STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF GASCARDIC ACID

WILLIAM LARRY BROWN

STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF GASCARDIC ACID

by

©William Larry Brown, B.Sc.

A Thesis submitted in partial fulfilment of the requirements of the degree of Master of Science.

Department of Chemistry
Memorial University of Newfoundland

July 1984

St. John's Newfoundland

Abstract

Various reactions directed toward the total synthesis of gascardic acid have been delineated. Unfortunately trisubstituted cyclopentadienes of type 31a and 31b would not partake in the desired intramolecular Diels-Alder reactions. In contrast, compounds 68 and 73 in which the sidechain substituents differ, cyclized to the requisite tricyclic skeletons.

A general method for inverting the stereochemistry of vinyl alcohols such as 20 and 37 has been developed. This involved a [2,3] sulfoxide rearrangement and will permit a broader application of the oxy-Cope rearrangement as illustrated by the conversion of 37 to 53 to 54.

Model studies of a suitable cyclohexane-cycloheptane ring expansion in which the keto-ester functionality is retained were commenced.

Acknowledgements

The author wishes to express his appreciation to Dr. Alex G. Fallis for the guidance, enthusiasm and patience he provided throughout this work, also Dr. Sandra Alward for helpful discussion and guidance.

The author would also like to thank Mr. Donald B. Parsons for the illustrations and Miss Teresa Barker for typing.

Thanks are also due to Ms. Marion Baggs for recording mass spectra, and to Mr. Avery Earle who recorded 80 MHz n.m.r. spectra.

Financial assistance from Memorial University is gratefully acknowledged.

Table of Contents

List of Tables

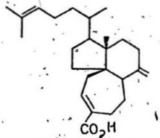
Introduction

Natural products have long fascinated organic chemists. However, in spite of the voluminous literature dealing with terpene structure elucidation and synthesis, the C_{25} class of sesterterpenes have until recently received relatively little attention.

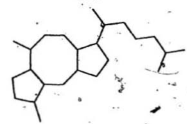
The sesterterpene gascardic acid (1) was first isolated from *Gascardia madagascariensis* by Broche and Polonsky in 1960[1]. The sesterterpene class of compounds includes a large variety of ring sizes and unique carbon skeletons. The most common structural class are the ophiobolanes 2[2,3], but other types range from monocyclic and acyclic polyenes to more complex systems such as the pentacyclic skeleton found in retigeranic acid 3[4,5].

The structure elucidation of gascardic acid was initially undertaken by Arigoni and Scartazzini[6]. They were able to assign the carbocyclic skeleton by extensive chemical and spectroscopic studies, but their studies failed to unambiguously establish the relative configuration of C-14 and C-18. They assigned the relative stereochemistry of these two centers based on a plausible biogenetic scheme. The relative stereostructure of gascardic acid was determined by Boeckman *et al.* by x-ray diffraction studies on the dicyclohexylammonium salt[7].

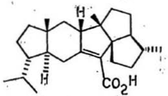
Boeckmann also verified the structure by developing a total synthesis[8]. The hydrindane system was constructed by a conjugate addition-annelation sequence using 2-methyl-2-cyclopentene-1-one and the mixed diorganocuprate reagent derived from copper *n*-pentyne and 6-methyl-5-pentenyllithium, to yield the hydindenone 4. The construction of the quaternary center at C-11 proved quite challenging.



(1)



(2)



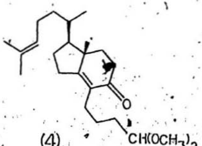
(3)

They had initially planned to use an intermolecular conjugate addition to construct this center, but after trying various nucleophiles and organometallic reagents without success, they abandoned this approach.

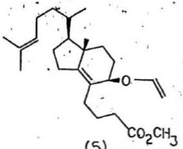
They then thought that the driving force for an intramolecular rearrangement would be sufficient to overcome any steric factors in functionalizing C-11. The hydrindenone 4 was transformed into the vinyl ether 5 through a series of transformations. Rearrangement of 5 afforded the olefinic aldehyde 6 which was converted to the keto diester 7. Methylenation of 7 by standard Wittig reaction afforded only poor yields. However, the methylene diester 8 was obtained by treatment of the diacid with N-methylphenylsulfonimidoylmethyllithium, followed by *in situ* reaction of the crude adduct with aluminum amalgam, and reesterification with diazomethane.

Completion of the ring system was achieved by a Dieckmann cyclization to give ketoester 9 which was converted into dl-methyl gascardate 10 by reduction of the ketone, followed by mesylation and elimination. The mixture of epimers (1:1) was resolved by LC, and finally saponification gave gascardic acid(1).

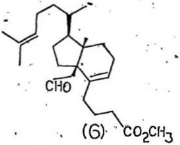
The tricyclic nucleus of gascardic acid is found in modified form in a variety of natural products including sesqui-, di- and sesterterpenes. We are developing a general strategy for the construction of these quaternary, spiro-fused tricyclic skeletons of varying ring size. Our approach relies on an intramolecular Diels-Alder: oxy-Cope rearrangement sequence. It provides stereochemical control and depending upon the final target (gascardic acid, retigeranic acid, pentalenic acid, laurenene, etc.), the length of the sidechain may be



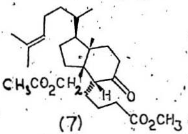
(4)



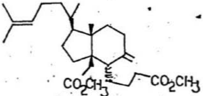
(5)



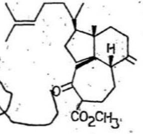
(6)



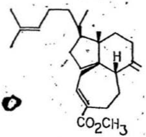
(7)



(8)



(9)



(10)

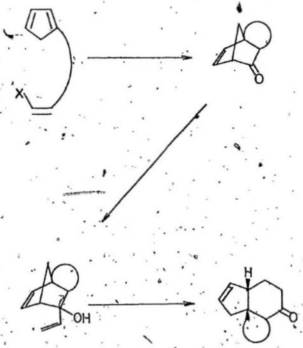
varied and the resulting cyclohexanone contracted or expanded as required. The general principle is outlined in Scheme I.

The original plan was to construct an intermediate keto-ester such as 11 which after Diels-Alder cycloaddition would afford the tricyclic adduct 12 containing a seven-membered ring[9]. Unfortunately these keto-esters would not cyclize; the reaction yielded either starting materials or decomposition products.

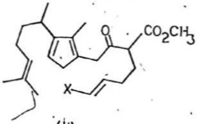
Systematic studies[9] revealed that entropy disfavours direct formation of a cycloheptane by this intramolecular sequence and that the presence of keto-ester functionality in the sidechain is deleterious even for the preparation of cyclohexanes. Internal cycloaddition proceeded to give six membered rings in the absence of the ester. These results were consistent with a marked conformational bias caused by through space interactions of the cyclopentadiene and sidechain functionality.

The effect of the ester group was deduced from the presence of an unusual infrared absorbtion band in the ketones which cyclized. The carbonyl band (1670 cm^{-1}) was not typical of a saturated ketone, but is consistent with a pseudo-conjugated carbonyl interacting with the π system of the diene. As illustrated in Scheme II, this creates the correct orientation of the diene and dienophile and aids in cyclization. When the ester is present, it apparently dominates the competition for this pseudo-conjugation and therefore holds the diene and dienophile in a conformation that makes it difficult for cyclization to occur.

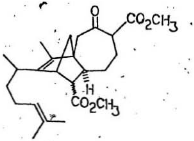
The validity of this analysis was confirmed by conducting the reaction under conditions which favour the correct geometry for cycloaddition. This was accomplished by the use of tetramethylethylene-



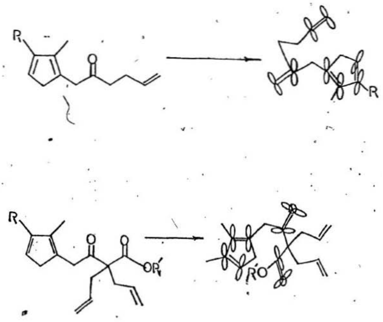
SCHEME I



(11)



(12)



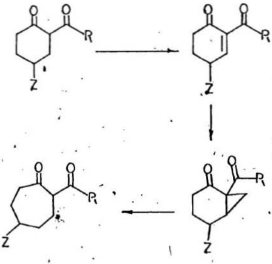
SCHEME II

diamine as a complexing agent[10]. The Diels-Alder reaction failed in the absence of tetramethylethylenediamine.

These results dictate that the approach to gascardic acid be modified. Clearly the route must proceed via a tricyclo[6.2.1.0^{1,6}]-undecene which is suitably functionalized for subsequent ring expansion to a cycloheptane. In general terms, this requires the insertion of a carbon into the cyclohexane system at the β-carbon. In principle this might be achieved via a cyclopropyl-ketone, in which controlled bond cleavage affords the requisite ring system as illustrated in Scheme III.

Ordinarily carbene insertions cannot be used to prepare such a cyclopropane since carbenes react much faster with unconjugated double bonds than with conjugated ones. Corey[11] has developed a method of adding dimethyl sulfoxonium methylide to electrophilic unsaturated linkages including C=O, C=N, C=S and C=C. This method was utilized by Mukaiyama[12] for the asymmetric synthesis of cyclopropanes and γ-butyrolactones. This procedure has been modified by Johnson[13], using (dialkyl amino) methyl sulfoxonium methylide which also adds to electrophilic unsaturated linkages. A slightly different method was developed by Annen[14], who used the anion of nitromethane to add to α,β-unsaturated nitriles.

Conventional methods of cyclopropane cleavage, such as catalytic hydrogenation[15], sodium in ammonia[16,17], etc., are likely to give a mixture of cleavage products with the desired ring expanded compound 13 as the minor isomer. Activated cyclopropanes may be cleaved with nucleophiles, both inter and intramolecularly[18]. Deslongchamps has shown that when the cyclopropyldiketone 14 is exposed to base it undergoes cyclopropane ring opening via a retro-Michael addition, to

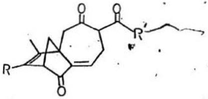


SCHEME III

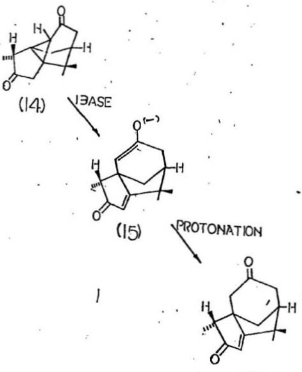
give the tricyclic enolate 15, which in turn gave the α,β-unsaturated ketone 16 upon protonation[19]. This study provides a reasonable analogy for gascardic acid and the route may now be adjusted to follow the sequence from 17 via 18 to 19.

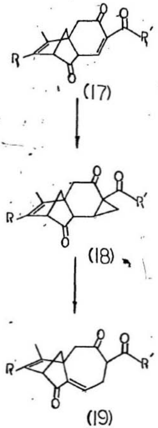
It is well established that nucleophilic addition to norbornanones occurs preferentially from the exo-face. We intend to add an allyl Grignard reagent to a norbornene, therefore, the stereochemistry must be corrected. Thus, the next stage of the synthesis requires a method for conversion of the endo-vinyl alcohol of type 20 into its epimer 21. A [2.3] sulfoxide rearrangement of the type described by Mislow[20,21] and further studied by Evans[22,23,24] should accomplish the required inversion. Evans and collaborators have applied this rearrangement to the synthesis of prostaglandin intermediates[25] and the total synthesis of (±)-bakkenolide A[26]. The allylic alcohol is transformed into the allylic sulfoxide followed by rearrangement to the other alcohol isomer as shown in Scheme IV.

The base accelerated oxy-Cope rearrangement should now be feasible. Evans increased the synthetic utility of the oxy-Cope rearrangement which originally required high temperature, with the discovery that the rate of this [3.3]-sigmatropic shift can be accelerated by a factor of 10^{10} to 10^{17} when the oxygen atom bears a negative charge[27,28]. This observation is a general one with widespread applications and implications, since all reactions which involve an α-bond cleavage should be accelerated by increasing the electron density on an adjacent atom. This anion oxy-Cope rearrangement has been used in the total synthesis of (±)-acoragermacrone, (±)-preisocalamendiol[29]; steroid analogues[30,31], as well as the stereoselective synthesis of (±)-juvabione[32]. For gascardic acid the desired cis-hydrindane nucleus will result from the oxy-Cope on 22 to give 23.



(13)

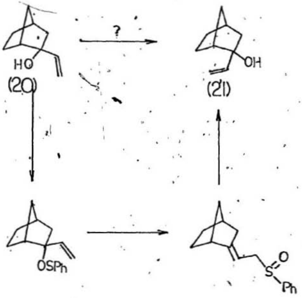




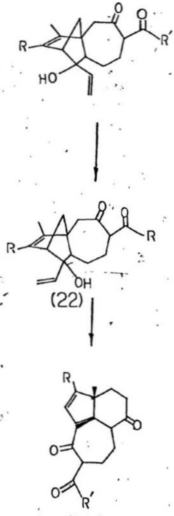
(17)

(18)

(19)



SCHEME IV



(22)

(23)

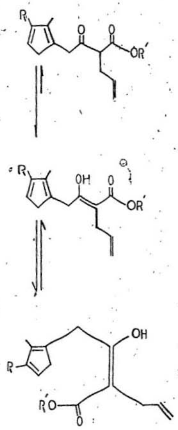
Results and Discussion

Part A: Preparation and Attempted Cyclization of Trisubstituted Cyclopentadienes.

