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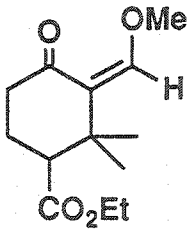
To My Grandmother

ABSTRACT

Studies directed towards the synthesis of the taxane skeleton is described. The synthesis and cyclopropanation of **170** was attempted, and the preparation and base induced cyclization of γ,δ-epoxyketone **187** and γ,δ-epoxyester **198** examined.

An unusual cycloaddition of ethyl vinyl ether to ketene carbonyls to form oxetanes was uncovered. The ketenes were generated from the cyclic diazoketones **210**, **211** and **213** and the acyclic system **215**. In all cases, with either $Rh_2(OAc)_4$, $Pd(OAc)_2$ or CuCl as catalyst, the oxetanes were the major products. Irradiation afforded the cyclobutanones **236**, **237**, **238** and **239**, while triplet sensitized photolysis afforded both oxetane and cyclobutanone. Less electron rich olefins followed literature precedent for metal catalyzed decomposition to yield cyclopropanes. These features are consistent with a zwitterionic intermediate such as **247**. (Scheme i illustrates these general features)

The preparation of the key radical cyclization precursor **282** and related compounds, **289** and **305** containing the taxol A and C ring models from enone **202** and subsequent radical cyclization to the taxane skeleton **284a** are also described.



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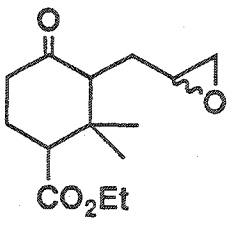

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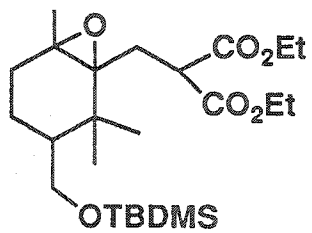

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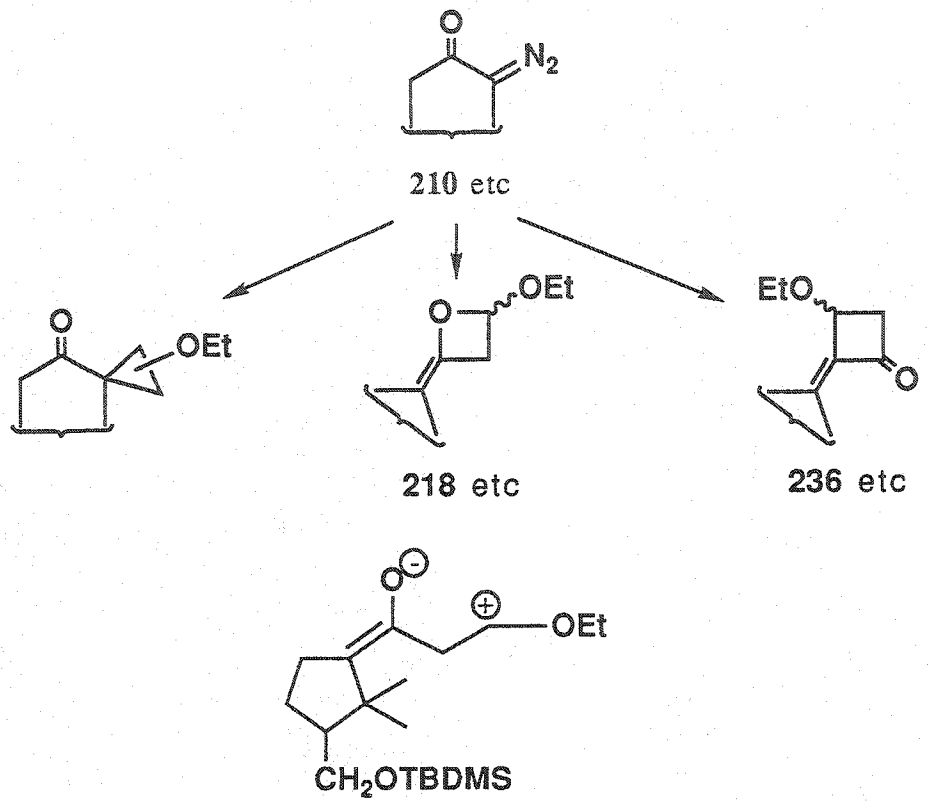
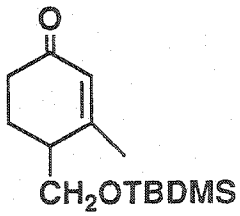


Scheme i



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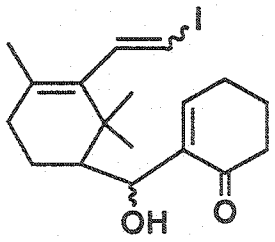

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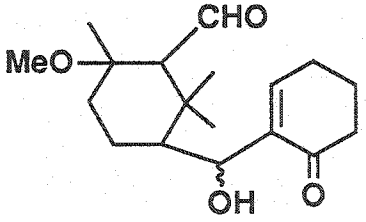

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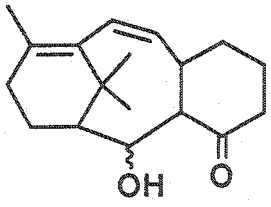
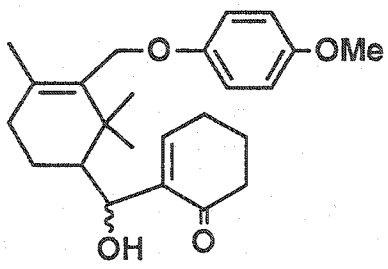


284a



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LIST OF ABBREVIATIONS

The following abbreviations have been used throughout this thesis.

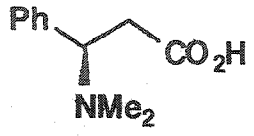
acac	=	2,4-pentanedione (acetylacetone)
t-Bu	=	*tert*-butyl
d	=	doublet
DABCO	=	diazabicyclo[5.4.2]undec-7-ene
DBU	=	1,8-diazabicyclo[2.2.2]octane
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	=	distortionless enhanced polarization transfer
DMAD	=	dimethyl acetylenedicarboxylate
DMF	=	*N*,*N*-dimethylformamide
DMSO	=	dimethyl sulfoxide
equiv	=	equivalent (s)
Et	=	ethyl
EtOAc	=	ethyl acetate
GC	=	gas chromatography
GCMS	=	gas chromatography mass spectroscopy
GLC	=	gas-liquid chromatography
h	=	hour (s)
hf(acac)	=	hexafluoroacetylacetone
HMPA	=	hexamethylphosphoramide
IR	=	infrared
LDA	=	lithium diisopropylamide

LiICA	=	lithium *N*-isopropylcyclohexylamide
M^+	=	parent molecular ion
m	=	multiplet
Me	=	methyl
MOM	=	methoxy methyl
MVK	=	methyl vinyl ketone
min	=	minute (s)
mmol	=	millimole
MS	=	mass spectrum
^{1}H NMR	=	proton nuclear magnetic resonance
NOE	=	nuclear Overhauser effect
$Pd(PPh_3)_4$	=	tetrakistriphenylphosphinepalladium(0)
Ph	=	phenyl
ppm	=	parts per million
c-Pr	=	cyclopropyl
i-Pr	=	isopropyl
q	=	quartet
s	=	singlet
t	=	triplet
TBDMS	=	*tert*-butyldimethylsilyl
TCNE	=	tetracyanoethylene
Th	=	thienyl
THF	=	tetrahydrofuran
TLC	=	thin-layer chromatography
TMS	=	tetramethylsilane
TPAP	=	tetrapropylammonium perruthenate

I. INTRODUCTION

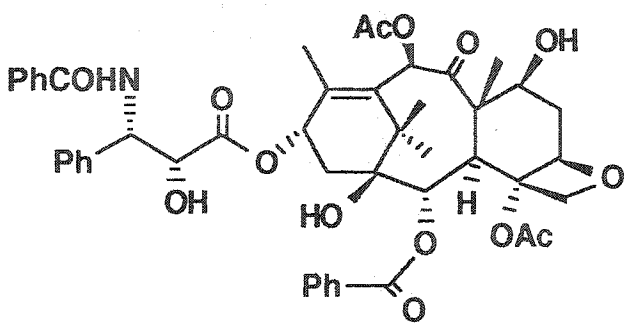
Taxol is obtained from the pacific yew tree, a slow growing evergreen belonging to the genus Taxus and family Taxaceae. It has been isolated from several taxus species including *Taxus baccata* (the most commonly encountered yew tree in Europe), *Taxus brevifolia* (a large tree native to the pacific North Western part of the United States and Canada), *Taxus cuspadata* and *Taxus Canadensis* found in Ontario and Quebec. The wood of the yew tree is dense and highly mould resistant. Consequently it has largely been used for decorative purposes and as Christmas trees in North America although its toxicity has been known for a very long time by native Americans who have used the tree as an anti-inflammatory medicine. In 1346 the English defeated the French with bows made of yew in the battle of Crecy.

The first reported work on taxol was in 1856 by Lucas[1] who isolated from the leaves the amorphous basic fraction called taxin. Subsequently Winterstein[2] in 1921 showed that 3-dimethylamino-3-phenyl propionic acid 1 called Winterstein's acid was a degradation product of taxin. Due to the relative instability of the extracts from



1

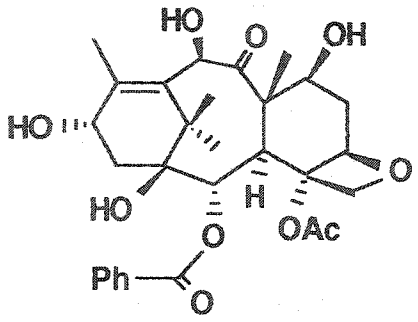
the yew tree and the highly complex structure of the diterpenes present, the structure of taxol (2) was not determined until 1971 when Wani and Wall[3] isolated taxol from the stem bark of the American yew, *Taxus brevifolia* and determined its structure.



Taxol 2

1.1 Isolation and Structure Elucidation

The most comprehensive isolation procedure[3,4] published to date was by Wani *et al.* According to this procedure, the powdered stem bark of *Taxus brevifolia* was extracted with ethanol, concentrated and partitioned between water and chloroform. The concentrated organic extract was chromatographed on Florisil, Sephadex LH-20 and silica gel respectively. Recrystallization from aqueous methanol gave taxol as needles in 0.02% yield. To obtain suitable samples for X-ray analysis taxol was subjected to a mild base catalyzed methanolysis at 0 ^{o}C producing compounds **3**, **4** and methyl acetate. Compounds 3 and 4 were recrystallized from chloroform and methanol respectively.



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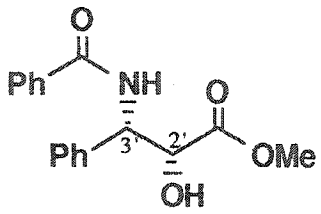
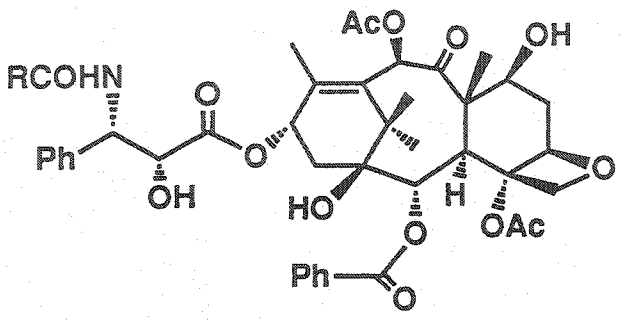


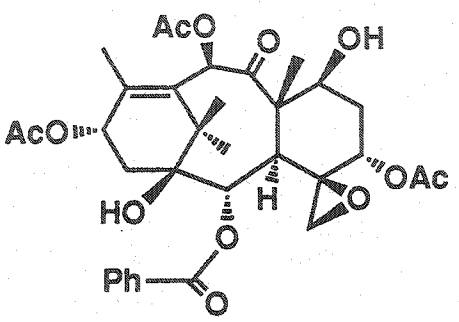
4

X-ray crystallography, NMR and mass spectroscopy are the principal techniques used for the structure elucidation of taxanes. Stimulated by the discovery of the antitumor activity of taxol, practically all taxus species, namely *T. baccata* L in Europe, *T. brevifolia* in North America, *T. canadensis* in Canada, *T. cuspidata*, *T. wallichiana* and *T. mairei* in Asia and *Austotaxus spiccata* Compton in New Caledonia have been screened for taxol.[5,6] It has been isolated from almost all these taxus species. Various derivatives of the taxane nucleus have also been isolated from the taxus species. These include taxinine, taxusin, 1β-hydroxybaccatin I, baccatin III, cephalomannine and taxagifine (Scheme 1).

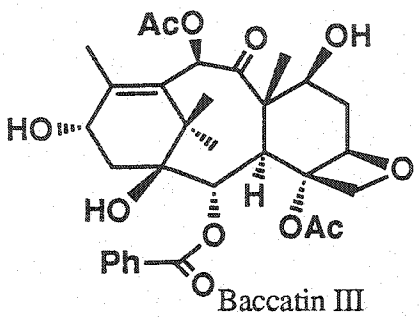
The isolation procedure is difficult, very low yielding and destructive of the source. Approximately 12,000 trees are required to obtain about 60,000 pounds of bark and a mere 2.5 Kg of taxol.[7] Thus continued harvest would lead rapidly to complete elimination of the taxus species and a serious environmental hazard. In addition to the rainfall pattern being adversely affected, species such as the endangered northern spotted owl which depend on the old-growth forest in the Pacific Northwest as their habitat, could face extinction before the turn of the century.



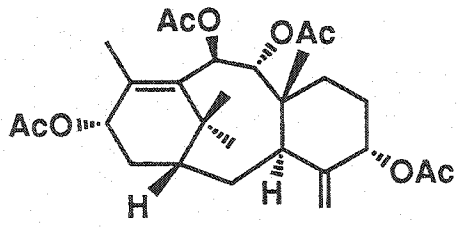
R = $CH_3CH{=}CHCH_3$, Cephalomanine



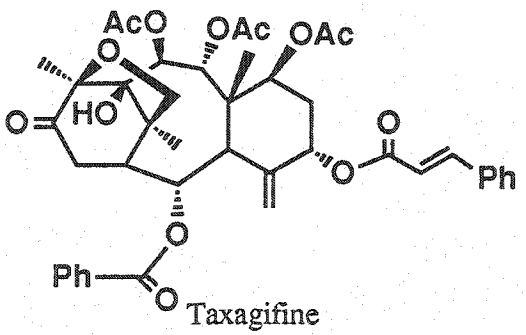
1β-hydroxybaccatin I



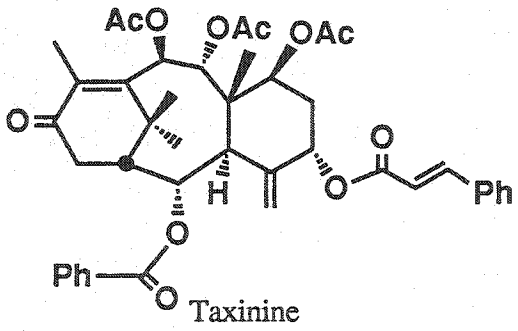
Baccatin III



Taxusin



Taxagifine



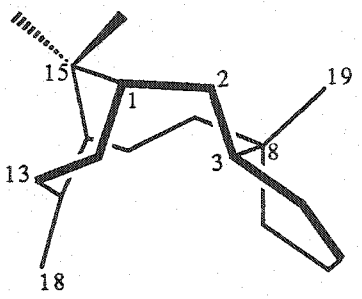
Taxinine

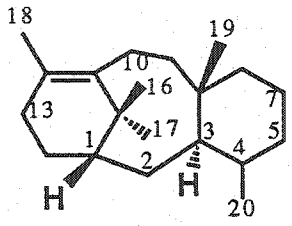
Scheme 1

1.2 Structure

The skeletal system of the taxoids is a tricyclic[9.3.1.$0^{3,8}$] pentadecene diterpene **5**. The two dimensional representation is

some what misleading since the conformation is highly folded (Scheme 2). The A ring, a distorted boat shape, is fused to the 8-membered ring which has a boat-chair conformation and is trans fused to the six membered C ring. The C ring is a distorted chair in the case of taxinine and baccatin derivatives.[6] MM2 calculations performed by Swindell *et al*[8] on a bicyclo[5.3.1]undec-1-ene have shown that the bridgehead double bond is stabilized by the presence of substituents in its vicinity and by conformational effects. These conclusions have been confirmed by NOE NMR measurements,[9] conformational calculations,[10] and by all X-ray diffraction studies done to date (recently Shea[11] has shown that the kinetic enolate of a C_2 ketone arose from C_1 hydrogen abstraction creating an intermediate with an additional bridgehead double bond).





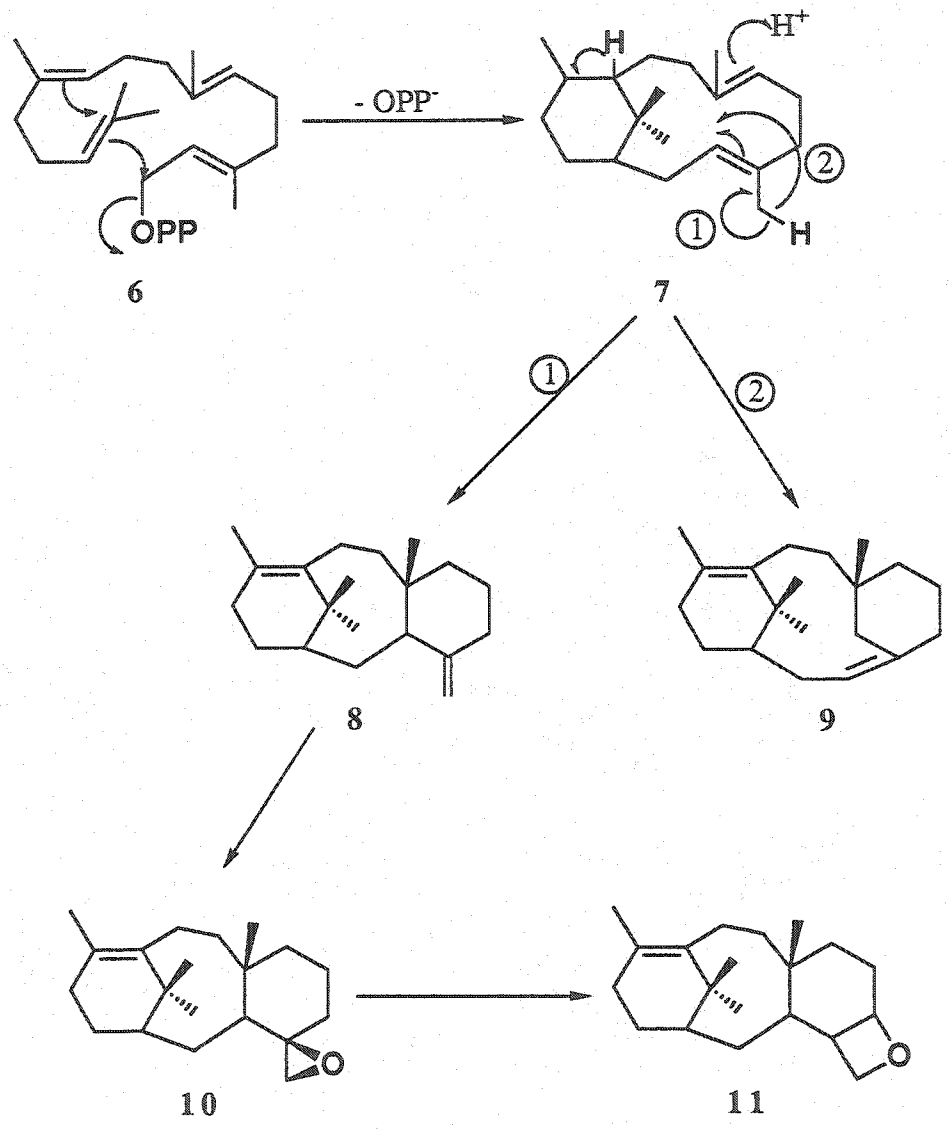
5

Scheme 2

1.3 Biosynthesis

There is a basic similarity in the carbon framework of the terpenes isolated from the various yew trees. They are classified into four main groups and are thought to have a common biogenetic origin. To satisfy the "common biogenetic origin" theory, Lythgoe *et al*[12] in 1966 proposed that all four basic taxane-type skeletons, **8**, **9**,

10, and **11** may originate from geranylgeraniol pyrophosphate through a series of cyclization reactions as shown in Scheme 3 below.

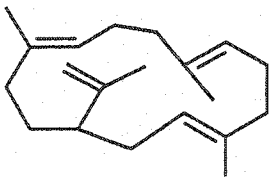


Scheme 3

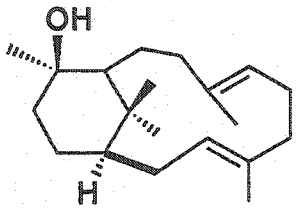
Hudder *et al*[13] expanded Lythgoe's proposal by suggesting that the taxol oxetane may originate from derivatives with an exocyclic

double bond at the C_4 - C_{20} position through regioselective epoxide formation. Opening of the epoxide followed by rearrangement may then result in the formation of the oxetane. Potier *et al*[14] have made similar proposals concerning the origin of taxol itself.

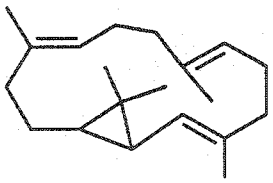
Other diterpenes that may be related to taxanes in terms of origin include the monocyclic diterpene, cembrene A[15] and the bicyclic diterpene alcohol verticillol[16] and casbene.



Cembrene A



Verticillol



Casbene

There is however no experimental evidence in support of the above proposals on the biosynthesis of taxanes.

1.4 Hemisynthesis

The high demand for taxol, the destructive nature of the collection method on the yew population and the difficulties of providing a short synthesis of a compound with such a complex array of functionalities, has stimulated alternative syntheses of taxol to meet the above demands.

Analysis of the various parts of the yew tree revealed that *Taxus brevifolia* leaves and heartwood contain between 20 ppm and 70 ppm of taxol and the bark 70 ppm to 400 ppm.[7] However the amount of leaves (in pounds) is about twice the amount of bark and

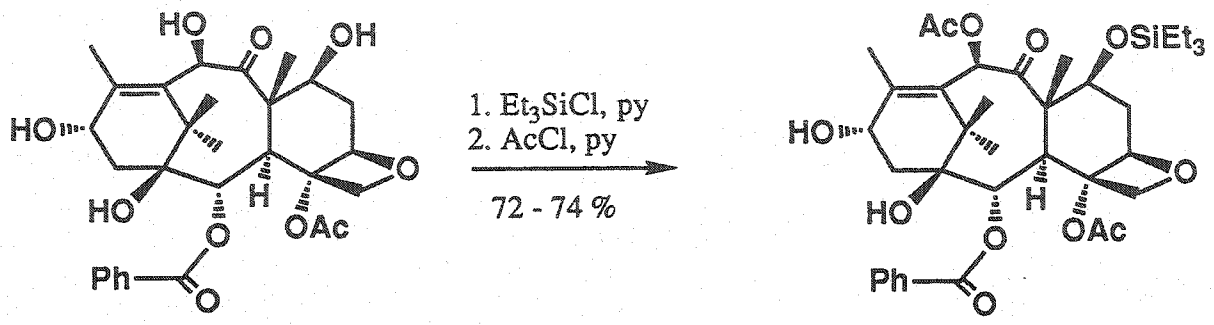
the amount of heartwood about ten times the amount of bark. The leaves have the added advantage that harvesting them does not kill the trees since they are quickly regenerated and as such do not create any environmental hazards.

In addition, 10-deacetylbaccatin III, (**12**) a precursor of taxol, was isolated in good yield (200 to 1000 mg/Kg of leaves) from the leaves of *Taxus baccata* by Potier *et al*[17] and converted by partial synthesis to taxol. Thus selective protection of **12** by silylation of the C_7 alcohol and acetylation at the C_{10} position followed by forced esterification of the C_{13} alcohol gave **14**. Deprotection of both the $C_{2'}$ and C_7 alcohol functions lead to taxol in 10% overall yield as shown in Scheme 4.

In a second and improved approach,[17c] a modified 10-deacetylbaccatin III, protected at both C_7 and C_{10} positions was converted to the cinnamoyl ester at C_{13}, **16**. Oxyamination by the Sharpless procedure gave four isomers one of which, the 2'R, 3'S isomer is converted to taxol in two steps involving deprotection and *N*-benzoylation in 26% yield from deacetylbaccatin III, Scheme 5. The weakness of this procedure is its poor diastereoselectivity but this is readily improved by the use of chiral ligands during the oxyamination reaction.

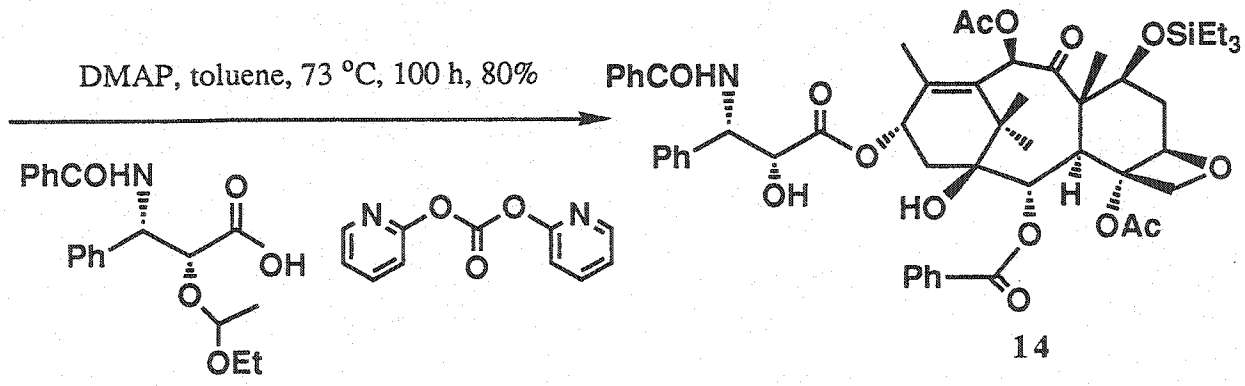
Taxotere (**18**), one of several taxol derivatives/analogues obtained in the course of this synthesis has been shown in clinical trials to be more effective and less toxic than taxol itself after the testing of forty taxol-like compounds.[17d] It is also claimed to have better bioavailability and solubility compared to taxol which has had formulation problems due to its low water solubility.[7] This

combination of isolation and hemisynthesis has solved the supply problem at least for Taxotere.



10-Deacetylbaccatin III, 12

13



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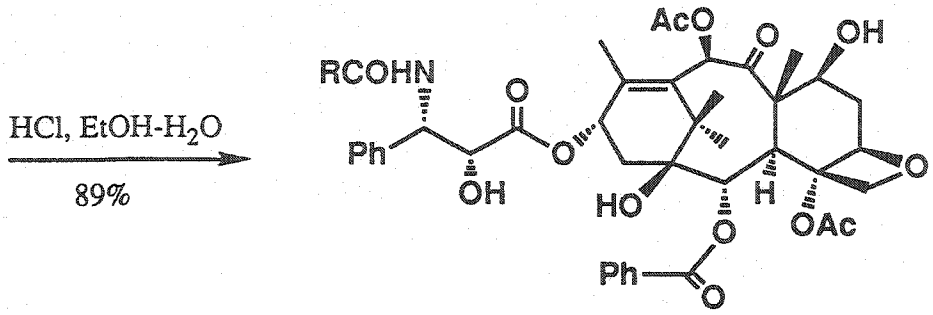
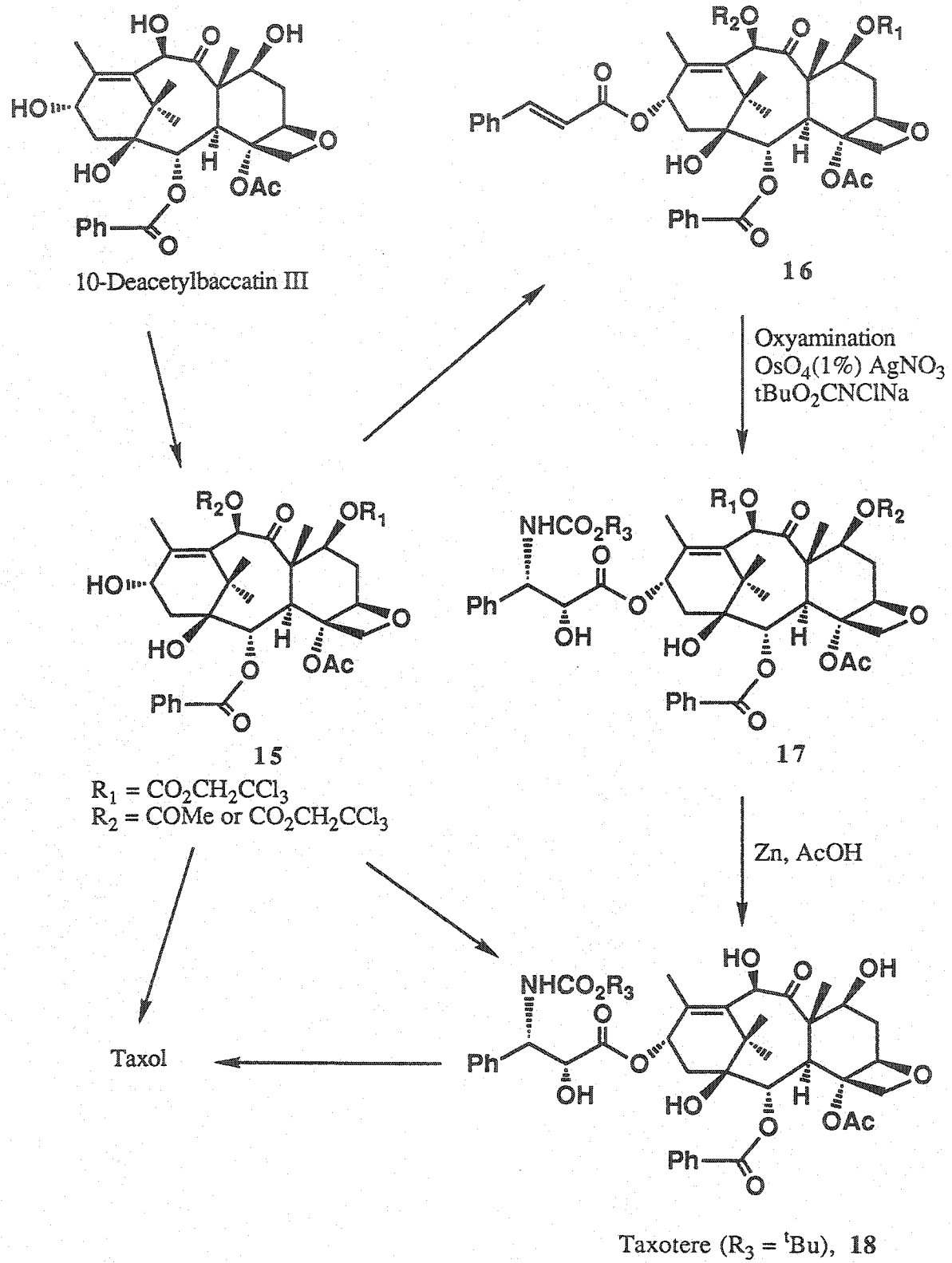


Taxol, R = Ph

Scheme 4


10-Deacetylbaccatin III
16
Oxyamination
OsO_4(1%) $AgNO_3$
$tBuO_2CNClNa$
15
$R_1 = CO_2CH_2CCl_3$
R_2 = COMe or $CO_2CH_2CCl_3$
17
Zn, AcOH
Taxol
Taxotere ($R_3 = {}^tBu$), 18

Scheme 5

The second strategy is the production of taxol from selected cultivers. It may be easier to grow selected taxol shrubs with high taxol content for pruning and harvesting (leaves) to attain the required biomass for taxol isolation with little or no adverse effect on the general yew tree population.

The third approach is through plant tissue culture, *i.e.*, production of taxol in cultures of cells grown in bioreactors. By this concept, a plant tissue culture capable of overproducing taxol is first selected and then optimized and integrated into a tissue culture which is stimulated to produce taxol. Some success in this area has already been reported by workers at USDA and by a company in San Carlos, California called ESCAgenetics.[7]

1.5 Pharmacological Activity

The toxicity and biological activity of the yew tree have been known since antiquity and native Americans have been known to have used the aqueous bark extract as an anti-inflammatory drug. However extensive study of the biological activity of the yew tree extracts began around 1968. This study included the antiovulatory effect of the leaf extracts of *Taxus baccata* described[18] in 1970, the tranquilizing effect on the central nervous system[19] caused by the administration of the extracts and the acute toxicity of taxin in mice especially with respect to the heart[20] where it is believed to be a calcium antagonist.

Potential anti-cancer properties were discovered during the initial screening tests of the stem bark extracts when Wani and Wall[3] found it to be quite active against rodent cancer cells. Of the large

number of taxol derivatives isolated from the extract, only taxol itself has given rise to a significant biological and pharmacological study. This is due in part to the strong anti-cancer activity of taxol and especially to the novel mechanism by which it disrupts cancer cells. This unique finding was first described in 1979 by Horwitz and co-workers[21] who showed that taxol binds to tubulin and acts to stabilize microtubules and to prevent depolymerization.

Tubulin is a heterodimeric protein (2 x 55,000 daltons) which upon polymerization forms microtubules and microfilaments. These microtubules together with associated fibers and proteins constitute the spindle. During mitosis,[22] the spindle plays a role in the distribution of chromatids to daughter cells resulting from normal cell division. Taxol has been shown to interfere with the microtubule organizing centers by lowering the critical concentration of tubulin needed for polymerization. This results in polymerization at many sites in addition to the microtubule organizing centers.[5] Buendia *et al*[23] have observed that *in vivo*, microtubules were not irreversibly stabilized by taxol but it instead seemed to promote the nucleation of microtubules that remained partially dynamic since at the beginning of mitosis the bundles were disrupted and replaced by asters.

Taxol is thus a unique member of a group of natural products including colchicine, podophillotoxin, vinblastine and their derivatives, collectively known as spindle poisons which impair cell division by inhibiting polymerization of tubulin into microtubules. Taxol on the other hand favour microtubule assembly into microfilament and spindle and inhibits its depolymerization.

Tubulin is the most probable target within the cell, although there is a possibility that mitotic spindle formation interference may perhaps not be essential to the antitumor activity of taxol.[6] In fact another mechanism has been put forward by Gupta and Dudani[24a] which suggests that taxol interacts with membrane bound tubulins of cytoplasmic organelles and alters the calcium regulation which as a side effect causes mitotic spindle disfunction.

At concentrations that effectively stop cell division, there is no known effect of taxol on DNA, RNA or protein synthesis whereas HeLa cells were blocked in late G_2 and/or M phase.[5] Because tumor cells multiply more rapidly than cancer cells, taxol inhibits tumor activity and is highly effective against human ovarian cell tumors[24b] and more recently has shown promise against breast and lung cancer.

Taxol is insoluble and must be administered intravenously but there are problems with obtaining a stable, homogeneous and nontoxic solution. Samples for human tests are prepared by adding cremophor, a polyethylated castor oil to an ethanol solution of taxol diluted with 5% dextrose in water or normal saline.[5] Cremophore is toxic and has been known to provoke serious allergies. Taxol is also neuropathic as a result of problems arising from nerve regeneration.

Structure activity studies have shown that the side chain at position C_{13} is essential for activity whereas the nature of the substituents on the hydroxyl groups at positions C_7 and C_{10} can be varied without a significant change in activity.[6] The importance of the oxetane ring for activity have been demonstrated by Kingston who showed that it facilitates binding to tubulin as well as

maintaining the conformation of the taxane skeleton perhaps for recognition at the cell binding site.[25a] Within the side chain itself the hydroxyl group at the 2' position has been shown to be essential.[25b]

2 Radical reactions

Radical reactions have increased in importance in synthetic organic chemistry during the last ten years. This is due in part to the detailed understanding of the reactivity, selectivity and stability of several types of organic radicals that have been studied especially by physical organic chemists. Recently however, synthetic organic chemists have been applying this understanding to solving synthetic problems involving highly complex natural products.

The most synthetically useful radical reactions are chain processes involving three main steps namely; radical initiation, chain propagation which may involve electron, atom or group transfer, addition, substitution or elimination and chain termination.

Radical reactions are initiated either directly by a thermal or photochemical step and to a lesser extent by redox activation. Indirectly an initiator is employed which in synthetic organic chemistry is frequently azobisisobutyronitrile (AIBN) or other related azocompounds. These initiators have the advantage of being safe, easy to handle and have decomposition rates that are independent of solvent.

Due to their very low enthalpy of activation, the propagation steps of radical reactions are very fast processes and whether or not products form will depend on the reactivity and the rates of the

various competing radical species. Thus if the rate of hydride abstraction, K_H is much much faster than K_C (rate constant for the intramolecular addition of the radical to the double bond), then only the reduced product **21** is formed (Scheme 6). Fortunately most of the important rate constants useful for synthetic planning have been determined and are independent of solvent for neutral radicals.[26] Radical reactions which constitute the chain termination step do not have favorable rate constants compared to propagation steps and are usually not very important in radical reactions for organic synthesis.

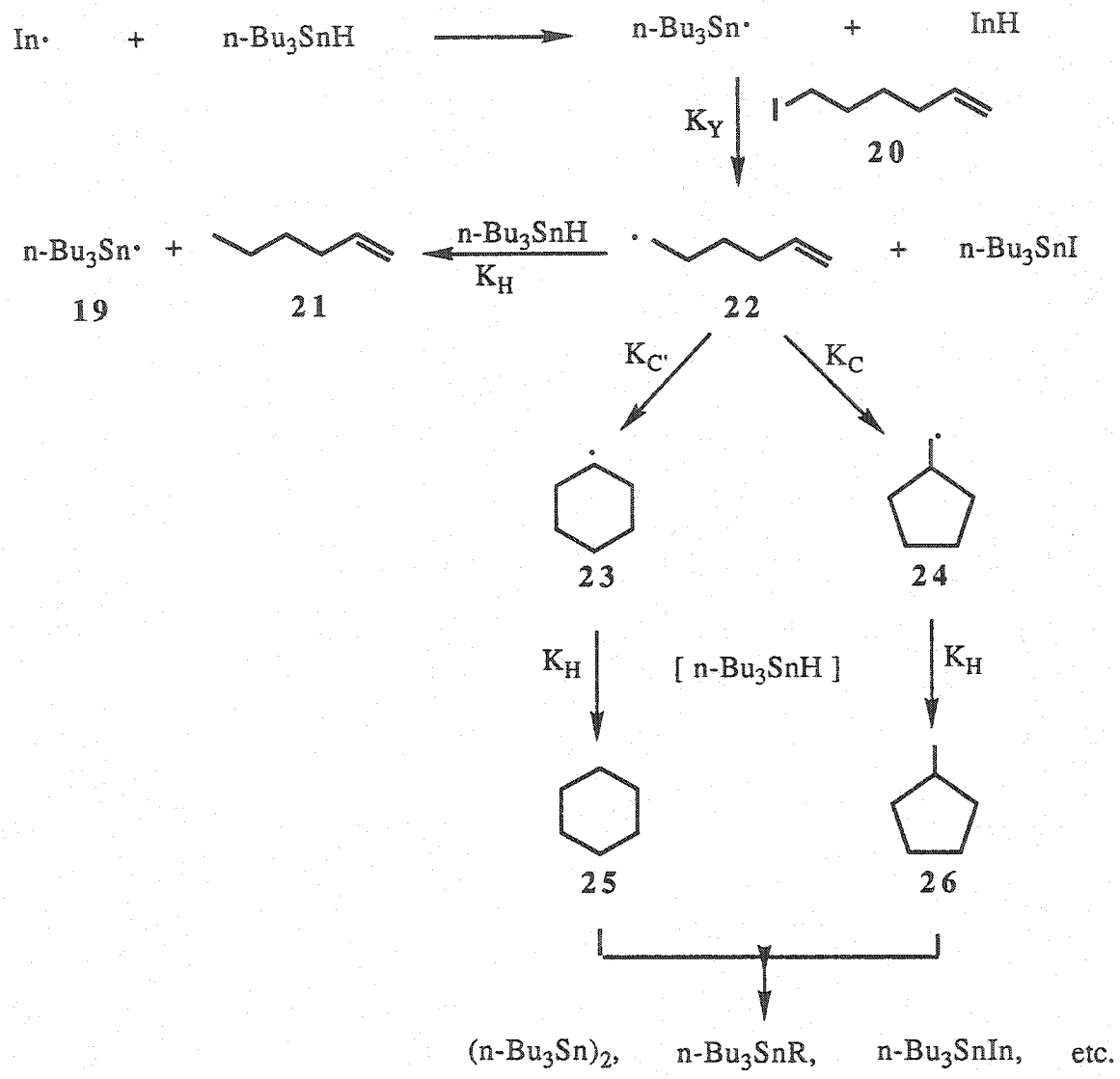
Compared to reactions conducted under ionic conditions using organometallic intermediates, radical reactions have the following advantages; a) solvents have little effect on the reaction rates of neutral radicals.

b) A wide range of functionalities are tolerated without protection. For example, homolytic cleavage of O-H and N-H bonds in aliphatic alcohols and amines and intermolecular addition to carbonyl bonds of ketones and esters by alkyl radicals is extremely slow at room temperature. Consequently these processes seldom interfere. Carbon centered radicals thus show high chemoselectivity.

c) Orbital interactions are more important in radical compared to ionic reactions since radicals attack exclusively at the carbon atom with the largest LUMO coefficient. Thus for addition reactions to α,β-unsaturated compounds the radical attacks exclusively at the β-olefinic carbon atom.

d) Steric crowding is tolerated especially on the radical center. Thus the *tert*-butyl radical adds to alkenes with rates comparable to

or faster than less substituted radicals due to its increased nucleophilicity.[26b]

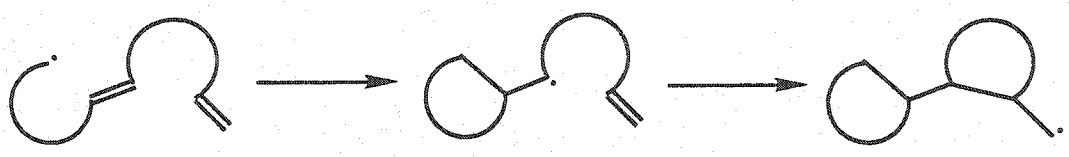


Scheme 6

e) The influence of remote substituent effects are minimal. Thus quite accurate information about a planned reaction may be inferred from simple models containing appropriate substitution

patterns. However the common technique of altering reaction variables such as temperature, solvent, counter ion and additives to improve the product ratio is of very little help in radical reactions that show little of no stereo or regioselectivity.[27]

f) Possibilities exist for tandem type cyclizations, one of the most important advances in radical chemistry in particular and synthetic chemistry in general. This is very important because it offers the unique possibility of performing two or more ring closures in one synthetic step.



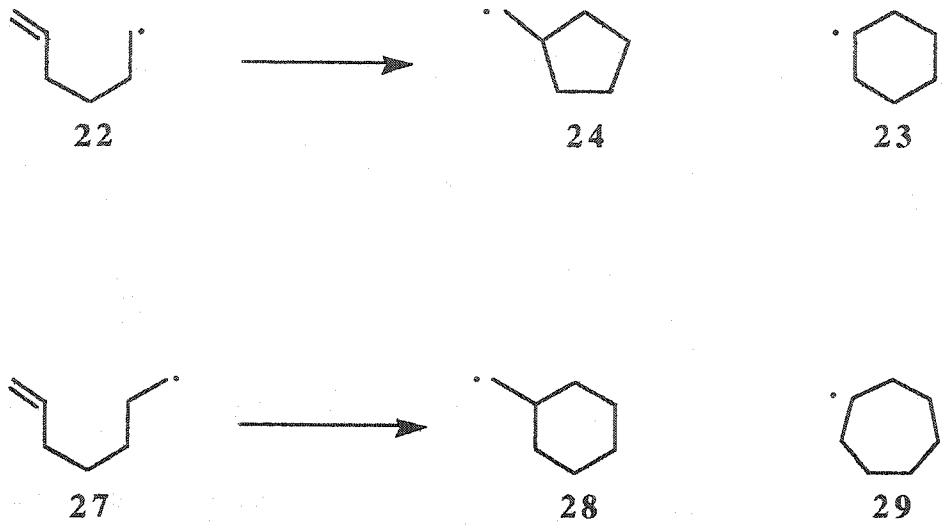
Tandem cyclization

For radical reactions to be synthetically useful, both the selectivity and reactivity requirements for chain reactions must be fulfilled thus an understanding of the reactivities of radicals is very important. Chain propagating radicals that give rise to resonance stabilized radicals are favoured and therefore are faster than those giving rise to unstabilized radicals. Also radical bearing carbon centers with electron withdrawing groups attached react preferentially with electron rich substrates and conversely radicals with electron donating groups react preferentially with electron deficient substrates. Thus radicals can be thought of as having electrophilic or nucleophilic properties or as electron acceptors or donors.[28a]

Steric factors are usually large and important in determining the success of radical reactions involving addition to multiple bonds but radical reactions involving hydrogen or halogen transfer (displacement reactions) usually show little sensitivity to steric effects. In radical displacement reactions if the intermediate radical is prochiral it may show preference for reaction at its less hindered face. Due to the existence of delocalization in allylic radicals, reaction may take place at either α or γ positions but generally the less hindered position is preferred.

Both regio- and stereoselectivities of radical reactions have been well studied but predicting their outcome in more complex situations is very difficult. In the case of intermolecular radical reactions, regioselectivity is determined by resonance, polarity and steric factors. Generally anti-Markovnikov addition is favoured by energetic and steric factors. Steric effects tend to be more important in aliphatic olefins and stereoelectronic factors in intramolecular reactions. Regioselectivity is enhanced in intramolecular reactions because they are controlled by molecular geometry.

The most synthetically useful radical reactions are the intramolecular reaction involving the 5-hexenyl radical system. Both 5-hexenyl and 5-heptenyl radicals **22** and **27** cyclize in the presence of tributyltin hydride in a highly regioselective manner to give the smaller rings **24** and **28** via the exo-cyclization mode (Scheme 7).

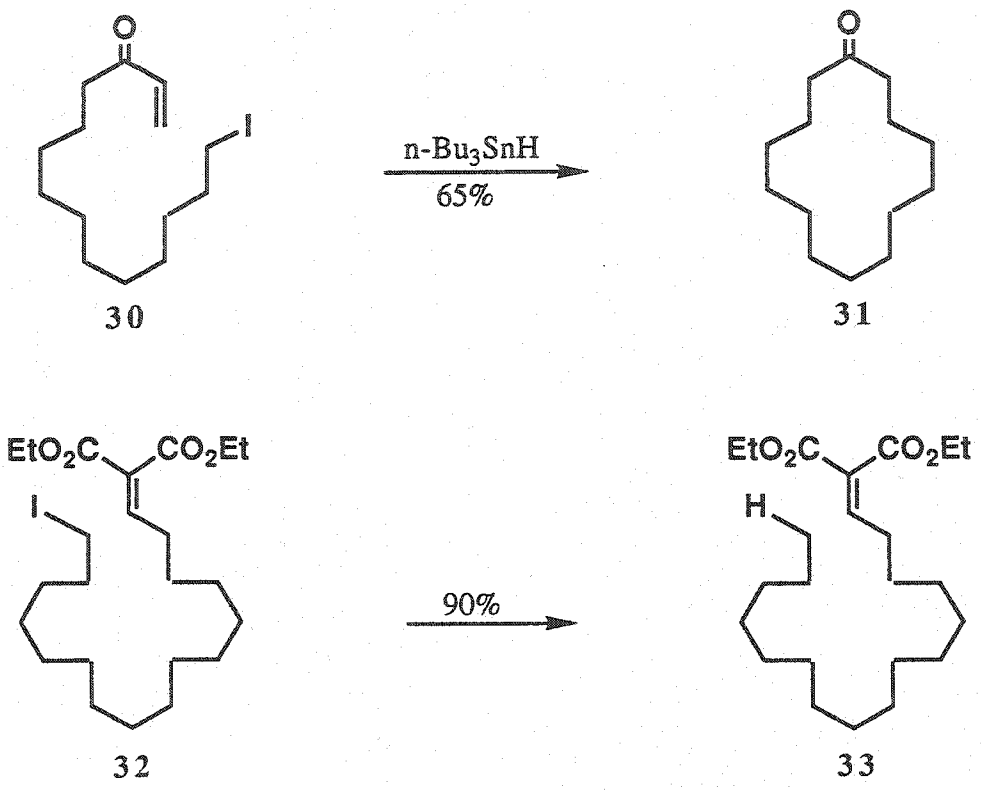


Scheme 7

According to the Baldwin rules,[28b,33] under kinetic control, ring closure occurs preferentially in an exo-mode. The degree of preference for exo-cyclization depends on the length of the carbon chain, n; when n is 1 or 2, the transition state for the endo process is highly strained and less favorable but when the chain is long and flexible, the difference in strain energy between the transition complexes leading to exo- and endo-cyclization diminishes thus increasing the favorability of endo-cyclization. Also structural features affect the ability of the double bond and the radical to accommodate the transition complex which influences the rate and regioselectivity of ring closure.

It has been suggested that the formation of medium rings via radical cyclization is not a useful synthetic route, however recent work by Porter,[29] has shown that large rings can be synthesized by radical cyclization. According to Porter, in macrocyclization reactions there is no preference for exocyclization (Scheme 8). Example **32** to **33** was designed to favour exo-cyclization, but no cyclized product

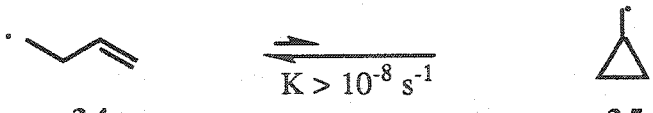
was observed. He also noted that use of iodides is a critical requirement to maximize yields.



Scheme 8

Pattenden[30] has recently published a synthesis of the taxol diterpene skeleton (*vide infra*) involving radical macrocyclization as shown in Scheme 20 which again relies on endo-cyclization. Also heteroatom radicals *e.g.*, silyl and germyl radicals cyclize in an endo fashion.[31] This is due in part to the increased chain length of the Si-C or Ge-C bond and the pyramidal configuration of the hetero atom radical as opposed to the planar carbon radical.

Small ring formation is favoured according to the Baldwin rules but neither three nor four membered rings can be synthesized because the cyclopropylmethyl and cyclobutylmethyl radicals **35** and **37** cleave much faster to form the more stable acyclic radical intermediates **34** and **36** respectively. The rate constant[32] for this process in the case of the cleavage of **34** is $> 10^{-8}$ s^{-1}.



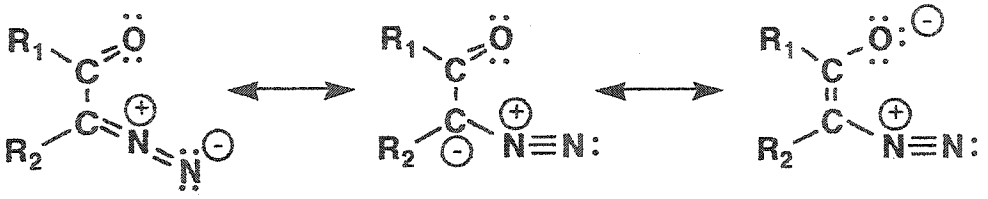
34 **35**

36 **37**

Finally the stereochemical outcome of the 5-hexenyl radical ring closure can be readily predicted using two guidelines formulated by Beckwith:[33] 1- or 3- substituted radicals afford preferentially cis disubstituted products and 2- or 4- substituted radicals afford mainly the trans product.

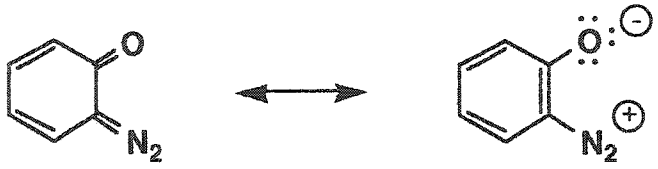
3 α-Diazo Carbonyl Compounds

α-Diazo carbonyl compounds **38** contain as a general feature the $CO\text{-}CN_2$ group which is capable of resonance as shown below:



38

When the carbon-carbon bond which may either be part of an aliphatic carbon chain or a cyclic system, is present in an aromatic ring an inner diazonium phenoxide **39** ("o-quinone diazide") is present. The attached R_1 groups may be occupied by heteroatoms *e.g.*, R_1 may be OR, NH_2, NHR, NR_2, etc. The most obvious analytical feature of a simple α-diazo carbonyl compound is the diazo band which occurs between 2090 and 2190 cm^{-1} in the IR spectrum.



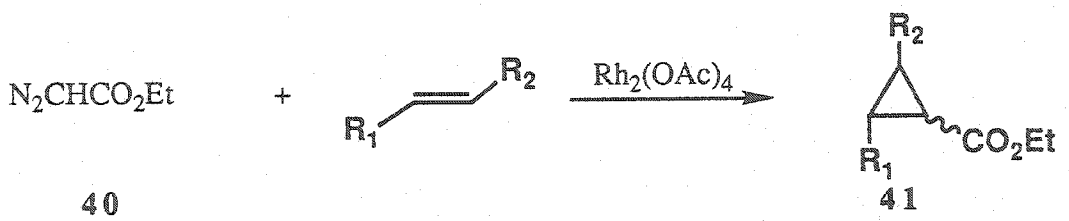
39

These compounds are very reactive species and their reaction which involves loss of nitrogen may be induced thermally, photochemically, catalytically (metals and salts) or by Lewis acids. Loss of nitrogen under photochemical or thermal conditions produce a carbene whereas under catalytic conditions, the free carbene is not formed. Instead the catalyst is bound in some way to the diazo carbonyl compound,[34] or the carbene derived from it[35] referred to as a carbenoid intermediate. Under both thermal and photochemical conditions the resulting carbene intermediates frequently undergo Wolff rearrangement giving rise to a ketene as the major product but

under catalytic conditions (especially rhodium, copper, and palladium), the resulting carbene is stabilized by the metal and Wolff rearrangement is a minor pathway. There are however a few examples of rhodium catalyzed Wolff rearrangement[36] (*vide supra*).

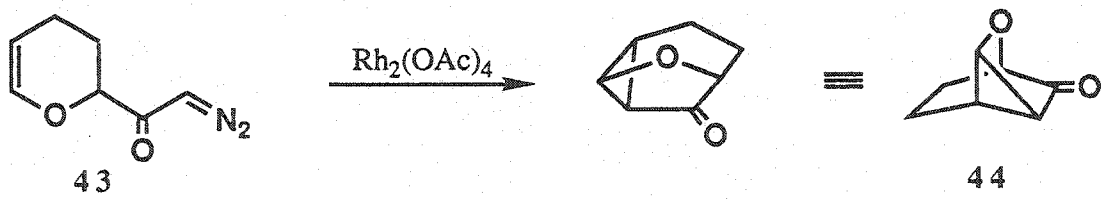
Generally the carbenoid intermediate generated from catalytic decomposition may undergo four main reactions namely a) cyclopropanation or cyclopropenation when allowed to react with olefins or acetylenes respectively, b) carbon-hydrogen bond insertion, c) heteroatom-hydrogen bond insertion and d) initial ylide formation with oxygen, sulfur and nitrogen followed by subsequent reactions. Cyclopropanes frequently occur in several natural products and they are especially useful in ring cleavage reactions leading to complex products. Thus their preparation has evolved into one of the important areas of organic synthesis.

The most widely used reaction of α-diazocarbonyl compounds involves the formation of cyclopropyl derivatives from alkenes. Copper (*e.g.* copper, copper sulphate) was the catalyst of choice until the early 1970's when work by Teyssie *et al*[37] showed that rhodium(II) carboxylates are more efficient catalysts for carbenoid mediated cyclopropanation. Representative examples are shown below for the formation of **41** and **42**. Rhodium(II) carboxylates have the advantage of a) being highly specific for cyclopropanation, b) have very high catalytic efficiency, requires about 1 to 3% catalyst by weight, c) reactions are carried out at ambient temperature and d) reaction rates are very rapid. To date however, no intermediate carbenoid complexes have been isolated and the actual detailed mechanism has not yet been determined.



40 41

40 42



43 44

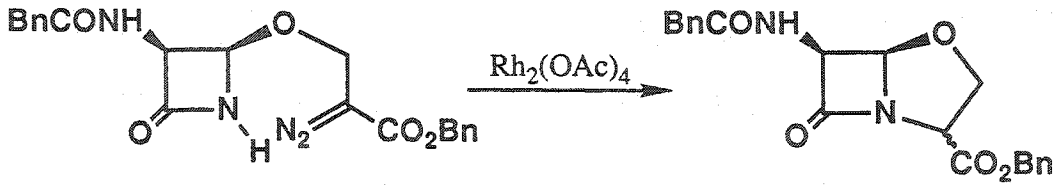
A study of alkene reactivity showed electron rich alkenes react faster and preferentially while electron deficient alkenes such as α,β-unsaturated carbonyl compounds frequently form pyrazolines rather than cyclopropanes. Acetylenes readily undergo rhodium mediated carbene addition to form the strained and reactive cyclopropenes. The most notable problems of these addition reactions are the lack of selectivity and dimerization of the carbenoid intermediate. The later problem is frequently solved by controlling the rate of addition of the diazo compound (by use of syringe pump) and/or by the use of excess olefin, usually as the solvent. Rhodium catalysts are finding

increased use in intramolecular cyclopropanations (*e.g.*, formation of **44**) which have extensive preparative utility.[38a,38c]

Rhodium catalyzed carbene insertion into the C-H bond has been utilized extensively by Taber *et al*[39] for the synthesis of cyclopentane derivatives. In a competitive study of C-H insertion and cyclopropanation, it was observed that with methine, insertion is selected over cyclopropanation but cyclopropanation occurs to a greater extent than insertion in the case of methylene.

In the case of hetroatom-H insertion, Teyssie[37] has reported that for both ethylene and acetylenic alcohols O-H insertion is favoured over cyclopropanation.

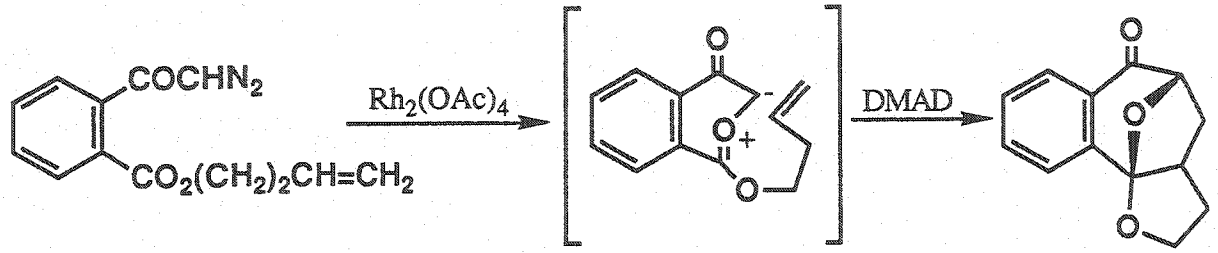
Rhodium catalyzed N-H insertion reactions have been utilized for the synthesis of β-lactam antibiotics as shown for the transformation of **45** to **46**.[40]



45 **46**

A carbonyl ylide is generated by the reaction of a keto carbenoid intermediate with the lone pair of electrons on the carbonyl oxygen. The resulting ylide *e.g.*, **48** is a 1,3-dipole species that can be trapped with olefins, acetylenes, carbonyls and heteromultiple bond dipolarophiles.[38b] This reaction has been successfully utilized by Padwa's group but it frequently occurs as a

side reaction in cyclopropanation reactions where free ketones and/or other heteroatoms such as sulfur and nitrogen are available.



47 48 49

4 Previous Synthesis

Taxol is the most functionally and stereochemically complex of the taxanes and thus the most synthetically challenging. Besides the vast array of functionalities, there are two stereocentres in the side chain, two in the A-ring, two in the B-ring and five in the C-ring. The skeleton itself, a combination of a highly strained 8-membered ring system with two stereochemically distinct 6-membered rings A and C attached poses a major synthetic problem. MM2 calculation indicated that whereas the gem dimethyl group causes extreme stress in the taxane nucleus, it hints that the bridge head double bond in the A-ring may decrease rather than increase the strain energy of the tricyclic system.[8] These views are supported by derivations of the natural product which show a remarkable stability of the bridge-head olefin.[8,12,41]

There have been several attempts by numerous groups but very few successful syntheses of the tricyclic framework with the correct stereochemical ring linkage.[42] A few synthesis of the less complex side chain at the C_{13} position[43] have appeared including a modified version that has been shown to give Taxotere a compound with significantly greater cancer chemotherapeutic potential than taxol itself.

Cyclization reactions

The approaches adapted for the taxane skeleton are as varied as one's imagination and to date there has been several different strategies which could be broadly divided into linear and convergent.

The convergent strategy is preferable because it is more efficient however most of the published synthesis of the taxane skeleton have involved the linear strategy because of difficulties involved in the development of an effective convergent synthesis. Swindell has recently published a comprehensive review[42] containing many partial synthesis therefore only a brief overview of the important approaches to methyl substituted tricyclic skeletons is given below.

4.1 Linear Strategies

A. Biomimetic Approaches

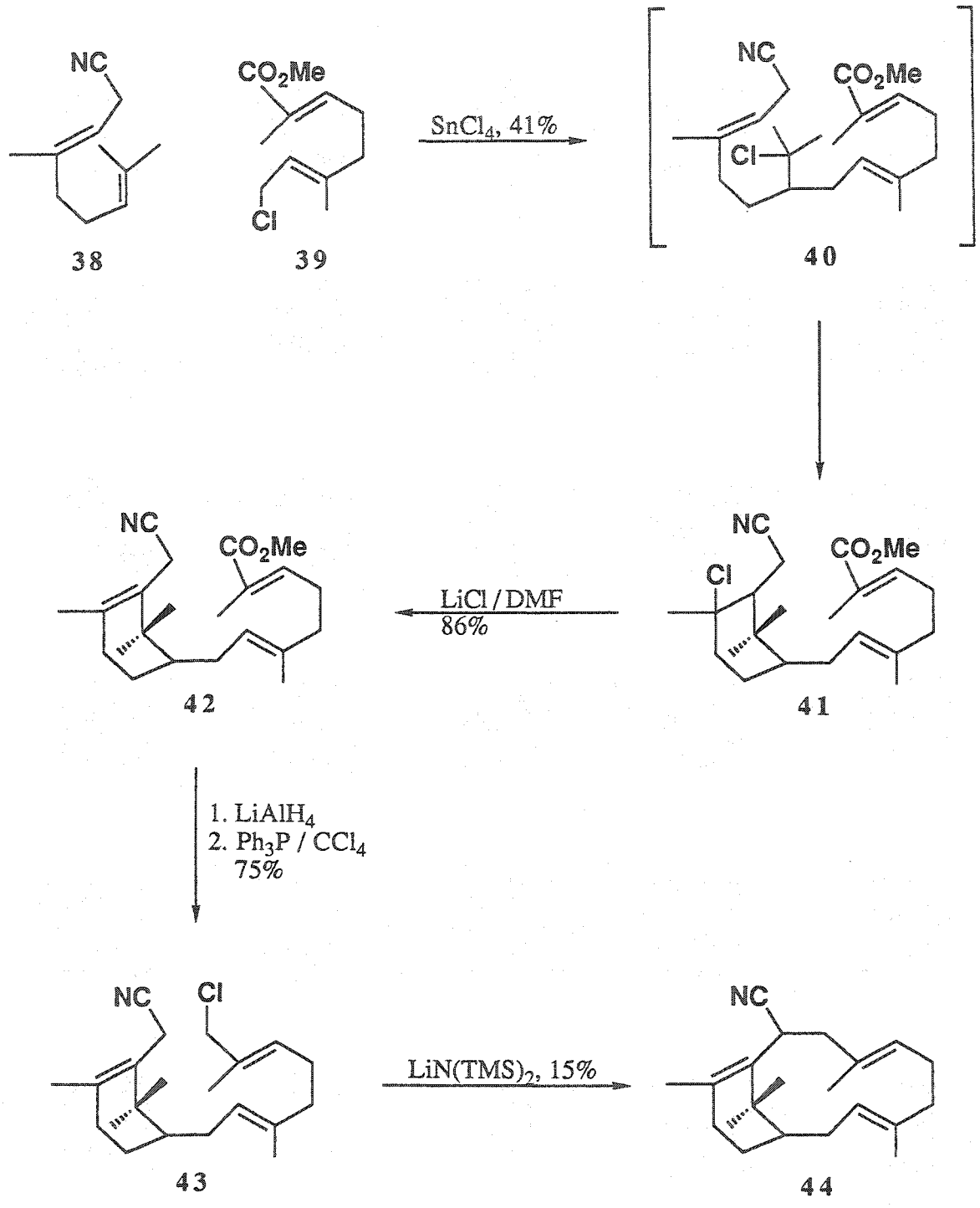
Most of these approaches are based on Lythgoe's[12a] biogenetic scheme for taxane.

4.1.1 Kato's Synthesis

In 1978 Kato and coworkers[44] devised a synthetic strategy based on a modification of Lythgoe's scheme such that the C_8 - C_9 bond of **5** is connected after connection of the A-ring by carbon - carbon bond formation between an isopropyl cation and the C_{10} position of the intermediate **40**. Two functionalized geranyl units are coupled in a head to tail fashion to obtain the seco-cembrene **40** at -78 °C and cyclized directly to **41** at -30 °C. Further modification afforded **43** in 75% yield and finally base induced ring closure gave the macrocyclic seco-taxane **44** in 15% yield (Scheme 9).

4.1.2 Pattenden's First Approach: Synthesis of verticillene and attempted transannular cyclization to form the C-ring.

Pattenden[45a,45b] reasoned that the taxane ring system **53** is probably derived in nature through a transannular cyclization across

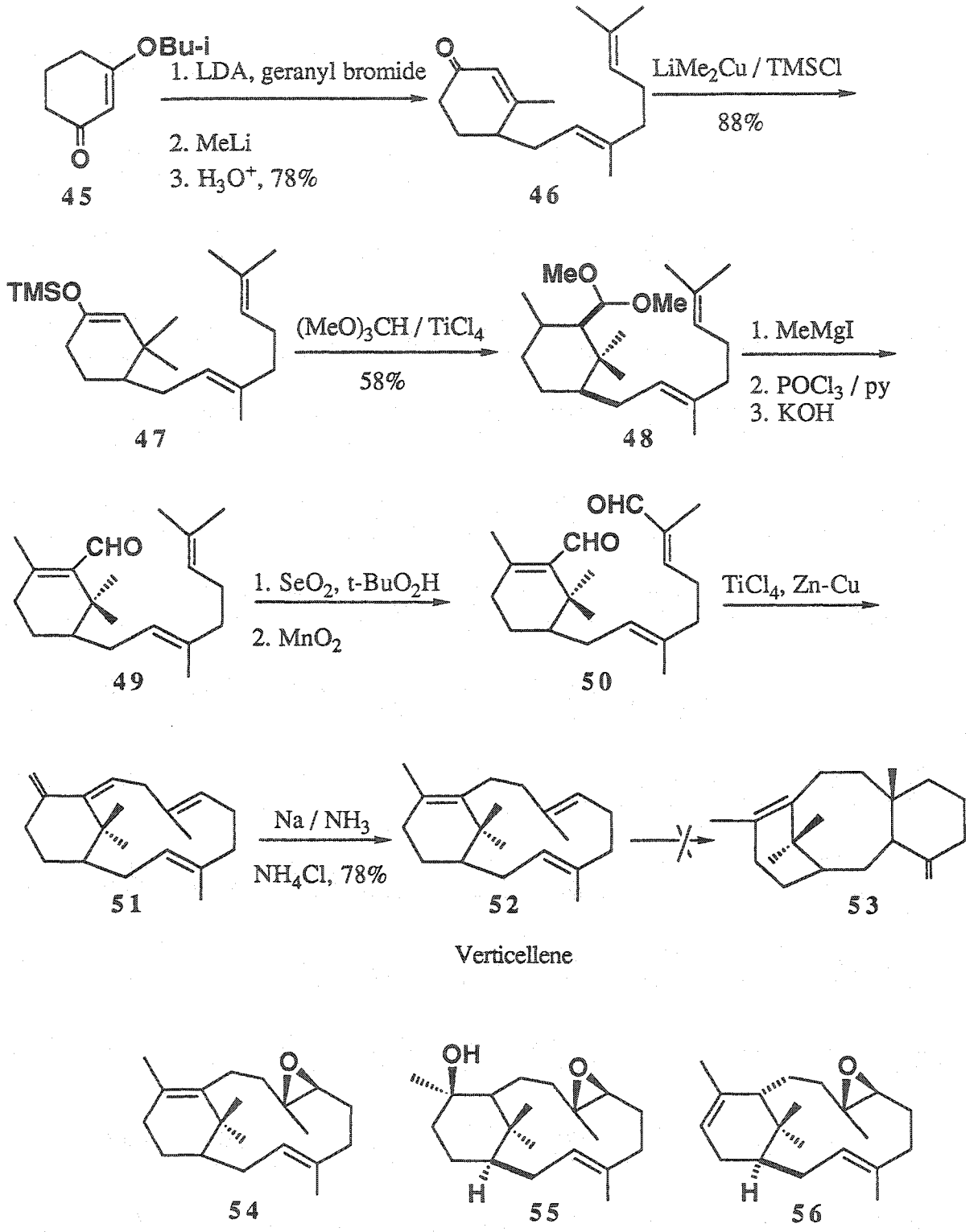

NC
CO2Me
Cl
SnCl4, 41%
38
39
40
LiCl / DMF
86%
1. LiAlH4
2. Ph3P / CCl4
75%
LiN(TMS)2, 15%
41
42
43
44

Scheme 9

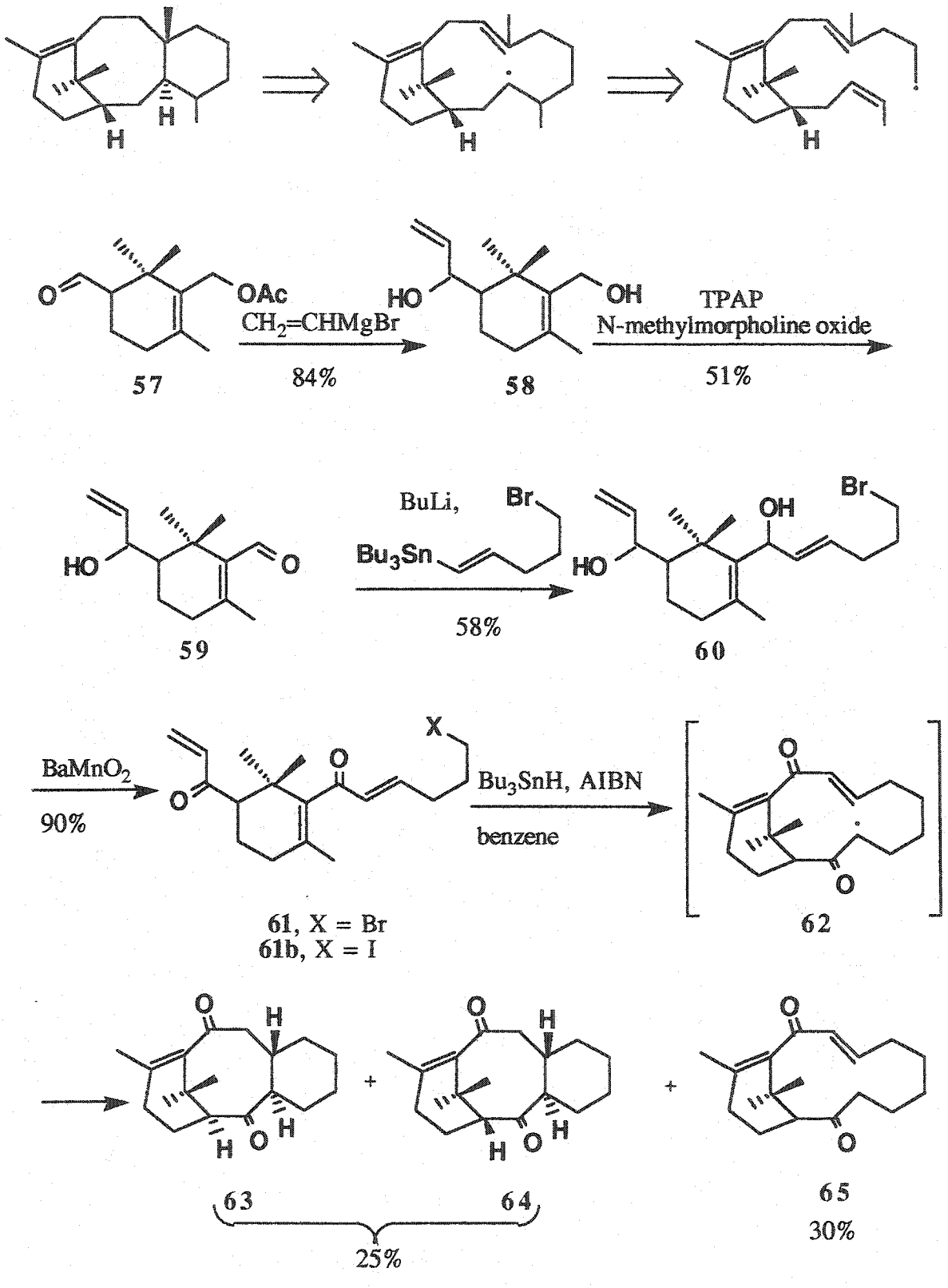
the verticillene, **54** 12-membered ring which "according to Lythgoe" is produced by macrocyclization of geranylgeranyl pyrophosphate. The starting material, dihydroresorcinol derivative, **45** was converted through a series of steps to the key bisaldehyde **50**, Scheme 10. In the presence of Ti(O) this underwent a McMurry dialdehyde condensation followed by a 1,5-H sigmatropic rearrangement to form a 12-membered macrocyclic ring, **51** (25%). Metal reduction gave E,E verticillene in 78% yield. All attempts to convert verticillene or other epoxide derivatives of verticellene, **57**, **58** and **59** to the 6-8-6 taxane skeleton via transannular cyclization in presence of Lewis acids failed to give the desired product. Decomposition or rearrangement of the epoxide rings in the substrate were obtained.

4.1.3 Pattenden's Second Approach: Tandem Radical Macrocyclization.

In a recent reported synthesis of the taxane ring system, Pattenden[30] described a unique synthesis based on his interest in the biomimetic-type approach and in the development of cascade radical ring forming reactions in target synthesis. Thus compound **60**, derived from a Diels-Alder reaction between acrolein and 2,4-dimethyl-3-(acetoxymethyl)penta-2,4-diene in $BF_3.OEt_3$ at -78 ^oC (79%) was converted in four steps to the radical precursor compound **61b**. This contained two conjugated enone moieties to allow the tandem 12-endo 8-endo cyclization desired. Iodide **61b** was converted to the desired compound **64** and its isomer **63** in 25%


OBu-i
1. LDA, geranyl bromide
2. MeLi
3. H_3O^+, 78%
45
46
$LiMe_2Cu$ / TMSCl
88%
TMSO
47
$(MeO)_3CH$ / $TiCl_4$
58%
MeO
OMe
48
1. MeMgI
2. $POCl_3$ / py
3. KOH
CHO
49
1. SeO_2, t-BuO_2H
2. MnO_2
OHC
CHO
50
$TiCl_4$, Zn-Cu
51
Na / NH_3
NH_4Cl, 78%
52
53
Verticellene
54
OH
H
55
H
56

Scheme 10


OAc
CH2=CHMgBr
84%
HO
OH
TPAP
N-methylmorpholine oxide
51%
57
58
59
60
BuLi,
Br
Bu3Sn
58%
BaMnO2
90%
X
Bu3SnH, AIBN
benzene
61, X = Br
61b, X = I
62
63
64
65
30%
25%

Scheme 11

yield in refluxing benzene, tributyltin hydride and AIBN. 30% of the uncyclized reduced product, **68** was also isolated, Scheme 11.

