“Synthesis of Imperatonin analogues and study their biological activity”

UGC-MRP by
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Final Report

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“Synthesis of Imperatonin analogues and study their biological activity”

A MINOR RESEARCH PROJECT PROPOSAL FOR FINANCIAL ASSISTANCE

Completion Report

UNIVERSITY GRANT COMMISSION

NEW DELHI

BY

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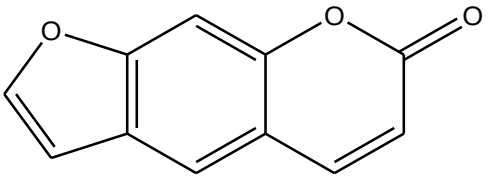
(AFFILIATED TO UNIVERSITY OF PUNE)

Title : "Synthesis of Imperatonin analogues and study their biological activity"

Introduction :

The linear parent furocoumarin is known as psoralen (**1**). It is one of the important naturally occurring furocoumarins. Psoralen (**1**) does not contain any substituent on any of the carbocyclic or heterocyclic ring.



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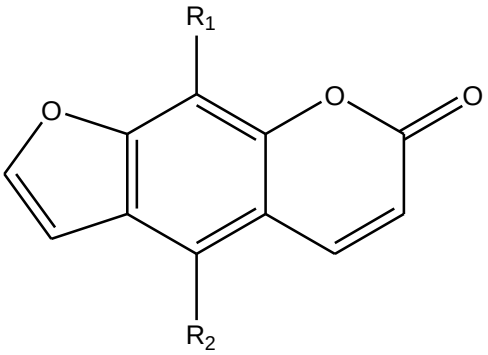


2

Psoralen (**1**) and substituted psoralens (**2**) possess important biological activities. It is used as the monofunctional reagent in photobinding with DNA. Psoralen (**1**) and some of its derivatives are used in photochemotherapy of skin disorder, particularly in the treatment of psoriasis disease.

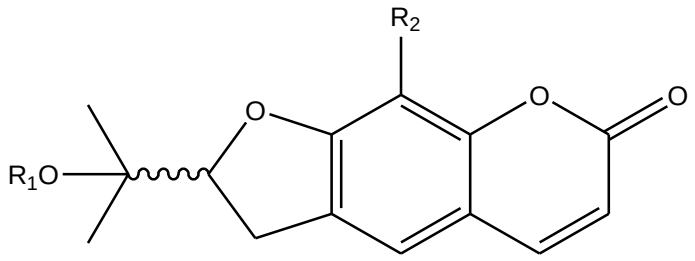
Natural liner dihydrofurocoumarins :

A variety of substituted liner dihydrofurocoumarin have been reported from natural souraces . They are commonly found in Umbelliferae family especially inangelica species. Dihydrofurocoumarins are very labile and are present as one of the compounds in very complex mixture . Therefore it is difficult to isolate these fourocoumarins in pure form.

Most of the naturally occurring linear dihydrofurocoumarins presented above contain either one or two substitunts in the furan ring . Some of them like **6** have substituents in both furan and pyran rings.

Reported methods for the synthesis of linear dihydrofurocoumarins :-

Various linear dihydrofurocoumarins having one, two or three substituents in furan ring have been synthesized. **7,8,9,10**. The examples of these syntheeetic furocoumarins (**8-12**) are presented below.



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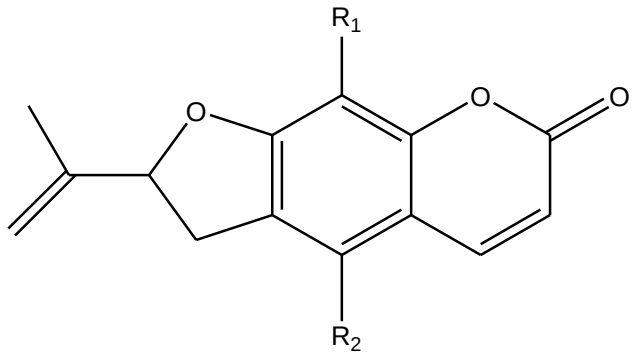

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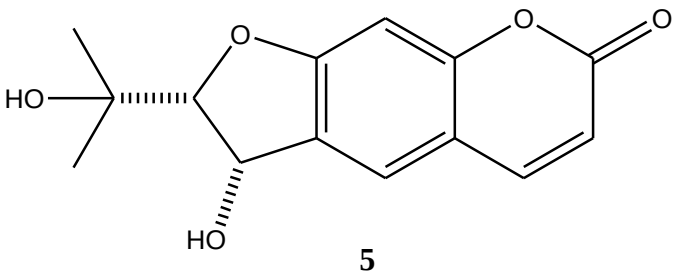

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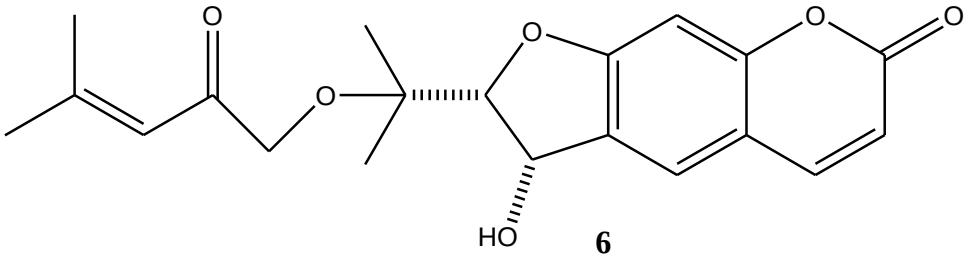