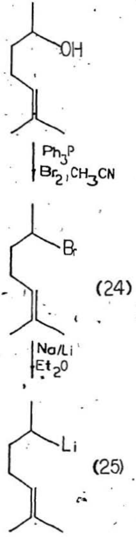
Our original plans required the preparation of suitable trisubstituted cyclopentadienes which could undergo Diels-Alder cyclizations to yield tricyclic adducts. It was anticipated that these tricyclic adducts could then be further developed into the skeleton of gascardic acid. As outlined earlier in the introduction, direct cyclization of these keto-esters was not possible, although removal of the ester moiety afforded smooth cyclization. It was originally thought that the enolization of the keto-ester system might be unfavourable and hold the dienophile in a conformation from which cyclization was disfavoured as shown in Scheme V.

To check this, trisubstituted cyclopentadienes were prepared in which this enolization was blocked. The thiophenyl group was selected to block this enolization, because it could later be oxidatively eliminated to provide the required double bond in the tricyclic system, for expansion of the six-membered ring.

The first model, the trisubstituted cyclopentadiene 31a was prepared as outlined in Scheme VI. The alkyllithium reagent 25 was prepared from 2-bromo-6-methyl-5-heptene (24) by reaction with freshly prepared 2% sodium/lithium alloy in ether while irradiating with an ultrasonic bath. This bromide was generated by treatment of 6-methyl-5-heptene-2-ol with triphenylphosphine and bromine at 0°C (63%). The enol ether 27, prepared from 2-methyl-1,3-cyclopentanedione in 91% yield, was condensed with 25 to give the enone 28a (70%) after aqueous acid work-up.



SCHEME V.


OH
Ph$_3$P
Br$_2$, CH$_3$CN
Br
(24)
Na/Li
Et$_2$O
Li
(25)

The ultrasonic bath was essential for the efficient preparation of the alkyllithium reagent as standard Grignard reaction conditions failed to give the desired product. As dimerization of the bromide was a competing side reaction, the use of two equivalents of the bromide resulted in a substantial increase in yield, from 37% to 70%.

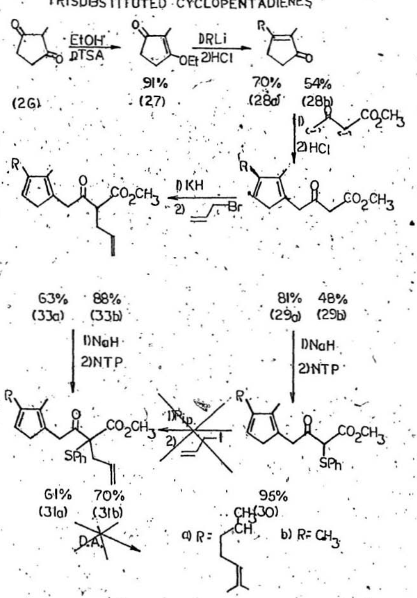
Weiler and Huckin[33] established that the optimum conditions for generation of the dianion of methyl acetoacetate involved using sodium hydride to abstract the first proton followed by n-butyllithium to abstract the second. Under these conditions the enone 28a was added rapidly to yield the desired cyclopentadiene 29a in 81% yield, after dehydration with 3N HCl.

The thiophenyl group was introduced into the keto-ester 29a by alkylation with N-thiophenylphthalimide[34] and sodium hydride was employed as the base to give the sulfide 30a in 95% yield. Unfortunately the allyl group could not now be introduced under a variety of conditions. This may be a result of steric hinderance or alternatively the lack of nucleophilicity of the highly delocalized anion. The reverse order of alkylation was investigated next. Alkylation of keto-ester 29a with allyl bromide gave 33a in 63% yield. A second alkylation with N-thiophenylphthalimide[35] afforded the target compound 31a in 61% yield.

Unfortunately this compound would not undergo the desired Diels-Alder cyclization. It was heated in toluene in a sealed tube at 180°C for three to five days but only decomposition products or starting material were obtained.

In some conformations the trisubstituted double bond appears to block the desired cycloaddition. To ascertain if this was a serious

SCHEME VI
PREPARATION AND ATTEMPTED CYCLIZATION OF TRISUBSTITUTED CYCLOPENTADIENES



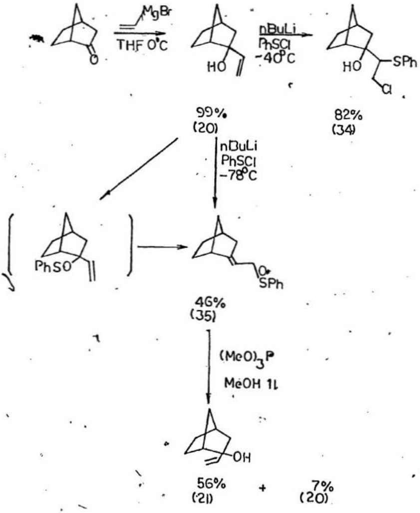
problem a simpler model (compound 31b) was investigated. This cyclopentadiene has a methyl group in place of the 2-methyl-2-heptenyl substituent. The synthetic route to compound 31b outlined in Scheme VI is analogous to that for compound 31a except that methyllithium replaced 25 in the initial addition to the enol ether 27.

As above, the keto-ester 29b is alkylated with allyl bromide to give 33b (88% yield), and further alkylated with N-thiophenyl phthalimide[35] to give the desired molecule 31b in 70% yield. Again the Diels-Alder cyclization did not occur. The reason for the failure of the cyclization was not enolization. It was found by a co-worker[9,10] that the keto-ester functionality in the side chain has a deleterious effect. Through space interactions between the ester and the cyclopentadiene place the dienophile in a conformation which inhibits cyclization as described above in the Introduction.

Part B: Epimerization of Vinyl Tertiary Alcohols.

It is well established that nucleophilic attack on norcamphor occurs preferentially from the exo-face. Thus in order to employ the "proposed" oxy-Cope rearrangement for the gascardic acid synthesis a method for controlling this addition or epimerizing the resulting endo-alcohol after vinyl magnesium bromide addition is required (Scheme VII). This potential difficulty was appreciated from the outset and there appeared to be a simple solution. This solution would take advantage of the [2,3] sulfoxide rearrangement in which the oxygen should migrate predominantly across the exo-surface to provide (in the presence of a thiophile) the desired exo-alcohol (Scheme VII).

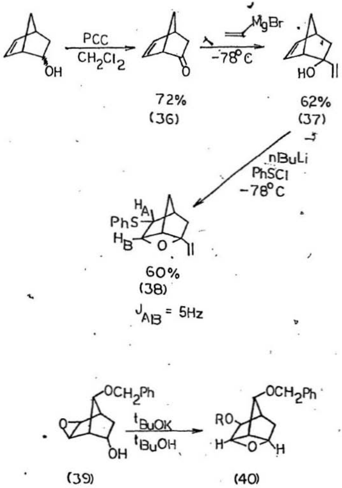
SCHEME VII


MgBr
THF 0°C
nBuLi
PhSCl
-40°C
HO
HO
SPh
Cl
O
99%
(20)
82%
(34)
nBuLi
PhSCl
-78°C
PhSO
O
SPh
46%
(35)
(MeO)$_3$P
MeOH 1L
OH
56%
(21)
+
7%
(20)

In order to test this hypothesis vinyl magnesium bromide was added to norcamphor to yield the endo-alcohol 20. It was found that by conducting the reaction at 0°C the endo-isomer was obtained exclusively in 99% yield. The next step involved oxygen alkylation and spontaneous rearrangement to the allylic sulfoxide. Initially it was intended to use vinyllithium in place of vinylmagnesium bromide, as Evans employed for his synthesis of (±)bakkenolide A[26]. This allows alkylation of the lithium salt directly with phenyl sulfenyl chloride[35] without isolating the alcohol. Unfortunately we had no luck in generating vinyllithium cleanly. Our attempts to alkylate the magnesium bromide salts of the alcohols directly failed under various conditions (Table 1). Also, using lithium salts at temperatures higher than -78°C or not freshly distilled phenyl sulfenyl chloride resulted in rapid addition across the double bond to yield endo-2-hydroxy-2-(1-thiophenyl-2-chloroethanyl) bicyclo[2.2.1] heptane(34) in 82% yield.

The allylic sulfoxide 35 was obtained in 45% yield when the temperature was lowered to -78°C and freshly distilled phenyl sulfenyl chloride was used. The allylic sulfoxide rearranged to give the exo-alcohol 21 in refluxing methanol in the presence of trimethyl phosphite in 56% yield. The ratio of exo to endo alcohols was 8:1.

The next model sequence (Scheme VIII) contained an endocyclic double bond so that after the stereochemistry was corrected an oxy-Cope rearrangement could occur. Bicyclo[2.2.1]hept-5-ene-2-ol was oxidized to bicyclo[2.2.1]hept-5-en-2-one with pyridinium chloro chromate[36] in 72% yield. Grignard reaction with vinyl magnesium bromide at -78°C gave only the endo-alcohol 37 in 62% yield. However,



OH
PCC
CH_2Cl_2
O
72%
(36)
MgBr
-78°C
HO
62%
(37)
nBuLi
PhSCl
-78°C
H_A
PhS
H_B
O
60%
(38)
J_{AB} = 5Hz
OCH_2Ph
O
OH
(39)
^tBuOK
^tBuOH
RO
H
O
H
OCH_2Ph
(40)

SCHEME VIII

TABLE 1

Attempted Alkylations of Alcohol 20

Counter Ion	Solvent	Temperature	Alkylating Agent	Result
MgBr$^{\oplus}$	Ether	-40°C	PhSCl	(34) 60%
"	"	-95°C	"	(34) 50%
"	DME	22°C	NTP[a]	N.R
Li$^{\oplus}$	Ether	0°C	PhSCl	(34) 40%
"	"	-40°C	"	(34) 82%
"	"	-78°C	"	(35) 46%
"	THF	66°C	NTP[a]	N.R

[a] NTP refers to N-thiophenyl phthalimide.[35]

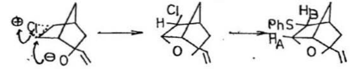
when the lithium anion was reacted with freshly distilled phenyl sulfenyl chloride at -78°C it did not give the desired O-alkylation. Instead oxetane 38 was formed exclusively. The structure was assigned by analogy to a similar oxetane 39 prepared by Ikegami et al[37] in which epoxide 40 was opened with the potassium anion of the alcohol. In addition Saksena et al[38] had shown that the alkoxide could not open the epoxide from the other side to give the twisted oxetane due to steric constraints.

Based on the stereochemistry of the product it appears that this product arose from association of the positive chlorine with the reactive norbornene double bond, followed by oxetane formation and finally displacement of the chlorine by thiophenolate. The stereochemistry was established from 'H nmr coupling constants by analogy with results for 41 and 42 in which JAB = 4.8 Hz and ~ 0.5 Hz respectively.

A series of bases and reaction conditions were used to try and enhance the desired O-alkylation (Table 2) but unfortunately all of these attempts failed.

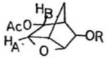
To establish the relative reactivity of the phenyl sulfenyl chloride it was added to norbornene at -78°C. The red colour of the phenyl sulfenyl chloride disappeared immediately to give compound 43 resulting from addition across the double bond.

Although initially disappointing differential functionalization of remote sites in the norbornene skeleton is often difficult and this oxetane forming reaction may be useful for the synthesis of thromboxanes such as thromboxane A_2 44 or related analogues such as 45. Thromboxanes



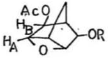
(38)

$J_{AB} = 5\,Hz$



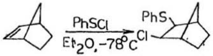
(41)

$J_{AB} = 4.8\,Hz$

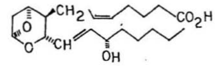


(42)

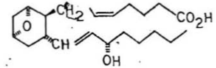
$J_{AB} < 0.5\,Hz$



(43)



(44)



(45)

TABLE 2

Attempted Alkylations of Alcohol 37

Base	Solvent	Temperature Time	Alkylating Agent	Result
nBuLi	Ether	-78°C/1 h	PhSCl	(38) 60%
"	"	0°C/22 h	[b]NTS	N.R.
"	DME	22°C/18 h	MeSSMe	N.R.
KH	DME	22°C/20 h	[a]NTP	N.R.
"	DME	85°C/18 h	[a]NTP 18-crown-6	N.R.
"	DME/HMPA	-78°C/1 h	PhSCl	(38) 40%
"	DME	22°C/16 h	MeSSMe	N.R.
"	"	22°C/16 h	MeSSMe 18-crown-6	N.R.
"	"	85°C/16 h	MeSSMe	N.R.
"	"	22°C/20 h	[b]NTS	N.R.

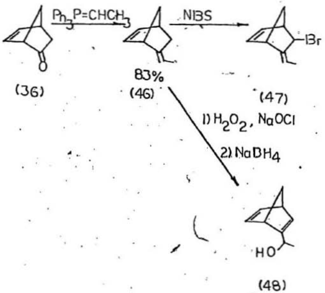
[a] NTP refers to N-thiophenyl phthalimide[35].

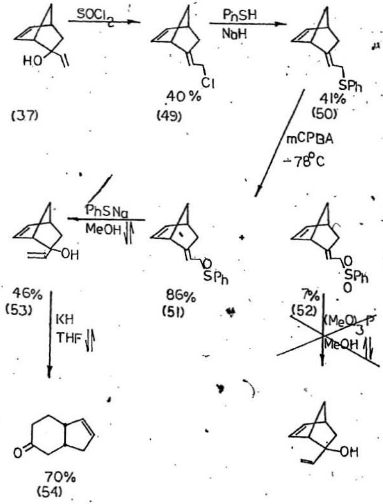
[b] NTS refers to N-thiophenyl succinimide[39].

have received considerable attention lately due to their potent blood platelet aggregating and vasoconstrictor properties. It has also been found that analogues of thromboxanes have similar activity and many have been synthesized.[37,40,41,42,43]

Another route to the allylic sulfoxide was required since the phenyl sulfenyl chloride added across the double bond faster than alkylation of the oxygen anion. Initially a number of Wittig reagents were tried on ketone 36 with functionality on C-2, but these all failed due to either formation of a di-Wittig reagent or elimination under the basic conditions necessary for formation of the ylid. Subsequently the simple unsubstituted ylid generated from ethyl triphenylphosphonium bromide was used to produce the olefin 46 in 83% yield. It was known that selenium dioxide would oxidize the secondary centre preferentially, so N-bromosuccinimide was used to attempt to functionalize the primary position but it only delivered the bromine in the secondary position to give bromide 47. Singlet oxygen which could have given us the desired exo-alcohol was investigated next but it unfortunately gave the secondary alcohol 48.

