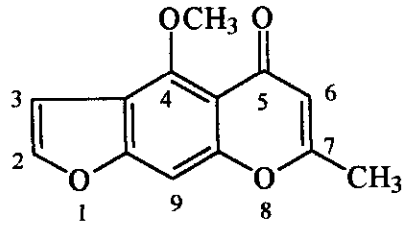
INTRODUCTION

2.1. THE CHEMISTRY OF VISNAGIN

Visnagin [Visnagidin, 4-methoxy-7-methyl-5H-furo[3,2-g]-1-benzo-pyran-5-one or 4-methoxy-2-methylfuro[3`,2`-6,7]chromone] **(1)**, $C_{13}H_{10}O_4$, m.p. 142-144°C is an important companion of khellin found in the fruits of *Ammi visnaga* L.[1]. Treatment of its solution with fuming nitric acid, led to the formation of a bright green crystalline oxonium nitrate which regenerate visnagin by hydrolysis .



(1)

2.1.1. Synthesis of Visnagin:

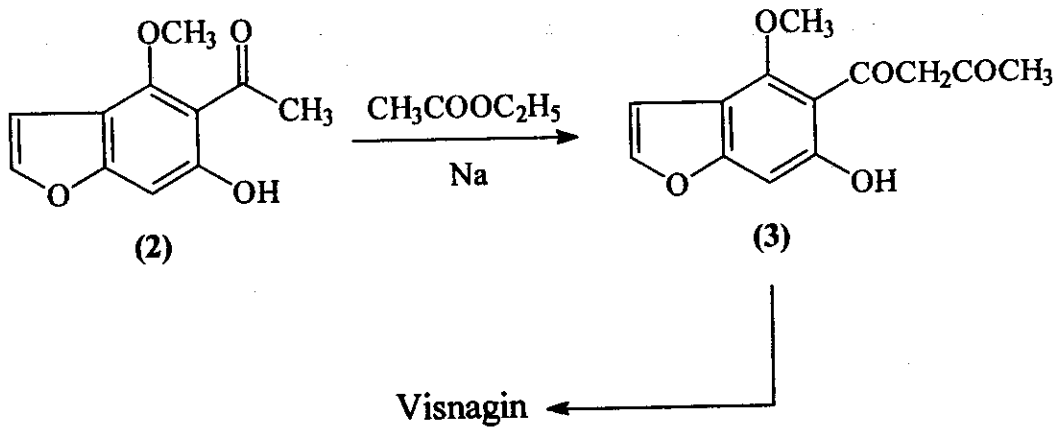
All routes followed towards visnagin synthesis have logically been concerned with either:

(a) The construction of a γ-pyrone ring onto the requisite benzofuran residue, or (b) The construction of a furan ring on the corresponding 2-methylchromone nucleus.

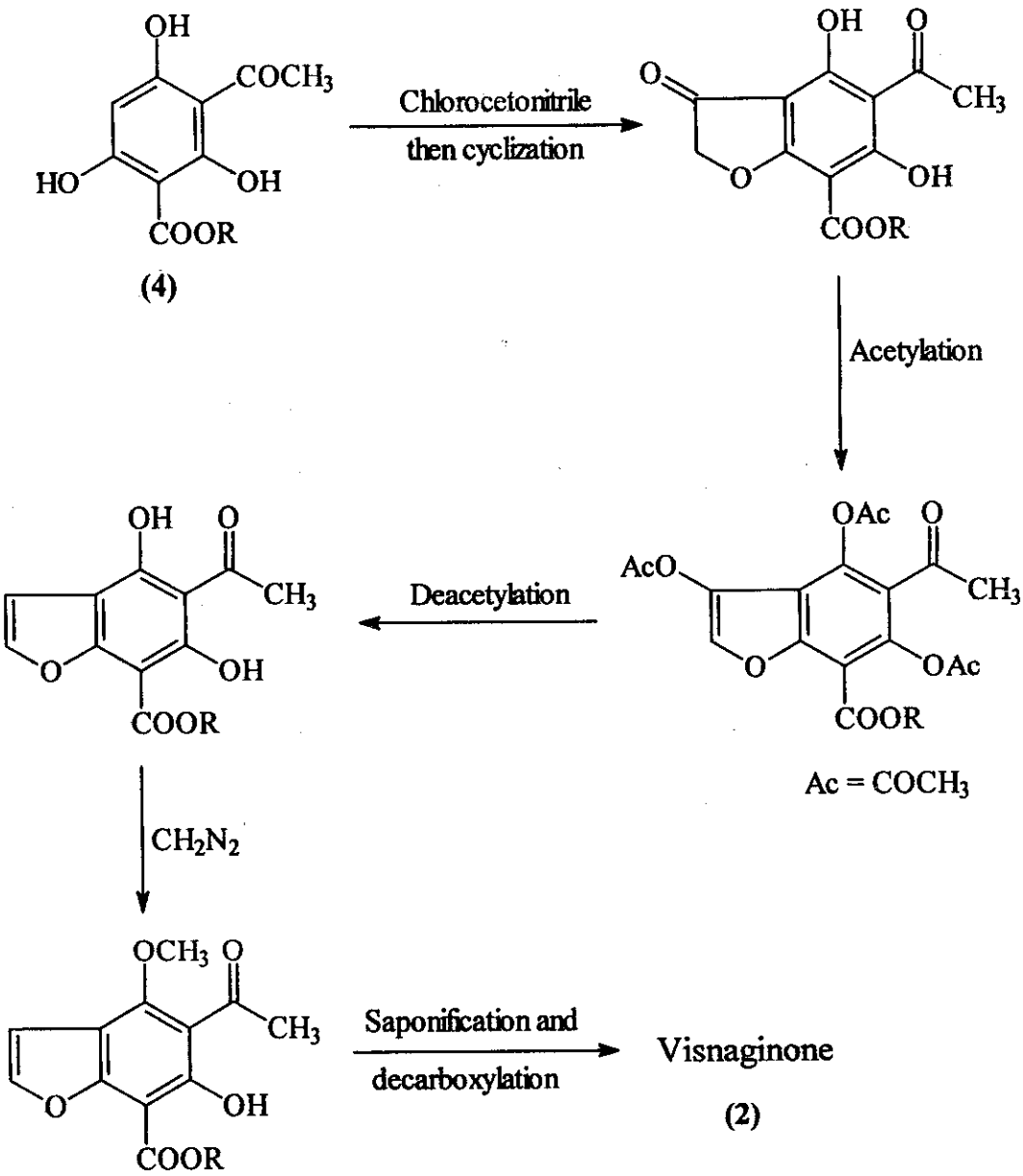
The latter route of synthesis follows more closely the process of biosynthesis in plants which could be expected to lead to a more efficient and a simpler route.

Interconversion of one furochromone into another was achieved as a convenient method for synthesis, hence, khellin has been prepared from visnagin and khellol could be easily converted into visnagin proving the idea that different chromones isolated from the same plant are in fact so closely related to each other that they can be more or less interconverted.

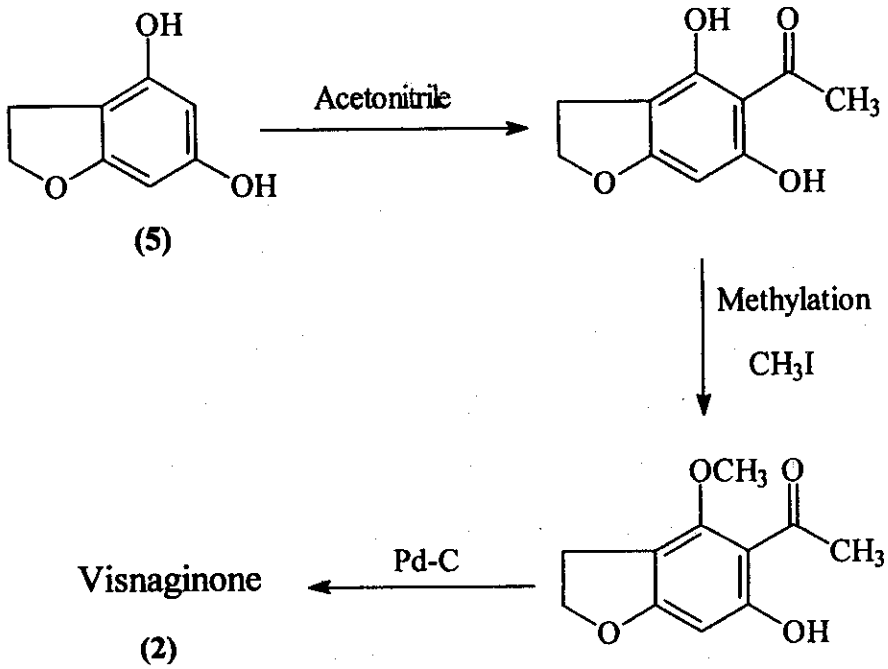
Visnagin has been partially synthesized from visnaginone **(2)** by cyclization of the diketone **(3)** resulting from the interaction of visnaginone (obtained from natural sources) with ethyl acetate in presence of sodium[2].



Gruber and Horvat[3] synthesized visnaginone beginning with phloroacetophenone carboxylic ester **(4)**, the key reaction was a Hoesch condensation.

