UNIVERSITY OF SOUTHAMPTON

SYNTHESES OF FURANOSESQUITERPENOID NATURAL PRODUCTS

by

Russell John Sims

Thesis presented for the degree of

Doctor of Philosophy

Department of Chemistry

October 1981

To

My Parents

ACKNOWLEDGEMENTS

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My thanks are due to my mother, Joyce Sims, for the excellent way in which she typed this thesis and to Dr. David Billington for proof-reading the manuscript.

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

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The effect of addition of a catalytic quantity of a crown ether in the reaction of a phosphonate anion with a carbonyl compound (Wadsworth-Emmons reaction) has been studied and found to greatly facilitate this reaction. This modification of the Wadsworth-Emmons reaction, using a catalytic amount of 15-crown-5, has been employed in the synthesis of the naturally occurring furanosesquiterpene Pallescensin-E. The structure of this compound has been confirmed by comparison of its spectral data with that of the synthesised isomer, 4,10-dihydro-7,8-dimethyl-10H-benzo[4,5]cyclohepta[1,2-b]furan.

Homosesquirosefuran, an analogue of the naturally occurring furanosesquiterpene Sesquirosefuran, has been synthesised via the dianion of methylacetoacetate.

An approach to the synthesis of Pinguisone (a component of the essential oil of the liverwort Aneura pinguis)has been attempted employing two Diels-Alder reactions to generate the four cis-methyl groups found in the natural product.

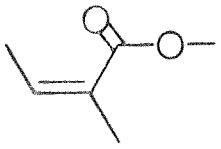
In a study of the reaction of π-(2-methylallyl)nickel bromide complex with a range of epoxides, this complex was found not only to react with reactive epoxides (e.g. styrene epoxide) but also with less reactive propylene epoxide.

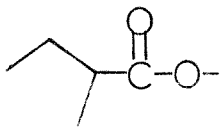
Substrates for possible intramolecular π-allylnickel cyclisation to generate an α-methylene-δ-valerolactone ring system have been prepared.

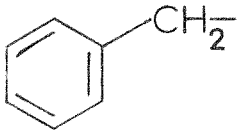
CONTENTS

ABBREVIATIONS

Throughout this thesis the following abbreviations have been used:-

Ang= 

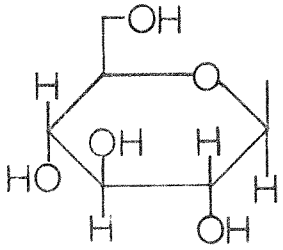
Meb= 

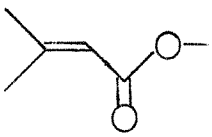
Bz= 

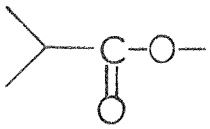
$Ni(COD)_2$= *bis*(1,5-cyclo-octadiene)nickel (0)

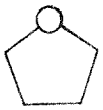
DMF= N,N-dimethylformamide

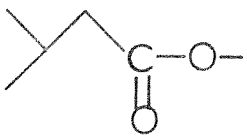
pcc= pyridinium chlorochromate

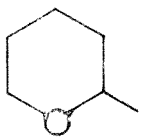
Glu= 

Sen= 

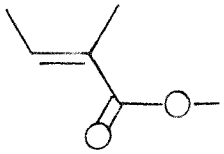
Ibu= 

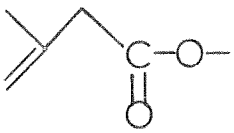
THF= 

Iva= 

THP= 

LAH= lithium aluminium hydride

Tig= 

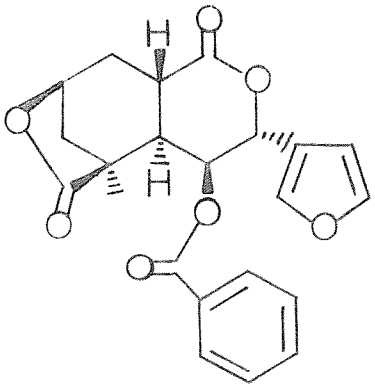
Mac= 

TMS= $Si(CH_3)_4$

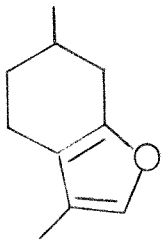
CHAPTER ONE INTRODUCTION

1. Isolation of Furanonatural Products

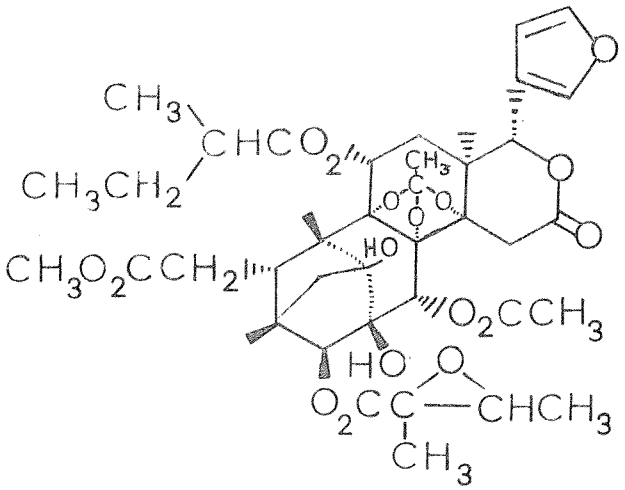
From the isolation of collybolide (1)[1] in 1911 to the present day, a large number of furanoid natural products have been isolated from a variety of sources.[2,3,4] These compounds represent a large and structurally varied group of natural products which range from the 'simple' monoterpenes (e.g. menthofuran (2)[5]) to the more complex triterpenes (e.g. utilin (3)[6]). The taxonomic distribution of furanoid natural products is wide and sources include sponges,[7] liverworts,[8] termites[9] and ants.[10]



collybolide (1)



menthofuran (2)



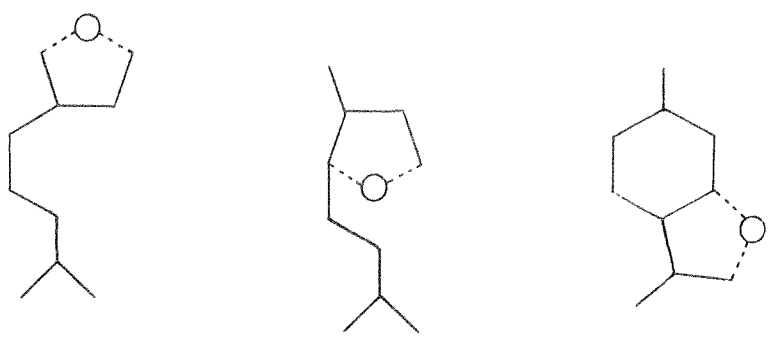
utilin (3)

Until 1960 only a few structures of furanoid natural products had been established. With the development of separation methods and physio-chemical techniques for structural investigations, rapid advances in the chemistry of furanoid natural products have taken place. Thus, during the 21 years from 1960 the number of furanoid natural products reported in the literature has risen rapidly. The majority of these compounds may be classified by the identification of the usual "isoprene" pattern in their carbon skeletons and thus are termed monoterpenoid, sesquiterpenoid etc. This, where appropriate, is the classification used in this review.

This review covers the isolation of all the furanoterpenoids known to date, including the sesterterpenoids, with a brief summary of the structural types found in the triterpenoids. In the majority of cases only one reference is given for each structure and this refers to the first isolation or structure determination. For brevity subsequent isolation sources have not been included.

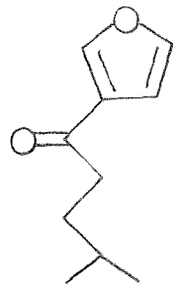
1.1. Monoterpenoid Furanonatural Products

The majority of furanomonoterpenoid natural products which have been isolated to date fall into two classes, those containing a 'linear' skeleton (4) or (5) and those containing a 'menthane' skeleton (6).

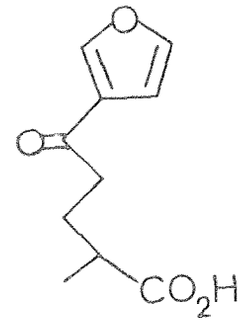


(4) (5) (6)

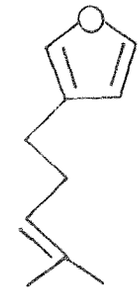
linear skeletons menthane skeleton



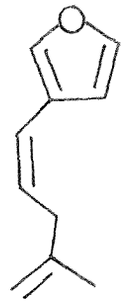
perilla ketone (7)
Perilla frutescens[11]



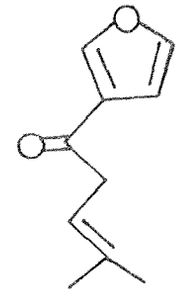
Batatic acid (8)
Ipomea sp.infected with *Ceratostomella fibriata*[12,13]



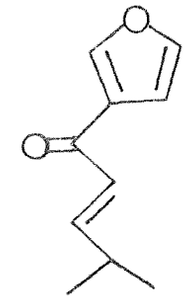
perillene (9)
Perilla frutescens[14]



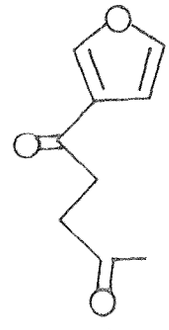
α-clausenane (10)[15]



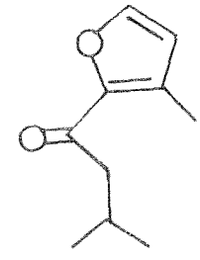
egomaketone (11)
Perilla frutescens[11]



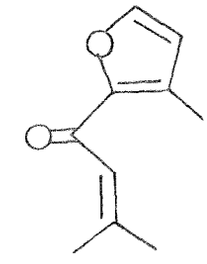
*iso*egomaketone (12)[16]
Perilla frutescens[17]



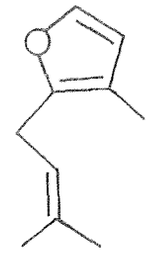
ipomeanine (13) from *Ipomoea batatas* infected with *Ceratostomella fibriata* or *Fusarium solani*[18]



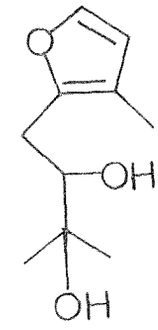
elsholtzione (14)[19]
Perilla frutescens[20]
Elsholtzia cristata



naginata ketone (15)[21]
Perilla frutescens[22]
Elsholtzia cristata



rosefuran (16)[23]



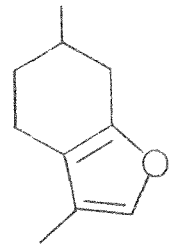
elsholtzidiol (17)
Elsholtzia densa[24]

1.1.1. Linear Skeleton

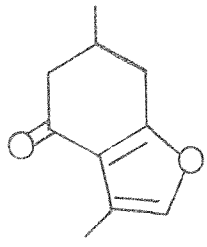
This has formed the largest of the two groups of furano monoterpenes (7-17). Batatic acid (8) has been isolated from sweet potatoes (*Ipomoea* sp.) infected with the black-rot fungus *Ceratostomella fimbriata*.[12] *Perilla frutescens* has been one of the best sources of monoterpenoid furanonatural products which include, egomaketone (11), perillaketone (7), perillene (9), naginata ketone (15) and *iso*-egomaketone (12).

1.1.2. Menthane Skeleton

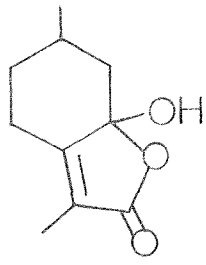
The two most common members of this group of furanoid natural products are menthofuran (2) and evodone (18). Menthofuran occurs in various peppermints and other oils,[25,26] together with its auto-oxidation product (19), the structure of which was established by Woodward in 1950.[27] Evodone (18) has been isolated from the leaves of *Evodia hortensis*.[28,29,30]



(2)
menthofuran



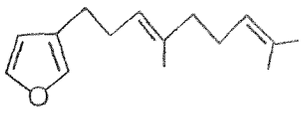
(18)
evodone



(19)

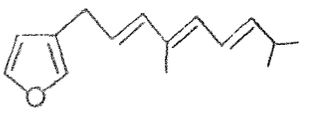
1.2. Sesquiterpenoid Furanonatural Products

Furanosesquiterpenoids are the largest group of furanonatural products and no attempt has been made to exhaustively cover the extensive literature of furanosesquiterpenoids in the following review, many aspects of which have been discussed elsewhere.[31-35]



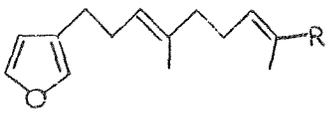
(20)

dendrolasin
Lasius fuliginosus[10]
Torreya nucifera[36]
Ipomoea sp.[37]



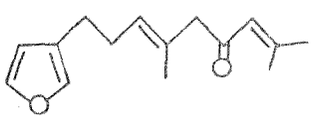
(21)

dehydrodendrolasin
Pleraplysilla spinifera[38,39]



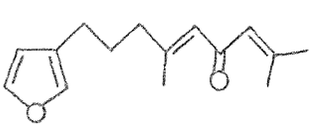
R=CH_2OH neotorreyol (22)
Torreya nucifera[36,40]

R=CHO torreyal (23)
Torreya nucifera[36,40]



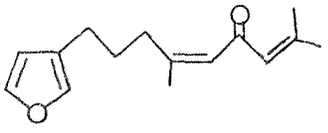
(24)

Athanasia crithmifolia
Lasiospermum radiatum[41]
Stilpnophytum linifolium[42,43]



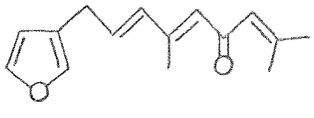
(25)

trans-dihydrophymaspermone
Athanasia acerosa
Athanasia crithmifolia[41]



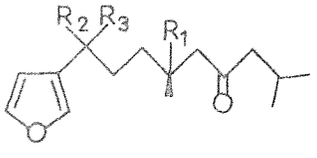
(26)

cis-dihydrophymaspermone
Athanasia acerosa
Athanasia crithmifolia[41]



(27)

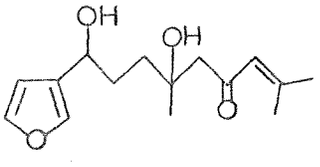
phymaspermone
Phymaspermum parvifolium[42,43]



R_1=R_2=R_3=H (28)
Ipomoea sp.[44]

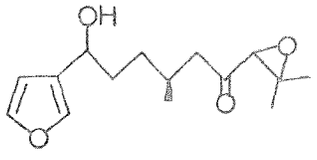
R_1=H, R_2,R_3=O
myoporone (31)[46]
Myoporum bontioides[45]
Myoporum deserti[19]

R_1=OH, R_2,R_3=O
4-hydroxymyoporone (32)
Ipomoea sp. infected with *Fusarium solani*[47,48]



(29)

Athanasia crithmifolia[44]

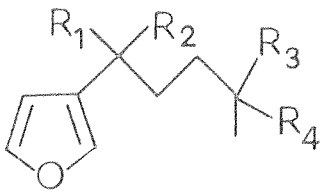


eumorphinone (30)[49]

1.2.1. Linear Skeleton

Many of the simplest, and most common, linear furanosesquiterpenoids have a structure based on dendrolasin (20). Dendrolasin (20) was initially isolated from the ant *Lasius fuliginosus*[10] and was the first example of a furanonatural product isolated from other than vegetable sources.[10] It has subsequently been isolated from plant sources (for example *Torreya nucifera*).[36]

Some of the furano monoterpenoids, e.g. batatic acid (8), may be derived from the dendrolasins.[13,50] Using ^{14}C labelling techniques 4-hydroxymyoporone (32) has been shown to be an intermediate in the production of the normonoterpenoids (13,33-35), by *Fusarium solani* infected sweet potatoes.[47]



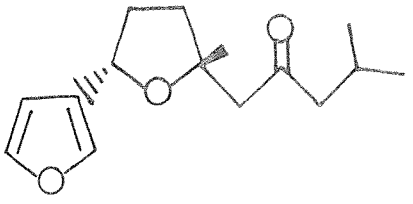
$R_1=R_3=H$, $R_2=R_4=OH$ (33)

$R_1,R_2=O$, $R_3=H$, $R_4=OH$ (34)

$R_1=H$, $R_2=OH$, $R_3,R_4=O$ (35)

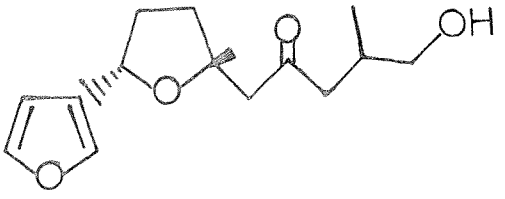
Close analogues of the dendrolasinsare the ipomeamarones (36-45) which have the inclusion of a tetrahydrofuran ring between C-4 and C-7. A typical representative, ipomeamarone (36), is the bitter principle produced by the tubers of *Ipomoea batatis* infected by the fungus *C. fimbriata* and other pathogens.[51-53] A significant feature of the ipomeamarones is the presence of the oxo-grouping at C-9 which may result in the formation of catabolites e.g. deisopropylngaione (46).[58]

Closely related to the ipomeamarones is eremoacetal (47),[8] which has been isolated from *Eremophila rotundifolia*, in which a further oxygen bridge has been formed.



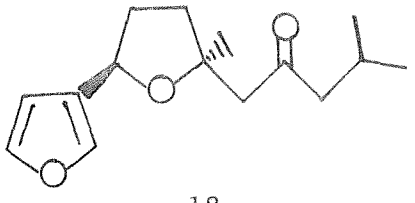
ipomeamarone (36)

Ipomoea sp. infected with pathogens[51-53]



ipomeamaronol (37)

Ipomoea sp. infected with *C. fimbriata*[54]



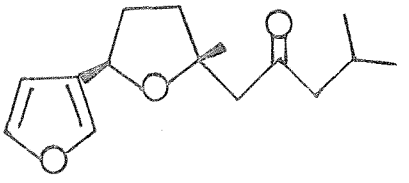
ngaione (38)[18]

Myoporum acuminatum

M. deserti[56]

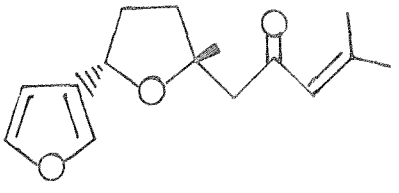
M. laetum[55]

Eremophila latrobei[53]



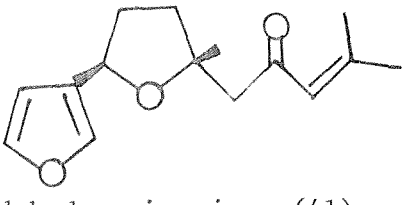
epingaione (39)

Myoporum deserti[57]



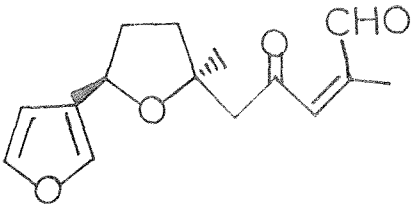
dehydroipomeamarone (40)

Ipomoea batatas infected with *C. fimbriata*[58,59]



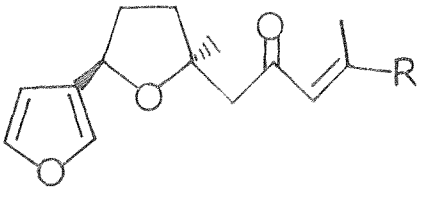
dehydroepingaione (41)

Myoporum deserti[57]



cis-dehydrongaional (42)

Athanasia crithmifolia[41]



R=CH_3 dehydrongaione (43)

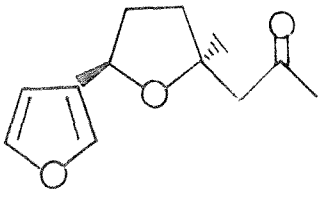
Myoporum deserti[57]

R=CH_2OAc (44)

Stilpnophytum linifolium[42,43]

R=CHO *trans*-dehydrongaional (45)

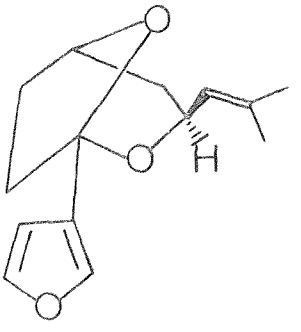
Athanasia crithmifolia[41]



(46)

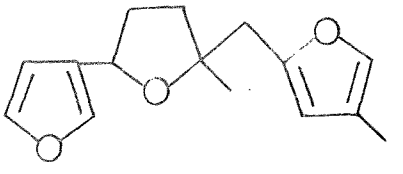
deisopropylngaione

Myoporum deserti[57]



eremoacetal (47)

Eremophila rotundifolia[58a]



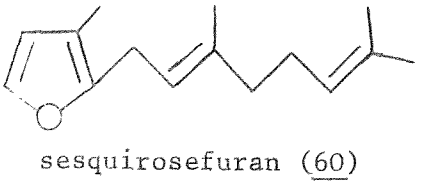
athanasin (48)

Athanasia crithmifolia[41]

The lasiospermans (49-59) may be considered to be derived from the dendrolasins by a further furan ring closure at the end of the dendrolasin (20) side chain. Similarly, athanasin (48)[41] may be considered to be derived from the lasiospermans by the introduction of a tetrahydrofuran ring. However athanasin could equally be considered to be derived from the ipomeamarones with the introduction of the second furan ring.

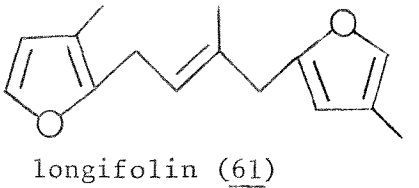
Freelingyne (57)[62] is one of a group of lactones which are analogues of the lasiospermans in which the furan ring has been replaced by an unsaturated γ-lactone or butenolide and is also the only furanosesquiterpenoid isolated to date to contain an acetylenic linkage.

Sesquirosefuran (60), an isomer of dendrolasin (20), has been isolated from *A.longifolia*[64] which is also a source of longifolin (61).[64] Longifolin (61) may be derived from sesquirosefuran (60) as dehydrolasiosperman (49) may be formed from dendrolasin (20).



sesquirosefuran (60)

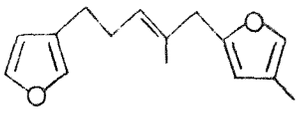
Actinodaphne longifolia[64]



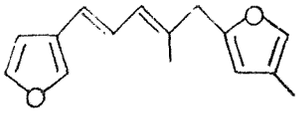
longifolin (61)

Actinodaphne longifolia[64]

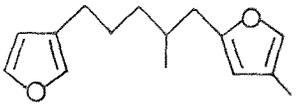
Asaemia axillaris[45]



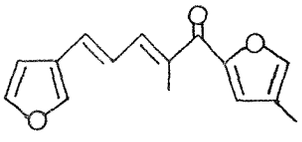
dehydrolasiosperman (49)
Athanasia incisa[41]
Lasiospermum radiatum[60]



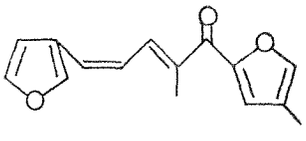
(50)
Lasiospermum radiatum[60]



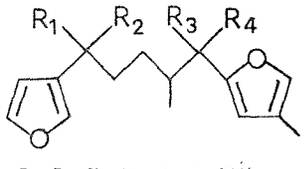
lasiosperman (51)
Lasiospermum radiatum[60]



(52)
Athanasia acerosa[41]
Athanasia parvifolia[41]
Lasiospermum sp.[41]

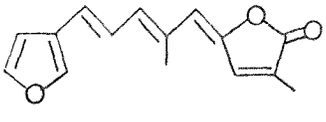


(53)
Athanasia acerosa[41]
Athanasia parvifolia[41]
Lasiospermum sp.[41]

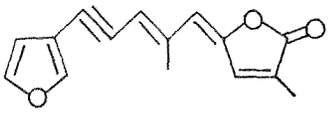


R_1=R_2=H, R_3,R_4=O (54)
Eumorphia dregeana[42,43]

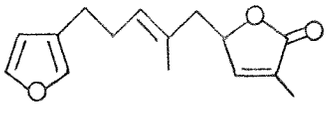
R_1,R_2=O, R_3=R_4=H (55)
Eumorphia sp.[49]



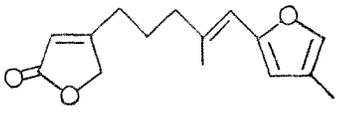
dihydrofreelingyne (56)
Eremophila freelingii[61]



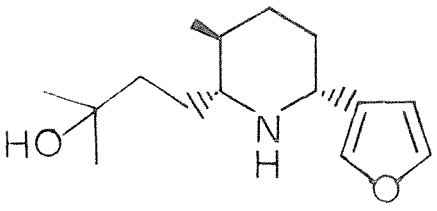
freelingyne (57)
Eremophila freelingii[62]



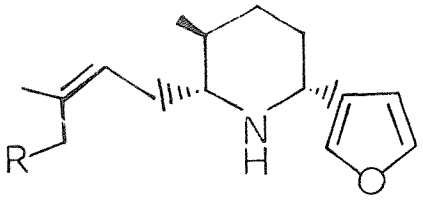
freelingnite (58)
Eremophila freelingii[63]



(59)
Athanasia sp.[63a]

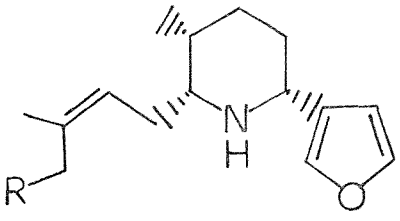


nupharamine (62)
Nuphar japonicum[69,70,71]



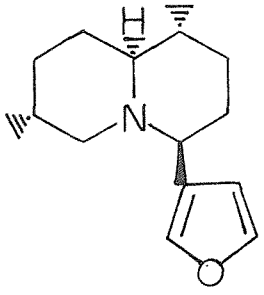
R=H anhydronupharamine (63)
Nuphar japonicum[72]

R=OH nuphamine (64)
Nuphar japonicum[73,74]

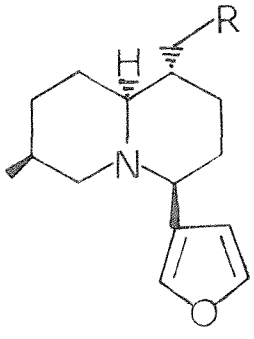


R=H nuphenine (65)
Nuphar variegatum[75]

R=OH 3-epinuphamine (66)
Nuphar luteum subsp. *variegatum*[76]



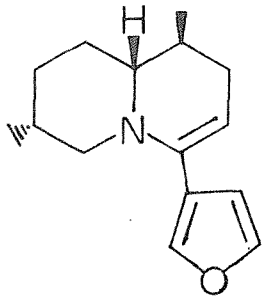
7-epidesoxynupharidine (67)
Nuphar luteum
subsp. *variegatum*[77]



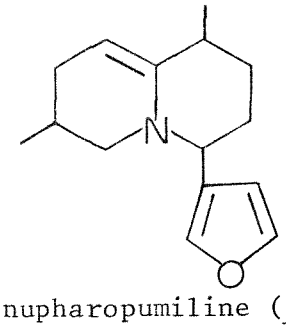
R=H desoxynupharidine (68)
Nuphar japonicum[78,79,80,81]

R=OH castoramine (69)
Castor canadensis[65,66,67,68]

R=H, N-oxide nupharidine (70)
Nuphar japonicum[78,79,80,82]



dehydrodeoxynupharidine (71)
Nuphar japonicum[83a]



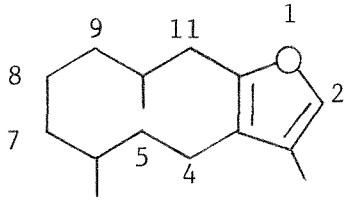
nupharopumiline (72)
Nuphar pumila[83b]

The nupharamines (62-66), isolated mainly from nymphaeaceous plants, can be considered to be derived from dendrolasin type intermediates by the formation of a nitrogen bridge. In each case the isoprene chain and the furan ring are *cis* whereas the stereochemistry of the methyl group at C-3 is dependant on the source.

A group of compounds, related to the nupharamines, which have also been isolated from nymphaeaceous plants is (67-72). In this group the isoprene side chain of the nupharamines has been cyclised on to the amine to form a quinolizidine nucleus. Castoramine (69) has been isolated from the scent gland of the beaver, *Castor canadensis*, and to date has been the only furanosesquiterpene isolated from a higher animal.[65,66,67,68]

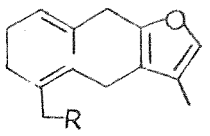
1.2.2. Germacrane Skeleton

All the furanogermacranes isolated to date possess a common skeleton (73) with the furan closure between C-2 and C-3a.

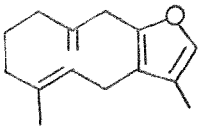


(73)

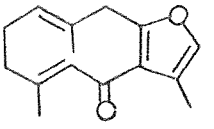
This group of furanosesquiterpenes is exemplified by furanodiene (74). Furanodiene has been isolated from the plant *Curcuma zeodoaria*[84] which has been a source of a number of furanosesquiterpenoids including pyrocurzerenone (266)[108] and curzerenone (102).[109] A simple anologue of furanodiene (74), is (76), isolated from an Australian soft coral,[87] other simple analogues include furanodienone (77) and isofuranodienone (78) in which C-4 has been oxidised to a ketone. In other furanogermacranes the methyl group at C-6 has been oxidised to form a series of lactones and esters. Further modification by oxidation of one or both of the double bonds has formed complex structures such as linderadine (96). The majority of furanogermacranes show oxidation to an alcohol or ketone moiety at C-4, however, the first examples to show oxidation at C-7 or C-8 (80,82,85) have been recently isolated from Myrrh.[92]



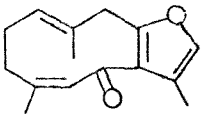
R=H furanodiene (74)
Curcuma zedoaria[84]
Eugenia uniflora[85]
Smyrnium olusatrum[86]



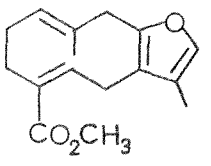
(76)[87]



furanodienone (77)
Curcuma zedoaria[88,89]

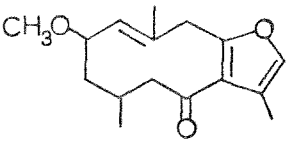


iso-furanodienone (78)
Curcuma zedoaria[88,89]

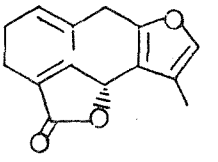


R=OAc neosericenyl acetate (75)
Lindera strychnifolia[90]

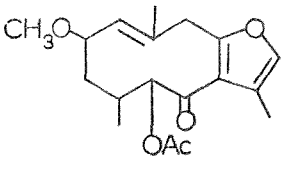
neosericenine (79)
Neolitsea sericea[91]



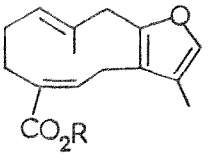
(80)[92]



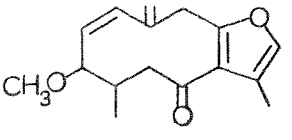
linderalactone (81)
Lindera strychnifolia[93]
Neolitsea aciculata[94]
N. sericea[34]
N. zeylanica[95]



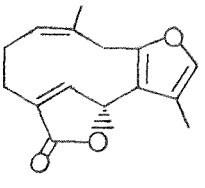
(82)[92]



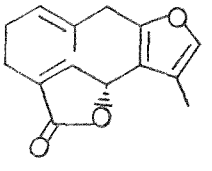
R=H sericenic acid (83)
R=CH_3 sericenine (84)
Neolitsea sericea[96]



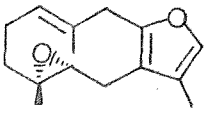
(85)[92]



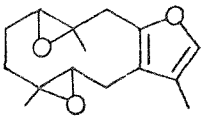
neolinderalactone (86)
Lindera strychnifolia[97,98]



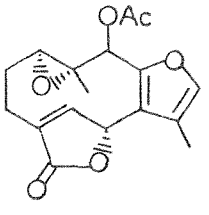
litsealactone (87)
Neolitsea aciculata[94,99]



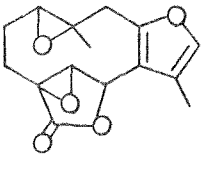
zederone (88)
Curcuma zedoaria[100,101,102]



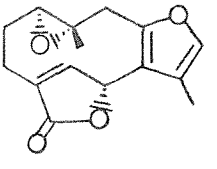
glechomafuran (89)
Smyrnium olusatrum[86]
Glechoma hederacea[103]



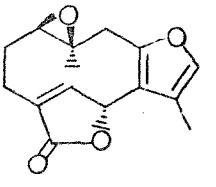
zeylanicine (90)
Neolitsea zeylanica[95,104]



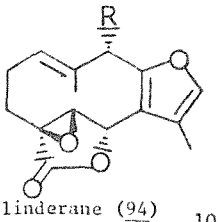
zeylanidine (91)
Neolitsea zeylanica[95,104]



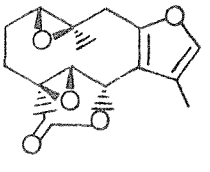
pseudoneolinderane (92)
Lindera strychnifolia[34]
Neolitsea aciculata[94]



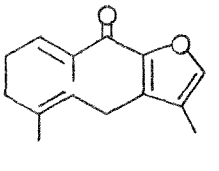
neolinderane (93)
Neolitsea aciculata[94]
N.zeylanica[95]



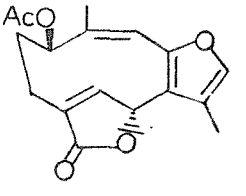
R=H linderane (94)
Lindera strychnifolia[105]
Neolitsea aciculata[94]
N. zeylanica[95]
R=OAc litseaculane (95)
N.aciculata[94,99]



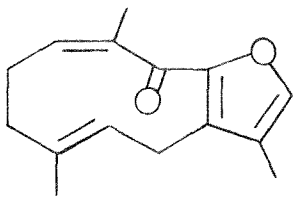
linderadine (96)
Neolitsea aciculata[94,106]



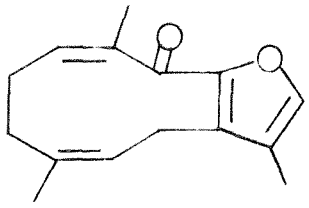
furanocaulesone-A (97)
Asarum caulescens[107]



zeylanine (98)
Neolitsea aciculata[94]
Neolitsea zeylanica[95]



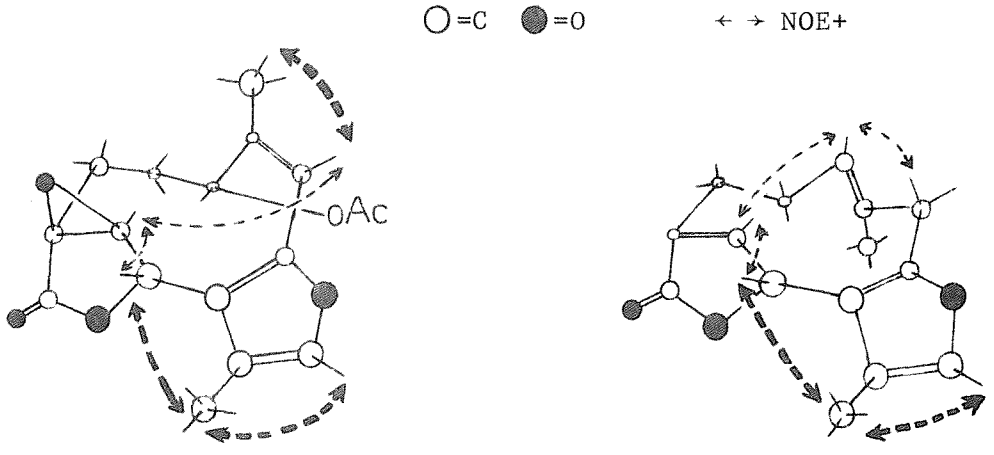
(99)
furanocaulesone-B
Asarum caulescens[107]



(100)
furanocaulesone-C
Asarum caulescens[107]

The conformation of the germacrane type ten-membered ring has been investigated by x-ray analysis of silver nitrate adducts.[110] The substitution pattern of a number of furanogermacranes has enabled easy identification of the protons in their ^{1}H nmr spectra from which their conformations have been elucidated by nuclear Overhauser techniques,[32] Figure 1.

Figure 1. The elucidation of the molecular conformations of zeylanane and linderalactone by means of the NOE technique.[32]



zeylanane (98)

linderalactone (81)

1.2.3. Elemane Skeleton

The furanoelemanes (101-108) can be considered to originate from furanogermacrane-type intermediates by a biogenetic Cope rearrangement.[32] The simplest representatives, *iso*furanogermacrene (101) and its oxygenated derivatives (102,103), correspond to the germacrane analogues (74,77,78) occurring in the same plant. The Cope rearrangement of some of the furanogermacranes to the elemane analogues has been shown to be very facile.[93,115] Linderalactone (81) has thus been isomerised to give a 2:3 mixture with *iso*linderalactone (106) at moderate temperatures (ca 170°) and even at room temperature linderalactone was found to be partially rearranged to *iso*-linderalactone (106).[93,115]

1.2.4. Eudesmane Skeleton

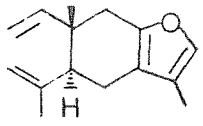
In contrast to the large number of eudesmane derivatives encountered as natural products only a few members (109-114) containing a furan nucleus have been isolated to date.

1.2.5. Lindenane Skeleton

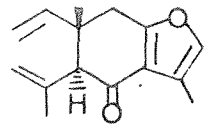
Several furanosesquiterpenoids (115-120) have been isolated containing the modified eudesmane or lindenane skeleton, all of which have been isolated from plants of the Lauraceae. Lindenenol (linderene) (116) was first obtained in 1925 from the tubers of *L.strychnifolia* and was one of the first furanonatural products to be isolated.[105]

1.2.6. Eremophilane Skeleton

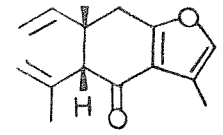
Furanosesquiterpenoids containing the eremophilane skeleton (262) are considerably more abundant than those containing any other skeleton and comprise some 140 examples (121-261). However, although numerous, this group shows little diversity of structural features.



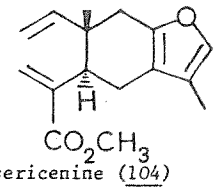
isofuranogermacrene, curzerene (101)
Curcuma zedoaria[84]
Lindera strychnifolia[111]
Smyrnium olusatrum[86]



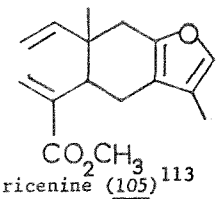
curzerenone (102)
Curcuma zedoaria[109]



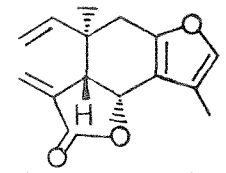
epicurzerenone (103)
Curcuma zedoaria[109]



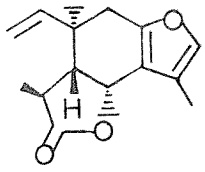
isosericenine (104)
Neolitsea sericea[112]



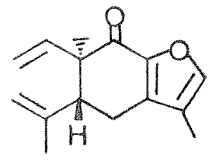
sericenine (105)[113]



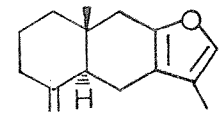
isolinderalactone (106)
Lindera strychnifolia[93,115]
Neolitsea aciculata[94]
N. sericea[34]



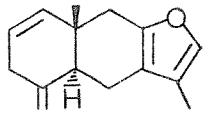
(107)
epidihydroisolinderalactone
Lindera strychnifolia[114]



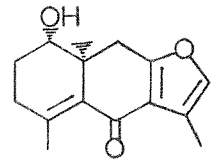
(+)-aoifuranone (108)
Asarum caulescens[107]



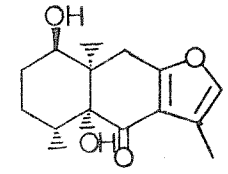
atractylon (109)[87]
Atractylodes sp.[116]
Atractylodes japonica[117]



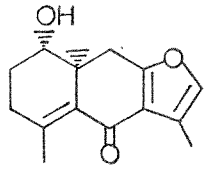
lindesterene (110)
Lindera strychnifolia[118]
Neolitsea sericea[34]



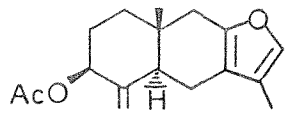
curcolone (111)
Curcuma zedoaria[119,120]



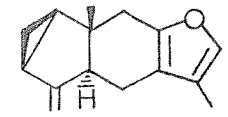
nehipediol (112)
Nepeta hindostana[121]



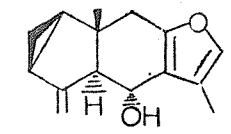
nehipetol (113)
Nepeta hindostana[121]



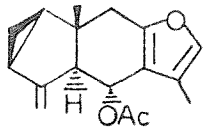
acetoxyatractylon (114)
Atractylodes lancea var. *chinensis* x *A. japonica*[122]



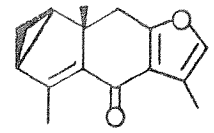
lindenene (115)
Lindera strychnifolia[123]
Neolitsea sericea[34]



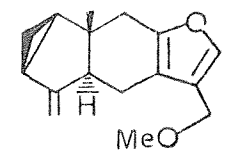
lindenenol (linderene) (116)[105]
Lindera strychnifolia



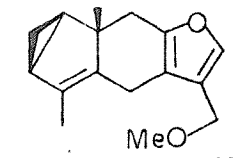
lindenenyl acetate (117)
Lindera strychnifolia[118]



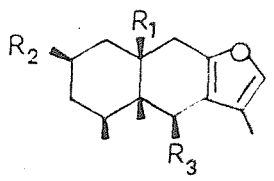
linderenone (118)
Lindera strychnifolia[98]



linderoxide (119)
Lindera strychnifolia[111]



isolinderoxide (120)[124]
Lindera strychnifolia



R_1=OH, R_2=H, R_3=H (121)
tetradymol
Tetradymia glabrata[125]

R_1=Ang, R_2=OH, R_3=H (122)
Euryops abrotanifolius[126]

R_1=OH, R_2=Mac, R_3=H (123)
Euryops linifolius[126]

R_1=OH, R_2=H, R_3=OH (124)
Lingularia japonica[127,128]
Othonna amplexicaulis[129]

R_1=OH, R_2=H, R_3=OMe (125)
Lingularia jaopnica[127,128]

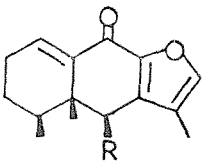
R_1=OH, R_2=H, R_3=Ang (126)
Othonna amplexicaulis[129]

R_1=OH, R_2=H, R_3=Tig (127)
Othonna amplexicaulis[129]

R_1=OH, R_2=H, R_3=Sen (128)
Furfugium japonicum[130]
Othonna amplexicaulis[129]

R_1=OH, R_2=H, R_3=Meb (129)
Lingularia japonica[127,128]
Othonna amplexicaulis[129]

R_1=OH, R_2=H, R_3=Iva (130)
Othonna amplexicaulis[127,128]



R=H (131)
9-oxoeuryopsin
Euryops virgeneus[126]

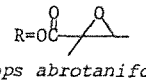
R=OAc (132)
decompositin
Cacalia decomposita[131]
Euryops othonnides[132]

R=Mac (133)
Euryops spathaceus[126]

R=Ibu (134)
Adenostylone
Adenostyles alliariae[133]

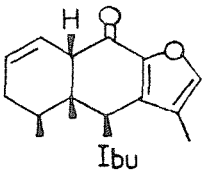
R=Ang (135)
neoadenostylone
Adenostyles alliariae[133]

R=Iva (136)
Senecio pterophorus[134]

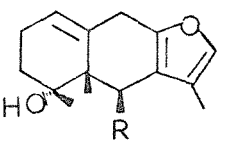


(137)
Euryops abrotanifolius[126]

$R=O\overset{O}{C}CH=C(CH_3)CH_2CH_3$ (138)
Senecio praecox[135]



(139)
isoadenostylone
Adenostyles alliariae[133]



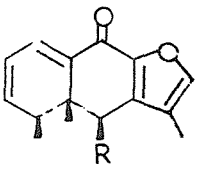
R=Ibu (140)
Euryops hebecarpus[126]

R=Ang (141)
Euryops tenuisissimus[126]

R=Tig (142)
Euryops virgineus[126]
Senecio elegans[134]

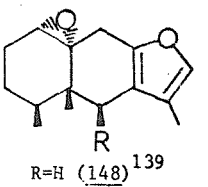
R=Sen (143), R=Meb (144)
Senecio elegans[134]

R=Iva (145)
Euryops hebecarpus[126]



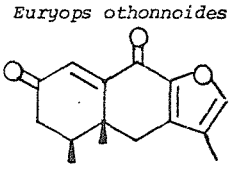
R=Mac (146)
Euryops spathaceus[126]

R=Ang (147)
Euryops spathaceus[126]

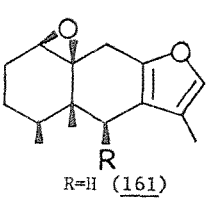


R=H (148)[139]
Senecio stylvaticus

R=OAc (149)[132], R=Ang (150)
Euryops othonnoides



(151)
Euryops tenuisissimus[126]



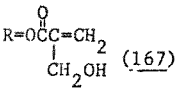
R=H (161)
Senecio glastifolius[134]

R=OH (162)
Ligularia fischeri[140]

R=OAc (163), R=Mac (164)
Senecio rigidus[134]

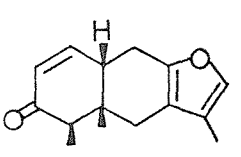
R=Ang (165)
Senecio nemorensis[141]

R=Sen (166)
Senecio rigidus[134]

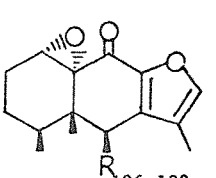


(167)
Ligularia fischeri[142]

$R=O\overset{O}{C}C(CH_3)=CHCH_2OH$ (168)
Ligularia vorobierii[143]



(152)[136]
10βH-furanoligularenone
Ligularia fischeri



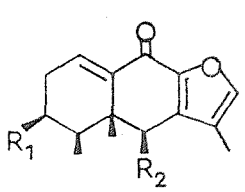
R=OAc (169)[126,132]
Euryops linifolius
Euryops othonnoides

R=Mac (170)[126]
Euryops spathaceus

R=Ibu (171)[132]
Euryops speciosissimus

R=Ang (172)[126]
Euryops linifolius
Euryops speciosissimus

R=Iva (173)[132]
Euryops speciosissimus



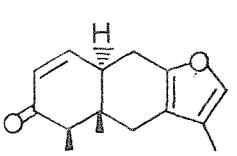
R_1=OH, R_2=Mac (153)
Euryops spathaceus[126]

R_1=OH, R_2=Ang (154)
Euryops spathaceus[126]

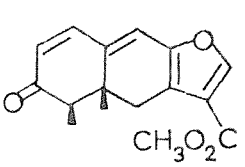
R_1=R_2=Mac (155)
Euryops spathaceus[126]

R_1=Mac, R_2=Ang (156)
Euryops spathaceus[126]

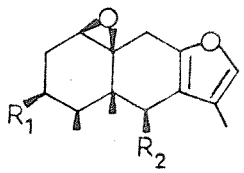
$R_1=O\overset{O}{C}CH=C(CH_3)CH_2CH_3$, R_2=H (158)
Senecio praecox[135]



furanoligularenone (159)
Aster tataricus[137]



warburgin (160)
Wargburgia ugandensis[138]

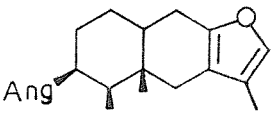


R_1=OH, R_2=Ibu (174)
nemosenin-C
Senecio nemorensis[141]

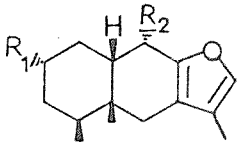
R_1=OH, R_2=Ang (175)
nemosensin-A
Senecio nemorensis[141]

R_1=OH, R_2=Meb (176)
nemosenin-B
Senecio nemorensis[141]

R_1=OAc, R_2=Ibu (177)
nemosenin-D
Senecio nemorensis[141]



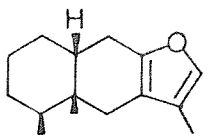
(178)
Othonna filicalis[129]



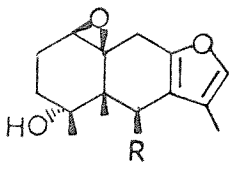
R_1=H, R_2=OH (179)
Petasites hybridus[144]

R_1=OH, R_2=OH (180)
furanopetasol
Petasites officinalis[145]

R_1=Ang, R_2=OH (181)
furanopetasin
Petasites officinalis[146]



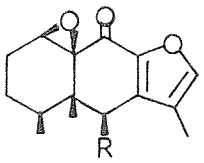
furanoeremophilane (190)
Petasites hybridus[146]
Petasites officinalis[147]



R=Ibu (182)
Euryops hebecarpus[126]

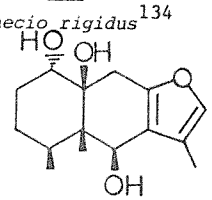
R=Ang (183)
Euryops abrotanifolius[126]

R=Iva (184)
Euryops abrotanifolius[126]

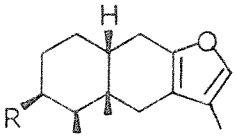


R=Ang (185)
Senecio glastifolius[134]

R=Sen (186)
Senecio rigidus[134]

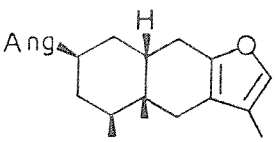


euryopsol (187)
Euryops floribundus[149]
Euryops tenuisissimus[149]

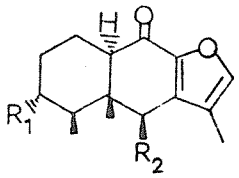


R=Ang (188)
Farfugium japonicum[130]

R=Mac (189)
Othonna macrophylla[148]



furanojaponin (191)
Petasites japonica[150]



R_1=R_2=H (192)
furanoeremophilone
Euryops othonnoides[132]
Petasites hybridus[151]

R_1=Mac, R_2=H (193)
Euryops linifolius[126]

R_1=Ibu, R_2=H (194)
Euryops speciosissimus[132]

R_1=Ang, R_2=H (195)
Euryops tenuisissimus[126]

R_1=Iva, R_2=H (196)
Euryops Speciosissimus[132]

R_1=OCC(=O)C(H)CH_3, R_2=H (197)
OH
Euryops speciosissimus[132]

R_1=H, R_2=Ibu (198)
Senecio umbellatus[134]

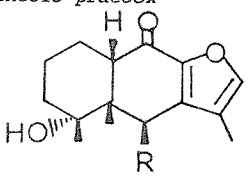
R_1=H, R_2=Ang (199)
Senecio umbellatus[134]

R_1=H, R_2=Iva (200)
Senecio umbellatus[134]

R_1=H, R_2=OCC(=O)CH=C(CH_3)CH_2CH_3
(201)
Senecio praecox[135]

R_1=H, R_2=Sen (202)
Senecio praecox[135]

R_1=H, R_2=OCC(=O)CH_2CH(CH_3)CH_2CH_3
(203)
Senecio praecox[135]

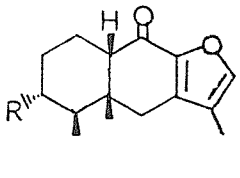


R=Ibu (214)
Euryops spathaceus[126]

R=Ang (215)
Euryops hebecarpus[126]

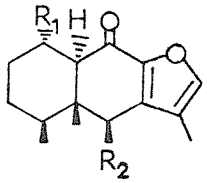
R=Tig (216)
Euryops virgineus[126]

R=Sen (217)
Euryops abrotanifolius[126]



R=H (204)
10βH-furanoeremophilone
Petasites albus[152]

R=OH (205)
euryopsonol
Euryops floribundies[153]



R_1=OH, R_2=Ibu (206)
Senecio umbellatus[134]

R_1=OH, R_2=Ang (207)
Senecio rigidus[134]

R_1=OAc, R_2=Ibu (208)
Senecio umbellatus[134]

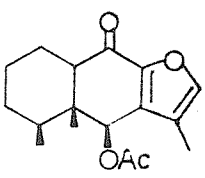
R_1=OAc, R_2=Ang (209)
Senecio rigidus[134]

R_1=OAc, R_2=Tig (210)
Senecio umbellatus[134]

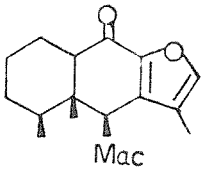
R_1=Ang, R_2=OAc (211)
Senecio rigidus[134]

R_1=OH, R_2=Tig (212)
Senecio umbellatus[134]

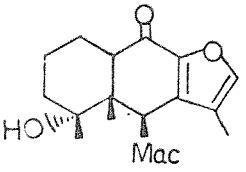
R_1=Sen, R_2=Ibu (213)
Senecio panduriformis[154]



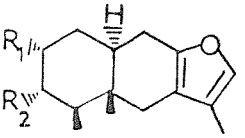
(218)
dihydrodecompositin
Euryops othonnoides[132]



(219)
Euryops spathaceus[126]



(220)
Euryops spathaceus[126]

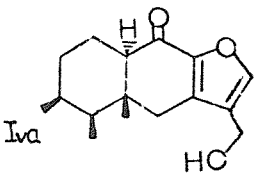


R_1=Ang, R_2=OAc (238)
Othonna bulbosa[129]

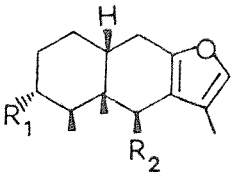
R_1=R_2=Ang (239)
Othonna bulbosa[129]

R_1=Ang, R_2=Sen (240)
Othonna bulbosa[129]

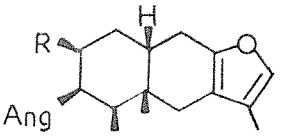
R_1=Sen, R_2=OAc (241)
Othonna bulbosa[129]



(248)
Euryops speciosissimus[132]

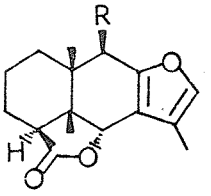


R_1=H, R_2=OH (221)
ligularol or petasalbin
Ligularia sibirica[155]
Petasites albus[152]



R=OAc (230)
Othonna barkerae[129]

R=Ang (231)
Othonna barkerae[129]

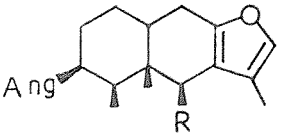


R=Tig (249)
Ligularia sp.[163]

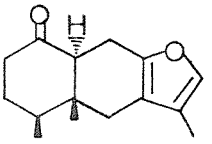
R=H (250)
Ligularia sp.[156,157]

R_1=H, R_2=OCH_3 (222)
Petasites japonicus[150]

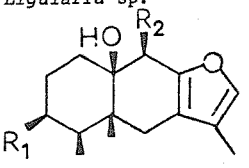
R_1=H, R_2=Sen (223)
Farfugium japonicum[130]

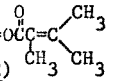


R=H (232)
Othonna filiculis[129]
R=OAc (233)
Othonna filiculis[129]



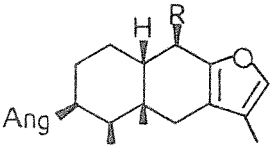
furanoeremophilone-(1)
(243)
Smyrnium olusatrum[86]



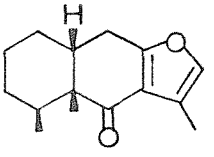
R_1=Tig, R_2= 
(252)
Farfugium japonicum[158]

R_1=Tig, R_2=H (253)
Farfugium japonicum[158]

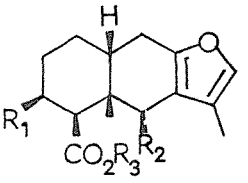
R_1=OH, R_2=OH (224)
furanofukinol
Farfugium hiberniflorum[144]
Petasites japonicum[150]



R=H (234)
Farfugium japonicum[130]
R=Sen (235)
Farfugium japonicum[130]



ligularone (244)
Ligularia sibirica[155]



R_1=Ibu, R_2=Ang, R_3=H
(254)
Othonna coronopifolia[129]

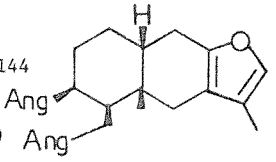
R_1=OH, R_2=OAc (225)
Petasites japonicus[150]

R_1=OH, R_2=Ang (226)
Farfugium hiberniflorum[144]
Petasites japonicum[150]

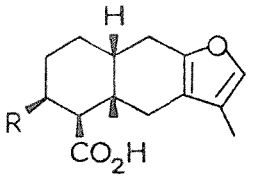
R_1=Ang, R_2=H (227)
Farfugium hiberniflorum[144]

R_1=Ang, R_2=OAc (228)
Farfugium hiberniflorum[144]

R_1=  , R_2=Ang (229)
Petasites japonicus[150]



(236)
Othonna amplexicaulis[129]



R=Mac (245)
Othonna amplexicaulis[129]

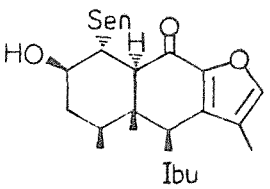
R=Ang (246)
Othonna dentata[129]

R_1=Ang, R_2=Ang, R_3=H
(255)
O. quercifolia[129]

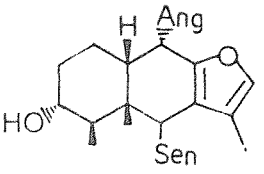
R_1=Sen, R_2=Ang, R_3=H
(256)
O. quercifolia[129]

R_1=Iva, R_2=Tig, R_3=H
(257)
Ligularia intermedia[159]

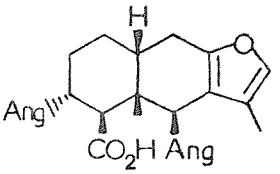
R_1=H, R_2=Ang, R_3=CH_3
(258)
Ligularia macrophylla[160]



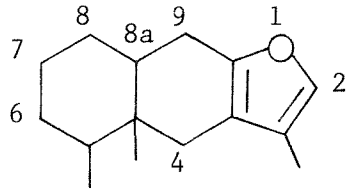
(251)
Senecio panduriformis[154]



kablicin (237)
Petasites kablikianus[145]

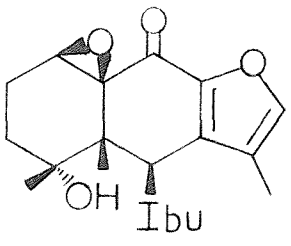


(247)
Othonna barkerae[129]



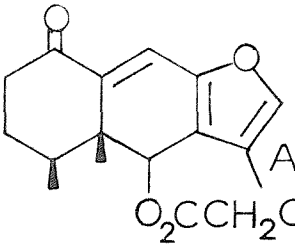
(262)

Among the furanoeremophilanes, the ones possessing the most basic structures are tetradymol (121) and furanoeremophilane (190). Oxidation at C-8, C-9 or C-4, together with occasional epoxide bridges (C-8 to C-8a) (e.g. nemosenin-C (174)) forms the majority of the furanoeremophilanes, with the substitution pattern, in general, being specific to certain types of plants. For example the C-8 to C-8a α-epoxide bridge (149,150,169-173) appears to be a characteristic of the *Euryops* sps. with only isolated examples of the bridge appearing elsewhere (e.g. (148) from *Senecio stylvaticus*[139]). Compounds isolated from *Othonna* sps. (245,246,254-256) in general show oxidation of the methyl group at C-5 and also functionalisation of C-6. One of the major characteristic features in the furanoeremophilanes is the predominance of the A/B ring junction *cis*-fused. Thus the 8a α-H furanoeremophilone analogues, which are occasionally found, may be artefacts and originally present as their 8a β-H furanoeremophilone counterparts, since the *cis*-ketone is easily epimerised to the *trans*-ketone.



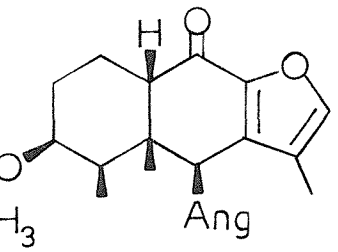
(259)

Senecio salignus[135]



(260)

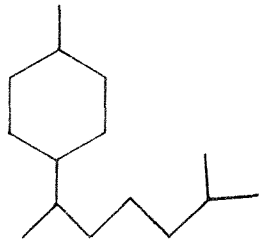
Senecio pampse[161]



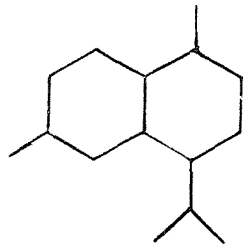
(261)

Gynoxys psilophylla[162]

1.2.7. Bisabolane and Cadinane Skeletons



(263)

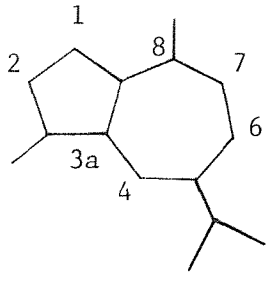


(264)

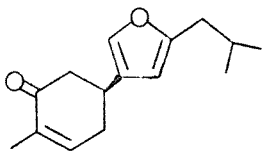
Although the bisabolane (263) and cadinane (264) skeletons are widespread throughout the sesquiterpenoids,[3] only a few examples (265-272) of these skeletons containing a furan nucleus have been isolated to date.

1.2.8. Modified Guaiane Skeleton

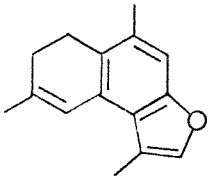
The group of furanosesquiterpenoids (273-276) can be considered derived from a guaiane skeleton (277) by cleavage between C-7 and C-8 and then furan ring formation between C-7 and C-4.