Allyl alcohols frequently afford rearranged chlorides upon treatment with thionyl chloride and the primary chloride 49 should be expected in this case. Indeed thionyl chloride gave 49 in 40% yield. This chloride was very unstable and impossible to purify completely. Thus the crude chloride was transformed into the thioether 50 by displacement with sodium thiophenolate (41%). The sulfide was oxidized with m-chloroperbenzoic acid at -78°C to give the sulfoxide 51 in 86% yield; this was accompanied by some of the corresponding sulfone 52 (7%) but none of the possible epoxides. In theory, rearrangement of


(36)
Ph3P=CHCH3
83%
(46)
NBS
Br
(47)
1) H2O2, NaOCl
2) NaBH4
HO
(48)


SOCl2
PnSH
NaH
HO
Cl
40 %
(49)
SPh
41%
(50)
(37)
mCPBA
-78°C
PhSNa
MeOH
OH
O
SPh
46%
(53)
86%
(51)
O
SPh
O
7%
(52)
(MeO)3P
MeOH
KH
THF
O
70%
(54)
OH

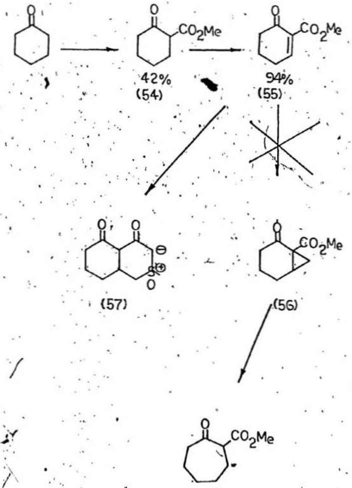
the sulfone to the exo-alcohol 53, should be possible but when it was refluxed in methanol in the presence of trimethyl phosphite for up to six days only starting sulfone 52 was recovered. This may be explained by the fact that the sulfones are obtained by heating sulfinates, the intermediate in the rearrangement to the exo-alcohol. It was shown by Hiroi et al that the equilibrium between allylic sulfinates and allylic sulfones is shifted toward the sulfone.[44] This would result in the sulfone being present almost exclusively and the rearrangement therefore cannot occur readily.

The allylic sulfoxide 51 was rearranged to the exo-alcohol 53 in 46% yield by refluxing in methanol in the presence of sodium thiophenolate. The ratio of exo to endo-alcohol obtained was 8.5:1. Refluxing the sulfoxide 51 in methanol in the presence of trimethyl phosphite gave some of the desired exo-alcohol 53 accompanied by significant decomposition. The cis-hydrindenone 54 was obtained cleanly in 70% yield when the potassium anion of the alcohol was refluxed in THF for 20 minutes. As expected, when the endo-alcohol was treated under the same conditions no reaction occurred.

Part C: Ring Expansion of Six to Seven-Membered Rings.

As discussed earlier direct Diels-Alder cyclization to give the seven-membered ring was not possible due to entropy disfavouring formation of the cycloheptane.[9] Thus a ring expansion method was required which would leave the keto-ester functionality intact and add the new carbon adjacent to the ester (Scheme IX). We chose to prepare a cyclopropane and cleave it by a retro-Michael addition type reaction.

SCHEME IX



The first model chosen was consistent with our earlier models. Methyl keto-ester 54 was prepared, a double bond was inserted by selenide formation and oxidative elimination to give the unsaturated keto-ester 55 in 94% yield. This was then reacted with the sulfur ylid prepared from trimethyl sulfoxonium iodide, which was expected to give the bicyclo[4.1.0] heptane system 56. However, as found by Corey et al[46,47] the sulfur ylid adds competetively to the α,β-unsaturated methyl and ethyl esters to give β-ketosulfoxonium ylides such as 57 (Scheme IX). Since this failed we tried the addition of the anion of nitromethane to the unsaturated keto-ester as shown by Annen[14]. This method gave none of the desired product; apparently this method requires the presence of at least one nitrile to activate the double bond.

The tertiary butyl ester was next synthesized. This proved challenging. Trans-esterification from methyl or ethyl ester to tertiary butyl ester failed, not even traces of the desired ester were found under various conditions. Direct acylation of cyclohexanone under similar conditions to these employed for the preparation of the methyl ester using di-t-butyl carbonate, t-butyl methyl carbonate etc. was studied under various conditions shown in Table 3, but these all failed. Thus, the methyl ester was reduced with LAH to the diol then oxidized to the keto-acid which was transformed into the acid chloride then to the t-butyl ester but this was very lengthy and yields were terrible. Alkylation of the dianion of t-butyl acetoacetate with 1,3-diiodopropane also failed to give the desired β-keto-t-butylester.

Finally a compound used to protect amines, di-t-butyldicarbonate was used to alkylate the sodium anion of cyclohexanone to give the

TABLE 3

Attempts to Prepare Tertiary Butyl Ester <u>58</u> from Cyclohexanone

Base	Solvent	Time	Temperature	Acylating Agent	Result
NaH	benzene	24 h	reflux	$^{t}\mathrm{BuO}\overset{\mathrm{O}}{\mathrm{C}}\mathrm{OMe}$	N.R.
"	toluene	23 h	"	"	N.R.
"	"	24 h	"	$^{t}\mathrm{BuO}\overset{\mathrm{O}}{\mathrm{C}}\mathrm{O}^{t}\mathrm{Bu}$	N.R.
"	"	24 h	"	$^{t}\mathrm{BuO}\overset{\mathrm{O}}{\mathrm{C}}\overset{\mathrm{O}}{\mathrm{C}}\mathrm{O}^{t}\mathrm{Bu}$	N.R.
"	"	24 h	"	$^{t}\mathrm{BuO}\overset{\mathrm{O}}{\mathrm{C}}\mathrm{O}\overset{\mathrm{O}}{\mathrm{C}}\mathrm{O}^{t}\mathrm{Bu}$	<u>58</u> 73%

desired keto-ester 58 in 73% yield. This was then transformed into the α,β-unsaturated keto-ester by preparation of the selenide and oxidative elimination to give 59 in 97% yield (Scheme X). The cyclopropane 60 was prepared by the addition of the ylid prepared from trimethyl sulfoxonium iodide to 59in 65% yield.

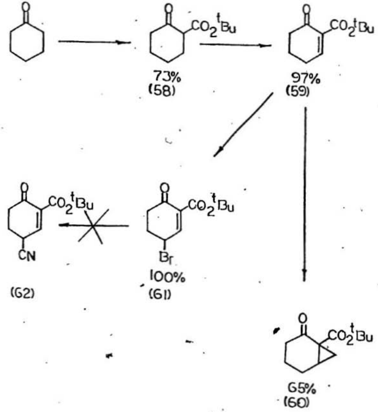
It remained to activate the 4-position so that a proton could be removed and retro-Michael addition could take place. The α,β-unsaturated keto-ester 59 was reacted with N-bromosuccinimide to give bromide 61 quantitatively. But when the bromide was reacted with sodium cyanide to give nitrile 62 only enolization occurred.

A better model is a compound where the position α to the cyclopropane would already be activated (Scheme XI). We chose to start with 2,2-dimethyl-1,3-cyclohexanedione and alkylate it with di-*t*-butyl-dicarbonate to give keto-ester 63 in 56% yield. The double bond was put in via the selenide as in the previous example to give 64 in 85% yield. This was then reacted with the sulfur ylid under a variety of conditions but the desired cyclopropane was not obtained. Unfortunately the model study could not be completed as anticipated but the principle seems valid and ultimately it should be possible to employ a related sequence in the total synthesis.

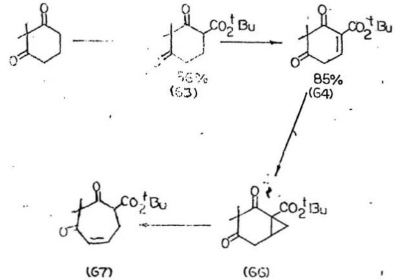
Part D: Modification of Trisubstituted Cyclopentadienes.

The preparation of a cyclopropane in the presence of the methyl ester was not feasible and thus the scheme toward gascardic acid was changed to include a tertiary butyl ester. We first reacted enone 28b

SCHEME X


O
CO2tBu
73%
(58)
O
CO2tBu
97%
(59)
O
CO2tBu
CN
(62)
O
CO2tBu
Br
100%
(61)
O
CO2tBu
65%
(60)

SCHEME XI



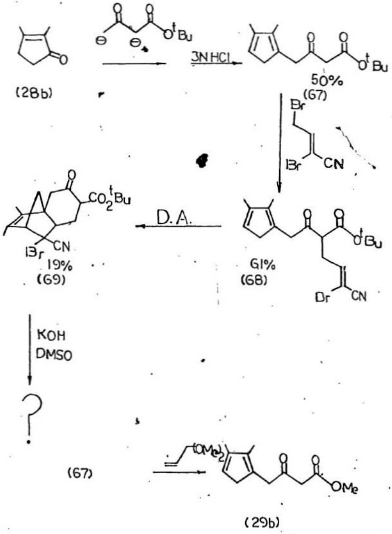
with the dianion of tertiary butyl acetoacetate to give keto-ester 67 in 50% yield. This was then alkylated with 1,3-dibromo-1-cyanopropene which was prepared by allylic bromination of the product of the Wittig reaction of acetaldehyde with bromocyanotriphenyl phosphine methylide[48] to give 68 in 61% yield (Scheme XII).

This was then heated in a sealed tube in toluene at 180°C for 24 h to give the Diels-Alder adduct 69 in 19% yield. Unfortunately when the bromo-nitrile was hydrolyzed to the ketone it appeared that the keto-ester was also hydrolyzed and decarboxylated, although this structural assignment is tentative.

Alkylation of keto-ester 67 with the dimethyl acetal of propenal in the presence of nickel acetoacetonate resulted in trans-esterification to methyl ester 29b.

We now chose to switch to the methyl ketone as opposed to the tertiary butyl ester. Unfortunately the dianion reaction with 2,4-pentanedione would not occur under the same conditions as the keto-esters. Finally two equivalents of lithium di-isopropyl amide in DME generated the dianion which was reatted with enone 28b to give diketone 71, but the yield was not very good (13%) (Scheme XIII). This method was pursued in hopes that the yield could later be improved. In keeping with earlier studies by Weiler and Huckin[33] it may be that benzyloxyacetone would be a better choice. Several attempts were made to alkylate this diketone (Table 4); the only reagent that would alkylate the diketone under normal conditions was allyl bromide which gave 72 in 95% yield.

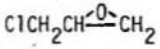
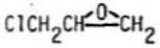
This was not of much use since we required functionality on the double bond which could be transformed into a ketone. We then tried


(28b)
O^tBu
3N HCl
50%
(67)
Br
Br
CN
D.A.
$CO_2{}^tBu$
Br
CN
19%
(69)
61%
(68)
O^tBu
Br
CN
KOH
DMSO
?
(67)
$(OMe)_2$
OMe
(29b)

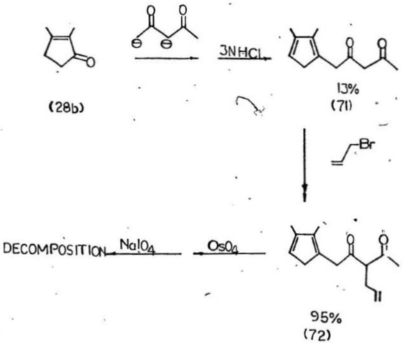
SCHEME XII

TABLE 4

Attempted Alkylations of 71

Base	Solvent	Alkylating Agent	Temperature/ Time	Yield
KH	DME	$BrCH_2CH=C(Cl)CN$	22°C/2 h	-
"	"	$ClCH_2CH(OMe)_2$	22°C/7 h	-
"	"	"	85°C/20 h	-
"	DMSO	"	27°C/20 h	-
"	DME	$CH_2=CHCH_2Br$	22°C/20 h	95%
"	"	$BrCH_2CH_2OH$	22°C/20 h	-
NaH	DMSO	 $ClCH_2CH\overset{O}{\frown}CH_2$	22°C/20 h	-
K_2CO_3	acetone	 $ClCH_2CH\overset{O}{\frown}CH_2$	56°C/20 h	-

SCHEME XIII



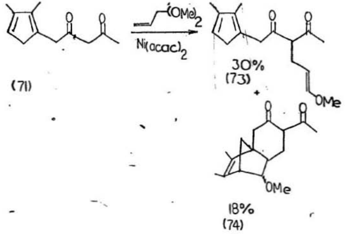
to cleave the double bond to give the aldehyde which could be reacted with a Wittig reagent to give the required functionality. But unfortunately when this cleavage was attempted with osmium tetroxide and sodium periodate only total decomposition resulted.

It was found that compound 71 could be alkylated with the dimethyl acetal of propenal, neat, at 200°C in the presence of nickel acetoacetonate to give 73 and also some of the cyclized product 74 (Scheme XIV). This route was no longer pursued because the yield of the dianion reaction could not be improved, although as suggested above benzyloxyacetone should be more reactive.