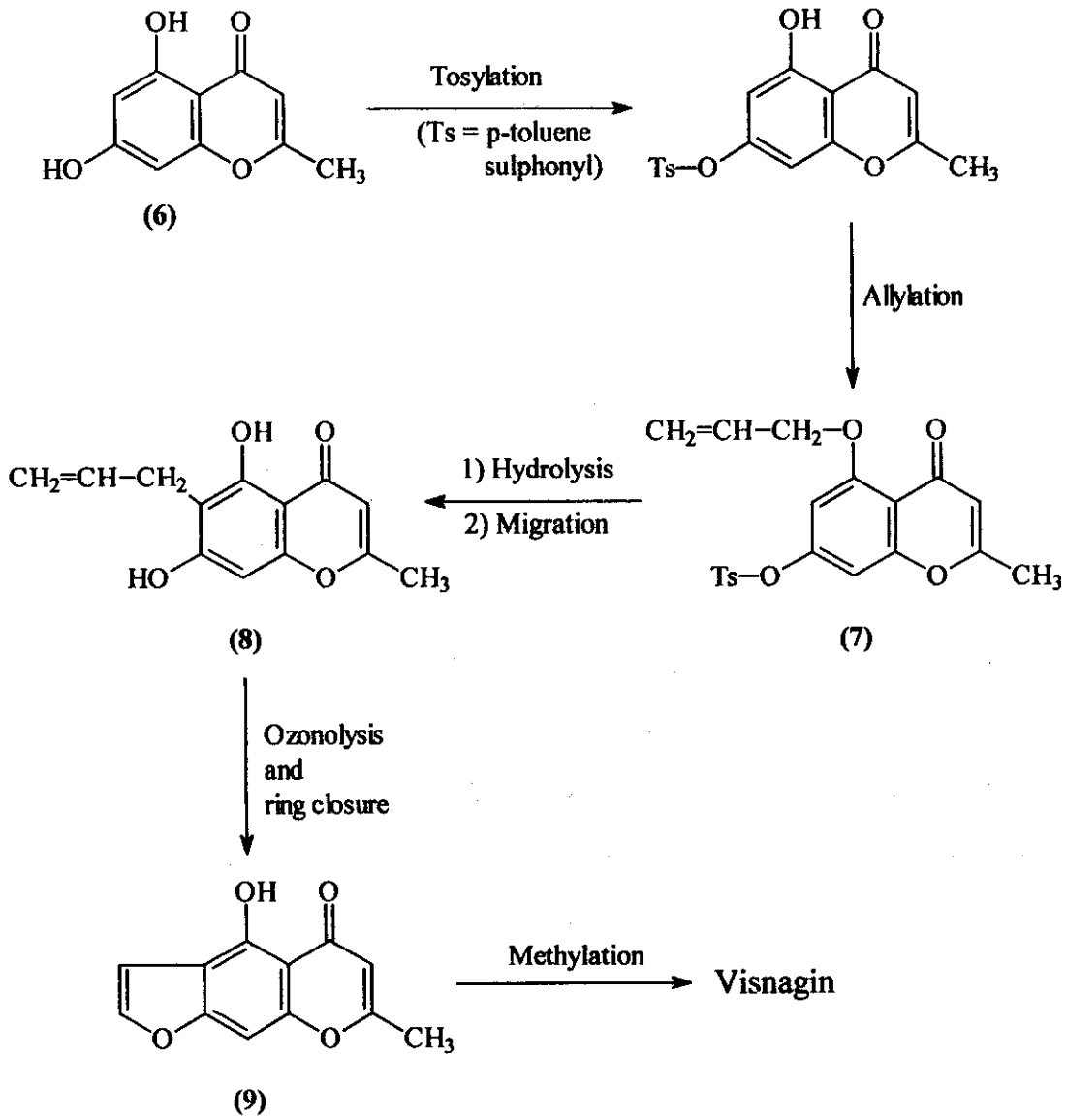


Total synthesis of visnaginone has also been achieved by Geissman and Henreiner[4] who started with 4,6-dihydroxycoumaran.



Thus, starting with 5,7-dihydroxy-2-methyl chromone **(6)**, visnagin could be synthesized[5]. The process involve the introduction of an allyl group in the 6-position by the Claisen migration of the 5-allyl ether **(7)** of 5,7-dihydroxy-2-methyl chromone, the 7-hydroxy group has to be protected by means of a group capable of easily elimination at a later stage, and in this a tosyl group was found to be superior.

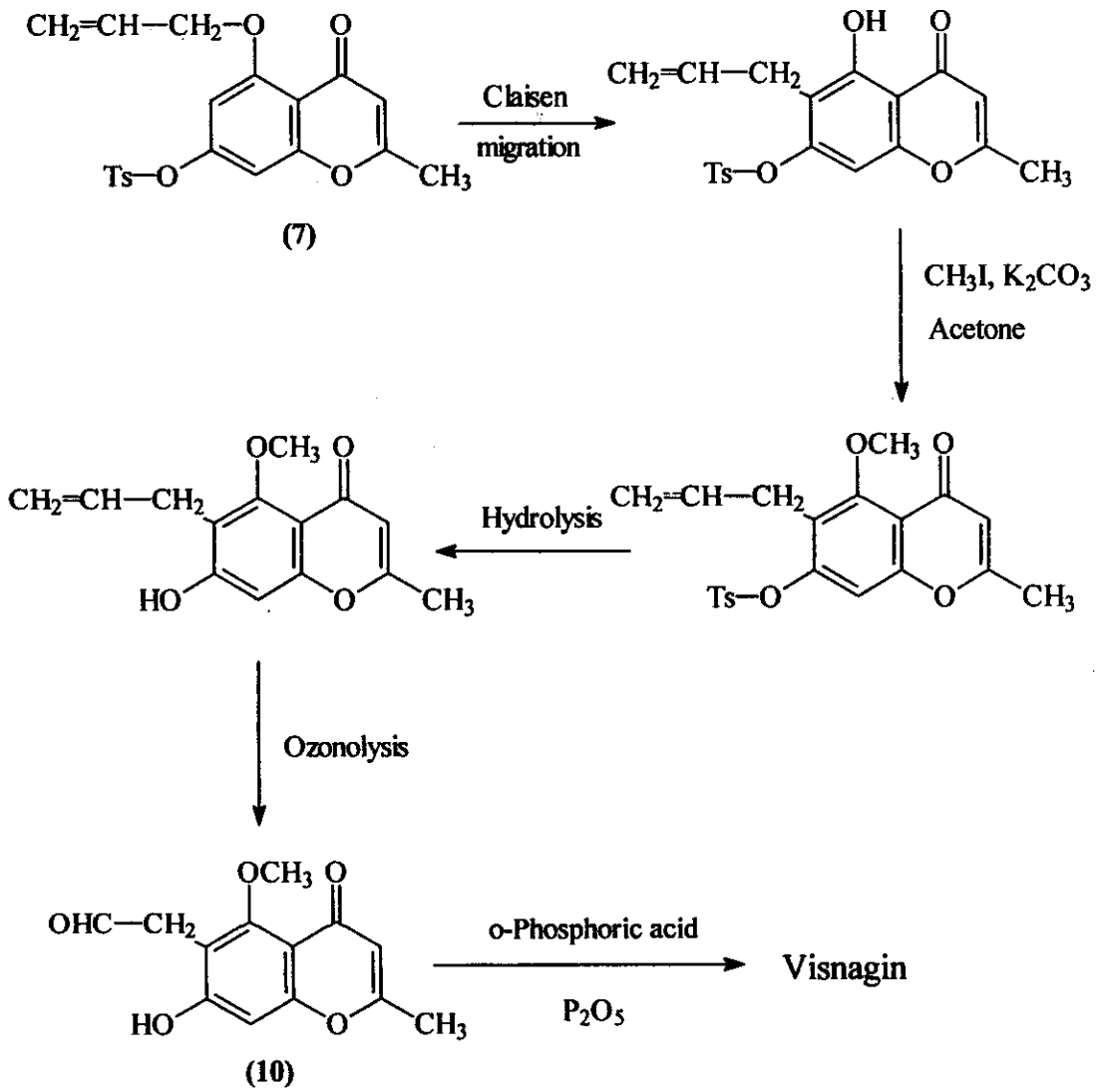
The C-allyl compound **8** when was subjected to ozonolysis and ring closure, gave norvisnagin **9**[6] in a poor yield.



Special mention should be made here, that the product of the furan ring closure in a single entity, in which cyclization has proceeded through the 7-hydroxyl group. The alternative ring closure involving the 5-hydroxyl group did not seem to proceed to any detectable extent indicating that the 5-hydroxyl is unreactive, due to its chelation.

In an alternative procedure, the tosyl group is removed just before ozonolysis, for this purpose the previous methylation of the 5-position is advantageous.

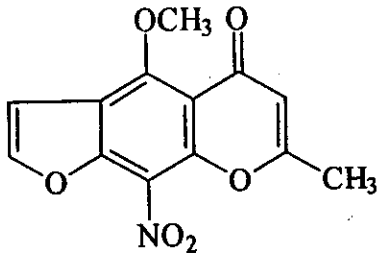
Subsequent stages of ozonolysis and ring closure of the 6-acetaldehydochromone afforded visnagin in good yield.



2.1.2. Electrophilic Substitution Reaction at Position-9

2.1.2.1. Nitration

Nitration of 4-norvisnagin with nitric acid followed by methylation affords 9-nitrovisnagin **11a**[7].

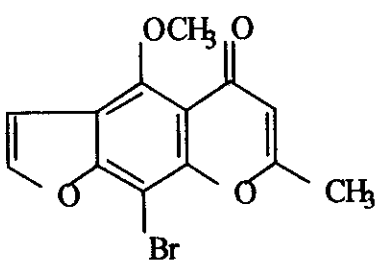


(11a)

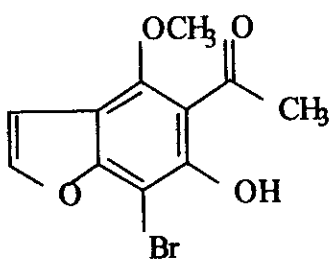
2.1.2.2. Halogenation

Visnagin reacts with bromine to give 9-bromovisnagin **11b**[8] whose structure was proved by alkaline degradation to 5-acetyl-7-bromo-6-hydroxy-4-methoxy coumarone **12** and oxidation to 8-bromo-6-formyl-7-hydroxy-5-methoxy-2-methyl chromone **13**[9].

On the other hand, visnagin forms deeply coloured crystalline adduct with iodine[84] which is decomposed by sodium thiosulphate solution.



(11b)



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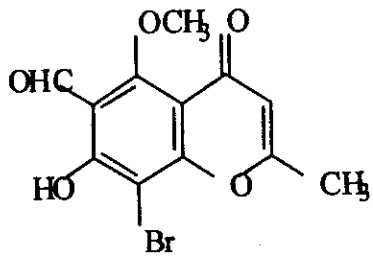
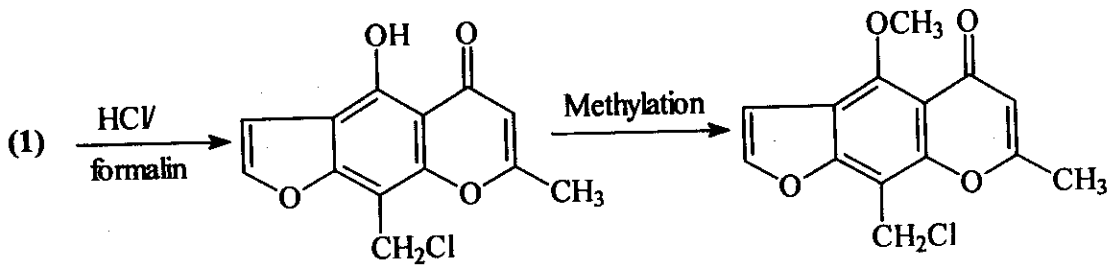


(13)

2.1.2.3. Chloromethylation

When 4-norvisnagin was treated with formalin in the presence of hydrogen chloride, it gives 9-chloromethyl derivative of 4-norvisnagin **14** which upon methylation affords the chloromethyl visnagin derivative **15**[10].