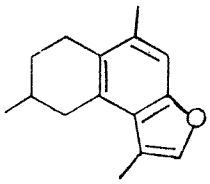
(277)



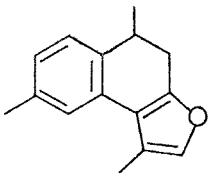
bilobanone (265)
Ginko biloba[164]



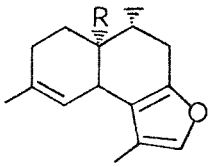
pyrocurzerenone (266)
Curcuma zedoaria[108]



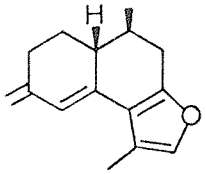
dihydropyrocurzerenone (267)
Chloranthus serratus[165]



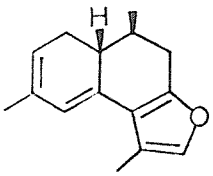
laevigatin (268)
Eupatorium laevigatum[166]



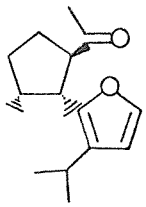
R=H (269)
R=OH (270)
Verbesima occidentalis[167]



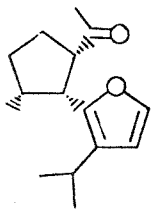
(271)
Chromolaena tumariensis[168]



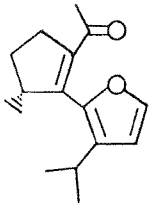
(272)
Chromolaena tumariensis[168]



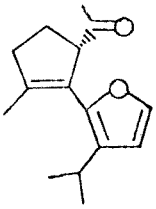
furopelargone-A (273)
Pelargonium roseum[169]
Geranium bourbon[170]



furopelargone-B (274)
Pelargonium roseum[169]
Geranium bourbon[170]



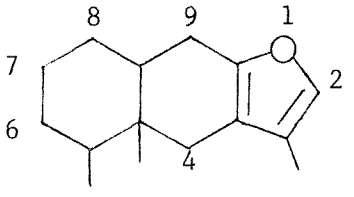
furopelargone-C (275)
Geranium bourbon[171]



furopelargone-D (276)
Geranium bourbon[171]

1.2.9. Modified Eremophilane Skeletons

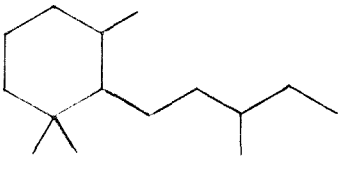
Furanosesquiterpenoids possessing modified eremophilane skeletons fall into four groups. The largest group, 'subgroup A' 278-293), possess a skeleton in which the C-4a methyl group of the furanoeremophilane skeleton (262) has undergone 1,2-migration to C-4.



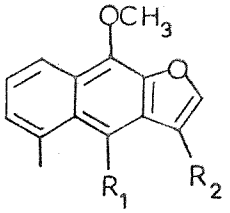
(262)

In maturinone (292) and maturone (293) the methyl group at C-4 has been replaced with a carbonyl group to form quinones. Cleavage between C-4a and C-5 of the furanoeremophilane skeleton forms 'subgroup B' (294-296) whereas cleavage between C-4 and C-4a forms 'subgroup C' (297-299). The last group, 'subgroup D' (300) is unusual in that the five carbon fragment generated by A-ring fission (C-4a/C-5) has been migrated to C-9.

1.2.10. Monocyclofarnesane Skeleton



(306)



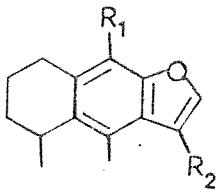
R_1=R_2=CH_3 (278)
O-methylcacaldienol
Cacalia auriculata var. *kamtschatica*[172]
Cacalia hastata[173]

R_1=CHO, R_2=CH_3 (279)
maturinin
Cacalia decomposita[174]

R_1=CHO, R_2=CH_2OH (280)
maturin
Cacalia decomposita[174]

R_1=CH_3, R_2=CHO (281)
isomaturinin
Senecio panduriformis[154]

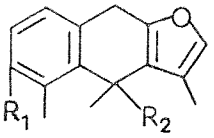
R_1=CHO, R_2=CHO (282)
Senecio panduriformis[154]



R_1=OAc, R_2=CH_3 (283)
cacalol acetate
Cacalia delphiniifolia[175]

R_1=OH, R_2=CH_3 (284)
cacalol
Cacalia decomposita[176]

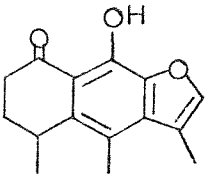
R_1=OH, R_2=Sen (285)
Cacalia delphiniifolia[175]



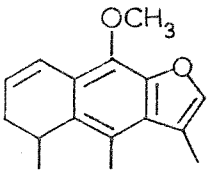
R_1=H, R_2=OH (286)
cacalonol
Cacalia auriculata[172]

R_1=H, R_2=OOH (287)
peroxycacalonol
Cacalia hastata var. *tanakae*[175,177]

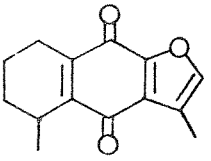
R_1=OCH_3, R_2=OH (288)
Cacalia hastata var. *tanakae*[175,177]



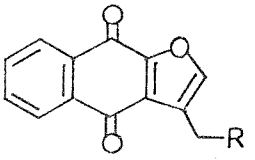
cacalone (289)
Cacalia decomposita[176]



(290)
Cacalia auriculata var. *kamtschatica*[172]
Cacalia hastata[173]
Euryops linifolius[126]

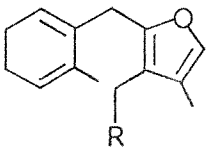


tetrahydromaturinone (291)
Cacalia delphiniifolia[175,177]



R=H (292)
maturinone
Cacalia decomposita[174]

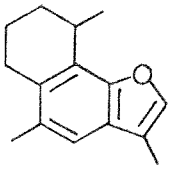
R=OH (293)
maturone
Cacalia decomposita[174]



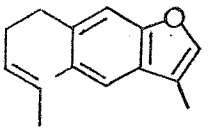
R=Mac (297)
Euryops hebecarpus
Euryops tenuisissimus[126]

R=Ang (298)
Senecio elegans[134]

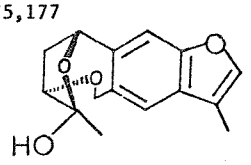
R=Sen (299)
Euryops hebecarpus[126]



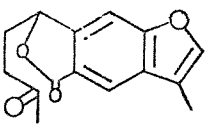
farfugin-A (300)
Farfugium japonicum[178]



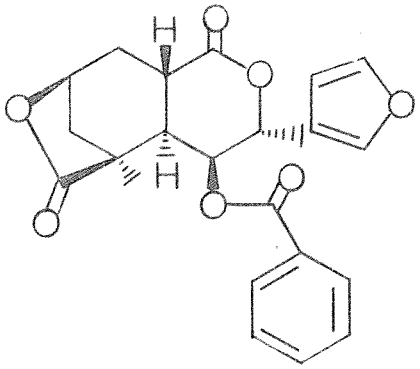
farfugin-B (294)
Farfugium japonicum[178]



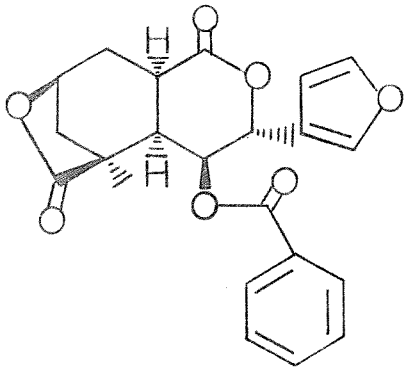
(295)
Euryops hebecarpus[126]



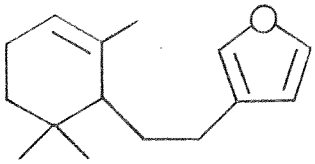
(296)
Euryops hebecarpus[126]



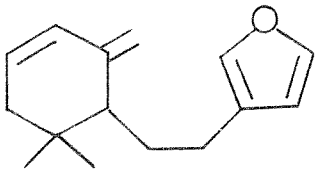
collybolide (1)
Collybia maculata[1,179]



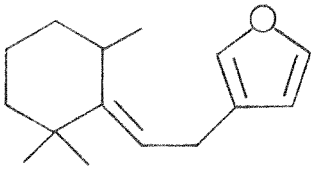
*iso*collybolide (301)
Collybia maculata[180]



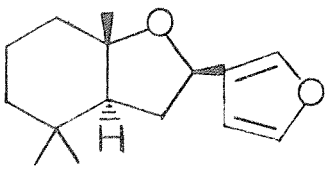
pallescensin-1 (302)
Disidea pallescens[181]



pallescensin-2 (303)
Disidea pallescens[181]



microcionin-3 (304)
Microciona toxtstila[182]



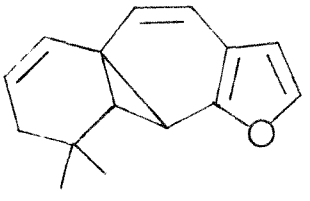
ancistrofuran (305)
Ancistrotermes cavithorax[9]

Collybolide (1) was first isolated in 1911[1], however its structure was not unambiguously assigned until 1974 by Bui.[179] Other furanosesquiterpenoids possessing the monocyclofarnesane (or farnesiferol[183]) skeleton (306) are pallescensins-1 (302) and -2 (303) from the marine sponge *Disidea pallescens*,[181] ancistrofuran (305) from the termite *Ancistrotermes cavithorax*[9] and micronin-3 (304) from another sponge *Microciona toxystila*.[182]

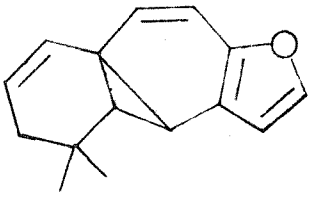
1.2.11. Furanosesquiterpenoids Possessing Less Common Skeletons

A number of furanosesquiterpenoid natural products possess structures which do not have a common terpene carbon skeleton and as such are difficult to classify. The simplest example, the furan ester (307), has been isolated from the Mediterranean sponge *Pleraplysilla spinifera*[38] and from the nudibranch *Chromodoris marislae*.[184] The sponge *Pleraplysilla spinifera* has also been a source of spiniferin-1 (314) and spiniferin-2.[38]

Cimino was unable to decide between the two structures (315) and (316) for spiniferin-2 as each structure was compatible with the chemical and physical data he obtained for spiniferin-2.[38] The structure of spiniferin-1 has been recently shown to be (314) by ^{13}C nmr spectroscopy[196] after it was incorrectly assigned as (348) or (349).[38]



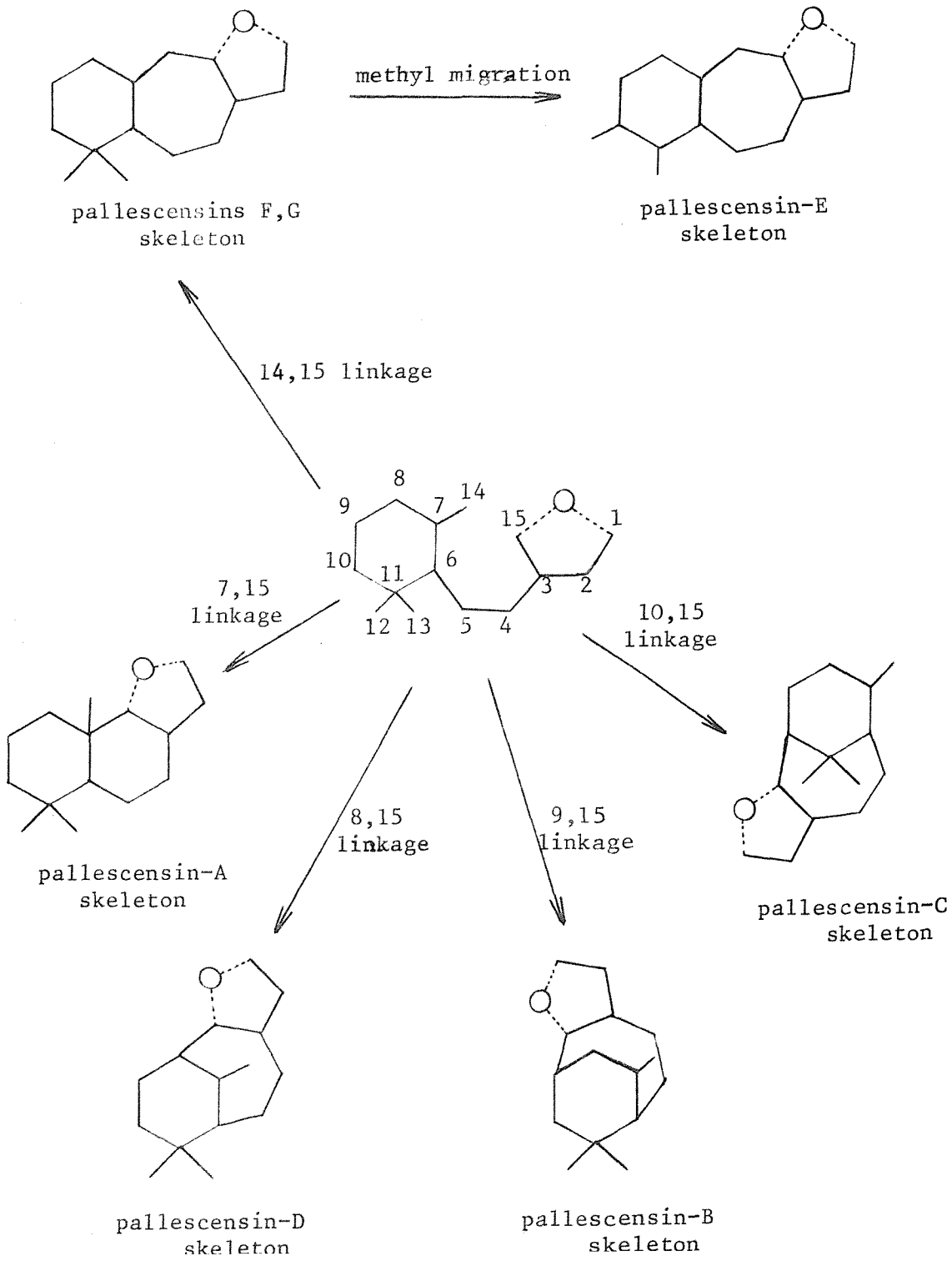
(348)

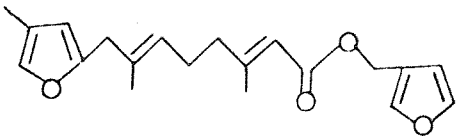


(349)

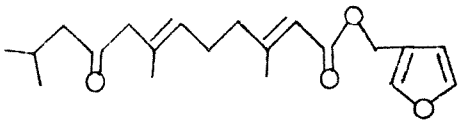
The pinguisones (328-332) form a group of structures which have all been isolated from liverworts, pinguisone (325) from *Aneura pinguis*[8] and the remainder (329-332) from *Pollera vernicosa*.[191] The marine sponge *Disidea pallescens* has been a rich source of furanosesquiterpenes with unusual structures (333-339) each of which could be considered derived from a monocyclofarnesyl skeleton with the appropriate ring closure, figure 2.[181,192]

FIGURE 2. Possible biogenetic scheme for the formation of pallescensins A-G

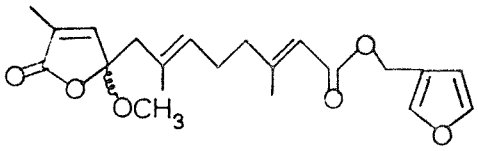




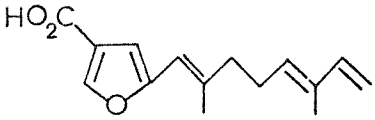
(307)
Pleraplysilla spinifera[38]
Chromodoris marislae[184]



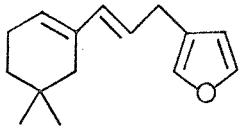
(308)
Chromodoris marislae[184]



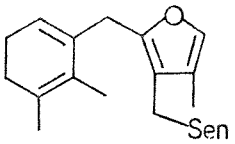
(309)
Chromodoris marislae[184]



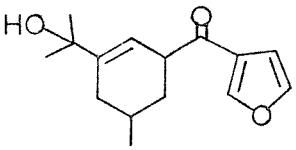
(310)
Sinularia gonatodes[185]



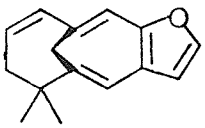
(311)
Pleraplysilla spinifera[38]



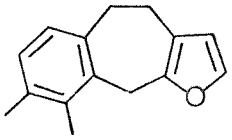
(312)
Senecio elegans[134]



(313)
Eumorphistonol
Eumorphia sp.[48b]

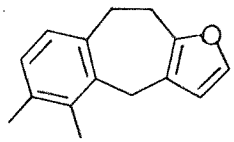


(314)
spiniferin-1
Pleraplysilla spinifera[38]



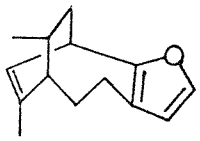
(315)

or

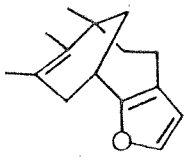


(316)

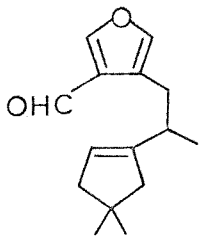
Pleraplysilla spinifera[38]



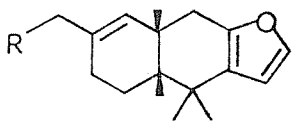
(317)
nakafuran-8
Hypselodoris godoffroyana[186]
Chromodoris maridadilus[186]
Dysidea fragilis[186]



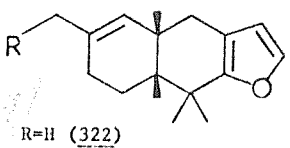
(318)
nakafuran-9
Hypselodoris godoffroyana[186]
Chromodoris maridadilus[186]
Dysidea fragilis[186]



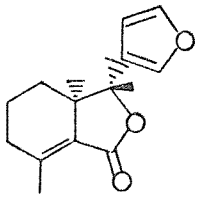
lactaral (319)
Lactarius vellereus[187]
L. pergamenus[188]



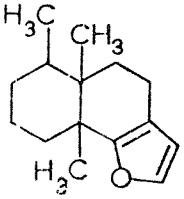
R=H (320)
furodysinin
R=SAc (321)
Dysidea herbacea[189]



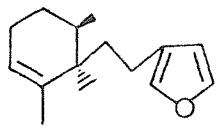
R=H (322)
furodysin
R=SAc (323)
Dysidea herbacea[189]



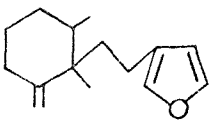
fraxinellone (324)
Dictamnus albus[190]



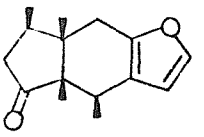
microcionin-1 (325)
Microciona toxystila[182]



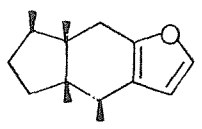
microcionin-2 (326)
Microciona toxystila[182]



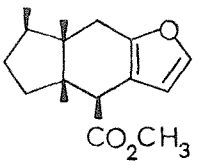
microcionin-4 (327)
Microciona toxystila[182]



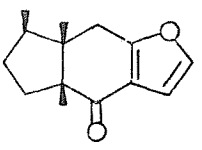
pinguisone (328)
Aneura pinguis[8]



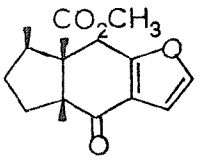
deoxopinguisone (329)
Ptilidium ciliare
Pollera vernicosa[191]



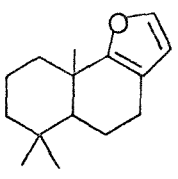
(330)
Pollera vernicosa[191]



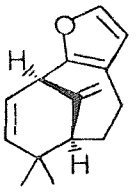
(331)
Pollera vernicosa[191]



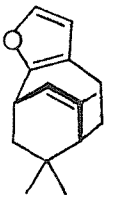
(332)
Pollera vernicosa[191]



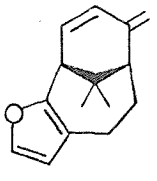
pallescensin-A (333)
Disidea pallescens[181,192]



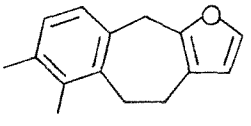
pallescensin-D (334)
Disidea pallescens[181,192]



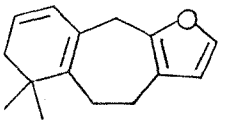
pallescensin-B (335)
Disidea pallescens[181,192]



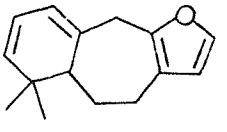
pallescensin-C (336)
Disidea pallescens[181.192]



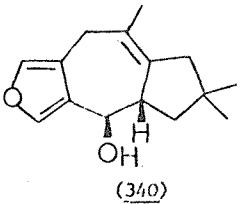
(337)
pallescensin-E
Disidea pallescens[7,181]



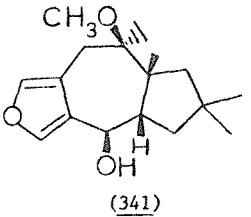
(338)
pallescensin-F
Disidea pallescens[7,181]



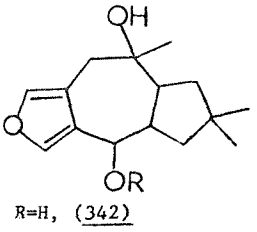
(339)
pallescensin-G
Disidea pallescens[7,181]



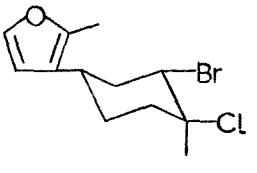
(340)
Formitopsis insularis[193]
Lactarius vellereus[194]



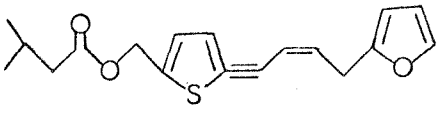
(341)
Lactarius vellereus[194]



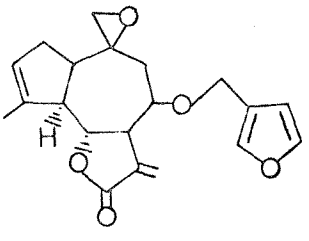
R=H, (342)
R=Ac (343)
Formitopsis insularis[193]



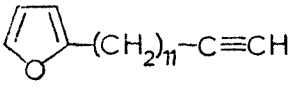
(344)
furocaespitane
Laurencia caespitosa[195]



(345)
Santolina rosmarinifolia[197]



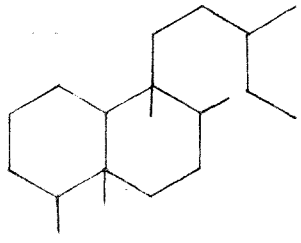
Bahifolin (346)
Bahia oppositifolia[198]



(347)
avocadypofuran
avocado pear[199,200]

1.3. Diterpenoid Furanonatural Products

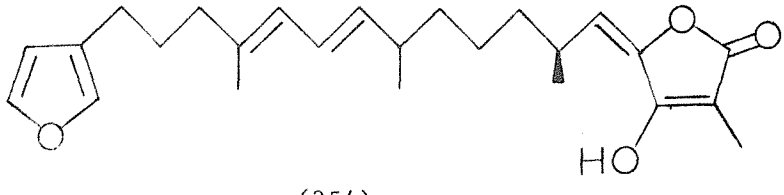
The large number of furanoditerpenoids can be classified into seven main skelatal types, with the kolevane skeletal (350) group containing the most members. Some furanoditerpenoid natural products have been previously reviewed by Baker.[201]



(350)

1.3.1. Linear Skeleton

Only three examples of furanoditerpenes with a linear skeleton have been isolated to date, (351) from the sponge *Dysidea amblica*,[202] phytofuran (352) from Burley tobacco,[203] and (353) from *Centipeda orbicularis*.[204] The large number of C_{21} furanoterpenoids, which have been mainly isolated from sponges (e.g. fasciculatin (354)), have been considered by Minale[207] to arise from biologically truncated sesterterpenes rather than extended diterpenes and so are included below under the sesterterpenoids.

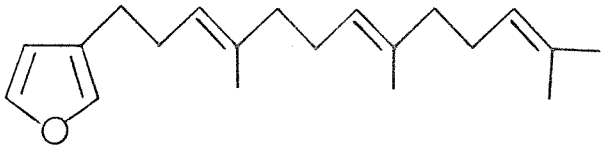


(354)

fasciculatin[296]

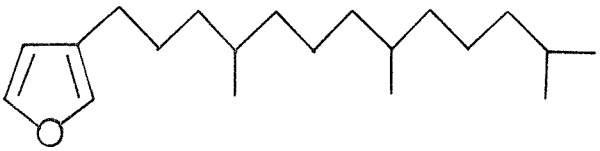
1.3.2. Labdane Skeleton

Furanoditerpenoids possessing the labdane skeleton can be considered to fall into two main groups. The first group (356-364)



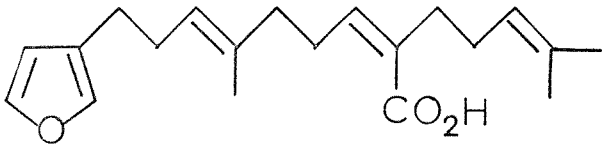
(351)

Dysidea amblia[202]



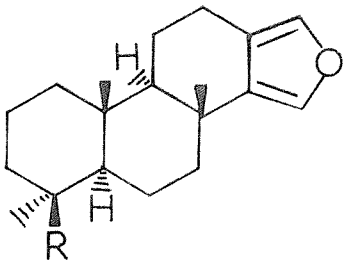
phytofuran (352)

'Burley tabacco'[203]



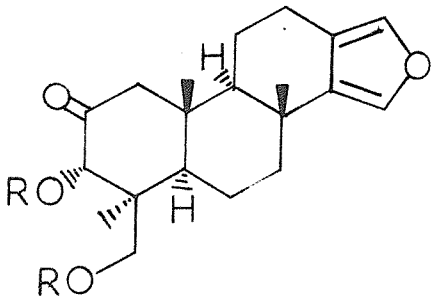
(353)

Centipeda orbicularis[204]



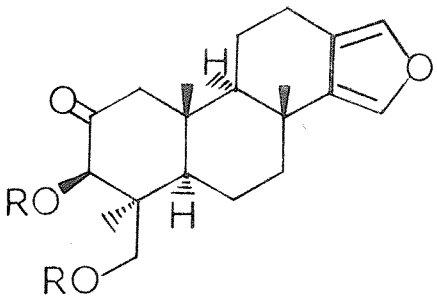
R=CO_2H (356)
R=CHO (357)
R=CH_3 (358)

Spongia officinalis[205]



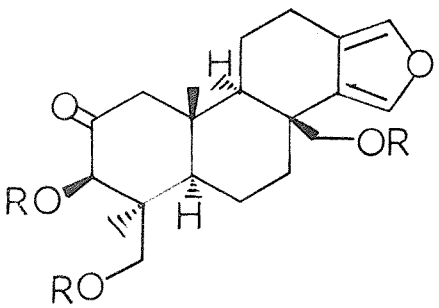
R=H (359)
R=OAc (360)

Spongia sp.[206]



R=H (361)
R=Ac (362)

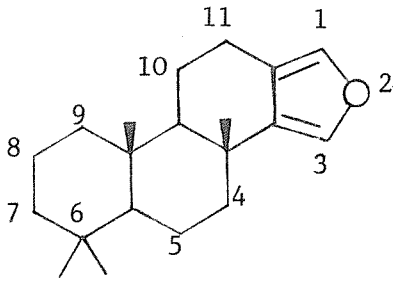
Spongia sp.[206]



R=H (363)
R=Ac (364)

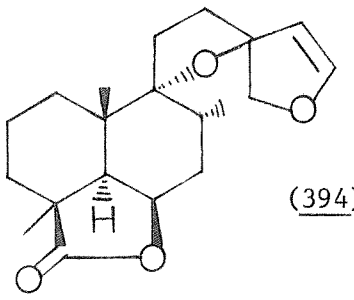
Spongia sp.[206]

possess the labdane skeleton (355) intact whereas in the second group (365-393) bond fission has occurred between C-3a and C-3b. In the majority of the group the *gem* dimethyl group at C-6 has been oxidised to an alcohol or acid moiety which may form a lactone with C-5, or the oxidised methyl group at C-9a. Compounds with functionalisation of the A-ring are rare, with only the ketones austrofolin (389) and ballonigrinone (391) as examples to date.



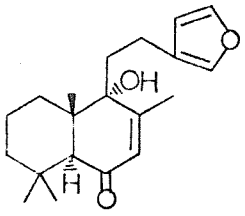
(355)
labdane skeleton

Laonigro has shown recently that the structure of the furanoditerpenoid marrubiin (374), possessing the modified labdane skeleton, is an artifact of the isolation procedure employed. The correct structure of the natural product is a spiroether (394) which readily rearranges to marrubiin (374) when heated in ethanol for a short time or is allowed to stand in chloroform.[233]

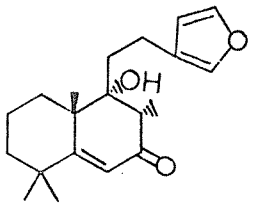


(394)

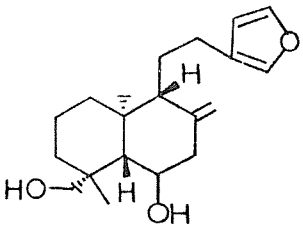
This result casts some doubt on the structure of some of the furanoditerpenoid 'natural products' (365,366 etc.) which may, in fact, be artifacts from the isolation procedure.



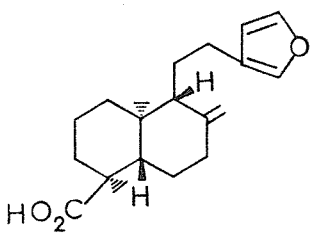
solidagenone (365)
Solidago canadensis[208]



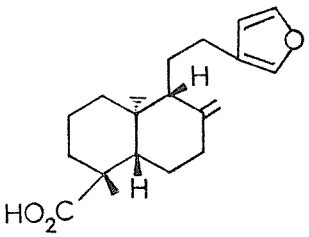
(366)
Leonotis leonurus[209]



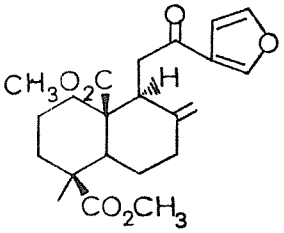
psiadiol (367)
Psiadia altissima[210]



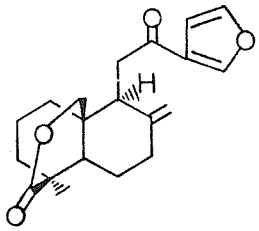
polyalthic acid (368)
Polyalthia fragrans[211]



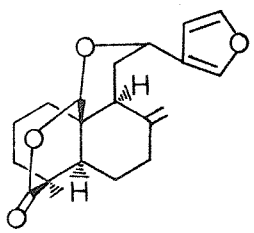
(-)-daniellic acid (369)
Daniella sp.[212]



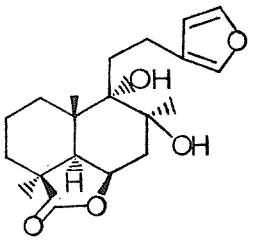
dimethyl sciadinonate (370)[213]



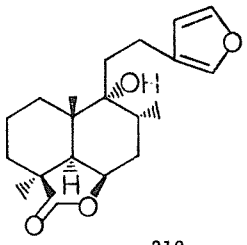
sciadinone (371)[214]



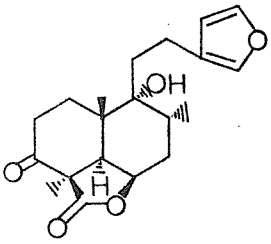
sciadine (372)
Sciadopitys verticullata[215]



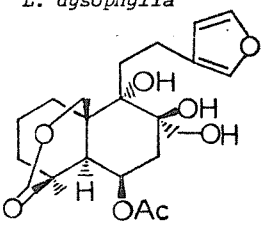
leonotin (373)
Leonotis nepetaefolia[216]
L. dysophylla[217]



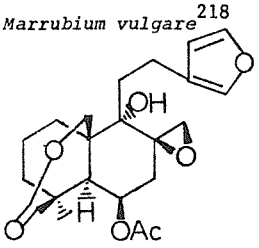
marrubiin (374)[218]
'horehound'
Marrubium vulgare[218]



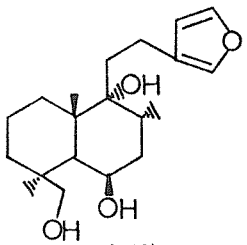
peregrinine (375)
Marrubium incanum[219]



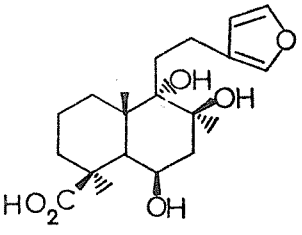
nepetaefuranol (376)
Leonotis nepetaefolia[220]



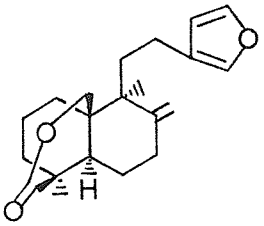
nepetaefuran (377)
Leonotis nepetaefolia[220]



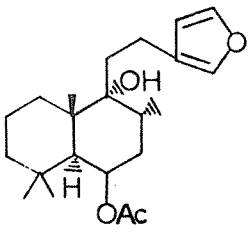
marrubenol (378)
Marrubium vulgare[221]



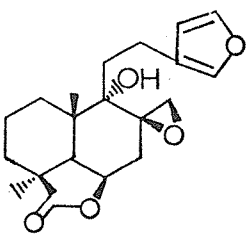
leonotic acid (379)
Leonotis nepetaefolia[216]



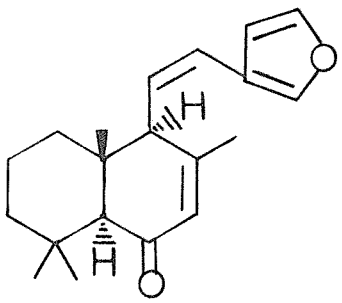
potamogetonin (380)
Potamogeton ferrugineus[222]



rotundifuran (381)
vitex rotundifolia[223]

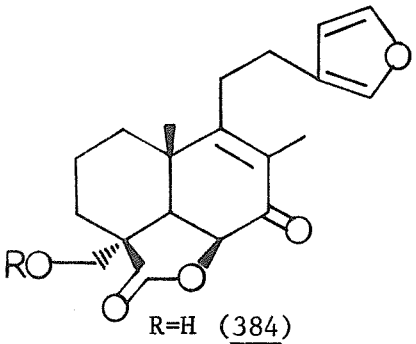


leonotinin (382)
Leonitis repetaefolia[224]



hedychenone (383)

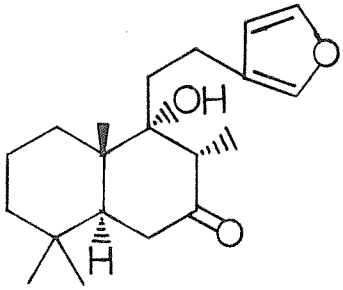
Hedychium spicatum[225]



R=H (384)

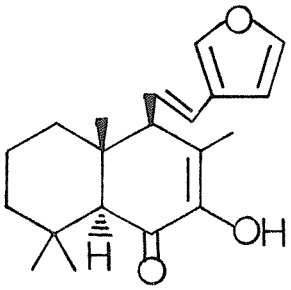
R=OAc (385)

Ballota acetobulosa[226]



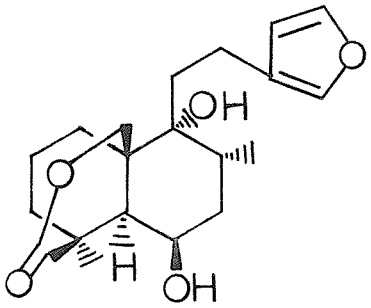
hispanolone (386)

Ballota hispanica[227]



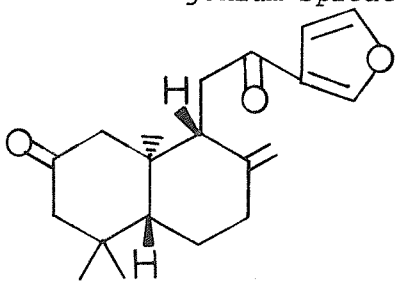
(387)

Hedychium spicatum[228]



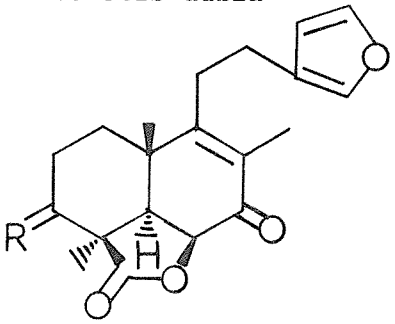
(388)

Leonotis dubia[229]



austrofolin (389)

Austroeupatorium inulae folium[230]



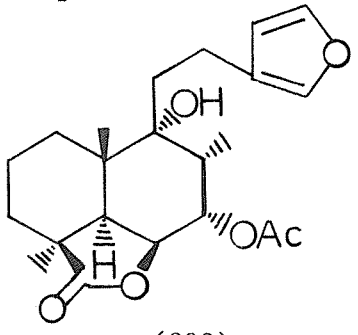
R=CH_3 (390)

ballonigrin

R=O (391)

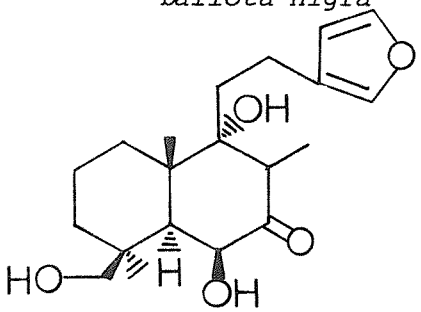
ballonigrinone

Ballota rupestris[231]



(392)

ballota nigra[232]



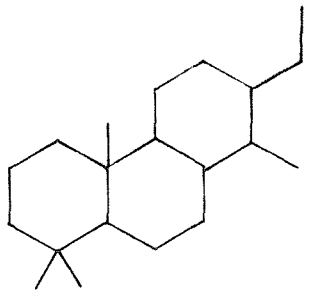
(393)

Ballota nigra[232]

1.3.3. Kolevane Skeleton

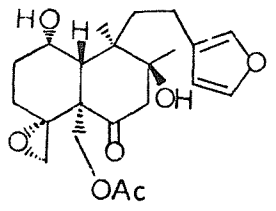
The group of furanoditerpenoids possessing the kolevane skeleton (350) can be divided into two main groups, those containing the complete skeleton (395-425), and the *nor* methyl series (426-441). Although the simplest member of the first group is (405) from *Solidago arguta*[240] the majority possess a variety of lactone and ether bridges. The *Teucrium* sps. has been a major source of furanoditerpenoids with both the complete kolevane skeleton and the *nor*-series being present.[234-239] X-ray techniques have played a key role in the elucidation of the stereochemistry of these structures which would have otherwise been difficult to assign.

1.3.4. Cassane Skeleton

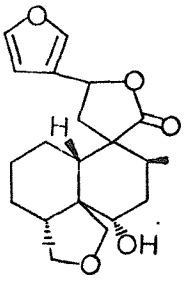


(442)

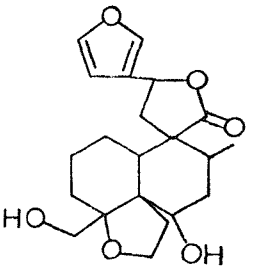
Furanoditerpenoids possessing the cassane skeleton (442) have been isolated from relatively few sources, with the majority of examples obtained from the fruits of *Pterodon emarginatus* (448-452)[270] and from *Caesalpina* sps. (443,444,446,447). The first example of a furanoditerpenoid to be isolated with the cassane skeleton was the ester (453) reported by Spoelstra in 1930 from the tree *Vouacapoua americana*.[274] This structure was assigned solely by chemical degradation, whereas the more recent examples have been assigned by x-ray techniques.[265]



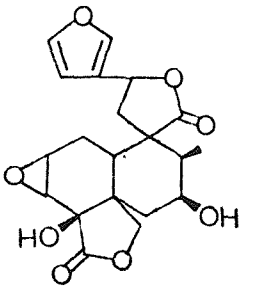
(395)
Teucrium fruticans[234]



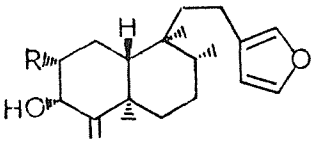
teucrin-E (401)
Teucrium chamaedrys[237]



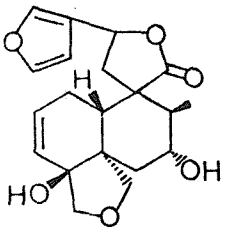
montanin-D (398)
Teucrium montanum[236]



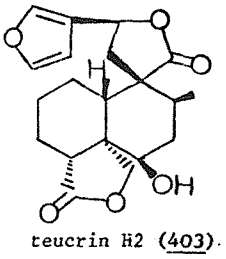
teucrin-G (399)
Teucrium chamaedrys[237]



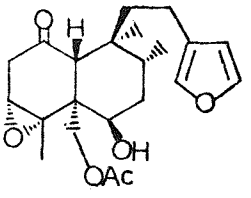
R=H agbaninol (396)
R=OH agbanindiol (397)
Gossweilerodendron balsamiferum[235]



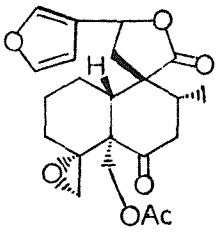
teucrin-F (400)
Teucrium chamaedrys[237]



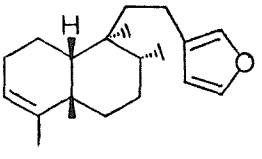
teucrin H2 (403)
Teucrium hyrcanicum[239]



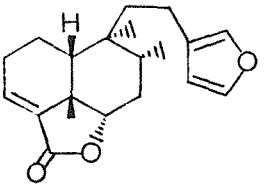
(402)
Teucrium fruticans[238]



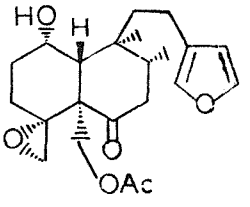
teucrin H3 (404)
Teucrium hyrcanicum[239]



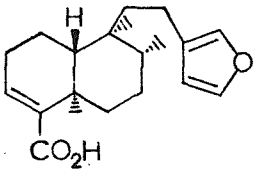
(405)
Solidago arguta[240]



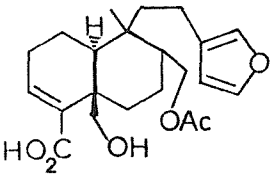
(406)
Solidago arguta[240]



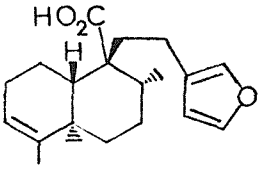
fruticolone (407)
Teucrium fruticans[238]



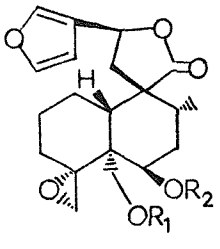
hardwickiic acid (408)
Hardwickia pinnata[241]



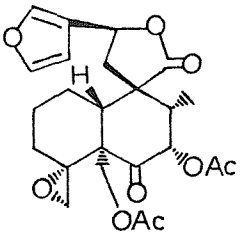
(409)
Dodonaea attenuata[245,246]



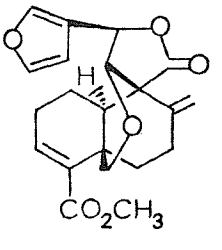
(410)
Solidago juncea[247]



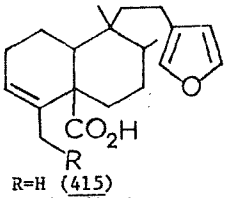
R_1=H, R_2=Ac (411)
R_1=Ac, R_2=H (412)
Teucrium polium[242]



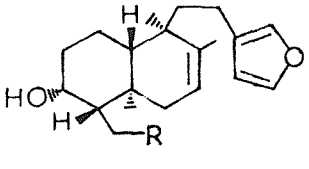
capitatin (413)
Teucrium capitatum[243]



croverin (414)
Croton verreauxii[244]

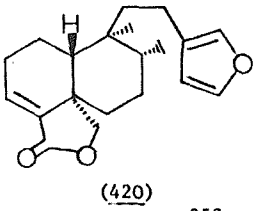


R=H (415)
R=Tig (416)
Solidago serotina[248-9]

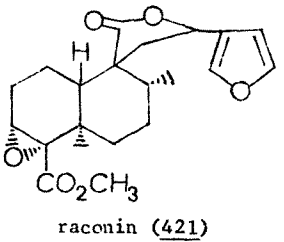


R=Iva (417)
R=Meb (418)
R=Ang (419)

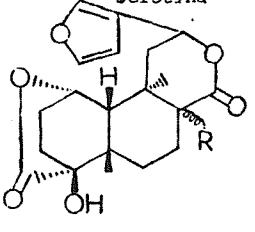
Hinterhubera imbricata[250]



(420)
Printzia laxa[252]

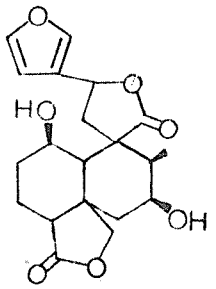


raconin (421)
Croton draco[253]

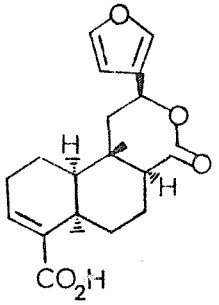


R=α-H (422)
columbin
R=β-H (423)
iso-columbin

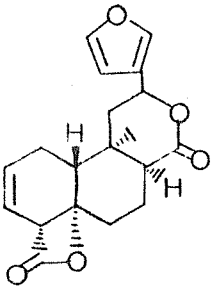
Dioscoreophyllum cumminsii[251]



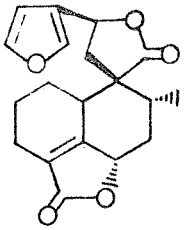
teucrin-B (424)
Teucrium chamaedrys[237]



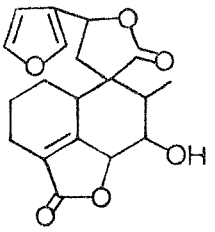
floribundic acid(425)
Evodia floribundia[254]



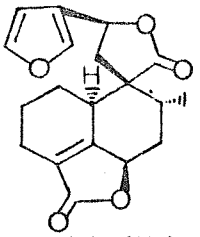
salviarin (426)
Salvia splendens[255]



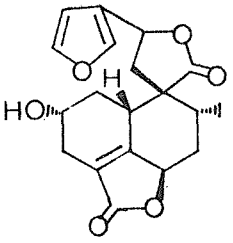
teucvin (427)
Teucrium viscidum[262]



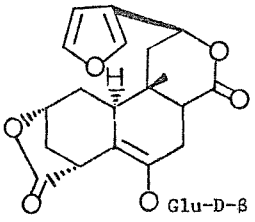
teucrin-A (428)
Teucrium chamaedrys[263]



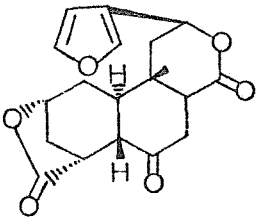
teucvidin (429)
Teucrium viscidum[264]



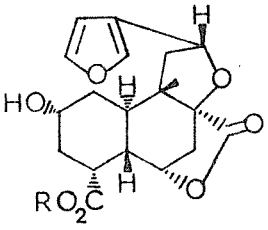
teucrin H4 (430)
Teucrium hyrcanicum[239]



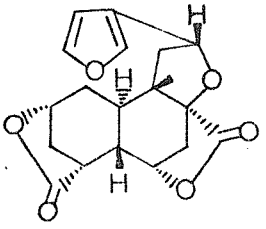
diosbulbinoside (431)
Dioscorea bulbifera[256]



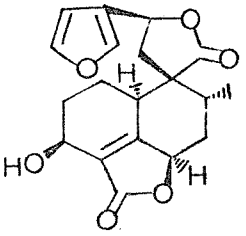
diosbulbin-D (432)
Dioscorea bulbifera[257]



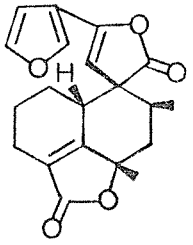
R=H diosbulbin-C (433)
R=CH_3 diosbulbin-A (434)
Dioscorea bulbifera[258-261]



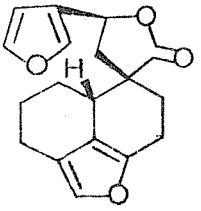
diosbulbin-B (435)
Dioscorea bulbifera[258,259,261]



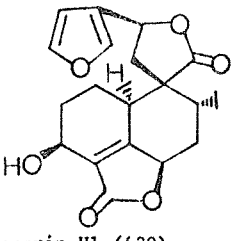
teuflidin (436)
Teucrium flavum[265,266]



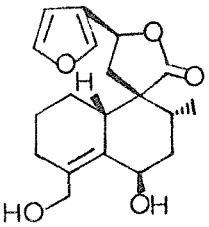
isocrotocaudin (437)
Croton caudatus[266]



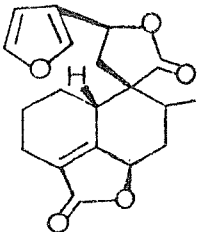
montanin-A (438)
Teucrium montanum[267]



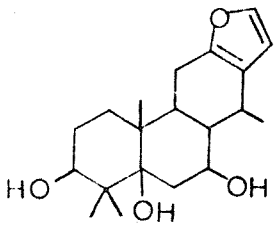
teucrin H1 (439)
Teucrium hyrcanicum[239]



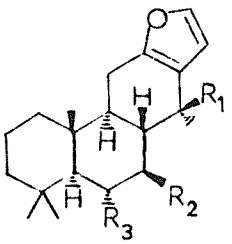
montanin-B (440)
Teucrium montanum[267]



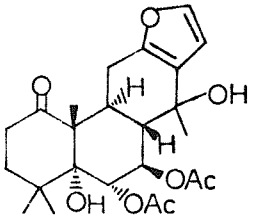
teuflin (441)
Teucrium flavum[268]



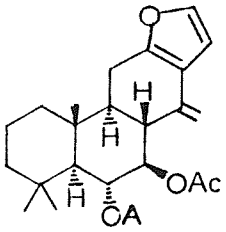
x-caesalpin (443)
Caesalpinia pulcherrima[269]



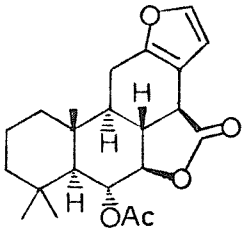
R_1=R_2=R_3=OH (448)
R_1=H, R_2=R_3=OH (449)
R_1=R_3=H, R_2=OH (450)
Pterodon emarginatus[270]



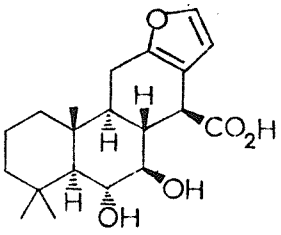
α-caesalpine (444)
Caesalpina bonducella[271-273]



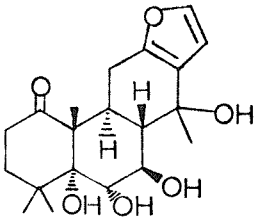
(451)
Pterodon emarginatus[270]



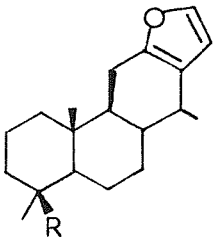
(445)
Pterodon emarginatus[270]



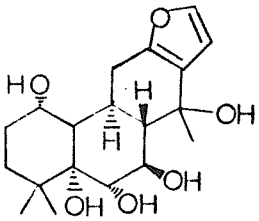
(452)
Pterodon emarginatus[270]



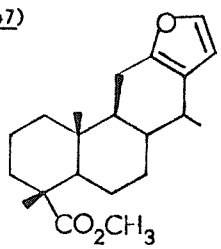
β-caesalpine (446)
Caesalpina bonducella[271-273]



R=CO_2CH_3 (453)[274]
R=CO_2H (454)
R=CH_2OAc (455)
Vouacapoua macropetala[275]



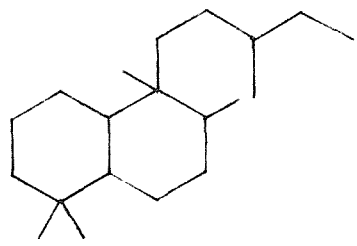
δ-caesalpine (447)



(456)
Vouacapoua macropetala[275]

1.3.5. Chettaphanin Skeleton

The chettaphanin skeleton (457) can be considered as a modified



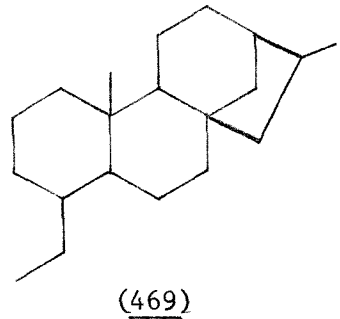
(457)

labdane skeleton (355), in which the methyl group at C-9a has migrated to C-9b and bond fission has occurred between C-3a and C-4a. Only three examples of furanoditerpenoids possessing this skeleton have been isolated to date (458-460), (458) from *Adenochlaena siamensis*,[278] (459) from *Maelotus repandus*[277] and diasin (460) from *Croton diasii*.[278]

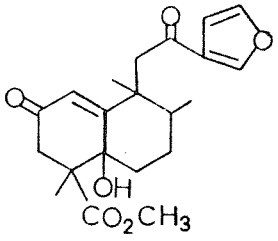
1.3.6. Cembrane Skeleton

Despite the large number of terpenoids possessing the cembrane skeleton[281] only four furanocembranoids have been isolated to date (461-464). Pukalide (461) from *Sinularia abrupta*[279] and the three compounds (462-464) from *Pachyclavularia violacea*.[280]

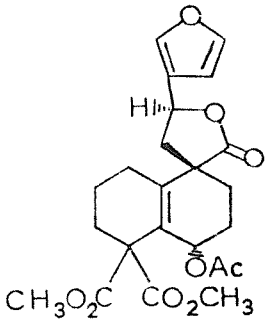
1.3.7. Cafestol Skeleton



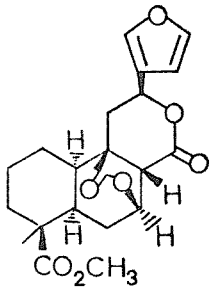
(469)



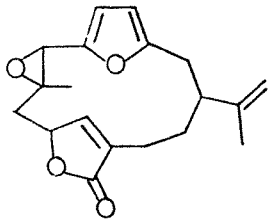
chettaphanin-1 (458)
Adenochlaena siamensis[276]



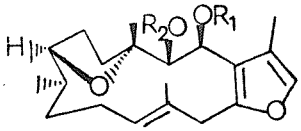
mallotucin-B (459)
Mallotus repandus[277]



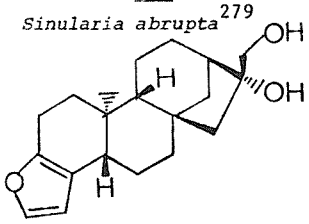
diasin (460)
Croton diasii[278]



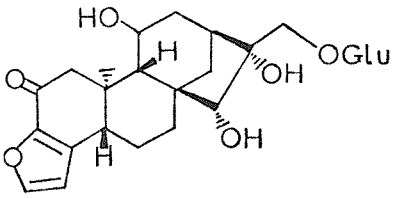
pukalide (461)
Sinularia abrupta[279]



R_1=R_2=H (462)
R_1=Ac, R_2=H (463)
R_1=R_2=Ac (464)
Pachyclavularia violacea[280]

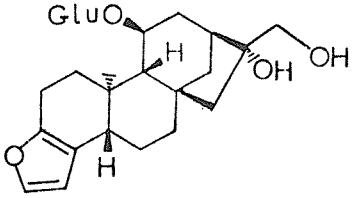


cafestol (465)
'coffee beans' [282]

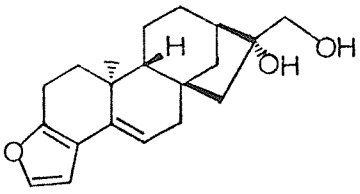


mascaroside (466)

Coffea vianneyi[283]



(467)
'green coffee beans' [284]



kahweol (468)
'coffee beans' [282]

Only four furanoterpenoids possessing the cafestol skeleton (469) have been isolated to date (465-468), all from coffee plants. The structure of mascaroside (466), the bitter principle of 'malagasy coffee' (*Coffea vianneyi*), was determined by x-ray techniques and was the first glucoside to be found in coffee.[283]

1.3.8. Furanoditerpenoids Possessing Less Common Skeletons

Although the furanoditerpenoids form a relatively large group of natural products, few compounds have structures which could be termed 'less common' (470-477). *Scytalium tentaculatum* has been a source of two compounds (476) and (477) which could be considered to contain a modified cembranoid skeleton.[291] (471) From *Adenochlaena siamensis* possesses a structure, determined by x-ray techniques, which could be considered to be a modification of the labdane skeleton (355).[287]

1.4. Sesterterpenoid Furanonatural Products

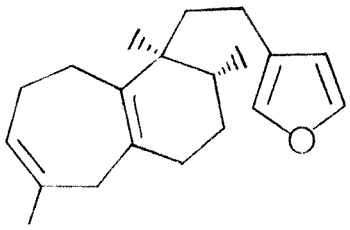
The furanosesterterpenoids (478-498) form a small group of natural products. All the examples of this group isolated to date possess a linear skeleton and the majority have been isolated from a small number of sponges.

1.5. Triterpenoid Furanonatural Products

The size of the group of triterpenoid furanonatural products has been rapidly approaching the size of the sesquiterpenoid group over the last ten years and so for brevity only a few examples of each ring system are included here.

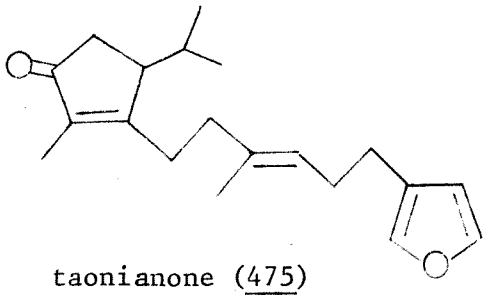
1.5.1. Linear Skeleton

Only two examples of triterpenoids with linear skeletons have been isolated to date, (499) and (501) from the sponge *Ircinia spinosula*.[293]



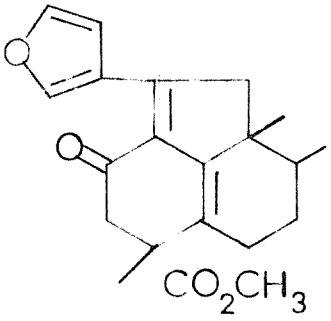
(470)

Printzia laxa[285]



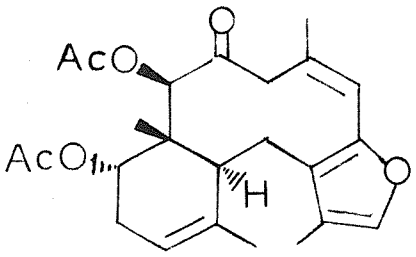
taonianone (475)

Taonia australasica[286]



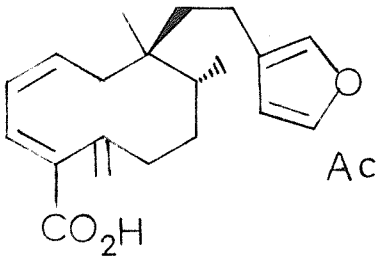
(471)

Adenochlaena siamensis[287]



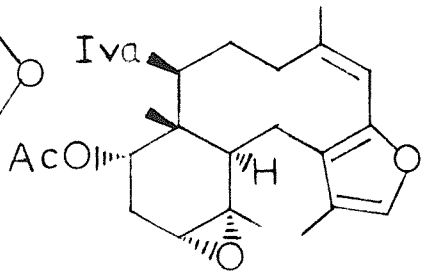
(476)

Scytalium tentaculatum[291]



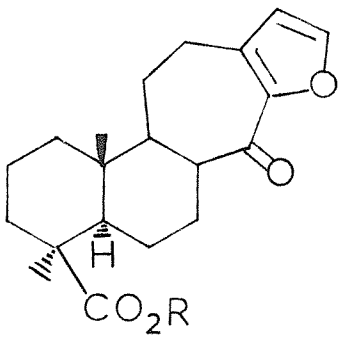
(472)

Conya stricta[288]



(477)

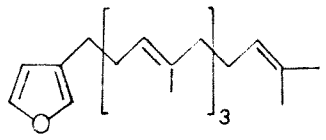
Scytalium tentaculatum[291]



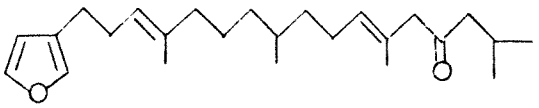
R=H (473)

R=CH_3 (474)

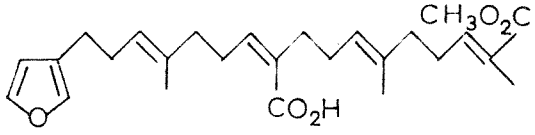
Ballota hispanica[289,290]



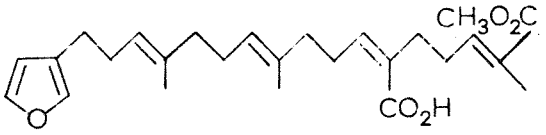
(478)
Spongia idia[292]
Ircinia spinosula[293]



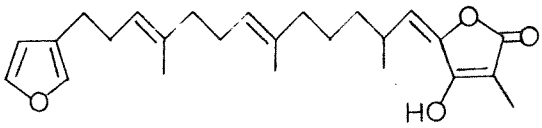
(479)
idiadione
Spongia idia[292]



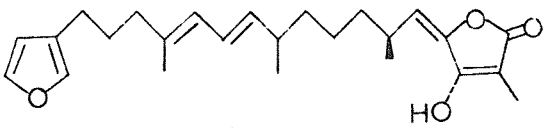
(480)
Spongia officinalis[294]



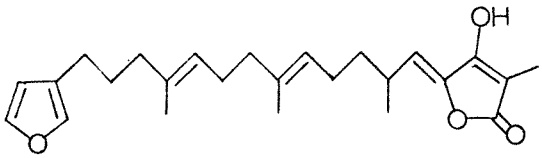
(481)
Spongia officinalis[294]



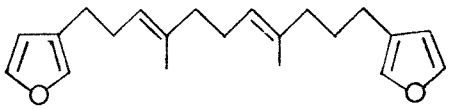
(482)
Ircinia variabilis[295]



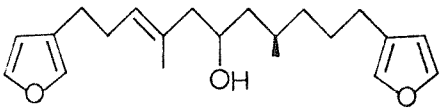
(354)
Ircinia fasciculata[296]



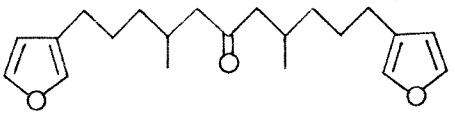
(483)
Ircinia strobilina[297]



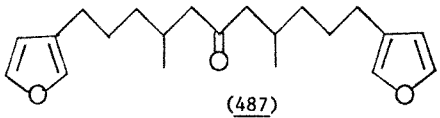
(484)
Spongia officinalis[298]



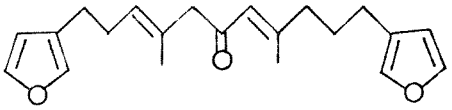
(485)
Spongia officinalis[298,299]



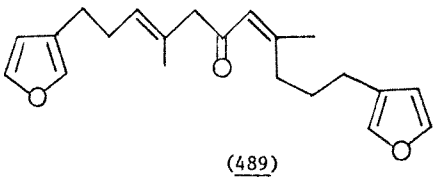
(486)
Spongia officinalis[298]



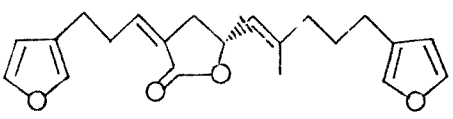
(487)
Spongia officinalis[298]



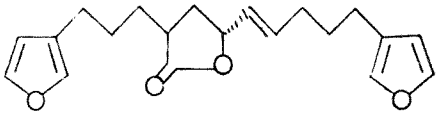
(488)
Spongia officinalis[298]



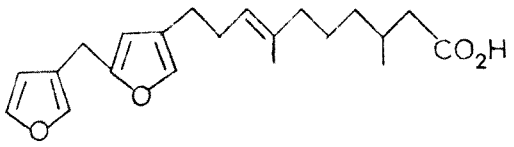
(489)
Spongia officinalis[298]



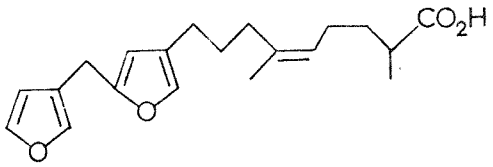
(490)
Spongia nitens[300]



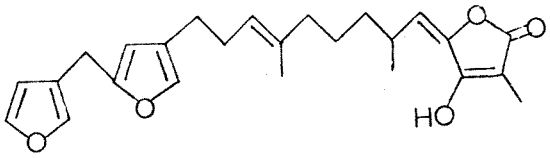
(491)
Spongia nitens[300]



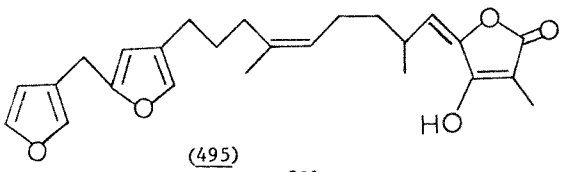
(492)
Ircinia oros[294]



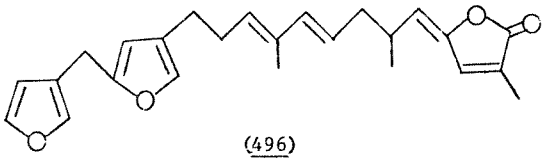
(493)
Ircinia oros[294]



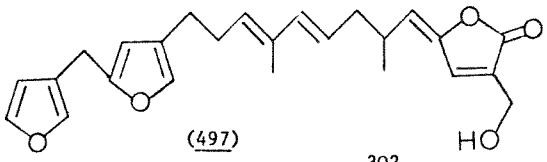
(494)
Ircinia oros[301]



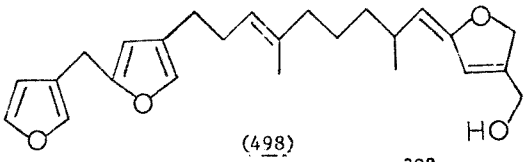
(495)
Ircinia oros[301]



(496)
Ircinolide
Thorecta marginalis[302]



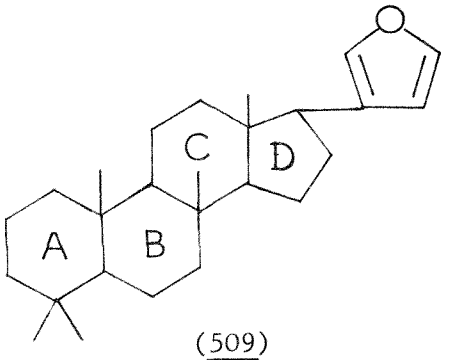
(497)
Thorecta marginalis[302]



(498)
Thorecta marginalis[302]

1.5.2. Melicane Skeleton

The furanonatural products possessing the melicane skeleton (509), form one of the largest groups of triterpenoids. The majority of examples possess the α-furan ring and the *gem* dimethyl group without functionalisation. A number of examples (e.g. (502-504), however, show oxidation of the *gem* dimethyl group to alcohols, acids etc.[303]



(509)

1.5.3. Andirobin Skeleton

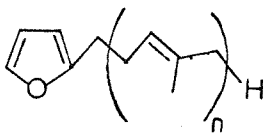
Cleavage of the B ring of the melicane skeleton (509) together with loss of the methyl group at the B/C ring junction and oxidation of the D ring to a lactone could be considered to form the andirobin skeleton of which (505)[306] and (506)[307] are examples.