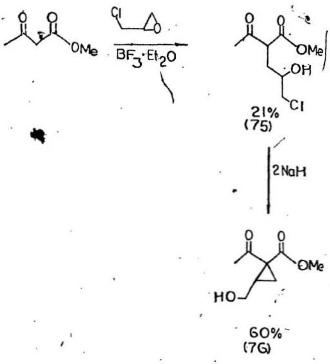
Direct cyclopropane formation from the keto-ester using the alkylation method developed by Weiler[49] for the first bond formation was examined next. Initially methyl acetoacetate was reacted with epichlorohydrin in the presence of boron trifluoride etherate to give chlorohydrin 75. This was then exposed to two equivalents of sodium hydride to give cyclopropane 76 (Scheme XV).

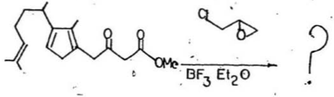
Application of this method to compound 29a, which contained a double bond in the side chain, appeared to result in an ene reaction between the side chain double bond and the cyclopentadiene. When this was tried on compound 67 which does not contain a sidechain double bond, it appeared that the cyclopentadiene portion reacted also. Clearly further experimentation is required in order to introduce the cyclopropane unit possibly via a diazoketone addition.

SCHEME XIV

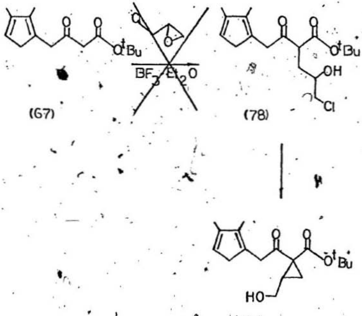


SCHEME XV





(29a)



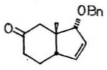
(67) (78)

(79)

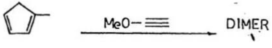
Part E: Vinyl Alcohol Epimerization Extension.

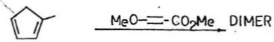
Jung[31] has used the oxy-Cope rearrangement to prepare the hydrindane portion of steroids. To accomplish this a lengthy sequence was required in order to ensure the correct stereochemistry of the norbornene-alcohol intermediate. It should be possible to prepare his intermediate more directly employing the [2,3] sulfoxide rearrangement sequence developed above. A brief start was made in this direction with the intention of preparing the steroid intermediate 80 synthesized by Jung and Hatfield[31] (Scheme XVI). The initial step required the Diels-Alder reaction of methyl cyclopentadiene with a suitably functionalized dienophile.

We could not chose a dienophile activated on one side, such as a ketene equivalent because the Diels-Alder adduct would have the functionality and the methyl group both on the same side which was unacceptable. Methoxy acetylene was not sufficiently reactive and even using a Lewis acid catalyst gave only dimer. Methyl-3-methoxypropionate, was also not active enough and thus maleic anhydride was employed which gave a mixture of regioisomers 81 and 82 (2:1). The two isomers were not easily separated chromatographically so the mixture was hydrolyzed to give diacids 83 and 84. The diacids were reacted with lead tetraacetate to give dienes 85 and 86. This part was then stopped due to lack of time, but the desired diene which is now symmetrical should be separable. Reaction with 9-BBN should give mainly the desired alcohol 87 which could after oxidation to ketone 88 be used to synthesize hybrindenone 80.

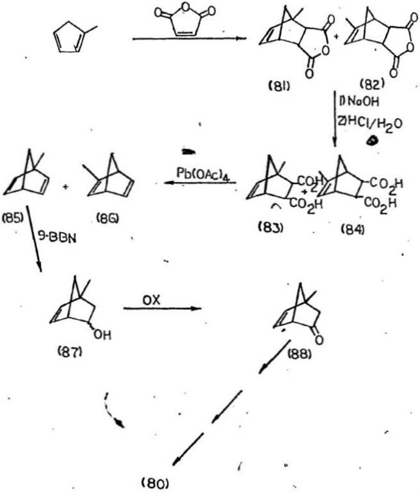


(80)





SCHEME XVI



Experimental

Infrared spectra were recorded on a Perkin-Elmer 237B or 451 grating spectrophotometer, and were calibrated with the 2850 and 1601 cm^{-1} bands of polystyrene film. Ultraviolet spectra were recorded on a Perkin-Elmer 202 uv-visible spectrophotometer and were calibrated with the 279.4 nm band of a Holmium oxide filter. Proton magnetic resonance spectra were measured at 80 MHz with a Bruker WP80 spectrometer employing a chloroform lock or at 60 MHz with a Varian EM 360 spectrometer or at 400 MHz with a Bruker WH 400 spectrometer at the University of Alberta. Signal positions are reported in ppm downfield from tetramethylsilane (delta scale) as an internal standard, the number of protons, multiplicity, coupling constants, and the proton assignments are indicated in parentheses. Mass spectra were determined on a V.G. Micromass 7070 HS instrument using an ionization energy of 70 electron volts.

Gas liquid chromatographic analyses were conducted on a Hewlett Packard 402B gas chromatograph equipped with a column (3m x 6 mm i.d.) containing 1.5% OV-17 supported on Gas Chrome Q using helium as the carrier gas. Thin layer chromatographic analyses were carried out on commercial precoated silica gel plates with fluorescent indicator (Eastman Kodak silica gel 13181). Preparative thin layer chromatography was conducted on 20 x 20 cm glass plates coated with silica gel $PF_{254 + 366}$ type 60 (E. Merck). Flash chromatography using BDH silica gel Kieselgel 60, 230-400 mesh was employed for all column chromatography.

Petroleum ether refers to a fraction of boiling range 30-60°C. Anhydrous diethyl ether (ether), tetrahydrofuran (THF), dimethoxyethane (DME), and dioxane were obtained by distillation from lithium aluminium hydride or potassium/benzophenone. Absolute ethanol and methanol were dried by distillation from magnesium. Dry hexamethylphosphoramide (HMPA), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and diisopropylamine were prepared by distillation from calcium hydride. Solutions in organic solvents were dried over anhydrous magnesium sulphate and stripped of solvent with a Buchi rotary evaporator connected to a water aspirator. Unless otherwise indicated all reactions were conducted under an atmosphere of dry nitrogen.

2-Bromo-6-methyl-2-heptene (24)

Bromine (43.60 g, 272.80 mmol) in acetonitrile (200 mL) was added dropwise to a stirred suspension of triphenylphosphine (71.20 g, 271.45 mmol) in acetonitrile (400 mL) at 0°C. The reaction mixture was allowed to warm to 22°C, and 6-methyl-5-heptene-2-ol (34.00 g, 265.16 mmol, Aldrich) in acetonitrile (100 mL) was added dropwise, stirring was continued for 1 h after addition was complete. The solution was concentrated, the residue was treated with petroleum ether (500 mL), shaken vigorously and cooled to precipitate the phosphine salt. The salt was removed by filtration, the filtrate was concentrated and the clear oil obtained, purified by distillation, b.p. 69-70°C/10 mm Hg, to give 24, 31.64 g (63%); ir (film): 2900 (H-C=), 1445 (C=C) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ: 1.60 (d, 6H), 1.70 (d, 3H), 2.00 (m, 4H), 4.09 (sextet, 1H, R_2CHBr), 5.09 (t, 1H, $R_2C=CHR$); M.S. (m/z): 191 (M^+), 193 (M+2).

3-Ethoxy-2-methyl-2-cyclopentene-1-one (27)

2-Methyl-1,3-cyclopentanedione (25.00 g, 222.96 mmol, Aldrich) and p-toluene sulfonic acid (1.5 g) in absolute ethanol (300 mL) were suspended in benzene (400 mL) and refluxed for 2 days, a pressure equalizing dropping funnel (250 mL) containing molecular sieves was placed between the reaction flask and the condenser to remove water. The solution was concentrated to afford a yellow oil which was purified by distillation, b.p. 90-93°C/0.4 mm Hg, to give enol ether 27, m.p. 36-38°C, 27.86 g (91%); ir (film): 2920 (C-H), 1685, 1628 (RO-C=C-C=O) cm^{-1}; 'H nmr ($CDCl_3$) δ: 1.46 (t, 3H, $OCH_2C\underline{H}_3$), 1.62 (t, 3H), 2.42 (m, 2H), 2.67 (m, 2H), 4.28 (q, 2H, OCH_2); M.S. (m/z): 140 (M^+), 112 ($M-C_2H_4$), 83 ($M-C_2H_3O$); Exact mass calculated for $C_8H_{12}O_2$: 140.0837, found: 140.0834.

3-(2-Methyl-2-heptenyl)-2-methyl-2-cyclopenten-1-one (28a)

Bromide 24 (21.51 g, 112.62 mmol) in anhydrous ether (200 mL) was added dropwise to a mixture of the enol ether 27 (7.90 g, 56.43 mmol) and 2% Na in Li alloy (6.4 g) in anhydrous ether (150 mL) suspended in an ultrasonic bath. The mixture was irradiated during addition and continued for a further 3 h. Any unreacted alloy was removed by filtration, and the filtrate quenched by the dropwise addition of 3N HCl at 0°C. The resulting ethereal solution was washed with a second portion of acid, the combined aqueous extracts were extracted with ether and the combined ethereal extracts washed with brine, dried, concentrated and the product purified by distillation, b.p. 89-91°C/ 0.05 mm Hg, to afford the enone 28a, 8.03 g, (70%); ir (film): 1700 and 1640 (α,β-unsaturated ketone) cm^{-1}; 'H nmr ($CDCl_3$) δ: 1.15 (d, 3H), 1.50 (m, 2H), 1.60 (s, 9H), 1.85 (m, 2H), 2.40 (m, 4H), 2.89 (sextet, 1H, R_2CHMe), 5.09 (t, 1H, $Me_2C=CHR$); Exact mass calculated for $C_{14}H_{22}O$: 206.1671, found: 206.1673.

Methyl-3-oxo-4-[2-methyl-3-(6-(2-methyl-2-heptenyl) cyclopentadienyl]-butyrate (29a)

Methyl acetoacetate (0.78 g, 6.72 mmol, Aldrich) in THF (10 mL) was added dropwise to a mixture of sodium hydride (0.38 g, 9.50 mmol, 60% suspension in oil, Aldrich) (washed with hexane) in THF (10 mL) at 0°C. After stirring for 10 min, a solution of n-butyllithium (4.06 mL, 9.66 mmol, 2.1 M, Aldrich) was added dropwise. Ten min later the enone 28a (1.38 g, 6.72 mmol) was added in one aliquot, stirred for 20 min and quenched with 3N HCl. The mixture was extracted twice with ether and the combined ether extracts stirred for 1 h with 3N HCl. The ether fraction was separated, the aqueous fraction extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and the product purified by flash chromatography (30% ether/hexanes), to yield 29a, 1.66 g (81%); ir (film): 1745, 1635, 1600 and 1570 (keto-ester and cyclopentadiene) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.10 (m, 8H, 1.60 (m, 9H), 2.45 (m, 2H), 3.00 (m, 2H, $C=CCH_2C=C$), 3.55 (s, 2H, $COCH_2COOR$), 3.75 (s, 3H, OCH_3), 5.11 (t, 1H, $HC=C(CH_3)_2$), 6.10 (t, 1H, $C=CHCH_2C=C$); Exact mass calculated for $C_{19}H_{28}O_3$: 304.2038, found: 304.2051.

Methyl-2-thiophenyl-3-oxo-4-[2-methyl-3-(6-(2-methyl-2-heptenyl)) cyclopentadienyl]butyrate (30a)

Keto-ester 29a (0.20 g, 0.69 mmol) in DME (5 mL) was added dropwise to a mixture of sodium hydride (0.04 g, 1.00 mmol, 60% suspension in oil, Aldrich) (washed with hexane) in DME (5 mL) at 0°C. After the addition was complete, the reaction mixture was warmed to 22°C and a solution of N-thiophenylphthalimide[34] (0.21 g, 0.82 mmol) in DME (15 mL) was added dropwise. After stirring for 24 h the reaction mixture was quenched by the addition of water, extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated, and the product purified by flash chromatography (30% ethyl acetate/petroleum ether) to yield 30a, 0.27 g (95%); ir (film): 1740, 1650, 1600 and 1560 (keto-ester and cyclopentadiene) cm^{-1}; 'H nmr ($CDCl_3$) δ: 1.10 (m, 8H), 1.60 (m, 9H), 2.45 (m, 2H), 3.00 (m, 2H), 3.70 (s, 3H, OCH_3), 5.05 (t, 1H, $CH{=}C(CH_3)_2$), 6.68 and 6.18 (each t, both isomers of cyclopentadiene), 7.15 (m, 5H, Ar-H), 14.14 (br.s., 1H, OH from enol).

Attempted Preparation of Methyl-2-thiophenyl-2-allyl-3-oxo-4-[6-(2-methyl-2-heptenyl)cyclopentadienyl]butyrate (31a)

Piperidine (0.05 g, 0.60 mmol) was added dropwise to a solution of keto-ester 30a (0.20 g, 0.50 mmol) in DME (5 mL) at 0°C. The solution was allowed to warm to 22°C and allyl iodide (0.08 g, 0.50 mmol, Aldrich) in DME (5 mL) was added dropwise and allowed to stir for 2 h; no reaction had occurred.

