Synthesis of Xanthones: An Overview

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Abstract: Among the known synthetic routes to obtain xanthones, the Grover, Shah, and Shah reaction, the cyclodehydration of 2, 2'-dihydroxybenzophenones and electrophilic cycloacylation of 2-aryloxybenzoic acids are the most popular methods. Due to important biological applications of xanthones, some synthetic strategies leading to more complex derivatives have been widely explored in the past years. Thus, the purpose of this review is to report some recent improvements of the classical synthetic methods as well as of some non-classical methods to obtain simple oxygenated xanthones. The strategies for introduction of substituents into the xanthonic nucleus are also summarized. Furthermore, different approaches used to synthesize complex structures, with an emphasis on the total synthesis of bioactive natural products, accomplished in the last twenty years, are also discussed. Besides the synthesis of xanthones, the reactivity of the xanthonic nucleus and its role as a key intermediate for the synthesis of other important classes of compounds are also highlighted.

Keywords: Xanthone, xanthenone, heterocycle, synthesis, benzophenone, diphenyl ether, xanthene.

1. INTRODUCTION

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds [1]. Chemically, xanthones (9*H*-xanthen-9-ones) are heterocyclic compounds with the dibenzo-γ-pyrone framework (Fig. (**1**)). Naturally-occurring xanthones, with nearly one thousand known members [2,3] contain different types of substituents in different positions, leading to a large variety of pharmacological activities [4]. As their biosynthetic pathways are a limiting factor for the structural variation of naturally-occurring xanthones, the synthesis of new derivatives can help rationalize the relation of structural features versus activity.

One of the first methods for the synthesis of xanthones was introduced by Michael and Kostanecki, which involved the distillation of a mixture of a phenol, a *o*-hydroxybenzoic acid, and acetic anhydride [5,6]. Since then, several other routes with higher yields and less drastic experimental conditions have been developed.

Some extensive reviews have reported the synthesis and biosynthesis of phytoxanthones [1,7-9], with emphasis on synthetic methods for preparation of simple polyoxygenated xanthones and natural prenylated xanthones. The methods for selective methylation/demethylation and protection/ deprotection of polyoxygenated xanthones, based on differences in acidity of the phenolic groups, have also been discussed [8,9].

Recently, there has been an increase in the interest in new xanthonic structures, partly due to diverse pharmacological activities exhibited by this type of compounds [4]. Also, in the field of Medicinal Chemistry, the groups of compounds that can bind to different classes of receptors have attracted much attention [10] and xanthones can be considered as potential structures in this field. Therefore, xanthones obtained by synthesis began to represent a significant part of the derivatives described in literature. The main objectives of xanthone syntheses are not only for the development of more diverse and complex bioactive compounds for biological activity and structure-activity relationship (SAR) studies, but also for other applications in Medicinal Chemistry, such as preparation of fluorescence probes, due to photochemical properties of xanthones.

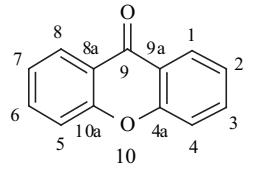

Fig. (1). Xanthone nucleus and numbering.

Hence, the following sections will describe new insights in the synthesis of simple xanthonic derivatives, such as polyoxygenated xanthones as well as the synthesis of more complex derivatives using non-conventional approaches to build the xanthone framework. In this perspective, some examples of total synthesis of natural products with caged/fused structures will be highlighted. Finally, the use of xanthones as synthetic precursors for other molecular frameworks will be emphasized.

2. SYNTHESIS OF SIMPLE XANTHONES

2.1. Classical Methods

Three traditional methods can be applied for the synthesis of simple xanthones: the Grover, Shah, and Shah (GSS) reaction, the synthesis *via* benzophenone, and the synthesis *via* diphenyl ethers intermediates. The GSS reaction (Scheme **1**) [11] offers a convenient method for preparing hydroxyxanthones and still enjoys a great

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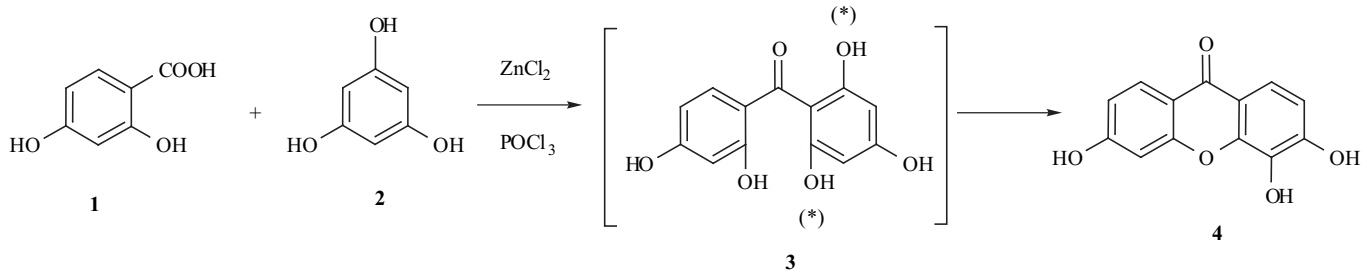
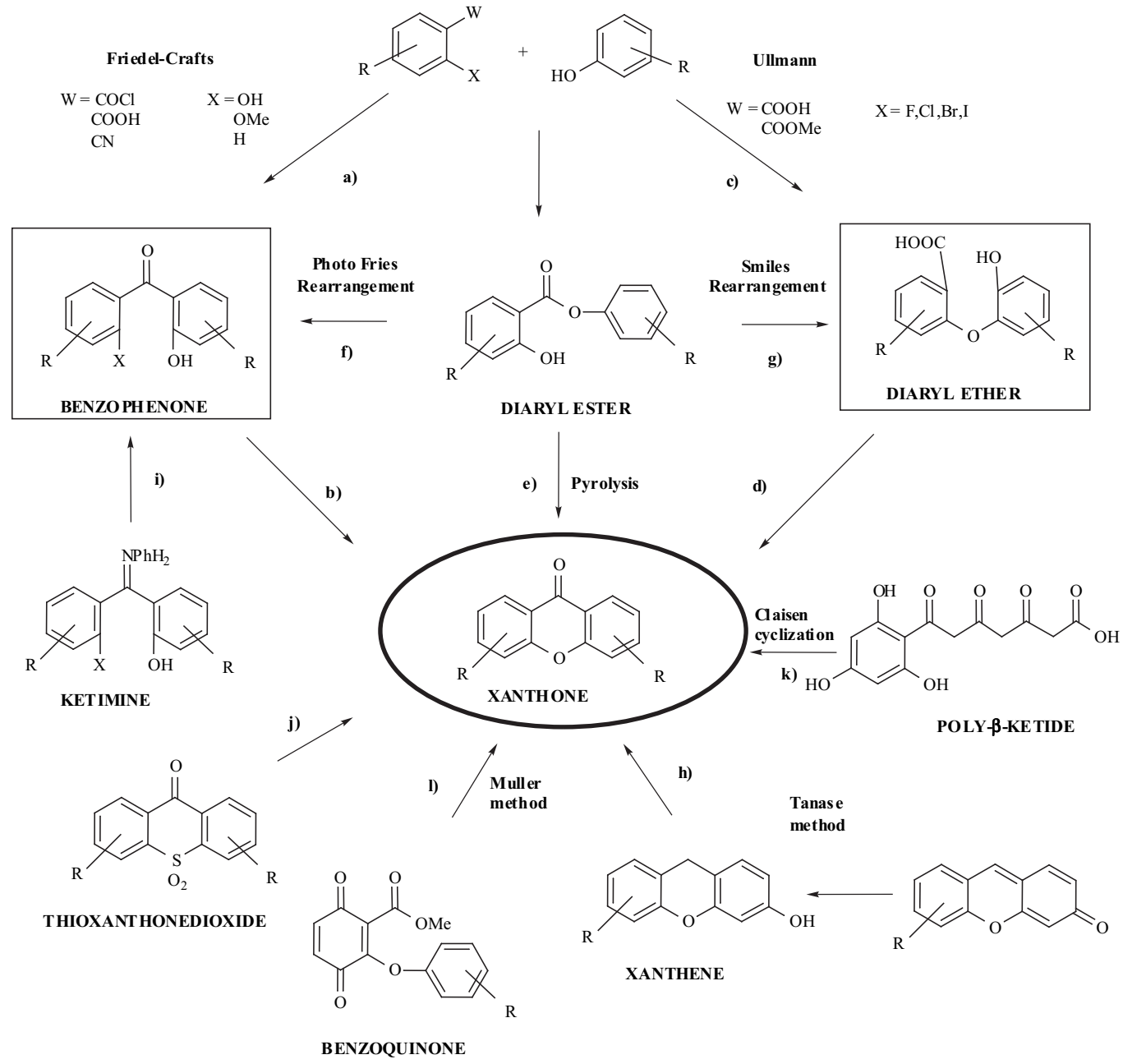


Scheme 1.



Scheme 2.

popularity, due to usually accessible materials [*for recent examples see* 12-25]. It requires a salicylic acid derivative (**1**) and a suitable phenol (**2**) that are heated together with zinc chloride in phosphoryl chloride as solvent. The Grover, Shah, and Shah (GSS) method can afford the xanthone skeleton (**4**), directly only if the benzophenone intermediate (**3**) carries another hydroxyl group at the 6 or the 6' position, *i.e.*, if an alternative site for cyclization is available ((*),

Scheme **1**). Due to a number of limitations of this process [8,9,26], other methods have taken over this one-pot synthesis of simple xanthones.

These methods include the route benzophenone **a)** → **b)** and the route diaryl ether **c)** → **d)** (Scheme **2**). The benzophenone derivatives are commonly accessible through condensation by Friedel–Crafts acylation **a)** [27] of an appropriate substituted benzoyl chloride with a phenolic derivative [28] and is followed by the cyclization step **b)** that involves a nucleophilic substitution [8,28] or a nucleophilic addition-elimination [29] of 2,2'-dioxygenated benzophenones, or an oxidative process (X=H) [30]. The diaryl ether synthesis (Ullmann condensation) **c)** [31] uses the reaction of sodium phenolates with benzoic acids bearing halogen in the *ortho* position, and the ring formation is accomplished by electrophilic cycloacylation of the 2-aryloxybenzoic acids **d)** [32]. Because intermolecular acylation reactions give generally higher yields than Ullmann ether syntheses, the most prevalent strategy for xanthone synthesis is acylation, followed by cyclization to form the heterocyclic ring [*for a practical comparative example see* 33]. The xanthone skeleton can also be formed directly from diaryl ester by pyrolysis **e)** [34,35] or through the above intermediates by photo Fries rearrangement **f)** [36-42], or by Smiles rearrangement **g)** [43,44], strategies that emerged in the last years.

Some less conventional methods for the synthesis of xanthones (in the lower half of Scheme **2**) have also been reported [9]. These include aryl anion addition to salicylaldehyde, followed by reduction to xanthene and eventual oxidation to xanthone (Tanase method) **h)** [45,46], synthesis of benzophenones involving ketimine intermediates **i)** (Robinson and Nishikawa synthesis) [47], synthesis from a thioxanthen-9-one-10,10-dioxide nucleus **j)** [34,48], from extended poly-β-ketides **k)** [49-51], and from the nucleophilic addition of phenols to alkoxycarbonyl-*p*-benzoquinones (method of Muller and coworkers) followed by reduction **l)** [52,53]. These general approaches are shown in Scheme **2**.

2.2. Modifications to the Classical Methods

Recent modifications to the experimental methods illustrated in Scheme **2** have been reported. In the Grover, Shah, and Shah (GSS) reaction (see Scheme **1**), better results were obtained using a mixture of phosphorus pentoxide–methanesulfonic acid (Eaton's reagent) instead of phosphorus oxychloride–zinc chloride as catalyst [46,54]. The former acylation catalyst was found to be an excellent condensing agent between phloroglucinol (**5**) and 3-methylsalicylic acid (**6**), providing high yields (90–95%) of the xanthone (**7**) and no detectable amounts of the possible benzophenone (**8**) (Scheme **3**). Later studies found that it was unnecessary to fuse zinc chloride prior to the coupling; this extra procedure actually decreased the reaction yield because of the insolubility of glass-like fused zinc chloride. To circumvent this step, the zinc chloride was heated in phosphorus oxychloride to 60ºC for 30 minutes prior to the addition of dimethoxy benzoic acid and the heat was maintained for an additional 30 minutes before the addition of the polyphenol [13].

Modifications of Friedel-Crafts reaction (Scheme **2**, **a)**) have included an acylation in the presence of trifluoroacetic acid anhydride, demethylation, and subsequent cyclization of the benzophenone (with elimination of methanol) in aqueous medium under pressure and heating [43]. Also, a method restricted to 1,3-dihydroxyxanthones included the acylation of an appropriate *O,O,O*-tris(trimethylsilyl)-substituted phenol with the benzoyl chloride in the presence of stannic chloride [46]. The use of Nafion®-H, a perfluorinated resinsulfonic acid catalyst, has also been applied in the synthesis of simple xanthones with excellent yields in the condensation step of benzoic acids (Scheme **2**, **a)**) [55,56]. The use of PPh_3/CCl_4 [57,58] to build the xanthone framework was the key cyclization reaction (Scheme **2**, **b)**) and constituted a new method for the total synthesis of α-mangostin (**13**) (Scheme **4**) [59]. The benzophenone (**12**), obtained through the parent alcohol (**11**) by a protected aryl (**9**) anion addition to benzaldehyde (**10**), furnished the natural xanthone (**13**). A slightly different approach involving a *ortho*-lithiation as the key step for the synthesis of benzophenones followed by classical cyclization to xanthones was accomplished [60].

Unexpected results in Friedel-Crafts reactions have also been observed. KF/Al_2O_3 conditions, while mediating the *O*-alkylation of 2-hydroxy-4,4'-bis(methylthio)-benzophenone, promoted an unusual tandem electrophilic-nucleophilic aromatic substitution and led to the xanthonic thioderivative (**14**) (Fig. (**2**)) [61]. Also, in the course of a study of copper-catalyzed oxidation reactions to obtain diaryl derivatives with electron-withdrawing substituents based on Ullmann condensation, a benzophenone was synthesized by oxidation of the corresponding bis(4-nitrophenyl)methane by refluxing with copper powder in *N,N*-dimethylformamide; the intermediate 2,2'-di-iodo-4,4'-dinitrobenzophenone furnished 3,6-dinitroxanthone in good yields [62]. Using Friedel-Crafts intramolecular cyclobenzylation in the preparation of xanthenes, by the action of dichloromethyl methyl ether and $TiCl_4$ on 4,4'-di-*tert*-butyldiphenyl ether has allowed an electrophilic substitution *ortho* to the diphenyl ether linkage and yielded 2,7-di-*tert*-butylxanthene in 38% along with 2,7-di-*tert*-butylxanthone in 38% [63].

