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NEOFLAVONES. 2. METHODS FOR SYNTHESIZING AND MODIFYING 4-ARYLCOUMARINS

M. M. Garazd,[1] Ya. L. Garazd,[2] and V. P. Khilya[2]

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Literature data up to 2003 were presented and information on methods for preparing and modifying natural 4-arylcoumarins and their synthetic analogs were systematized.

Key words: flavonoids, neoflavones, 4-phenylcoumarins, synthesis, modification.

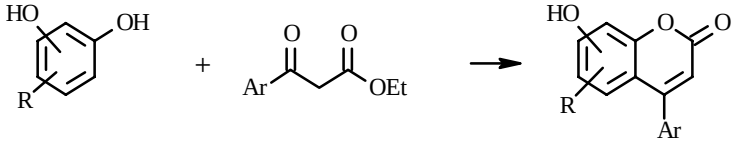
The first part of this review [1] presented data on the physicochemical and pharmacological properties of natural 4-arylcoumarins. Natural neoflavones and their synthetic analogs can be used as medical preparations because of their wide spectrum of biological activity and low toxicity. However, this necessitates the development of preparative synthetic methods. Therefore, the second part reviews completely all presently known synthetic approaches to the construction and modification of neoflavones.

1. METHODS FOR SYNTHESIZING 4-ARYLCOUMARINS

Most known methods for synthesizing 4-arylcoumarins can be divided into two groups: those in which the benzopyran-2-one ring is closed (Pechmann, Perkin, Ponndorf and other reactions) and those based on arylation of coumarins activated at the 4-position.

Pechmann reaction

Various modifications of the Pechmann reaction, which consists of the condensation of substituted phenols with esters of aroylacetic acids in the presence of mineral and Lewis acids, are most widely used to synthesize 4-arylcoumarins. The reaction leads usually in high yield to neoflavones **1** of various structures [2].



1

Phenols that have been used in the Pechmann condensation include resorcinol [1-15], 3-methylphenol [16, 17], 4-methylphenol [18, 19], 2,4-dimethylphenol [20], 3-methoxyphenol [7, 21], 2-methylresorcinol [10, 22-24], orcine [10, 14, 25], 4-chlororesorcinol [10, 26], 2-bromoresorcinol [27], 4-ethylresorcinol [28, 29], β-resorcinolic acid methyl ester [30], 5-pentadecylresorcinol [31], 4-ethyl-2-acetylresorcinol [28], 2-methylhydroquinone [32], 2-ethylhydroquinone [32], pyrogallol [5, 10, 11, 15, 33, 34, 59, 64], 4-ethylpyrogallol [35], pyrogallol-4-carboxylic acid ethyl ester [35], phloroglucinol [10, 11, 13,

1) Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, 02094, Ukraine, Kiev, ul. Murmanskaya, 1, e-mail: gmm@i.com.ua; 2) Taras Shevchenko Kiev National University, 01033, Ukraine, Kiev, ul. Vladimirskaya, 64. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 199-218, May-June, 2005. Original article submitted May 10, 2004.

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15, 33, 36-44], 1,3,5-triacetoxybenzene [41], 5-methoxyresorcinol [45-49], fluoroacetophenone [50, 51], 2-methylpropionylphloroglucinol [52], 2-methylbutyrylphloroglucinol [52], 3-methylbutyrylphloroglucinol [52, 53], butyrylphloroglucinol [54], 2,4-dihydroxy-6-methoxyacetophenone [50], 1,2,4-triacetoxybenzene [11, 55-59], 1,2,4-trihydroxybenzene [12, 60], 2-methoxyhydroquinone [60-62], 2,6-dimethoxyhydroquinone [63], 2,6-dihydroxy-1,4-dimethoxybenzene [45], 1,2-diacetoxy-3,5-dimethoxybenzene [45], 2-ethyl-3,5-dimethoxyphenol [65], 3,5-dimethoxy-2-propylphenol [65], 3,5-dimethoxy-2-pentylphenol [65], 3,5-dimethoxy-2-isopentylphenol [66], 3,5-dimethoxy-2-benzylphenol [67], 7-hydroxy-2,2,-dimethylchromane [68], 7-hydroxy-5-methyl-2,2-dimethylchromane [69], 7-hydroxy-8-methyl-2,2-dimethylchromane [70], 7,8-dihydroxy-2,2-dimethylchromane [68], 8-methyl-2-phenylchroman-7-ol [71], 6-acetoxycoumaran [72], 2,3-dihydro-1-benzofuran-6,7-diol [73].

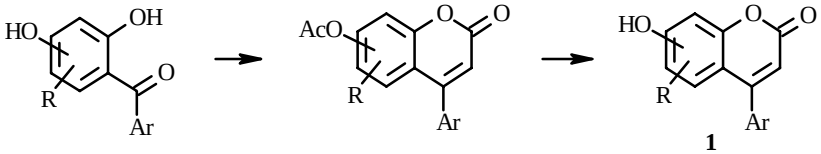
The Pechmann reaction has been carried out using esters of benzoylacetic [1-6, 13-16, 18-24, 26-38, 40, 43-46, 50-56, 59, 60, 63-73], 2-methoxybenzoylacetic [11, 13], 3-methoxybenzoylacetic [58], 4-methoxybenzoylacetic [11, 12, 14, 25, 39, 41, 45, 49], 4-ethoxybenzoylacetic [12], 2-isopropyloxybenzoylacetic [13], 3-isopropyloxybenzoylacetic [13], 2,4-dimethoxybenzoylacetic [11], 3,4-dimethoxybenzoylacetic [7, 8, 11, 57], 2,5-dimethoxybenzoylacetic [42], 2,5-diisopropylbenzoylacetic [13, 47], 3,4-diisopropylbenzoylacetic [47], trimethylgalloylacetic [9, 36], 2,3,4-trimethoxybenzoylacetic [42], 3-benzyloxybenzoylacetic [61], 4-benzyloxybenzoylacetic [39, 41, 49, 61], 4-methoxy-3-ethoxybenzoylacetic [62], 3-methoxy-4-ethoxybenzoylacetic [62], 3-methoxy-4-benzyloxybenzoylacetic [41], 4-methoxy-3-benzyloxybenzoylacetic [48, 49, 62], and 3-(1,3-benzodioxol-5-yl)-3-oxopropionic [41] acids. It should be mentioned that diethyl esters of benzoylmalonic acids have also been used in the Pechmann reaction to form 4-arylcoumarins [74].

Condensing agents in this reaction include sulfuric [1, 2, 4, 7, 9, 11, 16, 18, 20-22, 24, 26-28, 30, 32, 33, 35, 36, 40, 44, 49, 52-55, 59, 60, 61, 63, 66-73], phosphoric [5, 45], and trifluoroacetic acids [10], phosphoryl chloride in benzene [25], phosphorus pentoxide [34, 36, 37], boron trifluoride etherate [15, 29, 43], zinc chloride [1, 2, 33], a solution of HCl in absolute ethanol [3, 6, 8, 11-13, 31, 38, 39, 41, 45, 47-50, 57, 58, 61, 62, 65, 69], and HF [19].

Because of the simplicity and availability of reagents, this reaction is used more often than any other method to prepare polysubstituted natural neoflavones and their synthetic analogs.

Perkin condensation

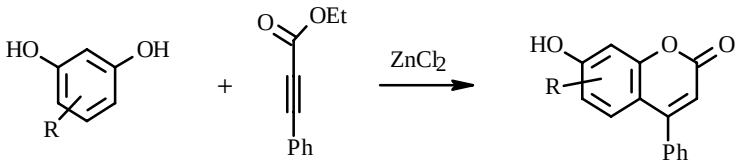
The Perkin reaction is also used to synthesize natural and synthetic neoflavones with complicated structures. The structures of the products from condensation of *o*-hydroxyarylketones and anhydrides of the corresponding acids in the presence of base depend on many factors. The starting materials for synthesizing substituted 4-arylcoumarins **1** are *o*-hydroxybenzophenones of various structure and acetic anhydride in the presence of potassium or sodium acetates [34, 37, 58, 75-94].



1

Syntheses based on propargylic acids

Condensation of polyphenols and the ethyl ester of phenylpropiolic acid in the presence of anhydrous zinc chloride gives the corresponding 4-phenylcoumarins **2** in low yields [95, 96].

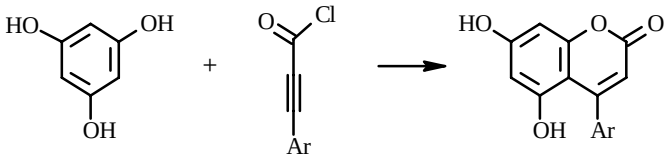


2

The condensing agent in this synthesis can also be concentrated sulfuric acid [95], 80% H_2SO_4 [97], P_2O_5, and trifluoroacetic acid [98, 99]. Condensation of 3,5-dimethoxyphenol and ethylphenylpropiolate in the presence of palladium acetate and sodium acetate in formic acid gave 5,7-dimethoxy-4-phenylcoumarin in 69% yield [100]. Reaction of the corresponding phenols and phenylpropiolic acids in the presence of montmorillonite K-10 and a catalytic amount of conc. H_2SO_4 gave with microwave irradiation substituted 4-phenylcoumarins in high yields [101].

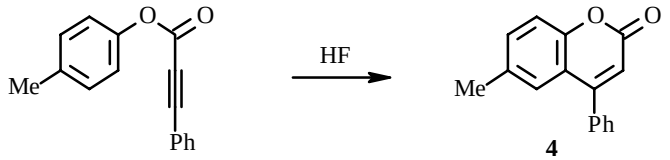
The catalysts for condensation of polyphenols and phenylpropiolic acid were polyphosphoric acid (PPA) [102-106], BF_3 etherate, HCl or HBr [107], P_2O_5 in methanesulfonic acid [108], and a mixture of PPA and thallium triacetate [109].

Reaction of phloroglucinol and acid chlorides of arylpropiolic acids in nitrobenzene in the presence of montmorillonite K-10 at room temperature for 12 h gave 5,7-dihydroxy-4-arylcoumarins **3** in high yields (74-85%) [110].



3

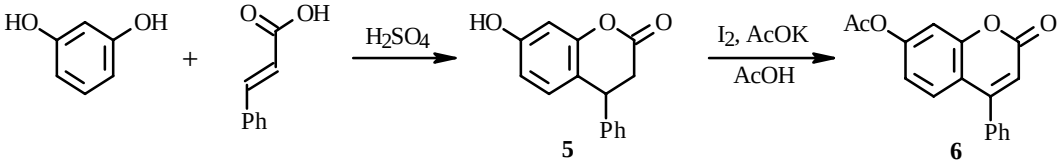
Cyclization of *p*-toluylphenylpropiolate using HF at 0°C formed 6-methyl-4-phenylcoumarin (**4**) [19].



4

Ponndorf reaction

The Ponndorf reaction of phenols with maleic or fumaric acids in the presence of H_2SO_4 at 150-160°C produces 3,4-dihydrocoumarins. For example, 3,4-dihydro-7-hydroxy-4-phenylcoumarin (**5**) was synthesized using cinnamic acid and resorcinol [111]. The condensing agents were PPA [105] and conc. H_2SO_4 [112]. The yields of coumarins increased in experiments with HCl because a significant quantity of sulfonation products formed if the condensation was carried out with H_2SO_4 [112]. Dehydrogenation of 3,4-dihydrocoumarin **5** by iodine and KOAc in boiling acetic acid gave 7-acetoxy-4-phenylcoumarin (**6**) [111].



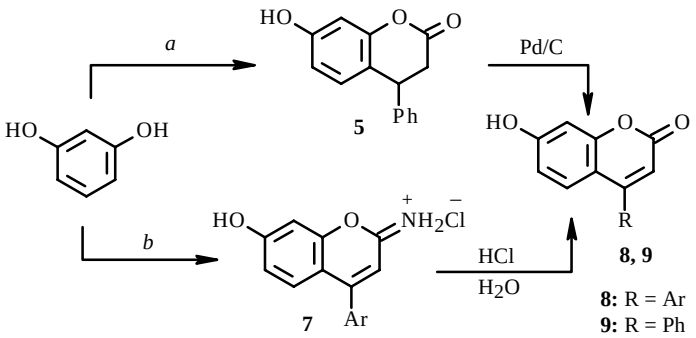
5 **6**

On the other hand, 3,4-dihydro-4-phenylcoumarins can be prepared in high yields by reacting substituted phenols and cinnamic acids in the presence of montmorillonite K-10 with microwave irradiation [101].

Condensation of resorcinol and methylcinnamate in the presence of anhydrous $AlCl_3$ and HCl gave 3,4-dihydrocoumarin **5**, dehydrogenation of which with heating in diphenyl ether with Pd gave 7-hydroxy-4-phenylcoumarin [113]. Sulfur was also used for the dehydrogenation [114].

Houben-Hoesch reaction

The Houben-Hoesch synthesis with aroylacetonitriles gives hydrochlorides of iminocoumarins **7**, acid hydrolysis of which produces 4-arylcoumarins **8** in high yields [115-121].



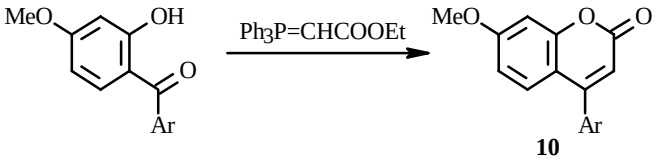
a. PhCH=CHCN, $ZnCl_2$, HCl; *b*. $PhCOCH_2CN$, $ZnCl_2$, HCl

Using ketimines of aroylacetonitriles in the Houben-Hoesch reaction gives the same results [122].

Condensation of resorcinol and the nitrile of cinnamic acid in the presence of $ZnCl_2$ or $AlCl_3$ and HCl gave 3,4-dihydrocoumarin **5** [123, 124], dehydrogenation of which with heating in diphenyl ether with 10% Pd on C gave 7-hydroxy-4-phenylcoumarin (**9**) [124].