Methyl-2-allyl-3-oxo-4[6-(2-methyl-2-heptenyl)cyclopentadienyl]-butyrate (33a)

Keto-ester 29a (0.70 g, 2.40 mmol) in DME (10 mL) was added dropwise to a mixture of potassium hydride (0.33 g, 2.98 mmol, 35%

suspension in oil, Aldrich) (washed with hexane) in DME (10 mL) at 0°C. The reaction mixture was allowed to warm to 22°C and allyl bromide (0.29 g, 2.40 mmol, Aldrich) was added in one aliquot. After stirring for 3 h the reaction mixture was quenched with water and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and the product purified by flash chromatography (20% ethyl acetate/petroleum ether), yield of <u>33a</u> 0.50 g (63%); ir (film): 1790, 1670, 1640 and 1575 (keto-ester and cyclopentadiene) cm^{-1}; 'H nmr ($CDCl_3$) δ: 1.10 (m, 8H), 1.55 (m, 9H), 2.50 (m, 4H), 2.97 (m, 2H, $C{=}C{-}CH_2{-}C{=}C$), 3.50 (m, 1H, COCHRCOOR), 3.68 (s, 3H, OCH_3), 5.00 (m, 4H, $CH{=}CH_2$ and $CH{=}C(Me)_2$), 5.98 (t, 1H, $C{=}C\underline{H}CH_2C{=}C$); Exact mass calculated for $C_{22}H_{32}O_3$: 344.2351, found: 344.2364.

<u>Methyl-2-thiophenyl-2-allyl-3-oxo-4-[6-(2-methyl-2-heptenyl)-cyclopentadienyl]butyrate (31a)</u>

Keto-ester <u>33a</u> (0.50 g, 1.74 mmol) in DME (10 mL) was added dropwise to a mixture of sodium hydride (0.08 g, 1.89 mmol, 60% suspension in oil, Aldrich) (washed with hexane) in DME (5 mL) at 0°C. After the addition was complete, the reaction mixture was warmed to 22°C and a solution of N-thiophenylphthalimide[34] (0.44 g, 1.80 mmol) in DME (15 mL) was added dropwise. After stirring for 3 days the reaction mixture was quenched with water and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and the product purified by flash chromatography (15% ethyl acetate/petroleum ether), to yield <u>31a</u> 0.41 g (61%); ir (film): 1730, 1665, 1640 and 1570 (keto-ester and cyclopentadiene) cm^{-1}; 'H nmr (CCl_4) δ: 1.10 (m, 8H), 1.60 (m, 9H), 2.50 (m, 4H), 3.00

(m, 2H, C=CCH$_2$C=C), 3.68 (s, 3H, OCH$_3$), 5.05 (m, 4H, CH=CH$_2$ and CH=(C(Me)$_2$), 6.05 (t, 1H, C=C<u>H</u>CH$_2$C=C), 7.19 (br.s., 5H, Ar-H).

Attempted Diels-Alder Cyclization of Methyl-2-thiophenyl-2-allyl-3-oxo-4-[6-(2-methyl-2-heptenyl)cyclopentadienyl]butyrate (31a)

A solution of triene <u>31a</u> (0.08 g, 0.20 mmol) in degassed toluene (15 mL) was placed in a sealed tube and heated at 180°C for 5 days, recovered mainly starting material and some decomposition.

2,3-Dimethyl-cyclopent-2-ene-1-one (28b)

Methyllithium (73.76 mL, 114.33 mmol, 1.55 M, Aldrich), was added to a solution of enol ether <u>27</u> (16.00 g, 114.28 mmol) in THF (50 mL) at 0°C, after the addition was complete the solution was warmed to 22°C. After stirring for 3 h the reaction mixture was quenched with 3N HCl and worked up as in <u>13</u>. The oil was purified by distillation, b.p. 78-84°C/10 mm Hg to give <u>28b</u>, 5.41 g (54%); ir (film): 2905 (C-H), 1700, 1655 (α,β-unsaturated ketone) cm^{-1}; 'H nmr (CCl$_4$) δ: 1.58 (s, 3H, CH$_3$-C=C-C=O), 2.02 (s, 3H, C=C(CH$_3$)C=O), 2.25 (m, 2H), 2.52 (m, 2H); M.S. (m/z): 110 (M$^+$); Exact Mass calculated for C$_7$H$_{10}$O): 110.0732, found: 110.0730.

Methyl-3-oxo-4[2,3-dimethyl cyclopentadienyl]butyrate (29b)

Methyl acetoacetate (3.03 g, 26.10 mmol, Aldrich) in THF (20 mL) was added dropwise to a mixture of sodium hydride (1.48 g, 37.00 mmol, 60% suspension in oil, Aldrich) (washed with hexane) in THF (20 mL) at 0°C. After stirring for 10 min, a solution of <u>n</u>-butyllithium (15.77 mL, 33.12 mmol, 2.1 M, Aldrich) was added dropwise. Ten min later the enone 28b (2.87 g, 26.10 mmol) was added in one aliquot, stirred for 30 min and quenched with 3N HCl and worked-up as in 29a. The oil was purified by flash chromatography to yield 29b, 2.57 g (48%), m.p. 47-48°C; ir (film): 3027 (C-H), 1735, 1720 and 1578 (keto-ester and cyclopentadiene) cm^{-1}; ^{1}H nmr (CCl$_4$) δ: 1.70 (s, 3H), 1.92 (s, 3H), 2.45 (m, 2H), 2.92 (m, 2H, C=CCH$_2$C=C), 3.40 (s, 2H, COCH$_2$COOR), 3.70 (s, 3H, OCH$_3$), 5.98 (t, 1H, C=C$\underline{H}$CH$_2$C=C); M.S. (m/z): 208 (M$^+$), 135 (M-73) (McLafferty rearrangement); Exact mass calculated for $C_{12}H_{16}O_3$: 208.1099, found: 208.1069.

Methyl-2-allyl-3-oxo-4[2,3-dimethyl-cyclopentadienyl]butyrate (33b)

Keto-ester 29b (2.57 g, 12.40 mmol) in DME (25 mL) was added dropwise to a mixture of potassium hydride (1.71 g, 14.90 mmol, 35% suspension in oil, Aldrich) (washed with hexane) in DME (25 mL) at 0°C. The reaction mixture was allowed to warm to 22°C and allyl bromide (1.50 g, 12.40 mmol, Aldrich) was added in one aliquot. After stirring for 3 h the reaction mixture was quenched with water and worked-up as in 33a. The oil was purified by flash chromatography (30% ethyl acetate/petroleum ether) to yield 33b, 2.70 g (88%); ir (film): 1770, 1700, 1600 and 1460 (keto-ester and cyclopentadiene) cm^{-1}; ^{1}H nmr (CCl$_4$) δ: 1.68 (s, 3H), 1.90 (s, 3H), 2.48 (m, 4H), 2.90 (m, 2H, C=C-CH$_2$-C=C), 3.35 (m, 1H, COCHRCOOR), 3.64 (s, 3H, OCH$_3$), 5.50-4.85 (br.m, 3H, CH=CH$_2$), 5.95 (t, 1H, C=CHCH$_2$C=C); M.S. (m/z): 248 (M$^+$), 135 (M-113) (McLafferty rearrangement); Exact mass calculated for $C_{15}H_{20}O_3$: 248.1412, found: 248.1421.

Methyl-2-thiophenyl-2-allyl-3-oxo-4[2,3-dimethyl cyclopentadienyl]-butyrate (31b)

Keto-ester 33b (2.65 g, 10.70 mmol) in DME (25 mL) was added dropwise to a mixture of sodium hydride (0.51 g, 12.80 mmol, 60% suspension in oil, Aldrich) (washed with hexane) in DME (25 mL) at 0°C. After the addition was complete, the reaction mixture was warmed to 22°C and a solution of N-thiophenylphthalimide[34] (2.81 g, 11.00 mmol) in DME (30 mL) was added dropwise. After stirring for 24 h the reaction mixture was quenched with water and worked-up as in 31a. The oil was purified by flash chromatography (20% ether/hexanes) to yield 31b, 2.61 g (70%); ir (film): 1725, 1660, 1630 and 1520 (keto-ester and cyclopentadiene) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.66 (s, 3H), 1.85 (s, 3H), 2.43 (m, 4H), 2.95 (m, 2H, $C{=}CCH_2C{=}C$), 3.60 (s, 3H, OCH_3), 5.48-4.85 (br.m., 3H, $CH{=}CH_2$), 6.62 and 5.73 (each t, both isomers of cyclopentadiene), 7.20 (m, 5H, Ar-H); M.S. (m/z): 356 (M^+), 135 (M-221) (McLafferty rearrangement); Exact mass calculated for $C_{21}H_{24}SO_3$: 356.1446, found: 356.1437.

Attempted Diels-Alder Cyclization of Methyl-2-thiophenyl-2-allyl-3-oxo-4-[2,3-dimethyl cyclopentadienyl]butyrate (31b)

A solution of triene 31b (1.00 g, 2.81 mmol) in degassed toluene (50 mL) was placed in a sealed tube and heated at 180°C for 24 h. After the solvent was removed it appeared that only decomposition had occurred.

endo-2-Hydroxy-2-vinyl bicyclo[2.2.1]heptane (20)

Norcamphor (5.00 g, 45.40 mmol, Aldrich) in THF (100 mL) was added dropwise to a solution of vinyl magnesium bromide (45.40 mL, 45.40 mmol, 1.0M, Aldrich) at 0°C. After stirring for 1 h the reaction mixture was quenched by the addition of 3N HCl and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and the product purified by flash chromatography (50% ether/petroleum ether), to yield 20, 6.22 g (99%) (only endo-isomer obtained); ir (film): 3348 (O-H), 1645 (RCH=CH$_2$) cm^{-1}; 'H nmr (CCl$_4$) δ: 0.90-2.65 (m, 10H), 3.40 (br.s., 1H, OH), 4.80-4.98 (dd, J = 2 Hz, 1H), 5.00-5.30 (dd, J = 2 Hz, 18.4 Hz, 1H), 5.88-6.30 (dd, J = 11 Hz, 18.4 Hz, 1H, RC<u>H</u>=CH$_2$); M.S. (m/z): 138 (M$^+$).

Reaction of the Lithium anion of Alcohol (20) with Phenyl Sulfenyl Chloride at -40°C

n-Butyllithium (0.49 mL, 4.96 mmol, 10.2M, Aldrich), was added dropwise to a solution of alcohol 20 (0.57 g, 4.13 mmol) in THF (40 mL) at 0°C. After stirring for 10 min the reaction temperature was lowered to -40°C and a solution of phenyl sulfenyl chloride[35] [prepared from thiophenol (0.55 g, 5.00 mmol, Aldrich) and sulfuryl chloride (0.67 g, 5.00 mmol, Aldrich)] in ether (20 mL), was added dropwise. After the addition was complete the reaction mixture was warmed to 22°C. After stirring for 2 h the reaction mixture was quenched with water and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and the product purified by flash chromatography (50% ether/petroleum ether). The phenyl sulfenyl chloride added across the double bond to give endo-2-hydroxy-2-(1-

thiophenyl-2-chloroethanyl) bicyclo[2.2.1]heptane 34, 0.95 g, (82%); ir (film): 3490 (O-H), 3050 (Ar-H), 2930 (C-H) cm^{-1}; ^{1}H nmr (CCl$_4$) δ: 1.00-2.50 (br.m., 10H), 3.70 (m, 3H), 4.55 (t, 1H, PhS-C$\underline{H}$CH$_2$Cl), 7.28 (m, 5H, Ar-H); M.S. (m/z): 282 (M$^+$), 283 (M+1) (18%), 284 (M+2) (38%); Exact mass calculated for $C_{15}H_{19}SOCl$: 282.0845, found: 282.0854.

Reaction of the Lithium anion of Alcohol (20) with Phenyl Sulfenyl Chloride at -78°C

n-Butyllithium (2.78 mL, 6.96 mmol, 2.5M, Aldrich), was added dropwise to a solution of alcohol 22 (0.80 g, 5.80 mmol) in THF (25 mL) at 0°C. After stirring for 10 min the reaction temperature was lowered to -78°C and a solution of phenyl sulfenyl chloride[35] (distilled) (0.83 g, 5.80 mmol) in ether (25 mL) was added dropwise over 45 min, stirring at -78°C was continued for 1.5 h, the reaction temperature was then allowed to warm to 22°C. After stirring for 12 h the reaction mixture was quenched with water and worked-up as above. The product was purified by flash chromatography (50% ether/petroleum ether) to yield 2-(1-oxo-1-phenyl-1-thiaphenyl)bicyclo[2.2.1]heptane (35) 0.66 g (46%); ir (film): 3045 (=C-H), 2930 (C-H), 1675 (C=C), 1040 (S=O) cm^{-1}; ^{1}H nmr (CCl$_4$) δ: 1.30 (br.m., 7H), 2.10 (m, 2H), 2.58 (br.s., 1H), 3.32 (d, 2H, J = 8 Hz, =CH-C$\underline{H}_2$), 5.18 (t, 1H, J = 8 Hz, =C$\underline{H}$-CH$_2$), 7.42 (m, 5H, Ar-H); M.S. (m/z): 244 (M$^+$); Exact mass calculated for $C_{15}H_{16}SO$: 244.0922, found: 244.0934.

Reaction of Sulfoxide (35) with Trimethyl Phosphite

The vinyl sulfoxide 35 (1.00 g, 4.07 mmol) and trimethylphosphite (4.78 mL, 40.65 mmol, Aldrich) in dry methanol (60 mL) were refluxed for 24 h. The solution was concentrated, the residue dissolved in ether, washed with water, brine, dried, concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethanol/ hexanes) yielding exo-2-hydroxy-2-vinyl bicyclo[2.2.1]heptane (21), 0.32 g (56%) and some endo-isomer 20, 0.04 g (7%); ^{1}H nmr (CCl_4) δ: 0.90 (m, 10H), 3.40 (br. s., 1H, O-H), 4.75-4.96 (dd, J = 2 Hz, J = 11 Hz, 1H), 4.95-5.25 (dd, J = 2 Hz, J = 18.4 Hz, 1H), 5.80-6.25 (dd, J = 11 Hz, J = 18.4 Hz, 1H, RCH=CH).

