SYNTHESIS AND CARBON-13 NMR SPECTROSCOPY OF DITERPENOIDS

SYNTHESIS AND CARBON-13 NMR SPECTROSCOPY OF DITERPENOIDS

by

JOHN WALLACE EASTON, B.Sc. (Hon.),
Diploma in
Chem. Tech.,
M.C.I.C.

A Thesis
Submitted to the Faculty of Graduate Studies
in Partial Fulfilment of the Requirements
for the Degree
Doctor of Philosophy

McMaster University
September 1973

Doctor of Philosophy (1973) McMaster University
(Chemistry) Hamilton, Ontario

TITLE: Synthesis and Carbon-13 NMR Spectroscopy of Diterpenoids

AUTHOR: John Wallace Easton; B.Sc.(Honors), McMaster University; Diploma in Chem. Tech., Ryerson Polytechnical Institute; M.C.I.C.

SUPERVISOR: Professor R.A. Bell

NUMBER OF PAGES: xii, 176

SCOPE AND CONTENTS:

With the view to functionalizing the C-20 angular methyl group of the ring C-aromatic diterpenoids, synthetic objectives centred on finding an easily accessible intermediate to which a 1,6-hydrogen transfer could be attempted by photolysis of the nitrite ester. Attempted functionalization through the 12β-hydroxy group in perhydropodocarpic acid 29b and through the C-7 alcohol group in methyl 7β-hydroxy-O-methylpodocarpate 37 and in 6β, 7β-dihydroxy-O-methyl-podocarp-19, 6β-lactone 48 were unsuccessful. Recourse to the normal 1, 5-hydrogen transfer through the nitrite ester of methyl 6β,7β-dihydroxy-O-methyl-podocarpate 95, a compound readily obtained in good yield after six steps from 12-acetoxypodocarpic acid 38, was inconclusive.

During the course of the synthesis, an improved procedure of benzylic oxidation of phenolic compounds, or easily hydroyzable derivatives, was developed.

The carbon-13 nuclear magnetic resonance spectra of

podocarpic acid 25, a ring C-aromatic diterpenoid, and a number of derivatives were recorded and analyzed. Substituent effects on the aliphatic carbons were determined for a variety of oxidation levels at carbon 19.

These substituent effects, among other techniques, are applied to the analysis of some labdane intermediates, ozonolysis products of podocarpic acid, and abietic acid and derivatives.

ACKNOWLEDGEMENTS

During the course of this work, significant contributions have been made by others to whom the author wishes to express his appreciation. Special thanks are accorded the following:

Dr. R.A. Bell (Research Director) for his friendship, ideas, guidance, and interest.

Drs. J. Warkentin and T. Neilson for their interest and helpful discussions.

Mr. B.G. Sayer for his help and co-operation.

To my parents for their interest and constant encouragement.

To my wife Cheryl for her patience and understanding during the many hours she spent alone and for her help in the completion of this thesis. To Jennifer and Margot for keeping the noise down to a dull roar while the thesis was being written.

To Gwyn and Susan Davies for their unselfish help in the typing, organization, and duplication of this manuscript.

To Dr. John Saunders of the Université de Sherbrooke for his friendship, co-operation, and helpful discussions.

Financial support through McMaster University and the Ontario Graduate Fellowships is gratefully acknowledged.

The author wishes to express his appreciation to the Department of Chemistry for allowing part of this work to be done on a part-time basis.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. GENERAL INTRODUCTION

1.1 Natural Products

The knowledge of the chemistry of compounds derived from plants and animals, the so-called natural products, has increased and diversified to an extent that, only a century ago, would have seemed unimaginable. From humble beginnings in the primitive technologies of dyeing, perfumery, and folk-medicine, the subject of natural products has become a precise science from which has evolved almost all of the present framework of structural and theoretical organic chemistry.

The ancient Egyptians, Romans, and Phoenicians made extensive use of dyes which were organic compounds: indigo derived from the colourless glucoside, indican, which is extracted from the leaves of the indigo and of the woad plants; alizarin, the principle colouring material of madder, a plant of the rubia tinctorum; Tyrian purple, the legendary dye ascribed to royalty, derived from glandular fluid expressed from the purple Mediterranean snail, Murex brandaris.

The fermentation of sugars to yield alcohol and the conversion of animal fat into soap have been known since ancient times. Alcohol is still prepared to-day by a similar method and it has only been in the last twenty-five years that organic chemists have been able to synthesize

detergents which could compete with soap.

Until the end of the seventeenth century, the interest of chemists has been directed almost entirely to the non-living mineral world. Although many natural compounds, mostly from vegetable sources, were isolated during the eighteenth century, their compositions remained unsolved and their chemistry ignored. Because of their association with living organisms("organized matter"), the chemicals of animal and vegetable origin were termed organic to differentiate them from those of the inanimate mineral realm termed inorganic.

Lavoisier had shown in 1784 by analysis of combustion products that most organic compounds contained the same small group of elements: carbon, hydrogen, oxygen, and nitrogen. Despite the existence of these elements in inorganic as well as organic matter, chemists believed that only a "vital force" inherent in a living cell could build complex compounds from the elements and, although inorganic matter could be prepared artificially in the laboratory, organic compounds could be produced only in living organisms. Contrary to this widely accepted belief, Berzelius was able to show in 1814 that the usual chemical laws governing the behaviour of organic materials, such as the laws of fixed and multiple proportions, applied as well to organic compounds.

The gulf between inorganic and organic compounds was bridged by Friedrich Wohler in 1828 when his evaporation

of an aqueous solution of ammonium cyanate yielded urea identical with the compound found in urine which had been known only as a product of animal metabolism. This observation was an obvious demonstration of the fallacy of the vital force theory. However, only the weight of accumulated evidence in succeeding years finally laid to rest the vitalistic theory.

During the latter half of the nineteenth century, the foundations of structural theory of both atomic organization and molecular shape were begun. The three-dimensional nature of molecules and the tetrahedral structure of the four bonds to carbon were proposed and have long since been universally accepted. The consequences of these theoretical developments have been a remarkable insight afforded chemists of the molecular architecture of the most complex molecules.

The rapid and continuous development in this area coupled with the discovery of new synthetic methods resulted in the preparation of many thousands of compounds of both theoretical interest and practical importance. Starting materials for the industrial production of dyes, pharmaceuticals, photographic chemicals, and explosives were realized from the constituents of coal tar.

During the present century, the growth of the organic chemical industry can be attributed to the many practical and socially beneficial uses to which these compounds have

been applied. The increased demand for products of nature provided an already flourishing industry with the impetus to produce in quantity synthetic analogs of natural materials of equal or better quality. Such dramatic progress represents only a continuation of the traditional curiosity of man about the natural world and his attempts to understand and exploit it.

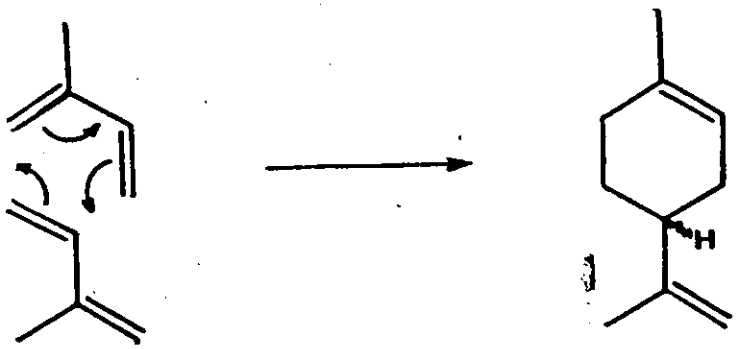
1.2 The Terpenoids

The odoriferous components of plants and, to a lesser extent, animals, known as the essential oils, have been extracted and used by man for hundreds of years, expecially in the areas of cosmetics, perfumery, and medicine. In recent times, these oils have also found application in the fields of paints, preservatives, and artificial flavourings.

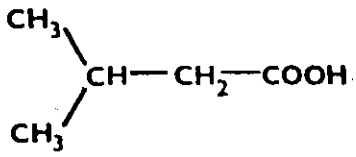
Although known to be a complex mixture of acyclic, alicyclic, aromatic, and heterocyclic compounds, a prominent constituent was found to be a series of isomeric unsaturated hydrocarbons of formula $C_{10}H_{16}$, known collectively as terpenes. The term, terpenoids, has since come to represent a wide variety of substance, many not of natural origin, having a variety of functional groups, but retaining a basic structural relationship to the original simple terpenes.

Subsquent to the discovery that the $C_{10}H_{16}$ terpenoids could be considered as head-to-tail dimers of isoprene C_5H_8 1 , higher molecular weight terpenoids were found, each having the isoprene unit as a common denominator. Coupled with the

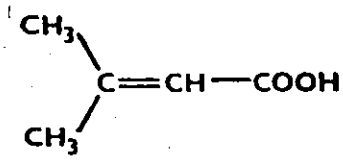
observation that thermal decomposition of almost all terpenes gave isoprene as one of the products, this evidence suggested that the skeleton structures of all terpenes could be built up from isoprene units. This isoprene rule (1), while not correct in all cases, has proved a useful guiding principle in structural studies of many natural products. Under appropriate conditions, for example, isoprene will dimerize to dl-limonene ii or polymerize to a rubber-like material. Although isoprene itself has never been found in nature, iso-valeric acid iii and senecioic acid iv have been found naturally.



i ii



iii

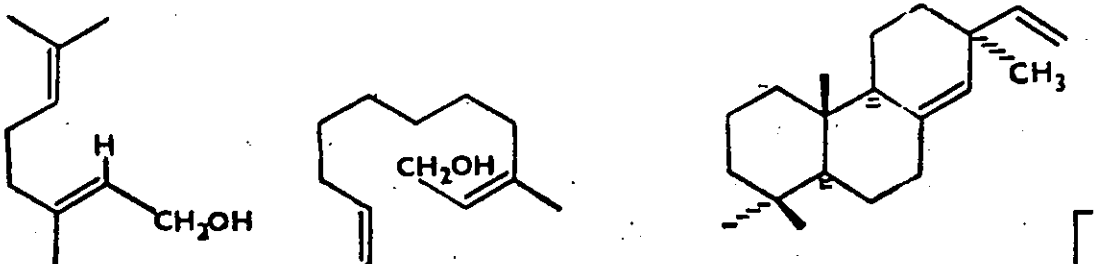


iv

The terpenoids are classified according th the number of isoprene units in the molecule.

TABLE I Classification of terpenoid compounds

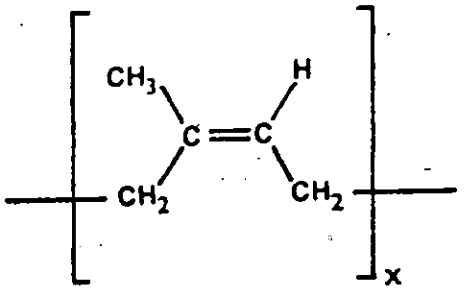
Number of Isoprene units	Number of Carbon units	Class	Example
10	2	monoterpenoids	geraniol v
15	3	sesquiterpenoids	farnesol vi
20	4	diterpenoids	pimaradiene vii
25	5	sesterpenoids	~~di~~mycinol viii
30	6	triterpenoids	squalene ix
40	8	tetraterpenoids	β-carotene x
>40		polyterpenoids	rubber xi



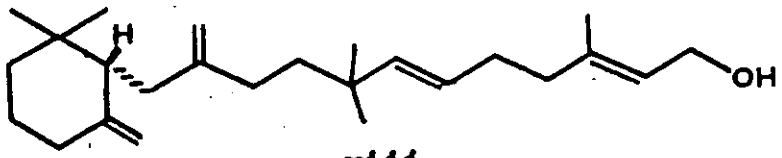
v

vi

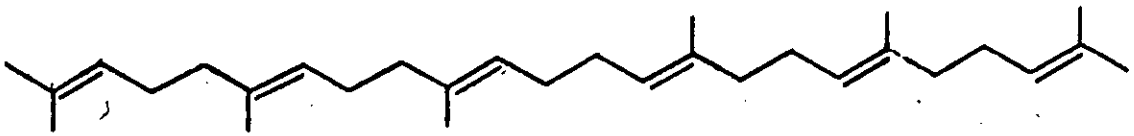
vii



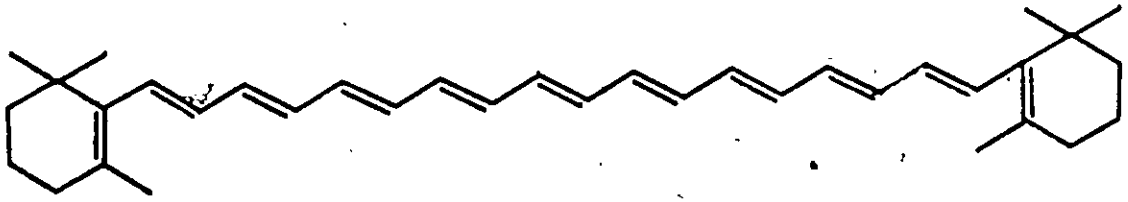
xi



viii



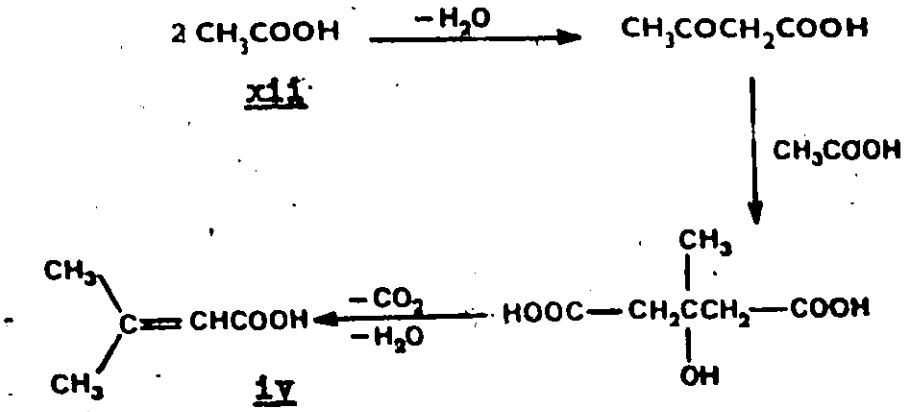
ix



x

FIGURE I Terpenoid compounds

Much work in recent years has been applied to information on how plants and animals are able to synthesize terpenoid substances. Bloch and his associates have shown that fatty acids could be biosynthesized in tissue from acetic acid (2) and that the same precursor is used by animal tissue in the synthesis of the sterol cholesterol (3-7). The implication is that acetic acid xii is the fundamental building unit from which the iso-pentane unit is derived, possibly by a scheme shown below.



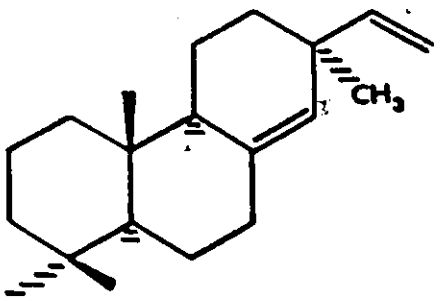
This hypothesis has been experimentally substantiated by the discovery that not only could the guayule plant incorporate labelled acetic acid into its rubber product (8), but the substitution of acetic acid by senecioic acid was also successful.

On this basis, one can formulate the condensation of two molecules of senecioic acid followed by reduction of the ketone function to give geraniol vi from which other

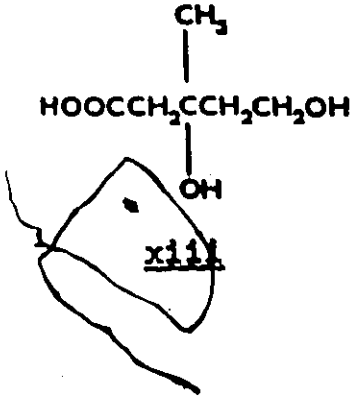
cyclic and acyclic monoterpenes could be derived.

A giant step in the studies of terpene biogenesis came with the discovery of mevalonic acid xiii (9) which is structurally closely related to senecioic acid. Mevalonic acid was found to be an efficient cholesterol precursor (10) as well as being incorporated readily into carotenoids (11), rubber (12), and other terpenoids, therefore, suggesting it to be the source of "active isoprene" in plant and animal tissues.

Analogous to the formation of the monoterpenes, the diterpenes are derived from the polyisoprenoid unit such as geranylgeraniol xiv, the cyclization of which yields a cationic intermediate xv which can stabilize by neutralization as by lactone or ether formation or hydration (giving scareol xvi (13,14), or proton loss (giving manoöl (xvii) or by rearrangement. Predictable rearrangements of polycyclic precursors possessing carbonium ion sites provide



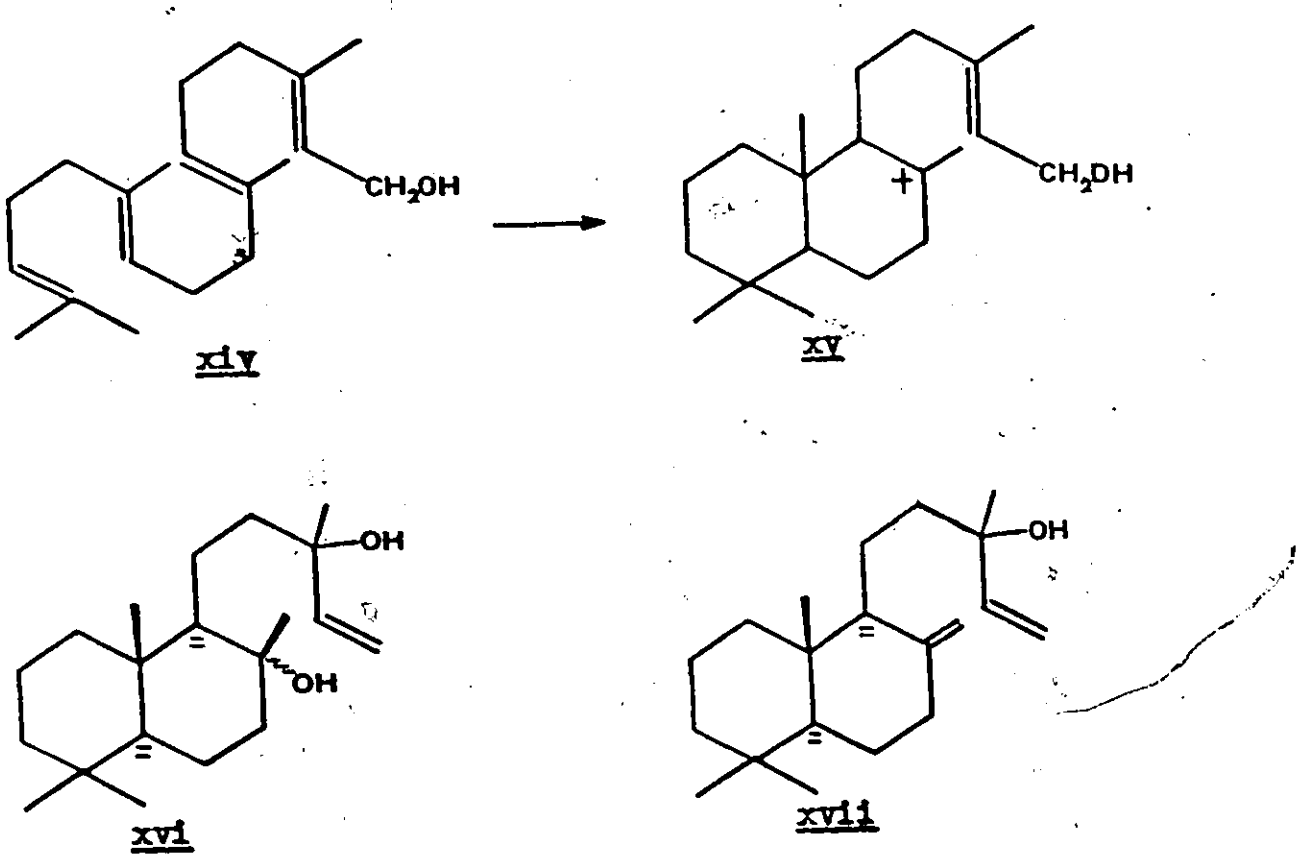
vii



xiii

reasonable pathways to most of the naturally occurring terpenoid cyclic skeltons. For example, a postulated ionization of the hydroxyl could lead, from the manoöl skelton, to the tricyclic diterpenoid structure, such as pimaradiene vii (15,16)

Natural products have received a great deal of attention from the structural and synthetic chemist. Originally the synthesis of terpenes was directed principally at confirmation of structure and at the challenge to the capabilities of the chemical principles. In recent years, synthesis has become a precursor to the development and understanding of the sequential application of reactions and reagents enabling chemists to optimize their choice



xiv xv xvi xvii

FIGURE 2 Diterpene biosynthesis

and sequence of reactions for the preparation of a desired product. The recent syntheses of cholesterol and vitamin B_{12} are the compendia of such predictions.

Other benefits from natural product syntheses have a accrued over the years. Products and intermediates, for example, may have biological significance and, hence, medical applications, where the necessary quantities from natural sources may be limited.

To the scientist, natural and synthetic terpenoids have found extensive application as model compounds. With their structural rigidity and variety of substitution, they have helped reveal the relationships between structure, mechanism and stereochemistry and have added to the fundamental understanding of chemical reactions, thus, not only improving the successful predictions of products in a given reaction sequence, but also bestowing upon the field of organic chemistry a theoretical unity which had, heretofore, been lacking.

In addition, their use as model compounds for the correlation of molecular structure with physical properties accounts, in part, for the rapid acceptance and growth of spectroscopic analytical techniques in the last few decades. Indeed much of the empirical data available to those working in the areas of ultraviolet, visible, infrared, and nuclear magnetic resonance spectroscopy has been gleaned from studies on known structures. Their application and modification to other molecular situations has accelerated both the

analysis of a given synthetic step and also the characterization of an unkown structure. Prime examples include the Woodward rules of ultraviolet spectroscopy and the substituent effects of various structural systems in nuclear magnetic resonance spectroscopy.

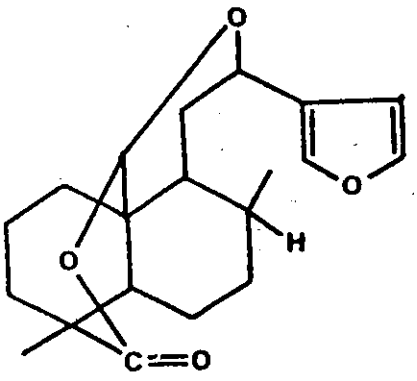
2. HISTORICAL INTRODUCTION

2.1 Sciadin - Structure and Related Derivatives

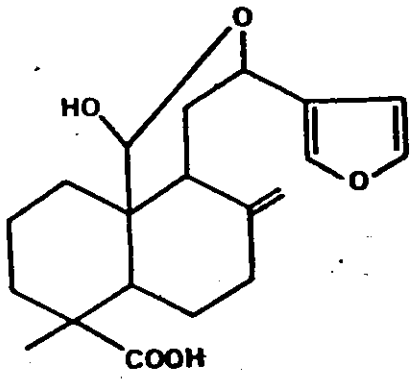
Sciadin 1, a diterpenoid bitter principle was first isolated from the heartwood of Sciadopitys Verticillata Sieb. et Zucc. found in central and western Japan (17).

The neutral compound from the methanolic extract gave a molecular formula of $C_{20}H_{24}O_4$ while chemical and spectroscopic evidence indicated the presence of a lactone ring, a furan ring, and a vinylidene group.

Hydrogenation of sciadin over Adam's catalyst in the presence of ethanol gave dihydrosciadin 2 whereas saponification with alcoholic potassium hydroxide yielded sciadinic acid 3.

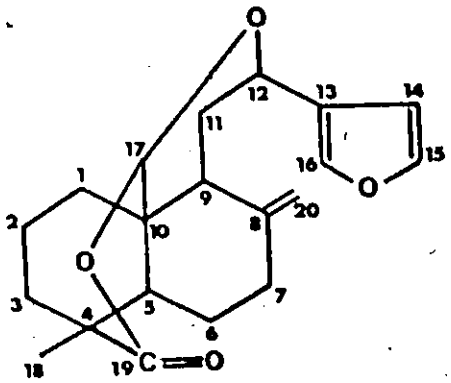


2

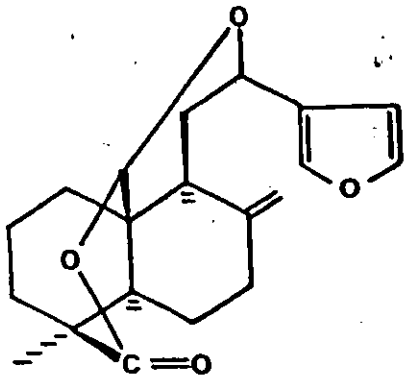


3

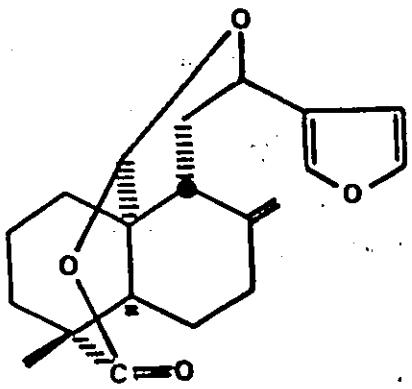
During the course of the chemical and physical investigations for functional groups, it became evident that sciadin was a bicarbocyclic compound. Wet chemical methods


O
12
13
14
11
17
16
15
1
9
O
2
10
8
20
O
3
4
5
6
7
18
19C=O

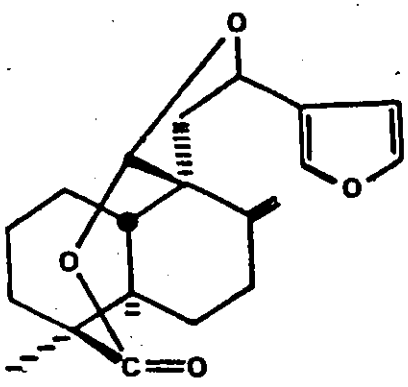
1


O
O
O
C=O

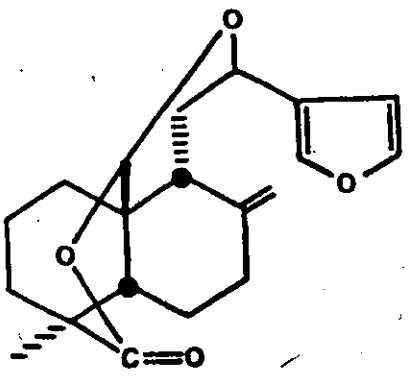
1A


O
O
O
C=O

1B

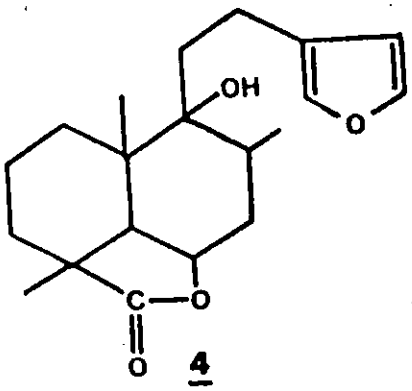

O
O
O
C=O

1C

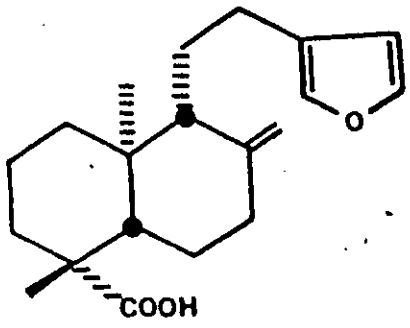

O
O
O
C=O

1D

suggested the similarity of the sciadin structure to that of manoöl xvii and possibly other known furanoid diterpenes such as marrubiin 4 and daniellic acid 5.



4

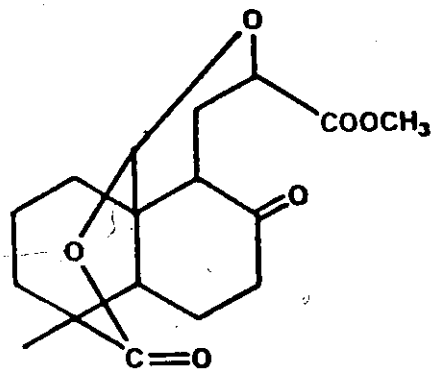


5

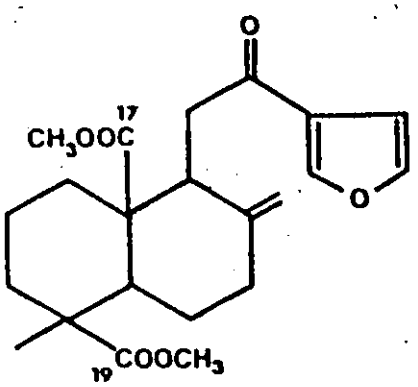
The conformation of sciadin can be represented by structures 1A and 1B, of which the former was favoured based on optical rotatory dispersion measurements on the ketoester 6. The negative Cotton effect suggested the structure having the lactonic and ether groups on the beta side of the molecule, a situation which would apply equally well to sciadin itself.

Kaneko and co-workers (18) isolated from the leaves of the same plant, in addition to sciadin, two related furanoid diterpenes, dimethylsciadinonate 7 and sciadinone 8. Appropriate chemical transformations confirmed the structural correlation between the three compounds. In addition, the authors confirmed the aforementioned structural proposal by Sumimoto and, in the process, excluded the possibility of structure 1C by proton magnetic resonance analysis.

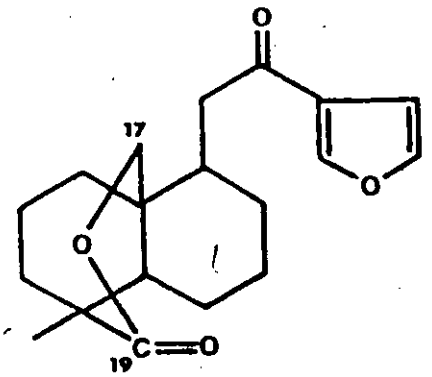
The same authors (19) established the relative configuration of sciadin through the application of a novel chemical reaction. Carbons 17 and 19 must be in a 1, 3-cis-


O
COOCH3
O
O
C=O

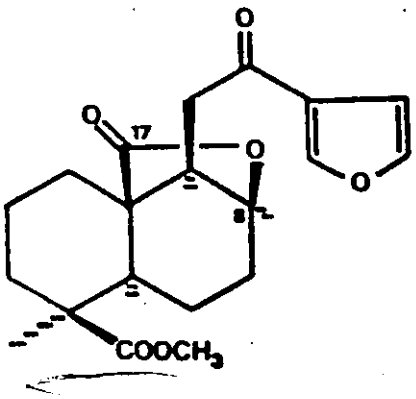
6


O
CH3OOC
17
O
19COOCH3

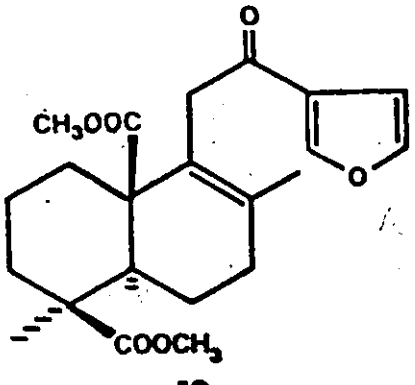
7


O
17
O
19C=O

8


O
O
17
O
O
COOCH3

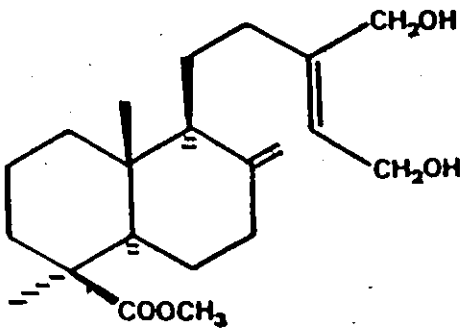
9


O
CH3OOC
O
COOCH3

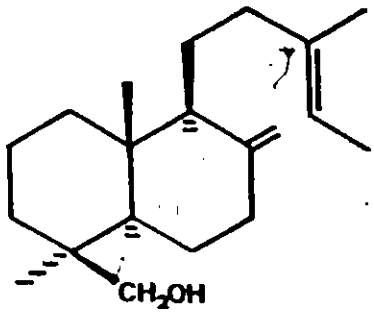
10

diaxial relation to one another and, considering the presence of the C-12, 17 ether link only two structures, 1A and 1D, are possible. Treatment of dimethylsciadinonate 7 with boron trifluoride-etherate in methanol yielded two products 9 and 10 identified by their spectral data. Formation of the former can only occur if C-17 and the C-8 oxygen bear a 1,3-cis-diaxial relationship to one another, thus, confirming the configuration given by structure 1A.

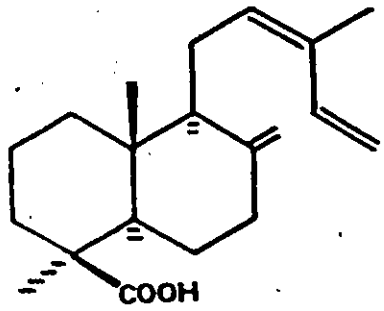
Miyasaka (20) reported the isolation of methyl sciadopate 11 from the heartwood of Sciadopitys Verticillata Sieb. et Zucc. and has determined its structure and absolute configuration. The chemical conversions of 11 into isodihydrocommunol 12 and into the enantioner of daniellic acid tended to support the theory that 11 was situated biogenetically between communic acid 13 and the furanoid diterpenes. Since the absolute configuration at C-9 in communic acid has been established (21), this confirmed the equatorial orientation of the C-9 side chain as in 1A.



11



12



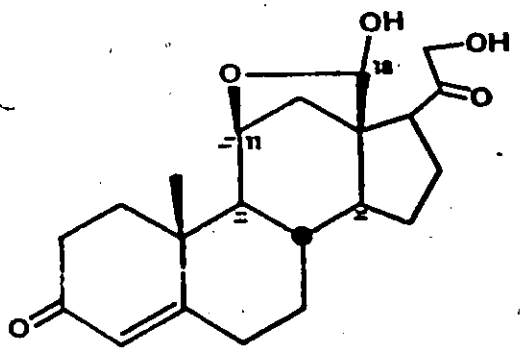
13

2.2 The Barton Reaction

Introduction

Aldosterone 15, the hormone of the adrenal cortex controlling salt retention was a natural product of interest to synthetic organic chemists because of the oxygenation of the angular C-18 methyl group to the aldehydic level. In addition to being a primary paraffin centre in a complex

molecule containing many methylene and methine carbon atoms, C-18 was quaternary linked and, therefore, not susceptible to activation in the conventional sense which, consequently, precluded the use of traditional ionic and free-radical reactions. There was a need, therefore, for a novel chemical reaction which would duplicate the known enzymatic selectivity for an isolated non-activated angular methyl group.



