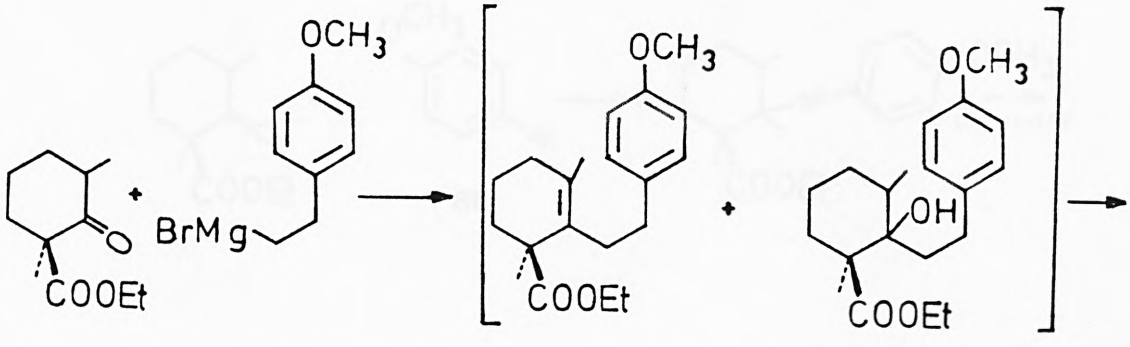


82 R=H, Desoxypodocarpic acid

83 R=  Callitrisic acid

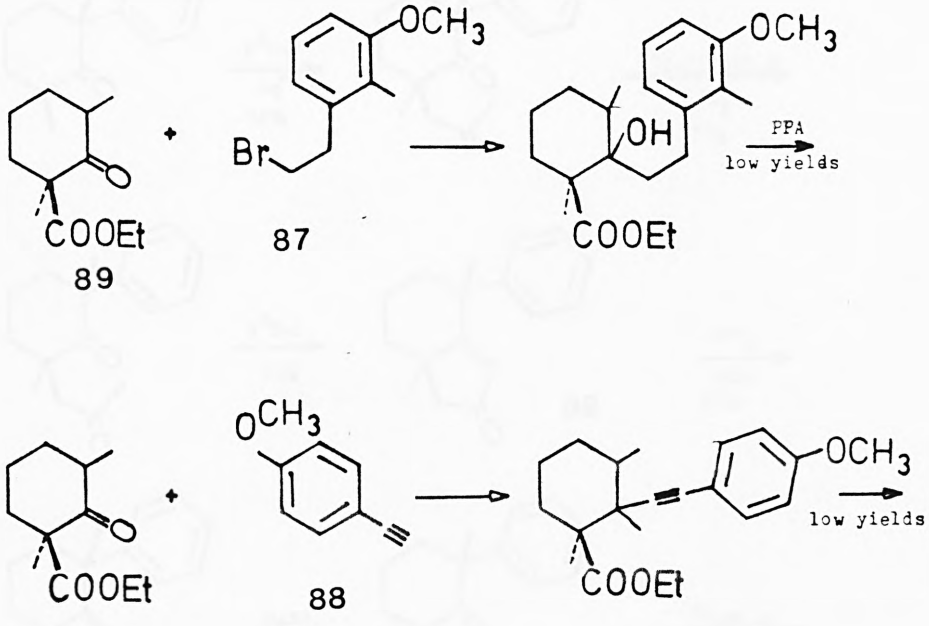
SCHEME VIII

Podocarpic acid (84) and O-methylpodocarpate (85) (first isolated by Oudemans[3] in 1873 from the resin of Podocarpus cupressinus) were prepared by Bhattacharyga, Haworth and Moore[4] using methods comparable to those in Scheme VIII. The structures were then confirmed by King, King, and Topliss[5]. Scheme IX.



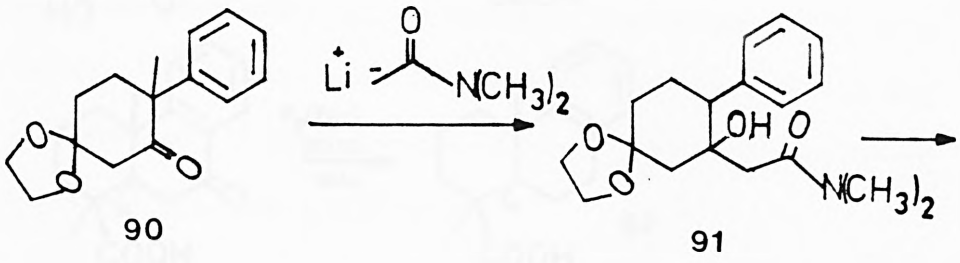
Non formation of isomeric compounds during the ring closure of (86) with an equatorial carbomethoxyl may be due to the presence of the SP_2-hybridised carbonyl of carbmethoxyl, the latter being sterically favoured to occupy an axial position as compared to the SP_3-methyl. The repulsion between the two polar methyl groups is also avoided thereby lowering the activation energy of the transition state complex.

Similarly Mancini et al.[7] reported in 1969 the synthesis of derivatives of podocarpic acid via Grignard condensation of β-(2-methyl-3-methoxy phenyl) ethyl bromide (87) or p-methoxyphenyl acetylene (88) with ethyl-1,3-dimethyl-2-oxocyclohexane carboxylate (89) and then cyclisation (Scheme XI).



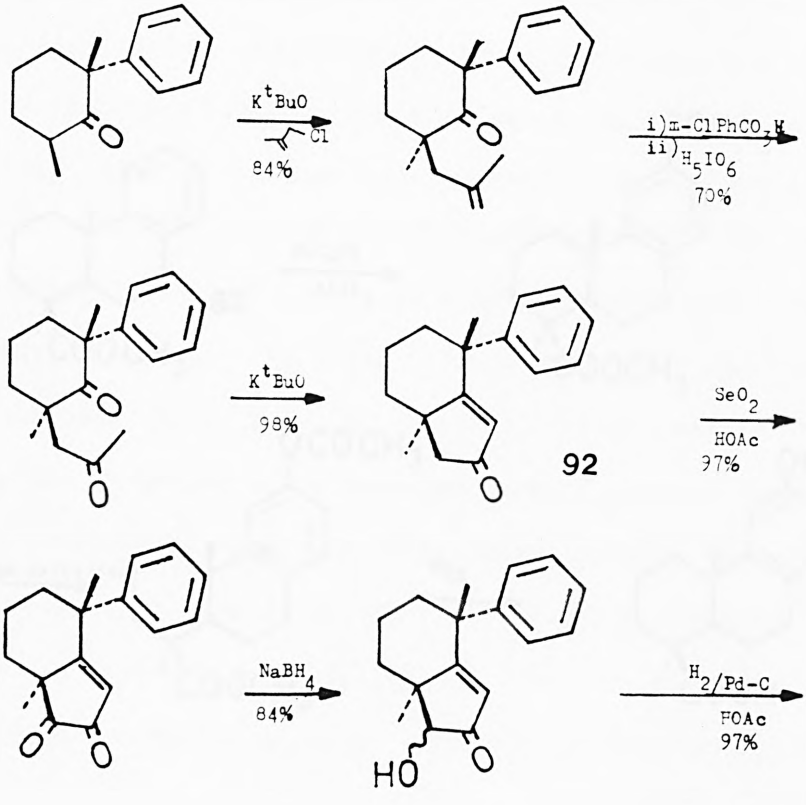
Scheme XI

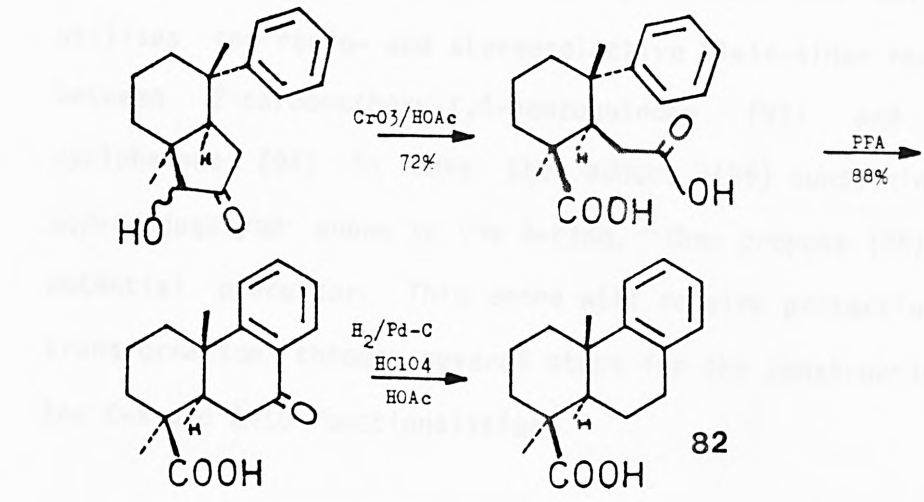
A slightly different approach by Japanese workers involves treating dioxaspirodecanone (90) with 2-lithio-N,N-dimethyl,acetamide to prepare (91) as a potential intermediate[8].



90 91

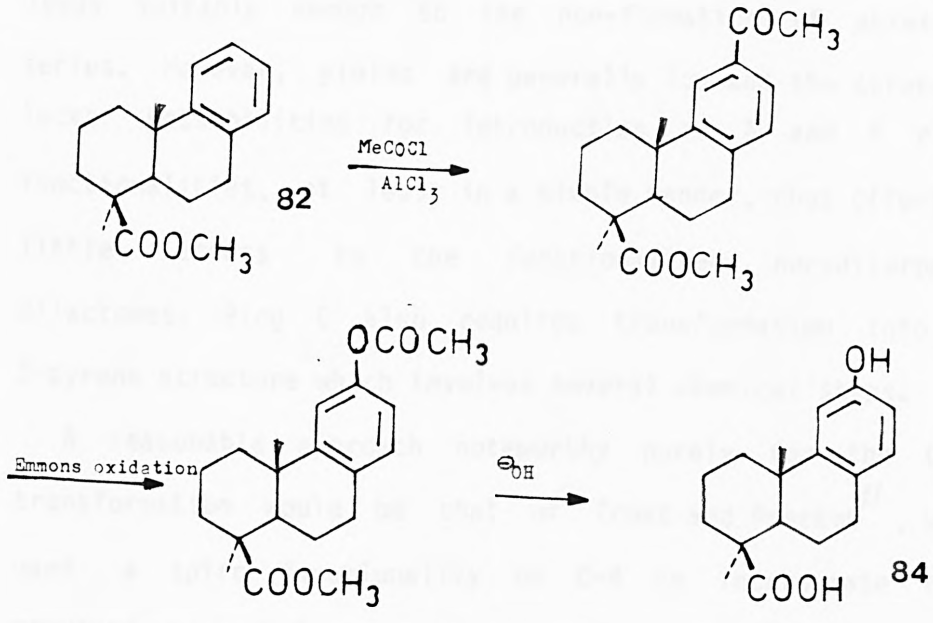
Giarrusso and Ireland[9] developed a novel hydrindenone precursor(92), which led to preparation of (±)-desoxypodocarpic acid in 11 stages with an overall yield of 21%.(Scheme XII).



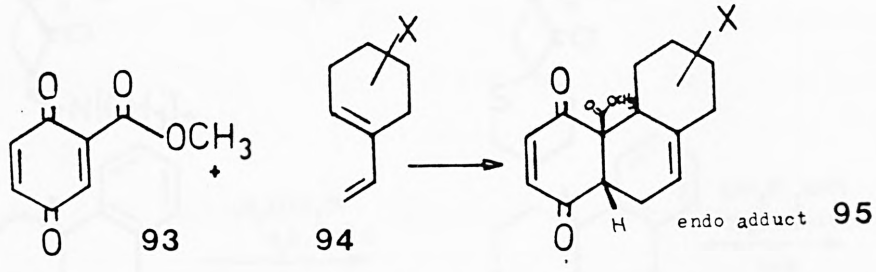


Scheme XII

d-Desoxypodocarpic acid can then be converted to podocarpic acid as follows:



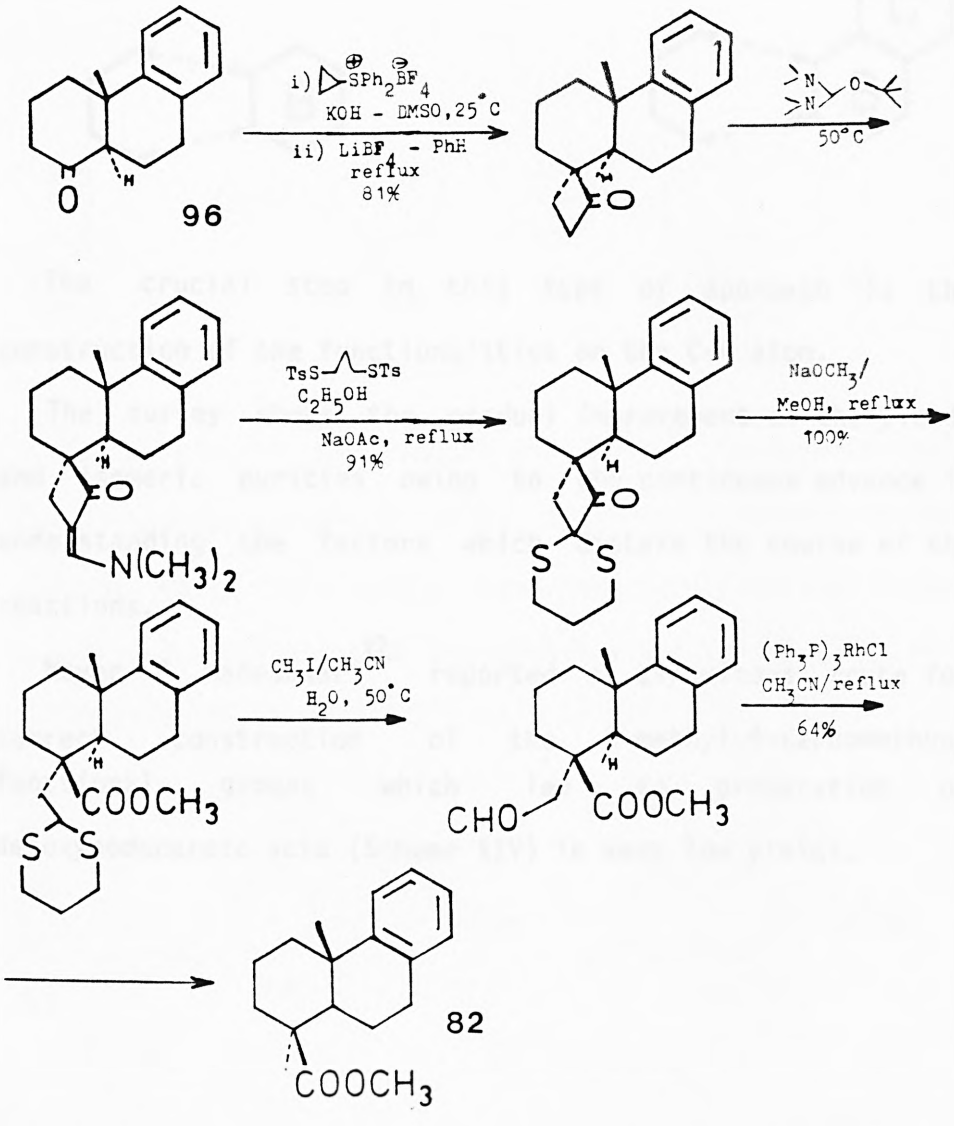
Finally, a recent approach by Orsini and Pelizzoni[10] utilises the regio- and stereoselective Diels-Alder reaction between 2-carbomethoxy-1,4-benzoquinone (93) and vinyl cyclohexene (94) to make the adduct (95) containing the α,β-conjugated enone in the A-ring. They propose (95) as a potential precursor. This enone will require protection and transformation through several steps for the construction of the C-4 and C-10 functionalities.



93 94 endo adduct 95

Knowledge available from this type of strategy enables construction of podocarpanes. The prerequisite condition for the cyclisation stage appears to be the aromatic C ring and leads suitably enough to the non-formation of abietane series. However, yields are generally low and the strategy lacks possibilities for introduction of A and B ring functionalities, at least in a simple manner, thus offering little access to the functionalised nor-diterpene dilactones. Ring C also requires transformation into a 2-pyrone structure which involves several chemical steps.

A reasonable approach noteworthy purely for the C-4 transformation would be that of Trost and Precket[11], who used a spiro functionality on C-4 to incorporate the required gem methyl carboxyl correctly in (96)(Scheme XIII).


i) SPh2BF4
KOH - DMSO, 25°C
ii) LiBF4 - PhH
reflux
81%
96
50°C
TsS STs
C2H5OH
NaOAc, reflux
91%
NaOCH3/
MeOH, reflux
100%
N(CH3)2
CH3I/CH3CN
H2O, 50°C
(Ph3P)3RhCl
CH3CN/reflux
64%
COOCH3
CHO
82

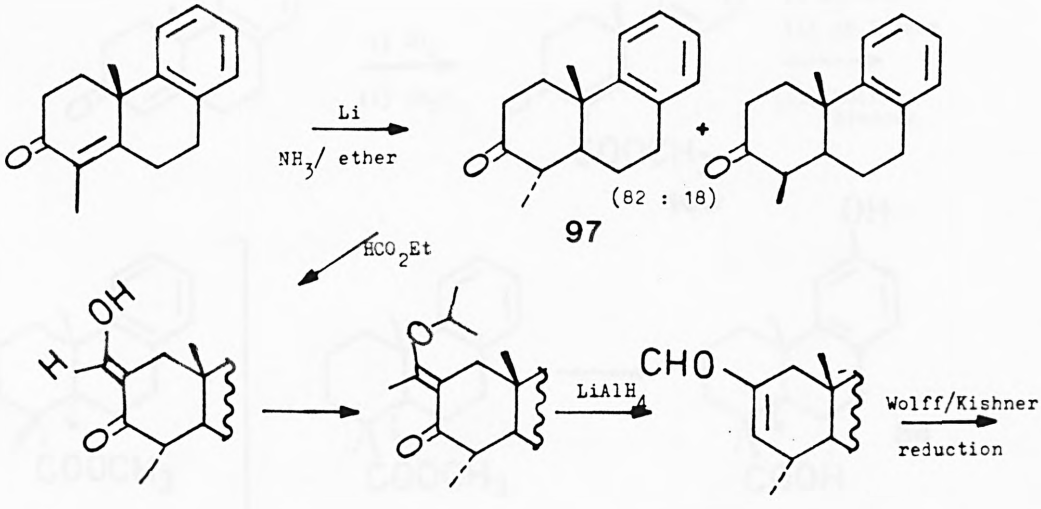
Scheme XIII

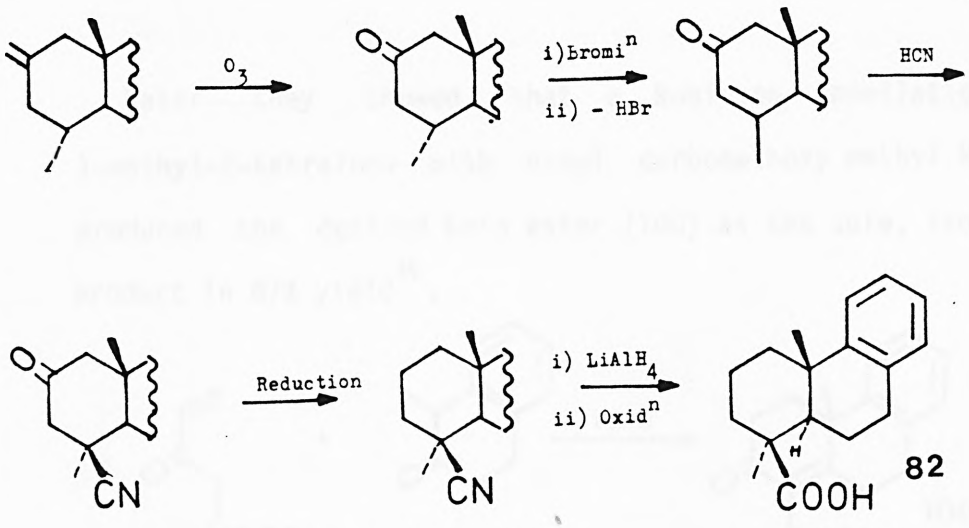
2.3.2 Type II

The crucial step in this type of approach is the construction of the functionalities on the C-4 atom.

The survey shows the gradual improvement of the yields and isomeric purities owing to the continuous advance in understanding the factors which dictate the course of the reactions.

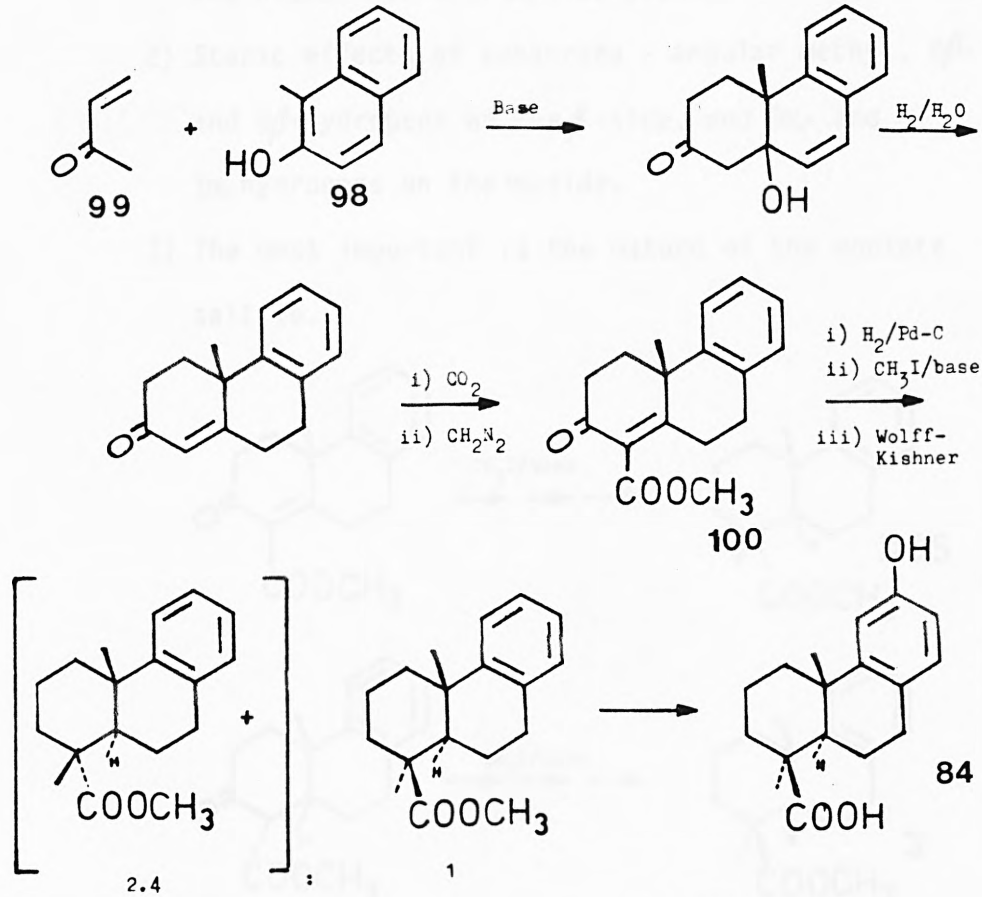
Meyer & Maheshwari[12] reported a circuitous route for correct construction of the 4-methyl-4-carbomethoxy functional groups which led to preparation of desoxypodocarpic acid (Scheme XIV) in very low yields.





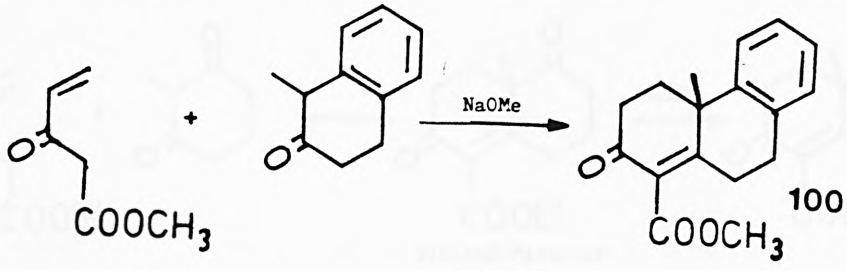
Scheme XIV

Early efforts by Wenkert and Tahara[13] to develop routes to a hydrophenanthrone (100) resulted in several methods, one of which involved a base-catalysed reaction between 1-methyl-2-naphthol (98) and methyl vinyl ketone (99), which ultimately led to podocarpic acid (Scheme XV)



Scheme XV

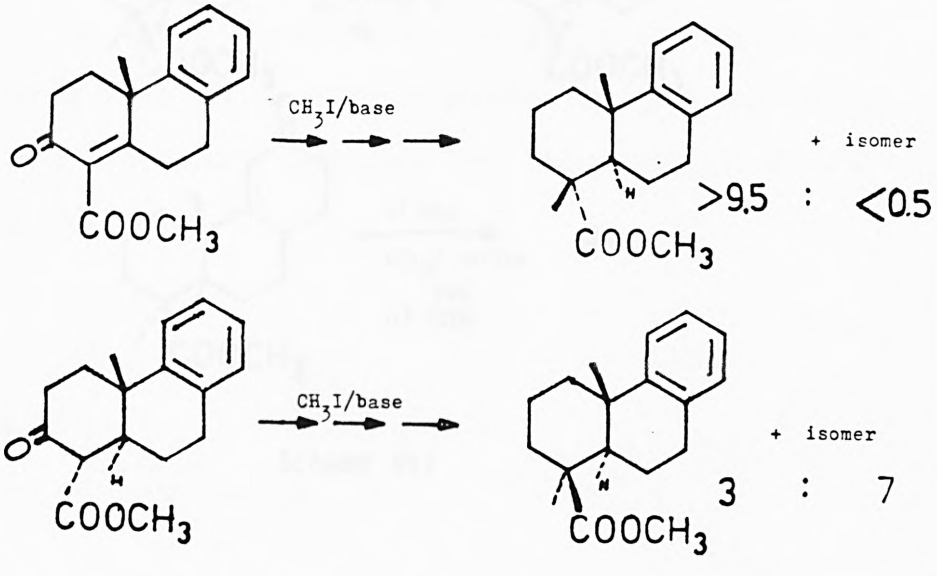
Later they showed that a Robinson annellation on 1-methyl-2-tetralone with vinyl carbomethoxy methyl ketone produced the desired keto ester (100) as the sole, isolable product in 87% yield[14].



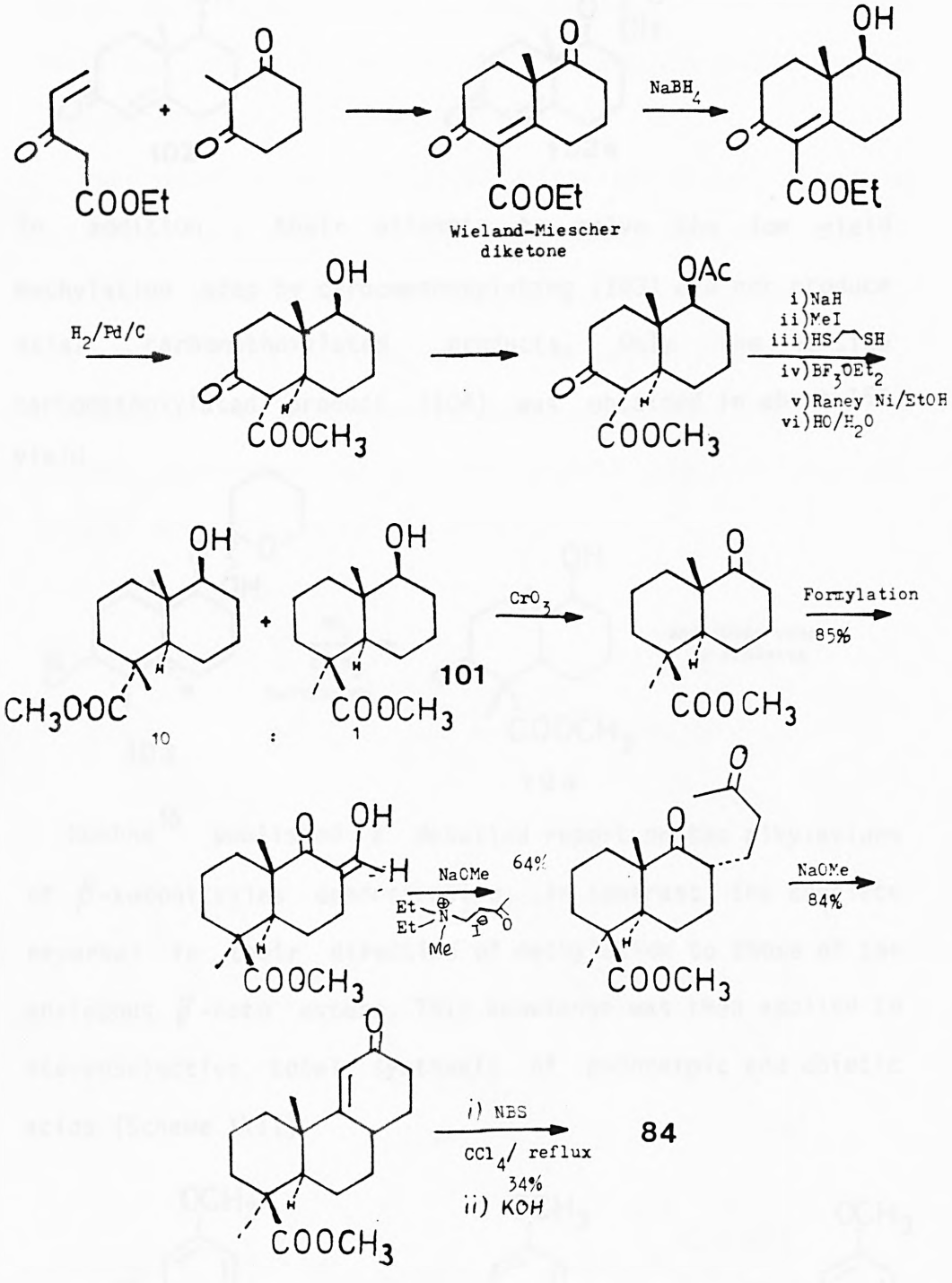
100

The factors influencing the non-stereospecific methylation step brought about by the attack of methylating agent from α- or β-side were shown experimentally to be;

1) The size of the methylating agent, (CH_3, $BrCH_2CO_2C_2H_5$, $(ClCH_2)_2S$), the larger the reagent, the higher ratio of α-side attack.
2) Steric effects of substrate - angular methyl, 2β- and 6β-hydrogens on the β-side, and 5α- and 1α-hydrogens on the α-side.
3) The most important is the nature of the enolate salt ie.

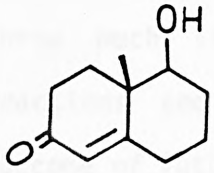


Spencer et al[15] working on the abietic series came across a minor product (101) which allowed access to the compounds in the podocarpic acid series (Scheme XVI).

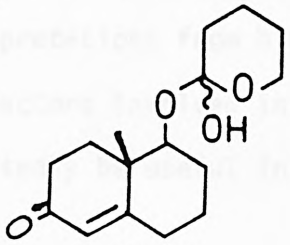


Scheme XVI

They showed that the yield from reductive carbomethoxylation of (102) can be increased from 12% to 30% by using the tetrahydropyranyl ether(102a).

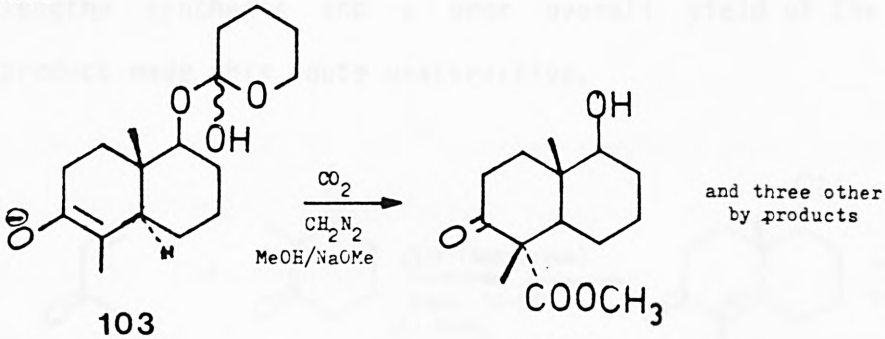


102



102a

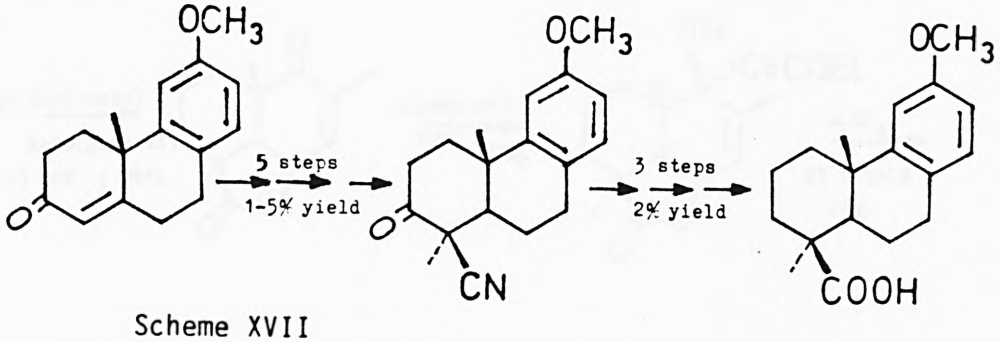
In addition , their attempts to solve the low yield methylation step by carbomethoxylating (103) did not produce axial carbomethoxylated products. Only the ∝-side carbomethoxylated product (104) was obtained in about 15% yield



103

104

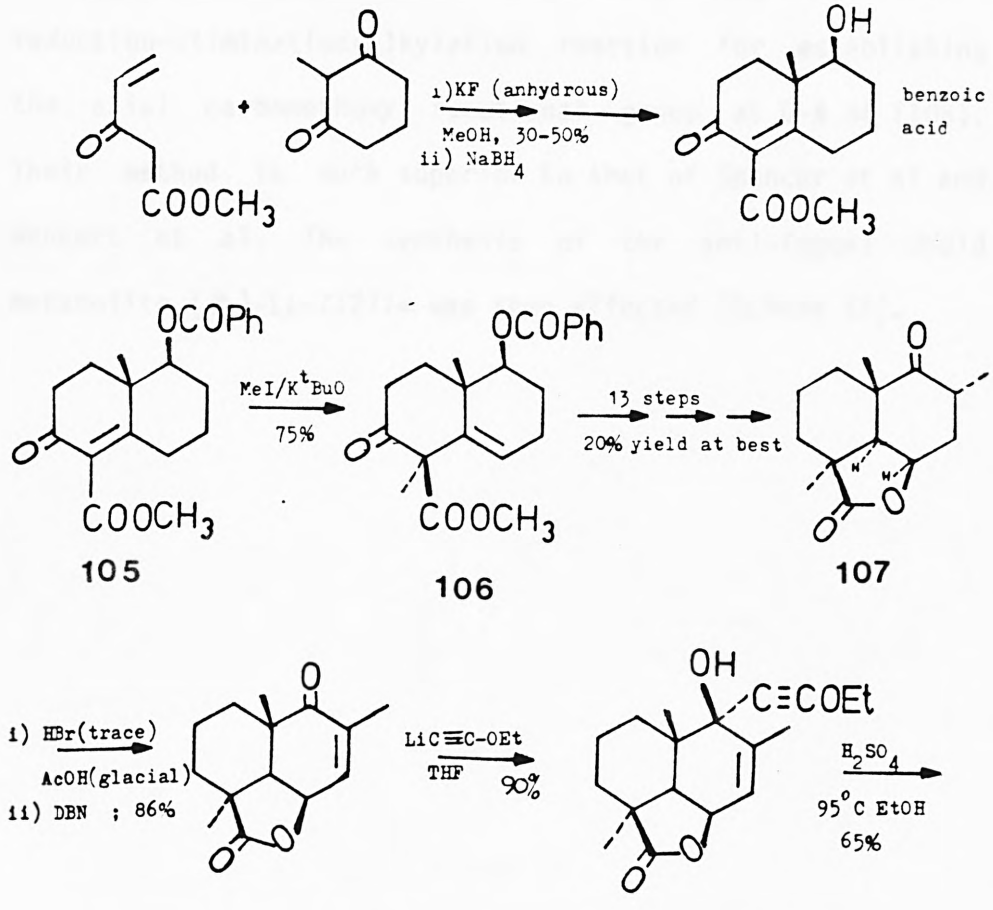
Kuehne[16] published a detailed report on the alkylations of β-ketonitriles demónstrating, in contrast, the complete reversal in their direction of methylation to those of the analogous β-keto esters. This knowledge was then applied to stereoselective total synthesis of podocarpic and abietic acids (Scheme XVII).

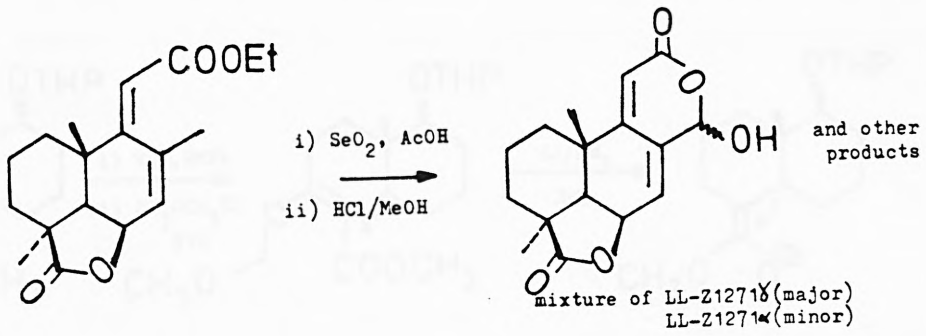


Scheme XVII

Clearly Scheme XVII is not practical owing to unacceptable yields. Nevertheless, Kuehne[17] has deduced valuable experimental interpretations from his results which throw much light on the factors involved in the alkylation reactions and will undoubtedly be useful in predicting the outcome of future reactions.

Two years after isolation of the anti-fungal dilactone LL-71271α its synthesis was described by Adinolfi et al[18]. The keto ester (106) was stereospecifically prepared from the ester (105), according to the method of Pelletier[19]. Although a few modifications were made (Scheme XIX) but the lengthy synthesis and a poor overall yield of the final product made this route unattractive.

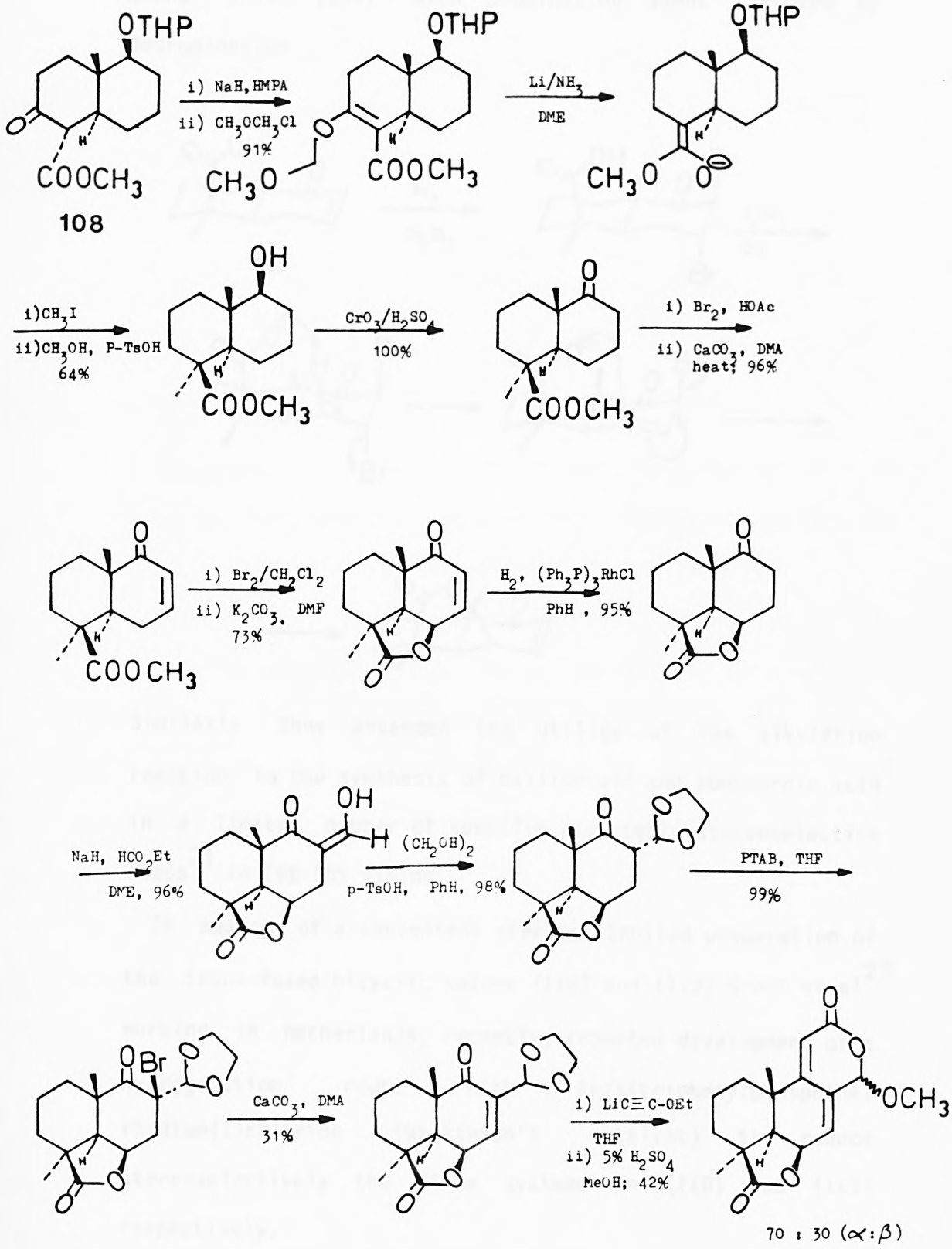




Scheme XIX

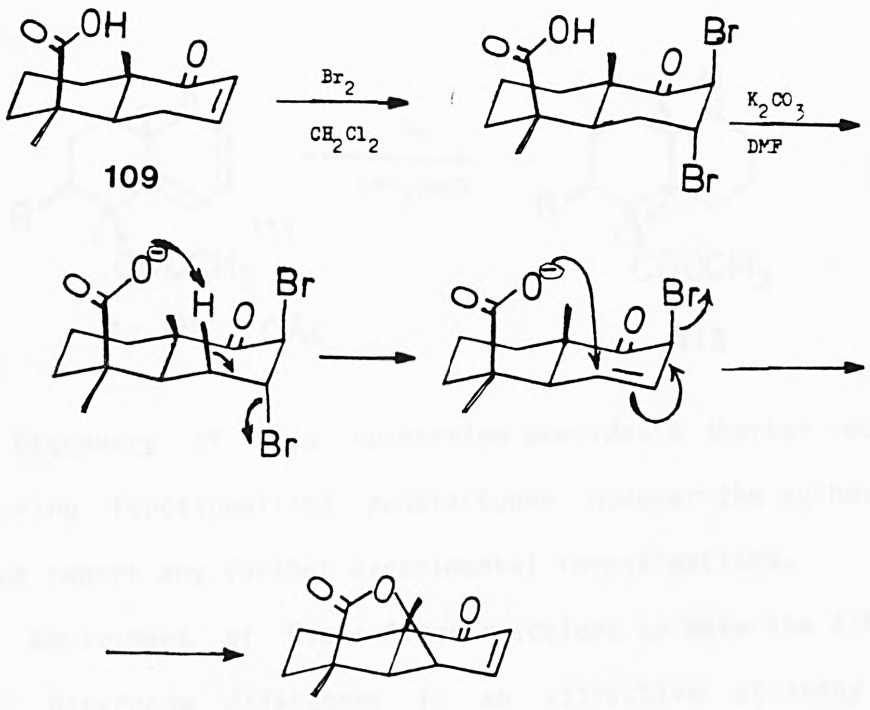
(107) is also accessible from degradation of naturally occuring Marrubin.

In 1977 Welch et al[20] reported a highly stereoselective reduction-elimination-alkylation reaction for establishing the axial carbomethoxy functional group at C-4 of (108). Their method is much superior to that of Spencer et al and Wenkert et al. The synthesis of the anti-fungal mould metabolite (±)-LL-Z1271α was then effected (Scheme XX).


OTHP
COOCH3
108
i) NaH, HMPA
ii) CH3OCH2Cl
91%
CH3O
Li/NH3
DME
i)CH3I
ii)CH3OH, P-TsOH
64%
OH
CrO3/H2SO4
100%
i) Br2, HOAc
ii) CaCO3, DMA
heat; 96%
i) Br2/CH2Cl2
ii) K2CO3, DMF
73%
H2, (Ph3P)3RhCl
PhH , 95%
NaH, HCO2Et
DME, 96%
(CH2OH)2
p-TsOH, PhH, 98%
PTAB, THF
99%
Br
CaCO3, DMA
31%
i) LiC≡C-OEt
THF
ii) 5% H2SO4
MeOH; 42%
OCH3
70 : 30 (α:β)

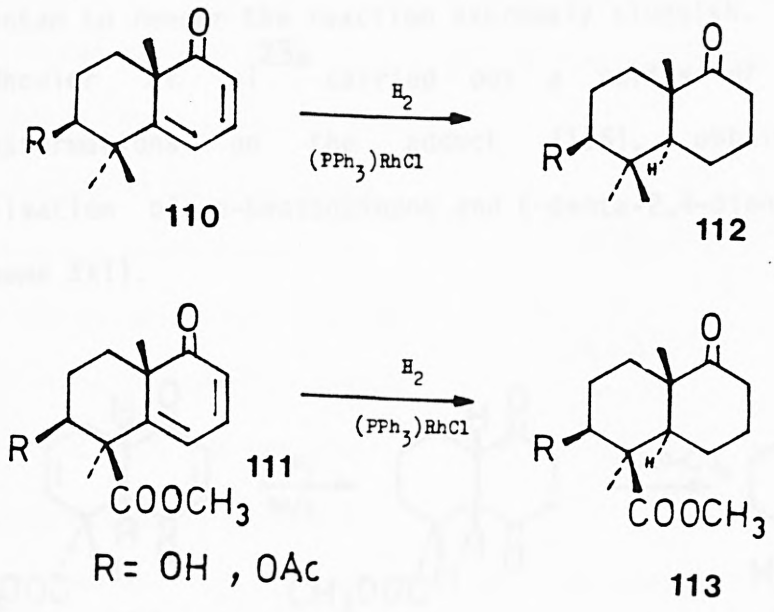
Scheme XX

The γ-lactone formation was effected by treating the enone acid (109) with brominating agent followed by debromination



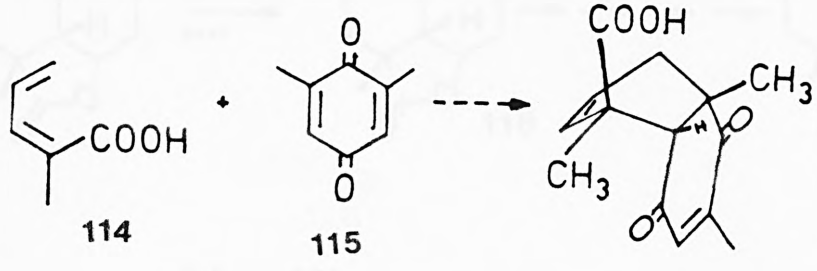
Similarly they extended the utility of the alkylation reaction to the synthesis of callitrisic and podocarpic acid in a limited number of specific and highly stereoselective steps[21] in 26%-50% yields.

In search of a convenient stereocontrolled preparation of the trans-fused bicyclic ketone (112) and (113) Groot et al[22] working in Netherlands, recently, reported development of a hydrogenation route with tris(triphenylphosphine) rhodium(I)chloride (Wilkinson's catalyst) to reduce stereoselectively the diene systems in (110) and (111) respectively.



Discovery of this conversion provides a shorter route to A-ring functionalised podolactones however the authors did not report any further experimental investigations.

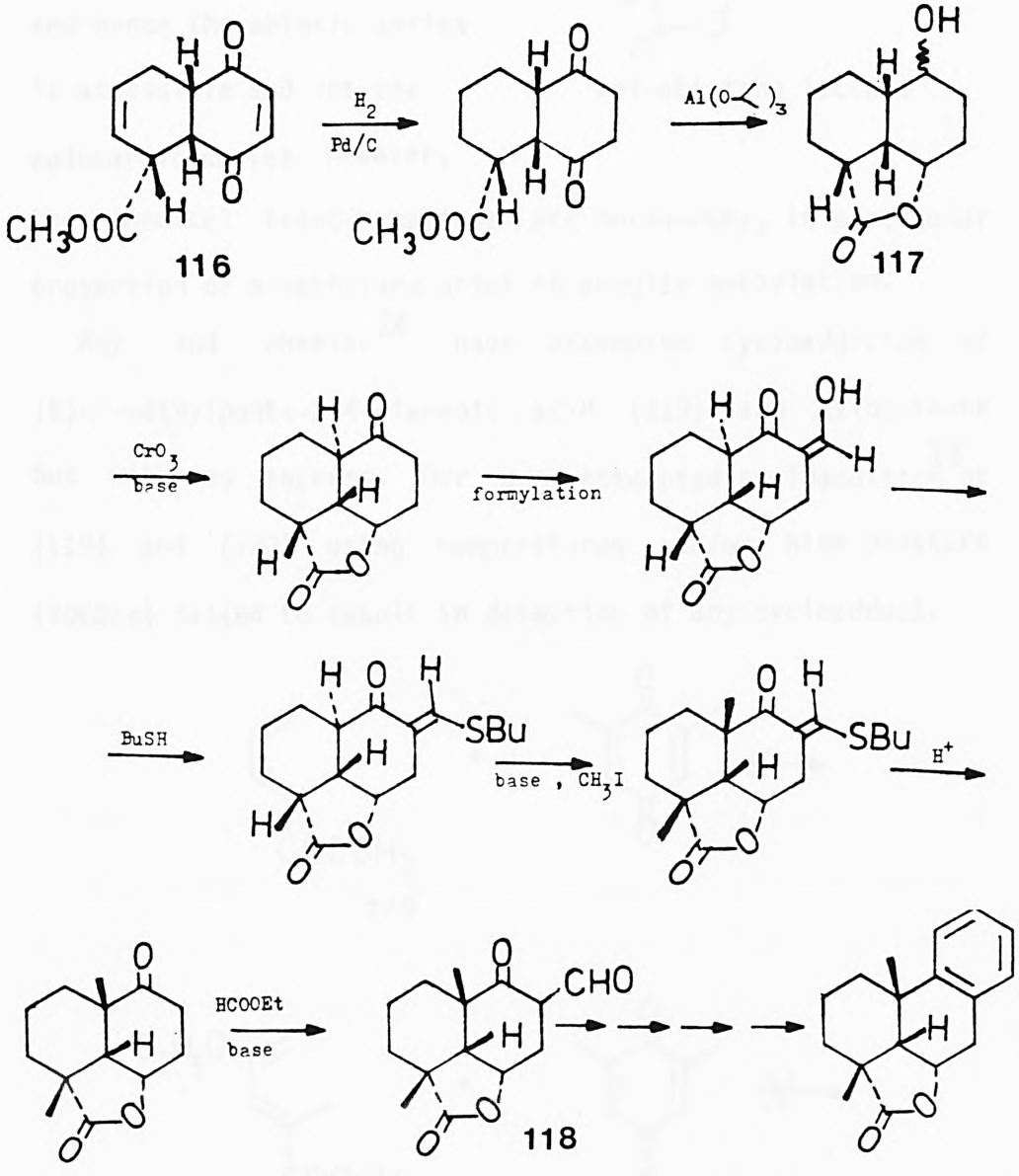
Employment of Diels-Alder reactions to make the A/B-ring of diterpene dilactones is an attractive strategy which offers the opportunity of constructing the correct stereochemistry of substituents on C-4, C-5 and C-10 in one step. For this (Z)-2-methyl-penta-2,4-dieneoic acid (114) and 1,3-dimethyl-2,5-dioxocyclohexa-3,6-diene (115) must cyclise to form a non-ortho/endo adduct.



However, presence of the geminal methyl carboxylic acid function on the diene and a methyl on the dieneophile is

expected to render the reaction extremely sluggish.

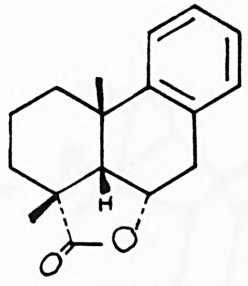
Wheeler et al[23b] carried out a series of chemical transformations on the adduct (116), obtained from cyclisation of p-benzoquinone and E-penta-2,4-dieneoic acid (Scheme XXI).



Scheme XXI

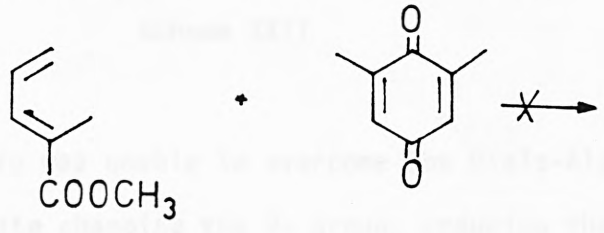
Compound (118) clearly has the wrong stereochemistry for the

synthesis of the podocarpanes and dilactones. However, it was taken through four more steps to the epi-abietane lactone. It is apparent that the methylation step gives the wrong stereochemistry of the methyl group on C-10 and hence the abietic series is accessible and not the podocarpic series. However, the chemical transformations are noteworthy, in particular protection of a-methylene prior to angular methylation.

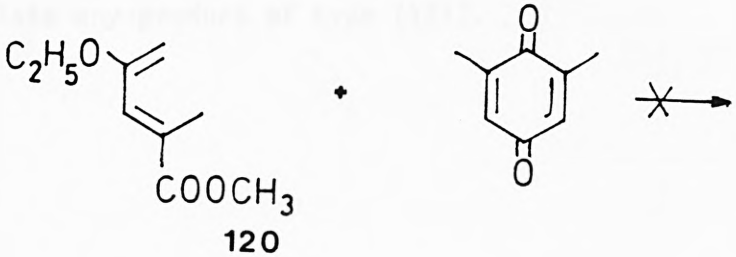


epi-abietane lactone

Roy and wheeler[24] have attempted cycloaddition of (E)-2-methylpenta-2,4-dieneoic acid (119) and xyloquinone but with no success. Our own attempted cycloaddition[25] of (119) and (120) using temperatures and/or high pressure (70KBar) failed to result in detection of any cycloadduct.



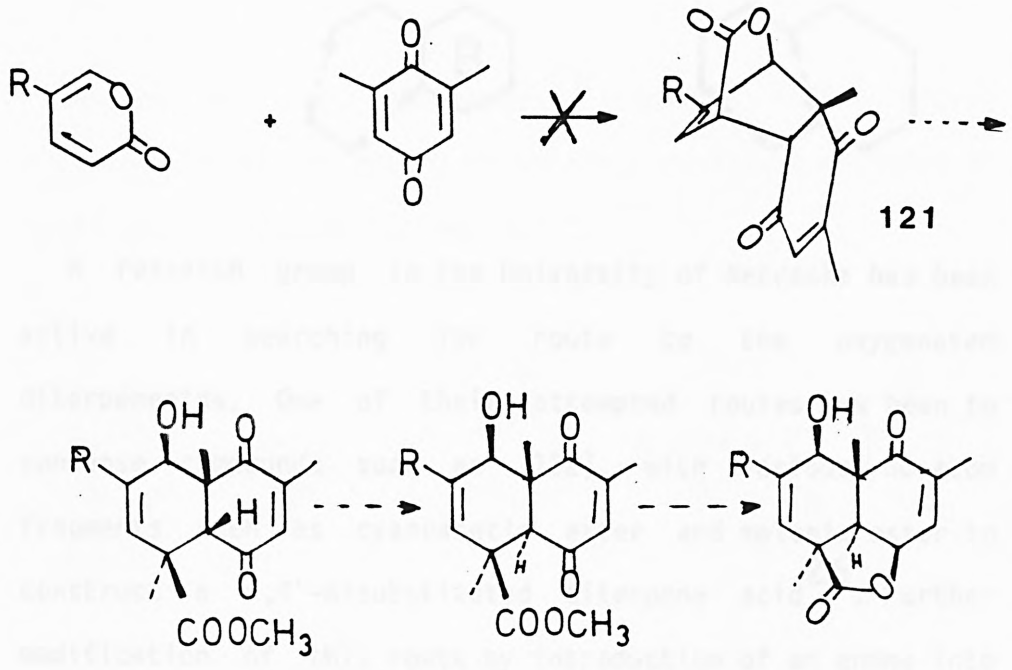
119



120

The idea of using a 2-pyrone as a configurationally locked diene was adopted by Liu in 1980[23a], who proposed to build a bicyclic bridge compound (121) which would be ring

opened, followed by epimerisation at C-5 to produce the correct trans-ring junction and stereochemistry at C-4 (Scheme XXII).

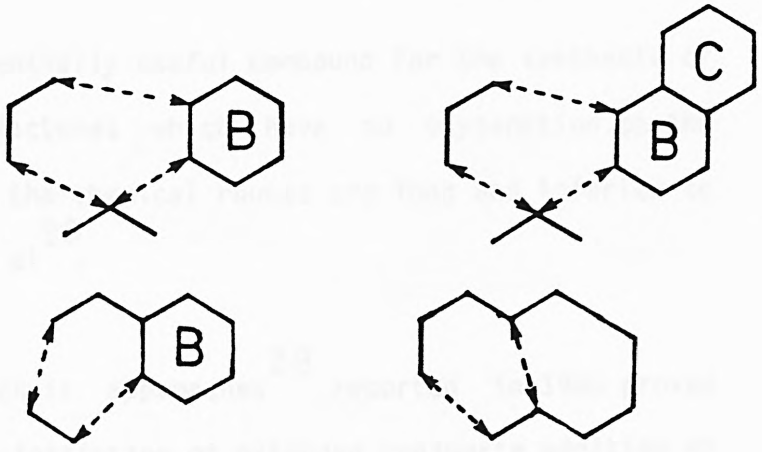


R=$COOCH_3$, -NHCOOR' , $-CH_3$, $-C_2H_5$, $-C(CH_3)_3$.

