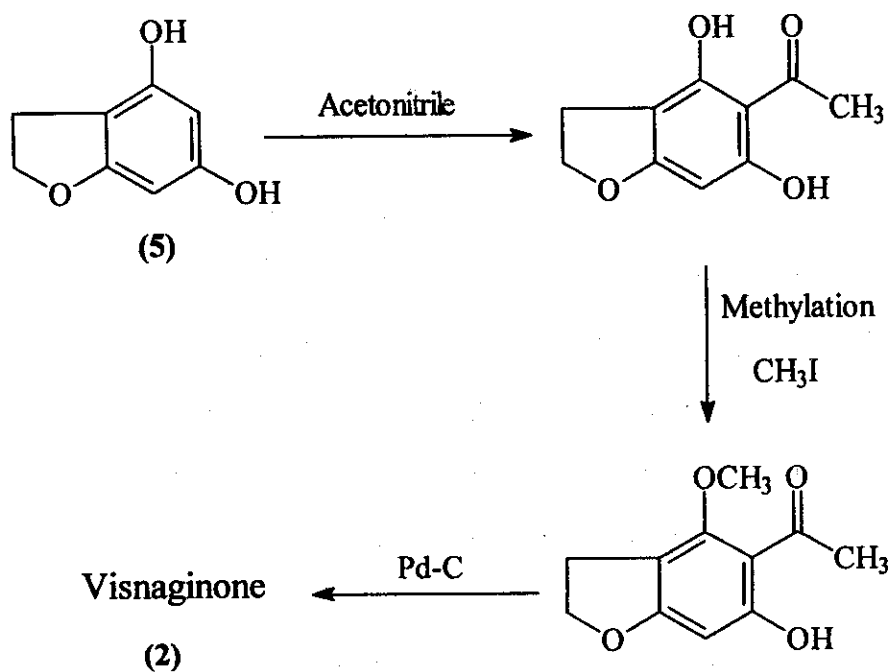
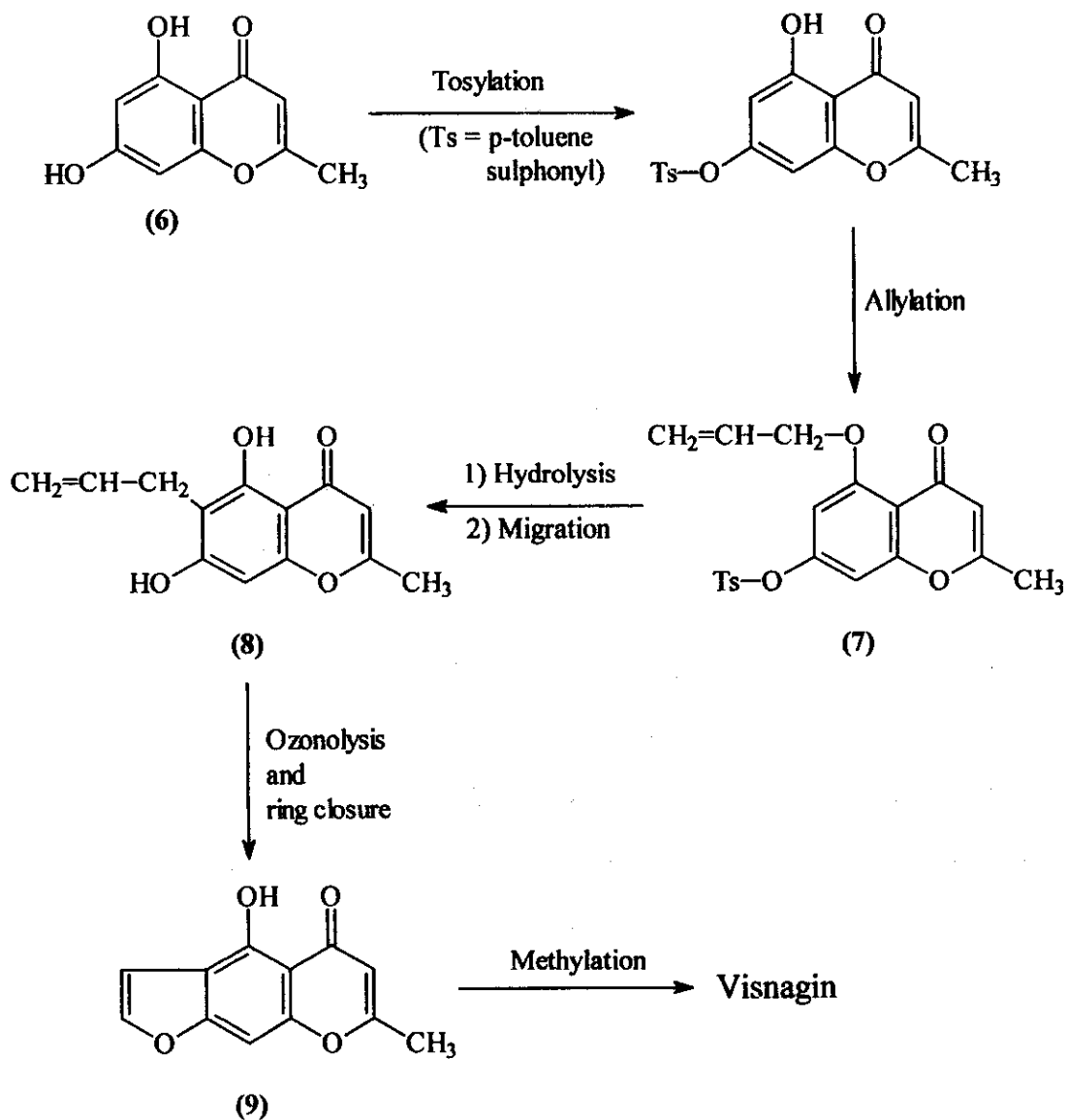




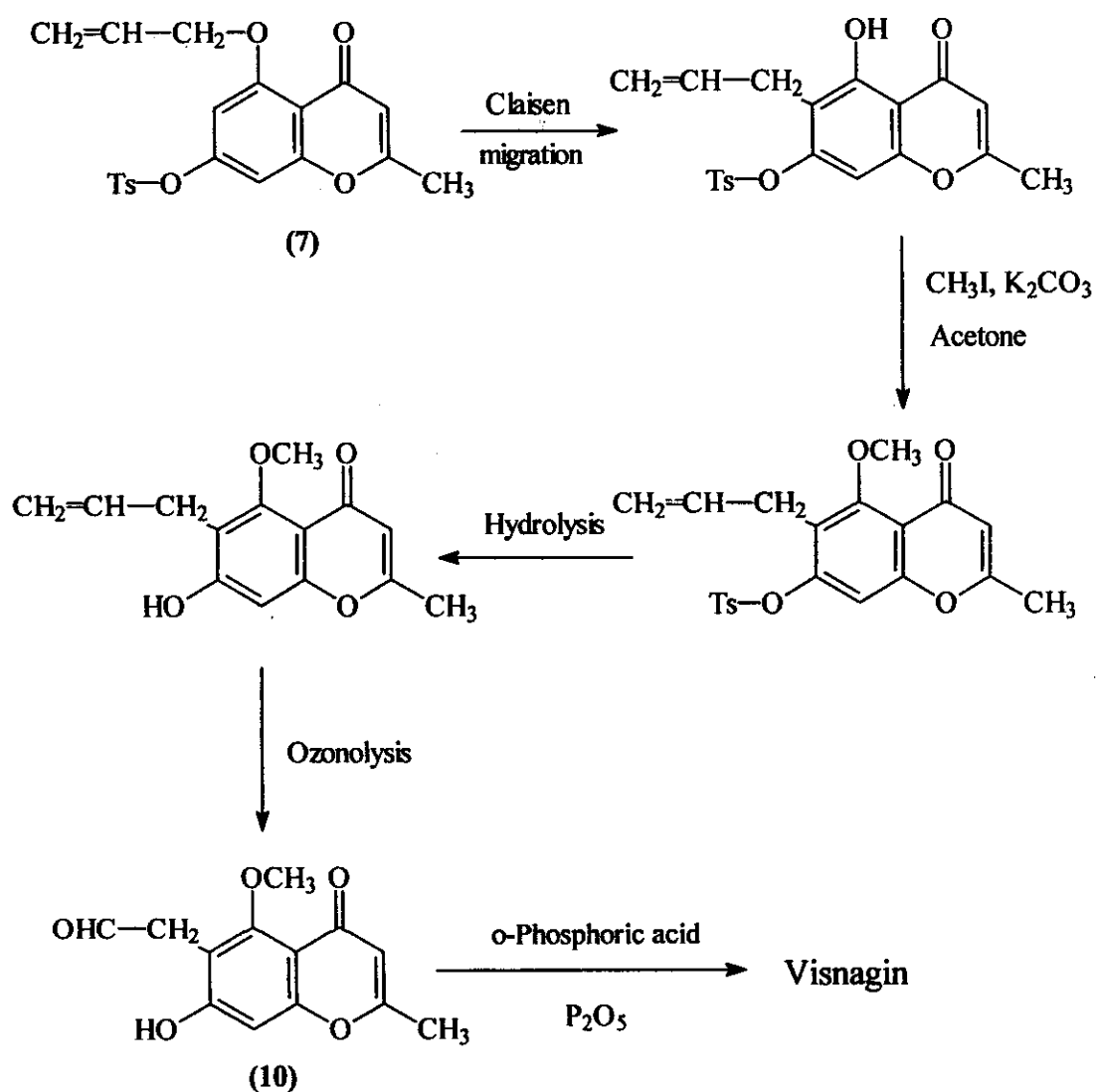
Thus, starting with 5,7-dihydroxy-2-methyl chromone (6), visnagin could be synthesized⁽⁵⁾. The process involve the introduction of an allyl group in the 6-position by the Claisen migration of the 5-allyl ether (7) of 5,7-dihydroxy-2-methyl chromone, the 7-hydroxy group has to be protected by means of 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.

