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SYNTHESIS OF WARBURGANAL

AND RELATED COMPOUNDS

a thesis presented by

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in partial fulfilment of the

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To my parents.

ABSTRACT

The Diels-Alder adduct between dimethylacetylene dicarboxylate and 1-vinyl-2,6,6-trimethylcyclohexene was obtained in 95% yield, and was reductively rearranged directly to the trans-fused decalin dimethyl-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[1β,4aα,8aβ]-naphthalene-1,2-dicarboxylate (94) by hydrogenation over a palladium catalyst. Compound (94) was reduced to the corresponding diol 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[1β,4aα,8aβ]-naphthalene-1,2-dimethanol (157), and this key intermediate was then oxidised with a variety of reagents to provide the drimane natural products cinnamolide (8) (57%), drimenin (17) (35%), polygodial (29) (57%) and warburganal (36) (20%) in the overall yields indicated.

The use of activated dimethylsulphoxide reagents was found to uniquely achieve the crucial oxidation of 1,4-diol systems like drimane diol (157) to the corresponding dialdehydes polygodial and warburganal, rather than to the normally obtained lactones, e.g., cinnamolide.

A number of terminally substituted Diels-Alder dienes were prepared in an effort to extend the scope of the cycloaddition reaction, but which provided no observable adducts with dimethylacetylene dicarboxylate.

Initial studies on the oxidation of compounds (157) and (29) with micro-organisms (e.g., Cunninghamella elegans or Aspergillus niger) gave C-3 hydroxylated products in high yield.

Methyl bicyclofarnesoate (198) prepared via the Stork cyclisation of farnesic acid, was used to prepare another drimane natural product

isotadeonal (27) by a short sequence of reactions in 32% overall yield. Enolate hydroxylation of the ester (198), followed by regioselective oxidation with selenium dioxide at C-12 provided 9-carbomethoxy warburganal, and the similar C-9 epimeric product in 49% and 9% overall yields respectively. Similar oxidation of 1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1α-hydroxy-[4aα,8aβ]-naphthalene-1-carboxaldehyde (211) did not provide warburganal (36) but gave instead the novel lactone 9-hydroxy-drimenin (212), in 65% yield.

A further three naturally occurring drimane sesquiterpenes were prepared starting from 5,5,9-trimethyl-trans-1-decalone (214). A three step sequence from (214) provided 4,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethyl-[5aα,9aβ]-naphtho[1,2-c]furan (euryfuran, 38) in 60% overall yield. This furan was oxidised with bromine in methanol and subsequently hydrolysed to provide confertifolin (9) in 69% yield from (38). Photooxygenation of (38) provided valdiviolide (35) as a mixture of isomers at C-11 in 90% yield.

ACKNOWLEDGEMENTS

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I would also like to thank Mr. J.N. Bilton for interesting and helpful discussions, and for high resolution mass measurements. I am similarly grateful to Mrs. J. Lee for excellent mass spectra; to Mr. D. Neuhaus for numerous 250 MHz ^{1}H n.m.r. spectra; to Mr. E.S. Pepper and Mr. R.V. Carter and his staff for technical assistance; to the mechanical and glass workshop engineers; to Mr. K.I. Jones and his staff for elemental analyses, and lastly to Mrs. B. Day for her efficient and friendly service in the Stores.

Finally, I thank the S.R.C. for financial support during the course of this work, Moira Shanahan for typing the manuscript, and Anne for her patience and tolerance. (Most of the time).

CONTENTS

	Page
INTRODUCTION AND REVIEW	7
RESULTS AND DISCUSSION	40
(A) The Diels-Alder Approach to Drimane Synthesis	40
(i) Preparation and Attempted Use of Heterosubstituted Dienes	42
(ii) Preparation of 1-Vinyl-2,6,6-trimethylcyclohexene	54
(iii) Use of 1-Vinyl-2,6,6-trimethylcyclohexene	61
(B) The Biomimetic Approach to Drimane Synthesis	94
(C) Miscellaneous Routes for Drimane Synthesis	104
EXPERIMENTAL	113
X-Ray and 250 MHz ^{1}H N.M.R. Spectra	154
REFERENCES	180

PREAMBLE

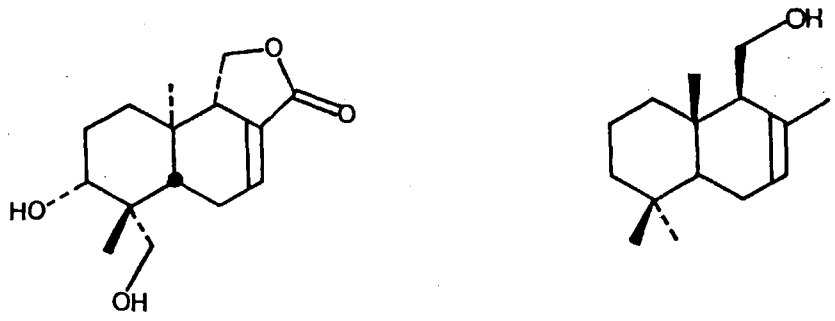
The literature concerning the drimane sesquiterpenes has been searched and reviewed from 1960 until July 1981. The structures of the compounds reported are presented (Figure 3) together with references to their isolation and synthesis (where applicable). Any biological activity which has been observed is also indicated. The approaches which have been employed to synthesise compounds of this type are critically discussed.

INTRODUCTION

Terpenoids represent one of the largest and most structurally diverse class of natural products. They exhibit a wide range of acyclic, monocyclic and fused-ring structures,[1-3] and since their occurrence in nature is often associated with a biological function, interest is generated not only in their synthesis but also in studies of their activity.

Sesquiterpenes form the largest division of the terpenoids, and themselves display a very wide variety of structural types.[4] They contain a fifteen carbon skeleton, derived in nature from farnesyl pyrophosphate, itself derived from acetyl CoA *via* mevalonic acid to isopentenyl (isoprenyl) pyrophosphate, which then couples with further isoprenyl units, in a head-to-tail fashion[2,3] through geranyl to farnesyl pyrophosphate.[5-7] The first example of a bicyclofarnesane having a steroidal type structure was iresin (1) (Figure 1), isolated by Djerassi *et al*. in 1954,[8] from the Mexican plant *Iresin celosioides*.

Although iresin was later shown to be of the " wrong" absolute configuration, it formed the missing link in terpene biogenesis since until that time it was suggested that steroid, di- and triterpene biosynthesis differed fundamentally from the mono- and sesquiterpenes.

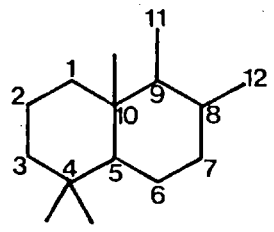


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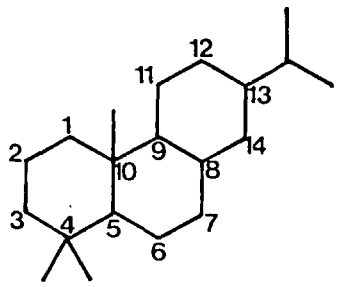
Figure 1

The first example of a bicyclofarnesane having the same configuration as the steroids and higher terpenes, was reported by Appel[9] and coworkers in 1959. They assigned structure (2) to a sesquiterpene alcohol isolated from the bark of a South American plant Drimys winteri Forst. Drimenol (2) (Figure 1) is the first member of this skeletal class of naturally occurring sesquiterpenes. Figure 2 also shows diterpenes with a similar skeleton to that of drimenol, namely the abietanes, sacculatanes and labdanes, from which the latter arguably give rise to some drimanes via natural degradation.

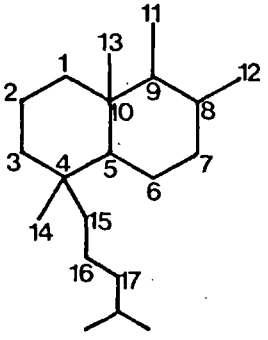
Since 1959, the number of naturally occurring drimane sesquiterpenes reported has grown steadily; at present there are over thirty true members of this class known (Figure 3), with several rearranged, one-carbon degraded or otherwise closely similar structures known, some



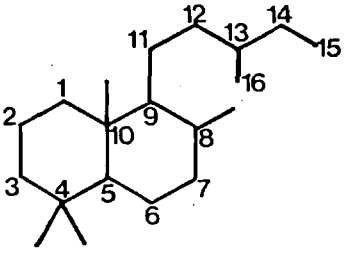
Drimane skeleton



Abietane skeleton



Sacculatane skeleton



Labdane skeleton

Figure 2

examples of which are shown in Figure 4. Also shown in Figure 4 are some examples of sacculatanes (58), (59) and labdanes (61)-(63), which contain similar, interesting functionality patterns to those found in the drimanes. All of the drimanes reported to date occur in the plant kingdom, with the majority isolated from the higher plants, in particular the families Winteraceae and Canellaceae. Of these the genera Warburgia, Cinnamosma and latterly that of Drimys have yielded the drimanes.

However, since 1967[10] there has been an increasing number of reports of drimane sesquiterpenes being isolated from the lower plant orders, namely mosses (for example Porella species are a rich source of drimane

sesquiterpenes, e.g., P. vernicosa contains (29) in ca. 30% by weight of crude extract[45]) and fungi. Furthermore, some examples of these compounds, i.e., (8), (9), (17), (18), (29) actually occur in both the higher and lower orders. The separate occurrence of the same or very similar compounds in such unrelated organisms suggests that they are the result of independent evolution. This indicates that these compounds may well be beneficial to the organism concerned, by for example, successfully mediating functions such as growth regulation, control of disease or phytophageous insects, etc., and thus further stresses their biological importance. Indeed, it is hard to imagine such highly functionalised compounds as are present in the drimane series, merely serving as reserve foodstuffs to be consumed when carbohydrate supplies are limited, or as " shunt" products from primary metabolism; these roles are often ascribed to secondary metabolites.

Although the activity of the majority of the drimanes has not been thoroughly studied, most of those which have been tested are active in some respect. In particular, warburganal (36) shows a very wide range of potent activities, for example, (36) along with muzigadial (51) and azadirachtin[83] (Fig. 5), are the three strongest anti-feedants against the African army worms Spodoptera exempta and S. littoralis found to date.

In view of this, and the presence of biological activity in other members of this class, warburganal and related compounds constitute desirable synthetic targets. Existing synthetic routes to these compounds do not provide good overall yields of material, and in some cases are rather long. A synthesis of the drimane skeleton which is

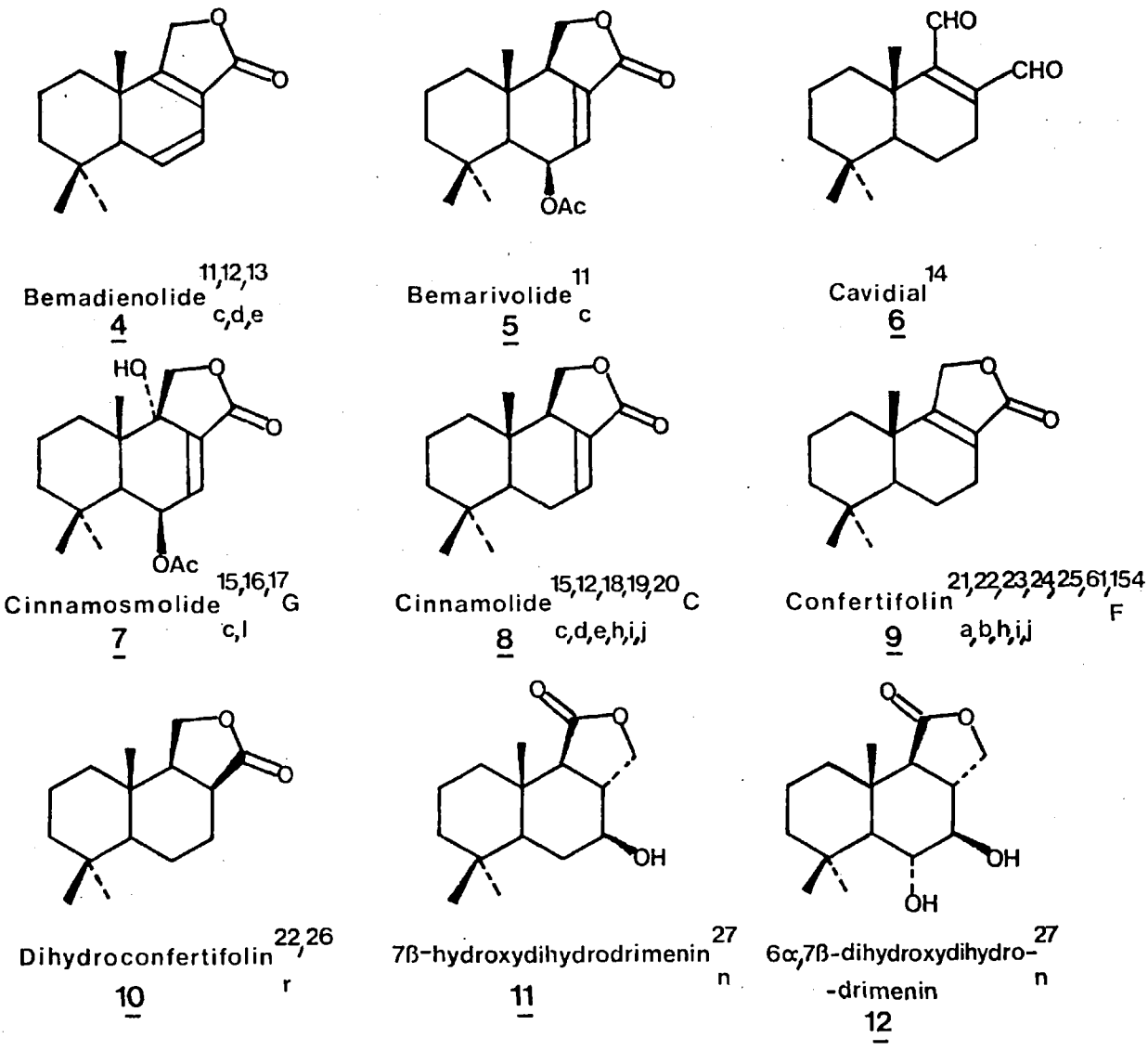
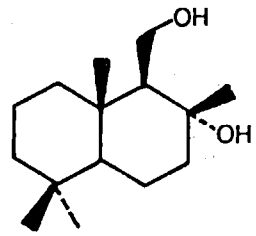


Figure 3. Naturally occurring drimane sesquiterpenes.

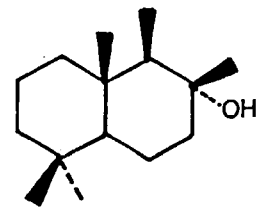
Occurrence: a = *Drimys winteri (Winteraceae);* b = *D. confertifolia;* c = *Cinnamosma fragans (Canellaceae);* d = *Warburgia stuhlmanii (Canellaceae);* e = *W. ugandensis;* f = *Nicotina Tabacum;* g = *Protowoodsia manchuriensis;* h = *Porella vernicosa (Hepaticae);* i = *P. macroloba;* j = *P. gracillima;* k = *Bazzania trilobata;* l = *Capsicodendron dinisii (Canellaceae);* m = *Polygonum hydropiper (Polygonaceae);* n = *Mycocalia reticulata (Nidulariaceae);* o = *Drimys lanceolata (Winteraceae);* p = *Fomes annosus;* q = *Lactarius uvidus (Russulaceae);* r = *Porella arboris-vitae (Porellaceae).*

Biological activity: A = insect antifeedant; B = antimicrobial; C = antifungal; D = molluscicidal; E = anticomplemental; F = plant growth regulation; G = cytotoxic.



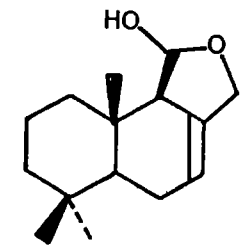
Driman-8,11-diol [28,29] f

13



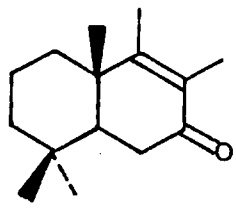
Driman-8-ol [28] f

14



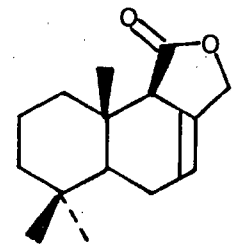
Drimeninol [18,26] i,j,r

15



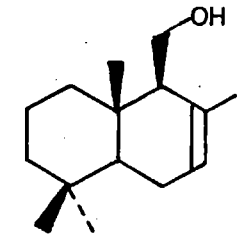
Drim-8-en-7-one [30] f

16



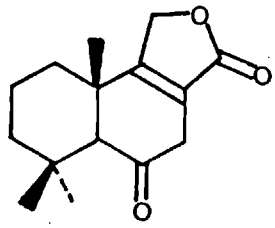
Drimenin [21,23,31,19,32,18,26,63] a,h,i,j,r

17



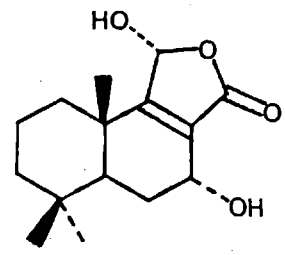
Drimenol [9,10,18,23,29,25,22,84,85,] a,h,k,q, F

18



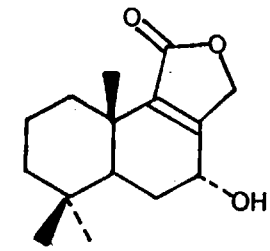
Fragrolide [11,13,33,49,61] c

19



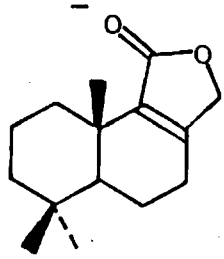
Fuegin [34] a,b

20



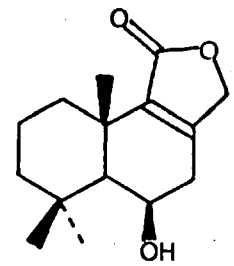
Futronolide [16,34,35] a,b,l

21



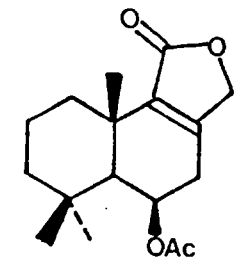
Isodrimenin [21,23,24,31,61,13] a

22



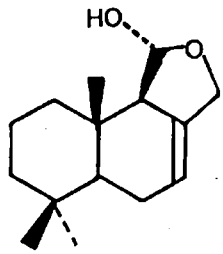
6ß-hydroxyisodrimenin [36] g

23



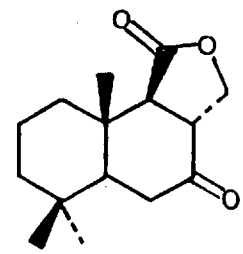
6ß-acetoxyisodrimenin [16] l

24



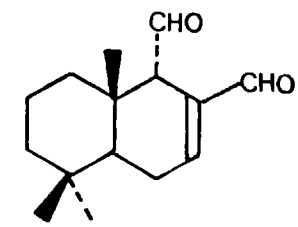
Isodrimeninol [37,26] m,r

25



7-ketodihydrodrimenin [27] n

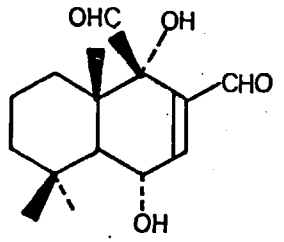
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Isotadeonal [38,37] m

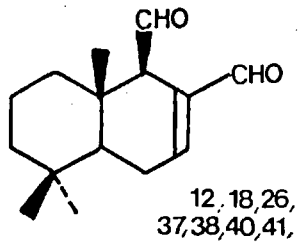
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Figure 3: continued



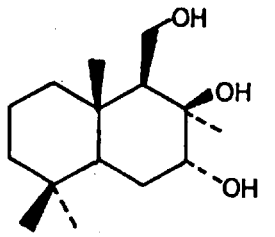
6α-hydroxywarburganal[39] d,e

28



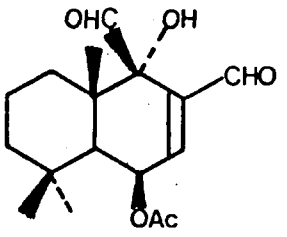
Polygodial[12,18,26,37,38,40,41,43,45,63,64] A,B,D,G,F

29 e,d,h,m,o,r



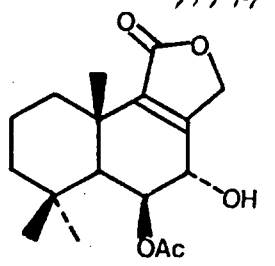
7α,8β-trihydroxydrimane[46] p

30



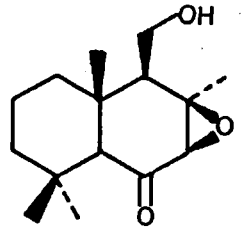
Cinnamodial[12,15,16,47,48,49] c,d,e,l A,G

31



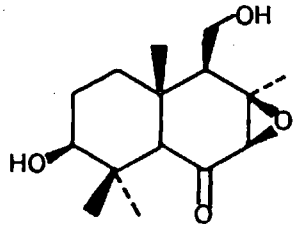
Ugandensolide[16,47] e,l

32



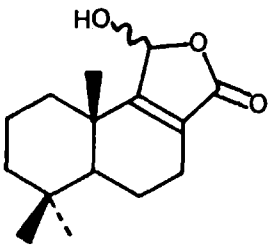
Uvidin A[50] q

33



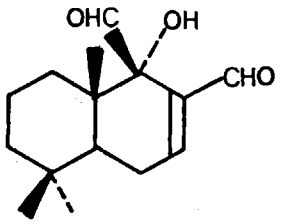
Uvidin B[50] q

34



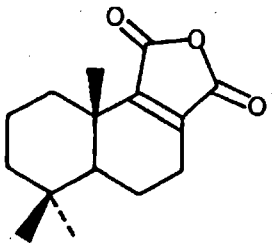
Valdiviolide[13,34] a,b

35



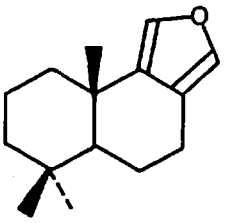
Warburganal[12,32,51–57,62] d,e A,B,C,D,E,F,G

36



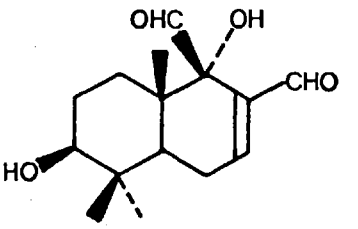
Winterin[13,24,34,58,59,61] a,b

37



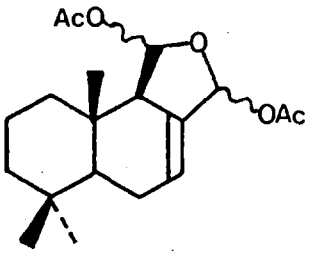
Euryfuran[18,24,37,60,61,65,155]

38

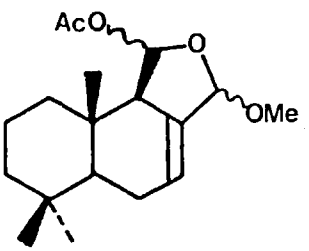


3β-hydroxywarburganal[32] d,e

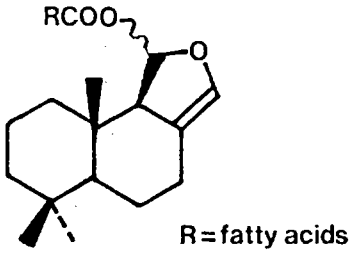
39



ref. 60

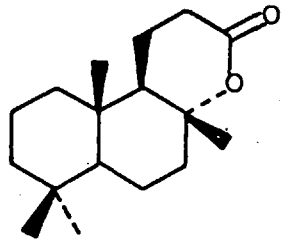


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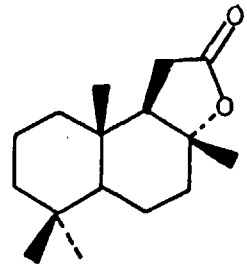
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Figure 3: continued



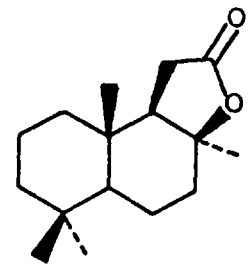
Ambreinolide[66]

40



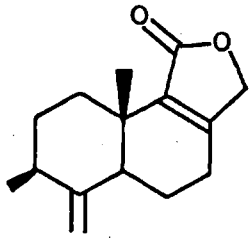
Norambreinolide[67]

41



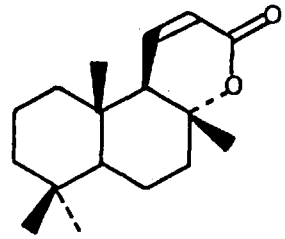
Norisoambreinolide[68]

42



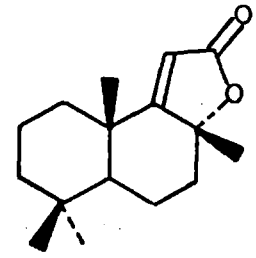
Colorata-4,(13),8-dienolide[69]

43



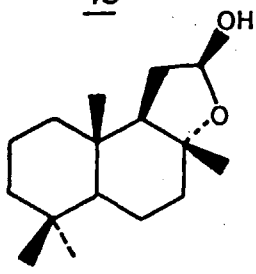
Dehydroambreinolide[70]

43



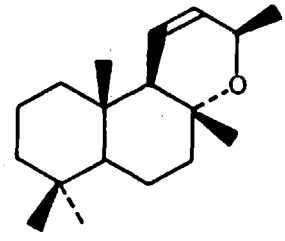
Dehydronorambreinolide[70]

44



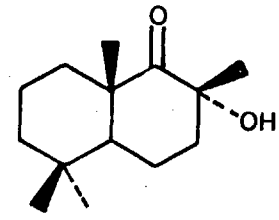
Sclaral[70]

46



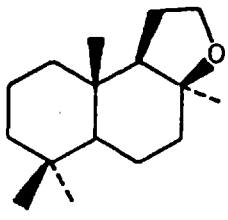
Sclareol oxide[70]

47



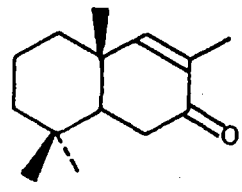
2-OH-2,5,5,8a-tetramethyl-trans-1-decalone[70]

48



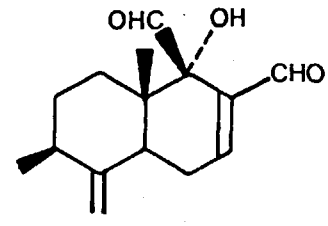
Isoambrox[68]

49



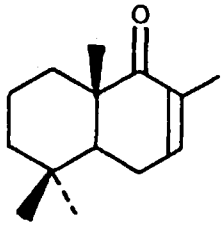
Isonordrimenone[71] F

50



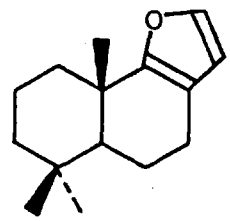
muzigadial[51,72] A,B,D

51



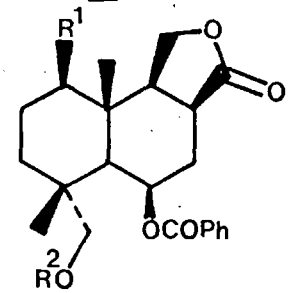
Nordrimenone[25,73]

52



Pallescensin A[13,74]

53



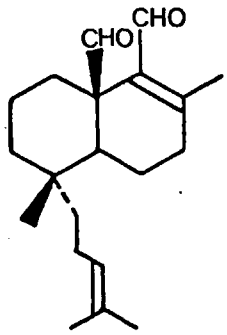
R^1=OH, R^2= Ac= Pebrolide[75,76]

R^1=H, R^2= Ac=1-deoxy "

R^1=OH, R^2=H= 1-desacetyl "

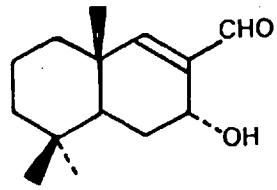
54

Figure 4. Related or similar compounds.



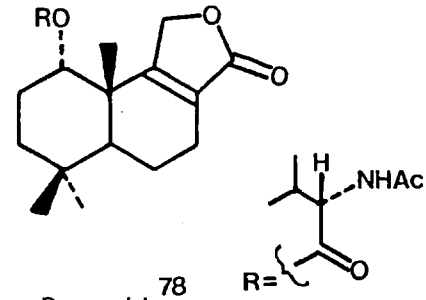
Perrottetianal A [77]

55



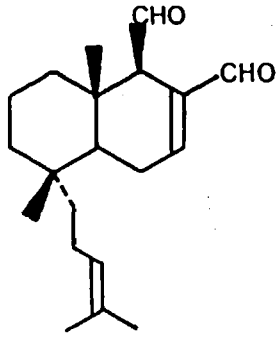
Polygonal [37] F

56



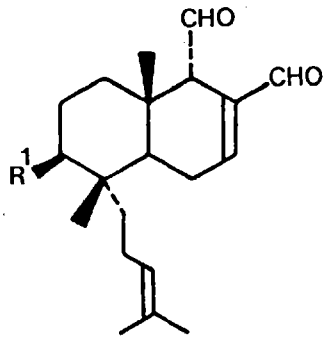
Purpuride [78]

57



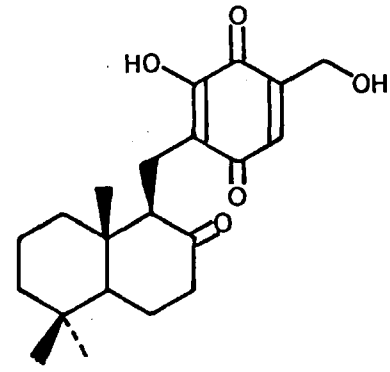
Sacculatal [44,79]

58



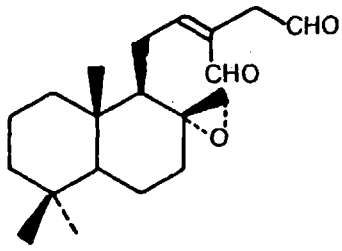
R^1=H= Isosacculatal [44,79]
R^1=OH=3ß-OH "

59



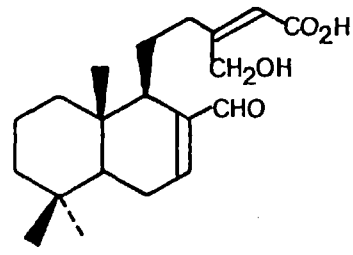
Tauranin [80]

60



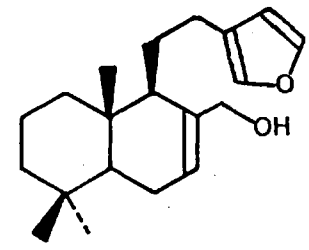
(E)-8ß,17-epoxylabd-12-ene-15,16-dial [81]

61



16-OH-17-oxo-labda-7,13E-dien-15-oic acid [82]

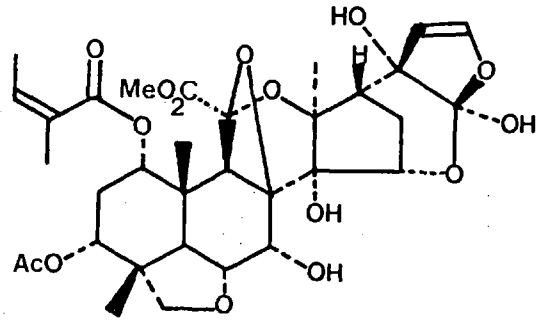
62



17-OH-isopolyalthine [82]

63

Figure 4: continued



3

Figure 5

both flexible enough to allow ready manipulation of functionality, thus permitting the preparation of both natural products and synthetic analogues, and efficient enough to provide reasonable quantitites of materials for biological evaluation, would be of considerable value.

Four synthetic approaches have been used for the construction of the drimane skeleton: biogenetic-type cyclisation, degradation of naturally occurring diterpenes, Diels-Alder cycloaddition, and transformation of synthetic intermediates. The remainder of this review deals with these approaches in turn and indicates the advantages and disadvantages of each in their application to the synthesis of drimane sesquiterpenes, with the main emphasis on warburganal (36) which has received much recent synthetic effort.[32,53-57]

Synthesis of drimanes via a biogenetic approach.

Although a biogenetic-type cyclisation was first achieved with farnesal to produce the corresponding aldehydes (64) and (65) (Figure 6) with undefined stereochemistry, the reaction conditions were rather vigorous (concentrated sulphuric and phosphoric acids respectively) and the yield of products was low (< 5%).[84]

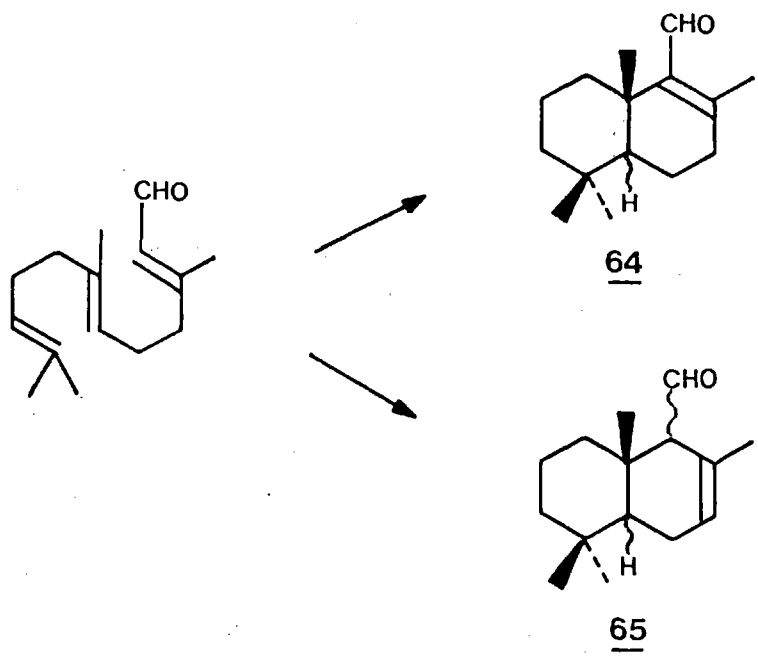
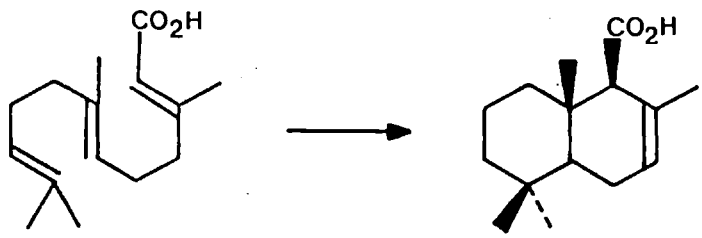


Figure 6

Caliezi and Schinz subsequently reported the cyclisation of farnesic acid using a formic-sulphuric acid mixture, to bicyclofarnesic acid (66) in 10% yield (Figure 7). (66) was reduced with LAH to provide an alcohol later[86] shown to be (±) drimenol. In 1955 Stork and Burgstahler[2] used BF_3 etherate in benzene solution to cyclise farnesic

acid and obtained (66) in 35% yield together with a small amount (2-5%) of its C-9 epimer. Although they erroneously assigned the products as cis-decalins, subsequent work[86] revealed the correct structures. In 1957, Stork and co-workers[86] reported the conversion of (66) to (±) drimenol via esterification (CH_2N_2) and LAH reduction.



66

Figure 7

In 1963 Van Tamelen and co-workers [84] showed that 3,4-epoxy farnesylacetate (67), prepared by selective terminal bromination with NBS in aqueous DME followed by base treatment of the resulting bromohydrin, could also be cyclised with BF_3 etherate to provide (68) and (69) (85%: 15%) in " modest" yield (Figure 8). These products were then converted by standard procedures (oxidation, thioketalisation, desulphurisation, LAH reduction) to (±) drimenol and (±) epi-drimenol respectively. In 1966, Van Tamelen also showed that methyl farnesoate could be directly cyclised with NBS in THF:H_2O to provide bromides (70) and (71) in minute yields (Figure 8). Subsequent LAH treatment again provided (±) drimenol and (±) epi-drimenol.

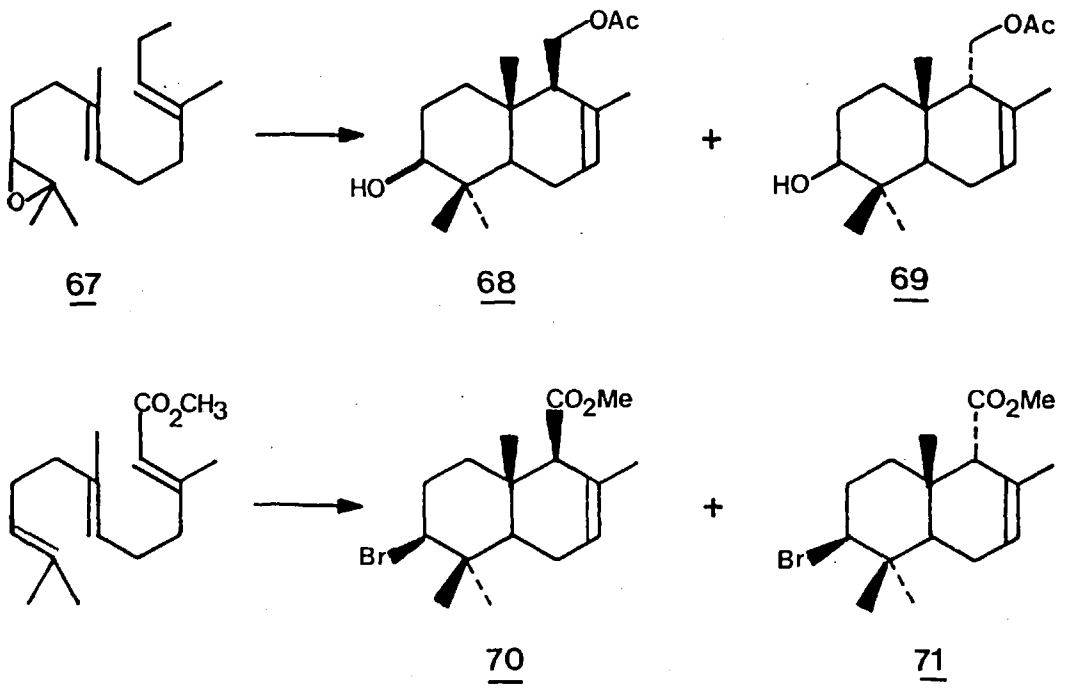
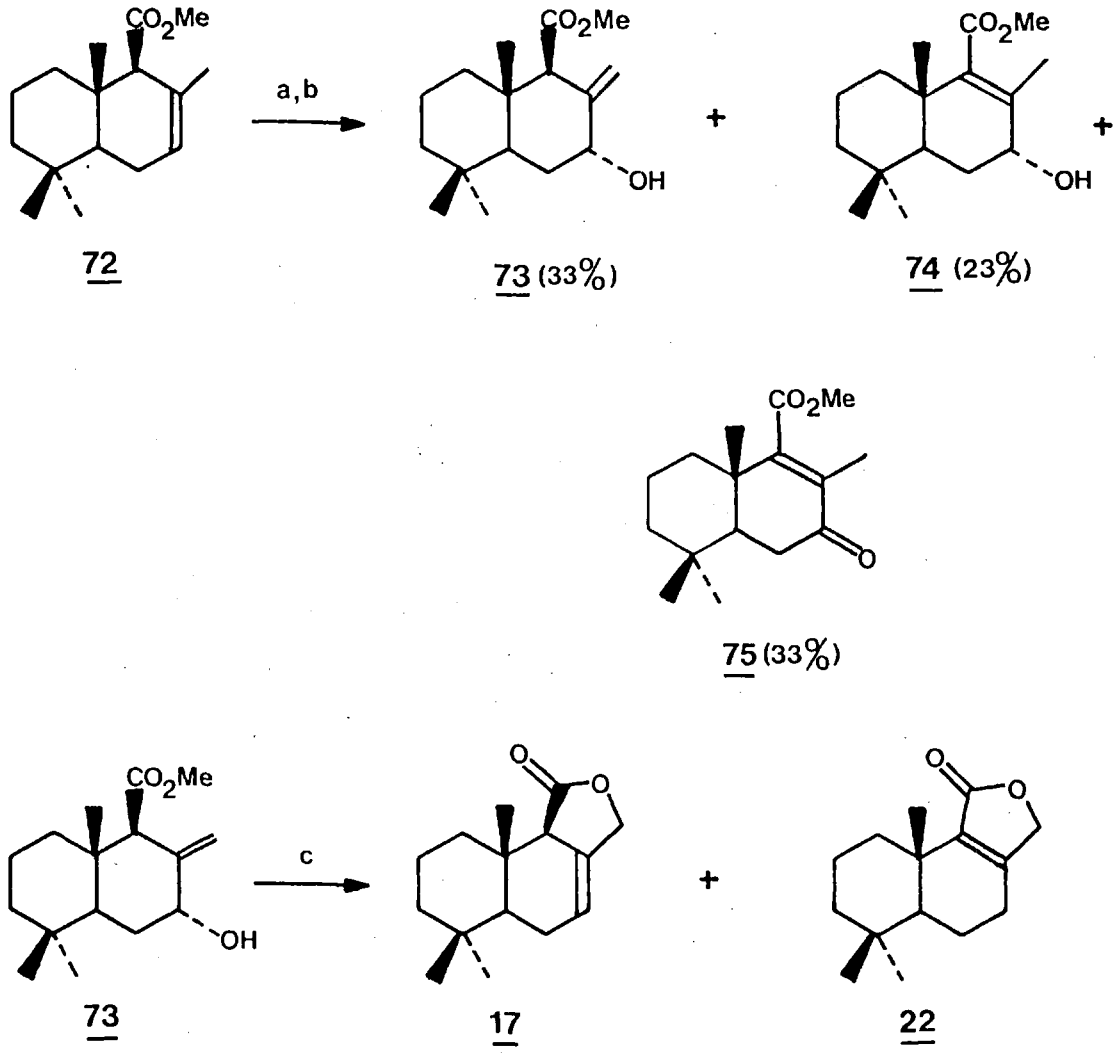


Figure 8

In 1969, Kitahara[31] reported an improved yield (55%) of (66) over that obtained by Stork by use of ether as a cosolvent for the reaction. Photo-oxidation of methyl drimenate (72) then gave products (73)-(75) in 89% yield (Scheme 1). Hydrolysis and simultaneous lactonisation of (73) gave drimenin (17) (69%) and isodrimenin (22) (11%). The overall yield to (17) from (72) was 23%.

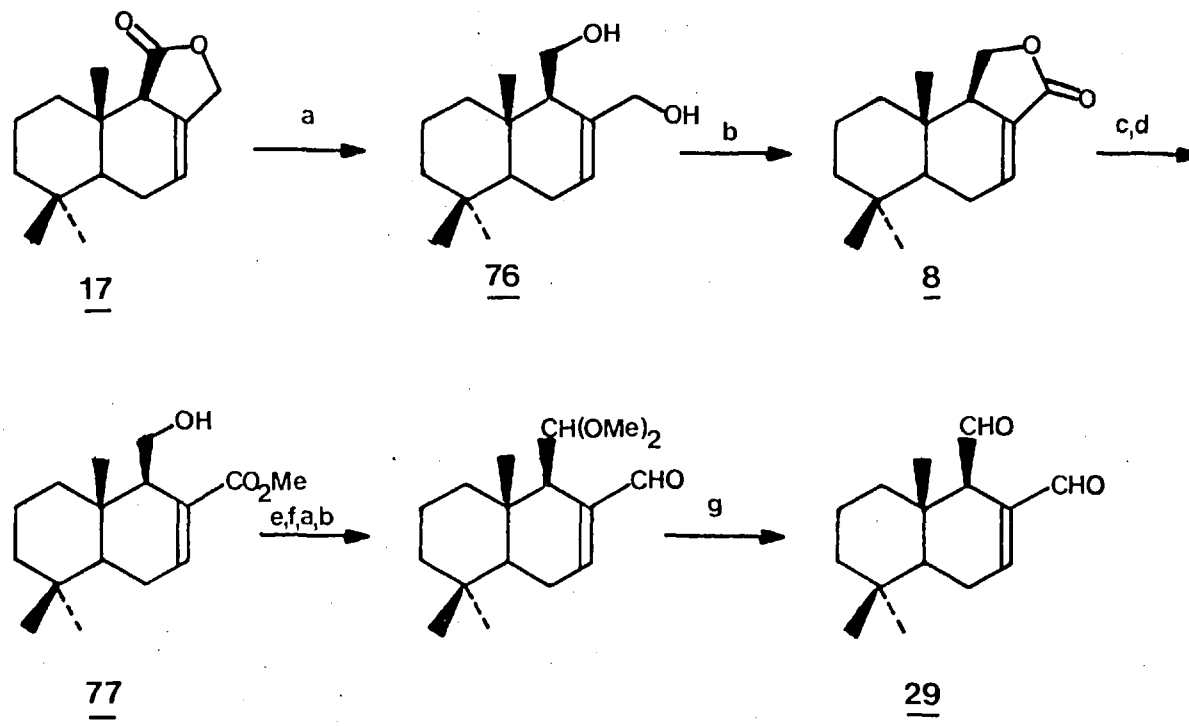


Scheme 1. a) $^1O_2$; b) KI; c) 6N H_2SO_4, dioxan (1:13), 90°C, 24 h.

These workers also showed[19] that (66) or (18) could undergo aerial oxidation at C-12 in the presence of palladium chloride after prolonged reflux (4 days) in aqueous DMF, to provide directly (17) or (8) respectively, in low yields (∿ 10%).

Kitahara and co-workers later reported[64] a converion of drimenin (17), prepared as above, into polygodial (29) (Scheme 2). Reduction of (17) gave diol (76) which was oxidised to cinnamolide (8). Saponi-

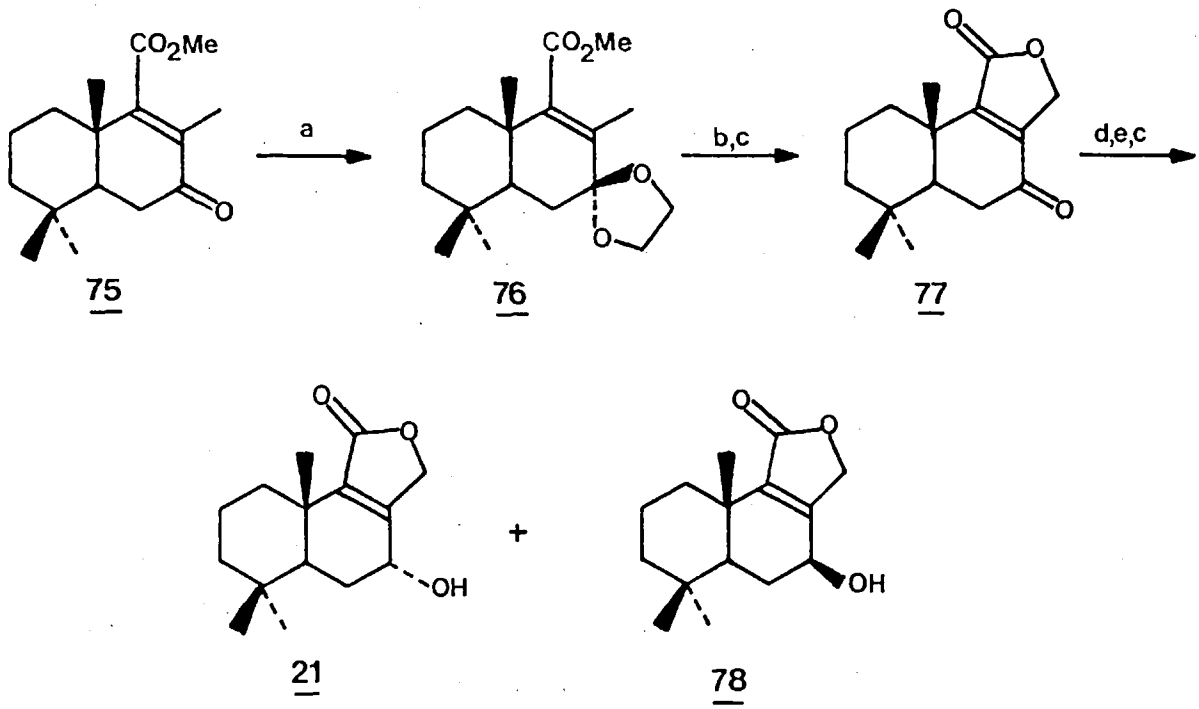
fication and esterification led to hydroxy ester (77), which was converted using a multi-stage procedure involving protection of a 9-CHO function into (29), isolated in an impure state only.



Scheme 2. a) LAH; b) MnO_2; c) KOH, MeOH; d) CH_2N_2; e) CrO_3.2Pyr; f) $HC(OMe)_3$, MeOH; g) oxalic acid, aq. acetone.

Kitahara later used product (75) (Scheme 1) in a synthesis of futronolide (21)[35] (Scheme 3). Ketalisation at C-7 followed by treatment with NBS and then hot water provided keto lactone (77) in 51% overall

yield. Unfortunately, reduction and bromination of (77) followed by hydrolysis gave a 1:1 mixture of futronolide (21) and the epimer (78) in an unstated yield, from which (21) was isolated by repeated recrystallisation.

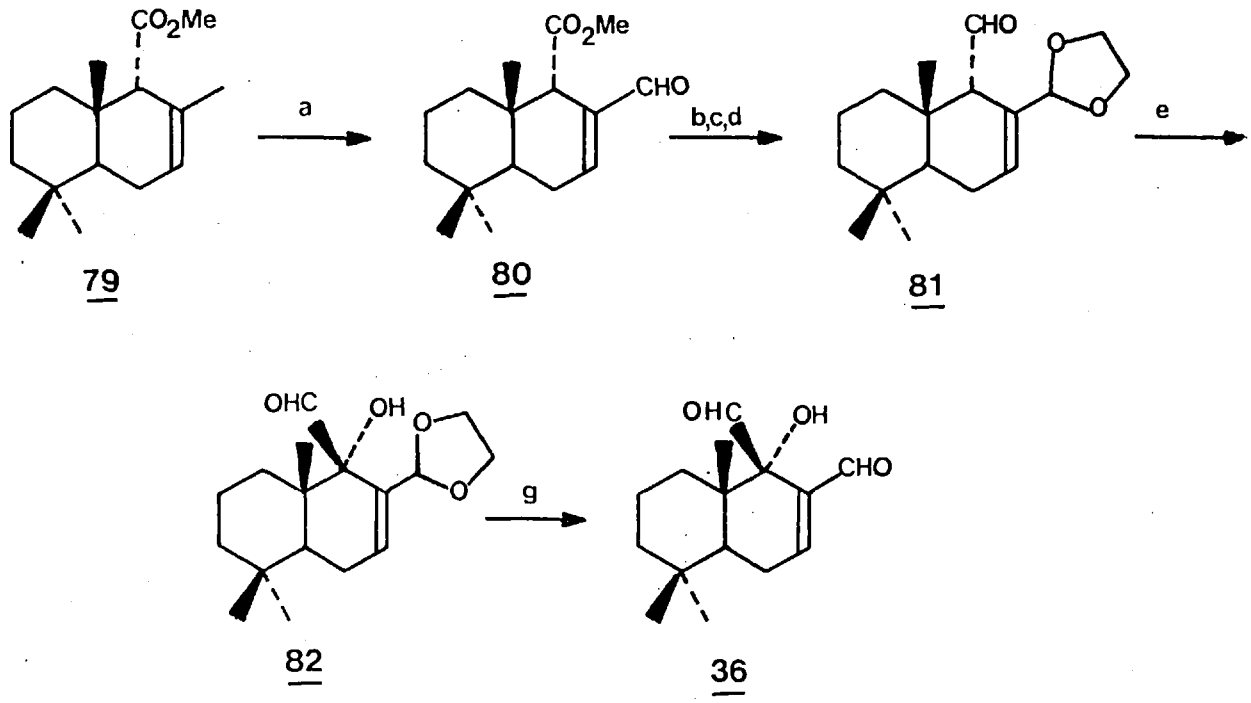


75 76 77 21 78

Scheme 3. a) $HO(CH_2)_2OH$; b) NBS; c) H_2O; d) $NaBH_4$, e) PBr_3.

The last example to date of a " biogenetically-styled" synthesis was that of (±) warburganal (36) and (±) isotadeonal (27) reported by Ohsuka and Matsukawa[5b] in 1979 (Scheme 4). Although their route utilised the much less readily available methyl (±)-9-epidrimenate (79) as starting

material, they achieved a direct regioselective oxidation with selenium dioxide, to afford (80) with the desired C-12 CHO group in reasonable yield (61%). Unfortunately this group required protection prior to conversion through to (81), the lithium enolate of which was then hydroxylated in poor yield (24%) to provide (82). Deprotection provided (36) in 10% overall yield in only 6 steps.



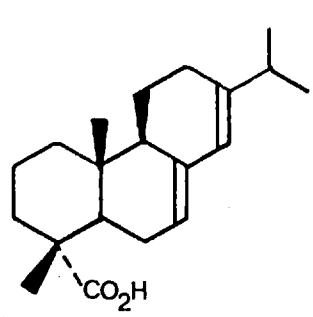
Scheme 4. a) SeO_2, dioxan; b) $HO(CH_2)_2OH$; c) LAH; d) $CrO_3.2Py$; e) LiHMDS-HMPA, then MoOPH; g) PTSA, acetone.

In summary, the biogenetic cyclisation provides a genuinely readily available, versatile starting material (72). Besides the easily accessible drimenol (18), seven other drimane natural products have

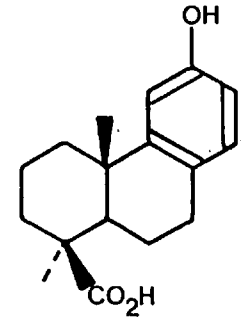
been prepared using this approach, i.e., the lactones (8), (17), (21), (22), and the dialdehydes (27), (29) and (36), albeit in low overall yields. Most of these syntheses have utilised a selective oxidation at the least hindered C-12 position as the key step. This thesis also describes further exploitation of this process to prepare (27) and analogues of warburganal (36) in a short, high yield sequence.

Synthesis of drimanes via a degradative approach.

Degradation of naturally occurring diterpenes, e.g., from the abietane and labdane groups, has provided a route to the drimane sesquiterpenes. Obviously, this approach carries the additional possibility of chiral synthesis. Wenkert and Strike[23] used the diterpene resin acids, abietic (83) or podocarpic acid (84) (Figure 9) to synthesise drimenin (17), confertifolin (9), and drimenol (18) in approximately 6% overall yield.



83

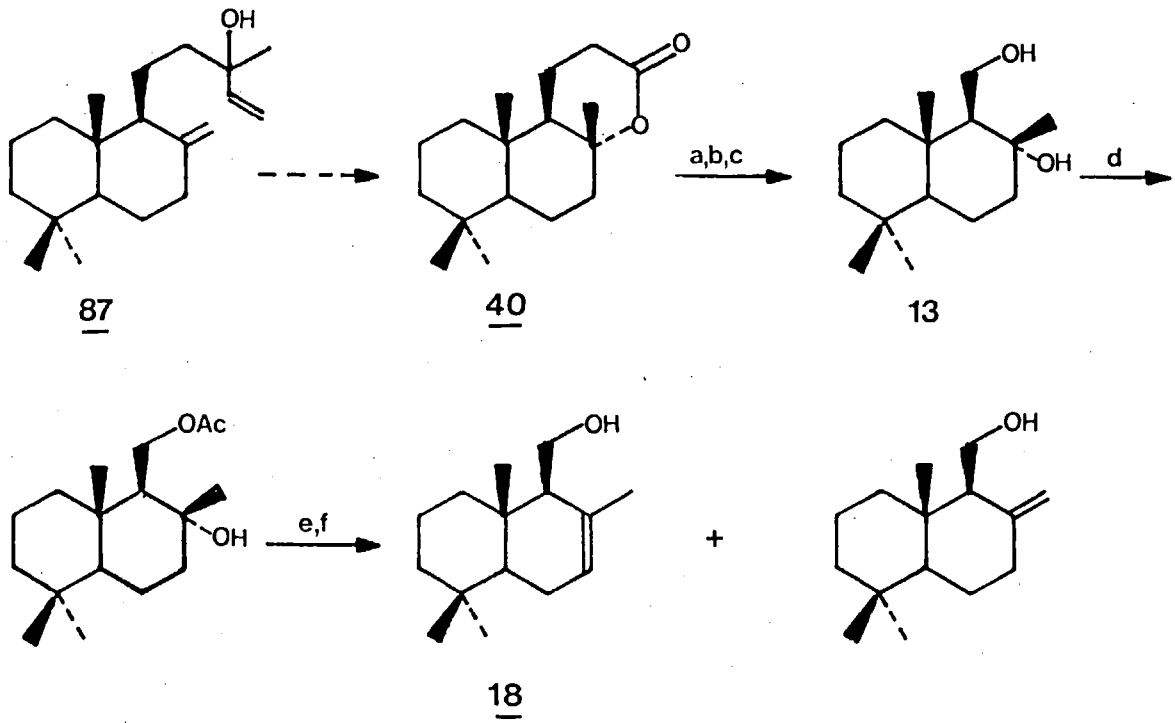


84

Figure 9

Dehydroabietane was obtained from abietic acid (83) and converted in a rather long sequence (> 20 steps) to the drimane natural products.

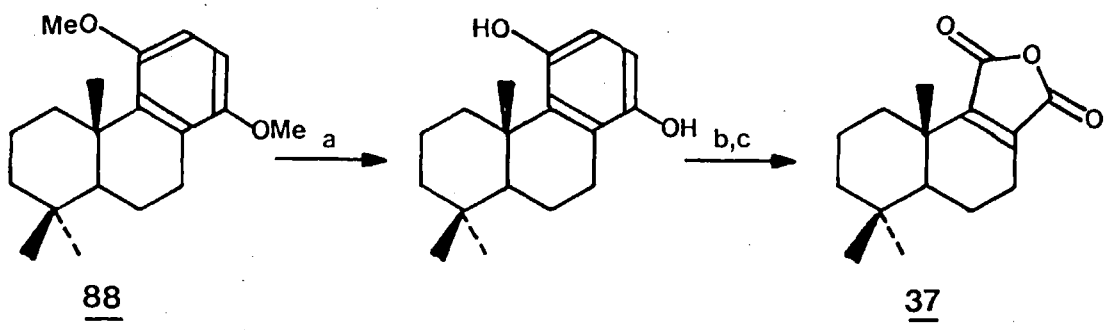
In 1975, Pelletier reported[66] a short synthesis of (+)-drimane-8,11-diol (13) and (-)-drimenol (18) from (+)-ambreinolide (40) which was obtained from the labdane manool (87). The products were obtained in 34% and 13% overall yields respectively (Scheme 6).



Scheme 6. a) DDQ; b) O_3; c) Red-Al; d) Ac_2O, py; e) $POCl_3$.py; f) KOH, MeOH.

[59]

In 1977, Pelletier and Ohtsuka also reported their studies on the degradation of variously substituted podocarpane derivatives. They converted the dimethoxy derivative (88) to winterin (37) in three steps in 20-31% yield (Scheme 7).