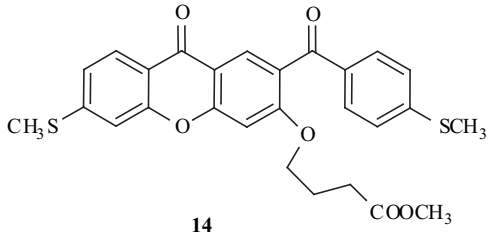


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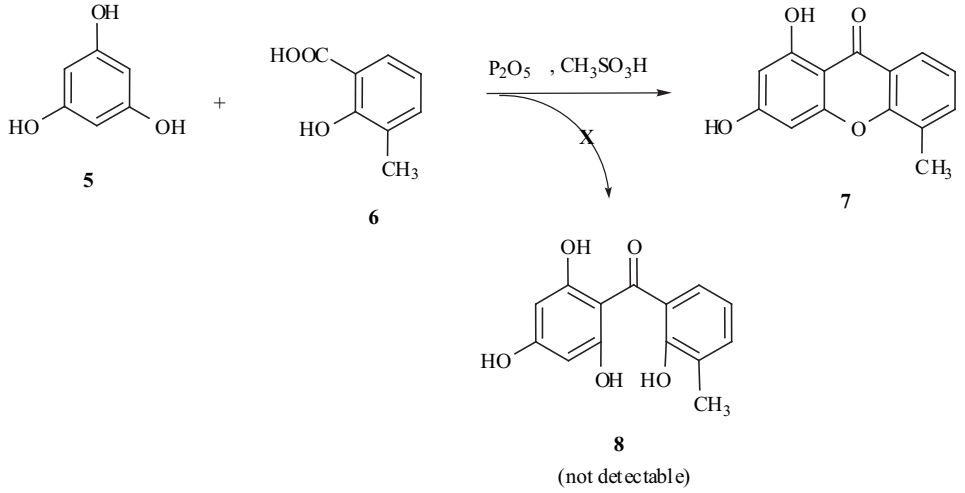
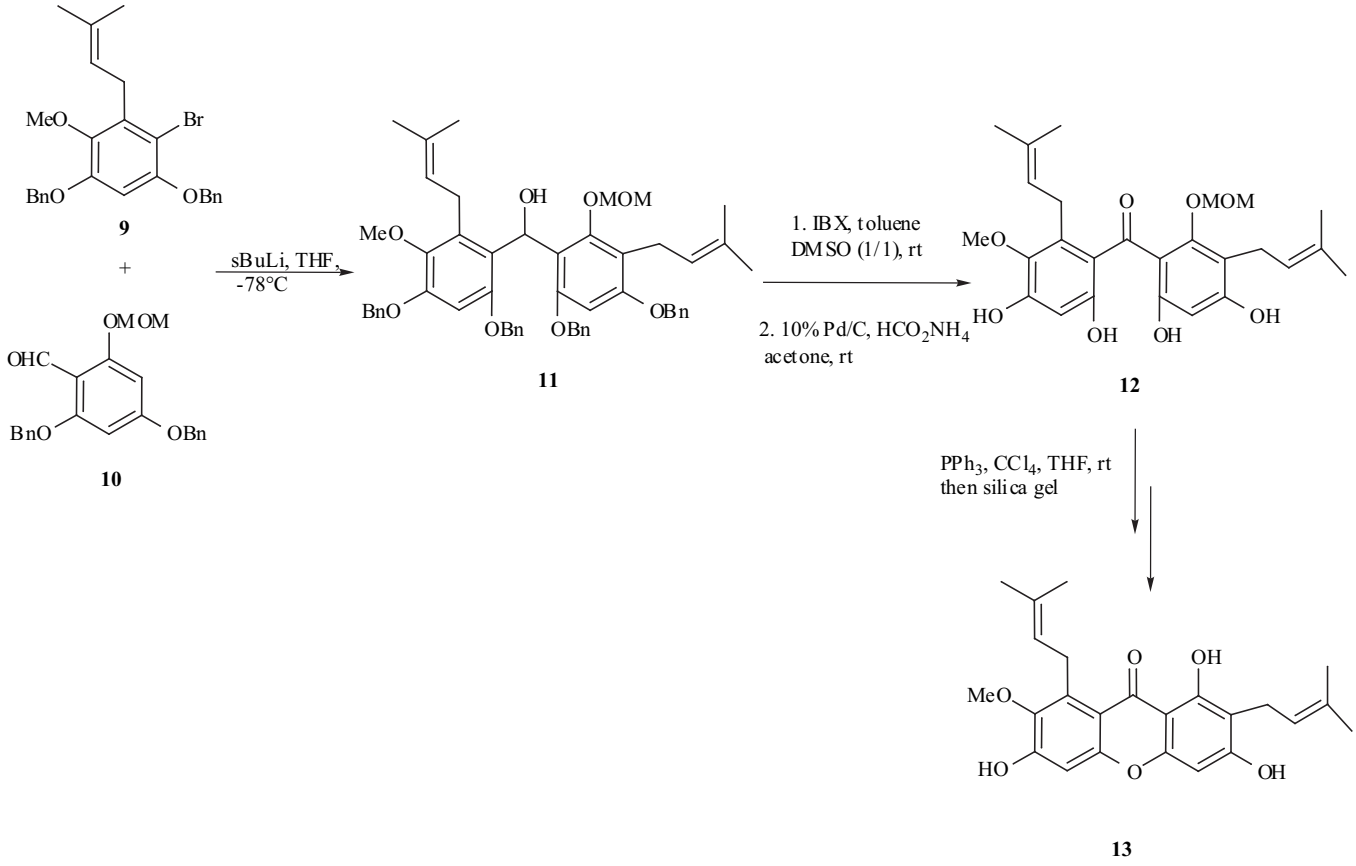
Fig. (2).

In the diaryl ether condensation (Scheme **2**, **c)**), microwave methodology has already assisted and replaced the common heating in the Ullmann reaction [17]. Microwave irradiation of a mixture of sodium 2-methoxyphenolate, sodium 2-chlorobenzoate, CuCl, and tris [2-(2-methoxyethoxy)-ethyl]amine gave 2-(2'-methoxy-phenoxy)benzoic acid, which was then treated with polyphosphoric acid to provide 4-methoxyxanthone in 41% yield. Another improvement in the Ullmann synthesis consisted in the coupling of aryl halides with phenols in the presence of phosphazene P_4-*tert*-butyl base and CuBr at



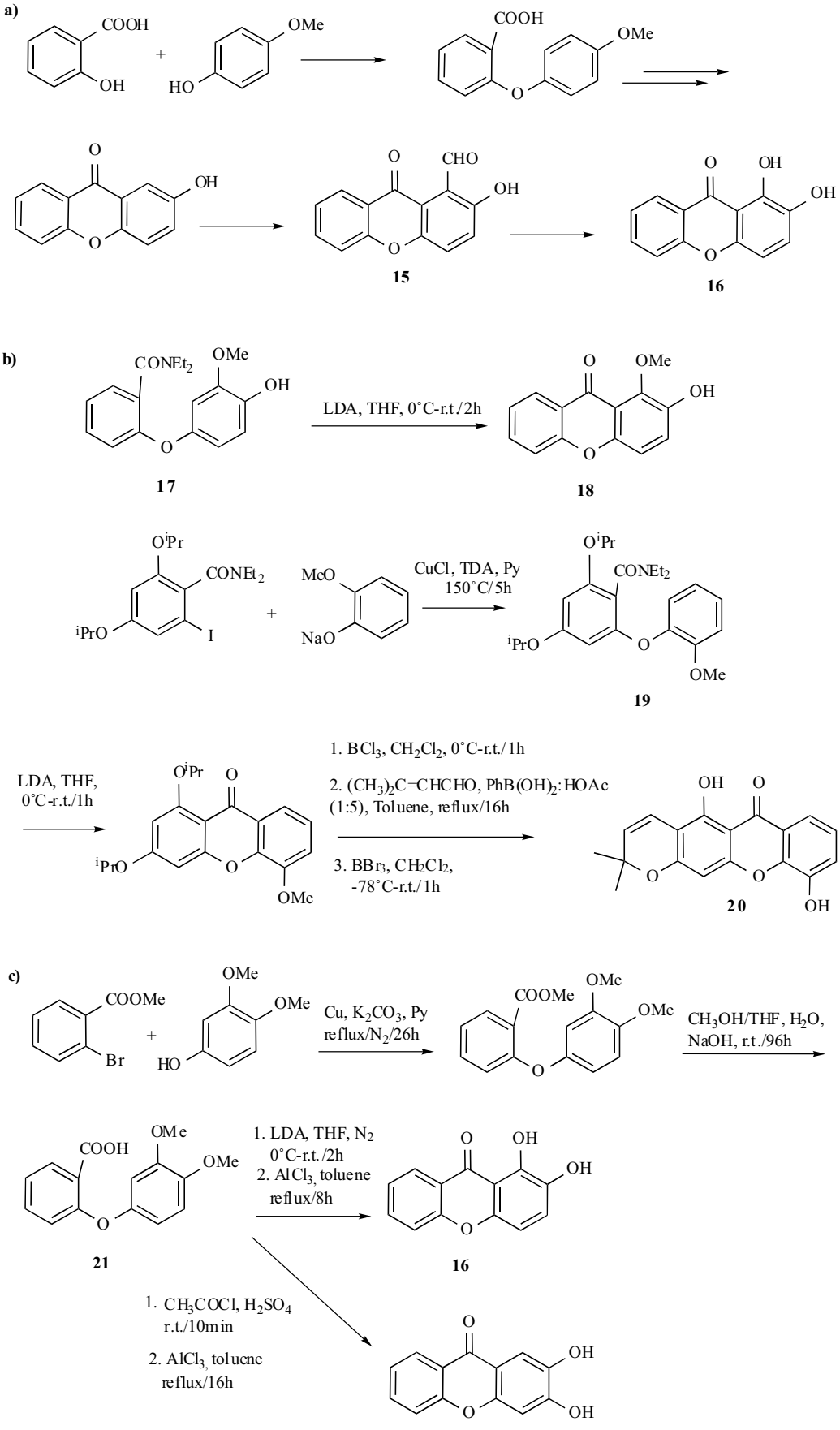
Scheme 3.



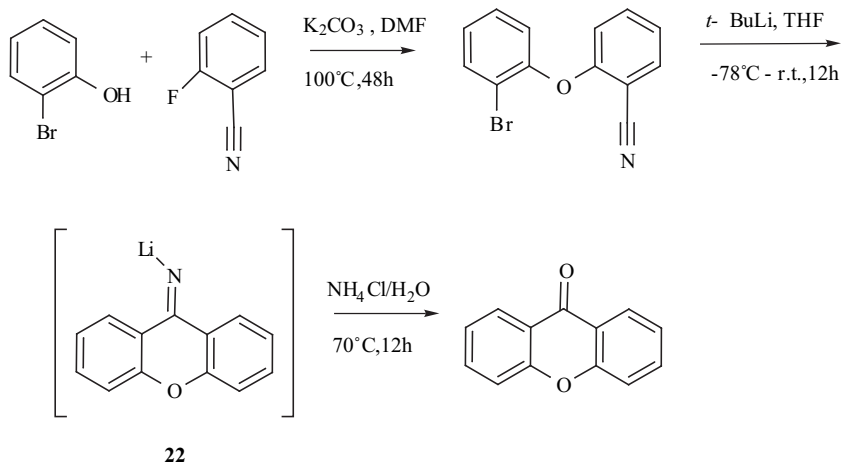
Scheme 4.

100ºC [64]. An improved synthesis of the anticancer drug 5,6-dimethylxanthone-4-acetic acid (DMXAA), which was achieved in 22% yield from 3,4-dimethylbenzoic acid, is also an example of an optimized strategy based on the Ullmann reaction [65].

Remarkable improvements have been achieved in the synthesis of 1,2-dioxygenated xanthones by application of a direct metalation on diphenyl ether intermediates (Scheme **2**, **d)**) using lithium di-isopropylamide (LDA) [66,67], a method similar to that developed for the synthesis of natural xanthones cervinomycin A1 and A2 (see Table **2**) [68]. An attempt to obtain 1,2-dihydroxyxanthone (**16**) by traditional Friedel-Crafts acylation or Ullmann reaction resulted in an isomeric mixture with very low yields of compound (**16**) [69]. Consequently, 1,2-dihydroxyxanthone (**16**) was first obtained as a major product by a multi-step synthesis through its intermediate 1-formyl-2-hydroxyxanthone (**15**) in very low yields (Scheme **5 a)**) [70]. Snieckus and co-workers have accomplished the LDA-mediated synthesis of the natural products 2-hydroxy-1-methoxyxanthone (**18**) and 6-deoxyjacareubin (**20**) from the appropriate diaryl ether 2-carboxamides (**17**) and (**19**), respectively (Scheme **5 b)**) [66]. The cyclization step is dictated by the coordination effects of


a)
COOH
OH
OMe
HO
O
CHO
15
16
b)
CONEt2
17
LDA, THF, 0°C-r.t./2h
18
O^iPr
MeO
NaO
CuCl, TDA, Py
150°C/5h
19
LDA, THF,
0°C-r.t./1h
1. BCl3, CH2Cl2, 0°C-r.t./1h
2. (CH3)2C=CHCHO, PhB(OH)2:HOAc
(1:5), Toluene, reflux/16h
3. BBr3, CH2Cl2,
-78°C-r.t./1h
20
c)
COOMe
Br
Cu, K2CO3, Py
reflux/N2/26h
CH3OH/THF, H2O,
NaOH, r.t./96h
21
1. LDA, THF, N2
0°C-r.t./2h
2. AlCl3, toluene
reflux/8h
1. CH3COCl, H2SO4
r.t./10min
2. AlCl3, toluene
reflux/16h

Scheme 5.

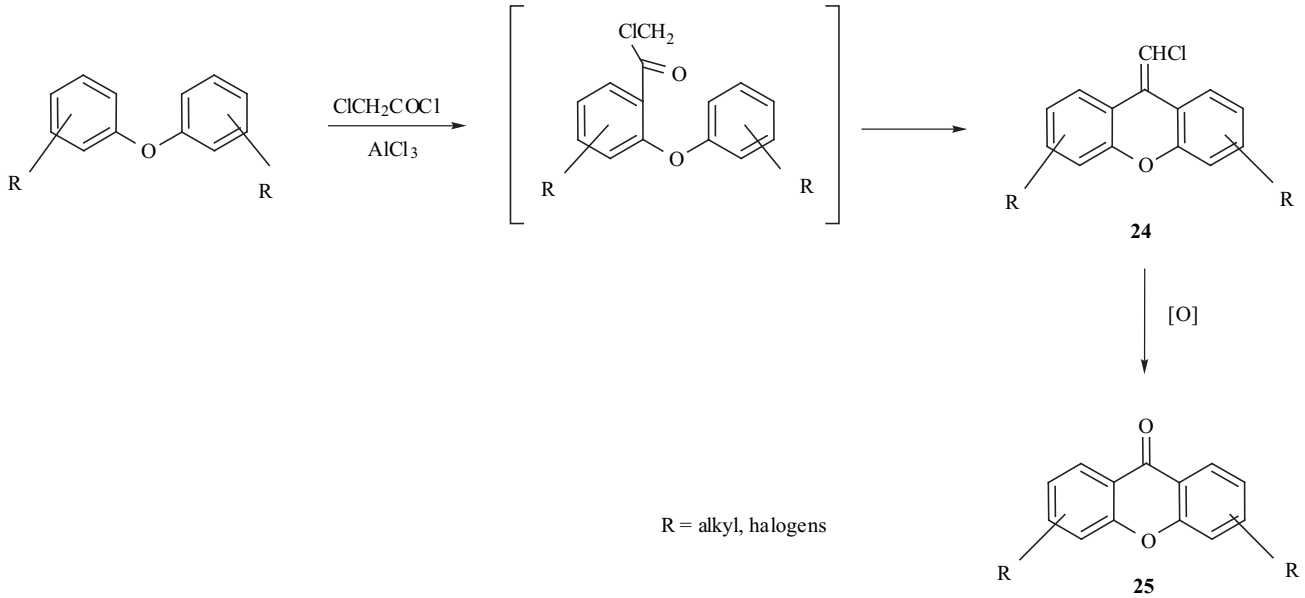


Scheme 6.

direct metalation groups in contrast with the electrophilic substitution of the corresponding carboxylic acids and is probably driven by the Complex Induced Proximity Effect (CIPE) [71]. A CIPE has also been attributed to the success of an anionic Fries rearrangement (Scheme **2**, **f)**), applied in the synthesis of dihydro-*O*-methylsterigmatocystin (see Table **2**) [38]. Moreover, the direct metalation has been applied in the synthesis of fluorenones [72], thioxanthones [73], and selenoxanthones [74]. This method was combined with important adjustments to the Ullmann reaction accomplished by Jackson *et al.* [75] to obtain 1,2-dihydroxyxanthone (**16**) by a direct lithiation [76] of the unprotected diaryl intermediate 2-(3',4'-dimethoxyphenoxy) benzoic acid (**21**) (Scheme **5 c)**) [67,77]. A direct lithiation has also been applied to synthesize 4,5-dihydroxyxanthone to be incorporated in crown-ether macrocycles (*see Section 3.2*) [78]. Kristensen *et al.* have described a ring closure of diphenyl ethers *via* an anionic cascade process initiated by a bromine-lithium exchange, using *tert*-butyllithium at -78 °C, and thus prepared xanthones and related compounds in high yields (Scheme **6**) [79]; the reaction proceeded *via* a sequential intramolecular trapping of a very reactive organolithium intermediate (**22**).