B. Intramolecular Diels-Alder Strategies

The presence in the unusual tricyclic carbon framework of two six-membered rings, ring A with a bridgehead double bond makes the Diels-Alder approach the most obvious strategy since it offers the unique possibility of forming both the 8- and 6-membered rings at the same time and at either ring A or C.

AB-Bicyclization.

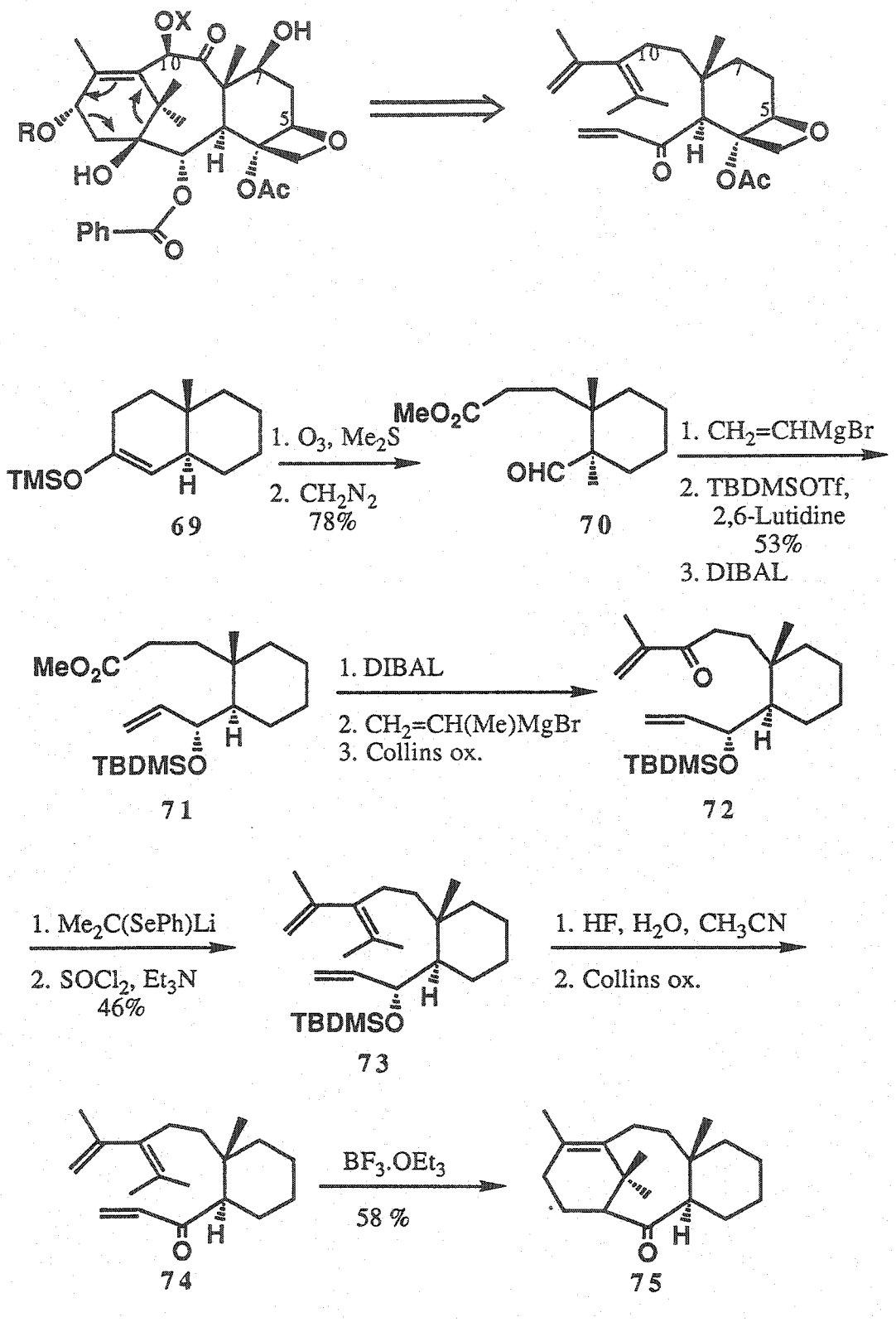
The AB ring closure with concomitant formation of the bridgehead double bond makes this the most obvious approach.

4.1.4 Jenkins' Approach

The approach via a Diels-Alder reaction by Jenkins and Bonnert[46] leads to one of the most functionalized taxol skeletons to date. The strategy developed concurrently with, and similar to that of Shea[47] and co-workers, was based on the synthesis of a trans disubstituted cyclohexane of known stereochemistry at C_3 and C_8 positions followed by Diels-Alder ring formation. This created the A-ring and introduced the bridgehead double bond (Scheme 12).

BC-Bicyclization.

Difficulties are anticipated if the bridgehead double bond is introduced before the Diels-Alder reaction. This is because conformational and entropy considerations due to the requirement for axial orientation of the diene, make direct formation of the C ring difficult.


OX
OH
RO
HO
OAc
Ph
TMSO
1. O_3, Me_2S
2. CH_2N_2
78%
69
MeO_2C
OHC
70
1. CH_2=CHMgBr
2. TBDMSOTf,
2,6-Lutidine
53%
3. DIBAL
MeO_2C
TBDMSO
71
1. DIBAL
2. CH_2=CH(Me)MgBr
3. Collins ox.
72
1. Me_2C(SePh)Li
2. $SOCl_2$, Et_3N
46%
73
1. HF, H_2O, CH_3CN
2. Collins ox.
BF_3.OEt_3
58 %
74
75

Scheme 12

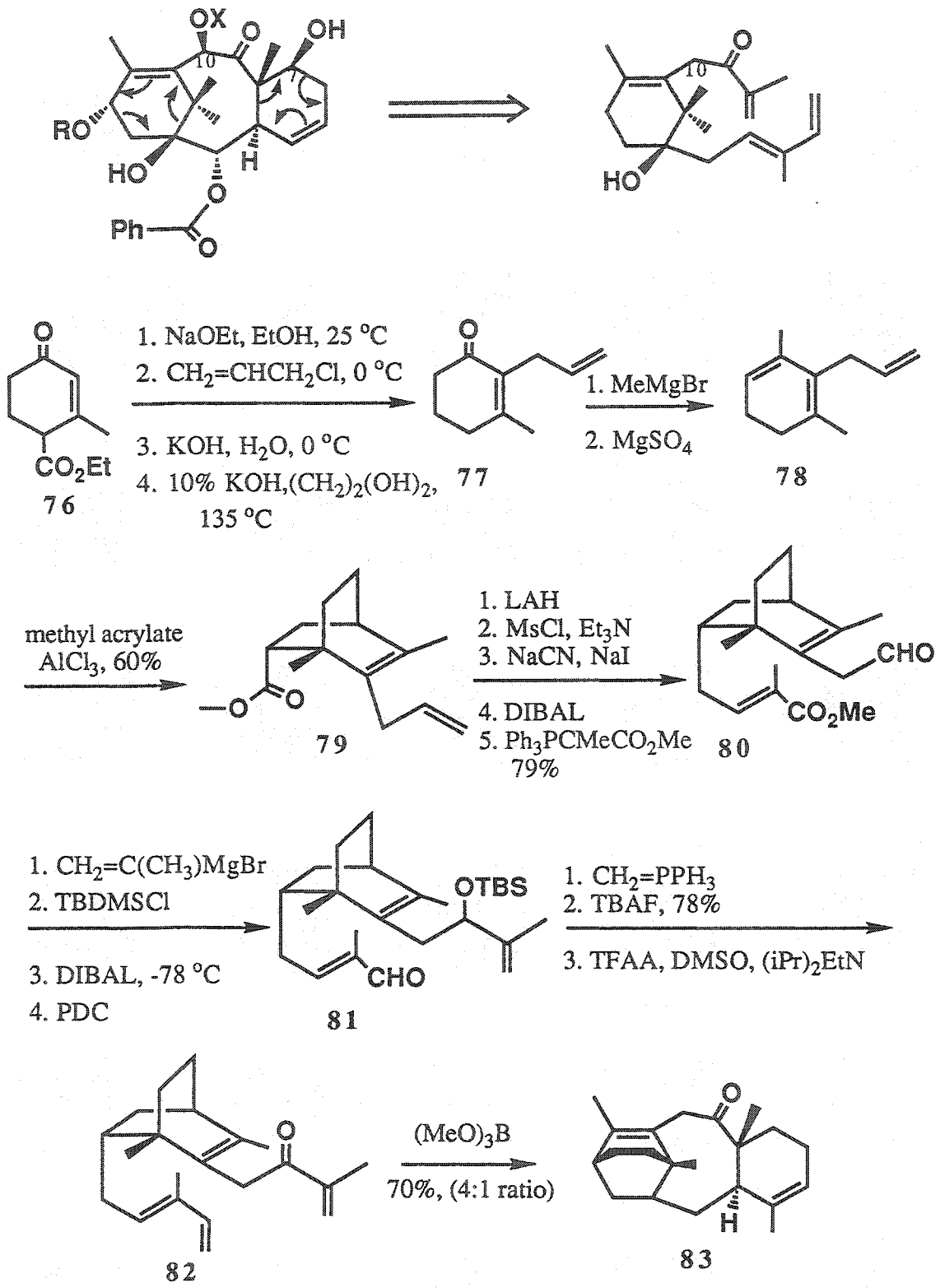
4.1.5 Sakan's Approach

Sakan and Craven[48] in 1983 published the first example of an intramolecular Diels-Alder BC bicyclization leading to the taxol-like skeleton. Commercially available Hagemann's ester (**76**) was converted through a series of steps to ketone **77** in 65% overall yield (Scheme 13). Treatment of **77** with MeMgBr at 0 ^{o}C followed by dehydration with anhydrous $MgSO_4$ in pentane at room temperature gave a 1:1 mixture of trienes which were converted to **79** in one step. Through a multistep synthesis **79** was converted to the key Diels-Alder intermediate **82** which upon cyclization in the presence of $(MeO)_3B$ catalyst gave a 70% yield of the desired product with the correct stereochemistry at the C_3 and C_8 positions.

According to Sakan earlier studies had shown that to get the system into the stereochemically correct but less favorable BC ring conformation, ring A must sit in a boat conformation. This requirement is satisfied in the synthetic strategy by the introduction of the rigid bridge through the formation of bicyclo[2.2.2]octene system. It is also widely belived that a substituted cyclohexene by itself will not cyclize but recent progress in our group has shown the additional ring is unnecessary.

4.2 AB TO ABC Strategies

It is generally well known that formation of medium rings (8, 9) via direct ring closure is very difficult thus several approaches to the taxol skeleton have relied on an indirect approach to the 8-membered ring via ring expansion.


OX
O
OH
10
1
RO
HO
H
O
Ph
O
O
10
HO
O
1. NaOEt, EtOH, 25 °C
2. CH2=CHCH2Cl, 0 °C
3. KOH, H2O, 0 °C
4. 10% KOH,(CH2)2(OH)2, 135 °C
CO2Et
76
77
1. MeMgBr
2. MgSO4
78
methyl acrylate
AlCl3, 60%
O
O
79
1. LAH
2. MsCl, Et3N
3. NaCN, NaI
4. DIBAL
5. Ph3PCMeCO2Me
79%
CHO
CO2Me
80
1. CH2=C(CH3)MgBr
2. TBDMSCl
3. DIBAL, -78 °C
4. PDC
OTBS
CHO
81
1. CH2=PPH3
2. TBAF, 78%
3. TFAA, DMSO, (iPr)2EtN
O
82
(MeO)3B
70%, (4:1 ratio)
O
H
83

Scheme 13

4.2.1 Holton's Approach

Holton published the first successful and complete synthesis of taxusin.[49] The synthetic strategy required building the AB system through fragmentation followed by later introduction of the C-ring by annulation. (-)-β-Patchoulene oxide (available commercially) was synthesized in two steps from patchouli alcohol and isomerized with $BF_3.OEt_3$ to tertiary alcohol, **84** according to the Buchi procedure. Due to steric bias, epoxidation of **84** with Ti(*i*-PrO)$_4$/*tert*-BuOOH occurs only from the α side to give unstable **85**, which rearranges in refluxing methylene chloride to the AB skeleton, **86**. This was converted to its TMS enol ether followed by reaction with a modified methyl vinyl ketone to form intermediate **88**. Aldol cyclization in the presence of bromomagnesium diisopropylamide formed the expected taxol framework, **89**. Due to the susceptibility of **89** to a retro aldol reaction, it was reduced *in situ* to the more stable compound **90** with Red-Al, Scheme 14.

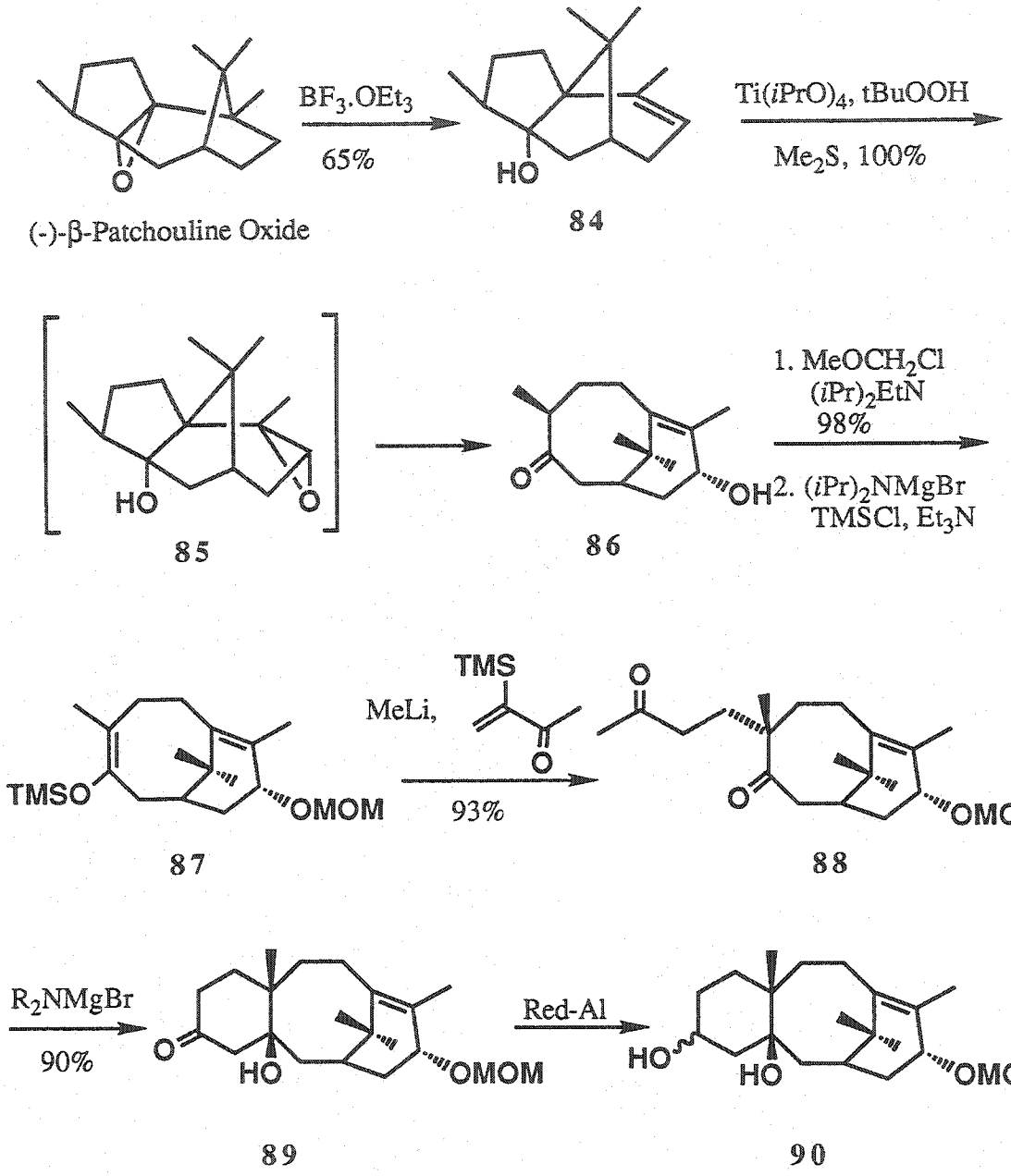
Holton then extended this strategy to the total synthesis of taxusin[49a] which was first published in 1988 as shown in Scheme 15.

4.3 BC to ABC Strategies

Only one complete example of this approach to the taxane skeleton has been published to date. This strategy required building the BC ring followed by later annulation to introduce the A ring.

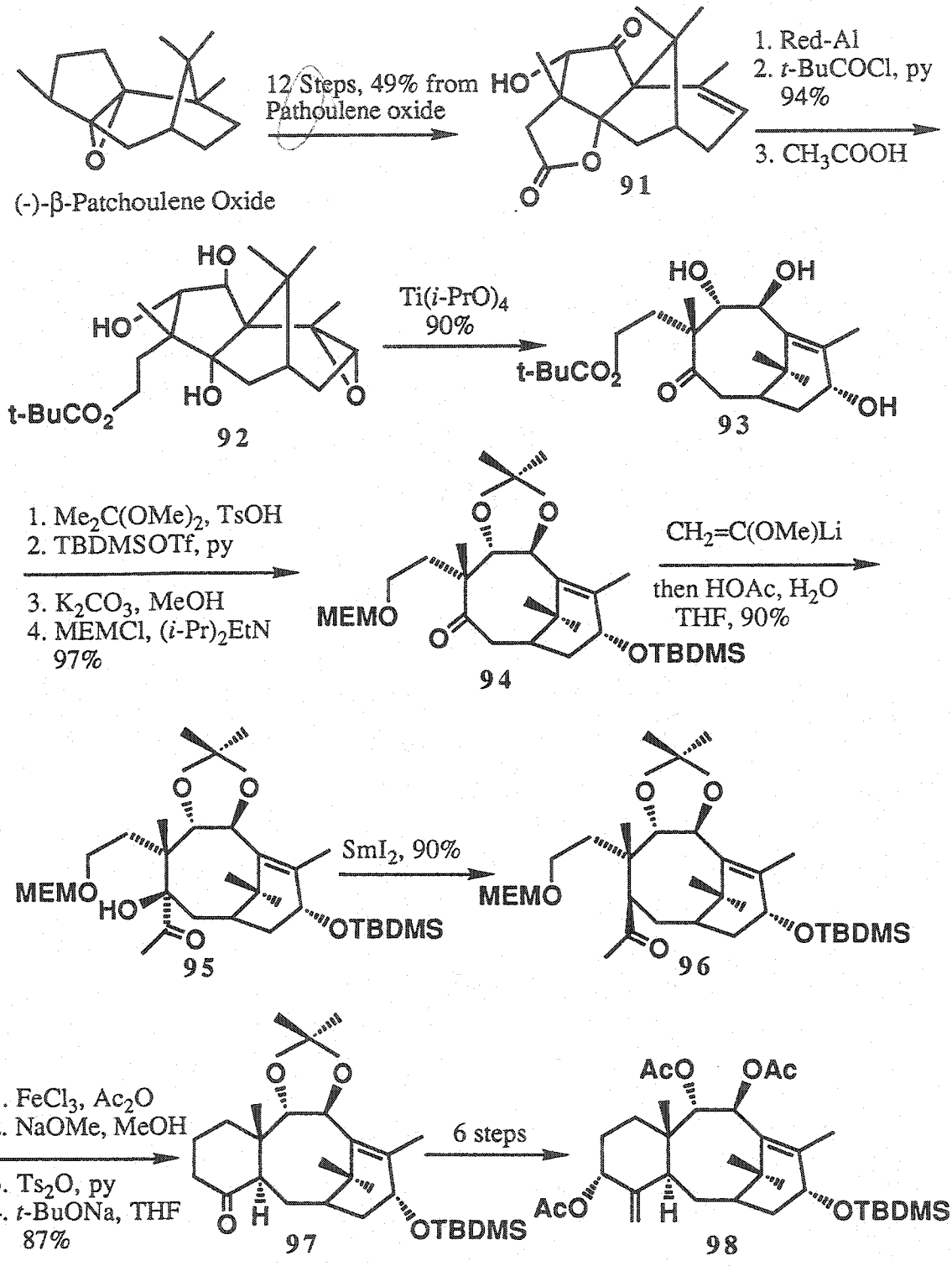
4.3.1 Swindell's Approach

In previous studies carried out during their studies of the taxane skeleton, Swindell and co-workers[50] showed that the natural stereochemistry at C_3 relative to C_1 and C_8 in natural taxol is the

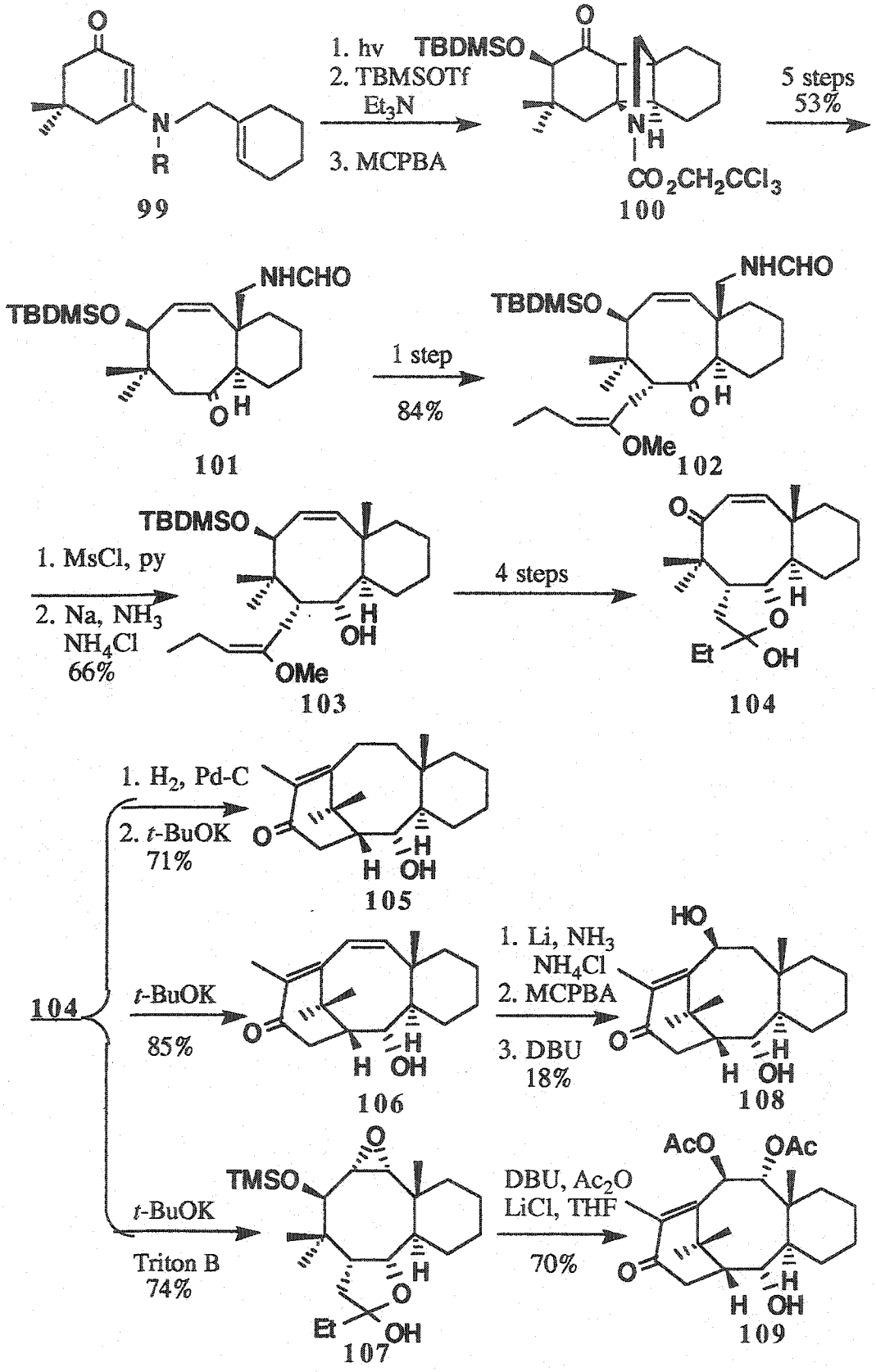


Scheme 14

thermodynamically prefered one. Compound **99** was prepared from dimedone and cyclohexanone cyanohydrin in three steps (87% yield). Photolysis followed by Rubottom oxidation gave the key compound **100** in which the future C_3 and C_8 stereochemistries were preserved. Ketone **100** was subjected to the standard Grob type fragmentation


(-)-β-Patchoulene Oxide
12 Steps, 49% from Patchoulene oxide
91
1. Red-Al
2. t-BuCOCl, py
94%
3. CH3COOH
92
Ti(i-PrO)4
90%
93
1. Me2C(OMe)2, TsOH
2. TBDMSOTf, py
3. K2CO3, MeOH
4. MEMCl, (i-Pr)2EtN
97%
94
CH2=C(OMe)Li
then HOAc, H2O
THF, 90%
SmI2, 90%
95
96
1. FeCl3, Ac2O
2. NaOMe, MeOH
3. Ts2O, py
4. t-BuONa, THF
87%
97
6 steps
98

Scheme 15


1. hv
2. TBMSOTf
Et3N
3. MCPBA
TBDMSO
5 steps
53%
99
100
CO2CH2CCl3
NHCHO
1 step
84%
101
102
OMe
1. MsCl, py
2. Na, NH3
NH4Cl
66%
103
4 steps
104
1. H2, Pd-C
2. t-BuOK
71%
105
t-BuOK
85%
106
1. Li, NH3
NH4Cl
2. MCPBA
3. DBU
18%
108
t-BuOK
Triton B
74%
TMSO
107
DBU, Ac2O
LiCl, THF
70%
AcO
OAc
109

Scheme 16

protocol to give the expected BC ring system, **101** with the correct stereochemistry at the C_3 and C_8 positions. After several steps the pivotal intermediate **104** was obtained in 38% yield from **101**. Epoxidation using *t*-BuOOH/Triton B gave the epoxide **107** which in the presence of DBU/Ac_2O/LiCl/THF formed the highly functionalized system **109**. Synthesis of **109** required 21 steps and gave a 3.2% overall yield.

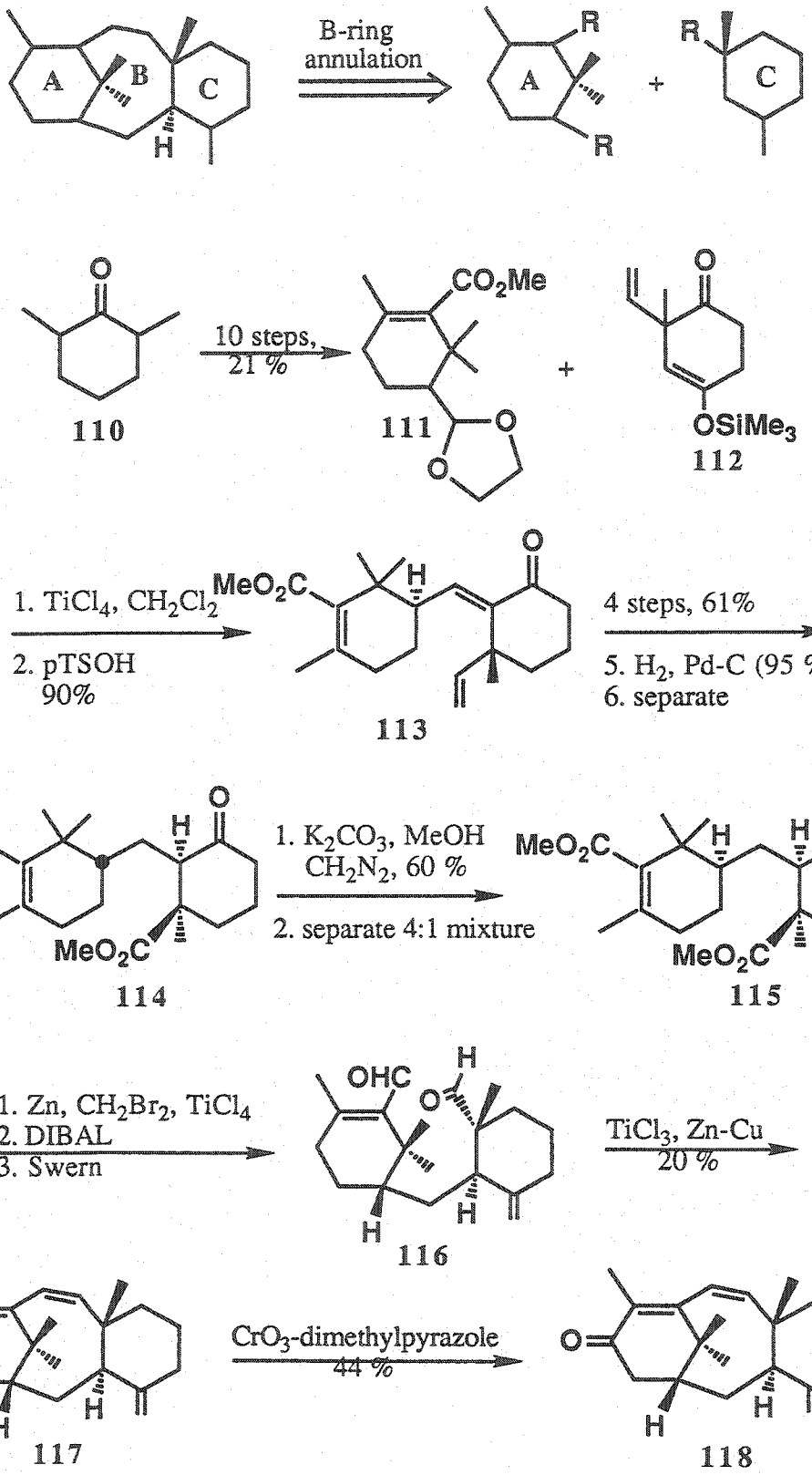
4.4 Convergent Strategies

4.4.1 AC to ABC strategies

The success of these types of approaches have, not surprisingly been quite limited due in part to the difficulties associated with the extra strain introduced by the presence of two 6-membered rings.

4.4.2 Kende's Approach

Kende and co-workers[51] in 1986 first published the most functionalized tricyclic taxane structure prepared to that date, possessing the full and stereochemically correct carbon framework of natural taxusin. In the synthesis, acetal **111**, prepared in 10 steps (21%) as shown in Scheme 17, underwent a directed aldol $TiCl_4$-mediated coupling with enol silane **112**. After acid hydrolysis this gave **113** in 90% yield as two Z diastereomers and two E diastereomers in a 2:1 (Z:E) ratio respectively. Oxidative vinyl cleavage in three steps followed by several modifications gave a mixture of compounds one of which, **114** possessed the correct stereochemistry and was converted through further reactions to the key dialdehyde **116**, a rather unstable compound. McMurry


A
B
C
H
B-ring
annulation
R
R
A
+
R
C
O
10 steps,
21 %
110
CO2Me
111
O
O
+
O
OSiMe3
112
1. TiCl4, CH2Cl2
2. pTSOH
90%
MeO2C
H
O
113
4 steps, 61%
5. H2, Pd-C (95 %)
6. separate
MeO2C
H
O
MeO2C
114
1. K2CO3, MeOH
CH2N2, 60 %
2. separate 4:1 mixture
MeO2C
H
H
O
MeO2C
115
1. Zn, CH2Br2, TiCl4
2. DIBAL
3. Swern
OHC
O
H
H
H
116
TiCl3, Zn-Cu
20 %
H
H
117
CrO3-dimethylpyrazole
44 %
O
H
H
118

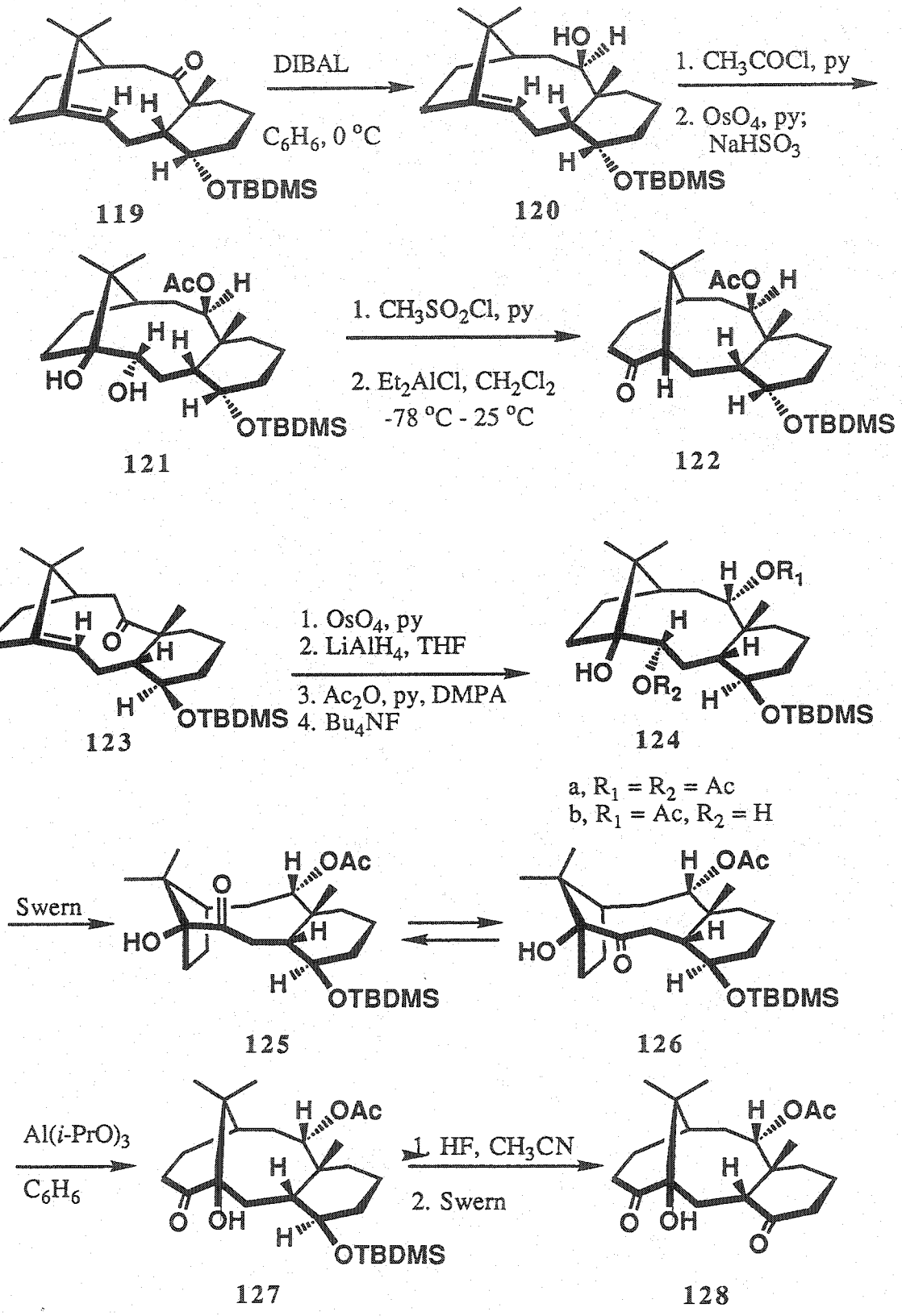
Scheme 17

dialdehyde coupling reaction with $TiCl_3$/Zn-Cu gave 20% of the desired tricyclic compound as the minor product. Allylic oxidation with CrO_3/dimethylpyrazole gave **118** in 40% yield. Overall yield for **118** was 0.1% in 24 steps.

4.4.3 A[B]C to ABC Strategies

4.4.4 Paquette's Approach

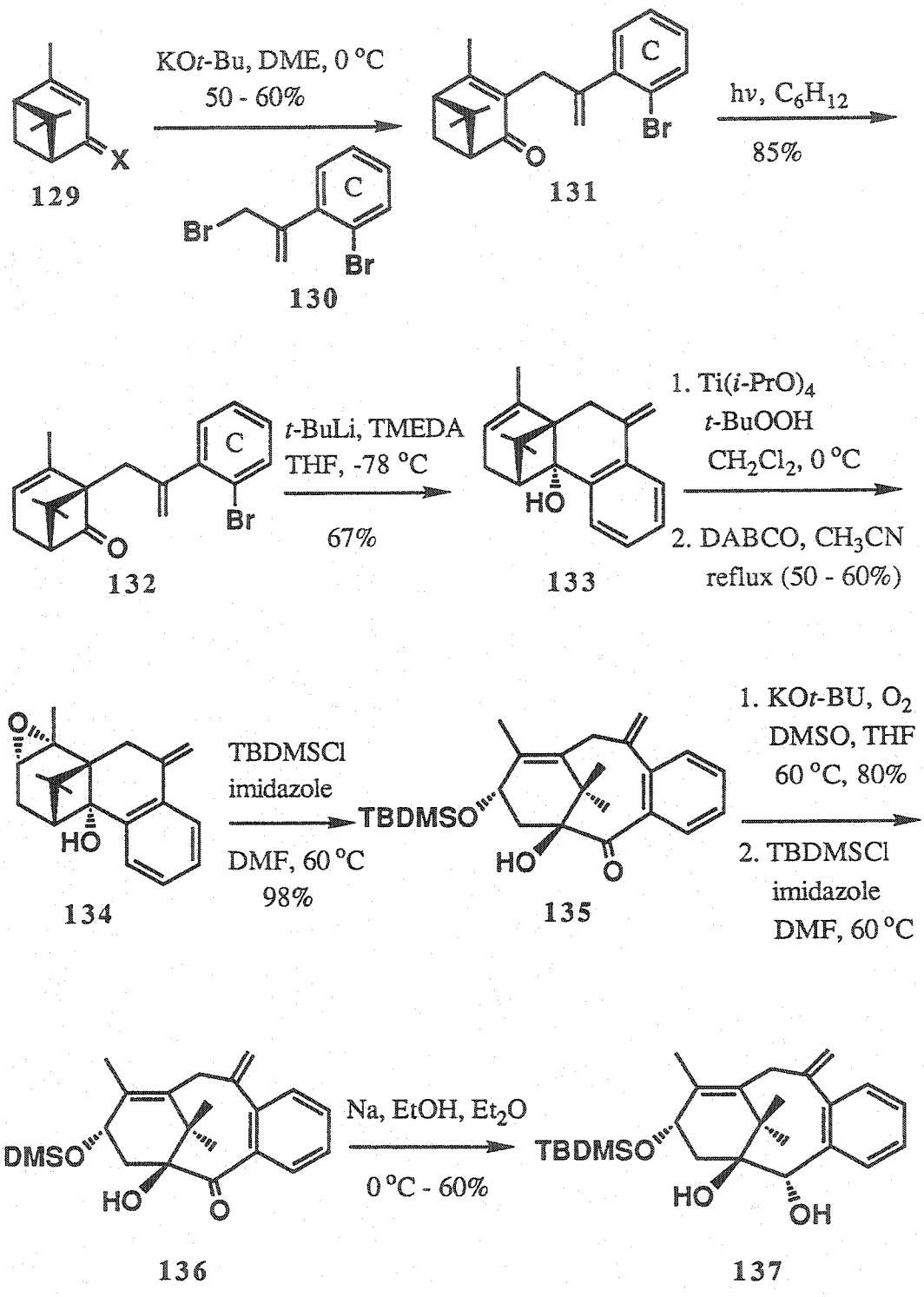
Much of Paquette's work has involved the oxy-Cope rearrangement and this is adapted to his approach to the taxane skeleton in which he solves the problem of setting the proper C_1 oxidation level on demand.[52] Thus compound **119** prepared in two steps from D-2-oxo-7,7-dimethyl-1,1-vinylbicyclo[2.2.1]heptane is converted to the key compound **121** in three steps. Diol **121** undergoes the key Wagner-Meerwein rearrangement in Et_2AlCl/CH_2Cl_2 at -78 °C to 25 °C to provide compound **122** with the correct taxane skeleton but no hydroxyl group at the 1-position. Starting from compound **123** (isomer of **119**) they showed that due to the "carbonyl down" bias exerted by the β-OTBDMS at C_5 as in **123**, generation of unsaturated carbinol is disallowed by direct 1,2-hydride addition. Thus **123** was converted in a series of steps to **126** which in refluxing $Al(i\text{-}PrO)_3/C_6H_6$ induced isomerization to the desired compound **127** in 90% yield. This compound was converted to the crystalline diketone, **128** for X-ray structure determination.


DIBAL
C_6H_6, 0 °C
1. CH_3COCl, py
2. OsO_4, py; $NaHSO_3$
1. CH_3SO_2Cl, py
2. Et_2AlCl, CH_2Cl_2
-78 °C - 25 °C
1. OsO_4, py
2. $LiAlH_4$, THF
3. Ac_2O, py, DMPA
4. Bu_4NF
a, $R_1 = R_2 = Ac$
b, $R_1 = Ac$, $R_2 = H$
Swern
$Al(i\text{-}PrO)_3$
C_6H_6
1. HF, CH_3CN
2. Swern
119
120
121
122
123
124
125
126
127
128

Scheme 18

4.4.5 Wender's Approach

Previously Wender's group prepared an unfunctionalized AB skeletal ring system by a unique nickel catalyzed 4+4 cycloaddition.[53a-53c] Their current aim is to produce a practical synthesis of taxol that could also be used to make analogues.[53d] They started with pinene, a cheap naturally available compound found in pine trees and a major component of industrial solvents such as turpentine. Pinene posses 10 of the 20 carbons of the taxol core and is available in either enantiomeric form. The first step of this synthesis is the addition of **130** to verbenone, **129** (the readily available air oxidation product of pinene) in the presence of potassium *tert*-butoxide in DME to form **131**. A photo induced 1,3 shift formed **132**. Treatment of **132** with *t*-BuLi led to the formation of the tetracyclic alcohol **133** which interestingly undergoes both stereo- and regiocontrolled epoxidation to form the labile key intermediate **134**. Grob fragmentation *in situ* in the presence of DABCO formed the 6-8-6 taxol framework **135**, with concomitant formation of the bridgehead double bond. The bridgehead hydroxyl group at C_1 was introduced in 80% yield when the *tert*-butyldimethylsilyl ether **135b** was treated with potassium *tert*-butoxide in THF at 60 °C in the presence of DMSO and oxygen gas for 30 minutes. Finally, thermodynamically controlled reduction of **136** in Na/Et_2O gave the diol **137** in 60% yield. Compound **137** contains one of the most functionalized taxol frameworks published to date and was prepared in 9 steps and 6.7% yield from verbenone.


KO*t*-Bu, DME, 0 °C
50 - 60%
129
130
131
hν, C_6H_{12}
85%
t-BuLi, TMEDA
THF, -78 °C
67%
132
133
1. Ti(*i*-PrO)$_4$
t-BuOOH
CH_2Cl_2, 0 °C
2. DABCO, CH_3CN
reflux (50 - 60%)
TBDMSCl
imidazole
DMF, 60 °C
98%
134
135
1. KO*t*-BU, O_2
DMSO, THF
60 °C, 80%
2. TBDMSCl
imidazole
DMF, 60 °C
Na, EtOH, Et_2O
0 °C - 60%
136
137

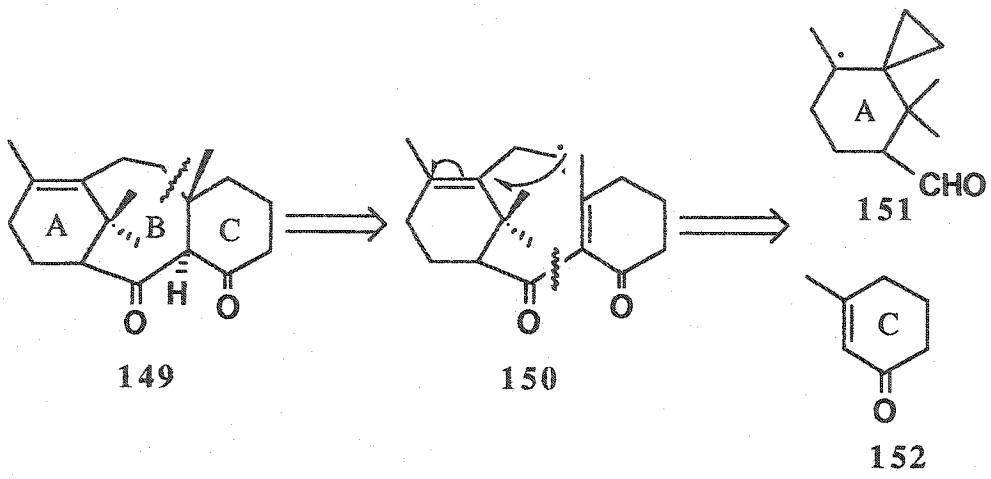
Scheme 19

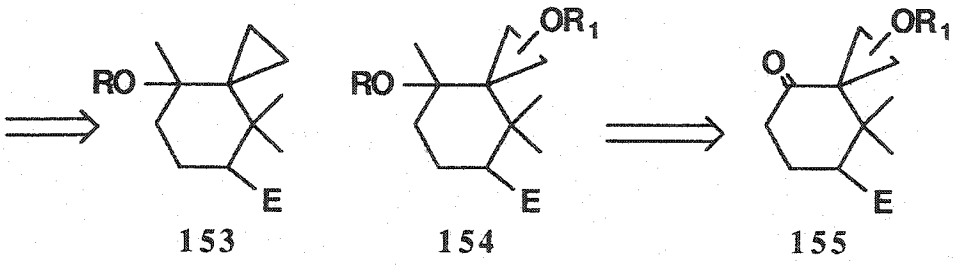
II. OUR PLAN

We mentally disconnected the molecule as shown in Scheme 20. Thus a convergent approach to the taxane skeleton was envisaged with the final B-ring closure taking place by intramolecular 8-endo radical cyclization (*vide infra*). Research in our group involves extensive use and development of radical chemistry and methodology for the synthesis of natural products. Thus we have examined free radical bond rupture to reveal latent functionality as part of a sesquiterpene synthesis and free radical induced cyclization of sulfur acetals.[54] Our interest in the use of cyclopropanes have been demonstrated in previous publications.[55]

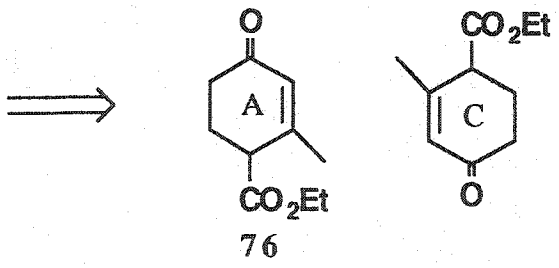
The unique characteristic of the 3-membered ring and the similarity of its chemistry to that of the olefinic double bond makes the use of cyclopropanes in organic synthesis particularly valuable. Thus cyclopropanes and their derivatives have been utilized in every synthetic sense. Their applications in the preparation of organic compounds are extensive[56] and their preparation has been reviewed several times.[57]

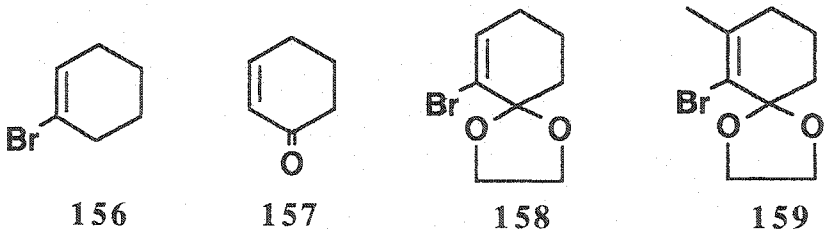
As dicussed above it is known from physical organic chemistry that rapid ring opening occurs when a radical center is generated adjacent to cyclopropane and cyclobutane rings leading to a new radical center. The rate constant for the cyclopropyl carbinyl system are known over a range of temperatures[58,59] and more importantly kinetic data are available for cyclopropyl carbinyl skeletons with





E = CH_3CH_2OCO-
R = radical precursor

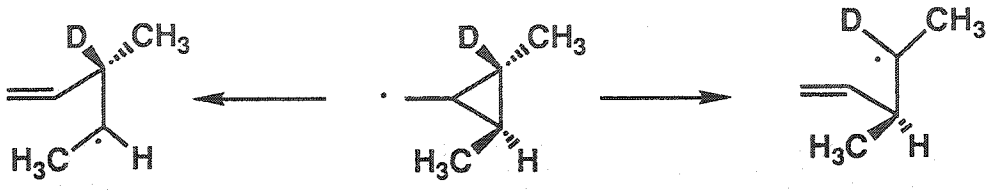




Scheme 20

substituents such as methyl, phenyl, and ethoxy carbonyl groups attached.[60]

Ring opening of **138** occurs by one of two possible routes leading to α- and β- deuterated butenyl radicals **139a** and **139b**. Work done by Mariano[61] and later Ratier *et al*[62] has shown the alkyl substituted effect on radical stability. Thus σ-bond-dissociation energies are not the controlling feature determining the direction of opening of unsymmetrically substituted cyclopropyl carbinyl radicals when there is no steroeoelectronic effect.

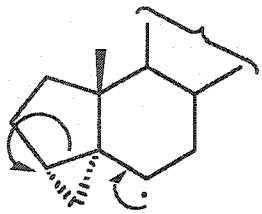


139a **138** **139b**

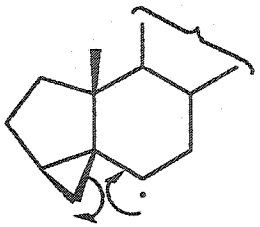
Instead a qualitative interpretation may be provided by the frontier molecular orbital theory. Thus for **140** to **141**, there is preferential interaction between the SUMO and the LUMO of the C_1 and C_3 bonds because the energy of the orbital of the C_1-C_2 bond is raised by the attached electron donating methyl group. According to Mariano, steric effects on the ring (*e.g.*, when the ring substituents are cis) can determined the reaction outcome, and reaction occurs via that conformation in which non bonded interactions are minimized.

140 **141**

Independent evidence from Dauben[63] and Davies *et al*[64] has shown that stereoelectronic factors were important in situations where the cyclopropane is fused to another cyclic structure because the cyclopropyl bond that overlaps effectively with the adjacent singly occupied orbital is the one that breaks. This is illustrated by the steroidal systems **142** and **143**.[65]



142

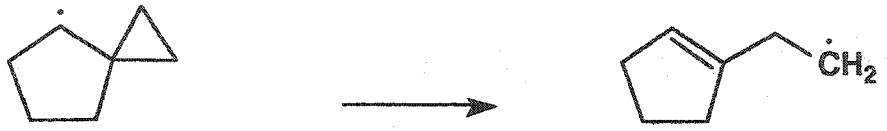


143

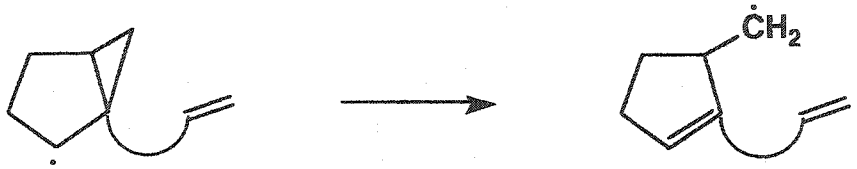
When the cyclopropyl carbinyl is part of a polycyclic system, the resulting rearrangement will provide a powerful method for the introduction of a reactive center at a remote site. The new radical may react further or be quenched to introduce new functionality (eg nitrile, sulfide) as illustrated for a simple spiro and fused cyclopentane-cyclopropane ring systems **144** and **145**.

The opening of cyclopropyl carbinyl radicals where the radical centre is itself part of a ring had received very little use in synthesis[66] when our work began in early 1988. There was no reported attempt to generalize and evaluate the synthetic potential offered by such reactions although radical opening of epoxides and azidirines had been studied quite extensively. However in 1991 Clive[32b] published what he called the first attempt at evaluation and generalization of the synthetic potential of these types of reactions (Scheme 21). He showed that radical ring opening of cyclopropyl

carbinyl proceeded efficiently in benzene under reflux when the non bridgehead carbon of the cyclopropane carries a strongly electron withdrawing substituent. Ring expansion interferes in the absence of such substituents unless the reaction is carried out at lower temperatures.



144



145

The advantages perceived in our approach were:

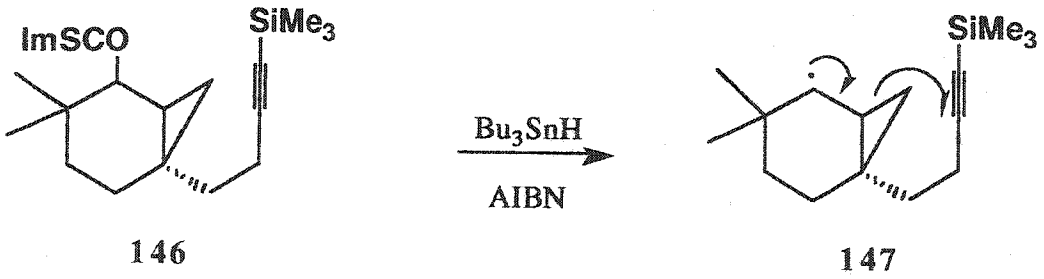
a) The unique possibility of introducing the potentially troublesome bridgehead double bond with concomitant ring closure to form the B ring in one step.

b) It opens new avenues for the synthesis of highly functionalized macrocyclic systems via radical reactions. This is important because reported examples of radical initiated macrocyclization only involved synthesis of rather simple 12- to 18-membered rings such as 31 and 33. Synthesis of 8-membered rings are especially challenging regardless of the the synthetic method

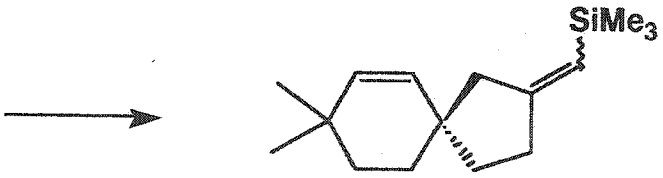
used. The importance of a simple and mild direct approach via radical chemistry cannot therefore be underestimated.

c) An extension of the understanding of the chemistry of radical reactions which has been restricted to the 5-hexenyl and more recently to the 5-heptenyl radicals could be realized in the course of this study.

d) Finally it offered the opportunity for evaluation and understanding spiro fused cyclopropyl-carbinyl-cyclohexane ring cleavage and its application to the synthesis of natural products.



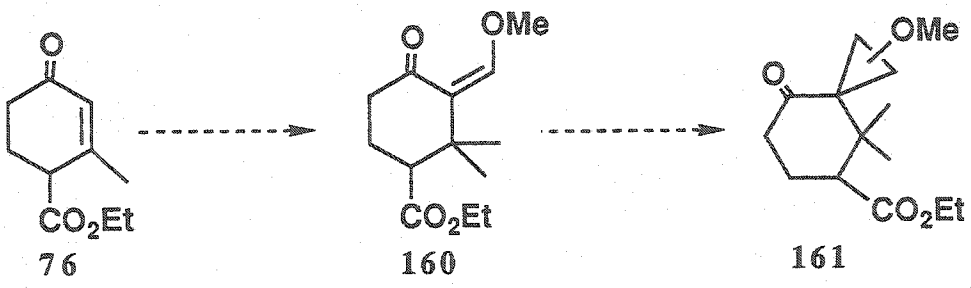
146 147



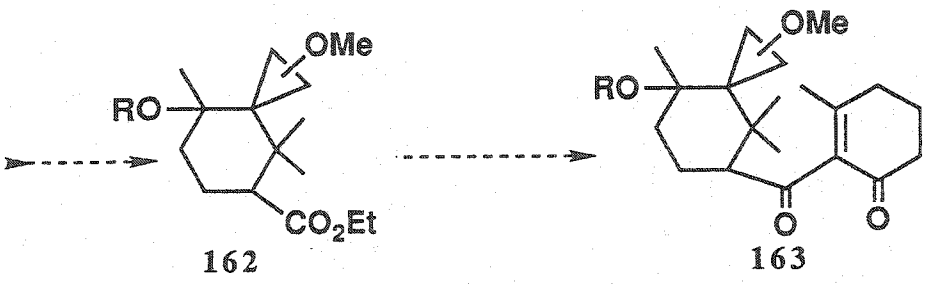
148

Scheme 21

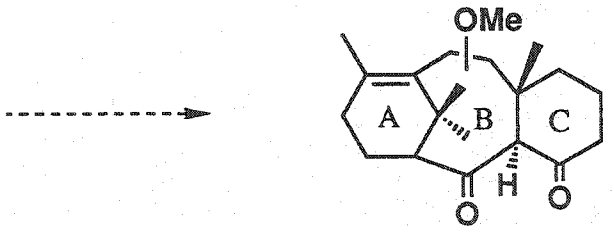
Initial examination of a model to check the practicality of this approach was to involve a conjugate addition of dimethylcuprate to Hagemann's ester and trapping of the enolate generated with ethyl formate followed by further modification to afford **161** (Scheme 22).



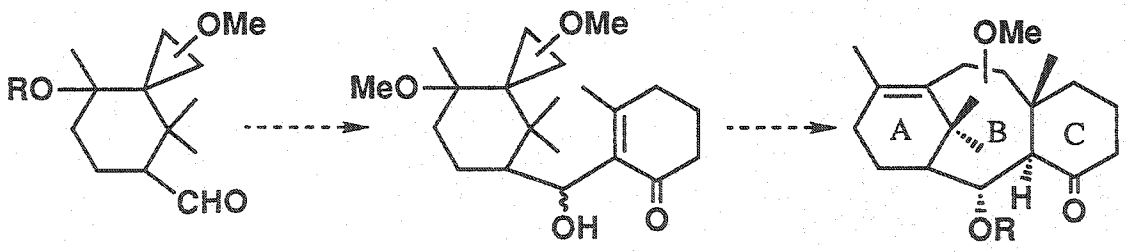
76 160 161



162 163



164



165 166 167

Scheme 22

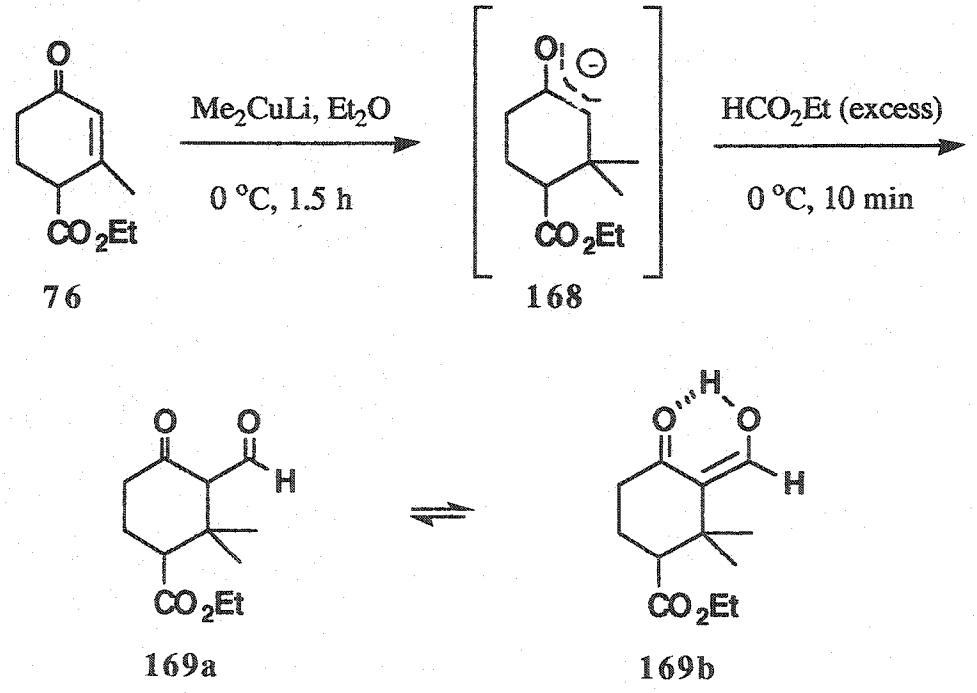
Simmons-Smith cyclopropanation followed by low temperature selective addition of methyl lithium and trapping of the resulting alkoxide with a radical precursor should lead to the A ring **162**. Condensation of the ester unit with cyclohexanone[67] should afford the unsaturated diketone **163**. Generation of the requisite tertiary radical using the method of Barton and Crich[68] is expected to provide the desired taxane nucleus **164** in a very direct manner with the correct taxane ring fusion. In a parallel series of experiments the vinyl anions related to **156**, **158**, and **159** (Scheme 20) could be added to the aldehyde **165** to examine the cyclization to **167**. Based on results obtained in our laboratory[54] the trans geometry was expected to predominate.

It is interesting to note that based on the proposed disconnection strategy, it is possible to use the same starting material, Hagemann's ester (**76**) for the construction of both the A and C rings. In the case of the C ring, the ester at the 4-position (Hagemann's ester) would eventually become the handle for the introduction of the hydroxyl group at the C_7 position of taxol.

III. DISCUSSION

6.1 Attempted cyclopropanation of alkyl enol ether

In order to develop the strategy outlined above the synthesis of ethyl 2,2-dimethyl-3-formal-4-oxocyclohexanecarboxylate, (**169**) from Hagemann's ester was examined. A direct one step synthesis of the cyclopropane precursor did not seem possible but an indirect approach via conjugate addition should be feasible. Thus addition of dimethylcopper lithium to **76** at 0 °C generated the enolate intermediate **168** which was trapped with purified ethyl formate to form an isomeric mixture of **169a** and **169b**.[69,70,71] The yield for this reaction was rather erratic, ranging from 25 to 55% but averaging 35%.



76 **168**

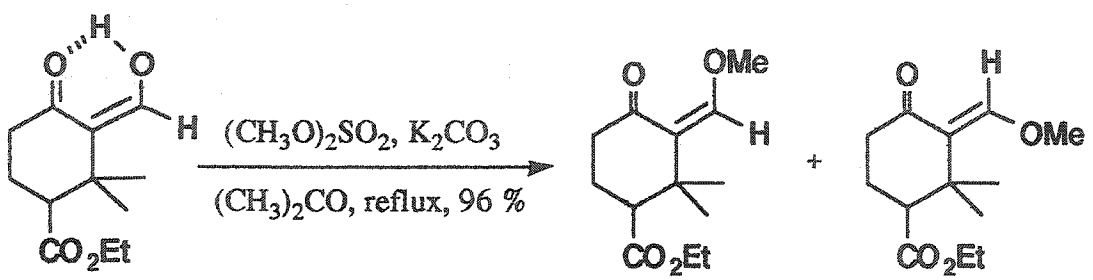
169a **169b**

Equation 1

These low yields were probably due to the extraction procedure which involved conversion of the crude β-keto-aldehyde to its sodium salt by extraction of the ether solution with aqueous 10% sodium hydroxide solution followed by regeneration of the keto-aldehyde by acidification with cold aqueous 50% HCl solution. Extraction of the acidified fraction gave the product. This type of extraction procedure is most useful when the compound to be extracted is moderately acidic. However **169a** and or its isomer required several extractions with aqueous 10% NaOH solution to convert **169** to its water soluble sodium salt. Yields of only 45% were also obtained in the literature examples. The crude product obtained after isolation was however quite pure and GCMS analysis indicated only one product. This material was therefore used without further purification.

Attempts to purify **169** were unsuccessful since it is extremely labile. Compound **169** was identified by its 60 MHz ^{1}H NMR spectrum which showed a characteristic singlet at δ 8.67 ppm that is assigned to the vinyl proton in **169b**. A feature also present in the 200 MHz ^{1}H NMR spectrum of a similar compound (*vide supra*). A six proton singlet at 1 ppm was assigned to the gem dimethyl at the C_3 position. The low resolution mass spectrum showed the molecular ion signal at *m/z* 226 with characteristic peaks at 211 and 183. The base peak (211) is due the loss of a methyl group and 183 corresponds to the loss of 43 mass units, a methyl group and a carbonyl functionality. The chemical composition of **169** was established by high resolution mass spectroscopy which showed that **169** had a molecular formula of $C_{12}H_{18}O_4$.

6.1.2 Preparation of the methyl enol ether



169 **170a** **170b**

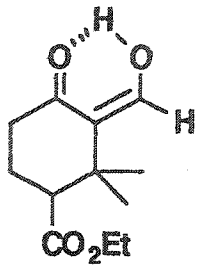
10 : 1

Equation 2

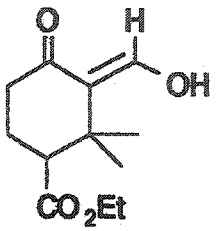
Methylation of **169** occur smoothly in refluxing acetone containing 1.1 equivalents of dimethyl sulfate and anhydrous potassium carbonate (Equation 2).[72,73,74] It was essential to use anhydrous acetone of high quality to obtain good yields. The reaction was quite clean, giving one spot on TLC. All attempts to purify the product by flash chromatography caused extensive decomposition so **170** was used without further purification. GCMS analysis of the crude material indicated 94% desired product and 6% **169**. The enol ether was composed of two isomers in a 10:1 ratio. Based on the stereochemistry of **169** it was predicted that H-bonding stabilization of **169b** should make it the dominate isomer and the Z-enone **170a**, would be the major compound in this methylation reaction. The outcome of this step could also depend on the rates of formation of 170a and the alternative E-enone (Curtin-Hermmett principle)

The 60 MHz NMR spectrum of **170** indicated a characteristic signal at 3.9 ppm due to the newly introduced methoxy group and a one-proton multiplet for the vinyl proton. This multiplet may be due

to the presence of an E/Z mixture since the pure compound should show a singlet for the vinyl proton.



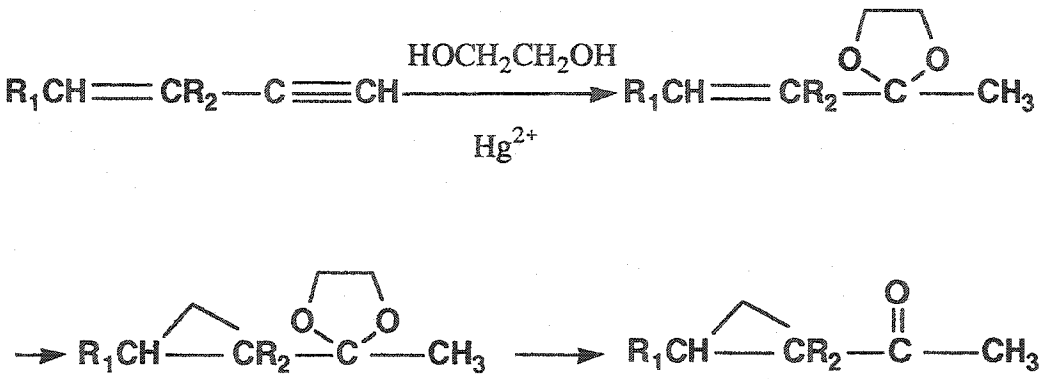
169b, Z



169c, E

All attempts to prepare the key cyclopropyl intermediate **161** via the Simmons-Smith reaction[57a] and its several modifications[75] including use of diethylzinc in both the presence and absence of oxygen[76] and trialkylaluminum-alkylidene iodide failed. Close examination of available literature indicated that although α,β-unsaturated ketones undergo the Simmons-Smith reaction to form cyclopropyl ketones,[77] these reactions are very dependent on the structure of the initial ketone.[77a,78] It has been suggested that the preferable method for the cyclopropanation of α,β-unsaturated ketones is to carry out the methylene transfer reaction on the corresponding ethylene ketal, followed by hydrolysis. This procedure has been utilized by Monti[79] for the conversion of several vinyl acetylenes to their cyclopropyl ketones (Scheme 23).

Most ethylene glycol ketalizations require an acid catalyst, thus ketalization of **170** is not feasible since the presence of catalytic amounts of acid quickly convert it to **169**.

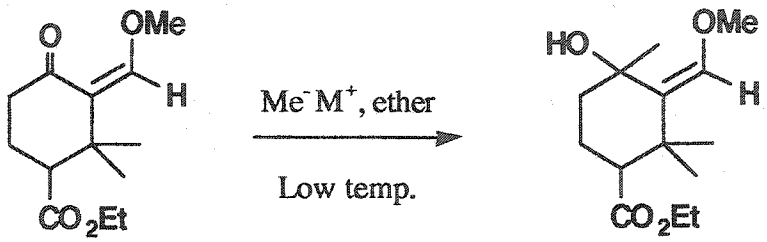


Scheme 23

The use of dimethyloxosulfonium methylide for the cyclopropanation of enones was a method developed by Corey and Chaykovsky.[80] It was later modified especially for Michael acceptors with electron donating substituents at the Michael receptor site[81] but failed to give the desired product when attempted on **170**. A later attempt at this reaction on a similar compound, **260** (*vide infra*) gave a low yield of the expected product which decomposes after a few days even when kept in the fridge (5 ^{o}C). It is probable that the expected compound **161** formed followed quickly by rearrangement, since α-cyclopropyl ketones substituted on the cyclopropyl ring by electron donating groups are known to undergo various rearrangements depending on the structure of the molecule.[32c]

The synthetic plan required the conversion of **161** to **162**. An alternative solution to the problem of cyclopropanation of **170** would be to convert the ketone function to a tertiary alcohol followed by the introduction of the cyclopropyl ring. This modification should afford an additional benefit since coordination of iodomethylzinc iodide to hydroxyl groups is known to facilitate and direct the methylene transfer reaction stereoselectively.[57a] Thus the low

temperature reaction with organometallic compounds (Equation 3) was attempted in order to generate the tertiary alcohol, **171** from **170.** Unfortunately no effective procedure was found in spite of numerous reactions examined under various temperature and solvent conditions.



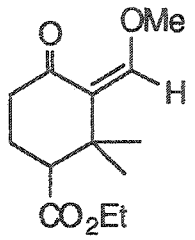
170 **171**

Equation 3

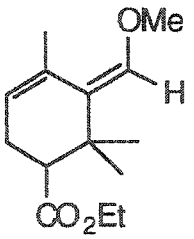
Table 1 gives a very brief summary of some of these reactions.

Table 1: Addition of Me^-M^+ to **170** under various conditions

Reaction Condition	% Yield **170**	**171b**	**172**	**173**
MeLi, toluene -78 °C, 10 min	1.9	10	27	57
MeLi (1.1 eq), ether -78 °C, 10 min.	87			13
MeLi $CeCl_3$, THF -78 °C, 4 h, 22 °C	9	10	66.8	14
MeMgCl (2 eq) ether, 0.5 h, 22 °C	40.7	5.4	39.6	7.6

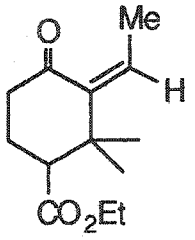


170

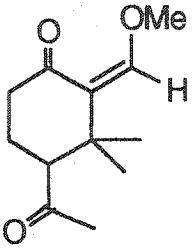


171b

m/z 240 210



172

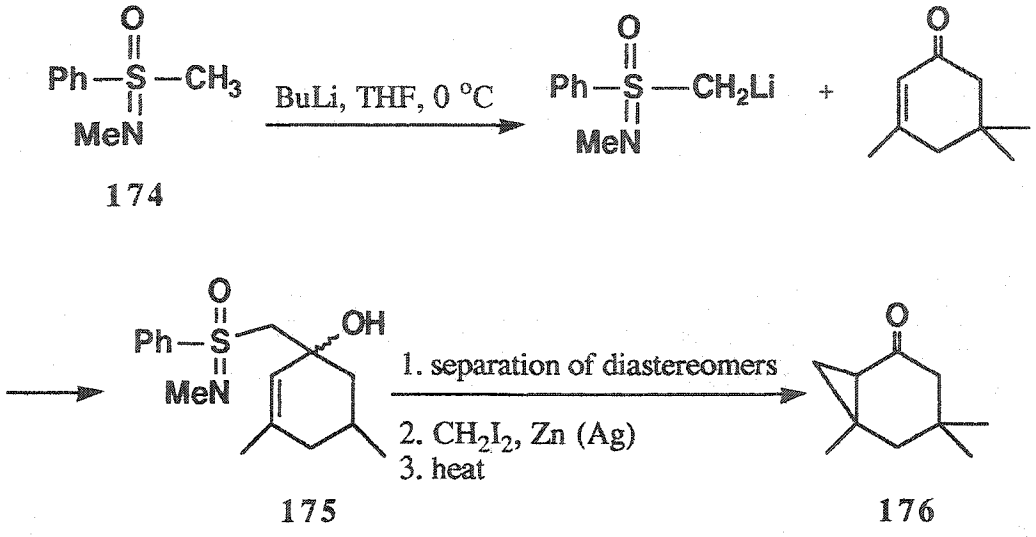


173

m/z 224 238

Scheme 24

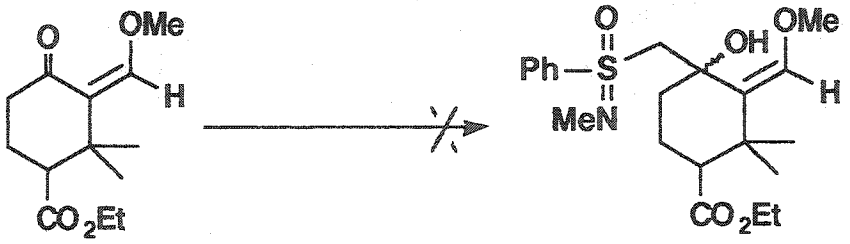
The structures of compounds **171**, **172** and **173** (Scheme 24) were not fully characterised but identified mainly from the ^1H NMR spectrum and GCMS analysis of the reaction products. It is obvious that this approach would not be feasible due to the rather low yield of the expected product. However work by Johnson and co-workers[82] had shown interesting synthetic applications of sulfoximines that seemed applicable to this situation. For example, some of Johnson's compounds such as **178** (Scheme 25) prepared from the enone via the sulfoximine procedure) were similar to **161** due to its spiro cyclopropyl-cyclohexanone skeleton. Attempted conversion of **171** to **179** via Johnson's procedure was unfortunately unsuccessful (Equation 4).



174 175 176

177 178

Scheme 25



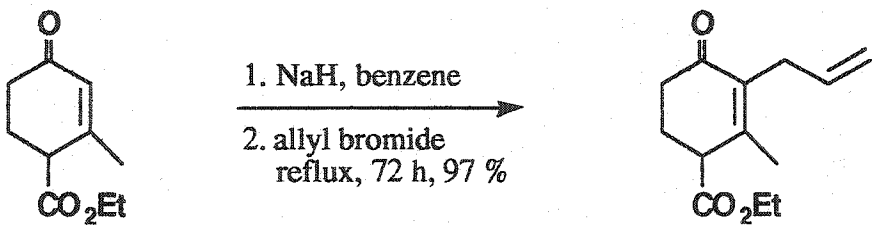
171 179

Equation 4

6.2 Base induced cyclopropanation of γ,δ-epoxyketone

6.2.1 Preparation of ethyl 2-methyl-3-(2-propenyl)-4-oxo- cyclohex-2-enecarboxylate (180)

A mixture of Hagemann's ester, NaH and allyl bromide in refluxing benzene gave **180** in 95% yield after three days following Marshall's procedure[83] (Equation 5).