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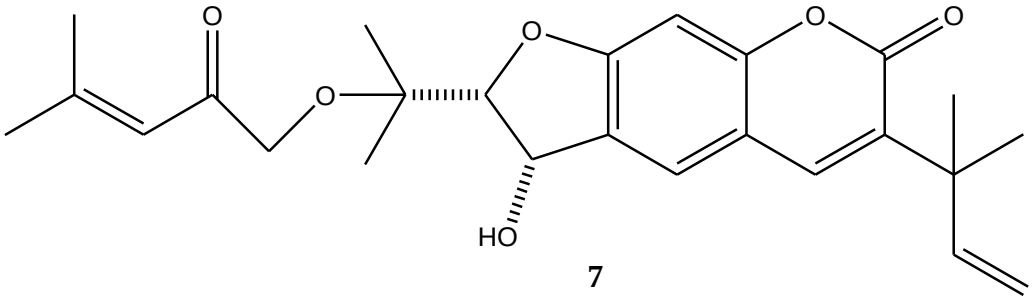
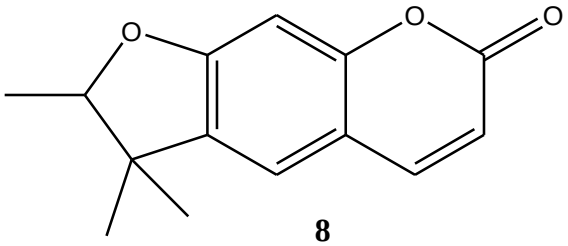


7

ReportedSynthesis : :



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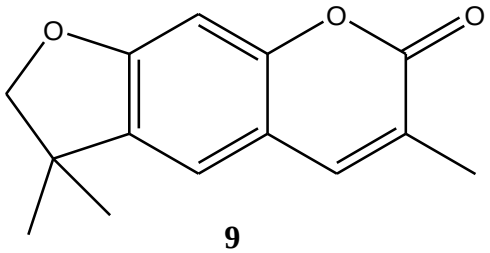

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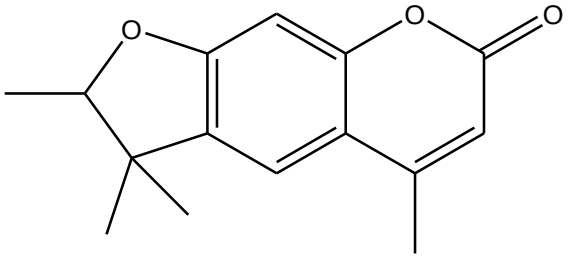

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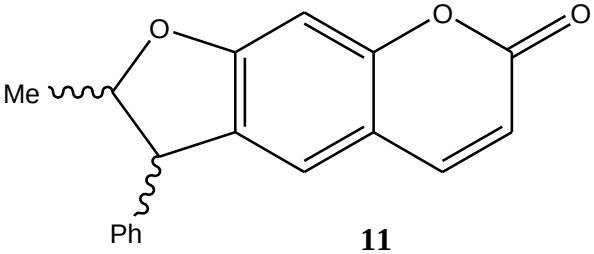

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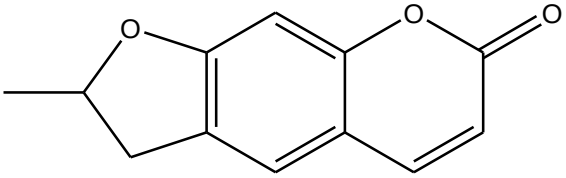
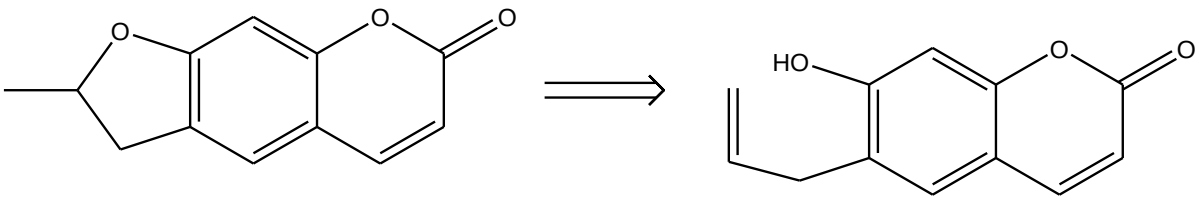


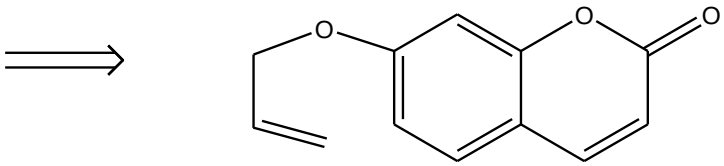
12

Retrosynthetic analysis of 7-methyl and 7-methyl-6,6-disubstituted dihydrofurocoumarins (**12** & **8**) are shown in Schemes I and II respectively. Thus the synthesis of 12 could be achieved from 7- allyloxycoumarins **14** via the intermediacy of **13**.

It is well known that allyloybenezenes on clasen rearrangement give 2- allylphenols. Hence it was expected that 7- allyloxy coumarin (14) on claisen rearrangement could also give 6-allyl-7-hydroxycoumarin (**13**). However, it is observed that under variety of conditions 7-allyloxycoumarin (**14**) gives 8- allyl-7-hydroxycoumarin (**15**) as a major product along with minor amount of the required 6- allyl-7- hydroxycoumarin (**13**).