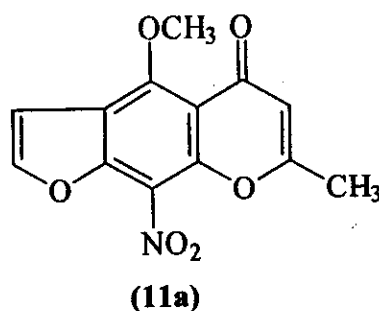
Subsequent stages of ozonolysis and ring closure of the 6-acetaldehydychromone afforded visnagin in good yield.



2.1.2. Electrophilic Substitution Reaction at Position-9

2.1.2.1. Nitration

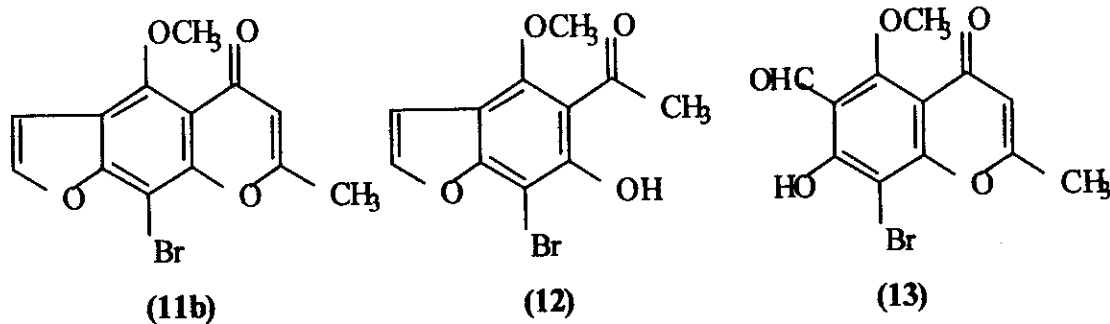
Nitration of 4-norvisnagin with nitric acid followed by methylation affords 9-nitrovisnagin **11a**⁽⁷⁾.



2.1.2.2. Halogenation

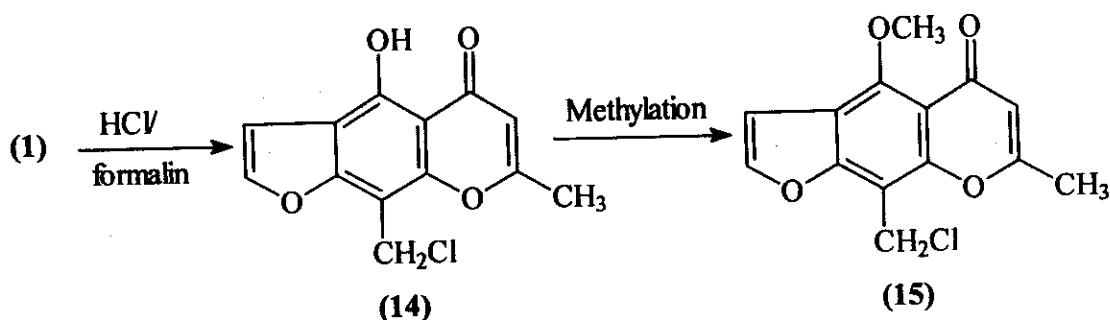
Visnagin reacts with bromine to give 9-bromovisnagin **11b**⁽⁸⁾ whose structure was proved by alkaline degradation to 5-acetyl-7-bromo-6-hydroxy-4-methoxy coumarone **12** and oxidation to 8-bromo-6-formyl-7-hydroxy-5-methoxy-2-methyl chromone **13**⁽⁹⁾.

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



2.1.2.3. Chloromethylation

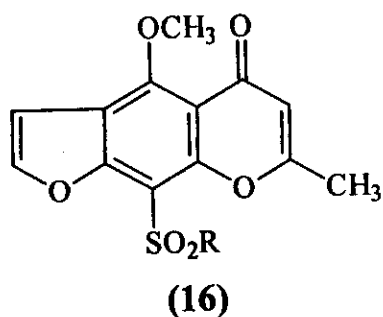
When 4-norvisnagin was treated with formalin in the presence of hydrogen chloride, it gives 9-chloromethyl derivative of 4-norvisnagin **14** which upon methylation affords the chloromethyl visnagin derivative **15**⁽¹⁰⁾.



2.1.2.4. Chlorosulphonated visnagin derivative **16** and its reactions

2.1.2.4.1. With amines:

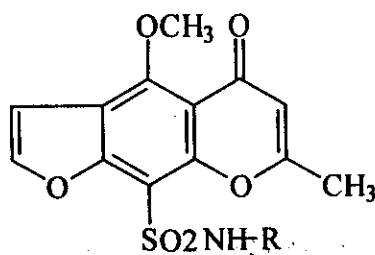
Treatment of visnagin with chlorosulphonic acid yields visnagin-9-sulphonyl chloride derivative **16**⁽¹¹⁾. Visnagin-9-sulphonyl chloride reacts with primary aliphatic, aromatic, heterocyclic and secondary amines forming the corresponding sulphonamides **17**⁽¹²⁻¹⁶⁾.



- 16**, R = Cl
17a, R = NH₂
b, R = NH-NH₂
c, R = NH-CH₃
d, R = NHCH(CH₃)₂-iso

- e**, R = NHC₄H₉-n
f, R = NHC₆H₁₁-cyclic
g, R = NHCH₂C₆H₅
h, R = NHCH=CH-CH₃

Also, compound **16** reacts with o, m and p-phenylenediamine 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⁾.

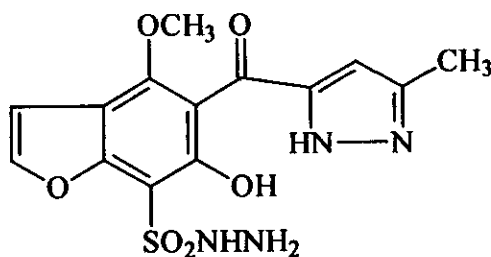


(18)

- | | | | |
|-------------|--|-----------|---|
| 18a, | R = p-C ₆ H ₄ -NH ₂ | d, | R = p-C ₆ H ₄ -(NH)SO ₂ -vis |
| b, | R = m-C ₆ H ₄ -NH ₂ | e, | R = m-C ₆ H ₄ -(NH)SO ₂ -vis |
| c, | R = o-C ₆ H ₄ -NH ₂ | f, | R = o-C ₆ H ₄ -(NH)SO ₂ -vis |

2.1.2.4.2. With hydrazine hydrate:

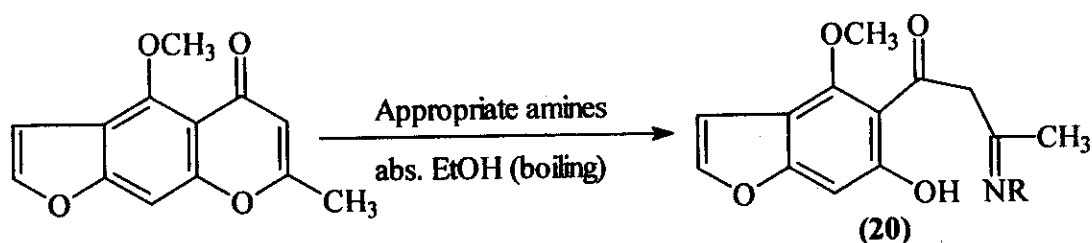
El-Sharief *et al.*⁽¹²⁾ reported that visnagin-9-sulphonyl chloride reacted with hydrazine hydrate to give **19**.