2.3. New Approaches to the Synthesis of the Xanthonic Tricyclic System

Different modes to construct the xanthone core have emerged in the last years. The strategies of these methods were to provide an advantage for building highly polyoxygenated xanthones with regioselectivity. Consequently, they were found to have a wide range of applications in xanthone synthesis. Phenoxymalonates (**23**) (Fig. (**3**)) obtained by condensation of chloromalonates and phenols were found to be the key intermediates for a new methodology to obtain diphenylethers by thermolytic ring closure at 240ºC. This method allowed the regioselective introduction of a methyl group into C4 of the xanthone framework by a three-step route [80].



Scheme 7.

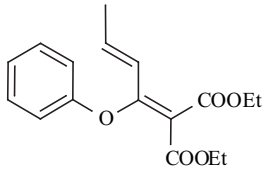


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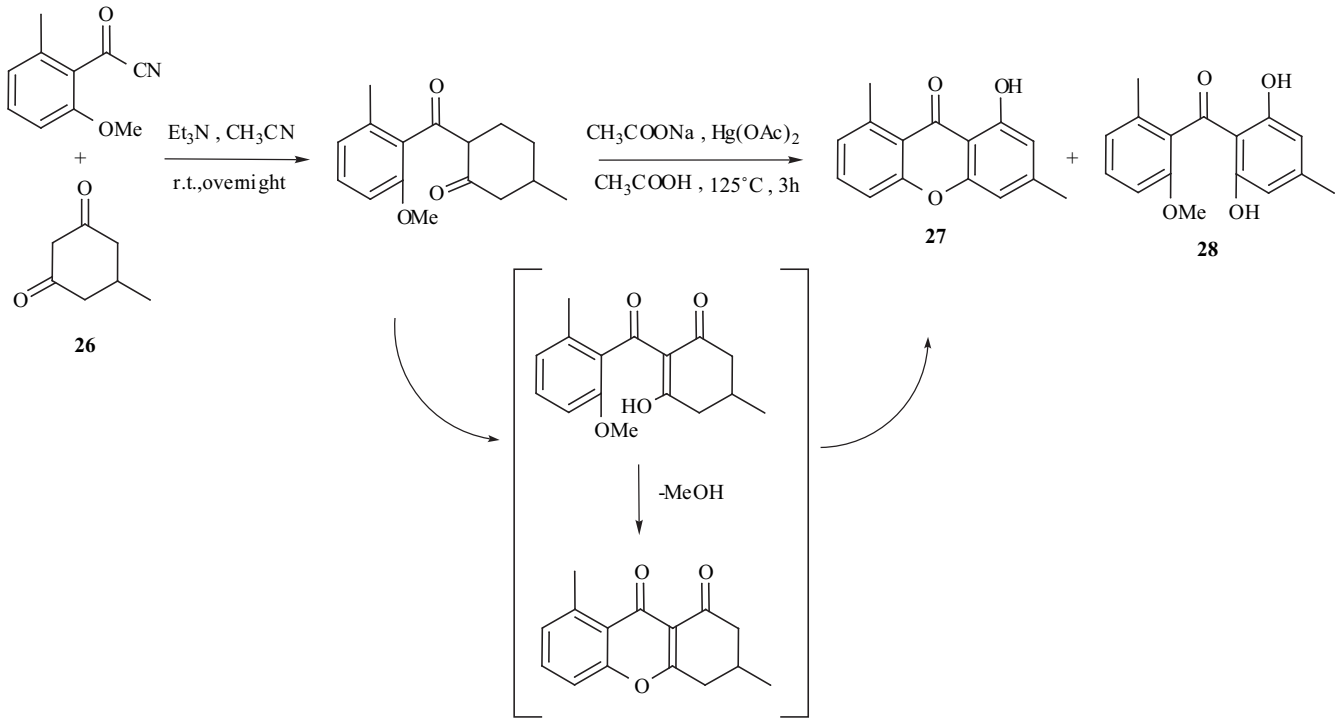
Fig. (3).

Several substituted 9-chloromethylenexanthenes (**24**) (Scheme **7**), prepared in good yields by Lewis acid catalyzed cyclodehydration of diarylethers followed by hydrolysis, were the key intermediates to obtain, by oxidative cleavage, xanthones with halogens and alkyl groups (**25**) [81]. The final oxidation step was accomplished by several reagents such as potassium permanganate, chromic acid, and *m*-chloroperbenzoic acid, by dye-sensitized photo-oxidation [81], or by Mg/tetrahydrofuran followed by air oxidation [82].

Several methyl salicylates were used to substitute halogenated benzoquinones regiospecifically in the presence of anhydrous potassium fluoride. The resulting phenoxybenzoquinones were then reduced and cyclized to form highly functionalized xanthones, such as 1,4-dihydroxy-2,3,7-trimethoxyxanthone [83].

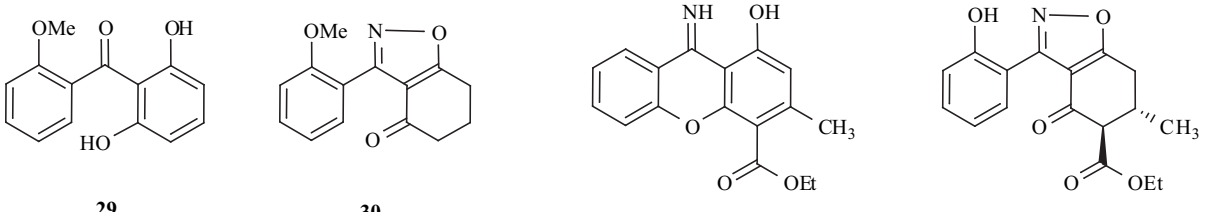
An unexpected formation of the xanthone system (**27**) (Scheme **8**) occurred by acylation of a 1,3-cyclohexanedione (**26**) in the synthesis of benzophenone (**28**) [60]. It was proposed that the simultaneous formation of xanthone (**27**) involved the loss of methanol during the aromatization process due to the presence of the Lewis acid mercuric acetate. Likewise, oxygenated benzophenone (**29**) and iminoxanthone (**31**) were synthesized from isoxazoles (**30**) and (**32**), respectively (Fig. (**4**)), which were previously obtained from *C*-chloro oximes and cyclic 1,3-diketones [84]. This new method was also proposed for the synthesis of highly oxygenated xanthones [84]. A systematic study of alkylation of cyclic-1,3-diketones (**34**) with 2-bromo-6-methoxybenzofuran-3-one (**33**) has led to a new method of formation of the xanthone core (Scheme **9**) [85]; the intermediate (**35**) of the reaction then reacted with *p*-substituted anilines to furnish the substituted xanthone derivatives (**36**) shown in Scheme **9**.

An alkylnitrilium modification of the Houben-Hoesch reaction (Scheme **10**) was applied to the synthesis of the xanthone derivative (**40**) based on the reactivity of *N*-alkyl



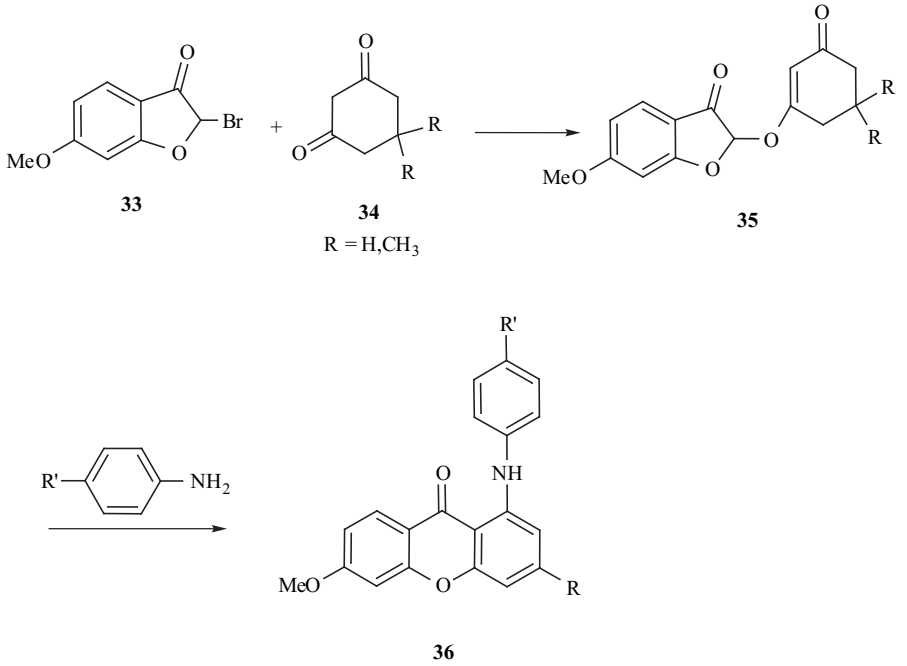
26 **27** **28**

Scheme 8.

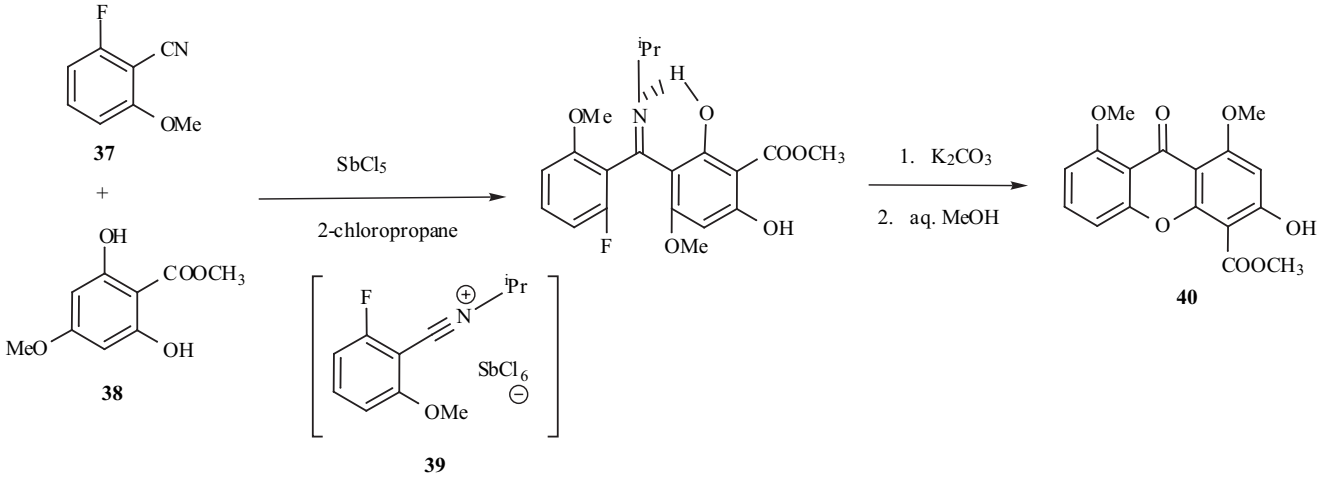


29 **30** **31** **32**

Fig. (4).



Scheme 9.

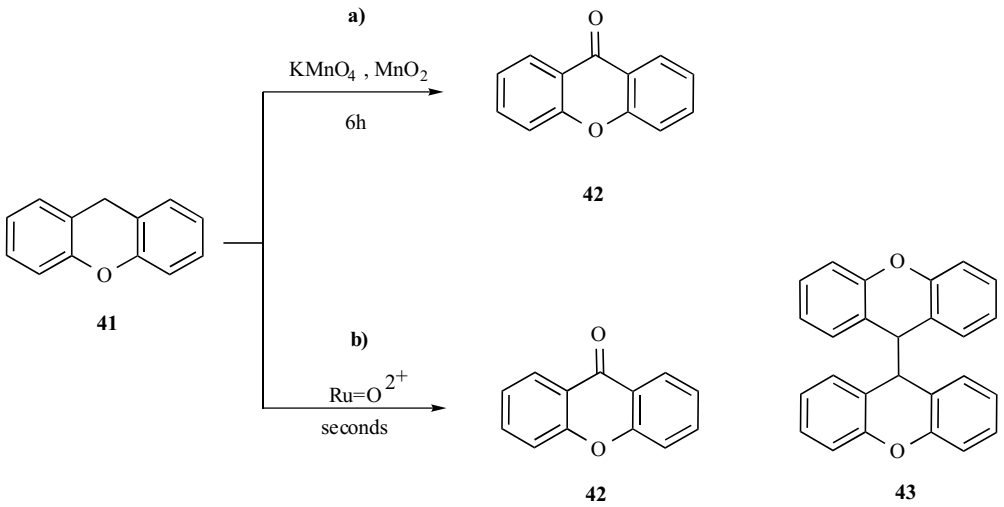


Scheme 10.

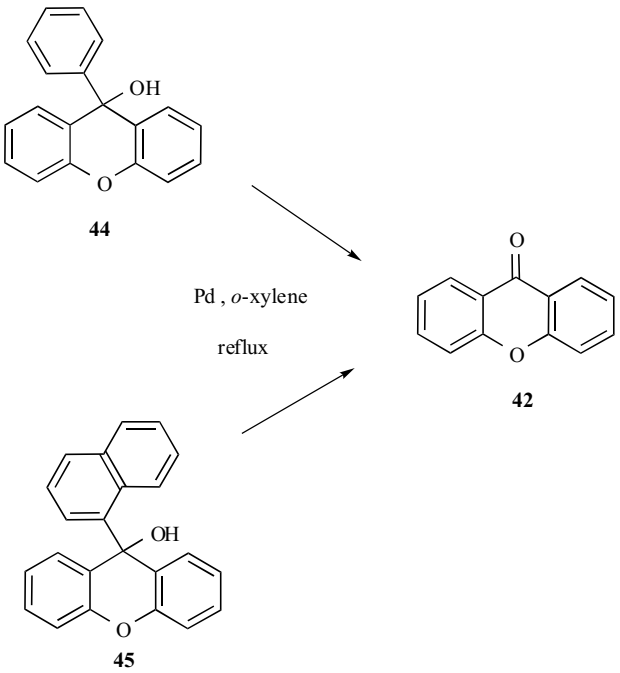
nitrilium salts (**39**) with activated aromatic rings in a Friedel-Crafts reaction [86]. This strategy consists in the reaction of an appropriate arylnitrile (**37**) and an excess of the benzoic methylesther (**38**) (Scheme **10**). In the same study, a new method was developed for xanthone carbonyl protection/deprotection, using *n*-butyllithium to convert xanthones into their corresponding alkenyl xanthenes and their efficient regeneration, at a later stage by dehydration. This strategy was applied to a wide range of reactions in the synthesis of *O*-methylsterigmatocystin [86] and 11-hydroxyl *O*-methylsterigmatocystin (see Table **2**) [87].

Methodologies in the synthesis of xanthones through the xanthene framework (Scheme **2**, **h)**) have also been investigated [88-91]. Green oxidations under heterogeneous or solvent-free conditions, by potassium permanganate supported on manganese dioxide (Scheme **11 a)**) [88,91] or montmorillonite K10 [89], were used effectively for the oxidation of xanthene (**41**) and its conversion into xanthone (**42**) at room temperature. Ultrasound and microwave methodologies have increased the rate at which the xanthone (**42**) was formed [88,89]. Investigations in anaerobic oxidations of xanthene by $[(bpy)_2(py)\text{-}Ru^{IV}O]^{2+}$ in acetonitrile solution furnished 9,9'-bisxanthene (**43**) by organic radical dimerization, and xanthone (**42**) by oxygen-atom transfer (Scheme **11 b)**) [90]. The xanthone (**42**) was obtained (>98%) from the oxidation of 9-arylxanthen-9-ols (**44-45**) by an appropriate palladium catalyst system in refluxing *o*-xylene (Scheme **12**) [92].

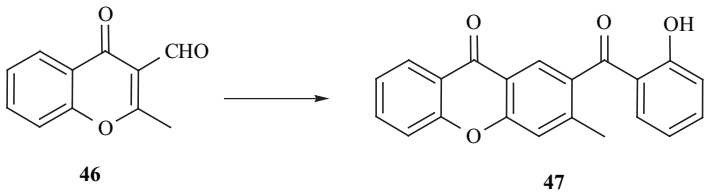
The synthesis of xanthones from benzopyran-4-ones [*for a general review see* 93], particularly from 3-acyl-2-methylchromones was of great interest in the last twenty years [94-96]. Ghosh *et al.* have introduced the strategy illustrated in Scheme **13**, in which 3-formyl-2-methylchromone (**46**) undergoes, in the presence of a base an intermolecular Michael initiated ring closure, the cycloaddition of a benzoxanthene, that on base catalyzed



Scheme 11.

