Chemistry of α-Santonin

GHULAM A.MIANA AND HAMAD A. AL-LOHEDAN,
Department of Chemistry, College of Science,
King Saud University, P.O.Box. 2455,
Riyadh, Saudi Arabia

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α-Santonin (1), a powerful anthelmintic, is one of the most well known and earliest studied sesquiterpene lactone [1,2,3]. It is found in a number of Artemisia species of the plant family Compositeae [4]. As a result of synthetic studies [5], (+)-santonin-A (2), (+)-santonin C(4), and (+)-santonin D(5) are also known. β-Santonin (6) also occurs in various Artemisia species [4].

The chemistry of α-santonin has been studied extensively and details of the earlier work may be found elsewhere [2,3]. This review is concerned with some of the reactions of α-santonin and covers the period since the last reviews.

Hydrogentation of α-santonin

Hydrogenation of (1) and the stereochemistry of the products has been studied [6]. Hydrogentation of (1) in non-polar solvents like benzene over Raney nickel gives dihydrosantonin A (7) in 30-40% yield [7]. Hydrogenation of (1) in ethyl acetate over 2% palladised strontium carbonate at room temperature, on the other handgives ɣ-tetrahydrosantonin (8) in 43% yield [7]. Hydrogentation of (1) over palladized carbon in acetic acid, however, gives tetrahydro isomers (8) and (9) in 56% and 22% yields, respectively [6].

Reduction of (1) with lithium in liquid ammonia gives [8] (10). In another publication [9], (11) has been reported to be formed.

Hydrogenation of the keto acid (12) in the presence of homogenous catalyst, tris(triphenylphosphine) chlorohdium, also gives (11) in excellent yield.

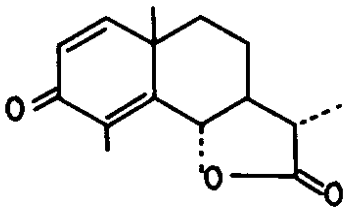
Epimerization

Ishikawa [11] has shown that α-santonin is epimerized at C(6) to give 6β-α santonin (13), when treated with hydrogen chloride in dimethylformamide. Barton [12] has similarly prepared 6α ,11β (H)-santonin (14) from 6β,β11 (H)-santonin (6). Tetrahydrosantonin (9) undergoes epimerization [13] at C(4) under the influence of hydrochloric acid in ethanol to give (8).

Epoxidation

Epoxidation of α-santonin was first reported by Wedekind and Tettweiler in 1931 [14] using perbenzoic acid and peracetic acid. The product named as α-epoxide was obtained in 68% yield. The correct structure (15) was given by Hendrickson et al. [7] in 1962. α-Epoxide can also be obtained [7] from corresponding santonin chlorohydrins by reaction with a base.

Recently, Fujimoto et al. [15] have reported the reaction of α-santonin with m-chloroperbenzoic acid in the presence of 4,4 -thiobis (6-t-butyl-3-methylphenol) as a radical inhibitor. They obtained α- (15) and β-epoxides (16) in 38.6% and 43.2% yields, respectively, together with small amounts of



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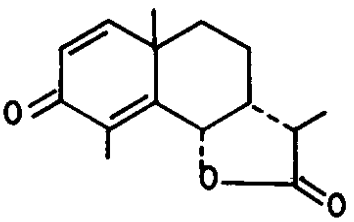

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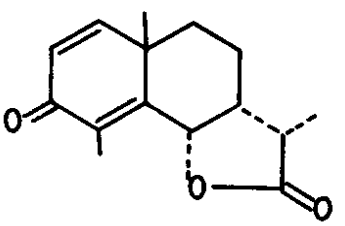

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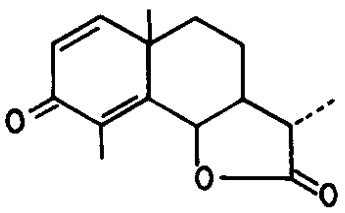

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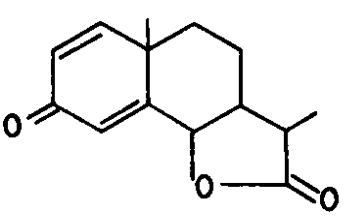

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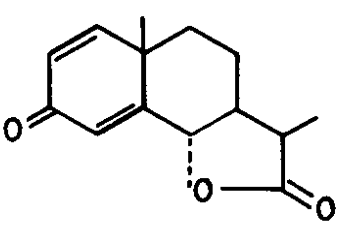

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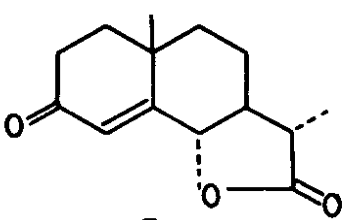

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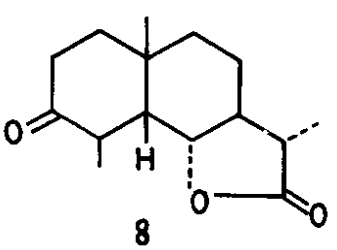

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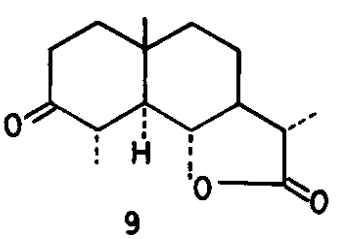

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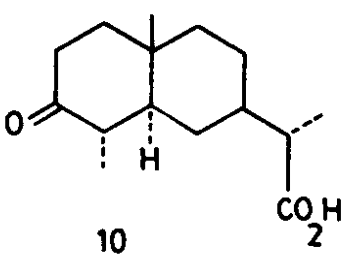

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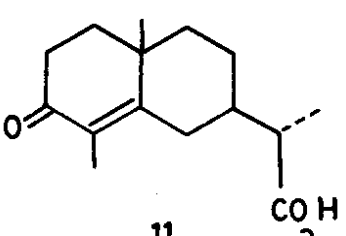

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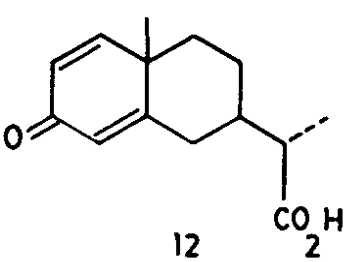

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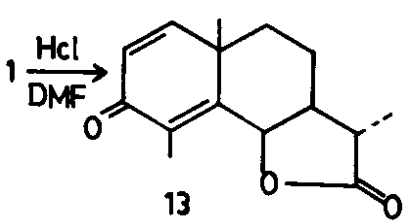

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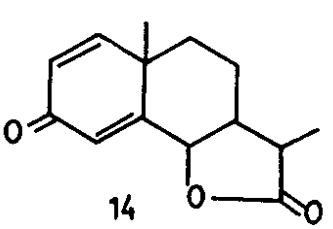

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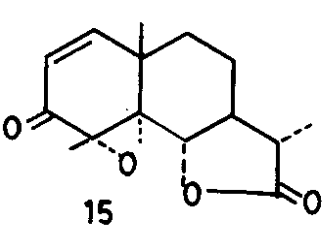

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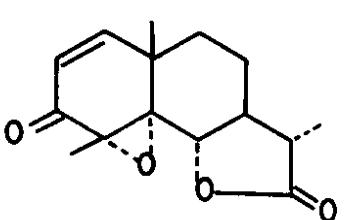

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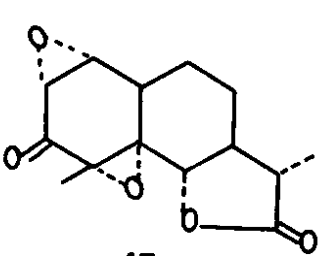

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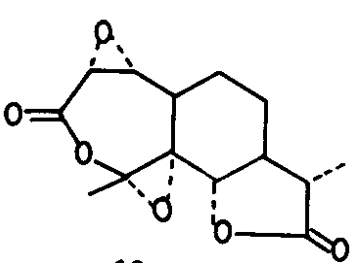

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diepoxides (17) and Baeyer-Villiger rearrangement product (18).

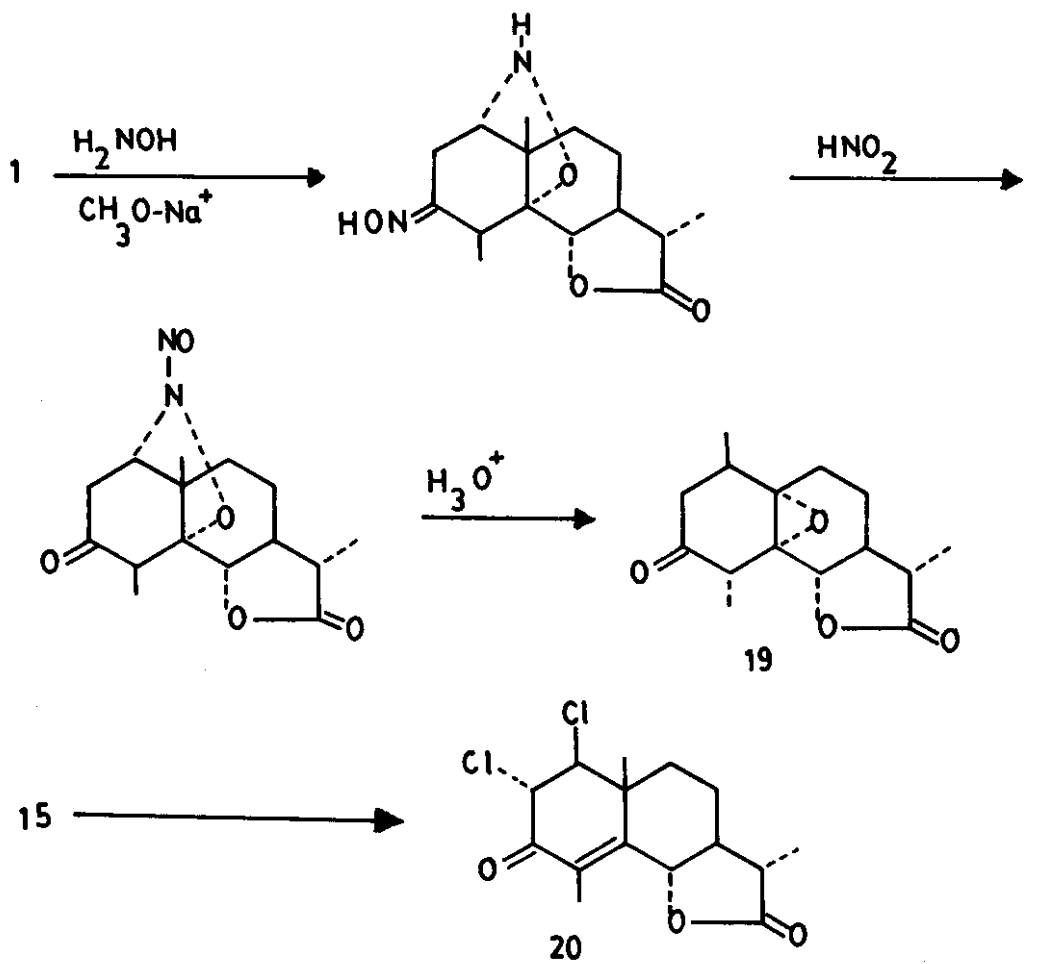
The novel epoxide (19) has been prepared [16] as shown in Scheme I. Fujimoto et al. (loc. cit) have utilized α and β-epoxides in the synthesis of dihydrocostunolide and derivatives (see later on).

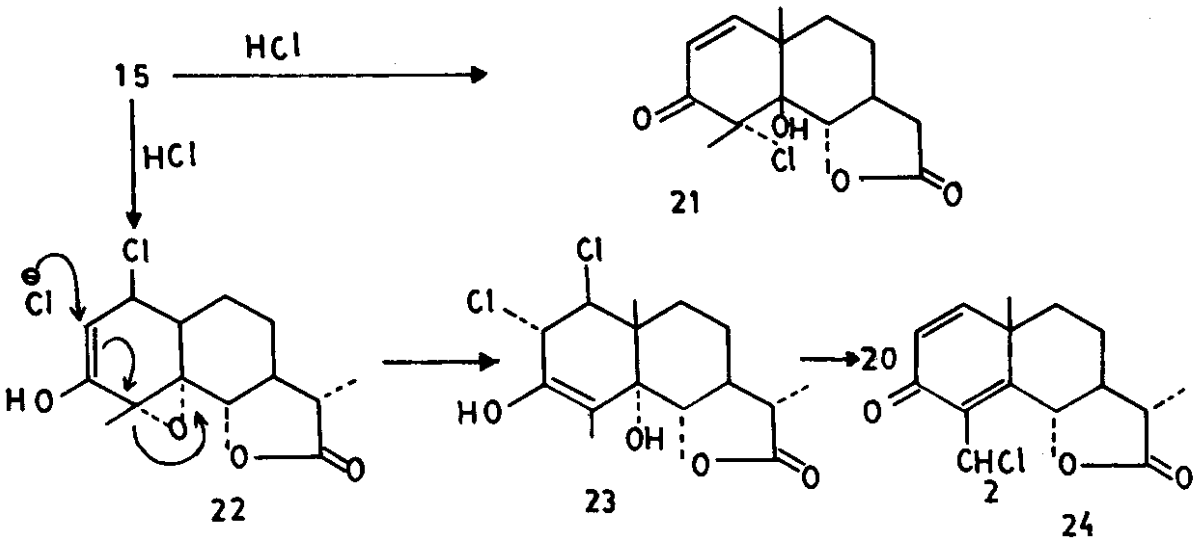
Wedekind et al. [14] as well as Hendrickson and Bogard [7] have reported an interesting conversion of α-epoxide (15) with hydrochloric acid into 1,2-dichlorosantonin (20).

It has been suggested by Hendrickson et al. [7] that the ditertiary epoxide is apparently sufficiently hindered to render normal opening to the α-isochlorohydrin (21) relatively difficult. However, 1,4- addition of hydrogen chloride to (15) can occur at position 1, to give enol (22). This allylic tertiary epoxide undergoes S_N2 displacement from below at position 2 by chloride ion to yield (23), and this enol is converted to santonin dichloride (20) on elimination of water (Scheme 2).

Santonin dichloride can be readily prepared [7,14] by the chlorination of santonin in chloroform.

On the other hand, Takayanagi et al. [17] have reported the isolation of 14-chlorosantonin (24) from the re-





action of santonin α-epoxide (15) with hydrogen chloride gas in methanol.

The suggested mechanism is shown in Scheme (7).

Chlorination of α-santonin

Wedeking and Tettweiler [14] first reported the chlorination of santonin. Hendrickson and Bogard [7] gave the stereochemical structure to the products. Chlorination of (1) in water gives (25). Chlorination of (1) in chloroform, however, gives santonin 1,2-dichloride (20).

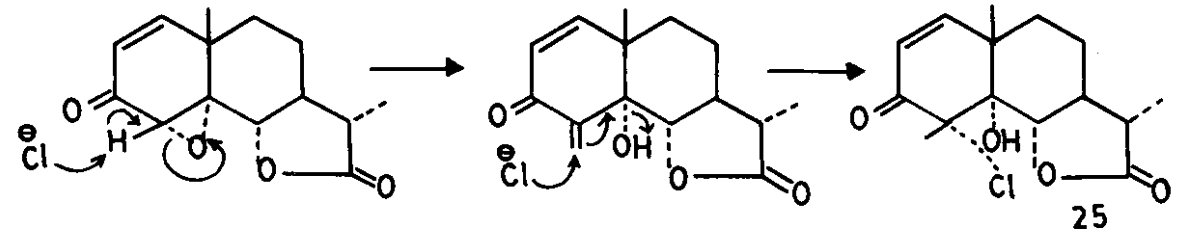
α-isochlorohydrin (21) has been prepared by dissolving -epoxide in hydrochloric acid; the other product of this reaction is (24) as discussed above [17].

Recently, Takayanagi et al. [18] have revised the stereostructures of santonin dichloride and santonin chlorohydrin to be (26) and (27), respectively, on the basis of x-ray analysis of the derivatives.

Santonin 1,2-dichloride undergoes easy elimination in the presence of a base to yield 2-chlorosantonin (28) [7].

Hydroxylation of (1)

Angeli and Morino [19] first reported the mild permanganate oxidation of (1) to afford 1,2-dihydroxy-santonin (29). Hendrickson and Bogard [7] later on revised the structure to (30). Further oxidation of (30) with permanganate gives an acid (31). The same acid has been reported to be formed by ozonolysis of the α-epoxide or of santonin [7].



Carbonyl Derivatives

Reaction of α-santonin (1) with phosphorous pentasulfide gives [20] 3-thio-α-santonin (32), the chemistry of which has not been studied as yet. The reaction of (1) with hydroxylamine hydrochloride in the presence of sodium methoxide was first studied by Francesconi and Cusmano [21,22] who reported the formation of 3 products. These were the expected α-santonin oxime (33) and the two isomeric α- and β-hydroxyl-amino santonin oximes (34).

Edward and Davis [16] have recently re-investigated the reaction and have given the structures (35) for the two isomeric hydroxylamine santonin oximes on the basis of their spectral analysis. The formation of epoxide (22) from (35) has already been discussed.

Treatment [16] of (19) with levulinic acid - hydrochloric acid at room temperature gives (35) and (36). Treatment of (19) with levulinic acid-hydrochloric acid at 100°C gives (37); more prolonged treatment results in the formation of (-) -α-desmotropo-santonin (38).

Reduction of the carbonyl group of α-santonin to the corresponding alcohols does not seem to have been reported. However, reduction of santonin α-epoxide [15] and other isomers with lithium aluminium hydride has been found to give products of the type (39).

Dienone-Phenol Rearrangement

The conversion of α-santonin to the (-)-α-desmotrope santonin (38) [29] was the first example of the dienonephenol rearrangement studied [23] and is brought about by heating (1) with concentrated hydrochloric acid in a sealed tube.