(19)

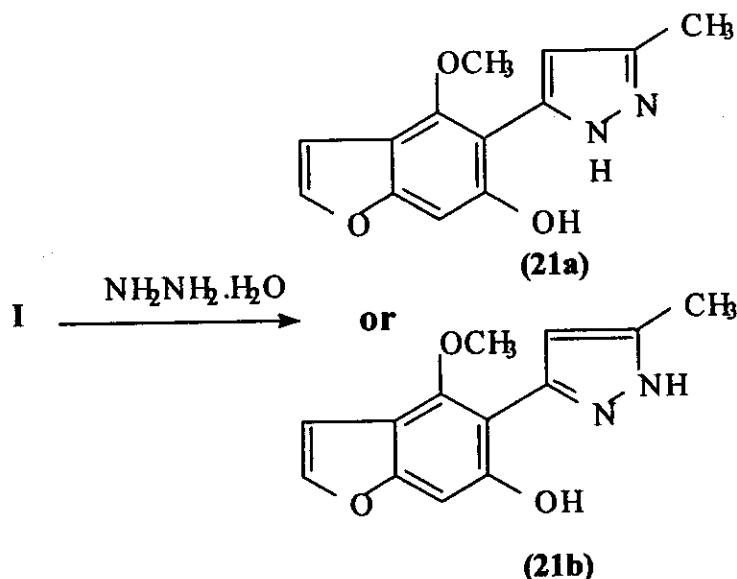
2.1.2.4.3. Action of amines:

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

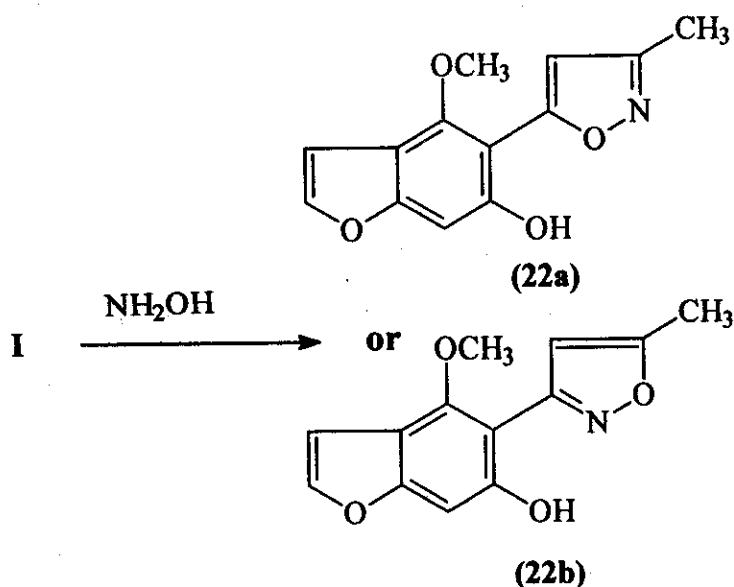


2.1.2.4.4. Action of hydrazine hydrate and hydroxyl amine hydrochloride:

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

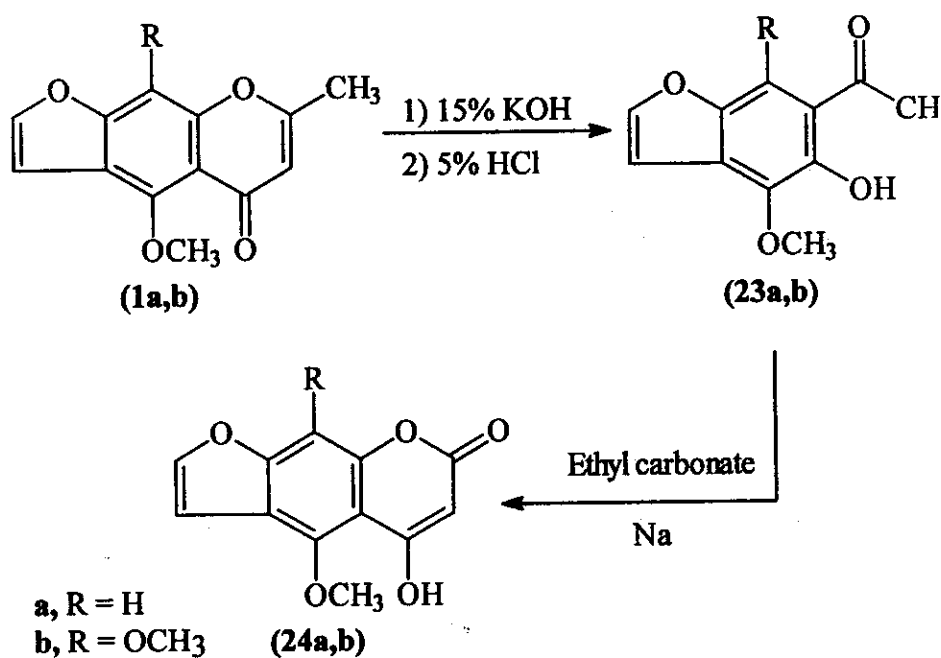


In contrast to its stability to hydroxyl amine hydrochloride in acetic acid at room temperature, visnagin reacts in boiling pyridine to give isoxazole derivatives (22a-b)⁽¹⁷⁾.



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.

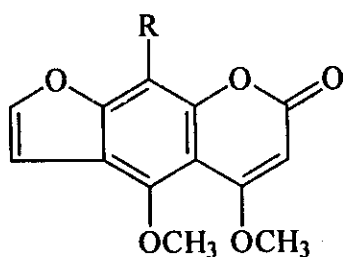
Special mention must be made that the coumarins in the family *Umbelliferae* (*Apiaceae*) which have been previously reviewed^(18,19). Also, a list of some prepared furocoumarins has been reported by Gevrenova⁽¹⁹⁾ and its biogenesis and biological activities were considered⁽²⁰⁾. Such biological activity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

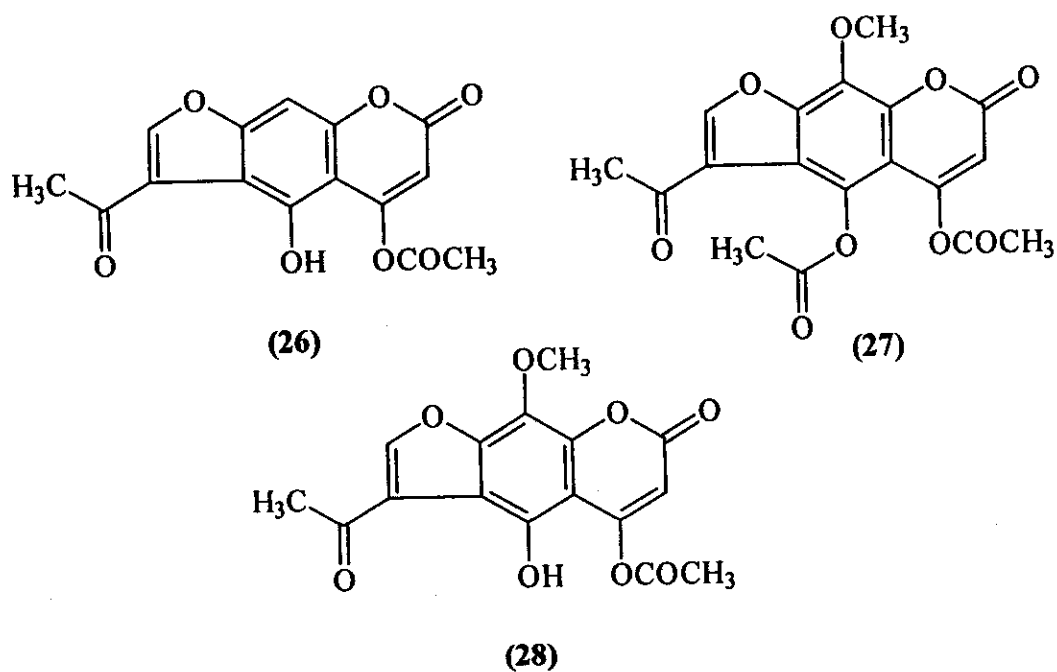
A number of 5-hydroxybergapten ether derivatives have been prepared by alkylation of bergaptol using either alkyl⁽²⁹⁾ or aryl⁽³⁰⁾ halides or by using diazoalkanes⁽³¹⁾.



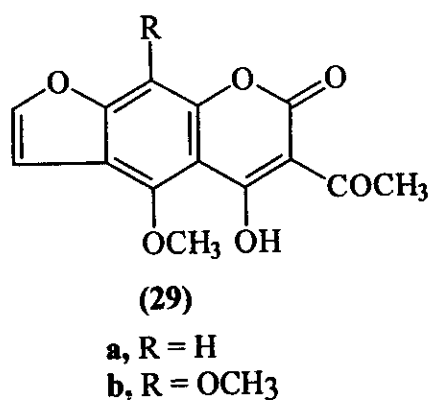
(25a,b) **a**, R = H
 b, R = OCH₃

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**.