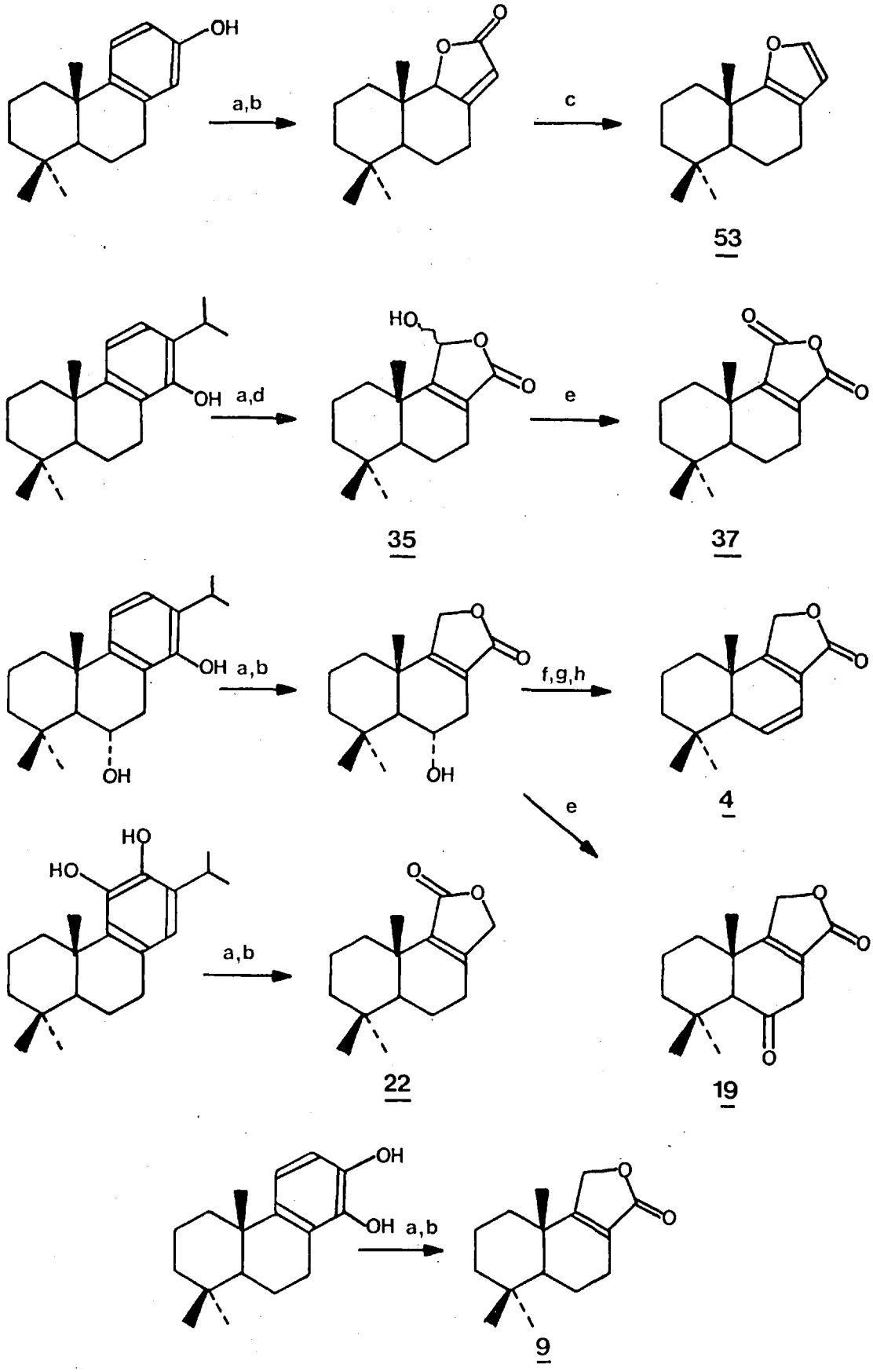


88 37

Scheme 7. a) BBr_3; b) O_3; c) Jones.

Finally, in 1978 Akita and Oishi reported their findings on the ozonolysis of a variety of phenolic dehydroabietic acid derivatives. The drimane natural products which were obtained are indicated in Scheme 8. Most of the yields were not quoted.

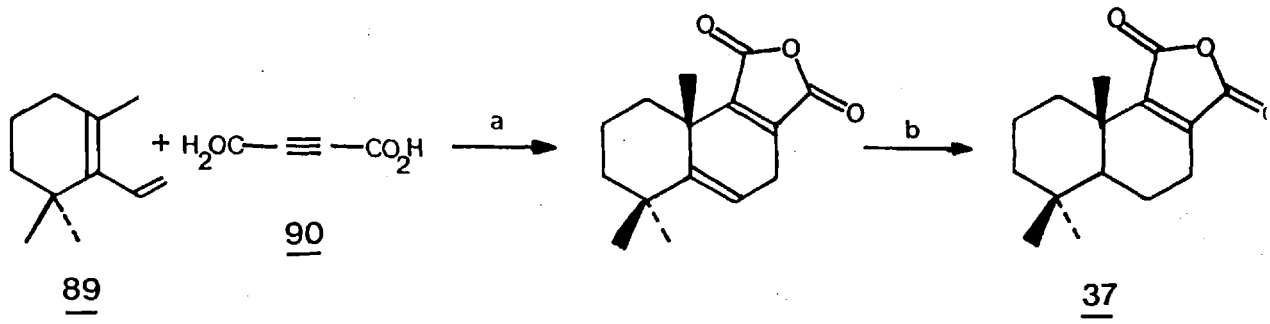
It is clear that the degradative approach to the drimanes has received little attention, compared to that of total synthesis. Apart from a few specific examples, e.g., (13), (37), (19), this approach offers little scope for the synthesis of a range of structures. Indeed, all of the drimanes obtained by degradation can be more efficiently obtained by alternative routes.



Scheme 8. a) O_3; b) $NaBH_4$; c) iBu_2AlH; d) Na_2SO_3; e) Jones; f) MsCl; g) PhSeNa; h) H_2O_2.

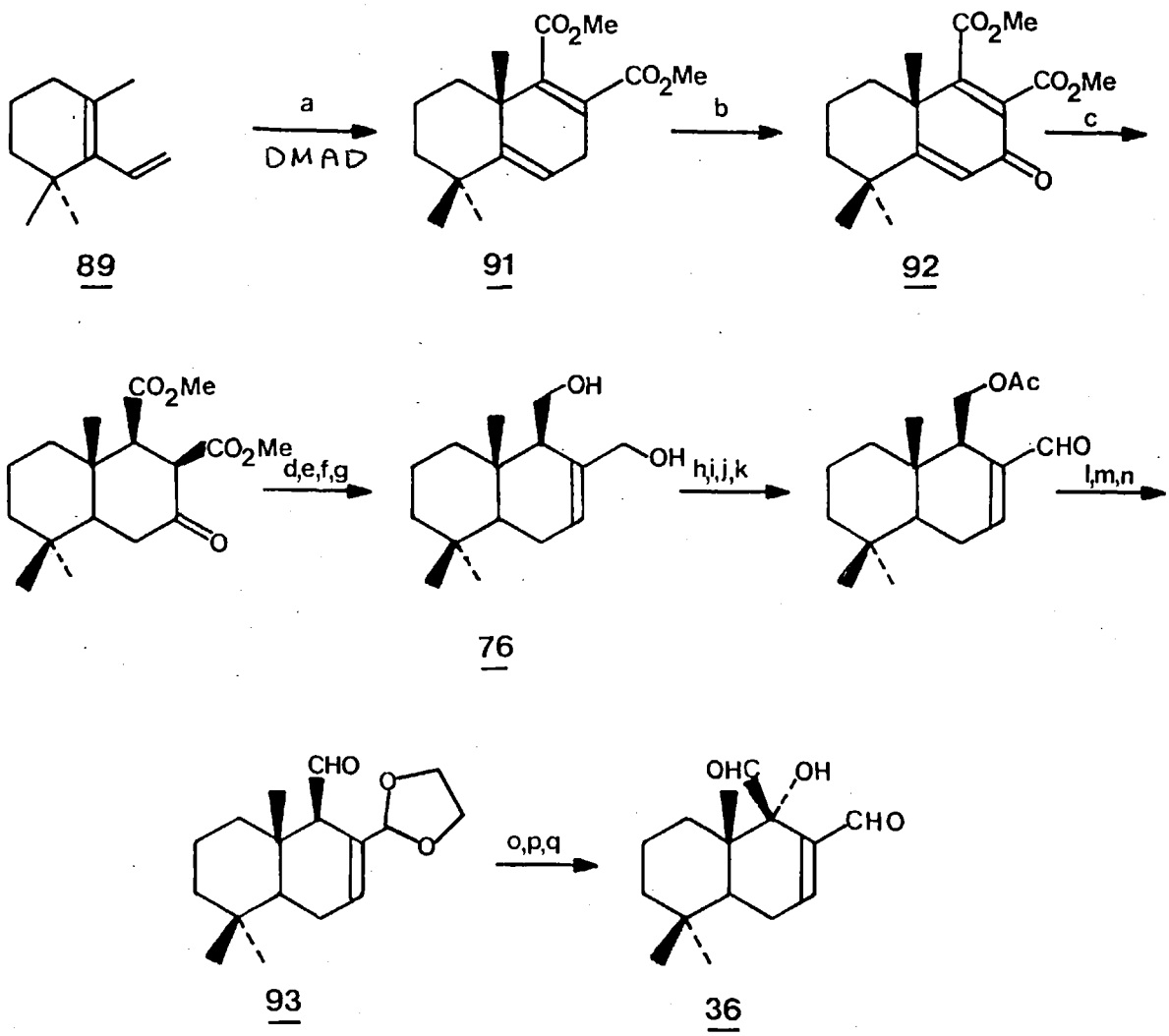
Synthesis of Drimanes via a Diels-Alder Approach.

The third approach to the construction of the drimane skeleton involves a Diels-Alder addition of a suitable dienophile to a diene such as (89) (Scheme 9). The approach was first used by Brieger[58] in 1965 in his synthesis of winterin (37) (Scheme 9). Unfortunately (90) was a poor choice as a dienophile and the addition proceeded in only 4% yield. Catalytic hydrogenation provided winterin in only 1.2% overall yield. Maleic anhydride was found to add in only slightly higher yields (21%).[87]



Scheme 9. a) 97°C, 24 h, diglyme; b) H_2, Pd/C.

Hence, although the route provided a direct entry into the drimane skeleton, the yields at this stage were low. However, Loperfido had reported[88] that dimethylacetylenedicarboxylate gave a 69% yield of adduct with diene (89), though he did not apply this to drimane synthesis. Tanis and Nakanishi later reported[32] the application of this reaction to the synthesis of (8), (17), (29) and (36) (Scheme 10).



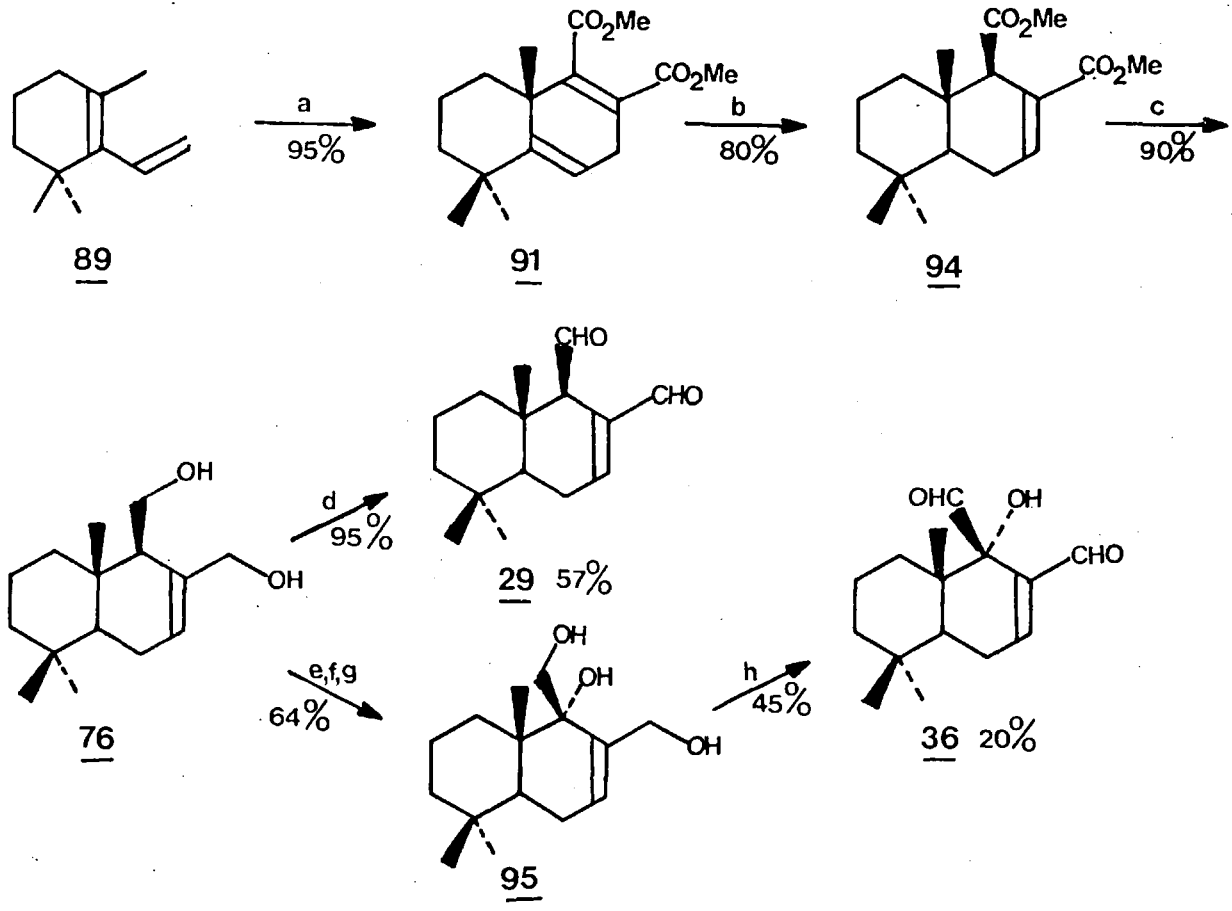
89 91 92 76 93 36

Scheme 10. a) 110°C, 16 h; b) $(CrO_3).2py$; c) H_2, Pd/C; d) $NaBH_4$; e) MsCl, Et_3N; f) DBU; g) LAH; h) t-BDMSCl; i) Ac_2O; j) nBu_4NF; k) PCC, l) $HO(CH_2)_3OH$; m) KOH, MeOH; n) CrO_3, py; o) LDA, then MoOPH; p) HCl.

They initially encountered problems in obtaining the correct A/B trans stereochemistry on hydrogenation of the 5,6 double bond in (91). A variety of platinum catalysts were tried in order to achieve this transformation but without success. Surprisingly, they did not try

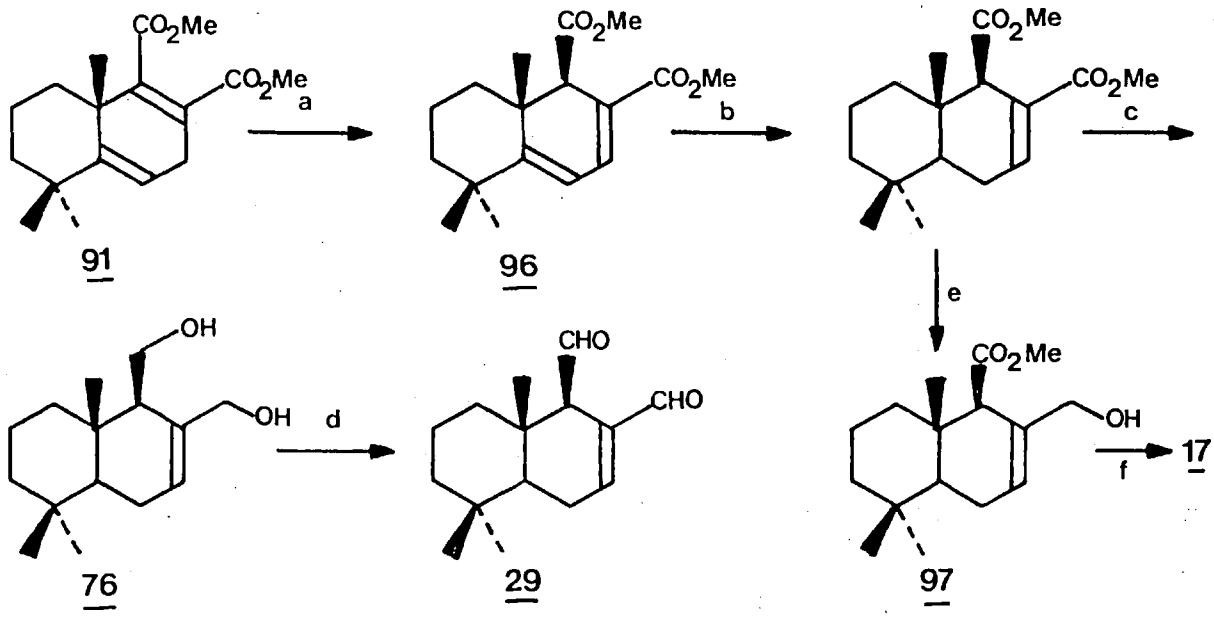
palladium catalysts, which have been later shown[89] to produce a trans-A/B system, even though these authors used palladium on carbon to hydrogenate (92). Nakanishi and Tanis also erroneously assigned the product of hydroboration of the 5,6 double bond in (91) as a cis-decalin,[49] and although they were able to epimerise this product at C-5 via a 6-keto function, they were then unable to effectively deoxygenate the 6-position.

With (92) in hand, a multistage procedure then provided the key diol (76), which was then further elaborated via a sequence of protection and deprotection to (93), which then led to (29), or (36) in 16% overall yeild from (89). Later reports from our laboratories[89,90] have indicated a much more direct route from (89) to (29) and (36) via the pivotal intermediate (76), in the overall yields indicated (Scheme 11).



Scheme 11. a) DEAD, 110°C, 22 h; b) H_2, 10% Pd/C, MeOH, H^+; c) LAH; d) DMSO-$(COCl)_2$ then Et_3N; e) Ac_2O, py; f) SeO_2, dioxan; g) K_2CO_3, MeOH; h) DMSO-TFAA then Et_3N.

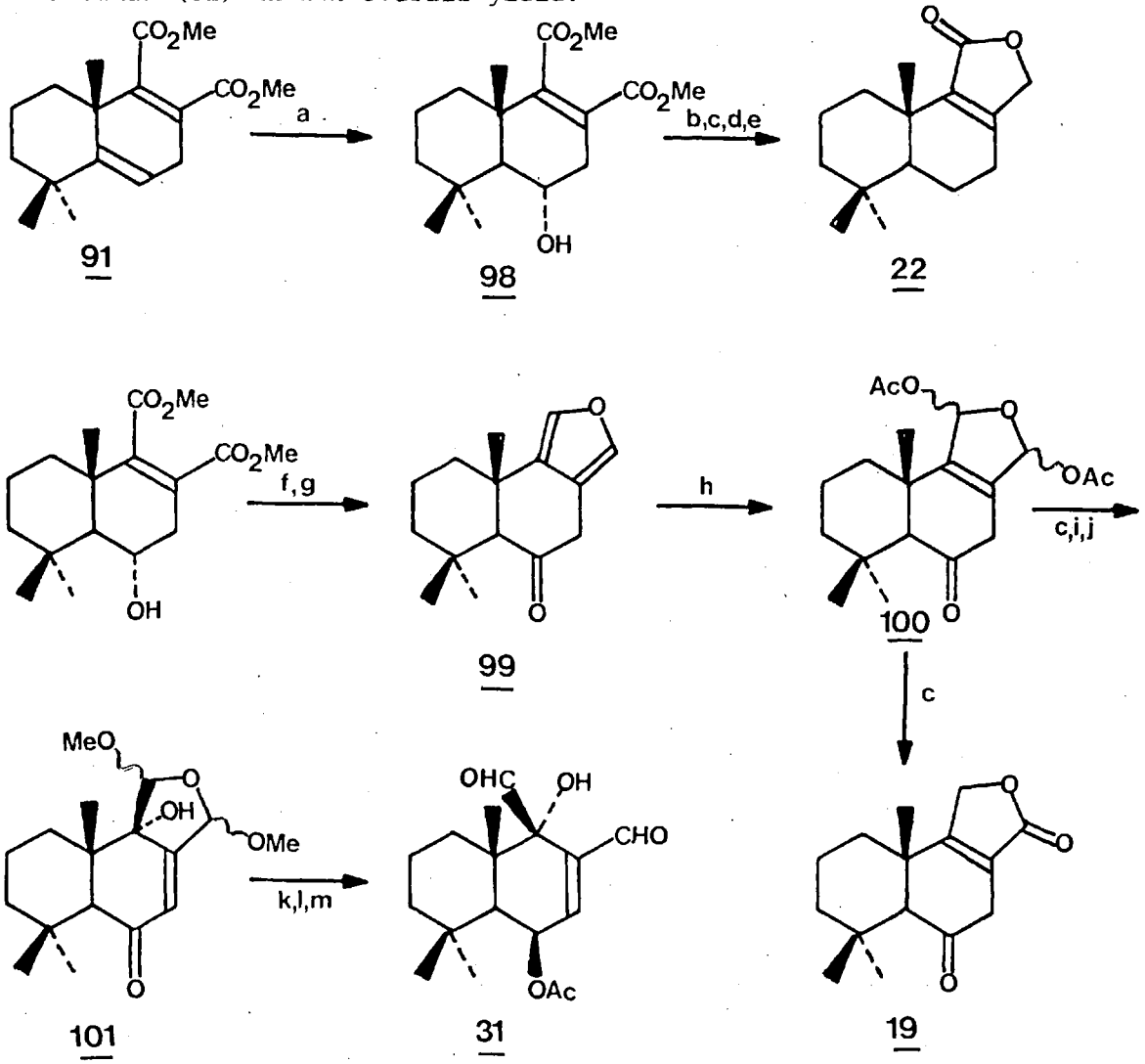
Lallemand and co-workers, also recently reported[63] a similar route to (29) in lower yield (37%) (Scheme 12). They too wrongly assigned the hydrogenation products arising from (91), using a palladium on carbon catalyst, as cis-fused compounds. Their route involved an isomerisation of (91) to (96) prior to hydrogenation. They achieved a selective reduction of the C-12 ester group to afford (97) which was subsequently lactonised to drimenin (17) in an unstated yield.



Scheme 12. a) LDA, -78°C, then H^+; b) H_2 Pd/C; c) LAH; d) DMSO-$(COCl)_2$ then Et_3N; e) iBu_2AlH, -78°C; f) PTSA, C_6H_6.

Burton and White[49] also recently used the Diels-Alder approach in their synthesis of cinnamodial (31), isodrimenin (22) and fragrolide (19) (Scheme 13). Hydroboration of (91) produced (98) (75%) which was

reduced with DIBAL and the resulting triol oxidised to the tricyclic furan (99) in 68% yield from (98). This oxidation is surprisingly high yielding in view of Henderson's[65] earlier report of the oxidation of the 6-deoxy-11,12-diol analogue of (98) using chromium trioxide-pyridine from which he predominantly obtained lactones. White also converted (98) to isodrimenin (22) in " high yield" . From the ketofuran (99), oxidation firstly to the diacetates (100) and then to the hydroxy bis acetal (101), gave after reduction, deprotection and acetylation, cinnamodial (31) in 14% overall yield.



Scheme 13. a) BH_3-THF, then H_2O_2-NaOH; b) MsCl, py; c) DBU; d) LAH; e) H_2; f) iBu_2AlH, toluene, $-78^oC \longrightarrow 0^oC$, 2 h; g) PCC; h) $Pb(OAc)_4$; i) m-CPBA-Na_2CO_3; j) MeOH, PTSA; k) iBu_2AlH, THF, -5^oC, 0.5 h; l) HCl, acetone; m) Ac_2O, py, DMAP.

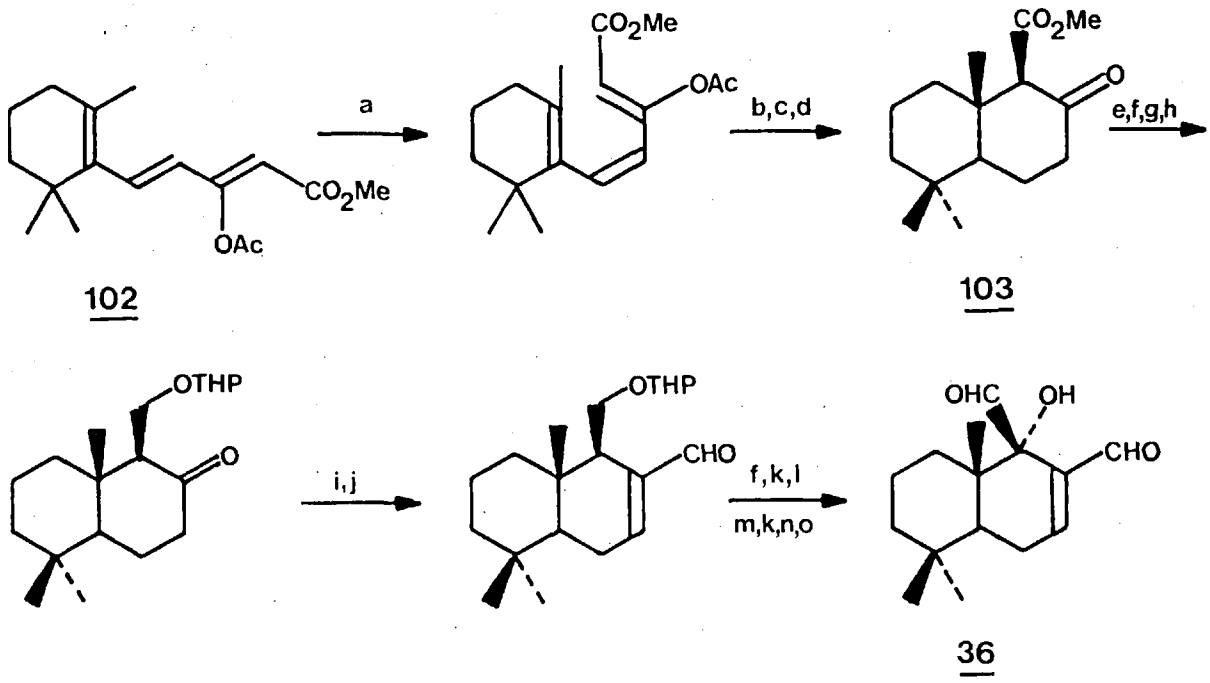
In view of the near quantitative yields of adduct (91) which can be obtained under simple conditions from the easily available addends (89) and DMAD, and its subsequent conversion into A/B trans systems which can now be achieved in high yields, the Diels-Alder approach to the drimane class of natural products must be considered the most direct and efficient route. Futhermore, the solution of the problems connected with the synthesis of compounds containing rather congested functionality for example by use of activated DMSO reagents for the oxidation of 1,4-diols, or the use of a furan as a 1,4-dialdehyde synthon, has enabled easy access to this group of biologically active natural products.

Synthesis of Drimanes from Synthetic Intermediates.

There have been other successful approaches to the drimanes in addition to those already discussed, which make use of synthetic starting materials or intermediates.

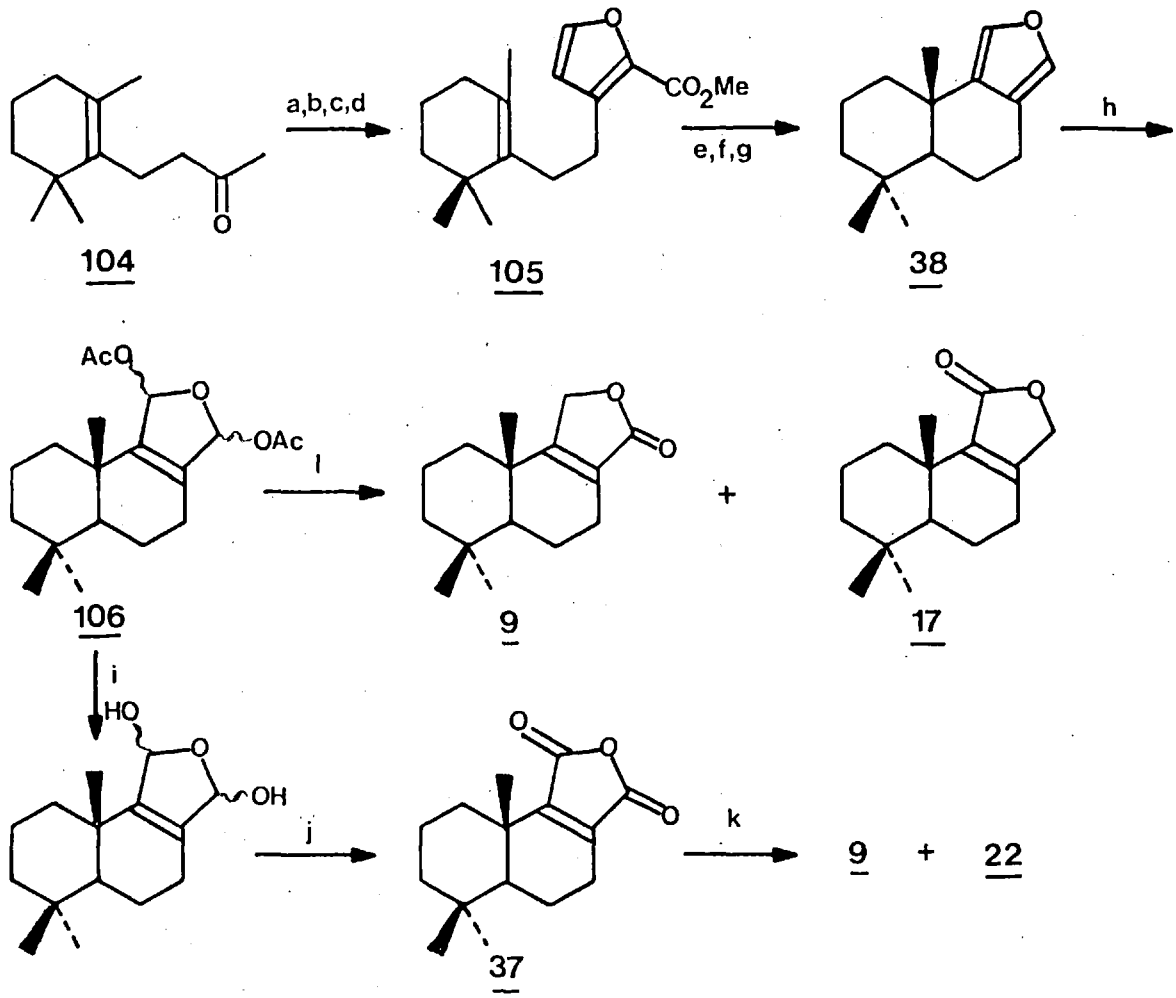
A model synthesis[91] of ring B of warburganal involved addition of 2-lithio-1,3-dithiane to a protected 2-formyl-6,6-dimethyl-2-cyclohexen-1-one and subsequent deprotection, but this has not yet been applied to the real system.

Kimura and Isoe[57] reported a lengthy (∿ 20 steps) synthesis of warburganal from (102), obtained from β-ionone, in 17% yield from (103) (Scheme 14). Their starting material (103) was not readily available and the length of the synthesis does not compare favourably with that of other routes.

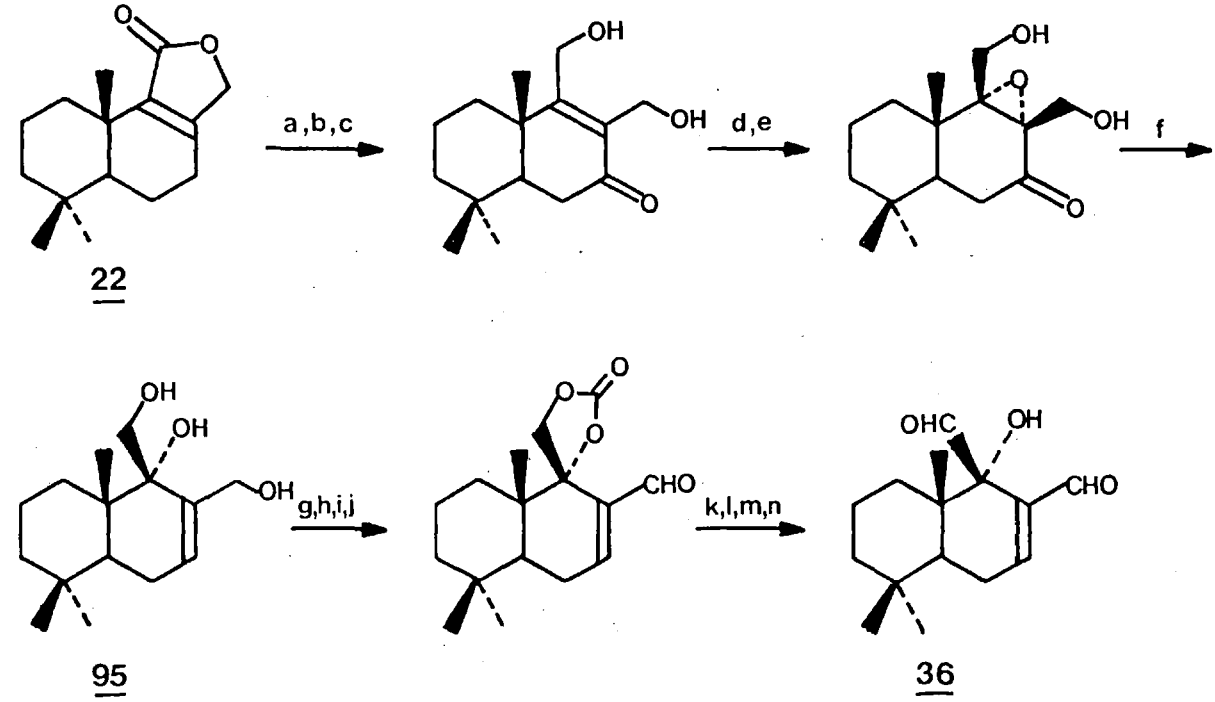


Scheme 14. a) hν, sens; b) Δ; c) NaOMe, MeOH; d) H_2, PtO_2, DME; e) $HO(CH_2)_2OH$, PTSA; f) LAH; g) AcOHaq; h) DHP; i) NH_2NHTS; j) nBuLi, TMEDA then DMF; k) H^+; l) Ac_2O, py; m) SeO_2; n) LAH; o) DMS-NCS, $AgBF_4$, then Et_3N.

β-Ionone has also been used for the synthesis of confertifolin (9) and isodrimenin (22) by Oishi and co-workers,[24,61] (Scheme 15). Selective reduction to dihydro β-ionone (104) was followed by a four step sequence to the furan (38). The blocking effect of the ester substituent directed the subsequent cyclisation via the 3- rather than the more facile 2-position. Pallescensin A (53) had been previously prepared by a similar cyclisation of the unsubstituted version of (105). Hydrolysis and decarboxylation of (105) gave furan (38) which was oxidised and then pyrolysed to give a mixture of confertifolin (9) (74%) and drimenin (17) (17%) separable by chromatography on silica gel, in 16% overall yield from (104).

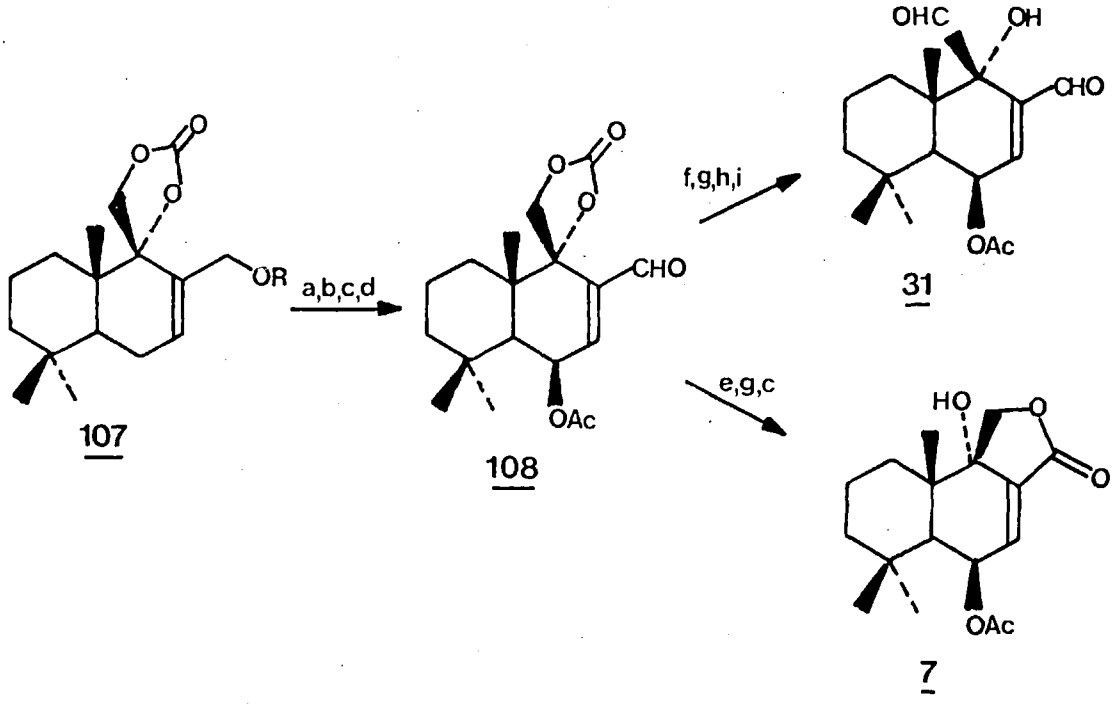


Scheme 15. a) $HClO_4$, $HC(OMe)_3$; b) Py.HBr, MeOH-THF-H_2O; c) $ClCH_2CO_2Me$, NaOMe; d) p-TsOH, C_6H_6; e) $SnCl_4$, CH_2Cl_2; f) KOH, MeOH-H_2O; g) Cu, quinoline; 220°C, h) $Pb(OAc)_4$, C_6H_6; i) KOH, dioxane-H_2O; j) Jones; k) $NaBH_4$, THF; l) 170°C, 1 h.



Scheme 16. a) CrO_3, AcOH; b) $HO(CH_2)OH$, p-TSA, C_6H_6; c) LAH; d) Ac_2O, py; e) H_2O_2, NaOH, MeOH; f) $NH_2NH_2.H_2O$; g) t-BDMSCl, DMF, imidazole; h) N,N'-carbonyldiimidazole, C_6H_6; i) CSA; j) Jones; k) $HO(CH_2)_3OH$, p-TSA, C_6H_6; l) NaOH, dioxan-H_2O; m) DMSO, py, DCC, TFA; h) p-TsOH, acetone.

Hydrolysis of diacetates (106) and then oxidation gave winterin (37) (16% overall yield). Reduction of (37) gave (9) and (22) in 14% and 81% yields respectively. These workers later reported a conversion of isodrimenin (22) into warburganal (36) as shown in Scheme 16.[53] The total synthesis of (36) from β-ionone via (22) required 25 steps and therefore is not a convenient route, and once again extensive use of protecting groups is made during the manipulation of C-8 and C-9 functionality in triol (95). The production of the key triol proceeded in low yield (23%), and the overall yield to warburganal was a mere 2.5%. Oishi has also demonstrated a conversion of this triol into cinnamodial (31) and cinnamosmolide (7)[48] (Scheme 17). Conversion of (95) into the protected



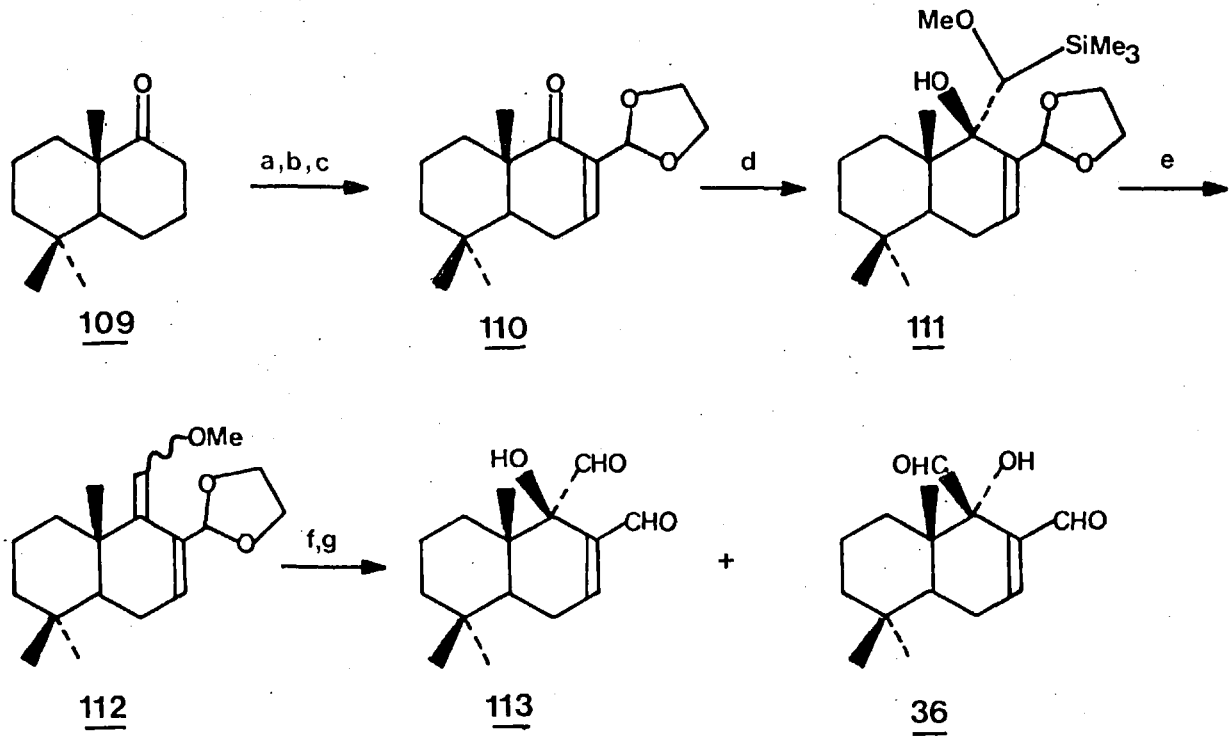
Scheme 17. a) CrO_3, AcOH; b) $Zn(BH_4)_2$; c) Ac_2O, py, DMAP; d) Zn, AcOH; e) Jones; f) $HO(CH_2CH_2)OH$; g) NaOH, dioxane-H_2O; h) DMSO-DCC; i) PTSA, acetone.

derivative (107, R = $CO_2CH_2CCl_3$) in a similar manner as before, was followed by chromium trioxide oxidation to the 6-keto derivative in 64% yield. Reduction of this acid labile ketone with zinc borohydride in ether led to acetate (108). Conversion of (108) took place to (7) and (31) in 16% and 7% yields from (22) respectively.

Finally, use has been made of 5,5,9-trimethyl-trans-1-decalone (109)[92] to synthesise warburganal and isotadeonal. This rather less readily available starting material is obtained by condensation of ethyl vinyl ketone with 2-methylcyclohexa-1,3-dione, followed by further elaboration (vide infra).

Kende and Blacklock[54] treated (110) obtained in 64% yield from (109) with lithium methoxy(trimethylsilyl)methylide to afford the homologated derivative (111) in 73% yield. A non-stereospecific elimination of trimethyl silanol produced enol ethers (112) (Z: E = 3:1), which could be further hydrolysed to isotadeonal (27) in 22.5% overall yield. Epoxidation of (112) followed by hydrolysis, gave a 3:2 mixture of epi-warburganal (113) and warburganal (36) in 22.5% and 13.5% overall yields, separated by silica gel chromatography (Scheme 18).

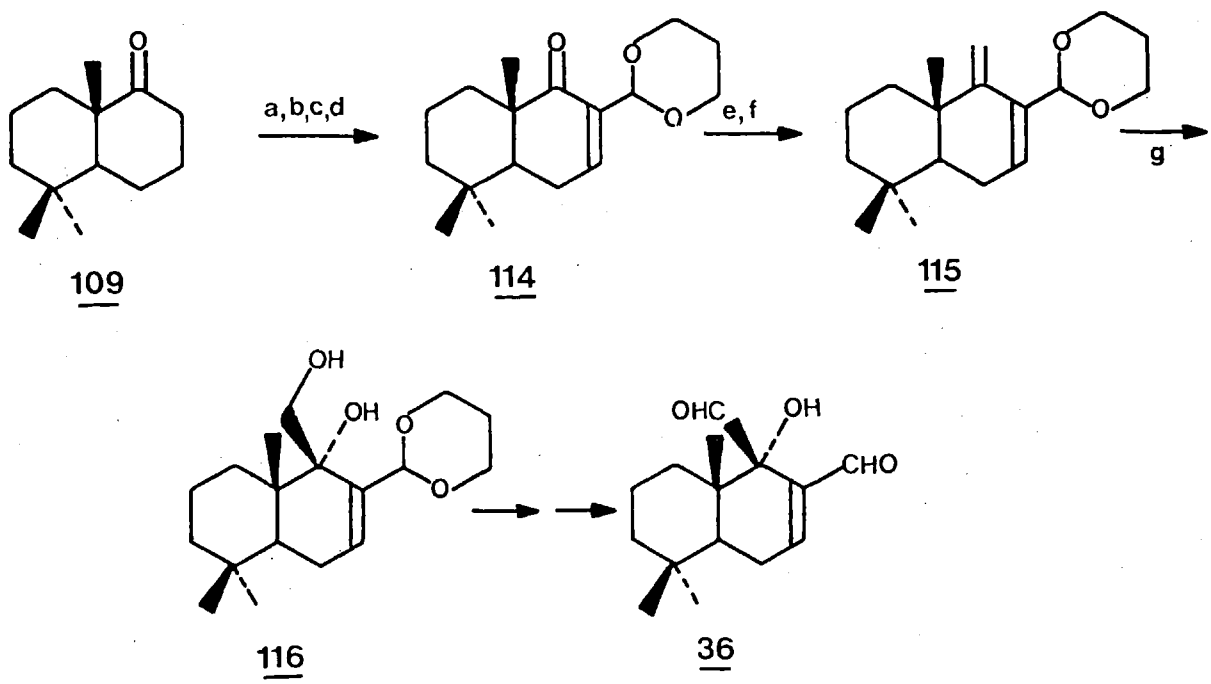
Shortly afterwards, Goldsmith and Kezar reported a similar approach.[55] This time treatment of (114), obtained in an improved yield (79%) from (109), with methyl lithium, followed by quantitative dehydration of the resulting carbinol using the Burgess reagent gave diene (115) in 94% yield from (114). Stereospecific osmylation produced diol (116) which was carried through without isolation to warburganal (36) by previously reported procedures, in 15% overall yield after 9 stages.



Scheme 18. a) HCOOEt, NaH, THF; b) DDQ, C_6H_6, 20°C, 15 min; c) $HO(CH_2)_2OH$; d) $LiCH(OMe)SiMe_3$, THF, -23°C, 30 min; e) KH, THF, 0°C, 20 min; f) m-CPBA, $NaHCO_3$; g) HCl, THF.

The synthesis had proceeded well up to (115) with an overall yield of 74%. Since the reported[53] procedures for oxidation and hydrolysis of (116) were of good yield (73%, 100%) the crucial osmylation of (115) to (116) must be of rather low yield (∿ 25%).

Although the decalone (109) has allowed very short syntheses of warburganal, their overall yields are still rather inferior when it is remembered that alternative routes which were twice as long provided comparable yields. Also, the starting material itself, which is not a particularly convenient one, should be regarded more as an intermediate since it incorporates almost all of the skeleton of the desired product.



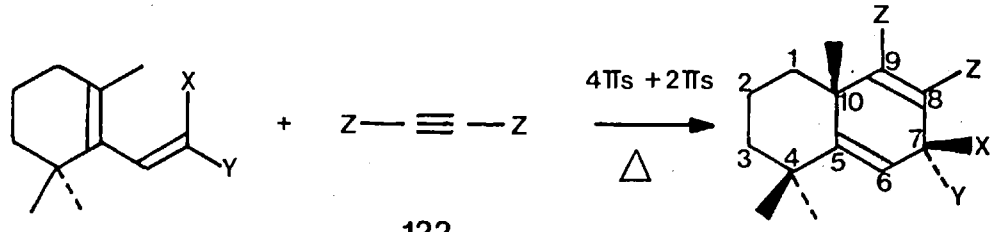
Scheme 19. a) HCOOEt, NaH, C_6H_6; b) PhSeCl, py, $CHCl_3$, 0°C; c) 30% H_2O_2, 0°C, 45 min; d) $HO(CH_2)_3OH$; e) MeLi, THF, HMPA, -78°C ⟶ R.T., 8 h; f) $MeO_2CNSO_2NEt_3$, Et_3N, THF, reflux, 2.5 h; g) OsO_4, py, Et_2O, R.T., 20 h.

Indeed, each of the warburganal syntheses reported so far suffers from at least one poor transformation or groups of transformations which dramatically reduced the efficiency of a potentially high yielding series of reactions. It is expected that the current sustained interest of synthetic organic chemists will provide still further improvements to the existing methods.

RESULTS AND DISCUSSION

A) Diels-Alder Approaches to Drimane Synthesis.

At the outset of this work, the strategy which was proposed for the synthesis of drimane related natural products involved a Diels-Alder reaction between a diene such as (117)-(121) and a dienophile (122) (Figure 10). The reason for this approach was that we sought to improve on the early Brieger work (scheme 9), by suitable modification of the Diels-Alder components, and the reaction conditions. At that time we were unaware of a paper by Loperfido[88] on the addition of dimethyl-acetylene dicarboxylate (DMAD) to (89) which was reported to proceed in good yield.



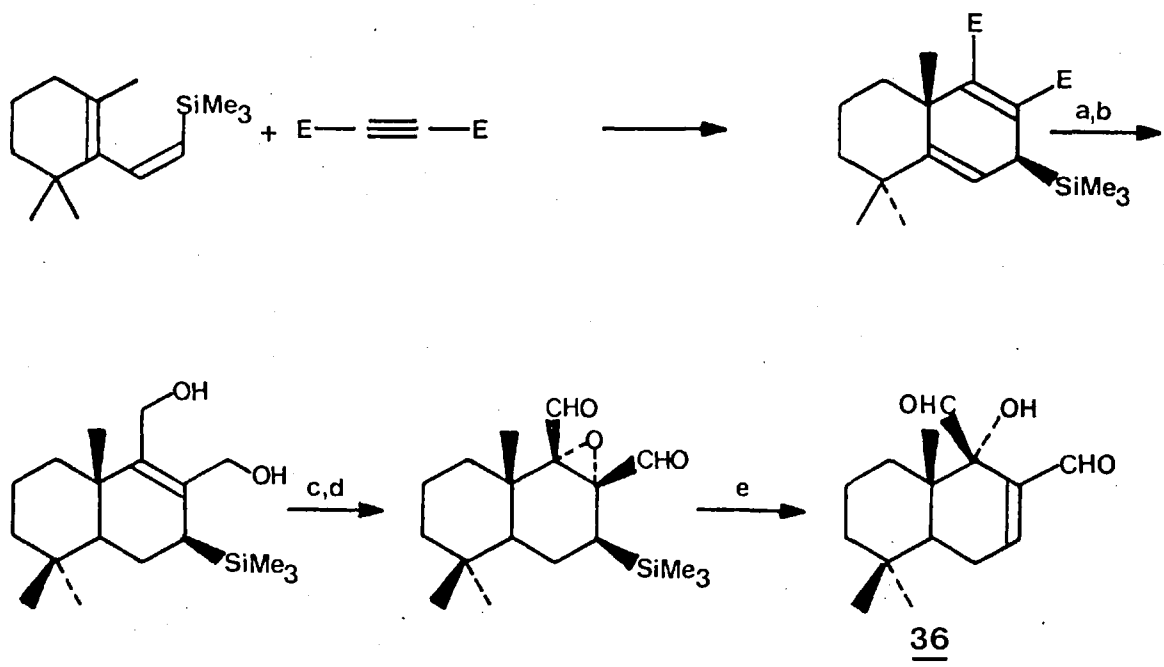
117 X=H,Y=$SiMe_3$
118 X=$SiMe_3$,Y=H
119 X=H,Y=OAc
120 X=H,Y=Br
121 X=OMe,Y=H
89 X=Y=H

122

123

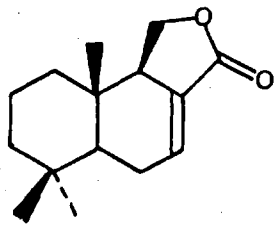
Figure 10

We had selected DMAD as a suitably functionalised, reactive dienophile and had speculated upon a range of appropriately substituted dienes from which the examples (117)-(121) appeared to be the best candidates for later modifications. It was argued that the oxygenated dienes (119) and (121) by virtue of their electron-rich nature should facilitate the Diels-Alder reaction, while the other hetero-dienes would give rise to adducts with 7-substituents which might be useful during the manipulation of functional groups on C-8 and C-9 (see below). An initial route proposed is shown in Scheme 20.

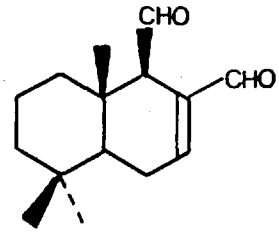


Scheme 20. a) H_2; b) LAH; c) tBuOOH-VO(acac)$_2$; d) [O]; e) nBu_4NF.

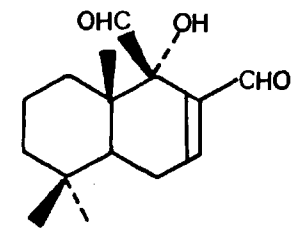
In the event however, no success was obtained as these dienes failed to react with DMAD. Futhermore, when it was discovered that the parent diene (89) readily afforded an adduct with DMAD without the need for its activation by means of hetero-substituents, it was clear that these compounds offered little advantage over the parent diene (89). Attention was therefore subsequently focussed on the adduct (123, X=Y=H) which led to efficient syntheses of cinnamolide (8) polygodial (29) and warburganal (36) (Figure 11). The first part of this thesis however, describes the preparation of these substituted dienes.



8



29



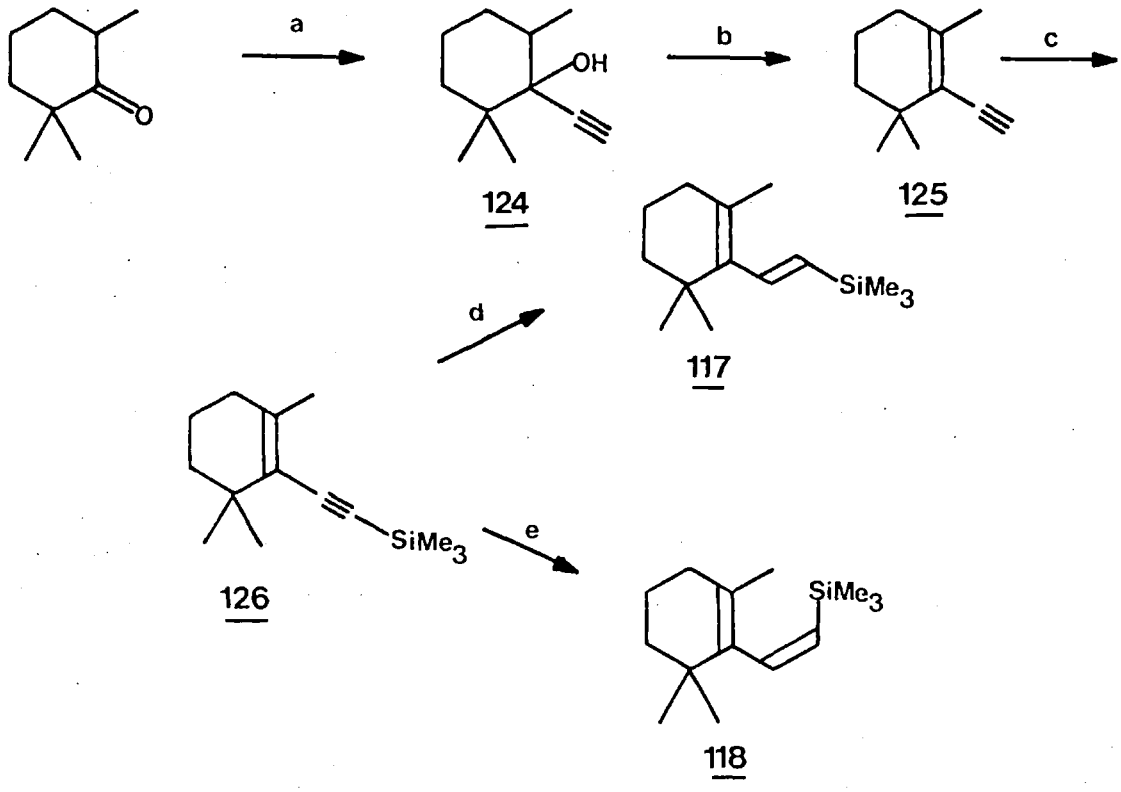
36

Figure 11

(i) Preparation and attempted use of heterodienes (117)-(121).

The starting material for all these syntheses was 2,6,6-trimethylcyclohexanone. Reaction of which with sodium acetylide in liquid ammonia produces acetylenic carbinols (124) (vide infra, Scheme 29) in near quantitative yield. Dehydration by refluxing in xylene in the presence of a small amount of copper(II) sulphate trihydrate gave the enyne (125), according to the previously described method of Julia.[93]

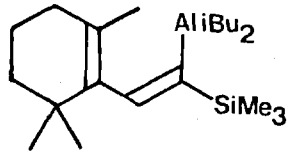
Since (125) was unstable at room temperature, it was immediately converted without isolation, to the stable trimethylsilyl derivative (126) in 70% yield from (124) by treatment with methyllithium and then trimethylsilyl chloride in ether at -78°C (Scheme 21).



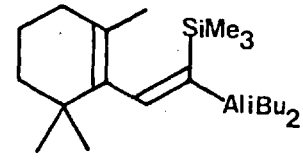
Scheme 21. a) NaC≡CH, liq. NH_3; b) $CuSO_4.3H_2O$, xylene, reflux; c) MeLi, Et_2O, -78°C then TMSCl; d) iBu_2AlH, toluene, -78°C ⟶ RT, 60 h; e) iBu_2AlH, THF, 55°C, 12 h.

Stereocontrolled reduction of (126) to either (117) or (118) in high yields could be achieved using DIBAL under different conditions, which had been reported by others to stereoselectively produce cis- or trans-

vinyl silanes.[94] This reaction however, had not been previously used with TMS-enynes. Thus it was found that addition of DIBAL in hexane or toluene to (126) followed by stirring at room temperature for 2-3 days gave (117) in essentially quantitative yield which was shown to be 90:10 trans:cis- by g.l.c. Conducting the reaction at higher temperatures led to more of the cis-isomer (118) being produced via the more thermodynamically stable alane intermediate (128) (Figure 12), the regiochemistry of which was assigned on the basis of previous precedence.



127



128

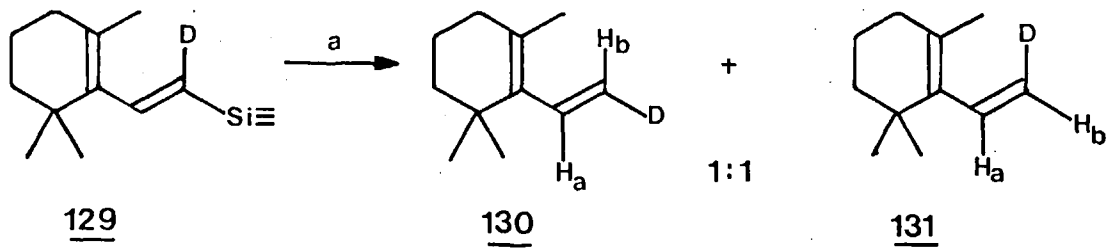
Figure 12

No interconversion of (127) to (128) was observed on heating (60°C, 12 h) and nor was (118) isomerised to (117) at 150° on a g.l.c. column. Diene (117) was ultimately prepared with 100:0 trans:cis-ratio from alcohol (148) (see later).

Modification[94] of the DIBAL reagent by addition of 1 equivalent of a Lewis base, e.g., THF, led to the less stable product (118) being formed. Addition of this reagent to (126) at slightly elevated temperatures (55-60°C), which favoured the formation of (128), afforded (118) (98:2 cis:trans-) in 75-95% conversion, and in 94% yield based on recovered

starting material. Interestingly, use of temperatures of 70°C or above led to reversal of reaction back to starting material.

It was hoped that (117) and (118) or the intermediates (127) and (128) could be used to obtain other functionalised dienes. The latter compounds would require a subsequent stereospecific protodesilylation if the product diene was to have a defined stereochemistry. Of the existing procedures available[95,96] for achieving this transformation, the method of choice for the removal of the TMS group involves brief treatment with hydriodic acid in benzene at room temperature.[95] However, when (129), obtained by deuterium oxide quench of (127), was treated with this reagent a completely non-specific loss of the TMS group occurred (Scheme 22). N.m.r. analysis of the product clearly showed a 1:1 mixture of (130) and (131). (131) had δ 6.0 (Ha, d, J = 11 Hz), 5.0 (Hb, d, J = 11 Hz) and (130) had δ 6.0 (Ha, d, J = 18 Hz), 4.75 (Hb, d, J = 18 Hz). Compound (118) stubbornly refused to lose its TMS group, even on prolonged treatment with HI. The results shown in Scheme 22 contrasts markedly to



129 130 131

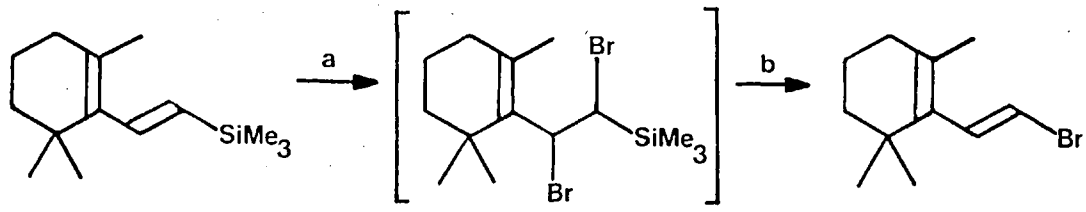
Scheme 22. a) HI, C_6H_6, RT, 30 min.

the case of other vinyl silanes, for which strict retention of stereochemistry is observed for electrophilic substitution of TMS by proton.[95] Examination of models and Newmann projections, fails to provide an adequate explanation for this observation.