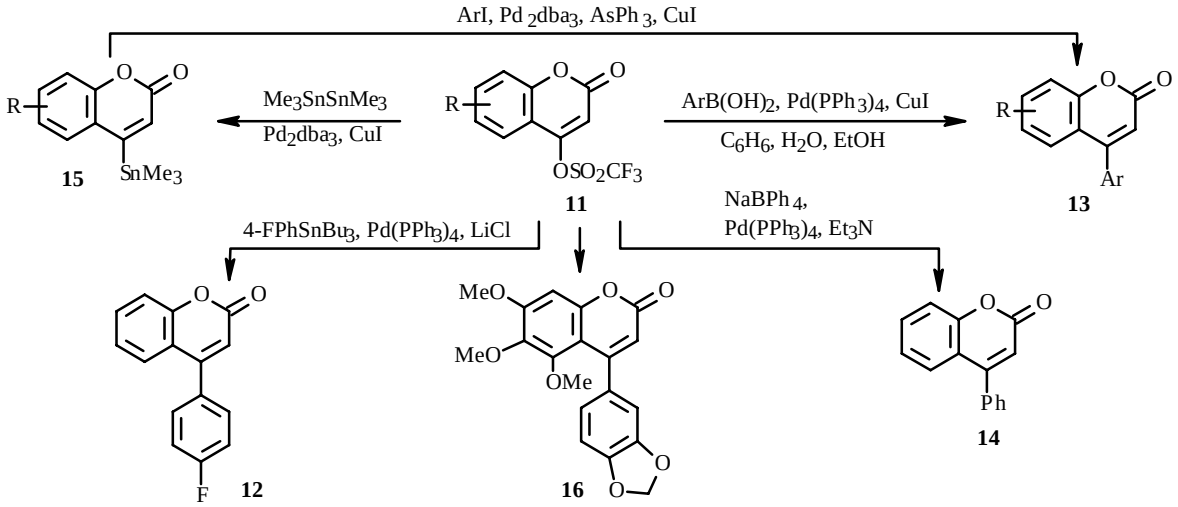
Wittig reaction

The method for synthesizing neoflavones that is based on the Wittig reaction includes condensation of 2-hydroxybenzophenones and ethoxycarbonylmethylenetriphenylphosphorane in absolute benzene [125]. Methoxy derivatives of 4-phenylcoumarins **10** were prepared using 2-hydroxy-4-methoxybenzophenones as starting materials.



Arylation of coumarins at the 4-position

Several methods for preparing polysubstituted 4-phenylcoumarins that are based on direct arylation using organometallic reagents of coumarins activated at the 4-position have been developed recently. 4-Trifluoromethanesulfonyloxycoumarins **11** are very convenient starting materials for synthesizing neoflavones. Thus, 4-(4-fluorophenyl)coumarin (**12**) was prepared in 79% yield by heating **11** (R = H) and tri-*n*-butyl-(4-fluorophenyl)stannane in dioxane in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] [126]. The yields were 30-40% if Cu(I) chloride or iodide was used as the catalyst.



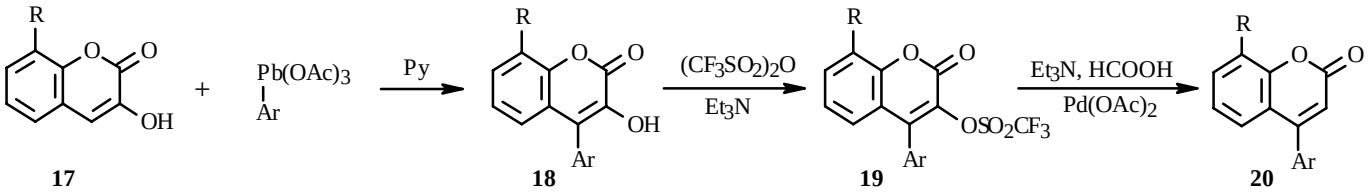
Polymethoxylated neoflavones **13** with cytotoxic activity were prepared in high yields (70-97%) under modified Suzuki-reaction conditions using substituted coumarins **11** and arylboronic acids in the presence of $Pd(PPh_3)_4$. CuI was used as a cocatalyst in the reaction [131, 127].

Reaction of **11** (R = H) and tetraphenylborate in the presence of $Pd(PPh_3)_4$ and triethylamine gave 4-phenylcoumarin (**14**) in 55% yield [128].

4-Stannylcoumarins **15** prepared by reaction of hexamethyldistannane and **11** in the presence of tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) and CuI have been used to prepare neoflavones [129]. Reaction of **15** and aryliodides in the presence of Pd_2dba_3, triphenylarsine, and CuI gave 4-arylcoumarins **13** in 67-81% yields.

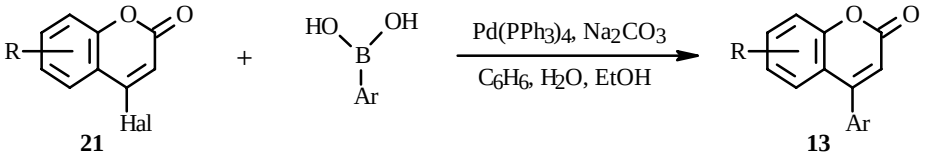
Using **11** and tributyl-3,4-methylenedioxyphenylstannane in the Stille reaction formed neoflavone **16** in 63% yield [127].

The reaction of 3-hydroxycoumarins **17** and arylleadtriacetates in $CHCl_3$ in the presence of pyridine at 40-60°C produced 4-aryl-3-hydroxycoumarins **18** in 58-92% yields. Treatment of these with trifluoromethanesulfonic acid anhydride in CH_2Cl_2 in the presence of triethylamine gave the corresponding triflates **19**. Reduction of the triflates by formic acid and triethylamine in the presence of palladium diacetate formed 4-arylcoumarins **20** [130].



17 **18** **19** **20**

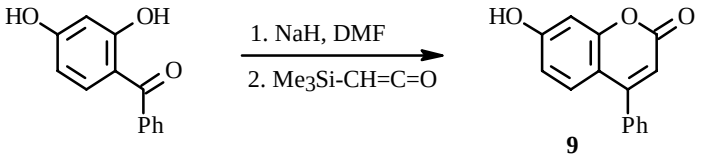
A method for preparing neoflavones that was based on the Suzuki reaction was also developed. Reaction of arylboronic acids with 4-chloro- or 4-bromocoumarins **21** in the presence of $Pd(PPh_3)_4$ and aqueous Na_2CO_3 solution gave 4-phenylcoumarins **13** in 72-95% yields [131].



21 **13**

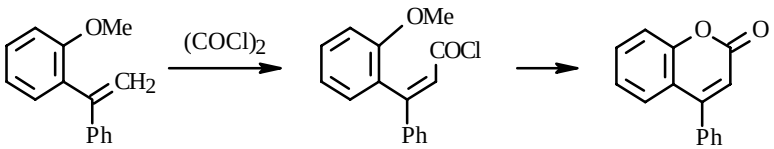
Other methods for synthesizing 4-arylcoumarins

Among the other methods used to construct the 4-phenylbenzopyran-2-one ring, the one-step conversion of *o*-acylphenols into coumarins should be mentioned. Thus, reaction of 2,4-dihydroxybenzophenone with NaH in DMF formed the phenoxide ion, which reacted with trimethylsilylketene to give 7-hydroxy-4-phenylcoumarin **9** in 90% yield [132].



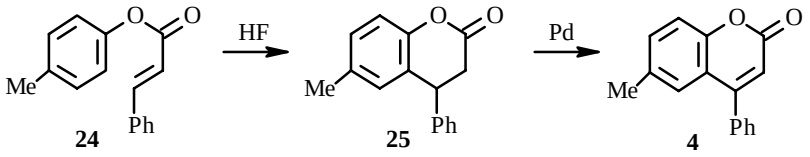
9

Ethylene derivatives have also been used to synthesize 4-phenylcoumarins. Thus, reaction of 1-phenyl-1-(*o*-anisyl)ethylene **22** with oxalyl chloride formed the acid chloride of β-phenyl-β-(*o*-anisyl)acrylic acid **23**, which cyclized into 4-phenylcoumarin **14** in 60% yield [133].



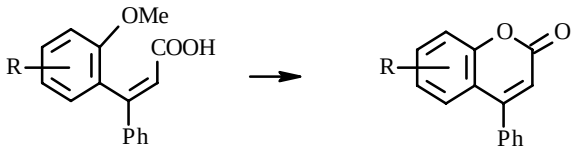
22 **23** **14**

Treatment of *p*-toluylcinnamate **24** with HF at 100°C produced dihydrocoumarin **25**, heating of which with palladium black formed 6-methyl-4-phenylcoumarin (**4**) [19].



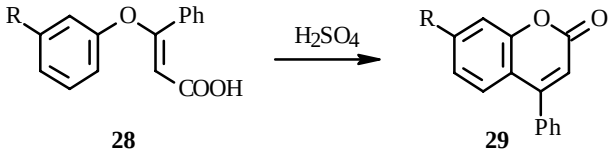
24 **25** **4**

Neoflavones **26** were prepared by cyclization of substituted 3-(2-methoxyphenyl)-3-phenylacrylic acids **27** using acetyl chloride [7, 134] or HI [135].



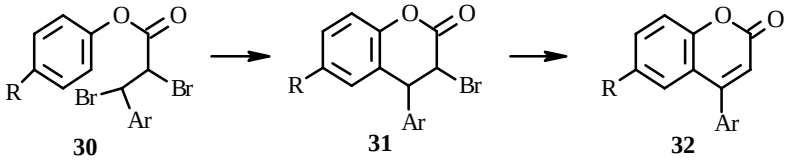
27 **26**

It should be noted that substituted *β*-phenoxyacrylic acids **28** underwent an unusual rearrangement into the corresponding 4-phenylcoumarins **29** upon reaction with 80-90% H_2SO_4 [136].



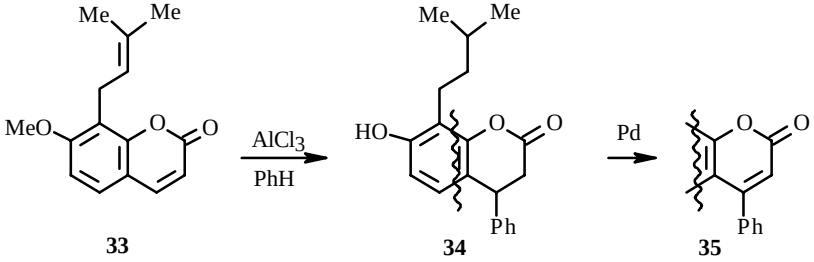
28 **29**

Treatment of phenyl esters of 2,3-dibromo-3-arylpropanoic acids **30** with conc. H_2SO_4 or $AlCl_3$ in chlorobenzene formed 4-aryl-3-bromo-3,4-dihydrocoumarins **31**, dehydrobromination of which by triethylamine in $CHCl_3$ gave 4-arylcoumarins **32** [137].



30 **31** **32**

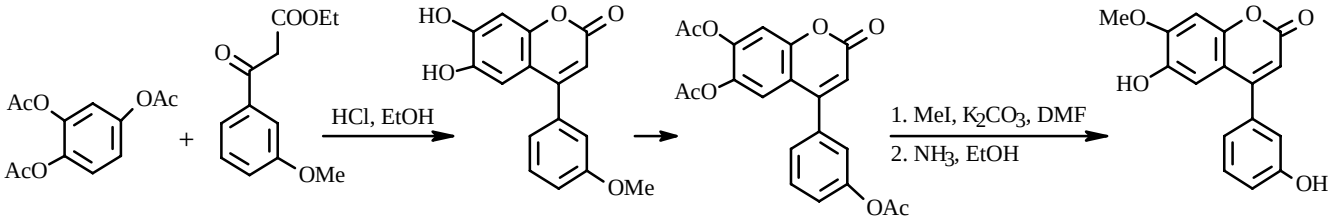
Osthole **33** gave under Friedel-Krafts conditions a mixture of products, one of which was 3,4-dihydro-4-phenylcoumarin **34**, dehydrogenation of which in the presence of 10% Pd on C in diphenyl ether gave 4-phenylcoumarin **35** [138].



33 **34** **35**

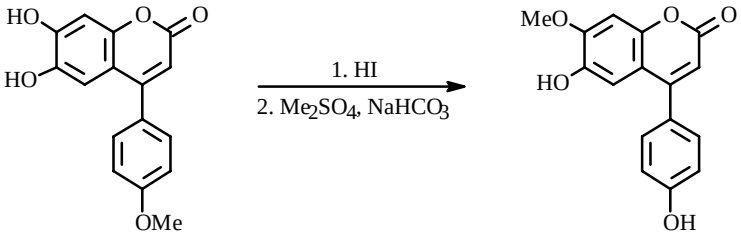
2. SYNTHESIS OF NATURAL NEOFLAVONES

One feature of natural neoflavones is their polyfunctional nature, namely, the presence of hydroxyls, methoxyls, prenyls, and acyls; glycoside units; and annelated furan and pyran heterocycles. Therefore, definite tactics and strategies are needed to synthesize such systems. For example, stevenin **36** was prepared by the Pechmann reaction starting from 1,2,4-triacetoxybenzene [58]. Coumarin **37** transformed into triacetate **38** upon successive treatment with HI and acetic anhydride in pyridine. Alkylation of intermediate **38** by methyl iodide in DMF in the presence of potash gave a mixture of diacetoxymethoxy-4-phenylcoumarins; its hydrolysis by aqueous ammonia produced a mixture of hydroxy derivatives, from which chromatography isolated stevenin **36** [58].



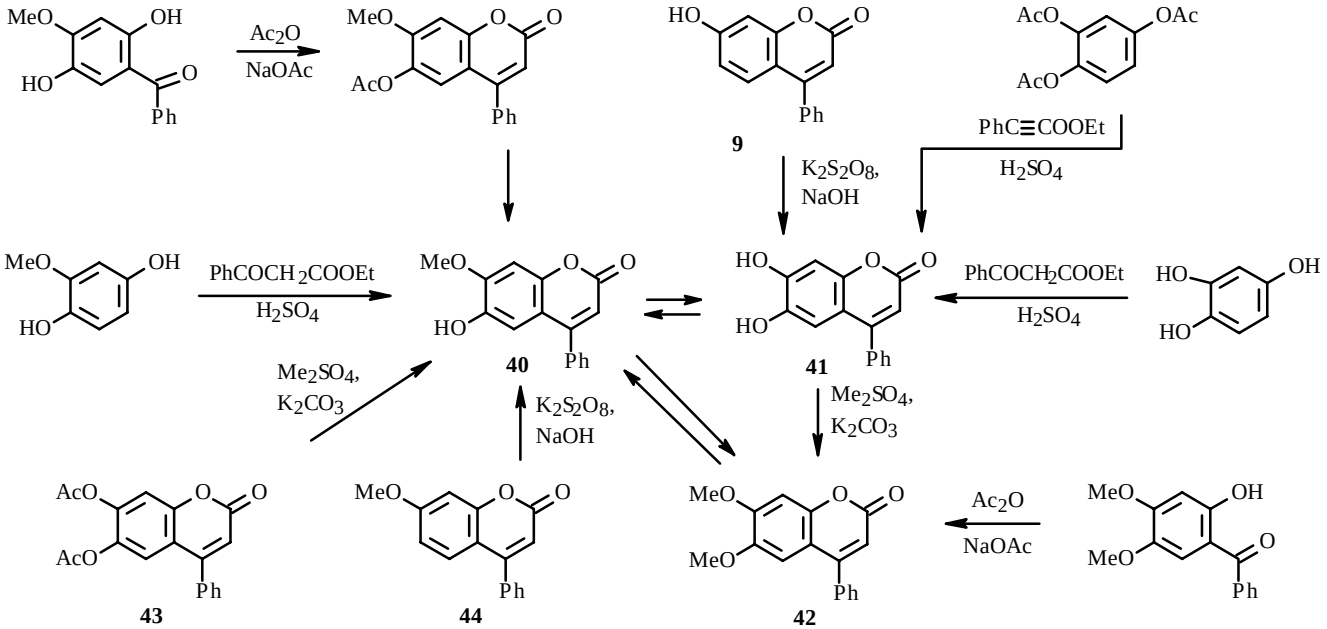
37 **38** **36**

Stevenin **36** and melanettin **39** were prepared by Pechmann condensation of 2-methoxyhydroquinone with 3-benzyl- and 4-benzyloxybenzoylacetoacetate, respectively, in absolute ethanol saturated with dry HCl [61]. Melanettin was also prepared by an alternate route as one of the products of partial methylation of 6,7-dihydroxy-4-(4′-hydroxyphenyl)coumarin by dimethylsulfate in the presence of $NaHCO_3$ [12].