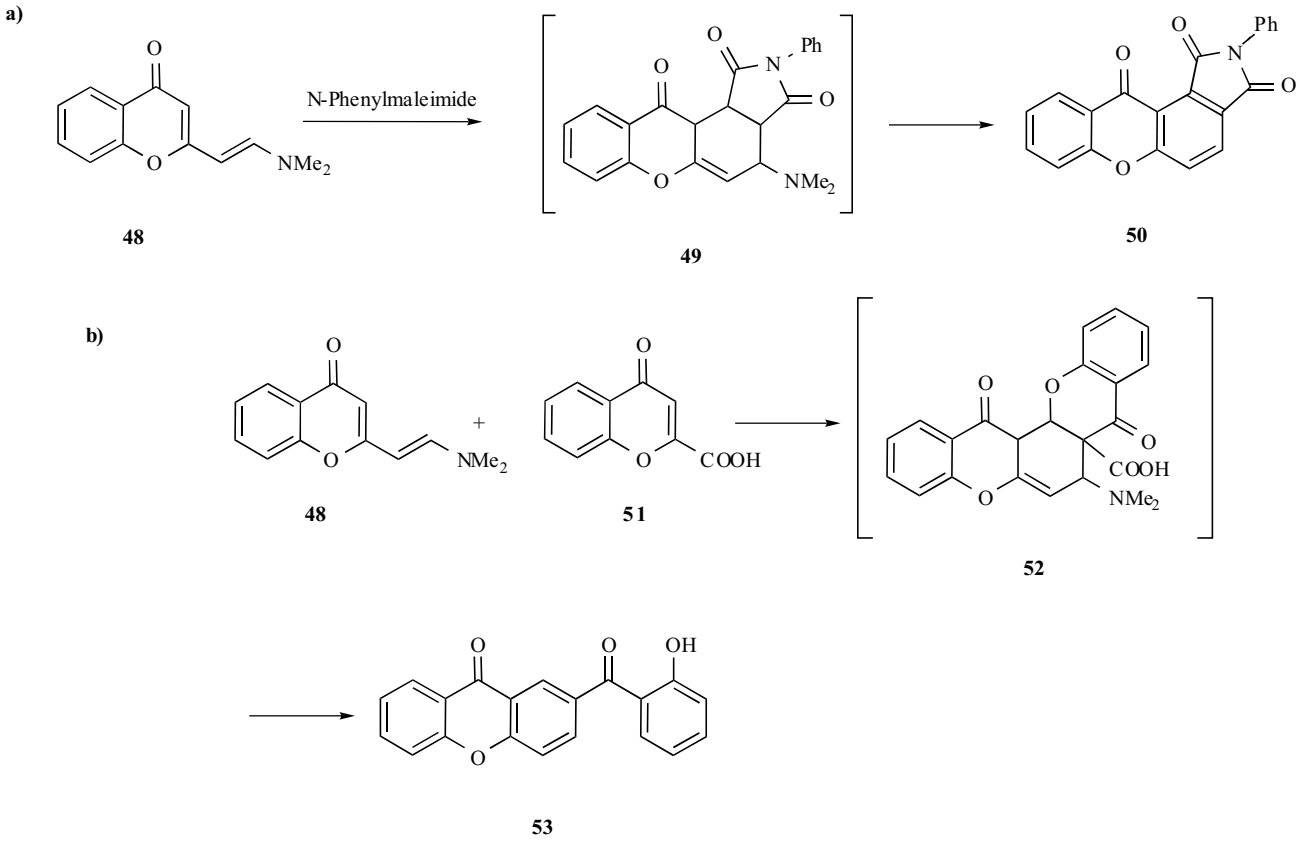


Scheme 12.

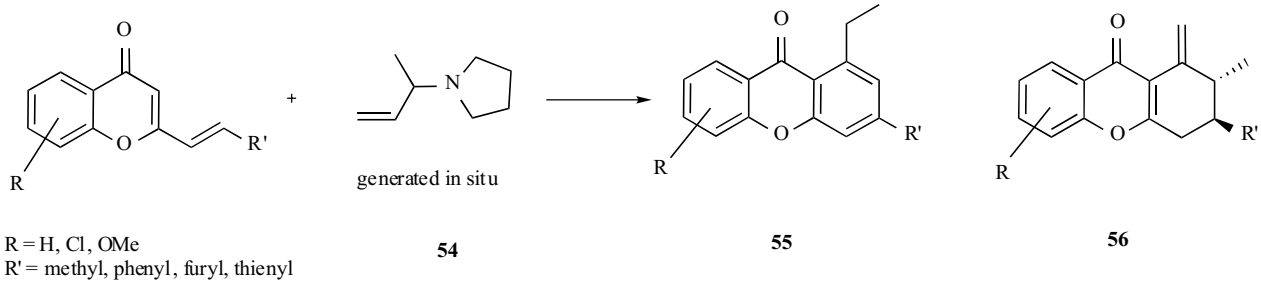


Scheme 13.

deacylative hydroxyl elimination and pyran ring opening, led to 3-methyl-2-salicyloylxanthone (**47**) [95]. This strategy was particularly useful in the synthesis of 1,2,3,4-tetrahydroxanthone derivatives [96,97]. Similarly, the 2-(2-dimethylaminovinyl)-1-benzopyran-4-one (**48**), with a strong electron-donating dimethylamino group, is a reactive diene likely to undergo [4+2] cycloaddition even with moderately active dienophiles and produced the xanthone (**50**) through the cycloadduct (**49**) (Scheme **14 a)**). The weak dienophile chromone-3-carboxylic acid (**51**) was found to react smoothly with the same diene (**48**) to give 2-salicyloylxanthone (**53**) through the cycloadduct (**52**) (Scheme **14 b)**).



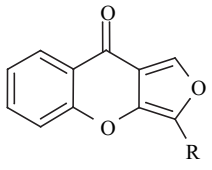
Scheme 14.



Scheme 15.

A novel approach to the synthesis of substituted xanthones was developed using the [4+2] cycloaddition reactions of enamines with aromatically substituted vinylchromones (Scheme **15**) [98]. With this method, 1-methyl- and 1-ethyl-xanthones (**55**) were obtained in a one-pot synthesis from the reaction of pyrrolidine enamines (**54**) obtained *in situ* from the corresponding alkyl ketones with vinylchromones, when taken as solvent a catalytic amount of pyrrolidine (Scheme **15**). 1-Methylidene- and 1-methylidene-2-methyl-substituted tetrahydroxanthones (**56**) were also obtained as byproducts (Scheme **15**) and were proposed as intermediates in the reaction, since they underwent facile conversion to 1-methyl- and 1,2-dimethylxanthones. Interestingly, the synthesis of 2-alkylxanthones has only been possible from an enamine generated from an aldehyde rather than from a ketone [98]. Additionally, cycloadditions of furanobenzopyrans with the general structure (**57**) furnished an entry to 2,3-disubstituted xanthones (**58**) and linear fused derivatives (**59**) (Fig. (**5**)) [99]. In another report, the reaction of dimethyl acetylene-dicarboxylate with 3,4-dehydroxanthones (**60**), in boiling bromobenzene gave a good yield of dimethyl xanthone-3,4-dicarboxylate (**62**) through the intermediate adduct (**61**) which, depending on the substituents, decomposed *via* thermal extrusion of ethylene or isobutenes (Scheme **16**) [100]. Moreover, dehydroxanthones obtained by a reaction between a cyclic ketone enamine and diacyl chloride, were transformed into xanthonic derivatives by catalytic dehydrogenation with Pd–C catalyst at atmospheric pressure in 70% yield [101].

Other syntheses of dehydroxanthones [*for a recent example see* 102,103], xanthenes [104], and benzophenones [40-42,105,106], could be highlighted due to the accessible transformation of these classes of compounds into xanthonic derivatives. Moreover, the synthesis of several isosters of xanthones, such as thioxanthenes [99,107,108], seleno-xanthenes [74], and azaxanthones [109,110], due to their similar reactivities could also be used for the synthesis of xanthones.



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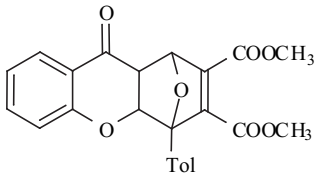

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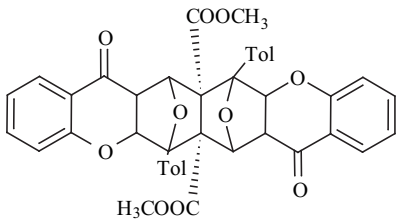
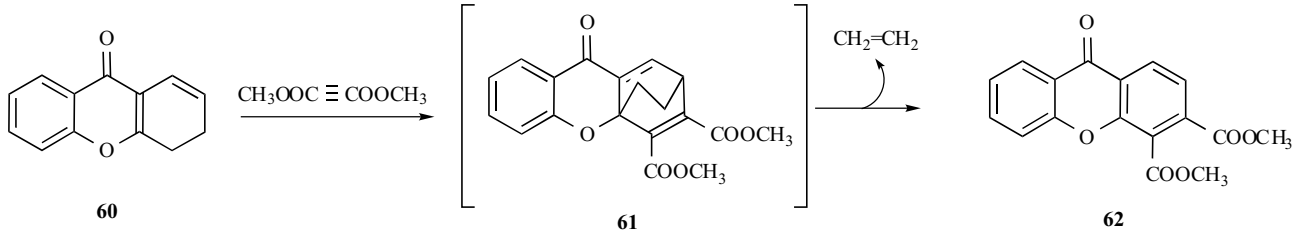


59

Tol = *p*-tolyl

Fig. (5).



60 **61** **62**

Scheme 16.

2.4. Strategies to Introduce Simple Substituents into the Xanthone Core

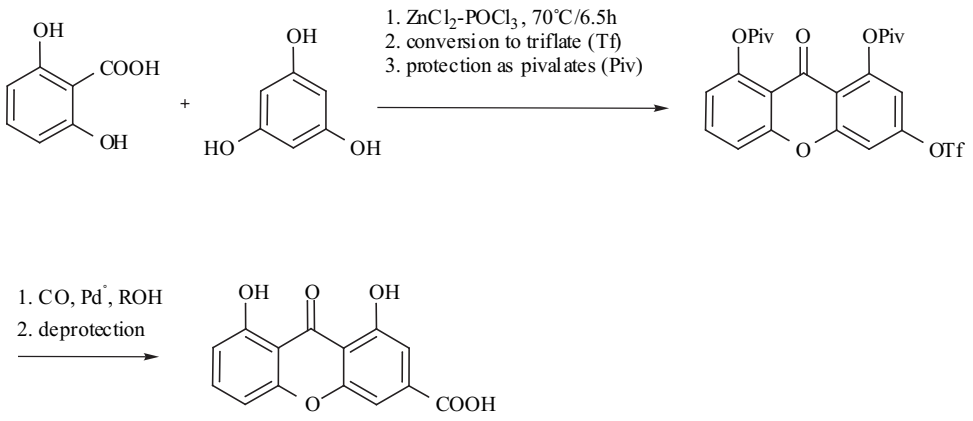
There are several strategies to provide the substitution pattern for the xanthone nucleus. The most flexible preparative route for xanthones provides small substituents in the aromatic ring of the building blocks prior to the formation of the pyrone ring; some substituents often serve the purpose of later molecular modification. Less frequently, the required substituents are directly introduced to the aryl moieties after the heteronucleus formation. In this case, the electronic effects of both the xanthone oxygen (O10) and the C9 carbonyl group (Fig. (**1**)) are normally responsible for the regioselectivity observed, *e.g.*, in the Claisen/Diels–Alder reactions (see Section 4).

Table **1** lists the common substituents used as groups to be replaced in the xanthone framework, as well as the references of the recent examples of activity-guided substitutions. From Table **1** can be outlined a recent strategy based on carbonylation of aryl triflates (Scheme **17**) that was developed to prepare new xanthone analogs of rhein [12]. The advantage of this approach is to avoid the oxidation step of methyl derivatives with toxic chromium salts. However, protection of the chelated phenol groups proved to be essential to carry out the palladium catalyzed carbonylation.

Table 1. Molecular Modifications After the Xanthone Nucleus Formation

Groups Modified	Final Substituents
acetyl	hydroxyl [8*]
amino	halogen [111*,112], cyano [112], hydroxyl [113]
bromo	hydroxyalkylamino [114,124-126,129], vinyltributyl [115]
chloro	methoxyl [116,117], dimethylamino [116], anilino [111*], diethylaminoalkoxyl [118,119]
formyl	1,4-dihydropyridinyl [120,131,132], carboxyl [121], arylhydrazonomethyl [54*]
hydroxyl	alkoxyl [122*,123,127,128,130,133,134], pyranones [135], tosylates[a] [136], α-methylene-γ-butyrolactones [137], triflates[b] [12*]
methyl	carboxyl [12*,138[c]], bromomethylene, cyanomethylene [35*], carboxymethyl [139]
nitro	amino [112,113,138,140]

* References cited in the text; [a] to obtain amines; [b] to obtain carboxyl groups; [c] xanthonecarboxylic acids were obtained by oxidation of the methyl group with potassium permanganate before the xanthone nucleus formation.



Scheme 17.

The substituents most frequently inserted in the aromatic rings after the xanthone nucleus formation are acetyl [141], formyl [121], halogens [54,115,142-145], and nitro groups [113,138]. Nevertheless, this strategy is limited because the pattern of substitution thus obtained often follows the electrophilic aromatic substitution rules and/or also depends on the presence of bulky groups.

Methods of glycosylation were used in xantho [2,3*g*]tetralins in which a modified Koenigs-Knorr procedure using mercuric bromide and mercuric cyanide as catalysts in the presence of the protected sugars, afforded the desired glycosides, in acceptable yields in contrast with the procedures employing silver carbonate or cadmium carbonate in the presence of calcium sulfate [146].

The strategies described above, as well as protecting/deprotecting methods have a crucial role in the pattern of substitution obtained and some of these approaches have already been discussed in a more detailed manner [8,9]. Nevertheless, interesting examples of selective etherifications in the synthesis of pyranoxanthones were recently reported [23,33]. These methods consist in the deactivation of the 1-hydroxyl group of the xanthone nucleus in the presence of a cuprous salt, as a catalyst. Selective etherification of the 3-hydroxyl group was achieved through the chelation of the cuprous ion with the hydroxyl group on C1 and the carbonyl at C9.

3. SYNTHESIS OF COMPLEX XANTHONES

Due to the important biological activities of xanthones, more complex derivatives have been prepared in recent years. The procedure used to synthesize complex xanthones does not always involve the initial construction of the xanthone. On the contrary, the xanthone core is usually constructed in the final steps of the synthetic pathway [*for example see* 147]. Recent advances in the synthesis of xanthones with fused rings such as prenylated xanthones (furano/pyrano), xanthonolignoids (linear/angular), and (di)benzoxanthones (linear/angular), as well as in the synthesis of miscellaneous xanthones such as dimers (C-O, C-C), polymers, and macrocyclic structures like crown ethers and calix[6]arenes incorporating xanthones have been accomplished.

3.1. Xanthones with Fused Rings

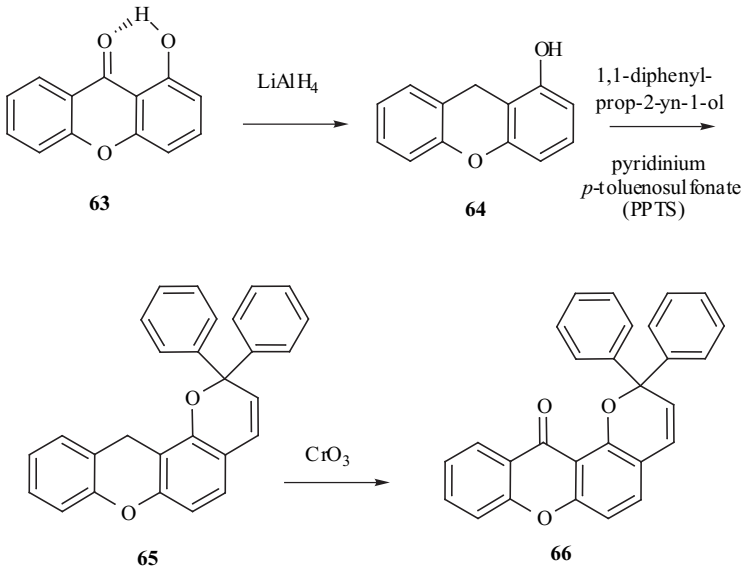
3.1.1. Pyranoxanthones and Furanoxanthones

Pyranoxanthones are essentially prepared by two methods. The first method involves the condensation of an appropriate chroman with a suitably substituted *o*-hydroxybenzoic acid followed by dehydration [148]. The second method deals with an initial nuclear prenylation of the xanthone followed by an oxidative ring closure [149]. Due to the formation of mixtures of isomeric products associated with both processes, some improvements in the synthesis of prenylated xanthones have been made.