With the demonstrated unsuitability of alanes (127) and (128) for use in the preparation of other specifically substituted dienes it was hoped that silyl dienes (117) and (118) themselves could be profitably employed. Attempted production of a vinyl anion from (117) or (118) by nucleophilic cleavage of the TMS group with, for example, t-butyllithium in DME at -78°C or even room temperature, met with failure. Tetra-n-butylammonium fluoride in refluxing acetonitrile or potassium hydroxide in refluxing methanol also failed to remove the silyl group.

Vinyl silanes are known[97] to stereo-specifically give vinyl halides with inversion on treatment with halogens and subsequent desilicohalogenation of the intermediate dihalide, cf. Scheme 23. Addition of one equivalent of bromine in methylene chloride to (117) at -78°C, gave complete consumption of starting material after 2-3 hours. As expected, this reaction was much slower than the instantaneous reaction of vinyl silanes with various halogens. The presumed intermediate dibromide which resulted was not stable to aqueous work up, giving rise to products of desilicohalogenation, dehydrobromination, hydrolysis, etc., as indicated by mass spectral analysis of the crude reaction product. The instability of intermediate (132) paralleled that of alcohol (149) (vide infra). Instead direct treatment with potassium fluoride in DMSO was found to provide an 87% yield of bromide (120) after work up (Scheme 23). Use of potassium fluoride: 18-crown-6: THF gave only partial reaction. Sodium

methoxide or alumina gave predominantly dehydrobromination. Product (120) was contaminated with approximately 10% of (118) (present in the starting material) which was found to react with bromine only after 4-5 hours at $0^{o}C$, and which could not be removed by distillation. The crude product was ∿ 85% pure by g.l.c. and was used directly.

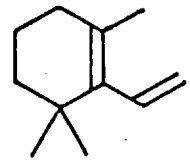


117 132 120

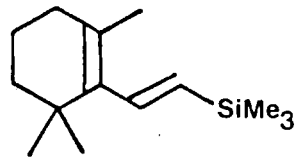
Scheme 23.a) Br_2, CH_2Cl_2, $-78^{o}C$, 2 h; b) KF, DMSO.

Unfortunately, the reaction of (118) with bromine was not as clean as with (117). The subsequent treatment with potassium fluoride in DMSO gave an even more complex mixture, and this approach was therefore abandoned. The sluggishness of the reaction of (118) versus (117) with electrophiles is thought to be due to the severely hindered nature of the p-orbitals on the silyl substituted double bond by the nearby methyl groups. By inspection of molecular models the two double bonds in the much more sterically congested isomer (118) are expected to be almost orthogonal to each other, however the compound still has an appreciable u.v. extinction coefficient as shown in Figure 13, indicating some degree

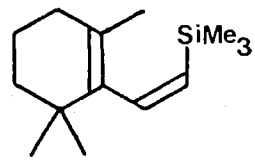
of planarity as would be required for a Diels-Alder reaction to occur with this substrate.



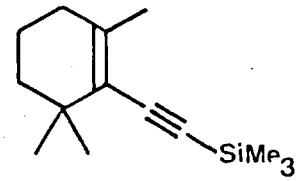
λ_{max}(nm)	ε
235	10,500



251	7,800



240	2,800



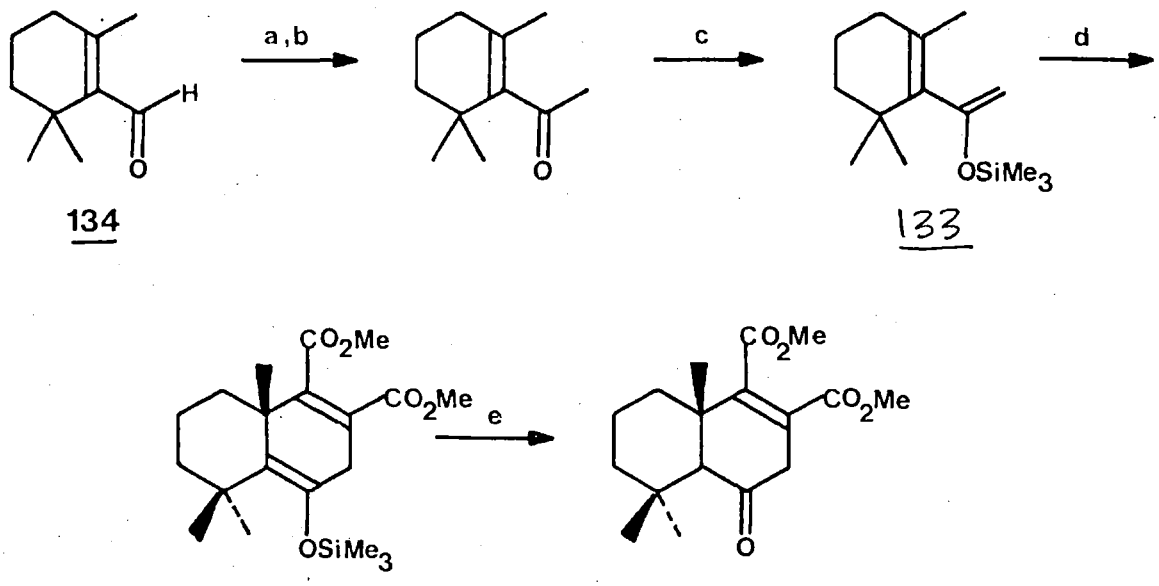
246	12,000

Figure 13

The results shown in Figure 13 deserve further comment. The calculated value of λ_{max} for diene (89) is 229 nm (214 nm + 3 alkyl residues), and therefore the longer observed value of 235 nm, coupled with its reduced intensity (ε 10,500 cf 20,000) agrees well with the

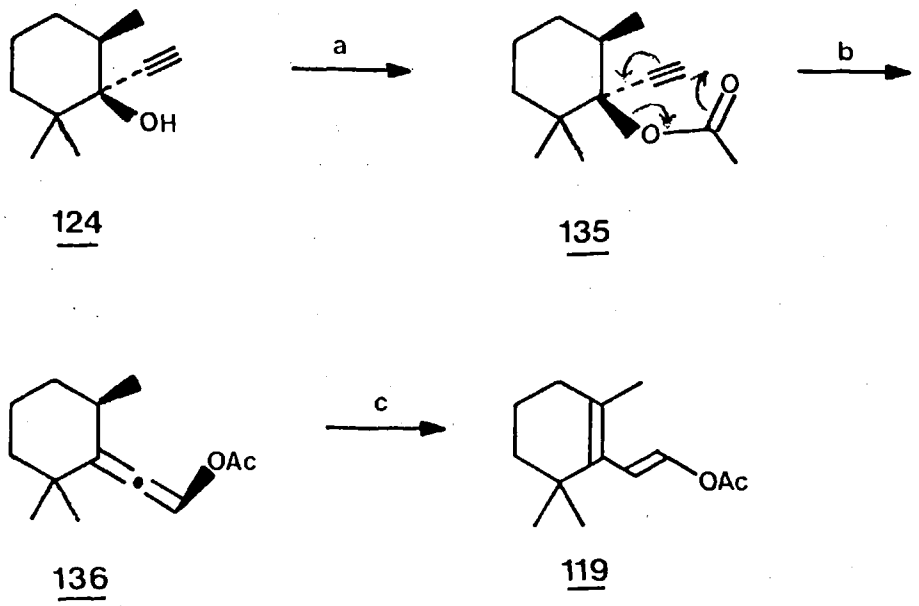
1,3-diene unit adopting an s-cis conformation rather than the usually more favoured s-trans conformation. This can be rationalised by considering the hindering effect of the 6,6-geminal dimethyl grouping being more important than that of the 2-methyl group. The s-cis conformation which is required for a (4 + 2) cycloaddition to occur is a favourable aspect of the structure of (89), although the 1,1-disubstituted arrangement might be expected to inhibit the Diels-Alder reaction. This effect is even more pronounced for diene (117) which, by virtue of the bulky TMS group, is now locked into a cisoid co-planar arrangement as indicated by the large red shift and still further reduced extinction coefficent in the u.v. spectrum. The serious obstruction to coplanarity of the diene unit in (118) caused by buttressing of the TMS and 2-methyl groups, results in a lowered wavelength maximum, and similar loss in spectral intensity. The possible effect of the silicon heteroatom in these compounds in the u.v. has been ignored.

Obviously then (118) is not an attractive " Diels-Alder" diene. For these reasons a proposed Diels-Alder reaction between diene (133), which should be easily obtained from β-cyclocitral (134) as indicated was not further investigated (Scheme 24). Even though the diene unit is now activated towards addition, the non-terminal 2-trimethylsiloxy substituent which would have favoured the requisite cis-co-planar conformation in an acylic system, is almost certain to make this arrangement impossible to achieve as a result of the serious interaction with the geminal dimethyl groups. This approach could have led to the trans-fused 6-oxo-11,12-dicarbomethoxy compound (Scheme 24) which has obvious potential for drimane synthesis.



Scheme 24. a) MeMgBr; b) PCC; c) LDA, -78°C then TMSCl; d) DMAD; e) H_3O^+

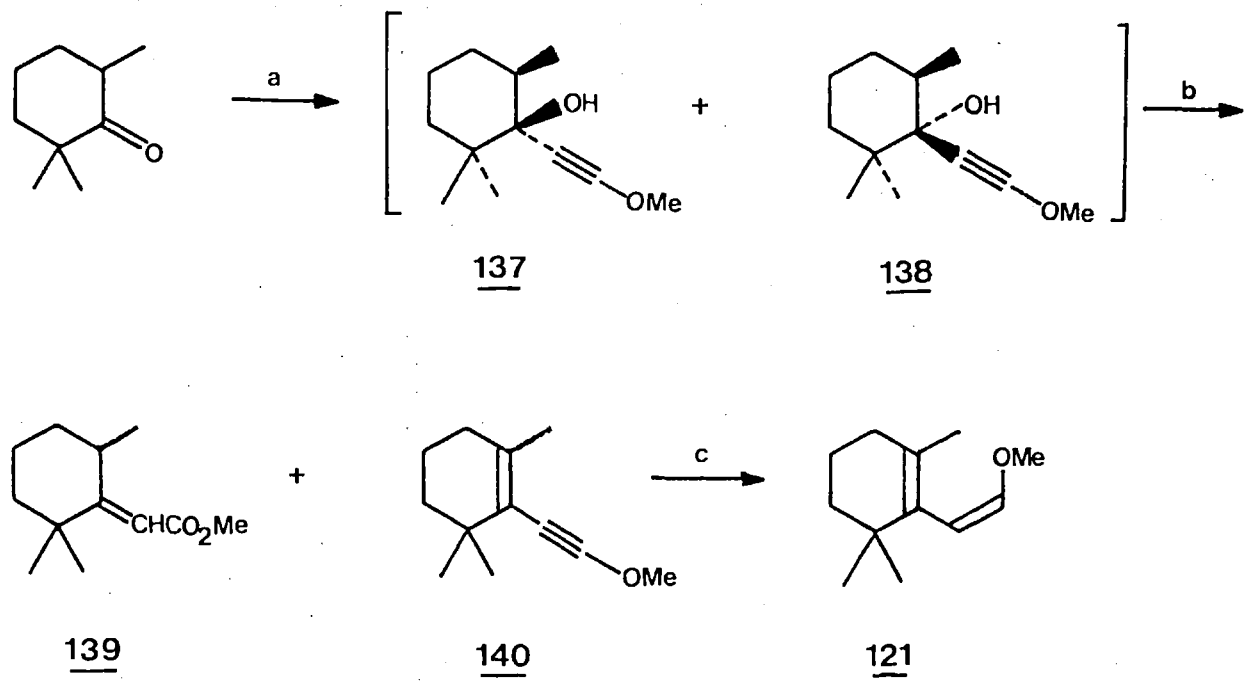
The reported[98] conversion of propargylic acetates into 1,3-dienyl-acetates via the intermediate allene prompted us to prepare (119) from (124). Acetylation[99] was followed by treatment with a range of π-acids including CuCl, $AgPF_6$, AgO_2CCF_3, $AgSbF_6$ and $AgBF_4$. All these reagents caused rapid [3,3] sigmatropic rearrangement to the intermediate allene on gentle warming in benzene. Use of $AgPF_6$ provided (136) quantitatively after a few minutes. Subsequent prolonged reflux with these reagents, in order to produce (119) by [1,3] prototropic shift, gave variable results. The best reagent was $AgSbF_6$, which provided a 68% yield of (119) after work up (Scheme 25). ^1H n.m.r. showed no observable cis isomer.



Scheme 25. a) Ac_2O, AcBr, 100°C, 16 h; b) $AgSbF_6$, C_6H_6, Δ; c) $AgSbF_6$, C_6H_6 reflux, 8 h.

Finally, preparation of diene (121) was accomplished in a manner similar to that for (118). Addition of lithium methoxyacetylide to 2,6,6-trimethyl cyclohexanone afforded the diastereomeric alcohols (137) and (138) (72%:28% respectively, cf. Scheme 29). in 94% yield. The reported use of ethyl magnesium bromide[99] to generate the anion from methoxyacetylene gave poorer results; the reagent thus prepared was an oily-solid suspension which was incompletely soluble in THF, even at reflux. The hitherto unreported use of n-butyllithium for this purpose was found to be far superior. Attempted dehydration of alcohols

(137) and (138) using the Julia method as before led predominantly (75%) to the unsaturated ester (139), presumably via 1,3 rearrangement and tautomerisation of the resulting allenol, although a small yield (15%) of the desired compound (140) was also isolated. Attempted suppression of this rearrangement by the addition of a small quantity of pyridine led to inhibition of reaction in refluxing benzene: in refluxing toluene only (139) was observed in reduced yield. Without investigating ways of improving the dehydration at this stage, the enyne (140) was then successfully converted to the dienol ether (121) by treatment with the deactivated DIBAL reagent as before in 69% yield (Scheme 26).



Scheme 26. a) LiC≡COMe, Et_2O, -20^oC, 0.5 h; b) $CuSO_4.3H_2O$, C_6H_6, reflux 3 h; c) iBu_2AlH, THF, RT, 72 h.

With the range of substituted dienes (117)-(121) to hand, attention was focussed on a possible Diels-Alder reaction with DMAD. Uncatalysed reactions were studied first. Samples of (117) and (118) were heated under nitrogen in the absence of solvent with an excess of DMAD (1.5-2 eq.). Initial runs were performed in n.m.r. tubes. Heating of the mixtures to temperatures of 80°, 95°, 110° and 125°C for periods of several hours each gave no observable products. The dienes were recovered in good yield, but the DMAD had suffered significant decomposition to brown polymeric material. Continued heating at 125°-150°C now produced substantial decomposition of (117), but (118) was still largely unreacted. At 150°C the DMAD rapidly became dark brown and was almost completely solidified. Use of freshly distilled DMAD made no difference to these results.

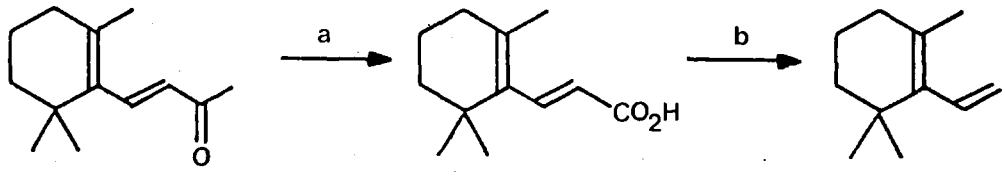
The reactions were then repeated using Florisil, magnesium bromide and zinc chloride as catalysts. Again, heating from RT to 110°C showed little difference by t.l.c. to the uncatalysed runs. The zinc chloride reaction apparently (t.l.c.) produced more decomposition of reactants than the others. Conditions of high pressure (5-15 Kbar), which is known[100-102] to accelerate Diels-Alder reactions were not investigated.

Dienes (119)-(121) were similarly investigated with and without solvent (methylene chloride, benzene, xylene) and catalysts for the reaction as before. Although minor products were observed, the mixtures were quite intractable and were therefore abandoned. The catalysed reactions actually appeared worse on t.l.c. than the uncatalysed ones.

Further efforts to achieve a Diels-Alder reaction with these compounds were not made and at this stage attention was turned to the reaction of diene (89).

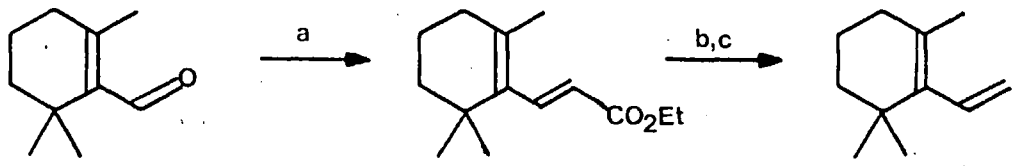
(ii) Preparation of 1-vinyl-2,6,6-trimethylcyclohexene (89).

Before we could embark on a programme of research using this route we obviously required an efficient, convenient synthesis of the diene (89). Brieger[58] had previously obtained (89) by thermal decarboxylation of ß-cyclocitrylideneacetic acid (142) obtained from β-ionone (141) by hypochlorite oxidation (Scheme 27). In our hands, this process was inconvenient and low-yielding, even when (142) was prepared independently in higher yield (44%) by Wittig reaction of β-cyclocitral (134) with carboethoxymethylene triphenylphosphorane and subsequent hydrolysis (Scheme 28).



141 **142** **89**

Scheme 27. a) KOCl; b) 240°C, Cu, quinoline.

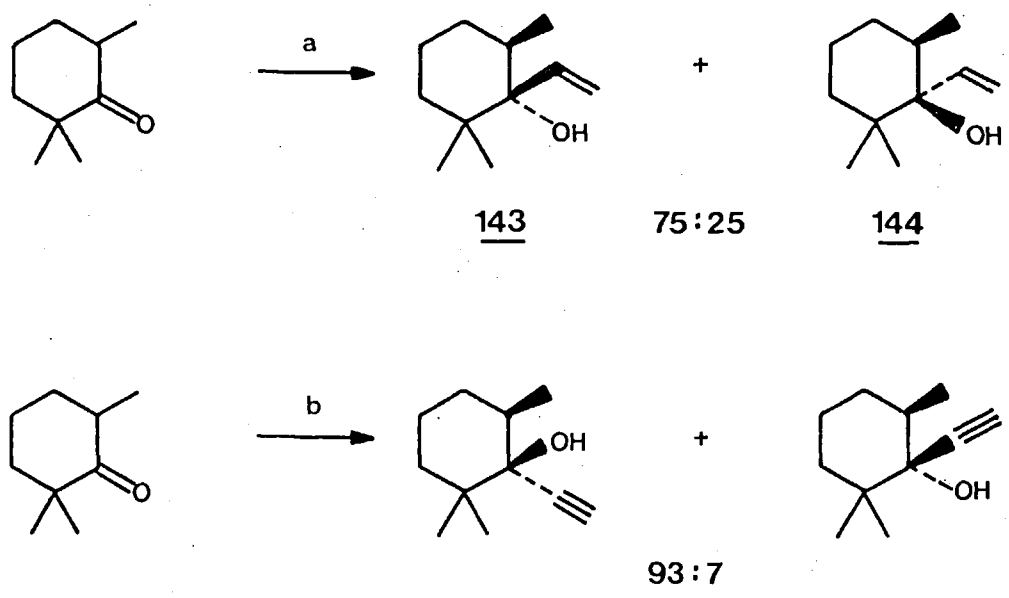


134 89

Scheme 28. a) Ph_3PCHCO_2Et, C_6H_6, reflux, 140 h; b) NaOMe, MeOH, H_2O; c) 240°C, Cu, quinoline.

Although direct olefination of β-cyclocitral[103] with, for example, methylenetriphenylphosphorane, is the obvious alternative, early trials on a small scale gave unsatisfactory results (however, later reactions on a larger scale showed this to be a viable route). A number of alternative possible procedures for the preparation of (89) were therefore investigated, and are briefly discussed below.

Reaction of 2,6,6-trimethylcyclohexanone with vinyl magnesium bromide gave vinyl carbinols (143) and (144) in 85-90% yield (Scheme 29). Even when an excess of Grignard reagent was used in these reactions, 10-15% of starting ketone was always reisolated, presumably caused by enolisation competing with nucleophilic addition to the hindered carbonyl group. An interesting comparison to the reaction of this ketone with sodium acetylide is also shown in Scheme 29. It is clear that the two reagents prefer to attack from opposite faces of the ketone, to provide the diastereoisomeric products in the ratios indicated. The results shown in Scheme 29 must be explained in terms of steric approach control since no equilibration can occur. The preferred conformation of this hindered

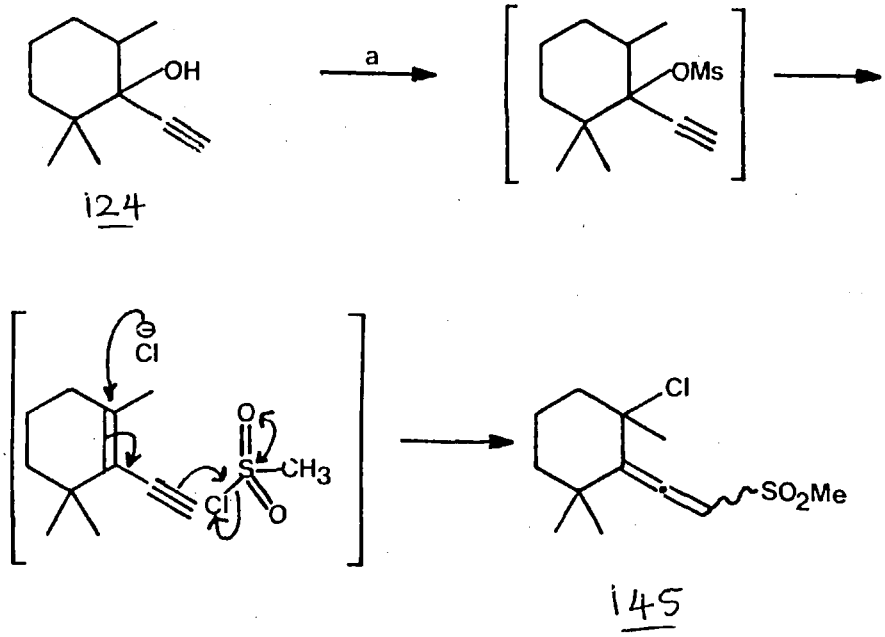


Scheme 29. a) CH_2=CHMgBr, THF; b) NaC≡CH, liq. NH_3.

ketone is with 2 pseudo-equatorial and 1 pseudo-axial methyl group orientations. The small steric requirement of the acetylide anion allows its attack from the same side as the " axial" methyl: the bulkier Grignard reagent with its larger counter-ion pair, attacks from the opposite side.

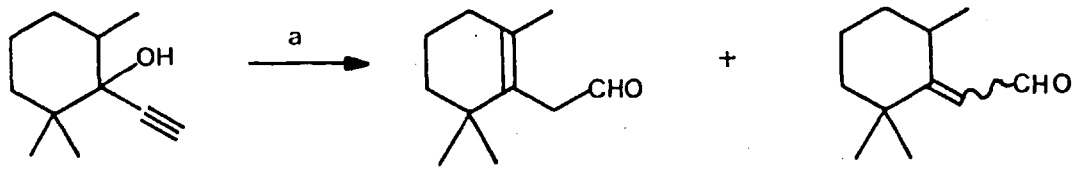
The stereochemistries were initially assigned on thin-layer and spectral properties, thus the axial alcohols in each case were the more polar, and exhibited less intense, sharp non-H-bonded OH absorptions at 3620 cm^{-1} relative to the broader intermolecular H-bonded absorptions at 3500 cm^{-1}. This assignment was additionally confirmed by the observed

rates of acetylation and subsequent elimination using DBU in benzene. Acetylation was achieved with acetyl chloride in ether in the presence of dimethylaniline and a small amount of DMAP. In each case the axial alcohols were (∿ 4X) more rapidly esterified and eliminated, although the latter reaction proceeded with poor conversion throughout. Indeed, all attempts to dehydrate either (143) or (144) ($SOCl_2$, py; $POCl_3$, py; I_2, xylene; H_2SO_4, pentane; pTsOH, benzene; MsCl, py then DBU) to (89) were unsuccessful. The acetylenic alcohols (124) also refused to dehydrate under these conditions. Also, use of phosphorous oxychloride in pyridine at elevated temperatures led to extensive methyl group migration. Attempted mesylation of (124) with methane sulphonyl chloride led to the unexpected novel sulphone (145) by the proposed route shown (Scheme 30).



Scheme 30. a) MsCl, py, 55°C, 12 h.

Another approach to (89) utilised a Meyer-Schuster rearrangement of the acetylenic alcohols (124) to β-homocyclocitral (146) (Scheme 31), which circumvented the previously encountered problems of alcohol dehydration.



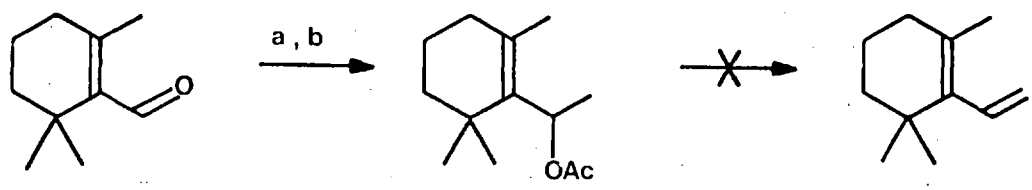
124 146 95:5 147

Scheme 31. a) $-(Ph_2SiO)V(=O)<$, toluene, reflux, 3 h.

Heating (124) in the presence of a polymeric organo-silyl vanadate catalyst[104,105] gave an 80% yield of aldehydes (146) and (147). The normally obtained α,β-unsaturated isomer is a minor product in this reaction since bond isomerisation to the more stable γ,δ-endocyclic isomer occurs. Unfortunately reduction of (146) to the corresponding alcohol and then esterification to the acetate or xanthate, or conversion to the o-nitrophenylselenide[106] could not be followed by an effective syn-elimination reaction to produce (89) in reasonable yield.

Returning to the more readily available β-cyclocitral, conversion to acetate (148) in 90% overall yield as shown followed by prolonged reflux in dioxan in the presence of triphenylphosphine and palladium(II)

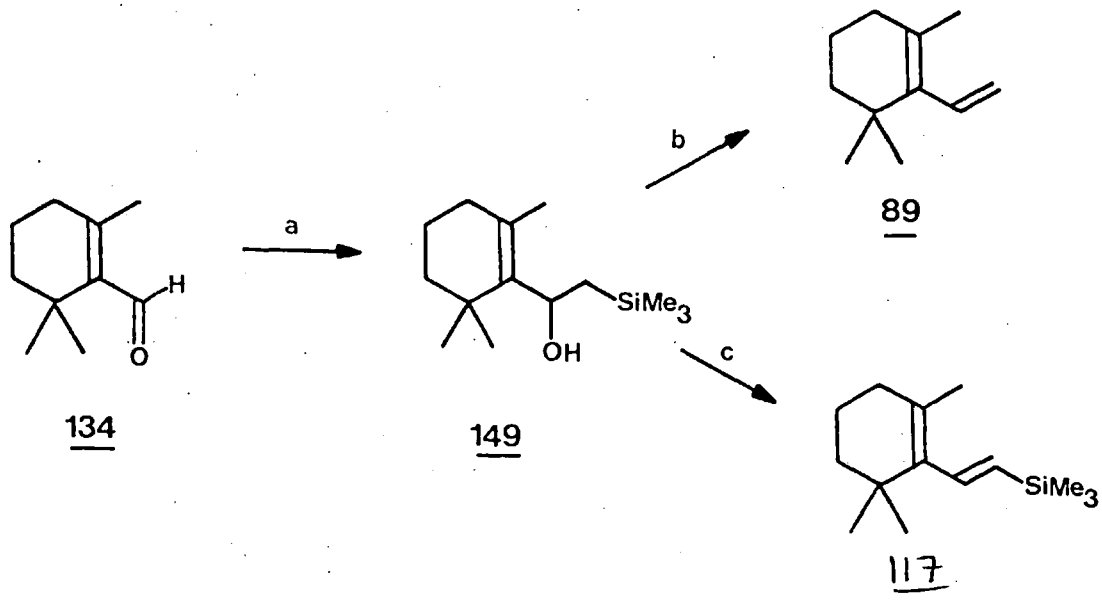
acetate[107] also failed to provide (89) (Scheme 32). Exchange of acetate to mesylate in (14) followed by treatment with DBU in refluxing benzene was also unsuccessful.



148

Scheme 32. a) MeMgBr; b) Ac_2O, py, DMAP.

A convenient, successful preparation of (89) from (134) was finally achieved by means of the Peterson olefination[108,109] which makes use of the Grignard reagent derived from chloromethyltrimethylsilane. This procedure is now the method of choice for the synthesis of (89). Addition of (134) to this reagent gave silyl alcohol (149) in essentially quantitative yield. After much investigation it was found that (149) could be converted selectively to (89) or the previously described (117) under appropriately different conditions, in high yields (96% and 84% respectively) (Scheme 33). Alcohol (149) is sensitive to mild acid or base and is unstable to chromatography at room temperature. It spontaneously decomposes to mixtures of (89) and (117) on standing at room temperature. This instability is due to an incipient carbonium ion in the -CHOH carbon atom, which has both allylic stabilisation and is



134 149 89 117

Scheme 33. a) $TMSCH_2MgCl$, Et_2O, RT; b) PTSA: H_2SO_4 (3:1), THF; c) KH, -78°C, Et_2O, 3 h, then TFAA, py, -78°C ⟶ 30°C, 6 h.

β- to the silicon atom. The usual conditions for elimination of trimethylsilanol from β-silyl alcohols, i.e., KH:THF or H_2SO_4:THF, provided in the first case a 1:1 mixture of (89):(117) and secondly (89) contaminated with 10-20% of (117). Eventually it was found that exclusive attack at silicon rather than the β-hydrogens (to the OH), to provide (89) free of (117) could be achieved by a rapid addition of (149) to a PTSA:H_2SO_4 mixture in THF. The product was ∿ 100% pure by g.l.c. analysis and the overall yield from (134) was excellent (95%).

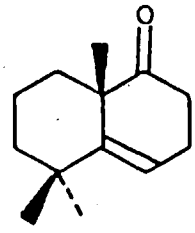
The more difficult task of selectively removing a β-hydrogen, in preference to the much more labile silyl group, in the overall elimination of water to provide selectively (117) was ultimately achieved by formation of the alkoxide of (149) with potassium hydride at low temperature to prevent internal displacement of silicon, subsequent esterification with trifluoroacetic anhydride and final elimination using pyridine. By using low temperatures and in the absence of nucleophiles for silicon, (117) was thus directly obtained in > 95% purity, 100% stereospecificity and 85% yield.

(iii) Use of 1-vinyl-2,6,6-trimethylcyclohexene.

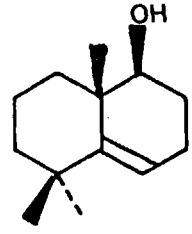
When the Diels-Alder reaction between (89) and DMAD was performed under the conditions used by Nakanishi,[32] inital runs on a small scale gave 60-80% yields of adduct (152) (Scheme 34). However, when the reaction was run on a large scale (0.25 mole) using pure, distilled (89) and 1.4 equivalents of freshly distilled DMAD, an improved 95% yield of (152) was obtained (literature = 83%). This product could be seeded and crystallised directly, after filtration of the crude material through a small amount of silica gel (1:3,w/w), which dispensed with the previous need for exhaustive chromatography or H.P.L.C. of the crude product. With supplies of (152) now readily available, its hydrogenation was subsequently investigated.

The reduction of systems like (152) (Scheme 34) containing a 4,4-dimethyl-Δ5,6 unit does not always proceed stereospecifically. Both the geometry and the nature of the substitution of the " B" ring are known[92,110] to markedly effect the accessibility of the α- and β-faces

of the molecule, and thus the direction of hydrogenation. For example, while the catalytic reduction of ketone (150) (Figure 14) proceeds predominantly to a cis-decalin, the 9β-hydroxy compound (151) provided exclusively a trans-fused product.[92]



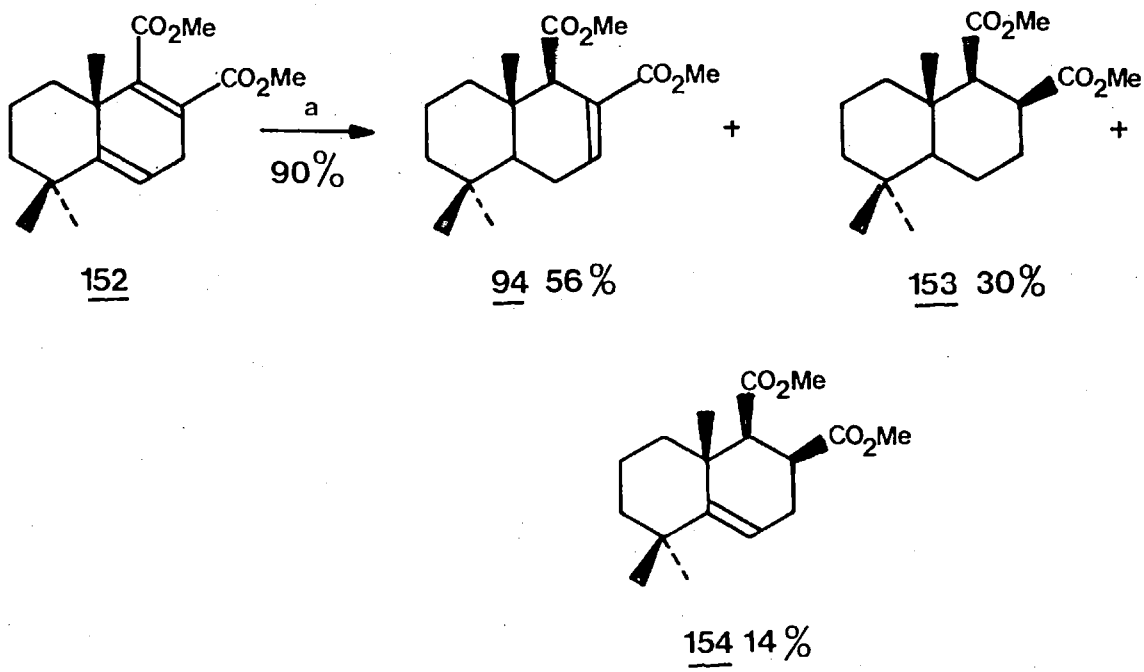
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151

Figure 14

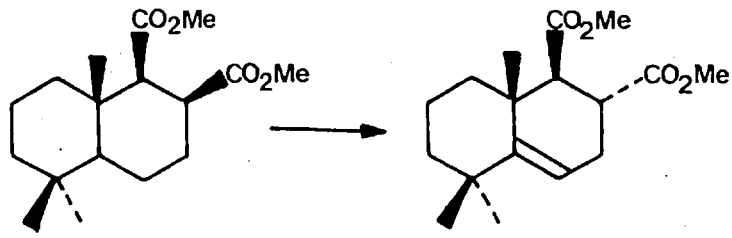
Reduction of (152) over platinum catalysts is reported to lead only to cis-fused derivatives.[32] Inspection of a model of (152) reveals the convex nature of the β-face. Changing C-7 from an sp^3 to an sp^2 centre had the effect of flattening the molecule and rendering the α-face less hindered than the β-face. In accord with this, reduction of compounds (92) or (96) (Schemes 10 and 12) indeed provided the required trans-fused ring junction. We argued that an active palladium-based catalyst should be capable of isomerising the 8,9-double bond to the fully conjugated 7,8-position and subsequent reduction should then provide the desired trans-ring junction. To our delight, when (152) was hydrogenated over 10% palladium on carbon in methanol solution, trans-fused products were indeed obtained (Scheme 34).



Scheme 34. a) H_2, 10% Pd/C, MeOH.

The three products isolated accounted for 90% of the product mixture, which was obtained in quantitative conversion. We had proposed an intermediate (96, Scheme 12) which was never observed, but which has since been shown[63] to provide (94) on catalytic hydrogenation. The observed products arising from hydrogenation of this common intermediate appeared at equal rates (g.l.c. monitor). Structure (94) was fully characterised by the usual methods and later confirmed by single crystal X-ray analysis (see p. 154). Structures (153) and (154) were also fully characterised, and it was further shown that (94) or (154) on hydrogenation provided a product identical to (153) by ^{1}H n.m.r. comparison at 250 MHz,

thus confirming the A/B trans stereochemistry in (153) and the C-8 and C-9 stereochemistry in (153) and (154). Furthermore, (153) was easily epimerised at C-8 by brief treatment with sodium methoxide in methanol at room temperature: the 9α-hydrogen at 2.35 ppm (d, J = 5.5 Hz) in (153) then showed the larger (12 Hz), diaxial coupling. Indeed, unless (153) was obtained in crystalline form the relief of the serious 1,3-diaxial interaction between the C-8 ester and C-10 methyl group led to a clean conversion of (153) to (155) merely on standing in air (Scheme 35). This structure was also characterised by all the usual methods, but was obvious from a comparison of its high field ^{1}H n.m.r. spectrum to that of (154). Thus the appearance of an olefinic resonance at 5.57 ppm (dd, J = 3.4, 4.5 Hz) matched that of the 6-hydrogen in (154): 5.58 ppm (dd, J = 3, 5 Hz). The three tertiary methyl singlets in (153) were shifted downfield to 1.08, 1.14 and 1.28 ppm, indicative of 5,6 unsaturation, similar to those in (154) [1.32 (3H), 1.10 (6H)]. Slight shift differences in the ester methyl singlets were apparent, along with the C-9 methine doublets, and the C-8 and C-7 protons (each ddd). The only striking difference was a large reduction from 12 Hz to 7 Hz in the coupling constant between the C-8 methine and one of the C-7 protons in the conversion of (153) to (155), indicating epimerisation at C-8. Compound (154) did not visibly change on treatment with base.



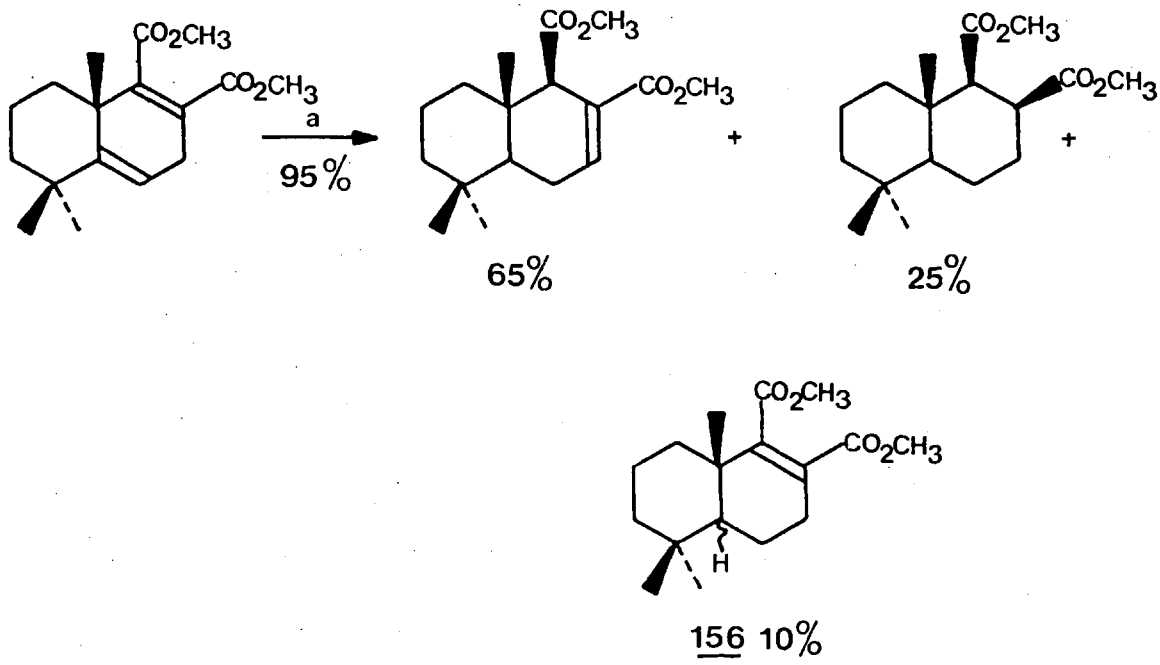
153 155

Scheme 35. a) RT, 1 week.

A study has been made in these laboratories[111] of the hydrogenation of (152) in an effort to improve the yield of (94). Thus, it was found that in the presence of a trace of acid and in dilute methanol solution, yields of 50-80% could be obtained. Although an 80% yield was obtained using hydrochloric acid, the reaction was slow, presumably due to deactivation of the catalyst, and we now prefer to use sulphuric acid which rapidly provides 55-65% yields of (94) on a large scale (50 g) (Scheme 36).

The rate of reaction was increased with increasing concentrations of acid, and thus it was observed that with approximately 0.1 ml sulphuric acid per 100 ml methanol, and with efficient agitation, 95% conversion of (152) occurred within thirty minutes at room temperature. Thereafter, the remaining (152) was not further consumed, but instead the tetrahydro diester (153) which is produced alongside (94) as the reaction proceeds, and constitutes the major byproduct, starts to accumulate at the expense of (94). This over-reduction is fortunately quite slow, under these conditions, but careful g.l.c. monitoring is nevertheless required to obtain optimum yields of (94).

Curiously, when the reaction was performed under acid promoted conditions, the initially isolated product (154) was no longer observed, instead dihydrodiesters (156) are obtained, which were shown to be a mixture of $\sim$ 2:1, cis:trans-fused decalins by reduction to the corresponding diols with LAH and comparison of the n.m.r. spectrum at 250 MHz with those of authentic cis- and trans-fused Δ8,9-11,12-diols.



Scheme 36. a) H_2, 10% Pd/C, dil. MeOH, H_2SO_4.

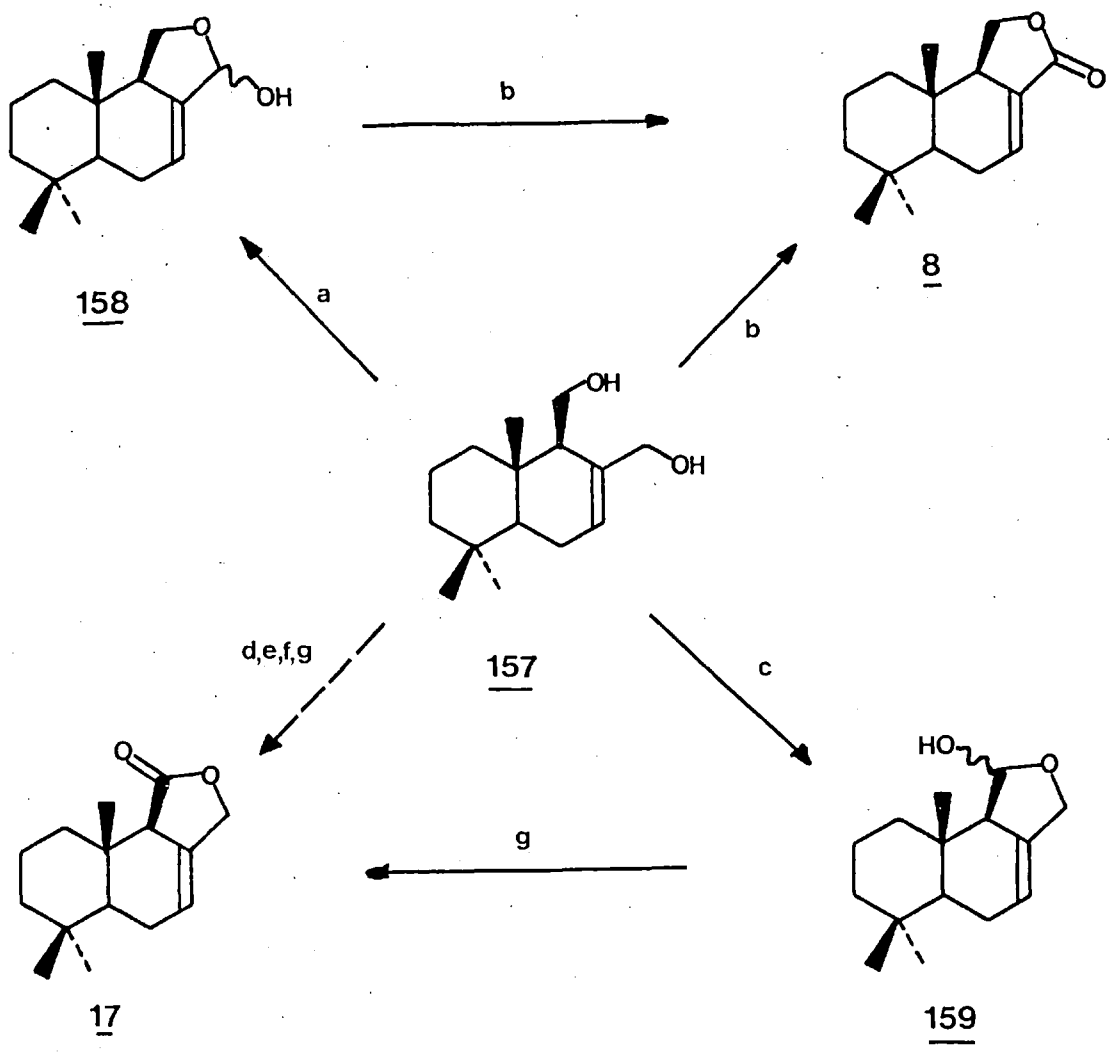
Most of (94) (75-80%) could be obtained by direct crystallisation; chromatographic separation was required to obtain the remainder which is produced. Reduction of (94) with LAH in ether furnished a 90% yield of the key drimane diol (157) (Scheme 37). Oxidation of this diol with various reagents was then investigated. It is well known that oxidation of 1,4-diol systems normally leads to lactones rather than dialdehydes, via cyclisation of the intermediate hydroxy-aldehyde, the mono-oxidation product, and then further oxidation of the lactol leads to the lactone. In diol (157), the hydroxy groups are ideally situated for lactone (lactol) formation, and this is indeed the product of oxidation with, for example, chromium reagents[32] or manganese dioxide.[20] Usually, a single product

is obtained since the more exposed primary allylic alcohol is selectively oxidised first. However, another worker[112] in these laboratories has shown that use of tetraphenylphosphoniumdioxoruthenium-trichloride leads to the isolation of rather low yields of lactol (159) (Scheme 37). Clearly, it is breakdown, rather than formation of the hindered ruthenate ester on C-11 which is the rate-determining process in this reaction.

Use of barium manganate[113] was found to give superior yields of (158) and (8) (92%, 94% respectively) in contrast to the moderate yields obtainable with chromium reagents (∿ 55%). The synthesis of the natural product cinnamolide (8) was thus achieved in an excellent 57% overall yield from (89).

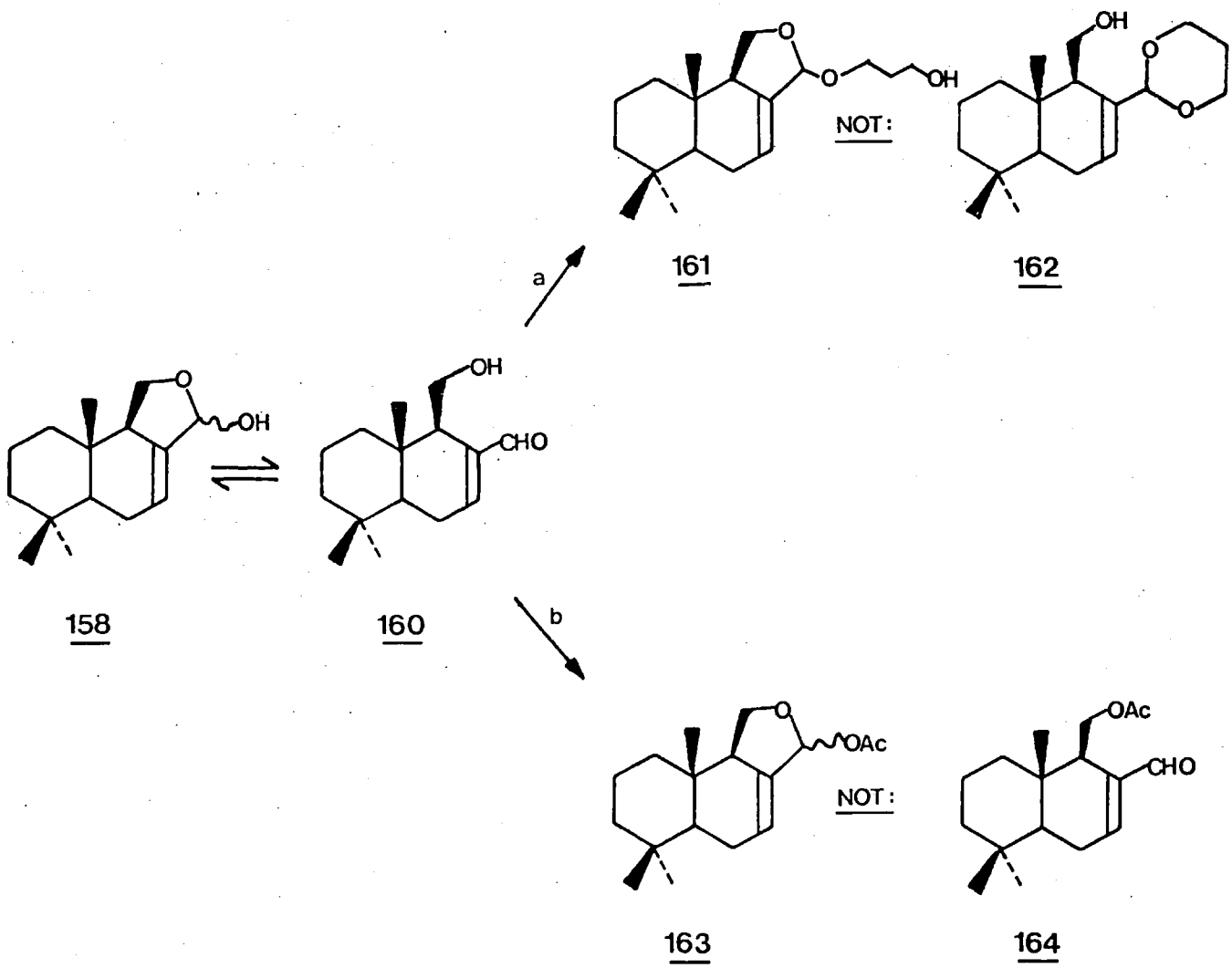
Similarly, oxidation of lactol (159) obtained directly from (157), or more efficiently via prior selective and quantitative protection of the C-12 alcohol in (157) as its tBDMS ether, oxidation at C-11 to the aldehyde (90%) and then deprotection (80%), provided drimenin (17) in 35% overall yield (Scheme 37).

That the lactol (158) is in equilibrium with hydroxy aldehyde (160) is indicated by an aldehyde signal in the n.m.r. (9.38 ppm, s), and i.r. (1670 cm^{-1}) spectrum (the ratio of (158):(160) is ∿ 1:1 in $CDCl_3$; and ∿ 95:5 in C_6D_6). It was attempted to trap out (160) by reaction either on the primary -OH, or aldehyde group as in Scheme 38. Treatment with propane-1,3-diol[111] did not provide the desired protected hydroxy aldehyde (162); rather the C-11 hydroxy readily cyclised onto the intermediate hemi-acetal to provide (161). Attempted silylation (tBDMSCl)

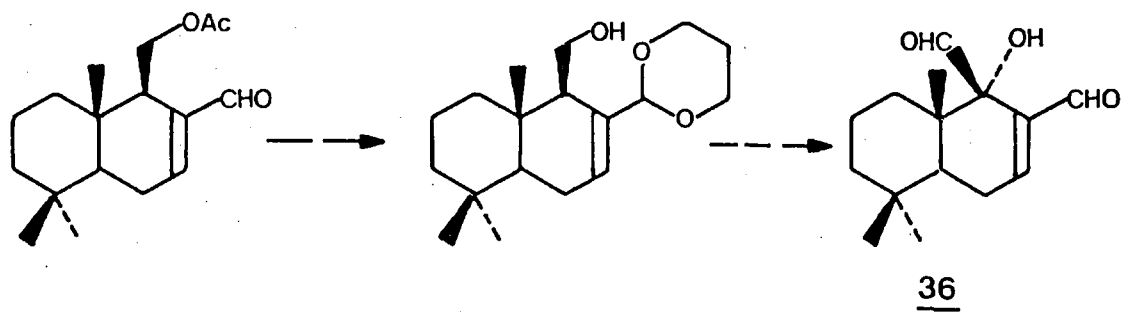


Scheme 37. a) $BaMnO_4$, 1-2 eq., CH_2Cl_2, RT, 4 h; b) $BaMnO_4$, 10-20 eq., CH_2Cl_2, RT, 24 h; c) $Ph_4PRuO_2Cl_3$; d) tBDMSCl, 1-1.2 eq., dil. DMF, imidazole; e) DMSO-$(COCl)_2$, -50°C, then Et_3N; f) nBu_4NF, THF; g) PCC.

or acetylation of the C-11 hydroxy also failed to provide (164); instead lactol acetate (163) resulted, which was amply supported by i.r., n.m.r. and m.s. analysis. Either (162) or (164) would have constituted a formal total sysnthesis of the important drimane natural product warburganal (36), in view of their intermediacy in the Nakanishi route (Scheme 10).[32]



Nakanishi:

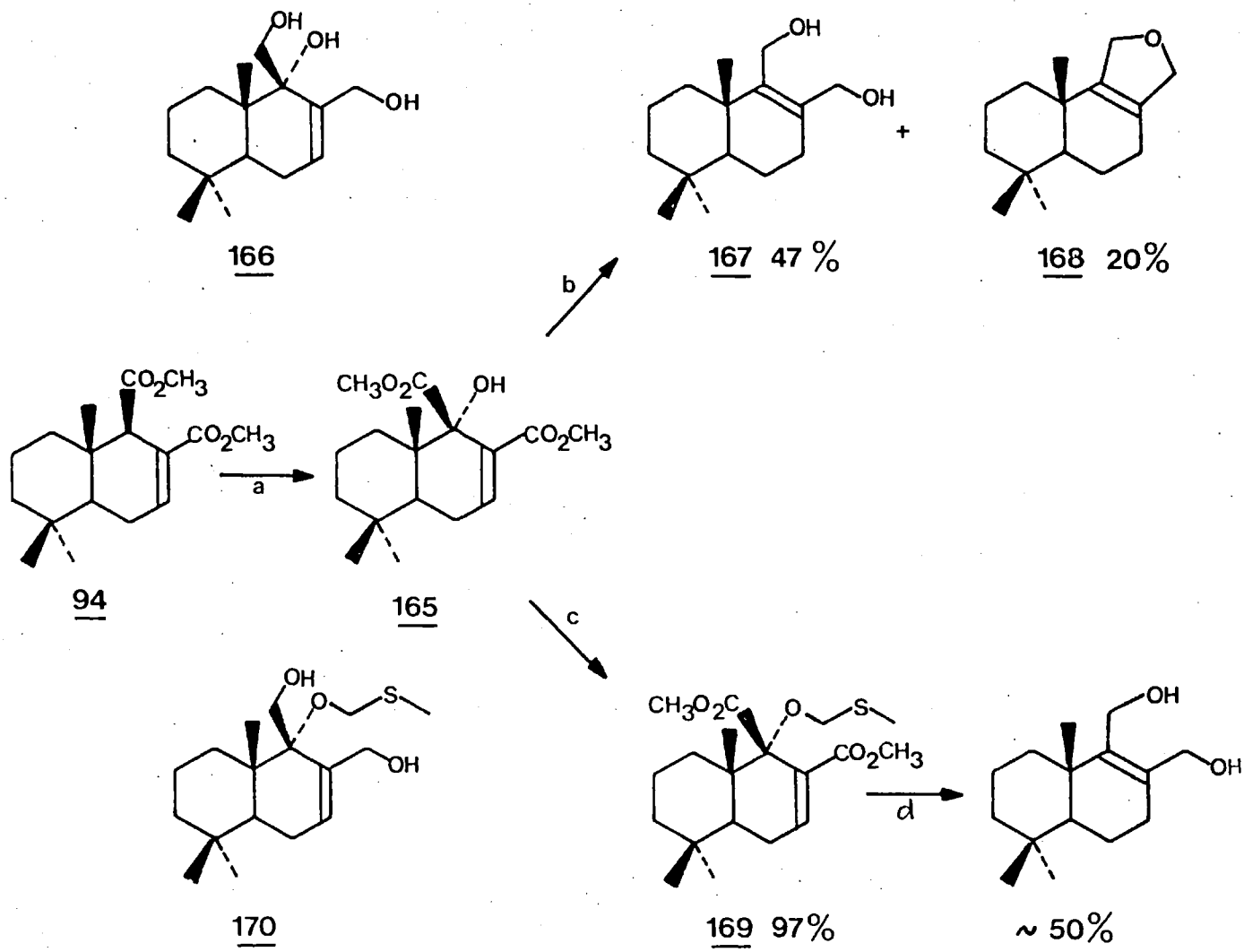


Scheme 38. a) $HO(CH_2)_3OH$; b) Ac_2O, py, $CHCl_3$.

In view of the selective reduction of (94) to (97) (Scheme 12) reported with DIBAL by Lallemand,[63] (162) should now be available by trivial oxidation and protection of the C-8 CHO group followed by reduction of the C-9 ester function.

Attention was then focussed on the problem of introducing the 9α-angular hydroxy function, common to several drimane natural products. Nakanishi's success in achieving this on the C-11 aldehydo-C12 propylenedioxy compound (93) (Scheme 10) led us to try this method with the diester (94). Smooth enolate formation with LDA at -78°C, was followed by quench with the Vedejs oxidant MoO_5.HMPA.py (MoOPH)[114] to provide the desired angularly hydroxylated product (165) in 90-95% yields (Scheme 39). The stereochemistry of the newly introduced -OH group was initially assumed on the basis of least hindered approach by the bulky reagent, and later confirmed by comparison of the n.m.r. spectrum of (165) to those of hydroxy-ester-aldehydes (201) and(202) derived from hydroxy-esters (199) and (200) which were assigned with the aid of n.O.e. experiments (see later).

Unfortunately, all attempts to reduce this compound (165) to the triol (166), led only to the rearranged diol (167),[21] together in some examples with a cyclised product, dihydrofuran (168) and other unidentified products (Scheme 39). The production of (167) is rationalised by internal hydride delivery via a C-9 aluminate intermediate, with resulting deoxygenation.



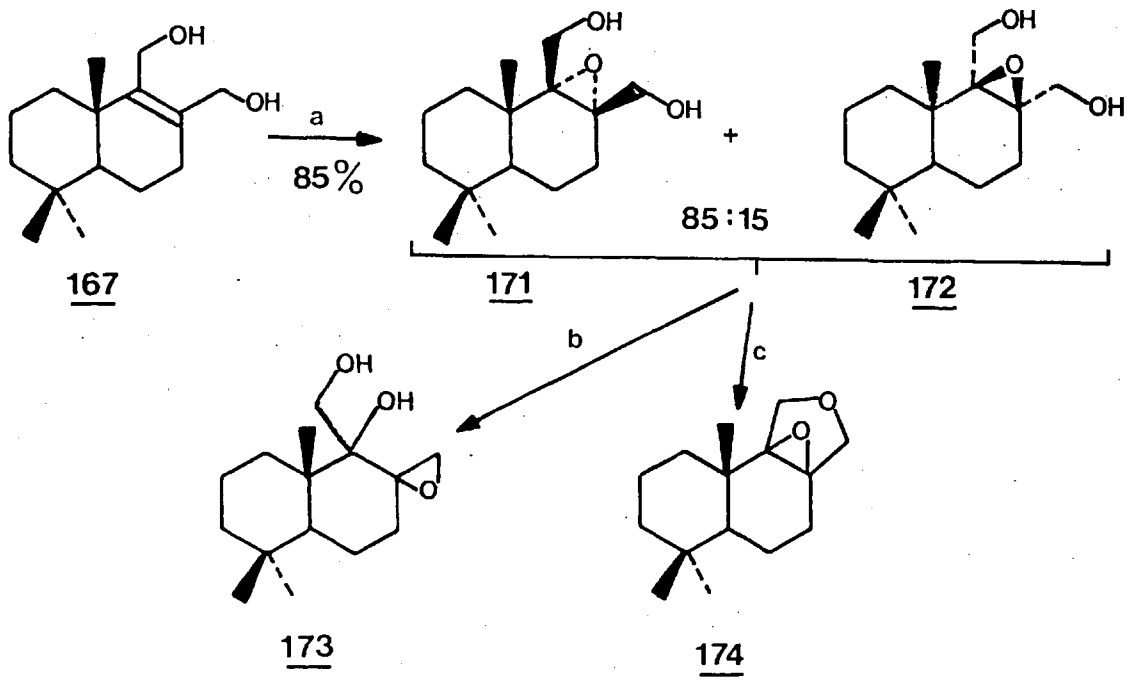
Scheme 39. a) LDA, THF, -78°C, then MoOPH; b) LAH; c) DMSO, Ac_2O, RT, 120 h; d) iBu_2AlH, -78°C, toluene, 1 h.