Bicyclo[2.2.1]hept-5-ene-2-one (36)

Bicyclo[2.2.1]hept-5-ene-2-ol (mixture of exo and endo) (10.00 g, 90.90 mmol, Aldrich) in dichloromethane (150 mL) was added in one aliquot to a slurry of pyridinium chlorochromate[36] (29.30 g, 136.40 mmol) in dichloromethane (150 mL), and a black slurry formed immediately. After stirring for 2 h, anhydrous ether (300 mL) was added and the supernatant decanted from the black gum. The black gum was washed with ether, the combined organic phases were filtered through fluorosil and concentrated to give a yellow oil. The oil was purified by distillation, b.p. 60-62°C/12 mm Hg to yield 36, 7.10 g (72%); ir (film): 3055 (=C-H), 2960 (C-H), 1740 (C=O), 1640 (C=C) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.75 (m, 2H), 2.05 (m, 2H), 2.90 (m, 1H), 3.18 (m, 1H), 6.05 (dd, J = 6 Hz, J = 3.6 Hz, 1H); 6.52 (dd, J = 6 Hz, J = 3 Hz, 1H); M.S. (m/z): 108 (M^+); Exact mass calculated for C_7H_8O: 108.0575, found: 108.0559.

endo-2-Hydroxy-2-vinyl bicyclo[2.2.1]hept-5-ene (37)

Ketone 36 (2.00 g, 18.52 mmol) in THF (50 mL) was added dropwise to a stirred solution of vinyl magnesium bromide (18.52 mL, 18.52 mmol, 1.0M, Aldrich) in THF (80 mL) at -78°C. After stirring at -78°C for 1 h and warming to 22°C the reaction mixture was quenched with 3N HCl and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated, the product purified by flash chromatography (50% ether/petroleum ether) to yield 37, 1.57 g (62%) (only endo-isomer obtained); ir (film): 3355 (O-H), 3050 (=C-H), 2910 (C-H), 1630 (C=C) cm^{-1}; 'H nmr (CCl_4) δ: 1.10 (dt, 1H), 1.48 (d, 2H), 1.75-2.10 (dd, 1H), 2.49 (br.s., 1H), 2.70 (m, 1H), 2.85 (br.s., 1H, O-H), 4.88-5.05 (dd, J = 2 Hz, J = 11 Hz, 1H), 5.10-5.45 (dd, J = 2 Hz, 18 Hz, 1H), 5.87-6.50 (m, 3H); M.S. (m/z): 136 (M^+).

Reaction of the Lithium anion of Alcohol (37) with Phenyl Sulfenyl Chloride

n-Butyllithium (3.52 mL, 8.82 mmol, 2.5M, Aldrich) was added slowly to a solution of alcohol 37 (1.00 g, 7.35 mmol) in THF (50 mL) at 0°C. After stirring for 10 min the reaction temperature was lowered to -78°C and a solution of phenyl sulfenyl chloride[35] (distilled) (1.05 g, 7.35 mmol) in ether (40 mL) was added over 1 h, the reaction temperature was then allowed to warm to 22°C. After stirring for 16 h the reaction mixture was quenched with water and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and product purified by flash chromatography (50% ether/petroleum ether). It appeared that the phenyl sulfenyl chloride had added across the cyclic double bond followed by displacement of the chloride by the oxygen anion to yield endo-2-thiophenyl-5-vinyl-2-oxatricyclo[3.2.1.$0^{2,6}$]octane 38, 1.08 g (60%); ir (film): 3050 (=C-H, Ar-H), 2940 (C-H), 1645 (C=C), 1090 (C-O-C), 960 (oxetane); 'H nmr (CCl_4) δ: 1.20-2.10 (m, 4H), 2.85 (m, 1H), 3.32 (dd, J = 5 Hz, J = 2 Hz, 1H, R_2CHSPh), 3.60 (d, J = 2 Hz, 1H), 4.25 (dd, 1H), 5.00 (dd, J = 10 Hz, J = 2.5 Hz, 1H, RHC=CHH,cis), 5.15 (dd, J = 16 Hz, J = 16 Hz, J = 2.5 Hz, 1H, RHC=CHH, trans, 1H), 5.80 (dd, J = 10 Hz, J = 16 Hz, 1H, $RCH=CH_2$), 7.20 (m, 5H, Ar-H); M.S. (m/z): 244 (M^+); Exact mass calculated for $C_{15}H_{16}SO$: 244.0922, found: 244.0934.

Reaction of Bicyclo[2.2.1]heptene with Phenyl Sulfenyl Chloride

Phenyl sulfenyl chloride[36] (distilled) (1.53 g, 10.64 mmol) in ether (20 mL) was added dropwise to a solution of bicyclo[2.2.1] heptene (1.00 g, 10.64 mmol) in ether (20 mL) at -78°C, the reaction was immediate, the red colour disappeared. After 10 min the reaction mixture was quenched and worked-up as above. Purification by flash chromatography (50% ether/petroleum ether) yielded 2-chloro-3-thiophenyl bicyclo[2.2.1]heptane 43, 2.04 g (90%); ir (film): 3050 (Ar-H) cm^{-1}; 'H nmr (CCl_4) δ: 1.15-2.10 (br.m., 6H), 2.30 (m, 2H), 3.05 (t, 1H, CHSPh), 3.95 (t, 1H, CHCl), 7.25 (m, 5H, Ar-H).

2-Vinyl bicyclo[2.2.1]hept-5-ene (46)

n-Butyllithium (12.36 mL, 33.36 mmol, 2.7M, Aldrich) was added slowly to a mixture of ethyltriphenylphosphonium bromide (12.36 g, 33.36 mmol) in THF (100 mL) at 0°C. After 15 min a solution of ketone

36 (3.00 g, 27.78 mmol) in THF (50 mL) was added dropwise, the reaction temperature was raised to 22°C. After stirring for 19 h the reaction mixture was diluted with pentane and filtered through a short column of silica. The solvent was concentrated and product purified by flash chromatography (30% ether/petroleum ether) to yield 46, 2.77 g (83%); ir (film): 1675 (C=C) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.15-1.85 (br.m., 7H), 3.00 (m, 1H), 3.45 (br.s., 1H), 5.20 (m, 1H, RR'C=CHR), 6.10 (m, 2H, RCH=CHR).

2-(1-Chloro Propenyl) bicyclo[2.2.1]hept-5-ene (49)

Alcohol 37 (0.44 g, 3.24 mmol) and thionyl chloride (0.46 g, 3.88 mmol, Aldrich) in hexanes (25 mL) were stirred at 0°C. After 16 h the reaction mixture was quenched with cold water and extracted with hexanes, the combined organic extracts were washed with water, brine, dried, concentrated and product purified by flash chromatography (30% ether/petroleum ether), (compound decomposes slightly on the column), to yield 49 0.20 g (40%); ir (film): 3020 (=C-H) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.45 (br.m., 2H), 2.00 (br.m., 2H), 3.05 (m, 1H), 3.52 (br.s., 1H), 3.92 and 4.08 (both d, together 2H, both cis and trans-isomers, =$CHCH_2Cl$), 5.50 (m, 1H, RR'C=CHR), 6.00 (m, 2H, RCH=CHR).

2-(1-Phenyl-1-thiapropenyl)bicyclo[2.2.1]hept-5-ene (50)

Thiophenol (4.10 g, 37.22 mmol) in DME (25 mL) was added dropwise to a mixture of sodium hydride (1.63 g, 40.93 mmol, 60% suspension in oil, Aldrich) (washed with hexane) in DME (50 mL) at 0°C. This was followed by the dropwise addition of chloride 49 (5.21 g, 33.83

mmol) in DME (50 mL), after the addition was complete the reaction mixture was allowed to warm to 22°C. After stirring for 18 h the reaction mixture was quenched by the addition of water and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and product purified by distillation, b.p. 105-110/0.05 mm Hg, to yield 50, 3.13 g (41%); ir (film): 3048 (=C-H), 2910 (C-H), 1675 ($R_2C=CRH$) cm^{-1}; 'H nmr (CCl_4) δ: 1.50 (br. s., 4H), 2.75 (br.s., 1H), 3.00 (br.s., 1H), 3.30 and 3.48 (both d, together 2H, both *cis* and *trans*-isomers, $=CHC\underline{H_2}SPh$), 5.20 (br, m., 1H, RR'C=CHR), 5.90 (m, 2H, RCH=CHR), 7.10 (m, 5H, Ar-H); M.S. (m/z): 228 (M^+); Exact mass calculated for $C_{15}H_{16}S$: 228.0973, found: 228.0985.

Oxidation of 2-(1-Phenyl-1-thiapropenyl)bicyclo[2.2.1]hept-5-ene (50)

Sulfide 49 (3.13 g, 13.87 mmol) and *m*-chloroperbenzoic acid (3.00 g, 13.87 mmol, 80%, Aldrich) in dichloromethane (50 mL) were stirred at -78°C. After stirring for 5 h the reaction mixture was filtered to remove *m*-chlorobenzoic acid, the filtrate was washed with water, 10% sodium sulfite, saturated sodium bicarbonate, brine, dried, concentrated and products purified by flash chromatography (60% ether/pentane) to yield 2-(1-oxo-1-phenyl-1-thiapropenyl)bicyclo[2.2.1]-hept-5-ene 51, 2.88 g (86%) and 2-(1,1-dioxo-1-phenyl-1-thiapropenyl) bicyclo[2.2.1]hept-5-ene(52) 0.25 g (7%); for sulfoxide 50 - ir (film): 3045 (=C-H, Ar-H), 2950 (C-H), 1675 ($R_2C=CHR$), 1040 (S=0) cm^{-1}; 'H nmr (CCl_4) δ: 1.30 (br. m., 4H), 2.75 (br. m., 1H), 3.30 (br. m., 3H, = $CHC\underline{H_2}SOPh$; $=CHCR\underline{H}C\underline{H}=$), 5.10 (br. m., 1H, RR'C=CHR), 5.90 (m, 2H, $RC\underline{H}=C\underline{H}R$), 7.45 (br.s., 5H, Ar-H); M.S. (m/z): no molecular ion, 119 (M-125, M-SOPh), 97 (M-147, $C_5H_5S^+$); for sulfone 51; ir (film): 3040 (=C-H, Ar-H), 2950 (C-H), 1676 (C=C), 1320, 1140 (SO_2) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.40 (br. m., 4H), 2.85 (m, 1H), 3.10 (br.s., 1H), 3.65 (two doublets, both isomers, 2H, =$CHCH_2SO_2Ph$), 5.20 (br. m., 1H, RR'C=CHR), 5.85 (br. s., 2H, RCH=CHR), 7.55 (br. m., 5H, Ar-H); M.S. (m/z): 260 (M^+); Exact mass calculated for $C_{15}H_{16}SO_2$: 260.0871, found: 260.0830.

Reaction of Sulfoxide (50) with Trimethyl Phosphite

Sulfoxide 50 (0.82 g, 3.40 mmol), and trimethyl phosphite (4.21 g, 34.00 mmol, Aldrich), in methanol (100 mL), were refluxed. After 24 h the solution was concentrated, the residue was dissolved in ether, washed with water, brine, dried and concentrated to yield only traces of the desired alcohol 53. Longer refluxes resulted only in decomposition.

Reaction of Sulfoxide (50) with Sodium Thiophenolate

Thiophenol (6.06 g, 54.94 mmol, Aldrich) in methanol (30 mL) was added slowly to sodium hydride (2.20 g, 54.94 mmol, 60% suspension in oil, Aldrich) (washed with hexanes). This was followed by the addition of the sulfoxide 50 (1.34 g, 5.49 mmol) in methanol (30 mL). After refluxing for 24 h, the reaction mixture was quenched with water and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and product purified by flash chromatography (30% ether/petroleum ether) yielding exo-2-hydroxy-2-vinyl bicyclo[2.2.1]hept-5-ene (53) 0.34 g (46%), and some endo-isomer 37, 0.04 g (5%); ir (film): 3360 (O-H), 1630 (C=C) cm^{-1};

^{1}H nmr (CCl_4) δ: 1.80-2.20 (m, 2H), 2.60 (m, 1H), 2.85 (br.s., 1H, O-H), 4.65-4.70 (dd, J = 2 Hz, J = 11 Hz, 1H), 4.95-5.35 (dd, J = 2 Hz, J = 18 Hz, 1H), 5.50-6.20 (m, 3H).

Reaction of Sulfone (52) with Trimethyl Phosphite

Sulfone 52 (0.25 g, 0.98 mmol) and trimethyl phosphite (1.21 g, 9.77 mmol, Aldrich) in methanol (30 mL) were refluxed. After 6 days the reflux was stopped, the solution was concentrated, the residue dissolved in ether, washed with water, brine, dried, concentrated to yield only starting sulfone 52.

Base Accelerated Oxy-Cope Reaction of Alcohol (53)

Alcohol 53 (0.10 g, 0.74 mmol) in THF (5 mL) was added to a mixture of potassium hydride (0.09 g, 0.81 mmol, 35% suspension in oil, Aldrich) (washed with hexane) in THF (10 mL) at 0°C. After refluxing for 20 min the reaction mixture was quenched with water and extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and product purified by flash chromatography (20% ether/petroleum ether) which yielded cis-3-oxo bicyclo[4.3.0]non-7-ene (54), 0.07 (70%); ir (film): 3025 (=C-H), 2875 (C-H), 1715 (C=O) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.50-2.30 (m, 6H), 2.40-3.20 (m, 4H), 5.30-5.80 (m, 2H); M.S. (m/z): 136 (M^+); Exact mass calculated for $C_9H_{12}O$: 136.0888, found: 136.0889.