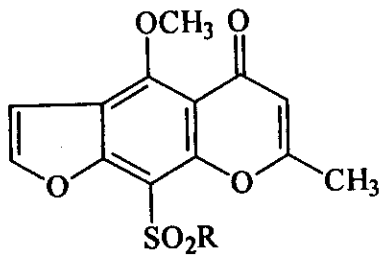


(14) **(15)**

2.1.2.4. Chlorosulphonated visnagin derivative 16 and its reactions

2.1.2.4.1. With amines:

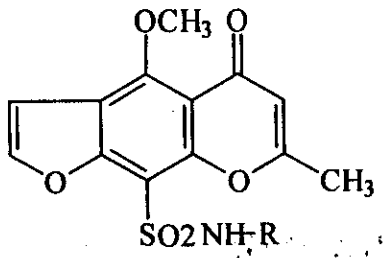
Treatment of visnagin with chlorosulphonic acid yields visnagin-9-sulphonyl chloride derivative **16**[11]. Visnagin-9-sulphonyl chloride reacts with primary aliphatic, aromatic, heterocyclic and secondary amines forming the corresponding sulphonamides **17**[12-16].



(16)

16, R = Cl
17a, R = NH_2
b, R = NH-NH_2
c, R = NH-CH_3
d, R = NHCH$(CH_3)_2$-iso
e, R = NHC_4H_9-n
f, R = NHC_6H_{11}-cyclic
g, R = $NHCH_2C_6H_5$
h, R = NHCH=CH-CH_3

Also, compound **16** reacts with o, m and p-phynylenediamine in equimolecular ratio to form the corresponding sulphonamide derivatives **18a-c**[15], but when it was allowed to react with the same reagents in a molecular ratio of (2:1) it forms bis-visnagin-9,9`-disulphonamide **18d-f**[15].

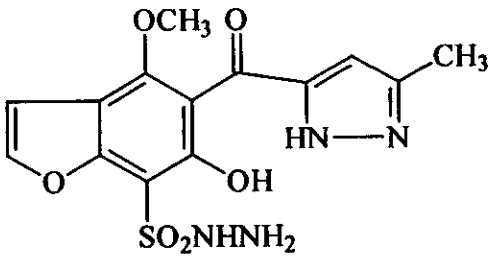


(18)

18a,	R = p-C_6H_4-NH_2	**d,**	R = p-C_6H_4-(NH)SO_2-vis
b,	R = m-C_6H_4-NH_2	**e,**	R = m-C_6H_4-(NH)SO_2-vis
c,	R = o-C_6H_4-NH_2	**f,**	R = o-C_6H_4-(NH)SO_2-vis

2.1.2.4.2. With hydrazine hydrate:

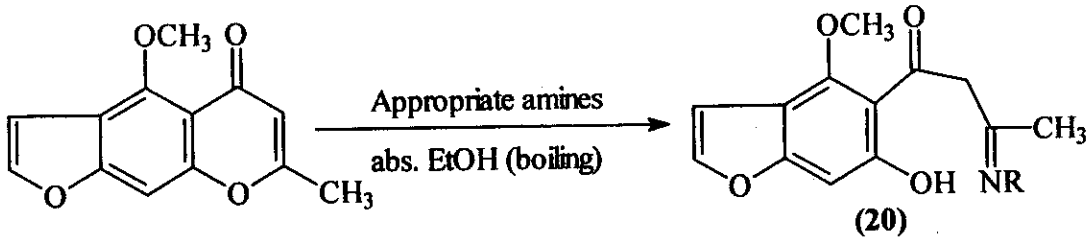
El-Sharief *et al.*[12] reported that visnagin-9-sulphonyl chloride reacted with hydrazine hydrate to give **19**.



(19)

2.1.2.4.3. Action of amines:

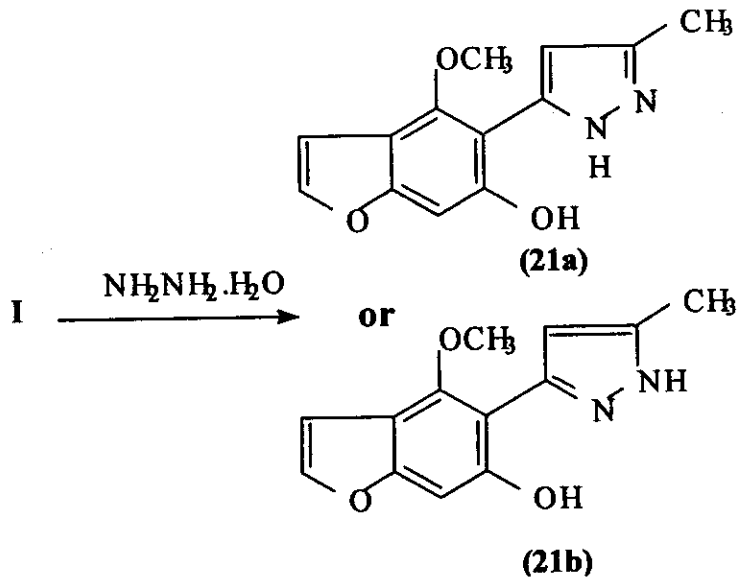
Visnagin reacts with primary aliphatic amines with γ-pyrone ring opening to give the corresponding enamines **20**.



(20)

2.1.2.4.4. Action of hydrazine hydrate and hydroxyl amine hydrochloride:

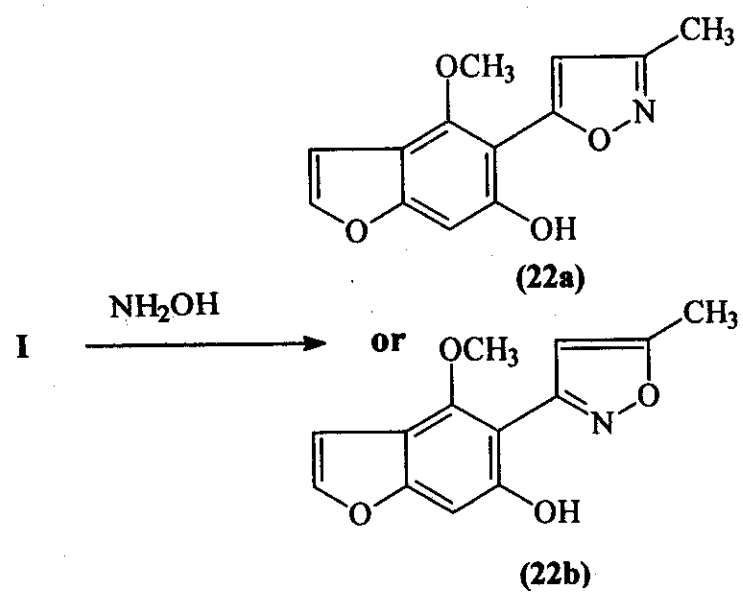
The γ-pyrone ring in visnagin is opened by hydrazine hydrate to give the pyrazole derivatives **(21a,b)**[17].



(21a)

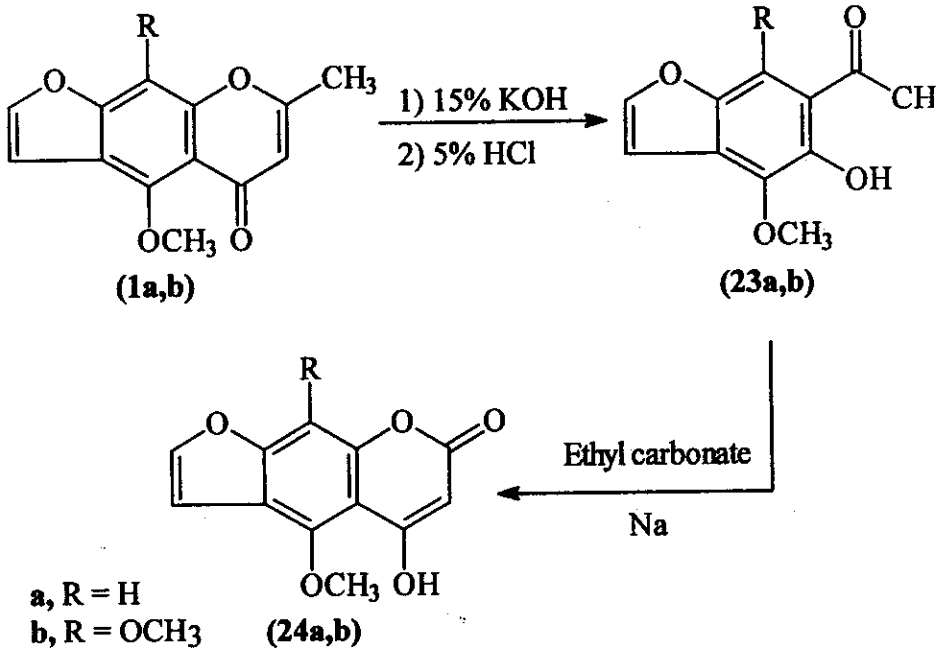
(21b)

In contrast to its stability to hydroxyl amine hydrochloride in acetic acid at room temperature, visnagin reacts in boiling pyridine to give isoxazole derivatives **(22a-b)**[17].



2.1.2.5 Alkaline hydrolysis of VISNAGIN :

The 5-hydroxyfurocoumarins derivatives **24** were prepared by alkaline hydrolysis of visnagin **1a** and khellin **1b** giving visnaginone **23a** and khellinone **23b**. The condensation of the latter compounds with ethyl carbonate[27] in the presence of sodium metal give 5-hydroxy bergapten **24a** and 5-hydroxy isopimpinellin **24b**.



2.1.2.6 Chemistry of hydroxyfurocoumarins

The coumarins could be classified to the ring oxygenation number and patterns. The carbon substituents are considered in order of increasing numbers of carbon atom and increasing oxidation level within each group.