In an attempt to suppress this deoxygenation reaction the angular hydroxy was therefore protected as its methylthiomethyl ether[115] (169) in near quantiative yield, but once again, reduction with for example, LAH, DIBAL, lithium-tri-s-butylborohydride (L-selectride), lithium triethylborohydride (" Super Hydride") or sodium bis-(2-methoxyethoxy)-

aluminium hydride (Red-Al), at -78°C or above led only to diol (167) as the major product, with no (170) observable by t.l.c. or n.m.r., in a yield of around 50%.

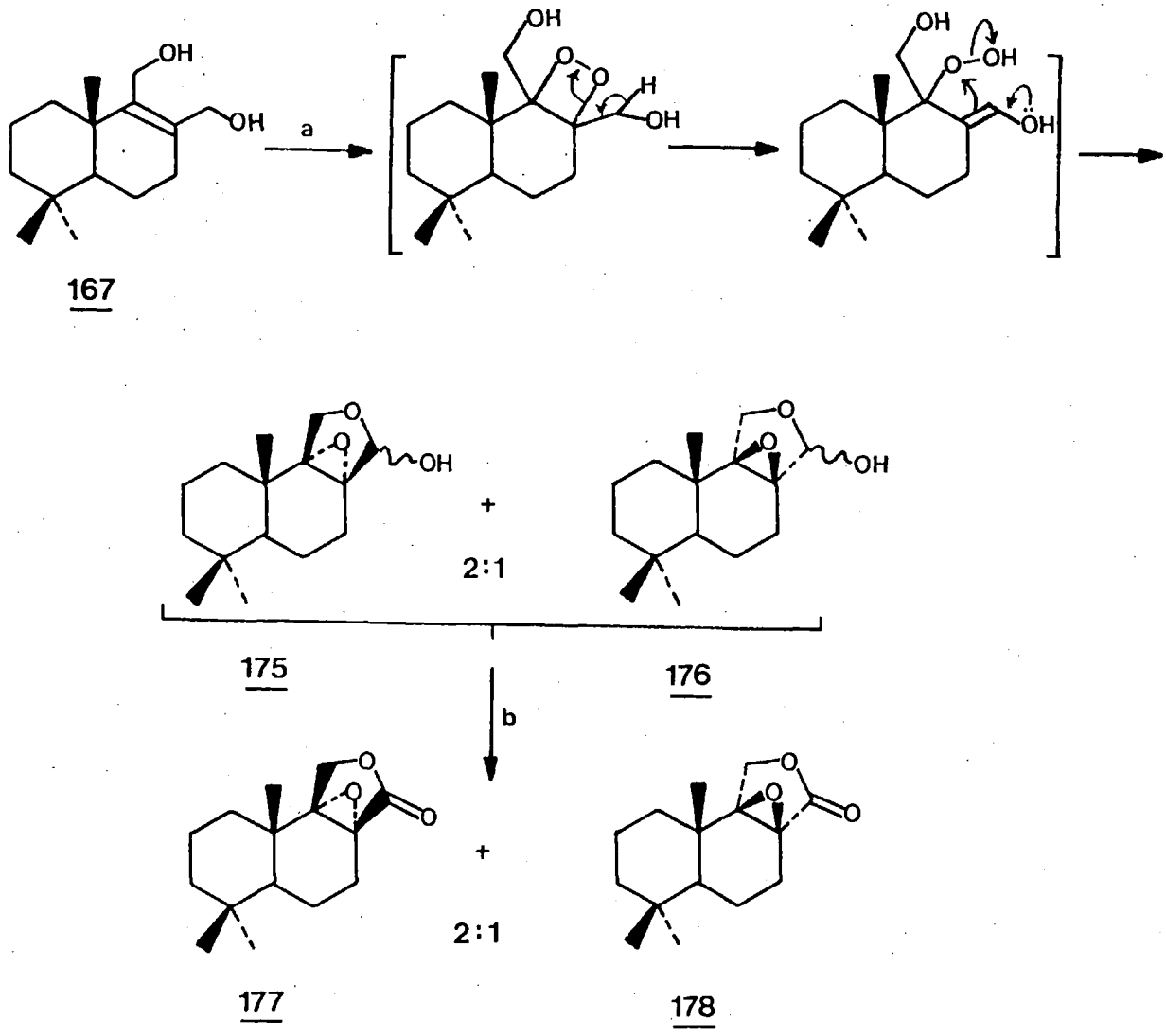
With an overall yield of 45-50% of diol (167) thus available from (94), it was then attempted to convert this material to the desired triol (166). Rearrangement of an epoxide such as (171) (Scheme 40) was thought to be a reasonable proposal. The mild method of epoxidation of allylic alcohols invented by Sharpless[116,117] was employed and gave smooth oxidation after 1 hour. Unfortunately, this reaction was only 70% stereospecific. ^{1}H n.m.r. analysis clearly showed 2 pairs of AB quartets for the C-11 and C-12 methylenes in the ratios indicated (Scheme 40), the major one of which at 3.62 and 3.89 ppm was assumed to correspond to the α-epoxide (171), on steric grounds. Treatment of these epoxides with excess (> 3 eq.) LDA in THF at 0°C for 30 minutes gave a major product which was less polar on t.l.c. than expected for structure (166). M.s. analysis showed this product to have the same molecular weight as the starting material, and no olefinic hydrogen was present in the n.m.r. spectrum. The product actually reverted to starting material on standing and is therefore postulated to be an isomeric epoxide, e.g., (173) (Scheme 40). Attempted protection of the hydroxy groups in (171) and (172) as their trimethylsilyl ethers by treatment with trimethylsilyl chloride in pyridine,[118] prior to base treatment led only to (174).

A final attempt to oxidise (167) to the triol (166) was made using singlet oxygen (Scheme 41). This reagent is known to attack allylic C-H bonds via the intermediate oxetane to provide allylic alcohols with net



Scheme 40. a) tBuOOH-VO(acac)$_2$, C_6H_6, RT, 1 h; b) LDA, THF, 0°C; c) TMSCl, py, RT, 1 h.

double bond inversion. Irradiation of (167) in methanol containing Rose Bengal, at 30-40°C using a 300 W quartz-iodine lamp and with efficient oxygen circulation, provided a 65% yield of product after chromatography. The n.m.r. spectrum however, showed no signal at ca. 5.9 ppm[53] for the triol (166) or indeed any olefinic resonance, and the m.s. showed no m/e 254, but instead a clear molecular ion at m/e 252 was observed (acc. mass: $C_{15}H_{24}O_3$). The 250 MHz n.m.r. showed signals at 3.5-4.1 ppm from which could be extracted two AB quartets centred at 3.93 and 3.84 ppm together with four singlets (∿ 0.5 H each), at 3.63, 3.93 and 3.59, 3.95 ppm. This data was in accord with the product being a ∿ 2:1 mixture of epoxy lactols (175) and (176) (Scheme 41).



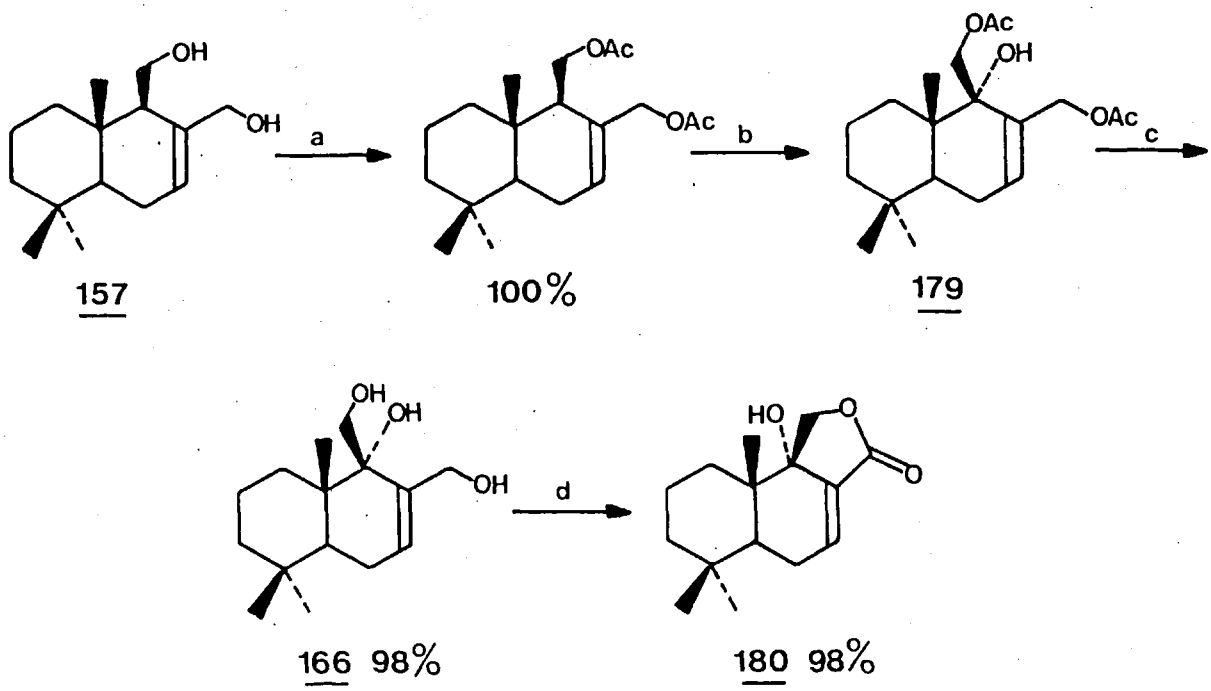
Scheme 41. a) $^1O_2$, 30-40°C, 72 h; b) Ag_2CO_3/Celite, C_6H_6, reflux, 3 h.

These products, which were not separated arose by loss of a proton from C-12 rather than from C-7 as indicated in Scheme 41. Although a model shows the 7β-hydrogen in (167) to be almost perpendicular to the p-orbitals of the 8,9-double bond and hence to the intermediate oxetane C-O bond, which is the preferred orientation for abstraction, the freely rotating methylene protons on C-12 can more precisely align themselves for reaction

and are thus lost preferentially. Attack of singlet oxygen occurs predominantly from the less hindered α-face and therefore the major isomer is assigned as the α-epoxide (175) (cf. oxidation of furan (38), see later). Breakdown of the intermediate oxetane leads to regiospecific lactol formation, and is assigned as shown in scheme 40 by loss of one of the more exposed, allylic methylenes on C-12 rather than on C-11, although no rigorous proof of the regiochemistry was obtained. Further confirmation of structures (175) and (176) was gained by oxidation to the corresponding epoxy ketones (177) and (178), which now showed disappearance of the lactol methine singlets and the appearance of two new AB quartets at 4.18 and 4.31 ppm (J = 11 and 10.5 Hz respectively).

Returning to drimane diol (157), it was argued that a reagent such as selenium dioxide should be capable of oxidising (157) at the more substituted end of the double bond and from the less hindered α-face to provide (166). Although oxidation of (157) itself led to a complex mixture, the simple expedient of acetylation previously used by Sharpless[119] in other systems followed by refluxing in dioxan with selenium dioxide provided a 65% yield of the desired angular hydroxy diacetate (179) after chromatography (Scheme 42). The simplification of the AB quartet of doublets for the C-11 methylene protons to an AB quartet, with the C-6 methylenes remaining intact, indicated the desired transformation had occurred.

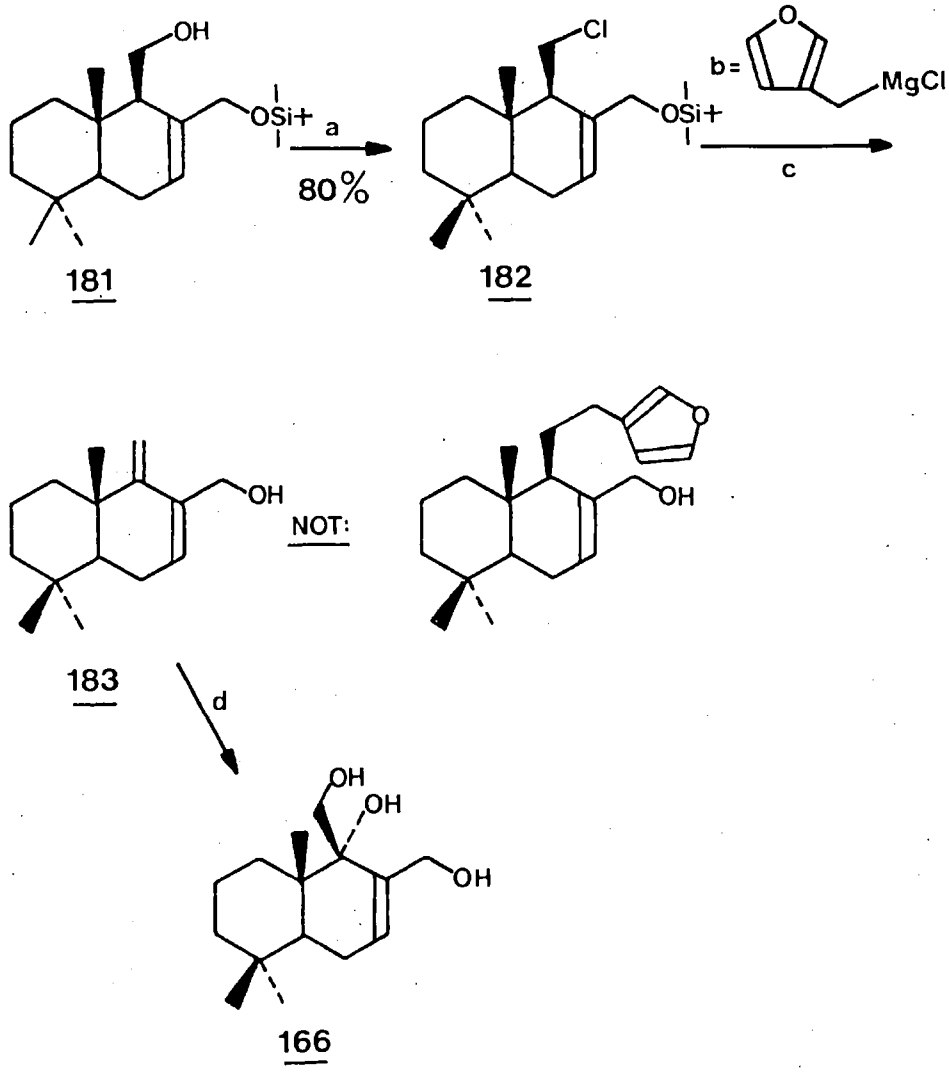
Deprotection using potassium carbonate in methanol[120] gave the desired triol (166) in essentially quantitative yield. Oxidation of this compound with barium manganate or Fetizon's reagent as before produced an almost quantitative yield of 9-hydroxy cinnamolide (180) (Scheme 42).



Scheme 42. a) Ac_2O, py, RT, 12 h; b) SeO_2, 1.2 eq., dioxan, reflux, 1 h; c) K_2CO_3, MeOH, RT, 10 min.; d) Ag_2CO_3/Celite, C_6H_6, reflux, 20 min.

In an attempt to further demonstrate the utility of diol (157) it was attempted to prepare the naturally occurring labdane, 17-hydroxy isopolyalthine[82] (63) (Figure 4). Mono-silyl ether (181), prepared as before (Scheme 37) was treated with triphenylphosphine in refluxing carbon tetrachloride to provide chloride (182). Treatement of (182) with excess 3-furyl magnesium chloride in the presence of Kochi's catalyst, dilithium tetrachlorocuprate (Li_2CuCl_4), followed by treatment with tetra-n-butylammonium fluoride did not provide the desired coupled product, but gave instead dehydrochlorination to diene (183) in moderate yield (Scheme 43). The high field n.m.r. of (183) showed an AB quartet at 4.27 ppm for the C-12 methylenes and the C-11 olefinic methylenes appeared as a singlet at 4.92 ppm. Surprisingly, the halide preferred

to undergo elimination rather than substitution by the Grignard reagent, presumably due to its hindered nature. It is thought that an aldehyde at C-11 would be a more reliable group for a coupling reaction: subsequent reduction of the resulting alcohol should provide (63). However, diene (183) was not completely without use since reaction with osmium tetroxide furnished triol (166) identical to the previously prepared material (t.l.c., n.m.r.), albeit in low yield (∿ 10-20%) (Scheme 43).



Scheme 43. a) CCl_4, Ph_3P, reflux, 2 h; b) 3-furyl-magnesium chloride, Li_2CuCl_4, THF, reflux 1-2 h; c) nBu_4NF, THF; d) OsO_4, Et_2O, py, RT, 0.5h, then Na_2SO_3, EtOH, H_2O.

At this stage, the problem of direct oxidation of 1,4-diol systems such as (157) was investigated. In view of the facile lactol and lactone formation which occurred with previously described reagents, we required a reagent which would react with both hydroxy groups to form a stable intermediate, which could then be converted to a dialdehyde in a second step. With the absence of a free hydroxy group during the production of a 1,4-situated aldehyde group there is no possibility for cyclisation to occur. A Moffat-type oxidation appeared to fulfil these requirements, in which elimination of dimethyl sulphide occurs from an intermediate sulphoxonium salt to produce the carbonyl group (Scheme 44).

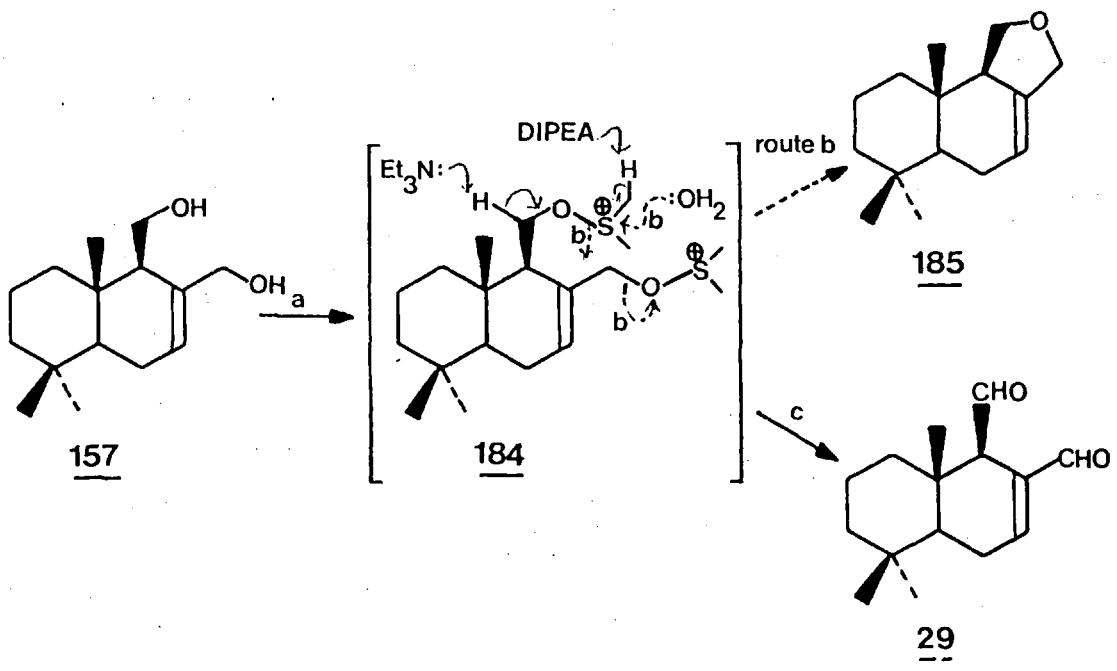
This approach was first used by Barton and co-workers[121] to oxidise butane-1,4-diol to succinaldehyde. Here, the necessary bis-sulphoxonium intermediate was obtained by reaction of DMSO with the bis-chloroformate derivative, obtained by treatment of the starting diol with phosgene; subsequent treatment with triethylamine then furnished the dialdehyde. Alkyl halides have been converted to their dimethylsulphoxonium salts by treatment with DMSO in the presence of silver tetrafluoroborate.[122] However, conversion of diol (157) to an intermediate bis-chloroformate or bis-bromide, is unattractive, especially in view of the known tendency of allylic chloroformates to rearrange by decarboxylation.

In recent years, methods have been reported for activating DMSO by use of electrophilic reagents which allow direct conversion of the alcohol into its corresponding sulphoxonium salt. One of the most effective of these "activators" reported so far is oxalyl chloride, developed by Swern.[123,124] A further advantage of this procedure is the use of low temperatures, in contrast to the higher reaction temperatures required previously.

Most gratifyingly, when diol (157) was treated with 2 equivalents (4 mole equivalents) of the Swern reagent at -50°C followed by 6 mole equivalents of triethylamine, a 95% yield of the desired dialdehyde polygodial (29), was obtained (Scheme 44). The overall yield from diene (89) to this biologically active sesquiterpene was 57%. The efficiency, brevity and convenience of this approach to (29) is a vast improvement on previously reported procedures.[32,64]

It was noted that the quantity of triethylamine used was crucial. Use of 4 mole equivalents of Swern reagent required the addition of 4 mole equivalents of triethylamine merely to quench the 2 equivalents of acid (HCl or HO_2CCOCl) produced during the formation of (184), and the 2 equivalents excess reagent (required to ensure complete reaction). Hence, addition of 0-4 equivalents of triethylamine to (184) thus produced, followed by aqueous work up led to a high yield (93%) of the cyclised material (185) (route b, scheme 44). Use of excess (> 6 equiv.) triethylamine led to the production of other side products, and a resulting lowered yield of (29). A virtual " titration" procedure for the addition of the last equivalent of base, with careful t.l.c. monitoring ensured optimum yields of polygodial. Attempted use of the hindered Hünigs base, diisopropylethylamine (DIPEA), led to large amounts of (185) being formed alongside (29), presumably by competing removal of S-methyl protons (cf. Pummerer rearrangement) rather than the less accessible methylene protons on C-11 and C-12.

With a high yield procedure now established for the synthesis of polygodial (29), an obviously attractive conversion would be that of direct angular hydroxylation to warburganal (36). The enolate



Scheme 44. a) DMSO-$(COCl)_2$, 4 equiv., CH_2Cl_2, -50°C, 1h; b) H_2O or 0-4 eq. NEt_3; c) 6 eq. NEt_3.

hydroxylation method of Vedejs, which had been highly successful when applied to diester (94), was attempted first. To check that the formation of the enolate would occur properly, (29) was treated with LDA in THF at -78°C, followed by quench with D_2O:THF (1:4), to provide on work up a 95% recovery of a compound showing 9.45 ppm (s) and 9.50 ppm (s), plus small singlets at 9.42 and 9.87 ppm. This indicated virtually quantitative incorporation of deuterium at C-9 in (29); The kinetically controlled protonation produced only ∿ 10% of the C-9 epimerised, more thermodynamically stable compound, isotadeonal (27). However, treatment of the same enolate with MoOPH at -78°C, followed by slow warming to 0°C with t.l.c. monitoring at regular intervals showed only starting material to be present and no warburganal[125] (t.l.c. comparison) was formed. At -50°C, the MoOPH reagent had dissolved to produce a green solution, typical of a normal hydroxylation, though

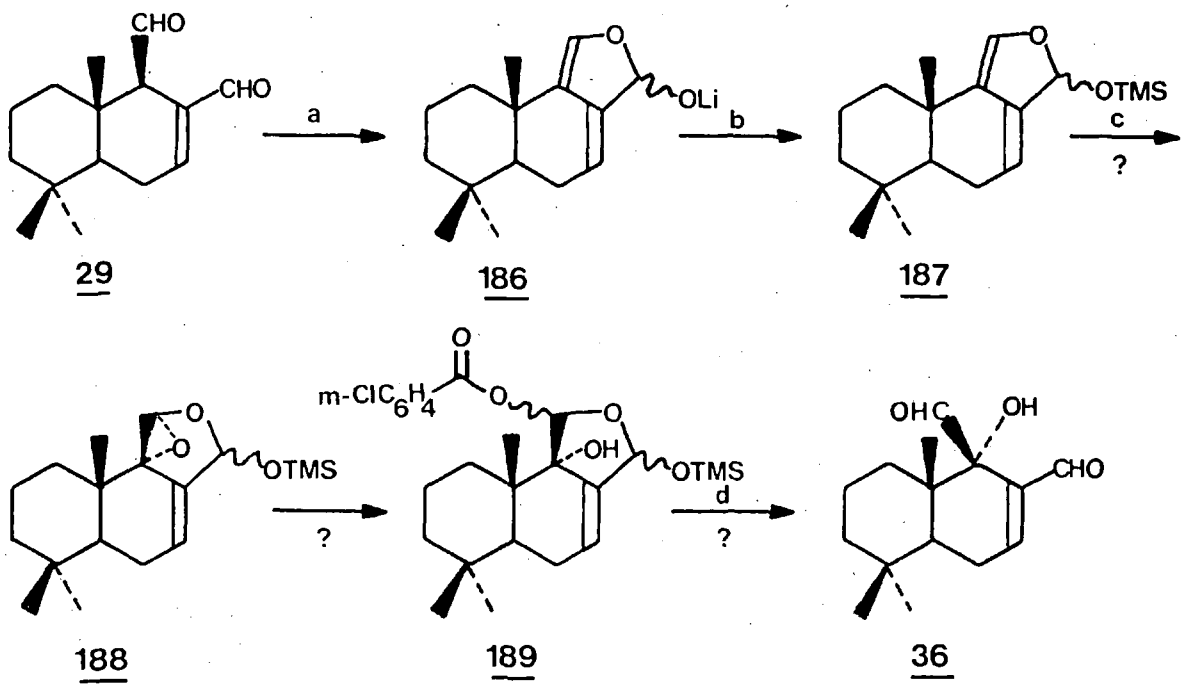
beyond 0°C the reaction mixture began to darken, with other products becoming apparent on t.l.c. Recooling and quenching provided a good recovery of polygodial as before. This unfortunate result could not be explained at this stage, but became clear as a consequence of later results.

There are several reports[114,126-129] of the oxidation of enolates directly with triplet oxygen to provide the α-hydroxy derivative after reduction of the intermediate hydroperoxide. Thus the enolate of (29) in THF, formed as before was treated with dry triethyl phosphite (dist. from sodium) and then rigorously dried oxygen ($CaCl_2$, then powdered 4A molecular seives, activated at 250°C at 0.1 mm for 48 h). Slow warming from -78°C to 0°C once again produced no observable warburganal (t.l.c.). Recooling and quench, this time with D_2O:THF, led to the recovery of an almost completely deuterated sample of (29) as before.

This result was even more surprising when it is considered that enolates usually react rapidly with molecular oxygen at -100°C. It was thought that the enolate could cyclise in a manner similar to that observed during the oxidation of (157) to (158) or (8) (Scheme 37) to provide (186) (Scheme 45). This lactenolate would now be reluctant to react with oxygen electrophiles, as was observed. In accord with this proposal, treatment of the enolate with trimethylsilyl chloride produced (187) (Scheme 45) in essentially quantitative yield (n.m.r.), amply supported by i.r., n.m.r., m.s., and acc. mass.

However, m-CPBA epoxidation of enol silyl ethers is a well known method[130] for the α-hydroxylation of ketones, although aldehydes are subject to the intervention m-chlorobenzoic acid to provide the masked

aldehyde as exemplified in Scheme 45; subsequent treatment with acetic anhdyride however, provided the α-acetoxy aldehyde. It was felt that a 9,11-α-epoxide, if selectively obtained, might be less susceptible to ring opening on steric grounds, and in any event, masked aldehydes at C-11 and C-12 should be capable of deprotection to provide (36) (Scheme 45). However, treatment of (187) with m-CPBA buffered with



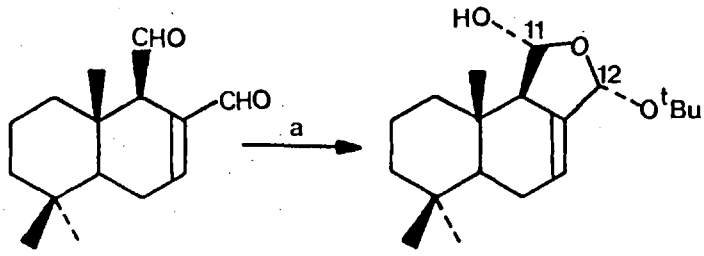
Scheme 45. a) LDA, THF, -78°C; b) TMSCl-Et_3N; c) m-CPBA, Na_2CO_3; d) H^+.

sodium carbonate in methylene chloride or ether at -20°C led to several products. T.l.c. and m.s. analysis at this stage or after further treatment with HCl in THF or nBu_4NF in THF, showed no warburganal

to be present. Substitution of a t-BDMS group for the TMS group in the extremely sensitive lactenol silyl ether (187), by work up of (186) with t-BDMS chloride, gave even worse results on oxidation - hydrolysis. The attempted conversion of (29) into (36) by an enolate oxidation approach was thus abandoned in favour of other possibilities.

Attempted direct hydroxylation using selenium dioxide, which previously had successfully produced the angular hydroxy diacetate (179) (Scheme 42), also failed to provide warburganal from polygodial. Thus gradual warming of (29) with SeO_2 in dioxan followed by reflux for several hours led only to decomposition of (29) with no (36) observed (t.l.c.). Similar treatment of (29) with benzeneseleninic anhydride[157] in chlorobenzene led to complex reaction mixtures. Attempts at a radical-type oxygenation of (29), with for example, iodoxybenzene ($C_6H_5IO_2$), to warburganal, were similarly unsuccessful. For example, refluxing (29) with 1-2 equivalents of this reagent in benzene led to two or three major products, none of which were (36), and were therefore not isolated. Use of the milder t-butylhydroperoxide-selenium dioxide reagent developed by Sharpless,[119] led to a rapid, clean addition of t-butanol to the dialdehyde system (Scheme 46). A clear molecular ion at m/e 308 was observed together with disappearance of the aldehyde signals in (29). The product was a mixture of two isomers (2.5:1); the regiochemistry of the major product indicated, was assigned both on steric grounds and from the lack of aldehyde absorptions in the i.r. or ^1H n.m.r. spectrum [cf. compound (158)]. The stereochemistry at C-11 was assigned from a signal at 5.48 ppm (d, J = 6 Hz) and by comparison to the literature values[37] for compounds (15) and (25) (Figure 3). The

C-12 stereochemistry was assumed on grounds of least hindered approach of t-butanol to the aldehyde group. The C-12 hydrogen thus resonated at 5.67 ppm (s) and the t-butyl residue at 1.28 ppm.



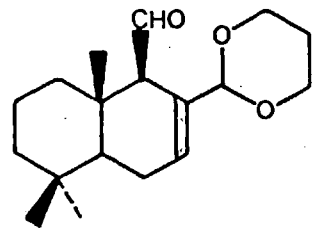
190 Major isomer

Scheme 46. a) t-BuOOH, SeO_2, CH_2Cl_2, RT.

Other reagents for achieving a direct oxidation were conceived, for example, ozone on silica gel,[131] cerium(IV) oxide - hydrogen peroxide,[132] thallium(II) nitrate or trifluoroacetate[133] with subsequent nitrate ester reduction or trifluoroacetate ester hydrolysis respectively, and lead tetraacetate[134] with subsequent acetate hydrolysis, but these approaches were felt to be insufficiently mild or direct and were thus not further investigated.

It was next attempted to selectively protect the C-12 aldehyde in polygodial (29) to produce for example, (93) (Scheme 10, Figure 15), which is known[32] to provide warburganal on oxidation and deprotection. Treatment of (29) with propane-1,3-diol in warm benzene containing a

trace of p-TSA rapidly gave 2 products in similar amounts and in high yield, but neither was the desired mono-protected aldehyde (93), (Scheme 47). The less polar u.v. active component (191) had an

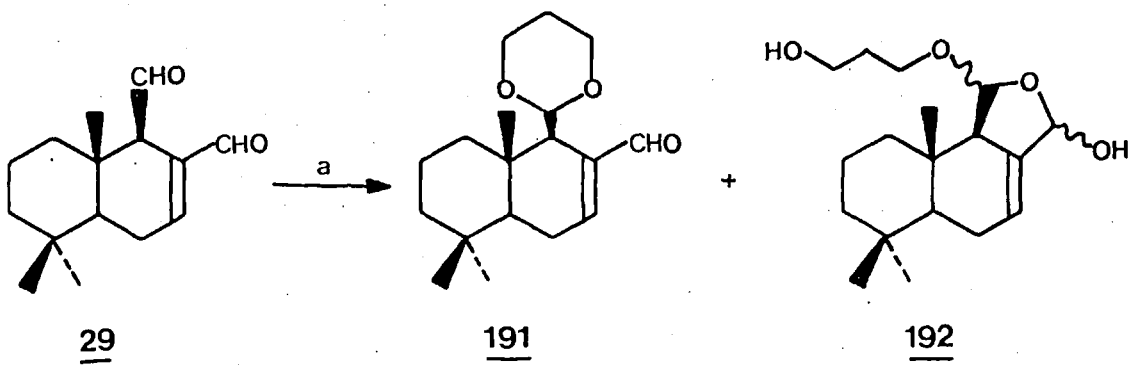


93

Figure 15

absorption at 9.80 ppm as a singlet, while compound (93) is reported to show a doublet at 9.70 ppm.[32] The crude n.m.r. spectrum of the mixture showed an 8:1 ratio of the CH_2-O protons to the aldehyde proton thus indicating the presence of (192) which was not u.v. active at 254 nm, and a single molecular ion at m/e 292 was observed. Hence reaction apparently occurred preferentially at the more reactive, although more hindered aldehyde function at C-11 rather than at C-12, and once again hemiacetal cyclisation occurred to produce (192) as with (190) and the previous lactols (158) and (159) (Scheme 37). For these reasons, no further effort was made to achieve a selective protection of the C-12 aldehyde as an approach to the synthesis of warburganal.

Success was finally achieved by oxidation of the previously prepared triol (166) (Scheme 42) using an activated DMSO reagent, to the desired hydroxy dialdehyde (36). (166) was initially thought to be an unsuitable substrate for such an oxidation in view of the expected



29 191 192

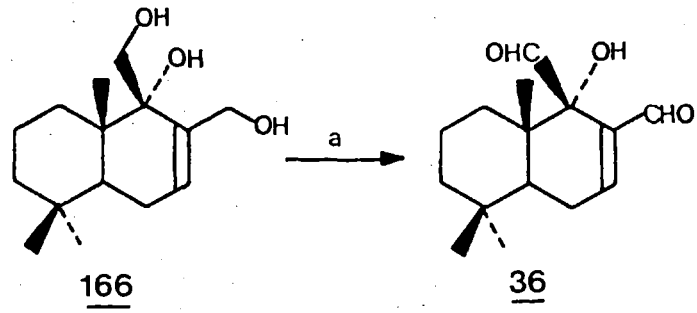
Scheme 47. a) $HO(CH_2)_3OH$, p-TSA, C_6H_6, Δ.

lability of the tertiary allylic -OH at C-9. Indeed, it has been shown that allylic alcohols can be rapidly converted to allylic halides in high yield by treatment of their dimethylsulphoxonium derivatives with halide ion at moderately low temperatures.[135] It was thus attempted to protect the tertiary hydroxyl group in (179) prior to hydrolysis and oxidation, in a manner similar to that achieved with (165). Unfortunately, repeated attempts with anhydrous reagents led only to ∿ 10% conversion to the presumed product, even after heating to 40-45°C for several days, and thus these attempts were abandoned.

The Swern reagent, although it had successfully oxidised both saturated and allylic primary alcohols in the diol (157) (Scheme 44) to the corresponding aldehydes with no discernible chloride formation, might therefore be expected to be an unsuitable reagent for the oxidation of (166) by virtue of the halide counter-ion. Indeed, treatment of (166) with the Swern reagent gave only 5-10% of warburganal (t.l.c. comparison) along with several other products. It was attempted to exchange the chloride counter-ion for the non-nucleophilic tetrafluoroborate anion,

by addition of silver tetrafluoroborate to the Swern reagent. When an excess of this in DMSO was added to the Swern reagent followed by (166), no products were formed. This was rationalised by complete decomposition of the reagent due to the silver-assisted removal of the chloro group present in the reagent. Attempted addition of an exactly equimolar amount of this highly hygroscopic silver salt still led to low yields (∿ 10%) of warbarganal (36). We subsequently learned of a report[57] that a modified Corey-Kim reagent, employing a similar procedure for the removal of the chloride ion, could be used to oxidise (166). However, in our hands this procedure gave equally poor results as the Swern reagent.

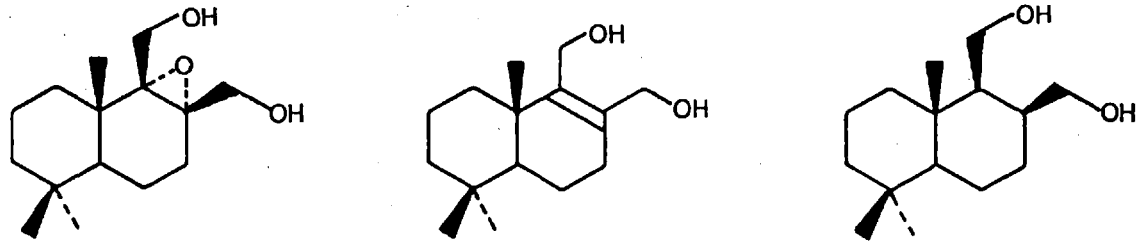
We considered that the best " activator" for use with DMSO in the oxidation of (166) was trifluoroacetic anhydride.[136] The reagent could be prepared and used at low temperature like the oxalyl chloride reagent but the counter-ion was now the poorly nucleophilic trifluoroacetate anion. Addition of (166) to 2 equivalents (6 mole equivalents) of this reagent and then 3 equivalents of triethylamine as before, gave at 45% yield of warburganal after column chromatography (Scheme 48). The product was identical (i.r., n.m.r., m.s.) to the authentic material.[125] The overall yield to warburganal from diene (89) was 20%, and the synthesis was completed after only seven steps. The previously highest yield reported was 16%, by Nakanishi and Tanis,[32] in sixteen stages also from (89). Our synthesis is therefore a significant improvement to the literature methods.[32,53-57, 62]



166 36

Scheme 48. a) DMSO-TFAA, 6 eq. CH_2Cl_2-DMSO, -50°C then Et_3N, 9 eq.

The oxidation of other 1,4-diol systems not containing a labile -OH group, with the Swern reagent, had been previously studied. Unfortunately, very poor results were obtained in contrast to the excellent oxidation of (157). Examples of these substrates are shown in Figure 16.



171 167 193

Figure 16

The oxidation of (171) to the corresponding epoxy dialdehyde and subsequent epoxide rearrangement was of interest as a possible route to warburganal. Addition of crude (171) to the Swern reagent as usual, followed by stirring for 3-4 hours at -50°C and then treatment

with triethylamine gave a complex mixture which was not separated. The crude mass spectrum showed a distinct molecular ion at m/e 250 (acc. mass: $C_{15}H_{22}O_3$) for the desired product and ν_{max} 1725 cm^{-1}. The 250 MHz ^1H n.m.r. spectrum showed 2 major singlets at 9.17 and 9.84 ppm and 2 minor singlets at 10.06 and 9.68 ppm (corresponding to (172) Scheme 39). The product from this reaction was not purified but instead treated with LDA at -78°C and warmed gradually to 0°C to give a complex mixture containing no warburganal by t.l.c. comparison. In a control reaction warburganal itself suffered ∿ 30-40% decomposition under the same reaction conditions as judged by t.l.c.

Similarly, addition of (167) to the Swern reagent followed by triethylamine after 1 hour, again led to a mixture of products which were not separated. The desired product (6), named cavidial, which has been isolated from termites,[14] was undoubtedly present but only in small amounts. Again, the crude mass spectrum showed m/e 234 (acc. mass: $C_{15}H_{22}O_2$). High field n.m.r. analysis showed 2 major singlets at 9.60-9.61 ppm, which are presumed to correspond to the aldehyde protons in (6). This oxidation was not further investigated due to lack of time.

Lastly, it was attempted to oxidise diol (193), obtained by LAH reduction of (153) to the corresponding dialdehyde, in a similar manner as before. Once again only a tiny yield of product was observed by ^1H n.m.r. at 250 MHz. Two small signals at 9.87 (d, J = 1 Hz) and 9.66 ppm (d, J = 3 Hz) were present together with other minor aldehyde resonances. An i.r. stretch at 1712 cm^{-1} was also observed together

with a molecular ion at m/e 236 (acc. mass: $C_{15}H_{24}O_2$). The saturated dialdehyde was required both for biological testing and as a possible precursor to (6) via dehydrogenation.

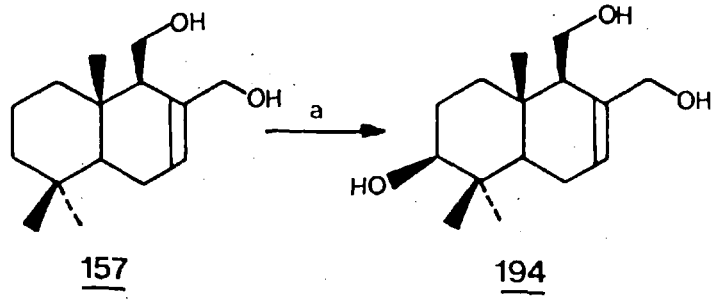
It is notable that each of the substrates indicated in Figure 16 gave very poor results with the Swern oxidant, while diol (157) was cleanly oxidised. The only explanation for these results is that the crowding between the dimethylsulphoxonium groups in the intermediate inhibits both their formation and subsequent elimination to the desired dialdehydes. Any such mutual repulsions are at a minimum in structure (157).

Finally, we became interested in the possibility of achieving a microbial hydroxylation of polygodial to warburganal (36). Oxidative transformations using micro-organisms are well-known though little-exploited processes in synthesis,[137-139] and have produced numerous dramatic stereospecific and enantiospecific oxidations, which could not possibly be achieved with conventional chemical reagents. There has however, been only little speculation, and no real explanation as to why these transformations should occur.

We selected polygodial (29) and drimane diol (157) as substrates for " feeding" experiments. We chose three species of fungi for use in these experiments, namely Cunninghamella elegans, Aspergillus niger, and A. ochraceous. A. niger was used as it is known to be a C-21 hydroxylator of progesterone,[140] which is roughly analogous to the angular hydroxylation required to prepare (36) from (29). C. elegans was selected since steroid literature includes several reports of allylic

hydroxylation occurrring with this fungus.[141] A. ochraceous is known to 11α-hydroxylate steroids[142] and this capability is relatively independent of oxygenated sites already present in the molecule.

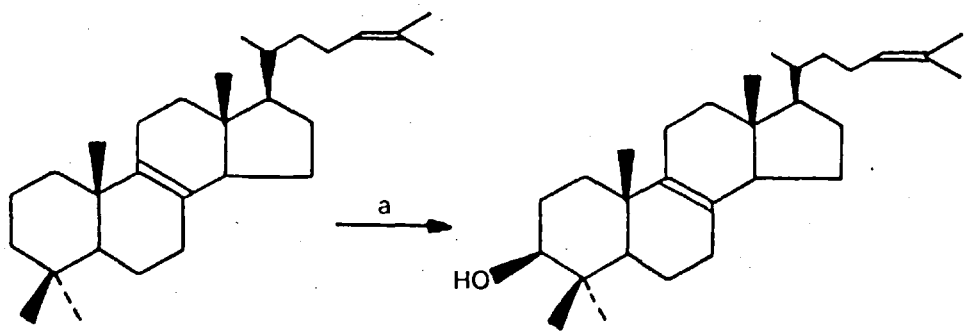
Most gratifyingly, incubation of a small sample (10 mg) of diol (157) with either C. elegans or A. niger for 3 days at 24°C led to the isolation of high yields (70-80%) of an oxidised product, but which unfortunately, was not the desired angularly hydroxylated triol (166). The 250 MHz ^{1}H n.m.r. spectrum was very similar to that of the starting material (157). The AB quartet systems for the C-11 and C-12 methylene hydrogens were unchanged, though slightly shifted. From the integral and multiplicity of the signals at 1.9-2.2 ppm, the C-6 methylene and the C-9 methine hydrogens were intact. The C-7 olefinic proton resonance at 5.80 ppm was also unchanged. The only new features of the spectrum were a signal at 3.28 ppm (1H, dd, J = 4.5, 11 Hz), and three methyl singlets, significantly shifted from their positions in (157). This, therefore, suggested a monohydroxylation of the A-ring had occurred at either C-1 or C-3. Since the methine proton geminal to the newly introduced hydroxyl group at 3.28 ppm showed typical axial-equatorial and axial-axial coupling constants, the configuration of this hydroxyl group was assigned as equatorial. The product was finally assigned as structure (194), i.e., the result of 3β-hydroxylation (Scheme 49).



157 194

Scheme 49. a) C. elegans or A. niger, 3 days, 24°C.

The introduction of the hydroxy group at C-3 was assigned by correlation of the methyl resonances in (194) with those in (157). Of the three resonances at 0.89, 0.87 and 0.75 ppm in (157) the highest field signal at 0.75 ppm could be assigned as the C-10 methyl by comparison to the saturated diol (193) (Figure 16), in which the 1,3-diaxial relation between the C-10 methyl and the axial $-CH_2OH$ group on C-8 causes a shift from 0.75 down to 0.82, with little change in the geminal dimethyl resonances. In the conversion of (157) to (194), one of the lower field, geminal methyl resonances in (157) was shifted down to 1.00 ppm in (194), with little change in the remaining two methyl singlets. These observations can only be rationalised by oxidation at C-3 and not C-1. A similar 3β-hydroxylation has been achieved with Saccharomyces cerevisiae in the conversion of lanosta-8,24-diene (195) to lanosterol (196) (Scheme 50).[144]

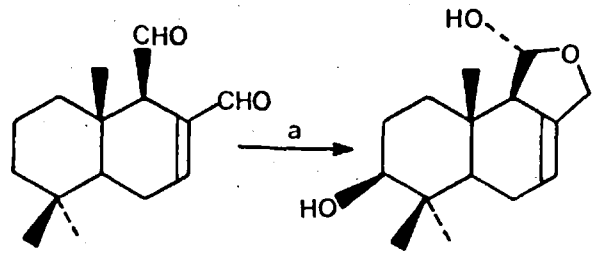


195 196

Scheme 50. a) S. cerevisiae, 30°C, 14 h.

It would therefore appear that 3β-hydroxylated steroids or similar compounds e.g., drimanes can be formed by either a simultaneous oxidative-cyclisation pathway, the cyclisation of epoxyfarnesyl pyrophosphate, or by cyclisation and then subsequent hydroxylation. Vita-Finzi mentions this point in his paper on the isolation of the fungal metabolites uvidins A and B (Figure 3).[50]

When polygodial (29) was added to a culture broth of C. elegans and the mixture swirled for 10 days under the previous conditions an even more impressive 90% yield of product was formed. The product was only weakly u.v. active and was quickly shown not to be (36). The mass spectrum now showed a molecular ion at 18 mass units higher than that of the starting material (29), as opposed to 16 m.u. for triol (194) which suggested net addition of the elements of water. The high field n.m.r. also showed disappearance of the aldehyde signals and appearance of a signal at 3.30 ppm suggesting 3β-hydroxylation as before, and the allylic hydrogens in the B-ring again appeared to be intact. The appearance of a finely coupled AB quartet centred at 5.33 ppm was unambiguously assigned to two C-12 methylene protons adjacent to oxygen by comparison with the values for (17) and (185). The appearance of a sharp doublet at 5.28 ppm (J = 5 Hz) was assigned, by comparison to the data reported[37] for (15) and (25) to a methine proton at C-11, bearing an α-oriented hydroxyl group. The structure was thus assigned as hydroxy lactol (195) (Scheme 51) which was the result of a simultaneous oxidation and reduction by the fungus, the latter process being much less commonly encountered among microbial transformations.



29 195

Scheme 51. a) C. elegans, 10 days, 24°C.

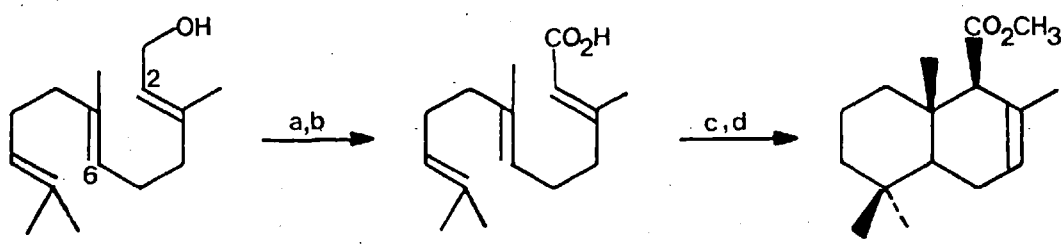
Research is being continued in these laboratories on the use of microorganisms during the synthesis of drimane natural products and related compounds.

B. Biomimetic Approaches to Drimane Synthesis.

The Stork cyclisation of farnesic acid (197) into bicyclofarnesic acid, and subsequent esterification has been used as the starting point for a number of drimane natural product syntheses (see Introduction). We felt that we could also exploit this approach for the preparation of warburganal analogues, with modified C-9 substituents.

The bicyclic ester (198) (Scheme 52) was prepared from the commercially available farnesol (196) by the literature procedure,[2] in 40% overall yield. The inital oxidation to farnesal was accomplished with PCC since the reported use of manganese dioxide[143] was found to be inconvenient on a large scale (0.1 mole).

Commercially available farnesol is a mixture of 2:1 6E, 2E (trans:trans-) and 6E, 2Z (trans:cis-) isomers, which can be readily separated on a reasonable scale by H.P.L.C.[144] The 6E, 2E isomer leads to (198)



196 197 198

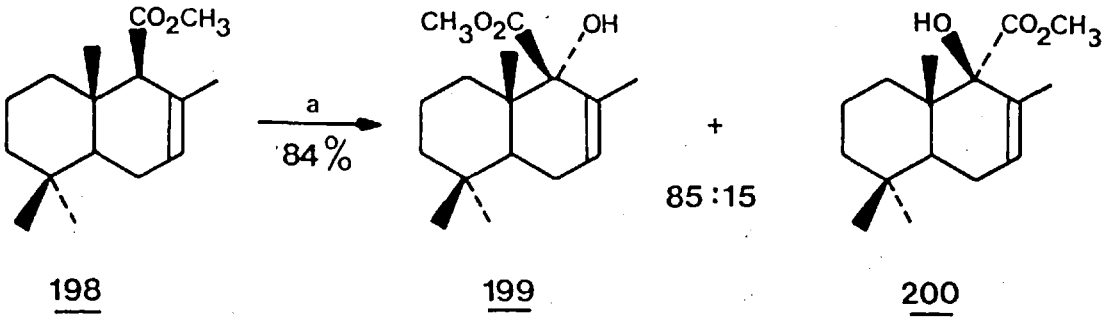
Scheme 52. a) PCC, CH_2Cl_2; b) Ag_2O, EtOH, H_2O; c) $BF_3.Et_2O$, C_6H_6, 35°C, 24 h; d) CH_2N_2, MeOH, 0°C.

on cyclisation of the corresponding acid and subsequent esterification with about 5% of the C-9 epimeric ester (205) (Scheme 55) being produced. The 6E, 2Z isomer produces only (205) on similar cyclisation. The farnesol isomers can be separated prior to the reaction sequence or simultaneously converted through to a mixture of (198) and (205) which may also be separated, although with greater difficulty. Purification was found to be necessary only for (198) and (205), i.e., after the final stage.

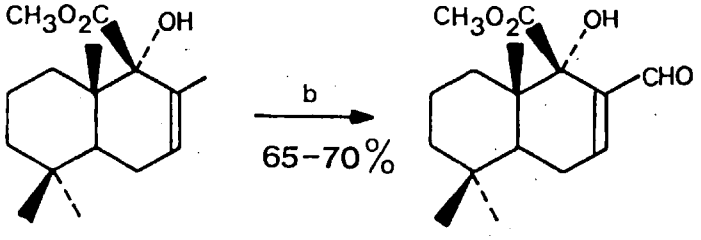
We felt that an enolate hydroxylation could be achieved with (198) in a manner similar to that with diester (94) (Scheme 39), to provide hydroxy ester (199). A regiospecific allylic oxidation of the less-hindered 9-methyl group with selenium dioxide should then furnish directly the desired hydroxy ester aldehyde (201). These expectations were indeed realised, and the results are shown in Scheme 53.

Compound (201) contains the intramolecularly H-bonded enal Michael centre present in warburganal (36) which is thought to be responsible for the potent biological activities of (36),[12] but the C-9 aldehyde

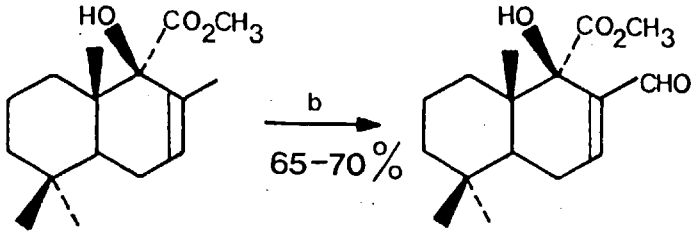
group is now replaced for the larger, less polar ester group. The C-9 aldehyde in (36) was suggested to be both H-bonded and act as a nucleophile acceptor,[12] and so by modification of the C-9 functional group it is conceivable that alternative, active compounds could be generated.



198 199 200



201



202

Scheme 53. a) KDA-LiO^{t}Bu, THF, -55°C, then MoOPH, -55°C ⟶ RT; b) SeO_2, dioxan, reflux, 4 h.

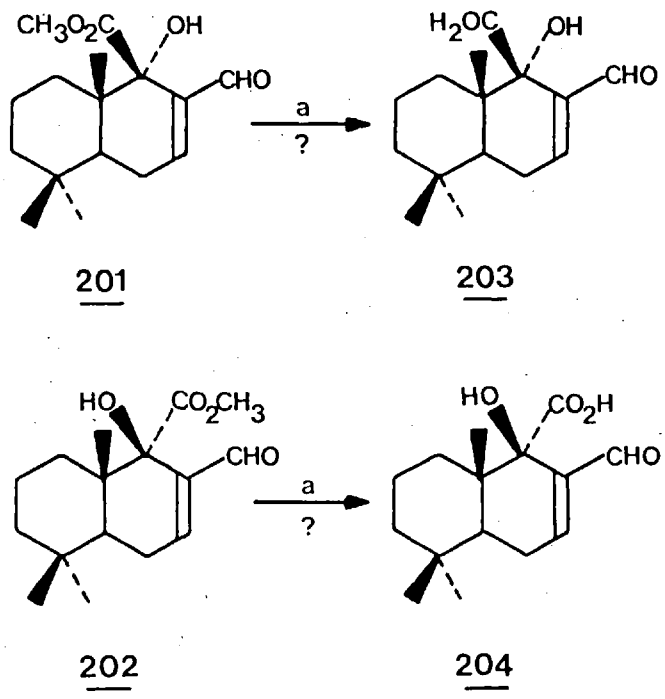
It was found that treatment of (198) with LDA at -78°C failed to deprotonate the 9-position in (198) as indicated by a virtually colourless reaction mixture and lack of oxidised products following the addition of MoOPH; instead a good recovery of (198) was obtained. Deprotonation indeed only occurred at -20 to -10°C with very dark reaction mixtures then being produced. Thus treatment of (198) with LDA at 0°C followed by cooling to -78°C, addition of MoOPH and warming to room temperature gave a 53% yield of an approximately 1:1 ratio of products (199) and (200) after chromatography, with substantial amounts of side products evident from t.l.c. Structures (199) and (200) were characterised by the usual methods. The stereochemistry of the 9-position was initially presumed from thin layer (the axial hydroxy compound (199) being the more polar) and spectral properties. Thus, the bridgehead proton at C-5 (dd, J = 5, 12 Hz) shows a larger downfield shift in (200) at 2.08 ppm compared to that in (199) at 1.75 ppm, by virtue of the greater deshielding effect of the 1,3-situated ester group over that of the hydroxy group.

More rigourous proof of these assignments were made with aid of n.O.e. experiments (see pp. 172 and 173). Thus, irradiation at the C-10 methyl group in (199) at 1.00 ppm gave a small (∿ 1%) enhancement of the ester methyl singlet and no effect on the -O<u>H</u> proton: irradiation at the C-10 methyl in (200) at 1.04 ppm showed no effect upon the ester methyl but a small (∿ 2%) (negative) enhancement of the angular hydroxyl proton. Irradiation at the other tertiary methyl positions caused the expected moderate (5-10%) enhancements of the C-5 and C-6 hydrogens which allowed their assignments as indicated.

Having established the structures of (199) and (200), there was a need to rationalise the formation of this mixture of hydroxylated products, especially in view of the previous stereospecific hydroxylation of (94) (Scheme 39). The specificity of the product from the oxidation of (94) or aldehyde (210) (see later), is accounted for by kinetic control of the approach of the bulky MoOPH reagent to an sp^2-like enolate in these substrates. This is analogous to the kinetic protonation of the enolate of (91) (Scheme 12) which produced (96) rather than the more thermodynamically stable C-9 epimer.[63] In the oxidation of (198), no such kinetic control was observed, and the products are thus accounted for by the generation of an equilibrating mixture of two less stabilised, sp^3-like carbanions and their subsequent oxidation. In order to reduce the amount of equilibration of an anion formed at C-9 which can occur, and hence obtain the maximum amount of product (199) which has the desired warburganal stereochemistry, we argued that the deprotonation should be conducted at as low a temperature as possible prior to addition of the oxidant. The reaction of MoOPH with these enolates occurs at approximately $-50^{\circ}C$, and so enolate formation should be conducted at or below this temperature. In accord with this, use of the more strongly basic KDA,[145] indeed allowed deprotonation at $-50^{\circ}C$ or below and subsequent treatment with MoOPH provided predominantly the desired hydroxy isomer (199) in an improved yield of 71% (Scheme 53).

Attempted hydrolysis of esters (201) and (202) to the corresponding 9-COOH derivatives (203) and (204), which also may be expected to be active compounds, using the mild method for hydrolysis of hindered esters

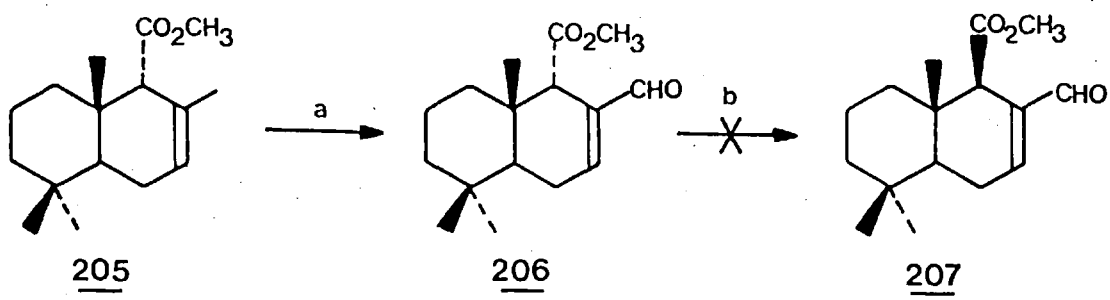
at ambient temperatures reported by Gassman[146] led to mixtures of products (Scheme 54).



Scheme 54. a) KO^{t}Bu, Et_2O, H_2O, RT.

