TOTAL SYNTHESIS OF METHYL O-METHYL-11-DESOXYCARNOSATE

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by

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SCOPE AND CONTENTS

Synthetic methods for the preparation of 2,7-dimethoxy-1-naphthoic acid are presented. The selective reduction of this acid with sodium in liquid ammonia to give 1,4-dihydronaphthoic acid is described.

The selective Birch reduction of 2,7-dimethoxynaphthalene to 1,4-dihydro-2,7-dimethoxynaphthalene has been accomplished. 2,7-Dimethoxy-3-isopropylnaphthalene was converted to 3-keto-12-methoxy-10-carbomethoxy-13-isopropylperhydrophenanthra-4,8,11,13-tetraene via, 1,2,3,4-tertrahydro-7-methoxy-6-isopropyl-1-carbomethoxynaphthalen-2-one. The transformation of 3-keto-12-methoxy-10-carbomethoxy-13-isopropylperhydrophenanthra-4,8,11,13-tetraene to methyl O-methyl-11-desoxycarnosate via methylation, thioketalisation, desulphurisation and hydrogenation is also described.

ACKNOWLEDGEMENTS

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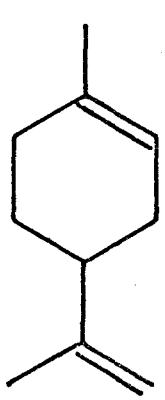
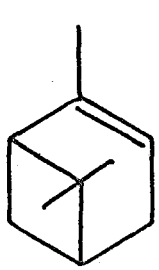
GENERAL INTRODUCTION

From early times many organic compounds derived from the plant and animal kingdoms have been well known to man. Such compounds of animal or plant origin are to-day referred to as natural products. It is probable that from the beginning of his history, man has been interested in the diverse and fragrant odours associated with certain plants. It was discovered that the active principles responsible for the odours of plants could be separated from the plant by gentle heating, steam distillation, or extraction. The oils thus isolated became known as "essential oils". It was found that in the more volatile fraction of many essential oils there were a number of hydrocarbons, all possessing the empirical formula $C_{10}H_{16}$. The general term terpene which is derived from the German terpentine, was eventually applied to these compounds. Biogenetically, terpenes are considered to be derived from isoprene (C_5H_8) units. Those compounds containing ten carbon atoms are termed monoterpenes. Limonene I and α-pinene II are typical examples of monoterpenes belonging to the monocyclic and bicyclic series respectively.



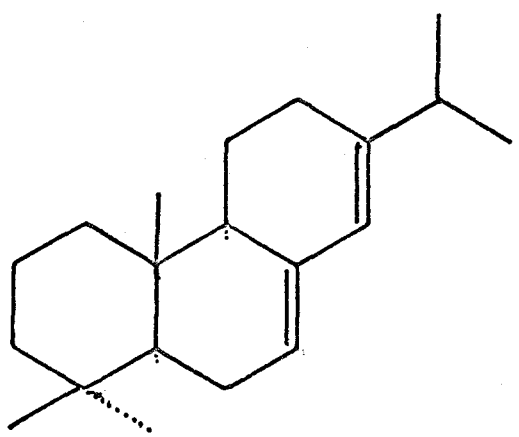
I



II

With the discovery of related substances containing a wide variety of other atoms (functional groups) the term terpene which was originally applied to hydrocarbons, has been replaced by the more general term terpenoid.

The higher boiling fractions from the distillation of essential oils were found to contain compounds with fifteen carbon atoms. These compounds, which are derived from three units of isoprene, are referred to as sesquiterpenes. Later it was found that many bitter principles consisted of compounds containing twenty carbon atoms. Such C-20 compounds are known as diterpenes. Abietane III is an example of a typical diterpene belonging to the tricyclic series.



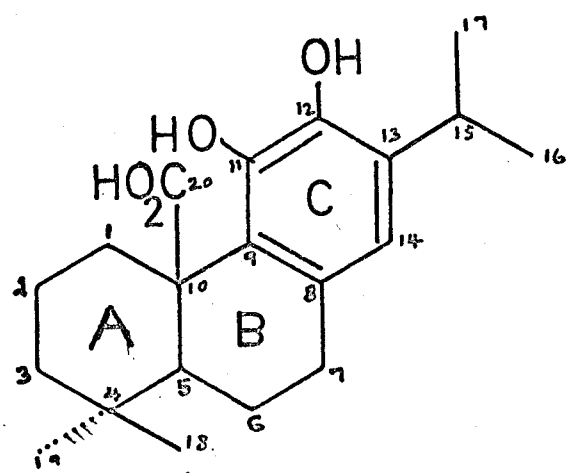
III

Triterpenes contain 30 carbon atoms and are derived from six isoprene units. They are often polycyclic in structure.

The isolation and characterization of natural products and the synthesis of compounds with the proposed structure are major activities of the natural products chemist. The accomplishment of the total synthesis of a natural product can help in confirming the proposed structure and stereochemistry. The synthetic natural

product workers are concerned with the building up of complex structures starting with simple molecules. This involves the creation of new carbon-carbon bonds with the help of new reagents or known reagents applied to new situations. The problem involved is the creation of a suitable carbon skeleton with the correct stereochemistry and with the substituents in the correct positions. The key functional groups can be either introduced after the creation of the carbon skeleton or more appropriately, the starting materials may contain the substituents and be converted into the required molecule. At each stage of the synthetic sequence all stable intermediates must be purified and characterized both by modern spectroscopic methods and microanalysis. Frequently the yield of a desired product from an organic reaction is poor because of the formation of other materials. Consequently, the quantity of material available for the next stage is greatly reduced. In a multi-step synthesis it is of paramount importance to devise reactions which will give the greatest possible yield at each step otherwise the attainment of the ultimate synthetic goal may be rendered impossible.

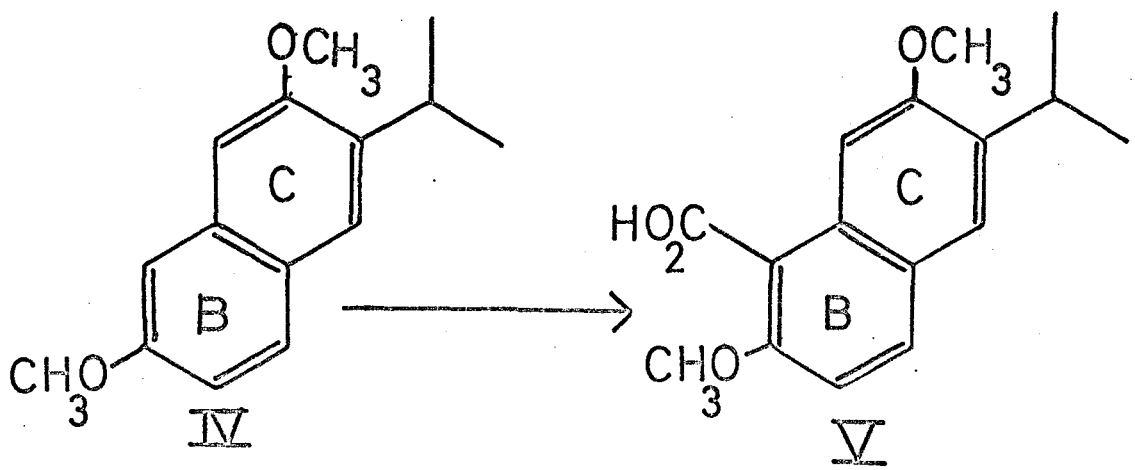
All the general problems discussed above were confronted with in the course of the present work. The object of the work was to devise a practical total synthesis of the diterpenoid carnosic acid 1e.

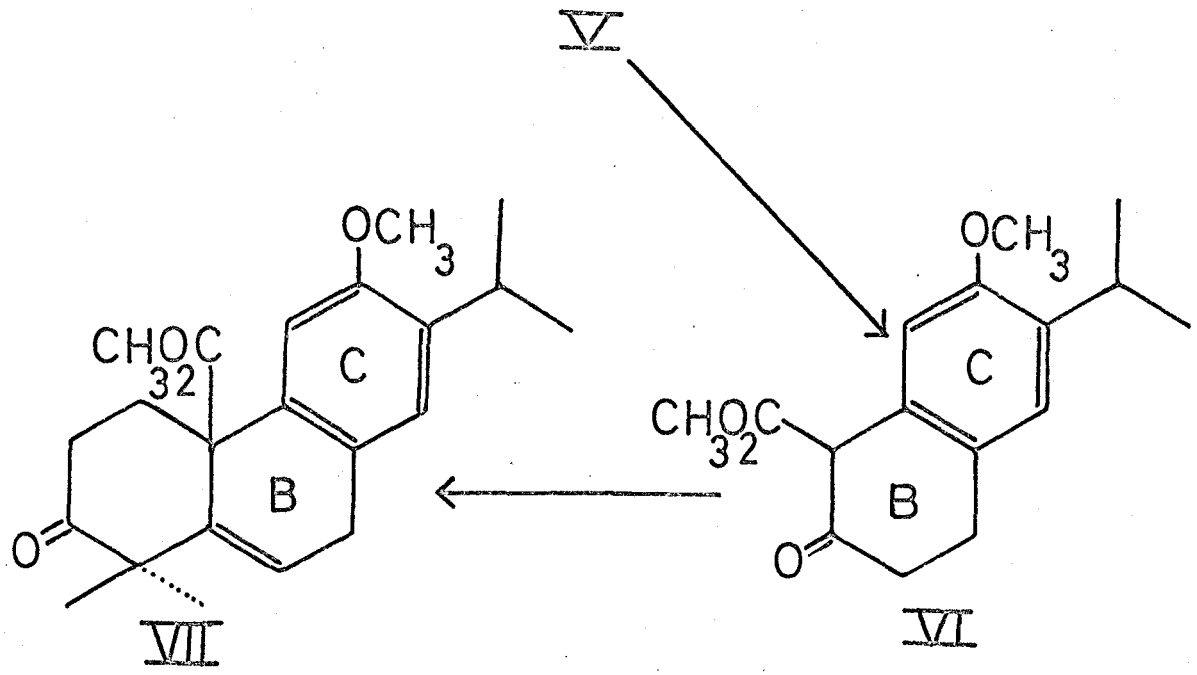


1e

This acid is a diterpenoid possessing the dehydroabietane carbon skeleton. It is a highly oxygenated molecule and the C-20 carboxyl group is an unusual structural feature among the known resin acids. The central problem of this synthetic work was expected to be the creation of this carboxyl group and its retention during the course of all of the reactions involved in the synthesis. Further, once a successful method of synthesis of carnosol is found it can be reasonably expected to be applicable to the synthesis of other more complex diterpenes and triterpenes. Such related but more complex terpenoids will be discussed in the Historical Section.

The proposed synthetic route consists of starting with a naphthalene system (IV) (representing the B and C rings of the final product), introducing a carboxyl group at the C-1 position (V) and modifying ring B by Birch reduction (VI). Ring A could then be attached by the addition of a four carbon chain and cyclization. Placing two methyl groups at C-4, removal of the 3-keto group, and removal of the 5,6-double bond are the remaining major steps to be accomplished (VII). In an alternate approach ring B of the naphthalene system may be reduced by the procedure of Birch and the carboxyl group could be introduced at C-1 of the modified B ring.





The actual timing of the placement of the carboxylic group has to await experimentation. Part I of the discussion is concerned with the carboxylation of the naphthalene system at C-1 and the conversion of the naphthoic acid to the carnosic acid system. Part II of the discussion is centred around the carboxylation at C-1 of the modified B ring of the A,B ring system.

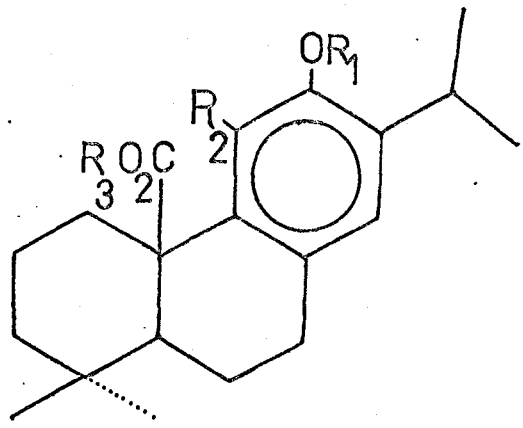
In the course of the present work a number of differently substituted tricyclic compounds with C-20 ester functions were synthesised. The tricyclic α,β-unsaturated ketones 85, 111 and 120 and the hindered esters 99 and 1a are the important compounds synthesised with C-20 carboxyl groups. The very fact that these different compounds with different structural features were made by essentially the same method illustrates

the generality, versatility and dependability of the method and hence its applicability to the synthesis of other terpenes.

HISTORICAL

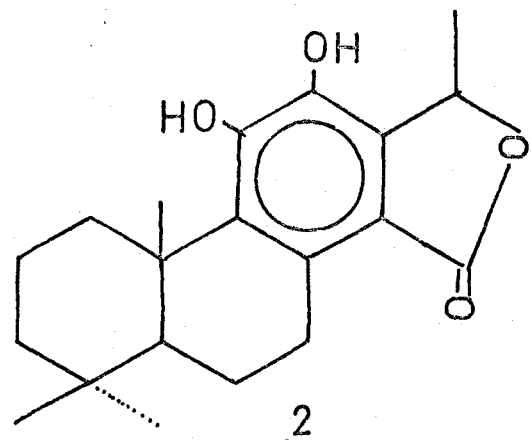
The elucidation of the structure of organic compounds of plant or animal origin - generally referred to as natural products - is an important aspect of organic chemistry. Terpenes and other compounds derivable from a five carbon unit are widely distributed in the plant and animal world, and have received much attention from the structural and synthetic chemist. In its early phases, the synthesis of terpenes was principally directed towards the confirmation of structure, but in recent years synthesis has become a convenient forum for the study of the sequential application of common reactions and reagents to new molecular situations.

The object of this work is the examination of reactions and intermediates which might lead to convenient synthesis of diterpenes (compounds containing 20 carbon atoms) with a carboxylic acid functional group in the C-20 position. Diterpenes functionalized in this manner are relatively rare in nature. Specifically a synthetic approach to methyl O-methyl -11- desoxy carnosate (1a) has been developed. The compound 1b which is a derivative of 1a, has been converted to ethyl O-methyl carnosate[1] (1c). Since 1c has been transformed into carnosic acid[1-5] 1e, the work described here constitutes a total synthesis of the natural product.



1

a, R_2=H, R_1=R_3=Me
b, R_1=R_2=H, R_3=Et
c, R_1=Me, R_2=OMe R_3=Et
d, R_1=Ac, R_2=OAc, R_3=H
e, R_1=R_3=H, R_2=OH
f, R_1=R_3=Me, R_2=OMe



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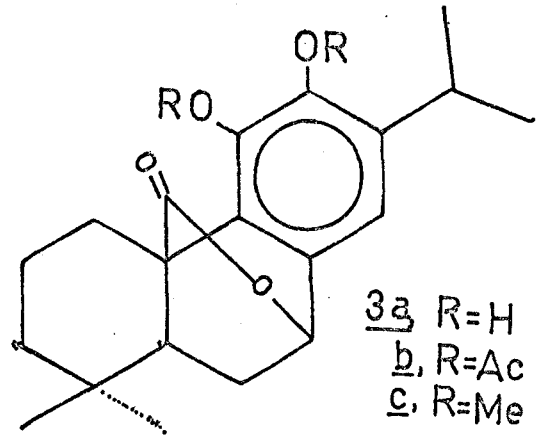


3a R=H
b, R=Ac
c, R=Me

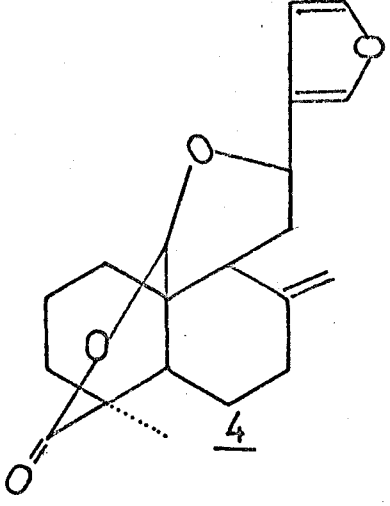
Over 25 years ago a bitter principle was isolated from Sage, Salvia carnosa D[6]. The natural product was named carnosol and noted to be a diphenolic ester with molecular formula $C_{19}H_{26}O_4$. Another bitter principle, Picrosalvin was isolated recently from two other species of sage, Salvia officinalis L. and Salvia triloba L[7,8] as well as from rosemary, Rosmarinus officinalis L.[9] Structure 2 was proposed for picrosalvin. The similarities in the physical and chemical properties of the two bitter principles suggested that they may be the same compound. A direct comparison of the two substances and their derivatives was made[9] and their identity established. In view of the priority of the work of White and Jenkins[6] the name carnosol

is retained. The elegant work of Wenkert et al.[9] has established that carnosol has structure 3a.

Recent studies by Wenkert, Fuchs and McChensey[3] have shown that carnosic acid 1e is the natural product and that carnosol is a product of oxidation of carnosic acid formed during its isolation. A hexane extract of rosemary leaves was acetylated and fractionated by column chromatography. The only product isolated in appreciable quantity proved to be the diacetate of carnosic acid, 1d, first prepared by the hydrogenolysis of carnosol diacetate (3b)[9] and recently reported in an investigation of the constituents of salvia officinalis L.[4]. Serious doubt regarding the natural product status of carnosol derived from observations of the presence of its diacetate in only small quantities among the products of acetylated extracts of rosemary leaves and its constant regeneration from solutions of extracts of sage[6]. The conversion of carnosic acid into carnosol by exposure of a methanolic solution of the acid to air for several weeks confirmed this hypothesis.

A novel diterpene, sciadin, was isolated by Sumimoto[10] from the powdered heartwood of S. Verticillata. It was assigned structure 4 from chemical and spectroscopic evidence. Aside from the presence of a furan ring, the most interesting feature in this compound is the presence of an oxygenated 20 -carbon atom.

A few diterpene alkaloids also contain functionalized 20 -carbon atoms. As a result of the pioneering researchers of Jacobs and Wiesner the structures of many alkaloids of tha atisine family such as veatchine (5)[11, 13],



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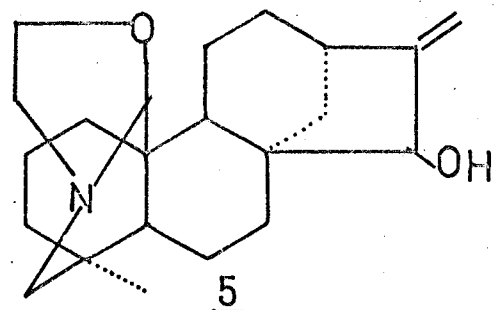

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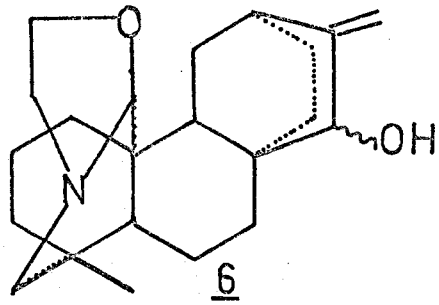

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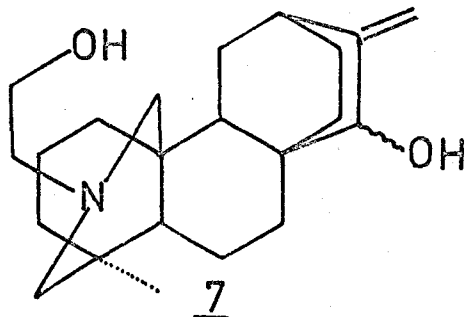

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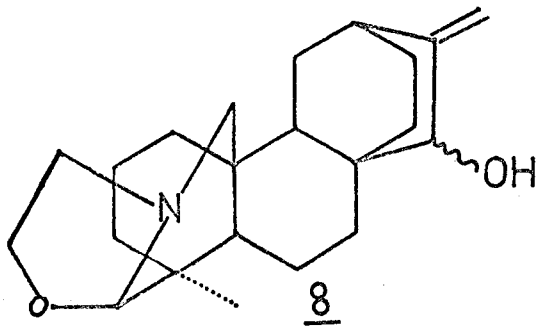

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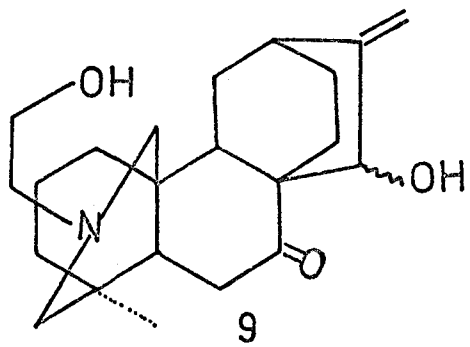

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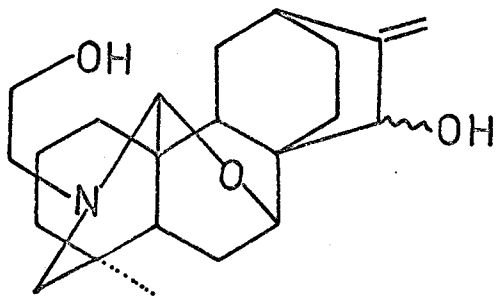

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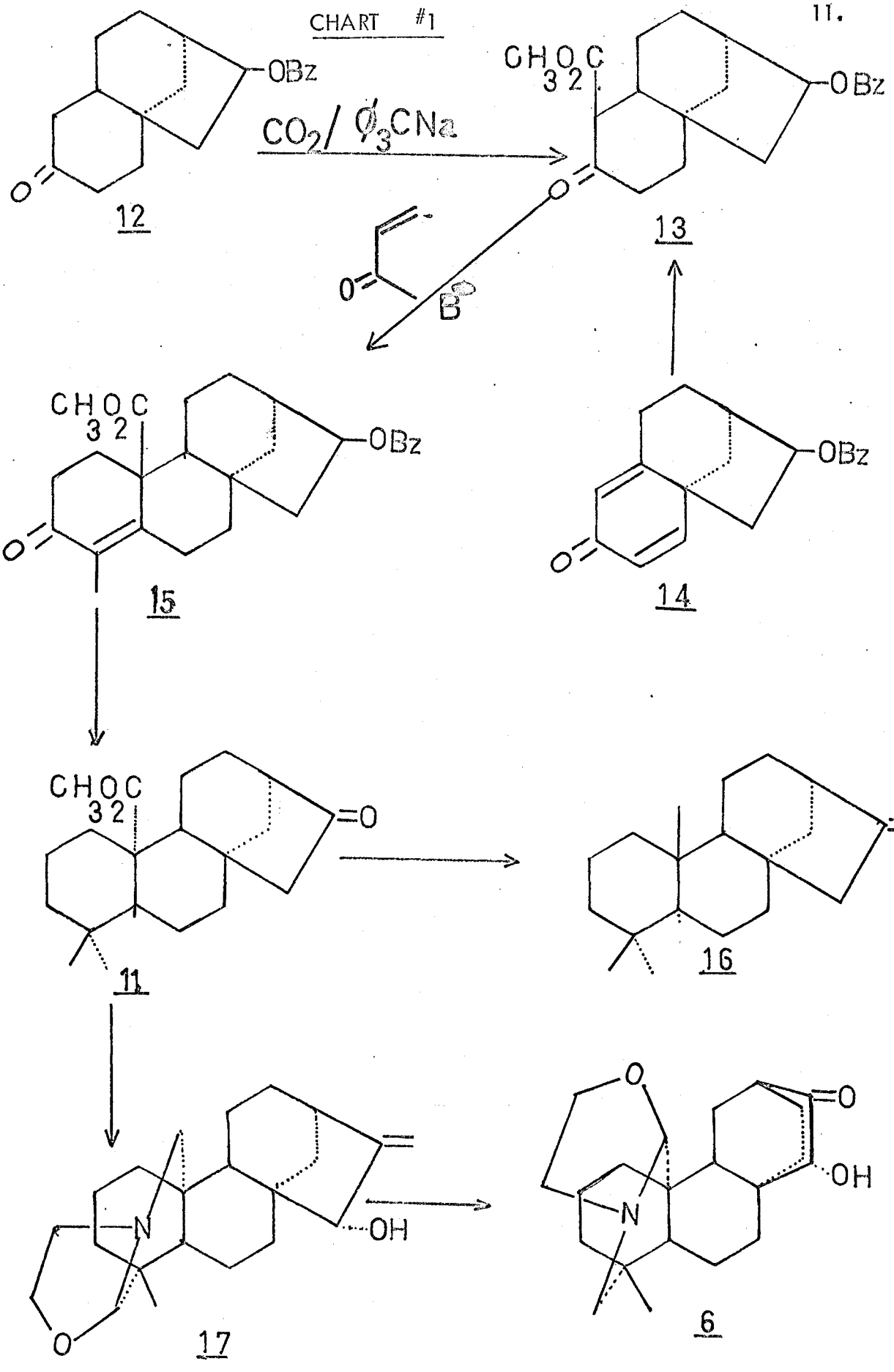
CHART #1



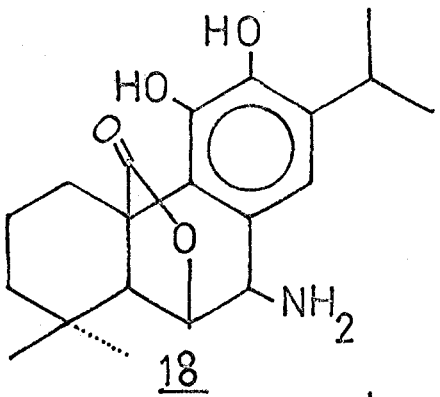
atisine (6)[12], dihydroatisine (7)[11], and isoatisine (8)[12] are now well established. Though the structures postulated by Wiesner were based mainly on analogy, subsequent study at the Rockefeller Institute and the National Research Council, Ottawa have provided further justification for these structures[14-20]. Pelletier[21] has shown that atidine (9) is a ketodihydroatisine. The delphinium alkaloid ajaconine was shown to have structure 10 by Edwards and Dvornik[22].

Masamune[23] carried out the synthesis of dl-16-keto-10-carboxy-17,20-bisnorkaurene 11, a diterpenoid containing a C-20 carboxyl function. Carbonation of the ketone 12 in the presence of triphenyl methyl sodium followed by methylation afforded the keto-ester 13. Alternatively 13 was obtained by a similar carbon-methylation of 14 followed by hydrogenation. Ring A was constructed by Michael addition to give the tetracyclic unsaturated ketone 15 containing the carbomethoxy group at the C-20 position. This tetracyclic compound 15 was converted into 11 in five steps. Masamune has also carried out the conversion of 11 to Kaurene (16)[24] and garryine (17)[25] and that of garryine to atisine[26]. (Chart #1).