1.5.4. Gedunin Skeleton

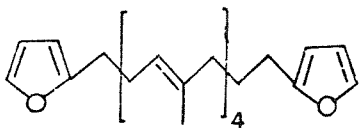
Oxidation of the D ring of the melicane skeleton (509) to a lactone could be considered to form the gedunin skeleton of which (507)[308] is a typical example.

1.5.5. Limonin Skeleton

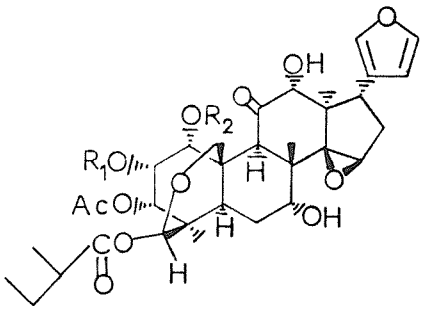
Oxidation of the D ring and cleavage of the A ring of the melicane skeleton (509) could be considered to form the limonin skeleton of which Calamin (508), from calamodin seeds, is a recent example.[309]



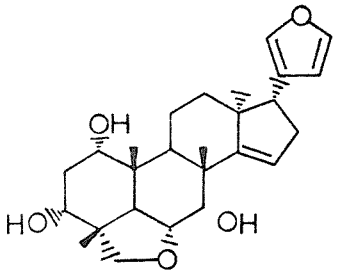
n=5 (499)
n=6 (500)
Ircinia spinosula[293]



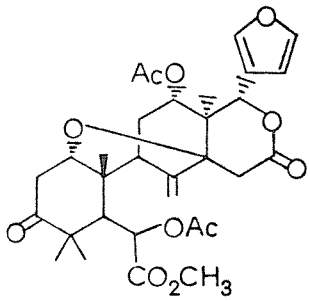
(501)
Ircinia spinosula[293]



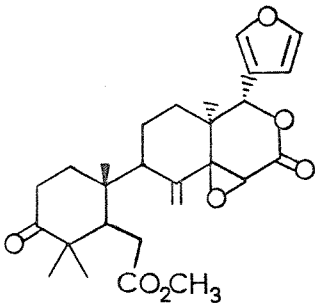
R_1=H, R_2=Ac (502)
R_1=Ac, R_2=H (503)
Trichilia raka[304]



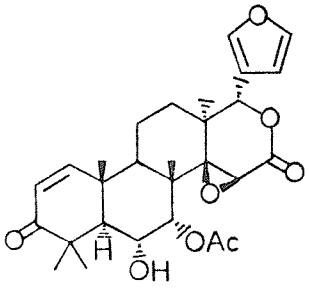
(504)
vilasinin
Azadirachta indica[305]



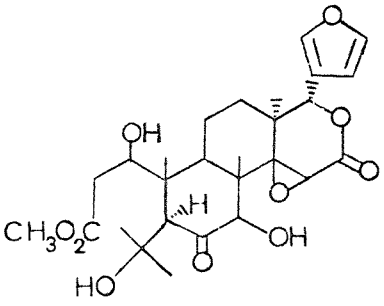
(505)
Guarea thompsonii[306]



(506)
Aphanamixis polystachya[307]



(507)
Carpa guianensis[308]



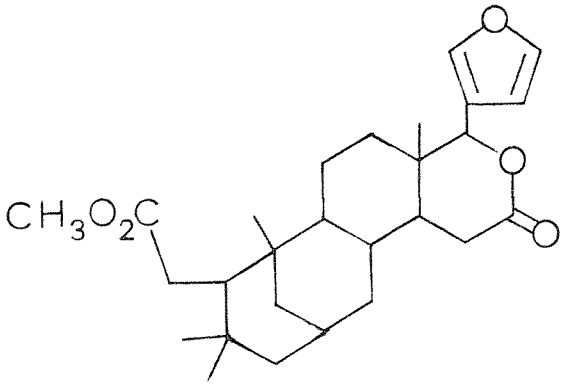
(508)
calamin
Citrus reticulata[309]

1.5.6. Nimbin Skeleton

Nimbolide (510) is a typical example of the nimbin skeleton which could be considered derived from the melicane skeleton (509) by cleavage of the C ring. This group also usually shows oxidation of the *gem* dimethyl group.

1.5.7. Swietenine and Utilin Skeletons

A large number of furanotriterpenoids possess the swietenine skeleton (517) (e.g. (511)) but all are very similar and only differ from each other by slight variations of the substituents.



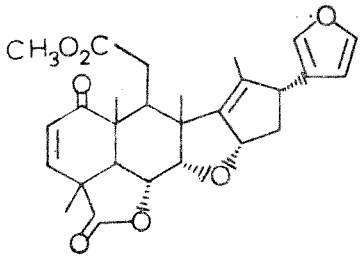
(517)

Closely related to the swietenines is the utilin group which usually possess complex substitution patterns e.g. utilin (3) and the busseins (512) and (513)

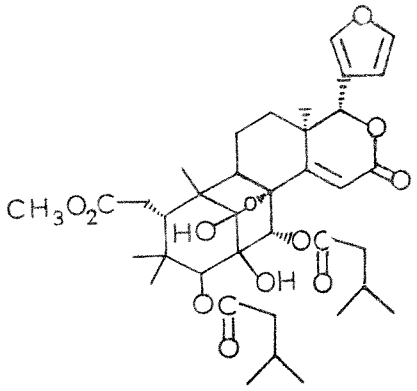
The terpenoid (500) has been isolated from the sponge *Ircinia spinosula* and is the only higher furanoterpenoid isolated to date.[293]

An unusual structure among the triterpenoids (which is usually classed as a dimeric sesquiterpenoid[2]) is nuphleine (514) a furano-alkaloid which has been isolated from *Naphar luteum*.[314]

A variety of furanosteroids (e.g. (515)) and furanoalkaloids (e.g. (516)) have also been isolated but are beyond the scope of this review.



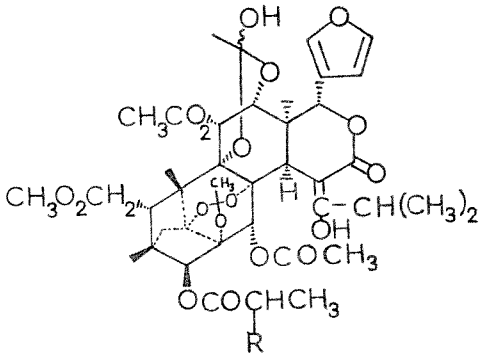
nimbolide (510)[310]



(511)

xyloccensin A

Xylocarpus moluscensis[311]

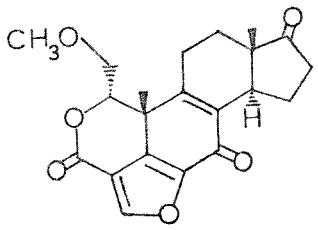


R=CH_2CH_3 (512)[312]

Bussein A

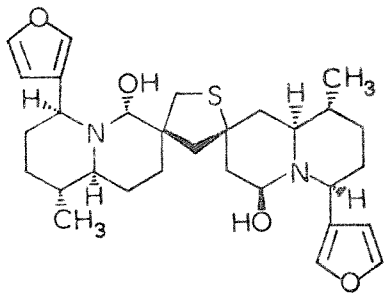
R=CH_3 (513)[312]

Bussein B



(515)

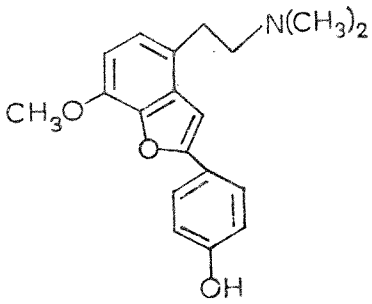
Penicillium funiculosum[313]



(514)

nuphleine

Nuphar luteum[314]

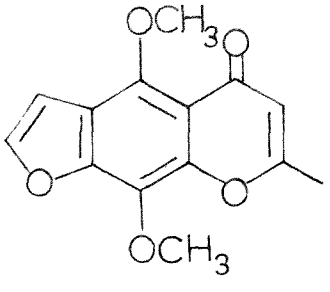


(516)[315]

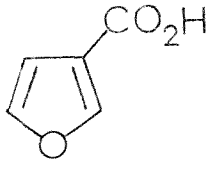
1.6. Biological Activities of Furanonatural Products

The small amounts of material available from the isolation of furanonatural products has, in the majority of cases, prohibited their testing for biological activity. A limited range of furanonatural products have, however, been tested.

The psoralens are a family of naturally occurring furocoumarins widely distributed in nature. The crude plant products have a long folkloric history as agents that promote the development of suntan and, unlike modern cosmetic tanning agents, are orally active. The psoralens have clinical utility in allowing extremely fair skinned individuals to develop a tolerance to sunshine.[316,317] The crude plant material from which khellin (517), related to the psoralens, has been isolated has been widely used since ancient times as a folk remedy and modern pharmacologic work has confirmed its bronchiodilating and antispasmodic activity.[320-322]



khellin (517)
Ammi visnaga[318,319]



(518)

Although much effort has been placed over the last 10-20 years in the synthesis of furano derivatives with antibacterial activity,[323] hypotensive activity,[324] enzyme inhibiting activity[324] and antifungal activity,[325] little investigation has been carried out of the naturally occurring furanoterpenoids. The few reports of biological activities of the furanoterpenoids have been mostly confined to the farnesane derivatives.

An aggressive substance and/or alarm pheromone expelled, together with formic acid, by the madibular gland of a *Lasius* ant[10] is dendrolasin (20) which exhibits remarkable toxicity against ants but not against other insects.

The norsesquiterpenoids (13,33-35) have been shown to be potent pulmonary toxins in laboratory animals and appear to be the causative substances in the atypical interstitial pneumonia occurring in cattle which have ingested mold-damged sweet potatoes.[326]

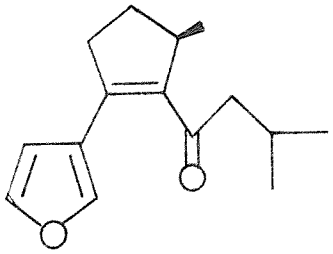
Ipomeamarone (36) and ipomeamaronol (37), along with batatic acid (8), ipomeanine (13) and 3-furoic acid (518), are phytoalexins which arise from infections of sweet potatoes by several pathogens and show antimicrobial activity at the infected region where they are biosynthesised.[327,328] Ipomeamarone (37) is also toxic to higher animals[329,330] and exhibits anthelmintic (antihelmintic) activity.[331] Ngaione (38), epingaione (39), dehydrongaione (43) and dehydroepingaione (41) when given intraperitoneally to mice resulted in the so called ngaione liver pathology.[332] A mixture of dehydrongaione (43) and dehydroepingaione (41) is toxic to sheep and mice.[332] Intraperitoneal administration to mice of deispropylngaione (46), a probable catabolite of ngaione (38), brings about liver and kidney degeneration.[332]

Although myoporone (31) is biologically inactive, its probable derivatives, dehydromyodesmone (521) and (522), are toxic to mice and cause the pathology typical of ngaione poisoning.[333]

Literature reports of the biological activities of furanosesquiterpenoids other than the furanofarnesanes are very limited, however tetradymol (121) has been shown to be a moderate hepatotoxin in mice, rats, gerbils, rabbits, guinea pigs and sheep.[125] Pinguisone (328) has been shown to be an antifeedant for the larvae of *Prodenia litura*.[335]

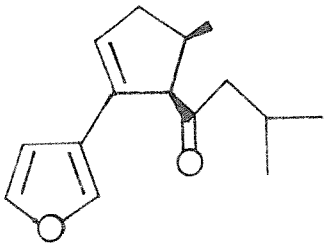
Nakafuran-8 (317) and nakafuran-9* (318) have been shown to be antifeedant substances of the nudibranchs, *Hypselodoris godeffroyana* and *Chromodoris maridadilus* together with their prey *Dysidea fragilis* against common reef fish, *Chaetodon* sp.[186] The furan esters (307-309) have been shown to be chemical defense compounds for the nudibranch *Chromodoris marislae*.[184]

* *Naka is the Hawaiian word for sea creature and is often used as a general prefix for various invertebrates.*



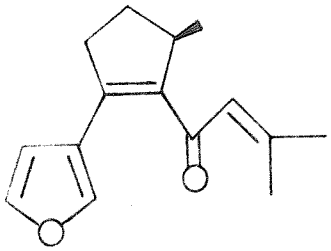
myodesmone (519)

Myoporum deserti[334]



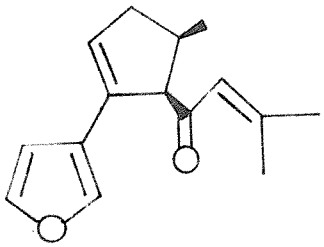
*iso*myodesmone (520)

Myoporum deserti[334]



dehydromyodesmone (521)

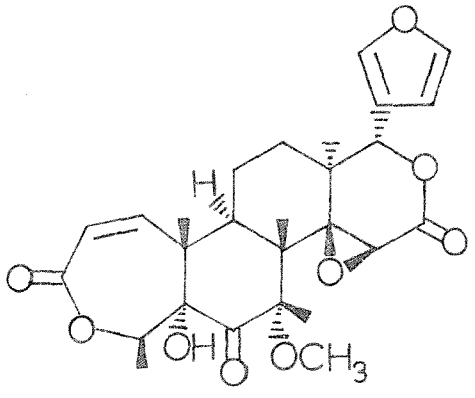
Myoporum deserti[333]



dehydroisomyodesmone (522)

Myoporum deserti[333]

Very few higher furanoterpenoids have been shown to have significant biological activity. (503) Has been shown to be an antifeedant against the southern army worm (*Spodoptera eridania*)[304] and against the mexican bean beetle (*Epilachna varivestis*).[304] Similarly (302) has also been shown to have cytotoxic[336] and antifeedant activity.[304] Harrisonin (523), from *Harrisonia abyssinica*,[337] has been shown to have antibiotic activity against *Bacillus sub tilis*.[338]



(523)

Despite the occurrence of biological activity, the great diversity of these compounds has precluded the determination of most of the free energy parameters required for a rigorous Hansch analysis. The structural features, which have been considered by Jacobi[339] to be significant for biological activity in furano compounds and α-methylene lactones are :-

(a) They either contain a furan ring or a functionality in principle derivable from a furan ring.

(b) The more biologically active compounds usually contain an oxygen functionality adjacent to the furan or lactone ring junction.

(c) Most of the stereochemically interesting features are contained about the periphery of a single ring.

CHAPTER TWO STUDIES ON A MODIFICATION OF THE WADSWORTH-EMMONS METHOD OF OLEFIN FORMATION USING A CROWN ETHER

2.1. Introduction

In Chapter Three two approaches to the synthesis of the furanosesquiterpene pallescensin-E (337) are described. The first approach (3.2.1.) was based on an intramolecular reaction of a π-allylnickel halide with an aldehyde, to form an α-methylene lactone and the pallescenain-E ring system, in one step. The second, more 'classical' approach, (3.2.2.) required the formation of a furanostilbene, by the Wadsworth-Emmons method, as the key reaction.

The wide variety of unsaturated compounds prepared by the Wittig reaction[340] (Scheme 1) have been augmented over the last twenty years by the reactions of phosphonyl-stabilised carbanions with carbonyl compounds to produce olefinic products (the Wadsworth-Emmons reaction),[341,342] (Scheme 2). The phosphonyl stabilised carbanions have become one of the most frequently employed organophosphorus reagents and as such have been the subject of a number of reviews.[342-4] The following review has been confined to a brief comparison of the Wadsworth-Emmons and Wittig reactions.

2.1.1. Comparison of the Wadsworth-Emmons reaction and the Wittig reaction

Olefin formation by means of phosphonyl-stabilised anions has a number of advantages over alternative methods. These advantages are particularly apparent when a direct comparison is made with alternative procedures involving phosphoranes (the Wittig reaction).

(a) Phosphoranes in general do not undergo smooth alkylation, whereas, numerous examples have been reported of both alkylation and acylation of phosphonyl-stabilised carbanions, (Scheme 3).[341,345-348]

(b) Phosphonyl-stabilised carbanions are, in general, more nucleophilic than the phosphoranes. Direct comparisons between phosphonyl-stabilised carbanions and phosphoranes have shown that, although the phosphonium salts are more acidic than the phosphonate analogues, the latter are more nucleophilic and thus more reactive than Wittig reagents.[342]

Phosphonate carbanions, with their negative charge stabilised by a carbonyl group, react readily with ketones, whereas their phosphorane counterparts are much less reactive. This was demonstrated by Jones who found that treatment of a mixture of (524), (525) and benzophenone with excess base resulted in formation of the olefin and a 70% recovery of the unchanged phosphonium salt (525) (Scheme 4).[349]

(c) Perhaps as a consequence of their low reactivity in olefin formation the Wittig reagents give more artifacts than the corresponding phosphonates.[350] The Wittig reaction of a *trans*-allylic phosphorane (526) and *n*-hexanal yields, not only the four possible geometric isomers of the expected diene (527), but also both geometric isomers of the diene (528) arising from γ-condensation, (Scheme 5).[351] In contrast, the analogous *trans*-phosphonate provided only the *trans*-2-*trans*-4 and *trans*-2-*cis*-4 isomers of the α-condensation product (527), in a 6:1 ratio.[351]

Not only is double bond migration more likely in products obtained from a Wittig reagent than those from phosphonate anions,[352] there is also a distinct difference in the isomer content of olefins prepared from phosphonates as compared to those from Wittig reagents. The former usually giving a much higher percentage of *trans*-isomer than the latter.[353,354,355]

(d) The workup of reaction mixtures and subsequent isolation of products are relatively simple when phosphonate anions are employed. The unsaturated product can be readily separated from the highly water soluble alkali metal phosphate salts. In contrast, phosphine oxides, the by-products of the Wittig reaction, normally have solubilities similar to those of olefins and hence elaborate separation procedures are often required.

In the preparation of heterocyclic stilbenes, analogues of the stilbene required to synthesise pallescensin-E (337), the elevated temperatures required for the reaction of the heteroarylmethane-phosphonates often result in decomposition and, therefore, low yields.[342,356]

Macrocyclic polyethers (crown ethers e.g. (529-531)) have the ability to solvate cations and in doing so, yield anions, unencumbered by strong solvation forces, which are potent nucleophiles.[357] This is exemplified by the reation of potassium acetate with benzyl

Scheme 1.

$$(R)_3P^{+}\!\!-\!\!CHR_1 \;+\; R_2R_3C{=}O \longrightarrow R_2R_3{=}CHR_1 \;+\; (R)_3P(O)$$

Scheme 2.

$$(RO)_2\overset{O}{\overset{\|}{P}}C^{-}HR_1 \rightleftharpoons (RO)_2\overset{O^-}{\overset{|}{P}}{=}CHR_1 \xrightarrow{R_2R_3C=O} R_2R_3C{=}CHR_1 \;+\; (RO)_2P(O)O^-$$

Scheme 3.

$$(RO)_2P(O)C^{-}HR_1 \xrightarrow{R_2X} (RO)_2P(O)CHR_1R_2 \xrightarrow[2.\,R_3R_4C=O]{1.\,\text{base}} R_3R_4C{=}CR_1R_2 \;+\; (RO)_2P(O)O^-$$

Scheme 4.

$$\underset{(524)}{(EtO)_2P(O)CH_2Ph} \;+\; \underset{(525)}{[(Ph)_3PCH_2Ph]^+\,Br^-} \xrightarrow[Ph_2CO]{t_{BuOK}} (Ph)_2C{=}CHPh \;+\; (Ph)_3P(O) \;+\; (EtO)_2POH$$

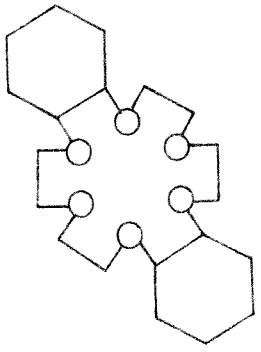
Scheme 5.

$$n\text{-}C_5H_{11}CHO \;+\; (Ph)_3P{=}CHC(CH_3){=}CHCO_2CH_3 \;\;(526) \longrightarrow$$

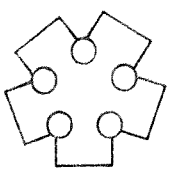
$$n\text{-}C_5H_{11}CH{=}CHC(CH_3){=}CHCO_2CH_3 \;\;(527)$$

$$+$$

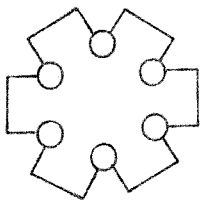
$$n\text{-}C_5H_{11}CH{=}C(CO_2CH_3)C(CH_3){=}CH_2 \;\;(528)$$



(529)



15-crown-5 (530)



18-crown-6 (530a)

chloride in acetonitrile. At room temperature, the reaction has a half life of 685h with no crown ether present, and a half life of 1.5h in the presence of dicyclohexyl-18-crown-6 (529).[358] Addition of a crown ether to the reaction of an unstabilised arylmethane-phosphonate anion could, therefore, enable shorter reaction times and lower temperatures to be employed, and consequently higher yield of stilbene products to be obtained.

2.2.

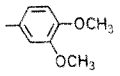
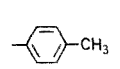
2.2.1. Effect of Crown Ether on the Yield of Stilbene Product[385]

For this study the convenient base sodium hydride was used to generate the anion from the phosphonate (531) in the presence of the carbonyl substrates (532a-g) and 15-crown-5 (530). The substrates (532a-g) were chosen such that stilbene products formed had been well characterised in the literature and, where possible, had been previously prepared by the Wadsworth-Emmons reaction.

The results (Table 1.) show that the addition of a catalytic quantity of a crown ether to the reaction mixture of a phosphonate anion with a carbonyl compound greatly facilitates this reaction. Nearly quantitative yields of olefin products were obtained in short reaction times and at lower temperatures than those conventionally used (0-25°C instead of 80°C).[342]

A similar result to this has recently been published by Aristoff[392] who found that the cyclisation of the ketone (534) to form the strained bicyclo[3.3.0]octenone (535) could not be accomplished by using standard methods. The cyclisation did, however, take place when the ketone (534) was treated with 1 equivalent of potassium carbonate and 2 equivalents of 18-crown-6 (530) in warm toluene, (Scheme 7).

Table 1. Stilbenes and Hetero Analogues (533) prepared

(533)	R_1	R_2	Reaction time[a] (h)	Yield[b] (%)	Yield (%) by Wadsworth-Emmons reaction	m.p. or b.p./torr (°C) found	m.p. or b.p./torr (°C) reported
a	H		16	98	85[359]	m.p. 123-125°	m.p. 124-125° [341]
b	H		2	99	c	m.p. 112-113°	m.p. 111° [360]
c			3	96	67[361]	m.p. 65-67°	m.p. 65-68° [361]
d	CH_3		16	86[d]	26[361]	m.p. 80-82°	m.p. 82° [362]
e	H		6	99	77[359]	m.p. 53-54°	m.p. 54-55° [359]
f	H		2	99	c	m.p. 119-120°	m.p. 119.5-120° [363]
g	H		2	90	c	b.p. 70°/0.01 (n_D^{15}: 1.6745)	b.p. 143-145°/0.15 [364] (n_D^{24}: 1.6822) [365]

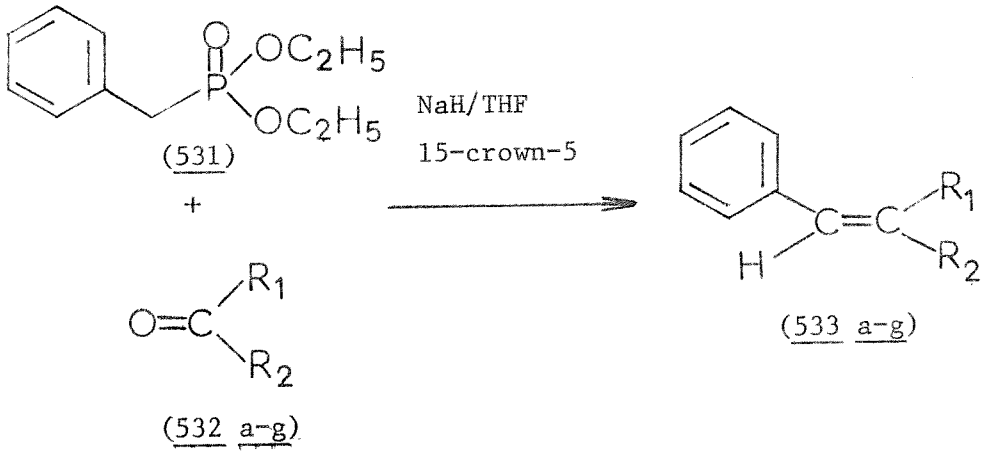
a Reaction started at 0° and allowed to attain room temperature over time shown.

b Yield of isolated product. All compounds have spectral data consistent with the assigned structure and published data.

c Not previously prepared by Wadsworth-Emmons reaction.

d After column chromatography on silica gel (MN-Kieselgel 60) using ether:petroleum ether (10:90) as eluent.

Scheme 6.



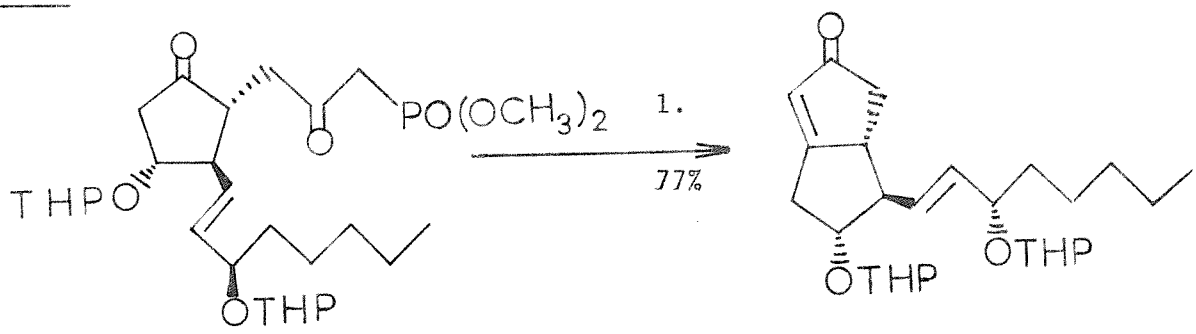
(531)

+

(532 a-g)

(533 a-g)

Scheme 7.



(534)

(535)

Reagents. 1. K_2CO_3, 18-crown-6 (530), toluene, Δ.

Table 2.

Entry	Reaction Temperature[a]	Crown Ether	Mole Equivalent Added	Yield (%)	Stilbene Products Mixture[c]	
					E (*trans*)	Z (*cis*)
1	53-5°C	-	0	e	98.4[d]	1.6
2	rt[b]	(530)	10^{-2}	e	98.4	1.6
3	rt	(530)	10^{-1}	e	98.7	1.3
4	rt	(530)	1	e	98.9	1.1
5	rt	-	0	5[f]	98.4	1.6
6	rt	HMPA	10^{-1}	8[f]	98.5	1.5
7	rt	HMPA	1	8[f]	98.6	1.6
8	rt	(530)	10^{-2}	6[f]	98.7	1.3

a All reactions conducted for 1h under argon.

b Room temperature.

c Product mixture analysed by G.C., FFAP, 248°C, N_2 carrier gas at 20ml/min. A standard mixture of E:Z ; 47:53 showed no change in composition under these conditions.

d Estimated error ± 0.3. e Yield not determined f Yield of Stilbene products by G.C.

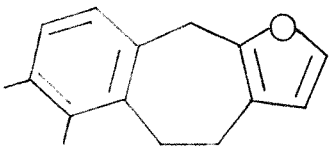
2.2.2. Effect of a Crown Ether on the E:Z Ratio of the Product in the Preparation of Stilbene (1,2-diphenylethene).

For this study sodium hydride was used to generate the anion from the phosphonate (531) in the presence of benzaldehyde (532a) and either a crown ether (15-crown-5 (530), 18-crown-6 (531)), or HMPA under the same conditions as 2.2.1. The crude reaction mixtures were analysed by G.C. (FFAP column, 248^{O}C) which showed that the E:Z ratio of the stilbene products was independant of the crown ether concentration, within experimental error, (Table 2) (entries 1-4). As expected the addition of either HMPA or 18-crown-6 (531) had little effect on the yield of products or their E:Z ratio, (Table 2) (entries 5-8).

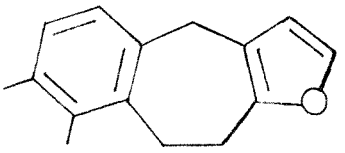
CHAPTER THREE SYNTHESIS of 5,10-dihydro-6,7-dimethyl-4*H*-benzo[5,6]cyclohepta[1,2-b]furan (pallescensin-E) (337) and analogues.

3.1. Introduction

Pallescensin-E (337) has been isolated, together with eight other furanosesquiterpenes (302, 303, 333-336, 338, 339), from the marine sponge *Disidea pallescens*.[7,181,192] The structure of pallescensin-E (337) was proposed on the basis of spectral and chemical data,[7] which failed however, to distinguish structure (337) from its isomer (536)[196] and the decision in favour of (337) was made on biogenetic grounds.[7]



(337)



(536)

An unambiguous synthesis of (337) should enable (337) to be distinguished from (536) and thus allow the structure of the natural product to be assigned. A successful general synthesis could also be extended to the preparation of a range of novel analogues of pallescensin-E, which might have biological activity.

3.2. Synthesis of Pallescensin-E

3.2.1. Synthetic Studies Towards (337) Based on an Intramolecular π-Allylnickel Cyclisation

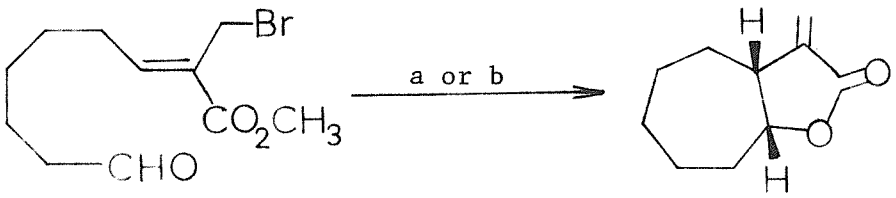
π-Allylnickel halides have been shown to be valuable reagents.[366-7] In polar, coordinating solvents, such as N,N-dimethylformamide, π-allylnickel halides have been shown to undergo reactions with a range of halides, aldehydes, epoxides[367] and quinones.[368]

Semmelhack has used the intramolecular cyclisation of a π-allylnickel halide (537) and an aldehyde to form the *cis* α-methylene lactone (538), (Scheme 8).[369] This cyclisation has also been carried out by the use of the Reformatsky reation in similar yield.[369]

An approach to the pallescensin-E ring system can be envisaged using cyclisation of the allylbromide (539) to form the α-methylene lactone (540), which could be reduced to the furan (541) by the methods of Grieco[370] and Birch[371] (Scheme 9). The allyl bromide (539) could be available from the aldehyde (545), (Scheme 10).

The first approach to the synthesis of the aldehyde (545) was *via* isocoumarin (1*H*-2-benzopyran-1-one) (551), (Scheme 11). This route failed when isocoumarin (551), prepared by the literature procedure [372-376] from phthalide (546), gave a complex mixture of products on treatment with sodium ethoxide. A second approach to (545) was by the route shown (Scheme 12). 2-Bromo-benzenepropanol (555) was prepared by the literature procedure from 1-bromo-2-bromomethyl-benzene (560).[377] Treatment of the alcohol (555) with sodium hydride and subsequent quenching of the alkoxide with benzylchloride gave the benzyl ether (556). The Grignard complex of (556) was reacted with ethylene oxide to give the alcohol (557) which was oxidised with pyridinium chlorochromate (pcc) to the corresponding aldehyde which was then protected as the 1,3-dioxolan (558). This approach to (545) again failed, however, as treatment of (558) under the usual literature conditions (Pd/C,EtOH)[378] and Pt/C,pTsOH,$(CH_2OH)_2$ failed to remove the benzyl protecting group.

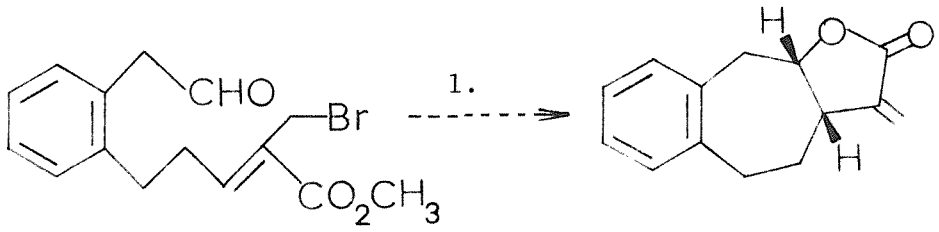
Scheme 8.



(537) (538)

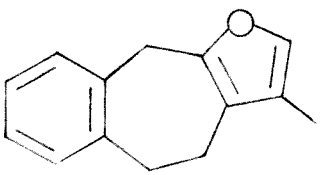
Reagents. a. Zn dust, 65°, THF, 10h. (60%)
b. $Ni(COD)_2$, -17°, THF, 8h. (52%)

Scheme 9.



(539) (540)

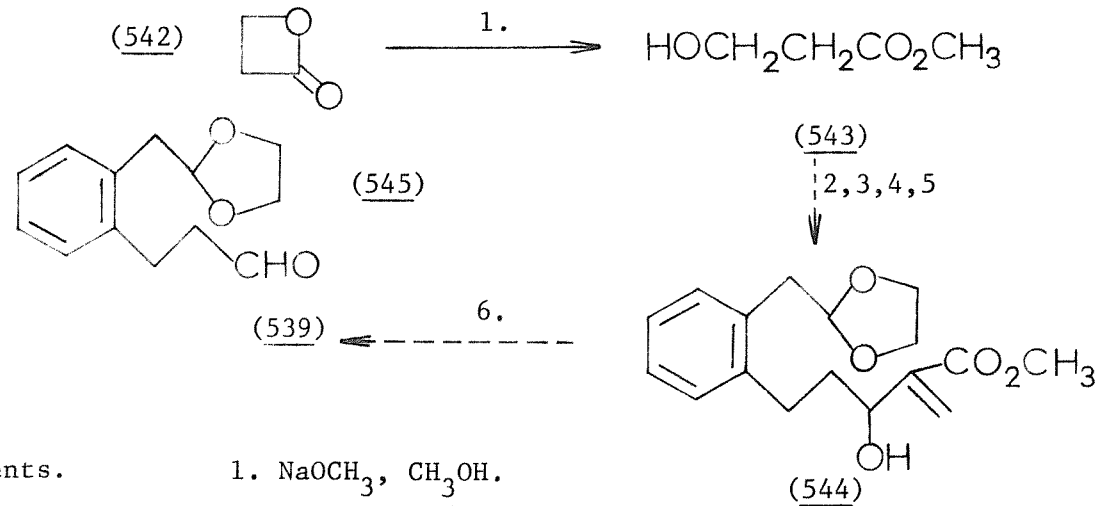
2,3,



(541)

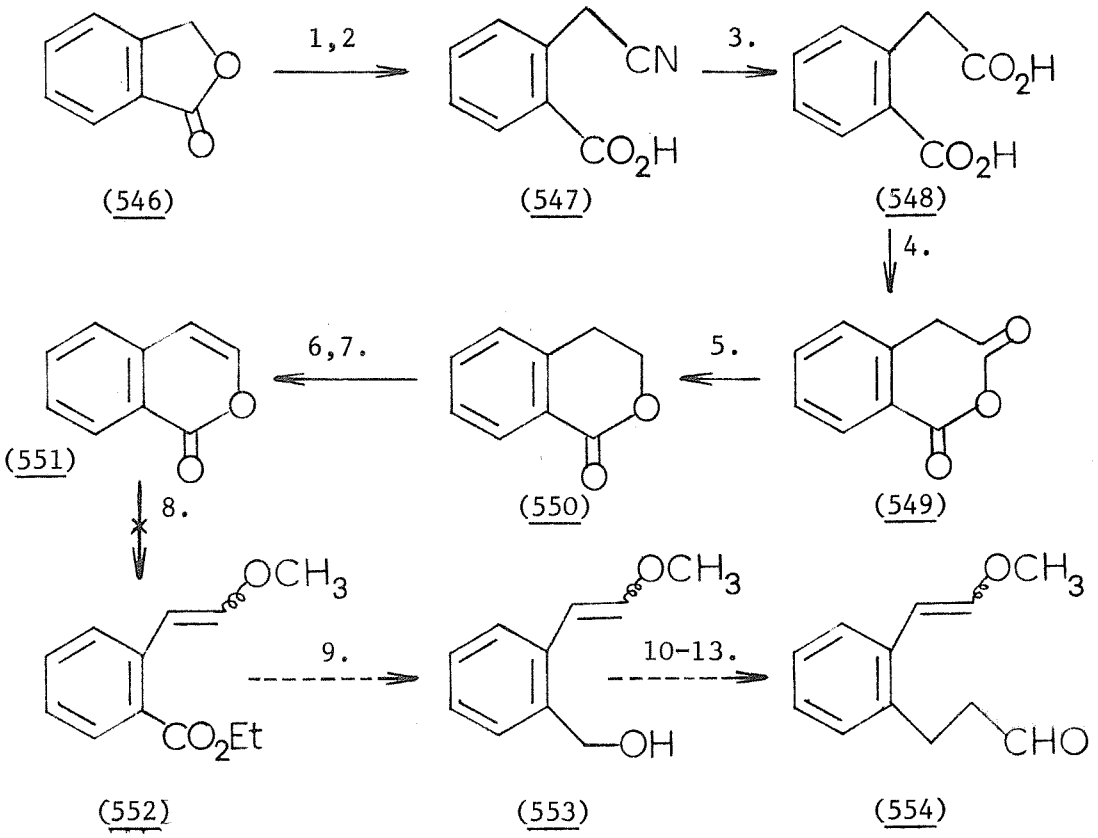
Reagents. 1. $Ni(COD)_2$
2. $(Ph_3P)_3RhCl$, O_2 (ref. 371)
3. $HAl(^iBu)_2$ (ref. 370)

Scheme 10.



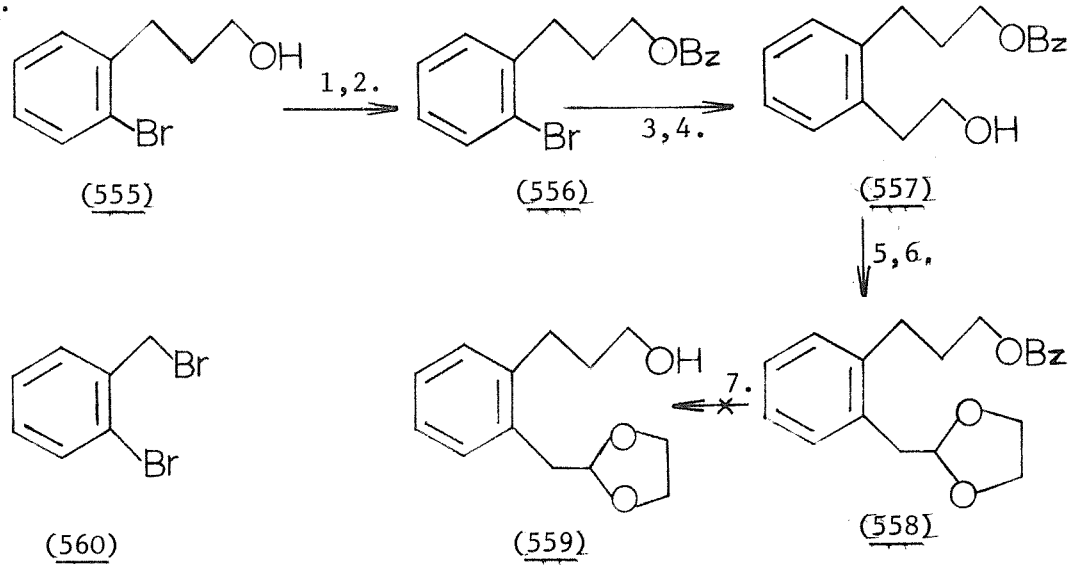
Reagents. 1. $NaOCH_3$, CH_3OH.
2. LDA, 3. (545). 4. TsCl.
5. DBU, Et_2O. 6. PBr_3.

Scheme 11.



Reagents. 1. KCN. 2. H^+, H_2O. 3. H^+, Δ. 4. Ac_2O.
5. $NaBH_4$, THF. 6. NBS, CCl_4. 7. NEt_3.
8. NaOEt, CH_3I. 9. LAH. 10. PBr_3. 11. Mg.
12.  . 13. pcc, CH_2Cl_2.

Scheme 12.



Reagents. 1. NaH, DMSO. 2. BzCl (561). 3. Mg, THF.
4.  . 5. pcc, CH_2Cl_2. 6. $(CH_2OH)_2$, H^+.
7. H_2/catalyst.

3.2.2. Synthesis of 5,10-dihydro-6,7-dimethyl-4*H*-benzo*[5,6]*-cyclohepta*[1,2-b]*furan (pallescensin-E) (337).

In the light of the difficulties encountered with the synthetic approaches to (337) outlined in 3.2.1. a more 'classical' approach to (337) was undertaken based on a synthesis of the benzo*[4,5]* cyclohepta*[1,2-b]*furan ring system by Bisagni,[379] (see 4.1.1.). The key step in the current synthetic approach is the Wadsworth-Emmons reaction[341,342] between the phosphonate (562) and the aldehyde (532h), (Scheme 13).

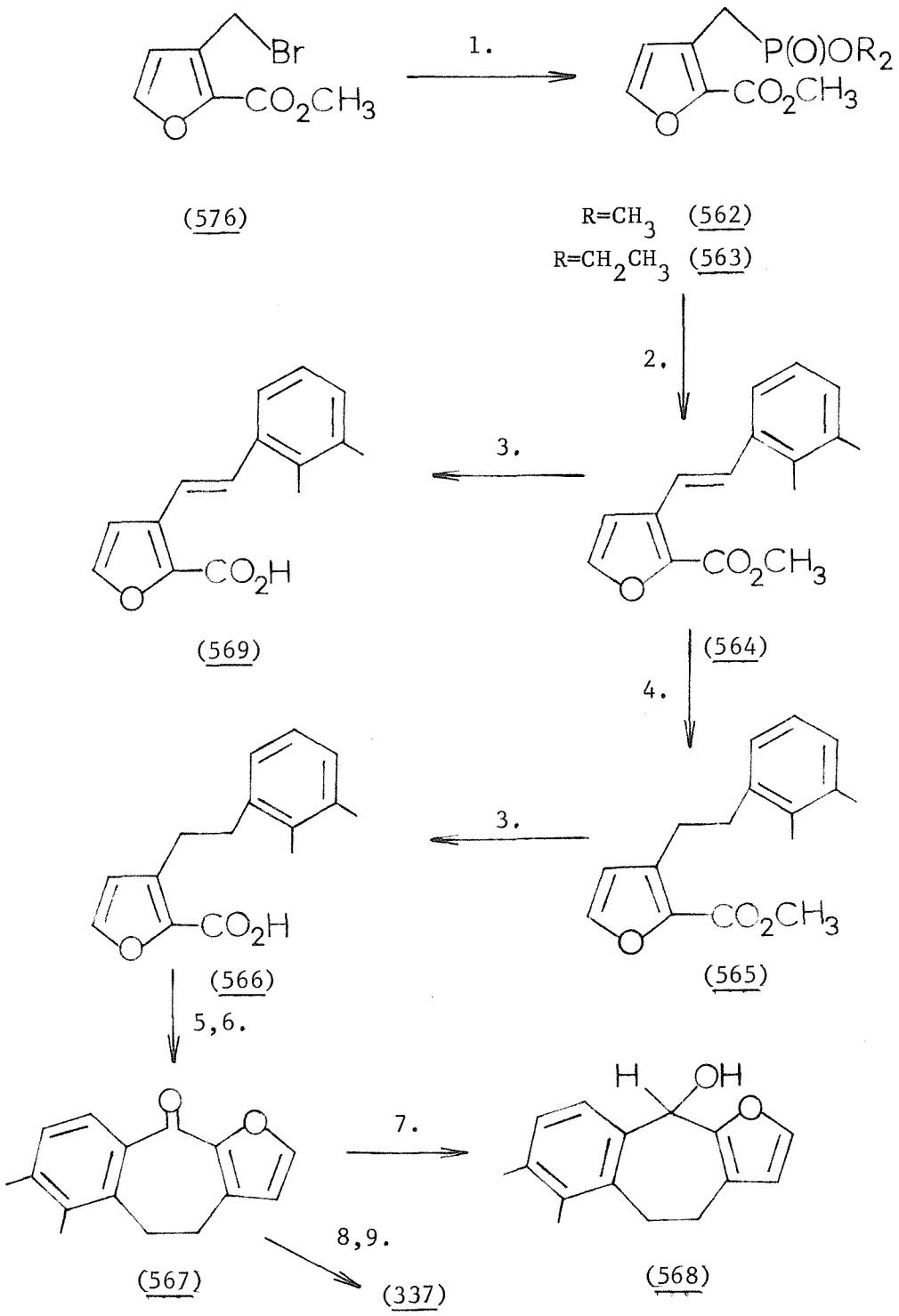
Hydrolysis of the commercially available nitrile (571) gave 2,3-dimethylbenzoic acid (572) which on reduction with lithium aluminium hydride gave the alcohol (574). Pyridinium chlorochromate oxidation of alcohol (574) gave 2,3-dimethylbenzaldehyde (532h). This three step route to (532h) was used as the more direct Stephen's reduction[380] of the nitrile (571) failed to yield the desired aldehyde (532h), and the iodide (575) failed to form the Grignard complex (which on reaction with formaldehyde would have given the desired alcohol (574)).

No reaction could be obtained between the phosphonate (563) and the aldehydes (532a,b,h) under the condition of Seus and Wilson[359] or a number of other literature conditions,[342] although low yields of stilbene products were obtained under more forcing conditions, (Table 3).

Alternative methods for this carbon-carbon bond formation failed to produce satisfactory results. For example, attempted alkylation of the selenide (577), prepared by the method of Reich,[381] failed to give the ester (580), (Scheme 15). Similarly, attempted alkylation of the acid (584) under the conditions of Tada[382,383] failed to form the required product (581), a result which has also been obtained by Knight,[384] although the isomeric acid (582) has been reported to alkylate readily.[382,383]

A study of the reaction of diethyl (phenylmethyl)phosphonate (531) with a number of aryl and furanyl aldehydes and ketones showed that the addition of a catalytic quantity of crown ether greatly facilitated this reaction (see Chapter 2).[385] Stilbene (564) was obtained in moderate yield when a catalytic amount of 15-crown-5 (530) was added to the reaction mixture containing phosphonate (562)

Scheme 13.



Reagents.

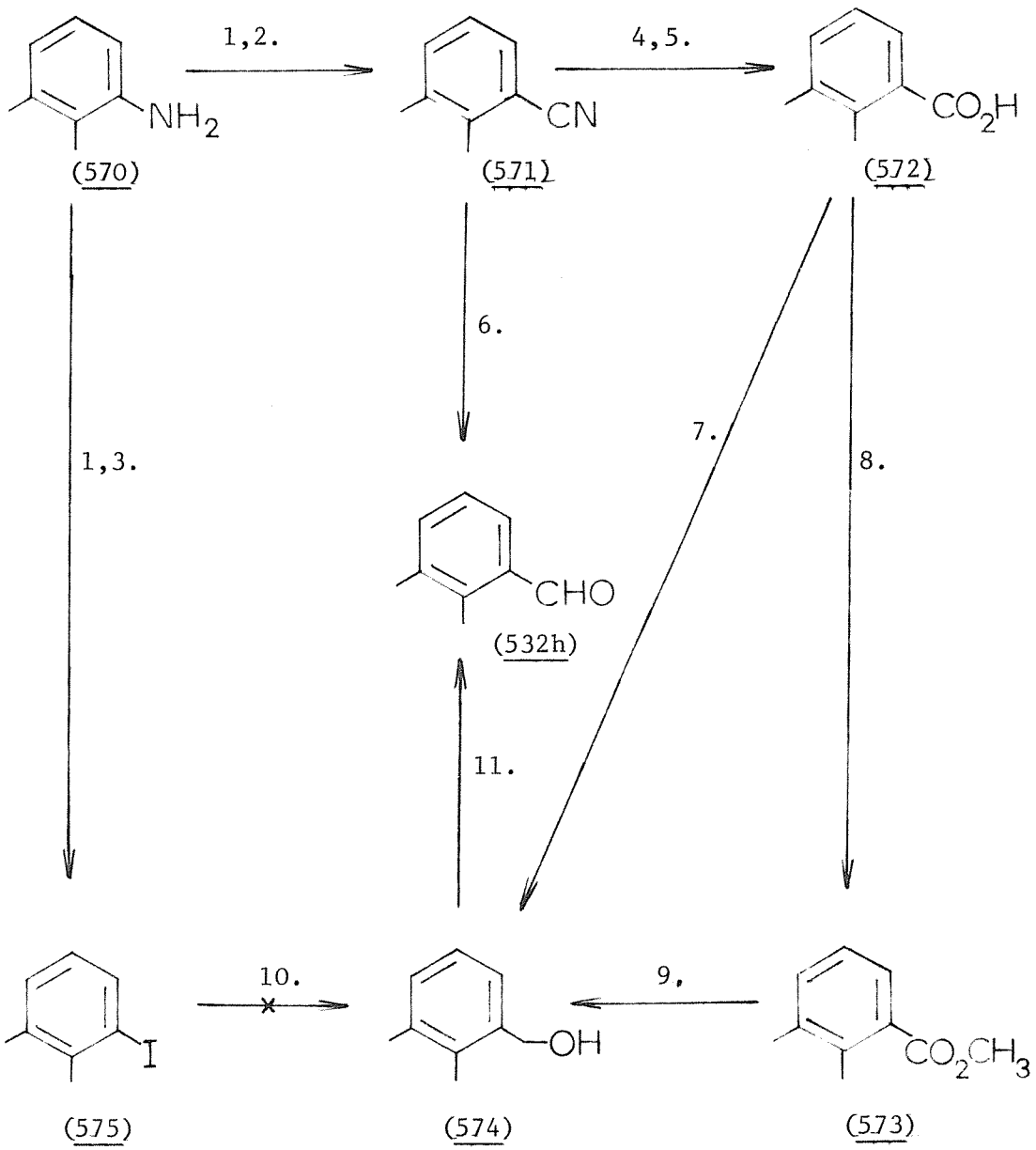
1. $P(OR)_3$. 2. NaH, diglyme, (532h). 3. OH^-.

4. $(Ph_3P)_3RhCl$, EtOH, benzene.

5. $SOCl_2$, benzene. 6. $AlCl_3$, $PhNO_2$. 7. $NaBH_4$.

8. $TsNHNH_2$, EtOH, H^+. 9. $NaCNBH_3$, DMF, H^+.

Scheme 14.



Reagents. 1. H^+, $NaNO_2$. 2. CuCN. 3. KI. 4. H_2O, KOH.

5. H^+. 6. $SnCl_4$, Et_2O. 7. LAH, THF.

8. CH_3OH, H_2SO_4. 9. LAH, Et_2O.

10. Mg, THF, $(CHO)_n$. 11. pcc, CH_2Cl_2.

Table 3.

Aldehyde[a]	Conditions		
	Base/Solvent/Temperature	Reference	Yield (%)
(532b)	NaH/THF/0°C	341	0
(532b)	NaH/diglyme/0-60°C	342	0
(532a)	NaH/diglyme/0-60°C	342	0
(532a)	NaH/THF/RT	341	0
(532b)	LDA/THF/$^{-}$78°-$^{-}$10°C	367	0
(532a)	$NaOCH_3$/DMF/RT	346	0
(532a)	$NaOCH_3$/DMF/0°C	-	0
(532a)	NaH/diglyme/80°C	342	3[b]
(532h)	NaH/diglyme/95°-100°C	342	3[b]

a In each case aldehyde (532a,b or h) was reacted with phosphonate (563) under the conditions shown.

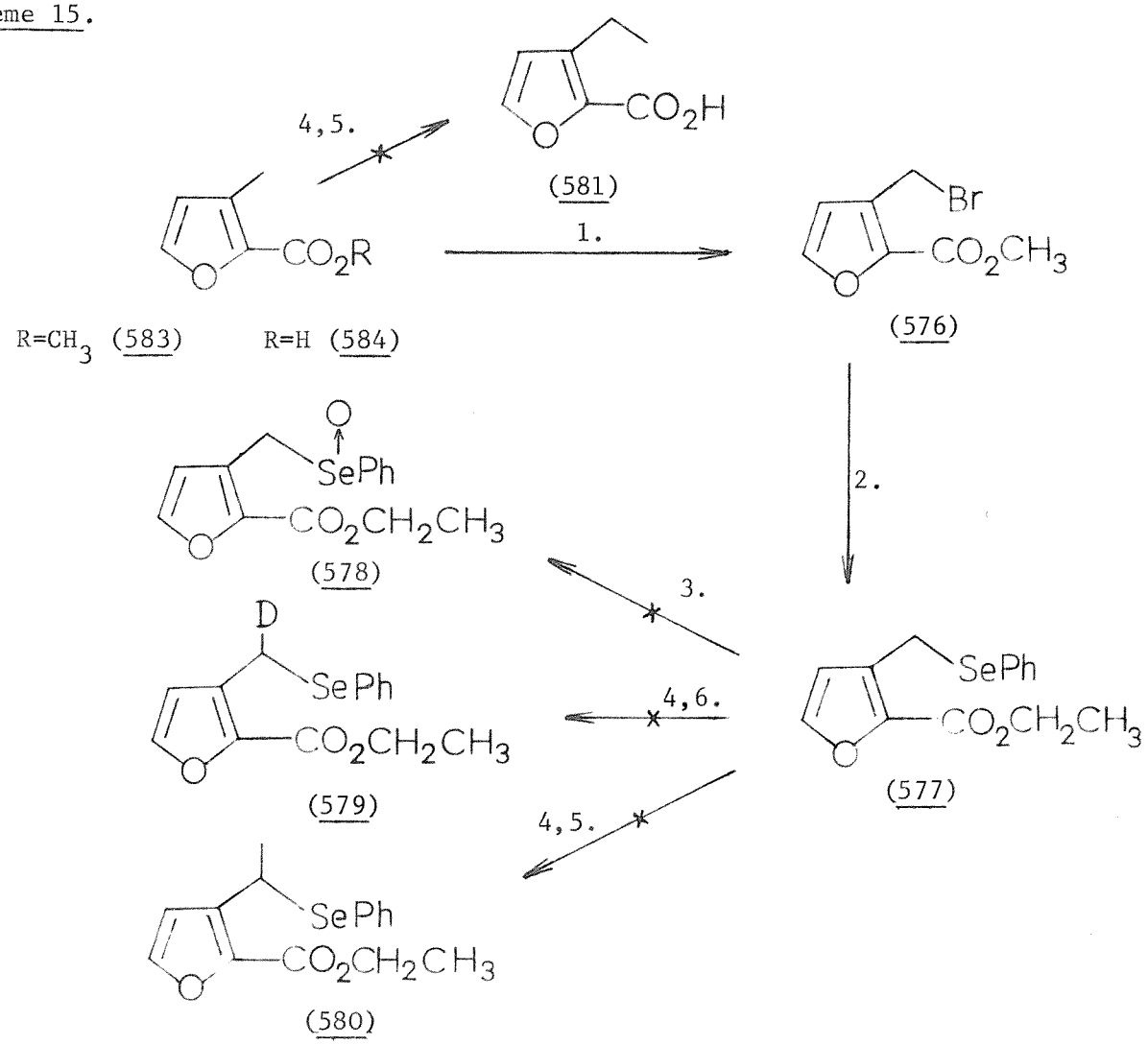
b The low yield obtained from the reaction of an unstabilised phosphonyl anion with an aldehyde or ketone has been fairly common (see reference 356 and Chapter 2).

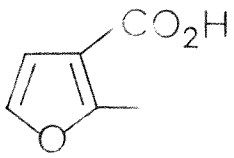
and aldehyde (532h).[386]

In a model study, catalytic hydrogenation of the stilbene acid (595a) was readily achieved over 5% platinum on charcoal, however the stilbene acid (569) was not reduced under these or similar conditions (Table 4). Reduction of the stilbene ester (564) was achieved using Wilkinson's catalyst[387] at high pressure, to give the ester (565) which was smoothly hydrolysed with aqueous sodium hydroxide solution to give the acid (566). Reaction of the acid (566) with thionyl chloride, followed by aluminium chloride cyclisation of the acid chloride obtained, gave the ketone (567), (Scheme 13).

Catalytic reduction of benzylic alcohols and ketones to the respective hydrocarbons has been well established.[390] Fluorenone (585) has been reduced in high yield to the hydrocarbon fluorene (586) by Micheel, who used the same conditions to reduce benzophenone (587) and diphenylmethanol (589) to diphenylmethane (588),[391] (Scheme 16). Thus catalytic hydrogenation of the ketone (567) or the alcohol (568) would have been expected to have afforded pallescensin-E (337). In a model study, hydrogenation of the ketone (597) (5%Pd/C,EtOH) returned starting material, whereas reduction of the alcohol (598) (5%Pd/C,benzene) gave a complex mixture of products. Further model studies on the sodium cyanoborohydride reduction of the 4-toluenesulphonyl hydrazones of fluorenone (585) and benzophenone (587) afforded the respective hydrocarbons in high yield, (Scheme 17). Treatment of the ketone (567) under the same conditions afforded the unstable light sensitive furan (337), which could be stored as the Diels-Alder adduct (592), (Scheme 18). The spectral data for the furan (337) was consistent with the assigned structure, and was identical to the published spectra for pallescensin-E.[7] In order to demonstrate that this allows the structure of pallescensin-E to be unambiguously assigned the structural isomer (536) was also synthesised. ^{1}H nmr spectroscopy showed that (536) was distinguishable from (337) (see Chapter 4).