Treatment [24] of (1) with acetyl chloride - acetic anhydride in the presence of small amounts of water gives an enol acetate, 3-acetoxy-eudesma-3,5,7-(11)-triene-6, 13-olide (40), trans-(41) and cis- desmotroposantonin acetate (42) and small amounts of 3-chloro-eudesma-3,5,7 (11)-triene-6, 13-olide (43) and the trans - and cis- chloro-demotroposantonins (44).

Reaction of 1 with phosphorous trichloride in acetic acid affords the same products as above, but the chloro compounds are obtained in much higher yield [25].

Phosphorous tribromide reacts with 1 and gives slightly different products: enol acetate (40), the desmotroposantonins (41,42) and two new compounds (45) and (46) are obtained [25].

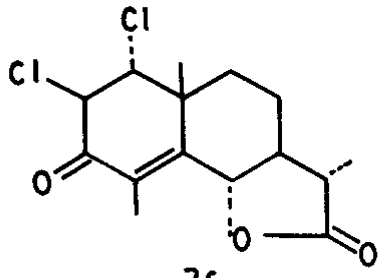
Partial aromatisation [26,27] of 1 with zinc and demethylformamide furnishes 6β (H), 7α (H),β (H)-1-desmethyl-troposantonin (47). Pyrolytic aromatization [28] of α- and β-santonins on the other hand, produce isomeric cis compounds (48) and (49), respectively.

It may be pertinent to point out here that the dienone (50) undergoes dienone-phenol rearrangement by two routes to give (51) and (52) [30], as shown in Scheme 4.

It may therefore be worthwhile to re-investigate the dienone-phenol rearrangement of 1 and especially of 6-epi-α-santonin (14), in view of the above results and look for similar compounds of the type (53).

Photochemistry of α-Santonin

The photochemistry of (1) has been studied as early as 1830, when it was isolated by Kahler [31]. The first



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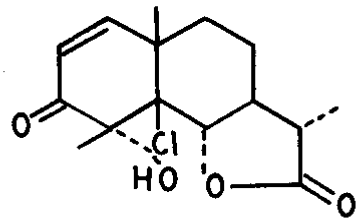

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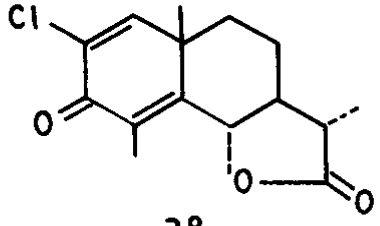

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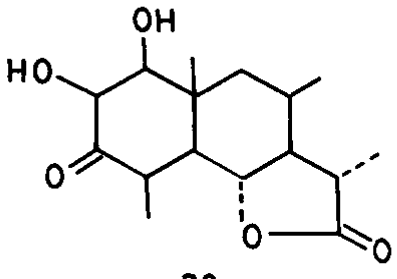

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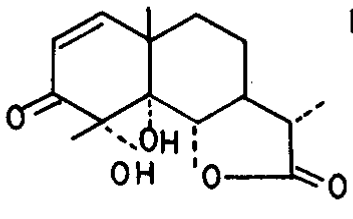

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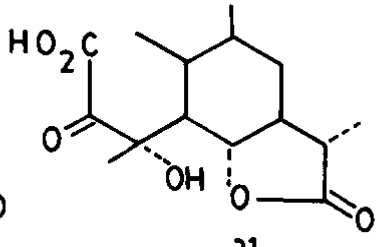

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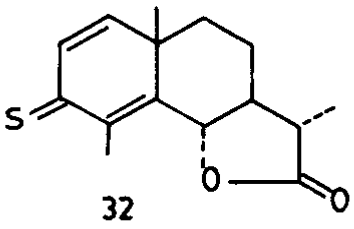

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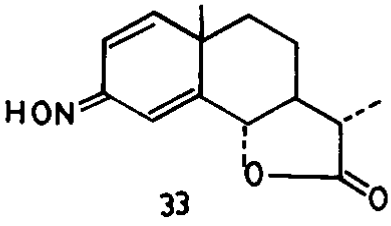

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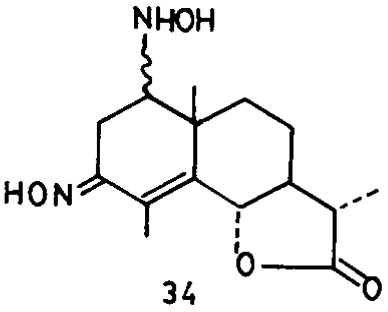

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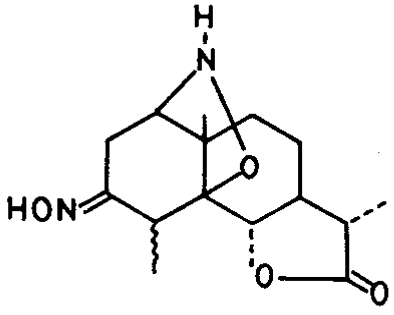

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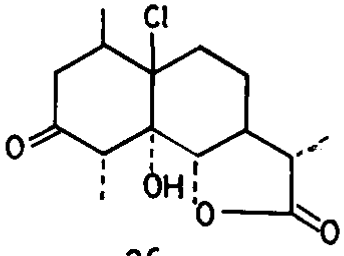

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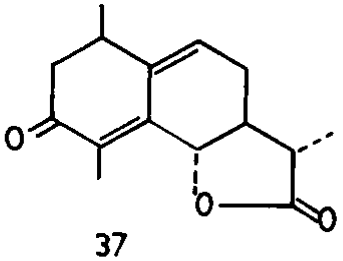

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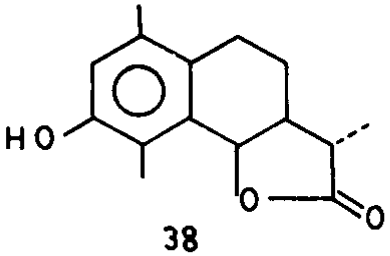

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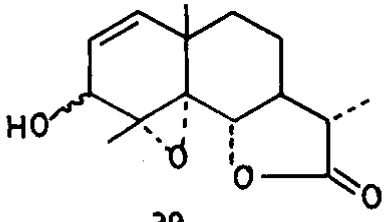

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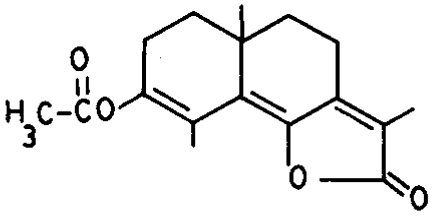

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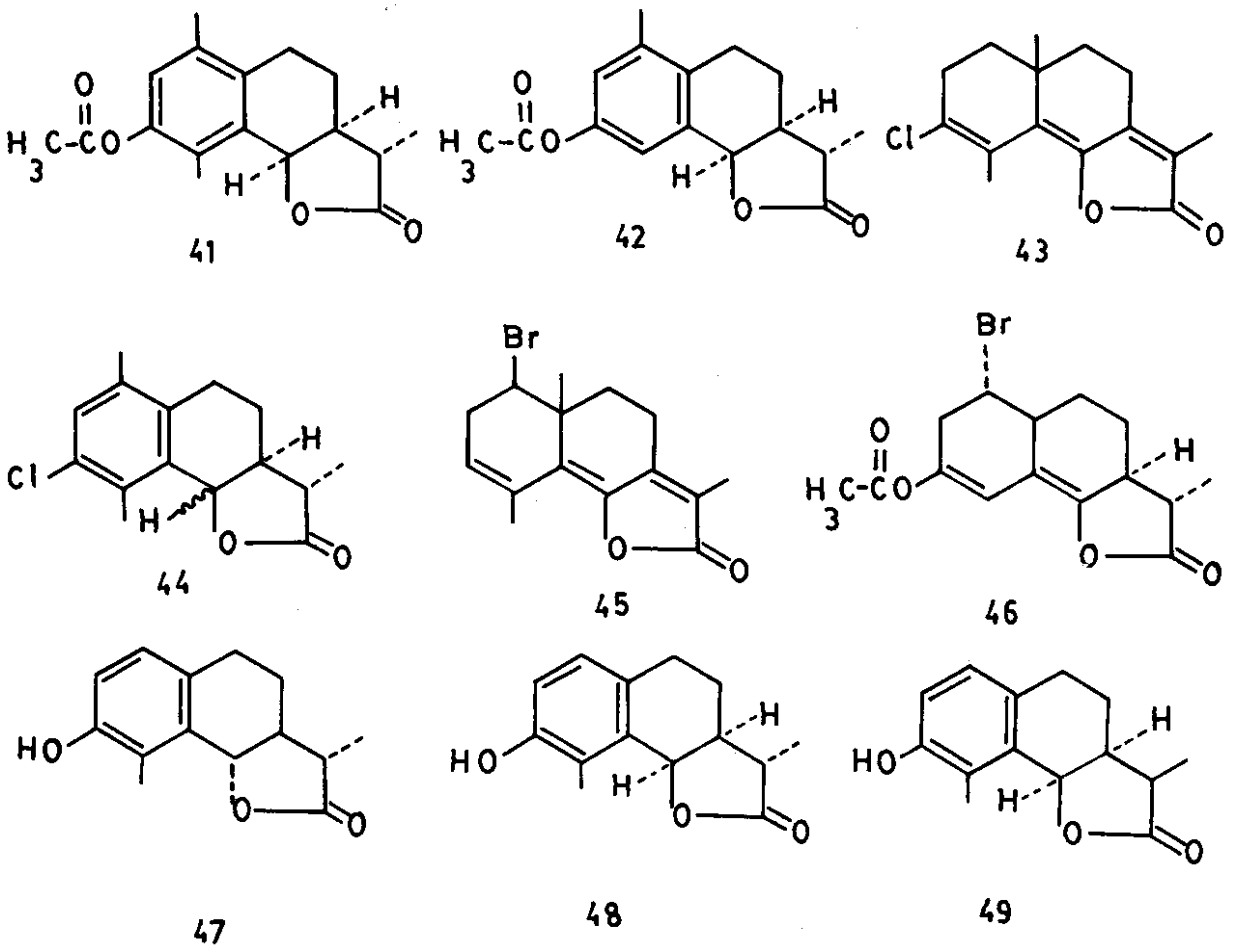


photoproudct isolated was called chromosantonin [31,32], which appears to be an impure form of santonin.

A large number of products have been discovered on irradiation of (1) in protic solvents, mostly alcohols or acetic acid. These are photosantonic acid (54), isophotosantonic acid (55), photosantoninic acid (56), and a myriad of related ethers, esters and acids.

Barton, de Mayo and Shafiq elucidated the structure of isophotosantonic acid (55) [33], and most of its derivatives. The structure of photosantonic acid was also assigned [33], which proved to be erroneous and the correct structure (54) was given by van Tamelen [34] and co-workers, mostly on the basis of NMR spectroscopy.

Lumisantonin (57) [35,36,37] was found to be a central intermediate on the pathway to other santonin photoproducts.

Photosantoninic acid (56) can be obtained from lumisantonin (57) on basic treatment; whereas (57) gives photosantonic acid and derivatives on irradiation. Perhydroazulene derivatives such as photosantonic acid (55) are obtained on treatment with acid. Lumisantonin (57) rearranges to the linearly conjugated dienone (58) called

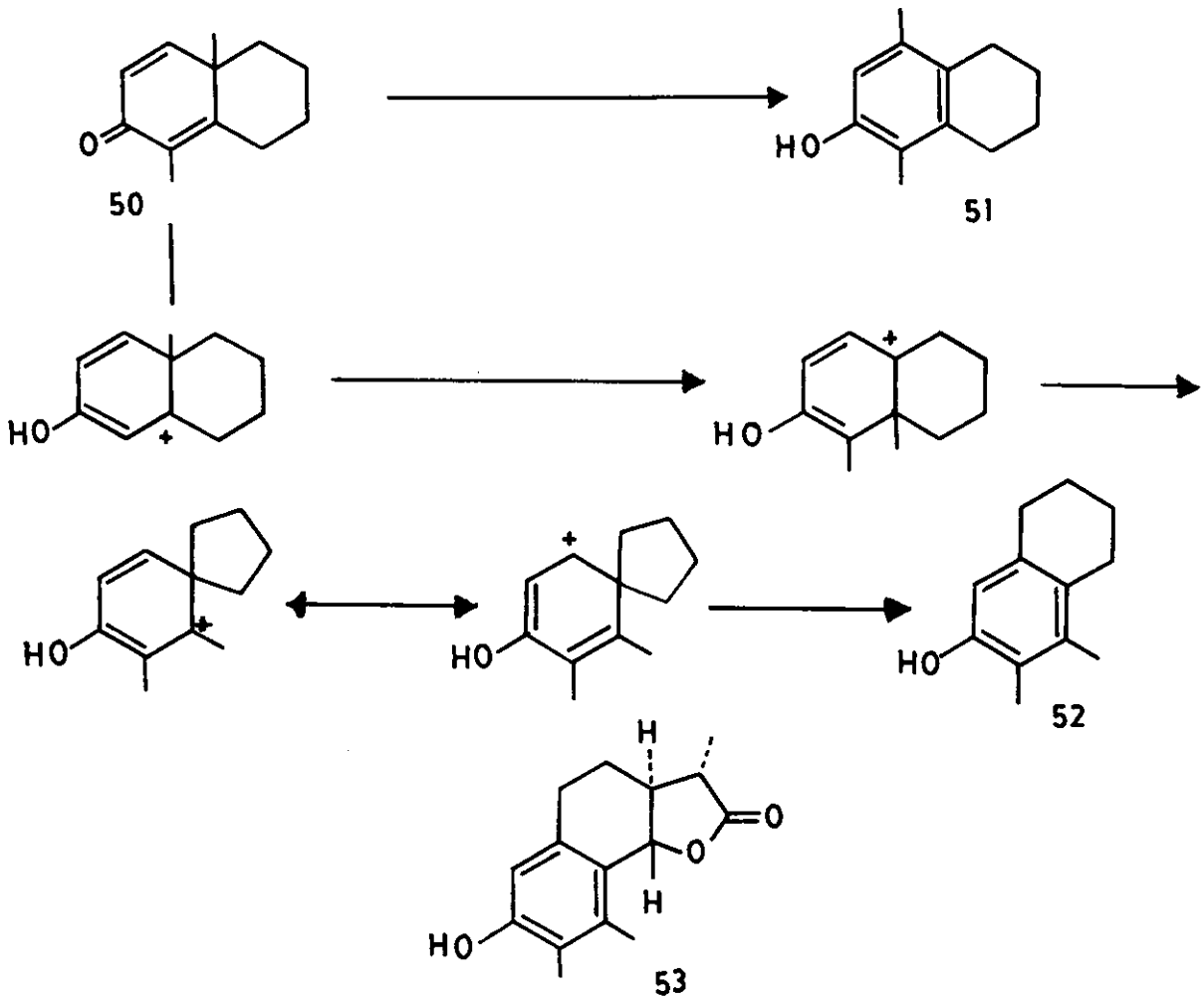
mazdasantonin on further irradiation [38], in the absence of any nucleophile. All these transformations are summarized in Scheme 5.

The photochemistry of 6-epi-α-santonin (14) has also been studied [38]. In neutral aprotic solvents the only product formed is 6-epilumisantonin (59). Further irradiation of (59) produces 6-epimazdasantonin (60) (25%). In aqueous acetic acid at 0°, the irradiation of 6-epilumisantonin gives spirodienone (61), phenol (62) and 6-epi-photosantonic acid (63).

The difference in the photochemistry of 6-epi-lumisantonin and that of lumisantonin can be interpreted as due to the nature of the lactone ring function. However, due to the low yield of spirodienone (61) and the phenol (62), it has been suggested that other stereochemical factors may be operative.