Recently an alkaloid rosmaricine was isolated from Rosmarinus officinalis L.[27, 28]. Wenkert, Fuchs and McChesney[3] assigned structure 18 for rosmaricine and have shown that rosmaricine is not a natural product but an artifact resulting from the treatment of the plant material with ammonia.

There are a few tricyclic naturally occurring diterpenoids which have an aromatic C-ring as in the case of carnosic acid. The most important of them are podocarpic acid (19a) and dehydroabietic acid (20). The structures of these compounds have been established by chemical methods and they have been

confirmed by total synthesis.



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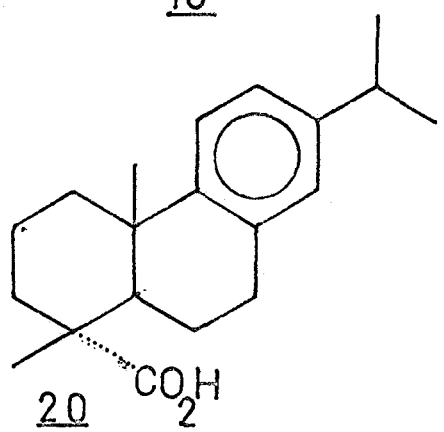

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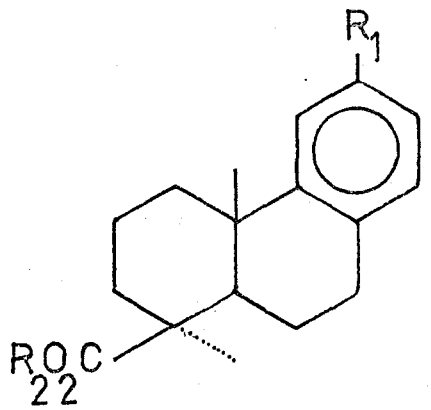


19

a, R_1 = OH, R_2 = H

b, R_1 = H, R_2 = Me

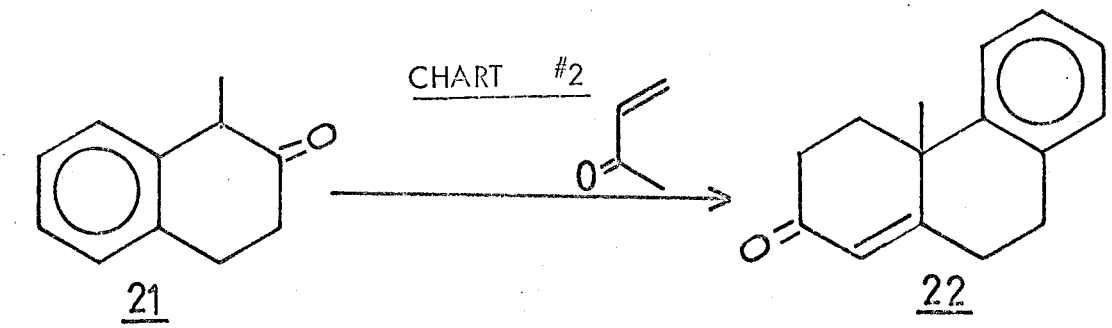
c, R_1 = R_2 = H

d, R_1 = OMe, R_2 = Me

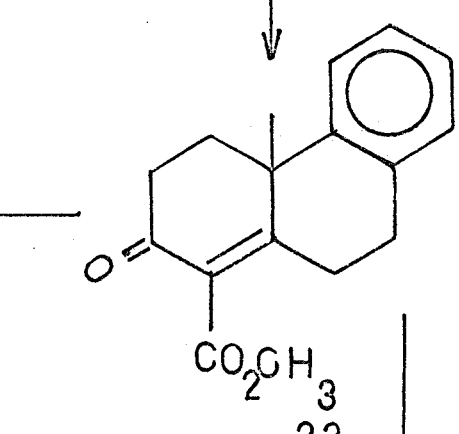
The total synthesis of podocarpic acid (19a) has been effected by a number of different groups of workers[29-35]. The initial synthetic methods [29-33] consisted in condensing together a suitably substituted cyclohexanone and a Grignard reagent containing the benzene ring to form an intermediate containing the A and C rings. This intermediate on cyclisation gave the perhydrophenanthra - 9,11,13- triene carbon skeleton.

The recent methods of synthesis[34, 35] of podocarpic acid have made use of Robinson's annelation reaction[36-40] to create the octahydrophenanthrene skeleton. Wenkert and his co-workers[35] have effected a total synthesis of (+)-podocarpic acid from 1-methyl-2-tetralone (21). The teralone was converted

CHART #2



21 22



$CO_2, \emptyset_3C^{\ominus}$

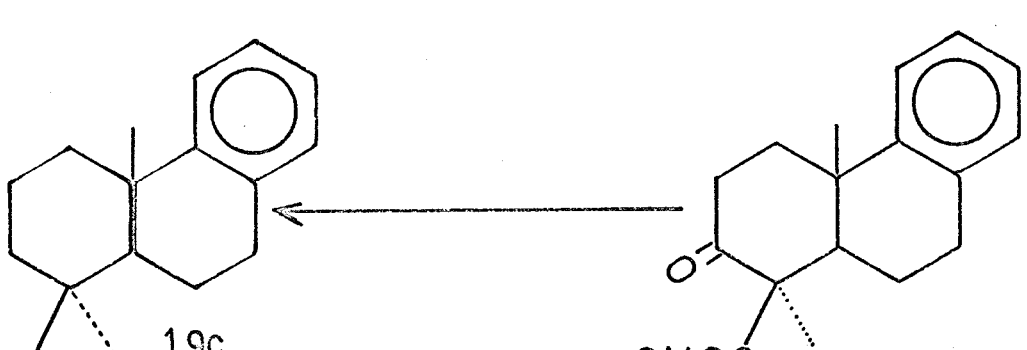
H_2

$CH_3I, B^{\ominus}$

$CH_3I, B^{\ominus}$

25 23

26



19c 24

to 22 by the Robinson annelation reaction. The product on carbonation in the presence of sodium triphenyl methide followed by esterification of the resultant acid, provided 23. Methylation of 23 using methyl iodide in the presence of potassium tertiary butoxide in tertiary butyl alcohol followed by hydrogenation afforded 24 as the exclusive product. On the other hand hydrogenation of 23 to 25 followed by methylation yielded 24 and 26 in the ratio 1 : 2.4. These methylation reactions illustrate most lucidly the importance of the nature of the enolate salt in determining the stereochemical course of alkylation. Thus in the absence of steric hindrance, stereoelectronic control (axial attack by the alkylating agent) governs the stereochemistry of alkylation. Clemmenson reduction of 24 afforded methyl 12-desoxy podocarpate (19b) and this amounted to a total synthesis of (+)-podocarpic acid (19a) as the oxygenation[41] of 19c and the resolution[42] of the dl-acid had been effected earlier. (Chart #2).

Stork and Schulenberg[43, 44] have achieved the total synthesis of dl-dehydroabietic acid (20) using the Robinson annelation[36-40] method for creating the tricyclic skeleton. They converted 6-isopropyl-2-naphthol (27) to the tetralone 28 by sodium in liquid ammonia reduction[45,46]. The tetralone was methylated at the 1-position by the enamine alkylation procedure[47]. The addition of ring A to the bicyclic ketone 29 was carried out by the addition of ethyl vinyl ketone in the presence of aqueous methanolic potassium hydroxide[40]. Alkylation of the resultant α,β-unsaturated ketone 30 using ethyl bromoacetate in the presence of potassium tertiary butoxide in tertiary butyl alcohol afforded 31 as the only product. The presence of the axial angular methyl group at C-20

CHART #3

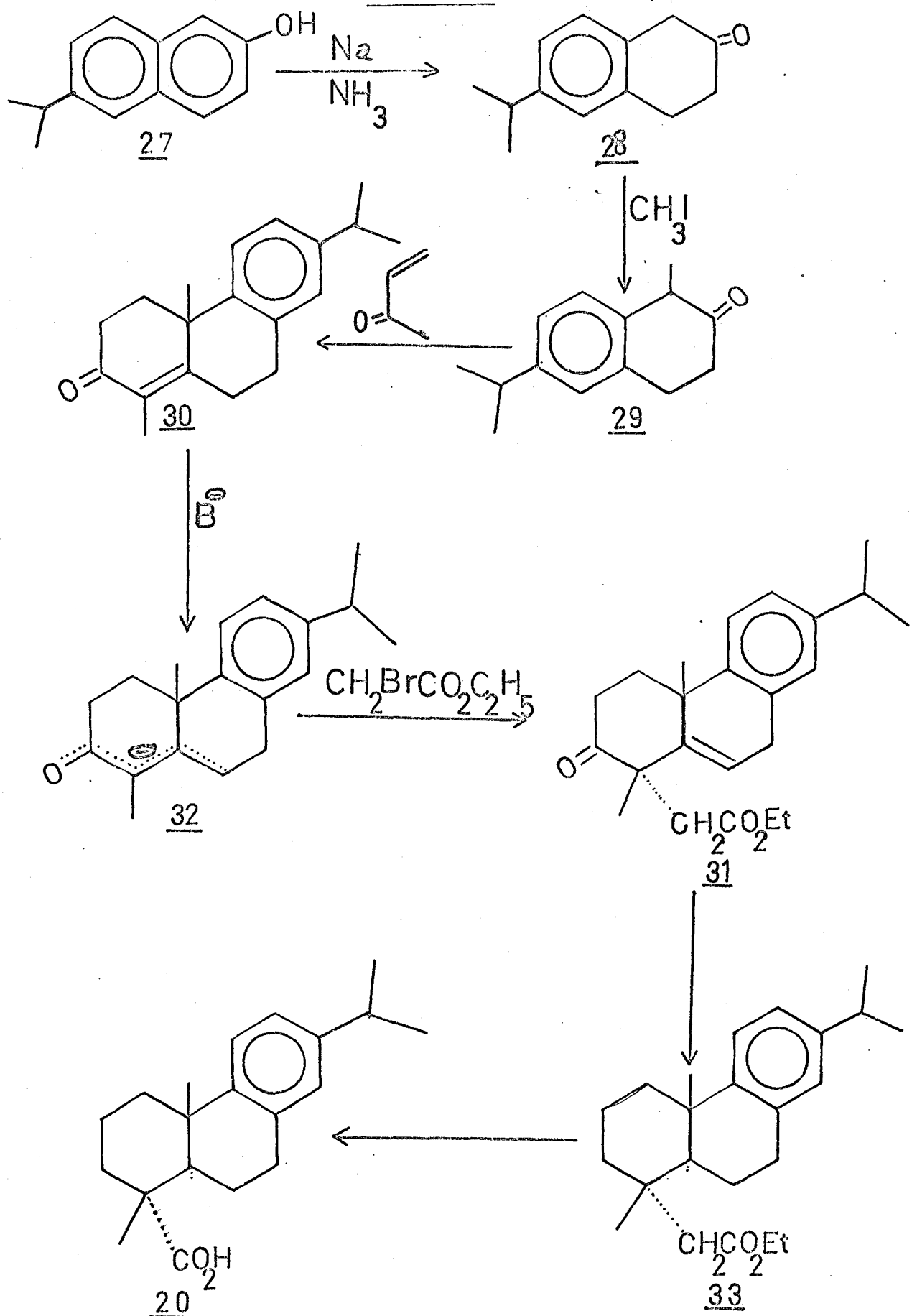
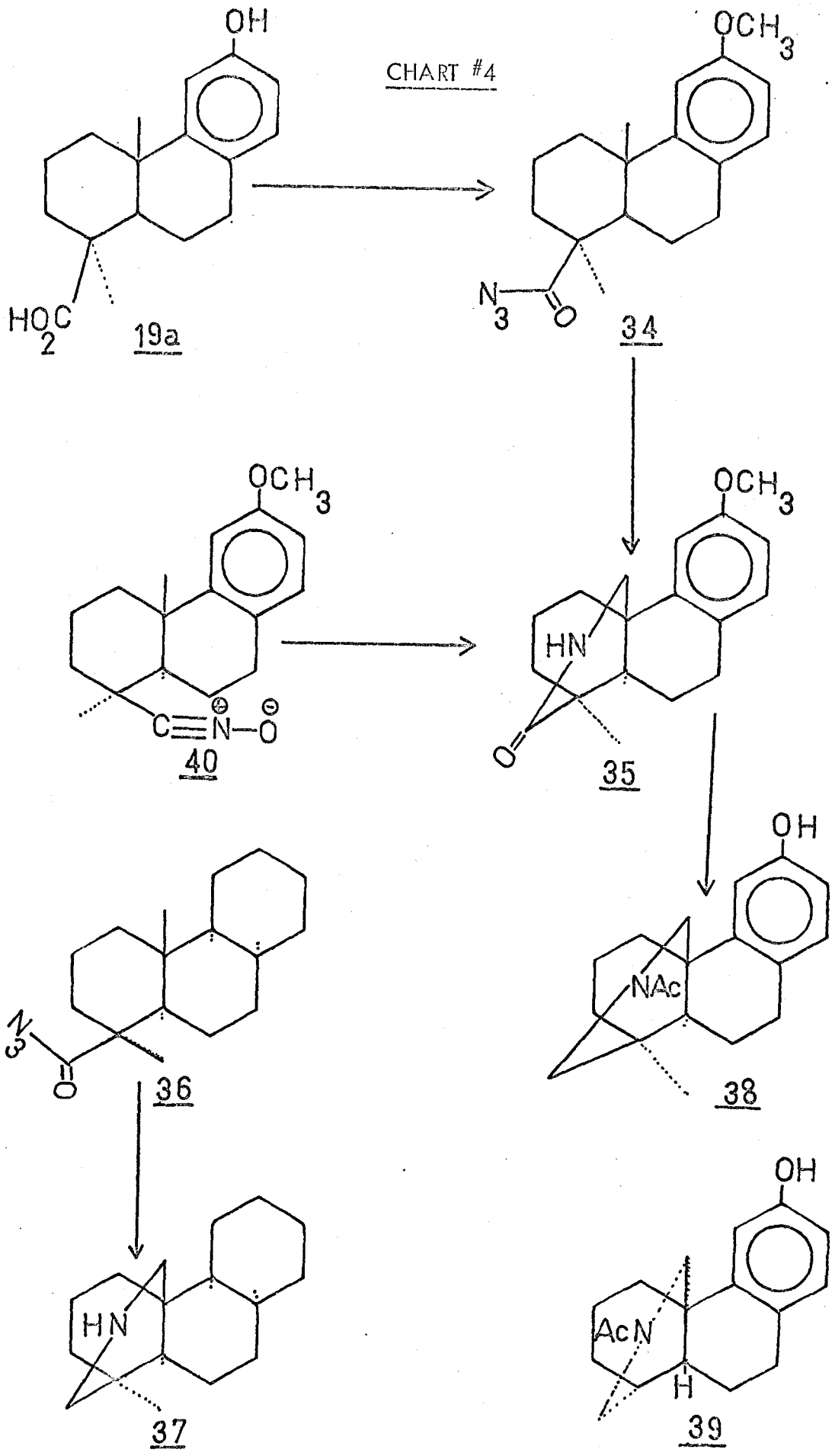

OH
Na
NH3
27
28
CH3I
O
O
O
30
29
B⊖
CH2BrCO2C2H5
32
O
CH2CO2Et
31
CO2H
20
CHCO2Et2
33

CHART #4


OH
HO2C
19a
OCH3
N3
O
34
OCH3
C≡N–O
40
OCH3
HN
O
35
OH
NAc
38
N3
O
36
HN
37
OH
AcN
H
39

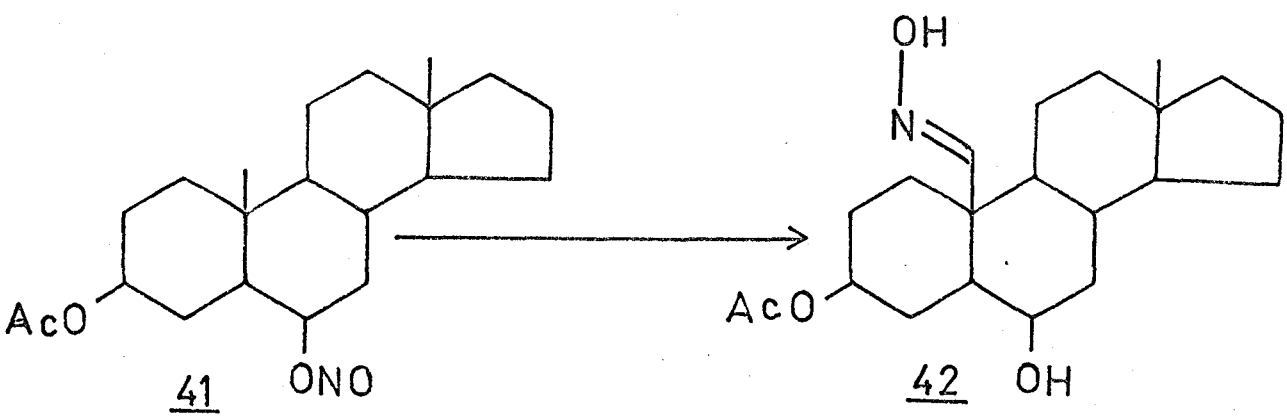
in the rigid enolate 32 was expected to make the transition state for alkylation in which the bromo ester would approach from the β -side of higher energy than the alternate approach from the α-side. The rigidity of the anion and the large size of the alkylating agent accounts for the observed stereospecificity of this alkylation. Removal of the 3-keto group by desulphurisation of the thioketal and hydrogenation to remove the double bond followed by Barbier-Wieland degradation of the resultant ester (33) afforded dl-dehydroabietic acid (20). (Chart #3.)

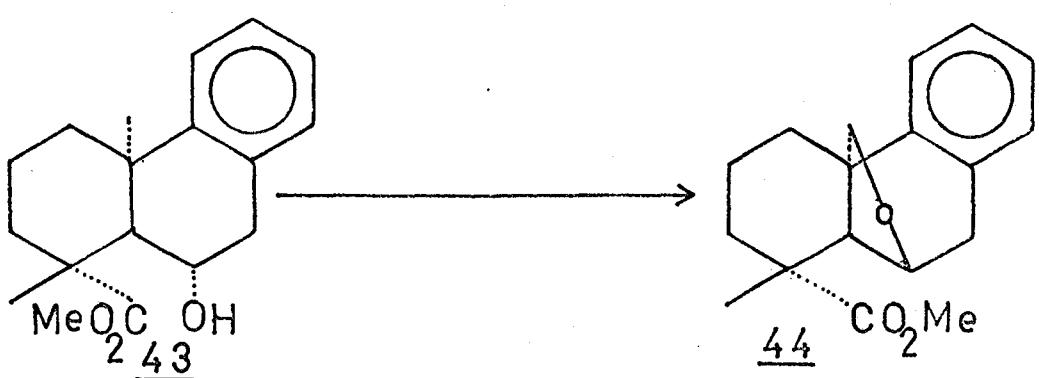
The placing of oxygenated functions in the axial and equatorial C-4 position of diterpenes has been effected by a number of methods[29-33]. However, functionalising the C-20 position has always been a more challenging problem. Apsimon and Edwards[48] have developed an ingenious method of functionalising the C-20 methyl group of podocarpic acid (19a). The azide of O-methyl podocarpic acid 34 on irradiation with ultraviolet light yielded a δ-lactam 35 in 25% yield. The azide 36 under similar conditions yielded the δ-lactam 37 in 25% yield. The lactam 35 was converted to the phenol 38 which was shown to be enantiomeric to the phenol 39 derived from atisine (6). (Chart #4.)

Recently Just and Zehetner[49] observed a bridging reaction similar to the one reported by Apsimon and Edward[48]. They prepared the stable O-methyl podocarponitrile oxide 40 by the lead tetra-acetate oxidation[50] of podocarpinal syn-oxime. The nitrile oxide 40 on irradiation in hexane solution afforded the δ-lactam 35 in 25% yield.

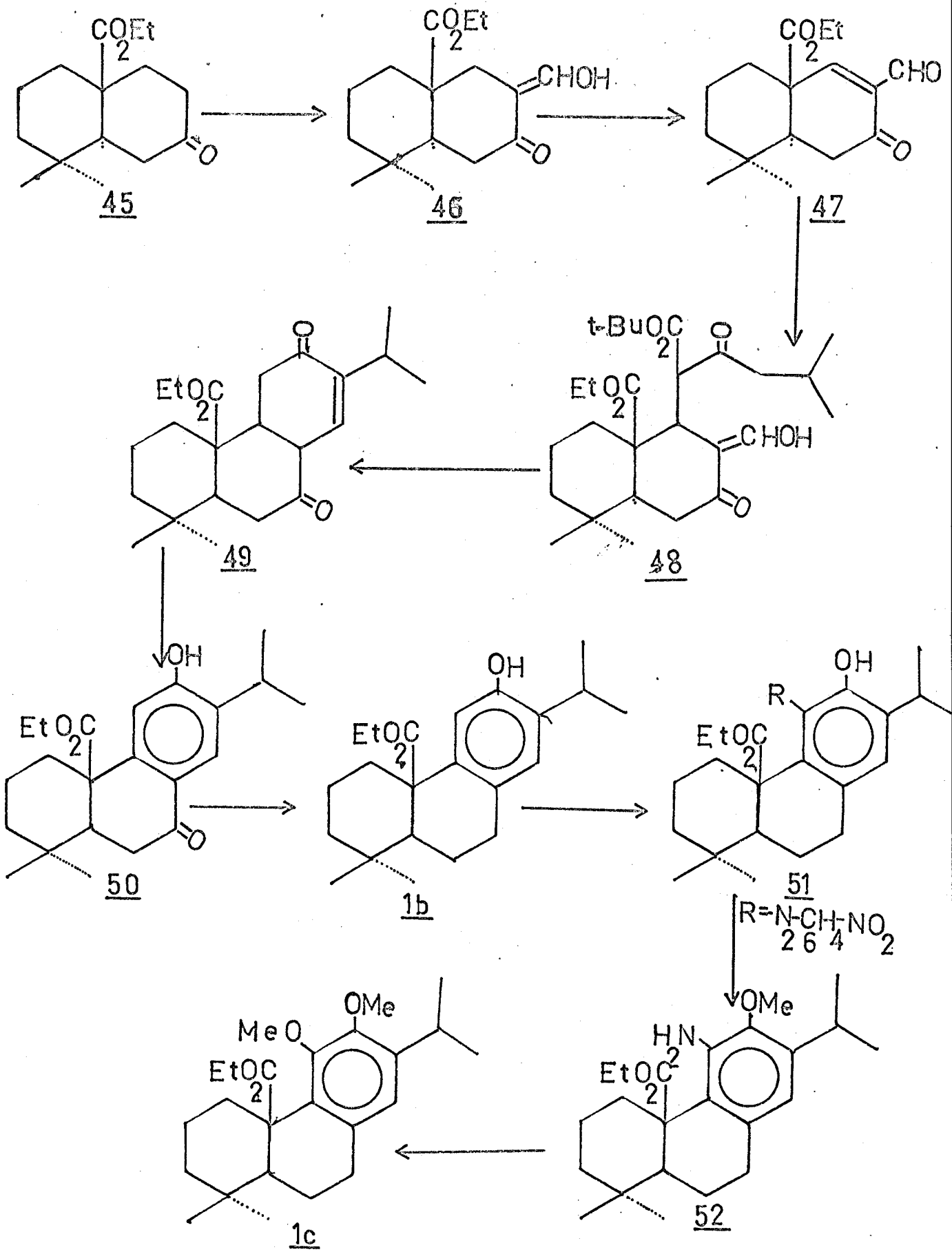
Barton[51,52] observed that the photolysis of suitably constituted organic nitrites provokes an intramolecular exchange of NO of the nitrite

residue with a hydrogen atom attached to a carbon atom in the γ-position. This ingenious reaction has been used in functionalising[53-56] many angular methyl groups which are difficult to attack by other methods. The resultant nitroso compounds can be rearranged to aldoximes. Thus photolysis of 3β -acetoxy-androstan-6β-ylnitrite (41)[57] in iso-octane or toluene gave the corresponding C-20 aldoxime 42. Similar photolysis of hypohalites has been employed recently for functionalising[58-63] angular methyl groups.





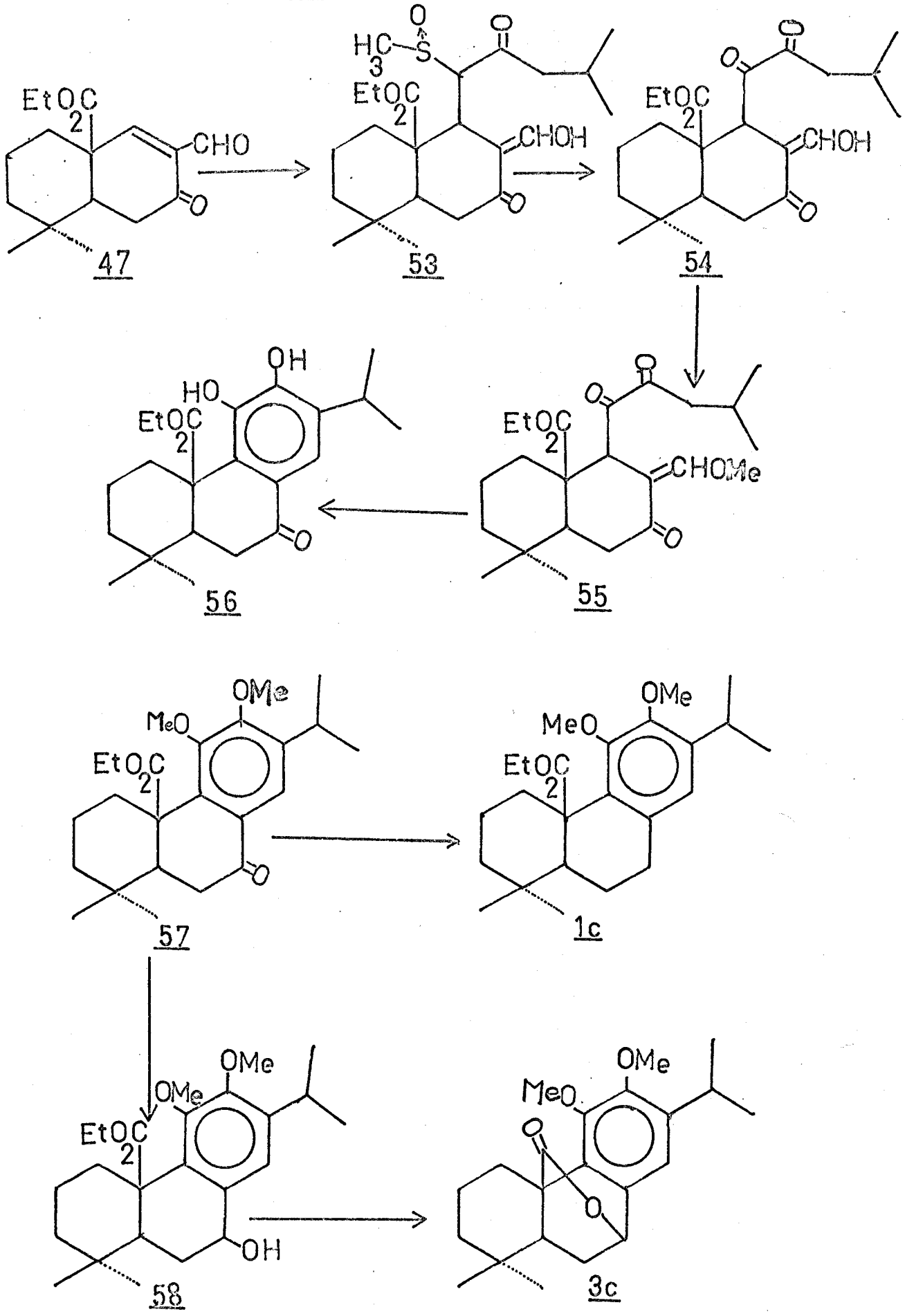
Following the application of the Barton principle to hypohalites[58-63], Mystre et.al.[64] reported a reaction of lead tetra-acetate and iodine with steroid alcohols in which the products corresponded to a Barton type intramolecular


COEt
2
CHOH
CHO
45
46
47
t-BuOC
2
EtOC
2
CHOH
O
49
48
OH
R
OMe
MeO
HN
R=N-CH-NO
2 6 4 2
50
1b
51
52
1c

substitution. Using this reaction a number of steroidal 6β, 2β, 4β, and 20-alcohols have yielded 18 - and 19- substituted compounds. Thus 6β-hydroxy steroids in a photo-induced reaction with lead tetra-acetate and iodine gave an ether bridging the C-6 and C-19 carbon atoms. Application of the same reaction to methyl 6 α-hydroxyenantiopodocarpa - 8,11,13-trien-16-oate (43) afforded the 17-epoxy compound 44.