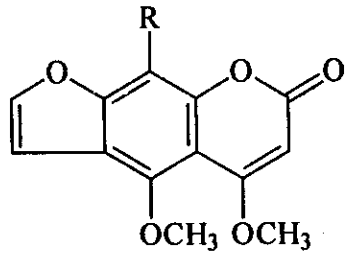
Special mention must be made that the coumarins in the family *Umbelliferae* (*Apiaceae*) which have been previously reviewed[18,19]. Also, a list of some prepared furocoumarins has been reported by Gevrenova[19] and it biogensis and biological activities were considered[20]. Such biological activity is linked to the furocomarinic nucleus and the existence of double bond in the furan and α-pyrone rings. Moreover, the linear structure of furocomarinic system is more active than the angular one. The introduction of hydroxyl, methoxy groups in 4 or 9 position and lengthing of the side chain deactivate the compound[21-26].

2.1.2.7 Reaction of 5-Hydroxyfurocoumarins:

2.1.2.7.1 Methylation:

5-Hydroxybergapten and 5-hydroxyisopimpinellin **24** have been methylated using methyl iodide[27] or dimethyl sulphate[28] in the presence of acetone and anhydrous potassium carbonate lead to the formation of 5-methoxy derivative **25**.

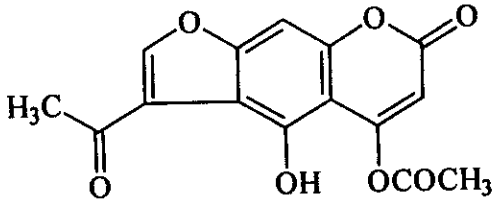
A number of 5-hydroxybergapten ether derivatives have been prepared by alkylation of bergaptol using either alkyl[29] or arayl[30] halides or by using diazoalkanes[31].



(25a,b) **a**, R = H
b, R = OCH_3

2.1.2.7.2 Acetylation:

When 5-hydroxybergapten **24a** was acetylated by 2 moles of acetyl chloride, the first acetylation occurs at C-3 and hydroxyl group attached at C-5. This was followed by demethylation of the methoxy group at C-4 to give **26**[32]. Acetylation of 5-hydroxyisopimpinellin **24b** gives either a diacetyl or triacetyl derivatives depending on the molar ratio of the acetylchloride used. Acetylation of the furan moiety at position-3 occurs in both cases, however when an excess of the reagent was used C-4 and C-5 were also acetylated to give 3-acetyl-4,5-diacetoxy-9-methoxy-psoralene **27**[32]. On the other hand, when two moles of acetylchloride were used, C-5 only was acetylated in addition to C-3 to produce 3-acetyl-4-hydroxy-5-acetoxy-9-methoxy-psoralene **28**.



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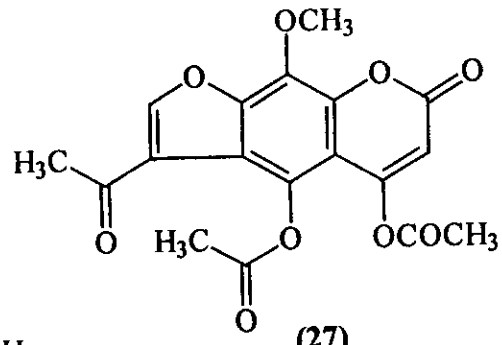

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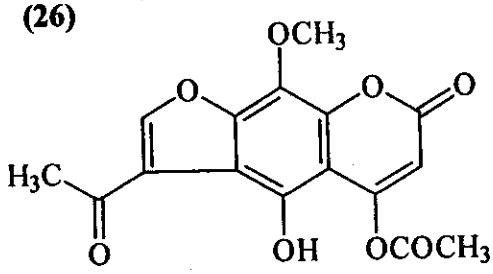
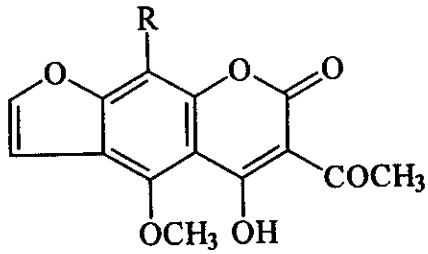


(28)

Also, 3-acetyl derivatives can be prepared by different conditions[33] to give **29**.

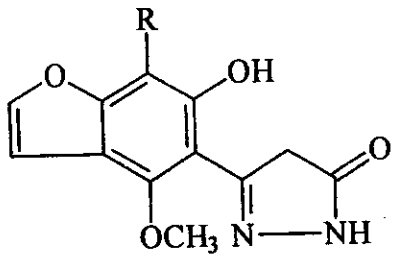


(29)

a, R = H
b, R = OCH_3

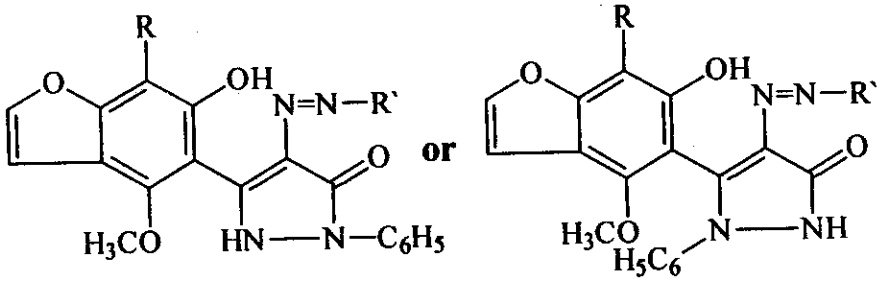
2.1.2.7.3 Action of Hydrazine Hydrate and Phenyl Hydrazine

5-Hydroxybergapten **24a** and 5-hydroxyisopimpinellin **24b** are opened by the action of hydrazine hydrate[34] to give 3-(5`-(4`-methoxy-6`-hydroxybenzofuryl)-5-pyrazolone **30a** and 3-(5`-(4`,7`-dimethoxy-6`-hydroxybenzofuryl)-5-pyrazolone **30b**[34].



30a, R = H
b, R = OCH_3

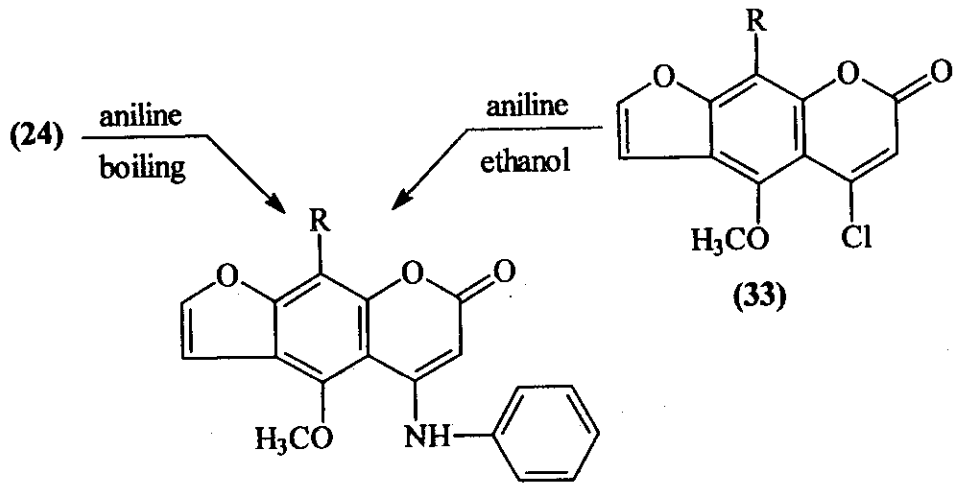
Also, the behaviour of **24** towards the action of phenyl hydrazine[34] lead to opening of the coumarin ring and formation of 1-phenyl-3`-(5`-(4`-methoxy-6`-hydroxybenzofuryl)-4-phenylazo-5-pyrazolone **31a** and 1-phenyl-3`-(5`-(4`,7`-methoxy-6`-hydroxybenzofuryl)-4-phenylazo-5-pyrazolone **31b** or the possible isomers.



31a, R = H
b, R = OCH_3

2.1.2.7.4. Action of Aniline:

5-Hydroxybergapten **24a** and 5-hydroxyisopimpinellin **24b** reacted with boiling aniline to give the corresponding 5-anilino derivatives **32** which was also obtained by the action of aniline on the corresponding 5-chloro derivative **33** in boiling ethanol[35].



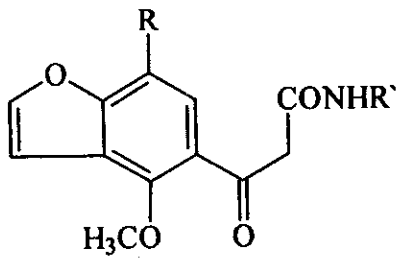
(33)

32a, R = H
b, R = OCH_3

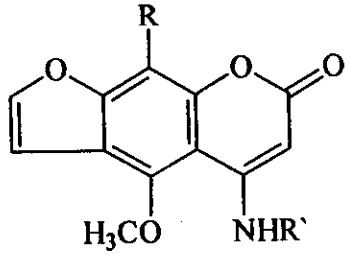
2.1.2.7.5. Action of Amines:

5-Hydroxybergapten **24a** and 5-hydroxyisopimpinellin **24b** were reacted with aliphatic, aromatic or heterocyclic amines in ethanol or without a solvent at 100°C, opening of the pyrone ring occurs leading to the formation of the corresponding α-(4-methoxy)- or α-(4,7-dimethoxy)-6-hydroxy benzofuran-5-carbonyl)acetamide **34**[36].

The reaction of **24a,b** with propylamine or benzylamine in ethanol under reflux gave the corresponding 5-amino derivatives**35**[37].

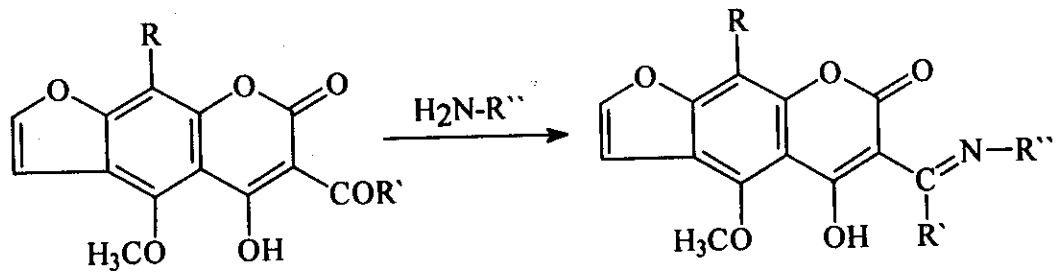


34a, R = H
b, R = OCH_3



35a, R = H; R` = C_3H_7
b, R = OCH_3; R` = C_3H_7
c, R = OCH_3; R` = $CH_2C_6H_5$

The action of aniline or ethylamine on 5-hydroxy-6-acyl bergapten and isopimpinellin **36** results in the formation of the amino derivatives **37**[35].