Use of α-Santonin in the Synthesis of Sesquiterpenes

α Santonin (1) has been used as starting material in the total synthesis of the following sesquiterpenes:



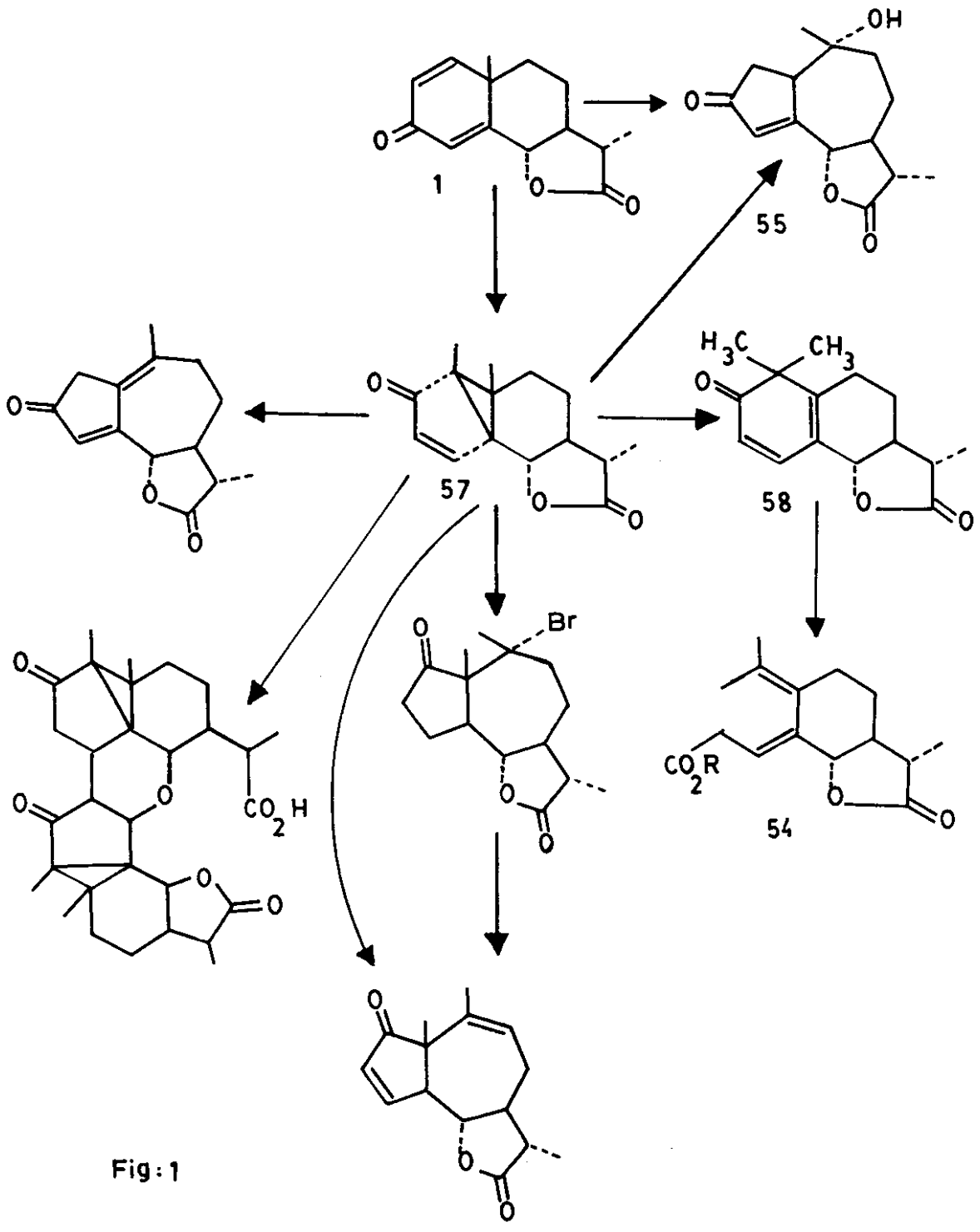
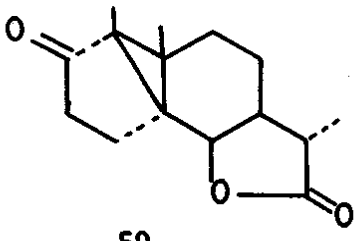


Fig : 1



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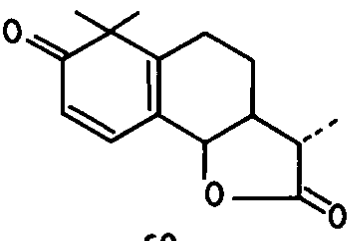

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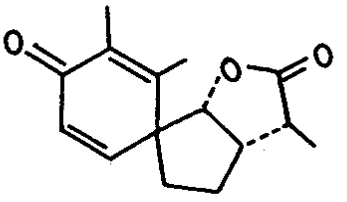

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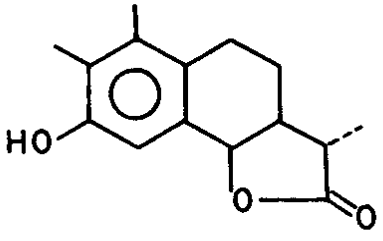

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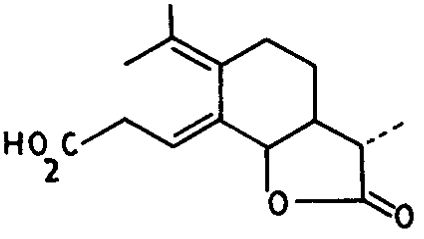

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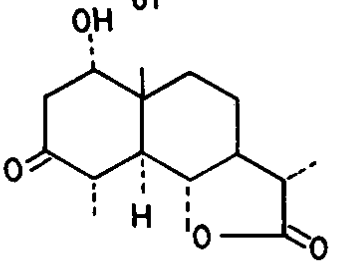

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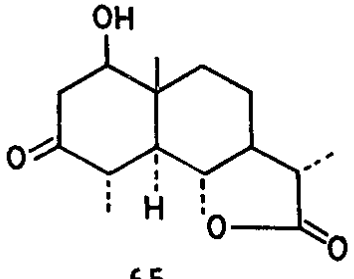

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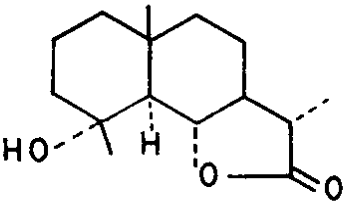

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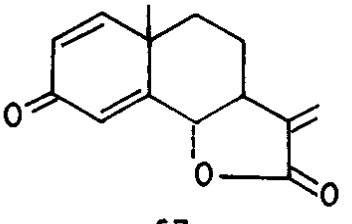

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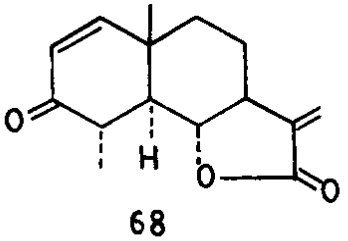

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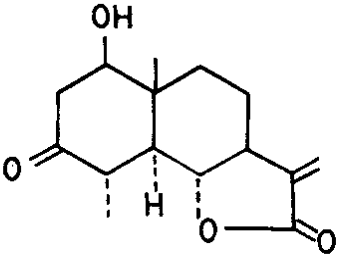

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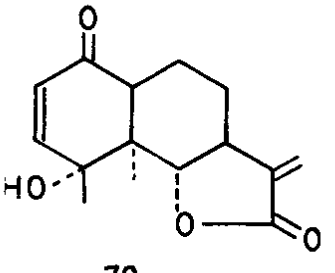

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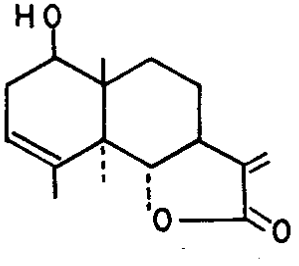

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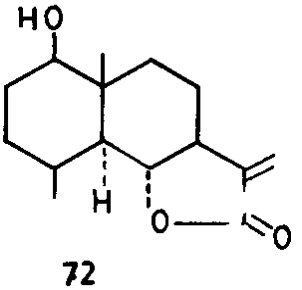

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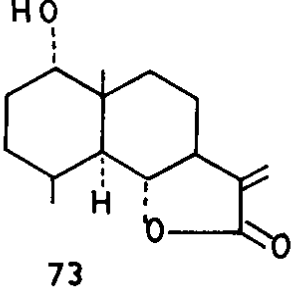

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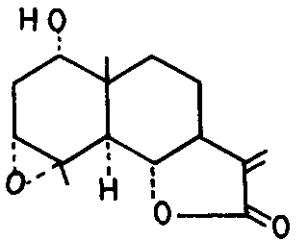

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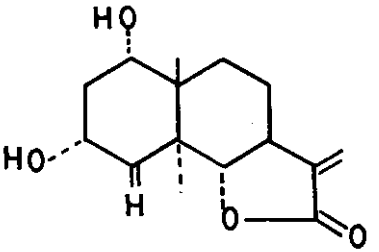

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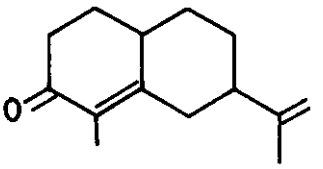

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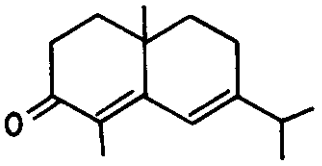

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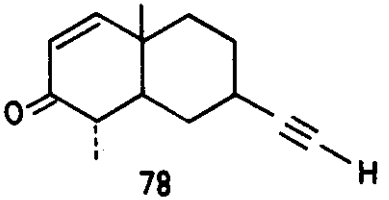

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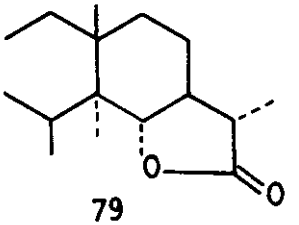

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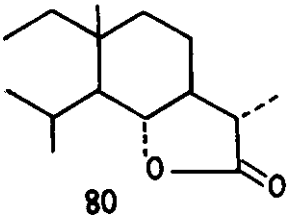

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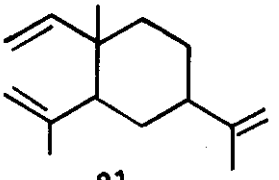

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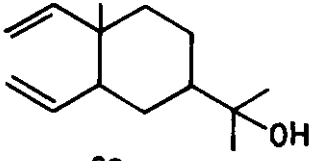

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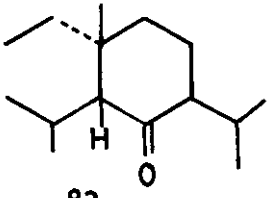

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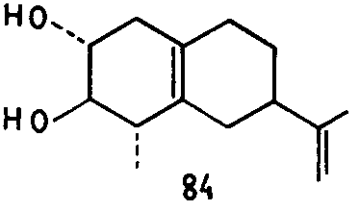

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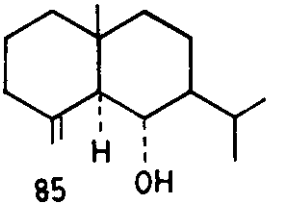

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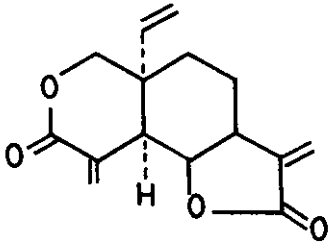

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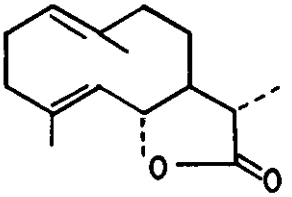

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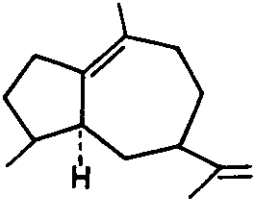

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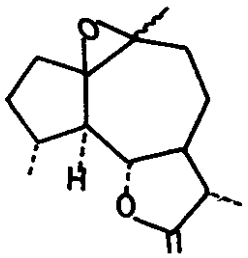
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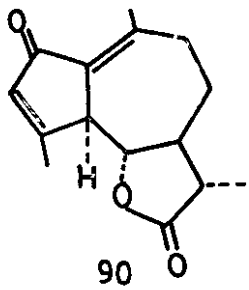
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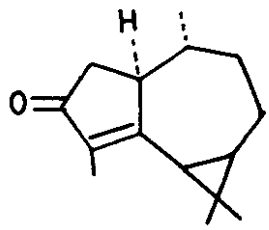
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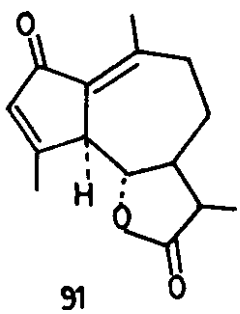
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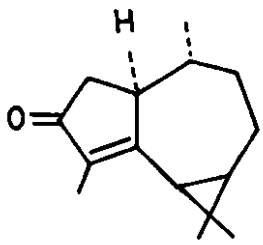
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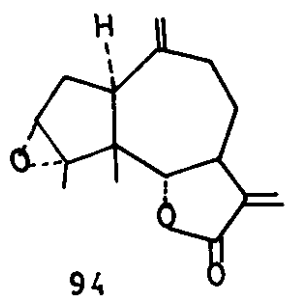

94

arsantin (64), arsanin (65), colartin (66), 11-exo-methylene-santonin (67), tuberiferin (68), artecalin (69), arglanine (70), santamarin (71), balchanin (72), douglanine (73), ludovicin A (74), ludovicin B (75), cyperone (76,77), chamaecynone (78), tetrahydrosaussurea lacton (79), saussurea lactune (80), β-elemene (81), and elemol (82), (-)shyobunone (83), rishitin (84), (+)-uneol (85), deoxyvernolepin (86), dihydrocostunolide (87), bulnesene (88), arborescin (89), deacetoxymatricarin (90), achillin (91), and epicyclocolorenone (92), (-), estafiatin (93).

Synthesis of Arsantin (64) [39]

α-Tetrahydrosantonin (8) was brominated and debrominated to give an enone (95). Epoxidation of (95) by 30% hydrogen peroxide in dioxan - sodium hydroxide solution gave stereoselectively an α-epoxide (96), in quantitative yield. Treatment of (96) with activated zinc dust in ethanol in the presence of small amount of acetic acid gave (64), which was not identical with natural (+)-arsantin in terms of IR spectrum and melting point (Scheme 6).

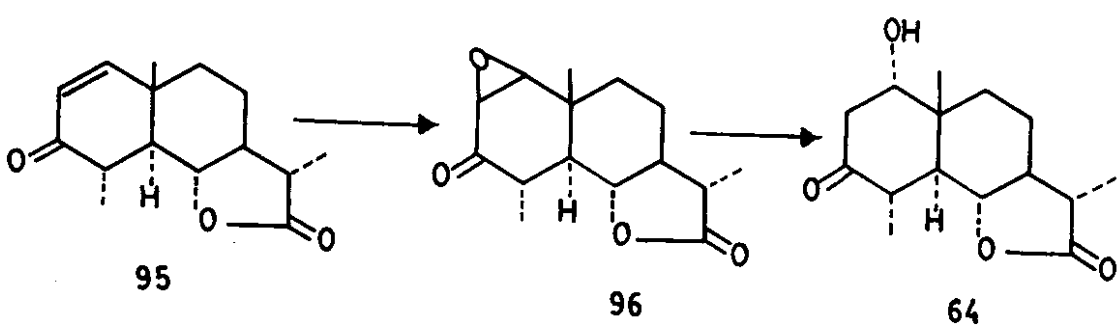

95 96 64

Fig : II

Synthesis of Arsanin (65) [39]

The enone (95) was reduced with lithium aluminium hydride at room temperature in ether to give 1-en-3-β.ol (97) in 46% yield, whereas the reduction in tetrahydrofuran at 5-10° gave (97) stereoselectively in high yield. Epoxidation of (97) by tert-butyl hydrogen peroxide in the presence of vanadyl acetylacetone in CH_2Cl_2 gave (98) in 47% yield together with the starting material (39%).

Oxidation of the α- and β-epoxide with chromium trioxide-pyridine complex gave α- and β-epoxyketone (99). Reductive cleavage of the β-epoxyketone with activated zinc dust gave 1β-hydroxy-α-tetrahydrosantonin in 74% yield, which was identical in all respects with the natural arsanin (65) (Scheme 7).

Synthesis of Colartin (66) [40]

1-oxo-3-ene (116) was converted into α-epoxide (100) by treatment with m-chloroperbenzoic acid in $CHCl_3$ in 71% yield. The Wolff-Kishner reduction of epoxyketone (100) gave 4α-hydroxy -1 (or 2) -ene (102) in 8.3% yield, which was reduced with 10% Pd-C in EtOAc to give colartin (66). Colartin could also be obtained in overall yield of 46.8%, by the route shown in Scheme 8.

Treatment of (101) with ethanedithiol in AcOH containing p-toluenesulfonic acid at room temperature for a day gave a thioketal (103) in 72% yield. Reductive desulfurization of (103) with Raney nickel in acetone gave colartin in 65% yield (Scheme 8).

11-Exo-Methylene-santonin (67) [41]

The synthesis of this compound has been reported in a recent Japanese patent, which was not available to us.

Synthesis of Tuberiferine (68) [42]

The enone (95) was treated with two eq. moles of lithium diisopropylamide (LDA) and then an eq. mole of diphenylselenide to give (104) in 15% yield. Treatment of (104) with 30% hydrogen peroxide in THF containing a few drops of acetic acid at 0° furnished α-methylene- γ-lactone (68);

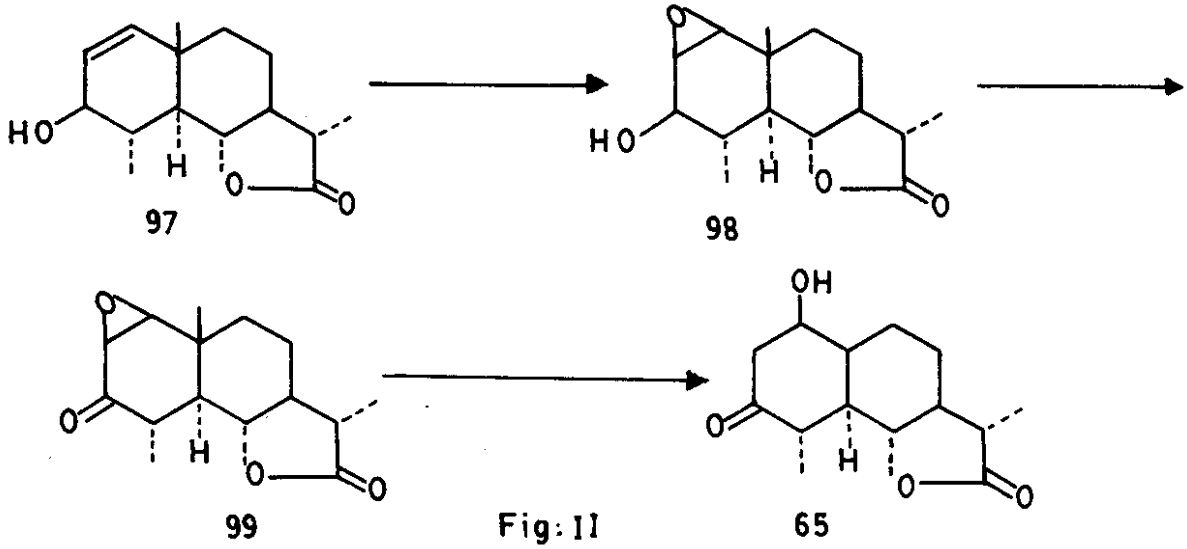


Fig: II

the IR and NMR spectra of (68) were identical with that of (+)-tuberiferine but not the melting point.

Alternatively, the reduction of (95) with $LiAlH_4$ in THF at -10° gave stereoselectively a 3β-ol (97). Phenylselenylation of acetate of (97) gave a phenylselenide (105) in 66.3% yield, which gave (68) on treatment with hydrogen peroxide (Scheme 9).