2-Carbomethoxycyclohexanone (54)

Cyclohexanone (30.00 g, 300.00 mmol, Aldrich) in benzene (60 mL) was added slowly to a refluxing mixture of sodium hydride (12.00 g, 301.18 mmol, 60% suspension in oil, Aldrich) (washed with hexane) and dimethyl carbonate (54.00 g, 600.00 mmol, Aldrich) in benzene (500 mL). After refluxing for 4 h and cooling, the reaction mixture was quenched with 3N HCl, washed with brine, dried and concentrated, the resulting yellow oil was purified by distillation, b.p. 104-106/12 mm Hg to give keto-ester 54 19.58 g (42%); ir (film): 2920 (C-H), 1750, 1720, 1660 (keto-ester) cm^{-1}; ^1H nmr (CCl_4) δ: 1.65 (m, 4H), 2.20 (m, 4H), 3.72 (s, 3H, CO_2CH_3), 11.98 (s, 1H, C=C-OH); M.S. (m/z): 156 (M^+).

2-Carbomethoxycyclohex-2-en-1-one (55)

Keto-ester 54 (17.86 g, 114.49 mmol) in THF (100 mL) was added over 30 min to a suspension of sodium hydride (7.21 g, 171.73 mmol, 60% suspension in oil, Aldrich) (washed with pentane) in THF (300 mL) at 0°C. After the addition was complete phenylselenenyl chloride (24.16 g, 125.94 mmol, Aldrich) in THF (60 mL) was added rapidly. After the addition was complete the reaction mixture was slowly added to a mixture of 50% ether:pentane (300 mL), saturated sodium bicarbonate (200 mL) and some ice. The aqueous fraction was extracted with 50% ether:pentane (100 mL), the combined organic extracts were washed with saturated sodium bicarbonate, dried and concentrated yielding the crude selenide.

Hydrogen peroxide (32.40 mL, 286.23 mmol, 30% water, Anachemia.) in water (30 mL) was added to the crude selenide in dichloromethane (300 mL) over a 30 min period, maintaining the temperature between 20°C and 30°C. After stirring an additional 10 min at 22°C the reaction mixture was poured into dichloromethane (250 mL) and 10% sodium carbonate (100 mL) with stirring. The aqueous fraction was extracted with dichloromethane, the combined organic extracts were washed with brine, dried and concentrated to yield 55 as a yellow oil, 16.48 g (94%); ir (film): 2950 (C-H) 1650, 1775 (α,β-unsaturated keto-ester) cm^{-1}; ^{1}H nmr (CCl_4) δ: 2.00 (m, 2H), 2.50 (m, 4H), 3.65 (s, 3H, CO_2Me), 7.52 (t, 1H, RCH=CR); M.S. (m/z): 154 (M^+).

Reaction of 55 with Dimethyl Sulfoxonium Methylide[11,12]

n-Butyllithium (1.43 mL, 3.00 mmol, 2.1 M, Aldrich) was added to trimethylsulfoxonium iodide[11] (0.66 g, 2.98 mmol) in THF (40 mL) at 0°C. The reaction mixture was heated to reflux to generate the ylid, then cooled to -78°C. The olefin 55 (0.50 g, 2.90 mmol) was added at once. After stirring for 2 h the reaction mixture was quenched by pouring into ice water, extracted with ether, the combined ether extracts were washed with brine, dried and concentrated. The desired product was not obtained.

Reaction of 55 with Nitromethane

Sodium (0.18 g, 7.82 mmol) was added to dry methanol (50 mL), this was followed by the addition of nitromethane (16.91 g, 277.13 mmol). After stirring for 10 min the olefin 55 (0.50 g, 3.25 mmol) in dry methanol (10 mL) was added. After refluxing for 3 h the reaction mixture was poured onto ice water-dichloromethane. The aqueous fraction was extracted with dichloromethane, the combined organic extracts were washed with brine, dried and concentrated, the desired product was not obtained.

2-Carbo-t-butoxy Cyclohexanone (58)

Cyclohexanone (1.00 g, 10.20 mmol, Aldrich) in toluene (50 mL) was added slowly to a refluxing solution of sodium hydride (0.49 g, 12.24 mmol, 60% suspension in oil, Aldrich) (washed with hexane) and di-*t*-butyl dicarbonate (2.22 g, 10.20 mmol) in toluene (60 mL). After refluxing for 20 h and cooling, the reaction mixture was quenched with 3N HCl, and worked-up as in 54. Purification by flash chromatography (50% ether/petroleum ether) to give 58 as a yellow oil, 1.47 g (73%); ir (film): 2925 (C-H, 1750, 1720, 1660 (keto-ester) cm^{-1}; 1.25 (m, 13H), 1.80 (m, 4H), 12.00 (s, 1H, C=C-OH); M.S. (m/z): 198 (M^+), 57 ($C(CH_3)_3^+$).

2-Carbo-t-butoxy Cyclohex-2-en-1-one (59)

Keto-ester 57 (1.47 g, 7.44 mmol) in THF (30 mL) was added over 30 min to a suspension of sodium hydride (0.47 g, 11.17 mmol, 60% suspension in oil, Aldrich) (washed with pentane) in THF (30 mL) at 0°C. After the addition was complete phenylselenenyl chloride (1.57 g, 8.18 mmol, Aldrich) in THF (30 mL) was added rapidly. After the addition was complete the reaction mixture was slowly added to a mixture of 50% ether:pentane (100 mL), saturated sodium bicarbonate (100 mL) and some ice. The reaction was worked-up as in 55.

Hydrogen peroxide (2.11 mL, 18.60 mmol, 30% in water, Anachemia) in water (25 mL) was added to the crude selenide in dichloromethane (100 mL) overa a 30 min period, maintaining the temperature between 20°C and 30°C. After stirring an additional 10 min at 22°C the reaction was worked-up as in 55 to yield 59 a yellow oil, 1.41 g (97%); ir (film): 2920 (C-H), 1750, 1650 (α,β-unsaturated keto-ester) cm^{-1}; 'H nmr (CCl_4) δ: 1.40 (m, 11H), 2.20 (m, 4H), 7.25 (t, 1H, $CH=C(COR)_2$).

1-Carbo-t-butoxybicyclo[4.1.0]heptan-2-one (60)

Trimethyl sulfoxonium iodide[11] (0.58 g, 2.68 mmol) was added to sodium hdyride (0.11 g, 2.68 mmol, 60% suspension in oil, Aldrich) in DMSO (20 mL). This was followed by the addition of olefin 58 (0.50 g, 2.55 mmol) in DMSO (15 mL). After stirring for 2 h at 22°C the reaction temperature was raised to 50°C for 30 min. The reaction was then quenched with water, extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and purified by flash chromatography (50% ether/petroleum ether) to yield 60, 0.35 g (65%); ir (film): 2950 (C-H), 1740 (ester), 1680 (ketone) cm^{-1}; 'H nmr (CCl_4) δ: 1.00 (m, 3H, cyclopropyl H's), 1.38 (s, 9H), 1.60 (m, 4H), 2.10 (m, 2H); M.S. (m/z): 210 (M$^+$), 57 $[C(CH_3)^+]$.

4-Bromo-2-carbo-t-butoxy cyclohex-2-en-1-one (61)

Keto-ester 57 (0.30 g, 1.53 mmol) and recrystallized N-bromo succinimide (0.33 g, 1.84 mmol) in CCl_4 (50 mL) with AIBN as free radical initiator were refluxed. After 3 h the reaction was cooled and filtered. The remaining oil was purified by flash chromatography (20% ether/hexane) to give 61 as a yellow oil 0.42 (100%); ir (film): 2980 (C-H), 1680, 1770 (α,β-unsaturated keto-ester) cm^{-1}; 'H nmr (CCl_4) δ: 1.50 (s, 9H), 1.80 (m, 2H), 2.15 (m, 2H), 4.50 (m, 1H), 7.20 (m, 1H).

4-Carbo-t-butoxy-2,2-dimethyl cyclohexan-1,3-dione (63)

2,2-Dimethyl cyclohexan-1,3-dione[45] (5.00 g, 35.71 mmol) in toluene (100 mL) was added slowly to a refluxing mixture of sodium hydride (1.71 g, 42.85 mmol, 60% suspension in oil, Aldrich) (washed with hexane) and di-tert-butyl dicarbonate (7.79 g, 35.71 mmol, Aldrich) in toluene (25 mL). After refluxing for 20 h and cooling, the reaction mixture was quenched with 3N HCl, washed with brine, dried and concentrated, the resulting yellow oil was purified by flash chromatography (50% ether/pentane) to give 63, 4.50 g (56%); ir (film): 2900 (C-H), 1750, 1655 (keto-ester) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.00 (m, 4[illegible], 1.30 (br.s, 15H); 2.50 (m, 1H); M.S. (m/z): 184 (M-isobutene), 57 ($C(CH_3)_3^+$) (100%).

2-Carbo-t-butoxy-6,6-dimethylcyclohex-2-en-1,5-dione (64)

Keto-ester 63 (2.35 g, 9.79 mmol) in THF (30 mL) was added over 30 min to a suspension of sodium hydride (0.59 g, 14.75 mmol, 60% suspension in oil, Aldrich) (washed with pentane) in THF (30 mL) at 0°C. After the addition was complete phenylselenenyl chloride (2.07 g, 10.78 mmol, Aldrich) in THF (30 mL) was added rapidly. After the addition was complete the reaction mixture was added slowly to a mixture of 50% ether:pentane (100 mL), saturated sodium bicarbonate (100 mL) and some ice. The reaction was worked up as in 55.

Hydrogen peroxide (2.77 mL, 24.44 mmol, 30% in water, Anachemia) in water (25 mL) was added to the crude selenide in dichloromethane (100 mL) over a 30 min period, maintaining the temperature between 20°C and 30°C. After stirring an additional 10 min at 22°C the reaction was worked-up as in 55, to yield 64 as a yellow oil, 1.98 g (85%); ir (film): 2925 (C-H), 1755, 1650 (α,β-unsaturated keto-ester) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.50 (br.s, 15H), 2.50 (m, 2H), 5.48 (t, 1H); M.S. (m/z): 137 ($M-CO_2{}^tBu$), 57 ($C(CH_3)_3$).

t-Butyl-3-oxo-4[2,3-dimethyl cyclopentadienyl] butyrate (67)

tert-Butyl acetoacetate (11.66 g, 73.77 mmol, Aldrich) in THF (50 mL) was added dropwise to a mixture of sodium hydride (2.95 g, 73.77 mmol, 60% suspension in oil, Aldrich) (washed with hexane) in THF (100 mL) at 0°C. After stirring for 10 min, a solution of n-butyllithium (30.98 mL, 77.46 mmol, 2.5 M, Aldrich) was added dropwise. Ten min later the enone 28b (5.41 g, 49.18 mmol) was added in one aliquot, stirred for 30 min and quenched with 3N HCl and worked-up as in 29a. The resulting oil was purified by flash chromatography (20% ether/hexane) to yield 67 as a yellow solid, 6.13 g (50%), m.p. 73-74°C; ir (film): 3025 (C-H), 1730, 1720 and 1575 (keto-ester and cyclopentadiene) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.40 (s, 9H, $C(CH_3)_3$), 1.70 (s, 3H), 1.95 (s, 3H), 2.40 (m, 2H), 2.95 (m, 2H), 3.20 (s, 2H), 5.95 (t, 1H, $C{=}\underline{CH}CH_2C{=}C$); M.S. (m/z): 250 ($M^+$), 135 (M-115) (McLafferty rearrangement), 57 [$C(CH_3)_3^{\ +}$].

t-Butyl-2-(3-bromo-3-cyano-2-butenyl)-3-oxo-4[2,3-dimehtyl cyclopentadienyl]butyrate (68)

Keto-ester 67 (1.22 g, 4.89 mmol) in DME (20 mL) was added dropwise to potassium hydride (0.78 g, 5.87 mmol, 35% suspension in oil, Aldrich) (washed with hexane) in DME (20 mL) at 0°C. After the addition was compelte the reaction mixture was allowed to warm to 22°C and 1,3-dibromo-1-cyanopropene (1.10 g, 4.89 mmol) was added in one aliquot. After stirring for 2 h the reaction was quenched with water, extracted with ether, the combined ether extracts were washed with water, brine, concentrated and product purified by flash chromatography (30% ether/hexane), to yield 68, 1.18 g (61%); ir (film): 2950 (C-H), 2250

(C≡N), 1725, 1715 and 1580 (keto-ester and cyclopentadiene) cm^{-1}; ^{1}H nmr (CCl$_4$) δ: 1.45 (s, 9H), 1.78 (s, 3H), 1.90 (br.s, 3H), 2.45 (m, 4H), 2.98 (m, 2H), 3.22 (m, 1H), 6.00 (m, 1H), 6.60 (m, 1H).

Diels-Alder reaction of 68

Triene 68 (0.52 g, 1.32 mmol) and tetramethyl ethylenediamine (0.15 g, 1.32 mmol, Aldrich) in toluene (20 mL) were refluxed. After 20 h the solvent was removed and product purified by flash chromatography (20% ether/hexane) to yield the Diels-Alder adduct 69, 0.10 g (19%); ir (film): 2920 (C-H), 2220 (C≡N), 1720, 1575 (keto-ester); ^{1}H nmr (CCl$_4$) δ: 1.30 (m, 3H), 1.60 (s, 9H), 1.75 (br.s, 3H), 1.90 (br.s, 3H), 2.50 (m, 3H), 2.98 (m, 2H), 3.75 (s, 1H).

Reaction of Keto-ester 67 with Acrolein dimethyl acetal

Keto-ester 67 (0.70 g, 2.80 mmol), acrolein dimethyl acetal (0.54 g, 5.32 mmol) and nickel acetoacetonate (5 mg) were heated in a sealed tube at 200°C. After 1 h the heating was stopped, product purified by flash chromatography (30% ether/petroleum ether) to yield methyl ester 29b, 0.28 g (64%).