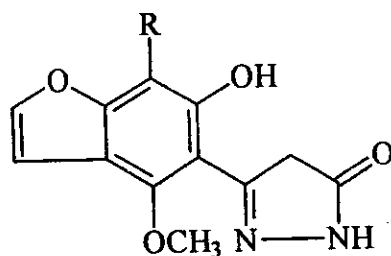
Also, 3-acetyl derivatives can be prepared by different conditions⁽³³⁾ to give 29.



2.1.2.7.3 Action of Hydrazine Hydrate and Phenyl

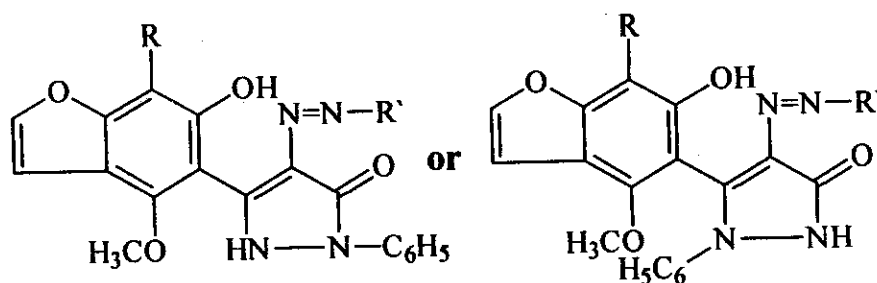
Hydrazine

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 = OCH₃

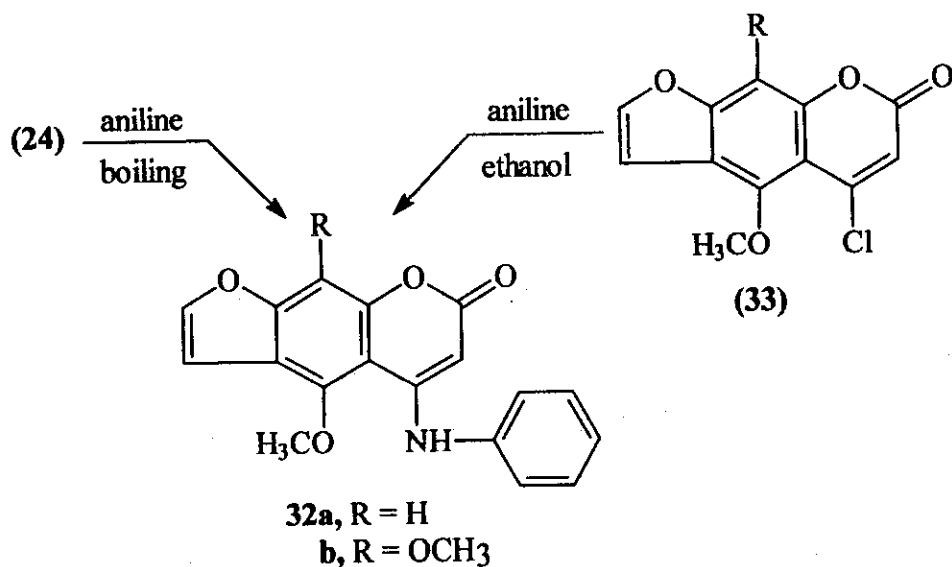
Also, the behaviour of 24 towards the action of phenyl hydrazine⁽³⁴⁾ lead to opening of the coumarin ring and formation of 1-phenyl-3'-(5'-(4'-methoxy-6'-hydroxybenzofuryl)-4-phenylazo-5-pyrazolone 31a and 1-phenyl-3'-(5'-(4',7'-methoxy-6'-hydroxybenzofuryl)-4-phenylazo-5-pyrazolone 31b or the possible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



31a, R = H
b, R = OCH₃

2.1.2.7.4. Action of Aniline:

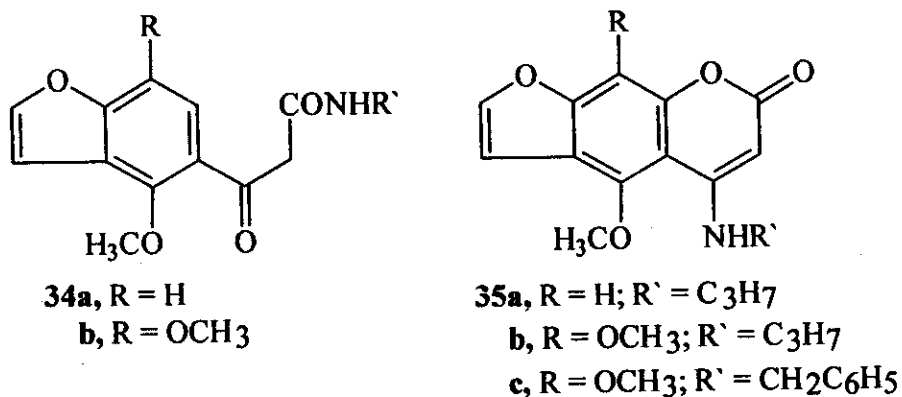
5-Hydroxybergapten 24a and 5-hydroxyisopimpinellin 24b reacted with boiling aniline to give the corresponding 5-anilino derivatives 32 which was also obtained by the action of aniline on the corresponding 5-chloro derivative 33 in boiling ethanol⁽³⁵⁾.



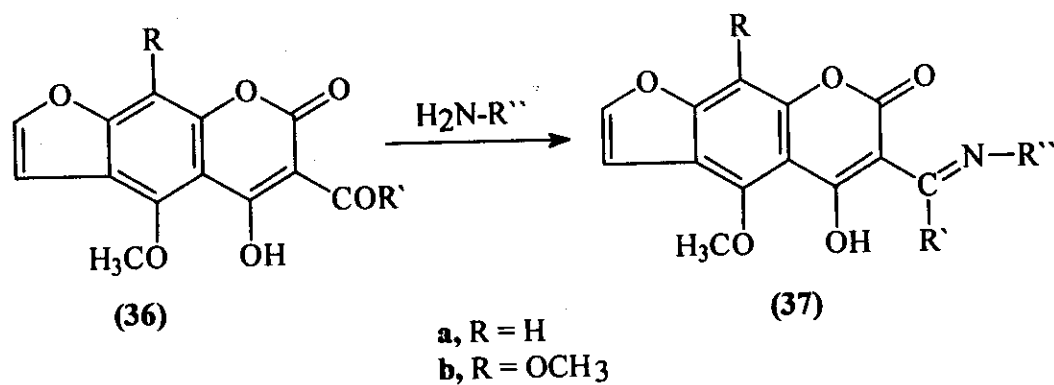
2.1.2.7.5. Action of Amines:

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⁾.

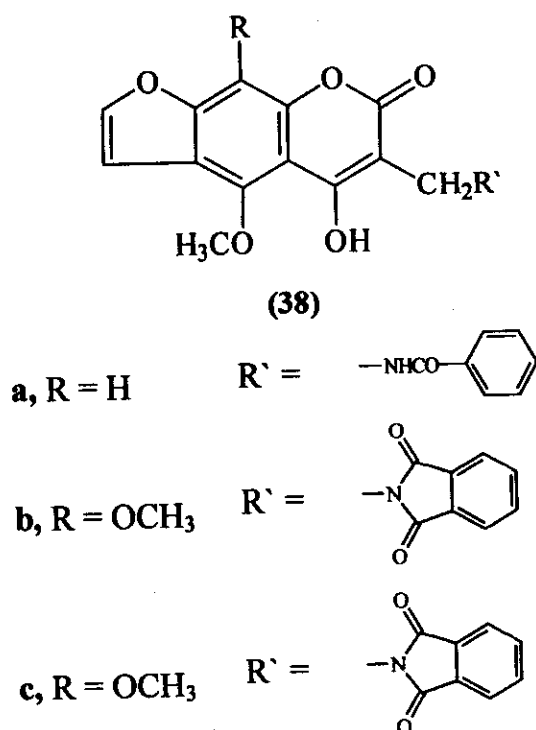


The action of aniline or ethylamine on 5-hydroxy-6-acyl bergapten and isopimpinellin **36** results in the formation of the amino derivatives **37**⁽³⁵⁾.



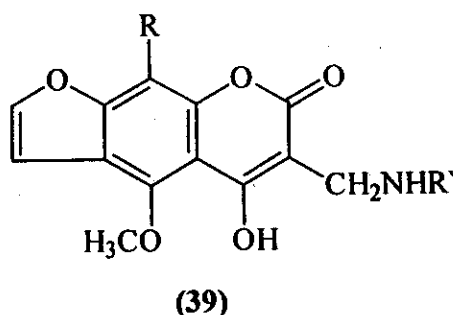
2.1.2.7.6. Acylaminomethylation:

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⁾.