Synthesis of Artecalin (69) [42].

The epoxide (98) was treated with LDA and then diphenyl diselenide to give a phenylselenide (106). Oxidation of (106) with activated MnO_2 gave a ketone (107), which was treated with 30% hydrogen peroxide in THF containing a few drops of acetic acid to give (108). Reductive cleavage of the β-epoxyketone with zinc dust in benzene containing a few drops of acetic acid furnished 3-oxo-1β-hydroxy-5α-sant-11-en-6,12-olide (69) in 95% yield, which was identical with the natural (+)- artecalin in all respects (Scheme 10).

Synthesis of Arglanine (70) [43]

The epoxyketone (96) was treated with 85% hydrazine hydrate in ethanol containing acetic acid and the solution

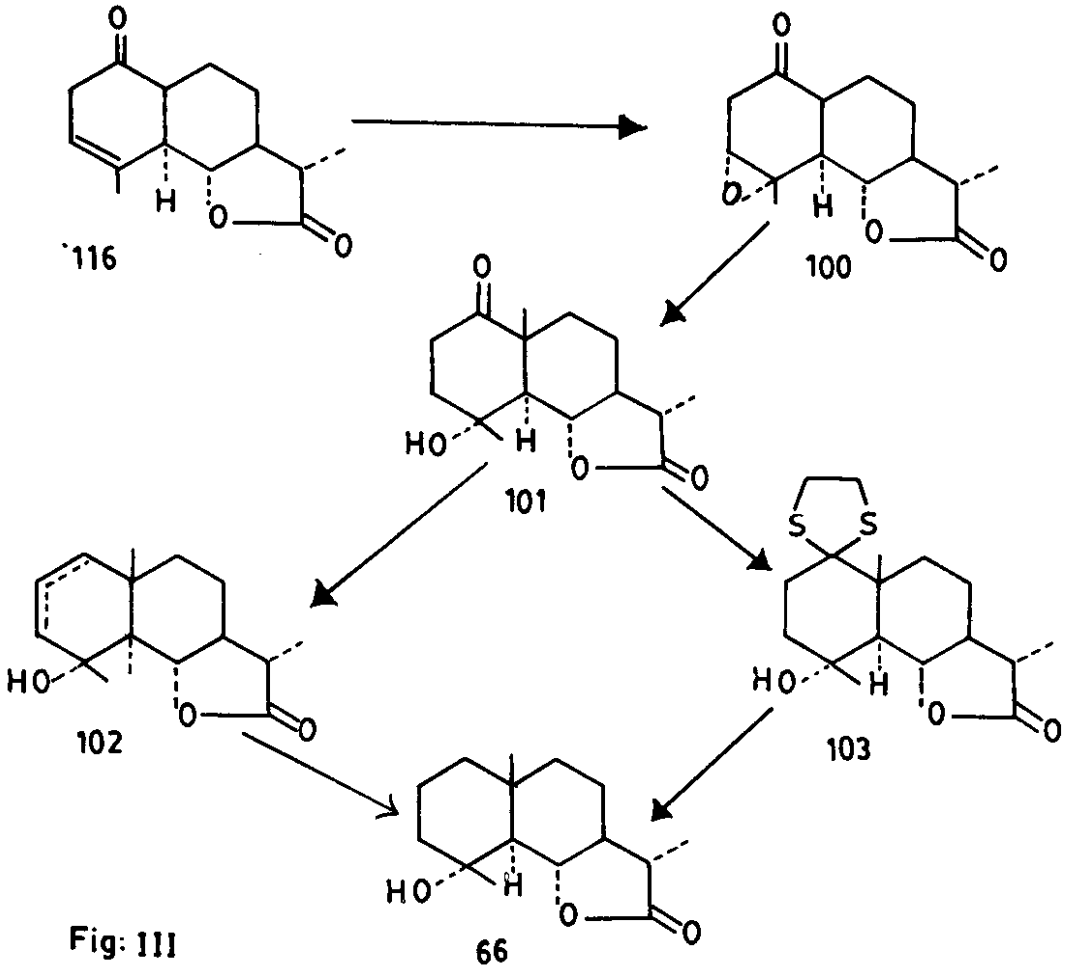
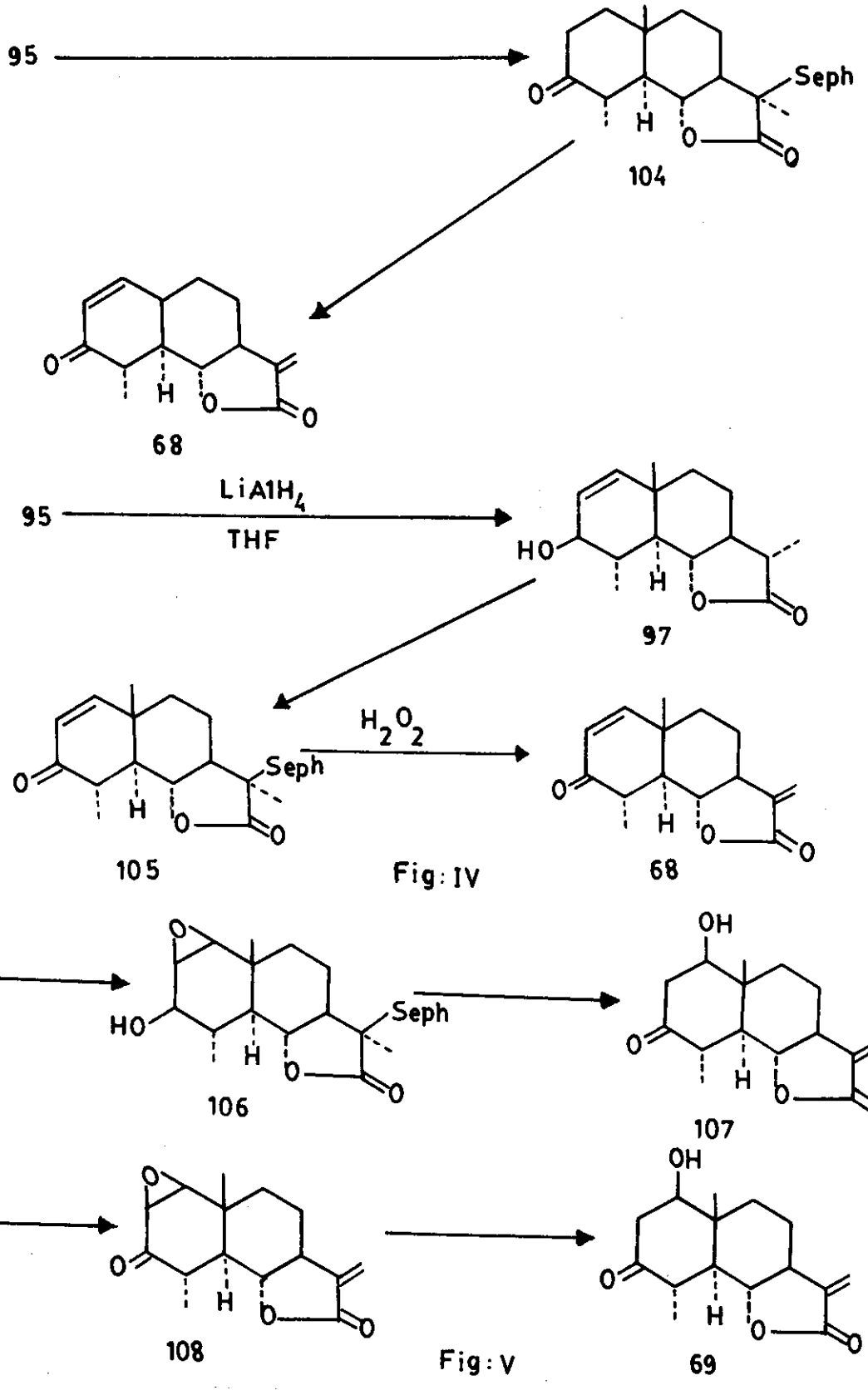


Fig: III


95
Seph
104
68
95
LiAlH4
THF
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H2O2
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Fig: IV
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107
108
OH
69
Fig: V

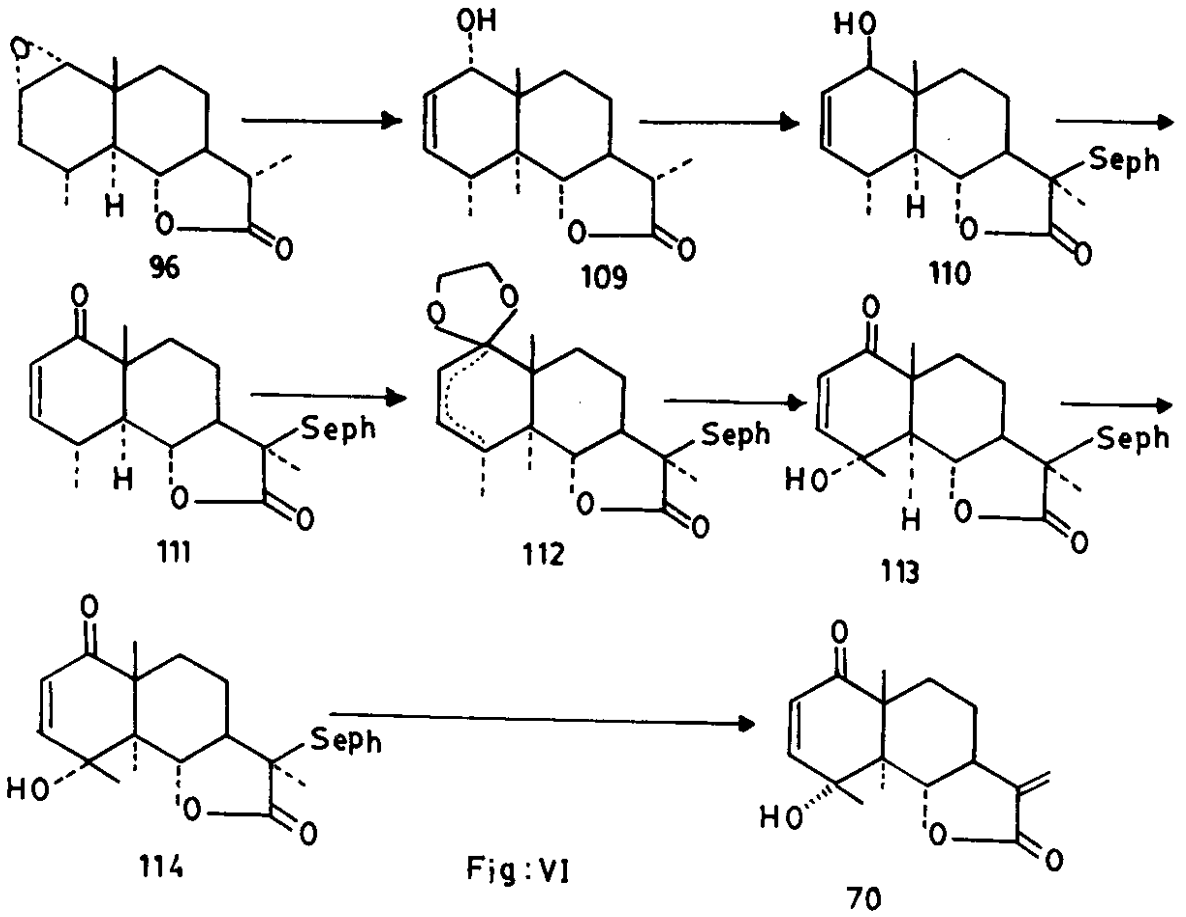


Fig : VI

warmed to 30-40° to give the allyl alcohol (109) in 22-33% yield. Phenylselenenylation of (109) afforded (110), which was oxidized with MnO_2 to give enone (111). The ketal (112) was prepared from (110) by reaction with ethylene glycol in the presence of p-toluenesulphonic acid in benzene. The hydroxy-enone (113) was formed in good yield by deketalization in the presence of O_2 gas. Oxidation of (113) with 30% H_2O_2 in THF-CH_3CO_2H at O° gave a selenoxide as an intermediate which underwent syn-elimination to give exo-methyelene (70), which was identical with natural arglanine in terms of IR and NMR spectra (Scheme 11).

Synthesis of Santamarine (71) [43]

The enol (104) was oxidized with Jones reagent to afford enone (114). Ketalization of (114) with bromoglycol gave a mixtures of isomeric bromoketal (115), from which (116) was obtained by deketalization by refluxing with zinc in methanol for 18 hours. Reduction of (116) with $NaBH_4$ in methanol at O° for 30 minutes afforded predominantly 1β-ol (117), which was converted into santamarine (71) by phenylselenenylation to give (118), followed by oxidative syn-elimination from (119), by reaction with hydrogen peroxide (Scheme 12).

Synthesis of Balchanin (72) [40]

Catalytic reduction of (116) gave 4 βmethyl-1-β-ol (120), which was identical with dihydrobalchanin. Phenylselenenylation followed by oxidactive syn-elimination gave (72), whose physical constants do not agree with those reported for (+)-balchanin. Thus