Scheme 15.





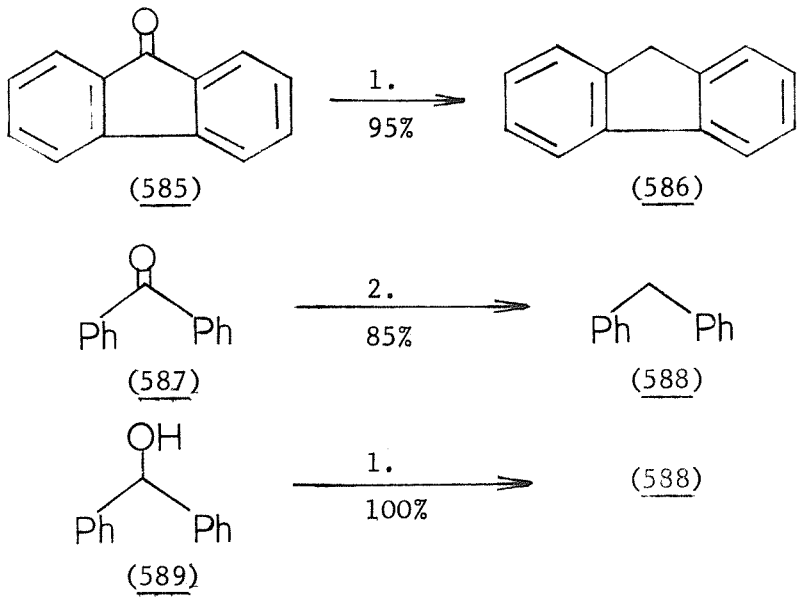
(582)

Reagents. 1. NBS, CCl_4, hν, rapid stirring, Δ.

2. $(PhSe)_2$, $NaBH_4$, EtOH. 3. mcpba, CH_2Cl_2.

4. LDA, THF. 5. CH_3I. 6. D_2O.

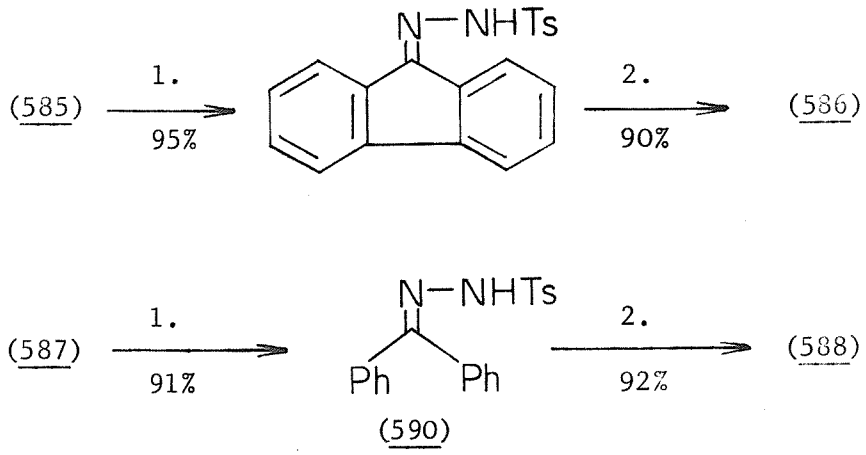
Scheme 16.



Reagents.

1. Pd/C/EtOH. 2. Pd/C/CH_3OH.

Scheme 17.



Reagents.

1. NH_2NHTs, TsOH, EtOH. 2. $NaCNBH_3$, DMF, TsOH.

Scheme 18.

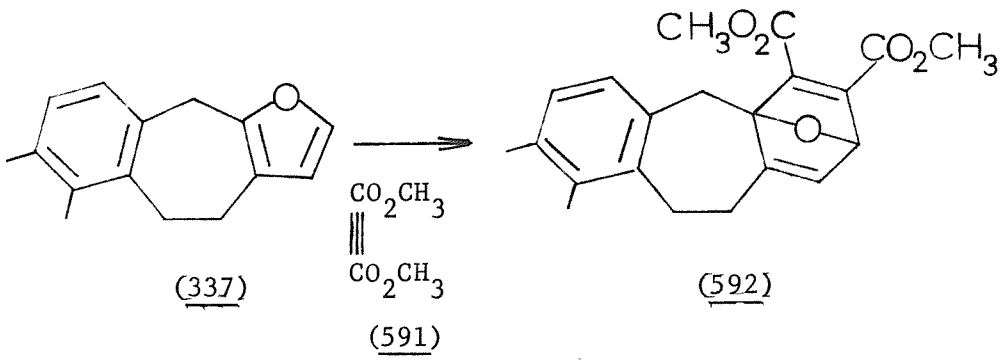


Table 4.

Entry	Stilbene	Catalyst, Solvent[a]	Yield (%)	Product	Reference
1	(595a)	Pt/C, EtOH	100	(596a)	-
2	(569)	Pt/C, EtOH	0	s.m.[c]	-
3	(569)	Pt/C, EtOAc	0	s.m.	-
4	(569)	Pt/C, MeOH/AcOH(1:1)	0	s.m.	-
5	(569)	Pd/C, EtOAc	0	s.m.	-
6	(569)	Pd/C, EtOAc + 2drops $HClO_4$	0	s.m. + decomposition	388
7	(569)	Rh/alumina, EtOH	0	complex mixture	-
8	(569)	Rh/C, Et_2O	0	s.m.	389
9	(564)	$(PPh_3)_3RhCl$, EtOH	0	s.m.	387
10[b]	(564)	$(PPh_3)_3RhCl$, EtOH/benzene(2:3)	65	(565)	-
11[b]	(593b)	$(PPh_3)_3RhCl$, EtOH/benzene(1:1)	100	(594b)	-

a Entries 1-9 at room temperature and atmospheric pressure.

b Entries 10 and 11 at 25atm and 50°C.

c Starting material.

3.3. Synthesis of Analogues of Pallescensin-E Intermediates

With a view to their possible biological activity, analogues of intermediates used in the preparation of pallescensin-E were prepared by the methods outlined in 3.2.2. (Scheme 19). Treatment of the aldehydes (532a,b,f,g) and phosphonate (563) with sodium hydride in the presence of 15-crown-5 (530) afforded the stilbenes (593a-d) in moderate yield, (Table 5)[386] Hydrogenation of the stilbene (593b) in the presence of Wilkinson's catalyst[387] gave the ester (594b) which was smoothly hydrolysed to the acid (596b) by aqueous base. The stilbene acid (595a) was hydrogenated over 5% platinum on charcoal to give the acid (596a) (Table 4).

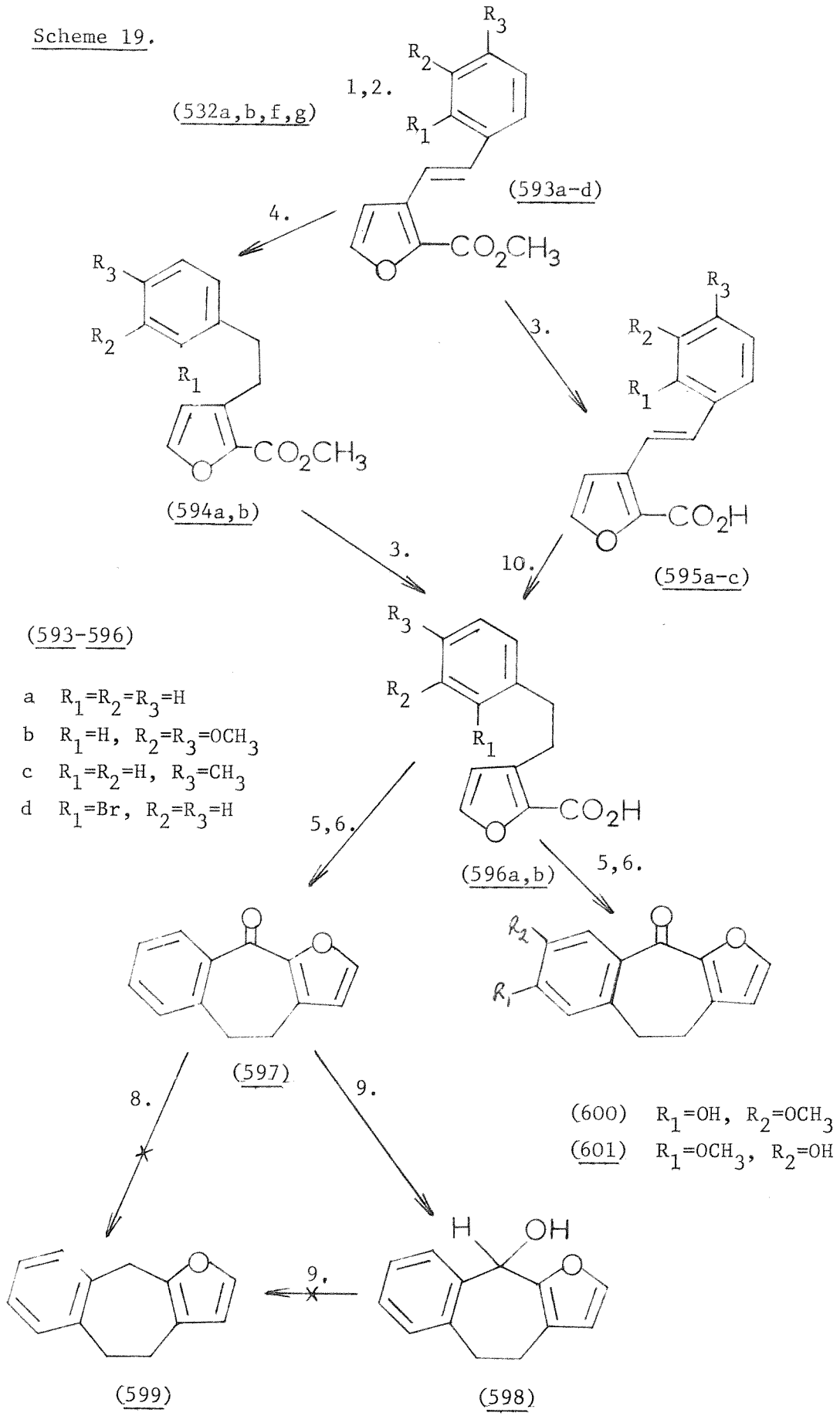
Reaction of the acid (596a) with thionyl chloride followed by aluminium chloride cyclisation of the acid chloride obtained gave the ketone (597), which was used in model studies for the catalytic removal of the ketone group to give (599) (see 3.2.2.).

The dimethoxy acid (596b) under the Friedel-Craft conditions employed gave a (3:7) mixture of two compounds by TLC, the ketones (600) and (601) which, after separation on silica gel, could not be distinguished by their ^{1}H nmr spectra. The two compounds were distinguished by the characteristic shift in the uv spectrum of (601) when the pH of the solution was changed from pH7 to pH13, which compared well with the literature examples,[393,394] (Figure 3). This structural assignment was confirmed by a nuclear Overhauser experiment.[395] Irradiation of the signal at 3.90δ, due to the methoxy group, afforded a 43% enhancement in the C-9 proton signal at 7.58δ. (Figure 4).

3.4. Conformation of Alcohol (598)

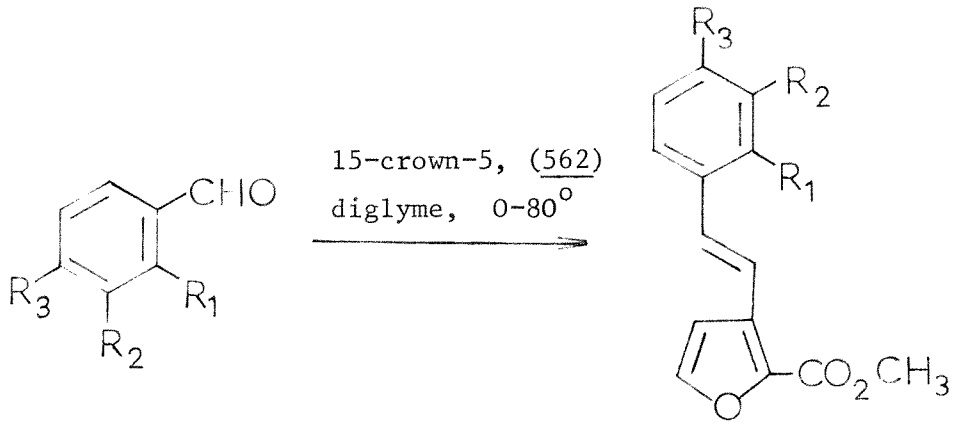
The ^{1}H nmr spectrum of the alcohol (598) showed two separate resonances for the benzylic protons H_w, H_x, H_y and H_z (Figure 6), a one proton multiplet at 3.6δ and a three proton multiplet at 2.7δ rather than the expected two proton multiplets as observed in the ^{1}H nmr spectrum of the ketone (597). A variable temperature ^{1}H nmr study of (598) showed no significant change between +50°C and -40°C which implied that (598) exists in solution as one fixed conformer.

Scheme 19.



Reagents. 1. (562). 2. NaH, diglyme. 3. OH^-.
4. $(Ph_3P)_3RhCl$. 5. $SOCl_2$, benzene. 6. $AlCl_3$. $PhNO_2$.
7. $NaBH_4$, THF. 8. H_2/Pd/C, EtOH. 9. H_2/Pd/C, benzene.
10. H_2/Pd/C.

Table 5.



(532a,b,f,g,h) (593a-d)

	R_1	R_2	R_3	Yield	(%)
(532a)	H	H	H	(593a)	49
(532b)	H	OCH_3	OCH_3	(593b)	54
(532f)	H	H	CH_3	(593c)	33
(532g)	Br	H	H	(593d)	51
(532h)	CH_3	CH_3	H	(559)	45

Figure 3. UV spectra of (601) in EtOH at pH=7 and pH=13.

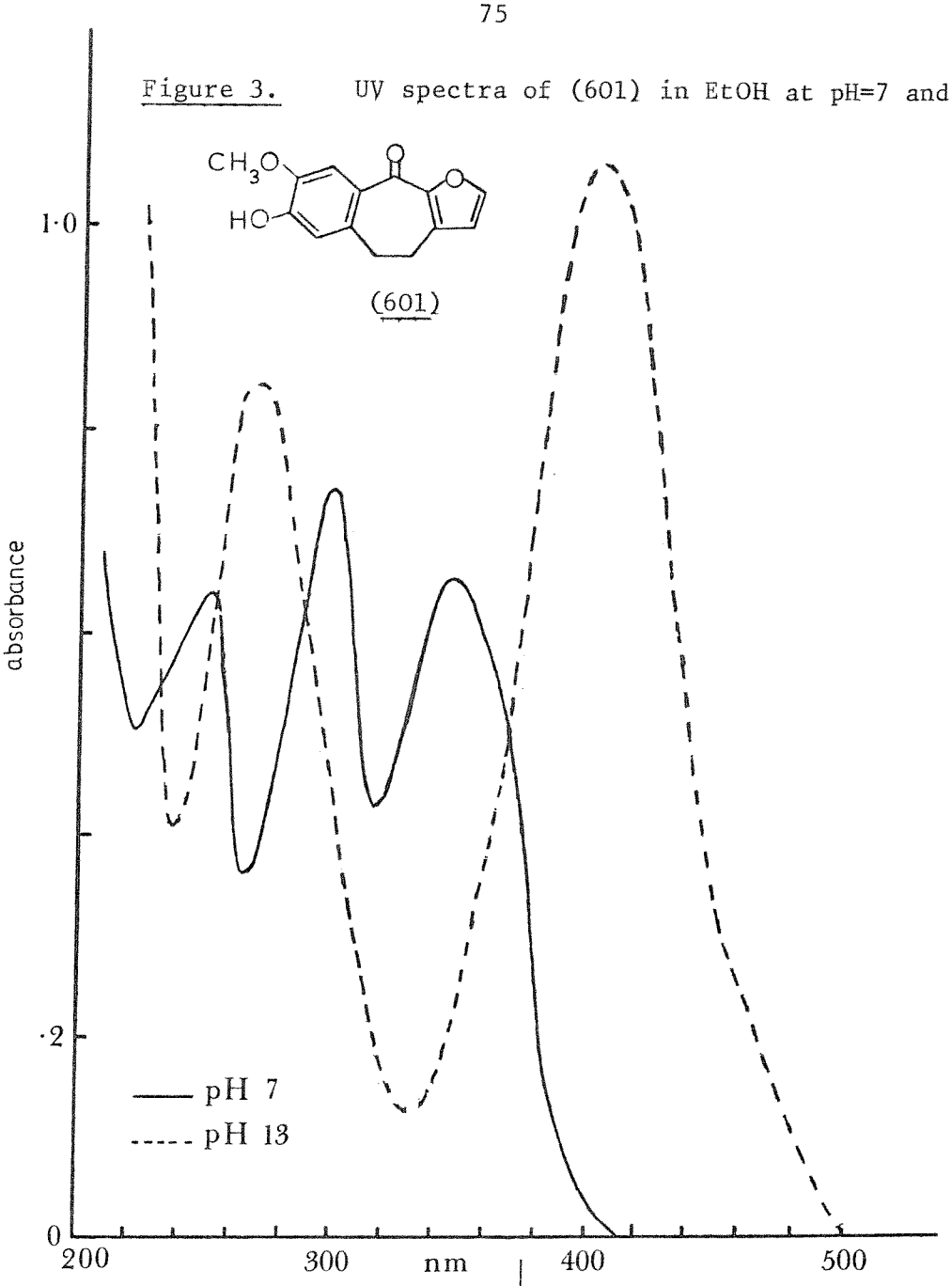
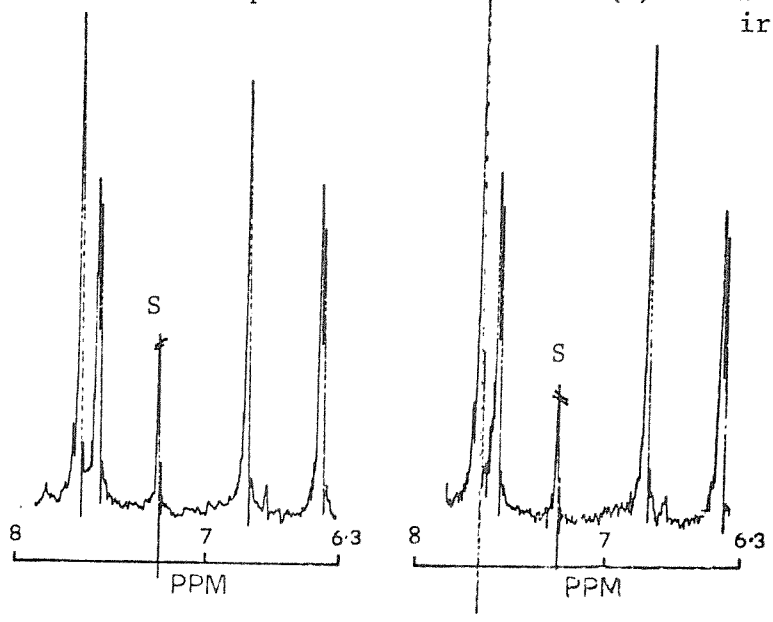


Figure 4. N.O.E. experiment on (601)

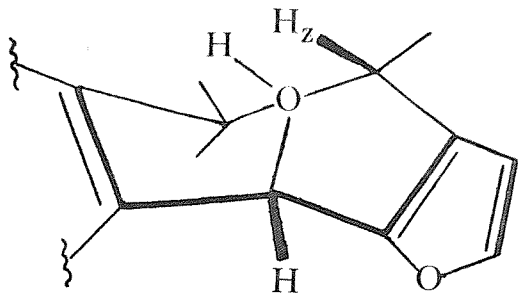
(a) Normal ^{1}Hnmr spectrum

(b) ^{1}Hnmr spectrum during irradiation at 3.90δ

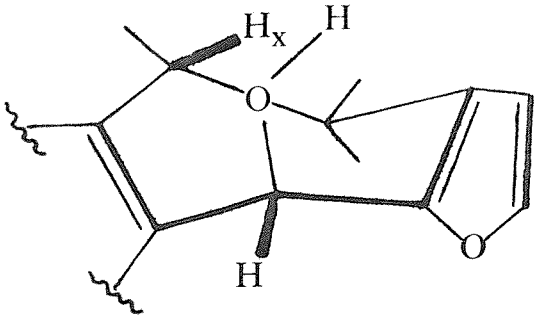


S=solvent ($CHCl_3$)

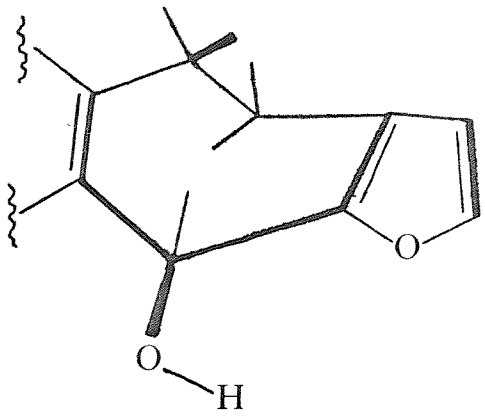
Figure 5.



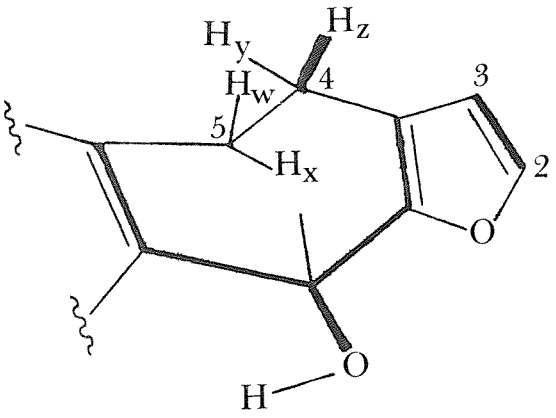
A



B

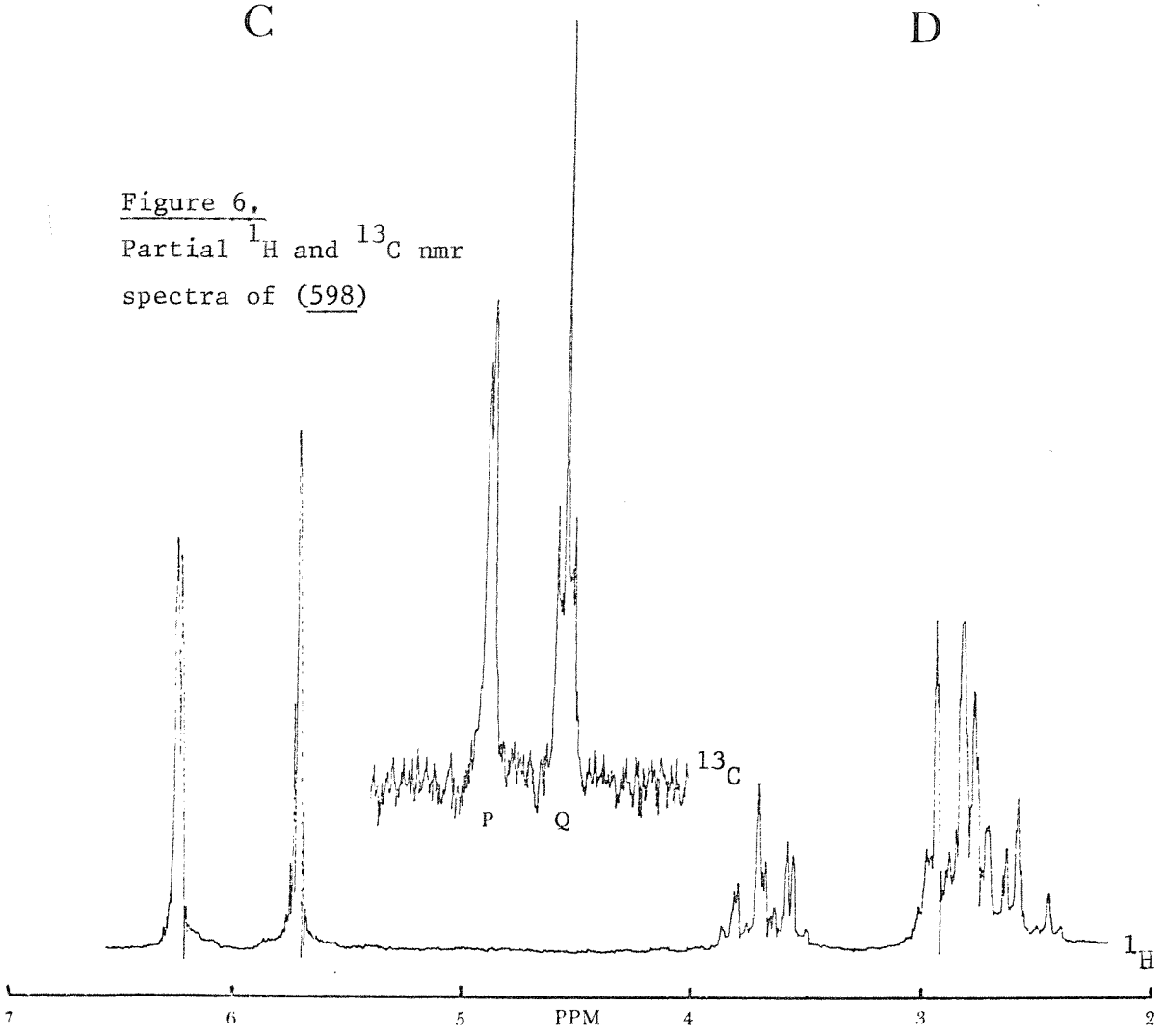


C



D

Figure 6.
Partial ^{1}H and ^{13}C nmr spectra of (598)



From a consideration of a 'Drieding' model of (598) four least energy conformations are possible, A-D (Figure 5). In two of these, conformations C and D, the alcohol moiety is not in close proximity to the protons H_{w-z}. In conformations A and B, however, the alcohol moiety is close to H_z and H_x respectively, thus the resonance at 3.6δ could arise from either H_z or H_x. In the ^{13}C nmr spectrum of (598) the resonances at 32.4δ (P) and 25.9δ (Q) can be assigned to C-5 and C-4 respectively by comparison with literature assignments.[396,397] The off-resonance spectrum showed both the resonances (P and Q) to be triplets, however, during selective ^{1}H decoupling[398,399] at 3.6δ the resonance at 32.4δ collapsed to a doublet whilst the resonance at 25.9δ remained as a triplet. Thus the proton at 3.6δ is attached to C-5, from which the conformation can be assigned to B.

The two signals P and Q do not appear as a true doublet and triplet as it was not found possible to irradiate at 3.6δ without some disturbance of the signals at 2.7δ.

CHAPTER FOUR SYNTHESIS of 4,10-DIHYDRO-7,8-DIMETHYL-10*H*-BENZO[4,5]CYCLOHEPTA[1,2-b]FURAN (536) and HOMO-SESQUIROSEFURAN (628) : THE STRUCTURES of PALLESCENSIN-E and SPINIFERIN-2.

4.1. Synthesis of 4,10-dihydro-7,8-dimethyl-10*H*-benzo[4,5]cyclohepta[1,2-b]furan (536).

4.1.1. Introduction

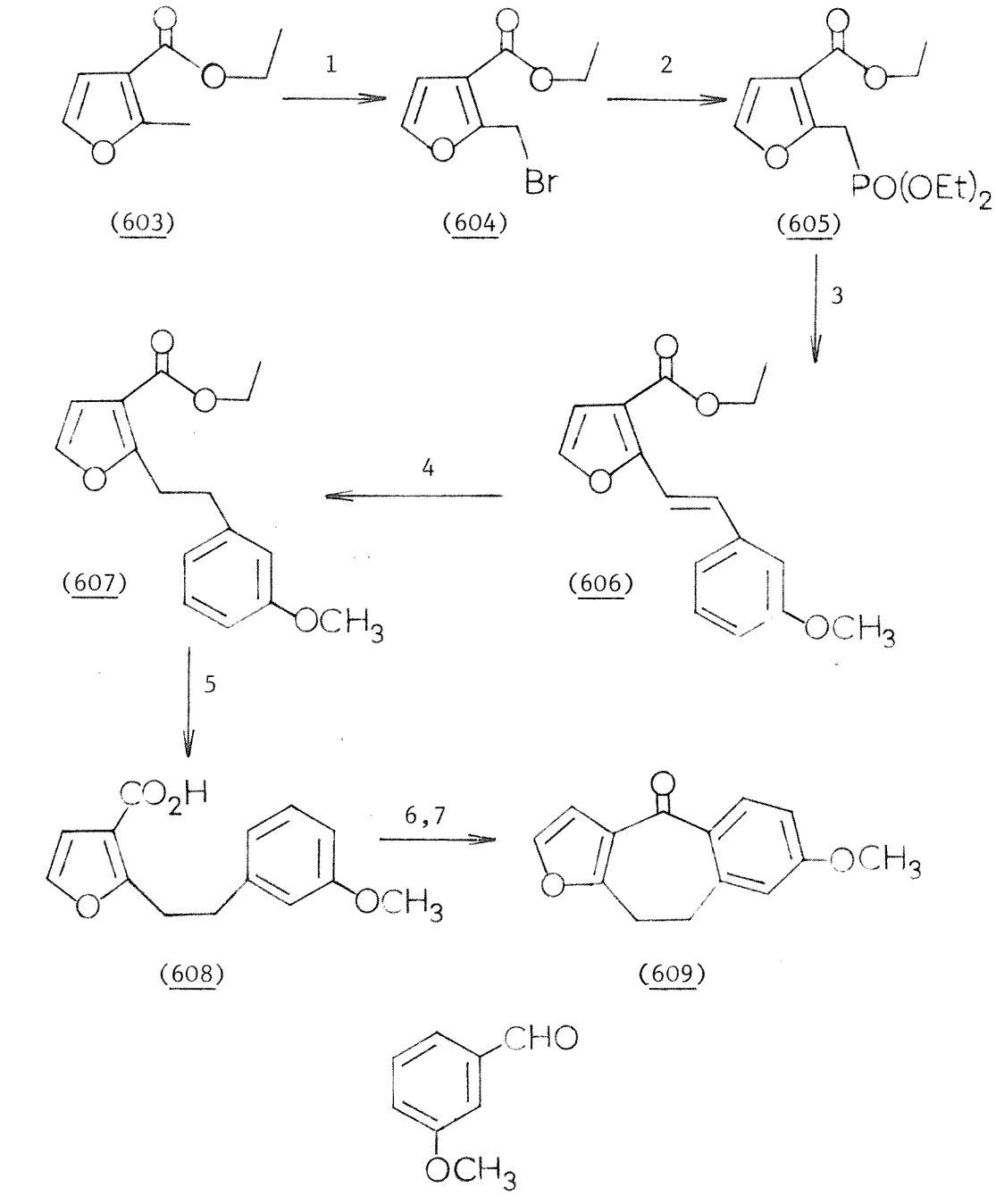
In 1975 Bisagni reported the synthesis of the benzo[4,5]cyclohepta[1,2-b]furan ring system (609) by a six step synthesis *via* the phosphonate (605),[379] (Scheme 20). The phosphonate (605) was prepared from the methyl furan (603) by bromination followed by treatment of the resulting bromide with triethylphosphite. Wadsworth-Emmons reaction[341,342] of the phosphonate (605) with the aldehyde (610) gave the stilbene (606) which was hydrogenated to give the key intermediate ester (607). The ester (607) was hydrolysed by ethanolic potassium hydroxide to give the acid (608) which was cyclised under Friedel-Craft conditions to give the target ring system (609).

The key intermediate in this approach to the benzo[4,5]cyclohepta[1,2-b]furan ring system is the ester (607), an analogue of which, (615), is required for the preparation of (536), (Scheme 21). This key intermediate (615) could be prepared by alkylation of the dianion of methyl acetoacetate[401] (613) with the bromide (619) followed by annulation of the resulting ketoester (614) with chloroacetaldehyde.

4.1.2. Synthesis of (536)

Treatment of the dianion of methyl acetoacetate (613), generated by the method of Weiler,[401] with the benzyl bromide (619) gave the ketoester (614) which was annulated with chloroacetaldehyde to give the furan (615), (Scheme 21). These two steps can be combined to give a "one pot" preparation of furan esters of the type (621) (see 4.1.3.) without isolation of the intermediate ketoesters. Aqueous base

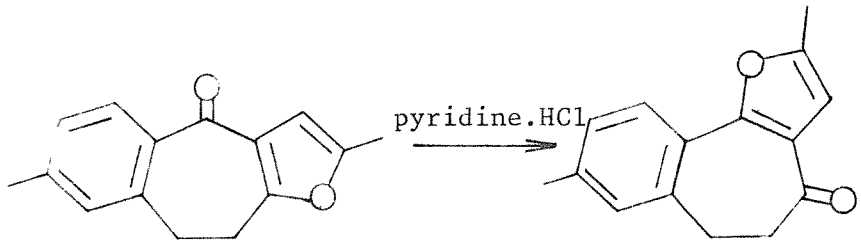
Scheme 20.



(603) (604) (605) (606) (607) (608) (609) (610)

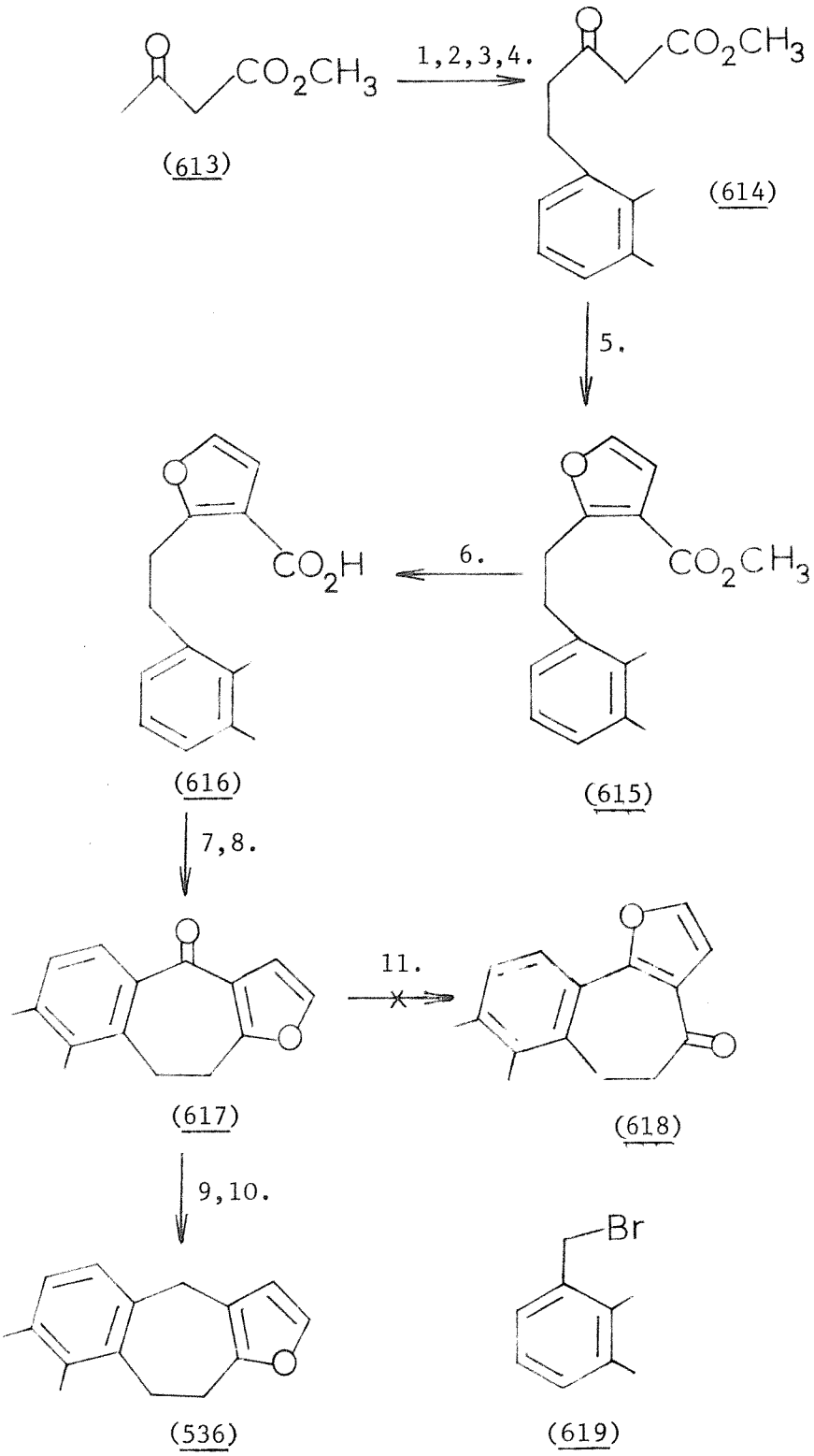
Reagents.

1. NBS, benzene. 2. $P(OEt)_3$. 3. NaH, DME, (610).
4. 30%Pd/C, H_2, EtOH. 5. KOH, EtOH. 6. PCl_5, benzene.
7. $AlCl_3$, CH_2Cl_2.



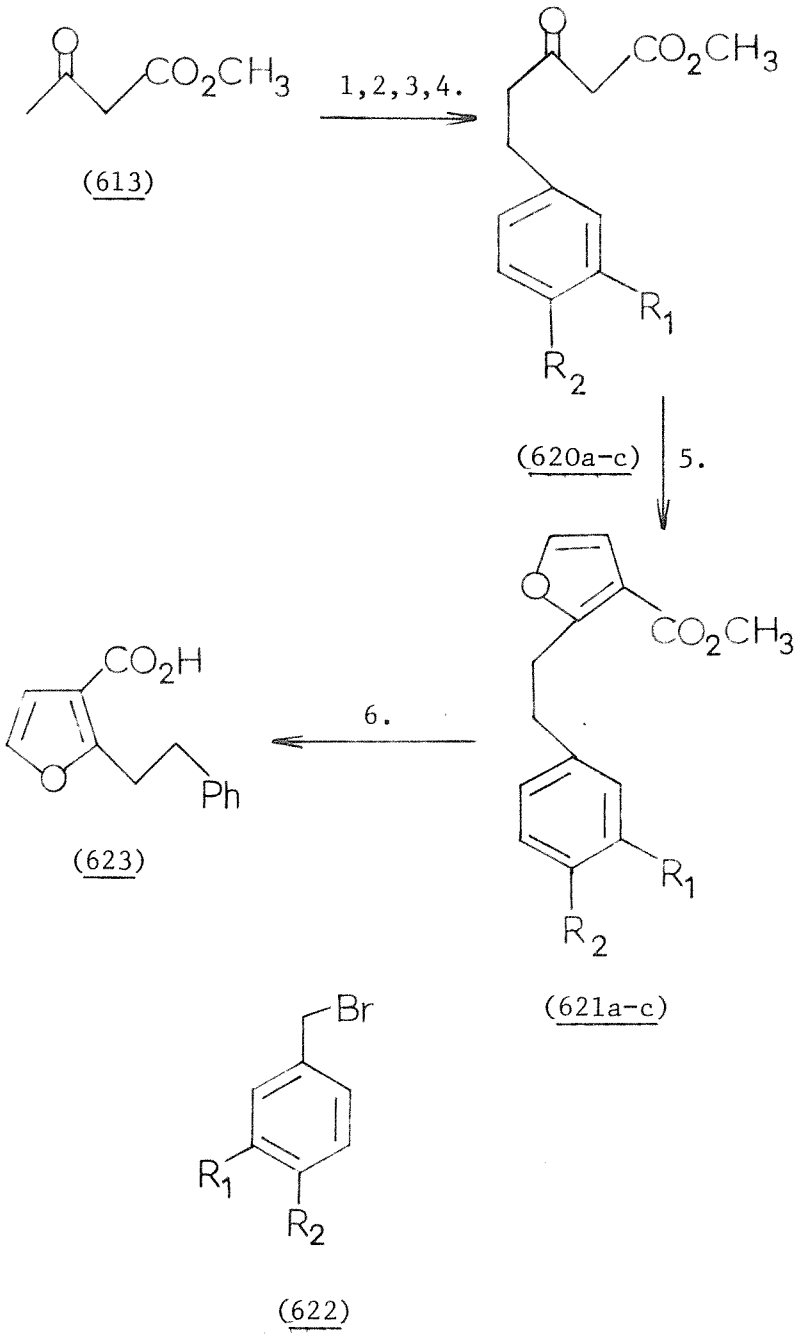
(611) (612)

Scheme 21.



Reagents. 1. NaH, THF. 2. *n*-BuLi. 3. (619). 4. H^+.
5. $ClCH_2CHO$, pyridine. 6. KOH, H_2O.
7. $SOCl_2$ benzene. 8. $AlCl_3$, $PhNO_2$. 9. $TsNHNH_2$, H^+, EtOH. 10. $NaCNBH_3$, DMF. 11. pyridine.HCl.

Scheme 22.



(613)

(620a-c)

(621a-c)

(623)

(622)

Reagents.

1. NaH, THF,
2. *n*-BuLi.
3. (622a-c)
4. H^+.
5. $ClCH_2CHO$, pyridine.
6. KOH, H_2O.

(620-622)

a $R_1=R_2=H$

b $R_1=H$, $R_2=Br$

c $R_1=Br$, $R_2=H$

hydrolysis of the ester (615) gave the acid (616). Cyclisation of the acid (616) followed by reduction of the resulting ketone (*ut supra*, Chapter 3), gave the novel furanoterpenoid (536).

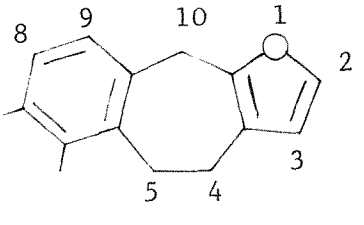
Bisagni reports that ketones of the type (611) readily rearrange, either under Friedel-Craft conditions or under acid catalysis, to give the isomeric ketones (612).[379] In contrast to this no evidence was found for the formation of (618) during the Friedel-Craft cyclisation of (616) or by acid catalysed rearrangement of (617), (Scheme 21).

4.1.3.

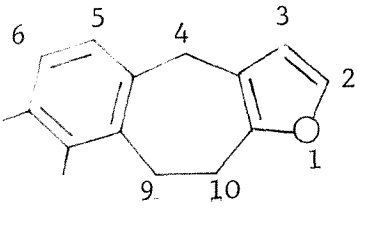
With a view to their possible biological activities, analogues of intermediates used in the preparation of (536) were prepared by the methods outlined in 4.1.2., (Scheme 22).

Treatment of the dianion of methyl acetoacetate (613)[401] with the benzyl bromides (622a-c) gave the ketoesters (620a-c) which were annulated with chloroacetaldehyde to give the furans (621a-c). Aqueous base hydrolysis of the ester (621a) gave the acid (623) which had previously been prepared by Bisagni.[379] (620a) Was prepared in 20% yield in a "one pot" procedure by quenching the mono-anion of methyl acetoacetate (which remains after the addition of benzyl bromide (622a)) with chloroacetaldehyde.

4.2. Structure of Pallescensin-E



(337)



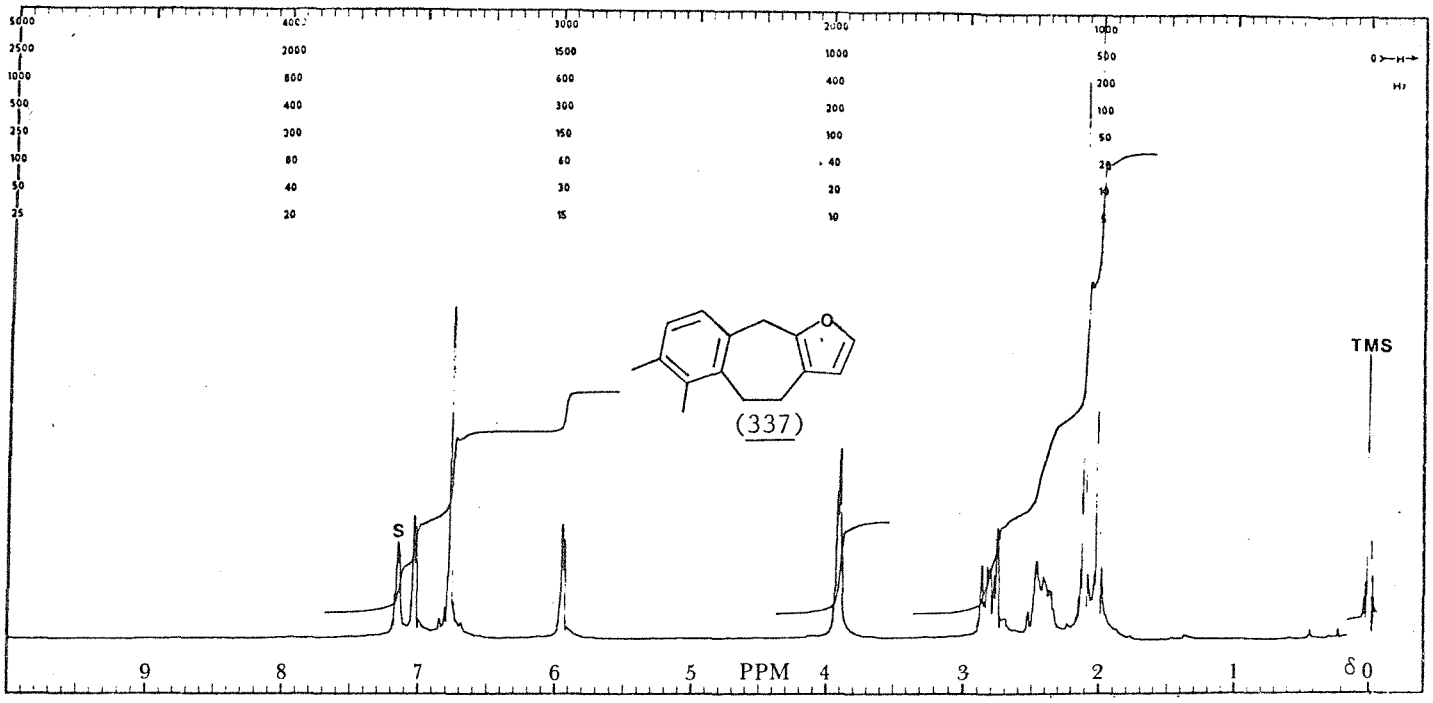
(536)

Table 6. Comparison of Spectral Data for Pallescensin-E[a] and (337).

	(337)	Pallescensin-E
^{1}Hnmr $\delta(C_6{}^2H_6)$		
	2.01(3H,s)	2.10
	2.10(3H,s)	2.11
	2.42(2H,m)	2.44
	2.82(2H,m)	2.80
	3.91(2H,brs)	3.90
	5.94(1H,d,J=2Hz)	5.94
	6.77(2H,s)	6.78
	7.01(1H,d,J=2Hz)	7.09
uv $\lambda_{max}^{EtOH}(\varepsilon)$		
	217nm(12,600)	222,225(10,300 and 11,900)
ms m/e(% base peak)		
	213($\underline{M}^+$+1,15)	
	212($\underline{M}^+$,95)	212($\underline{M}^+$,90)
	198(15)	
	197(100)	197(100)
	183(14)	183(13)
	169(27)	169(28)

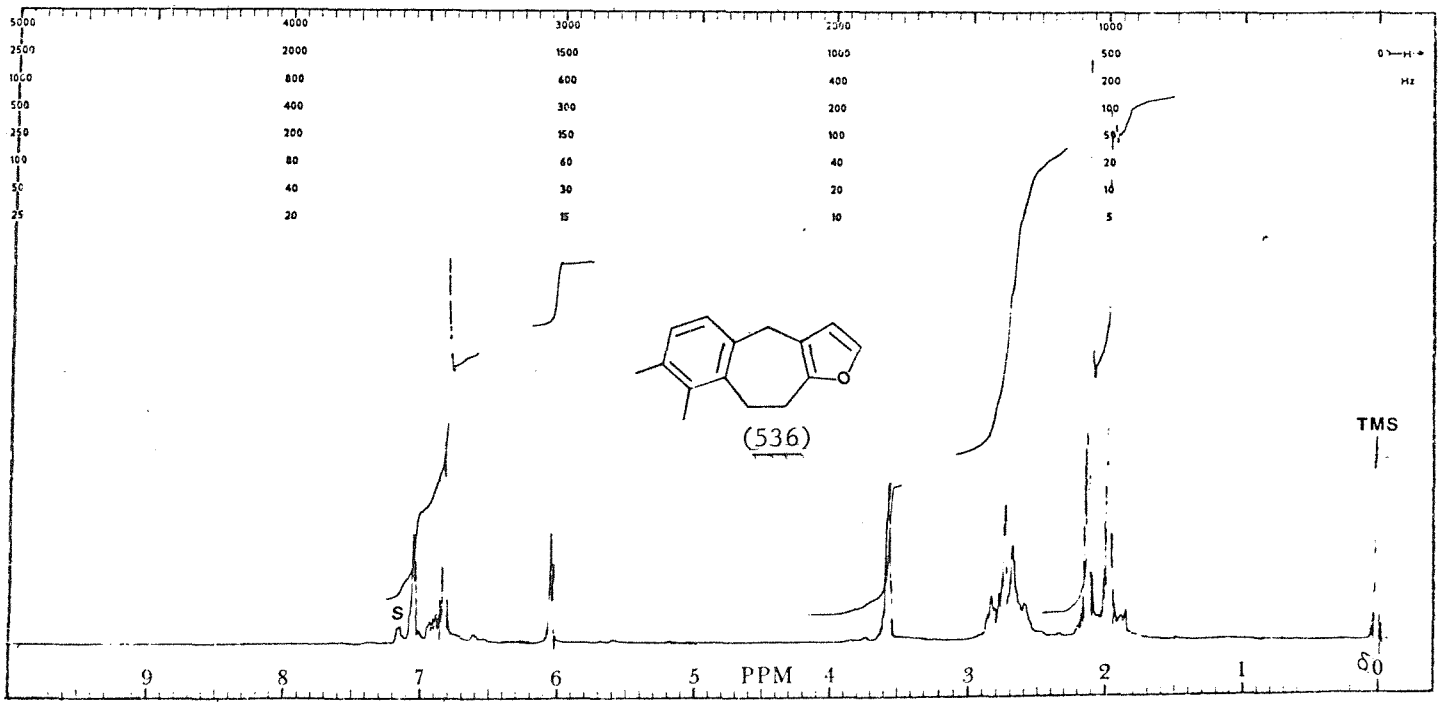
a Spectral data for pallescensin-E taken from reference 7.

Figure 7. 100MHz ^{1}H nmr spectra of (337) and (536).



(337)

S= solvent (C_6D_6)

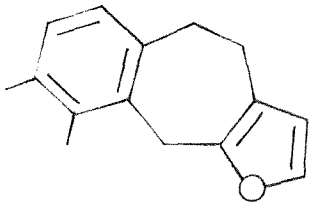


(536)

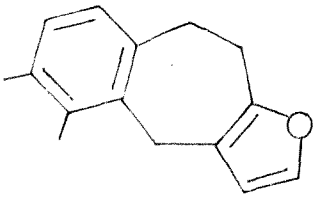
The ^{1}H nmr spectrum of (337) and (536) exhibited many similarities but they were markedly different in two regions, (Figure 7). The ^{1}H nmr spectrum of (536) showed a broad singlet for the two "dibenzylic protons" (C-4) at 3.57δ whereas the spectrum of (377) showed a broad singlet for the "dibenzylic protons" (C-10) at 3.91δ, in good agreement with the published value of 3.90δ for pallescensin-E.[7] The spectrum of (536) also showed a single four proton multiplet for the "mono benzylic proton" (C-9 and C-10) at 2.72δ, whereas the spectrum of (337) showed a pair of two proton multiplets, at 2.82 and 2.42δ, again in good agreement with the published values of 2.80 and 2.44δ for pallescensin-E.[7] The remaining spectral data for (337) was in good agreement with the published data,[7] (Table 6). Thus the structure of pallescensin-E is (337) and not (536).

4.3. Structure of Spiniferin-2

Spiniferin-2 (315 or 316) was isolated along with spiniferin-1 (314) and longifolin (61) in 1976 by Cimino.[38] Both structures, (315) and (316) were compatable with the collected chemical and physical data for spiniferin-2 but the authors were unable to unambiguously assign the structure.[196,402] The slight differences in the ^{1}H nmr spectral data between (337) and (536) should allow the structure of spiniferin-2 to be assigned (c.f.pallescensin-E). The ^{1}H nmr data for (337), (536) and spiniferin-2 are shown in Table 7 and are similar in many respects. The ^{1}H nmr spectrum of (536) showed a signal at 3.58δ for the two dibenzlic protons (C-4), whereas (337), pallescensin-E, showed a signal at 3.90δ close to the value of 4.02δ for spiniferin-2.[402] The spectrum of (536) also showed a single four proton multiplet for the monobenzylic proton at C-9 and C-10 whereas (337) showed a pair of two proton multiplets similar to that observed from spiniferin-2. Thus, from arguments similar to those for pallescensin-E, the structure of spiniferin-2 can be tentatively assigned as (315) rather than (316).



(315)



(316)

Table 7. Comparison of ^{1}H nmr Data for (337), (536) and Spiniferin-2.

Pallescensin-E (337)[a,b] $CDCl_3$, δ	(536)[a,b] $CDCl_3$, δ	Spiniferin-2[196,402] CCl_4, δ
3.90(s)[c]	3.58(s)	4.02(s)
7.00(s)	7.05(s)	7.03(s)
5.90(d)[d]	6.05(d)[d]	5.96(d)[d]
2.42 and 2.82(2xm)	2.72(m)	2.61 and 2.92(2xm)
2.00 and 2.10(2xs)	2.00 and 2.12(2xs)	2.21 and 2.25(2xs)
6.76(d)[d]	6.82(d)[d]	6.82(d)[d]

a Spectra for (337) and (536) were run in $CDCl_3$ due to their rapid (under 2 minutes) decomposition in CCl_4.

b The different solvents ($CDCl_3$ v CCl_4) can be expected to cause at most a variation in chemical shift of ±0.1ppm for C-H proton.[403]

c s=singlet, d=doublet, m=multiplet.

d J=2Hz in each case.

4.5. Synthesis of Homosesquirosefuran (628)

4.5.1. Introduction

The common occurrance of biological activity among furanonatural products (Chapter 1.) has encouraged many groups of workers to prepare various furano analogues of natural products and analogues of furanonatural products. Recent examples include a range of furano prostanoids,[404] furano carotenoids[405] and furano fatty acids.[406]

With a view to possible biological activity (628), an analogue of sesquirosefuran (60), was prepared to exemplify the use of the dianion of methylacetoacetate (613) in furan synthesis.

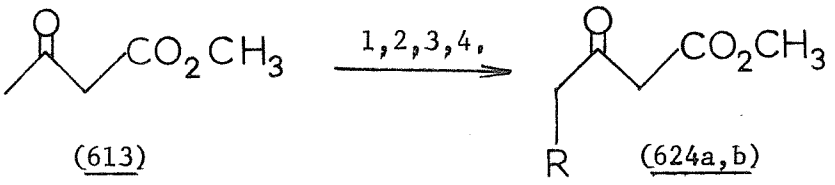
4.5.2. Synthesis of Homosesquirosefuran (628)

In a model study the dianion of methyl acetoacetate (613) was reacted with allyl bromide (626b), by the method of Weiler[401] to give the ketoester (624b) which was annulated with chloroacetaldehyde to yield the furan (625b), (Scheme 23). The furan (625a) was prepared by the same procedure and reduced with lithium aluminium hydride to give the alcohol (627). Treatment of the alcohol (627) with 4-toluenesulphonyl chloride in pyridine gave the corresponding tosylate which was reduced with lithium aluminium hydride to give the novel methylfuran (628).

4.5.3. Future Work

The above procedure (4.5.2.) could allow easy preparation of a range of analogues of the type (628) for biological activity screening as well as convenient synthesis of insecticidal β-ketoesters of the type (624)[407] (e.g. 624a).[408]

Scheme 23.



(613) (624a,b)

RBr

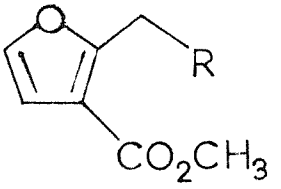
(626a,b)

5.

(624-626)

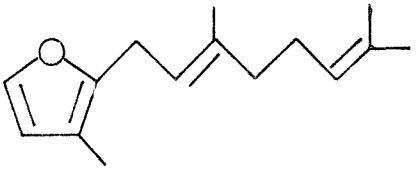
R= (b)

R= (a)



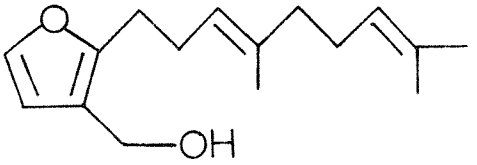
(625a,b)

6.



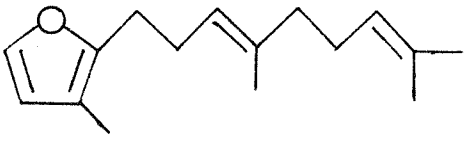
sesquirosefuran

(60)



(627)

7,6.



(628)

Reagents.

1. NaH, THF.
2. BuLi.
3. R-Br (626a,b).
4. H^+
5. $ClCH_2CHO$, pyridine.
6. LAH.
7. pTsCl, pyridine.

CHAPTER FIVE AN APPROACH TO THE SYNTHESIS OF PINGUISONE

5.1. Introduction

Pinguisone (328), a component of the essential oil of the liverwort *Aneura pinguis*, was first isolated in 1969 by Šorm *et al.*[8] Since then a number of natural products belonging to the pinguisane group have been isolated from liverworts (329-332).[191]

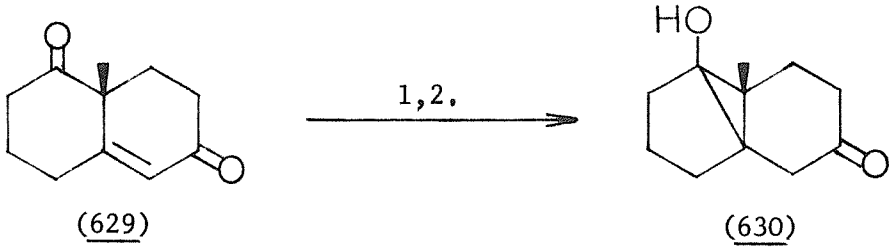
One of the first synthetic approaches to pinguisone was that of Venkataramani, which failed, however, when the *trans* ring junction (631) was obtained from the acid catalysed rearrangement of the cyclopropane alcohol (630), (Scheme 24).[409]

While this thesis was in preparation Jommi[410] reported a synthesis of (+)-7-*epi*-pinguisone (639) from the chiral dione[411] (633),(Scheme 25). Robinson cyclisation of the triketone (632)[412] in the presence of a catalytic amount of (S)-(-)-proline gave the (S)-(+)-diketone (633) which on treatment with lithium dimethylcuprate gave the *cis*-dimethylindanone (634). Dibromination of (634) with bromine in acetic acid followed by dehydrobromination with calcium carbonate in dimethylacetamide afforded the *bis*-enone (636). Methylation of the more reactive double bond in the five membered ring of (636), by lithium dimethylcuprate, gave only the α-methyl group (637). Treatment of (637) with lithium dimethylcuprate and trapping of the resulting enolate with chloroacetyl chloride yielded the furanone (638) which was reduced with 9-BBN to (+)-7-*epi*-pinguisone (639).

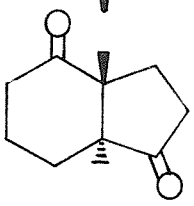
5.2. Initial Synthetic Considerations

Any synthetic approach to one or all of the pinguisones must enable the stereospecific introduction of the *cis* methyl groups. From a consideration of pinguisone (328), if the C-7 methyl group could be 'pinned' to the C-5 ketone to create an ethylene bridge, this retro synthetic step would yield a cyclohexane ring which could be considered derived from the [2.2.1.]bicycloheptane (640) *via* a Diels-Alder reation, (Figure 8). In this approach its success depends on the cycloaddition reaction occurring as in (a) and not (b),(Figure 9).

Scheme 24.



(629) (630)



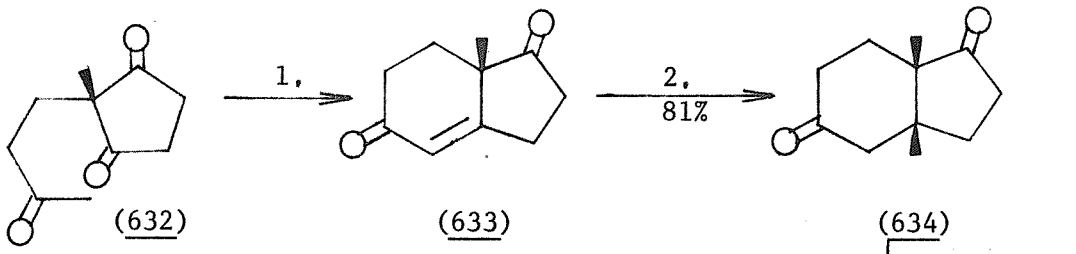
(631)

Reagents. 1. Li, NH_3, Et_2O.

2. NH_4Cl.

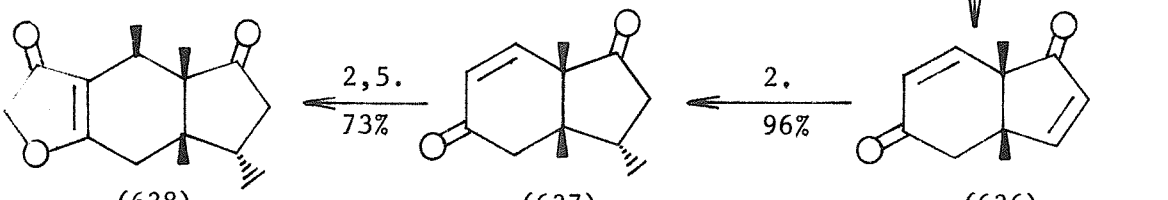
3. pTsOH, PhH, Δ.

Scheme 25.



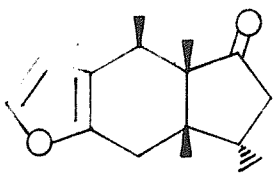
(632) (633) (634) (635)

51% 4.



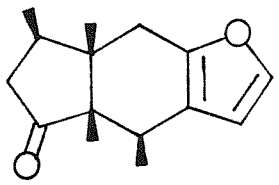
(638) (637) (636)

6.