At the intiation of this work, the only total synthesis of a diterpenoid with a C-20 oxygenated function which has been accomplished was that of dl-16-keto-10-carboxy-17,20- bisnorkaurene (11) by Masamune[23]. While the present work was in progress Meyer and Schindler[1] reported the total synthesis of ethyl dl-carnosate dimethyl ether (1e). These authors employed a general diterpenoid synthesis[65] following an A→ B→ C sequence. Condensation of 4,4-dimethyl-10-carbethoxy-trans-7-decalone (45)[66] with ethyl formate resulted in the hydroxy methylene ketone 46 and the latter compound was dehydrogenated with 2,3-dichloro- 5',6-dicyanoquinone[67,68]. Michael addition of tertiary butyl-5-methyl-3-ketohexanoate to the unsaturated aldehyde 47, followed by treatment of the adduct 48 with p-toluene sulphonic acid afforded the enedione 49. which dehydrogenated over palladium on charcoal to the ketophenol 50. Palladium catalysed hydrogenolysis of 50 afforded the phenolic ester 1b. (Chart #5).

The 11-methoxy group was introduced[1] by an adaptation of the sequence applied in the structure elucidation of carnosol[9]. Treatment of the phenol 1b as its sodium salt with diazotised p-nitroaniline afforded the azocompound 51 which was methylated and reduced with dithionite to the methoxyamine 52.


EtOC
2
CHO
O
47
HC
3
O
S
EtOC
2
CHOH
53
EtOC
2
CHOH
54
EtOC
2
CHOMe
55
OH
HO
EtOC
2
56
OMe
MeO
EtOC
2
57
OMe
MeO
EtOC
2
1c
OMe
OMe
EtOC
2
OH
58
OMe
MeO
O
3c

Diazotisation and methanolysis of 52 yielded ethyl dl-carnosate dimethyl ether (1c).

More recently, Meyer and Shew[69] have developed a new method of constructing the 11,12-dihydroxylated C-ring of carnosic acid. The new method has the advantage that it avoids the lengthy procedure of introducing the 11-oxygen and that the 7-oxygen could be retained for synthesis of compounds like carnosol (3a)[4,9]. The sodium enolate of 1-methyl sulphonoxy-4-methyl-2-pentanone, prepared by the condensation of dimethylsulphoxide with ethyl isovalerate[70], when added to the unsaturated keto aldehyde 47[1] yielded the adduct 53 as a pair of crystalline diastereomeric racemates. Addition of 50% aqueous acetic acid[71] to either adduct resulted in the formation of the α-diketone 54, the methyl enol-ether of which (55) underwent cyclization in methanolic sodium methoxide to produce the keto-catechol 56. Hydrogenolysis of the corresponding dimethyl ether (57) afforded ethyl dl-carnosate dimethylether (1c), identical with a sample synthesised by the earlier method[1].. Reduction of the keto-dimethyl ether 57 with sodium borohydride followed by lactonisation of the hydroxy ester 58 with potassium tertiary butoxide in benzene[4] afforded dl-carnosol dimethyl ether 3c. (Chart #6.)

DISCUSSION AND RESULTS

PART I - The Synthesis of Naphthoic Acids

The initial approache to the octahydrophenanthrene diterpenes was geared to the preparation of suitably substituted naphthoic acids. The carboxyl group of these acids would constitute the C-20 functionality of the tricyclic skeleton. The first part of this thesis is devoted to attempts to carboxylate 2,7-dimethoxynaphthalene (59) at the 1-position. Subsequent Birch reduction of the resultant naphthoic acid and Michael addition of methyl vinyl ketone to the tetralone ester would create the tricyclic skeleton with a C-20 carbomethoxy function.

Accordingly 2,7-dihydroxynaphthalene (60) was used as the starting material. This was converted into the dimethoxy derivative 59 in 85% yield by methylation with dimethyl sulphate and sodium hydroxide[72]. Bromination according to the procedure or Roger Adams[73] proceeded in 92% yield. Lithiation of the 1-bromo-2,7-dimethoxynaphthalene (61) with butyl lithium in anhydrous ether followed by carbonation at low temperature resulted in the formation of 2,7-dimethoxy-1-naphthoic acid (62). However, extensive purification of the naphthoic acid was required and was finally accomplished by conversion to the methyl ester[74], followed by alkaline hydrolysis. The

overall yield of the reaction was only 49% and was much lower than the reported yield[73] of 68%, presumably because the previously prepared acid was impure. All attempts to improve the yield of this reaction failed.

In an alternative approach to prepare 62, 2,7-dimethoxynaphthalene (59) was converted to the 1-formyl derivative by the reaction of 59 with dimethyl formamide and phosphorus oxychloride in toluene[75]. Hydrolysis of the resultant immine yielded 2,7-dimethoxy-1-naphthaldehyde (63) in 85% yield. This aldehyde was oxidised to the corresponding naphthoic acid 62 with alkaline silver oxide[76] in methanol. The yield of the oxidation reaction was poor probably because of complications arising from the formation of naphthaquinones. The presence of 62 in the reaction product was shown by its conversion to the methyl ester with diazomethane and the mass spectrometric detection of the molecular ion at m/e 246. The contaminants however, prevented the isolation of 62 in pure form in any reasonable yield and after a number of trial experiments with other oxidising agents, this approach to 62 was not further explored. Adams[73] has noted similar, very low yields in the permanganate oxidation of 63 and Buu-Hoi has made a similar observation in the silver oxide oxidation of 63.

The Friedel-Crafts acylation of 2,7-dimethoxynaphthalene (59) with acetyl chloride and anhydrous aluminium chloride in methylene chloride was attempted. The complex pattern of absorptions from 6.5 to 8.0 ppm in the pmr spectrum of the reaction products indicated that they were a mixture

of isomers. The crude mixture of these acetyl naphthalenes was oxidised to the corresponding naphthoic acids with sodium hypochlorite. The product obtained was a mixture of 62 and 2,7-dimethoxy-3-naphthoic acid (64) in a ratio of 1:2.5 respectively. From this mixture a pure sample of the 3-acid 64, was obtained as an ether insoluble material. The ether-soluble fraction was shown from its pmr spectrum to be a 1:1 mixture of the two naphthoic acids. Buu-Hoi[76] has reported that the acylation of 59 in nitrobenzene resulted in the sole formation of the 3-acetyl compound 65. Since 62 was only a minor product in the above reaction this method was not pursued further.

CHART #7

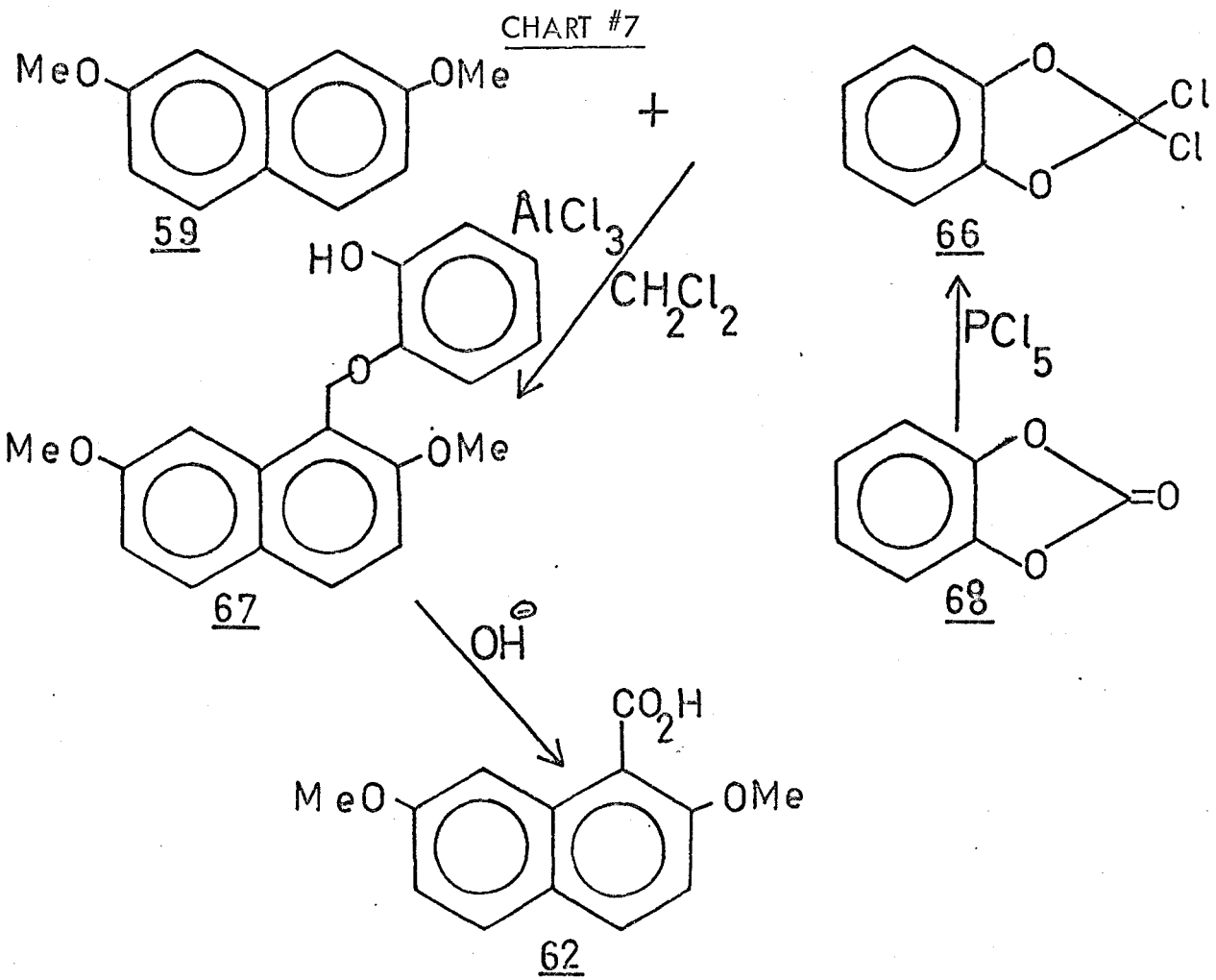
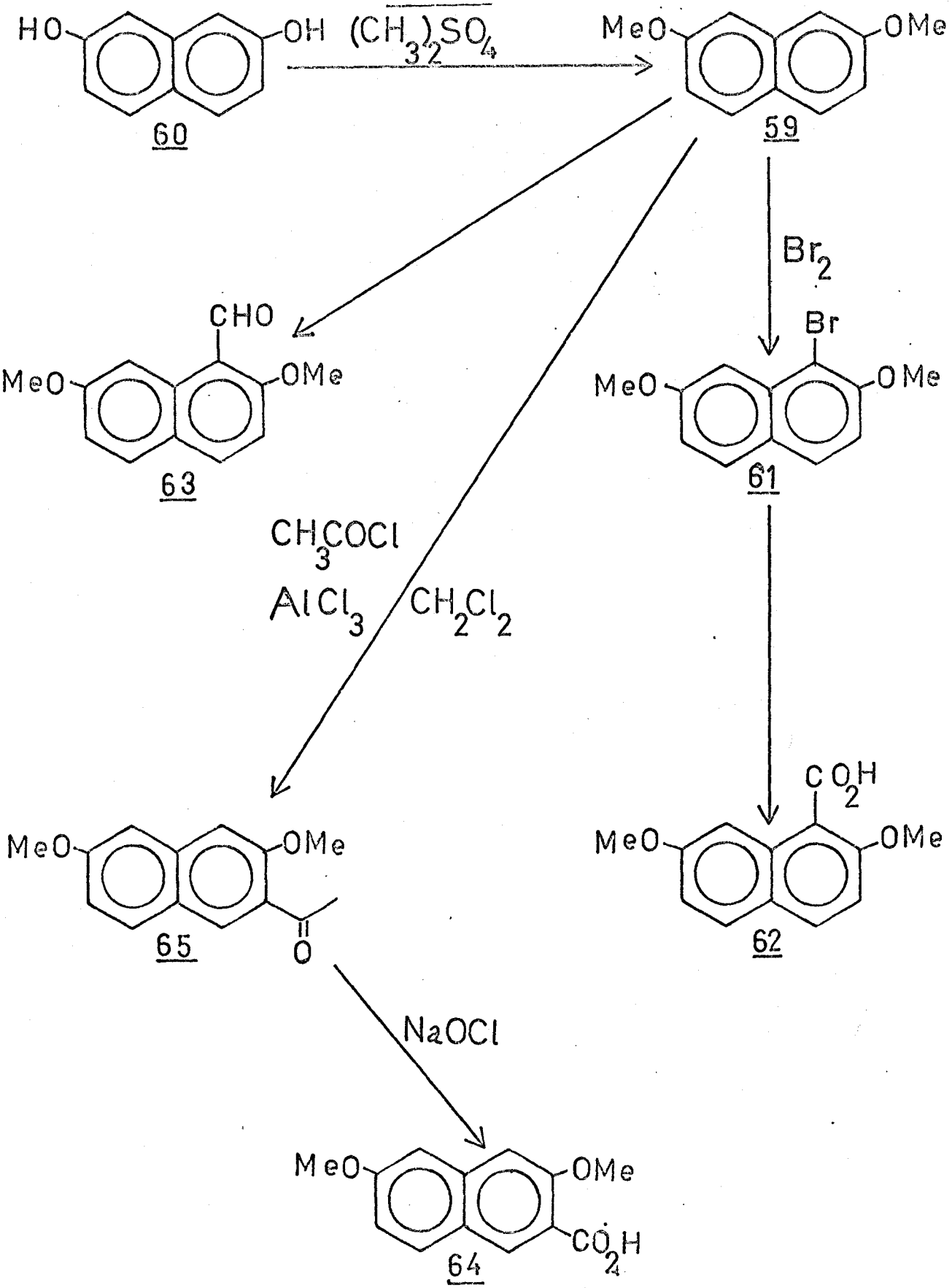


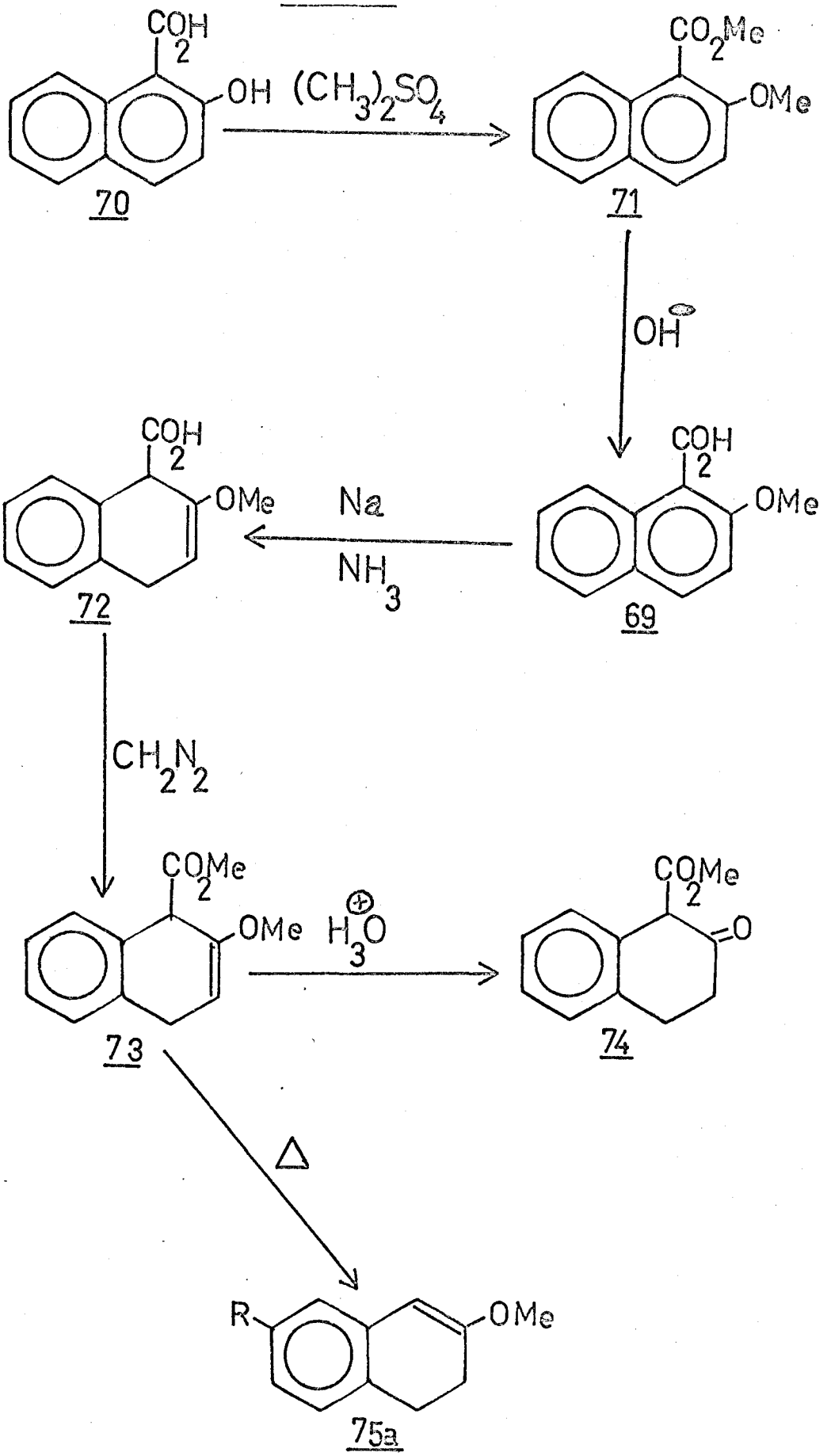
CHART #7


HO
OH
$(CH_3)_2SO_4$
60
MeO
OMe
59
Br_2
CHO
MeO
OMe
63
Br
MeO
OMe
61
CH_3COCl
$AlCl_3$
CH_2Cl_2
MeO
OMe
65
O
CO_2H
MeO
OMe
62
NaOCl
MeO
OMe
CO_2H
64

A more successful method of preparation of the acid 62 proved to be a Friedel-Crafts acylation by the method of Gross[77]. The reaction of 2,7-dimethoxynaphthalene and catechol-dichloromethylene acetal (66) in the presence of anhydrous aluminium chloride in methylene chloride yielded the catechol ester of 2,7-dimethoxy-1-naphthoic acid (67). This catechol ester on alkaline hydrolysis in the presence of sodium dithionite provided 62. The purification of this acid was tedious and difficult as it was contaminated with large quantities of catechol and catechol oxidation products. Hot water crystallisation of the crude acid gave a pure sample of the acid in an overall yield of 48%. The chloro compound 66 used in this reaction was prepared[77, 78] by the action of catechol carbonate (68) and phosphorus pentachloride. (See Chart #7.)

The further utilization of the substituted naphthoic acid 62 required the specific reduction of only one ring of the naphthalene system. The presence of the 1-carboxylic acid would be expected to direct reduction to the carboxylate-substituted ring when a metal-ammonia system was used as the reducing agent[45]. In order to study the experimental conditions necessary for this specific reduction, the simple and more readily available 2-methoxy-1-naphthoic acid (69) was used as a model. A sample of 69 was prepared in 54.5% from 2-hydroxy-1-naphthoic acid (70) by methylation with dimethyl sulphate and sodium hydroxide, followed by alkaline hydrolysis of the resultant methyl ester 71. The naphthoic acid 69 was reduced to the dihydro acid 72 with sodium in liquid ammonia according to the procedure of Birch[45]. In

CHART #8


COH2
OH
(CH3)2SO4
CO2Me
OMe
70
71
OH⊖
COH2
OMe
Na
NH3
72
69
CH2N2
COMe2
OMe
H3O⊕
O
73
74
Δ
R
OMe
75a

order to protect the carboxyl group, the dihydro acid 72 was first esterified with diazomethane and the enol-ether-ester 73 was then hydrolysed with dilute hydrochloric acid in acetone solution to yield the β-keto ester 74. In the purification of the enol-ether ester 73 by vacuum distillation 3,4-dihydro-2-methoxy-naphthalene (75a) was obtained as a low boiling fraction (25% in yield). This might have arisen as a result of the pyrolytic decomposition of the ester group followed by rearrangement. The conversion of the naphthoic acid 69 to the keto ester 74 proceeded in an overall yield of 71%. (See Chart #8.)

In view of the reasonable results obtained for the reduction of 69, the same procedure was adopted in the conversion of the naphthoic acid 62 to 1,2,3,4-tetrahydro-7-methoxy-1-carbomethoxynaphthalen-2-one (76). The Birch reduction of the acid 62 followed by treatment with diazomethane resulted in the ester 77 in 73.7% yield. The acid hydrolysis of the ester 77 yielded the keto ester 76 in 66.3%. Attempts to crystallise 77 were unsuccessful probably because of contamination by 7-methoxy-2-tetralone (78) which arose from the decomposition of the keto-ester 76 during its distillation.

In an attempt to create the tricyclic skeleton with the C-20 ester function, Michael addition of methyl vinyl ketone to the keto ester 76 in the presence of sodium methoxide in absolute methanol[35] was attempted. Only a poor yield of a pale yellow crystalline compound could be obtained. The absence of any vinylic proton in the pmr spectrum of the compound, unexpectedly high molecular weight (m/e 338), and the presence of an α,β-unsaturated ketone

grouping suggested by the infrared spectrum, implied an unexpected structure for the product. On the basis of the spectral data and the carbon-hydrogen analysis a tetracyclic structure 79 has been proposed for the compound. The observed value of the ultraviolet absorption maximum (335 $m\mu$) agrees well with the value calculated for structure 79 using Woodward's rules[79]. The ultraviolet spectrum of another compound with a similar chromophore, 2-acetyl-5,5-dimethyl cyclohexadiene-1,3 (80), has been studied by Meinwald[80] and close agreement between the experimental and theoretical values of the ultraviolet absorption maximum has been observed.

Anomalous Michael addition products such as 79 resulting from the addition of two molecules of methyl vinyl ketone to one molecule of the substrate, have been observed earlier[81]. House[81] has obtained a tricyclic diketone 81 by the reaction of cyclo-hexaxnone enamine (82) and methyl vinyl ketone in ethanol followed by acid hydrolysis in 50% yield along with several octalones.