15

In general, means were chosen to generate a highly reactive species of high energy content proximate to the methyl group so as to achieve the desired direct and selective attack. The photolysis of nitrite esters as a potentially useful tool for this transformation was proposed by D.H.R. Barton and co-workers (22) in 1960 and experimentally verified by the conversion of 3β-acetoxy-5α-

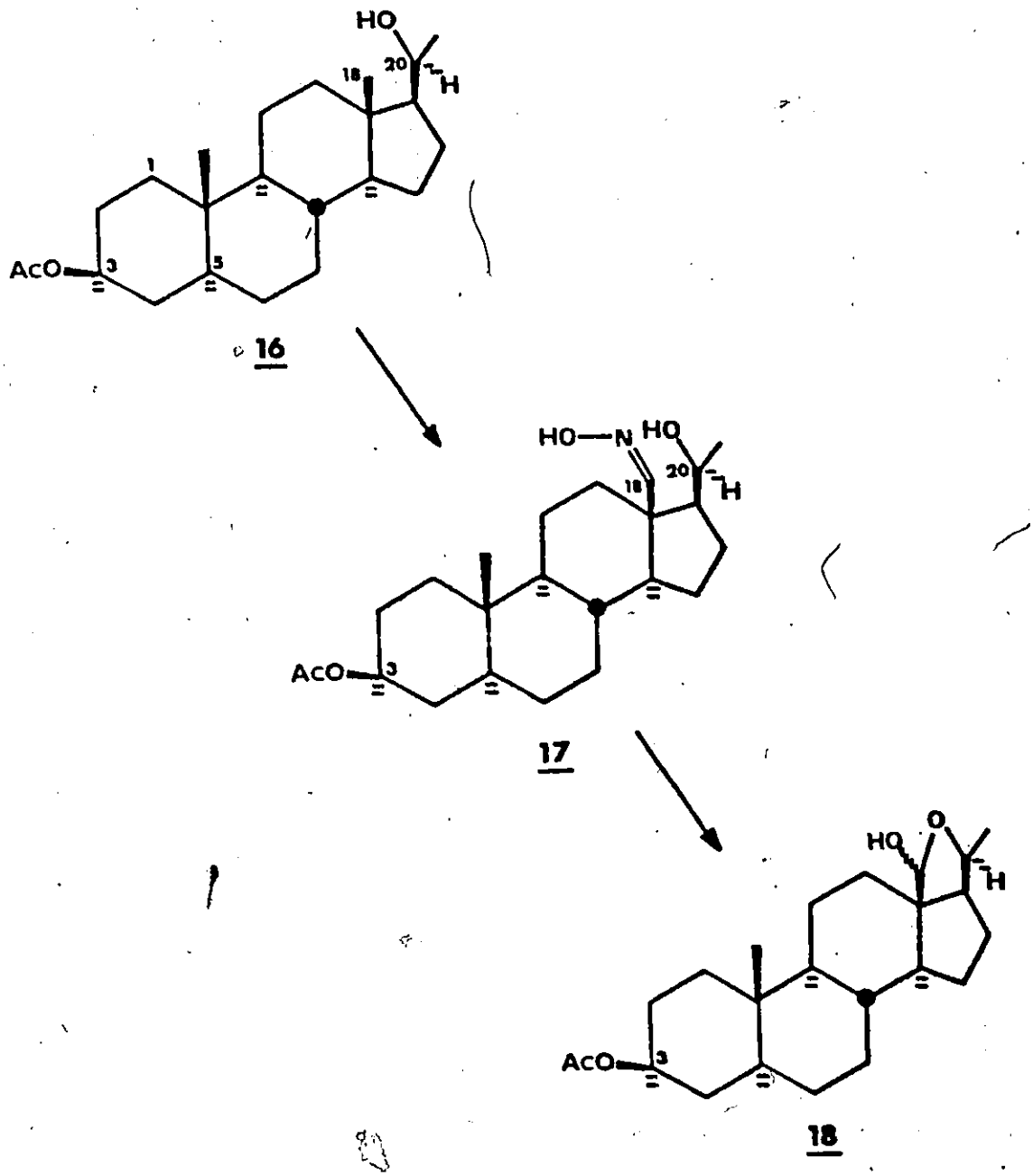


FIGURE 3 Angular methyl functionalization by the Barton reaction (22)

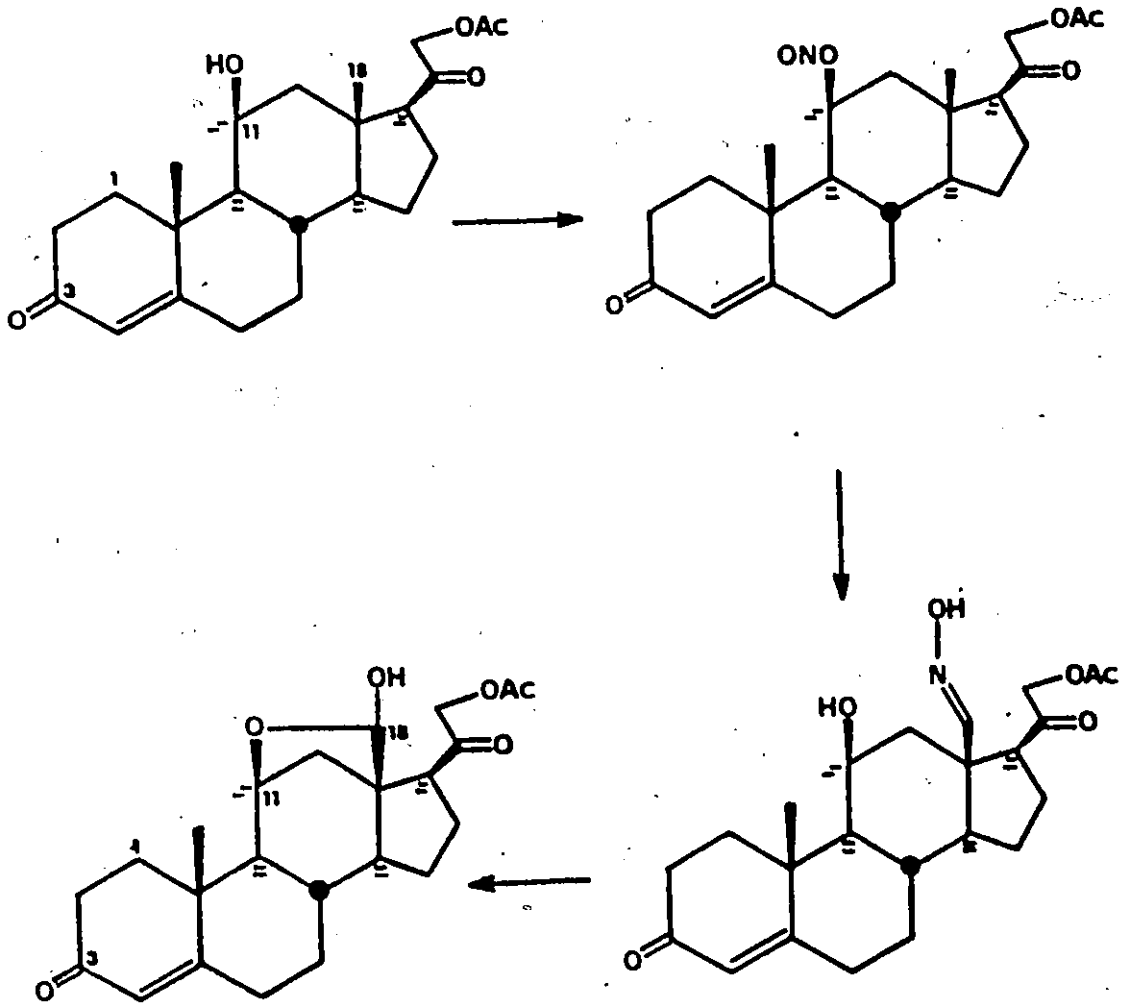
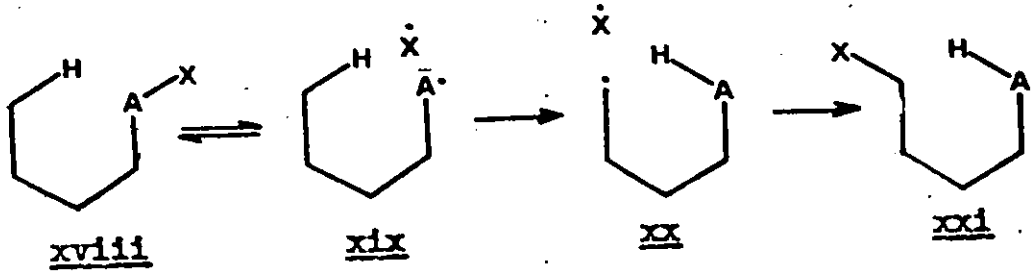


FIGURE 4 Synthesis of aldosterone acetate (23)

pregnan-20β-ol 16 to 18-oximino-5α-pregnane-3β, 20β-diol 3-acetate 17 and thence to the masked aldehyde 18.

Shortly thereafter, Barton and Beaton reported the synthesis of aldosterone acetate 19 from corticosterone (23).

The general mode of reaction commences with homolytic cleavage of the A-X bond (Figure 5: A=O, X=NO) in the substrate xviii to give the radical xix which can abstract a hydrogen atom from a conformationally proximate carbon to give the rearranged radical xx. The recombination of radicals to give xxi effectively accomplishes a ligand exchange between the two reaction centres in question.



xviii xix xx xxi

FIGURE 5 General mode of the Barton reaction

Accumulated evidence has so far substantiated the discrete stages of the reaction as shown above.

The Alkoxyl Radical

Aliphatic nitrites absorb ultraviolet light in two principal regions: 220-230 nm and 310-385 nm. Absorption in the former region leads to highly reactive intermediates and complex reaction mixtures, whereas, absorption of the lower energy radiation leads to efficient O-NO homolysis and the Barton reaction.

Once generated, the reactive alkoxyl radical may stabilize in one or more of the following ways:

(a) association $RO\cdot + X\cdot \longrightarrow ROX$

(b) α-cleavage $RR'O\cdot \longrightarrow R{=}O + R'\cdot$

(c) disproportionation $2(RCHO\cdot) \longrightarrow R{=}O + RHOH$

(d) dimerization $2(R\text{-}O\cdot) \longrightarrow R\text{-}O\text{-}O\text{-}R$

(e) intermolecular hydrogen abstraction $R\text{-}O\cdot + XH \longrightarrow ROH + X\cdot$

(f) intramolecular hydrogen abstraction $HC\text{-}C\text{-}C\text{-}C\text{-}R\dot{O} \rightarrow \dot{C}\text{-}C\text{-}C\text{-}C\text{-}ROH$

The latter process, having received attention only recently, has been found to predominate in systems where a suitable geometry will facilitate the hydrogen transfer. In almost all cases this has involved a 6-membered transition state and, consequently, a 1,5-hydrogen transfer (Figure 5).

Experimental verification for the presently accepted mechanism of the Barton reaction was achieved by Akhtar and Pechet (24) through a series of nitrogen - 15 labelled compounds. Their results from the photolysis of a mixture of

two nitrite esters, one from the androstane series, and one from the cholestane series, with the latter being isotopically labelled, established that the mechanism did indeed involve free radicals and that the overall reaction did not take place in a solvent cage. Similar experiments, establishing the nitrogen-15 scrambling in the initial nitrite esters, confirmed the reversible nature of the step xviii ⟷ xix.

The Hydrogen Abstraction Reaction

The hydrogen transfer step is an intramolecular process governed primarily by the steric factors as evidenced by the formation of 4-nitroso-5-phenyl-1-pentanol 21 and the absence of the 5-nitroso-compound 22 in the photolysis of 5-phenyl-1-pentyl nitrite 20 (Figure 6). Abstraction of the benzylic hydrogen would be expected to prevail if the reaction was intermolecular or if carbon-hydrogen bond energies were of paramount importance (26). Obviously the six-membered transition state is most favourable although, in special circumstances, 1,6-hydrogen transfers have been reported. Even where 6-membered cyclic transition states are possible, however, the appropriate conformer must be energetically favourable (27), and the sensitivity of this process to steric effects has been reported in numerous cases (24).

In rigid systems of undistorted geometry, a 1,3-diaxial relationship between reaction centres is particularly favourable (although other 6-membered arrangements have been observed). In steroids and related structures, then, carbon-

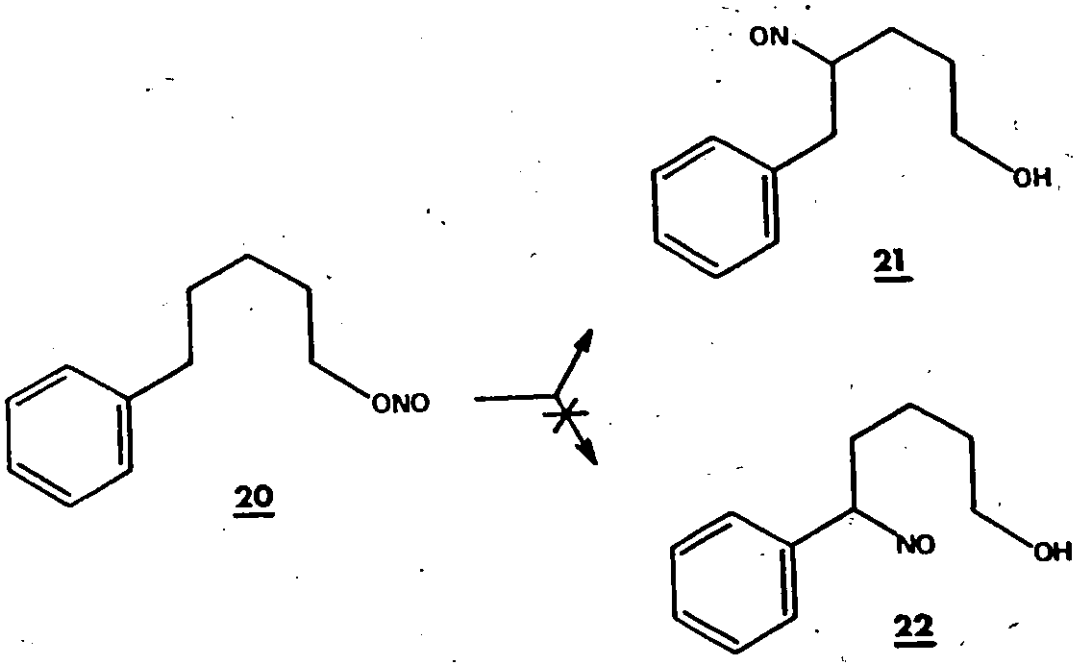
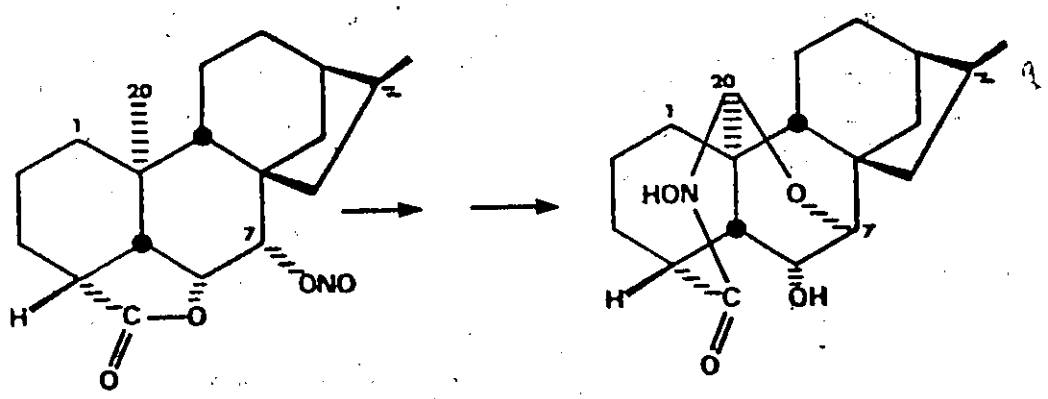


FIGURE 6 Steric requirements for the Barton reaction

20 functionalization through the Barton reaction is best served by the β-alcohols at carbons 2,4,6, and 8. Distortions to the ring geometry, however, have been known to alter the course of the Barton reaction. In their review of intramolecular reactions, Heusler and Kalvoda (29) concluded that these reactions are much more rapid than intermolecular free-radical reactions, in the aforementioned rigid systems, if the distance between the oxygen radical and the carbon bearing the abstractable hydrogen atom in between 2.5 and 2.7 Å. Evidence is illustrated dramatically by the 1,6-hydrogen transfer in the carbon-20 functionalization of the norditerpene 23 leading to compound 24. The lactone ring has apparently

distorted ring B to an extent that has forced the C-7 alkoxyl radical into closer proximity to the angular C-20 methyl group facilitating hydrogen transfer (30).



23 24

The inference is therefore clear that the proximity of an alkoxyl radical and a particular hydrogen facilitates transfer of that hydrogen to the radical.

The Alkyl Radical and Termination

Alkyl radicals in solution tend to stabilize rapidly through cleavage, dimerization, association, or, in some cases, rearrangement. However, in the Barton reaction, the alkyl radical tends to react quickly with the nitric oxide in a chain-terminating reaction to form the tautomer of the oxime.

Although deviations from the normal termination of the Barton reaction have been reported (31), most are of a specialized nature and do not lessen the wide-ranging applicability of this reaction.

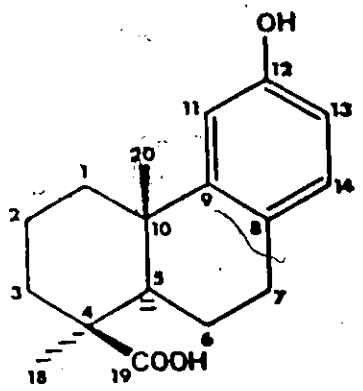
Related Reactions

Other reactions very similar to the Barton reaction have recently been observed. These include the hypoiodite reaction (Figure 5: A=O, X=I) (29), the lead tetraacetate and iodine reaction proceeding through the hypoiodite formed in situ (32) and the reactions of N-halo-(33) and N-nitroso-amides (34). The Barton reaction of nitrates (35) has also been reported. (see also 169).

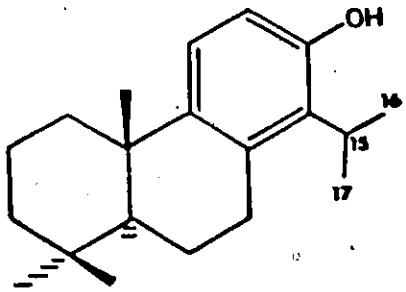
The Hofmann-Loffler-Freytag reaction, known since the turn of last century, is another interesting mode of functionalizing an inactive carbon which is closely related, in principle, to the Barton reaction (Figure 5: A=N, X=halogen). Recently, Corey and Hertler (36) have reported the functionalization of C-18 in steroids using this reaction.

2.3 Podocarpic Acid as a Synthetic Precursor

Podocarpic acid 25, $C_{17}H_{22}O_3$, is not strictly a diterpenoid, but its chemistry resembles that of the resin acids and, biogenetically, it appears to be a product of deisopropylation of the totarol skelton 82. The compound was first isolated by Oudemans (37) from the resin of *podocarpus cupressinum* and has since been found to occur in other resins.



25



82

The structure was first suggested in 1939 (38), but it was not until 1957 that stereochemical formula was unequivocally established (39). During the intervening years, much effort by many researchers was expended in the structural elucidation and total synthesis (40-48) of podocarpic acid, with the stereochemistry of C-4 being the major stumbling block.

Because of its ready availability and its functionality, podocarpic acid has become a popular starting material for the synthesis of other natural products. Numerous conversions have been reported which have centred primarily on the reactivity of aromatic ring C (49-54), of the C-7 oxygenated materials in ring B (55,56) or the C-4 carboxylic acid group in ring A (57-59).

2.4 Synthetic Objectives and Plans

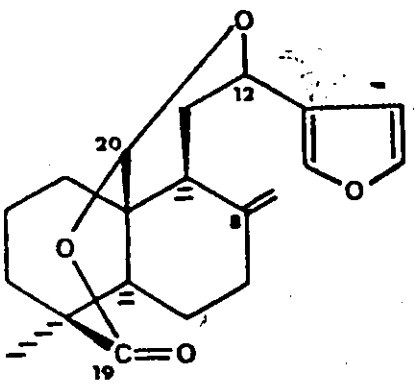
The synthesis of sciadin 1A from podocarpic acid 25 would involve three explicit transformations.

(i) oxidation of the aromatic ring and the attachment of the 3-furyl side chain (60).

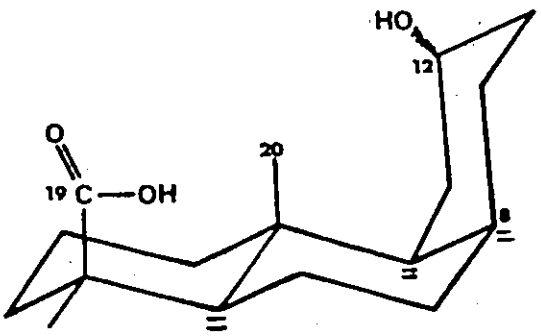
(ii) generation of the C-8 exocyclic methylene (54).

(iii) oxidation of C-20 to an aldehyde and thence formation of the 19→20 lactone and 20→12 ether.

On the basis of reported results, application of the Barton reaction to the latter transformation seemed encouraging and initial interest centred on the use of the alcohol function at C-12. Hydrogenation of podocarpic acid to give perhydro-podocarpic acid 26 would give a configuration where the C-12 oxygen and the C-20 were separated



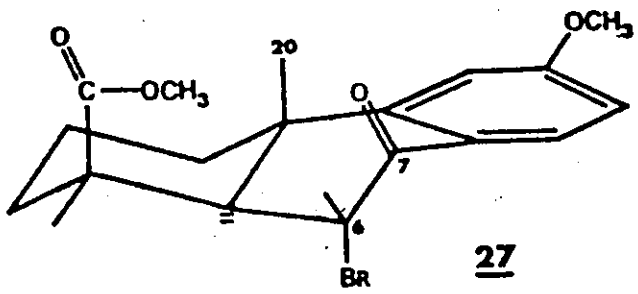
1A



26

by a distance of 1.44 Å (undistorted) and 2.08 Å (distorted) providing the trans-anti-cis conformation was realized (61). Considering the proximity of the two reaction centres, photolysis of the nitrite ester of 26 would give an alkoxyl radical which would then abstract a hydrogen atom from the methyl group. The resulting C-20 nitroso compound, when converted to the oxime by refluxing in iso-propanol, would then be susceptible to attack by the favourably situated C-19 ester function to give the lactone ring essential to the sciadin structure.

About the same time, results on the Nuclear Overhauser Effects (NOEs) of 6α-bromo-7-oxoditerpenoids (62) established that ring B existed in a boat conformation (Figure 7) and molecular models suggested that a 7β- alcohol

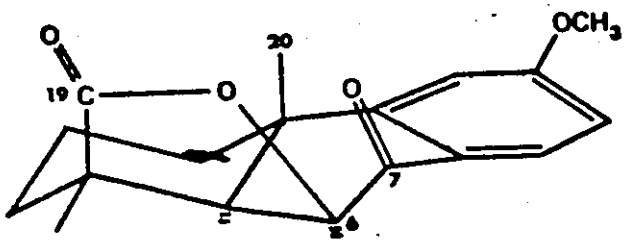


27

FIGURE 7. Stereostructure of 6α-bromo-7-oxoditerpenoids

was sufficiently proximate to C-20 to allow a Barton reaction be feasible between these centres. Considering the ready oxidation of benzylic carbon (55), this potential pathway appeared to be both efficient and of general application.

If the Barton reaction proved unsuccessful for the 7β-nitrite ester, then formation of the C-19, 6β-lactone 28 would, perhaps, distort the ring B boat conformation to an entent that would force C-7 even closer to the C-20 methyl group.



28

In the event that functionalization of C-20 via the C-12 or C-7 hydroxyl radicals, which would involve 1,6-hydrogen transfers, failed further recourse could be made to the more normal 1,5-hydrogen transfer by opening of the lactone ring of 28 and utilization of the 6β-alcohol group.

Although the functionalization of C-20 by 6β-alcohols has sound procedence in the norsteroid series (24), it was not the primary objective of the work in this thesis.

B. CARBON-13 NUCLEAR MAGNETIC RESONANCE

3.1 Historical Development

The initial experiments of the NMR phenomena in bulk materials occurred in 1945 when Bloch (70) at Stanford and Purcell (71) at Harvard, working independently, observed the proton spectra of water and paraffin wax, respectively. Their pioneering achievements were rewarded in 1952 by their sharing of the Nobel Prize for Physics.

Potential applications of NMR principles to the solution of chemical problems were realized in 1950 with the discovery that precise resonance absorptions for a nucleus were dependent on the chemical environment of that nucleus. This phenomenon, now referred to as the "chemical shift" culminated in 1951 by the resolving of the spectrum of ethanol into three absorption peaks. Shortly thereafter, the first commercial high resolution NMR spectrometer was marketed by Varian Associates.

Since that time, proton magnetic resonance spectroscopy (p.m.r.) has been rivalled only by gas chromatography in its general and rapid acceptance as an analytical tool and by its multifarous applications to the solution of diverse chemical problems.

In 1957, Lauterbur (72) and Holm (73) reported from independent laboratories, the first NMR observations of

carbon-13 nuclei. To organic chemists, the direct observation of carbon nuclei in molecular systems was significantly more advantageous than proton observations. Despite the advantages, the growth of carbon-13 NMR was delayed for many years by inadequate instrumentation, poor spectral resolution, and the requirement for highly soluble, low molecular weight materials.

The development of field-frequency controlled spectrometers partially overcame these difficulties while wideband proton decoupling, available in 1965, eliminated the coupling between the carbon and hydrogen nuclei, thereby reducing complex multi-peak spectra to simple spectra where each absorbance peak corresponded to each chemically non-equivalent carbon nucleus in the sample.

Development in the late 1960's of Fourier transform techniques has brought carbon-13 NMR almost to the level of proton NMR----in terms of versatility, spectral quality, amount of sample required, and sampling times----with the result that C^{13} NMR literature should grow tremendously over the next few years.

3.2 Carbon-13 NMR Theory

Difficulties in C^{13} NMR

The most abundant isotope of carbon, atomic weight 12, has no nuclear spin and, therefore, is not observable by NMR techniques. Carbon isotope 13, however, has a nuclear spin of $\frac{1}{2}$; its low natural abundance (1.1%), while advantageous

because C^{13}-C^{13} and C^{13}-H^1 coupling interactions do not significantly complicate C^{13} NMR and H^1 NMR spectra, respectively, does, in fact decrease the sensitivity of the C^{13} NMR experiment.

The magnetogyric ratio, γ, of the C^{13} nucleus is about ¼ that of the H^1 nucleus which further decreases the sensitivity of the C^{13} nucleus relative to that of the H^1 by a factor of $(\frac{1}{4})^3$ (74, page 4). Overall then, the C^{13} nucleus has a sensitivity of about 1/6000 the value for the proton.

Compounding this difficulty is the relatively long relaxation times which are typical of carbon-13 nuclei. The nucleus is, therefore, easy to saturate resulting in decreased signal intensity. This situation can be overcome by rapid sweep rates and lower radio frequency power settings; however, the former reduces resolution and the latter reduces signal intensity, both of which are also undesireable.

Advantages in C^{13} NMR

Despite the aforementioned difficulties which beset the observations of the C^{13} nucleus in NMR experiments, there are considerable advantages over p.m.r. spectroscopy which make it attractive to the solution of chemical problems.

The variation in carbon shieldings in neutral organic compounds is about 20X greater than that of protons. The total range, from carbon tetraiodide to cations on the extremities, extends over approximately 600 p.p.m. with the

result that resolution in not only enhanced, but also, in most cases, each carbon nucleus can be associated with a single absorbance peak. Recently reported (75) was the C^{13} spectrum of a derivative of vitamin B_{12} in which 55 discrete absorbances, some of these double and triple resonances, were observed.

Carbon-13 NMR spectroscopy also has the advantage of directly observing molecular backbones and particular carbon reaction sites of interest, both of which allow for greater intimacy in the probing of atomic nuclei for the solution of practical problems in conformation, kinetics, and mechanism. Obviously, the experiment can be extended to systems having functional groups bearing no hydrogen atoms (carbonyls, nitriles, thiocyanates, etc.), the direct analysis of which previously required methods other than NMR. Carbon resonances are also extremely sensitive to the nature of the chemical bond such that, in terms of chemical shifts with respect to a tetramethylsilane standard, $sp^3 < sp^2 < sp$.

Broad-band decoupling removes not only C^{13}- H directly bonded interactions, but also long-range coupling with the result that narrower resonance lines are available to C^{13} spectra than are the case for normal p.m.r. spectra. This decoupling technique has the further advantage, by virtue of the nuclear Overhauser effect that the C^{13} absorption peaks are considerably enhanced. The dominant relaxation mechanism for carbon nuclei is C^{13}- H^1 dipole-dipole relaxation (except

for quaternary carbons) and the partial or complete saturation of the protons causes a favourable shift in carbon nuclei energy level populations to the α-state. This means that more radio frequency energy can be absorbed by the C^{13} nucleus with a concomitant increase in signal. The maximum NOE enhancement for a C^{13} nucleus is 2.998 (76,page 31) which means that a carbon absorption peak area will be 2.998 times the total resonance signal area in the absence of proton irradiation.

Experimental Techniques

Early C^{13} studies employed the rapid-passage, dispersion-mode operation which allowed the use of powerful radio frequency fields to partially overcome the weak C^{13} signals. Although, under these conditions, the signal resembled closely the typical absorption-mode signal, line distortions, broadening, and shifts reduced accurate line positions. In most cases, signal positions were obtained by scanning the field in both directions and averaging the line positions for each carbon.

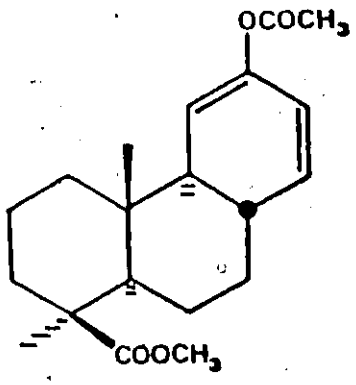
The introduction of audio modulation techniques using phase detection for base line stability allowed the use of slow-sweep absorption-mode operations along with larger samples and spinning of the sample. This type of spectrometer employs a field-frenquency control on a signal which is of the same nuclear species as the nucleus being observed (homonuclear lock), a continuous sweep (continuous

wave or CW) of the magnetic field for recording of the spectra, and a heteronuclear decoupling unit. Use of the latter enhances the signal intensity by the NOE and by the collapsing of multiplets due to C^{13}-H^{1} coupling into single peaks for each proton-bearing carbon. The spectra are usually obtained by multiple scans, each being recorded in a Computer of Average Transients (CAT) with the result that carbon absorbances will accumulate much faster than random noise. The improved signal-to-noise (S/N) ratio from such a technique is proportional to the square root of the total scans n. For accurate results over long scan times, optimum stability of the field-frequency unit is of prime importance.

The continuous wave NMR is rather inefficient when one considers that, at any instant, only one frequency is observed. The inefficiency is overcome by Fourier transform (FT) NMR (77) which utilizes a short radio frequency pulse to excite a finite bandwidth of frequencies. The use of high radio frequency power which is pulsed over a short period of time (about 50 μsec) is enough to excite a bandwidth of 5000 Hz which is wide enough to simultaneously excite the entire range of precession frequencies of the C^{13} nuclei. These nuclei are analogous to a set of tuning forks, each tuned to different frequencies (78). A shock, such as striking the base with a hammer, causes all the tuning forks to oscillate simultaneously. The nuclei, like the tuning forks, once excited, generate a signal which

decays in a characteristic fashion to zero, at which point equilibrium is re-established (Figure 8). This free-induction decay (FID) is a periodic function, the Fourier transformation of which gives the normal steady-state resonance spectrum. The advantage of Fourier transform NMR, then, is one of time; there is about a ten-fold increase in signal-to-noise over CW experiments for the same total time. This allows the data accumulation on small samples or low solubility samples where the time required for adequate accumulation under CW conditions would be beyond the stability capabilities of the spectrometer. An additional advantage is the obtaining of narrower line-widths which are broadened in the CW mode by sweep conditions. A number of articles of a more detailed nature on FT NMR have recently been published (79,80).

A number of advantages are inherent in the technique of off-resonance decoupling in which the proton noise decoupling frequency is offset from its optimum value by 100-600 Hz. Under these conditions, a significant NOE enhancement remains and the splittings for the methyl, methylene, and methine carbons become discernible although with only a partial splitting (J_r). Methyl and methine carbons are readily identified due to the absence of a peak in the off-resonance spectrum at the same position as that in the noise-decoupled spectrum. Methylene carbons give a triplet, the position of the central absorption peak



93

FIGURE 8. Free induction decay (FID) for compound 93

corresponding to the absorption peak in the noise-decoupled spectrum. Quaternary carbons are little affected by the decoupling frequency and are readily identified. The latter effect has been utilized frequently in CW mode systems and on complex molecular systems, such as natural products (81), to determine non-protonated carbon centres.

The partial splitting, J_r, is related to other parameters by (3.1)

$$J_r \simeq \frac{\Delta f \; J}{\gamma H_2/_{2\pi}} \qquad (3.1)$$

where J = true C^{13} -H^1 coupling constant

$\gamma H_2/_{2\pi}$ = strength of the decoupling field

Δf = the difference between the resonance frequency of a given H^1 signal and the applied decoupling frequency.

Equation (4.1), therefore, correlates the perturbed C^{13} multiplets with specific proton absorptions. This is a technique which has been used for spectral assignments. In addition, single-frequency proton decoupling of a single proton signal causes only the carbon attached to that proton to collapse to a singlet, thereby identifying that carbon.

During the early years of C^{13} NMR development, a number of reference standards, both internal and external, were utilized. Recently (76), there appears to be wide acceptance of tetramethylsilane (TMS) as the reference for which all spectra will be reported. Levy and Cargioli (82) have reported the chemical shifts for a variety of solvents

based on the TMS scale (Table 2) and have found solvent effects to be generally less than 1 p.p.m.

TABLE 2 TMS-based C^{13} chemical shifts (82)

Solvent	Chemical Shift
cyclohexane	27.51
acetone	30.43
dimethylsulfoxide	40.48
methylene chloride	54.02
dioxane	67.40
chloroform	77.17
carbon tetrachloride	95.99
benzene	128.53
acetic acid (CO)	178.27
CS_2	192.8
CS_2 capillary	193.7

Carbon-13 Chemical Shifts

The general trends for a variety of neutral organic species is shown in Figure 13. In hydrocarbons, the shieldings are dramatically related to bond hybridization with sp^3 carbons at high fields and sp^2 carbons at low fields, with sp carbons generally at intermediate positions. Electronegative substituents, as expected, produce downfield shifts.

A great deal of information has been obtained on C^{13} chemical shifts. Only data relevant to this thesis will be summarized in the following pages. It is noted that one of the most interesting and useful results is the additivity

relationships between C^{13} shieldings in related series allowing the estimation and prediction of carbon shieldings with extraordinary precision.

(a) alkanes

Early studies on alkanes established initially the extraordinary additivity relationships of C^{13} chemical shifts. Grant and Paul (84), for example, found that alkanes absorb over a range of -2 to 43 p.p.m. and that the shieldings for linear alkanes can be described by equation (3.2)

$$\delta^i = B + \sum_j A_j \, n_{ij} \qquad (3.2)$$

where

δ^i = shielding of carbon i

A_j = additive shift parameter for the position j

n_{ij} = number of atoms in the position j

B = constant whose value is close to the methane carbon shielding of -2.1 p.p.m. (85)

The same authors (84) found that, for highly substituted and adjacent carbons, anomalous predicted shieldings resulted unless additional terms were incorporated into the calculations to account for chain branching. With these corrective measures, the agreement between predicted and experimental shifts has been amazing.