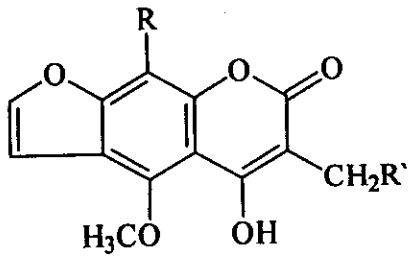


(36) **(37)**

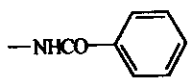
a, R = H
b, R = OCH_3

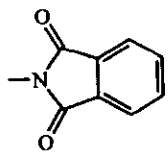
2.1.2.7.6. Acylaminomethylation:

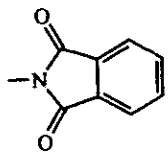
5-Hydroxybergapten **24a** and 5-hydroxyisopimpinellin **24b** were condensed with different N-hydroxy methyl carboxamides to give the corresponding 6-acylamino methyl derivatives **38**[38].



(38)

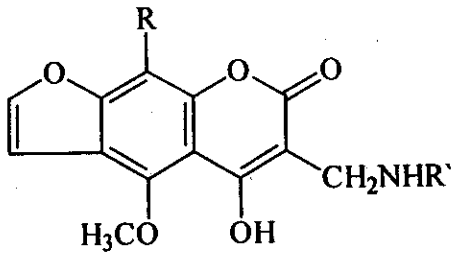
a, R = H R` = 

b, R = OCH_3 R` = 

c, R = OCH_3 R` = 

2.1.2.7.7. Mannich Reaction:

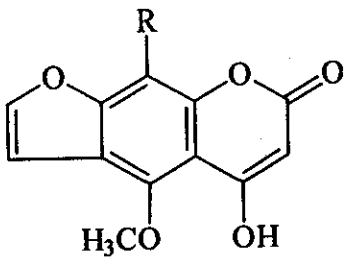
The reaction of **(24.a-b)** with primary and secondary amines (e.g. n-propylamine, 2-aminopyrazine, 2-benzimidazolamine, 2-aminophenol, morpholine and piperdine) in the presence of formaldehyde yields the corresponding 6-substituted amino methyl derivatives **39**[39]. All compounds were evaluated against *Bacillus subtilis*, *Sarcina lutea*, *Staphylococcus aureus*, *E. coli* and *Micrococcus philis*, using the disc agar diffusion method[40]. Sveral compounds were found to possess a broad spectrum activity.



(39)

2.1.2.7.8. Reaction with β-Keto Esters:

Reaction of 5-hydroxybergapten **24a** and 5-hydroxyisopimpinellin **24b** with β-keto esters in the presence of ammonium acetate gave the corresponding condensed compounds **40**[41,42]. The reaction of 5-hydroxy fuorocoumarin derivatives **(24.a-b)** with ethylcyclopentanone-2-carboxylate in the presence of ammonium acetate led to the corresponding furobenzodipyran derivatives **41**[41].

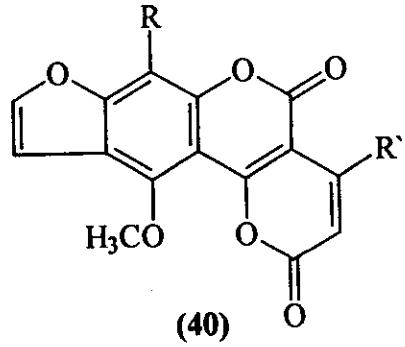


a, R = H
b, R = OCH_3

NH_4OAc

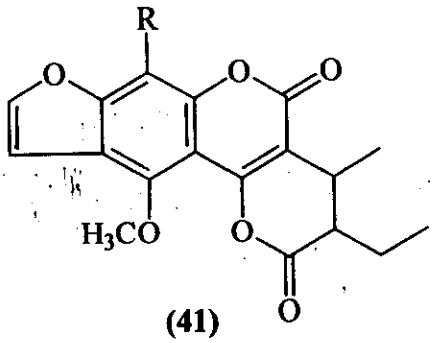
$R`CH_2COOC_2H_5$

a, R` = $COCH_3$
b, R = COC_6H_5
c, R` = $COOC_2H_5$



(40)

a, R = H; R` = CH_3
b, R = H; R` = C_6H_5
c, R = H; R` = OH
d, R = OCH_3; R` = CH_3
e, R = OCH_3; R` = C_6H_5
f, R = OCH_3; R` = OH

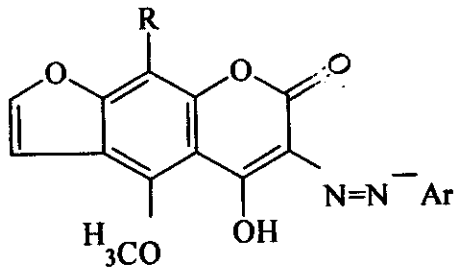


(41)

a, R = H
b, R = OCH_3

2.1.2.7.9. Action of Aryl Diazonium Chlorides:

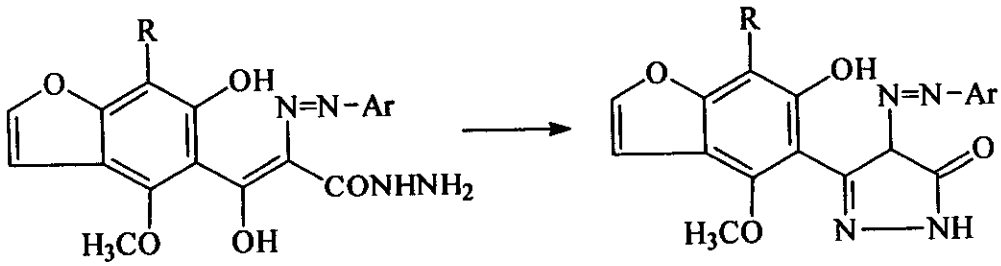
The reaction **(24.a-b)** with aryl diazonium chlorides in the presence of alcoholic sodium carbonate give the corresponding 6-arylazo derivatives **42**[43].



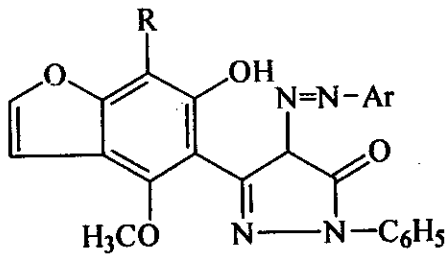
(42)

a, R = H
b, R = OCH_3

When the 6-arylazo derivatives **42** were reacted with hydrazine hydrate[43] in the presence of glacial acetic acid, the pyrone ring was opened with the formation of the intermediate o-hydroxy acid hydrazide **43** followed by cyclization involving the substituent in the 5-position to yield 4-arylazo-3-[5`-(4`methoxy-6`-hydroxy)benzofuryl]-5-pyrazolone **45**[43].



(43) a, R = H; b, R = OCH_3 **(44)**



(45)

a, R = H
b, R = OCH_3

B.I.I. The Triterpenoids:

The triterpenoids are a class of naturally occurring compounds containing, as a basic criterion thirty carbon atoms arranged in six isopentane units. The vast majority of the triterpenoids occur in the plant knigdom, often in association with phytosterols[44], where they occur in resins and saps either in the free state, as esters, or glycosidically linked with a sugar as saponins. They have been isolated from almost all order of the natural vegetational hierachy. Indeed, a few triterpenoids have been

also isolated from petroleum[45] and from peat[46-48]. very few triterpenoids have been isolated from animal sources.

Although the isolation of many well-known triterpenoids dates back to the last century, the first correct structures were not assigned until the time of the Second World War. Thus, the parent substances β-amyrin, α-amyrin and lupeol were correctly formulated respectively in 1937[49], 1949[50] and 1951[51].

Triterpenoids together with steroids have played an important part in laying the foundations of "New Organic Chemistry". In particular they provided excellent experimental basis for the principles of conformational Analysis[52-53]. The biogenetic Isoprene rule for terpenoids emerged via the pioneering investigations of zurich school of Ruzicka, Arigoni and Simonsen[54-56]. This postulates that each class of terpenoids is formed from an cyclic precursor which is cyclized and further elaborated according to a limited number of well-defined stereoelectronic principles. The conceptual edifice of the biogenetic Isoprene Rule is matched and complemented by the biochemical investigations of Bloch, Lynen, cornforth, pijak who have elucidated in extraordinary detail the precise mechanism for steroid and terpenoid biogensis[57-59].

The interest in the chemistry of triterpenoids has in recent years assumed vast dimensions as judged by the avalanche of publications emerging from numerous schools all over the world. The volume of the literature, concerning new isolations, novel, types and constitutional elaborations, is growing at such as a rate that it may be a fair statement that the bulk of achievements made in the past 20 years excit all that which has been made before. Comprehensive reviews on the occurence,

structures, reactions and interrelationship of the triterpenoids are available[56, 60-64].

B.I.1.1 The pentacyclic triterpenoids:-

Until a few years ago it was customary to classify the pentacyclic triterpenoids into three groups:-

1) Oleanane, β-amyrin or oleanolic acid group.
2) Ursane, α-amyrin or ursolic acid group.
3) Lupane, lupeol or betulic acid group.