76 **180**

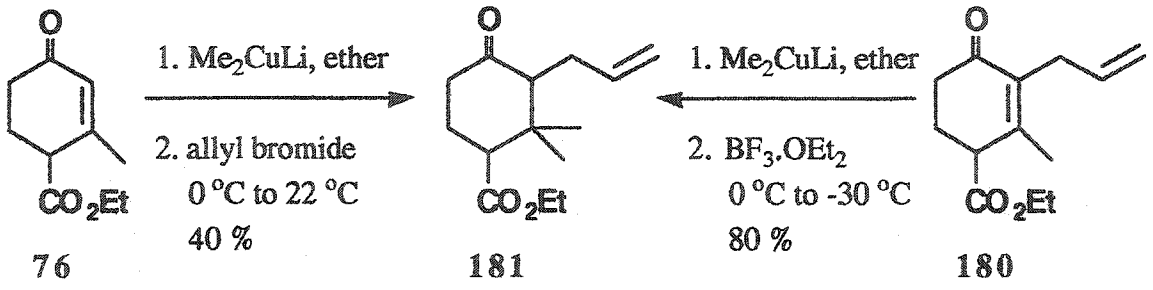
Equation 5

Alkyl iodides generally give better yields of 'C' alkylation products in enolate alkylation reactions because both I^- and the carbon centre of the enolate are soft bases. The overall yield of the reaction decreased however when allyl iodide was used instead of allyl bromide. This may be due to extensive decomposition of the allyl iodide under the reaction conditions.

6.2.2 Preparation of ethyl 2,2-dimethyl-3-(2-propenyl)-4- oxocyclohexanecarboxylate (181)

Cyclohexanone **181** was made either by dimethylcuprate addition to Hagemann's ester followed by enolate trapping with allyl bromide or allyl iodide, or via **180** (Equation 6). Trapping of the

enolate obtained after addition of dimethylcuprate to Hagemann's ester with allyl bromide gave after workup and chromatography a maximum of 40% yield of **181**.



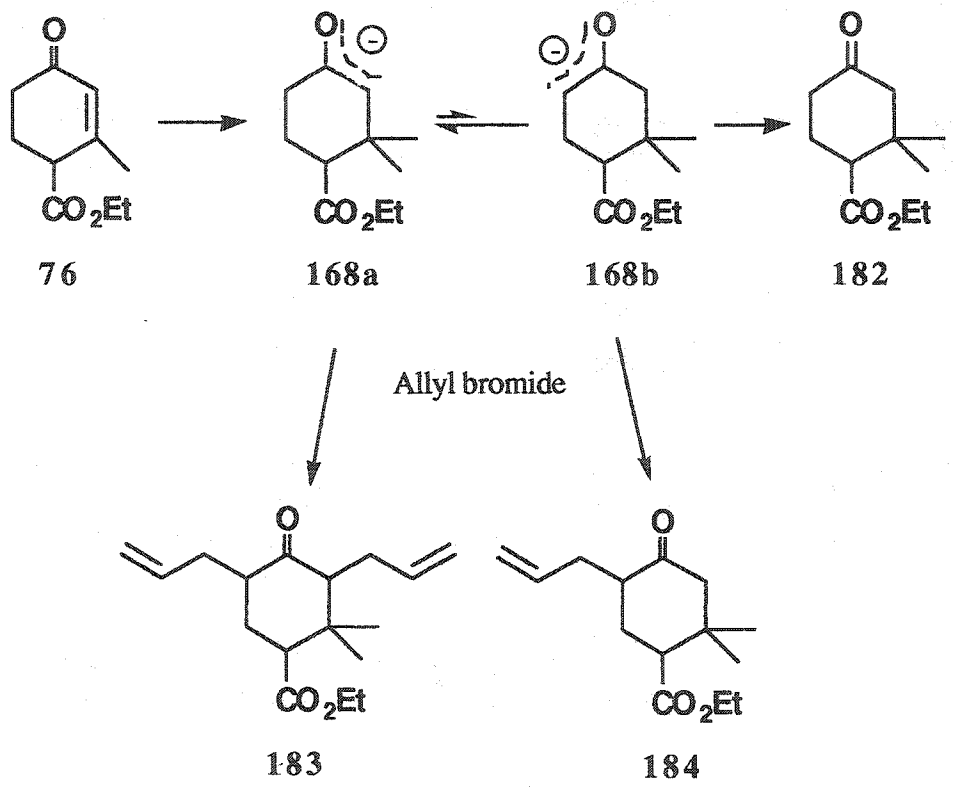
76 **181** **180**

Equation 6

Conjugate addition of the methyl group to **76** was very efficient since the enone was never isolated from the reaction. In contrast enolate trapping was inefficient and a large amount of the unreacted ketone, **182** (up to 50%) was always isolated. The other side products arose from dialkylation to form **183** which was isolated in about 15% yield and sometimes **184** in minor quantities. Compound **183** is formed via an undesired α-proton exchange between the enolate and **181** followed by alkylation while **184** arose from α'-substitution by allyl bromide on the enolate **168b**, itself formed from enolate equilibration (Equation 7).

Efforts were made to improve this reaction and reduce the byproducts. Studies on cuprate enolate alkylation have revealed that variation of reaction time, solvent, cosolvent and especially temperature can have a profound influence on the nature of a product.[71c] For the cyclopentanone system Posner concluded that longer reaction times led to larger amounts of polyalkylation

products while lower temperatures (either with or without cosolvent) generated significant amounts of allylically rearranged cyclopentanones. However variation of temperature, solvent, cosolvent and reaction time in various combinations did not lead to any dramatic improvement in the yield of **181**.

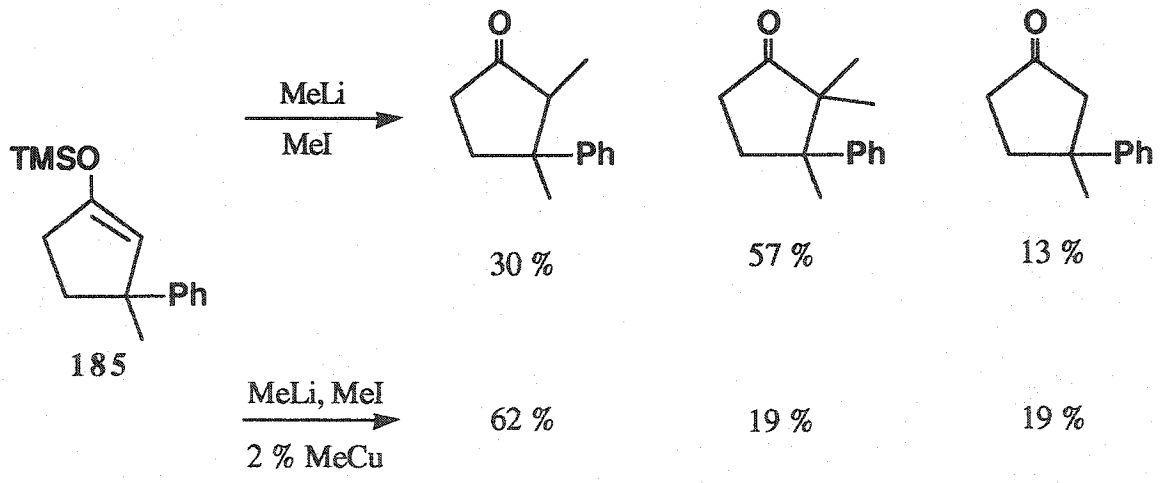


Equation 7

Noyori and co-workers[84] also reported that addition of both HMPA and diethylzinc promotes a smooth and selective monoalkylation. This approach was successfully applied to the synthesis of prostaglandins where polyalkylation products dropped from 15% to 0.5% after the addition of 3 equivalents HMPA and 0.2 equivalents of diethylzinc. No mechanistic study was done to provide

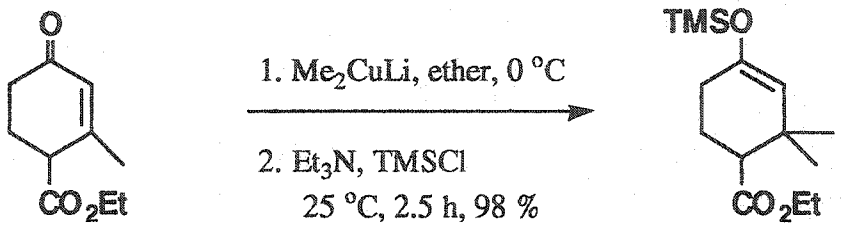
an insight into why polyalkylation was suppressed and the role of dialkylzinc is not fully understood. This procedure also did not lead to improved yields of **181** when applied to the transformation of **76** to **181**.

It has been shown by Posner[71d] that the course of enolate reaction of electrophiles with allyl bromide or methyl iodide was distinctively and reproducibly different in the absence or presence of copper(I). Thus small amounts of Cu(I) (*e.g.*, 0.2 % CuCN) caused a dramatic decrease in the amount of dimethylated product from 57% to 19% when **185** was methylated in the absence and presence of Cu(I) respectively (Scheme 26). The TMS-enol ether, **186** was synthesized from Hagemann's ester (Equation 8) in an effort to improve the overall yield of the desired material.



Scheme 26

6.2.3 Preparation of ethyl 2,2-dimethyl-4-trimethylsiloxycyclohex-3-enecarboxylate (186)



76 186

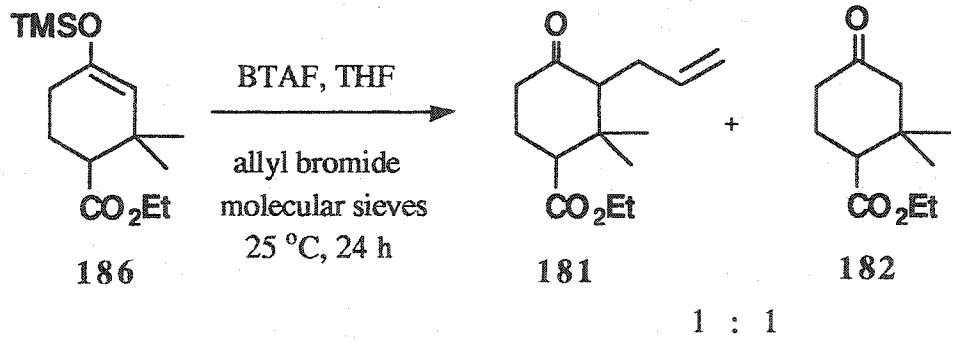
Equation 8

Dimethylcuprate addition to **76** followed after 1.5 h by addition of freshly distilled triethylamine and chlorotrimethylsilane gave 96% isolated yield of **186**. Both the ^{1}H and ^{13}C NMR spectral data were consistent with the assignment of the structure of **186**. Thus the ^{1}H NMR spectrum showed the characteristic nine proton TMS- singlet at 0.14 ppm and the singlet due to the vinyl proton at 4.6 ppm. The possibility of an indirect preparation of **181** via the enol ether **186** was attractive because of its ease of preparation, isolation, high yield and availability of simple methods of cleavage of TMS-enol ethers to provide high yields of monoalkylation products.[70,71d]

Also Kuwajima[85] had shown that treatment of enol silyl ethers with alkyl halides in the presence of benzyltrimethylammonium fluoride (BTAF) and molecular sieves in DMF or THF at room temperature gave very high yields of the corresponding

monoalkylated products with high regioselectivity and with little or no polyalkylated products.

In spite of careful preparation of the highly hygroscopic BTAF, analysis of the reaction product indicated that although cleavage of the enol silyl ether was very effective, a 1:1 ratio of **181** and **182** were obtained and no polyalkyation products were observed (Equation 9). Sadly less than 50% yield of **181** in two steps is not much better than 40% in one step from **76**. The conventional solution to the above problem requiring the introduction of blocking and activating groups[86] was not applicable to this particular problem.



186 **181** **182**

1 : 1

Equation 9

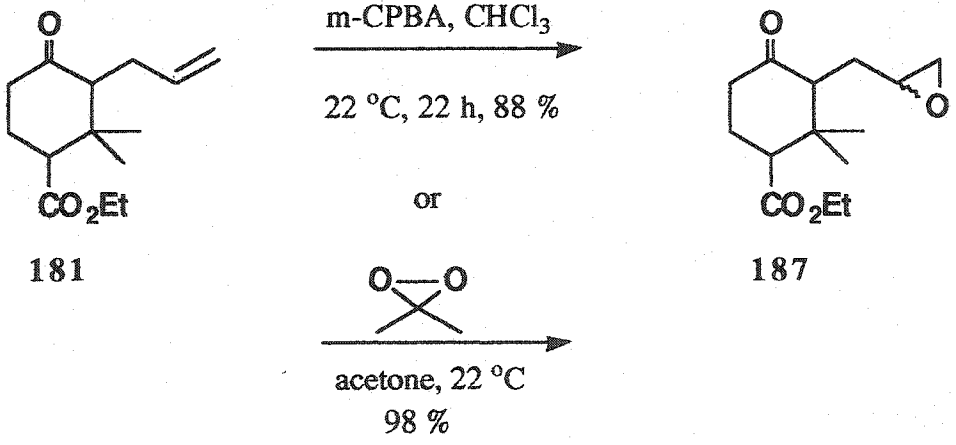
Due to the low yields and the tedious separation associated with direct one step synthesis of **181** from **76**, a second and better approach via **180** became necessary. Preparation of **181** from **180** required a simple dimethylcuprate addition to **180** but gave low yields of **181**.

Organocuprate addition to β,β-disubstituted and α,β-disubstituted enones are known to sometimes give poor conjugate addition products.[71b,87a,88] Organocuprate conjugate additions

promoted with Lewis acids have been shown to be effective when dealing with sterically hindered enones.[87,88,89]

Thus addition of a mixture of **180** and BF_3.OEt in ether at 0 °C to a cold (-30 °C) suspension of dimethylcuprate in ether followed by stirring for 1 h gave after workup and isolation an 80% yield of **181**. The ^1H and ^{13}C NMR spectra were consistent with the assigned structure for **181**.

6.2.4 Preparation of ethyl 2,2-dimethyl-3-(2,3-epoxypropanyl)-4-oxocyclohexanecarboxylate (187)



181 **187**

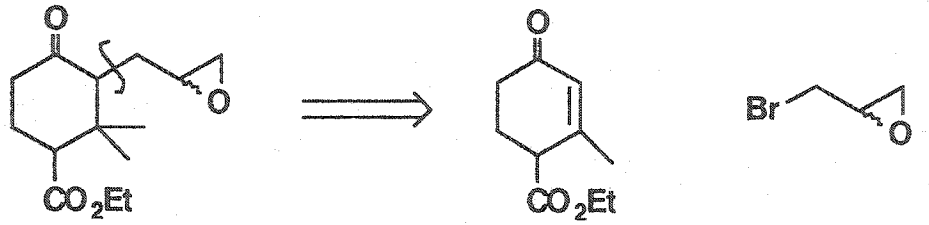
Equation 10

Epoxide **187** was prepared in 88% yield by stirring a mixture of **181** and *meta*-chloroperoxybenzoic acid (85%) in chloroform at room temperature for 10 h (Equation 10). Attempts to purify **187** by flash column chromatography lead to extensive decomposition thus it was used without further purification. Structural assignment was

based on ^1H NMR and mass spectral data. The vinyl signals present in the ^1H NMR spectrum of **181** were absent and a new one proton multiplet at 2.9 to 3 ppm assigned to the methine proton of the oxirane ring was present.

The first report of the use of dimethyldioxirane, the peroxide reactive intermediate that is generated from the addition of potassium peroxomonosulfate (oxone, $KHSO_5$) to ketones, as a reagent for the epoxidation of olefins appeared in 1980.[90] This method has gained wide usage in synthesis. The procedure used to generate dimethyldioxirane was tedious and time consuming but it was highly efficient and always gave a quantitative yield of **187**. The reaction was very fast (usually complete in 10 min) and clean. The concentration of dioxirane dropped considerably when stored for several days in the freezer thus only freshly prepared samples were used for the epoxidation.

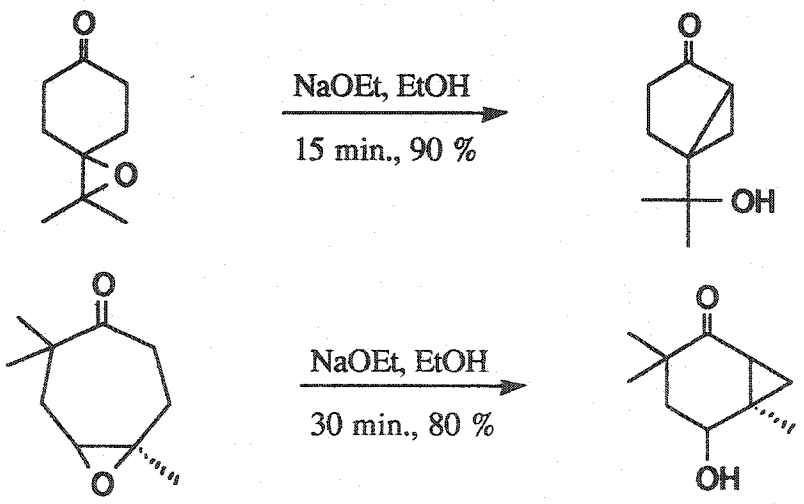
The structure of **187** seemed to indicate that it should be possible to prepare it in one step from **76** with epibromohydrin via the cuprate reaction (Scheme 27). The use of epoxides as trapping agents in cuprate reactions is known and occurs in moderate to good yields.[91] Also, the structure of epibromohydrin is such that enolate trapping by either bromine displacement or attack on the epoxide will generate **187**. Attempts to trap the enolate generated by the dimethylcuprate addition to **76** with epibromohydrin under various conditions (time, temperature and cosolvent) failed to furnish the expected product. Reaction of **186** and epibromohydrin in the presence of methyllithium also failed to give **188**. Compound **182** was always the major product isolated in these experiments.



187 76

Scheme 27

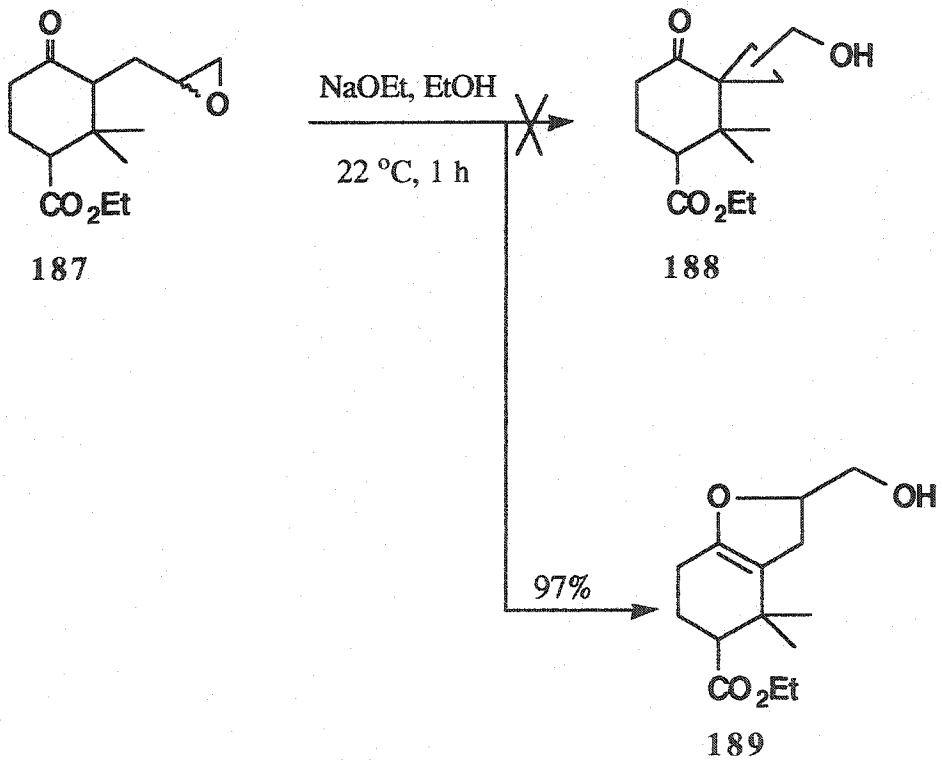
Bifunctional molecules containing both an epoxide and a nucleophile may undergo an intramolecular epoxide ring opening to generate a new carbocycle.[55a,92] Most examples of these approaches have generally involved the formation of three-membered,[55a,93,95,95] five-membered[55a,96] and six-membered rings[55a,97] but a few examples of the formation of ten and fourteen membered rings have also been reported.[98] Gioni has shown that these reactions are very useful for the formation of cyclopropyl rings and good to excellent yields are obtained (Scheme 28).



Scheme 28

6.2.5 Synthesis of 2-hydroxymethyl-4,4-dimethyl-5-carbethoxy-2,3,4,5,6,7-hexahydrobenzofuran (189)

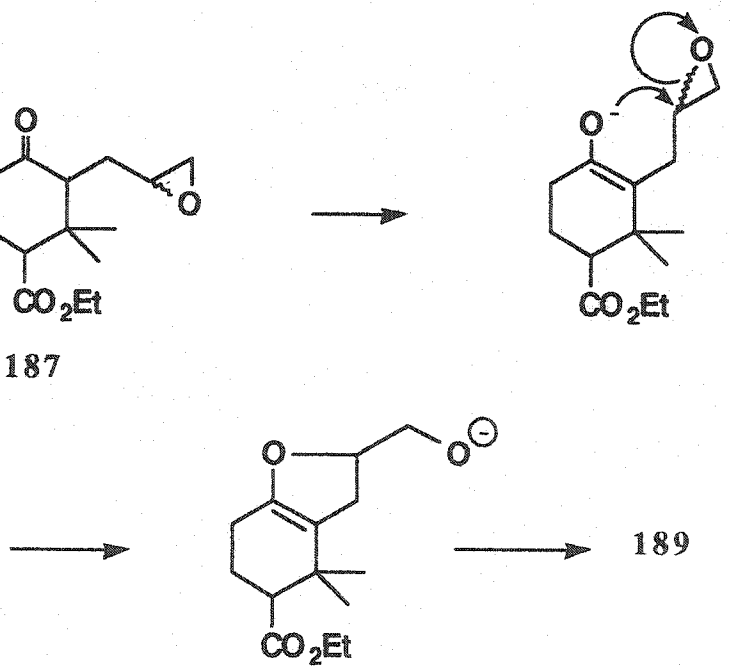
Epoxide **187** dissolved in dry ethanol was added to a solution of sodium ethoxide in ethanol at room temperature and stirred for one hour to furnish **189** (after purification by column chromatography) instead of the expected compound, **188** (Equation 11). Hexahydrobenzofuran **189** arose from attack by the enolate oxygen on the epoxide as shown in Scheme 29.



Equation 11

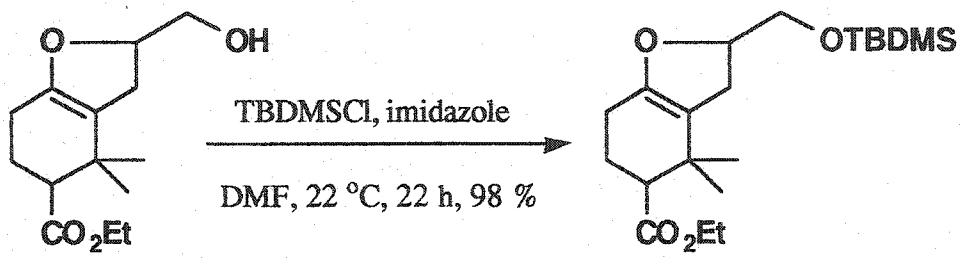
The ^{1}H NMR spectrum showed among other signals a two proton multiplet at 3.6 to 3.75 ppm that was assigned to $C\underline{H_2}OH$ and a

one proton multiplet at 4.65 ppm that was assigned to the methine proton of the hexahydrofuran at C_2 and next to the oxygen at C_1. This signal cannot be accounted for in compound **188**. The ^{13}C NMR spectrum was more characteristic of **189**, showing four low field signals (*i.e.*, > 77 ppm) at 81.5, 102.5, 149.2, and 174.4 ppm. The signal at 174 ppm is attributed to the ester functionality while those at 149.2 ppm and 102.5 ppm must be olefinic signals. The C_8 olefinic carbon atom adjacent to the oxygen gave rise to the peak at 149.2 and $\underline{C}H_2$-OH was assigned to the signal at 81.5. The IR spectrum confirmed the presence of both the alcohol and ester functionalities with signals at 3350 cm^{-1} and 1737 cm^{-1} respectively. The mass spectrum (EI) was not very helpful in the structural assignment since all the significant peaks could be accounted for by both structure **188** and **189**.



Scheme 29

Unfortunately **189** was rather unstable and a high resolution mass spectrum could not be obtained. Thus to confirm the assignment it was converted to its *tert*-butyldimethylsilyl protected ether, **190** (Equation 12) according to the procedure developed by Corey.[99] The ^{13}C NMR spectrum of **190** showed the characteristic olefinic signals at 148.7 ppm and 112.4 ppm and the C_2 carbon at 81 ppm. HRMS analysis (EI, $C_{20}H_{48}O_4$ - CH_3) confirmed structure **190**.



189 **190**

Equation 12

Attempts to improve the C/O alkylation ratio by varying the type of counterion in favour of smaller counterion such as Li and also modify solvent effects to encourage H-bonding to the enolate oxygen[86,100,101] were not very successful. Miller and Clark[102] reported that treatment of a number of β-dicarbonyl compounds with short chain alkyl iodides in the presence of tetra-alkylammonium fluorides give high yields of mono-C-alkylated derivatives with no apparent 'O' alkylation or other side reactions. They inferred that in the presence of the powerful hydrogen-bonding electron donor fluoride anion, the β-dicarbonyl compound behaves as a hydrogen bond electron acceptor thus forming a tightly

bonded complex anion with fluoride. This probably leads to shielding of the oxygen atom both by the large cation and also by the enol hydroxy-fluoride bond.

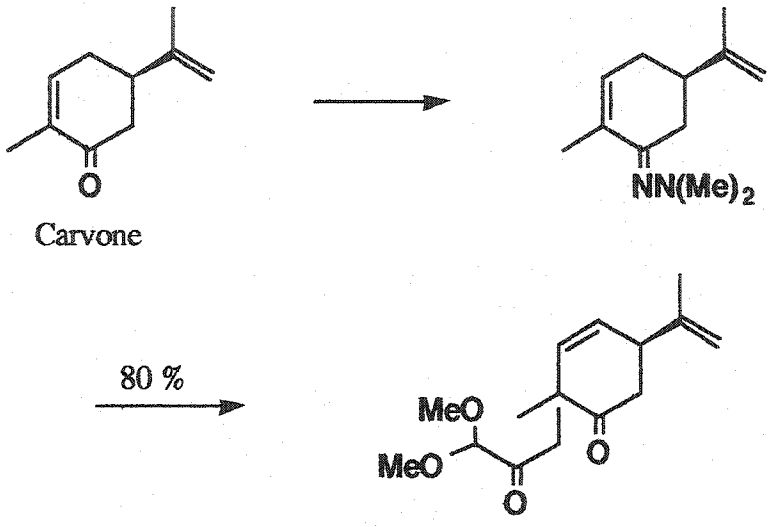
Reaction of **187** and tetramethylammonium fluoride in THF according to the procedure of Clark and Miller **189** (50%), **187** (5%) and some unidentified products. Possible reasons for failure to form the enol hydroxy-hydrogen bond and thus enhance 'C' alkylation may be that intramolecular reaction through oxygen is much faster than intermolecular hydrogen bond formation.

N,N-Dimethylhydrazones, obtained from the reaction of *N,N*-dimethylhydrazines with carbonyl compounds have been developed by Corey[103] as enolate ion equivalents in synthesis via α-lithiation. This procedure is claimed to have the following advantages: (1) efficiency of formation and lack of side reactions observed with enolate generation from free carbonyl compounds, (2) stability (in absence of oxygen, carbon dioxide, water *etc*) even at 25 °C, (3) much higher reactivities than enolates towards electrophiles such as oxirans and halides, (4) formation of only mono-substituted products with electrophiles and (5) unique stereoselectivities.

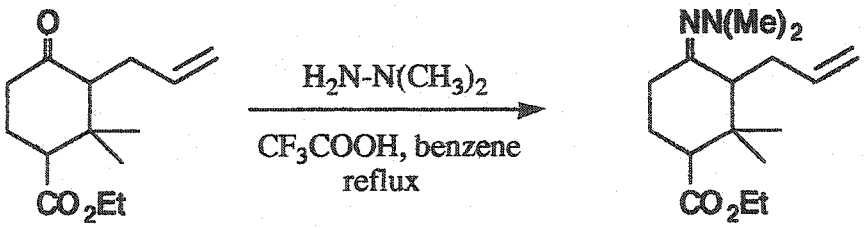
This procedure was used to synthesize picrotoxin. The transformation in Scheme 30 of carvone could not be realized using any of the currently available conditions for direct alkylation and therefore an indirect approach became necessary.

However transformation of **181** to **191** (Equation 13) was not clean and a large amount of **181** was still present after two days. Chromatography was not possible due to the sensitivity of **191** to

silica gel (tailing was observed even on TLC), thus **191** could not be carried further. It has been claimed that epoxidation with MCPBA does not usually affect the C=N of the hydrazone[104] although attempted epoxidation of a mixture of **191** and **181** gave rise to a mess!



Scheme 30

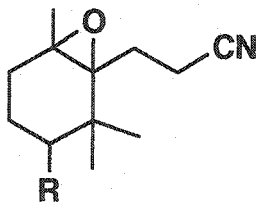


181 **191**

Equation 13

6.3 Attempted base induced cyclopropanation of γ,δ-epoxynitrile

At this point it was obvious that cyclization of epoxyketone, **187** was not possible by the literature methods available perhaps due to the geometry of the molecule. According to Baldwin,[28c] stereoelectronic control of the alkylation of ambident nucleophiles requires approach of the electrophile perpendicular to the plane of the enolate for carbon alkylation, while oxygen alkylation requires approach in the plane of the enolate. Stork[105a] had shown that this problem is readily overcome by the choice of γ,δ-epoxynitriles. It was demonstrated that in these cases, the rate of cyclopropanation is such that it is produced preferentially to the cyclobutane regardless of the relative degree of substitution of the oxetane ring. Thus an attempt was made to synthesize compounds such as **192**.



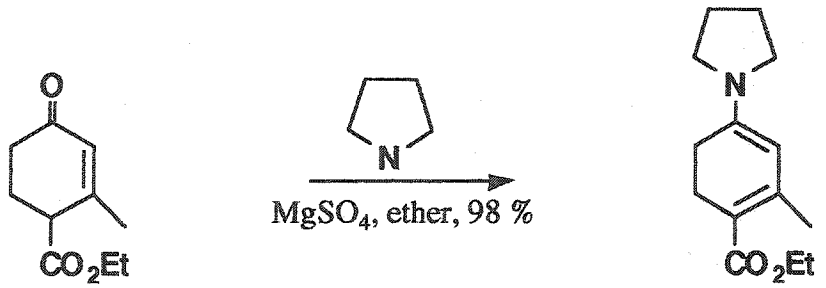
192

6.3.1 Attempted preparation of ethyl 2,2,4-trimethyl-3-(2-cyanoethyl)-3,4-epoxycyclohexanecarboxylate (194)

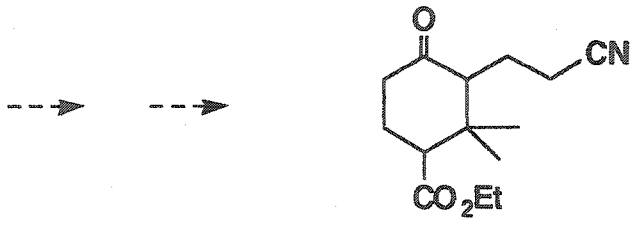
An attempt was made to prepare **194** through the enamine **193** which was synthesized in 98% yield by stirring a mixture of **76**, pyrrolidine and and a small amount of magnesium sulfate in ether for 3 h at 22 °C (Equation 14). When spotted on a TLC plate, the

crude product decomposes, showing mainly **76** as the major product however, both the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture after concentration showed a quantitative yield of **193**. The ^{1}H NMR spectrum showed a characteristic vinyl signal at 4.5 ppm while the ^{13}C NMR spectrum indicated among others, four olefinic signals at 152.6, 150.9, 105.2 and 97.4 ppm which were characteristic of the assigned structure for **193**.

A Michael type addition of **193** to acrylonitrile was unsuccessful although Stork and co-workers[105b] have reported the addition of the enamines of simple carbonyl compounds to acrylonitrile in fair to good yields. Other attempts such as direct trapping of acrylonitrile or 2-bromocyanopropane by the cuprate reaction intermediate, **168** under various conditions failed.



76 **193**

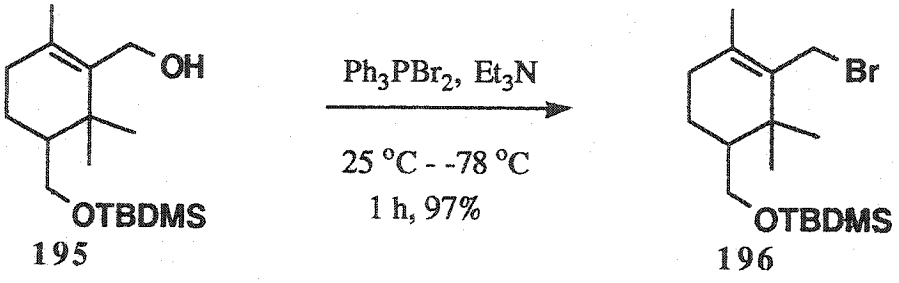


194

Equation 14

6.3.2 Preparation of oxirane (198)

A solution of **195** in methylene chloride was added to a cold (-78 °C) mixture of triphenylphosphine dibromide (prepared by the dropwise addition of bromine to triphenylphosphine in methylene chloride) and triethylamine and stirred for 1 h at 22 °C according to the procedure of Fallis and co-workers[55a] to furnish **196** after workup in almost quantitative yield (Equation 15).

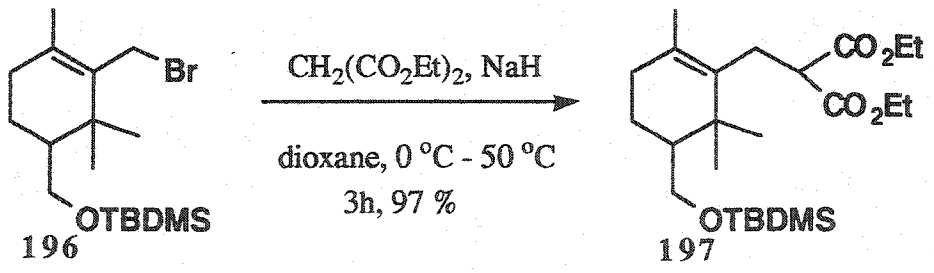


Equation 15

The ^1H NMR spectrum of **196** was in agreement with the structural assignment. An AB quartet at 4 ppm with coupling constant, J = 9.9 Hz was assigned to the exocyclic methylene protons between C_2 and the bromine atom. These methylene protons are diastereotopic and although free rotation is possible about the C_2 - CH_2Br bond, it is likely that this is slowed down considerably due to steric interaction between the bromine atom and the gem dimethyl substituents at C_3. The other exocyclic methylene protons at C_4, being next to a chiral center are chemically non equivalent and therefore, they are coupled to each other, and to the methine proton at C_4. Each gave rise to a doublet of doublets, one at 3.3 ppm with J = 10 Hz, 8.75 Hz and the other at 3.7 ppm with J = 10 Hz, 4 Hz. The geminal

coupling constant is 10 Hz while the vicinal coupling constant is 8.75 Hz for the syn protons and 4 Hz for the anti protons.

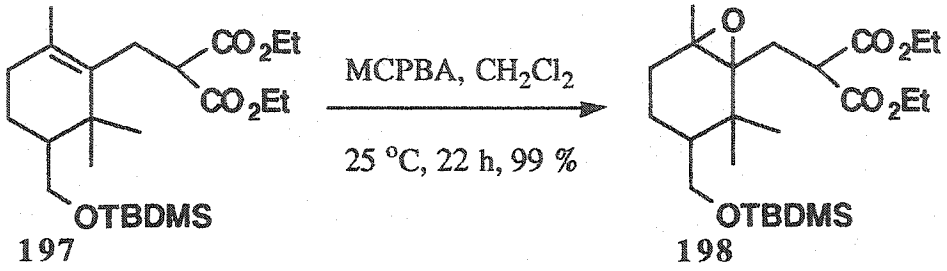
S_N2 displacement of bromine by diethyl malonate was achieved smoothly by the dropwise addition of **196** to a cold (0 °C) solution of diethyl malonate, dioxane and sodium hydride and warmed to 50 °C for 3 h (Equation 16). Workup and chromatography gave **197** in 97% yield. Structural assignment of **197** was based on the ^1H and ^{13}C NMR spectra and on the low and high resolution mass spectral data. Both the low and high resolution mass spectra did not indicate the molecular ion peak (M^+) but instead showed the M^+ - 57 peak which is due to the loss of the *t*-Bu group from silicon. It is very well known that molecules containing the TBDMS-O- group frequently do not give the M^+ peak but instead show the M^+ - *t*-Bu- peak. The base peak was due to the loss of *t*-Bu- and $-CH(CO_2Et)_2$ groups. These are all consistent with the structural assignment for **197**.



Equation 16

meta-Chloroperbenzoic acid (85%) was added to a stirred solution of **197** in chloroform to afford **198** after 22 h at 22 °C in 99% yield (Equation 17). Low resolution mass spectral analysis gave a signal at *m/z* 399 (2.6 %) which was attributed to the loss of *t*-Bu-

from the molecular ion. The proton NMR spectrum matched the structure given to **198**.

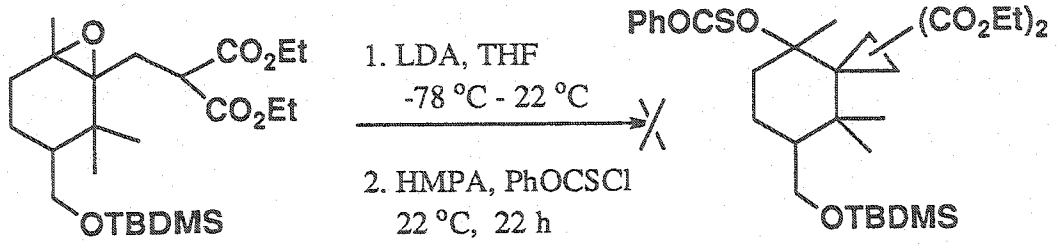


197 **198**

Equation 17

6.3.3 Attempted intramolecular cyclization of 198

All attempts to effect the base induced cyclopropanation of **198** in the presence or absence of phenyl chlorothionoformate (Equation 18) were unsuccessful. Cyclopropane **199** is sterically very congested and this may inhibit cyclization of **198**. In addition the presence of CN- of CO_2Et- substituents on the cyclopropane ring would not be practical for the final ring closure to form the taxol skeleton (Scheme 22) because electron withdrawing substituents attached to radical centers slow down addition to the double bonds of enones (*vide infra*). However, they could be modified or used directly to study the ring cleavage of spiro cyclopropyl carbinyl systems (*vide infra*).



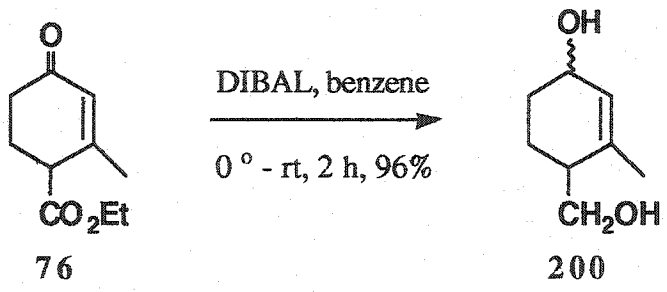
198 **199**

Equation 18

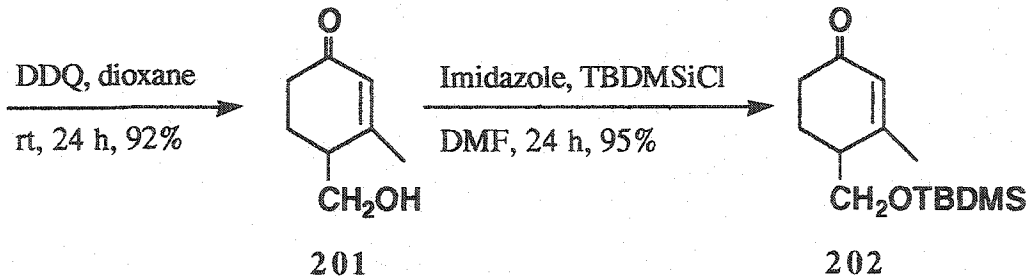
6.4 Ketene carbonyl cycloaddition

6.4.1 Preparation of 4-(*tert*-butyldimethysilyloxy)-methyl-3-methyl-2- cyclohexenone (202)

In our synthetic plan introduction of the methyl substituent at C_{12} of the taxol skeleton was envisaged to proceed via methyllithium attack on the ketone carbonyl group (*vide infra*) in the presence of the ester function (Equation 3). The products of this reaction did not however favour the expected compound (Table I) thus modification of the ester functionality was required. Hagemann's ester **76** was converted to the *tert*-butyldimethylsilyl protected enone **202** according to Scheme 31.



76 **200**



201 **202**

Scheme 31

Diisobutylaluminum hydride reduction of **76** at 0 °C in methylene chloride occured smoothly after 2.5 hours to give the diol **200** as a colorless oil in 96% yield. The structure of **200** was confirmed from the ^{1}H and ^{13}C NMR spectra and low and high resolution mass spectral data. A solution of DDQ in dioxane was added to a stirred solution of **200** in dioxane at 22 °C for 22 hours to furnish unsaturated ketone **201** in 98% yield.[106] The literature procedure for purification after DDQ reaction required precipitation of the insoluble 2,3-dichloro-5,6-dicyanohydroquinone by addition of petroleum ether and or column chromatography on silica gel.

Compound **201** however was insoluble in petroleum ether and all the solvents tried that dissolve **201** also dissolved DDQ and its byproducts. Flash column chromatography was unsuccessful due to massive tailing of the DDQ and other byproducts. Column chromatography (20% acetone/petroleum ether) on alumina (neutral) effectively stops the flow of DDQ and 2,3-dichloro-5,6-dicyanohydroquinone through the column and gave **201**, after concentration of the eluent, as a colorless oil.

MnO_2 the reagent of choice for allylic alcohol oxidation[55b] gave very low yields of **201**. This reagent has been prepared and used successfully in our laboratory however its success depends on the nature and quality of the charcoal used. All the Aldrich charcoal tried gave low yields of the isolated product. TLC of the crude reaction mixture before isolation indicated total conversion to **201** however the yield of the actual isolated product was always less than 40%. Jones reagent also gave low yields of **201** even when performed at 0

^{o}C. A large amount of the primary alcohol was also oxidized, either to the aldehyde or further to the acid.

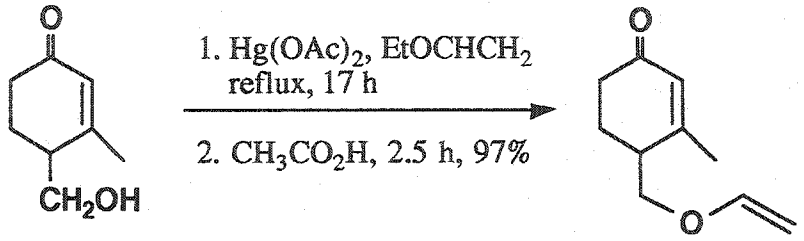
Addition of imidazole followed by TBDMSCl to a solution of the enone in DMF at 25 ^{o}C for 24 h furnished after workup and chromatography 98% of the *tert*-butyldimethylsilyl protected enone **202**. The ^{1}H NMR spectrum of **202** showed the characteristic six and nine proton singlets of the *tert*-butyldimethylsilyloxy group at 0 ppm and 0.85 ppm respectively. A one proton singlet at 5.9 ppm was assigned to the vinyl proton and a two proton doublet at 3.7 ppm was assigned to the methylene protons attached to the C_4 carbon.

The ^{13}C NMR spectrum showed ten signals, including the ketone at 199.4, and two olefinic signals at 162.5 ppm and 128 ppm. The signal at 199.4 ppm is typical of the carbonyl carbons of conjugated ketones which are usually equal to or lower than 200 ppm compared to isolated ketones which are usually greater than 200 ppm. The signal observed for the β-carbon of conjugated enones is at a much lower field than that of the α-carbon. High resolution mass spectral data showed that **202** has the molecular formula $C_{10}H_{17}O_2Si$ - C_4H_9. The elemental analysis was in agreement with this formula.

6.4.2 Preparation of 4-(ethyleneoxy)methyl-3-methyl-2-cyclohexene-1-one (203)

Enone **203** was prepared according to the procedure of Ireland and Dawson[107] by refluxing a mixture of **201**, ethyl vinyl ether and mercuric acetate for 17 h. Acetic acid was then added at room temperature for 2.5 h followed by workup and chromatography to afford **203** in 97% yield (Equation 19). The IR spectrum showed the

conjugated ketone at 1652 cm^{-1} and no alcohol signal. The ^{13}C NMR spectrum showed four olefinic signals at 161.5 ppm, 151.5 ppm, 128.6 ppm, and 87 ppm which were characteristic of the structure assigned to **203**. High resolution mass spectral data confirmed the molecular formula for **203** as $C_{10}H_{14}O_2$.



201 **203**

Equation 19

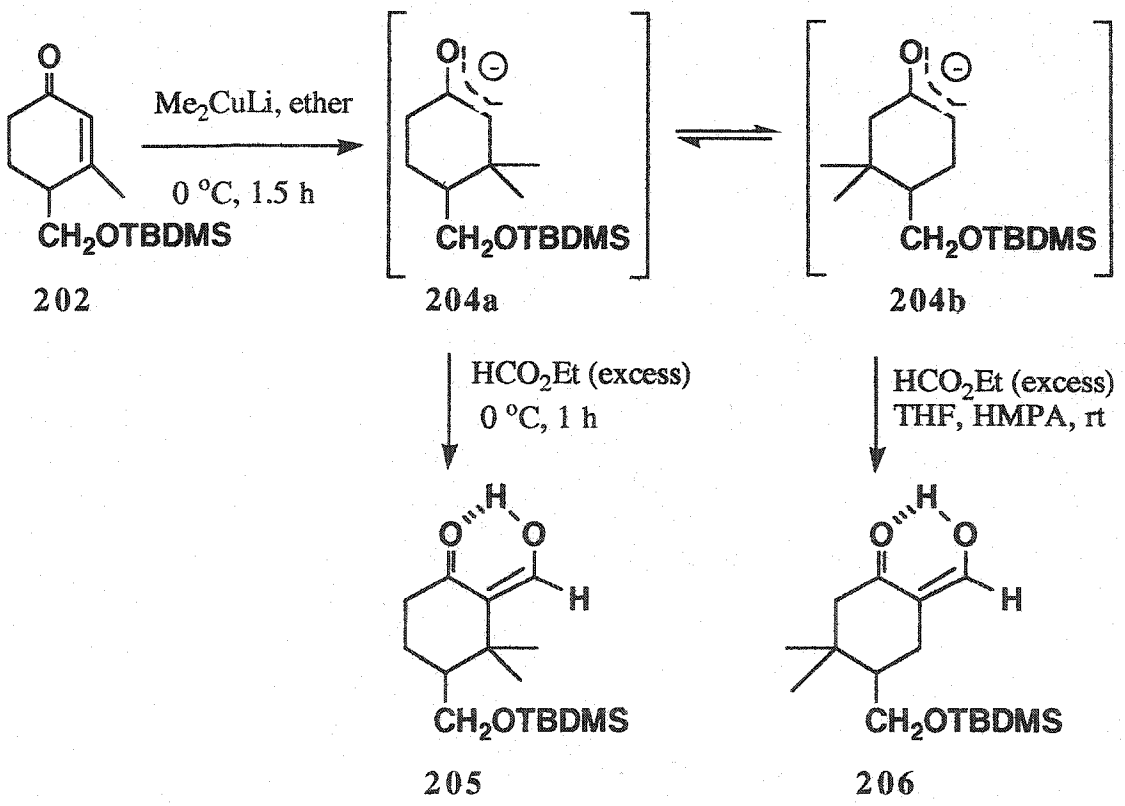
6.4.3 Preparation of β-keto aldehydes:

a) via cuprate reactions.

Dimethylcuprate addition to **202** followed by trapping with ethyl formate (*vide infra*) gave the keto aldehyde **205** in about 30% yield (Equation 20). In an attempt to improve the yield, THF followed by HMPA was added just before the addition of ethyl formate. There was a large improvement in the product yield from about 30% to 78%. However the product isolated was **206**, the isomer of **205** that arises as a result of enolate equilibration (*vide infra*) leading to the favoured, less sterically hindered product. The ^1H NMR spectrum of the two isomers were distinguishable in that **206** showed a distinct two proton doublet at 2.1 ppm with J = 11.4 ppm due to the C_6 methylene protons that was absent in the spectrum of **205**. Both spectra showed a doublet at 15 ppm, J = 1.6 Hz that was shown by

proton irradiation experiments and the value of the coupling constant to be coupled to the vinyl proton.

These observations indicate that **205** and **206** occur as the more stable keto-enol tautomer due to the presence of H-bonding between the ketone and the enol alcohol. Keto enol ether **207** was also made in a similar fashion (Table III). During the preparation of **207** the presence of THF and or HMPA was essential for product formation. Thus all attempts to prepare the isomer of **207** through enolate **204a** in the absence of cosolvent only gave the cuprate reaction intermediate without trapping ethyl formate.

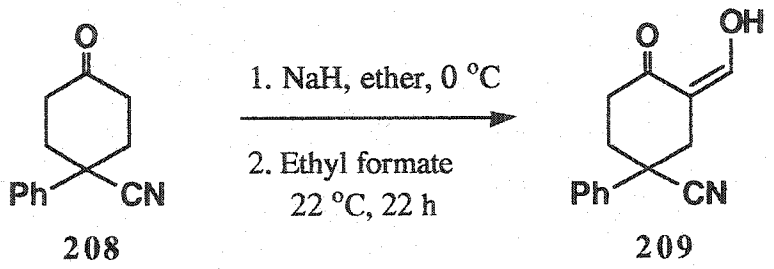


Equation 20

b) From the ketone

Preparation of 3-formyl-4-oxo-1-phenylcyclohexanecarbonitrile (209)

β-Keto-aldehyde **209** was prepared from ketone **208**, sodium hydride, a small amount of ethanol and ethyl formate according to the procedure of Ainsworth.[108] The crude product after workup was used without further purification for the next step (Equation 21).



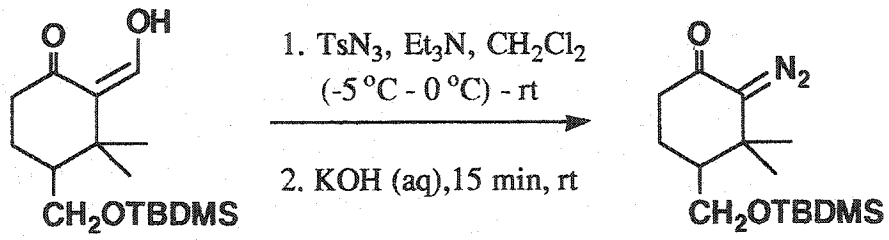
208 **209**

Equation 21

6.4.4 Preparation of α-diazoketones from β-keto enol ether(s)

α-Diazoketones constitute an important precursor for the generation of cyclopropanes via catalytic decomposition in the presence of olefins (*vide infra*).[113,114] In keeping with the desire to synthesize derivatives such as **163** as precursors to the taxol skeleton and also for studying the ring opening reactions of cyclopropyl carbinol systems, it was hoped that the required compounds could be readily generated via diazoketones. The required spiro cyclopropyl cyclohexane system could be prepared using this procedure according to one of two possible routes (Scheme 34) without too much change in the overall synthetic plan.

The α-diazo ketones were synthesized from the corresponding β-keto enol ethers (Equation 22) by the slow addition of *p*-toluenesulfonyl azide to a solution of the enol ether and freshly distilled triethylamine in methylene chloride at 0 °C to 22 °C for 3 hours. An aqueous potassium hydroxide solution was then added for 15 minutes followed by workup and chromatography to afford the product (Table III). All of the diazoketones showed the characteristic IR signal around 2100 cm^{-1} to 2110 cm^{-1} which is due to the diazo group and the spectra obtained were in agreement with the structure assignment.



205 **210**

Equation 22

α-Diazoketones **210** and **211** were readily distinguishable from each other by their proton NMR spectra which shows a two proton singlet at 2 ppm due to the C_6 protons in **211** while the C_6 proton in **210** appears as a multiplet at 2.4 ppm. α-Diazoketone **212** had a rather interesting ^1H and COSY NMR spectra due to coupling among the protons at C_3, C_4 and the protons of the methylene substituent attached to C_4. Apart from the methylene protons at C_6

which appear as a singlet, all the other protons occur as doublets of doublets due to coupling with two other protons.

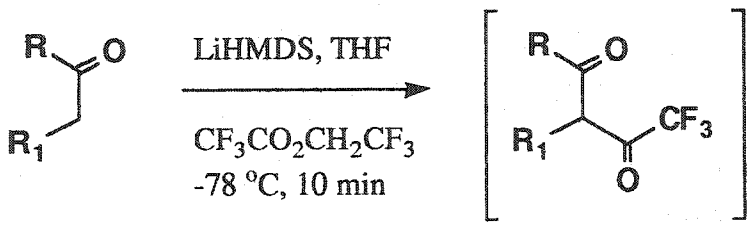
Diazoketone **215** was prepared in quantitative yield by stirring a solution of the acid chloride **214** and diazomethane (prepared from *N*-nitrosomethylurea and aqueous 50% potassium hydroxide[109a] in ether (0 °C to 21 °C) for 3 h.[109b] The diazoketone required for the taxol synthesis is **210** which is obtained in rather low yields.

There are very few reports of direct diazo transfer to ketone enolates. For example, Lombardo and Mander[110a] reported diazo transfer from 2,4,6-triisopropylphenylsulfonyl azide to enol derivatives of hindered cyclic ketones under phase transfer conditions and Evans and Britton[110b] transfered the diazo group fromp-nitrobenzenesulfonyl azide (PNBSA) to the enol derivatives of a benzyl ester and an *N*-acyloxazolidinone. Generally such processes are not very practical.[111]

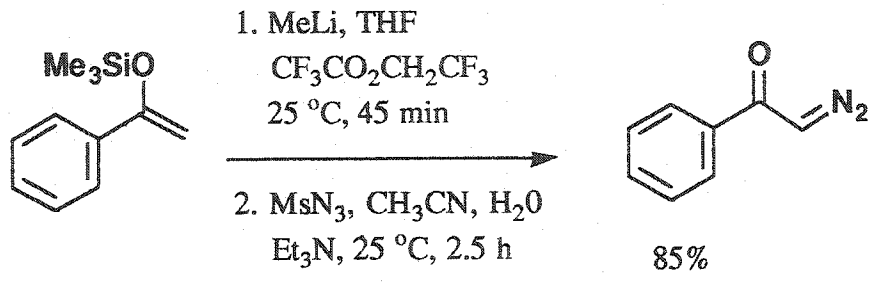
Tosyl azide has been the the azide transfer reagent of choice for most diazo transfer reactions however it has been suggested by Taber[112] that methanesulfonyl azide is a superior reagent, having the following advantages, a) it affords an easier and more effective workup because excess mesyl azide and and other formamide by-products are readily separated from the products by dilute base extraction and b) it is inexpensive and easy to prepare.

Danheiser and co-workers[111] have published an improved procedure for generating α-diazoketones. The key feature of this method is the activation of the ketone starting material as the corresponding trifluoroacetyl derivative followed by treatment with methanesulfonyl azide at room temperature (Scheme 32). It was also

shown that variants of this diazo transfer strategy based on other methods of generating kinetic enolates was also possible. Thus cleavage of TMS enol ethers with methyl lithium provides another useful route for specific enolates which can be trapped with trifluoroethyl trifuoroacetate (TFEA) and converted to the diazo derivative (Scheme 33). Application of Danheiser's procedure did not improve the yield of **210** as dramatically as would have been expected from the report of Danheiser and co-workers.



Scheme 32



Scheme 33

Table II: Preparation of keto-aldehydes

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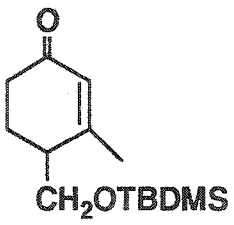
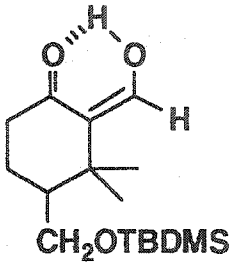
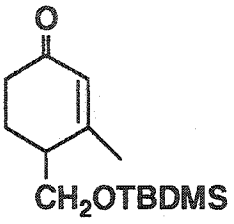
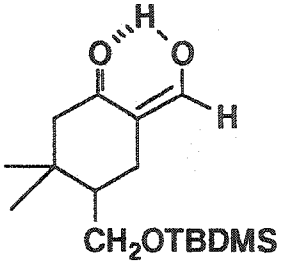
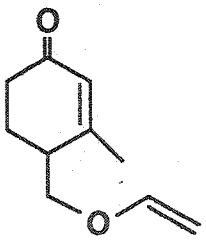
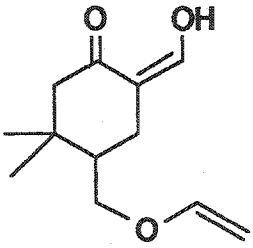
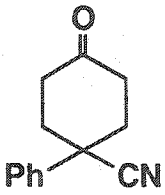
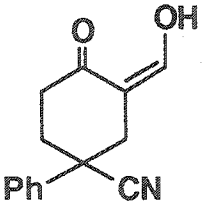
1	 202	 205	< 30%
2	 202	 206	78%
3	 203	 207	nd
4	 208	 209	nd

[I] Yield of purified product.

nd Yields were not determined.

Table III: Diazo transfer reactions

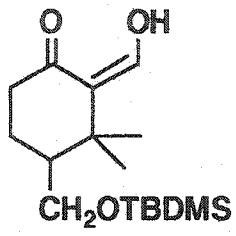
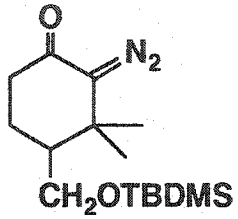
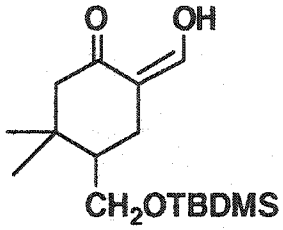
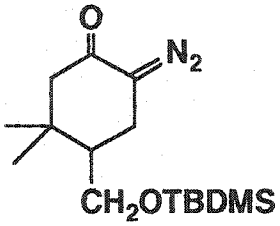
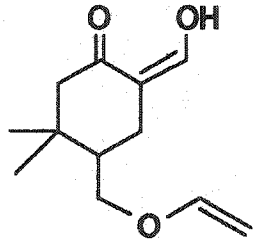
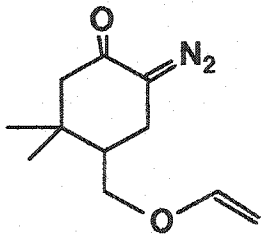
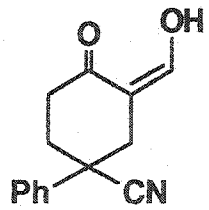
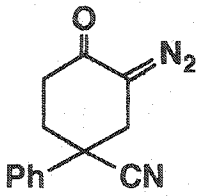
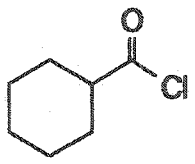
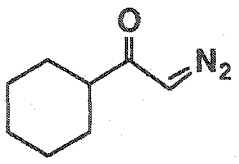
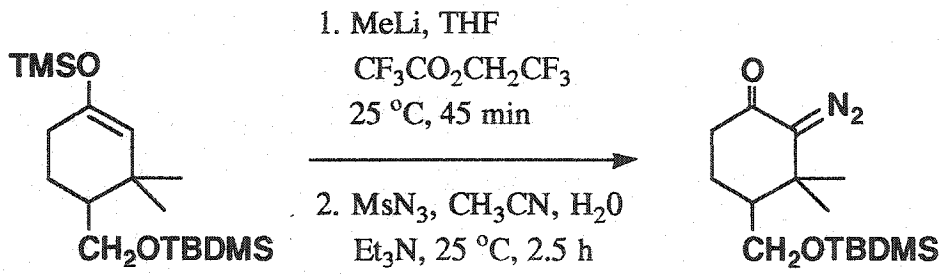
Entry	Substrate	Product	Yield[I] (%)
1	 205	 210	20[I]
2	 206	 211	78[I]
3	 207	 212	85[I]
4	 209	 213	40[I]

Table III. continued

5			98
	214	**215**	

[I] Yields are based on the starting enone (entries 1 - 3) and Ketone (entry 4).

Attempts to generate **210** via the silyl enol ether **216** (Equation 23) gave rather low yields. It is likely that severe steric hiderance caused by the gem dimethyl substituent at C_3 prevents the introduction of bulky substituents such as trifluoromethyl acetate at the 2-position thus lowering the yield of **210**.



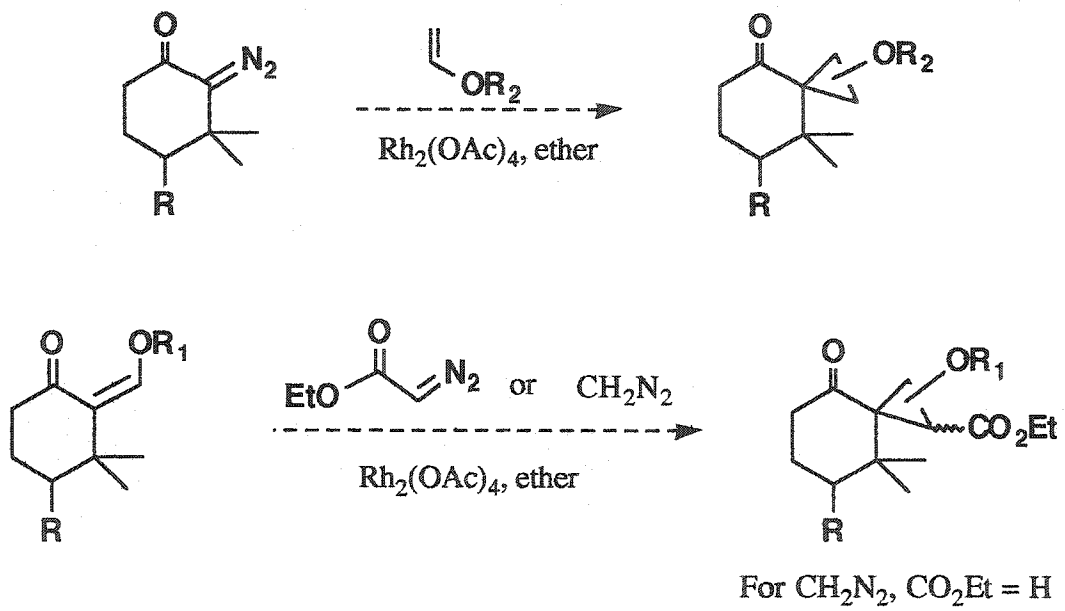
216 **210**

Equation 23

6.4.5 Catalytic decomposition of α-diazoketones

Initial cyclopropanation attempts by reaction of diazoketone **210** and vinyl acetate in catalytic amounts of rhodium acetate were unsuccessful and no identifiable products were obtained however,

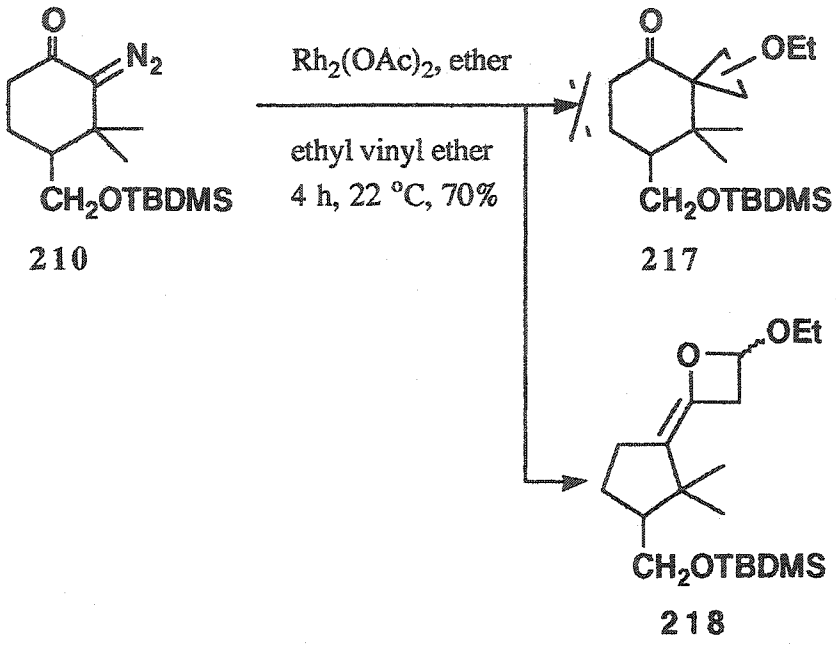
rather interesting products were obtained with ethyl vinyl ether as the olefin source. Thus addition of an ether solution of the diazoketone **210** to a suspension of rhodium(II) acetate in ethyl vinyl ether over four hours via syringe pump afforded a 70% yield of oxetane **218** and not the expected cyclopropanation product **217** (Equation 24).



Scheme 34

The IR spectra of oxetane **218** lacked the carbonyl signal expected for **217**. Instead it showed a very strong band at 1100 cm^{-1} due to asymmetric C-O-C stretching vibrations. The ^{1}H NMR spectrum showed a characteristic one proton multiplet at 5.4 ppm that was assigned to the C_2 oxetane methine (between the two oxygen atoms) proton. The ^{13}C NMR spectrum showed two olefinic signals at 148 ppm and 104.6 ppm these being the oxetane C_4 and cyclopentane C_1 respectively in addition to a signal at 102 ppm that

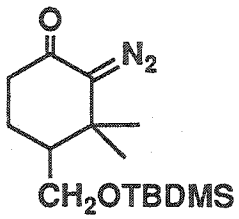
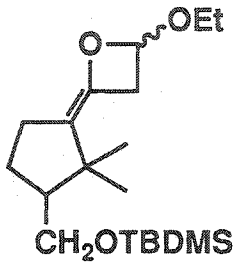
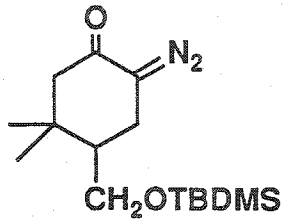
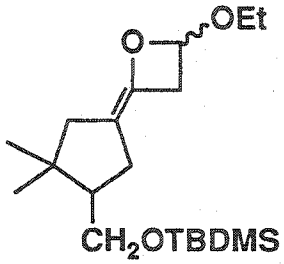
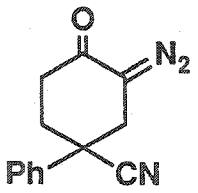
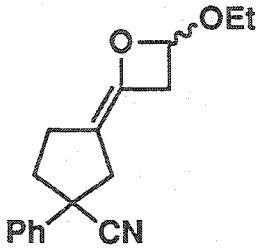
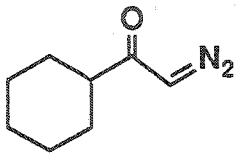
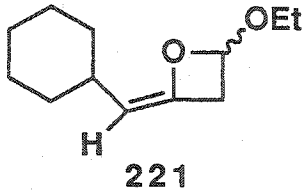
was assigned to the oxetane C_2, between the two oxygen atoms. High resolution mass spectroscopy confirmed the molecular formula of **218** as $C_{19}H_{36}O_2Si$.



Equation 24

Initially we were of the opinion that **218** which probably arose via the ketene addition (*vide supra*) to the ethyl vinyl ether occured because of steric hindrance by the gem dimethyl substituent at C_3. This may retard direct formation of cyclopropane and permit the Wolff rearrangement. In addition, the catalyst may play a role in the formation of the oxetane (*vide supra*). However synthesis of diazoketone **213** and its subsequent decomposition leading to **219** (Table IV) indicated that steric hindrance due to the gem dimethyl had negligible influence on the course of the reaction.

Table IV:Rhodium acetate catalyzed decomposition of Diazoketones.

Entry	Substrate	Product	Yield (%)
1	 210	 218	70
2	 211	 219	75
3	 213	 220	40
4	 215	 221	71[I]

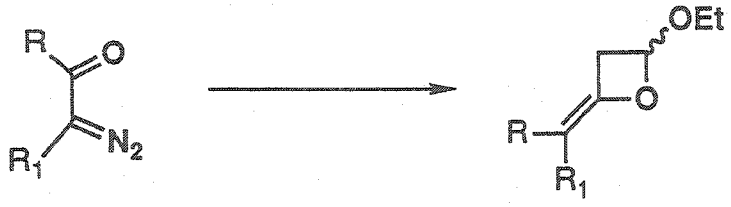
[I] Yield determined by GCMS.

To answer the question of whether or not this observation was unique to cyclic systems **215** was synthesized and decomposed as described above. The product from this reaction was extremely labile and could not be isolated and fully characterized although the crude ^1H NMR spectrum showed the presence of the characteristic one proton multiplet at 5.4 ppm due to the methine signal between the the two oxygen atoms. Also GCMS analysis of the crude mixture indicated that the major product of the reaction had a mass corresponding to oxetane **215**. These reactions are thus not unique to cyclic diazoketones.

Several other catalysts also effect the cyclopropanation of diazoketones. In an attempt to determine the importance of the rhodium(II) acetate catalyst for oxetane formation, the reactions were repeated using first palladium(II) acetate as the catalyst[115] and then copper(I) chloride (Table V) as a representative of the copper based catalysts. It has been reported by Anceaux[113] and by other workers[116,117] that copper triflate is a better copper based catalyst however it causes rapid polymerisation of ethyl vinyl ether under the reaction conditions and thus could not be used. As Table V indicates, the same products (although in lower yields especially for for the copper(I) chloride catalyst) were obtained with palladium(II) acetate and copper(I) chloride catalysts showing that rhodium(II) acetate was not essential for the formation of the observed products.

It is known that the nature of the substituent attached to the olefin frequently influences the course of the catalytic diazoketone decomposition reaction.[116] The reaction was thus repeated in various olefins (Table VI) however only a few gave products that could be

Table V: Decomposition of diazoketones in $Rh_2(OAc)_4$, $Pd(OAc)_2$ and CuCl



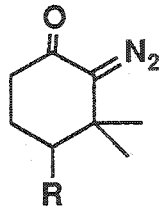
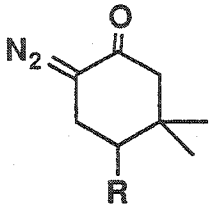
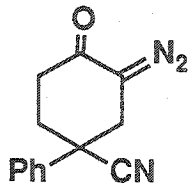
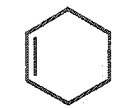
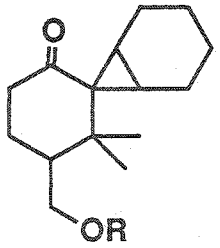
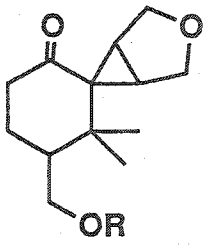
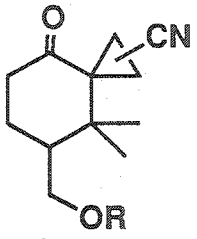
Entry	Substrate	Catalyst and % Yield		
		$Rh_2(OAc)_4$	$Pd(OAc)_2$	CuCl
1	 **210**	70	72	30
2	 **211**	75	72	35
3	 **213**	40	36	10

Table VI: Decomposition of **210** in different olefins under catalytic or thermal conditions

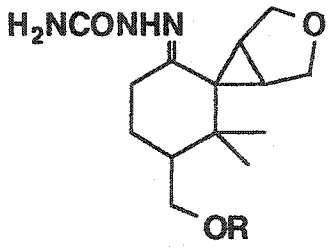
Entry	Olefin	Product	Yield (%)
1	 $Rh_2(OAc)_4$	 **222**	25
2	 $Rh_2(OAc)_4$	 **223**	65[I]
3		 **225**	75

[I] Best yield obtained. Yields were generally erratic.

R = TBDMS

readily identified. The yield of product was either too low, too many products (TLC analysis) or the products decomposed rapidly.

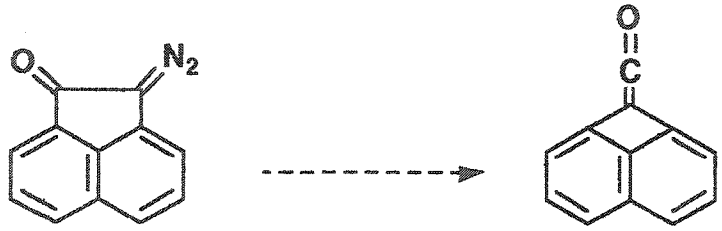
Spiro cyclopropanes **222** and **223** were successfully prepared via rhodium(II) acetate catalyzed decomposition of **210** in cyclohexene and dihydrofuran respectively. Structural assignments were based on the ^1H NMR spectra and on the high and low resolution mass spectra which confirmed the molecular formula of **222** as $C_{21}H_{38}O_2Si$. Both the EI and CI mass spectral data of **223** did not indicate the molecular ion. Attempts were thus made to prepare suitable crystal derivatives of **223**. The semicarbazone **224** was prepared but the crystals isolated were not suitable for X-ray studies. Structural assignments for **224** were based on its ^1H NMR spectral data.



224

In studies directed towards the preparation of derivatives of **227** via Wolff rearrangement of **226** (Scheme 35), Schecter and co-workers[118] observed that although thermal or photochemical cyclopropanation of ethyl vinyl ether or cyclohexene with **226** were unsuccessful, thermal decomposition or irradiation in acrylonitrile gives the Z and E spirocyclopropyl products in moderate yields. These thermal reactions were conducted either in refluxing acrylonitrile

with trace amounts of palladium(II) acetate or in refluxing toluene and acrylonitrile.



226 227

Scheme 35

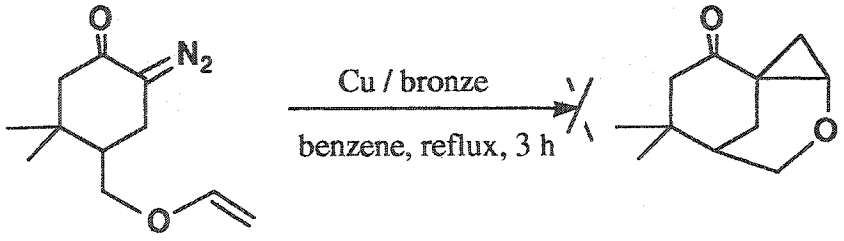
Refluxing a mixture of **210** and acrylonitrile in toluene for 24 h gave after chromatography a 75% yield of **225** as a mixture of isomers. The IR spectrum indicated the presence of both ketone and nitrile functionalities with signals at 1708 cm^{-1} and 2239.8 cm^{-1} respectively. Due to the presence of an isomeric mixture of products, the ^{13}C NMR spectral data indicated more signals than expected for a single compound however these included the ketone and nitrile carbon signals at 206 ppm and 117 ppm respectively as the only signals above 77 ppm.