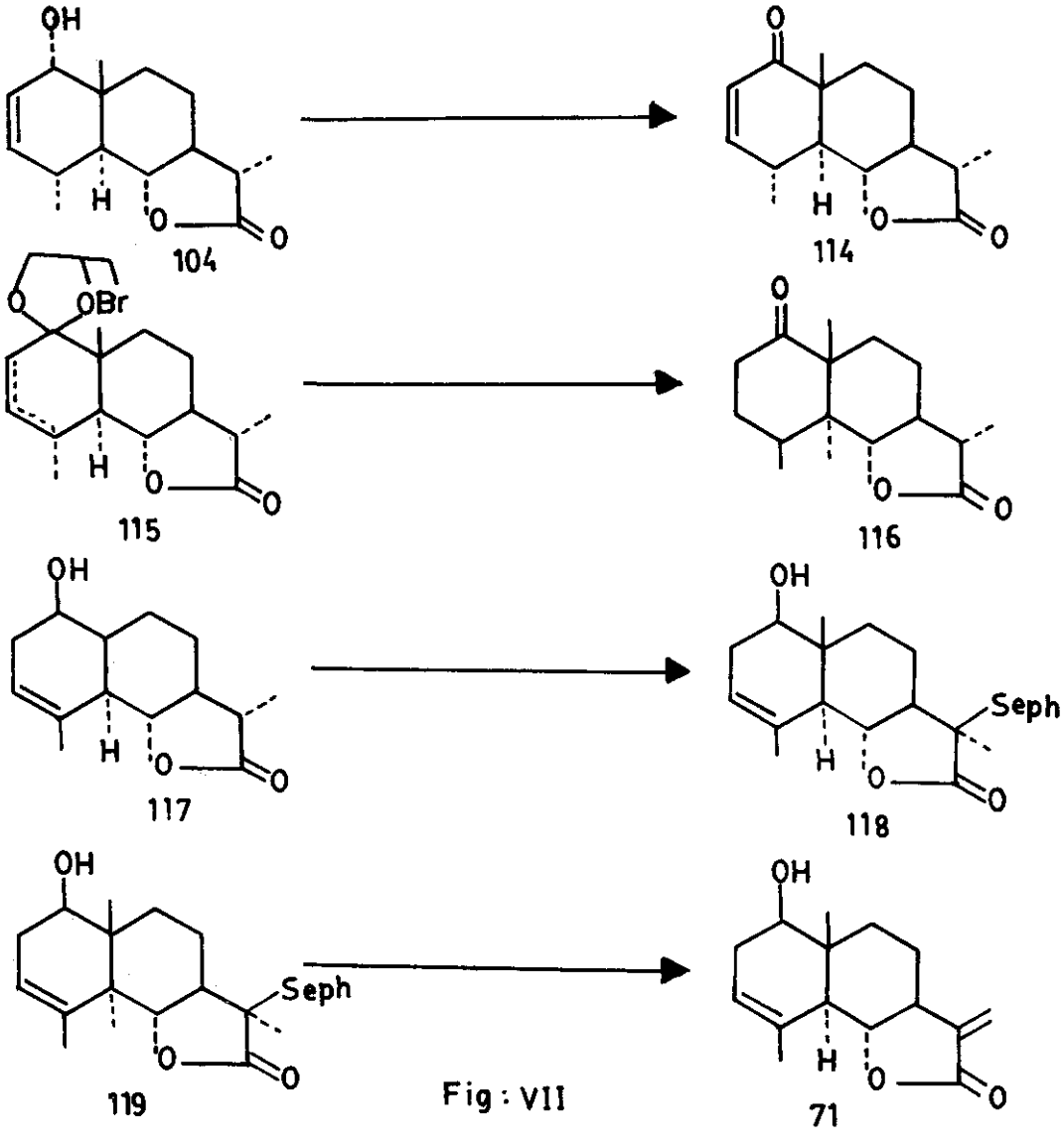


Fig : VII

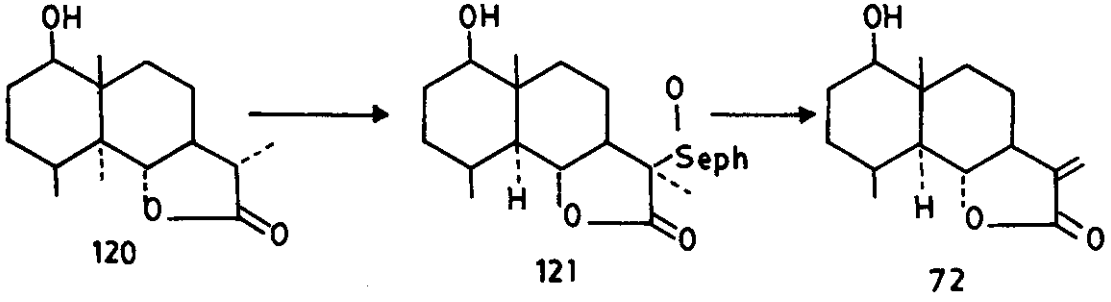


Fig : VIII

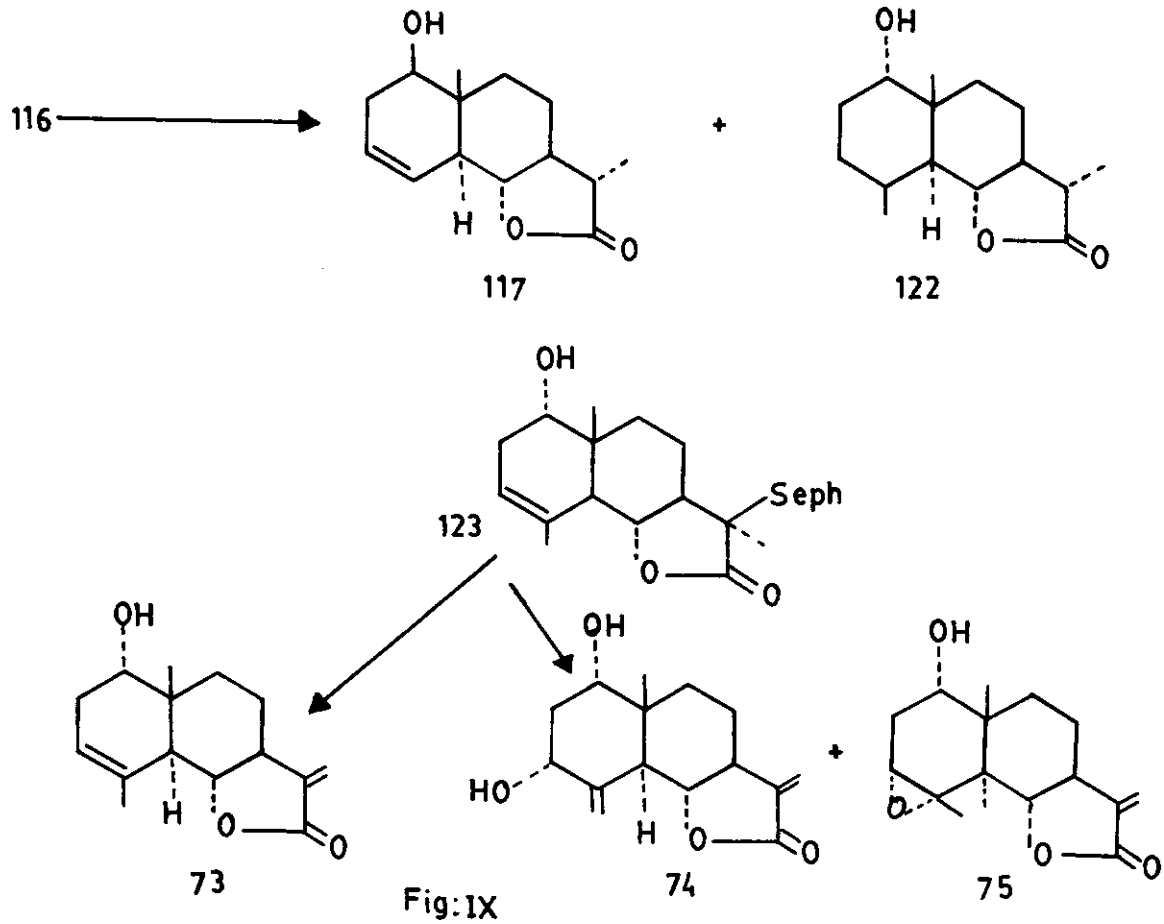


Fig:IX

the structure of balchanin should be reconsidered.

Synthesis of Douglanine (73) [44] and Ludovicin A and B (74,75) [44]

Reduction of enone (116) with lithium tri-tert-butoxy-aluminium hydride gave a mixture of 1β-ol (117) and 1 α-ol(122) in 73.6% and 12.4% yield, respectively. These were separated by preparative TLC. Phenylselenenylation of 1α-ol (122) according to the procedure of Grieco et al gave a phenylselenide (123). Oxidation of 123 with 2 molar equivalents of 30% H_2O_2 in THF-AcOH at 0° produced a selenoxide as an intermediate which underwent facile syn-elimination to give the natural douglanine (73).

Similarly, oxidation of (123) with an excess of 30% H_2O_2 in THF-AcOH gave a mixture of exo-methylene compounds, which were separated by column chromatography to give (74) (22% yield) and (75) (36% yield), which were identical with natural ludovicin A and ludovicin B respectively (Scheme 4).

The keto acid (12) was esterified to give (124) which was selectively hydrogenated using Wilkinson's catalyst to give (125) Reduction of (125) by $LiAlH_4$ produced a mixture of diasteromeric diols (126). The allylic hydroxyl in (126) was selectively oxidized using dichlorodicyanoquinone to the enone-alcohol (127). Reaction of (127) with $ClCO_2Et$ in pyridine gave

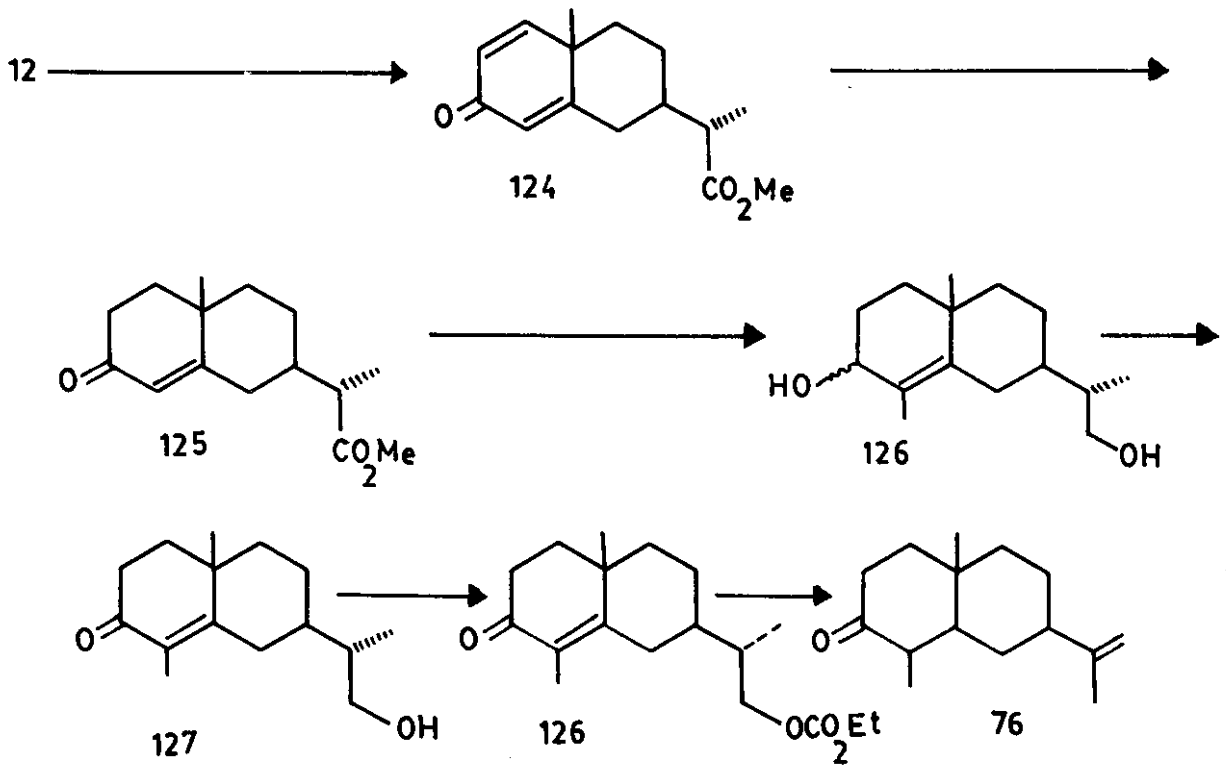

12
O
124
CO2Me
O
125
CO2Me
HO
126
OH
O
127
OH
O
126
OCO2Et
O
76

Fig : X

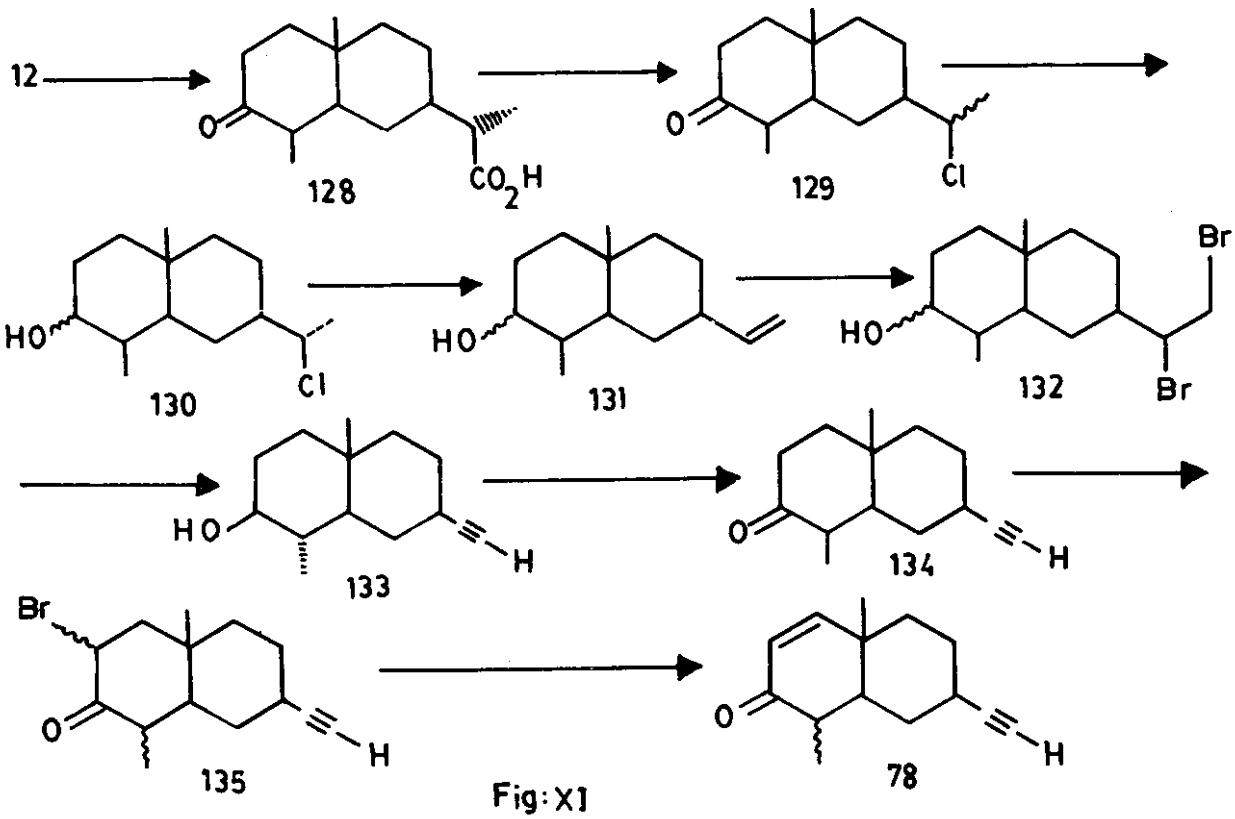

12
O
128
CO2H
O
129
Cl
HO
130
Cl
HO
131
HO
132
Br
Br
HO
133
H
O
134
H
Br
O
135
H
O
78
H

Fig : XI

carbonate ester, which was pyrolyzed at 400° to effect elimination, and gave α-cyperone(76) in 61% yield, plus 32% of enone-alcohol (127) (Scheme 15).

Synthesis of Chamaecynone (78) [45]

Hydrogenation of (12) in the presence of 1% NaOH gave saturated ketone (128). Chlorodecarboxylation of (128) gave the chloride (129), which is a mixture of diastereomers. To avoid aldol condensation in the reaction of (129) with potassium t-butoxide, the carbonyl group was temporarily reduced giving a mixture of diastereomeric chlorides (130) which were dehydrochlorinated in the presence of strong base to give the unsaturated alcohol (131). Bromination and dehydrobromination of (132) gave a mixture of acetylenic alcohols (133). Oxidation of (133) gave ketone (134) which was brominated and the resultant mixture of bromoketones (135) was dehydrobrominated to give chamaecynone (78) (Scheme (16).

Synthesis of Tetrahydroaussurea lactone (79) [46,47]

α-Tetrahydrosantonin (8) was converted into keto-oxide (138) via (136) and (137). The A ring was cleaved by ozonolysis of the derived benzylidine or furfuralidine derivative. The resulting diacid (139) was converted to its diester and reduced with lithium aluminium hydride to give diol (140).

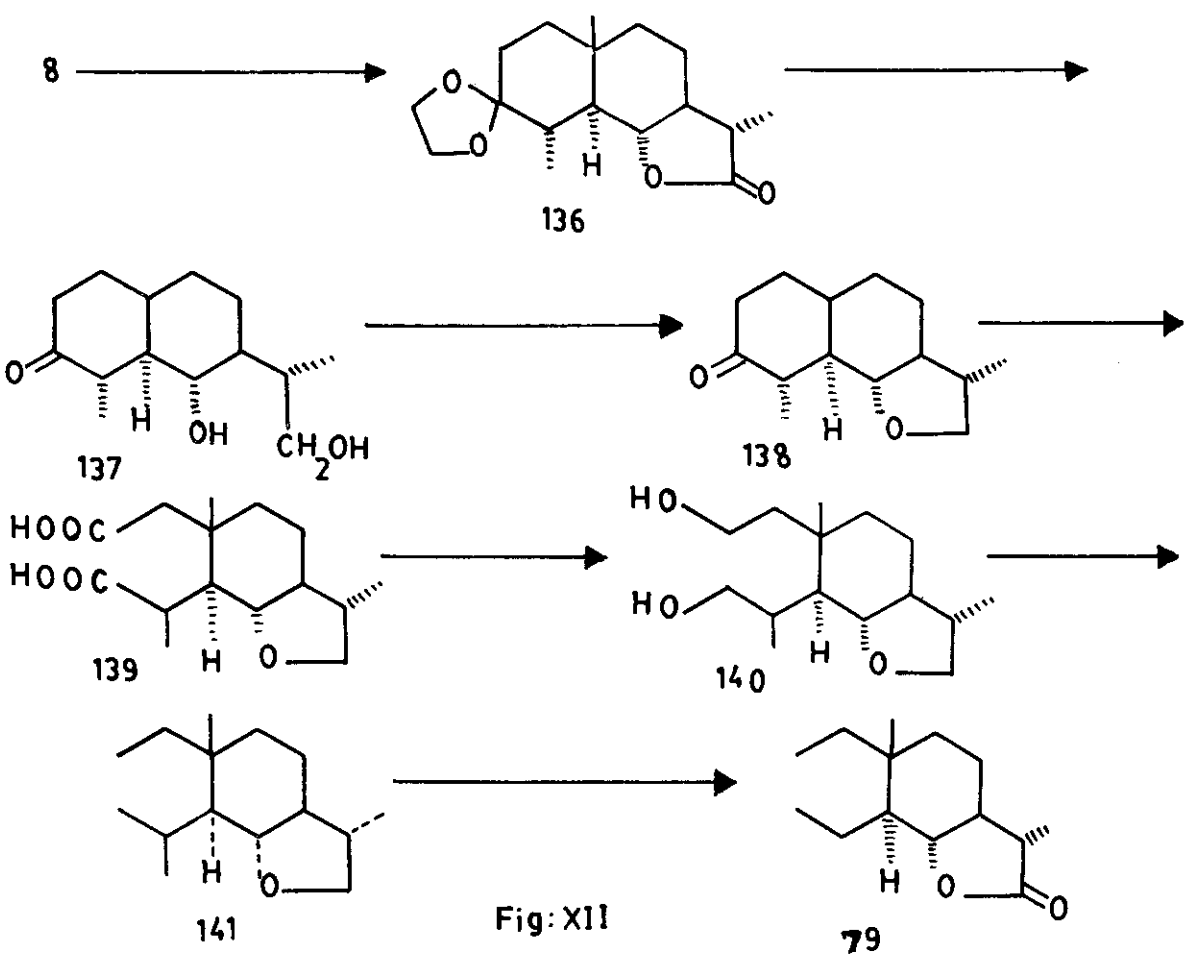


Fig: XII

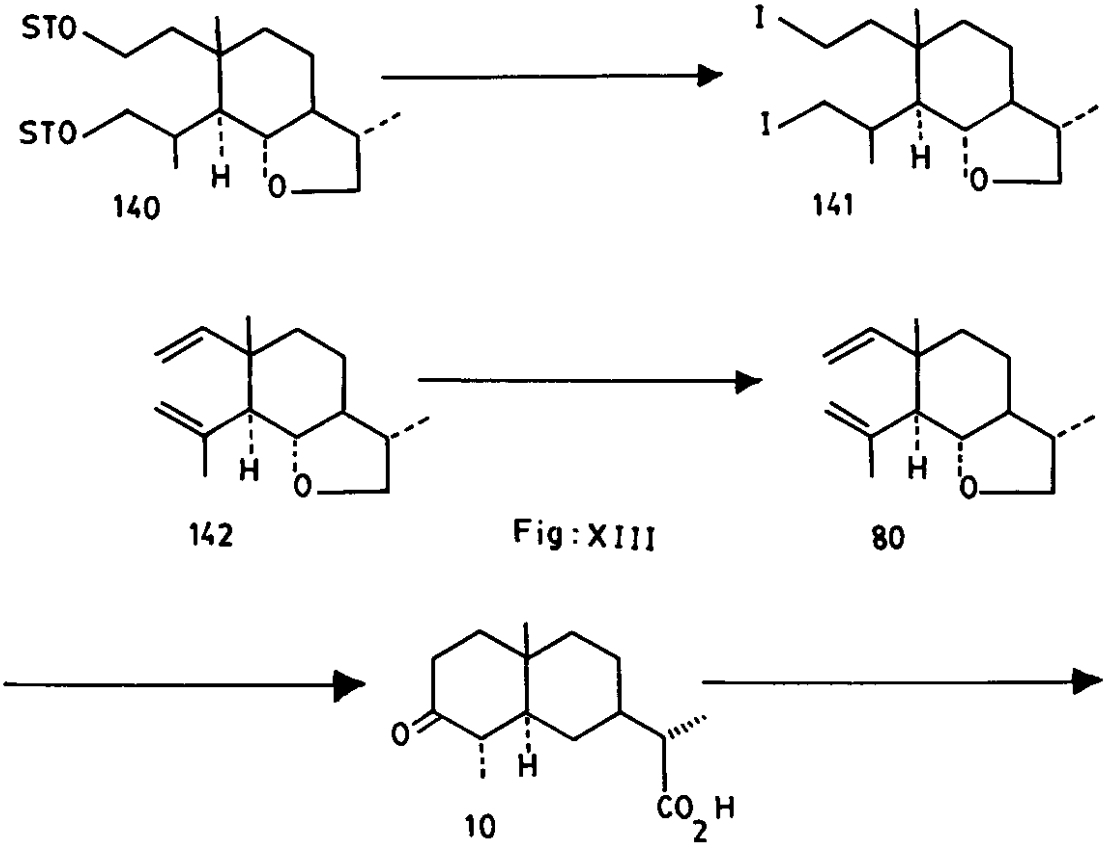


Fig: XIII

Fig: XIV

This was converted into a ditosylate, which was reduced by hydride to (141). Oxidation of (141) gave tetrahydrosaussuresa lactone (79) in high yield (Scheme 17).