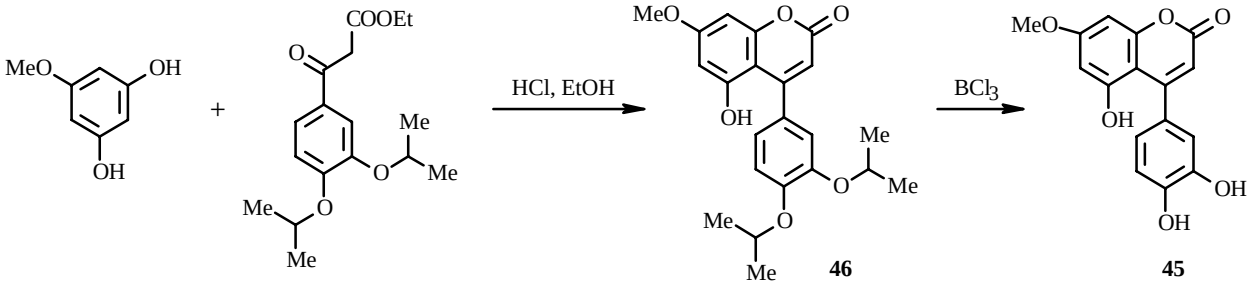


39

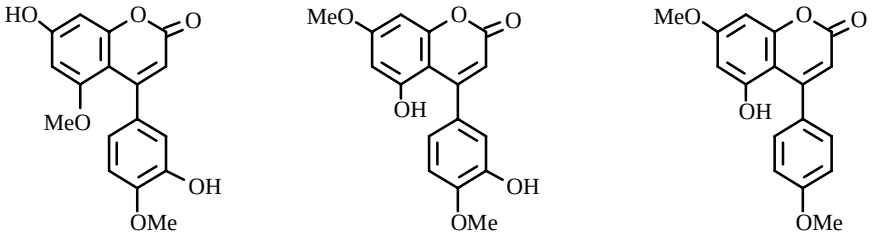
Considering the similarity of the dalbergin **40**, nordalbergin **41**, and O-methyldalbergin **42** structures, several methods for mutual conversion of these related natural compounds were developed. Dalbergin **40** was prepared in 65% yield by condensation of methoxyhydroquinone and ethylbenzoylacetate in the presence of conc. H_2SO_4 [60]. Demethylation of neoflavone **40** by BBr_3, 48% HBr, or anhydrous $AlCl_3$ produced **41**, which was also prepared by Pechmann condensation starting from 1,2,4-trihydroxybenzene [56, 60]. Methylation of **41** [56] and **40** [139] by dimethylsulfate in the presence of potash gave **42**. 2,5-Dihydroxy-4-methoxy- and 2-hydroxy-4,5,-dimethoxybenzophenones were converted by the Perkin reaction into the corresponding neoflavones **40** and **42** [90]. Partial demethylation of **42** by a mixture of HBr and glacial acetic acid or HI in acetic anhydride produced **40** [90]. Neoflavone **40** was prepared by partial methylation of nordalbergin diacetate **43** [57] and **41** using dimethylsulfate in the presence of $NaHCO_3$ and by oxidation of 7-methoxyneoflavone **44** using potassium persulfate in NaOH solution [140]. Coumarin **41** was formed by oxidation of **9** using potassium persulfate in NaOH solution [140] and condensation of hydroquinone triacetate and the ethyl ester of phenylpropiolic acid [95].



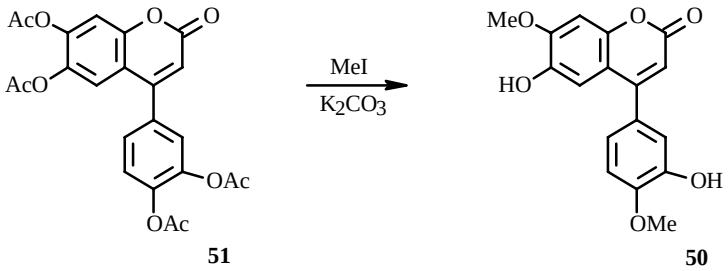
The structure of **45** isolated from *Coutarea hexandra* was finally proved by synthesis. Pechmann condensation of monomethylphloroglucinol and ethyl-3,4-diisopropyloxybenzoylacetate produced a mixture of products, one of which was coumarin **46**. Removal of the isopropyl from **46** by BCl_3 in CH_2Cl_2 at -70°C formed **45** [47].



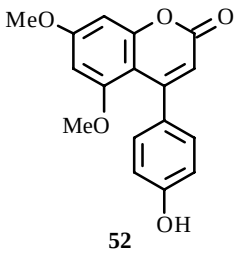
Reaction of ethyl-4-methoxy-3-benzyloxybenzoylacetate and phloroglucinol monomethyl ester in the presence of dry HCl in absolute ethanol formed a mixture of the two isomeric natural 4-phenylcoumarins seshadrin **47** and neoflavone **48**, which were separated chromatographically [48, 49]. 5-Hydroxy-7,4′-dimethoxyneoflavone **49**, which is produced by *Exostema acuminatum*, were prepared as one of the Pechmann-condensation products of 5-methoxyresorcinol and 4-methoxy-benzoylacetate [49].



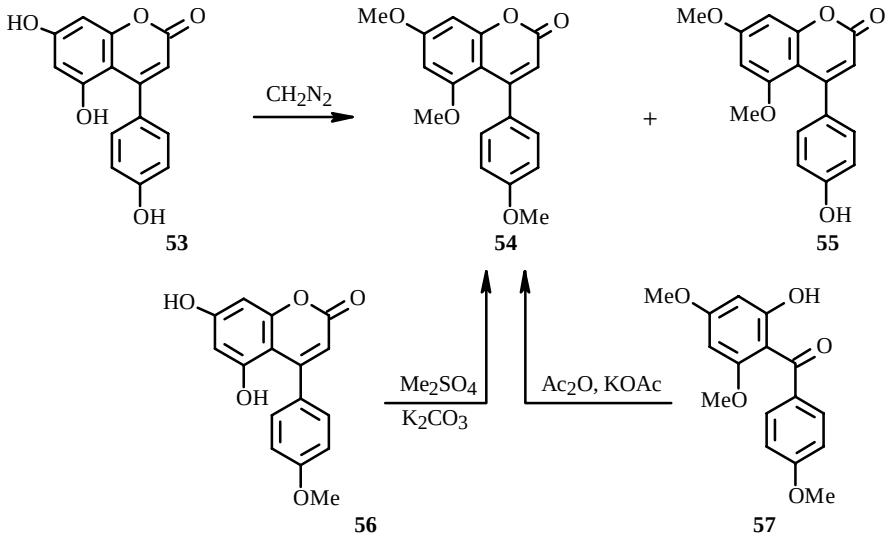
Melannein **50** was formed as one of the products of partial methylation of 6,7,3′,4′-tetraacetoxyneoflavone **51** using methyl iodide in the presence of potash [57]. Another version of the total synthesis of **50** was based on Pechmann condensation of 2-methoxyhydroquinone and ethyl-4-methoxy-3-benzyloxybenzoylacetate in the presence of dry HCl in absolute ethanol [62].



5-Methoxyresorcinol was used as the starting material to synthesize 4′-hydroxy-5,7-dimethoxy-4-phenylcoumarin **52**, which was isolated from *C. hexandra* and *E. mexicanum* [49].

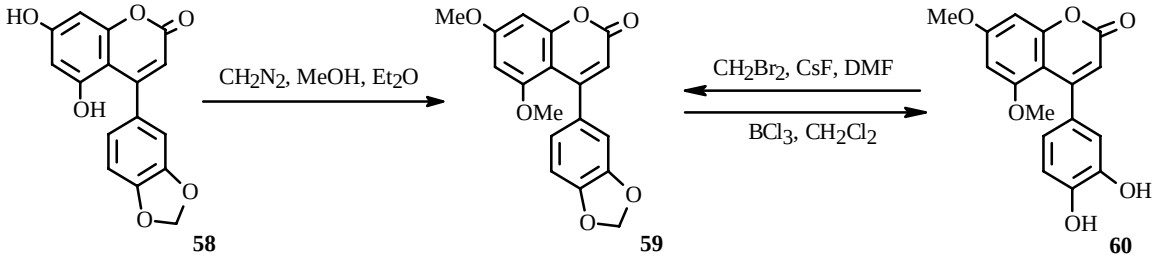


Pechmann condensation of ethyl-4-benzyloxybenzoylacetate and phloroglucinol produced 5,7,4′-trihydroxyneoflavone **53**, methylation of which using diazomethane gave 4-phenylcoumarins **54** and **55**, which were isolated from *C. hexandra* [39, 41]. Neoflavone **54** was also isolated by condensation of ethyl-4-methoxybenzoylacetate and phloroglucinol in absolute ethanol in the presence of dry HCl with subsequent alkylation of **56** using dimethylsulfate in the presence of potash [39, 41]. An alternate approach was based on Perkin condensation of the corresponding benzophenone **57** [41].



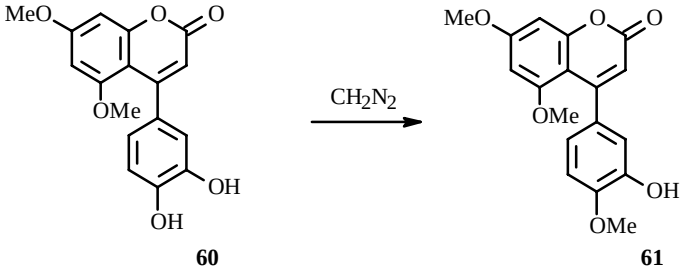
53 **54** **55** **56** **57**

Pechmann condensation of phloroglucinol and ethyl-3-(1,3-benzodioxol-5-yl)-3-oxopropanoate and subsequent methylation of the resulting 5,7-dihydroxycoumarin **58** using diazomethane in methanol:diethylether gave 4-phenylcoumarin **59** [41]. Another version of the synthesis included alkylation of **60** using dibromomethane [141]. Partial demethoxylation of **60** using BCl_3 in CH_2Cl_2 formed **59** [41].



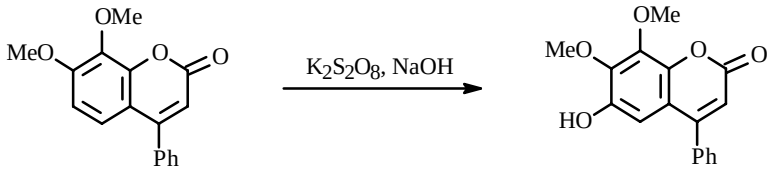
58 **59** **60**

3′-Hydroxy-5,7,4′-trimethoxyneoflavone **61** appeared as a product of partial methylation of **60** using diazomethane in methanol:diethylether [142].



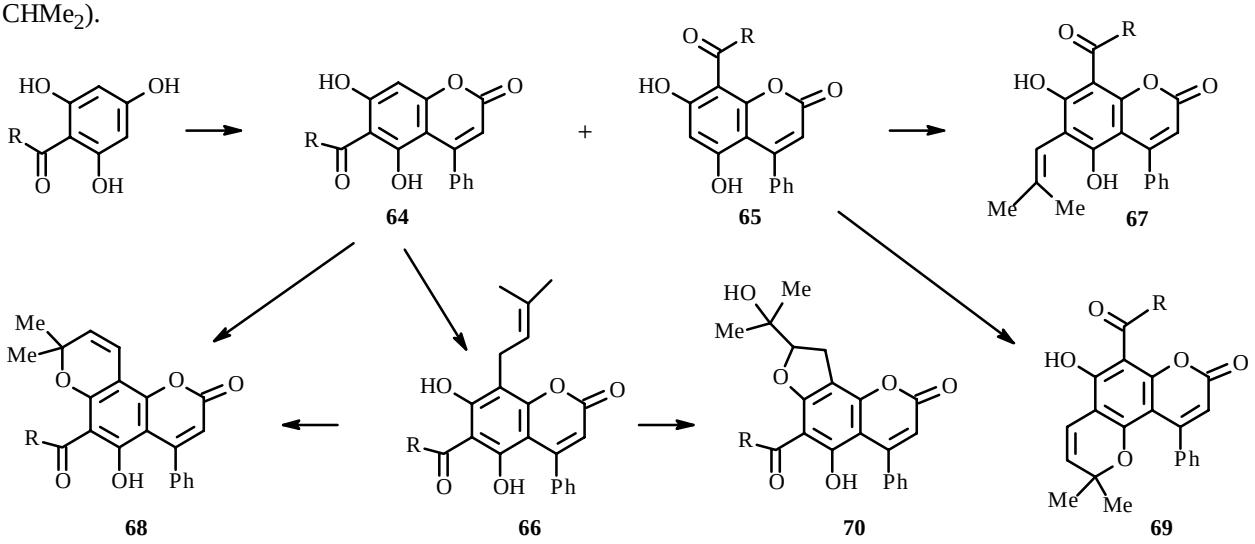
60 **61**

Kulmannin **62** was prepared by oxidation of 4-phenylcoumarin **63** using potassium persulfate in NaOH solution [63]. 7,4′-Dimethoxyneoflavone reacted analogously to form natural 6-hydroxy-7-methoxy-(4-methoxyphenyl)coumarin [12].