A simple preceding methylation of a hydroxyl group of the xanthone nucleus with the subsequent cyclization has facilitated the manipulation of the resulting mixture of isomers and allowed better yields in the preparation of pyranoxanthones [23,150]. Also, a xanthene framework was successfully used as the initial substrate to modify the regioselectivity of the aryl moieties in the synthesis of tetracyclic angular pyranoxanthones [151]. The pyranoxanthene thus formed, was then converted to the corresponding xanthone by oxidation with SeO_2/xylene or ceric ammonium nitrate.

In order to investigate the photochromic properties of pyranoxanthones, their synthesis was achieved by condensation of 1,1-diphenylprop-2-yn-1-ol with the appropriate hydroxyxanthone under pyridinium *p*-toluenosulfonate (PPTS) catalysis [17]. However, 1-hydroxyxanthone (**63**), due to the hydrogen bonding between the hydroxyl group on C1 and the carbonyl at C9, failed to react with 1,1-diphenylprop-2-yn-1-ol in the presence of PPTS to give the pyranoxanthone (**66**). To circumvent this problem, a synthetic strategy was devised (Scheme **18**). This involved the reduction of 1-hydroxyxanthone (**63**) to the corresponding xanthene (**64**) followed by reaction with 1,1-diphenylprop-2-yn-1-ol in the presence of PPTS to give pyranoxanthene (**65**), which was then oxidized to form the pyranoxanthone (**66**).

Synthetic methods were designed to prepare the pyrano and furano analogs of 5,6-dimethylxanthenone-4-acetic acid (DMXAA) for bioactivity studies. These involved the formation of pyrano and furano rings either through the reaction of the xanthonic derivative and an alkyl halide,

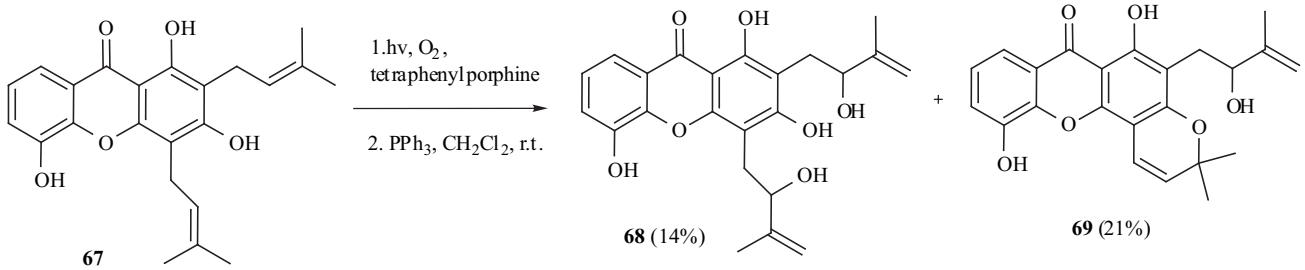


63 **64** **65** **66**

Scheme 18.

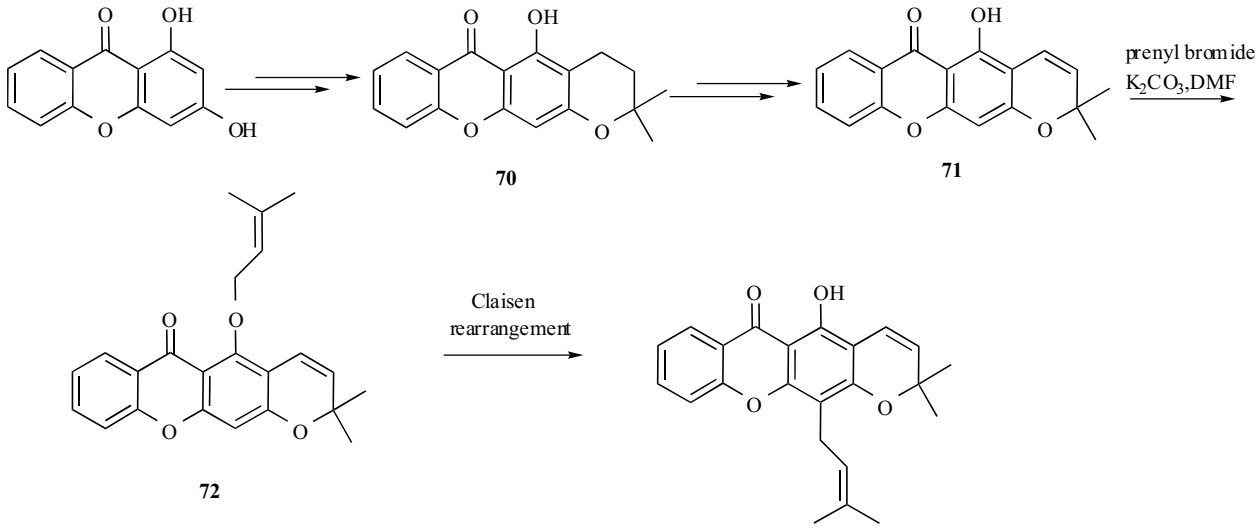
followed by cyclization by heating, or by direct heating of the appropriate xanthone in pyridine with an alkyl aldehyde [117].

Recently, an oxidative ring closure afforded prenylated (**68**) and pyranoxanthone (**69**) with the application of a new photo-oxidation–reduction methodology from the *o*-prenylphenol precursor (**67**) (Scheme **19**). The oxidation products distribution was shown to be dependent on the large group effect [152]. In the studies on the synthesis of natural products, a new synthesis of pyranoxanthones was described. This involved the preparation of a linear dihydropyranoxanthone (**70**), its conversion into the pyranoxanthone (**71**) and into pyranoxanthone (**72**), followed by a Claisen rearrangement (Scheme **20**) [15].



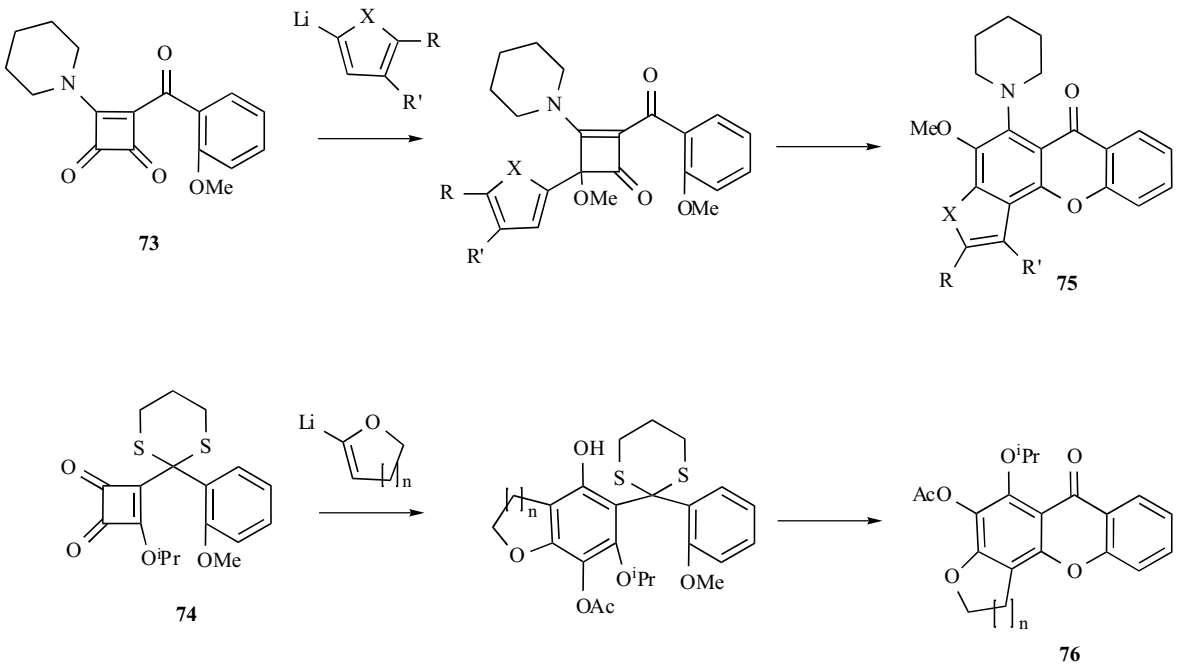
67 **68** (14%) **69** (21%)

Scheme 19.



70 **71** **72**

Scheme 20.



Scheme 21.

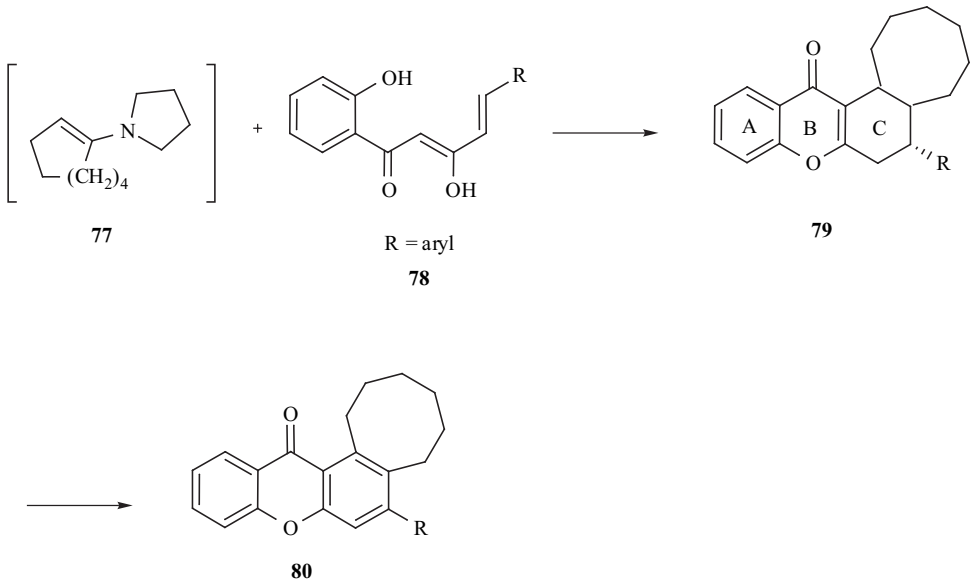
The original method for the syntheses of furanoxanthones involved the preparation of angularly-fused xanthones as illustrated in Scheme **21**. This method was based on the vinylketene-based benzannulation of 3-(*o*-anisoyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-diones (**73**) and 3-alkoxy-4-(2-(*o*-anisyl)-1,3-dithian-2-yl)-3-cyclobutene-1,2-diones (**74**), followed by the classic intramolecular loss of methanol and cyclization to xanthones (**75**) and (**76**), respectively [153]. Following this strategy, the regiocontrolled nucleophilic addition of heteroaryl-, cycloalkenyl-, and alkenyl-lithiates, followed by a cascade of electrocyclizations with subsequent deprotection in cases of dithiane derivatives and cyclization of the *o*-anisoylphenols, has afforded a variety of xanthones with unique structures [153,154].

The reaction of (*E*)-(2-hydroxyphenyl)-5-arylpent-4-ene-1,3-diones (**78**) with cycloalkanones/pyrrolidine (**77**) in refluxing dichloromethane also represents a new method for the synthesis of cycloalkana[*d*]xanthones (**80**) (Scheme **22**) [155]. Treatment of the dehydroxanthone intermediate (**79**) with pyrrolidine in boiling ethanol causes the ring C to readily aromatize and provide xanthone (**80**).

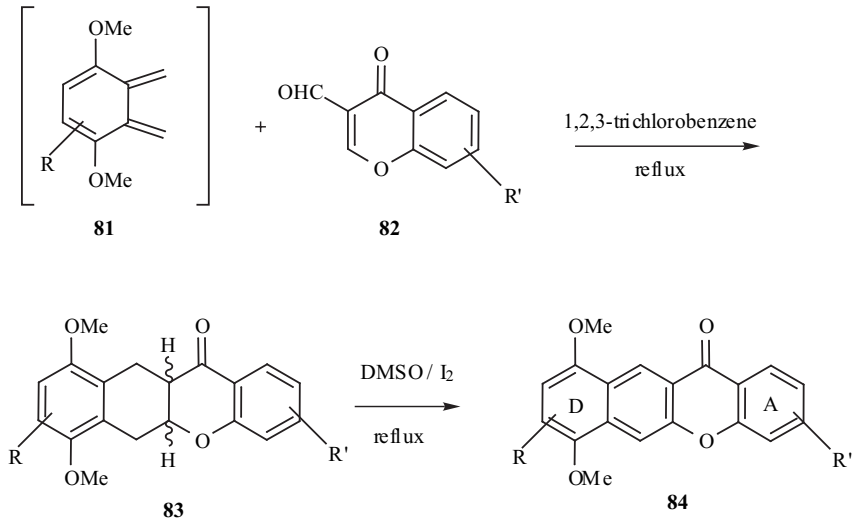
The synthesis of angular and linear xanthonolignoids, with a fused dioxane ring in the xanthonic structure, was recently reviewed [156].

3.1.2. Benzoxanthones

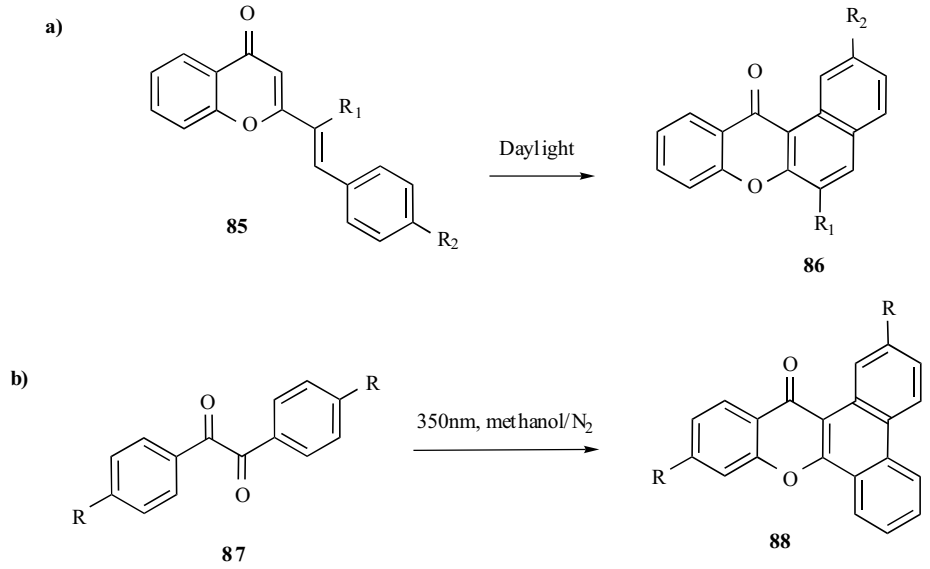
General construction of linear and angular benzoxanthones uses the naphatalene framework instead of



Scheme 22.



Scheme 23.



Scheme 24.