Synthesis of Saussurea Lactone (80) [47]

Saussurealactone (80) was synthesized from the diol (140). (140) was converted into a di-iodide (141) via ditosylate of (140). Di-iodide (141) was treated with potassium t-butoxide in DMSO to yield the oxide (142). Oxidation of (142) with CrO_3 in acetic acid gave (80) in 15% yield (Scheme 18).

Synthesis of β-Elemene (81) and Elemol (82) [48]

α-Santonin was reduced by Li-NH_3 to the keto-acid (10), which was oxidized by HNO_3 and ammonium vanadate to give triacid (144). The corresponding triester was reduced to elemon-2,3,12-triol (145), which was converted via its tritosylate into iodide (146). Dehydroiodination of (146) in the presence of base catalyst gave β-elemene(81). Selective epoxidation of β-elemene followed by hydride reduction yielded alcohol (147) and the required elemol (82) (Scheme 19).

Synthesis of Shyobunone (83) [49].

Dihydroxy-acetal (148), obtained from (1) by the method of Simonovic et al was acetylated and carefully hydrolyzed to the hydroxymonoacetate (149). Treatment of (149) with methane sulfonyl chloride - pyridine followed by reaction with excess sodium iodide gave an iodo-acetate (150), which was reduced and then heated in aqueous acetic acid to produce, in 68% yield, the acetoxy-ketone (151). The enol acetate (152) was ozonized and the product reduced with lithium aluminium hydride to give a triol (153). Dihydroxymonoacetate (154) was obtained from (153) by acetylation and careful hydrolysis, and it was converted into a monoacetoxydimesylate (155). The dimesylate (155) gave the diiodoacetate (156) on treatment with sodium iodide under vigorous conditions. Dehydrohalogenation of (156) was effected with 1,5-diazobicyclo-(3.4.0)undec-5-ene to give an oily acetoxydiene (157), which was quantitatively converted into shyobunone (83) on treatment with LAH followed by oxidation with Jone's reagent (Scheme 20).

Synthesis of Rishitin (84) [50]

Δ^2-3-ol acetate (158) was obtained from (9) on treatment with isopropenyl acetate in the presence of acid. Oxidation of (158) with perbenzoic acid in chloroform at 0° for 24 hours afforded 2α -3α -epoxy-3β -acetate (159), which was rearranged to (160) by heating at 170 C° for 10 minutes. The acetoxy ketone (160) was then epimerized with hydrobromic acid in acetic acid at room temperature to give (161). It could also be obtained from (9) by a one step oxidation reaction with lead tetracetate and borontrifluoride. Reduction of (161) with sodium borohydride in methanol at 0° afforded a mixture of diastereoisomeric alcohols, which were separated to give 3 β - alcohol (162). Reduction of (162) with LAH gave tetraol (164), which was transformed into an acetate (164) and then into 6-nitrite (165) by treatment with nitrosyl chloride in pyridine.

Irridiation of the 6-nitrite (165) followed by refluxing in 1:1 mixture of THF and 2-propanol resulted in functionalization at C_{15} and gave a mixture from which 15-oxime (166) was

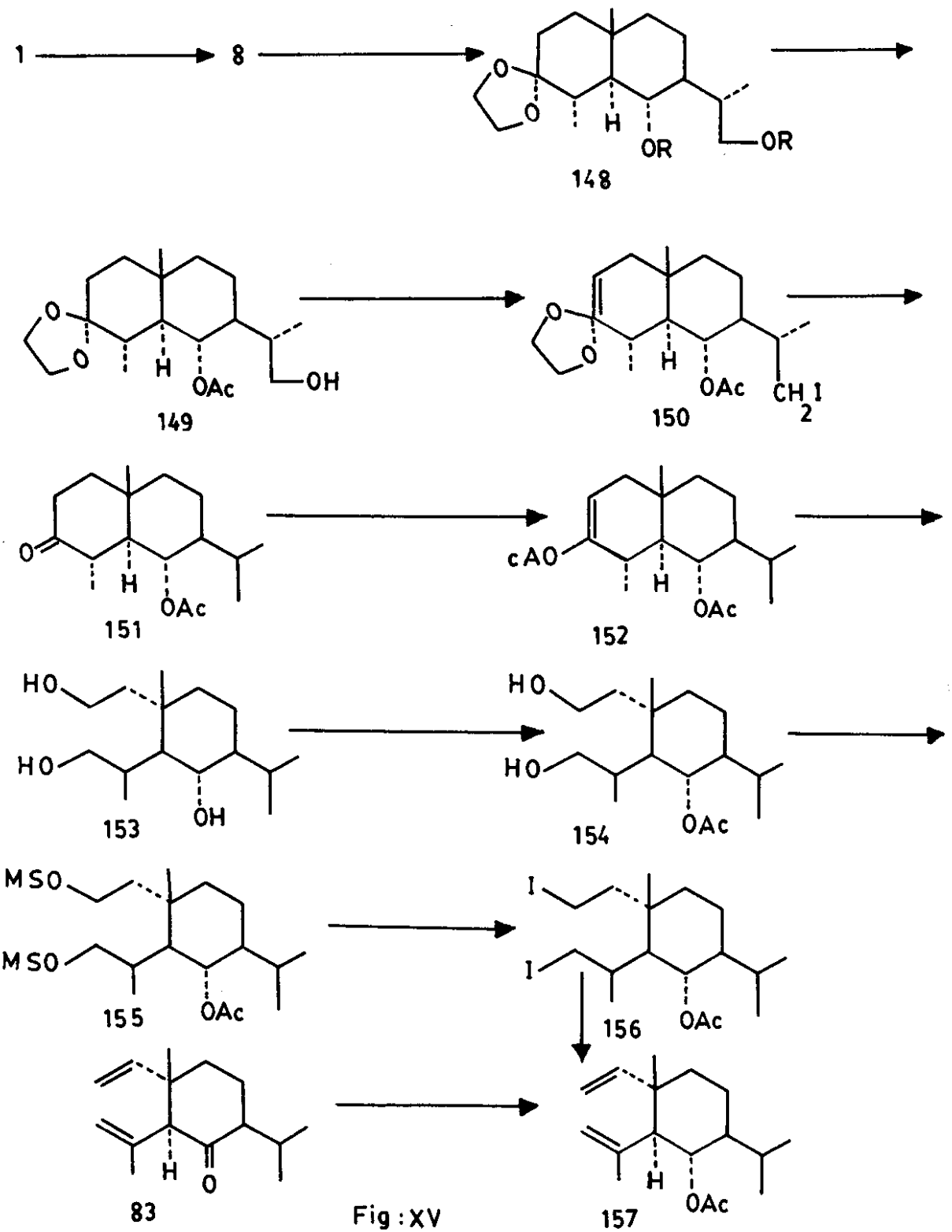


Fig : XV

obtained in 78% yield. Treatment of (166) with acetic anhydride in pyridine gave 6 β-hydroxy-10-nitrile (167) in 89% yield. Dehydration of (167) gave a mixture of Δ^5 - (168) and Δ^6 - 10-nitriles. Treatment of (168) with sodium in toluene containing ethanol under reflux effected reductive decyanation with concurrent migration of the double bond to give Δ^5(10)-triol (169), which was converted into 2,3-acetonide and treated with tosyl chloride in pyridine and then with sodium iodide in acetone to give the 12-iodide (170). The 12-iodide (170) was treated with KOH in refluxing methanol to give a mixture from which (171) was obtained by chromatographic separation. Hydrolysis of the acetonide with 0.5% phosphoric acid in ethanol under reflux gave (84), which was identical with natural rishitin (Scheme 21).

Synthesis of Juneol (85) [51] and Acolamone (179)

The acetoxy ketone (172) was reduced with $NaBH_4$ to give a mixture of α-(173) and β-hydroxy (174) compounds in 27% and 71% yield, respectively. The β-hydroxy compound was mesylated (175) (98% yield) and directly converted into a trisubstituted olefin (176). The epoxidation of (176) with m-chloroperbenzoic acid, followed by $LiAlH_4$ reduction gave (177) which was acetylated and treated with $POCl_3$ -pyridine at 0° for 1 hour to give (178) which was then reduced with $LiAlH_4$ to give, in a quantitative yield, (+)-juneol (85). Further oxidation of (85) with pyridinium chlorochromate in CH_2Cl_2 afforded acolamone (179) in 78% yield (Scheme 22).

Synthesis of (+)-Deoxyvernolepin (86) [52]

Treatment of tetrahydrosantonin (9) with lead tetraacetate in the presence of boron trifluoride gave a mixture of 2α -acetoxy (180) and 2β -acetoxytetrahydrosantonin (181). Treatment of mixture of (180) and (181) with tetramethylammonium acetate in glyme at reflux for 8 hours gave 2-oxo-3β-acetoxy-5α -santonolide (182) in 85% yield. Reduction of (182) with $NaBH_4$ afforded an alcohol (183) in quantitative yield. Oxidation of (183) with mercuric oxide-iodine gave an ether (184). Hydrolysis of the acetyl group of (184), followed by oxidation gave the ketone (185). Treatment of (185) with zinc powder in refluxing

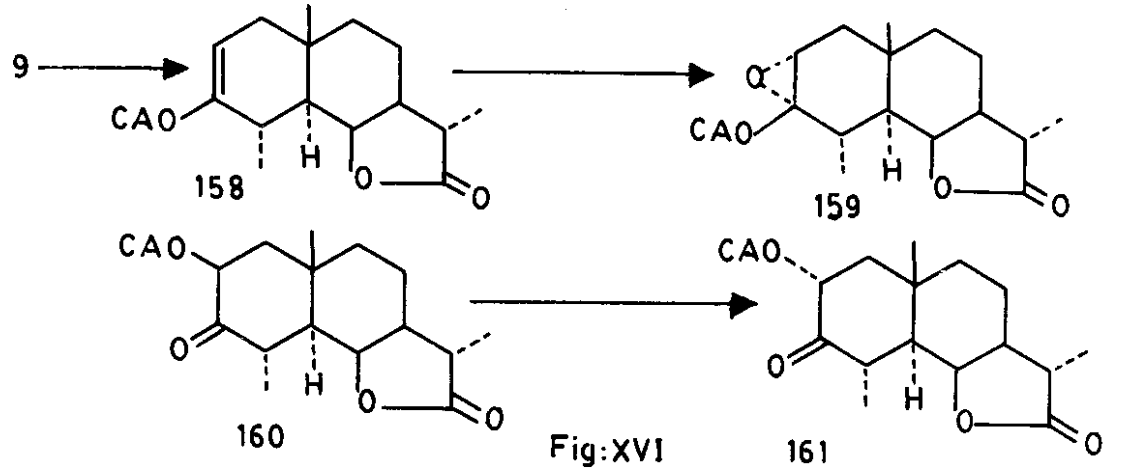
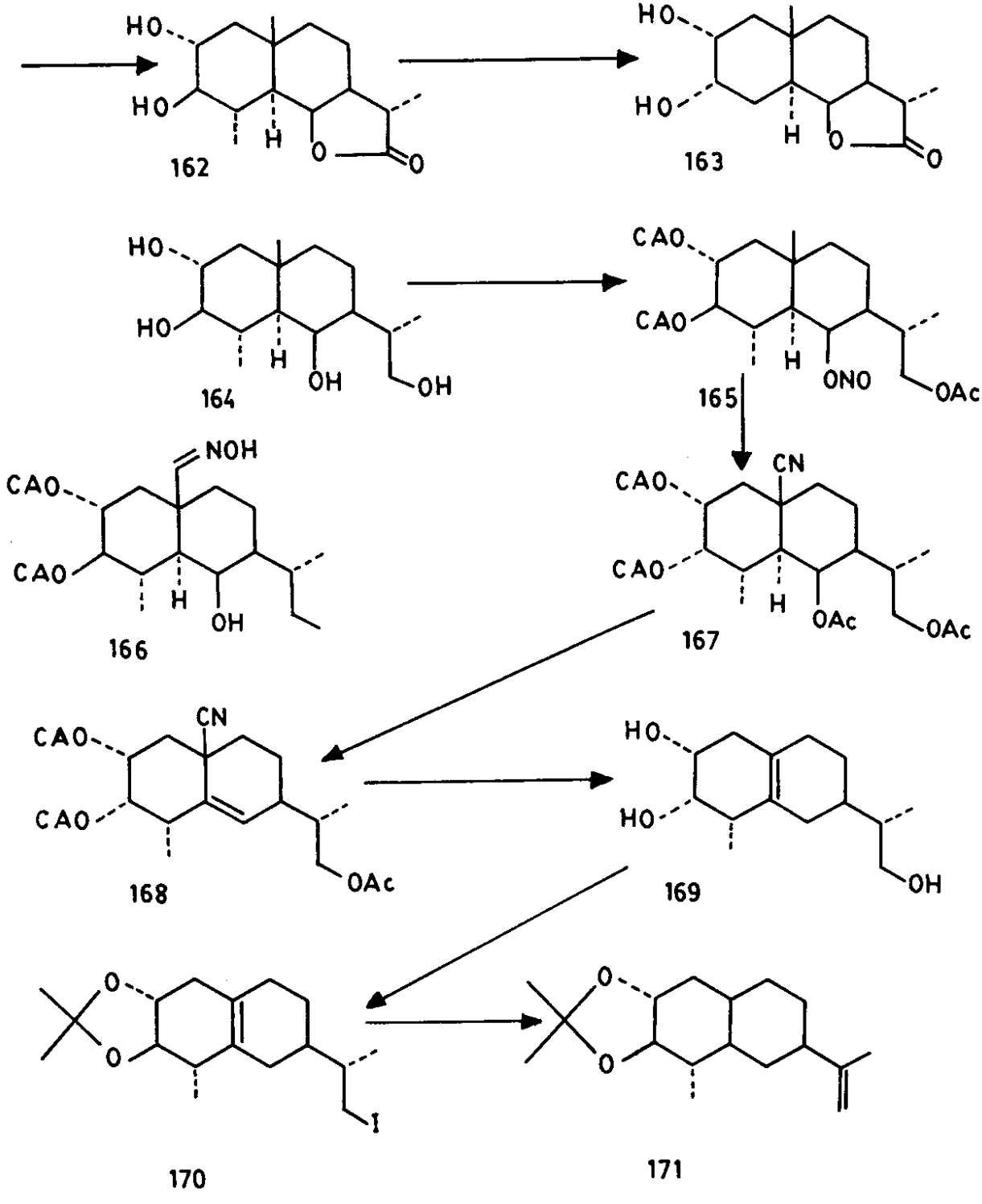


Fig:XVI


HO
HO
H
O
O
162
HO
HO
H
O
O
163
HO
HO
H
OH
OH
164
CAO
CAO
H
ONO
OAc
165
NOH
CAO
CAO
H
OH
166
CN
CAO
CAO
H
OAc
OAc
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OAc
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HO
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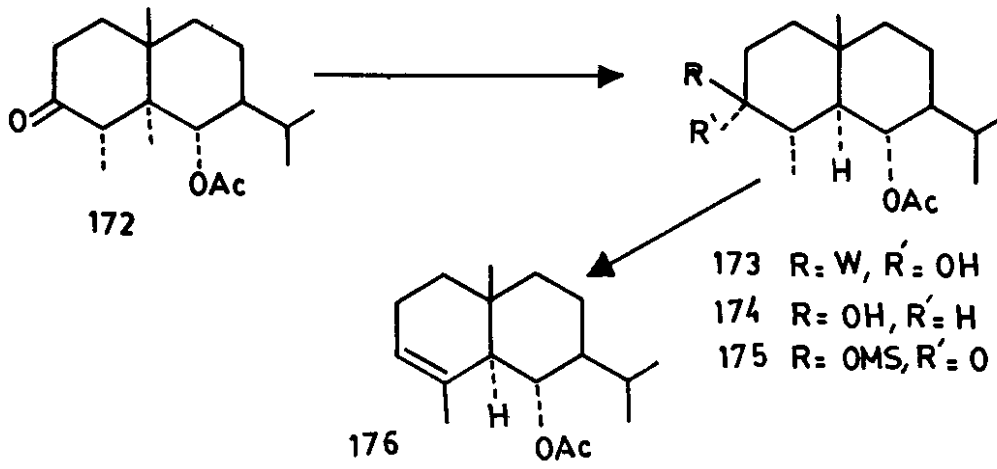
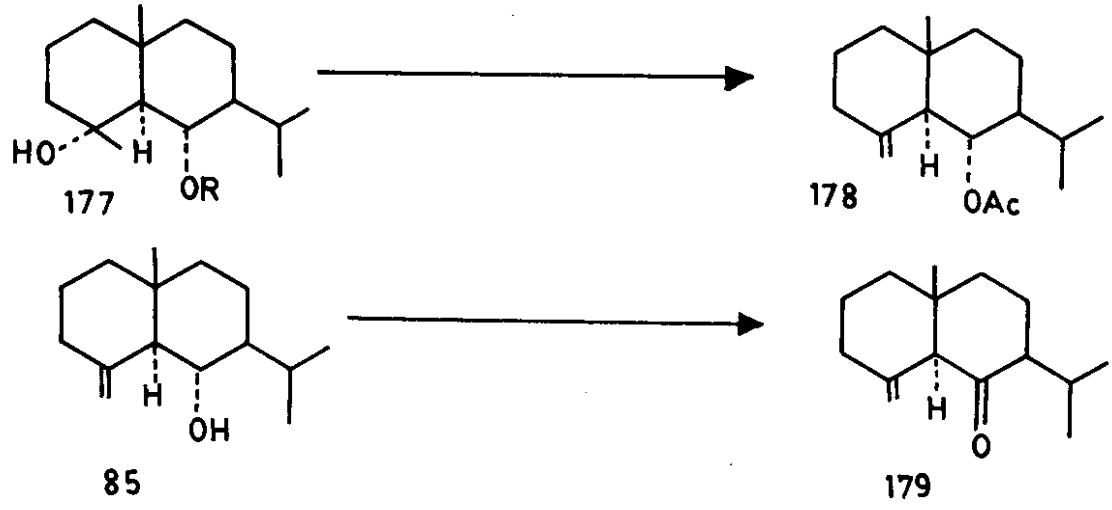
OH
169
O
O
I
170
O
O
171



acetic acid in the presence of zinc iodide and zinc chloride gave the keto alcohol (186 a) in 55% yield and the keto-acetate (186b) in 26% yield. Reaction of (186b) with methyl orthoformate in the presence of pyridinium p-toluenesulphonate in methanol afforded a mixture of enol ether (188) and dimethylketal. Ozonization of (188) followed by reduction with $NaBH_4$ provided an ester (189), which was transformed to a dilactone (190), by refluxing in MeOH and 10% HCl. The dilactone (190) was converted into a selenide by reaction with o-nitrophenyl selenocyanate-tri-n-butylphosphine and oxidized with 30% H_2O_2 to afford deoxytetrahydrovernolepin (191). Dienolate formation (lithium diisopropylamide, THF,-78°) from (191), followed by reaction with phenylselenyl chloride gave a mixture of selenide (192). Oxidation of (192) with 30% H_2O_2 gave (+)-deoxyvernolepin (86) in 82% yield (Scheme 23)..