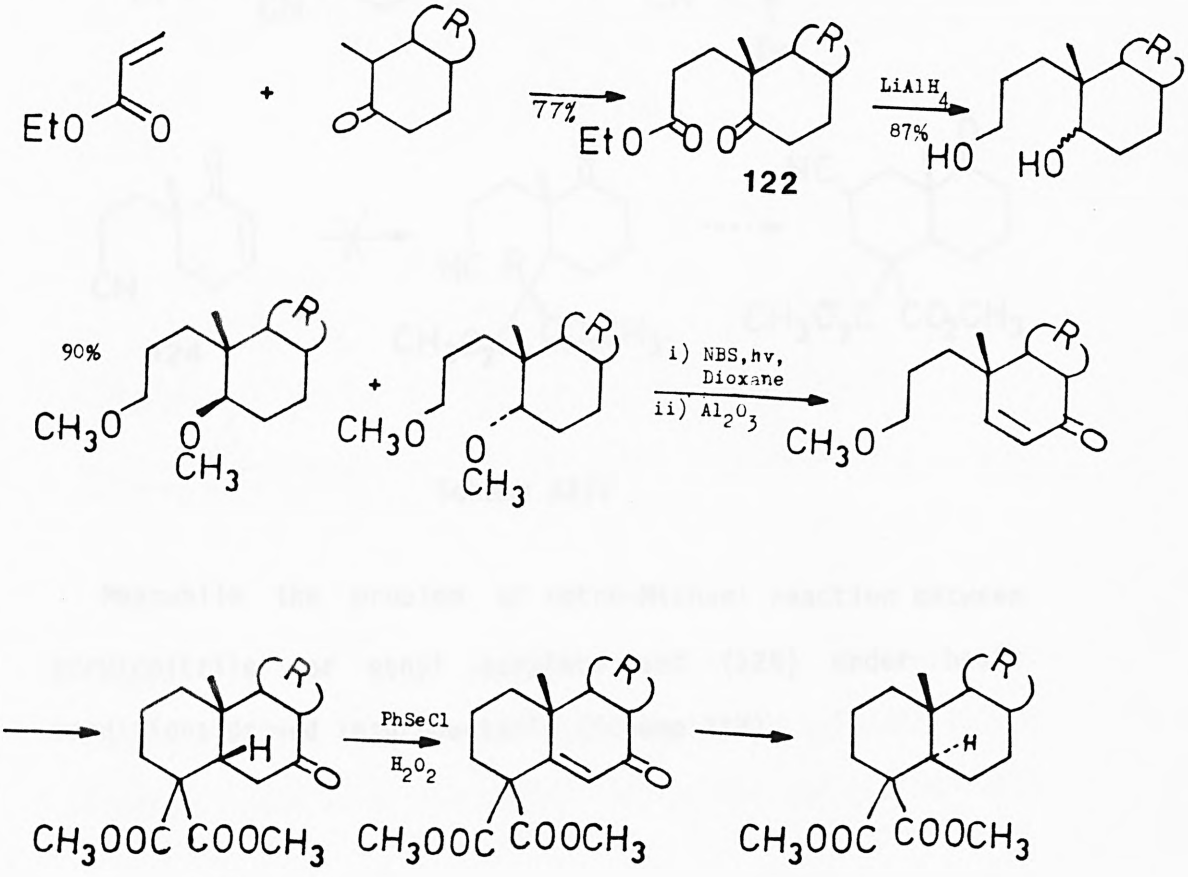
Scheme XXII

However, Liu was unable to overcome the Diels-Alder energy barrier despite changing the R- group, reducing the carbonyl of the pyrone, or using Lewis acids as catalyst, and failed to isolate any product of type (121).

2.3.3 TYPE III



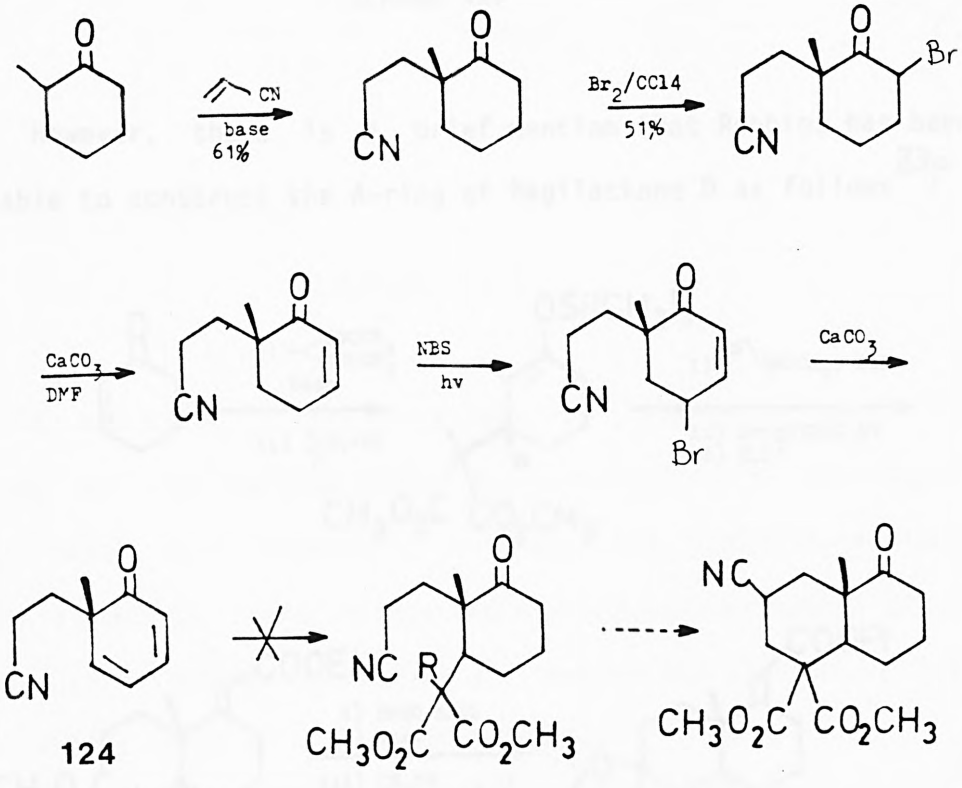
A research group in the University of Nebraska has been active in searching for route to the oxygenated diterpeneoids. One of their attempted routes has been to condense compounds such as (122), with various 3C atom fragments such as cyanoacetic ester and malonic ester to construct a 4,4'-disubstituted diterpene acid[26]. Further modification of this route by introduction of an enone into the system improved yields[27] (Scheme XXIII).



Scheme XXIII

(123) is a potentially useful compound for the synthesis of norditerpene dilactones which have no oxygenation on the A-ring. However the chemical routes are long and inferior to that of Welch et al[20].

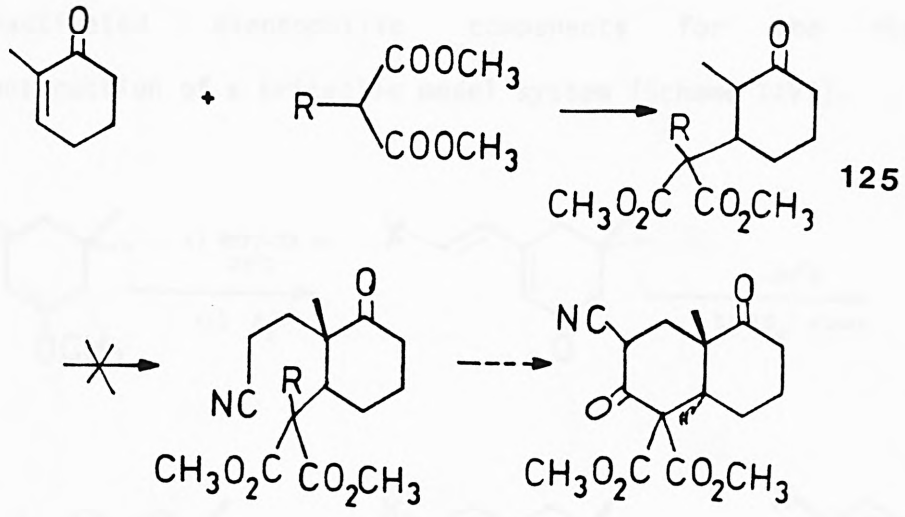
Another of their approaches[28] reported in 1980 proved fruitless since initiation of extended conjugate addition on (124) did not proceed (Scheme XXIV).



124

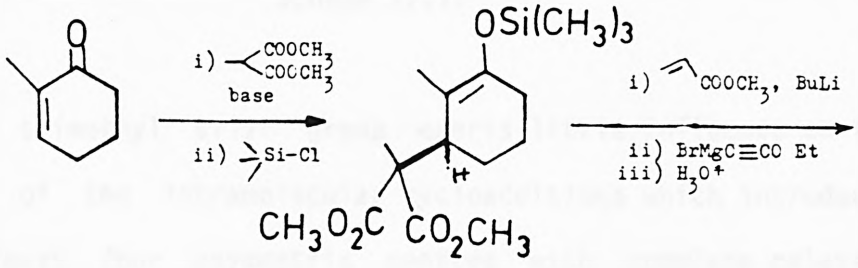
Scheme XXIV

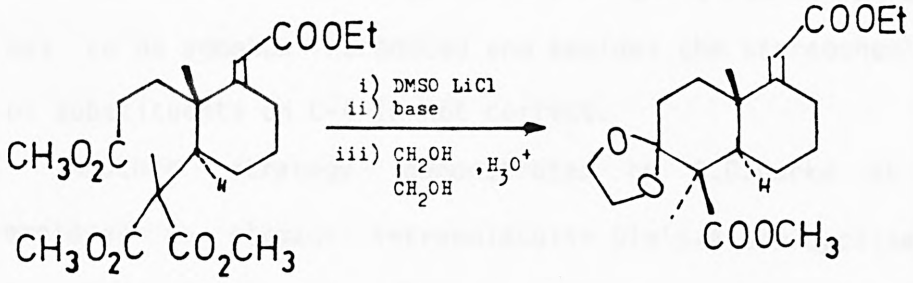
Meanwhile the problem of retro-Michael reaction between acrylonitrile or ethyl acrylate and (125) under basic conditions proved insurmountable (Scheme XXV).



Scheme XXV

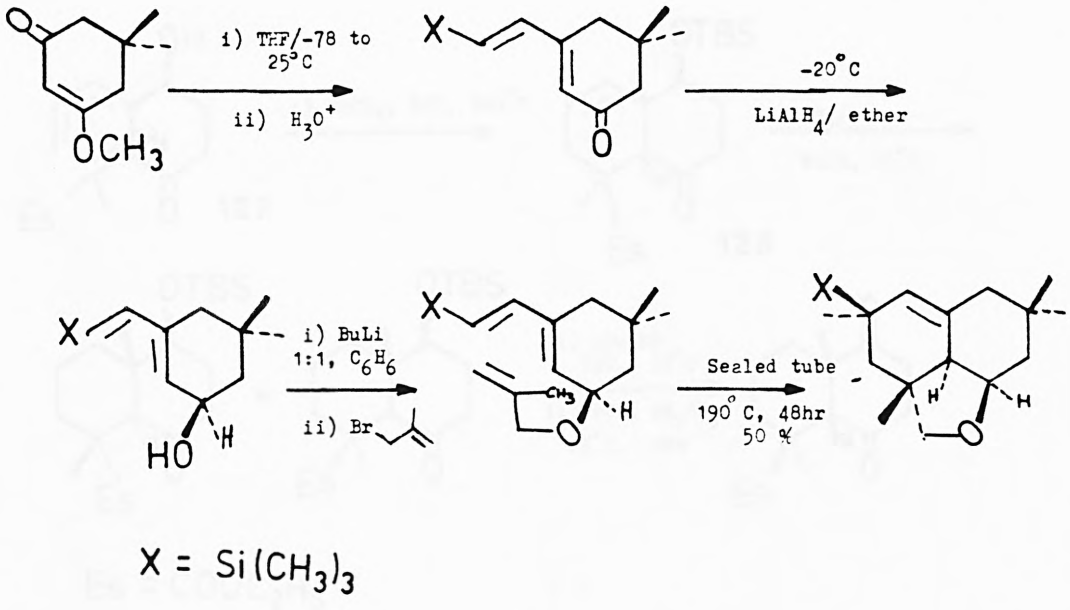
However, there is a brief mention that Robbins has been able to construct the A-ring of Nagilactone D as follows[23a]:





Burke et al[29] have reported preliminary studies that demonstrate the viability of the trimethyl silyl-substituted butadiene unit as an intramolecular Diels-Alder partner with

unactivated dieneophilic components for the rapid construction of a tricyclic model system (Scheme XXVI).

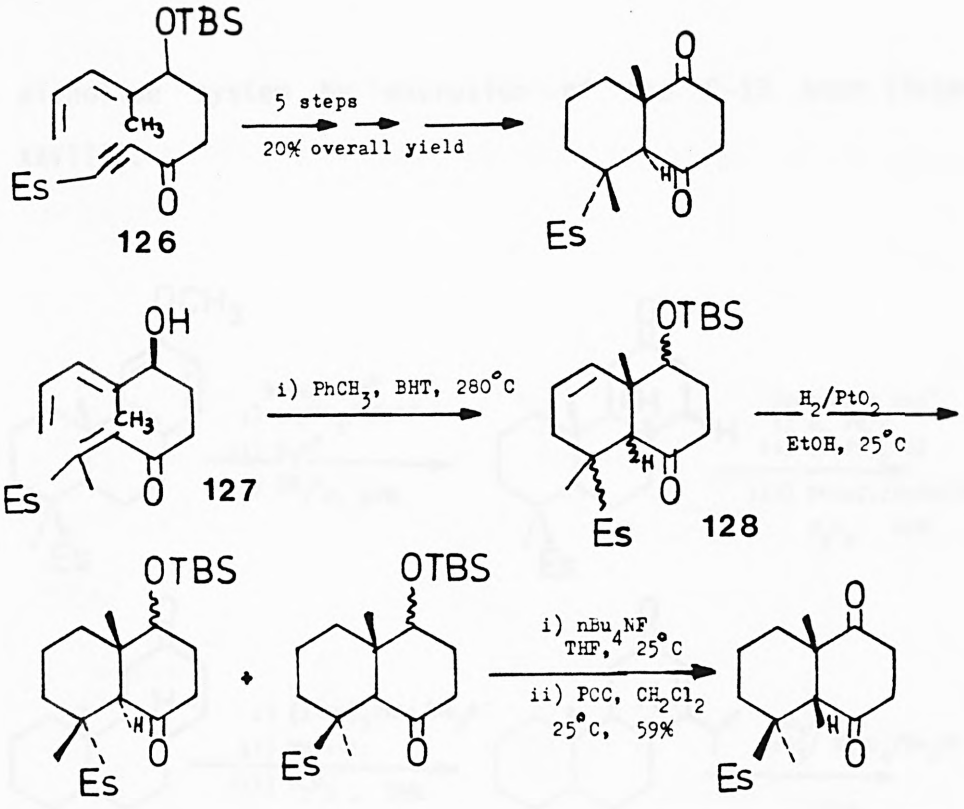


X = $Si(CH_3)_3$

Scheme XVIII

The trimethyl silyl group exerts little influence on the rate of the intramolecular cycloadditions which introduced at least four asymmetric centres with complete relative stereocontrol. Nevertheless the missing angular methyl group has to be somehow introduced and besides the stereochemistry of substituents on C-4 in not correct.

Another strategy demonstrated by S.D.Burke et al.[30] employes an elegant intramolecular Diels-Alder cyclisation to construct the A and B rings simultaneously. Use of the acetylenic moeity in the precursor (126) allows entry to the abietic series while (127), a substituted olefinic group renders the podocarpic series accessible from the minor product obtained from hydrogenation of (128) as shown in Scheme XXVII



Es = $COOC_2H_5$

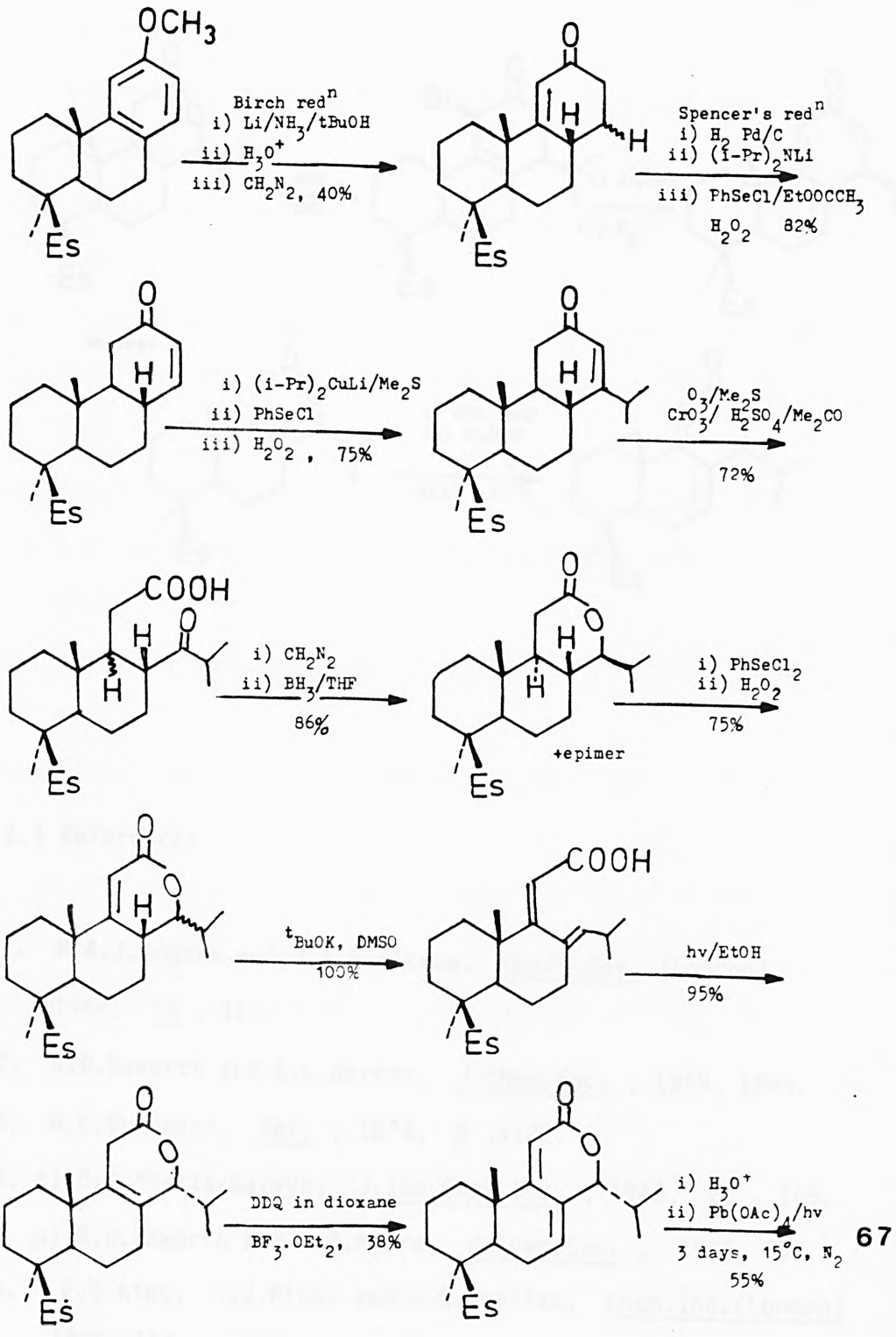
TBS = t-butyldimethylsilyl ether

Scheme XXVII

Clearly the chemical steps involved and yields obtained (10% overall yields from (127)) limit the synthesis as a viable route to such compounds.

Appropriate to the close of the chapter, Hayashi et al.[31] has reported the first and so far the only total synthesis of a plant norditerpene dilactone, Nagilactone F, (67), (synthesis of a 13,15,16,17-tetranorditerpenoid, an antifungal mould metabolite is the only precedent for a synthesis of this type of dilactone). The ten step synthetic route from (+)podocarpic acid includes a stereo-controlled introduction of an isopropyl group of the C-14 position, and transformation of the B/C ring part of the resin acid to the

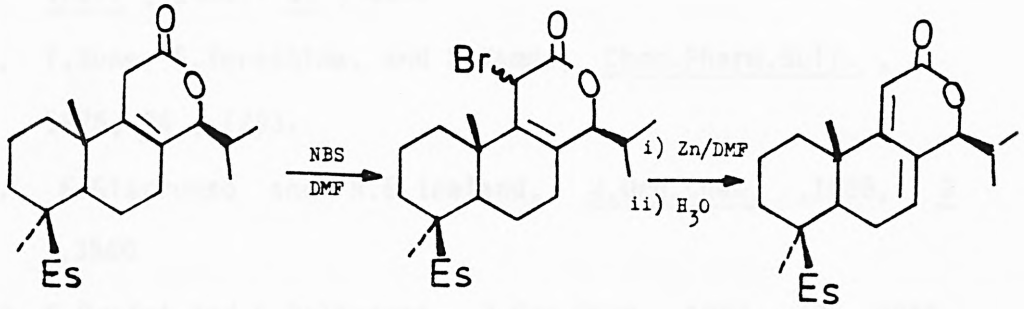
dienolide system by extrusion of the C-13 atom (Scheme XXVIII).



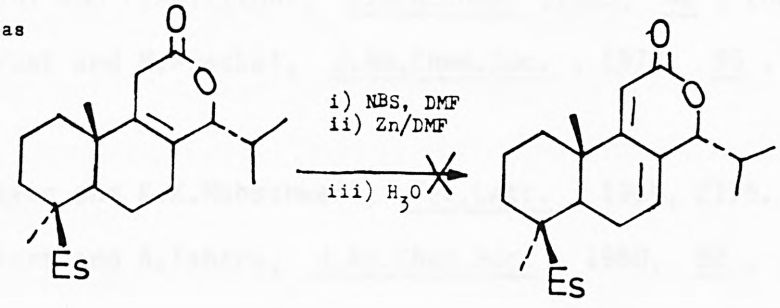
67

Scheme XXVIII

It is note worthy to include a side route which was reported not to lead to the formation of the expected products.



Whereas



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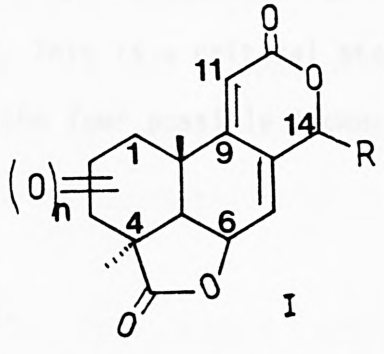
CHAPTER 3. A SYNTHETIC STRATEGY

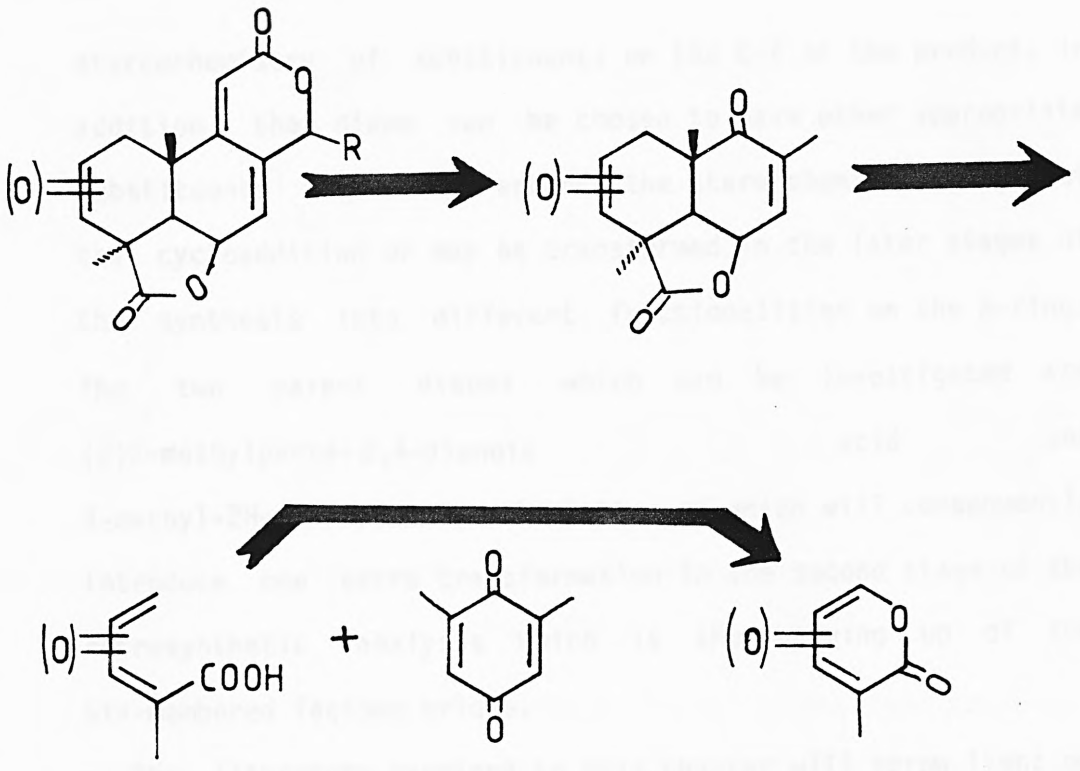
3.1 Introduction.

Short and versatile synthetic routes towards A-ring functionalised norditerpene dilactones are not available and as a result a detailed study of their biological activities has not been possible. This chapter proposes a plausible synthetic route which has been arrived at by a retrosynthetic analysis of the target compounds. The available background information necessary for predicting the viability of the Diels-Alder reactions has been included in this chapter.

3.2 Retrosynthetic Analysis.

The target structures (I) vary in their substitutents on C-14 eg. alkyls and alkoxides; functionalities on A-ring eg. hydroxides, epoxides and enes; and position of the double bonds in the diene system. There are a number of ways of fragmenting to the appropriate synthons required for the synthesis. Construction of the AB ring system prior to that of C-ring has been the commonly adopted strategy. Scheme XXIX shows a possible retrosynthetic analysis.





Scheme XXIX

The major stages of the scheme are as follows:

1) Construction of the C-ring,

2) Construction of the A-ring with a cycloaddition which is regio- and stereo-chemically specific. This is a critical step of the synthesis because only one of the four possible isomers has the correct structure,

3) Synthesis of the starting materials.

2,6-Dimethyl—p-benzoquinone is the dieneophile which is a structurally suitable synthon. The diene must have a Z-double bond, which after the cycloaddition results in the correct

stereochemistry of substituents on the C-4 of the product. In addition, the diene can be chosen to have other appropriate substituents which may enhance the stereochemical outcome of the cycloaddition or may be transformed in the later stages of the synthesis into different functionalities on the A-ring. The two parent dienes which can be investigated are (Z)2-methylpenta-2,4-dienoic acid and 3-methyl-2H-pyran-2-one, the latter of which will consequently introduce one extra transformation in the second stage of the retrosynthetic analysis which is the opening up of the six-membered lactone bridge.

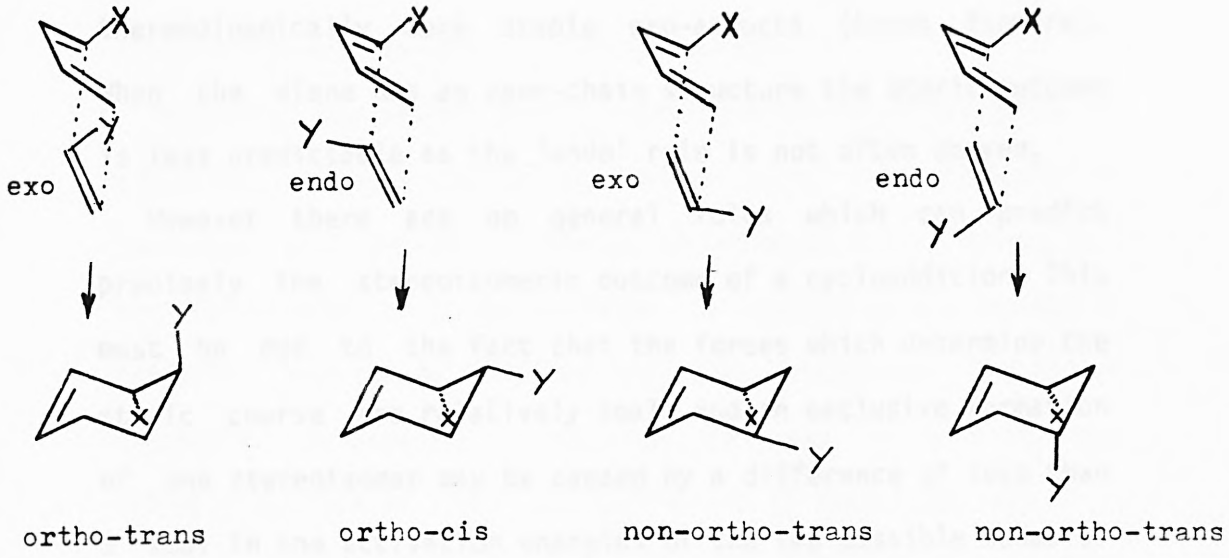
The literature examined in this chapter will throw light on the cycloaddition stage of the synthesis, the efficiency of which will be of utmost importance to this proposed synthetic approach.

3.3 Review of Diels-Alder reactions

3.3.1 (4 + 2) cycloadditions

The cycladdition between butadiene and ethylene leads to the formation of cyclohexene. Presence of substituent(s) in the diene and/or dieneophile results in the formation of isomeric cycloaddition products owing to the nature of the reaction which may occur via different orientations of the starting materials.

As can be seen from the scheme XXX, four isomers - ortho and non-ortho, and cis and trans - can theoretically be formed, from a 1-substituted diene and a mono-substituted dieneophile.



Scheme XXX

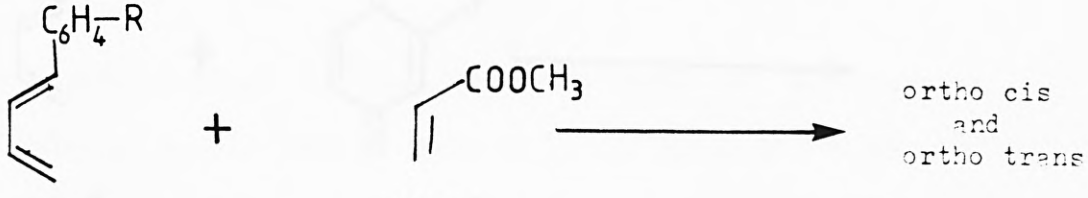
Examination of published data by Titov[1] shows that the meta-isomers are usually formed in small quantities but in all cases the ortho- isomers predominate in the resulting mixture of adducts, for the following substituents : in the diene -R(alkyl), Ph-, $C_6H_4NO_2$, C_6H_4Br, CN, COOH, OR, CH_3COO, $N(C_2H_5)_2$, and $SiMe_3$[2] and in the dieneophile - COOH, COCl, $CONH_2$, CHO, CN, COR, and C_6H_5. Further more each of the substituents have their own degree of "orienting power" and it has been found that the ortho- "orienting power" decreases in the following order when substituent is on the diene : C_6H_5 > COOH > CH_3 > H .

The investigation of the two stereochemical alternatives - cis and trans isomers - has been carried out in many different systems[3] . The "endo" rule proposed by Alder is quite closely obeyed in the addition of cyclic dienes to cyclic dienophiles to yield kinetically favourable endo adducts (cis isomers) and if the cycloaddition is reversible then increase of the reaction temperature allows isomerisation to the

thermodinamically more stable exo-adducts (trans isomers). When the diene has an open-chain structure the steric outcome is less predictable as the 'endo' rule is not often obeyed.

However there are no general rules which can predict precisely the stereoisomeric outcome of a cycloaddition. This must be due to the fact that the forces which determine the steric course are relatively small and an exclusive formation of one stereoisomer may be caused by a difference of less than 3 Kcal in the activation energies of the two possible modes of addition.

Ansell et al.[4] have investigated the ratio of cis- and trans-ortho isomers of (129) and (130) and found the following isomeric ratios:



129 130

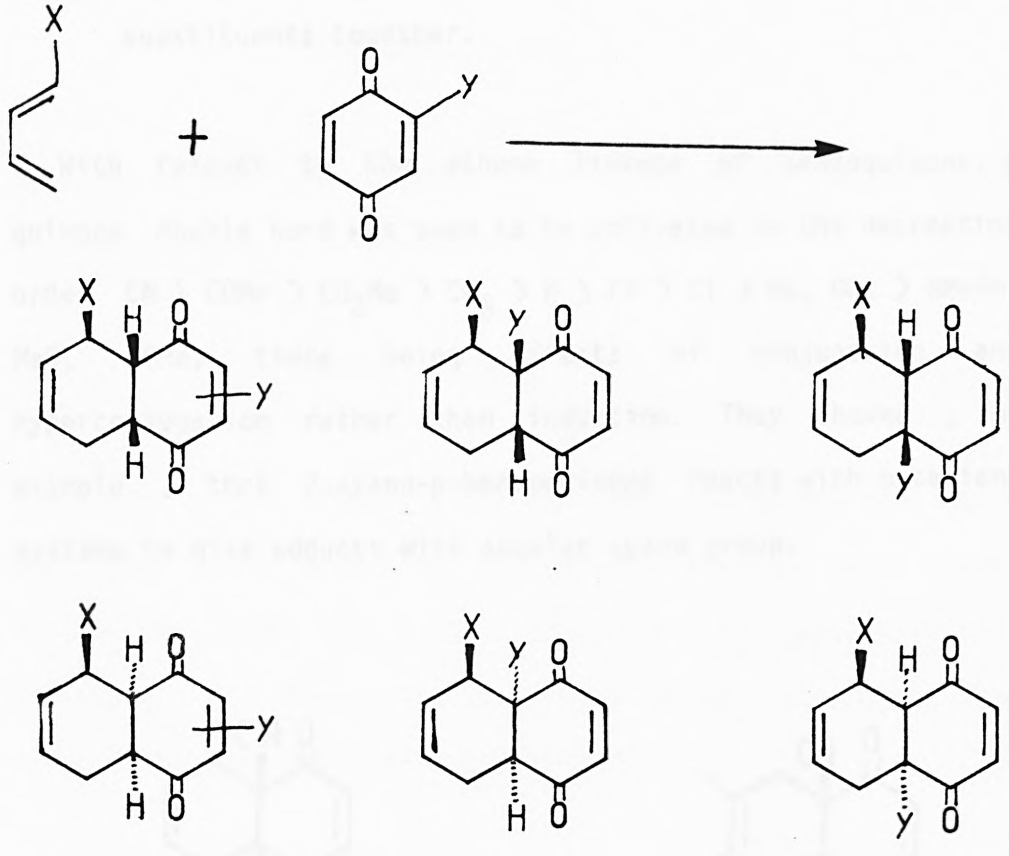
diene R=	%cis	%trans
1-(p-methoxy-phenyl)	57	43
1-(phenyl)	62	38
1-(p-nitro-phenyl)	72	28

Product composition for Diels-Alder reaction of methyl acrylate

3.3.2 Cycloaddition with quinonoid systems.

Quinones and substituted quinones are an important group of ene-dione synthons which are often used in cycloaddition reactions with variety of dienes to build up target molecules. The usefulness of these reactions is limited by the degree of isomeric purity of the cycloadducts produced. To devise synthetic strategies, knowledge of ways to control the isomeric outcome of their cycloadditions is thus required.

Symmetrical quinones with symmetrical dienes can produce two stereoisomeric adducts - exo and endo adducts. Presence of substituents leads to the formation of a number of possible adducts as depicted in scheme XXXI



Scheme XXXI

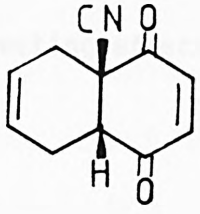
Unsymmetrical p-benzoquinones often only undergo cycloaddition with their more reactive ene side. A detailed investigation by Ansell et al.[5] was reported in 1964 which showed that the Diels-Alder reactions of a number of mono-, di-, tri-, and tetra- substituted p-benzoquinones mostly with 2,3-dimethylbutadiene occur specifically at one of the ethene linkages of a quinone. They suggested three factors for this observation :

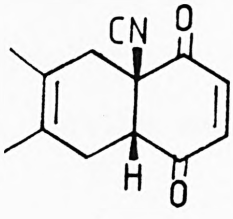
I) electronic nature of quinone substituents

II) steric considerations of the quinone sustituents alone

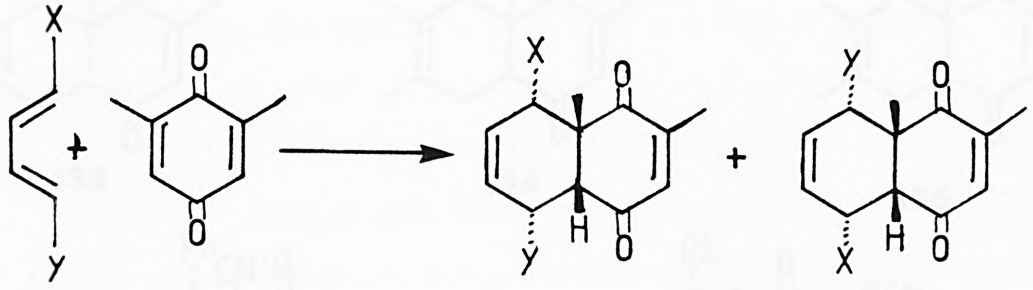
III) steric considerations of the quinone and diene substituents together.

With respect to the ethene linkage of benzoquinone, a quinone double bond was seen to be activated in the decreasing order CN > COMe > CO_2Me > CF_3 > H > F? > Cl > Me, OAc > NMePh, MeO, SMe, these being effects of conjugation and hyperconjugation rather than induction. They showed , for example , that 2-cyano-p-benzoquinone reacts with butadiene systems to give adducts with angular cyano group.





The other aspect which involves substitution on the diene was examined by Ansell et al[6] and Schmidt et al[7]. Orientation studies demonstrated that the ortho-directing influence of either an electron-donating group (acetoxy) or an electron-withdrawing group (Carbomethoxy) is more powerful than that of a methyl group in the 1,4-disubstituted dienes.



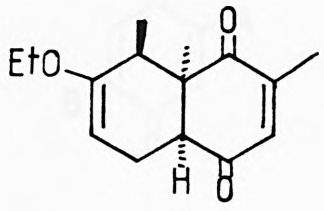
1) $Y=COOCH_3$, $X=CH_3$

2) $Y=OCOCH_3$, $X=CH_3$

Examination of the product's isomeric ratio suggested the following order of ortho-orienting influence:

$$COOCH_3 > OCOCH_3 > CH_3$$

Synthesis of the adducts (131) and (132) led to the conclusion that the ortho directing influence of terminal substituents follow the order $OCH_3 > CH_3 > H$,[8] and that the para- directing influence of 2-substituted ethoxy group is weaker than ortho-directing effect of 1-substituents.



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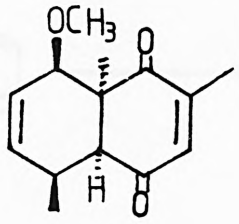

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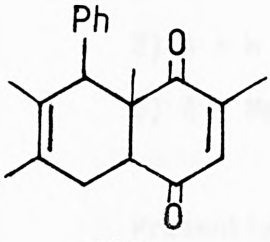

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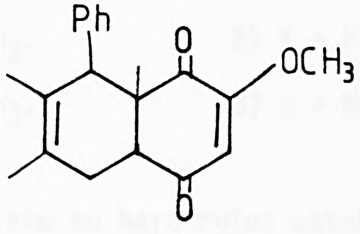

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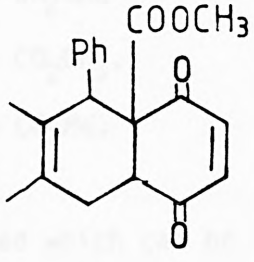

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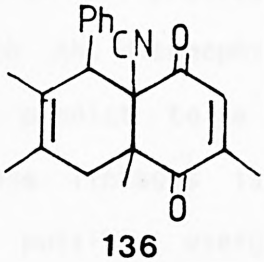

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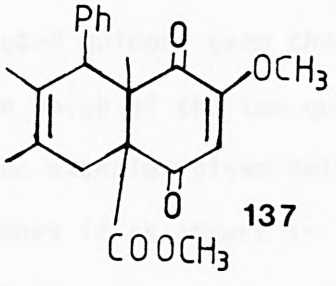
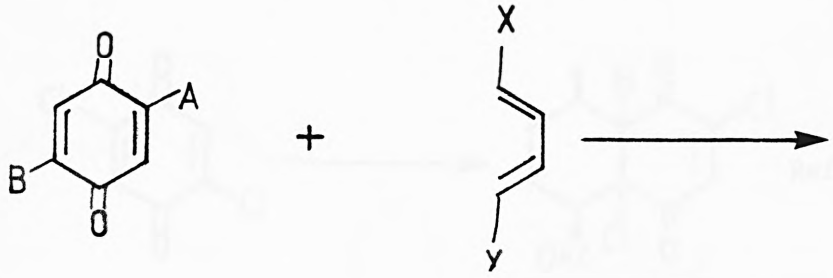


137

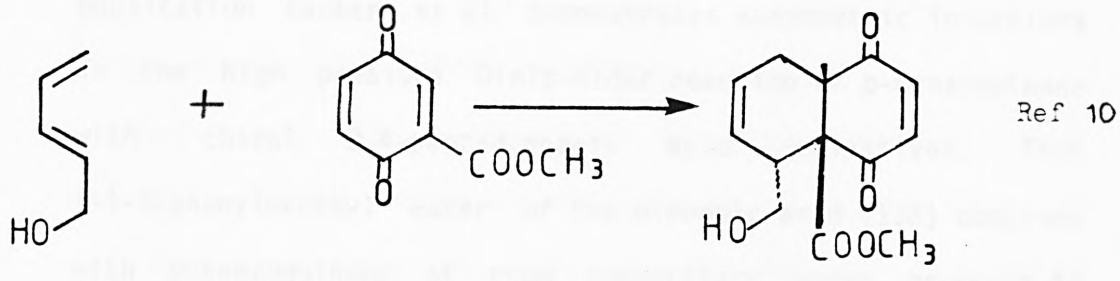
Isolation of the adducts (133) , (134) and (135) from the appropriate starting materials does appear to follow the trend suggested by Ansell. Consideration of the structures (136) and (137) and (135) suggests that multisubstitution on starting materials upsets the rules of addition. A cyano group and a carboxyl group are found in different orientations in these adducts. Other authors have also carried out cycloaddition with quinones[9] and found that none of the assumed models is fully in agreement with the experimental results and presumed that steric factors seem to be mostly more important than the electronic situations. The paper also includes some useful spectroscopic data for the adducts.



1) A = Me, B = Me.
2) A = H , B = OCH_3.
3) A = Me, B = OCH_3.

1) X = H, Y = CH_2OAc
2) X = H, Y = CO_2CH_3.
3) X = Me, Y = CO_2Me.

Presently, there are no hard rules established which can be applied to predict the isomeric outcome of a cycloaddition in which the dieneophile is a substituted quinone even though one can predict to a limited degree which of the two quinonoid ethene linkages is more active. The examples given below show the possible usefulness of quinones if an adduct is formed whose regio- and/or stereochemistry is correct for the synthetic route.



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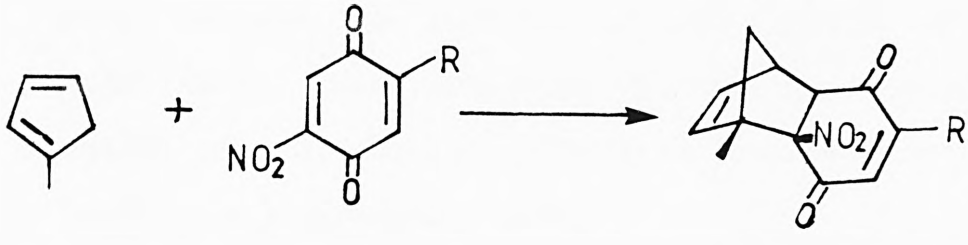

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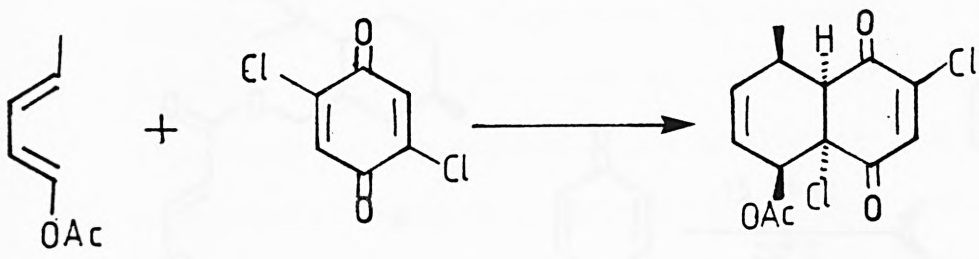
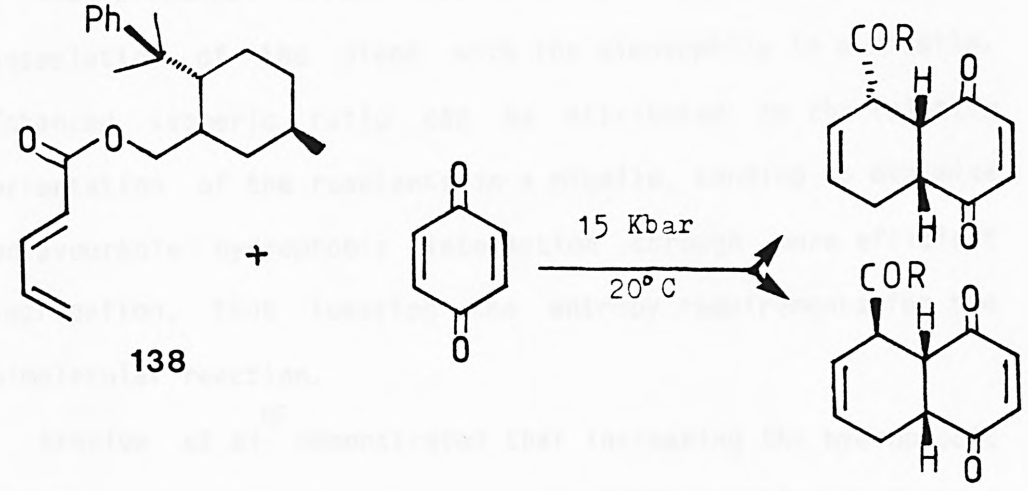


Ref 12

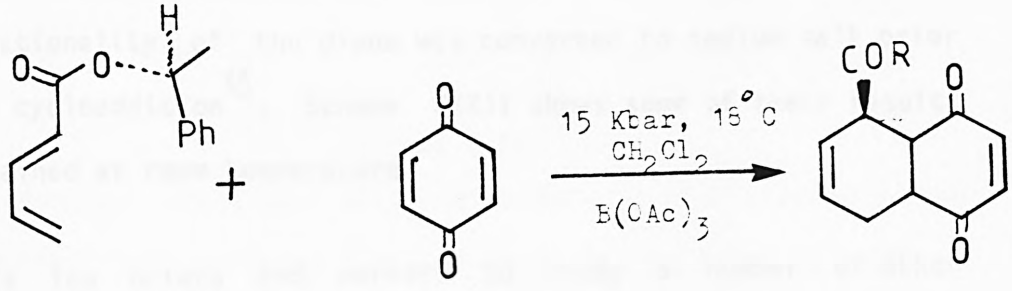
Recently thermal and catalysed cycloadditions between six unsymmetrical quinones and three alkyl-substituted butadienes has led to collection of some unexpected results. The theoretical molecular orbital prediction of isomeric ratios as well as calculations taking into account secondary orbital overlaps are quantitatively correct only in 5 of the 15 examples given[13].

3.3.3 High pressure Diels-Alder reactions.

The utility of high pressure in the Diels-Alder synthesis of heat sensitive adducts is well established. In a recent publication Dauben et al.[14] demonstrates asymmetric inductions in the high pressure Diels-Alder reaction of p-benzoquinone with chiral 2,4-pentadieneoic acid derivatives. Thus (-)-8-phenylmenthyl ester of the dieneoic acid (138) combines with p-benzoquinone at room temperature under pressure to yield 50% ee of the adduct.



He also claimed that the failure of cycloaddition of (-)-1-phenylethyl,dienoic acid ester in the presence of a Lewis acid ($B(OAc)_3$) can be overcomed by applying pressure to yield the adduct quantitatively with 18% ee.



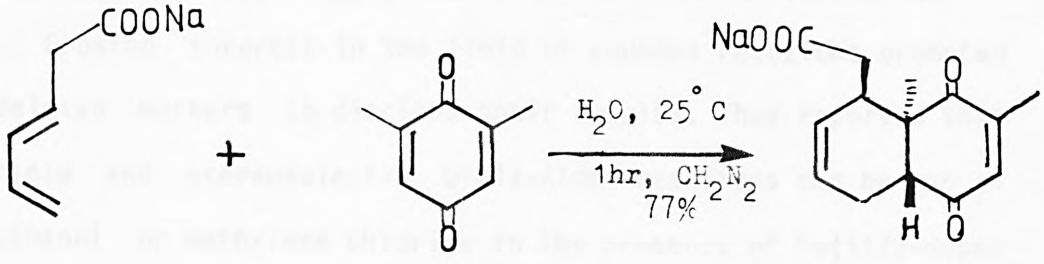
3.3.4 Aqueous Diels-Alder reactions.

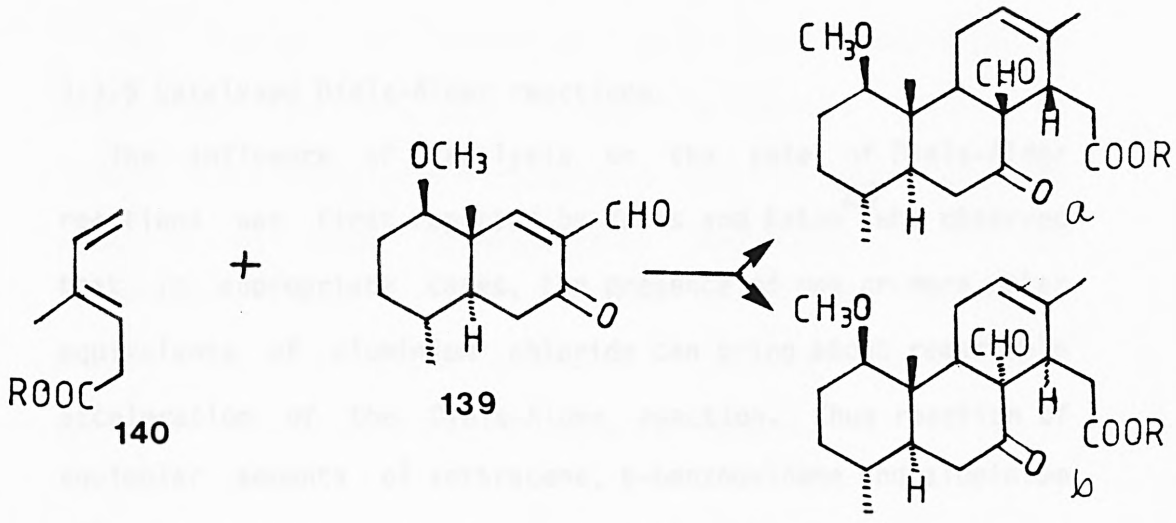
Very large rate acceleration of some common Diels-Alder reactions in water solution has added an interesting dimension to the field of synthesis by cycloaddition. This provides an alternative for carrying out reactions at lower temperatures which increases the stability of some starting materials. Futher more, water media appear to affect the stereoisomeric outcome of the reaction, offering a means of enhancing the formation of a particular isomer.

The principal effect has been ascribed to hydrophobic association of the diene with the dieneophile in a micelle. Enhanced isomeric ratio can be attributed to the relative orientation of the reactants in a micelle, tending to minimise unfavourable hydrophobic interaction through more efficient aggregation, thus lowering the entropy requirements for the bimolecular reaction.

Breslow et al.[15] demonstrated that increasing the hydrophobic effects of water by addition of lithium chloride further accelerated the reaction rate between N-ethyl maleamide and hydroxymethyl anthracene. By contrast guanidinium perchlorate had the opposite effect as a result of its lowering of the hydrophobic effect. Grieco observed an increase in the reaction rate of (139) and (140) when the carboxylic acid functionality of the diene was converted to sodium salt prior to cycloaddition[16]. Scheme XXXII shows some of their results obtained at room temperature.

This led Grieco and workers to study a number of other reactions including cycloaddition of xyloquinones and sodium(E)-3,5-hexadienoate[17,18].





R	solvent	conc. of diene	time	yield	a/b ratio
H	neat	-	30h	80%	1.4
H	water	1.0M	17h	85%	1.5
H	water-dioxane(1:1)	1.0M	104h	100%	0.8
Na	water	1.0M	8h	83%	2.0

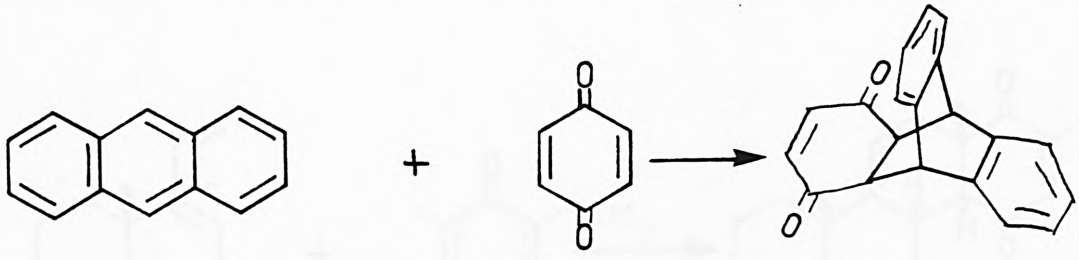
Scheme XXXII

In general reactions were conducted at 25°C with vigourous stirring and employing 5.0 equivalent of the diene in a 2M aq. solution. Critical factors were found to be excess and concentration of diene as well as absence of co-solvents which may dissolve the substrates. The reactions proceeded efficiently with excellent regiochemical control tending to favour, in this particular case, the endo-adduct formation.

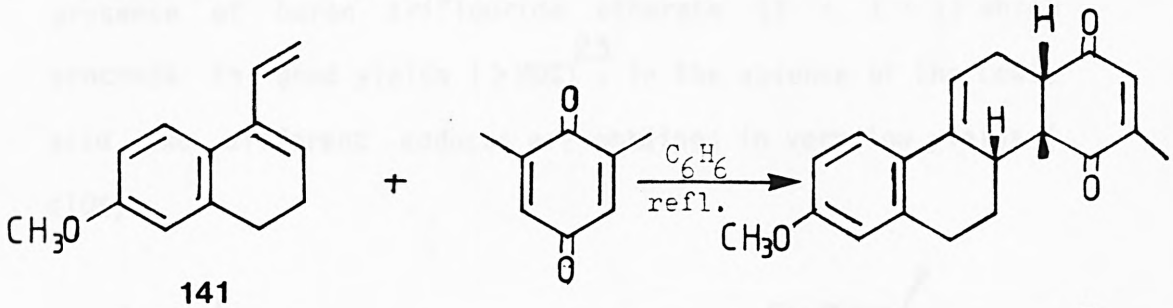
Growing interest in the field of aqueous reactions prompted Belgian workers to disclose their results. They reported that rapid and stereoselecive Diels-Alder reactions can be run in ethanol or methylene chloride in the presence of Fe(III)-doped K10 montmorillonite[19].

3.3.5 Catalysed Diels-Alder reactions.

The influence of catalysis on the rate of Diels-Alder reactions was first reported by Yates and Eaton[20] who observed that in appropriate cases, the presence of one or more molar equivalents of aluminium chloride can bring about remarkable acceleration of the Diels-Alder reaction. Thus reaction of equimolar amounts of anthracene, p-benzoquinone and aluminium chloride dissolved in methylene chloride (a solution of 0.0625mol of each) at room temperature was complete in less than 15min, giving the 1 : 1 adduct reproducibly in 90% yield.



In search of a stereospecific synthesis of ring A-aromatic steroids, Dickinson et al.[21] utilised boron-triflouride as a Lewis acid for affecting an orientation inversion of cycloaddition between (141) and (120) to yield the non-ortho adduct as the major adduct.



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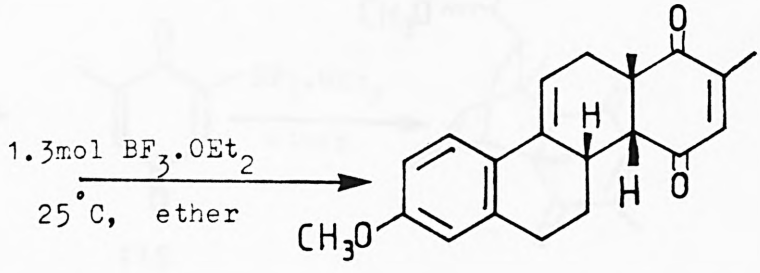
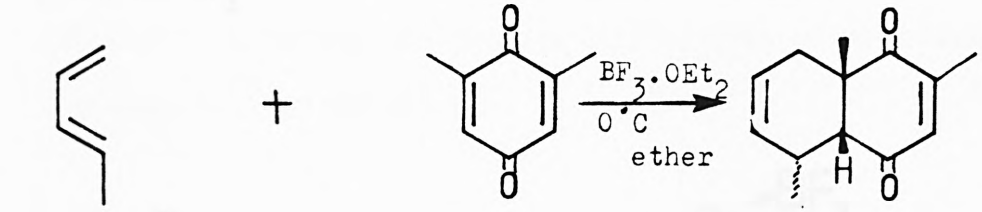
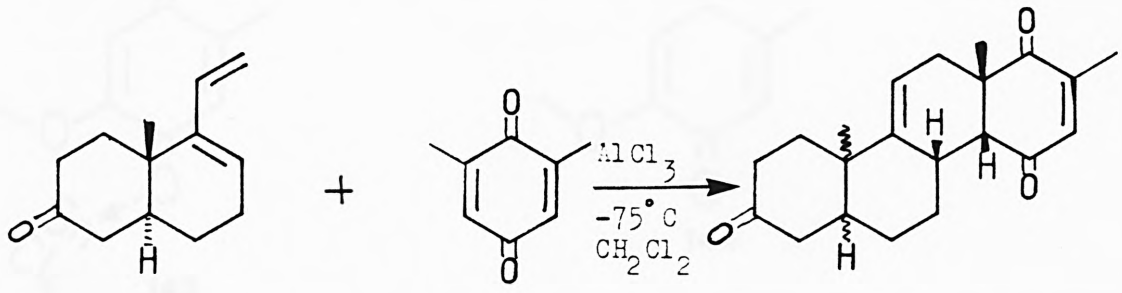
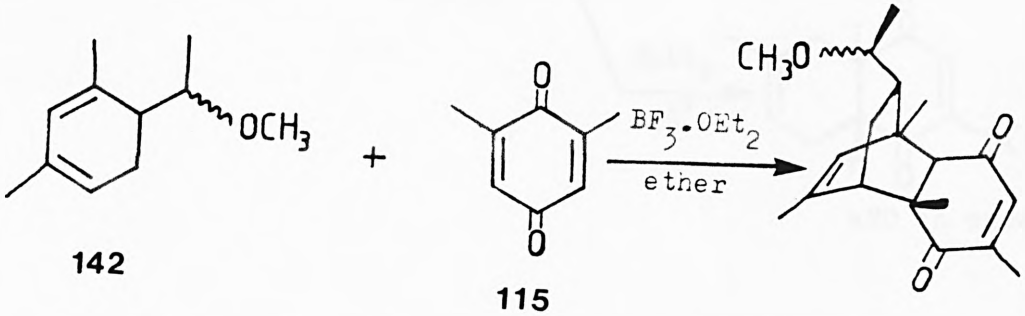


The concept of catalysed orientation reversals in Diels-Alder reactions was followed by Valenta et al.[22]. He showed 2,6-dimethyl-1,4-benzoquinone and toluquinone cycloadd with 1-substituted 1,3-butadienes and with 1,2- and 1,3-dialkyl dienes in the presence of $AlCl_3$ or $BF_3.OEt_2$ to yield the non-ortho adducts, contrary to thermal cycloadditions which produced the ortho-adducts.