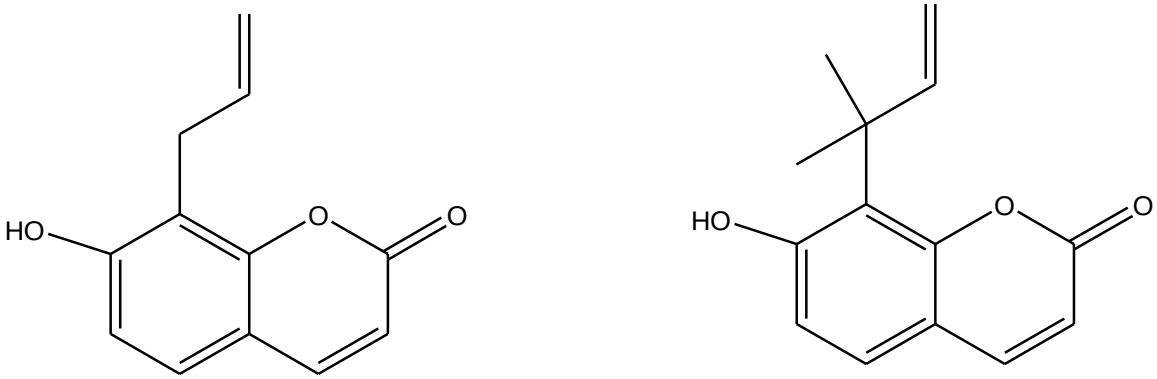


12 **13**

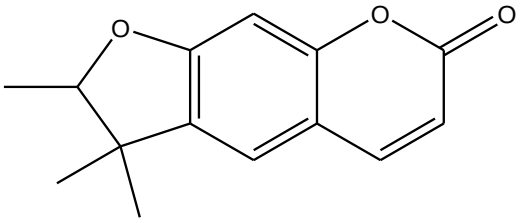


14

The synthesis of trisubstituted prenyloxycoumarin linear dihydrofurocoumarin (**8**) is visualized in scheme-2 from 7- (**17**). In this sequence also claisen reagent of (**17**) is visualized. It is reported that claisen rearrangement of (**7**) prenyloxycoumarin **18** as a major product along with a minor amount of 16.



15 **16**



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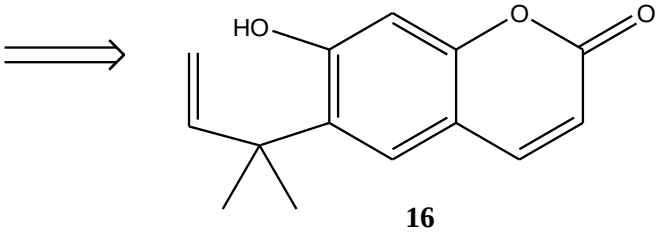

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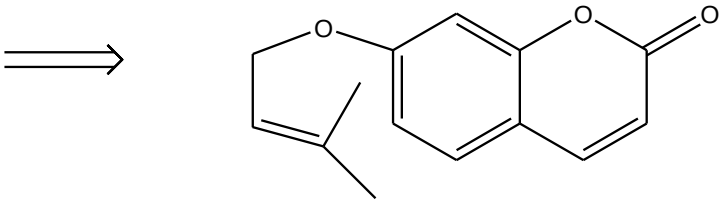
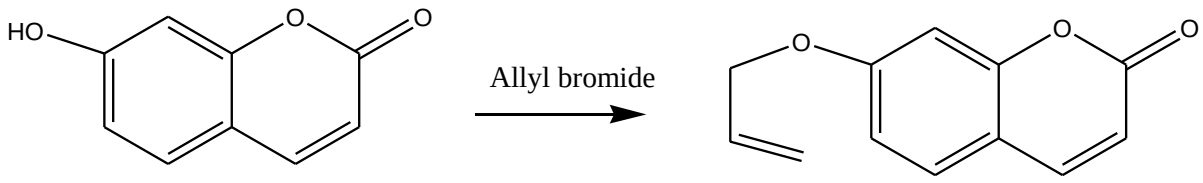


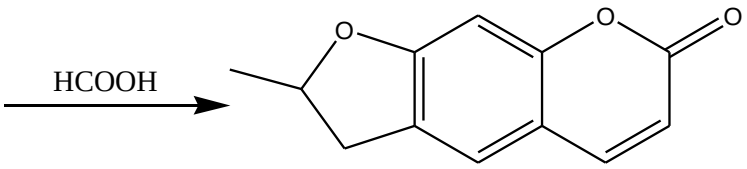
17

As described aboe the 7-allyloxycoumarin (**14**) & (**7**) prenyloxycoumarin could not provide furocoumarins in a good yield.

Allylation of 7-hydroxycoumarin (**19**) with allyl bromide in 90% formic acid gives (**14**) in a poor yield10 (25%) which on cyclization could give (**12**) as shown in a scheme 3.