Ester (202) had reacted completely within a few minutes at room temperature; 50% conversion of (201) had occurred after 14 hours at room temperature. Although the crude mass spectra indicated the presence of the product acids (m/e 266, acc. mass: $C_{15}H_{22}O_4$), and the n.m.r. spectra showed signals at 9.3-9.5 ppm, the mixtures were not further characterised or other methods for the hydrolysis of (201) to (203) investigated, due to lack of time.

It was attempted to achieve an epimerisation at C-9 of ester aldehyde (206) (Scheme55) obtained in higher yield (90%) than that reported by Ohsuka by oxidation of methyl-9-epidrimenate (205), by a kinetic protonation similar to that achieve with the C-9 epimer of (96) (Scheme 12) by Lallemand.[63]



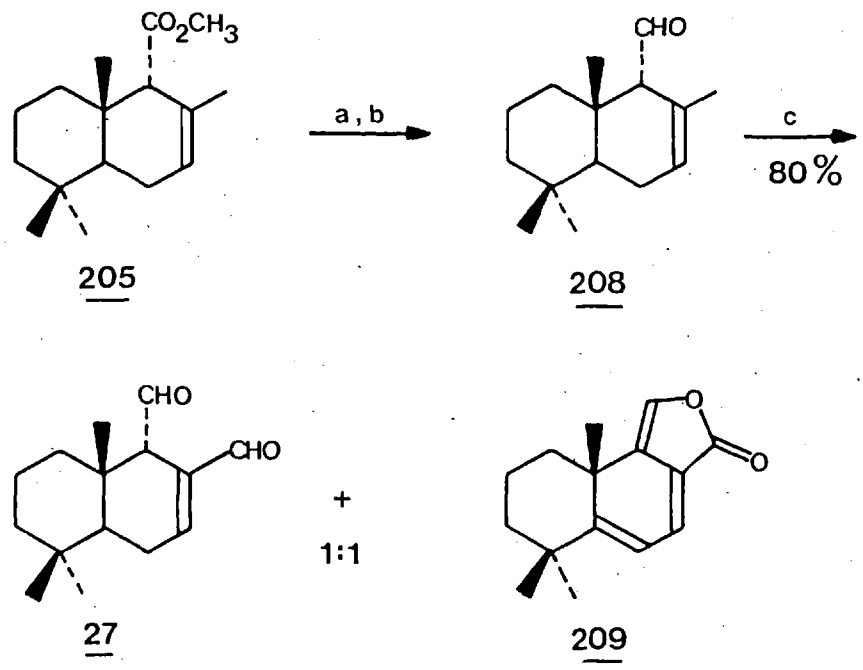
205 206 207

Scheme 55. a) SeO_2, dioxan, reflux, 3 hrs;
b) LDA, THF, -78°C, then 1 N H_2SO_4 in THF.

Unfortunately, treatment of (206) with LDA at -78°C followed by addition of 1 N H_2SO_4 in THF to the resulting orange-red enolate provided only starting material back. This result was readily deduced by the reappearance of the sharp doublet at 3.09 ppm (d, J = 2 Hz) for the 9β-hydrogen in (206) which couples only to the 6α-hydrogen at 2.19 ppm (dddd, J = 2, 2, 11, 20 Hz); the 9α-hydrogen in the C-9 epimerised compound (207) would appear as a broader signal at 60 MHz by coupling with the 6α-,6β- and 7-hydrogens. The biological evaluation of (207) would have been of interest.

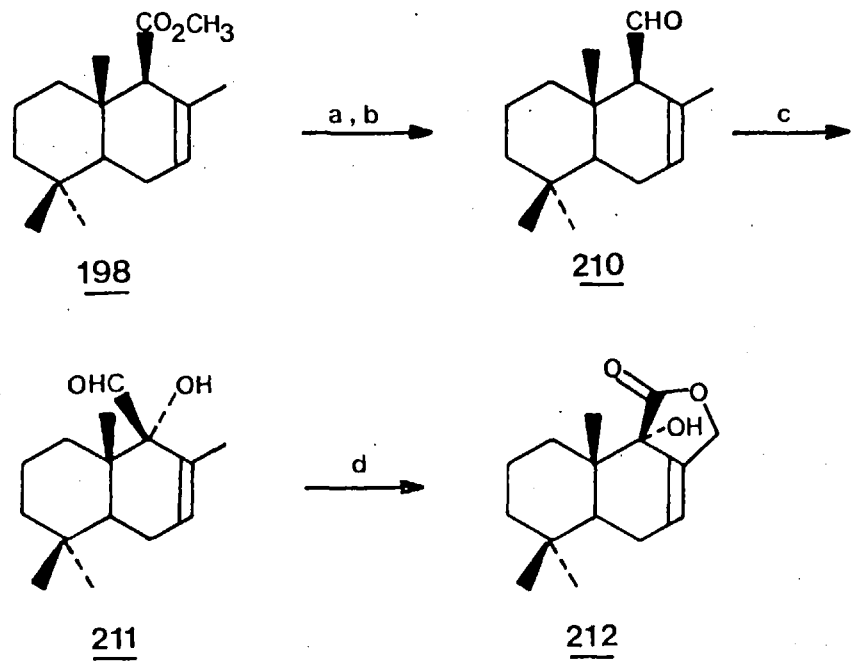
It should be noted that selenium dioxide oxidation of either (198) or (210) (see later) gave only complex mixtures. A 9α-oriented group would seem to be required for useful oxidation at C-12, presumably due to its hindering effect on the vulnerable C-9 allylic carbon-hydrogen bond. However, when the aldehyde (208), derived from (205) by the same procedure as that used to obtain (210) from (198) (Scheme 57), was treated with selenium dioxide, an 80% yield of two products in the ratio (1:1) were obtained and were assigned as isotadeonal (27) and the novel unsaturated lactone (209) (Scheme 56). The overall yield from (205) to isotadeonal was 32% which thus compares favourably with other synthetic routes.[54,56] The structure of (209) was clearly evident from its n.m.r. spectrum. Thus, three tertiary methyl signals at 1.24, 1.34 and 1.55 indicated 5,6-unsaturation [cf. compounds (152), (154) and (155)]. The only other signals below 2.2 ppm were a singlet at 6.29 ppm and an AB quartet at 7.68 ppm (J = 2 Hz) which were assigned to the C-11 proton and the C-6 and C-7 protons respectively. Compound (27) was not converted into (209) by similar treatment with selenium dioxide, which was thought to arise via competing oxidation at C-6, and then elimination to provide a Δ 5,7-dienyl intermediate which would encourage tautomerism of the C-11 CHO to the enol form, for cyclisation onto a subsequently formed aldehyde at C-12.

At an earlier stage we had thought that the enolate hydroxylation of an aldehyde at C-11 derived from ester (198), followed by regiospecific oxidation with selenium dioxide as before could provide warburganal



Scheme 56. a) LAH, Et_2O; b) PCC, CH_2Cl_2; c) SeO_2, dioxan, reflux, 2 h.

(Scheme 57). Thus reduction of (198) provided drimenol (18) which was oxidised to the desired aldehyde (210) in 80% overall yield from (198). Deprotonation of (210) at -78°C with LDA followed by oxidation with MoOPH provided hydroxy aldehyde (211) in 65% yield. Oxidation of (211) with SeO_2 gave a 60% yield of a product which was not warburganal. The 250 MHz n.m.r. spectrum of this compound showed a further coupled AB quartet centred at 4.37 ppm, an olefinic multiplet at 5.73 ppm and no aldehyde signals. The appearance of ν_{max} 3500 and 1740 cm^{-1} in the i.r. spectrum led to the assignment of the product as the novel 9-hydroxy drimenin (212) (Scheme 57).



Scheme 57. a) LAH, Et_2O; b) PCC, CH_2Cl_2; c) LDA, THF, $-78^{o}C$, then MoOPH $-78^{o}C \longrightarrow$ RT; d) SeO_2, dioxan, reflux, 1 h.

The unexpected formation of (212) is rationalised by a facile addition of the selenium-oxygen bond of the intermediate selenide, produced by initial " ene" reaction and [2,3] sigmatropic rearrangement as usual, to the C-11 aldehyde before collapse to a carbonyl group with loss of elemental selenium could occur. Subsequent breakdown of the cyclised intermediate yields the lactone.

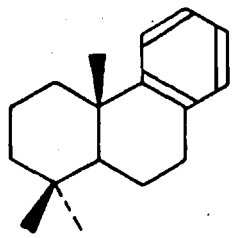
Attempted direct oxidation of (211) to warburganal with benzeneseleninic anhydride in chlorobenzene caused decomposition with no major products observed (t.l.c.). Allylic carbon-hydrogen bonds can be oxidised directly to ketones with NBS in wet THF, via hydrolysis of the

geminal dibromide.[158] However, treatment of (211) under these conditions produced a mixture of products containing no warburganal (t.l.c., 250 MHz n.m.r.). The less direct route involving oxidation of a monobromide at C-12 with DMSO-$AgBF_4$ and subsequent elimination with triethylamine[122] was not attempted.

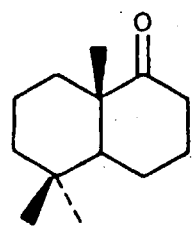
It was finally attempted to protect the C-11 aldehyde prior to oxidation at C-12, to avoid the possibility of lactonisation. However, (206) stubbornly resisted ketal formation using propane-1,3-diol, even in refluxing toluene with PTSA as catalyst. Treatment of (206) with trimethyl orthoformate in methanol with a trace of PTSA gave a mixture of products, presumably due to participation by the neighbouring hydroxy group. The possible use of (206) as a precursor to warburganal was not further investigated.

C. Miscellaneous Routes for Drimane Synthesis.

In addition to the approaches previously described we had proposed the use of other suitable precursors for drimane synthesis. The known bicyclic compounds (213) and (214) are ideal candidates (Figure 17).



213

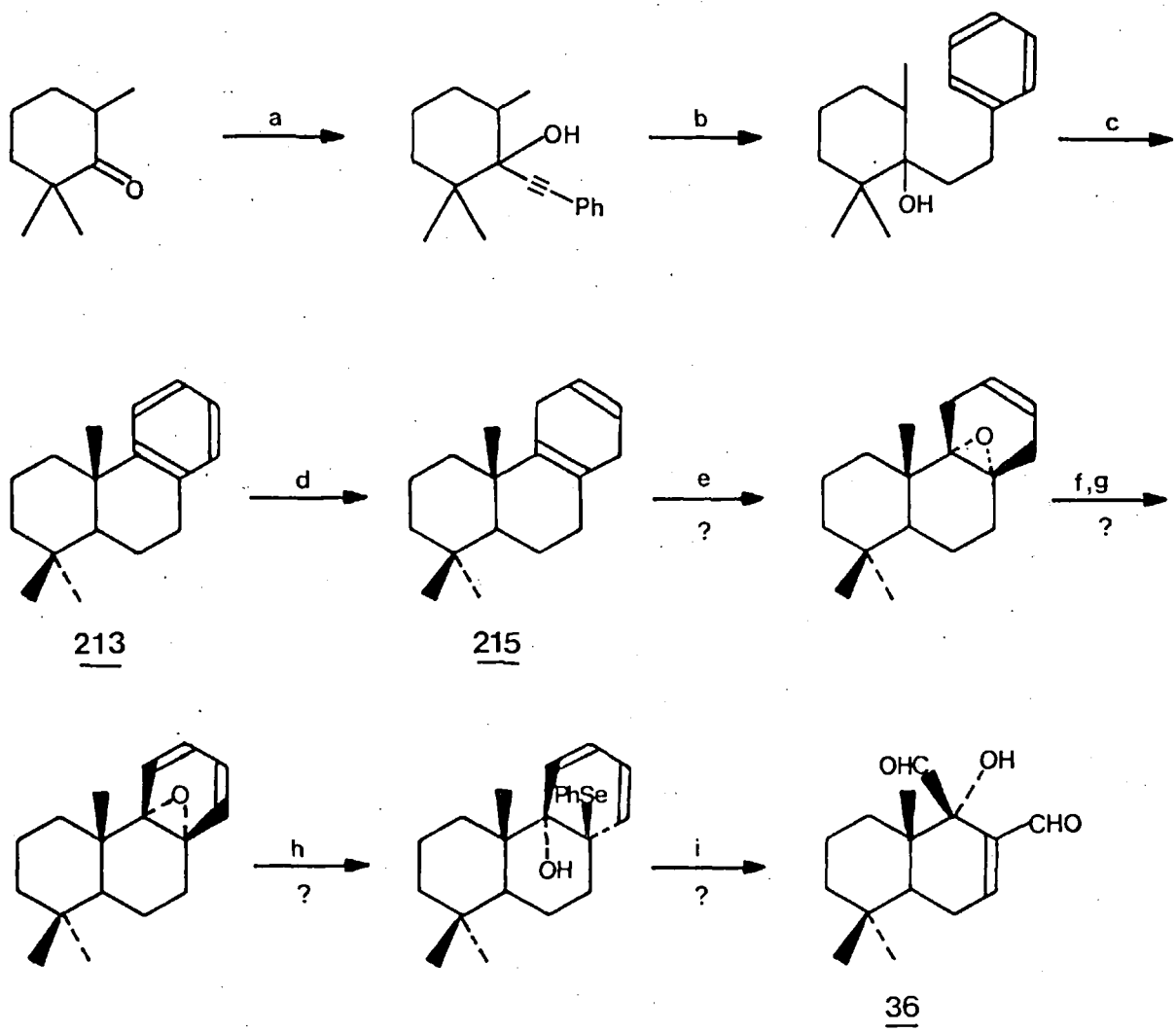


214

Figure 17

The synthesis of (213) was easily and rapidly achieved from 2,6,6-trimethylcyclohexanone on a large scale (75 g) in a greatly improved overall yield of 85% compared to 37% originally reported by Barltrop and Rogers,[147] by the initial use of sodium phenyl acetylide rather than the potassium derivative, and polyphosphoric acid for the final dehydration-cyclisation (Scheme 58). An example of the proposed strategy is outlined in the scheme (58), and involves a stereospecific epoxidation and a subsequent ozonolysis to produce the desired functionality. The Birch reduction of (213) using lithium in ethylamine[148] indeed showed the desired diene (215) to be produced (m.s., n.m.r.). However, the synthesis was discontinued at this early stage in favour of other more attractive approaches to the target compounds. In retrospect the epoxidation of (215) with, for example, m-CPBA is not expected to be greated than ∿ 50% stereospecific, by comparison to the oxidation of diol (167) and furan (38) (see later) with ^{t}BuOOH-VO(acac)$_2$ or singlet oxygen. Also, the remainder of the route shown contains some rather speculative transformations, but could nonetheless still accomodate changes of the synthetic manipulations.

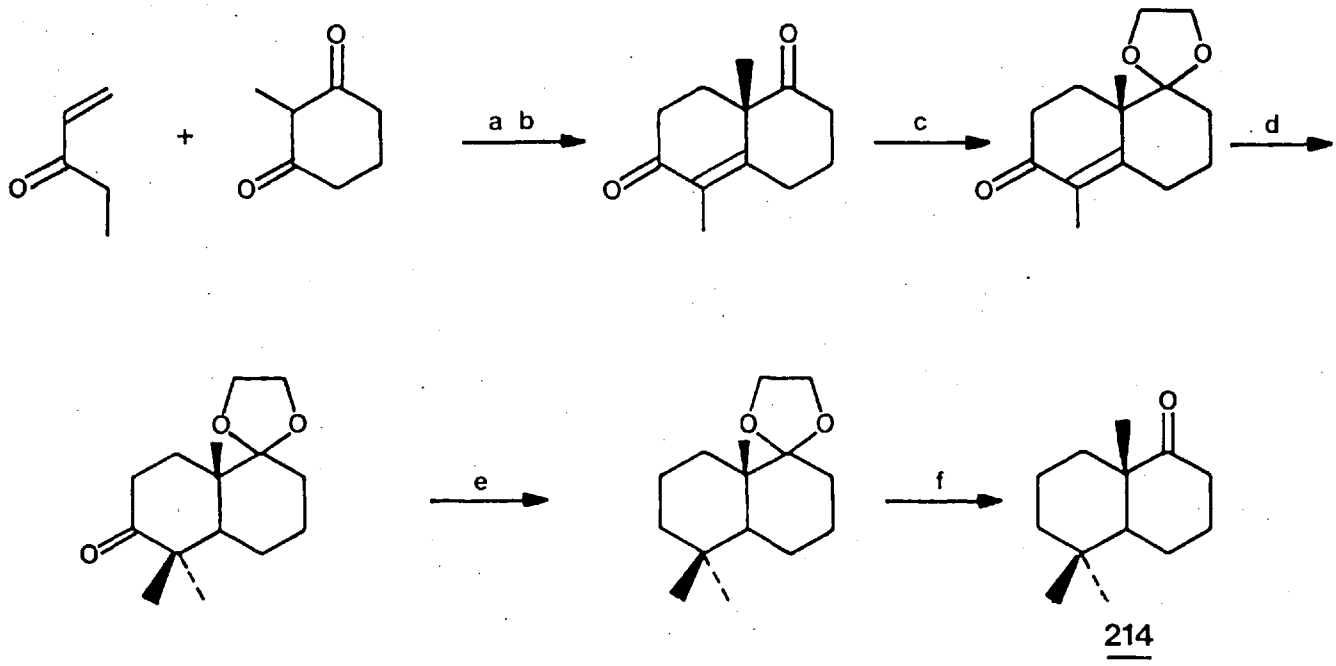
The second intermediate studied was the decalone (214), which was prepared as shown in Scheme 59.[149] The utility of (214) as a precursor to drimane natural products is illustrated by two recent syntheses of warburganal (Schemes 18 and 19).[54,55] We had conceived possible ways of converting (214) into warburganal (36) for example, by the conjugate addition of 1,3-dithiane to a homologated aldehyde [from a Shapiro reaction on (214)] and stereospecific oxidation of the resulting enolate. However, these approaches were felt to offer insufficient improvement over the existing routes from (214) (Scheme 60).



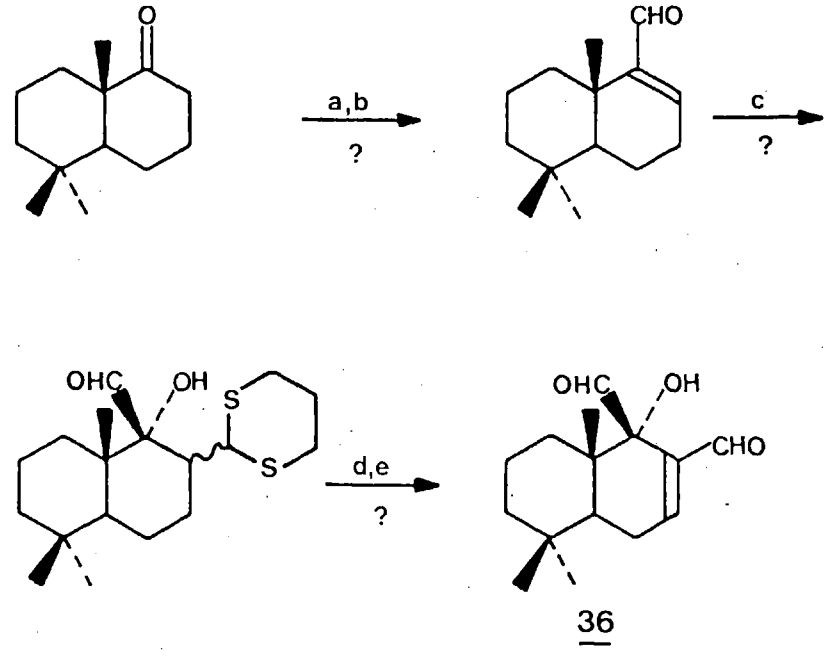
Scheme 58. a) NaC≡CPh, liq. NH_3; b) H_2, 5% Pd/C, EtOAc; c) PPA, 100°C, 1 h; d) Li, $EtNH_2$, tBuOH; e) m-CPBA;) Br_2;) LiCl, Li_2CO_3, DMF;) PhSeNa;) O_3.

Instead, we turned our attention to the synthesis of the tricyclic furan (38) (Figure 3) which we felt could act as a 1,4-dialdehyde synthon, and thus as a possible precursor to warburganal (36) or cavidial (6) (Figure 3).

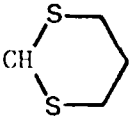
The reported conversion of ketones into 3- and 3,4-substituted furans via their n-butylthiomethylene derivatives[150] appeared to offer a direct route from (214) to the desired furan (38) named euryfuran,



Scheme 59. a) KOH, MeOH, reflux, 4 h; b) pyrrolidine, C_6H_6, reflux, 20 h; c) $HO(CH_2)_2OH$, PTSA, C_6H_6, reflux, 12 h; d) Li, NH_3, then MeI; e) $NH_2NH_2.H_2O$, $NH_2NH_2.2HCl$, trigol, 140°C, 1.5 h, then 200°C for 2.5 h; f) 1 M HCl, AcOH, THF (1:2:3), RT, 2 h.



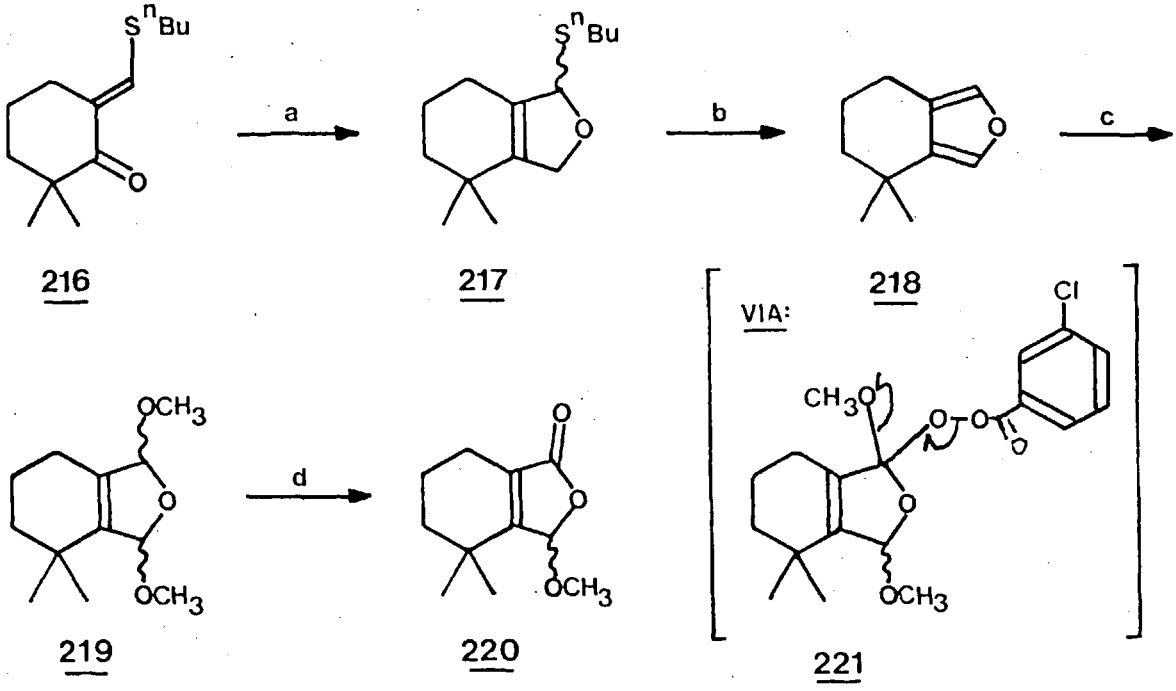
Scheme 60. a) $TrSO_2NHNH_2$; b) nBuLi, TMEDA, then DMF; c) LiCH HMPA, THF, then MoOPH; d) $AgNO_3$; e) [O].



which has recently been isolated[60] from the nudibranchs Cadlina luteomarginata, C. limbaughorum, Hypselodoris porterae and H. californiensis and also from an unidentified sponge of the genus Euryspongia. This compound along with the related oxidation products from Doriopsilla albopunctata (40) and (41) (Figure 3) are the first examples of drimane sesquiterpenes isolated from sources outside the plant kingdom.

As a model study it was decided to investigate the conversion of 2,2-dimethylcyclohexanone[151] into the corresponding furan (218) and its subsequent oxidation. Thus, treatment of the n-thiobutylmethylene derivative (216), obtained in a standard way,[150] with dimethylsulphonium methylide at -78°C, gave clean conversion to the dihydrofuran (217) (via rearrangement of the intermediate epoxide) in 88% yield (Scheme 61). Brief treatment of (217) with mercuric sulphate in DME caused elimination of n-butanethiol to provide the furan (218) in 90% yield.

Furan (218) was unstable at room temperature after removal of the solvent. However, it could be readily oxidised in DME solution at 0°C, by direct treatment with a solution of bromine in methanol[152] to provide the more stable dimethoxy derivatives (219) in 90% yield. Assuming this process could be successfully applied to the real system (214), we were then interested by the possibility of epoxidation of the double bond corresponding to that in (219) with a reagent such as m-CPBA to provide an 8,9-β-epoxide. Rearrangement of this epoxide to the allylic alcohol and subsequent hydrolysis of the bis-acetal could provide warburganal. However, when (219) was treated with m-CPBA at 0°C, a high yield (∿ 90%) of product was obtained which was not the expected epoxide but the unsaturated lactone (220), amply supported by i.r., n.m.r., and m.s.



Scheme 61. a) $CH_3\overset{+}{S}\overset{-}{C}H_2$, DME, -78°C, 1 h; b) $HgSO_4$, DME, RT, 10 min; c) Br_2, MeOH, 0°C, 5 min; d) m-CPBA, CH_2Cl_2, 0°C, 1 h.

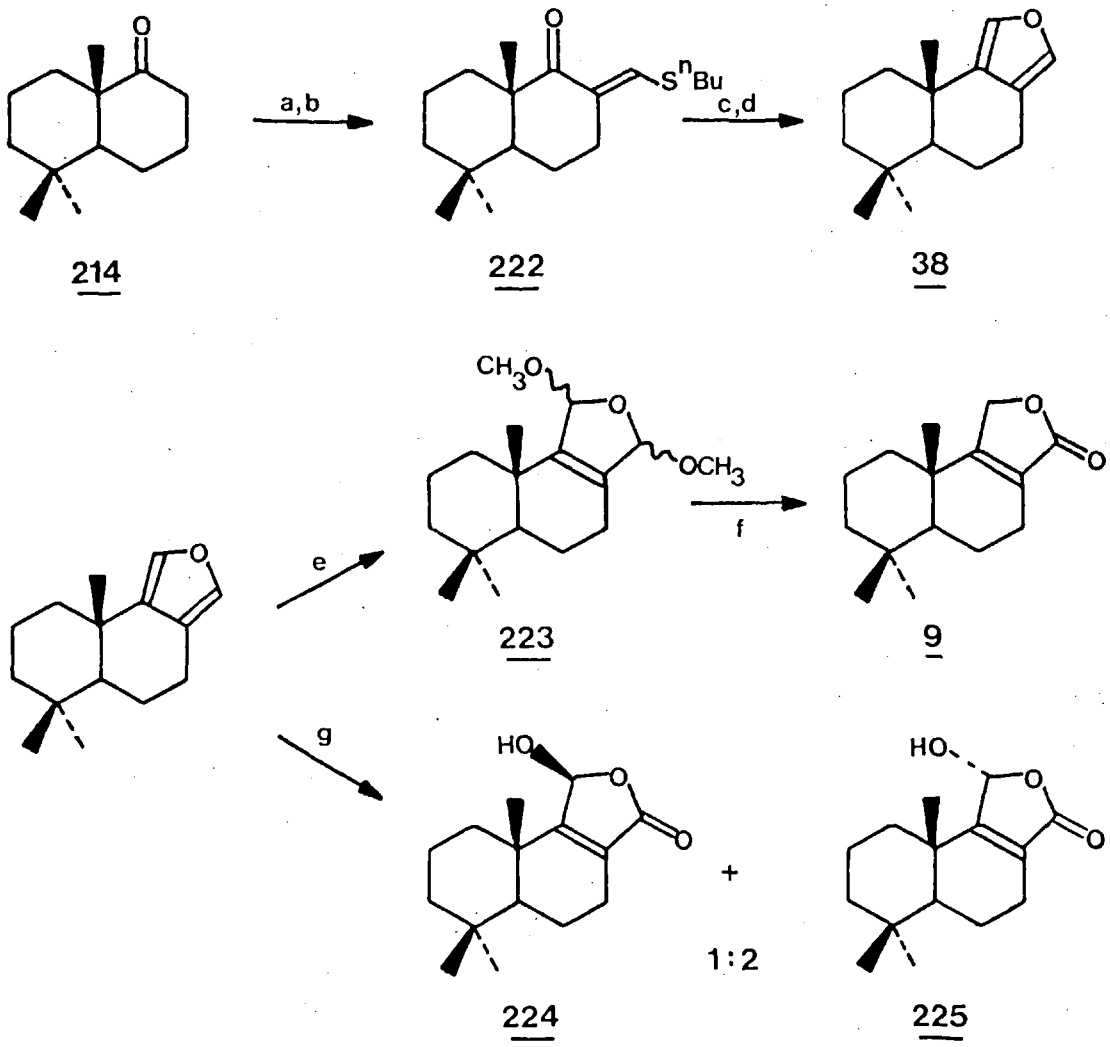
The lactone formation is thought to proceed via a radical mechanism involving breakdown of an intermediate such as (221) (Scheme 61). The regiospecificity of the reaction is evident from the reduction of the number of methoxy proton singlets from 8 at 3.3-3.4 ppm in (219), indicating a mixture of all possible isomers, to only 2 at 3.43, 3.47 ppm in (220) and the formation of the lactone is assumed to occur furthest away from the dimethyl groups on steric grounds.

Treatment of (219) with either hydrochloric acid in THF or PTSA in aqueous acetonitrile failed to provide a dialdehyde. Treatment with lithium chloride in anhydrous DMF at 80°C again led to (220) as the only observable product.

Undiscouraged by these results we proceeded to subject the ketone (214) to this series of transformations. Conversion of (214) to the

known[54,55,110] α-formyl derivative in 90% yield was followed by condensation with n-butanethiol to provide n-butylthiomethylene ketone (222) in 85% overall yield as shown in Scheme 62. Treatment with excess (5 equiv.) dimethylsulphonium methylide at -78°C for 10 min provided the dihydrofuran corresponding to (217) which on standing (35°C, 12 h) or brief treatment with mercuric sulphate gave euryfuran (38) in 70% yield from (124) after filtration through silica. The product had an identical n.m.r. spectrum at 250 MHz with that of the natural material.[60]

With this furan to hand, oxidation with bromine in methanol provided dimethoxy compounds (223) again as a mixture of all possible isomers in 92% yield. Hydrolysis of (223) with hydrochloric acid did not provided the expected dialdehyde cavidial (6) but led instead to a lactone (9) in 75% yield, shown to be identical to confertifolin by comparison (i.r., n.m.r., m.s.) to the authentic material.[153] High field ^{1}H n.m.r. methods revealed the presence of ∿ 10% of isodrimenin (22) (Figure 3), the other regioisomer. The mechanism and regioselectivity of this reaction is rationalised by a facile 1,4-elimination of methanol from (223) via removal of the more accessible proton on C-12 and the more sterically congested methoxy group on C-11 to give initially 12-methoxy euryfuran, which is subsequently hydrolysed to (9). This result contrasts markedly with the hydrolysis of the Δ7,8-dimethoxy compounds (Scheme 13) to the corresponding dialdehyde achieved by White.[49] Obviously, the position of the double bond, and hence the relative geometries of the C-8, C-12 and C-9, C-12 bonds in these compounds is the governing factor in this reaction. By comparison, confertifolin was also prepared by oxidation of diol (167) with barium manganate as for diol (157). This reagent produced a 95% yield of product, which



214 222 38

223 9

224 225

Scheme 62. a) HCOOEt, C_6H_6, RT, 12 h; b) nBuSH, C_6H_6, PTSA, reflux, 2 h; c) $CH_3S^+CH_2^-$, DME, -78°C, 10 min; d) 35°C, 12 h or $HgSO_4$, 1 equiv., DME, RT, 10 min; e) Br_2, MeOH, 0°C, 30 min; f) 10% HCl, acetone, RT, 30 min; g) O_2, hν, eosin, 25°C, 4 h, tBuOH:2,6-lutidine (2:1).

was a mixture of ∿ 6:1 (9): isodrimenin (22), by ^{1}H n.m.r. at 250 MHz. The overall yield of confertifolin in this case was 27% from (89). Alternative ways of achieving the deprotection of (223) to a dialdehyde were not further investigated.

Treatment of (223) with m-CPBA is expected to provide not an epoxide but a lactone, corresponding to (220) obtained from the model system,

i.e., the methyl ether of valdiviolide (35). We anticipated that valdiviolide could be obtained directly from euryfuran (38) via a singlet oxygen oxidation, by analogy to Corey's work on the synthesis of camptothecin.[154] Thus, it was expected that attack of singlet oxygen should occur predominantly from the underside of (38) to give an α-endoperoxide, which should then collapse by removal of the less hindered proton on C-12 to regiospecifically provide (35) with predominantly the 11α-configuration. These expectations were indeed fulfilled, with a 90% yield of product obtained as a 2:1 mixture of 11α:11β-hydroxy isomers (224) and (225) (Scheme 62). The product mixture showed two signals at 5.84 and 6.09 ppm (integration 1:2) assigned as the 11α- and 11β-methine protons on (224) and (225) respectively; the authentic material[152] showed the signal at 6.09 ppm only, and is therefore assigned as the 11α-hydroxy compound (225). The syntheses of the three drimane natural products euryfuran, confertifolin and valdiviolide were thus achieved in 60%, 41%, and 54%overall yields respectively from decalone (214).

EXPERIMENTAL

General Techniques.

Anhydrous solvents were obtained by distillation as follows: ether, benzene, DME, triethylamine, pyridine, DMSO (red-press), DMF (red-press.), all from powdered calcium hydride; toluene from sodium; THF from sodium benzophenone ketyl; methanol and ethanol from the respective magnesium alkoxides. Other reagents were purified by standard procedures. Petrol refers to 60-80 petroleum ether.

Unless otherwise stated, all reactions were magnetically stirred under a nitrogen atmosphere. The reaction vessel for use with air/moisture sensitive reagents, e.g., LDA, Grignard reagents, etc., was flame dried and immediately evacuated and flushed with dry argon several times *via* a three way tap. Other glassware used was oven dried (150°C, 12 h) and cooled in a vacuum desiccator (P_2O_5) immediately prior to use.

" Usual" treatment or work up refers to dilution of the reaction with water, extraction with ether, washing with saturated sodium chloride solution and drying over anhydrous sodium sulphate. Removal of solvents refers to rotary evaporation under reduced pressure or vacuum below 50°C. Column chromatography was performed on silica gel 60 H (< 40 μm) slurry packed, and eluted at a linear flow rate of approximately 2.5 cm/min. under low pressure (3-25 p.s.i.), with the solvents mentioned. Usually, gradient elution through the polarity required for Rf ∿ 0.2 on t.l.c. was employed. Sample application was achieved either in the smallest volume of petrol or less commonly by preadsorption onto a small quantity

of M.F.C. silica (acetone). P.l.c. and t.l.c. was performed on Merck Kieselgel $60F_{254}$ (0.2 mm coated aluminium sheets).

G.l.c. analysis [of, for example, compounds (89) or (94)] was carried out on a Perkin-Elmer Sigma 3 machine using a 4 m 10% Carbowax 20 M on Chromosorb WA 80-100 mesh, or 2 m 10% silicone OV-1 on Chromosorb W AW DMCS 80-100 mesh columns, at 150° and 200°C isothermal column temperatures respectively.

Melting points were determined on a Kofler Hot-stage apparatus and are uncorrected. U.v. spectra were recorded on a Pye-Unicam SP 1800 machine, in 95% ethanol solution. I.r. spectra were obtained on a Perkin-Elmer 298 spectrometer as neat films (oils, liquids, low-melting solids) or chloroform solutions (solids). Routine mass spectra were recorded on an A.E.I. M.S. 9 or V.G. Micromass 7070 instrument at 70 eV. ^{1}H n.m.r. spectra were recorded on a Varian EM 360A or Bruker WH 250 FT machine with 16k transforms, in deuterochloroform solutions with TMS as internal reference. In n.m.r. descriptions, s = singlet, d = doublet, t = triplet, br = broad, m = multiplet, dm = doublet of multiplets, etc. The abbreviation " t" is used only for coupling by magnetically equivalent protons, otherwise " dd" is used. AB systems are described as pairs of doublets, with the chemical shift of each reported as the arithmetic mean of the respective line positions. Observed coupling constants are quoted throughout to the nearest 0.5 Hz. Assignments were often made with aid of decoupling experiments on typical compounds.

Microanalyses and high resolution mass measurements were carried out within the Chemistry Department of Imperial College.

Preparation of 1-ethynyl-2,6,6-trimethylcyclohexanol (124).

Purified acetylene was bubbled into a stirred suspension of sodamide (from 9.5 g sodium) in liquid ammonia (500 ml). After 1 h, 2,6,6-trimethylcyclohexanone (52 g, 0.37 mole) in ether (50 ml) was added over 30 min to the resulting grey suspension with mechanical stirring. After a further 2 h, ammonium chloride (25 g) and subsequently ether (200 ml) was added, and the ammonia evaporated with a warm water bath. The mixture was filtered and the ethereal solution dried and evaporated. Distillation gave (124) (59.3 g, 98%), b.p. 50°C, 0.5 torr; ν_{max} 3450, 3290 and 2050 cm^{-1}; δ (60 MHz) 0.95, 1.0, 1.05 (9H, 3s), 1.3-1.7 (7H, m), 1.9 (1H, s, OH), and 2.33 (1H, s); m/e 166 (M^+) 151, 140, 125, 123, 110, 95 and 92. (Found: C, 79.27; H, 10.96. $C_{11}H_{18}O$ requires C, 79.46; H, 10.91%).

Preparation of 1-trimethylsilylethynyl-2,6,6-trimethylcyclohexene (126).

(124) (20 g, 0.12 mole) was refluxed in xylene (200 ml) in the presence of copper sulphate trihydrate (2.2 g) for 6 h using a Dean-Stark trap. A fractionating column was attached, and 180 ml of xylene was distilled under nitrogen at atmospheric pressure. The residue was decanted and dissolved in dry ether (60 ml) and cooled to -78°C. Methyllithium (100 ml, 1.24 M in ether) was added and the mixture stirred for 1 h. Trimethylsilylchloride (16.5 ml, 0.13 mole) was added and the mixture stirred for a further 2 h at -78°, before being allowed to warm to room temperature. Addition of water (80 ml) with ice cooling was followed by extraction with petrol. Drying and removal of the solvents followed by distillation gave (126) (19.38 g, 70%) b.p. 70°C, 0.5 torr; ν_{max} 2960,

2930, 2900, 2860, 2830, 2130, 1620 and 1450 cm^{-1}; δ (60 MHz) 0.2 (9H, s) 1.05 (6H, s), 1.80 (3H, s) and 1.0-2.0 (6H, m); m/e 220 (M^+) 205, 177, 164 and 149. (Found: C, 76.28; H, 11.21. $C_{14}H_{24}Si$ requires C, 76.28; H, 10.97%).

Preparation of 1-(trans-trimethylsilylvinyl)-2,6,6-trimethylcyclohexene (117).

(126) (3 g, 11.26 mmol) was treated with DIBAL (17 ml, 1 M in hexane, 1.5 equiv.) at -78°C under argon. The mixture was warmed to room temperature, stirred for 60 h, and water (0.4 ml, 2 equiv.) added. Filtration was followed by drying and evaporation of the solvents to give (117) (3.0 g, 98%) b.p. 64°C ∿ 1 torr; ν_{max} 2960, 2930, 2860, 2130, 1595, 1460, and 1250 cm^{-1}; δ (60 MHz) 0.1 (9H, s), 0.9 (6H, s), 1.5 (3H, s), 0.9-2.0 (6H, m), and 5.4, 6.25 (2H, 2d, J 19Hz; 19 Hz); m/e 222 (M^+), 207, 148, 133, 124, 99, and 73. (Found: C, 75.54; H, 11.96. $C_{14}H_{26}Si$ requires C, 75.59; H, 11.78%).

Preparation of 1-(cis-trimethylsilylvinyl)-2,6,6-trimethylcyclohexene (118).

(126) (3 g, 11.26 mmol) was heated to 55°-60°C under argon and treated with DIBAL (380 mg, 1.35 equiv.) in THF (0.215 ml, 1.35 eq.) in one portion and stirred for 12 h. Addition of water (0.4 ml, 2 equiv.), filtration and evaporation gave a clear liquid (480 mg) which was chromatographed on silica H (20 g) eluting with petrol to give (126) (5%) and (118) (2.70 g, 94%); ν_{max} 2960, 2920, 2860, 2130 and 1600 cm^{-1}; δ (60 MHz) 0.05 (9H, s), 0.95 (6H, s), 1.65 (3H, s), 0.9-2.0 (6H, m) and 5.6, 6.6 (2H, 2d, J 16 Hz; 16 Hz). (Found: C, 75.54; H, 11.96. $C_{14}H_{26}Si$ requires C, 75.59; H, 11.78%).

Preparation of 1-(trans-bromovinyl)-2,6,6-trimethylcyclohexene (120)

A solution of (117) (1 g, 4.5 mmol) in methylene chloride (25 ml) at -78°C was treated with a solution of bromine in methylene chloride (0.75 M, 6 ml, 1 equiv.) over 10 min. After 2.5 h at -78°C, the reaction mixture was quickly transferred to a cooled saturated solution of potassium fluoride in dimethylsulphoxide (40 ml) with rapid stirring. After 4 h at room temperature, the reaction was diluted with water and extracted with petrol. Drying and removal of solvent gave (120) (0.89 g, 87%); ν_{max} 1600, 1460, 990, 870, 840 and 740 cm^{-1}; δ (60 MHz) 1.03 (6H, s), 1.6 (3H, s), 0.9-2.0 (6H, m), and 5.9, 6.5 (2H, 2d, J 15 Hz; 15 Hz); m/e 288.0517 (M^+), 213, 148, 135, 109, ($C_{14}H_{26}Br$ requires 228.0514).

Preparation of 1-(trans-acetoxyvinyl)-2,6,6-trimethylcyclohexene (119).

Acetate (135) (0.25 g, 4.8 mmol) was warmed in benzene (5 ml) in the presence of a catalytic amount of silverhexafluoroantimonate for 1-2 min to produce (136) (100%); ν_{max} 3060, 1920, and 1750 cm^{-1}; δ (60 MHz) 0.97 (3H, d, J 6 Hz), 1.07, 1.17 (6H, 2s), 1.0-1.7 (7H, m), 2.06 (3H, s), and 7.3 (1H, d, J 2.5 Hz); m/e 208 (M^+), 193, 166, 151 and 133. (Found: C, 75.04; H, 9.96. $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68%).

Further reflux for 8 h followed by filtration and evaporation of the solvent and filtration through Florisil gave (119) (0.17 g, 68%), ν_{max} 1760, 1690, 1655, 1450, 1365, and 1220 cm^{-1}; δ (60 MHz) 1.05 (6H, s), 1.55 (3H, s), 0.9-1.8 (6H, m), and 5.70, 6.85 (2H, 2d, J 13 Hz; 13 Hz); m/e 209.1467 (M^+), 193, 166, 148 and 133 ($C_{13}H_{20}O_2$ requires 208.1463).

Preparation of 1-methoxyethynyl-2,6,6-trimethylcyclohexanol (137) and (138).

To a solution of methoxyacetylene (0.875 g, 15.63 mmol) in ether (10 ml) at -78°C under argon was added dropwise n-butyllithium (106 ml, 1.4 M in hexane, 15 mmol). After 15 min the white suspension was warmed to -20°C and 2,6,6-trimethylcyclohexanone (1.5 g, 7 mmol) in ether (5 ml) was added over 5 min. After a further 30 min, the reaction was warmed to 0°C for 1 h and worked up as usual to provide a pale yellow oil which was chromatographed on silica H (45 g, ether:hexane, 3:93) to give (138) (550 mg, 28%), ν_{max} 3620, 3500, 2260, 1450 and 1240 cm^{-1}; δ (60 MHz) 0.92 (3H, d, J 6Hz), 0.95, 1.03 (6H, 2s), 1.57 (1H, s, OH), 0.9-1.9 (7H, m), and 3.85 (3H, s); m/e 196.1461 (M^+), 181, 153, 139, 125 and 97, ($C_{12}H_{20}O_2$ requires 196.1463), and (137) (1.42 g, 72%), ν_{max} 3620, 3500, 2255, 1450, and 1230 cm^{-1}; δ (60 MHz) 0.98 (3H, d, J 6 Hz), 1.03 (6H, s), 0.9-1.9 (7H, m), and 3.82 (3H, s); m/e 196.1461 (M^+), 181, 153, 139, 125 and 97 ($C_{12}H_{20}O_2$ requires 196.1463).

Preparation of 1-methoxyethynyl-2,6,6-trimethylcyclohexene (140).

(137) (3.5 g, 17.8 mmol) in benzene (100 ml) together with copper sulphate trihydrate were refluxed for 3 h. Filtration and evaporation of the solvent gave an oil which was chromatographed (silica H, 10 g, petrol then ether-petrol) to give (140) (475 mg, 15%), ν_{max} 2255, 1455, 1315, 1250, 1110, and 1010 cm^{-1}; δ (60 MHz) 1.03 (6H, s), 1.72 (3H, s), 0.9-2.0 (6H, m), and 3.82 (3H, s); m/e 178.1360 (M^+), 163, and 151 ($C_{12}H_{18}O$ requires 178.1358); and 139 as a mixture of isomers (1.85 g, 54%), ν_{max} 1720, 1625, 1430, and 1265 cm^{-1}; δ (60 MHz), 1.15 (3H, s), 1.15 (3H, d, J 4Hz), 1.28 (3H, s), 0.9-1.9 (7H, m), 3.60 (3H, s), and 5.60 (1H, s); m/e 196.1461 (M^+), 181 and 169 ($C_{12}H_{20}O_2$ requires 190.1463) and (0.75 g, 21%), ν_{max} 1730, 1640, 1625, and 1200 cm^{-1}; δ (60 MHz) 1.05

(3H, d, J 6 Hz), 1.18 (6H, s), 0.9-1.9 (7H, m), 3.60 (3H, s), and 5.35 (1H, s); m/e 196.1461 (M^+), 181 and 169 ($C_{12}H_{20}O_2$ requires 190.1463).

Preparation of 1-(cis-methoxyvinyl)-2,6,6-trimethylcyclohexene (121).

A solution of (140) (0.25 g, 1.4 mmol) in hexane (5 ml) at -78°C under argon was treated with DIBAL (35 mg, 1.4 mmol, 1 equiv.) in THF (1 equiv.) and the solution allowed to reach room temperature. Stirring for a further 3 d was followed by addition of water (2 equiv.) and filtration through Florisil to provide (121) (175 mg, 69%), ν_{max} 1630, 1450, 1250, 1055 and 1010 cm^{-1}; δ (60 MHz) 1.10 (6H, s), 1.5 (3H, s), and 4.55, 7.10 (2H, 2d, 18 Hz; 18 Hz); m/e 180.1511 (M^+), 165, and 153 ($C_{12}H_{20}O$ requires 180.1514).

Preparation of 1-methylsulphonyl-allenyl-2-chloro-2,6,6-trimethyl-cyclohexane (145).

(124) (1 g, 6 mmol) together with methane sulphonyl chloride (0.8 ml, 10 mmol) in pyridine (4 ml) were heated to 55°C for 12 h. Addition to hydrochloric acid (10%, 100 ml), followed by washing with saturated sodium bicarbonate solution and usual work up gave an oil (800 mg) which was chromatographed (silica H 10 g, petrol, then ether-petrol) to provide colourless prisms of (145) m.p. 60-62°C (250 mg, 20%), ν_{max} 1940, 1460, 1380, 1305, 1150 and 1125 cm^{-1}; δ (60 MHz) 1.0, 1.10, 1.12, 1.15, 1.17, 1.24 (9H, 6s), 1.0-2.4 (6H, m), 4.33 (3H, s), and 6.05 (1H, m); m/e 262.0795 (M^+), 247, 206, 185, 183, 149, 148 and 133 ($C_{12}H_{19}SO_2Cl$ requires 262.0793). (Found: C, 54.51; H, 7.35; S, 12:28. $C_{12}H_{19}SO_2Cl$ requires C, 54.85; H, 7.29; S, 12.20%).

Preparation of ß-homocyclocitral (146).

(124) (10 g, 60 mmol) together with the polymeric organosilyl-vanadate catalyst (8 g),[105] were refluxed in toluene (25 ml) under argon for 3 h. Hexane (100 ml) was added to the cooled reaction mixture, and the precipitate filtered using Celite. The solvent was removed and the product chromatographed (silica H 250 g, ether:hexane, 1:99) to provide (146) (8.0 g, 80%) b.p. 41°-42°C, 0.08 torr, ν_{max} 2700, 1720, 1420, 1400 and 1390 cm^{-1}; δ (60 MHz) 0.96 (6H, s), 1.55 (3H, s), 1.4-1.8 (4H, m), 2.0 (2H, m), 3.0 (2H, m), and 9.42 (1H, t, J 2.5 Hz); m/e 166 (M^+), 151, 137, 133, 123, 109. (Found: C, 79.20; H, 11.21. $C_{11}H_{18}O$ requires C, 79.46; H, 10.91%).

Alternative Preparation of 1-(trans-trimethylsilylvinyl)-2,6,6-trimethylcyclohexene (117).

To (149) (100 mg, 0.45 mmol) in ether (15 ml) at -78°C under argon was added oil free potassium hydride (2-3 equiv.) and the mixture stirred for 4 h. A solution of trifluoroacetic anhydride (5 equiv.), pyridine (2 equiv.) in ether (5 ml) was then added dropwise at -78°C. The mixture was allowed to warm to -30°C, stirred for 6 h, warmed to 0°C and added to ice-water (100 ml). Extraction with petrol followed by drying and removal of solvent gave (117) (0.78 g, 84%) (> 95% pure by g.l.c.) identical to the previous sample.

Preparation of 1-vinyl-2,6,6-trimethylcyclohexene (89).

ß-cyclocitral:[103] Commercial citral (228 g) in ether (200 ml) was added dropwise to aniline (140 g, redistilled from calcium hydride under reduced

pressure) in ether (100 ml) and the mixture stirred for 1 h at room temperature. The ethereal layer was decanted, and added over 30 min to 95% sulphuric acid (1.5Kg) under argon, at 0°C internal temperature (cooling bath -20°C). After stirring for a further 30 min, the mixture was poured onto ice (3 Kg), saturated with sodium chloride and worked up as usual. The crude product was dissolved in methanol (100 ml) at 0°C and treated with a solution of potassium hydroxide (50 g) in methanol (600 ml) for 10 min. The mixture was washed with saturated sodium chloride and extracted with ether as usual to provide a dark red oil. Distillation gave β-cyclocitral (110 g, 48%) b.p. 73°-80°C, 5 torr, contaminated with small (< 5%) amounts of the corresponding acid (by aerial oxidation), and α-cyclocitral.

Alcohol (149): β-cyclocitral (52 g, 0.34 mole) in ether (50 ml) was added to a solution of trimethylsilylmethylmagnesium chloride [1.05 equiv., from magnesium (8.6 g) and chloromethyltrimethylsilane (52 ml, 0.36 mole)] in ether (100 ml), and the mixture stirred for a further 1 h, at room temperature, and then transferred to ice-saturated ammonium chloride solution, and worked up as usual. Drying and evaporation of the solvent gave (149) (80.8 g, 98.5%) purified (for microanalysis) by low temperature (-78°C) chromatography (silica H - Celite 4:1, ether hexane, 2:98), ν_{max} 3630, 3500, 1460, 1380, 1245 and 1030 cm^{-1}; δ (60 MHz) 0.95, 1.10, (6H, 2s), 1.20 (1H, s, OH), 1.1-1.8 (8H, m), 1.85 (3H, s), and 4.50 (1H, m); m/e 240, 223, 208, 190, 143 and 133. (Found: C, 69.88; H, 11.98. $C_{14}H_{28}SiO$ requires C, 69.93; H, 11.74%).

The crude alcohol (149) (80 g) in THF (200 ml) was added all at once to a vigorously stirred solution of p-TSA (3 equiv.) and sulphuric acid (1 equiv.) in THF (1 ℓ). After a further 5 min the mixture was transferred to saturated sodium bicarbonate solution and extracted with petrol. Drying and removal of the solvent followed by distillation gave (89) (48 g, 96%) b.p. 54°C, 5 torr, ν_{max} 3040, 1620, 1390, 1370, 990 and 910 cm^{-1}; δ (250 MHz) 1.0 (6H, s), 1.4-1.7 (4H, m), 1.69 (3H, m), 1.98 (2H, m), 4.96 (1H, dd, J 3, 18 Hz), 5.22 (1H, dd, J 3, 12 Hz), and 6.21 (1H, ddm, J 12, 18 Hz); m/e 150, 135, 119 and 107. (Found: C, 87.87; H, 12.18. $C_{11}H_{18}$ requires C, 87.93; H, 12.07%).

Preparation of Dimethyl-3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (152).

Diene (89) (35 g, 0.23 mole, distilled) together with freshly distilled DMAD (44 g, 1.4 equiv.) were heated together under argon in a sealed vessel at 110°C for 22 h. The reaction mixture was then cooled, dissolved in hexane (80 ml) and filtered through silica (250 g) using ether:hexane (2:3), to provide an almost colourless oil. Seeding (if necessary) and trituration with a little methanol followed by cooling (< -50°C) and filtering provided (152) (56.3 g) of white crystals, m.p. 53°-54°C. Chromatography of the mother liquors provided another 7.7 g of (152) (total yield 94%), ν_{max} 1720, 1660, 1620 and 1250 cm^{-1}; δ (250 MHz) 1.14 (3H, s), 1.19 (3H, s), 1.43 (3H, s), 1.2-1.9 (6H, m), 2.78 (1H, dd, J 3, 23 Hz), 3.16 (1H, dd, J 6, 23 Hz), 3.73 (3H, s), 4.01 (3H, s), and 5.70 (1H, dd, J 3, 6 Hz); m/e 292 (M^+), 261 and 245. (Found: C, 69.66; H, 8.37. $C_{17}H_{24}O_4$ requires C, 69.84; H, 8.27%).

Hydrogenation of Dimethyl-3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (152).

Adduct (152) (1 g, 3.42 mmol) was dissolved in methanol (200 ml), 10% Pd/C (150 mg) added, and the mixture was stirred vigorously under an atmosphere of hydrogen. After 1 h, 1.2 equiv. of hydrogen had been absorbed and further uptake was very slow. The mixture was then filtered and the solvent removed to provide 1.0 g (100%) of product mixture which was chromatographed on silica H (100 g, ether-hexane mixtures) to give (94) (507 mg, 50%) m.p. 82.5°-83°C, ν_{max} 2890, 1730, 1725, 1650, 1460, 1280 and 1245 cm^{-1}; δ (250 MHz) 0.89 (3H, s), 0.92 (3H, s), 0.95 (3H, s), 1.24 (1H, dd, J 5, 12 Hz), 1.0-1.7 (5H, m), 1.85 (1H, dm, J 13 Hz), 2.10 (1H, dddd, J 3, 4, 12, 20 Hz), 2.29 (1H, dddd, J 2.5, 5, 6, 20 Hz), 3.20 (1H, ddd, J 2, 2.5, 4 Hz), 3.67 (3H, s), 3.70 (3H, s), and 7.06 (1H, ddd, J 2,3, 6 Hz); m/e 294 (M^+), 279, 262, 234. (Found: C, 69.19; H, 8.82. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%). [Crystals of (94) are triclinic, a = 7.052(1), b = 10.468(2), c = 11.513(2)Å, α = 74.94(1), β = 81.84(1), γ = 86.90(2)°, U = 812Å^3, space group $P\bar{1}$, Z = 2, D_c = 1.21 g cm^{-3}. DAta were measured using monochromatised Cu-K_α radiation (graphite monochromator) on a Nicolet R3m diffractometer. A total of 1953 independent reflections were measured ($\theta \leq 50°$) using the omega scan measuring routine and of these 106 had $F_o < 3\sigma(F_o)$ and were classed as unobserved. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The hydrogen atoms, with the exception of the five methyl groups which were refined as rigid bodies, were placed at calculated positions and allowed to ride on their parent carbons.

Refinement was terminated at a final R = 0.050. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system]; and (153) (270 mg, 27%) m.p. 68°-70°C, ν_{max} 1735, 1465, 1435, 1210, 1160, and 910 cm^{-1}; δ (250 MHz) 0.82 (3H, s), 0.85 (3H, s), 1.05 (3H, s), 1.0-1.7 (9H, m), 2.23 (1H, ddd, J 2.5, 5, 13 Hz), 2.33 (1H, m), 2.34 (1H, d, J 5 Hz), 3.04 (1H, ddd, J 2, 5, 5 Hz), 3.63 (3H, s) and 3.65 (3H, s); m/e 296 (M^+), 281, 264, 249, 208 and 1.45. (Found: C, 69.07; H, 9.20. $C_{17}H_{28}O_4$ requires C, 68.89; H, 9.52%) and (154) (127 mg, 12.6%) m.p. 78°-79°C, ν_{max} 1735, 1430, 1200 and 910 cm^{-1}; δ (250 MHz) 1.10 (6H, s), 1.32 (3H, s), 1.2-1.9 (6H, m), 2.31 (1H, ddd, J 5, 7, 18 Hz), 2.69 (1H, ddd, J 3, 12, 18 Hz), 2.74 (1H, d, J 4 Hz), 3.07 (1H, ddd, J, 4, 7, 12 Hz), 3.62 (1H, d, J 4 Hz), 3.07 (1H, ddd, J 4, 7, 12 Hz), 3.62 (3H, s), 3.69 (3H, s,) and 5.59 (1H, dd, J 3, 5 Hz); m/e 294 (M^+), 281, 279, 262, 235, 219 and 175. (Found: C, 69.20; H, 8.83. $C_{17}H_{26}O_4$ requires, C, 69.36; H, 8.90%).

Product from (153) on standing: m.p. 73-74°C, ν_{max} 1745, 1650, 1435, 1200, 1170, 1020; δ (250 MHz), 1.08 (3H, s), 1.14 (3H, s), 1.27 (3H, s), 1.0-1.7 (6H, m). 2.01 (1H, dm, J 13 Hz), 2.30 (1H, ddd, J 4.5, 7.5, 17 Hz), 2.64 (1H, d, J 5 Hz), 2.77 (1H, ddd, J 3.5, 5, 17 Hz), 3.12 (1H, ddd, J 5,5,7.5 Hz), 3.65 (3H, s), 3.68 (3H, s), and 5.57 (1H, dd, J 3.5, 4.5 Hz); m/e 294.1825 (M^+), 279, 234 and 105 ($C_{17}H_{26}O_4$ requires 294.1831).

Preparation of Dimethyl-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-naphthalene-1,2-dicarboxylate (94).

Adduct (152) (55 g, 0.19 mole) was dissolved in methanol (20 ℓ) containing sulphuric acid (98%, 20 ml). 10% Pd/C (5 g) was added and hydrogen passed into the solution (via sintered frit) with efficient mechanical stirring, at room temperature. After 30 min, g.l.c. indicated optimum yield of the desired product. Sodium bicarbonate (2 equiv.) was added and the mixture stirred for 5 min before filtering and removal of the solvent. The residue was taken up in ether (500 ml) and treated as usual to give a pale yellow oil. Seeding and trituration with a little methanol caused crystallisation of the desired product. The mixture was then cooled (< -60^{o}C) and the resulting sludge filtered rapidly, washing through with small volumes of cold methanol, to provide (94) (29.2 g) identical to the previous sample. Chromatography of the mother liquors provided another 7.3 g (combined yield = 66%).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[1β,4aα,8aβ]-naphthalene-1,2-dimethanol (157).

A solution of diester (94) (2.05 g, 7 mmol) in ether (25 ml) was added dropwise to LAH (0.27 g, 4 equiv.), in ether (100 ml) at 0^{o}C under argon. After a further 15 min at 0^{o}C, the mixture was transferred to ice - 5% sulphuric acid (250 ml). The ethereal layer was washed with saturated sodium bicarbonate solution and worked up as usual to provide a colourless oil (1.7 g). Seeding and trituration with cold methanol

(< -60°C) followed by rapid filtration gave (157) (1.2 g, 80%) as white crystals, m.p. 73°-74°C. Chromatography (silica H, ethyl acetate petrol mixtures) gave another 0.29 g of (157) (combined yield = 90%), ν_{max} 3620, 3420, 1665, 1460, 1440, 1370, 1040 and 990 cm^{-1}; δ (250 MHz, after D_2O exchange) 0.75 (3H, s), 0.87 (3H, s), 0.89 (3H, s), 1.1-1.7 (7H, m), 1.8-2.2 (3H, m), 3.65 (1H, dd, J 7.5, 10.5 Hz), 3.89 (1H, dd, J 2, 10.5 Hz), 3.94 (1H, d, J 12 Hz), 4.23 (1H, d, J 12 Hz) and 5.79 (1H, m); m/e 238 (M^+), 220, 207, 205 and 190. (Found: C, 75.76; H, 11.13. $C_{15}H_{26}O_2$ requires C, 75.58; H, 10.99%).