Addition of methyl vinyl ketone to the keto-ester 76 in the presence of triethyl amine in absolute methanol was attempted according to the procedure of Ireland[82]. The change in the A_2B_2 pattern of the addition product when compared to that of the starting keto-ester 76 and the appearance of a sharp singlet (3H) at 1.85 ppm in the pmr spectrum of the addition product, suggested that it was the bicyclic alkylation product 83. Cyclisation of this material with sodium methoxide in methanol was not attempted, as the previous Michael

CHART #9

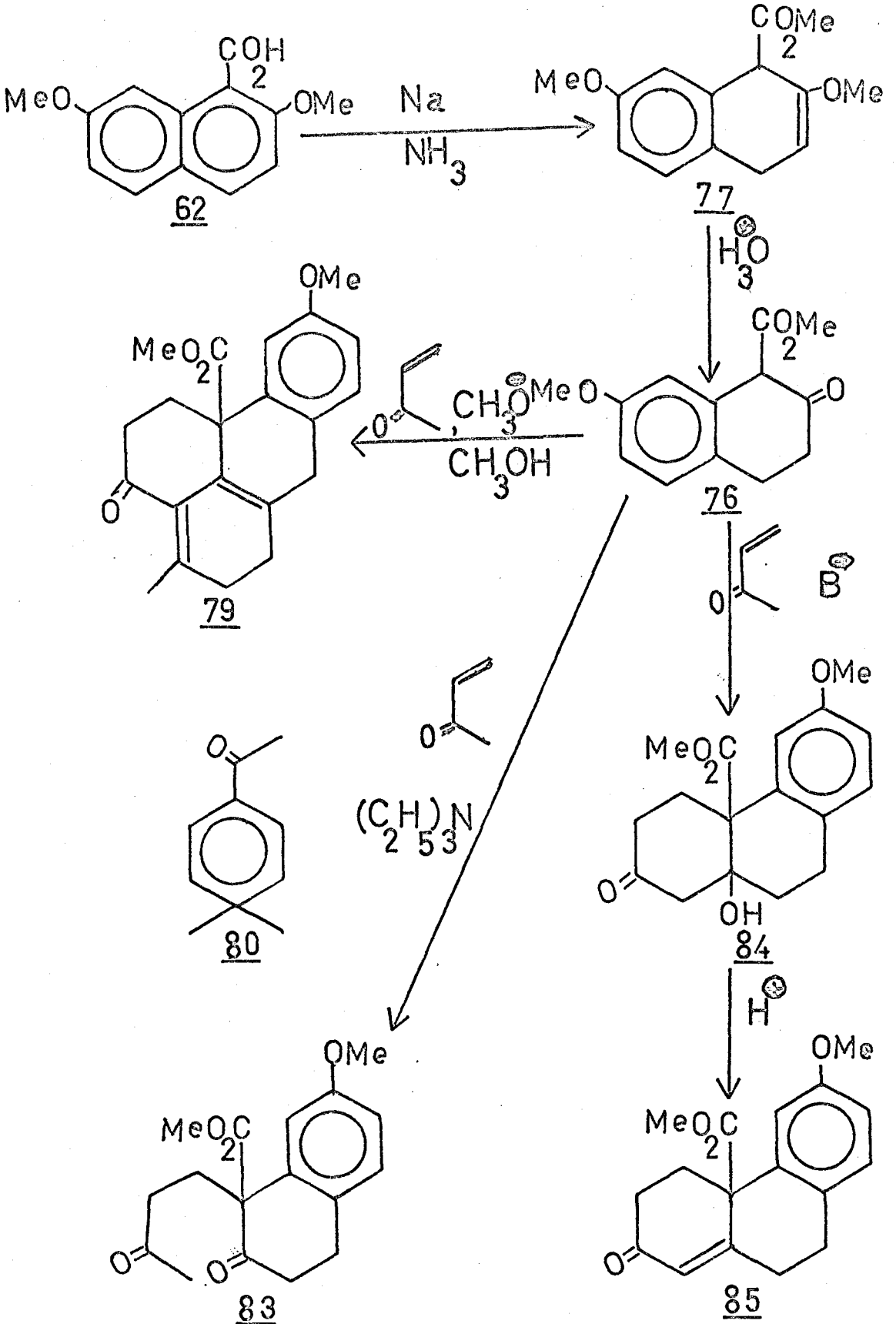
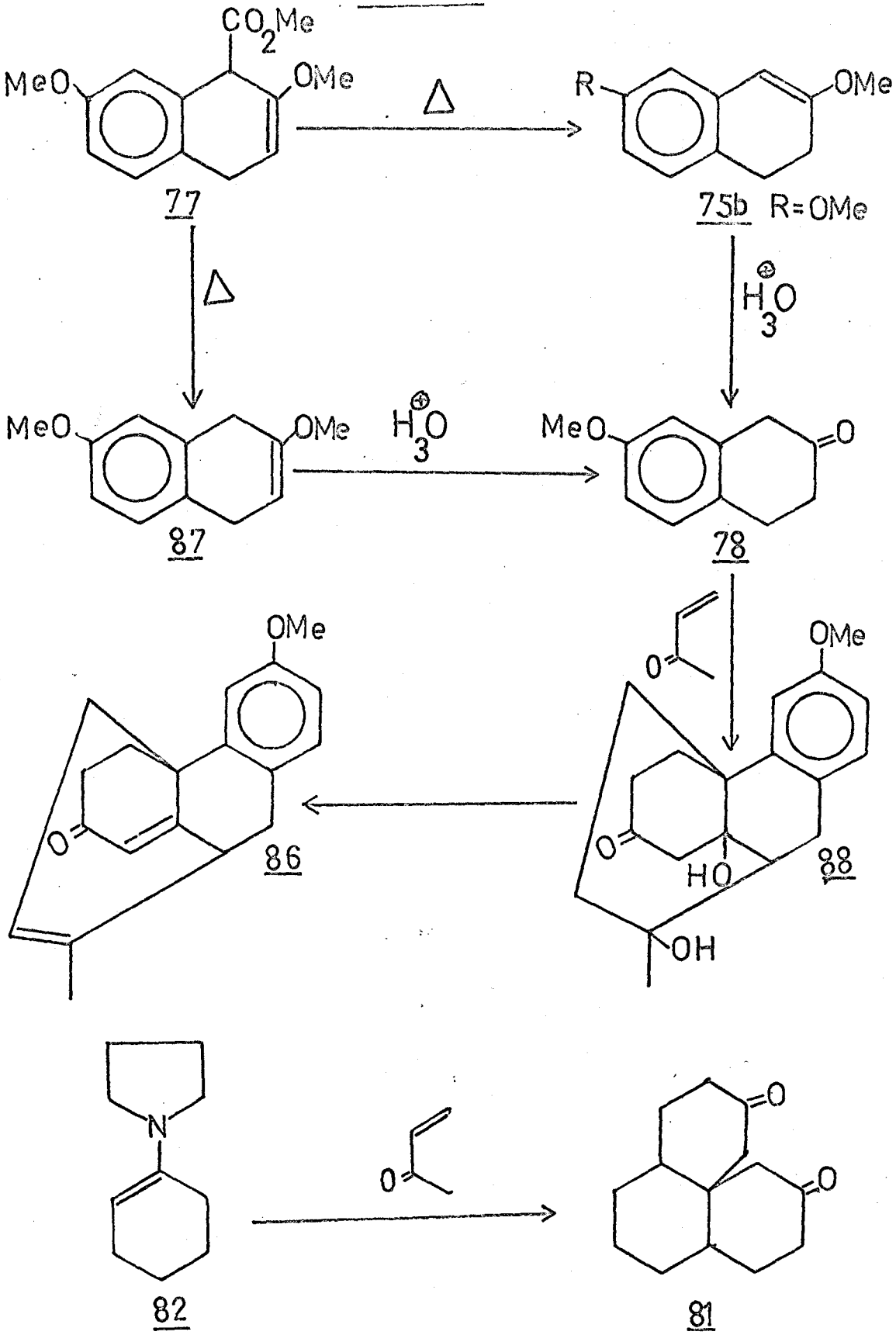

COH
2
MeO
OMe
Na
NH3
62
COMe
2
MeO
OMe
77
H3O
COMe
2
MeO
O
CH3O
CH3OH
76
OMe
MeO2C
O
79
B
O
OMe
MeO2C
OH
84
O
80
(C2H5)3N
H
OMe
MeO2C
O
O
83
OMe
MeO2C
O
85

CHART #10


CO2Me
MeO
OMe
Δ
R
OMe
77
75b R=OMe
Δ
H3O⊕
MeO
OMe
H3O⊕
MeO
O
87
78
OMe
O
OMe
O
O
HO
OH
86
88
N
O
O
O
82
81

addition experiments had resulted in multiple reaction.

The tricyclic α,β-unsaturated ketone with the C-20 ester function was finally prepared by the addition of methyl vinyl ketone to the β-keto-ester 76 in the presence of benzyl-trimethylammonium methoxide[83-85] in absolute methanol followed by dehydration of the resultant tricyclic ketol 84 with p-toluene sulphonic acid in refluxing toluene. The reaction proceeded to give 85 in an overall yield of 21% (See Chart #9.).

In experiments aimed at large scale preparation of the tricyclic ketone 85 starting from crude 2,7-dimethoxy-1-naphthoic acid (62) a side product was isolated in considerable quantities along with poor yields of 85. On the basis of its spectroscopic properties and microanalytical data a tetracyclic structure 86 has been assigned to it. The formation of 86 can be rationalised by assuming that during the distillation of 1,4-dihydro-2,7-dimethoxy-1-carbomethoxynaphthalene (77) pyrolytic decarboxymethylation has taken place leading to 1,4-dihydro-2,7-dimethoxynaphthalene (87) (or its $\Delta^{1,2}$ isomer 75b) which on acid hydrolysis produced 7-methoxy-2-tetralone (78). The addition of two molecules of methyl vinyl ketone to 78 followed by dehydration would yield 86. (See Chart #10.) It is noteworthy that in the purification of 1,4-dihydro-2-methoxy-1-carbomethoxy-naphthalene (73) by vacuum distillation described above 3,4-dihydro-2-methoxy-naphthalene (75a) was isolated in 25% yield. Similar tetracyclic ketol formation has been observed by Johnson[86] in Michael addition reactions involving methyl vinyl ketone. The slow rate of dehydration of the tetracyclic ketol 88 to yield 86 also supports the structure of the dehydration product, since the driving force for the elimination of the C-15 hydroxyl group would be low.

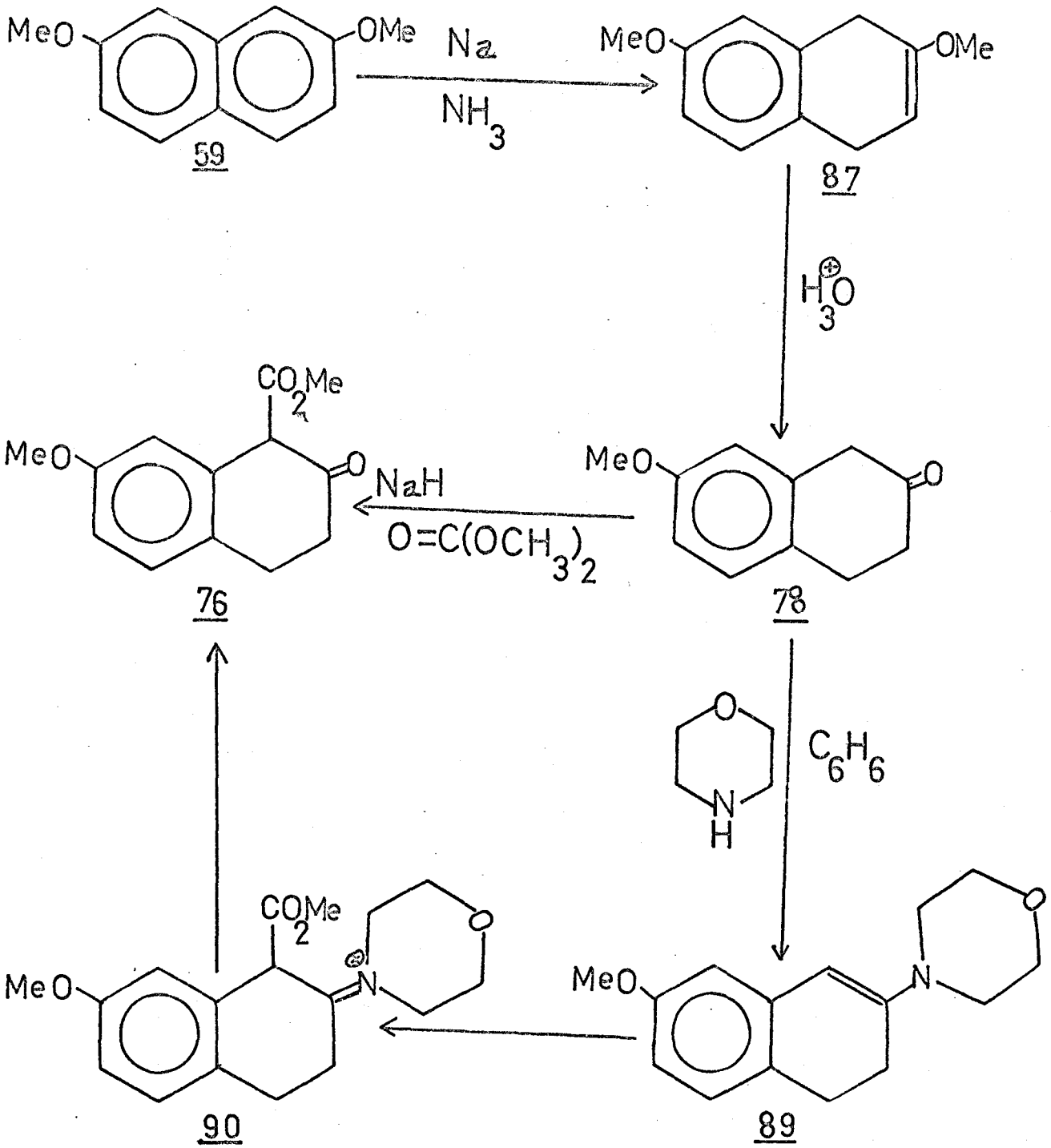
DISCUSSION AND RESULTS

PART II - Synthesis of Methyl O-methyl-11-desoxy-carnosate

The poor overall yield of the tricyclic unsaturated ketone 85 combined with the formation of unwanted side products in the above reaction sequence necessitated the search for improved methods of creating the tricyclic skeleton with a C-20 oxygenated function.

The second part of this thesis is devoted to the study of an alternative synthetic pathway which does not involve the introduction of the carboxyl group into the intact naphthalene nucleus. Rather, it was found possible to first selectively reduce 2-methoxynaphthalenes to tetrahydro derivatives and then to introduce the carbomethoxy function in excellent yield. In general outline, the synthetic sequence developed consisted of the Birch reduction of 2,7-dimethoxy-naphthalene, hydrolysis of the resultant enol-ether, carboxymethylation of the tetralone at the 1-position and addition of methyl vinyl ketone to the resultant keto-ester. The tricyclic α,β-unsaturated ketone on methylation followed by removal of the 3-keto group and the $\Delta^{5,6}$ double bond created the carnosic acid carbon skeleton. The above sequence of reactions were repeated using 1,7-dimethoxy-naphthalene and 2,7-dimethoxy-3-isopropylnaphthalene.

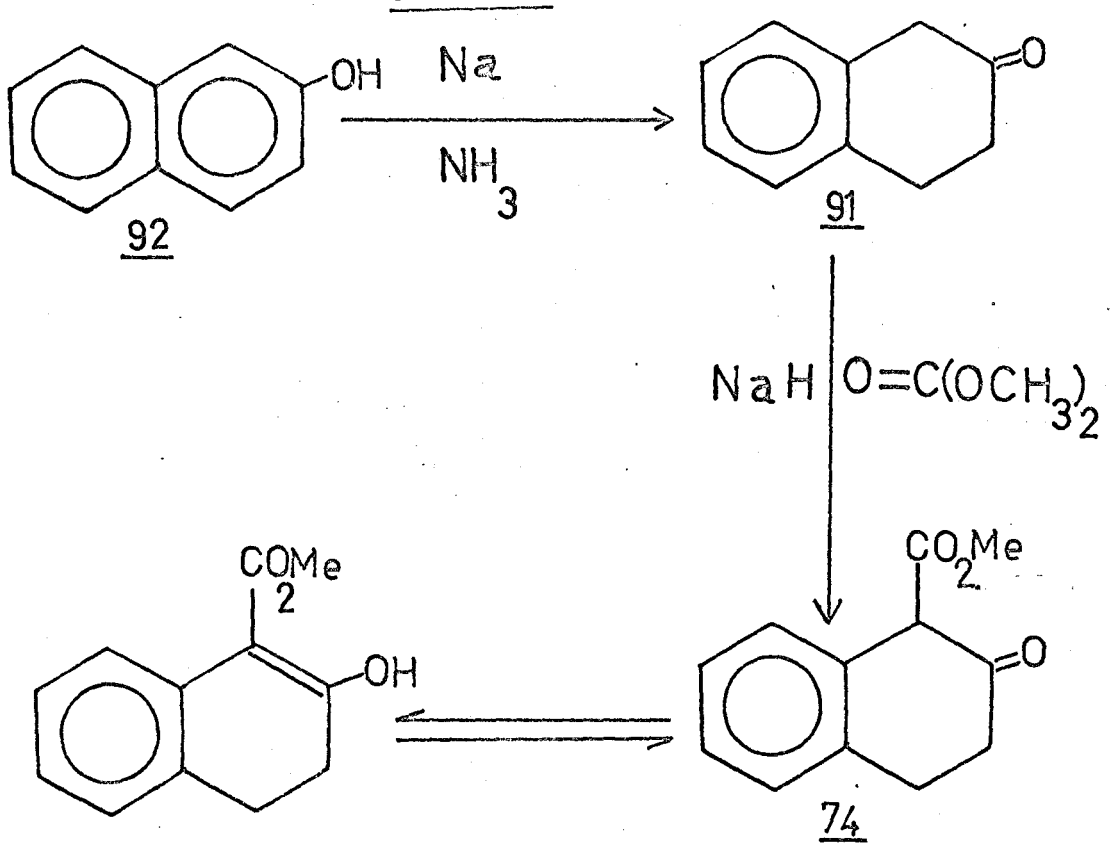
CHART #11

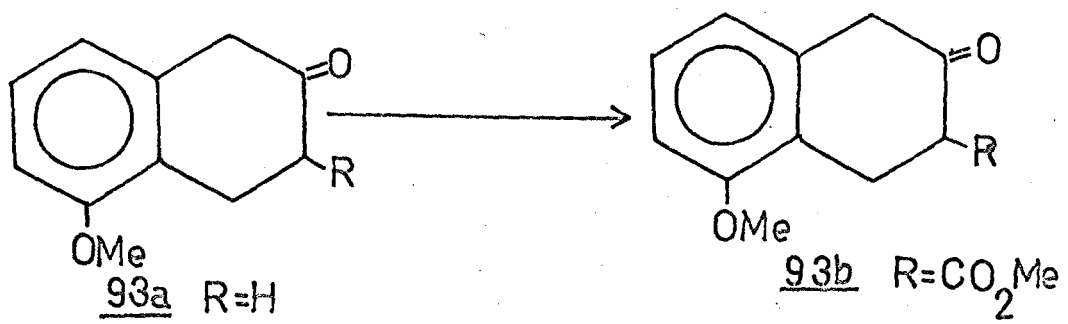


An investigation of the sodium in liquid ammonia reduction of naphthalenes following the general method of Huckel[87] showed that when 2.45 equivalents of sodium metal were employed quite satisfactory yields of tetrahydro reduction products could be obtained. This selective reduction is presumably a consequence of the reduction being a stepwise process where the first ring is rapidly reduced but where the second ring, being effectively a highly substituted benzene nucleus, is reduced at a relatively slow rate. The reduction of 2,7-dimethoxynaphthalene (59) with 2.45 equivalents of sodium in liquid ammonia gave the 1,4-dihydronaphthalene 87 which was hydrolysed with dilute hydrochloric acid in acetone to the tetralone 78. The purified tetralone 78 was obtained in an overall yield of 78% from 59.

In an attempt to carboxymethylate the tetralone 78 at the 1-position, 78 was converted to the morpholine enamine 89 by the elegant procedure of Stork[47, 88]. The enamine was allowed to react with chloromethyl formate in the presence of dry calcium carbonate. The progress of the reaction was followed by pmr spectroscopy and the refluxing continued until the vinylic absorption of 5.42 ppm (C-1 H) had disappeared. The resultant enamine of the keto-ester 90 was hydrolysed under mild acid conditions. However, the product isolated was mainly the starting tetralone 78 and the yield of keto-ester 76 was only 12.4%. The poor yield of the reaction may be a consequence of the hydrolysis and decarboxylation of the ester function during the final hydrolysis of the morpholine moiety. In the event, this reaction was not

CHART #12


OH
Na
NH3
O
92
91
NaH
O=C(OCH3)2
COMe
2
OH
CO2Me
O
74


O
R
OMe
93a R=H
O
R
OMe
93b R=CO2Me

pursued further for the preparation of the keto-ester 76 because of the poor yield. (see Chart #11)

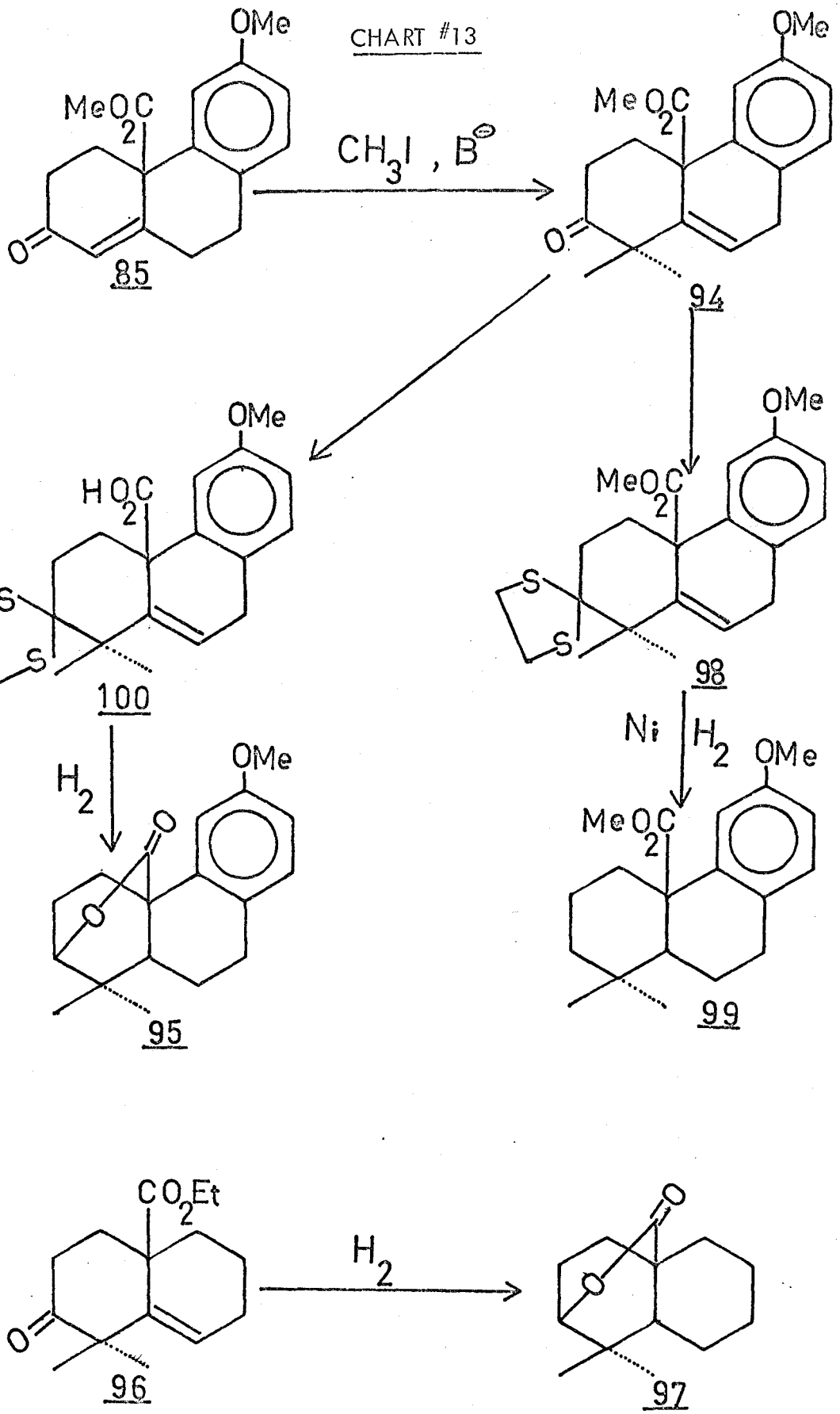
In an attempt to explore other methods of carboxymethylation of tetralones a more readily accessible 2-tetralone (91) was prepared. The Birch reduction of β-naphthol (92)[43] with sodium in liquid ammonia yielded 91 in 57% yield. The reaction of the tetralone 91 with dimethyl carbonate and sodium hydride was carried out by a modification of the procedure of Rhoads[89,90] for the carboxyethylation of cyclic ketones. The reaction proceeded in an overall yield of 85%. The highly enolic nature of this keto-ester implies that the steric interaction between the C-1 ester group and C-8 hydrogen atom is not sufficient to destabilise the enolic form of 74. The dimethylcarbonate reaction was repeated using 7-methoxy-2-tetralone (78). The reaction proceeded in 92% yield producing the highly enolic keto-ester 76. It is interesting to note that the reaction of methyl magnesium carbonate on 5-methoxy-2-tetralone (93a) has been reported[91] to result in carboxymethylation at the 3-position only. (See Chart #12.)

To construct the tricyclic carbon skeleton the Michael addition of methyl vinyl ketone to the keto-ester 76 was carried out in methanol in the presence of triton B methoxide. On this occasion the reaction afforded the tricyclic ketone 85 in a relatively pure form, unaccompanied by any tetracyclic side products, in 50.5% yield. This improved result can be ascribed to the high state of purity of 76 when obtained from the dimethyl carbonate reaction.

The methylation of the tricyclic α,β-unsaturated ketone 85 with methyl iodide in the presence of potassium tertiary butoxide in tertiary butyl alcohol was carried out according to the general procedure of Barton[92]. This procedure has been applied to systems similar to the one under study, by Meyer[66] and also by Stork[93]. The reaction afforded the unstable methylation product 94 in 94% yield. The crude methylation product contained in addition to 94, minor quantities of polymethylation products as evidenced by the mass spectrum. Attempts to hydrogenate the crude methylation product at atmospheric pressure in the presence of 5% palladium-on-charcoal in glacial acetic acid resulted in a complex mixture of compounds containing products of reduction of the 5,6-double bond and 3-keto group. Hydrogenation at high pressures in the presence of 5% palladium-on-charcoal in glacial acetic acid yielded the saturated 3-lactone 95. In the hydrogenation of a similar bicyclic ketone 96 in the presence of platinum oxide in acetic acid Meyer[66] obtained the 3-lactone 97.