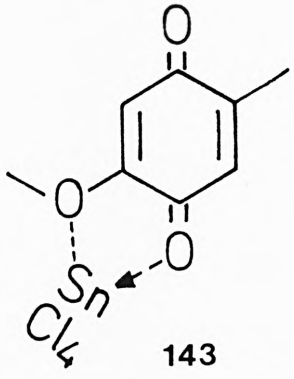


Utility of such catalysis is clearly demonstrated in a reported reaction between diene (142) and quinone (115) in the presence of boron triflouride etherate (1 : 1 : 1) which proceeds in good yields (>80%)[23]. In the absence of the Lewis acid two different adducts are obtained in very low yields (<10%).



142 115

The landmark study by Valenta and coworkers demonstrating a clean reversal of regioselecivity on the reactions of 2,6-dimethyl-quinone with various dienes in the presence of Lewis acid catalysts was further extended by Tou et al[24] who noted that methoxybenzoquinone responds differently to the two Lewis acids, $SnCl_4$ and BF_3. They explained their observations by proposing a catalyst-quinone complex (143) for $SnCl_4$ and (144) for BF_3



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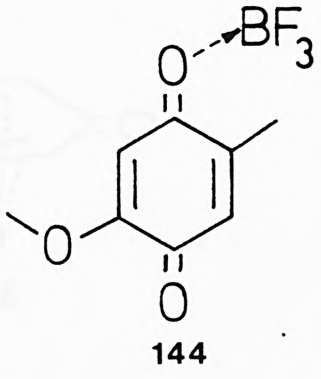

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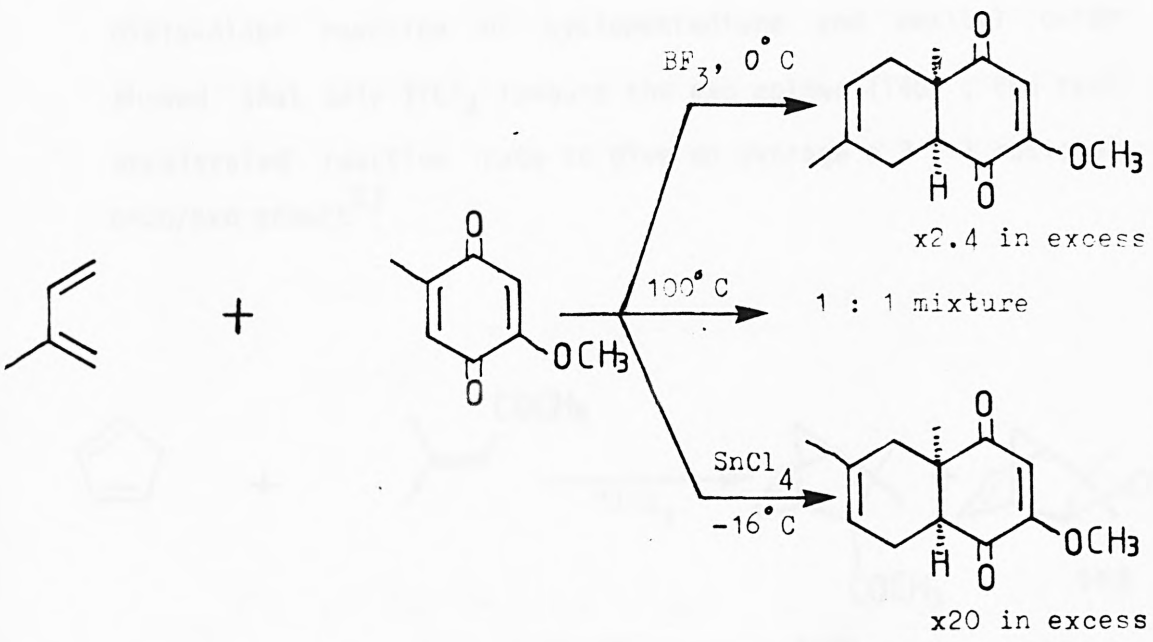
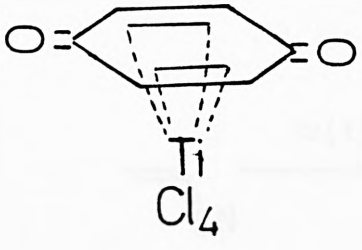
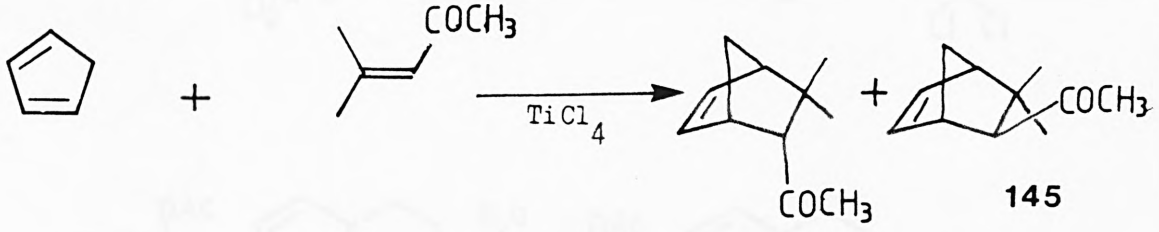


In contrast, comparison of BF_3, $AlCl_3$, and $TiCl_4$ catalysed cycloaddition of quinones and butadienes[13] failed to produce a totally coherent picture of mechanisms involved in catalysed cycloaddition. Infact some of the results obtained are not consistant with the Lewis acid-quinone complex explanation given by Reusch. $TiCl_4$ was found to increase reaction rate without altering the regioselectivity and was assumed to centrally bond to the whole π-face of the quinone without especially altering the bonding coefficients which direct the regiochemistry of the product.



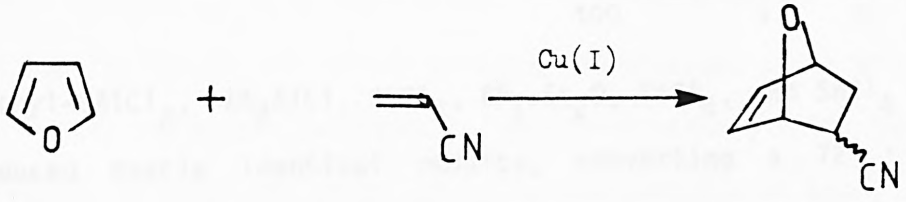
A study of the influence of nine Lewis acids on the Diels-Alder reaction of cyclopentadiene and mesityl oxide showed that only $TiCl_4$ favours the exo epimer (145) ; the rest accelerated reaction rate to give on average a 3 : 1 ratio of endo/exo adduct[25];



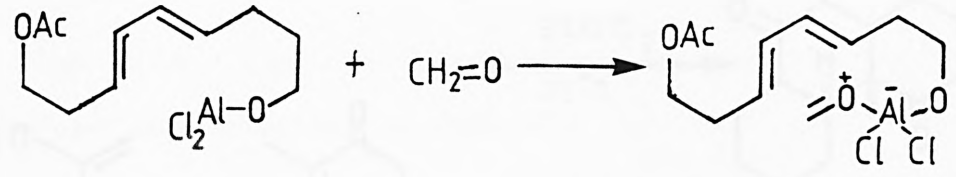
145

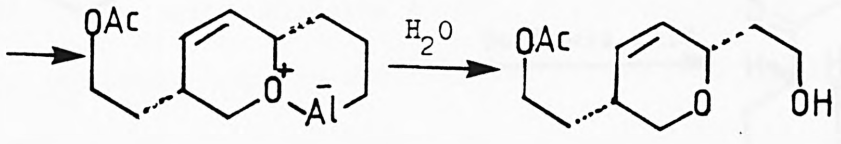
endo : exo
1 : 3

Hydroquinone is often used as polymerisation retardant in reaction mixtures. However, Moore et al.[26] noticed that effect of cupric flouroborate as Lewis acid on the cycloaddition of furan and 2-chloroacrylonitrile is greatly enhanced in the presence of hydroquinone as a result of reduction of Cu(II) to Cu(I) by hydroquinone. Moreover, tetrakis(acetonitrile) copper(I)flouroborate was also an effective catalyst on the Diels-Alder reactions with furan. Use of Lewis acids such as ferric choride, stannic chloride and zinc chloride led to formation of resinous products.

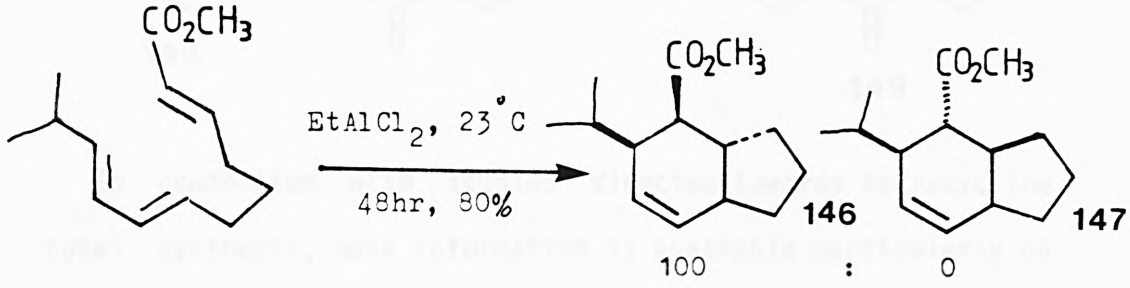


In a "quasi-intermolecular" Lewis acid catalysis the Lewis acid binds covalently to the diene and complexes to the dieneophile, providing regiochemical control and reaction rate accelaration.[27]



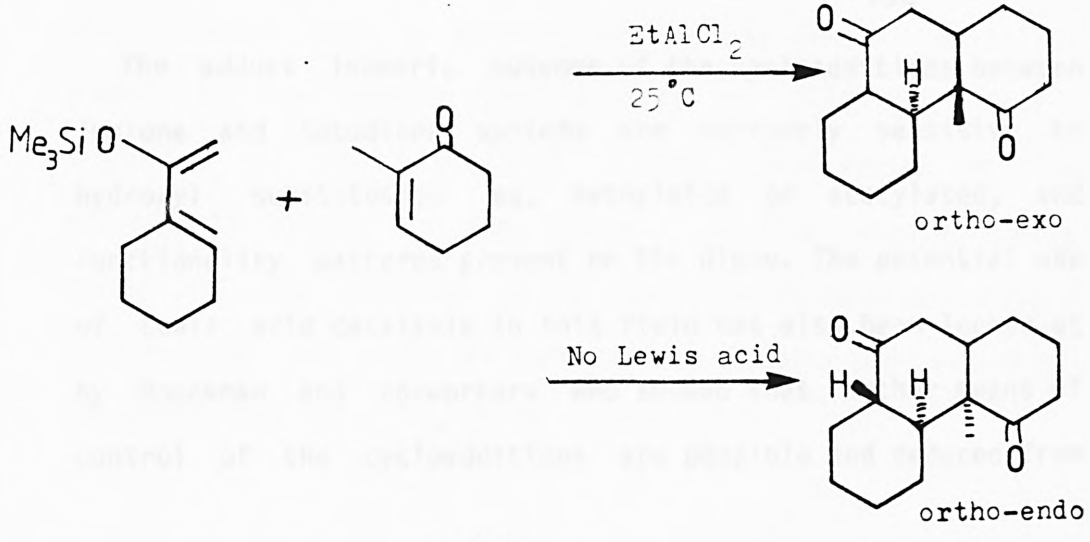


The first significant example of rate accelaration and product selectivity in a catalysed intra-molecular reaction was comprehensively dealt with by Rousch et al.[28] who presented a series of results comparing thermal and catalysed reaction rates and products. A few of organometalic Lewis acids such as menthoxyaluminium and ethylaluminium dichloride were favoured because of their mildness and ease of handling and were used with equal success.

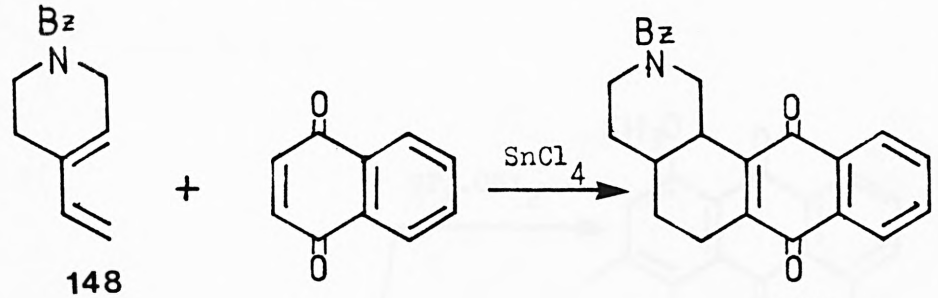


Menthyl-$OAlCl_2$, Et_2AlCl, $AlCl_3$, $BF_3.Et_2O$, $TiCl_4$, and $SnCl_4$ all produced nearly identical results, converting a 72 : 28 product ratio to 100 : 0 (146 to 147), both of which have the same favoured regiochemistry.

While examining methods for the construction of the quassinoid diterpenes, the observation was made that presence of a Lewis acid led to the formation of the product derived from an exo transition state[29].

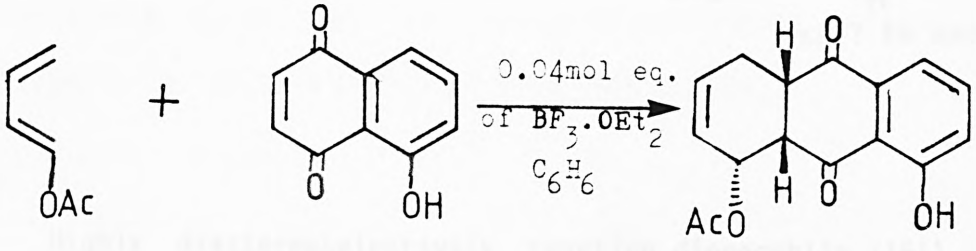


To effect a cycloaddition between naphthoquinone and the unreactive dieneophile (148), anhydrous stannic chloride was used as catalyst in equimolar quantities under reflux to produce 55% yield of (149)[30].



148 149

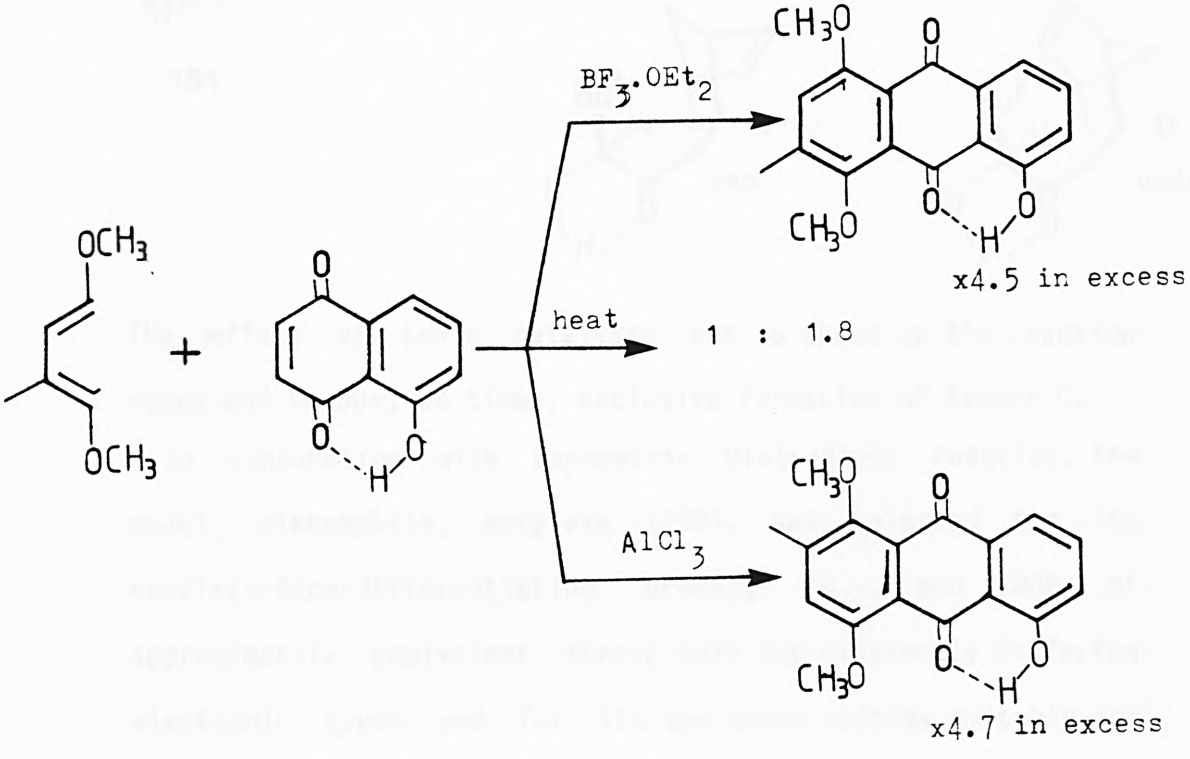
In connection with studies directed towards tetracycline total synthesis, much information is available particularly on the cycloaddition of substituted naphthoquinones and dienes. A >94 :0.5 ratio of regioisomeric purity of adduct (150) can be effected by addition of $BF_3.OEt_2$. In the absence of Lewis acid the regioisomeric ratio becomes 3 : 2[31].



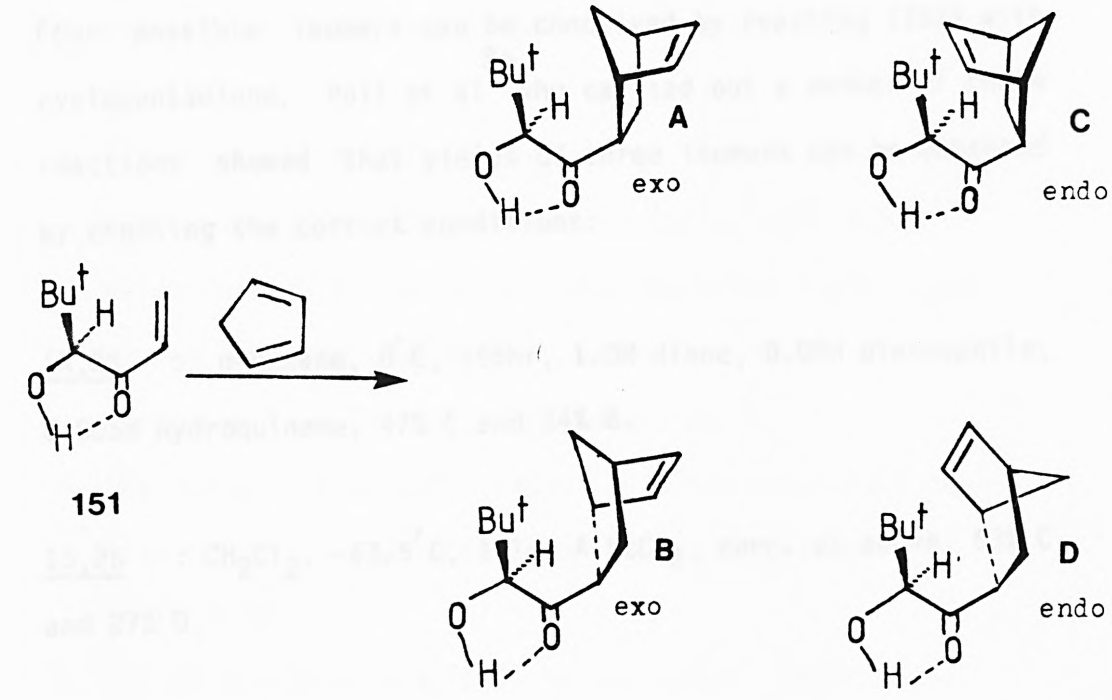
150

The adduct isomeric outcome of the cycloadditions between juglone and butadiene systems are extremely sensitive to hydroxyl substitution eg. methylated or acetylated, and functionality patterns present on the diene. The potential use of Lewis acid catalysis in this field has also been looked at by Boeckman and co-workers who showed that further means of control of the cycloadditions are possible and deduced from

their results that $BF_3.OEt_2$ and $AlCl_3$ favour different isomeric adducts presumably due to having different complexation sites[32]

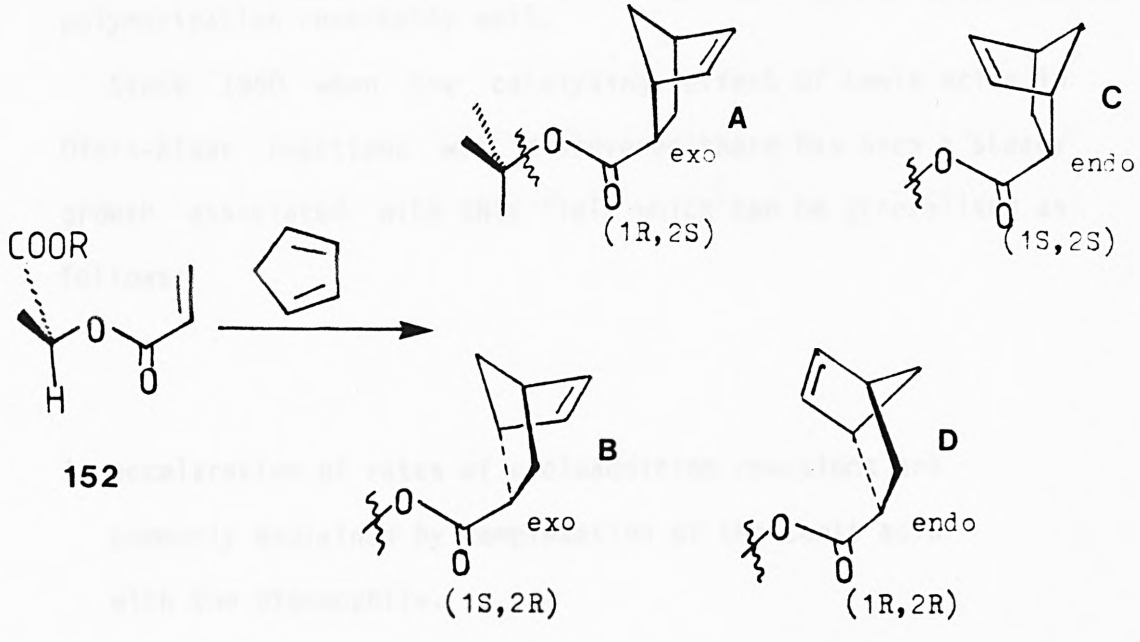


Highly diastereoselectively reacting dieneophile (151) has been studied with a wide variety of both achiral and chiral dienes in the absence and presence of $Ti(O\text{-}iPr)_4$, $ZnCl_2$, $BF_3.OEt_2$ as Lewis catalysts[33]. The concentration of the exo-adducts formed in the thermal reaction were generally below 18% and addition of the catalysts in combination with lowering of the reaction temperatures reduced the exo-adduct concentrations to as low as 3% in some cases.



The effect of Lewis catalysts was to speed up the reaction rates and favour, at times, exclusive formation of isomer C.

In conjunction with asymmetric Diels-Alder reactios, the model dieneophile, acrylate (152), was selected for its acrylate-face-differentiating groups, CH_3-, and COOR, of approximately equivalent steric bulk but distinctly differing electronic types and for its two donor centres suitable for formation of chelate complexes with Lewis acids.



Four possible isomers can be conceived by reacting (152) with cyclopentadiene. Poll et al[34] who carried out a number of these reactions showed that yields of three isomers can be enhanced by choosing the correct conditions:

1R,2S : n-hexane, 0°C, 186hr, 1.0M diene, 0.05M dieneophile, 0.005M hydroquinone, 47% C and 34% B.

1S,2S : CH_2Cl_2, -63.5°C, 1.1eq $AlEtCl_2$, conc. as above, 63% C and 27% D.

1R,2R : n-hexane/CH_2Cl_2 (9:11), -63.5°C, 0.75eq $TiCl_4$, 0.046M dieneophile, 91% D.

They also found that while $TiCl_4$ and $SnCl_4$ caused enrichment of isomer D, $BF_3.OEt_2$, AlX_3, $ZrCl_4$ and non-catalysed reactions effected enrichment of isomer C. Furthermore, to reduce polymerisation of diene in the presence of Lewis acid, they used CH_2Cl_2/n-hexane mixtures as solvent which suppressed polymerisation remarkably well.

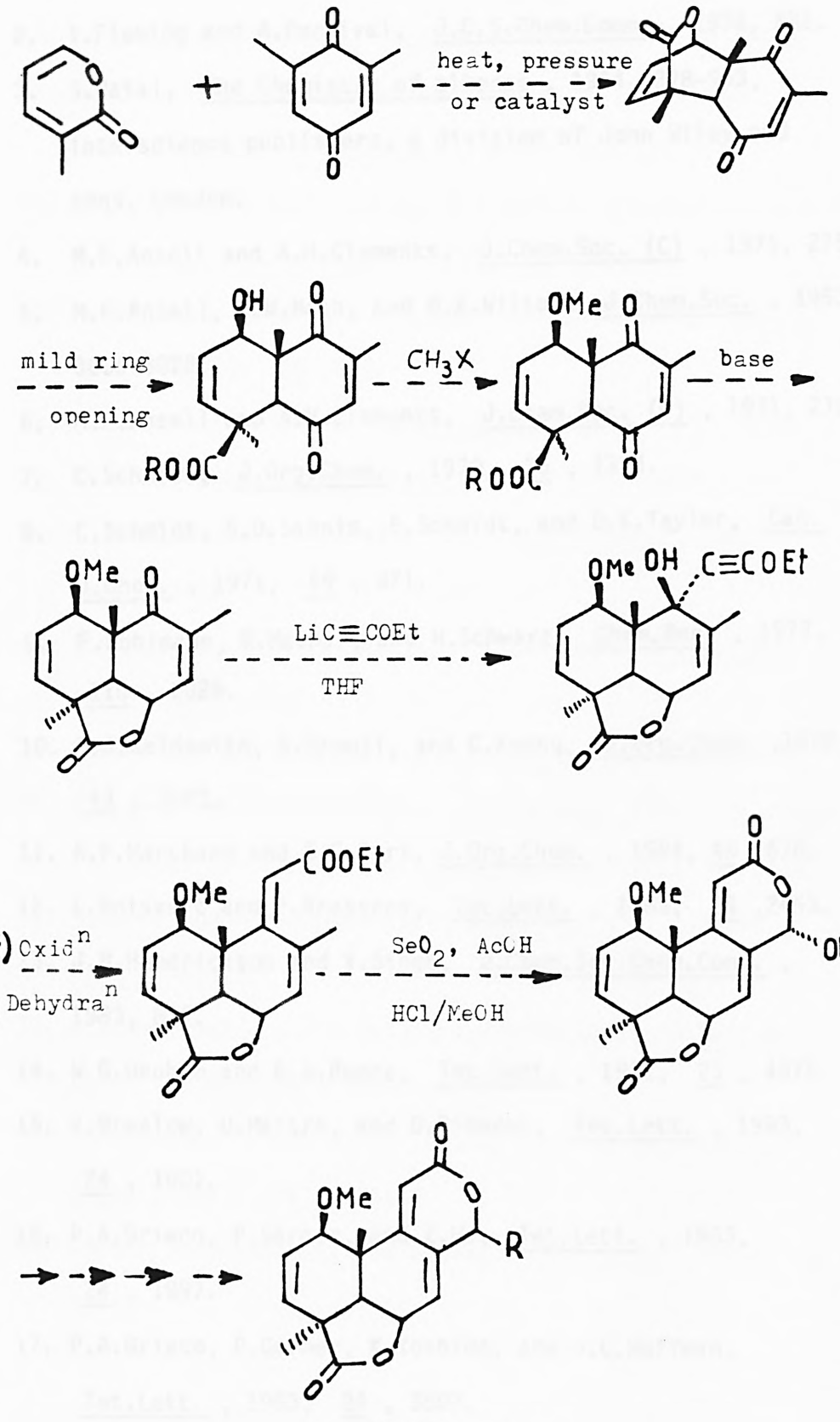
Since 1960 when the catalysing effect of Lewis acids in Diels-Alder reactions was discovered there has been a steady growth associated with this field which can be generalised as follows:

1. accelaration of rates of cycloaddition reactions are commonly explained by complexation of the Lewis acid with the dieneophile.

2. orientation inversion of cycloaddition can often be obtained in the presence of a Lewis acid.
3. different Lewis acids favour one of the two possible structures (ortho- or non-ortho-) but a Lewis acid which favours formation of, say, non-ortho regio-isomer in one cycloaddition may not favour the same regio-structure in a different cycloaddition.
4. the concentration and ratio of endo/exo components can also be influenced to some extent by the choice of a Lewis acid.
5. the mechanism of catalysis is not totally understood.

3.4 A Synthetic Strategy

The majority of the norditerpene dilactones have oxygenated substituents on their A-rings as well as some on their B-rings. The synthetic route outlined below has been devised in such a way to allow possible synthesis of analogue compounds in the minimum number of chemical steps. Appropriately protected functional groups (including oxygenated ones) can be introduced into the diene as well as the dieneophile to modify, respectively, the substituents on the A and B-rings of the target dilactones (Scheme XXXIII)



Scheme xxxiii

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SECTION B

SYNTHESIS OF DIENES AND DIENEOPHILES

Chapter 4: Acyclic dienes

4.1 Introduction.

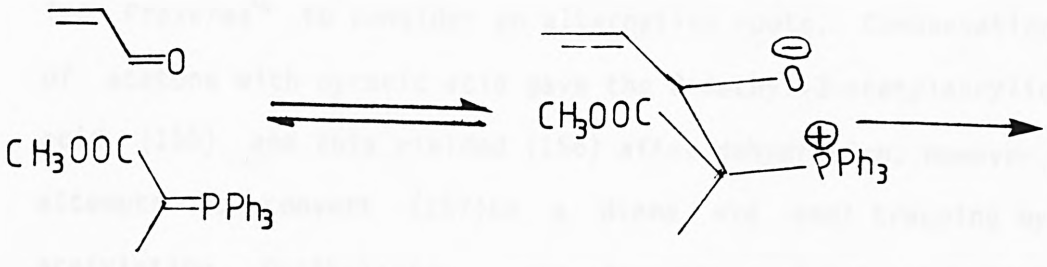
The central objective portrayed in this chapter is synthetic approaches towards dieneoic esters and in particular the (Z)-2-methylpenta-2,4-dienoic ester (114a). The latter represents the simplest example of a possible group of synthons which, via a Diels-Alder reaction with xyloquinone, produce the basic carbon skeleton required for a norditerpene dilactone precursor. However, it is well recognised that dienes which have a cis substituted terminal carbon atom are reluctant to undergo Diels-Alder reactions under normal conditions. Thus this approach was pursued with the expectation that use of high pressure as well as catalysed reactions would have to be explored.

One of the chemical steps in a diene synthesis involves photo-oxygenation of furanoid systems. The mechanism of the photolysis has been discussed to explain the formation of the products. The products have been separated by high pressure liquid chromatography and their structures confirmed by spectroscopic methods.

4.2 Previous Synthetic routes to dieneoic esters

Wittig reactions of simple alkylidene phosphoranes can often be used for the production of cis-olefins[1]. However, stabilised ylides such as (153) give exclusively products of E-stereochemistry[2].

The explanation is generally accepted to rely on the fact that where the betaine formation is reversible, the thermodynamically more stable isomer (the trans olefin) will be prominantly formed before elimination occurs (Scheme XXXIV).



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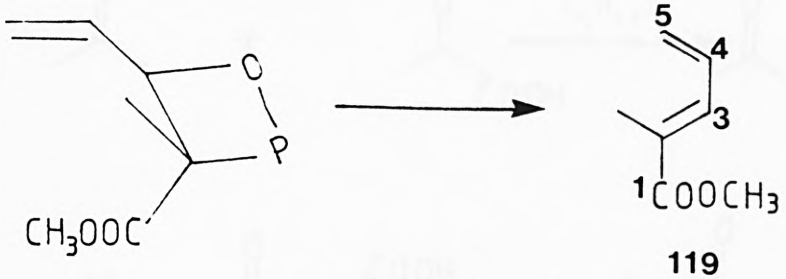

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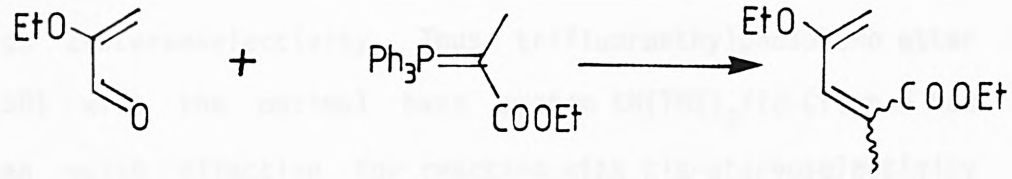
Scheme XXXIV

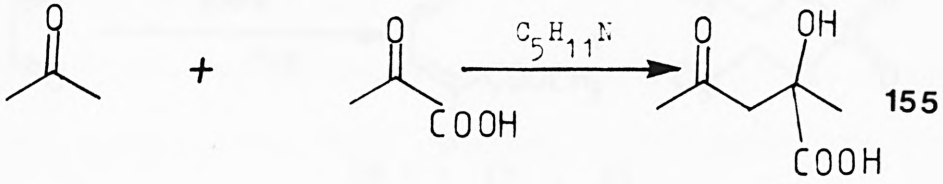
Indeed it is found that ylides containing stabilizing groups or formed from trialkylphosphines give trans-olefins[3]. However, ylides formed from triaryl phosphines and not containing stabilizing groups often give cis or mixture of cis and trans olefins, eg. trialkoxy phosphines produce more

reactive ylides. Furthermore , substituents on the aldehyde or ketone play a part too. For instance, the presence of an alkoxide in 2-ethoxyacrolein results in a loss of stereoselectivity in the witting reaction of the stabilised phosphorane[4].



154

The instability and reactivity of 2-ethoxyacrolein(154) and the formation of a mixture of cis and trans isomeric products led Prazeres[4] to consider an alternative route. Condensation of acetone with pyruvic acid gave the 2-methyl-3-acetylacrylic acid (155) and this yielded (156) after dehydration. However, attempts to convert (157)to a diene via enol trapping by acetylation, O-alkylation , or formation of trimethylsilyl enol ether failed. Scheme XXXV



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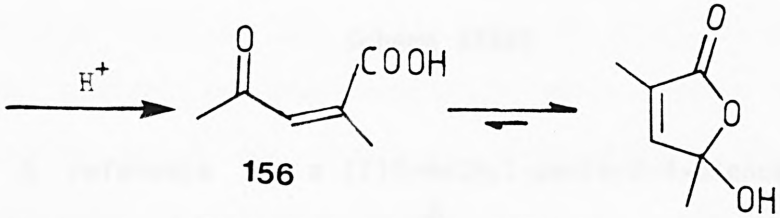

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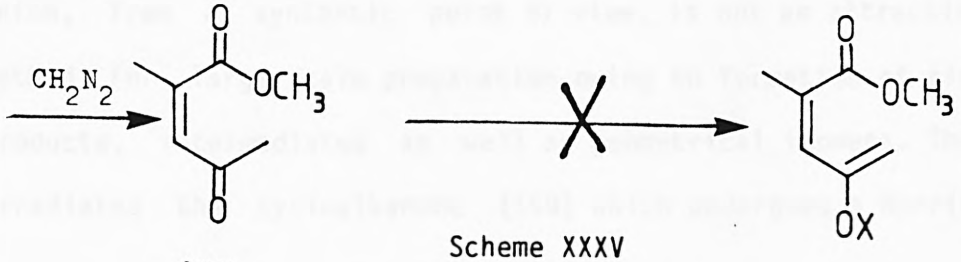
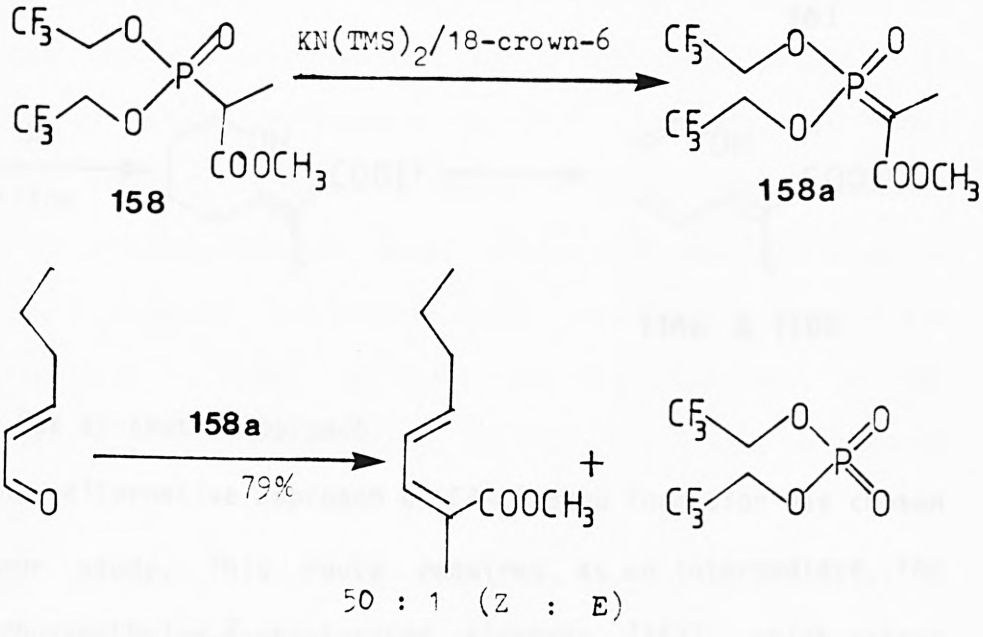


157

Scheme XXXV

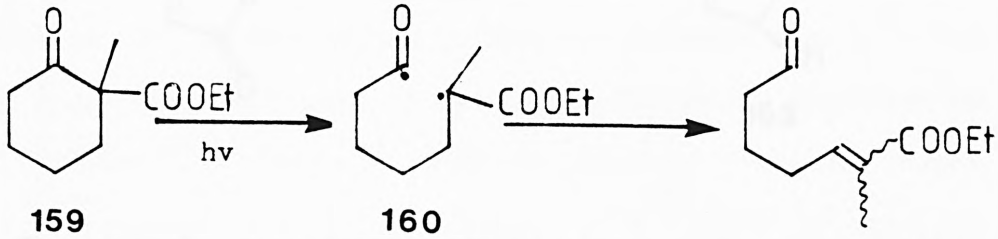
When acrolein is condensed with the ylide (153), the undesirable E isomer is formed. However Still and Gennari[5] have developed the use of new phosphono-ester reagents which enable preparation of the unsaturated esters from a variety of aromatic, saturated and unsaturated aliphatic aldehydes with high Z-stereoselectivity. Thus trifluoroethylphosphono ester (158) with the optimal base system $KN(TMS)_2$/18-Crown-6 has been quite effective for reacting with cis-stereoselectivity (Scheme XXXVI).



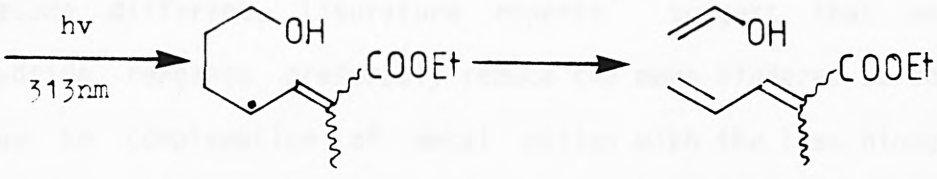
Scheme XXXVI

A reference to a (Z)2-methyl-penta-2-4-dienoate structure (114a) by J.Kassangi et al.[6] describes a photosynthetic route which, from a synthetic point of view, is not an attractive method for large scale preparation owing to formation of side products, intermediates as well as geometrical isomers. They irradiated the cycloalkanone (159) which undergoes a Norrish

type I reaction via a biradical intermediate (160) to the aldehyde (161). This aldehyde under selective wavelength irradiation subsequently undergoes a Norrish type II reaction from the excited singlet state. E- and Z- isomers produced were separated by distillation and their ^{1}H-NMR spectra were reported.



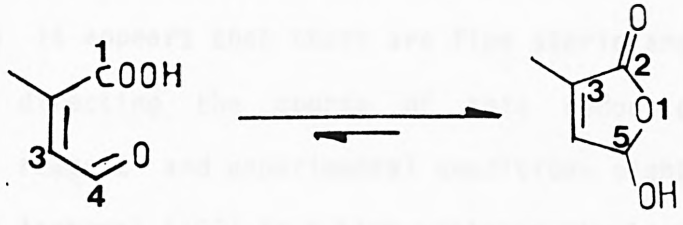
159 160 161



114a & 119b

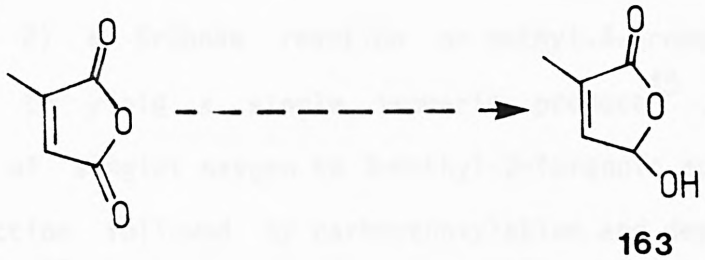
4.3 Our synthetic Approach

The alternative approach of C4-C5 bond formation was chosen in our study. This route requires, as an intermediate, the Z-carboxymethyl-α,β-unsaturated aldehyde (162), which exists in the cyclised form as the lactonol (163). In this strategy, the problem of stereochemistry about C-2 is resolved at an earlier stage and therefore eliminates a stereocontrolled Wittig reaction in the final step.



162 163

The most attractive method of γ-lactonol (163) synthesis must be a single step stereoselective reduction of citraconic anhydride.



163

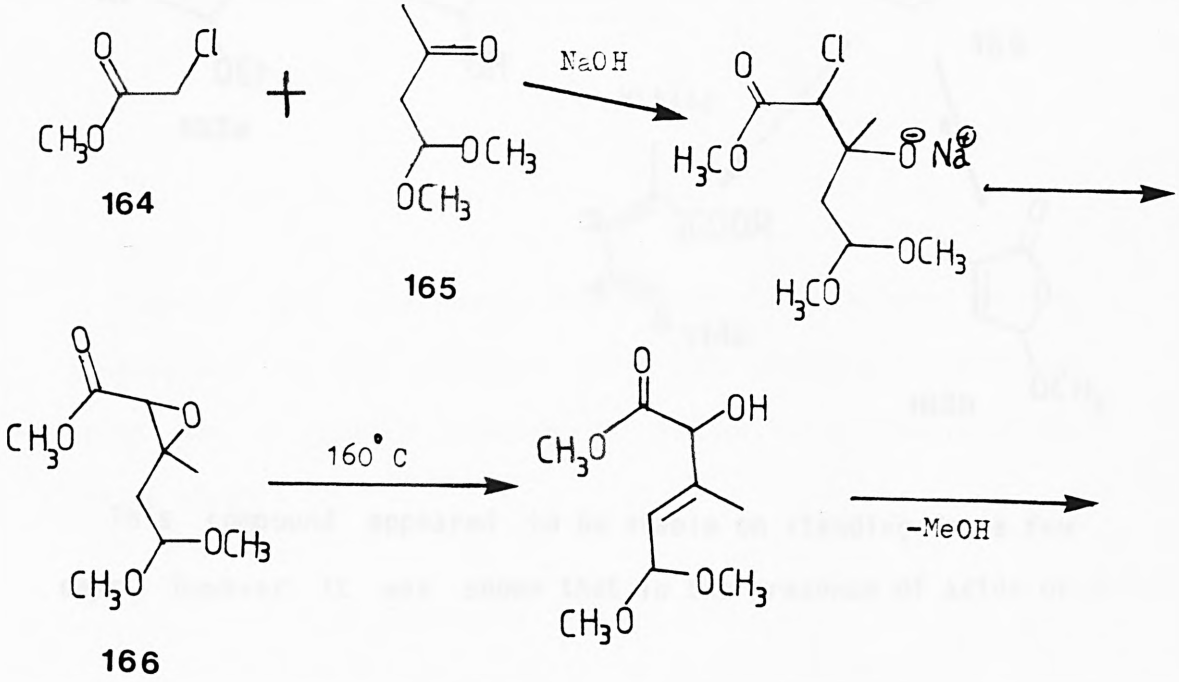
The methyl group in the anhydride causes the suseptibility of the two carbonyl carbons to attack by nucleophiles to become different. Liturature reports[7] suggest that metal hydride reagents preferably reduce the more hindered carbonyl due to complexation of metal cation with the less hindered carbonyl. However, in such reactions, usually both centres are reduced and in some instances complete reduction of the carbonyl to a methylene occurs, thus resulting in a mixture of products.

$NaBH_4$[8], $LiAlH_4$[9] and $Li(t\text{-}BuO)_3AlH$[10] result in a mixture in which the products from an attack on the more hindered carbonyl predominate (8 : 1). $Li(CH_3O)_3AlH$ behaves similarly (3 : 1). On the other hand, K-selectride (K-tri-S-butyl borohydride) recently has been claimed to reduce , in almost quantitative yields, the less hindered carbonyl to methylene[11]. Hence it appears that there are fine steric and electronic factors directing the course of this reduction. Choice of correct reagent and experimental conditions might produce the required lactonol (163) in a high yielding single step.

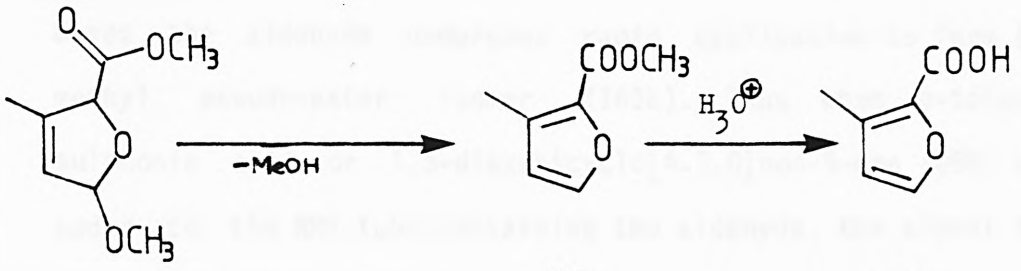
Available chemical routes to γ-lactonol (163), which was required in good yield without isomeric complications, were 1) N-bromosuccinimide bromination of 2-methylbutenolide followed by silver acetate treatment (which gives a mixture of isomers)[12], 2) a Kröhnke reaction on methyl-4-bromo-2-methyl crotonate to yield a single isomeric product[13], 3) the addition of singlet oxygen to 3-methyl-2-furanoic acid[14], and 4) protection followed by carboethoxylation and deprotection of crotonal[10]. Farina's photo-oxygenation route was chosen which required 3-methyl-2-furanoic acid[15] (168) as starting material.

4.3.1. Preparation of methyl furanoic acid

Condensation of 4,4-dimethoxy-2-butanone (165) with methyl chloroacetate (164) in the presence of sodium methoxide yielded the glycidic ester (166) which eliminated two moles of methanol under heating at 160°C to form the furanoic ester. Hydrolysis of (167) yielded the acid in overall yield of 50% (Scheme XXXVII).



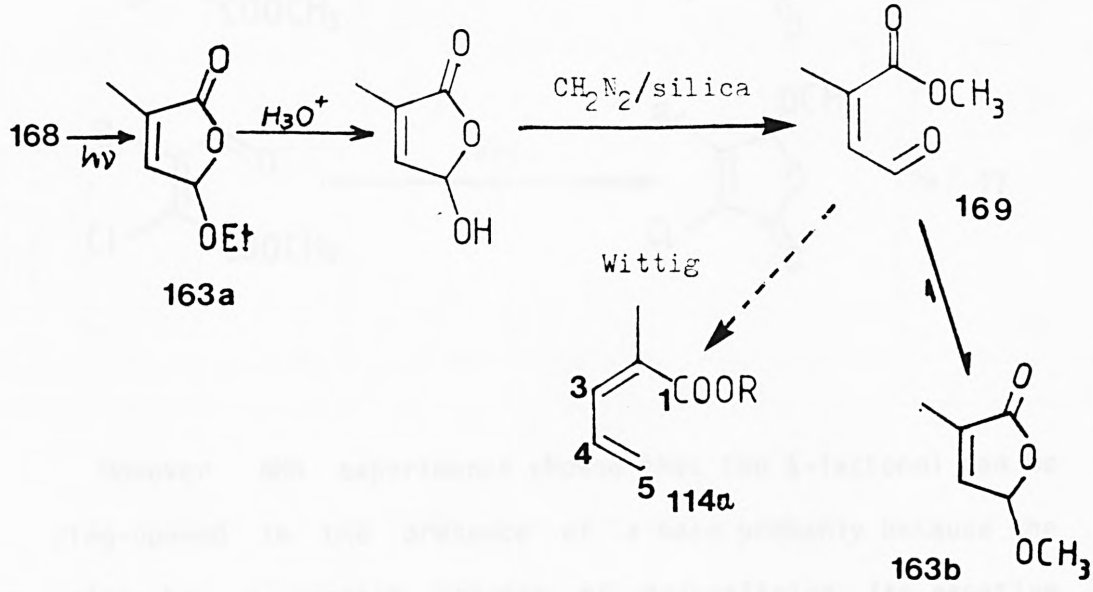
164 165 166



Scheme XXXVII

4.3.2 Preparation of the dieneoic acid (114)

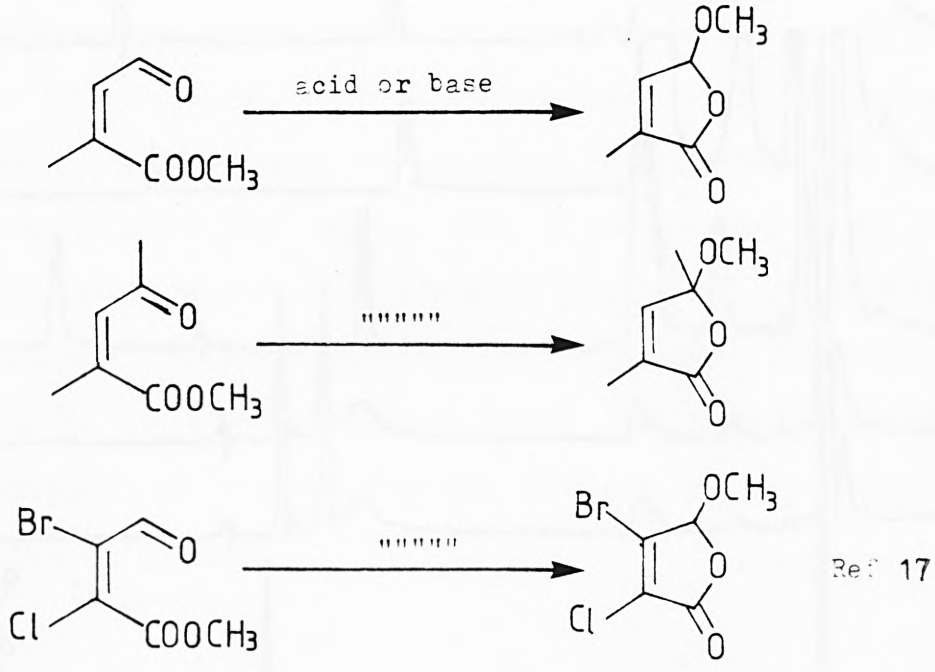
Farina's photo-oxygenation of (168) in absolute ethanol in the presence of eosine and vanadium pentoxide produced (163a) which upon hydrolysis yielded (163) as the only isolable isomer. The γ-lactonol was ring-opened and cleanly methylated using diazomethane and catalytic quantities of silica[16]. Above 90% yield of the aldehyde (169) was obtained as yellow liquid and was purified by distillation.



This compound appeared to be stable on standing for a few days. However it was shown that in the presence of acids or

bases the aldehyde undergoes rapid cyclisation to form the methyl pseudo-ester isomer (163b). Thus when p-toluene sulphonic acid or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) was added to the NMR tube containing the aldehyde, the signal due to the aldehydic hydrogen disappeared.

In conjunction with this observation the IR spectrum showed a strong absorption at 1795cm^{-1} due to the presence of the lactone ring, after exposing the aldehyde to acidic or basic condition. This is a common behaviour of similar structures.



However NMR experiments showed that the γ-lactonol can be ring-opened in the presence of a base probably because the anion has a greater freedom of delocalising its negative charge (Figure 1).

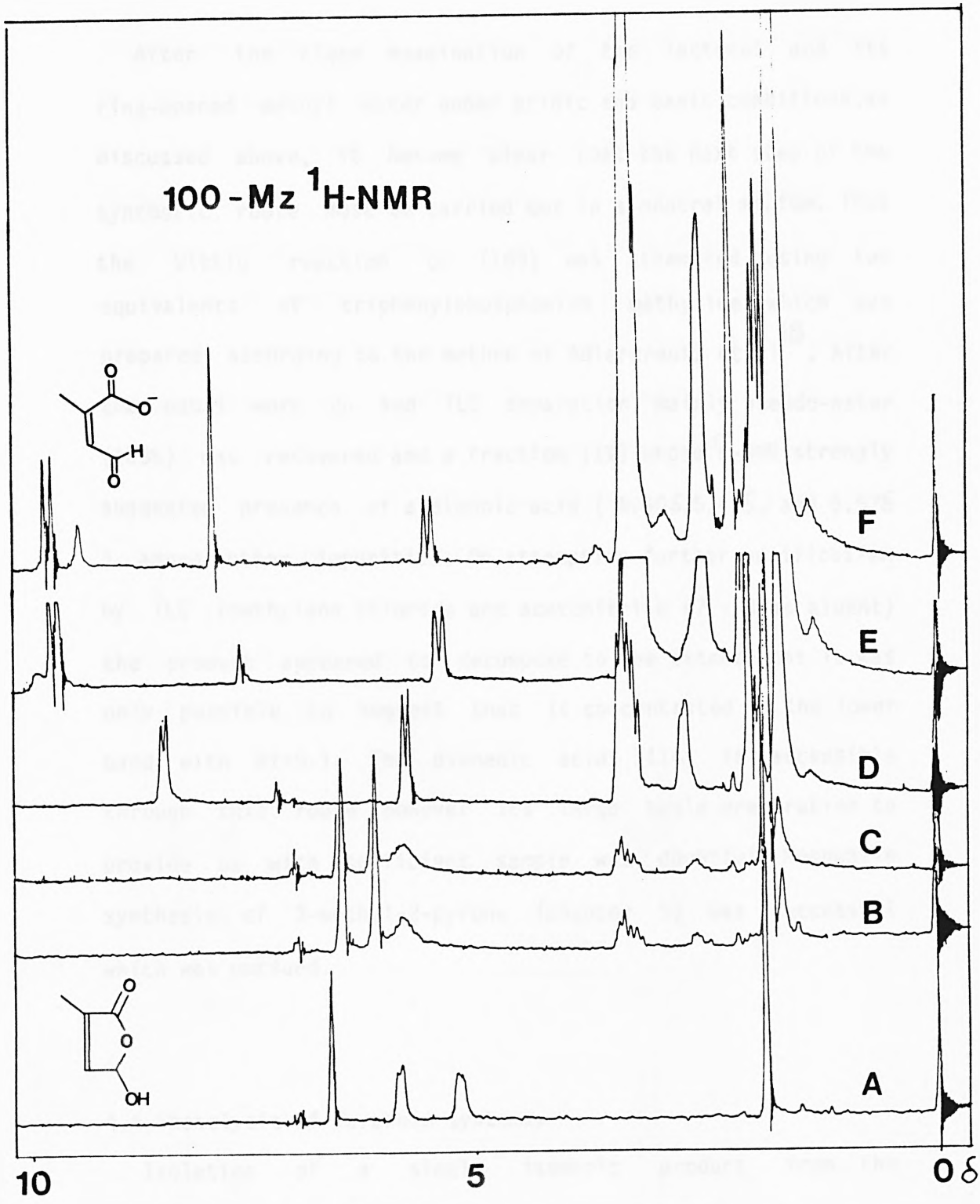


Figure 1 : The ^{1}H-NMR shows the effect on the interconversion of two structures when A) 0μl, B) 50μl, C) 50μl,2hr, D) 100μl, E) 200μl, F) 500μl of DBN was added to 30mg of γ-lactonol in 1.0ml of $CDCl_3$. Equilibrium is reached in seconds.

After the close examination of the lactonol and its ring-opened methyl ester under acidic and basic conditions,as discussed above, it became clear that the next step of the synthetic route must be carried out in a neutral medium. Thus the Wittig reaction on (169) was attempted using two equivalents of triphenylphosphonium methylide which was prepared according to the method of Adlercreutz et al[18]. After the usual work up and TLC separation mainly pseudo-ester (163b) was recovered and a fraction (1%) whose ^{1}H-NMR strongly suggested presence of a dienoic acid (5.40δ,5.41δ, and 6.57δ) among other impurities. On attempting further purification by TLC (methylene chloride and acetonitrile 97 : 3 as eluent) the product appeared to decompose to the extent that it was only possible to suggest that it concentrated in the lower band with Rf=0.1. The dieneoic acid (114) is accessible through this route however its large scale preparation to provide us with sufficient sample was doubtful. Meanwhile synthesis of 3-methyl-2-pyrone (chapter 5) was successful which was pursued.

4.4 Photolysis of furanoid systems.

Isolation of a single isomeric product from the photooxygenation of 3-methyl-2-furoic acid with singlet oxygen suggested a mechanism which had to be influenced by the presence of the carboxyl and/or methyl substituents on the furan ring. Surprisingly, Farina[14] has reported that 3-methyl-furan also gives only one isomer (163). To

investigate this point further the examination was continued by decarboxylating the furanoic acid[19] using copper/quinoline/ heat and subjecting the product, 3-methylfuran, to similar photolysis. This time a mixture of isomeric products was obtained which was shown by ^{1}H-NMR and HPLC to be (163) and (170) in the ratio of 2 : 1. With the aid of preparative HPLC the two isomers were separated. Figure 2 shows the analytical and preparative HPLC traces for the two isomers on silica.

Once pure sample of each isomer was obtained the molecular structure of each was identified. This was established using ^{1}H-NMR and ^{13}C-NMR spectroscopy. In (163) the ^{13}C signal of C-2 is a quartet of doublet of doublet which confirms that the methyl group is located on the C-3 carbon (Figure 3).