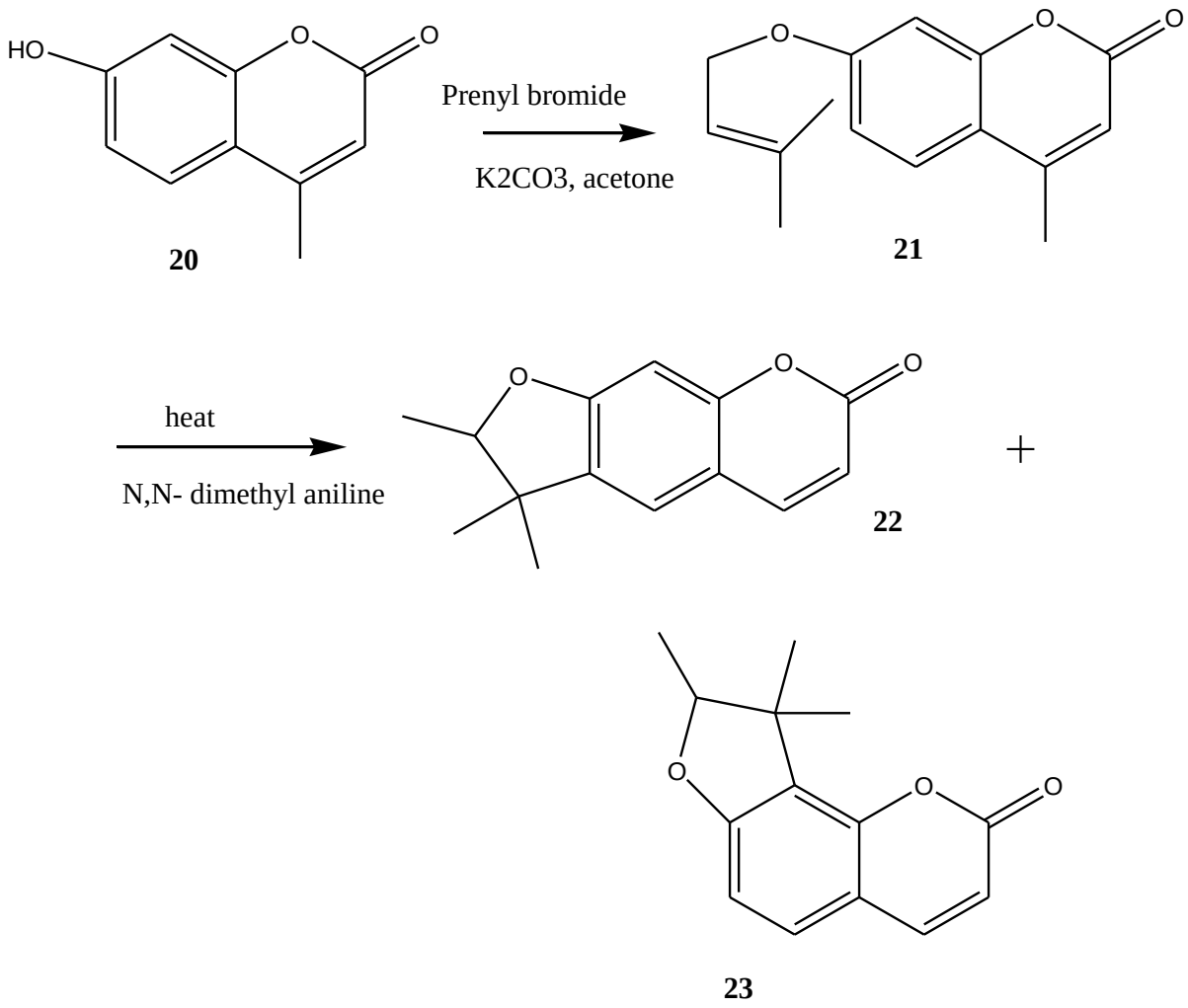


19 **14**



15

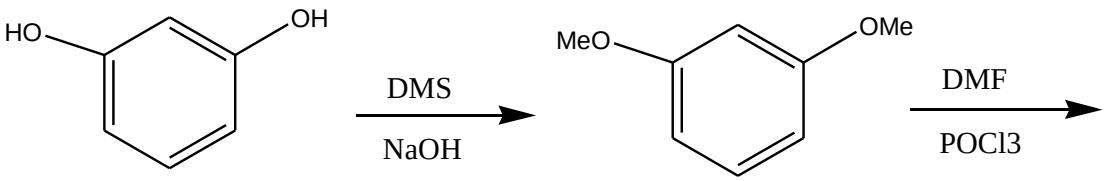
The synthesis of trisubstituted dihydro linear furocoumarin (**22**) is also reported in the literature scheme 4. The 7- prenyloxy 4- methylcoumarin (**21**) require for this purpose was prepared from 4- methylumbeliferon (**20**) by reacting it with prenyl bromide in the presence of potassium carbonate in acetone solution. On claisen rearrangement, by heating (**21**) in N,N- dimethyl aniline gave a mixture of two products **22** and **23**.

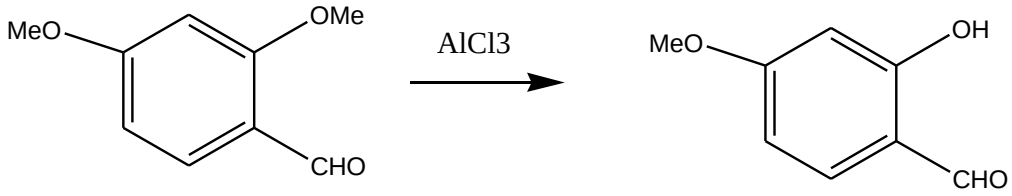


20 **21** **22** **23**

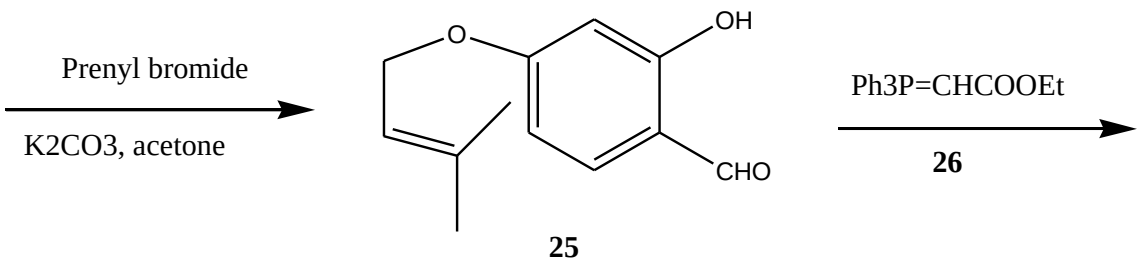
The synthesis of dihydro furocoumarins (**8**) and (**27**) has been reported from our laboratory from resorcinol (scheme 5). Resorcinol was first converted11 to its dimethyl ether which on Vilsmeier Haack reaction followed by demethylation provided aldehyde **24** in 93% yield. It was then prenylated by creating it with prenyl bromide in presence of potassium carbonate in refluxing acetone solution as reported in the literature.