Five of these substituent parameters for the alkanes are shown in Table 3 and represent the effect of replacing

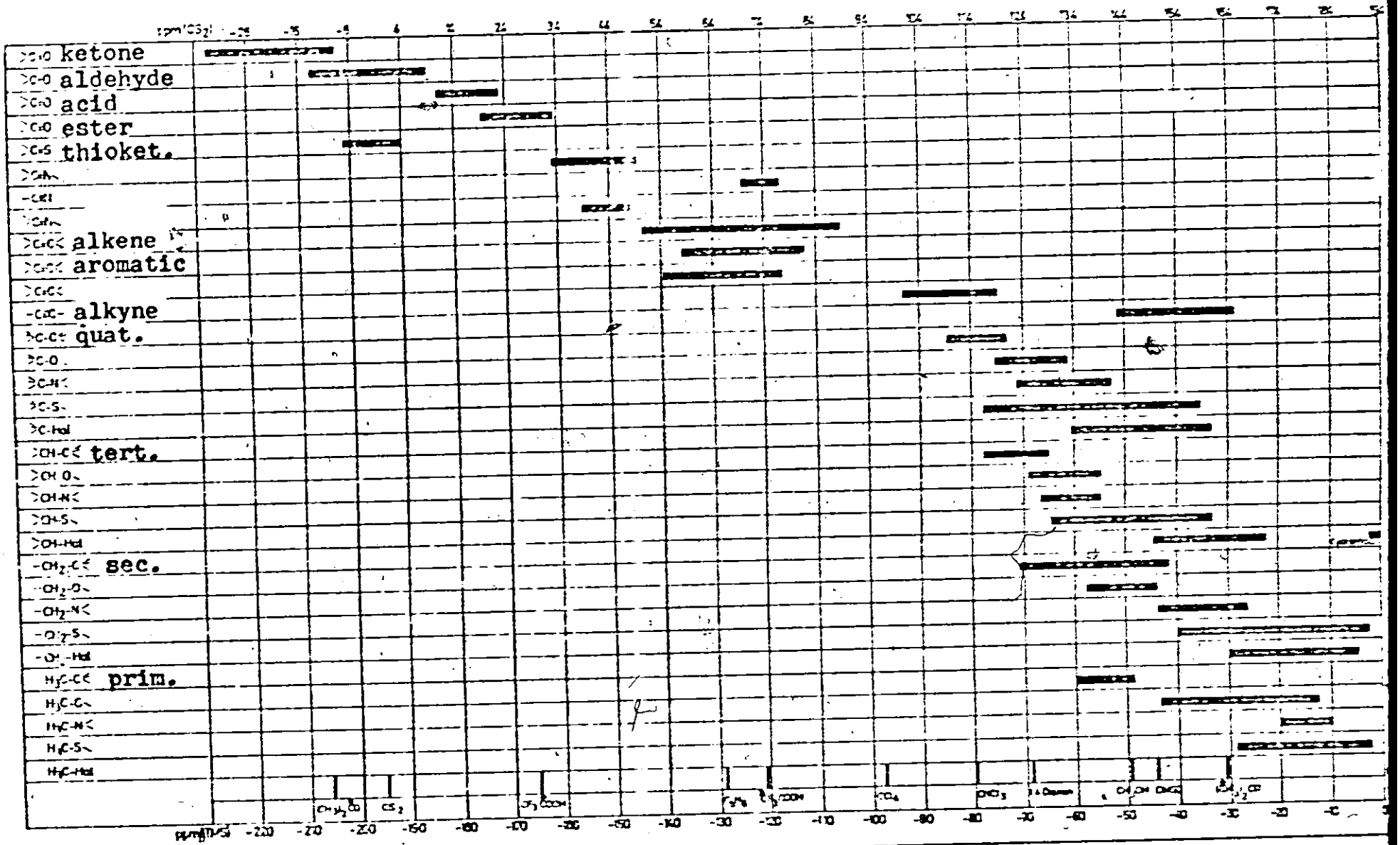


FIGURE 9 Functional group carbon-13 NMR shifts

a hydrogen atom by a methyl group in the indicated position. These parameters appear to be typical of all organic compounds although the values may differ from one class of compound to another. The general observation that substituents tend to shield the δ-position appears to have conformational applications since it has been attributed to steric interactions (86).

Savitsky and Namikawa (87) reported

TABLE 3 Substituent parameters for alkanes (84)

Substitution	Effect	Shift (p.p.m.)
C-H ⟶ C-CH_3	α	9.1±0.1
C-CH ⟶ C-C-CH_3	β	9.1±0.1
C-C-CH ⟶ C-C-C-CH_3	γ	-2.5±0.1
C-C-C-CH ⟶ C-C-C-C-CH_3	δ	0.3±0.1
C-C-C-C-CH ⟶ C-C-C-C-C-CH_3	ε	0.1±0.1

adequate predictability of carbon shieldings using bond parameters although results are less precise than those by Grant and Paul. In any case, the existence of simple additivity relationships and their useful application to shift assignments is clear (98,99).

(b) cycloalkanes

Aside from cyclopropane (-2.6 p.p.m.), most cycloalkanes differ only slightly from the chemical shift value of 27.7 p.p.m. for cyclohexane (88). Substituent effects and additivity relationships become increasingly important for cyclo-

hexane in view, not only of the geometrical and conformational features, but also the extensive occurence of this ring system in organic compounds. The importance of conformational effects is evident from the results of methyl substitution (Table 4) in the cyclohexane system (89,90,103) and the low temperature conformational effects of methylcyclohexane (91).

TABLE 4 Substituent effects for methylcyclohexanes(89)

Substituent	α	β	γ	δ
equat-CH_3	5.6	8.9	0.0	-0.3
axial-CH_3	1.1	5.2	-5.4	-0.1
gem-$(CH_3)_2$	-3.4	-1.2		
vic-$(CH_3)_2$ (e,e)	-2.3			
vic-$(CH_3)_2$ (a,e)	-3.1			

Use of the substituent effects in Table 4 have been used to satisfactorially analyze the spectra for cis- and trans-decalin on the assumption that incorporation of the second ring on cyclohexane introduces interactions which are similar to those from methyl substitution.

Oxygenated derivatives of cycloalkanes have also received much attention (92,93,94,95). The alpha effect for the hydroxyl group has been reported as 43 p.p.m. and 39 p.p.m. for equatorial and axial conformation, respectively, whereas the corresponding beta effects are 8 p.p.m. and 5 p.p.m. The carbinyl carbon shieldings appear to reflect the hydroxyl group orientation and have been applied to conforma-

tional free energy calculations (96). In cyclohexanones, the average substituent effects for a series of monosubstituted derivatives are: α +13.3; β -0.6; δ -2.6 p.p.m. Although these may not be accurate for any given system, the large α-effect has obvious advantages for spectral assignments.

(c) alkenes

Carbons of sp^2 hybridization appear considerably downfield relative to alkanes in the range 100-165 p.p.m. Additivity relationships, while not quite as good as for the alkanes, have been reported for a diverse group of substituted alkenes, both cyclic and acyclic (92,93,94,95,96,97). In acyclic olefins, the substitution of a hydrogen atom by a methyl group gives an effect on nearby carbon absorbances which depends on whether the transmission of that effect has been through sigma bonds or through pi bonds. For example, methyl substitution on one of the olefinic carbons deshields the substituted carbon, as expected, but shields the adjacent olefin carbon (reverse β-effect).

Results for a series of alkylcyclohexenes (76,page 84) indicate a substituent effect pattern resembling qualitatively that for alkanes. As expected, the most pronounced changes in the olefinic shielding occur with direct substitution on the olefinic carbon.

(d) aromatics

Aromatic hydrocarbons absorb over a fairly narrow range of 123-142 p.p.m. with benzene, itself, absorbing at

128.53 p.p.m. (82). Substitutions on the ring alter shifts in a regular manner consistent with other aforementioned systems. In toluene, for example, C-1 is deshielded by +9.1 p.p.m. and C-4 shielded by -3.1 p.p.m. with only small changes at the ortho and meta positions. Using these parameters in other polymethylbenzenes, correlation between predicted and experimental chemical shifts is good and the effects are additive, except when substituents are ortho to one another (104). Similar results were obtained by the same authors for other alkylbenzenes (104).

Aryl carbon shieldings are sensitive to the electronic effects of polar substituents with the substituted carbon exhibiting the largest shift changes. The results of twenty-five monosubstituted benzenes (76, page 197) show that C-1 varies from as high as -31.8 p.p.m. upfield from benzene to as low as +39.8 p.p.m. while the ortho and para carbons exhibit shifts which vary from 20-25 p.p.m. As in toluene, the meta position is affected only slightly. The results for aryl carbon shieldings for a number of substituents appropriate to this thesis are recorded in Table 5 (See also 100-102).

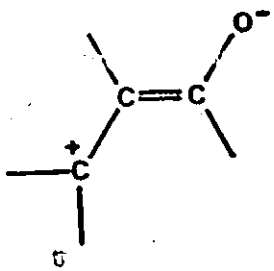
TABLE 5 Aryl carbon shieldings for monosubstituted benzenes, C_6H_5X

Substituent (X)	Shielding Effect from Benzene				Reference
	C-1	ortho	meta	para	
OH	+26.9	-12.6	+1.8	-7.9	(105)
OCH_3	+30.2	-15.5	0.0	-8.9	(106)
$OCOCH_3$	+23.0	-6.4	+1.3	-2.3	(107)

(e) carbonyl compounds

The overall shift range of the carbonyl carbon is 162-222 p.p.m. relative to TMS which is considerably downfield and away from any interfering carbon resonances in the usual organic compounds. Ketones are typically at 197-217 p.p.m; aldehydes, 187-202 p.p.m.; carboxylic acids, 172-182 p.p.m.; and esters, 162-172 p.p.m. (108).

The effect of α,β -conjugation on the ketone carbonyl resonance is a shift upfield (109) attibuted to contributions made by the mesomeric structure below.



The same structure rationalizes the dramatic deshielding effect on the β -carbon.

Assignment Techniques

A number of valuable techniques are available to the spectroscopist which aid in the assignment of absorption peaks to specific carbon nuclei. Although detailed explainations are beyond the scope of this report, some of these techniques are listed below.

(i) off-resonance spin decoupling (section 3.2)

(ii) selective decoupling (single frequency proton decoupling; section 3.2)

(iii) additivity rules (see section 3.2)

(iv) chemical shift range (see Figure 9)

(v) steric shifts

Carbon atoms that are sterically perturbed usually appear at higher field than similar carbon atoms undergoing no steric compression (149)

(vi) chemical shift reagents

The addition of lanthanide shift reagents to NMR samples has resulted in differential shifts among similar protons thereby simplifying otherwise complex spectra (110-114). The shifts are ascribed to a pseudocontact interaction between the metal atom and a substrate atom possessing one or more lone electron pairs. The magnitude of the shift is expressed by

$$\Delta\delta = \frac{K\,(3\cos^2\theta - 1)}{r^3} \qquad (3.3)$$

where K = constant for a particular complex at a given temperature,

θ = proton-metal-coordination site internuclear angle,

and r = proton-metal distance.

Recently, applications to the analysis of C^{13} NMR spectra have been reported (115-118) and, although shift reagents do not yield the same benefits as

obtained in proton magnetic resonance, the shift measurements aid in spectral assignments.

(vii) specific deuteration

The signal for a deuterated carbon essentially disappears at the signal-to-noise ratios of most CW mode instruments because of quadrupole broadening, spin-spin splitting, and decreased NOE enhancement.

(viii) relaxation

The application of measured T_1 values to spectral assignments has been reported (74, page 83) for substituted biphenyl compounds. Preferred molecular rotations about axes bisecting large substituents results in shorter T_1 values for carbons on those axes. (see also 160-163)

(ix) nuclear overhauser effect (NOE) (see Reference 164)

(x) integration

A quantitative relationship exists between signal intensity and the number of carbon-13 nuclei when the NOE is suppressed (165-168).

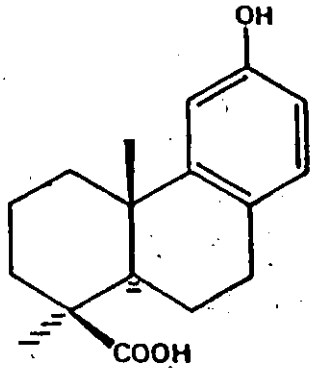
4. DISCUSSION AND RESULTS (SYNTHETIC)

4.1 Attempted C-20 Functionalization Through the C-12 Alcohol, via C-19 Ester

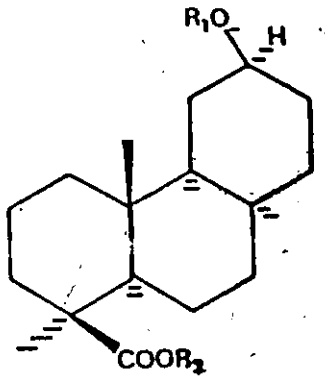
Reduction of the aromatic ring of podocarpic acid 25 using 5% Rhodium on Alumina (Englehard Industries Inc.) in ethanol containing one percent acetic acid (60) was found to be more efficient than previously reported conditions (61). When catalyst-to-substrate in the ratio of 1 to 3 was used, with hydrogen pressures of 40-50 psi, uptake of hydrogen was complete in forty hours. Intuitively, it was expected that the sterically congested β-face of the molecule would give rise to the predominance of the B/C-cis ring juncture and the C-12β hydroxyl group. Proton magnetic resonance on the crude reaction mixture confirmed the former expectation; peak integration established the ratio of cis-to-trans ring junctions to be 85:15 (60). The desired cis-hydroxy acid was readily obtained by crystallization from ethyl acetate.

Attempts to prepare the nitrite ester of the perhydro derivative (29b; R_1 = NO, R_2 = H) by bubbling nitrosyl chloride into a cold pyridine solution of the cis-hydroxyacid proved unsuccessful. At the time, it was reasonable to assume that hydrolysis occurred in the work-up (119) or that steric congestion at C-12 prevented formation of the ester.

If the latter factor was important, then free-radical

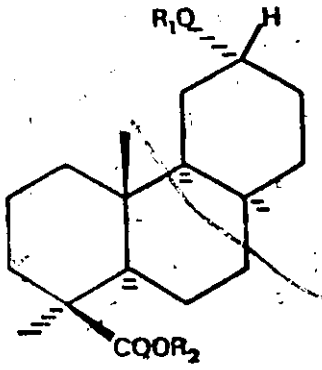


25



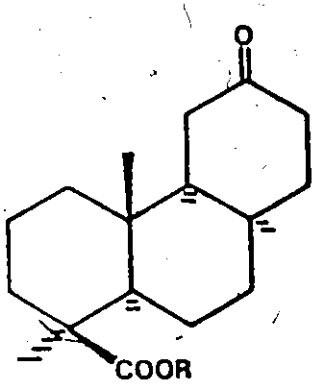
29

a $R_1 = R_2 = H$
b $R_1 = NO$; $R_2 = H$
c $R_1 = H$; $R_2 = CH_3$
d $R_1 = Ac$; $R_2 = CH_3$



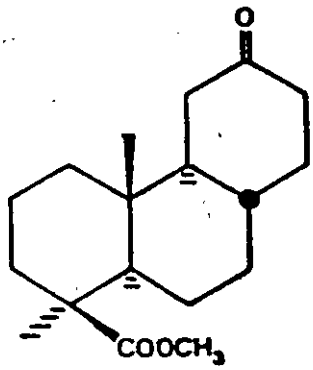
30

a $R_1 = R_2 = H$
b $R_1 = Ac$; $R_2 = H$
c $R_1 = H$; $R_2 = CH_3$



31

a R = H
b R = CH_3



32

FIGURE 10 Ring C-aromatic reduction of podocarpic acid 25

generation a C-12 could still be effected by alternate means. Photolysis of 30a with lead tetraacetate-iodine after 4h showed two major species by thin layer chromatographic analysis, one the starting material 30a and the other cis-ketoester 31b. Identification was made by comparing the R_f-values of pure samples of 30a and 31b (0.16 and 0.32, respectively) with those in the crude photolysis mixture when eluted through alumina with 9:1 petroleum ether-ethyl acetate solution. Reduction of the reaction mixture with sodium borohydride elimimated the spot at 0.32.

A further attempt at free radical hydrogen abstraction at the C-20 methyl was made using the lead tetraacetate thermolytic method, but this, too, was unsuccessful. Analysis of the reaction mixture indicated the keto ester and starting material to be once again the major products.

At this point, doublts were raised that hydrogenation of podocarpic acid did indeed give the anticipated 12 - hydroxyl. It was felt that perhaps some investigation into the two epimers would be of some value. A sample of the perhydropodocarpic acid was oxidized to the keto acid 31a and 31b using the Jones reagent (120) (8N chromic acid in acetone) at 25°. The trans-anti-cis stereoisomer could be preferentially crystallized from the reaction mixture using aqueous alcohol. After methylation, a pure sample of 31 was obtained by preparative gas-liquid chromatography for physical analysis.

Reduction of the cis-keto acid with sodium borohydride was expected to give primarily the 12 - alcohol 29a (R_1=R_2=H) from the consideration that the carbonyl group will be attacked by the metal hydride anion from the less hindered side (121). Consequently, reduction followed by methylation of the reaction product, gave a material whose p.m.r. spectrum indicated the predominant C-20 methyl absorption peak at 0.77 p.p.m.

Reduction of the cis-keto acid with sodium in alcohol, followed by methylation, gave a product whose p.m.r. spectrum included a predominant high field absorption peak at 0.82 p.p.m. Since the latter reduction was expected to yield the two epimers in a ratio of their thermodynamic stabilities, the peak at 0.82 p.p.m. was assumed to be due to the C-20 methyl of the 12 -hydroxyl derivative 30c (R_1=H; R_2=CH_3) while the predominant peak at 0.77 p.p.m. in the previously mentioned reduction corresponded to the C-20 methyl in the epimeric alcohol 29c (R_1=H; R_2=CH_3). It is a convenient practice in structure determination to utilize the changes in shift of the quaternary methyl groups because of their readily discernible nature in complex spectra and their frequent sensitivity to structural changes elsewhere in the molecule (122, 123).

The bandwidths of the C-12 hydrogen atoms substantiate the assignments for the two epimers. The bandwidths at one-half peak height for the 12α- and 12β- alcohols are, respectively, 4 H_z and 2.5 H_z and it is generally known that equator-

ial hydrogens have narrower bandwidths than do axial hydrogens. The magnitude of the bandwidth for the 12-axial hydrogen is smaller than usual for similar systems and suggests that ring C is in a boat or twist conformation.

Each of the epimers was converted to the corresponding acetate using either the acetic anhydride-hydrochloric acid or the acetic anhydride-pyridine methods. Three recrystallizations gave a large crystal (m.p. 120.0-120.5°) whose p.m.r. spectrum suggested as being the 12α- equatorial epimer. This compound was predominant in the spectrum of the crude acetylation mixture from the sodium-alcohol reduction. The C-20 methyl absorbance was 0.90 p.p.m. and analysis of the p.m.r. spectrum of the crude material for the sodium borohydride reduction showed a peak at 0.78 p.p.m. attributed to the C-20 methyl in the 12β-axial epimer. Thus, C-20 methyl assignments for the two epimeric acetates, 29d (R_1 = Ac; R_2 = CH_3) and 30c (R_1 = Ac; R_2 = CH_3) were established. It is prudent at this time to indicate that, in the acid-catalyzed acetylation, no interconversion of epimers was detected.

Acetylation of the crude reaction mixture from the rhodium catalyzed hydrogenation of podocarpic acid, followed by methylation, gave a product mixture whose p.m.r. spectrum indicated the presence of both α- and β- epimeric acetates in the ratio of 5:3 respectively.

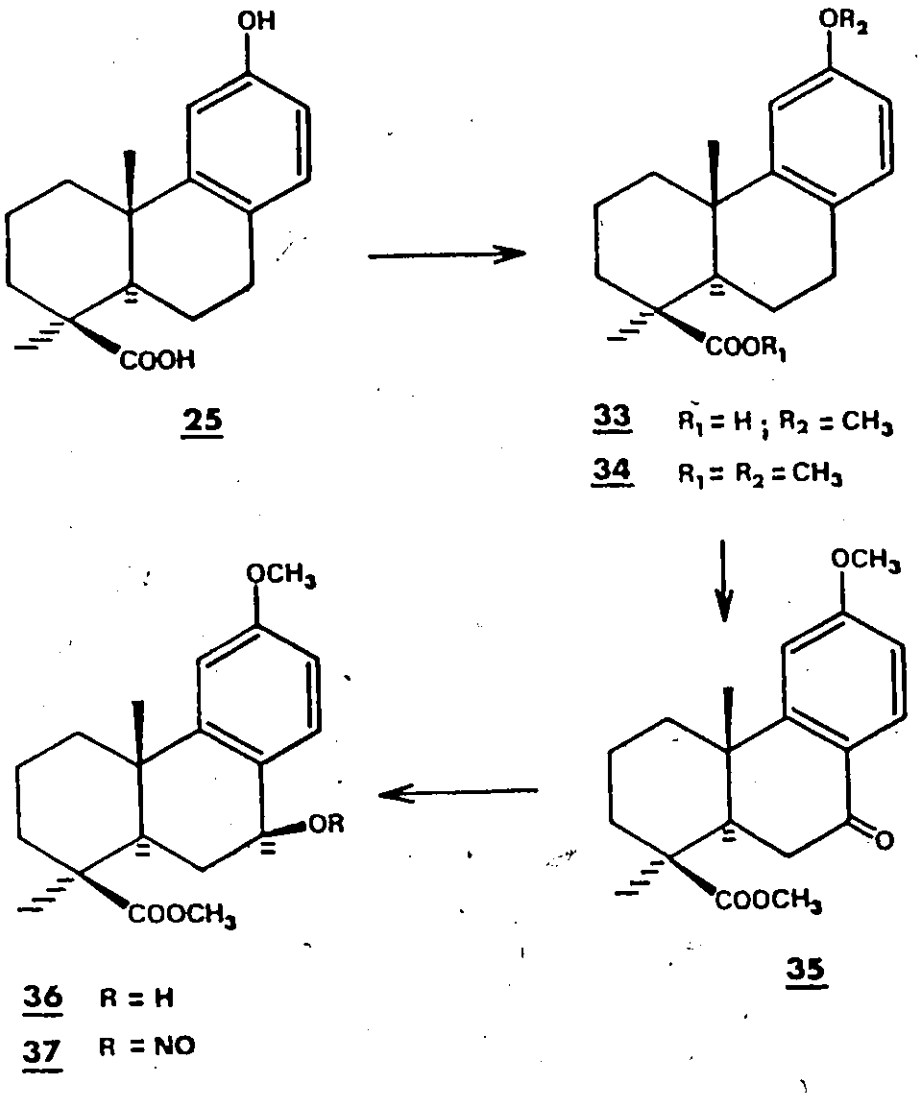
The failure of the Barton reaction for compound 29

has been studied. The presence of the trans-anti-cis conformation and the 12β -axial alcohol have been established. Although molecular models establish the proximity of the C-12 hydroxyl and the C-20 methyl necessary for free-radical hydrogen abstraction, the abstraction failure can be attributed to a twist conformation assumed by ring C to overcome the extensive interactions within the molecular framework. Certainly, the p.m.r. analysis of the C-12 hydrogens is consistent with a twist conformation for the 12β-alcohol. If this is the case, free-radical functionalization of the C-20 methyl group, via the C-12 alcohol, would be impossible.

4.2 Attempted C-20 Functionalization Through the C-7 Alcohol, via the C-19 Ester

The relatively low energy barrier, evident in molecular models, to the twisting of carbons 6 and 7 in podocarpic acid suggested the possibility of ring B assuming a twist conformation (boat-type), in which a beta-oriented hydroxyl group on C-7 might be close enough to the C-20 methyl to effect hydrogen abstraction by the Barton reaction. The NOE results (section 2.4) on oxygenated diterpenoids gave added impetus to the potentiality of this pathway.

Podocarpic acid was converted to the O-methyl derivative 33 by dimethyl sulfate in basic media, after which, the product was esterified to give 34. Chromium trioxide-



25

33 $R_1 = H$; $R_2 = CH_3$

34 $R_1 = R_2 = CH_3$

35

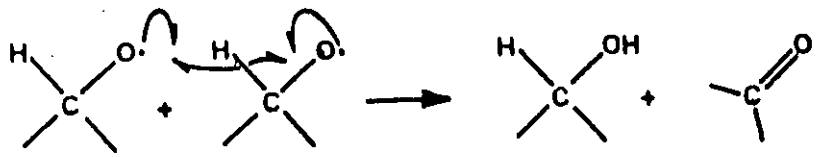
36 R = H

37 R = NO

FIGURE 11. Synthetic route to nitrite ester 37

acetic acid oxidation (124) at the C-7 benzylic position gave 35 in good yield, from which, the 7β-alcohol 36 was obtained by sodium borohydride reduction.

The conversion of 36 to the nitrite ester 37 was only partially completed. However, photolysis of the crude mixture for 4.5h indicated the absence of any nitrite ester starting material and the almost equal generation of the alcohol 36 and the ketone 35. The implication is that the free-radical of 37, unable for conformational reasons to effect the hydrogen abstraction from the C-20 methyl, abstracts the C-7 hydrogen from a second free-radical species generating alcohol and ketone in equal amounts as shown below.

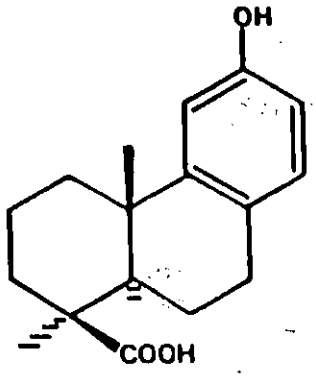


It is remarkable that this intermolecular reaction should have proceeded so efficiently as efforts were made to conduct the photolysis at as low as practicable concentrations in order to slow down the rates of any intermolecular, bimolecular process.

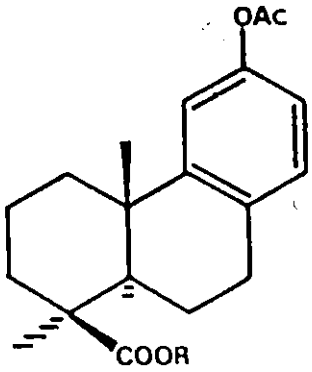
4.3 Attempted C-20 Functionalization Through C-7 Alcohol, via C-19, 6β -Lactone

Molecular models indicate that ring B can be forced

FIGURE 12. Synthetic route from podocarpic acid 25 to keto-lactones 44-46

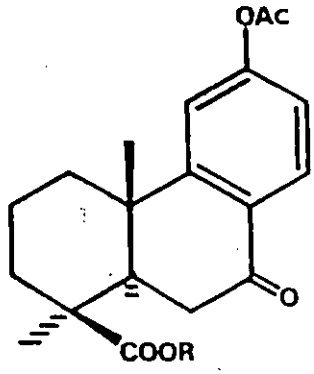


25



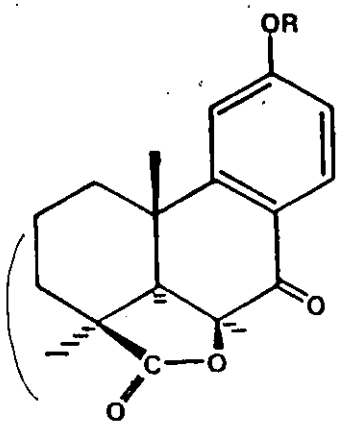
38 R = H

39 R = CH_3



40 R = H

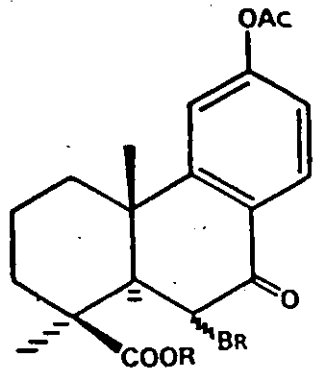
41 R = CH_3



44 R = Ac

45 R = H

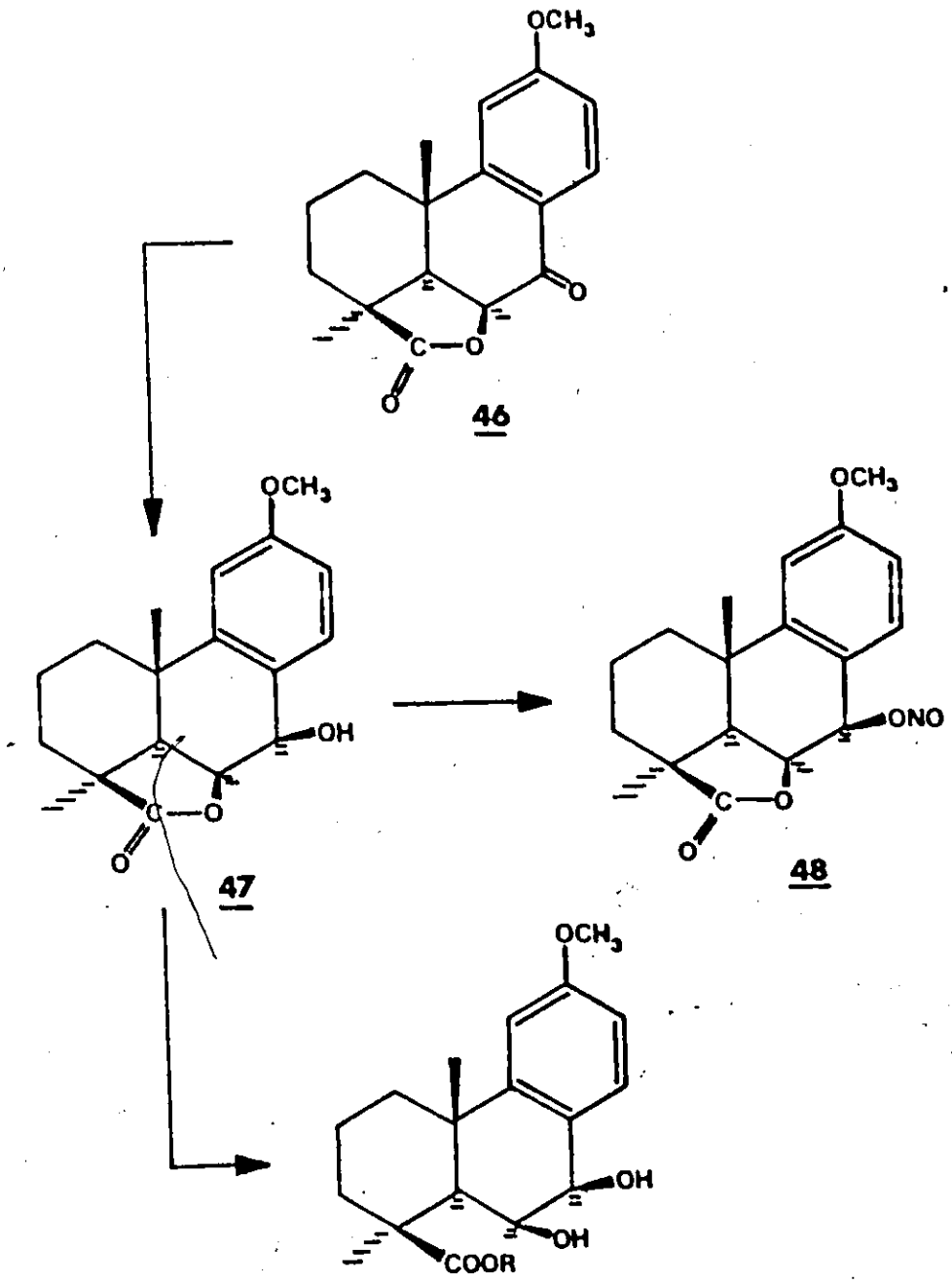
46 R = CH_3



42 R = H

43 R = CH_3

FIGURE 13 Synthetic route to 6β - and 7β - alcohol lactones



94 R = H

95 R = CH_3

into a boat-type conformation by locking it into place with a lactone ring between carbons 19 and 6. The Barton reaction on closely related systems has been reported (30). Podocarpic acid was acetylated, to deactivate the ring to bromine attack in a later step, and oxidized by a modification of the method of Wenkert (Section 4.4). Bromination of the C-6 position was accomplished by the dropwise addition of bromine to an acetic acid solution of 40 containing a few drops of 16% hydrobromic acid to initiate the reaction (55). Lactonization to 44 occurred readily under basic conditions. Pure compound 42 was only obtained by careful work-up to avoid spontaneous lactonization.

Hydrolysis of the acetate under basic conditions and diazomethane methylation of the acidic phenol gave the keto-lactone 46. Sodium borohydride reduction, as before, and nitrosylation of the 7β -alcohol yielded the nitrite ester 48.

Photolysis of the nitrite ester as a two per cent solution in benzene gave, after 15 h, a mixture containing mainly the starting alcohol 47 with evidence of the keto-lactone 46 each identified by the comparison of the pmr spectrum with those of the pure compounds. There was no indication of the occurrence of the Barton reaction between the C-7 oxygen and the angular C-20 methyl as evidenced by the absence of both the decreased intensity of the pmr spectrum of the C-20 peak and also the expected AB quartet

of the anticipated C-20 methylene. Similar results were obtained when the photolysis was conducted in pyridine or in 1:1 pyridine-cyclohexane.

The lactone ring was readily hydrolyzed under basic conditions to give acid 94 which was readily esterified to give methyl 6β,7β-di hydroxy-O-methyl podocarpate 95. Nitrosylation and photolysis in benzene gave, after evaporation, a residue whose pmr spectrum indicated three compounds, one being starting material 95. A low field doublet at 8.0 p.p.m. suggests one compound to have a ketonic function at C-7 and an indication that some intermolecular reaction has occurred. The decreased intensity of the C-20 methyl peak suggested that the Barton reaction has occurred although the anticipated AB quartet of the C-20 methylene could not be identified among the peaks between 3.8 and 4.8 p.p.m.

4.4 Improved Procedure for Benzylic Oxidation in Diterpene Synthesis

The synthesis of substantial quantities of C-7 OH compounds necessitated an efficient oxidation procedure for this carbon. The use of excess chromium trioxide in glacial acetic acid containing a trace of water to effect such a transformation has been reported (48,55,124). Our results were such that, although the desired oxidation at C-7 was realized, recovery of the product from the chromium salts was difficult and tedious. This can be rationalized by the partial acid

hydrolysis of the acetate to give the phenolic compound which can then form troublesome insoluble chromium salts. It was obvious, then, that to expedite the oxidation stage of the synthesis, a modification of the general chromic acid oxidation of Wenkert (124), developed successfully on non-phenolic tricarbocyclic diterpenes, was necessary.

The oxidation of 12-acetoxypodocarpic acid 38 followed by quenching of excess oxidant and concentration of the solution on the rotary evaporator gave a dark green solution containing 7-oxo-12-acetoxypodocarpic acid 40. The tedious and time-consuming column chromatographic separation of 40 from interfering materials has been reported (48) and excellent yields of 40 were only obtained with the use of large quantities of absorbent (SiO_2) and massive volumes of eluent. Similar yields have been obtained in this laboratory, however, by a different approach which eliminates the large quantities of expensive materials.

The oxidation of 12-acetoxypodocarpic acid 38 followed by oxidant quenching and evaporation of the solvent gave a dark green product which was simply hydrolyzed with a minimum quantity of 10-15 per cent sodium hydroxide. The generated phenolic compound readily separated from other neutral materials, particularly chromium salts, as its sodium salt. Subsequent regeneration of the 12-acetate with acetic anhydride and pyridine gave the 7-oxo-12-acetoxypodocarpic acid 40 as an easily purified crystalline material in excellent (80-90%) yields.

Further work on the 6β,7β-diol was abandoned in view of the fact that ring B may not be in a chair conformation and, therefore, the 6β-alcohol and the C-20 methyl group may not be suitably orientated for efficient 1,5-hydrogen transfer. Although a successful 1,5-hydrogen transfer preceded by removal of the 7β-hydroxy group by hydrogenolysis would be a valuable set of reactions in the synthsis of diterpenoid systems, this was beyond the scope of this work.

5. CARBON-13 NUCLEAR MAGNETIC RESONANCE OF RING C-AROMATIC DITERPENOIDS

5.1 Aliphatic Carbon Assignments

The aliphatic carbon-13 NMR chemical shifts for a number of appropriate model compounds along with those for derivatives of podocarpic acid 25 are given in Tables 6 and 7, respectively. It should be noted that closely separated resonances have been assigned based on most probable chemical shift considerations but, unless unequivocal identification was possible (Section 3.2), reversed assignments are equally valid. In each table, space limitations do not allow the correct name of each compound to be printed under the appropriate heading; in many cases, a simplified term has been used which, at least, will identify to the reader the type of substitution in a particular molecular system. Alternatively, the compound number will identify the correct structure which is located elsewhere in the thesis.

It is obvious from both tables that a number of frequently appearing carbon groups give relatively constant chemical shifts and can be assigned immediately. The aryl methoxyl, for example, in all relevant compounds exhibits absorbance signals at 55.2 ± 0.6 p.p.m. comparable to the reported value of 54.0 p.p.m. for anisole (125). In addition, acetates gave rise to signals at 20.5 ± 0.9 p.p.m. and

169 ± 0.6 p.p.m. for the methyl and carbonyl carbons respectively, consistent with reported values of 20.5 and 169.2 p.p.m. for estrone acetate (126). The methoxyl carbons in the C-19 methyl esters absorb at 51.7 ± 1.0 p.p.m. a range which encompasses the average value of 51.0 p.p.m. reported for a number of aliphatic methyl esters (127).