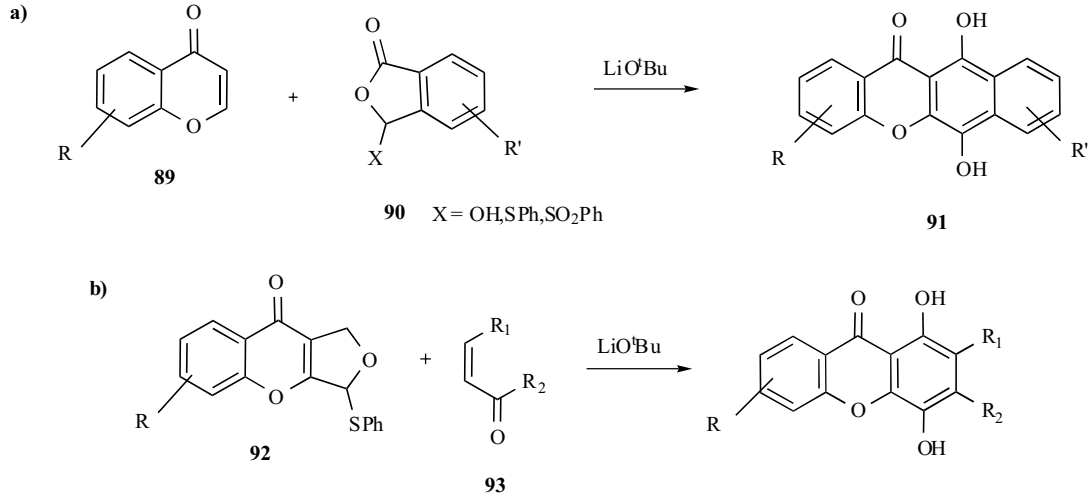
the benzene ring (building blocks on top of the Scheme **2**) [*for a review in literature see* 157, *for a recent example see* 116,158]. A new route to linear benzo[*b*]xanthones (**84**), by cycloaddition reactions of chromone-3-carboxaldehydes (**82**) with the *o*-benzoquinodimethane (**81**), followed by adducts (**83**) oxidation, was recently explored (Scheme **23**) [157,159]. In order to prepare benzo[*b*]xanthones for structure-activity relationships (SAR) studies as well as to investigate this synthetic methodology, novel benzo[*b*]xanthones with substituents in the A (R') [157,159] and D (R) rings were synthesized [157]. Interestingly, the same authors have previously discovered that the induced daylight photo-oxidative cyclization of some (*E*)-2-styrylchromones (**85**) gave benzo[*a*]xanthones (**86**), while studying an exposure to daylight of chloroform solutions of (*E*)-2-α-alkylstyrylchromones (**85**) (Scheme **24 a)**) [160]. Likewise, angular dibenzoxanthones (**88**) were produced from aromatic α-diketones (**87**) by a photochemical method (350 nm, methanol/N_2) (Scheme **24 b)**) [161].

Hauser *et al.* have described the condensation of a phthalide (**90**) with a benzopyranone (**89**), to regiospecifically provide a highly oxygenated natural benzo[*b*]xanthone (**91**) (Scheme **25 a)**) [162]. This methodology was extended to angular polycyclic xanthones and simple xanthones by condensation of a benzopyranonaphthalide (**92**) with various Michael acceptors (**93**), as general exemplified in Scheme **25 b)** [163].

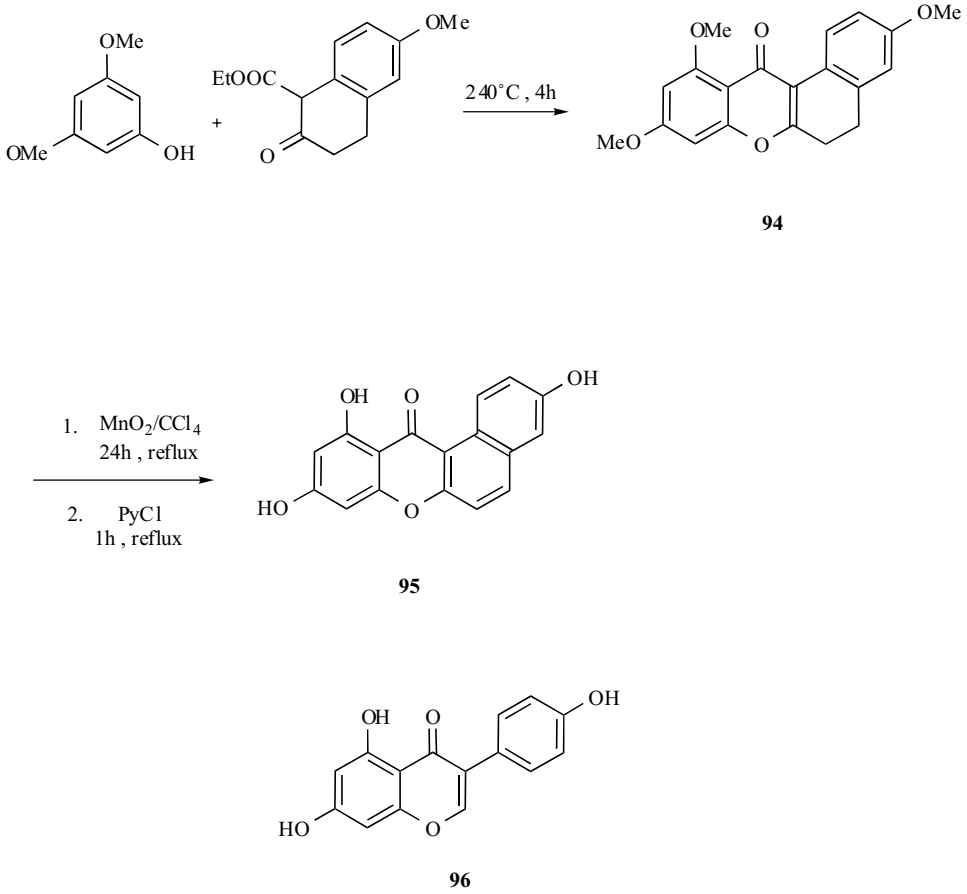
In the synthesis of the genistein (**96**) analogs for investigation of their effects on epidermal growth factor receptor tyrosine kinase, the benzoxanthone (**95**) was obtained from 5,6-dehydrobenzoxanthone (**94**) by oxidation with MnO_2 in CCl_4 followed by demethylation (Scheme **26**) [164].

3.2. Miscellaneous Xanthones

The synthesis of tetramethylenebis(oxy)- (**97**) and hexamethylenebis (oxy)-3-linked xanthones (**98**) was developed,



Scheme 25.

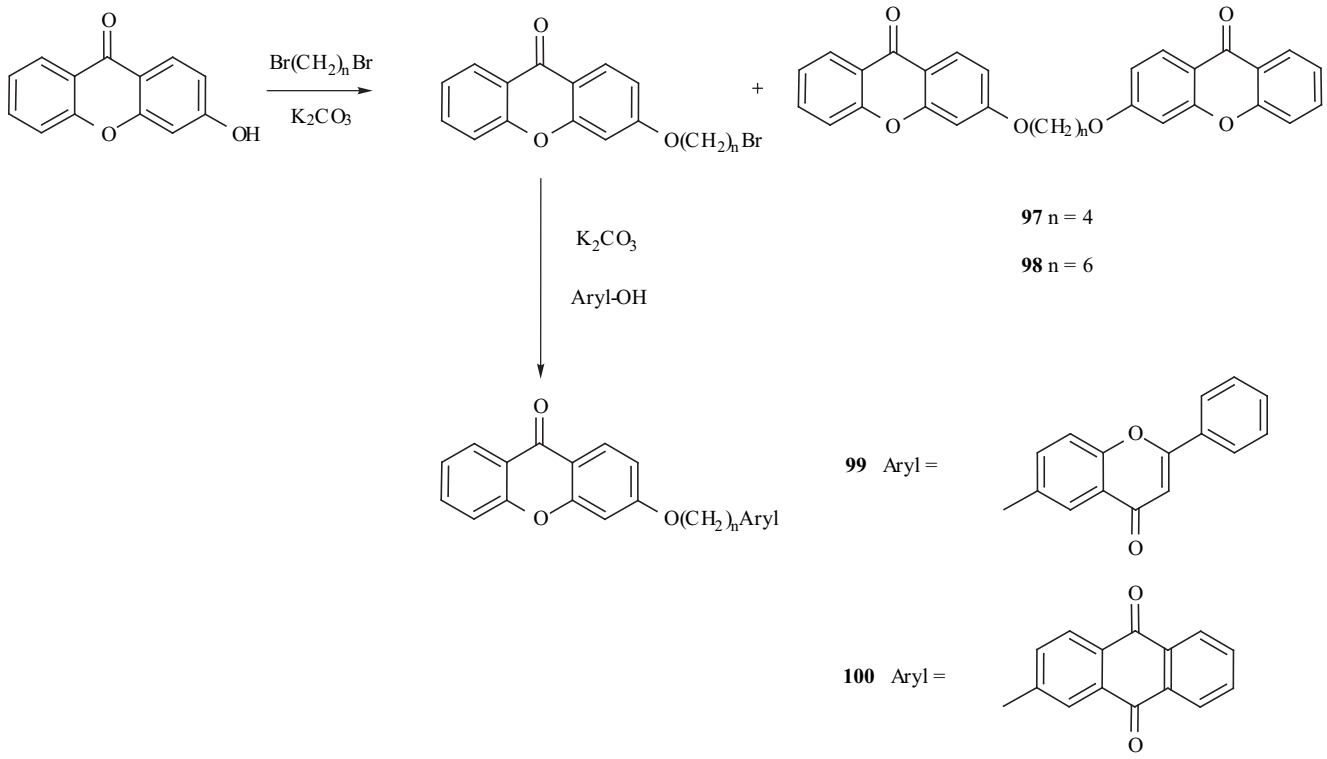


Scheme 26.

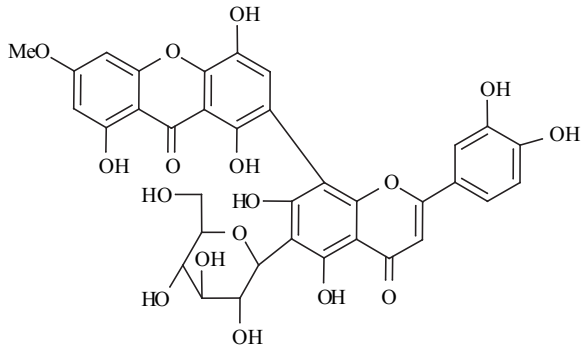
by the classical procedure described in Scheme **27**, to obtain xanthones for the evaluation of their cytotoxicity as potential bis-intercalators. The same method was also used for the preparation of the unsymmetrical bis-intercalators xanthone-flavone (**99**) and xanthone-anthraquinone (**100**) [122].

Many natural products with interesting biological activity contain symmetrical or unsymmetrical diaryl units (with a C-C linkage). An elucidative example of such molecules is swertifrancheside (**101**) (Fig. (**6**)), the first flavone-xanthone *C*-glycoside isolated from Nature, that acts as inhibitor of HIV-1 reverse transcriptase [165].

The total synthesis of the secalonic acids is yet another example of a construction of dehydroxanthones with a symmetrical diaryl unit. This was carried out by a homo-coupling reaction of the functionalized dehydroxanthene (**102**) (Scheme **28**) [166]. Further studies on the scope of this reaction, as well as on its application in the total synthesis of the secalonic acids were undertaken [166].



Scheme 27.



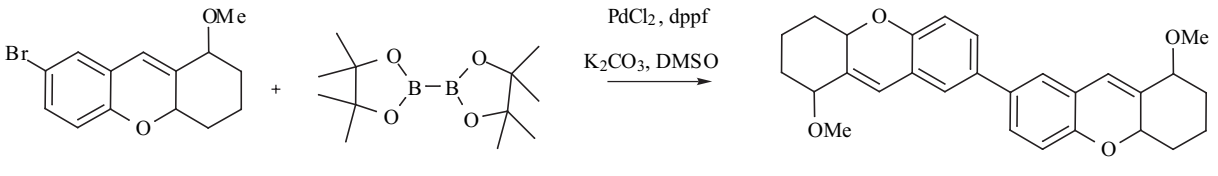
101

Fig. (6).

A new approach to the synthesis of xanthones (**105-106**) and poly(dixanthone)s with good yields was carried out through cyclization of 2-aryloxybenzonitriles (**103-104**) in trifluoromethanesulfonic acid (Scheme **29**). Nucleophilic condensation of a bisphenol with 2-fluorobenzonitrile or 3,3'-difluoro-4,4'-diphenyldicarbonitrile resulted in xanthone-iminium triflates, which were then converted to xanthone dimers by superacid-promoted Houben-Hoesch cyclization [167]. This synthetic approach was investigated for a novel series of polynuclear dixanthones (**105-106**) (Scheme **29**) as well as for a high molecular weight polyxanthone (**107**) (Fig. (**7**)).

In the process of evaluation of the chelating capacity of macrocyclic compounds, a new chelating agent, 2,7-dimethyl-4,5-bis(salicylidene amino-methyl)xanthone (**108**) (Fig. (**8**)) was prepared by treatment of 2,7-dimethylxanthone with *N*-hydroxymethylphthalimide, followed by hydrolysis to 2,7-dimethyl-di(aminomethyl) xanthone dihydrobromide and condensation with salicylaldehyde in the presence of an alkali [168].

Xanthones have been incorporated into the macrocyclic compounds used as molecular hosts. The calix[*n*]arenes are macrocyclic compounds capable of hosting small molecules in their molecular cavity. An annular modification of the calixarenes was based on dehydration of two adjacent hydroxyl groups of *p-tert*-butylcalix[6]arene, resulting in the



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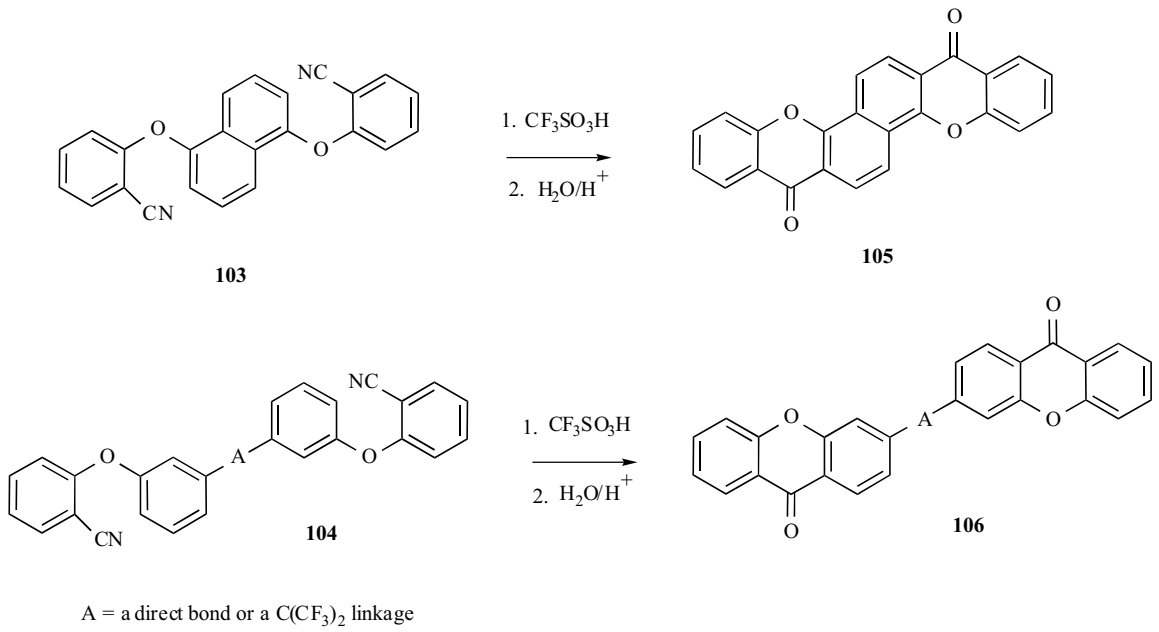
ddpf = 1,1'-bis(diphenylphosphino)ferrocene

Scheme 28.



Scheme 29.

formation of calixarene xanthene derivative (**109**) (Fig. (**8**)) [169]. The related xanthone calix[6]arene derivative (**110**) (Fig. (**8**)) was prepared by *O*-methylation of the phenol groups followed by CrO_3 oxidation of the xanthene methylene group and deprotection of the hydroxyl groups. McMurry coupling of calixanthone (**110**), after protection of their hydroxyl groups, afforded the dixanthylene (**111**) (Fig. (**8**)). These compounds (**109-111**) possess structural features of two of the most intensively investigated families of molecular hosts: the calixarenes and the crown ethers [169].