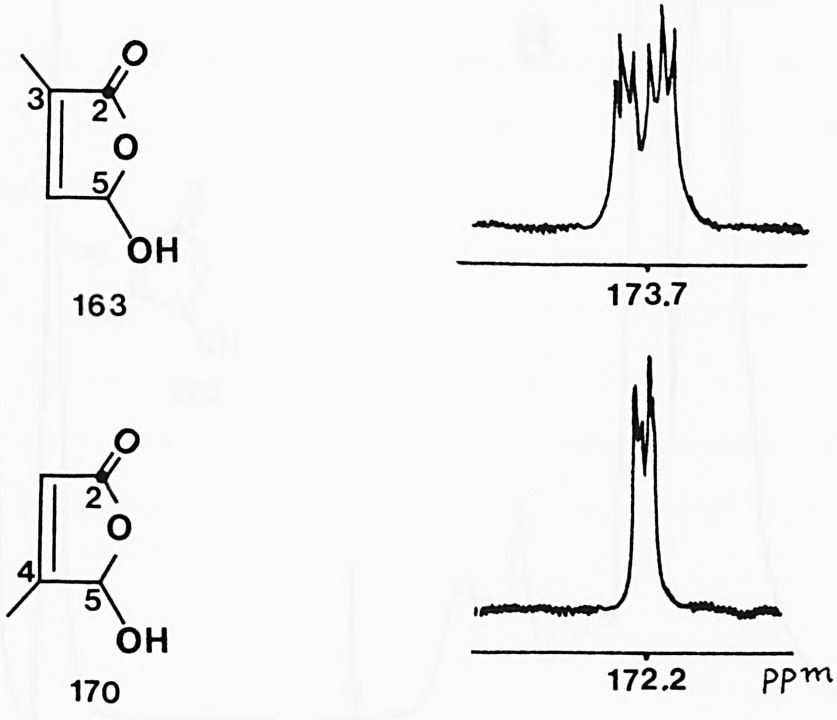
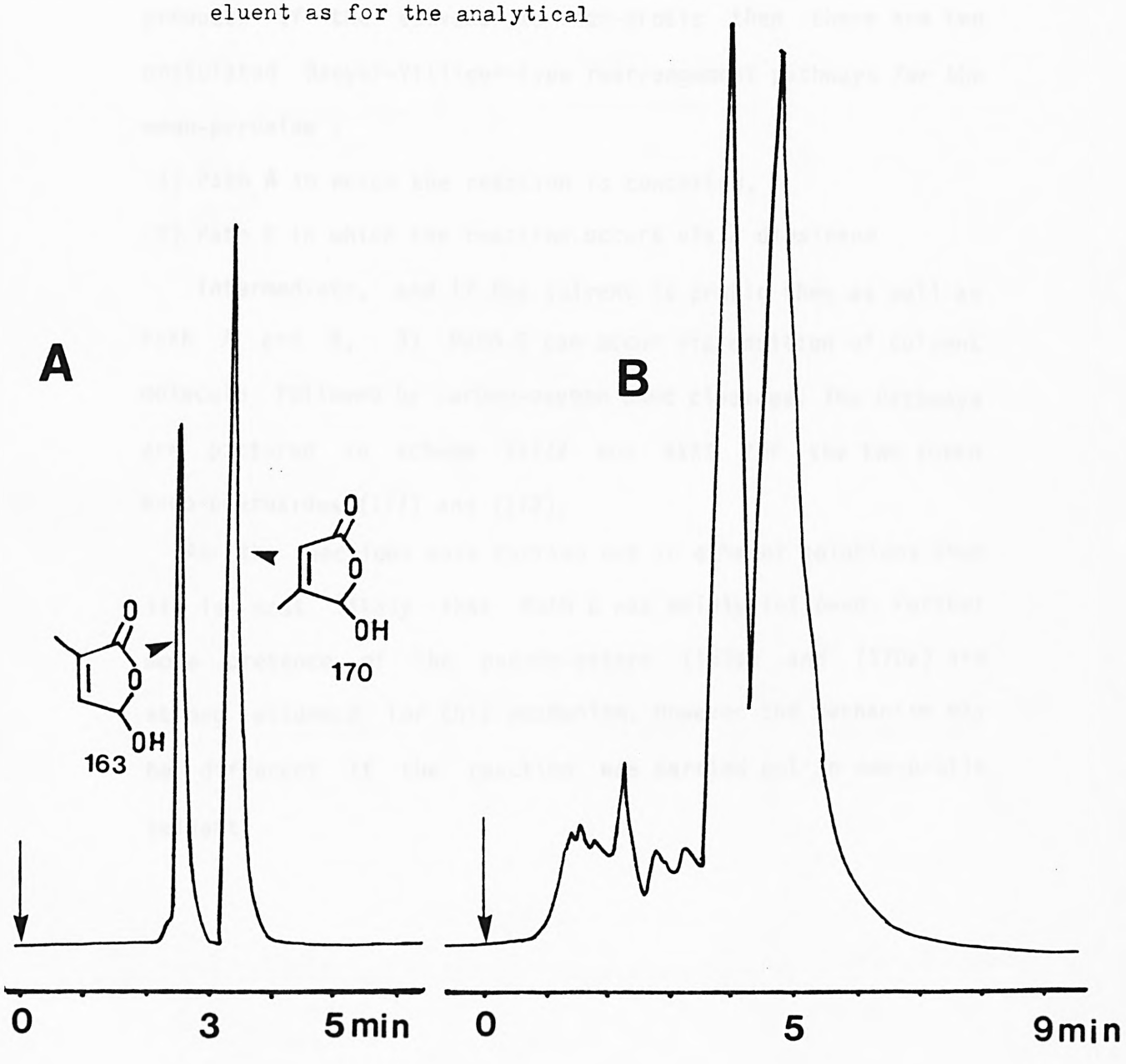


Figure 3 60MHz ^{13}C-NMR H-coupled signals for the carbonyl carbon in the two γ-lactonol isomers

Figure 2 HPLC traces for A) analytical and B) preparative separations of the lactonol isomers

A) spherisorb silica (5μm), 25 X 0.45 cm ID
230nm, 4ml/min, 1cm/min,
CH_2Cl_2 : CH_3CN : AcOH (97:2.7:0.3)

B) Lichrosorb silica (7μm), 25 X 2 cm ID
230nm, 19.9ml/min, 1cm/min,
100mg of sample loaded on column and
eluent as for the analytical

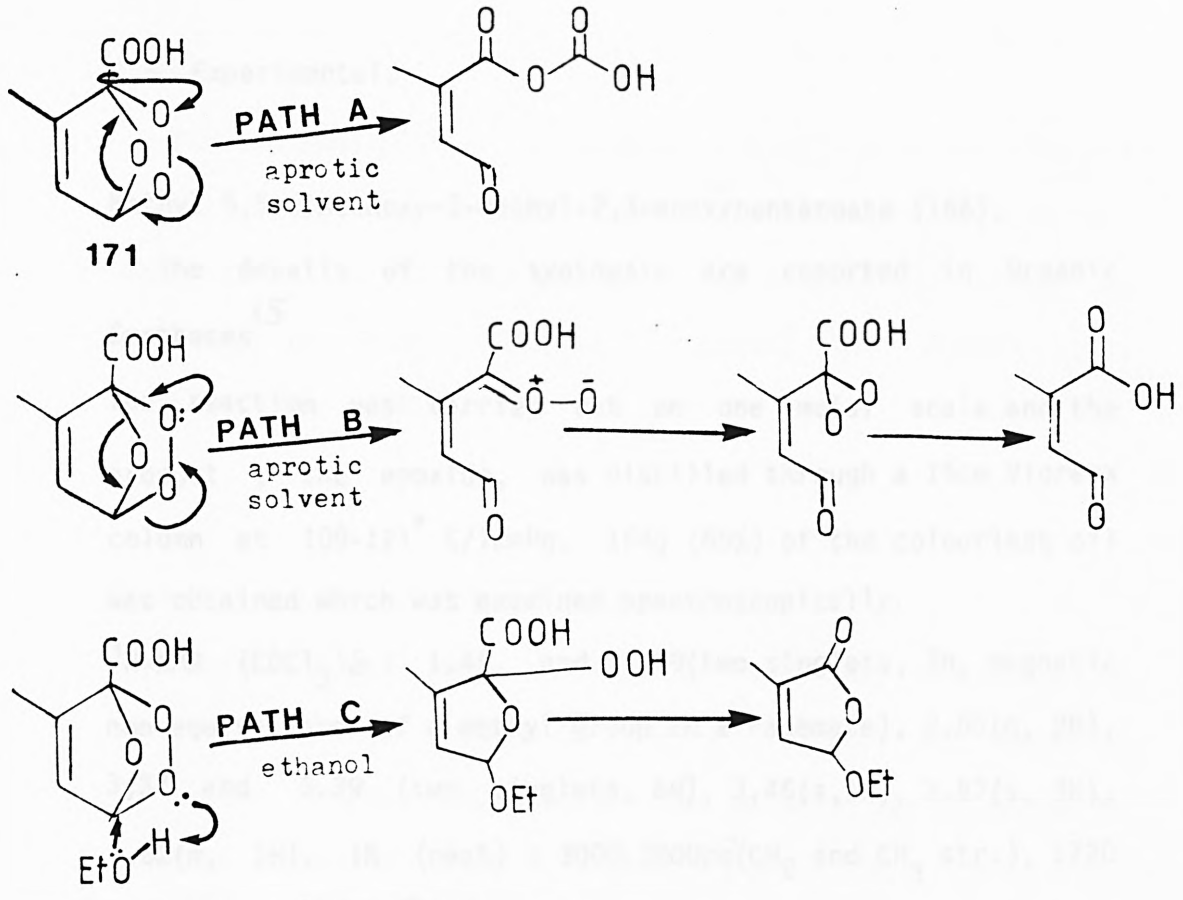


The mechanism of photo-oxidation of furans has been the subject of much investigation in recent years. In particular the ability of furan endoperoxides to oxidise olefins to epoxides, sulphides to sulphoxide and adamantane to its lactone has caused a growing interest for elucidation of mechanistic details involved. The work carried out by Feringa et al[20] and Adam et al[21] clearly show that the solvent in which photolysis is performed affects the outcome of the product. If the solvent is non-protic then there are two postulated Baeyer-Villiger-type rearrangement pathways for the endo-peroxide :

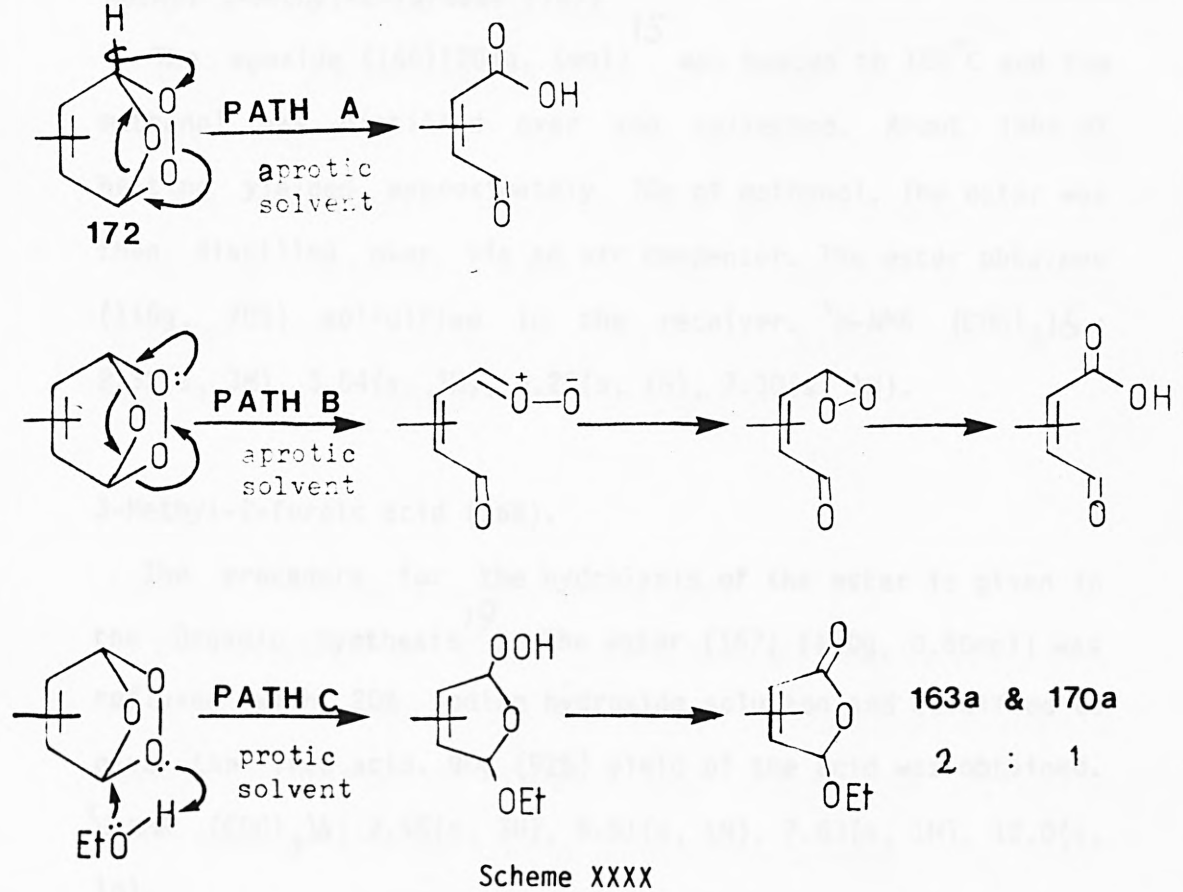
1) Path A in which the reaction is concerted,

2) Path B in which the reaction occurs via a dioxirane intermediate, and if the solvent is protic then as well as Path A and B, 3) Path C can occur via addition of solvent molecule followed by carbon-oxygen bond cleavage. The Pathways are pictured in scheme XXXIX and XXXX for the two furan endo-poeroxides (171) and (172).

As the reactions were carried out in ethanol solutions then it is most likely that Path C was mainly followed. Further more presence of the pseudo-esters (163a) and (170a) are strong evidence for this mechanism. However the mechanism may be different if the reaction was carried out in non-protic solvent.



Scheme XXXIX



Scheme XXXX

4.5 Experimental.

Methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate (166).

The details of the synthesis are reported in Organic Syntheses[15].

The reaction was carried out on one molar scale and the product , the epoxide, was distilled through a 15cm Vigreux column at 109-121° C/7mmHg. 164g (80%) of the colourless oil was obtained which was examined spectroscopically.

^{1}H-NMR ($CDCl_3$)δ : 1.44, and 1.49(two singlets, 3H, magnetic non-equivalence of a methyl group in a racemate), 2.03(m, 2H), 3,37 and 3.39 (two singlets, 6H), 3.46(s,1H), 3.87(s, 3H), 4.62(m, 1H). IR (neat) : 3000-2800cm^{-1}(CH_2 and CH_3 str.), 1720 and 1710 and 1750cm^{-1}(C=O str.).

Methyl 3-methyl-2-furoate (167)

The epoxide (166)(204g, 1mol)[15] was heated to 160°C and the methanol was distilled over and collected. About 14hr of heating yielded approximately 70g of methanol. The ester was then distilled over via an air condenser. The ester obtained (110g, 70%) solidified in the receiver. ^{1}H-NMR ($CDCl_3$)δ : 2.32(s, 3H), 3.84(s, 3H), 6.25(s, 1H), 7.30(s, 1H).

3-Methyl-2-furoic acid (168).

The procedure for the hydrolysis of the ester is given in the Organic Synthesis[19]. The ester (167) (110g, 0.80mol) was refluxed with 20% sodium hydroxide solution and acidified to give the free acid. 90g (92%) yield of the acid was obtained. ^{1}H-NMR ($CDCl_3$)δ: 2.45(s, 3H), 6.51(s, 1H), 7.63(s, 1H), 12.0(s, 1H).

3-Methyl furan

The decarboxylation of 3-methyl-2-furoic acid was effected according to the reported method[19]. 60% yield was obtained with 25.2g (0.2mol) of the acid. The product was redistilled at 65-66° C. ^{1}H-NMR ($CDCl_3$)δ : 2.06(bd, 3H), 6.29(bs, 1H), 7.25(bs, 1H), 7.38(bs, 1H).

3-Methyl,5-ethoxy,3-butenol-lactone (163a)

Furoic acid (168) (18.75g, 0.15mol) was dissolved in absolute ethanol (1250cc). Eosine (0.21g) and Vanadium pentoxide (0.21g) were added and the solution was subjected to visible radiation from 8 Cryselco 20W Daylight lamps. After 70hr the reaction was stopped and ethanol was evaporated to about 200ml and to this was added 4g of anhydrous stannous chloride (prepared from hydrated SnCl4 by adding acetic anhydride) and refluxed for one hour. Ethanol was removed on a rotary evaporator and the residue was distilled. 11.2g (60%) of the pseudo-ester was obtained at 80-90°C/13mmHg. Only one isomer was detected. ^{1}H-NMR ($CDCl_3$)δ: 1.29(t, 3H, J = 6.5Hz), 1.95(bdd, 3H), 3.86(m, 2H, J = 6.5Hz), 5.90(b, 1H), 6.97(b, 1H). IR (neat) : 1750cm^{-1}(C=O str), 1675(C=C str).

3-Methyl,5-hydroxy,3-butenolactone (163)

The pseudo-ester (163a) (10.5g, 0.07mol) was refluxed with water for one hour. Water was removed by distillation and the residue solidified in freezer over night.Recrystallisation from benzene yielded a white crystalline product (7.5g, 88%).

M.Pt. : 73-75° C(lit 75-77°C)[14]. ^{1}H.NMR ($CDCl_3$)δ: 1.97(bd, 3H), 5.70(bd, 1H), 6.24(bd, 1H), 7.06(bdq, 1H), signal at 5.70 disappeared and the signal at 6.24 collapsed to a singlet on D20 shake. ^{13}C-NMR ($CDCl_3$)δ: 10.4(dq, J = 129, 3Hz), 97.4(dd, J = 174, 7.5Hz), 133.7(m, J = 7.8Hz), 145.4(dm, J = 176,4Hz), 173.7(dqq, J = 13, 4Hz). IR (nujol) : 3310cm^{-1}(OH str), 1765(C=O str of lactone), 1670cm^{-1}(C=C str).

4-Methyl,5-hydroxy,3-butenolactone (170)

3-Methyl furan (10g, 0.12mol) obtained from decarboxylation was subjected to visible radiation using the conditions which were used for photolysis of 3-methyl-2-furoic acid. After the solvent was removed on rotary evaporator NMR check showed presence of pseudo-ester (170a). Water was added and the mixture was refluxed for one hour. The mixture was dried on a rotary evaporator to leave a dark brown oily residue which did not solidify in freezer. Preparative HPLC separation was carried out using methylene chloride, acetonitrile and acetic acid (97 : 2.7 : 0.3) on a silica column. ^{1}H-NMR ($CDCl_3$)δ : 2.17(bd, 3H), 5.35(b, 1H), 5.81(bs, 1H), 5.98(bs, 1H), signal at 5.35 disappeared on D20 shake. ^{13}C-NMR ($CDCl_3$)δ : 13.32(qd, J = 132, 3Hz), 99.93(dq, J = 172, 8Hz), 118.38(bd, J = 181, 4.5Hz), 166.00(bd, J = 3, 6Hz), 172.24(bm, J = 4, 1H).

Methyl,2-methyl,cis-3-formylacrylate (169)

The hydroxy-butenolactone (7.5g, 0.065mol) was dissolved in

dried ether (150ml) and excess diazomethane was added in the presence of silica (7.5g). Above 90% yield of the aldehyde was obtained and the yellow liquid was distilled at 42-46°C/2mmHg and characterised. ^{1}H-NMR ($CDCl_3$)δ: 2.22(d, 3H), 3.90(s, 3H), 6.30(dq, 1H, J = 6.8Hz), 11.0(d, 1H, J = 6.8Hz). IR (neat) : 2745cm^{-1}(CH str), 1735 and 1695cm^{-1}(C=O str), 1640cm^{-1}(C=C str). This compound was unstable and readily reverted to the pseudo-ester (163b).

4.6 References

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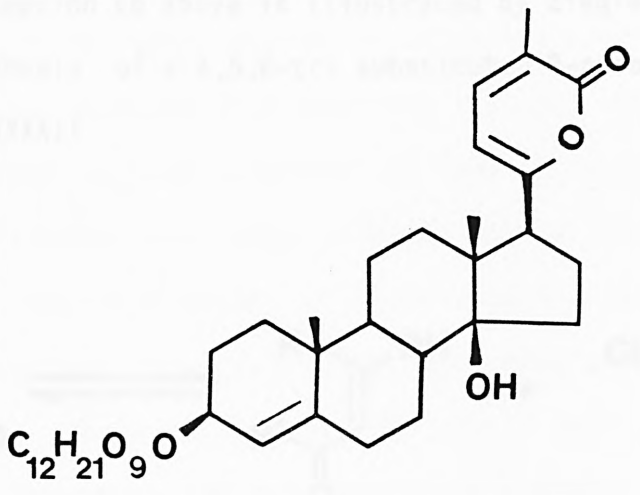
CHAPTER 5 : PYRONES

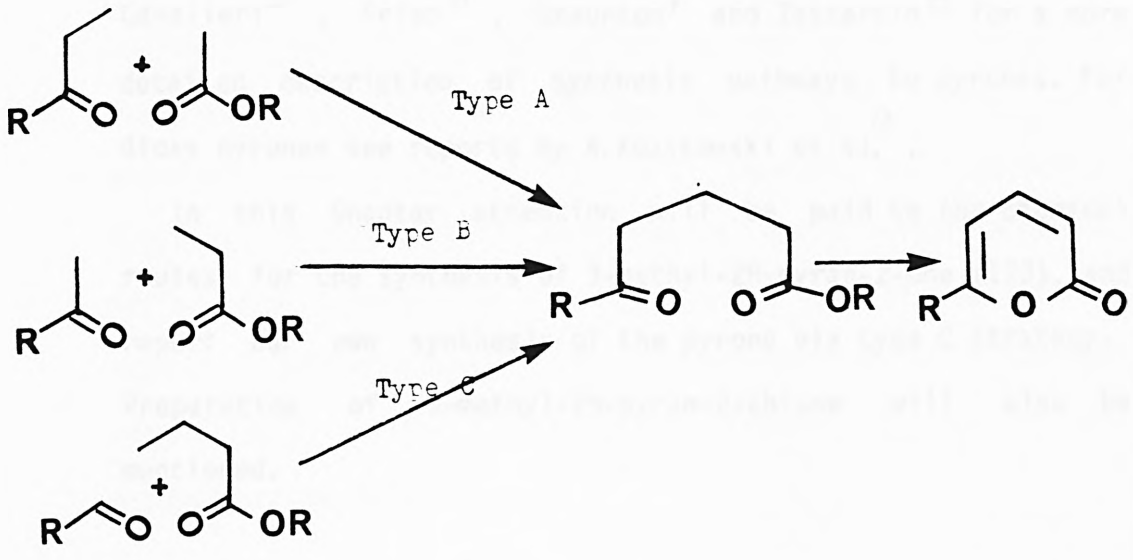
5.1 Pyrones and their synthesis

Naturally occurring 2-pyrones isolated from plants and animals are heavily substituted and have a wide range of biological activities[1] . For example, the steroidal 2-pyrone , scillaren A, is an active ingredient of the poisonous secretion found in the skin of certain toads[2]. Norditerpeneoid 2-pyrones isolated from Podocarpus plants show important biological activities discussed in chapter 1 .



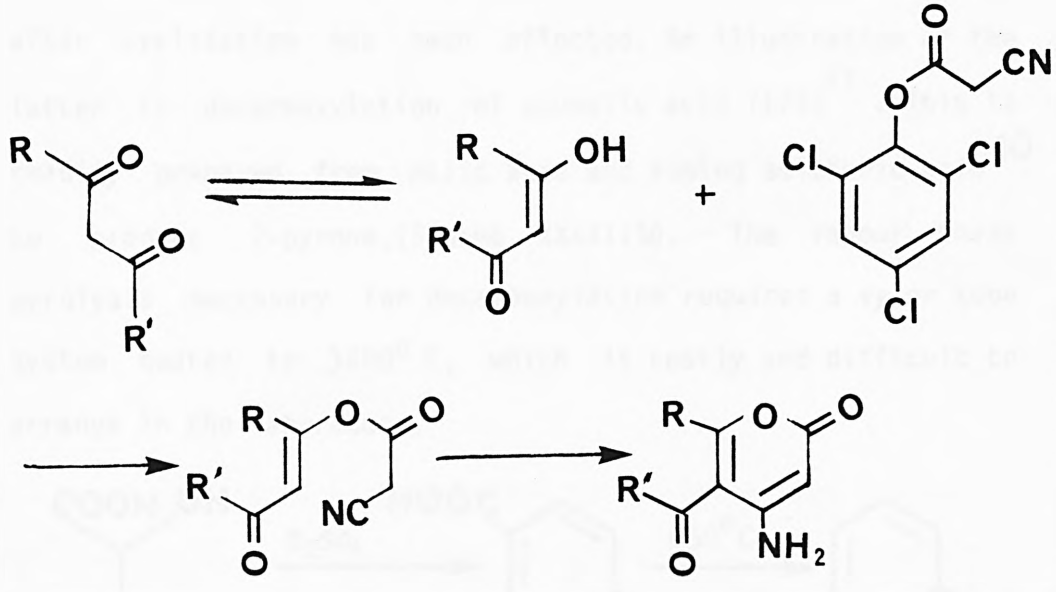
SCILLAREN A

As a result of their structural complexity, there is a diversity of approaches to the synthesis of 2-pyrones . All of the methods exhibit limitation in terms of the number of steps involved, chemical yields, functional group compatibility, and the pattern and type of substituents that can be introduced. However, synthesis of simple parent pyrones are also varied and follow roughly one of the three main strategies depicted in scheme XXXXI .



Scheme XXXXI

One exception to above is illustrated by Ziegler et al.[3] in their synthesis of a 4,5,6-tri substituted 2-pyrone, as shown in scheme XXXXII



Scheme XXXXII

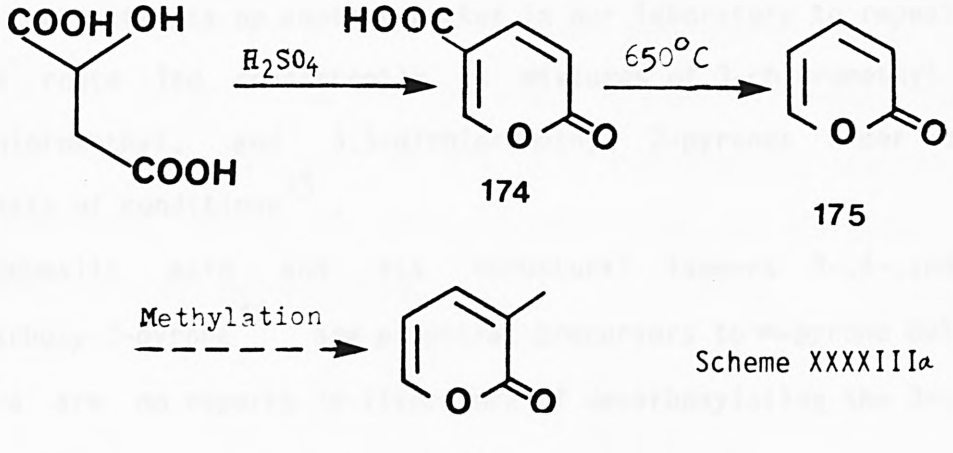
A recent paper explains how to exploit the ∝-oxoketone dithio-acetal functionality for a versatile and efficient

synthesis of annulated and simple 2-pyrones[4]. See reviews by Cavalieri[5], Fried[6], Staunton[7] and Zakharkin[8] for a more detailed description of synthetic pathways to pyrones. For dioxy pyrones see reports by A. Kozikowski et al.[9].

In this Chapter attention will be paid to the chemical routes for the synthesis of 3-methyl-2H-pyran-2-one (173), and report our own synthesis of the pyrone via type C strategy. Preparation of 3-methyl-2H-pyran-2-thione will also be mentioned.

5.2 Synthesis of 3-methyl-2H-pyran-2-one and/or its precursors.

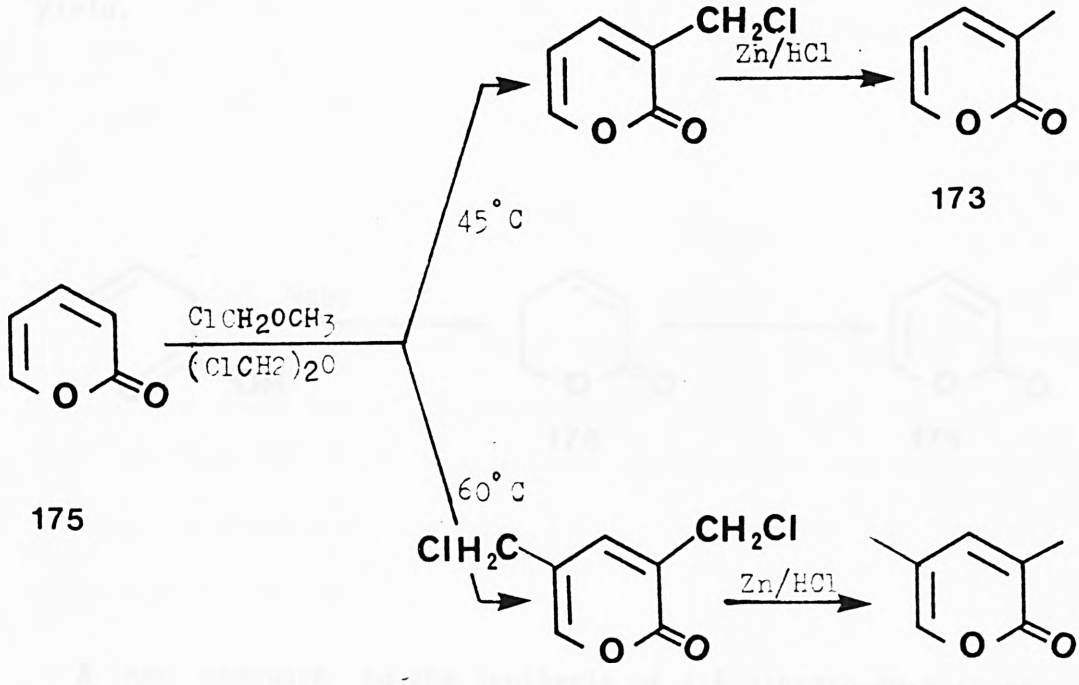
The insertion of a methyl group at the position 3 of 2-pyrone can be made before or after the ring closure. In addition the presence of a functionality, eg; -COOH group, on the ring can also be tolerated as long as it can be removed after cyclization has been effected. An illustration of the latter is decarboxylation of coumalic acid (174)[11]. This is readily prepared from malic acid and fuming sulphuric acid[10] to produce 2-pyrone, (Scheme XXXXIIIa). The vapour phase pyrolysis necessary for decarboxylation requires a vycor tube system heated to $>600^{\circ}$ C, which is costly and difficult to arrange in the laboratory.



174 175 173

Scheme XXXXIIIa

Furthermore the methyl group has then to be introduced in the 2-pyrone molecule. Shusherina et al.[12], reported a procedure for alkylation in 1977. However, their method of treating 2-pyrone with chloromethyl methyl ether in acidic medium and maintaining the temperature at 45°C or 60°C to obtain 3-chloromethyl or 3,5-bis(chloromethyl)-2-pyrone respectively leaves doubts as to isomeric purity of the product(Scheme XXXXIV).



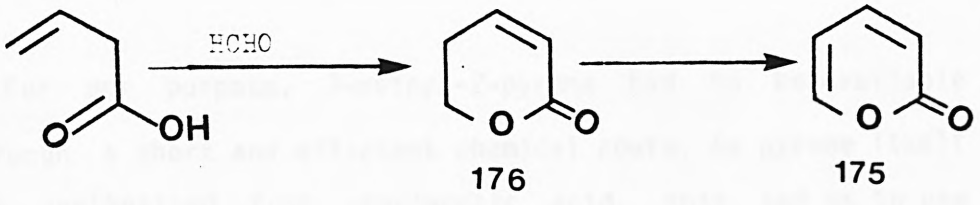
Scheme XXXXIV

In fact attempts by another worker in our laboratory to repeat this route led consistently to mixtures of 3-chloromethyl, 5-chloromethyl, and 3,5-dichloromethyl 2-pyrones under a variety of conditions[13].

Coumalic acid and its structural isomers 3-,4-,and 6-carboxy-2-pyrone[14] are potential precursors to α-pyrone but there are no reports in literature of decarboxylating the 3-,

and 4-carboxy-2-pyrone[12]. Methylating C-3 of cumalic acid using a liturature method[16] has failed.

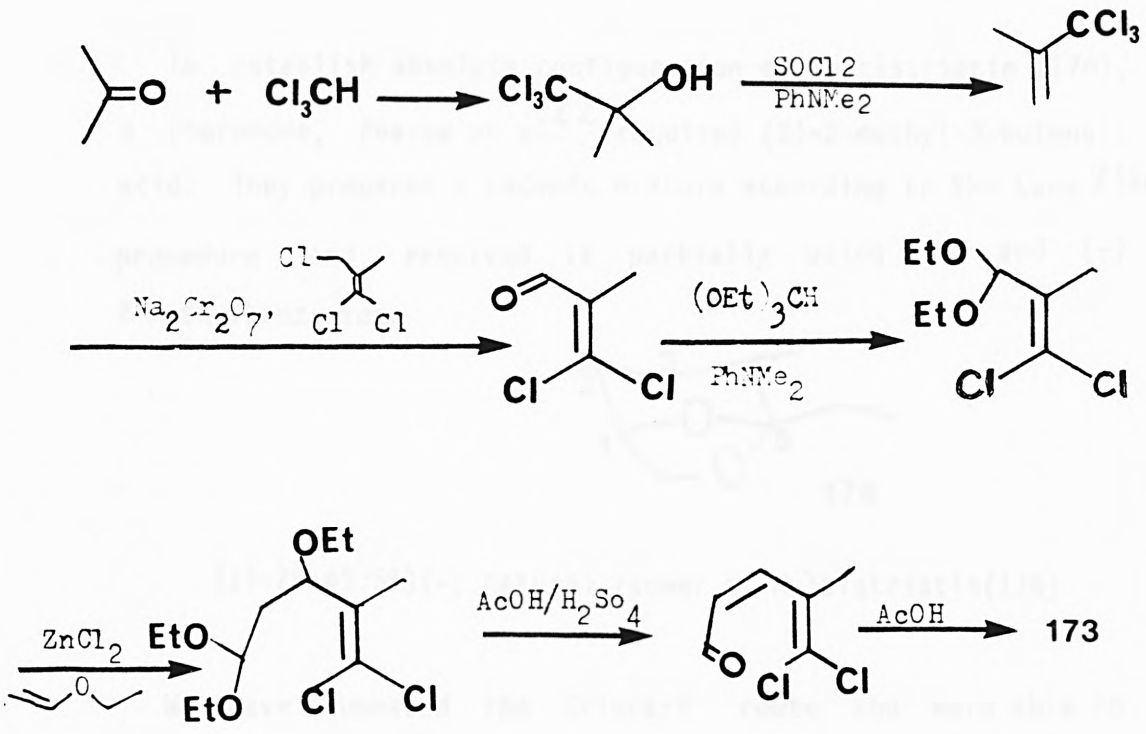
A convenient approach via type C strategy to the synthesis of 5,6-dihydro-2-pyrone and 2-pyrone from commercially available chemicals was reported by Nakagawa et al.[17]. By condensing vinyl acetic acid with formaldehyde in the presence of a catalytic amount of conc. sulphuric acid in boiling acetic acid they obtained (176). Subsequently bromination-dehydrobromination yielded 2-pyrone in 25% overall yield.



176 175

A new approach to the synthesis of 4,5-dihydro-2H-pyrones has been reported recently which uses pyridinium chlorochromate to oxidise the 5,6-dihydropyrans.

Representative of a 'type A' strategy was reported by Julia et al.[19] who developed a direct route to 3-methyl-pyrone. The route required handling of six oily and sometimes unstable intermediate, making the synthesis inefficient and the overall yield very poor. Scheme XXXXV.

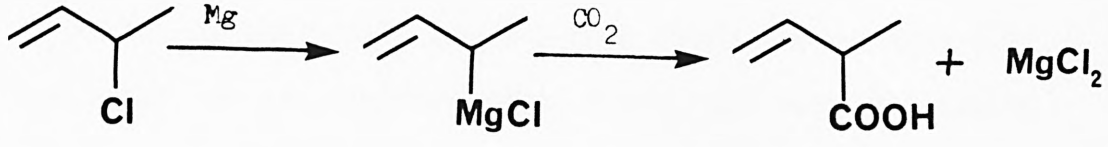


Scheme XXXXV

For our purpose, 3-methyl-2-pyrone had to be available through a short and efficient chemical route. As pyrone itself was synthesised from vinylacetic acid, this led us to use 2-methyl-2-vinyl-acetic acid (177) to prepare the methyl substituted 2-pyrone[20].

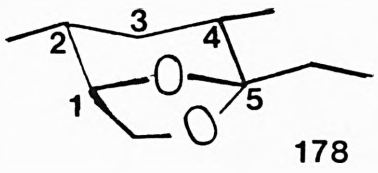
5.3 Preparations of 2-methyl-but-3-eneoic acid (177)

a) Via Grignard reaction : American workers[21] have reported that a Grignard reaction of crotyl magnesium halide with carbon dioxide afforded 2-methyl,but-3-enoic acid in up to 82% yield.



177

To establish absolute configuration of Multistriatin (178), a pheromone, Pearse et al.[22] required (S)-2-methyl-3-butenoic acid. They prepared a racemic mixture according to the Lane[21b] procedure and resolved it partially using (+) and (-) 2-methylbenzamide.

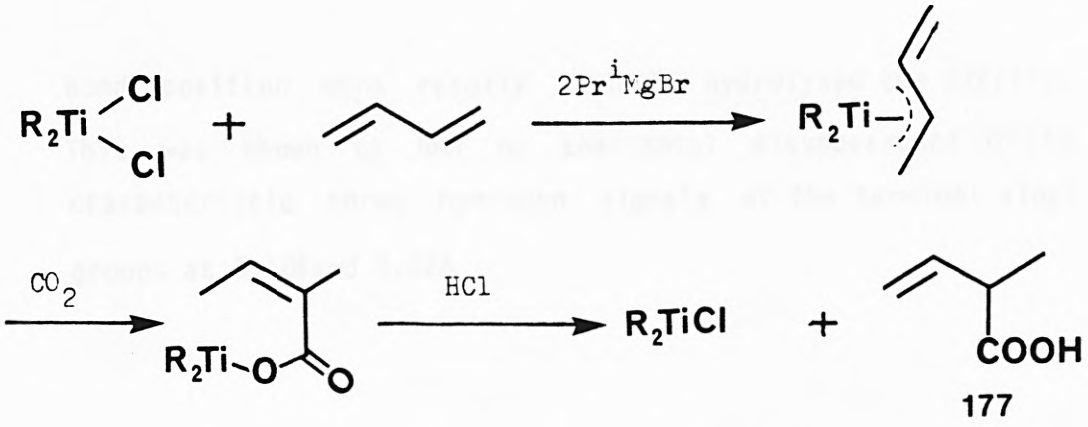


178

(1S:2R:4S:5R)(-) natural isomer of Multistriatin(178)

We have repeated the Grignard route and were able to obtain the required racemic acid in up to 30% yield, However the method suffers from a number of disadvantages since the crotyl halides are not cheap; the reaction is erratic and on a number of occasions produced large amounts of resinous by-product; and is limited in scale by the need to work in dilute ether solution. This approach was therefore not considered suitable for our purpose.

b) Via butadiene : With the advent of π-allyl titanium(III) and palladium complexes, Sara et al[23] recently reported an asymmetric carbon dioxide insertion into a butyl group to form the optically pure acid.



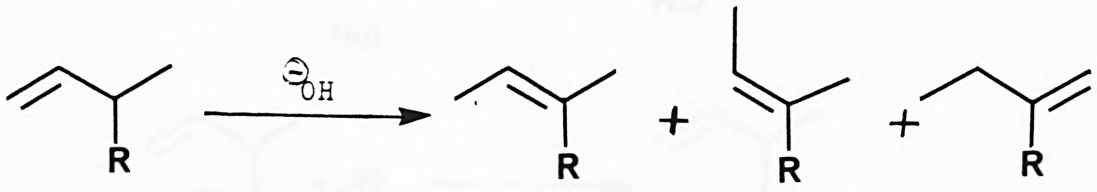
R = (η^5-C5H5), racemic, 85% yield.

R = ( ), (S) 18.9%ee, 70% yield.

c) Via nitrile : Fluka sells technical grade 2-methyl,3-buteneonitrile (179). Hydrolysis of nitriles to the corresponding acids are well known reactions, Standard methods are acid or alkali hydrolysis and several other methods have been used depending on whether the nitrile is aromatic or primary , secondary or tertiary aliphatic[24] . The only reference in the literature to hydrolysis of 2-methyl-3-butenonitrile (179) reported the use of conc. HCl under reflux. However we found that those conditions reported led to extensive charring with no detectable quantity of the acidic product.We therefore carried out a detailed examination of the hydrolysis reaction to establish suitable conditions for a clean, high-yield conversion of the nitrile (179) to the acid (177).

It became immediately apparent that alkaline conditions (KOH in water or in 2-hydroxy ethyl ether) rearranged the double

bond position more readily than they hydrolysed the nitrile. This was shown by NMR by the total disappearance of the characteristic three hydrogen signals of the terminal vinyl groups at 5.10δ and 5.82δ

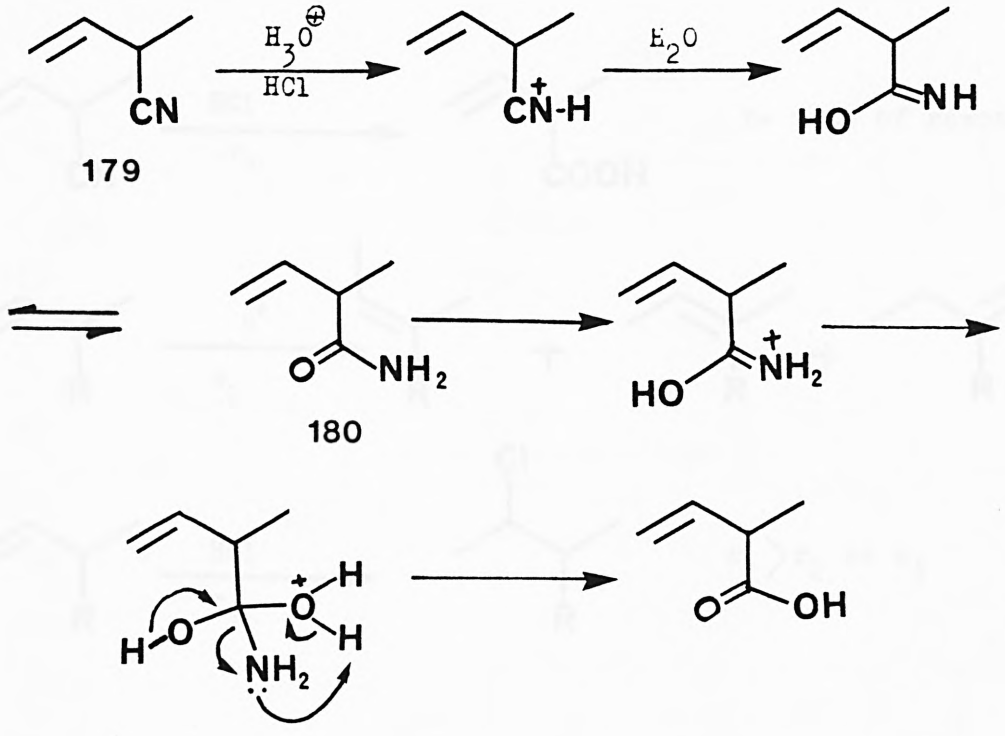


R=CN, $CONH_2$, COO-

Possible isomeric products.

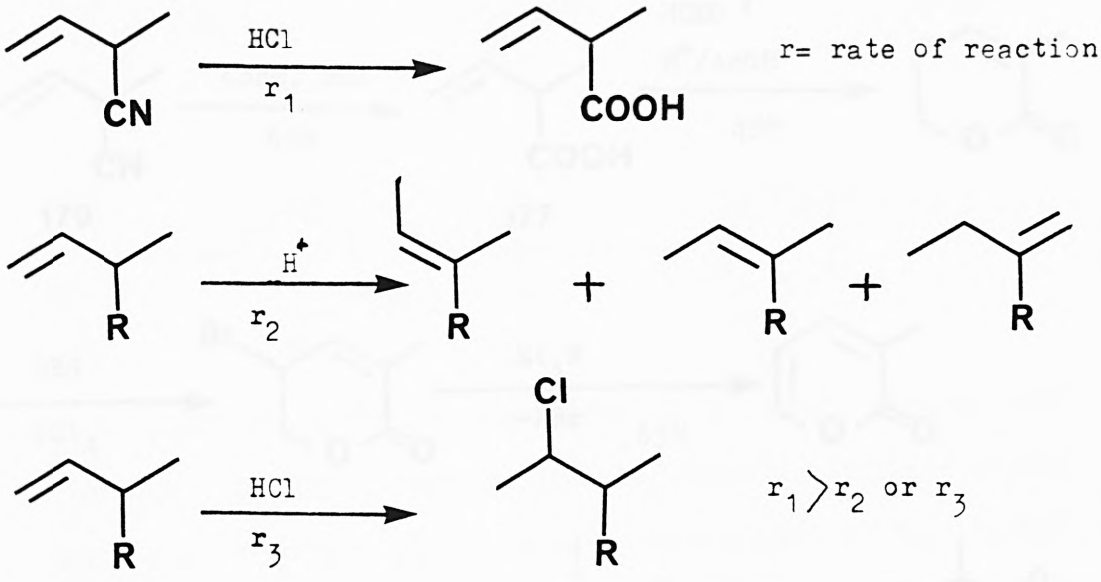
The second route examined was the use of polyphosphoric acid (PPA). PPA has been used to convert nitriles to the acids in good yields[24]. However in the present case when 100% PPA was employed at 120-150°C , 2-methyl-3-buteneamide (180) was obtained in 21% yield. Conversion of the amide to the acid was not explored since it was not considered attractive to use a two-step procedure for the overall hydrolysis.

Unlike alkaline hydrolysis, which rearranged the double bond, acid medium appeared suitable. 66% Sulphuric acid produced a mixture of several products as shown by NMR, some of which encouragingly had their terminal vinyl group intact. The detailed examination of the by-products was abandoned in favour of the study of the hydrolysis with conc. HCl (Scheme XXXXVI)



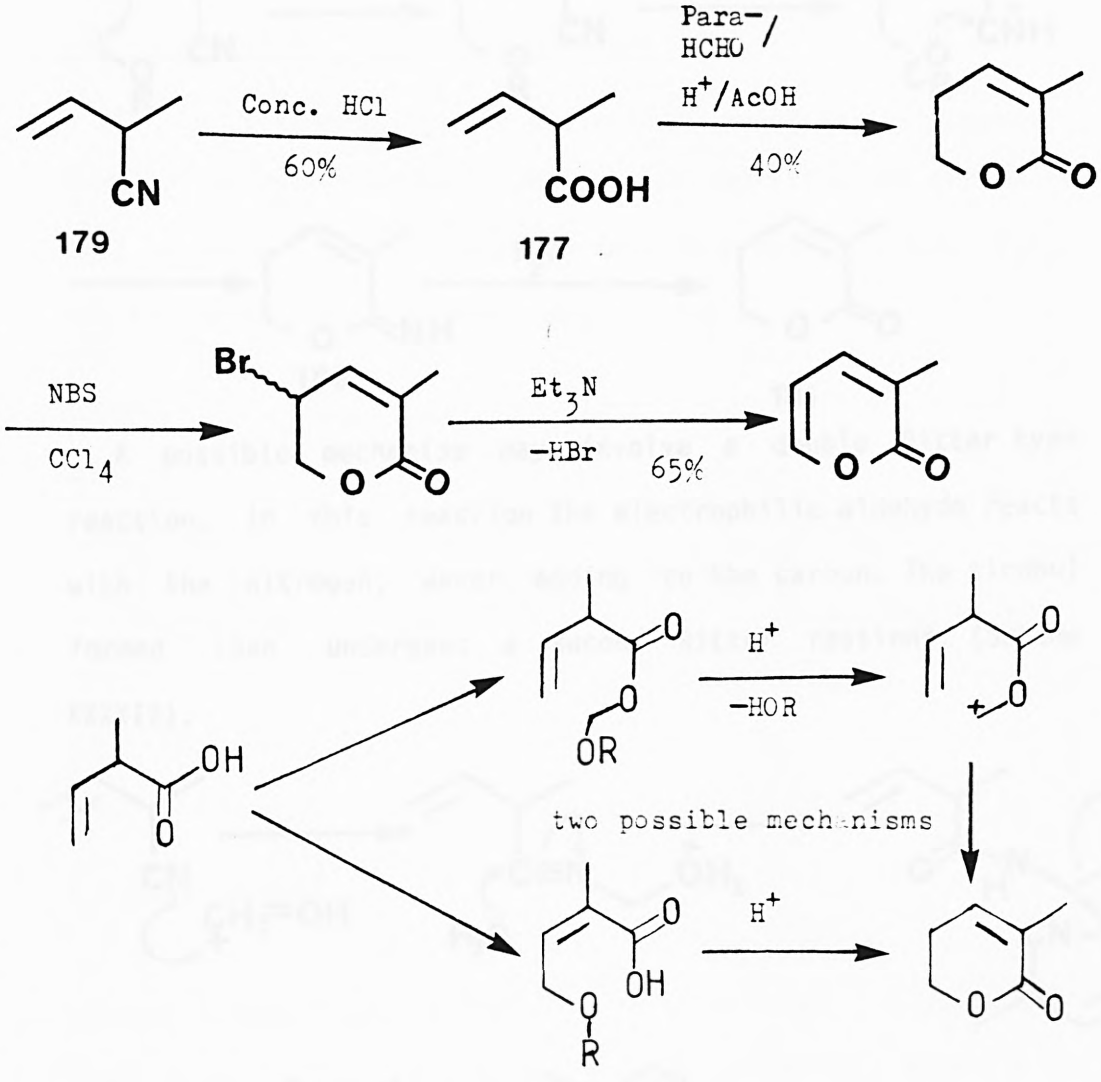
Scheme XXXXVI

A trial run of conc. HCl mixed with the nitrile (179)and left stirring at 60-65° C over the weekend produced a white precipitate of NH_4Cl. The NMR spectrum after work up showed the presence of the desired acid as the major component. A series of experimental conditions were examined, establishing that a 1 : 1.2 (vol/vol) mixture of the nitrile and conc. HCl stirred for 3hr at 65° C yielded 50-60% of the 2-methyl-3-buteneoic acid. Isomeric impurities and other by products (Scheme XXXXVII) were suppressed by lowering the reaction time and reducing the amount of concentrated HCl suggesting that the rate of hydrolysis of C≡N under acidic conditions is faster than double bond rearrangement (by protonation and deprotonation) and faster than the rate of possible hydro- halogenation of the double bond.



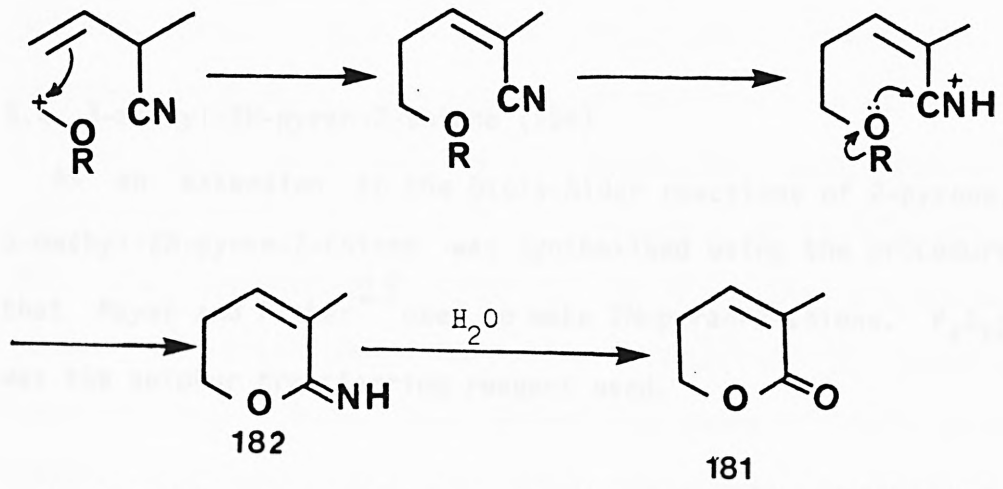
Scheme XXXXVII

Once 2-methyl-3-buteneoic acid was available cheaply and in large quantities, the problem of synthesis of 3-methyl-2-pyrone (173) was solved. 3-methyl-5,6-dihydro-2-pyrone (181) was prepared using slight modification of the procedure of Nakagawa et al.[17]. Distillation of the dihydropyrone (crude) also produced higher boiling oil fractions with similar N M R spectra and acidic odours but their structures were not investigated. Bromination- dehydrobromination of the dihydropyrone was effected smoothly using N-bromosuccinimide and triethylamine to make the required 2-pyrone in 30-35% overall yield from the acid (Scheme XXXXVIII). The 3-methyl-2-pyrone prepared, was stable in triflouroacetic acid at 40°C for four days.



Scheme XXXXVIII

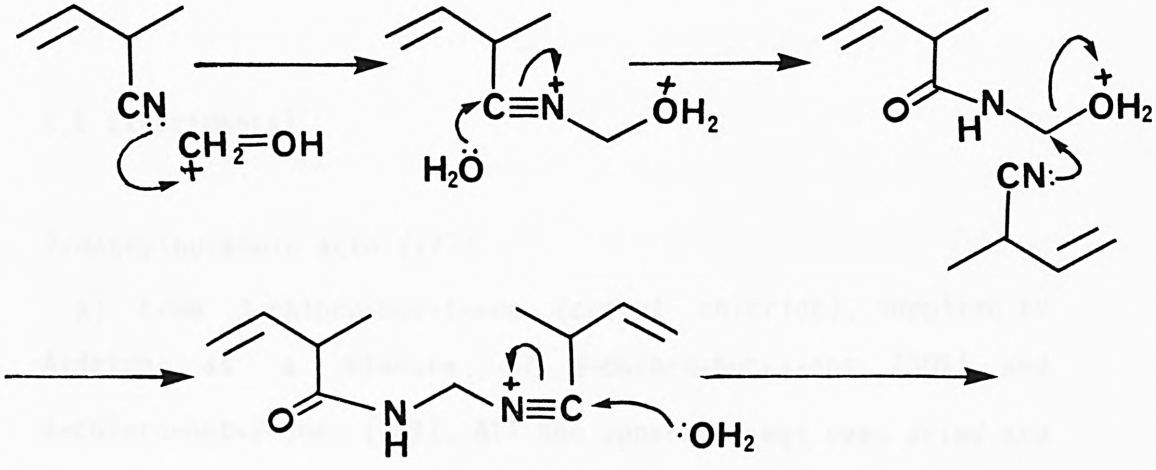
During the course of the above investigation it was reasoned that the nitrile (179) could cyclise with paraformaldehyde to give an unstable imine (182) which could be converted into the dihydro-pyrone (181).



182

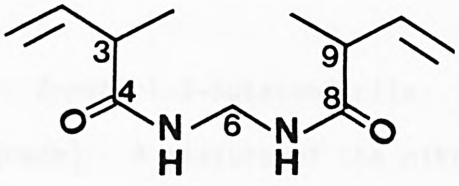
181

A possible mechanism may involve a double Ritter type reaction. In this reaction the electrophilic aldehyde reacts with the nitrogen, water adding to the carbon. The alcohol formed then undergoes a second Ritter reations (Scheme XXXXIX).



Scheme XXXXIX

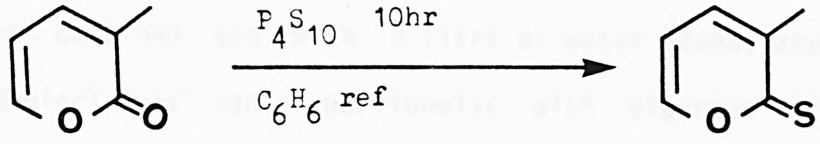
In an attempt to effect this route to the dihydro-pyrone, 2-methylbut-3-enonitrile was used instead of the corresponding acid. A white crystalline solid was obtained with spectroscopic data confirming the structure to be (183).



183

5.4 3-methyl-2H-pyran-2-thione (184)

As an extension to the Diels-Alder reactions of 2-pyrone, 3-methyl-2H-pyran-2-thione was synthesised using the procedure that Mayer and Fisher[25] used to make 2H-pyran-2-thione. P_4S_{10} was the sulphur transferring reagent used.



184

5.5 Experimental

2-Methylbutenoic acid (177)

a) From 3-chloro-but-1-ene (crotyl chloride), supplied by Aldrich as a mixture of 3-chloro-but-1-ene (30%) and 4-chloro-but-2-ene (70%). All the apparatus was oven dried and the starting materials distilled and dried. The procedure of Young and Lane[21b] was followed using 118.5g of the halide. Distillation of crude product at atmospheric pressure produced several fractions of which the 170-185°C fraction (26.2g) was mainly the acid as shown by NMR and IR. Several runs gave a range of 15-30% yields.

b) From 2-methyl-3-butenonitrile supplied by Fluka (Technical grade). A mixture of the nitrile (810g, 10mol) and conc. HCl (1.2litre) was stirred mechanically in a 3-necked,

3-litre flask, fitted with thermometer and condenser. Whilst stirring vigorously, the temperature was raised to 65°C using an oil bath. Once the reaction began, the temperature was controlled using an ice bath to maintain it at 55-70°C. After 2hr, the temperature dropped to 35 C and the reaction was worked up after 3hr. The white precipitate of ammonium chloride was filtered and washed with ether (2x50ml). Water (200ml) was added and the ether phase was separated. The aqueous phase was washed with ether (4x100ml). Ether fractions were combined and with 2 litre of water added, aqueous NaOH (30molar) was added portionwise with vigorous stirring to avoid overheating, until the aqueous phase was just alkaline (pH=8). The aqueous phase was then washed with ether (5x100ml) and was then re-acidified with conc. HCl slowly with efficient stirring and cooling. The organic acid phase was removed and the aq. phase washed with ether (3x200ml). The combined ether extracts were dried over Na_2SO_4 and evaporated to give 702g of crude oil.

Distillation at 53mmHg produced several fractions and the acidic major fraction was collected at 110 -125°C (490g, 49%)(lit=170-180° C atm. pressure;93-94°C at 33mmHg, and 95.5 C at 35mmHg)[22,23]. Yields on several runs were in the range 50-60%. ^{1}H-NMR ($CDCl_3$)δ : 1.35(d, 3H, J=8.5Hz), 3.16(m, 1H), 5.10(m, 1H), 5.82(m, 2H), 11.20 (bs, 1H). IR (neat) : 3100-3000cm^{-1} (CH_2, CH_3 str.), 3600-3400cm^{-1} (OH vib.), 1725cm^{-1} (C=O str), 1660cm^{-1}(C=C), 920cm^{-1}(OH bend out of plane.

A higher boiling fraction (130-150° C) solidified in the condenser and proved to be tiglic acid (60g). M.pt. = 64-65°C (lit. = 64.5-65°C). ^{1}H-NMR (CDCl3)δ: 1.82(m, 6H, two methyls), 6.99(m, 1H, =C-H str).

2-Methylbut-3-enamide (180)

To 57g of phosphoric acid 100%(prepared by mixing 24g of P2O5 and 33g of 88% orthophosphoric acid and stirring at 110-150 C for 2hrs) was added 4.05g (0.05 mole) of the nitrile and the mixture stirred for further 1.5hr at the same temperature. After cooling, 200ml of distilled water was added and the aqueous mixture of the phosphoric acid was brought to pH=7-8 with aqueous KOH and extracted with 4x50ml ether. Combined ether fractions were dried over Na_2SO_4 and evaporated down to an oily residue, 3.47g. Recrystalization from benzene-hexane mixture yielded 2.2g (21% yield) of white plates. M.Pt= 97-98°C (lit. 98°C)[216]. ^{1}H-NMR($CDCl_3$)δ: 1.34(d, 3H, J=8.1Hz), 3.17(m, 1H), 5.40(m, 1H), 6.08(m, 1H), 6.62(bs, 1H). IR (neat) : 3400-3200cm^{-1}($CONH_2$ str), 1650cm^{-1}(O=CNH_2 str), 1000 and 920cm^{-1}(H_2C=CH def). Mass spect.(20eV) : 99.0645(99.0778, m+), 55, 44. Elemental analysis : Cal. C 60.60 H 9.16 N 14.14, Fou. C 60.40 H 9.07 N 13.95.