These groups cover most of pentacyclic triterpenoids together with scattered cases of natural products with modified carbocyclic skeletal constitutions isomeric with the typical skeleta which include:-

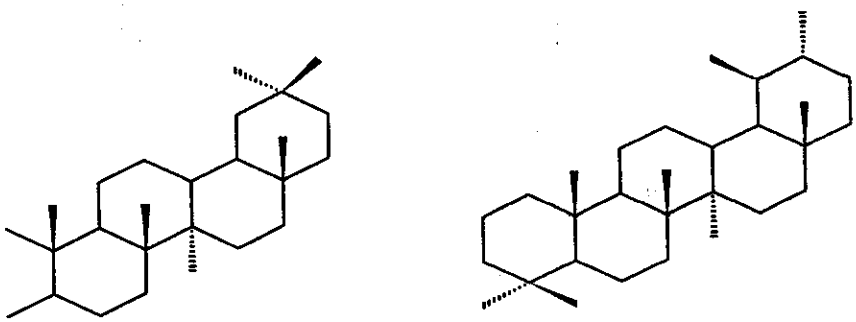
1) Hopane group	(e. g. Hopane)
2) Dammarane group	(e. g. Dammarne)
3) Lanostane group	(e. g. Lanosterol)
4) Holostane group	(e. g. Halostanol)
5) Euphane group	(e. g. Euphane)
6) Tarxastane group	(e. g. Traxasterol)
7) Allobetulin group	(e. g. Allobetulin)
8) Friedelane group	(e. g. Friedelene and epifriedelol)
9) Glutinane group	(e. g. Glutinane)

(Chart I)

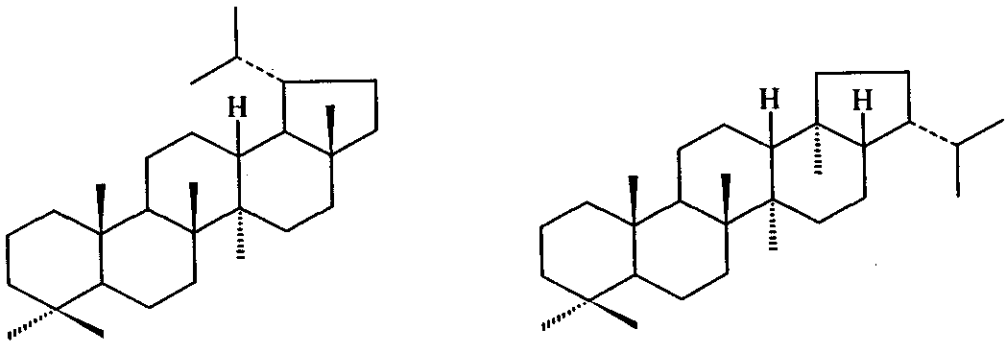
β- Amyrin is the parent compound of the oleanane group while α-amyrin and ursolic acid are the most representative examples of the ursane group. Finally, lupane is the parent compound of the lupane group.

It is true that the basic skeleta oleanane, ursane and lupane represent the vast majority of the so-far identified and established natural

pentacyclic triterpenoids. The advent in the past few years of new types of natural triterpenoids possessing modified constitutions departing radically from the basic skeleta of the above three types makes it, however, unnecessary to regard such types as mere "exceptions" any longer.



Ursane



Hopane

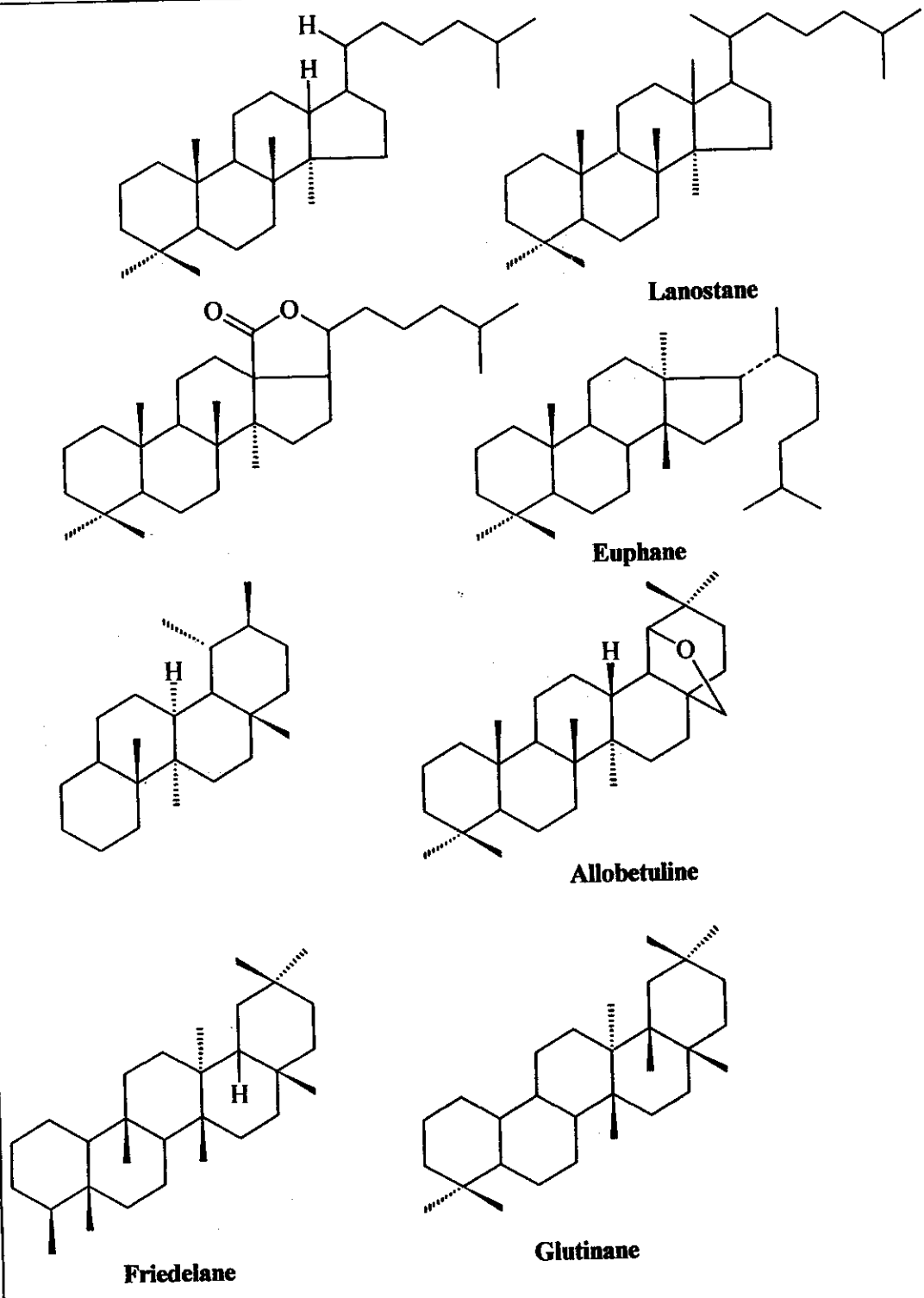
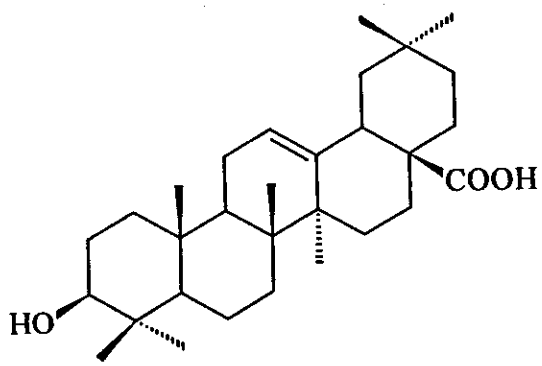

H
H
Lanostane
O
O
Euphane
H
H
O
Allobetuline
H
Friedelane
Glutinane

Chart I

Numerous proposals[66-70] have previously been advanced for the modified nomenclature of fundamental triterpenoid types both of natural and synthetic origin and have received varied degrees of acceptance. The most recent proposal, to the best knowledge of the author, is that made by Qurisson and Allard[71] in which they proposed four fundamental types, oleanane, ursane, lupane and gammacerane. Moreover, the designations D-friedo-, D: C:-friedo, D: B:-friedo and D: A:-friedo-were proposed to denote the modified structures, arising from transposed skeleta of the previous four fundamental types, of the unknown natural modes but which, however, biogentically possible.

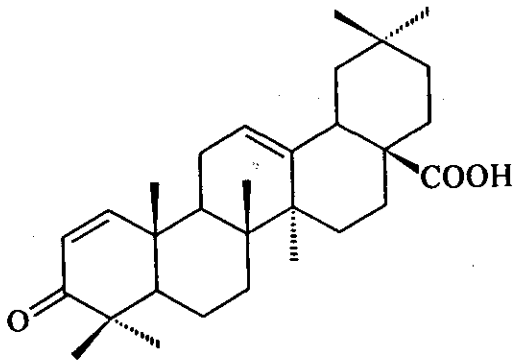
Oleanolic acid (**46**) is a pentacyclic triterpene containg C-28 carboxylic acid moiety, β-hydroxyl and Δ^{12} ene functionalities.



(46)

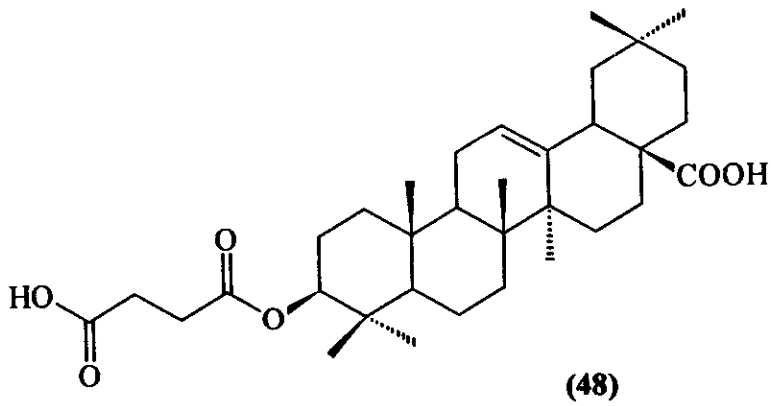
It present separate in olive trees, and with ursolic acid in Eucalptus trees, also it present as aglucone in partiner of many glucosides in most plants[72].

Honda et al[72] prepared the 3-oxo-olean-12-en-28-oic acid (4) that showed significant inhibitory activity against interferon-γ-induced nitric oxid production in mouse macr when assayed at the 1 u M level.



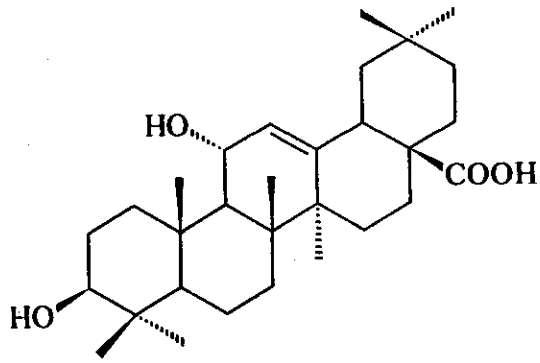
(47)

3-[(2-Carboxy ethyl) carbonyloxy] olean-12-en-28-oic acid (**48**) was synthesized by reacting oleanolic acid with succinic anhydrid in pyridine to improve the solubility and bioavilability of oleanolic acid, it has been used as anti inflammatory and anti lepatitis drug in east Asia[73].