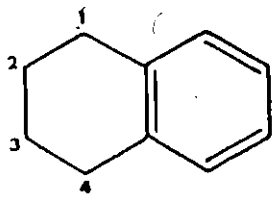
The first three compounds in Table 6 provide the carbon skeleton for rings B and C of the tricyclic diterpenoids series. Tetralin 60, or 1,2,3,4-tetrahydronaphthalene, gives rise to a pair of aliphatic absorbance signals corresponding to the two pairs of chemically equivalent carbon nuclei. In view of the deshielding effect of the benzene nucleus (76, page 98), the low field absorbance at 29.7 p.p.m. is assigned to those carbons alpha to the fused aryl ring while the two beta carbons are assigned the absorbance at 23.8 p.p.m.

Introduction of a 6-methoxyl group has very little effect on the saturated ring carbons and only to the extent that the peaks for each of the four carbons are resolved.

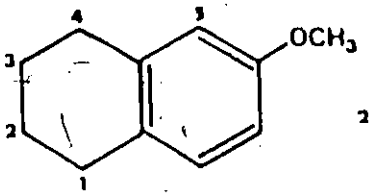
On the other hand, direct substitution of a carbonyl into the cyclohexane ring dramatically alters chemical shifts for the substituted and adjacent carbons as evidenced by the changes on going from 53 to 52. As expected the substituted carbon appears at very low field, 196.0 p.p.m., while C-2 is deshielded by 15.4 p.p.m., comparable to the deshielding of 15.2 p.p.m. for C-2 in 3-cholestanone (126). Noticeably absent is the anticipated β- effect at C-4, having a value

TABLE 6 Chemical shifts and assignments for the aliphatic carbon-13 NMR spectra of model compounds

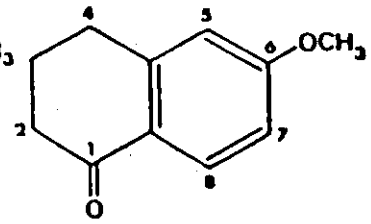
Compound number	name	Carbon 1	2	3	4	5	6	7	10	20	CH_3
60	tetralin	29.7	23.8	23.8	29.7	-	-	-	-	-	-
53	6-methoxytetralin	28.8	23.6	23.8	29.8	-	-	-	-	-	54.7
52	6-methoxy-1-tetralone	196.0	39.0	23.9	30.4	-	-	-	-	-	55.0
61	2-oxohexahydrophenanthrene	37.5	35.1	197.3	124.4	168.8	31.6	31.7	39.6	28.1	
49	6-methoxy-2-oxohexahydrophenanthrene	37.1	34.8	197.2	124.5	168.8	30.4	31.4	39.6	27.5	55.2
50	6-methoxy-2-oxo-octahydrophenanthrene	38.3	37.7	208.6	42.5	44.6	26.2	29.0	36.8	21.1	55.2
51	6-methoxyoctahydrophenanthrene	38.2	22.8	26.4	26.8	42.8	28.9	29.6	37.4	21.7	55.0



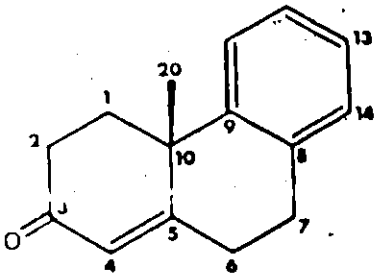
60



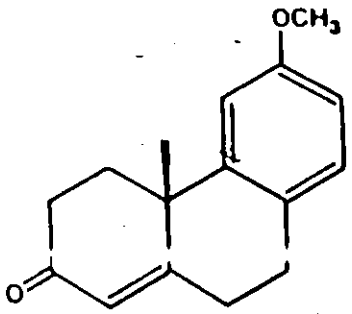
53



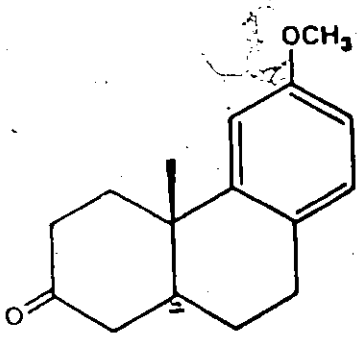
52



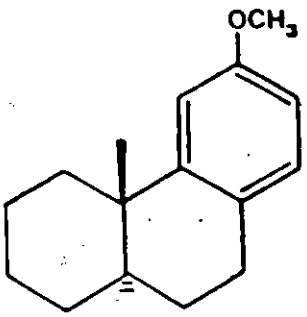
61



49



50



51

FIGURE 14 Structures of model compounds

of -3.6 p.p.m. in cyclohexanone (94), which can be attributed to geometric constraints on the cyclohexane ring by the energetically favourable coplanarity of the ketonic and aromatic π-systems thereby reducing H,H-interactions involving C-4.

Extension of the model system to 49-51 and 61 completes the basic tricyclic structure for the podocarpic acid series by the attachments of ring A and the angular methyl group at C-10. In each of these compounds, the latter group, designated as C-20 in view of its analogous position in the diterpoid series, was assigned to the high field absorbance in accordance with usual methyl shift positions and in consideration of steric perturbations between C-20 and carbons 2 and 6. Off-resonance decoupling readily identified the quaternary centre, C-10, to which the angular methyl is attached.

Reduction of compound 49 results in the disappearance of signals at 124.5 and 168.8 p.p.m. attributed to C-4 and C-5, respectively. The latter is assigned the low field position in consideration of the resonance structure shown in Section 4.2. The simultaneous appearance of peaks at 42.5 and 44.6 p.p.m. in 50 establish C-4 and C-5, respectively, with the latter, a tertiary centre, expected to resonate at the lower field position. The low field position for C-5 is maintained in 51.

Assignments for carbons 6 and 7 follow from comparison of the shift changes on going from cyclohexane to trans-decalin with the shift changes on going from 53 to 51. Carbon 6, being adjacent to the ring junction, is expected to be

TABLE 7 Predicted chemical shifts of the B-aliphatic carbons in compound 51

Carbon	δ_c in 53	αeq	αax	βeq	βax	γeq	γax	δeq	δax	$(CH_3)_2$ gem.	$(CH_3)_2$ vic.	δ_c in 51 predict.	δ_c in 51 actual
5	23.8	+5.6	-	+17.8	+5.2	-	-5.4	-	-	-	-2.3	44.1	42.8
6	23.6	-	-	+ 8.9	-	0.0	-5.4	-	-	-	-	27.1	28.9
7	28.8	-	-	-	-	0.0	-	-0.3	-0.1	-	-	28.4	29.6
10	29.8	+5.6	+1.1	+17.8	-	-	-5.4	-	-	-3.4	-5.4	40.1	37.4

deshielded by about 7-8 p.p.m. or a shift change from 23.6 to about 31 p.p.m. The carbon beta to the junction, C-7, is expected to be minimally affected and remain essentially at 29 p.p.m. In the spectra of these compounds (53-55, 65), only two absorbance peaks are present in this region.

Additional confirmation of the assignments for carbons 5,6, and 7 is shown in Table 7 in which the chemical shifts for each are predicted using the methyl substituent parameters of Dalling and Grant (89). It is tacitly assumed that hydrogen interactions between the two rings are comparable to those introducted by methyl substitution on the cyclohexane ring (Table 4). The signal assigned to C-10 is upfield by 2.7 p.p.m. from its predicted value possibly attributable to an accentuated γ-effect reported elsewhere for rigid carbon skeletons (127).

Noteworthy as well are the upfield shifts of carbons 6 and 10 upon reduction of the double bond in 49. The increased shielding is expected in consideration of the increased steric perturbations between carbons 4,6, and 10 and of the decreased electronegativity of C-5 on assuming sp^3 hybridization.

Assignment of C-3 in compounds 49,50, and 61 is unequivocal because of its extremely deshielded position. Loss of conjugation in 50 results in decreased shielding of the carbonyl as expected from other reports (128).

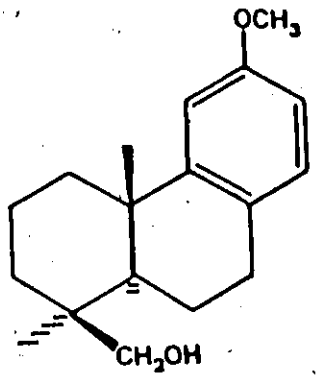
Three resonances of compound 50 change significantly upon reduction of the C-3 carbonyl function. Absorbances at

37.7 and 42.5 p.p.m. appear in 51 at 21.7 and 26.8 p.p.m., respectively, and are assigned to C-2 and C-4. The new peak at 26.4 p.p.m. in 51 is assigned to C-3 and, as expected, is close to the chemical shift of cyclohexane. A small deshielding of 1.7 p.p.m. in C-20 is an additional consequence of C-3 reduction and is comparable to the deshielding by 1.6 p.p.m. of the methyl resonances on going from 4,4-dimethylcyclohexanone (94) to 1,1-dimethylcyclohexane (89).

Carbon 1 in the four compounds (49-51, 61) is expected to undergo minimal chemical shift changes and is assigned the values between 37.1 and 38.3 p.p.m. The remaining unassigned resonances at 35.1 and 34.8 p.p.m. in compounds 61 and 49, respectively, are associated with C-2. The upfield shift of C-2 when beta to a double bond is consistent with results reported for cyclohexene (126).

The aliphatic carbon-13 NMR chemical shifts for podocarpic acid and derivatives are contained in Table 8. Included in the table is a list of substituents and their positions on the basic tricyclic structure (below) to facilitate the mental correlation of compound number and structure.

Initial assignments for the ring C-aromatic diterpenoids were based on examination of one of the compounds, O-methylpodocarpinol 55, and its interaction with praseodynium tris (dipivalomethane),$Pr(DPM)_3$ (Section 3.2). The upfield pseudo-contact induced shifts for various complex concentrations are shown in Table 9 and the observed rate of change of chemical shift for each absorbance peak shown in T le 10.



55

The calculated upfield shifts based on the relationship

$$\frac{\Delta H}{H} = \frac{3\cos^2\theta - 1}{r^3} \quad \text{(5.1)}$$

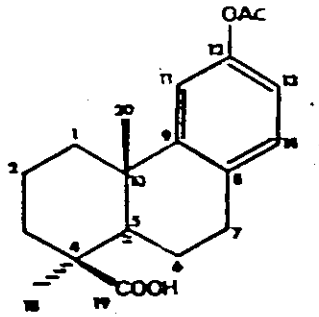
are shown in Table II with internuclear distances (r) and angles (θ) determined from Dreiding molecular models and with the praeseodynium atom at a distance of 3.0 A away from the oxygen atom. Graphical representations of the shift changes are shown in Figures 25 and 26 where the line positions have been corrected according to the ApSimon method (129). Although the errors in this experiment are estimated to be of the order of ten per cent, it was considered not worthwhile to further refine the data because the oxygen atom at C-19 can adopt two conformations (Figure 15). Although conformer A is anticipated to be the predominant one, contributions made to the induced shifts by conformer B are

TABLE 8 Chemical shifts and assignments for non-aromatic C^{13} spectra of ring C-aromatic diterpenoids

	Ring substituents					Carbon														
no:	19	6	7	12	other	1	2	3	4	5	6	7	10	18	19	20	OCH_3	$COOCH_3$	other	
25	COOH	-	-	OH	-	38.1	20.8	40.0	44.3	53.3	21.9	31.7	39.2	29.1	179.7	23.7	-	-	-	-
33	COOH	-	-	OCH_3	-	38.0	20.6	39.8	44.1	53.1	21.7	31.4	39.1	28.9	180.7	23.4	55.1	-	-	-
34	$COOCH_3$	-	-	OCH_3	-	37.8	20.3	39.5	44.0	53.0	21.4	31.2	38.7	28.2	177.6	22.8	54.7	50.7	-	-
57	CHO	-	-	OCH_3	-	34.1	19.6	38.9	48.8	52.1	19.8	30.7	38.7	24.4	204.3	24.4	55.2	-	-	-
55	CH_2OH	-	-	OCH_3	-	35.9	19.7	39.5	39.2	51.7	19.9	30.5	38.3	27.3	64.8	25.9	55.0	-	-	-
56	CH_2OAC	-	-	OCH_3	-	36.6	19.6	39.3	37.6	51.7	20.0	30.6	38.3	27.6	66.1	25.9	55.1	-	20.9	170.6
58	CH_3	-	-	OCH_3	-	39.0	19.5	41.9	33.6	50.6	19.5	29.7	38.1	33.3	19.5	24.6	54.9	-	-	-
35	$COOCH_3$	-	C=O	OCH_3	-	37.6	20.0	38.5	44.0	50.4	37.4	195.9	38.9	27.8	176.8	21.4	55.2	51.1	-	-
36	$COOCH_3$	-	OH	OCH_3	-	37.5	20.2	39.7	43.9	50.6	31.8	71.1	39.5	28.0	178.6	22.7	55.0	50.9	-	-
59	$COOCH_3$	C=C	C=C	OCH_3	-	36.2	19.4	37.5	43.6	51.5	148.7	125.2	38.4	27.6	177.5	20.0	54.9	50.9	-	-
62	$COOCH_3$	-	-	OCH_3	3-OH	38.1	29.6	65.3	49.4	52.4	21.2	31.1	38.3	22.6	-	23.4	54.8	50.6	-	-
63	$COOCH_3$	-	-	OCH_3	13-i-PrOH	38.0	20.4	39.9	44.2	53.2	21.6	31.6	38.9	28.5	177.5	23.1	55.4	50.9	56.3	73.6
																				22.3
64	$COOCH_3$	OH	OH	OH	-	37.9	20.3	38.9	45.2	66.5	67.1	71.9	42.0	29.2	182.1	25.3	-	52.8	-	-
46	19,6 -lactone		C=O	OCH_3	-	28.3	24.7	30.7	42.1	49.8	76.1	191.3	35.4	28.3	179.9	17.4	55.4	-	-	-
96	$COOCH_3$	-	-	OCH_3	13-$COCH_3$	37.9	20.2	39.7	44.3	52.8	21.2	31.7	39.4	28.7	177.4	22.9	55.8	51.2	31.1	198.6
65	$COOCH_3$	C=C	-	OCH_3	5-C=C 3-C=O	31.5	35.3	206.9	60.2	141.5	125.3	30.1	39.5	27.4	172.3	22.1	55.3	52.6	-	-

TABLE 8 Chemical shifts and assignments for non-aromati- C^{13} spectra of ring C-aromatic diterpenoids

	Ring substituents					Carbon											acetate		
no:	19	6	7	12	other	1	2	3	4	5	6	7	10	18	19	20	$COCH_3$	CO	CH_3
38	COOH	-	-	OAC	-	38.0	20.7	39.7	44.0	52.8	21.6	31.6	39.1	28.7	183.6	23.4	-	169.6	20.7
39	$COOCH_3$	-	-	OAC	-	38.2	20.6	39.1	44.5	53.0	22.0	31.8	39.9	28.7	177.3	23.4	51.2	168.9	21.1
40	COOH	-	C=O	OAC	-	37.6	21.1	38.7	43.9	50.1	28.3	197.1	39.4	28.3	178.1	21.5	-	168.4	22.4
41	$COOCH_3$	-	C=O	OAC	-	37.9	20.3	38.8	44.0	50.5	30.6	196.0	39.4	28.1	177.0	21.7	51.6	168.6	21.0
43	$COOCH_3$	Br	C=O	OAC	-	36.9	19.4	38.3	45.5	52.1	48.2	193.6	39.3	29.4	177.0	24.7	50.6	169.0	21.2



38

TABLE 9 Spectral data for the O-methylpodocarpinol-Pr(DPM)$_3$ complexes

Percent Composition of Pr (DPM)$_3$

Carbon	0	1.9	3.5	6.2	7.4
2	19.7	18.8	18.8	17.8	17.8
6	19.9	19.1	19.1	18.3	18.3
20	25.9	25.3	25.4	24.5	24.7
18	27.3	26.2	26.1	25.1	24.7
7	30.5	29.6	30.0	29.2	29.4
1	35.9	34.8	34.7	33.3	33.3
10	38.3	37.6	37.5	36.1	36.0
4	39.2	37.8	37.7	36.7	36.5
3	39.5	38.7	38.7	38.0	38.1
5	51.7	50.8	50.9	49.9	49.8
OCH_3	55.0	54.7	54.7	54.0	54.2
$\sum \delta_{ij}$	383.9	373.4	373.6	362.9	362.8

TABLE 10 Pr(DPM)3 shifts for O-methylpodocarpinol (55)

carbon	$\Delta H_{1:1}$ complex	$\Delta H/H$	$\Delta H/\Delta$ concentration ($\times 10^{-2}$)
1	10.8	0.30	21.6
2	7.2	0.37	14.4
3	6.3	0.16	12.5
4	11.0	0.28	21.9
5	8.0	0.15	15.9
6	6.9	0.35	13.8
7	4.5	0.15	9.0
10	8.9	0.23	17.8
18	9.6	0.35	19.2
20	6.2	0.24	12.3

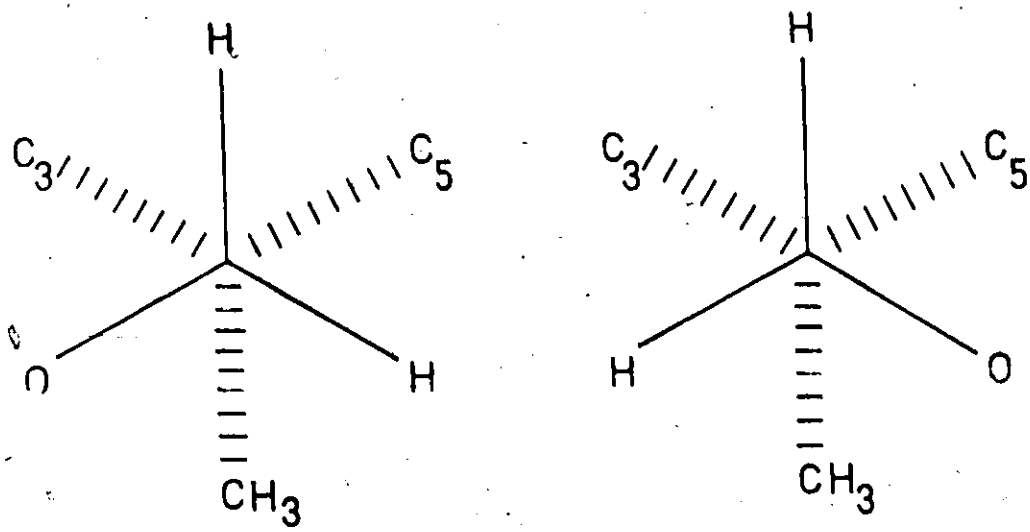
TABLE 11 Calculated data for the O-methylpodocarpinol-Pr (DPM)3 complex[a]

carbon	r(Å)	r^3	X	cos X	$3\cos^2X-1$	$3\cos^2X-1/r^3$ (X 104)
1	6.9	329	22	0.93	1.79	55
2	5.9	205	24	0.91	1.72	84
3	5.7	185	13	0.97	1.91	103
4	-	-	-	-	-	-
5	6.3	250	35	0.82	1.46	58
6	6.4	262	35	0.82	1.46	56
7	7.8	475	28	0.88	1.64	35
10	6.5	275	34	0.83	1.49	54
18	5.6	175	15	0.97	1.91	109
20	5.3	149	34	0.83	1.49	100

a Pr-O bond length taken as 3.0 A

difficult to assess. Calculations (Table 11) were done on conformation A.

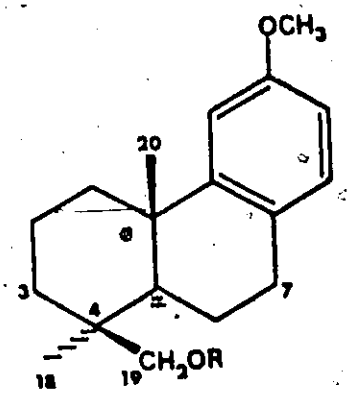
FIGURE 15 Conformations of C-19 oxygen in O-methylpodocarpinol-Pr(DPM)3 complexes



Despite the errors, the $\Delta H/H$ values, both calculated and experimental clearly fall into three groups. The peaks

with lowest slopes must be associated with carbons most distant from C-19 and those with highest slopes associated with carbons proximate to C-19. The peak of lowest slope, and obviously isolated from the bulk of the shift data in Tables 10 and 11, can be assigned to C-7. On the other hand, the peaks with the highest slopes must correspond to carbons 3,4,18, and 20. Intermediate to these ranges is a large group of resonances comprising the remainder of the aliphatic carbon nuclei, 1,2,5,6, and 10. Off-resonance decoupling to locate the quaternary carbons shows that one lies in the intermediate set and one lies in the high slope set, therefore, carbons 4 and 10 are located.

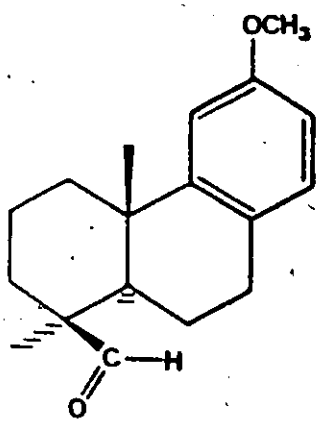
For the definite assignment of the remaining aliphatic carbons recourse was made to the chemical shift data for the variously substituted podocarpic acid derivatives shown in Table 8 and to some of the assignment techniques indicated in Section 3.2.



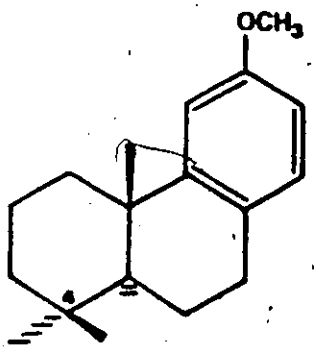
55 R = H

56 R = AC

In all cases, for example, off-resonance decoupling established the quaternary centres at C-4 and C-10. The low field resonance, except in compounds 56 and 58, was assigned to C-4 in consideration of the inductive effect of the adjacent carbonyl group (94). Of the two exceptions, the methyl group in 58 is expected to shield the C-4 carbon (93) and C-4 is, therefore, assigned to the high field quaternary position. In compound 56, assignment was confirmed by comparison of data from acetylation of cis-4-t-butylcyclohexanol (126) in which the carbinol carbon, upon acetylation, is deshielded by 3.1 p.p.m., whereas, the adjacent carbons are shielded by 2.9 p.p.m. Acetylation of O-methylpodocarpinol 55 results in an upfield shift of one quaternary carbon by 1.6 p.p.m. (39.2 → 37.6 p.p.m.) thereby assigning C-4. The second quaternary carbon at C-10 was unaffected as expected. Also noted is the deshielding of the C-19 carbon by acetylation by 1.3 p.p.m. which, although smaller than values earlier reported, follow a similar trend.

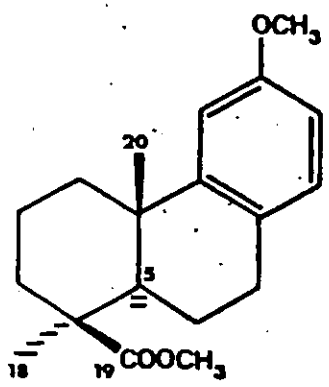


57

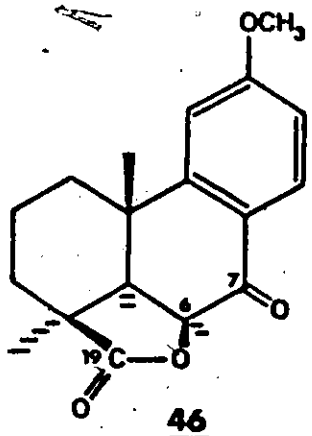


58

Off resonance decoupling of methyl O-methylpodocarpate 34 using the Fourier transform technique established the splitting patterns for the remainder of the aliphatic carbons. Excluding the methoxyl groups only three carbons of the ten did not exhibit corresponding absorbances at the same positions in each of the partially and completely decoupled spectra. A doublet at 53.0 p.p.m. was unequivocally assigned to C-5 and its low-field position is not only expected, but also maintained in the remaining derivatives, by virtue of its substitution. Two quartets of 28.2 and 22.8 p.p.m. are assigned to the methyl groups at C-18 and C-20, respectively, the latter owing its high field position to steric interactions with carbon 2,4, and 6. The shift difference of 5.4 p.p.m. for the axial and equatorial methyl groups compares favourably with the value of 6.0 p.p.m. reported for the two conformations of methylcyclohexane (91). The chemical shift of C-18 in the remaining diterpenoids changes only



34



46

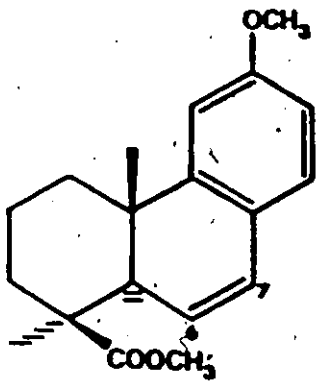
slightly. Most noticeable is the upfield shift of C-18 when an equatorial hydroxyl group is introduced at C-3. The upfield shift of C-18 of -5.6 p.p.m. is comparable to the shifts of 6.8 p.p.m. when comparing methylcyclohexane (89) with cis-2-methylcyclohexanol (90) and is probably associated with non-bonded interactions between the oxygen and the methyl hydrogen atoms which has been referred to earlier as the γ-effect. In the same way, C-20 remains relatively constant at about 24 p.p.m. throughout the series. It does, however, noticeably mirror substitution at carbons 6 and 7, again with steric implications. In addition, formation of the lactone ring in 46 increases the steric interactions between C-20 and carbons 6,7, and 19 resulting in a substantial shielding effect.

The five remaining carbons, 1,2,3,6, and 7, unaccounted for so far in 34, show up as triplets in the off-resonance experiment. Two triplets are at the extreme high field positions and could only be carbons 2 and 6 since they are the only carbons with obvious steric interactions with other centres.

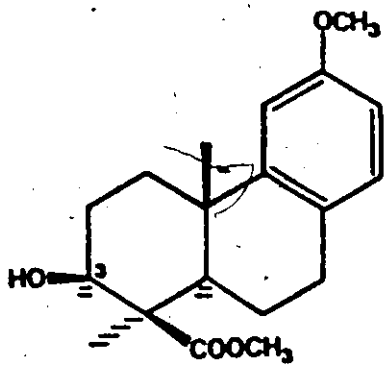
Both C-6 and C-7 can be identified by comparisons of compounds containing substitution on those carbons with compounds that do not. Comparison of 34 and 35, for example, show that, with the introduction of a ketone function at C-7, two absorbances originally in the spectrum of 34, completely disappear from their general regions. The C-7 absorbance, in

34, at 31.2 p.p.m. is now located at 195.9 p.p.m. and the peak at 21.4 p.p.m., assigned to C-6, is now located at 37.4 p.p.m. The deshielding of C-6 by 16.0 p.p.m. by an adjacent electron-withdrawing carbonyl is comparable to the 15-16 p.p.m. deshieldings reported for steroid compounds (126). The disappearance of the peak at 37.4 p.p.m. upon deuteration substantiates the initial assignment. The latter material, after sodium borohydride reduction giving C-6 deuterated 36, established the correct assignment of both carbons in that compound. Of an obvious nature is the disappearance of two absorbance peaks on going from 34 to 59 which accounts for both assignments. A carbonyl at C-7 or an olefinic bond between carbons 6 and 7 have a shielding effect on C-5 of -2.6 p.p.m. and -1.5 p.p.m, respectively, consistant with reports for 4-methylcyclohexanone (94) and for cyclohexene (126) respectively.

Assignment of the three remaining carbons 1,2, and 3, can be made by comparison of 34 with 62 or 65. Introduction of a hydroxyl group at C-3 alters dramatically only three

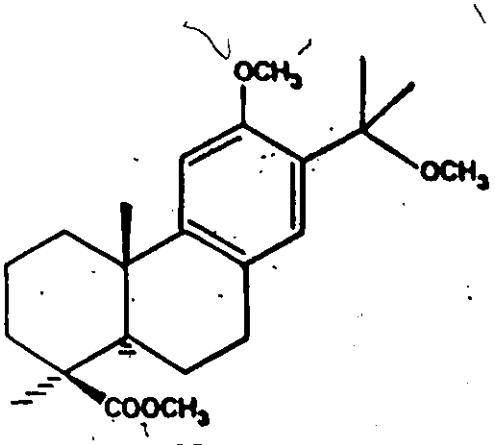


59

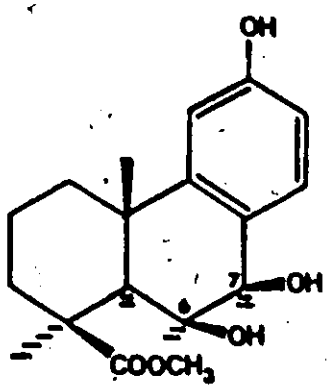


62

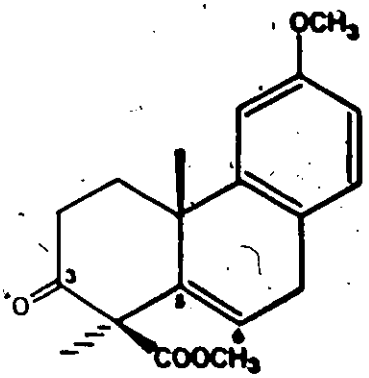
absorbances from 34 which can only be carbons 2,3, and 4. The disappearance of the peak at 39.5 p.p.m. in 34 clearly establishes C-3 which resonates at 65.3 p.p.m. in 62. The new peak at 29.6 p.p.m. can be assigned to C-2 having been deshielded, by the strong inductive influence of the C-3 hydroxyl, from its peak position of 20.3 p.p.m. in 34. The magnitude of the deshielding, +9.3 p.p.m., is consistent with the value of +8.1 p.p.m. reported elsewhere (90).



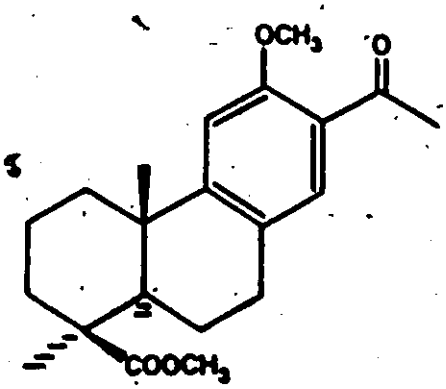
63



64



65



96

The remaining carbon, C-1, in 34 is assigned 37.8 p.p.m. Aside from compounds 46 and 65, the C-1 resonance varies only slightly from the region 36-40 p.p.m. The lactone ring in 46 and the exocylic double in 65 result in substantial shielding at C-1 attributable to steric interactions in the former and possibly rehybridization factors in both.

5.2 Aromatic Carbon Assignments

The chemical shifts of the aromatic carbons are shown in Tables 12 and 13. The assignments are simpler than in the case of the aliphatic carbons because of the presence of the C-12 oxygen function and the ready identification of the fully substituted carbons 8 and 9 by off-resonance experiments. The carbon-13 spectrum of anisole itself shows a simple four line pattern interpretable in terms of inductive and resonance effects (130) with the ortho carbons being at higher field than expected because of the steric interaction of the methoxyl group with the ortho hydrogens (125). Thus the carbon-13 anisole spectrum shows the ortho carbons at 113.0 p.p.m., the para carbon at 119.6 p.p.m., the meta carbons at 128.6 p.p.m. and the substituted carbon at 158.8 p.p.m. The close additivity relationship between simple model compounds and more complex molecular systems, so valuable in peak assignments, is illustrated in Table 14.

In view of the results shown in Table 14, the similarity in aryl chemical shifts of the tricyclic model compounds (Table 12) and of the corresponding aryl carbons in

TABLE 12 The chemical shifts and assignments for the aromatic carbon-13 spectra of model compounds

number	compound	carbon 8	9	11	12	13	14
60	tetralin	137.2	137.2	129.4	125.8	125.8	129.4
53	6-methoxy tetralin	129.3	138.2	114.3	158.6	112.3	130.1
52	6-methoxy-1-tetralone	126.8	147.1	113.4	164.1	113.1	129.5
61	2-oxo-hexahydrophenanthrene	135.1	144.5	127.1	126.3	126.3	128.8
49	6-methoxy-2-oxo-hexahydrophenanthrene	127.2	145.5	112.3	159.2	112.4	129.8
50	6-methoxy-2-oxo-octahydrophenanthrene	127.4	147.3	111.4	158.7	112.2	130.5
51	6-methoxy-octahydrophenanthrene	127.6	149.6	110.7	158.5	111.5	130.2

TABLE 13 Chemical shifts and assignments for the aromatic carbon-13 spectra of ring C-aromatic diterpenoids

Ring Substituents			Carbon					
no.	12	13	8	9	11	12	13	14
25	OH	-	126.7	149.6	112.3	155.0	113.6	130.1
33	OCH_3	-	127.9	149.7	111.6	158.3	112.1	130.1
34	OCH_3	-	127.8	149.9	111.6	158.8	112.0	130.2
57	OCH_3	-	127.1	149.1	111.3	158.4	112.2	130.2
55	OCH_3	-	127.2	151.4	110.7	158.5	111.7	130.0
56	OCH_3	-	127.1	150.9	110.1	158.4	111.1	130.0
58	OCH_3	-	126.3	151.7	110.4	155.3	113.1	129.9
35	OCH_3	-	125.9	157.3	110.4	164.4	112.4	129.9
36	OCH_3	-	128.6	149.5	111.0	159.3	112.3	132.2
59	OCH_3	-	126.3	150.6	110.0	160.1	110.7	127.6
62	OCH_3	-	-	-	-	-	-	-
63	OCH_3	$-C(CH_3)_2OH$	126.6	147.9	107.8	155.6	130.0	127.7
64	OH	-	128.2	147.5	111.7	155.5	114.1	129.1
46	OCH_3	-	125.2	155.5	108.1	164.4	111.6	130.8

TABLE 13 (Cont'd) Chemical shifts and assignments for the aromatic carbon-13 spectra of ring C-aromatic diterpenoids

Ring Substituents			Carbon					
no.	12	13	8	9	11	12	13	14
47	OCH_3	$COCH_3$	127.9	154.2	108.8	157.3	130.9	131.1
65	OCH_3	-	127.0	145.0	109.9	158.5	110.7	128.6
38	OAC	-	130.1	149.5	118.6	149.5	119.2	132.8
39	OAC	-	130.0	149.5	118.5	149.5	119.0	132.9
40	OAC	-	120.7	155.4	118.2	156.6	120.2	129.0
41	OAC	-	128.7	155.7	118.2	156.9	120.2	129.2
43	OAC	-	129.8	155.0	116.3	152.9	120.5	130.0

TABLE 14 Aromatic chemical shifts for methoxyl substituted compounds

compound	compound	chemical shift change, carbon					
		9(14)	10(13)	5	6	7	8
60	53	-7.9	+1.0	-15.1	+32.8	-13.5	+0.7
61	49	-7.7	+2.8	-15.7	+32.4	-14.1	+1.7
benzene	anisole[1]	-8.9	0.0	-15.5	+30.2	-15.5	0.0

[1]shifts reported for corresponding carbons of models with values from reference (125)

the 12-methoxypodocarpic acid is not surprising. The general range of shifts is best illustrated with reference to a specific compound, O-methylpodocarpic acid 33. The two ortho carbons, C-11 and C-13, occur at 111.6 and 112.1 p.p.m.; the meta carbons, C-9 and C-14, absorb at 149.7 and 130.1 p.p.m.; the para carbon, C-8, resonates at 127.9 p.p.m.; and the substituted carbon, C-12, shows up at 158.3 p.p.m. The large discrepancy between the shifts of the two meta positions, C-9 and C-14, was of interest. The large downfield shift of C-9 is similar in magnitude (+24.0 p.p.m.) to that shown by the substitution of anisole by a tertiary butyl group (125).

The substitution of the 12-methoxyl group by a 12-acetoxyl group gives a pattern, shown in Table 15, which is qualitatively similar for the simple system (anisole) and for the more complex diterpenoid structures (illustrated using 34 and 35.