High resolution mass spectral data confirmed the molecular formula for **225** as $C_{14}H_{22}O_2NSi$. Elemental analysis also showed an agreement between the observed and calculated C, H and N for $C_{14}H_{22}O_2NSi$. The above procedure was repeated using maleic anhydride as the electron poor olefin however unlike acrylonitrile, excess maleic anhydride was difficult to remove (either by column chromatography or precipitation of the anhydride) thus the reaction products could not be isolated.

The results obtained so far seemed to indicate three reaction pathways, namely: a) catalytic decomposition of diazoketone **210** at room temperature in the presence of unactivated olefins gave cyclopropanation products in poor yields, b) use of activated or electron rich olefins gave oxetanes in good yields and c) thermolysis of **210** in electron poor olefins gave cyclopropanation products in good yields.

Intermolecular reactions of α-diazoketones and olefins require a high concentration of the olefin because dimerization of the olefin is usually a faster reaction than cyclopropanation.[113,119] This limitation is solved experimentally by a slow addition of the diazoketone via a syringe pump to a suspension of the catalyst in excess olefin (usually the solvent) and has been exploited in an intramolecular sense[38c,112,120] thus avoiding the carbene dimerization problem.

Intramolecular reactions are usually faster than the corresponding intermolecular reaction thus it was hoped that the resulting keto-carbenoid species would add much more rapidly to an internal double bond than rearrange.



212 **228**

Equation 25

Attempts to cyclize **212** to **228** (Equation 25) were unsuccessful although several different catalysts were tried under

various temperature and solvent conditions. No products were successfully identified from this reaction.

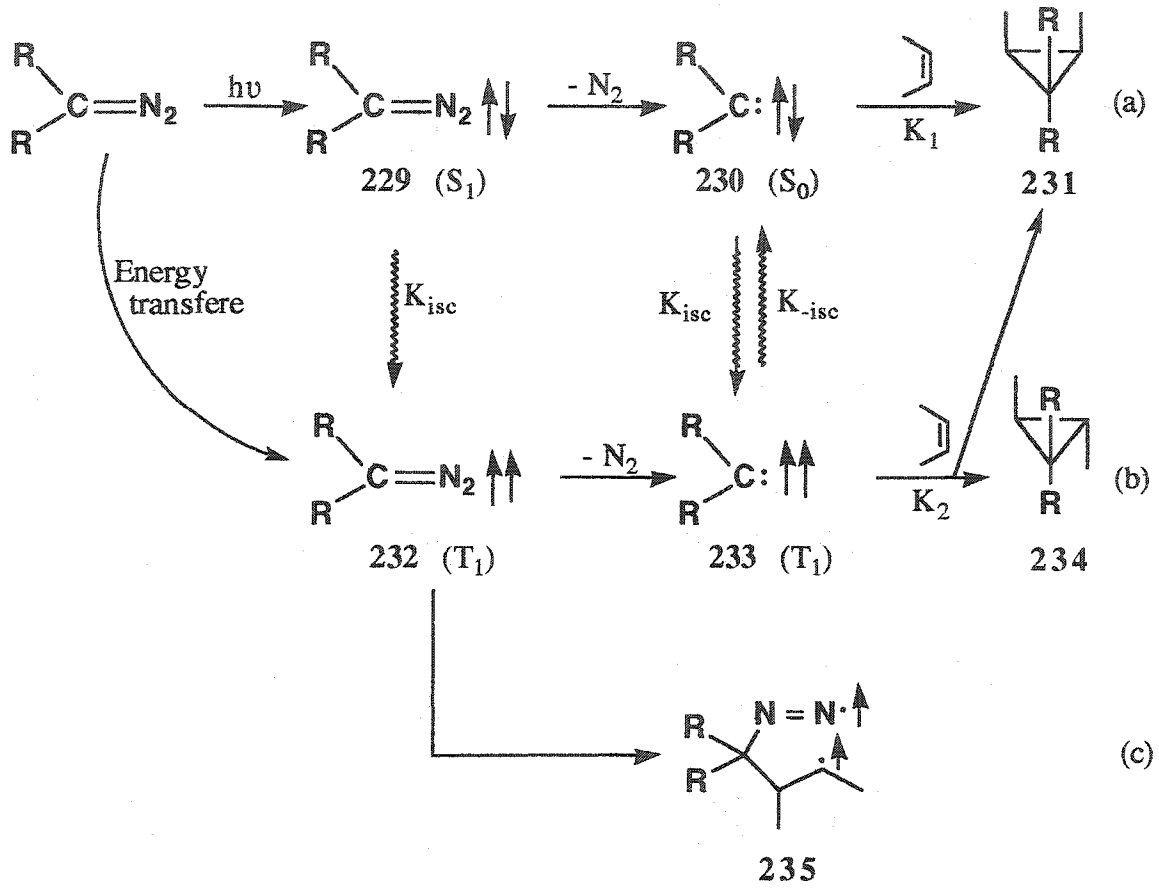
6.4.6 Photochemical decomposition of α-diazoketones

Photoexcitation of the long wave bands of diazo compounds (they absorb between 400 nm and 500 nm with a low extinction coefficient $\varepsilon = 10$) give rise to an excited singlet state of the diazo compound **229** which may react according to three possible pathways (Scheme 36): 1. Undergo intersystem crossing to the triplet diazo compound. 2. Revert to the starting compound by internal conversion in a radiationless decay process. 3. Decompose to a singlet carbene.

Loss of nitrogen from **229** forms the singlet carbene **230** (S_o state) which may add directly to cis butene if K_1 is large in a stereospecific manner to form cyclopropane **231**. If on the other hand, intersystem crossing **230** to **233** (*i.e.*, K_{isc} is large) competes favourably with **230** to **231**, then the triplet state of the carbene is populated, and the carbene can add non-stereospecifically to the olefin to give **231** and **234**.[117]

Photolysis of diazoketones to form ketenes via the Wolff rearrangement is a well known useful synthetic reaction and it frequently provides a valuable method for making strained cyclic systems by ring contraction.[117] The reaction seemed to fail in cases where contraction would result in excessively strained systems such as **227**. The rearrangement competes with direct carbene addition to the double bond forming cyclopropanes. However if rearrangement is

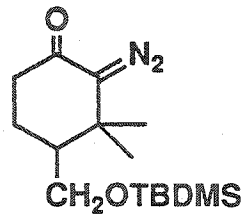
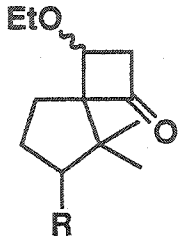
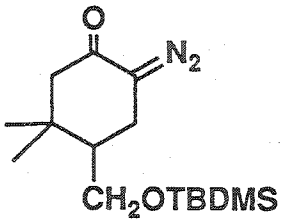
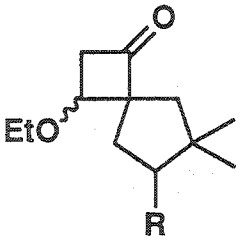
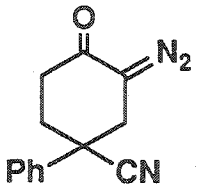
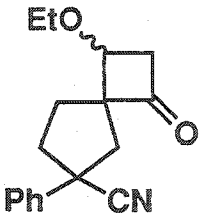
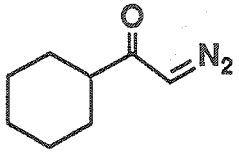
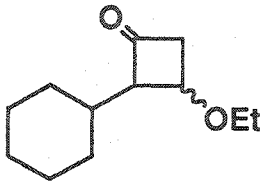
possible, it may predominate, frequently being the preferred pathway.



Scheme 36

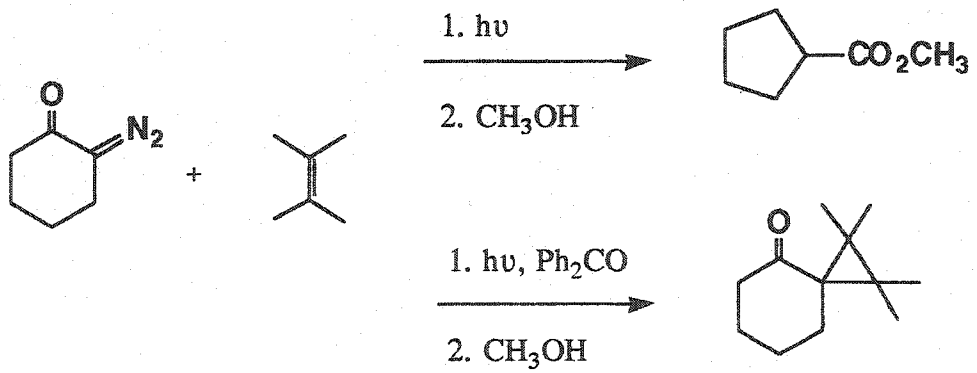
Thus, attempts to effect cyclopropanation of the diazoketone under photochemical conditions in the presence of ethyl vinyl ether should provide the ketene and posibly the oxetane observed previously. Instead high yields of the cyclobutanones as a mixture of isomers (Table VII) via the Wolff rearrangement were obtained. In a typical experiment, a degassed solution of the diazoketone in ethyl

Table VII: Photochemical decomposition of Diazoketones.

Entry	Substrate	Product	Yield (%)
1	 210	 236	88
2	 211	 237	88
3	 213	 238	60
4	 215	 239	80

vinyl ether was irradiated for about 3 h followed by chromatography to afford the cyclobutanones which were readily identified by the characteristic IR signal at 1780 cm^{-1} attributed to the ketone. General structural assignments were based on ^1H NMR spectra and the low and high resolution mass spectral data.

Several reports indicate that the Wolff rearrangement results only from the singlet carbene[121a,121b] while the triplet gives addition or hydrogen abstraction products.[121b,121d,122] Jones and Ando[121b] have shown that Wolff rearrangement is suppressed when the triplet carbene is generated by energy transfer via a triplet sensitizer. Thus Jones and Sohn[121c] showed excellent suppression of rearranged and insertion products compared to cyclopropanation (Scheme 37) when the reaction was carried in the presence and in the absence of triplet sensitizer. According to Yamamoto[122] an equilibrium existed between the triplet and singlet carbene states in the presence of a sensitizer thus to ensure triplet state reaction, a large excess of benzophenone was required.



Scheme 37

In accordance with the above reports, the photochemical reactions were repeated in the presence of 10 equivalents of benzophenone. For the same substrate, the reaction required twice as much time for complete decomposition (TLC check and/or reaction mixture changes color from yellow to colorless). The crude ^{1}H NMR spectra and TLC analysis indicated that the product was composed of an equal amount of the cyclobutanone and oxetane products previously isolated and characterized. Product isolation was made impossible by the presence of a large amount of benzophenone used to ensure the triplet carbene reaction.

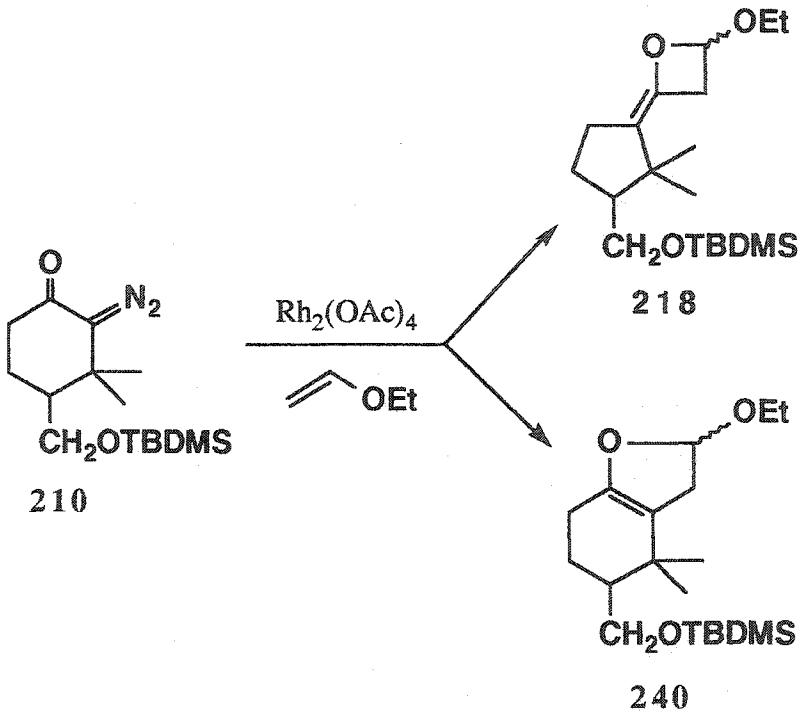
The triplet carbene must have been formed predominantly in the presence of the sensitizer although reaction may take place from both the triplet and the higher energy but nearby singlet state assuming an equilibrium exists between them. An equilibrium may occur if the triplet carbene is long lived. This may be supported by the longer reaction time required in the presence of the sensitizer and the nature of the products.

6.4.7 Possible mechanistic explanation for the formation of oxetanes

Based upon the NMR spectral data (^{1}H and ^{13}C) and also the mass spectral data, two possible structures may be proposed for the product of catalytic decomposition of the α-diazoketones (Equation 26).

Both compounds **218** and **240** have the same number of methine, methylene and methyl groups in the molecule thus the DEPT experiment could not distinguish one from the other. Due to the

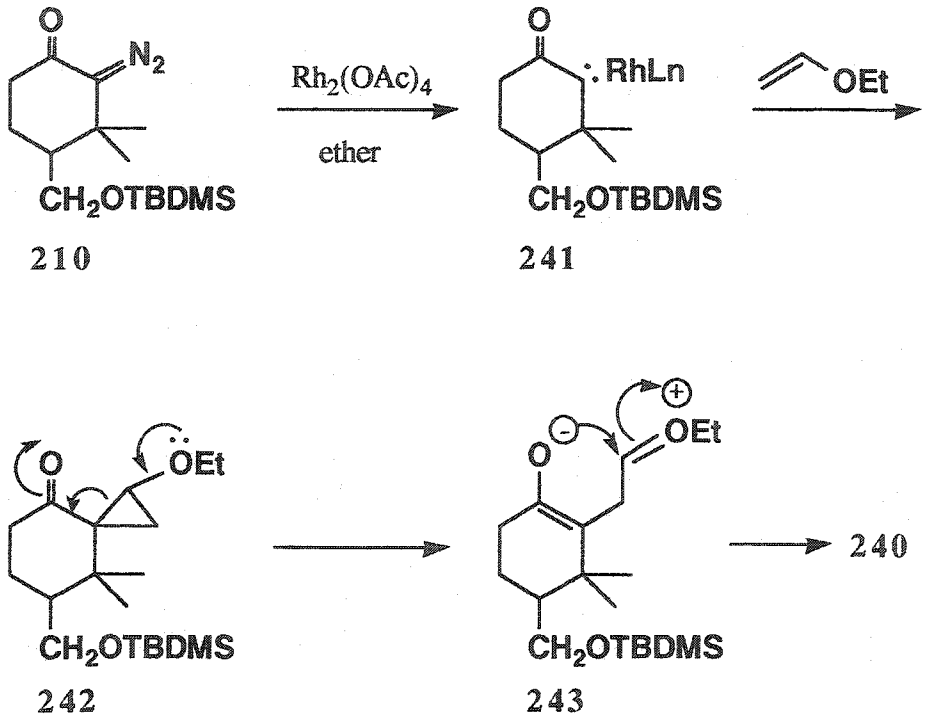
complicated nature of the ^1H NMR spectrum, use of COSY and HETCOR (C-H correlation NMR) were not helpful because the signals were too close to each other making the connections difficult to follow unambigiously. Compound **240** may arise via two possible mechanistic routes (Scheme 38 and Scheme 39) and the oxetane via a different route (Scheme 40).



Equation 26

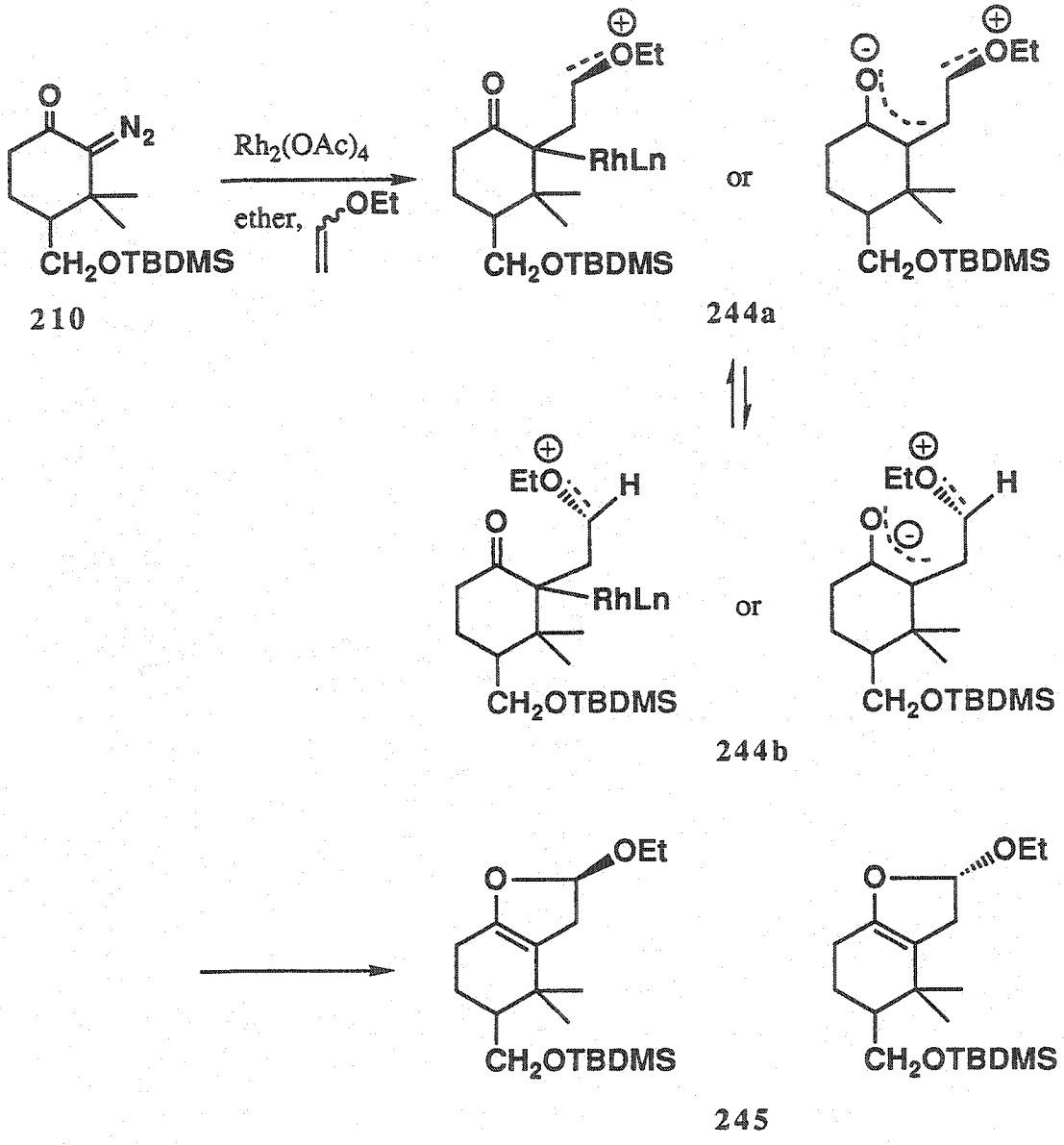
Available literature evidence indicated that although α-diazoketones are known to be useful cyclopropane precursors, a different reaction mode emerges when certain α-diazoketones (mainly diazopyruvates) are combined with enol ethers and dihydrofurans rather than cyclopropanes are isolated.[116] It has however been observed that with unactivated olefins *e.g.*, styrene,

indene, cyclohexene and cyclohexadiene, alkyl diazopyruvates behave like simple diazoketones and give cyclopropanes.[124] Wenkert[123] and Alonso[124a] have synthesized a number of natural products products containing a furan ring based on this carbenoid reaction in the presence of copper catalyst such as $Cu(acac)_2$.

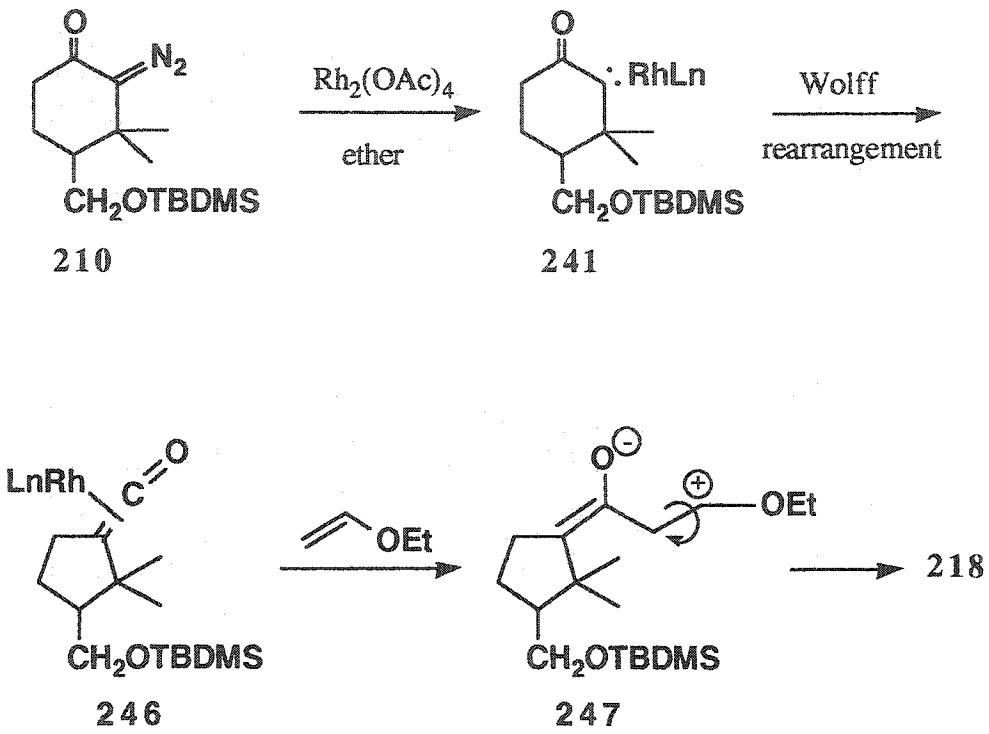


Scheme 38

Alonso and co-workers have proposed a mechanistic pathway for these reactions (Scheme 41). They suggested the dipolar intermediate **248a** as precursor to both dihydrofuran and acyclic products **251** however the role of the copper catalyst in **248a** has not been proven. Apparently 1,5-cyclization of **248a** must be easier than the 1,3-ring closure leading to cyclopropane **249**.


O
N2
Rh2(OAc)4
ether,
OEt
CH2OTBDMS
210
RhLn
or
244a
EtO
H
244b
245

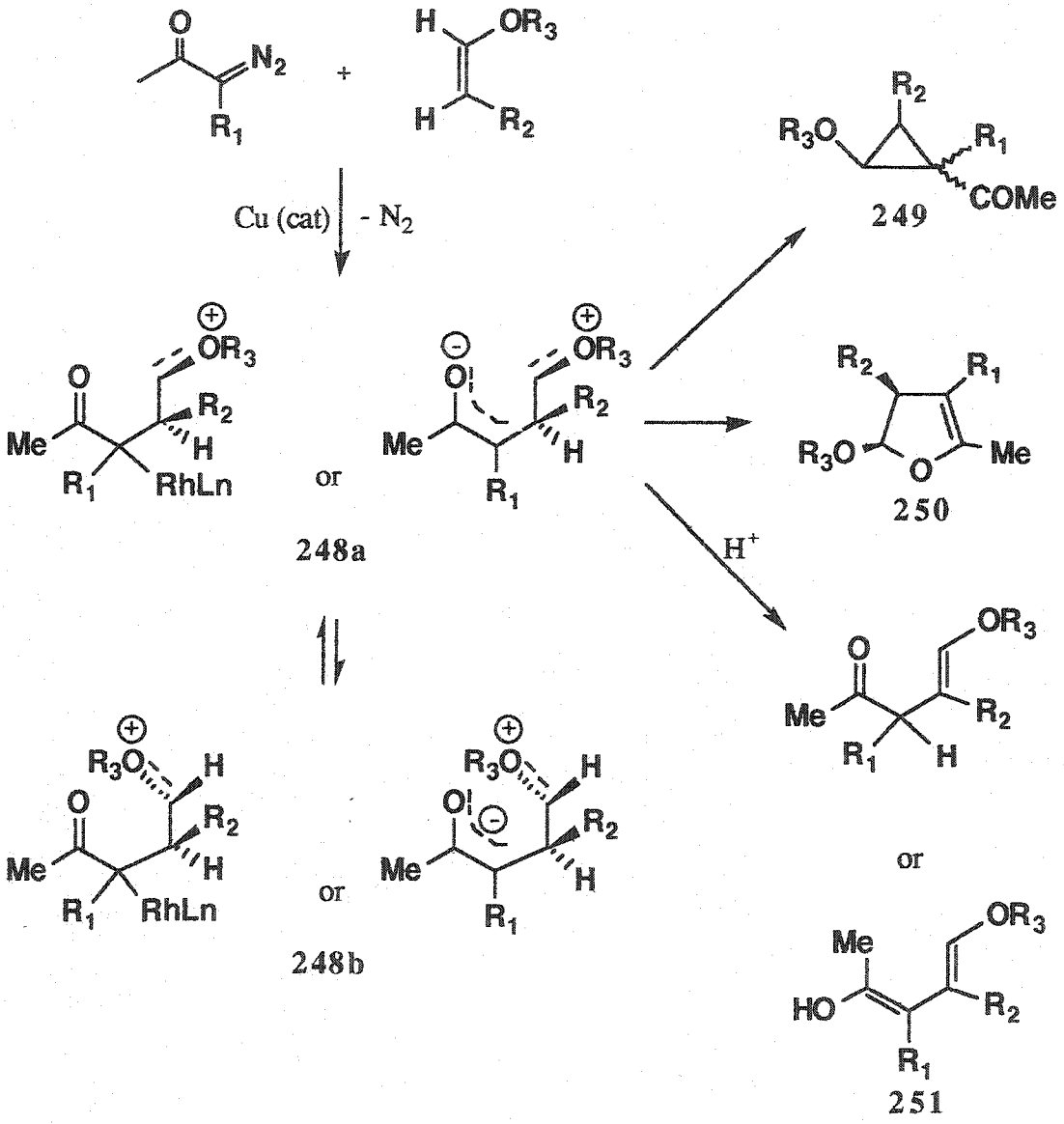
Scheme 39



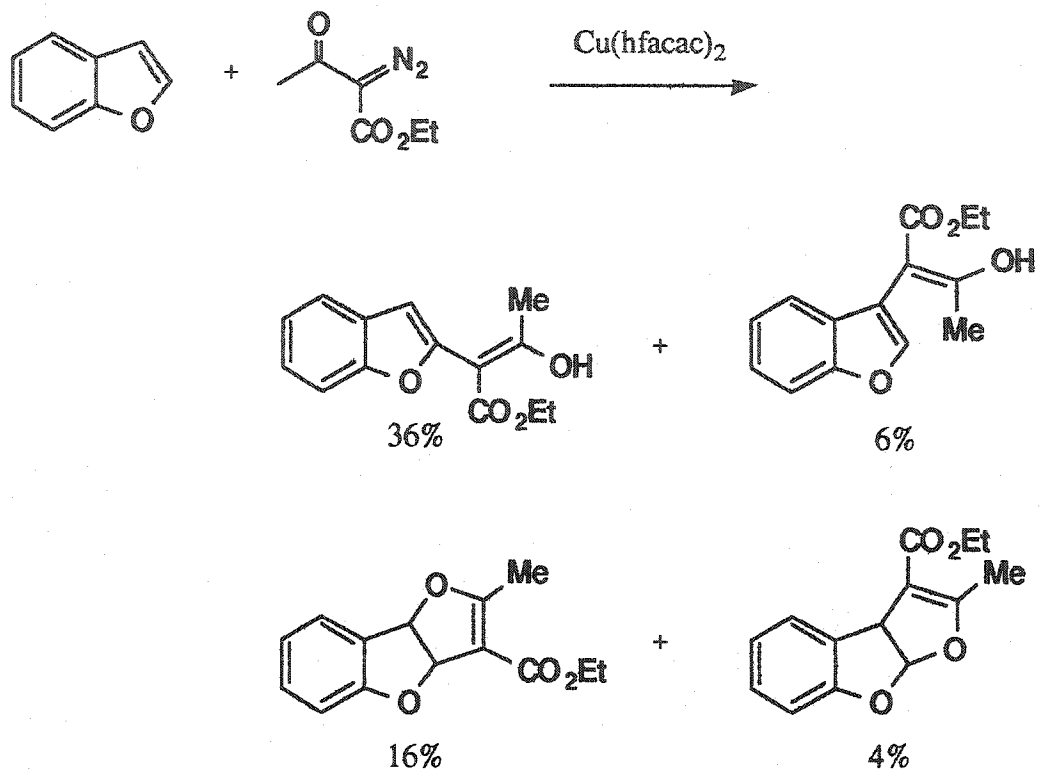
Scheme 40

The regioselectivity of the [3 + 2] cycloaddition reaction arises due to the presence of partial charges in the ketocarbenoid species and a corresponding polarization of the olefinic bond. The only exception to this occurred with benzofuran which according to Alonso[124] was in agreement with the behavior of the carbenoid derived from ethyl-2-diazo-3-oxobutyrate (Scheme 42). It is assumed that the 1,5-cyclization products are always formed stereospecifically as shown by the representative examples given in Scheme 43. It is therefore implied by stereospecific stepwise formation of the dihydrofuran that the ring closure of **248a** is distinctly faster than the carbon-carbon bond rotation about the

former enol ether double bond *i.e.*, the equilibration of 248a and 248b is very much slower than product formation from 248a.

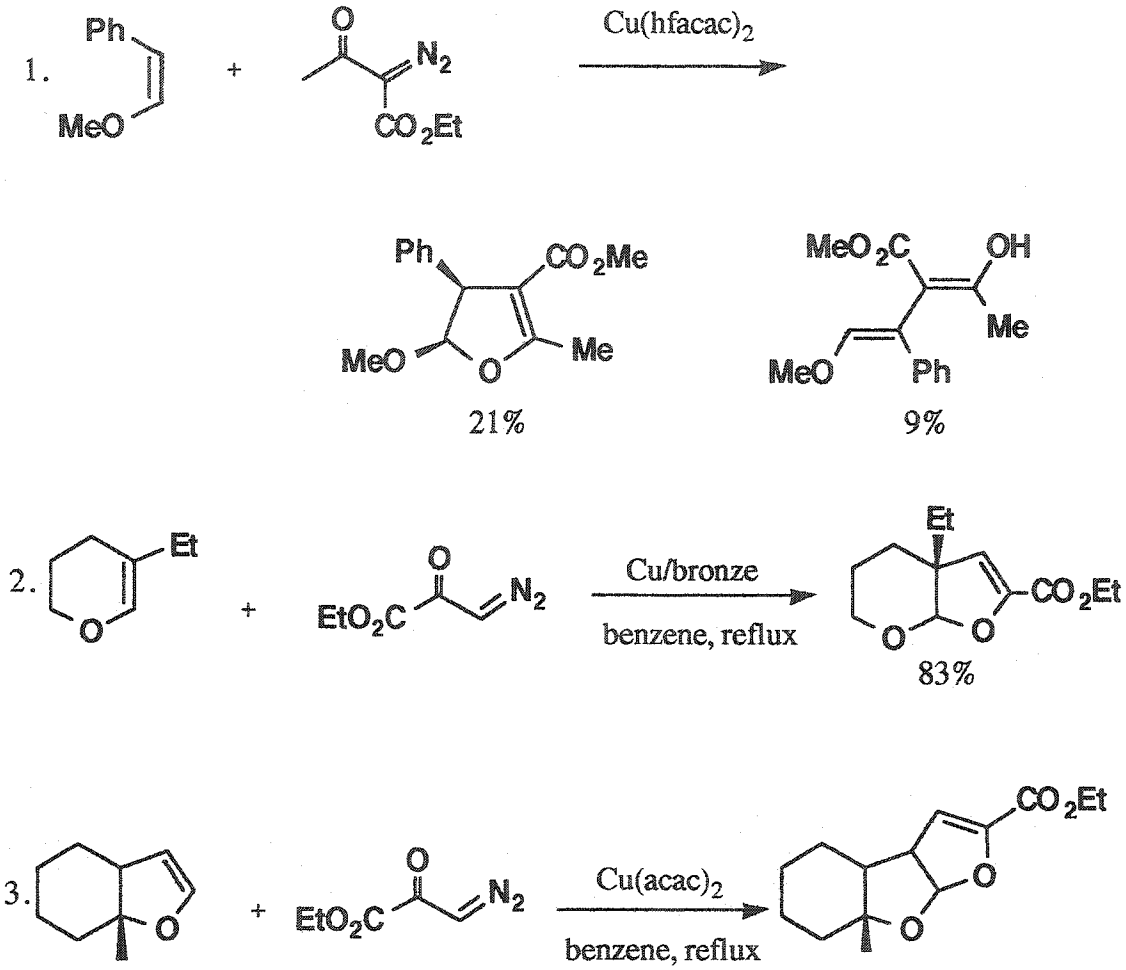


Scheme 41



Scheme 42

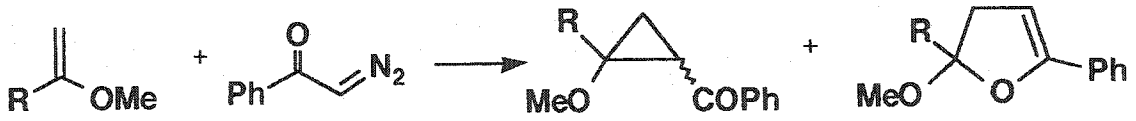
Other pathways leading to the dihydrofuran **240** are excluded with some certainty. Thermal or copper catalyzed ring expansion of a primary formed cyclopropane has been ruled out by control experiments with identical cyclopropanes which do not rearrange to dihydrofurans under authentic reaction conditions (heating with fluorobenzene with of without the copper catalyst). Also their pyrolysis at elevated temperature leads to stereoisomeric dihydrofurans in which the stereochemical information furnished by the olefin had been lost. Finally, it has been proven that the dihydrofurans do not result from isomerization of the β,γ-unsaturated carbonyl compounds **251** or their tautomers.



Scheme 43

Generally metal catalyzed decomposition of simple diazoketones in the presence of enol ethers, enol acetates and enol silyl ethers yield cyclopropanes in parallel with unactivated alkenes whereas dihydrofurans usually result from reaction with ketene acetals.[125] An interconnection between these alternatives exists since product formation seems to depend on the nucleophilicity of the enolate oxygen in **248a**. The more nucleophilic the oxygen the more favorable the 1,5- compared to 1,3- ring closure.

Thus the rhodium(II) acetate catalysed decomposition of ω-diazoacetophenone in the presence of ethyl vinyl ether produces mainly the cyclopropane and a small amount of dihydrofuran (Scheme 44). The products of these reactions were not interconvertible under the reaction conditions and the product ratio is neither affected by catalytic concentration nor reaction time.[119b] Both products arise from the same dipolar reaction intermediate (*e.g.*, **248a**). Changing the olefin from methyl vinyl ether to 2-methoxy propene or α-methoxystyrene cause an increase in the yield of the furan product.



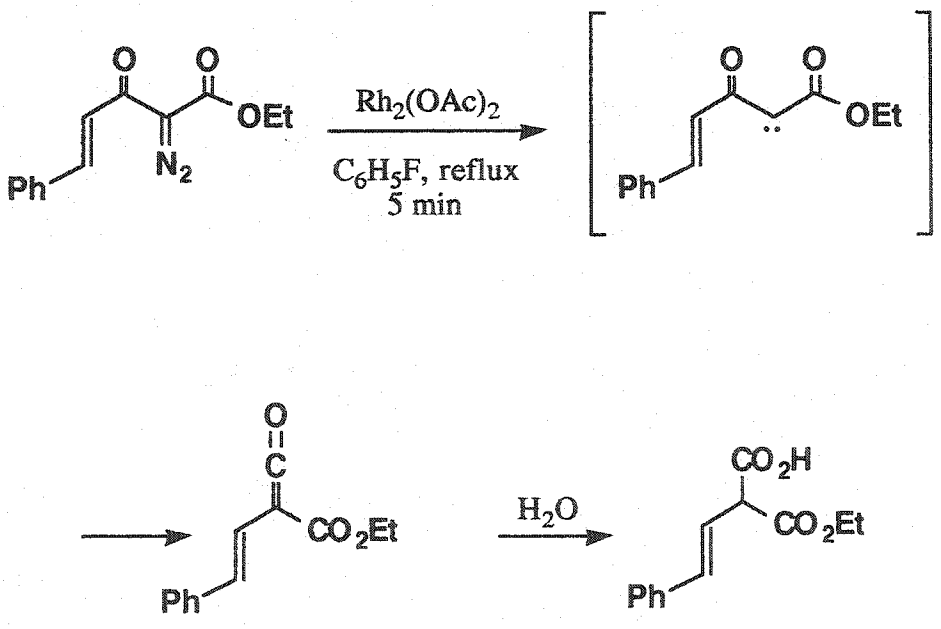
R = H	76%	6.6%
R = Ph	67%	29%
R = Me	-	32%

Scheme 44

Based on the above arguments, the mechanism shown in Scheme 38, requiring first the formation of a cyclopropane derivative followed by rearrangement can be ruled out (see also Scheme 48). On the other hand precedent for the formation of furans from diazoketones has been shown although it occurs to a very limited extent (as a minor product) and under special circumstances (*e.g.*, with ketene acetals) (*vide infra*) for simple α-diazoketones related to

210. Synthesis of dihydrofurans from simple α-diazoketones or α-diazoesters and an alkyl vinyl ether is not a preparative procedure.[116]

The reaction mechanism proposed in Scheme 40 required that the Wolff rearrangement occur under catalytic conditions followed by a [2+2] cycloaddition between the enol ether and the ketene carbonyl bond via a zwitterion intermediate **247**. As a result of the presumed complex formation between the carbene and metal catalyst in the metal catalyzed decomposition of diazoketones (*vide infra*) the Wolff rearrangement is usually suppressed and no longer occurs or becomes very difficult. However precedent exist for metal catalyzed Wolff rearrangements involving use of silver salts, copper salts and in one example platinum.[126] An example of a rhodium acetate catalyzed decomposition of an α-diazoketone resulting in a wolff rearrangement has been reported by Taylor[36] (Scheme 45).



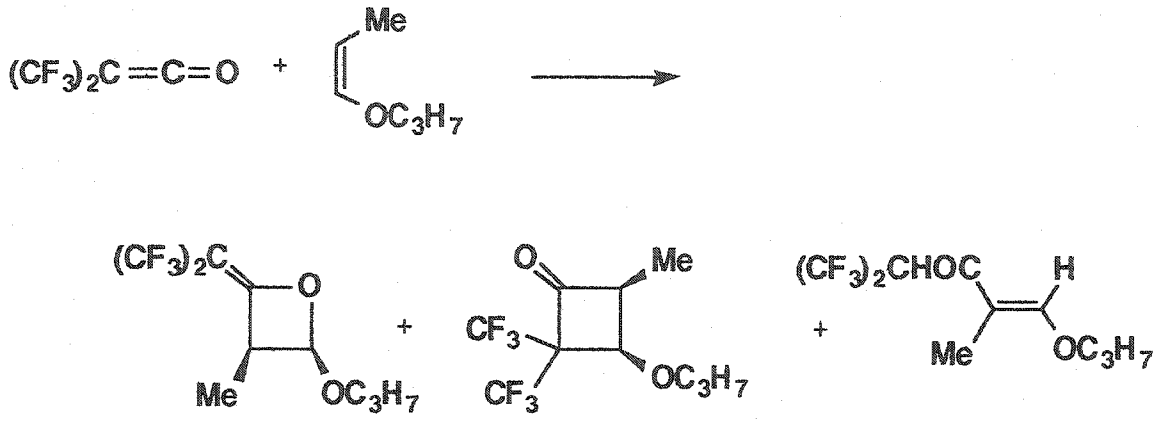
Scheme 45

Furthermore, metal catalyzed decomposition of β,γ-unsaturated diazoketones leading to γ,δ-unsaturated esters via the so called vinylogous Wolff rearrangement[127] is another example of a metal influenced Wolff rearrangement. Mechanistic studies established the existence of a β,γ-unsaturated ketene in the course of this reaction.

Ketenes normally form cyclobutanones with very reactive olefins as well as with simple alkenes[128] although there are examples of ketene dimerization leading to the formation of β-lactones.[129] According to Webster and co-workers,[129] with the exception of ketene itself, spontaneous dimerization of ketenes probably affords 1,3-cyclobutanones as major primary products. They proposed that the formation of β-lactone type dimers can be facilitated by the presence of a catalyst, and strong Lewis acids such as $AlCl_3$ and $ZnCl_2$. Until 1970 the only example of a 1,2-cycloaddition to a ketene carbonyl group to form an oxetane appeared to be with bis(trfluoromethyl)ketene scheme 46.[130]

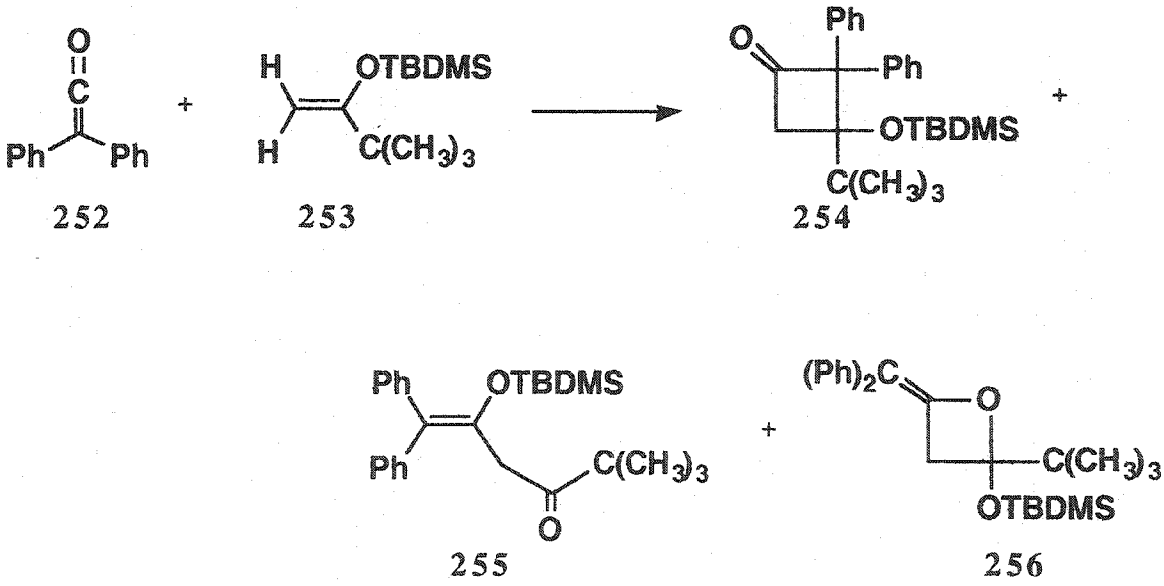
England and Krespan[130] demonstrated that [2+2] cycloaddition to the ketene carbonyl bond proceeded through dipolar intermediates of a finite lifetime. Martin and co-workers[131] have also reported an example of a ketene carbonyl reaction in a [2+4] cycloaddition to a diene, while diphenyl diazomethane has been shown to react with diphenyl ketene in what was referred to as 'the abnormal sense' to furnish methylene oxadiazole.[132]

The reaction of diethyl ketene and diphenyl ketene with various silyl enol ethers and the chemistry of some of the reaction products have been investigated by Reynolds and DeLoach[133] (Scheme 47 and 48).



Scheme 46

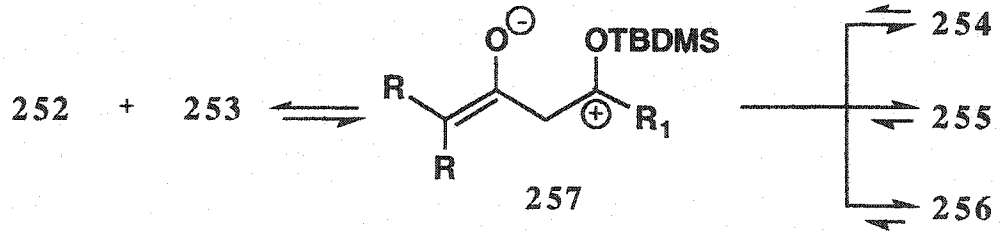
These reactions were studied with various R and R_1 groups. When R = $C(CH_3)_3$ and R_1 = Ph, only **255** and oxetane **256** were isolated although with most other R groups cyclobutanones were the major product and a very small amount of the unsaturated ketone **255**, without any oxetane formation (Scheme 47).



Scheme 47

They proposed that the ketene **253** reacts with silyl enol ether **252** via a stepwise mechanism to afford an intermediate, probably a zwitterion **257** which may undergo four possible processes namely reversal, rearrangement, and the two modes of ring closure, depending upon steric and electronic factors (Scheme 48). Other possible routes for the generation of **254**, **255** and **256** were not ruled out, however it was noted that support for the proposed mechanism could be achieved if the reaction intermediate **257** could be generated by an independent route preferably via the expulsion of molecular nitrogen from a suitably designed diazo compound.

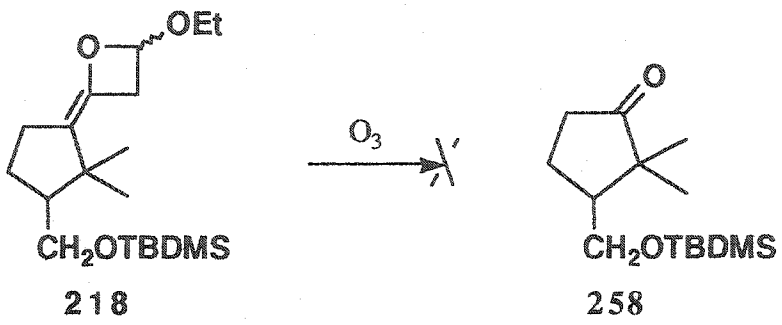
The above discussions indicate that Scheme 40 is highly probable. The exact role of the rhodium acetate is not known but it may complex to the ketene double bond and facilitate the formation of the zwitterion intermediate **247**.



Scheme 48

6.4.8 Reactions of oxetane 218

Ozonolysis of **218** should provide unambiguous proof of its structure since the cyclopentanone could be isolated and identified (Equation 27). Ozonolysis however did not furnish any identifiable products.

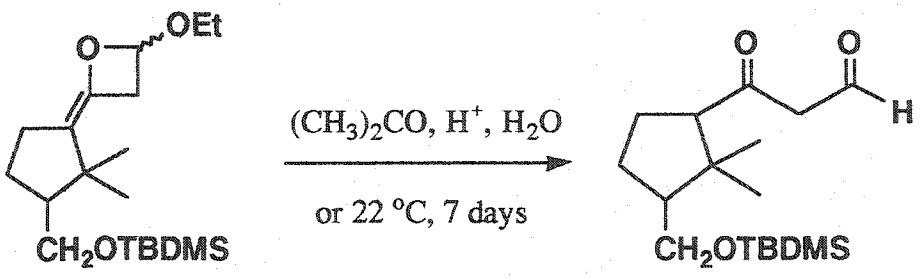


218 **258**

Equation 27

Reynolds and DeLoach[133] had shown that formation of **256** occured via an equilibrium reaction upon thermolysis of **256** to furnish **252**, **253** and **255**. Thermolysis of **218** in dry toluene containing molecular sieves in a sealed tube at 100 °C for 2 days did not furnish any new products.

When **218** was stirred in aqueous acetone containing catalytic amounts of acetic acid it was converted to the keto aldehyde **259** (Equation 28). When **218** was left in wet ether or benzene at room temperature for 7 days **259** was obtained.



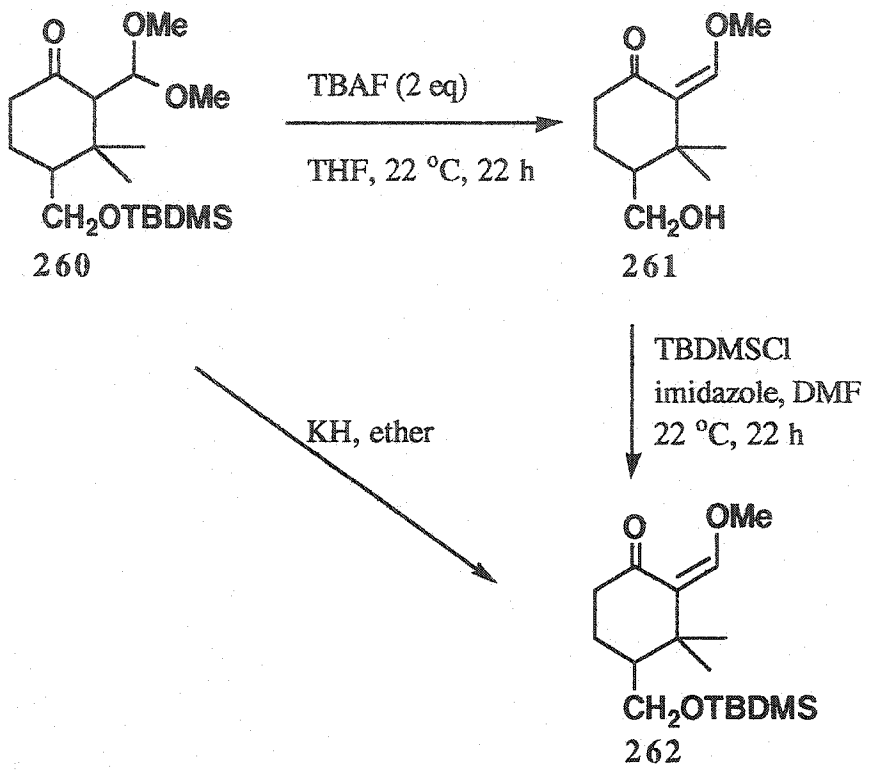
218 **259**

Equation 28

Furthermore, a minor product that was found in some of the rhodium acetate catalyzed decomposition reactions was shown by crude ^1H NMR spectra and TLC analysis to be the same keto-aldehyde (*e.g.*, **259**) obtained after hydrolysis. This compound could only arise from oxetane **218** and lends support to a dipolar intermediate such as **247**. The structure of **259** was determined from the ^1H and ^{13}C NMR spectral data and the high and low resolution mass spectral data.

6.5 Preparation of hexahydrobenzofuran (263)

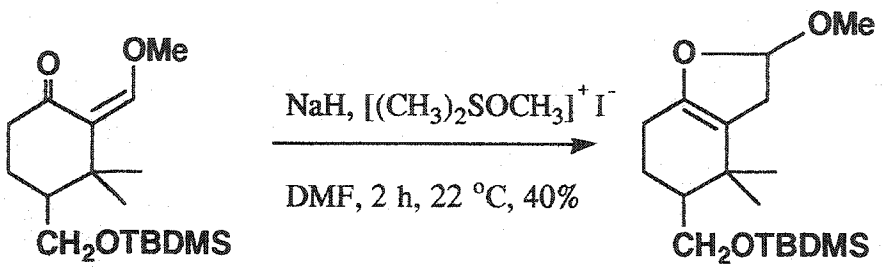
Attempted deprotection of the *tert*-butyldimethylsilyl ether **260** to the alcohol with 2 equivalents of tetrabutylammonium fluoride in THF at room temperature gave the unexpected alcohol **261** after workup and chromatography in quantitative yield (Equation 29). The fluoride ion acted as a base causing the formation of an enolate which eventually eliminates one of the methoxy groups leading to the formation of **261**. The alcohol **261** was identified by its ^1H and ^{13}C NMR, IR and the high and low resolution mass spectral data. The IR displayed strong bands at 3398 cm^{-1} and 1666 cm^{-1} that were attributed to the alcohol and the α,β-unsaturated ketone respectively. The ^1H NMR spectrum in acetone-d_6 indicated a singlet at 7.2 ppm due to the vinyl proton and the ^{13}C NMR spectrum showed two olefinic signals at 161 ppm and 123 ppm indicating an olefin conjugated to a ketone. Reprotection of **261** according to Corey's procedure[99] afforded **262** in quantitative yield. Base catalyzed (NaH, or NaOMe) reaction of **260** in ether at room temperature for 3 h also afforded **262** in quantitative yield.



Equation 29

A solution of dimethyloxosulfonium methylide was prepared by the addition of trimethyloxosulfonium iodide (prepared according to the procedure of Corey and Chaykovsky[80] to a suspension of sodium hydride in THF or DMF and **262** dissolved in THF or DMF added. Workup after 2 h followed by chromatography gave the labile hexahydrobenzofuran **263** as the only isolatable product (Equation 30) in about 40% yield. Two other products were indicated by TLC but they were extremely unstable and could not be isolated. One of the TLC spots is likely to be **265** because the intensity decreases while that due to **263** increases after silica gel column chromatography.

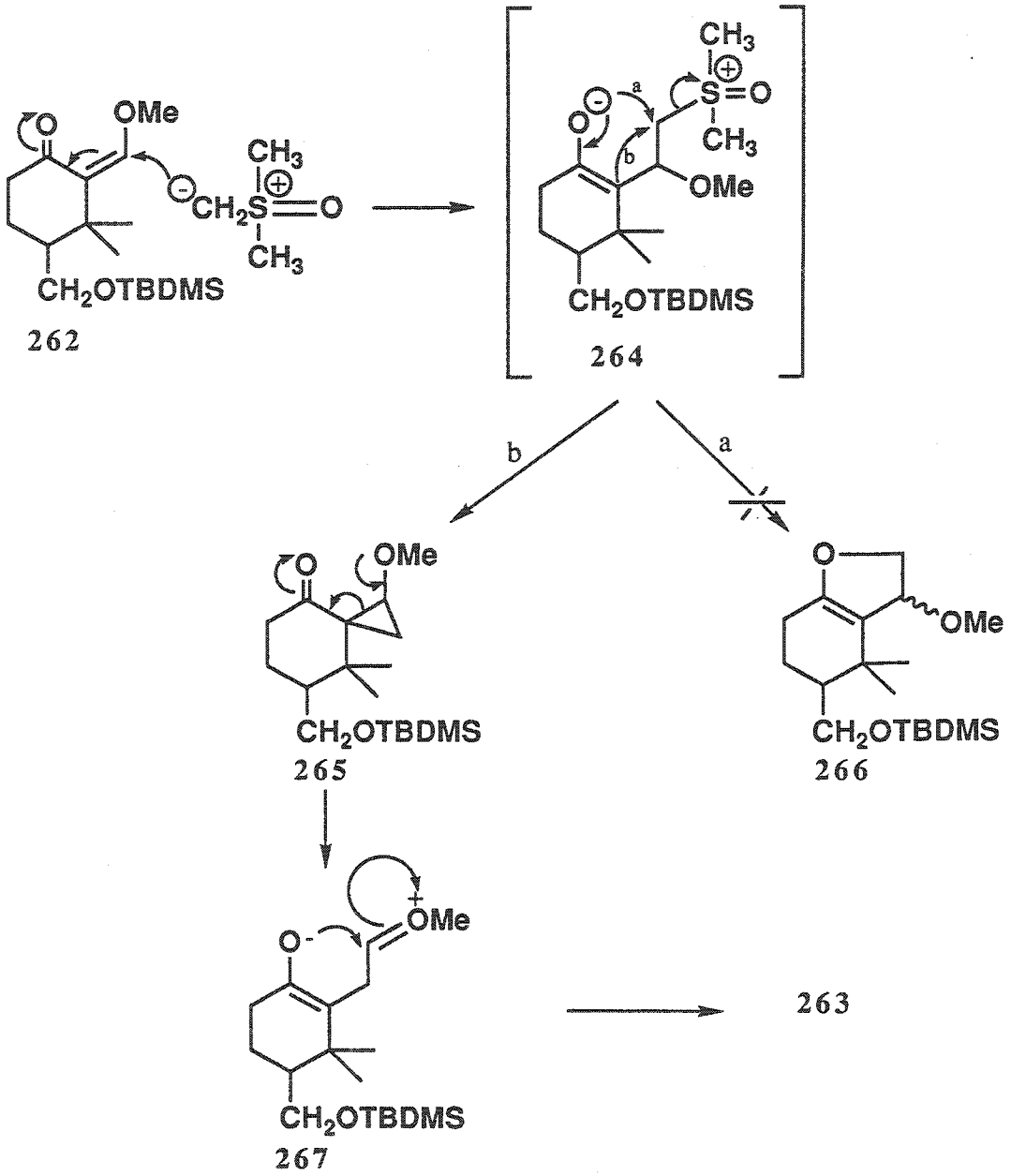
Hexahydrobenzofuran **263** was stereochemically pure although the exact stereochemistry was not determined. The methine proton at C_2 in the ^1H NMR spectrum gave rise to a doublet of doublets, J = 2.5 Hz, 7.5 Hz at 5.3 ppm. The ^{13}C NMR spectrum showed two olefinic signals at 148 ppm and 113 ppm which are assigned to C_8 and C_9 respectively. A signal at 105.6 ppm was assigned to C_2 which lies between two oxygen atoms in the five-membered ring. The high resolution mass spectrum indicated that hexahydrobenzofuran **263** has the molecular formula $C_{18}H_{34}O_3$.



262 **263**

Equation 30

A possible mechanistic origin of **263** is proposed in Scheme 49. Addition of dimethyloxosulfonium methylide in Michael fashion to **262** generated the dipolar intermediate **264** which may undergo cycloaddition according to two possible pathways, a and b. Path a, would result in hexahydrobenzofuran **266** (which does not form), while path b, gave the spiro cyclopropane adduct **265** which rearranged through dipolar intermediate **267** to hexahydrofuran **263**.


OMe
CH3
CH2S=O
CH3
CH2OTBDMS
262
CH3
S=O
CH3
OMe
CH2OTBDMS
264
a
b
b
a
OMe
CH2OTBDMS
265
O
OMe
CH2OTBDMS
266
OMe
O
CH2OTBDMS
267
263

Scheme 49

6.6 Comparison of some representative ^{1}H and ^{13}C NMR spectral data for 218 and 263

There is a small shift towards low field for the gem dimethyl signal of **263** at 0.86 ppm and 1.03 ppm compared to that of **218** which appears at 0.85 ppm and 0.95 ppm, however this shift is quite small and could be due to other factors. The ^{13}C NMR spectra on the other hand, shows a big difference in the position of the olefinic signals. In hexahydrobenzofuran **263** the C_2, C_8 and C_9 signals are at 105.6 ppm, 148.3 ppm and 113 ppm respectively while the corresponding carbon atoms in **218**, $C_{3'}$, $C_{1'}$ (in the oxetane ring) and C_1 (five-membered ring) fell at 102.4 ppm, 104.6 ppm and 148 ppm respectively. In both **218** and **263** the chemical shifts of the methine carbon between the two oxygen atoms *i.e.*, $C_{3'}$ and C_2 respectively are similar in value, having a difference of only 3 ppm.

The olefinic carbons bearing oxygen (=C-O) are identical at 148 ppm however there is a difference of 9 ppm between C_9 in **263** and C_1 in **218**. This difference is too big for the same hexahydrobenzofuran differing only in the ethoxy and methoxy substituents. Also unlike oxetane **218**, hexahydrobenzofuran **263** required more drastic conditions (about 50 ^{o}C, and longer reaction time) to hydrolyze. Furthermore the ^{1}H NMR spectrum obtained for this hydrolysis product was not identical to that of the hydrolysis product of **218**. Mechanistic studies have indicated (*vide infra*) that when dipolar intermediates are formed in the catalyzed decomposition of diazoketones (Scheme 41) cycloaddition to form a dihydrofuran is faster than rotation of the former enol ether double bond and that these additions are stereoselective.

Oxetane **218** is a stereoisomeric mixture and may arise via a different mechanism. Moreover Maas[116] points out that for simple α-diazoketones[125c] and α-diazoesters[125d] catalytic decomposition in the presence of enol ethers and enol silyl ethers results in cyclopropanes just as is the case for unactivated ketones. Further work is required for the unambiguous stereochemical assignment of **218**.

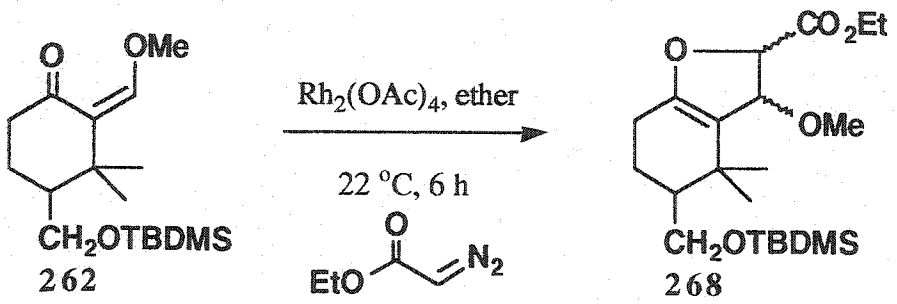
6.7 Attempt at cyclopropanation of 262

Diazocarbonyl compounds usually undergo [3+2] cycloaddition to electron poor alkenes under thermal conditions to form pyrazolines. Palladium(II) acetate has however been shown to be an effective catalyst for cyclopropanation with ethyl diazoacetate and diazomethane.[115b,134,135] According to Vorbruggen,[115b] these reagents add stereospecifically cis to α,α- or α,β-disubstituted α,β-unsaturated ketones or esters in excellent yield but fail to react with trisubstituted unsaturated α,β-unsaturated carbonyl compounds.

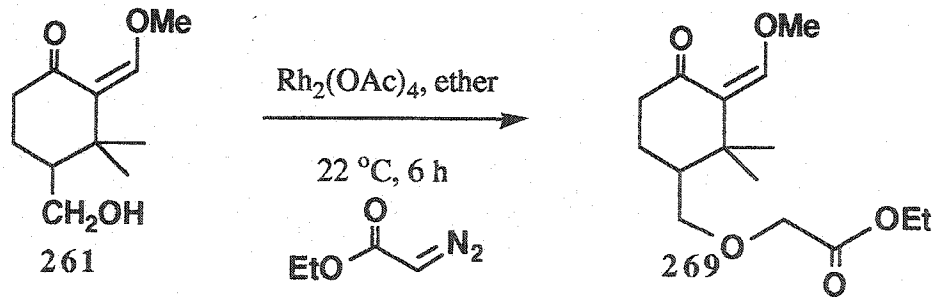
Not surprisingly, dry diazomethane failed to add to **262** in either palladium(II) acetate or rhodium(II) acetate. Ethyl diazoacetate however reacted with **262** in the presence of rhodium(II) acetate catalyst at room temperature to furnish after workup and chromatography, a 45% yield of hexahydrobenzofuran **268** (Equation 31). Structural assignments for **268** were based on the ^{1}H and ^{13}C NMR and the DEPT spectral data.

Hexahydrobenzofuran **268** was a mixture of isomers and showed the C_2 methine proton as a characteristic multiplet at 4.7 ppm (this shift is usually greater than 5 ppm when it occurs between two oxygen atoms as in **263**). The C_3 methine proton appears as a

multiplet at 4.5 ppm since it is allylic and C_3 bears the methoxy substituent. Since **268** was an isomeric mixture, there were more signals than expected for the pure compound in the ^{13}C NMR spectrum however the presence of two olefinic carbon peaks was clearly indicated. The DEPT experiment showed that C_2 and C_3 were methine carbons. The mass spectral data (EI) was consistent with structure **268** showing loss of -OMe (367, 3%), $-C(CH_3)_3$ (341, 27%), $-CO_2Et$ (325, 9%), and the high resolution mass spectra data confirmed that M^+ - $(CH_3)_3C$- was $C_{17}H_{29}O_5Si$.

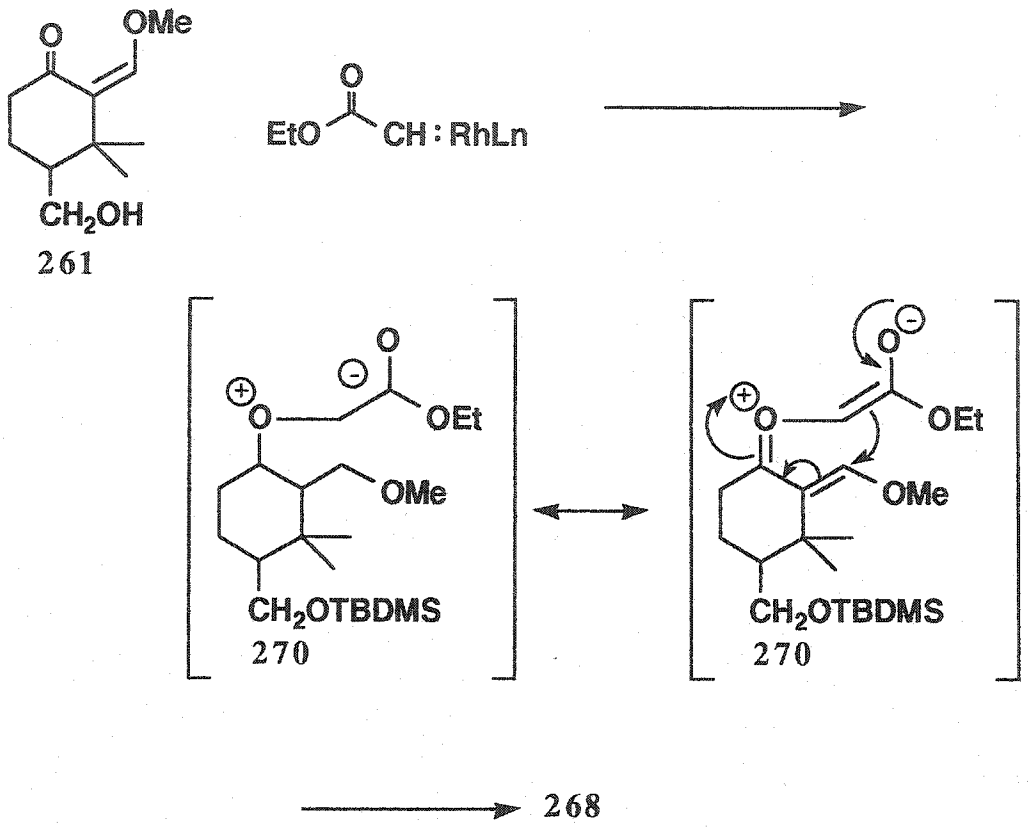


Equation 31



Equation 32

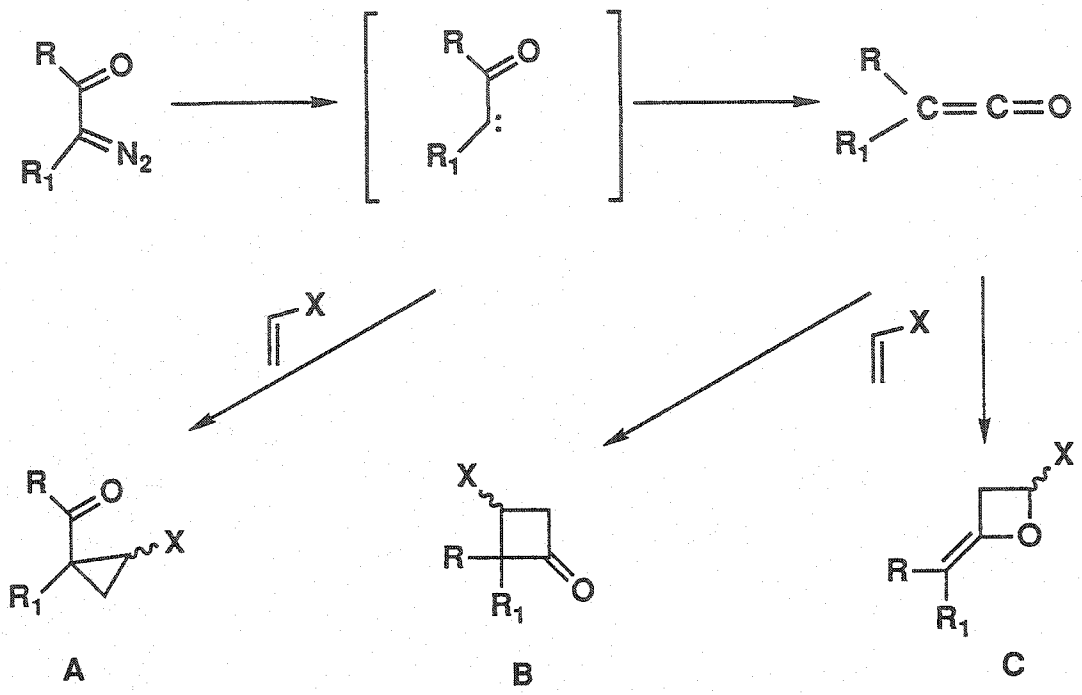
A possible mechanistic explanation of the formation of **268** via ylide **270** is shown in Scheme 50. Examples of such ylides have been detected in recent years.[136]



Scheme 50

Attempted cyclopropanation of the unsaturated alcohol **261** with ethyl diazoacetate and rhodium(II) acetate resulted in insertion into the alcohol O-H bond forming **269** (Equation 32) in 80% yield.

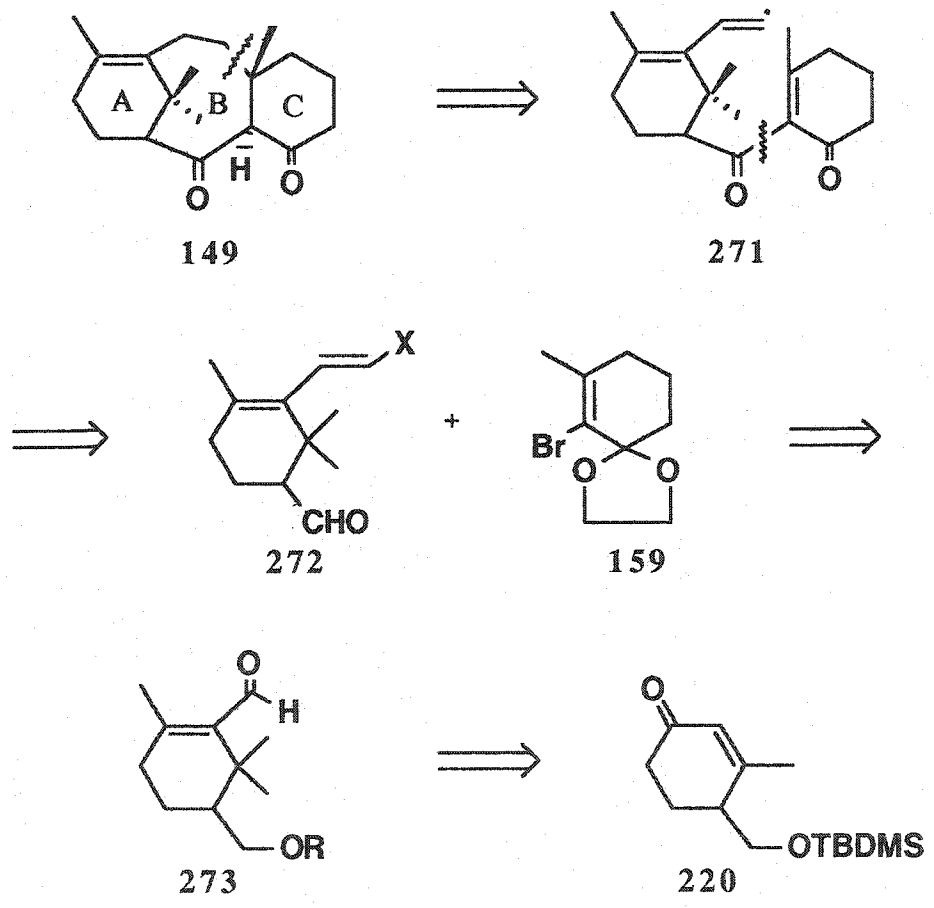
The results of the α-diazoketone reactions are summarized in Scheme 51 below.



Scheme 51

7 Taxol skeleton by direct vinyl radical cyclization

It is evident from the aforementioned discussions that the preparation of cyclopropyl carbinyl precursor **161** was far more challenging than expected. Consequently a direct radical cyclization route to the taxol skeleton was envisaged using some of the same precursors prepared for the previous approach according to the disconnections shown below (Scheme 52).

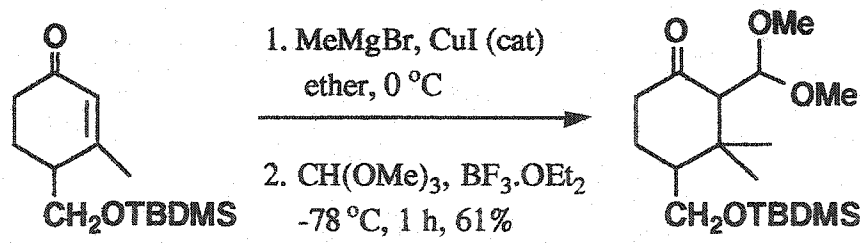


Scheme 52

The advantages offered by this approach are: a) it does not differ very much from Scheme 20, thus in principle with very little modification new precursors could be prepared in a relatively short time and b) connection of the A and C rings would result after a few steps in the key radical precursor to the taxol skeleton and allow a quick test of this model as a possible route to taxanes.

7.1 Preparation of ring A models (275, 276, 277 and 280)

tert-Butyldimethylsilyloxy protected α,β-unsaturated cyclohexenone **202** was chosen as the starting material because introduction of the C_1 methyl in **272** could be achieved without the problems encountered in the previous attempt to prepare tertiary alcohol **171** (Equation 3). Enone **202** was converted via the cuprate reaction to the enolate (*vide infra*) and trapped at -78 °C with trimethyl orthoformate in the presence of boron trifluoride etherate to afford a 61% yield of the acetal **260** (Equation 33).