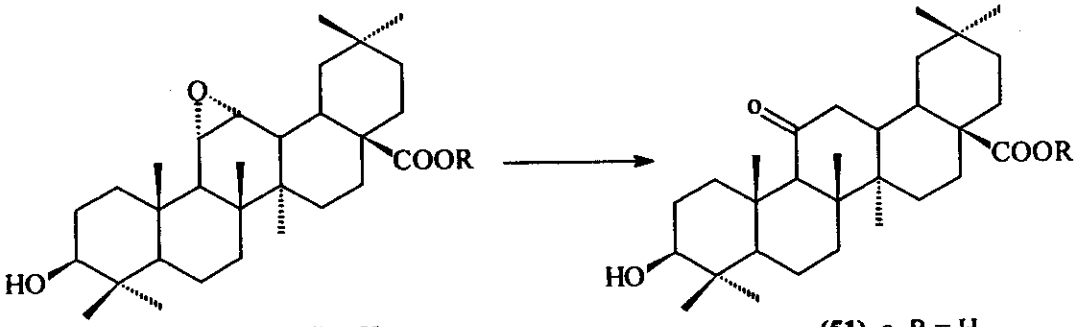
(48)

A novel allylic hydroxylation by mcpBA of oleanolic acid is catalyzed by Fe(PFPP)Cl give the 11α-hydroxy oleanolic acid (**49**)[74].



(49)

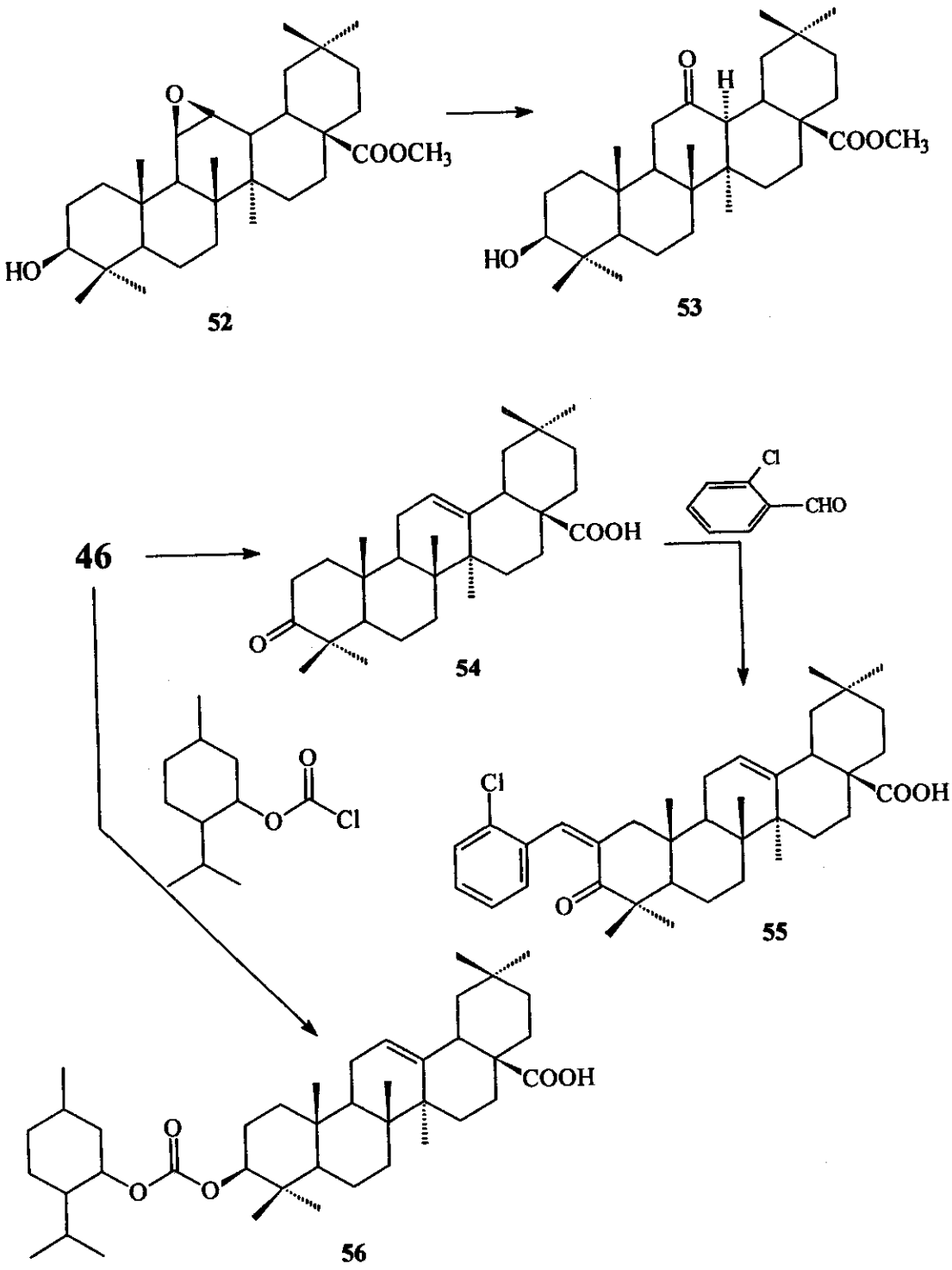
Hydrogen peroxide-selenium dioxide in-t butanol has been found to be a good reagent for the prepration of 11^{α}, 12^{α}-oxidotriterpenoids of oleanolic acid and its methyl esters[75], they under acid conditions gives the 11-oxo function.



(50), a, R = H
b, R = CH_3

(51), a, R = H
b, R = CH_3

Reaction of oleanolic acid bromolactone with methanolic potassium affords methyl-3β-hydroxy-12β,13β-epoxyolean-28-oate, which rearranged, under mild conditions, to the novel 12-oxo derivatives possessing the 13^{α} configuration[76].

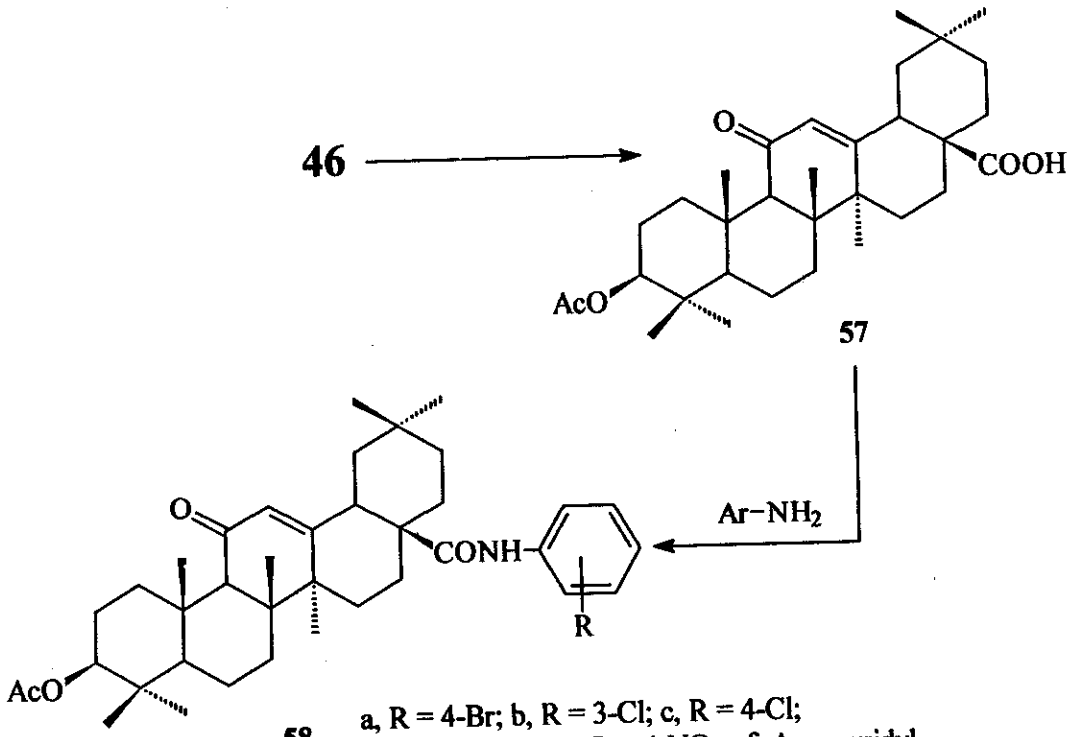


The synthesis of oleanolic acid-2-chlorobenzylidene derivative (**55**) consists of oxidizing the 3β-hydroxy group into the corresponding 3-one (**54**) by rillion's reagent followed by aldol condensation with 2-

chloro benzaldhyde in aqueous alcoholic 30% KOH Compound **(55)** show both anti inflammatory and anti ulcerogenic activities.