63 **62**

Good methods for synthesizing coumarins of the Mammea A series have been developed. Convenient synthons for preparing these are acylphloroglucinols of various structure [52-54]. Condensation of them with benzoylacetic ester in glacial acetic acid in the presence of conc. H_2SO_4 gave a mixture of 6- and 8-acylcoumarins **64** and **65**, which were separated chromatographically. C-prenylation into the aromatic ring of 4-phenyl-5,7-dihydroxy-6-isovalerylcoumarin (**64**, R = CH_2CHMe_2) using 2-methylbut-3-en-2-ol in BF_3 etherate gave mammeisin (**66**, R = CH_2CHMe_2) [53]. The 6-butyrylcoumarin (**66**, R = $CH_2CH_2CH_3$) was prepared analogously [54]. C-prenylation was also achieved by alkylation of **64** and **65** using 3,3-dimethylallyl bromide in KOH solution (10%) under a N_2 atmosphere [52]. This method prepared in low yields (20-22%) Mammea A/AA (mammeisin) (**66**, R = CH_2CHMe_2), mammea A/AB (**66**, R = $CHMeCH_2Me$), mammea A/AD (**66**, R = $CHMe_2$), mammea A/BA (**67**, R = CH_2CHMe_2), mammea A/BB (**67**, R = $CHMeCH_2Me$), and mammea A/BD (**67**, R = $CHMe_2$).



64 **65** **67**

68 **66** **70** **69**

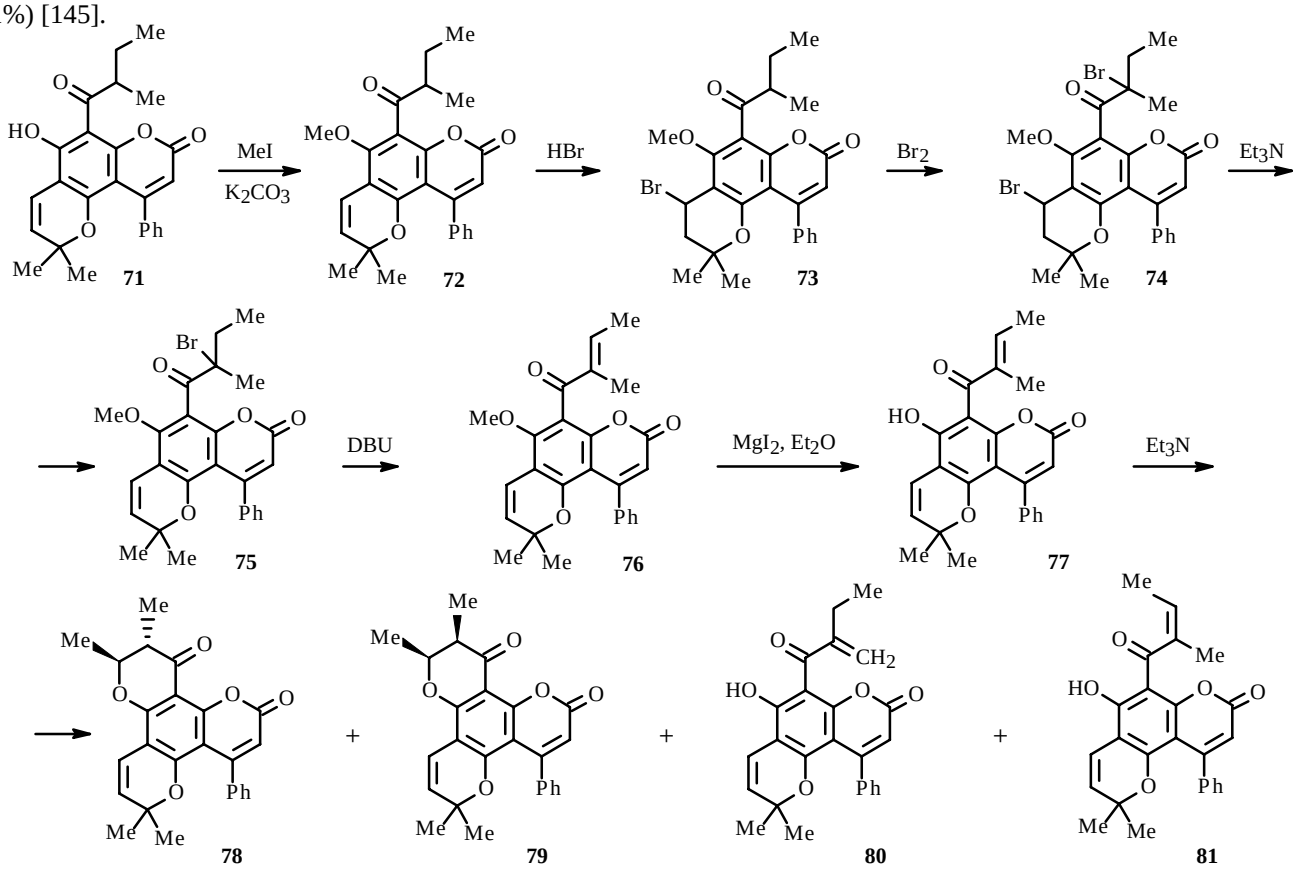
Several methods have been used to annelate the 2,2-dimethylpyran ring. Thus, oxidative cyclization of mammeisin (**66**, R = CH_2CHMe_2), neoflavone (**66**, R = $CH_2CH_2CH_3$), and mesuol (**66**, R = $CHMe_2$) using dichlorodicyanobenzoquinone (DDQ) at room temperature produced in high yields mammeigin (**68**, R = CH_2CHMe_2) [53, 143], 6-butyryl-5-hydroxy-4-phenylseselin (**68**, R = $CH_2CH_2CH_3$) [54], and mesuagin (**68**, R = $CHMe_2$) [53], respectively. Isomesuagin (**68**, R = $CHMe_2$) was prepared analogously using the corresponding coumarin (**65**, R = $CHMe_2$) [144].

An alternate synthesis of neoflavone (**68**, R = $CH_2CH_2CH_3$) included reaction of a coumarin (**66**, R = $CH_2CH_2CH_3$) with 3-methyl-2-butenal in pyridine [54]. Mammea A/BB cyclo D (ponnalide) (**69**, R = $CHMeCH_2Me$) and mammea A/AB cyclo D (MAB 5) (**68**, R = $CHMeCH_2Me$) were prepared by condensation of the corresponding 8-acylcoumarins and 1,1-dimethoxy-3-methylbutan-3-ol in dry pyridine [52, 145].

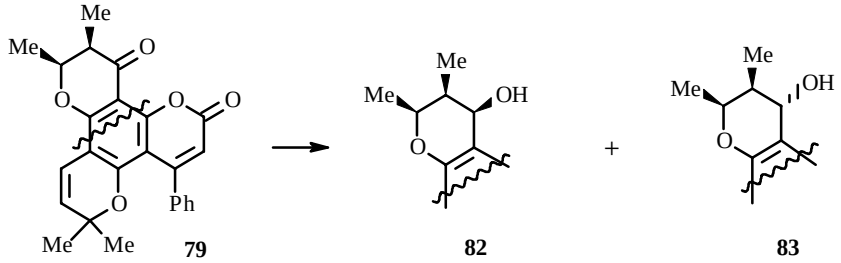
Mammea A/AA cyclo F (**70**, R = CH_2CHMe_2) and mammea A/AB cyclo F (**70**, R = $CHMeCH_2Me$), which contain a condensed dihydrofuran ring, were prepared by oxidative cyclization of mammea A/AA (mammeisin) (**66**, R = CH_2CHMe_2) and mammea A/AB (**66**, R = $CHMeCH_2Me$), respectively, using *m*-chloroperbenzoic acid in dry CH_2Cl_2 at room temperature [52, 146].

Several methods for synthesizing neoflavones of complicated structure that were isolated from natural sources have been developed. In these, ponnalide **71** and MAB 5 **87** were used as convenient synthons [145]. Alkylation of **71** using methyl iodide produced 5-methoxycoumarin **72**, which was converted using HBr in CCl_4 to 4-bromopyranocoumarin **73**. Intermediate **73** reacted with one Br equivalent to form dibromocoumarin **74**, storage of which with triethylamine at room temperature gave bromoacylpyranocoumarin **75**. Treatment of **75** with diazobicyclo[5.4.0]undecen-7-ene (DBU) at room temperature caused dehydrobromination to form the (*E*)-2-methylbut-2-enoyl derivative, which produced caliphyllolide **76** in 53% yield.

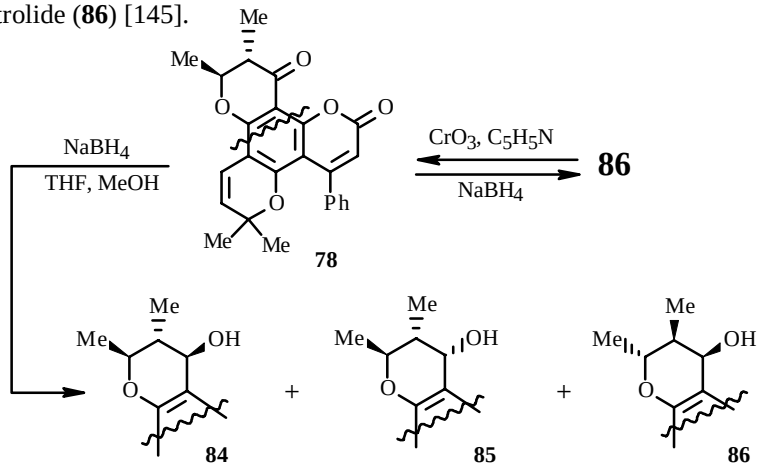
Demethylation of **76** using MgI_2:diethylether complex gave 5-hydroxycoumarin **77**, cyclization of which using triethylamine produced a mixture of (±)-inophyllum C (**78**, 39% yield), (±)-inophyllum E (**79**, 59% yield), and coumarins **80** (0.7%) and **81** (1%) [145].



Reduction of **79** using $NaBH_4$ gave a mixture of two chromanols, (±)-inophyllum A (**82**, 51%) and (±)-inophyllum D (**83**, 1%) [145].

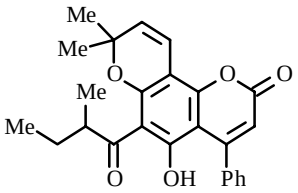


Reduction of **78** under analogous conditions formed (±)-inophyllum B (**84**, 28%) and a mixture of enantiomers of inophyllum P (**85**) and soulattrolide (**86**) [145].



Oxidation of **86** using CrO_3 in pyridine produced inophyllum C (**78**), reduction of which using $NaBH_4$ in methanol formed a mixture of **86** and its epimer [147].

MAB 5 (**87**) was transformed into coumarin **88**, (±)-tomentolide A (**89**), and its (±)-*cis*-isomer (**90**) [145]. The physical and spectroscopic constants of **88**, the structure of which was earlier ascribed to apetatolide, did not correspond with those of apetatolide reported in the literature. These data prompted a reexamination of the structure of apetatolide [145].



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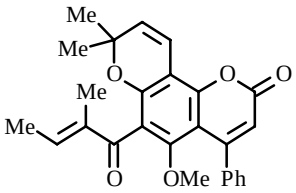
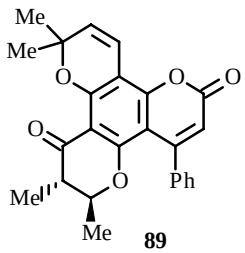


88



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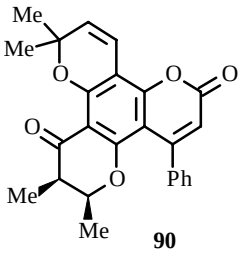
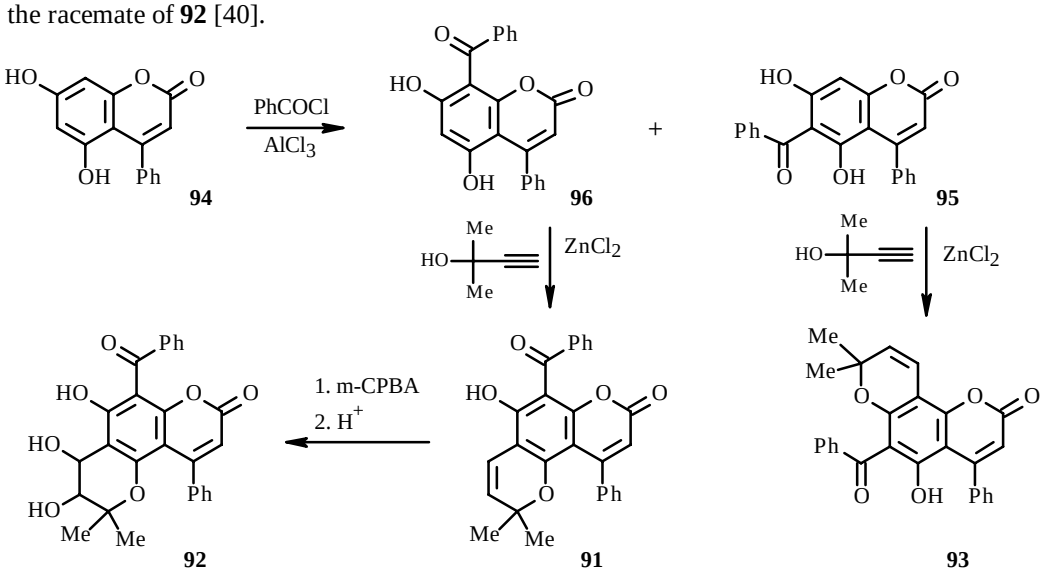


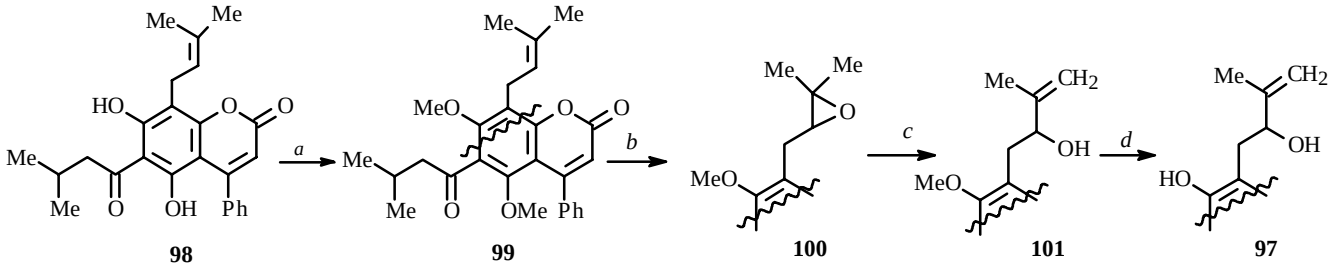
90

The biomimetic synthesis of calanone (**91**), the racemate of 7,8-dihydroxycalanone (**92**), and isocalanone (**93**) was carried out starting from 5,7-dihydroxy-4-phenylcoumarin (**94**), benzoylation of which using benzoylchloride in a CS_2:nitrobenzene mixture and in the presence of $AlCl_3$ produced a mixture of 6- and 8-benzoylcoumarins **95** and **96** [40]. Condensation of **95** and **96** with 2-methylbut-3-yn-2-ol in the presence of $ZnCl_2$ caused annelation of the 2,2-dimethylpyran ring to form **91** and **93**. Epoxidation of **91** using *m*-chloroperbenzoic acid (*m*-CPBA) produced the 7,8-epoxide, hydrolysis of which formed the racemate of **92** [40].