202 **260**

Equation 33

The IR spectrum showed the saturated ketone functionality at 1720 cm^{-1}. The ^1H NMR spectrum showed two characteristic three

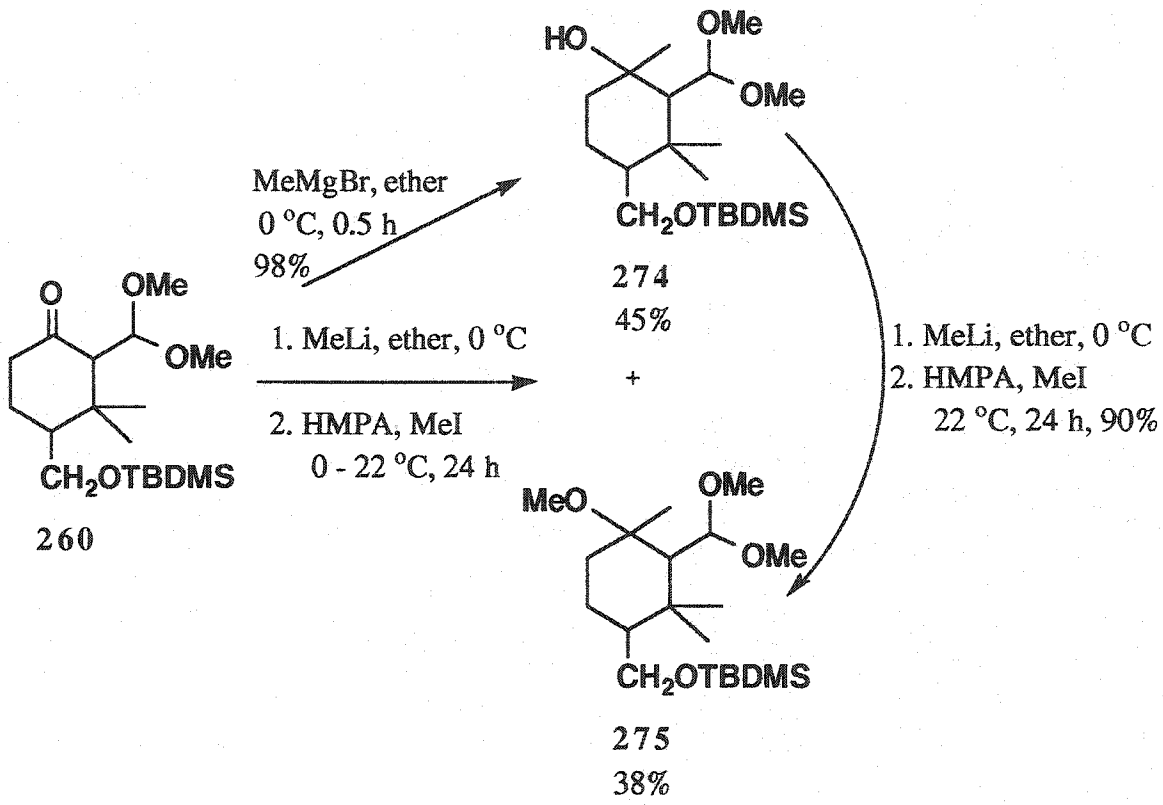
proton singlets at 3.27 ppm and 3.29 ppm which were assigned to the two acetal methoxy groups and a one proton doublet at 4.7 ppm with J = 7 Hz due to the methine proton attached to C_2. The mass spectrum (EI) does not show the molecular ion but instead the (M^+ - CH_3) and (M^+ - $(CH_3)_3C$-) peaks which are all consistent with the structure assigned to **260**.

Addition of methylmagnesium bromide to a solution of **260** in ether at 0 °C for 30 min gave a quantitative yield of tertiary alcohol **274**. Attempts to effect acid catalyzed dehydration of **274** to **276** gave a mixture of alkenes in addition to partial removal of the *tert*-butyldimethylsilyl group. Unpublished results of the ongoing research in our group directed towards the total synthesis of taxol have shown that hydroxyl elimination from **274** to **276** is best accomplished by first converting the tertiary alcohol to a methyl ether. Thus the required compound **275** was made either directly from **260** in one step or in two steps via tertiary alcohol **274** (Equation 34).

The one-step procedure was accomplished by adding methyl lithium to an ether solution of **260** at 0 °C followed by the addition of 2 equivalents of HMPA and then MeI. Workup followed by chromatography furnished **275** and **274** in 38% and 45% yield respectively. The two-step procedure afford a quantitative yield for the first step and about 90% yield for the second step. This procedure was therefore superior to the first and less problems were encountered during product isolation.

The IR spectra of tertiary alcohol **274** showed a strong absorption band in the O-H stretching region at 3550 cm^{-1}. The

newly introduced methyl group resonated at 1.3 ppm as a singlet in the ^1H NMR spectrum. All of the spectral data obtained were consistent with the assigned structure. The IR spectrum of **275** did not show any O-H stretching band and the ^1H NMR spectrum indicated the presence of three methoxy singlets at 3.10 ppm, 3.31 ppm and 3.35 ppm due to the methoxy substituent at C_1 and the two acetal methoxy groups respectively.

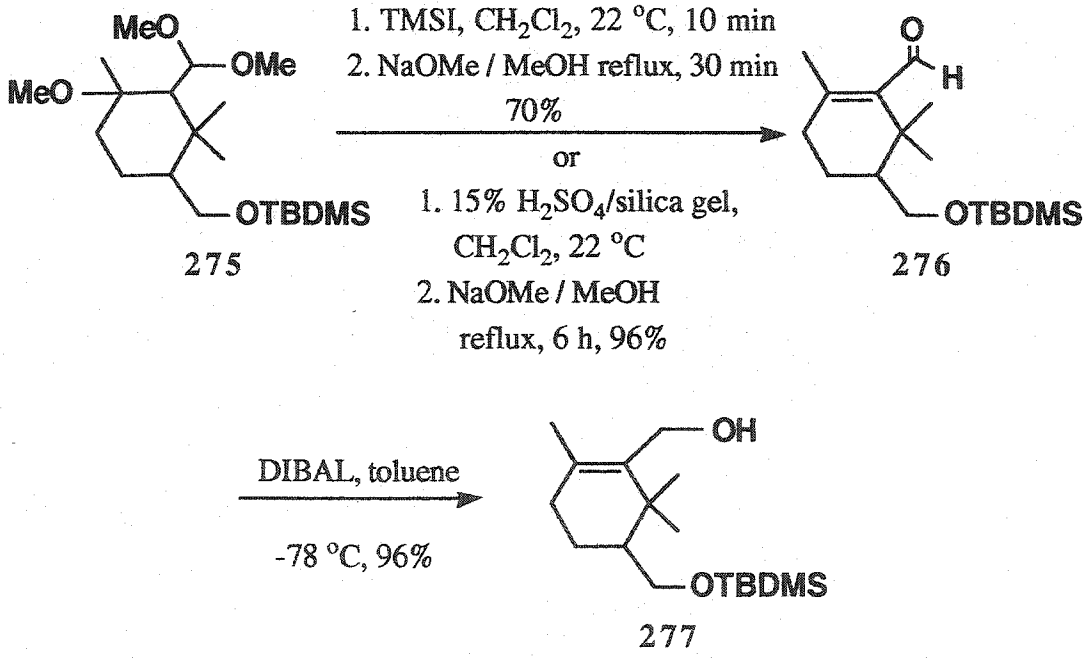


Equation 34

α,β-Unsaturated aldehyde **276** was prepared (Equation 35) by the addition of sodium iodide followed by trimethylsilyl chloride to a solution of **275** in dichloromethane with propylene gas bubbling through for 5 min at room temperature according to the procedure of

Jung and co-workers.[137] After workup the crude product was refluxed for 30 min in a methanol / sodium methoxide solution to afford a 70% yield after chromatography. Unfortunately the yield of **276** obtained by this procedure was erratic and a different two step approach was developed.

First the dimethoxy acetal was deprotected by stirring **275** in a suspension of silica gel in dichloromethane containing a catalytic amount of aqueous 15% sulfuric acid[138] to afford a quantitative yield (determined by the NMR spectra of the crude product) of the intermediate aldehyde. Sodium methoxide was then added to a solution of the crude aldehyde in methanol and refluxed for 8 h to furnish **276** in 96% yield from **275**.



Equation 35

The IR spectrum showed a strong carbonyl C=O stretching band at 1698 cm^{-1} which was due to the α,β-unsaturated aldehyde. The

aldehyde signal appeared in the ^1H NMR spectrum at 10.6 ppm as a singlet. The allylic methylene protons displayed multiplets at 2.1 to 2.2 ppm. No methoxy signals were detected. The ^{13}C NMR spectrum indicated the presence of the conjugated aldehyde which appears at 192 ppm and two olefinic signals at 156 ppm and 140 ppm. The fragmentation pattern indicated by the mass spectral data (EI) was consistent with the assigned structure. Finally high resolution mass spectral (EI) data confirmed the molecular formula of **176** - $(CH_3)_3C$- as $C_{13}H_{23}O_2Si$.

α,β-Unsaturated aldehyde **276** underwent diisobutyl aluminium hydride reduction (Equation 35) at -78 °C to furnish the allylic alcohol **277** in quantitative yield. The IR spectrum showed the alcohol stretching band at 3368 cm^{-1}. No carbonyl bands were detected in the IR spectrum. The ^1H and ^{13}C NMR spectral data as well as the both low and high resolution mass spectral (EI) data were consistent with the structure assigned to allylic alcohol **277**.

The vinyl iodide **278** was prepared by a dropwise addition of a solution of **276** and iodoform in THF to a suspension of anhydrous chromium(II) chloride in THF at 0 °C and warmed to room temperature for 2 h to afford **278** in 40% yield after workup and chromatography[139] (Scheme 53). Yields of this reaction were as low as 20% when the reaction was scaled up (*i.e.*, greater than 180 mg of the starting aldehyde **276**). Product isolation was particularly difficult because **278** and iodoform had identical R_f's in various solvent systems and the iodoform which was present in excess tailed extensively on the column.

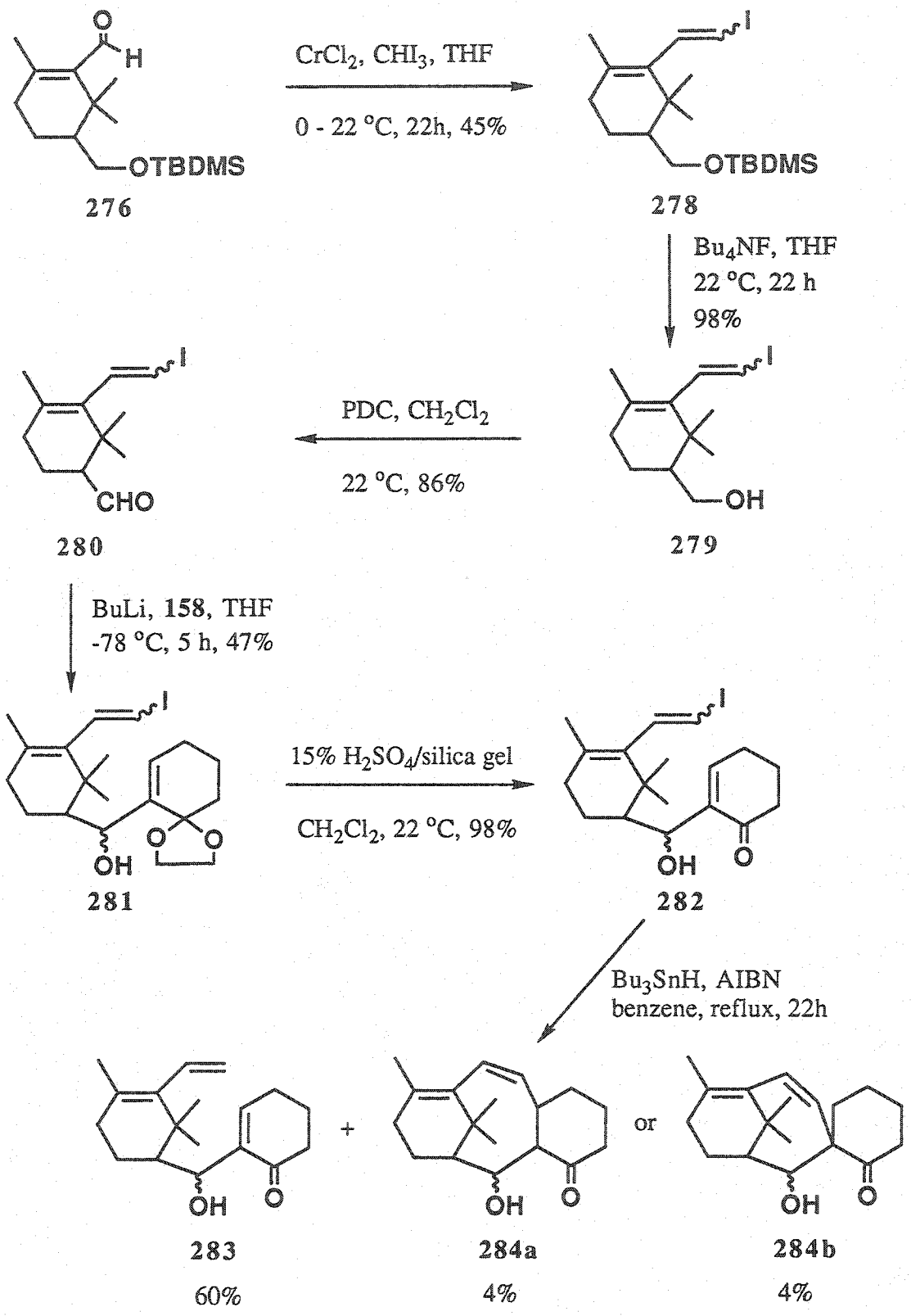
Thus although TLC check after workup indicated about 50% **278**, and 50% **276**, the actual yield of product isolated after column chromatography was very low. Also the aldehyde that did not undergo reaction decomposed and could not be isolated and recycled. Evans and Black[140] prepared a vinyl iodide by the above reaction using a 6:1 ratio of dioxane / THF as the solvent to obtain a 90% yield however using this solvent system did not cause any dramatic improvement in the yield of **278**. All attempts to prepare the vinyl bromide or vinyl gem dibromide by various procedures[141-148] were unsuccessful or gave very low yields although all these methods worked on a model aldehyde, 1,2,5,6-tetrahydrobenzaldehyde. For example dibromoalcohol **278b** (see experimental section) was prepared from **276** according to the procedure of Williams[145] and Tugushi[146] in only 25% yield. The aldehyde functionality may be severly hindered by the gem dimethyl substituent at C_3 in **276** thus preventing attack by the bulky Wittig reagents.

The ^1H NMR spectrum of **278** indicated two vinyl protons as a multiplet at 5.8 to 6.4 ppm. The ^{13}C NMR spectrum showed the characteristic vinyl iodide signal[149] at 74.7 ppm and three other olefinic signals at 145 ppm, 132.7 ppm and 130 ppm assigned to C_2, C_1 and $C_{2'}$ respectively. The fragmentation pattern of the low resolution mass spectrum (EI) were characteristic of the assigned structure. High resolution mass spectra could not be determined because **278** was too volatile. Vinyl iodide **278** was extremely labile thus all spectra data had to be obtained soon after it was prepared. The E/Z isomer ratio of **278** was not determined but according to

Takai[139] the chromium(II) chloride / iodoform reaction affords the E isomer as the major product.

Addition of two equivalents of tetrabutylammonium fluoride to a THF solution of **278** at 22 °C for 22 h gave the alcohol **279** in quantitative yield after chromatography. Care was taken to exclude light from the overnight reaction since all the vinyl iodide containing compounds decomposed quite rapidly in light. The IR spectrum of **279** showed the alcoholic stretching band at 3325 cm^{-1}. The ^{1}H NMR, ^{13}C NMR and low resolution mass spectral data were all consistent with the structure assigned to **279**. The high resolution mass spectrum (EI) confirmed **279** as $C_{12}H_{19}IO$.

The alcohol **279** was immediately oxidized by stirring a mixture of **279** and pyridinium dichromate in dichloromethane at 22 °C for 22 h. Workup according to the procedure of Corey[150] afforded the labile aldehyde **280** in 86% yield. There was a drastic drop in product yield to about 35% when the reaction was scaled up (when more than 450 mg of **279** is used). Aldehyde **280** decomposes when stored in the deep freeze for a prolonged period thus it was used immediately after its preparation. The IR spectrum indicated the presence of a strong carbonyl stretching band at 1717 cm^{-1} while the proton NMR spectrum showed a doublet at 9.8 ppm with J = 2.8 Hz due to the aldehyde proton which is coupled to the methine proton at C_4.

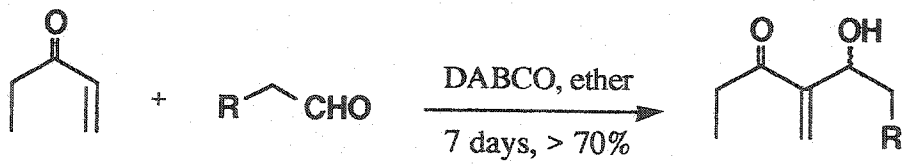

O
H
OTBDMS
276
CrCl2, CHI3, THF
0 - 22 °C, 22h, 45%
I
OTBDMS
278
Bu4NF, THF
22 °C, 22 h
98%
I
OH
279
PDC, CH2Cl2
22 °C, 86%
I
CHO
280
BuLi, 158, THF
-78 °C, 5 h, 47%
I
O
O
OH
281
15% H2SO4/silica gel
CH2Cl2, 22 °C, 98%
I
O
OH
282
Bu3SnH, AIBN
benzene, reflux, 22h
OH
O
283
60%
+
OH
O
284a
4%
or
OH
O
284b
4%

Scheme 53

7.2 Preparation of the model C-ring (158)

Construction of α-substituted enones directly from the parent α,β-unsaturated carbonyl compound in good yields and without intervention of the thermodynamic enolate has been a synthetic problem for quite some time.[154] Independently Corey,[155] Fuchs[156] and Stork[157] had each developed an umpolong strategy for the α-alkylation and α-arylation of α,β-unsaturated ketones that was dependent on the generation of an effective latent equivalent for α-ketovinyl cation. These approaches were limited in their application because they depended upon the available of the requisite alkyl or aryl organometallic reagent.

It has been reported that 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyses the addition of aldehydes to Michael acceptors[158] (Equation 39) however this procedure fails to work for more complex enones and aldehydes and is of little use in the synthesis of more complex natural products. For example, the reaction failed to work when a mixture of cyclohexene, 2,3,5,6-tetrahydrobenzaldehyde and DABCO was stirred in ether for 7 days (Scheme 54).

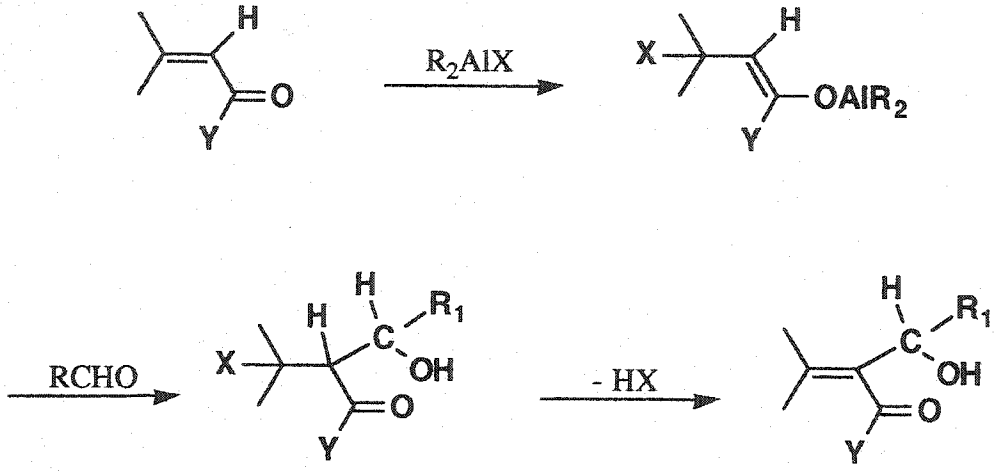


Scheme 54

Oshima[159] has developed a solution to the above recurring problem by a 1,4-addition of organoaluminium reagents of the type R_2AlX (X = -SPh, -SeMe) followed by reaction of the resulting

aluminium enolate with aldehydes to give the Aldol adducts in fair to good yields. Formal elimination of HX from these adducts provide α-substituted α,β-unsaturated carbonyl compounds (Scheme 55).

Under Oshima's reaction condition, the acetal in aldehyde **286** is rapidly converted to the aldehyde thus a complex mixture of products was obtained.



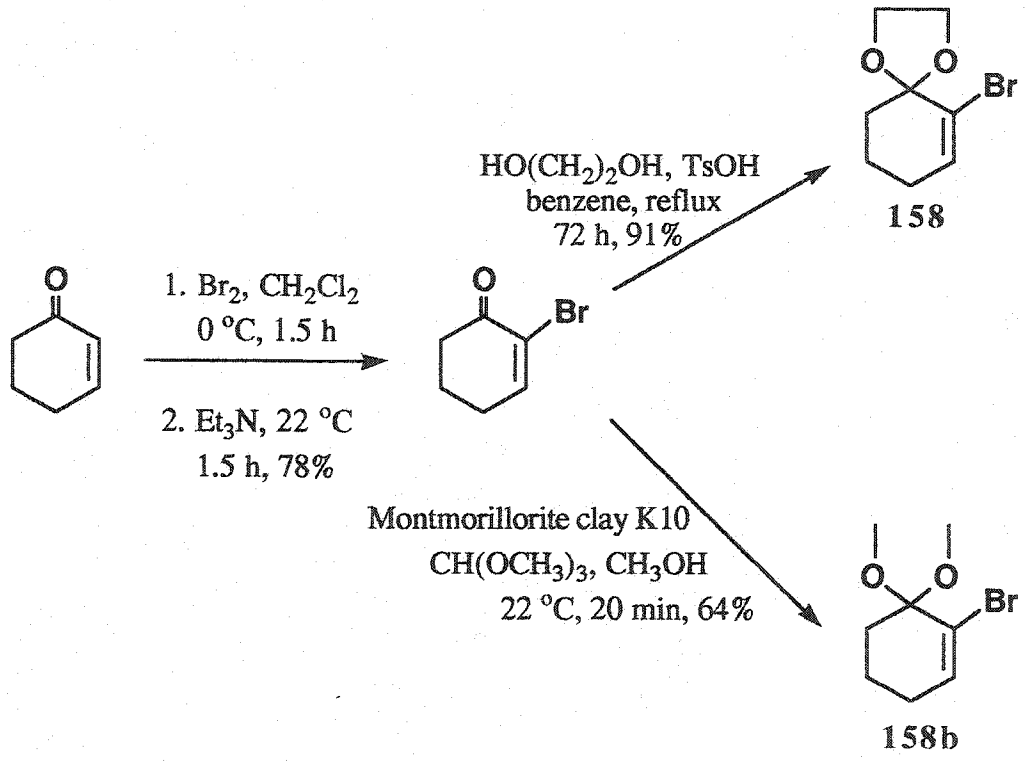
Scheme 55

A procedure developed by Noyori and co-workers[160] relies on a one pot conjugate addition of phenyl silyl selenide to the enone to form the silyl enol ether followed by trapping the aldehyde, masked as an acetal in catalytic trimethylsilyl trifluoromethanesulfonate. This approach was not applicable to the present problem.

The approach by Smith[151] which relies on the generation of a latent α-ketovinyl anion equivalent offered the best approach to the introduction of ring C.

α-Bromoketal **158** was therefore prepared from cyclohexenone according to the procedure of Smith.[151] Bromine was added dropwise to a solution of cyclohexenone in carbon tetrachloride at 0 °C

followed by a slow addition of triethylamine over 10 min. The reaction mixture was stirred at room temperature for 2 h to afford after workup and recrystalization from ether a 78% yield of 2-bromocyclohexenone as white needles. All the spectral data were consistent with the literature values.



Equation 35

A mixture of this enone, benzene, ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid was heated at reflux with azeotropic removal of water (Dean-Stark trap) to afford after workup and rapid chromatography 91% yield of **158** as a colorless oil. This

compound decomposes slowly turning reddish in color after prolonged exposure to light and was flushed through a short column to obtain the pure colorless sample. All the spectra data obtained were in agreement with the literature values.[151a]

Dimethoxy ketal **158b** would be much faster and easier to deprotect than the corresponding ketal **158**.[152] Ketal **158b** was thus prepared as a better alternative to **158** by stirring a mixture of 2-bromocyclohexenone, montmorillorite clay K10, trimethyl orthoformate and methanol in carbon tetrachloride for 20 min.[153] Chromatography furnished **158b** in 64% yield as a colorless oil. The ^{1}H NMR spectrum showed the presence of the two methoxy groups as a six proton singlet at 3.3 ppm and the vinyl proton as a triplet at 6.3 ppm with J = 4 Hz. α-Bromo ketal **158b** was extremely labile and unfortunately decomposed after about 5 h (Equation 35).

7.3 Connection of the A- and C-rings

The α-ketovinyl anion equivalent was generated by dropwise addition of a solution of **158** in THF to a -78 °C solution of butyllithium in THF. After one hour excess HMPA was added followed by a dropwise addition of a THF solution of aldehyde **280**. Workup after 5 h followed by chromatography gave the labile alcohol **281** in 47% yield as a colorless gum and 20% of **280**.

The IR spectrum of **281** showed a strong O-H stretching band at 3475 cm^{-1}. The ^{1}H NMR spectrum showed the following characteristic signals: a four proton broad singlet at 3.9 ppm to 3.97 ppm due to the two methylene protons of the dioxolane ring, a one proton broad singlet at 4.6 ppm that arises from the proton of the

hydroxy bearing methine and three separate vinyl proton multiplets at 5.8 to 5.94 ppm, 6.3 ppm to 6.5 ppm due to the protons of the vinyl iodide side chain at C_2 and 6 ppm to 6.15 ppm due to the C-ring vinyl proton. The ^{13}C NMR spectrum showed five olefinic signals at 145 ppm, 140 ppm, 133 ppm, 130.3 ppm, 130.1 ppm including the characteristic vinyl iodide carbon (=C-I) at 74.8 ppm. The signal at 107.7 ppm was characteristic of $C_{1'}$ which is attached to two oxygen atoms in ring C. The mass spectrum (EI) did not give the M^+ peak however the CI spectrum showed the $M^+ + 1$ peak at *m/z* 445.

Alcohol **281** hydrolyzed to **282** when left in the freezer for about 4 days. Immediate deketalisation by the procedure of Conia and co-workers (*vide infra*) afforded the key radical reaction precursor **282** in quantitative yield. A degassed solution of tributyltin hydride, azobisisobutyronitrile and benzene was added over 10 h by syringe pump to a refluxing degassed solution of **282** and a catalytic amount of azobisisobutyronitrile in benzene.

Workup after 22 h followed by chromatography gave the reduced alcohol **283** in 57% yield. GCMS Analysis of the isolated product indicated two compounds in a 9.3:1 ratio with the same molecular ion but different fragmentation patterns. The signals in the ^1H NMR spectrum between 4.8 ppm and 6.8 ppm (Appendix 1) are consistent with the GCMS analysis. These compounds, **283** and **284a** or **284b** had the same R_f from TLC analysis and could not be separated. Based upon work by Baldwin,[28b] Porter[30] and Pattenden[31] intramolecular radical addition to the enone should favour the formation of **284a** and not **284b**.

To improve the radical cyclization reaction and increase the possibility of having products (cyclized and uncyclized) with different R_f's after the radical cyclization step, we felt that the alcohol functionality in **282** should be oxidized to the diketone **350** (Scheme 54). In addition to improving the overall yield of the key radical precursor **282**, the introduction of the troublesome and low yielding vinyl iodide step should come just before the cyclization reaction (Scheme 59). This would reduce the number of steps through which the labile vinyl iodide had to be carried.

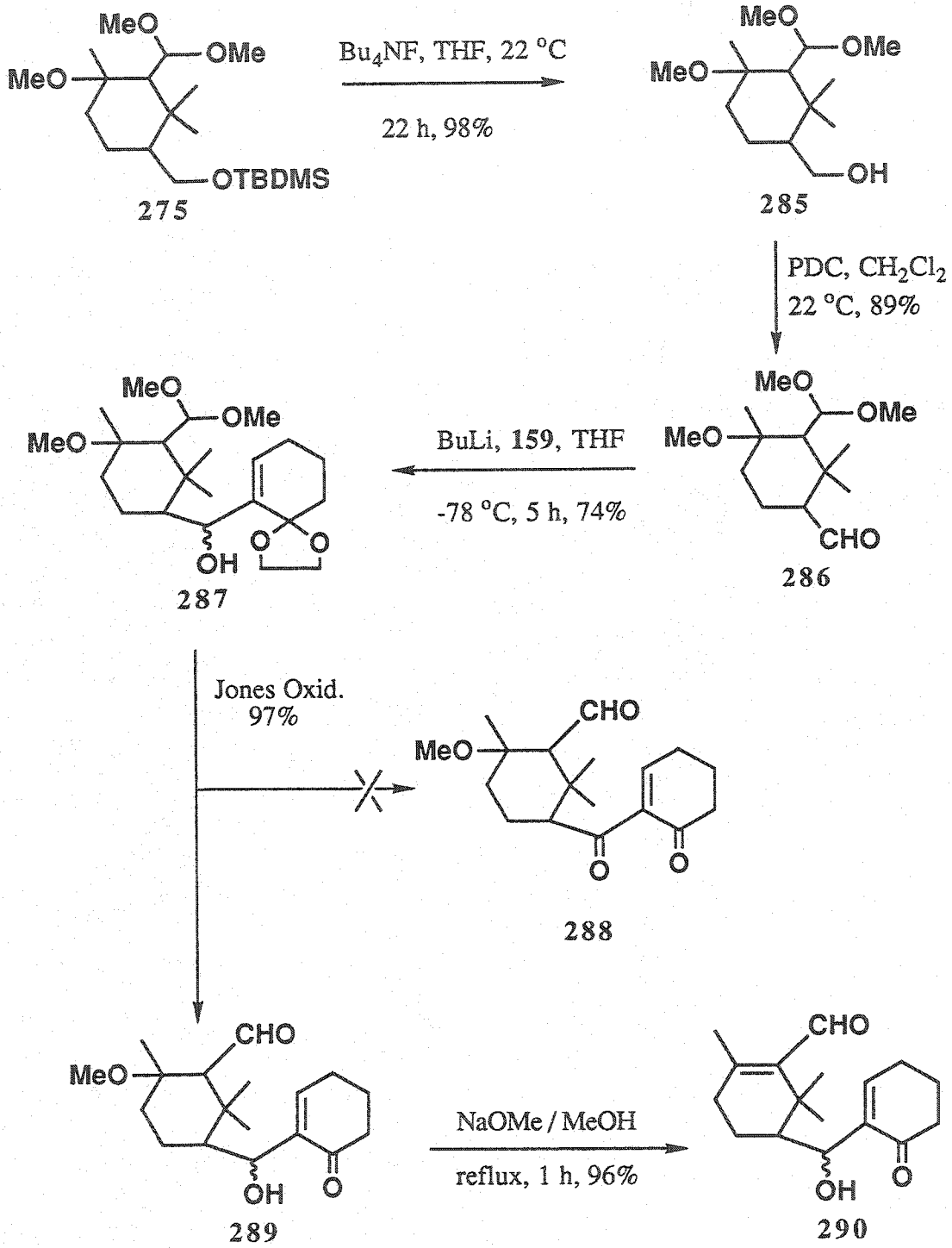
To test this model, *tert*-butyldimethylsilyloxy protected acetal **275** was converted to the alcohol **285** by reaction with tetrabutylammonium fluoride (*vide infra*) in quantitative yield. Alcohol **285** was oxidized with pyridinium dichromate in dichloromethane (*vide infra*) to afford the aldehyde **286** in 89% yield after workup. Structure assignment for **285** and **286** were consistent with the ^{1}H, ^{13}C and the low and high resolution (EI) mass spectral data.

Connection of **286** and **159** according to the method of Smith (*vide infra*) furnished alcohol **287** in 74% yield as a colorless gum (Scheme 56). The IR spectrum indicated the presence of the alcohol function with an O-H stretching band at 3421 cm^{-1}. A few hours after **287** was prepared the acetal and ketal groups started decomposing to the aldehyde and ketone functions, respectively. This was observed from the proton NMR spectrum taken a day after the preparation of **287** although in **275** the acetal is very stable and the compound has been kept in the fridge for over six months without any sign of decomposition.

It was hoped that Jones oxidation[161] of **287** would lead to oxidation of the alcohol functionality and deprotection of the labile acetal and ketal in one step to furnish **288**. Instead, alcohol **289** was obtained after the Jones oxidation. The IR spectrum indicated the presence of the alcohol, aldehyde and ketone functionalities at 3422 cm^{-1}, 1729 cm^{-1} and 1690 cm^{-1} respectively. The ^1H NMR spectrum displayed the C_1 methoxy substituent as a singlet at 3.3 ppm and the proton of the hydroxy bearing methine at 4.85 ppm as a broad singlet. The vinyl proton in the now α,β-unsaturated C-ring had shifted downfield from 6 ppm in **287** to 6.9 to 7 ppm in **289**. Alcohol **289** was successfully converted to **290** in refluxing methanol containing sodium methoxide in quantitative yield.

Simple ylides are highly reactive, reacting with oxygen, water, alcohols as well as carbonyl compounds and esters thus these reactions are run under conditions where these materials are absent.[101] In the presence of the alcohol functionality in **290**, the introduction of the vinyl iodide by Takai's procedure (*vide infra*) could not be achieved.

An alternative solution to the above problem was to protect aldehyde **276** as the acetal or to protect the alcohol **277** with protection groups that could be readily removed and very stable such as *p*-anisyl ether or benzoyl ester. The advantages of this approach are: a) The low yielding and highly unstable vinyl iodide could be introduced very late in the synthesis, b) it is more likely that there will be a bigger difference in R_f's between iodoform and


MeO
OMe
MeO
OTBDMS
275
Bu4NF, THF, 22 °C
22 h, 98%
MeO
OMe
MeO
OH
285
PDC, CH2Cl2
22 °C, 89%
MeO
OMe
MeO
CHO
286
BuLi, 159, THF
-78 °C, 5 h, 74%
MeO
OMe
MeO
OH
O
O
287
Jones Oxid.
97%
CHO
MeO
O
O
288
CHO
MeO
OH
O
289
NaOMe / MeOH
reflux, 1 h, 96%
CHO
OH
O
290

Scheme 56

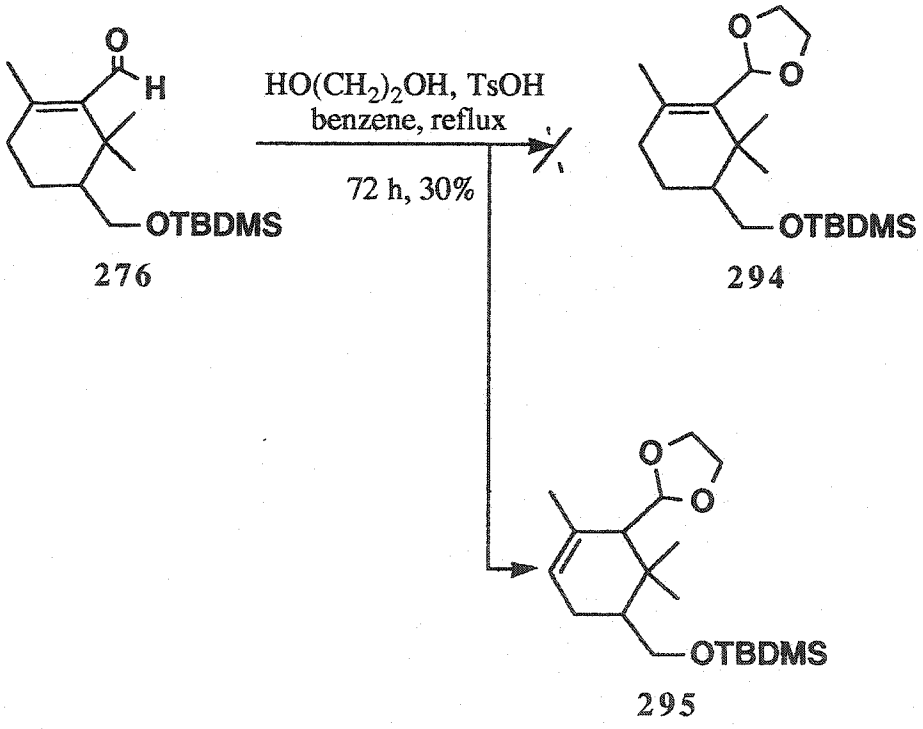
the product thus make isolation by chromatography much easier, c) the NMR spectra would be simplified and d) loss of product due to decomposition of the vinyl iodide would be reduced.

Protection of aldehyde **276** by refluxing a mixture of ethylene glycol, *p*-toluenesulfonic acid and **276** in benzene (*vide infra*) afforded **295** in 30% yield (Equation 36). Double bond isomerization during the protection of α,β-unsaturated enones is known to occur in certain molecules and may be reduced or eliminated by using milder acid catalyst such as oxalic acid and pyridinium*p*-toluene sulfonate acid.[152,162] With oxalic acid as catalyst, double bond isomerisation did not occur however very little product was formed after four days. Protection of 276 as its acetal using Montmorillorite clay K10 and trimethylorthoformate according to the procedure of Taylor[153] gave instead the diene **296** in 65% yield (Equation 47).

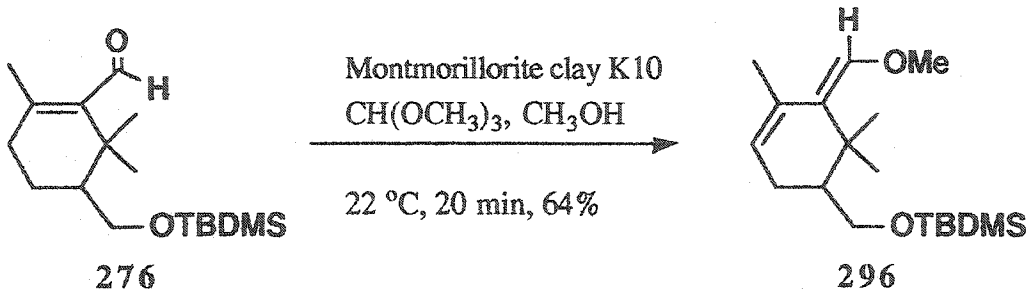
The problem of double bond migration, although a nuisance, could be effectively utilized to introduce the C_{13} hydroxy group in Taxol (Scheme 57) via epoxidation followed by epoxide ring opening by base with concomitant formation of the required A-ring double bond.

Pyridinium dichromate oxidation of 2.5 g of alcohol **285** afforded, in addition to the aldehyde **286**, about 1.5 g of the acid **298** which was purified by chromatography and identified by its ^1H NMR spectrum. Acid **298** was converted to the methyl ester **299** in quantitative yield by the addition of an ether solution of diazomethane to a stirred solution of **298** in ether at 0 ^oC for 2 h followed by chromatography. The presence of the ester functionality was detected in the IR, ^1H and ^{13}C NMR spectra at 1731 cm^{-1}, a

three proton singlet at 3 ppm and a signal at 176 ppm respectively. Deacetylation followed by base elimination of the methoxy group (*vide infra*) and sodium borohydride reduction furnished the alcohol **300** which was converted to the highly stable *p*-anisyl ether **301** in 90% yield according to the procedure developed by Fukuyama.[163] Thus a mixture of alcohol **300**, *p*-methoxy phenol, triphenylphosphine and diethylazodicarboxylate (DEAD) was stirred at 22 °C for 30 min followed by workup and chromatography to give **301** as a colorless oil (Scheme 58).

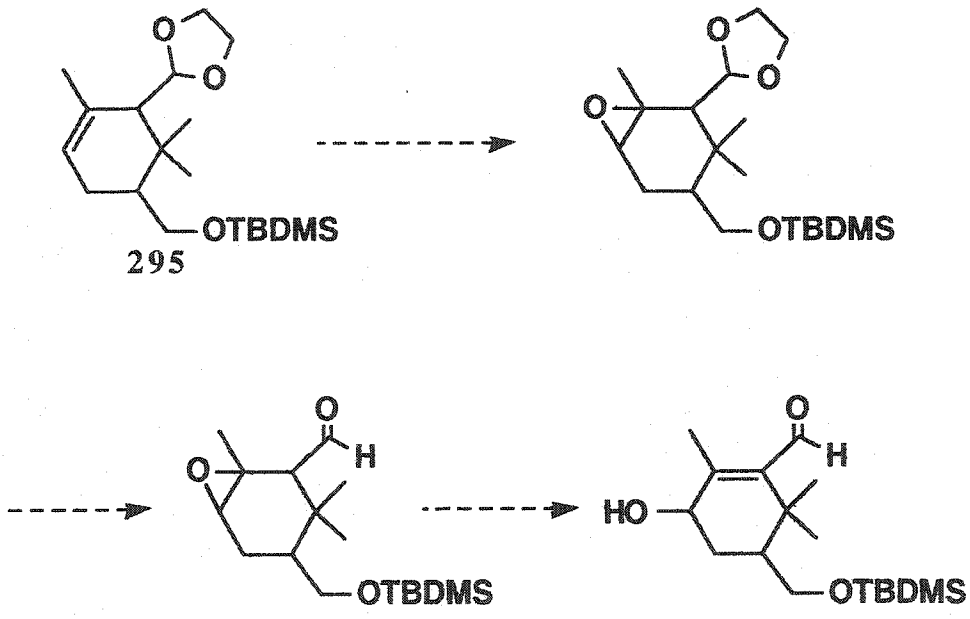


Equation 40



276 296

Equation 47



295

Scheme 57

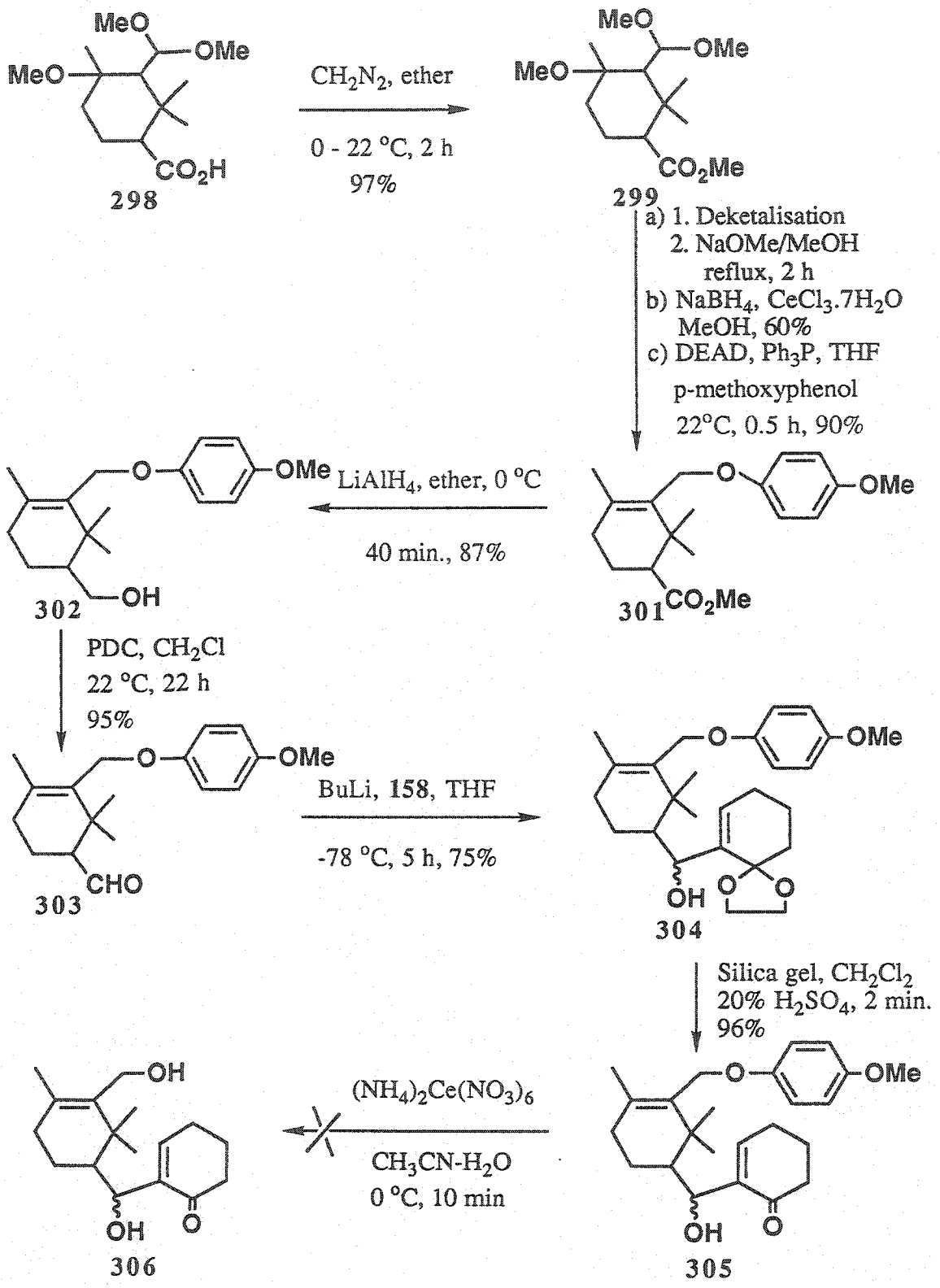
The ^1H NMR spectrum showed the protons of the methylene groups attached to C_2 and *p*-methoxyphenol as a pair of AB doublets with J = 10 Hz and the p-methoxy group at 3.7 ppm as a singlet. Four aromatic protons were indicated by a multiplet at 6.7 ppm to 6.9 ppm.

Lithium aluminum hydride reduction of the ester functionality in **301** afforded the alcohol **302** as a colorless oil after stirring in an ether solution for 40 min. The presence of an alcohol O-H stretching band at 3379 cm^{-1} confirmed **302** as an alcohol. The ^{1}H and ^{13}C NMR spectra were consistent with the structure assignment for **302**. Pyridinium dichromate oxidation (*vide infra*) of **302** furnished the aldehyde **303** in 95% yield. Condensation of **303** and **158** (*vide infra*) gave **304** in 75% yield as colorless gum after chromatography. The IR spectra of **304** showed the characteristic alcohol band at 3357 cm^{-1}. The four methylene protons of the five membered ring of the ketal appeared in the proton NMR as a singlet at 3.8 ppm while the *p*-methoxy showed up at 3.7 ppm as a singlet. The C-ring vinyl proton was shifted downfield at 6.94 to 6.98 ppm compared to the other alcohols (**281** and **287**) possessing the A- and C-rings. This may be due to the presence of the *p*-anisyl ether. The vinyl proton in the C-ring may be just outside the aromatic ring and is influenced by the ring current or anisotropy effect of the benzene ring.

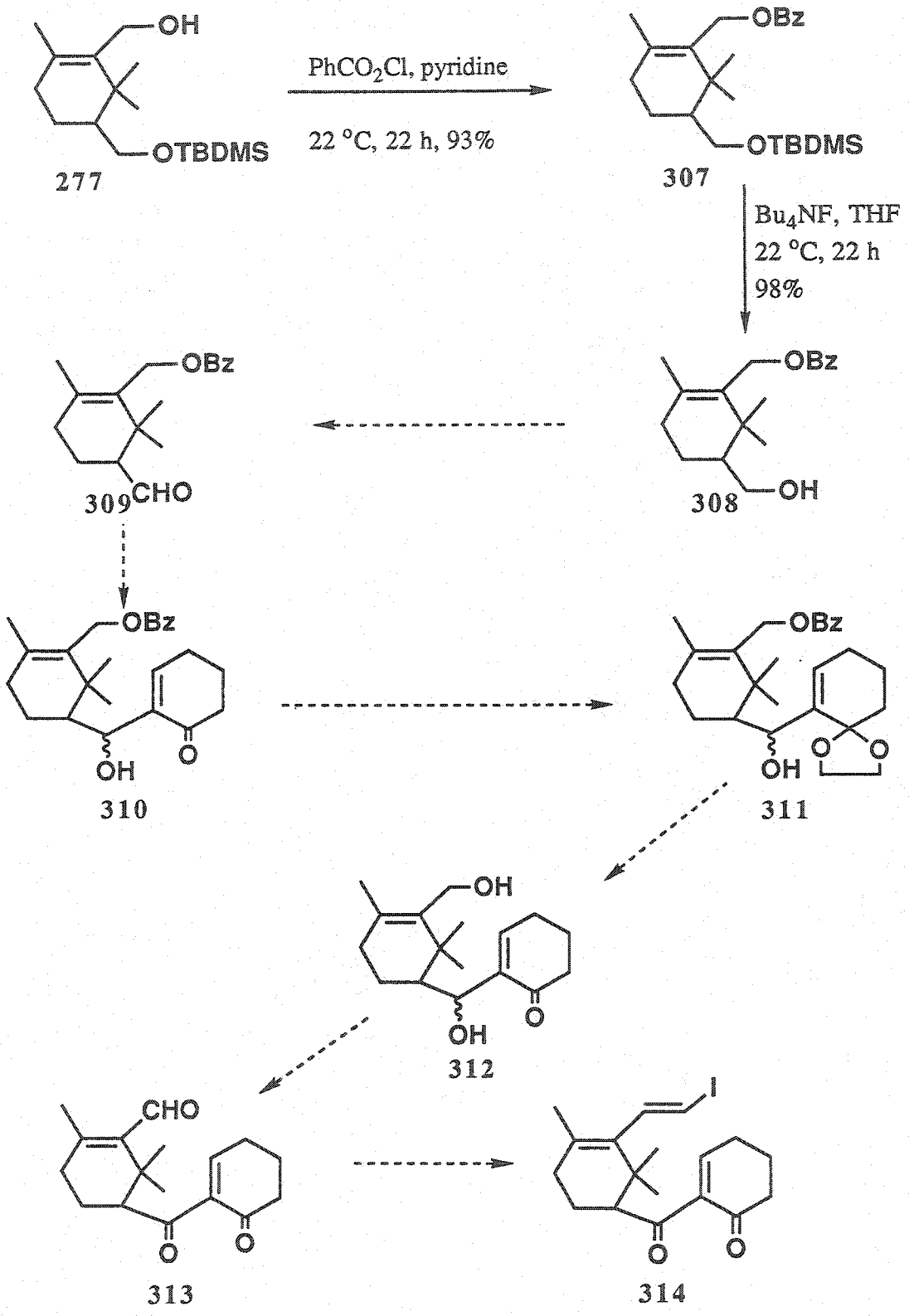
Deketalization of **304** occurs slowly in the fridge but generally it was accomplished using wet silica gel according to the procedure of Conia (*vide infra*) to afford **305**. Deprotection of *p*-anisyl ether by treatment with ceric ammonium nitrate (CAN) in aqueous acetonitrile at 0 ^{o}C afforded a product after workup and chromatography which has not as yet been identified. The IR of this compound did not indicate the presence of an alcohol although the *p*-anisyl group was successfully removed as indicated by the proton NMR which does not show any aromatic signals or the *p*-methoxy group.

Benzoyl ester protection of alcohol **277** was achieved by stirring **277** and benzoyl chloride in pyridine at room temperature for 20 h. Chromatography gave **307** as a colorless oil in 93% yield (Scheme 59). Deprotection of the *tert*-butyldimethylsilyloxy group (*vide supra*) by tetrabutylammonium fluoride furnished a quantitative yield of the alcohol **308**. Conversion of this alcohol in six steps would furnish the requisite vinyl iodide in good yield to allow a study of the radical cyclization reaction.

Thus in spite of extensive study this project concludes with several question related to taxoids unresolved. The original intent to utilize a cyclopropyl ring opening cyclization sequence could not be employed due to difficulties encountered in synthesizing a suitable precursor. Nevertheless the discovery of the vinyl enol ether-ketene carbonyl cycloaddition has more than compensated for this and opened new doors for further investigations. The tantalizing results from the cyclization of **282** suggested that this radical route to taxanes is possible but this area requires additional study before a definitive conclusion can be drawn.


MeO
OMe
MeO
CO2H
298
CH2N2, ether
0 - 22 °C, 2 h
97%
MeO
OMe
MeO
CO2Me
299
a) 1. Deketalisation
2. NaOMe/MeOH
reflux, 2 h
b) NaBH4, CeCl3.7H2O
MeOH, 60%
c) DEAD, Ph3P, THF
p-methoxyphenol
22°C, 0.5 h, 90%
O
OMe
CO2Me
301
LiAlH4, ether, 0 °C
40 min., 87%
O
OMe
OH
302
PDC, CH2Cl
22 °C, 22 h
95%
O
OMe
CHO
303
BuLi, 158, THF
-78 °C, 5 h, 75%
O
OMe
OH
O
O
304
Silica gel, CH2Cl2
20% H2SO4, 2 min.
96%
O
OMe
OH
O
305
(NH4)2Ce(NO3)6
CH3CN-H2O
0 °C, 10 min
OH
OH
O
306

Scheme 58


OH
OTBDMS
277
PhCO2Cl, pyridine
22 °C, 22 h, 93%
OBz
OTBDMS
307
Bu4NF, THF
22 °C, 22 h
98%
OBz
OH
308
OBz
CHO
309
OBz
OH
O
310
OBz
OH
O
O
311
OH
OH
O
312
CHO
O
O
313
I
O
O
314

Scheme 59

IV. EXPERIMENTAL

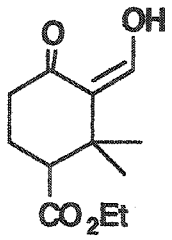
General:

Melting points were determined in capillary tubes with a Thomas-Hoover Unit-Melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 783 spectrometer or a Bomem MB 100 FTIR spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were measured at 60 MHz with a Varian spectrometer or at 200 MHz with a Varian Gemini spectrometer or at 300 MHz with a Varian XL-300 spectrometer in deuterochloroform unless otherwise stated. Carbon magnetic resonance spectra (^{13}C NMR) were measured at 50 MHz (Varian Gemini) or at 75 MHz (Varian XL-300). The residual signal ($CHCl_3$) was used as an internal lock; $CHCl_3$; ^{1}H: δ 7.262, $CDCl_3$; ^{13}C: δ 77.0. Chemical shifts are reported in ppm downfield from trimethylsilane (δ scale). The multiplicity, number of protons, coupling constants and proton assignments are indicated in parentheses. Mass spectra (MS) were determined on a V.G. micromass 7070 HS instrument using an ionization energy of 70 eV. Gas chromatography mass spectra (GCMS) were determined on an HP 5971A MSD/HP 5890 Series II Gas Chromatograph. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, AZ, USA. Analytical thin layer chromatography (TLC) employed commercial aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Flash column chromatography using E. Merck silica gel 60 (70-230 or 230-400 mesh) was employed for all column chromatography.

Petroleum ether refers to a fraction with boiling range 30 - 60 °C. Anhydrous diethyl ether (ether) and diisopropylamine were

obtained by distillation from $LiAlH_4$ and anhydrous tetrahydrofuran (THF) from potassium/benzophenone. Absolute ethanol was dried by distillation from magnesium. Dry benzene, dimethylformamide (DMF) and carbon tetrachloride (CCl_4) were prepared by distillation from phosphorous pentoxide. Anhydrous hexamethylphosphoramide (HMPA) was obtained by distillation from calcium hydride, and acetone was dried by distillation from anhydrous K_2CO_3. Dioxane was distilled from $LiAlH_4$ and stored over Linde type 4A molecular sieves. CuI (99.999%, Aldrich) was purified by repeated soxhlet extraction with THF and dried (80 ^oC) under vacuum for 7 h. Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvents with a Büchi rotatory evaporator connected to a water aspirator. Unless otherwise stated all reactions were conducted under an atmosphere of dry nitrogen in flame dried flasks equipped with a magnetic stirring bar and rubber septa.

Ethyl 2,2-dimethyl-3-hydroxymethylidene-4-oxocyclohexanecarboxylate (169)

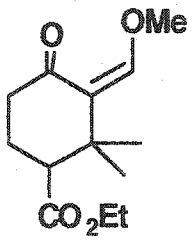


169

Methyllithium (7.14 mL, 10 mmol, 1.4 M solution in diethyl ether, Aldrich) was added to a suspension of purified CuI (952 mg, 5

mmol) in ether (30 mL) at 0 °C and after 10 min, 4-carbethoxy-3-methyl-2-cyclohexene-1-one **76** (Hagemann's ester) (0.43 mL, 2.5 mmol, Aldrich) was added. After 90 min ethyl formate (2.1 mL, 25 mmol) was added and stirring continued for 10 min. The reaction mixture was poured into aqueous 10% NH_4Cl solution and extracted with ether. The ether extracts were further extracted with aqueous 10% NaOH solution, the alkaline extract acidified with ice-cold aqueous 50% HCl and extracted with ether (3x). The ether fraction was concentrated and dried to give the product (0.31 g, 54.6%). GCMS analysis of the crude product indicated no contaminants were present. ^1H NMR (60 MHz), δ 1.06 (s, 6 H, 2(CH_3)), 1.29 (t, 3 H, J = 7 Hz, $C\underline{H}_3$-CH_2), 2.20 - 2.75 (m, 5 H), 4.15 (q, 2 H, J = 7 Hz, $C\underline{H}_2$-CH_3), 8.76 (s, 1 H, CHO); MS (EI) *m/z* 226 (61.1%), 211 (100%), 183 (25%), 153 (61.9%), 109 (89%). HRMS (EI) calcd. for $C_{12}H_{18}O_4$ 226.1204, found 226.1204.

Ethyl 2,2-dimethyl-3-methoxymethylidene-4-oxocyclohexanecarboxylate (170)

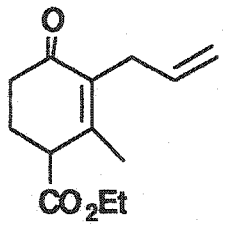


170

Anhydrous K_2CO_3 (112.5 mg, 0.814 mmol) was added to a solution of **169** (184 mg, 0.814 mmol) in dry acetone (5 mL)

followed by dimethyl sulfate (81.5 μL, 0.814 mmol) in one portion. The reaction mixture was refluxed for 2.5 h, filtered and concentrated to give the crude product which was used for the next reaction without further purification. GCMS analysis of the product indicated 94% desired product and 6% **169**. ^{1}H NMR, (60 MHz), δ 1.08 (s, 6 H, 2(CH_3)), 1.28 (t, 3 H, J = 7 Hz, $C\underline{H}_3$-CH_2), 2.15 - 2.70 (m, 5 H), 3.89 (s, 3 H, OCH_3), 4.05 (q, 2 H, J = 7 Hz, $C\underline{H}_2$-CH_3), 7.30 (m, 1 H, =CH).

Ethyl 2-methyl-3-(2-propenyl)-4-oxocyclohex-2-enecarboxylate (180)

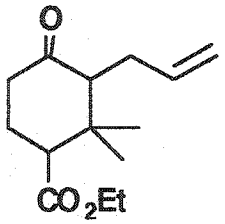


180

A mixture of **76** (Hagemann's ester) (2.3 mL, 13.73 mmol) and NaH (0.339 g, 13.73 mmol) in toluene (15 mL) was heated to 110 °C for 1 h during which time hydrogen evolution occured forming a brownish foamy mixture. The reaction was then cooled, allyl bromide added and refluxed for 3 days. The reaction mixture was cooled in an ice bath and acetic acid (0.12 mL) added followed by water (18 mL) and the organic layer separated. The aqueous layer was extracted with ether and the combined ether extract dried and concentrated. Chromatography gave **180** (3 g, 97%). ^{1}H NMR (200 MHz), δ 1.25 (t, 3 H, J = 7.1 Hz, $C\underline{H}_3$-CH_2O), 1.98 (s, 3 H, CH_3), 2.22 - 2.72 (m, 4 H), 3.07

(m, 2 H, =C-CH_2-C=), 3.30 (m, 1 H, CH-C=O), 4.23 (q, 2 H, J = 7 Hz, CH_2-CH_3), 4.90 - 5.03 (m, 2 H, =CH_2), 5.83 (m, 1 H, =CH); ^{13}C δ 197.1 (conjugated ketone), 172.2 (ester), 151.7 (=$C(CH_3)R$), 134.9 (=C), 129.4 (=CH), 114.6 (=CH_2), 61.1 (OCH_2), 47.6, 34.3, 28.9, 25.4, 20.2, 13.9; MS (EI) *m/z* 222 (16.2%) (M^+), 149 (100%).

Ethyl 2,2-dimethyl-3-(2-propenyl)-4-oxocyclohexanecarboxylate (181)

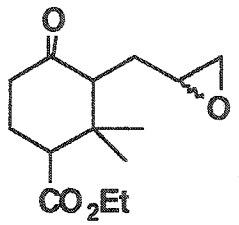


181

Method A. Hagemann's ester **76** (0.43 mL, 2.5 mmol) was added to a solution of lithium dimethylcuprate {prepared from MeLi (7 mL, 10 mmol) and CuI (952 mg, 5 mmol)} in anhydrous ether (30 mL) and stirring continued for 1.5 h. THF (14 mL) was added followed by a rapid addition of excess allyl bromide (1 mL). The reaction mixture was allowed to warm to 22 °C and stirring continued for 20 h. The reaction was poured into aqueous 10% NH_4OH solution, the organic layer separated and washed successively with 10% NH_4OH solution, water and brine. The organic solution was dried, concentrated and chromatographed (10% Et_2O/petroleum ether) to afford **181** (238 mg, 40%).

Method B. Methyllithium (28.5 mL, 40 mmol) was added to a suspension of CuI (3.89 g) in ether (120 mL) at 0 °C. After 30 min at 0 °C, the reaction mixture was cooled to -30 °C and a mixture of the enone **180** (2.26 g, 10 mmol) and $BF_3.OEt_2$ (4.63 mL, 50 mmol) in ether (5 mL) at 0 °C was added dropwise. Stirring was continued for 1 h. Aqueous 10% NH_4OH solution was added, the organic layer separated and washed consecutively with 10% aqueous NH_4OH solution, water and brine. The ether solution was dried, concentrated and chromatographed (10% Et_2O/petroleum ether) to give the product **181** (1.9 g, 80%). ^1H NMR (200 MHz), δ 0.86 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.20 (t, 3 H, J = 7 Hz, $C\underline{H}_3$-CH_2), 1.60 - 2.41 (m, 6 H), 2.41 - 2.72 (m, 2 H, allylic CH_2), 4.11 (q, 2 H, J = 7 Hz, $C\underline{H}_2$-CH_3), 4.96 (m, 2 H, $=CH_2$), 5.72 (m, 1 H, =CH); ^{13}C δ 209.8, 173.5, 138.0, 115.4, 60.8, 60.2, 53.4, 41.8, 40.7, 27.1, 26.7, 25.7, 16.2, 14.0; MS (EI) *m/z* 238 (17%) (M^+), 223 (33%) (M^+ - 15), 193 (20.5%) (M^+ - OEt), 165 (12.5%) (M^+ - CO_2Et), 41 (100%); HRMS (EI) calcd. for $C_{14}H_{22}O_3$ 238.1568, found 238.1560.

Ethyl 2,2-dimethyl-3-(2,3-epoxypropanyl)-4-oxocyclohexanecarboxylate (187)

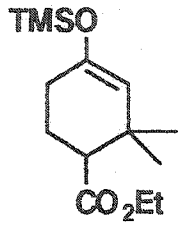


187

Method A. *m*-Chloroperbenzoic acid (90 mg, 0.36 mmol, 85% Aldrich) was added to the olefin **181** (71.2 mg, 0.3 mmol) in chloroform (2 mL) at 22 °C and stirring continued for 18 h. Water was added and the mixture extracted with CH_2Cl_2. The combined organic extract was dried and concentrated to afford **187** (67.4 mg, 88%) which was used without further purification. Some starting material remained but attempted chromatography caused decomposition of the product.

Method B. A cold solution of dimethyl dioxirane dissolved in acetone was added to a solution of the the olefin **181** (71 mg, 0.3 mmol) in acetone (1 mL) and the mixture allowed to warm to 22 °C. TLC indicated the reaction was complete. It was dried and concentrated to afford the product **187** (76 mg, 100%). ^{1}H NMR (200 MHz), δ 0.91 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.33 (t, 3 H, J = 7 Hz, $C\underline{H_3}$-CH_2), 1.62 - 2.70 (m, 8 H), 2.70 - 2.81 (m, 2 H, OCH_2), 2.90 - 3.13 (m, 1 H, OCH), 4.24 (q, 2 H, J = 7 Hz, O-CH_2CH_3). MS (EI) *m/z* 254 (18%) (M^+), 239 (100%) (M^+ - 15), 209 (25.4%) (M^+ - OEt), 181 (10.6%) (M^+ - CO_2Et), 165 (19%) (M^+ - CO_2Et - CH_3); HRMS (EI) calcd. for $C_{14}H_{22}O_4$ 254.1517, found 254.1515.

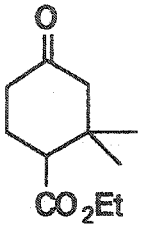
Ethyl 2,2-dimethyl-4-trimethylsilyloxycyclohex-3-enecarboxylate (186)



186

Methyl lithium (7.1 mL, 10 mmol) was added to a suspention of copper(I) iodide (0.95 g, 5 mmol) in ether (100 mL) at 0 °C. After 15 min, enone **76** (0.46 g, 2.5 mmol) was added dropwise and stiring continued for 1 h. Triethylamine (1 mL, 7.5 mmol) and chlorotrimethylsilane (0.95 mL, 7.5 mmol) were added in succession and the resulting mixture stirred for 3 h at 22 °C. The mixture was poured on to saturated NH_4Cl solution and extracted with ether (3 x 15 mL). Chromatography (5% acetone/petroleum ether) on Florisil afforded enol silyl ether **186** (0.6 g, 90%) as a colorless oil. ^1H NMR (200 MHz) δ 0.11 (s, 3H, $Si(CH_3)_3$), 0.90 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.23 (t, 3 H, J = 7 Hz, $CH_2C\underline{H}_3$), 1.64 - 2.03 (m, 4 H, (CH_2-CH_2)), 2.20 - 2.33 (m, 1 H, C<u>H</u>-CO_2Et), 4.01 - 4.20 (m, 2 H, C<u>H</u>$_2CH_3$), 4.60 (s, 1 H, =C-H); ^{13}C NMR δ 172.2 (<u>C</u>O_2Et), 146.4 (TMSO-C=), 114.1 (=C), 57.0, 48.0, 32.0, 28.3, 26.6, 23.2, 20.0, 12.2, -2.1 ($Si(CH_3)_3$).

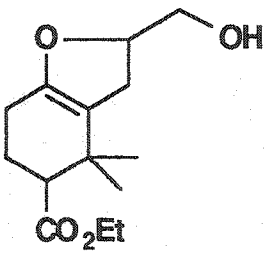
Ethyl 2,2-dimethyl-4-oxocyclohexanecarboxylate (182)



182

Obtained as a byproduct in the preparation of **181**. ^{1}H NMR (200 MHz) δ 0.90 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.20 (t, 3 H, J = 7Hz, CH_3-CH_2), 1.91 - 2.02 (m, 7 H), 4.54 (q, 2 H, J = 7Hz); ^{13}C NMR δ 210.2 (C=O), 174.0 ($\underline{C}O_2Et$), 60.4, 54.5, 50.3, 38.1, 37.0, 29.1, 25.0, 23.2, 14.0.

2-Hydroxymethyl-4,4-dimethyl-5-carbethoxy-2,3,4,5,6,7-hexahydrobenzofuran (189)

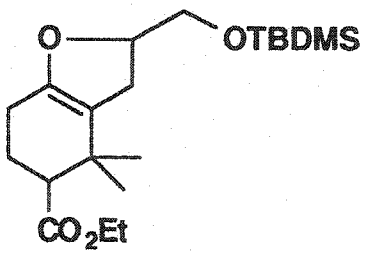


189

Sodium metal (15.2 mg) was added to ethanol (2.5 mL) and the epoxide **187** (168.4 mg, 0.66 mmol) in ethanol (0.5 mL) added. Stirring was continued for 30 min, the reaction was quenched with water, the ethanol removed, ether added and washed with water and brine. The ether solution was dried, concentrated and

chromatographed (5% acetone/petroleum ether) to give **189** (163 mg, 96%). IR (neat) 3350, 2938, 1737, 1472 cm^{-1}; ^1H NMR (200 MHz), δ 0.98 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.43 (t, 3 H, J = 7 Hz, $C\underline{H}_3$-CH_2), 1.71 - 2.74 (m, 7 H), 3.61 - 3.80 (m, 2 H, $C\underline{H}_2$-OH), 4,15 (q, 2 H, J = 7 Hz, $OC\underline{H}_2$-CH_3), 4.65 (m, 1 H, $OC\underline{H}$-CH_2OH); ^{13}C δ 174.4, 149.2, 102.5, 81.5, 65.7, 60.0, 49.4, 36.8, 34.0, 33.6, 28.5, 24.8, 22.0, 14.0; DEPT (200 MHz) δ 81.5 (CH), 65.7 (CH_2), 60.0 (CH_2), 49.4 (CH), 36.8 (CH_2), 34.0 (CH_2), 28.5 (CH_3), 24.8 (CH_2), 22.0 (CH_3), 14.0 (CH_3); MS (EI) *m/z* 254 (14.6%) (M^+), 236 (23%) (M^+ - H_2O), 209 (1.8%) (M^+ - OEt), 180 (17%) (M^+ - CO_2Et), 163 (17%) (M^+ - H_2O - CO_2Et).

2-(*tert*-Butyldimethylsilyloxy)methyl-4,4-dimethyl-5-carbethoxy-2,3,4,5,6,7-hexahydrobenzofuran (190)

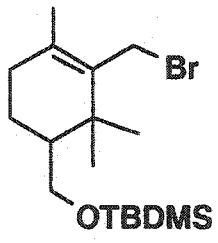


190

The alcohol **189** (190 mg, 0.75 mmol), imidazole (127.3 mg, 1.5 mmol) and TBDMSCl (134.6 mg, 0.84 mmol) in DMF (2 mL) were stirred overnight. Ether was added and the mixture washed with small amounts of water (2x1 mL). The ether solution was dried and concentrated. Chromatography (5% Et_2O/petroleum ether) afforded the product **190** (270 mg, 98%). IR (neat) 2950, 1735 (br), 1469, 1260 cm^{-1}; ^1H NMR (200 MHz), δ 0.15 (s, 6 H, Si-$(CH_3)_2$), 0.85 (s, 9 H,

$(CH_3)_3$), 0.96 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.25 (t, 3 H, J = 7 Hz, $C\underline{H}_3$-CH_2), 1.82 - 2.68 (m, 7 H), 3.6 - 3.75 (m, 2 H, CH_2-OSi), 4.15 (q, 2 H, J = 7 Hz, $C\underline{H}_2$-CH_3), 4.55 (m, 1 H, O-C$\underline{H}$-CH_2O); ^{13}C δ 174.5, 148.7, 112.4, 85.5 (O-CH), 65.3, 59.8, 51, 33.9, 30.5, 27.3, 25.5, 22.4, 22.3, 22.1, 18.1, 14.1, -5.6; DEPT (200 MHz) 85.5 (CH), 65.3 (CH_2), 59.8 (CH_2), 51 (CH), 30.5 (CH_2), 27.35 (CH_3), 25.5 (CH_2), 25.5 (CH_3), 22.4 (CH_3), 22.3 (CH_2), 14.1 (CH_3), -5.6 (CH_3); MS (EI) *m/z* 368 (6.4%) (M^+), 353 (14%) (M^+ - 15), 311 (50%) (M^+ - 57), 323 (14%) (M^+ - OEt), 295 (3.2%) (M^+ - CO_2Et), 237 (24%) (M^+ -57 - 73), 73 (100%) (CO_2Et); HRMS (EI) calcd. for $C_{19}H_{33}O_4$ - CH_3 353.2147, found 353.2110.

2-Bromomethyl-1,3,3-trimethyl-4-(*tert*-butyldimethylsilyl-oxy)methylcyclohexene (196)

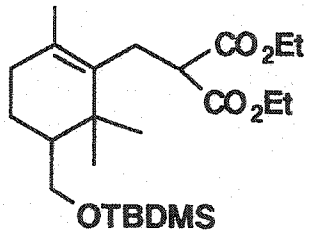


196

Bromine was added dropwise to a solution of Ph_3P (106.5 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) at 22 °C until a slight yellowish colour persisted followed by Et_3N (154 μL, 1.1 mmol). After stirring for 5 min the reaction mixture was cooled to -78 °C and the alcohol **277** (109.3 mg, 0.36 mmol) dissolved in CH_2Cl_2 (0.5 mL) was added dropwise. Stirring was continued for 1 h and petroleum ether was added. The white precipitate produced was filtered, the filtrate

concentrated and the process of precipitation and filtration repeated until no more precipitate formed upon concentration (4x). Further concentration afforded the product **196** (129 mg, 98%). ^{1}H NMR (200 MHz), δ 0.16 (s, 3 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $(CH_3)_3$), 0.09 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.41 - 1.50 (m, 2 H), 1.70 (s, 3 H, $=C-CH_3$), 1.73 - 2.02 (m, 1 H), 2.02 - 2.05 (m, 2 H, allylic CH_2), 3.33 (dd, 1 H, J = 8.75, 10 Hz, CH-OSi), 3.70 (dd, 1 H, J = 4, 10 Hz, CH-OSi), 4.14 (AB q, 2 H, J = 9.9 Hz, CH_2-Br).

Diethyl 7-(*tert*-butyldimethylsilyloxy)methyl-4,8,8-trimethylcyclohex-3-enemethylmalonate (197)

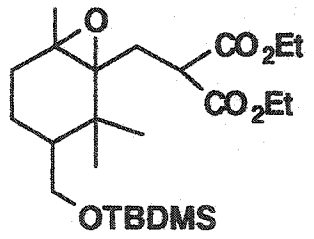


197

A solution of diethyl malonate (47.6 μL, 0.3 mmol) in dioxane (0.5 mL) was added dropwise to a cold (0 °C) suspension of NaH (5.5 mg, 0.23 mmol, 80% oil, Aldrich) (washed twice with hexane) in dioxane (1 mL). After hydrogen evolution had ceased, the reaction mixture was warmed to 22 °C and the bromide **196** (75 mg, 0.2 mmol) dissolved in dioxane (0.5 mL) added dropwise. The temperature was raised to 50 °C with an external oil bath and stirring continued for 3 h. The product was obtained after quenching the reaction with water, extraction with ether and dried.

Concentration and chromatography (5% EtOAc/petroleum ether) gave **197** (85.4 mg, 97%). ^{1}H NMR (200 MHz), δ -0.20 (s, 6 H, $Si(CH_3)_2$), 0.81 (s, 3 H, CH_3), 0.93 (s, 9 H, $(CH_3)_3$), 1.02 (s, 3 H, CH_3), 1.20 (overlapping t, 6 H, J = 7 Hz, $(C\underline{H}_3\text{-}CH_2)_2$), 1.37 - 1.43 (m, 2 H), 1.52 (s, 3 H, $=C\text{-}CH_3$), 1.73 - 1.92 (m, 3 H), 2.70 (d, 2 H, J = 6.91 Hz, $(=C\text{-}C\underline{H}_2\text{-}CH)$), 3.30 (dd, 1 H, J = 8.75, 10 Hz, CH-OSi), 3.40 (t, 1 H, J = 6.9 Hz, $(C\underline{H}\text{-}CO_2Et)$), 3.71 (dd, 1 H, J = 3.5, 10 Hz, CH-OSi), 4.14 (overlapping q, 4 H, J = 7 Hz, $(OC\underline{H}_2\text{-}CH_3)_2$); ^{13}C δ 170.0, 169.9, 133.8, 130.8, 63.4, 61.2, 47.0, 36.9, 31.0, 27.6, 26.8, 25.7, 22.5, 20.9, 20.4, 18.0, 13.8, -5.6; MS (EI) *m/z* 383 (25%) (M^+ - 57), 217 (100%) (M^+ - 57 - $CH(CO_2Et)$; HRMS (EI) calcd. for $C_{20}H_{35}O_5Si$ (M^+ - C_4H_9) 383.2253, found 383.2256.