1-(2,3-Dimethyl cyclopentadienyl)-2,4-pentanedione (71)

n-Butyllithium (47.17 mL, 117.91 mmol, 2.5 M, Aldrich), was added slowly to diisopropylamine (16.48 mL, 117.91 mmol, Aldrich) in DME (50 mL) at 0°C. After 20 min 2,4-pentanedione (5.60 g, 56.16 mmol, Aldrich) in DME (50 mL) was added dropwise. After 10 min enol 28b (4.12 g, 37.45 mmol) was added in one aliquot. After stirring for 1 h at 0°C the reaction mixture was quenched by the addition of 3N HCl, extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and purified by flash chromatography (50% ether/petroleum ether) to give 71 as a yellow solid 0.93, (13%); ir (film): 2950 (C-H), 1720, 1630 (diketone); 'H nmr ($CDCl_3$) δ: 1.75 (br.s, 3H), 1.90 (br.s, 3H), 2.05 (s, 3H, $RCOCH_3$), 2.50 (m, 2H), 3.05 (m, 2H), 5.50 (s, 1H, RC<u>H</u>=CROH), 5.55 (t, 1H, C=CHCHC=C); M.S. (m/z): 192 (M^+), 135 (M-57) (McLafferty rearrangement); Exact mass calculated for $C_{12}H_{16}O_2$: 192.1150, found: 192.1156.

1-(2,3-Dimethyl cyclopentadienyl) 3-allyl-2,4-Pentanedione (72)

Dike[illegible] (0.46 g, 2.40 mmol) in DME (20 mL) was added dropwise to potassium hydride (0.30 g, 2.64 mmol, 25% suspension in oil, Aldrich) (washed with hexane) in DME (20 mL) at 0°C. After 10 min the reaction was allowed to warm to 22°C and allyl bromide (0.29 g, 2.40 mmol, Aldrich) was added in one aliquot. After 20 h the reaction was quenched with water, extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and product purified by flash chromatography (30% ether/petroleum ether) to yield 72, 0.53 g (95%); ir (film): 2980 (C-H), 1730, 1630 (diketone); 'H nmr (CCl_4) δ: 1:70 (br.s, 3H), 1.85 (m, 3H), 2.05 (s, 3H), 2.45 (m, 2H), 2.95 (m, 2H), 3.25 (d, 1H), 4.70-5.95 (br.m, 4H).

Reaction of Diketone 71 with Acrolein dimethyl acetal

Diketone 71 (0.37 g, 1.92 mmol), acrolein dimethyl acetal (0.22 g, 2.16 mmol) and nickel acetoacetonate (5 mg) were heated at 200°C in a sealed tube. After 15 h the products were purified by flash chromatography (50% ether/petroleum ether) to yield compounds 73, 0.15 g (30%)

and 74 0.09 g (18%). For compound 73 ^{1}H nmr (CCl_4) δ: 1.60 (br.s, 3H), 1.90 (br.s, 3H), 2.00 (s, 3H), 2.50 (m, 4H), 2.95 (m, 2H), 3.40 (s, 3H), 4.30 (two t, 1H, both isomers), 5.80 (m, 1H), 6.20 (m, 2H); M.S. (m/z): 262 (M^+), 230 (M-MeOH), 220 (M-CHCO), 135 (McLafferty rearrangement). For compound 74 ^{1}H nmr (CCl_4) δ: 0.80-1.30 (m, 7H), 1.40-2.10 (m, 8H), 250 (m, 3H), 3.25 (s, 3H), 3.40 (s, 1H); M.S. (m/z): 244 ($M-H_2O$), 230 (M-MeOH).

1-Chloro-2-hydroxy-4-carbomethoxy hexan-5-one (75)

Methyl acetoacetate (1.00 g, 8.62 mmol, Aldrich), epichlorohydrin (0.96 g, 10.32 mmol, Aldrich) and boron trifluoride etherate (5 drops) in dichloromethane (2[illegible] mL) were stirred at 22°C. After 2 h the reaction was quenched with water, extracted with dichloromethane, the combined organic extracts were washed with water, brine, concentrated and product purified by flash chromatography (50% ether/petroleum ether) to yield 75, 0.34 g (21%); ir (film): 3500 (O-H), 2840 (C-H), 1730, 1660 (keto-ester) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.20 (t, 2H), 190 and 230 (both s, 3H, keto-enol forms of $CH_3\overset{O}{C}-$), 3.50 (m, 4H), 3.70 (s, 3H), 4.95 and 11.95 (both m, 1H, keto-enol); M.S. (m/z): 208 (M^+), 210 (M+2).

1-Carbomethoxy-1-acetyl-2-hydroxymethylcyclopropane (76)

Chlorohydrin 75 (0.30 g, 1.56 mmol) in THF (10 mL) was added dropwise to sodium hydride (0.14 g, 3.49 mmol, 60% suspension in oil, Aldrich) in THF (15 mL). After stirring for 2 h the reaction was quenched with saturated ammonium chloride, extracted with ether, the combined ether extracts were washed with water, brine, dried, concentrated and product purified by flash chromatography (50% ether/pertoleum ether) to yield 76, 0.15 g (60%); ir (film): 3420 (O-H), 2960 (C-H), 1740 (ester), 1710 (ketone) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.00-1.60 (br.m, 3H, cyclopropyl), 2.20 (s, 3H), 3.50 (m, 2H), 3.75 (s, 3H), 8.20 (m, 1H, O-H); M.S. (m/z): 163 (M+H), 145 (M+H-H_2O).

endo-1-Methyl bicyclo[2.2.1]hept-2-en-5,6-dicarboxylic acid anhydride (81)

Maleic anhydride (0.85 g, 8.62 mmol, Aldrich), methyl cyclopentadiene (0.90 g, 11.21 mmol, Aldrich) and iron (5 mg) in dichloromethane (15 mL) were stirred at 0°C. After 1 h the iron was removed by filtration, solvent was removed and product purified by flash chromatography (30% ether/petroleum ether) to yield 81 and its' 2-methyl isomer 82 (2:1), 0.90 g (59%); ir (film): 2975 (C-H), 1860, 1780, 1230 (anhydride) cm^{-1}; ^{1}H nmr (CCl_4) δ: 1.70 and 1.90 (both s, 3H, two isomers), 1.80 (m, 2H), 3.30 (m, 2H), 3.70 (m, 2H), 5.70-6.40 (m, 2H); M.S. (m/z): 178 (M^+).

endo-1-Methyl bicyclo[2.2.1]hept-2-en-5,6-dicarboxylic acid (83)

Anhydrides 81 and 82 (0.90 g, 5.06 mmol) were placed in 10% sodium hydroxide and stirred. After 10 h the mixture was acidified, extracted with ether, the combined ether extracts were washed with saturated sodium bicarbonate, the aqueous phase was neutralized to yield 83 and its' 2-methyl isomer 84, 0.70 g (78%); ^{1}H nmr (CCl_4) δ: 1.20 (m, 2H), 1.70 (s, 3H), 2.80 (m, 2H), 3.20 (m, 1H), 5.80 (m, 2H), 11.70 (s, 2H).

1-Methyl bicyclo[2.2.1]hept-2,5-diene (85)

Diacids 84 and 85 (0.70 g, 3.93 mmol) and lead tetraacetate (2.00 g, 4.52 mmol, BDH) in pyridine (20 mL) were stirred at 22°C for 10 min, then heated to 80°C for 1 h. The reaction mixture was poured into 0.3N HCl and [illegible]ted with petroleum ether, the combined organic extracts were washed with 10% sodium bicarbonate, water, dried and concentrated to give 85 and some 86 0.10 g (24%); ^{1}H nmr ($CDCl_3$) δ: 1.55 (m, 2H), 1.80 (s, 3H), 4.10 (m, 1H), 5.20-5.90 (m, 4H); M.S. (m/z): 106 (M^+), 80 (M-acetylene).

Conclusion

These studies have increased our knowledge of the reactions required for an intramolecular Diels-Alder:oxy-Cope approach to diverse ring systems such as gascardic acid. It is now clear that a subtle blend of reactivities is required in order to introduce a suitably functionalized sidechain which is amenable to intramolecular cycloaddition. The vinyl alcohol inversion procedure has widespread application both for the gascardic acid synthesis and related fused ring systems. Although incomplete, it appears likely that the cyclopropane based ring expansion will follow the desired course and provide a general method for ring expansions of this type.

Bibliography

1. G. Brochure and J. Polonsky, Bull. Soc. Chim. Fr. 963 (1960).
2. G. Cordell, Phytochem. 13, 2343 (1974).
3. S. Nozoe and M. Moriasaki, Chem. Commun. 1319 (1969).
4. M. Kaneda, R. Takahashi, Y. Iitaka and S. Shibuta, Tetrahedron Lett. 4609 (1972).
5. H. Khan, A. Zanian, G. Chetty, A. Gupta and S. Dev, Tetrahedron Lett. 443 (1971).
6. R. Scartazzani, Ph.D. Dissertation, ETH (Zurich), 1966.
7. R. Boeckman, D. Blum, E. Arnold and J. Clardy, Tetrahedron Lett. 4609 (1979).
8. R. Boeckman, D. Blum and S. Arthur, J. Am. Chem. Soc. 101, 5060 (1979).
9. S.J. Alward and A.G. Fallis, Can. J. Chem. 62, 121 (1984).
10. S.J. Alward and A.G. Fallis, unpublished results.
11. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc. 87, 1353 (1960).
12. T. Mukaiyuma, K. Fujimoto and T. Takeda, Chem. Lett. 1207 (1979).
13. C.R. Johnson and P.E. Rogers, J. Org. Chem. 33, 1793 (1973).
14. K. Annen, H. Hofmeister, H. Laurent, A. Seeger and R. Weichert, Chem. Ber. III, 3094 (1978).
15. W.J. Irwin and F.J. McQuillan, Tetrahedron Lett. 2195 (1968).
16. W.G. Dauben and E.J. Deviny, J. Org. Chem. 31, 3794 (1966).
17. W.G. Dauben and R.E. Wolf, J. Org. Chem. 35, 374 (1970).
18. S. Danishefsky, Acc. Chem. Res. 12, 66 (1979).
19. P. Deslongchamps, J. Lafontaine, L. Ruest and P. Soucy, Can. J. Chem. 55, 4117 (1977).
20. P. Bickart, F.W. Carson, J. Jacobs, E.G. Miller and K. Mislow, J. Am. Chem. Soc. 90, 4869 (1968).
21. R. Tang and K. Mislow, J. Am. Chem. Soc, 92, 2100 (1970).
22. D.A. Evans, G.C. Andrews and C.L. Sims, J. Am. Chem. Soc. 93, 4956 (1971).

23. D.A. Evans and G.C. Andrews, J. Am. Chem. Soc. 94, 3672 (1972).

24. D.A. Evans and G.C. Andrews, Acc. Chem. Res. 7, 147 (1974).

25. D.A. Evans, T.C. Crawford, T.T. Fujimoto and R.C. Thomas, J. Org. Chem. 39, 3176 (1974).

26. D.A. Evans, C.L. Sims and G.C. Andrews, J. Am. Chem. Soc. 99, 5453 (1977).

27. D.A. Evans and A.M. Golob, J. Am. Chem. Soc. 97, 4765 (1975).

28. D.A. Evans, D.J. Baillargeon and J.V. Nelson, J. Am. Chem. Soc. 100, 2242 (1978).

29. W.C. Still, J. Am. Chem. Soc. 99, 4186 (1977).

30. M.E. Jung and J.P. Hudspeth, J. Am. Chem. Soc. 100, 4309 (1978).

31. M.E. Jung and G.L. Hatfield, Tetrahedron Lett. 2931 (1983).

32. D.A. Evans and J.V. Nelson, J. Am. Chem. Soc. 102, 774 (1980).

33. S. Huckin and L. Weiler, J. Am. Chem. Soc. 96, 1082 (1974).

34. M. Behforuz and J.E. Kerwood, J. Org. Chem. 34, 51 (1969).

35. I.W.J. Still, G.W. Kutney and D. McLean, J. Org. Chem. 47, 560 (1982).

36. E.J. Corey and J.W. Suggs, Tetrahedron Lett. 2647 (1975).

37. M. Shibasaki, A. Nishida and S. Ikegami, Tetrahedron Lett. 3061 (1980).

38. A.K. Saksena, P. Mangiaracina and R. Brambilla, Tetrahedron Lett. 1729 (1978).

39. W. Groebel, Chem. Ber. 93, 284 (1980).

40. S.M. Roberts and F. Scheinmann, "New Synthetic Routes to Prostaglandins and Thromboxanes", Academic Press, London, 1982.

41. K.C. Nicolau, G.P. Gasic and W.E. Barnette, Angew. Chem. 17, 295 (1978).

42. M.F. Ansell, M.P.L. Caton, M.N. Palfreyman and K.A.J. Stuttle, Tetrahedron Lett. 4497 (1979).

43. V.N. Kale and D.J. Clive, J. Org. Chem. 49, 1554 (1984).

44. K. Hiroi, R. Kitayama and S. Sato, Chem. Commun. 1470 (1983).

45. S. Swaminathan, R. Ramachandran and S.K. Sankarappa, Tetrahedron 20, 1119 (1964).

46. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc. 86, 1639 (1964).

47. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc. 86, 1640 (1964),

48. J.M.J. Tronchet and O.R. Martin, Helv. Chim. Acta 62, 1401 (1979).

49. P.E. Sum and L. Weiler, Can. J. Chem. 57, 1475 (1979).