(639)

Reagents. 1. base.
2. Me_2CuLi, Et_2O.
3. Br_2, CH_3CO_2H.
4. $CaCO_3$, CH_3CONMe_2
5. $ClCH_2COCl$.
6. 9-BBN, THF.



(328)

pinguisone[8]

Figure 8.

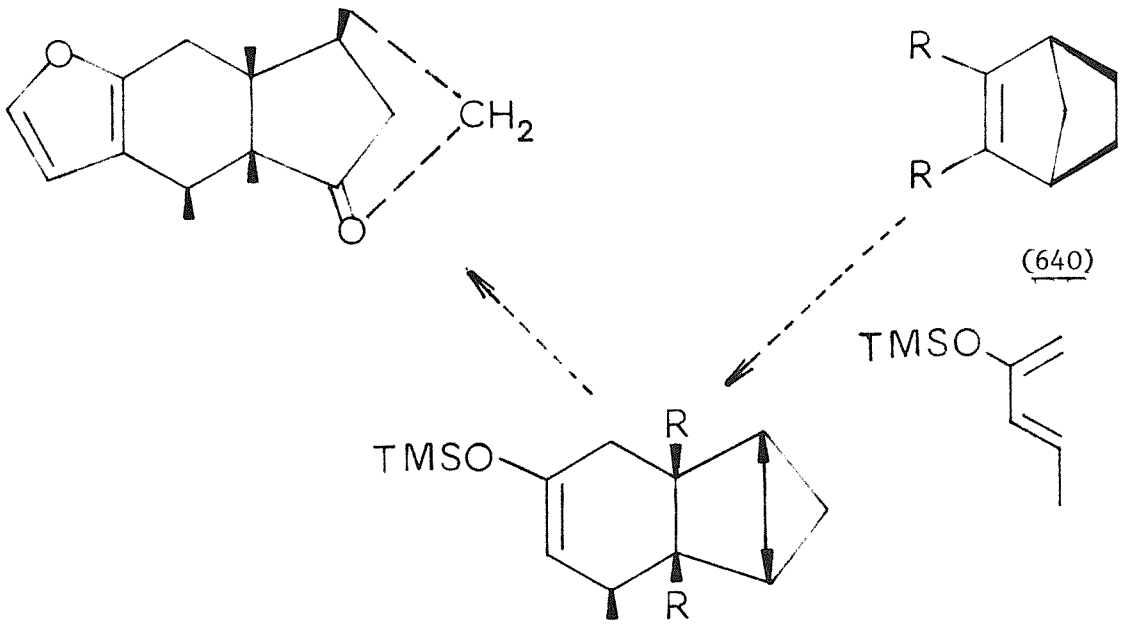
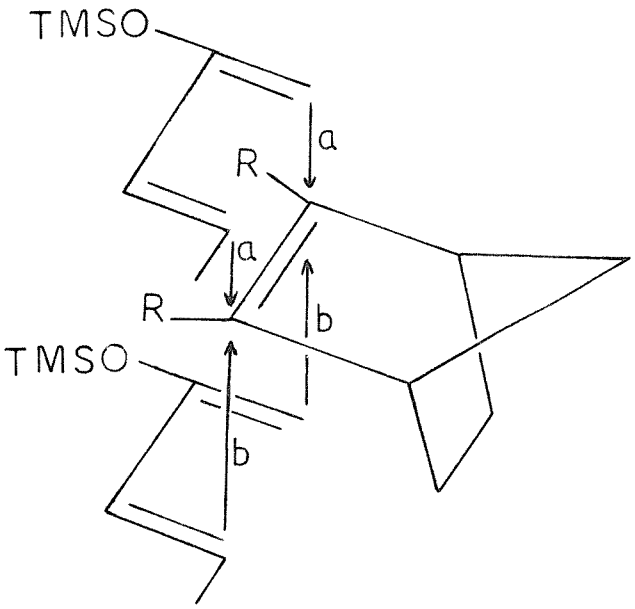
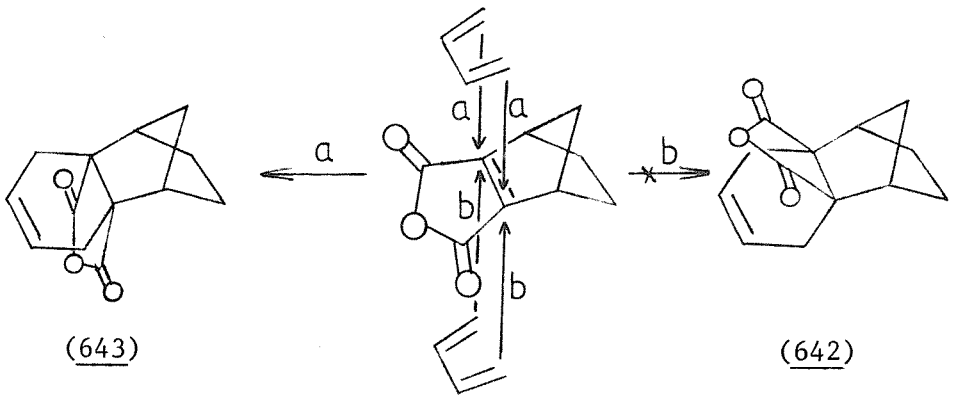


Figure 9.



Scheme 25.



(643) (641) (642)

A significant precedent for this reaction to occur as in (a) exists in the results of Simmons, who found that 1,3-butadiene reacted with the anhydride (641) to give the adduct (643) rather than (647),[413] (Scheme 25).

Thus an approach to pinguisone (328) can be envisaged where an acetonide is used to mask the C-5 ketone and C-7 methyl functionalities, (Schemes 26 and 31).

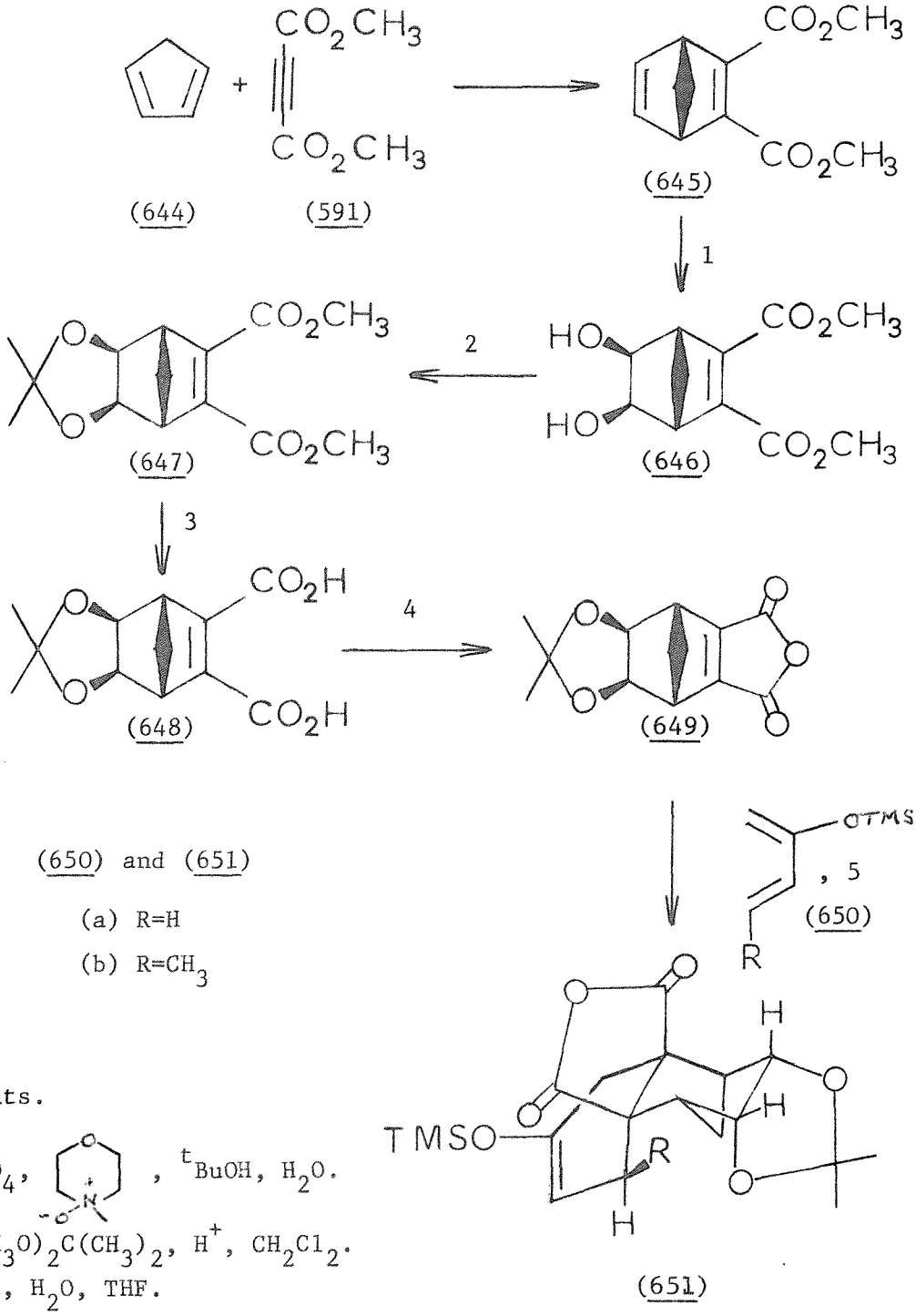
5.3. Synthetic Studies

The readily available diene[414] (645) was converted to the diol (646) by the action of catalytic osmium tetroxide which was continuously recycled by conducting the reaction in the presence of N-methyl morpholine N-oxide.[415] The diol (646) was converted to the acetonide ester (647) which was then hydrolysed to the corresponding acetonide acid (648) by aqueous potassium hydroxide. The crystalline anhydride (649) was prepared under the literature conditions from the acid (648).[416]

In a model study of the proposed Diels-Alder reaction the anhydride (649) was treated with 2-(trimethylsilyl)oxy-buta-1,3-diene[417] (650a), which gave the expected adduct (651a). In an initial small scale study, of the cycloaddition reaction of the diene (650b) (prepared by Scheme 28) with (649), however, a mixture of the ketone (653) and the unexpected adduct (654) was obtained, (Scheme 27). The adduct (654) could result from a cycloaddition between (649) and the rearranged diene (652), which could have arisen from a [1,5]hydrogen shift in the diene (650b), (Scheme 27). [1,5]hydrogen shifts in dienes are well known and there is evidence to support the view that they are concerted reactions.[418] The stereospecific suprafacial nature of the migration has been demonstrated with the diene (658).[419] Here the optically active starting material (658) gave the two isomers expected from a suprafacial [1,5] shift (659) and (660) but gave neither of the isomers that would result from an antarafacial migration.[419,420]

In a subsequent large scale preparation of the adduct (651b) formation of the isomer (654) was not observed. The product (651b)

Scheme 26.



(650) and (651)

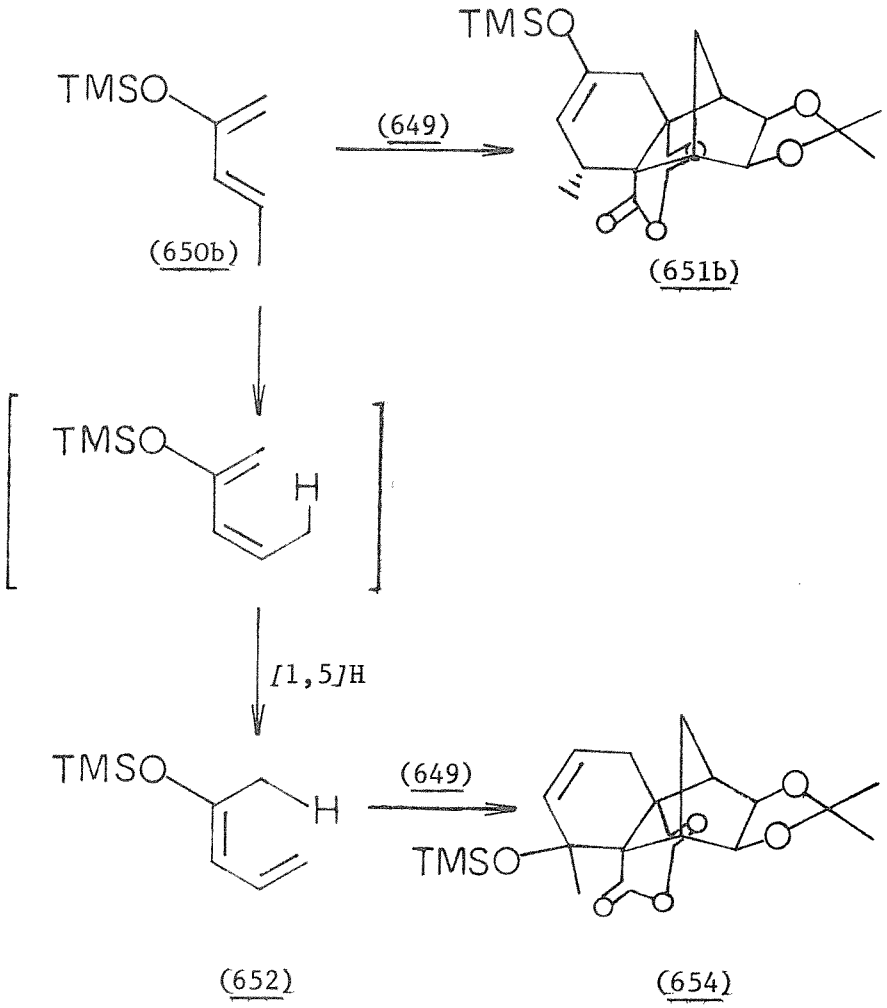
(a) R=H

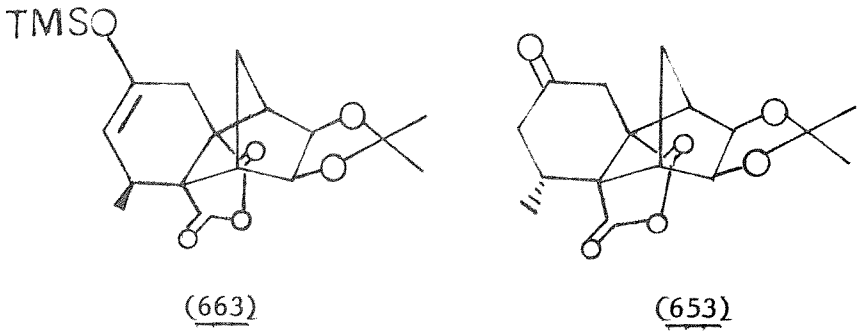
(b) R=CH_3

Reagents.

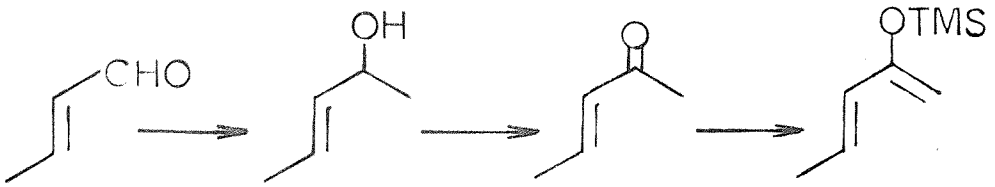
1. OsO_4, , ^tBuOH, H_2O.
2. $(CH_3O)_2C(CH_3)_2$, H^+, CH_2Cl_2.
3. KOH, H_2O, THF.
4. EtOC≡CH, CH_2Cl_2.
5. $PhCH_3$, Δ.

Scheme 27.


TMSO
(649)
TMSO
(650b)
(651b)
TMSO
H
[1,5]H
TMSO
H
(649)
TMSO
(652)
(654)


TMSO
(663)
(653)

Scheme 28.

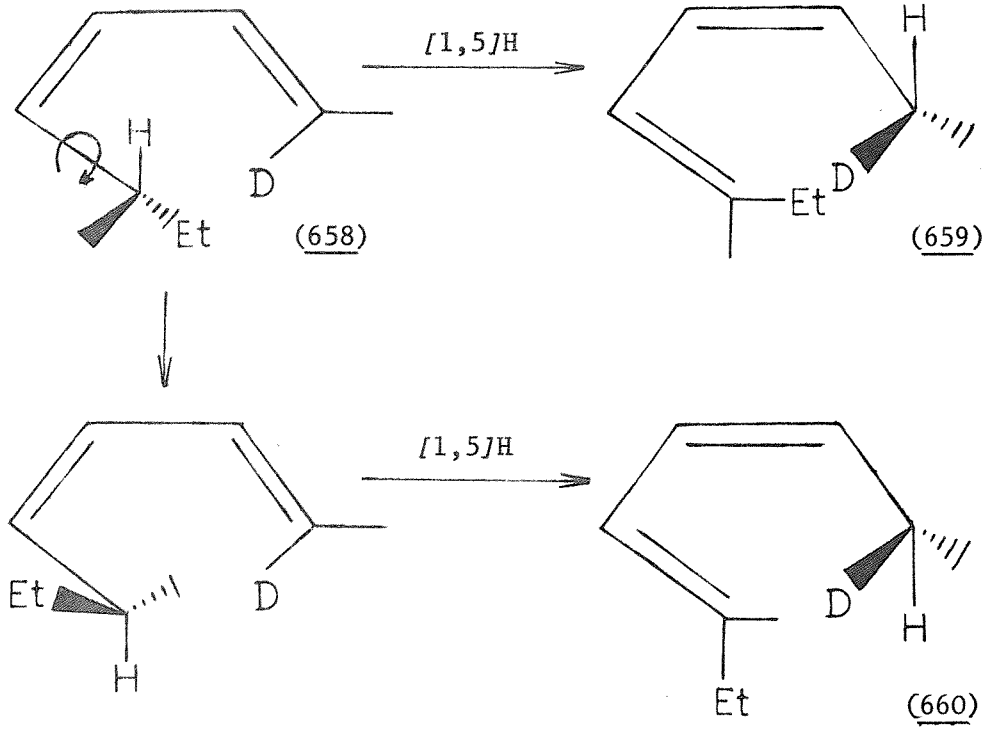


(655) (656) (657) (650b)

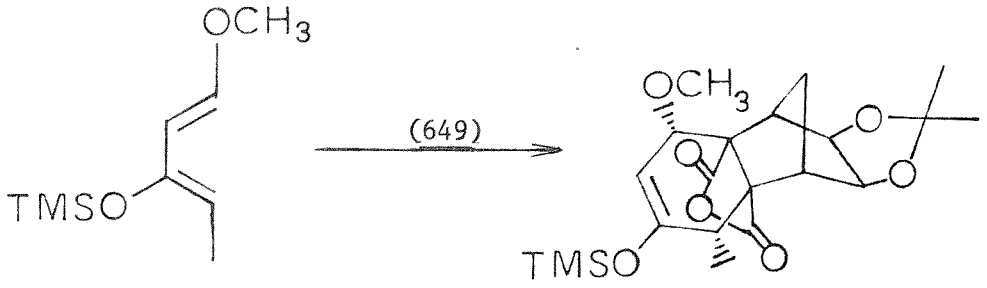
Reagents,

1. CH_3MgI, Et_2O.
2. pcc, CH_2Cl_2.
3. TMSCl, NEt_3, benzene, $ZnCl_2$.

Scheme 29.



Scheme 30.



(661) (662)

Figure 10a.
Partial ^{1}Hnmr spectrum of (651b) showing a doublet of doublets (→) (J_1=7Hz, J_2=1Hz) for the C_5-$\underline{CH}_3$ group which collapses to single doublet on irradiation at 4.5δ (inset).

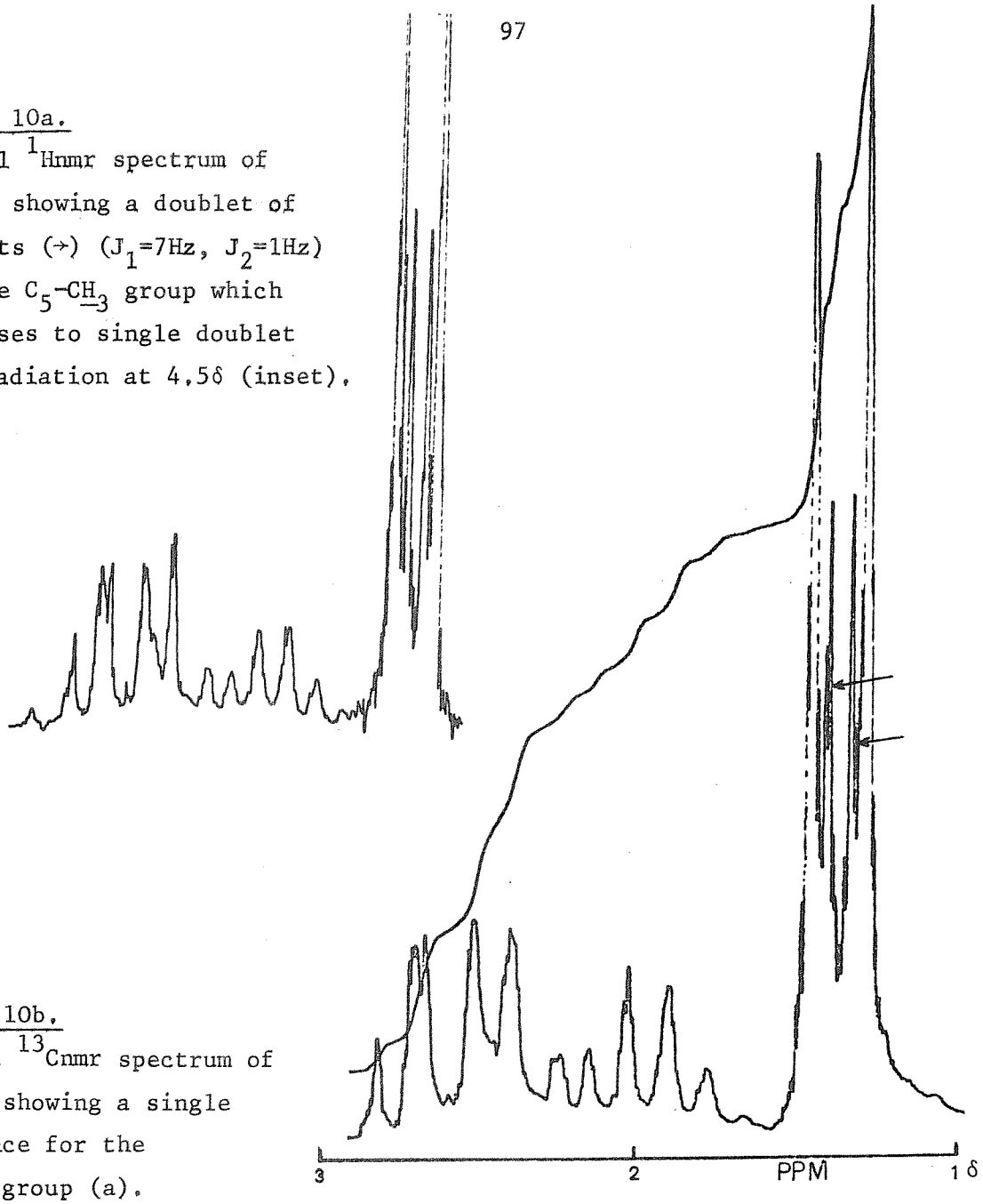
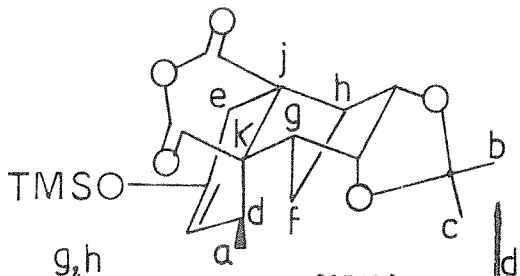
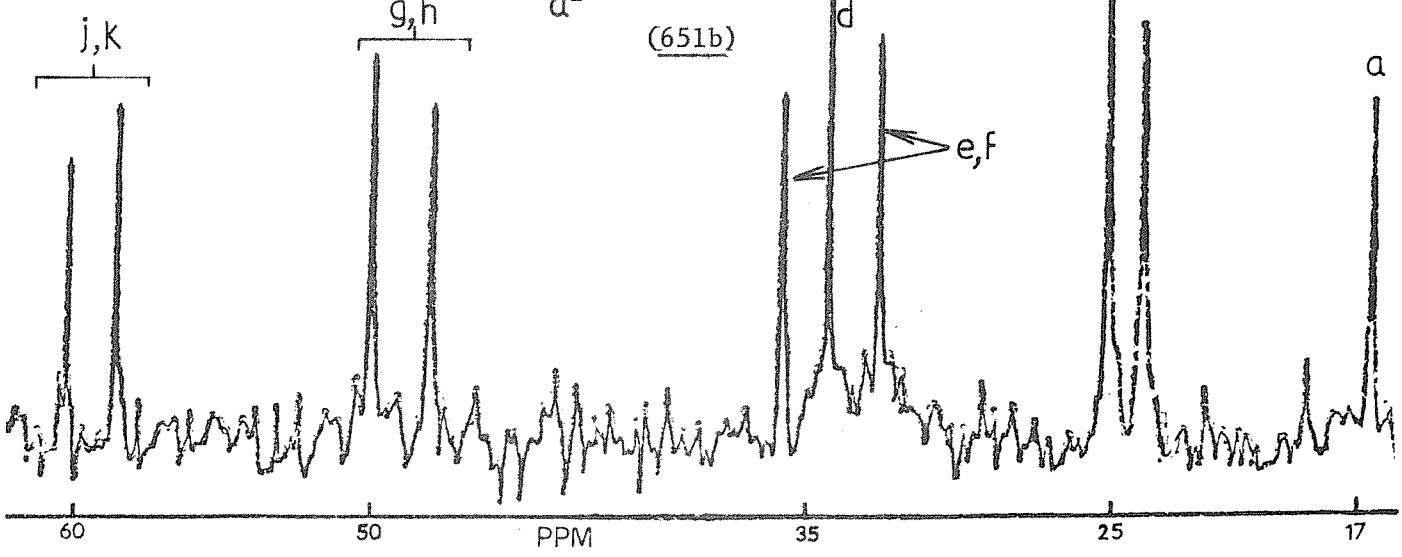


Figure 10b.
Partial ^{13}Cnmr spectrum of (651b) showing a single resonance for the C_5-$\dot{C}H_3$ group (a).



(651b)



showed a single resonance for the methyl group at C-5 in both the ^{1}H and ^{13}C nmr spectra (Figure 10) and was thus believed to be the 5α-methyl compound (651b), analogous to the single product (662) obtained by Gombatz[421] from diene (661) and anhydride (649), (Scheme 30), and not the 5β-methyl isomer (663).

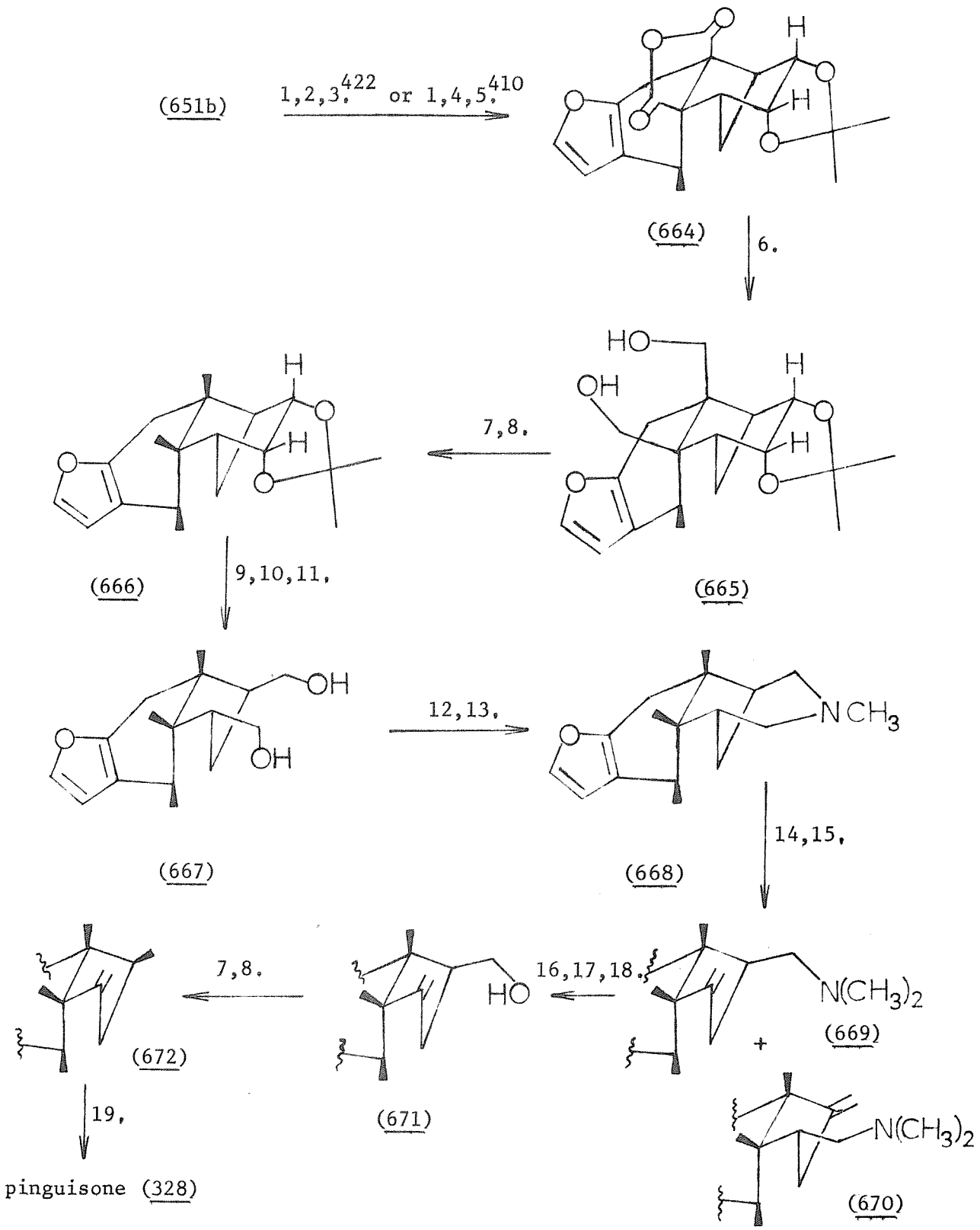
5.4. Future Work

Further work on this approach to pinguisone (328) was not possible in the time available, but future work could proceed as outlined (Scheme 31). Treatment of the enol ether (651b) with tertiary butyl lithium followed by elaboration of the resulting enolate either by the method of Yoshikoshi[442] or by the method of Jommi[410] (see 5.1.) should afford the furan (664). These procedures could most conveniently be initially attempted on the adduct (674) which is readily available from maleic anhydride (673) and 2-(trimethylsilyl)oxy-buta-1,3-diene[417] (650a), (Scheme 32). The furan product (675) would also be useful as a model for the reduction of the anhydride (664) to give the diol (665),[423] and subsequent reduction of the *bis*-alcohol mesylate to the dimethyl analogue[424] (666), (Scheme 31).

Removal of the acetonide protecting group by the method of Danishefsky,[416] followed by manganese dioxide oxidation[416] and then sodium borhydride[416] reduction of the resulting dialdehyde, should afford the diol (665).

Bromination of the diol[425] (665), followed by treatment of the dibromide product with methylamine, should yield the amine (668).[426] Hofmann elimination[426,427] of the amine (668) should give a mixture of the two amines (669) and (670) which should be separable. Quaternisation of the amine (669) followed by treatment with base and a crown ether should afford the alcohol[357] (671) which could be reduced to the C-7 methyl group (672) *via* the corresponding mesylate, as above.[424] Ozonolysis of the methylene group should then yield pinguisone (328).

Scheme 31.



Reagents. 1. ^{t}BuLi. 2. $=^{NO_2}_{SPh}$. 3. $NaIO_4$, MeOH, Δ. 4. $ClCH_2COCl$, 5. 9-BBN. 6. LAH, THF. 7. $MeSO_2Cl$, pyridine. 8. LAH, NaH, (1:1), Et_2O. 9. CH_3CO_2H, H_2O. 10. MnO_2, $CHCl_3$. 11. $NaBH_4$, MeOH. 12. PBr_3, LiBr, collidene. 13. NMe_2H, Δ. 14. MeI. 15. AgO. 16. EtBr, EtOH. 17. NaOAc, HOAc, 15-crown-5. 18. NaOH, MeOH. 19. O_3.

CHAPTER SIX PRELIMINARY STUDIES OF THE FORMATION OF LACTONES *via* THE INTRAMOLECULAR REACTION OF π-ALLYLNICKEL HALIDES WITH EPOXIDES

6.1. π-Allylnickel Halides in Organic Synthesis

π-Allylnickel halides are valuable reagents since they can be prepared by a number of methods and are easily purified and stored in the absence of oxygen for several weeks.[366,367] High yields (up to 90%) of π-allylnickel complexes can be obtained by heating allylhalides with nickel tetracarbonyl in benzene[428,367] or by reaction of *bis*(1,5-cyclooctadiene)nickel (0)[367,429] with allyl halides at -10°C.[429]

In polar coordinating solvents, such as N,N-dimethylformamide, π-allylnickel halides have been shown to undergo reactions with a range of functional groups, including halides,[367,430] ketones,[367] aldehydes,[367] quinones[368] and epoxides.[367]

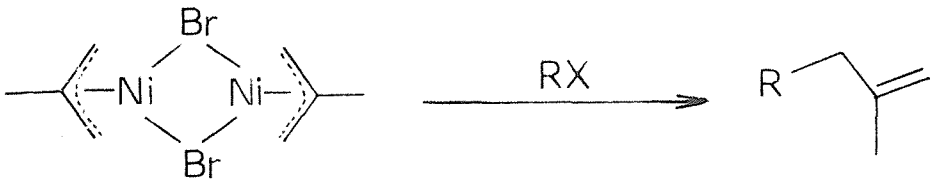
6.1.1. Reaction of π-Allylnickel Halides with Organic Halides

Corey and Semmelhack have shown that in polar aprotic media π-allylnickel halides (e.g.(678)) react with organic halides to produce allyl substituted molecules and nickel II halides, (Table 8 and Scheme 33).[430] The efficient reaction of π-allylnickel halides with allyl halides has been exemplified by the synthesis of α-santalene (681).[430] Conversion of 1-bromo-3-methyl-2-butene (679) to the corresponding π-allylnickel complex (680) followed by reaction with the tricyclic iodide (682) produced α-santalene (681) in 80% overall yield.[430] By comparison, the coupling of the Grignard reagent from (682) and allyl bromide (679) gave only a 20% yield of α-santalene (681).[431]

6.1.2. Reaction of π-Allylnickel Halides with Aldehydes, Ketones and Quinones

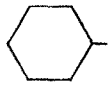
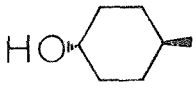
In its reaction with alkyl and aryl halides, the π-allyl ligand does not show the normal characteristics of a nucleophilic

Scheme 33.



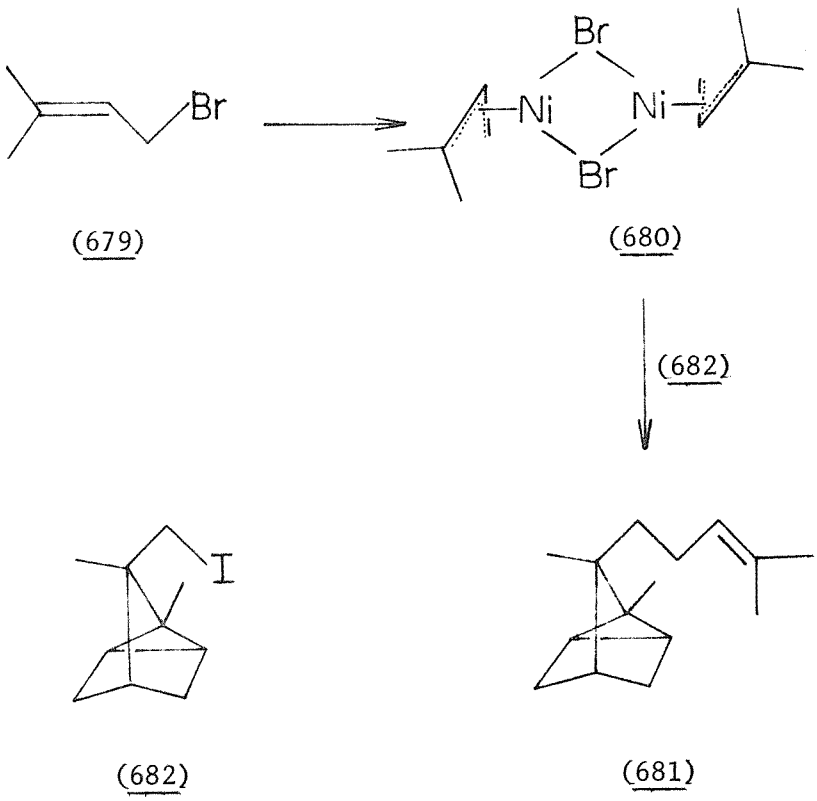
(678)

Table 8. Coupling of π-methallylnickel Bromide (678) with Halides in N,N-Dimethylformamide.[430]

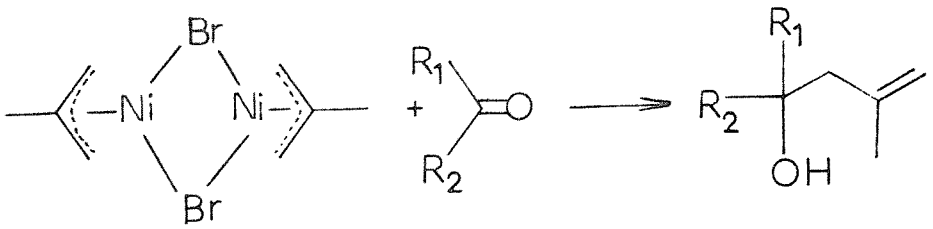
R	X	Reaction time h (temperature °C)	Yield (%)
Me	I	10(22)	90
Me	Br	19(22)	90
	I	3(22)	91
	I	10(22)	88[a]
t-Bu	I	24(22)	25
Ph	I	1(22)	98
CH_2=CH-	Br	13(22)	70
$PhCH_2$-	Br	6(60)	91
$PhCH_2CH_2CH_2$-	Br	46(65)	92

a Mixture of *cis* and *trans* isomers.

Scheme 34.



Scheme 35.



eg. R_1-R_2= -(CH_2)-

R_1=H, R_2=Ph (532a)

R_1=H, R_2= -CH=CH_2

reagent.[430,367] Under more vigorous conditions π-allylnickel halides behave more like other organometallic species (e.g. Grignard reagents,[432] alkyl lithiums[433] etc) in attacking carbonyl groups and epoxide rings.[366,367,430] For example, benzaldehyde, cyclopentanone and acrolein undergo allylation with π-allylnickel halides in moderate to high yield, in strongly polar media at 50-60°C, with acrolein undergoing 1,2-addition,[367] (Scheme 35).

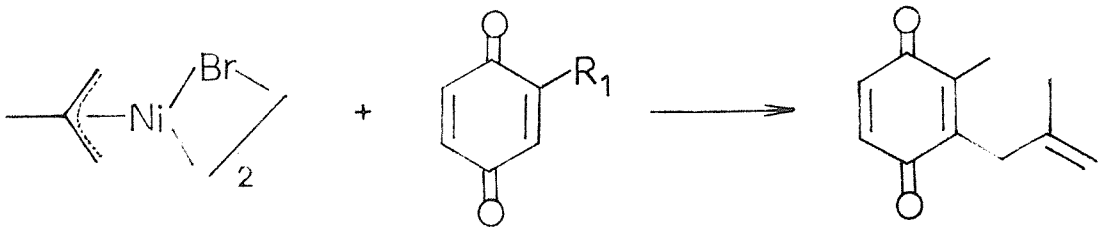
The addition of an allyl ligand to a carbonyl group has found synthetic application in the synthesis of *cis*-fused α-methylene lactones by the intramolecular cyclisation of a 2-carbomethoxy π-allylnickel species onto an aldehyde,[369] (see Chapter 3.2.1. Scheme 8).

Alkylation of quinones by π-allylnickel halides has been shown to depend on the substitution of the quinone.[368] p-Benzoquinone (683a) reacts to produce allyl-substituted hydroquinones (685a,b), while substituted quinones produce the corresponding allyl quinones (Table 9). The major side product in the alkylation of quinones by π-allylnickel halides has been the hydroquinone arising from reduction of the substrate. This reduction has been most extensive with p-benzoquinone (683a) but has been observed to a lesser degree with the other substrates in Table 9. Quinones having a methyl group adjacent to an unsubstituted position (e.g. 2-methylbenzoquinone (683b)) suffered attack at the methylated position as well as attack at the unsubstituted position (Scheme 36) although no attack at the methylated position of quinones with adjacent methyl groups (e.g.2,3-dimethylbenzoquinone) was observed.[368] The synthetic utility of this reaction has been demonstrated by Hegedus by the synthesis of coenzyme Q_1 (687) in 30% yield and plastoquinone (688) in 61% yield, (Table 9).[368]

6.1.3. Reaction of π-Allylnickel Halides with Epoxides

Semmelhack has reported the only reaction of a π-allylnickel species with an epoxide to date.[367] Styrene oxide (689) reacted with π-(2-methlyallyl)nickel bromide (678) in N,N-dimethylformamide at 60°C to give the primary alcohol (690) in 60% yield,[367] (Scheme 37). As simple nucleophilic attack would be expected to occur at the 1 position in styrene oxide,[434] the nickel could be assisting the opening of the epoxide ring.[367]

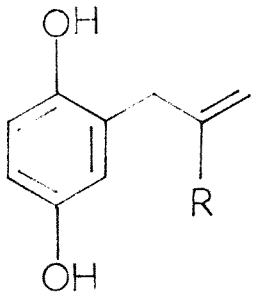
Scheme 36.



(678) (683) (684)

R_1=H (683a)

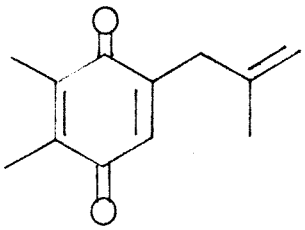
R_1=CH_3 (683b)



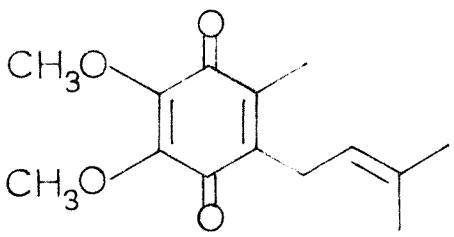
(685)

R=H (685a)

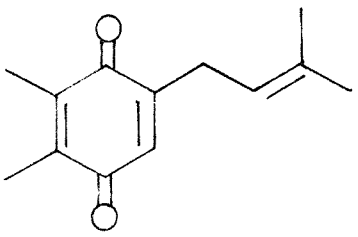
R=CH_3 (685b)



(686)



(687)



(688)

Table 9. Alkylation of Quinones with π-Allylnickel Bromide Complexes.[368]

π-Allylnickel bromide	Quinone	Product	Yield (%)
Allyl	(683a)	(684a)	58
(678)	(683a)	(685b)	86
(678)	1,4-Naphthoquinone	2-(2-Methyl-2-propenyl)-1,4-naphthoquinone	39
(678)	(683b)	(684)	45
(678)	2,3-Dimethylbenzoquinone	(686)	82
1,1-Dimethylallyl	2,3-Dimethylbenzoquinone	Plastoquinone (688)	61
1,1-Dimethylallyl	2,3-Dimethoxy-5-methylbenzoquinone	Coenzyme Q_1 (687)	30

6.2. Natural Products Possessing the α-Methylene-δ-Valerolactone Structural Unit

The α-methylene-γ-butyrolactone structural unit, and to a lesser extent the α-methylene-δ-valerolactone unit, characterise a rapidly expanding group of biologically active natural products (e.g. 691-694), together with a number of natural products with a lactone ring that could be considered derived from an α-methylene-δ-valerolactone moiety (695-697).[435,441]

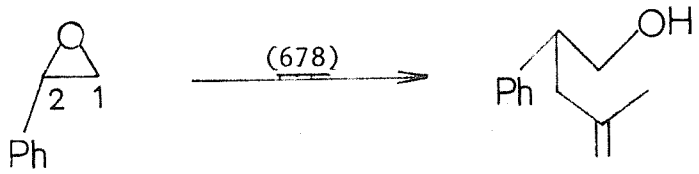
Numerous synthetic approaches for the introduction of the α-methylene-γ-butyrolactone group have been developed,[455,456] but in most the introduction of the α-methylene-δ-valerolactone moiety is based on the functionalisation of a preformed δ-valerolactone, (e.g. Schemes 38[457] and 39[458]). Groutas has developed a method for the introduction of the α-methylene-δ-valerolactone moiety based on lactonisation of the diketone (702) followed by elimination of phenylselenic acid to generate the α-methylene group (705),[459] (Scheme 40).

6.3. Basis for the Proposed Study

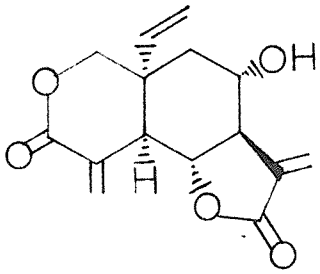
A simple, one step introduction of the α-methylene-δ-valerolactone structural unit can be envisaged based on the reaction of π-(2-carboethoxyallyl)nickel halide (706) with an epoxide, followed by lactonisation of the intermediate anion, (Scheme 41). This approach would enable a novel approach to α-methylene-δ-valerolactones such as secocrispiolide (693),[451] (Scheme 42). This approach to secocrispiolide (693) could also lead to the formation of the lactone (710), formed by the opening of ethylene oxide by the terminal end of the π-allyl complex (709).

An intramolecular cyclisation of a π-(2-carbomethoxyallyl) nickel halide onto an epoxide could lead to the formation of two rings in one step, (Scheme 43). This approach may be particularly useful for the preparation of medium sized rings, as if there is indeed an interaction between the epoxide and the nickel species, as suggested by Semmelhack,[367] this may facilitate the intramolecular opening of the epoxide compared to the corresponding intermolecular

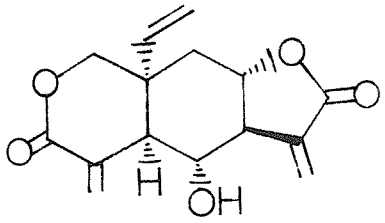
Scheme 37,



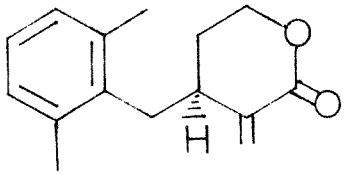
(689) (690)



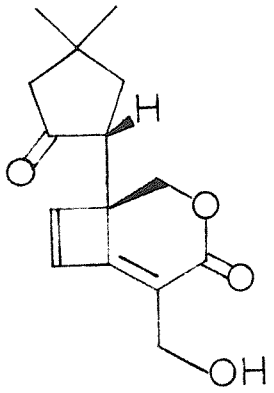
vernolepin (691)
Vernonia hymenolepis[450]



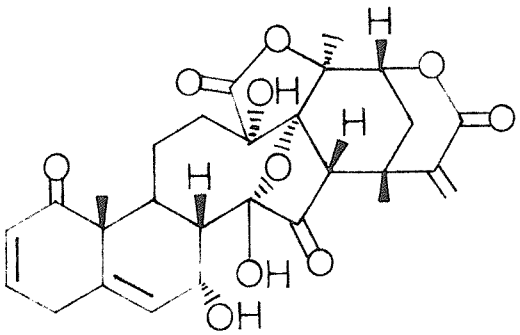
vernomenin (692)
Vernonia hymenolepis[450]



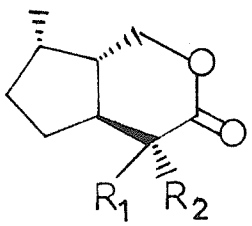
secocrispiolide (693)
Palicaria crispa[451]



fomannosin (695)
Fomes annosus[453]

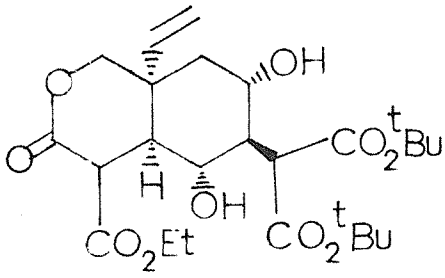


physalin-A (694)[452]



R_1=H, R_2=CH_3 (696)
R_1=CH_3, R_2=H (697)
Actinidia polygama[454]

Scheme 38.



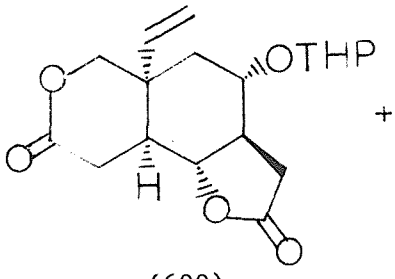
(698)

1,2,3. →

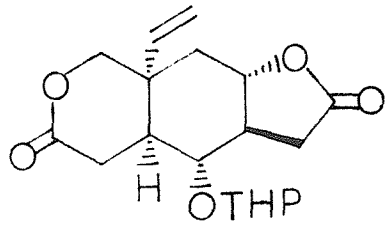
(691) vernolepin 22% + (692) vernomenin 5%

Reagents. 1. amberlite IRA400, MeOH.
2. TFA:water (1:1).
3. Et_2NH, HCHO, H_2O.

Scheme 39.



(699) +

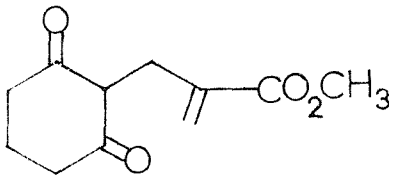


(700)

1,2,3,4,5. → (691) + (692)

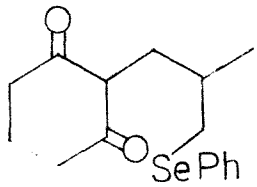
Reagents. 1. LDA, THF. 3. $MeSO_2Cl$, pyridine.
2. HCHO (gas). 4. DBU, benzene.
5. CH_3CO_2H, H_2O.

Scheme 40.



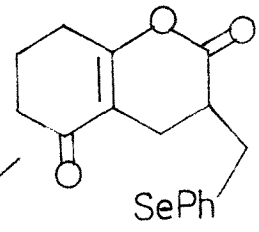
(701)

1,2. →



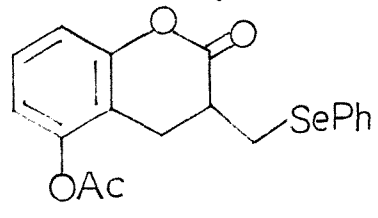
(702)

3. →



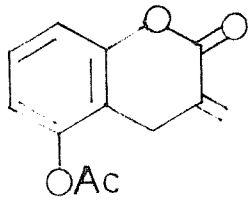
(703)

4. ↓



(704)

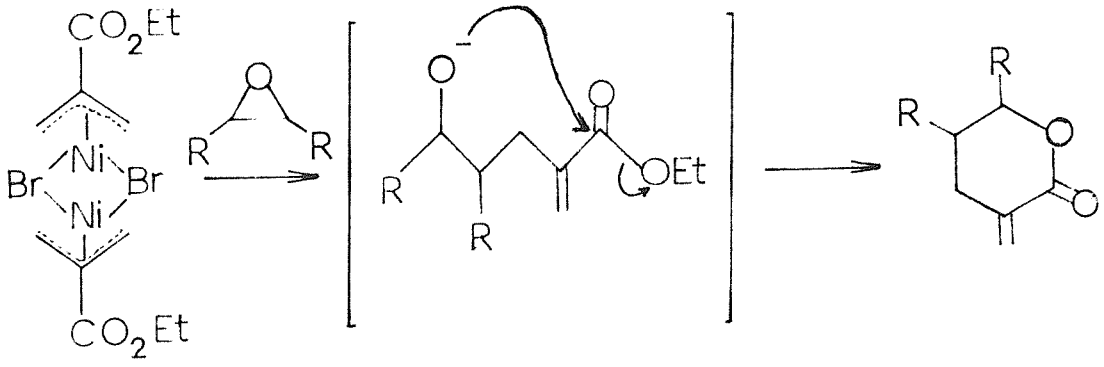
5. ←



(705)

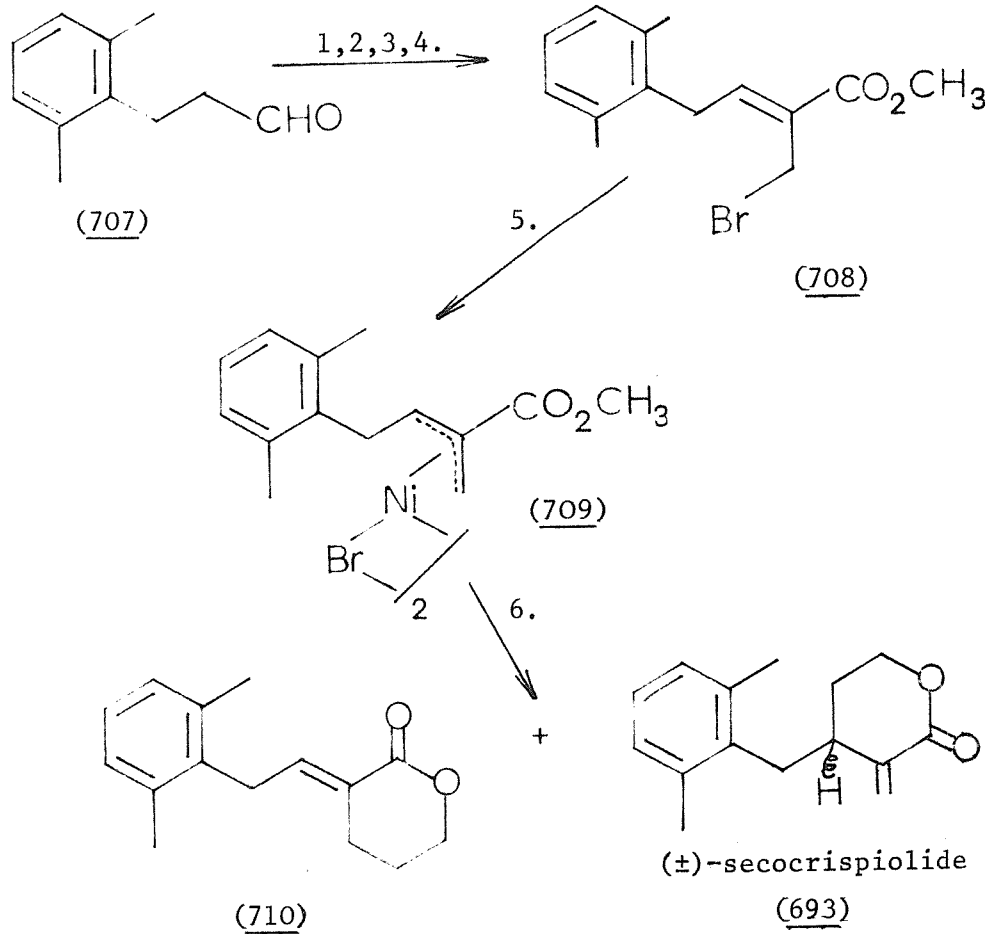
Reagents. 1. $PhSe^-$, EtOH. 2. H_3O^+. 3. TFAA, 4. HOAc, Ac_2O, H_2SO_4.
5. 30% H_2O_2.

Scheme 41.



(706)

Scheme 42.



(707) (708) (709) (710) (693)

Reagents. 1. $2Li^{+}.(OCH_2CHCO_2CH_3)^{2-}$, THF. 2. TsCl. 3. DBU. 4. PBr_3. 5. $Ni(CO)_4$. 6.  , DMF.

(±)-secocrispiolide

opening. There are four possible products from the intramolecular opening of an epoxide ring (Scheme 43), (712) and (714) are particularly interesting as they could lead to the formation of the α-methylene-lactones (713) and (715) respectively, which contain the characteristic features of natural products such as vernolepin (691) and physalin-A (694).

To enable the condition of the ring closure reaction to be studied a short synthesis of an allyl bromide-epoxide (711) is necessary (6.5) together with model studies on the reactions of π-allylnickel complexes with epoxides (6.4).

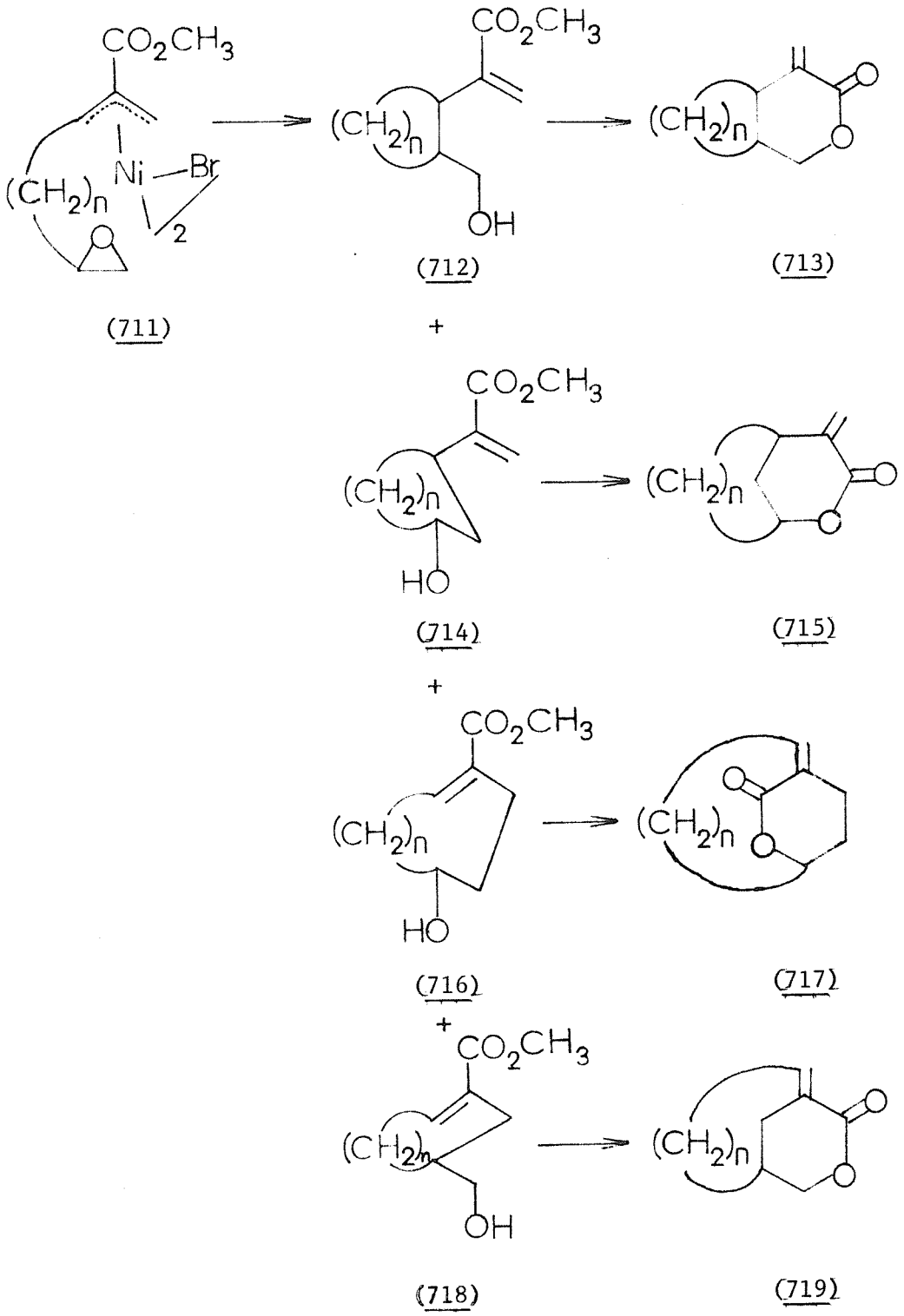
6.4. Investigation of the Reaction of π-(2-Methylallyl)Nickel Bromide (678) with Epoxides

For the following study the well characterised complex π-(2-methylallyl)nickel bromide (678)[428] was prepared from nickel tetracarbonyl and 1-bromo-2-methyl-2-propene[367] and stored at 4°C in a Schlenk tube under a positive pressure of argon.

In each of the experiments (Table 10) the complex (678) was transferred under a stream of argon into a tared, flamed dry, argon flushed flask. The flask was reweighed and the complex dissolved in anhydrous, argon purged N,N-dimethylformamide (DMF) to give a burgundy red solution.[367] A solution of the epoxide (689, 721, 723, 726, 730 or 731) in DMF was then added to the solution of the complex and the mixture stirred at 60-70°, under argon, until the solution became dark green. The reaction mixture was poured into water, which was then extracted with ether and the ethereal extracts examined by TLC. The components of the solution were then separated by flash column chromatography and identified from analysis of their ^{1}H nmr, ir and mass spectra (see Chapter 7).

Treatment of styrene epoxide (689) with (678) gave a mixture of two isomeric alcohols (690) and (720) in 85% yield. This is in contrast to the results of Semmelhack who only obtained the primary alcohol (690) under the same conditions.[367] *trans*-Stilbene epoxide (721) gave a low yield of the alcohol (722) as the only product, similarly 4-methoxy-styrene epoxide (723) gave a 27% yield of the

Scheme 43.



(711) (712) (713)

+

(714) (715)

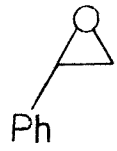
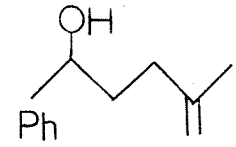
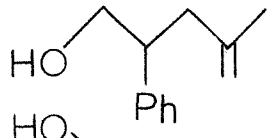
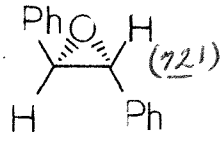
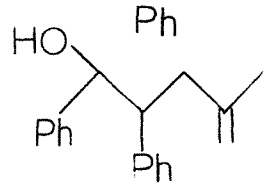
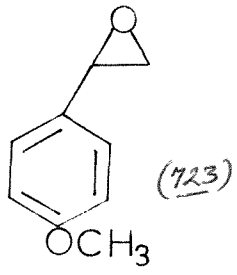
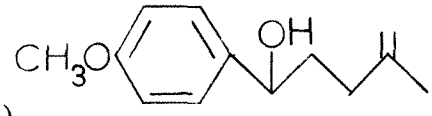
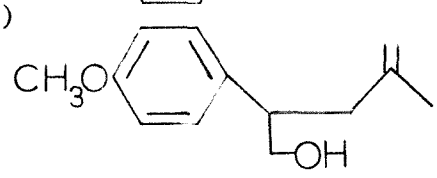
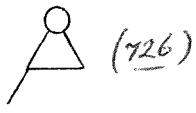
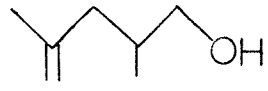
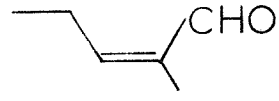
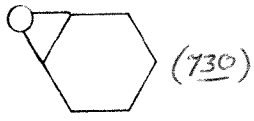
+

(716) (717)

+

(718) (719)

Table 10. Reaction of π-(2-methylallyl)nickel Bromide (678) with Epoxides.