5,7-Diaza-3,9-dimethylundeca-1,10-diene-4,8-dione (183)

2-Methyl-3-butenonitrile (20g, 0.25mol) was placed in a similar reaction mixture to that which was used to cyclise 2-methyl-3-butenoic acid. Using the same experimental conditions the reaction was refluxed for 15hr. After the work up procedures white crystalline needles appeared which were filtered off. On standing, the filterate produced more solid. TLC and NMR checks did not reveal the presence of any dihydro-pyrone.

The solid isolated was insoluble in petroleum ether, sparingly soluble in ether and readily soluble in chloroform. M.Pt. : 167.5-169° C. ^{1}H-NMR ($CDCl_3$)δ: 1.26(d, 6H, J = 6.7Hz), 3.04(m, 2H,J = 7.7, 6.7, 0.9Hz), 4.63(t, 2H, J = 6.1Hz), 5.22(t, 2H, J = 17.0, 10.2, 1.2Hz), 5.93(t, 2H, J = 17.0), 7.20(bt, 2H).IR (KBr disc) : 3300cm^{-1}(N-H str), 3070cm^{-1}(=C-H str), 2970cm^{-1}(C-H str), 1695-1600cm^{-1}(C=O str), 1120cm(C≡N str), 1000 and 920cm(-H and C=CH def). Mass spec.(20eV) : 210.139(210.156, m+),155, 112, 83, 55. Elem. Anal. : Cal C 62.86 H 8.57 N 13.33, Fou. C 62.58 H 8.60 N 13.15.

3-Methyl-5,6-dihydro-2H-pyran-2-one (181)

A mixture of 2-methylbut-3-enoic acid (100g, 1mol), paraformaldehyde (60g, 2mol) and conc. sulphuric acid (4ml) in acetic acid (200ml) was refluxed for 9hr. The solvent was removed under vacuum after addition of anhydrous sodium acetate (20g). The residue was neutralised (pH=8) with aqueous sodium hydrogen carbonate and extracted with methylene chloride. (3x200ml). The methylene chloride fractions were dried over anhydrous sodium sulphate and evaporated to give

46g of a crude oil. Distillation at 1.5mmHg/65-75°C or at 4mmHg/80-86° C or 20mmHg/114° C, yielded the cyclic product(35.5g, 32%) as a sweet smelling colourless liquid which solidified in the freezer. ^{1}H-NMR ($CDCl_3$)δ: 1.93(d, 3H, J = 2.0Hz), 2.46(m, 1H), 4.30(t, 1H, J= 7Hz), 6.69(m, 1H). IR (neat) : 3000-2900cm^{-1}(CH_2, CH_3 def.), 1720cm^{-1}(C=O conj). Mass spec.(20eV) : 112.0419(112.0626, M+), 82, 67, 54, 39(100%). Elem. Anal. : Cal C 59.98, H 8.05, Fou. C 58.90 H 7.91.

3-Methyl-2H-pyran-2-one (173)

A mixture of dihydropyrone (112g, 1mol), 200g of finely powdered N-bromosuccinimide (1.2mol), and benzoyl peroxide (1g), in carbon tetrachloride(5000cc) was refluxed until the orange colour which developed had faded (1 to 2.5 hr). The reaction mixture was filtered to remove succinimide and the filtrate was evaporated to give the crude bromide. ^{1}H-NMR ($CDCl_3$)δ : 1.95(d, 3H), 4.55-4.90(m, 3H), 6.72(m, 1H). Mass spec. (20eV) : 190.9619(190.9636, M+), 161, 159, 118, 111, 83, 55, 39.

The bromide was added gradually to stirred triethylamine (2000cc) at 60°C. After the completion of addition (.5hr), the triethylammonium bromide was filtered and the solid washed with benzene (4x100cm). The solvent was evaporated. Ether (1000cc) was added to the crude oil and the solution was washed with saturated brine (3x100ml). The ether was dried over anhydrous sodium sulphate and evaporated to leave a crude dark red oil (97g). Vacuum distillation yielded a colourless oil (62.5g, 56%) at 60-66°C/2-3mmHg or 74-79°C/5mmHg. M.Pt. : 12-15° C. ^{1}H-NMR ($CDCl_3$)δ: 2.12(dd, 3H, J = 2.0Hz), 6.20(dd, 1H,

J = 8.0, 6.5Hz), 7.16(ddq, 1H, J = 2.5, 8.0, 2.0Hz), 7.45(ddq, 1H, J = 6.5, 2.5, 2.0Hz). ^{1}H-NMR (CF_3COOH)δ: 2.16(s, 3H), 6.52(dd, 5Hz, 6.5Hz), 7.6(m, 2H). The pyrone is stable in trifluoroacetic acid. IR (neat) : 1750-1735cm^{-1}(C=O str.of 6-mem. lactone ring), 1650 and 1600cm^{-1}(C=C vib conj diene). Mass spec.(20eV) : 110.0349(110.0466, M+), 82, 81, 54, 53. UV (absolute ethanol) : 216nm, 291nm.

3-Methyl-2H-pyran-2-thione (184)

3-Methylpyrone (2g, 0.018mol) in benzene (50ml) was refluxed with P2S5 (5g, 0.023mol) for 24hr. Diphosphorous pentasulphide was decanted and further 5g of fresh batch of the reagent was added and the solution refluxed for 24hr. After cooling the residue was decanted, washed with benzene (2x10ml) and the washings combined with the supernatant liquid. Hot water was added (50ml) and the mixture shaken. The water was extracted with ether and the ether washings dried over anhydrous sodium sulphate and evaporated to give yellow needle crystals (1.4g, 61%) with a strong smell and a tendency to sublime. The thiopyrone was further purified on silica (100g, Kieselgel H, type 60) using methylene chloride as carrier (Rf=0.7). M.Pt : 55-56°C. ^{1}H-NMR ($CDCl_3$)δ: 2.32(dd, 3H, J = 2.0, 1.0Hz), 6.54(dd, 1H, J = 6.5, 5Hz), 7.20(ddq, 1H, J = 6.5, 2.0, 1.9Hz), 7.87(ddq, 1H, J = 5.0, 1.9, 1.0Hz). IR (melt) : 3100cm^{-1}(C=C-H str), 3000-2900cm^{-1}(CH_3 str.), 1620 and 1540cm^{-1}(C=C str), 1180cm^{-1}(S=C-O- str).

Elem. Anal. : Cal C 57.11 H 4.79 S 25.40, Fou. C 56.92 H 4.75 S 25.26.

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CHAPTER 6 : Synthesis of quinones

6.1 Introduction

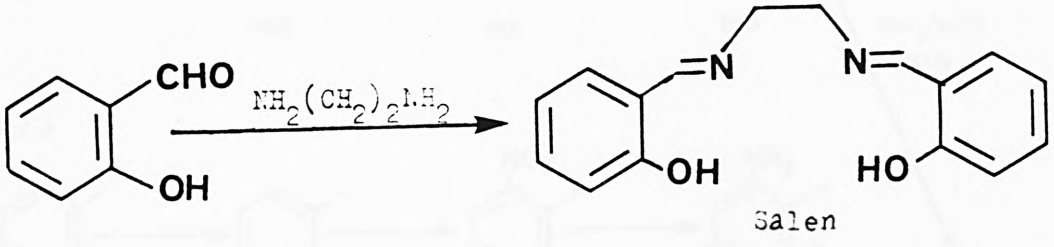
Oxidation of phenols, quinols, aromatic amines or diamines has been the only completely general method for the synthesis of quinones[1]. A variety of oxidizing agents has been used, eg Fremy salt[2]. Chromic acid, silver carbonate on celite, silver oxide, ferric chloride, lead tetraacetate, nitric acid, peracetic[3] or trifluoroperacetic acid, thallium (III) trifluoroacetate, ruthenium (III) chloride[4] and anodic oxidation have been employed.

The literature on the synthesis of quinones is not reviewed here exhaustively. Musgrave has reviewed the oxidation of alkyl,aryl ethers[5]. A Russian paper describes oxidation of phenols to quinones by cupric nitrate, discussing their homogeneous oxidation mechanism in the absence of oxygen[6].

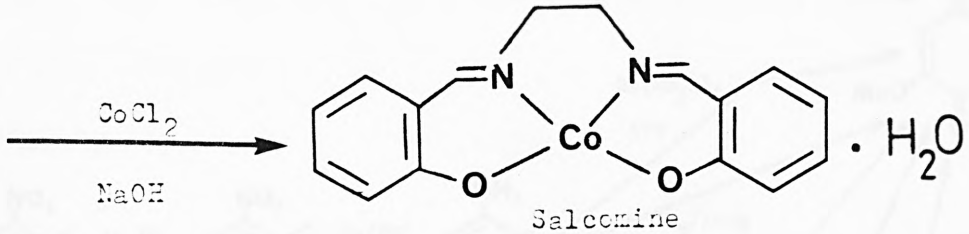
During the course of this project it was necessary to synthesise a number of quinoes to investigate their modes of reaction with 3-methyl-2-pyrone. The reaction of 2,6-dimethyl-p-benzoquinone with 3-methyl-2-pyrone proved difficult and it was felt that limitations of this reaction would be better understood after studying the reactions of other quinones with the pyrone. The purpose of this chapter is to discuss the preparative routes to the quinones which were synthesised.

6.2 2,6-Dimethyl-p-benzoquinone (115).

Literature preparations of this compound involve use of a range of reagents to oxidise 2,6-dimethyl phenol. The method adopted in this laboratory has been the air oxidation of the phenol, using salcomine as catalyst.[7] Salcomine (185) is the cobalt (II) derivative of N,N'-disalicylalethylene diamine, a schiff base prepared from salicylaldehyde and ethylenediamine. This method gave xyloquinone in excellent yield (90%) and purity.

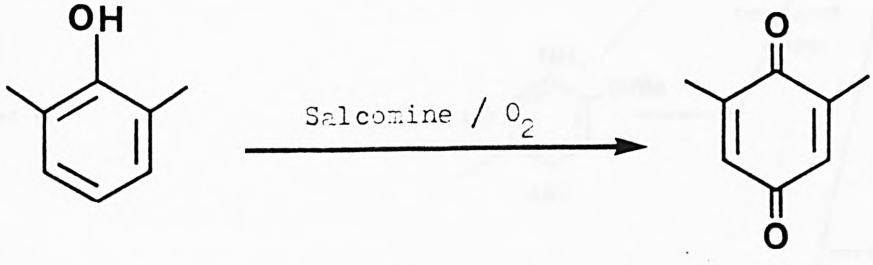


Salen



Salcomine

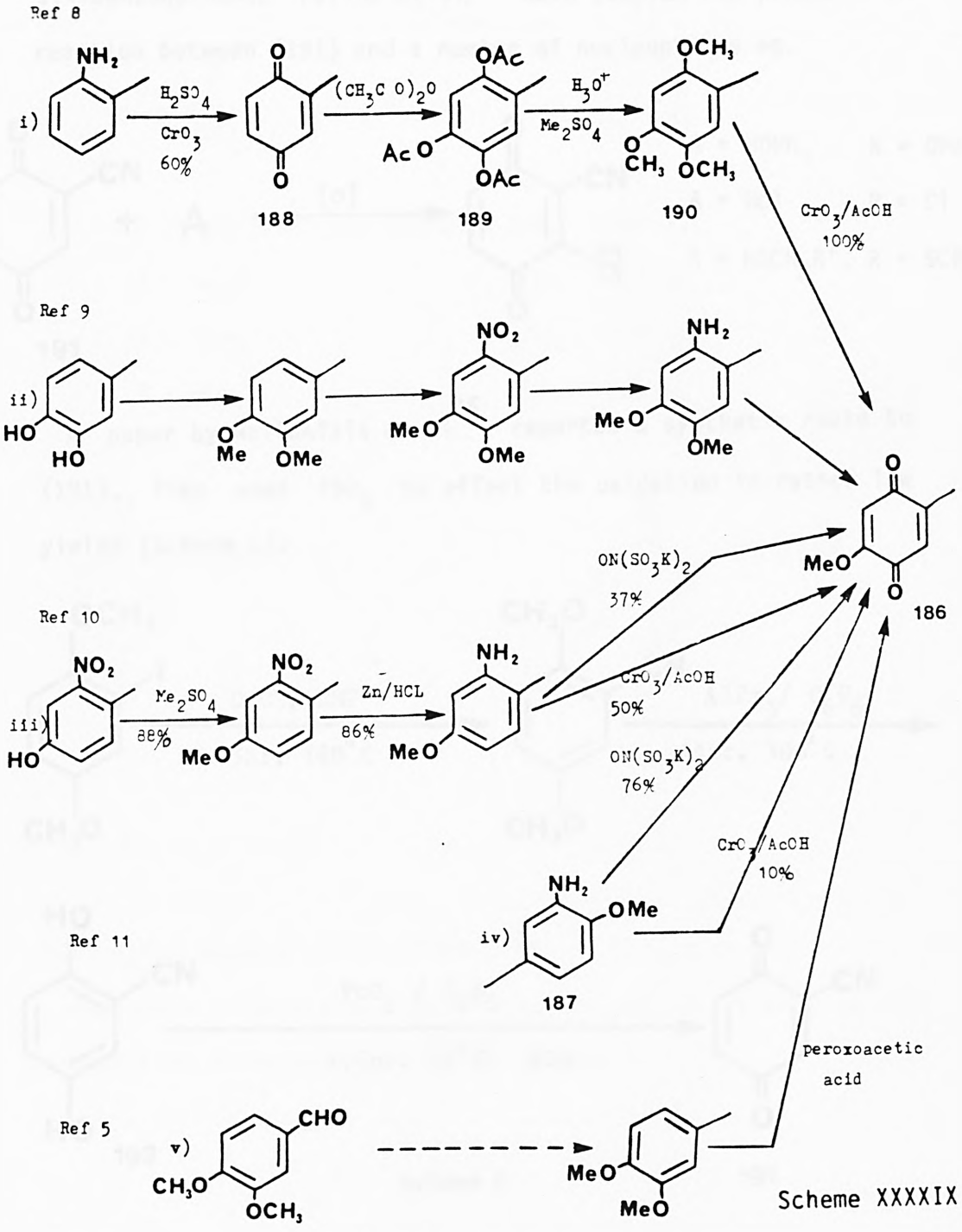
185



115

6.3 2-Methoxy-5-methyl-p-benzoquinone (186)

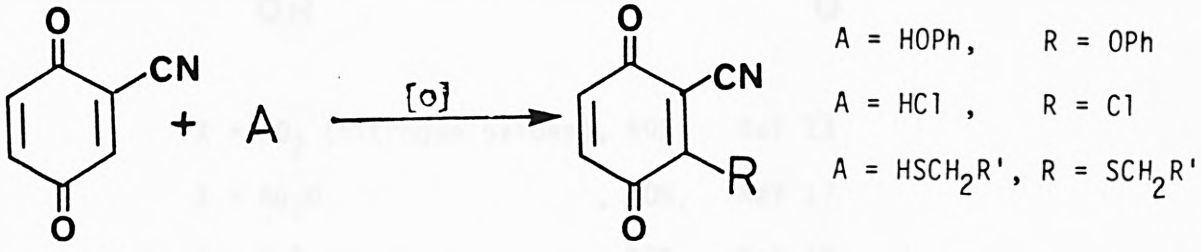
Scheme XXXXIX outlines the reported literature synthetic routes to this quinone. One step synthesis from 2-methoxy-5-methyl-aniline (187)[11] [available from Aldrich] using Fremy's radical ($O=N(SO_3K)_2$) appears to be most suited for large scale preparations. However, route i) was chosen because toluquinone (188) was a useful intermediate for other purposes.



Scheme XXXXIX

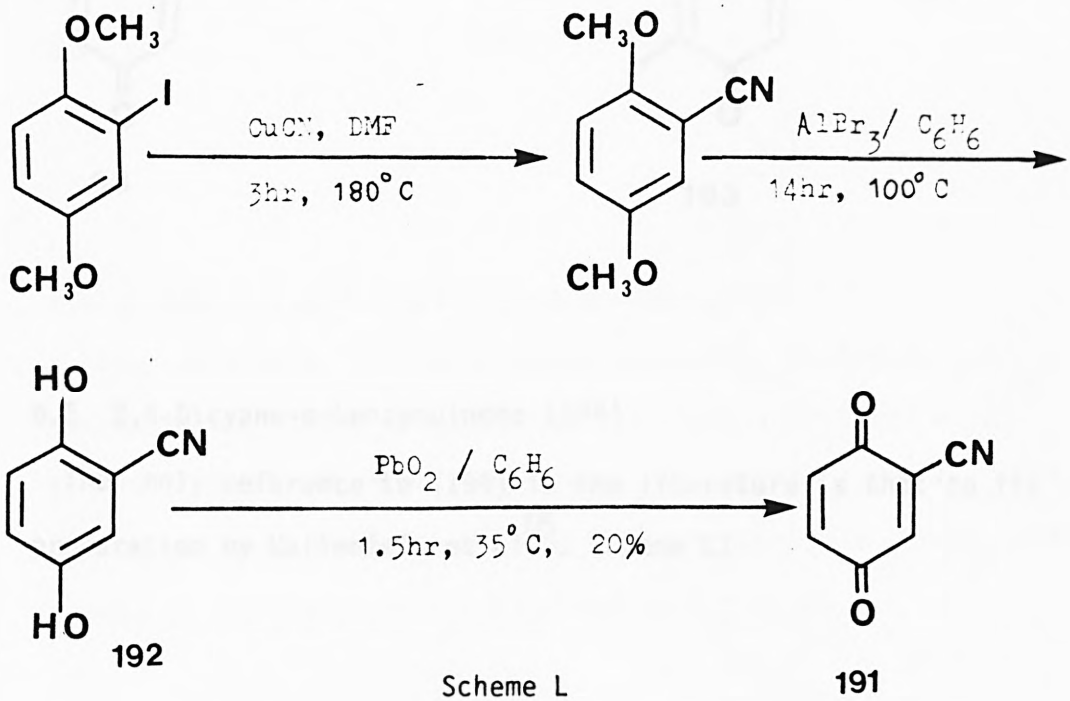
6.4 2-Cyano-p-benzoquinone (191).

This compound is one of the less investigated simple quinones. Cyanoquinones are known to form charge transfer complexes readily and have high electron affinities[12]. Hammond[13] has studied the latter property of many mono-substituted benzoquinones, and has obtained correlation data for substituted effects on the acceptor properties of 1,4-benzoquinone. Farina et al.[14] have studied the products of reaction between (191) and a number of nucleophiles eg.



191

A paper by Wallenfals et al.[15] reported a synthetic route to (191). They used PbO_2 to effect the oxidation in rather low yields (Scheme L).

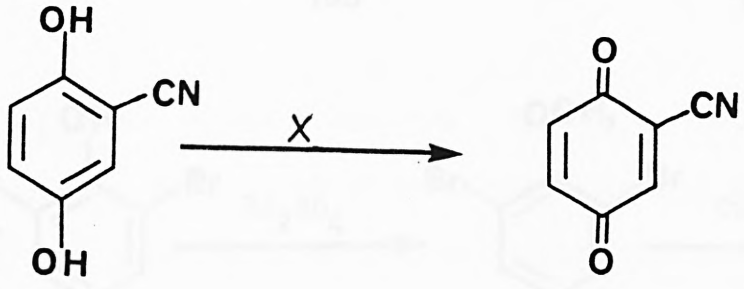


192

Scheme L

191

Bruce et al[16] have recently showed that MnO_2 is a good and cheap catalyst for oxidation of quinols. They prepared (191), (193), (93) and seven other quinones from their quinol precursors.So far cyano-hydroquinol (192) has been the only precursor to cyano-benzoquinone.

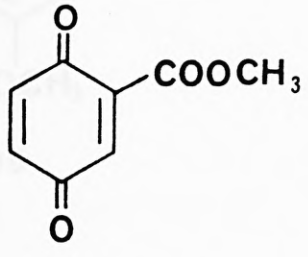


X = NO_2 (nitrogen oxides), 50%, Ref 13

X = Ag_2O , 50%, Ref 17

X = MnO_2 , 90%, Ref 16

X = PbO_2 , 20%, Ref 15



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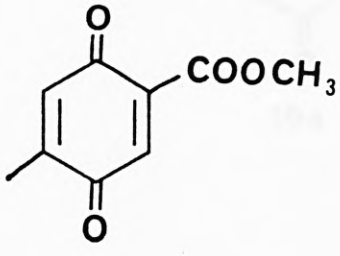
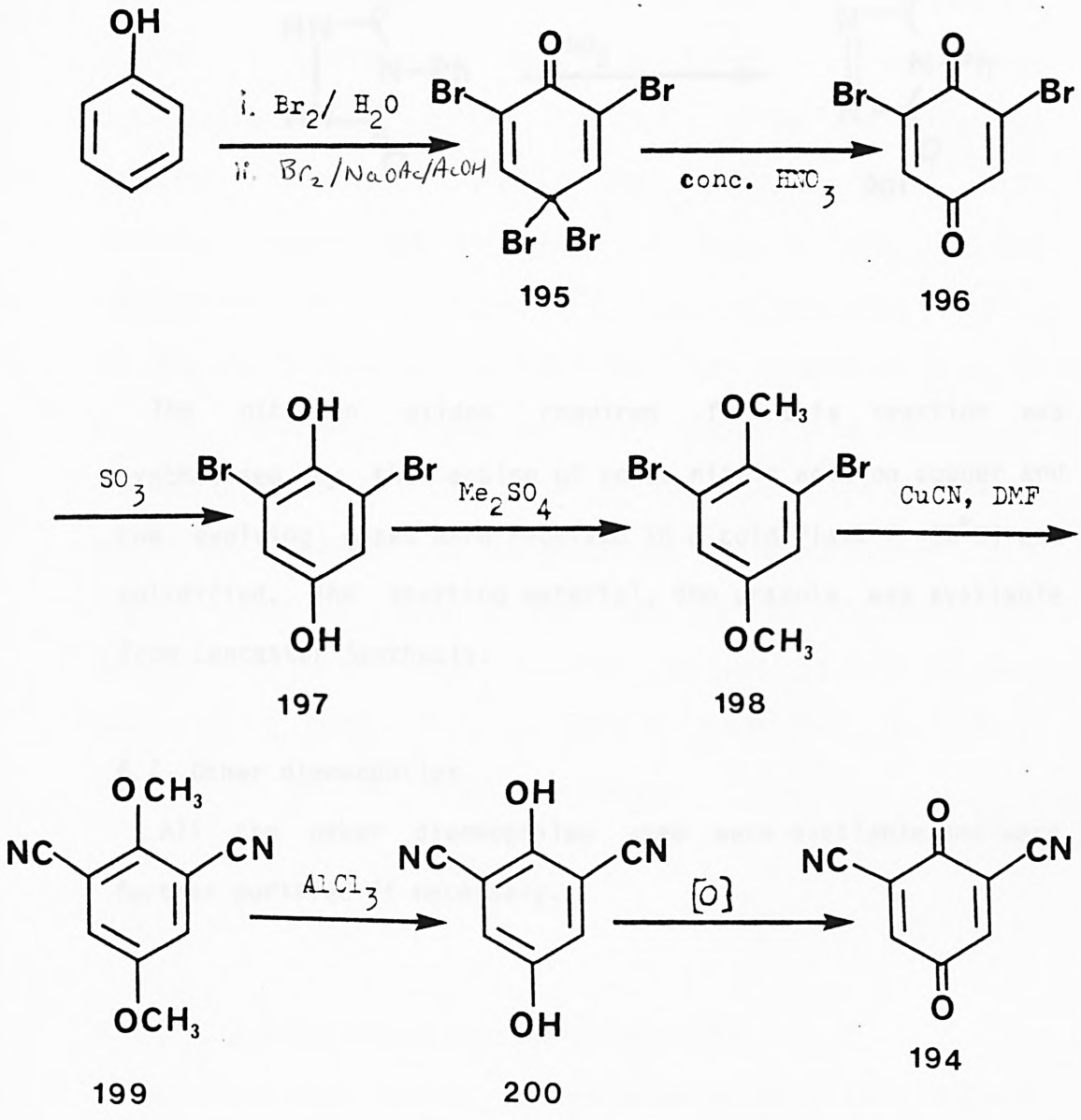


193

6.5 2,6-Dicyano-p-benzoquinone (194)

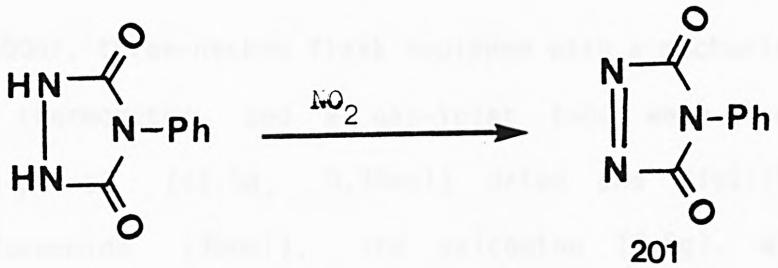
The only reference to (194) in the literature is that to its preparation by Wallenfels et al[18]. Scheme LI



Scheme LI

6.6 N-Phenyl-1,2,4-Triazoline-3,5-dione (201)

The synthesis of this dione requires oxidation of the corresponding 1,2,4-triazolidine-3,5-dione. Stickler et al.[19] showed that nitrogen tetroxide is superior to all the previously cited oxidising agents in convenience, yield, and purity of the isolated 1,2,4-triazoline-3,5-dione.



201

The nitrogen oxides required for this reaction was synthesised by the action of conc. nitric acid on copper and the evolving gases were received in a cold flask (-50°C) and solidified. The starting material, the urazole, was available from Lancaster Synthesis.

6.7 Other dieneophiles

All the other dieneophiles used were available and were further purified if necessary.

6.8 Experimental

All the quinones were purified by sublimation before use.

2,6-Dimethyl-2,5-cycloheaxadiene-1,4-dione (115).[20]

a) Preparation of salcomine. This compound was synthesised using the procedure described by Diehl and Hack[7] . Results were reproduced ie: disalicylalethylene diamine or SALEN (5g, 0.019mol) afforded salcomine (5.5g, 68%).

b) In a 500ml, three-necked flask equipped with a mechanical stirrer, a thermometer, and a gas-inlet tube were placed 2,6-dimethyl-phenol (42.5g, 0.35mol) dried and distilled dimethyl formamide (300ml), and salcomine (2.5g). With stirring, oxygen was introduced at such a rate that the temperature did not exceed 45°C. This was continued for 3hr. At the end of the reaction the temperature dropped to about 28° C. The reaction mixture was then poured onto crushed ice (500g) and 4M HCl (15ml). A yellow precipitate was formed which was filtered and washed on the filter with 1M HCl (3 x 50ml), water (3 x100ml), and cold ethanol (2 x 25ml). The product was dried under reduced pressure at 50°C for 3hr. Yield 42.6g (90%), M.Pt. : 70-71°C. ^{1}H-NMR ($CDCl_3$)δ: 2.08(s, 2H), 6.60(s, 1H). IR (nujol) : 1655cm^{-1}.

2-Methyl-2,5-cyclohexadiene-1,4-dione (188)

The literature method for the preparation of this compound was used.[21]

MS: 122.0241(122.0462 , M+), 94(100%), 82, 68, 66, 54.

2,4,5-Triacetoxytoluene[9] (189)

Toluquinone (20g, 0.164) was gradually dissloved in acetic anhydride (60g) and 1.5cm3 of conc. sulphuric acid so that the temperature did not exceed 50-60°C. After cooling, the mixture was poured into water and the precipitate was filtered and crystallised from alcohol. White crystals of metling point

114-115° C were obtained. Yield : 83%. ^{1}H-NMR ($CDCl_3$).δ, 2.32(b, 3H), 2.38(s, 6H), 2.39(s, 3H), 7.69(s, 1H), 7.78(s, 1h).

2,4,5-trimethoxy toluene (190)

The triacetate (24g, 0.09moles), 1ml conc. sulphuric acid, and 30ml of methanol were mixed and refluxed for 1hr. After cooling, 50g of dimethyl sulphate was added under nitrogen and 60-65ml of 40% NaOH was added very slowly, with vigorous stirring, so that the temperature did not exceed 45°C. The mixture was then extracted with ether (4 x 50ml) after addition of 200ml of water. The combined ether extracts were dried and evaporated to give (190) with a yield of 90-95%. Melting point: 55 C (lit 55 C) as a pale brown solid. ^{1}H-NMR : δ($CDCl_3$),2.31 (s, 3H), 4.02 (s,3H), 4.08 (s, 3H), 4.12 (s, 3H), 6.91 (b, 1H), 7.12 (b, 1H). Elemental analysis: cal., C 65.91, H 7.74; fou., C 65.69, H 7.78. MS : 182.0807 (182.1088, M+, 100%), 167, 139, 124, 109, 107, 79, 77,69,66,65,53,50.

2-Methoxy-5-methyl-2,5-cyclohexadiene-1,4-dione (186)

2,4,5-Trimethoxy toluene (190) (10g, 0.055mol) in 100ml of glacial acetic acid was mixed with 100ml of 4M sulphuric acid. Chromium trioxide (110g, 1.1mol) dissolved in little water was added with stirring and the solution turned green. After a few minutes 450ml of water was added upon which the product (186) precipitated as golden crystals. The crude yield was 8.2g (98%). ^{1}H-NMR (CDC13) δ , 2.20 (d, 3H), 4.50(s, 3H), 6.23 (s, 1H), 6.89 (q, 1H). Elemental Analysis : cal., C 63.15, H 5.30; fou., C 62.87, H 5.28. MS : 152.0344 (152.0614, M+), 139, 124, 122, 69, 66, 52.

2,4,4,6-Tetrabromocyclohexa-2,5-dienone[22] (195)

Bromine (82g, 0.51mol) in acetic acid (500ml) was added dropwise to a solution of tribromophenol (170g, 0.51mol) and sodium acetate (69g, 0.51mol) in the same solvent (1000ml) at room temperature. After 30min the mixture was poured onto ice. The lemon yellow solid was filtered off and crystallised from chloroform. 206.5g of solid was obtained (98% yield). Melting point = 139-141°C (lit 140-141°C). Mass spec. : 409.6312 (409.6297, M+), 329.7656 (329.7639, 100%, M+-Br), 140, 69, 62, 53.

1,3-Dibromo-2,5-dioxo-3,6-cyclohexadienone[23] (196)

Tribromophenol bromide (205g, 0.5mol) was added to fuming nitric acid (683g), under cooling with vigorous stirring. After the completion of gas evolution, the reaction mixture was poured on ice-water, filtered and the yellow crystals of dibromoquinone were recrystallised from absolute ethanol. Melting point = 131°C (lit 132° C). Yield was 100g (75%). Elemental analysis : cal., C 27.10 H 0.76 ; fou., C 27.01, H 0.68. Mass spec. : 265.8701 (265.8146, M+), 186, 158, 80, 77, 69, 58.

2,6-Dibromo-1,4-dihydroxybenzene (197)

2,6-Dibromobenzoquinone (90g, 0.38mol) was suspended in 1000ml of water and the mixture stirred in cold while sulphur dioxide was bubbled through until the red colour first produced had almost disappeared. The mixture was then gradually warmed to 100° C, filtered and allowed to cool to produce 85g (93.7%) of powdery pure white 2,6-dibromohydroquinone. Melting point = 160-161° C (lit

162-163° C). Elemental analysis : cal., C 29.90, H 1.50; fou., C 27.15, H 1.51. Mass spec. : 269.8, 267.8528 (267.8384, M+), 265.8, 160, 131, 119, 91, 83, 79, 69, 57, 55, 53, 51.

2,6-Dibromo-1,4-dimethoxybenzene (198)

2,6-dibromo-1,4-dihydroxybenzene (79g, 0.3mol) was dissolved in 300ml of ethanol. The solution was heated to 60°C and to this hot solution under stirring were alternately added in five installments aqueous sodium hydroxide (31g in 90ml) and dimethyl sulphate (92g). The heat evolved during the reaction made the solution boil. After the addition was complete, the mixture was made alkaline by the further addition of aqueous sodium hydroxide (9g in 20ml) and was allowed to reflux on the water-bath for 3hr. The dark mixture was distilled to remove ethanol, water was added (500ml), and the mixture was ether extracted (5 x 100ml). The ether phase was dried over anhydrous sodium sulphate and evaporated to give 51g (84%) of the dimethylated product. Melting point = 38-39°C (lit 38-39°C and after several days 53-56°C). ^{1}H-NMR ($CDCl_3$)δ: 6.99 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H). Mass spec. : 295.8748 (295.87, M+), 282.87, 281, 159, 157, 80, 62, 52, 50.

2,6-Dicyano-1,4-dimethoxybenzene (199)

Dibromo-dimethoxybenzene (45g, 0.17mol) and potassium cyanide (36g, 0.55mol) were stirred in 90ml of absolute dimethyl formamide for 14hr at 140°C. The solution had turned brown. 120g of ferric chloride in 30ml conc. HCl and 180ml of

water were added and the mixture stirred for 1hr at 80°C. HCN was evolved and the mixture was evaporated to dryness. 200ml of water was added and the solution extracted with methylene chloride (10 x 50ml). The methylene chloride fractions were combined and dried over anhydrous sodium sulphate to give 9.23g of a crude product. Column chromatography using silica gel (500g, Kieselgel 60, 70-230 mesh) and methylene chloride as solvent produced 7.72g (27%) of an off-white fluffy solid (Rf=0.45). Melting point = 192-193° C and sublimed at 160°C (lit 195-196° C). ^{1}H-NMR (CD_3CN/$(CD_3)_2CO$)δ, 7.58 (s, 2H), 4.21 (s, 3H), 3.91 (s, 3H). Elemental analysis : cal., C 63.83, H 4.28, N 14.87; fou., C 63.91, H 4.58, N 13.96. IR (KBr disc) : 3100-2800cm^{-1} (CH str.), 2240cm^{-1} (CN str.), 1600,1590cm^{-1} (C=C str.). Mass spec. : 188.0595 (188.0754, M+), 173 (100%), 145, 90, 66, 63, 51.

2,6-Dicyano-1,4-dihydroxybenzene (200)

Anhydrous aluminium chloride (50g, 0.37mol), dried and finely powdered sodium chloride (10g, 0.17mol), and dimethoxy compound (199) (5g, 0.03mol) were stirred in a flask heated to 180-185° C on an oil bath. The colour of the mixture turned dark red. After 20min the mixture was added gradually to ice-water upon which the solution fluoresced green-blue. Diethyl ether (5 x 100ml) was used to extract the product. The combined ether extracts were dried and evaporated to give 3.6g of a reasonably pure product. Purification by column chromatography on silica gel(200g, Kieselgel 60, 70-230mesh) using 1:1 mixture of methylene chloride and acetonitrile

(Rf=0.5) yielded 3.4g (58%) of a yellow powder. Melting point = 228-230° C (lit 220-230°C). Mass spec. : 160.0266 (160.0438, M+, 100%), 132, 105, 77, 53, 52.

2,5-Dioxo-1,3-dicarbonitrile-3,6-cyclohexadiene (194)

All operations were carried out under nitrogen atmoshere. The quinol (200) (3g, 0.019mol) was suspended in 50ml of HPLC grade CCl_4 and stirred and cooled in an ice-salt bath. Nitrogen oxides (mainly dioxide) were bubbled into the flask during which the dirty green colour began to turn dark red. Stirring was continued for 1hr and the reaction was followed by H-NMR. After the reaction was compelete, the contents were filtered and the yellow-red solid was dried overnight in a dessicator during which time it turned bright yellow. The product turned red in the presence of moisture and appeared to break down on silica TLC plates. ^{1}H-NMR ($CDCl_3/CD_3CN$)δ, 7.90 (s,2H). IR (nujol): 3080cm^{-1} (C=C-H cycl. str.), 2250cm^{-1}(CN str.), 1670,1690cm^{-1} (CO str.),1600 (C=C str.). Mass spect. : 158.0115 (158.0281, M+), 130, 107, 102, 87, 80 79, 69, 67, 51(100%).

2,5-Dihydroxybenzonitrile (192)

2,5-Dimethoxybenzonitrile (10g, 0.06mol, Lancaster synthesis) in 400ml of absolute benzene, and 4g of aluminium tribromide in 300ml of absolute benzene were mixed together and refluxed for 14hr with stirring. Further 36g of aluminium tribromide was added and solution refluxed for further 14hr (an oily layer at the bottom of flask was always present). The

cooled mixture was added to water (1l). The benzene layer was discarded and the aqueous layer acidified with conc. HCl and extracted with ether (9 x 100ml) to remove all the product. The combined ether fractions were dried over anhydrous sodium sulphate and evaporated to give 9.3g of an off-white powder.Column chromatography on silica gel using 1:1 mixture of methylene chloride and acetonitrile as solvent yielded 6.23g (75%) of a white solid. Melting point = 170-174°C (lit 169-173° C). IR (KBr disc): 3000-3500cm^{-1}(OH str.), 2220cm^{-1}(CN str), 1600cm^{-1} (C=C arm.). ^{1}H-NMR ($(CD_3)_2CO$)δ, 7.00 (m, 3H), 7.30 (broad, 2H).^{1}H-NMR (CD_3CN)δ, 7.20 (m, 3H), 8.60 (b, 1H), 9.20 (b,1H). Mass spec. : 135.0356 (135.045, M+, 100%), 107, 80, 79, 53, 52, 51.

3,6-Dioxo-1-carbonitrile-1,4-cyclohexadiene (191)

The benzonitrile (192) (3g, 0.022mol) was oxidised with silver oxide in benzene (50ml) , boiling the mixture for 45min to afford 1.6g(50%) of a yellow brown solid after filtering the suspensions and removing the solvent on rotary evaporator. Melting point = at 110° C begins to sublime, melt, and decompose up to 120° C (lit 124-125°C).^{1}H-NMR (CD_3CN)δ, 7.03 (d, 2H, 1Hz), 7.50 (dd, 1H, 1Hz).

4-Phenyl-1,2,4-triazoline-3,5-dione (201)

Gaseous nitrogen tetroxide was bubbled through a cold suspension of the urazole (1.00g , 5.6mmol) and 10g of anhydrous sodium sulphate in methylene chloride (50ml). The solution was kept cold during the 1hr of reaction. The sodium

sulphate was removed by filt ration and the red solution was evaporated to dryness at reduced pressure to give 0.9g (90%) of the crude product. A portion of the red crystalline solid was sublimed (1mmHg, 40°C) to obtain analytically pure sample.

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SECTION C

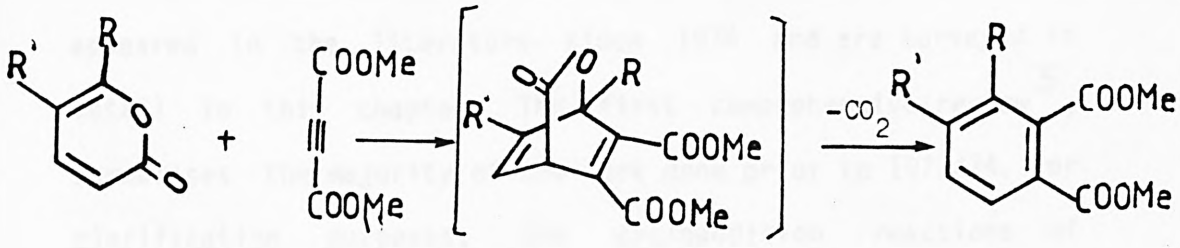
CYCLOADDITION ADDUCTS

Chapter 7 : A Literature Review of Cycloaddition Reactions of Pyrones

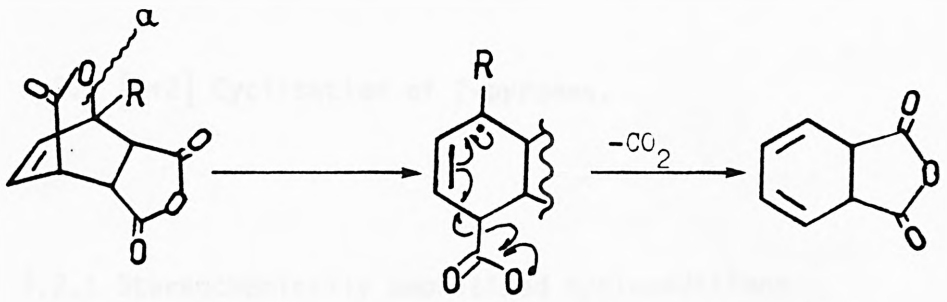
7.1 Introduction

Ever since Diels and Alder observed the cycloaddition of 2-pyrone and 5-methoxy carbonyl-2-pyrone with maleic anhydride in 1931[1], there has been a sporadic and increasing number of reports illuminating the fact that the family of 2-pyrone compounds are suitable precursors for the introduction of a C4H4 carbon skeleton. The carboxyl group of a pyrone locks the diene into the necessary cisoid conformation for cycloaddition. Thus, activation energies for the reactions are lowered, particularly in cases where the presence of a bulky functional group on the carbon skeleton may not favour the cis arrangement in a butadiene type molecule.

A classical example which demonstrates the behaviour of pyrones in cycloaddition reactions is addition of acetylenic dieneophiles with 2-pyrones[2]. The cycloadducts produced initially in these reactions are not isolated, since they immediately split off the endo oxy-carbonyl bridge (because it is in the β-position with respect to two double bonds) and are converted into aromatic compounds;



Some of the bridged adducts formed can be stable at temperatures above 150° C (see page 169, compound 216) Primary isotope effect studies of carbon and oxygen for the monoadducts of 2-pyrone with maleic anhydride have suggested that the elimination of carbon dioxide is a two-stage process, which begins with the dissociation of bond a. The resulting biradical (202) is then converted further into the more stable cyclohexadiene system (203)[3]



202 203

This hypothesis concerning the course of the thermolysis explains the instability of monoadducts with substituents at the bridgehead (R=alkyls or aryl) by the stabilisation of the biradical (202) owing to +I and +M effects of the substituents. On the other hand, even weak electron-accepting groups ($R=CH_2Br$) in this position appreciably increase the stability of the monoadduct[4].

Many interesting cycloaddition examples of 2-pyrones have appeared in the literature since 1974 and are surveyed in detail in this chapter. The first comprehensive review[5], summarises the majority of the work done prior to 1973/74. For clarification purposes, the cycloaddition reactions of 2-pyrones have been categorised as follows:

i) Diels-Alder reactions in which the stereochemistry of the adduct is emphasised which may be a prerequisite for a synthetic route.

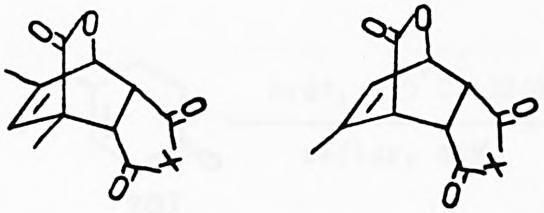
ii) Diels-Alder reactions involving a dieneone eg quinones

iii) Diels-Alder reactions which are followed by loss of a carbon dioxide molecule, resulting in a single or racemic product, or yield unexpected products.

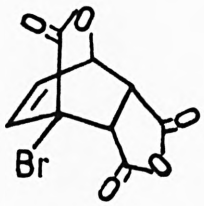
7.2. [4+2] Cyclisation of 2-pyrones.

7.2.1 Stereochemically emphasised cycloadditions

Formation of endo adducts are usually favoured in the cycloaddition of pyrones. Russian workers have established, using ^{1}H-NMR spectroscopy, that only endo-adducts (shown in Scheme LII) are produced when the appropriate starting materials are cyclised[6]. The expected J2,3 coupling constant for an endo adduct is 3.5-4.5Hz whereas for that of an exo adduct is lower and in the region of 2.0-2.5Hz.



X= O, NPh



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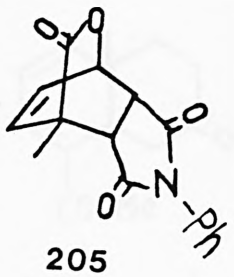

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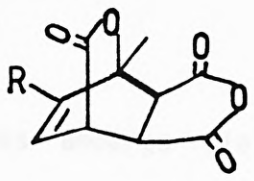
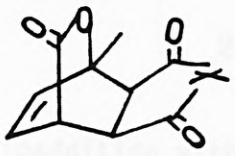
Scheme LII

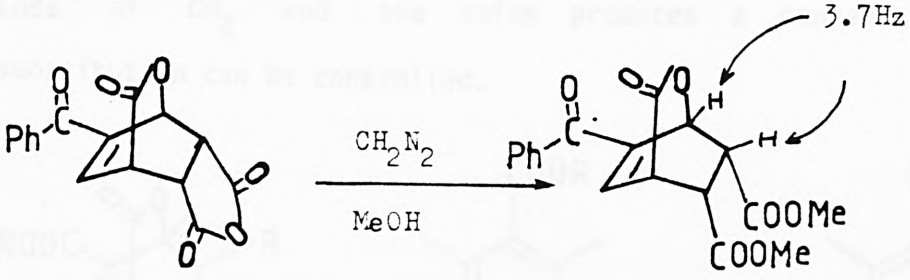
Presence of a methyl group on C-6 results in formation of exo-adducts.





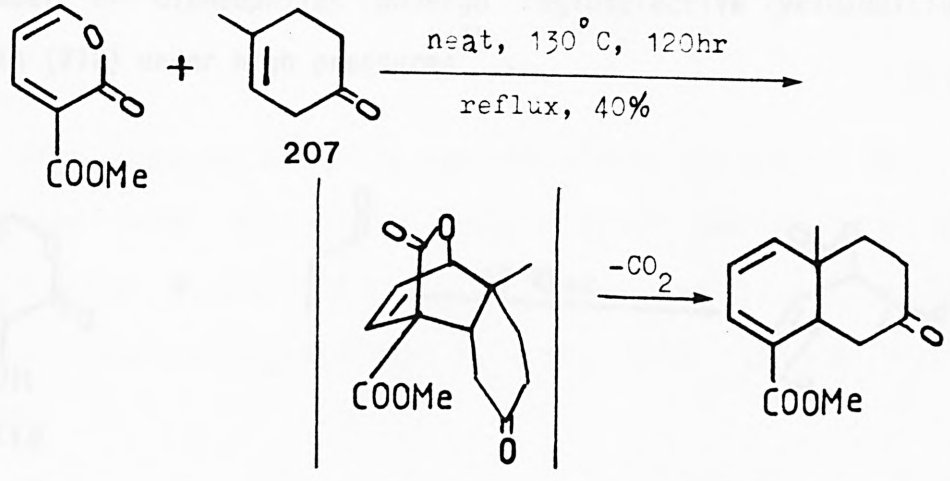
X= O, NPh

Formation of adduct (206) followed by methylation was reported to give a product having J2,3 coupling of 3.7Hz, which is characteristic of endo adducts[7].



206

Electron withdrawing substituents in the 3-position of 2-pyrones deactivate the pyrone ring towards cycloaddition. This was observed by Watt who cyclised 3-carboxypyrone with 4-methylcyclohex-3-ene-1-one (207)[8] .Under similar conditions analogues of (207) such as (208) ,(209), and (210) were unreactive.



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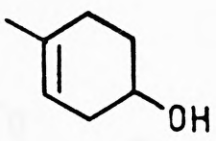

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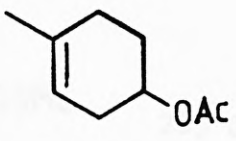

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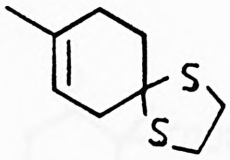

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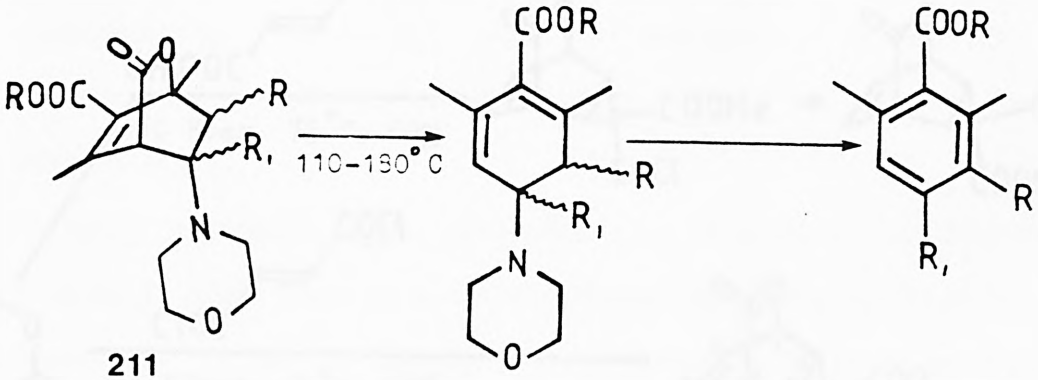
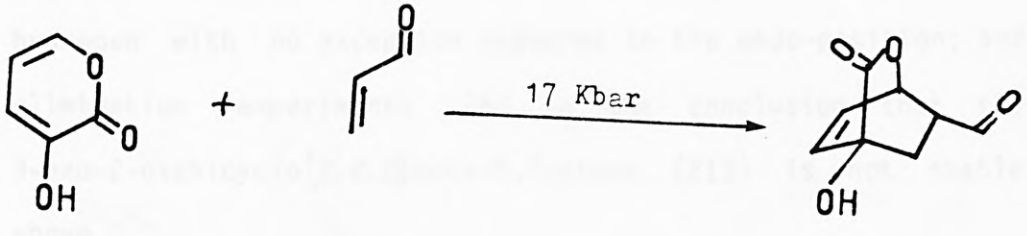
Enamines undergo Diels-Alder cycloaddition with 2-pyrones and the adduct formed can, under certain circumstances, be forced to eliminate the amine. Gingrich et al.[9] examined this in detail and showed that presence of a morpholino group on a dieneophile causes formation of a regiospecific adduct (211). Loss of CO_2 and the amine produces a benzene whose substitution can be controlled.



211

Another example of a substituent playing a dominant role in determining the outcome of a Diels-Alder reaction is a hydroxyl group on C-3 of 2-pyrone. It has been shown that a number of dieneophiles undergo regioselective cycloaddition with (212) under high pressures[10].



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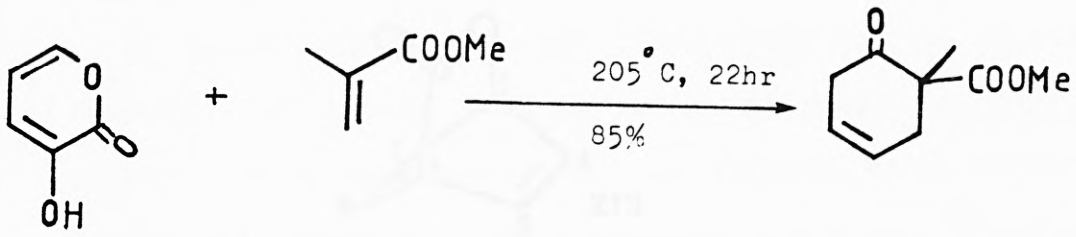
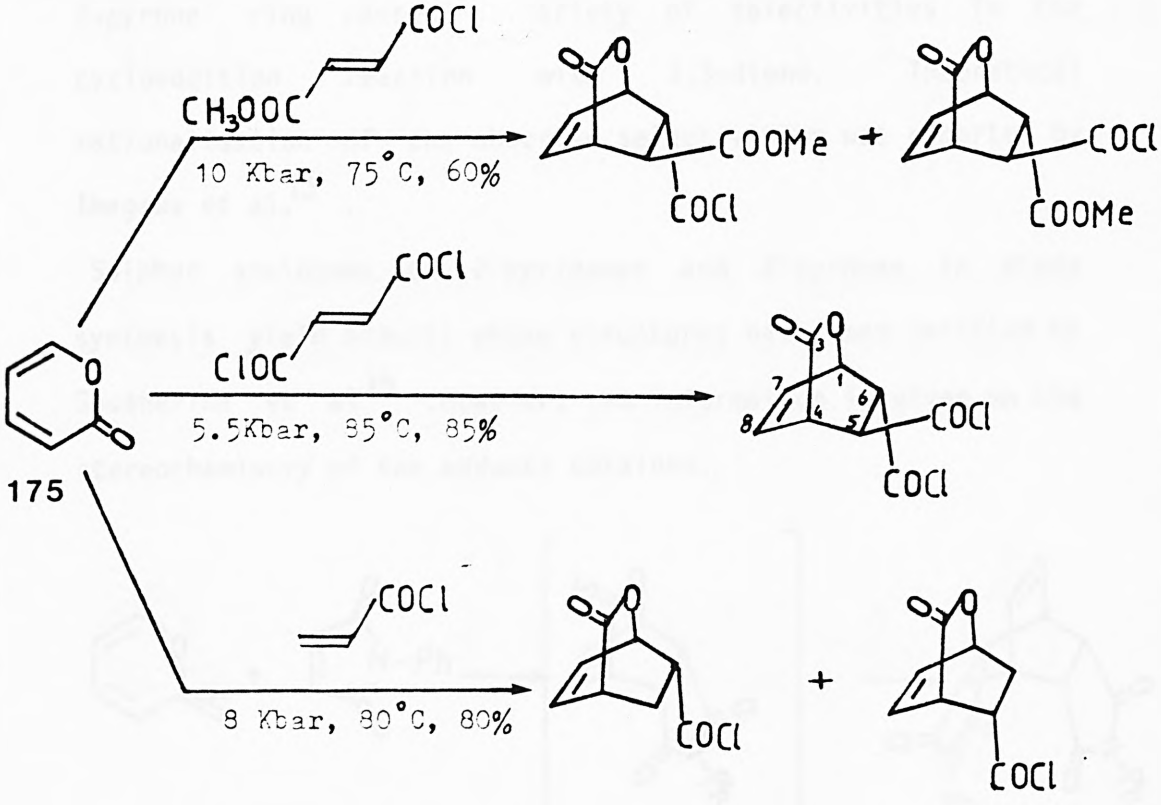
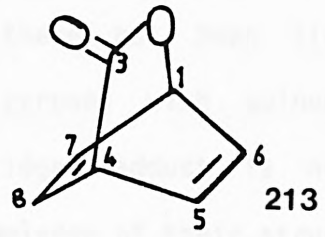


High pressure Diels-Alder studies and adduct derivatisation approaches carried out by Pfaff[11], have led to interesting findings about the constitution and configuration of the cycloaddition products.



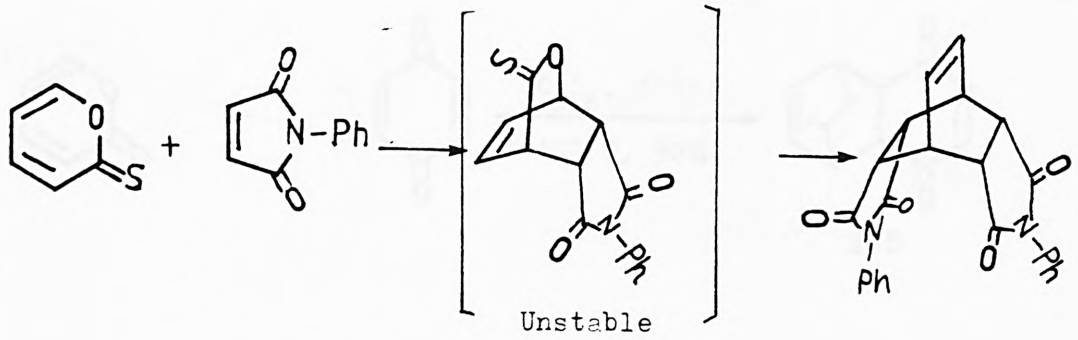
High pressure primarily improved yields and purity; the C-6 hydrogen with no exception appeared in the endo-position; and elimination experiments led to the conclusion that the 3-oxo-2-oxabicyclo[2.2.2]octa-5,7-diene (213) is not stable above 0°C.

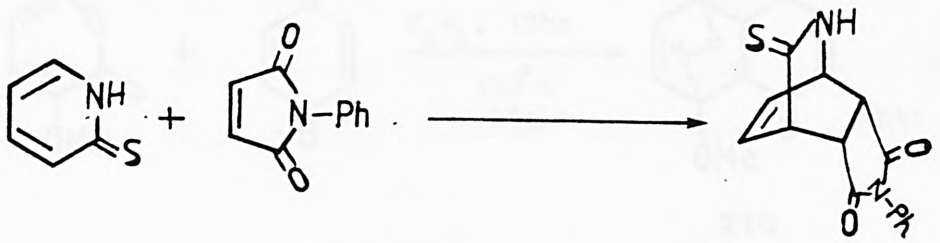


213

Several substituted 2-pyrones have been subjected to dimerisation which appears to be reversible and reluctant to occur[12] . The nature of the pyrone as a diene is largely dependent on the substituents it bears. For instance, the sequential introduction of methoxycarbonyl groups onto a 2-pyrone ring causes a variety of selectivities in the cycloaddition reaction with 1,3-diene. Theoretical rationalisation of the observed selectivities was reported by Imagawa et al.[13] .

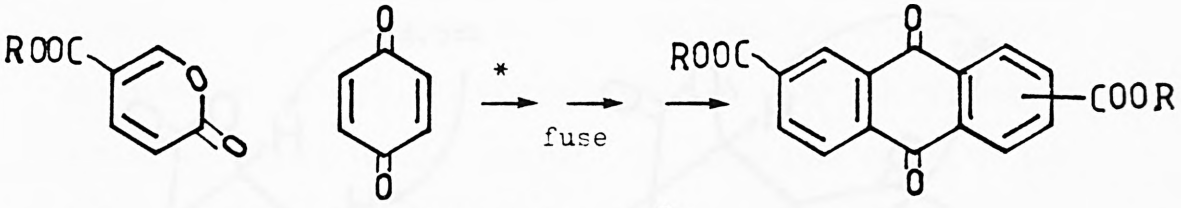
Sulphur analogues of 2-pyridones and 2-pyrones in diene synthesis yield adducts whose structures have been verified by Shusherina et al.[14] .However, no information is given on the stereochemistry of the adducts obtained.





7.2.2 [4+2] Cycloadditions with dieneone systems

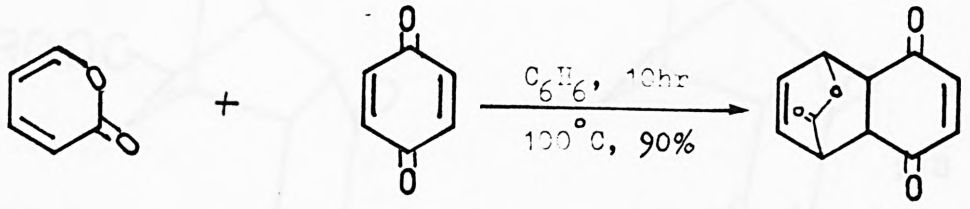
In general there has been little investigation of the reactions of pyrones with quinones. In these reactions, usually the bridged adduct is not isolated, which further limits the knowledge of their structure. For example[15] alkyl coumalates react with p-benzoquinone, when fused together over a flame, to give dimethyl anthraquinone-2,6-dicarboxylic acid (214). The reaction involves extrusion of carbon dioxide and addition of a second dieneophile molecule.