94 **96** **95** **92** **91** **93**

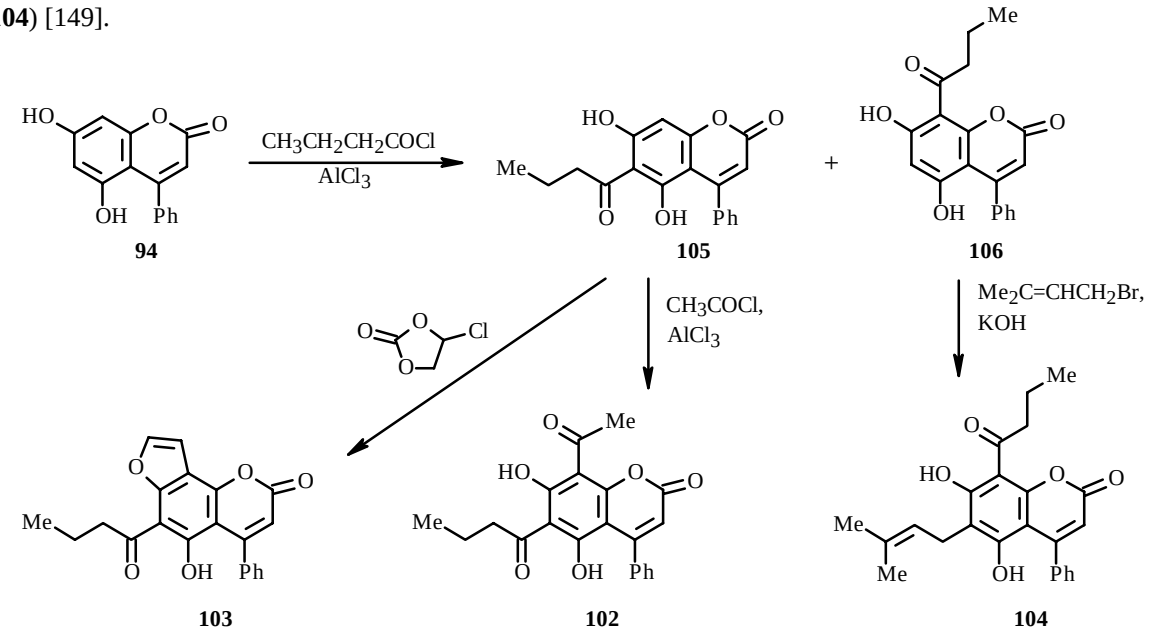
Mammeisin (**98**) was used as starting material for the synthesis of disparinol A (**97**) [148]. Oxidation of dimethyl ether **99** using *m*-CPBA gave epoxide **100**, rearrangement of which using aluminum isopropoxide in xylene gave a 2-hydroxy-3-methylbut-3-enyl substituent in coumarin **101**. Demethylation of the coumarin using BBr_3:Me_2S produced **97** [148].



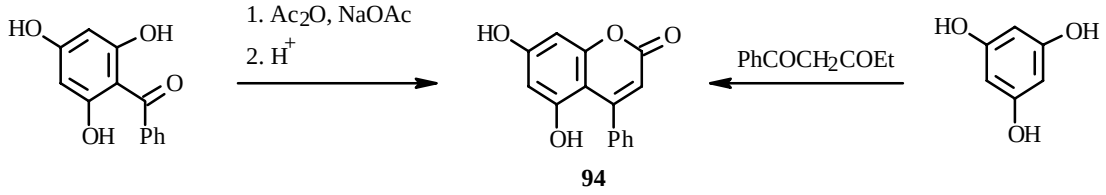
98 **99** **100** **101** **97**

a. Me_2SO_4, K_2CO_3; *b*. m-CPBA; *c*.Al(OiPr)$_3$; *d*. $Me_2S\cdot BBr_3$

The starting material for the synthesis of racemosone (**102**), furanoracemosone (**103**), and mammea A/BC (**104**) was 5,7-dihydroxy-4-phenylcoumarin (**94**) [149], Friedel-Krafts acylation of which produced 6- and 8-butanoylcoumarins **105** and **106**. Acylation of **105** using acetylchloride in the presence of $AlCl_3$ formed **102** in 11% yield. It should be noted that the synthesis of **103** is interesting and convenient. It consists of heating a mixture of **105** and 4-chloro-1,3-dioxolan-2-one at 150-165°C. C-prenylation of **106** using 3-methylbut-2-enylbromide in the presence of KOH solution (10%) produced mammea A/BC (**104**) [149].



Serratin (**94**) was readily prepared by reacting phloroglucinol and benzoylacetic ester using Pechmann conditions or by Perkin condensation of 2,4,6-trihydroxybenzophenone and acetic anhydride [92].

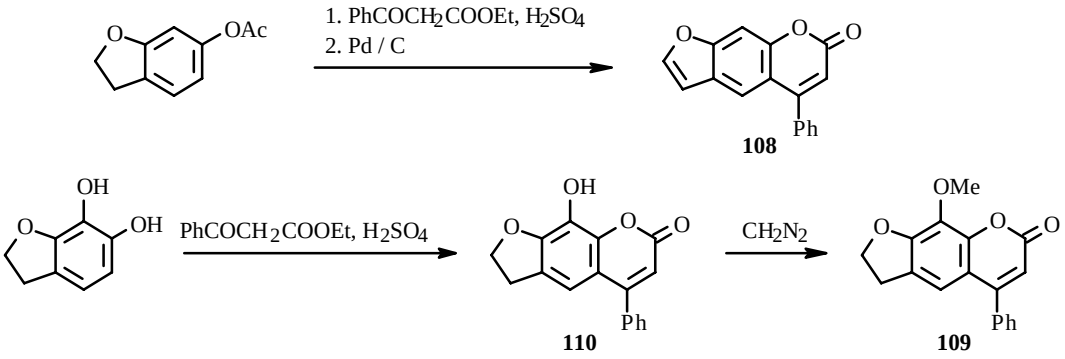


3. METHODS OF MODIFYING 4-ARYLCOUMARINS

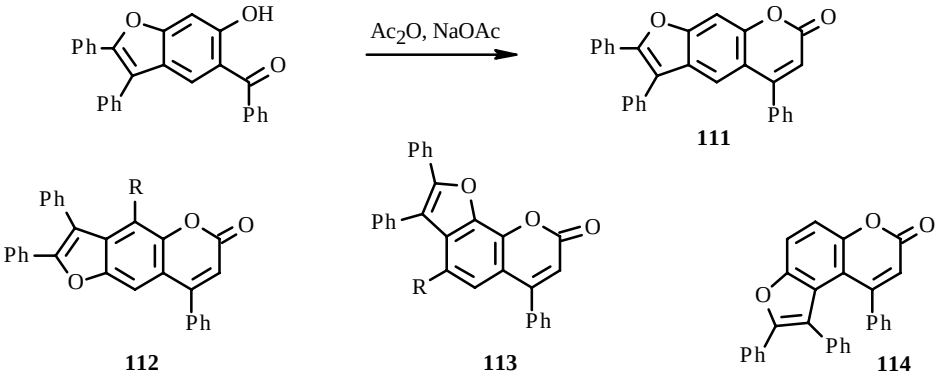
Natural neoflavones and their synthetic analogs are considered to have unique preparative potential because they contain several reactive centers. They can act as convenient synthons for synthesizing various functionalized derivatives and condensed heterocyclic systems based on them. The methods for modifying neoflavones can be divided into several categories, the most important of which are annelation of the heterocycles, substitution in the aromatic ring, and reaction of the hydroxyls.

Coumarins condensed with heterocycles such as furan, pyran, and others are often found in the plant world. Therefore, methods for annelating these structural fragments to the coumarin system are definitely of interest for preparing natural compounds and their structural analogs.

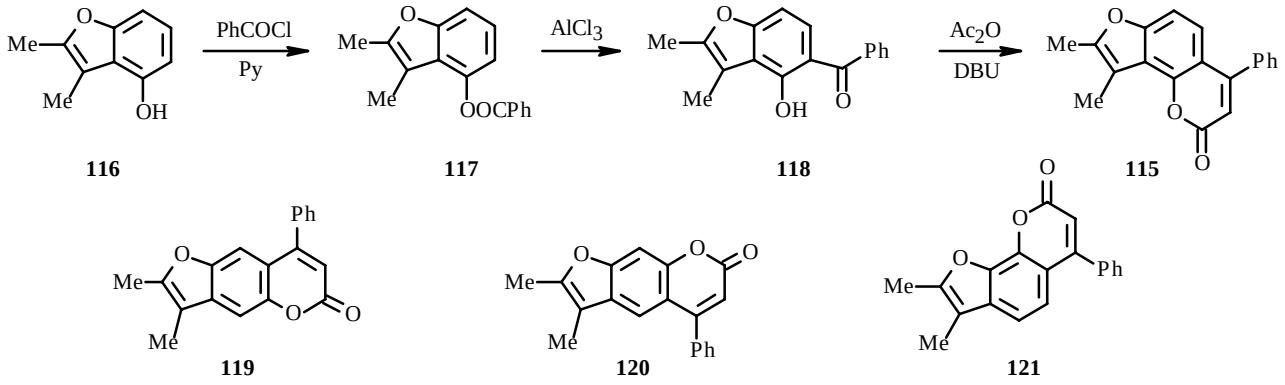
Furocoumarins based on 4-phenylbenzopyran-2-one have been prepared by various methods that can be divided into two groups: 1) attachment of a coumarin system to a benzofuran derivative and 2) annelation of a furan ring to the benzopyran system. Thus, Spaeth synthesis of linear furocoumarins consists of condensation of 6-acetoxycoumaran and ethylbenzoylacetate under Pechmann conditions with subsequent dehydrogenation of dihydrofurocoumarin **107** by Pd in diphenylether. Transformations such as these produced 4-phenylpsoralen (**108**) [72]. 4-Phenyldihydroxanthotoxin (**109**) was prepared using 2,3-dihydro-1-benzofuran-6,7-diol and subsequent methylation of **110** using diazomethane [73].



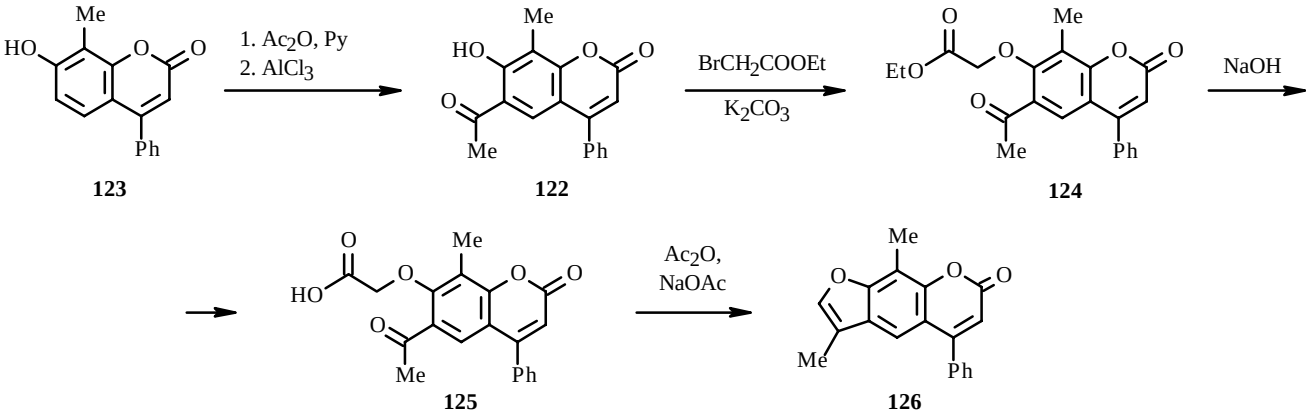
Several methods in which the starting materials for constructing the furocoumarin system were substituted *o*-hydroxybenzophenones have been developed. Thus, Perkin condensation of *o*-hydroxy-2,3-diphenylbenzofuranylphenylketone produced triphenylfurocoumarin **111**. This transformation was also used successfully to synthesize linear and angular furocoumarins **112-114** [150-154].



A convenient synthon for synthesizing 2,3-dimethylfurocoumarin **115** is 4-hydroxy-2,3-dimethylbenzofuran **116** [155]. Treatment of **116** with benzoylchloride in pyridine formed **117**. Benzoylation was also carried out using benzoic acid in the presence of PPA at 90-100°C. Fries rearrangement of **117** prepared from the benzofuran by $AlCl_3$ at 120-130°C gave *o*-hydroxyketone **118**, which reacted readily with acetic anhydride in the presence of DBU to give furocoumarin **115** [155]. Similar transformations were used to synthesize isomeric furocoumarins **119-121**.

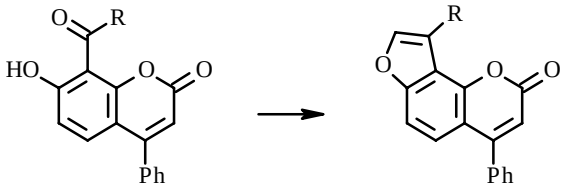


6-Acylcoumarins have served as key intermediates for constructing substituted furocoumarins. 6-Acetyl-4-phenylcoumarin (**122**) was prepared by acetylation of 7-hydroxycoumarin **123** with subsequent Fries rearrangement using $AlCl_3$. Alkylation of **122** produced ester **124**. The key step in this synthesis was Perkin cyclization of **125**, which was prepared by alkaline hydrolysis of **124**. The transformations formed furocoumarin **126** [24]. Analogous transformations were carried out using 6-propionyl- and 6-benzoyl-7-hydroxy-8-methyl-4-phenylcoumarin.