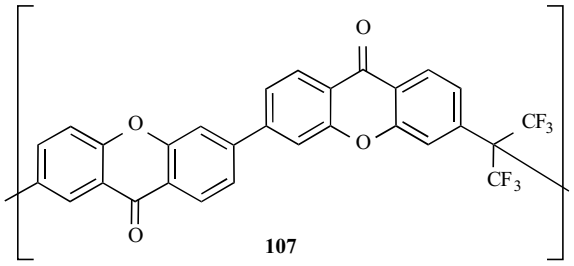
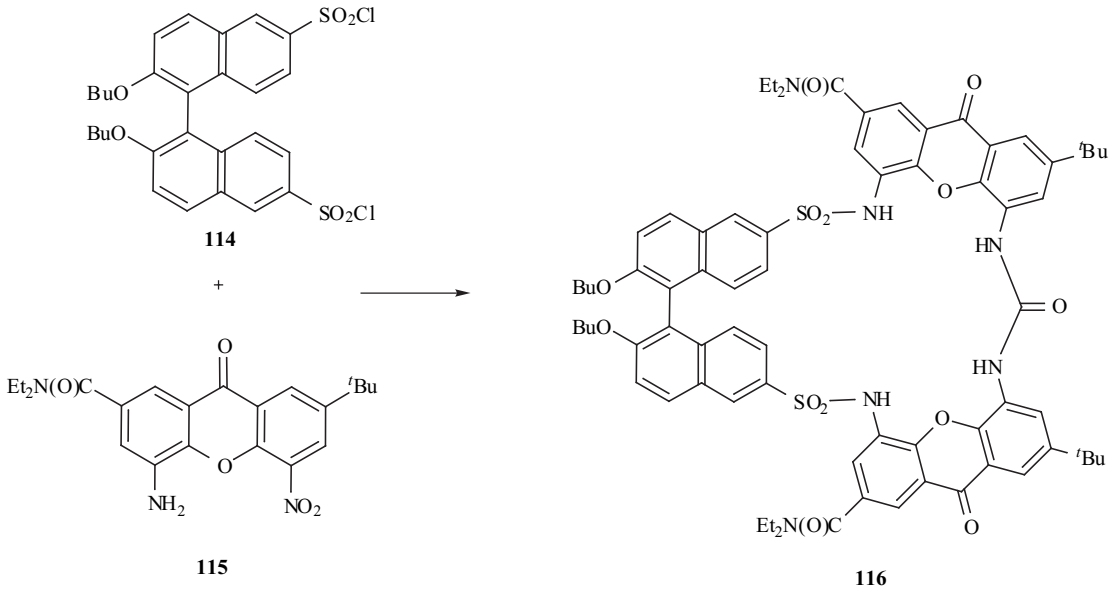
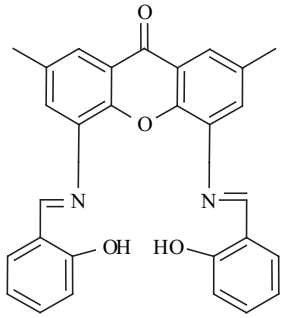


Fig. (7).

Moreover, syntheses of crown ethers with an incorporated xanthonic core have already been described [78,140,170-172]. An efficient preparation of 4,5-dioxyxanthone (**112**) [78] and 1,8-dioxyxanthone derivatives (**113**) [171,172] was accomplished by attachment of an appropriate polyethylene oxide chain to the corresponding dihydroxyxanthones with the incorporation into crown ethers with 18-, 21-, and 24-membered macrocyclic arrays (n = 3, 4, and 5) (Fig. (**9**)). Photophysical properties of xanthones have suggested that



Scheme 30.



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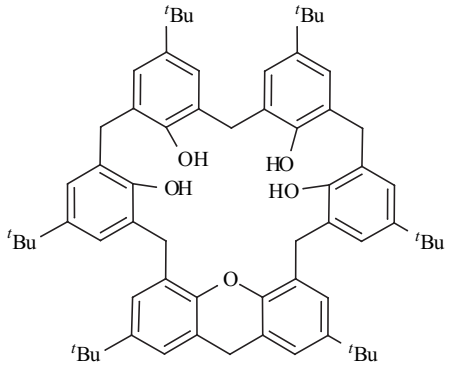

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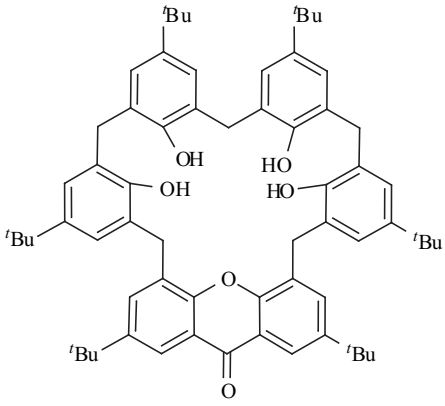

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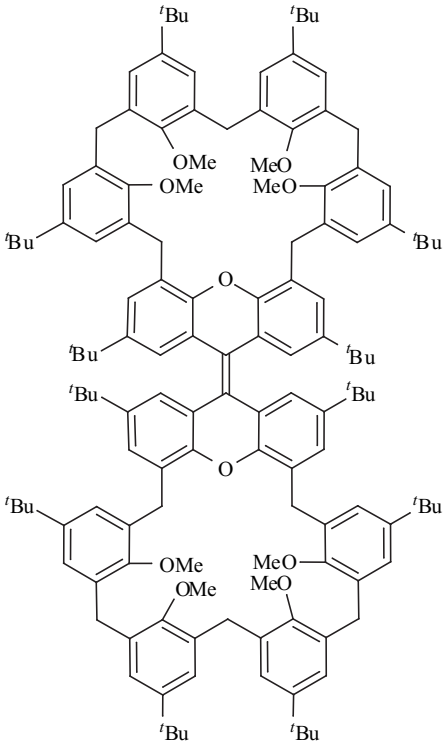


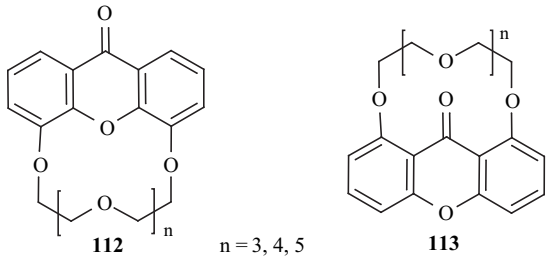
111

Fig. (8).

their incorporation into the crown ethers (**112-113**) or related structures would yield ionophores with desirable features [78].

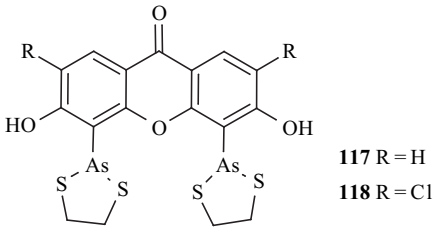
A macrocyclic receptor (**116**) formed by two xanthone units bonded to a dinaphthyl has shown to be able to extract enantioselectively zwitterionic amino acids from water in the presence of the well-known 18-crown-6 ether [170]. The receptor (**116**) was prepared using dinaphthyl derivative (**114**) and xanthone (**115**) as starting materials (Scheme **30**). Although the receptor (**116**) alone was unable to extract enantiomerically pure zwitterionic amino acids from water to chloroform, the addition of the 18-crown-6 ether to the biphasic system made this extraction possible. These authors have already combined an analog of compound (**115**) and 1-aza-18-crown-ether-6 that provided a receptor for phenylalanine extraction from water [140].

A miscellaneous xanthone-peptide-naphthalene derivative was synthesized to measure an intrachain contact formation in poly(glycine-serine) chains by applying the method of triplet–triplet energy transfer between xanthone and 1-naphthyl alanine [173]. The triplet donor xanthone, contrary to thioxanthone, was enabled to perform all measurements in water and to additionally test the influence of various solvents on chain dynamics. In another study for site-specific fluorescent labeling of recombinant proteins in living cells, blue-fluorescing bisarsenicals (**117**) and (**118**) (Fig. (**10**)) were generated by the usual mercuration and subsequent *trans*-metalation reactions upon 3,6-dihydroxyxanthone and its 2,7-dichloro derivative, respectively. These compounds (**117-118**) have furnished a substantial enhancement of fluorescence upon binding with a tetracysteine peptide [21].



112 n = 3, 4, 5 **113**

Fig. (9).



117 R = H

118 R = Cl

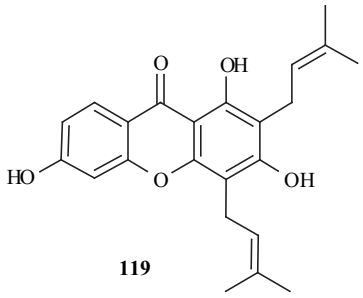
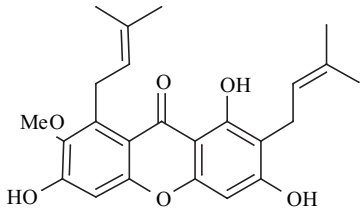
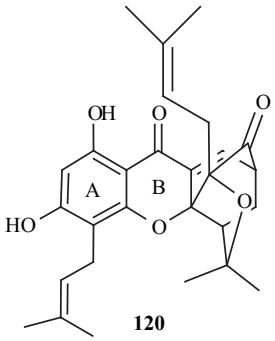
Fig. (10).

4. SYNTHESIS OF NATURAL PRODUCTS

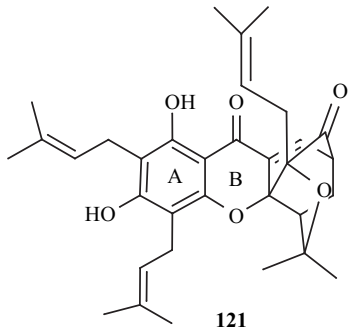
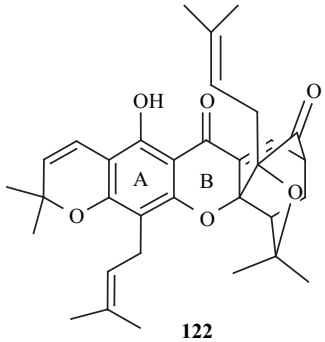
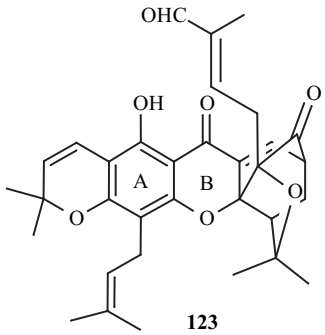
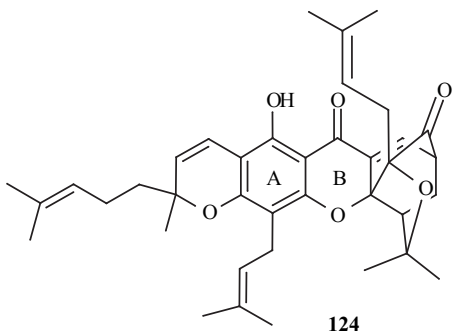
The total synthesis of natural products especially those with interesting biological activities and unusual structures still remains a challenge. Table **2** presents natural products whose syntheses have been reported in the last twenty years by the reasons stated above. Nevertheless, in the 80s and 90s, several studies still reported syntheses of xanthones as a methodology to assign unambiguously the structures of isolated compounds [174-176]. For previous studies, considering the synthesis of phytoxanthones, see references [8,9].

The continuing phytochemical studies especially of *Garcinia* species led to the isolation of several xanthone-derived natural products which possess unusual molecular architectures and diverse biological properties. The structural motif of many of these compounds is an intriguing 4-oxatricyclo[4.3.1.0]decan-2-one framework attached onto a

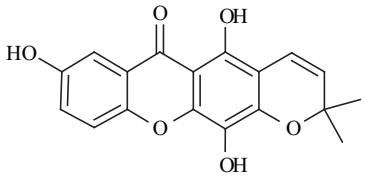
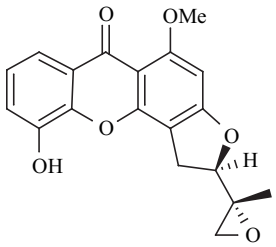
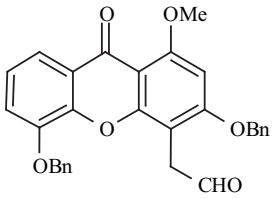
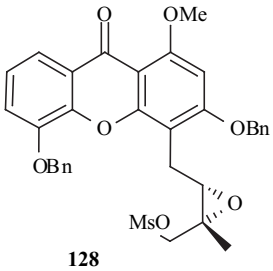
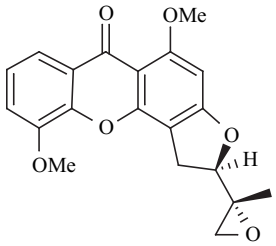
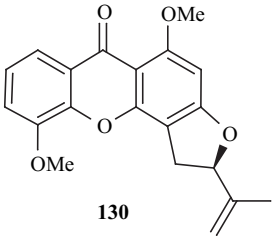
Table 2. Synthetic Strategies for More Complex Natural Xanthones

Natural Xanthones	Strategies in the Synthetic Pathway
Garcinone A  **119** [183]	- reaction of l,3-dihydroxy-6-methoxy- and 1,3,6-trihydroxyxanthone with 1-bromo-3-methylbut-2-ene in presence of methanolic sodium methoxide, to give the corresponding 3-methylbut-2-enylated xanthones; - synthetic xanthone (**119**) was found to be different from natural garcinone A.
α-Mangostin  **13** [59*]	- protected aryl anion addition to benzaldehyde furnishes through the parent alcohol, the corresponding benzophenone (Scheme **4**); - effective activation and/or protection of the hydroxyl groups; - because prenyl groups tend to cyclize, all of the reaction steps have been manipulated under mild reaction conditions; - PPh_3/CCl_4 [57*,58*] used for the cyclization and simultaneous removal of the methoxymethyl (MOM) group.
Forbesione  **120** [14*,184]	- Grover, Shah, and Shah reaction; - inspired in the proposed biosynthetic scenario; - tandem/regioselective Claisen/Diels–Alder/Claisen reaction; - 2-chloro-2-methylbutyne in the presence of KI and K_2CO_3 under CuI catalysis [185] essential for selective alkylation/propargylation of the 1,3,5,6-tetrahydroxyxanthone; - functionalization of the C1 hydroxyl group of the starting xanthone affected the regioselectivity of the cascade reaction *via* remote electronic effects; - the C-ring Claisen/Diels–Alder rearrangement was followed by the A-ring Claisen rearrangement [14*]; - the C9 carbonyl group, the O10, and the C18 dimethylallyl substituent were strategically placed to facilitate the building of the regular caged motif, by stabilizing the polar transition state of the C-ring Claisen rearrangement.

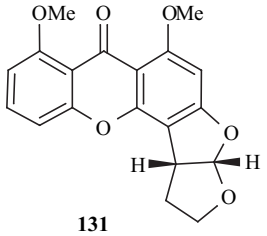
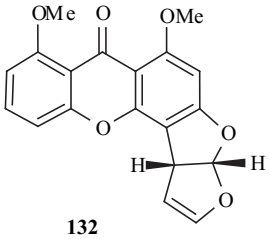
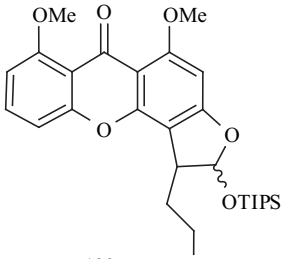
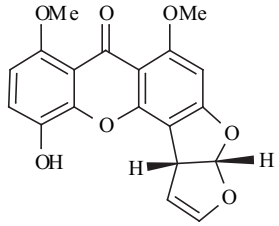
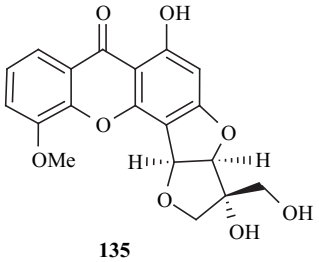
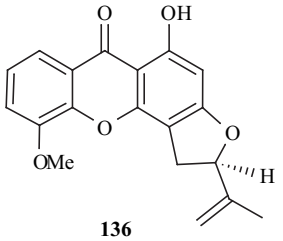
(Table 2)contd.....

Natural Xanthones	Strategies in the Synthetic Pathway
Desoxygaudichaudione  **121** [14*]	- propargylation of the C3 phenol of forbesione (**120**), followed by Lindlar reduction and Claisen rearrangement of the resulting alkene.
Desoxymorellin  **122** [14*,184]	- propargylation of the C3 phenol of forbesione (**120**), followed by Claisen rearrangement of the resulting alkyne.
Morellin  **123** [15*,186]	- application of the Alder–Rickert process for the synthesis of 5,5-dimethyl-methoxy-4-oxatricyclo[4.3.1.0]decan-2-one moiety.
Gambogin  **124** [14*]	- condensation of forbesione (**120**) with citral by using triethylamine and $CaCl_2.H_2O$ in methanol.