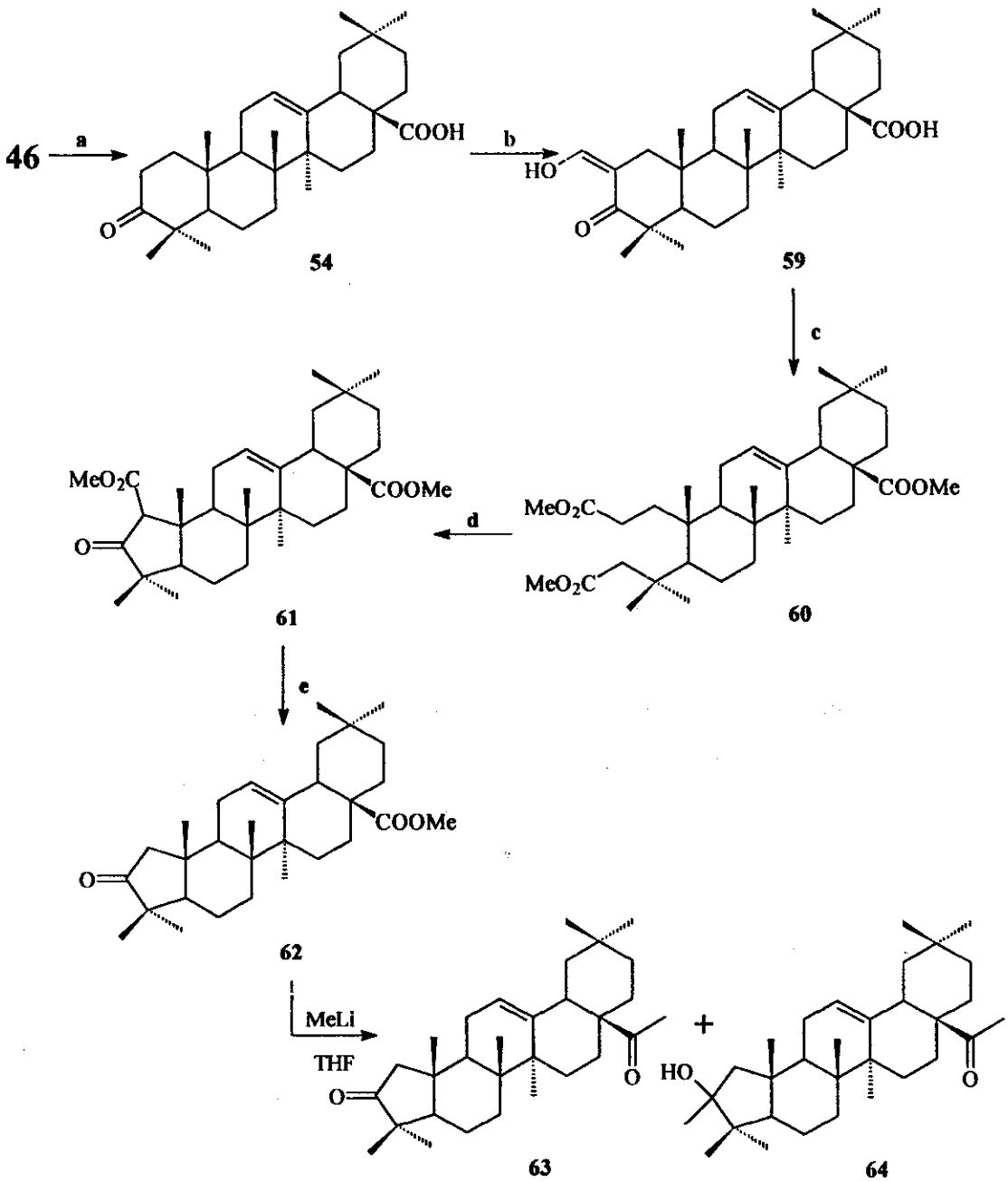
Menthol show anti ulcerogenic activities, in atrial to combine add its activity to oleanolic acid, they combined in carboxy bridge (compound **56**) via treating oleanolic acid with 3-chlorocarbonate esters of methanol in refluxing dioxane-triethylamine, compounds **56** exhibit good anti inflammatory and anti ulcerogenic activities.

In a chemical array to increase the anti inflammatory activities of oleanolic acid, by the 3-acetyl oleanolic acid was condensed with different aniline derivatives via mixed anhydride techniques to obtain the corresponding anilineds that have marked anti inflammatory activities**(58)**.



58 a, R = 4-Br; b, R = 3-Cl; c, R = 4-Cl;
d, R = 2-OCH_3; e, R = 4-NO_2; f, Ar = pyridyl

There have been established procedures for labeling steroids, and in most of them isotopic carbon was introduced into the 4-position. However, we failed to label the 4-position of **46** by the known method, and we next explored another strategy for introducing isotopic carbon on 2-position utilizing ^{13}C-MeLi as an isotope source,[6,7] and we found a successful one. Our procedure was shown in Scheme 1 and Scheme 2 using non labeled MeLi as a model study. We prepared cyclopentanone **62** starting from (**46**) by a known process (Scheme 1). Compound **46** was oxidized to ketone **54** by Jones reagent, and **54** was condensed with ethyl formate to give 2-hydroxymethylene-oleanolic acid **59**. The A ring of **59** was cleaved by alkaline hydrogen peroxide to give a tricarboxylic acid, which was esterified by diazomethane to yield trimethyl ester **59**. Dieckmann condensation of **60** (t-BuOK/benzene) gave 5-membered keto ester **61**. Saponification of the methoxycarbonyl group on the 1-position and subsequent decarboxylation of the transient carboxylic acid under a thermal condition gave cyclopentanone **62**. Methyl ester on the 28-position remained intact during the saponification because of exterme steric hindrance around this position. Having key precursor **62** for labeling, we tried to add the labeled one-carbon unit onto the 2-keto group by treating several methylmetal species under various conditions. However, starting ketone **62** was recovered unchanged in every attempt. Under forcing conditions such as treating **62** with a large excess of MeLi (10 eq.), 28-methyl ketone **63** was obtained as main product along with small amount of methyl adduct **64** derived from **64**. A facile enolate formation seemed to be the cause of sluggish sddition of methyllithium to the cyclopentanone moiety of **62**, and this was supported by an observation that more basic and bulkier butyllithium did not add to **62**.

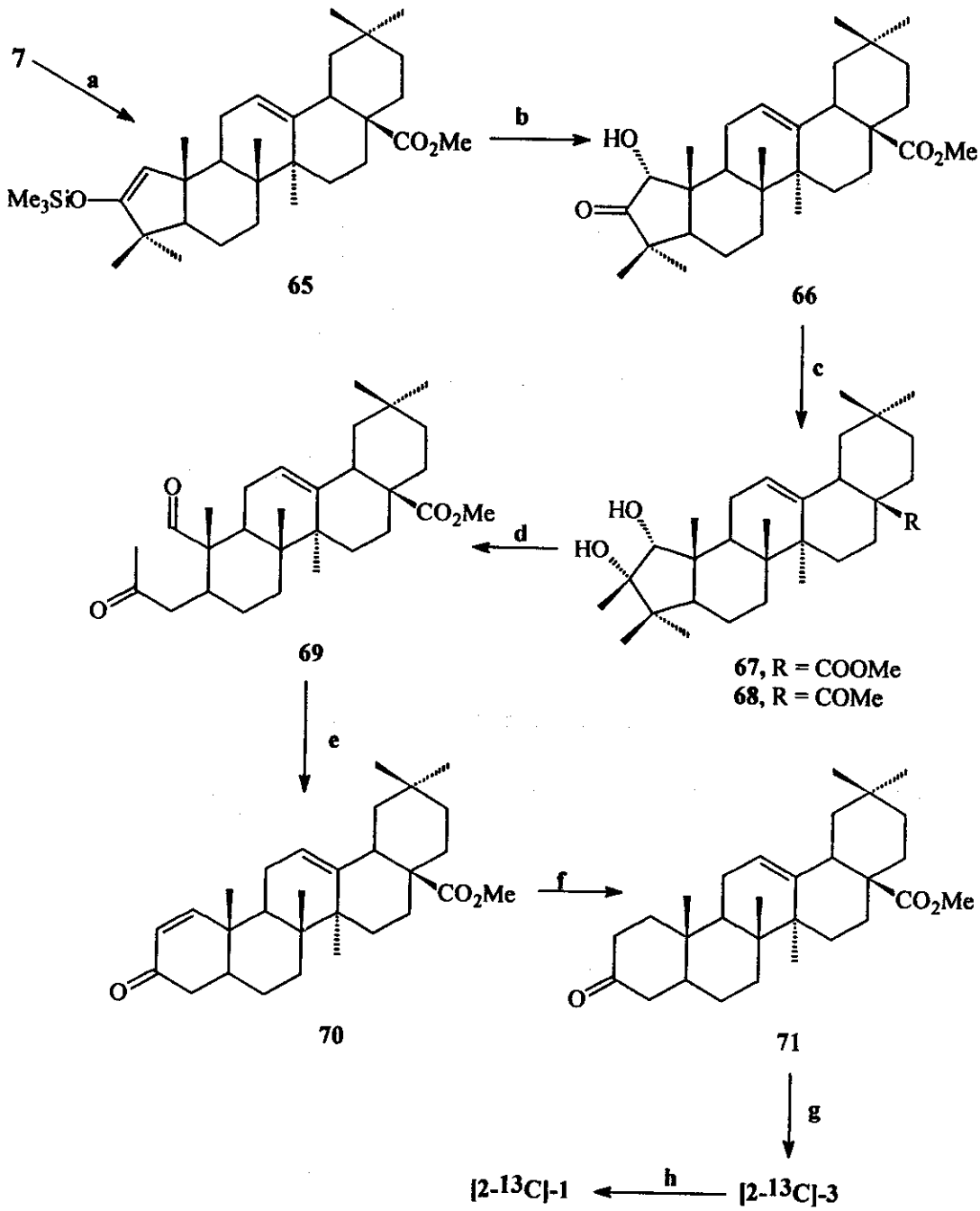


i) Jones reagent, CH_2Cl_2-acetone; b) HCOOEt, 28% NaOEt, benzene;
c) 1) 30% H_2O_2, 28% NaOEt, 2) CH_2N_2, MeOH 58% from 1;
d) t-BuOK, benzene, 78%; e) 50% aq. KOH, dioxane, 90%.

In order to circumvent the sluggish addition of methyllithium, we then took advantage of the facile enolization of ketone **62** and converted the enolate to a derivative which would undergo addition of

methyllithium (Scheme 2). The enolate generated by deprotonating(**62**) by BuLi was treated with Me_3SiCl to give silyl enol ether **65**, which was treated with m-CPBA in aqueous $KHCO_3$ buffer[12,13] to give hydroxy ketone **66**. In contrast to **62**, hydroxy ketone **66** underwent a preferential MeLi addition to 2-keto group to give syndiol 12 with a small amount of methyl ketone **68** (6.5:1). Addition of MeLi to the cyclopentanone skeleton from the β-side can be explained by the chelating effect of the lithium alkoxide to the 2-ketone accelerating the addition of methyllithium from the unhidered β-side. Structures of **66** and **67** were determined by X-ray crystallography. Diol **67** was cleaved oxidatively by treatment with lead tetraacetate to give ketoaldehyde **69**, which was cyclized under a condition of aldol condensation and yielded 6-membered unsaturated ketone **70** regeneration the 3-ketooleanolic acid skeleton with 1,2-double bond. Final sequence of reactions to oleanolic acid **1** was a conventional one; the hydrogenation of 1,2-double bond, the methyl ester deprotection by LiI and the reduction of the 3-keto group by $NaBH_4$.

The whole sequence of the conversion was efficient in terms of total yield (5.9%) and labeling. We followed the whole procedure using ^{13}C-MeLi (20% enrichment).[14] Final oleanolic acid **1** prepared was shown to contain 20% ^{13}C on the 2-position by LSIMS and ^{13}C-NMR.



i) BuLi, TMSCl, THF; b) m-CPBA, $KHCO_3$, hexane, 57% from 7;
ii) MeLi, THF; d) $Pb(OAc)_4$, $CHCl_3$-AcOH, 59% from 11;
e) 50% aq. KOH, dioxane, 78%; f) H_2, 10% Pd-C, 99%; g) LiI, 2,6-lutidine, 80%;
h) $NaBH_4$, THF-MeOH, 70%.