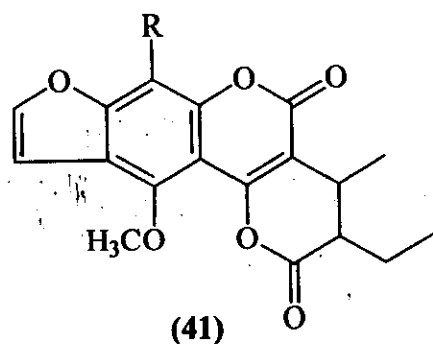
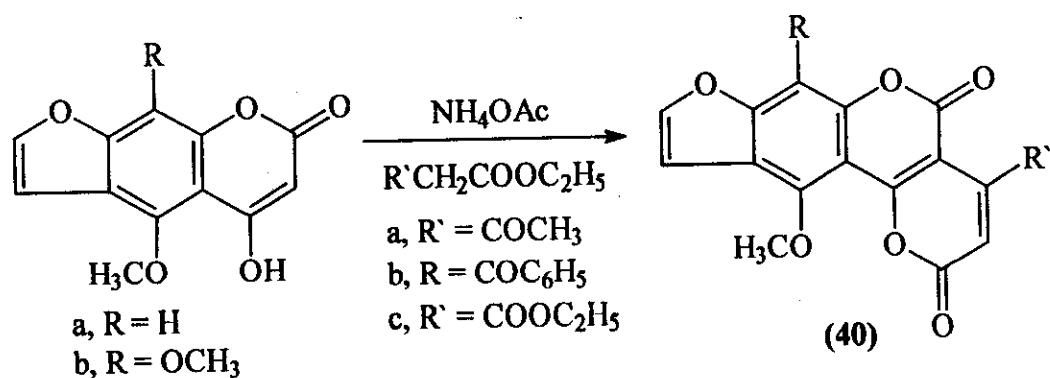
2.1.2.7.7. Mannich Reaction:

The reaction of (24.a-b) with primary and secondary amines (e.g. n-propylamine, 2-aminopyrazine, 2-benzimidazolamine, 2-aminophenol, morpholine and piperidine) 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.



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 fluorocoumarin derivatives (24.a-b) with ethylcyclopentanone-2-carboxylate in the presence of ammonium acetate led to the corresponding furobenzodipyran derivatives 41⁽⁴¹⁾.

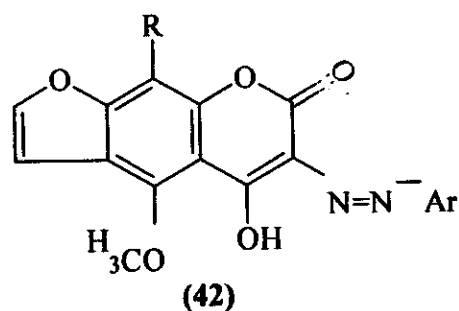


a, $\text{R} = \text{H}$
 b, $\text{R} = \text{OCH}_3$

a, $\text{R} = \text{H}; \text{R}' = \text{CH}_3$
 b, $\text{R} = \text{H}; \text{R}' = \text{C}_6\text{H}_5$
 c, $\text{R} = \text{H}; \text{R}' = \text{OH}$
 d, $\text{R} = \text{OCH}_3; \text{R}' = \text{CH}_3$
 e, $\text{R} = \text{OCH}_3; \text{R}' = \text{C}_6\text{H}_5$
 f, $\text{R} = \text{OCH}_3; \text{R}' = \text{OH}$

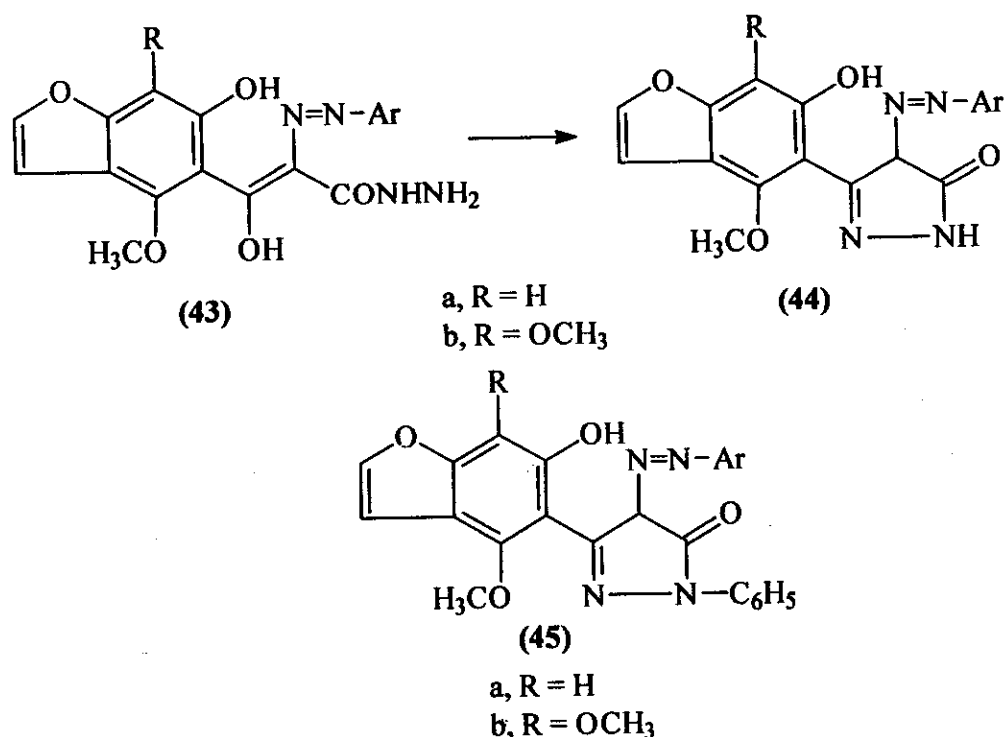
2.1.2.7.9. Action of Aryl Diazonium Chlorides:

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



a, $\text{R} = \text{H}$
 b, $\text{R} = \text{OCH}_3$

When the 6-aryazo 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-aryazo-3-[5'-(4'-methoxy-6'-hydroxy)benzofuryl]-5-pyrazolone **45**⁽⁴³⁾.



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 kingdom, often in association with phytosterols⁴⁴, 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 hierarchy. Indeed, a few triterpenoids have been

also isolated from petroleum⁴⁵ and from peat⁴⁶⁻⁴⁸. 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 1937⁴⁹, 1949⁵⁰ and 1951⁵¹.

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 Analysis⁵²⁻⁵³. The biogenetic Isoprene rule for terpenoids emerged via the pioneering investigations of zurich school of Ruzicka, Arigoni and Simonsen⁵⁴⁻⁵⁶. 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 biogenesis⁵⁷⁻⁵⁹.

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 a rate that it may be a fair statement that the bulk of achievements made in the past 20 years excite all that which has been made before. Comprehensive reviews on the occurrence,

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:-

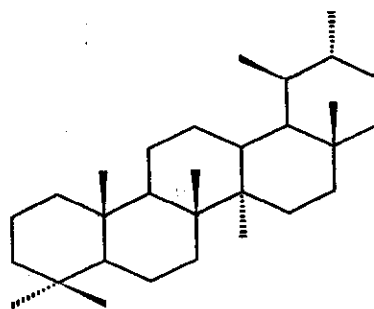
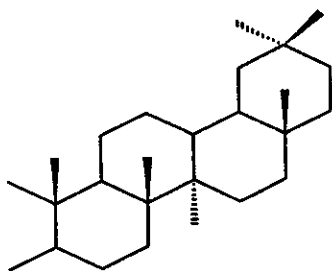
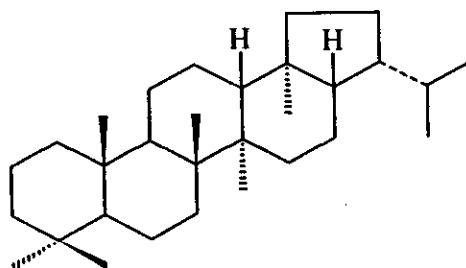
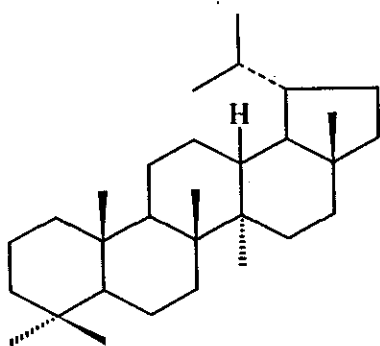
- | | |
|----------------------|-------------------------------------|
| 1) Hopane group | (e. g. Hopane) |
| 2) Dammarane group | (e. g. Dammarne) |
| 3) Lanostane group | (e. g. Lanosterol) |
| 4) Holostane group | (e. g. Halostanol) |
| 5) Euphane group | (e. g. Euphane) |
| 6) Tarxastane group |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