Preparation of 1,3,5,5a,6,7,8,9,9a,9b-decahydro-6,6,9a-trimethyl-[5aα,9aβ,9bβ]-naphtho[1,2-c]furan-3(1H)-ol (158).

Diol (157) (100 mg, 0.42 mmol) was stirred with barium manganate (160 mg, 1.5 equiv.) in methylene chloride (4 ml) for 4 h. Filtration through Celite gave (158) (91 mg, 92%) after removal of the solvent, m.p. 95°-98°C, further purification could be performed by silica gel chromatography if desired. ν_{max} 3580, 3390, 2930, 2860, 2713, 1670 and 1630 cm^{-1}; δ (250 MHz) hydroxy aldehyde form: 0.72 (3H, s), 0.91 (3H, s), 0.93 (3H, s), 1.0-1.7 (7H, m), 1.9-2.5 (3H, m), 3.46 (1H, ddd, J 2.5, 7, 11.5 Hz), 3.79 (1H, ddd, J 11.5, 11.5, 12 Hz), 4.70 (1H, dd, OH, J 2.5, 12 Hz), 7.04 (1H, ddd, J 2, 3, 5 Hz) and 9.38 (1H, s); m/e 236.1770 (M^+), 221, 218, 206, 133, 124 and 109 ($C_{15}H_{24}O_2$ requires 236.1776).

Preparation of 5,5a,6,7,8,9,9a,9b-octahydro-6,6,9a-trimethyl-[5aα,9aβ,9bβ]-naphtho[1,2-c]furan-3(1H)-one (Cinnamolide) (8).

Diol (157) (100 mg, 0.42 mmol) was stirred with barium manganate (1.06 g, 10 equiv.) in methylene chloride (4 ml) for 24 hours at room temperature. Filtration through Celite and removal ofsolvent gave crystals of (8) (92 mg, 94%) m.p. 78-80°C (hexane) ν_{max} 2940, 2900, 2860, 2840, 1760, 1705 and 1860 cm^{-1}; δ (250 MHz) 0.82 (3H, s), 0.93 (3H, s), 0.95 (3H, s), 1.40 (1H, dd, J 5.5, 12 Hz), 1.10-1.70 (6H, m), 2.12 (1H, dddd, J 3.5, 5, 12, 19 Hz), 2.42 (1H, dddd, J 4, 4, 5.5,19 Hz) 2.82 (1H, ddddd, J 3.5, 4, 5, 9.5, 9.5 Hz), 4.04 (1H, dd, J 9.5, 9.5 Hz), 4.38 (1H, dd, J 9.5, 9.5 Hz), and 6.88 (1H, ddd, J 3.5, 3.5, 4 Hz); m/e 234 (M^+), 219, 201, 191, 124 and 109. (Found: C, 76.94; H, 9.51. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[1β,4aα,8aβ]-naphthalene-1-methanol-2-t-butyldimethylsiloxymethyl (181).

To a solution of diol (157) (0.22 g, 0.92 mmol) in DMF (25 ml) at 0°C under argon was added t-butyldimethylsilyl chloride (166 mg, 1.1 equiv.) and imidazole (125 mg, 2 equiv.) and the resulting mixture stirred for 24 h at room temperature. Dilution with water (100 ml) and usual work up gave an oil (0.35 g) which was chromatographed (silica H 10 g, ether-hexane mixtures) to provide (181) (0.327 g, 100%)[32] as an oil, ν_{max} 3350, 2900, 1660, 1465, 1255 and 1045 cm^{-1}; δ (60 MHz) 0.1 (6H, s), 0.89 (18H, s), 0.9-2.4 (10H, m), 3.7 (2H, m), 4.15 (2H, m) and 5.75 (1H, m); m/e 352 (M^+), 321, 313, 277, 203, 191, 189 and 147.

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[1β,4aα,8aβ]-naphthalene-1-carboxaldehyde-2-t-butyldimethylsiloxymethyl.

(181) (0.32 g, 0.9 mmol) in methylene chloride (5 ml) was added to the Swern reagent (2 equiv.) in methylene chloride (10 ml) at -50°C under argon. After 30 min, triethylamine (0.37 ml, 3 equiv.) was added and the mixture worked up as usual to provide the aldehyde (0.285 g, 90%),[32] ν_{max} 3920, 2860, 1720, 1670 and 1255 cm^{-1}; δ (60 MHz) 0.1 (6H, s), 0.95 (15H, s), 1.1 (3H, s), 1.1-2.0 (7H, m), 2.1 (1H, m), 2.8 (1H, m), 4.1 (2H, m), 5.9 (1H, m), and 9.7 (1H, d, J 5 Hz).

Preparation of 1,3,5,5a,6,7,8,9,9a,9b-decahydro-6,6,9a-trimethyl-[5aα,9aβ,9bβ]-naphtho[1,2-c]furan-1(3H)-ol (159).

To the above (0.28 g, 0.8 mmol) in THF (5 ml) at 0°C under argon was added tetra-n-butylammonium fluoride (1.6 ml, 2 equiv., 1 M in THF), and stirred for 2 h at room temperature. Usual work up provided an oil which was filtered through silica to provide (159) (0.15 g, 80%)[32] ν_{max} 3620, 3450, 2930, 2870, 1700, 1460, and 1260 cm^{-1}; δ (60 MHz) 0.85 (6H, s), 0.9 (3H, s), 1.05-2.2 (9H, m), 4.05 (1H, m), 4.4 (1H, m), 5.15 (1H, m), and 5.45 (1H, m).

Preparation of 5,5a,6,7,8,9,9a,9b-octahydro-6,6,9a-trimethyl-[5aα,9aβ,9bβ]-naphtho[1,2-c]furan-1(3H)-one (Drimenin) (17).

To a solution of (159) (0.15 g, 0.64 mmol) in methylene chloride (10 ml) was added PCC (0.2 g, 1.5 equiv.) and the mixture stirred for 20 min at room temperature. Dilution with ether (100 ml) and filtration through Celite gave a dark oil which was chromatographed (silica H, 20 g, ether:hexane 1:9) to provide (17) (75 mg, 50%) as colourless

needles m.p. 96°-98°C (hexane), ν_{max} 2920, 2840, 1780, 1465, 1455 and 1130 cm^{-1}; δ (250 MHz) 0.88 (3H, s), 0.90 (3H, s), 0.92 (3H, s), 1.36 (1H, dd, J 5.5, 11.5 Hz), 1.1-1.7 (5H, m), 1.98 (1H, ddddm, J 3, 4.5, 11.5, 18 Hz), 2.20 (1H, ddddm, J 3.5, 3.5, 5.5, 18 Hz), 2.49 (1H, ddd, J 3, 6, 13 Hz), 2.78 (1H, dddm, J 3, 3.5, 3.5 Hz) 4.68 (2H, m) and 5.73 (1H, dddm, J 3.5, 3.5, 4.5 Hz); m/e 234 (M^+) 219, 201 and 124. (Found: C, 76.90; H, 9.52. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%).

Preparation of Dimethyl-1,4,4a,5,6,7,8,8a-octahydro-1α-hydroxy-5,5,8a-trimethyl-[4aα,8aβ]-naphthalene-1,2-dicarboxylate (165).

A solution of diester (94) (3 g, 10.2 mmol) in THF (50 ml) was added dropwise to a solution of LDA [1.1 equiv., from diisopropylamine (1.53 ml), and n-butyllithium (7.2 ml, 1.55 M in hexane)] in THF (10 ml) at -78°C under argon. To the resulting deep red enolate solution was added MoOPH (5.75 g, 1.3 equiv.) and the mixture allowed to reach room temperature over 2-3 h. The resulting green solution was quenched with sodium thiosulphate solution (10%, 20 ml) and the mixture transferred to ether (100 ml). Usual work up gave a crystalline product which was triturated with a little cold (< -60°C) methanol and filtered to provide a white solid (165) (2.4 g, 80%). A further 0.6 g could be obtained by chromatography of the mother liquors (combined yield 95%) m.p. 138°-140°C (hexane), ν_{max} 3440, 2920, 1730, 1435, 1255 and 1080 cm^{-1}; δ (250 MHz) 0.93 (3H, s), 0.97 (3H, s), 0.98 (3H, s), 1.87 (1H, dd, J 5, 12 Hz), 1.1-1.9 (6H, m), 2.13 (1H, ddd, J 2.5, 12, 19.5 Hz), 2.31 (1H, ddd, J 5, 5.5, 19.5 Hz), 3.72 (3H, s), 3.73 (3H, s), 3.88 (1H, s, OH) and 7.23 (1H, dd, J 2.5, 5.5 Hz); m/e 310 (M^+), 278, 251, 219, 233, 186, 163, 124 and 109. (Found: C, 65.70; H, 8.67. $C_{17}H_{26}O_5$ requires C, 65.78; H, 8.44%).

Preparation of 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[4aα,8aβ]-naphthalene-1,2-dimethanol (167).

A solution of hydroxy diester (165) (0.266 g, 0.86 mmol) in ether (20 ml) was added dropwise to a suspension of LAH (0.2 g, 5 equiv.) in ether at 0°C under argon. After a further 15 min the mixture was transferred to ice - 5% sulphuric acid (100 ml) and ether (25 ml). The ethereal layer was washed with sodium bicarbonate solution and worked up as usual to provide an oil (183 mg) which was chromatographed (silica H, 15 g, ether eluent) to provide (167) (96 mg, 47%) m.p. 123-124°C (benzene), ν_{max} 3350, 1460, 1380 and 1100 cm^{-1}; δ (250 MHz) 0.86 (3H, s), 0.92 (3H, s), 1.0 (3H, s), 1.0-1.8 (9H, m), 1.88 (1H, dm, J 11.5 Hz), 2.34 (2H, m), 4.04 (1H, d, J 11.5 Hz), 4.17 (1H, d, J 11.5 Hz), 4.13 (1H, d, J 12 Hz), and 4.23 (1H, d, J 12 Hz); m/e 238, 220, 205, 189, 139, 127, 124 and 109. (Found: C, 75.56; H, 11.03. $C_{15}H_{26}O_2$ requires C, 75.58; H, 10.99%); and compound (168) (37 mg, 20%) as an oil, ν_{max} 2980, 2840, 1660, 1460, 1440, and 1260 cm^{-1}; δ (250 MHz) 0.92 (6H, s), 0.98 (3H, s), 1.1-1.85 (9H, m), 1.9-2.25 (2H, m), 4.17 (2H, m), and 4.57 (2H, m); m/e 220.1826 (M^+), 206, 205, 192, 177, 149, 123 and 109, ($C_{15}H_{24}O$ requires 220.1827).

Preparation of Dimethyl-1,4,4a,5,6,7,8,8a-octahydro-1α-methylthiomethoxy-5,5,8a-trimethyl-[4aα,8aβ]-naphthalene-1,2-dicarboxylate (169).

Hydroxy diester (165) (1 g, 3.2 mmol) was stirred with DMSO (15 ml) and acetic anhydride (15 ml) for 120 h at room temperature. The solution was then evaporated at 40°C under vacuum and then high vacuum (2×10^{-3} Torr) to provide a crystalline product. Trituration with a little cold (< -50°C) methanol and filtering afforded (169) (1.0 g, 84%).

A further 0.15 g was obtained by chromatography (silica H, 15 g, ether) of the mother liquors (total yield = 97%), m.p. 126°-127°C (hexane), ν_{max} 2950, 2870, 1760, 1730, 1655, 1435, 1250 and 1070 cm^{-1}; δ (60 MHz) 0.95 (9H, s), 1.0-2.4 (9H, m), 2.20 (3H, s), 3.69 (3H, s), 3.74 (3H, s), 4.5 (1H, d, J 10.5 Hz), 4.85 (1H, d, J 10.5 Hz) and 7.30 (1H, m); m/e 370 (M^+), 311, 295, 262 and 223. (Found: C, 61.88; H, 7.96; S, 8.38. $C_{19}H_{30}O_5S$ requires C, 61.80; H, 8.16; S, 8.65%).

Preparation of 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1,2-epoxy-naphthalene-1,2-dimethanol (171) and (172).

A solution of (167) (20 mg, 0.084 mmol) in benzene (1 ml) was added dropwise to a solution of t-butylhydroperoxide (11.3 mg, 1.5 equiv.) in benzene (2 ml) containing vanadyl acetyl acetonate (ca. 3-4 mg). After 1 h, the solvent was evaporated to provide almost pure crude epoxy diols (171) and (172) (18 mg, 85%), unstable to chromatography at room temperature. A purified sample was obtained by low temperature (-78°C) chromatography (silica H-Celite, 4:1, ethyl acetate-hexane) ν_{max} 3380, 2980-2840, 1460, 1380, 1260, 1140 and 1060 cm^{-1}; δ (250 MHz) (major isomer) 0.83 (3H, s), 0.86 (3H, s), 1.14 (3H, s), 1.1-1.9 (11H, m), 3.56 (1H, d, J 11.5 Hz), 3.67 (1H, d, J 11.5 Hz), 3.65 (1H, d, J 12 Hz), and 4.11 (1H, d, J 12 Hz); m/e 254.1887 (M^+), 236, 239, 223, 205, 193, 190, 179, and 163 ($C_{15}H_{26}O_3$ requires 254.1882).

Preparation of 1,3,4,5,5a,6,7,8,9,9a-decahydro-6,6,9a-trimethyl-1,2-epoxy-[5aα,9aβ]-naphtho[1,2-c]furan-3(1H)-ol (175) and (176).

A solution of diol (167) (15 mg, 0.063 mmol) in methanol (5 ml) containing Rose Bengal (0.5 mg) was irradiated for 72 h with a 300 W

quartz-iodine lamp at 4 cm distance, with efficient oxygen circulation, at 30°-40°C (cold finger). Evaporation of the solvent, followed by chromatography (silica H, 4 g, ether-hexane mixtures) gave (175) and (176) (10 mg, 65%), ν_{max} 3320, 1460, 1380, 1360, 1200, 1050 and 800 cm^{-1}; δ (250 MHz) major isomer: 3.78 (1H, d, J 10 Hz), 4.07 (1H, d, J 10 Hz), 3.63, 3.93 (1H, 2s); minor isomer: 3.59 (1H, d, J 10.5 Hz), 4.09 (1H, d, J 10.5 Hz), and 3.59, 3.95 (1H, 2s); mixture: 0.83, 0.85, 0.96, 0.88, 0.89, 1.15, 1.16, 1.19 (9H, 8s), and 1.0-2.0 (11H, m); m/e 252.1726 (M^+), 237, 234, and 109 ($C_{15}H_{24}O_3$ requires 252.1726).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1α-hydroxy-1,2-diacetoxymethyl-naphthalene (179).

The diacetate of (157) (3.8 g, 1.18 mmol) was refluxed with selenium dioxide (1.63 g, 1.25 equiv.) in dioxan (100 ml) for 1 h. The reaction mixture was cooled, diluted with water (200 ml) and worked up as usual to provide the crude product (49). Chromatography (silica H, 140 g, ether-hexane) gave (179) (2.60 g, 65%) as an oil, ν_{max} 3500, 2970, 2860, 1740, 1670, 1460, 1365, 1240 and 1080 cm^{-1}; δ (250 MHz) 0.92 (6H, s), 0.95 (3H, s), 1.82 (1H, dd, J 5, 12 Hz), 1.0-1.7 (6H, m), 2.06 (3H, s), 2.07 (3H, s), 1.97 (1H, m), 2.16 (1H, m), 4.21 (1H, d, J 11.5 Hz), 4.29 (1H, d, J 11.5 Hz), 4.60 (2H, m), and 6.06 (1H, m); m/e 338 (M^+), 322, 278, 265, 218, 214 and 154.

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1α-hydroxy-[4aα,8aβ]-naphthalene-1,2-dimethanol (166).

Hydroxy diacetate (179) (2 g, 5.9 mmol) was stirred with anhydrous potassium carbonate (5 g) in methanol (100 ml) at room temperature for

30 min. Filtration and evaporation of the solvent provided (166) (1.49 g, 99%) m.p. 140°-141°C (ether), ν_{max} 3620, 3500, 3420, 1664, 1460, 1440, 1250, 1040, and 990 cm^{-1}; δ (250 MHz) 0.82 (3H, s), 0.91 (3H, s), 0.93 (3H, s), 1.73 (1H, dd, J 5, 12 Hz), 1.1-1.9 (6H, m), 1.91 (1H, ddd, J 2, 12, 18 Hz), 2.13 (1H, ddd, J 5,6,18 Hz), 2.88 (1H, s, O<u>H</u>), 2.99 (1H, dd, J 6.5, 6.5 Hz, <u>OH</u>), 3.27 (1H, dd, J 6.5, 6.5 Hz, O<u>H</u>), 3.72 (1H, dd, J 6.5, 11.5 Hz), 3.77 (1H, dd, J 6.5, 11.5 Hz), 4.11 (1H, dd, J 6.5, 12 Hz), 4.31 (1H, dd, J 6.5, 12 Hz), and 5.91 (1H, dd, J 2, 5Hz); <u>m/e</u> 254 (M^+), 237, 225, 218, 205. (Found: C, 70.62; H, 10.33. $C_{15}H_{26}O_3$ requires C, 70.83; H, 10.30%).

<u>Preparation of 5,5a,6,7,8,9a,9b-octahydro-6,6,9a-trimethyl-1α-hydroxy-[5aα,9aβ]-naphtho[1,2-c]furan-3(1H)-one (180).</u>

Triol, (166) (50 mg, 0.2 mmol) was refluxed with the Fetizon reagent (5 equiv.) in benzene (10 ml) for 20 min. Cooling and filtration through Celite followed by evaporation of the solvent gave (180) (48 mg, 98%) as white needles m.p. 175°-178°C (ethyl acetate), ν_{max} 3440, 2980, 2840, 1745, 1720, 1680, 1460, 1415, 1230, 1100; δ (250 MHz) 0.91 (3H, s), 0.97 (3H, s), 0.99 (3H, s), 1.86 (1H, dd, J 5.5, 12 Hz), 1.20-2.05 (6H, m), 2.15 (1H, ddd, J 3.5, 12, 20.5 Hz), 2.45 (1H, ddd, J 5, 5.5, 20.5 Hz), 2.17 (1H, d, J 1 Hz, O<u>H</u>), 4.23 (1H, d, J 10 Hz), 4.37 (1H, dd, J 1, 10 Hz), and 7.04 (1H, dd, J 3.5, 5.0 Hz); <u>m/e</u> 250.1571 (M^+), 233, 232, 217 and 114 ($C_{15}H_{22}O_3$ requires 250.1569). (Found: C, 71.54; H, 8.85. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[1β,4aα,8aβ]-naphthalene-1,2-dicarboxaldehyde (Polygodial) (29).

A solution of diol (157) (0.4 g, 1.7 mmol) in methylene chloride (5 ml) was added dropwise to the Swern reagent (6.8 mmol, 4 equiv., prepared by adding a solution of DMSO (1 g) in methylene chloride (2 ml) to a solution of oxalyl chloride (862 mg, 6.8 mmol) in methylene chloride (15 ml) at -50°C) under argon at -50°C, and stirred for 1 h at -50°C. Addition of triethylamine (1.03 ml, 6 equiv.) and usual work up gave a crystalline product (0.4 g), which was recrystallised from hexane to give (29) (373 mg, 95%) m.p. 91°-92.5°C, ν_{max} 2915, 2870, 2850, 2710, 1720, 1680, and 1645 cm^{-1}; δ (250 MHz) 0.93 (3H, s), 0.96 (3H, s), 0.97 (3H, s), 1.27 (1H, dd, J 5, 11.5 Hz), 1.15-1.65 (5H, m), 1.85 (1H, dm, J 12 Hz), 2.32 (1H, dddd, J 3, 4, 11.5 20 Hz), 2.52 (1H, dddd, J 2, 5, 6, 20 Hz), 2.83 (1H, dddd, J 2, 2.5, 4, 5 Hz), 7.14 (1H, ddd, J 2.5, 3, 6 Hz), 9.47 (1H, s), and 9.54 (1H, d, J 5 Hz); m/e 234 (M^+), 219, 218, 217, 216, 206, 191, 121 and 109. (Found: C, 76.75; H, 9.56. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%). Omission of triethylamine before work up gave compound (185) (93%) as an oil, after chromatography (silica H, hexane) ν_{max} 2980-2840, 1660, 1460, 1380, 1365, 1260 and 1120 cm^{-1}; δ (250 MHz) 0.88 (3H, s), 0.89 (3H, s), 0.90 (3H, s), 1.1-1.7 (7H, m), 1.85-2.20 (3H, m), 3.83 (1H, dd, J 5, 11.5 Hz) 3.96 (1H, dd, J 3, 11.5 Hz), 4.13 (1H, d, J 10.5 Hz), 4.45 (1H, ddd, J 1, 2, 10.5 Hz), and 5.98 (1H, m); m/e 220.1825 (M^+), 205, 202, 190, 189, 187, 175, 124 and 109, ($C_{15}H_{24}O$ requires 220.1827).

Preparation of 3,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethyl-[5aα,9aβ]-naphtho[1,2-c]-3-trimethylsiloxy-furan (187).

A solution of polygodial (42 mg, 0.18 mmol) in THF (1.3 ml) was added dropwise to a solution of LDA (0.23 mmol, 1.3 equiv.) in THF (0.25 ml) at -78°C under argon. After a further 5 min trimethylsilyl chloride (0.11 ml, 5 equiv., distilled from pyridine onto triethylamine) in triethylamine (1:1), after centrifugation of the hydrochloride, was added and the mixture warmed to 0°C and the solvent removed. Usual work up gave a white gum (55 mg, 100%) ν_{max} 2980-2840, 2740, 2600, 2500, 1480, 1440 and 1390 cm^{-1}; δ (60 MHz) 0.25 (9H, s), 0.8-1.2 (9H, 6s), 1.0-2.5 (9H, m), 5.20 (1H, m), and 5.50 (2H, m); m/e 307.2094 (M + 1), 288, 278, 260, 218, 203 and 109 ($C_{18}H_{31}O_2Si$ requires 307.2093); cf. quench with t-butyldimethylsilyl chloride m/e: 349.2573 (M + 1), 291, 207, 206, 149, 133, 132 and 109 ($C_{21}H_{37}O_2Si$ requires 349.2563).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[5aα,9aβ]-1α-hydroxy-naphthalene-1,2-dicarboxaldehyde (Warburganal) (36).

A solution of triol (166) (45 mg, 0.18 mmol) in DMSO-methylene chloride (1:1, 2 ml) was added to the Swern reagent (1.08 mmol, 6 equiv., prepared by the addition of trifluoroacetic anhydride (260 mg, 0.175 ml) in methylene chloride (2 ml) to DMSO (0.5 g) in methylene chloride (10 ml) at -50°C under argon) dropwise under argon at -50°C. After 30 min at -50°C, triethylamine (0.215 ml, 9 equiv.) was added, and the reaction worked up as usual. Chromatography of the product mixture (silica H 15 g, ether-hexane) gave (36) (20 mg, 45%). Charcoaling (ethanol) and

recrystallisation (hexane) gave m.p. 96-98°C, ν_{max} 3440, 3420, 3000-3840, 1715, 1680, 1645, 1460, 1120 and 1040 cm^{-1}; δ (250 MHz) 0.94 (3H, s), 0.99 (3H, s), 1.09 (3H, s), 1.15-1.75 (6H, m), 1.89 (1H, dd, J 5, 12 Hz), 2.34 (1H, ddd, J 2.5, 12, 21 Hz), 2.58 (1H, ddd, J 5, 6, 21 Hz), 4.09 (1H, d, J 1 Hz, O<u>H</u>), 7.27 (1H, dd, J 2.5, 6 Hz), 9.42 (1H, s), 9.74 (1H, d, J 1 Hz); <u>m/e</u> 250 (M^+), 232, 221, 189, 161, 124, 109 and 105. These data were identical to an authentic sample.[125]

<u>Preparation of 1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-[1β,2β, 4aα,8aβ]-naphthalene-1,2-dimethanol (193)</u>.

Tetrahydrodiester (153) (0.71 g, 2.4 mmol) in ether (10 ml) was added to LAH (365 mg, 4 equiv.) in ether (25 ml) at 0°C under argon. After a further 30 min the mixture was transferred to ice-sulphuric acid (5%, 100 ml) and the ethereal layer washed with bicarbonate. Usual work up then gave an oil which was filtered through silica H (10 g, ethyl acetate) to provide (193) (0.55 g, 95%) m.p. 135°-137°C, ν_{max} 3300, 3000-2860, 1460, 1380, 1360 and 1010 cm^{-1}; δ (250 MHz) 0.82 (3H, s), 0.85 (3H, s), 0.87 (3H, s), 0.9-2.2 (13H, m), 2.70 (2H, br, O<u>H</u>), 3.55 (1H, dd, J 7, 10.5 Hz), 3.80 (1H, dd, J 5, 10.5 Hz), and 3.88 (1H, dd, J 6, 10.5 Hz); <u>m/e</u> 240.2081 (M^+), 220, 207, 205, 189, 175, 123, 119 and 109, ($C_{15}H_{28}O_2$ requires 240.2089). (Found: C, 75.32; H, 11.87; $C_{15}H_{28}O_2$ requires C, 74.95, H, 11.74%).

(and 3·70 (1H, dd J 10·5, 10·5 Hz).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-3β-hydroxy-[1β,4aα,8aβ]-naphthalene-1,2-dimethanol (194).[136]

Cultures of C. elegans (on Czapek Dox agar) were plated out on petri dishes at 25°C for 5-6 d before needed to ensure healthy growth. The flasks containing the medium were then innoculated with approximately 1 cm^2 of mycelial growth. The fungus was grown on a medium of glucose (5 g), sucrose (2 g), beef extract (1 g), malt extract (1 g), yeast extract (1 g), distilled water (to 1 litre), and the pH adjusted to 5.5 with dilute hydrochloric acid. The flasks, each containing 100 ml liquid culture medium were autoclaved at 120°C for 15 min, before use. The cultures were then incubated for 3 days at 24°C, using a rotary shaker (200 r.p.m.) until a healthy growth had occurred. Diol (157) (10 mg, 0.042 mmol) in hot ethanol (0.5 ml) was then added via sterile syringe. After 9 d, t.l.c. indicated complete conversion. The fermentation broth was then salt saturated, and the mycelia filtered off. Thorough extraction with ethyl acetate (4 x 50 ml), followed by drying and removal of the solvent gave the crude product, which was subjected to p.l.c. (ethyl acetate, 2 elutions) to provide (194) (8 mg, 75%) m.p. 170-173°C, ν_{max} 3300, 3980-2840, 1650, 1450, 1380 and 1090 cm^{-1}; δ (250 MHz), 0.78 (3H, s), 0.87 (3H, s), 1.00 (3H, s), 1.2-2.2 (8H, m), 2.83 (3H, br, OH), 3.28 (1H, dd, J 4.5, 11 Hz), 3.71 (1H, dd, J 7.5 10.5 Hz), 3.92 (1H, dd, J 2, 10.5 Hz), 4.01 (1H, d, J 12 Hz), 4.37 (1H, d, J 12 Hz), and 5.82 (1H, m); m/e 254.1875 (M^+), 236, 234, 223, 218, 188, 173 and 107, ($C_{15}H_{26}O_3$ requires 254.1882).

Preparation of 1,3,5,5a,6,7,8,9,9a,9b-decahydro-6,6,9a-trimethyl-3β-hydroxy-[5aα,9aβ,9bβ]-naphtho[1,2-c]furan-1α(3H)-ol (195).

A solution of (29) (10 mg, 0.042 mmol) in hot ethanol (0.5 ml) was added to 100 ml culture medium containing a healthy growth of C. elegans as before, and incubated for 10 d at 24°C. Work up as before provided the crude product, purified by p.l.c. (ethyl acetate, 2 elutions) to provide (195) (9 mg, 90%) m.p. 126-128°C, ν_{max} 3390, 2970-2840, 1725, 1670, 1440, 1365, 1080 and 970 cm^{-1}; δ (250 MHz) 0.81 (3H, s), 0.90 (3H, s), 1.01 (3H, s), 1.1-2.4 (8H, m), 3.29 (1H, dd, J 5.5, 10 Hz), 4.20 (1H, dm, J 11Hz), 4.50 (1H, dm, J 11Hz), 5.28 (1H, d, J 4.5 Hz), and 5.54 (1H, m); m/e 252.1719 (M^+), 234, 219, 217, 188, 173, 169 and 119 ($C_{15}H_{24}O_3$ requires 252.1725).

Preparation of Methyl-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-[1β,4aα,8aβ]-naphthalene-1-carboxylate (198).

Farnesal: Commercial farnesol (22.2 g, 0.1 mole) in methylene chloride (25 ml) was added to a suspension of PCC (35 g, 1.5 equiv.) in methylene chloride (200 ml) at room temperature. After a further 30 min the solution was diluted with ether (1 ℓ) and the mixture filtered through silica H under pressure (20 p.s.i.). Evaporation of the solvent provided farnesal (20.2 g, 92%) as a mixture of isomers, ν_{max} 1675, 2740, 1630, 1610, 1190 and 1115 cm^{-1}; δ (60 MHz) 1.62 (3H, br s), 1.70 (3H, brs), 1.97 (3H, br s), 2.17 (3H, br s), 1.9-2.8 (8H, m), 5.10 (2H, m), 5.82 (1H, dm, J 8.5 Hz), 9.93 (major) and 9.86 (1H, 2d, J 8.5 Hz).

Farnesic acid: Crude farnesal (20 g, 0.09 mole) in ethanol (40 ml) was added dropwise to a solution of silver nitrate (32 g) in water (300 ml) at room temperature. The mixture was then treated dropwise with a solution of potassium hydroxide (19.3 g) in water (300 ml) with mechanical stirring and ice-salt cooling (internal temperature 0^{o}-5^{o}C). After a further 36 h stirring at room temperature the mixture was filtered, washing through with hot water. The cooled filtrate was then treated with 50% sulphuric acid (250 ml) and extracted with ether. The organic layer was worked up as usual to provide the crude product (197) (18.64 g, 86%), ν_{max} 3500-2500, 1700, 1640, 1440, 1380, 1295, 1250, and 1170 cm^{-1} ; δ (60 MHz) 1.67 (3H, br s), 1.70 (6H, br s), 2.01 (3H, br s), 2.17 (3H, brs), 1.0-2.6 (8H, m), 5.0 (2H, m), 5.6 (1H, m), and 8.7 (1H, m).

Bicyclofarnesic acid: Crude farnesic acid (18 g, 0.076 mole) in benzene (180 ml) was added dropwise to a rapidly stirred solution of boron trifluoride-diethyletherate (180 ml, redistilled) in benzene (720 ml) under nitrogen at 35^{o}C over 2-3 h. After allowing to stir for a further 14 h at this temperature, the mixture was poured into ice-water (1.5 ℓ) and worked up as usual to provide the crude acids (19.3 g), ν_{max} 3600, 2400, 1770, 1700, 1640, 1450, and 1160 cm^{-1}; δ (60 MHz) 0.93 (6H, s), 1.03 (3H, s), 0.9-2.8 (10H, m), 5.50 (1H, m), and 9.8 (1H, br s).

Methyl drimenate (198): The crude bicyclic acids (19.3 g) were dissolved in methanol, cooled to 0^{o}C and treated with excess ethereal diazomethane (from N-methyl, N-nitrosourea). After 30 min, excess

reagent was decomposed with acetic acid. Drying and evaporation of the solution gave the crude product (18.75 g) which was chromatographed on silica H (125 g, ether-hexane, 2:98) to provide 10.04 g of yellow oil (> 90% pure by t.l.c.). Further chromatography of this oil on silica H (1:150 loading, 0.5, 1.0, 1.5% ether gradient in hexane) provided (198) (6.3 g, 25% overall yield) m.p. 46-48°C, ν_{max} 2960-2835, 1740, 1460, 1440 and 1160 cm^{-1}; δ (250 MHz), 0.88 (3H, s), 0.91 (3H, s), 0.96 (3H, s), 1.1-1.7 (7H, m), 1.60 (3H, m), 1.80-2.15 (3H, m), 2.92 (1H, br s), 3.68 (3H, s), and 5.55 (1H, m); and (205) (3.6 g, 15% overall yield) as an oil, ν_{max} 2960-2850, 1740, 1430, 1155, and 1015 cm^{-1}; δ (250 MHz) 0.89 (6H, s), 0.96 (3H, s), 1.61 (3H, m), 1.1-1.7 (7H, m), 1.8-2.2 (3H, m), 2.49 (1H, s), 3.70 (3H, s), and 5.63 (1H, m). (Found: [mixture of (198) and (205)] C, 76.74; H, 10.58. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%).

Preparation of Methyl-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-hydroxy-[4aα,8aβ]-naphthalene-1-carboxylate (199) and (200).

A solution of (198) (1.5 g, 6 mmol) in THF (35 ml) was added dropwise to a solution of potassium diisopropylamide-lithium-t-butoxide [9 mmol, 1.5 equiv., prepared by the addition of n-butyllithium (6.0 ml, 1.5 M in hexane) to a solution of potassium t-butoxide (1.16 g, 10.3 mmol) in THF (17 ml) at -78°C under argon] in THF (17 ml) at -55°C under argon. After a further 10 min, MoOPH (4.4 g, 1.7 equiv.) was added to the red enolate solution, and the mixture allowed to reach room temperature over 2 h. Addition of sodium thiosulphate solution (10%, 50 ml) with ice cooling, followed by washing with sodium bicarbonate solution and

usual work up gave the crude product which was chromatographed on silica H (100 g, ether-hexane) to provide (200) (207 mg, 13%) as an oil, ν_{max} 3510, 3000-2840, 1720, 1460, 1435, 1255, 1170, 1120 and 109 cm^{-1}; δ (250 MHz) 0.90 (3H, s), 0.94 (3H, s), 1.04 (3H, s), 1.1-1.8 (6H, m), 1.57 (3H, m), 1.9-2.15 (2H, m), 2.08 (1H, dd, J 4, 12 Hz), 3.50 (1H, s, OH), 3.82 (3H, s), and 5.70 (1H, m); m/e 266.1883 (M^+), 207, 142, 124, and 109 ($C_{16}H_{26}O_3$ requires 266.1882); and (199) (1.13 g, 71%) m.p. 49°-50°C, ν_{max} 3520, 3000-2840, 1720, 1680, 1460, 1250, and 1075 cm^{-1}; δ (250 MHz), 0.90 (3H, s), 0.95 (3H, s), 1.0 (3H, s), 1.64 (3H, m), 1.1-1.8 (6H, m), 1.84 (1H, dd, J 5, 11.5 Hz), 1.85-2.10 (2H, m), 3.58 (1H, s, OH), 3.80 (3H, s), and 5.73 (1H, m), m/e 266 (M^+) 207, 142, 119 and 109. (Found: C, 72.29; H, 9.82; $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84%).

Preparation of Methyl-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1α-hydroxy-[4aα,8aβ]-naphthalene-2-carboxaldehyde-1-carboxylate (201).

Hydroxy ester (199) (0.5 g, 1.88 mol) was refluxed with selenium dioxide (1.04 g, 5 equiv.) in dioxan (25 ml) for 4 h. Cooling and addition of the reaction mixture to water (100 ml) and usual work up gave a red oil which was purified on silica H (80 g, ether-hexane) to provide (201) (358 mg, 68%) m.p. 121°-123°C, ν_{max} 3500, 2980-2840, 1722, 1687, 1645, 1465, 1250 and 1170 cm^{-1}; δ (250 MHz) 0.94 (3H, s), 0.96 (3H, s), 0.99 (3H, s), 1.1-1.9 (6H, m), 1.92 (1H, dd, J 4.5, 12 Hz), 2.27 (1H, ddd, J 2.5, 12, 21 Hz), 2.47 (1H, dd, J 4.5, 5, 21 Hz), 3.74 (3H, s), 3.78 (1H, s, OH), 7.06 (1H, dd, J, 2.5, 5 Hz) and

9.37 (1H, s); m/e 280 (M^+), 262, 221, 203, 157, 124 and 109. (Found: C, 68.35; H, 8.64 . $C_{16}H_{24}O_4$ requires C, 68.55; H, 8.64%).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1β-hydroxy-[4aα,8aβ]-naphthalene-2-carboxyaldehyde-1-carboxylate (202).

Hydroxy ester (200) (0.2 g, 0.75 mmol) was refluxed with selenium dioxide (0.4 g, 5 equiv.) in dioxan (10 ml) for 4 h. Work up and purification as for (201) gave (202) (145 mg, 70%) m.p. 100°-101°C, ν_{max} 3510, 1730, 1675, 1645, 1465, 1415, 1240, 1115 and 1090 cm^{-1}; δ (250 MHz), 0.94 (3H, s), 0.99 (3H, s), 1.06 (3H, s), 1.1-1.9 (6H, m), 2.06 (1H, dd, J 4.5, 10.5 Hz), 2.28 (1H, ddd, J 2.5 10.5, 21 Hz), 2.50 (1H, ddd, J 4.5, 5, 21 Hz), 3.78 (3H, s), 4.14 (1H, s, OH), 7.04 (1H, dd, J 2.5, 5.5 Hz), and 9.34 (1H, s); m/e 280 (M^+), 262, 221, 203, 157, 124 and 109. (Found: C, 68.49; H, 8.2. $C_{16}H_{24}O_4$ requires C, 68.55; H, 8.63%).

Preparation of Methyl-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[1α,4aα,8aβ]-naphthalene-2-carboxaldehyde-1-carboxylate (206).

(205) (0.2 g, 0.8 mmol) was refluxed with selenium dioxide (180 mg, 2 equiv.) in dioxan (10 ml) for 3 h. Work up as for (201) gave (206) (0.185 g, 90%) m.p. 63°-64°C, ν_{max} 3000-2810, 2710, 1730, 1680, 1650, 1460, 1330, 1200, 1160 and 1000 cm^{-1}; δ (250 MHz) 0.92 (3H, s), 0.95 (6H, s), 1.0-1.7 (6H, m), 1.88 (1H, dd, J 5, 11 Hz), 2.19 (1H, dddd, J 2, 2, 11, 20 Hz), 2.56 (1H, ddd, J 5,5,20 Hz), 3.09 (1H, d, J 2 Hz) 7.06 (1H, dd, J 2, 5 Hz), and 9.43 (1H, s, OH); m/e 264 (M^+), 205, 187, 124 and 109. (Found: C, 72.80; H, 9.18. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-[1α,4aα, 8aβ]-naphthalene-1,2-dicarboxaldehyde (isotadeonal) (27), and 6,7,8,9-tetrahydro-6,6,9a-trimethylnaphtho[1,2-c]furan-3-one (209).

(208) (0.3 g, 1.36 mmol) was refluxed with selenium dioxide (450 mg, 3 equiv.) in dioxan (20 ml) for 2 h. Work up as for (201) and chromatography (silica H, 20 g, ether-hexane) provided (27) (127 mg, 40%) m.p. 59°-61°C (hexane), ν_{max} 2960-2840, 1725, 1680, 1580, 1450 and 1250 cm^{-1}; δ (250 MHz) 0.92 (3H, s), 0.94 (3H, s), 0.97 (3H, s) 1.1-1.95 (5H, m), 1.79 (1H, dm, J 12 Hz), 2.22 (1H, dddd, J 1.5, 2.5, 11.5, 20.5 Hz), 2.56 (1H, ddd, J 5, 5, 20.5 Hz), 3.26 (1H, dd, J 1.5, 2.5 Hz), 7.10 (1H, dd, J 2.5, 5 Hz), 9.42 (1H, s), and 9.87 (1H, d, J 2.5 Hz); m/e 234 (M^+) 219, 216, 206, 191 and 109. (Found: C, 76.96; H, 9.53. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%); and compound (209), (125 mg, 40%) m.p. 120-121°C, ν_{max} 2860-2840, 1720, 1685, 1655, 1590, 1530, 1460, 1320, and 1125 cm^{-1}; δ (250 MHz) 1.24 (3H, s), 1.34 (3H, s), 1.55 (3H, s), 1.2-2.2 (6H, m), 6.29 (1H, s), 7.37 (1H, d, J 2 Hz), and 7.98 (1H, d, J 2 Hz); m/e 230.1307 (M^+), 215, 212, 197, 162, 106 and 91 ($C_{15}H_{18}O_2$ requires 230.1307). (Found: C, 77.48; H, 8.00. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-[1β,4aα,8aβ]-naphthalene-1-methanol (drimenol) (18).

(198) (2 g, 8 mmol) in ether (20 ml) was added to a suspension of LAH (0.6 g, 2 equiv.) in ether (100 ml) at 0°C under argon. After a further 30 min the mixture was poured onto ice - 5% sulphuric acid (250 ml) and the ethereal layer washed with saturated sodium bicarbonate

solution and worked up as usual to provide an oil purified on silica H (50 g ethyl acetate-hexane) to provide (18) (1.65 g, 93%), ν_{max} 3350, 2900, 2840, 1460 and 1030 cm^{-1}; δ (250 MHz) 0.86 (3H, s), 0.87 (3H, s), 0.89 (3H, s), 1.78 (3H, m), 0.95-2.10 (10H, m), 1.67 (1H, s, OH), 3.73 (1H, dd, J 3.5, 11 Hz), 3.85 (1H, dd, J 5, 11 Hz) and 5·54 (1H, m); m/e 222 (M^+), 204, 189, 124 and 109.

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-[1β,4aα,8aβ]-naphthalene-1-carboxaldehyde (210).

(18) (1.15 g, 5.2 mmol) in methylene chloride (2 ml) was added to a suspension of PCC (1.7 g, 1.5 equiv.) in methylene chloride (20 ml) and stirred for a further 30 min at room temperature. Ether (100 ml) was added and the mixture filtered through Celite, and the solvent removed. Chromatography of the residue (silica H, 20 g, ether:hexane 2:98) gave (210) (980 mg, 86%) as an oil, ν_{max} 2960-2840, 2710, 1720, 1670, 1460, 1440, 1390 and 1110 cm^{-1}; δ (60 MHz) 0.87 (3H, s), 0.93 (3H, s), 1.05 (3H, s), 1.0-2.5 (10H, m), 1.60 (3H, m), 5.60 (1H, m), and 9.65 (1H, d, J 5.5 Hz).

Preparation of 1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1α-hydroxy-[4aα,8aβ]-naphthalene-1-carboxaldehyde (211).

(210) (330 mg, 1.5 mmol) in THF (8 ml) was added dropwise to a solution of LDA (2 mmol, 1.3 equiv.) in THF (1.7 ml) at -78°C. After a further 10 min, MoOPH (1 g, 0.5 equiv.) was added and the solution allowed to reach room temperature over 2 h, and then quenched with sodium thiosulphate solution (10%, 20 ml) with ice cooling. Usual

work up gave an oil (32 mg) which was chromatographed (Silica H:Celite, 4:1, 20 g, -78°C, ether-hexane mixtures) to provide (211) (230 mg, 65%) ν_{max} 3490, 2960-2840, 1718, 1675, 1460, 1445, 1380 and 1265 cm^{-1}; δ (60 MHz) 0.88 (3H, s), 0.95 (3H, s), 1.22 (3H, s), 1.0-2.3 (9H, m), 1.54 (3H, m), 3.70 (1H, d, J 1.5 Hz, OH), 5.83 (1H, m), and 9.75 (1H, d, J 1.5 Hz); m/e 236.1770 (M^+), 207, 124, 119, 109 and 95, ($C_{15}H_{24}O_2$ requires 236.1776).

Preparation of 3,5,5a,6,7,8,9a,9b-octahydro-6,6,9a-trimethyl-1α-hydroxy-[5aα,9aβ]-naphtho[1,2-c]furan-1(3H)-one (212).

(211) (9 mg) in dioxane (1 ml) was refluxed with selenium dioxide (10 mg, 2 equiv.) for 1 h. The reaction mixture was worked up as usual and purified by p.l.c. (ether-hexane) to afford (212) (6 mg, 60%) m.p. 120°-122°C; ν_{max} 3420, 1740, 1460, 1440, 1380, 1260, 1150, 1075 and 1060 cm^{-1}; δ (250 MHz) 0.92 (6H, s), 0.97 (3H, s), 0.8-1.8 (6H, m), 1.8 (1H, dd, J, 5, 11 Hz), 1.9-2.3 (2H, m), 4.19 (1H, ddd, J 2, 4, 12 Hz), 4.58 (1H, dddd, J 0.5, 3.5, 6, 12 Hz), and 5.74 (1H, m); m/e 250.1571 (M^+), 234, 223, 206, 124 and 109 ($C_{15}H_{22}O_3$ requires 250.1569).

Preparation of 1,2,3,4,9,10,11,12-octahydro-1,1,12-trimethylphenanthrene (213).

Phenyl acetylene (47 g, 0.5 mole) in ether (100 ml) was added dropwise to a mechanically stirred solution of sodamide (from 12 g sodium) in liquid ammonia (500 ml), over 40 minutes. The mixture turned light brown from pale grey. Liquid ammonia (to 600 ml) and subsequently trimethylcyclohexanone (70 g, 0.5 mole) in ether (100 ml) was added.

The darkened mixture was then stirred rapidly for 3 h and then ammonium chloride (24 g) was added cautiously over 15 min. The ammonia was evaporated using a warm water bath, ether (100 ml) was added and the mixture filtered, and washed with saturated sodium metabisulphite solution (150 ml) and dried. Removal of the solvent gave 119.1 g (98.5%) of 2,6,6-trimethyl-1-phenylethynylcyclohexanol, which crystallised on standing. ν_{max} 3450, 2200, 1700, 1600, 1585 and 1490 cm^{-1}; δ (60 MHz) 1.05 (3H, d, J 6Hz), 1.0 (3H, s), 1.15 (3H, s), 1.0-2.2 (7H, m), 1.95 (1H, s, OH) and 7.1-7.4 (5H, m). The above product (113.7 g) in ethyl acetate (500 ml) was hydrogenated over 5% Pd/C (8 g) until no more hydrogen was absorbed (21.8 ℓ). Filtration through Celite and removal of the solvent gave 2,6,6-trimethyl-1-phenylethyl-cyclohexanol (113.8 g, 98%) as an almost colourless liquid, ν_{max} 3550, 1950, 1600, 1590, 1500, 1450 and 760 cm^{-1}; δ (60 MHz), 0.93 (3H, s), 0.96 (3H, s), 0.97 (3H, d, J 6 Hz), 1.2-1.80 (11H, m), 1.85 (1H, s, OH), 2.4-2.8 (2H, m), and 7.1 (5H, br s); m/e 246 (M^+), 176, 175, 162, 105 and 91.

The above product (92 g) was stirred with polyphosphoric acid (1.5 kg) at 100°C for 1 h under argon. The mixture was then poured into water (6 ℓ) and extracted with ether, the combined extracts were washed with 5% potassium hydroxide solution (250 ml), and worked up as usual to provide a yellow liquid (81.7 g). Distillation gave (213) (75 g, 88%), b.p. 77°-78°C, 2 x 10^{-4} torr, ν_{max} 3050, 1495, 1440, and 765 cm^{-1}; δ (60 MHz) 0.9 (6H, s), 1.1 (3H, s), 0.8-2.5 (9H, m), 2.8 (2H, m), and 6.85 (4H, m). (Found: C, 89.25; H, 10.82. $C_{17}H_{24}$ requires C, 89.41; H, 10.59%).

Preparation of 5,5,9-trimethyl-*trans*-1-decalone (214).[149]

2-Methylcyclohexa-1,3-dione (24.3 g, 0.19 mmol) was dissolved in warm methanol (75 ml) containing potassium hydroxide (1.3 g). To the resulting solution was added EVK (25.1 g, 0.3 mole) and the mixture refluxed for 4 h. Cooling and removal of solvent and excess EVK (by repeated azeotroping with benzene 3 x 50 ml) gave a pale yellow oil which was dissolved in benzene (125 ml) containing pyrollidine (2 ml) and the solution refluxed for 20 h using a Dean-Stark trap. The cooled solution was washed with sulphuric acid (0.5 M, 2 x 50 ml), and worked up as usual to provide a pale brown oil. Distillation gave 2,3,4,7,8,8a-hexahydro-5,8a-dimethylnaphthalene-1,6-dione (21.2 g, 58%), b.p. 124°-140°C, 0.6 torr, ν_{max} 1715 and 1670; δ 1.4 (3H, s), 1.75 (3H, s) and 1.9-2.7 (10H, m). A solution of the above (20.4 g), ethane-1,2-diol (6.7 g, distilled from sodium) and PTSA (0.5 g) in benzene (250 ml) was refluxed for 12 h using a Dean-Stark trap. The cooled reaction mixture was washed with sodium bicarbonate solution and treated as usual to give a yellow oil (24.2 g), which was chromatographed (silica H, 80 g, ether-hexane 3:7) to provide 2,3,4,7,8,8a-hexahydro-5,8a-dimethyl-1-ethylenedioxynaphthalene-6-one (23 g, 94%), ν_{max} 1670 cm^{-1}; δ (60 MHz), 1.3 (3H, s), 1.7 (3H, s), 1.9-2.6 (10H, m) and 3.75 (4H, m).

A solution of the above (2.25 g) and t-butanol (0.75 g, distilled from sodium) in THF (30 ml) was added to liquid ammonia (300 ml, distilled from sodium) under argon. Lithium wire (168 mg) was added with efficient mechanical stirring. The initial blue colour was quenched but reappeared after 2-3 min, persisted for 5-6 min, and then faded to produce an almost colourless solution. Dry methyl iodide

(14.2 g, 6.2 ml) was added and the mixture stirred for 1.5 h before evaporating the ammonia with a warm water bath under an argon stream, over 1 h. Water (150 ml) was added and the solution extracted with ether, and treated as usual to provide an oil (2.33 g). Chromatography (silica H, 60 g, ether-hexane 1:4) provided 2,3,4,7,8,8a-hexahydro-5,5,8a-trimethyl-1-ethylenedioxy-naphthalene-6-one (1.50 g, 63%), m.p. 37°-42°C, ν_{max} 1715 cm^{-1}; δ (60 MHz), 1.02 (3H, s), 1.08 (3H, s), 1.25 (3H, s), 1.9-2.5 (10H, m), and 3.8 (4H, m). A solution of the above (1.83 g), hydrazine hydrochloride (0.815 g) and hydrazine hydrate (9.5 ml) in trigol (34 ml, distilled from sodium) heated to reflux (138°C) under nitrogen for 1.5 h until the hydrazone formation was complete. Powdered potassium hydroxide (2.7 g) was added and then excess hydrazine and water distilled until the solution refluxed freely at 190°-200°C. After a further 3 h, nitrogen evolution had ceased and water (75 ml) was added to the cooled reaction mixture. Extraction with petrol followed by drying and removal of solvent gave an oil (1.65 g), which was dissolved in 1M hydrochloric acid-acetic acid-THF (1:2:3) (35 ml) and stirred at room temperature for 2 h. Addition of sodium bicarbonate solution and usual work up gave the crude product (1.3 g). Chromatography (silica H, 50 g, ether-hexane 1:9) gave 2,3,4,4a,5,6,7,8-octahydro-5,5,8a-trimethyl-naphthalene-1-one (214) (1.16 g, 82%), m.p. ~ 30°C, ν_{max} 1710 cm^{-1}; δ (60 MHz), 0.88 (6H, s), 1.05 (3H, s), and 1.0-2.5 (13H, m); m/e 194 (M^+), 179, 178, 176, 162, 161, 152, 151, 123 and 109.

Preparation of 1,3,4,5,6,7-hexahydro-4,4-dimethyl-1-n-butylthio-isobenzofuran (217).

To trimethylsulphonium tetrafluoroborate[150] (1.65 g, 10 mmol) in DME (40 ml) was added n-butyllithium (3.80 ml, 2.65 M in hexane) over 2-5 min at -20°C under argon. After a further 15 min the white suspension-solution was cooled to -78°C and treated with a solution of 2,2-dimethyl-α-n-butylthiomethylene-cyclohexanone (216) (450 mg) in DME (5 ml) dropwise. After 2 h at -78°C, water (25 ml) was added and the mixture worked up as usual. Chromatography (silica H, 25 g, ether-hexane) gave (217) (421 mg, 88%) as an oil, ν_{max} 1625, 1460, 1360, 1050 and 1010 cm^{-1}; δ (60 MHz) 0.9-2.0 (13H, m), 1.05 (6H, s), 2.50 (2H, m), 4.10 (2H, m) and 5.68 (1H, m); m/e 240.1547 (M^+), 183, 151, 133, 105 and 81 ($C_{14}H_{24}OS$ requires 240.1548).

Preparation of 4,5,6,7-tetrahydro-4,4-dimethyl-isobenzofuran (218).

A solution of (217) (250 mg, 1.04 mmol) in DME (2.5 ml) was added to rapidly stirred mercuric sulphate (0.3 g) in DME (3 ml). After 10 min addition of ether (10 ml) and filtration gave a solution of (218). (Evaporation of the solvent gave 140 mg, 90% of product). (219) was unstable to chromatography and was used immediately without removal of the solvent. ν_{max} 1660, 1450, 1040, 910, 890 and 730 cm^{-1}; δ (60 MHz) 0.9-2.5 (6H, m), 1.23 (6H, s), 7.05 (1H, m), and 7.18 (1H, m); m/e 150.1044 (M^+), 135, 107, 91, 79 and 77, ($C_{10}H_{24}O$ requires 150.1045).

Preparation of 1,3,4,5,6,7-hexahydro-4,4-dimethyl-1,3-dimethoxy-isobenzofuran (219).

A solution of (218) (125 mg, 0.83 mmol) in DME (1.5 ml) was cooled to 0°C under argon, and treated with a solution of bromine in methanol (2 ml, 1.2 equiv, 0.5 M) dropwise. After a further 5 min, the reaction was treated with water (20 ml) and worked up as usual to provide (219) (180 mg, 90%), ν_{max} 1460, 1360, 1195, 1140, 1120, 1100, 1070 and 985 cm^{-1}; δ (60 MHz) 0.9-2.2 (6H, m), 1.15 (6H, m), 3.3-3.4 (6H, m), and 5.2-5.8 (2H, m); m/e 212.1403 (M^+), 197, 181, 153, 137 and 121 ($C_{12}H_{20}O_3$ requires 212.1412).

Preparation of 4,5,6,7-tetrahydro-4,4-dimethyl-3-methoxy-isobenzofuran-1-one (220).

A solution of (219) (60 mg, 0.28 mmol) in methylene chloride (2 ml) at 0°C was treated with m-CPBA (1-2 equiv) portionwise. Warming to room temperature for 40 min was followed by washing with sodium bicarbonate solution and usual work up to provide (220) (52 mg, 93%), ν_{max} 1770, 1675, 1260, 1215, 910 and 735 cm^{-1}; δ (60 MHz) 0.9-2.0 (4H, m), 1.1-1.2 (6H, 4s), 2.15 (2H, m), 3.40 (1.5H, s), 3.45 (1.5H, s), and 5.5 (1H, m); m/e 196.1096 (M^+), 181, 178, 168, 165, 164, 149, 121 and 109 ($C_{11}H_{16}O_3$ requires 196.1099).

Preparation of 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-2-n-butyl-thiomethylene-[4aα,8aβ]-naphthalene-1-one (222).

(213) (4.5 g, 23 mmol) was stirred with ethylformate (2.5 g, 1.5 equiv) and sodium hydride (1.44 g, 50% in oil, 1.3 equiv.) in benzene (120 ml) for 12 h at room temperature. The reaction mixture was then

transferred to 5% hydrochloric acid (50 ml) and extracted with ether. Usual work up provided 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-2-formyl-[4aα,8aβ]-naphthalene-1-one as an oil (4.63 g, 90%), ν_{max} 2960-2840, 1730, 1700, 1640, 1590, 1460, 1330, 1030 and 680 cm^{-1}; δ (60 MHz) 0.85 (3H, s), 0.90 (3H, s),1.10 (3H, s), 1.0-2.5 (11H, m), 7.28 (1H, br), and 8.40 (1H, br).

The above product (4 g, 18 mmol) was refluxed with n-butanethiol (2.88 ml, 1.5 equiv.) and p-TSA (50 mg) in benzene (50 ml) for 4 h using a Dean-Stark trap. The solution was then evaporated and the residual oil chromatographed (silica H, 130 g, ether-hexane) to provide (222) (4.50 g, 85% overall yield) m.p. 60-62°C, ν_{max} 2960-2850, 1675, 1550, 1460, 1430, 1300, 1230, 1140 and 810 cm^{-1}; δ (60 MHz) 0.9 (6H, s), 1.08 (3H, s), 0.9-2.8 (20H, m), and 7.45 (1H, m). (Found: C, 73.18; H, 10.28; S, 11.09. $C_{18}H_{30}SO$ requires C, 73.41; H, 10.27; S, 10.89%).

Preparation of 4,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethyl-[5aα,9aβ]-naphtho[1,2-c]furan (Euryfuran) (38).

A solution of (222) (0.1 g, 0.34 mmol) in DME (5 ml) was added dropwise to a solution of trimethylsulphonium methylide [5 equiv., generated as for (217)] in DME (40 ml) at -78°C under argon. After 10 min, water (25 ml) was added, and the mixture worked up as usual to provide the dihydrofuran as an oil, ν_{max} 2980-2860, 1620, 1460, 1380, and 1100 cm^{-1}; δ (60 MHz) 4.5 (2H, m), and 5.7 (1H, m). Standing at 35°C for 12 h or brief treatment with mercuric sulphate (0.1 g) in DME (2 ml) gave, after filtration through silica H (5 g, hexane), (38) (52 mg,

70% overall yield) as an oil, ν_{max} 2960-2850, 1460, 1430, 1380, and 890 cm^{-1}; δ (250 MHz), 0.91 (3H, s), 0.94 (3H, s), 1.21 (3H, s), 1.2-2.0 (9H, m), 2.50 (1H, dddd, J 2, 7.5, 11.5, 16 Hz), 2.77 (1H, ddm, J 6.5, 16 Hz), 7.05 (1H, dd, J 1.5, 2.5 Hz), and 7.07 (1H, d, J 1.5 Hz); m/e 218.1671 (M^+), 203. ($C_{15}H_{22}O$ requires 218.1671).

Preparation of 1,3,4,5,5a,6,7,8,9,9a-decahydro-6,6,9a-trimethyl-1,3-dimethoxy-[5aα,9aβ]-naphtho[1,2-c]furan (223).

A solution of (38) (15 mg, 0.069 mmol) in methanol (2 ml) at 0°C was treated with a solution of bromine in methanol (1.7 ml, 0.05 M, 1.2 equiv.). After a further 30 min at room temperature, the reaction was diluted with water and worked up as usual to provide (223) (18 mg, 92%) as an oil, ν_{max} 2960-2840, 1760, 1670, 1460, 1370 and 1190 cm^{-1}; δ (60 MHz) 0.90, 1.1-1.2 (9H, m), 1.0-2.4 (11H, m), 3.3-3.5 (6H, 8s), and 5.2-5.8 (2H, m); m/e 280.2046 (M^+), 279, 265, 264, 249, 235, 234, 219, 189, 156 and 143, ($C_{17}H_{28}O_3$ requires 280.2038).

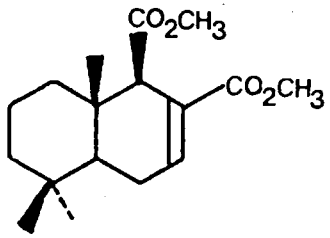
Preparation of 1,4,5,5a,6,7,8,9-octahydro-6,6,9a-trimethyl-[5aα,9aβ]-naphtho[1,2-c]furan-3(1H)-one (Confertifolin) (9).