Synthesis of Dihydrocostunolide (87) [53]

Selective reduction of the α-epoxide (17) with $LiAlH_4$ afforded a mixture of corresponding α(193) and β-alcohols (194), respectively. Mesylation (or tosylation) of (193) and (194) with



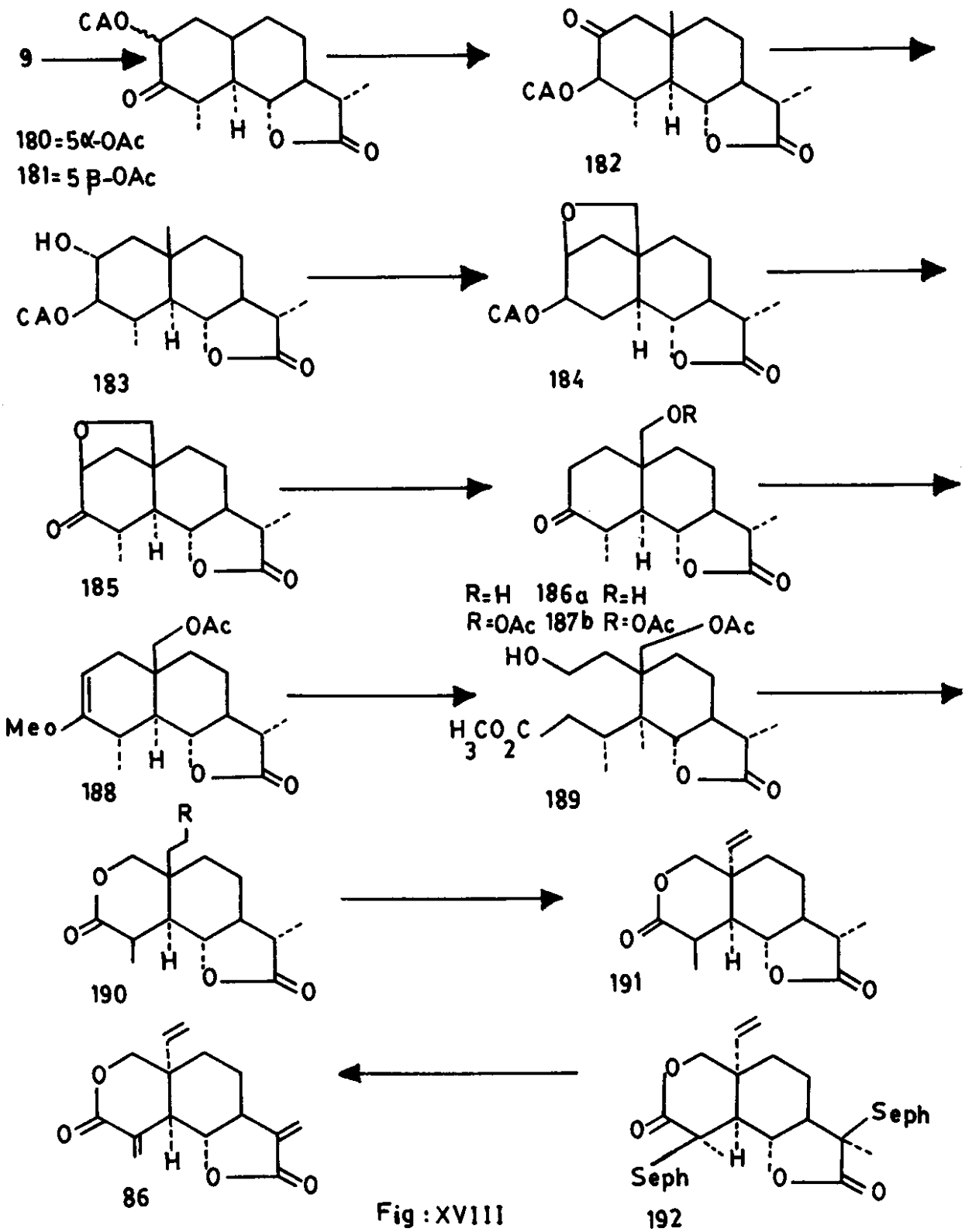

9
CAO
180=5α-OAc
181=5β-OAc
182
HO
183
184
185
OR
R=H 186a R=H
R=OAc 187b R=OAc
OAc
Meo
188
HO
H3CO2C
189
R
190
191
86
Seph
192

Fig : XVIII

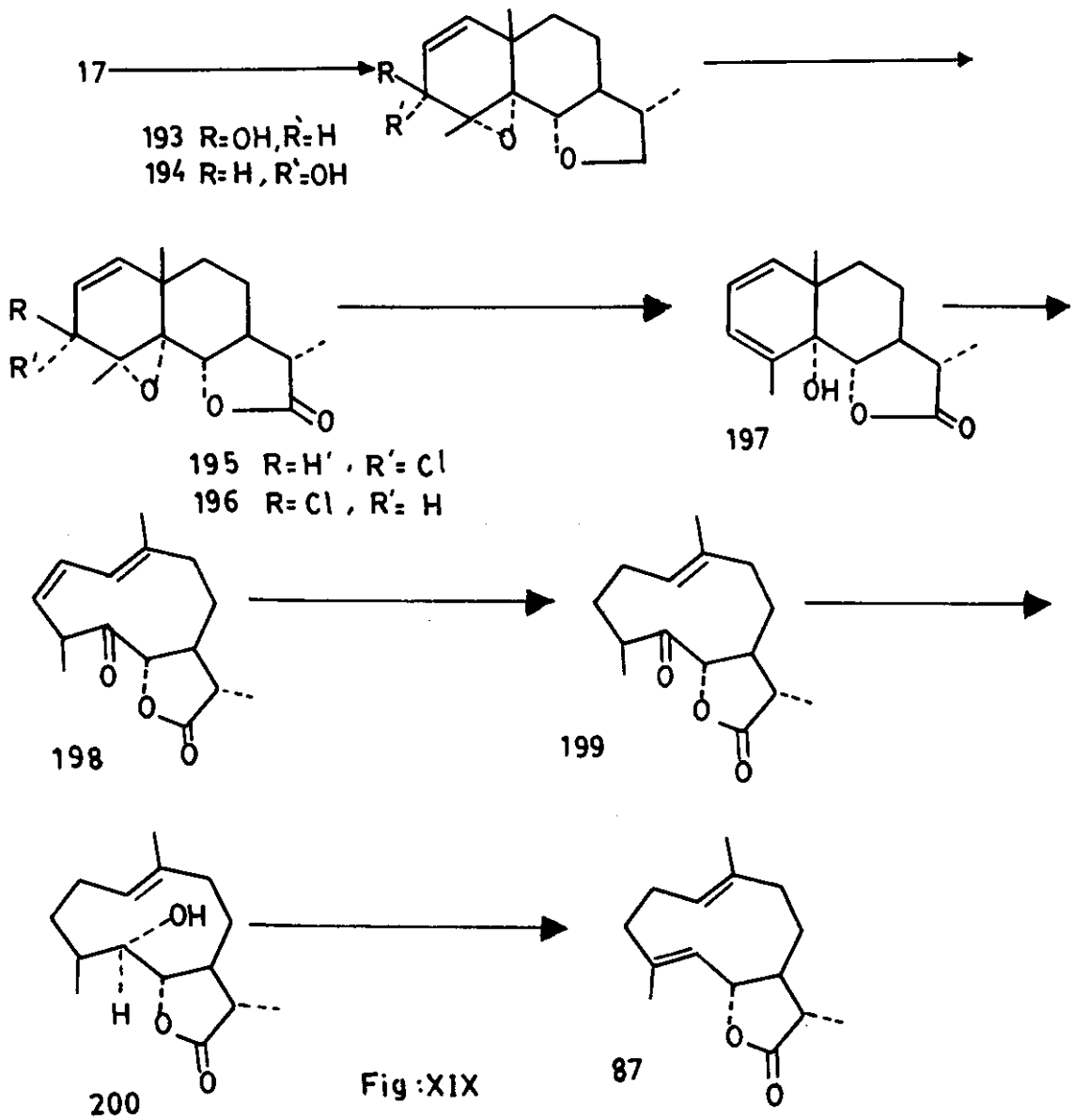


Fig :XIX

MsCl or TsCl-pyridine gave, stereospecifically, chlorides (195) and (196), respectively. Treatment of (195) with sodium iodide in refluxing acetone gave a dienol (197) in 67% yield. Irradiation of 197 with a 7W low pressure mercury lamp provided a mixture of dienones, from which (198) was obtained in 45% yield, together with a guaianolide type compound and a conjugated dienone.

Hydrogenation of (198) over Pd/C gave the dihydro derivative (199) and other compounds. Reduction of (199) with $NaBH_4$ produced an α-alcohol (200, 86.5%), which was mesylated, and then treated with tetra-butylammonium oxalate to give dihydrocostunolide (87) (Scheme 24).

Corey's Synthesis of Dihydrocostunolide (87) [54]

The enol (201) was prepared from santonin (1). The basic idea in the synthesis of dihydrocostunolide involves the scission of the central bond

in a 1,2-fused bicyclic system, leading to a new ring corresponding in size to the periphery of the old bicyclic compound. This was done in this case by photolysis of the crucial diene (202). The initial product of the photolysis (203) was hydrogenated in the presence of Raney Nickel at -18° to give dihydrocostunolide (87) (Scheme 25)

Synthesis of α-Bulnesene (88) [55]

Photolysis of (12) in H_2O-HOAc gave the photo product (204). Acetylation of (204) gave (205) which was hydrogenated in the presence of catalyst to give the saturated ketone (206). Reduction of (206) yielded a mixture of epimeric alcohols (207) which was treated with p-toluenesulfonyl chloride in pyridine to effect dehydration. Compound (208) was obtained in 55% yield. When (208) was hydrogenated in the presence of homogeneous catalyst tris(tripheylphosphine)rhodium (1) chloride, the reduction, selectively, yielded isomer (209). Reduction of (209) with $LiAlH_4$ gave a diol (210) which was treated with methyl chlorocarbonate to give carbonate ester at the less hindered primary position. Dehydration of the t-alcohol gave (211) which was pyrolysed at 400° to give a mixture of olefin α-Bulnesene (88) was isolated from these olefins by preparative gpc (Scheme 26).

Synthesis of Arborescin (89) [56]

o-Acetyldihydroisophotosantonic lactone (212) was obtained from α-santonin by Barton's method. Reduction of (212) by $NaBH_4$ gave a mixtureof alcohols (213). Reaction of (213) with benzoyl chloride gave a mixture of benzoates (214) which was treated with BF_3 to eliminate acetic acid and produce an olefin (215). Epoxidation of 215 gave an ether (216) which was pyrolyzed at 210°. Arborescin (89) was isolated from pyrolysate by chromatography (Scheme 27).

Synthesis of Desacetoxymatricarin (90) [57] and Achillin (91) [58].

White et al. synthesized desacetoxymatricarin (90) and achillin (91) starting from a mixture of diastereomeric

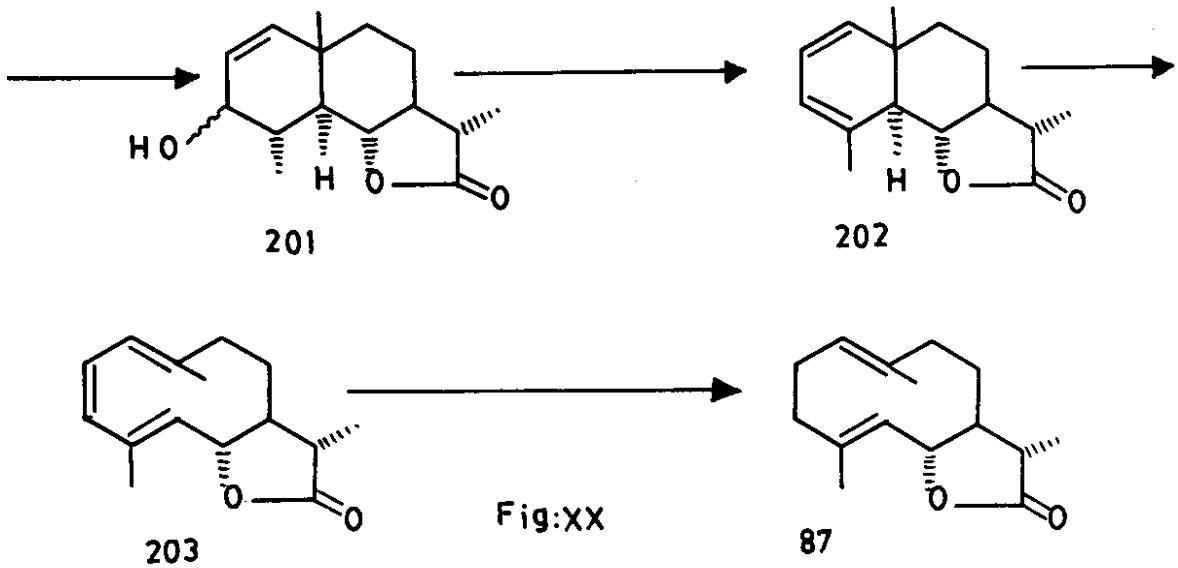


Fig:XX

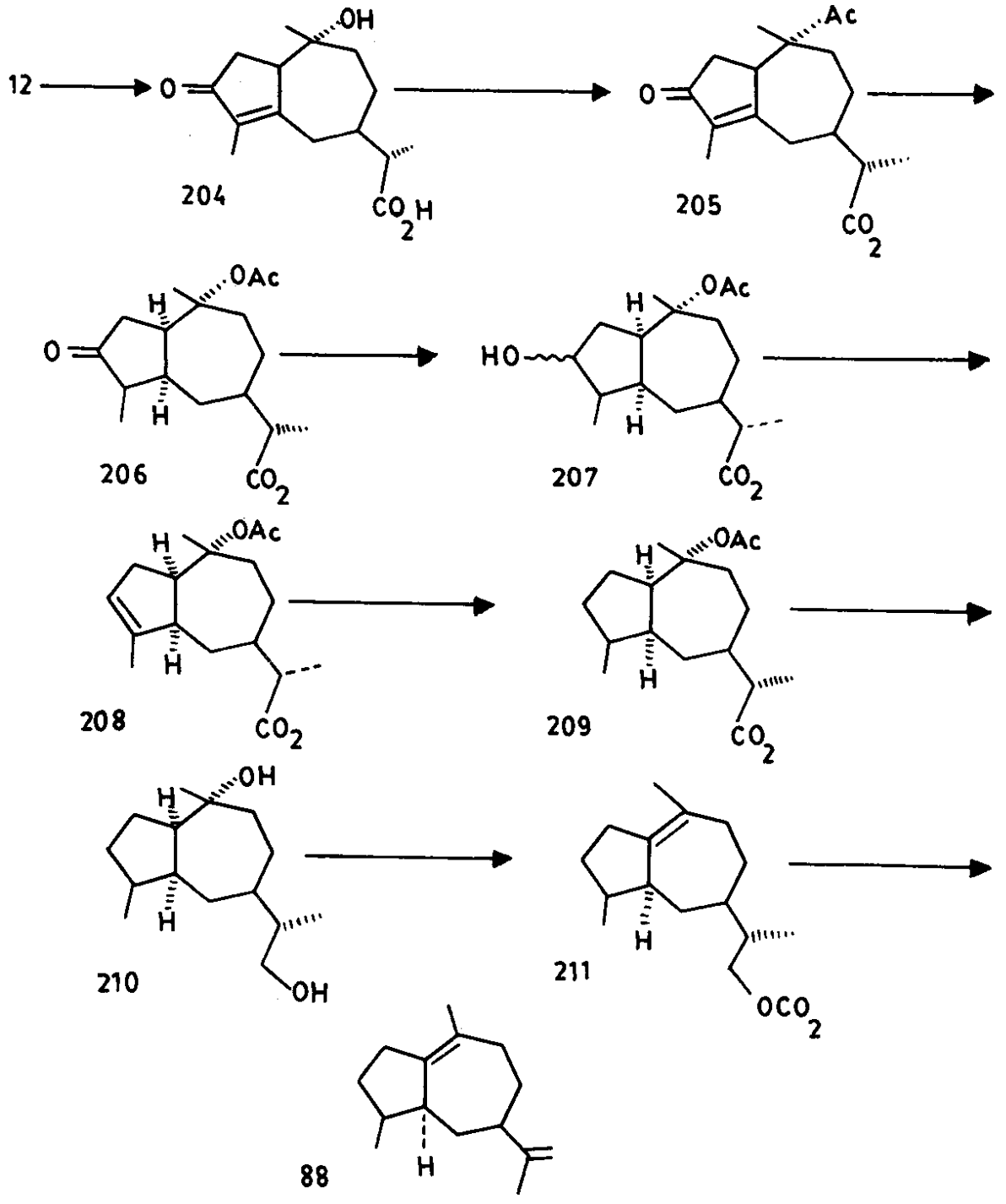

12
OH
O
204
CO2H
Ac
O
205
CO2
OAc
H
O
H
206
CO2
OAc
H
HO
H
207
CO2
OAc
H
H
208
CO2
OAc
H
H
209
CO2
OH
H
H
210
OH
211
H
OCO2
88
H