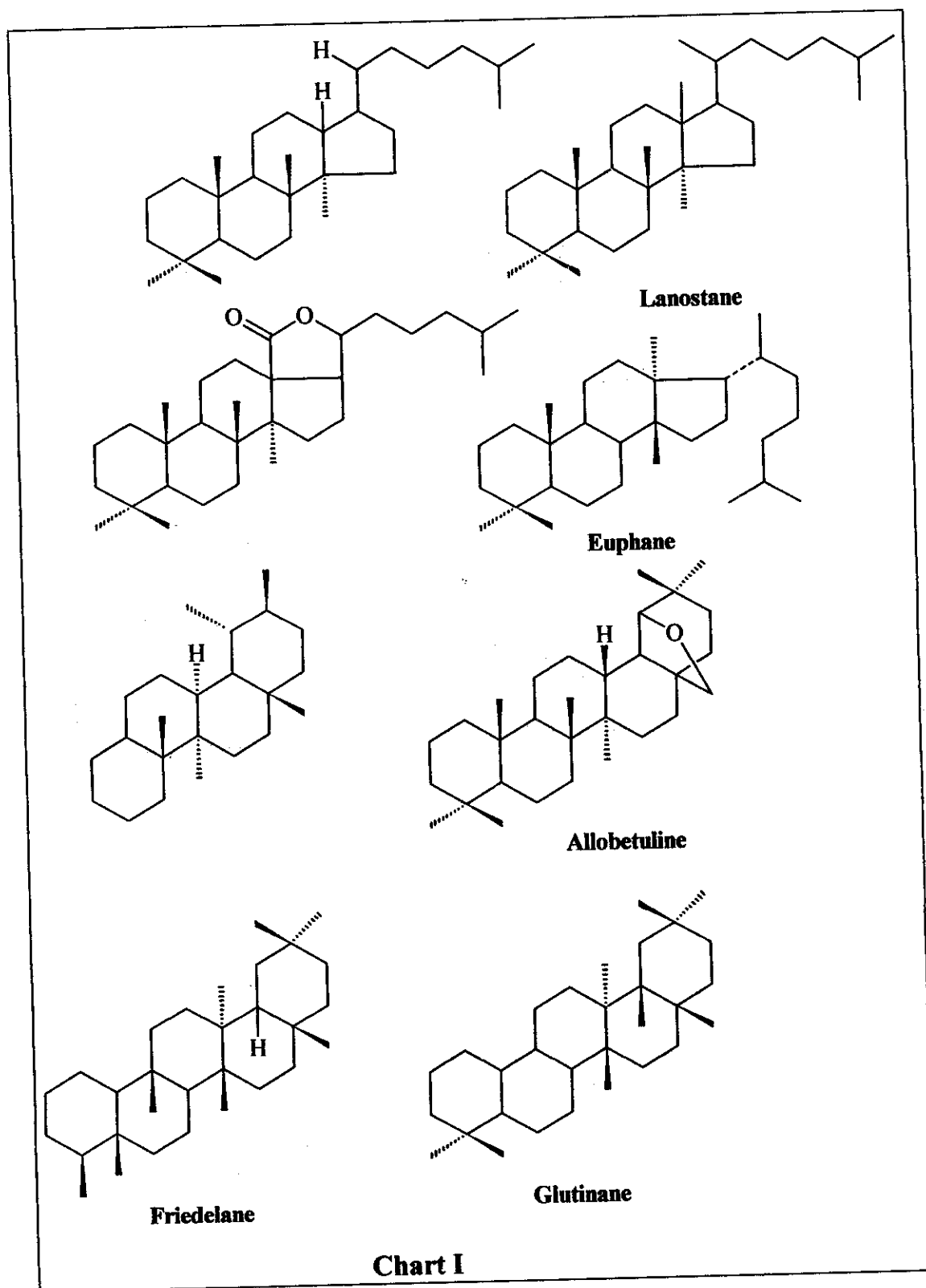
(Chart I)

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

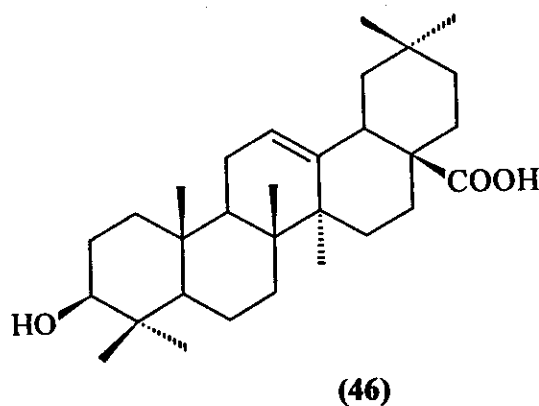
pentacyclic triterpenoids. The advent in the past few years of new types of natural triterpenoids possessing modified constitutions departing radically from the basic skeleta of the above three types makes it, however, unnecessary to regard such types as mere "exceptions" any longer.

**Ursane****Hopane**



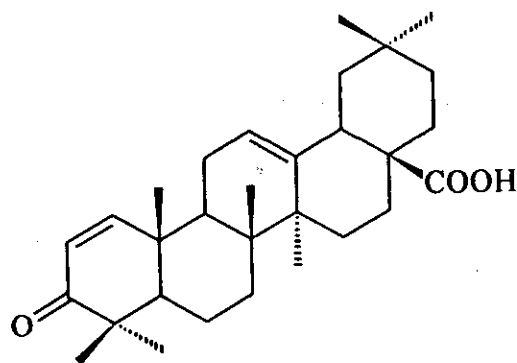
Numerous proposals⁶⁶⁻⁷⁰ have previously been advanced for the modified nomenclature of fundamental triterpenoid types both of natural and synthetic origin and have received varied degrees of acceptance. The most recent proposal, to the best knowledge of the author, is that made by Qurisson and Allard⁷¹ 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, biogenetically possible.

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



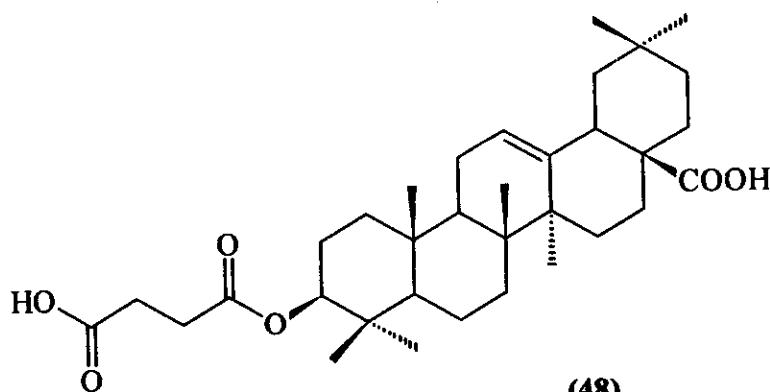
It present separate in olive trees, and with ursolic acid in Eucalptus trees, also it present as aglucone in partiner of many glucosides in most plants⁷².

Honda et al⁷² 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 macrophages when assayed at the 1 μ M level.



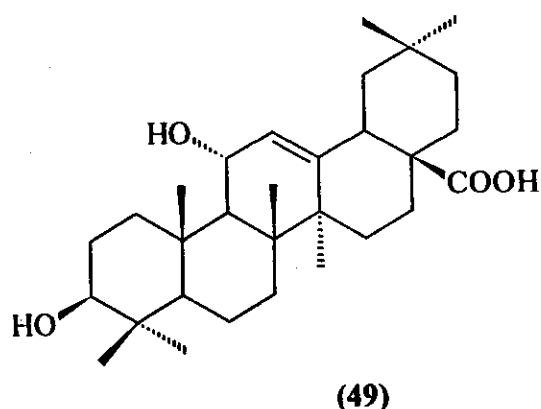
(47)

3-[(2-Carboxy ethyl) carbonyloxy] olean-12-en-28-oic acid (48) was synthesized by reacting oleanolic acid with succinic anhydride in pyridine to improve the solubility and bioavailability of oleanolic acid, it has been used as anti inflammatory and anti hepatitis drug in east Asia⁷³.