Diethyl 3,4-epoxy-7-(*tert*-butyldimethylsilyloxy)methyl-4,8,8-tri-methylcyclohexanemethylmalonate (198)

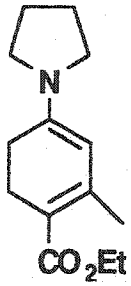


198

m-Chloroperbenzoic acid (45 mg, 0.15 mmol, 85% Aldrich) was added to a solution of the starting material **197** (43.5 mg, 0.098 mmol) in $CHCl_3$ at 22 °C and stirred for 22 h. Dichloromethane was added and the mixture washed sequentially with saturated $NaHCO_3$ solution, water, brine and dried. The solvent was evaporated to

afford the product (43 mg, 95%) which was used for the next step without further purification. ^{1}H NMR (200 MHz), δ -0.24 (s, 6 H, $Si(CH_3)_3$), 0.80 (s, 9 H, $(CH_3)_3$), 0.87 (s, 3 H, CH_3), 1.02 - 1.15 (m, 2 H), 1.20 - 1.33 (m, 9 H), 1.42 - 2.50 (m, 5 H), 3.24 - 3.30 (m, 1 H, CH-OSi), 3.49 - 3.61 (m, 2 H), 4.11 - 4.20 (m, 4 H); MS (EI) *m/z* 399 (2.6%) (M^+ - 57), 129 (71%), 77 (100%).

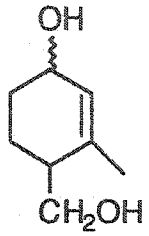
Ethyl-3-methyl-5-*N*-Pyrrolidinyl-2,4-cyclohexadiene carboxylate (193)



193

Hagemann's ester **76** (0.5 g, 2.7 mmol), pyrrolidine (2 mL, excess) and anhydrous $MgSO_4$ were stirred at 22 °C in ether (2 mL) for 6 h. Filtration followed by concentration afforded **193** (0.63 g, 98%) as a yellowish oil. ^{1}H NMR (200 MHz) δ 1.23 (t, 3 H, J = 7.1 Hz, OCH_2CH_3), 1.84 - 1.95 (m, 4 H, CH_2-CH_2 (pyrrolidine ring)), 2.20 (s, 3 H, CH_3), 2.20 - 2.33 (m, 2 H, CH_2), 2.41 - 2.50 (m, 2 H, CH_2), 3.20 - 3.25 (m, 4 H, CH_2-N-CH_2), 4.01 (q, 2 H, J = 7.1, OCH_2-CH_3), 4.50 (s, 1 H, =CH); ^{13}C, δ 168.8, 152.6, 150.9, 105.3, 97.4, 58.7, 47.3, 26.9, 24.9, 23.9, 22.2, 14.4.

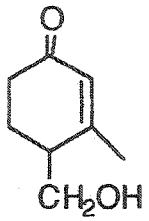
4-Hydroxymethyl-3-methyl-2-cyclohexen-1-ol (200)



200

Diisobutylaluminium hydride (1 M solution in toluene, 16.46 mL, 16.46 mmol) was added dropwise to a solution of Hagemann's ester 76 (1 g, 5.5 mmol) in benzene (5 mL) and the mixture stirred at 0 °C for 2 h. The aluminium salts were decomposed at 5 °C by dropwise addition of excess methanol (20 mL). The resulting white precipitate was removed by fltration and washed several times with hot methanol. The combined filtrate and washings were evaporated to give a thick oil and a gel-like precipitate which was removed by a second filtration. The crude product was chromatographed (50% acetone/petroleum ether) to afford the diol (770 mg, 98%). In subsequent experiments the crude product was used directly. IR (neat) 3350 (OH), 1660 (C=C) cm^{-1}; ^{1}H NMR (200 MHz), δ 5.65 (m, 1 H, CH=C), 4.16 (br s, 1 H, CH-O), 3.79 (m, 2 H, CH_2-O), 1.79 (s, 3 H, CH_3-C=C), 2.15 (m, 1 H, H-4), 1.5-2 (m, 6 H). ^{13}C NMR; δ 136.8 (C-3), 127.7(C-2), 65.3 (C-1), 63.2 (CH_2-OH), 41.1 (C-4), 30.6 (C-6), 29.3 (C-5), 21.4 (CH_3). MS: *m/z* 142, 124, 109, 91, 79, 77, 69, 55, 41, 39, 27. HRMS calcd. for $C_8H_{12}O$ - H_2O 124.0888, found 124.0890.

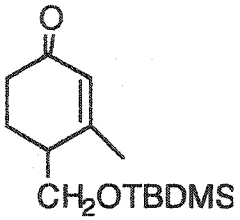
4-(Hydroxy)methyl-3-methyl-2-cyclohexenone (201)



201

The diol **200** (3.8 g, 26.8 mmol) was dissolved in dry dioxane (10 mL) and a dioxane solution of dichlorodicyanoquinone (7.92 g, 34.9 mmol) was added dropwise by syringe. The reaction was stirred at 21 °C overnight (23 h, reaction complete by TLC). The reaction was concentrated, diluted with ether, filtered through celite, and washed several times with ether until the washings were colourless. Concentration of the crude filtrate and chromatography (20% acetone/petroleum ether) on alumina (basic or neutral) gave the ketone (3.5 g, 92%). IR (neat) 3300 (br s, OH), 1665 (C=O) cm^{-1}; ^1H NMR, (200 MHz), δ 5.92 (s, 1 H, CH=C), 3.79 (m, 2 H, CH_2-O), 1.98 (s, 3 H, =C-CH_3); ^{13}C, δ 199.5, 162.1, 128.5, 70.0, 42.1, 34.2, 24.9, 22.7. MS: *m/z* 140, 122, 110, 95, 79. Anal. calcd for $C_8H_{14}O_2$: C, 68.54; H, 8.6; found: C, 67.91; H, 8.7.

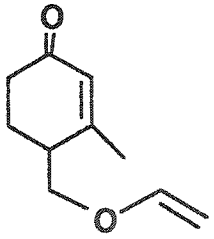
4-(*tert*-Butyldimethylsilyloxy)methyl-3-methyl-2-cyclohexen-1-one (202)



202

The alcohol (0.97 g, 6.82 mmol) was dissolved in DMF (2 mL) and imidazole (1.16 g, 17.0 mmol) followed by *tert*-butyldimethylsilyl chloride (1.23 g 8.18 mmol, Aldrich) added and the mixture stirred overnight (23 h) at 21 °C. The reaction was diluted with ether and washed with small portions of water (2x2 mL) to give the product. Chromatography (5% ethyl acetate/petroleum ether) gave **202** (1.7 g, 98%). IR (neat) 1675 (C=O) cm^{-1}; ^1H NMR (200 MHz), δ 5.87 (s, 1 H, CH=C), 3.72 (d, 2 H, J = 5.49 Hz, H_2C-O), 2.39 (m, 3 H, CH_3 -C=C), 2.02 (m, 2 H) 0.85 (s, 9 H, Me_3C), 0.02 (s, 6 H, Me_2Si) ^{13}C δ 199.4, 162.5, 128.1, 63.3, 42.7, 34.3, 25.5, 22.7, 17.8, -5.3. MS (EI) *m/z* 239, 224, 197 (M^+ - 57), 165, 81, 75, HRMS (EI) calcd for $C_{10}H_{17}O_2Si$ - C_4H_9, 197.1013, found 197.1013. Anal. calcd. for $C_{14}H_{26}O_2Si$: C, 66.08; H, 10.3; found: C, 65.91; H, 9.51.

4-(Vinyloxy)methyl-3-methyl-2-cyclohexenone (203)

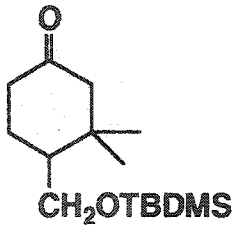


203

A mixture of the alcohol **201** (210 mg, 1.5 mmol), $Hg(OAc)_2$ (0.48 g, 1.5 mmol) and ethyl vinyl ether (8 mL) was refluxed for 17 h and then cooled to ambient temperature. Acetic acid (37.4 μL, 0.65 mmol) was added and stirring continued for 2.5 h. The mixture was poured into aqueous NaOH (30 mL) overlaid with petroleum ether

(90 mL) and separated. The aqueous layer was extracted with petroleum ether (2 x 30 mL) and the combined organic extracts dried, concentrated and chromatographed (5% EtOAc/petroleum ether) to give the product **203** (249 mg, 97%). IR (neat) 2929, 1652, 1444 cm^{-1}; ^1H NMR (200 MHz), δ 1.95 (s, 3 H, CH_3), 2.01 - 2.20 (m, 2 H), 2.20 - 2.51 (m, 2 H, CH_2-C=O), 2.57 - 2.62 (m, 1 H), 3.76 - 3.81 (m, 2 H, OCH_2), 4.02 (dd, J = 2.4, 6.82 Hz, 1 H, =CH), 4.22 (dd, J = 2.4, 14.5 Hz, 1 H, =CH), 5.90 (s, 1 H, O=C-CH=), 6.40 (dd, J = 6.8, 14.5 Hz, 1 H, OCH=C); ^{13}C δ 22.6, 25.3, 34.4, 39.3, 67.6, 86.9, 128.6, 151.5, 161.5, 199.3; MS (EI) *m/z* 166 (1.8%) (M^+), 151 (2.3%) (M^+ - 15), 123 (8.5%) (M^+ - $OCH=CH_2$), 109 (8.3%) (M^+ - CH_2-$OCH=CH_2$), 96 (100%); HRMS (EI) calcd. for $C_{10}H_{14}O_2$ 166.0993, found 166.0992.

3,3-Dimethyl-4-(*tert*-butyldimethylsilyloxy)methylcyclohexanone (204)

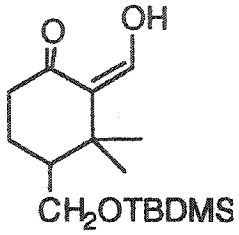


204

^1H NMR (200 MHz) δ 0.02 (s, 6 H, $Si(CH_3)_2$), 0.81 (s, 3 H, CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 1.01 (s, 3 H, CH_3), 1.53 - 1.84 (m, 2 H, CH_2), 2.02 - 2.41 (m, 5 H), 3.45 (dd, 1 H, J = 8.4, 5.29 Hz, CH-0) 3.82 (dd, 1 H, J = 4.3, 8.7 Hz, CH-O); ^{13}C δ 212.0, 63.3, 55.1, 47.0, 40.0, 37.2, 30.3, 25.6, 25.4, 22.0, 18.3, -5.7; MS (EI) *m/z* 255 (0.9%) (M^+ - CH3), 213 (28.4%)

(M^+ - $C(CH_3)_3$); HRMS (EI) calcd. for $C_{15}H_{30}O_2Si$ - $C(CH_3)_3$ 213.12665, found 213.1266.

2-Hydroxymethylidene-3,3-dimethyl-4-(*tert*-butyldimethylsilyloxy)methylcyclohexanone (205)

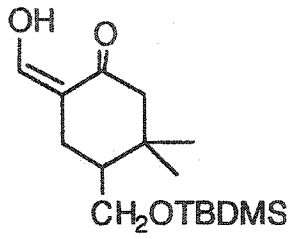


205

A suspension of copper(I) iodide (3.80 g, 20 mmol) in ether (200 mL) was cooled to 0 °C and methyllithium (28.6 mL, 40 mmol) introduced and stirring continued for 15 min. An ether solution of the enone **202** (2.56 g, 20 mmol) was added dropwise during 10 min. After 90 min, ethyl formate (9 mL) was added and after 20 min at 0 °C it was poured into aqueous 10% NH_4Cl solution (150 mL). The organic layer was washed (3x) with dilute aqueous 1% HCl solution, dried and concerntrated. Chromatography (5% ethyl acetate/petroleum ether) gave **205** (0.64 g, 20%). ^1H NMR (200 MHz), δ 0.03 (s, 6 H, $(CH_3)_2$-Si), 0.90 (s, 9 H, $C(CH_3)_3$), 1.11 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.55 (m, 2 H, CH_2), 1.95 (m, 1 H, CH), 2.40 (m, 2 H, CH_2-CO), 3.42 (dd, 1 H, J = 8.4, 5.3 Hz, CH-0), 3.83 (dd, 1 H, J = 4.3, 8.7 Hz, CH-O), 8.90 (d, 1 H, J = 3.2 Hz, =CH-O), 15.22 (d, 1 H, J = 3.2 Hz, O-H); ^{13}C δ 188.3, 185.6, 117.9 62.5, 46.0, 33.3, 30.2, 29.0, 25.6, 19.9, 18.0, -5.7; MS (EI) *m/z* 283 (M^+ - 15), 257, 241 (M^+ - 57), 237, 213, 199,

185, 171, 107, 75; HRMS (EI) calcd. for $C_{12}H_{21}O_3Si$ 241.1259, found 241.1252.

2-Hydroxymethylidene-5,5-dimethyl4-(*tert*-butyldimethylsilyloxy)methylcyclohexanone (206)

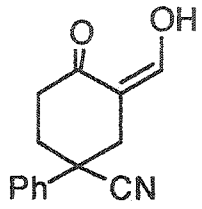


206

A suspension of cuprous iodide (3.80 g, 20 mmol) in ether (200 mL) was cooled to 0 °C and methyllithium (28.6 mL, 40 mmol) introduced and stirring continued for 15 min. An ether solution of the enone **202** (2.56 g, 20 mmol) was added dropwise during 10 min. After 1.5 h, THF (27.2 mL) followed quickly by ethyl formate (9 mL) were added and the reaction allowed to warm to room temperature (22 °C) over 4 h then poured into aqueous 10% NH_4Cl solution (150 mL). The organic layer was washed (3x) with dilute aqueous 1% HCl solution, dried and concerntrated. Chromatography (5% ethyl acetate/petroleum ether) gave **206** (2.5 g, 78%). ^1H NMR (200 MHz), δ 0.02 (s, 6 H, $(CH_3)_2$-Si), 0.85 (s, 12 H, $C(CH_3)_3$, CH_3), 0.98 (s, 3 H, CH_3), 1.55 (m, 1 H, CH), 2.09 (d, 2H, J = 11.4 Hz, CH_2-CO), 2.51 (dd, 1 H, J = 5.8, 15.7 Hz, H-3), 3.41 (dd, 1 H, J = 8.4, 5.3 Hz, CH-0), 3.75 (dd, 1 H, J = 4.3, 8.7 Hz, CH-O), 8.73 (d, 1 H, J = 1.6 Hz, =CH-O), 15.0 (d, 1 H, J = 1.6 Hz, O-H); ^{13}C δ 188.3, 185.6, 117.9 62.5, 46.0,

33.3, 30.2, 29.0, 25.6, 19.9, 18.0, -5.7; MS: *m/z* 283 (M^+ - 15), 257, 241 (M^+ - 57), 237, 213, 199, 185, 171, 107, 75; HRMS (EI) calcd. for $C_{12}H_{21}O_3Si$, 241.1259, found 241.1254.

3-Formyl-4-oxo-1-phenylcyclohexanecarbonitrile (209)



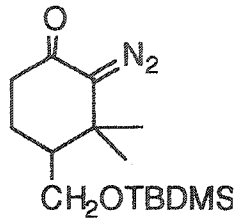
209

A stirred mixture of sodium hydride (0.376 g, 12.55 mmol, 80% in mineral oil, Aldrich), anhydrous ether (100 mL), and ethyl alcohol (0.25 mL) was cooled (0°C) and a solution of 4-cyano-4-phenylcyclohexanone (2.5 g, 12.5 mmol, Lancaster) and redistilled ethyl formate (1.52 ml, 18.8 mmol) were added dropwise during 1 h. Stirring was continiued for 66 h, and the solution allowed to stand overnight. Ethanol (1 mL) was added and the mixture stirred for 1 h. Water (10 mL) was added and the mixture poured into a 500 mL separatory funnel. The organic layer was separated, washed with water (5 mL) and the combined aqueous extract washed with ether (100 mL). The aqueous layer was acidified with 6 N HCl (4 mL) and the mixture extracted twice with ether (30 mL). The combined ether solutions were washed with brine (25 mL), dried, filtered and concentrated to give the product (2.5 g), which was used directly in the next step.

General procedure for the synthesis of 2-diazocyclohexanones.

2-Hydroxymethylidene-3,3-dimethyl-4-(*tert*-butyldimethylsilyloxy)methylcyclohexanone **205** (3.6 g, 12 mmol) was dissolved in dichloromethane (25 mL) and freshly distilled triethylamine (3.37 ml 0.024 mmol) added. The solution was cooled by an external ice-salt bath (-10°C) and *p*-toluenesulfonyl azide (1.8 g, 10 mmol) (prepared from *p*-toluenesulfonyl chloride and sodium azide) was added with vigorous stirring over a period of approximately 1 h. Stirring was continued for an additional 2 h as the cooling bath melted and the temperature rose to 0 °C. A solution of KOH (0.672 g, 12 mmol) in water (25 mL) was added and the mixture stirred at 21 °C for 15 min. The resulting emulsion was placed in a 100 mL separatory funnel, the dichloromethane layer separated and the aqueous alcoholic layer washed twice with dichloromethane (5 mL). The combined dichloromethane extracts were washed with aqueous KOH solution (0.05 g in water (15 mL), with water and dried over anhydrous $NaSO_4$. Concentration and chromatography (5% ethyl acetate/petroleum ether) gave the product.

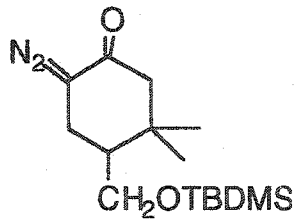
2-Diazo-3,3-dimethyl-4-(*t*-butyldimethylsilyloxy)methylcyclohexanone (210)



210

20% Yield from **202**. IR (neat) 2100 ($C{=}N_2$), 1740 (C=O) cm^{-1}; ^1H NMR (200 MHz), δ 3.85 (dd, 1 H, J = 10.0, 4.4 Hz, CH-O) 3.54 (dd, 1 H, J = 10.0, 7.5 Hz, CH-O), 2.41 (m, 2 H, CH_2-CO), 2.1 (m, 1 H, H-4), 1.71 (m, 2 H, CH_2), 1.39 (s, 3 H, CH_3), 11.17 (s, 3 H, CH_3), 0.93 (s, 9 H, Si-$C(CH_3)_3$), 0.1 (s, 6 H, Si-$(CH_3)_2$); ^{13}C δ 193.9, 62.5, 62.2, 51.4, 44.2, 32.6, 28.4, 25.6, 22.3, 17.9, -5.8; MS (EI) *mz* 268 (M^+ - 28), 253, 240, 211 (M^+ - 28 - 57), 181, 171, 107, 89, 75; HRMS (EI) calcd. for $C_{15}H_{28}O_2Si$ 268.1858, found 268.1865.

2-Diazo-4-(*tert*-butyldimethylsilyloxy)methyl-5,5-dimethylcyclohexanone (211)

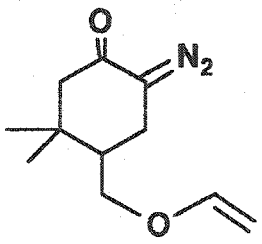


211

78% Yield from **202**. IR (neat) 2100 ($C{=}N_2$), 1740 (C=O) cm^{-1}; ^1H NMR (200 MHz), δ 3.82 (dd, 1 H, J = 10.0, 4.4 Hz, CH-O), 3.5 (dd, 1 H, J = 10.0, 7.5 Hz, CH-O), 2.85 (dd, 1 H, =C-CH), 2.60 (dd, 1 H, =C-CH)

2.08 (s, 2 H), 1.68 (m, 1 H, H-4), 0.97 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 0.85 (s, 9 H, Si-$C(CH_3)_3$), 0.15 (s, 6 H, Si-$(CH_3)_2$; ^{13}C δ 193.9, 62.5, 62.2, 51.4, 44.2, 32.6, 28.4, 25.6, 22.5, 17.9, -5.8; MS: *m/z* 268, 253, 239, 211, 181, 171, 107, 93, 75; HRMS (EI) calcd. for $C_{15}H_{28}O_2Si$ 268.1858, found 268.1865.

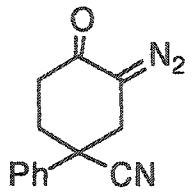
2-Diazo-5,5-dimethyl-4-(vinyloxy)methylcyclohexanone (212)



212

The diazotization reaction described previously was employed to obtain the product (85%). IR (neat) 2932, 2087 (C=N_2), 1756 (very weak), 1624 cm^{-1}; ^1H NMR (200 MHz), δ 0.95 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.92 - 2.06 (m, 1 H, CH-CH_2-O-R), 2.16 (s, 2 H, CH_2-C=O), 2.62 (dd, J = 9.55, 14.3 Hz, 1 H, CH-C=N_2), 2.92 (dd, J = 5.65, 14.3 Hz, 1 H, CH-C=N_2), 3.55 (dd, J = 9.4, 9.74 Hz, CH-OR), 3.89 (dd, J = 3.99, 9.74 Hz, 1 H, CH-OR), 4.01 (dd, J = 2.2, 6.82 Hz, 1 H, =CH), 4.17 (dd, J = 2.2, 14.95 Hz, 1 H, =CH), 6.45 (dd, J = 6.82, 14.95 Hz, 1 H, O-CH=C); MS: *m/z;* 180 (13) (M^+ - N_2), 165 (1.4) (M^+ - N_2 - 15), 153 (10) (M^+ - N_2 - $CH=CH_2$), 137 (M^+ - N_2 - $OCH=CH_2$); HRMS (EI) calcd. for $C_{11}H_{16}O_2$ (M^+ - N_2) 180.115, found 180.1133.

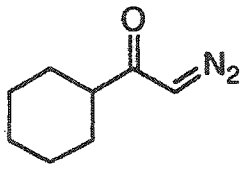
2-Diazo-4-oxo-1-phenylcyclohexanecarbonitrile (213)



213

40% Yield from the parent ketone **208**; IR (CCl_4) 2238 (CN), 2110 (C=N_2), 1727 (C=O) cm^{-1}; ^1H NMR (200 MHz), δ 2.34 (dd, 1 H, J = 8.1, 4.2, CH_2-CO), 2.57 (dt, 1 H, J = 18.4, 4.1, CH-C(CN)Ph), 2.80 (dt, 1 H, J = 18.7, 9.5 Hz, CH-C(CN)Ph), 3.22 (s, 2 H, =C-CH_2), 7.42 (m, 5 H, Ph); ^{13}C δ 190.4, 137.7, 129.5, 129.0, 125.5, 120.8, 62.5 (C-2), 41.2, 34.3, 33.7, 32.2; MS (EI) *m/z* 224.9, 197, 168, 154, 141, 129.

Diazoacetylcyclohexane (215)

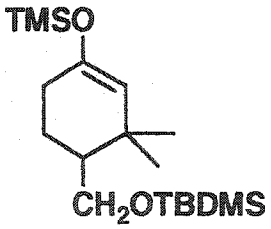


215

Oxalyl chloride (4.8 mL, 54.6 mmol) was added dropwise to a stirred solution of cyclohexanecarboxylic acid (1 g, 7.8 mmol) in benzene (40 mL). Concentration gave the acid chloride (97%) which was reacted directly with an ethereal solution of diazomethane to generate the diazoketone **215**. IR (neat) 2104 (C=N_2), 1636 (C=O) cm^{-1}; ^1H NMR (200 MHz), δ 1.25 (m, 6 H, $(CH_2)_3$), 1.71 (m, 4 H, $(CH_2)_2$-

C), 5.22 (s, 1 H, =CH), 2.10 (br, 1 H, CH-CO); ^{13}C δ 198.5, 29.1, 25.6; MS (EI) *m/z* 153.1, 152, 124, 123, 109, 97, 95, 83, 67, 41, 39; HRMS (EI) calcd. for $C_8H_{12}N_2O$ 152.0950, found 152.0942.

Trimethylsilyloxy-3,3-dimethyl-4-(*tert*-buthyldimethylsilyloxy)methylcyclohexene (216)



216

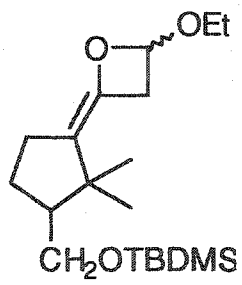
Trimethylsilyl enol ether **216** (300 mg, 0.8 mmol) was prepared according to the procedure used for the preparation of TMS enol ether **186**, in 93% yield. IR (neat) 2930, 1250 cm^{-1}; ^1H NMR (200 MHz), δ 0.01 (s, 6 H, $Si(CH_3)_2$), 0.14 (s, 9 H, $Si(CH_3)_3$), 0.78 (s, 3 H, CH_3), 0.86 (s, 9 H, $C(CH_3)_3$), 1.02 (s, 3 H, CH_3), 1.37 - 1.42 (m, 2 H, C_5), 1.83 - 1.92 (m, 1 H, C_4), 1.93 - 1.96 (m, 2 H, C_6), 3.30 (dd, 1 H, J = 8.4, 5.29 Hz, CH-0) 3.72 (dd, 1 H, J = 4.3, 8.7 Hz, CH-O), 4.50 (s, 1 H, =CH); MS: (EI) 342 (0.3) (M^+), 327 (23.5%) (M^+ - CH_3), 285 (26.3%) (M^+ - *t*-Bu); HRMS (EI) calcd. for $C_{18}H_{38}O_2Si_2$ 327.2127, found 327.2127.

General procedure for metal catalyzed cyclopropanation and oxetane formation.

An anhydrous diethyl ether (1.5 mL) solution of the diazoketone (100 mg, 0.34 mmol) was added over 4 h via syringe

pump (Sage model 341A) to a stirred solution of the catalyst {(4.49 x 10^{-3} mmol, 1 mg palladium(II) acetate) or (1.68 x 10^{-3} mmol, 0.7 mg rhodium(II) acetate) or (1.68 x 10^{-2} mmol, 1.66 mg cuprous chloride)} and excess alkene (1 mL) at room temperature (21 °C). The needle of the syringe was placed just below the surface of the reaction solution. Once the addition was complete, the mixture was concentrated, flushed through a small amount of silica gel (70 - 230 mesh) and reconcentrated. The product was purified by chromatography (5% ethyl acetate/petroleum ether).

2,2-Dimethyl-1-(2-oxa-3-ethoxycyclobutylideneyl)-3-(*tert*-butyldimethylsilyloxy)methylcyclopentylidene (218)

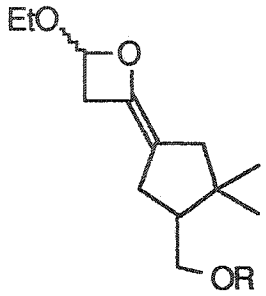


218

70% Yield from **210**. IR (neat) 1100 (vs, C-O) cm^{-1}; ^1H NMR (200 MHz) δ 0.15 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $Si\text{-}C(CH_3)_3$), 1.05 (s, 3 H, CH_3), 1.24 (t, 3 H, J = 7.1, $O\text{-}CH_2\text{-}C\underline{H}_3$), 1.27 (s, 3 H, CH_3), 1.71 - 2.80 (m, 7 H), 3.35 (m, 1 H, CH-O), 3.50 (m, 1 H, CH-O), 3.75 (m, 2 H, $O\text{-}C\underline{H}_2\text{-}CH_3$), 5.45 (m, 1 H, O-CH-O); ^{13}C δ 148.3, 104.6, 102.4, 63.4, 63.2, 45.7, 39.5, 39.4, 32.6, 28.8, 25.7, 23.8, 23.0, 18.0, 15.0, -5.7; DEPT (200 MHz) δ 104.6 (CH), 63.4 (CH_2), 63.2 (CH_2), 45.7 (CH), 39.5 (CH_2), 38.4 (CH_2), 28.8 (CH_3), 25.7 (CH_3), 23.8 (CH_2), 23.0 (CH_3), 15.0 (CH_3), -5.7

(CH_3); MS (EI) *m/z* 340, 325, 295, 279, 255, 237, 208, 163, 98 (100%); HRMS (EI) calcd. for $C_{19}H_{36}O_2Si$ 340.2433, found 340.2433.

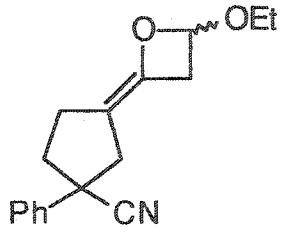
3,3-Dimethyl-1-(2-oxa-3-ethoxycyclobutylideneyl)-4-(*tert*-butyldimethylsilyloxy)methylcyclopentylidene (219)



219

75% Yield from diazoketone **211**. IR (neat) 1100 (vs, C-O) cm^{-1}; ^1H NMR (200 MHz) δ 0.15 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $Si\text{-}C(CH_3)_3$), 0.853 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.19 (t, 3 H, J = 7.1, $O\text{-}CH_2\text{-}C\underline{H}_3$), 1.70 (m, 7 H), 1.91 - 2.60 (m, 6 H), 3.35 (m, 1 H, CH-O), 3.53 (m, 1H, CH-O), 3.75 (m, 2 H, $O\text{-}C\underline{H}_2\text{-}CH_3$), 5.50 (m, 1 H, O-CH-O); ^{13}C δ 148.3, 104.6, 102.4, 63.5, 63.2, 45.7, 39.5, 39.4, 32.6, 28.8, 25.7, 23.8, 23.0, 18.0, 15.0, -5.67; MS (EI) *m/z* 340, 325, 295, 279, 255, 237, 208, 163, 98 (100%); HRMS (EI) calcd. for $C_{19}H_{36}O_2Si$ 340.2433, found 340.2433.

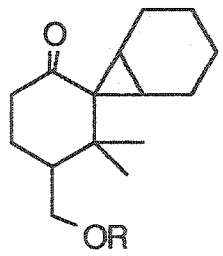
1-Phenyl-3-(2-oxa-3-ethoxycyclobutylideneyl)cyclopentyl-idenecarbonitrile (220)



220

40% Yield from **213**. IR (CCl_4) 1098 (C-O), 2241 (CN) cm^{-1}; ^1H NMR (200 MHz) δ 1.23 (t, 3 H, J = 7.1 Hz, 3 H, $C\underline{H}_3$-CH_2), 2.40 (m, 8 H), 3.71 (m, 2 H, O-CH_2-CH_3), 5.55 (m, 1 H, O-CH-O), 7.33 (m, 5 H, Ph); ^{13}C δ 149.3, 139.9, 129.0, 102.0, 64.0, 39.3, 35.9, 32.8, 21.2, 14.9; MS: *m/z* 270, 269, 243 (M^+ - CN), 224 (M^+ - 45), 196, 195, 192 (M^+ - Ph) 180, 167, 165, 152, 129, 105, 72, HRMS (EI) calcd for $C_{17}H_{19}NO_2$ 269.1411, found 269.1382.

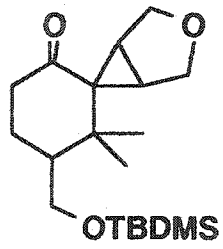
6,6-Dimethyl-5-(*tert*-butyldimethylsilyloxy)methylcyclohe-xan-2-onespiro[4.1.0]heptane (222)



222

25% Yield from **210**. IR (neat) 1710 (C=O). 1093 (C-O) cm^{-1}; ^1H NMR (200 MHz) δ 0.04 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 12 H, $Si\text{-}C(CH_3)_3$, CH_3),,1.03 (s, 3 H, CH_3), 1.06 - 2.31 (m, 15 H), 3.84 (m, 1 H, CH-O); MS (EI) *m/z* 350, 332, 293, 275, 232, 218, 210, 107, 75; HRMS (EI) calcd. for $C_{21}H_{38}O_2Si$ 350.2641, found 350.2661.

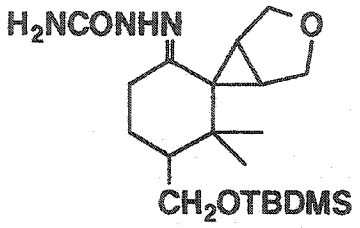
6,6-Dimethyl-5-(*tert*-butyldimethylsilyloxy)methylcyclohexan-2-onespiro[3.1.0]pentahydrofuran (223)



223

Same procedure as for the preparation of **200**. (25%). ^1H NMR (200 MHz), δ 0.0 (s, 6 H, $CH_3\text{-}Si\text{-}CH_3$), 0.81 (s, 3 H, CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 1.21 (s, 3 H, CH_3), 1.23 - 1.50 (m, 2 H), 1.9 (m, 1 H), 2.1 - 2.7 (m, 4 H), 3.31 - 3.60 (m, 2 H), 3.70 - 3.85 (m, 2 H), 4.21 (m, 1 H), 4.70 (m, 1 H); ^{13}C δ 210.2, 75.0, 62.7, 54.0, 46.0, 38.5, 36.1, 33.0, 29.5, 26.0, 21.2, 18.0, -6.4; MS (EI) 338 (0.5%) (M^+), 320 (6.5%), (M+ - H_2O), 281 (12.5%) (M^+ - $C(CH_3)_3$), 263 (3.7%) (M^+ - H_2O - $C(CH_3)_3$); HRMS (EI) calcd. for $C_{19}H_{34}O_3Si$ - H_2O 320.2099, found 320.2097.

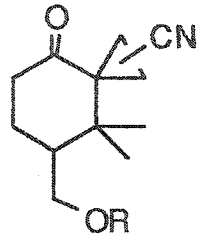
6,6-Dimethyl-5-(*tert*-butyldimethylsilyloxy)methylcyclohexan-2-simicarbazonespiro[3.1.0]pentahydrofuran (224)



224

Semicarbazide hydrochloride (18mg, 0.16 mmol) and sodium acetate (24 mg, 30 mmol) was dissolved in a few drops of water and compound **223** in ethanol (5 drops) added. The crystals which formed were filtered, redissolved in ethanol and allowed to recrystallize. Filtration and drying (under vacum) afforded **224** (85%, 17 mg) as a white powder. ^{1}H NMR δ 0.02 (s, 6 H, CH_3-Si-CH_3), 0.81 (s, 3 H, CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 1.10 (s, 3 H, CH_3), 1.23 - 1.40 (m, 1 H), 1.61 - 1.82 (m, 4 H), 2.40 - 2.54 (m, 1 H), 3.43 - 3.82 (m, 5 H), 4.01 - 4.20 (m, 1 H), 4.82 - 5.82 (br, 1 H), 8.30 (s, 1 H); ^{13}C δ 157.5, 152.6, 70.8, 63.1, 45.8, 40.0, 36.5, 36.1, 29.2, 25.7, 25.6, 20.4, 18.1, -5.7.

Cyano-8,8-dimethyl-7-(*tert*-butyldimethylsilyloxy)methyl-spiro[2.5]octan-2-one (225)



225

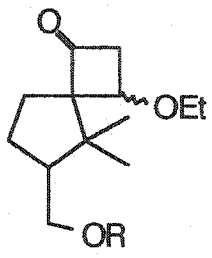
Acrylonitrile (1.5 mL) and **210** (100 mg, 0.34 mmol) in toluene (8 mL) were refluxed for 24 h. Chromatography (5% ethyl acetate/petroleum ether) gave the cyclopropane product **225** as a mixture of isomers in 75% yield. IR (neat) 2240 (CN), 1708 (C=O), 3, 1098 (C-O) cm^{-1}; ^1H NMR (200 MHz) δ 0.02 (s, 6 H, Si-$(CH_3)_2$), 0.85 (s, 9 H, Si-$C(CH_3)_3$), 1.07 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.47 - 2.32 (m, 8 H), 3.42 (m, 1 H, CH-O), 3.86 (m, 1 H, CH-O); ^{13}C δ 206.0, 117.2, 62.7, 61.4, 55.9, 52.1, 46.7, 36.1, 35.5, 33.9, 31.2, 29.4, 25.9, 21.48, 18.2, 16.7, 14.21, -5.38; MS (EI) *m/z* 306, 264 (M^+ - 57), 234, 200, 172, 155, 107, 91; HRMS (EI) calcd for $C_{14}H_{22}NO_2Si$ - C_4H_9 264.1419, found 264.1420. Anal. calcd. for $C_{18}H_{31}NO_2Si$: C, 67.24; H, 9.71; N, 4.37, found: C, 67.34; H, 9.61; N, 4.49.

General procedure for photochemical reactions of the diazoketones.

A solution of the diazoketone (100 mg, 0.34 mmol) in ethyl vinyl ether (5 mL) was degassed by bubbling dry argon through the solution for about 10 min then irradiated (medium pressure Hanovia

Hg lamp) for 3 h until the reaction was complete by TLC analysis. Concerntration followed by chromatography (10% ethyl acetate/petroleum ether) afforded the product. For all sensitized photolyses, benzophenone (943 mg, 3.34 mmol) was added.

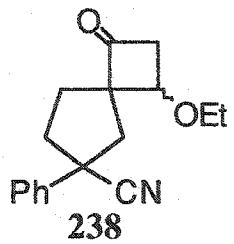
5,5-Dimethyl-3-ethoxy-6-(*tert*-butyldimethylsilyloxy)methylspiro[3.4]heptan-1-one (236)



236

88% Yield from **210**. IR (neat) 1780 (C=O), 1100 (C-O) cm^{-1}; ^1H NMR (200 MHz) δ 0.15 (s, 6 H, Si-$(CH_3)_3$), 0.85 (s, 12 H, Si-$C(CH_3)_3$, CH_3), 1.05 (s, 3 H, CH_3), 1.20 (m, 3 H), 1.71 (m, 4 H, $(CH_2)_2$), 2.11 (m, 1 H, CH), 3.02 (m, 2 H, CH_2-CO), 3.45 (m, 4 H, CH_2-O, Si-O-CH_2), 3.87 (m, 1 H, CH-O); MS (CI) *mz* 340.9 (100%); MS (EI) *m/z* 283, 237, 211, 166, 129, 75; HRMS (EI) calcd. for $C_{19}H_{36}O_3Si$ 283.1734, found 283.1715.

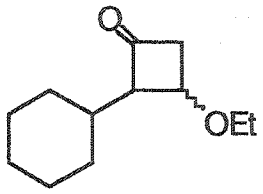
6-Phenyl-6-cyano-3-ethoxyspiro[3.4]heptan-1-one (238)



238

60% Yield from **213**. IR (CCl_4) 2234 (CN), 1779 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ 1.23 (m, 3 H, CH_3), 2.52 (m, 6 H), 3.19 (m, 2 H, CH_2-CO), 3.63 (m, 2 H, O-CH_2), 4.11 (m, 1 H, CH-O), 7.34 (m, 5 H , Ph); MS (EI) *mz* 269, 242, 241, 227, 216, 196, 168, 143, 142, 129, 128, 98; HRMS (EI) calcd. for $C_{17}H_{19}O_2N$ 269.1411, found 269.1411.

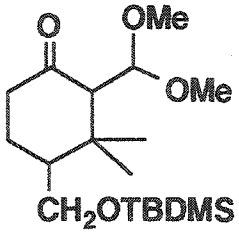
2-Cyclohexyl-3-ethoxycyclobutanone (239)



239

80% Yield from **215**. IR (neat) 1780 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ 1.00 (m, 9 H), 1.83 (m, 5 H), 2.91 (m, 3 H, CH_2-CO, CH-CO), 3.45 (m, 2 H, O-CH_2), 4.15 (m, 1 H, CH-O); MS (EI) *mz* 197, 196, 168, 154, 150, 132, 122, 108, 80, 67; Too volatile for HRMS.

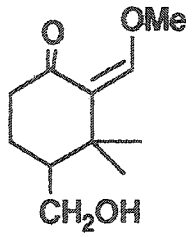
2-(Dimethoxy)methyl-3,3-dimethyl-4-(*tert*-butyldimethylsilyloxy)methylcyclohexanone (260)



260

MeMgBr (16.65 mL, 23.4 mmol) was added to a stirred suspension of CuI (0.29 g, 1.56 mmol) in ether (180 mL) at 0 °C. After 5 min the starting enone **202** (4 g, 15.6 mmol) in ether (5 mL) was added dropwise and after 30 min at 0° C the reaction mixture was cooled to -78 °C and $CH(OMe)_3$ (4.95 mL, 46.8 mmol) followed by $BF_3.Et_2O$ (5.74 mL, 46.8 mmol) added. The reaction was quenched after 1 h at -78 °C, washed with 10% NH_4Cl solution, brine, dried and concentrated. Chromatography (5% Et_2O/petroleum ether) gave **260** (3.34 g) in 61% yield. About 1 g of the intermediate **204** (without the acetal protected side chain) was also obtained. IR (neat) 2970, 1720, 1475, 1120, 880, 780 cm^{-1}; ^1H NMR, (200 MHz), δ 0.018 (s, 6 H, $Si(CH_3)_2$), 0.78 (s, 3 H, CH_3), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.03 (s, 3 H, CH_3), 1.45 - 1.70 (m, 1 H), 2.01 - 2.60 (m, 5 H), 3.27 (s, 3 H), 3.29 (s, 3 H), 3.42 (dd, 1 H, J = 8.75, 10 Hz, CH-OSi), 3.85 (dd, 1 H, J = 3.7, 10 Hz, CH-OSi), 4.71 (d, 1 H, J = 7 Hz O-CH-O); ^{13}C δ 210.0, 101.1 ($CH(OMe)_2$), 64.7, 63.3, 53.1, 52.6, 43.2, 39.9, 38.0, 25.9, 25.9, 25.7, 22.9, 17.9, -5.6; MS (EI) *mz* 329 (M^+ - CH_3), 287 (M^+ - $C(CH_3)_3$), 256 (M^+ - $C(CH_3)_3$ -OMe); HRMS (EI) calcd. for $C_{18}H_{36}O_4Si$ (M^+ - $C(CH_3)_3$) 287.1683, found 287.1680. Anal. calcd. for $C_{18}H_{36}O_4Si$: C, 62.75; H, 10.53; found C, 62.83; H, 10.43.

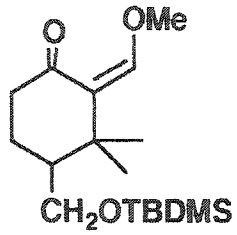
2-(Methoxy)methylidene-3,3-dimethyl-4-hydroxymethyl-cyclohexanone (261)



261

Tetrabutylammoniun fluoride (1.16 mL, solution in THF, 1.16 mmol) was added to a cold (0 °C) solution of the starting material (0.2 g, 0.58 mmol) in THF (3.5 mL). The reaction mixture was allowed to warm to 22 °C and stirring continued overnight. Water was added, the reaction extracted with ether and the combined ether extracts dried and concentrated to afford the product (114 mg, 99%). IR (neat) 3399, 2931, 1665, 1569, 1253 cm^{-1}; ^1H NMR (Acetone-d_6, 200 MHz), δ 1.03 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.40 - 2.51 (m, 6 H), 3.3 - 3.35 (m, 1 H, C<u>H</u>-OH), 3.79 - 3.88 (m, 4 H, OCH_3 and C<u>H</u>-OH), 7.23 (s, 1 H, =CH); ^{13}C ($CDCl_3$) δ 202.2, 161.1, 123.4, 62.11, 62.1, 48.0, 37.9, 36.0, 26.6, 20.7, 20.7; MS (EI) *m/z* 198 (31.5%) (M^+), 183 (30%) (M^+ - CH_3), 166 (32%) (M^+ - OMe); HRMS (EI) calcd. for $C_{11}H_{18}O_3$ 198.1255, found 198.1248.

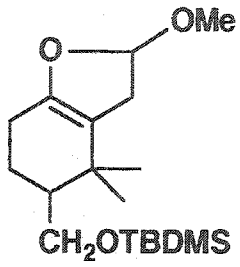
2-(Methoxy)methylidene-3,3-dimethyl-4-(*tert*-butyldimethylsilyloxy)methylcyclohexanone (262)



262

KH (0.64 mg, 35% mineral oil) was added to **261** (20 mg, 0.057 mmol) in ether (1 mL) at 22 °C for 3 h. The reaction was quenched with aqueous 10% NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with brine and dried. Concentration followed by chromatography gave the product **262** (174 mg, 98%). ^1H NMR (Acetone-d_6 200 MHz) δ 0.08 (s, 6 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $(CH_3)_3$), 1.11 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.56 - 2.32 (m, 5 H), 3.50 (dd, 1 H, J = 8.15, 10 Hz, CH-OSi), 3.85 - 3.92 (m, 4 H, CH-OSi and OCH_3), 7.22 (s, 1 H, =CH); ^{13}C δ 201.8, 160.6, 123.5, 62.7, 61.9, 47.8, 37.1, 36, 26.9, 25.8, 21.1, 20.7, 18.2, -5.4; MS (EI) *m/z* 279 (2.9%) (M^+ - 15), 255 (100%) (M^+ - 57); HRMS (EI) calcd. for $C_{13}H_{23}O_3$ (M^+ - 57) 255.1416, found 255.1409.

2-Methoxy-4,4-dimethyl-5-(*tert*-buthyldimethylsilyloxy)-methyl-2,3,4,5,6,7-hexahydrobenzofuran (263)

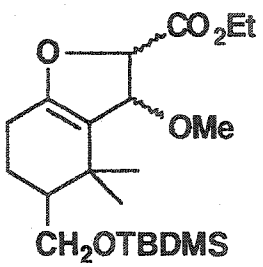


263

Trimethyloxosulfonium iodide ($(CH_3)_2SOCH_2I$) (38.15 mg, 0.17 mmol) in DMF (0.5 mL) was added to a suspension of NaH (4 mg) in DMF (1 mL) at 22 °C. After stirring for 20 min **262** (53 mg, 0.17 mmol) dissolved in DMF (0.5 mL) was added in one portion and stirring continued for 2 h. Cold water was added and the reaction mixture extracted several times with ether. The combined ether extracts were washed with water then brine and dried with anhydrous $NaSO_4$. Concentration followed by chromatography (5% Et_2O/petroleum ether) gave **263** (22 mg, 40%). ^1H NMR (300 MHz), δ 0.02 (s, 6 H, Si-$(CH_3)_2$), 0.86 (s, 3 H, CH_3) 0.87 (s, 9 H, $(CH_3)_3$), 1.1 (s, 3 H, CH_3), 1.43 - 1.50 (m, 2 H), 1.90 - 1.96 (m, 1 H), 2.04 - 2.09 (m, 2 H, allylic CH_2, 5-membered ring), 2.38 - 2.35 (m, 1 H), 2.64 - 2.68 (m, 1 H), 3.40 (dd, 1 H, J = 8.79, 10 Hz, CH-OSi), 3.42 (s, 3 H, OCH_3), 3.75 (dd, 1 H, J = 3.65, 10 Hz, CH-OSi), 5.34 (dd, 1 H, J = 2.57, 7.25 Hz, O-C<u>H</u>-OCH_3); ^{13}C δ 148.2, 113.2, 105.6, 63.5, 55.4, 47, 35.4, 26.9, 25.9, 22.4, 22.18, 22, 21.8, -5.3; DEPT (75 MHz) δ 105.6 (CH), 63.5 (CH_2), 55.4 (CH_3), 47 (CH), 35.4 (CH_2), 26.9 (CH_3), 25.9 (CH_3), 22.4 (CH_2), 22.2 (CH_2), 22 (CH_3), -5.3 (CH_3); MS (EI) *m/z* 326 (1%) (M^+) 311 (36%) (M^+

- 15), 269 (27%) (M^+ - 57), 237 (10%) (M^+ - 15 - OCH_3); HRMS (EI) calcd. for $C_{18}H_{34}O_3$ 326.2276, found 326.2285.

2-Carbethoxy-3-methoxy-4,4-dimethyl-5-(tert-buthyldimethylsilyloxy)-methyl-2,3,4,5,6,7-hexahydrobenzofuran (268)

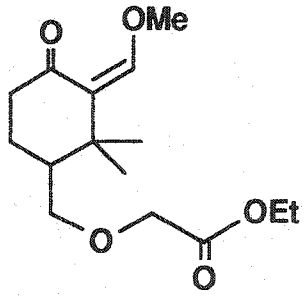


268

To a suspention of enone **262** (189.5 mg, 0.6 mmol) and rhodium(II) acetate (2.6 mg, 0.006 mmol) in ether (3 mL) was added ethyldiazo acetate (191 μL, 1.8 mmol) in ether (2.5 mL) dropwise over 6 h by syringe pump. The crude product was concentrated and chromatographed (5% ethyl acetate/petroleum ether) to furnish **268** (108 mg, 46%) as a colourless oil. IR (neat) 2924, 1742, 1465, 1075 cm^{-1}; ^1H NMR (300 MHz) δ 0.01 (s, 6 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $C(CH_3)_3$), 0.90 (overlapping s, 3 H, CH_3), 1.11 (overlapping s, 3 H, CH_3), 1.23 (overlapping t, 3 H, J = 7 Hz, $OCH_2C\underline{H}_3$), 1.30 - 1.62 (m, 2 H, C_6), 1.90 - 1.98 (m, 1 H, C_5), 2.10 - 2.22 (m, 2 H, allylic CH_2), 3.31 (m, 4 H, OCH_3 + CH-OSi), 3.73 (m, 1 H, CH-OSi), 4.10 - 4.21 (m, 2 H, $OC\underline{H}_2CH_3$), 4.50 (m, 1 H, CH-OMe) 4.70 (m, 1 H, O-CH-CO_2Et); ^{13}C NMR δ 170.4, 170.3, 156.7, 114.0, 113.0, 87.1, 86.5, 82.6, 82.4, 63.2, 62.3, 61.4, 61.3, 54.9, 54.7, 47, 46.7, 33.1, 33, 28.4, 26.7, 25.9, 25.8, 23, 22.9,

22.7, 21.8, 21.6, 18.2, 14.1, -5.3, -5.4. DEPT (200 MHz) δ 87.0 (CH), 86.5 (CH), 82.6 (CH), 82.4 (CH), 63.2 (CH_2), 62.3 (CH_2), 61.4 (CH_2), 61.3 (CH_2), 54.9 (CH_3), 54.7 (CH_3), 47.0 (CH), 46.7 (CH), 33.1, 33, 28.4 (CH_3), 26.7 (CH_3), 25.9, 25.8 (CH_3), 23.0 (CH_3), 22.9 (CH_2), 22.7 (CH_3), 21.8 (CH_2), 21.6 (CH_2), 21.2 (CH_2), 18, 14 (CH_3), -5.3 (CH_3), -5.4 (CH_3). MS (EI) 383 (1.3%) (M^+ - CH_3), 367 (3%) (M^+ - OMe), 341 (27.3%) (M^+ - *t*-Bu), 309 (16%) (M^+ - OMe - *t*-Bu), 325 (9.1%) (M^+ - CO_2Et), 267 (10%) (M^+ - *t*-Bu - CO_2Et); HRMS (EI) calcd. for $C_{21}H_{38}O_5Si$ - $C(CH_3)_3$ 341.1756, found 341.1756.

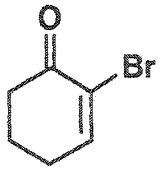
Ethyl 5-[6,6-dimethyl-7-methoxymethylidene-8-oxo-2-oxymethyl]cyclohexanecarboxylate (269)



269

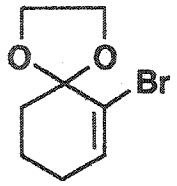
Enone **269** was prepared from alcohol **261** according to the procedure described above for the preparation of **268** in 60% yield. IR (neat) 2933, 1746, 1671, 1575, 1454 cm^{-1}. ^1H NMR (200 MHz), δ 1.10 (s, 3 H, CH_3), 1.25 (t, 3 H, J = 7 Hz, $OCH_2C\underline{H}_3$), 1.30 (s, 3 H, CH_3), 1.61 - 1.73 (m, 2 H), 2.12 - 2.53 (m, 3 H), 3.30 (dd, 1 H, J = 8.79, 10 Hz, CH-OSi), 3.65 (dd, 1 H, J = 3.65, 10 Hz, CH-OSi), 3.80 (s, 3 H, OCH_3), 4.10 (s, 2 H, O-$C\underline{H}_2$-CO_2Et), 4.20 (q, 2 H, J = 7 H, $OC\underline{H}_2CH_3$), 7.23 (s, 1 H, =CH).

2-Bromocyclohex-2-ene-1-one



Bromine (5.29 mL, 103.2 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 30 min to a stirred solution of 2-cyclohexene (10 mL, 8.7 mmol) in CH_2Cl_2 (250 mL) maintained at 0 °C. The solution was stirred at 0 °C for a further 1.5 h, and then Et_3N (23 mL, 123 mmol) was added dropwise. The solution was stirred at room temperature for 1.5 h. It was washed with aqueous 3% HCl (2 x 50 mL) and saturated brine (50 mL). The mixture was dried and the solvent evaporated to afford the crude solid. Recrystallization from ethyl acetate/hexanes afforded 15.2 g (78%) of the previously reported 2-bromocyclohex-2-ene-1-one as white crystals (m.p. 75-76 °C, Lit. m.p.[151a] 74 °C). IR ($CHCl_3$) 1690, 1600 cm^{-1}; ^1H NMR, (200 MHz), δ 2.05 (m, 2 H), 2.38 - 2.47 (m, 2 H), 2.59 - 2.62 (m, 2 H), 7.40 (t, 1 H, J = 4 Hz).

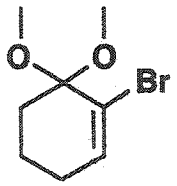
6-Bromo-1,4-dioxaspiro[4.5]dec-6-ene (158a)



158a

A mixture of 2-bromocyclohex-2-ene-1-one (2.81 g, 16 mmol), benzene (115 mL), ethylene glycol (2.32 mL, 41.6 mmol) and TsOH (28 mg) was heated at reflux with azeotropic removal of water (Dean-Stark trap) for 72 h. The reaction mixture was cooled to room temperature, 0.5 g K_2CO_3 added and the mixture filtered through a cake of silica gel on $MgSO_4$ with the aid of CH_2Cl_2. Concentration followed by chromatography (5% Et_2O/petroleum ether) gave 3.7 g (91%) of the product **158a** as a colorless oil. IR (neat) 2922 cm^{-1}; ^1H NMR (200 MHz), δ 1.70 - 1.82 (m, 2 H), 1.85 - 1.91 (m, 2 H), 2.00 - 2.12 (m, 2 H), 3.90 - 3.98 (m, 2 H), 4.10 - 4.18 (m, 2 H), 6.30 (t, 1 H, J = 7 Hz); ^{13}C δ 136.0, 124.5, 105.8, 65.8, 65.79, 35.0, 27.1, 20.2; MS (EI) *m/z* 219.9 (M^+ + 2), 219, 218 (M^+), 189.9, 188 (M^+ - CH_2O), 139 (M^+ - Br).

1,1-Dimethoxy-2-bromocyclohex-2-ene (158b)

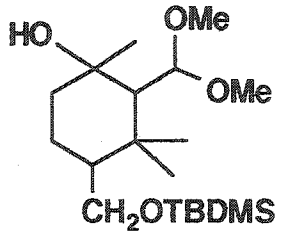


158b

A Montmorillorite clay K 10 (Aldrich) orthoformate/methanol reagent was prepared by stirring K-10 Montmorillorite clay (1 g) with a mixture of trimethyl orthoformate (0.8 mL) in methanol (0.8 mL) and filtration. The carbonyl substrate (500 mg, 2.87 mmol) was added to a suspension of the resultant filter cake in CCl_4 (3 mL) and stirred for 20 min followed by filtration. The filtrate was washed with saturated aqueous $NaHCO_3$ solution then brine. Concentration

followed by chromatography (5% Et_2O/petroleum ether) gave **158b** (400 mg, 64% yield) as a colourless oil. IR (neat) 2945, 2831 cm^{-1}; ^1H NMR, (200 MHz), δ 1.70 - 1.84 (m, 2 H), 1.85 - 1.90 (m, 2 H), 2.01 - 2.12 (m, 2 H), 3.30 (s, 6 H), 6.30 (t, 1 H, J = 4 Hz,); ^{13}C δ 136.1, 122.6, 96.9, 50.1, 50.0, 32.1, 28.3, 19.2.

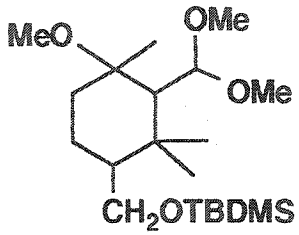
2-Dimethoxymethyl-1,3,3-trimethyl-4-(*tert*-butyldimethylsilyloxy)methylcyclohexanol (274)



274

MeMgBr (7.15 mL, 10 mmol) was added to ketone **260** (2.65 g, 7.7 mmol) in ether (20 mL) at 0 °C and stirring continued for 30 min. The reaction was quenched with aqueous 10% NH_4Cl solution and extracted (3x) with ether. The combined ether extracts were dried and concentrated to give the product **274** (2.68 g) in 97% yield. IR (neat) 3550, 2977 cm^{-1}; ^1H NMR, (200 MHz), δ 0.01 (s, 6 H), 0.85 (s, 9 H), 0.98 (s, 3 H), 1.21 (s, 3 H), 1.30 (s, 3 H), 3.30 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.56 - 3.80 (m, 2 H, CH_2-OSi), 3.97 (br s, 1 H, OH), 4.40 (s, 1 H, C<u>H</u>$(OMe)_2$); ^{13}C δ 109.6 ($CH(OMe)_2$), 72.1 (R_3COH), 62.2 (CH_2-OSi), 56.7 (OMe), 55.8 (OMe), 51.3, 47.4, 35.9, 34.6, 31.6, 28.4, 26.2, 25.7, 19.6, 17.9, -5.7. Anal. calcd. for $C_{19}H_{40}O_4Si$: C, 63.28; H, 11.18; found: C, 63.34; H, 11.11.

2-Dimethoxymethyl-1-methoxy-1,3,3-trimethyl-4-(*tert*-butyldimethylsilyloxy)methylcyclohexane (275)



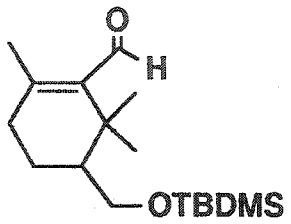
275

Method A. MeLi (9.34 mL, 13.08 mmol) was added to a solution of **260** (3 g, 8.72 mmol) in ether (50 mL) at 0 °C. HMPA (3.03 mL, 17.44 mmol) was added followed by MeI (1.08 mL, 17.44 mmol) and the reaction mixture was allowed to warm to 22 °C and stirring continued overnight. The reaction was quenched with water and washed several times with saturated aqueous NH_4Cl solution, dried and concentrated. Chromatography (5% Et_2O/petroleum ether) gave **275** (1.27 g) and the intermediate tertiary alcohol **274** (1.5 g) in 38% and 45% yield respectively.

Method B. The above procedure was repeated on the intermediate tertiary alcohol to give 94% of **275** after chromatography (5% Et_2O/petroleum ether). IR (neat) 2979, 1465, 1200 cm^{-1}; ^1H NMR (200 MHz), δ 0.02 (s, 6 H), 0.85 (s, 9 H), 0.96 (s, 3 H), 1.20 (s, 3 H), 1.19 (s, 3 H), 1.31 - 1.73 (m, 6 H), 3.10 (s, 3H), 3.31 (s, 3 H), 3.35 (s, 3 H), 3.55 (dd, 1 H, J = 8.77, 10 Hz, SiOCH), 3.75 (dd, 1 H, J = 4, 10 Hz, Si-OCH), 4.51 (d, 1 H, J = 3.7 Hz, MeO-C<u>H</u>-OMe); ^{13}C δ 108.5, 75.8, 61.2, 56.0, 54.7, 54.2, 48.7, 47.8, 35.5, 28.87, 28.7, 26.4,

25.7, 24.9, 18.5, 18.0, -5.6. Anal. calcd. for $C_{20}H_{42}O_4Si$: C, 64.12; H, 11.3, found C, 64.19; H, 11.47.

5-(tert-Butyldimethylsilyloxy)methyl-2,6,6-trimethyl-1-cyclohexenecarboxaldehyde (276)



276

Method I: Propylene gas was bubbled through a solution of **275** (650 mg, 1.69 mmol) in CH_2Cl_2 (3 mL) at room temperature. NaI (279 mg, 1.86 mmol) was added followed by trimethylsilylchloride (0.24 mL, 1.86 mmol) and stirring continued for 5 min after which the reaction was quenched with water, washed with water, aqueous 6% $Na_2S_2O_4$ and brine. The organic layer was concentrated to give the product which was used for the next step without further purification.

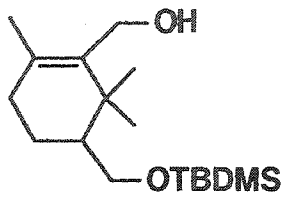
This material was dissolved in MeOH, NaOMe (91.3 mg, 1.69 mmol) added and the reaction refluxed for 30 min. The mixture was concentrated, ether added and washed with water and brine. Concentration followed by chromatography (5% Et_2O/petroleum ether) gave **276** (350 mg) in 70% yield from the acetal.

Method II: An aqueous 15% H_2SO_4 solution (1.2 g) was added with continuous stirring to a suspension of silica gel (70 - 230 mesh,

12 g) in CH_2Cl_2 (15 mL). After 3 min when the aqueous phase had disappeared, a solution of **275** in CH_2Cl_2 (2 mL) was added and stirring continued at room temperature for 2 min during which the reaction was completed. $NaHCO_3$ (0.1 g) was then added and stirring continued for 5 min followed by filtration of the reaction mixture through a small plug of $MgSO_4$. Concentration gave the product which was used directly without further purification for the next step.

NaOMe (140 mg, 2.6 mmol) was added to a solution of the aldehyde (876 mg, 2.6 mmol) in MeOH (10 mL). The mixture was refluxed for 8 h, concentrated, ether added and the ether extracts washed with water, brine and dried. Concentration and chromatography (5% Et_2O/petroleum ether) gave the aldehyde **276** (846 mg) in 96% yield. IR (neat), 2921, 1698 cm^{-1}; ^1H NMR, (200 MHz), δ 0.01 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H), 1.01 (s, 3 H), 1.30 (s, 3 H), 1.36 - 1.20 (m, 2 H, CH_2), 1.84 - 1.87 (m, 1 H, CH), 2.02 (s, 3 H, CH_3), 2.10 - 2.20 (m, 2 H, allylic CH_2), 3.33 (dd, 1 H, J = 8.75, 10, CH-O), 3.83 (dd, 1 H, J = 3.65, 10, CH-O), 10.62 (s, 1 H, CHO); ^{13}C δ 192.3 (conjugated CHO), 156.3, 140.4, 62.9, 47.8, 35.3, 34.6, 26.3, 25.9, 21.4, 20.7, 19.4, 18.0, -5.3; MS (EI) *mz* 281 (M^+ - 15), 239 (M^+ - 57), 210 (M^+ - $C(CH_3)_3$ - CHO); HRMS (EI) calcd. for $C_{13}H_{23}O_2Si$ 239.1467, found 239.1466.

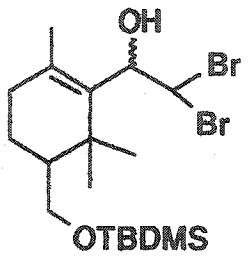
6-(*tert*-butyldimethylsilyloxy)methyl-3,7,7-dimethyl-2-cyclohexenemethanol (277)



277

Diisobutylaluminum hydride (1M solution in toluene, 53.6 μL, 0.08 mmol) was added to a solution of the aldehyde **276** (20 mg, 0.067 mmol) in toluene (1.5 mL) at -78° C and the mixture stirred for 1.5 h at -78 °C. The reaction was warmed to 0 °C and MeOH was added until a white precipitate formed. The crude product was filtered through Celite and washed free of remaining product with hot MeOH. Concentration gave **277** (20 mg), 99% yield which was used without further purification. M.p. 53.5 - 55 °C. IR ($CHCl_3$) 3620, 2960, 1260, 1090, 840 cm^{-1}; ^1H NMR (200 MHz), δ 0.02 (s, 6 H, $Si(CH_3)_2$), 0.84 (s, 3 H, CH_3), 0.86 (s, 9 H, $C(CH_3)_3$), 1.10 (s, 3 H, CH_3), 1.22 - 1.40 (m, 3 H), 1.70 (s, 3 H, =C-CH_3), 1.94 - 1.98 (m, 2 H, allylic CH_2), 3.32 (dd, 1 H, J = 8.75, 10 Hz, CH-OSi), 3.78 (dd, 1 H, J = 3.65, 10 Hz, CH-OSi), 4.11 (AB q, 2 H, J = 9.89 Hz, C$\underline{H_2}$-OH); ^{13}C δ -5.3 ($Si(CH_3)_2$), 18.3 (CH_3), 19.9 (CH_3), 21.4 (CH_2), 22.2 (vinyl CH_3), 25.9, 26.7, 31.7 (allylic CH_2), 36.3, 46.8, 60.9, 63.7, 132.0, 136.5; MS (EI) *m/z* 280 (1.8%) (M^+ - 18), 233 (25%) (M^+ - 75), 75 (100%) (H_2O + $C(CH_3)_3$); HRMS (EI) calcd. for $C_{17}H_{23}O$ 233.15179, found 233.1523. Anal. calcd. for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48, found C, 68.50; H, 11.26.

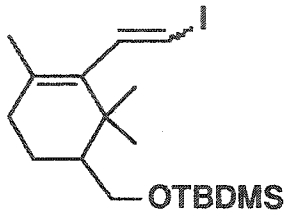
7-(*tert*-Butyldimethylsilyloxy)methyl-4,8,8-trimethyl-cyclohex-3-ene-1,1-dibromo-2-ethanol) (278b)



278b

n-Butyllithium (0.48 mL, 1.2 mmol) was added to a solution of dicyclohexylamine (242 μL, 1.2mmol) in THF (2 mL) at 0 °C. The resulting lithium dicyclohexylamide was added over a period of 15 min to a solution of dibromomethane (85 μL, 1.2 mmol) and the aldehyde **276** (180 mg, 0.6 mmol) in THF (2 mL) at -78 °C for 1 h. Workup followed by chromatography (5% Et_2O/petroleum ether) gave the alcohol **278** (60mg, 22%); IR (neat) 3480, 2916, 1722, 1466, 1375, 1253 cm^{-1}; ^1H NMR (200 MHz), δ 0.01 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 1.02 (s, 3 H), 1.20 (s, 3 H) 1.22 - 1.40 (m, 4H), 1.81 (s, 3 H, $=C-CH_3$), 2.02 (m, 2 H, allylic CH_2), 3.40 (dd, 1 H, J = 8.75, 10, CH-O), 3.80 (dd, 1 H, J = 3.65, 10, CH-O), 4,60 (d, 1 H, J = 9.8 Hz), 6.20 (d, 1 H, J = 9.8 Hz); ^{13}C δ 136.1, 135.2, 76.7, 64.0, 51.5, 58.0, 37.3, 34.2, 27.0, 26.1, 23.4, 21.3, 21.0, 18.1, -5.1; MS (EI) *m/z* 455 (2.5%) (M^+ - CH_3), 413 (1.6%) (M^+ - $C(CH_3)_3$), 395 (1.3%) (M^+ - $C(CH_3)_3$ - H_2O), 319 (4.4%) (M^+ - Br - $C(CH_3)_3$ - H_2O).

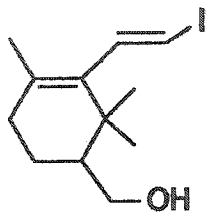
3-(2-Iodoethenyl)-1,3,3-trimethyl-4-(*tert*-butyldimethylsilyloxy)methylcyclohexene (278)



278

Aldehyde **276** (0.29 g, 0.98 mmol) and iodoform (0.77 g, 1.99 mmol) in THF (3.5 mL) was added dropwise over 15 min to a stirred suspension of $CrCl_2$ (0.72 g, 5.88 mmol) in THF (20 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into water (12.5 mL) extracted with ether and the combined ether extracts dried and concentrated. Chromatography (5% Et_2O/petroleum ether) gave **278** (189 mg, 45%) and starting material **276** (118 mg, 40%). The yield of the pure product after chromatography decreased to about 20% as the reaction was scaled up. IR (neat) 2916, 1467, 1362, 1253, 1094 cm^{-1}; ^1H NMR, (200 MHz), δ 0.01 (s, 6 H), 0.84 (s, 3 H), 0.86 (s, 9 H), 1.01 (s, 3 H), 1.30 - 1.46 (m, 2 H, CH_2), 1.50 (s, 3 H, vinyl CH_3), 1.72 - 1.91 (m, 2 H), 2.73 (m, 1 H, allylic CH), 3.31 (dd, 1 H, J = 8.75, CH-O,), 3.72 (dd, 1 H, J = 3.7, 10, CH-O), 5.81 - 6.45 (m, 2 H, vinyl CH); ^{13}C δ 145.3, 132.7, 130.0, 74.7 (=CHI), 63.9, 47.1, 37.1, 34.6, 31.5, 27, 25.9, 22.0, 21.6, 20.0, 18.3, -5.1; MS (EI) *mz* 402, 389, 377, 363 (M^+ - $C(CH_3)_3$), 302, 287.

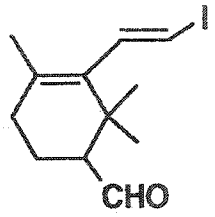
3-(2-Iodoethenyl)-2,2,4-trimethyl-3-cyclohexenylmethanol (279)



279

Tetrabutylammonium fluoride (1.74 mL, 1.79 mmol, 1 M solution in THF, Aldrich) was added to **278** (376.8 mg, 0.89 mmol) in THF (5 mL) at 0 °C and the reaction stirred overnight at 22 °C. The reaction mixture was poured into water (3 mL) and extracted with ether (3 x 10 mL). The combined ether extracts were dried, concentrated and chromatographed (20% ethyl acetate/petroleum ether) to give **279** (270 mg) in 98% yield as a colourless oil. IR (neat) 3325, 2920.8 cm^{-1}; ^1H NMR, (200 MHz), δ 0.75 - 2.08 (m, 13 H), 2.30 - 2.42 (m, 1 H, allylic CH), 2.71 - 2.92 (m, 1 H, allylic CH), 3.30 - 3.45 (m, 1 H, CH-OH), 3.80 - 3.88 (m, 1 H, CH-OH), 5.82 - 6.72 (m, 2 H, vinyl protons); ^{13}C δ 145.0, 132.0, 130.2, 74.9 (C bearing vinyl iodide), 63.5, 47.4, 37.0, 34.3, 31.2, 27.3, 22.0, 21.0, 20.0; MS (EI) *mz* 307 (M^+ + 1), 306 (M^+), 288.9 (M^+ - H_2O), 179.1 (M^+ - I), 161 (M^+ - (I + H_2O) 153 (M+ - CH=CHI); HRMS (EI) calcd. for $C_{12}H_{19}IO$ 306.04805, found 306.0480.

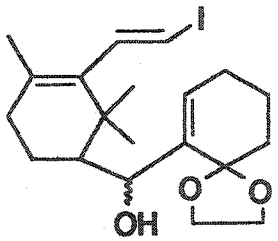
3-(2-Iodoethenyl)-2,2,4-trimethyl-3-cyclohexenecarboxaldehyde (280)



280

Pyridinuim dichromate (432 mg, 1.14 mmol) was added to the alcohol **279** (234.3 mg, 0.76 mmol) in CH_2Cl_2 (1.5 mL) at 22 °C and the mixture stirred overnight. Ether was added and the mixture filtered through celite. Last traces of chromium salts were removed by a second filtration through a small plug of $MgSO_4$ on silica gel (70 - 230 mesh). The resulting product **280** (200mg, 86%) was used without further purification. IR (neat) 2934, 1717 cm^{-1}; ^1H NMR (200 MHz), δ 0.81 - 1.32 (m, 8 H), 1.58 - 2.20 (m, 6 H), 2.79 - 2.81 (m, 1 H, CH-CHO), 5.91 - 6.01 (m, 1 H, =CH), 6.30 - 6.41 (m, 1 H, =CH), 9.80 (d, 1 H, J = 2.8, CHO).

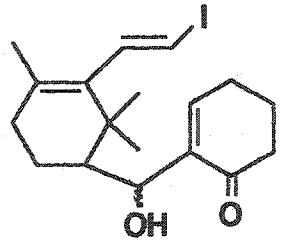
3'-(2'-iodoethenyl)-2',2',4'-trimethyl-3'-cyclohexenyl-1,4-dioxaspiro[4.5]dece-6-en-6-ylmethanol (281)



281

6-Bromo-1,4-dioxaspiro[4.5]dec-6-ene **158a** (148 mg, 0.67 mmol) in THF (2 mL) was added dropwise over 5 min to a cold (-78 °C) solution of *n*-BuLi (0.27 mL, 0.68 mmol) in THF (10 mL). The resulting solution stirred for 1 h and treated with excess HMPA (1 mL, 6.2 mmol) followed by dropwise addition of aldehyde **280** (159 mg, 0.52 mmol) in THF (2 mL). After 5 h at -78 °C, the reaction was quenched with aqueous 10% NH_4Cl, warmed to room temperature, diluted with ether (50 mL) and washed with water and brine. The ether solutuion was dried, concentrated and chromatographed (15% EtOAc/petroleum ether) to give **281** (108 mg, 47% yield) as a mixture of isomers. No attempt was made to separate the isomers. IR (neat) 3475, 2918 cm^{-1}; ^1H NMR (200 MHz), δ 0.80 - 1.38 (m, 8 H), 1.42 - 1.86 (m, 7 H), 1.90 - 2.01 (m, 2 H), 2.02 - 2.20 (m, 2 H, allylic CH_2 in the C-ring), 2.70 - 2.85 (m, 2 H, allylic CH_2 in the A ring), 3.90 - 3.97 (br s, 4 H, O-CH_2CH_2-O) 4.58 (br s, 1 H, CH-OH), 5.80 - 5.94 (m 1 H, vinyl proton), 6.05 - 6.15 (m, 1 H, vinyl proton, C ring), 6.30 - 6.52 (m, 1 H, vinyl proton); ^{13}C δ 145.3, 139.7, 133.0, 130.3, 130.1, 107.7, 74.8, 67.3, 64.2, 64.0, 47.8, 38.9, 35,3, 32.8, 27.0, 25.0, 22.6, 20.1, 17.2; MS (CI) 445 (M^+ + 1).

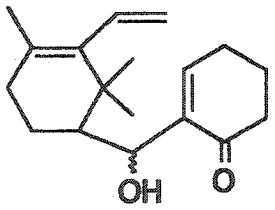
2-(Hydroxy(3-(2-iodoethenyl)-2,2,4-trimethyl-3-cyclohex-enyl)methyl-2-cyclohexenone (282)



282

Aqueous 20% H_2SO_4 (70 mg) was added to a stirred suspension of silica gel (700 mg) in CH_2Cl_2 (1 mL) After 3 min when all the aqueous phase had disappeared, a solution of **281** (71 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) was added and stirring continued at room temperature for 1 h. Solid $NaHCO_3$ (10 mg) was added and stirring continued for another 5 min. Filtration of the crude mixture through a small plug of $MgSO_4$ gave the product **282** (63 mg) in 98% yield. IR (neat) 3419, 2921, 1668 cm^{-1}; ^1H NMR (200 MHz), δ 0.74 - 1.73 (m, 12 H), 1.76 - 2.20 (m, 5 H), 2.25 - 2.50 (m, 3 H), 2.71 - 2.80 (m, 1 H), 4.80 - 4.90 (m, 1 H), 5.82 - 6.42 (m, 2 H, vinyl protons, A ring), 6.90 - 6.95 (m, 1 H, vinyl proton, C ring); ^{13}C δ 145.5, 145.5, 141.0, 133.2, 130.0, 74.8 (=CHI), 68.3, 48.1, 39.3, 35.5, 32.5, 27.5, 26.0, 23.0, 20.8, 17.2.

2-(Hydroxy(3-ethenyl)-2,2,4-trimethyl-3-cyclohexenyl)methyl-2-cyclohexenone (283)

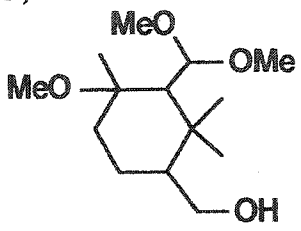


283

A solution of azobisisobutyronitrile (AIBN) (3 mg, 0.01 mmol), tributyltin hydride (28.2 uL, 0.1 mmol) in benzene (2 mL) was added over 10 h via syringe pump to a refluxing solution of azobisisobutylonitrile (1 mg) and **282** (35 mg, 0.09 mmol) in benzene. Concentration followed by chromatography (5% ethyl

acetate/petroleum ether) after 22 h afforded **283** and **284a** or **284b** (9.3:1) as a colourless UV active gum (14 mg, 57%). IR (neat) 3438, 2917, 1661, 1457 cm^{-1}; ^1H NMR (200 MHz) δ 0.90 - 2.11 (m, 17 H), 2.30 - 2.42 m, 4 H), 2.81 (m, 1 H), 4.90 - 5.32 (m, 3 H), 5.60 - 6.32 (m, 1 H), 6.90 - 7.01 (m, 1 H).