The prenyloxy benzaldehyde (**25**) thus obtained was reacted with phosphorane **26** to give a mixture of furocoumarins (**8** and **27**) as shown in scheme 5.


HO
OH
DMS
NaOH
MeO
OMe
DMF
POCl3

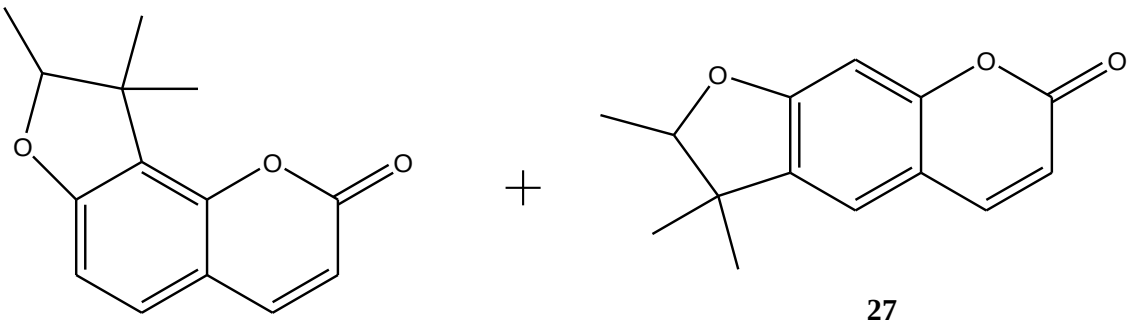

MeO
OMe
CHO
AlCl3
MeO
OH
CHO

24


Prenyl bromide
K2CO3, acetone
O
OH
CHO
Ph3P=CHCOOEt

25

26

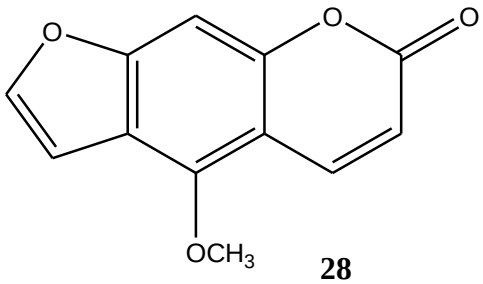

O
O
O
O
O
O

8

27

Present work:

As described furocoumarins are used photosensitising agent. Even as earliest 1938 Kuske found that substituted furocoumarins are photodynamically active. Furocoumarins like xanthotoxin (**28**), imperatonin (**29**) and Bergapten (**30**) where isolated from fruits of Ammi majus plant which has been used for long time in the treatment of leukoderma.



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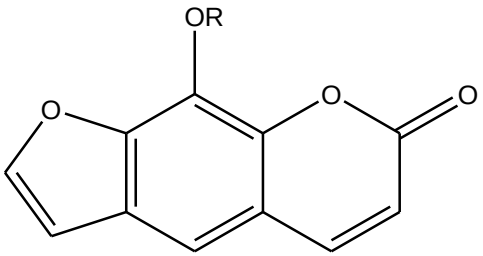


29, R=Prenyl
30, R= CH_3

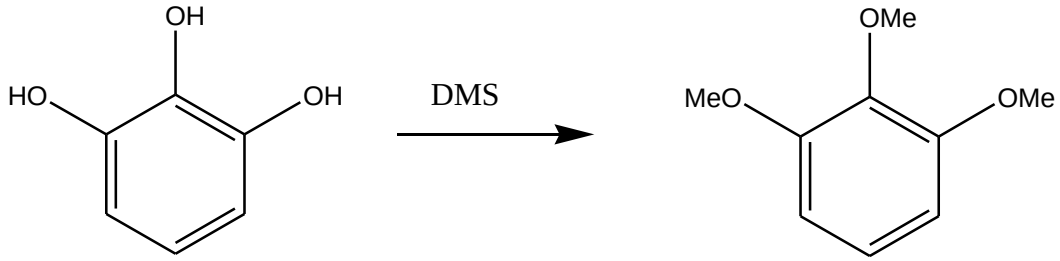
Musajo et al have examined many furocoumarin for their photodynamic activity and have shown that linear furocoumarins are more active than the angular furocoumarins .

In this chapter, our work on the synthesis of linear dihydro furocoumarins and 6-methylformyl-7,8 dimethoxycoumarins, a valuable intermediate for the synthsis of linear furocoumarins, is described.

As described in scheme 1-3, during the synthesis of furocoumarins, the construction of furan ring is found to be difficult task, as nuclear substitution of 7-oxygenated coumarins occurs chiefly at C8 position. The reported synthesis of substituted linear dihydro furocoumarin uses 7-oxygenated coumarins.

As described above 7-substituted-9-hydroxy-6,7-dihydrolinear furocoumarins (3f) and 9-alkoxy linear7-furocoumarins, imperatonin (**29**) Bergapten (30) have been isolated from natural sources. It was planned to develop methods the synthesis 7-substituted-9-hydroxy-6,7-dihydrolinear coumarins and for linear furocoumarins (**29** and **30**). The synthesis of furocoumarin (**31**) is planned as outlined in scheme 6.