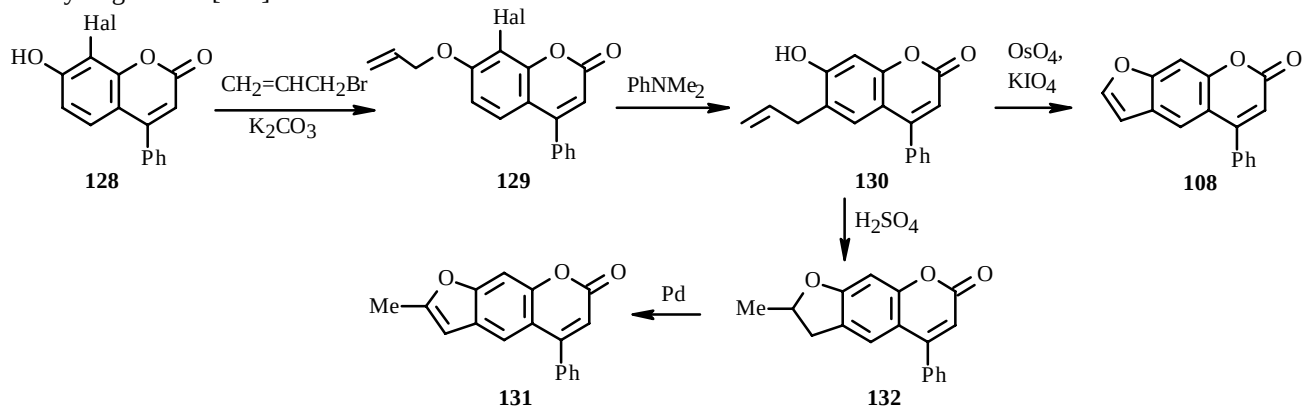
123 **122** **124** **125** **126**

A similar transformation was used to synthesize the angular furocoumarins **127** (R = Me, Ph) [156].



127

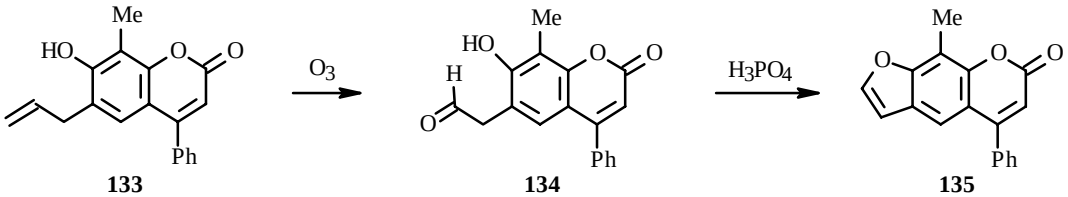
The Claisen rearrangement was used to synthesize 4-phenylpsoralens from 8-bromo- or 8-iodo-7-hydroxy-4-phenylcoumarins **128** [27, 157]. Alkylation of **128** produced the corresponding allyl ethers **129**, heating of which in N,N-dimethylaniline caused Claisen rearrangement with elimination of halogen to form 6-allylcoumarin **130**. Oxidative cyclization of **130** using OsO_4 and KIO_4 gave **108** [157]. Furocoumarin **131** was prepared by treating **130** with H_2SO_4 with subsequent dehydrogenation of **132** using 10% Pd on C in diphenylether [27]. DDQ in benzene was also used successfully for the dehydrogenation [158].



128 **129** **130** **108** **131** **132**

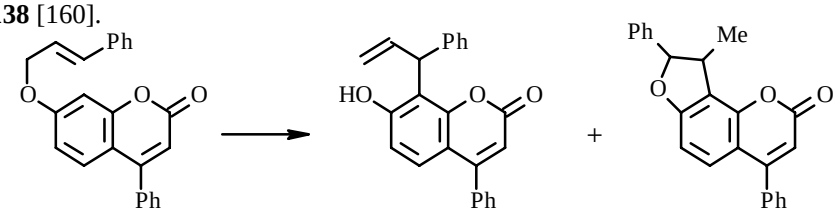
The analogous method using 7-hydroxy-8-methyl-4-phenylcoumarin as starting material isolated 2,9-dimethyl-5-phenylfuro[3,2-*g*]chromen-7-one [159].

Ozonolysis of 6-allylcoumarin **133** produced 6-acetaldehyde **134**, treatment of which with *ortho*-phosphoric acid caused cyclization into the corresponding furocoumarin **135** [159].



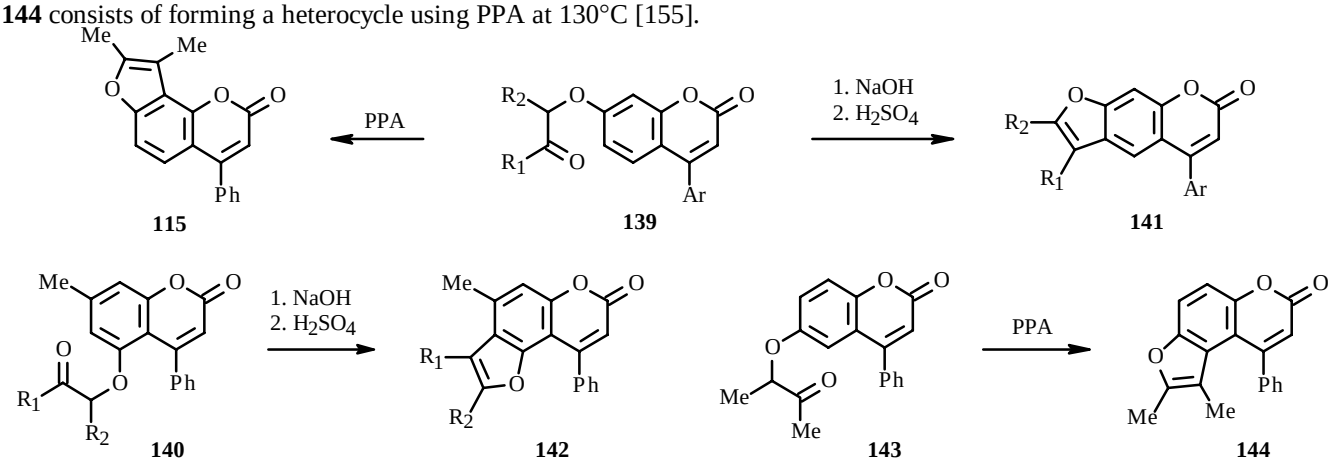
133 **134** **135**

Claisen rearrangement of 7-cinnamyloxy-4-phenylcoumarin **136** with boiling in *N*,*N*-dimethylaniline or heating in vacuo formed a mixture of two compounds, 7-hydroxy-8-(1-phenyl-2-propenyl)-4-phenylcoumarin (**137**) and dihydrofurocoumarin **138** [160].



136 **137** **138**

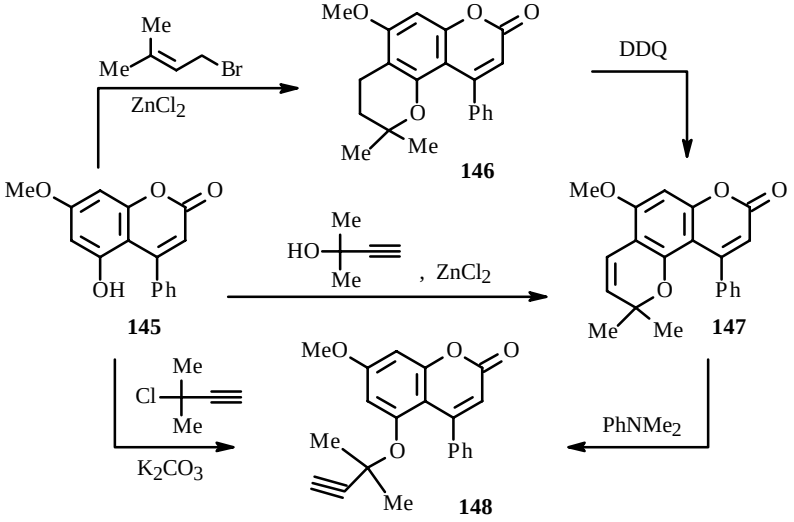
MacLeod cyclization is an effective method for synthesizing substituted linear and angular furocoumarins. Alkylation of 7-hydroxy- and 5-hydroxy-4-phenylcoumarins by α-haloketones produced the corresponding ketones **139** and **140**, heating of which in alkaline solutions caused smoothly and in high yields cyclization into the corresponding furocoumarins **141** and **142** [161-163]. Another method for transforming **139** and **143** into the corresponding angular dimethylfurocoumarins **115** and **144** consists of forming a heterocycle using PPA at 130°C [155].



115 **139** **141**

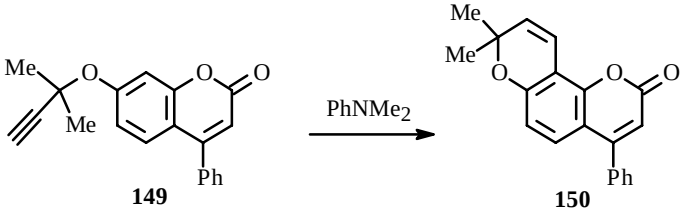
140 **142** **143** **144**

The wide range of methods for synthesizing pyranocoumarins is based on the ability to annelate the 2,2-dimethylpyran ring to 4-phenylcoumarin using various structural moieties, namely, both functionalized neoflavones and chromane derivatives. Several methods are known for constructing pyranocoumarins based on 4-arylcoumarins. For example, reaction of **145** and 3,3-dimethylallylbromide in the presence of anhydrous $ZnCl_2$ formed chromane **146**, dehydrogenation of which using DDQ caused transformation into pyranochromenone **147** [164]. Another synthesis of **147** is based on condensation of **145** and 2-methyl-3-butyn-2-ol in the presence of $ZnCl_2$ [164]. The propargyl ether of 4-phenylcoumarin **148**, which was prepared by etherification of **145** using 3-chloro-3-methyl-1-butyne, underwent Claisen rearrangement with heating in N,N-dimethylaniline with subsequent cyclization into pyranocoumarin **147** [165].



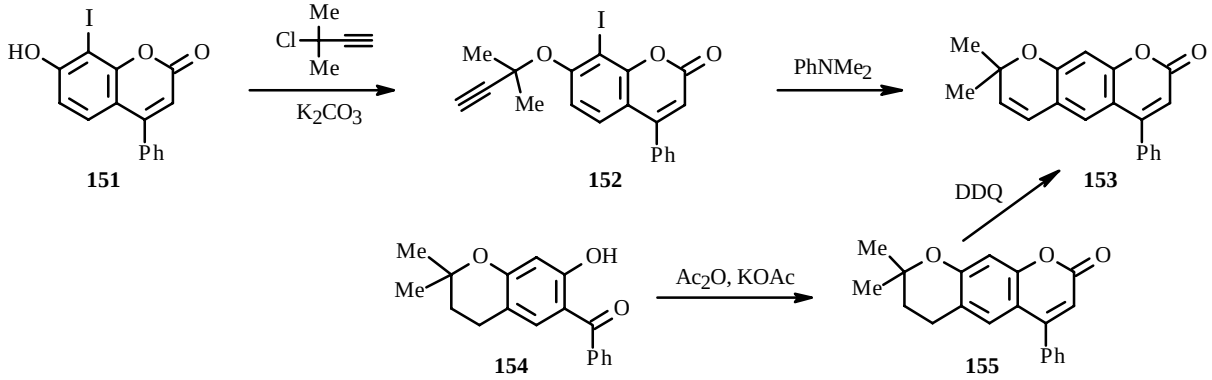
145 **146** **147** **148**

Claisen rearrangement of ether **149** in N,N-dimethylaniline [165] or N,N-diethylaniline [166] produced exclusively angular pyranocoumarin **150**.



149 **150**

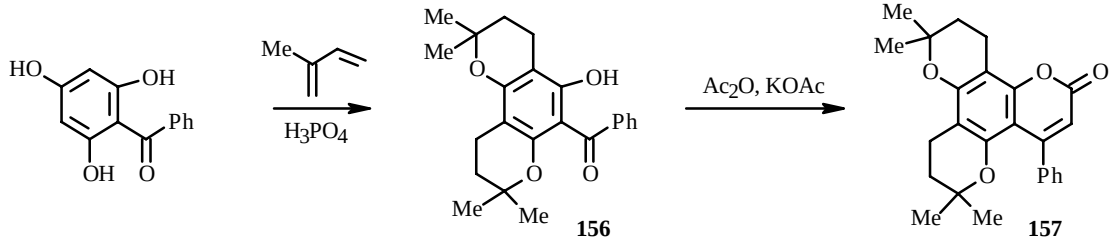
Therefore, the 8-position of the coumarin system must be blocked in order to synthesize the linear isomers. 8-Iodocoumarin **151** has been used successfully as a convenient synthon for this. Claisen rearrangement of **152** produced 4-phenylxanthyletin **153** with simultaneous elimination of the I atom [167].



151 **152** **153** **154** **155**

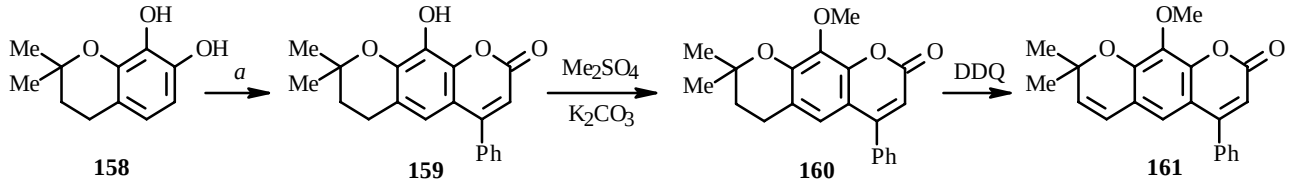
An alternate synthesis of **153** was based on the use of a hydroxy chromane as the starting material. Perkin condensation of benzoylchromane **154** gave dihydropyran **155**, subsequent aromatization of which using DDQ in absolute benzene formed **153** [94].

o-Hydroxybenzophenone **156** reacted analogously to form tetrahydrodipyranocoumarin **157** [93].



156 **157**

Pechmann condensation of 7,8-dihydroxy-2,2-dimethylchromane (**158**) and ethylbenzoylacetate with subsequent methylation of the hydroxy derivative **159** using dimethylsulfate formed intermediate **160**, dehydrogenation of which produced 10-methoxy-4-phenylxanthyletin **161** [68].