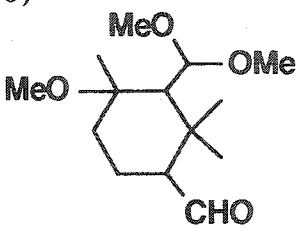
(3-Dimethoxymethyl-4-methoxy-2,2,4-trimethylcyclo-hexyl)methanol (285)



285

The removal of TBDMSi- group with tetrabutylammonium fluoride described above for the preparation of **279** was repeated on a 3 g scale to give 98% yield of **285** after chromatography from **275**. IR (neat) 3387, 2929, 1062 cm^{-1}; ^1H NMR, (200 MHz), δ 0.85 - 1.60 (m, 15 H), 1.71 - 1.85 (m, 1 H), 3.10 (s, 3 H), 3.25 (s, 3 H), 3.35 (s, 3 H), 4.50 (d, 1 H, J = 3.6 Hz, MeO-CH-OMe).

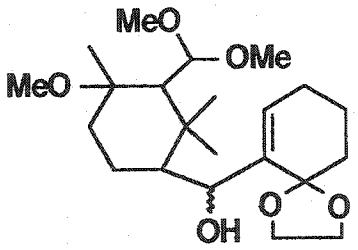
3-Dimethoxymethyl-4-methoxy-2,2,4-trimethylcyclohexane carboxaldehyde (286)



286

The alcohol **285** was converted to the aldehyde **286** in 89% yield according to the procedure described above for the preparation of **280** using PDC. IR (neat) 2938, 2826, 1717 cm^{-1}; ^1H NMR, (200 MHz), δ 1.22 (s, 9 H), 1.59 - 1.86 (m, 5 H), 2.11 - 2.14 (m, 1 H, C<u>H</u>-CHO), 3.10 (s, 3 H), 3.30 (s, 3 H), 3.37 (s, 3 H), 4.61 (d, J = 3.9 Hz, 1 H), 9.90 (d, 1 H, J = 2.2 Hz, CHO); ^{13}C δ 206.0 (CHO), 107.4 ($CH(OMe)_2$), 75.7, 60.1, 56.2, 55.0, 53.3, 48.1, 35.3, 30.0, 29.4, 26.0, 24.9, 18.6; MS (CI) *mz* 259 (M^+ + 1).

3'-(dimethoxymethyl)-4-methoxy-2',2',4'-trimethylcyclohexanyl-1,4-dioxaspiro[4.5]dece-6-en-6-ylmethanol (287)

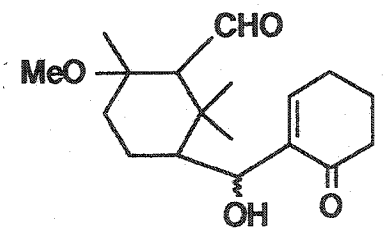


287

6-Bromo-1,4-dioxaspiro[4,5]dec-6-ene **158a** (236.4 mg, 1.08 mmol) in THF (2 mL) was added dropwise over 5 min. to a cold (-78 °C) solution of *n*-BuLi (0.43 mL, 1.09 mmol) in THF (15 mL). The resulting solution was allowed to stir for 1 h and treated with excess HMPA (1 mL, 6.2 mmol) followed by the dropwise addition of **286** (233.3 mg, 0.904 mmol) in THF (2 mL). The reaction was allowed to proceed for 5 h at -78 °C, quenched with 10% aqueous NH_4Cl solution, warmed to 22 °C and diluted with Et_2O (50 mL). The ether solution was washed with water, brine, dried and concentrated.

Chromatography (15% EtOAc/petroleum ether) gave **287** as a mixture of isomers (230.8 mg) in 74% yield. IR (neat) 3422, 2928, 2827, 1729 (weak) cm^{-1} (This signal increases after a couple of days due to the decomposition of the acetal with time to the aldehyde even when the sample was kept in the fridge); ^1H NMR, (200 MHz), δ 1.11 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.50 - 1.75 (m, 10 H), 1.98 (d, 1 H, J = 3.9 Hz), 2.10 (m, 2 H), 3.10 (s, 3 H, OMe), 3.30 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.96 (br s, 4 H, $(OCH_2)_2$), 4.58 (d, 1 H, J = 2.93 Hz, $CH(OMe)_2$), 4.71 (m, 1 H, CH-OH), 6.08 (m, 1 H, =CH); ^{13}C δ 140.5, 130.2, 108.9 ($CH(OMe)_2$), 107.7 ($R_2C(OCH_2)_2$), 76.5 (R_3COMe), 69.2, 64.5, 64.3, 56.2, 54.6, 54.7, 48.0, 46.6, 36.8, 33.5, 31.7, 28.7, 27.6, 25.3, 25, 20.2, 17.5; MS (EI) m/z 367 (0.3%) (M^+ - OMe), 334 (1.8%) (M^+ - H_2O - Me_2O), 290 (0.5%), (M^+ - H_2O - $(CH_2)_2O$).

(2-(Hydroxy(3-(carboxaldehyde-4-methoxy)-2,2,4-trimethyl-3-cyclo-hexenyl)methyl)cyclohexenone (289)

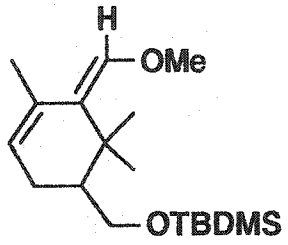


289

The Jones' reagent was added dropwise from a burette to the alcohol **287** (25 mg, 0.062 mmol) dissolved in acetone (0.5 mL) at 0 °C until a greenish colour was produced (2 drops). The crude reaction mixture was concentrated, water added and the mixture extracted

with ether. The combined ether extracts were dried and concentrated. Chromatography (20% EtOAc/petroleum ether) gave a UV active product **289** (18.4 mg) in 97% yield. IR (neat) 3422, 2929, 1729 (CHO), 1690 cm^{-1}; ^1H NMR, (200 MHz), δ 0.76 - 2.60 (m, 22 H), 3.22 (s, 3 H, OMe), 4.85 (br s, 1 H, CH-OH), 6.93 - 7.02 (m, 1 H, =CH), 9.85 (overlapping doublet, 1 H, J = 3 Hz, CHO).

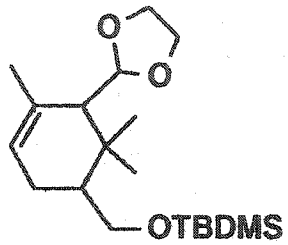
2,4,4-Trimethyl-3-(methoxymethylidene)-5-(*tert*-butyl-dimethylsilyloxy)methylcyclohexene (296)



296

A mixture of **276** (35 mg, 0.12 mmol), montmorillorite clay K 10 (0.1g, Aldrich), trimethyl orthoformate (0.2 mL), and hexanes (2 mL) was stirred for 10 min at 22 °C. Filtration followed by chromatography (5% ethyl acetate/petroleum ether) afforded **296** (22 mg, 60%); ^1H NMR (200 MHz) δ 0.01 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $Si(CH_3)_3$), 1.50 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 1.40 - 1.50 (m, 1 H), 1.72 (s, 3 H, $=C-CH_3$), 2.10 - 2.22 (m, 2 H, allylic CH_2), 3.31 (dd, 1 H, J = 8.77, 10 Hz, O-CH), 3.60 (s, 3 H, OMe), 3.71 (dd, 1 H, J = 4, 10 Hz, O-CH), 5.32 (m, 1 H, =CH), 6.01 (s, 1 H, =CH-O); ^{13}C δ 143.0, 130.0, 123.2, 121.5, 62.2, 60.1, 48.2, 38.0, 27.0, 26.0, 24.5, 24.3, 21.2, 18.3, -6.1.

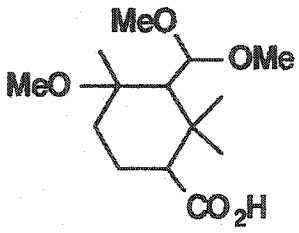
2,4,4-Trimethyl-3-(1,4-dioxapentanyl)-5-(*tert*-butyldimethylsilyloxy)methylcyclohexene (295)



295

Aldehyde **276** (60 mg, 0.2 mmol), ethylene glycol (29 uL, 0.5 mmol) and *p*-toluenesulfonic acid (1.1mg, 0.006 mmol) in toluene (2 mL) was refluxed for 3 h. Workup (see **159**), concentration and chromatography (5% ethyl acetate/petroleum ether) gave the labile compound **295** (14 mg, 20%) as a colourless oil. ^{1}H NMR (200 MHz) δ 0 (s, 6 H, $Si(CH_3)_2$), 0.80 (s, 3 H, CH_3), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.01 (s, 3 H, CH_3), 1.51 - 2.51 (m, 7 H), 3.30 - 3.52 (m, 2 H), 3.73 - 4.01 (m, 4 H), 5.02 (d, 1 H, J = 4 Hz, 0-CH-0), 5.51 (broad s, 1 H, =CH).

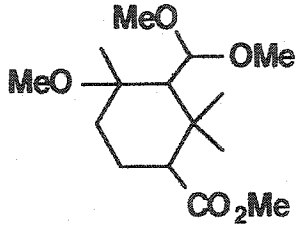
3-Dimethoxymethyl-4-methoxy-2,2,4-trimethylcyclohexanecarboxylic acid (298)



298

Obtained as a by-product from the oxidation of alcohol **285**. ^{1}NMR (200 MHz), δ 1.10 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.30 - 2.02 (m, 4 H), 2.10 (d, J = 2.95 Hz, 1 H), 2.25 (m, 1 H), 3.02 (s, 3 H, OCH_3), 3.21 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 4.62 (d, 1 H, J = 2.95 Hz, $CH(OMe)_2$), 8.45 (very br s, 1 H, COOH).

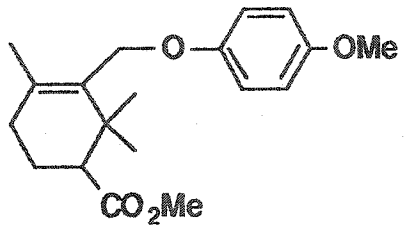
3-Dimethoxymethyl-4-methoxy-2,2,4-trimethylcyclohexane carboxylate (299)



299

Excess diazomethane in ether (prepared from 2.6 g of N-nitrosomethyl urea) was added to a solution of acid **298** (1 g, 3.6 mmol) in ether (5 mL) at 0 °C. After 2 h H_2O was added and the reaction mixture extracted with ether (3x). The combined ether extracts were dried and concentrated. Chromatography (5% ethyl acetate/petroleum ether) gave the pure product (1 g, 97%). IR (neat) 2931, 1731 (w), 1507, 1223 cm-1; ^{1}H NMR (200 MHz), δ 0.85 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.25 - 1.90 (m, 4 H), 2.1 - 2.21 (m, 2 H), 2.98 (s, 3 H, OCH_3), 3.21 (s, 3 H, OCH_3), 3.20 (s, 3 H, OCH_3), 3.51 (s, 3 H, CO_2CH_3), 4.55 (d, 1 H, J = 2.94 Hz, C<u>H</u>$(OCH_3)_2$); ^{13}C δ 175.8, 106.8, 75.6, 55.4, 53.5, 52.0, 51.3, 50.6, 47.9, 35.0, 29.4, 29.2 25.0, 24.8, 20.5.

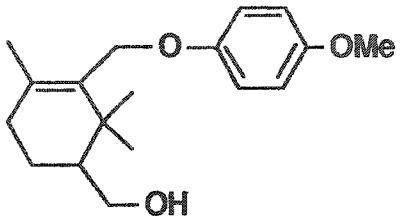
Methyl-3-(4-methoxyphenoxy)methyl-2,2,4-trimethyl-3-cyclohexanecarboxylate (301)



301

A mixture of the intermediate alcohol (57 mg, 0.26 mmol), *p*-methoxyphenol (100 mg, 0.806 mmol), triphenylphosphine (91 mg, 0.35 mmol) and diethyl azodicarboxylate (DEAD, 55.05 μL, 0.35 mmol) in CH_2Cl_2 (1 mL), was stirred at 22 °C for 30 min. Ether was added to precipitate the triphenylphosphine. This procedure was repeated three times. Concentration and chromatography (5% ethyl acetate/petroleum ether) afforded the ether **301** (74 mg, 90%). IR (neat) 2931, 1732, 1535 cm^{-1}; ^1H NMR (200 MHz), δ 1.01 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.20 - 1.31 (m, 2 H), 1.71 (s, 3 H, vinyl CH_3), 2.02 - 2.06 (m, 2 H, allylic CH_2), 2.47 (dd, 1 H, J = 3.4, 10.99 Hz, $CHCO_2CH_3$), 3.60 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, C_6H_4-OCH_3), 4.35 (AB q, 2 H, J = 10 Hz, CH_2-OC_6H_4), 6.70 - 6.91 (m, 4 H, aromatic); ^{13}C δ 14.2, 19.3, 22.0, 23.0, 26.8, 26.9, 31.3, 36.1, 41.0, 51.1, 51.3, 55.0, 64.9, 114.5, 115.6, 132.7, 135, 153.3, 153.8, 175.2.

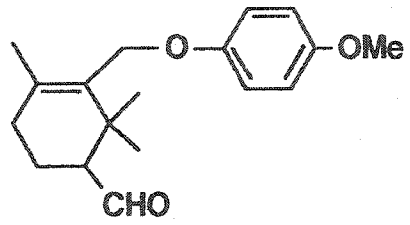
(3-(4-Methoxyphenoxy)methyl-2,2,4-trimethyl-3-cyclohex-enyl)methanol (302)



302

Solid $LiAlH_4$ (15.13 mg, 0.39 mmol) was added to **301** (180 mg, 0.57 mmol) in ether (4 mL) at 0 °C and the mixture stirred for 40 min. After quenching with water, the mixture was poured into aqueous 10% HCl (2 mL) and extracted with ether, dried and concentrated. Chromatography (10% EtOAc/petroleum ether) gave 302 (142 mg, 87%). IR (neat) 3379, 2926, 1505 cm^{-1}; ^1H NMR (200 MHz), δ 0.88 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.42 - 1.51 (m, 4 H), 1.70 (s, 3 H, vinyl CH_3), 3.41 (dd, 1 H, J = 8.6, 10.45 Hz, C<u>H</u>-OH), 3.74 (s, 3 H, O-CH_3), 3.86 (dd, 1 H, J = 3.45, 10.45 Hz, C<u>H</u>-OH), 4.34 (AB q, 2 H, J = 9.96 Hz, -C<u>H_2</u>-0$C_6H_4OCH_3$), 6.74 - 6.90 (m, 4 H, aromatic); ^{13}C δ 153.8, 153.4, 135.9, 133.2, 115.7, 114.6, 65.2, 63.7, 55.7, 47.2, 36.4, 31.6, 26.8, 22.5, 21.6, 19.9.

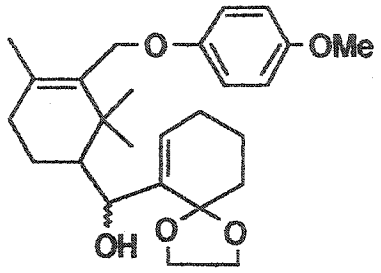
(3-(4-Methoxyphenoxy)methyl-2,2,4-trimethyl-3-cyclohexane)carboxaldehyde (303)



303

Pyridinium dichromate was added to a stirred solution of the alcohol **302** (130 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) at 25 °C. Ether was added after 24 h and the reaction mixture filtered through Celite. The remaining traces of chromium salts were removed by a second filtration through a small amount of $MgSO_4$ on silica gel (70 - 230 mesh) to give the product **303** (122 mg, 95%). IR (neat) 2927, 1718, 1507, 1379, 1224 cm^{-1}; ^1H NMR (200 MHz), δ 1.07 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.70 (s, 3 H, vinyl CH_3), 1.75 - 2.08 (m, 4 H), 2.21 - 2.29 (m, 1 H, CH-CHO), 3.70 (s, 3 H, OCH_3), 4.41 (AB q, 2 H, J = 10.1 Hz, $C\underline{H_2}$-$OC_6H_4OCH_3$), 6.78 - 6.91 (m, 4 H, aromatic), 9.86 (d, 1 H, J = 2.6 Hz, CHO).

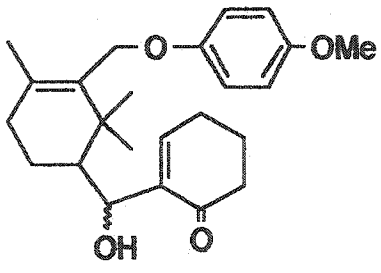
3'-(4-Methoxyphenoxy)methyl-2',2',4'-trimethyl-3-cyclohexenyl-1,4-dioxaspiro[4.5]dece-6-en-6-ylmethanol (304)



304

Procedure same as for the preparation of **281**, yield 75%. IR (neat) 3357, 2940, 1776 (weak), 1660, 1510, 1228 cm^{-1}; ^1H NMR (200 MHz), δ 1.11 (s, 3 H, CH3), 1.21 (s, 3 H, CH3), 1.45 - 1.76 (m, 7 H), 1.92 - 2.04 (m, 4 H), 2.35 - 2.43 (m, 4 H, allylic CH_2), 3.74 (s, 4 H, $(OCH_2)_2$), 3.75 (s, 3 H, OCH_3), 4.35 (AB q, 2 H, J = 10 Hz, CH_2-$OC_6H_4OCH_3$), 4.91 (br s, 1 H, CH-OH), 6.74 - 6.89 (m, 4 H, aromatic), 6.94 - 6.98 (m, 1 H, vinyl CH).

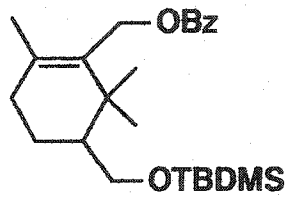
1'-hydroxy-4'-(4-Methoxyphenoxy)methyl-3',3',5'-trimethyl-4-cyclohexenyl-2-cyclohexenone (305)



305

Procedure: same as for the preparation of **282**, yield 96%. IR (neat) 3335, 2941, 1664, 1510, 1235 cm^{-1}; ^1H NMR (200 MHz), δ 1.10 (s, 3 H, CH3), 1.20 (s, 3 H, CH3), 1.45 - 1.76 (m, 7 H), 1.92 - 2.04 (m, 4 H), 2.35 - 2.54 (m, 4 H, allylic CH_2), 3.75 (s, 3 H, OCH_3), 4.36 (AB q, 2 H, J = 10 Hz, CH_2-$OC_6H_4OCH_3$), 4.95 (br s, 1 H, CH-OH), 6.95 - 6.89 (m, 4 H, aromatic), 6.98 - 7.1 (m, 1 H, vinyl CH).

5-(*tert*-butyldimethylsilyloxy)methyl-2,6,6-trimethyl-1-cyclohexenylmethylbenzoate (307)

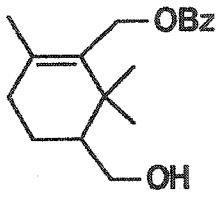


307

Pyridine (1 mL) was added to the alcohol **277** (20 mg, 0.067 mmol) followed by benzoyl chloride (11.6 μL, 0.1 mmol) and the reaction stirred at room temperature for 20 h. Water was added to the reaction mixture which was then extracted with a 3:1 toluene/ether mixture (3 x 3 mL), Dried and concentrated. Chromatography (5% ethyl acetate/petroleum ether) gave **307** (25 mg) in 93% yield as a colourless oil. IR (neat) 2917, 1718, 1264 cm^{-1}; ^1H NMR (200 MHz), δ 0.03 (s, 6 H), 0.88 (s, 12 H, CH_3 and Si-$C(CH_3)_3$), 1.10 (s, 3 H, CH_3), 1.45 - 1.50 (m, 3 H), 1.71 (s, 3 H, vinyl CH_3), 1.85 - 2.02 (m, 2 H, allylic CH_2) 3.40 (dd, J = 8.4, 10 Hz, 1 H, CH-OSi), 3.79 (dd, 1 H, J = 3.8, 10.1 Hz, CH-OSi), 4.80 (AB q, 2 H, J = 9.9 Hz, C$\underline{H_2}$-OBz),

7.35 - 7.75 (m, 3 H, aromatic), 7.97 - 8.02 (m, 2 H, aromatic); ^{13}C δ 166.8, 136.7, 132.0, 130.5, 129.8, 129.5, 63.7, 61.4, 46.0, 36.2, 31.0, 27.0, 25.9, 23.1, 21.5, 19.9, 18.2, -5.2; MS (EI) *mz* 281 (M^+ - OBz), 223 (M^+ - OBz - $C(CH_3)_3$).

5-Hydroxymethyl-2,6,6-trimethyl-1-cyclohexenylmethyl-benzoate (308)



308

The removal of the *tert*-butyldimethylsilyl group was accomplished according to the procedure already described above for the preparation of **280** to give **308** in 97% yield. IR (neat) 3406, 2925, 1708, 1268 cm^{-1}; ^1H NMR (200 MHz), δ 0.89 (s, 3 H), 1.12 (s, 3 H), 1.49 - 1.53 (m, 2 H), 1.71 (s, 3 H, vinyl CH_3), 1.90 - 2.01 (m, 1 H), 2.01 - 2.05 (m, 2 H, allylic CH_2), 3.42 (dd, J = 8.75, 10.1 Hz, 1 H, CH-OH), 3.86 (dd, J = 3.65, 10.1 Hz, 1 H, CH-OH), 4.80 (AB q, J = 9.89 Hz, 2 H, CH_2-OBz), 7.31 - 7.50 (m, 3 H, aromatic), 7.96 - 8.01 (m, 2 H, aromatic); ^{13}C δ 168.0, 136.7, 132.7, 132.0, 130.4, 129.5, 128, 63.6, 61.1, 47,4, 36.2, 31.1, 27.0, 22.0, 21.3, 19.1.

Claims to Original Research

1. γ,δ-Epoxyketone **187** and γ,δ-epoxyester **198** were successfully prepared in good yield. In the presence of base, the oxygen nucleophile (of the ambident ion) favoured attack to form hexahydrofuran **188**. In compounds such as **198**, steric factors prevented cyclization.
2. Enone **202** was prepared as a key building block for several studies. A useful experimental procedure employed neutral alumina (Aldrich) for purification after DDQ reaction.
3. Cuprate enolate trapping reactions of unsymmetrical enones was effected at either the α or α' position depending upon the presence or absence of THF as co-solvent. Presence of THF as co-solvent favours α' alkylation at room temperature, forming **206** and **207** while in its absence at 0 °C, α alkylation is favoured in lower yields (*e.g.*, **205**).
4. Diazoketones **210**, **211**, **212**, **213**, and **215** were prepared and studied under catalytic conditions leading to the formation of oxetane or cyclopropane derivatives. Oxetanes **218**, **219**, **220**, and **221** were prepared from the corresponding α-diazoketone under catalytic conditions in the presence of ethyl vinyl ether. With cyclohexene and dihydrofuran as the olefin source, cyclopropane adducts were obtained. Under thermal conditions, acrylonitrile reacts with **210** to form the cyclopropane adduct **224** as a mixture of isomers.
5. Dimethyloxosulfonium methylide was added to methyl enol ether **262** to form hexahydrofuran **263** instead of the

cyclopropanation adduct. It was shown that **263** resulted via the expected cyclopropanation adduct through a rearrangement.

6. Hexahydrofuran **268** was prepared under rhodium acetate catalyzed conditions in the presence of ethyl diazo acetate instead of the expected cyclopropane adduct.
7. Cyclobutanones **236, 237, 238** and **239** were prepared by photochemical decomposition of the corresponding diazoketones. The photochemical reactions were repeated in the presence of benzophenone forming a 1:1 ratio of oxetane and cyclobutanone products.
8. Taxol A ring models **276, 277, 278, 301** and **307** were prepared.
9. Taxol ring systems containing the A and C rings (**287, 289** and **305**) were prepared by condensation of **158a** and the corresponding A ring using technology developed elsewhere and for a different purpose.
10. Radical cyclization of the key taxane skeleton precursor **287** in Bu_3SnH, AIBN and refluxing toluene was studied, and preliminary evidence was consistent with a low yield of the tricyclic[9.3.1.$0^{3,8}$]undecene nucleus **284a**.

CONFERENCE PRESENTATIONS

1. A. G. Fallis and I. A. Kennedy, Ketene Carbonyl Cycloadditions with Alkenes, Abstract No. ORGN 669, 74th Canadian Chemical Conference of the C.S.C., Hamilton, Ontario, June 1 - 4, 1991.
2. A. G. Fallis and I. A. Kennedy, Unusual Cycloadditions to Ketene Carbonyls, Ontario/Quebec Minisymposium in Synthetic/Bioorganic Chemistry, University of Toronto, Toronto, Ont., October 20 - 21, 1991.
3. A. G. Fallis, Y-F Lu and I. A. Kennedy, Yew versus Us: A Synthetic Challenge for the 90's, First Canadian-Chinese Organic Chemistry Conference, Banff, Alberta, May 28 - 31, 1992.
4. A. G. Fallis, Y-F Lu and I. A. Kennedy, Ketene Carbonyl Cycloadditions and Enediyne Building Blocks, Third French-American Chemical Society Meeting on Synthetic Organic and Bioorganic Chemistry, Aussois, France, June 15 - 18, 1992.
5. A. G. Fallis, Y-F Lu and I. A. Kennedy, Yew versus Us: Synthetic Approaches to Taxol, Abstract No. TJ-26, 9th International Conference on Organic Synthesis, Montreal, Quebec, June 28 - July 2, 1992.

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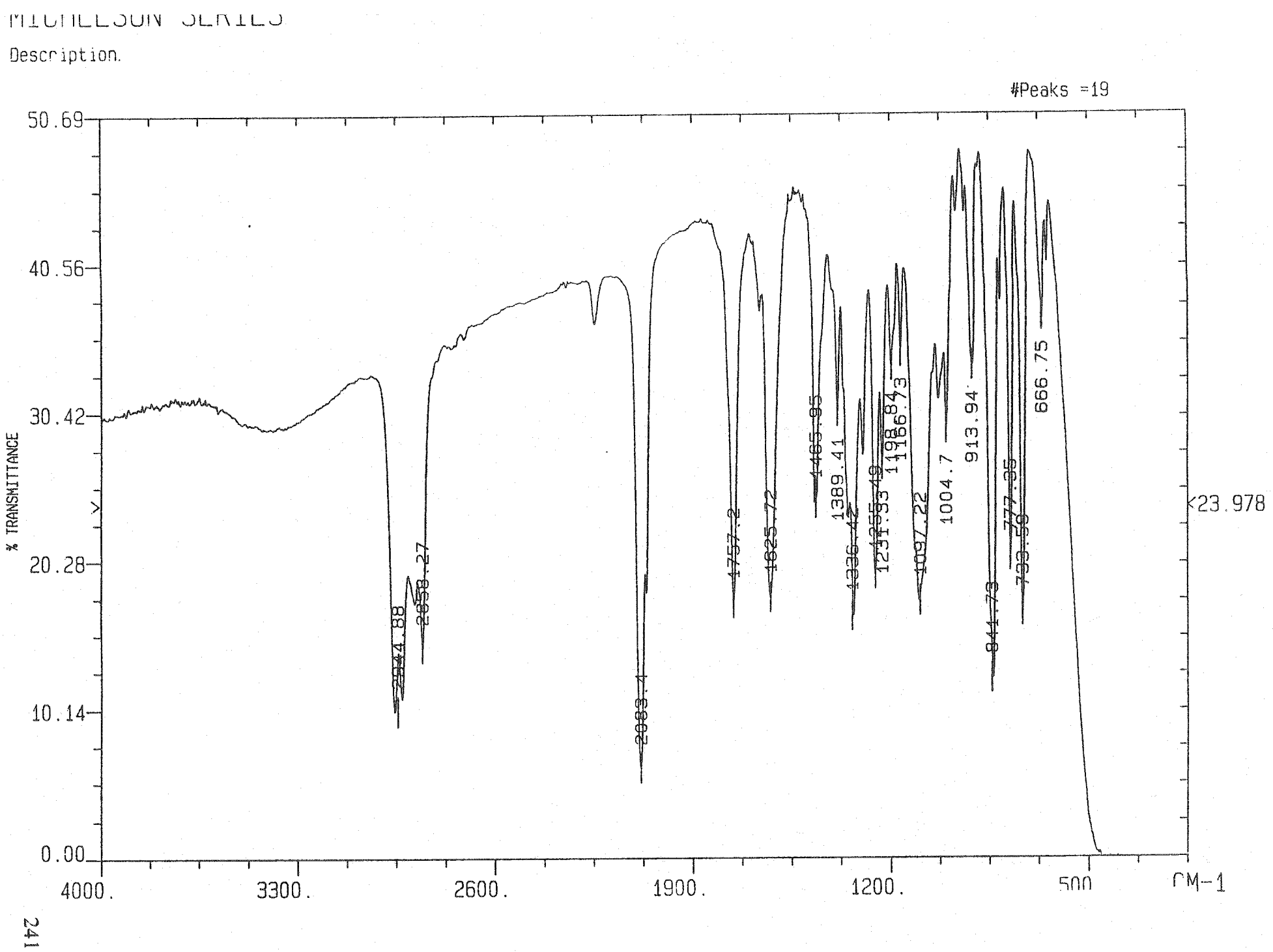
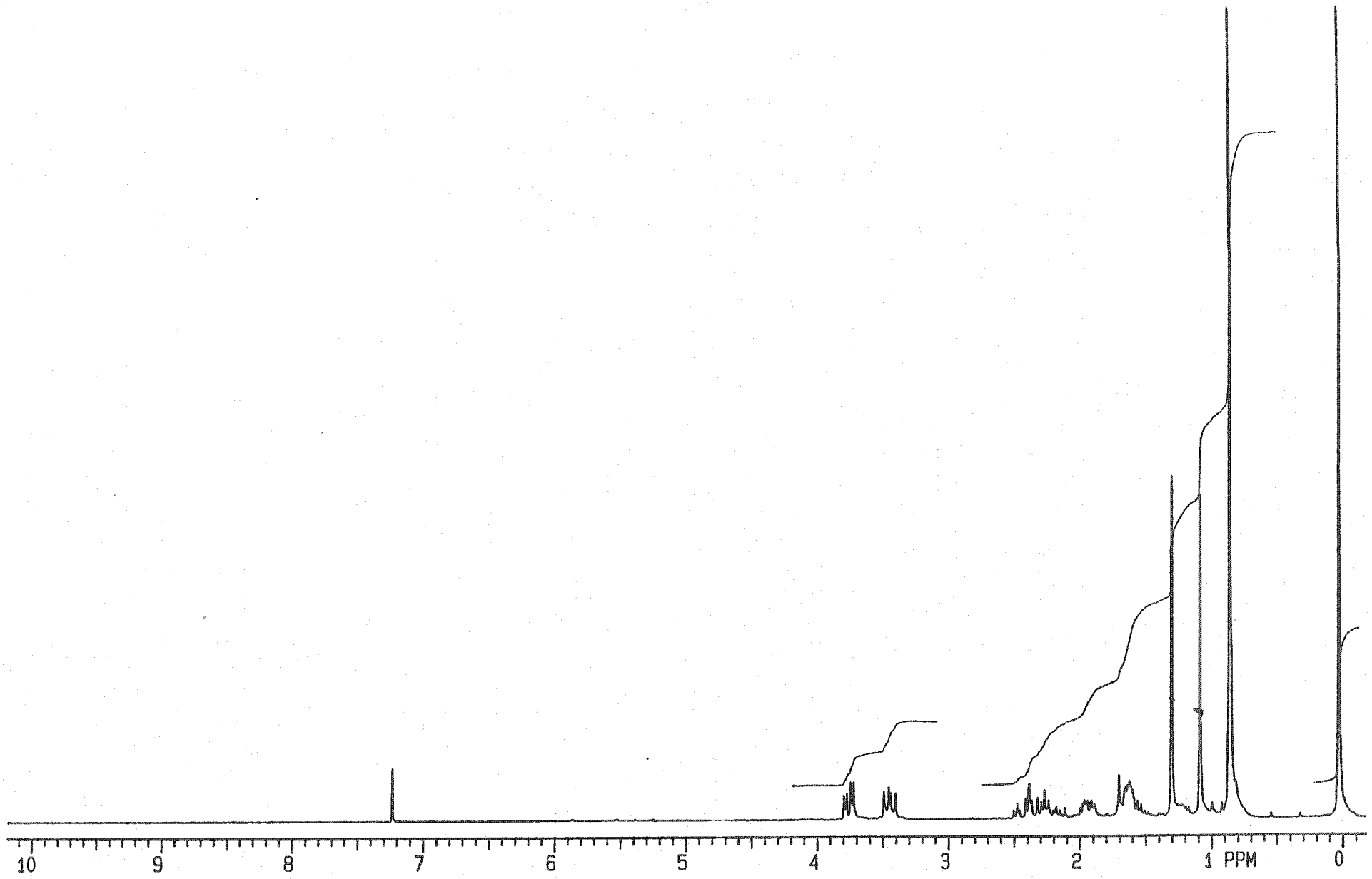
VII. SPECTRA

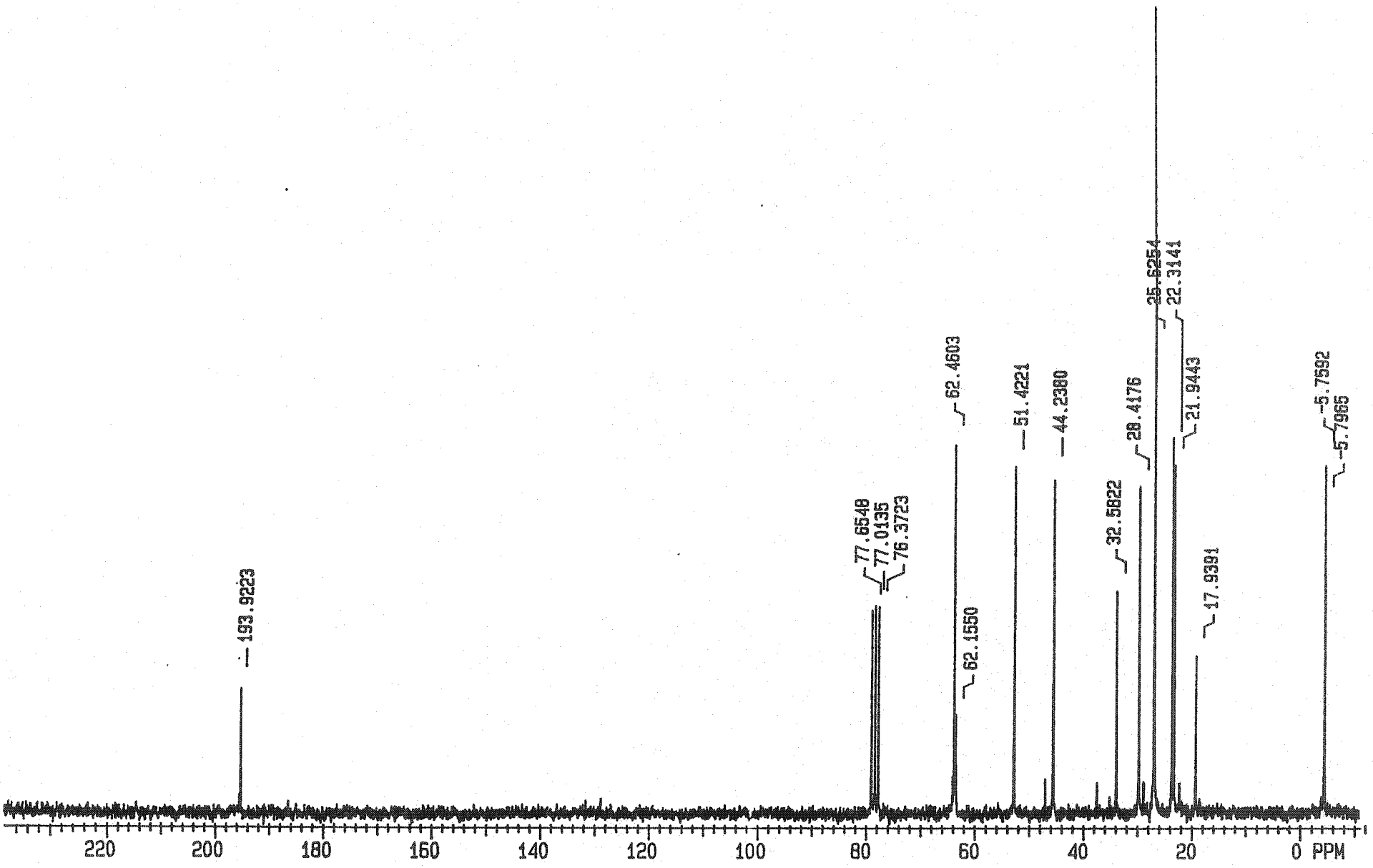
IR, ^{1}H NMR, ^{13}C NMR and or DEPT spectra of some key intermediates are listed here.



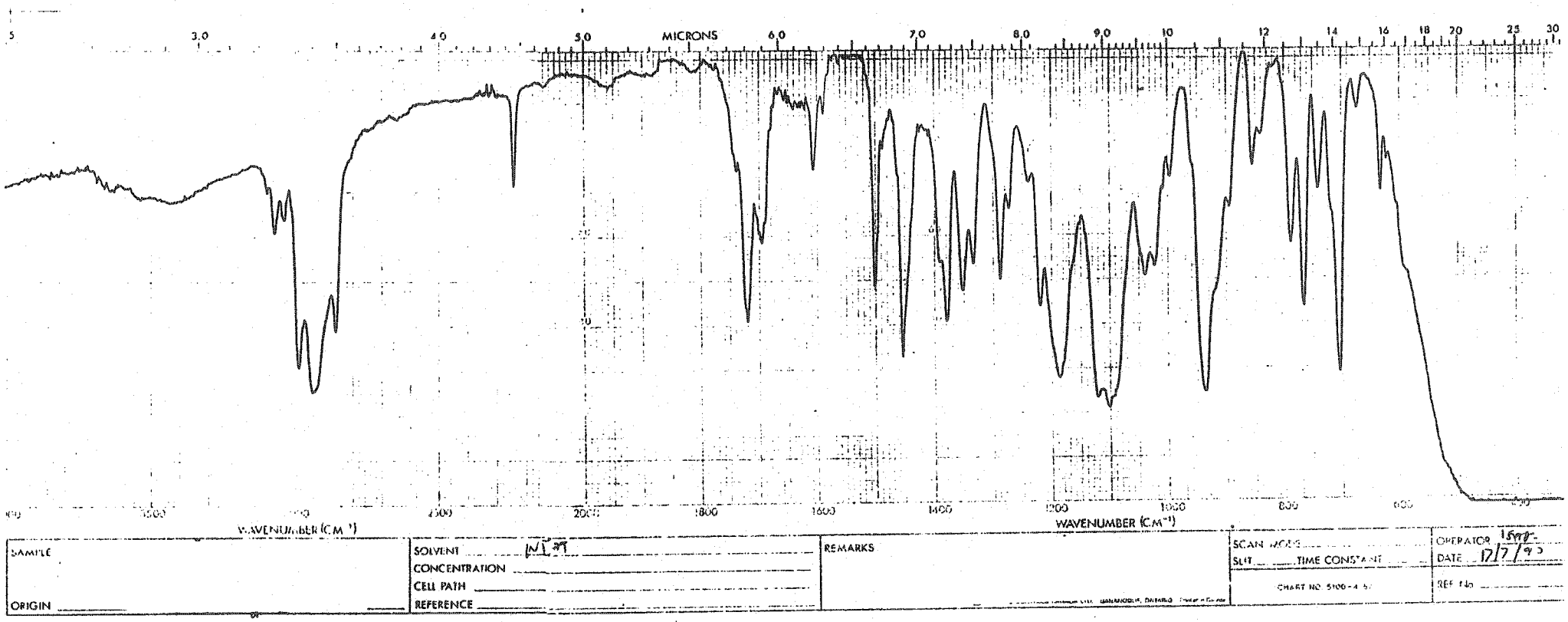
Figuure 1. The IR Sectrum of Diazoketone 210



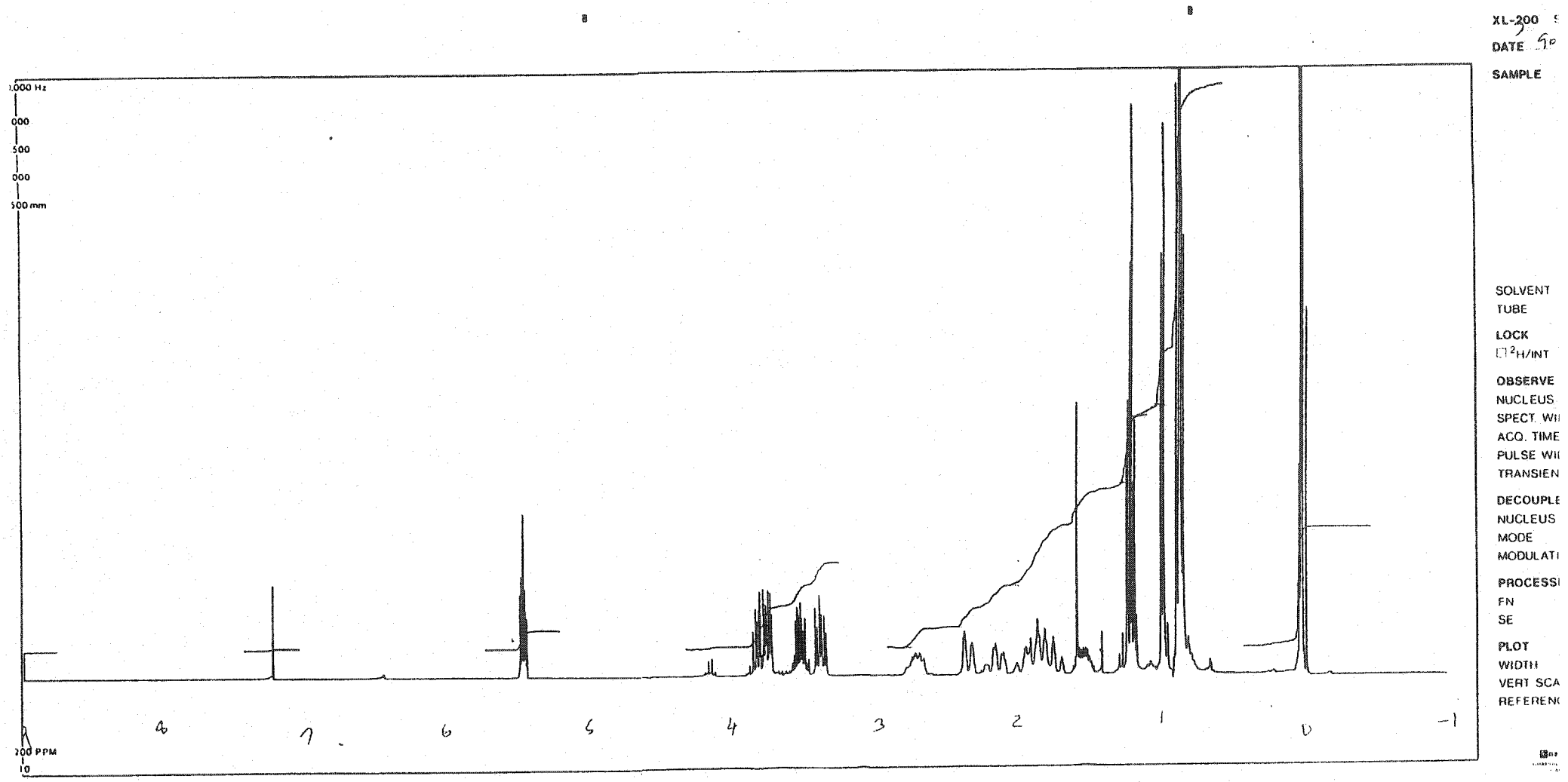
Figuure 2. The 200 MHz ^{1}H NMR Spectrum of **210**



Figuure 3. The 200 MHz ^{13}C NMR Spectrum of **210**



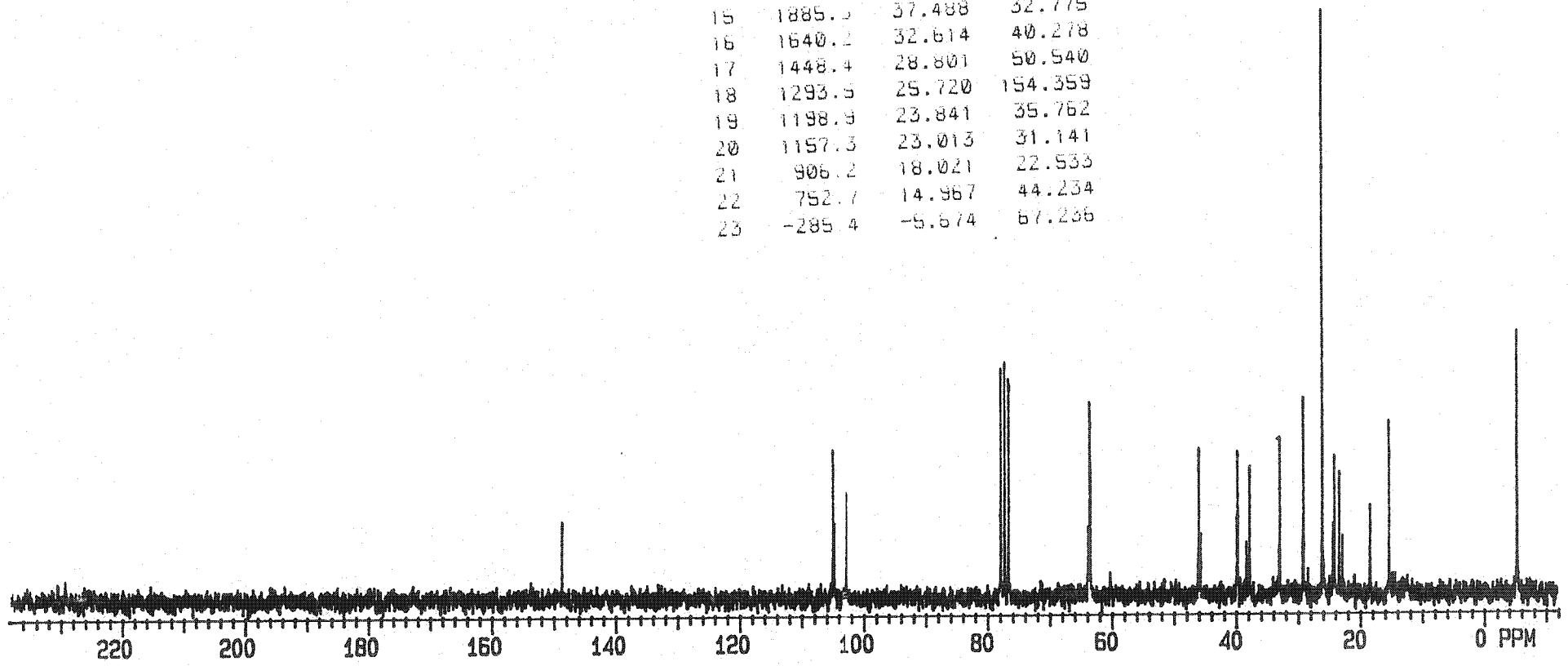
Figuure 4. The IR Sectrum of Oxetane 218



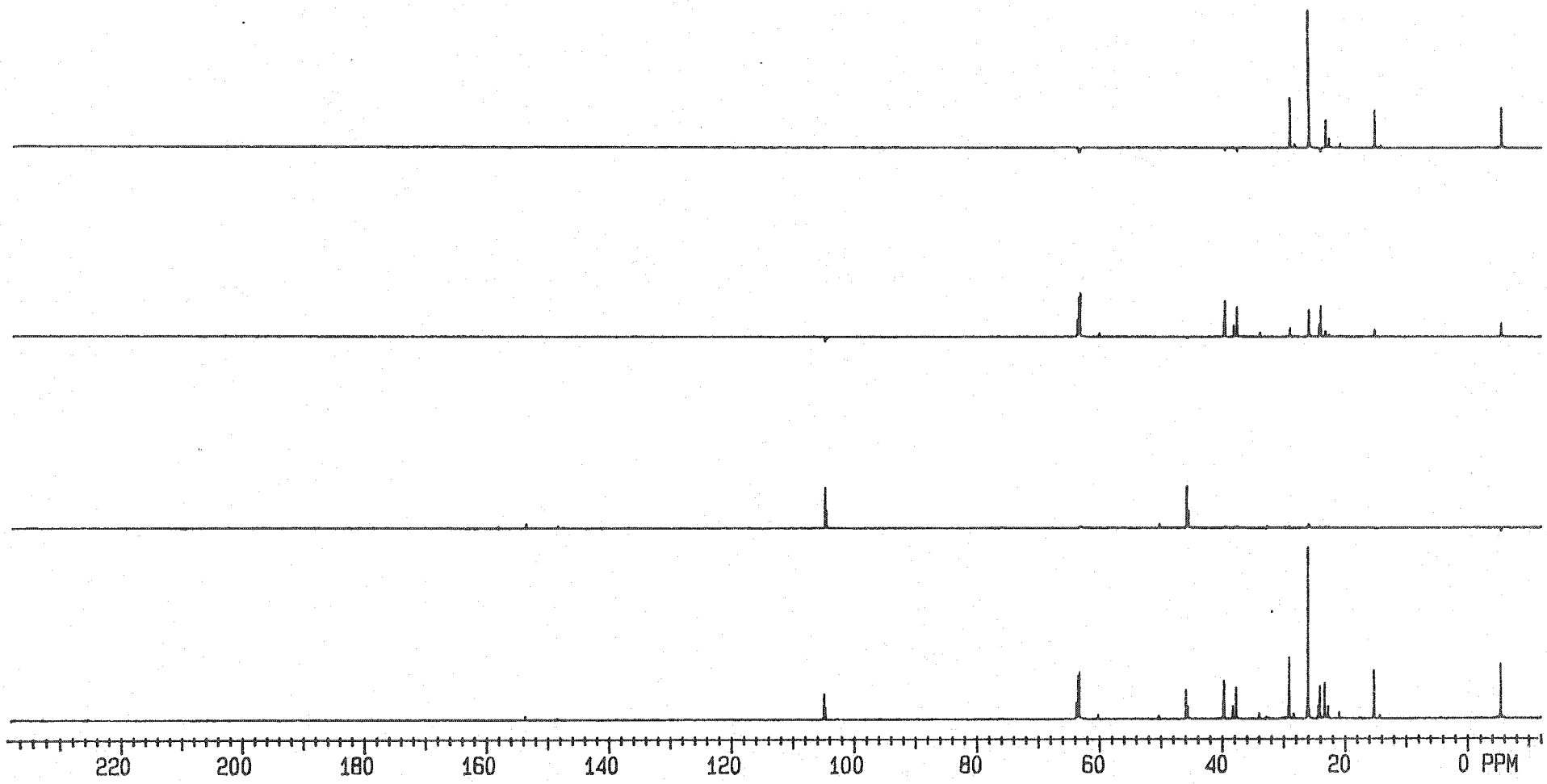
Figuure 5. The 300 MHz ^{1}H NMR Spectrum of **218**

RFL= 610.9 RFP= 0

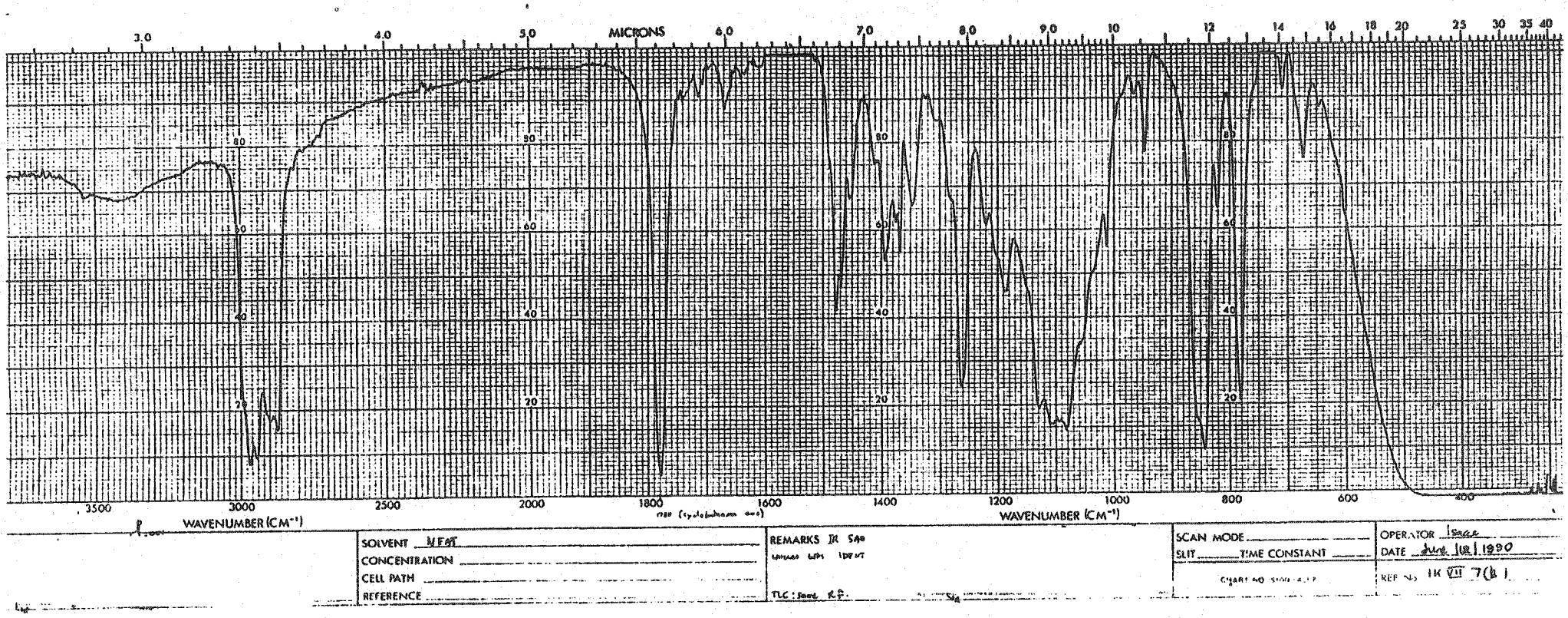
INDEX	FREQ	PPM	INTENSITY
01	7457.6	148.297	19.388
02	5260.5	104.613	38.274
03	5253.4	104.464	18.734
04	5150.6	102.420	26.796
05	3899.3	77.548	58.121
06	3867.6	76.910	60.577
07	3835.9	76.277	55.894
08	3191.3	63.471	17.371
09	3179.7	63.217	50.552
10	3173.8	63.098	45.610
11	2296.2	45.660	38.747
12	2282.7	45.391	15.535
13	1988.9	39.544	19.796
14	1981.9	39.403	38.021
15	1885.9	37.488	32.775
16	1640.2	32.614	40.278
17	1448.4	28.801	50.540
18	1293.5	25.720	154.359
19	1198.9	23.841	35.762
20	1157.3	23.013	31.141
21	906.2	18.021	22.533
22	752.7	14.967	44.234
23	-285.4	-5.674	67.236



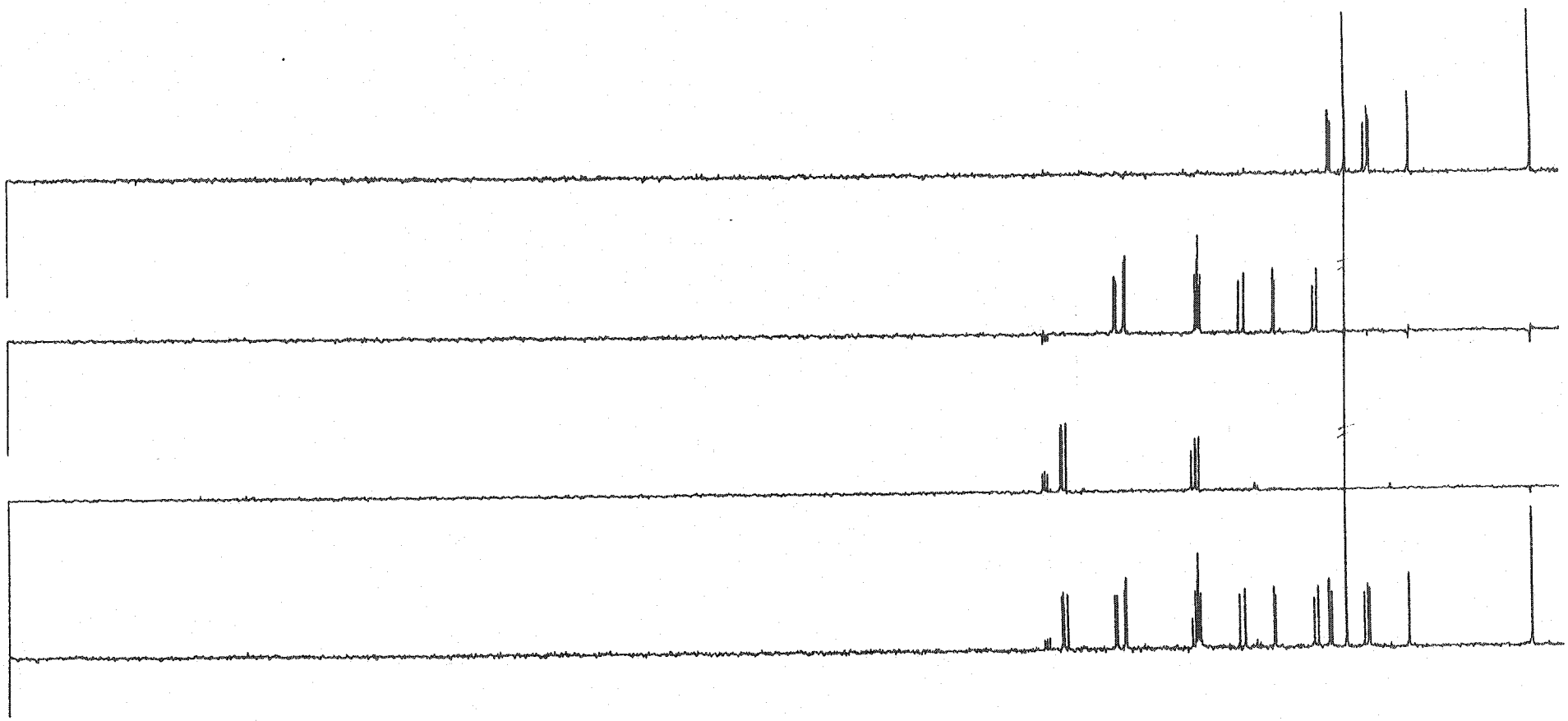
Figuure 6. The 200 MHz ^{13}C NMR Spectrum of **218**



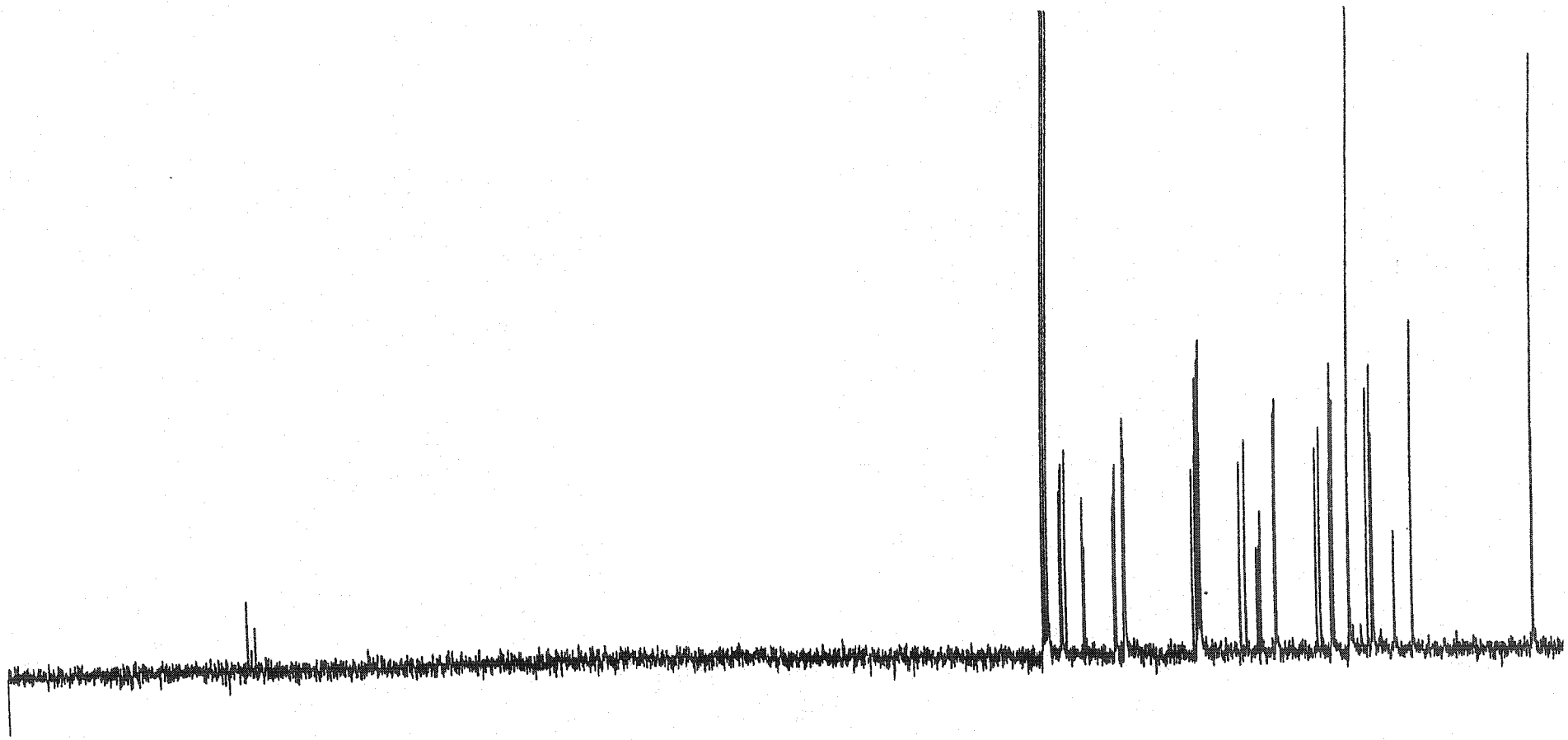
Figuure 7. The 200 MHz DEPT Spectrum of **218**



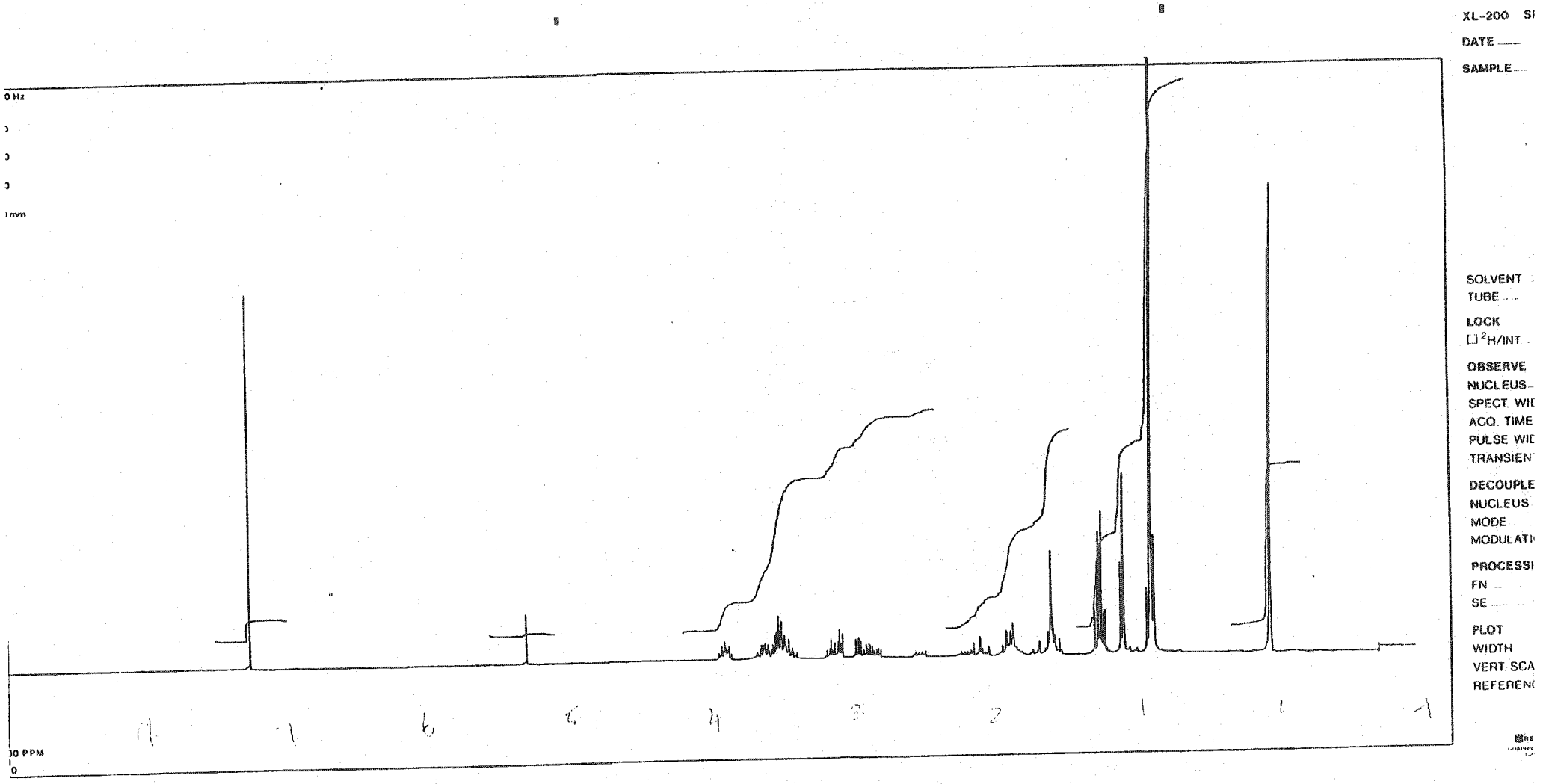
Figuure 8. The IR Sectrum of Cyclobutanone 236



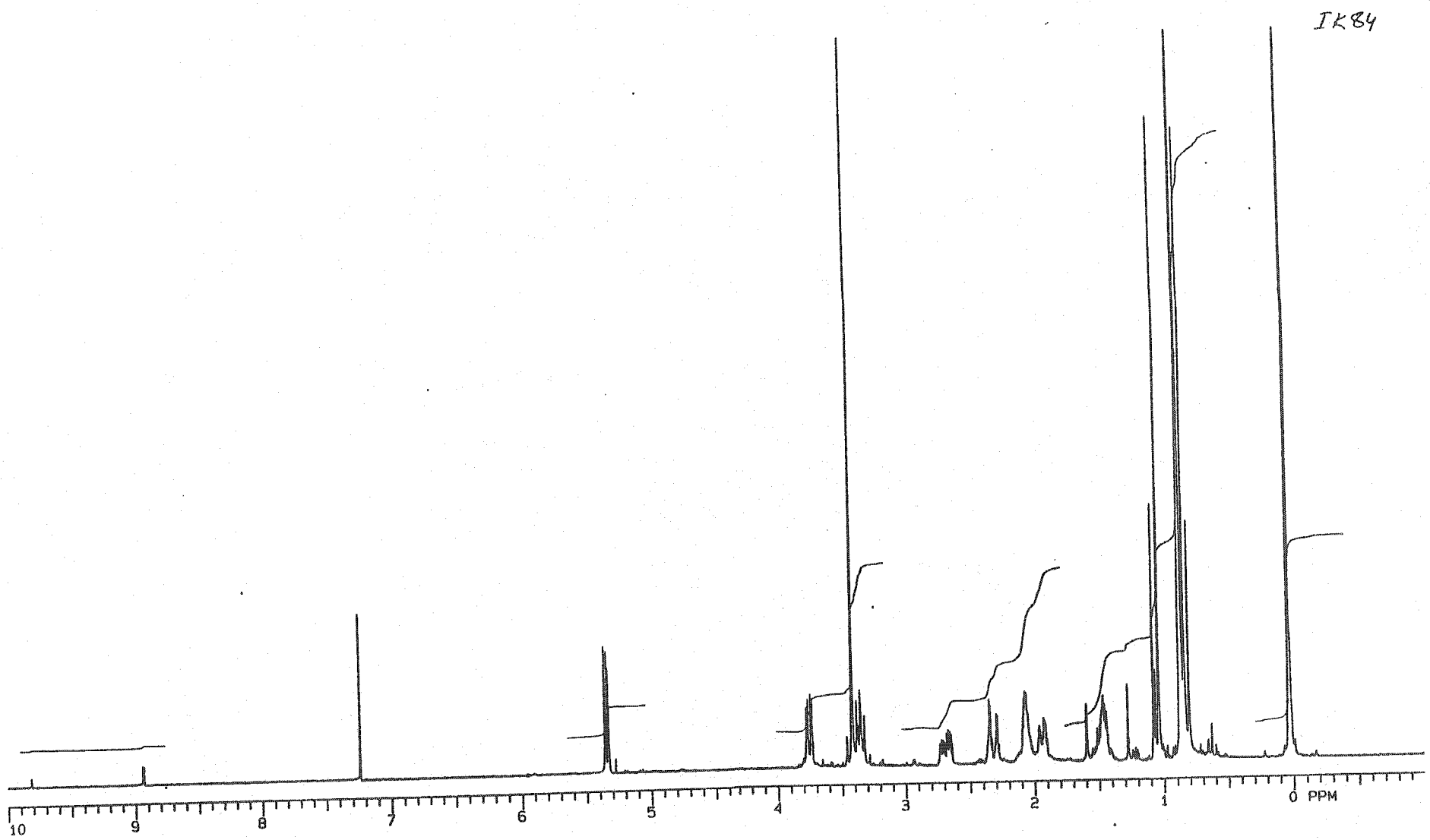
Figuure 9. The 300 MHz ^{1}H NMR Spectrum of 236



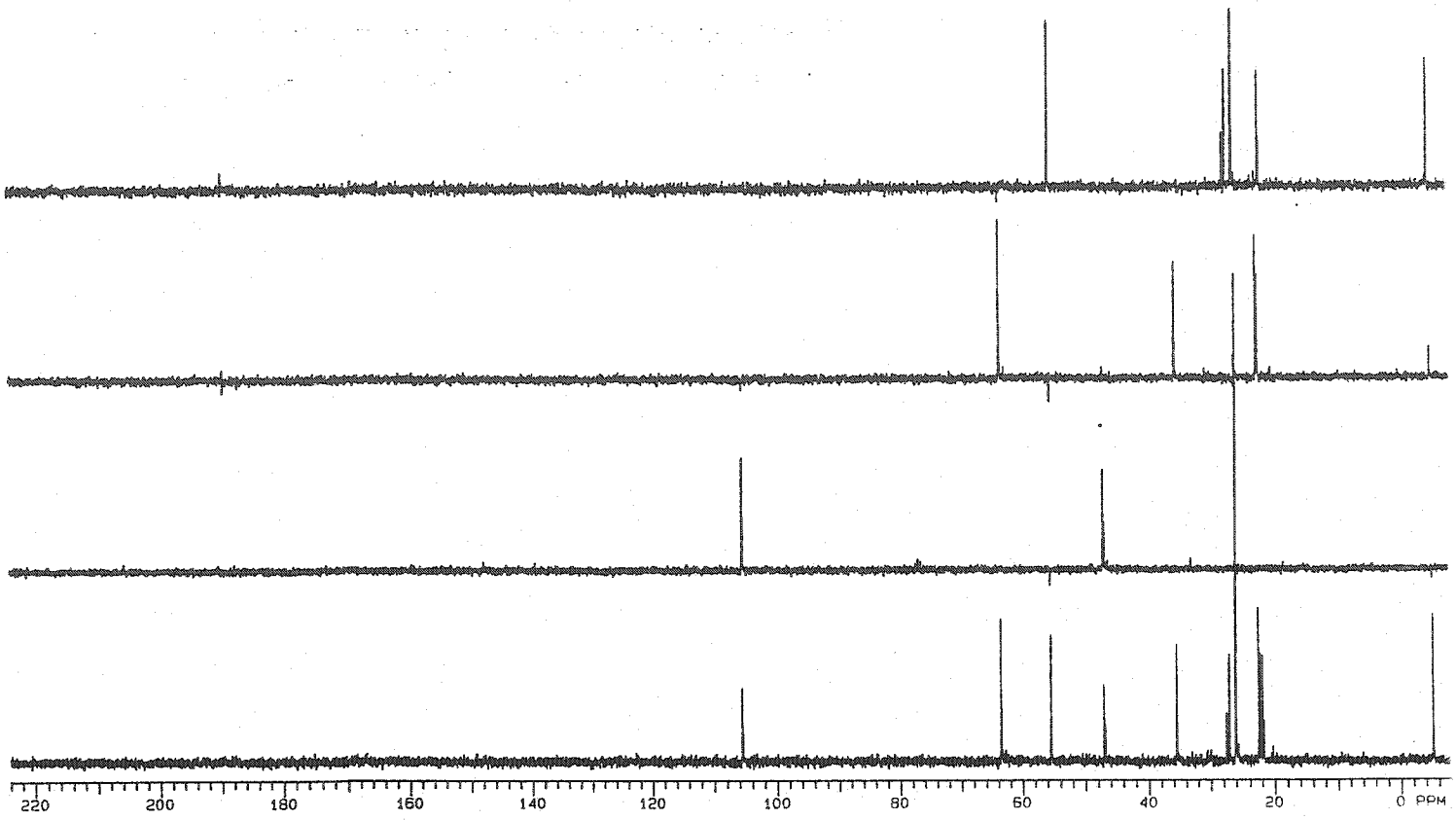
Figuure 10. The 300 MHz ^{13}C NMR Spectrum of 236