Thus , the synthesis of furocoumarin **31** could be achieved from pyrragallol as depicted in scheme 6.



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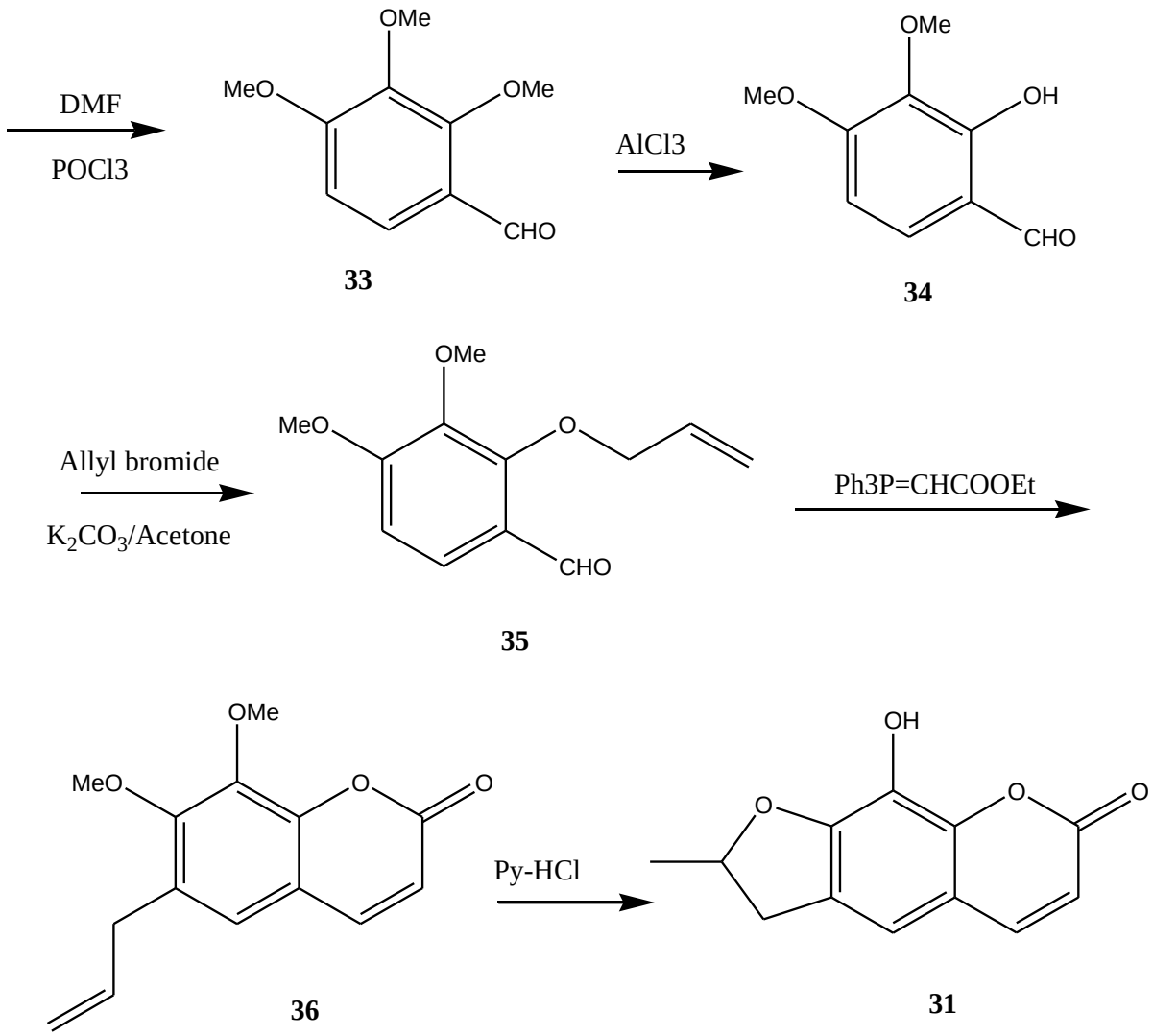
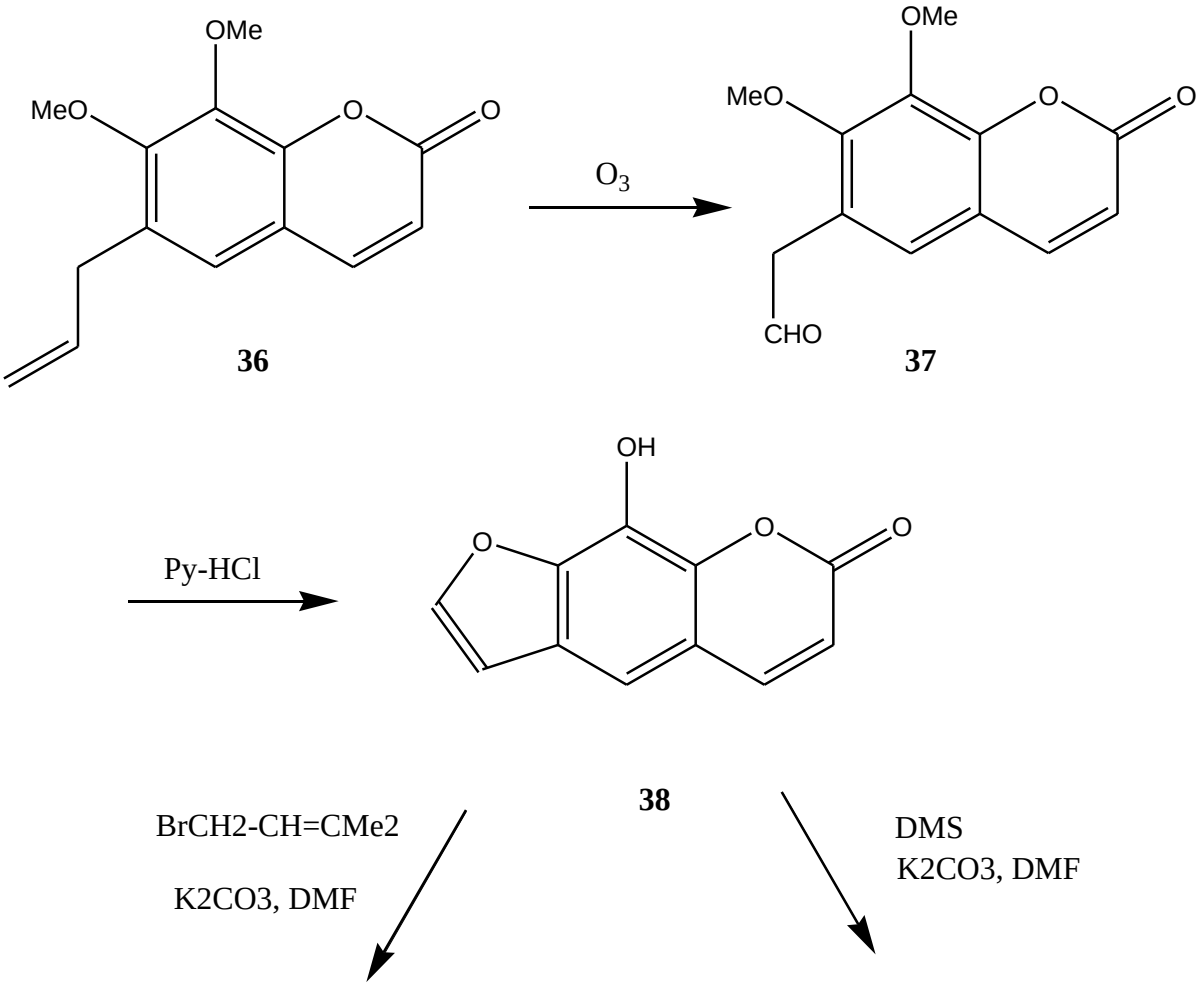