In order to avoid the complicating effects of the 3-keto group during hydrogenation, the methylation product 94 was converted to the thioketal 98 by treatment with ethane-1,2-dithiol and borontrifluoride etherate in acetic acid. The procedure adopted was that of Stork[93, 94]. The reaction gave a crystalline 3-thioketal in 88.5% yield. Desulphurisation of the thioketal was effected by refluxing with W-2 Raney Nickel catalyst suspended in absolute ethanol according to the procedure of Stork[93,94]. The pmr spectrum of

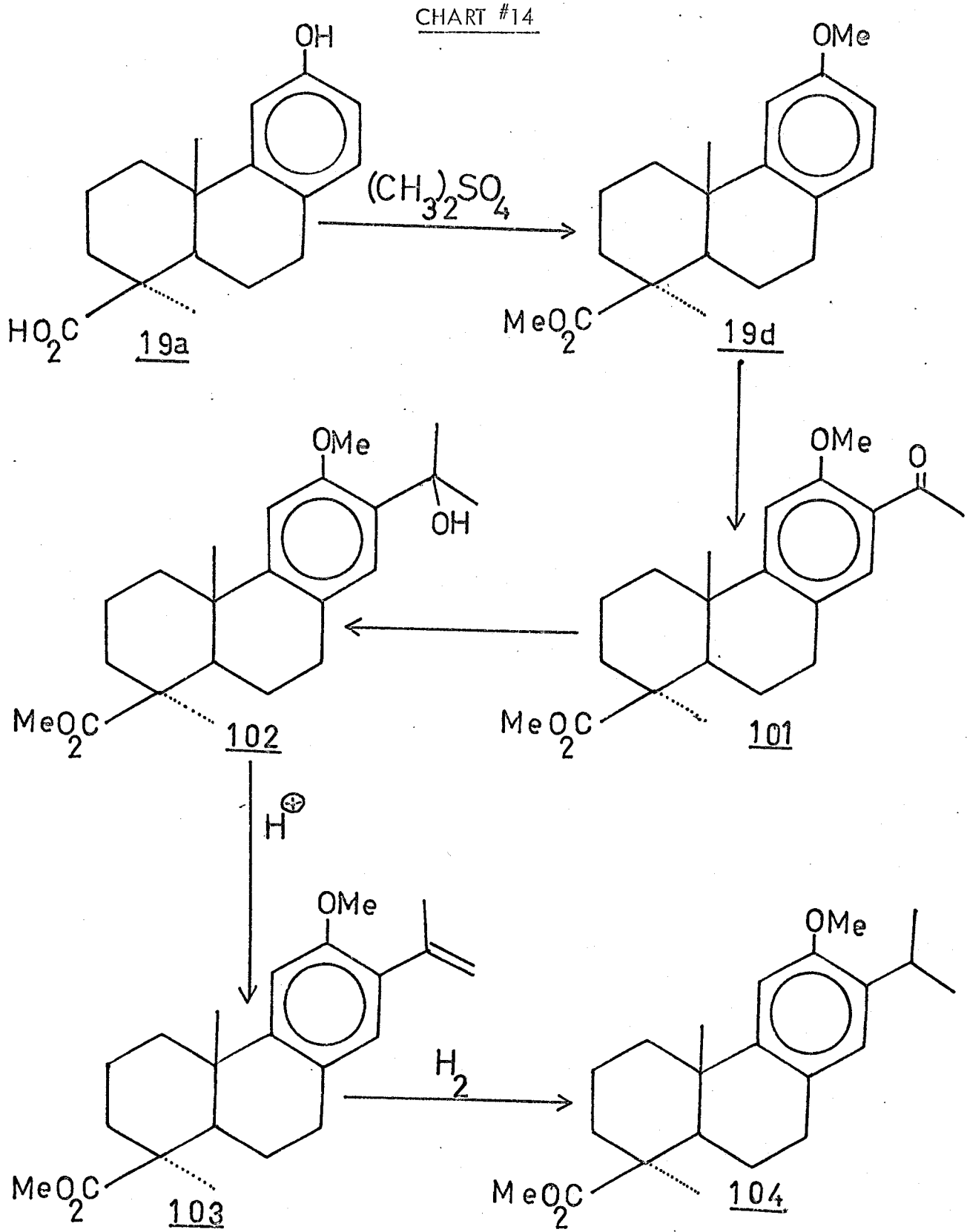
CHART #13



the desulphurisation product showed that the double bond in the 5,6-position had undergone partial reduction by the Raney Nickel treatment. In similar tricyclic compounds with a C-20 methyl group the reduction of the 5,6-double bond has been found[93, 94] to occur concommitantly with the desulphurisation of the thioketal group. The rationalisation of the resistance of the 5,6-double bond to reduction in compounds with C-20 ester functions is rather difficult. The crude desulphurisation product was hydrogenated in the presence of platinum oxide in glacial acetic acid to give the octahydrophenanthrene skeleton. The reaction proceeded in 59.5% yield. The sample of methyl O-methyl-13-deisopropyl-11-desoxy carnosate (99) obtained was contaminated with small quantities of the 3-lactone 95. This must have arisen during the Raney Nickel reaction from the thioketal acid 100 which accompanied the thioketal ester 98. The thioketal acid 100 must have been formed by the demethylation of the C-20 ester group during the boron trifluoride etherate ethane dithiol treatment. Such acid catalysed demethylations of hindered esters have been observed in other systems[95]. (See Chart #13).

If oxygenation at C-11 and isopropylation at C-13 could be effected on methyl O-methyl-13-deisopropyl-11-desoxycarnosate (99) methyl O-methyl carnosate (1f) could be prepared. Methyl O-methyl podocarpate (19d) was chosen for a model study of isopropylation at C-13. Direct isopropylation of 19d using isopropyl iodide in methylene chloride in the presence of anhydrous aluminium chloride[96] resulted in a monoisopropyl derivative which was shown by its

CHART #14

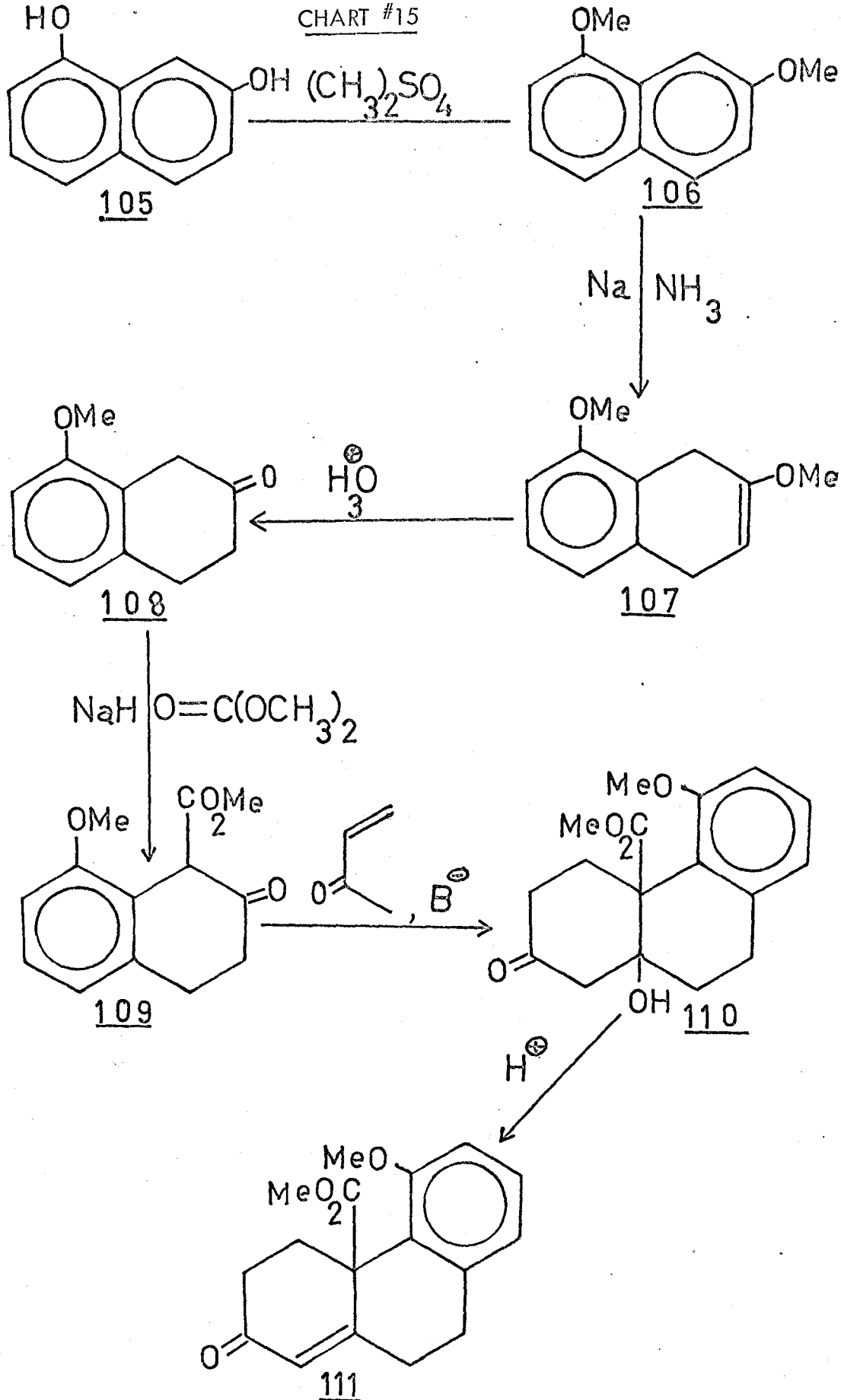

OH
HO2C
19a
(CH3)2SO4
OMe
MeO2C
19d
OMe
O
MeO2C
101
OMe
OH
MeO2C
102
H⊕
OMe
MeO2C
103
H2
OMe
MeO2C
104

pmr spectrum and vpc analysis to be a mixture of isomers. This can be explained by assuming that the C-13 isopropyl derivative underwent isomerisation in the presence of the Lewis acid leading to C-14 or even C-11 derivatives. Since the direct isopropylation of 19d appeared to be impractical, the isopropylation was effected by a modification of the procedure of Campbell and Todd[97] in four steps. Acetylation of 19d at C-13 was effected by acetylchloride in the presence of anhydrous aluminium chloride in methylene chloride. The reaction proceeded in 85% yield. The 13-acetyl derivative 101 reacted with methyl magnesium bromide in anhydrous ether giving the 13-isopropanol derivative 102 in 98% yield. The dehydration of 102 was effected by refluxing with glacial acetic acid and the isopropenyl derivative 103 was isolated in 92% yield. The hydrogenation of 103 was carried out in the presence of 5% palladium on charcoal in glacial acetic acid and proceeded in 97% yield. (See Chart #14.)

An attempt was made to effect the acetylation of methyl O-methyl-13-deisopropyl-11-desoxy carnosate (99) at C-13 by the procedure described above for the podocarpate model system. However, no acetyl derivative could be isolated. The only product isolated in poor yield was the 3-lactone 95 which might have been a contaminant of the carnosate 99. The pmr spectra of the mother liquors indicated the presence of minor quantities of acetylated products. Thus alternate methods had to be explored for effecting isopropylation at C-13.

In an attempt to make tricyclic compounds with C-11 oxygenation and

CHART #15


HO
OH
$(CH_3)_2SO_4$
OMe
OMe
105
106
Na
NH_3
OMe
OMe
$H_3O^{\oplus}$
O
OMe
OMe
108
107
NaH
$O{=}C(OCH_3)_2$
OMe
$COMe_2$
O
O
$B^{\ominus}$
MeO
MeO_2C
O
OH
109
110
$H^{\oplus}$
MeO
MeO_2C
O
111

a C-20 ester function which might serve as a precursor to carnosic acid (1e), 1,7-dihydroxynaphthalene(105) was chosen as the starting material. The methylation of 105 was effected in 96% yield with dimethyl sulphate and sodium hydroxide. The Birch reduction of 1,7-dimethoxynaphthalene (106) with sodium in liquid ammonia followed by hydrolysis of the dihydronaphthalene 107 provided 8-methoxy-2-tetralone (108) in an overall yield of 49%. The tetralone 108 on reaction with dimethyl carbonate in the presence of sodium hydride afforded the ketoester 109 in 93% yield. The addition of methyl vinyl ketone to the keto-ester 109 in the presence of triton B methoxide followed by dehydration of the resultant tricyclic ketol 110 yielded the tricyclic unsaturated ketone 111. The reaction proceeded in 57% yield. The procedure adopted in the above sequence of reactions was the same as that employed in the case of the 7-methoxy analog. It is interesting to note that this reaction sequence has made available in reasonable yield a hindered 11-substituted hexahydrophenanthrene which is difficult to otherwise prepare. (See Chart #15.)

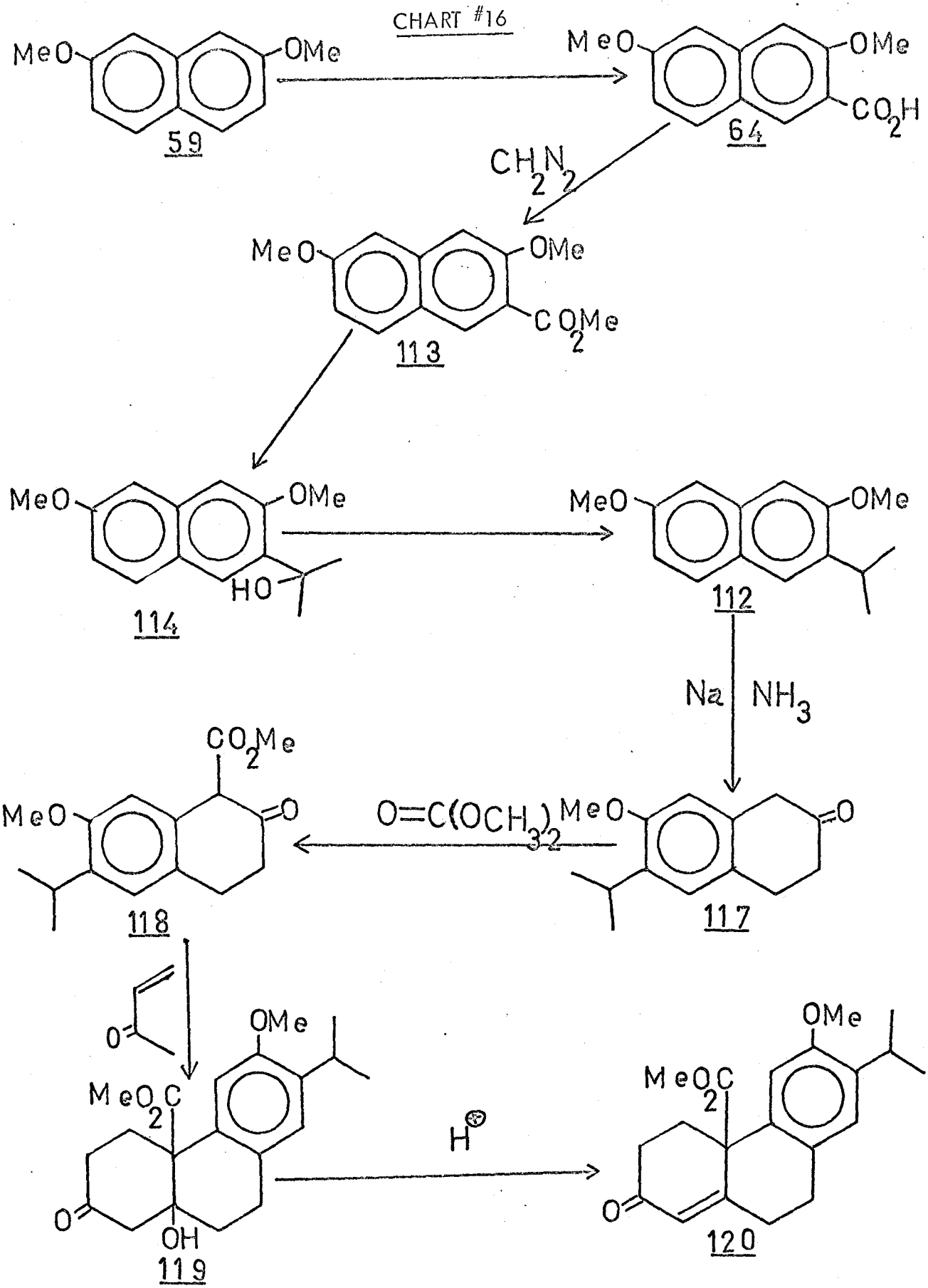
The keto-ester 109 differed from the 7-methoxy isomer 76 in that the 8-methoxy keto-ester 109 was non-enolic and existed almost completely in the keto form. This was indicated by the weak infrared absorption at 1652 cm^{-1}, low extinction coefficients for ultraviolet absorption maxima, and the peak at 4.55 ppm in the pmr spectrum corresponding to C-1 H. On the other hand the pmr spectrum of the 7-methoxy keto-ester 76 showed no absorption for the C-1 proton but only an absorption for a hydroxylic proton at 13.3 ppm. This

can be explained as due to the destabilisation of the enolic form of the 8-methoxy keto-ester (109) resulting from the highly unfavourable steric interaction between the C-1 ester group and the C-8 methoxyl group. Similar destabilisation of the enolic form, due to steric interactions of substituents in 1,8-positions and consequent predominance of the keto-form have been observed by Wenkert[98] in the case of the keto-esters of the decalone series, although other factors such as ring distortion are operative in this example.

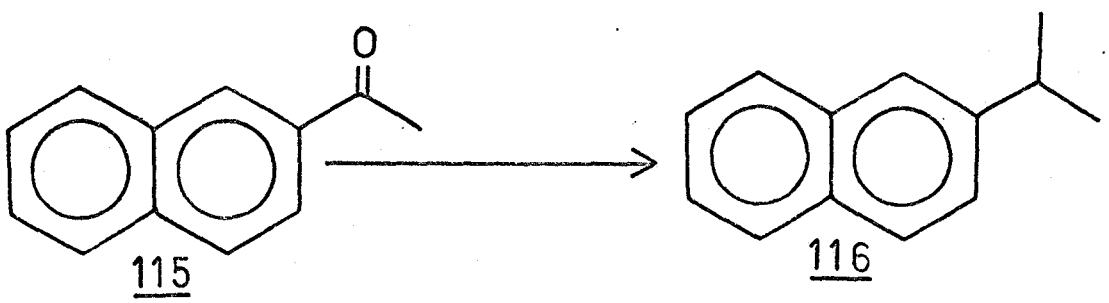
As the isopropylation of 13-deisopropyl-11-desoxycarnosate systems was unsuccessful, attempts were made to synthesise the 11-desoxycarnosate system using a suitably substituted starting material. The material chosen was 2,7-dimethoxy-3-isopropylnaphthalene(112) which was prepared from 2,7-dimethoxy-naphthalene (59) in five steps.

When 59 was lithiated with butyl lithium in ether and the lithiation product carbonated with Dry Ice, 2,7-dimethoxy-3-naphthoic acid 64 was obtained in 64.2% yield. The procedure adopted was a modification of that of Gilman[99]. The naphthoic acid 64 was esterified by Fisher's method[74] using a trace of concentrated sulphuric acid in absolute methanol and proceeded in 93% yield. The methyl ester 113 was treated with methyl magnesium iodide in anhydrous ether to give the tertiary alcohol 114 in 99% yield. The tertiary alcohol was then dehydrated by refluxing with glacial acetic acid and the unsaturated product was hydrogenated in the presence of 5% palladium-on-charcoal in acetic acid. The reaction proceeded in an overall yield of 98.5%, giving

CHART #16


MeO
OMe
59
MeO
OMe
CO2H
64
CH2N2
MeO
OMe
CO2Me
113
MeO
OMe
HO
114
MeO
OMe
112
Na
NH3
CO2Me
MeO
O
118
O=C(OCH3)2
MeO
O
117
O
OMe
MeO2C
O
OH
119
H⊕
OMe
MeO2C
O
120

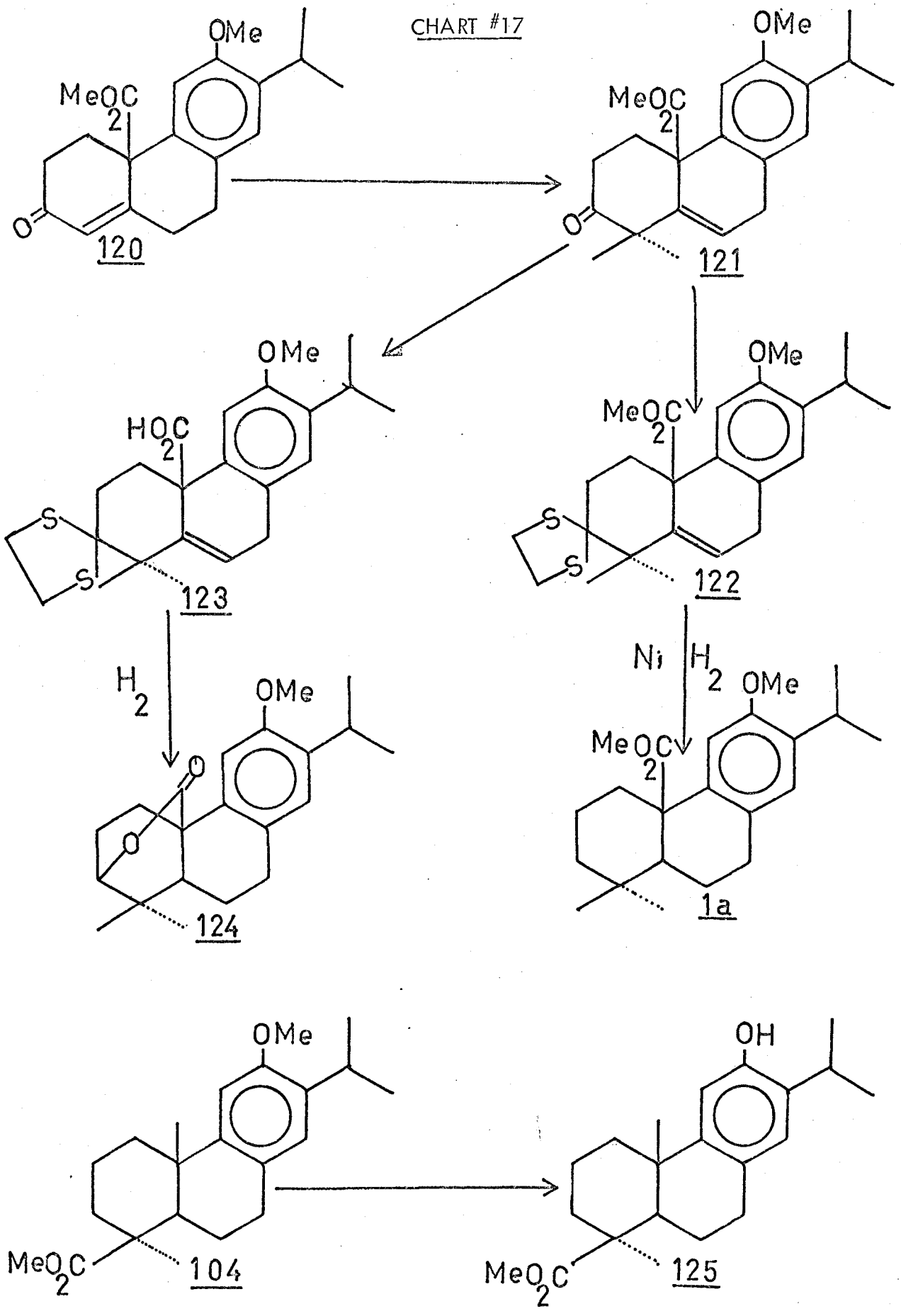
2,7-dimethoxy-3-isopropylnaphthalene (112). The procedure employed in the above reaction sequence was similar to Bergmann's method[100] of converting 2-acetyl naphthalene 115 to 2-isopropylnaphthalene 116. (See Chart #16.)



115 116

The sequence of reactions employed in the conversion of 2,7-dimethoxy-naphthalene into methyl O-methyl-13-deisopropyl-11-desoxy carnosate (99) were applied with little change to 2,7-dimethoxy-3-isopropylnaphthalene (112). The Birch reduction and hydrolysis of 112 gave 7-methoxy-6-isopropyl-2-tetralone (117) in 67.1% yield. The tetralone 117 was carboxymethylated at the 1-position, with dimethyl carbonate and sodium hydride, in 80% yield. The resultant enolic keto-ester 118 on Michael addition followed by dehydration of the tricyclic ketol 119, afforded the tricyclic unsaturated ketone 120 in 41.5% yield. The unsaturated ketone 120 was methylated with methyl iodide in the presence of potassium tertiary butoxide in tertiary butyl alcohol and the unstable methylation product 121 converted into the thioketal 122 with ethane-1,2-dithiol and

CHART #17



borontrifluoride etherate in glacial acetic acid. Thioketalisation was accompanied by partial demethylation of the C-20 ester group. The thioketal acid-thioketal ester mixture on treatment with diazomethane in ether afforded the thioketal ester 122 in a pure form. The reaction proceeded in an overall yield of 80.4% from the unsaturated ketone 120.

In experiments where the thioketal 122 was contaminated with the C-20 carboxylic acid 123, desulphurisation with W-2 Raney Nickel was very fast and the only product isolated in pure form was the saturated 3-lactone 124. As the desulphurisation of 122 with W-2 Raney Nickel was slow a very active variety of the catalyst was prepared by the method of Burgstahler[101]. Desulphurisation of 122 with this Raney Nickel catalyst proceeded smoothly. However, desulphurisation was accompanied by partial reduction of the 5,6-double bond. The reduction of the 5,6-double bond was completed by refluxing the mixture obtained from the previous treatment with a large excess of the same active Raney Nickel in a current of hydrogen. Methyl O-methyl-11-desoxy carnosate (1a) was thus obtained in 62.4%.yield from the thioketal 122. An authentic sample of 1a was not available for comparison. Hydrogenation of the above desulphurisation product in the presence of platinum oxide suspended in acetic acid also yielded 1a in a less pure state. (See Chart #17.)

Desulphurisation of the thioketal 122 with W-2 Raney Nickel was slow. However, a sample of the thioketal contaminated with the C-20 acid 123 underwent rapid desulphurisation and the only product isolated in a pure

state was the saturated 3-lactone 124. This relatively fast desulphurisation of the thioketal acid must be the result of nucleophilic assistance offered by the free carboxylic acid group.

The remaining problem in the synthesis of the carnosic acid system is oxygenation of the C-11 position. Many attempts at functionalising C-11 with a nitro group were made using the methyl-13-isopropylpodocarpate (125) model system. Methyl O-methyl-13-isopropylpodocarpate (104) on refluxing with hydrobromic acid in acetic acid followed by treatment with diazomethane afforded 125 in 87% yield. Nitration of 125 with a copper nitrate solution in acetic anhydride according to the procedure of Hodges and Raphael[102], and the rearrangement procedure of nitration according to the method of Zabik and Schuetz[103] were attempted. The reaction of 125 with 35% nitric acid-benzene mixture was also studied[102]. In all these cases the products obtained were very complex mixtures as judged from their pmr spectra. Attempts were also made to hydroxylate 125 with Fe^{+++}-catechol[104], Fe^{+++}-hydroquinone[104] and the Udenfriend hydroxylating systems[104 - 109] according to the procedure of Hamilton and Friedman[104]. The mass spectra of these products indicated that the reaction had not occurred.

Oxygenation of the C-11 position of the 11-desoxycarnosate system has been effect by Meyer and Schindler[1] by an adaptation of Wenkert's procedure[9] of oxygenating C-11 of the ferruginol system. This has been accomplished by demethylating the C-12 methoxyl group, effecting a coupling

reaction at C-11 with diazotised p-nitroaniline, reducing the azo group to an amino group, and diazotisation and solvolysis of the amino group. Since oxygenation of the C-11 position of methyl O-methyl-11-desoxycarnosate (1a) has been achieved and the demethylation of the C-20 ester[1,2] and C-12 methyl ether[3-5] have been carried out, the total synthesis of methyl O-methyl-11-desoxycarnosate (1a) completes the total synthesis of dl-carnosic acid (1e). Thus, only the resolution of the two enantiomers remains to be explored for a total synthesis of the natural product.

GENERAL CONCLUSIONS

The synthesis of methyl O-methyl-11-desoxycarnosate and the related C-20 carboxy-tricyclic compounds demonstrates the validity of the general approach devised in this work.