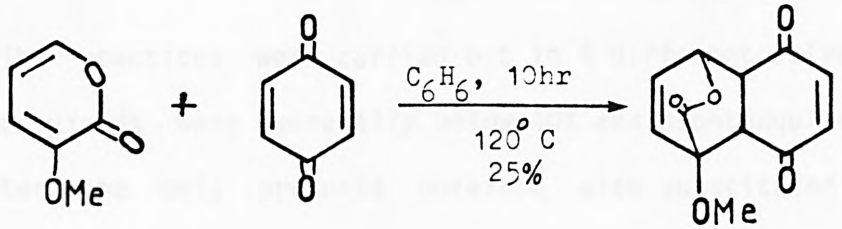
* no reaction in solvent below 100° C

214

2-Pyrone and 3-methoxy-2-pyrone react[16] with benzoquinone in a tubing bomb in the presence of benzene as solvent to give the mono adducts (215) and (216). No ^{1}H-NMR data were given.



215

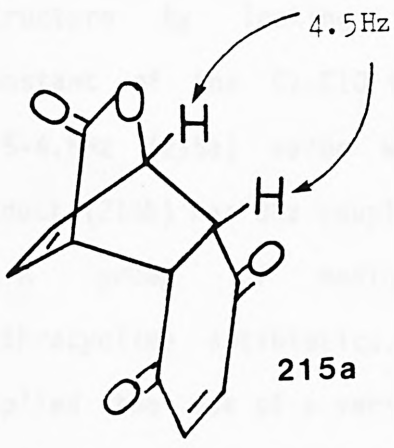


Mpt: 180-185° C

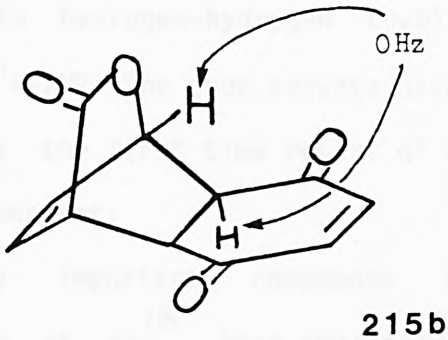
216

The monoadducts (215) and (216) lost the bridge when heated in refluxing acetic anhydride or when refluxed in ethyl acetate with active manganese dioxide to give the corresponding naphthoquinones.

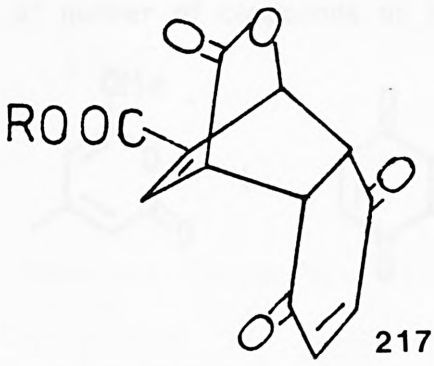
A more comprehensive paper was published by Japanese workers[17] who studied the thermal reactions of substituted 2-pyrones with several p-benzoquinones. The following bridged adducts were isolated and their spectroscopic data were reported



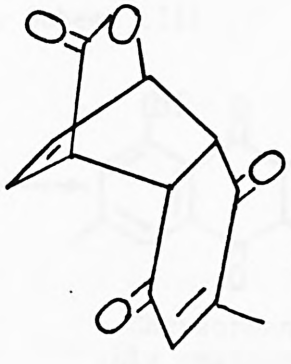
215a



215b



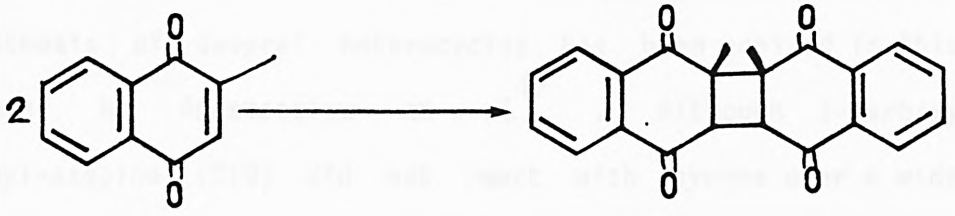
217



218

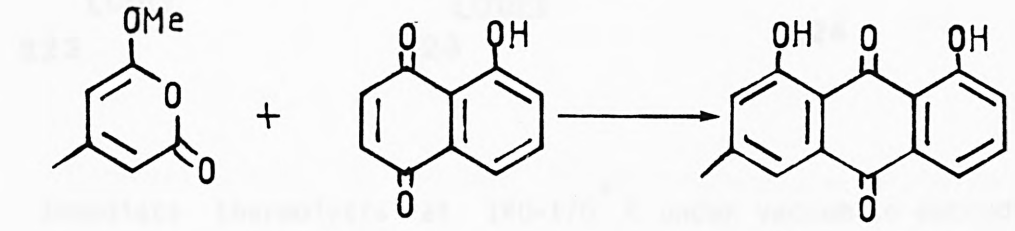
The reactions were carried out in 4 different solvents, and the yields were generally below 40% and naphthoquinones were often the only products obtained with substituted starting

materials. In addition they reported that 2-methyl-1,4-naphthoquinone thermally and photochemically gave 2 + 2 cycloaddition dimers.

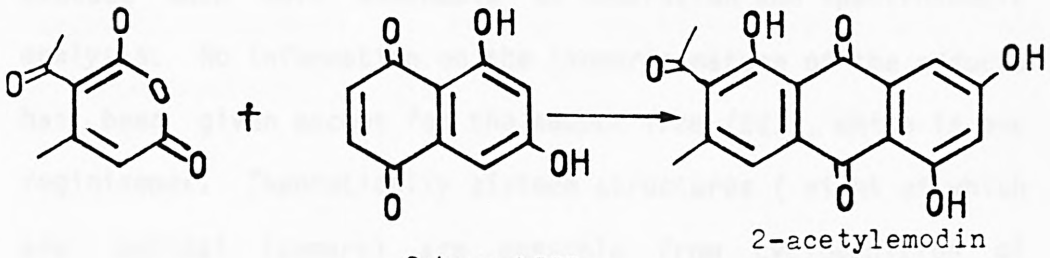


A 39:1 ratio of endo:exo mixture of adducts was obtained when reacting p-benzoquinone with 2-pyrone. The spectroscopic data reported provide a confident way of establishing the isomeric structure by looking at the hydrogen-hydrogen coupling constant of the C1-C10 in the ^{1}H-NMR. The endo adducts have a 3.5-4.5Hz (215a) value whereas the first time report of exo adduct (215b) has 0Hz coupling constant.

A group of medicinally important compounds are anthracycline antibiotics. Jung et al.[18] have successfully applied the use of a variety of substituted 2-pyrones through Diels-Alder cycloaddition and CO_2 elimination to the synthesis of number of compounds of this group . Scheme LIII



Chrysophanol
only regioisomer

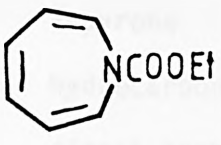


2-acetylemodin

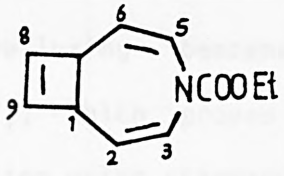
Scheme LIII

7.2.3 [4+2] cyclisation followed by CO_2 loss

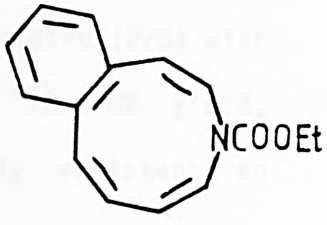
When properly utilised, 2-pyrone cycloaddition offers a unique method for realising two-step C4H4 introduction with overall construction of a 1,3-cyclohexadiene function. Synthesis of several heterocycles has been achived in this manner by Anastassiou et al.[19]. Although 1-carboxy ethyl-azepine (219) did not react with pyrone over a wide temperature range (70-110° C), acetyl-4-azabicyclo[5.2.0] (220), carboxymethyl-trans benzozonine (221), carboxyethyl -2-azabicycle[3.2.0] (222), carboxyethyl-2,3-diazabicycle [3.2.0] (223), and 2-oxa- bicycle[3.2.0] (224) cyclised.



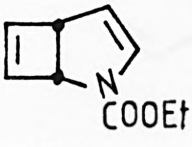
219



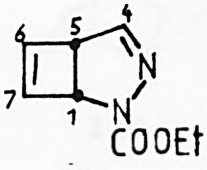
220



221



222

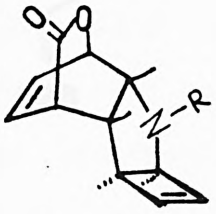


223

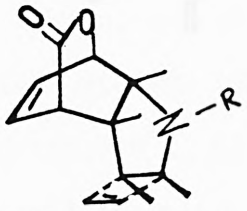
224

Immediate thermolysis at 140-170° C under vacuum to extrude CO_2 reduced the number of possible isomers, resulting in a product much more ammenable to separation and spectroscopic analysis. No information on the isomeric nature of the adducts has been given except for the adduct from (221), which is one regioisomer. Theoretically sixteen structures (eight of which are optical isomers) are possible from cycloaddition of

2-pyrone to only one of the double bonds of (222). However after decarbonylation only racemic 225 was obtained.



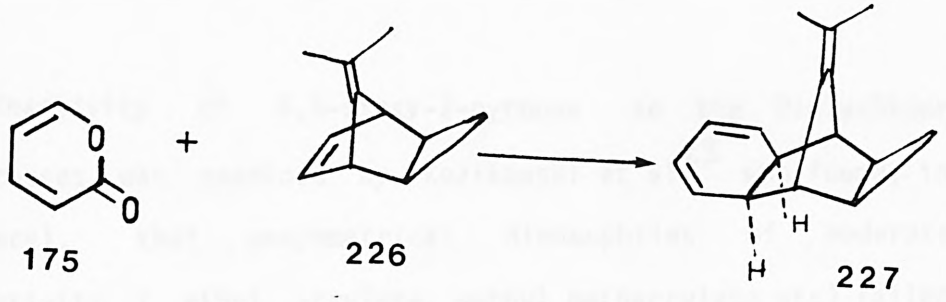
225
Anti conformer
allowed



Cis conformer
not allowed

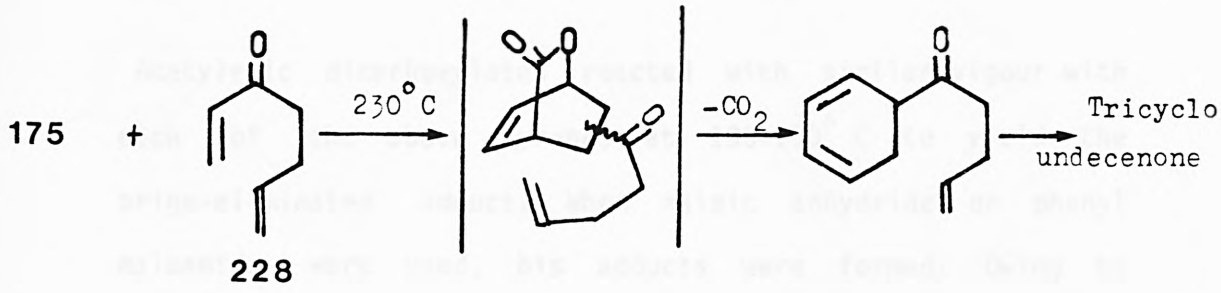
The cis configuration is not produced in detectable quantities in most cases owing to steric crowding.

Battiste et al.[20] showed that reaction of olefin (226) with 2-pyrone in refluxing benzene affords, in 70% yield, hydrocarbon (227), which proved surprisingly resistant to direct aromatisation using standard reagents



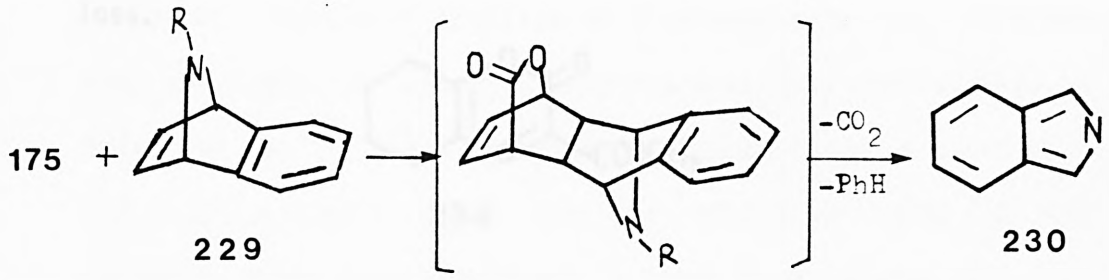
175 226 227

A novel route to bridged tricycloundecenones achieved by heating 2-pyrone with 1,6-heptadiene-3-one (228) involves formation of an intermediate product whose stereochemistry appears unimportant to the outcome of the synthesis at such high temperatures[21].



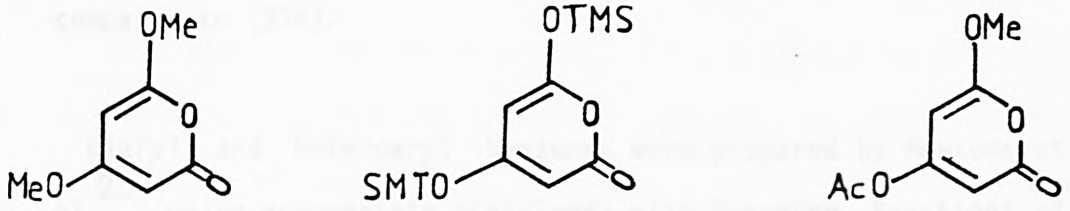
228

The cycloaddition of 7-azabenzonorbornadiene (229) with 2-pyrone, under reflux in toluene for 70hrs, initially forms isoindole (230) by successive loss of carbon dioxide and benzene[22] and this undergoes further addition.



229 230

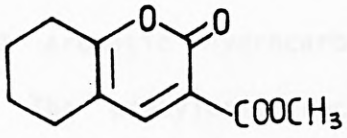
Reactivity of 4,6-dioxy-2-pyrones in the Diels-Alder processes was examined by Kozikowski et al.[23] who found, in general, that unsymmetrical dieneophiles of moderate reactivity (ethyl acrylate, methyl methacrylate etc) failed to give isolable products with these pyrones (231), (232), and (233).



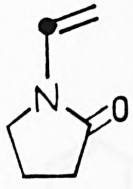
231 232 233

Acetylenic dicarboxylates reacted with similar vigour with each of the above pyrones at 100-150° C to yield the brige-eliminated adduct. When maleic anhydride or phenyl maleamide were used, bis adducts were formed. Owing to critical decarbonylation temperatures of 100-140°C, no primary adduct was isolated and thus no data on the stereoselectivity of the reaction was reported.

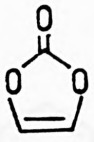
3-Carbomethoxy-2-pyrone underdgoes an inverse electron demand Diels-Alder cycloaddition[24] with (235-238) followed by CO2 loss.



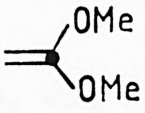
234



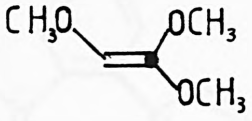
235



236



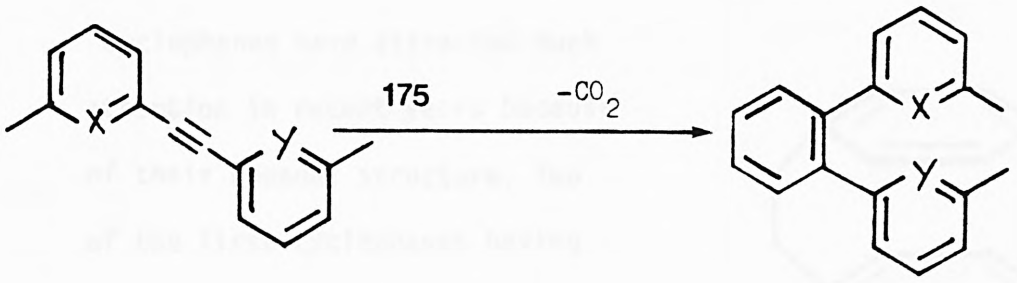
237



238

Experimental results suggest (237) is the most reactive dieneophile above, and the unsymmetrical structure of (235) may be a factor in its higher reactivity towards (234) as compared to (236).

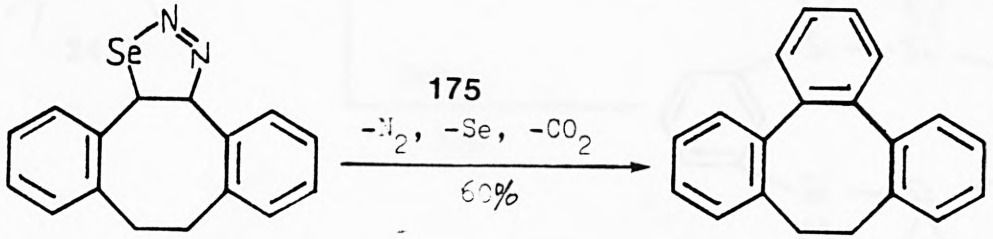
Diaryl and heteroaryl benzenes were prepared by Newkome et al.[25] using appropriate acetylenes with 2-pyrone. Reactions of this type, particularly because they are carried out at high temperatures, require radical scavengers to improve yields (Scheme LIV)



X=N, Y=CH	220°C	72hr	80%
X=N, Y=N	220°C	9hr	56%
X=Y, Y=CH	310°C	120hr	40%

Scheme LIV

Another example of addition of 2-pyrones to a C≡C bond for the synthesis of aromatic hydrocarbons was demonstrated by Meier et al.[26]. The acetylenic decomposition product of a 1,2,3-selenadiazole (239) cyclises with substituted 2-pyrone to yield, after decarbonylation, a fused ring (Scheme LV).

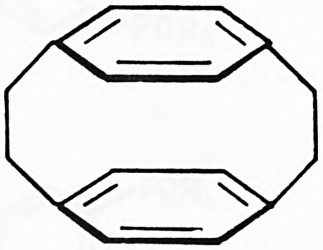


239

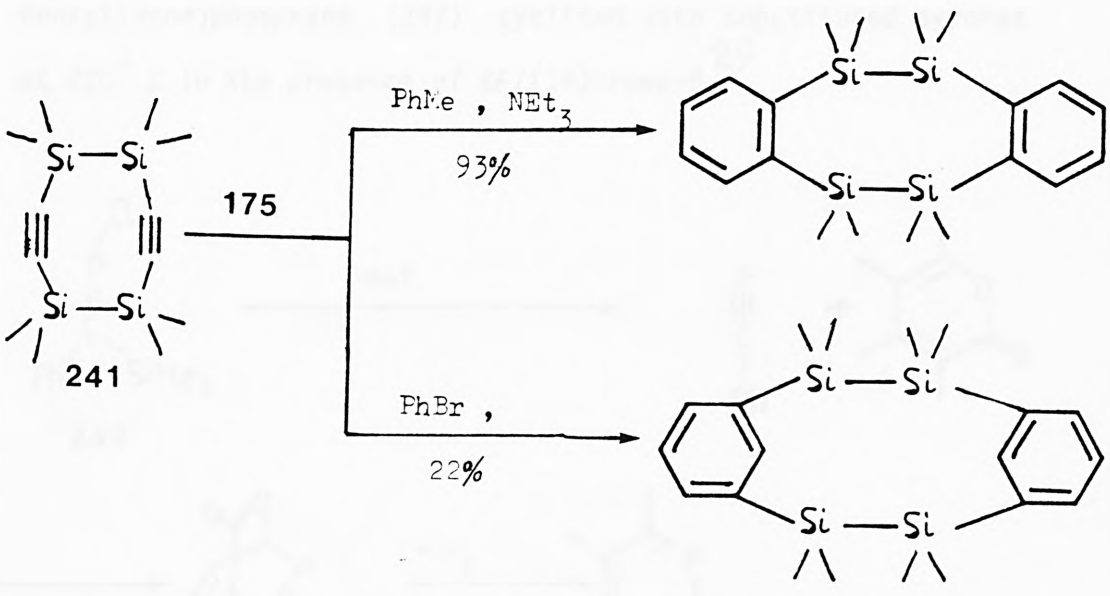
Scheme LV

2-Pyrone, 5-carboxy-2-pyrone, 4,6-dimethyl-5-carboxy and 4,6-dimethyl-5-carbomethoxy pyrone reacted to yield varying quantities of adduct but 4-methoxy-6-methyl-2-pyrone proved unreactive towards (239).

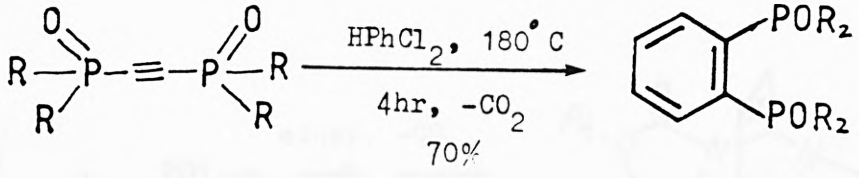
Cyclophanes have attracted much attention in recent years because of their unusual structure. Two of the first cyclophanes having silicon-silicon bonds as a bridge, instead of C-C bonds, were prepared by Sakurai et al.[27] who reacted 2-pyrone with (241). Formation of m-cyclophane is characteristic of isomerisation of 1,2-bis(trimethylsilyl)benzene.



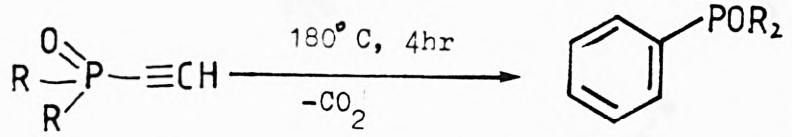
240
Para-cyclophane



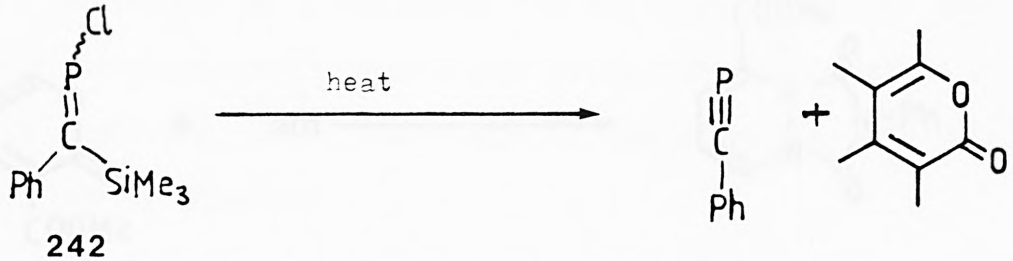
The study into novel synthesis of s1,2-diphosphorylbenzenes, by Kyba et al.[28] showed that only a single activating group on the alkyne is necessary for the cycloaddition to occur with 2-pyrone whereas the symmetrical dieneophile $Ph_2PC{\equiv}CPPh_2$ failed to react under a variety of conditions, including Lewis acid catalysis.



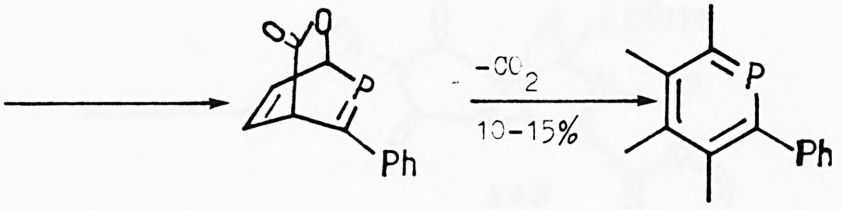
175 +



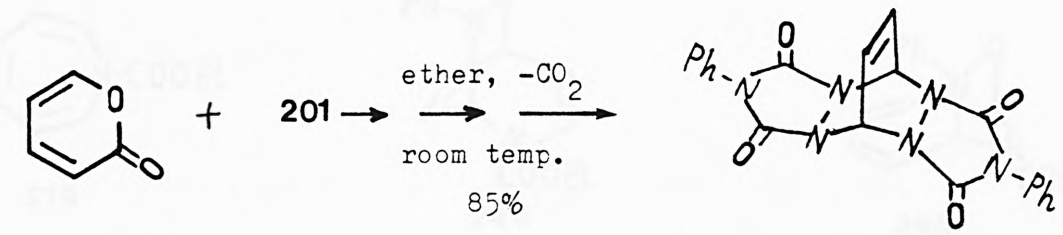
A novel [4+2]-cycloaddition utilises C≡P functionality to afford λ^3-phosphorins . P-Chloro(∝-trimethylsilyl benzylidene)phosphane (242) cyclised with substituted pyrones at 220° C in the presence of KF/(18)crown-6[29]

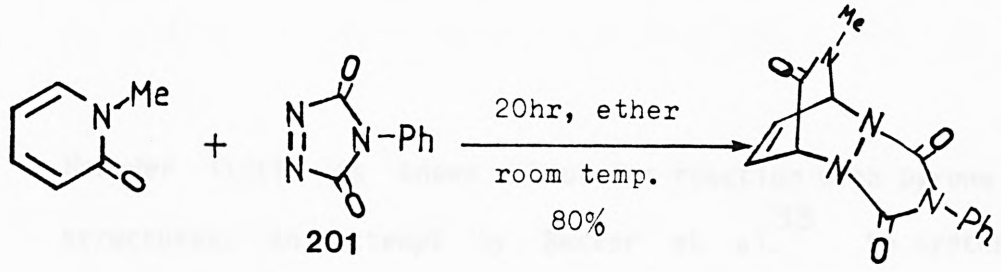


242

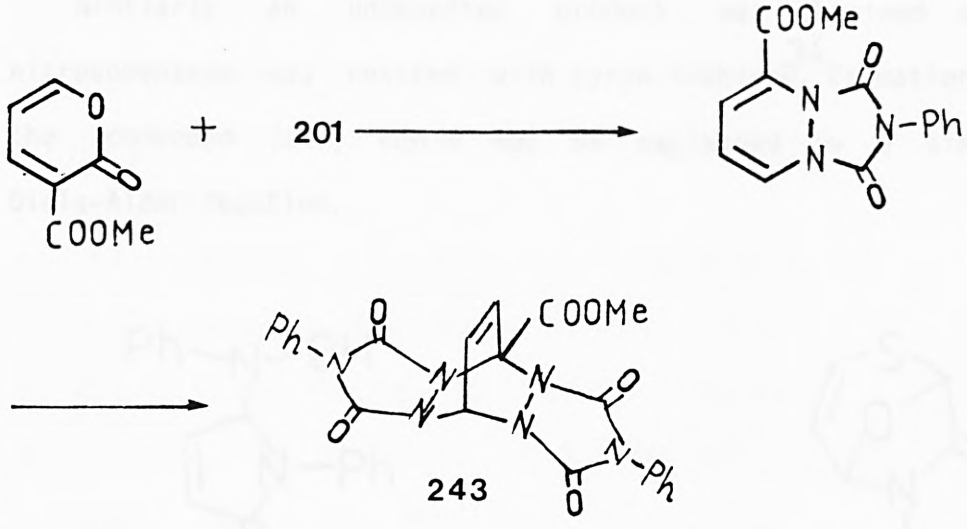


N-Phenyl-1,2,4-triazoline-3,5-dione (201)readily undergoes cycloaddition reaction with 2-pyrone and N-methyl-2-pyridone to yield bis- and mono-adducts respectively. The crystalline products were isolated readily after the completion of the reactions which was judged by the disappearance of the red colouration of the dieneophile[30] .

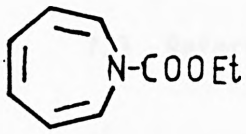




Bicyclic 1,2-dihydropyridazine (243) was prepared by Diels-Alder reaction of 2-pyrones with cyclic azo-dieneophiles.[31]



The N=O- functionality of nitrosobenzene can be regarded as a dieneophile which may undergo Diels-Alder cycloadditions. For instance, reaction of PhNO with the azopine (219) gave, together with the brown 1,6-cycloadduct (244), the stable 1,4-cycloadduct (245)[32].



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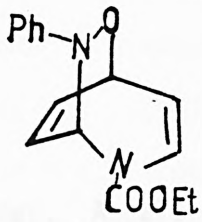
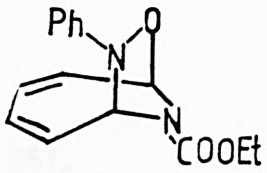


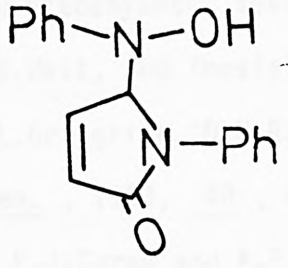
244



245

However little is known about its reaction with pyrone type structures. An attempt by Becker et al.[33] to synthesise N-phenyl-1,2-oxazine failed to yield an adduct or indeed any product which could be mechanistically accounted for by simple 4 + 2 dipolar cycloaddition. Instead they isolated 24% yield of colourless solid (246)

Similarly an unexpected product was obtained when nitrosobenzene was reacted with pyran-2-thione.[34] Formation of the compound (247) could not be explained by a simple Diels-Alder reaction.



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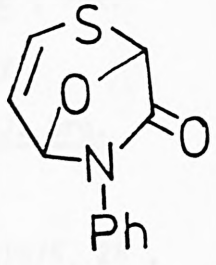

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Chapter 8 : Cycloadditions of 3-methyl-2-pyrone

8.1 Introduction

The success of our proposed synthetic route for nor-diterpene dilactones depended largely on causing an efficient cycloaddition reaction between 3-methyl-2-pyrone (173) and 2,6-dimethyl-p-benzoquinone (115) to give the adduct with correct geometrical and stereochemical isomeric structure. It was therefore felt necessary to investigate a wider range of cycloaddition reactions of the pyrone with purpose-chosen dieneophiles. The results then gave us better understanding of the limitations of the cycloaddition and helped to judge the necessary experimental conditions to achieve success.

This chapter presents the data obtained on all the adducts synthesised including the target adduct (262)

To classify the cycloaddition reactions of 3-methyl-2-pyrone, division has been made between quinonoid dienes and non-quinonoid dienes. A tabulated summary of all the cycloaddition reactions is also presented in Appendix I. Also selected spectroscopic data is presented in Appendix II and Appendix III.

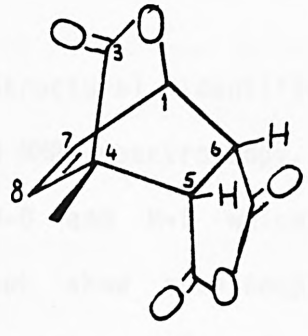
8.2 Cycloaddition with non-quinonoid compounds

8.2.1 Formation of 8-Oxabicyclo[2.2.2]oct-4-en-7-one derivatives.

In this section seven dieneophiles which reacted with

3-methylpyrone to produce the bridged structure, 8-oxabicyclo[2.2.2]oct-5-en-7-one, are discussed. The ability of structures of this type to extrude a carbon dioxide molecule is well established. However CO_2 extrusion does not usually occur below 100° C and this was found to be true for all except one of the adducts, which lost the bridge at room temperature.

A) Maleic anhydride and N-Phenyl maleamide: Cycloaddition of maleic anhydride and N-phenylmaleamide with 3-methyl-2-pyrone were performed in the absence of solvents to afford adducts (248) and (205) with yields of greater than 80%.
The spectroscopic data were all in accord with the adducts having a six-membered lactone ring and an endo-configuration.



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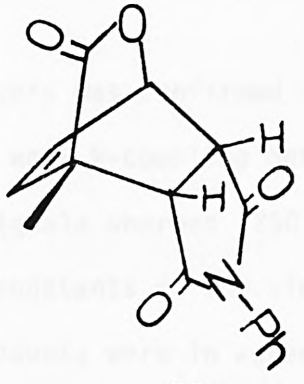
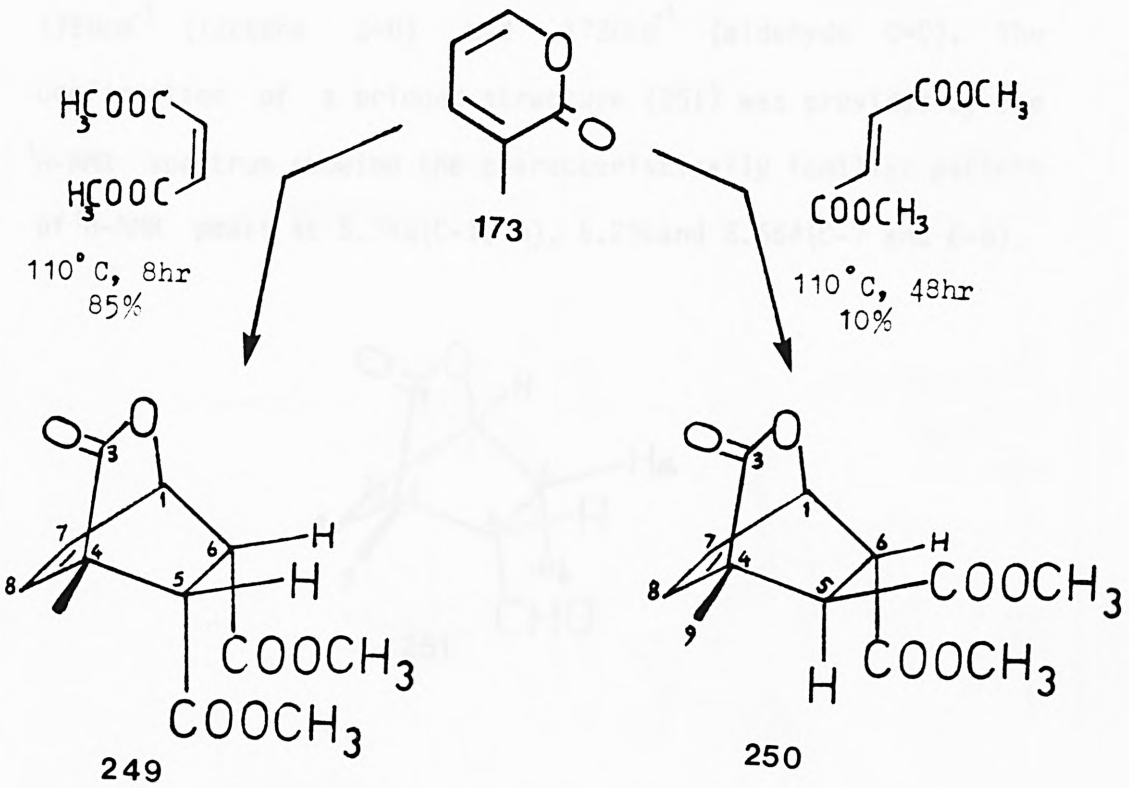


205

B) Dimethyl maleate and dimethyl fumarate : Comparative study of the two geometrical isomers, dimethyl maleate and dimethyl fumarate, clearly indicate the importance of steric factors in their cycloaddition reactions with 3-methylpyrone. Thus the cis isomer resulted in 85% yield of the maleate adduct (249) when stirred at 110 C with the pyrone for 4hr, whereas

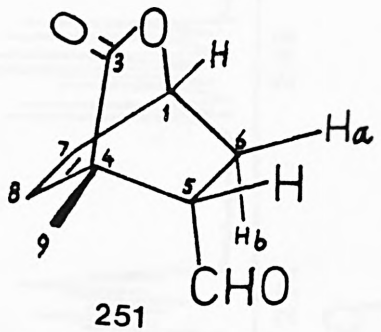
sixfold increase in the duration of cycloaddition of the trans isomer under similar conditions yielded only 10% of the crystalline fumarate adduct (250).



Structural identification of these adducts was confirmed using ^{1}H-NMR spectroscopy. (249) exhibited a weak W-coupling between H-8 and H-5 which broadened their signals whereas (250) did not show such coupling. The coupling constants of the vicinal protons, H-5 and H-6, in the two adducts were in agreement with the prediction based on Karplus equation and were 11Hz in (249) and 5.5Hz in (250).

C) Prop-2-enal (acrolein) : The cycloaddition with acrolein was carried out without solvent at room temperature by stirring for a few weeks. Heating was avoided because acrolein could polymerise. Removal of excess acrolein under vacuum

produced an oil, which was purified by column chromatography on silica with ether as eluent to produce a single product (Rf=0.5) whose infra-red spectrum showed an absorption at 1750cm^{-1} (lactone C=0) and 1720cm^{-1} (aldehyde C=0). The confirmation of a bridged structure (251) was provided by the ^{1}H-NMR spectrum showing the characteristically familiar pattern of ^{1}H-NMR peaks at 5.34δ(C-1, m), 6.29δand 6.66δ(C-7 and C-8).



251

The geometry can be deduced from the coupling pattern with the aid of hydrogen decoupling technique as follows (Figure 4):

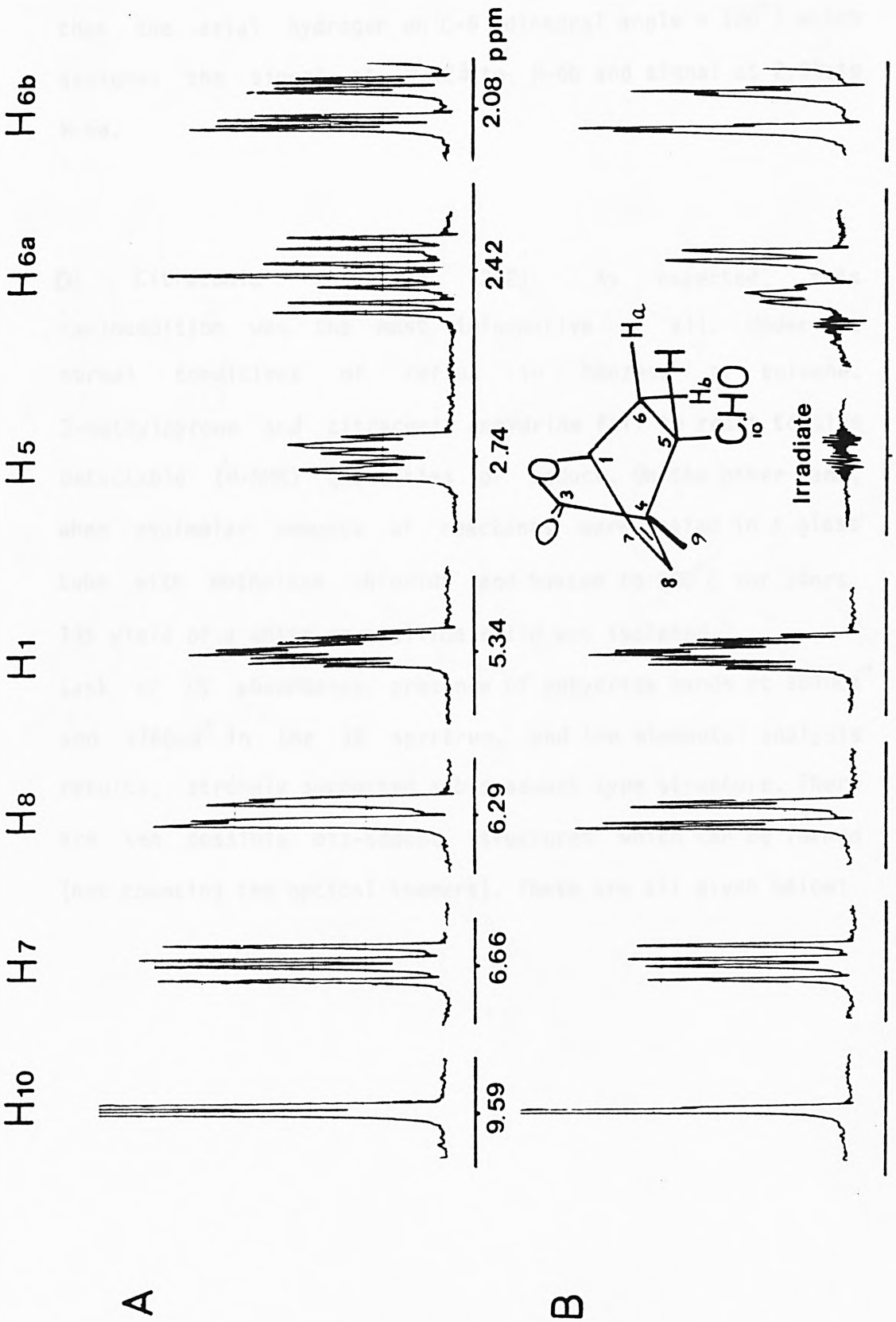
a) geminal coupling of 14Hz observed in the signals at 2.08δ and 2.42δ establishes that these signals belong to two hydrogens on the same carbon atom from acrolein fragment (H-6a and H-6b).

b) as the rest of the peaks are easily assignable the signal at 2.74δ is due to the third hydrogen from acrolein fragment

c) irradiation at 2.74δ has no effect on H-1 and thus are not ortho to each other. Hence, signal at 2.74δ is due to the hydrogen on the C-5 and furthermore the geminal hydrogens are on C-6

d) irradiation at 2.74δsharpens the signal at 6.29δ (H-8)

Figure 4 : 220MHz ^{1}H-NMR spectrum of acrolein adduct (251); A) coupled spectrum, B) H-5 decoupled spectrum. Methyl signal has been ommitted.

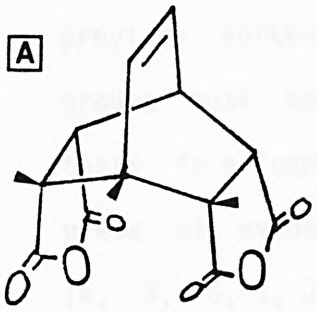


suggesting presence of a weak W-coupling between H-8 and H-5 which is only observed if the H-5 is in the equatorial position as in (251). The coupling constant between H-5 and the equatorial hydrogen on C-6 is larger (dihedral angle= 0°) than the axial hydrogen on C-6 (dihedral angle = 120°) which assignes the signal at 2.42δ to H-6b and signal at 2.08δ to H-6a.

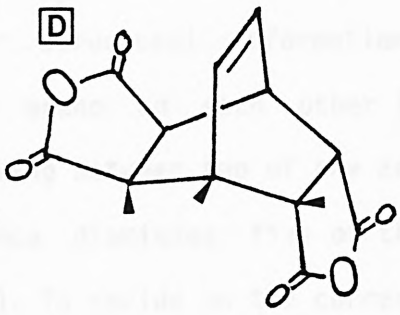
D) Citraconic anhydride (252): As expected, this cycloaddition was the most informative of all. Under the normal conditions of reflux in benzene or toluene, 3-methylpyrone and citraconic anhydride fail to react to give detectable (^{1}H-NMR) quantities of adduct. On the other hand, when equimolar amounts of reactants were sealed in a glass tube with methylene chloride and heated to 200°C for 24hrs, 13% yield of a white crystalline solid was isolated.

Lack of UV absorbance, presence of anhydride bands at 1840cm^{-1} and 1780cm^{-1} in the IR sprctrum, and the elemental analysis results, strongly supported a bis-adduct type structure. There are ten possible bis-adduct structures which can be formed (not counting the optical isomers). These are all given below:

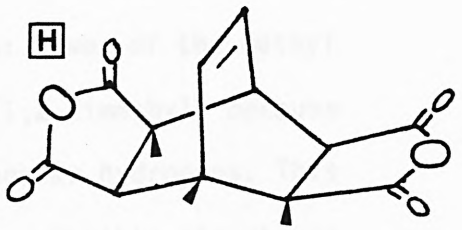
A



D



H



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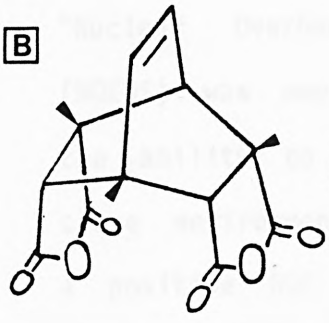
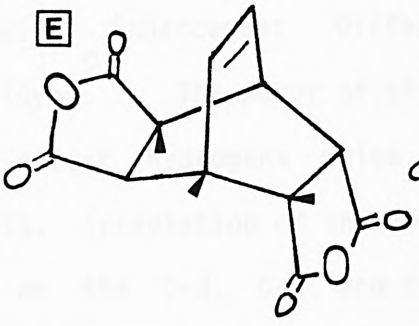
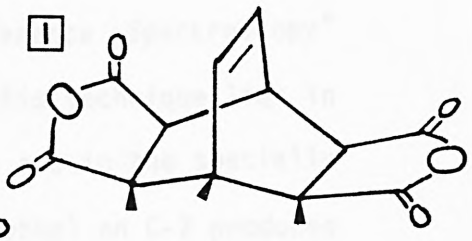
B



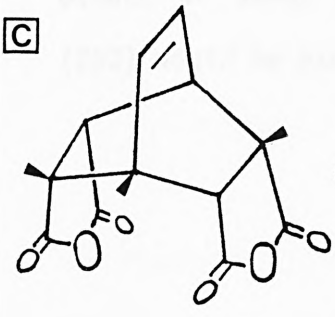
E



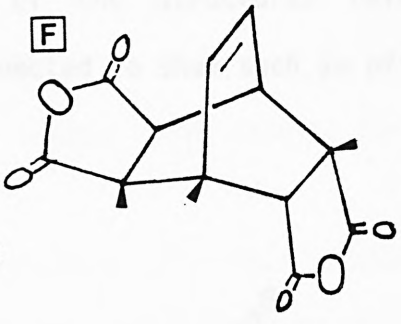
I



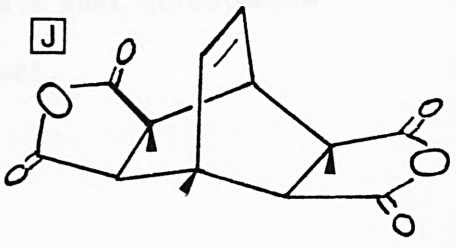
C



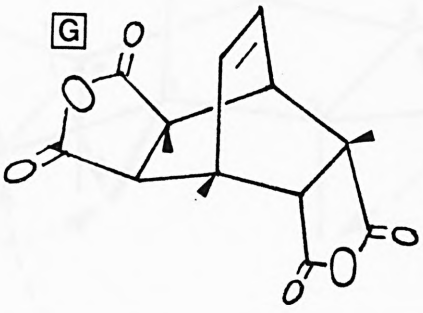
F



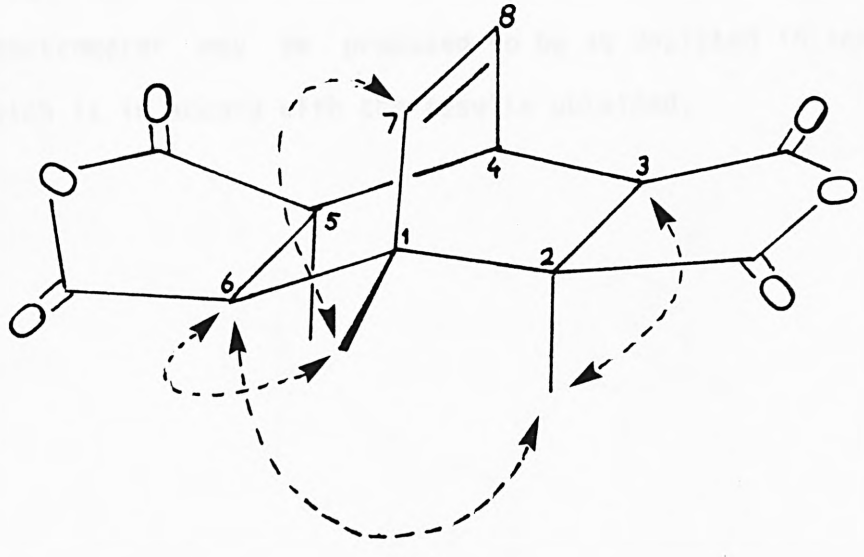
J



G



The ^{1}H-NMR is consistant with a bis-adduct structure and provides further structural information: two of the methyl groups must be ortho to each other (1,2-dimethyl) because there is a coupling between two of the angular hydrogens. This piece of evidence dismisses five of the possible structures (A, B, G, I, J). To decide on the correct molecular structure out of the remaining five configurations, the technique of "Nuclear Overhauser Enhancement Difference Spectroscopy" (NOEDS) was employed[2]. The power of this technique lies in the ability to detect hydrogens which are in the spatially close environments. Irradiation of the methyl on C-2 produces a positive NOE on the C-3, C-6, and C-1(methyl) hydrogens which suggests that these hydrogens must be close to each other. A study of the structures reveals that structure H (253) would be expected to show such an effect.



253

Irradiation of other hydrogens has been carried out and the results are given in Table 5.

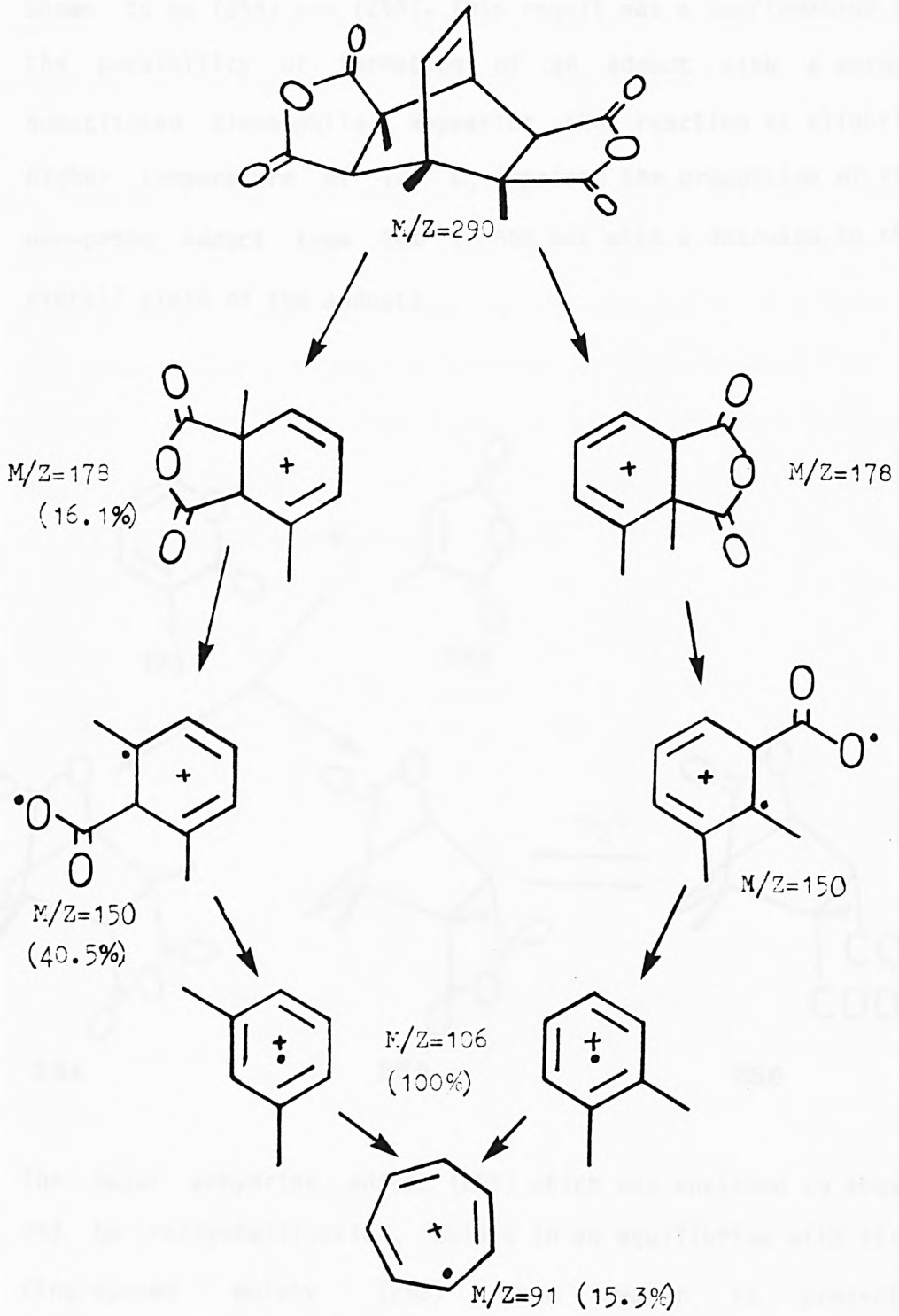
Assig	δ	coupling constants Hz	NOE
1 (Me)	1.68	-	6, 7, 2 (Me)
2 (Me)	1.48	------	6, 3, 1 (Me)
3	3.30	3.3	2 (Me), 5 (Me)
4	3.34	3.3, 6.0, 1.4	8, 3, 5 (Me)
5 (Me)	1.53	-----	6, 3, 4
6	3.02		5 (Me), 2 (Me), 1(Me)
7	6.16	8.3, 1.4	1 (Me)
8	6.42	8.3, 6.0	4

Table 5 : 400MHz ^{1}H-NMR results for structure (253)

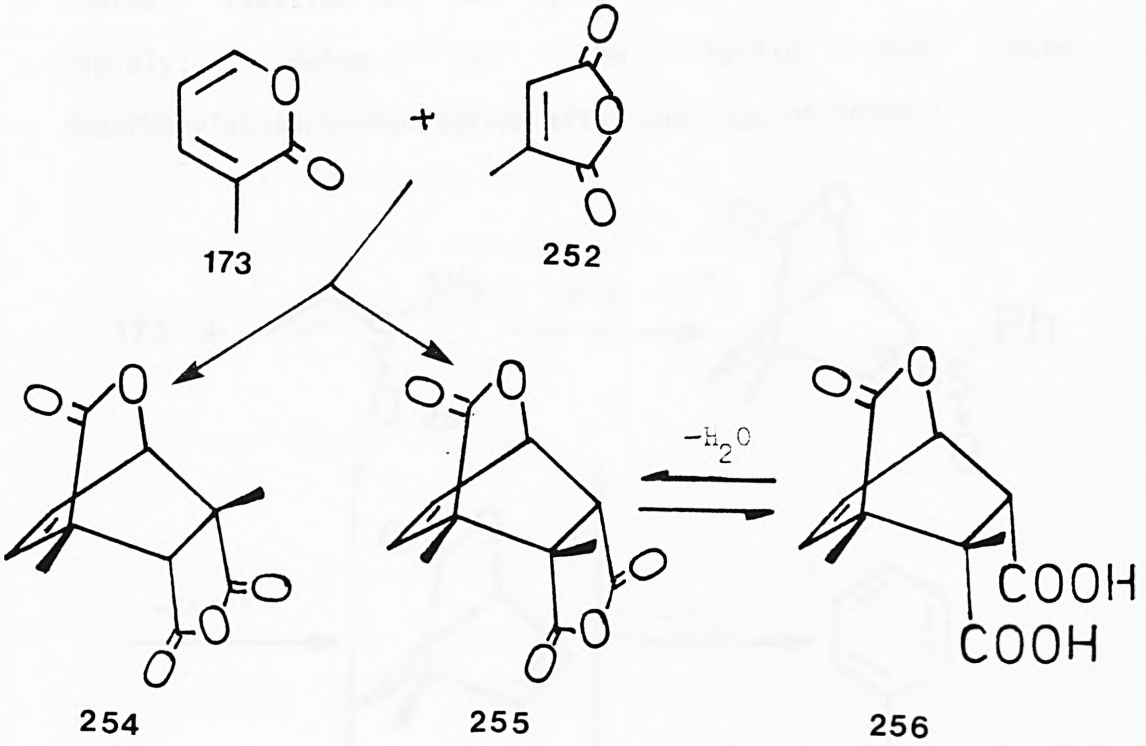
Fragmentation pattern of this compound in the mass spectrometer may be proposed to be as depicted in scheme LVI which is in accord with the results obtained.

Scheme LVI : MS fragmentation pattern of

the bis-adduct (253)



When the cycloaddition with (252) was carried out in the absence of solvent at 100-110° C, approximately 10% yield of a mixture of isomeric adducts was obtained as shown and detected by ^{1}H-NMR spectroscopy. After isolation of the products and examination by spectroscopic techniques the products were shown to be (254) and (255). This result was a confirmation of the possibility of formation of an adduct with a methyl substituted dieneophile. Repeating the reaction at slightly higher temperature of 120° C, improved the proportion of the non-ortho adduct from 20% to 50% but with a decrease in the overall yield of the adducts

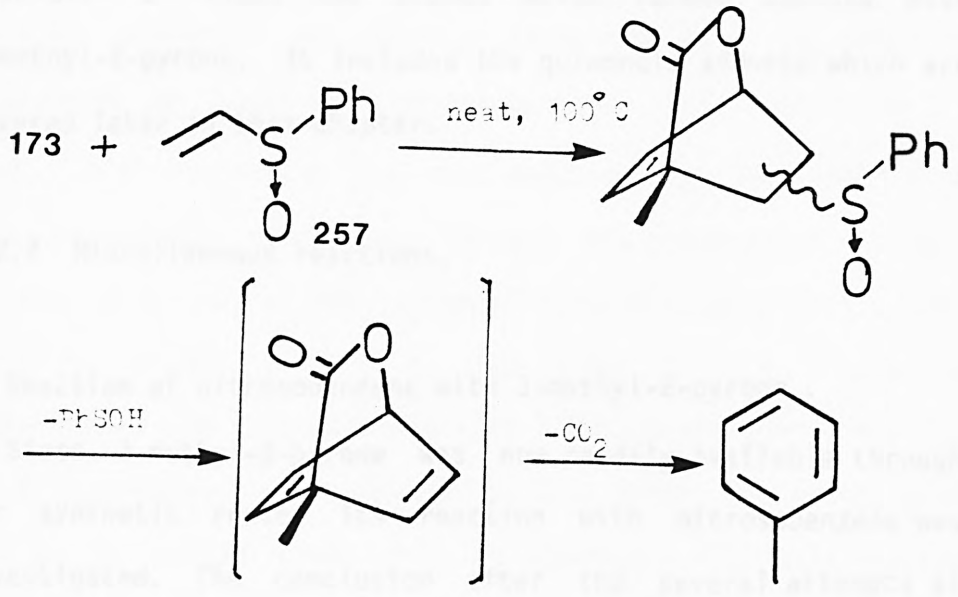


The major anhydride adduct (255) which was enriched to above 95% by recrystallisation, exists in an equilibrium with its ring-opened moiety (256) when water is present. Recrystallisation of (255) from water produces cubical

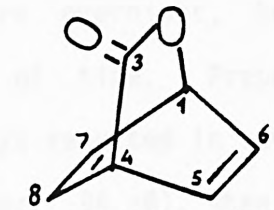
crystals of the acid with one mole of water of crystallisation. This acid recyclised from acetonitrile.

Cycloaddition of 3-methyl-2-pyrone and citraconic anhydride was repeated as above but in the presence of an equimolar amount of $BF_3.OEt_2$ as Lewis acid catalyst. No adduct could be detected by ^{1}H-NMR which showed disappearance of the diene. Hence, it was deduced that $BF_3.OEt_2$ retarded the cycloaddition reaction and caused gradual decomposition of the diene.

E) Phenyl vinyl sulphoxide (257) : This was the only dieneophile which did not lead to formation of a stable bridged adduct when cyclised with 3-methyl-2-pyrone. Indeed the adduct was not detected by ^{1}H-NMR in a sample taken from a thermal reaction at 100° C,and appeared to form toluene rapidly, owing to the facile one step decarbonylation/aromatisation after the loss of PhSOH :



The parent structure (213) is also known to decompose around 0° C.



213 unstable above freezing point

F) Other dieneophiles.