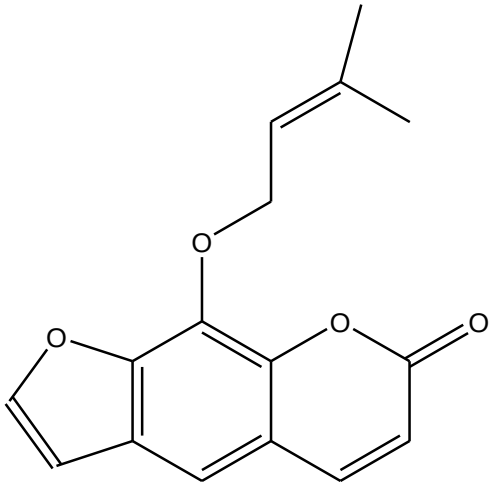
Pyrragallol on methylation gave the trimethyl ether **32** which on Vilsmier Haack reaction provided 2,3,4-trimethoxy benzaldehyde (**33**). Selective dimethylation of **33** gave hydroxyl aldehyde which on allylationfurnished the allyloxy aldehyde **35** in good yield. In reaction of allyloxy aldehyde 35 with phosphorane **26** gave 6-allyl-7,8 dimethoxy coumarin (**36**). The

next step of **36** into the target molecule using dimethylating cyclization approach. For this purpose 6-allyl-7,8 dimethoxy coumarin (**36**) was heated with pyridine hydrochloride at 423-428K for two hours under nitrogen atmosphere. After completion of reaction on acididc workup, a white solid (M.P 157^0 C) was obtained.

The linear furocoumarin, imperatonin **29** and Bergapten **30** have prenyloxy and methoxy group at C9 position. Both these coumarins could be prepared from 9 hydroxyfuro coumarins (**38**). Hence it was decided to synthesize **38** from 6-allyl-7,8 dimethoxy coumarin was visualized i scheme 7.