The method of introducing the carboxyl function at the C-1 position, after modifying the B ring of the naphthalene has been found to be superior to the alternate approach of introducing the carboxyl group into the naphthalene system directly.

In the course of the work a number of reactions were attempted which by precedent in the literature should have proceeded well, but which failed to yield the desired products. In some cases it was very difficult to rationalize the lack of reactivity or change in reaction course. One such example was the attempted acylation of methyl O-methyl-11-desoxycarnosate. This reaction did not proceed at all under a wide variety of reaction conditions. Under much milder reaction conditions methyl O-methylpodocarpate was found to react readily giving a high yield of the 13-acetyl derivative. The immediate steric and electronic environments of the C-13 position in both molecules are apparently the same and one is forced to conclude that the position of the ester group must be the critical factor.

A similar observation which is difficult to rationalize was the very low yields obtained during attempts to convert the tetralone 78 to the ketoester 76 via the enamine. The hydrolysis of the enamine of the ketoester 76 even under very mild

acid conditions resulted in loss of 85-90% of the carbomethoxy groups. Previous work recorded in the literature on ester-enamines makes no comment on the excessive loss of ester groups during hydrolysis of the enamine moiety.

Unexpected products were obtained during some reactions. One such example is the formation of the tetracyclic ketone 79 by the Michael addition of methyl vinyl ketone to the ketoester 76. From the behaviour of similar tetralones under identical conditions the product expected was the unsaturated tricyclic ketone 85. It is remarkable to find that the presence of a methyl or a carbomethoxy group at the C-1 position of β-tetralone directs the course of the Michael addition reactions in such diverse fashions.

EXPERIMENTAL

Part I - Synthesis of Naphthoic Acids

Apparatus, Methods, Materials

Melting points were recorded on a Kofler Micro hot stage melting point apparatus and are corrected unless otherwise stated.

The infrared spectra were recorded on Bechmann Model IR-5 recording Spectrophotometer and Perkin-Elmer 337 grating infrared spectrophotometer in carbontetrachloride, chloroform or dimethyl sulphoxide solvents.

The ultraviolet spectra were measured in methanol on a Bausch and Lomb spectromic 600 ultraviolet spectrophotometer.

The microanalyses were performed by the Spang Microanalytical laboratory, Ann Arbor, Michigan, U.S.A.

The mass spectra were determined on an Hitachi-Perkin-Elmer RMU 9 and a C.E.C. high resolution mass spectrometer.

The proton magnetic resonance spectra were recorded on a Varian associates A-60 spectrometer and an HA-100 nmr spectrometer in deuteriochloroform solutions with tetramethyl silane as internal standard unless otherwise stated. The symbols s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet are used in the recording of spectra.

2,7-Dimethoxynaphthalene (59)

The preparation of 2,7-dimethoxynaphthalene (59) was carried out by a modification of the method of Vogel[72].

To a solution of 160 g of 2,7-dihydroxynaphthalene (60) in 2-l of 3N sodium hydroxide solution was added dropwise 700 g (525.5 ml) of dimethyl sulphate during 2 - 2.5 h. The temperature of the reaction mixture was kept below 50°. The mixture was stirred for 18 h and then heated to 50° for about 2 h . The residue was collected by filtration after cooling the reaction mixture to room temperature. It was then washed with 5% sodium hydroxide solution, cold water until free of alkali, and dried to yield 183 g of crude methylation product. The crude product was chromatographed on 500 g of alumina to yield 160 g (85%) of pure 2,7-dimethoxynaphthalene, m.p. 138°; reported[110], 133 - 134°.

2,7-Dimethoxy-1-bromonaphthalene (61)

Bromination of 2,7-dimethoxynaphthalene (59) was carried out by the procedure of Roger Adams[73]. The reaction proceeded in 92% yield. An analytically pure sample was obtained by one crystallisation from methanol and two crystallisations from hexane-ether (3:1) mixture, m.p. 87 - 88.5°; reported[73], 88 - 89°.

2,7-Dimethoxy-1-naphthoic Acid (62)

Conversion of 2,7-dimethoxy-1-bromonaphthalene (61) to the corresponding naphthoic acid was effected by the method of Adams[73].

To 8.1 ml of a 15.2% solution of butyllithium in hexane was added 25 ml of anhydrous ether. A solution of 3.18 g of 2,7-dimethoxy-1-bromonaphthalene in 50 ml of anhydrous ether was added dropwise to the ethereal solution of butyllithium. The reaction mixture was stirred at room temperature for 30 minutes in an atmosphere of nitrogen and the resultant solution cooled to 0° and carbonated by pouring it into a slurry of powdered 'Dry Ice' in anhydrous ether. The naphthoic acid 62 was separated from the neutral material using a saturated solution of sodium bicarbonate. The crude acid obtained was purified by conversion to the methyl ester by Fisher's [74] method, chromatography of the methyl ester on alumina, and alkaline hydrolysis of the ester to the acid 62. By this procedure, 0.83 g of the acid was obtained. Two crystallisations from a 1:1 benzene-hexane mixture afforded an analytical sample of 2,7-dimethoxy-1-naphthoic acid m.p. 121 - 122°; ν_{max}^{dioxan} 1700 cm^{-1} (acid); pmr, δ 3.88 (3H) (s, C-7 methoxyl), 3.94 (3H) (s, C-2 methoxyl), 7.01 (1H) (d, C-3 H, $J_{3,4}$ = 9 Hz), 7.01 (1H) (q, C-6 H, $J_{5,6}$ = 9 Hz, $J_{6,8}$ = 2,5 Hz), 7.62 (1H) (d, C-5 H, $J_{5,6}$ = 9 Hz), 7.76 (1H) (d, C-4 H, $J_{3,4}$ = 9 Hz), 7.78 (1H) (d, C-8 H, $J_{6,8}$ = 2.5 Hz), 11.025 (1H) (s, acid proton); reported[76], m.p. 122°.

2,7-Dimethoxy-1-naphthaldehyde (63)

The conversion of 2,7-dimethoxynaphthalene (59) to the 1-formyl derivative was effected by the method of Buu-Hoi and Lavit[75].

A mixture of 5.3 g of 2,7-dimethoxynaphthalene (59), 2.75 g dimethyl-

formamide, 4.9 g of phosphorus oxychloride and 10 ml of dry toluene was heated at 100° for 16 h on an oil bath under a nitrogen atmosphere. The resultant dark liquid was then boiled for 45 minutes with a concentrated solution of sodium acetate. The reaction mixture was cooled to room temperature and isolation via ether extraction yielded 6.9 g of the crude aldehyde. Two crystallisations from ethanol afforded 5.2 g (85%) of the aldehyde as colourless crystals, m.p. 95 - 97° (reported[75], 98°); mol.wt., 216, mass spectrum; ν_{max}. 1650 cm^{-1} (aldehyde); pmr,δ 3.86 (3H) (s, C-7 methoxyl), 3.94 (3H) (s, C-2 methoxyl), 10.67 (1H) (s, aldehyde). This sample of the aldehyde was sufficiently pure for further reaction.

2,7-dimethoxy-1-naphthoic Acid (62)

The oxidation of 2,7-dimethoxy-1-naphthaldehyde (63)[76] was effected with silver oxide. To a solution of 1 g of the aldehyde in 30 ml of hot methanol was added a solution of 1.58 g of silver nitrate in 5 ml of water. A 10% solution of sodium hydroxide was then added until the reaction mixture was distinctly alkaline. The reaction mixture was kept agitated on a steam bath for 1 h and the silver oxide residue filtered off. The filtrate, after cooling to room temperature, was extracted with ether to remove neutral materials. The ether layer was washed with water and saturated brine and evaporated to dryness to yield 0.39 g of neutral material. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ether.

The ether solution was washed with water and saturated sodium chloride solution and was evaporated to dryness to yield 0.53 g of a dark liquid. The ethereal solution showed a great tendency to darken on warming; crystallisation was effected from carbon tetrachloride giving 0.21 g of 2,7-dimethoxy-1-naphthoic acid. Two more crystallisations from the same solvent gave a pure sample of the acid, m.p. 121-122° (reported[76], 122°); $\nu_{max}^{CHCl_3}$ 1700 cm^{-1} (carboxylic acid); pmr, δ 3.88 (3H) (s, C-7 methoxyl), 3.94 (3H) (C-2 methoxyl), 7.01 (1H) (d, C-3 H, $J_{3,4}$ = 9 Hz), 7.01 (1H) (q, C-6 H, $J_{5,6}$ = 9 Hz, $J_{6,8}$ = 2.5 Hz), 7.62 (1H) (d, C-5 H, $J_{5,6}$ = 9 Hz), 7.76 (1H) (d, C-4 H, $J_{3,4}$ = 9 Hz), 7.78 (1H) (d, C-8 H, $J_{6,8}$ = 2.5 Hz), 11.025 (1H) (s, acid proton).

A small quantity of the acid was dissolved in ether and treated with diazomethane in ether and the ether solution evaporated to dryness. A mass spectrum of the resultant methyl ester was recorded and showed a molecular ion at m/e 246. (Calculated for $C_{14}H_{14}O_4$, mol.wt. 246.)

2,7-Dimethoxyacetylnaphthalenes

To an ice cold suspension of 14 g of anhydrous aluminium chloride in 50 ml of methylene chloride was added 8 g of reagent grade acetyl chloride and the mixture stirred in an ice bath for 15 minutes. A clear solution of the complex of acetyl chloride and aluminium chloride resulted. To this was added dropwise a solution of 19.1 g of 2,7-dimethoxynaphthalene (59) in 200 ml of methylene chloride over a period of 30 minutes. The reaction

mixture was then kept at room temperature for 1 h , refluxed for 10 minutes and allowed to stand overnight at room temperature. It was decomposed by the addition of an ice cold 10% solution of hydrochloric acid and extracted with ether. The ether extract was washed with 5% sodium bicarbonate solution, water and saturated brine. Evaporation of the ether yielded 21.6 g of a dark green solid. A pmr spectrum of this crude reaction product showed that it contained 60% of acetylated compounds. From the complexity of the absorptions from 6.5 to 8 ppm the reaction products appeared to be a mixture of isomers. No attempt was made to separate and characterise the components. The crude reaction mixture was directly used in the next stage to produce the corresponding naphthoic acids.

2,7-Dimethoxynaphthoic Acids

To a solution of 17 g of the crude acylation product of 2,7-dimethoxy-naphthalene (obtained as described above) in 100 ml of 95% methanol at 5° was added 222 mmoles of sodium hypochlorite (296 ml of 'Javex') dropwise during 30 minutes. The reaction mixture was cooled in an ice bath to prevent any temperature increase. During the addition of the hypochlorite solution, precipitation of the organic material took place and the addition of more methanol was required to maintain homogeneity. After the addition of the hypochlorite the reaction mixture was tested periodically with starch-iodide paper. After 30 minutes no hypochlorite was detected and the reaction mixture

was allowed to stand overnight. Part of the unreacted 2,7-dimethoxynaphthalene which had separated out was filtered off and dried. It weighed 3.5g. The filtrate was evaporated to remove the bulk of the methanol and more cold water was added to the residue. More 2,7-dimethoxynaphthalene separated and was filtered off, washed with water, dried and weighed (4.6 g). The aqueous solution remaining after the removal of the neutral naphthalene was cooled in ice and acidified with a 10% solution of hydrochloric acid. The acid which separated was collected by filtration. The filtrate was extracted with ether and the ether layer washed with water and saturated brine and evaporated to dryness. The combined yield of the crude naphthoic acid collected was 9.1 g. This acid was agitated with 20 ml of ether and separated into an ether-soluble and an ether-insoluble fraction. The ether-soluble fraction amounted to 5.3 g and was found to be a 1:1 mixture of 2,7-dimethoxy-1-naphthoic acid (62) and 2,7-dimethoxy-3-naphthoic acid (64). The composition of this mixture was established by an examination of its pmr spectrum. No attempt was made to separate the two naphthoic acids. The ether-insoluble fraction (3.8 g) was found to be 2,7-dimethoxy-3-naphthoic acid (64) from its pmr spectrum in trifluoroacetic acid solvent. Two recrystallisations from 1:1 ethylacetate-hexane and one crystallisation from benzene-hexane (2:1) afforded an analytical sample, m.p. 185 - 186°; ν_{max}^{dioxan} 1708 cm^{-1} (acid); pmr, δ (in CF_3CO_2H) 3.54 (3H) (s, C-2 methoxyl), 3.64 (3H) (s, C-7 methoxyl), 6.63 (3H) (m, C-1, C-6 and C-8 H), 7.2 (1H) (d, C-5 H, $J_{5,6}$ = 9.5 Hz), 7.96 (1H) (s, C-4 H); reported[99], m.p. 185.5°.

A preferred procedure for the preparation of 2,7-dimethoxy-3-naphthoic acid was the direct lithiation and carbonation of 2,7-dimethoxynaphthalene (see Experimental - Part II).

ortho-Phenylene Carbonate (68)

ortho-Phenylene carbonate was prepared by the low temperature reaction of phosgene and catechol[78] in sodium hydroxide solution. To a solution of 88 g of sodium hydroxide in 250 ml of deaerated distilled water was added 110 g of freshly recrystallised catechol. The solution was cooled with a mixture of ice and salt and maintained under an atmosphere of nitrogen. An ice cold solution of 280 g of phosgene in 750 ml of toluene was then added over a period of two hours. Care was taken to ensure that the temperature of the reaction mixture did not exceed 5°. The reaction mixture was cooled for further 2 h and then allowed to warm to room temperature. It was left at room temperature overnight and the precipitated sodium chloride filtered under suction. The toluene layer of the filtrate was separated and the toluene solution was heated with the solid sodium chloride collected earlier to dissolve any additional o-phenylene carbonate contained within it. The warm toluene solution was filtered to remove residual sodium chloride and on concentration and cooling yielded 99.0 g of o-phenylene carbonate. It was dried under vacuum. The mother liquor on evaporation yielded a second crop of 10.2 g (total yield, 80.3%). A pure sample of 68 was obtained by recrystallisation from toluene, m.p. 118.5 - 120°, $\nu_{max}^{CHCl_3}$ 1840 cm^{-1}; reported[78], m.p. 119 - 120°.

Catechol Dichlormoethylene acetal (66)

A mixture of 104.1 g of o-phenylene carbonate and 159.7 g of phosphorus pentachloride[77] was heated to 130° for 2 h in an oil bath under an atmosphere of nitrogen. The temperature was then slowly raised to 170° and maintained there for 2-3 h and the phosphorus oxychloride was allowed to distill over at the rate at which it was formed. When the rate of distillation of the oxychloride declined (6-7 h) the reaction mixture was distilled at reduced pressure. The fraction distilling at 82 - 89° (12 mm) was collected. The distillate was allowed to stand for one day and a small amount of residual phosphorus pentachloride was removed by filtration through glass wool. In this manner 106.7 g (73%) of the catechol dichloromethylene acetal (66) was obtained.

2,7-Dimethoxy-1-naphthoic Acid (62)

The procedure of Gross and co-workers[77] was employed with some slight modifications.

To a solution of 18.8 g of 2,7-dimethoxynaphthalene (59) in 300 ml of methylene chloride (freshly distilled over phosphorus pentoxide) was added 21.01 g (1.1 equivalent) of pyrocatechol dichloromethylene acetal. The reaction mixture was cooled in ice and was stirred under an atmosphere of nitrogen. Thirty grams of anhydrous aluminium chloride was then added portion-wise. The reaction mixture was kept ice-cold for about 15 minutes,

at room temperature for 2 h and then refluxed for 10-15 minutes. It was allowed to cool to room temperature, decomposed by pouring into ice-cold 5% hydrochloric acid and extracted with ether. The ether layer was washed with water, saturated brine and evaporated to dryness to yield 31.0 g of crystalline solid. Its mass spectrum showed a molecular ion at m/e 324, corresponding to the catechol ester of 2,7-dimethoxy-1-naphthoic acid (67)[77]. The infrared spectrum of this compound had peaks at $\nu_{max}^{CHCl_3}$ 3245 (hydroxyl), 1730 (ester) cm^{-1}. No attempt was made to further purify this compound as it was deemed sufficiently pure for the next stage.

To 30 g of the above catechol-ester, under a nitrogen atmosphere, was added 250 mg of sodium dithionite and 100 ml of a 20% solution of potassium hydroxide. The reaction mixture was refluxed for 1 h, cooled in ice and acidified with 5% hydrochloric acid and extracted with ether. The ether layer was repeatedly washed with cold water to remove the bulk of the catechol. The ether solution was then extracted with 5% solution of sodium hydroxide to remove the acidic materials and the ether layer again washed with water and saturated brine. The ethereal solution of neutral material was evaporated to dryness to yield 4.2 g of solid. The aqueous alkaline solution was cooled in ice and acidified with 10% hydrochloric acid and extracted with ether. The ether layer was washed repeatedly with cold water to remove as much catechol as possible, and then washed with saturated sodium chloride solution. Evaporation to dryness yielded 15.5 g of crude 2,7-dimethoxy-1-naphthoic acid. This sample

of the naphthoic acid was contaminated with catechol and found difficult to purify. A fairly pure sample of the acid was obtained by one crystallisation from hot water, giving 8.6 g of the acid as colourless needles. Three recrystallisations from 1:1 hexane-benzene mixture afforded an analytical sample, m.p. 121 - 122°; ν_{max}^{dioxan} 1700 cm^{-1} (acid); pmr, δ 3.88 (3H) (s, C-7 methoxyl), 3.94 (3H) (s, C-2 methoxyl), 7.01 (1H) (d, C-3 H, $J_{3,4}$ = 9 Hz), 7.01 (1H) (q, C-6 H, $J_{5,6}$ = 9 Hz, $J_{6,8}$ = 2.5 Hz), 7.62 (1H) (d, C-5 H, $J_{5,6}$ = 9 Hz), 7.76 (1H) (d, C-4 H, $J_{3,4}$ = 9 Hz), 7.78 (1H) (d, C-8 H, $J_{6,8}$ = 2.5 Hz), 11.025 (1H) (s, acid proton); reported[76], m.p. 122°.

2-Methoxy-1-naphthoic Acid (69)

To a solution of 8 g of sodium hydroxide in 65 ml of water was added 6.9 g of 2-hydroxy-1-naphthoic acid (Practical grade, Aldrich Chemical Company, Inc.). The mixture was stirred in an atmosphere of nitrogen and 23.1 g of dimethyl sulphate was added dropwise over a 1.5 h period. During the addition of dimethyl sulphate the temperature was not allowed to exceed 50°. When all the dimethyl sulphate was added the solution was maintained at 70 - 80° until it became acidic. It was then made alkaline with 2N sodium hydroxide solution, cooled to room temperature and the oily product extracted with ether. The ether solution was washed with water, saturated sodium chloride and evaporated to dryness to yield 4.7 g of the oily ester. The ester was refluxed with 50 ml of 20% potassium hydroxide solution until all oily materials had disappeared. The reaction mixture was then cooled to room temperature and acidified with 5% hydro-

chloric acid. The 2-methoxy-1-naphthoic acid (69) which separated was collected by filtration, washed with water and dried to yield 4.04 g 69. Two crystallisations from 1:2 water-ethanol afforded an analytical sample, m.p. 178-179° (reported[111] 176 - 177°).

1,4-Dihydro-2-methoxy-1-carbomethoxynaphthalene (73)

To a solution of 2.02 g of 2-methoxy-1-naphthoic acid (69) in 8 ml of absolute ethanol and 50 ml of tetrahydrofuran (freshly distilled over calcium hydride) was condensed 200 - 250 ml of liquid ammonia. The reaction mixture was stirred with a mechanical stirrer. Clean metallic sodium (552 mg) was then added in small pieces. Each piece of sodium was added after the green colour caused by the addition of the previous piece had disappeared. The reaction mixture was left overnight in an atmosphere of nitrogen. When most of the ammonia had evaporated, about 200 ml of cold water was added and the solution acidified to pH5 by the addition of a 10% solution of sodium dihydrogen phosphate. The reaction mixture was extracted with ether and the ethereal layer was washed with water, saturated brine and evaporated to dryness to yield 2.1 g of impure dihydronaphthoic acid as an off-white crystalline solid.

No attempt was made to purify the dihydronaphthoic acid. To an ether solution of the acid was added an ethereal solution of diazomethane and the mixture stirred for five minutes. The ether was removed by evaporation and the residue was fractionated by vacuum distillation. The first fraction (b.p. 90 - 95°, 0.6 mm) weighed 0.5 g and its pmr spectrum indicated that

it was 3,4-dihydro-2-methoxynaphthalene (75a). The second fraction (b.p. 125 - 130°, 0.6 mm) weighed 1.5 g and was 1,4-dihydro-2-methoxy-1-carbomethoxy-naphthalene (73), $\nu_{max}^{CHCl_3}$, 1668, 1725 cm^{-1} (ester carbonyl); pmr, δ 3.38 (6H) (s, C-1 ester and C-2 methoxyl protons), 3.4 (2H) (m, C-4 H), 4.27 (1H) (t, C-1 H, $J_{1,4}$ = 3.5 Hz), 4.81 (1H) (m, C-3 H, $J_{3,4}$ = 4.5 Hz, $J^{1}_{3;4}$ = 3.5 Hz), 7 (4H) (m, C-5, C-6, C-7 and C-8 aromatic protons); λ_{max}^{MeOH} 264 (ε, 1,090), 272 mμ (ε, 1,190).

To 400 mg of the 1,4-dihydro-2-methoxy-1-carbomethoxynaphthalene (73) was added 200 mg of 5% palladium on charcoal and the whole heated to 180° for 1 h under an atmosphere of nitrogen. The reaction mixture was cooled to room temperature and the residue extracted with ether. The ether solution on evaporation afforded 151 mg of 2-methoxy-1-carbomethoxynaphthalene (71) as a crystalline solid. Its identity was demonstrated by comparison of its infrared, ultraviolet and pmr spectra with those of an authentic sample.

1,2,3,4-Tetrahydro-1-carbomethoxynaphthalen-2-one (74)

To a solution of 1.5 g of 1,4-dihydro-2-methoxy-1-carbomethoxy-naphthalene (73) in about 25 ml of acetone was added 5 ml of 3N hydrochloric acid. The reaction mixture was refluxed for 15 minutes in an atmosphere of nitrogen, cooled to room temperature, diluted with 100 ml of cold water and extracted with ether. The ether solution was washed with water, saturated brine and evaporated to dryness. The crude product was distilled in vacuum to yield 1.45 g of the ketoester 74, b.p. 115 - 120° (0.15 mm); $\nu_{max}^{CHCl_3}$

1630, 1719^{cm-1} (enolic β-ketoester); λ_{max}^{MeOH} 225 (sh) (ε , 15,460), 275 (ε , 16,320), 302 mμ (ε , 8,710); pmr, δ 2.4 (4H) (m, C-3, C-4 H, A_2 B_2 system), 3.64 (3H) (s, C-1 ester methyl), 6.92 (3H) (m, C-5, C-6 and C-7 H), 7.45 (1H) (m, C-8 H), 13.2 (1H) (s, C-2 enolic H). Reported[112], b.p. 126° (2mm).

1,4-Dihydro-2,7-dimethoxy-1-carbomethoxynaphthalene (77)

The Birch reduction[45] of 2,7-dimethoxy-1-naphthoic acid (4.64 g) was effected by the same procedure adopted in the reduction of 69 and is described above. The naphthoic acid was reduced using 2.4 equivalents of metallic sodium in a mixture of liquid ammonia, ethanol and tetrahydrofuran. The dihydro acid was esterified with diazomethane in ether solution. The ether on evaporation followed by distillation of the crude product afforded 3.72 g (73. 75%) of 77, b.p. 140 - 150° (0.6 mm). Three recrystallisations from ether afforded an analytical sample m.p. 91- 92°; $\nu_{max}^{CHCl_3}$ 1610 (w), 1680 (w), 1725 (s) cm^{-1}; λ_{max}^{MeOH} 278 (ε , 2,390), 287 mμ (ε ,2,210); pmr, δ 3.49 (3H) (s, C-7 methoxyl), 3.51 (2H) (m, C-4 H), 3.55 (3H) (s, C-2 methoxyl), 3.63 (3H) (s, C-1 ester methyl), 4.16 (1H) (t, C-1 H, $J_{1,4}$ = 3.5 Hz), 4.87 (1H) (q, C-3 H, $J_{3,4}$ = 5 Hz, $J'_{3,4}$ = 3.5 Hz), 6.63 (1H) (d, C-6 H, $J_{5,6}$ = 8 Hz), 6.67 (1H) (s, C-8 H), 6.93 (1H) (d, C-5 H, $J_{5,6}$ = 8 Hz).

1,2,3,4-Tetrahydro-7-methoxy-1-carbomethoxynaphthalen-2-one (76)

The hydrolysis of 1,4-dihydro-2,7-dimethoxy-1-carbomethoxynaphthalene

(76) was effected by refluxing with dilute hydrochloric acid in acetone following the procedure described above for the preparation of 74. The reaction proceeded in an overall yield of 66.3% to give the ketoester 76, b.p. 130 - 140° (0.15 mm); $\nu_{max}^{CHCl_3}$ 1600 (s), 1635 (s), 1715 (w) cm^{-1}; λ_{max}^{MeOH} 217 (ε, 29,000), 232 (sh) (ε, 20,800), 258 (sh) (ε, 13,900), 270 (ε, 15,200), 297 mμ (ε, 14,300); pmr, δ 2,36 (4H) (m, C-3 H and C-4 H, A_2 B_2 system), 3.51 (3H) (s, C-7 methoxyl), 3.63 (3H) (s, C-1 ester methyl), 6.33 (1H) (q, C-6 H, $J_{5,6}$ = 8 Hz, $J_{6,8}$ = 2.5 Hz), 6.74 (1H) (d, C-5 H, $J_{5,6}$ = 8 Hz), 7.1 (1H) (d, C-8 H, $J_{6,8}$ = 2.5 Hz).