TABLE 15 Aromatic substitution effects for aryl acetates

compound	compound	chemical shift change, carbon					
		8	9	11	12	13	14
34	39	+2.2	-0.4	+6.9	-9.3	+7.0	+2.7
35	41	+2.8	-1.6	+7.8	-7.5	+7.8	-0.7
anisole	phenyl-acetate	+6.6	+1.3	+9.1	-6.8	+9.1	+1.3

5.3 Discussion

Aliphatic Chemical Shifts

The chemical shift assignments made it of interest to examine the effect of substituents on the tricyclic ring system, and to ascertain how they compare with substituent effects in simpler alicyclic ring systems. As a test case, comparison of the chemical shifts of the 10-methyl compound 51 and the 4,4,10-trimethyl compound 58 and using the shift parameters deduced for the methyl cyclohexanes by Dalling and Grant (89), the expected chemical shifts of 58 can be estimated (Table 16).

Excepting carbon 6 and the two carbons at ring junctions (C-5, C-10), the agreement between predicted and observed values is good (all within $\pm$ 1.5 p.p.m.). The question of why the shifts aforementioned digress from predicted values is significant and is attributed to the backbone distortion of the tricyclic system caused by severe C-10 axial methyl, C-4 axial methyl interaction. This view is supported by X-ray structural analysis on diterpenoids

TABLE 16 Predicted aliphatic chemical shifts for A,B - ring carbons in 58

C	δ_c in 51	αeq	αax	βeq	βax	γeq	γax	δeq	δax	$(CH_3)_2$ gem.	$(CH_3)_2$ vic.	δc in 58 pred.	δc in 58 act.
1	38.2	-	-	-	-	-	-	-0.3	-0.1	-	-	37.8	39.0
2	22.8	-	-	-	-	0.0	-5.4	-	-	-	-	17.4	19.5
3	26.4	-	-	+8.9	+5.2	-	-	-	-	-1.2	-	39.3	41.9
4	26.8	+5.6	+1.1	-	-	-	-	-	-	-3.4	-	30.1	33.6
5	42.8	-	-	+8.9	+5.2	-	-	-	-	-1.2	-	55.7	50.6
6	28.9	-	-	-	-	0.0	-5.4	-	-	-	-	23.5	19.5
7	29.6	-	-	-	-	-	-	-0.3	-0.1	-	-	29.2	29.7
10	37.4	-	-	-	-	0.0	-5.4	-	-	-	-	32.0	38.1

(131) where ring A has a flattened chair shape and the two axial methyls in question distort outwards from one another. Carbon-10 retains essentially tetrahedral angles, but carbon-5 bears the brunt of ring distortion with the bond angles C-10, C-5, and C-6, C-10, C-5, and C-4, C-4, C-5, and C-6 being 112°, 116°, and 113°, respectively. Thus C-5 has effectively rehybridized with an increase in s-character and, therefore, appears at higher field (by 5.1 p.p.m.) than predicted. Carbon 6 will be affected by two factors of which one, the rehybridization at C-5, is difficult to assess. The other, outward distortion of the C-19 methyl and the concomitant downward motion of the C-18 methyl, reduces the steric perturbations between the hydrogen atoms of carbons 18 and 6 causing the decreased shielding in the latter.

Anomalous shifts for the quaternary carbons, C-4 and C-10, result because there are no adequate parameters available to describe these changes. Both, however, undergo paramagnetic shifts (7.2 p.p.m. for C-4 and 0.7 p.p.m. for C-10) consistent with the paramagnetic shifts noted for carbons bearing 1,3-diaxial methyl groups (89).

The availability of compounds with differing C-4 axial substituents lends itself to the analysis of substituent effects which can be of value in diterpenoid structure determination (Table 17).

The β-shifts at C-5 show a change on going from an sp^3 carbon substituent to an sp^2 carbon which must reflect

a small distortion at C-5 necessary to accomodate the flattening of the ring A. The γ-effects at C-2 and C-6 are consistent with the latter expected to show accentuated changes with substituent changes at C-4. The consistent paramagnetic shifts of C-10 have been mentioned above and need no further elaboration. The δ-carbon shifts at C-1 and C-7 are difficult to assess and must be attributed primarily to the distortion introduced into the tricyclic structure by the C-4 and C-10 axial substituents.

Aromatic Chemical Shifts

The substituent effects of the methoxyl group on the carbons of the aromatic ring have been used to assign all six carbon resonances and dramatically illustrate the application of substituent effects in simple systems to analysis of analogous carbons in more complex systems. This effect lead to the logical comparison of methyl O-methyl-7-oxopodocarpate 35 with p-methoxy-acetophenone 98 (132) allowance being made for the additional substituent at C-9 (Table 18).

The predicted shifts for 99 were calculated using the methyl shift parameters on going from benzene to toluene and assuming similar changes in 98. It was noted that use of larger alkoxyl groups (for sample 4-methoxy-propiophenone) did not alter the aryl shifts from those given for 98 (133).

TABLE 17 Experimental substituent effects at C-4 axial position in diterpenoid compounds[1]

compound	substituents C-18	C-19	C-4	C-3	C-5	C-2	C-6	C-10	C-1	C-7
51	H	H	0	0	0	0	0	0	0	0
58	CH_3	CH_3	+1.2	+6.6	-1.1	-3.3	-9.4	+1.3	+1.1	+0.4
55	CH_3	CH_2OH	+6.8	+4.2	0	-3.1	-9.0	+0.9	+1.6	+1.2
56	CH_3	CH_2OAC	+5.2	+4.0	0	-3.2	-8.9	+0.9	-1.3	+1.3
57	CH_3	CHO	+16.4	+3.6	+0.4	-3.2	-9.1	+1.3	-3.8	+1.4
33	CH_3	COOH	+11.7	+4.5	+1.4	-2.2	-7.2	+1.7	+0.1	+2.1
34	CH_3	$COOCH_3$	+11.6	+4.2	+1.3	-2.0	-7.5	+1.3	+0.2	+2.4

[1] calculated after subtracting the substituent effects for the equatorial $-CH_3$ at C-4 (89)

TABLE 18 Predicted chemical shifts for 7-oxo diterpenoids

compound	chemical shifts 8	9	11	12	13	14
p-methoxyaceto-phenone 99	129.8	130.1	113.3	163.1	113.3	130.1
2-methyl-4-methoxy-acetophenone 99 (predicted)	130.4	139.2	113.9	162.9	110.2	129.9
compound 35	125.9	157.3	110.4	164.4	112.4	129.9
6-methoxy tetralin 53	129.3	138.2	114.3	158.6	112.3	130.1

The basic chemical shifts of carbons 8,11,12,13 and 14 are reproduced remarkably well for the model 99 and the substrate 35. Moreover, the predicted chemical shifts of 99 show remarkable agreement with the aryl shifts for 6-methoxytetralin 53. So good are the results tha the discrepancy in the shift at C-9 of 18.1 p.p.m. must be accounted for by some other factors. The unusual shift changes at C-9 are exemplified in the conversion of 34 to 35 and of 53 to 52 where attendant deshielding is +7.4 and +8.9 p.p.m., respectively.

Inspection of molecular models failed to reveal the introduction of any geometrical constraints by the inclusion of a carbonyl into the cyclohexane ring. In addition, no other spectroscopic data indicated any unusual character-

istics of the benzylic ketones. Consideration that the orientation of the carbonyl was the critical factor was discounted on p.m.r. evidence. The intense anisotropy of the carbonyl double bond is expected, however, to deshield C-14 in 6-methoxy-1-tetralone (as is H-14) and thus C-14 should exhibit a significant paramagnetic shift while C-9 should show a smaller effect in the same direction. Experimentally, the reverse is true and it is suggested that this situation arises from the diamagnetic effect of the carbonyl oxygen atom.

It has recently become clear that the variation in the diamagnetic shielding term, σ_d, for nuclei other than hydrogen is significant (134), particularly those effects generated by directly bonded atoms. The carbonyl group is highly polarized and has a strong electron-withdrawing effect in both the σ- and π- bonding frameworks. The directly bonded ring carbon, C-8, for example, is deshielded by 8.0 p.p.m. when compared to benzene and the para carbon, C-12, moves downfield by 3.0 p.p.m., but the ortho carbons are virtually unchanged which is a situation suggesting the existence of an additional factor countervailing the inductive effect. The suggested rationale is a through space, diamagnetic effect of the oxygen atom where, in a cyclic molecule such as 52, there should be a differential paramagnetic effect shown by the more distant of the two ortho carbons. A calculation of the σ_d contribution of the oxygen

atoms using (5.2) and internuclear distances of O to C-14 and O to C-9 of 2.80 A and 3.55 A, respectively, gives a difference of +8.3 p.p.m. between carbons 9 and 14.

$$\sigma_{AV}\,(k) = \sigma_{AV}\ \text{(free atom)} + \frac{e^2}{2mc^2}\sum_{\alpha}\frac{Z_\alpha}{r_\alpha} \qquad (5.2)$$

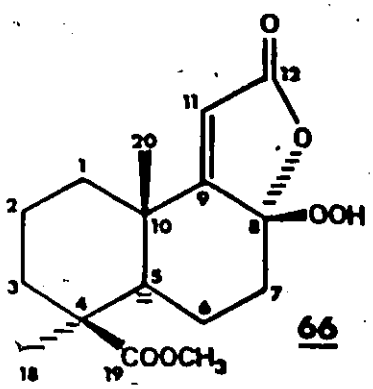
Thus, C-9 is predicted to be deshielded relative to C-14 by 8.3 p.p.m. which is in remarkable agreement with the experimental value of +8.7 p.p.m. for 6-methoxy-1-tetralone. While agreement here may be fortuitous, the results point out a factor which has hitherto been largely disregarded in consideration of upfield shifts of carbon atoms caused by proximate atoms. It is not unreasonable to ascribe a diamagnetic effect of a compressing atom to making a significant contribution to the upfield γ-effect.

6 CARBON-13 NUCLEAR MAGNETIC RESONANCE OF NORDITERPENOID BICYCLIC LACTONES

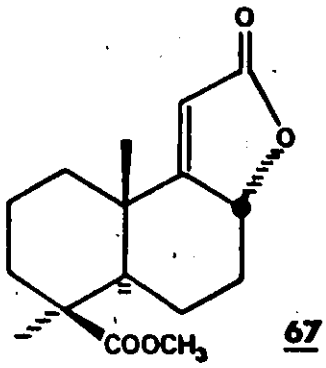
The slow ozonolysis of podocarpic acid 25 or methyl podocarpate 54 in hydroxylic solvents conducted at low temperatures results in the isolation of a variety of crystalline products which depend on the work-up conditions employed (135). Direct isolation, by the careful removal of all solvent and volatile materials, of the crude ozonolysis products of 54 gave a residue, the recrystallization of which gave a pure compound. Spectroscopic and chemical analysis identified the compound as having the structure given by 66. The lack of an NOE between the C-20 methyl and H-11 established the β-configuration of the C-8 hydroperoxide group (68).

When the crude ozonolysis mixture was treated directly with sodium borohydride, the major products were the lactones 67 and 68. On the other hand, oxidation of the ozonolysis mixture with aqueous alkaline hydrogen peroxide gave the lactone acid 69a.

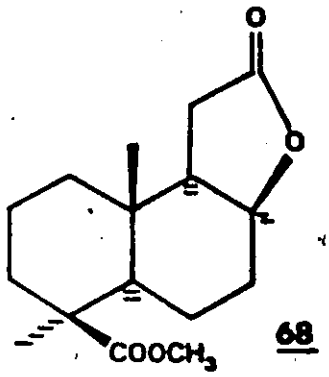
The reduction of 67 using hydrogen over 5% palladium-on-carbon gave the saturated lactone 70 whereas reduction of the same compound using sodium and 2-propanol gave the epimeric lactone 71 (136). In all cases, the NOE experiments established the configurations at the appropriate carbon centres (62,68).



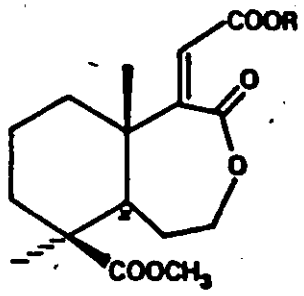
66



67



68

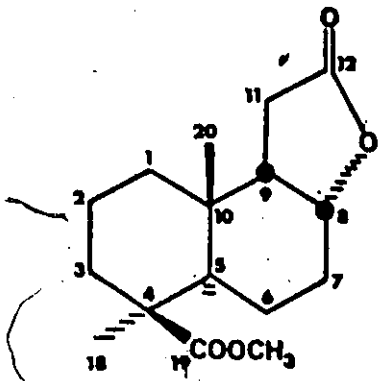


69

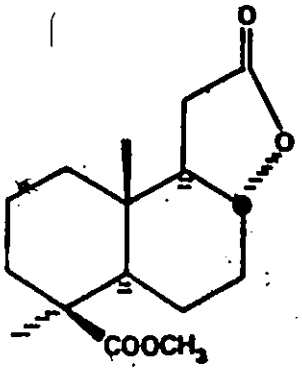
a R = H

b R = CH_3

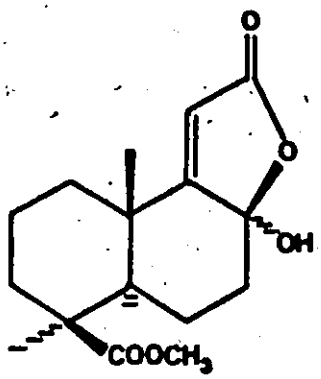
FIGURE 16 Structures of lactones derived from ozonolysis of podocarpic acid



70



71



72

FIGURE 17 Structures of lactones derived from ozonolysis

TABLE 19 Chemical shifts and assignments for carbon-13 spectra of norditerpenoid bicyclic lactones

Carbon	Compound and Chemical Shifts				
	67	68	70	71	72
1	37.0	40.7	38.9	39.8	37.8
2	21.2	18.7	21.2	22.1	20.6
3	38.1	38.1	38.4	38.5	39.2
4	44.4	43.7	43.9	44.1	44.1
5	55.0	53.4	51.2	55.6	55.8
6	19.4	18.4	20.2	19.1	18.7
7	35.4	34.4	36.8	32.0	37.2
8	79.5	79.9	78.5	79.6	105.6
9	172.9	49.2	47.8	57.1	171.3
10	39.8	36.2	36.4	36.9	40.0
11	110.2	28.6	29.3	30.5	112.4
12	176.8	177.4	175.7	174.6	177.2
18	29.2	28.6	28.6	28.6	28.6
19	181.1	177.8	177.1	175.5	177.9
20	18.3	13.8	19.4	12.5	15.6
$COOCH_3$	51.4	51.3	49.7	51.3	51.6

In view of the widespread application of carbon-13 NMR to problems of stereochemistry (76, Chapter 11), it seemed judicious to investigate the chemical shifts of these lactones 68-72 having a variety of configurations.

At the same time the magnitude of the NOE, being a measure of proton internuclear distances, may itself show some correlation with carbon-13 chemical-shifts since steric compression generally results in diamagnetic shifts.

The carbon-13 nuclear magnetic resonance results and assignments are given in Table 19. Assignments were based primarily on chemical shift data (Chapters 3 and 5) although off-resonance decoupling was used to establish the quaternary centres. A number of carbons, having been assigned in the podocarpic acid series, were not expected to change drastically with changes at ring C in this series. For example, the carbon nuclei in ring A (carbons 1,2,3,4, 5, and 18) change only slightly from their general regions shown in Table 8 and these are readily assigned. The ester methoxyl group can be identified by comparison with the podocarpic methyl esters and the carbonyls were readily identified by their extreme low field positions. In the latter case, the lactone carbonyl was assigned the higher field position in view of general pattern recorded elsewhere (76 page 300), although positive identification was impossible and a reverse assignment is equally valid. Of the high field carbon nuclei (C-2,6, and 20), carbon-20 was expected to show the greatest shift changes considering the adjacent conformational changes and, therefore, it was assigned the high field positions. Carbon-6, as expected, remains fairly constant throughout the series.

The predominant changes occur at the remaining

carbons 7,8,9, and 11. Carbon-8 was readily assigned by its low field position either as the hydroxyl part of the lactone (78-80 p.p.m.) or as a hemiacetal (105.6 p.p.m.). Carbon-7 was assigned in compounds 67 and 72 since both 9 and 11 were unsaturated and their peaks disappeared from the aliphatic region leaving only one unassigned absorbance. In addition, this C-7 assignment was consistent with the downfield shift in 72 resulting from the inductive effect of the C-8 hydroxyl group and the expected upfield shift in 70 resulting from increased steric perturbations between the now axial 11-carbon and the C-7α hydrogen atom. Thus 1,3-diaxial relationships on the α-side of the molecule apply to C-5 as well and it has been shielded by about 2 p.p.m. as expected. The remaining two carbons 9 and 11 in compounds 68-71 are then readily identifiable since the highly β-substituted methine would be expected to be highly deshielded and close in value to C-5 ($\simeq$50 p.p.m.) whereas the C-11 methylene should be much farther upfield. Of note is the highly deshielded position of C-9 in 71 the explanation of which is not readily obvious from molecular models.

The data comparing the NOE values between protons on carbons 8 and 20 with their respective carbon-13 chemical shifts is given in Table 20. There is, quite obviously, no apparent correlation between the two parameters. While the C-20 methyl does show its maximum upfield shifts in compound 71 also having the highest NOE value, its high field location

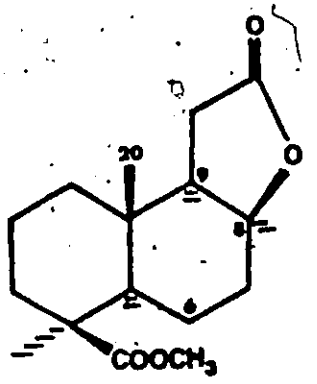
TABLE 20 Comparison of NOE results and chemical shifts for norditerpoid bycyclic lactones

Compound	Irradiated	Observed	NOE	Chemical Shifts C-20	C-8
67	CH_3-20	H-8β	18%	18.3	79.5
	CH_3-20	H-11	0%		
68	CH_3-20	H-8β	0%	13.8	79.9
70	CH_3-20	H-8β	13%	19.4	78.5
71	CH_3-20	H-8β	21%	12.5	79.6

in 68 is coupled with no measurable NOE value at all.

The lack of any correlation between proton NOE values and C^{13} chemical shifts is not in itself surprising. When one views the semi-empirical analysis of those factors affecting nuclear screening (159) one sees a variety of individual factors which are not necessarily independent of one another. Conformational changes in rigid systems, for example, may reduce steric compression by causing nuclei to move away from one another and, yet, on the other hand, the change could also alter the hybridization proximate to the nucleus in question. Since each of these factors, can independently, change dramatically the chemical shift of a given nucleus, there is no way of identifying their individual contributions to the shielding of a given nucleus when they are both operative. It is, therefore, impossible to relate the C^{13} chemical shift values for C-8 and C-20 with the NOE values between these two

nuclei because the 1,3,-diaxial relationship between the H-6β substituent and the C-10β methyl (C-20) is only one contributor to any shift changes of C-20. A good example of the contervailing factors from the lactones in Table 20 is 68. Formation of the C-8β, 9β cyclopentanolide ring is attendant with distortion in ring B necessary to accomodate the five number ring. The result is to increase the eclipsing of the two aforementioned bond positions which, in effect, causes the C-8β hydrogen atom to move outward and, therefore, decrease its steric interaction with C-20. However, molecular models indicate that with this adjustment of bond angles at carbons 8 and 9, the H-6β ~~atom~~ is forced inward toward C-20 and, consequently, increases the steric interactions between the two. These two effects are themselves countervalent and the NOE values of H-8 atoms cannot measure the contribution of one to the exclusion of the other.



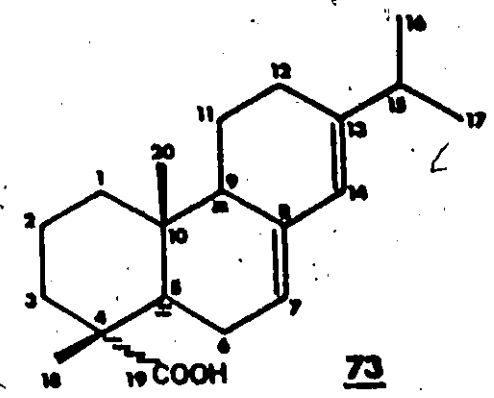
68

7. CARBON-13 NUCLEAR MAGNETIC RESONANCE OF ABIETIC ACID AND RELATED DITERPENOIDS

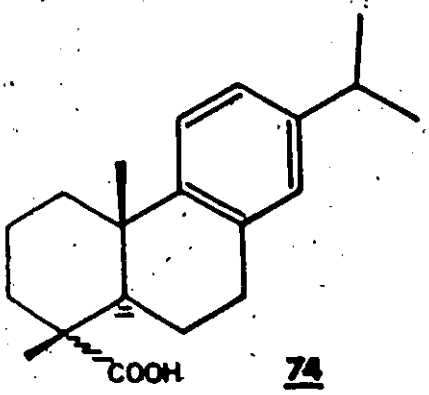
Abietic acid 73 is the isomerization product of a number of labile natural precursors, among them pimaric acid 77 and neoabietic acid 79, of which, the latter two compounds are major constituents of most pine rosins. Interest in these compounds, and in those listed in Table 22, results from their tricarbocyclic structure with suitable functionalization to make them useful starting materials in synthetic chemistry. For many years, interest was focussed on unequivocal establishment of the C-4 configuration which has been shown to be the opposite to that of podocarpic acid (128, pages 192-197).

Initial assignments were made by comparison of the spectra of compounds 51 and 74 taking into account the required substituent effects (Table 4) in addition to off-resonance experiments to establish the quaternary centres.

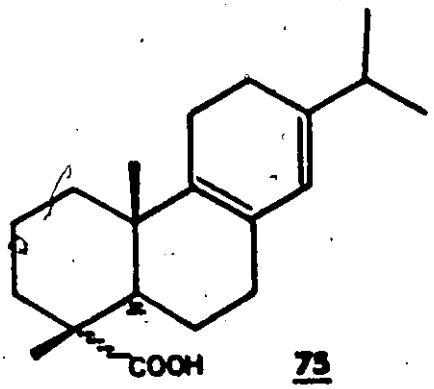
The results shown in Table 21 indicate a good correlation between predicted chemical shifts and experimental shifts using the parameters of Dalling and Grant and those developed for the podocarpic acid series. Estimates for the inductive effect for the carboxyl group on C-4 and the 1,3-interactions with C-6 are given in the table. The differentiation between the C-19,20 methyl groups was based on the effect of the equatorial C-4 carboxyl group. The



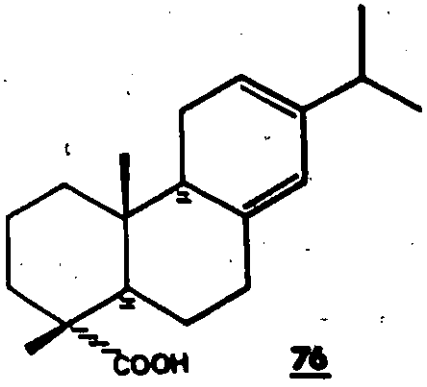
73



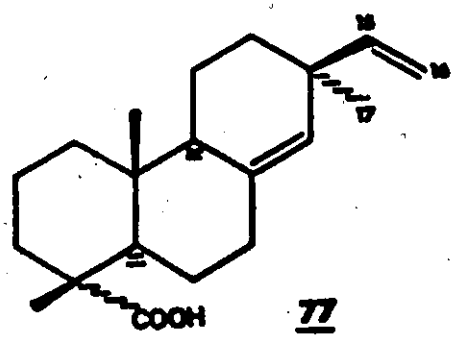
74



75

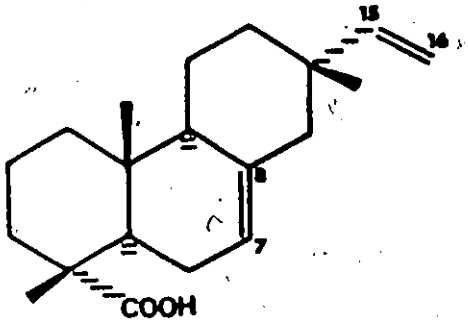


76

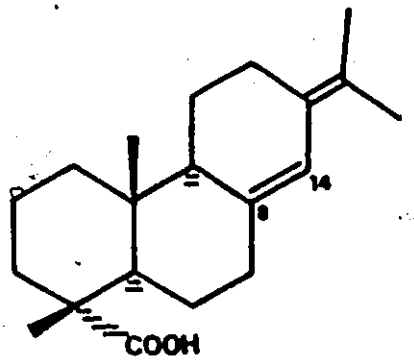


77

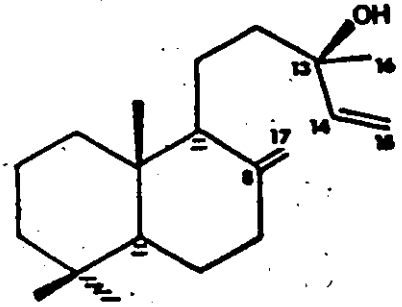
FIGURE 18 Structure of abietic acid 73 and related diterpenoids



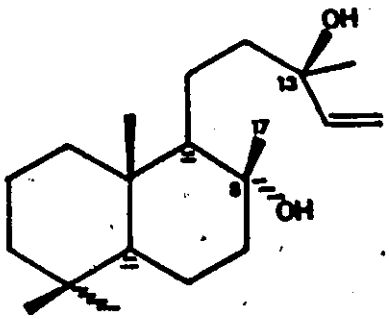
78



79



80



81

FIGURE 19 Structures of diterpenoids

aromatic substituent effects for the methoxyl group (125) and the 2-propyl group have been used to assign the aromatic peaks with reasonable success. Unequivocal assignments for carbons 9 and 13 was not possible, however, from these results.

It is not anticipated that there will be significant changes in the shifts of carbons 1-8,10,18,19, and 20 in the group of compounds 73-79 aside from C-7 in abietic acid 73 itself. Comparison with podocarpic acid 25 (Table 8) indicates a strong correlation between the chemical shifts of corresponding carbons aside from the large upfield shifts of carbons 19 and 20 anticipated from the increased steric bulk of the sp^3 methyl group over the sp^2 carbonyl in the C-4 axial position. On this basis, carbons 19 and 20 were assigned the high field resonances in all compounds in the series.

The low field aliphatic region 44-52 p.p.m. contained two resonances, identified in the podocarpic acid series as being carbons 4 and 5 in addition a third resonance peak which, because of its extensive degree of substitution, both directly and beta to it, has been assigned to C-9. The low field position of C-9, relative to C-8, even as an sp^2 carbon is maintained based on similar substitution arguments.

In the high field region of the spectrum, 12-22 p.p.m., the following carbons are intuitively expected to be contained: carbons 2,6,11,19, and 20. Since all but

TABLE 21: Chemical shifts and assignments of aliphatic C^{13} spectra of 74 using model compound 51

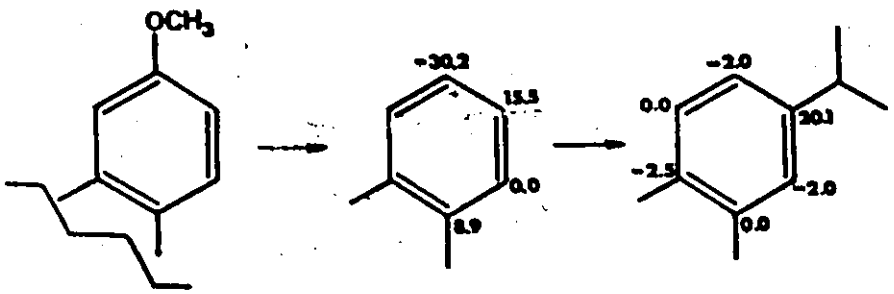
Compound and substituents	Carbons 1	2	3	4	5	6	7	10	19	20	CH_3
	38.2	22.8	26.4	26.8	42.8	28.9	29.6	37.4	-	21.7	55.0
51											
C-4 axial CH_3	-0.1	-5.4	+5.2	+ .1	+5.2	-5.4	-0.1	-5.4	-	0.0	-
C-4 equat. CH_3	-0.3	0.0	+8.9	+5.6	+8.9	0.0	-0.3	0.0	-	-0.3	-
				+12[a]		-6[b]					
Predicted chemical shifts for aliphatic carbons of 74	37.8	17.4	40.5	45.5	56.9	17.5	29.2	32.0	-	21.4	55.0
Experimental shifts	36.8	17.0	43.9	46.5	-	14.8	28.6	35.8	22.5	20.3	
Compound 33	38.0	20.6	39.8	44.1	53.1	21.7	31.4	39.1	28.9[c]	23.4	

a) Estimated correction for inductive effect of carboxyl group relative to methyl group from Table 8. b) Estimated effect of C-18α carboxyl group c) shift for C-18

TABLE 22. Chemical shifts and assignments for C^{13} spectra of abietic acid and related diterpenoids

	Carbons																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
73	36.0	16.8	37.2	45.1	43.8	26.1	123.0	145.5	50.0	33.2	20.3	-	136.1	121.0	33.5	24.5	24.5	186.4	15.3	12.6
74	36.8	17.0	43.9	46.5	-	14.8	28.6	135.5	146.8	35.8	124.5	124.5	148.1	127.5	32.1	23.6	23.6	184.9	22.5	20.3
75	35.8	19.4	34.3	46.4	45.1	20.4	28.9	137.7	143.7	36.0	20.1	20.0	125.2	120.6	33.1	21.2	25.0	185.1	17.0	14.9
76	35.8	16.4	35.5	46.3	48.2	24.6	34.3	139.5	48.6	37.9	-	119.7	140.0	115.1	31.7	24.6	24.6	186.8	14.7	12.3
77	36.2	16.9	--	46.2	48.1	23.6	34.3	138.8	50.7	37.4	17.8	34.6	36.8	128.8	148.4	112.5	28.1	186.0	15.7	13.7
78	37.9	16.8	36.1	45.3	--	20.4	35.2	136.4	51.3	34.0	18.9	35.2	35.7	121.7	151.5	109.5	23.7	185.5	16.0	13.8
79	36.2	17.0	37.6	46.4	47.9	19.0	24.7	138.9	50.8	36.8	18.4	34.5	126.1	122.4	133.4	23.8	21.3	184.9	15.7	14.0
80	40.6	16.6	41.3	32.5	56.8	13.2	37.4	146.4	45.0	38.9	18.2	38.2	73.0	149.7	111.6	23.3	106.6	-	20.5	26.7
81	41.0	17.1	43.2	31.9	55.4	14.0	44.0	74.1	61.1	38.2	17.7	38.6	72.9	147.4	111.0	22.8	20.1	32.2	19.1	25.4

TABLE 23 Chemical shifts and assignments of aromatic carbons in compound 74 using model compounds



51 74

Aromatic Carbon-13 Shifts

Carbon	51	74 predicted	74 experimental
8	130.2	139.1	135.5
9	149.6	147.1	146.8
11	110.7	126.2	124.5
12	158.5	126.3	124.5
13	111.5	147.1	148.1
14	130.2	128.2	127.5

C-11 are known, assignment of the peaks in the region of 17.8-20.3 p.p.m. in the series to carbon 11 is complete.

The remaining carbons, in ring C and the side chain, were assigned from shift differences expected for olefinic carbons in different environments as well as from expected chemical shift changes with variance in substitution. Carbon 12, for example, is expected to be at lower field in 78 being adjacent to a tertiary centre than in 75 where the cyclohexadiene system tends to strongly shield the remaining sp^3 carbons.

In the olefinic region, quaternary centres were readily identified leaving assignments at other centres subject to substitution considerations.

Assignments for manoöl 80 and sclareol 81 were initially made by comparison of the latter with trans-decalin taking into account the various substitutions on the ring. The chain at C-9 equatorial was assumed to have interactions similar to those of a methyl group. Coupled with off-resonance experiments, agreement between predicted and experimental shifts is good with the exception, as usual, of the C-5 ring junction.

After assignments of the sp^2 carbons on the C-9 side chain and the quaternary centre at C-13, only four resonances remained unassigned : 17.7,20.1,22.8, and 38.6 p.p.m. In consideration of steric perturbations with C-1 hydrogens, the high field peak must be C-11. The two methyl groups

TABLE 24: Chemical shifts and assignments for C^{13} spectra of sclareol 81

Model and substituents	Carbons												
	1	2	3	4	5	6	7	8	9	10	18	19	20
	35.5	28.0	28.0	35.5	44.9	35.5	28.0	28.0	35.5	44.9			
trans-decalin													
+ C-10 axial CH_3	+5.2	-5.4	-0.1	-5.4	+8.9	-5.4			+8.9				
+ C-4 axial CH_3	-0.1	-5.4	+5.2	+1.1	+8.9	-5.4				-5.4			
+ C-4 equat. CH_3	-0.3	0.0	+8.9	+5.6	+5.2	-5.4[a]							
gem $(CH_3)_2$				-3.4									
+ C-8 axial CH_3						-5.4	+5.2		+8.9	-5.4			
+ C-9 equat. CH_3									+5.6	+8.9			
+ alpha-hydroxyl							+10[b]		+10[b]				
Predicted shifts for Sclareol 81	40.6	17.2	42.0	34.4	67.9	13.9	43.2	-	68.9	43.0	33[c]	22[c]	25[c]
Experimental values	41.0	17.1	43.2	31.9	55.4	14.0	44.0	74.1	61.1	38.2	32.2	19.1	25.4

a) 1,3-diaxial interaction between two ring positions b) estimates for hydroxyl inductive effect

c) estimated values from analogous podocarpic acid compound

must be at 20.1 and 22.8 and although definitive assignment is impossible, the C-17 methyl was expected to be at higher field because of its axial conformation. The remaining absorbance at 38.6 p.p.m. is then due to C-12.

While this work was in prgress, the carbon-13 NMR spectral data of a variety of pimaradienic substances was reported by Wenkert (67). The compounds reported included two of those which are given in Table 22, specifically compounds 77 and 78 which are pimaric acid and sandaracopimaric acid, respectively.

8. CARBON-13 NUCLEAR MAGNETIC RESONANCE OF LABDANE INTERMEDIATES

Intermediates from the synthesis of labdane diterpenoids (60) provided an interesting series of related compounds upon which the applicability of our substituent effects (Chapter 6) and other appropriate effects could be tested. The structures of the compounds analyzed are given in Figures 20 and 21 along with the carbon-13 NMR data in Table 25.

Assignments of several absorbances were facilitated by comparison with analogous carbons in the podocarpic acid series. The C-19 ester carbonyl absorptions, for example, were in the range 175.2-177.6 p.p.m. and the ester methyl group appeared in the region of 54-56 p.p.m. In addition the low field position of C-5 (about 51 p.p.m. in the podocarpic acid series) was maintained throughout the labdane-type compound series as was the C-18 equatorial methyl group as 28-29 p.p.m. Recourse to off-resonance decoupling experiments readily established the quaternary centres C-4 and C-10 with the former assigned to the low field position.