Entry[b]	Epoxide	Time h (temperature °C)	Products	Yield[a] (%)
1	 (659)	24 (60-70)		(720) (30)
				(690) (55)
2	 (721)	95 (55-70)		(722) (23)
3	 (723)	72 (65)		(724) (27)
				(725) (0)
4	 (726)	48 (70)		(727) (16)
				(728) (12)
				(729) (72)
5	 (730)	184 (70)		-
6	 (731)	184 (60)		-

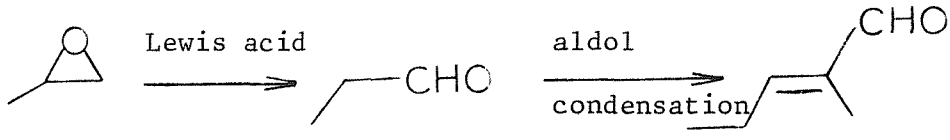
a Yield of isolated product after column chromatography.

b Entries 1-3. Reaction carried out in a round bottom flask fitted with a paraffin-oil bubbler to maintain an argon atmosphere.

Entries 4-6. Reaction carried out under an argon atmosphere in a sealed tube.

alcohol (724). Propylene epoxide (726) afforded a mixture of three compounds, two alcohols and an aldehyde which were identified as (727), (728) and (729) from their ^{1}H nmr ir spectra. Presumably (729) arises from a rearrangement of the epoxide (726) to the aldehyde (732)[460-1] followed by an aldol condensation (Scheme 44). No product from the reaction of propionaldehyde (732) or (729) with (678) was observed, a reaction which should proceed more readily than the epoxide opening.[367] Both cyclohexene epoxide (730) and cyclopentene epoxide (731) failed to react with allyl (678). This data demonstrates that a π-allylnickel complex will not only react with reactive epoxides (e.g. styrene epoxide (689)), but will also react with less reactive epoxides (e.g. propylene epoxide (726)). It was not found possible to repeat the above study with π-allylnickel complex (706) in the time available.

Scheme 44



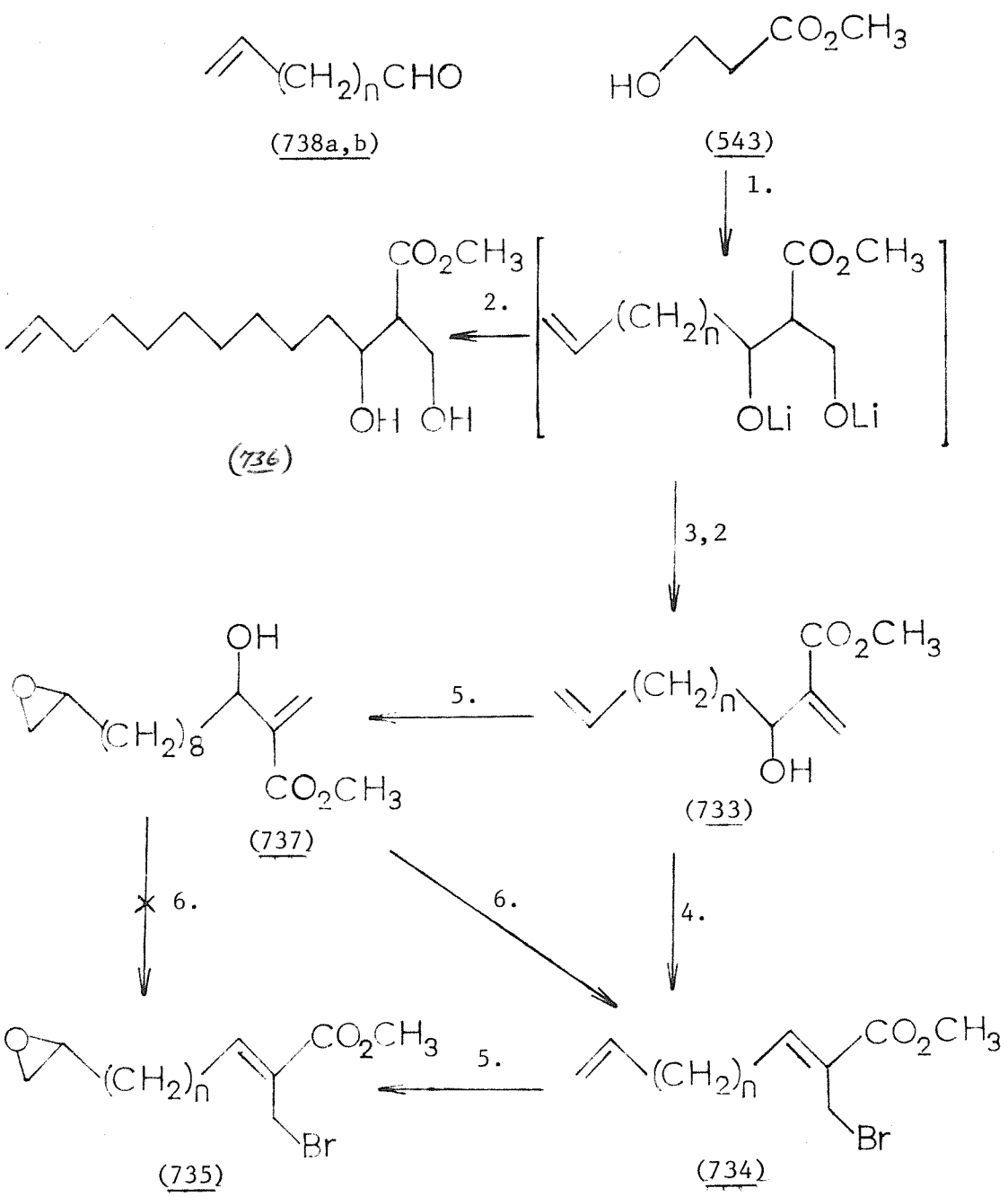
(726) (732) (729)

6.5. Preparation and Reaction of Substrates

6.5.1. Preparation of Substrates

The synthetic approach used to prepare substrates for possible intramolecular reaction of a π-allylnickel species to generate the

Scheme 45.



(733-735, 738) a n=2

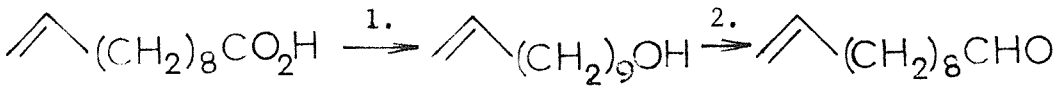
b n=8

Reagents.

1. LDA, THF, (738). 2. NH_4Cl. 3. TsCl.

4. PBr_3, Et_2O. 5. mcpba, CH_2Cl_2. 6. CBr_4 Ph_3P, Et_2O.

Scheme 46.



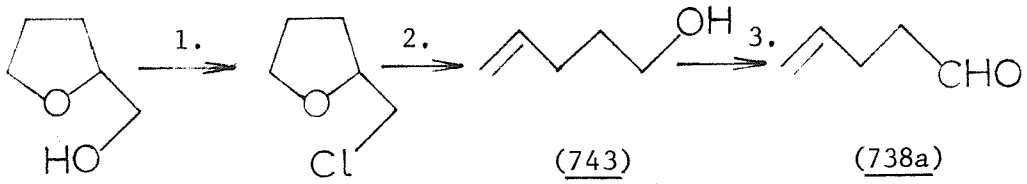
(739) (740) (738b)

Reagents.

1. LAH, Et_2O.

2. pcc, CH_2Cl_2.

Scheme 47.



(741) (742) (743) (738a)

Reagents.

1. $SOCl_2$, pyridine,

2. Na, toluene.

3. pcc, CH_2Cl_2.

α-methylene-γ-valerolactone moiety is shown (Scheme 45). For this approach to the substrates (735a,b), 'ω-enals' (738a and b) were required. 10-Undecenal (738b) was readily available by reduction of 10-undecenoic acid (739), followed by oxidation of the resulting alcohol (740) with pyridinium chlorochromate (pcc), (Scheme 46).

4-Pentenal (738a) was prepared (Scheme 47) from 2-hydroxymethyl-tetrahydrofuran (741). Chlorination of (741) with thionylchloride in pyridine gave the chloride (742)[462] which on treatment with sodium sand in toluene gave 4-penten-1-ol (743).[462] Oxidation of (743) with pcc gave the required aldehyde (738a).

Reaction of the dianion of 3-hydroxy-propanoic acid, methyl ester (543) with 10-undecenal (738b) followed by treatment with one equivalent of 4-toluenesulphonyl chloride and solid ammonium chloride gave the allyl alcohol (733b).[369] The alcohol (733b) was brominated with phosphorus tribromide to give the allylic bromide (734b)[369] which on treatment with mcpba gave the epoxide (735b). An alternative approach *via* (737) failed when bromination of the epoxy-alcohol (737) gave the bromide (734b).[463,464] The analogous substrate (735a) was prepared from 4-pentenal by the same procedure as that used for (735b).

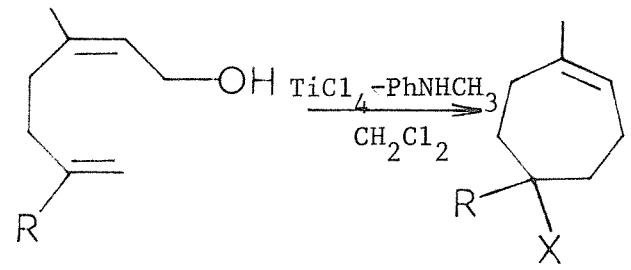
6.5.2. Reaction of Allyl Alcohol (733b) with $TiCl_4$ - $PhNHCH_3$ Complex.

Saito has reported the intramolecular cyclisation of an allyl alcohol onto a double bond by means of a $TiCl_4$-$PhNHCH_3$ complex,[465] (Scheme 48). Treatment of alcohol (733b) under the same conditions afforded one major product which was identified as the amine (744) by ^1H nmr, ^{13}C nmr, ir and mass spectroscopies, (Scheme 49).

6.5.3. Reaction of the π-Allylnickel Complex of (734b) with Benzaldehyde (532a).

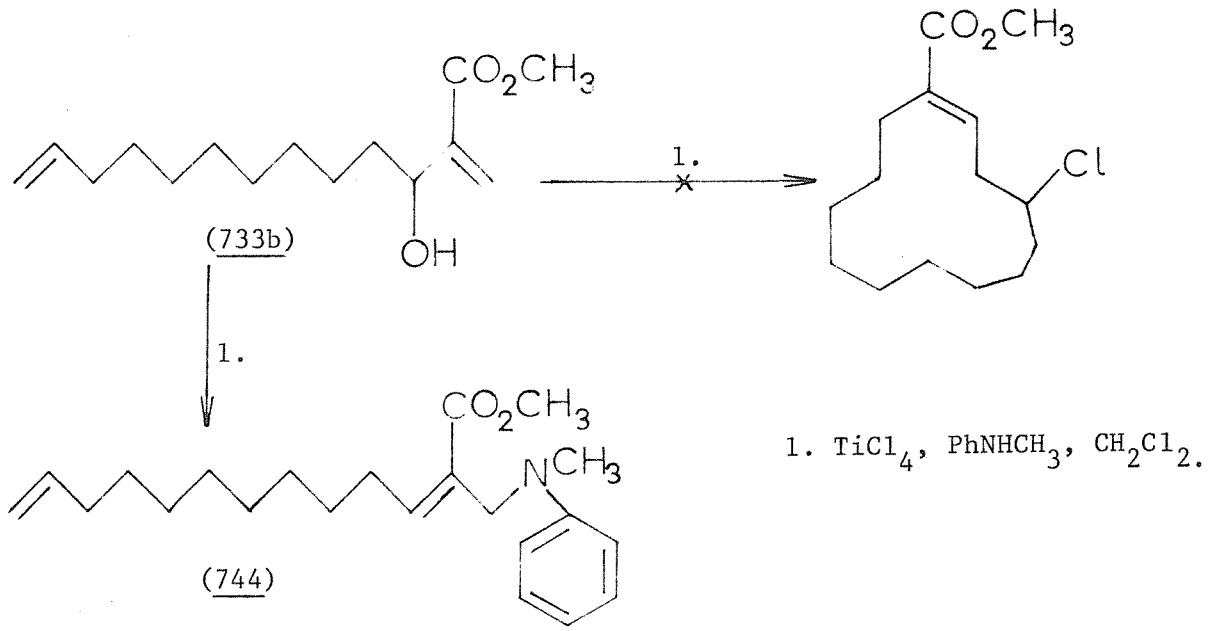
The π-allylnickel complex of the allyl bromide (734b) was generated by treating a suspension of $Ni(COD)_2$ in THF at -15^oC with the allyl bromide (734b) and allowing the suspension to warm to -7^oC over 3.5h.[367] Benzaldehyde (532a) was then added to the red solution and the mixture stirred for 16h at room temperature to afford a dark

Scheme 48.



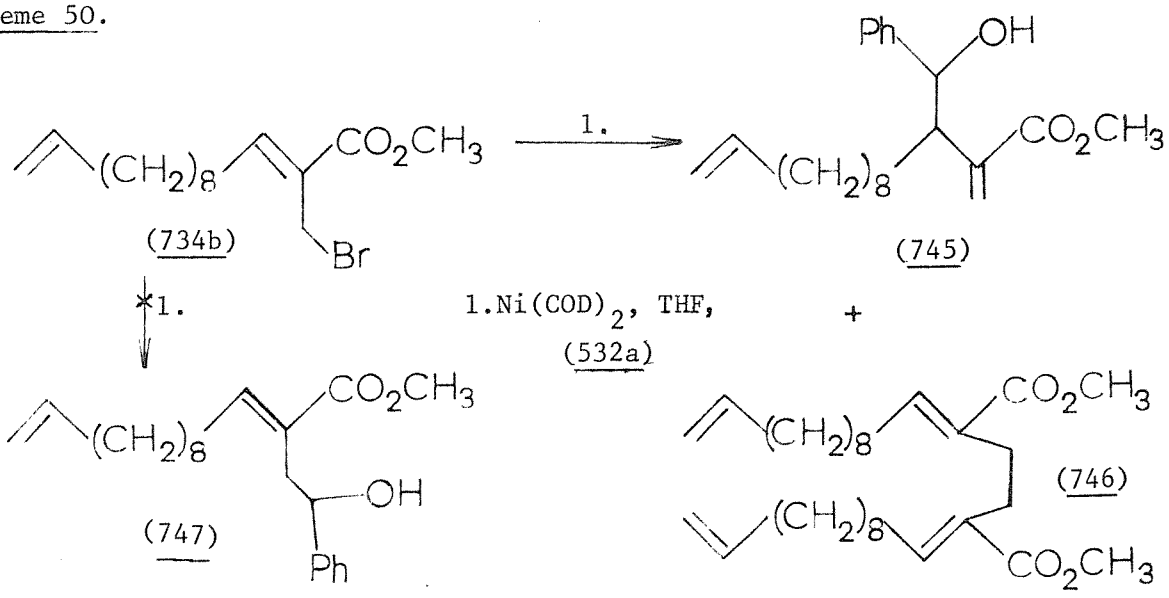
R	X	yield %
H	Cl	65
CH_3	Cl	66
Cl	Cl	18

Scheme 49.



1. $TiCl_4$, $PhNHCH_3$, CH_2Cl_2.

Scheme 50.



green solution. The solution was diluted with hydrochloric acid, extracted with ether and the ethereal extracts evaporated to give an oil which afforded the alcohol (745) and dimer (746) after column chromatography, (Scheme 50). There was no evidence (TLC, ^{1}H nmr) of reaction occurring at the terminal end of the allyl species, which would have afforded the isomeric alcohol (747), (Scheme 50).

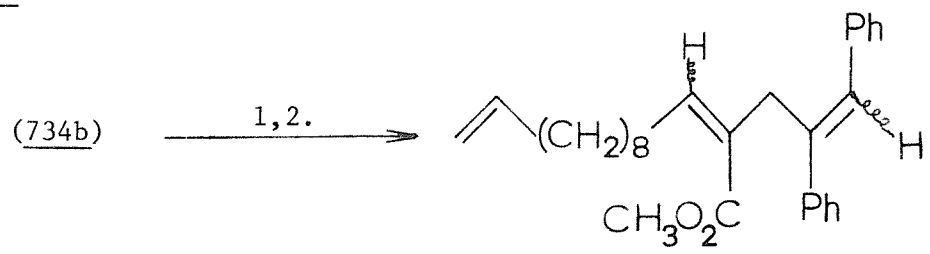
6.5.4. Reaction of the π-Allylnickel Complex of (734b) with *cis*-Stilbene Epoxide (748)

The π-allylnickel complex of (734b) was generated from (734b) as outlined above (4.5.3.) and treated with a solution of *cis*-stilbene epoxide (748) in DMF. The mixture was stirred at 60°C for 16h[367] and then the solvent removed *in vacuo* to give a green gum which was treated with hydrochloric acid. The aqueous suspension which resulted was extracted with ether and the ethereal extracts evaporated to give an oil which afforded the stilbene (749) as colourless crystals, after column chromatography, (Scheme 51).

6.5.5. Conclusions and Suggestions for Future Work

From the above experiments it appears that the reaction of a π-(2-carbomethoxyallyl)nickel species with an epoxide could form a short, viable approach to α-methylene-δ-valerolactones. The series of reactions that have been carried out with (678) (Table 10) should be repeated with (706) to establish the reactivity of (706) towards epoxides. These results could then lead to a synthesis of secocrispiolide (693) (Scheme 42). The aldehyde (707) being readily available from 2,6-dimethylbenzaldehyde (750)[466] by an aldol condensation with acetaldehyde, followed by reduction of the double bond (757) (Scheme 52).[467]

Scheme 51.

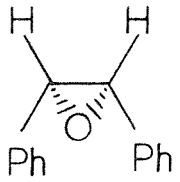


(749)

Reagents.

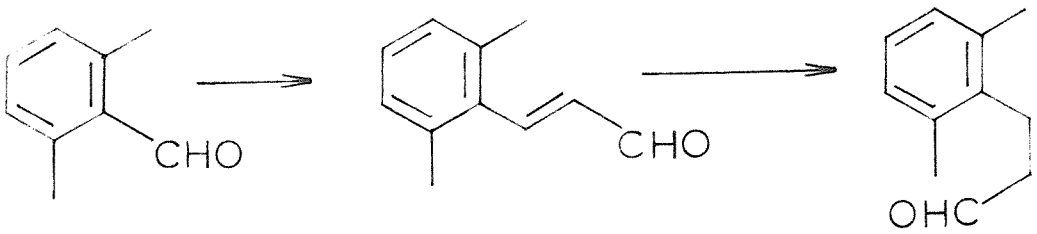
1. $Ni(COD)_2$, THF.

2.



(748)

Scheme 52.



(750) (751) (707)

CHAPTER SEVEN EXPERIMENTAL

7.1. Purification of Reagents

The methods that were used to dry the majority of reagents employed are shown in Table 11. Triphenylphosphine was recrystallised from dry pentane under an argon atmosphere and used to prepare Wilkinson's catalyst $[(Ph_3P)_3RhCl]$ by the method of Read.[468] N-bromosuccinimide was recrystallised from water and dried over P_2O_5 under high vacuum.[469,470] Other reagents were purified by standard procedures. *Bis*(cycloocta-1,5-dienyl)nickel (0) was prepared by the method of Winton.[471]

7.2. General Procedures

Evaporation of solvents was carried out at reduced pressure using a rotary evaporator. As far as possible all reactions were carried out under an atmosphere of oxygen-free nitrogen, except organometallic reactions involving π-allylnickel species which were carried out under an atmosphere of argon.[472,473,474]

7.3. Chromatographic Techniques

Gas-liquid chromatography was performed on a Pye Unicam GCD chromatograph fitted with a flame ionisation detector. In all cases a 5% FFAP column (3m x 2mm) was used with oxygen-free nitrogen as the carrier gas at 20ml/min.

'Flash' column chromatography refers to the method of Still *et al*,[480] using MN Kieselgel 60 230-400 mesh silica gel. Preparative thin layer chromatography was carried out on 20 x 20cm glass plates which had been coated with an aqueous slurry of alumina GF_{254}(Type 60/E) (Merck) to a depth of 0.75mm. Analytical TLC was carried out on pre-coated silica gel or alumina plates (Merck, Type 25 UV_{254}). Visulisation of chromatographs was effected by a combination of uv fluorescence, iodine vapour or spraying with an aqueous solution of potassium permanganate or methanolic 2,4-dinitrophenylhydrazine.

Table 11. Purification of Reagents

Reagent	Drying Agent	Reference
Pentane[a]	$LiAlH_4$	475,476
Benzene[b]	CaH_2	
Toluene[b]	CaH_2	
Diethyl ether[a]	$LiAlH_4$	475,476
N,N-Dimethylformamide[c]	CaH_2	
THF[a]	$LiAlH_4$	475.476
Diglyme[c]	CaH_2	475,476
Methanol	Mg/I_2	477
Ethanol	Mg/I_2	477
Nitrobenzene[d]	$CaCl_2$	477
Pyridine[h]	KOH	
CH_2Cl_2[i]	P_2O_5	
DMSO[c]	CaH_2	
CCl_4[i]	P_2O_5	
$P(OMe)_3$, $P(OEt)_3$[e]	5%Na	478
NEt_3[h]	KOH	
$HOCH_2CH_2OH$[f]	1%Na	
$^iPr_2NH$[c]	CaH_2	
$SOCl_2$	$P(OPh)_3$	479
$MeO_2CCH_2CCH_3$[g]	2%NaH	

(a) Predried over CaH_2 for 16h then distilled from $LiAlH_4$ at atmospheric pressure.

(b) Distilled from CaH_2 at atmospheric pressure.

(c) Distilled from CaH_2 at reduced pressure.

(d) Fractionated at atmospheric pressure then stored over $CaCl_2$.

(e) 5% Sodium was dissolved in the reagent over 16h then the reagent distilled at atmospheric pressure.

(f) 1% Sodium was dissolved in the reagent and then the reagent distilled at reduced pressure.

(g) 2% Sodium hydride was dissolved in the reagent and then the reagent distilled at reduced pressure.

(h) Stirred over KOH for 16h then distilled at reduced pressure.

(i) Stirred over P_2O_5 for 16h then distilled at atmospheric pressure.

7.4. Spectroscopic Techniques

^{1}H nmr spectra were recorded at 60MHz on a Perkin-Elmer R-12A spectrometer, or at 100MHz on a Varian Associates XL-100-12 (deuterium-lock) spectrometer. In all cases TMS was used as an internal standard. Signals have been described using the following abbreviations, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad and are quoted as δ values (TMS=0). Coupling constants (J) are given in Hz.

Noise decoupled ^{13}C nmr spectra were recorded at 25.2MHz on a Varian Associates XL-100-12 spectrometer. Peak positions are reported using the δ scale (TMS=0).

Mass spectra were recorded on a Kratos MS30 spectrometer equipped with the DS 50S Data System. Spectra were recorded at 70eV and are quoted as m/e values. The major ion fragmentations are reported as percentages of the base peak (100%).

Infra-red spectra were recorded using a Perkin-Elmer 157-G grating spectrometer, as thin films, Nujol mulls or in chloroform solution. The absorbtion bands are given in cm^{-1} relative to a polystyrene standard.

Ultra-violet spectra were recorded on a Pye-Unicam SP800 spectrometer and are quoted in the form $\lambda_{max}^{nm}(\varepsilon_{max})$.

7.5. Melting Points and Analyses

Melting points were determined using an Electrothermal electrically heated block, and are uncorrected.

Elemental analyses were carried out at the micro-analytical laboratory, University College, London.

To enable ease of reference, compounds prepared are listed in structure number order in this section.

7.6.1. 5,10-Dihydro-6,7-dimethyl-4H-benzo[5,6]cyclohepta[1,2-b]furan.[181] (337) [56881-471-1]

A mixture of 4,5-dihydro-6,7-dimethyl-10H-benzo[5,6]cyclohepta[1,2-b]-furan-10-one (567) (1.0g, 4.4mmol), 4-toluenesulphonylhydrazine (0.82g, 4.4mmol) and 4-toluenesulphonic acid (50mg) in ethanol (2ml) was heated at 80°C for 16h. The solvent was removed from the resulting suspension *in vacuo* to yield a paste which was dissolved in dimethylformamide (5ml). To the resulting solution sodium cyanoborohydride (1.0g, 14.7mmol) was added and the mixture heated at 120° for 12h.[481] The mixture was poured into water (100ml) and extracted with ether/petroleum ether (40-60°) (1:4) (3x25ml). The organic extracts were dried over potassium carbonate and evaporated to give a mixture as a red oil (1.1g) which was separated by flash column chromatography. Elution with petroleum ether (40-60°) gave a two component mixture as an oil (920mg) which was separated by flash column chromatography. Elution with petroleum ether (60-80°C) gave 5,10-dihydro-6,7-dimethyl-4H-benzo[5,6]cyclohepta[1,2-b]furan[181] (337) as a colourless oil (290mg, 31%) (Found: $\underline{M}^+$ 212.1188. $C_{15}H_{16}O$ requires: 212.1201).

uv λ_{max}^{nm} (EtOH) (ε) 217(12,600).

^{1}H nmr δ($C_6{}^2H_6$) 2.01(3H,s,Ar-C$\underline{H}_3$), 2.10(3H,s,Ar-C$\underline{H}_3$), 2.42(2H,m,C$\underline{H}_2$), 2.82(2H,m,C$\underline{H}_2$), 3.91(2H,brs,furan-C$\underline{H}_2$-Ar), 5.94(1H,d, J=2Hz,furan β-$\underline{H}$). 6,77(2H,s,2xaromatic-$\underline{H}$), 7.01(1H,d, J=2Hz,furan α-$\underline{H}$).

^{13}C nmr δ($C_6{}^2H_6$) 15.3, 20.9, 24.6, 27.5, 33.8, 112.6, 117.7, 125.9, 127.1, 127.8, 129.0, 135.0, 137.4, 139.4, 148.8.

ms m/e 213($\underline{M}^+$ +1, 15), 212($\underline{M}^+$, 95), 198(15), 197(100), 183(14), 167(27).

7.6.2. Diethyl (phenylmethyl)phosphonate (531) [1080-32-6]

(531) Was prepared by the method of Kagan and Berkenmeyer.[482] A mixture of bromomethyl-benzene (11.9ml; 17.1g; 0.1mol) and triethyl phosphite (28.6ml ; 27.7g ; 0.16mol) was heated at 160°C for 16h and then distilled *in vacuo* to give diethyl (phenylmethyl)phosphonate (531) as a colourless oil (19.6g; 86%) 160-2°C/13mm Hg (Lit.[482] 160-4°C/15mm Hg).

7.6.3. (E)-1,1[1]-(1,2-ethenediyl)*bis*-benzene (533a) [103-30-0]

A solution of benzaldehyde (532a) (0.53g; 5mmol) and diethyl (phenylmethyl)phosphonate (531) (1.14g; 5mmol) in tetrahydrofuran (10ml) was added to a stirred suspension of sodium hydride (0.12g; 5mmol) in tetrahydrofuran (20ml) containing 15-crown-5 (30mg) at 0°C.[385] The suspension was stirred at room temperature for 16h and water (100ml) added. The aqueous phase was separated and extracted with ether (3x25ml). The combined organic extracts were washed with sodium hydrogen sulphite solution (10%, 2x20ml) and saturated sodium chloride solution (2x20ml) and dried over potassium carbonate. The solvent was evaporated to give (E)-1,1[1]-(1,2-ethenediyl)*bis*-benzene (533a) as white microcrystals (0.886g; 98%), m.p. 123-5°C (ethanol) (Lit.[341] 124-5°C).

7.6.4. (E)-1,2-Dimethoxy-3-(2-phenylethenyl)-benzene (533b)

A solution of 3,4-dimethoxybenzaldehyde (532b) (0.83g; 5mmol) and diethyl (phenylmethyl)phosphonate (531) (1.14g; 5mmol) in tetrahydrofuran (10ml) was added to a stirred slurry of sodium hydride (0.12g; 5 mmol) in tetrahydrofuran (20ml) containing 15-crown-5 (530) (3.0mg) at 0°C.[385] A rapid evolution of hydrogen was observed and the solution developed a gelatinous orange precipitate. The suspension was stirred at room temperature for 2h and poured into water (100ml). The separated aqueous phase was extracted with ether (3x25ml) and the combined organic extracts washed with sodium hydrogen sulphite solution (10%, 2x20ml) and saturated sodium chloride solution (2x20ml), and dried over

potassium carbonate. The solvent was evaporated to give (E)-1,2-dimethoxy-3-(2-phenylethenyl)-benzene (533b) as colourless needles (1.19g; 99%) m.p. 112-3°C(ethanol) (Lit.[360] m.p. 111°C).

7.6.5. 1,1',1''-(1-Ethenyl-2-ylidene)*tris*-benzene (533c)[58-72-0]

A solution of diphenyl-methanone (532c) (0.91g; 5mmol) and diethyl (phenylmethyl)phosphonate (531) (1.14g; 5mmol) in tetrahydrofuran (10ml) was added to a stirred suspension of sodium hydride (0.12g; 5 mmol) in tetrahydrofuran (20ml) containing 15-crown-5 (30mg) at 0°C.[385] The suspension was stirred at room temperature for 3h and poured into water (100ml). The aqueous phase was separated and extracted with ether (3x25ml). The combined organic extracts were washed with sodium hydrogen sulphite solution (10%, 2x20ml) and saturated sodium chloride solution (2x20ml) and dried over potassium carbonate. The solvent was evaporated to give an oil which was distilled *in vacuo* to give 1,1',1''-(1-ethenyl-2-ylidene)*tris*-benzene (533c) as a colourless oil, (1.20g; 96%), b.p. 70°C/0.01mm Hg which crystallised on standing, m.p. 65-7°C (Lit.[361] 65-8°C).

7.6.6. (E)-1,1[1]-(1-methyl-1,2-ethenediyl)*bis*-benzene (533d)[833-81-8]

A solution of 1-phenyl-ethanone (532d) (0.75g; 5 mmol) and diethyl (phenymethyl) phosphonate (531) (1,14g; 5 mmol) in tetrahydrafuran (10ml) was added to a stirred suspension of sodium hydride (0.12g; 5 mmol) in anhydrous tetrahydrofuran (20ml) containing 15-crown-5 (30mg) at 0°C.[385] The suspension was stirred for 16h at room temperature and water (100ml) added. The aqueous phase was separated and extracted with ether (3x25ml). The combined organic extracts were washed with sodium hydrogen sulphite solution (10%, 2x20ml) and saturated sodium chloride solution (2x25ml), and dried over potassium carbonate. The solvent was evaporated to give a pale yellow oil (0.99g) which was purified by flash column chromatography.[480] Elution with ether/petroleum ether (40-60°C)(1:9) gave (E)-1,1[1]-(1-methyl-1,2-ethenediyl)*bis*-benzene (533d) as a colourless oil (0.83g; 86%) which crystallised on standing, m.p.80-2°C (Lit.[362] 82°C).

7.6.7. (E)-2-(2-phenylethenyl)-furan (533e) [18138-87-9]

A solution of 2-furancarboxaldehyde (0.48g; 5mmol) and diethyl (phenylmethyl)phosphonate (531) (1,14g; 5mmol) in tetrahydrofuran (10ml) was added to a stirred suspension of sodium hydride (0.12g; 5mmol) in tetrahydrofuran (20ml) containing 15-crown-5 (33mg) at $0^{o}C$.[385] The suspension was stirred at room temperature for 6h and water (100ml) added. The aqueous phase was separated and extracted with ether (3x25ml). The combined organic extracts were washed with sodium hydrogen sulphite solution (10%,2x20ml) and sodium chloride solution (2x20ml) and dried over potassium carbonate. The solvent was evaporated to give (E)-2-(2-phenylethenyl) -furan (533e) as white micro crystals (0.844g; 99%), m.p. 53-4^{o}C (Lit.[359] 54-5^{o}C).

7.6.8. (E)-1-Methyl-4-(2-phenylethenyl)-benzene (533f) [1860-17-9]

A solution of 4-methyl-benzaldehyde (532f) (0,60g; 5 mmol) and diethyl (Phenymethyl) phosphonate (531) (1.14g; 5 mmol) in tetrahydrofuran (10ml) was added to a stirred suspension of sodium hydride (0.12g; 5 mmol) in tetrahydrofuran (20ml) containing 15-crown-5 (30mg) at $0^{o}C$.[385] The suspension was stirred at room temperature for 2h and poured into water (100ml). The aqueous phase was separated and extracted with ether (3x25ml). The combined organic extracts were washed with sodium hydrogen sulphite solution (10%, 2x25ml) and saturated sodium chloride solution (2x20ml) and dried over potassium carbonate. The solvent was evaporated to give (E)-1-methyl-(2-phenylethenyl)-benzene (533f) as colourless microcrystaline plates (0.912g; 99%) m.p. 119-20% (ethanol) (Lit.[363] 119.5-120^{o}C).

7.6.9. (E)-1-Bromo-2-(2-phenylethenyl)-benzene (533g) [54737-45-0]

A solution of 2-bromo-benzaldehyde (532g) (0.93g; 5mmol) and diethyl (phenylmethyl)phosphonate (531) (1.14g; 5 mmol) in tetrahydrofuran (10ml) was added to a stirred suspension of sodium hydride (0.12g; 5mmol) in tetrahydrofuran (20ml) containing 15-crown-5 (30mg) at $0^{o}C$.[385] The suspension was stirred at room temperature for 2h and

poured into water (100ml). The aqueous phase was separated and extracted with ether (3x25ml). The combined organic extracts were washed with sodium hydrogen sulphite solution (10%, 2x25ml) and saturated sodium chloride solution (2x20ml) and dried over potassium carbonate. The solvent was evaporated to give an oil which was distilled *in vacuo* to afford (E)-1-bromo-2-(2-phenylethenyl)-benzene (533g) as a colourless oil (1.129g; 90.7%) b.p. 65°C/0.1mm Hg (Lit.[364] 143-5°C/0.15mm Hg), η_D^{15}:1.6745 (Lit.[365] η_D^{24}:1.6822).

7.6.10 Dimethylbenzaldehyde (532h) [5779-93-1]

A solution of 2,3-dimethyl-benzenemethanol (574) (13.6g;0.1mol) in methylene chloride (20ml) was added to a suspension of pyridinium chlorochromate[483] (24g; 0.112mol) in methylene chloride (20ml). The mixture was stirred for 1h, poured into ether (300ml) and the solid residue washed with ether (3x20ml). The pale green suspension thus obtained was filtered through silica gel (Merck Kieselgel GF_{254} (Type 60)) (20g) and evaporated to yield a pale green oil which was distilled *in vacuo* (bulb to bulb) to give 2,3-dimethyl-benzaldehyde (532h) as a colourless oil (13.1g; 98%) b.p. 90°C/13mm Hg (Lit.[484] 86-8°C/10mm Hg).

7.6.11. 4,10-Dihydro-7,8-dimethyl-10H-benzo[4,5]cyclohepta[1,2-b]furan[196] (536)

A mixture of 9,10-dihydro-7,8-dimethyl-4H-benzo[4,5]cyclohepta [1,2-b]furan-4-one (617) (0.50g; 2.21mmol), 4-toluenesulphonyl hydrazine (0.41g; 2.21mmol) and 4-toluenesulphonic acid (50mg) was heated at 80°C for 2.5h. The solvent was removed from the resulting suspension *in vacuo* to give an orange paste which was dissolved in dry dimethylformamide (3ml). Sodium cyanoborohydride (0.48g; 7.6mmol) and 4-toluenesulphonic acid (20mg) were added to the solution and the mixture heated at 120°C for 8h.[481] The solution was allowed to stand at room temperature for 16h, poured into water (20ml) and extracted with ether/petroleum ether (40-60°C) (1;9) (3x10ml). The extracts were washed with saturated sodium chloride solution (2x10ml), dried over potassium carbonate and evaporated to give a mixture a pale yellow

oil (0.410mg), which was separated by flash column chromatography.[480] Elution with ether/petroleum ether (40-60°C) (1:9) gave a mixture as a colourless oil (253mg) and 9,10-dihydro-7,8-dimethyl-4H-benzo [4,5] cyclohepta [1,2-b]furan-4-one (617) (30mg; 6%). The mixture was purified by flash column chromatography,[480] elution with petroleum ether (40-60°C) gave 4,10-dihydro-7,8-dimethyl-10H-benzo[4,5]cyclohepta [1,2 b]furan[196] (536) as a colourless oil (211mg;45%).
(Found: M^+,212.1080, $C_{15}H_{16}O$ requires 212.1201).

^{1}H nmr δ($C_6^2H_6$) 1.98(3H,s,Ar-CH_3),2.12(3H,s,Ar-CH_3), 2.72(4H,m, 2xCH_2), 3.57(2H,brs,Ar-CH_2-furan), 6.05(1H,d,J=2Hz, furan β-H), 6.83(2H,brs,2 x aromatic-H), 7.03(1H,d,J=2Hz, furan α-H).

ms m/e 212(M^+,92%), 197(100), 169(33), 149(27), 91(42),77(25).

7.6.12. 3-Hydroxy-propanoic acid, methyl ester (543) [547-64-8]

3-Hydroxy-propanoic acid, methyl ester (543) [547-64-8] was prepared by the method of Bartlett.[485] Treatment of 2-oxetanone (542) (36g;0.5mol) with sodium methoxide (from sodium (0.46g;0.02mol) in methanol (100ml) yielded 3-hydroxy-propanoic acid, methyl ester (543) as a colourless liquid (32.37g;62%), b.p. 66-70°C/13mm Hg (Lit.[485] 78-81°C/18mm Hg).

7.6.13. 2-(Cyanomethyl)-benzoic acid (547)[6627-91-4]

2-(Cyanomethyl)-benzoic acid (547)[6627-91-4] was prepared by the method of Price and Rogers.[372,373] Treatment of (546) (50g;0.37mol) with powdered potassium cyanide (50g;0.7mol) yielded 2-(cyanomethyl)-benzoic acid (547) as a tan solid (54.1g;90%) m.p. 95-9°C (Lit.[372] 113-5°C).

7.6.14. 2-Carboxy-benzeneacetic acid (548) [89-51-0]

2-Carboxy-benzeneacetic acid (548)[89-51-0] was prepared by the method of Price and Rogers.[372,373] Hydrolysis of 2-(cyanomethyl)-benzoic acid (547) (136.5g;0.85mol) with sulphuric acid (50%;150ml) gave 2-carboxy-benzeneacetic acid (548) as yellow crystals (149.7g; 98%) m.p. 184-7°C (Lit.[486] 180-1°C).

7.6.15. 1H-2-benzopyran-1,3(4H)-dione (549) [703-59-3]

1H-2-benzopyran-1,3(4H)-dione (549)[703-59-3] was prepared by the method of Grummitt.[487] 2-Carboxy-benzeneacetic acid (548)(6.0g; 0.033mol) was treated with acetic anhydride (3.1ml;0.033mol) to yield 1H-2-benzopyran-1,3(4H)-dione (549) as a white solid (4.0g;74%) m.p. 150-2°C (Lit.[487] 140-1°C).

7.6.16. 3,4-Dihydro-1H-2-benzopyran-1-one (550) [4702-34-5]

3,4-Dihydro-1H-2-benzopyran-1-one (550)[4702-34-5] was prepared by the method of Bailey.[374] Reduction of 1H-2-benzopyran-1,3(4H)-dione (15.0g;0.093mol) by sodium borohydride (3.75g;0.094mol) afforded 3,4-dihydro-1H-2-benzopyran-1-one (550) as a colourless oil (6.37g; 47%) b.p. 115-120°C/0.1 mm Hg (Lit.[374] 177-8°C/13 mm Hg).

7.6.17. 1H-2-Benzopyran-1-one (551) [491-31-6]

A solution of 3,4-dihydro-1H-2-benzopyran-1-one (550) (6.2g; 0.042mol), N-bromosuccinimide (9.3g;0.052mol) and benzoyl peroxide (30mg) in dry carbon tetrachloride (150ml) was heated under reflux for 20h under a 150 watt lamp. The solution was cooled to room temperature, filtered and evaporated to yield a pale orange oil (4.2g) which was dissolved in carbon tetrachloride (25ml). Triethylamine (4ml) was added to the solution and the mixture heated under reflux for 1h. The solvent was evaporated *in vacuo* to give a brown paste

which was triturated with ether (100ml) and the suspension filtered. The filtrate was dried over sodium sulphate and evaporated to give a brown oil (2.5g) which was distilled *in vacuo* to yield 1H-2-benzopyran-1-one (551) as a colourless oil (1.53g;24%) b.p. 110-20°C/0.2mm Hg (Lit.[489] 285-6°C/719mm Hg).

7.6.18. 2-Bromo-benzenepropanal (555)[52221-92-8].

A suspension of magnesium turnings (3.84g;0.16mol) in ether (10ml) was treated with 1,2-dibromoethane (1ml) and the suspension warmed under a salt/ice condenser until reaction commenced. A solution of 1-bromo-2-(bromomethyl)-benzene (560)(40g;0.16mol) in ether (100ml) was then added dropwise, at such a rate as to maintain reflux, over 30 min. The solution which resulted was diluted with ether (600ml), stirred for 15 min, cooled to -5°C and a solution of ethylene oxide (25ml; 0.28mol) in ice cold ether (25ml) added rapidly. The suspension was stirred at room temperature for 16h, saturated ammonium chloride solution (100ml) added and the two phases stirred for a further 2h. The separated aqueous phase was extracted with ether (2x100ml). The combined organic material was washed with saturated sodium bicarbonate solution (50ml) and saturated sodium chloride solution, dried over magnesium sulphate and evaporated to give a yellow oil which was distilled *in vacuo* to give a colourless oil (15g), b.p. 125-130°C/0.1mm Hg (75% pure by ^{1}H nmr).

The combined material from three preparations (63g) was distilled *in vacuo* to give 2-bromo-benzenepropanol (555) as a colourless oil (51.7g), b.p. 98-101°C/0.1mm Hg (Lit.[489] 106-8°C/0.5mm Hg).

7.6.19. [3-(2-bromo-phenyl)propoxy]methylbenzene (556)

A solution of 2-bromo-benzenepropanol (555) (8.6g;0.04mol) in dimethyl sulphoxide (20ml) was added to a stirred suspension of sodium hydride (80% dispersion in oil) (1.2g;0.04mol) in dimethyl sulphoxide (20ml) and the mixture stirred for 20hrs. A solution of benzyl chloride (5.2ml,0.042mol) in dimethyl sulphoxide (5ml) was added to the solution and the mixture stirred at room temperature for 8h. The resulting

suspension was poured into ice cold saturated sodium chloride solution (50ml) and extracted with ether (3x50ml). The extracts were washed with saturated sodium chloride solution (20ml), dried over magnesium sulphate and evaporated to give a pale yellow oil (11.4g) which was distilled *in vacuo* to give [3-(2-bromo-phenyl)propoxy]methylbenzene (556) as a colourless liquid (7.6g;62%) b.p. 160-2°C/0.1mm Hg.

Analysis — Found : C, 63.2; H, 5.9
$C_{16}H_{17}BrO$ requires : C, 63.0; H, 5.8%

ir — γ_{max} (liquid film) 1100cm^{-1}, 1025cm^{-1}, 750cm^{-1}, 700cm^{-1}

^{1}H nmr — $\delta(C^{2}HCl_3)$ 1.78-2.10 (2H,m,Ar $CH_2\underline{CH}_2CH_2O$),
2.85(2H,t,J=8Hz,Ar $\underline{CH}_2CH_2CH_2O$),
3.49(2H,t,J=7Hz,Ar $CH_2CH_2\underline{CH}_2O$), 4.51(2H,s,$O\underline{CH}_2Ph$),
6.88-7.42 (8H,m,3xaromatic $\underline{H}$),
7.50 (1H,d,J=8Hz, aromatic $\underline{H}$).

^{13}C nmr — $\delta(C^{2}HCl_3)$ 29.7, 32.8, 69.3, 72.8, 124.5, 127.4, 127.5, 128.4, 130.5, 132.8, 138.6, 141.3

ms — m/e 306($\underline{M}^{+}$,0.7%), 304($\underline{M}^{+}$,0.7), 225(19), 171(25), 169(26), 91(100).

7.6.20. 2-(3-Propoxymethylbenzene)-benzenethanol (557)

1,2-Dibromoethane (2 drops) was added to a suspension of magnesium turnings (0.7g;0.026mol) in tetrahydrofuran (5ml) and the mixture warmed until reaction commenced. To the resulting suspension a solution of (556) (7.1g;0.023mol) in tetrahydrofuran (10ml) was added at such a rate as to maintain reflux, and then the solution diluted with

tetrahydrofuran (30ml). Ethylene oxide (8ml) was added to the solution at -10°C, the solution stirred at room temperature for 2h and saturated ammonium chloride solution (50ml) added. The separated aqueous phase was extracted with ether (3x20ml). The combined organic extracts were dried over magnesium sulphate and evaporated to give a pale yellow oil which was purified by column chromatography. Elution with ether/petroleum (40-60°C) (1;3) gave (557) as a colourless oil (3.0g;41%).

ir γ_{max} (liquid film) 3,400cm^{-1}, 740cm^{-1}, 690cm^{-1}

^{1}H nmr $\delta(C^{2}HCl_3)$,1.65-2.10(2H,m,$ArCH_2-\underline{CH_2}-CH_2O-$), 2.25(1H, brs,O$\underline{H}$), 2.62(2H,t,J=6Hz,$ArC\underline{H_2}CH_2CH_2O-$), 2.88(2H,t,J=7Hz, $ArC\underline{H_2}CH_2OH$), 3.51(2H,t,J=6Hz, $ArCH_2CH_2C\underline{H_2}-O-$), 3.77(2H,t,J=7Hz,$ArCh_2C\underline{H_2}OH$), 4.51(2H,s,$OC\underline{H_2}Ph$), 7.05-7.45(9H,m,9x aromatic-$\underline{H}$)

^{13}C nmr $\delta(C^{2}HCl_3)$ 29.1, 31.1, 35.7, 63.2, 69.6, 72.9, 126.1, 126.5, 127.4, 127.6, 127.7, 128.0, 128.4, 129.5,129.9, 136.3, 138.4, 140.3

ms m/e 270($\underline{M}^{+}$, 0.4%), 252(1), 240(10), 179(4), 161(7), 149(26), 146(33), 131(63), 105(52), 104(9), 91(100), 77(9).

7.6.21. Preparation of (558)

A solution of (557) (3.0g;0.01mol) in dry methylene chloride (50ml) was added to a stirred suspension of pyridinium chlorochromate (9.0g;0.042mol) in methylene chloride (100 ml) and the suspension stirred for 5h. To the suspension dry ether (250ml) was added and the mixture filtered through 'HYFLO'. Evaporation of the orange

filtrate gave a brown oil which was dissolved in ether (50ml) and filtered through 'HYFLO'. Evaporation of the filtrate gave a yellow/green oil (2.8g) which was treated with dry ethylene glycol (0.68g; 0.011mol), 4-toluenesulphonic acid (10mg) and benzene (100ml). The mixture was boiled under 'Dean and Stark' conditions for 72h. The solution which resulted was washed with water (2x10ml), dried over magnesium sulphate and evaporated to give (558) as a pale green oil (3.0g;90%)

ir γ_{max} (liquid film) 695, 750, 1,140cm.$^{-1}$

^{1}H nmr $\delta(C^{2}HCl_3)$, 1.70-2.18 (2H,m,$ArCH_2\underline{CH_2}CH_2O$), 2.81(2H,t,J=9Hz,$ArCH_2CH_2CH_2O$), 3.04(2H,d,J=4Hz, $ArCH_2CH\langle^{O}_{O}\rangle$), 3.87(4H,m,$OCH_2CH_2O$), 4.54(2H,s,$OCH_2Ph$), 5.07(1H,t,J=4Hz,$ArCH_2CH\langle^{O}_{O}\rangle$), 6.94-7.66(9H,m,9x aromatic -H).

^{13}C nmr $\delta(C^{2}HCl_3)$, 29.3, 31.0, 37.1, 64.8, 69.6, 72.8, 104.7, 125.9, 126.8, 127.5, 127.6, 128.3, 129.3, 130.7, 134.2, 138.7, 140.7

ms m/e 312(M^+, 4%), 117(13), 105(17), 91(31), 73(100).

7.6.22. 1-Bromo-2-(bromomethyl)-benzene (560)[3433-80-5]

A mixture of 2-bromo-methylbenzene (4.65g;0.027mol) and benzoylperoxide (20mg), at 110°C under a 150 watt lamp, was treated with bromine (1.5ml;4,65g;0.029mol). The solution was stirred at 110°C for 1h, cooled to room temperature and stirred for 1h. The resulting pale yellow solution was distilled *in vacuo* to yield 1-bromo-2-(bromomethyl)-benzene (560) as a pale yellow oil (6.244g; 92%) b.p. 124-130°C/15mm Hg (Lit.[365] 120-130°C/13mm Hg).

7.6.23. Dimethyl (2-Carbomethoxy-3-furylmethyl)phosphonate (562)

Dimethyl (2-carbomethoxy-3-furylmethyl)phosphonate (562) was prepared by the method outlined below for (563). Treatment of (576) (5.79;0.026mol) with trimethylphosphite (3.12ml;0.026mol) gave (562) as a colourless liquid (6.54g;99%) b.p. 124°C/0.02mm Hg.

ir γ_{max} (liquid film) 1712cm^{-1}

^{1}H nmr $\delta(CCl_4)$ 3.58 and 3.75(6H, 2xs, 2xOCH_3),3.42 (2H,d, J=24Hz,CH_2P) 6.65(1H,m,furan β-H) 7.55(1H,m,furan α-H).

7.6.24. Diethyl (2-carbomethoxy-3-furylmethyl)phosphonate (563)

A solution of 3-bromomethyl-2-furancarboxylic acid, methyl ester (576) (78g;0.35mol) in triethylphosphite (70g;0.40mol) was heated at 160-170° for 4h and the bromoethane formed removed by distillation.[379,490] The residue was distilled to give diethyl (2-carbomethoxy-3-furylmethyl)phosphonate (563) as a pale yellow oil (51.5g;56%), b.p. 220-4°C.

^{1}H nmr $\delta(C^2HCl_3)$ 1.37(6H,t,J=8Hz, 2xOCH_2CH_3)
3.36(2H,d,J=24Hz, -CH_2P)
3.98(3H,s,CO_2CH_3), 4H multiplet centred at ≃4.15ppm collapsing to two signals at 4.10 and 4.19ppm on irradiating at 1.37ppm (2xOCH_2CH_3), 6.95(1H,d, J=2Hz, C_4-H), 7.57 (1H,d,J=2Hz, C_5-H).

7.6.25. (E)-3-[2-(2,3-dimethylphenyl)ethenyl]-2-furancarboxylic acid, methylester (564)

A solution of dimethyl (2-carbomethoxy-3-furylmethyl)phosphonate (562) (23.1g;0.093mol), 2,3-dimethylbenzaldehyde (532h) (13.5g;0.1mol)

and 15-crown-5 (50mg; 0.2mmol) in dry diglyme (50ml) was added dropwise to a suspension of sodium hydride (50% dispersion in oil, 4.8g;0.1mol) in diglyme (150ml) at 80°C over 0.5h.[385,386] After stirring at 80°C for 1h and at room temperature for 1h the orange suspension which resulted was poured into saturated sodium chloride solution (500ml) and the mixture extracted with ether (3x200ml). The combined organic extracts were washed with sodium bisulphite solution (10%, 2x50ml), saturated sodium chloride solution (2x100ml), dried over magnesium sulphate and evaporated *in vacuo* to give a brown oil which was distilled *in vacuo* to give (E)-3-[2-(2,3-dimethylphenyl)ethenyl]-2-furancarboxylic acid, methyl ester (564) as a pale yellow oil (11.5g;45%), b.p. 158-164°C/0.1mm Hg, which crystallised on standing, m.p. 64-5°C.

Analysis — Found : C, 74.9; H, 6.4
$C_{16}H_{16}O_3$ requires : C, 75.0; H, 6.3%

uv — λ_{max}^{nm} (EtOH)(ε) 302(11,900), 246(10,700), 213(13,200).

ir — ν_{max} (CCl_4 solution) 1710cm^{-1}.

^{1}H nmr — δ(CCl_4) 2.27(6H,s,2xAr-CH_3), 3.86(3H,s,CO_2CH_3), 6.84(1H,d,J=2Hz,furan β-H), 6.98-8.62(6H,m,furan α-H, -CH=CH-, 3 x aromatic-H).

^{13}C nmr — δ(C^2HCl_3) 15.4, 20.6, 51.7, 109.5, 120.1, 124.3, 126.9, 129.9, 132.2, 132.6, 134.5, 136.1, 136.9, 139.7, 145.5, 159.8.

ms — m/e 256(M^+, 82%), 197(100), 182(54), 169(60), 153(36), 105(36).

7.6.26. 3-[2-(2,3-Dimethylphenyl)ethyl]-2-furancarboxylic acid, methyl ester (565)

A solution of (E)-3-[2-(2,3-dimethylphenyl)ethenyl]-2-furancarboxylic acid, methyl ester (564) (30.5g;0.12mol) and tris-(triphenylphosphine)chlororhodium[387] (1g) in ethanol/benzene (1:1) (800ml) was degassed with argon and then hydrogenated at 70°C under 160 atm. for 14 days. The solution was evaporated *in vacuo* to give a black oil which was dissolved in ethanol (200ml), filtered through silica gel (Kieselgel) GF 254 (Type 60) and evaporated *in vacuo* to give a mixture as a light brown oil. The mixture was separated by flash column chromatography.[480] Elution with ether/petroleum ether (40-60°C) (1:4) gave 3-[2-(2,3-dimethylphenyl)ethyl]-2-furancarboxylic acid, methyl ester (565) as colourless microcrystals (16.6g;54%), m.p. 34-6°C.

Analysis — Found : C, 74.1; H, 7.1.
$C_{16}H_{18}O_3$ requires : C, 74.4; H, 7.0%

uv — λ_{max} nm (EtOH)(ε) 216(12,900), 253(12,600).

ir — ν_{max} (liquid film) 1715cm^{-1}.

^{1}H nmr — δ(C^2HCl_3) 2.27 and 2.31 (6H,2xs,2xAr-CH_3), 2.74-3.17 (4H,m,2xCH_2), 3.89(3H,s,CO_2CH_3), 6.33(1H,d,J=2Hz, furan β-H), 7.10(3H,brs, 3 x aromatic-H), 7.41(1H,d,J=2Hz, furan α-H).

^{13}C nmr — δ(C^2HCl_3) 14.9, 20.7, 26.8, 34.3, 51.6, 114.0, 125.5, 127.1, 128.0, 134.6, 135.3, 136.9, 139.3, 139.9, 145.0, 159.8.

ms — m/e 258(M^+,9%), 226(5), 120(10), 119(100), 91(6),77(4).

7.6.27. 3-[2-(2,3-Dimethylphenyl)ethyl]-2-furancarboxylic acid (566)

A solution of 3-[2-(2,3-dimethylphenyl)ethyl]-2-furancarboxylic acid, methyl ester (0.80g;0.31mol) in ethanol (10ml) was treated with sodium hydroxide solution (10%, 50ml) and the mixture boiled under reflux for 1h. The mixture was cooled on ice, acidified and filtered to give a white solid which was crystallised from ethanol/water to yield 3-[2-(2,3-dimethylphenyl)ethyl]-2-furancarboxylic acid (566) as white microcrystals (0.53g; 69%), m.p. 174-6°C.

Analysis — Found : C, 73.5; H, 6.7.
$C_{15}H_{16}O_3$ requires : C, 73.8; H, 6.6%

uv — λ_{max} nm (EtOH)(ε) 245(11,800), 215(12,800).

ir — ν_{max} (Nujol) 1680^{-1}.

^{1}H nmr — δ($(C^2H_3)_2SO$) 2.23 and 2.26 (6H,2xs,2xAr-C$\underline{H}_3$), 2.64-3.15 (4H,m,2xC$\underline{H}_2$), 6.56 (1H,d,J=2Hz, furan β-$\underline{H}$), 6.99(3H,brs,3 x aromatic-$\underline{H}$), 7.77(1H,d,J=2Hz,furan α-$\underline{H}$).

^{13}C nmr — δ($(C^2H_3)_2SO$) 14.5, 20.4, 26.5, 33.8, 114.0, 125.2, 126.8, 127.7, 134.2, 136.2, 139.3, 140.1, 145.3, 160.3.

ms — m/e 244 ($\underline{M}^+$,7%), 120(8), 119(100), 91(6), 77(3), 41(3).

7.6.28. 4,5-Dihydro-6,7-dimethyl-10H-benzo[5,6]cyclohepta [1,2-b] furan-10-one (567)

A suspension of 3-[2-(2,3-dimethylphenyl)ethyl]-2-furancarboxylic acid (566) (10.36g;0.042mol) in benzene (300ml) was treated with thionyl chloride (6.3ml;10.3g;0.086mol) and the mixture boiled under reflux for 2h. The solvent was removed from the mixture *in vacuo* to give an orange solid which was dissolved in nitrobenzene (300ml). The resulting solution was cooled to 0°C and aluminium chloride (15g;0.11mol) added. The mixture was stirred at room temperature for 16h, at 80°C for 4h, poured into water and extracted with ether 3x100ml). The organic extracts were washed with sodium hydroxide solution (10%, 1x50ml), saturated sodium hydrogen carbonate solution (1x50ml), saturated sodium chloride solution (2x100ml) and dried over magnesium sulphate. The solvent from the extracts was evaporated *in vacuo* to give a black oil which was concentrated to c.a. 20ml by distillation at reduced pressure. The residue was dissolved in ether/petroleum ether (40-60°C) (1:4), passed down a short silica gel column (2") and evaporated to give a brown oil (9g) which crystallized on standing. The solid mixture (3x3g) was separated by flash column chromatography.[480] Elution with ether/petroleum ether (40-60°C) (1:4) gave 4,5-dihydro-6,7-dimethyl-10H-benzo[5,6]cyclohepta[1,2-b]-furan-10-one (567) as colourless microcrystals (7.52g, 78%), m.p. 143-5°C.

Analysis Found : C,79.2; H, 6.1
$C_{15}H_{16}O_3$ requires : C,79.6; H, 6.2%.

uv λ_{max} nm (EtOH) (ε) 212(7,600), 279(7,200,sh), 236(3,600), 306(10,200).

ir ν_{max} ($CHCl_3$ solution) 1630 cm^{-1}.

^{1}H nmr $\delta(C^2HCl_3)$ 2.33 and 2.36(6H,2xs,2xAr-C$\underline{H}_3$), 2.70-2.96 (2H,m,C$\underline{H}_2$), 3.04-3.26(2H,m,C$\underline{H}_2$). 6.46(1H,d,J=2Hz, furan β-$\underline{H}$), 7.08(1H,d,J=8Hz,C_8-$\underline{H}$), 7.50(1H,d,J=2Hz, furan α-$\underline{H}$), 7.67(1H,d,J=8Hz,C_9-$\underline{H}$).

^{13}C nmr $\delta(C^2HCl_3)$ 15.9, 21.7, 25.2, 29.5, 113.4, 127.3, 128.5, 134.0, 136.9, 137.7, 141.8, 146.5, 149.3, 181.9.

ms m/e 226($\underline{M}^+$, 100%), 225(31), 211(25), 197(21), 183(21), 155(21).

7.6.29. 5,10-Dihydro-6,7-dimethyl-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-ol (568)

Sodium borohydride (0.2g;5.2mmol) was added to a stirred solution of 4,5-dihydro-6,7-dimethyl-10H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (567)(223mg;0.99mmol) in tetrahydrofuran (10ml) and the mixture stirred at room temperature for 16h. The mixture was poured into water (50ml) and solid ammonium chloride (5g) added. The solution which resulted was extracted with ether (3x10ml). The extracts were washed with saturated sodium chloride solution (1x20ml) dried over potassium carbonate and evaporated to give 5,10-dihydro-6,7-dimethyl-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-ol (568) as an orange microcrystalline powder (222mg;99%), m.p. 75-7°C.

ir ν_{max} (CCl_4 solution) 3,450cm^{-1},

^{1}H nmr $\delta(CCl_4)$, 2.19(6H,s,2xC$\underline{H}_3$), 2.41-3.79(5H,m,2xC$\underline{H}_2$+O$\underline{H}$), 5.35(1H,s,C$\underline{H}$OH), 6.01(1H,d,J=2Hz, furan β-$\underline{H}$), 6.79(2H,s,2 x aromatic-$\underline{H}$), 7.12(1H,d,J=2Hz,furan α-$\underline{H}$).

ms m/e 228($\underline{M}^+$, 12%), 226(66),211(100),210(68),209(54), 195(40), 155(29).

7.6.30 (E)-3-[2-(2,3-Dimethylphenyl)ethenyl]-2-furancarboxylic acid (569)

(E)-3-[2-(2,3-Dimethylphenyl)ethenyl]-2-furancarboxylic acid (569) was prepared by the method outlined for (566). Treatment of (564) (0.3g;1.2mol) with sodium hydroxide solution (10%,10ml) gave (569) as orange crystals (0.24;85%), m.p. 194-6°C.

uv λ_{max}^{nm} (EtOH)(ε) 216(10,000), 240(9,780), 325(12,800).

ir ν_{max} (Nujol mull) 1680cm.$^{-1}$

^{1}H nmr δ((C^{2}H$_3$)$_2$SO)2.28 and 2.32(6H;2xS;2xCH$_3$) 6.90-7.78(6H,m, 3 x aromatic-H + furan β-H and 2 x olefinic-H), 7.84(1H,d,J=2Hz, furan α-H), 9.35(1H,brs,CO$_2$H).

^{13}C nmr δ((C^{2}H$_3$)$_2$SO)15.1, 20.3, 109.7, 120.6, 123.5, 125.7, 130.9, 130.5, 129.5, 134.3, 136.7, 136.0, 141.2, 145.6, 160.8.

ms m/e 243(M^++1,3%), 242(M^+,24), 197(24), 196(21), 169(20), 111(31), 95(32), 83(48), 71(63), 69(60), 57(100).