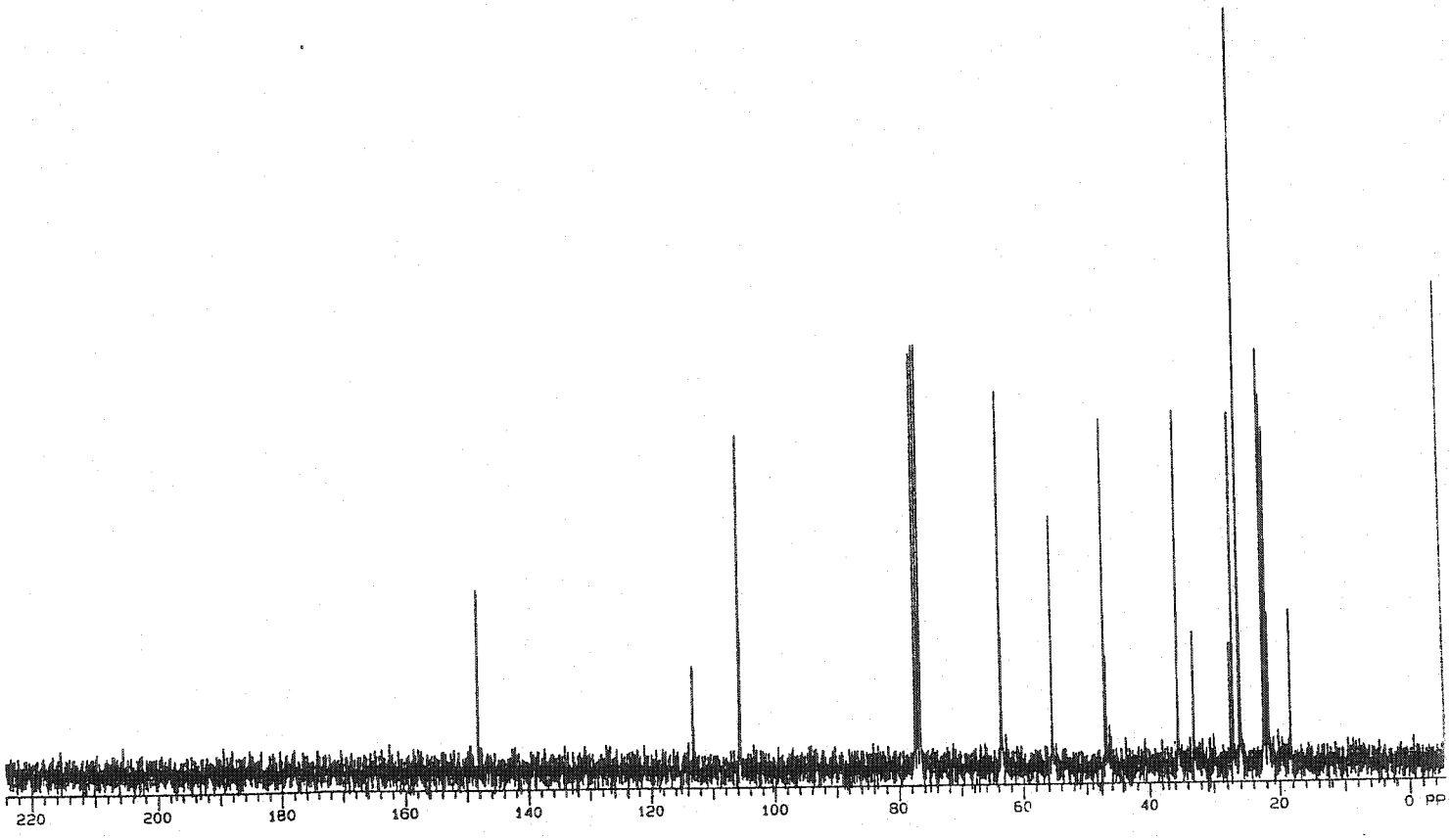


Figuure 11. The 300 MHz DEPT Spectrum of 236

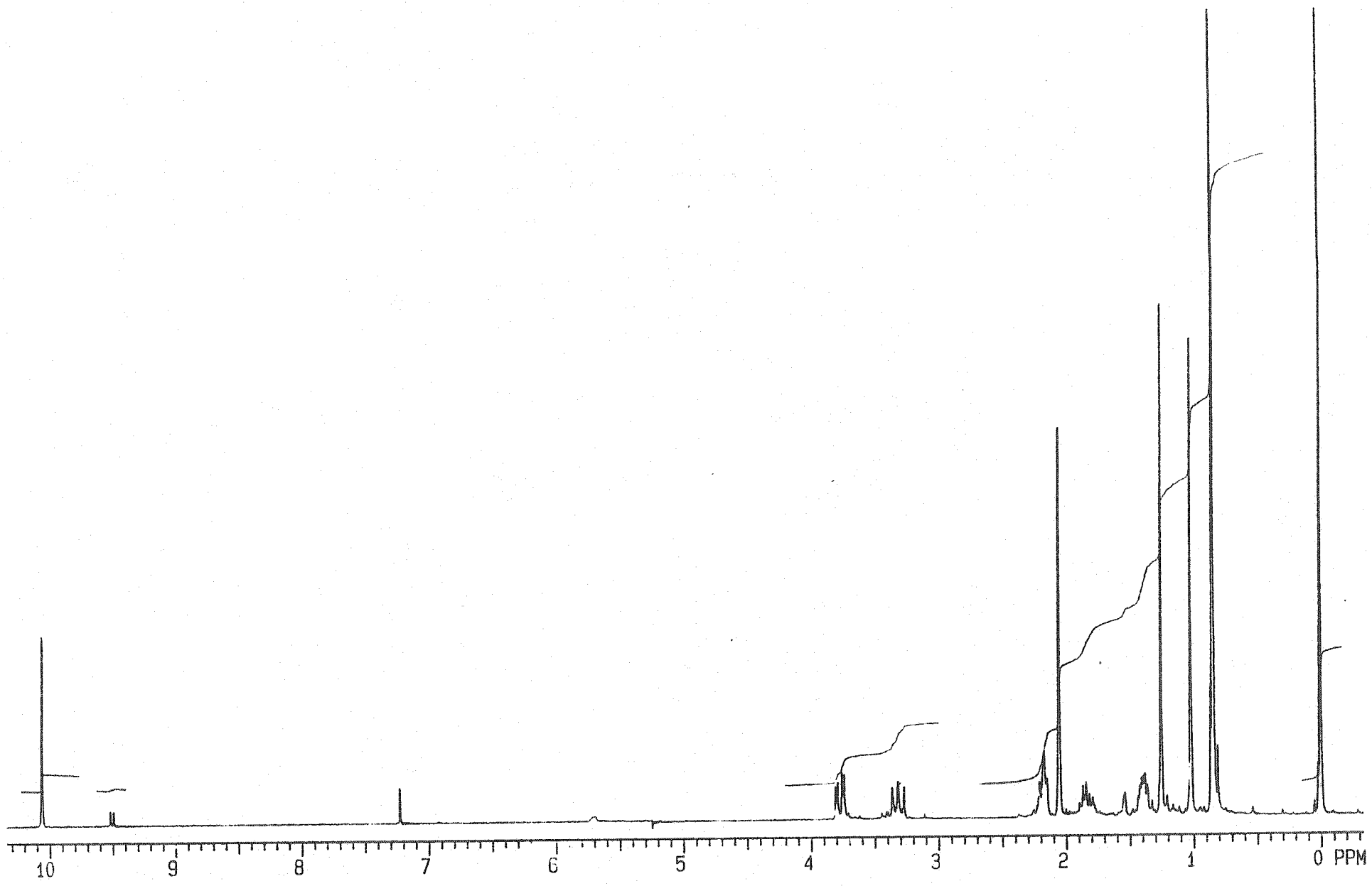


Figuure 12. The 300 MHz ^{1}H NMR Spectrum of Hexahydrofuran 263





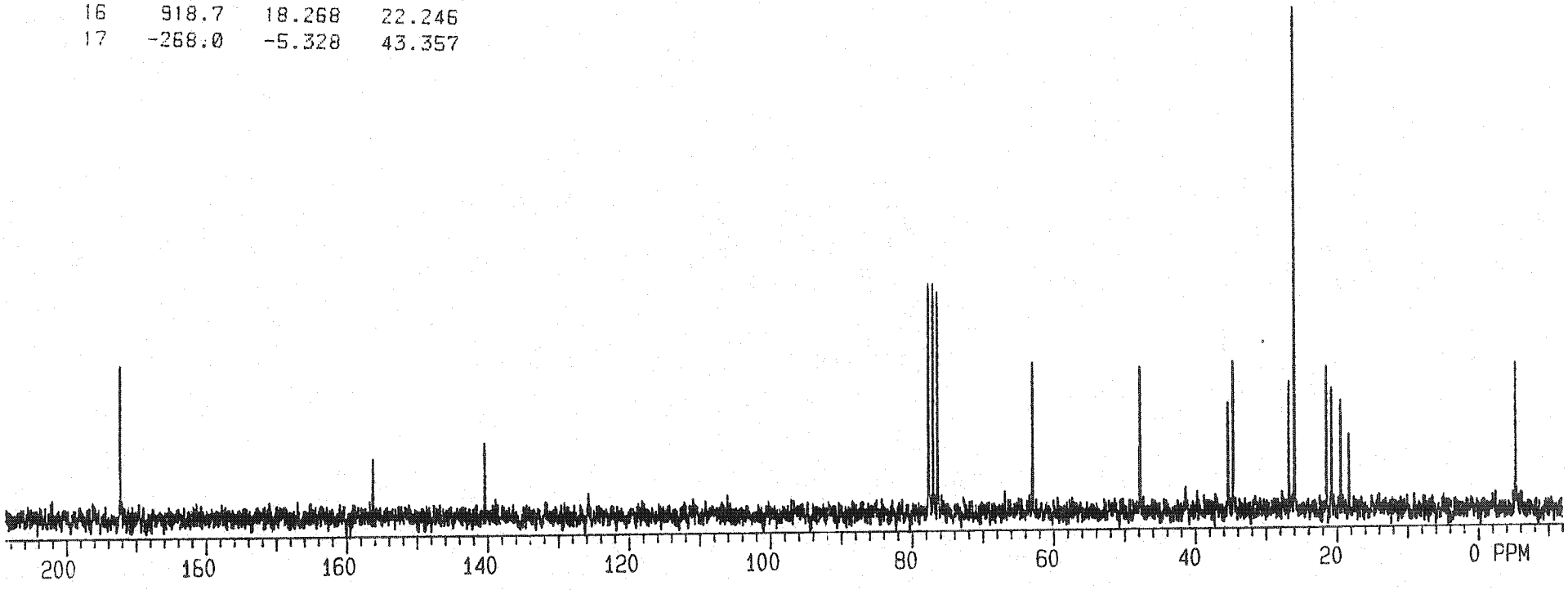
Figuure 13. The 300 MHz ^{13}C NMR and DEPT Spectra of **263**



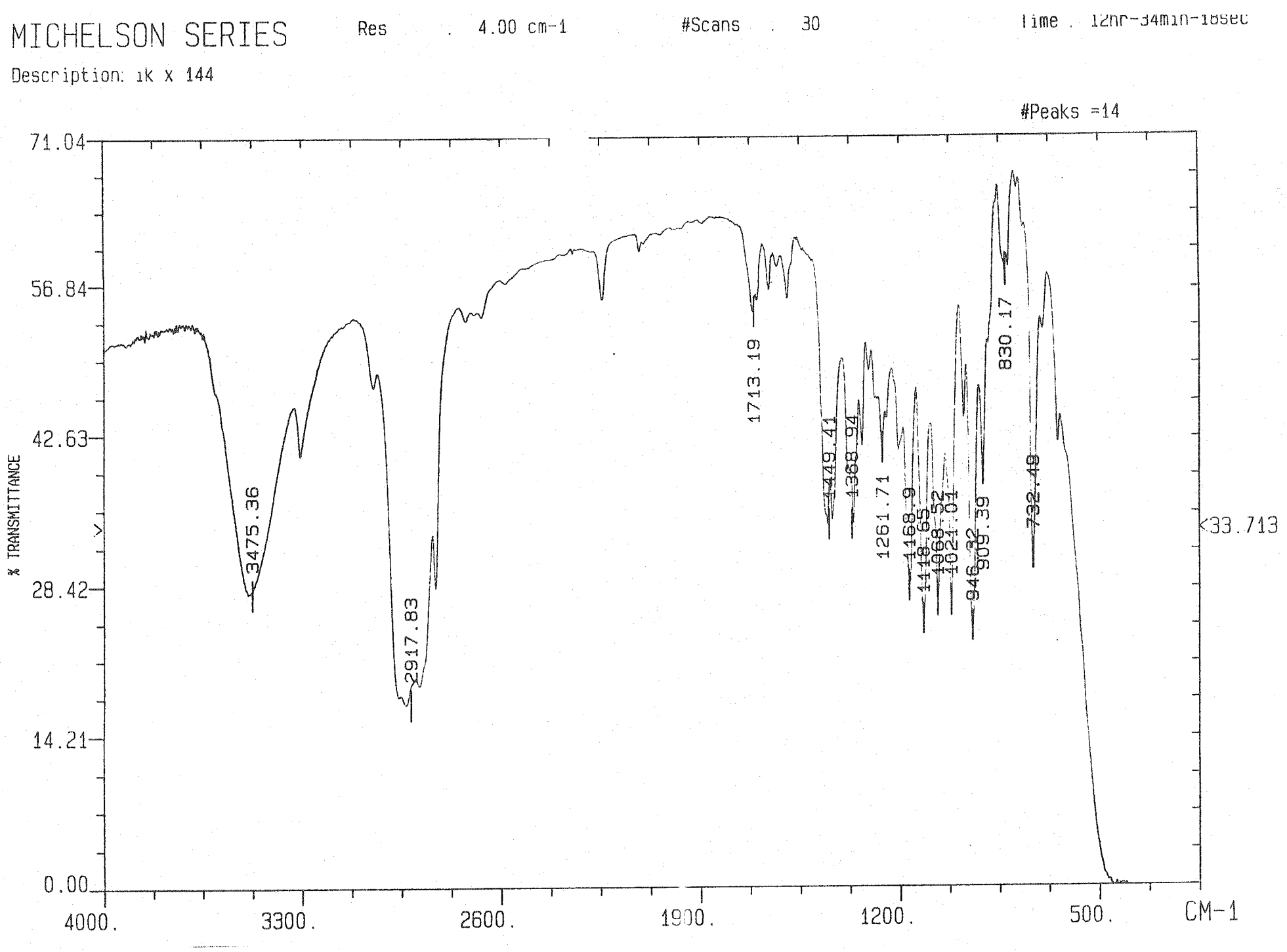
Figuure 14. The 200 MHz ^{1}H NMR Spectrum of Aldehyde **276**

SPECTRAL LINES FOR TH= 14.36
RFL= 610.9 RFP= 0

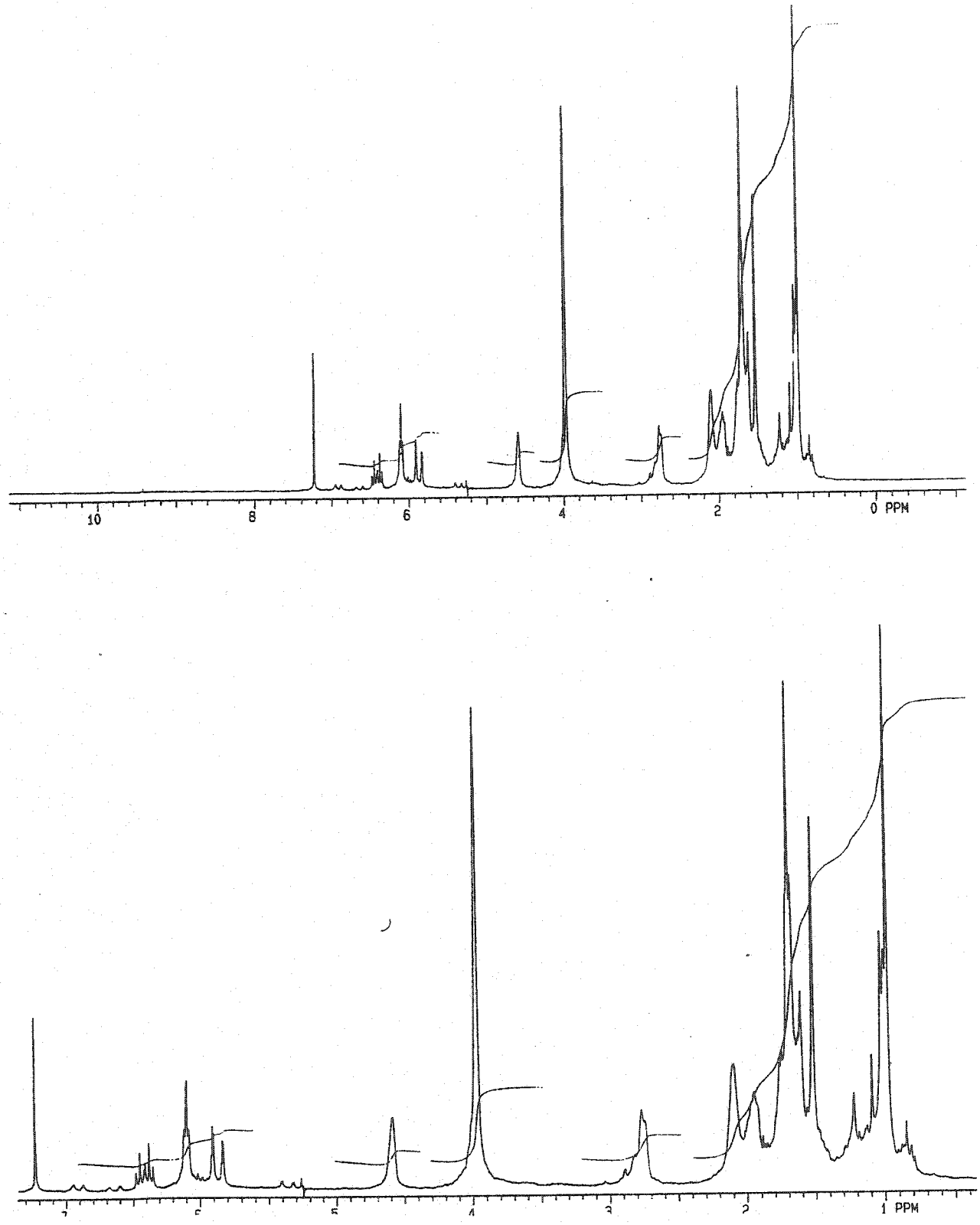
INDEX	FREQ	PPM	INTENSITY
01	9675.1	192.389	44.901
02	7860.1	156.297	16.830
03	7062.9	140.446	22.031
04	3904.4	77.639	67.641
05	3872.4	77.002	68.462
06	3840.5	76.367	67.324
07	3167.2	62.979	44.696
08	2404.5	47.814	45.663
09	1776.9	35.334	31.298
10	1741.1	34.621	45.302
11	1343.5	26.716	41.911
12	1303.9	25.927	150.250
13	1077.3	21.422	43.434
14	1041.7	20.714	38.831
15	978.4	19.456	32.040
16	918.7	18.268	22.246
17	-268.0	-5.328	43.357



Figuure 15. The 200 MHz ^{13}C NMR Spectrum of Aldehyde 276



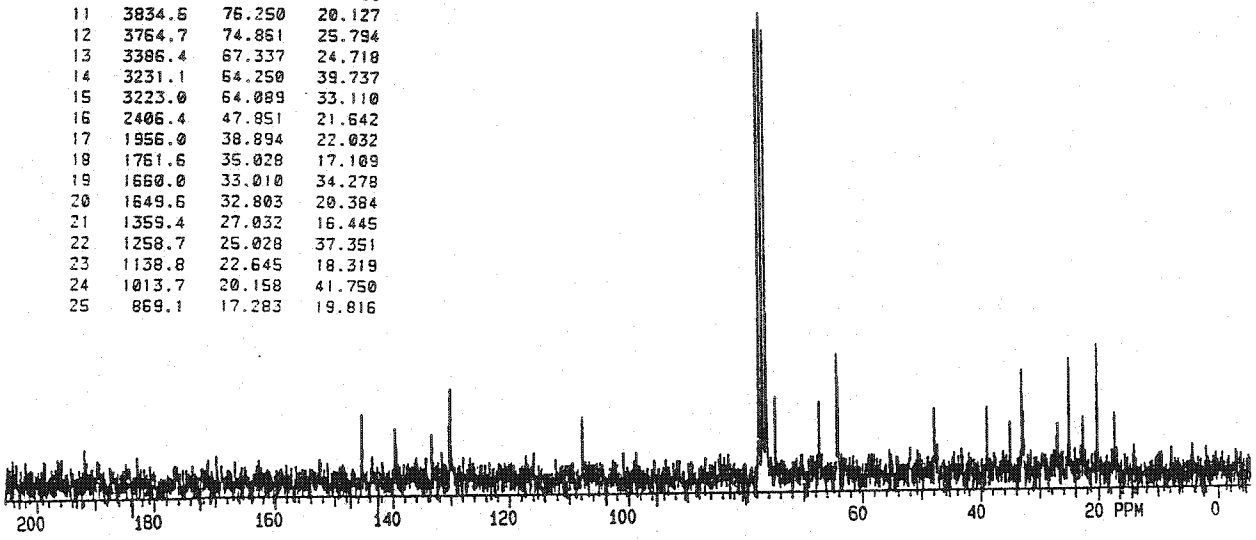
Figuure 16. The IR Sectrun: of Alcohol 281

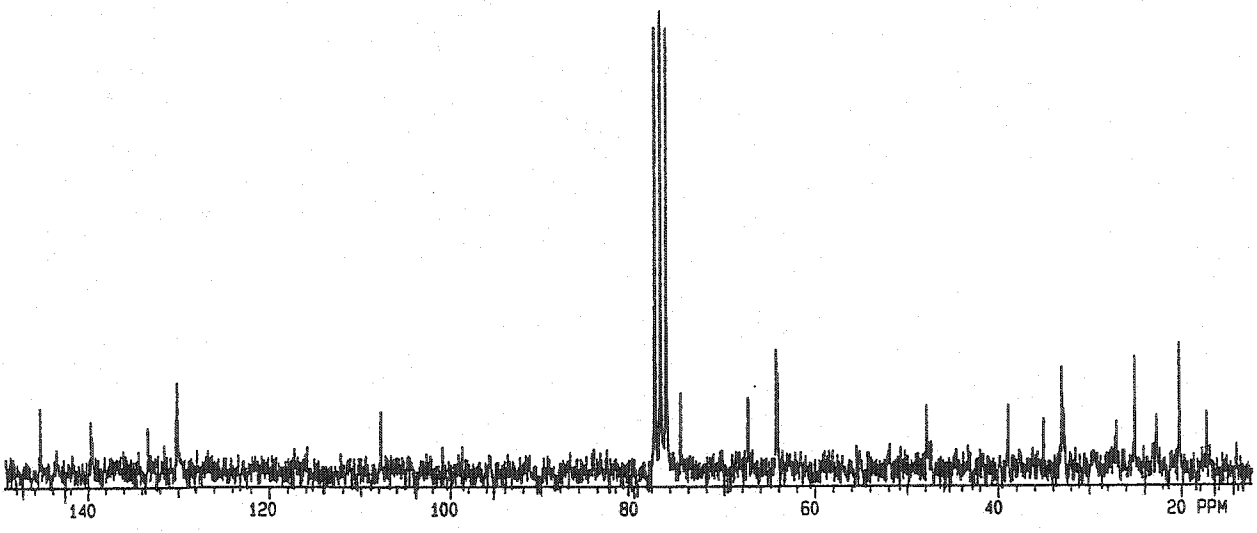


Figuure 17. The 200 MHz ^{1}H NMR Spectrum of **281**

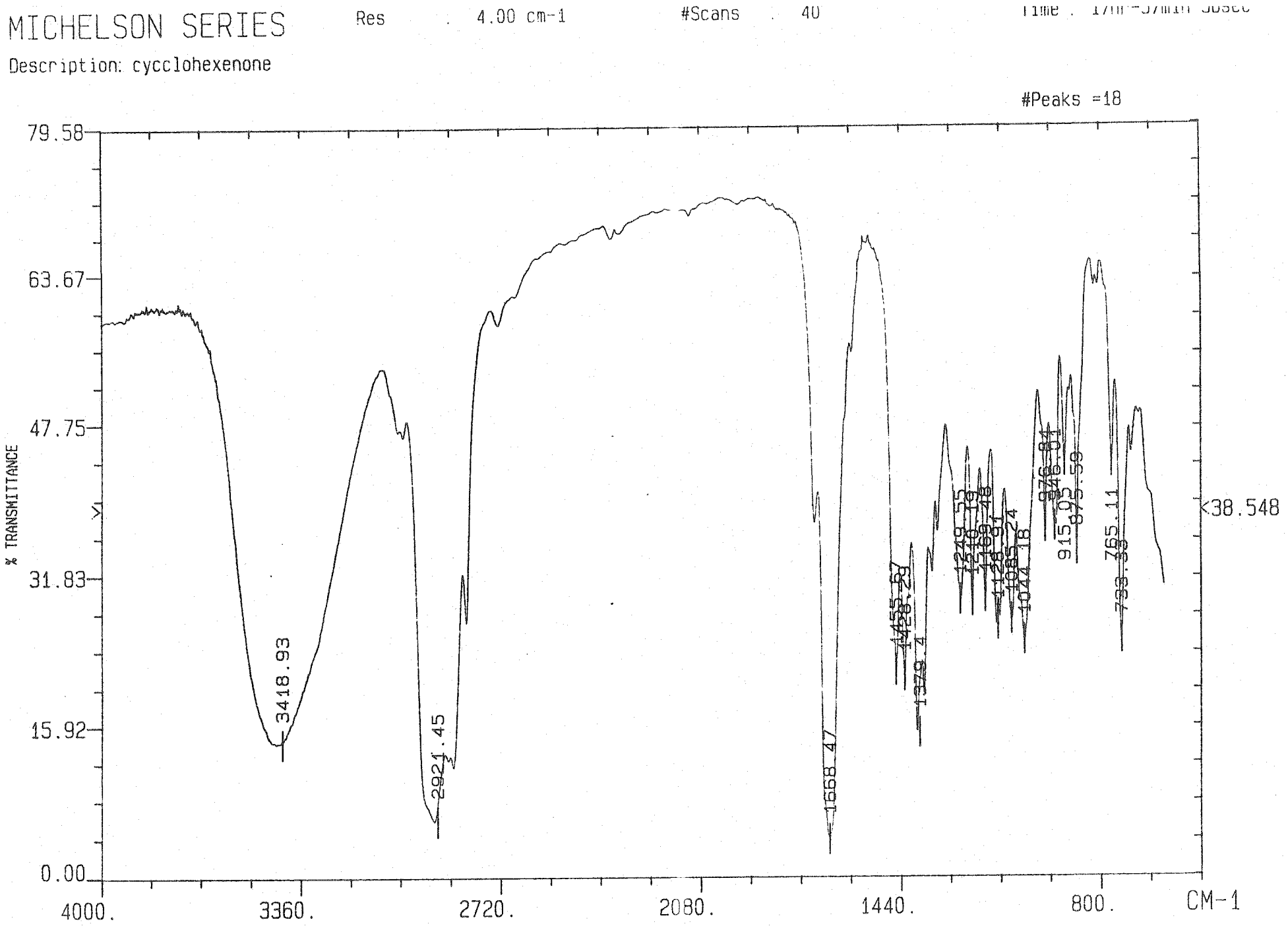
SPECTRAL LINES FOR TH= 14.10
RFL= 610.9 RFP= 0

INDEX	FREQ	PPM	INTENSITY
01	7311.7	145.392	22.077
02	7024.5	139.683	17.332
03	6707.2	133.372	15.916
04	6554.0	130.325	17.500
05	6544.1	130.129	29.547
06	5421.2	107.799	20.331
07	3905.2	77.655	144.649
08	3883.5	77.224	17.930
09	3873.2	77.019	153.349
10	3841.4	76.386	144.798
11	3834.6	76.250	20.127
12	3764.7	74.861	25.794
13	3386.4	67.337	24.718
14	3231.1	64.250	39.737
15	3223.0	64.089	33.110
16	2406.4	47.851	21.642
17	1956.0	38.894	22.032
18	1761.6	35.028	17.109
19	1660.0	33.010	34.278
20	1649.6	32.803	20.384
21	1359.4	27.032	16.445
22	1258.7	25.028	37.351
23	1138.8	22.645	18.319
24	1013.7	20.158	41.750
25	869.1	17.283	19.816

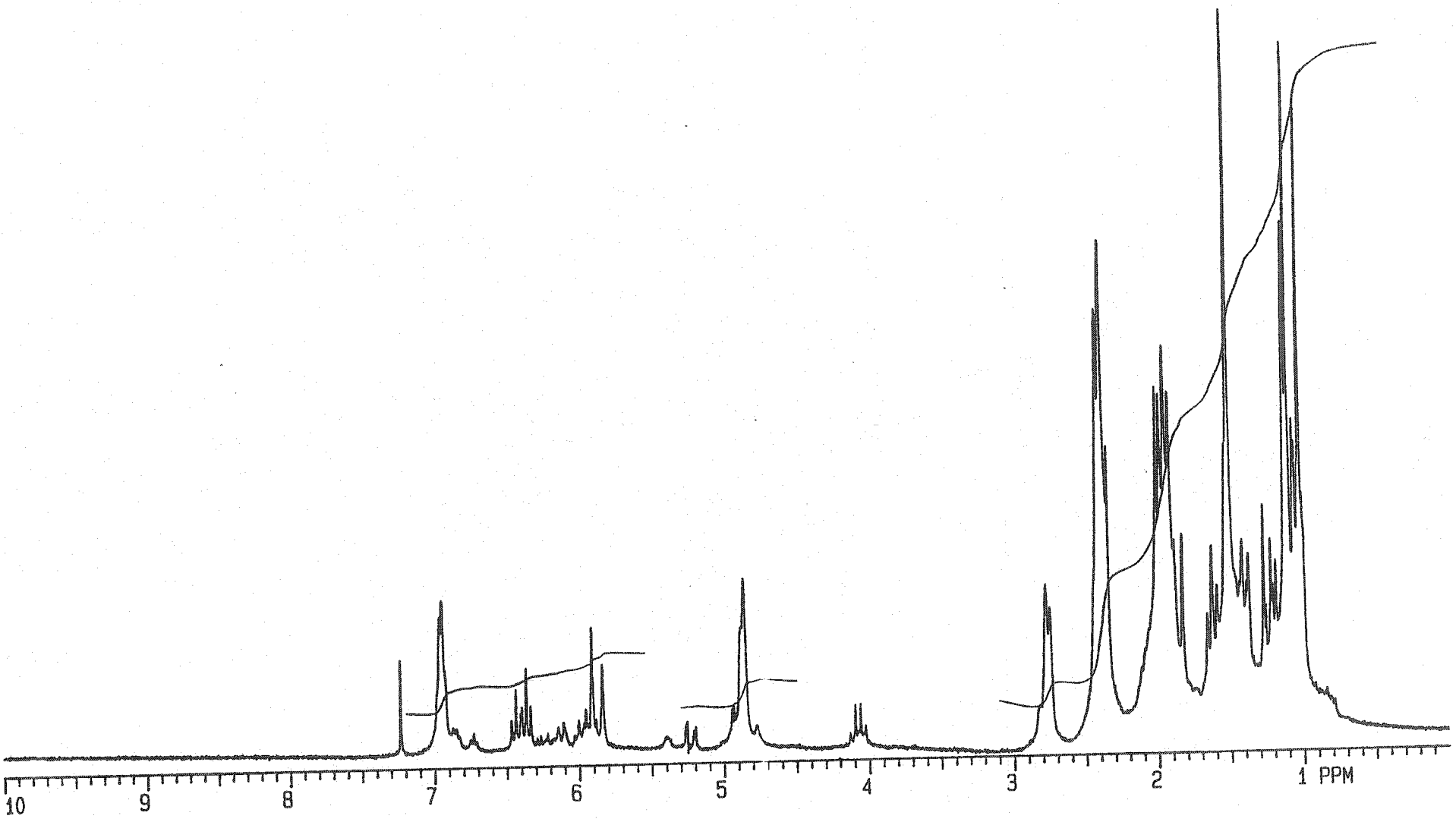




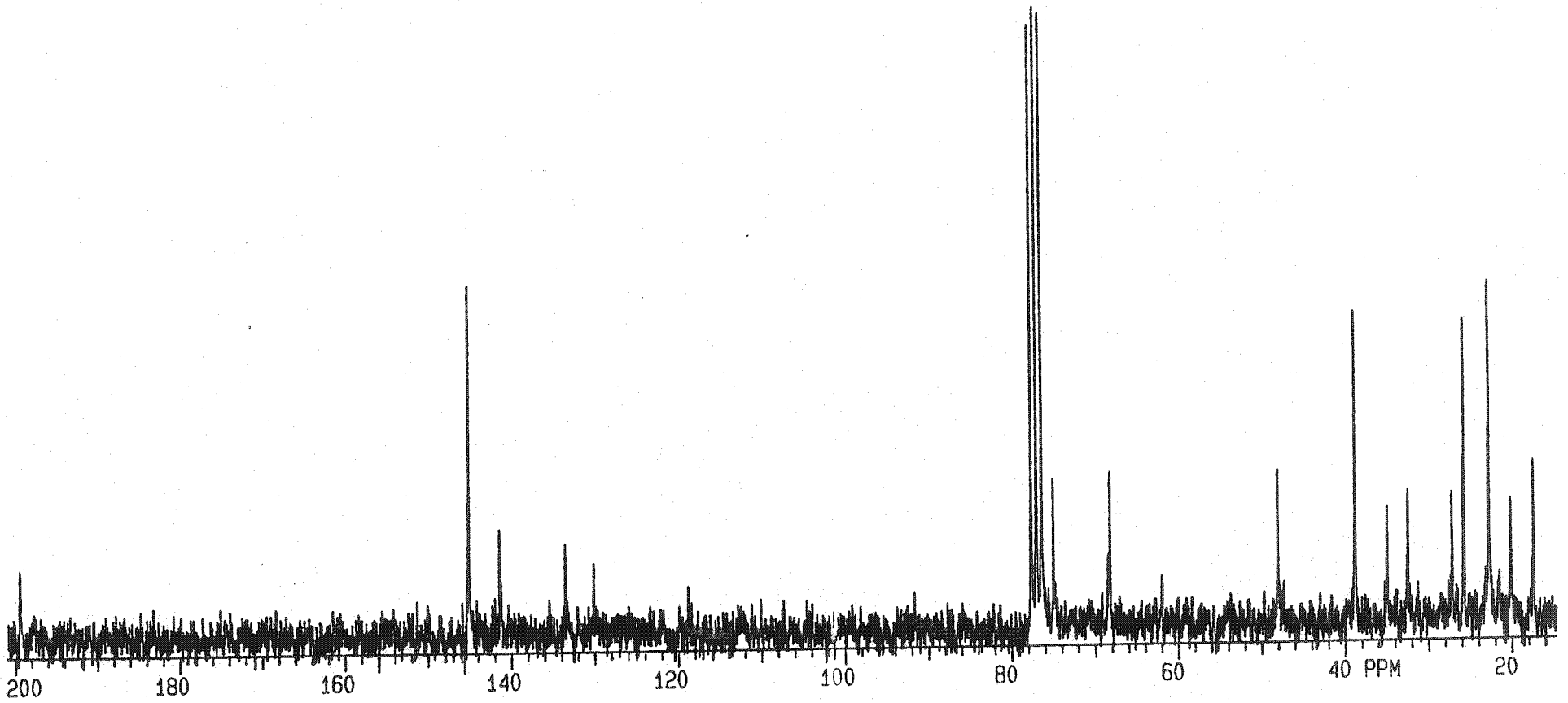
Figuure 18. The 200 MHz ^{13}C NMR Spectrum of 281



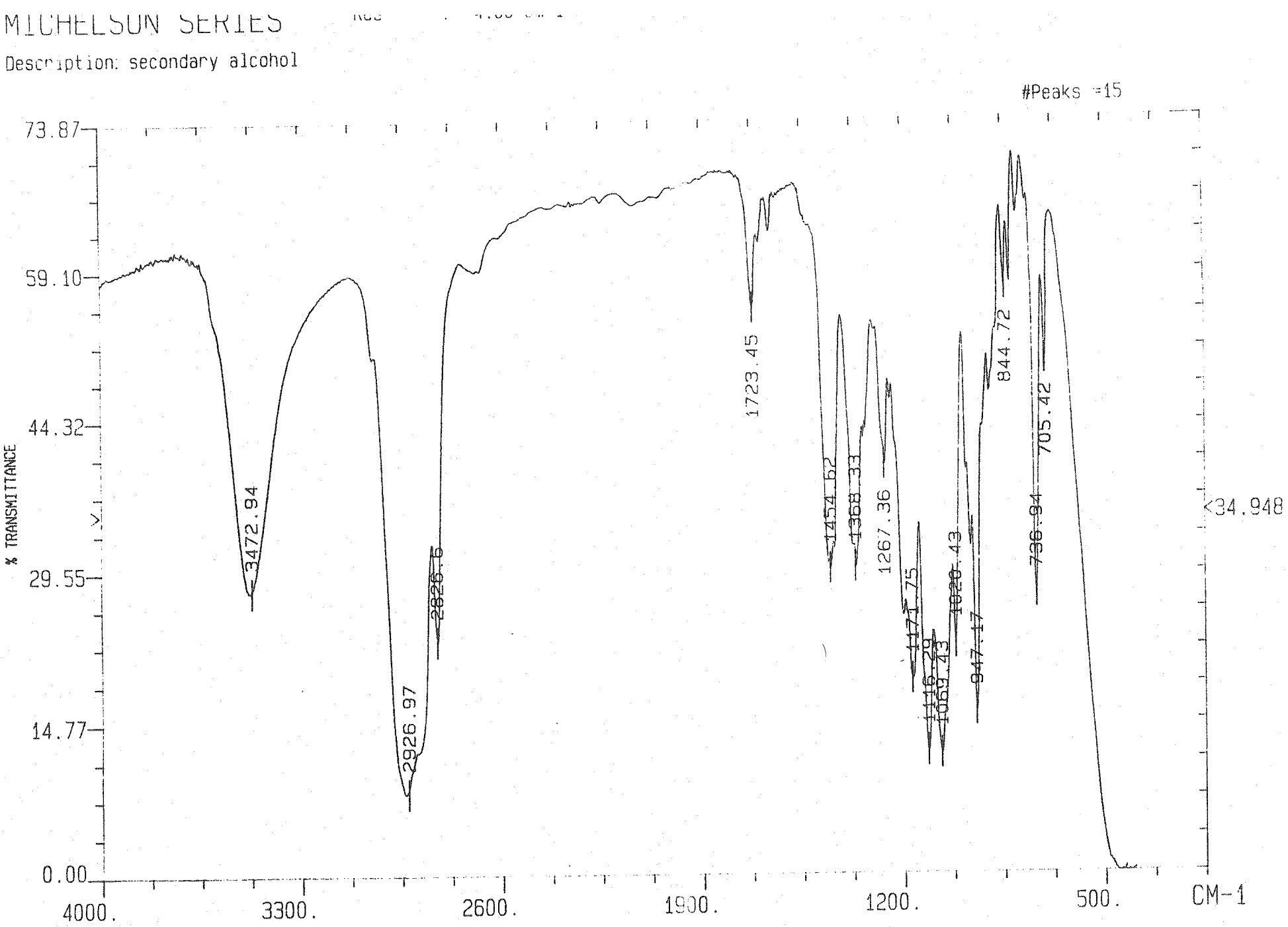
Figuure 19. The IR Sectrum of Alcohol 282



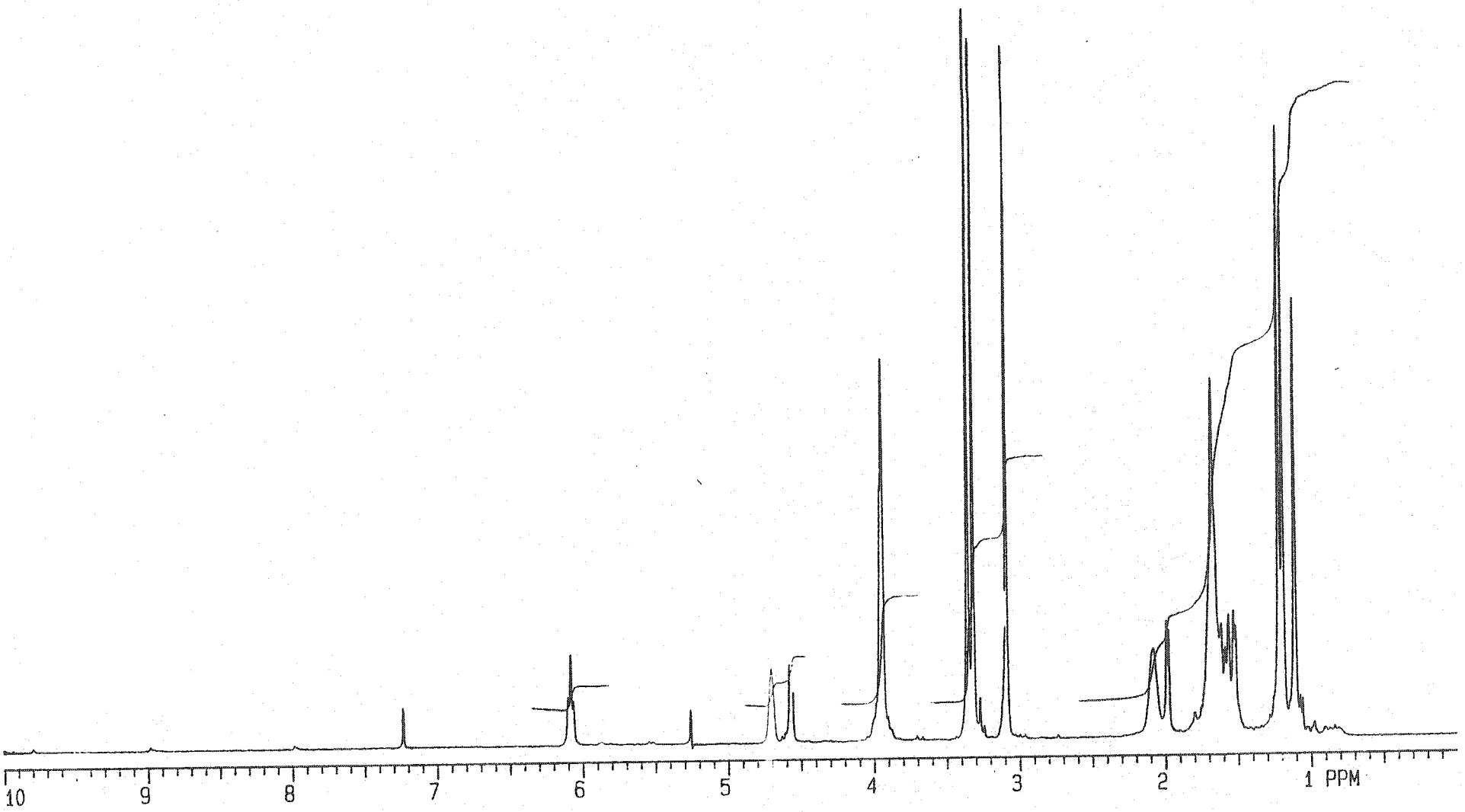
Figuure 20. The 200 MHz ^{1}H NMR Spectrum of **282**



Figuure 21. The 200 MHz ^{13}C NMR Spectrum of **282**



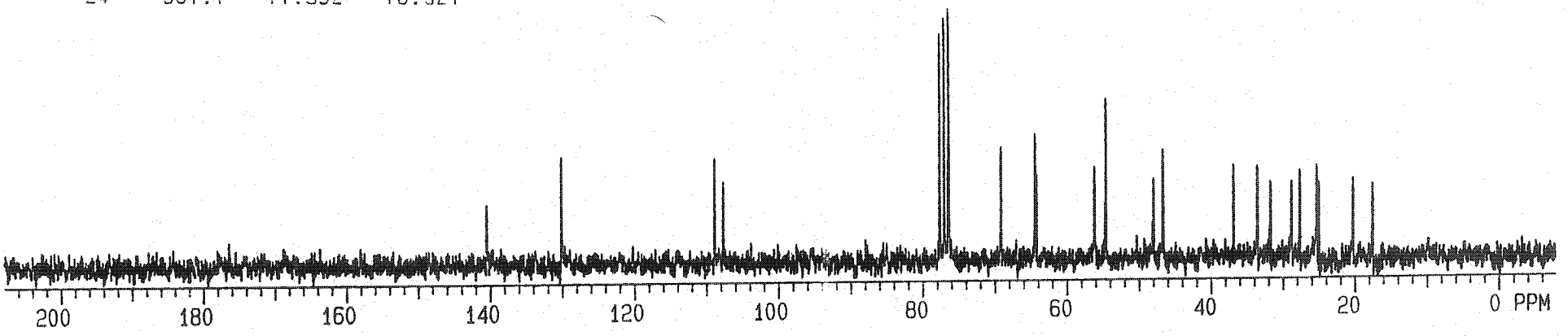
Figuure 22. The IR Sectrum of Alcohol **287**



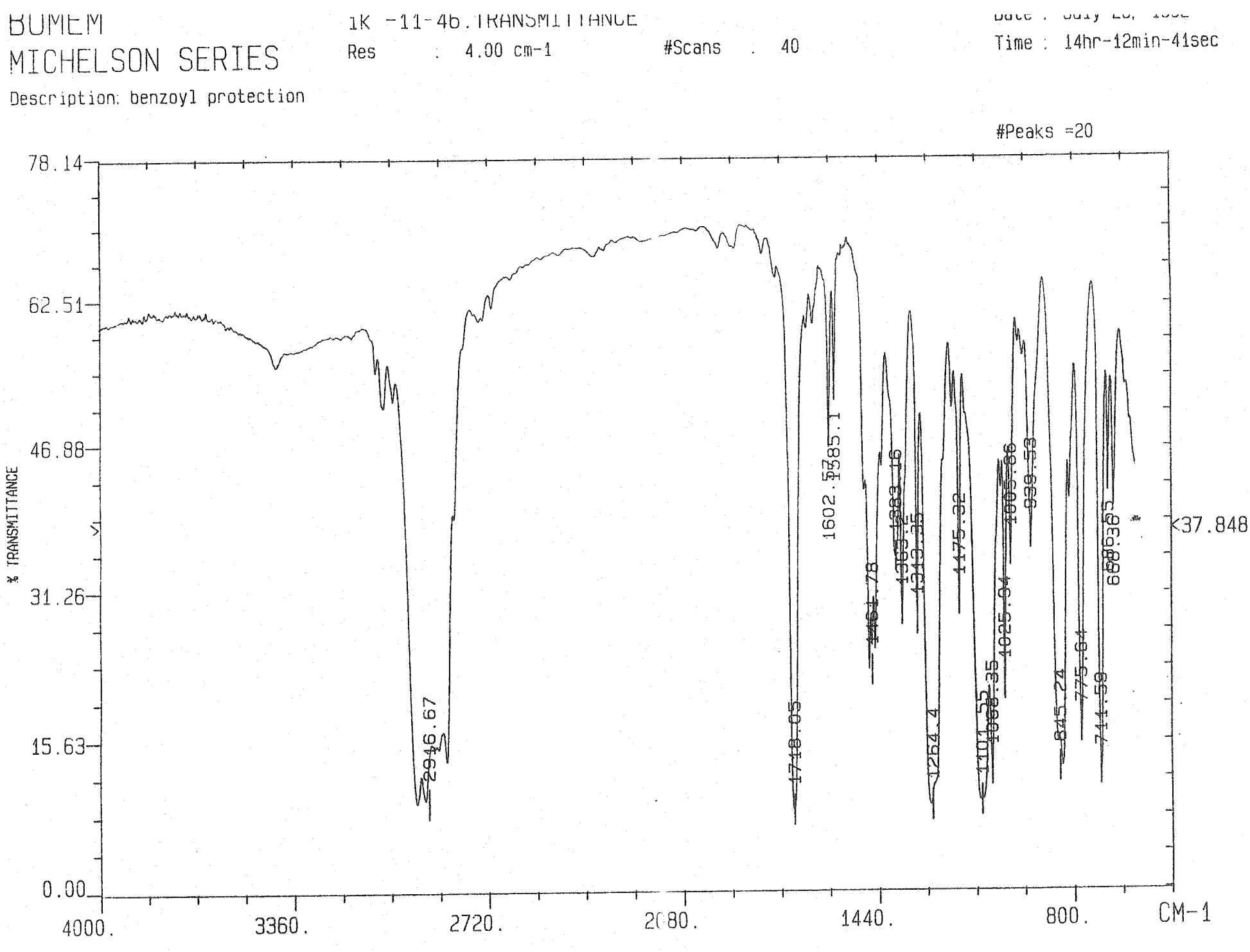
Figuure 23. The 200 MHz ^{1}H NMR Spectrum of **287**

SPECTRAL LINES FOR TH= 12.03
RFL= 610.9 RFP= 0

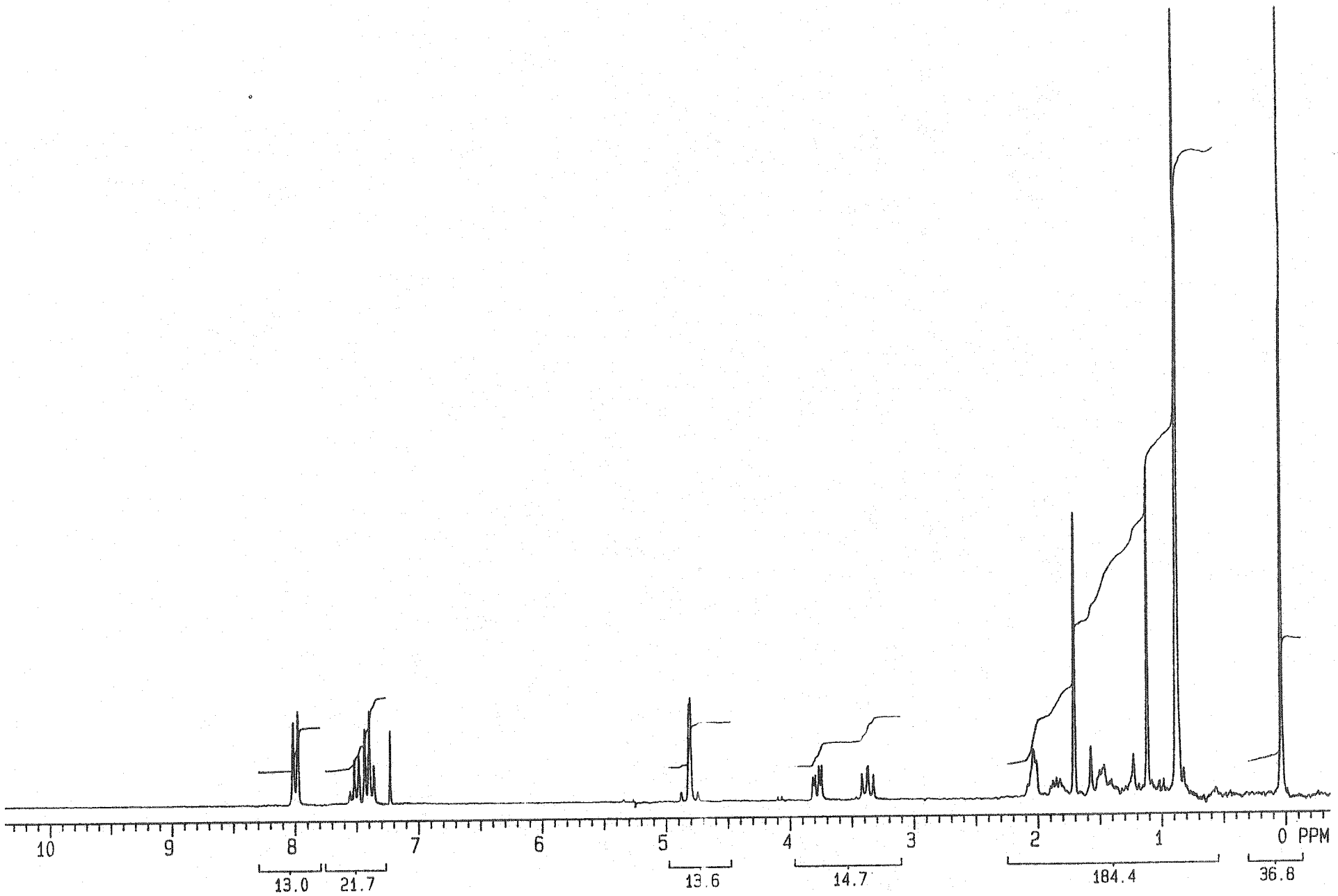
INDEX	FREQ	PPM	INTENSITY
01	7067.1	140.529	15.652
02	6546.4	130.174	27.523
03	5477.5	108.921	26.938
04	5415.6	107.689	21.340
05	3905.6	77.662	60.978
06	3873.6	77.025	63.663
07	3846.3	76.483	31.303
08	3841.6	76.389	65.567
09	3478.9	69.178	29.715
10	3241.8	64.464	32.741
11	3234.0	64.308	26.348
12	2825.7	56.189	23.955
13	2748.0	54.643	42.059
14	2415.5	48.031	21.096
15	2347.5	46.679	28.346
16	1853.7	36.860	24.164
17	1687.6	33.558	24.493
18	1598.0	31.776	19.783
19	1447.6	28.786	19.903
20	1390.7	27.654	22.876
21	1272.8	25.310	24.758
22	1259.0	25.035	20.678
23	1018.7	20.256	21.786
24	881.7	17.532	18.921



Figuure 24. The 200 MHz ^{13}C NMR Spectrum of **287**



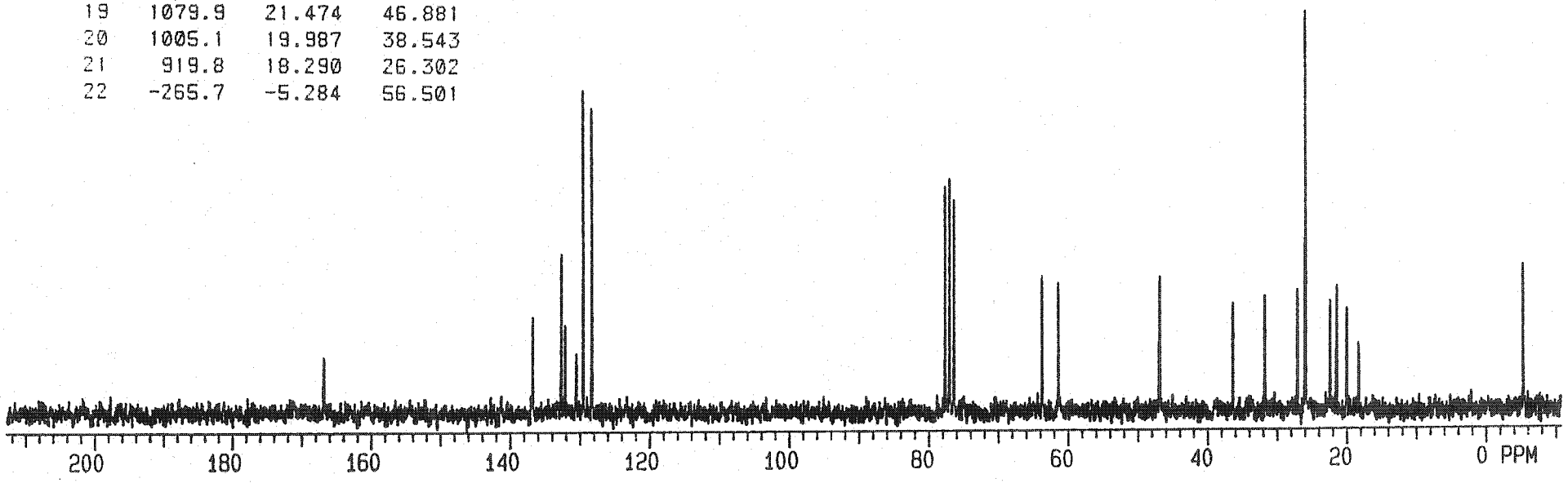
Figuure 25. The IR Sect um of Benzoyl Ester 307



Figuure 26. The 200 MHz ^{1}H NMR Spectrum of **307**

SPECTRAL LINES FOR TH= 18.92
RFL= 610.9 RFP= 0

INDEX	FREQ	PPM	INTENSITY
01	8389.4	166.823	22.453
02	6877.4	136.756	35.743
03	6673.2	132.695	59.887
04	6646.6	132.168	34.973
05	6567.1	130.587	21.922
06	6513.9	129.528	127.843
07	6450.8	128.274	123.463
08	3905.0	77.651	85.346
09	3873.0	77.014	87.585
10	3841.1	76.379	82.823
11	3205.7	63.745	50.777
12	3088.1	61.407	49.201
13	2359.4	46.917	52.705
14	1830.1	36.392	42.484
15	1598.4	31.783	45.616
16	1360.9	27.062	45.718
17	1305.5	25.960	150.000
18	1125.1	22.372	40.917
19	1079.9	21.474	46.881
20	1005.1	19.987	38.543
21	919.8	18.290	26.302
22	-265.7	-5.284	56.501



Figuure 27. The 200 MHz ^{13}C NMR Spectrum of 307

IX. APPENDIX

IR and ^1H NMR spectra of 283 and 284a or 284b including the expanded ^1H NMR spectrum are listed here. The 200 MHz ^1H NMR spectrum of 218 is also shown here.

BOMEM
MICHELSON SERIES Res . 4.00 cm-1 #Scans . 28 Time . 14hr-48min-17sec

Description. RADICAL CYCLIZATION PRRODUCT

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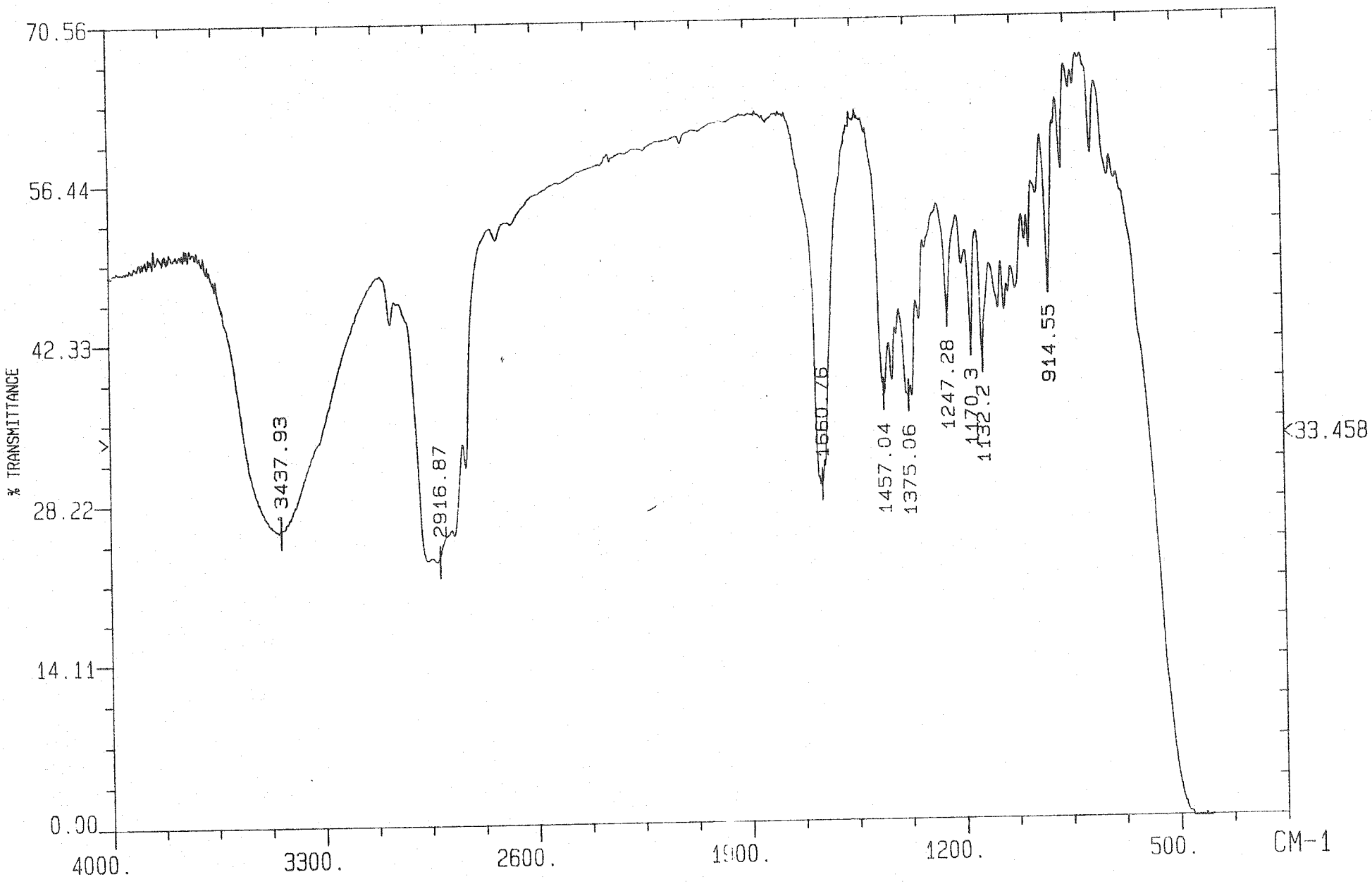
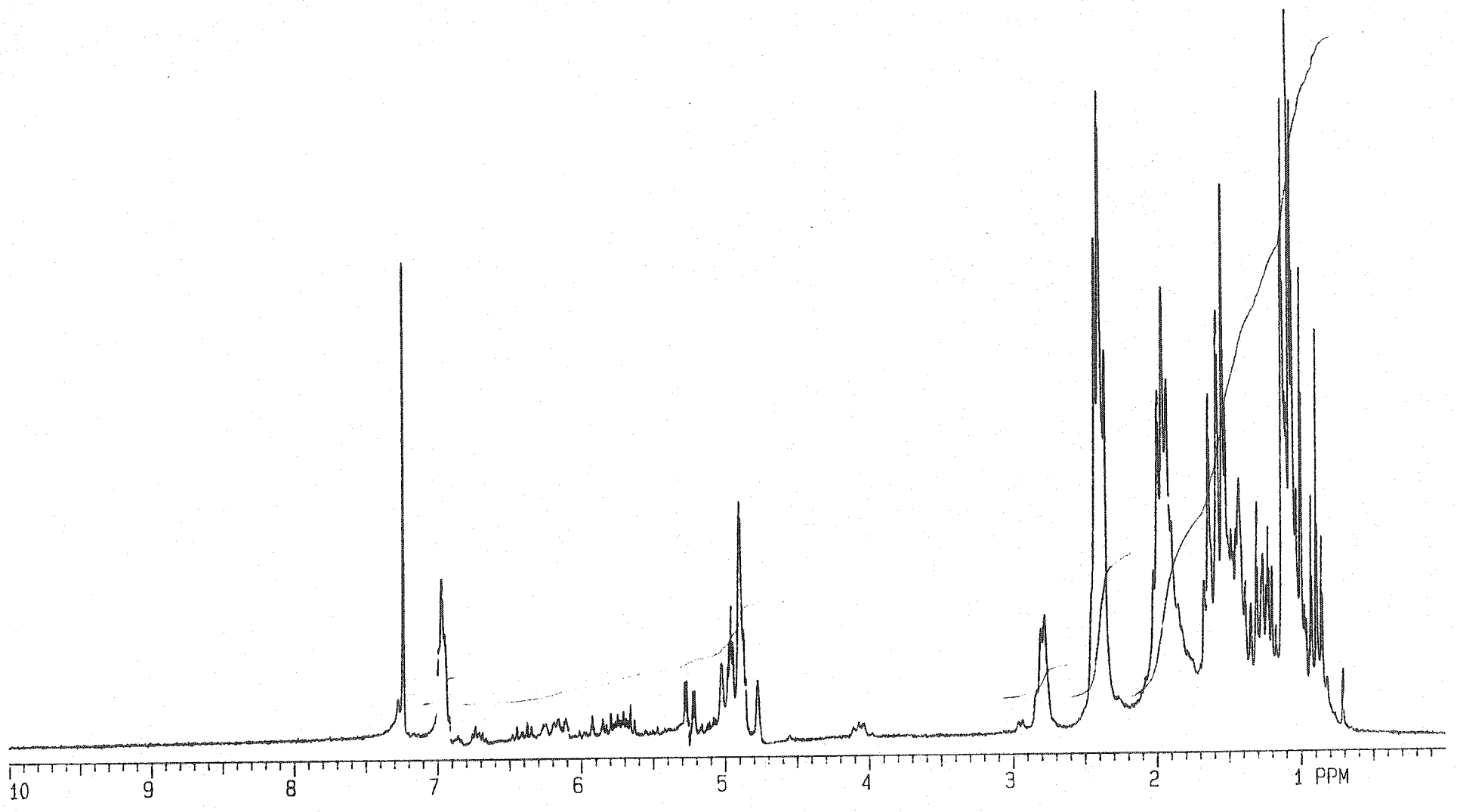
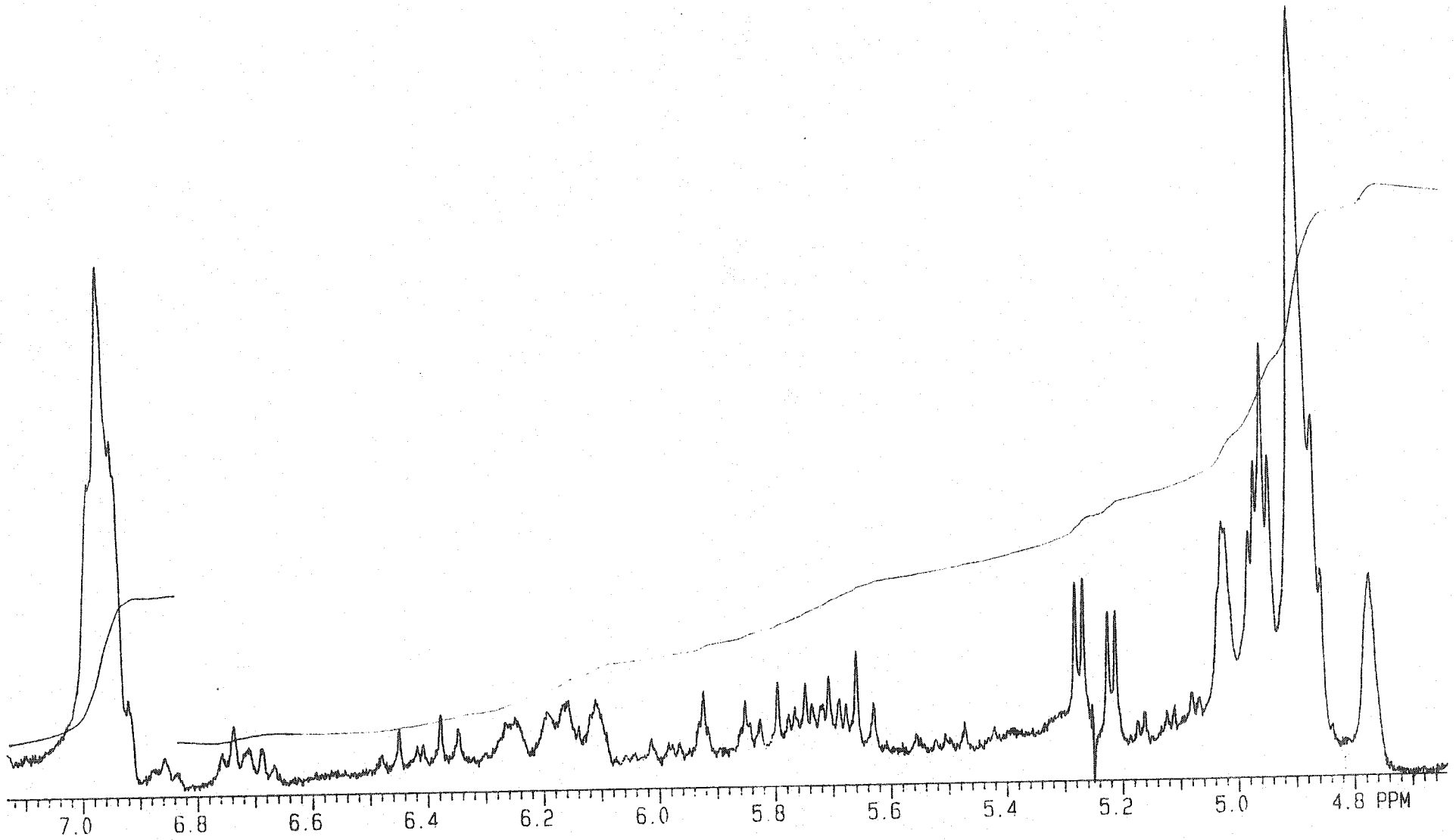
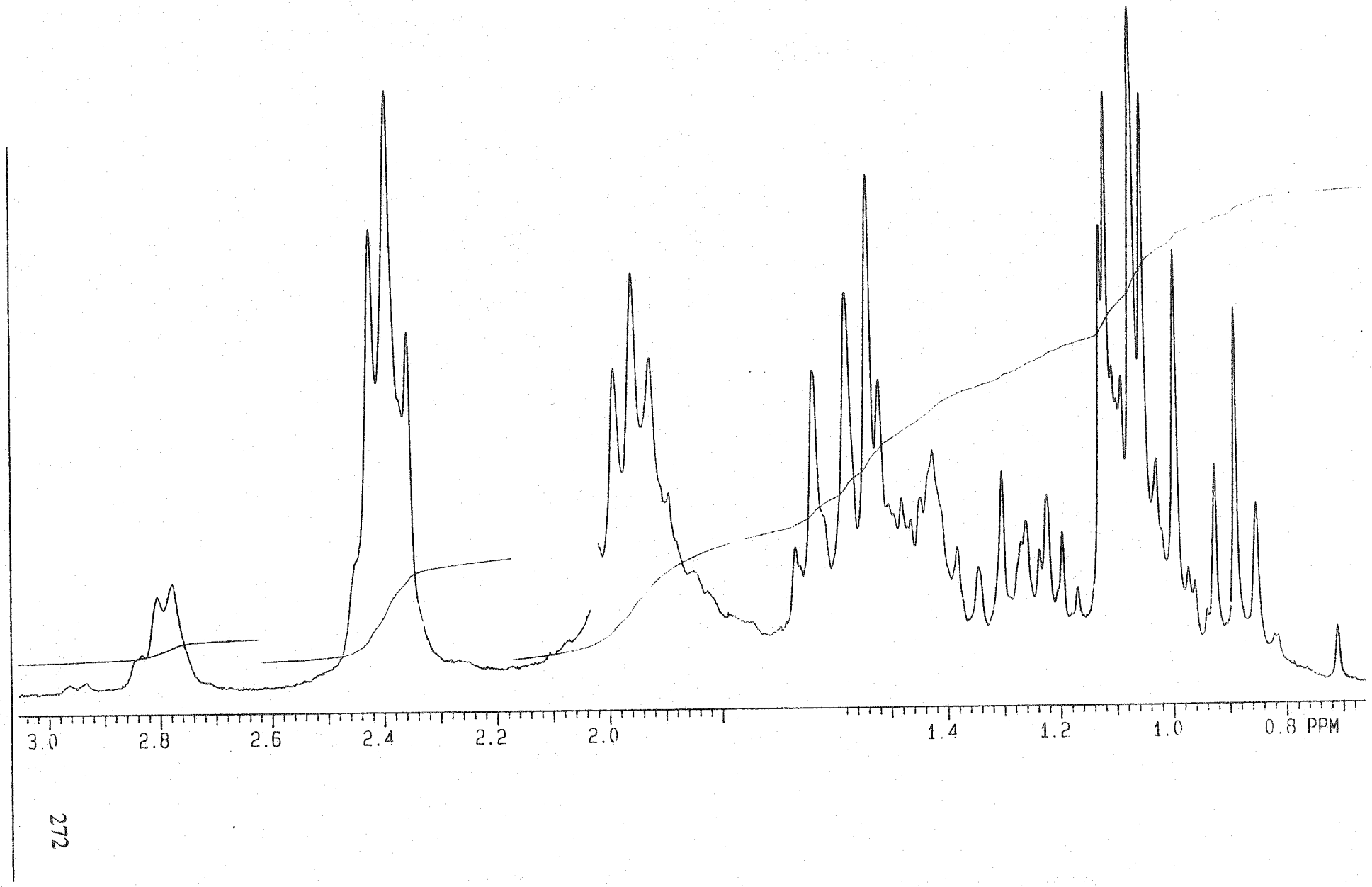


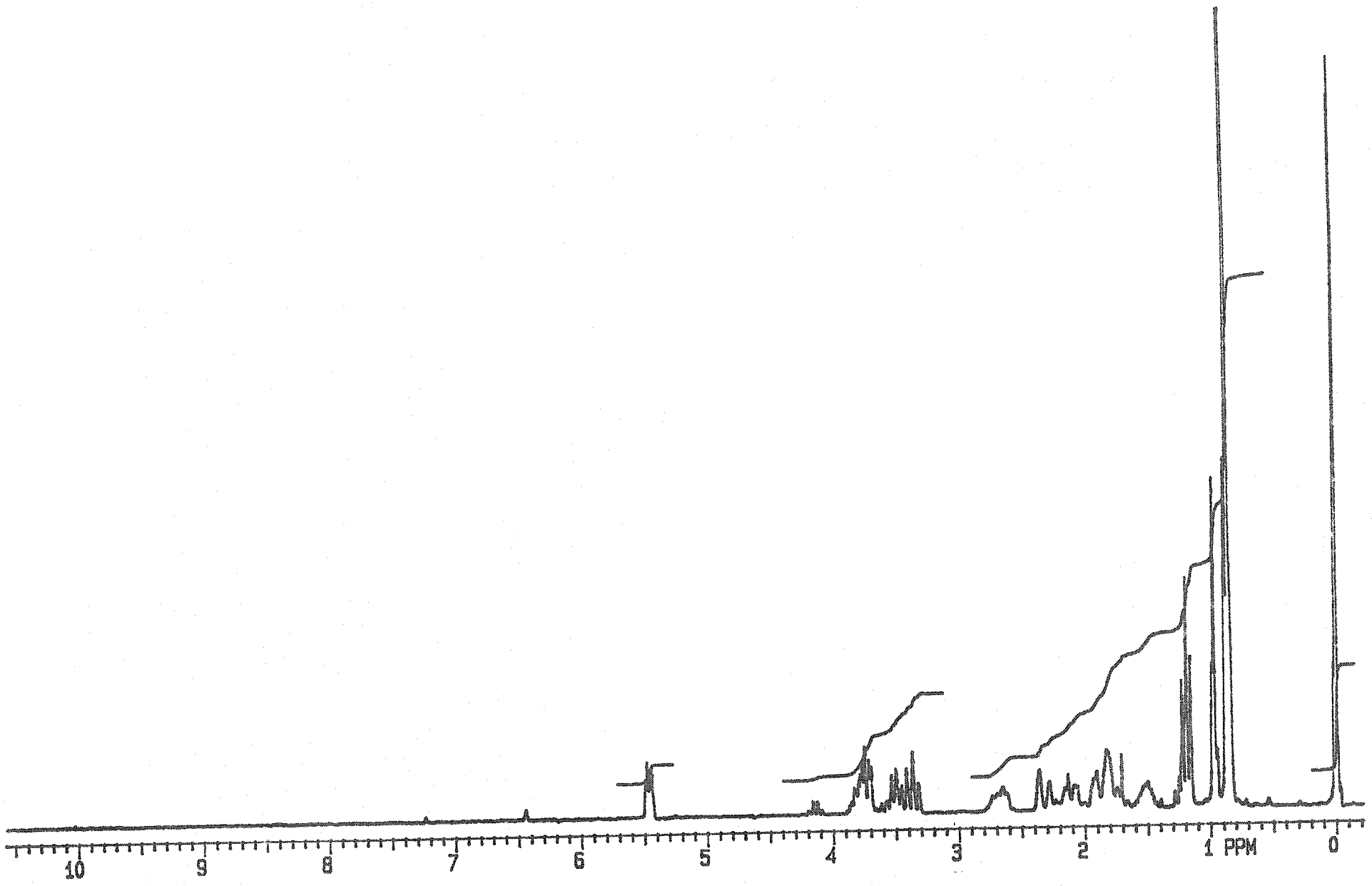


270


7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8 PPM



272



The 200 MHz ^{1}H NMR Spectrum of 218