The remaining resonances of the bicyclic ring carbons in compounds 83-87 can readily be identified by the application of appropriate substituent effects to *trans*-decalin, the peaks of which have been assigned by Lippmaa

TABLE 25 Chemical shifts and assignments for carbon-13 spectra of labdane-type intermediates

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	CH_3 (19-ester)	CH_3	18	19	20
83	38.3	20.0	39.5	44.5	51.2	25.3	42.3	207.7	59.2	42.0	27.7	171.8	-	-	54.8	51.3	28.7	175.2	13.5
84	38.1	19.8	39.3	44.0	51.1	25.1	41.9	210.0	59.1	42.2	27.2	177.2			54.7		28.6	175.3	13.5
85	38.4	20.0	39.1	44.6	51.2	25.9	30.7	149.2	50.9	39.7	26.5	171.8	106.7	-	56.3	52.4	28.5	177.1	12.6
86	39.7	20.3	39.9	44.4	51.0	26.0	38.2	148.5	50.5	39.7	38.4	201.8	108.0	-	56.2	-	28.8	177.0	13.2
87	38.9	20.4	39.4	44.5	52.4	22.5	38.2	148.8	51.0	40.2	28.9	61.8	118.8	-	56.7	-	28.9	177.0	13.0
88	38.2	19.9	39.2	44.3	51.0	26.0	31.7	162.9	50.6	41.6	29.9	177.9	111.9	167.6	56.2	54.3	28.4	177.9	12.7
89	38.1	19.5	38.5	44.0	50.8	22.6	31.3	46.4	48.0	38.1	33.8	173.7	175.7	-	55.3	51.0 51.1	28.5	177.5	12.3
90	38.1	19.3	38.5	46.4	51.3	22.6	31.0	47.7	51.6	38.5	34.2	179.4	176.0	-	55.3	51.6	28.8	177.6	12.4
91	36.9	19.8	37.9	44.5	51.0	23.3	34.6	35.5	174.2	41.1	121.2	197.1	35.7	29.5	54.5	-	28.4	177.2	19.7
92	38.1	19.4	38.5	43.9	51.0	25.2	36.0	138.3	53.2	40.4	36.0	210.7	38.5	116.3	55.5	-	28.6	177.3	12.8
93	37.0	19.3	38.2	43.9	51.0	23.6	34.7	32.7	52.9	38.2	112.6	146.7	135.4	122.4	55.2	20.8	28.5	177.2	14.8

TABLE 26: Chemical shifts and assignments using substituent effects for compound 83

Compound and substituents	Chemical shifts and substituent effects									
	1	2	3	4	5	6	7	8	9	10
trans-decalin	35.5	28.0	28.0	35.5	44.9	35.5	28.0	28.0	35.5	44.9
C-4 equat. CH_3	-0.3	0.0	+8.9	+5.6	+8.9	0.0	0.0	0.0	0.0	0.0
C-4 axial $COOCH_3$	+0.2	-2.0	+4.2	+11.6	+1.3	-7.5	+2.4	0.0	0.0	+1.3
C-10 axial CH_3	+5.2	-5.4	-0.1	-5.4	+5.2	-5.4	-0.1	-5.4	+5.2	+1.1
C-8 oxo group	0.0	0.0	0.0	0.0	-3.6	-0.9	13.0	+181.0	13.0	-0.9
C-9 equat. CH_3	0.0	0.0	0.0	0.0	0.0	-0.3	0.0	+8.9	+5.6	+8.9
predicted shift in 83	40.6	20.6	41.1	47.3	56.7	21.4	43.3	212.4	59.3	55.3
actual shifts in 83	38.3	20.0	39.5	44.5	51.2	25.3	42.3	207.7	59.2	42.0

and Pehk (137). The predicted chemical shifts of compound 83 along with the experimental shifts are given in Table 26 and show a remarkable correlation in spite of the fact that the C-4 carbomethoxy group substituent effect was determined in ring C-aromatic diterpenoids. Noticeable exceptions are carbons 1 and 6 along with the carbons at the ring junction, C-5 and C-10. Discrepancies between predicted and experimental shifts in the latter two carbons are consistent with the unusual diamagnetic shieldings of the bridgehead carbons in adamantane (127). In view of the arguments in Chapter 6, these discrepancies can be attributed to a rehybridization at C-5 as well as what is apparently an accentuated γ-effect in rigid carbon skeletons.

The diamagnetic C-1 shift is probably related to the interactions with the hydrogens of the C-11 methylene as well as to the essentially 1,3-diaxial interaction between the H-1 equatorial atom and the equatorial C-9, 11 bond. The effects on carbon-6, however, are qualitatively, more difficult to assess. Comparison of cyclohexene going to cyclohexane would predict the C-6, on going from a $\Delta^{8,9}$ system, albeit aromatic in 34, to the saturated system would be deshielded by about 4 p.p.m. Countervalent to this paramagnetic effect is the resulting interaction between the C-18 equatorial methyl group and the C-6 equatorial hydrogen atom upon ring B assuming a cyclohexane chair structure. The latter effect would, however, be reduced by the outward distortion and downward movement of

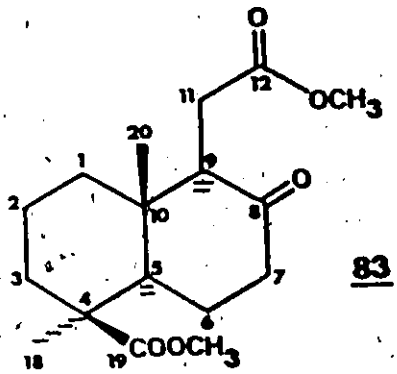
C-19 and C-18, respectively, as mentioned previously in O-methyl podocarpinol (page 92) and, therefore, the deshielding effect is expected to predominate resulting in the +3.9 p.p.m. discrepancy.

The remaining carbons 11 and 20 were then assigned readily since the latter, subject to a multitude of steric interactions, including those hydrogens at C-11, would be expected to resonate at high field. The resonance position assigned to C-11 (27.7) is in the region of analogous α-methylene absorptions from the analysis of a series of methyl esters (138).

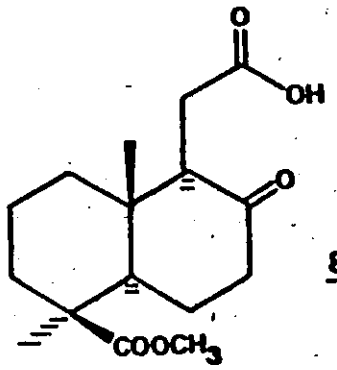
The exocylic methylene in compounds 85-87 and the various oxidation levels of C-12 expectedly change only the proximate carbon resonance positions. Carbon 1-6,18,20, and 10 maintain their general resonance positions established in compound 83. Carbons 8 and 9 are identified by their extremely deshielded positions with C-8 having the low field position based on its degree of substitution and its quaternary nature. Carbon 12 is identified by the typical ranges of ester and aldehyde carbonyls and the carbinol carbon. The carbons adjacent to C-8 are identified by their definite upfield shifts on going from the ketone function to the exocyclic methylene at carbon 8 leaving the remaining aliphatic carbon as C-11.

In compounds 88-90, only molecular changes at C-8 occur and, therefore, resonances in the ring carbons and the

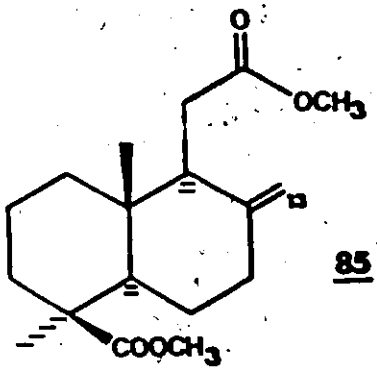
FIGURE 20 Structures of labdane intermediates



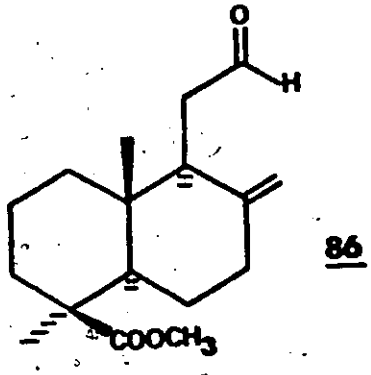
83



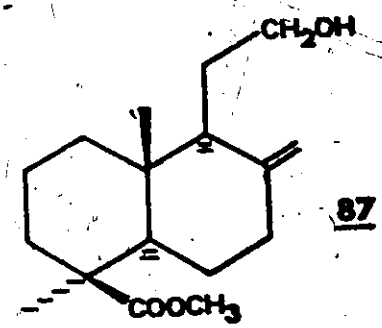
84



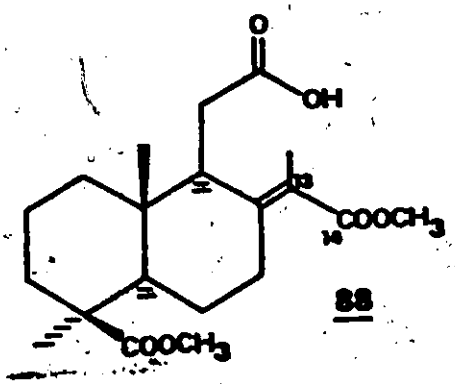
85



86

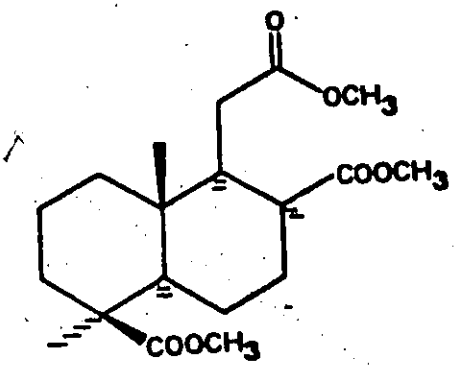


87

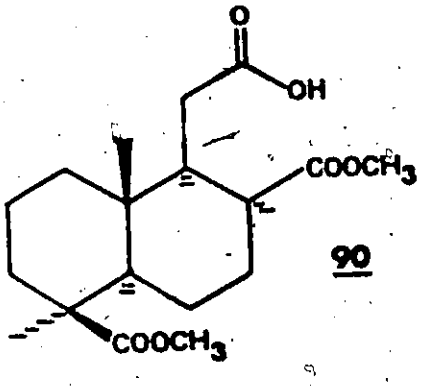


88

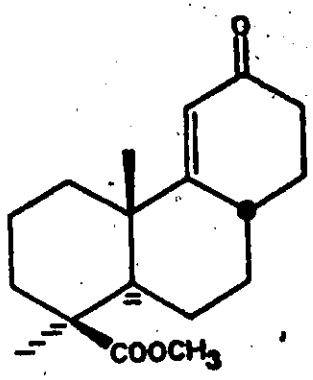
FIGURE 21 Structures of labdane intermediates



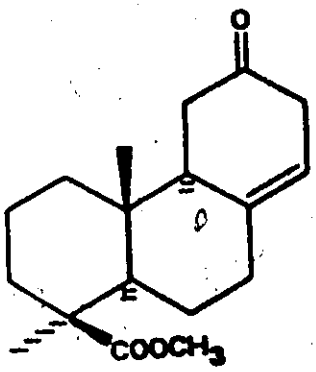
89



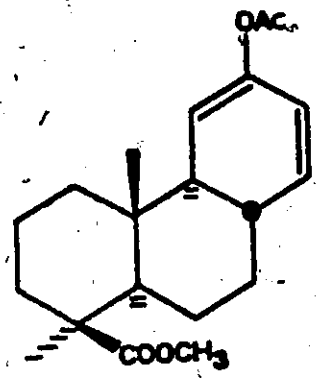
90



91



92



93

C-11β chain are expected to be small. Comparison of 89 with 85 establishes all resonances except for carbons 8,9, and 11. Carbons 8 and 9 are expected at low field due to their degree of substitution with carbon 9 given the lower assignment because of the proximity to the quaternary centre at C-10. The remaining peak at 33.8 must be attributed to C-11, its low field position probably a result of decreased steric interactions between the freely rotating C-8 carbomethoxy group in 89 and 90, and C-11, in comparison to the 8,17-double bond of 88.

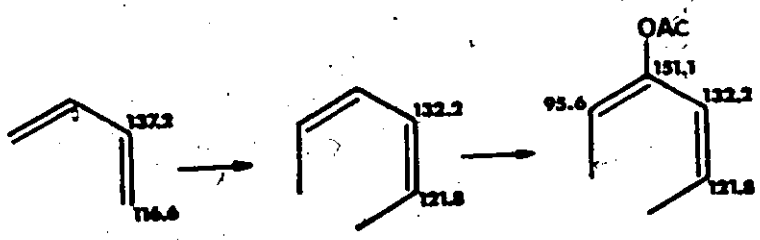
In the tricyclic diterpenoids represented by structures 91-93, all carbon resonances can be assigned by comparison with others in the series except for those carbons directly involved in ring C, carbons 8,9,11,12,13, and 14. In 91, carbons 9 and 11 are readily assigned, being the only sp^2 non-oxygenated carbons, with the β-carbon (C-9) having the characteristically deshielded position relative to C-11. This leaves four peaks unaccounted for; 8,12,13, and 14. The carbonyl is at 197.1 p.p.m. and readily identified while the C-8 methine and the C-13 methylene are expected to be the low field peaks of the remaining absorbances at 35.5,35.7, and 29.5 p.p.m. leaving the latter as the C-14 absorbance.

The isomeric unsaturated ketone 92 shows predictable changes from 91. Carbons 8,12, and 14 are assigned immediately based on previous arguments. Carbon 13 now

being α to a double bond instead of β to it, is expected to move downfield by roughly 2 p.p.m. from its position of 35.7 p.p.m. in 91 and is assigned to 38.5 p.p.m. The latter two peaks at 36.0 and 53.2 p.p.m. can be assigned to carbons 11 and 9, respectively, since steric interactions between the C-11, 1-methylenes would expectedly shield C-11 whereas extensive substitution adjacent to C-9 would expectedly deshield it.

The enol-acetate 93 shows only two aliphatic carbons that cannot be assigned by comparison with other compounds in the series at 32.7 and 52.9 p.p.m. Once again, adjacent substitution dictates the latter to be C-9 leaving the former to be assigned to C-8.

Analysis of the sp^2 carbons was somewhat less than definitive. The inclination was to initially assign C-12 the low field position based on substitution of the acetoxy group. Recourse to the substitution of 1,3,-butadiene by terminal methyl groups to give 2,4-hexadiene gives predicted shifts shown below using methyl substituent effects of



Friedel and Retcofsky (139). On the assumption that an acetate at C-12 would show a trend similar to that shown on going from ethylene to vinylacetate (140) (α +18.9, β -26.2 p.p.m.) the crude predicted shifts of the olefinic carbons in 93 are given. A beta effect through the sigma bond is expected to lower further the C-13 predicted resonance but, beyond that, any other effects are insignificant. The results, however crude, allow the assignment of those olefinic carbons directly involved in the acetate substitution and a probable distinction between carbons 13 and 14.

9. EXPERIMENTAL

Apparatus, Methods, and Materials

All melting points were determined on a Kofler micro hot-stage apparatus and are uncorrected.

Infrared spectra were obtained on Beckmann IR-5 and IR-8 infrared spectrophotometers in chloroform solutions, as nujol mulls, or as potassium bromide discs.

Proton magnetic resonance (pmr) spectra were recorded on Varian Associates HA-100, T-60, and A-60 spectrometers and in deuterochloroform solution unless otherwise stated. In all cases, tetramethylsilane (TMS) was used as internal reference. Standard symbols in the recording of spectra were used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

Carbon-13 spectra were recorded on a Varian Associates HA-100 spectrometer at 23.5 kG and 25.1 MHz. Field/frequency stabilization was achieved by use of an external (1.5 mm capillary) $^{13}CS_2$ lock. A sample volume of 0.3-0.5 ml was used in a 5 mm o.d. sample tube using a 1:1 mixture of dioxane and chloroform as solvent. The operating probe temperature was +55° C. Chemical shifts were related to internal dioxane and benzene and reported to internal tetramethylsilane (TMS). Normally a signal accumulation of 50-200 scans with a Varian Associates C-1024 time averaging computer was necessary for adequate signal-to-noise

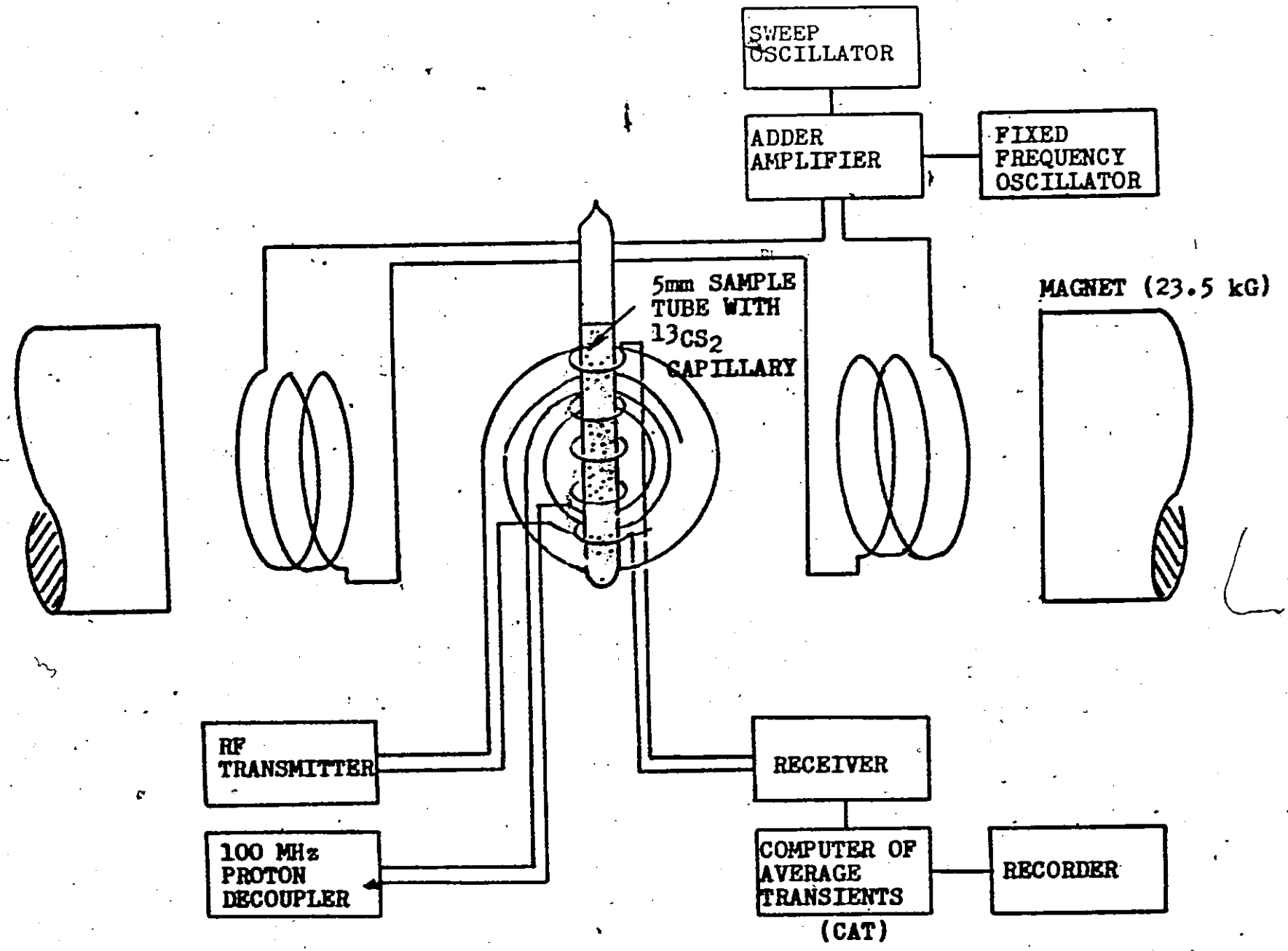


FIGURE 22 Varian HA-100 NMR system adapted to C-13 NMR capabilities

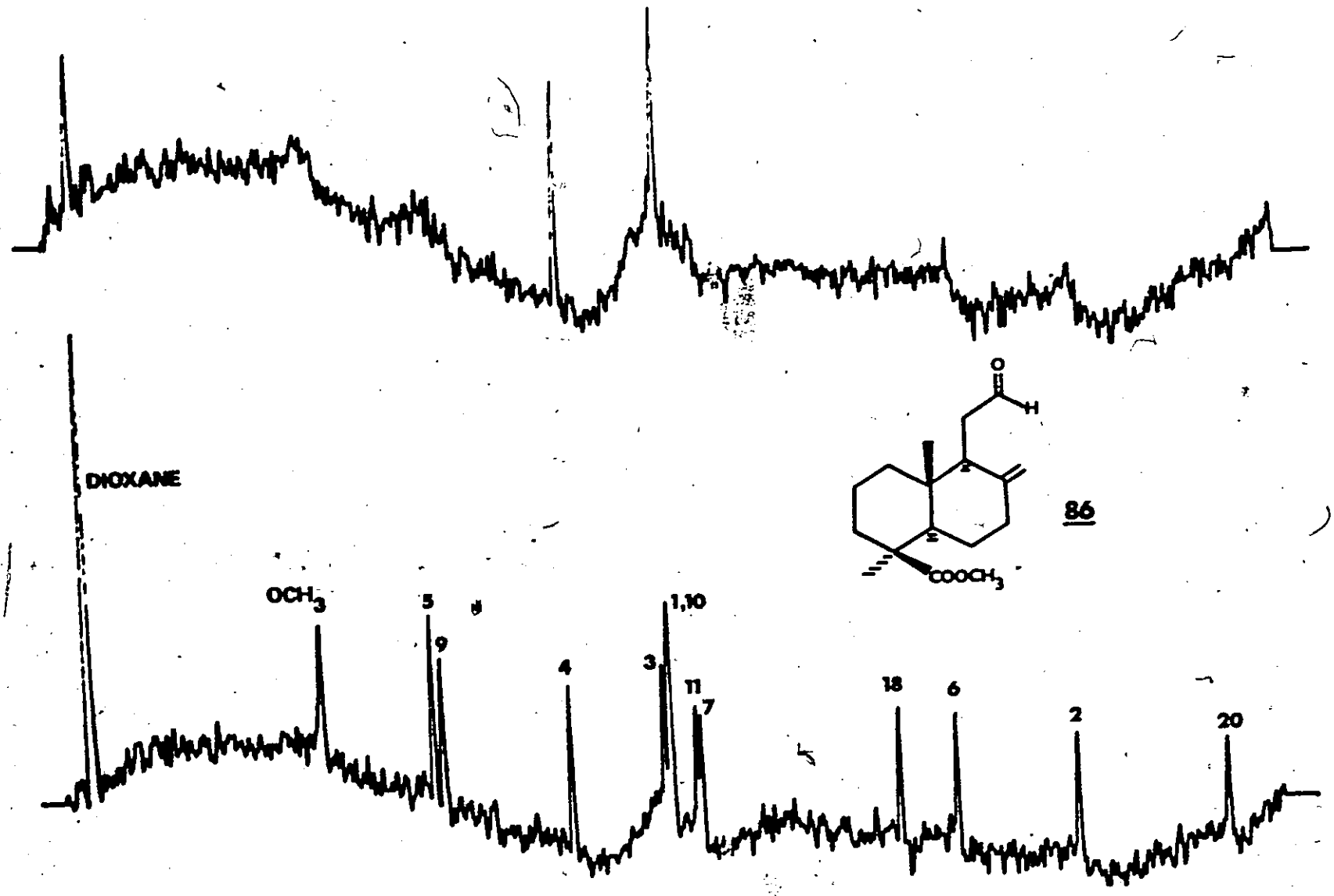


FIGURE 23 Spectrum of compound 86 using HA-100 CW mode system

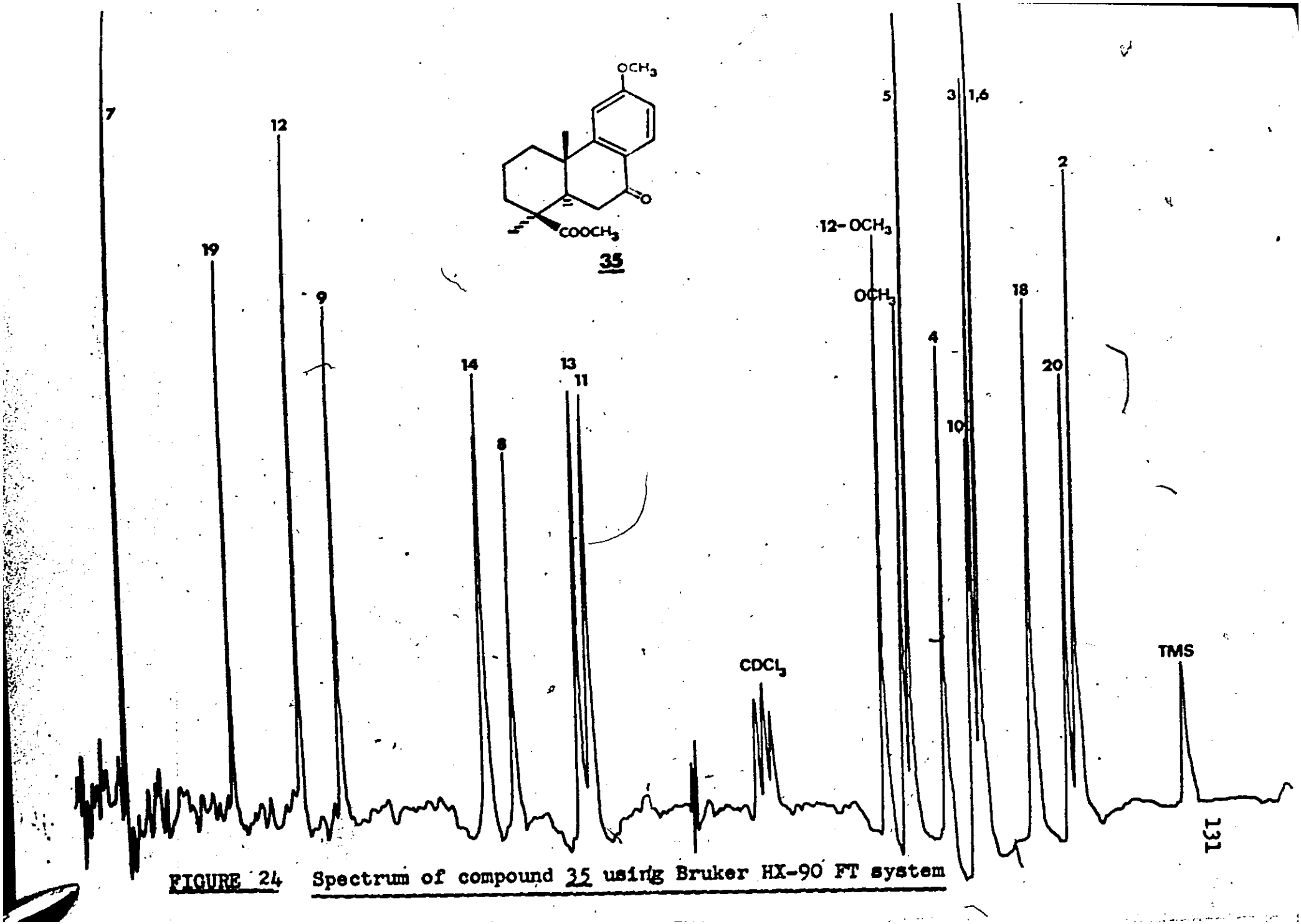


FIGURE 24 Spectrum of compound 35 using Bruker HX-90 FT system

enhancement. Proton decoupling was carried out using a Varian Associates V-3512-1 noise decoupler (Figures 22 and 23).

Fourier analysis was carried out on a Bruker HX-90 spectrometer operating at 22.63 MHz using a Nicolet 1083 instrument computer. Protons were decoupled at 90 MHz. Samples were contained in 10 mm sample tubes with pulse deuterium lock on the solvent $CDCl_3$ containing a few drops of tetramethylsilane (TMS) as internal reference. The probe temperature was +37°C (Figure 24).

Ultraviolet spectra were obtained in 95% ethanol solution using a Pye-Unicam SP-8000 spectrophotometer.

The phrase ".... worked-up in the usual manner ..." refers to the isolation of the organic substrates using an appropriate solvent (2x) followed by washing of the combined organic extracts with water, saturated brine, followed by drying over anhydrous sodium sulfate. The solvent was removed on a Büchi-Rotavapor 'R'-rotary evaporator using a water bath at 40-70° C.

Numerous methylations were carried out using diazomethane. The procedure of T.J. de Boer and H.J. Backer (144) was used, utilizing Diazald (N-methyl-N-nitroso-p-toluenesulphonamide).

Deuteration of keto compounds was carried out by the following general method; the compound (0.5 g) was dissolved in 5 ml of dioxane, and 4 ml of deuterium oxide and 0.100 g of sodium methylate added. The solution was

stirred at room temperature for 12-16 h, refluxed for 0.5 h, and poured into 10 ml of aqueous sodium dihydrogen phosphate. The product was extracted with diethyl ether and worked-up in the usual manner. The residue was recrystallized from a suitable solvent.

The compounds listed below were made available by other sources (references to structure proof are given where pertinent).

25 Podocarpic acid; New Zealand Timber Products Limited, P.O. Box 5748, Auckland, New Zealand.

28 Methyl 3-oxo-O-methylpodocarpate; R.A. Bell and E.N.C. Osakwe (48).

49 6-Methoxy-2-Oxohexahydrophenanthrene; Aldrich Chemicals Limited.

52 6-Methyoxy-1-tetralone; Eastman Kodak Limited.

60 1,2,3,4-Tetrahydronaphthalene (tetralin); Eastman Kodak Limited.

61 2-Oxohexahydrophenanthrene; Aldrich Chemicals Limited.

63 Methyl ether of methyl 13-isopropoxy-O-methylpodocarpate; R.A. Bell and P.K. Oomman (64).

65 Methyl 3-oxo-$\Delta^{5,6}$-O-methylpodocarpate; R.A. Bell and E.N.C. Osakwe (48).

67 8α-Hydroxy-(13→17)-pentanorlabd-9(11)-ene-12, 19-dioic acid 19-methyl ester 8 → 12-lactone; R.A.Bell and M.B.Gravestock (135).

68 8β-Hydroxy-(13→17)-pentanorlabdan-12,19-dioic acid 19-methyl ester 8→12-lactone; R.A.Bell and M.B.Gravestock (135).

70 8α-Hydroxy-(13→17)-pentanor-9-labdan-12,19-dioic acid 19-methyl ester 8→12-lactone; R.A.Bell and V.Taguchi (83).

71 8α-Hydroxy-13→17)-pentanor-9-labdan-12,19-dioic acid 19-methyl ester 8→12-lactone; R.A.Bell and V. Taguchi (83).

72 8,8-Dihydroxy-(13→17)-pentanorlabd-9 (11)-ene 12,19-dioic acid 19-methyl ester 8→12-lactone; R.A.Bell and M.B.Gravestock (60).

73 Abietic acid.

74 Dehydroabietic acid.

75 Palustric acid.

76 Levopimaric acid.

77 Pimaric acid.

78 Sandaracopimaric acid.

79 Neoabietic acid.

80 Manool.

81 Sclareol.

Compounds 73-81 were supplied by Professeur M. Fētizon, Laboratoire de Stēréochimie, Faculté des Sciences d'Orsay, Université de Paris.

83 Dimethyl 8-Oxo-(13→17)-pentanorlabdan-12,19-dioate; R.A.Bell and M.B.Gravestock (60).

84 8-Oxo(13→17)-pentanorlabdan-12,19-dioic acid 19-methyl ester; R.A.Bell and M.B.Gravestock (135).

85 Dimethyl (13→16)-Tetranorlabd-8(17)-ene-12,19-dioate; R.A.Bell, M.B.Gravestock, and V.Y. Taguchi (54).

86 Methyl 12-Oxo-(13→16)-tetranorlabd-8(17)-en-19-oate; R.A.Bell, M.B.Gravestock, and V.Y. Taguchi (54).

87 Methyl 12-Hydroxy-(13→16)-tetranorlabd-8(17)-en-19-oate; R.A.Bell, M.B.Gravestock, and V.Y. Taguchi (54).

88 17-Carbomethoxy-(13→16)-tetranorlabd-8(17)E-ene-12,19-dioic acid; R.A.Bell, M.B.Gravestock, and V.Y. Taguchi (54).

89 Trimethyl (13→16)-Tetranor-8 -labda-12,17,19-trioate; R.A.Bell and M.B.Gravestock (60).

90 (13→16)-Tetranor-8 -labda-12,17,19-trioic acid 17,19-dimethyl ester; R.A.Bell and M.B.Gravestock (160).

91 Methyl 12-OxOpodocarp-9(11)-en-19-oate; R.A.Bell and M.B.Gravestock (135).

92 Methyl 12-Oxopodocarp-8(14)-en-19-oate; R.A.Bell and M.B.Gravestock (53).

93 Methyl 12-Acetoxypodocarp-11(12),13(14)-diene -19-oate; R.A.Bell and M.B.Gravestock (60).

96 Methyl 13-Acetyl-O-methylpodocarpte; R.A.Bell P.K. Oomman (14).

Mass spectra were determined on a Hitachi-Perkin-Elmer RMU-6A spectrometer. High resolution mass spectra were recorded on a C.E.C. 21-110 high resolution mass spectrometer by Mister F.A. Ramelan.