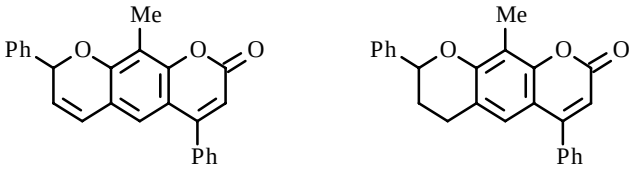


158 **159** **160** **161**

a. $PhCOCH_2COOEt$, H_2SO_4

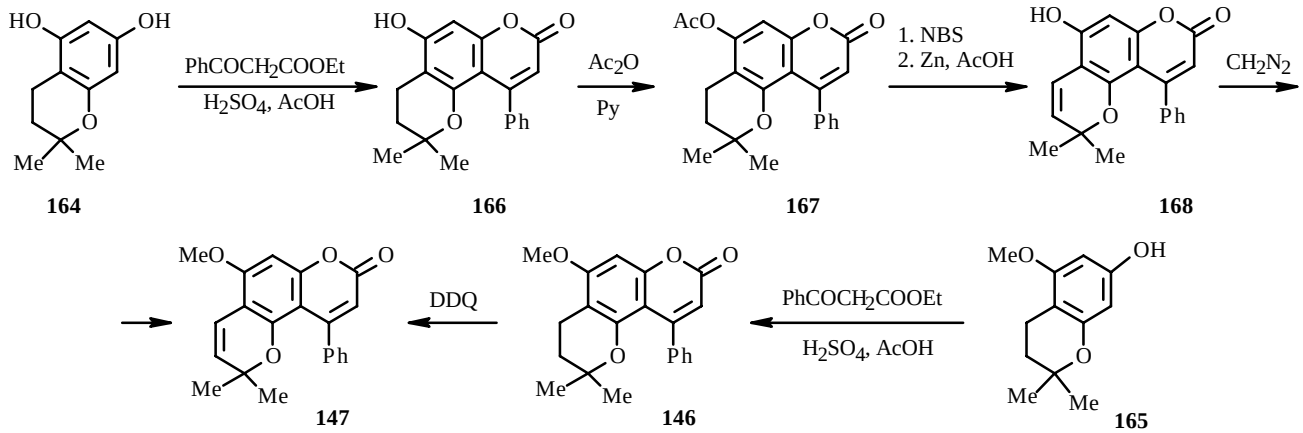
5-Methyl- and 9-methyl-4-phenylxanthyletins were prepared analogously [69, 70]. The dihydro intermediate was aromatized using DDQ in benzene and N-bromosuccinimide (NBS) in the presence of benzoyl peroxide in CCl_4.

Similar methods produced other neoflavone pyranocoumarins. Such a method was used to prepare diphenylpyranochromene **162** [71]. It should be noted that both the Pechmann reaction and the Perkin condensation have been used to construct the key pyran precursor **163**.



162 **163**

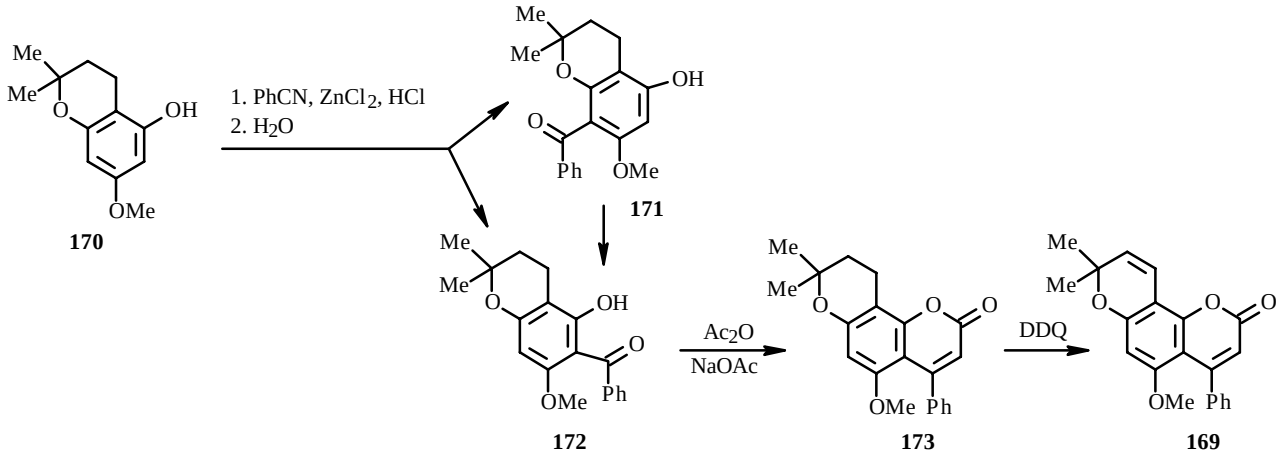
Dimethylchromanols and dimethylchroman-4-ones have also turned out to be convenient synthons for synthesizing angular phenylpyranocoumarins [168]. Pechmann condensation of chromanols **164** and **165** in acetic acid in the presence of H_2SO_4 produced coumarins **166** and **146**. Bromination of acetate **167** using NBS in benzene with subsequent treatment using Zn dust in acetic acid gave pyranochromenone **168**. Methoxypyran **147** was formed by dehydrogenation using DDQ of **146** and by methylation of hydroxy derivative **168** [168].



164 **166** **167** **168**

147 **146** **165**

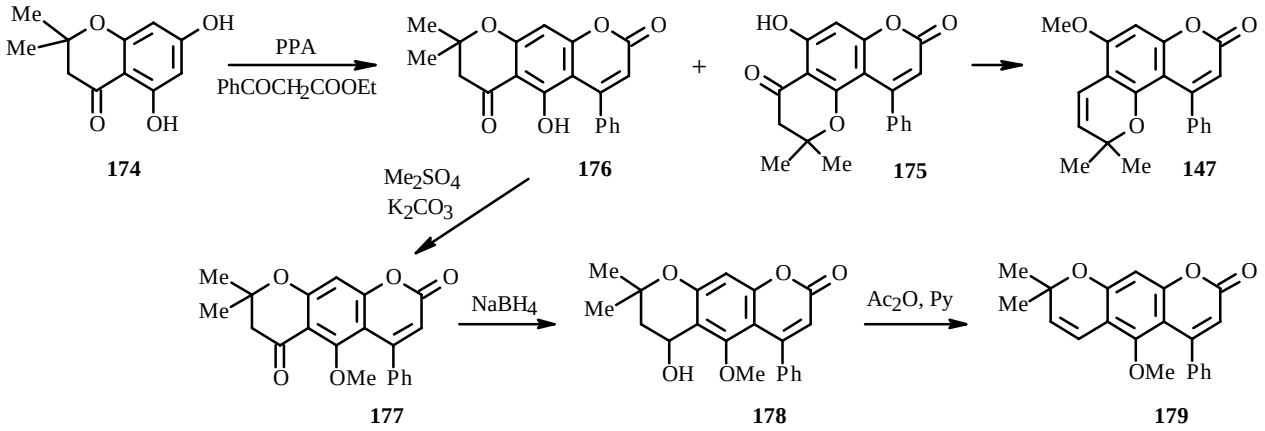
A different method was used to synthesize the isomeric pyranocoumarin **169**. Hoesch reaction of dimethylchromanol **170** and benzonitrile in the presence of $ZnCl_2$ formed a mixture of benzoylchromanes **171** and **172**. Transformation of **171** into **172** was carried out using acid catalysts (H_2SO_4 or $AlCl_3$). Perkin heterocyclization of **172** produced dihydro derivative **173**, aromatization of which gave pyranochromene **169** [168].



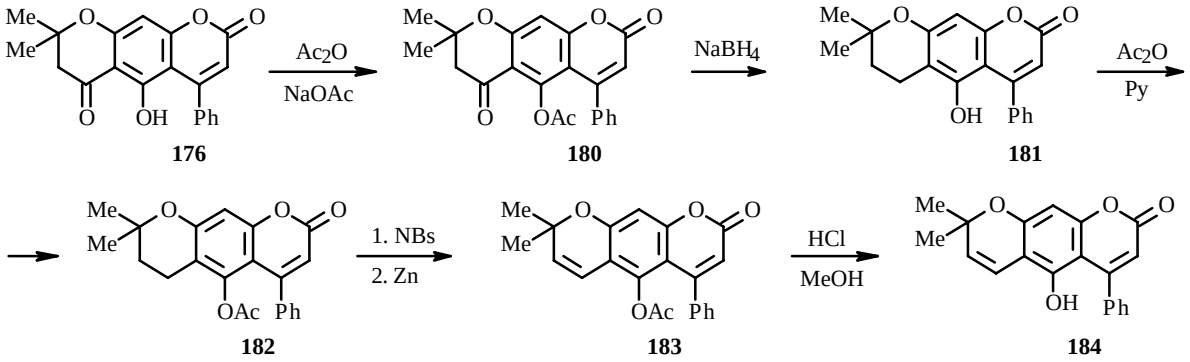
170 **171**

172 **173** **169**

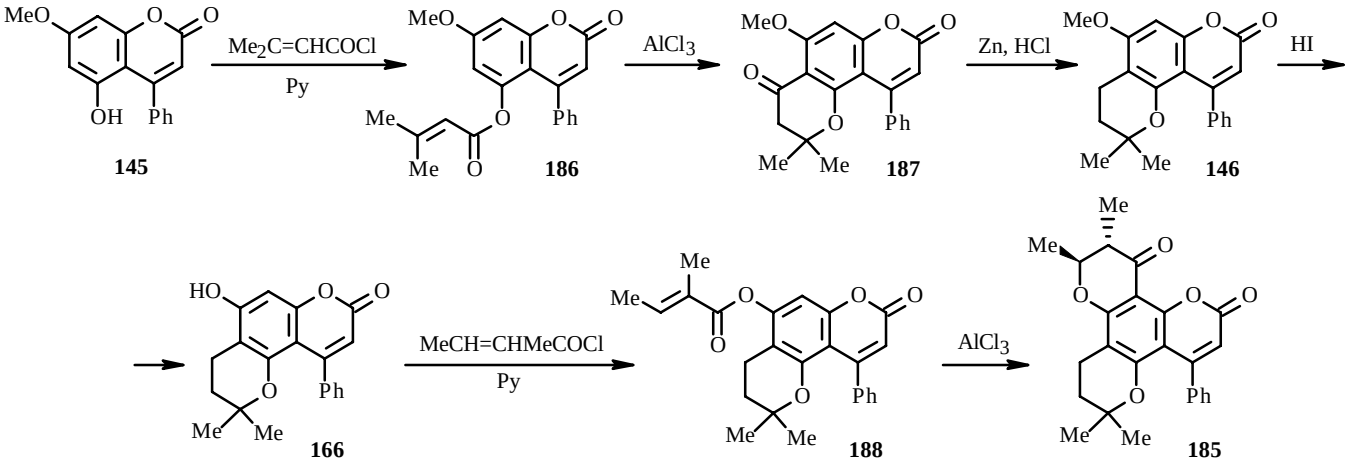
The use of 5,7-dihydroxychromanone **174** as starting material turned out to be exceedingly convenient for synthesizing both linear and angular pyranocoumarins. Reaction of **174** and ethylbenzoylacetate in the presence of PPA at 75-80°C produced a mixture of chromanocoumarins **175** and **176**, which were separated chromatographically. Reduction of methoxy derivative **177** using $NaBH_4$ in ethanol formed alcohol **178**, dehydration of which formed linear pyranocoumarin **179**. Chromanocoumarin **175** was transformed into angular pyranocoumarin **147** in the same way [168].



Treatment of acetate **180** with $NaBH_4$ produced dihydropyran **181**. Bromination of acetate **182** using NBS with subsequent debromination using Zn dust gave dehydro product **183**, deactylation of which produced hydroxypyranocoumarin **184** [168].

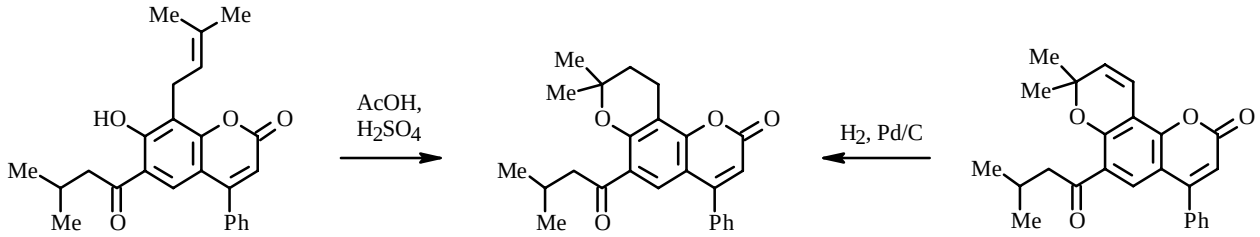


The key role in the synthesis of dihydroinophyllolide **185** was a Fries rearrangement [45]. Acylation of methoxycoumarin **145** by 3,3-dimethylacryloylchloride in pyridine formed ester **186**, Fries rearrangement of which using $AlCl_3$ in nitrobenzene gave chromanone **187**.



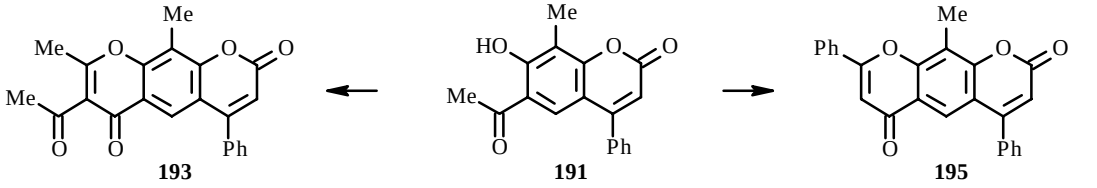
Clemensen reduction of ketone **187** gave chromane **146** [169]; its demethylation, hydroxycoumarin **166**. Acylation of **166** using tigloylchloride in pyridine with subsequent Fries rearrangement of ester **188** using $AlCl_3$ completed formation of dihydroinophyllolide **185** [45].

Dihydromammeigin (cyclomammeisin) **189** was prepared by cyclization of mammeisin **98** in glacial acetic acid in the presence of catalytic amounts of conc. H_2SO_4 [143, 170] and catalytic hydrogenation of mammeigin **190** [170].

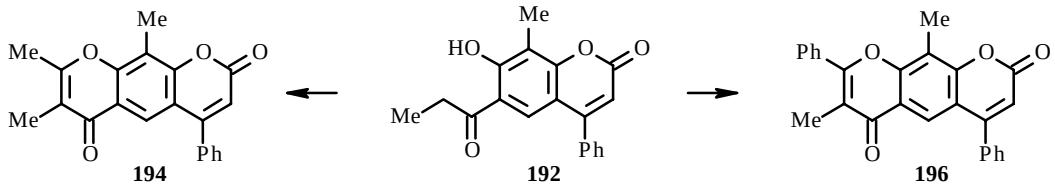


98 **189** **190**

o-Hydroxyacylcoumarins have great potential for constructing polyheterocyclic systems based on the 4-phenylcoumarin core. Thus, acetylation and Kostanetsky—Robinson benzoylation of 6-acetyl- and 6-propionyl-4-phenylcoumarins **191** and **192** were used to annelate a pyran-4-one moiety to form substituted pyrano[3,2-*g*]chromen-2,6-diones **193-196** [171].