Addition of methyl vinyl ketone to 1,2,3,4-Tetrahydro-7-methoxy-1-carbomethoxynaphthalen-2-one (76)

To an ice-cold solution of sodium methoxide in absolute methanol derived from 465.3 mg of clean metallic sodium, was added 4.734 g of the ketoester 76 in 10 ml of absolute methanol. Methyl vinyl ketone (1.6993 g) was then added and the reaction mixture was kept at the ice bath temperature for 1 h and then at room temperature for 2 h under an atmosphere of nitrogen. The resultant mixture was refluxed for 30 minutes, cooled to room temperature, neutralised by the dropwise addition of 10% acetic acid and extracted with ether. The ether solution was washed with 10% sodium bicarbonate solution, water and saturated brine and evaporated to dryness. The crude product was chromatographed on alumina to yield 482.6 mg of yellow crystalline solid. Two crystallisations from ether-hexane (4:1) followed by recrystallisation from ethyl acetate-petroleum ether (1:2) afforded an analytical sample of 79, m.p. 178.5 - 180°, $\nu_{max}^{CHCl_3}$ 1645,

1722 cm^{-1}; λ_{max}^{MeOH} 215 (sh) (ε , 6,760), 335 mμ (ε, 4,500); pmr, δ 1.98 (3H) (s, C-18 methyl), 2.45 (8H) (m, C-1, C-2, C-15 and C-16 H), 3.3 (2H) (m, C-7 H), 3.62 (3H) (s, C-12 methoxyl), 3.82 (3H) (s, C-19 ester methyl), 6.82 (1H) (q, C-13 H, $J_{13,14}$ = 8 Hz, $J_{13,11}$ = 2.5 Hz), 7.07 (1H) (d, C-11 H, $J_{11,13}$ = 2.5 Hz), 7.14 (1H) (d, C-14 H, $J_{13,14}$ = 8 Hz); mol.wt., 338, mass spectrum; Anal. calcd. for $C_{21}H_{22}O_4$: C,74.5; H, 6.5. Found : C, 74.66; H, 6.5. On the basis of the above evidence the compound $C_{21}H_{22}O_4$ is assigned the tetracyclic structure 79.

1,2,3,4-Tetrahydro-7-methoxy-1-carbomethoxy-1-(3-keto n-butyl)-naphthalen-2-one (83)

The condensation between the β-ketoester 76 (246.4 mg) and methyl vinyl ketone (88.2 mg) in the presence of triethyl amine (106 mg) in absolute methanol (20 ml) was attempted according to the procedure of Church, Ireland and Shridhar[82]. The reaction mixture was left at room temperature for 48 h in an atmosphere of nitrogen. The bulk of the methanol was evaporated under reduced pressure and the residue dissolved in ether. The ether solution was washed with 5% hydrochloric acid, 10% sodium bicarbonate solution, water and saturated brine and evaporated to dryness to yield 270 mg of crude product as a viscous liquid. It showed no tendency to crystallise. The following pmr and ir spectral data suggested structure 83 for the condensation product. $\nu_{max}^{CHCl_3}$ 1617 (w), 1673 (w), 1723 (s) cm^{-1}; pmr, δ 1.85 (3H) (s, sidechain $-CO-CH_3$ protons), 2.45 (2H) (m, C-3 H), 2.97 (2H) (m, C-4 H), 3.59 (3H)

(s, C-1 ester methyl), 3.62 (3H) (s, C-7 methoxyl), 6.6 (1H) (q, C-6 H, $J_{5,6}$ = 8 Hz, $J_{6,8}$ = 2.5 Hz), 6.88 (2H) (m, C-5 and C-8 H).

3-Keto-12-methoxy-10-carbomethoxy-perhydrophenanthra-4,8,11,13-tetraene (85)

To a solution of 3.859 g (16.49 mmoles) of the ketoester 76 in 200 ml of ice-cold absolute methanol under an atmosphere of nitrogen was added dropwise 1.3834 g of methyl vinyl ketone. Triton B (386 mg) (40% solution of benzyltrimethyl ammonium methoxide in methanol) was then added and the reaction mixture cooled for a further 15 minutes and then left at room temperature for 24 h. The progress of the reaction was followed by periodic testing with ferric chloride. After 20 - 24 h a negative test was obtained. The reaction was stopped by the addition of a few drops of 10% solution of acetic acid until the solution became neutral. The bulk of the methanol was evaporated under reduced pressure and the residue diluted with 100 ml of water and extracted with ether. The ether solution was washed with water, saturated sodium chloride, and was evaporated to dryness. The ir and pmr spectra of the product indicated that it was a hydroxy-keto ester. No attempt was made to further characterise this material.

It was refluxed with p-toluene sulphonic acid (5% by weight) in toluene solution using a Dean-Stark water separator. After 16 h the reaction mixture was cooled to room temperature and washed with 10% sodium bicarbonate, water, and saturated brine. The toluene solution was evaporated to dryness

and the crude α, β-unsaturated ketone was purified by chromatography on an alumina column. In this way, 988 mg (21%) of the unsaturated ketone were obtained as pale yellow crystals. Three recrystallisations from 4:1 hexane-ether afforded an analytical sample, m.p. 92 - 93.5°; $\nu_{max}^{CCl_4}$ 1611, 1678, 1728 cm^{-1}; λ_{max}^{MeOH} 230 (ε, 20,650), 245 (sh) (ε, 15,250), 288 mμ (ε, 3180); pmr, δ 2.5 (8H) (m, C-1, C-2, C-6 and C-7 H), 3.74 (3H) (s, C-12 methoxyl), 3.83 (3H) (s, C-20 ester methyl), 6.03 (1H) (s, C-4 H), 6.81 (1H) (q, C-13 H, $J_{13,14}$ = 7.5 Hz, $J_{11,13}$ = 2.5 Hz), 7.06 (1H) (d, C-11 H, $J_{11,13}$ = 2.5 Hz), 7.13 (1H) (d, C-14 H, $J_{13,14}$ = 7.5 Hz); Anal. calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found : C, 71.25; H, 6.23.

In experiments where the sample of 2,7-dimethoxy-1-naphthoic acid (62) used was impure and the reduction of the naphthoic acid 62 and subsequent reactions leading to the tricyclic α, β-unsaturated ketone 85 were carried out on a large scale, the yield of 85 was lower (approximately 10%). In addition a tetracyclic compound 86 was obtained in approximately 17% as a side product. Three recrystallisations from 5:1 hexane-ether provided an analytical sample of 86, m.p. 112 - 113.5°; $\nu_{max}^{CHCl_3}$ 1610, 1655 cm^{-1}; λ_{max}^{MeOH} 230 (ε, 1450), 279 (ε, 1200), 288 (ε, 1110), 310 mμ (ε, 180); pmr, δ 1.7 (3H) (d, C-18 methyl, $J_{16,18}$ = 1.5 Hz), 2.5 (9H) (m, C-1, C-2, C-6, C-7 and C-17 H), 3.73 (3H) (s, C-12 methoxyl), 5.38 (1H) (s, C-16 H, $W^{h/2}$ = 8.5 Hz) 5.68 (1H) (s, C-4 H), 6.6 (1H) (q, C-13 H, $J_{13,14}$ = 8.5 Hz, $J_{11,13}$ = 2.5 Hz), 6.74 (1H) (d, C-11 H, $J_{11,13}$ = 2.5 Hz), 6.91 (1H) (d, C-14 H, $J_{13,14}$ = 8.5 Hz). Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found C, 81.49; H, 7.26.

EXPERIMENTAL - PART II

Synthesis of Methyl O-methyl-11-desoxycarnosate

1,2,3,4-Tetrahydro-7-methoxynaphthalen-2-one (78)

To a solution of 30 g of 2,7-dimethoxynaphthalene (59) in 120 ml of absolute ethanol, 150 ml of tetrahydrofuran (freshly distilled over calcium hydride), and 750 ml of anhydrous ether was condensed nearly 2 litres of liquid ammonia using a Dry Ice condenser. Nine grams of clean sodium were then added in small pieces so that the addition of each piece of sodium was carried out after the blue colour caused by the previous piece had disappeared. When the reaction was completed as judged by the disappearance of the blue colour, 10 g of solid ammonium chloride was added and the reaction mixture left overnight to permit the ammonia to evaporate off. About 250 ml of water was added to the residue and the solution acidified (pH5) with 10% hydrochloric acid. It was repeatedly extracted with ether and the ether extracts washed with saturated sodium bicarbonate solution, water and saturated brine. Evaporation of the ether yielded 31.8 g of crude dihydroenol ether. No attempt was made to purify the material.

The above dihydronaphthalene 87 was dissolved in 150 ml of acetone and 30 ml of 3N hydrochloric acid was added. The reaction mixture was refluxed under nitrogen for 30 minutes and the acetone evaporated off. The residue was diluted with 200 ml of water and extracted repeatedly with ether.

The ether solution was washed with saturated sodium bicarbonate solution, water and saturated brine and the ether evaporated to yield 27 g of crude 7-methoxy-2-tetralone (78).

The crude tetralone was dissolved in 40 ml of ethanol and the solution slowly added to a vigorously stirred solution of 65 g of sodium bisulphite in 115 ml of water. Almost immediately a bulky precipitate separated out. Stirring was continued for another 5 minutes and the mixture was left at the refrigerator temperature overnight. The precipitate was filtered under suction, washed with 80 ml of an ice-cold 1:1 mixture of ethanol and water, 80 ml of benzene and finally with 80 ml of dry ether. The precipitate was air dried at the filter pump to yield 57.7 g of bisulphite adduct.

The bisulphite adduct was suspended in 250 ml of water and treated with 300 ml of a saturated solution of sodium bicarbonate. The mixture was kept stirring for 30 minutes and extracted several times with ether. The ether solution was washed with water and saturated brine and evaporated to dryness to yield 23.5 g of the tetralone. This was distilled in vacuo to yield 21.95 g of 7-methoxy-2-tetralone, (78), b.p. 115 - 125° (0.15 mm); $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}; pmr, δ 2.17 (2H) (t, C-3 H, $J_{3,4}$ = 6.5 Hz), 2.69 (2H) (t, C-4 H, $J_{3,4}$ = 6.5 Hz), 3.22 (2H) (s, C-1 H), 3.52 (3H) (s, C-7 methoxyl), 6.45 (1H) (d, C-8 H, $J_{6,8}$ = 2.5 Hz), 6.55 (1H) (q, C-6 H, $J_{5,6}$ = 8 Hz, $J_{6,8}$ = 2.5 Hz), 6.91 (1H) (d, C-5 H, $J_{5,6}$ = 8 Hz); reported[113] b.p. 123 - 125° (0.4 mm).

1,2,3,4-Tetrahydro-7-methoxy-1-carbomethoxy-naphthalen-2-one (76) Enamine method :

To a solution of 3.4 g of 7-methoxy-2-tetralone (78) in 150 ml of anhydrous benzene was added 5 ml of freshly distilled morpholine. The resultant mixture was refluxed for 48 h in an atmosphere of nitrogen using a Dean-Stark water separator. The ultraviolet spectrum and pmr spectrum indicated the formation of a morpholine enamine. No attempt was made to purify the resultant enamine.

The enamine solution was cooled in an atmosphere of nitrogen and 5 g of pure, dry calcium carbonate (freshly heated to 200°) and 5 ml of chloromethyl formate were added. The reaction mixture was heated to reflux and the progress of the reaction was followed by pmr spectoscopy. After 10 h the pmr spectrum showed a substantial absorption at 5.42 ppm (vinylic H) and a further 10 ml of the chloroformate was added and the mixture refluxed for another 14 h. Examination of a further aliquot indicated the presence of some unreacted enamine and a further 5 ml of chloroformate was added and the reaction mixture refluxed for 6 h. At the end of this period most of the enamine had reacted. The reaction mixture was filtered to remove the calcium carbonate and the residue washed with benzene. The filtrate was refluxed with 50 ml of 3N hydrochloric acid for 5 minutes and the resultant solution cooled to room temperature. The benzene solution was washed with 10% sodium bicarbonate solution, water and saturated brine and evaporated to dryness to yield 5.6 g

of product. A pmr spectrum of this crude product indicated that it was only 10% ketoester (12.4% yield) and was 90% starting material. No further attempt was made to purify the product.

1,2,3,4-Tetrahydronaphthalen-2-one (β-Tetralone) (91)

β-Tetralone was prepared essentially by the method of Birch[45]. The reduction of β-naphthol by sodium in liquid ammonia gave 57% yield of β-tetralone, b.p. 140 - 145° (13 mm). Reported[45], b.p. 140° (14 mm).

1,2,3,4-Tetrahydro-1-carbomethoxynaphthalene-2-one (74)

A solution of 1.295 g of β-tetralone (91) in 25 ml of freshly distilled dimethylcarbonate (n_D^{20} 1.3690) was cooled in an ice-bath. A sample of 700 mg of sodium hydride in mineral oil (51%) was washed three times with 10 ml portions of anhydrous ether and then suspended in 10 ml of dimethyl carbonate. This supsension was added slowly to the tetralone solution under a nitrogen atmosphere. The reaction mixture was kept at ice-bath temperature for 15 minutes and at room temperature for 48 h. It was then refluxed for 30 minutes, cooled to room temperature and the excess sodium hydride destroyed by pouring the reaction mixture into ice-cold 10% hydrochloric acid. The organic material was extracted with ether and the ether layer washed with sodium bicarbonate solution, water and saturated sodium chloride solution and the ether evaporated to dryness to yield 1.75 g of crude keto-ester. Distillation in vacuo afforded 1.543 g of the keto-ester as a pale yellow liquid, b.p. 115 - 120° (0.15 mm); $\nu_{max}^{CHCl_3}$ 1600, 1629, 1714 (w) cm^{-1};

λ_{max}^{MeOH} 208 (ε, 26,200), 225 (sh) (ε, 15,460), 275 (ε, 16,320) 302 mμ (ε, 8,710); pmr, δ 2.5 (4H) (m, C-3 and C-4 H), 3.74 (3H) (s, C-1 ester CH_3) 6.9 (3H) (m, C-5, C-6, and C-7 H), 7.5 (1H) (d, C-8 H, $J_{6,7}$ = 7 Hz). Reported[112], b.p. 126° (2 mm).

1,2,3,4-Tetrahydro-7-methoxy-1-carbomethoxy naphthalen-2-one (76)

This compound was prepared by the reaction of 7-methoxy-2-tetralone (78) and dimethyl carbonate in the presence of sodium hydride. The procedure followed was exactly the same as adopted in the preparation of 1,2,3,4-tetrahydro-1-carboxmethoxynaphthalen-2-one (74) from 2-tetralone. This reaction gave the keto-ester b.p. 130 - 140° (0.15 mm) in an overall yield of 91.8%. An analytical sample of this keto-ester was prepared by three crystallisations from absolute methanol giving the keto-ester as colourless crystals, m.p. 46 - 47° (uncorr.); $\nu_{max}^{CCl_4}$ 1600, 1636, 1717 (w) cm^{-1}; λ_{max}^{MeOH} 217 (ε, 29,000), 232 (sh) (ε, 20,800), 258 (sh) (ε, 13,870), 270 (ε, 15,170), 297 mμ (ε, 14,300); pmr, δ 2.51 (4H) (m, C-3 and C-4 H), 3.66 (3H) (s, C-7 methoxyl), 3.81 (3H) (s, C-1 ester CH_3), 6.4 (1H) (q, C-6 H, $J_{5,6}$ = 8 Hz, $J_{6,8}$ = 2.5 Hz), 6.81 (1H) (d, C-5 H, $J_{5,6}$ = 8 Hz), 7.12 (1H) (d, C-8 H, $J_{6,8}$ = 2.5 Hz). Anal. calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found : C, 66.58; H, 6.05.

3-Keto-12-methoxy-10-carbomethoxy-perhydrophenanthra-4,8,11,13-tetraene (85)

The addition of methyl vinyl ketone to the keto-ester 76 (prepared by the action of 7-methoxy-2-teralone and dimethylcarbonate in the presence of sodium hydride) in the presence of triton B in absolute methanol was carried out

by the procedure described above for the unsautrated ketone 85. The crude sample of the unsaturated ketone 85 obtained from 1.7417 g of 76 was chromatographed on 50 g of alumina. The fractions eluted by 90% benzene - 10% ether gave on evaporation 1.076 g (50.5%) of the unsaturated ketone as pale yellow crystals. Two recrystallisations from 80% hexane - 20% ethyl acetate gave 0.8182 g of an analytical sample, m.p. 92 - 93.5° (corr.); $\nu_{max}^{CCl_4}$ 1611, 1678, 1728 cm^{-1}; λ_{max}^{MeOH} 230 (ε, 20,655), 245 (sh) (ε, 15,253), 288 mμ (ε, 3,180); pmr, δ 3.74 (3H) (s, C-12 methoxyl), 3.83 (3H) (s, C-20 ester methyl), 6.03 (1H) (s, C-4 H), 6.81 (1H) (q, C-13 H, $J_{13,14}$ = 7.5 Hz, $J_{11,13}$ = 2.5 Hz), 7.06 (1H) (d, C-11 H, $J_{11,13}$ = 2.5 Hz), 7.13 (1H) (d, C-14 H, $J_{13,14}$ = 7.5 Hz); Anal. calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found : C, 71.25: H, 6.23.

Methyl O-methyl-3-keto, Δ^5-13-deisopropyl-11-desoxycarnosate (94)

The methylation of the tricyclic ketone 85 was carried out by a modification of Stork's procedure[93].

To a solution of 572 mg of dry 3-keto-12-methoxy-10-carbomethoxy perhydrophenanthra-4,8,11,13-tetraene (85) in 20 ml of tertiary butyl alcohol (freshly distilled over calcium hydride) was added a solution of 672 mg of potassium tertiary butoxide in 20 ml of tertiary butyl alcohol with stirring. During the addition of the tertiary butoxide the pale yellow solution became deep orange in colour. Methyl iodide (0.78 ml, 1.704 g) was then added

and after a short interval the solution became turbid because of the precipitation of potassium iodide. The reaction mixture was left at room temperature under an atmosphere of nitrogen for 48 h and then stopped by the addition of 10% hydrochloric acid. The bulk of the tertiary butyl alcohol was evaporated off under reduced pressure, 50 ml of water was added to the residue and the residue extracted repeatedly with ether. The ether solution was washed with water, saturated brine and evaporated to dryness to yield 590 mg of dark brown liquid, pmr, δ 1.25 (6H) (s, C-4 methyl groups), 3.7 (3H) (s, C-20 ester methyl), 3.72 (3H) (s, C-12 methoxyl), 6.01 (1H) (q, C-6 H). As this compound appeared to be very unstable no attempt was made to purify it.

The crude methylation product was dissolved in 25 ml of glacial acetic acid and hydrogenated in the presence of 100 mg of 5% palladium on charcoal catalyst for 24 h at atmospheric pressure. The catalyst was then filtered off the filtrate evaporated to dryness, and the residue extracted with ether. The ether solution was washed with 10% sodium bicarbonate solution, water and saturated brine and evaporated to dryness to yield 566 mg of a pale yellow liquid. No single pure compound was isolated from this reaction product. The mass spectrum of this material contained a major peak at m/e, 316 corresponding to dimethylation and peaks of smaller intensity at m/e, 330 and m/e 344 indicating some polymethylation. The infrared spectrum of this substance had a peak at 3450 cm^{-1} indicating partial reduction of the keto group and the pmr spectrum showed no vinylic protons. No serious attempt was made to

separate the constituents of the hydrogenation product. In hydrogenation attempts at high pressure the product was found to have lost the ester function (pmr spectrum) probably as a result of the formation of the 3-lactone 95. The product was not characterised.

Thioketal 98

The methylation of the tricyclic ketone 85 was repeated using 650 mg of the unsaturated ketone yielded 705 mg of crude product. The thioketal derivative of this ketone was prepared by the method of Ireland[94]. The methylation product (705 mg) was dissolved in 7 ml of glacial acetic acid, cooled to 5° and kept under a nitrogen atmosphere. To this well-stirred solution was added 2 ml of ethane-1,2-dithiol and then, dropwise, 2 ml of borontrifluoride-etherate over a 10 minute period. The reaction mixture developed a deep orange colour and the thioketal derivative separated out. Stirring was continued at 5° for 30 minutes and at room temperature for 1 h. The mixture was again cooled to 5° and filtered under suction. The product was washed with a few drops of cold methanol and sucked dry at the pump. This treatment afforded 784 mg (88.5%) of the thioketal as colourless crystals sufficiently pure for further reaction. Two crystallisations from ethanol afforded an analytical sample, m.p. 190 - 191° (sealed tube); λ_{max}^{MeOH} 227 (ε, 7,200) 280 (ε, 2,010), 287 mμ (ε, 1,905); pmr, δ 1.21 (3H) (s, C-4 axial CH_3), 1.51 (3H) (s, C-4 equatorial CH_3) 3.21 (4H) (m, thioketal H), 3.51 (3H)

(s, C-20 ester methyl), 3.72 (3H) (s, C-12 methoxyl), 6.10 (1H) (t, C-6 H), 6.75 (1H) (q, C-13 H, $J_{13,14}$ = 8.5 Hz, $J_{11,13}$ = 2.5 Hz), 6.8 (1H) (s, C-11 H, $W^{h/2}$ = 3.5 Hz), 7.05 (1H) (d, C-14 H, $J_{13,14}$ = 8.5 Hz); Anal. calcd. for $C_{21}H_{26}O_3S_2$: C, 64.6; H, 6.71; S, 16.40. Found: C, 64.45; H, 6.65; S, 16.36.

Methyl O-methyl-13-deisopropyl-11-desoxycarnosate (99)

To a suspension of 8 g of W-2 Raney Nickel in 50 ml of absolute ethanol was added a solution of 784 mg of the thioketal in 100 ml of absolute ethanol. The mixture was then stirred and refluxed in an atmosphere of nitrogen for 48 h. The reaction mixture was cooled, filtered, the nickel exhaustively washed with ethanol, and the filtrate evaporated to dryness to yield a viscous liquid. The mass spectrum of this material showed two major peaks at m/e, 300 and m/e 302. A pmr spectrum showed a triplet at δ 5.88 (C-6 H, area less than one third that of the aromatic protons) indicating that it was a mixture of the saturated compound 99 and its $\Delta^{5,6}$-unsaturated derivative.

The deketalisation product was dissolved in 10 ml of glacial acetic acid and hydrogenated in the presence of 70 mg of platinum oxide at atmospheric pressure. After 12 h the platinum was filtered off, the acetic acid evaporated under reduced pressure, and the residue diluted with 50 ml of water and extracted with ether. The ether layer was washed with 10% sodium bicarbonate, water and saturated brine and the ether evaporated. The residue was filtered through a micro-column of 5 g of alumina with n-hexane. Evaporation of the

hexane yielded 359 mg of crystalline 99. Three crystallisations afforded 218 mg of the methoxy-ester, m.p. 234 - 235° (sealed tube); mol.wt., 302, mass spectrum; $\nu_{max}^{CHCl_3}$ 1610, 1715 cm^{-1}; pmr, δ 1.05 (3H) (s, C-4 axial CH_3), 1.14 (3H) (s, C-4 equatorial CH_3), 3.65 (3H) (s, C-20 ester methyl), 3.72 (3H) (s, C-12 methoxyl), 6.58 (1H) (d, C-11 H, $J_{11,13}$ = 2.5 Hz), 6.6 (1H) (q, C-13 H, $J_{13,14}$ = 9 Hz, $J_{11,13}$ = 2.5 Hz), 6.87 (1H) (d, C-14 H, $J_{13,14}$ = 9 Hz); Anal. calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.29; H, 8.48.

An attempt was made to carry out a Friedel-Crafts acylation on 99. The reaction was carried out by the addition of a solution of 99 in methylene chloride to the complex of acetyl chloride and anhydrous aluminium chloride in methylene chloride and allowing the mixture to stand at room temperature in an atmosphere of nitrogen for 48 h. The product on work up via ether extraction and three crystallisations from 2:1 hexane-ether gave an analytical sample of the 3-lactone 95, m.p. 145 - 146.5°; $\nu_{max}^{CHCl_3}$ 1734 cm^{-1} (lactone); λ_{max}^{MeOH} 220 (ε, 2,430), 225 (ε, 2,255), 280 (ε, 750), 288 mμ (ε, 720); pmr, δ 1.15 (3H) (s, C-4 axial methyl), 1.23 (3H) (s, C-4 equatorial methyl), 2.8 (2H) (m, C-7 H), 3.82 (3H) (s, C-12 methoxyl), 4.27 (1H) (t, C-3 H, $J_{2,3}$ = 3 Hz), 6.82 (1H) (q, C-13 H, $J_{13,14}$ = 9 Hz, $J_{11,13}$ = 3 Hz), 6.84 (1H) (d, C-11 H, $J_{11,13}$ = 3 Hz), 7.08 (1H) (d, C-14 H, $J_{13,14}$ = 9 Hz); Anal. calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found : C, 75.54 ; H, 7.86.

The mother liquors from the crystallisation of the lactone contained

components possessing an acyl function as judged from their pmr spectra.

An attempt was made to effect Friedel-Crafts acylation of the lactone 95 by adding a solution of the lactone in methylene chloride to the complex of acetyl chloride and aluminium chloride in methylene chloride and allowing the reaction to proceed for 72 h at room temperature. The pmr and ir spectra indicated that acylation had not occurred. Refluxing the above reaction mixture for a few hours did not result in the formation of acylated products.

1,7-Dimethoxynaphthalene (106)

Methylation of 1,7-dihydroxynaphthalene (105) was carried out using dimethyl sulphate and sodium hydroxide as recorded above for the preparation of 2,7-dimethoxynaphthalene (59). The crude product was extracted with ether, washed with 5% sodium hydroxide, water and saturated brine and finally evaporated to dryness. The residue was purified by chromatography on alumina giving the dimethoxyether as a liquid (96% yield) with a green fluorescence, b.p. 100 - 105° (0.05 mm) n_D^{22} 1.616; ν_{max}^{neat} 1600, 1625 cm^{-1}; reported[114], b.p. 123 - 130° (0.4 mm).

1,2,3,4-Tetrahydro-8-methoxynaphthalen-2-one (108)

The conversion of 1,7-dimethoxynaphthalene (106) to 108 was effected by the same method as adopted in the synthesis of 7-methoxy-2-tetralone (78) described above. This tetralone was purified by preparation of the bisulphite adduct, regeneration of the tetralone with saturated sodium bicarbonate solution and extraction with ether. The ether solution was evaporated to dryness and

the residue on distillation under reduced pressure afforded 8-methoxy-2-tetralone in an overall yield of 49%, b.p. 125° - 140° (0.1 mm); m.p. 59.5 - 61°; n_D^{22} 1.559; $\nu_{max}^{CCl_4}$ 1717 cm^{-1}; pmr, δ 2.38 (2H) (m, C-3 H), 2.95 (2H) (m, C-4 H), (A_2B_2 system), 3.33 (2H) (s, C-1 H), 3.75 (3H) (s, C-8 methoxyl), 6.45 - 7.2 (3H) (m, C-5, C-6 and C-7 H) (A, A', B system). Reported[115], b.p. 108 - 111° (0.03 mm).