FIGURE 25 Praeseodynium induced shifts for O-methylpodocarpinol (17-31 p.p.m. region)

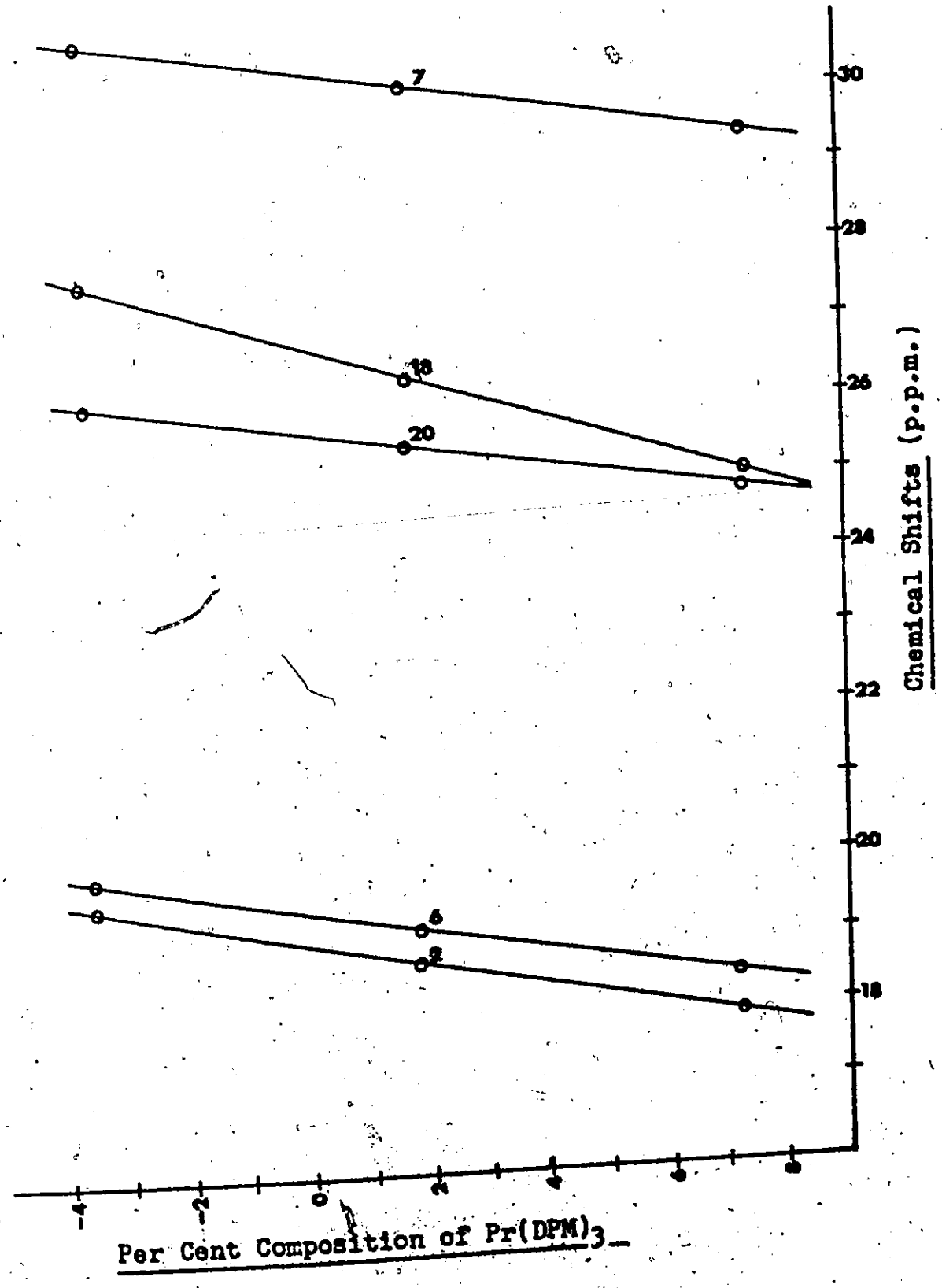
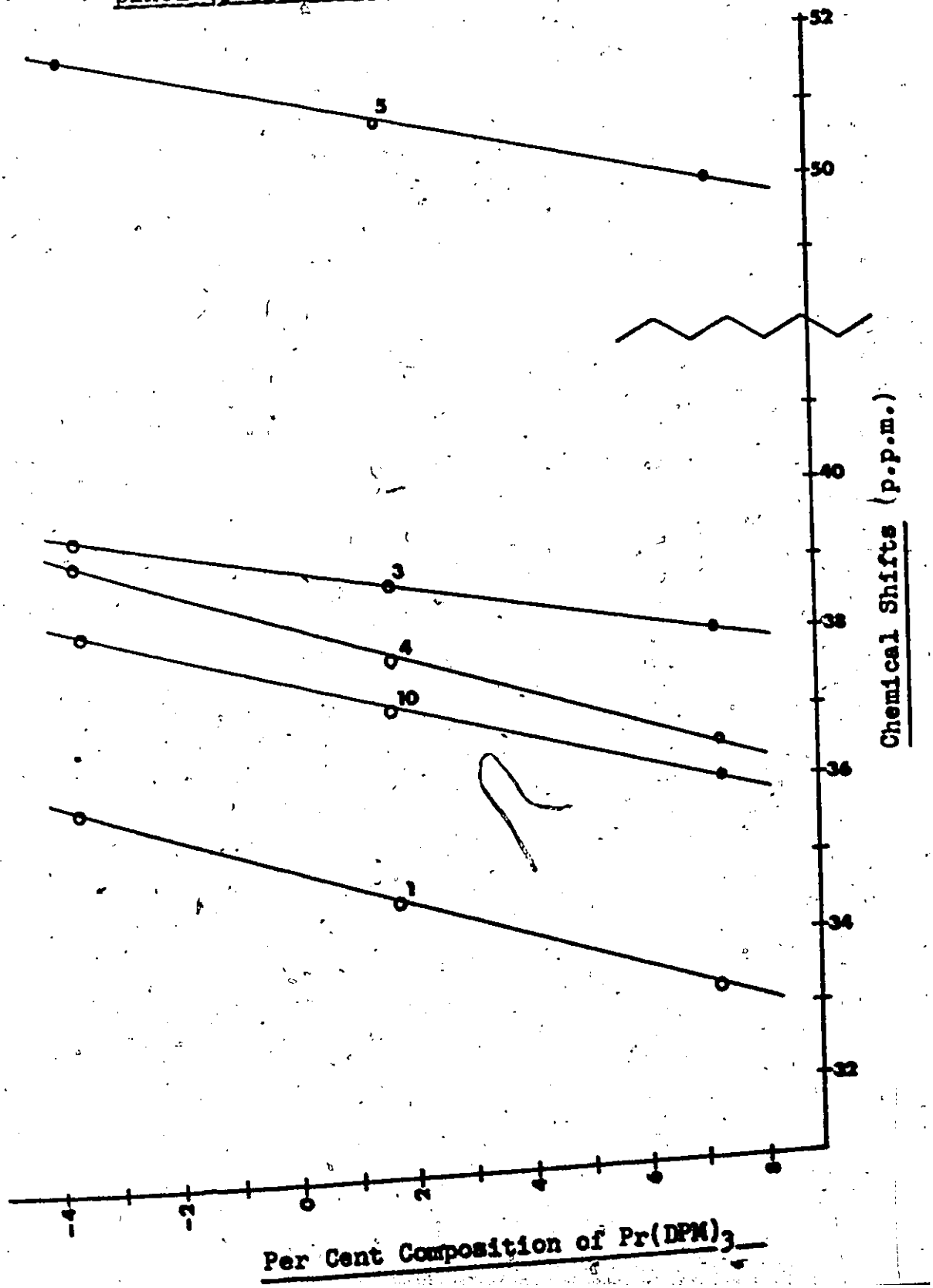


FIGURE 26 Praeseodynium induced shifts for O-methylpodocarpinol (32-52 p.p.m. region)



10.1 Attempted C-20 Functionalization through C-12 Alcohol, via C-19 Ester

1. Purification of Podocarpic Acid 25

Podocarpic acid[a] (50g,0.182 mol) was dissolved in 150 ml of refluxing methanol and the solution treated with 5 g of activated charcoal. After filtration through celite, the amber filtrate was set aside for 3-4 days during which time large transparent crystals were formed. These were collected, crushed, washed with 2x75 ml 1:10 water-methanol, and dried in vacuo. After three crops, a total yield of 40 g of podocarpic acid was realized; m.p. 195-197°; i.r. νmax (KBr) 3330 (broad), 2960, 1695, 1612, 1585, 1500, 1100-1300 cm^{-1} (broad); p.m.r. (trifluoracetic acid) δ 1.20 (s, 3H, C-20 CH_3), 1.45 (s, 3H, C-18 CH_3), 2.8-3.0 (broad, 2H, C-7 benzylic), 6.63-6.97 (3H, C-11,13,14 aromatic) p.p.m., (Lit (142) m.p. 193°).

[a]Available from New Zealand Timber Products Ltd., P.O. Box 5784, Auckland, New Zealand.

2. 12β-Hydroxy-8α- podocarpan-19-oic acid 29 a

The general procedure of Meyers (143) was used. Podocarpic acid (30.0 g, 0.110 mol) in 150 ml of 95% ethanol containing 2 ml of glacial acetic acid was hydrogenated at room temperature over 8.0 g of 5% rhodium-on-alumina at 40-50 psi in a Parr apparatus. After 40h, the uptake of hydrogen had ceased; recovery of the catalyst by filtration followed by evaporation of the solvent and

and subsequent recrystallization of the residue from ethyl acetate gave 9.9 g (32.4%) of white flakes, m.p. 233-236°, lit (61) 234.5-236°. A second crop of product (17.4 g, 56.9%) was also realized on further solvent evaporation.

A sample of the hydroxy-acid obtained was analyzed as the methyl ester after treatment with an ethereal solution of freshly-prepared diazomethane; p.m.r. ($CDCl_3$) δ 0.77 (s, 3H, C-20 CH_3), 1.18 (s, 3H, C-18 CH_3), 3.67 (s, 3H, C-19 $COOCH_3$) p.p.m. (previously prepared by Gravestock (60).)

3. Nitrite Ester of 12β -Hydroxy - 8α- podocarpan-19-oic acid 29b

The general method of Barton (151) was used.

The 12β-hydroxy-acid (0.50 g, 00018 mol) was dissolved in 6 ml of pyridine. The solution was cooled to to 0° and treated with nitrosyl chloride until a deep brown colour persisted. The reaction mixture was then poured into 10 ml of ice-water and worked up in the usual manner using benzene as extractant. The solvent was evaporated and the crude residue esterified using diazomethane. Spectroscopic analysis on the crude product indicated the product to be only methylated starting material.

4. Photolysis of Methyl 12β-Hydroxy -8α - podocarpan -19-oate 29c, Lead Tetraacetate-Iodine Method

Methyl 12β-hydroxy-8α-podocarp-19-oate 29c (1.00 g, 0.0034 mol) was dissolved in 100 ml of benzene (distilled from P_2O_5, deaerated with nitrogen) in a 250 ml Pyrex flask.

Lead tetraacetate (5.9 g, 0.013 mol) and iodine (2.9 g, 0.011 mol) were added and the stirred suspension subjected to the radiation from a 450 watt Hanovia mercury lamp. After 4 h, the dark brown solution was extracted with 2x100 ml of water, 2x100 ml of 10% sodium thiosulfate, and, finally, with 100 ml of water.

The organic layer was dried and the solvent evaporated giving a crystalline residue, the thin layer chromatogram of which indicated the major products to be starting material and keto-ester. This was confirmed by p.m.r. ($CDCl_3$) δ 0.65 (C-20 CH_3, ketone), 0.79 (C-20 CH_3, starting material), 1.15 (C-18 CH_3, ketone), 1.19 (C-18 CH_3, starting material)p.p.m.

5. Thermolysis of Methyl 12β-Hydroxy-8α-podocarpan-19-oate 29a, Lead Tetraacetate method

To a suspension of lead tetraacetate (1.6 g, 0.0036 mol) and calcium carbonate (0.4 g, 0.004 mol) in 10 ml of dry, deaerated benzene was added a solution of methyl 12β-hydroxy-8α-podocarpan-19-oate (1.08 g, 0.0037 mol) in 5 ml of dry deaerated benzene. After refluxing for 18 h, the reaction mixture was filtered and the filtrate extracted with 2x10 ml aliquots of 10% sodium bicarbonate solution followed by 2x10 ml of water.

Evaporation of the organic layer gave a solid residue, the analysis of which, by thin layer chromatography, indicated the presence of keto ester and starting material.

6. 12-Oxo-8α-podocarpan-19-oic Acid 31a

To a solution of 12-hydroxy-8α-podocarpan-19-oic acid (5.0 g, 0.018 mol) in 50 ml of acetone cooled to 10° was added, with stirring, a solution of chromium trioxide (6.8 g, 0.068 mol) in 5.5 ml of concentrated sulfuric acid and 20 ml of water until an orange-brown colour persisted. After continued agitation for 1 h, excess oxidizing agent was destroyed by addition of 2-propanol.

The solvent was removed in vacuo at 40-50° and, after the addition of 50 ml of water, the product was extracted with two portions of diethyl ether. The usual work-up followed by recrystallization of the crude residue from diethyl ether gave 4.5 g, (91%) of cis-keto acid 31a as a gray-white powder.

A second recrystallization from methanol yielded a first crop of 2.0g of cis-keto acid as colourless plates, m.p. 164-167°; ir: ν_{max} (nujol) 3100-2600, 1720,1670 cm^{-1}; p.m.r.($CDCl_3$-pyridine) δ 0.78 (s,3H, C-20 CH_3), 1.24 (s, 3H, C-18 CH_3) p.p.m.; (Lit(61) m.p. 167.5-174°).

Treatment of the acid with an ethereal solution of diazomethane ultimately yielded 2.1 g (100%) of cis-keto ester 31b; i.r. max(nujol)1715(broad)cm^{-1}, p.m.r. ($CDCl_3$) δ 0.69 (s,3H,C-20 CH_3) 1.19 (s, 3H, C-18 CH_3), 3.61 (s, 3H, C-19 $COOCH_3$) p.p.m.

Pure cis-keto ester 31b was obtained by gas-liquid chromatography (SE30-20% on 60/80 Chromosorb, 240°, 60

ml/min flowrate of helium, 5 µl injections in acetone). The product was collected in a liquid nitrogen cooled nmr tube after a retention time (t_R) of 18 min. The colourless flakes had a m.p. 107-110°; p.m.r. ($CDCl_3$) δ 0.69 (C-20 CH_3), 1.19 (C-18 CH_3), 3.62 (C-19 $COOCH_3$) p.p.m.

A sample of the residue from evaporation of the recrystallization mother liquor was analyzed by gas-liquid chromatography under similar conditions. Two peaks were recorded, one at a retention time of eighteen minutes, (cis-keto ester) and another at a retention time of fifteen minutes (trans-keto ester 32), p.m.r. ($CDCl_3$) δ 0.79 (C-20 CH_3), 1.19 (C-18 CH_3) p.p.m. Integration of the C-20 methyl peaks gave a ratio of 2.5:1 for trans:cis in the recrystallization mother liquor. (see also Gravestock (53).)

7. Sodium Borohydride Reduction of cis-12-Oxo-8α-podocarpan-19-oic Acid 31a

The cis-keto acid (1.23 g, 0.0044 mol) was dissolved in 15 ml of methanol and treated, dropwise, with a solution of sodium borohydride (0.77 g, 0.0204 mol) in 5 ml of methanol. The solution was stirred at room temperature for one hour before the addition of 10 ml of water and extraction with diethyl ether. The usual work-up gave 1.21 g, (98%) of colourless flakes; ir νmax (nujol) 3300 (broad), 1680 cm^{-1}.

The product was esterified using an ethereal solution of diazomethane; p.m.r. ($CDCl_3$) δ 0.77 (C-20 CH_3) 1.25

(C-18 CH_3), (C-12β-epimer); 0.82 (C-20 CH_3), 1.19 (C-18 CH_3) (C-12α-epimer) p.p.m.

8. Sodium/Alcohol Reduction of cis-12-Oxo- 8α-podocarpan-19-oic Acid 31a

The cis-keto acid (1.24 g, 0.0045 mol) was added to 65 ml of freshly-distilled 1-propanol and brought to reflux. Sodium metal (6.5 g, 0.28 mol) was added through the condenser as rapidly as possible and refluxing maintained for 1.5 h. After an additional 15 h at room temperature, the reaction mixture was acidified with 10% hydrochloric acid and the precipitate collected, water-washed until the filtrate was neutral, and oven-dried. The colourless flakes (1.26 g, 100%) obtained were methylated using ethereal diazomethane; p.m.r..($CDCl_3$) δ 0.77 (C-20 CH_3), 1.25 (C-18 CH_3) (C-12β-epimer); 0.82 (C-20 CH_3), 1.19 (C-18-CH_3) (C-12α -epimer) p.p.m.

9. Methyl 12-Acetyl-8α-podocarpan-19-oate 29d,30b

(a) base-catalyzed acetylation

A 500 mg sample of methyl 8α-podocarpan-19-oate from the sodium borohydride reduction of cis-keto acid (followed by methylation) was dissolved in 3 ml of pyridine and 4 ml of acetic anhydride. After refluxing for 1.5 h, 5 ml of water was added and the product extracted with diethyl ether. The organic layer was washed with 10% hydrochloric acid, followed by water, and then evaporated in vacuo to give colourless flakes, p.m.r. ($CDCl_3$) δ 0.78 (C-20 CH_3),

1.18 (C-18 CH_3) (C-12β -epimer); 0.90 (C-20 CH_3), 1.28 (C-18 CH_3) (C-12α-epimer) p.p.m.

(b) acid-catalyzed acetylation

Similar results were obtained by this procedure. Methyl 8α-podocarpan-19-oate (100 mg) was refluxed for 1 h in a solution of 1 ml of acetic anhydride containing one drop of concentrated hydrochloric acid. Four ml of water was added and the product extracted with chloroform. Work-up in the usual manner yielded colourless flakes of the 12-acetylated compound.

(c) A 500 mg sample of hydroxy-ester from the sodium-alcohol reduction of the cis-keto acid (followed by methylation) was acetylated by the base-catalyzed method given above and yielded product as colourless flakes, p.m.r. ($CDCl_3$) δ 0.90 (C-20 CH_3), 1.18 (C-18 CH_3), 2.00 (C-12 $OCOCH_3$), 3.64 (C-19 $COOCH_3$), 4.7-5.2 (broad, C-12 CH(axial)) p.p.m. Recrystallized from methanol, m.p. 120°-120.5°; mass spectrum (80eV) m/e 336 (M+ calcd. for $C_{20}H_{32}O_4$: 336.2300; found: 336.2271).

10.2 Attempted C-20 Functionalization through C-7 Alcohol via C-19 Ester

1. O-Methylpodocarpic Acid 33

The method of Bennett and Cambie (144) was used. Podocarpic acid (5.0 g, 0.018 mol) in 20 ml of 2M sodium hydroxide was treated dropwise with dimethyl sulfate

(7 ml, 0.072 mol) at room temperature.

The precipitate was collected by filtration, dried, and then heated under reflux with 250 ml of petroleum ether for 3 h. The solid was collected and washed with warm organic solvent.

The sodium salt was suspended in water and acidified with 12% hydrochloric acid. After filtration, the product was washed with water until the filtrate was neutral, then dried and recrystallized from methanol to give 3.9 g (74.5%) of white flakes, m.p. 156-157.5°; ir νmax (KBr) 3500-2400 (b), 1695,1612,1570,1500,1375,1265 (b) cm^{-1}; p.m.r. ($CDCl_3$) δ 1.13 (s, 3H, C-20 CH_3), 1.33 (s, 3H, C-18 CH_3) 2.6-2.9 (broad, 2H, C-7 CH_2), 3.72 (s,3H, C-12 OCH_3), 6.5-70 (m, 3H, C-11,13,14 aromatic protons), 9.0 (broad, C-19 COOH) p.p.m. (Lit. (144) m.p. 158°)

2. Methyl O-Methylpodocarpate 34

O-methyl podocarpic acid (10.0 g, 0.0347 mol) suspended in diethyl ether was treated with an excess of ethereal diazomethane solution and stirred overnight at room temperature.

Evaporation of the solvent in vacuo and recrystallization of the crude product from diethyl ether gave 9.8 g (93.1%) of white flakes, m.p. 128-128.5°; ir νmax (KBr) 2940, 2850, 1710, 1605, 1500, 1375 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.00 (s, 3H, C-20 CH_3), 1.23 (s, 3H, C-18 CH_3), 2.6-2.9 (broad, 2H, C-7 CH_2), 3.53 (s, 3H, C-19 $COOCH_3$), 3.63 (s,2H , C-12

OCH_3) 6.4-6.9 (m,3H, C-11,13,14 aromatic protons) p.p.m. (Lit. 144) m.p. 127-128°)

3. Methyl 7-Oxo-O-methylpodocarpate 35

The general method of Wenkert (55) was used.

Methyl O-methylpodocarpate (20.0 g, 0.067 mol) in 150 ml of glacial acetic was stirred at 0-10° during the dropwise addition of a solution of chromium trioxide (25.0 g, 0.250 mol) in 200 ml of 4:1 acetic acid-water. After 48 h, 250 ml of saturated brine was added and the solution extracted with 2x200 ml of 25% ethyl acetate in benzene.

Work-up in the usual manner followed by recrystallization of the crude organic residue from 95% ethanol gave 16.0 g (77%) of canary yellow flakes of methyl 7-oxo-O-methyl podocarpate, m.p. 124-125.5°; ir νmax (KBr) 3010, 2940,2860,1725,1680,1602,1570,1490,1375,1275 cm^{-1}; u.v. λmax 206 (13,100), 224 (12,400), 276 (14,500) nm; p.m.r. ($CDCl_3$) δ 1.13 (s, 3H, C-20 CH_3), 1.28 (s,3H, C-18 CH_3), 3.70 (s, 3H, C-12 OCH_3), 3.85 (s, 3H, C-19 $COOCH_3$), 6.7-6.9 (m, 2H, C-11, 13 aromatic protons), 8.0 (q, J= 7.5 H_3, 1H, C-14 aromatic proton) p.p.m. (Lit. (55) m.p. 121-123°)

4. Methyl 7β-Hydroxy-O-methylpodocarpate 36

To a solution of methyl 7-oxo-O-methylpodocarpate (4.0 g, 0.013 mol) in 40 ml of 95% ethanol containing sodium hydroxide (0.40 g, 0.010 mol) was added dropwise sodium borohydride (2.0 g, 0.053 mol) in 8 ml of water. After 2 h at room temperature, the solvent was evaporated and to the residue was added 20 ml of water. Extraction with diethyl

ether in the usual manner and recrystallization of the crude hydroxy-ester from aqueous methanol gave 3.5 g (87%) of 36 as a white powder, m.p. 104-106°; ir ν_{max} 3390, 3010, 2950, 2860, 1720, 1600, 1570, 1495, 1380, 1230 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.09 (s,3H, C-20 CH_3), 1.25 (s,3H, C-18 CH_3), 3.65 (s, 3H, C-12 OCH_3), 3.76 (s,3H C-19 $COOCH_3$), 6.6-6.9 (sextet, 2H, C-11, 13 aromatic protons), 7.5 (d, J=7.5 H_3, 1H, C-14 aromatic proton) p.p.m. (Lit. (155) m.p.110-112°)

5. Nitrite Ester of Methyl O-methyl-7β-hydroxy-podocarpate 37

The hydroxy-ester 36 (5.0 g, 0.016 mol) in 25 ml of freshly-distilled pyridine was cooled to -30° and treated with nitrosyl chloride until a red-brown colouration persisted. Ice-water was added and the mixture extracted with diethyl ether, the evaporation of which gave 5.0 g of off-white product; p.m.r. ($CDCl_3$) δ 1.08 (C-20 CH_3), 1.26 (C-18 CH_3)(7-hydroxy compound), 1.12 (C-20 CH_3), 1.33 (C-18 CH_3) (nitrite ester) p.p.m.

6. Photolysis of the Nitrite Ester of Methyl 7β-Hydroxy-O-methyl podocarpate 37

Crude nitrite ester of methyl 7β-hydroxy-O-methyl-podocarpate (about 1 g) in 100 ml of dry benzene was subjected to 4.5 h of ultraviolet radiation through a Pyrex filter from a 450 watt Hanovia mercury lamp, after which, a small volume was evaporated for analysis; p.m.r. ($CDCl_3$) δ 1.10 (C-20 CH_3), 1.30 (C-18 CH_3), 3.69 (C-12 OCH_3), 3.85

(C-19 $COOCH_3$), 8.0 (q, C-14 aromatic proton) (7-oxo derivative); 1.07 (C-20 CH_3), 1.24 (C-18 CH_3), 3.65 (C-12 OCH_3), 3.76 (C-19 $COOCH_3$), 7.5 (d, C-14 aromatic proton) (7-hydroxy derivative) p.p.m.

10.3 Attempted C-20 Functionalization through C-7 Alcohol, via C-19, 6β-lactone

1. 12-Acetoxypodocarpic Acid 38

The method of Sherwood and Short (142) was used.

Podocarpic acid (20.0 g, 0.073 mol), acetic anhydride (28.0 g, 0.30 mol) and 1 g of anhydrous sodium acetate were mixed and refluxed for 1 h. Excess acetic anhydride was destroyed by adding 25 ml of water and warming the solution for 20 min. The solution was poured over 300 g of ice and extracted with 2x100 ml of diethyl ether.

Work-up in the usual manner followed by recrystallization of the crude product from diethyl ether gave 22.0 g (95.5%) of 12-acetoxypodocarpic acid 38 as white needles; m.p. 180-181°; ir νmax (KBr) 3290,2940, 2860, 1740 (b), 1615, 1585, 1495, 1375, 1240, (b) cm^{-1}; u.v. λmax 203 (14,000), 217 (s,7100) nm; p.m.r. ($CDCl_3$) δ 1.28 (s,3H, C-20 CH_3), 1.35 (s,3H, C-18 CH_3), 2.27 (,3H, C-12 $OCOCH_3$), 2.85 (broad, 2H, C-7 CH_2), 6.9 (m, 3H, C-11,13,14 aromatic protons) p.p.m.; (Lit. (145) m.p. 180-182°).

2. Methyl 12-Acetoxypodocarpate 39

A solution of 12-acetoxypodocarpic acid (0.330 g, 1,05 mol) in 2 ml of diethyl ether was treated with an excess

of ethereal diazomethane solution. After 1 h, evaporation of the solvent gave 0.338 g (98%) of white powder, m.p.122-124°; i.r. ν_{max} (KBr) 3020, 2970, 2870, 1760, 1720, 1610, 1585, 1490, 1370 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.00 (s, 3H, C-20 CH_3), 1.23 (s, 3H, C-18 CH_3), 2.18 (s, 3H, C-12 $OCOCH_3$), 2.83 (broad, 2H, C-7 CH_2), 3.92 (s, 3H, C-19 $COOCH_3$) 6.6-7.1 (m,3H,C-11,13,14 aromatic protons)p.p.m.(Lit.(152)m.p.122-123.5°)

3. 7-Oxo-12-Acetoxypodocarpic acid 40

A modified version of the method of Wenkert and Jackson (124) was used.

A solution of 12-acetoxypodocarpic acid 38 (15.0 g, 0.0475 mol) in 150 ml of glacial acetic acid was stirred with cooling during the dropwise addition of a solution of chromium trioxide (11.5 g, 0.115 mol) in 150 ml of glacial acetic acid and 5 ml of water.

After 45 h at room temperature, excess oxidant was destroyed by the dropwise addition of 25 ml of 2-propanol, after which the solvent was removed on the rotary evaporator. The residue was treated with 500 ml of 10% sodium hydroxide for 2 h after which the green chromium salts were removed by filtration.

The bright yellow aqueous filtrate was acidified with 15% hydrochloric acid and extracted with 3x200 ml of 3:1 ethyl acetate-benzene, the evaporation of which gave 12.0 g of crude keto-phenol.

Acetylation was accomplished by refluxing the phenolic

compound for 1 h with 35 ml of acetic anhydride and 0.5 g sodium acetate. Excess anhydride was destroyed by the addition of 25 ml of water and warming the solution for ½ h, after which, the solution was poured over ice and extracted with 2x200 ml of ethyl acetate. Work-up in the usual manner gave 13.5 g (86.0%) of white crystals of 7-oxo-12-acetoxypodocarpic acid 40, m.p. 193-195°; i.r. νmax (KBr) 3270, 2930, 2850, 1740, 1715, 1670, 1595, 1570, 1365, 1230 - 1150 (b) cm^{-1}; u.v. λmax 206 (22,500), 253 (13,000) nm; p.m.r. ($CDCl_3$) δ 1.21 (s, 3H, C-20 CH_3), 1.31 (s, 3H, C-18 CH_3), 2.27 (s, 3H, C-12 $OCOCH_3$), 3.04 (d, J=4.0 Hz, 2H, C-6 CH_2), 6.9-7.1 (m, 2H, C-11, 13 aromatic protons)[a], 7.98 (d, J=8.0 Hz, 1H, C-14 aromatic proton) p.p.m. (different procedure (48) m.p.178°)

4. Methyl 7-oxo-12-acetoxypodocarpate 41

A solution of 7-oxo-12-acetoxypodocarpic acid (0.297 g, 0.900 mmol) in 2 ml of diethyl ether was treated with excess ethereal diazomethane. After 1 h, evaporation of the solvent gave 0.302 g (97.7%) of white powder, m.p. 130.5 -131°; i.r. ν max (KBr) 3010, 2950, 2890, 1765, 1720, 1685, 1601, 1575, 1450 (b), 1370, 1190 (b) cm^{-1}; p.m.r. ($CDCl_3$)δ 1.10 (s, 3H, C-20 CH_3), 1.23 (s, 3H, C-18 CH_3), 2.27 (s, 3H, C-12 $OCOCH_3$), 3.10 (m, 2H, C-6 CH_2), 3.67 (s, 3H, C-19 $COOCH_3$), 6.9-7.2 (m, 2H, C-11,13 aromatic protons), 8.0 (d, J=8.0 Hz, 1H, C-14 aromatic proton) p.p.m.; (Lit.(55) m.p. 136-138°)

5. 6α-Bromo-7-oxo-12-acetoxypodocarpic acid 42

The method of Wenkert et al (55) was used.

To a solution of 7-oxo-12-acetoxypodocarpic acid (8.0 g, 0.024 mol) in 24 ml of glacial acetic acid containing 3 drops of 16% hydrobromic acid was added dropwise a solution of bromine (4.4 g, 0.028 mol) in 15 ml of glacial acetic acid. After 15 minutes at room temperature, the reaction mixture was evaporated at reduced pressure yielding 9.4 g (95%) of a light yellow crystalline product which was then recrystallized from methanol, m.p. 90-92.5°; p.m.r. ($CDCl_3$) δ 0.95 (s, 3H, C-20 CH_3), 1.60 (s, 3H, C-18 CH_3), 2.28 (s, 3H, C-12 $OCOCH_3$), 2.6 (1H, d, J=7.0 H_3, C-5H), 5.9 (1H,d, J=7.0 H_3, C-6H), 6.8-7.2 (m, 2H, C-11, 13 aromatic protons), 7.75 (d, J=9.0 H_3, 1H, C-14 aromatic proton) p.p.m. (Lit.(48) m.p.89-92°).

A small sample was treated with an ethereal solution of diazomethane which yielded, after 12 h, upon evaporation of the solvent, a quantitative amount of methyl ester 43, m.p. 129.5-131.5°; i.r. ν_{max} (KBr) 2940, 1770, 1690, 1600, 1570, 1480, 1385 cm^{-1}; p.m.r. ($CDCl_3$) δ 0.85 (s, 3H, C-20 CH_3), 1.53 (s, 3H, C-18 CH_3), 2.28 (s, 3H, C-12 $OCOCH_3$), 2.48 (d, J=7.0 H_3, 1H, C-5H), 3.67 (s, 3H, C-19 $COOCH_3$), 5.77 (d, J=7.0 H_3, 1H, C-6H), 7.0-7.3 (m, 2H, C-11, 13 aromatic protons), 7.67 (d, J=9.0 H_3, 1H, C-14 aromatic proton) p.p.m.; (Lit. (55) m.p. 130-132°)

6. 6β-Hydroxy-7-oxo-12-acetoxypodocarpic-19, 6β-lactone 44

The method of Wenkert (55) was used.

A solution of 6α-bromo-7-oxo-12-acetoxypodocarpic acid (6.8 g, 0.017 mol) in 25 ml of chloroform was treated with 1.5 ml of pyridine and stirred for 18 h at room temperature.

After extraction with 2x25 ml of 1% hydrochloric acid, the organic layer was washed with 2x25 ml of water and, finally, with 25 ml of saturated brine. Evaporation of the solvent at reduced pressure gave 5.5 g (100%) of the keto-lactone, m.p. 162-164°; i.r. νmax (KBr) 3040 (s), 2970, 2940 (s), 1780, 1695, 1600, 1580, 1370, 1200 (b) cm^{-1}; p.m.r. ($CDCl_3$) δ 1.07 (s, 3H, C-20 CH_3), 1.32 (s, 3H, C-18 CH_3), 2.30 (s, 3H, C-12 $OCOCH_3$), 2.32 (d, J=6.0 H , 1H, C-5 CH), 4.93 (d, J=6.0 H_3, 1H, C-6 CH), 6.95-7.35 (m, 2H, C-11, 13, aromatic protons), 7.75 (d, J=9.0 H_2, 1H, C-14 aromatic proton) p.p.m. (Lit. (55) m.p. 161-164°).

7. 6β-Hydroxy-7-oxo-O-methylpodocarpic-19, 6β-lactone 46

A mixture of 6β-hydroxy-7-oxo-12-acetoxypodocarpic-19,6β-lactone (5.3 g, 0.016 mol) in 100 ml of 10% sodium hydroxide was agitated at room temperature for 1 h, at which time, the solution was acidified with dilute hydrochloric acid and extracted with 2x100 ml of ethyl acetate. Evaporation of the solvent in vacuo gave 4.5 g (97%) of keto-lactone phenol 45; m.p. 199.5-200.0°.

The keto-lactone phenol was suspended in 100 ml

of diethyl ether to which was added an excess of ethereal diazomethane. After 12 h, the solvent was evaporated and the crude product recrystallized from ether, m.p. 197-198°; i.r. ν_{max} (KBr) 3030, 2960, 2880, 1765, 1690, 1600, 1570, 1490, 1385 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.11 (s, 3H, C-20 CH_3), 1.33 (s, 3H, C-18 CH_3), 2.32 (d, J=6.0 H_3, 1H, C-5 CH), 3.85 (s, 3H, C-12 OCH_3), 4.85 (d, J=6.0 H_3, 1H, C-6 CH), 6.70-6.95 (m, 2H, C-11,13 aromatic protons), 7.72 (d, J=8.0 H_3,1H, C-14 aromatic proton) p.p.m.; (Lit. (55) m.p. 195-197.5°)

8. 6β, 7β -Dihydroxy-O-Methylpodocarpic-19, 6β -lactone 47

A solution of 7-oxo-O-methylpodocarpic-19, 6β -lactone (1.2980 g, 0.0043 mol) in 15 ml of methanol was added, with stirring, to a suspension of sodium borohydride (0.2899 g, 0.0077 mol) in 15 ml of methanol maintained at 0°C.

After 24 h, the pH was reduced to 4 by the addition of dilute hydrochloric acid and the product extracted with 3x25 ml of diethyl ether. Evaporation of the solvent gave 1.1708 g (89.8%) of the 7β -hydroxy compound as white flakes, m.p. 133-134.5°; i.r. ν_{max} ($CHCl_3$) 3590, 2950, 1780, 1615, 1580, 1500, 1390 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.33 (s, 3H, C-20 CH_3), 1.40 (s, 3H, C-18 CH_3), 1.87 (d, J=5 H_3, 1H, C-5 CH), 3.00 (s, 1H, broad, C-7 OH), 3.78 (s, 3H, C-12 OCH_3), 4.8-5.3 (m, 2H, C-6 and C-7 CH), 6.6-6.8 (m, 2H, C-11, 13 aromatic protons), 7.25 (d, J=9 H_3, 1H, C-14 aromatic proton) p.p.m. (Lit.(155) m.p. 150-151°).

9. Nitrite Ester of 6β,7β -Dihydroxy-O-methyl-podocarpic - 19, 6β -lactone 48

The hydroxy-lactone 47 (0.9870 g, 0.0033 mol) was dissolved in 10 ml of dry pyridine (ex. CaH_2) and cooled to -25°C. The temperature was maintained during the addition of nitrosyl chloride until a permanent yellow-brown colouration developed. Dry nitrogen was bubbled through the solution for 5 min at which time 10 ml of water was added and the product extracted with 2x20 ml of benzene. Work-up in the usual manner gave 1.0502 g (97.5%) of nitrite ester, p.m.r. ($CDCl_3$) 1.17 (s, 3H, C-20 CH_3), 1.23 (s, 3H, C-18 CH_3), 1.78 (d, J=5.0 H_3, 1H, C-5H) 3.72 (s, 3H, C-12 OCH_3), 4.9-5.2 (m, 2H, C-6 and C-7CH), 6.4-6.7 (m, 2H, C-11,13 aromatic protons), 7.1 (d, J=9.0 H_3, 1H C-14 aromatic proton) p.p.m.

10. Photolysis of the Nitrite Ester of 6β, 7β -Dihydroxy-O-methylpodocarpic -19, 6β-lactone 48

The nitrite ester 48 (1g) was dissolved in 50 ml of dry benzene (ex. Ca H_2) and subjected to ultraviolet radiation through a Pyrex filter from a 450 watt Hanovia mercury lamp for 15 h. A sample volume was evaporated for pmr analysis of the residue; p.m.r. ($CDCl_3$) δ 1.33 (s, C-20 CH_3), 1.40 (s, C-18 CH_3), 3.78 (s, C-12 OCH_3), 4.8-5.3 (m, C-6 and C-7 CH) (7-hydroxy lactone 47); 1.10 (s, C-20 CH_3), 1.33 (s, C-18 CH_3), 3.85 (s, C-12 OCH_3) (7-keto lactone 46) p.p.m.

11. Methyl 6β, 7β - Dihydroxy-O-methyl-podocarpate 95

Lactone hydrolysis was carried out according to the method of Tahara (150).

Pure 6β,7β-dihydroxy-O-methyl-podocarpic-19, 6β-lactone 47 (1.7728 g, 0.0059 mol) suspended in 25 ml of 15% sodium hydroxide was treated with methanol until complete dissolution. The solution was refluxed for 5h and the methanol removed on the rotary evaporator.

The cooled solution was acidified with 10% hydrochloric acid and the organic material extracted with 2 x 25 ml of ethyl acetate. Work up in the usual manner gave 1.6912g (95.6%) of pale yellow crystals of the dihydroxy acid 94.

The acid was dissolved in a minimum volume of methanol and treated with an ethereal solution of diazomethane. After 15h at room temperature, the evaporation of solvent and recrystallization of the crystalline material from methanol gave the methyl ester 95, m.p.129-131° ; i.r. ν_{max} 3550, 2940, 2850, 1710, 1605, 1500, 1375 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.25 (s, 3H, C-20 CH_3), 1.33 (s, 3H, C-18 CH_3), 3.72 (s, broad, 6H, C-12 OCH_3 and C-19 $COOCH_3$), 4.5-4.7 (2H, m, C-6H and C-7H), 6.5-6.7 (m, 2H, C-11, 13 aromatic protons), 7.45 (d, J=9 H_3, 1H, H-14 aromatic)p.p.m.(Lit.(155)m.p.131-132°).