A solution of (223) (0.015 g, 0.53 mmol) in ether (0.1 ml) was added to vigorously stirred 10% hydrochloric acid in acetone (2 ml). After 30 min at room temperature the mixture was transferred to sodium bicarbonate solution and ether (20 ml) and the ethereal layer treated as usual to give a crystalline product. Recrystallisation from hexane gave (9) (9.5 mg, 75%) m.p. 120°-123°C, ν_{max} 2960-2840, 1760, 1670, 1460, 1380, 1090 and 1000 cm^{-1}; δ (250 MHz) 0.92 (3H, s), 0.96 (3H, s),

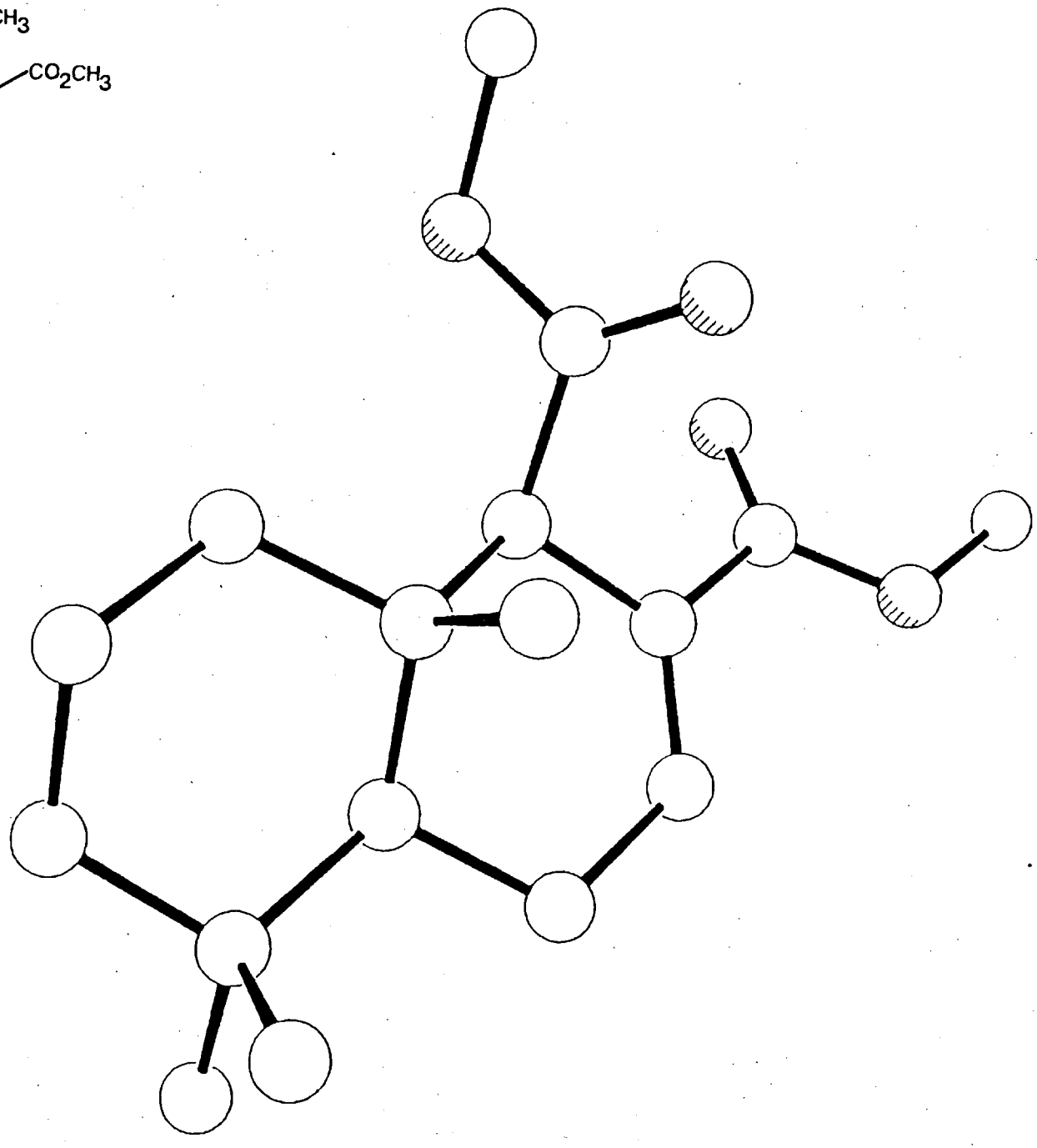
1.17 (3H, s), 1.1-2.0 (9H, m), 1.80 (1H, ddm, J 7.5, 13 Hz), 2.15 (1H, dm, J 18 Hz), 2.40 (1H, dm, J 18 Hz), 4.65 (1H, ddd, J 2, 3.5, 17.5 Hz), and 4.75 (1H, ddd, J 3, 3, 7 Hz); m/e 234 (M^+), 229, 189, 178, 123, 112, 110 and 109. (Found: C, 76.66; H, 9.47. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%).

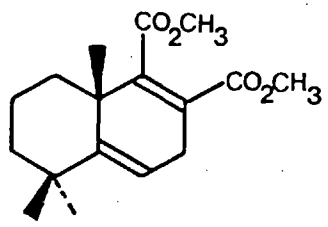
Preparation of 1,4,5,5a,6,7,8,9-octahydro-6,6,9a-trimethyl-1-hydroxy-[5aα,9aβ]-naphtho[1,2-c]-furan-3(1H)-one (Valdiviolide) (35).

(38) (17 mg, 0.078 mmol) in t-butanol-lutidine (5 ml, 2:1) containing eosin (ca. 0.5 mg) was irradiated with a 300 W quartz-iodine lamp at 25°C (cold finger) for 4 h with efficient oxygen circulation. The mixture was then evaporated and chromatographed on silica H (4 g, ether-hexane) to provide (35) (16 mg, 90%) as an oil which crystallised (m.p. 160°-168°C) on standing. Major isomer: ν_{max} 3360, 2980, 2860, 1755, 1675, 1460, 1390, 1150, 1015 and 910 cm^{-1}; δ (250 MHz) 0.91 (3H, s), 0.92 (3H, s), 1.25 (3H, s), 1.1-2.0 (9H, m), 2.13 (1H, m), 2.38 (1H, m), 3.95 (1H, s, OH) and 6.09 (1H, m); m/e 250.1564 (M^+), 232, 217, 205, 203, 135 and 123, ($C_{15}H_{22}O_3$ requires 250.1569).

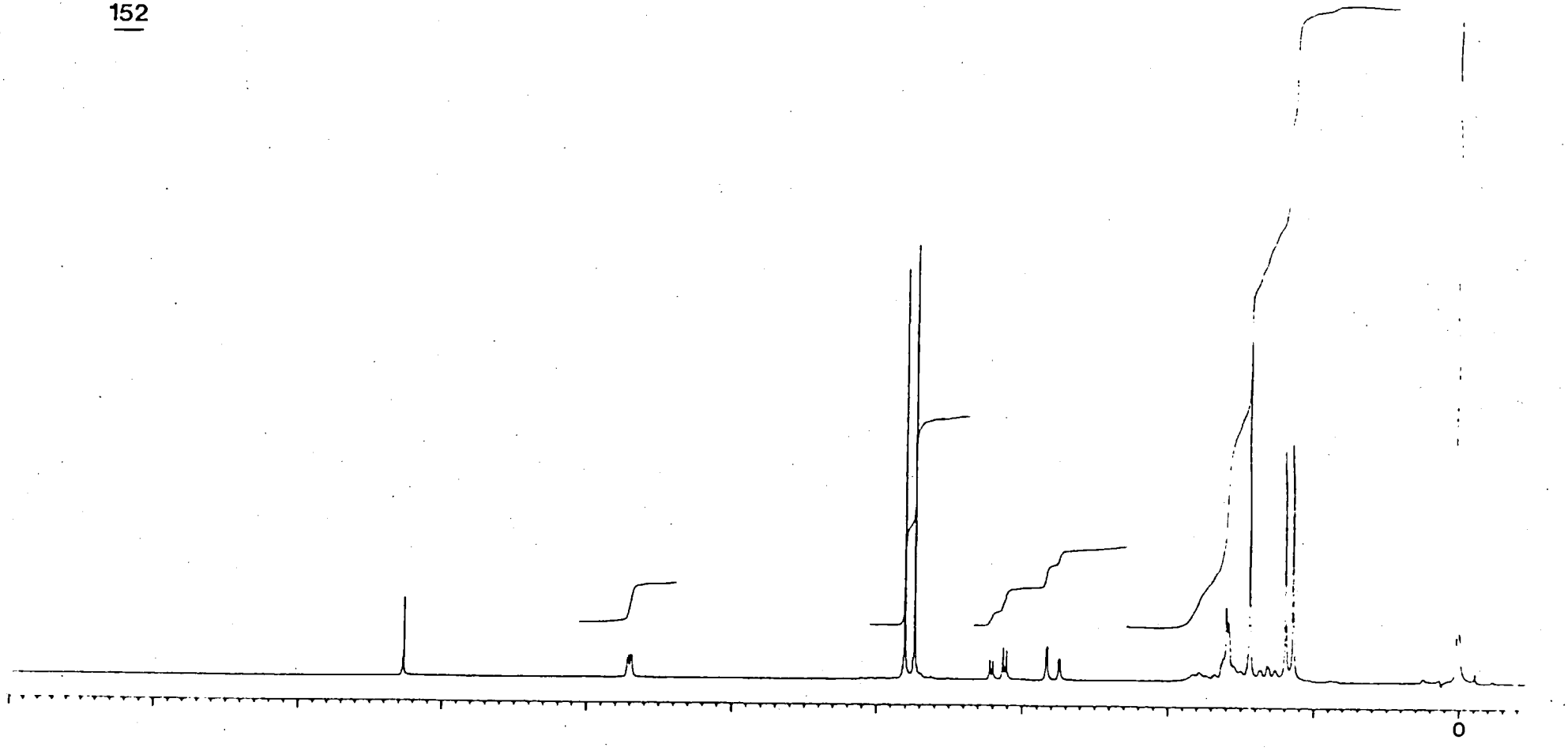


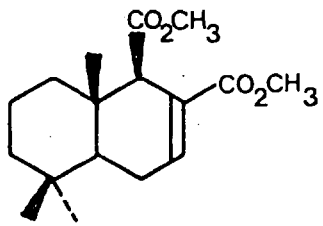
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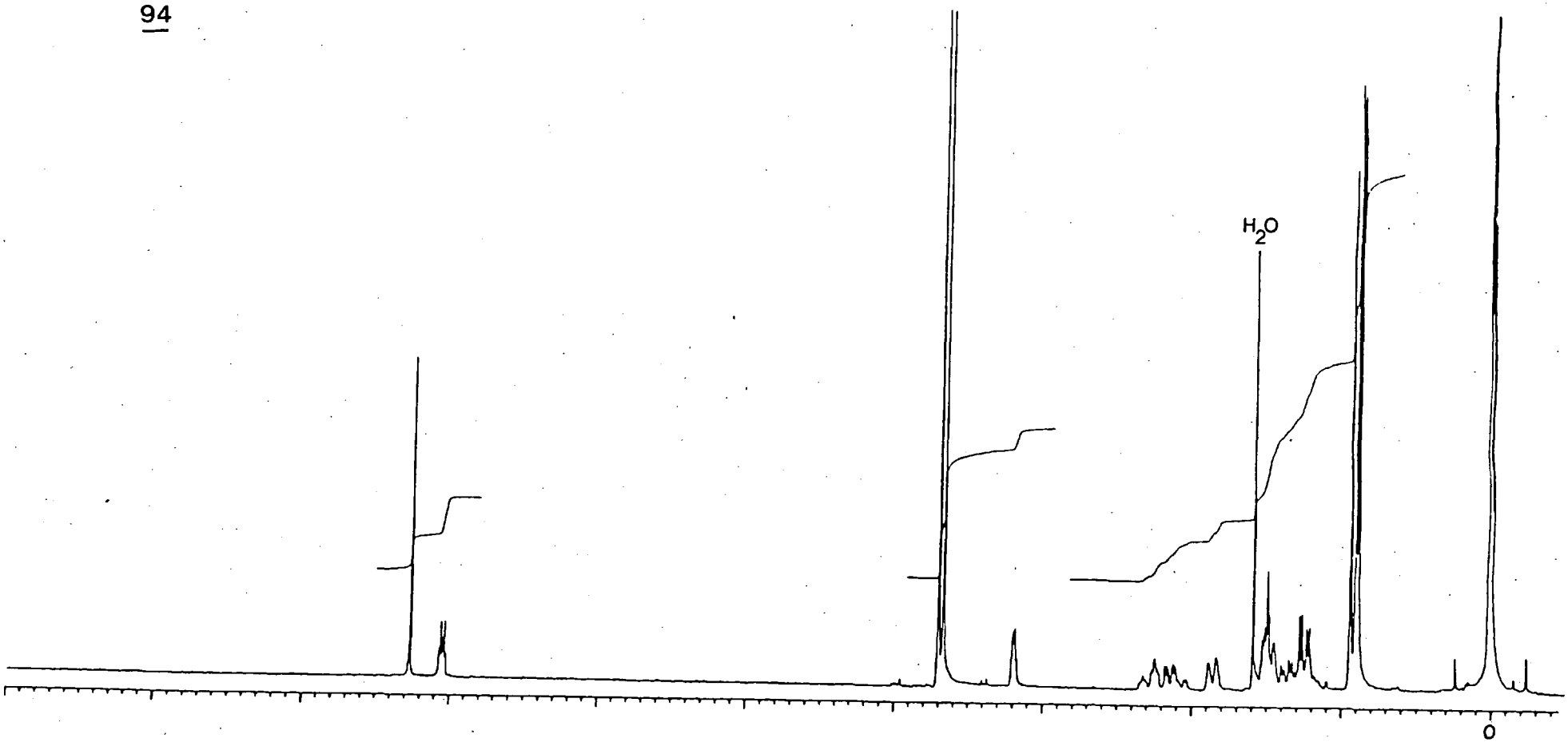


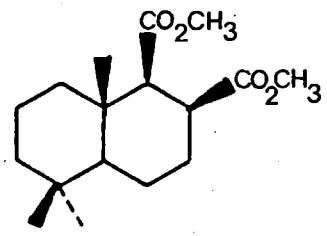
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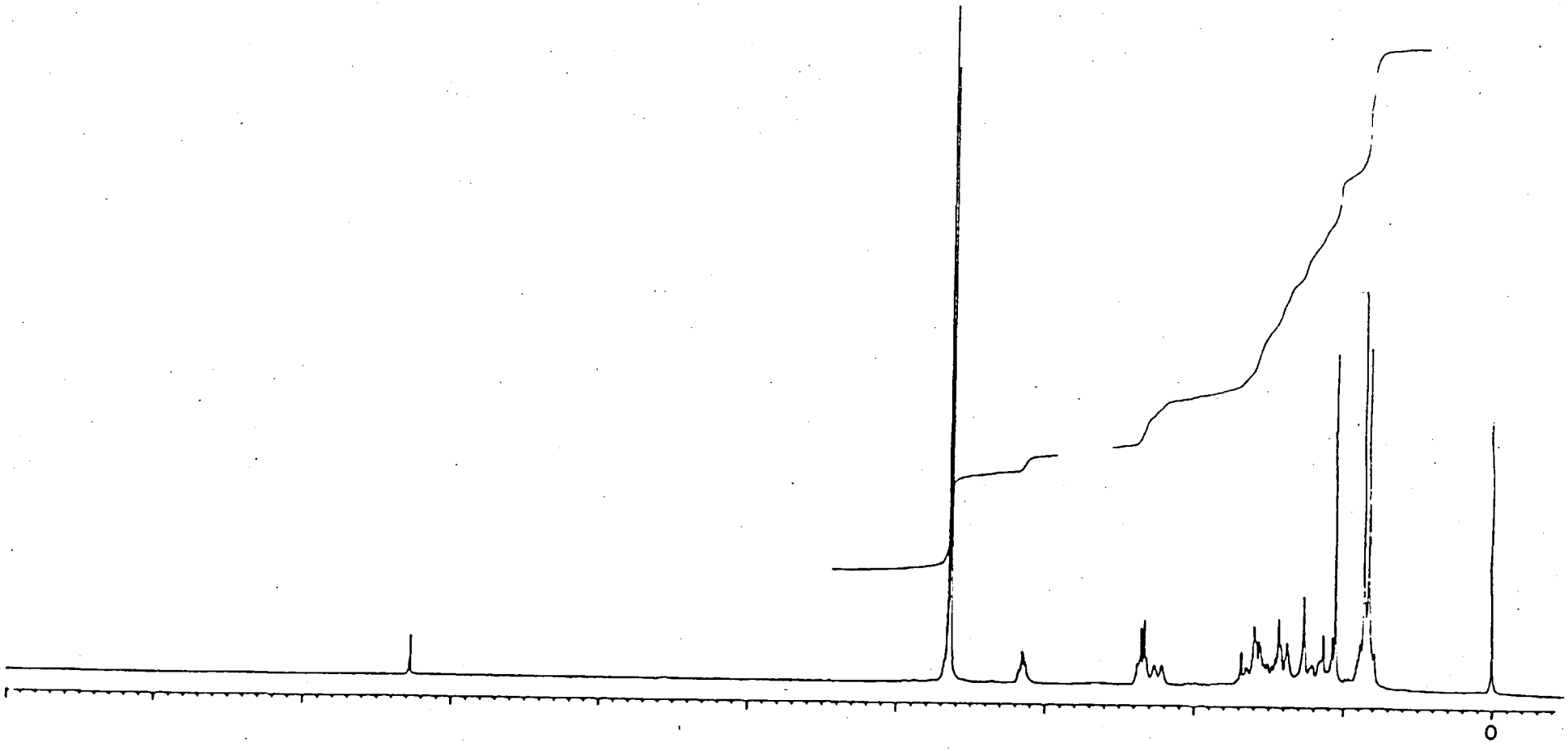


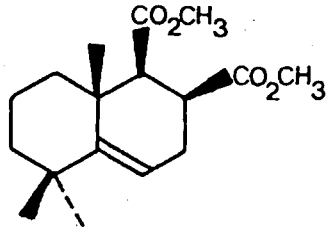
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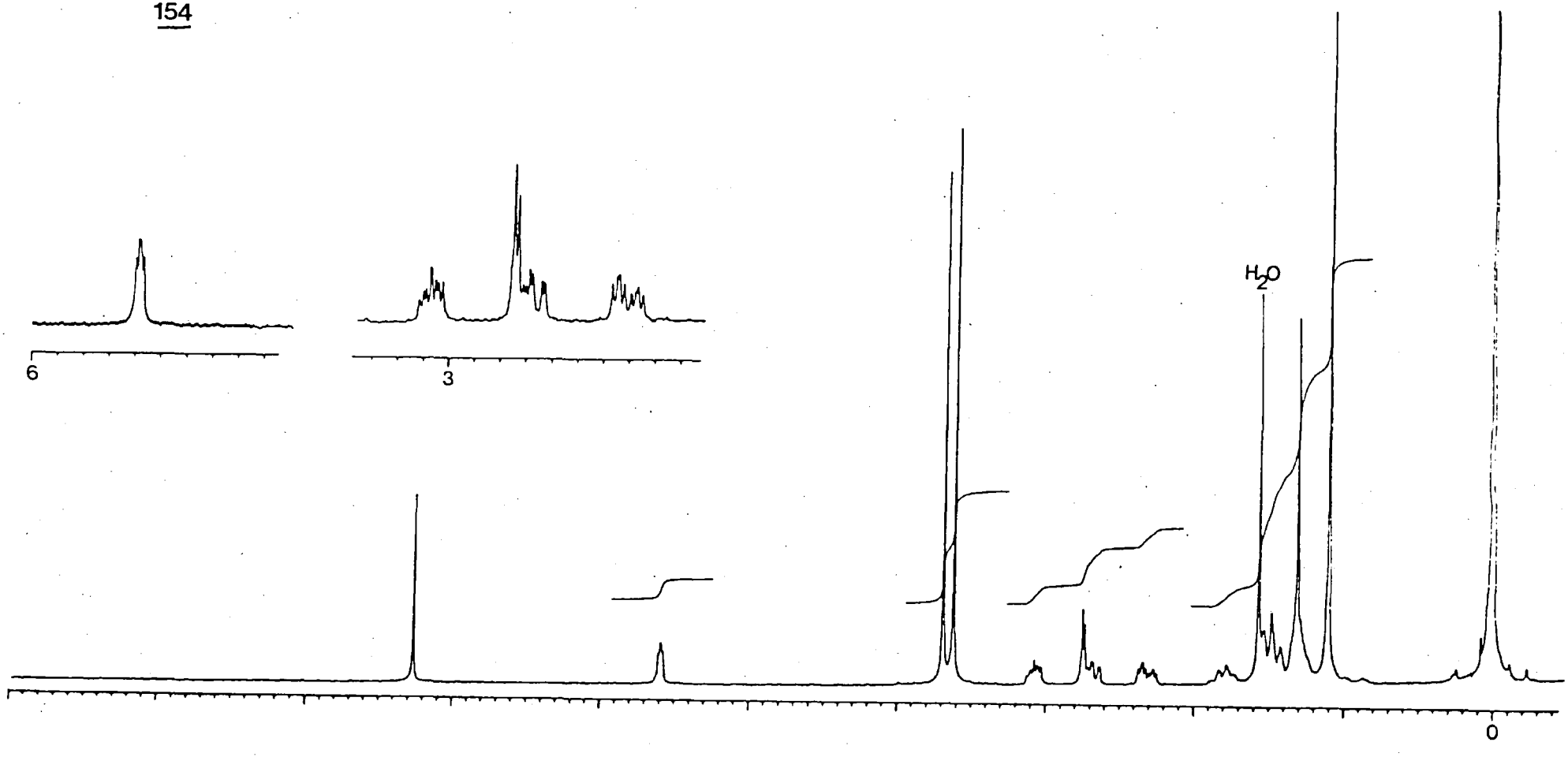


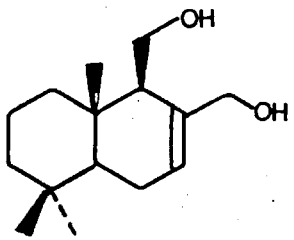
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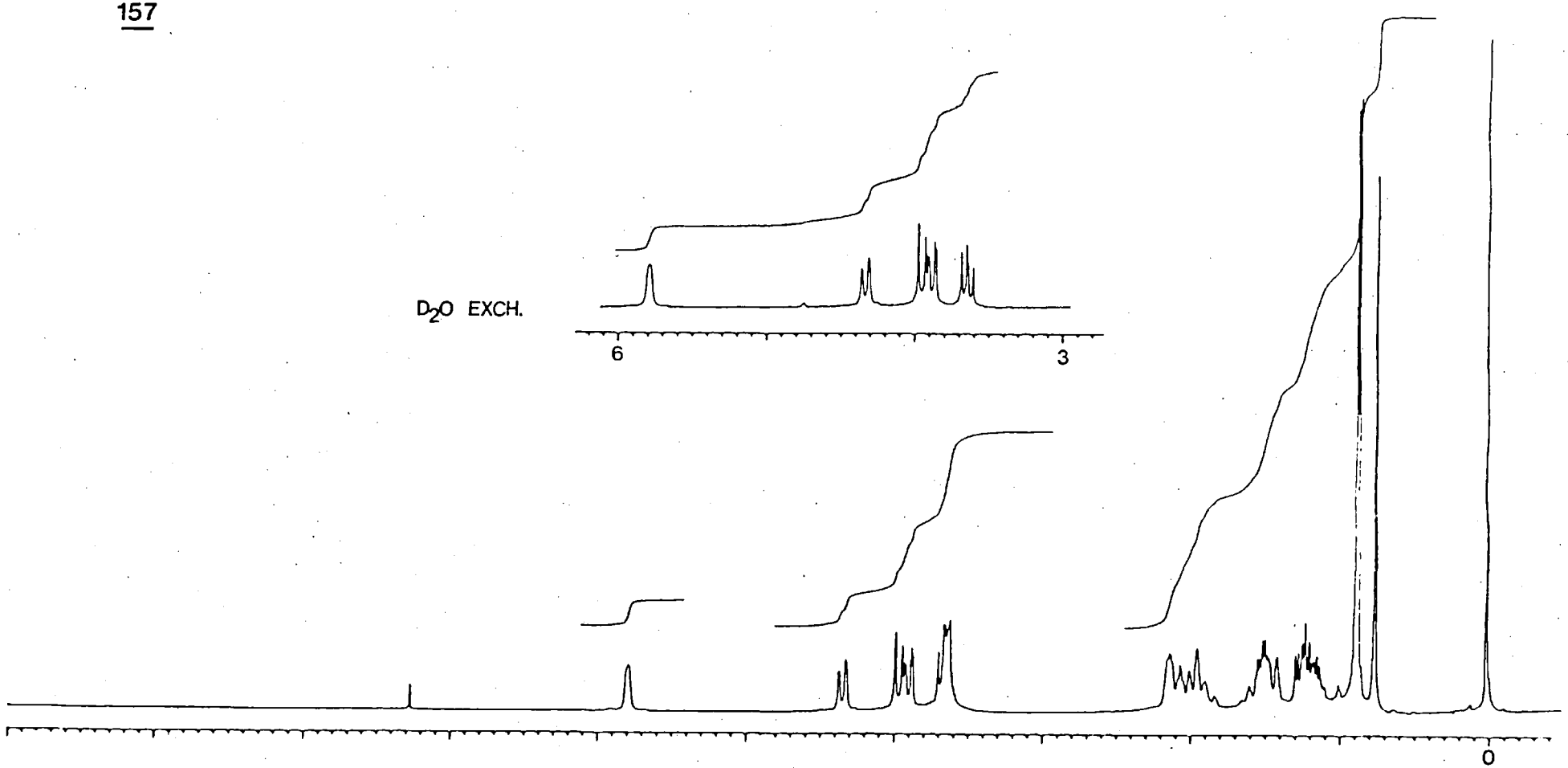


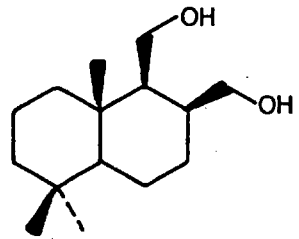
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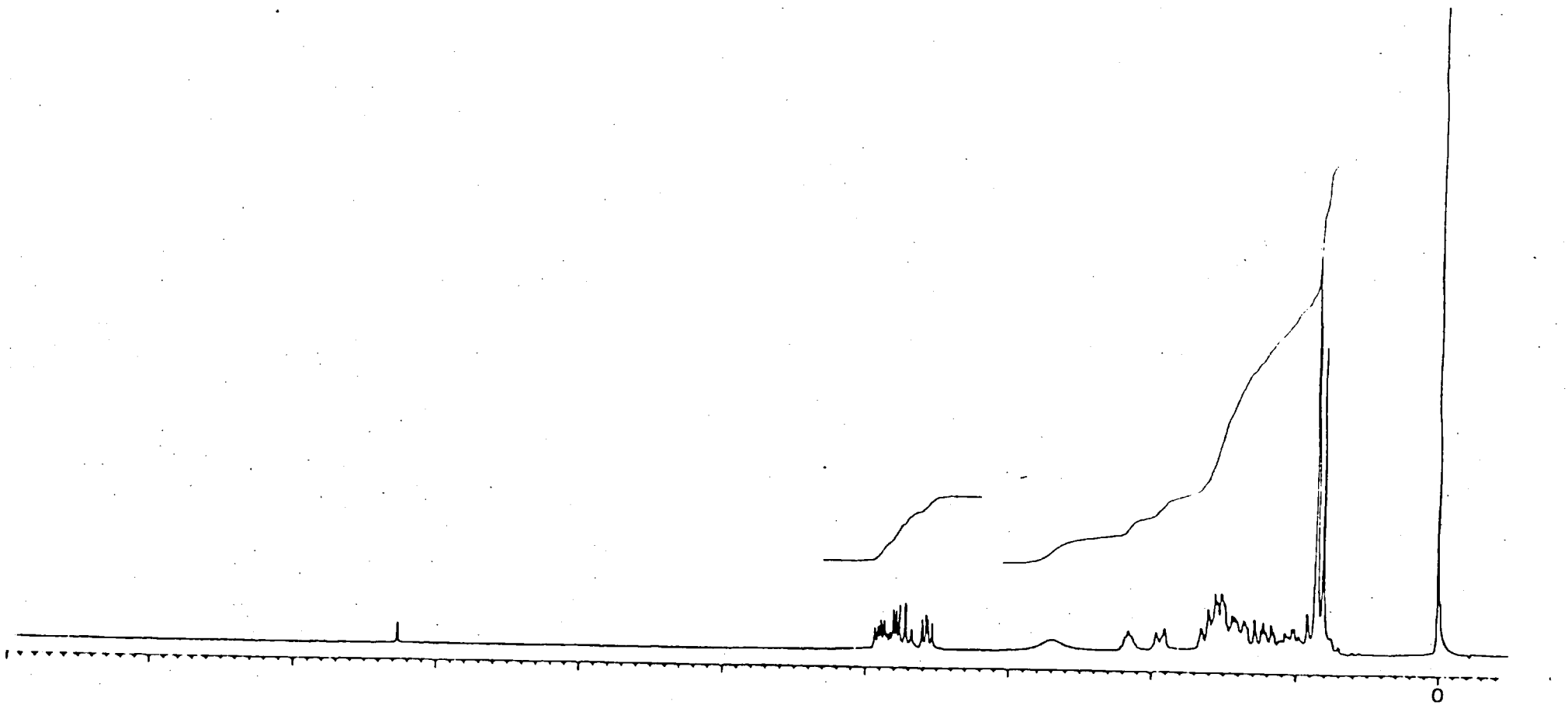


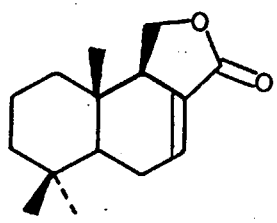
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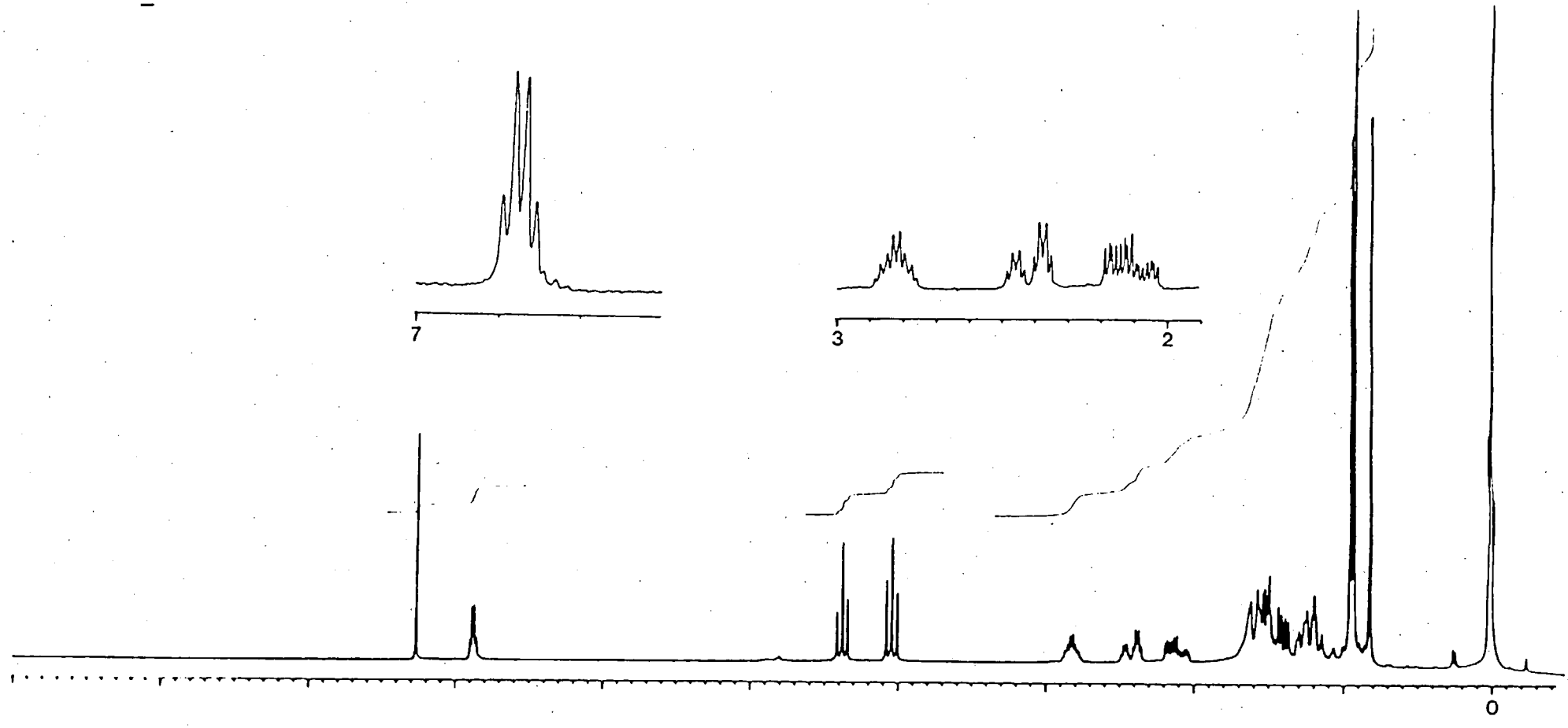


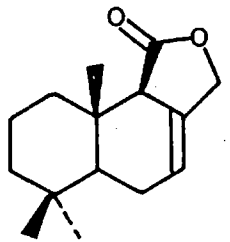
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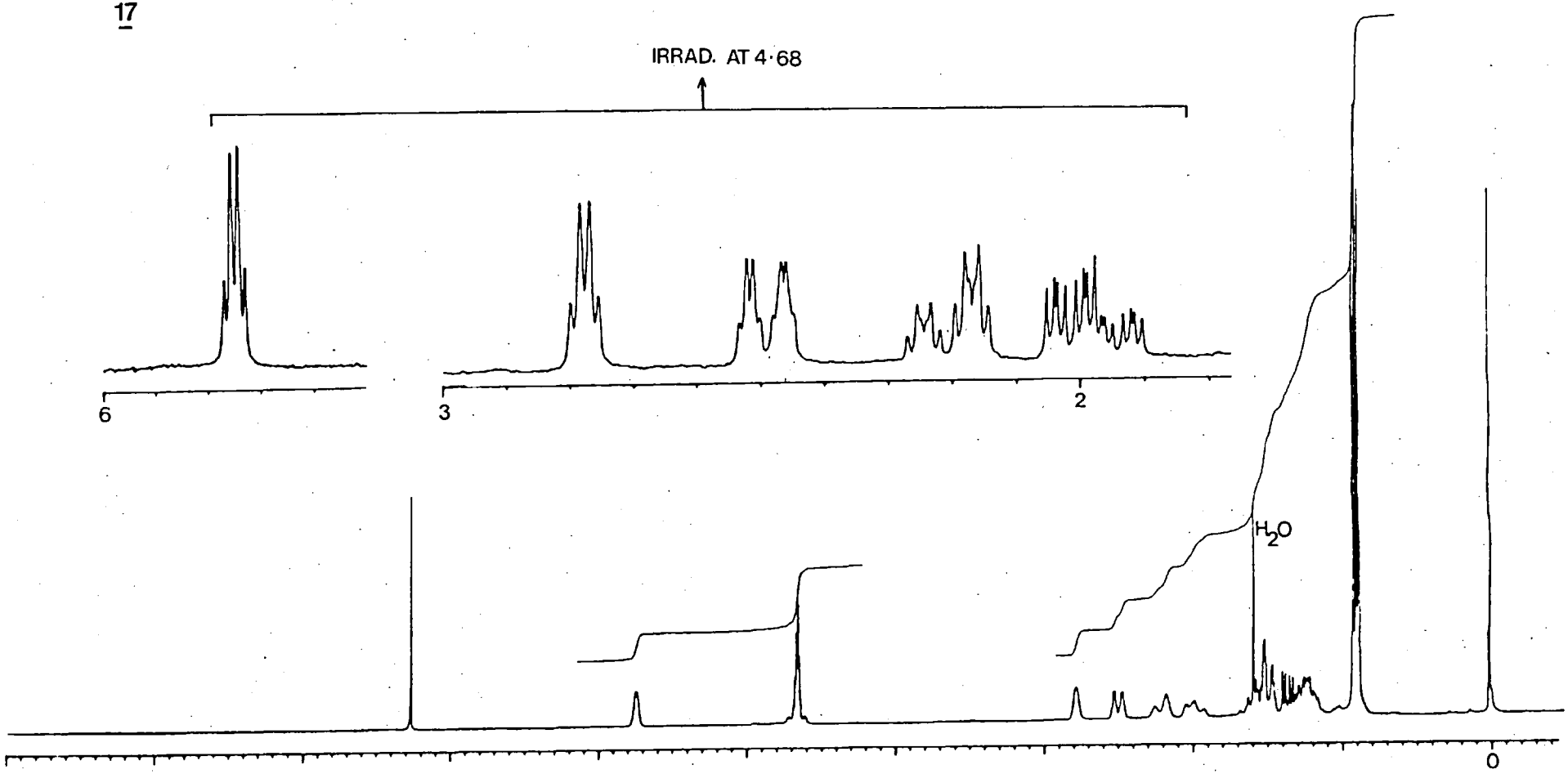


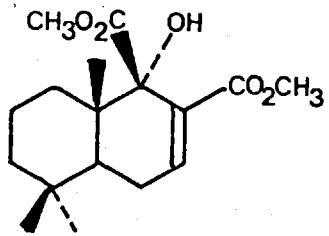
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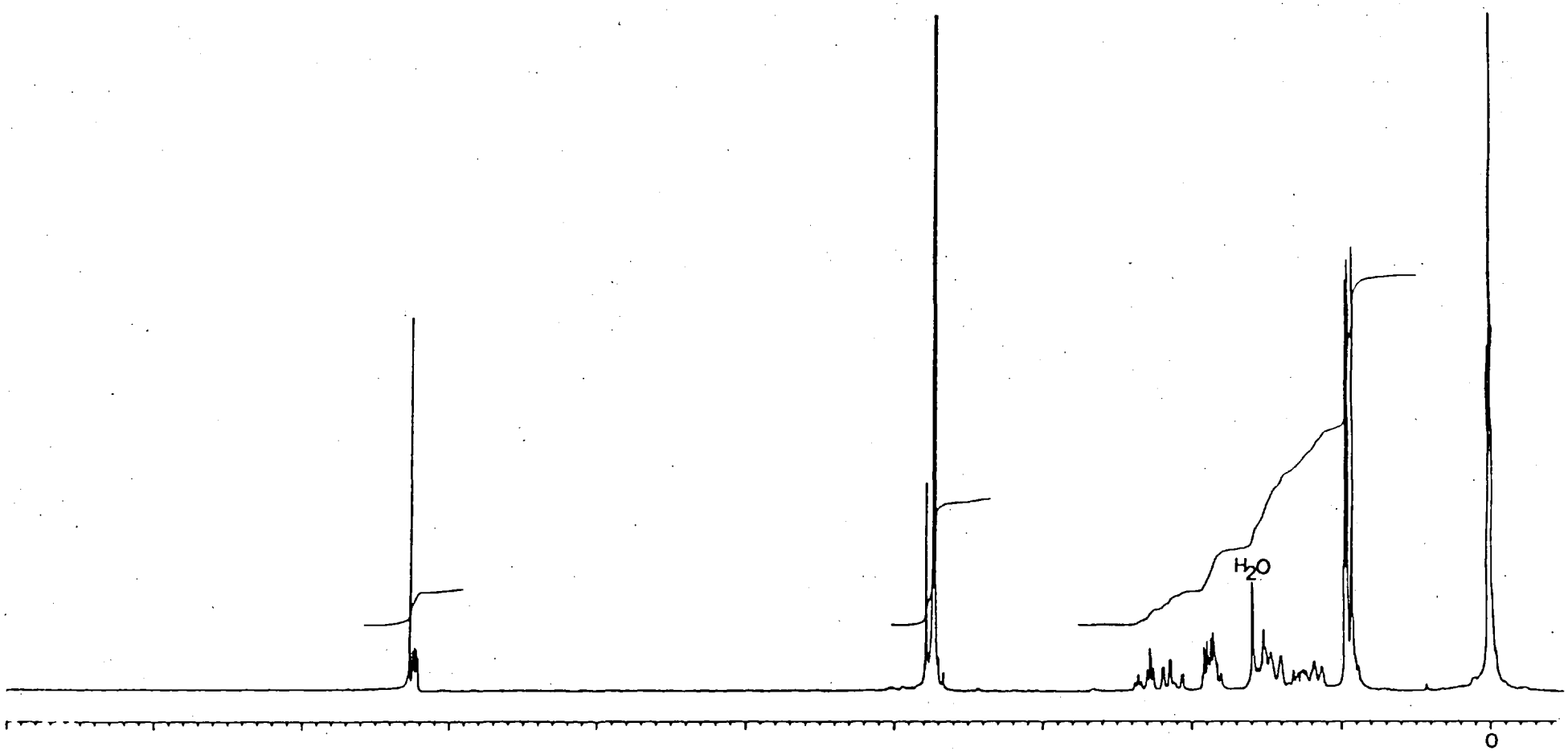


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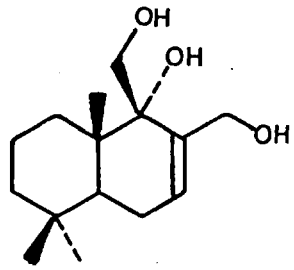




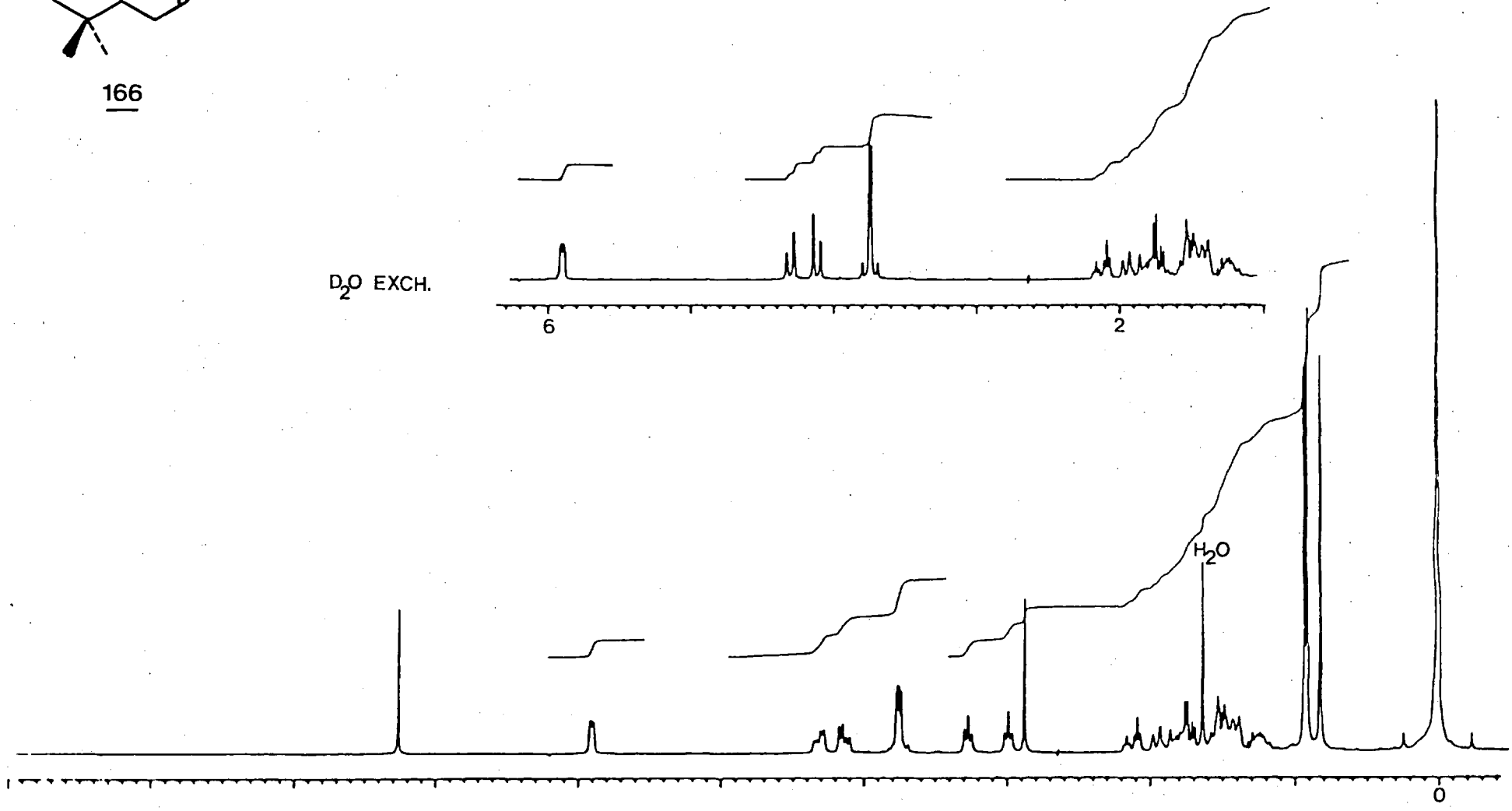
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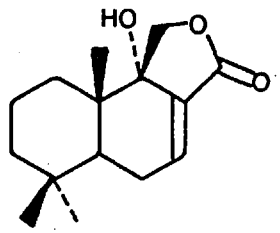


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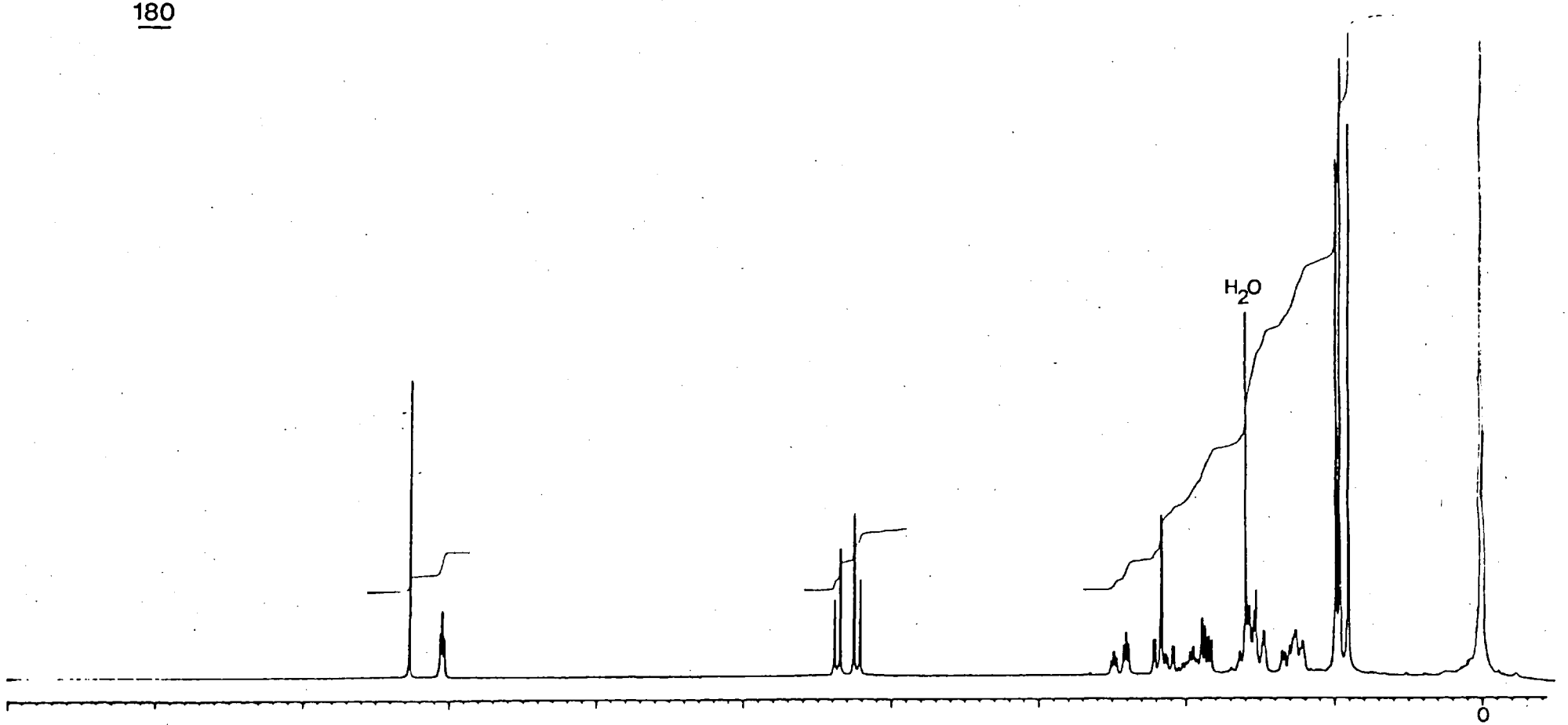


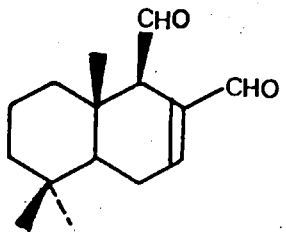
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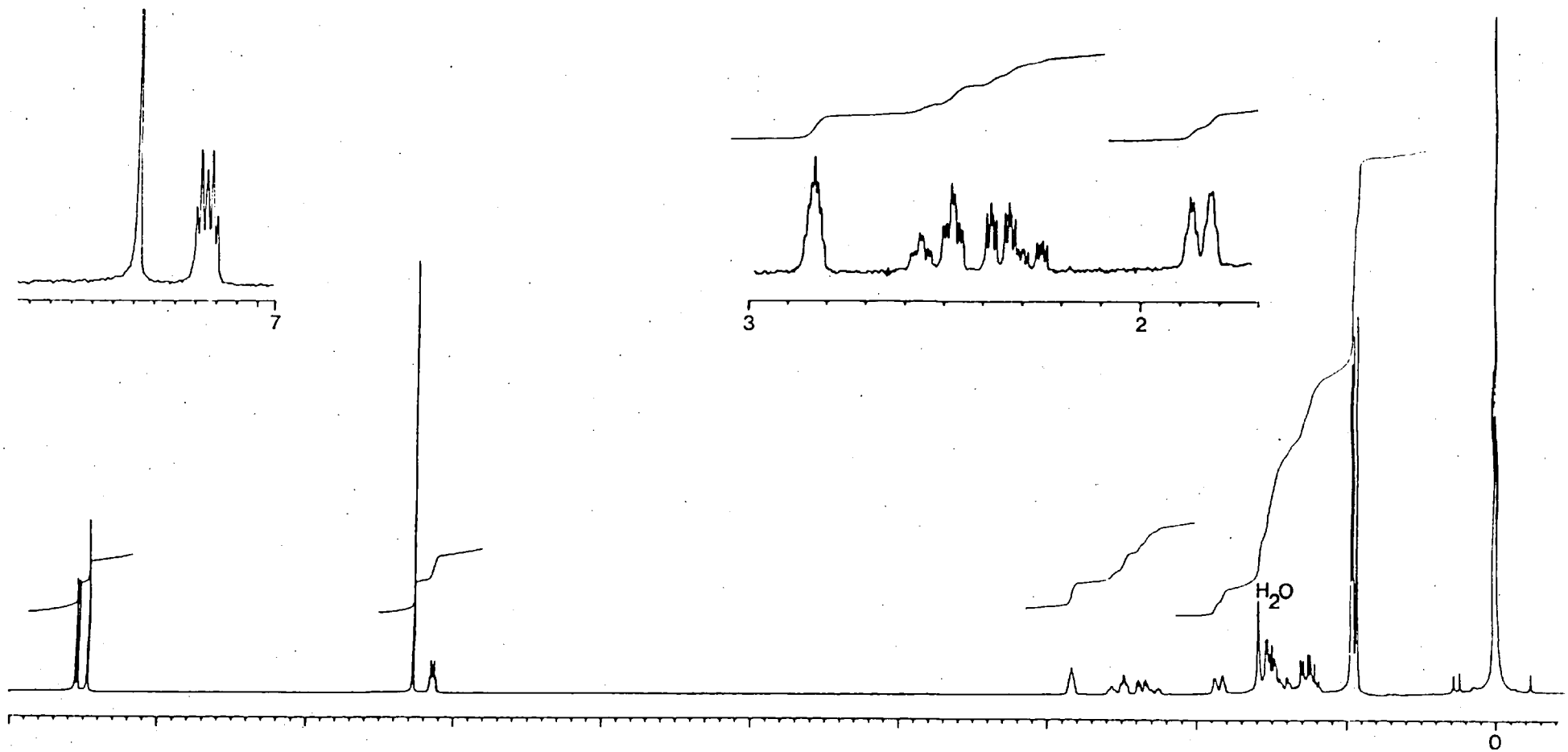


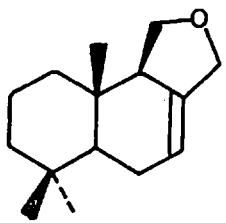
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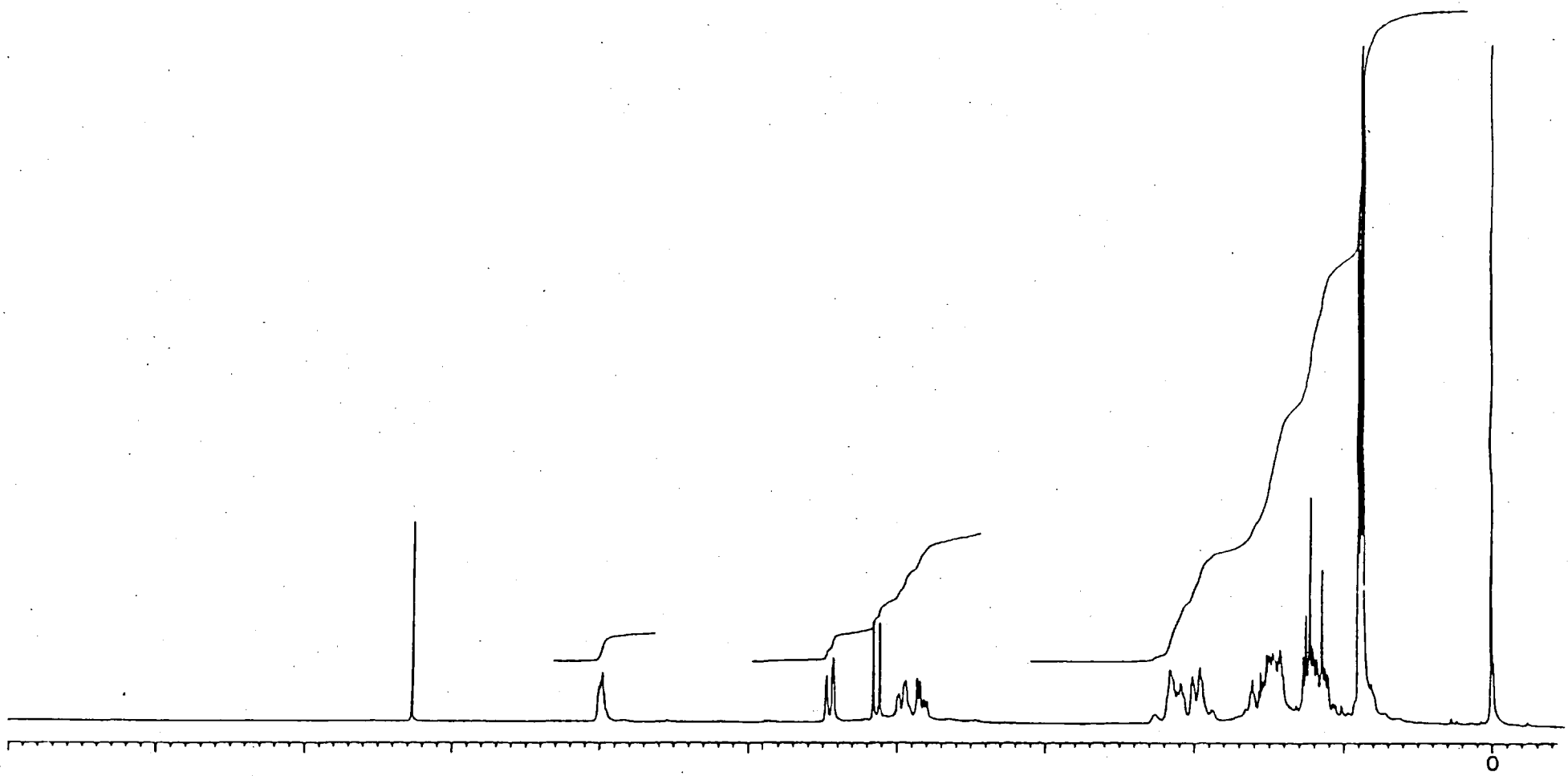


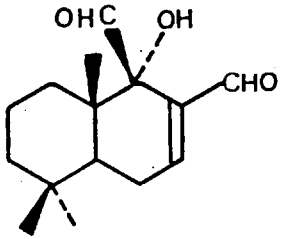
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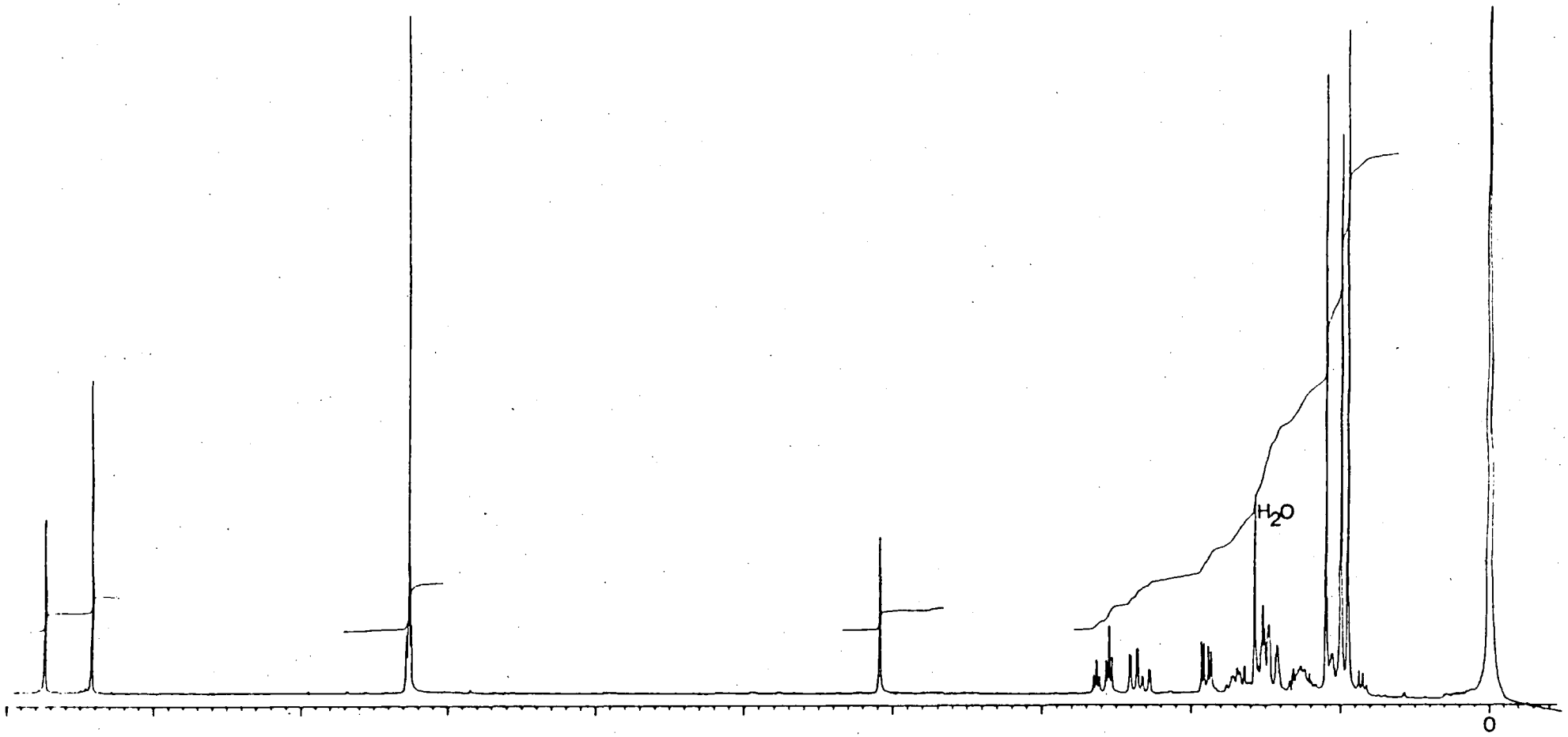