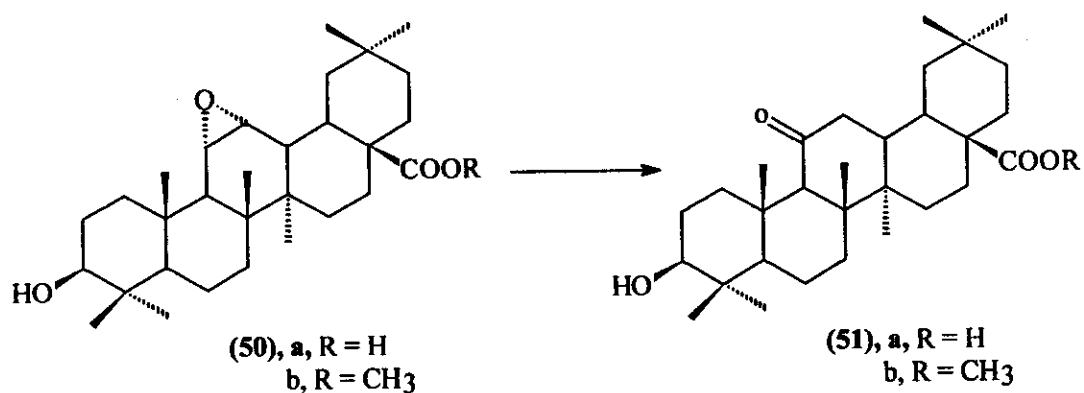


(48)

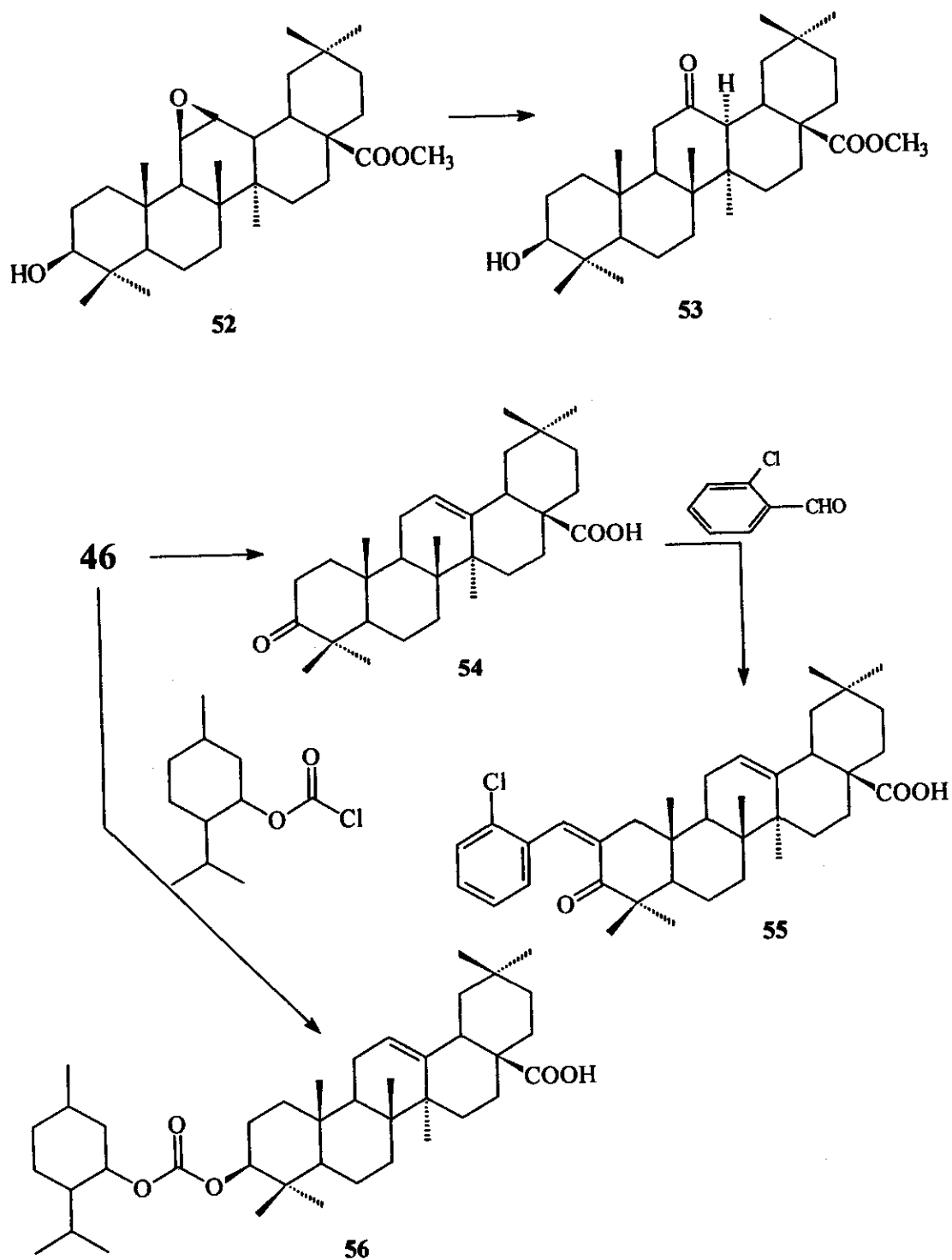
A novel allylic hydroxylation by mcpBA of oleanolic acid is catalyzed by Fe(PFPP)Cl give the 11 α -hydroxy oleanolic acid (49)⁷⁴.



Hydrogen peroxide-selenium dioxide in *t*-butanol has been found to be a good reagent for the preparation of 11^α, 12^α-oxidotriterpenoids of oleanolic acid and its methyl esters⁷⁵, they under acid conditions gives the 11-oxo function.



Reaction of oleanolic acid bromolactone with methanolic potassium affords methyl-3 β -hydroxy-12 β ,13 β -epoxyolean-28-oate, which rearranged, under mild conditions, to the novel 12-oxo derivatives possessing the 13^α configuration⁷⁶.

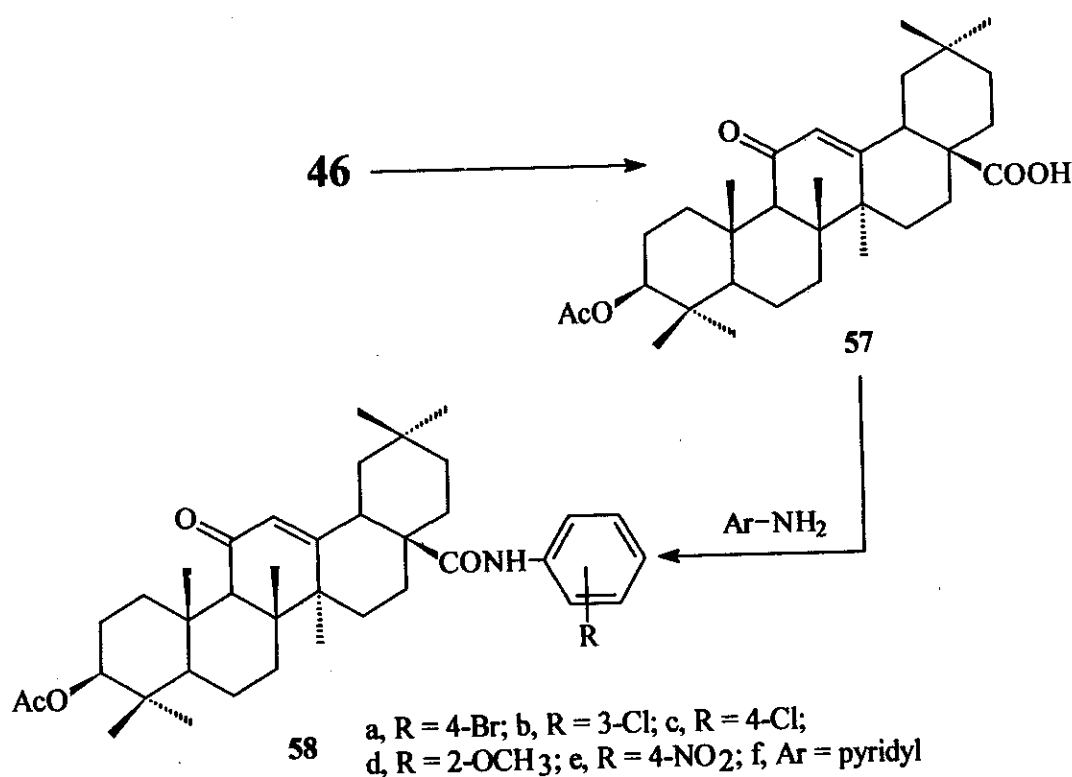


The synthesis of oleanolic acid-2-chlorobenzylidene derivative (**55**) consists of oxidizing the 3 β -hydroxy group into the corresponding 3-one (**54**) by rillion's reagent followed by aldol condensation with 2-