A number of other dieneophiles were examined for their reaction with 3-methyl-2-pyrone. Dimethyl citraconate , but-2-enal and vinyl acetate did not undergo cycloaddition under the most vigourous conditions (130° C,neat, 24hrs) allowed by product stability. At the end of this chapter, Appendix I lists the dienes which formed adducts with 3-methyl-2-pyrone. It includes the quinonoid adducts which are covered later in this chapter.

8.2.2 Miscellaneous reactions.

a) Reaction of nitrosobenzene with 3-methyl-2-pyrone .

Since 3-methyl-2-pyrone was now readily available through our synthetic route, its reaction with nitrosobenzene was investigated. The conclusion after the several attempts at reacting the pyrone with nitrosobenzene was that some sudden reaction occurred during evaporation of the solvent, methylene chloride,after the reagents were mixed, even with scrupulous exclusion of atmospheric oxygen from the reaction vessel.

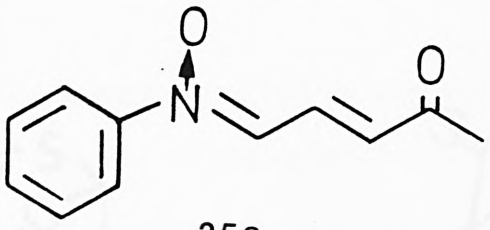
Similar observations were made when the reaction was left at room temperature overnight, but not if in freezer for a much longer period of time. Preparative TLC separation of the crude oil always resulted in several bands (methylene chloride : diethyl ether, 94 :6). When the bands were removed, washed and concentrated ,all of them decomposed/polymerised as shown by TLC and their ill-defined ^{1}H-NMR spectra, except one band which seemed to be an impure solid (5%). Addition of little ether left colourless needles in the flask. Larger quantities of the compound were purified using preparative HPLC on a silica column with methylene chloride/acetonitrile (92/8) as eluent and 240nm as monitoring wavelength. Some of the crystals of this compound appeared colourless and some appeared half red and half green under polarised light and melted at 133-135° C. The compound seemed to decompose gradually in solution in chloroform . The elemental analysis results suggested an empirical formula of $C_{11}H_{11}NO_2$ which was supported by exact mass measurements by field ionisation (FI) and field desorption (FD) mass spectroscopy. The 400MHz ^{1}H-NMR and decoupling experiments showed the presence of a singlet methyl at 2.42δ; an ABC system of three hydrogens with 9.5Hz (Ja,b), 15.5Hz (Jb,c), and 0.5Hz (Jc,a) coupling constants; and two multiplets at 7.51δ(3 hydrogens) and 7.73δ (2 hydrogens) which coupled to each other. The methyl group is on a carbon atom with no hydrogens. The mass spectrum exhibits M/Z = 189 (6%, M+), 173 (6%, M+ - O), 149 (12%), 146 (98%), 130 (23%), 118 (26%), 117 (16%), 104 (15%), 93 (53%), 91 (45%), 82 (32%), 77 (100%, C6H5+). In the infra-red spectrum, ester and lactone peaks were absent, but a strong

peak at 1650cm^{-1} suggested an unsaturated ketone or an amide. The IR spectrum also exhibits characteristic bands for a mono-substituted benzene ring at 690 and 775cm^{-1}. The UV absorption spectrum shows absorption at 352nm (ε = 4016), 270nm (ε = 1867), 240 (ε = 980), 210nm (ε = 1950).

In accord with the above spectroscopic data a molecular structure can be derived from the following deductions:

1. The ^{1}H-NMR suggested presence of a mono-substituted benzene ring, a remote methyl group, and a downfield three-hydrogen-system including a possible trans olefinic structure.
2. The loss of 16amu from the parent molecule (189amu) in the mass spectrometer is often observed if a nitrone functionality is present.
3. A highly conjugated system is suggested by the UV spectrum (352nm).

The proposed structure (258) fits all the spectroscopic data obtained.

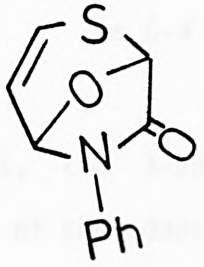


258

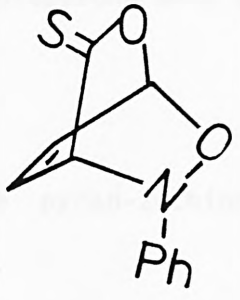
b)Reaction of nitrosobenzene with 3-methyl-2-thiopyrone.

It was recently reported by Augelmann et al.[1] that pyran-2-thione reacts with nitrosobenzene in dichloromethane at room temperature to give the adduct (247) quantitatively, instead of the expected [4+2] cycloaddition product (259). The

structure of the adduct (247) was confirmed by X-ray crystallography. It was suggested as a tentative mechanistic hypothesis that the formation of the adduct (247) involves a slow Diels-Alder cycloaddition affording (259) followed by some rapid rearrangement step, the nature of which was not specified. However, this mechanistic hypothesis presents a number of problems: the lack of stability of the supposed intermediate (259) seems surprising when compared with analogous cycloadducts of 2-pyrone and various dieneophiles; the presence of the supposed intermediate (259) could not be detected by NMR; it is very difficult to provide a mechanism for the rearrangement of (259) to (247). We therefore considered an alternative pathway for the formation of the product (247). This involves a "walk" of the sulphur atom around the pyran ring to give the oxonium ylide intermediate (247a) which then attacks the nitrosobenzene to give the oxizirane (247b). This zwitterionic intermediate, in which an intramolecular 1,3-dipolar cycloaddition to the aldehyde group is conceivable, furnishes the final product (247) as shown in scheme LVII.

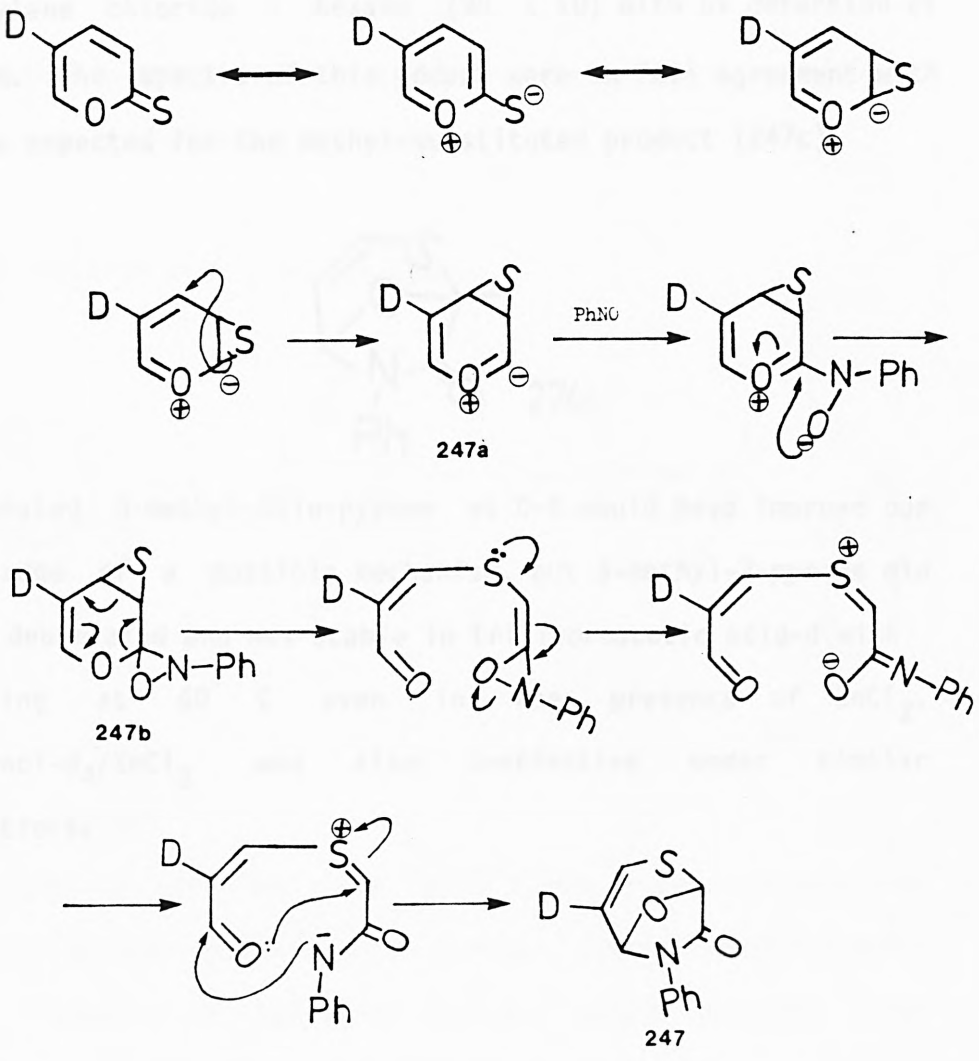


247



259

As evidence for this mechanism, we have examined the behaviour of 3-methyl-pyran-2-thione (184). As indicated in

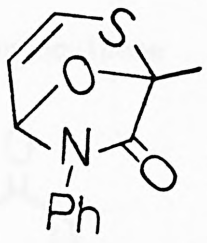


Scheme LVII: Deuterium on C-5 of thiopyrone ends up on C-4 of the product

scheme LVII, the 3-position of the pyran-2-thione should provide C-1 of the adduct.

3-Methyl-pyran-2-thione (184) was prepared by sulphur transfer to 3-methyl-2-pyrone (173). When this was treated with nitrosobenzene in dichloromethane, a single 1 :1 adduct could be isolated by direct vacuum sublimation from the crude

reaction product, or preparative hplc on silica using methylene chloride : hexane (90 : 10) with UV detection at 241nm. The spectra of this adduct were in full agreement with those expected for the methyl-substituted product (247c).



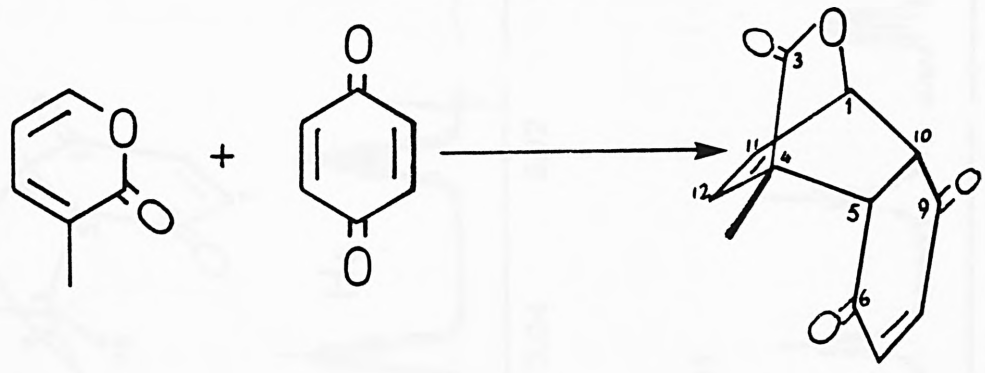
274c

Deuterated 3-methyl-thio-pyrone at C-5 would have improve our knowledge of a possible mechanism, but 3-methyl-2-pyrone did not deuterated and was stable in trifluoroacetic acid-d with stirring at 60° C even in the presence of $ZnCl_2$. Methanol-d_4/$ZnCl_2$ was also ineffective under similar conditions.

8.3. Cycloadditions with quinonoid compounds.

H-NMR spectroscopic data for eight quinonoid adducts are presented in appendix III.

8.3.1 Reaction with p-benzoquinone



260

8.3.1.1 Thermal

Evaluation of the ease with which p-benzoquinone and 3-methyl-pyrone cycloadd was carried out and showed clearly that reaction in refluxing toluene and/or benzene under nitrogen atmosphere yielded <10% of the adduct. However in the absence of solvents, improved yields of up to 80% were obtained after the solidified mass was crushed and washed with ether and recrystallised from ethyl acetate. All the spectroscopic data were consistant with an endo bridged adduct (260). Figure 5 represents a typical example of a high resolution H-NMR spectrum which was obtained for the benzoquinone adduct. Irradiation in the region of 3.05δto 3.00δ ppm decoupled the effect of H-5 which is shown in Figure 6 and allowed unequivocal assignment of the coupling patterns in the molecule.

Figure 5 : High resolution 400MHz ^{1}H-NMR spectrum of (260).

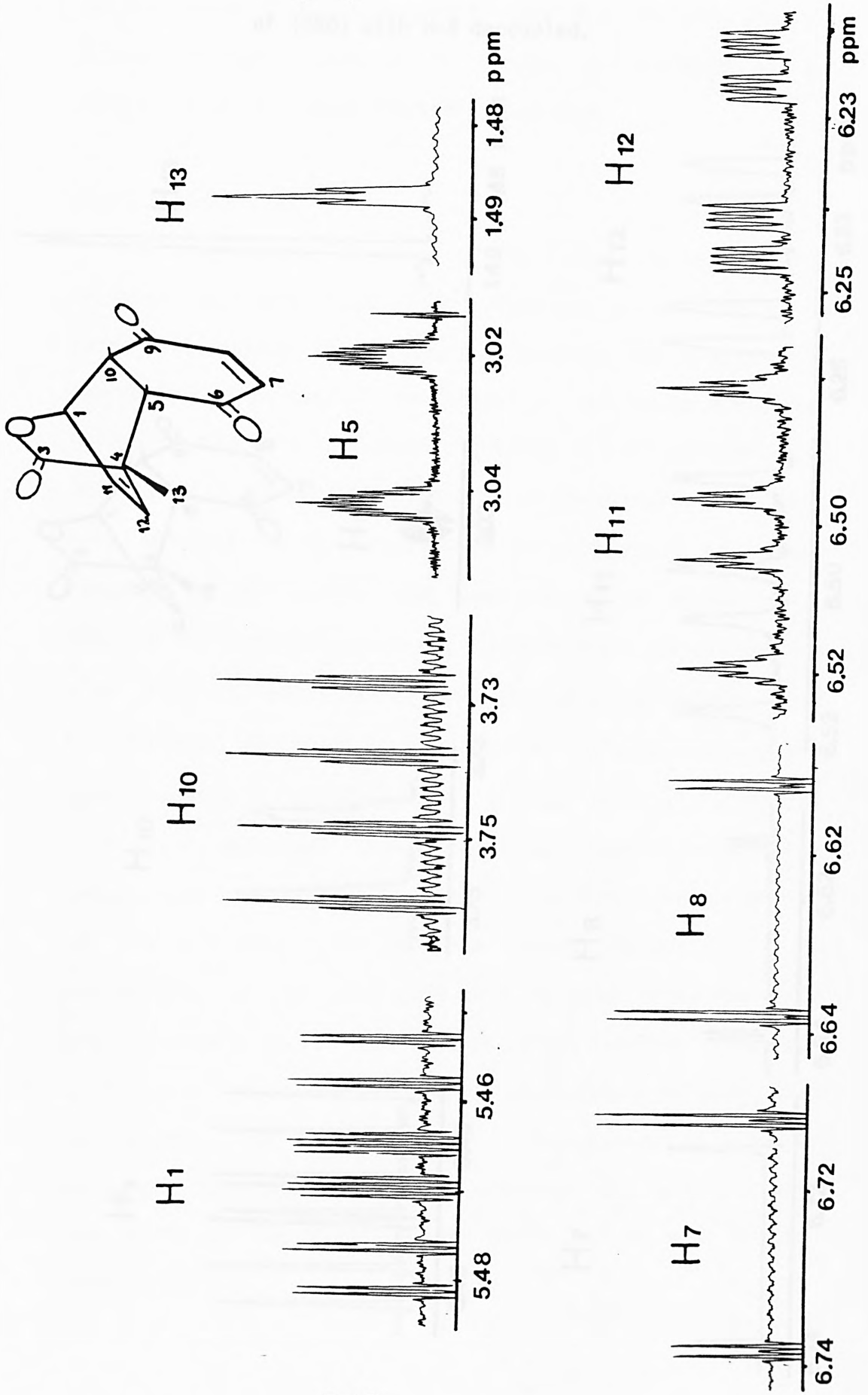
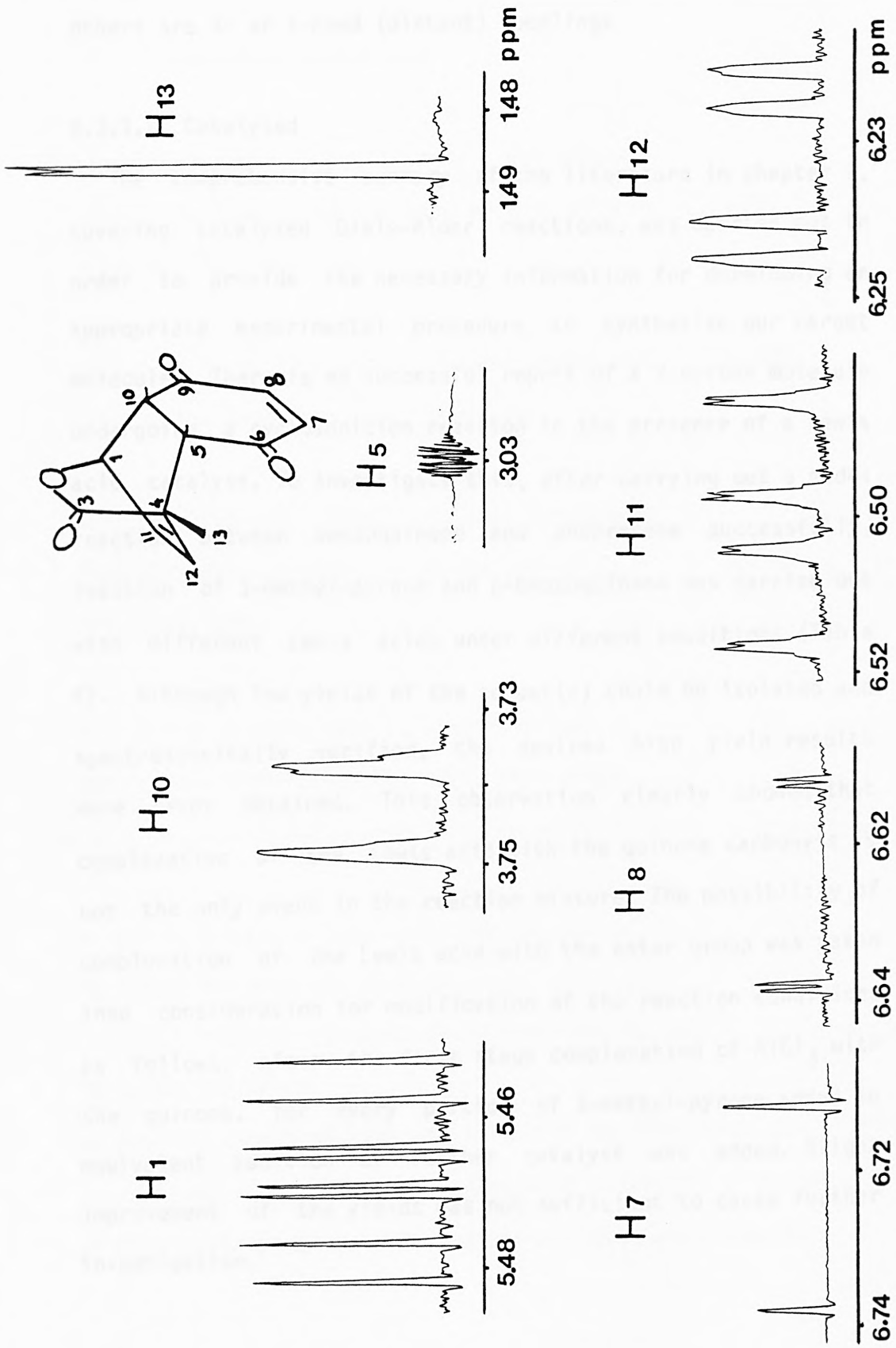


Figure 6 : High resolution 400MHz ^{1}H-NMR spectrum of (260) with H-5 decoupled.



H-5 appears to couple with all the hydrogens except H-8. H-1 couples with H-11, H-10, H-12, and H-5. The only apparent 5-bond (distant) coupling is between H-5 and H-11; all the others are 3- or 4-bond (distant) couplings

8.3.1.2 Catalysed

The comprehensive summary of the literature in chapter 7, covering catalysed Diels-Alder reactions, was carried out in order to provide the necessary information for developing an appropriate experimental procedure to synthesise our target molecule. There is no successful report of a 2-pyrone molecule undergoing a cycloaddition reaction in the presence of a Lewis acid catalyst. To investigate this, after carrying out a model reaction between benzoquinone and anthracene successfully, reaction of 3-methyl-pyrone and p-benzoquinone was carried out with different Lewis acids under different conditions (Table 6). Although low yields of the adduct(s) could be isolated and spectroscopically verified, the desired high yield results were never obtained. This observation clearly showed that complexation of the Lewis acid with the quinone carbonyls is not the only event in the reaction mixture. The possibility of complexation of the Lewis acid with the ester group was taken into consideration for modification of the reaction conditions as follows: after the first stage complexation of $AlCl_3$ with the quinone, for every portion of 3-methyl-pyrone added an equivalent addition of further catalyst was added. Slight improvement of the yields was not sufficient to cause further investigation.

Table 6 Summary of catalysed cycloadditions attempted with p-benzoquinone

EXPERIMENTAL CONDITIONS	YIELD
$AlCl_3$(1eq) added to CH_2Cl_2(100ml) and ethanol (25ml). Quinone added and then pyrone. Mixture stirred. 3hr, room temp.	1-5%
$AlCl_3$(1eq in CH_2Cl_2(200ml). Quinone added and then pyrone dropwise. 1hr, room temp.	5-10%
$AlCl_3$(1eq) in $CHCl_3$(200ml). Quinone added and then alternate portions of pyrone and $AlCl_3$. 2hr, room temp.	10-15%
$AlCl_3$(1eq) in ether(50ml). Quinone added. Pyrone then added dropwise. 1hr, room temp.	0%

a. solvents were all dried before use

b. reactions were all stirred

c. 1:1:1 ratio of catalyst:diene:dieneophile used

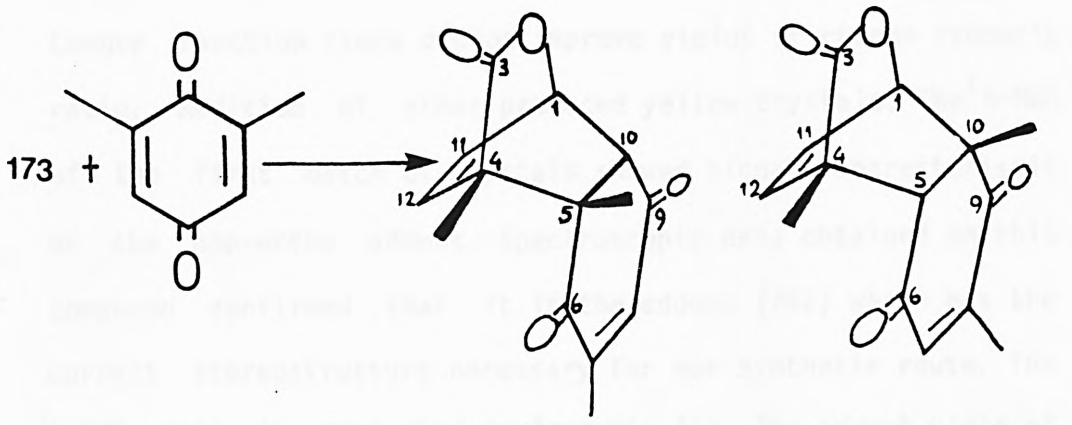
d. 0.05molar scale

e. quinone complexed with Lewis acid in solvent prior to addition of pyrone (accompanied with deepening of colour

f. white ppt appeared which was pyrone+Lewis acid complex.

8.3.2 Reaction with 2,6-dimethyl-p-benzoquinone

The target adduct (262) was finally synthesised but in low yields. All sorts of conditions were examined which are discussed below.



8.3.2.1 Thermal reaction

Several attempts were made to carry out the cycloaddition of xyloquinone with the substituted pyrone, 3-methyl-2H-pyran-2-one, thermally under nitrogen atmosphere by fusing the mixture at 100°C with stirring and by refluxing in different solvents (eg isopropanol, toluene, and xylene). The failure of the formation of any adduct, judged by TLC, H-NMR and HPLC was attributed to the low reaction temperatures necessary to avoid breakdown of the quinone and of any bridged adducts formed. Serious decomposition of the xyloquinone was observed above 120° C, causing blackening of the reaction mixtures. 3-Methyl-2-pyrone ,however, appeared stable and could be retrieved chromatographically.

The reaction was carried out neat in a sealed glass tube at 115° C for 80hr, and the rate of quinone decomposition was

decreased by scrupulous exclusion of oxygen (nitrogen bubbled and degased several times). Upon the removal of the starting materials by vacuum distillation a black residue was obtained. Crude mixture was examined on a HPLC silica column with methylene chloride / acetonitrile (98 : 2), which showed a 2 : 3 mixture of ortho- (261): non-ortho- (262) was detected. Longer reaction times didnot improve yields or change isomeric ratio. Addition of ether produced yellow crystals. The ^{1}H-NMR of the first batch of crystals showed signals characteristic of the non-ortho adduct. Spectroscopic data obtained on this compound confirmed that it is the adduct (262) which has the correct stereostructure necessary for our synthetic route. The ^{1}H-NMR data is presented in Appendix III. The adduct yield of this reaction was about 5%.

The non-crystallised portion of the product was reexamined by analytical hplc to show presence of both adducts as well as a third minor component. After the development of a better analytical hplc system (Figure 7) preparative HPLC separation of components, a, b, and c was attempted with difficulty because overloading occured at very low levels (Figure 8). Adduct (261) was obtained and spectroscopically examined. Two H-NMR distinguishing features of the adducts (261) and (262) are:

1) a W-coupling between H-12 and H-5 in (262) which is absent in (261)
2) (262) exhibits a broad singlet at 2.57δ for H-5 suggesting an endo isomer. (261) exhibits a doublet at 3.31δ for H-10, with a coupling constant of 4.5Hz (endo isomer), thus rendering the coupling pattern of H-1 in (261) more complex.

Figure 7 : Change of retention time of components by the choice of eluent.

A) CH_2Cl_2 : CH_3CN

97 : 3

B) CH_2Cl_2 : CH_3CN : ν-OH : C_6H_{14}

1 : 3 : 2 : 94

Hypersil silica 5µm

(25 X 0.46cm)

10mm/min

3ml/min

λ_{max} = 235nm

a = non-orth-adduct (262)

b = ortho-adduct (261)

c = unknown

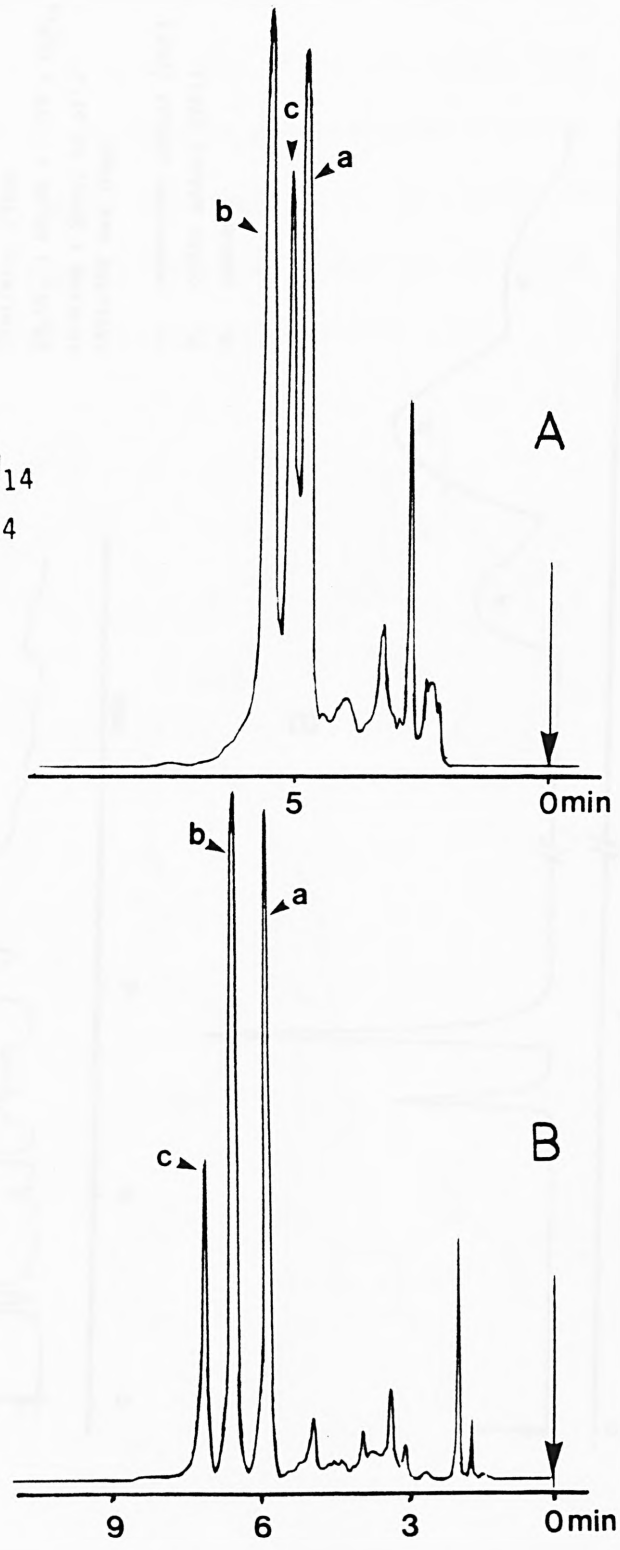
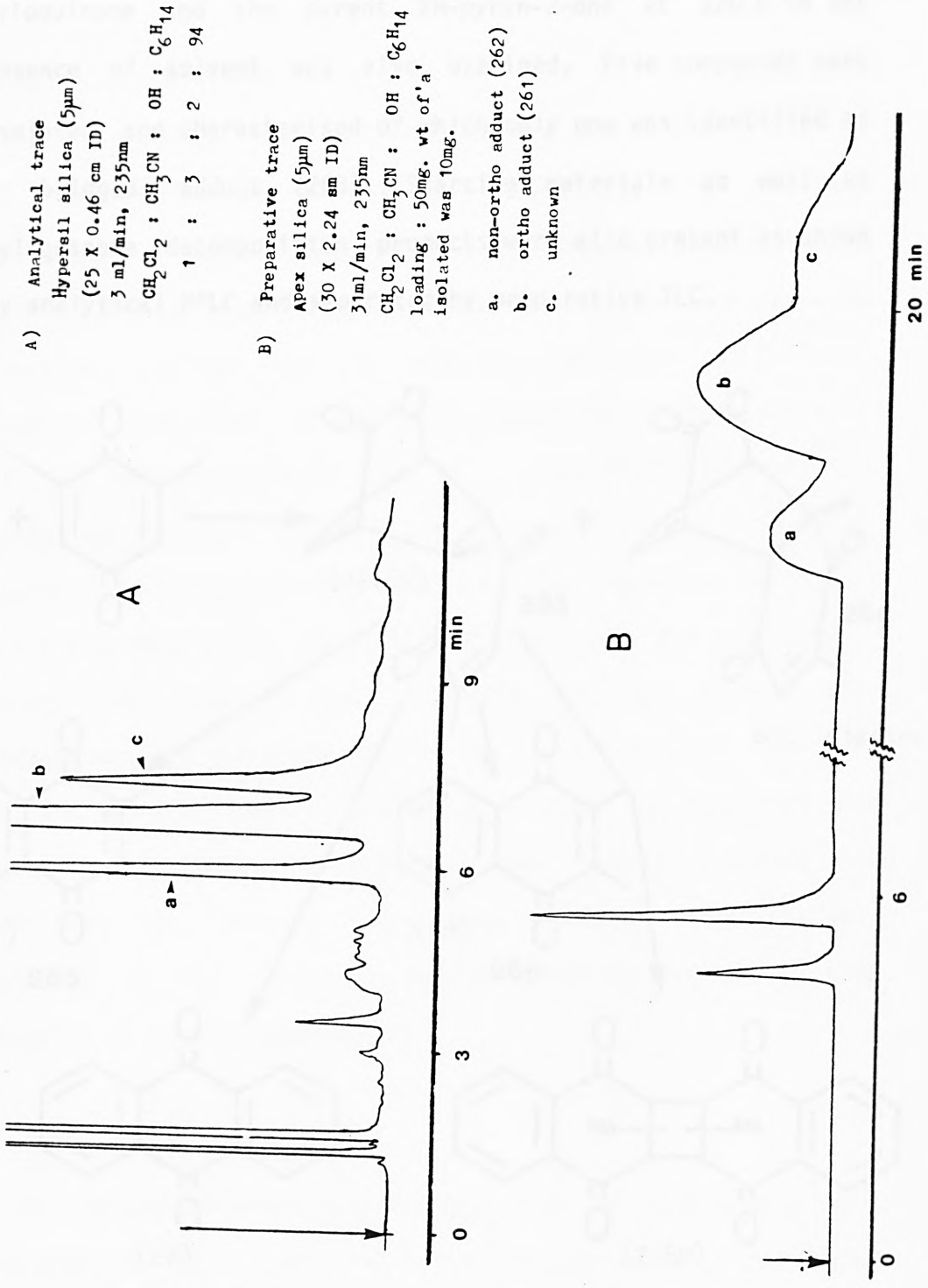
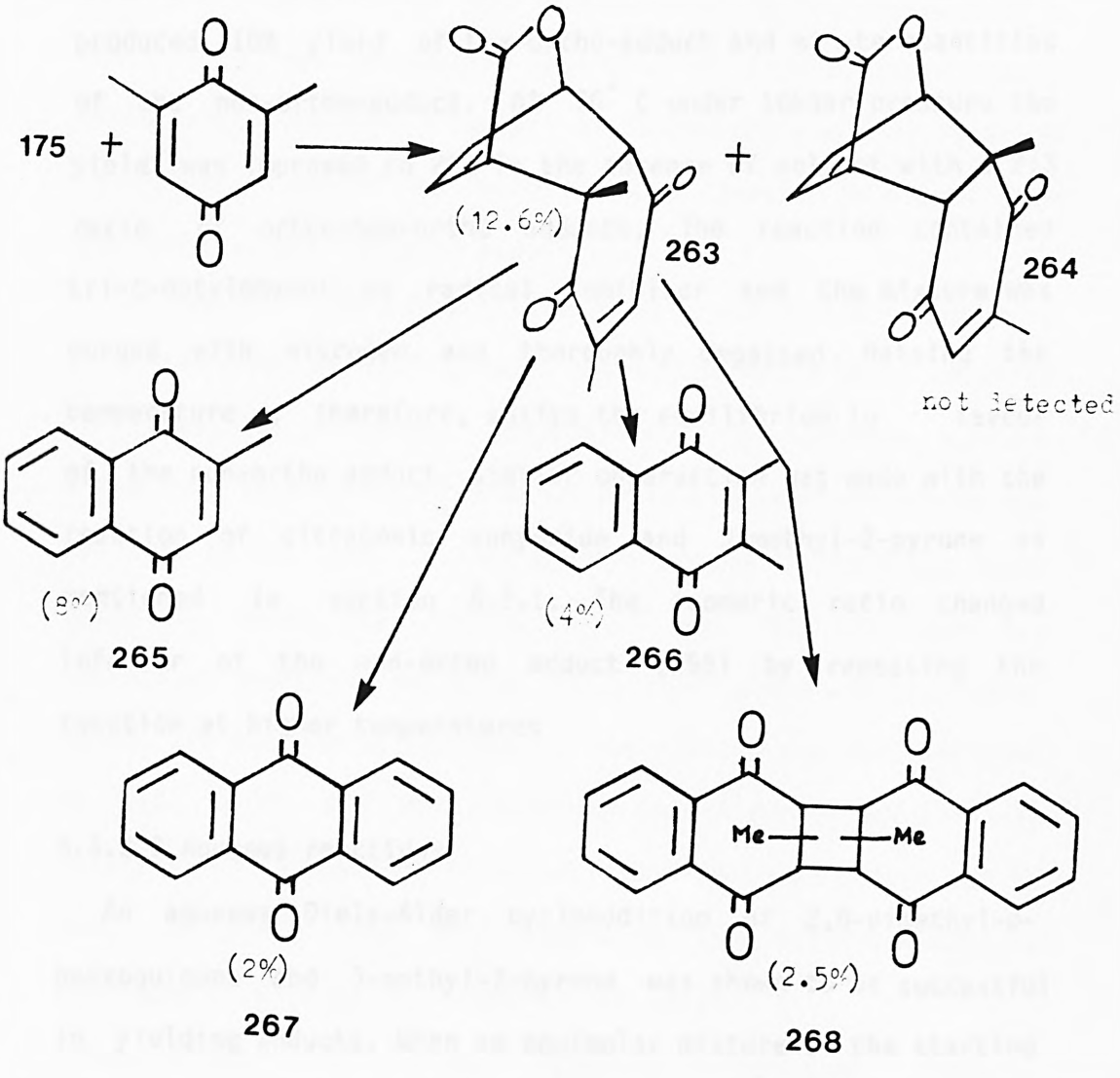


Figure 8 : Preparative HPLC separation of the xyloquinone adducts.



Mass spectrum of the third component, c, was obtained. Further investigation was abondoned owing to lack of sufficient sample.

During our investigations the thermal reaction between xyloquinone and the parent 2H-pyran-2-one at 120°C in the absence of solvent was also examined. Five compounds were isolated and characterised of which only one was identified as a bridged adduct (263). Starting materials as well as xyloquinone decomposition products were also present as shown by analytical HPLC and separated by preparative TLC.



Radical reactions, double cycloadditions, as well as decompositon reactions occur simultaneously and these account for such variety of by-products and their low yields. It is likely that (268) is a secondary by-product formed from dimerisation of (265).

8.3.2.2 High pressure reactions.

High pressure reactions were carried out at the University of Southampton and University of Reading. High pressure reactions of 3-methyl-2-pyrone and 2,6-dimethyl-p-benzoquinone were examined under varying conditions. A cold high pressure reaction carried out in methylene chloride as solvent, produced 10% yield of the ortho-adduct and minute quantities of the non-ortho-adduct. At 70° C under 10kbar pressure the yield was improved to 20% in the absence of solvent with a 2:3 ratio of ortho:non-ortho adducts. The reaction contained tri-t-butylphenol as radical inhibitor and the mixture was purged with nitrogen and thoroughly degassed. Raising the temperature , therefore, shifts the equilibrium in favour of the non-ortho adduct. Similar observation was made with the reaction of citraconic anhydride and 3-methyl-2-pyrone as mentioned in section 8.2.1. The isomeric ratio changed infavour of the non-ortho adduct (255) by repeating the reaction at higher temperatures

8.3.2.3 Aqueous reactions

An aqueous Diels-Alder cycloaddition of 2,6-dimethyl-p-benzoquinone and 3-methyl-2-pyrone was shown to be successful in yielding adducts. When an equimolar mixture of the starting materials was stirred vigorously in 50M of water at 50-60°C

for 100hrs, 10% yield of the crystalline product was isolated after removal of excess starting materials by distillation, followed by crystallisation from ether. The spectroscopic data was identical to that of the crystals from the high pressure reaction identified as the ortho-adduct, and analytical HPLC examination provided further confirmation that only trace quantities of non-ortho-adduct were formed in the aqueous reaction (Figure 9).

8.3.2.4 Catalysed reaction

The possibility of acceleration of the reaction between 3-methyl-2H-pyran-2-one and xyloquinone in the presence of a Lewis acid was thoroughly investigated. Five different Lewis acids were examined. A summary of conditions used are reported in Table 7. Some of the reactions were repeated to ensure that the results obtained were genuine.

In general, the Lewis acid was dissolved in the volume of a dried solvent and then quinone was added, which often resulted in formation of bright colourations. For instance, quinone added to stannic chloride solution in nitromethane turned the mixture bright red. To this mixture pyrone solution was added dropwise. After the completion of the reaction, water was added to hydrolyse the acid. The organic phase was separated, dried and evaporated to dryness. The residue was then analysed by TLC, ^{1}H-NMR and HPLC. Antimony pentaflouride was the only catalyst which appeared to cause formation of an adduct but in about 5% yield. The HPLC retention time and H-NMR signals suggested this to be the ortho-adduct (261).

Examination of high pressure reactions between

Table 7 : Summary of catalysed cycloadditions attempted with xyloquinone

EXPERIMENTAL CONDITIONS	YIELD
$BF_3.OEt_2$(1eq) in CH_2Cl_2 (10ml). Quinone added then pyrone dropwise (0.5hr) and refluxed (4.5hr)	non
$AlCl_3$(1eq), powder suspension in CH_2Cl_2(25ml). Quinone added and then pyrone. a) 1hr,0°C, b) 24hr, 0°C, c) 72hr, room temp.	non
$AlCl_3$(1eq) in excess CH_2Cl_2 or $CHCl_3$. Quinone added and then pyrone. 2hr, room temp.	non
$SnCl_4$(1eq) in CH_3NO_2 (25ml). Quinone added and then pyrone dropwise (1hr). 2hr, 0°C	non
$SnCl_4$(1eq) in CH_3NO_2 (25ml). Quinone and pyrone added and refluxed. a) 1hr, 25°C b) 72hr, 100°C	non
$TiCl_4$(1eq) in CH_2Cl_2 (50ml). Quinone added and then pyrone dropwise (1hr). 2hr, room temp.	non
SbF_5(1eq) in $CHCl_3$ (100ml). Quinone added and then pyrone dropwise (1hr). 2hr, room temp	traces of (261)

a. solvents were all dried before use

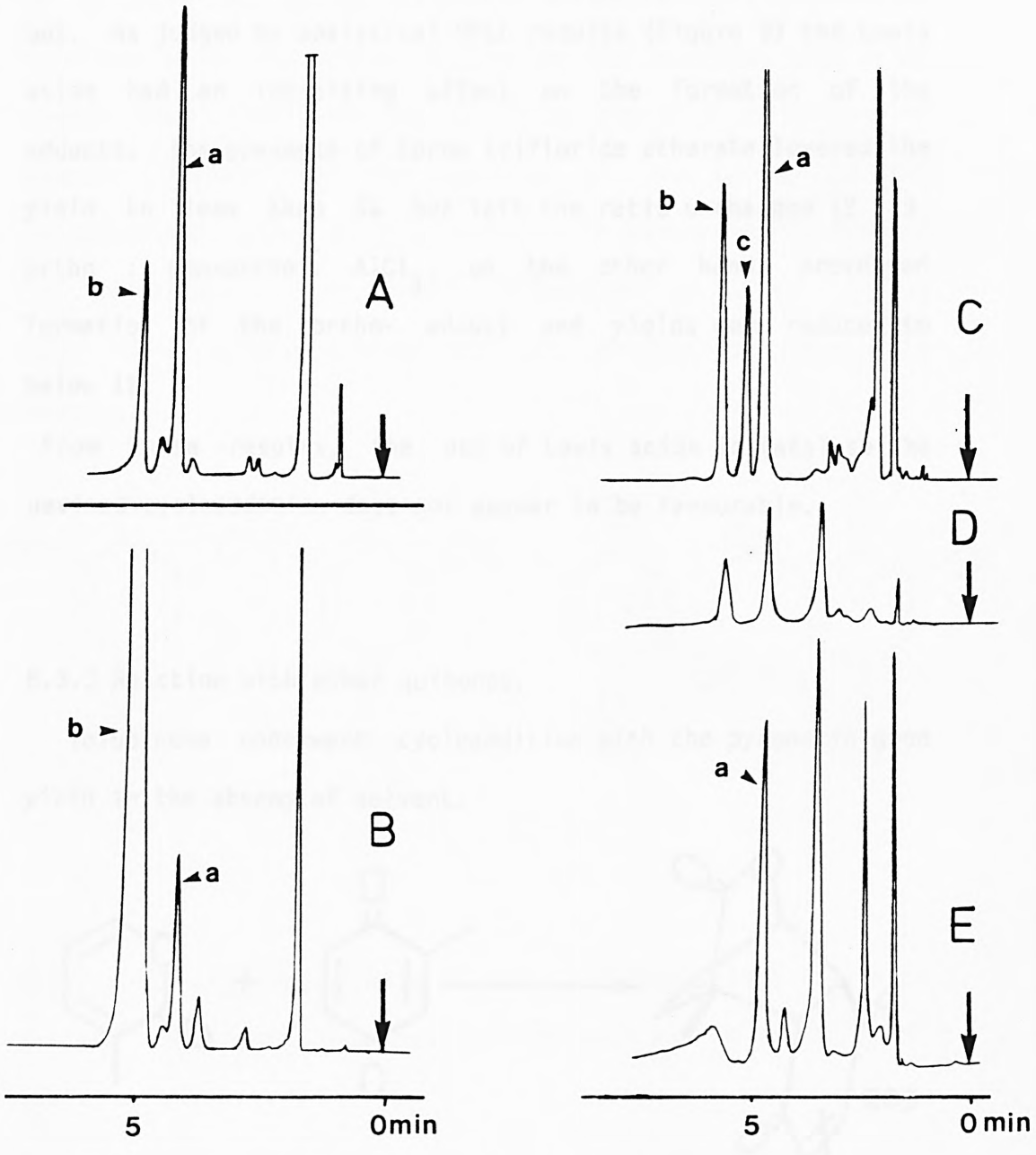
b. reactions were all stirred

c. 1:1:1 ratio of catalyst:diene:dieneophile used

d. 0.05molar scale

e. quinone complexed with Lewis acid in solvent prior to the addition of pyrone

Figure 9 : HPLC analysis of products of reaction between 3-methyl-2-pyrone and xyloquinone performed under



A) high press., 70°C 48hr B) H_2O, 40°C, 48hr(1:1:1),

C) sealed tube, 115°C, 48hr, (1:1),

D) high press., 70°C $BF_3.OEt_2$ cat., (1:1:1),

E) high press., 70°C, $AlCl_3$cat., (1:1:1)

a = non-ortho (262), b = ortho (261), c = unknown,

Hypersil silica 5µm, 25 X .46cm, 235nm, 2ml/min,

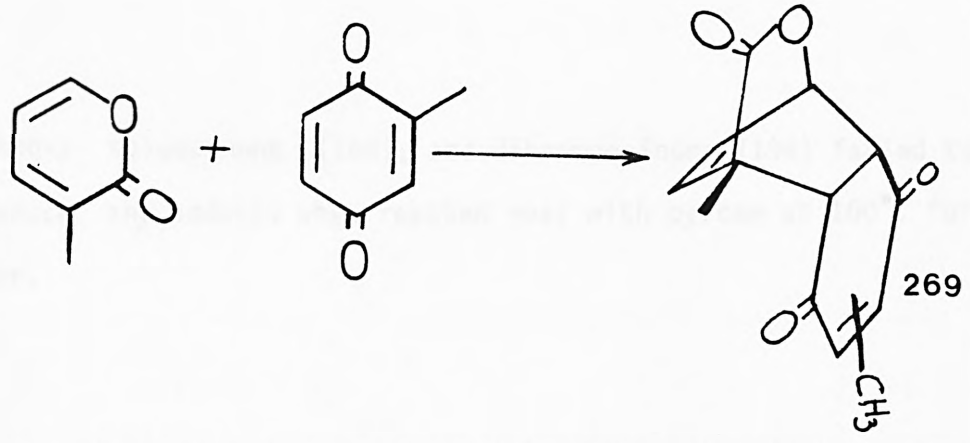
CH_2Cl_2/CH_3CN 98 : 2, 10mm/min

3-methyl-2-pyrone and xyloquinone in the presence of equimolar amounts of the Lewis acid $AlCl_3$ and $BF_3.OEt_2$ were also carried out. As judged by analytical HPLC results (Figure 9) the Lewis acids had an inhibiting effect on the formation of the adducts. The presence of boron trifloride etherate lowered the yield to less than 5% but left the ratio unchanged (2 : 3 ortho : non-ortho). $AlCl_3$, on the other hand, prevented formation of the ortho- adduct and yields were reduced to below 1%.

From these results, the use of Lewis acids to catalyse the devised cycloaddition does not appear to be favourable.

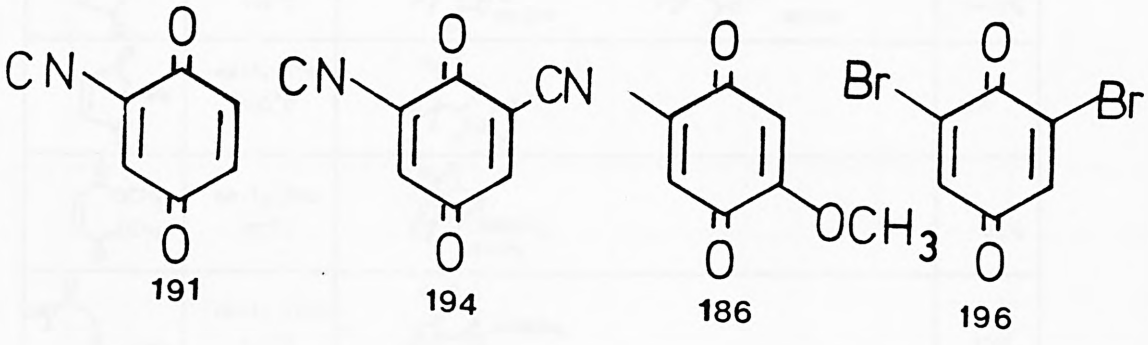
8.3.3 Reaction with other quinones.

Toluqinone underwent cycloaddition with the pyrone in good yield in the absence of solvent.



The analyses result suggested formation of a single isomer. No signal was detected which could have been due to isomeric impurity. Characteristic IR bands at 1760cm^{-1} (CO str. lactone), and 1675cm^{-1} (CO str. ketone) were present. The adduct (269) was crystalline and attempts to determine the orientation of the cycloadduct using high field ^{1}H-NMR and ^{13}C-NMR analysis failed

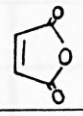
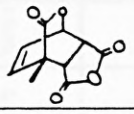
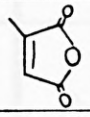
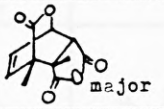
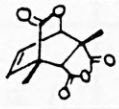
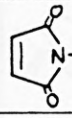
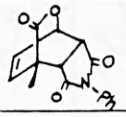
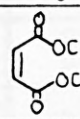
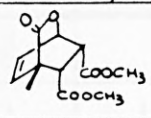
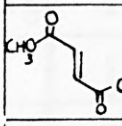
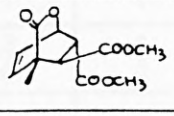
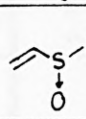
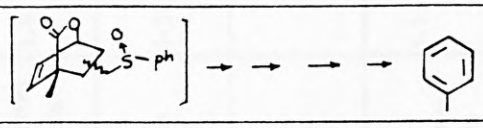
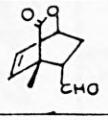
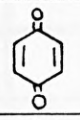
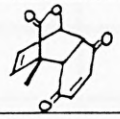
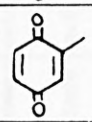
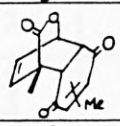
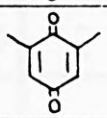
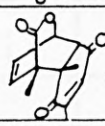
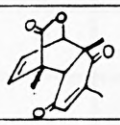
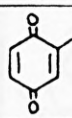
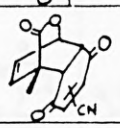
Mono- and di- cyano-quinones (191) and (194) were found to be unstable and decomposed during the attempted cycloaddition reaction with the pyrone. Monitoring the reactions with ^{1}H-NMR showed that (191) reacted to give possibly a mixture of adducts formed from the addition of the pyrone to the unsubstituted side of the quinone. On attempting to isolate the cycloadducts the product decomposed on silica. On the other hand dicyano-quinone did not produce any detectable adduct.



Methoxy toluquinone (186), and dibromoquinone (196) failed to produce any adducts when reacted neat with pyrone at 100°C for 12hr.

Appendix I

Successful cycloaddition reactions of 3-methyl-2-pyrone

	Condition	Product	Yield
	neat, 1hr 110°C		80%
	neat, 24hr 110°C	 major  minor	5-10%
	neat, 10hr 100°C		80%
	neat, 8hr 100°C		85%
	neat, 48hr 100°C		10%
	neat, 48hr 100°C		60%
	neat, 4 wk room temp	 + small amount of other isomer(s)	80%
	neat, 8hr 85°C		75%
	neat, 8hr 85°C		50%
	neat, 72hr 110°C	 major  minor	5%
	neat, 8hr 100°C	 decomposed	

Appendix II

Comparison of spectroscopic data of pyrone adducts

$ values of CO lactone str given in cm^{-1}

Coupling constants quoted in Hz

	$J_{1,6}$		W cplg	IR$ CO str		$J_{1,6}$		W cplg	IR$ COstr		$J_{1,10}$		W cplg	IR$ COstr
	4.9	Endo	0.6			3.8	Endo	bd	1750		4.4	Endo	0.25	1760
	5.0	Endo	---			3.5	Endo	2.0	1760		4.8	Endo	1.0	1760
	---	Endo	bd			3.6	Endo	---	1760		4.5	Endo	---	1750
*	4.5	Endo	--	1750		3.5	Endo	---			--	Endo	0.6	1760
	4.5	Endo	?	1760							---	Endo	bd	1760
*	---	Exo		1750	*	3.2	Endo	0.7	1770	*	4.0	Endo		1755
	5.0	Endo	bd	1765	*	3.7	Endo	---		*	0.0	Exo		1744
										*	4.0	Endo		1745

Appendix III

^{1}H-NMR data for the quinonoid adducts.

		H1	H4	H5	H7	H 8	H10	H11	H12	Coupling Constant (Hz)
	a	5.47	1.48 **Me**	3.03	6.73	6.63	3.74	6.50	6.24	$J_{1,10}$ =4.4 $J_{5,10}$ =8.7 $J_{12,5}$ =0.25 $J_{1,11}$ =5.0 $J_{12,11}$=7.7 $J_{1,12}$ =2.0 $J_{8,7}$ =10.4
	a	5.49	1.46 **Me**	3.05	1.92 **Me**	6.52	3.74	6.53	6.24	$J_{1,10}$ =4.8 $J_{5,10}$ =8.5 $J_{12,5}$ =1.2 $J_{1,11}$ =5.0 $J_{12,11}$=7.8 $J_{1,12}$ =2.0 $J_{8,7}$ =1.5
	a	5.35	1.46 **Me**	1.32 **Me**	1.94 **Me**	6.56	3.31	6.45	6.20	$J_{1,10}$ =4.5 $J_{1,11}$ =5.5 $J_{12,11}$=8.0 $J_{1,12}$ =2.0 $J_{8,7}$ =1.5
	a	5.10	1.46 **Me**	2.57	6.66	1.89 **Me**	1.38 **Me**	6.49	6.13	$J_{12,5}$=0.6 $J_{1,11}$ =5.0 $J_{12,11}$=7.6 $J_{1,12}$ =1.9 $J_{8,7}$ =1.5
	a	5.33	3.94	2.96	6.74	1.94 **Me**	1.50 **Me**	6.59	6.45	$J_{12,5}$= 0.5 $J_{1,11}$ =4.9 $J_{12,11}$=7.5 $J_{4,12}$ =6.0 $J_{1,12}$ =2.0 $J_{8,7}$ =1.6 $J_{4,5}$ =2.5
	c	5.88	4.40	3.66	6.98	6.98	3.98	6.66	6.66	$J_{1,10}$ =4.0 $J_{5,10}$ =9.0
★	b	5.69	4.24	3.44	6.80	6.80	3.77	6.54	6.54	$J_{1,11}$ =3.0 $J_{4,12}$ =4.0 $J_{1,12}$ =3.0 $J_{4,11}$ =4.0 $J_{4,5}$ =3.0
	c	5.92	4.28	3.34	7.12	7.12	3.34	6.80	6.80	$J_{1,10}$ =0.0 $J_{5,10}$ =9.5
★										$J_{1,11}$ =3.5 $J_{4,11}$ =4.0 $J_{1,12}$ =3.5 $J_{4,5}$ =0.0
	b	5.68	4.20	3.38	6.68	2.00	3.74	6.52	6.52	$J_{1,10}$ =4.0 $J_{5,10}$ =9.5 $J_{1,11}$ =3.5 $J_{4,12}$=3.5 $J_{1,12}$ =3.5 $J_{4,11}$ =3.5 $J_{4,5}$ =3.0
★										

4-Methyl-2-oxa-3-oxobicyclo[2.2.2]oct-7-ene-5,6-dicarboxylic anhydride (248)

A mixture of the pyrone (0.25g, 0.00225mol), maleic anhydride (0.22g, 0.00225mol) and dried toluene (15ml) was refluxed for 11hr. After cooling a white precipitate was formed. Toluene was removed under reduced pressure and the residue washed with ether. After drying (vac. oven, 40°, 24hr) 370mg (80%) yield of the white crystalline cycloadduct was obtained. M.Pt. = 190-192°C. ^{1}H-NMR (400MHz) (CD_3CN)δ: 1.64 (s, 3H), 3.47 (dd, 1H, J = 0.6, 8.4Hz), 4.12 (dd, 1H, J = 4.9, 8.4Hz), 5.57 (dt, 1H, J = 2.0, 4.9, 4.9Hz), 6.42 (ddd, 1H, J = 2.0, 7.8, 0.6Hz), 6.66 (dd, 1H, J = 4.9, 7.8Hz). IR (KBr disc) : 2950cm^{-1}, 1900-1680cm^{-1} (C=O str ester and anhydride), 1230cm^{-1}, 1190cm^{-1}, 980cm^{-1}, 904cm^{-1}. Elem. Anal. : cal C 57.70, H 3.87; fou. C 57.69, H 3.85. Mass spect. : 164.0489(164.0639, M+ - CO2), 162, 137, 136, 134, 118, 110, 93, 92 and 91 (100%), 90, 82, 79, 58.

N-Phenyl-4-methyl-2-oxa-3-oxobicyclo[2.2.2]oct-7-ene-5,6-dicarboxamide (205)

The literature procedure was repeatable . However, yields can be improved further from 60% to 80% by not using any solvent. The pyrone (0.55g, 0.005mol) and N-phenyl maleamide (0.865g, 0.01mol) were stirred together at 90-100°C under nitrogen for 10hr. The solid was powdered and washed with ether. 1.1g (80%) of adduct was obtained. The white solid was recrystallised from methanol. M.Pt. : 175-177°C (lit 173-175° C). ^{1}H-NMR (220MHz)(CD_3CN)δ : 1.74 (s,3H), 3.21 (bd, 1H, J = 8.0Hz), 3.93 (dd, 1H, J = 5.0, 8.0Hz), 5.60 (ddd, 1H, J = 2.0, 5.0, 5.0Hz), 6.46 (bdd, 1H, 2.0, 7.8Hz), 7.22 (m,

2H), 7.52 (m, 3H). IR (KBR disc) : 3090-3050cm^{-1}, 3000-2900cm^{-1}, 1765cm^{-1} (CO str. lactone), 1700cm^{-1}, 1600-1490cm^{-1}. Mass spec. : 283.0833(283.1091, M+), 240, 239, 238, 237, 209, 193, 119, 93, 92 and 91 (100%), 90, 89, 77, 65, 64, 63, 51. Elem. Anal. : cal. C 67.84 H 4.62 N 4.94, fou. C 67.79 H 4.56 N 4.84. ^{13}C-NMR (DMSO-d_6, decoupled, TMS as reference) δ : 16.01(Me), 42.17, 45.84(C-4), 46.37, 72.00 (C-1), 127.55 and 129.51 and 129.75 (phenyls), 131.66 (C-8), 132.47 (quaternary C in Ph), 137.52 (C-7), 173.65 and 173.90 and 174.75 (C=O).