7.6.31 2,3-Dimethyl-benzonitrile[491] (571) [5724-56-1]

2,3-Dimethyl-benzonitrile[491] (571) [5724-56-1] was prepared by the method of Vogel.[477] 2,3-Dimethyl-benzenamine (570) (19g;0.074mol) was treated with concentrated hydrochloric acid (40ml) and water (40ml) and the mixture stirred at 0°C for 0.5h. Sodium nitrite (19g) was then added to the mixture while keeping the temperature below 5°C. This

mixture was then added to a solution of copper (1) cyanide[477] (from copper sulphate (50g)) and potassium cyanide (25g) in water (60ml) at 60°C. The mixture was heated on a steam bath for 1h, cooled to room temperature and extracted with ether (4x100ml). The organic extracts were washed with saturated sodium chloride solution, dried over magnesium sulphate and evaporated to give a brown oil which was distilled *in vacuo* to give (571) as a white solid b.p. 115-8°C/15mm Hg (Lit.[492] 118-122.5°C/34mm Hg).

7.6.32. 2,3-Dimethylbenzoic acid (572) [603-79-2]

A suspension of 2,3-dimethylbenzonitrile (571) (48g;0.36mol) in aqueous potassium hydroxide solution (30%;300ml) was boiled under reflux 50h.[477] The solution was poured onto ice (800g) and slowly acidified with concentrated hydrochloric acid. The resulting suspension was cooled on ice for 1h, filtered, and the separated white solid washed with ice water (2x100ml). Drying at 80°C for 2h and at 20°C/0.1mm Hg for 2.5h gave 2,3-dimethylbenzoic acid (572) as a white powder (53.0g;96%) m.p. 144-145.5°C (Lit.[492] 141.5-144°C).

ir ν_{max} (Nujol) 1670cm.$^{-1}$

^{1}H nmr $\delta((C^2H_3)_2SO)$ 2.29(3H,s,C_2-C$\underline{H}_3$), 2.44(3H,s,C_3-C$\underline{H}_3$), 7.03-7.39(2H,m,C_5-$\underline{H}$ and C_4-$\underline{H}$), 7.52-7.68(1H,m,C_6-$\underline{H}$).

ms m/e ($\underline{M}^+$,100%), 132(88), 105(82), 91(27), 77(37).

7.6.33. 2,3-Dimethyl-benzoic acid, methylester (573) [15012-36-9]

A solution of 2,3-dimethyl-benzoic acid (572) (59g;0.39mol) in methanol (250ml) containing concentrated sulphuric acid (5ml) was boiled under reflux for 5h.[493] The mixture was cooled to room temperature, evaporated and poured into water. The aqueous solution

was extracted with ether (3x200ml). The organic extracts were washed with sodium hydrogen carbonate (2x50ml), dried over magnesium sulphate and evaporated to give a pale yellow oil (55g) which was distilled *in vacuo* to give 2,3-dimethyl-benzoic acid, methyl ester (573) as a colourless oil (16.3g;25%) b.p. 110-1°C/13mm Hg (Lit.[494] 104-5°C/12 mm Hg).

7.6.34. 2,3-Dimethyl-benzenemethanol (574) [13651-14-4]

A suspension of 2,3-dimethylbenzoic acid (572) (50.0g;0.33mol) in dry tetrahydrofuran (250ml) was added dropwise, over 0.5h to an ice cold suspension of lithium aluminium hydride (10g;0.33mol) in anhydrous ether (30ml). The resulting suspension was stirred for 4h and allowed to stand at room temperature for 3 days. Ethyl acetate (5ml) was added and the mixture stirred for 20min. Saturated ammonium chloride solution (20ml) was then added followed by hydrochloric acid (6N,180ml). The aqueous phase was separated and extracted with ether (3x100ml). The combined organic extracts were washed with potassium hydroxide solution (20%, 2x50ml), saturated sodium hydrogen carbonate solution (1x50ml) and saturated sodium chloride solution (3x100ml), and dried over magnesium sulphate. The solvent was removed by distillation at atmospheric pressure and the pale yellow residue distilled at reduced pressure to give 2,3-dimethylbenzenemethanol (574) as a colourless oil (28g;62%) b.p. 128-131°C/13mm Hg (Lit.[495] 128-130°C/12mm Hg) which crystallised on standing m.p.63-6°C (Lit.[496] 64°C).

ir ν_{max} (liquid film) 3620cm^{-1}, 3450cm^{-1}

^{1}H nmr $\delta(C^2HCl_3)$ 2.17(3H,s,C_2-CH_3), 2.24(3H,s,C_3-CH_3), 2.57(1H,s,OH), 4.54(2H,s,CH_2OH), 7.08(3H,brs,C_4-H, C_5-H, C_6-H).

ms m/e 136(M^+ 47%), 118(100), 117(35), 93(38), 91(49), 77(30).

7.6.35. 1-Iodo-2,3-dimethyl-benzene (575) [51599-60-7]

2,3-Dimethyl-benzenamine (570)(26.6g;0.22mol) was dissolved in concentrated hydrochloric acid (55ml) and ice (55g).[497] The mixture which resulted was stirred in a salt/ice bath for 1h and a solution of sodium nitrite (16g) in water (80ml) added dropwise below the level of the solution at such a rate as to maintain the temperature below 5°C. The solution was stirred at 0°C for 15 min and a solution of potassium iodide (36g) in water (40ml) added. The mixture was stirred and allowed to attain room temperature over 3h. The solution which resulted was extracted with ether (4x100ml). The organic extracts were washed with potassium hydroxide solution (20%,2x50ml), water (1x100ml), sodium bisulphite solution (10%. 3x25ml) and saturated sodium chloride solution, dried over potassium carbonate and evaporated to give a dark oil. The oil was distilled *in vacuo* to give (575) as an orange oil (22.65g;44%), b.p. 111-113°C/13mm Hg (Lit.[498] 125-6°C/15 mm Hg).

7.6.36. 3-Bromomethyl-2-furoic acid, methyl ester (576) [23268-19-1]

N-Bromosuccinimide (53g;0.3mol) was added to a rapidly stirred solution of 3-methyl-2-furoic acid, methyl ester (583) in carbon tetrachloride (250ml) containing benzoyl peroxide (0.5g). The mixture was boiled under reflux for 4h. cooled to room temperature and filtered. Evaporation of the filtrate gave an orange oil which was distilled *in vacuo* to give 3-bromomethyl-2-furoic acid, methyl ester[499,500] (576) is a colourless oil (62.7g;96%), b.p. 138-141°C.

uv λ_{max}^{nm} (EtOH)(ε) 224(sh)(4,460), 258(7,360)

ir ν_{max} (liquid film) 1720cm^{-1}

^{1}H nmr δ(CCl_4), 3.87(3H,s,$CO_2\underline{CH}_3$), 4.66(2H.s.$\underline{CH}_2Br$), 6.60(1H,d,J=2Hz,furan β-$\underline{H}$), 7.57(1H,d,J=2Hz,furan α-$\underline{H}$).

7.6.37 3-(Phenylselenylmethyl)-2-furancarboxylic acid, ethyl ester (577).

Powdered sodium borohydride (0.20g;5.5mmol) was added to a stirred solution of diphenyl diselenide (0.78g;2.5mmol) in dry ethanol (45ml).[381] The mixture was stirred for 15min to give a colourless solution and 3-(bromomethyl)-2-furancarboxylic acid, methyl ester (576) (1.09g;5mmol) added. The resulting mixture was boiled under reflux for 20h, cooled to room temperature and poured into dilute hydrochloric acid (1M,100ml). The aqueous solution was extracted with pentane (3x25ml). The organic extracts were washed with saturated sodium chloride solution (1x20ml), dried over magnesium sulphate and evaporated to give a yellow oil which was distilled *in vacuo* to yield 3-(phenylselenylmethyl)-2-furancarboxylic acid, ethyl ester (577) as a pale yellow oil (1.25g;85%), b.p. 154-6°C/0.02mm Hg.

uv λ_{max} nm(EtOH)(ε), 209(11,240), 249(11,240).

ir ν_{max} (liquid film) 1712cm.$^{-1}$

^{1}H nmr δ(CCl_4) 1.23(3H,t,J=8Hz, $CO_2CH_2\underline{CH_3}$), 4.12(2H,q,J=8Hz, $CO_2\underline{CH_2}CH_3$), 4.14(2H,s,$\underline{CH_2}Se$), 6.24(1H,d,J=2Hz,furan β-$\underline{H}$) 7.05-7.62(6H,m,furan α-$\underline{H}$ and 5x aromatic-$\underline{H}$).

^{13}C nmr δ(C^2HCl_3) 14.3, 21.2, 60.7, 114.0, 127.7, 128.9, 129.2, 129.3, 131.5, 132.7, 134.3, 140.1, 144.9, 159.1.

ms m/e 310($\underline{M}^+$,5), 153(21), 125(100), 77(15), 52(16), 51(22).

7.6.38. 3-Methyl-2-furancarboxylic acid, methyl ester (583) [6141-57-7]

3-Methyl-2-furancarboxylic acid, methyl ester (583) [6141-57-7] was prepared by the method of Burness.[501] Treatment of a mixture of

4,4-dimethoxy-butan-2-one (132g;1mol) and chloroacetic acid, methyl ester (131g;1.2mol) with sodium methoxide (66g;1.2mol) gave 3-methyl-2-furancarboxylic acid, methyl ester (583) as a colourless oil (85.8g; 61%), b.p. 89-91°C/13mm Hg (Lit.[501] 72-8°C/8mm Hg).

ir ν_{max} (liquid film) 1710cm^{-1}.

^{1}H nmr $\delta(C^2HCl_3)$ 2.36(3H,s,$C\underline{H}_3$), 3.92(3H,s,$CO_2C\underline{H}_3$), 6.40(1H,d,J=2Hz, C_4-$\underline{H}$), 7.51(1H,d,J=2H_2, C_5-$\underline{H}$).

7.6.39. Reduction of 9H-fluoren-9-one (585) *via* its 4-toluenesulphonylhydrazone derivative : preparation of (586).

A mixture of 9$\underline{H}$-fluoren-9-one (585) (1.8g;0.01mol), 4-toluenesulphonylhydrazine (1.9;0.011mol) and 4-toluenesulphonic acid (10mg) in ethanol (2ml) was heated at 80°C for 5 min. The solvent was removed from the resulting suspension *in vacuo* to yield a yellow solid which was crystallized from ethanol/water to give (589) as yellow crystals (3.321g;95%) m.p. 183-5°C.

A solution of (589) (696mg;2.0mmol) and sodium cyanoborohydride (0.5g;8.0mmol) in anhydrous N,N-dimethylformamide (5ml) was heated at 120°C and 4-toluenesulphonic acid (100mg) added in 10mg portions.[481] The mixture was heated at 120°C for 2.5h and the resulting paste poured into water (10ml). The aqueous suspension was extracted with petroleum ether (40-60°C) (3x10ml). The extracts were dried over magnesium sulphate and evaporated to give (586) as pale yellow crystals (300mg; 90.4%) m.p. 111-3°C (Lit.[488] 116°C).

7.6.40. Reduction of diphenyl-methanone (587) *via* its 4-toluenesulphonylhydrazone derivative : preparation of (588)

The 4-toluenesulphonylhydrazone derivative of diphenyl-methanone (587) was prepared by the method outlined for 9H-fluoren-9-one (585). Treatment of diphenyl-methanone (1.8g; 0.01mol) (587) with 4-toluene-

sulphonylhydrazine (1.9g;0.011mol) and 4-toluenesulphonic acid (10mg) in ethanol (2ml) gave(590) as colourless needles (3.214g;91%) m.p. 191-3°C.

A solution of (590) (50mg;0.14mol) and sodium cyanoborohydride (0.05g;0.8mmol) in anhydrous N,N-dimethylformamide (1ml) was heated at 120°C and 4-toluenesulphonic acid (10mg) added.[481] The mixture was heated at 120°C for 2.5h and the resulting paste poured into water (10ml). The aqueous suspension was extracted with petroleum ether (3x10ml). The extracts were dried over magnesium sulphate and evaporated to give diphenylmethane (588) as a waxy crystalline solid (22.0mg;92%) m.p. 21-2°C (Lit.[488] 26-7°C).

7.6.41. Butyndioic acid, dimethyl ester (591)

Butyndioic acid, dimethyl ester (591) was prepared the method of Huntress.[502] Treatment of butyndioic acid, monopotassium salt (100g; 0.65mol) with concentrated sulphuric acid (111ml) and methanol (510ml) gave (591) in a colourless liquid (86.1g;92%) (Lit.[502] 95-8°C/19mm Hg).

7.6.42. 6,7-Dimethyl-2,4a-epoxy-2,4a,10,11-tetrahydro-5H-dibenzo[a,d]cycloheptane-3,4-dicarboxylic acid, dimethyl ester (592).

A mixture of 5,10-dihydro-6,7-dimethyl-4H-benzo[5,6]cyclohepta[1,2b]furan (337)(39mg;0.18mmol) and 2-butyndioic acid, dimethyl ester (50mg;0.35mmol) in ether (5ml) was allowed to stand at room temperature for 2 days. The solvent was removed *in vacuo* to give a colourless oil. The oil was triturated with petroleum ether (40-60°C) to give (592) as colourless crystals (62.1mg;99%) m.p. 132-4°C.

ir ν_{max} ($CHCl_3$ solution) 1725cm.$^{-1}$

^{1}H nmr $\delta(C_6{}^2H_6)$ 1.95 and 2.06(6H,2xs,2xCH_3), 2.37-3.14(4H,m, 2xCH_2), 3.26 and 3.38(6H,2xs,2xCO_2CH_3),

3.80(2H,m,C_5-H), 5.46(1H,d,J=2Hz,C_2-H), 6.26(1H,m, C,-H), 6.90(2H,ABq,C_6-H and C_7-H).

^{13}C nmr — $\delta(C_6{}^2H_6)$15.2, 21.0, 25.8, 27.4, 35.7, 51.5, 51.7, 82.5, 96.6, 127.1, 128.1, 128.5, 129.0, 133.5, 133.7, 135.6, 137.2, 139.5, 158.4, 162.7, 165.9.

ms — m/e 354(M^+,31%), 322(31), 293(59), 212(96), 211(100), 197(71), 132(33).

7.6.43. (E)-3-(2-Phenylethenyl)-2-furancarboxylic acid, methyl ester (593a)

A solution of dimethyl (2-carbomethoxy-3-furylmethyl)phosphonate (562)(21g;0.085mol), benzaldehyde (532a)(9.01g;0.085mol) and 15-crown-5(100mg) was added dropwise to a stirred suspension of sodium hydride (4.08g;0.085mol)(50% dispersion in oil) in diglyme (150ml) at 80°C.[385-6] The mixture which resulted was stirred at 80°C for 1h, at room temperature for 16h and poured into saturated sodium chloride solution (500ml). The aqueous suspension was extracted with ether (3x100ml). The extracts were washed with sodium hydrogen sulphite solution (10%, 2x50 ml and saturated sodium chloride solution (2x100ml), dried over magnesium sulphate and evaporated to give an oil. The oil was distilled *in vacuo* to give (E)-3-(2-phenylethenyl)-2-furancarboxylic acid, methyl ester (593a) as a light yellow oil (7.2g;37%), b.p. 154-7°C/ 0.05mm Hg.

G.C. — R_T(160°C) 3.0min

uv — λ_{max}nm (EtOH)(ε) 210(8,900), 252(13,600), 303(sh) (9,400), 311(9,900), 320(sh)(7,500).

ir — ν_{max} (liquid film) 1713cm.$^{-1}$

^{1}H nmr $\delta(C^{2}HCl_3)$ 3.93(3H,s,$CO_2\underline{CH}_3$), 6.74(1H,d,J=2Hz, furan β-H, 6.96(1H,d,J=16Hz, olefinic-H), 7.10-7.58(6H,m, 5 x aromatic-H+furan α-H), 7.70(1H,d,J=16Hz,olefinic-H).

^{13}C nmr $\delta(C^{2}HCl_3)$ 51.7, 109.4, 118.4, 127.8, 128.3, 126.9, 128.7, 132.3, 133.4, 136.7, 145.5, 159.7.

ms m/e 228 (M^{+},100), 169(80), 168(83), 141(99), 117(40), 115(36).

7.6.44. (E)-3-[3,4-Dimethoxyphenyl)ethenyl]-2-furancarboxylic acid, methyl ester (593b).

A solution of 3,4-dimethoxy-benzaldehyde (532b)(15.4;0.093mol), dimethyl (2-carbomethoxy-3-furylmethyl)phosphonate (562)(23g;0.093mol) and 15-crown-5 (50mg) in diglyme (20ml) was added dropwise (over 0.5h) to a stirred suspension of sodium hydride (4.8g;0.1mol)(50% dispersion in oil) in diglyme (180ml) at 80°C.[385,386] The mixture was stirred at 80°C for 1h, at room temperature for 1h and poured into saturated sodium chloride solution (500ml). The aqueous suspension was extracted with ether (3x200ml). The extracts were washed with sodium hydrogen sulphite solution (10%,2x50ml) and saturated sodium chloride solution (2x100ml), dried over magnesium sulphate and evaporated to give an oil. The oil was distilled *in vacuo* to give (E)-3-[2-(3,4-dimethoxyphenyl) ethenyl]-2-furancarboxylic acid, methyl ester (593b) as a pale yellow oil (14.67g;54%), b.p. 194-200°C/0.1mm Hg.

uv λ_{max}nm (EtOH)(ε) 222(10,700), 256(9,730), 316(8,560).

ir ν_{max} (liquid film) 1715cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$, 3.80(9H,brs,$CO_2\underline{CH}_3$ and 2x$O\underline{CH}_3$), 6.86-7.25(4H,m,3 x aromatic-H+furan β-$\underline{H}$), 7.22(1H,d, J=18Hz, olefinic-$\underline{H}$), 7.62(1H,d,J=18 Hz, olefinic-$\underline{H}$), 7.90(1H,d,J=2Hz,furan-α$\underline{H}$).

ms m/e 288($\underline{M}^+$,79%), 229(26), 166(37), 157(35), 149(100), 71(47), 57(73).

7.6.45. (E)-3-[2-(4-Methyl-phenyl)ethenyl]-2-furancarboxylic acid, methyl ester (593c)

(E)-3-[2-(4-Methyl-phenyl)ethenyl]-2-furancarboxylic acid, methyl ester (593c) was prepared by the method outlined for (564).[385,386] Diethyl (2-carbomethoxy-3-furylmethyl)phosphonate (563) (2.76g;0.01mol) was reacted with 4-methyl-benzaldehyde (532f) (1.2g;0.01mol) and sodium hydride (0.24g;0.01mol) in the presence of 15-crown-5 (30mg) to yield an orange oil. The oil was distilled *in vacuo* to give (593c) as a colourless oil (0.345g;33%), b.p. 105-110°C/0.01mm Hg, which crystallised on standing, m.p. 40-2°C.

G.C. R_T(160°C) 4.6min.

uv λ_{max}nm (EtOH)(ε) 212(7,500), 234(sh)(9,900), 244(13,200), 256(13,500), 304(sh)(17,800), 316(19,900).

ir ν_{max} (liquid film) 1705cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 2.33(3H,s,$C\underline{H}_3$), 3.92(3H,s,$CO_2\underline{CH}_3$), 6.72(1H,d,J=2Hz,furan β-$\underline{H}$), 6.94(1H,d,J=16Hz, olefinic-$\underline{H}$), 7.02-7.51(5H,m,4 x aromatic-$\underline{H}$ and furan α-$\underline{H}$), 7.77(1H,d,J=16Hz, olefin-$\underline{H}$).

^{13}C nmr $\delta(C^{2}HCl_3)$ 21.2, 51.7, 109.3, 117.4, 126.8, 129.5, 133.4, 132.5, 133.9, 138.3, 139.4, 145.5, 159.8.

ms m/e 242($\underline{M}^+$,100%), 183(88), 182(83), 155(87), 153(33), 128(20).

7.6.46. (E)-3-[2-(2-Bromo-phenyl)ethenyl]-2-furancarboxylic acid, methyl ester (593d)

A solution of 2-bromo-benzaldehyde (532g)(4.07g;0.022mol), diethyl (2-carbomethoxy-3-furylmethyl)phosphonate (563) (6.07g; 0.022mol) and 15-crown-5 (30mg) in diglyme (20ml) was added dropwise (over 20min) to a stirred suspension of sodium hydride (1.0g;0.022mol) (50% dispension in oil) in diglyme (5ml) at 60°C.[385,386] The mixture was stirred at 60°C for 1.5h and poured into saturated sodium chloride solution (100ml), neutralised with 1M hydrochloric acid and extracted with ether (3x50ml). The extracts were washed with sodium hydrogen sulphite solution (10%, 2x25ml) and saturated sodium chloride solution (2x25ml), dried over magnesium sulphate and evaporated to give an oil. The oil was distilled *in vacuo* to give (E)-3-[2-(2-bromo-phenyl)ethenyl]-2-furancarboxylic acid, methyl ester (593d) as a pale yellow oil (3.98g;59%), b.p. 158-60°C/0.02mm Hg.

G.C. R_T(160°C) 9.6min.

uv λ_{max}nm (EtOH)(ε) 213(15,900), 244(12,100), 300(13,200), 355(6,300).

ir ν_{max} (CCl_4 solution) 1712cm.$^{-1}$

^{1}H nmr $\delta(CCl_4)$ 3.87(3H,s,$CO_2\underline{CH}_3$), 6.86(1H,d,J=2Hz, furan β-$\underline{H}$), 7.04-7.93(7H,m,4 x aromatic-$\underline{H}$+2x olefinic-$\underline{H}$+furan α-$\underline{H}$).

^{13}C nmr $\delta(C^2HCl_3)$ 51.8, 109.6, 121.0, 124.2, 127.1, 127.7, 129.5, 131.8, 131.8, 133.1, 136.4, 140.0, 145.6, 159.7.

ms m/e 308($\underline{M}^+$,^{81}Br,15%), 306($\underline{M}^+$,^{79}Br,16%), 169(17), 168(100), 155(26), 140(25), 139(35).

7.6.47. 3-[2-(3,4-Dimethoxyphenyl)ethyl]-2-furancarboxylic acid, methyl ester (594b)

3-[2-(3,4-dimethoxyphenyl)ethyl]-2-furancarboxylic acid, methyl ester (594b) was prepared by the method outlined for (565). A mixture of (E)-3-[2-(3,4-dimethoxyphenyl)ethenyl]-2-furancarvoxylic acid methyl ester (593b)(12.0g;0.042mol) and *tris*-(triphenylphosphine)chlororhodium[387] (0.5g) was hydrogenated at 50°C and 25 atm for 2 days to give 3-[2-(3,4-dimethoxyphenyl)ethyl]-2-furancarboxylic acid, methyl ester (594b) as a light brown oil (12.01g;99.4%). An analytical sample was prepared by distillation of 1.2g *in vacuo* to give a colourless oil (0.91g), b.p. 154°C/0.1mm Hg.

ir ν_{max} (liquid film) 1720cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 3.01(4H,m,2x$\underline{CH}_2$), 3.87(6H,s,2x$O\underline{CH}_3$), 3.90(3H,s,$CO_2\underline{CH}_3$), 6.35(1H,d,J=2Hz,furan β-$\underline{H}$), 6.80(2H,s,2 x aromatic-$\underline{H}$), 7.49(1H,d,J=2Hz,furan α-$\underline{H}$).

ms m/e 290($\underline{M}^+$,8%), 152(12), 151(100), 149(7), 107(5).

7.6.48. (E)-3-(2-Phenylethenyl)-2-furancarboxylic acid (595a).

(E)-3-(2-phenylethenyl)-2-furancarboxylic acid (595a) was prepared by the method outlined for (566). Treatment of (593a) (0.23g;1mmol) with potassium hydroxide (10%,10ml) gave (595a) as a white powder (0.14g;65%) m.p. 210-14°C.

Analysis — Found : C,72.9; H,4.7,
$C_{13}H_{10}O_3$ requires : C,72.8; H,4.8%

uv — λ_{max} nm (EtOH)(ε) 211(14,100), 233(sh)(16,300), 239(17,000), 246(15,210), 295(sh)(28,000), 307(30,900), 320(21,000).

ir — ν_{max} (Nujol mull) 1,665cm.$^{-1}$

^{1}H nmr — δ($(C^2H_3)_2SO$) 7.14(1H,d,J=2Hz, furan β-H), 7.26-7.85(7H,m,5 x aromatic-H and 2 x olefinic-H), 7.87(1H,d,J=2Hz,furan α-H).

^{13}C nmr — δ($(C^2H_3)_2SO$) 109.7, 118.5, 126.6, 128.9, 128.3, 131.2, 133.0, 136.6, 140.1, 146.4, 160.3.

ms — m/e 215(M^++1,13), 214(M^+,79%), 169(52), 168(59), 141(81), 85(48), 71(62), 65(55), 57(100), 55(60).

7.6.49. (E)-3-[2-(3,4-Dimethoxyphenyl)ethenyl]-2-furancarboxylic acid (595b)

(E)-3-[2-(3,4-Dimethoxyphenyl)ethenyl]-2-furancarboxylic acid (595b) was prepared by the method outlined for (566). Treatment of (593b)(0.41g;1.4mmol) with sodium hydroxide (10%;10ml) gave (595b) as

a light tan powder (0.33g;85%) m.p. 188-90°C.

Analysis — Found : C,65.7; H,5.2
$C_{15}H_{14}O_5$ requires : C,65.7; H,5.1%

ir — ν_{max} (Nujol mull) 1675cm.$^{-1}$

^{1}H nmr — $\delta((C^2H_3)_2SO)$ 3.84 and 3.88 (6H,2xs,2xOC$\underline{H}_3$), 6.88-7.40(5H;m,3 x aromatic-$\underline{H}$, furan β-$\underline{H}$, olefinic-$\underline{H}$) 7.65(1H,d,J=15Hz, olefinic-$\underline{H}$),7.89(1H,d,J=2Hz, furan α-$\underline{H}$).

^{13}C nmr — $\delta((C^2H_3)_2SO)$ 55.5, 119.8, 109.7, 109.8, 116.4, 112.0, 129.6, 131.7, 133.2, 149.4, 149.1, 139.6, 146.3, 160.4.

ms — m/e 275($\underline{M}^+$+1,17), 274(100), 230(7), 229(14), 228(12) 213(6).

7.6.50. (E)-3-[2-(4-Methylphenyl)ethenyl]-2-furancarboxylic acid (595c)

(E)-3-[2-(4-Methylphenyl)ethenyl]-2-furancarboxylic acid (595c) was prepared by the method outlined for (566). Treatment of (593c) (0.25g;1.0mmol) with sodium hydroxide solution (10%. 10ml) gave (595c) as pale yellow needles (0.211g;92%) m.p. 195-8°C.

uv — λ_{max}nm (EtOH)(ε) 214(12,700), 250(8,000), 292(12,700), 322(sh)(6,500).

ir — ν_{max} (Nujol mull) 1680cm.$^{-1}$

^{1}H nmr $\delta((C^{2}H_3)_2SO)$ 2.32(3H,s,C$\underline{H}_3$), 7.16(1$\underline{H}$,d,J=2Hz, furan β-$\underline{H}$), 7.21 and 7.48 (4H,ABq,J=7Hz,4 x aromatic-$\underline{H}$), 7.26 and 7.74 (2H,ABq,J=16Hz,2 x olefin-$\underline{H}$), 7.88(1H,d, J=2Hz, furan α-$\underline{H}$).

^{13}C nmr $\delta((C^{2}H_3)_2SO)$ 20.9, 109.7, 117.5, 126.6, 129.6, 131.5, 133.9, 133.0, 137.9, 139.9, 146.3, 160.4.

ms m/e 229($\underline{M}^{+}$+1,16%), 228($\underline{M}^{+}$,100), 183(59), 182(69), 168(32), 155(94), 141(38), 115(33), 57(43).

7.6.51. 3-(2-Phenylethyl)-2-furancarboxylic acid (596a)

A mixture of (E)-3-(2-phenylethenyl)-2-furancarboxylic acid (595a)(2.4g;11mmol), 5% platinum on charcoal (200mg) and ethanol (20ml) was hydrogenated at atmospheric pressure for 46h. The suspension was filtered and evaporated to give (596a) as a pale yellow solid (2.4g). An analytical sample was prepared by recrystallisation of a small sample (250mg) from water to give (596a) as pale yellow crystals (233mg), m.p. 167-9°C.

uv λ_{max}(EtOH)(ε) 213(6,000), 245(11,520).

ir ν_{max} (Nujol mull) 1685cm.$^{-1}$

^{1}H nmr $\delta((C^{2}H_3)_2SO)$ 3.00(4H,m,2xC$\underline{H}_2$), 6.56(1H,d,J=2Hz, furan β-$\underline{H}$), 7.27(5H,brs, 5 x aromatic-$\underline{H}$), 7.75(1H, d,J=2Hz,furan α-$\underline{H}$).

^{13}C nmr $\delta((C^{2}H_3)_2SO)$ 27.1, 35.5, 113.9, 125.9, 128.3, 134.0, 141.4, 145.3, 160.4.

ms m/e 216($\underline{M}^+$,17%), 141(25), 91(100).

7.6.52. 3-[2-(3,4-Dimethoxyphenyl)ethyl]-2-furancarboxylic acid (596b)

A solution of 3-[2-(3,4-dimethoxyphenyl)ethyl]-2-furancarboxylic acid, methyl ester (594b)(11.0g;0.038mol) in ethanol (10ml) was treated with sodium hydroxide solution (10%;100ml) and the mixture boiled under reflux for 5h. The cooled solution was washed with ether (2x10ml), acidified and extracted with chloroform (4x20ml). The extracts were dried over magnesium sulphate and evaporated to give (596b) as a viscous oil, which could not be induced to crystallise, (9.3g;89%).

uv λ_{max}nm (EtOH)(ε) 207(13,200), 231(13,200), 245(sh), (9,300), 276(sh)(3,400).

ir ν_{max} (liquid film) 1695cm.$^{-1}$

^{1}H nmr δ(C^2HCl_3) 2.76-3.20(4H,m,2x$\underline{CH}_2$), 3.85(6H,s,2x$O\underline{CH}_3$), 6.41(1H,d,J=2Hz, furan β-$\underline{H}$), 6.76(3H,brs, 3 x aromatic -$\underline{H}$), 7.51(1H,d,J=2Hz, furan α-$\underline{H}$).

ms m/e 276($\underline{M}^+$,7%), 196(3), 152(10), 151(100), 149(4).

7.6.53. 5,10-Dihydro-10H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (597)

A suspension of 3-(2-phenylethyl)-2-furancarboxylic acid (594a) (0.216g;1mmol) in benzene (10ml) was treated with thionyl chloride (0.2ml;0.32g;3mmol) and the mixture boiled under reflux for ½h. The solvent was removed from the mixture *in vacuo* to give a tan oil which was dissolved in nitrobenzene (10ml). The resulting solution was cooled to 0°C and aluminium chloride (270mg;2mmol) added. The mixture was

stirred at 100°C for 20 min, at room temperature for 16h, poured into hydrochloric acid (1M,20ml). The organic phase was diluted with methylene chloride(50ml) and the layers separated. The separated aqueous phase was extracted with methylene chloride (2x50ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2x50ml), saturated sodium chloride solution (1x50ml) and dried over magnesium sulphate. The solvent from the extracts was evaporated to give a dark oil which was concentrated to c.a.4ml by distillation at reduced pressure. The residue was separated by flash column chromatography. Elution with ether/petroleum ether (40-60°C)(3:7) gave 5,10-dihydro-10H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (597) as a light mauve oil (81.7mg;41%), which crystallised on standing m.p. 64-6°C.

uv λ_{max}nm (EtOH)(ε) 212(8,300), 250(6,000), 296(13,700).

ir ν_{max}($CHCl_3$ solution) 1632cm.$^{-1}$

^{1}H nmr δ(C^2HCl_3) 3.01(4H,symmetrical m,2xCH_2), 6.43(1H,d, J=2Hz,C_3-H), 7.16-7.56(3H,m,C_6-H.C_7-H,C_8-H), 7.49 (1H,d,J=2Hz,C_5-H), 8.00-8.14(1H,m,C_9-H).

^{13}C nmr δ(C^2HCl_3) 25.8, 35.3, 113.7, 127.1, 130.2, 132.6, 137.0, 139.9, 146.9, 149.3, 180.3.

ms m/e (M^+,100%), 197(28), 170(25), 169(32), 142(18), 141(71), 115(30).

7.6.54 5,10-Dihydro-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-ol(598)

Sodium borohydride (53mg;1.4mmol) was added to a stirred solution

of 4,5-dihydro-10H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (597) (140mg;0.7mmol) in anhydrous tetrahydrofuran (15ml) and the mixture stirred at room temperature for 24h. The emulsion which resulted was poured into water (25ml), acidified with dilute hydrochloric acid (0.01M) to pH=8 and extracted with ether (4x25ml). The combined organic material was washed with saturated sodium chloride solution (1x50ml), dried over potassium carbonate and evaporated to give a light orange gum (97mg) which was purified by preporative TLC (Merck aluminium oxide, 60 CF_{254}, neutral type E). Elution with ether/petroleum ether (40-60^{0}C)(1:3) gave 5,10-dihydro-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-ol (598) as a viscous oil (91mg,65%).

ir ν_{max}(CCl_4 solution) 3610cm.$^{-1}$

^{1}H nmr δ(C^2HCl_3) 2.36-3.16(3H,m,2xC_4-H+C_5-H) 3.44-3.86 (1H,m,C_5-H) 5.67(1H,s,C_{10}-H) 6.20 (1H,d,J=2H,C_3-H) 7.02-7.68(5H,m,C_6-H,C,-H,C_8-H,C_9-H,C_2-H)

^{13}C nmr δ(C^2HCl_3) 25.9, 32.4, 70.9, 112.5, 121.7, 126.5, 128.5, 130.4, 139.7, 140.5, 141.2, 149.3.

ms m/e 200(M^+,100%), 184(16), 183(100), 182(24), 181(11), 155(13), 152(12), 115(21).

7.6.55. 4,5-Dihydro-7-hydroxy-8-methoxy-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (601) and 4,5-dihydro-8-hydroxy-7-methoxy-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (600)

A suspension of 3-[2-(3,4-dimethoxyphenyl)ethyl]-2-furan-carboxylic acid (596b)(9.3g;0.034mol) in benzene (100ml) was treated with thionyl chloride (2.48ml;3.6g;0.034mol) and the mixture boiled under reflux for 1h. The solvent was removed *in vacuo* to give a

dark brown paste which was dissolved in nitrobenzene (30ml). The resulting solution was cooled to 0°C and aluminium chloride (6g;0.045mol) added. The mixture was stirred at 80°C for 2h, at room temperature for 16h, poured into water (200ml) and extracted with ether (3x50ml). The extracts were dried over magnesium sulphate and evaporated to give a brown oil. The oil was dissolved in ether : petroleum ether (1:4) (200ml) and passed down a short silica gel column (1"). The silica gel was washed with ether (2x100ml) and the solvent evaporated to give a mixture as a brown oil which was separated by flash column chromatography. Elution with ether gave 4,5-dihydro-7-hydroxy-8-methoxy-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (601)(1.1g;13%) as the fore running material and 4,5-dihydro-8-hydroxy-7-methoxy-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (600)(1.5g;17%). 4,5-Dihydro-7-hydroxy-8-methoxy-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (601), orange plates, m.p. 158-160°C.

Analysis — Found : C,68.4; H,5.0
$C_{14}H_{12}O_4$ requires : C,68.8; H,4.9%

uv — λ_{max}nm(EtOH,pH=7)(ε) 236(sh)(9,100), 249(10,600), 257(11,800), 297(12,600), 346(11,000).

λ_{max}nm (EtOH,pH=13)(ε) 267(14,300), 292(9,100), 415(18,500).

ir — ν_{max}($CHCl_3$ solution) 3,540cm.$^{-1}$; (Nujol mull) 3,180cm.$^{-1}$ 1,630cm.$^{-1}$

^{1}H nmr — δ($(C^2H_3)_2SO$) 2.76-3.18 (4H,m,2xCH_2), 3.90(3H,s,OCH_3), 6.52(1H,d,J=2Hz, furan β-H), 6.78(1H,s,C_6-H), 7.58(1H,s,C_9-H), 7.71(1H,d,J=2Hz, furan α-H).

^{13}C nmr — δ($(C^2H_3)_2SO$) 26.2, 35.4, 56.3, 114.0, 114.4, 117.8, 129.9,136.0, 136.8, 147.3, 147.4, 151.3, 178.7, 206.3.

ms m/e 245($\underline{M}^+$+1,16), 244($\underline{M}^+$,100), 215(18), 20(20), 115(18), 51(16).

4,5-Dihydro-8-hydroxy-7-methoxy-4H-benzo[5,6]cyclohepta[1,2-b]furan-10-one (600), orange plates, m.p. 141-3°C.

ir ν_{max}(Nujol mull) 3,500cm.$^{-1}$

^{1}H nmr $\delta((C^2H_3)_2SO)$, 2.95(4H,m,2xCH_2), 3.98(3H,s,OCH_3), 6.51(1H,d,J=2Hz, furan β-H), 6.90(1H,s,C_6-H), 7.70(1H,s,C_9-H), 7.71(1H,d,J=2Hz, furan α-H).

7.6.56. 2,3-Dimethyl-γ-oxo-benzenepentanoic acid, methyl ester (614)

A solution of dry 3-oxo-butanoic acid, methyl ester (613) (8.3g; 0.07mol) in anhydrous tetrahydrofuran (20ml) was added dropwise to a suspension of sodium hydride (50% dispersion in oil, 3.36g;0.07mol) in dry tetrahydrofuran (200ml) at -5°C.[401] The mixture was stirred for 15 min. at 0°C, n-butyl lithium (1.6M solution in hexane, 43ml, 0.069mol) added dropwise and the yellow/orange solution was stirred for 15 min at 0°C. A solution of 1-bromomethyl-2,3-dimethyl-benzene (619)(14.3g;0.07mol) in tetrahydrofuran (30ml) was added to the solution over 5 min. The resulting pale yellow suspension was stirred at 0°C for 15 min and at room temperature for 5 min. To the mixture a solution of concentrated hydrochloric acid (14ml) in water (35ml) was added and the suspension stirred for 2 min. The aqueous phase was separated and extracted with ether (2x25ml). The combined organic extracts were washed with saturated sodium chloride solution (2x250ml), dried over magnesium sulphate and evaporated to give 2,3-dimethyl-γ-oxo-benzenepentanoic acid, methyl ester (614) as a pale yellow oil (15.1g;92%). An analytical sample was prepared by distillation of 1.0g *in vacuo* to give a colourless oil (0.75g) b.p. 152°C/0.1mm Hg which was chromatographed by flash colum chromatography. Eluting with ether/petroleum ether (40-60°C)(1:4) gave a colourless oil (0.52g).

Analysis — Found : C, 72.1; H, 7.6.
$C_{14}H_{18}O_3$ requires : C, 71.8; H, 7.7%.

uv — λ_{max} nm (EtOH)(ε) 214(10,600), 248(1,550)

ir — ν_{max}(liquid film) 1,722, 1,752cm.$^{-1}$

^{1}H nmr — δ(C^2HCl_3) 2.20 and 2.28(6H,2xAr-CH_3), 2.26-3.10(4H, m,2xCH_2), 2.44(2H,s,$CH_2CO_2CH_3$), 3.72(3H,s,CO_2CH_3), 7.05(3H,brs,3 x aromatic-H).

ms — m/e 234(M^+, 0.3%), 216(29), 142(47), 133(32), 119(100), 118(48), 117(23), 91(24).

7.6.57. 2-[2-(2,3-Dimethylphenyl)ethyl]-3-furancarboxylic acid methyl ester (614)

A mixture of 2,3-dimethyl-γ-oxo-benzenepentanoic acid, methyl ester (614) (14.1g;0.06mol), pyridine (4.8ml; 4.7g;0.06mol) and chloroacetaldehyde (50-55% solution in water, 9.5ml) was stirred at room temperature for 16h. The mixture was poured into saturated sodium chloride solution (200ml) and extracted with ether (3x100ml). The organic extracts were washed with saturated sodium chloride solution (2x50ml), dried over magnesium sulphate and evaporated to give a pale yellow oil (18.1g) which was distilled *in vacuo* to yield 2-[2-(2,3-dimethylphenyl)ethyl]-3-furancarboxylic acid, methyl ester (615) as a colourless oil (11.5g;74%) b.p. 195°C/0.1mm Hg. An analytical sample was prepared by crystallisation from diisopropyl ether to give colourless microcrystals (425mg), m.p. 81-3°C.

Analysis — Found : C, 74.1; H, 7.0.
$C_{16}H_{18}O_3$ requires : C, 74.4; H, 7.0%.

uv λ_{max}nm (EtOH)(ε) 214(9,700), 247(6,200).

iv ν_{max} (liquid film) 1712 cm.$^{-1}$

^{1}H nmr δ($C^{2}HCl_3$) 2.26 and 2.29(6H,2xs,2xAr-CH_3), 2.84-3.38 (4H,m,2xCH_2), 3.80(3H,s,CO_2CH_3), 6.64(1H,d,J=2Hz,furan β-H), 7.01(3H,s,3 x aromatic1H), 7.26(1H,d,J=2Hz, furan α-H).

^{13}C nmr δ($C^{2}HCl_3$) 164.3, 162.2, 140.7, 138.9, 136.9, 128.2, 127.1, 125.5, 113.3, 110.8, 51.2, 32.6, 28.9, 20.7, 14.8.

ms m/e 259(M^{+}+1,2), 258(M^{+},11%), 226(10), 139(5), 120(10), 119(100),

7.6.58. 2-[2-(2,3-Dimethylphenyl)ethyl]-3-furancarboxylic acid (616)

Potassium hydroxide solution (10%,50ml) and ethanol (5ml) were added to a suspension of 2-[2-(2,3-dimethylphenyl)ethyl-3-furan-carboxylic acid, methyl ester (615) (10.5g;0.041mol) in water (20ml). The mixture was boiled under reflux for 1h, cooled to room temperature and allowed to stand for 16h. The solution was acidified with 2M hydrochloric acid and filtered to give a yellow powder (8.1g). The powder was crystallised from ethanol/water to yield (616) as a light tan powder (5.5g;55%) m.p. 152-4°C (dec).

Analysis Found : C,73.5; H,6.8
$C_{15}H_{16}O_3$ requires : C,73.8; H,6.6%

uv λ_{max}nm (EtOH)(ε) 215(14,900), 202(6,800),

ir ν_{max} (Nujol) 1684cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 2.27 and 2.29(6H,2xs,2xAr-CH_3), 3.00(2H,m, CH_2), 3.25(2H,m,CH_2), 6.70(1H,d,J=2Hz, furan β-H), 7.01(3H,s,3 x aromatic-H), 7.30(1H,d,J=2Hz, furan α-H).

ms m/e 244(M^+,7%), 226(3), 120(8), 119(100), 91(8).

7.6.59. 9,10-Dihydro-7,8-dimethyl-4H-benzo[4,5]-cyclohepta[1,2-b] furan-4-one (617)

A suspension of 2-[2-(2,3-dimethylphenyl)ethyl]-3-furan-carboxylic acid (616) (4.21g;0.017mol) in benzene (50ml) was treated with thionyl chloride (1.4ml;1.63g;0.019mol) and the mixture boiled under reflux for 1.5h. The solvent was removed *in vacuo* to give an orange/brown paste which was taken up in nitrobenzene (200ml) and aluminium chloride (4.6g,0.034mol) added. The resulting mixture was stirred at 95-90°C for 16h, poured into water (300ml) and extracted with ether (3x100ml). The organic extracts were washed with saturated sodium bicarbonate solution (2x50ml) and saturated sodium chloride (1x100ml). The extracts were dried over potassium carbonate and evaporated to give a black oil. The oil was dissolved in ether (200ml) and passed through a silica gel (Kieselgel GF254 (Type 60)) column (1"x4" dia.) and evaporated to give a brown oil. This oil was concentrated at 0.1mm Hg to ca. 5ml and separated by flash column chromatography. Elution with ether/petroleum ether (40-60°C)(1:4) gave 9,10-dihydro-7,8-dimethyl-4H-benzo[4,5]cyclohepta[1,2-b]furan-4-one (617) as colourless microcrystals (1.00g:26%) m.p. 79-81°C.

Analysis Found : C,79.6; H,6.3
$C_{15}H_{14}O_2$ requires : C,79.7; H,6.2%

uv λ_{max}nm (EtOH)(ε) 215(19,400), 226(14,500,sh), 267(9,900), 395(7,800).

ir ν_{max} (Nujol) 1638cm.$^{-1}$

^{1}H nmr $\delta(C^{2}HCl_3)$ 2.31 and 2.34(6H,2xs,Ar-CH_3), 2.92-3.30 (4H,m,2xCH_2), 6.83(1H,d,J=2Hz, furan β-H), 7.10 (1H,d,J=8Hz,C_6-H), 7.26(1H,d,J=2Hz, furan α-H), 7.54(1H,d,J=8Hz,C_5-H).

^{13}C nmr $\delta(C^{2}HCl_3)$ 15.8, 21.6, 27.2, 110.5, 123.8, 126.8, 128.6, 133.9, 136.4, 138.8, 141.2, 163.4, 188.7.

ms m/e 226(M^+,100), 225(45), 211(57), 183(47), 169(59), 155(47), 115(51), 91(41).

7.6.60. 1-Bromomethyl-2,3-dimethyl-benzene (619)

A solution of phosphorus tribromide (5.6ml;16.1g;0.060mol) in dry ether (30ml) was added to a solution of 2,3-dimethylbenzenemethanol (574)(17.1g;0.126mol) in dry ether (30ml) at 0°C. The mixture was stirred at room temperature for 16h and poured into water (100ml). The resulting suspension was neutralised with sodium hydrogen carbonate and extracted with ether (3x30ml). The organic extracts were dried over sodium sulphate and evaporated to give an orange oil which was distilled *in vacuo* to give 1-bromomethyl-2,3-dimethyl-benzene (619) as a light orange oil (14.3;57%) b.p. 115°C/13mm Hg (Lit.[503] b.p.112°C/12mm Hg) which crystallised on standing m.p. 43-5°C.

^{1}H nmr $\delta(C^{2}HCl_3)$ 2.30(6H,s,2xCH_3), 4.54(2H,s,CH_2), 7.13 (3H,s,3 x aromatic-H).

ms m/e 200(M^+,^{81}Br,5%), 198(M^+,^{79}Br,5%), 120(24), 119(100), 105(11), 91(22), 72(13).

7.6.61. γ-Oxo-benzenepentanoic acid, methyl ester (620a) [65248-41-1]

A solution of dry 3-oxo-butanoic acid, methyl ester (613) (11.6g;0.1mol) in anhydrous tetrahydrofuran (10ml) was added dropwise to a stirred suspension of sodium hydride (50% dispension in oil, 4.8g;0.1mol) in dry tetrahydrofuran (250ml) at 0°C.[401] The mixture was stirred at 0°C for 15 min, n-butyl lithium (1.6M solution in hexane, 63ml;0.1mol) added dropwise and the yellow/orange solution stirred at 0°C for 15 min. A solution of benzyl bromide (622a) (12.6g; 0.1mol) in tetrahydrofuran (10ml) was added to the solution, the mixture stirred at 0°C for 15 min at room temperature for 5 min. A solution of concentrated hydrochloric acid (40ml) in water (30ml) was added to the mixture and the suspension stirred for 2 min. The aqueous phase was separated and extracted with ether (3x100ml). The combined organic extracts were washed with saturated sodium chloride solution (2x250ml), dried over magnesium sulphate and evaporated to give a yellow oil. The oil was distilled *in vacuo* to give γ-oxo-benzenepentanoic acid, methyl ester (620a) as a colourless oil (15.26g;74%) b.p. 121°C/0.1mm Hg (Lit.[401] 102-3°C/0.4mm Hg).

7.6.62. 3-Bromo-γ-oxo-benzenepentanoic acid, methyl ester (620b)

3-Bromo-γ-oxo-benzenepentanoic acid, methyl ester (620b) was prepared by the method outlined for (620a).[401] Treatment of a solution of the dianion of 3-oxo-butanoic acid methyl ester (from 3-oxo-butanoic acid, methyl ester (613) (2.3g;0.02mol), sodium hydride (0.48g;0.02mol) and n-butyl lithium (12.5ml;0.02mol)) in tetrahydrofuran (30ml) with 1-bromo-3-bromomethyl-benzene (622b)(5.0g;0.02mol) gave a pale yellow oil. The oil was distilled *in vacuo* to give (620b) as a colourless liquid (1.6g;28%) b.p. 163°C/0.1mm Hg.

7.6.63. 4-Bromo-γ-oxo-benzenepentanoic acid, methyl ester (620c)

4-Bromo-γ-oxo-benzenepentanoic acid, methyl ester (620c) was prepared by the method outlined above for (620a).[401] Treatment of a solution of the dianion of 3-oxo-butanoic acid methyl ester (from 3-oxo-butanoic acid, methyl ester (613)(2.3g;0.02mol), sodium hydride (0.48g;0.02mol) and n-butyl lithium (12.5ml;0.02mol)) in tetrahydrofuran (30ml) with 1-bromo-4-bromomethyl-benzene (622c) (5.0g;0.02mol) gave (620c) as a pale yellow oil (4.2g;73%) which was used undistilled to prepare (621c).

7.6.64. 2-(2-Phenylethyl)-3-furancarboxylic acid, methyl ester (621a)

A mixture of γ-oxo-benzenepentanoic acid, methyl ester (620a) (2.06g;0.01mol), pyridine (5.0ml) and chloroacetaldehyde (50-55% solution in water, 3.7ml) was stirred at room temperature for 16h. The mixture was poured into water (50ml) and extracted with ether (2x20ml). The organic extracts were washed with saturated sodium chloride solution (1x50ml), dried over potassium carbonate and evaporated to give a mauve oil which was distilled *in vacuo* to give 2-(2-phenylethyl)-3-furancarboxylic acid, methyl ester[379] (621a) as an amber oil (1.22g; 53%), b.p. 120-2°C/0.1mm Hg.

ir ν_{max} (liquid film) 1722 $cm.^{-1}$

^1H nmr $\delta(C^2HCl_3)$ 3.12(4H,m,2xCH_2), 3.68(3H,s,CO_2CH_3), 6.64(1H,d,J=2Hz, furan β-H), 7.21(6H,brs,5 x aromatic-H + furan α-H).

ms m/e 230(M^+,12%), 198(18), 139(69), 109(17), 91(100), 65(16).

7.6.65. 2-[2-(3-Bromophenyl)ethyl]-3-furancarboxylic acid, methyl ester (621b)

2-[2-(3-Bromophenyl)ethyl]-3-furancarboxylic acid, methyl ester (621b) was prepared by the method outlined above for (621a). Treatment of (620b) (1.6g;5.6mmol) with chloroacetaldehyde (3ml) and pyridine (4ml) gave (621b) as a pale yellow oil (1.53g;90%) b.p. 168°C/0.1mm Hg.

ir ν_{max} (liquid film) 1720cm.$^{-1}$

^{1}H nmr $\delta(C^2CH_1{}_3)$ 3.14(4H,m,2xCH_2), 3.71(3H,s,CO_2CH_3), 6.68(1H,d,J=2Hz, furan β-H), 6.97-7.27(5H,m, 4 x aromatic-H and furan α-H).

7.6.66. 2-[2-(4-Bromophenyl)ethyl]-3-furancarboxylic acid, methyl ester (621c)

2-[2-(4-Bromophenyl)ethyl]-3-furancarboxylic acid, methyl ester (621c) was prepared by the method outlined above for (621a). A mixture of 4-bromo-γ-oxo-benzene-pentanoic acid, methyl ester (620c) (4.2g;0.015mol), pyridine (5ml) and chloroacetaldehyde (50-55% solution in water)(4ml) was stirred at room temperature for 40h. The resulting mixture was poured into saturated sodium chloride solution (25ml) and extracted with ether (3x25ml). The combined organic extracts were washed with saturated sodium chloride solution (1x25ml), dried over magnesium sulphate and evaporated to give a brown oil (3.1g). The oil was distilled *in vacuo* to give a pale yellow oil (2.61g), b.p. 173°C/0.1mm Hg, which was purified by flash column chromatography,[480] Elution with ether/petroleum ether (40-60°C)(3:17) gave (621c) as a colourless oil (2.01g;44%).

ir ν_{max} (liquid film) 1718cm.$^{-1}$

^{1}H nmr δ(CCl_4) 3.07(4H,m,2xCH_2), 3.70(3H,s,CO_2CH_3), 6.53(1H,d,J=2Hz, furan β-H), 7.02(2H,d,J=12Hz, 2 x aromatic-H), 7.17(1H,d,J=2Hz, furan α-H), 7.44(2H,d, J=12Hz,2 x aromatic-H).

ms m/e 310(M^+,^{81}Br,6%), 308(M^+, ^{79}Br,7%), 278(5), 276(5), 171(44), 169(43), 139(100), 90(18).

7.6.67. 2-(2-Phenylethyl)-3-furancarboxylic acid (623)[60300-16-5]

Potassium hydroxide solution (10%,50ml) was added to a suspension of 2-(2-phenylethyl)-3-furancarboxylic acid, methyl ester (621a) (7.71g;0.034mol) in ethanol (5ml). The mixture was boiled under reflux for 1h, cooled to room temperature and acidified with 2M hydrochloric acid. The tan solid which separated was crystallised from ethanol/ water to yield 2-(2-phenylethyl)-3-furancarboxylic acid (623) (4.60g; 63%), m.p. 111-3°C (Lit.[379] 111°C).

ir ν_{max}(Nujol mull) 1682 cm.$^{-1}$

^{1}H nmr δ(C^2HCl_3)2.86-3.44(4H,m,2xCH_2), 6.69(1H,d,J=2Hz, furan β-H), 7.25(6H,brs,5 x aromatic-H and furan α-H), 10.20(1H,brs,CO_2H).

^{13}C nmr δ(C^2HCl_3) 29.8, 34.1, 111.0, 113.0, 126.3, 128.5, 140.8, 140.9, 163.7, 169.9.

ms m/e 216(M^+,7), 198(7), 125(19), 91(100), 65(11).

7.6.68. (E,E)-7,11-Dimethyl-3-oxo-6,10-dodecadienoic acid, methyl ester (624a) [56523-17-2]

3-Oxo-butanoic acid, methyl ester (613)(11.6g;0.1mol) was added dropwise to a stirred suspsension of sodium hydride (50% dispersion in oil;4.8g;0.1mol) in anhydrous tetrahydrofuran (120ml) at 0°C,[401,504] The mixture was stirred at room temperature for 15 min, cooled to 0°C to give a clear solution and n-butyl lithium (1.6M solution in hexane; 62.5ml;0.1mol) added dropwise. The yellow/orange solution which resulted was stirred for 15 min at 0°C and a solution of (E,E)-1-bromo-3.7-dimethyl-2.6-octadiene (626a)(20.6g;0.1mol) in anhydrous tetrahydrofuran (30ml) added dropwise to afford a pale yellow suspension. The suspension was stirred at 0°C for 15 min, at room temperature for 5 min and then cooled to 0°C. An ice cold solution of concentrated hydrochloric acid (20ml) in water (50ml) was added to the suspension and the resulting mixture stirred for 2 min. The aqueous phase was separated and extracted with ether (3x50ml). The combined organic extracts were washed with saturated sodium chloride solution (2x250ml), dried over magnesium sulphate and evaporated to yield (E,E)-7,11-dimethyl-3-oxo-6,10-dodecadienoic acid, methyl ester (624a) as a pale yellow oil (24.8g;98%). An analytical sample was prepared by distillation of 1g *in vacuo* to give a pale yellow oil (o.71g) b.p. 110°C/0.1mm Hg (Lit.[505] 140-4°C/0.6mm Hg) which was chromatographed by flash column chromatogaphy.[480] Elution with ether/petroleum ether (40-60°C)(15:85) gave (624a) as a colourless oil (0.62g).

ir ν_{max} (liquid film) 1720cm.$^{-1}$, 1750cm.$^{-1}$

^{1}H nmr $\delta(CCl_4)$ 1.48-1.79(9H,m,3x CH_3), 1.85-2.77(8H,m, 4xCH_2), 3.30(2H,s,$COCH_2CO_2CH_3$), 3.71(3H,s,CO_2CH_3), 4.90(brs from enol form), 5.04(2H,m,2 x olefinic-H).

ms m/e 252(M^+,2), 109(69), 93(26), 81(51), 69(100), 41(59).

7.6.69. 3-Oxo-6-heptenoic acid, methyl ester (624b)[30414-57-4]

3-Oxo-6-heptenoic acid, methyl ester (624b)[30414-5714] was prepared by the method of Weiler.[401] Treatment of 3-oxo-butanoic acid, methyl ester (613)(2.3g;0.02mol) with 1-bromo-2-propene (626b) (2.4g;0.02mol) gave a colourless oil. The oil was distilled *in vacuo* to give 3-oxo-6-heptenoic acid, methyl ester (624b) as a colourless liquid (1.90g;61%) b.p. 105°C/13mm Hg (Lit.[401] 99-100°C/15mm Hg).

7.6.70. (E)-2-(4,8-Dimethyl-3,7-nonadienyl)-3-furancarboxylic acid, methyl ester (625a)

A mixture of (E)-7,11-dimethyl-3-oxo-dodecadienoic acid, methyl ester (624a)(27.5g;0.11mol), pyridine (69ml;70g;0.9mol) and chloroacetaldehyde (50-55% solution in water, 20ml) was stirred at room temperature for 40h and poured into a mixture of ether (100ml) and water (200ml). The aqueous phase was separated and extracted with ether (3x50ml). The combined extracts were washed with sodium bisulphite solution (10%,1x25ml), saturated sodium chloride solution (2x50ml), dried over magnesium sulphate and evaporated to give a mixture as a brown oil (21g). The mixture was separated by flash column chromatography. Elution with ether/petroleum ether (40-60°C) afforded (E)-2-(4,8-dimethyl-3,7-nonadienyl)-3-furancarboxylic acid, methyl ester (625a) as an unstable pale yellow oil (4.56g;15%).

ir ν_{max} (liquid film) 1712cm.$^{-1}$

^{1}H nmr $\delta(CCl_4)$1.42-1.74(9H,m,3xCH_3), 1.94(4H,m,-C(H)=C(CH_3)CH_2CH_2C(H)=C(CH_3)$_2$), 2.32(2H,m,furan-CH_2-CH_2-) 2.98(2H,m,furan-CH_2-CH_2), 3.76(3H,s,CO_2CH_3), 5.08(2H,m,2 x olefinic-H), 6.51(1H,d,J=2Hz, furan β-H) 7.16(1H,d,J=2Hz, furan α-H).

ms m/e 276(M^+,1), 233(17), 139(29), 81(30), 69(100),41(31).

7.6.71. 2-(3-Butenyl)-furancarboxylic acid, methyl ester (625b)

A mixture of 3-oxo-6-heptenoic acid, methyl ester (624b)(1.9g; 0.012mol), pyridine (5ml) and chloroacetaldehyde (50-55% solution in water, 3.7ml) was stirred at room temperature for 16h. The mixture was poured into water (50ml) and extracted with ether (3x25ml). The extracts were washed with saturated sodium chloride solution (2x50ml), dried over magnesium sulphate and evaporated to give a mauve oil which was distilled *in vacuo* to afford a colourless oil (2.1g) b.p. 105°C/15mm Hg. The oil was chromatographed by flash column chromatography,[480] elution with ether/petroleum ether (40-60°C)(15:85) gave 2-(3-butenyl)-furancarboxylic acid, methyl ester (625b) as a colourless oil (1.10g;50%).

ir ν_{max} (liquid film) 1711cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 2.46(2H,m,$C\underline{H}_2CH=CH_2$), 3.10(2H,m,$C\underline{H}_2CH_2CH=CH_2$) 3.80(3H,s,$CO_2C\underline{H}_3$), 4.82-5.23(2H,m,$CH_2CH=C\underline{H}_2$), 5.56-6.12(1H,m,$C\underline{H}=CH_2$), 6.64(1H,d,J=2Hz, furan β-$\underline{H}$), 7.24(1H,d,J=2Hz, furan α-$\underline{H}$).

ms m/e 180($\underline{M}^+$,16), 148(10), 139(100), 109(28), 91(8), 85(7).

7.6.72. (E)-2-(4,8-Dimethyl-3,7-nonadienyl)-3-furanmethanol (627)

A solution of (E)-2-(4,8-dimethyl-3,7-nonadienyl)-3-furancarboxylic acid (625a)(3.50g;12.7mmol) in ether (50ml) was added dropwise to a stirred solution of lithium aluminium hydride (0.5g; 12.8mmol) in ether (50ml), and the mixture stirred at room temperature for 4h. Celite (2g) was added to the mixture and the suspension stirred for 5 min. Water (1ml) was added to the resulting suspension, the mixture stirred for 5 min and magnesium sulphate added. The

suspension was filtered and evaporated to give a colourless oil (3.14g; 98%) which was chromatographed by flash column chromatography.[480] Elution with dichloromethane gave (E)-2-(4,8-dimethyl-3,7-nonadienyl)-3-furanmethanol (627) as a colourless oil (2.05g;65%).

ir ν_{max} (liquid film) 3,320cm.$^{-1}$

^{1}H nmr $\delta(C^{2}HCl_3)$ 1.48-1.72(9H,m,3xCH_3), 1.88(1H,brs,CH_2OH), 2.00(4H,m,-C(H)=C(CH_3)-CH_2CH_2-C(H)=), 2.35(2H,m,furan-CH_2-CH_2-), 2.66(2H,m,furan-CH_2-CH_2-), 4.41(2H,s,CH_2-OH), 5.12(2H,m,2 x olefinic-H), 6.33(1H,d,J=2Hz,furan β-H), 7.25(1H,d,J=2Hz,furan α-H).

ms m/e 248(M^+,1), 124(23), 111(53), 81(30), 69(100), 41(26).

7.6.73. (E)-2-(4,8-Dimethyl-3,7-nonadienyl)-3-methyl-furan (628).

4-Toluenesulphonyl chloride (0.77g;4.0mmol) was added to a solution of (E)-2-(4,8-dimethyl-3,7-nonadienyl-3-furanmethanol (627) (1.0g;4.0mmol) in pyridine (2.5ml) at 0°C and the solution stirred at 0°C for 4h. Sulphuric acid (2N,2.5ml) was added to the mixture and the resulting solution extracted with ether (3x10ml). The extracts were dried over magnesium sulphate and evaporated to give a pale yellow oil (1.63g). The oil was dissolved in tetrahydrofuran (20ml) and lithium aluminium hydride (0.3g;0.76mmol) added. The mixture was stirred at room temperature for 3 days, water (2ml) was added followed by sulphuric acid (2N,3ml). The aqueous phase was separated and extracted with ether (4x20ml). The combined extracts were washed with saturated sodium chloride solution (2x10ml), dried over magnesium sulphate and evaporated to give an orange oil (1.7g). The oil was dissolved in ether (5ml) and passed down a short plug of silica gel, MN-Kieselgel 60(230-400 mesh), and then chromatographed by flash column chromatography.[480] Elution with petroleum ether (40-60°C) gave (628) as a colourless oil (175mg;19%).