36 **37** **38**



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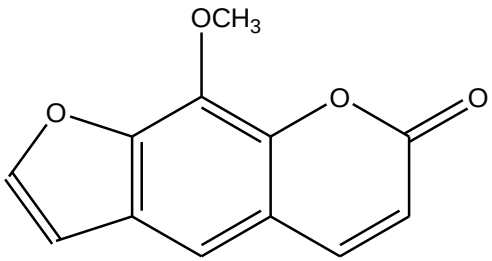
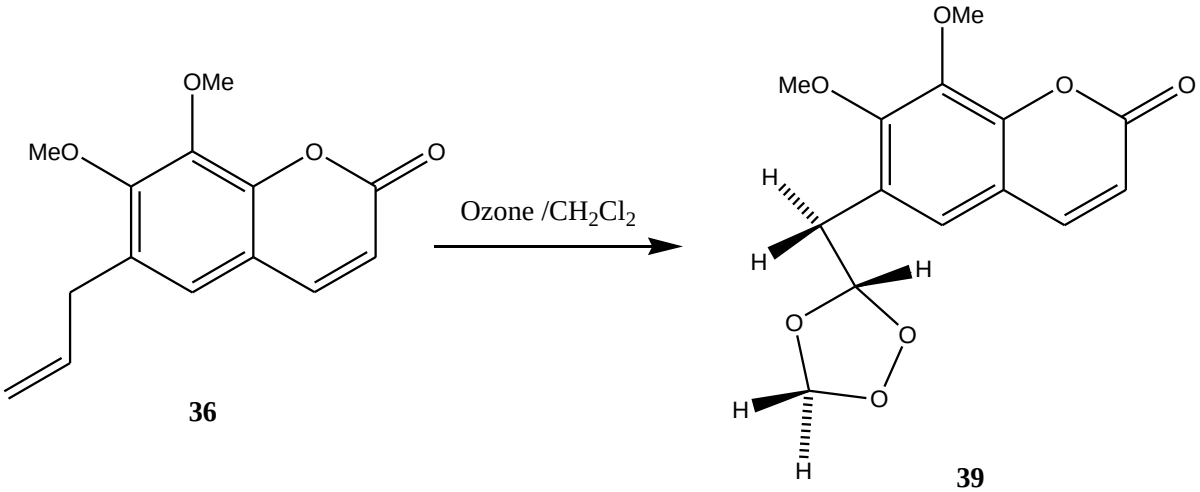


29

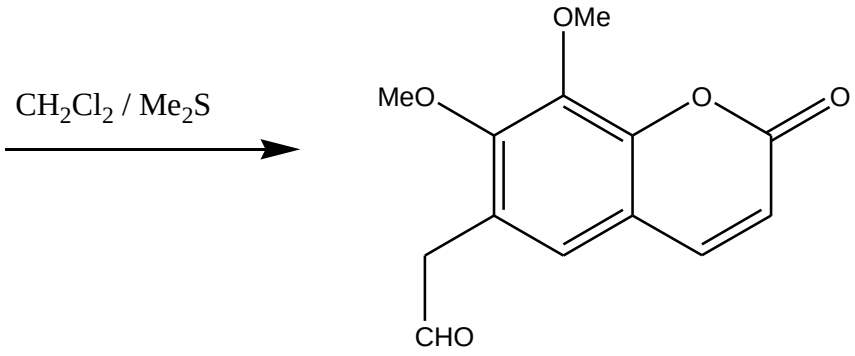
Ozonolysis experiments have been ued for synthesis of angelicin. Similarly the ozonolysis of **36** could give aldehyde **37** which on demethylation and cyclization could furnish coumarin **38**.

To achieve the synthesis of aldehyde **37**, ozonolysis of 6-allyl-7,8 dimethoxy coumarin **36** was carried out in dry methylene chloride at -78 0c. The course of reaction was followed by TLC. The TLC shown single spot compound different than starting compound within 3 minutes, hence the reaction was worked out. Evaporation of solvent afforded a white solid which on purification gave, a crystalline product, M.P.81^0 C .

It was then felt that inadvertently this step has been omitted. To check this possibility ozonolysis of **36** was once again repeated without using dimethyl sulphide scheme 8. The compound M.P 81^0 C , obtained from this reaction was found to be identical (TLC, superimposable IR) with the product obtained in the previous experiment.



36 **39**



37

The ozonide **39** was then stirred with dimethyl sulphide in methylene chloride for two hours. The course of reaction was followed by TLC.After stirring for two hours at room temp. The solvent was evaporated and the product odtained was purified by passing it through silica gel column.

A white solide ,m.p.175 ^{0} C ,was obtained from this reaction.

Ozonolysis of **36** was then carried out in methylene chloride, for 3 mins, at -78 ^{0}C. Till a faint blue colour appeared. Dimethyl sulphide was then added and mixture was stirred at room temperature for 1 hr. After removal of solvent the product obtained was purified by passing it through silica gel column. The white solid product **37**, M.P. 175 ^{0} C obtained in 72% yield from this reaction was identical (TLC, M.P) with the authentic sample obtained in the decomposition of ozonide (**39**).

As visualized in scheme 7 the next step was the demethylative cyclization of **37** to obtain 9-hydroxy furocoumarin (**38**). The demethylation of **37** with pyridine hydrochloride at 150 ^{0} C . However under this condition the starting compound is recovered from this reaction. The reaction was then repeated by increasing the reaction temperature (upto 180 ^{0} C) and also by increasing reaction time. In these reaction also starting compound **37** was recovered. This result is surprising since **36** is converted to **31** in good yield.

Eventhough the theoretical postulation was correct. Surprisingly the desired conversion of **37** into **38** could not be achieved.

Conclusion :

A convenient synthesis of 6,7-dihydro-7-methyl-9-hydroxypsoralen (**31**) and 6-formylmethyl-7,8-dimethoxycoumarin (**37**) is described from 6-allyl-7,8-dimethoxycoumarin (**36**).

Synthesis

Expt.2.1: Preparation of 1, 2, 3 – trimethoxybenzene (1)

Expt.2.2: Preparation of 2, 3, 4-trimethoxybenzaldehyde (2).

Expt.2.3:prepration of 2-hydroxy-3,4-dimethoxybenzaldehyde (3).

Outcome of the project :

Work presented in International conference :

1. **Synthesis of imperatonin analogue and study of its antimicrobial activity**
   2nd Internatinal conference on Herbal and Synthetic drugs studies, (HSDS-2014) 10-12 Feb 2014, organised by Interdisciplinary science and technology research academy (ISTRA) Azam campus, Pune. P-105 , Page No. 78, Vidya Kalyankar[a], , Omkar Pawar[a], Priyanka Dagade[a] **, Nalini Pandhare[a]**and **Shobha Waghmode[a*]**,