1,2,3,4-Tetrahydro-8-methoxy-1-carbomethoxy-naphthalen-2-one (109)

The 8-methoxy-ester 109 was prepared from 8-methoxy-2-tetralone (108) by the reaction of dimethyl carbonate in the presence of sodium hydride. The procedure adopted was the same as that used for the preparation of the 7-methoxy analog described above. This reaction proceeded in an overall yield of 93%. Two distillations under reduced pressure yielded an analytical sample, b.p. 145 - 150° (0.4 mm); $\nu_{max}^{CCl_4}$ 1652 (weak, hydrogen bonded ester carbonyl), 1720 (keto group, intense), 1753 (ester carbonyl, intense), 3400 cm^{-1} (enolic OH, weak, broad); λ_{max}^{MeOH} 230 (ε, 553), 277 (ε, 553), 330 mμ (ε, 266); pmr, δ 2.45 (2H) (m, C-3 H), 3.14 (2H) (m, C-4 H), (A_2B_2 system), 3.59 (3H) (s, C-1 ester methyl), 3.73 (3H) (C-8 methoxyl), 4.55 (1H) (C-1 H), 6.58 - 7.28 (3H) (m, C-5, C-6 and C-7 H) (A,A',B system). Anal. calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found : C, 66.80; H, 6.02.

3-Keto-11-methoxy-10-carbomethoxyperhydro-phenanthra-4,8,11,13-tetraene (111)

The unsaturated ketone 111 was prepared by the Michael addition of

methyl vinyl ketone to 1,2,3,4-tetrahydro-8-methoxy-1-carbomethoxynaphthalen-2-one (109) in the presence of Triton B methoxide in methanol followed by dehydration with p-toluene sulphonic acid in refluxing toluene. The procedure adopted was essentially the same as that employed in the preparation of the 12-methoxy isomer 85 and is described above. The dehydration of the ketol from the 8-methoxy tetralone ester 110 required refluxing with p-toluene sulphonic acid in toluene for 96 h. The tricyclic unsaturated ketone 111 was obtained in an overall yield of 57%. Three crystallisations from 1:1 hexane -ethyl acetate afforded an analytical sample, m.p. 155 - 156°; $\nu_{max}^{CHCl_3}$ 1668, 1718 cm^{-1}; λ_{max}^{MeOH} 223 (ε , 16,575), 240 (sh) (ε, 13,000), 272 (ε , 2,568), 279 (ε, 2,405), 338 mμ (ε, 481); pmr, δ 3.62 (3H) (s), 3.76 (3H) (s), (C-20 ester methyl and C-11 methoxyl), 5.97 (1H) (s, C-4 H), 6.68 - 7.22 (3H) (m, C-12, C-13 and C-14 H) (A,A',B system); Anal. calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found : C, 71.18; H,6.33.

2,7-Dimethoxy-3-naphthoic Acid (64)

The method employed was essentially the same as that followed by Sunthankar and Gilman [99].

The crude naphthoic acid 64 contaminated with valeric acid was purified by repeatedly washing with cold water, followed by dissolution in alkali and reprecipitation with dilute hydrochloric acid. The reaction proceeded in 64.2% yield. Two crystallisations from 1:1 benzene-ethanol

afforded an analytical sample, m.p. 185 - 186°; reported[99] m.p. 185.5°.

2,7-Dimethoxy-3-carbomethoxynaphthalene (113)

The methylation of the naphthoic acid 64 was carried out by the Fisher method[74]. To a solution of 22 g of the acid 64 in 1200 ml of absolute methanol was added 15 ml of concentrated sulphuric acid and the mixture refluxed for 22 h in an atmosphere of nitrogen. The reaction mixture was cooled to room temperature, neutralised with saturated sodium bicarbonate and the bulk of methanol removed by evaporation under reduced pressure. The residue was diluted with 100 ml of water and extracted with ether. The ether layer was washed with water, saturated brine and evaporated to dryness. The residue on crystallisation from 1:1 benzene-hexane afforded 22.6 g (93%) of the ester 113. One more crystallisation from the same solvent afforded an anlytical sample, m.p. 101 - 102°; $\nu_{max}^{CHCl_3}$ 1627, 1722 cm^{-1} (ester carbonyl); pmr, δ 3.83 (3H) (s, C-7 methoxyl), 3.87 (3H) (s, C-2 methoxyl), 3.92 (3H) (s, C-3 ester methyl), 6.94 (1H) (q, C-6 H, $J_{5,6}$ = 9.5 Hz, $J_{6,8}$ = 2 Hz), 6.95 (1H) (d, C-8 H, $J_{6,8}$ = 2 Hz), 7.03 (1H) (s, C-1 H), 7.62 (1H) (d, C-5 H, $J_{5,6}$ = 9.5 Hz), 8.19 (1H) (s, C-4 H); Anal. calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found : C, 68.32; H, 5.77.

2,7-Dimethoxy-3-(2'-hydroxy-2'-methyl ethyl) -naphthalene (114)

A solution of 17.5 g of methyl 2,7-dimethoxynaphthalene-3-carboxylate (113) in about 700 ml of anhydrous ether was added to 100 ml of a stirred

solution of methyl magnesium bromide in ether containing 0.43 g of the Grignard reagent per ml. As the reaction progressed a white precipitate separated out. When all the ester solution was added the reaction mixture was refluxed for one hour. The mixture was allowed to cool to room temperature and decomposed with 10% acetic acid. The ether layer was separated and the aqueous layer further extracted with ether. The combined ethereal solution was washed with 10% sodium bicarbonate, water and saturated brine. The ether on evaporation yielded 17.3 g (99%) of naphthalene alcohol 114, which was sufficiently pure for further reaction. A small portion of the naphthalene alcohol was dissolved in hexane and filtered through a small column of alumina. The filtrate on evaporation yielded 114 as colourless crystals and two crystallisations from hexane and one from hexane-ether (3:1) gave an analytical sample, m.p. 104.5 - 106°; $\nu_{max}^{CHCl_3}$ 1630, 3533 (OH, broad, intramolecularly H-bonded OH), 3650 cm^{-1} (s) (free OH); pmr δ 1.68 (6H) (s, C-3 isopropanol, CH_3), 3.77 (3H) (s), 3.81 (3H) (s) (C-2 and C-7 methoxyl groups), 4.1 (1H) (s, OH, $W^{h/2}$ 7.5 Hz), 6.95 (1H) (q, C-6 H, $J_{5,6}$ = 9.5 Hz, $J_{6,8}$ = 2.5 Hz), 6.97 (1H) (d, C-8 H, $J_{6,8}$ = 2.5 Hz), 6.99 (1H) (s, C-1 H), 7.57 (1H) (d, C-5 H, $J_{5,6}$ = 9.5 Hz), 7.69 (1H) (s, C-4 H); Anal. calcd. for $C_{15}H_{18}O_3$: C, 73.14; 7.37. Found : C, 73.21; H, 7.45.

2,7-Dimethoxy-3-isopropylnaphthalene (112)

A solution of 17 g of the naphthalene alcohol 114 in 150 ml of glacial

acetic acid was refluxed for 30 minutes in an atmosphere of nitrogen. The bulk of acetic acid was then allowed to distill off. When the volume of the residual solution had reached about 25 ml the mixture was cooled to room temperature. No attempt was made to isolate the isopropenylnaphthalene but the material was immediately hydrogenated in the presence of 1.8 g of 5% palladium on charcoal at 60 p.s.i. for 24 h. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was diluted with 100 ml of water, extracted with ether and the ether solution washed with 10% sodium bicarbonate, water and saturated brine. The ether was evaporated to yield 15.3 g of the crude isopropylnaphthalene 112. This was dissolved in benzene and filtered through a column containing 60 - 65 g of alumina. The filtrate on evaporation afforded 15.62 g (98.5%) of the isopropylnaphthalene (112). Three crystallisations from n-hexane-petroleum ether 30 - 60° (3:1) gave an analytical sample, m.p. 95 - 96°; $\nu_{max}^{CHCl_3}$ 1602, 1623 cm^{-1}; pmr, δ 1.28 (6H) (d, C-3 isopropyl CH_3, J = 7 Hz), 3.52 (1H) (m, C-3 isopropyl methine H, J = 7 Hz), 3.7 (3H) (s, C-7 methoxyl), 3.74 (3H) (s, C-2 methoxyl), 6.85 (1H) (s, C-1 H), 6.88 (1H) (d, C-8 H, $J_{6,8}$ = 2.5 Hz), 6.89 (1H) (q, C-6 H, $J_{5,6}$ = 9.5 Hz, $J_{6,8}$ = 2.5 Hz), 7.43 (1H) (s, C-4 H), 7.51 (1H) (d, C-5 H, $J_{5,6}$ = 9.5 Hz); Anal. calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88.
Found : C, 78.35; H, 7.86.

1,2,3,4-Tetrahydro-7-methoxy-6-isopropyl-naphthalen-2-one (114)

The conversion of 2,7-dimethoxy-3-isopropylnaphthalene (112) to 7-methoxy-6-isopropyl-2-tetralone (117) was effected by the same procedure adopted for the preparation of 7-methoxy-2-tetralone (78) described above. From 6.4346 g of 2,7-dimethoxy-3-isopropylnaphthalene (112) 4.336 g of the tetralone (114) was obtained. It was further purified by fractional distillation under reduced pressure. The 7-methoxy-6-isopropyl-2-tetralone (114) was obtained as a colourless liquid, 4.0961 g (67.1%), b.p. 120 - 125° (0.33 mm), $\nu_{max}^{CHCl_3}$ 1711 cm^{-1}; pmr, δ 1.16 (6H) (d, C-6 isopropyl methyl, J = 6.5 Hz), 2.4 (2H) (t, C-3 H, $J_{3,4}$ = 6.5 Hz), 2.92 (2H) (t, C-4 H, $J_{3,4}$ = 6.5 Hz), 3.22 (1H) (m, C-6 isopropyl methine H, J = 6.5 Hz), 3.38 (2H) (s, C-1 H), 3.75 (3H) (s, C-7 methoxyl), 6.46 (1H) (s, C-8 H), 6.88 (1H) (s, C-5 H); Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.87; H, 8.19.

1,2,3,4-Tetrahydro-7-methoxy-6-isopropyl-1-carbomethoxynaphthalen-2-one (118)

The method employed for the conversion of 7-methoxy-6-isopropyl-2-tetralone (117) to 7-methoxy-6-isopropyl-1-carbomethoxy-2-tetralone (118) was the same as that used in the preparation of 7-methoxy-1-carbomethoxy-2-teralone (76) from 7-methoxy-2-tetralone (78) and is described above. The isopropyl-keto-ester 18 was obtained as a pale yellow liquid (80%), b.p. 165 - 175° (0.05 mm). Two vacuum distillations afforded an analytical sample as a colourless liquid, b.p. 150 - 160° (0.03 mm); $\nu_{max}^{CHCl_3}$ 1587, 1629 (hydrogen

bonded ester carbonyl) (s), 1700 (w), 1723 (w) cm^{-1}; λ_{max}^{MeOH} 212 (ε, 47,240) 248 (ε, 15,040), 255 (sh) (ε, 12,430), 292 (ε, 6,340), 300 (ε, 6,216), 315 mμ (sh) (ε, 3,730); pmr, δ 1.17 (6H) (d, C-6 isopropyl CH_3, J = 7 Hz), 2.55 (4H) (m, C-3 and C-4 H, A_2B_2 system), 3.31 (1H) (m, C-6 isopropyl methine H, J = 7 Hz), 3.75 (3H) (s, C-7 methoxyl), 3.85 (3H) (s, C-1 ester methyl), 6.81 (1H) (s, C-8 H), 7.17 (1H) (s, C-5 H), 12.96 (1H) (s, C-2 enolic H); Anal. calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.20. Found: C, 69.66; H, 7.20.

3-Keto-12-methoxy-10-carbomethoxy-13-isopropylperhydrophenanthra-4,8,11,13-tetraene (120)

The Michael addition reaction of methyl vinyl ketone to the keto-ester 118 and the dehydration of the resultant cyclic ketol 119 were carried out by the procedure described above for the deisopropyl compounds. The unsaturated ketone 120 was purified by chromatography on alumina and was obtained as pale yellow crystals in 41.5% yield. Three crystallisations from hexane-ether (8:1) yielded an analytical sample, m.p. 94 - 95°; $\nu_{max}^{CHCl_3}$ 1661, 1722 cm^{-1}; λ_{max}^{MeOH} 230 (ε, 22,960), 282 mμ (ε, 2,950); pmr, δ 1.18 (6H) (d, C-16 and C-17 methyl, $J_{15,16}$ = 7 Hz), 3.23 (1H) (m, C-15 H, $J_{15,16}$ = 7 Hz), 3.65 (3H) (s, C-20 methoxyl), 3.78 (3H) (s, C-10 ester methyl), 5.99 (1H) (s, C-4 H), 6.87 (1H) (s, C-11 H), 6.89 (1H) (s, C-14 H); Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.17; H, 7.46.

Methyl O-methyl-3-keto-11-desoxy-Δ^5-carnosate (121)

The methylation of the unsaturated ketone 120 with methyl iodide in

the presence of potassium tertiary butoxide in anhydrous tertiary butyl alcohol was carried out by the procedure adopted for the methylation of the 13-deisopropyl ketone 85 described above. No attempt was made to characterise this methylation product as it appeared to be unstable. The crude reaction product was immediately used for the preparation of the thioketal derivative.

Thioketal 122

The procedure adopted was the same as that used for the thioketalisation of the 13-deisopropyl ketone 94 and is described above. The thioketal 122 was purified by crystallisation from acetone. It was obtained in an overall yield of 80.4% from the unsaturated ketone 120. Three recrystallisations from acetone afforded an analytical sample, m.p. 206 - 207.5°; λ_{max}^{MeOH} 238 (ε, 1,850) 280 (ε, 1,235), 285 mμ (ε, 1,235); pmr, δ 1.18 (6H) (d, C-16 and C-17 methyls, J = 6.5 Hz), 1.22 (3H) (s), 1.51 (3H) (s), (C-4 methyl groups), 3.2 (4H) (m, C-3 thioketal CH_2), 3.53 (3H) (s, C-20 ester methyl), 3.77 (3H) (s, C-12 methoxyl), 6.12 (1H) (m, C-6 H), 6.73 (1H) (s, C-11 H), 6.93 (1H) (s, C-14 H), Anal. calcd. for $C_{24}H_{32}S_2O_3$: C, 66.65; H, 7.46; S, 14.80. Found: C, 66.52; H, 7.34; S, 14.82.

Methyl O-methyl-11-desoxycarnosate (1f)

A solution of 57.6 mg of the thioketal 122 in 20 ml of ethanol was heated to reflux in an atmosphere of nitrogen. To the boiling solution was added 5 g of active Raney Nickel prepared according to the procedure of Burgstahler[101]. The reaction mixture was refluxed for 30 minutes, cooled to room temperature,

and the catalyst filtered off under suction in an atmosphere of carbon dioxide. The filtrate was evaporated to dryness and a pmr spectrum of the product indicated partial reduction of the 5,6-double bond. The material was dissolved in 20 ml of ethanol and refluxed with 5g of active Raney Nickel for a further 5 h in an atmosphere of hydrogen. The reaction mixture was cooled to room temperature the catalyst filtered off and the filtrate evaporated to dryness. The residue was dissolved in benzene and the benzene solution washed with water, saturated brine and evaporated to dryness. The residue on crystallisation from ethanol afforded 28.6 mg (62.4%) of methyl O-methyl-11-desoxy carnosate (1f). Two crystallisations from ethanol yielded an analytical sample of 1f, m.p. 108 - 109.5° (uncorr.); $\nu_{max}^{CHCl_3}$ 1605 (w); 1707 (s) cm^{-1}; λ_{max}^{MeOH} 230 (sh) (ε, 5,733), 280 (ε, 2,380), 287 mμ (ε, 2,350); pmr,δ 0.8 (3H) (s, C-4 axial CH_3), 0.98 (3H) (s, C-4 equatorial CH_3), 1.18 (6H) (d, C-16 and C-17 H, $J_{15,16}$ = 6.5 Hz), 3.2 (1H) (heptet, C-15 H, $J_{15,16}$ = 6.5 Hz), 3.55 (3H) (s, C-20 ester methyl), 3.75 (3H) (s, C-12 methoxyl) 6.72 (1H) (s, C-11 H), 6.86 (1H) (s, C-14 H); mass spectrum, mol.wt. calcd. for $C_{22}H_{32}O_3$, 344.235131; observed, 344.235609; mass calcd. for $C_{22}H_{31}O_3$, $(M-1)^+$ion, 343.227307; observed, 343.225957; mass calcd. for $C_{21}H_{29}O_3$, $(M-15)^+$ion, 329.211657; observed, 329.213040. Anal. calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.80; H, 9.43.

Hydrogenation of the initial desulphurisation product obtained from the thioketal 122 in the presence of platinum oxide suspended in glacial acetic

acid also yielded 1f. The pmr spectrum of this hydrogenation product indicated it to be of lower purity than the material obtained by Raney nickel reduction. However, two crystallisations from ethanol of the platinum catalysed hydrogenation product afforded an analytically pure sample.

Isopropylation at C-13 of Methyl O-methyl podocarpate

The isopropylation at C-13 of the methyl O-methyl podocarpate (19d) model system was effected in four steps by a modification of the method of Campbell and Todd[97]. Methyl O-methyl podocarpate (19d) was acylated at C-13 using acetyl chloride in methylene chloride in the presence of anhydrous aluminium chloride at room temperature. The reaction was stopped after 48 h and the product on work up and purification by crystallisation from hexane afforded the 13-acyl derivative 101 in 85% yield. Three crystallisations from hexane afforded an analytical sample, m.p. 119 - 120°; $\nu_{max}^{CCl_4}$ 1605, 1673 (carbonyl), 1723 (ester) cm^{-1}; pmr, δ1.0 (3H) (s, C-20 methyl), 1.25 (3H) (s, C-4 methyl), 2.5 (3H) (s, C-13 acyl CH_3), 3.72 (3H) (s, C-4 ester methyl), 3.95 (3H) (s, C-12 methoxyl), 7.0 (1H) (s, C-11 H), 7.55 (1H) (s, C-14 H). Reported[97], m.p. 119 - 119.5°.

The reaction of 101 with methyl magnesium bromide in anhydrous ether proceeded in 98% yield. A very pure sample of the tertiary alcohol 102 was obtained by three crystallisations from hexane, m.p. 148 - 149.5°; $\nu_{max}^{CHCl_3}$ 1608 (w), 1714 (ester), 3500 cm^{-1} (OH); pmr, δ 1.08 (3H) (s, C-20 methyl), 1.23 (3H) (s, C-4 methyl), 1.55 (6H) (s, C-13 isopropanol, methyl), 3.71 (3H)

(s, C-4 ester methyl), 3.92 (3H) (s, C-12 methoxyl), 4.13 (1H) (s, broad, C-13 isopropanol, OH), 6.95 (1H) (s, C-11 H), 7.125 (1H) (s, C-14 H). Reported[97], m.p. 148 - 150°.

An attempt to carry out hydrogenolysis of the isopropanol derivative 102 using 5% palladium on charcoal in acetic acid containing a trace of perchloric acid resulted in a complex mixture of compounds as judged from its pmr spectrum.

The dehydration of the isopropanol derivative 102 was effected by refluxing with glacial acetic acid for 30 minutes. The isopropenyl compound 103 was obtained in 92% yield. It was purified by crystallisation from hexane, m.p. 120 - 121°; $\nu_{max}^{CCl_4}$ 1613, 1633 (w), 1723 (ester) cm^{-1}; pmr, δ 0.92 (3H) (s, C-20 CH_3), 1.13 (3H) (s, C-4 CH_3), 2.0 (3H) (s, C-13 isopropenyl CH_3), 3.6 (3H) (s, C-4 ester methyl), 3.71 (3H) (s, C-12 methoxyl), 5.03 (2H) (s, 13-isopropenyl, vinylic H), 6.76 (1H) (s, C-11 H), 6.86 (1H) (s, C-14 H), Reported[97], m.p. 120.5 - 121.5°.

The hydrogenation of the isopropenyl compound 103 was carried out in glacial acetic acid in the presence of 10% by weight of 5% palladium on charcoal. It proceeded in 97% yield. An analytical sample of the isopropyl compound 104 was obtained by three crystallisations from hexane, m.p. 108 - 109.5°; $\nu_{max}^{CCl_4}$ 1613 (w), 1723 (ester) cm^{-1}; pmr, δ 1.1 (3H) (s, C-20 methyl), 1.23 (6H) (d, C-13 isopropyl CH_3, J = 7 Hz), 1.325 (3H) (s, C-4 CH_3), 3.8 (3H) (s, C-4 ester methyl), 3.93 (3H) (s, C-12 methoxyl), 6.99 (1H)

(s, C-11 H), 7.11 (1H) (s, C-14 H). Reported[97], m.p. 109 - 109.5°.

An attempt was made to effect the direct isopropylation of methyl O-methyl podocarpate (19d) at C-13 under Friedel-Crafts conditions[96]. The reaction of 19d with isopropyl iodide in methylene chloride in the presence of anhydrous aluminium chloride yielded a monoisopropyl derivative as judged from the mass spectrum of the crude reaction product. The pmr spectrum and vpc analysis indicated that the product was a mixture of isomers. No satisfactory reagent or reaction conditions could be found which led to the desired C-13 monoisopropyl derivative 104.

Attempted Hydroxylation at C-11 of Methyl-13-isopropylpodocarpate

To a solution of 3.096 g of methyl O-methyl-13-isopropylpodocarpate (104) in 10 ml of glacial acetic acid was added 6 ml of a 48% solution of hydrobromic acid. The solution was degassed by evacuation and was refluxed under nitrogen for 25 h. The reaction mixture was cooled to room temperature diluted with 50 ml of water, and extracted with ether. The ether solution was washed with 10% sodium bicarbonate, water and saturated brine. The ethereal solution was treated with an ether solution of diazomethane and allowed to stir for five minutes and then the ether was evaporated. A benzene solution of the methyl ester was filtered through a small column of alumina. The filtrate on evaporation yielded 2.91 g of fairly pure methyl-13-isopropyl-podocarpate 125. An analytical sample was obtained by three crystallisations

from ether, m.p. 180 - 181°; $\nu_{max}^{CHCl_3}$ 1615(w), 1710 (ester), 3350 (bonded OH), 3580 (free OH) cm^{-1}; pmr, δ 1.01 (3H) (s, C-20 CH_3), 1.22 (6H) (d, C-13 isopropyl CH_3, J = 7 Hz), 1.25 (3H) (s, C-4 CH_3), 3.17 (1H) (heptet, C-13 isopropyl methine H), 3.65 (3H) (s, C-4 ester methyl), 4.87 (1H) (s, C-12 OH, broad), 6.62 (1H) (s, C-11 H), 6.82 (1H) (s, C-14 H).

An attempt was made to carry out the nitration of 125 at C-11 using a solution of copper nitrate in acetic anhydride according to the procedure of Hodges and Raphael[102]. The reaction of 125 with 35% nitric acid-benzene mixture was also studied. In these two reactions the infrared spectra indicated that some nitration had taken place. But the pmr spectra indicated that the products obtained were very complex mixtures and no attempt was made to purify them.

In an alternative approach the rearrangement method of nitration according to the procedure of Zabik and Schuetz[103] was attempted. To an ice-cooled solution of 1.32 g of 125 in 100 ml of benzene was added 0.54 ml of liquid phosgene and 0.54 ml of N,N-dimethylaniline. The reaction mixture was left at room temperature for 2 h. The aniline hydrochloride was filtered off and the filtrate evaporated to dryness giving 1.4 g of pale yellow crystals, $\nu_{max}^{CHCl_3}$ 1717, 1766 (chloroformate). The crude chloroformate was dissolved in 25 ml of acetonitrile and was added to an ice-cold solution of 1.4 g of silver nitrate in 25 ml of acetonitrile. The reaction mixture developed a green

colouration and was left at room temperature for 24 h. To the resultant deep yellow solution 50 ml of water was added and the whole extracted with ether. The ether extract was washed with water, saturated brine and evaporated to dryness to yield 1.45 g of a viscous liquid. The pmr spectrum of the crude product indicated that it was largely the starting material in admixture with a number of other ill-defined components. Separation and characterisation of the required product did not appear feasible.

Attempts were made to hydroxylate 125 using the following hydroxylating systems according to the procedure of Hamilton and Friedman[104].

(i) Fe^{+3}-catechol: hydrogen peroxide, ferric salt, catechol, acetate buffer pH 4.3.

(ii) Fe^{+3}-hydroquinone: hydrogen peroxide, ferric perchlorate, hydroquinone, acetate buffer pH 4.3.

(iii) Udenfriend system: ferrous sulphate, ethylene diamine tetra acetic acid, ascorbic acid, phosphate buffer pH 6.7, oxygen.

In all these cases no reaction was found to occur as judged from the mass spectra of the products. Attempts to improve the efficiency of these reactions by increasing the solubilities of the organic reactants by the addition of tetrahydrofuran failed to yield any hydroxylated products.

SUMMARY

Initial attempts were aimed at carboxylating 2,7-dimethoxynaphthalene at the 1-position. Methods involving lithiation and carbonation of 2,7-dimethoxy-1-bromonaphthalene and oxidation of 2,7-dimethoxy-1-naphthaldehyde gave poor yields of the acid. The acid 62 was prepared from 59 by Friedel-Crafts reaction involving catechol dichloromethylene acetal and hydrolysis of the catechol ester. The selective reduction of naphthoic acids was accomplished with sodium in liquid ammonia and resulted in the reduction of the ring with the carboxylic acid substituent. Acid hydrolysis of the methyl ester of the resultant dihydroacid led to the β-keto-ester 76 and the Michael addition of methyl vinyl ketone to 76 yielded the unsaturated ketone 85. The same reactants in the presence of sodium methoxide led to the synthesis of the tetracyclic compound 79.

The selective Birch reduction of 2,7-dimethoxynaphthalene to the 1,4-dihydro derivative and its hydrolysis to the tetralone 78 are described. Carboxymethylation of the β-tetralone 78 at C-1 was accomplished with dimethyl carbonate and sodium hydride. The keto-ester 76 was obtained in a pure state in excellent yield. Michael addition of 76 with methyl vinyl ketone led to the formation of the unsaturated ketone 85. By the same sequence of reactions 1,7-dimethoxynaphthalene was converted to the unsaturated ketone 111. The preparation of 2,7-dimethoxy-3-isopropylnaphthalene from 2,7-dimethoxynaphthalene was carried out. This material was transformed to the

unsaturated ketone 120. The conversion of 120 to methyl O-methyl-11-desoxycarnosate was effected by methylation, thioketalisation, desulphurisation and hydrogenation. Thioketalisation of 120 was accomplished by partial demethylation of the C-20 ester group and the desulphurisation of the resultant mixture led to the formation of the lactone 124. Isopropylation of the methyl O-methyl podocarpate model system at C-13 via acylation is described. Similar experiments on the 11-desoxy-13-deisopropylcarnosate system failed. Attempts to hydroxylate the 11-desoxy-carnosate system at C-11 were unsuccessful.

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