^{1}H nmr $\delta(C^2HCl_3)$ 1.54-1,78 (9H,m,3xCH_3), 1.96(3H,s,Ar-CH_3),
2.00 (4H,m,$CH_2C(H)=C(CH_3)CH_2CH_2C(H)=C(CH_3)_2$),
2.34(2H,m,$CH_2C(H)=C(CH_3)CH_2CH_2C(H)=$),
2.60(2H,m,furan-$CH_2CH_2C(H)=$)
5.12(2H,m,2 x olefinic-H), 6.14(1H,d,J=2Hz, furan β-H),
7.20(1H,d,J=2Hz, furan α-H).

ms m/e 232(M^+,1%), 96(100), 81(15), 69(49), 55(18), 41(30).

7.6.74. Bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid, dimethyl ester (645)[947-57-9].

A mixture of 1,3-cyclopentadiene (644)(65g;0.98mol), butyndioic acid, dimethyl ester (591)(127g;0.89mol) and ether (500ml) was heated under reflux for 1.75h. The solvent was removed *in vacuo* to yield (645) as a colourless liquid (176.2g;95%) b.p. 134-8°C/13mm Hg (lit.[414] 134-5°C/10mm Hg).

7.6.75. (exo,exo)-5,6-Dihydroxy-bicyclo[2.2.1]hepta-2-ene-2,3-dicarboxylic acid, dimethyl ester (646)[72603-07-7].

(exo, exo)-5,6-Dihydroxy-bicyclo[2.2.1]hepta-2-ene-2,3-dicarboxylic acid, dimethyl ester (646)[72603-07-7] was prepared by the method of Danishefsky.[416] Treatment of a mixture of N-methyl morpholine-N-oxide (100g;0.74mol) (prepared by the method of van Rheenan[415]),osmium tetroxide (1g), t-butyl alcohol(1,500ml), water (300ml) and tetrahydrofuran with a solution of bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid, dimethyl ester (645)(105g;0.72mol) in tetrahydrofuran (100ml) gave (646) as a light brown oil (151.3g;87%).

7.6.76. (3aα,4β,7β,7aα)-3a,4,7,7a-tetrahydro-2,2-dimethyl-4,7-methano-1,3-benzodioxole-5,6-dicarboxylic acid, dimethyl ester (647)[72627-49-7].

2,2-Dimethoxy-propane (102ml;86g;0.82mol) was added dropwise

(over 1h) to a solution of (exo, exo)-5,6-dihydroxy-bicyclo[2.2.1]hepta-2-ene-2,3-dicarboxylic acid, dimethyl ester (646)(148g;0.61mol) in methylene chloride (200ml), containing 4-toluenesulphonic acid (200mg), at 0°C. The mixture was stirred at room temperature for 1h and the solvent removed *in vacuo* to give (3aα,4β,7β,7aα)-3a,4,7,7a-tetrahydro-2,2-dimethyl-4,7-methano-1,3-benzodioxole-5,6-dicarboxylic acid, dimethyl ester [416] (647) as a light brown oil (171g;99%).

7.6.77. (3aα,4β,7β,7aα)-3a,4,7,7a-Tetrahydro-2,2-dimethyl-4,7-methano-1,3-benzodioxole-5,6-dicarboxylic acid (648).

A suspension of (647)(102g;0.36mol) in aqueous potassium hydroxide solution (62.7g;1.1mol in 2,000ml) was stirred at room temperature for 18h. The orange solution which resulted was acidified to pH=2 with concentrated hydrochloric acid and extracted with ethyl acetate (8x500ml). Evaporation of the sodium sulphate dried extracts gave (648) as light tan crystals (81.0g;88%) m.p. 229-231°C (Lit.[416] 230-231°C).

7.6.78. (3aα,4β,8β,8aα)-3a,4,8,8a-Tetrahydro-2,2-dimethyl-4,8-methanofuro[3,4-f]-1,3-benzodioxole-5,7-dione(649)[68695-15-8].

Ethoxyacetylene (prepared by the method of Jones[506]) (9.5g; 0.14mol) was added to a suspension of (3aα,4β,7β,7aα)-3a,4,7,7a-tetrahydro-2,2-dimethyl-4,7-methano-1,3-benzodioxole-5,6-dicarboxylic acid (648)(10.0g;0.039mol) in methylene chloride (500ml).[413] The resulting mixture was boiled under reflux for 16h, charcoal was then added and the mixture boiled under reflux for a further 2h. The suspension was cooled to room temperature and filtered through HYFLO. The solvent was evaporated to give a brown paste which was triturated with ether:petroleum ether (1:20) to give (649) as white crystals (5.6g;60%), m.p. 158-160°(Lit.[416] 159-160°C).

^{13}C nmr $\delta(C^2HCl_3)$ 24.5, 25.9, 44.5, 48.2, 79.8, 116.1, 161.2.

7.6.79. 2-(Trimethylsilyl)oxy-1,3-butadiene (650a)[38053-91-7].

2-(Trimethylsilyl)oxy-1,3-butadiene(650a)[38053-91-7] was prepared by the method outlined below for (650b).[416] Treatment of 1-buten-3-one (25g;0.36mol) with zinc chloride (200mg), triethylamine (55.7ml;40.5g;0.4mol) and trimethylchlorosilane (51ml;43.4g;0.4mol) gave a pale yellow oil. The oil was distilled *in vacuo* to give (650a) as a colourless oil (21.2g;42%) b.p. 60-4°C/50mm Hg (Lit.[417] 50-3°C/ 50mm Hg).

7.6.80. 2-(Trimethylsilyl)oxy-1,3-pentadiene (650b).

A suspension of anhydrous zinc chloride (200mg) in dry triethylamine (28.5ml;21g;0.21mol) was stirred for 1h to give a fine suspension.[416] To the suspension 3-penten-2-one (657)(15.0g;0.18mol) was added and the mixture stirred for 10min at room temperature to give an orange suspension. To the suspension a solution of trimethylchlorosilane (22.8ml;19.5g;0.18mol) in benzene (25ml) was added and the mixture stirred at 40°C for 16h. The suspension was cooled to room temperature, poured into dry ether (400ml) and filtered through celite. The filtrate was distilled to give (650b) as a colourless liquid (12g) b.p. 68-70°C/ 28mm Hg containing ≈20% benzene by ^{1}H nmr.

^{1}H nmr $\delta(CCl_4)$ 0.12(9H,s,Si($\underline{CH}_3$)$_3$), 1.67(3H,brd,$\underline{CH}_3$), 4.04(2H,brs,$\underline{CH}_2$=C(OTMS)-), 5.78(2H,brs,$CH_3\underline{CH}$=$\underline{CH}$-).

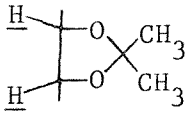
7.6.81. (3aα, 4β, 4aα, 8aα, 9β, 9aα)-(±)-3a,4,5,8,9,9a-Hexahydro-2,2-dimethyl-7-[(trimethylsilyl)oxy]-4,9-methano-4a,8a-(methanoxymethano)naphtho[2,3-d]-1,3-dioxole-11,13-dione (651a).

A solution of (649)(0.5g;2.1mmol) and 2-(trimethylsilyl)oxy-1, 3-butadiene (0.5g;3.5mmol) in toluene (20ml) was boiled under reflux for 16h. The solvent was removed *in vacuo* to give a pale yellow oil. The oil was induced to crystallised under ether/petane (1:5) and

filtered under nitrogen to give (649) as a tan solid (160mg). The filtrate was evaporated under nitrogen to give (651a) as a white microcrystalline solid (310mg;57%), m.p. 132-4°C.

ir ν_{max} (Nujol mull) 1782cm.$^{-1}$, 1844cm.$^{-1}$

^{1}H nmr $\delta(C^{2}HCl_3)$0.17(9H,s,Si($\underline{CH}_3$)$_3$), 1.28 and 1.45(6H,2xs, 2x$\underline{CH}_3$), 168-3.00(8H,m,3x$\underline{CH}_2$+2x$\underline{CH}$), 4.22(2H,brs,



, 4.70-4.91(1H,m, TMSO>=<$\underline{H}$).

^{13}C nmr $\delta(C^{2}HCl_3)$24.0, 25.2, 29.9, 32.9, 35.6, 50.2, 50.6, 56.6, 57.2, 78.5, 99.1, 110.6, 151.1, 173.9, 174.4.

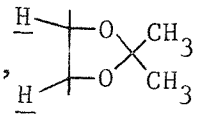
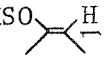
ms m/e 378($\underline{M}^{+}$,26%), 364(21), 363(68), 75(31), 73(100), 43(42).

7.6.82. (3aα,4β,4aα,5α,8aα,9β,9aα)-(±)-3a,4,5,8,9,9a-Hexahydro-2,2,5-trimethyl-7-[(trimethylsilyl)oxy]-4,9-methano-4a,8a-(methanoxymethano)naphtho[2,3-d]-1,3-dioxole-11,13-dione (651b).

A solution of (649)(3.7g;156mmol) and 2-(trimethylsilyl)oxy-1,3-pentadiene (7.5g;48mmol) in toluene (250ml) was boiled under reflux for 2 days. The solvent was removed *in vacuo* to give a light tan solid which was triturated with petroleum ether (60-80°C) gave (651b) as a light tan cystalline powder (5.23g;87%) m.p. 127-8°C.

Analysis Found : C,61.50;H,7.13,
$C_{20}H_{28}SiO_6$ requires : C,61.22;H,7.14%

ir ν_{max} (Nujol mull) 1770cm.$^{-1}$, 1832cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.28 and 1.48 (6H,2xs,2x$\underline{CH}_3$), 1.39(3H,d of d, J_1=7Hz,J_2=1Hz,$>$CH$\underline{CH}_3$), 1.62-3.00(7H,m,2x$\underline{CH}_2$+3x$\underline{CH}$), 4.25(2H,brs, ), 4.58(1H,brs, ),

^{13}C nmr $\delta(C^2HCl_3)$0.5, 16.3, 24.0, 25.2, 32.8, 34.5, 36.1, 48.1, 50.1, 58.7, 60.3, 78.3, 78.8, 105·5, 110.5, 150.5, 173.8.

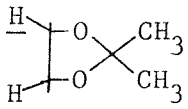
ms m/e 392($\underline{M}^+$,23), 377(82), 141(56), 75(39), 73(100), 43(55).

7.6.83. (3aα,4β,4aα,5α,5β,8aα,9β,9aα)-(±)-3a,4,5,8,9,9a-Hexahydro-2,2,5-trimethyl-5-[(trimethylsilyl)-oxy]-4,9-methano-4a,8a-(methanoxymethano)naphtho-[2,3-d]-1,3-dioxole-11,13-dione (654) and (3aα,4β,4aα,5α,8aα,9β,9aα)-(±)-3a,4,5,6,7,8,9,9a-octahydro-2,2,5-trimethyl-4,9-methano-4a,8a-(methanoxymethano)naphtho-[2,3-d]-1,3-dioxole-7,11,13-trione (653).

A mixture of 2-(trimethylsilyl)oxy-1,3-pentadiene (650b) (1.6g; 10mmol), (649)(2.0g;8.5mmol) and toluene (180ml) was boiled under reflux for 72h. The solvent was evaporated to give a solid which was triturated with petroleum ether (40-60°C). Filtration gave a light tan solid (649)(1.1g;55%). The filtrate was evaporated to give a mixture as a light brown gum which was separated by flash column chromatography. Elution with chloroform gave (654) as colourless crystals (578mg;38%), m.p. 121-3°C, and (653) as pale yellow crystals (243mg;20%), m.p. 82-4°C.

(3aα,4β,4aα,5β,8aα,9β,9aα)-(±)-3a,4,5,8,9,9a-Hexahydro-2,2,5-trimethyl-5-[(trimethysilyl)oxy]-4,9-methano-4a,8a-(methanoxymethano)naphtho-[2,3-d]-1,3-dioxole-11,13-dione (654).

ir ν_{max} (Nujol mull) 1725cm.$^{-1}$, 1820cm.$^{-1}$

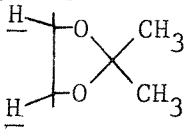
^{1}H nmr — $\delta(C^{2}HCl_3)$ 0.11(9H,s,-Si($\underline{CH}_3$)$_3$), 1.23 and 1.44 (6H,2xs, 2xC_2 $\underline{CH}_3$), 1.62(3H,s,C_5—$\underline{CH}_3$), 1.58-2.92(6H,m,2x$\underline{CH}_2$ and 2x$\underline{CH}$), 4.18(2H,m, ), 5.98(2H,m,2xolefinic-$\underline{H}$)

^{13}C nmr — $\delta(C^{2}HCl_3)$ 0.0, 22.3, 23.3, 25.0, 27.1, 31.6, 45.8, 46.5, 53.4, 56.1, 62.6, 69.2, 77.1, 108.7, 129.5, 136.2, 169.6, 172.7.

ms — m/e 392($\underline{M}^{+}$,3%), 377(50), 156(100), 75(29), 73(50), 43(44).

(3aα,4β,4aα,5α,8aα,9β,9aα)-(±)-3a,4,5,6,7,8,9,9a-octahydro-2,2,5-trimethyl-4,9-methano-4a,8a-(methoxymethano)-naphtho-[2,3-d]-1,3-dioxole-7,11,13-trione (653).

ir — ν_{max} (Nujol mull) 1707cm.$^{-1}$, 1770cm.$^{-1}$, 1835cm.$^{-1}$

^{1}H nmr — $\delta(C^{2}HCl_3)$ 1.28 and 1.46 (6H,2xs,2xC_2—$\underline{CH}_3$), 1.37(3H,d,J=6Hz,C_5—$\underline{CH}_3$), 170-2.18 (8H,m,3x$\underline{CH}_2$ and 2x$\underline{CH}$), 4.22(2H,m, ).

^{13}C nmr — $\delta(C^{2}HCl_3)$ 15.9, 24.0, 25.1, 32.0, 32.4, 43.2, 43.9, 47.7, 50.7, 54.0, 57.5, 78.4, 110.6, 170.3, 172.3, 196.6.

ms — m/e 320($\underline{M}^{+}$,0%), 306(16), 305(100), 91(19), 85(18), 83(24), 43(89).

7.6.84. (E)-3-Penten-2-ol (656)[507] [1549-50-2].

A solution of (E)-2-butenal (655)(35g;0.5mol) in ether (30ml) was added to a solution of methylmagnesium bromide (from magnesium (13.5g;0.5mol) and methyl iodide (25.4ml,57.9g;0.5mol)) in ether (250ml). The mixture was stirred at room temperature for 4h and then ammonium chloride solution (100ml) added dropwise. The separated aqueous phase was extracted with ether (3x50ml). The combined organic extracts were washed with saturated sodium chloride solution (2x50ml), dried over magnesium sulphate and evaporated to give a pale yellow mobile liquid which was distilled at atmospheric pressure to give (656) as a pale yellow oil (19.1g;44%) b.p. 120-2°C/751mm Hg (Lit.[488] 64°C/62mm Hg).

7.6.85. (E)-3-Penten-2-one[508] (657) [625-33-2].

A solution of (E)-3-penten-2-ol(19.1;0.22mol) in methylene chloride (10ml) was added to a suspension of pyridinium chlorochromate (68g;0.31mol) in methylene chloride (250ml) and the mixture stirred at room temperature for 3h. The mixture was poured into ether (800ml) and suspension which resulted filtered through TLC silica gel (50g). The filtrate was concentrated to ≈100ml by evaporation and then distilled at atmospheric pressure to give (657) as a colourless liquid (15.0g;80%) b.p. 120-3°C (Lit.[488] 122°C).

7.6.86. Preparation of Complex (678).

1-Bromo-2-methyl-2-pentene (24g;0.17mol) was added to a solution of nickel tetracarbonyl (11ml;0.085mol) in benzene (100ml) and the mixture heated at 40°C for 3h. The resulting red suspension was cooled to room temperature and the solvent removed *in vacuo* to give a brick red solid which triturated with pentane (3x15ml). The suspension was filtered to give (678) as a brick red solid (11g;29%).

7.6.87. Phenyl-oxirane (689) [96-09-3].

A solution of ethenyl-benzene (10.4g;0.1mol) in methylene chloride (100ml) was treated with 3-chloroperbenzoic acid (17.5g; 0.1mol) and the mixture stirred at room temperature for 16h. The resulting mixture was washed with in turn, saturated sodium hydrogen carbonate solution (20ml), sodium thiosulphate solution (10%,20ml), sodium hydrogen carbonate solution (20ml) and saturated sodium chloride solution (1x30ml), dried over magnesium sulphate and evaporated to give a colourless oil. The oil was distilled *in vacuo* to give phenyl-oxirane (689) as a colourless oil (10.95g;91%), b.p. 78-80°C/ 15mm Hg (Lit.[509] 71-3°C/10mm Hg).

7.6.88. *Trans*-2,3-diphenyl-oxirane (721) [1439-07-2].

A solution of (E)-1,1'-(1,2-ethenediyl)*bis*-benzene (533a) (1.15g;4.4mmol) in methylene chloride (30ml) was treated with 3-chloroperbenzoic acid (1.54g;8.9mmol) and the mixture stirred at room temperature for 20h. The suspension which resulted was filtered and the filtrate washed with saturated sodium hydrogen carbonate solution (2x20ml), sodium thiosulphate solution (10%,2x20ml) and saturated sodium chloride solution (2x20ml). The organic phase was dried over potassium carbonate and evaporated to give (721) as colourless crystals (1.06g;85%) m.p. 69-71°C (ethanol)(Lit.[510] 69-70°C)..

7.6.89. Reaction of phenyloxirane (689) with complex (678).

A solution of dry phenyl oxirane (689)(180mg;1.5mmol) in dry N,N-dimethylformamide (8ml) was added to complex(678)(300mg;0.87mmol). The burgundy red solution which resulted was stirred at 60-70°C for 24h and dilute hydrochloric acid (1M,5ml) added. The solution was extracted with ether (3x25ml) and the extracts washed with saturated sodium chloride solution (2x10ml). The organic extracts were dried over potassium carbonate and evaporated to give a mixture as a pale yellow oil (303mg) which was separated by flash column chromatography.

Elution with methylene chloride gave (690)[367] as a pale pink oil (27mg;55%) and (720) as a colourless oil (15mg;30%).

(690)[367]

ir ν_{max} ($CHCl_3$ solution) 3350cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.52(1H,brs,OH), 1.72(3H,s,CH_3), 2.40(2H,m,$CH_2C(CH_3)=CH_2$), 3.10(1H,quintet, CH), 3.75(2H,d of d,J_1=7Hz,J_2=2Hz,CH_2OH), 4.70(2H,m,CH_2=),7.26(5H,brs,5 x aromatic-H).

ms m/e 176 (M^+,1%), 145(100), 121(53), 120(22), 103(35), 91(22).

(720)

ir ν_{max} ($CHCl_3$ solution) 3400cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.76(4H,brs,OH and CH_3), 2.10-2.86(4H,m, 2xCH_2), 3.97(1H,m,CH-OH), 4.86(2H,m,=CH_2) 7.27(5H, brs,5 x aromatic-H).

ms m/e 176(M^+,0), 175(7), 92(100), 107(75), 121(75), 91(50).

7.6.90. Reaction of *trans*-diphenyl oxirane (721) with complex (678): 1,2-diphenyl-4-methyl-4-penten-1-ol (722).

A mixture of *trans*-diphenyl oxirane (721)(550mg;2.8mmol), complex

(678)(616mg;1.38mmol) and dimethylformamide (10ml) was heated at 55-70°C for 95h. The mixture was poured into water (20ml) and extracted with ether (3x20ml). The extracts were washed with saturated sodium chloride solution (2x10ml), dried over potassium carbonate and evaporated to give a mixture as a pale green oil, which was separated by flash column chromatography. Elution with methylene chloride gave (721)(249mg) and (722) as a colourless oil (91mg;23%).

ir ν_{max} ($CHCl_3$ solution) 3,450cm.$^{-1}$

^{1}H nmr δ(C^2HCl_3), 1.59(3H,s,CH_3), 2.08-2.68(3H,m,CH_2 and OH), 3.00-3.34(1H,m,CHPh), 4.44-4.86(3H,m,=CH_2 and CH-OH), 7.18(10H,m,10 x aromatic -H).

ms m/e 252(M^+,0%), 146(41), 131(34), 107(100), 91(56), 79(49), 77(42).

7.6.91. Reaction of 4-methoxy-phenyl oxirane (723) with complex (678).

A mixture of 4-methoxy-phenyl oxirane[511,512] (723)(702mg;4.7mmol), complex (678)(1.04g;2.3mmol) and dimethylformamide (10ml) was heated at 65°C for 72h. The mixture was poured into water (50ml) and extracted with ether (3x25ml). The exracts were washed with saturated sodium chloride solution (3x25ml) dried over magnesium sulphate and evaporated to give a mixture as a pale green oil which was separated by flash column chromatography. Elution with methylene chloride gave (723)(350mg;50%) and (724) as a colourless oil (122mg;27%).

ir ν_{max}($CHCl_3$ solution) 3,400cm.$^{-1}$

^{1}H nmr δ(C^2HCl_3) 1.75(3H,s,CH_3), 2.12-2.78(4H,m,2xCH_2), 3.78(4H,brs,OCH_3 and CHOH), 4.72(2H,m,CH_2=C(CH_3)-), 6.74-7.24(4H,m,4 x aromatic-H).

ms m/e 206($\underline{M}^+$,10%), 150(22), 137(43), 122(79), 121(100), 77(25).

7.6.92. Reaction of methyl oxirane (726) with complex (678).

A mixture of methyl oxirane (726)(0.5g;8.6mmol), complex (678) (1.3g;2.9mmol) and dimethylformamide (8ml) was heated in a sealed tube at 70°C for 48h. The mixture was poured into water (50ml) and exracted with ether (3 x 25ml). The exracts were washed with saturated sodium chloride solution (2x25ml), dried over magnesium sulphate and evaporated to give a mixture as pale green oil which was separated by flash column chromatography. Elution with methylene chloride gave (E)-2-methyl-2-pentenal[513] (729)(281mg;72%), 2,4-dimethyl-4-penten-1-ol[514] (727)[30457-95-5](162mg;16%) and 5-methyl-5-penten-2-ol[515,516] [50551-88-7](124mg;12%).

7.6.93. 3-Hydroxy-2-methylene-6-heptenoic acid, methyl ester (733a).

n-Butyl lithium (1.5M solution in hexane)(134ml;0.1mol) was added to a solution of diisopropylamine (20.2g;0.2mol) in tetrahydrofuran (400ml) at -10°C. The solution was stirred at 10°C for 10min, cooled to -40°C and a solution of 3-hydroxy-propanoic acid, methyl ester (543)(10.6g;0.1mol) in tetrahydrofuran (20ml) added dropwise. The 'milky' solution which resulted was stirred at -35°C for 1h, cooled to -40°C and a solution of 4-pentenal (738a)(7.4g;0.089mol) in tetrahydrofuran (20ml) added dropwise. The solution was stirred for 16h, during which time it became clear and warmed to 0°C, cooled to -10°C and a solution of 4-toluenesulphonyl chloride (17g;0.089mol) in tetrahydrofuran (100ml) added dropwise over 15min. The mixture was allowed to warm to 0°C over 1h, solid ammonium chloride (10g) was added and the suspension stirred for 2h. The suspension was filtered, cooled to -5°C and DBU (15.2g;0.1mol) added. The resulting mixture was stirred for 2h at room temperature, during which time it formed heavy precipitate, and the supernatant liquid decanted. The liquid was evaporated to give a brown oil which was dissolved in ether/petroleum

ether (40-60°C)(1:4) and passed down a short plug of silica gel (1"x4" diameter). Elution with ether/petrol ether (40-60°C)(1:4) gave a mixture of 3-hydroxy-2-methylene-6-heptenoic acid, methyl ester (733a) and its isomer (E)-2-hydroxymethyl-2,6-heptadienoic acid, methyl ester (10:1) as an unstable colourless oil (14.1g;84%) which was used without separation to prepare (734a).

^{1}H nmr $\delta(CCl_4)$ 0.92(2H,m,$\underline{CH}_2CH(OH)$-),2.12(2H,m,$\underline{CH}_2CH=CH_2$), 3.10(1H,brs,$\underline{OH}$), 3.73(3H,s,$CO_2\underline{CH}_3$). 4.14(1H,t,J=6Hz, $\underline{CH}OH$), 4.80-5.24(2H,m,$\underline{CH}_2$=CH-), 5.44-6.15(1H,m,CH_2=$\underline{CH}$-) 5.82 and 6.18 (2H,2xs,$CH_2=C(R)(CO_2CH_3)$).

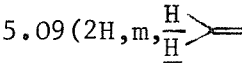
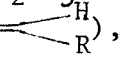
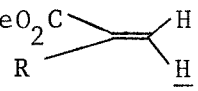
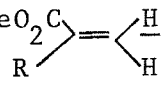
7.6.94. 3-Hydroxy-2-methylene-12-tridecenoic acid, methyl ester (733b).

n-Butyl lithium (1.5M solution in hexane)(29.3ml;0.044mol) was added to a solution of diisopropylamine (4.4g;0.044mol) in tetrahydrofuran (30ml) at -10°C. The solution was stirred at -10°C for 10min, cooled to -35°C and a solution of 3-hydroxy-propanoic acid, methyl ester (543)(2.29g;0.022mol) in tetrahydrofuran (30ml) added dropwise. The 'milky' solution which resulted was stirred at -35°C for 15min., cooled to -45°C and a solution of 10-undecenal (738b)(3.64g;0.022mol) in tetrahydrofuran (30ml) added dropwise. The solution was stirred for 16h, during which time it became clear and warmed to 0°C, cooled to -15°C and a solution toluene-4-sulphonylchloride (4.2g;0.022mol) in tetrahydrofuran (20ml) added. The clear solution was allowed to warm to room temperature over 2h, solid ammonium chloride (5g) added and the suspension stirred for 2h. The suspension was filtered and evaporated to yield a pale green gum (8.3g). The gum was treated with chloroform (300ml), stirred for 1h and filtered. Evaporation of the filtrate afforded a pale green oil (5.1g) which was distilled *in vacuo* to give 3-hydroxy-2-methylene-12-tridecenoic acid, methyl ester (733b) as a colourless oil (1.3g;23%) b.p. 138-142°C/0.3mm Hg.

Analysis Found : C,71.3; H,10.5

$C_{15}H_{26}O_3$ requires : C,70.9; H,10.3%.

ir ν_{max} (liquid film) 3420cm.$^{-1}$, 3090cm.$^{-1}$, 1715cm.$^{-1}$

^{1}H nmr $\delta(C^{2}HCl_3)$ 1.10-1.75(14H,m,7x$\underline{CH}_2$), 1.88-2.20(2H,m,CH_2=CH$\underline{CH}_2$), 3.80(3H,s,$CO_2\underline{CH}_3$), 4,41(1H,t,J=5Hz,-$CH_2\underline{CH}$(OH)-), 4.90-5.09(2H,m, ), 5.62(1H,m, ), 5.82(1H,s, ), 6.24(1H,s, ).

^{13}C nmr $\delta(C^{2}HCl_3)$ 25.9, 29.0, 29.2, 29.5, 33.9, 36.5, 51.7, 71.1, 114.2, 124.6, 139.1, 143.2, 167.1.

ms m/e 254($\underline{M}^{+}$,0%), 223(0.5), 208(0.8), 236(1.3), 193(1.1), 115(100).

7.6.95. (Z)-2-Bromomethyl-2,6-heptadienoic acid, methyl ester (734a).

A solution of 3-hydroxy-2-methylene-6-heptenoic acid, methyl ester (733a) and (E)-2-hydroxymethyl-2,6-heptadienoic acid, methyl ester (1.35g;7.9mmol) in ether (20ml) was treated with a phosphorus tribromide (0.6ml;1.7g;6.4mmol) and the mixture stirred at room temperature for 16h. The solution which resulted was poured into saturated sodium hydrogen carbonate solution (100ml) and the layers separated. The aqueous phase was extracted with ether (3x20ml). The organic extracts were washed with saturated sodium hydrogen carbonate solution (1x20ml), dried over potassium carbonate and evaporated to give a white opaque oil. The oil was dissolved in petroleum ether (40-60^{o}C)(100ml) and passed down a short silica gel plug (1"x4" diameter). Elution with ether/petroleum ether (40-60^{o}C)(1:4) gave (Z)-2-bromomethyl-2,6-heptadienoic acid, methyl ester (734a) as a colourless oil (1.8g;97%).

ir ν_{max} ($CHCl_3$ solution) 1,720cm.$^{-1}$

^{1}H nmr $\delta(CCl_4)$ 2.33(4H,m,2x$\underline{CH}_2$), 3.76(2H,s,$\underline{CH}_2$Br), 4.19(3H,s,$CO_2\underline{CH}_3$), 4.82-5.28(2H,m,$\underline{CH}_2$=CH-), 5.45-6.12(1H,m,CH_2=$\underline{CH}$-), 6.88(1H,t,J=7Hz,-$\underline{CH}$=C(CH_2Br)-CO_2CH_3).

7.6.96. (Z)-2-Bromomethyl-2,12-tridecadienoic acid, methyl ester (734b).

A solution of phosphorus tribromide (0.2ml;2mmol) in ether (10ml) was added to a solution of 3-hydroxy-2-methylene-12-tridecenoic acid, methyl ester (733b)(508mg;2mmol) in ether (10ml) and the mixture stirred at room temperature for 48h. The mixture was poured into ice cold saturated sodium bicarbonate solution (50ml), ether (40ml) was added and the separated aqueous phase extracted with ether (2x10ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (1x10ml) and saturated sodium chloride solution (2x10ml), dried over magnesium sulphate and evaporated to give a colourless oil(504mg) which was chromatographed by flash column chromatography. Elution with ether/petroleum ether (40-60°C)(5:95) gave (E)-2-bromomethyl-2,12-trideca-dienoic acid, methyl ester (734b) as a colourless oil (462mg;73%).

ir ν_{max} ($CHCl_3$ solution) 1712cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.31(12H,brs,6x$\underline{CH}_2$), 1.90-2.44 (3H,m,CH_2=CH$\underline{CH}_2$- and -$\underline{CH}_2$CH=C(CH_2Br)CO_2CH_3), 3.80(3H,s,$CO_2\underline{CH}_3$), 4.24(2H,s,$\underline{CH}_2$Br), 4.84-5.12(2H,m, $\underline{CH}_2$=CH-), 5.61-6.40(1H,m,CH_2=$\underline{CH}$-), 6.99(1H,t,J=5Hz, =$\underline{CH}$(CH_2Br)CO_2CH_3).

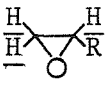
^{13}C nmr $\delta(C^2HCl_3)$, 24.2, 28.2, 28.9, 29.1, 29.4, 33.8, 52.1, 114.2, 129.3, 139.1, 148.5, 166.1.

ms m/e 318($\underline{M}^+$,0), 177(17), 95(66), 81(73), 69(55), 67(60), 55(100).

7.6.97. (Z)-β-Bromomethyl-β-oxiranepentenoic acid, methyl ester (735a).

A solution of (Z)-2-bromomethyl-2,6-heptadienoic acid, methyl ester (734a)(1.8g;7.7 mmol) in methylene chloride (15ml) was treated with 3-chloroperbenzoic acid (1.7g;10mmol). The mixture was stirred at room temperature for 16h and partitioned between methylene chloride (20ml) and potassium carbonate solution (20%,20ml). The organic phase was separated and washed with sodium thiosulphate solution (10%,2x20ml) and saturated sodium hydrogen carbonate solution (2x20ml). The organic phase was dried over potassium carbonate and evaporated to give (735a) as a pale yellow oil (0.62g;32%).

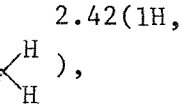
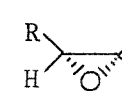
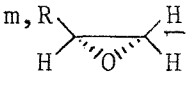
ir ν_{max} (CCl_4 solution) 1712cm.$^{-1}$

^{1}H nmr $\delta(CCl_4)$ 1.80(4H,m,2xCH_2), 2.21-3.05(3H,m, ),
3.78(3H,s,$CO_2\underline{CH}_3$), 4.22(2H,s,$\underline{CH}_2Br$),
6.95(1H,t,J=7Hz, olefinic -H).

7.6.98. (Z)-β-Bromomethyl-β-oxiraneundecenoic acid, methyl ester (735b).

A solution of (Z)-2-bromomethyl-2,12-tridencadienoic acid, methyl ester (734b)(1.9g;6mmol) in methylene chloride (20ml) was treated with 2-chloro-perbenzoic acid (1.0g;6mmol). The mixture was stirred at room temperature for 16h and partitioned between methylene chloride (10ml) and saturated sodium hydrogen carbonate solution (20ml). The separated organic phase was washed with saturated sodium hydrogen carbonate solution (2x20ml) and saturated sodium chloride solution (1x20ml). The extracts were dried over magnesium sulphate and evaporated to give (735b) a pale yellow oil (1.2g;75%).

ir ν_{max} (CCl_4 solution) 1722cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.04-1.72(14H,brs,7xCH_2), 2.14(2H,m,-$\underline{CH}_2$-CH=), 2.42(1H,m, ), 2.70(1H,m, ), 2.86(1H,m, ), 3.79(3H,s,$CO_2\underline{CH}_3$), 4.21(2H,s,$\underline{CH}_2$Br), 6.92(1H,t,J=8Hz, olefinic-$\underline{H}$).

^{13}C nmr $\delta(C^2HCl_3)$, 24.3, 26.0, 28.1, 28.6, 28.8, 29.3, 32.5, 46.9, 52.2, 129.3, 148.5, 166.0.

ms(25ev) m/e 333($\underline{M}^+$-1,0.6%), 317(1), 237(12), 141(33), 139(100), 95(37), 93(33).

7.6.99. 3-Hydroxy-2-(hydroxymethyl)-12-tridecenoic acid, methyl ester (736).

n-Butyl lithium (1.5M solution in hexane)(8.0ml;12mmol) was added to a solution of diisopropylamine (1.22g;12mmol) in tetrahydrofuran (10ml) at -10°C. The solution was stirred -10°C for 10mins. cooled to -40°C and a solution of 3-hydroxy-propionic acid, methyl ester (543)(0.62g;6mmol) in tetrahydrofuran (10ml) added dropwise. The solution was stirred at -40°C for 4h, during which time it became clear, and allowed to warm to room temperature over 16h. Saturated ammonium chloride solution (20ml) was added to the solution and the two phases stirred for 2h. The separated aqueous phase was extracted with ether (2x20ml). The combined organic extracts were washed with saturated sodium chloride solution (20ml), dried over magnesium sulphate and evaporated to give a pale yellow oil (1.54g) which was distilled *in vacuo* to give 3-hydroxy-2-(hydroxymethyl)-12-tridecenoic acid, methyl ester (736) as a colourless oil (0.53g;33%) b.p. 158-162°C/ 0.2mm Hg.

ir ν_{max} (liquid film) 3400cm.$^{-1}$, 3080cm.$^{-1}$, 1730cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.10-1.80(14H,m,7x$\underline{CH}_2$), 1.85-2.20(2H,m, CH_2=CH-$\underline{CH}_2$-), 2.42-2.84(1H,m,>$\underline{CH}CO_2CH_3$) 3.54-4.18(5H,m,$CH_2\underline{CH}(\underline{OH})CH(CO_2CH_3)\underline{CH}_2\underline{OH}$) 3.74(3H,s,$CO_2\underline{CH}_3$), 4.90-5.15(2H,m,$\underline{CH}_2$=CH-) 5.60-6.05(1H,m,$CH_2$=$\underline{CH}$-).

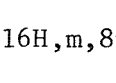
^{13}C nmr $\delta(C^2HCl_3)$ 25.9, 26.0, 29.1, 29.2, 29.6, 33.9, 35.4, 52.6, 52.8, 61.0, 61.7, 70.9, 71.4, 114.3, 139.1,174.2.

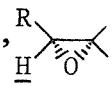
ms m/e 272($\underline{M}^+$,0%), 241(0.5), 223(1.7), 205(0.3), 177(1.7), 133(63), 104(100).

7.6.100. α-Hydroxy-β-methylene-oxiraneundecanoic acid, methyl ester (737).

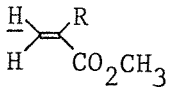
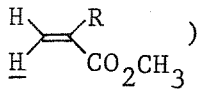
3-Chloro-perbenzoic acid (240mg;1.4mmol) was added to a stirred solution of 3-hydroxy-2-methylene-12-tridecenoic acid, methyl ester (733b)(254mg;1mmol) in methylene chloride (10ml) and the mixture stirred at room temperature for 40h. The mixture was poured into potassium carbonate solution (10%;50ml) and the organic phase separated. The aqueous phase was extracted with methylene chloride (2x10ml). The combined organic material was washed with potassium carbonate solution (10%,20ml), sodium thiosulphate solution (10%,20ml) and water (2x10ml), dried over potassium carbonate and evaporated to afford α-hydroxy-β-methylene-oxiraneundecanoic acid, methyl ester (737) as a colourless oil (242mg;90%).

ir ν_{max}($CHCl_3$ solution) 3540cm.$^{-1}$, 1710cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.30(16H,m,8xCH_2), 2.41(1H,m, ),

2.69(1H,m, ), 2.75(1H,m, ),

3.13(1H,brs,O<u>H</u>), 3.75(3H,s,$CO_2C\underline{H}_3$), 4.41(1H,m, >C<u>H</u>OH),

5.81(1H,d,J=2Hz, ), 6.17(1H,d,J=2Hz, ).

^{13}C nmr $\delta(C^2HCl_3)$ 25.8, 26.0, 29.5, 32.5, 36.5, 47.0, 51.7, 52.4, 70.8, 124.4, 143.4, 167.0.

ms m/e 270($\underline{M}^+$,0%), 115(100), 83(52), 81(18), 67(17), 55(37), 41(26).

7.6.101. 4-Pentenal[517] (<u>738a</u>) *[2100-17-6]*.

A solution of 4-penten-1-ol (<u>743</u>)(17.2g;0.2mol) in methylene chloride (50ml) was added to a stirred suspension of pyridinium chlorochromate[483] (50g;0.23mol) in methylene chloride (150ml) and the mixture stirred for 2h. The mixture was poured into ether (800ml) and the suspension filtered through HYFLO. The light green solution which resulted was evaporated to give light green oil (16g) which was distilled at atmospheric pressure to give 4-pentenal (<u>738a</u>) as a colourless oil (7.4g;44%) b.p. 105-8°C(Lit.[488] 103-4°C/749mm Hg).

7.6.102. 10-Undecenal (<u>738b</u>) *[112-45-8]*.

A solution of 10-undecen-1-ol (<u>740</u>)(35g;0.2mol) in methylene chloride (50ml) was added to a stirred suspension of pyridinium chlorochromate[483] (57g;0.26mol) in methylene chloride (800ml) and the mixture stirred for 2.5h. The mixture was poured into ether (1,500ml) and the suspension filtered through HYFLO. The light brown

solution which resulted was evaporated to give a dark brown oil which was taken up in ether (500ml). The solution was filtered through HYFLO, dried over magnesium sulphate and evaporated to give a pale green oil (33.2g;95%) which was distilled *in vacuo* to give 10-undecenal (738b) as a colourless oil (16.0g;46%) b.p. 120-3°C/13mmHg (Lit.[518] 67-8°C/0.6mm Hg), 2,4-dinitrophenylhydrazone m.p. 88-90°C (Lit.[519] 92°C).

7.6.103. 10-Undecen-1-ol (740) [112-43-6].

A solution of 10-undecenoic acid (739)(50g;0.27mol) in tetrahydrofuran (250ml) was added dropwise (over 3h) to a stirred suspension of lithium aluminium hydride (11g;0.28mol) in ether (200ml), allowing the suspension to boil under reflux. The suspension was heated under reflux for 3h and allowed to stand at room temperature for 16h. The suspension was cooled in a salt/ice bath, a solution of ethyl acetate (10ml) in tetrahydrofuran (50ml) added dropwise and the suspension stirred for 10mins. Saturated ammonium chloride solution (1000ml) was added to the suspension, the mixture stirred for 1h and the organic phase separated. The separated aqueous phase was extracted with ether (2x200ml). The combined organic material was washed with saturated sodium chloride solution (2x100ml), dried over magnesium sulphate and evaporated to give a pale yellow oil (47g) which was distilled *in vacuo* to give 10-undecen-1-ol (740) as a colourless oil (39g;85%) b.p. 148-151°C/20mm Hg (Lit.[520] 130-5°C/15mm Hg).

7.6.104. 2-(Chloromethyl)tetrahydrofuran (742) [3003-84-7].

2-(Chloromethyl)tetrahydrofuran (742) [3003-84-7] was prepared by the method of Brooks and Snyder.[462] Treatment of a solution of 2-(hydroxymethyl)tetrahydrofuran (741)(408g;4mol) in pyridine (348g;4.4mol) with thionyl chloride (500g;4.2mol) gave 2-(chloromethyl)-tetrahydrofuran (742) as a colourless oil (304g;63%), b.p. 50-1°C/15mmHg (Lit.[462] 47-8°C/15mm Hg), homogeneous by G.C. R_T(167°C)=1.6min.

7.6.105. 4-Penten-1-ol(743)[821-09-0].

4-Penten-1-ol(743)[821-09-0] was prepared by the method of Brooks and Snyder.[462] Treatment of 2-chloromethyl-tetrahydrofuran (742)(310g;2.5mol) with powdered sodium (112g;4.9mol) in anhydrous ether (700ml) gave 4-penten-1-ol as a colourless liquid (186g;80%) b.p. 137-9°C (Lit.[462] 134-7°C).

7.6.106. N,Methyl,N-phenyl 2-aminomethyl-2,12-tridecadienoic acid, methyl ester (744).

A solution of N-methyl benzenamine (0.12g;1.1mmol) in dichloromethane (10ml) was added to a solution of titanium tetrachloride (0.1ml;1mmol) in dichloromethane (10ml) and the mixture stirred at 0°C for ½h.[465] A solution of 3-hydroxy-2-methylene-12-tridecenoic acid, methyl ester (733b) (0.254g;1.0mmol) in dichloromethane (5ml) was added to the solution at -30°C. The resulting wine red mixture was stirred at -30°C for 3h and allowed to attain room temperature over 16h. The solution was poured into saturated sodium chlorate solution, the layers were separated, and the aqueous phase was extracted with ether (2x10ml). The combined organic ectracts were dried over magnesium sulphate and evaporated to give a mixture as a pale yellow oil (280mg) which was separated by preparative thin-layer chromatography on silica gel. Elution with petroleum ether (40-60°C)/ether (15:85) yielded N-methyl,N-phenyl 2-aminomethyl-2, 12-tridecadienoic acid, methyl ester (744) as a pale yellow oil (106mg; 32%).

ir ν_{max} ($CHCl_3$ solution) 1720cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.01-1.76(12H,brs,6xCH_2), 1.85-2.18(2H,m, CH_2=CH-CH_2), 2.25-2.62(2H,m,CH_3CO_2C=CH-CH_2)
2.92(3H,s,N-CH_3), 3.74(3H,s,CO_2CH_3),
4.09(2H,t,J=1.5Hz,-CH_2-N(CH_3)Ph)
4.98-5.15(2H,m,CH_2=CH-)
5.60-6.40(2H,m,CH_2=CH- and CH_3CO_2C =CH-)
6.59-7.36(5H,m, 5 x aromatic-H).

^{13}C nmr $\delta(C^{2}HCl_3)$ 29.2, 29.3, 33.8, 37.9, 51.2, 55.9, 112.4, 114.2, 116.7, 126.8, 129.1, 139.2, 142.7, 149.5, 167.8.

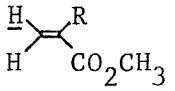
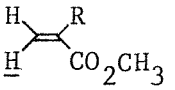
ms m/e 334($\underline{M}^+$+1,15%), 343($\underline{M}^+$,59), 329(7), 328(23), 205(3),204(19), 120(86), 107(100).

7.6.107. 3-[Hydroxy(phenyl)methyl]-2-methylene-12-tridecenoic acid, methyl ester (745).

A solution of (Z)-2-bromomethyl-2,12-tridecadienoic acid, methyl ester (734b)(429mg;1.35mmol) in tetrahydrofuran (3ml) was added to a suspension of *bis*(cycloocta-1,5-dienyl)nickel (0)[471] (371mg; 1.35mmol) in tetrahydrofuran (10ml) at -15°C. The mixture was stirred at -15° to -7°C for 3.5h during which time it became deep red in colour. A solution of benzaldehyde (532a)(150mg;1.4mmol) in tetrahydrofuran (5ml) was added and the mixture stirred at room temperature for 16h to give a dark green solution. Hydrochloric acid (0.1M;10ml) was added to the solution and the mixture stirred for 20min to give a pale green solution. The solution was extracted with ether (3x20ml) and the combined extracts washed with saturated sodium chloride solution (2x20ml). The extracts were dried over magnesium sulphate and evaporated to give a mixture as a pale yellow oil (350mg) which was separated by flash column chromatography.[480] Elution with ether/ petroleum ether (40-60°C)(1:4) gave 2-bromomethyl-2,12-tridecadienoic acid, methyl ester (734b)(210mg;49%) and the dimer (746)(82mg;34%).

3-[Hydroxy(phenyl)methyl]-2-methylene-12- tridecenoic acid, methyl ester (745)

ir ν_{max} (CCl_4 solution) 3480cm.$^{-1}$, 1740cm.$^{-1}$

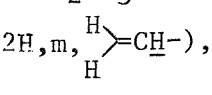
^{1}H nmr $\delta(C^{2}HCl_3)$ 0.98-1.74(14H,m,7x$\underline{CH}_2$), 2.00(3H,m, CH_2=CH$\underline{CH}_2$+-$\underline{CH}$(Ph)-C(=$\underline{C}$$CO_2CH_3$)-), 2.76-3.06(2H,m,-C(Ph)$\underline{H}$-O$\underline{H}$), 3.70(3H,s,$CO_2\underline{CH}_3$), 4.75-5.08(2H,m,$\underline{CH}_2$=CH-), 5.40(1H,s, ), 5.49-6.00(1H,m,CH_2=C$\underline{H}$-), 6.18(1H,s, ), 7.16(5H,s,5xaromatic-$\underline{H}$).

^{13}C nmr $\delta(C^{2}HCl_3)$ 27.4, 27.5, 28.9, 29.1, 29.4, 29.5, 33.8, 49.4, 52.0, 76.4, 114.2, 126.6, 127.0, 127.2, 128.0, 128.5, 139.2, 142.8, 168.5.

ms m/e 344 ($\underline{M}^{+}$, 0%), 238(16), 107(100), 105(50), 95(60), 81(64), 55(59).

Dimer (<u>746</u>).

ir ν_{max} (CCl_4 solution) 1735cm.$^{-1}$

^{1}H nmr $\delta(C^{2}HCl_3)$ 1.32(32H,brs,16x$\underline{CH}_2$), 2.07(4H,brs,2x$\underline{CH}_2$), 3.67(6H,s,2x$CO_2\underline{CH}_3$), 4.73-5.14(4H,m,$\underline{H}$>C=CH-), 5.48-6.08(2H,m,H>C=C$\underline{H}$-), 6.74(2H,t,J=7Hz, ).

ms m/e 474($\underline{M}^{+1}$,2), 442(16), 383(19), 107(37), 105(43), 95(48), 67(55), 55(100).

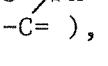
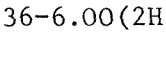
7.6.108. *Cis*-2,3-diphenyl-oxirane (748) [1689-71-0].

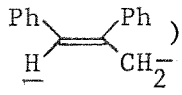
Cis-2,3-diphenyl-oxirane (748) [1689-71-0] was prepared by the method outlined for (721). Treatment of (Z)-1,1'-(1,2-ethenedyl)*bis*-benzene(1.63g;9.1mmol) with 3-chloroperbenzoic acid (2.25g;13mmol) in methylene chloride (30ml) gave (748) as a colourless oil (1.60g;90%) which crystallised on standing, m.p. 38-40°C (Lit.[488] 42°C).

7.6.109. 2-(2,3-Diphenyl-2-propenyl)-2,12-undecadienoic acid, methyl ester (749)

A solution of (Z)-2-bromomethyl-2,12-tridecadienoic acid, methyl ester (734b)(0.50g;1.6mmol) in tetrahydrofuran (5ml) was added to a suspension of *bis*(cycloocta-1,5-dienyl)nickel (0)[471](0.43g;1.6mmol) in tetrahydrofuran (5ml) at -7°C. The mixture was stirred at -7°C for 3h to give a deep red solution. A solution of *cis*-2,3-diphenyl-oxirane (748)(588mg;3mmol) in N,N-dimethylformamide (10ml) was added to the red solution and the mixture stirred at 60°C for 16h. The solvent was removed *in vacuo* to give a pale green gum to which water(10ml) and dilute hydrochloric acid (0.1M;30ml) were added. The mixture was stirred for 0.5h to give two layers which were separated and the separated aqueous phase extracted with ether (3x10ml). The combined organic extracts were washed with saturated sodium chloride solution (2x10ml), dried over magnesium sulphate and evaporated to give a mixture as a pale yellow viscous oil (0.81g). The mixture was separated by flash column chromatography. Elution with ether/petroleum ether (40-60°C)(1:9) gave 2-(2,3-diphenyl-2-propenyl)-2,12-undecadienoic acid, methyl ester (749) as colourless crystals (30.6mg;5%), m.p.54-5?).

ir ν_{max} ($CHCl_3$ solution) 1715cm.$^{-1}$

^{1}H nmr $\delta(C^2HCl_3)$ 1.00-2.62(16H,m,8xCH_2), 3.71(3H,s,CO_2CH_3), 3.82(2H,s $=C(CO_2CH_3)-CH_2-C(Ph)=$), 4.82-5.10(2H,m, ), 5.36-6.00(2H,m, and ),

7.04-7.58(11H,m,10 x aromatic-H and ).

^{13}C nmr $\delta(C^{2}HCl_3)$ 28.6, 28.9, 29.1, 29.5, 33.8, 62.9, 114.2, 125.6, 126.6, 127.7, 128.4, 128.6, 128.7, 137.2, 137.4, 139.2.

ms m/e 416(M^+,0%), 383(17), 304(10), 95(66), 91(35), 81(66), 55(100).

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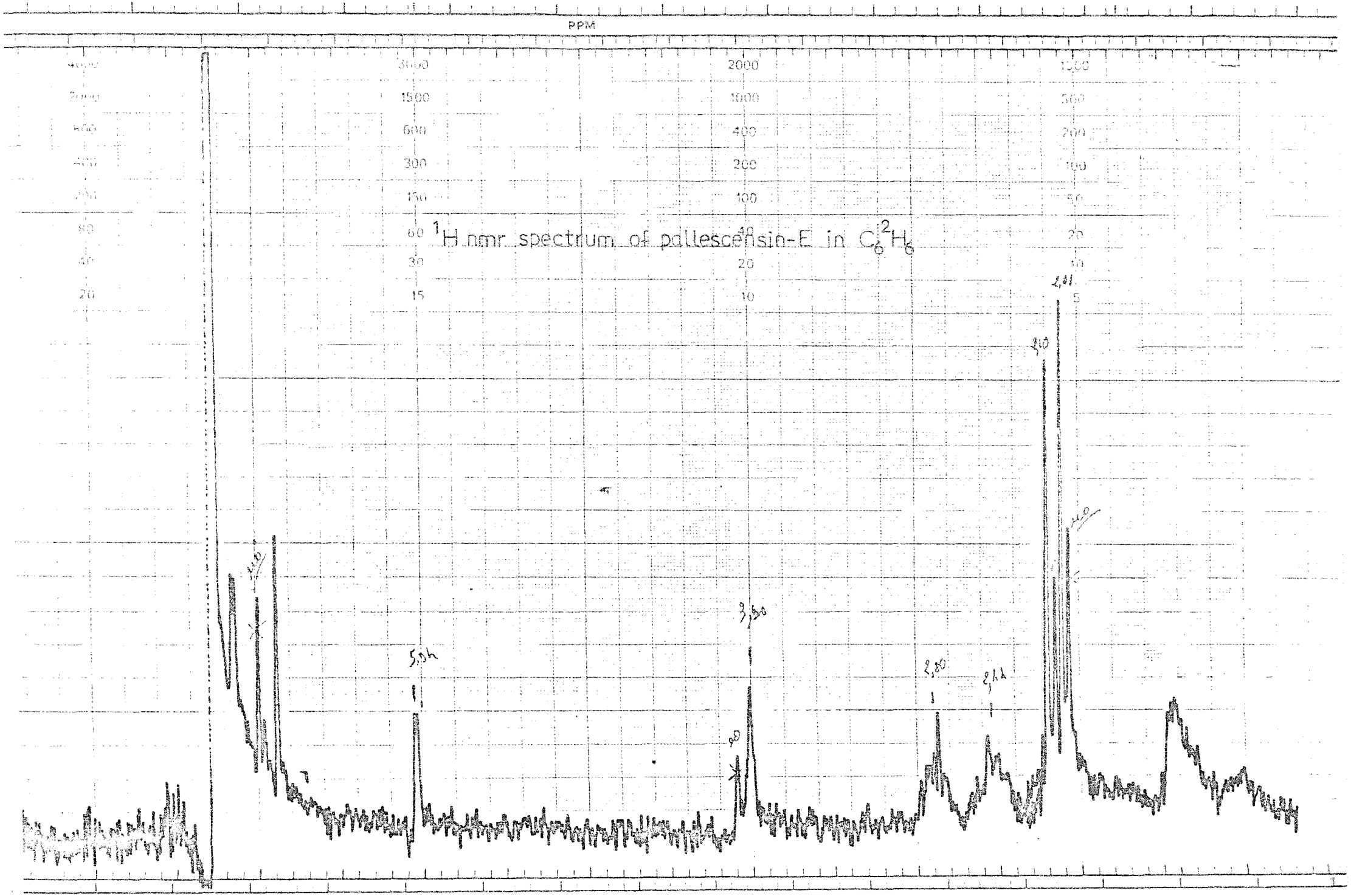
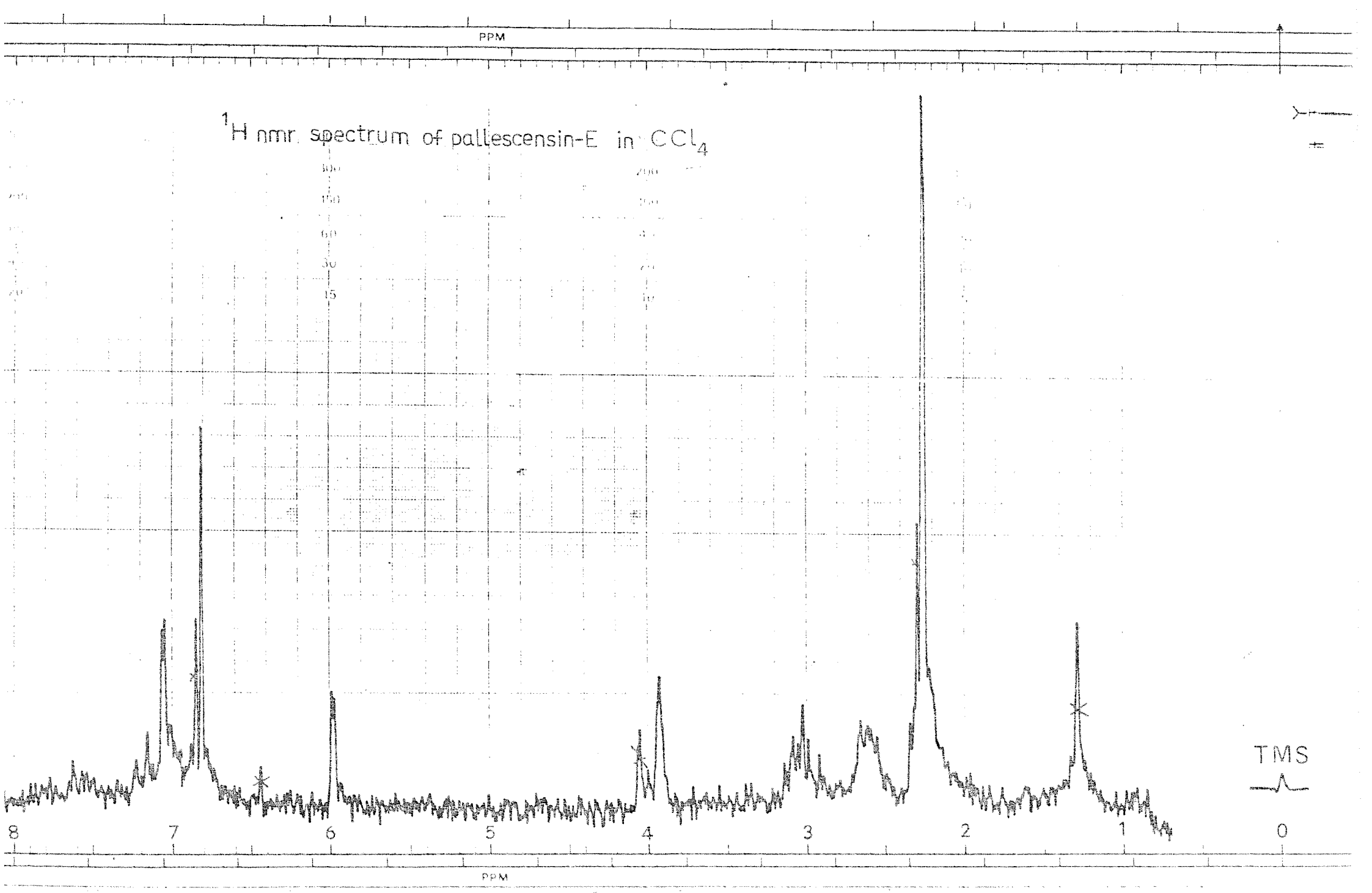
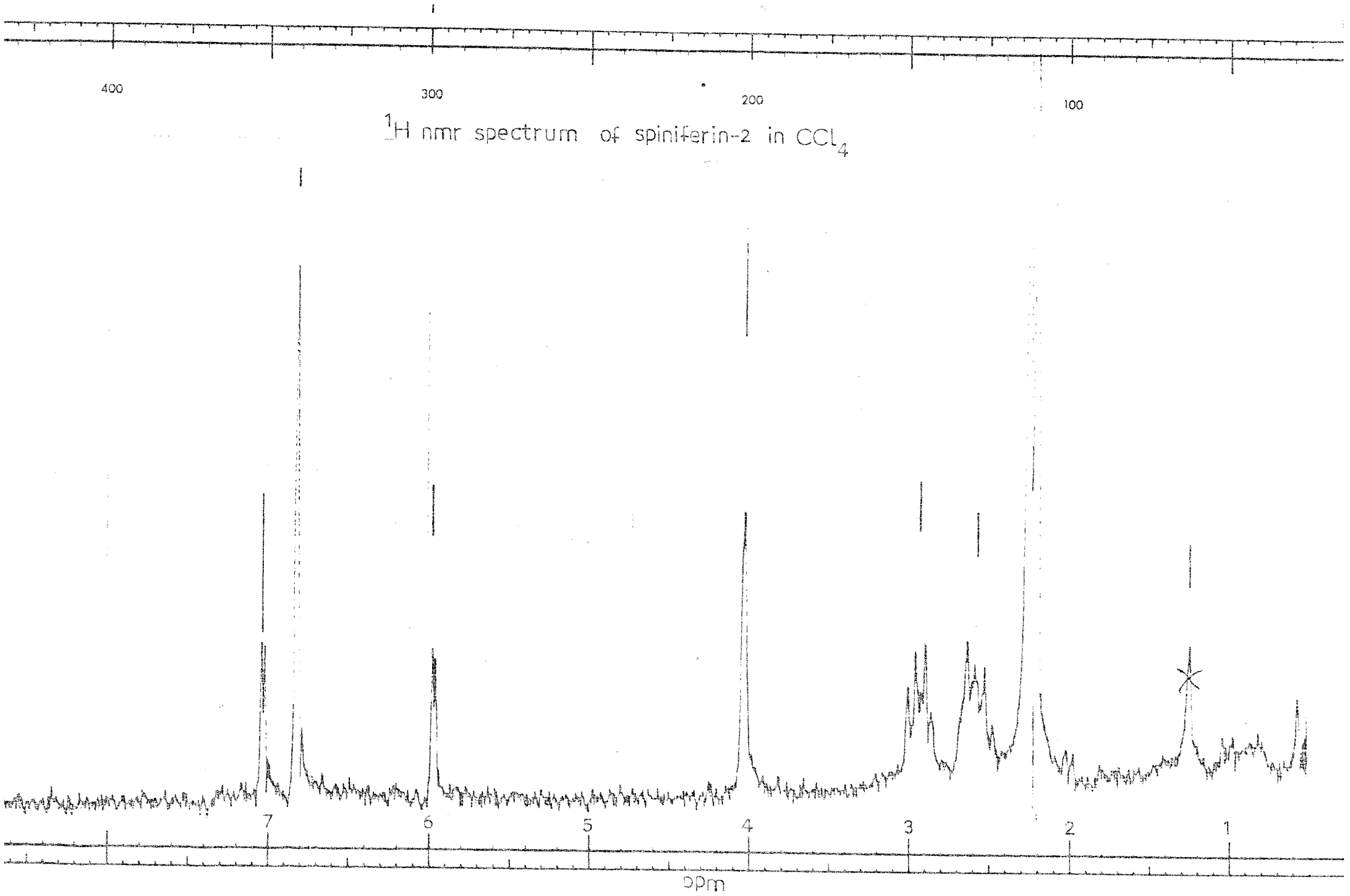
APPENDIX

^{1}H n.m.r. spectra of naturally occurring Pallescensin-E and Spiniferin-2*

* The Author thanks Professor G. Cimino for copies of spectra of naturally occurring Pallescensin-E and Spiniferin-2.


PPM
^{1}H nmr spectrum of pallescensin-E in $C_6^2H_6$
5,04
3,80
2,80
2,44
4,01
4,10


PPM
^{1}H nmr spectrum of pallescensin-E in CCl_4
TMS
8
7
6
5
4
3
2
1
0
PPM



^{1}H nmr spectrum of spiniferin-2 in CCl_4