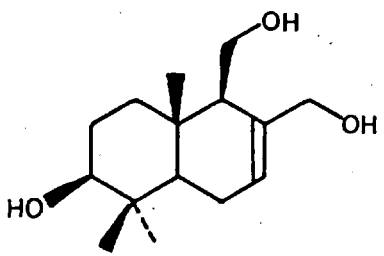
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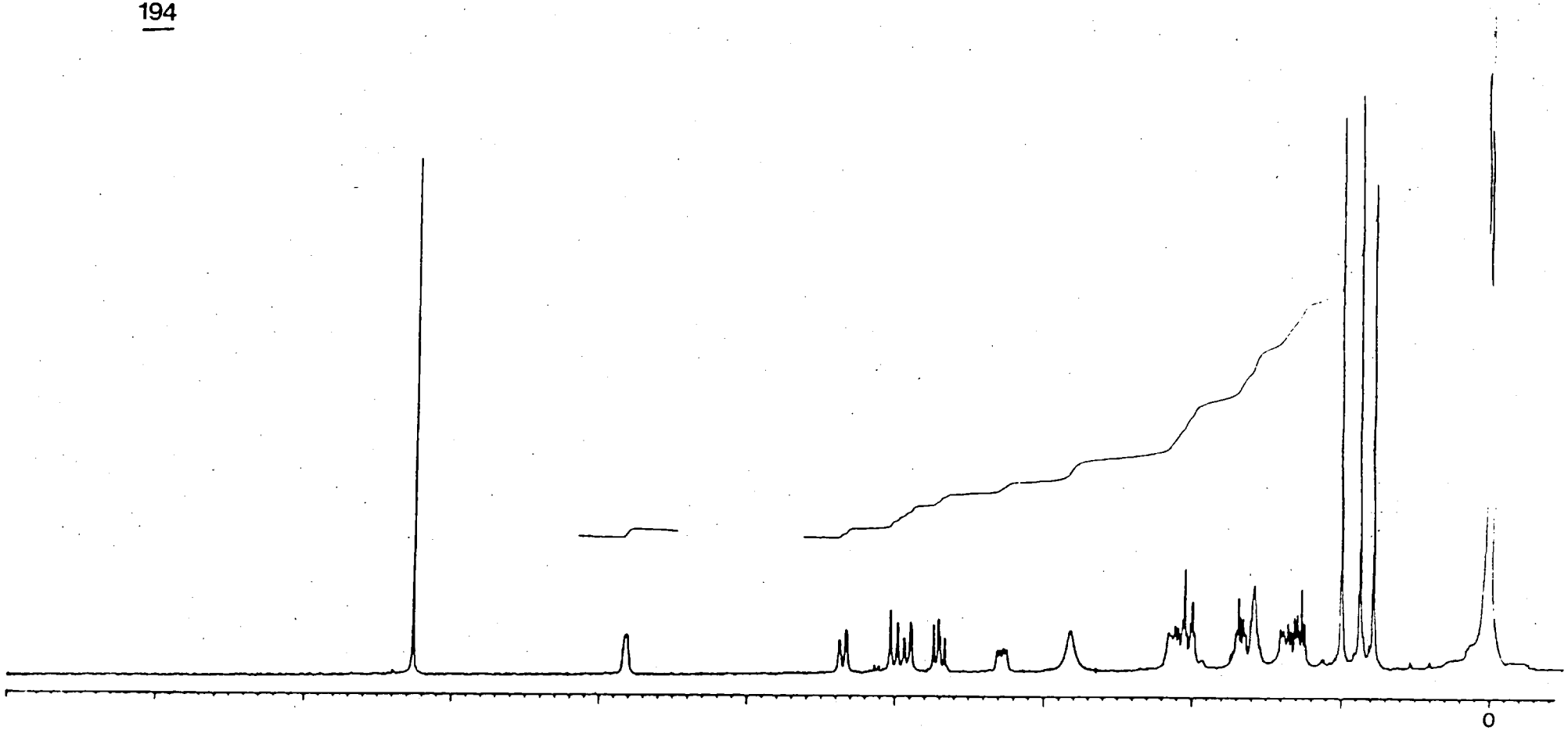


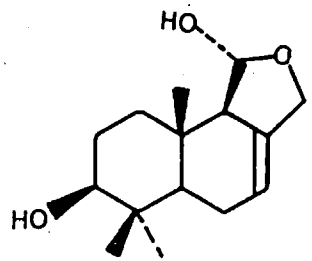
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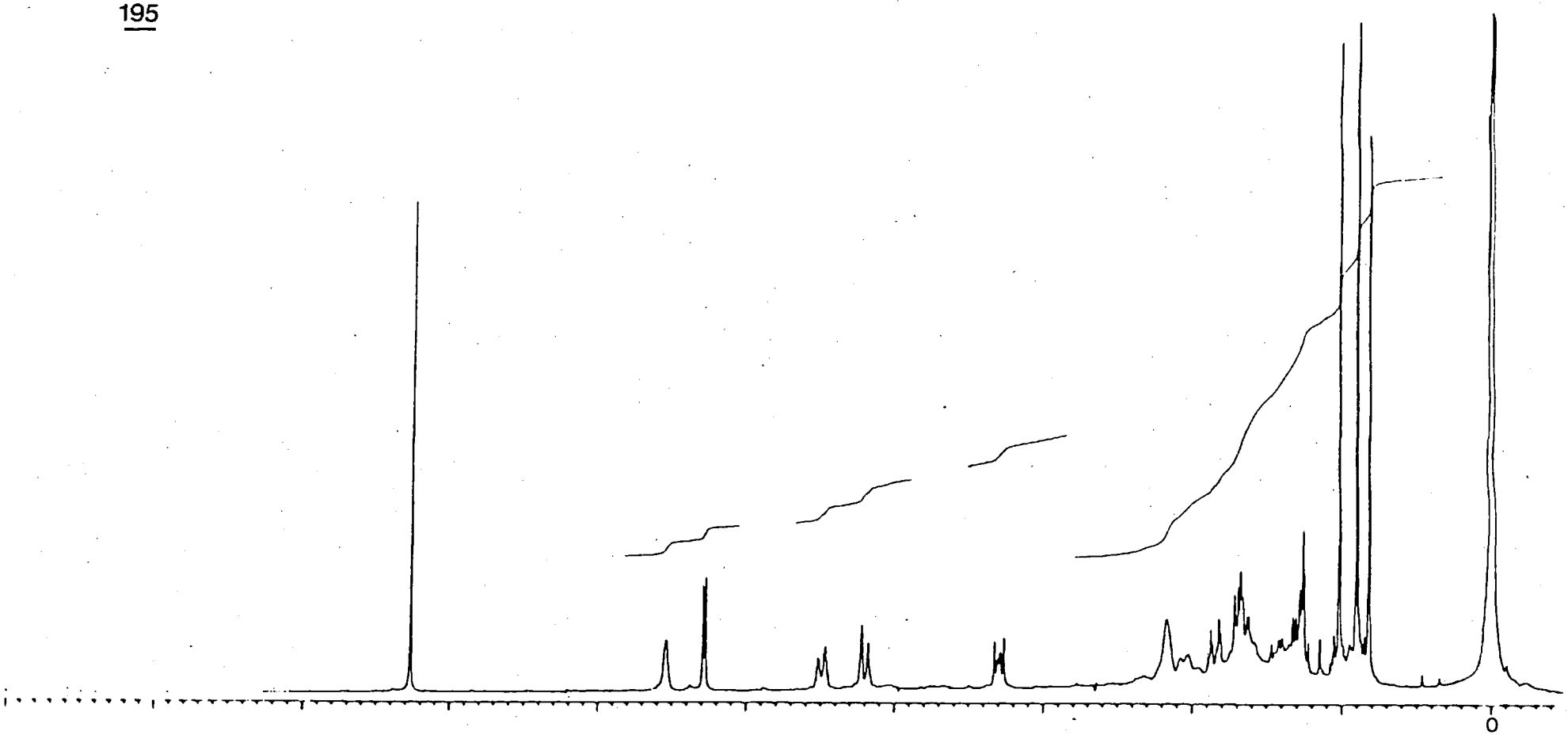


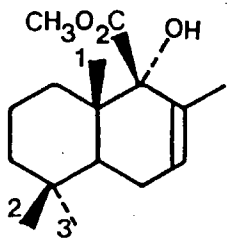
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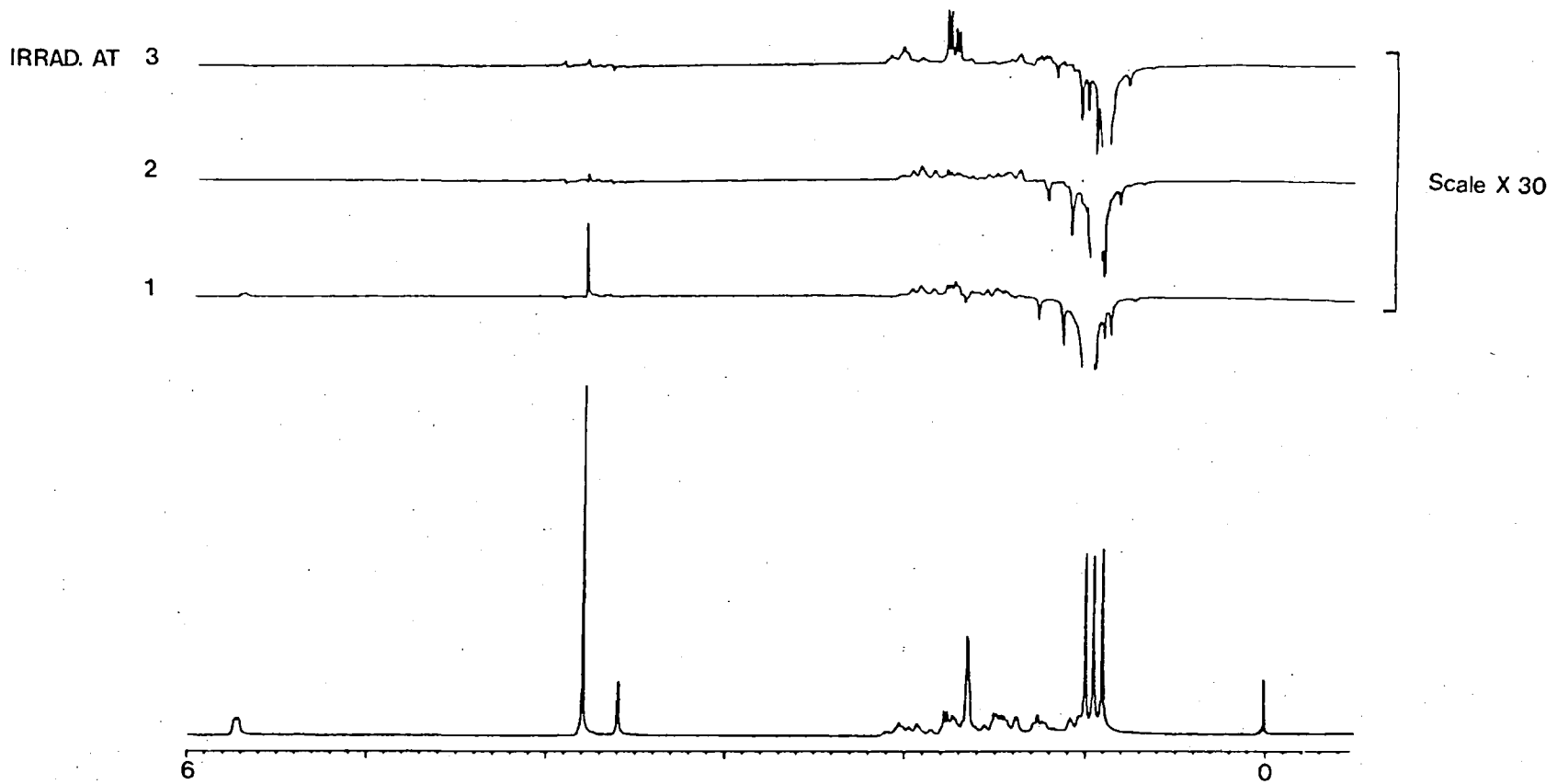


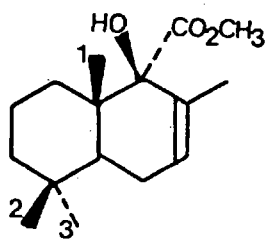
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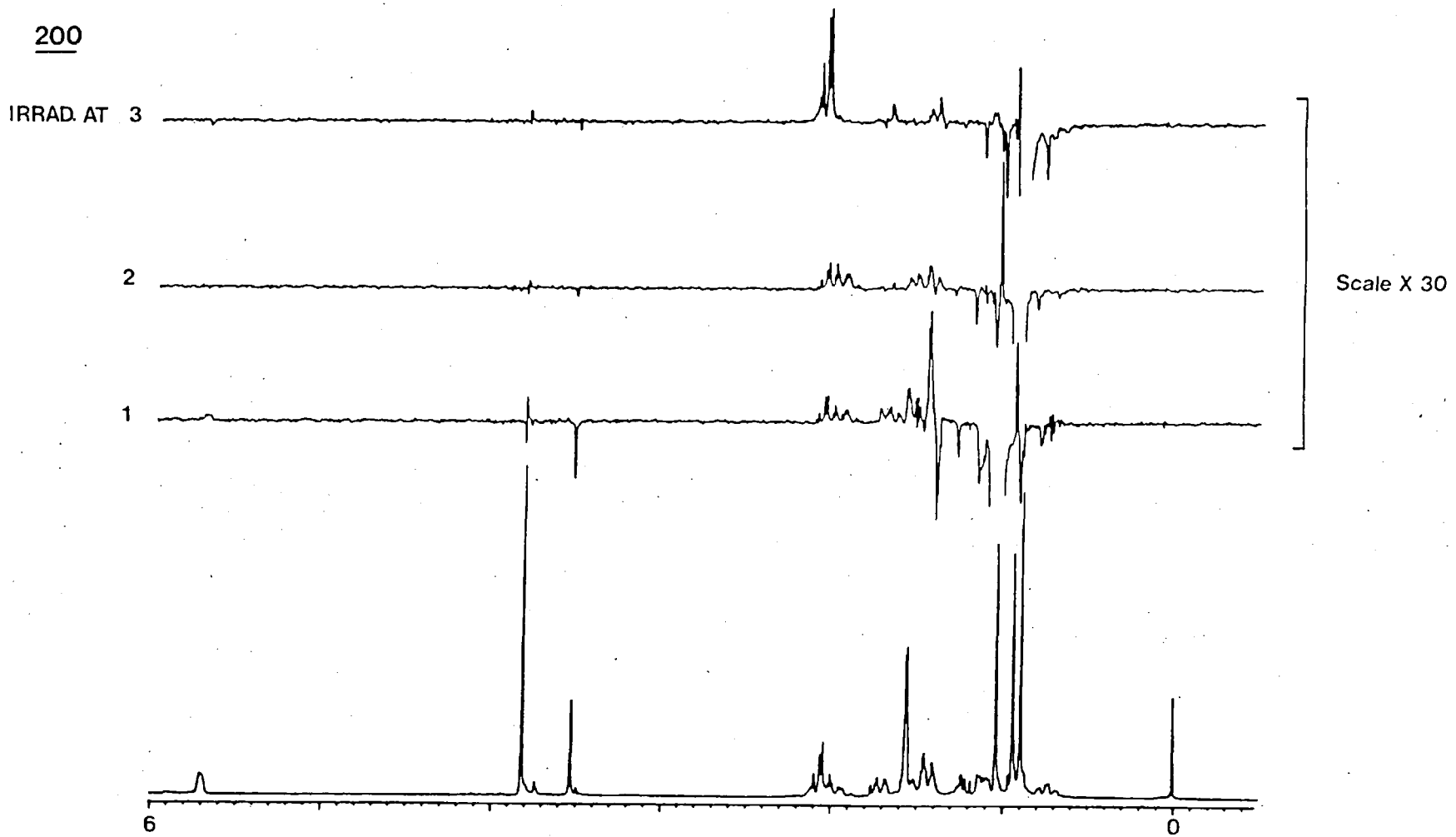


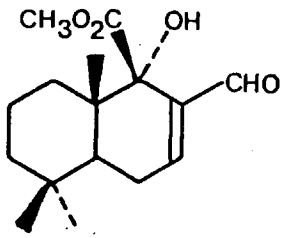
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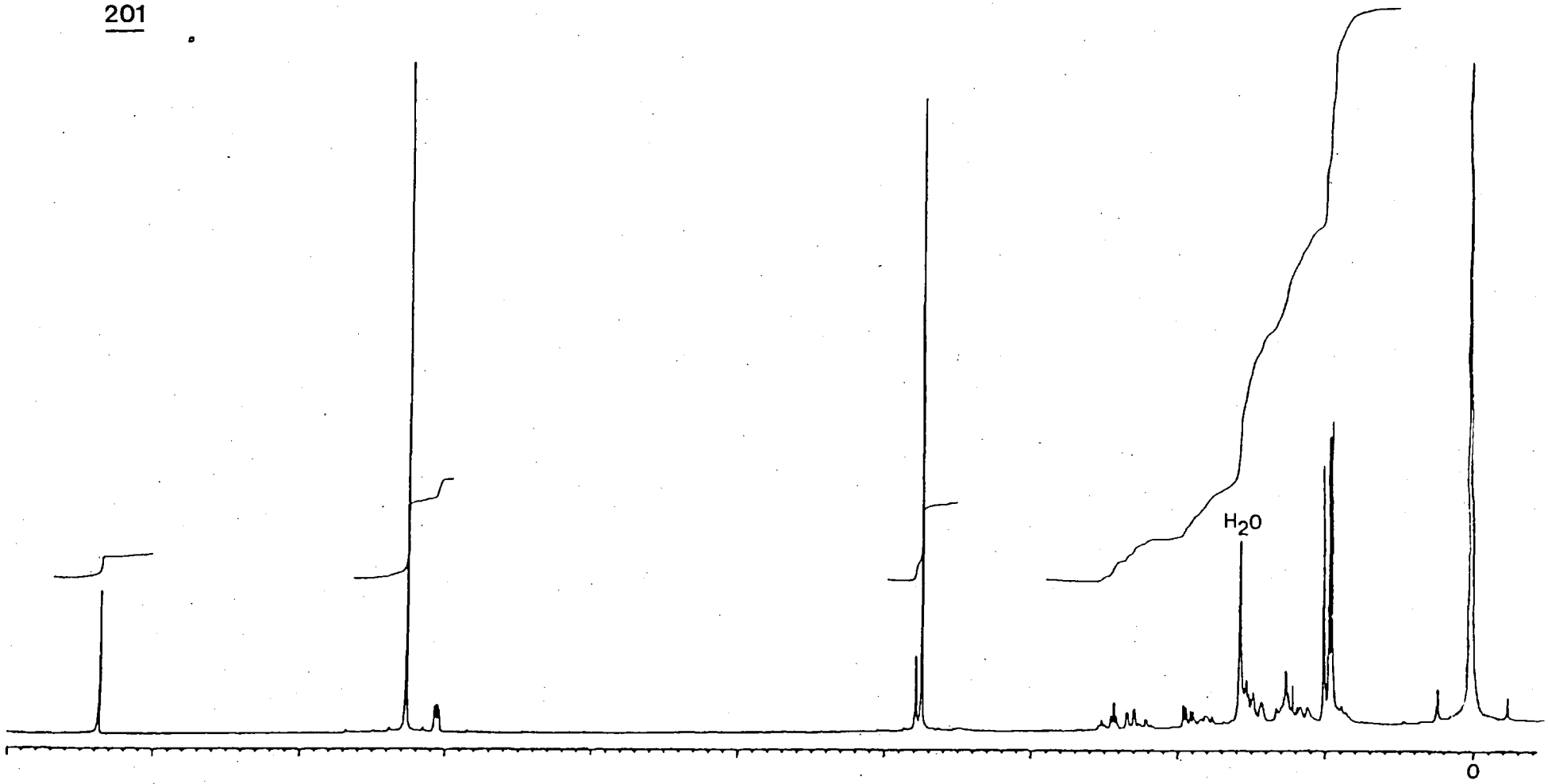


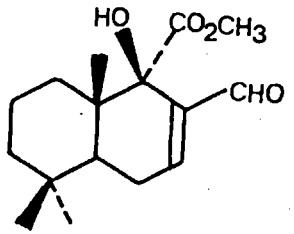
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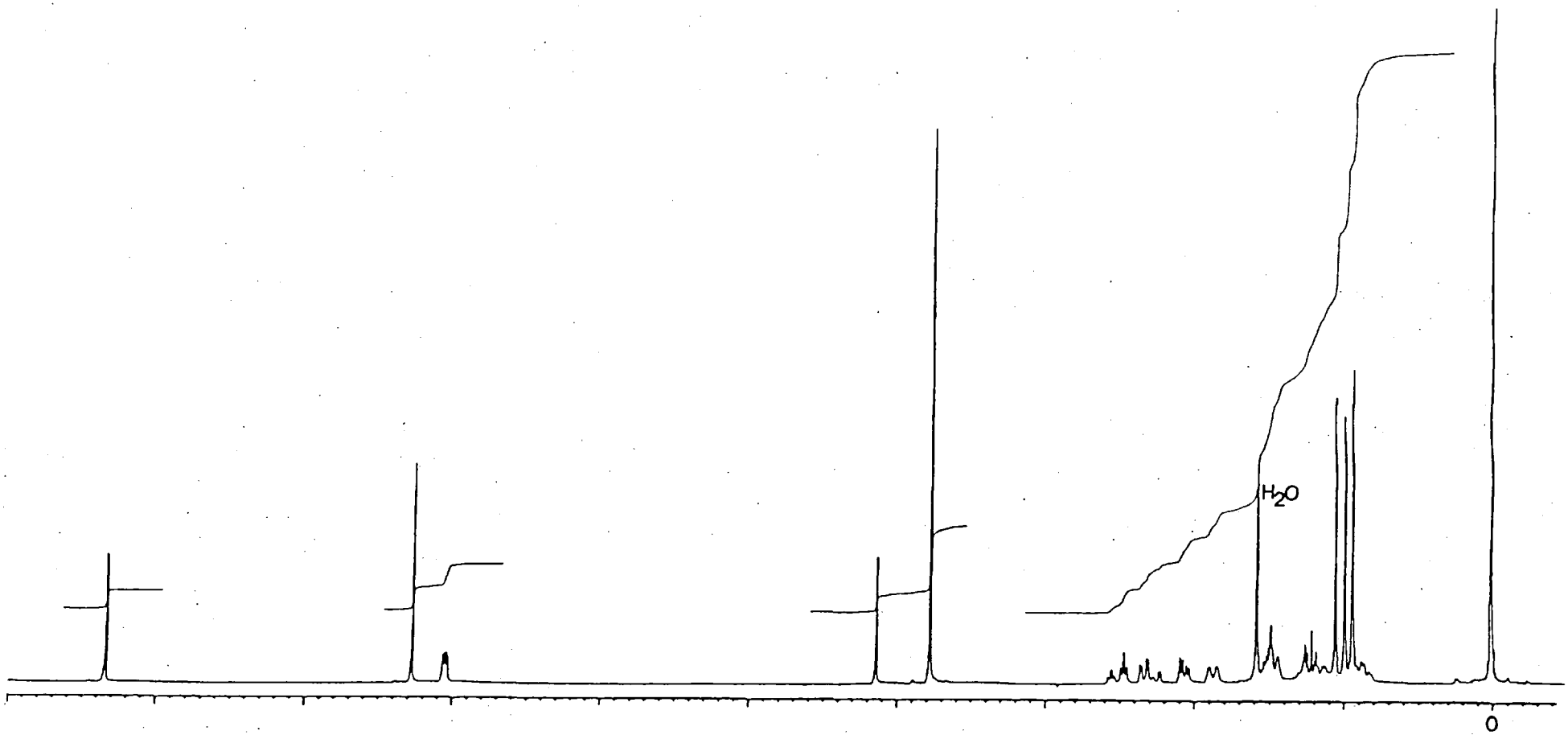


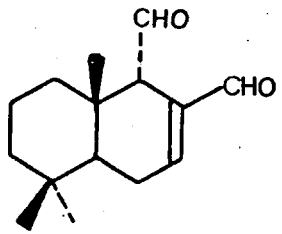
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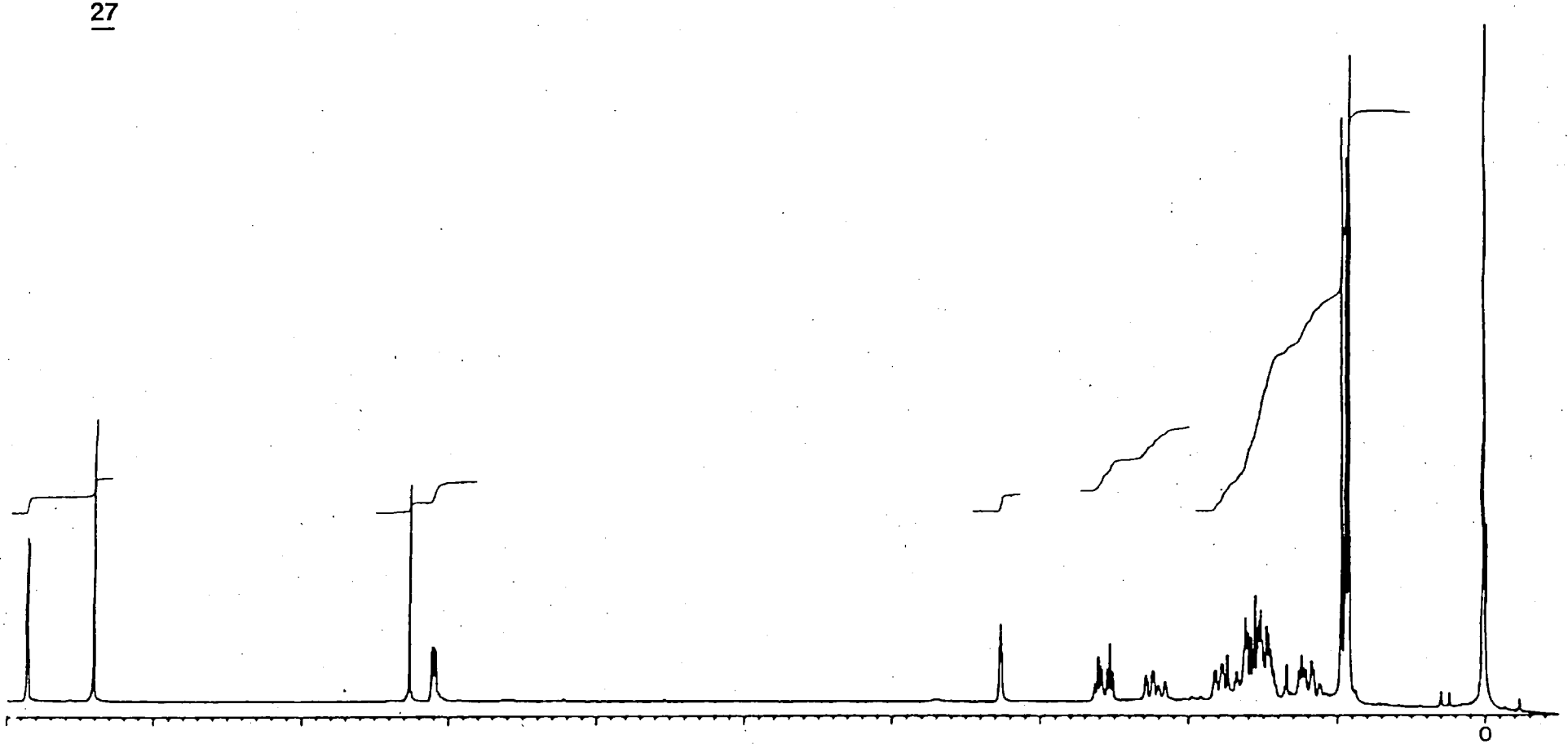


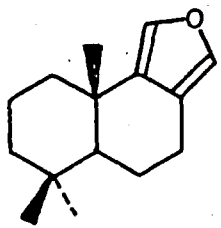
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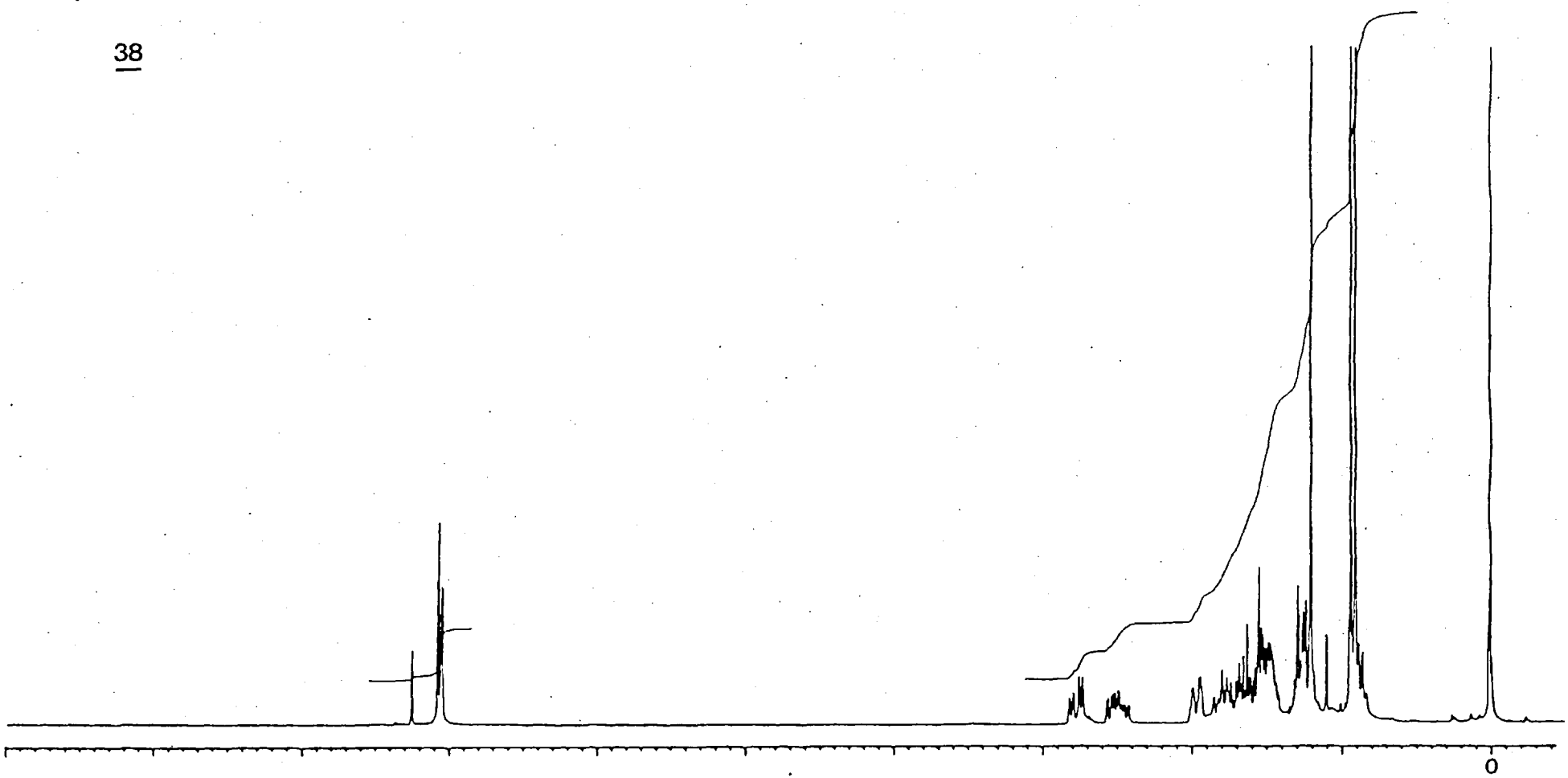


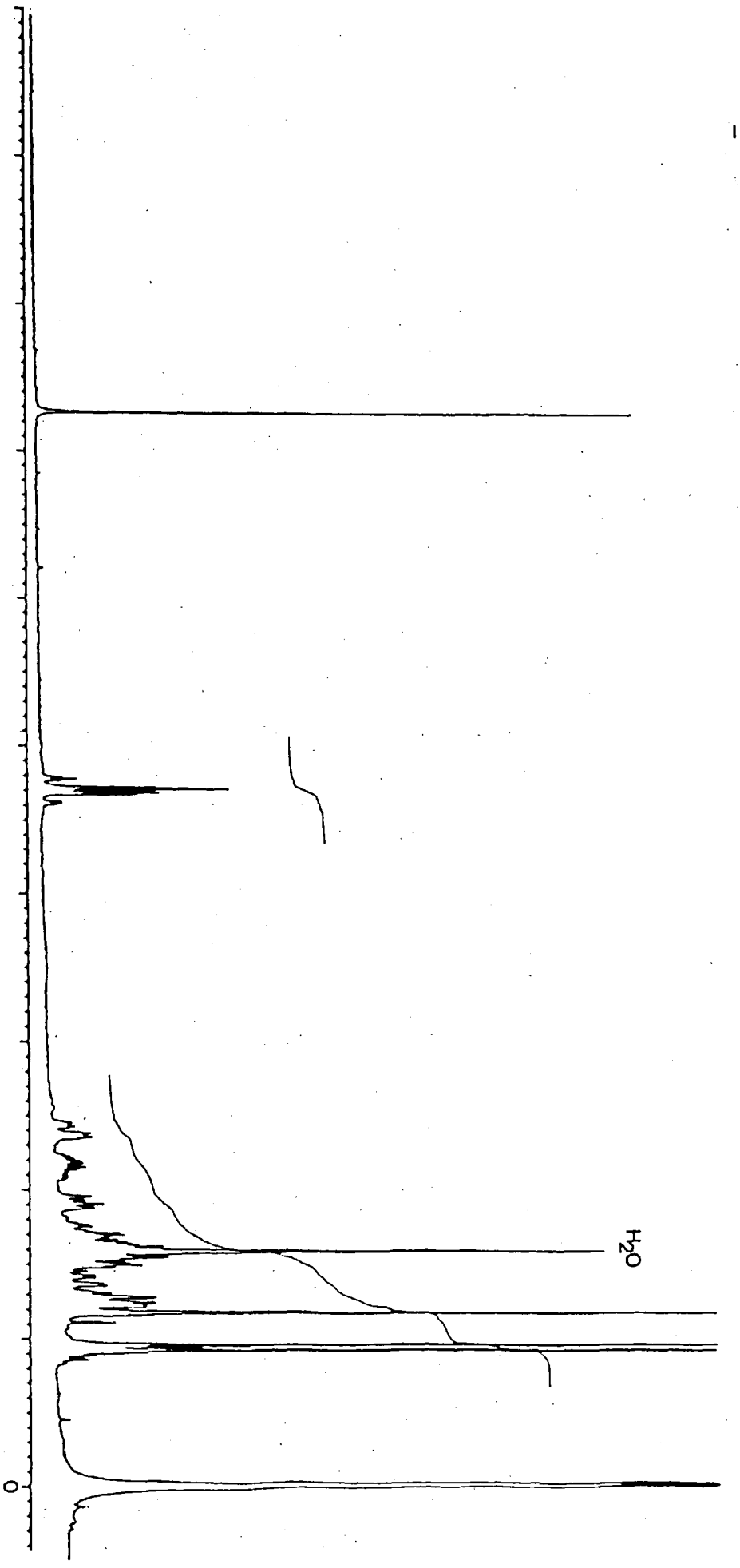
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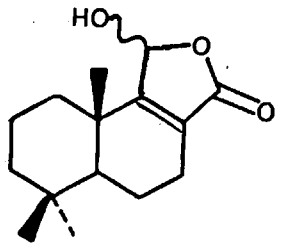


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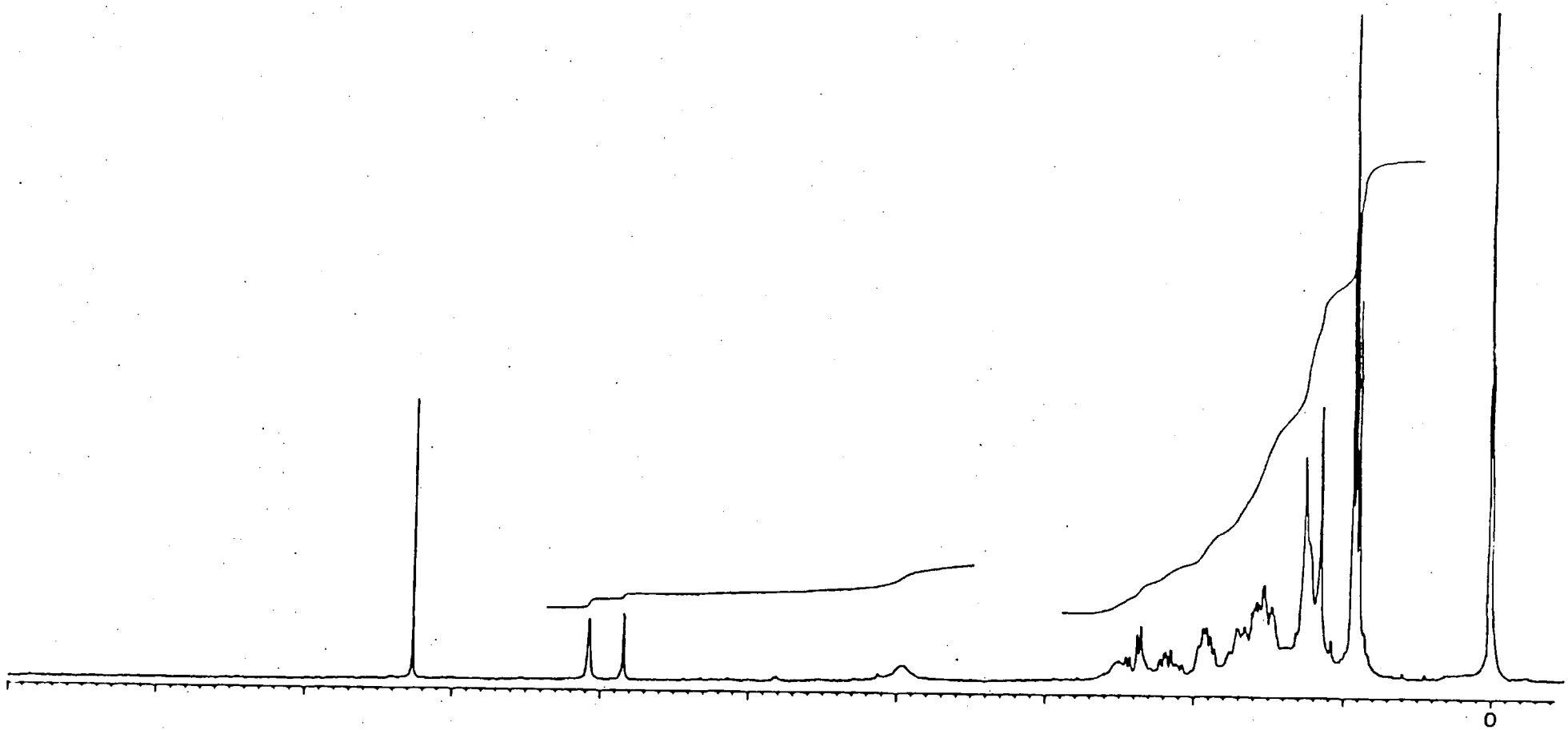




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35



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Synthesis of Cinnamolide and Polygodial

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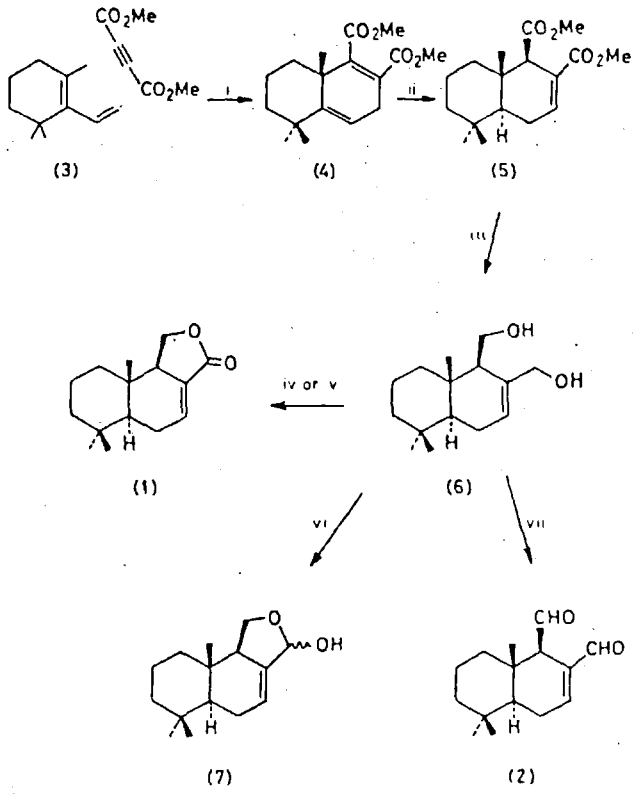
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Chemical Communications 1981

Synthesis of Cinnamolide and Polygodial

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Summary Starting from 2,6,6-trimethyl-1-vinylcyclohex-1-ene a short synthesis of the sesquiterpenes cinnamolide and polygodial has been achieved with 60% and 57% overall yields, respectively.

PREVIOUS synthetic routes to cinnamolide (**1**)[1] and the potent insect antifeedant polygodial (**2**)[1b,2] are unattractive, especially if reasonable quantities of material are required. Here we report a short, highly efficient synthesis



SCHEME. i, 110 °C, 24 h; ii, 1 atm of H_2, Pd/C 10%, trace of HCl, dil. methanol; iii, $LiAlH_4$; iv, 10—20 equiv. of $BaMnO_4$, CH_2Cl_2, 24 h; v, Ag_2CO_3/Celite; vi, 1—2 equiv. of $BaMnO_4$, CH_2Cl_2, 4 h; vii, dimethyl sulphoxide/$(COCl)_2$ 4 equiv., — 50 °C, 1 h, and then 6 equiv. of NEt_3.

of these natural products starting from the readily available diene (3).† Our route employs a similar strategy to that of Nakanishi;[1b] however, by a careful choice of reagents we can avoid the use of protecting groups.

Diels–Alder reaction of (3) with dimethyl acetylenedicarboxylate readily affords (4) in 83% yield (Scheme). Hydrogenation of (4) under isomerising conditions[2] (1 atm of H_2, Pd/C, trace of HCl, methanol) led directly to the *trans*-fused decalin‡[1b] (5) in high yield (80%). Reduction of (5) with lithium aluminium hydride gave the key drimane diol (6) (90%), m.p. 73—74 °C (lit.[1b] 73—74 °C). Oxidation of this diol with an excess of barium manganate[4] gave cinnamolide (1) in 94% yield, or quantitatively using Fetizon's reagent.[5] Compound (1) was identical in all respects to the previously prepared material.[1b] Oxidation of (6) using only 1—2 equiv. of barium manganate gave the known lactol (7) (92%) (m.p. 95—98 °C, lit.[1c] 95—97 °C).

In order to achieve specific oxidation of (6) to polygodial (2) as opposed to (1) or (7), special reaction conditions were required. Thus, it was found that the Swern method[6] (dimethyl sulphoxide/oxalyl chloride) uniquely effected this transformation in 95% yield. The polygodial produced was identical to authentic material {^{1}H n.m.r. δ 0·93 (s, 6H), 0·95 (s, 3H), 1·1—2·0 (m, 7H), 2·4 (m, 2H), 2·8 (m, 1H), 7.1 (m, 1H), 9·45 (s, 1H), and 9·5 (d, 1H); m.p. 91·0—92·5 °C; lit.[1b] 93—94 °C}.

We thank the S.R.C. and I.C.I. Plant Protection, Jealott's Hill, for research studentships (M. M. and S. C. H., C.A.S.E. award).

(*Received, 24th February* 1981; *Com.* 210.)

† Prepared in 95% yield from β-cyclocitral by treatment with trimethylsilylmethyl magnesium chloride in ether at room temperature followed by toluene-*p*-sulphonic acid in tetrahydrofuran at room temperature or in 90% yield according to ref. 1b.

‡ This structure has been confirmed by *X*-ray crystallographic determination. We thank Dr. D. J. Williams, Imperial College, for this result.

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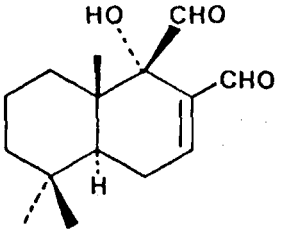
SYNTHESIS OF (±)WARBURGANAL

By Steven V. Ley* and Michael Mahon

(Department of Chemistry, Imperial College, London SW7 2AY.)

SUMMARY: From readily available starting materials a short stereospecific synthesis of the biologically active molecule warburganal (1) has been achieved in 20% overall yield.

Since its isolation in 1976[1] warburganal (1) has been shown to possess a wide spectrum of biological activity including insect antifeeding, plant growth regulation, cytotoxic, antimicrobial, molluscicidal, and anticomplemental properties. For these reasons its synthesis has attracted considerable attention[2].



(1)

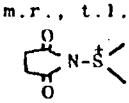
However, the syntheses reported so far are either excessively long, require the extensive use of protecting groups or make use of starting materials which are not readily available.

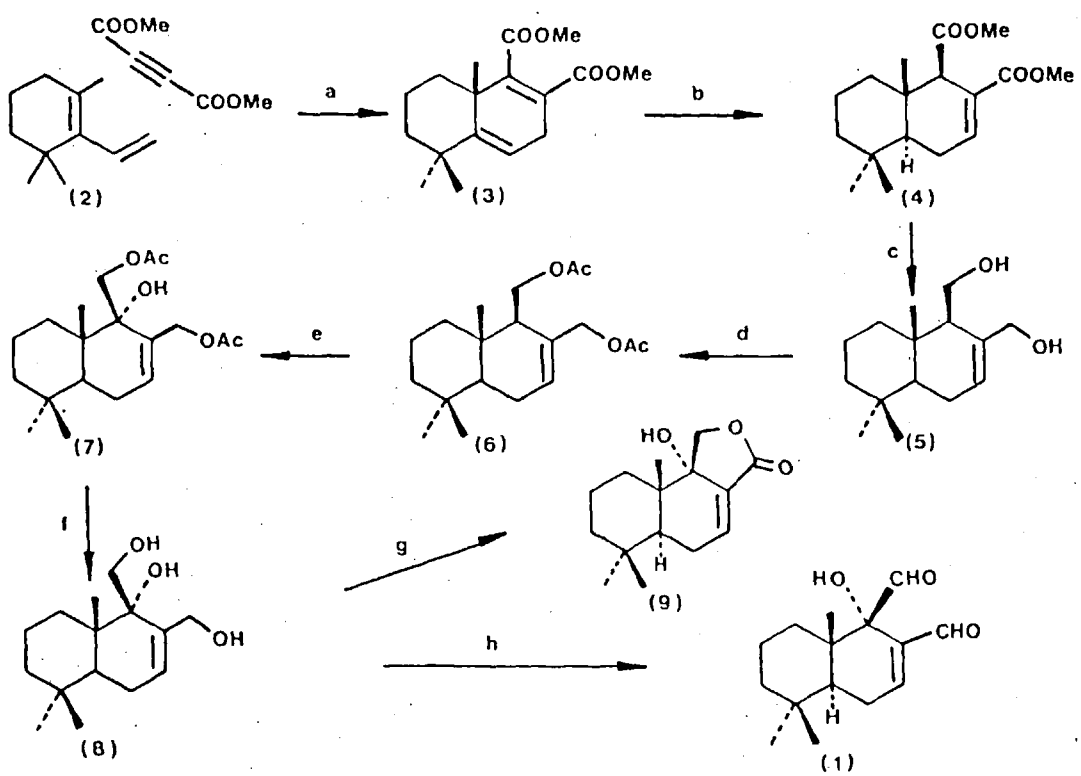
We recently reported[3] a short highly efficient preparation of two other drimane related natural products, polygodial and cinnamolide, and now show that this route can also be applied to warburganal synthesis.

Diels Alder reaction of dimethyl acetylene dicarboxylate with the easily prepared diene (2) gave (3) in 95% yield on a 100 g scale. This adduct was reductively rearranged directly to the diester (4) and converted to the diol (5) in 75% yield as before[3]. This diol now forms the starting point for the present warburganal synthesis.

Quantitative diacetylation of (5) produced (6) which was then regio- and stereoselectively oxidised by SeO_2 in dioxan at reflux to the desired angular hydroxy diacetate (7) which

was isolated as an oil in 65% yield. Quantitative deprotection of (7) using K_2CO_3/methanol gave the triol (8) m.p. 140-141°C. With this compound to hand, its oxidation by a variety of methods was subsequently studied.

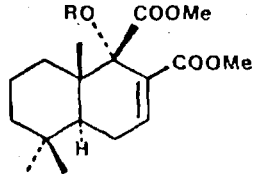
Oxidation of (8) by the Fetizon reagent[4] gave 9-hydroxy-cinnamolide (9), m.p. 175-178°, in excellent yield (98%). However, direct oxidation to warburganal (1) using a number of activated dimethylsulphoxide methods[5] gave variable results. The best procedure was found to be D.M.S.O./trifluoroacetic anhydride[6] which gave (1), identical by n.m.r., t.l.c. and i.r. to the natural product,[†] in 45% yield. A modified Corey-Kim reagent,  has been reported[2d] to achieve this transformation but was less successful in our hands. The overall yield to warburganal at this point is 20% from (2) which is an improvement over existing routes.[2]



SCHEME

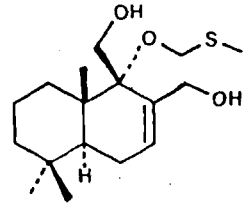
(a) 110°, 22h; (b) H_2, 1 atmos, 10% PdC, dil MeOH, trace H^+; (c) $LiAlH_4$; (d) Ac_2O/Py, RT, 12h; (e) SeO_2, 1.2 eq., dioxan, reflux 1 h; (f) K_2CO_3/MeOH, RT, 10 min; (g) Ag_2CO_3/celite, 5 eq., benzene reflux 20 min; (h) D.M.S.O./T.F.A.A. 6 eq., 0.5h, -50°C then Et_3N 10 eq., -50°C to RT.

In an effort to improve the overall yield of (1), it was attempted to protect the labile tertiary hydroxyl group in (6). However, methylthiomethyl ether[7] formation prior to oxidation failed, although similar protection (DMSO/Ac_2O, RT, 120 h) of the hydroxy diester (10) (m.p. 138-140°C) which was prepared in 95% yield by enolate hydroxylation of (4) (LDA, THF, -78° then MoOPH,[8] -78°C to RT), gave (11) in 97% yield (m.p. 126-127°C). Unfortunately all attempts to reduce (11) (or 10) to the protected triol (12) led to the rearranged diol (13)[9] (m.p. 123-124°C).

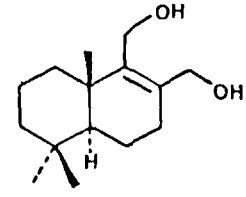


(10) R = H

(11) R = CH_2SCH_3

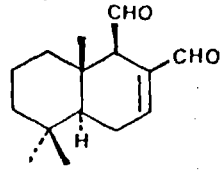


(12)

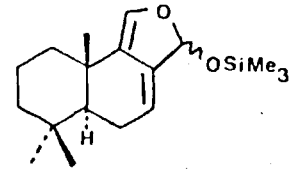


(13)

Finally, we have investigated various possibilities for direct oxidation of polygodial (14) to (1). For example, treatment of the enolate of (14) with MoOPH or O_2 gave only recovered polygodial upon work-up. The lack of reactivity of this enolate must be due to it being present in a cyclized form, i.e. as the lactenolate. In accord with this proposal, work-up of the enolate by treatment with trimethylsilyl chloride gave (15) quantitatively.



(14)



(15)

Attempted conversion of (15) via mCPBA oxidation and treatment with Bu_4NF also failed to provide (1).

We thank the S.R.C. for financial support, the Royal Society for an equipment grant, D. Neuhaus for high field ^1H n.m.r. studies and J.N. Bilton for useful discussions.

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† All new compounds were characterised by spectroscopic methods, acc. mass and/or microanalysis.

‡ We thank Professor I. Kubo, University of California, for a generous sample of the authentic material.

Compound (7) δ after D_2O exch 0.82 (3H, s), 0.91 (3H, s), 0.93 (3H, s), 1.73 (1H, dd, J 5, 12 Hz), 1.91 (1H, dd, J 2, 12, 18 Hz), 2.13 (1H, ddd, J 5, 6, 18 Hz), 3.72 (1H, d, J 11.5 Hz), 3.78 (1H, d, J 11.5 Hz), 4.12 (1H, d, J 12 Hz), 4.31 (1H, d, J 12 Hz), and 5.90 (1H, dd, J 2, 5 Hz).

Compound (9) δ 0.91 (3H, s), 0.97 (3H, s), 0.99 (3H, s), 1.86 (1H, dd, J 5.5, 12 Hz), 2.15 (1H, ddd, J 3.5, 12, 20.5 Hz), 2.45 (1H, ddd, J 5, 5.5, 20.5 Hz), 2.17 (1H, d, J 0.75 Hz -OH), 4.23 (1H, d, J 10 Hz), 4.37 (1H, dd, J 0.75, 10 Hz), and 7.04 (1H, dd, J 3.5, 5 Hz).

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SYNTHESIS OF EURYFURAN, VALDIVIOLIDE, AND CONFERTIFOLIN

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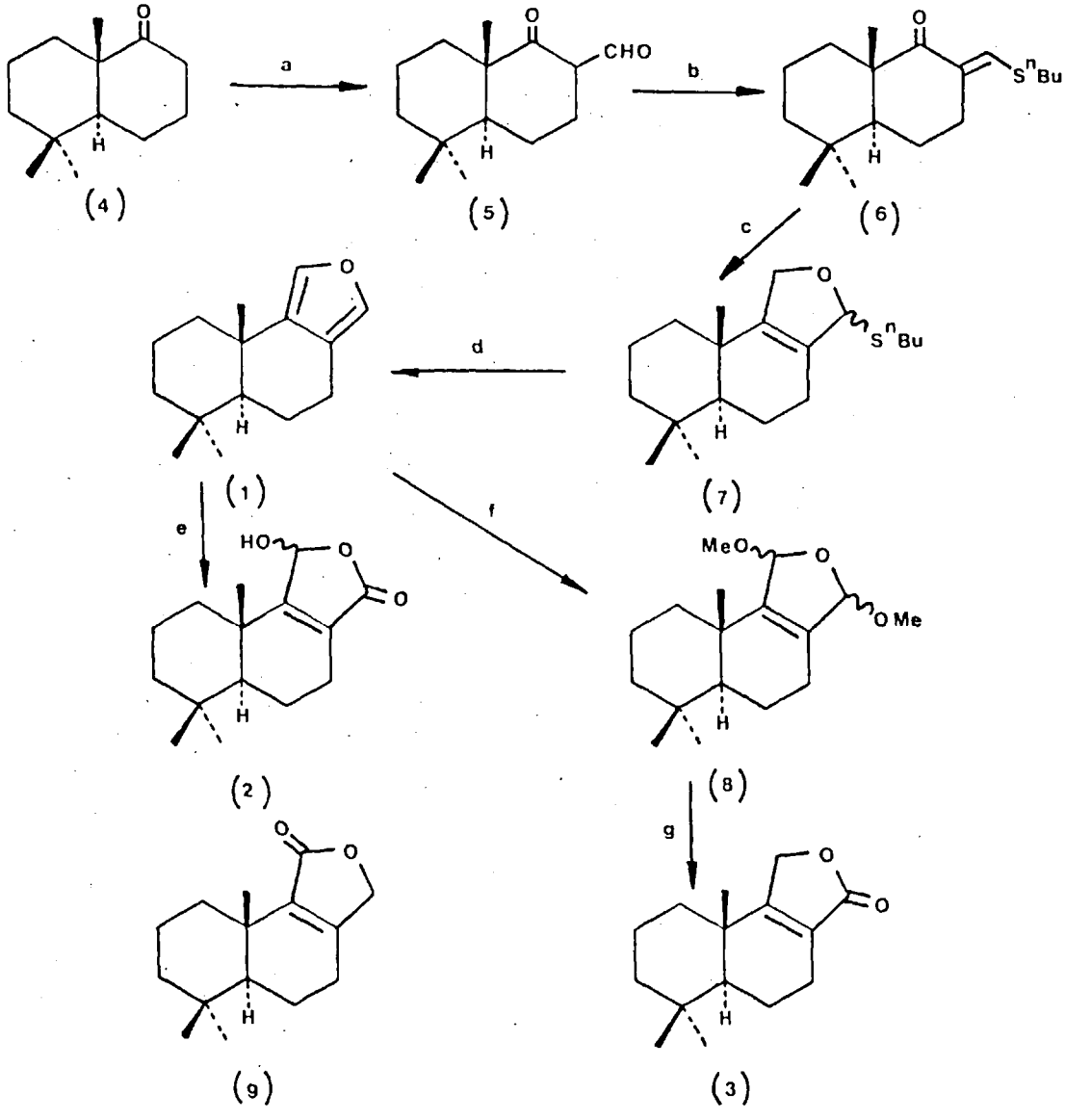
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SUMMARY: Starting from 5,5,9-trimethyl-trans-1-decalone (4), short and highly efficient syntheses of three drimane natural products, euryfuran (1), valdiviolide (2), and confertifolin (3) have been developed.

The biological activity associated with a number of drimane natural products has stimulated considerable recent interest in their synthesis[1]. Here, we report the preparation of euryfuran (1) and show how this molecule can also be used as a precursor for two other natural compounds (2) and (3).

The trans-decalone (4)[2] was formylated in the usual way with ethylformate/NaH to give (5)[1e,f,3] after 12 h at room temperature. This compound was subsequently converted to the n-butylthiomethylene derivative (6), m.p. 60-62°C, in 85% overall yield from (4). Treatment of (6) with trimethylsulphonium methylide in dimethoxyethane at -78°C gave the dihydrofuran (7)[4] (via rearrangement of the intermediate epoxide) which on standing (35°C, 12 h), or brief treatment with $HgSO_4$, gave euryfuran (1) directly in 70% yield as an oil after flash chromatography. The high field (250 MHz) ^1H n.m.r. spectrum of (1) was identical in all respects to the natural product which has been recently isolated from a number of marine sources[1k,5,†].

Photooxygenation of (1) in the presence of 2,6-lutidine[6] gave valdiviolide (2), m.p. 160-168°C, as a 2:1 mixture of 11α:11β hydroxy isomers in 90% yield. The authentic natural material, isolated from Drimys winteri[7†], was shown to have specifically the 11α configuration. The formation of (2) from (1) was expected on mechanistic grounds in that the initial attack of singlet oxygen should lead predominantly to the α-endoperoxide, by addition to the least hindered face, which then, on removal of the more exposed methine proton at C-12, collapses to (2).



(a) HCO_2Et, NaH, benzene, RT, 12 h; (b) nBuSH, pTSA, benzene, 2h, Δ; (c) $(CH_3)_2\overset{+}{S}-\bar{C}H_2$, -78°C, 10 min; (d) 35°C, 12 h or $HgSO_4$, 1 eq, DME, RT, 10 min; (e) O_2, hν, eosin, 25°C, 4h, 300 watt quartz iodine lamp, ^tBuOH : 2,6-lutidine, 2 : 1; (f) Br_2, MeOH, 0°C, 30 min; (g) 10% HCl in acetone, RT, 30 min.

Oxidation of euryfuran (1) with bromine in methanol gave (8) in 92% yield as a mixture of all possible isomers. Treatment of (8) with 10% hydrochloric acid gave confertifolin (3), m.p. 120-123°C, in 75% yield, again identical to the natural product[8†]. Also isolated from this reaction was a small amount (10%) of the other regioisomer, i.e. isodrimenin (9). The formation of (3) from (8) is rationalised as a facile 1,4-elimination of methanol via loss of the more accessible proton and sterically more congested methoxyl group. Further reactions of (1) will be reported in full at a later date.

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NOTES

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250 MHz ^{1}H n.m.r. ($CDCl_3$)

Euryfuran: 0.91 (3H, s), 0.94 (3H, s), 1.21 (3H, s), 1.2-2.0 (9H, m), 2.5 (1H, ddd, J 2, 7.5, 11.5, and 16 Hz), 2.77 (1H, dddd, J 1, 1.5, 6.5, and 16 Hz), 7.05 (1H, dd, J 2,2 Hz), 7.07 (1H, d, J 2 Hz).

Valdiviolide: 0.91 (3H, s), 0.92 (3H, s), 1.25 (3H, s), 1.1-2.0 (9H, m), 2.13 (1H, m), 2.38 (1H, m), 3.95 (1H, brs -OH), 6.09 (1H, m).

Confertifolin: 0.92 (3H, s), 0.96 (3H, s), 1.17 (3H, s), 1.1-2.0 (9H, m), 2.15 (1H, m), 2.4 (1H, m), 4.65 (1H, ddd, J 2, 3.5, and 17.5 Hz), 4.75 (1H, ddd, J 3, 3, and 17.5 Hz).