12. Nitrite Ester of Methyl 6β,7β -Dihydroxy-O-methyl-podocarpate and photolysis

The dihydroxy ester 95 (1g) was dissolved in 10

ml of dry pyridine (ex. CaH_2) and cooled to -25°C. The low temperature was maintained during the addition of nitrosyl chloride until a permanent yellow brown colour developed. Dry nitrogen was bubbled through the solution for 5 min after which 40 ml of dry pyridine was added and the solution subjected to ultraviolet radiation from a 450 watt Hanovia mercury lamp for 15 hr. A sample was removed for analysis; p.m.r. ($CDCl_3$)δ 1.25 (s, C-20 CH_3), 1.34 (s, C-18 CH_3), 3.77 (s, C-12 OCH_3 and C-19 $COOCH_3$), 7.45 (d, J=9 H_3, C-14 aromatic proton) (dihydroxy ester 95); 1.11 (s), 1.37 (s), 3.75 (s), 4.63 (s,broad), 8.0 (d, J=9 H_3) (unidentified compounds) p.p.m.

10.4 Various Model Compounds

1. 2-Oxo-6-methoxy-4aβ -methyl -1,2,3,4,4a,9,10,10a -octahydrophenanthrene 50

The general procedure of Stork and Darling (146) was used.

A solution of 2-oxo-6-methoxy-4aβ-methyl - 2,3,4, 4a,9,10,- hexahydrophenanthrene 49 (0.5914 g, 0.0024 mol) in 3 ml dry dioxane and 3 ml anhydrous diethyl ether was added dropwise to 25 ml of ammonia containing lithium wire (0.0724 g, 0.0103 mol).

After 5 minutes, ammonium chloride (2.12 g) was added and the ammonia allowed to evaporate. To the residue was added 10 ml of water and the ketone extracted with 3x15 ml of benzene. Removal of the solvent gave 0.5767 g (97%)

of product, m.p. 119-120°; p.m.r. ($CDCl_3$) δ 1.23 (s, 3H, C-4a CH_3), 3.72 (s, 3H, C-6 OCH_3), 6.5 - 7.1 (m, 3H, C-5, 7, 8 aromatic protons) p.p.m.; (lit.(169)m.p. 130°).

2. 6-Methoxy-4aβ -Methyl-1,2,3,4,4a,9,10,10a - octahydrophenanthrene 51

A mixture of 2-oxo-6-methoxy-4aβ-methyl-1,2,3,4, 4a,9,10,10a - octahydrophenanthrene (o.4942 g, 0.0020 mol), 8 ml of 95% hydrazine, and 12 ml of freshly distilled ethylene glycol (108°/50 mm) was heated to 140° for 2 h.

On cooling, potassium hydroxide (5 g) was added and the reaction heated to 200-205° and maintained for 3 h.

Dimethyl sulfate (0.75 g, 0.0060 mol) was added to the cooled mixture. After agitating for 24 h, fifty ml of water was added and the product extracted with 2x25 ml of benzene and 2x25 ml of diethyl ether. Evaporation of the solvent in vacuo gave 0.4521 g (97.5%) of a dark viscous liquid ; i.r. νmax ($CHCl_3$) 2930, 2860, 1610, 1575, 1520, 1375 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.03 (s, 3H, C-4a CH_3), 2.4-2.8 (m,2H, C-9 CH_2), 3.67 (s, 3H, C-6 OCH_3), 6.5-7.0 (m, 3H, C-5,7,8, aromatic protons) p.p.m.;(Lit.(170)b.p.120/10mm)

3. 6-Methoxytetralin 53

A mixture of 6-methoxy-1-tetralone 52 (0.5322 g, 0.0030 mol), 6 ml of 95% hydrazine, and 12 ml of freshly-distilled ethylene glycol was heated to 140° and maintained for 4 h.

At room temperature, potassium hydroxide (5.0 g,

0.089 mol) was added and the temperature maintained at 200-210° for 5 h. Upon cooling, dimethyl sulphate (0.75 g, 0.0060 mol) was added and the solution agitated for 15 h before pouring into an equal volume of water. The product was extracted with 3x20 ml of benzene, the evaporation of which gave 6-methoxytetralin as a dark liquid, p.m.r. ($CDCl_3$) δ 1.5-1.8 (m, 4H, C-2,3 CH_2), 2.4-2.8 (broad, 4H, C-1,4 CH_2), 3.63 (s, 3H, C-6 OCH_3), 6.4-6.9 (m, 3H, C-5,7,8 aromatic protons) p.p.m.; (Lit.(157) b.p. 129-131/11mm).

4. Methyl Podocarpate 54

Recrystallized podocarpic acid 25 (0.65 g, 0.0025 mol) was suspended in 10 ml of diethyl ether at room temperature and a freshly prepared ethereal solution of diazomethane was added. Additional diazomethane solution was added at intervals to maintain an excess as indicated by the yellow colouration. After 4 h, the volume of the mother liquor was reduced until crystallization. Further cooling followed by collection and drying of the white crystals gave 0.65 g (95%) of methylpodocarpate 54, m.p. 208-209°; i.r. ν max (KBr) 3450, 2960, 2860, 1690, 1610, 1505, 1380, 1250-1150 (broad) cm^{-1}; p.m.r. ($CDCl_3$-pyridine) δ 1.00 (s, 3H, C-20 CH_3), 1.23 (s, 3H, C-18 CH_3), 2.70-3.00 (broad, 2H, C-7 CH_2), 3.58 (s, 3H, C-19 $COOCH_3$) p.p.m.;(Lit. (152) m.p. 211.5-212.0°)

5. O-Methylpodocarpinol 55

The method of Zeiss and co-workers (147) was used. A suspension of lithium aluminum hydride (10.0 g,

0.263 mol) in 150 ml of dry diethyl ether was stirred and cooled in an ice bath during the dropwise addition of methyl O-methylpodocarpate (20.0 g, 0.0663 mol) in 300 ml of dry ether.

After 60 h at room temperature, the solution was carefully poured over ice and acidified with 5% sulfuric acid. The ether layer was collected and the aqueous layer further extracted with 200 ml of ether.

Work-up of the combined organic extracts in the usual manner gave 18.1 g (99.5%) of crude product which was recrystallized from ether yielding 14.7 g (80.5%) of O-methylpodocarpinol, m.p. 92.0-92.5°; i.r. νmax (KBr) 3400(b), 2940, 2880, 1612, 1580, 1495, 1380, 1100-1000 (b) cm^{-1}; p.m.r. ($CDCl_3$) δ 1.05 (s, 3H, C-20 CH_3), 1.19 (s, 3H, C-18 CH_3), 2.83 (broad, 2H, C-7 CH_2), 3.71 (q, J=11.5 H_3, 2H, C-19 CH_2), 3.73 (s, 3H, C-12 OCH_3), 6.6-7.1 (m, 3H, C-11,13 14 aromatic protons) p.p.m.; (Lit. (147) m.p. 91°)

6. O-Methylpodocarpinol Acetate 56

O-methylpodocarpinol (1.2048 g, 0.0042 mol) was dissolved in 1 ml of pyridine and to this solution was added 1 ml of acetic anhydride. After ½ h on a steam bath and 36 h at room temperature, an equal volume of water was added and the product extracted with 2x5 ml of ether. The combined extracts were washed with 2x5 ml of 5% hydrochloric acid, 2x5 ml of water, and then evaporated in vacuo to give 1.3546 g (97.5%) of acetate, m.p. 69-72°; i.r. νmax (KBr) 2980,

2890, 1730, 1605, 1580, 1490, 1370, 1250, 1235 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.03 (s, 3H, C-20 CH_3), 1.22 (s, 3H, C-18 CH_3), 2.07 (s, 3H, C-19CH_2OCO $\underline{CH_3}$), 2.87 (m, 2H, C-7 CH_2), 3.77 (s, 3H, C-12 OCH_3), 4.20 (q, J=11.0 H_3, 2H, C-19 $\underline{CH_2}$ $OCOCH_3$), 6.9-7.2 (m, 3H, C-11, 13, 14)p.p.m.(Lit.(156) m.p. 72-73°).

7. O-Methylpodocarpinal 57

The method of Bible (153) was used with some modifications. Chromic anhydride (1.50 g, 0.015 mol) in 15 ml of dry pyridine was added dropwise, with cooling, to a solution of O-methylpodocarpinol (2.0014 g, 0.0073 mol) in 15 ml of dry pyridine. After 1.5 h at room temperature, the product was extracted with 2x25 ml of diethyl ether. The combined ether extracts were washed with 25 ml of 10% hydrochloric acid, and, finally, with 2x15 ml of water. Drying of the ethereal solution over anhydrous magnesium sulfate followed by evaporation of the solvent in vacuo gave 1.8142 g (91.5%) of the aldehyde, m.p. 131.5-133°; i.r. ν max (KBr) 3000, 2960, 2850, 2790, 2770, 1715, 1612, 1575, 1505, 1385 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.03 (s, 3H, C-20 CH_3), 1.08 (s, 3H, C-18 CH_3), 2.88 (broad, 2H, C-7 CH_2), 3.73 (s, 3H, C-12 OCH_3), 6.5-7.0 (m, 3H, C-11,13,14 aromatic protons), 9.75 (s, 1H, C-19 CH) p.p.m. (lit (148) m.p. 133-135°).

8. O-Methylpodocarpane - 58

The method of Wenkert (154) was used with modifications. O-Methylpodocarpinal (1.1087 g, 0.0041 mol), 10 ml of 95% hydrazine, and 15 ml of freshly-distilled ethylene glycol were heated and maintained at 140° for 4 h. After

cooling to room temperature, potassium hydroxide (9.0 g, 0.16 mol) was added and the mixture heated to 200° for 9 h.

Excess dimethyl sulfate was added to the cooled mixture and agitation continued for 24 h at room temperature. Fifty ml of water was added and the product extracted with 2x25 ml of benzene and 25 ml of diethyl ether. Evaporation in vacuo gave 0.8991 g (85.5%) of O-methylpodocarpane as an oil, i.r. ν max ($CHCl_3$) 2980, 2910, 1612, 1585 (sh), 1505, 1390, 1380, 1360 cm^{-1}; p.m.r. ($CDCl_3$) δ 0.92 (s, 3H, C-19 CH_3), 1.17 (s, 3H, C-20 CH_3), 1.23 (s, 3H, C-18 CH_3), 2.80 (broad, 2H, C-7 CH_2), 3.73 (s, 3H, C-12 OCH_3), 6.5-7.0 (m, 3H, C-11,13,14 aromatic protons) p.p.m.(Lit.(154)m.p.31-32°).

9. Methyl O-methyl - $\Delta^{6,7}$ - podocarpate 59

Methyl O-methyl-7-oxopodocarpate 35 (1.08 g, 0.0034 mol) in 10 ml of 95% ethanol containing 0.1 g sodium hydroxide was treated in a dropwise manner by a solution of sodium borohydride (0.5 g, 0.013 mol) in 2 ml of water.

After 15 h at room temperature, the reaction was acidified with 10% hydrochloric acid and the product extracted with diethyl ether. Evaporation of the solvent gave a residue which was then recrystallized from methanol to give 0.70 g (68.3%) of white crystals, m.p. 80.0-81.5°; p.m.r. ($CDCl_3$) δ 0.87 (s, 3H, C-20 CH_3), 1.30 (s, 3H, C-18 CH_3), 3.68 (s, 3H, C-12 OCH_3), 3.79 (s, 3H, C-19 $COOCH_3$), 6.38-7.1 (m, 5H, C-6H, 7H, C-11, 13, 14 aromatic protons) p.p.m. (Lit.(155) mp. 85-86°).

10. Methyl 3β-Hydroxy-O-methylpodocarpate 62

Methyl 3-oxo-O-methylpodocarpate (0.300g, 0.95 mmol) dissolved in 20 ml of methanol was treated with a solution of sodium borohydride (0.100 g, 2.63 mmol) in 10 ml of methanol. After 1 h, the solvent was evaporated and 10 ml of water added to the residue. The organic material was extracted with 2X 10 ml of diethyl ether. Evaporation of the solvent gave 0.299 g (99.8%) of a white powder identified as 62 by its pmr spectrum; p.m.r. ($CDCl_3$) δ 1.07 (s, 3H, C-20 CH_3), 1.50 (s, 3H, C-18 CH_3), 2.7-2.9 (broad, 2H, C-7 CH_2), 3.72 (s, 3H C-19 $COOCH_3$), 3.78 (s, 4H, C-12 OCH_3 and C-3 CH), 6.6-7.1 (m, 3H, C-11,13,14 aromatic protons) p.p.m.; mass spectrum (80eV)m/e 318(M+,calcd. for $C_{19}H_{26}O_4$: 318.1831; found: 318.1837).

11. 6β, 7β-Dihydroxypodocarpic-19, 6β-lactone 97

A solution of 6β-hydroxy-7-oxo-12-acetoxypodocarpic -19, 6β-lactone 44 (1.28 g, 0.0040 mol) in 10 ml of 95% ethanol was cooled to 0-10°C. and treated with a suspension of sodium borohydride (0.300 g, 0.0080 mol) in ethanol. After 15 h, the solvent was evaporated and 25 ml of 10% hydrochloric acid added to the residue. Extraction with ethyl acetate and work-up in the usual manner gave 1.0 g (89%) of 6β,7β- dihydroxypodocarpic - 19, 6β-lactone 97; m.p. 203-207°; i.r.ν_{max} (KBr) 3490, 3370; 3040, 1780, 1600 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.28 (s, 3H, C-20 CH_3), 1.36 (s, 3H, C-18 CH_3), 2.25 (d, 1H, J=6H_3, C-5 CH), 2.90 (broad, 1H, OH), 5.10 (m, 2H, C-6H and C-7H), 6.5-6.8 (m, 2H, C-11,13 aromatic protons), 7.1 (d, 1H, J=9 H_3, C-14 aromatic proton) p.p.m.

12. Methyl 6β,7β- Dihydroxypodocarpate 64

Hydrolysis of the lactone was carried out by the method recorded on page 178 for compound 47.

Dihydroxy-lactone 97 (1.00 g, 0.0033 mol) was converted into the free acid which was immediately treated with an ethereal solution of diazomethane to give, after evaporation of the solvent, compound 64 (1.01 g, 95.1%) which was recrystallized from methanol, m.p. 142-144.5°; i.r νmax (KBr) 3550, 3300, 3030, 1750, 1600, 1500 cm^{-1}; p.m.r. ($CDCl_3$) δ 1.07 (s, 3H, C-20 CH_3), 1.32 (s, 3H, C-18 CH_3), 2.35 (d, 1H, J=6 H_3, C-5 CH), 3.72 (s, 3H, C-19 $COOCH_3$), 4.82 (m, 2H, C-6H, C-7H), 6.7-6.9 (m, 2H, C-11, 13 aromatic protons), 7.60 (d, 1H, J=9H_3, C-14 aromatic proton) p.p.m.; mass spectrum (80eV) m/e 320 (M+calcd. for $C_{18}H_{24}O_5$: 320.1624; found: 320.1645).

10. GENERAL CONCLUSIONS

10.1 Synthetic

The functionalization of the C-20 methyl group of the tricyclic diterpenoid system by means of a 1,6-hydrogen transfer using the Barton reaction has been unsuccessful despite the apparent proximity of the two nitrite ester centres, C-7 and C-12, to the angular methyl group in question.

The major synthetic objective of this work was to derive a substrate, in a minimum number of steps, upon which the Barton reaction could be performed. Obvious centres of interest in this regard were the C-12 and C-7 alcohol functions which were readily and efficiently generated by reduction of the aromatic ring and by oxidation of the benzylic position, respectively, of the podocarpic acid system. The failure of the Barton reaction on the C-12 alcohol was attributed to a twist conformation of ring C as suggested by coupling data.

Efforts to functionalize carbon-20 through the C-7 alcohol were also unsuccessful. Formation of the C-19, 6β-lacton in an attempt to force the two reaction centres closer together did not alter the final result.

It became obvious that recourse to the 6β-alcohol through the opening of the lactone ring in 47 would have to be made. Despite the extra steps involved, the overall process of converting podocarpic acid 25 to the 6β, 7β-diol

95 is carried out readily and in good yield. Although photolysis of the 6β-nitrite ester 95 gave results which were inconclusive, successes reported elsewhere for similiar systems indicate this to be the preferred pathway to C-20 functionalization.

In view of the progress made on attachment of the 3-furyl groups and on the generation of the exocyclic methylene at C-8 (60), it is reasonable to assume that generation of th 19→20 lactone and 20→12 ether through, in part by the Barton reaction may be close at hand and synthesis of the sciadin structure may be soon realized.

10.2 Carbon-13 Nuclear Magnetic Resonance

Substituent effects for a variety of functional groups have been developed for the oxygenated diterpenoids of the podocarpic acid series. The useful application of simple model compounds to study analogous effects in more complex molecular situations has been employed and illustrated rather dramatically in the compounds reported in this thesis. As more and more data is accumulated on substituent effects in a variety of molecular environments, the facility for semi-quantitatively assigning the chemical shift of a given carbon becomes easier. Ultimately it would be desireable to readily calculate all factors for a given carbon atom in a particular system, whether those factors be electric, steric, or magnetic, and apply these to some reference chemical shifts to obtain the shift value for that carbon.

At this stage, however, the development of Fourier transform NMR instruments coupled with the experimental techniques described (Section 3.2) and used throughout this work illustrate dramatically the application of C^{13} NMR to the analysis of compounds previously impossible to analyze by other magnetic resonance techniques.

REFERENCES

1. L. Ruzicka. Proc. Chem. Soc. 341 (1959).
2. D. Rittenburg and K. Bloch. J. Biol. Chem. 160, 417 (1945).
3. H.N. Little and K. Bloch. J. Biol. Chem. 183, 33 (1950).
4. J. Würsch, R.L. Huang, and K. Bloch. J. Biol. Chem. 195, 439 (1952).
5. K. Bloch, E. Borek, and D. Rittenburg. J. Biol. Chem. 162, 441 (1946).
6. K. Bloch and D. Rittenburg. J. Biol. Chem. 145, 625 (1942).
7. K. Bloch and D. Rittenburg. J. Biol. Chem. 159, 45 (1945).
8. A.R. Pinder. The Chemistry of The Terpenes. Chapman and Hall, Limited, London. 1960.
9. D.E. Wolf, C.H. Hoffman, P.E. Aldrich, H.R. Skeggs, L.D. Wright, and K. Folkers. J. Amer. Chem. Soc. 78, 4499 (1956).
10. P.A. Tavormina, M.H. Gibbs, and J.W. Huff. J. Amer. Chem. Soc. 78, 4498 (1956).
11. G.D. Braithwaite and T.W. Goodwin. J. Biochem. 67, 13 (1957).
12. R.B. Park and J. Bonner. J. Biol. Chem. 233, 340 (1958).
13. L. Ruzicka, C.F. Seidel, and L.L. Engel. Helv. Chim. Acta. 25, 621 (1942).
14. J.A. Barltrop and D.B. Bigley. Chem. and Ind. 1378 (1959).
15. L.H. Briggs, B.F. Cain, and J.K. Wilmshurst. Chem. and Ind. 599 (1958).
16. R.E. Ireland and P.W. Schiess. Tetrahedron Lett. 37 (1960).

17. M. Sumimoto. Tetrahedron, 19, 643 (1963).

18. C. Kaneko, T. Tsuchiya, and M. Ishikawa. Chem. Pharm. Bull. 11, 271 (1963).

19. C. Kaneko, T. Tsuchiya, and M. Ishikawa. Chem. Pharm. Bull. 11, 1346 (1963).

20. T. Miyasaka. Chem. Pharm. Bull. 12, 744 (1964).

21. V.P. Arya, H. Erdtman, and T. Kubota. Tetrahedron, 16, 255 (1961).

22. D.H.R. Barton, J.M. Beaton, L.E. Geller, and M.M. Pechet. J. Amer. Chem. Soc. 82, 2640 (1960).

23. D.H.R. Barton and J.M. Beaton. J. Amer. Chem. Soc. 82, 2641 (1960); ibid. 83, 4083 (1961).

24. M. Akhtar and D.H.R. Barton. J. Amer. Chem. Soc. 86, 1528 (1964).

25. M. Akhtar and M.M. Pechet. J. Amer. Chem. Soc. 86, 265 (1964).

26. P. Kabasakalian, E.R. Townley, and M.D. Yudis. J. Amer. Chem. Soc. 84, 2716 (1962).

27. P. Kabasakalian and E.R. Townley. J. Amer. Chem. Soc. 84, 2724 (1962).

28. A.L. Nussbaum and C.H. Robinson. Tetrahedron, 17, 35 (1961); A.L. Nussbaum, R. Wayne, E.R. Yuan, O. Zagneetko, and E.P. Oliveto. J. Amer. Chem. Soc. 84, 1070 (1960).

29. K. Heusler and J. Kalvoda. Angew. Chem. Intern. Ed. Engl. 3, 525 (1964).

30. D.H.R. Barton and J.R. Hanson. Chem. Commun. 117 (1965).

31. R.H. Hesse. Adv. Free Radical Chem. 3, 83 (1969).

32. C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein. Experimenta, 17, 475 (1961); C. Meystre, J. Kalvoda, G. Anner, and A. Wettstein. Helv. Chim. Acta. 46, 2844 (1963).

33. D.H.R. Barton and A.J.L. Beckwith. Proc. Chem. Soc. 335 (1963).

34. L.P. Kuhn, G.G. Kleinspehn, and A.C. Duckworth. J. Amer. Chem. Soc. 89 3858 (1967).

35. J.S. Mills. J. Chem. Soc. (c) 2261 (1966).

36. E.J. Corey and W.R. Hertler. J. Amer. Chem. Soc. 80, 2903 (1958).

37. A.C.Oudemans. Ber. 6, 1122,1125 (1873).

38. L.F. Fieser and W.P. Campbell. J. Amer. Chem. Soc. 61, 2528 (1939).

39. W.P. Campbell and D. Todd. J. Amer. Chem. Soc. 79, 573 (1957).

40. B.K. Bhattacharga. J. Indian Chem. Soc. 22, 105 (1945).

41. R.D. Haworth and B.P. Moore. J. Chem. Soc. 633 (1946).

42. F.E. King, T.J. King, and J.G. Topliss. Chem. and Ind. 113 (1956).

43. U.R. Ghatak. Tetrahedron Lett. 19 (1959).

44. U.R. Ghatak, D.K. Datta, and S.C. Ray. J. Amer. Chem. Soc. 82, 1728 (1960).

45. W.L. Meyer and K.K. Maheswari. Tetrahedron Lett. 2643 (1964).

46. E. Wenkert, A. Afonso, J.B-son Bredenberg, C. Kaneko, and A. Tahara. J. Amer. Chem. Soc. 86, 2038 (1964).

47. T.A. Spencer, R.J. Friary, W.W. Schmiegel, J.F. Simeone, and D.S. Watt. J. Org. Chem. 33, 719 (1968).

48. E.N.C. Osakwe. Ph.D. Thesis, McMaster University (1969).

49. E. Wenkert, V.I. Stenberg, and P. Beak. J. Amer. Chem. Soc. 86, 96 (1964).

50. K. Mori and M. Satsui. Tetrahedron Lett. 2347 (1965).

51. B.R. Davis and W.B. Watkins. Tetrahedron 24, 2165 (1968).

52. K. Crowshaw, R.C. Newstead, and N.A.J. Rogers. Tetrahedron Lett. 2307 (1964).

53. R.A. Bell and M.B. Gravestock. Can. J. Chem. 47, 3661 (1969).

54. R.A. Bell, M.B. Gravestock, and V.Y. Taguchi. Can. J. Chem. 50, 3749 (1972).

55. E. Wenkert, P. Beak, R.W.J. Carney, J.W. Chamberlin, D.B.R. Johnston, C.D. Roth, and A. Tahara. Can. J. Chem. 41, 1924 (1963).

56. R.A. Bell and E.N.C. Osakwe. Chem. Commun. 1093 (1968).

57. C.R. Bennett, R.C. Cambie, and T.J. Fullerton. Aust. J. Chem. 21, 2473 (1968)

58. J.W. ApSimon and O.E. Edwards. Can. J. Chem. 40, 896 (1962).

59. L.H. Zalkow and N.N. Girotra. Chem. and Ind. 704 (1964).

60. M.B. Gravestock. Ph.D. Thesis, McMaster University (1969).

61. R.H. Bible and R.R. Burtner. J. Org. Chem. 26, 1174 (1961).

62. R.A. Bell and J.K. Saunders. Topics in Stereochemistry. John Wiley and Sons, Inc., New York, 1972.

63. E.D. Becker. High Resolution NMR Academic Press, New York, 1969.

64. P.K.Oomman, Ph.D. Thesis, McMaster University 1968.

65. A.Eschenmoser. Quarterly Reviews, 24, 366 (1970).

66. J.H.Krieger. Chemical and Engineering News, March 12, 1973.

67. E.Wenkert and B.L.Buckwalter. J. Amer. Chem. Soc. 94, 4367 (1972).

68. J.K.Saunders. Ph.D. Thesis, McMaster University (1970).

69. R.E.Ireland and L.N.Mander. J. Org. Chem. 34, 142 (1969).

70. F. Bloch, W.W. Hansen, and M.E. Packard. Phys. Rev. 69, 127 (1946).

71. E.M. Purcell, H.C. Torrey, and R.V. Pound. Phys. Rev. 69, 37 (1946).

72. P.C. Lauterbur. J. Chem. Phys. 26, 217 (1957).

73. C.H. Holm. J. Chem. Phys. 26, 707 (1957).

74. G.C. Levy and G.L. Nelson. Carbon-13 Nuclear Magnetic Resonance for Organic Chemists. Wiley-Interscience, New York, 1972.

75. A. Allerhard. Lecture presented at Symposium on Nuclear Magnetic Resonance, University of Waterloo, Ontario, Canada, June 7-11, 1971.

76. J.B. Stothers. Carbon-13 NMR Spectroscopy. Academic Press, New York, 1972.

77. R.R. Ernst and W.A. Anderson. Rev. Sci. Inst. 37, 93 (1966).

78. J.E. Pearson. J. Chem. Ed. 50, 243 (1973).

79. H. Hill and R. Freeman. Introduction to Fourier Transform NMR. Varian Associates Analytical Instrument Division, Palo Alto, 1970.

80. T.C. Farrar and E.D. Becker. Pulse and Fourier Transform NMR. Academic Press, New York, 1971.

81. E. Wenkert, A.O. Clouse, D.W. Cochran, and D. Doddrell. J. Amer. Chem. Soc. 91, 6880 (1969).

82. G.C. Levy and J.D. Cargioli. J. Mag. Res. 6, 143 (1972).

83. V.Y.Taguchi. Ph.D. Thesis, McMaster University, 1973.

84. D.M. Grant and E.G. Paul. J. Amer. Chem. Soc. 86, 2984 (1964).

85. H. Spiesecke and W.G. Schneider. J. Chem. Phys. 35, 722 (1961).

86. J.B. Stothers. Applied Spec. 26, 1 (1972).

87. G.B. Savitsky and K. Namikawa. J. Phys. Chem. 68, 1956 (1964).

88. J.J. Burke and P.C. Lauterbur. J. Amer. Chem. Soc. 86, 1870 (1964).

89. D.K. Dalling and D.M. Grant. J. Amer. Chem. Soc. 89, 6612 (1967).

90. J.D. Roberts, F.J. Weigert, J.I. Kroschwitz, and H.J. Reich. J. Amer. Chem. Soc. 92, 1338 (1970).

91. F.A.L. Anet, C.H. Bradley, and G.W. Buchanan. J. Amer. Chem. Soc. 93, 258 (1971).

92. M. Christl, H.J. Reich, and J.D. Roberts. J. Amer. Chem. Soc. 93, 3463 (1971).

93. J.D. Roberts, F.J. Weigert, J.I. Kroschwitz, and H.J. Reich. J. Amer. Chem. Soc. 92, 1338 (1970).

94. F.J. Weigert and J.D. Roberts. J. Amer. Chem. Soc. 92, 1347 (1970).

95. T. Pehk and E. Lippmaa. Org. Mag. Res. 3, 679 (1971).

96. G.W. Buchanan, D.A. Ross, and J.B. Stothers. J. Amer. Chem. Soc. 88, 4301 (1966).

97. D.E. Dorman, M. Jautelat, and J.D. Roberts. J. Org. Chem. 36, 2757 (1971).

98. L.P. Lindeman and J.Q. Adams. Anal. Chem. 43, 1245 (1971).

99. J.B. Grutzner, M. Jautelat, J.B. Dence, J.A. Smith, and J.D. Roberts. J. Amer. Chem. Soc. 92, 7107 (1970).

100. G.E. Maciel. J. Phys. Chem. 69, 1947 (1965).

101. K.S. Dhami and J.B. Stothers. Can. J. Chem. 43, 510 (1965).

102. R.A. Friedel and H.L. Retcofsky. J. Amer. Chem. Soc. 85, 1300 (1963).

103. D.K. Dalling, D.M. Grant, and L.F. Johnson. J. Amer. Chem. Soc. 93, 3678 (1971).

104. W.R. Woolfender and D.M. Grant. J. Amer. Chem. Soc. 88, 1496 (1966).

105. G.E. Maciel and R.V. James. J. Amer. Chem. Soc. 86, 3893 (1964).

106. K.S. Dhami and J.B. Stothers. Can. J. Chem. 44, 2855 (1966).

107. G.E. Maciel and J.J. Natterstad. J. Chem. Phys. 42, 2427 (1965).

108. J.B. Stothers and P.C. Lauterbur. Can. J. Chem. 42, 1563 (1964).

109. D.H. Marr and J.B. Stothers. Can. J. Chem. 43, 596 (1965).

110. C.C. Hinckley. J. Amer. Chem. Soc. 91, 5160 (1969).

111. P.V. DeMarco, T.K. Elzey, R.B. Lewis, and E. Wenkert. J. Amer. Chem. Soc. 92, 5734 (1970).

112. P.V. DeMarco, T.K. Elzey, R.B. Lewis, and E. Wenkert. J. Amer. Chem. Soc. 92, 5737 (1970).

113. J.K.M. Saunders and D.H. Williams. Chem. Commun. 422 (1970).

114. J. Briggs, G.H. Frost, F.A. Hart, G.P. Moss, and M.L. Staniforth. Chem. Commun. 749 (1970).

115. W.B. Smith and D.L. Deavenport. J. Mag. Res. 6, 256 (1972).

116. E. Wenkert, D.W. Cochran, E.W. Hagaman, R.B. Lewis, and F.M. Shell. J. Amer. Chem. Soc. 93, 6271 (1971).

117. O.A. Gansow, M.R. Willcott, and R.E. Lenkinski. J. Amer. Chem. Soc. 93, 4295 (1971).

118. I. Morishima, K. Okada, and T. Yonezawa. J. Amer. Chem. Soc. 94, 1425 (1972).

119. D.H.R. Barton. Personal Communication.

120. K. Bowden, J.M. Heilbron, E.R.H. Jones, and B.C.L. Weedon. J. Chem. Soc. 39 (1946).

121. H.O. House. Modern Synthetic Reactions. W.A. Benjamin, Inc., New York, 1965.

122. R.F. Zurcher. Helv. Chim. Acta. 44, 1380 (1961).

123. R.F. Zurcher. Helv. Chim. Acta. 46, 2054 (1963).

124. E. Wenkert and B.G. Jackson. J. Amer. Chem. Soc. 80, 217 (1958).

125. C.H. Yoder, R.H. Tuck, and R.E. Hess. J. Amer. Chem. Soc. 91, 539 (1969).

126. H.J. Reich, M. Jautelat, M.T. Messe, F.J. Weigert, and J.D. Roberts. J. Amer. Chem. Soc. 91, 7445 (1969).

127. E. Lippmaa, T. Pehk, and J. Past. Eesti NSV Tead. Akad. Toim. Fuus. Mat 16, 345 (1967).

128. L.F. Fieser and M. Fieser. Topics in Organic Chemistry, Reinhold Publishing Co., New York, 1963.

129. J.W. ApSimon, H. Beierbeck, and A. Fruchier. Can. J. Chem. 50, 2725 (1972).

130. H. Spiesecke and W.G. Schneider. J. Chem. Phys. 35, 731 (1961).

131. K. Bjamer, G. Ferguson, and R.D. Melville. Acta. Cryst. B24, 855 (1968).

132. K.S. Dhami and J.B. Stothers. Can. J. Chem. 43, 479 (1965).

133. K.S. Dhami and J.B. Stothers. Can. J. Chem. 43, 498 (1965).

134. J. Mason. J. Chem. Soc. A1038 (1971).

135. R.A. Bell and M.B. Gravestock. Can. J. Chem. 48, 1105 (1970).

136. R.A. Bell and V. Taguchi. Private Communication.

137. E. Lippmaa and T. Pehk. Eesti NSV Tead. Akad. Toim. Keem. Geol. 17, 287 (1968).

138. E. Lippmaa and T. Pehk. Eesti NSV Tead. Akad. Toim. Keem. Geol. 17, 210 (1968).

139. R.A. Friedel and H.L. Retcofsky. J. Amer. Chem. Soc. 85, 1300 (1963).

140. G.E. Maciel. J. Phys. Chem. 69, 1947 (1965).

141. T.J. deBoer and H.J. Backer. Rec. Trav. Chim. Pays-Bas. 73, 229 (1954).

142. I.R. Sherwood and W.F. Short. J. Chem. Soc. 1006 (1938).

143. A.I. Meyers, W. Beverung, and C.A. Garcia-Munoz. J. Org. Chem. 29, 3427 (1964).

144. C.R. Bennett and R.C. Cambie. Tetrahedron, 23 927 (1967).

145. K. Mori, M. Matsui, and N. Fujisawa. Tetrahedron, 24, 3125 (1968).

146. G. Stork and S.D. Darling. J. Amer. Chem. Soc. 86, 1761 (1964).

147. H.H. Zeiss, C.E. Slimowicz, and V.Z. Pasternak. J. Amer. Chem. Soc. 70, 1981 (1948).

148. W.P. Campbell and D. Todd. J. Amer. Chem. Soc. 64, 928 (1942).

149. D.M. Grant and B.V. Cheney. J. Amer. Chem. Soc. 89, 5315 (1967).

150. A. Tahara, K. Hirano, and Y. Hamakazi. Tetrahedron, 21, 2133 (1965).

151. D.H.R. Barton, J.M. Beaton, L.E. Geller, and M.M. Pechet. J. Amer. Chem. Soc. 83, 4076 (1961).

152. L.H. Briggs, R.C. Cambie, R.N. Seelye, and A.D. Warth. Tetrahedron, 7, 270 (1959).

153. R.H.Bible, Jr. Tetrahedron, 11, 22 (1960).

154. E.Wenkert, V.I.Stenberg, and P.Beak. J. Amer. Chem. Soc. 83, 2320 (1961).

155. C.R.Bennett, R.C.Cambie, and W.A.Denny. Aust. J. Chem. 22, 1069 (1969).

156. G.F.Burkinshaw and B.R.Davis. Tetrahedron, 23, 4147 (1967).

157. G.Stork. J. Amer. Chem. Soc. 69, 578 (1947).

158. P.Gray and A.Williams. Chem. Rev. 59, 239 (1959).

159. A.Saika and C.P.Slichter. J. Chem. Phys. 22, 26 (1954).

160. G.C.Levy, J.D.Cargioli, and F.A.L. Anet. J. Amer. Chem. Soc. 95, 1527 (1973).

161. A.Allerhand, D.Doddrell, and K.Komoroski. J. Chem. Phys. 55, 189 (1971).

162. A.Allerhand, D.Doddrell, V.Glushko, D.W.Cochran, E.Wenkert, P.J.Lawson, and F.R.N.Gurd. J. Amer. Chem. Soc. 93, 544 (1971).

163. F.W.Wehrli. J. Chem. Soc. Chem. Commun., 379 (1973).

164. A.J.Jones, D.M.Grant, and K.F.Kuhlmann. J. Amer. Chem. Soc. 91, 5013 (1969).

165. D.F.S.Natusch. J. Amer. Chem. Soc. 93, 2566 (1971).

166. H.S.Gutowsky and D.F.S.Natusch. J. Chem. Phys. 57, 1203 (1972).

167. G.N.LaMar. J. Amer. Chem. Soc. 93, 1040 (1971).

168. G.L.Blackmer and R.L.Roberts. J. Mag. Res. 10, 380 (1973).

169. F.H.Howell and D.A.H.Taylor. J. Chem. Soc. 1248 (1958).

170. A.Buzas, M.Osowiecki, and G.Regnier. Compte. Rend. 248, 1397 (1959).