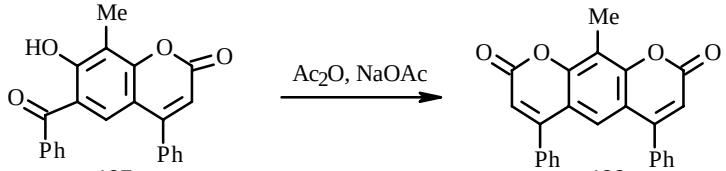


193 **191** **195**



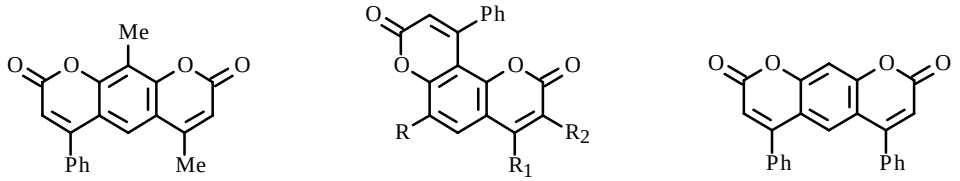
194 **192** **196**

Pyrano[3,2-*g*]chromen-2,8-diones can be prepared from the corresponding benzophenones containing an *o*-hydroxyl. Pyranocoumarin **198** was formed by Perkin condensation using **197** as the starting coumarin [172].

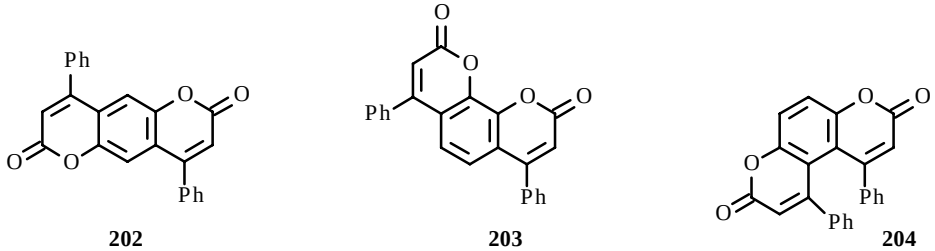


197 **198**

Angular and linear pyranochromendiones **199**-**204** were prepared under analogous conditions starting from the corresponding benzoylcoumarins [150-154, 171, 173-177].



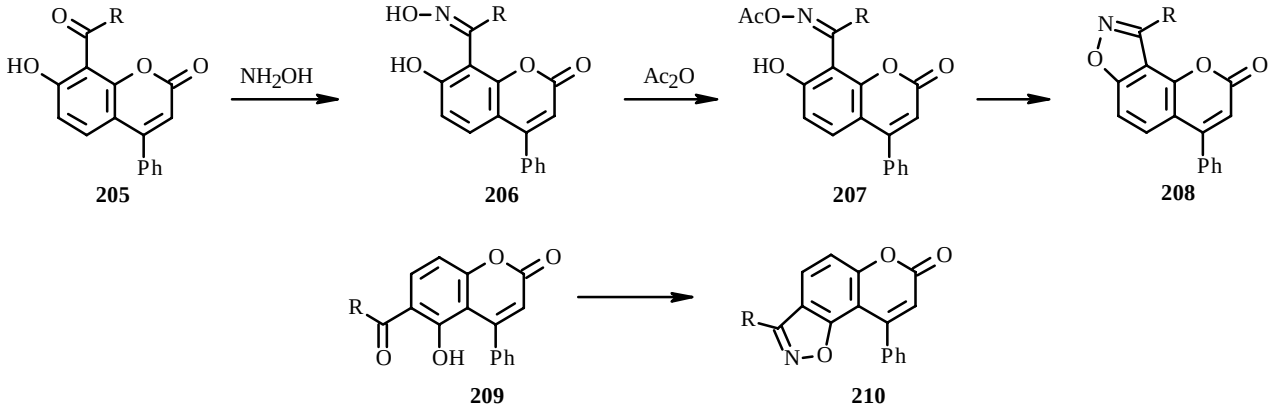
199 **200** **201**



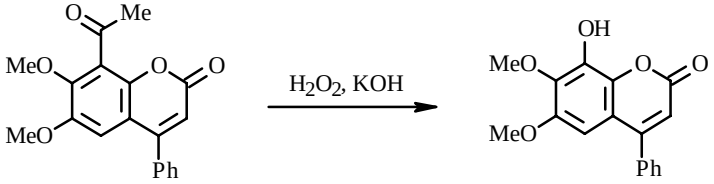
202 **203** **204**

7-Hydroxy-8-acyl-4-phenylcoumarins **205** were transformed into oximes **206** upon treatment with hydroxylamine. Reaction of these with acetic anhydride gave the corresponding acetates **207**. Pyrolysis at 140°C and reduced pressure (70 mm)

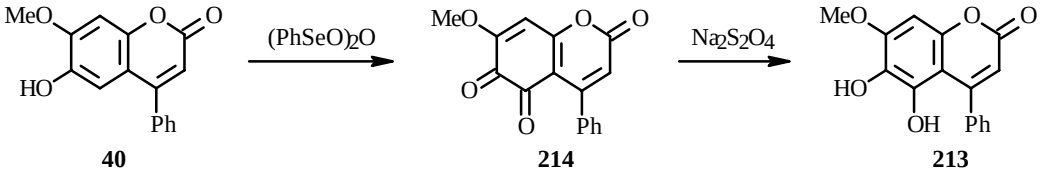
of the resulting oxime acetates annelated the isoxazole ring to form substituted angular pyrano[1,2]benzisoxazoles **208** [178]. 5-Hydroxy-6-acyl-4-phenylcoumarins **209** were converted into the corresponding derivatives **210** in a similar manner.



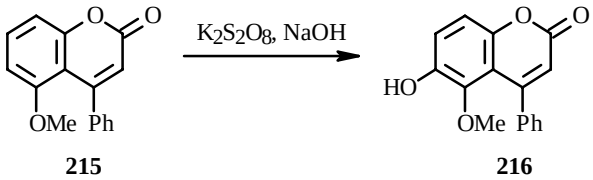
Among the other methods for modifying neoflavones, oxidation should be mentioned. It can introduce into the coumarin ring an additional hydroxyl. Thus, Dakin oxidation of 8-acetylcoumarin **211** using H_2O_2 in KOH solution produced 5,7-dimethoxy-8-hydroxy-4-phenylcoumarin (**212**) [50].



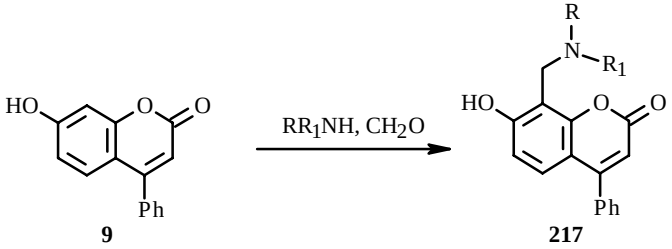
Dihydroxycoumarin **213** was prepared by oxidation of dalbergin (**40**) using phenylseleninyl anhydride in CH_2Cl_2 with subsequent reduction of 5,6-diketocoumarin **214** by sodium dithionite [179].



Allodalbergin **216** was synthesized by oxidation of 5-methoxy-4-phenylcoumarin (**215**) using $K_2S_2O_8$ in NaOH solution [90].

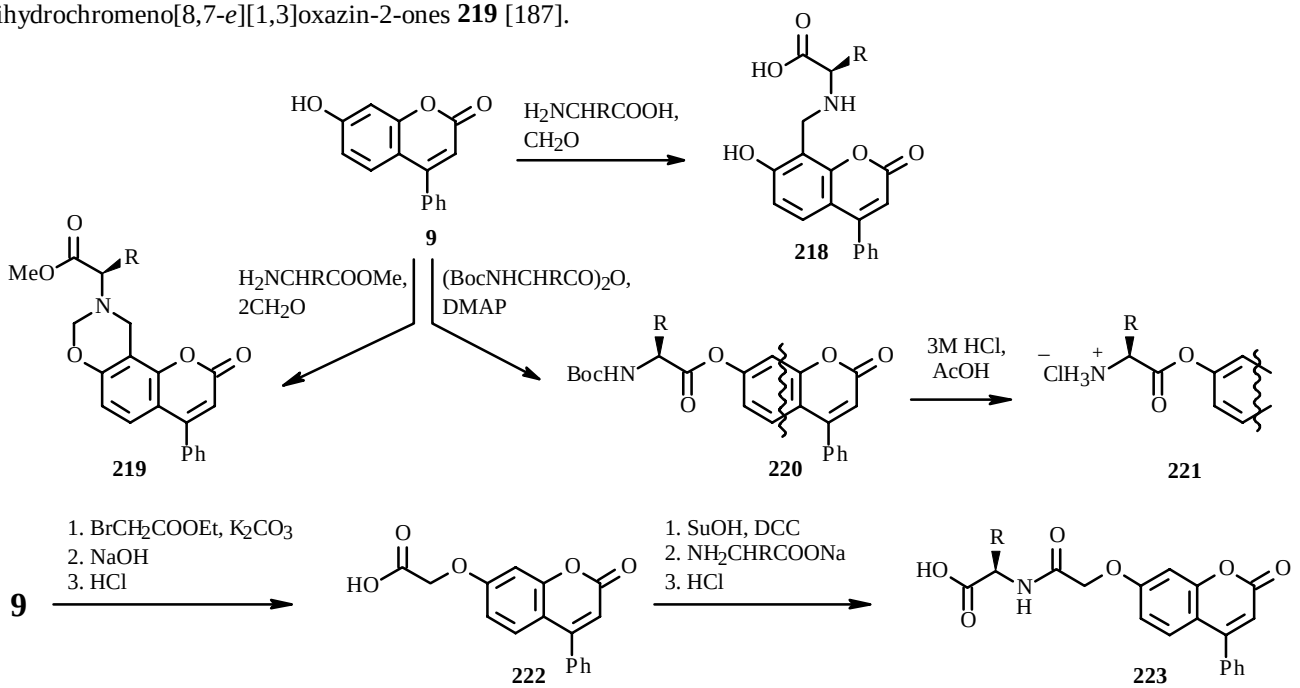


Methods for introducing the important dialkylaminomethyl pharmacophore into the neoflavone core have also been developed. Thus, 8-aminomethyl derivatives of 4-phenylcoumarin **217**, which possess analeptic activity and act as antagonists to barbiturates and CNS stimulants [180-183], were prepared by the Mannich reaction by heating a mixture of 7-hydroxy-4-phenylcoumarin, formaldehyde, and the appropriate amine in acetic acid at 100°C [184] or absolute ethanol [185, 186].



On the other hand, condensation of 5- and 7-hydroxy-4-phenylcoumarins and substituted 1,1-diaminomethanes produced Mannich bases containing the aminomethyl group in the 6- and 8-positions of the neoflavone [187].

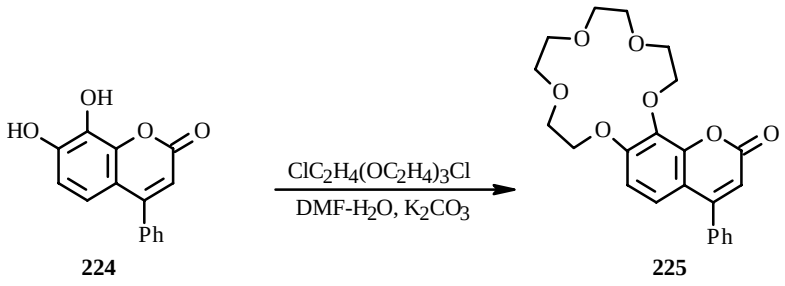
Considering the important role of amino acids in metabolic processes of organisms, several methods for modifying neoflavones with amino-acid type substituents have been proposed [188, 189]. The first method is based on the Mannich aminomethylation reaction. 7-Hydroxy-8-(N-aminoacyl)methyl-4-phenylcoumarins **218** were formed by heating a mixture of 7-hydroxy-4-phenylcoumarin, an equivalent amount of formaldehyde, and the appropriate amino acid in aqueous alcohol solutions [187, 190]. Condensation of 7-hydroxy-4-phenylcoumarin, a double equivalent of 35% formalin solution, and an alkyl ester of an amino acid in dioxane at 100°C annelated the dihydrooxazine ring to form 4-phenyl-9,10-dihydrochromeno[8,7-*e*][1,3]oxazin-2-ones **219** [187].



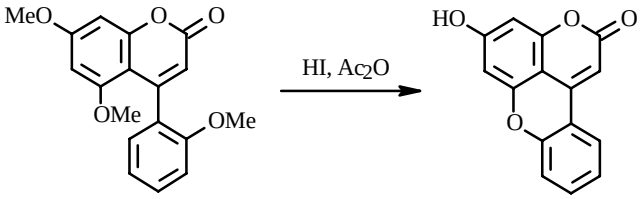
The second method is based on the formation of an ester of the amino acid and a phenol hydroxyl. Acylation of 7-hydroxyneoflavone by symmetric anhydrides of N-Boc-protected amino acids in the presence of catalytic amounts of DMAP at 0°C produced 7-O-Boc-aminoacylcoumarins **220**. Removal of the protecting group formed hydrochlorides **221** was carried out by acidolysis using HCl (3 M) in glacial acetic acid at 0°C.

The third method for modification is based on activated esters. Alkylation of 7-hydroxyneoflavone by ethylbromoacetate formed an ether, saponification of which gave the corresponding acid **222**. Reaction of the resulting coumarinyloxyacetic acid **222** and N-hydroxysuccinimide in the presence of DCC as a condensing agent formed an activated ester. The N-[2-(4-phenylcoumarin-7-yloxy)acetyl]amino acids **223** were prepared by condensation of the activated esters and sodium salts of the appropriate amino acids in aqueous dioxane at room temperature with subsequent acidolysis of the salts [191].

Reaction of 7,8-dihydroxycoumarin **224** and *bis*-[2-(2-chloroethoxy)ethyl]ether in the presence of potash at 85-95°C in DMF:water (85:15) produced 15-crown-5-ether **225**, which contains a 4-phenylcoumarin unit [192].



Natural neoflavones also include a series of 4-phenyl-5,2′-oxidocoumarins. The methods for synthesizing and modifying this series are poorly studied. The literature contains only one method for synthesizing 4-phenyl-5,2′-oxidocoumarins **226**. The key step is demethylation of 5-methoxy-4-(2-methoxyphenyl)coumarins **227** using HI in acetic anhydride at 110-115°C [42].



227 **226**

In conclusion, it should be noted that the simplicity of preparation and the capability for extensive chemical modification of functionalized derivatives of 4-arylcoumarins make this class of compounds exceedingly attractive in organic synthesis. Various annelated heterocyclic systems based on them are readily prepared. Certain representatives of these compounds are convenient starting reagents for synthesizing unique natural neoflavones and their modified analogs that possess various pharmacological properties. From this viewpoint, this area can be considered one of the most interesting and promising in the chemistry of benzopyran heterocycles. It can be assumed that further study of methods for synthesizing and modifying neoflavones will expand their sphere of use.

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