5,6-Dicarbomethoxy-4-methyl-2-oxa-3-oxobicyclo[2.2.2]-oct-7-ene (249) 3-Methyl-2-pyrone (0.5g, 0.0045mol), and dimethyl maleate (0.655g, 0.0045mol) were stirred together at 100-110 C for 8hr under nitrogen. The solid obtained was left under vacuum at 50°C to remove unreacted starting materials. 0.98g (85%) was obtained which was recrystallised from ether/hexane to give white needles of melting point : 153-155° C. ^{1}H-NMR (CD_3CN) (400MHz) δ: 1.37 (s, 3H), 3.23 (dd, 1H, J = 2.0, 11.0Hz), 3.55 and 3.62 (2s, 6H, $COOCH_3$ hydrogens), 3.75(dd, 1H, J = 11.0, 3.5Hz), 5.37 (ddd, 1H, J = 5.0, 3.5, 1.0Hz), 6.18 (ddd, 1H, J = 7.9, 2.0, 1.0Hz), 6.66 (dd, 1H, J = 7.9, 5.0Hz). IR (KBr disc) : 3500-3400cm^{-1}(C=C-H str.), 3000-2900cm^{-1}, 1760cm^{-1}, 1730cm^{-1}, 1220cm^{-1}. Mass spect. : 223, 210.0668(210.1104, M+ $-CO_2$), 178, 151, 150, 119, 113, 110, 107, 105, 92, 91(100%), 84, 82, 77, 65, 63, 59. Elemental Analysis : cal. C 56.69 H 5.55; fou. C 56.46 H 5.48.

5,6-Dicarbomethoxy-4-methyl-2-oxa-3-oxobicyclo[2.2.2] oct-7-ene (250)

3-Methyl-2-pyrone (0.5g 0.0045mol) and dimethyl fumarate

(0.655g, 0.0045mol) were stirred together at 100-110°C for 48hr under nitrogen. After the removal of excess starting materials with distillation under vacuum, 0.120g of a crystalline substance was obtained. This was recrystallised from ether/hexane. Although prior to removal of the starting materials ^{1}H-NMR showed presence of another minor adduct isomers, only the major one was obtained after the final stage of purification by applying vacuum for 6hr at 65°C. M.Pt. : 105-106° C. ^{1}H-NMR (CD_3CN)δ(220MHz) : 1.36 (s, 3H), 2.94 (d, 1H, J = 5.5Hz), 3.60 (dd, 1H, J = 5.5, 3.6Hz), 3.60 and 3.68 (2s, 6H, $COOCH_3$ hydrogens), 5.48 (ddd, 1H, J = 5.5, 2.0, 3.6Hz), 6.36 (dd, 1H, J = 7.7, 2.0Hz), 6.60 (dd,1H, J = 7.7, 5.5Hz). IR (KBr disc) : 3500-3400cm^{-1}(C=C-H str), 3020-2900cm^{-1}, 1760cm^{-1}, 1730cm^{-1}, 1215cm^{-1}. Mass Spect. : 223, 210.0918(210.1104, M+ -CO2), 178, 152, 151, 150, 119, 113, 110, 92, 91(100%), 777, 69, 65, 63, 59, 51. Elemental analysis : cal, C 56.69 H 5.54; fou C 56.89 H 5.55.

5-Formyl-4-methyl-2-oxa-3-oxobicyclo[2.2.2]oct-7-ene (251)

3-Methyl-2-pyrone (0.5g, 0.0045mol) and excess amount of acrolein (5ml) were mixed together and stirred for one week at room temperature. After removing the excess starting material under vacuum the crude residue was chromatographed on silica (Rf = 0.5) with diethyl ether as eluent. 0.6g (80%) yield of an adduct was obtained as colourless oil which solidified in fridge. M.Pt. : 52-57° C. ^{1}H-NMR (CD_3CN) (220MHz)δ: 1.58 (s, 3H), 2.08 (ddd, 1H, J = 14.0, 3.8, 1.5Hz), 2.42 (ddd, 1H, J = 14.0, 10.0, 3.8Hz), 2.74 (bddd, 1H, J = 10.0, 3.8, 3.0Hz), 5.34 (dddd, 1H, J = 5.0, 3.8, 2.0, 1.5Hz), 6.29 (bdd, 1H, J =

7.5, 2.0Hz), 6.66 (dd, 1H, J = 7.5, 5.0Hz), 9.59 (d, 1H, J = 3.0Hz). IR (melt) : 3500-3400cm^{-1} (C=C-H str.), 3000-2700cm^{-1}, 1750cm^{-1}, 1720cm^{-1}, 1620cm.$^{-1}$

1,2,5-trimethylbicyclo[2.2.2]oct-7-ene-2,3;5,6-tetra-carboxylic dianhydride (253)

3-Methyl-2-pyrone (0.57g,0.0052mol) and citraconic anhydride (0.58g, 0.005mol) were dissolved in methylene chloride(10ml) and heated at 200°C for 24hr in a tubing bomb. On evaporation of the solvent an oil appeared which on addition of little ether produced crystals, which were filtered to give 0.1g (13%) of the white crystalline bis-adduct (253). M.Pt. : 236-238°C(little sublimation from 180° C). ^{1}H-NMR (CD_3CN)δ (400MHz) : 1.48 (s, 3H), 1.53 (s,3H), 1.68 (s, 3H), 3.02 (s, 1H), 3.30 (d, 1H, J = 3.3Hz), 3.34 (ddd, 1H, J = 6.0, 3.3, 1.4Hz), 6.16 (dd, 1H, J = 8.3, 1.4Hz), 6.42 (dd, 1H, J = 8.3, 6.0Hz). IR (KBr disc) : 3000-2900cm^{-1} (-Me, $-CH_2$ str.), 1840 and 1780cm^{-1}, 1450 and 1400cm^{-1}, 1290-1190cm^{-1}, 1050-900cm^{-1}, 750cm^{-1}, 720cm^{-1}, 700cm^{-1}. Mass Spec. : 218, 178.0503(178.0058), 151, 150, 113, 107, 106(100%), 105, 91. Elem. Anal : cal. C 62.07 H 4.84; fou. C 62.04 H 4.85.

4,5-Dimethyl-2-oxa-3-oxobicyclo[2.2.2]oct-7-ene-5,6-dicarboxylic anhydride (255)

1) without catalyst

A number of attempts using benzene and toluene as solvents under reflux failed to produce any detectable amounts of adducts. However when the reaction was done with no solvent two anhydride adducts were obtained. 3-Methyl-2-pyrone (0.5g,

0.0045mol) was mixed with excess of citraconic anhydride (5ml). After the mixture was stirred under nitrogen for 24hr at 100° C, excess anhydride was removed by distillation under vacuum and the residue was mixed with little ether and placed in freezer. After a day white crystals were formed which were filtered and dried under vacuum (24hr, 25°C), to give 0.15g (15%) yield of a mixture of adducts. ^{1}H-NMR examination of the crude residue suggested a ratio of 5 : 1 and spectroscopic data obtained on the major isomer, separated by differential recrystallisation, confirmed the structure to be ortho, (255). M.Pt. : 120-175° C(crystals - powder - glass - melt). ^{1}H-NMR (CD_3CN) (220MHz) δ : 1.48 (s, 3H), 1.62 (s, 3H), 3.82 (d, 1H, J = 5.0Hz), 5.60 (ddd, 1H, J = 5.0, 4.7, 2.0Hz), 6.46 (dd, 1H, J = 7.6, 2.0Hz), 6.76(dd, 1H, J = 7.6, 4.7Hz). IR (nujol) : 1870-1740cm^{-1} (COO str lactone and anhydride), 1230cm^{-1}, 1190cm^{-1}, 960cm^{-1}, 930cm^{-1}. Mass Spect. :(222.0767, M+, absent), 178, 162, 150, 106 and 91 (100%), 77, 65, 63, 53, 51.

The anhydride (255) is in equilibrium with the diacid (256) in the presence of water and the acid recyclised in CD_3CN after two days. Recrystallisation from hot water produced cubical crystals which contained equivalent mole of water. M.Pt. : 150-175° C(crystals - glass - melt). ^{1}H-NMR (CD_3CN) (220MHz) δ : 1.35 (s, 3H), 1.38(s, 3H), 3.28 (d, 1H, J = 3.5Hz), 4.00 (b, acidic hydrogens), 5.34 (ddd, 1HY, J = 3.5, 2.0, 5.0Hz), 6.21 (dd, 1H, J = 7.5, 2.0Hz), 6.66 (dd, 1H, J = 7.5, 5.0Hz). IR (Nujol) : 3540 and 3480cm^{-1}(hydroxyl str in COOH), 1700 and 1740cm^{-1}(CO str in lact. and acid). Elemental Analysis : cal C 51.16, H 5.45(+1mole of water); fou C 50.99, H 5.37.

Repeating the cyclisation reaction at 120° C under similar conditions was shown by ^{1}H-NMR to prduce a mixture of adducts with a isomeric ratio of 1 : 1 .

2) with catalyst

Distilled 3-methyl-2-pyrone (0.5g, 0.0045mol), the anhydride (0.5g, 0.0045mol), and boron trifluoride etherate (0.64g, 0.0045mol) were mixed together in a flask and stirred under anhydrous conditions at 60-90°C for 24hr. The ^{1}H-NMR of the mixture at this stage showed presence of only starting materials. Further heating at 120°C over weekend did little as , when the H-NMR was taken in CD_3CN, no sign of adduct was present. The starting material had decomposed slightly. In comparison, in the absence of Lewis acid at 120°C after 10hr, a mixture of isomeric adducts were formed which are readily detectable in crude mixture by ^{1}H-NMR. Thus the Lewis acid added to the cyclisation lowered the yield of the products to undetectable levels.

Reaction with phenyl vinyl sulphoxide

3-methyl-2-pyrone (0.4g, 0.0036mol) and phenyl vinyl sulphoxide (1g, 0.0066mol) were mixed together and stirred at 100° C for 48hr under nitrogen. The reaction was monitored by running ^{1}H-NMR spectra in $CDCl_3$ at 2hr intervals which showed the gradual disappearance of the pyrone and formation of a major product. This was shown to be toluene using ^{1}H-NMR and analytical HPLC on silica with hexane as eluent. 60% yield of toluene was estimated by ^{1}H-NMR.

Reaction with nitrosobenzene to give (258)

3-Methyl-2-pyrone (0.5g, 0.0045mol), was dissolved in methylene chloride (100ml) and its temperature lowered to -10°

C. Dropwise over a period of 1hr, solution of nitrosobenzene (0.48g, 0.0045mol) in methylene chloride (50ml) was added under nitrogen atmosphere. The mixture was stirred magnetically and allowed to warm up to room temperature (1hr). The yellow-green solution was evaporated down which turned yellow-brown. The residual oil was subjected to preparative TLC separation (methylene chloride : ether 94 : 6). Several bands were obtained, only one of which appeared to be reasonably stable to be characterised (Rf = 0.25). The yield of this band after several runs was 10-30mg. Preparative hplc separation to obtain analytically pure sample was carried out on a silica column with methylene chloride : acetonitrile (92 : 8) as eluent and flow rate of 5ml/min. 10mg samples were efficiently purified on a 25cm X 1cm ID column. M.Pt. : 128-130° C. ^{1}H-NMR ($CDCl_3$) δ (400MHz) : 2.42 (s, 3H), 6.68 (bd, 1H, J = 15.5Hz), 7.51 (m, 3H), 7.73 (m,2H), 7.82(dd, 1H, J = 15.5, 9.5Hz), 7.90(bd, 1H, J = 9.5Hz). IR (nujol) : 1650cm^{-1}, 1510cm^{-1}, 1250cm^{-1}, 1060cm^{-1}. Mass spect. : 189.0682(189.0924, M+), 173, 149, 146(100%), 130, 118, 117, 107, 104, 91, 82, 77. Elemental Analysis : cal C 69.82 H 5.81 N 7.4 (based on $C_{11}H_{11}NO_2$ formula); fou. C 69.82 H 5.84 N 7.77).

1-Methyl-6-phenyl-2-thia-6-aza-8-oxa-7-oxobicyclo[3.2.1] oct-3-ene (247c)

3-Methyl-thio-pyrone (0.4g, 0.00318mol), was dissolved in dry methylene chloride (10ml) under nitrogen. The green solution of nitrosobenzene (0.34g, 0.00314mol) in methylene chloride (5ml) was added dropwise over ten minutes with stirring. Yellow solution turned green and, after 10hr, dark

brown-green. Solvent was evaporated and the residue chromatographed on silica using benzene as carrier (Rf = 0.35). This band contained a crude amount of a white substance (0.11g, 14.8%). Analytical HPLC examination of the crude product on silica column with methylene chloride : hexane (90 : 10), flow rate of 2ml/min, and monitored at 241nm showed a single peak whose H-NMR suggested a mixture of two products. Similarly result was obtained on an analytical APS-silica column with methylene chloride : hexane (10 : 90). Sublimation under 0.5mm at 100°C yielded a white solid (a yellow subtance co-sublimed at slightly higher temperature which was avoided carefully), 20mg of which was analytically pure. M.Pt. : 111-112° C (sublimes at 0.5mmHg/100°C). ^{1}H-NMR (CD_3CN)δ(220MHz) : 1.93 (s, 3H), 5.88(dd, 1H, J = 1.0, 4.0Hz), 6.32 (dd, 1H, J = 10.0, 4.0Hz), 6.59 (db, 1H, J = 10.0, broad), 7.08 (dd,1H, J = 7.3, 1.0Hz), 7.48 (dd, 2H, J = 7.3, 7.2Hz), 7.62 (dd, 2H, J = 7.5, 1.5Hz). IR (nujol) : 1705cm^{-1}(C=O str amide), 1600cm^{-1} (C=C conj). UV (Abs. Eth.) : 206nm(ε=8210), 240nm(ε=9360). Mass spect. : 233.0455 (233.1524, M+), 191, 190, 162, 104, 86, 77, 59, 51. Elem. Anal. : cal. C 61.78 H 4.75 N 6.00; fou. C 61.72 H 4.74 N 5.93.

4-Methyl-3,6,9-bioxa-2-oxatricyclo[4.4.0.2^{1,4}]dodec-7,11-diene (260)

1) Thermal reaction

3-Methyl pyrone (0.5g, 0.0045mol), 0.5g of p-benzoquinone, and dried benzene (10ml) were mixed and refluxed for 6hrs under anhydrous nitrogen atmosphere. The contents of flask was

concentrated and little ether was added. Pale yellow crystals appeared which were filtered. 100mg (10%) yield of the yellow crystals was obtained.

Reaction repeated in dried toluene led to isolation of slightly lower yields of adduct perhaps owing to slight decomposition of product. Reaction repeated in the absence of solvent at 100°C with little 2,4,6-tri-t-butyl phenol as inhibitor and stirring under dried nitrogen atmosphere solidified overnight. The solid mass was crushed and washed with little ether on Buchner funnel and then recrystallised from ethyl acetate. 0.81g (81%) yield of the mono-adduct obtained was analysed. MPt= 135-143°C. ^{1}H-NMR (CD_3CN)δ: 1.48(d, 3H, J=0.25Hz); 3.03(m, 1H, J= 8.7, 0.25,0.5Hz); 3.74(dd, 1H, J= 8.7, 4.4, 0.3Hz); 5.47(ddd, 1H, J= 5.0, 2.0, 4.4, 0.25Hz); 6.24(dd, 1H, J= 7.7, 2.0, 0.25Hz); 6.50(dd, 1H, J= 7.7, 5.0, 0.25Hz); 6.63(d, 1H, J= 10.4, 0.4Hz); 6.73(d, 1H, J= 10.4, 0.5Hz). IR(KBr disc) : 3100-2900cm^{-1}(C-H str.); 1760cm^{-1}(CO str. lactone); 1670cm^{-1}(CO str. ketone); 1350-1450cm^{-1}; 1300-1100cm^{-1}, 1000cm^{-1}. Mass Spec.(20ev) : 218.0611 (218.0785, M+), 174, 172, 131, 119, 118, 115, 110, 107, 91, 90, 82(100%), 69, 63, 58, 54, 53, 51. Elemental analysis : cal C 66.05, H 4.62; Fou C 65.75, H 4.59.

2) Catalysed

(0.5g, 0.0038mol) of granular $AlCl_3$ was put in 200ml of $CHCl_3$ (dried over P_2O_5 and distilled) and crushed until powdered.(0.38g,0.0035mol) of quinone was added. The solution was shaken until all the $AlCl_3$ dissolved. This took about 20min during which all the colour of the solution turned dark

purple. Solution of the pyrone (0.4g, 0.0035mol) in 50ml of methylene chloride was added portion-wise and the 1litre flask stoppered and shaken. The reaction was continued for 1hr after which 200ml water was added and the mixture shaken in a separating funnel. The organic layer was removed and the aqueous phase washed with two 50ml methylene chloride portions. The organic phases were combined and concentrated to leave an oil. When little ether was added crystals slowly appeared. They were filtered, washed and dried to give 80mg (10%) yield of the cycloadduct. This product was identical to the one obtained from the thermal reaction.

8,10-Dimethyl-2-oxa-3,6,9-trioxotricyclo[4.4.0.$2^{1,4}$]dodec-7,11-diene (263)

2-Pyrone (0.5g, 0.0045mol; Purified on silica with methylene chloride : acetonitrile 99 : 1) and 2,6-dimethyl-p-benzoquinone (0.69g, 0.005mol; purified by sublimation) were mixed together in a 5ml flask under anhydrous, oxygen free, nitrogen atmosphere. 30mg of 2,4,6-tri-tert-butyl phenol was added as an inhibitor and the mixture was stirred magnetically for 48hr at 120° C. The darkened reaction mixture was chromatographed on silica (prep TLC) using methylene chloride : acetonitrile 95 : 5. Further necessary purification with normal as well as reverse phase HPLC (methanol : water , 60 : 40) on semi-preparative columns yielded all-together five pure components which accounted for 29% yield of the products of the reaction and were all characterised. 0.18g of 2-pyrone was recovered while all of xyloquinone had been consumed.

compound 1 = yellow solid adduct (263). M.Pt. = 92-97° C(decom.). ^{1}H-NMR (CD_3CN) (220MHz)δ: 1.50 (s, 3H), 1.94 (d, 3H, J = 1.6Hz), 2.96 (d, 1H, J = 2.5Hz), 3.94 (ddd, 1H, J = 6.0, 2.5, 1.5Hz), 5.33 (dd, 1H, J = 4.9, 2.0Hz), 6.45 (ddd,1H, J = 7.5, 6.0, 2.0Hz), 6.59 (ddd, 1H, J = 4.9, 7.5, 1.5Hz), 6.74 (q, 1H, J = 1.5Hz). IR (nujol) : 1760cm^{-1}, 1670cm^{-1}, 1629cm^{-1} 1179cm^{-1} 719cm^{-1}. UV (Abs. Eth.) : 230nm.

compound 2 = HPLC retention times, UV absorption, ^{1}H-NMR, IR ,and Mass Spectrum of this compound was identical to published data on 3-methyl-1,4-naphthoquinone (265). Yield : 0.1g (8%).

compound 3 = White solid (268) with a melting point of 239-241° C (rhombic crystals). ^{1}H-NMR ($CDCl_3$) (400MHz)δ: 1.60 (s, 6H), 3.81 (s, 2H), 7.91 (s, 4H), 7.78 (s, 4H). IR (nujol) : 1690cm^{-1}, 1600cm^{-1}. Mass Spect. : 344 (M+), 196, 172(100%), 150, 144, 122, 115, 104, 76, 57, 50. UV (Abs. Etha.) : 238nm, 259nm, 302nm. Yield : 0.03g (2.5%).

Compound 4 = M.Pt. : 124-127°C(lit 127°C). UV absorption, ^{1}H-NMR data, Mass Spectrum and infrared results were all identical with the reported literature data for 2,3-dimethyl-1,4-naphthoquinone (266). Yield : 0.05g (4%).

compound 5 = ^{1}H-NMR data, mass spectroscopy data, UV absorption and melting point of this compound were identical to the literature data on 5,10-anthraquinone (267). Yield : 0.02g (2%).

4,8,10-trimethyl-2-oxa-3,6,9-trioxotricyclo[4.4.0.$2^{1,4}$]dodec-7,11-diene (262) or 4,5,7-trimethyl-2-oxa-3,6,9-trioxotricyclo[4.4.0.$2^{1,4}$]dodec-7,11-diene (261)

1) thermal

3-Methyl-2H-pyran-2-one (5.5g, 0.05mol), xyloquinone (6.8g, 0.05mol), and tri-t-butyl phenol (0.1g) were mixed together with 2ml of methylene choride to homogenise the mixture. Dry and oxygen free nitrogen was bubbled through this followed by freezing the mixture and applying vacuum for few minutes. This process was repeated several times to ensure total removal of dissolved oxygen in the media which was then placed in a heavy walled glass tube and sealed. The tube was left in an oven at 108°C for 80hr. When tube was cooled and opened, the slightly darkened residue was examined by ^{1}H-NMR which showed the presence of cycloadducts. The major bulk of the residue which was starting materials was removed by distillation under vacuum at 50°C. The concentrated residue was subjected to chromatography on silica using methylene chloride/ acetonitrile (95/5) as eluent and the cycloadduct band was collected. After evaporation of the solvent an oily residue (1.15g, 9%) remained which still contained some starting material. Further purification with preparative HPLC provided pure cycloadduct mixture (410mg, 3.5%) whose analysis on analytical HPLC showed a 2 : 3 mixture of ortho- : non-ortho. Partial crystallisation with ether separated some of the non-ortho adduct (262) which was fully characterised. M.Pt. : 135-140°C. ^{1}H-NMR (CD_3CN) (400MHz)δ: 1.38 (s, 3H), 1.46 (s, 3H), 1.89 (d, 3H, J = 1.5Hz), 2.57 (bd, 1H, J = 0.6, 0.6Hz), 5.10 (dd, 1H, J = 5.0, 1.9Hz), 6.13 (ddd, 1H, J = 7.6,

1.9, 0.6Hz), 6.49 (dd, 1H, J = 7.6, 5.0Hz), 6.66 (dq, 1H, J = 1.5, 0.6Hz). Mass Spect. : 246.0773 (246.1092, M+), 218, 149, 131, 125, 122, 110, 108, 106, 96(100%), 94, 91, 82, 79, 77, 68, 65, 53. ^{13}C-NMR (CD_3CN, TMS as reference)δ: 15.17 and 16.02 (C8-and C4-methyls), 22.83(C10-methyl), 47.46 (C10), 52.80(C4), 54.63(C5), 78.97(C1), 132.88(C11), 136.00(C7), 139.78(C12), 150.52(C8), 173.56(C3), 193.56(C6), 198.89(C9).

The mass spectrum of a third component c (Figure 7) was also obtained : 322.1014, 246.0431, 202, 187, 183, 175, 159, 149, 141, 138, 133, 127, 125, 119, 111, 110, 105, 99, 96(74%), 91, 85, 83, 77, 69, 68(81%), 55, 43.

2) high pressure

a) at room temperature/with solvent : 3-Methyl-2-pyrone (0.5g,0.0045mol) and xyloquinone (0.62g, 0.0048mol) were placed in a pressure vessel (10T/sq.inc., RT, 4 days) with methylene chloride (10ml). The resulting product was evaporated to remove solvent and ^{1}H-NMR of the crude suggested presence of adduct. Preparative TLC separation on silica plates (methylene chloride as eluent) yielded starting materials as well as a band (Rf = 0.2) which yielded 0.12g (11%) of a pale yellow powder identified as the ortho-adduct (261). M.Pt. : 88-90°C. ^{1}H-NMR (CD_3CN) (400MHz)δ: 1.32 (s, 3H), 1.46 (s,3H), 1.94 (d, 3H, J = 1.5Hz), 3.31 (d,1H, J = 4.5Hz), 5.35 (ddd, 1H, J = 5.5, 4.5, 2.0Hz), 6.20 (dd, 1H, J = 8.0, 2.0Hz), 6.45 (dd, 1H, J = 8.0, 5.5Hz), 6.56 (q, 3H, J = 1.5Hz). IR (KBr disc) : 3000-2900cm^{-1}(CH_3, CH_2 str), 1750cm^{-1}, 1660cm^{-1}, 1450-1350cm^{-1}, 1300-1100cm^{-1}, 1000cm^{-1}. Mass Spect. : 246.0823(246.1092,M+), 202, 187, 180, 172, 159, 155, 149,

146.9, 138, 137, 136, 131, 118.9, 110, 108, 107, 96, 91, 82, 79, 68, 54, 53, 51. Elem. Anal. : cal. C 68.28 H 5.73; fou. C 68.04 H 5.69.

b) at 70° C/no solvent : 3-methyl-2-pyrone (0.55g, 0.005mol), 2,6-dimethyl-p-benzoquinone (0.68g, 0.005mol), methylene chloride (0.5ml), and 2,4,6-tri-t-butyl-phenol (0.001g) as radical inhibitor were mixed together and degassed to remove any oxygen trace prior sending. At Southampton University the reaction was carried out under pressure (10kbar/sq.inc., 70° C, 7 days). On return the sample was vacuum dried (30° C, 24hr). The residue (0.33g) was purified by preparative TLC (CH_2Cl_2 : CH_3CN, 95 : 5) and the isomeric mixture of the adduct collected as one band (0.30g, 24%). Analytical HPLC examination of this band suggested a 3 : 2 mixture of non-ortho : ortho adduct. Differential crystalisation from ether yielded a pure sample of the non-ortho adduct (0.14g).

3) aqueous

Water (25ml) was added to a mixture containing 3-methyl-2-pyrone (1.5g,0.0136mol) and xyloquinone (1.84g, 0.0136mol) with little 2,4,6-tri-t-butyl phenol. After degasing the mixture was stirred vigourously under nitrogen for 60hr at 50-70° C. Upon distillatin of reaction mixture at 60° C under vacuum 0.32g (10%) of a residue remained which crystallised with addition of ether. The crystals were filtered and dried (o.2g). Analysis showed that only the ortho adduct(261) was formed. Minute quantities of the non-ortho adduct were detectable by hplc.

4)catalysed

The experiments were all carried out with exclusion of moisture under oxygen free nitrogen atmosphere. The solvents used were all dried prior to use. The quinones were sublimed where possible to purify and the pyrone used was distilled to a colourless liquid. A typical reaction was carried out as follows:

Antimony pentaflouride (0.82g, 0.004mol), was transfered into a flask containing dried and distilled chloroform (100ml). Xyloquinone (0.5g, 0.004mol) was added and the solution turned pale orange-red; an indication for the formation of the quinone complex. Then the pyrone (0.4g 0.004mol) in chloroform (20ml) was added gradually to the stirred solution of quinone-complex. The solution turned paler and more cloudy as reaction continued. After 12hr of stirring at room temperature, water (100ml) was added to hydrolyse the acid. The organics were removed with methylene chloride (3 x 50ml). The combined organic fractions were dried over anhydrous sodium sulphate which was then filtered. After the solvent was evaporated the residue was analysed by TLC, and ^{1}H-NMR. Under high amplitudes the ^{1}H-NMR showed presence of signals belonging to the ortho-adduct. Judged by this there was less than 5% yield of this component.

4,7(or 8)-Dimethyl-2-oxa-3,6,9-trioxotricyclo$[4.4.0.2^{1,4}]$ dodec-7,11-diene (269)

The cycloaddition with toluquinone was carried out (on a 0.01molar scale) as that for benzoquinone. Recrystalisation from acetonitrile/ether yielded 1.17g (50%) of the pale

yellow crystaline solid. M.Pt.= 164-168° C(170° C decomp., 140-164° C slight sublimation). ^{1}H-NMR (CD_3CN)δ: 1.46(s, 3H), 1.92 (d, 3H, J = 1.5Hz), 3.05 (bd, 1H, J = 8.5, 1.0Hz), 3.74 (dd, 1H, J = 8.5, 4.8 Hz), 5.49 (ddd, 1H, J = 2.0, 4.8, 5.0 Hz), 6.24 (ddd, 1H, J = 7.8, 2.0, 1.0 Hz), 6.52 (q, 1H, J = 1.5 Hz), 6.53 (dd, 1H, J = 7.8, 5.0Hz). IR ($CHCl_3$) : 3060-2920cm^{-1}, 1760cm^{-1} (CO str. lactone), 1675cm^{-1}(CO str. ketone), 1630cm^{-1}. Elem. Anal. : cal C 67.23, H 5.21, fou. C 67.41, H 5.24. Mass spec. : 232.0868 (232.0944, M+), 188, 186 (100%), 173, 171, 158, 145, 143, 141, 129, 122, 119, 118, 115, 110, 105, 96, 94, 91, 90, 82, 81, 77, 68, 66, 63. ^{13}C-NMR (DMSO-d_6, TMS as reference)δ : 16.080 and 16.796(C4- and C8-methyls), 45.64(C10), 47.07(C4), 49.94(C5), 73.96(C1), 131.83(C12), 136.65(C7), 138.02(C11), 153.12(C8), 173.56(C3), 193.87(C6), 195.44(C9).

8.5 References

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2. J.K.M.Sanders, Prog.Nucl.Magn.Reson.Spectrosc., 1983, 15 , 123.
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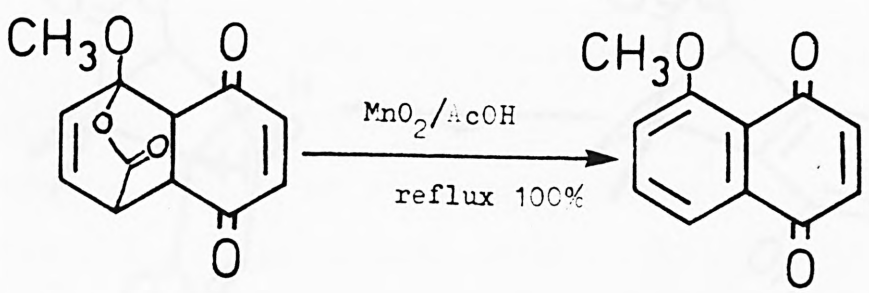
Chapter 9 : The chemistry of quinone-pyrone adducts

9.1 Introduction.

The synthesis of adducts of pyrone with quinones has been discussed in previous chapters. The succesful isolation of our intended adduct (262), albiet in poor yield, prompted us to consider the next step of the synthesis towards norditerpene dilactones and our findings are reported here. The stability of the adduct has been examined and a method for the opening of the ester bridge has been developed. Optimisation of the reaction yields followed by application of literature synthetic methods will allow access to A-ring functionalised norditerpene dilactones.

9.2 Results and discussion

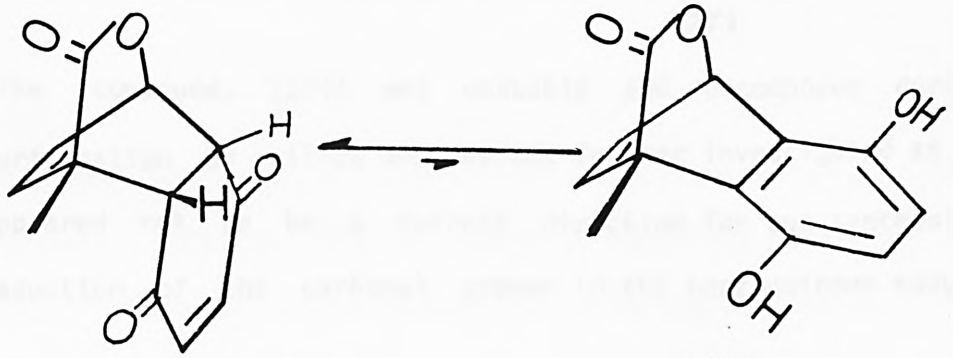
No information is available in the literature on the chemistry of bridged-adducts except that thermal treatment of the quinonoid adducts leads to aromatisation via loss of carbon dioxide. This can also be achieved in the presence of activated manganese dioxide.[1]



9.2.1 Chemistry of benzoquinone adduct (260).

Access to much larger quantities of the benzoquinone adduct through our Diels-Alder synthesis prompted us to carry out the priliminary studies on this compound. It was shown that saponification of the ester bridge using sodium methoxide/methanol mixture immediately caused the decomposition of the starting material into products with aromatic character. Failure of detection of any bridge-opened adduct signified that starting material is sensitive to basic conditions. Other bases such as sodium hydrogen carbonate in water and triethyl amine were also shown by ^{1}H-NMR to cause decomposition of the adduct. The stability of the adduct (260) was also checked in acidic media and found to be extremely good. Concentrated HCl was stirred with the crystals of (260) at room temperature for a long time (10hr) before break down took place. Tosic acid did not cause any apparent decomposition of adduct in acetonitrile and a solution of (260) in trifluoroacetic acid also showed remarkable stability for a week at room temperature.

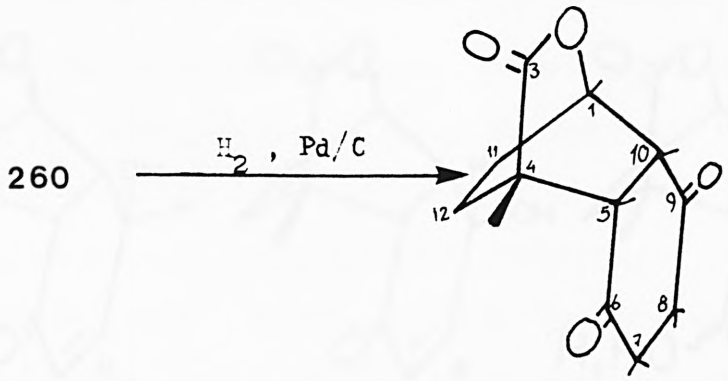
The driving forces behind the aromatisation and the loss of the lactone bridge are the C11-C12 double bond and enolisation of the carbonyl groups in the presence of a base.



260 270

The enol form (270) was not detected for adduct (260). The explanation must be that the molecule is made rigid by the presence of the ester bridge and the enol form in not energetically favoured. However, once the bridge is opened the enolisation can occur readily and leads to aromatisation. Presence of angular methyl group must stop aromatisation occurring, but it may not necessarily stop the loss of lactone bridge. Thus prevention of aromatisation and loss of lactone bridge in (260) was thought to be possible either by hydrogenating the C11-C12 and/or C7-C8 double bonds or converting the carbonyls into hydroxyl groups.

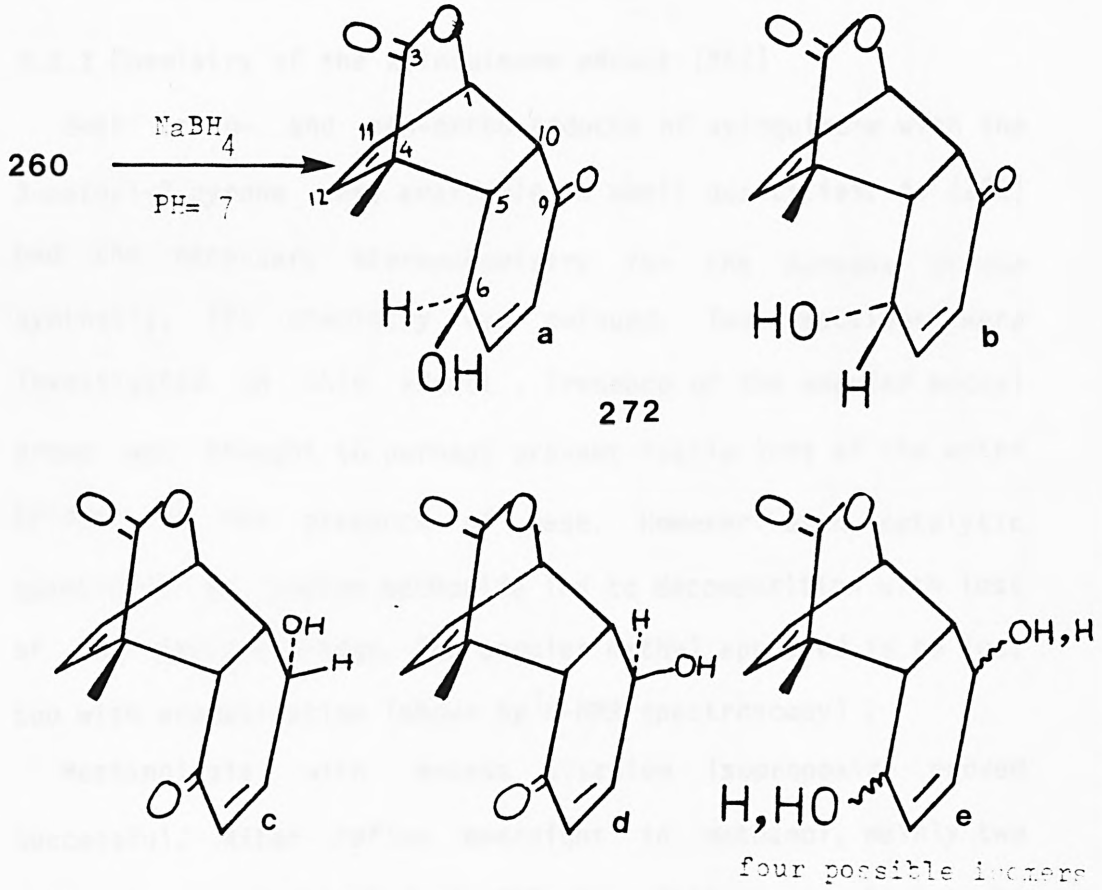
Hydrogenation of the adduct (260) was carried out in the presence of Palladium on charcoal and it was found that the product obtained had both double bonds hydrogenated. This was shown by the disappearance of the olefinic hydrogen signals in the ^{1}H-NMR spectrum and persistance of a broad triplet at 5.40 δ due to the C10 hydrogen.



271

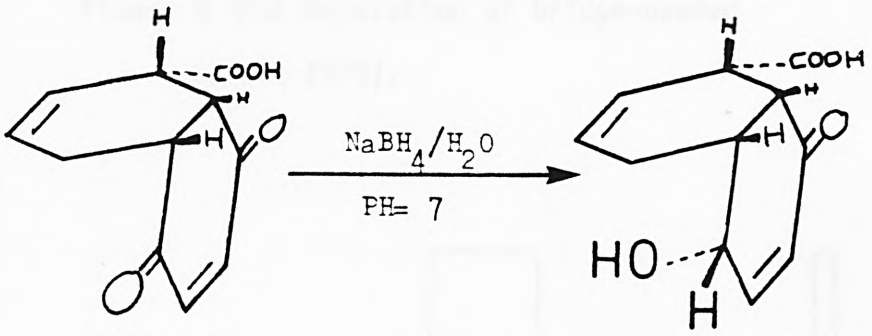
The compound, (271) was unstable and decomposed during purification on silica and was not further investigated as it appeared not to be a correct direction for our synthesis. Reduction of the carbonyl groups in the benzoquinone adduct

was examined next. As expected, unbuffered sodium borohydride reduction led to immediate decomposition of the starting material because as the reduction proceeds the media becomes progressively alkaline. A buffered media prevented decomposition and a good yield of a mixture of isomeric products were obtained. The evidence for an intact bridge was the ^{1}H-NMR signal in the region of 5.12δ and a multiplet due to H-10. Chromatographic purification of the crude product on silica yielded two bands one of which composed of at least two isomers. The presence of the C11-C12 double bond could also be confirmed.



However lack of a long-wavelength chromophore in (272) compounds hampered the separation of bands and hplc analysis. One or both of the carbonyls can be reduced but it is likely

that the reduction is selective as was a reduction of (273), reported by Woodward et al.[2] to give only one product.



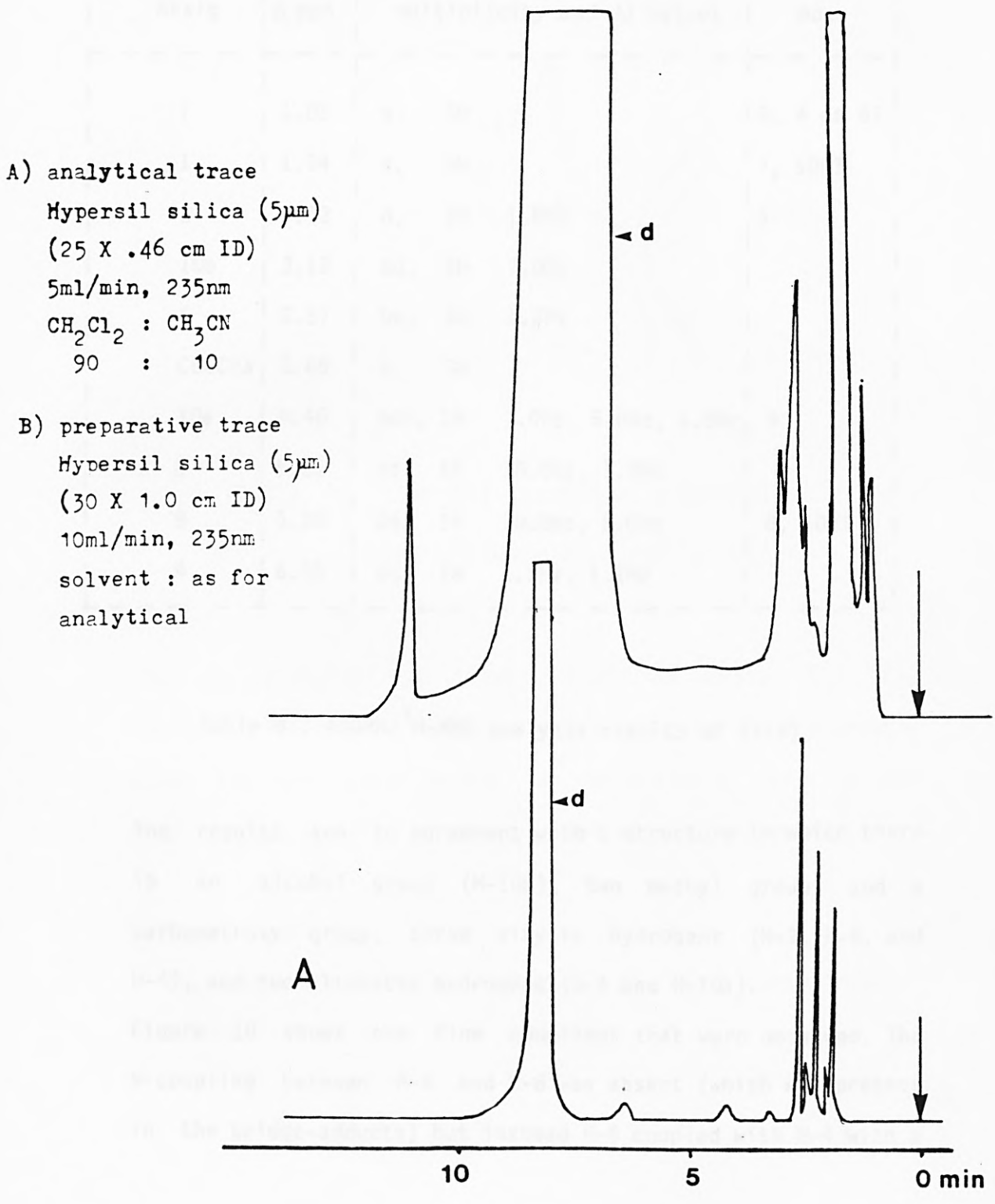
273

9.2.2 Chemistry of the xyloquinone adduct (262)

Both ortho- and non-ortho adducts of xyloquinone with the 3-methyl-2-pyrone were available in small quantities. As (262) had the necessary stereochemistry for the purpose of our synthesis, its chemistry was pursued. Two reactions were investigated on this adduct . Presence of the angular methyl group was thought to perhaps prevent facile loss of the ester bridge in the presence of base. However even catalytic quantities of sodium methoxide led to decomposition with loss of the lactone bridge. The angular methyl appeared to be lost too with aromatisation (shown by ^{1}H-NMR spectroscopy) .

Methanolysis with excess titanium isopropoxide proved successful. After reflux overnight in methanol, mainly two compounds were detected by TLC. One of these was shown to be the starting material (Rf=0.8 in 95:5 methylene chloride: acetonitrile) and the other was the bridge-opened adduct (Rf=0.15). After clean up using preparative TLC the product was further purified using semipreparative HPLC (See Figure 9)

Figure 9 HPLC separation of bridge-opened adduct (274).



The compound (274) was also examined by 400MHz ^{1}H-NMR spectroscopy (Table 8).

Assig	δ ppm	multiplicity and JJ values	noe
7	1.03	s, 3H	9, 4 or 6?
1	1.34	s, 3H	7, 10b?
3	1.93	d, 3H 1.5Hz	4
10b	3.12	bd, 1H 7.0Hz	
6	3.57	bs, 1H 1.2Hz	
COOCH3	3.66	s, 3H	
10a	4.40	bdd, 1H 7.0Hz, 5.0Hz, 1.0Hz	9
8	5.61	dd 1H 10.0Hz, 1.0Hz	
9	5.94	dd 1H 10.0Hz, 5.0Hz	8, 10a?
4	6.55	dq 1H 1.5Hz, 1.2Hz	

Table 8 : 400MHz ^{1}H-NMR analysis results of (274)

The results are in agreement with a structure in which there is an alcohol group (H-10b), two methyl groups and a carbomethoxy group, three vinylic hydrogens (H-9, H-8, and H-4), and two aliphatic hydrogens (H-6 and H-10a).

Figure 10 shows the fine couplings that were observed. The W-coupling between H-6 and H-8 was absent (which was present in the bridge-adducts) but instead H-6 coupled with H-4 with a

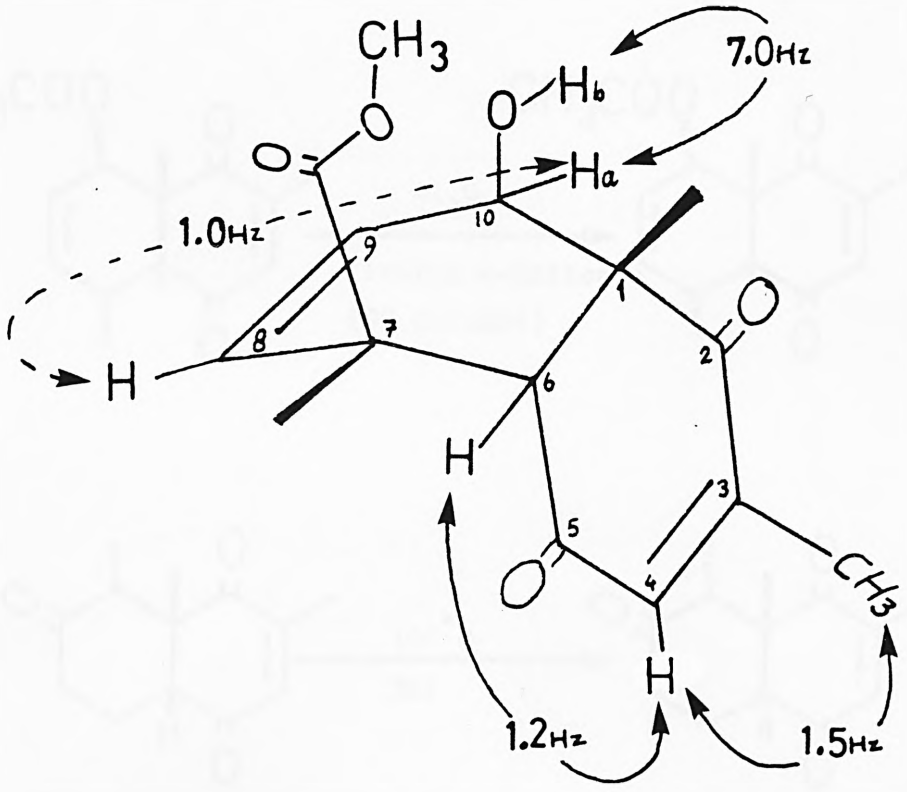
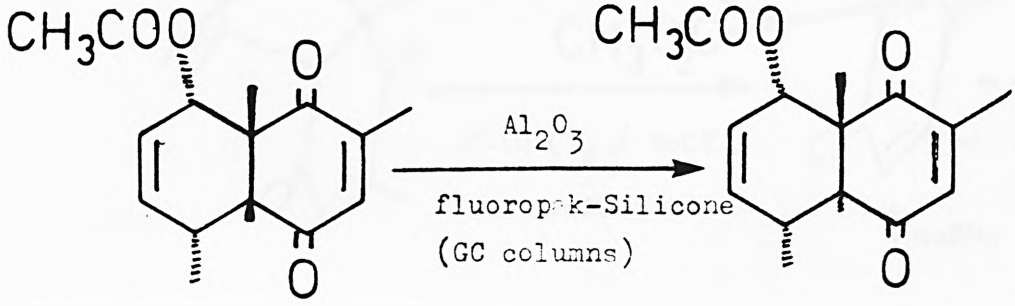


Figure 10 Fine H-H couplings obvserved in 400MHz ^{1}H-NMR spectrum of (274).

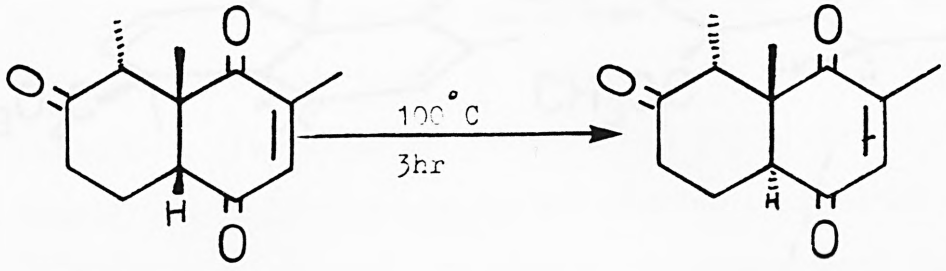
coupling constant of 1.2Hz). Based on these, the only ambiguous feature of the structure is the stereochemistry about the C-6 which cannot be definitively assigned. The molecular ion was also observed in the mass spectrometer.

9.3 Future work

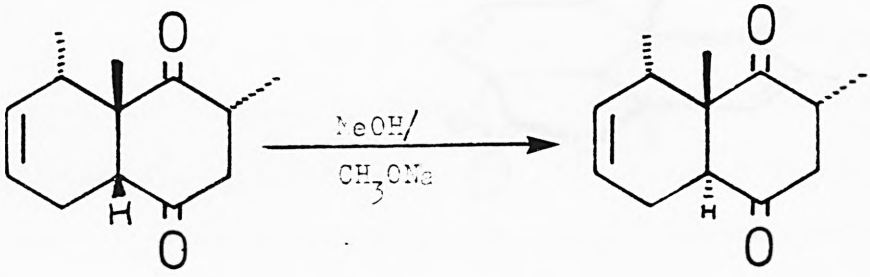
Cis/trans isomerisation about C1-C6 is a transformation which occurs readily in model compounds;



ref. 3



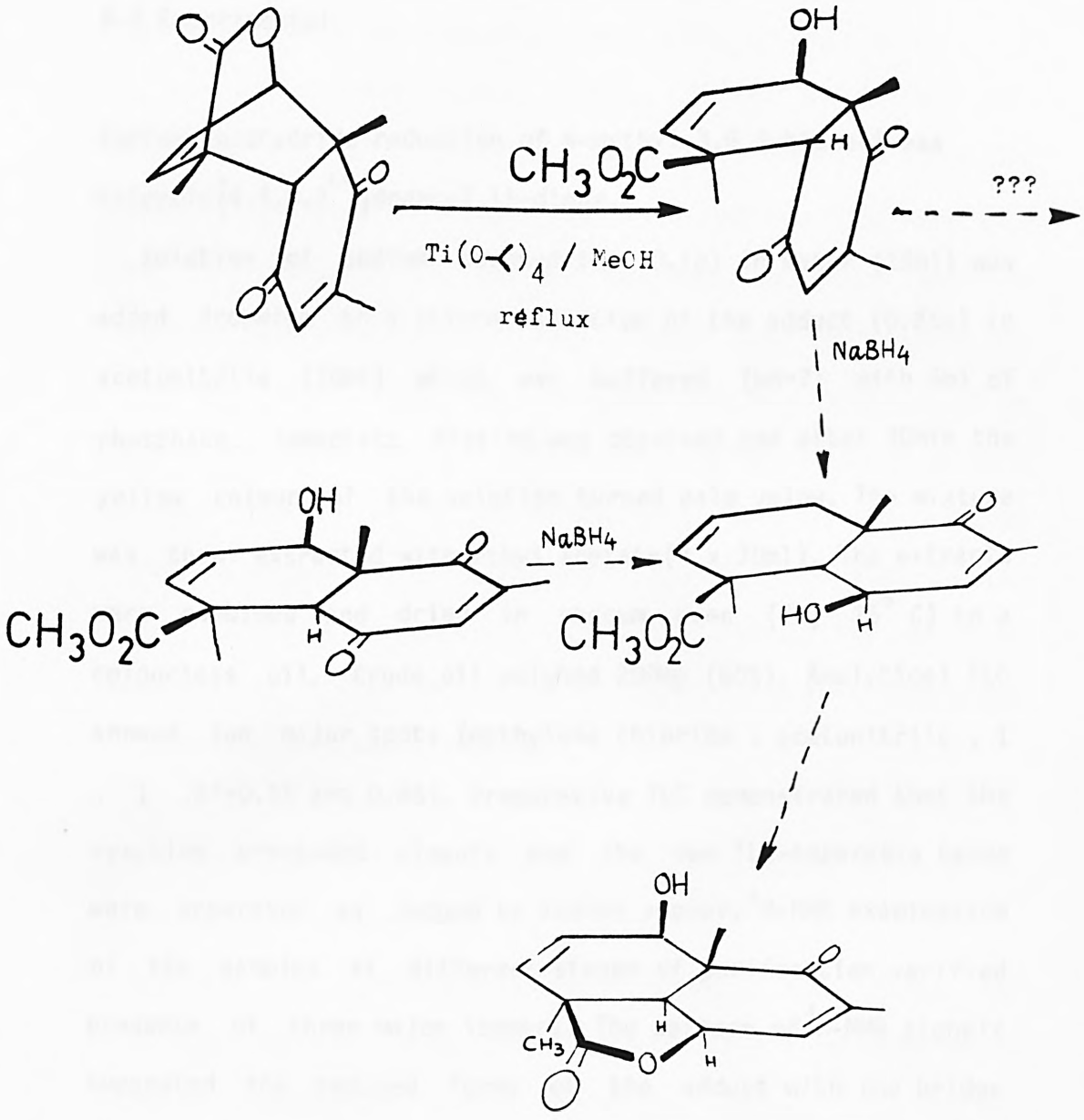
ref. 4



ref. 5

Presence of the angular methyl group prevents continuation of reaction to aromatisation. Absence of the angular methyl group, therefore, renders such compounds very sensitive to any pH other than pH=7.

Bridge-opened adduct (274) is expected to be easily amenable to trans isomerisation under very mild conditions ie;



Reduction of C-5 carbonyl should be a surmountable step which if carried out on the adduct (274) may also affect the trans-isomerisation and further cause the formation of γ-lactone

The established chemical methods for construction of the C-ring moiety for similar systems are expected to be readily applicable.

9.4 Experimental

Sodium borohydride reduction of 4-methyl-3,6,9-bioxo-2-oxa tricyclo$[4.4.0.2^{1,4}]$dodec-7,11-diene.

Solution of sodium borohydride (0.1g) in water (15ml) was added dropwise to a stirred solution of the adduct (0.25g) in acetonitrile (30ml) which was buffered (pH=7) with 5ml of phosphate. Immediate fissing was observed and after 30min the yellow colour of the solution turned pale yelow. The mixture was then extracted with ethyl acetate(4 x 30ml). The extracts were combined and dried in vaccum oven (2h, 25° C) to a colourless oil. Crude oil weighed 200mg (80%). Analytical TLC showed two major spots (methylene chloride : acetonitrile , 1 : 1 ,Rf=0.55 and 0.65). Preparative TLC demonstrated that the reaction proceeded cleanly and the two TLC-separable bands were separated as judged by iodine vapour. ^{1}H-NMR examination of the samples at different stages of purification verified presence of three major isomers. The pattern of ^{1}H-NMR signals suggested the reduced forms of the adduct with the bridge intact. Samples were reasonably stable during purification procedure. Component with the higher Rf value appeared to be mainly a mixture of two isomers. ^{1}H-NMR (CD_3CN)δ: 1.42 and 1.60 (two methyl singlets), 2.80(m, 1H), 3.40(dd, 1H), 4.20(m, 1H), 5.12(m, 1H), 6.00-6.60 (m, olefinic).

The component with the lower Rf value (0.55) which foamed on drying appears to be mainly a single compound. ^{1}H-NMR (CD_3CN)δ: 1.40(3H, methyl), 1.80-2.62(m, 3H), 4.06(b) , 5.10(m,1H), 6.00-6.42(m, 2H). IR (neat)cm^{-1}: 3600-3100 (OH str.), 3000-2850, 1700-1750.

Hydrogenation of benzoquinone adduct (260) to give (273)

The benzoquinone adduct, (260), (0.1g, 0.00045mol) was dissolved in ethyl acetate (70ml) and 10% Pd/C (25mg) was added. The flask was connected to a hydrogenating apparatus and the mixture was stirred magnetically under positive pressure of hydrogen for 24hr. About 11cm^3 of hydrogen was consumed. After filtering the catalyst, the original yellow colour of solution had disappeared. Evaporation of solvent yielded 0.102mg of a colourless oil. This oil was examined spectroscopically. ^{1}H-NMR($CDCl_3$)δ : 1.40(s, 3H), 1.50-2.20(m, 4H), 2.30-3.80(m, 6H), 5.40(bt, 1H).Unstability of this compound on silica prevented isolation of a pure sample and further analysis was abondoned.

2,5-Dioxo-7-carbomethoxy-10-hydroxy-1,3,7-trimethyl-bicyclo [4.4.0]dec-3,8-diene (274)

Crystals of compound (262) (0.040g) and dried and distilled methanol (30ml) were placed in a flask with dried nitrogen atmosphere and a condenser. Excess titanium(IV) iso-propoxide (1ml) was delivered into the reaction flask and after the disappearance of slight precipitation the contents were refluxed (16hr). After cooling methanol was removed on a buchi and water was added (20ml). Methylene chloride (5 x 20ml) was used to extract the organics from the aqueous layer. The combined organic layers were dried using anhydrous sodium sulphate which was then removed by filteration. Evaporation of the solvent yielded a clear yellow oil. TLC silica examination

using methylene chloride and acetonitrile (95:5) revealed two major spots (Rf= 0.8 and Rf=0.15). Preparative HPLC separation of the crude oil on a 5μm Hypersil silica column (see figure 9) yielded two components one of which was shown to be starting material (Rf=0.8, 20mg). The other component (Rf=0.15) was obtained as a colourless oil (5mg, 12%) Which was analysed spectroscopically. ^{1}H-NMR (CD_3CN)δ:1.03 (S, 3H), 1.34(S, 3H), 1.93 (d, 3H, 1.0Hz), 3.12 (bd, 1H, 7.0Hz), 3.57 (b, 1H), 3.66(s, 3H), 4.40(dd, 1H, 5.0Hz, 7.0Hz), 5.61(dd, 1H, 10.0Hz, 1.0Hz), 5.94(dd, 1H, 10.0Hz, 5.0Hz), 6.33(dq, 1H, 1.2Hz, 1.0Hz). Mass Spec.: 278.1392(278.1240, m+), 219, 204, 203, 201, 191, 176, 173, 142, 141, 138(100%), 137, 110, 96, 82, 68, 53, 39

9.5 References

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