Fig:XXI

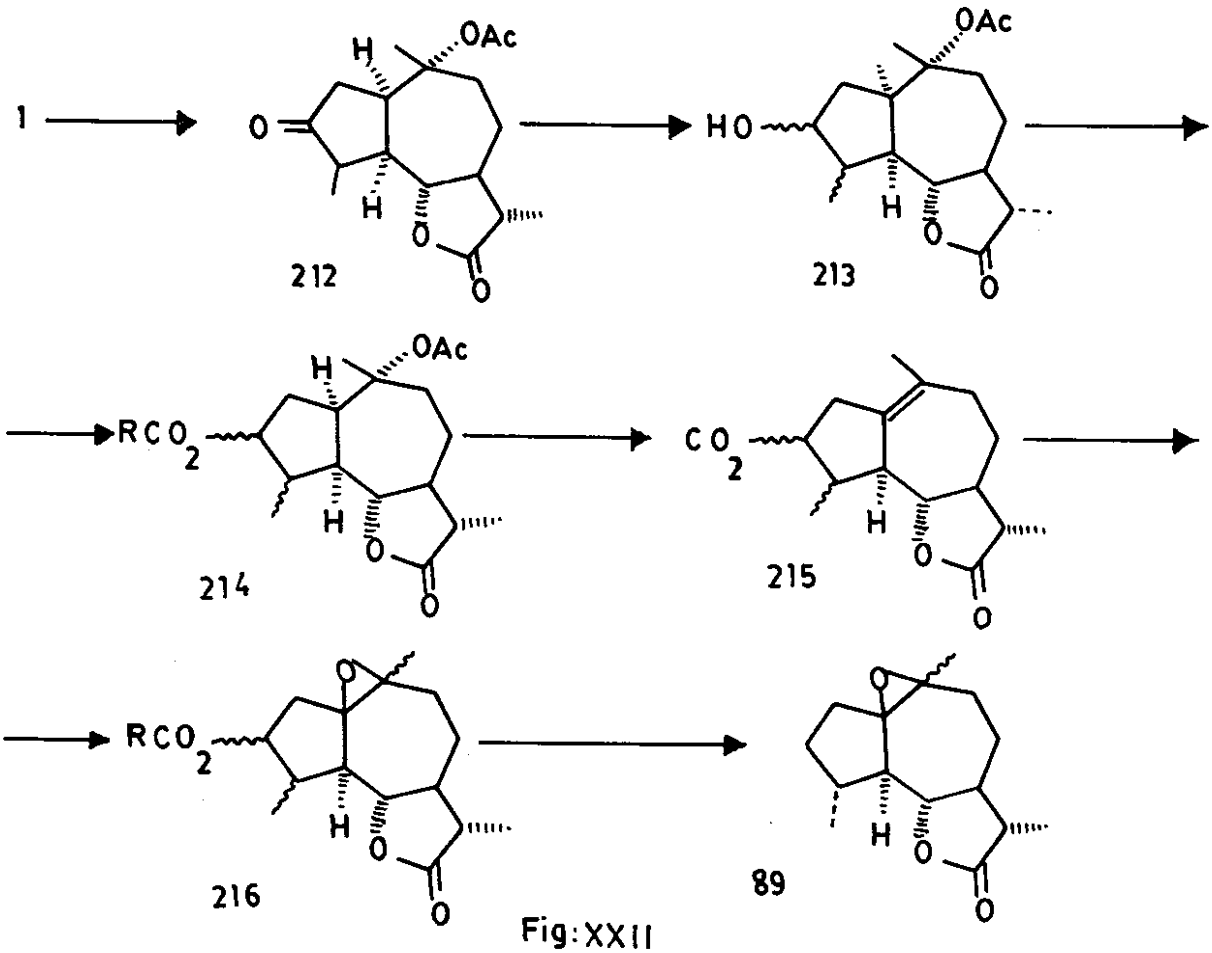


Fig:XXII

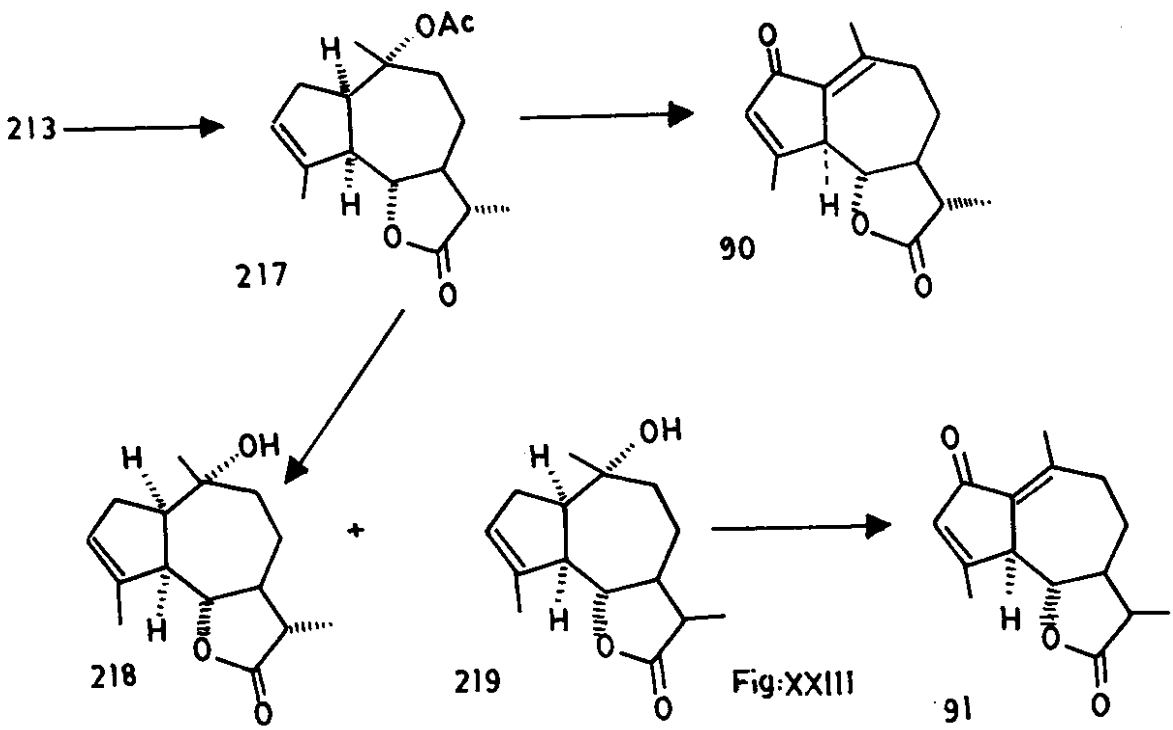


Fig:XXIII

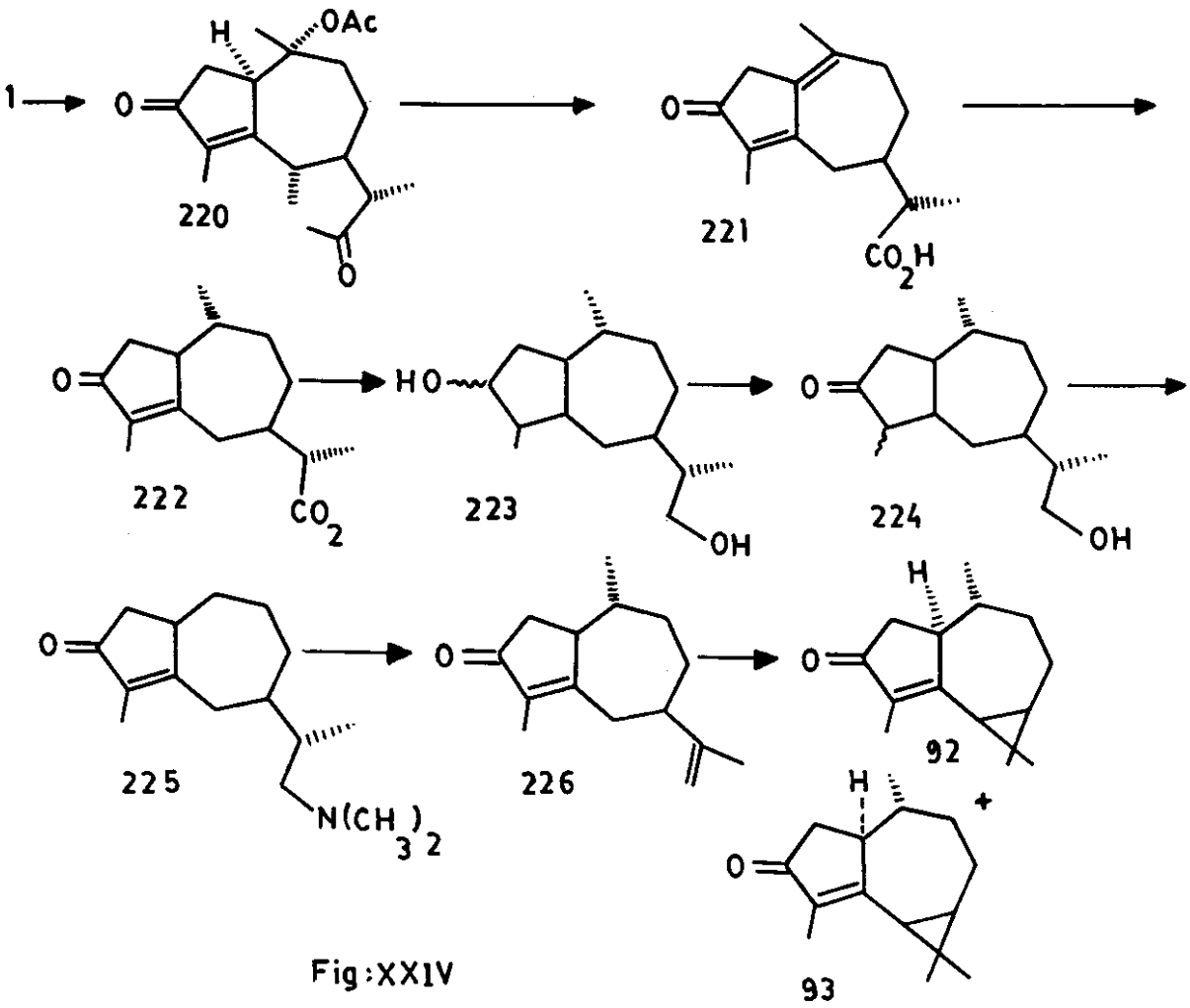


Fig:XXIV

alcohols (213) which was treated with methane-sulfonyl chloride in pyridine at room temperature for 24 hours to give olefine (217) in 45% yield. Allylic oxidation of (217) using t-butyl chromate in HOAc/NaOAc gave desacetoxymatricarin (90) in 15-20% yield. When (217) was treated with t-BuOK, epimerization at C-11 occurred along with acetate hydrolysis producing an equimolar mixture of isomers (218) and (219). Allylic oxidation of (219) gave achillin (91) in 5% yield (Scheme 28).

Synthesis of Epicyclocolorenone (92) [59]

O-Acetylphotosantonic acid lactone (220) was treated with chromous chloride to yield dienone (221). Partial hydrogenation of (221) produced mainly the dihydroisomer (222). Esterification and reduction of the ester with $LiAlH_4$ gave a diol (223). Reoxidation of (223) with dichlorodicyanobenzoquinone gave the hydroxy enone (224). Reaction of the derived p-bromobenzenesulfonate with dimethylamine gave an amino ketone (225). Cope elemination of the corresponding N-oxide produced dienone (226). Addition of HBr to (226) followed by dehydrobromination in the presence of KOH-MeOH gave (92) which is the stable epimer of natural cyclocolorenone (93) (Scheme 29).

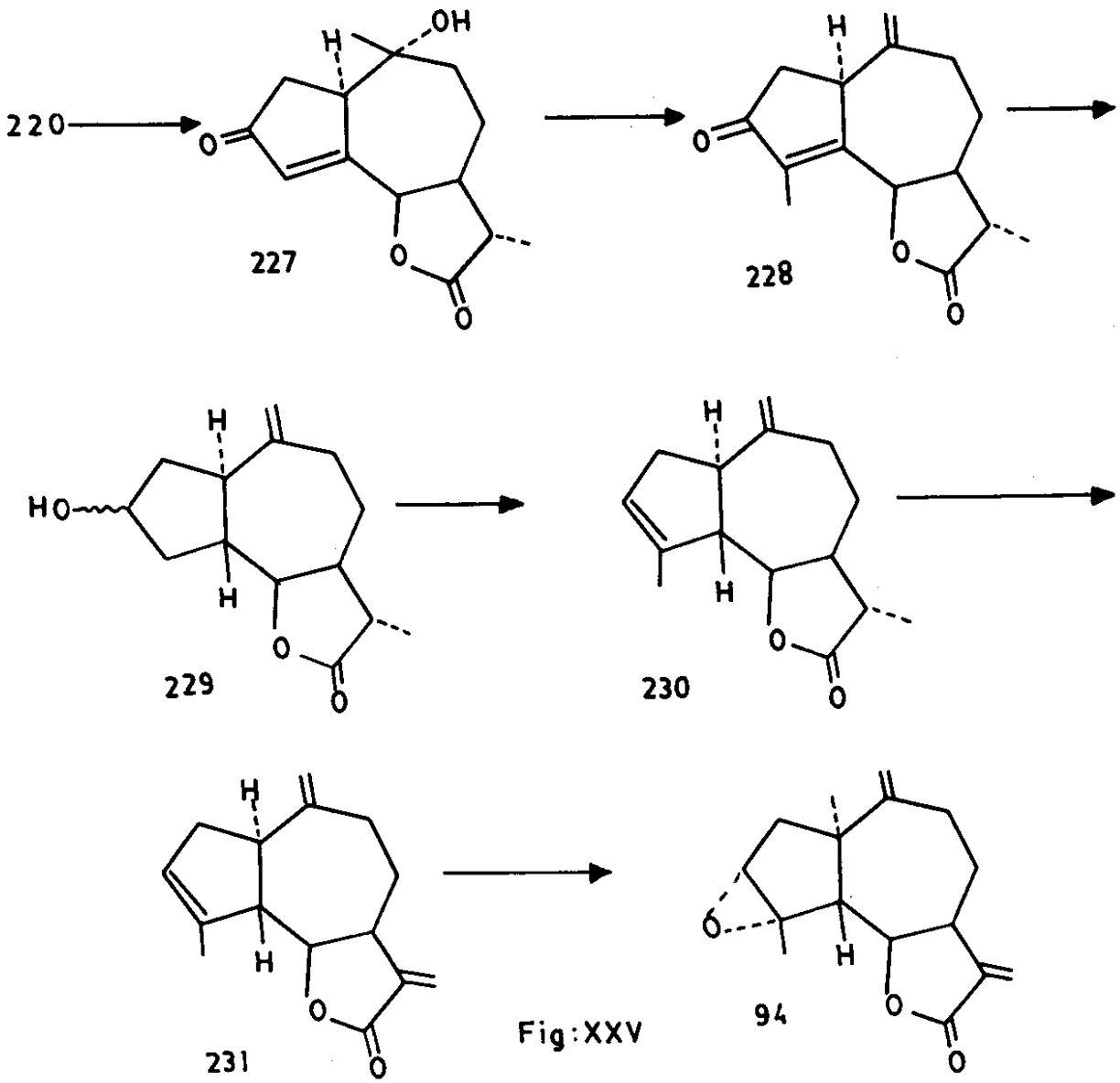


Fig:XXV

Stereoselective synthesis of (-) - Estafiatin (94) [60]

O-Acetylisophotosantonic lactone (220) obtained from -santonin by photolysis, was transformed via the alcohol (227) to the dienone lactone (228). Reduction of (228) with $NaBH_4$ in pyridine gave the alcohols (229). Dehydration of (229) in hexamethylphosphonic triamide afforded a mixture of tri- and disubstituted olefins (230) in 1.4:1 ratio, which were separated on silver impregnated silica gel. Alkene (230) was converted to the corresponding α-methylenelactone (231) by α-phenylselenenylation and oxidation. Selective epoxidation of the triene (231) produced (94) in 80% yield (Scheme 30).

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