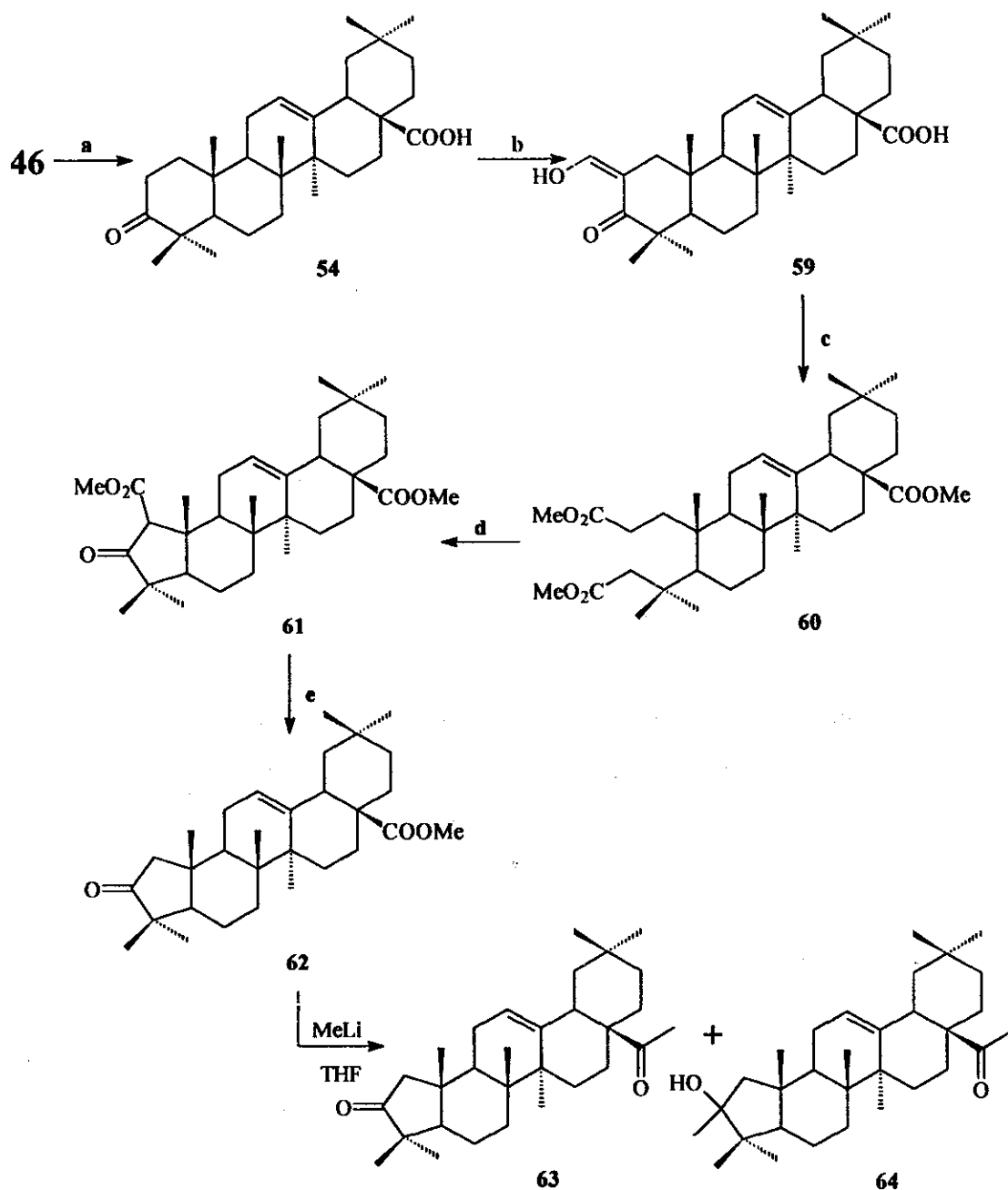
chloro benzaldehyde in aqueous alcoholic 30% KOH Compound (55) show both anti inflammatory and anti ulcerogenic activities.

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).



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 extreme 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 addition 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**.



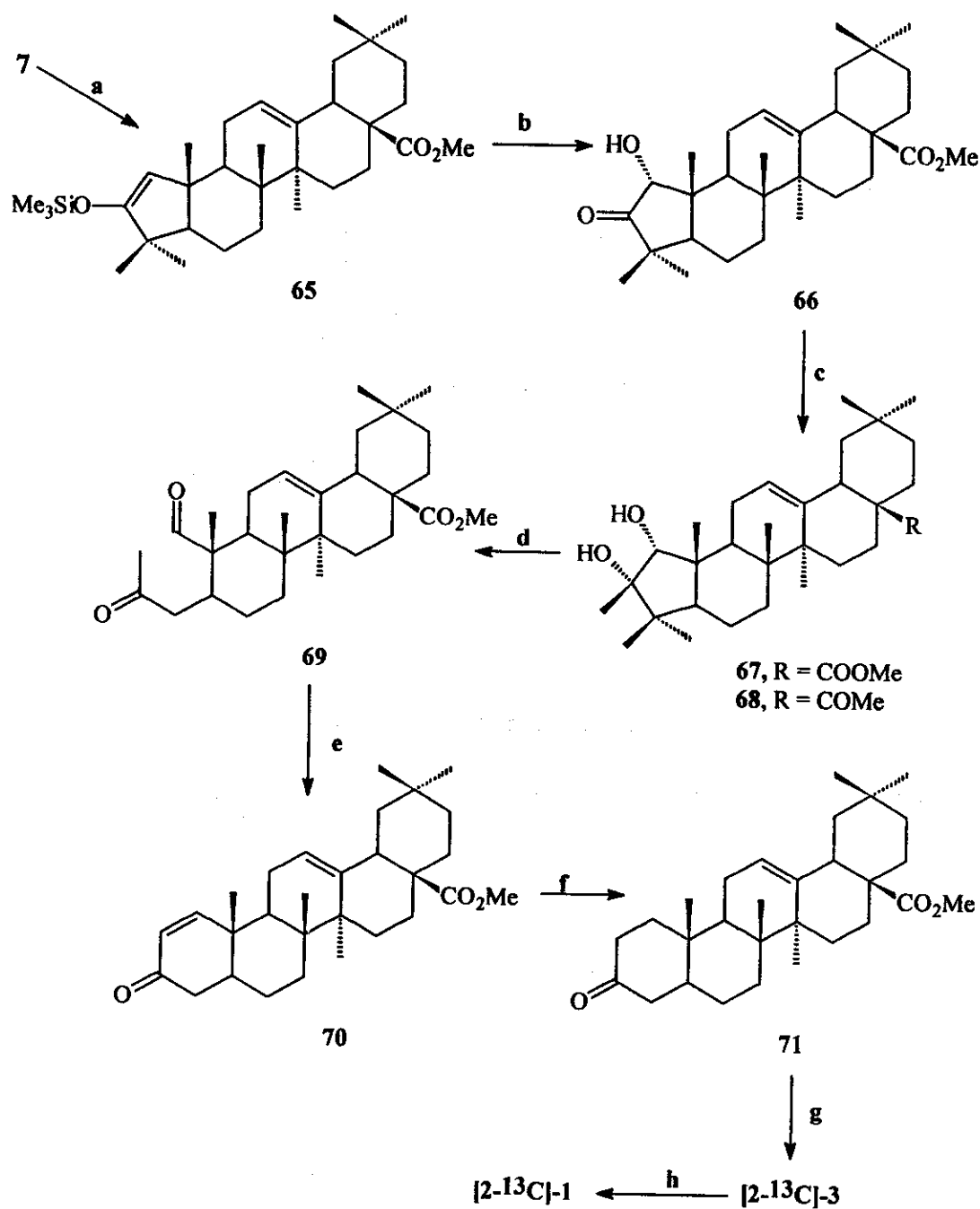
- i) Jones reagent, CH_2Cl_2 -acetone; b) HCOOEt , 28% NaOEt , benzene;
 c) 1) 30% H_2O_2 , 28% NaOEt , 2) CH_2N_2 , MeOH 58% from 1;
 d) $t\text{-BuOK}$, benzene, 78%; e) 50% aq. KOH , dioxane, 90%.

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

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methylolithium (Scheme 2). The enolate generated by deprotonating (62) by BuLi was treated with Me₃SiCl to give silyl enol ether 65, which was treated with m-CPBA in aqueous KHCO₃ 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 methylolithium from the unhindered 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 NaBH₄.

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



- i) BuLi, TMSCl, THF; b) m-CPBA, KHCO₃, hexane, 57% from 7;
 ii) MeLi, THF; d) Pb(OAc)₄, CHCl₃-AcOH, 59% from 11;
 e) 50% aq. KOH, dioxane, 78%; f) H₂, 10% Pd-C, 99%; g) LiI, 2,6-lutidine, 80%;
 h) NaBH₄, THF-MeOH, 70%.