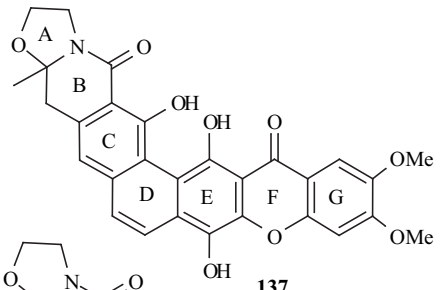
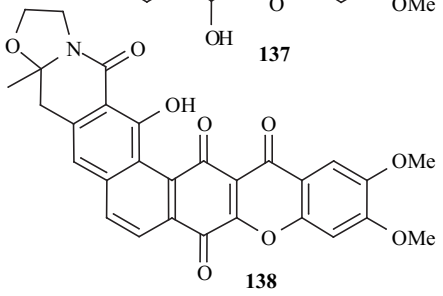
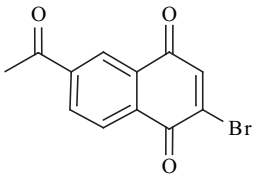
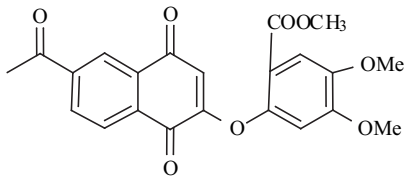
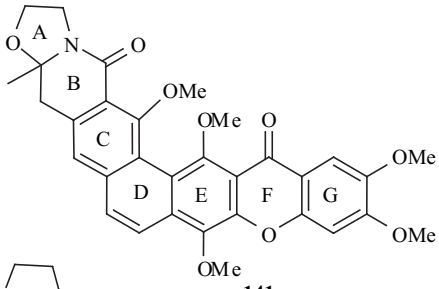
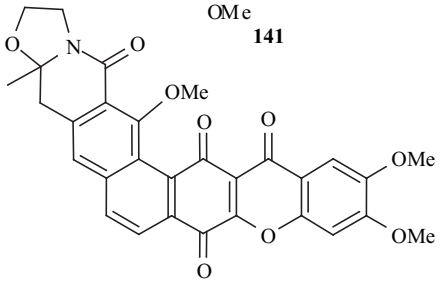
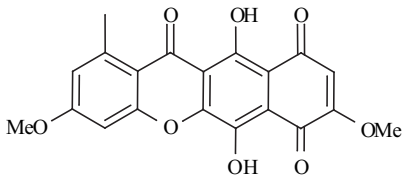
(Table 2)contd.....

Natural Xanthones	Strategies in the Synthetic Pathway
Atroviridin  **125** [187]	- the tetracyclic xanthone structure has been constructed by coupling an appropriate aryl bromide with an aldehyde and subsequent intramolecular conjugate addition on a quinone precursor; - the appropriate aryl bromide has been produced from aldehyde *via* a sequence of steps involving Baeyer–Villiger oxidation and Claisen cyclization; - use of a cerium ammonium nitrate-mediated oxidative demethylation and tandem Claisen cyclization to form the chromenequinone; - a final deprotection with concomitant annulation to form atroviridin has been based on the proposed biosynthetic pathway to xanthonoid natural products.
Psorospermin  **126** [13*,188,189]	- Grover, Shah, and Shah reaction; - key intermediates in the sequence:  **127**  **128** - 13 steps with an overall yield of 1.7%; - the use of polar solvents decreased the ratio of the rearrangement occurring at the 4-position in the Claisen rearrangement; - the key to the sequence was the di-demethylation and subsequent selective 3,5-bisbenzylation and the reductively cleavage of both benzyl groups (Bn) without reduction of the resulting epoxide; - the formation of the *Z*-olefin has been efficiently carried out by the method of Still and Gennari; - at the end, the use of stoichiometric Raney Nickel with potassium carbonate in a 1:1 mixture of ethyl acetate and ethanol at 60ºC afforded psorospermin (**126**).
Psorospermin methyl ether  **129** [190]	- Grover, Shah, and Shah reaction; - key intermediate in the sequence:  **130** - the key to the sequence involved installing the cyclic ether moiety in the down right hand quadrant of the molecule; - the double bond of the key intermediate (**130**) was oxidized to the diol using OsO_4; treatment of the diol with MsCl selectively activated the less hindered alcohol; subsequent treatment with K_2CO_3 has led to formation of the epoxide (3 steps); - in a previous study, deoxydehydropsorospermin methyl ether (**130**) has been obtained by the reaction of cuprous isopropenylacetylide with 4-bromo-1,5-dimethoxy-3-hydroxyxanthone [191].

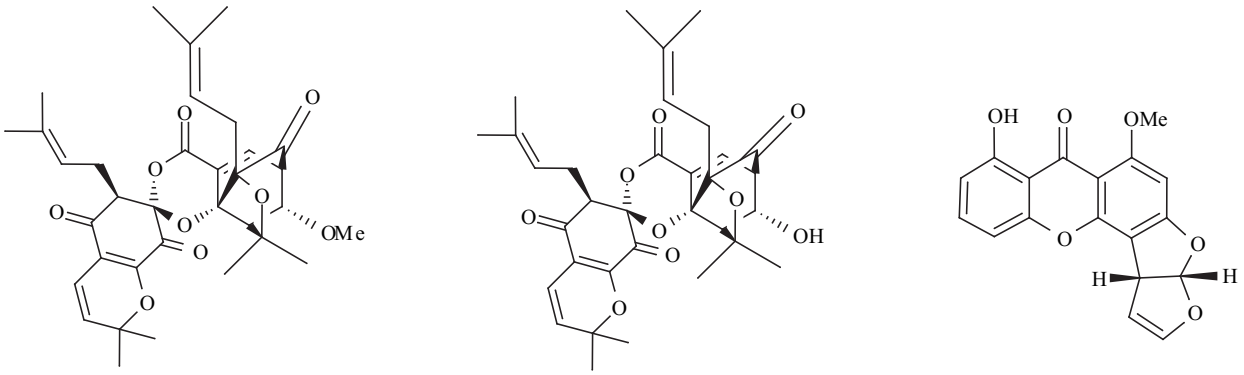
(Table 2)contd.....

Natural Xanthones	Strategies in the Synthetic Pathway
Dihydro-*O*-methylsterigmatocystin  **131** [38*]	- anionic Fries rearrangement; - the success of the anionic Fries rearrangement was dependent on the presence of a remote methoxyl substituent and was due to the Complex Induced Proximity Effect (CIPE); - the bisfuran structure has been incorporated into the phenol building block before the formation of the xanthone nucleus.
***O*-Methylsterigmatocystin**  **132** [86*]	- the imino-acylation reaction (*see* Scheme **10**); - key intermediate in the sequence:  **133** - applied a xanthone carbonyl protection/deprotection method (*see* Section 2.3.); - the butylene group has been oxidized to a xanthenyl spiroepoxide through the intermediate (**133**); - after acid-catalyzed oxirane hydrolysis, 3-chloroperbenzoic acid has carried out the initial epoxidation in the presence of 4 Å molecular sieves to form xanthone (**133**) exclusively.
11-Hydroxyl *O*-Methylsterigmatocystin  **134** [86*,87*]	- the imino-acylation reaction (*see* Scheme **10**) - total synthesis required 14 steps and was completed in >13% overall yield; - the xanthone carbonyl has been protected as a butylene to allow further elaboration of the molecule, and then compound (**134**) has been restored by peracid deprotection (butylene protection/deprotection tactics); - *O*-protection with methoxymethyl chloride (MOMCl) was not selective in contrast with silylation.
Isohydroxypsorofebrin  **135** [145*]	- key intermediate in the sequence:  **136** - based on the biosynthesis; - the 1-hydroxyl group is required to enable formation of the quinone methide and to yield the phenolic functionality in the final product; - the Heck reaction anion capture of the protected 1,3-dihydroxyiodoxanthones; - the key intermediate furanoxanthone (**136**) has been subjected to SeO_2-mediated allylic oxidation conditions; optimization of the reaction conditions using acetic acid as a co-solvent gave a more useful yield; oxidative cyclization of this material (**136**) gave the *exo*-alkene; - dihydroxylation, under phase-transfer conditions, gave (±)-isohydroxypsorofebrin (**137**) as a single diastereomer.

(Table 2)contd.....

Natural Xanthones	Strategies in the Synthetic Pathway
Cervinomycin A1 (137) and A2 (138)  **137**  **138** [68*]	- coupling of a *o*-bromo-naphthoquinone (**139**) with an appropriate *o*-hydroxybenzoic methyl ether in the presence of K_2CO_3; cyclization of the diphenylether (**140**) with polyphosphate ester;  **139**  **140** - Et_3N:BCl_3 conditions were found to be the best to cleave the methylether in C1 - cervinomycin A1 (**137**) has been obtained by reduction ($NaBH_4$) of cervinomycin A2 (**138**) - in another study [192], the oxazolo-isoquinolinone fragment (ABC rings) and the xanthone fragment (EFG rings) have been assembled first and coupled through a Wittig reaction; the key step has been the final construction of the central ring D through photochemical electrocyclization.
Cervinomycin A1-trimethyl ether (141) and cervinomycin A2-methyl ether (142)  **141**  **142** [193]	- heptacyclic framework of cervinomycin antibiotics (**141**,**142**) has been constructed through a C+EFG → CEFG → CDEFG → ABCDEFG approach; the photochemical generation of ring D was the key step.
Bikaverin  **143** [162*]	- condensation of (phenylsulfonyl)isobenzofuranones (**90**) with chromones (*see* Scheme **25 a)**) regiospecifically.

* References cited in the text.



144 **145** **146**

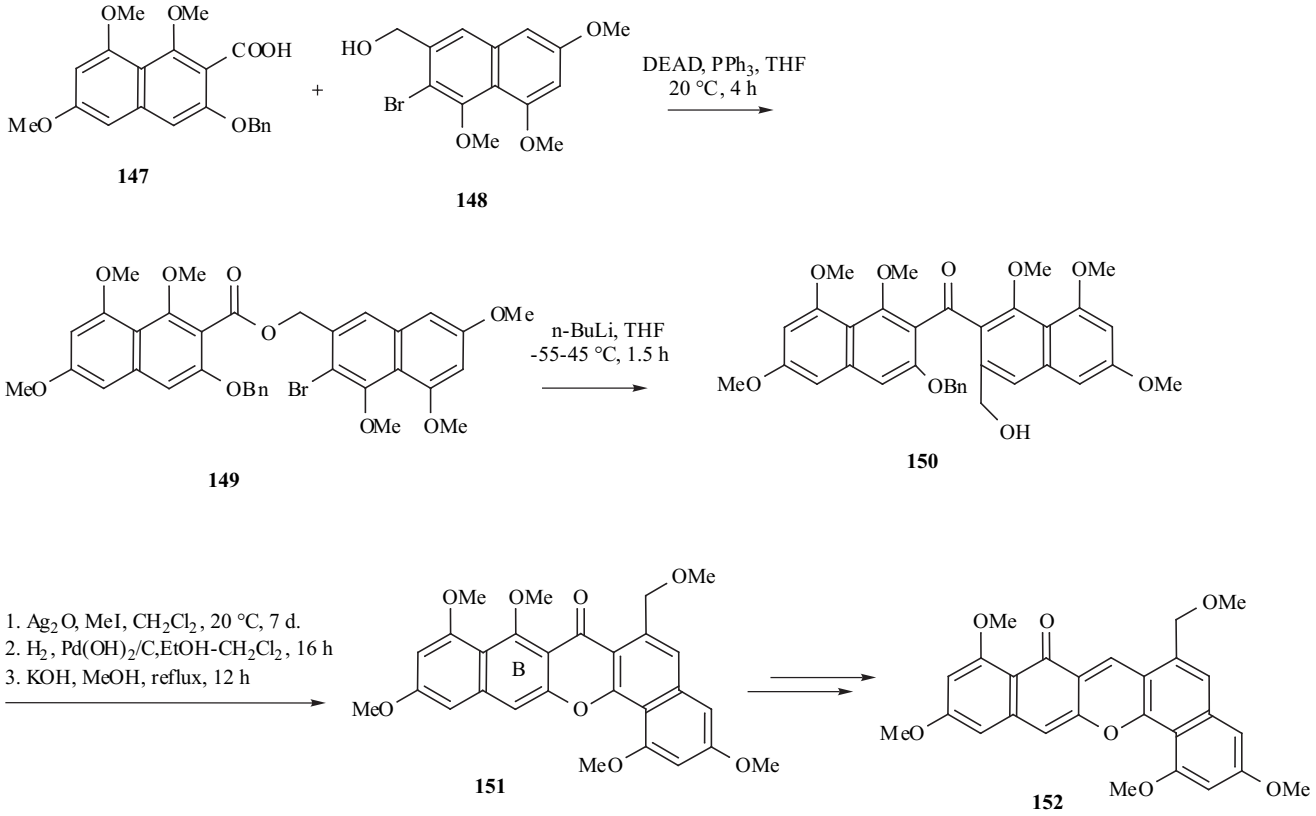
Fig. (11).

common xanthonoid ring system, such as in the case of forbesione (**120**), desoxygaudichaudione (**121**), desoxymorellin (**122**), morellin (**123**), and gambogin (**124**) natural products represented in Table **2** [177]. The total synthesis of 1-*O*-methyllateriflorone (**144**) (Fig. (**11**)), a xanthonoid structurally related to the previously mentioned compounds (**120-124**) was described by Nicolaou *et al.* with an interesting cascade sequence involving facile 6π electrocyclizations leading to the complex benzopyran system [177]. However, Tisdale *et al.* have previously achieved a regioselective synthesis of the tricyclic core of lateriflorone (**145**) (Fig. (**11**)) [178] *via* intramolecular aryl acrylate cycloadditions [179].

The fused bisfuran/heterocycle natural products, such as sterigmatocystin (**146**) (Fig. (**11**)) and the related compounds (**131-132, 134-135**) (Table **2**) have also been the targets of total syntheses which were carried out by Townsend's group [86,87].

As the majority of the compounds listed in Table **2** consist of highly functionalized xanthones units, they are synthetically challenging targets. In fact, some of the syntheses of natural xanthones have been the inspiring examples for a synthesis of new chemical structures for biological-activity evaluation, as in the case of psorospermin-quinobenzoxazine hybrids [180].

Another remarkable example is the synthesis of a topoisomerase I inhibitor, hypoxyxylerone, in which xanthone derivative (**151**) is a key intermediate [181]. This synthesis (Scheme **31**) involves a Mitsunobu coupling of



147 **148** **149** **150** **151** **152**

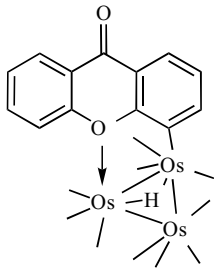
Scheme 31.

naphthyl partners (**147**) and (**148**) to form the ester (**149**), which was then converted to the dinaphthyl ketone (**150**) by anionic homo-Fries rearrangement. Debenzylation and cyclization of the compound (**150**) afforded the xanthone (**151**), which was reduced to penta(*O*-methyl)hypoxyxylerone (**152**). Interestingly, the conversion of the xanthone (**151**) into penta(*O*-methyl)hypoxyxylerone (**152**) in the final step required the application of a reduction-oxidation strategy, which involved a selective demethylation of the methoxy group on ring B, and the reduction of the carbonyl group with an excess of borane in dichloromethane. Silylation of the free hydroxyl group, followed by Saegusa-Ito dehydrosilylation with palladium(II) acetate furnished penta(*O*-methyl)hypoxyxylerone (**152**) [182].

5. REACTIVITY / THE XANTHONE CORE AS KEY INTERMEDIATE

In this section, recent studies on the reactivity of xanthones and their application as key intermediates in the synthesis of highly functionalized structures will be discussed. This strategy is mainly associated with the reactivity of the carbonyl group [111,194-202] and in a lesser extent, to the ether function [203]. Although some studies represent a new strategy for preparing xanthone-related compounds such as benzophenones [203], a major part deals with the construction of complex structures carrying a xanthene framework [196,198-202,204]. Moreover, the xanthone nucleus was found to be involved in many key-intermediates in the synthesis of fused naphthalenes [205] as well as of isoquinolines [111,115,195,206].

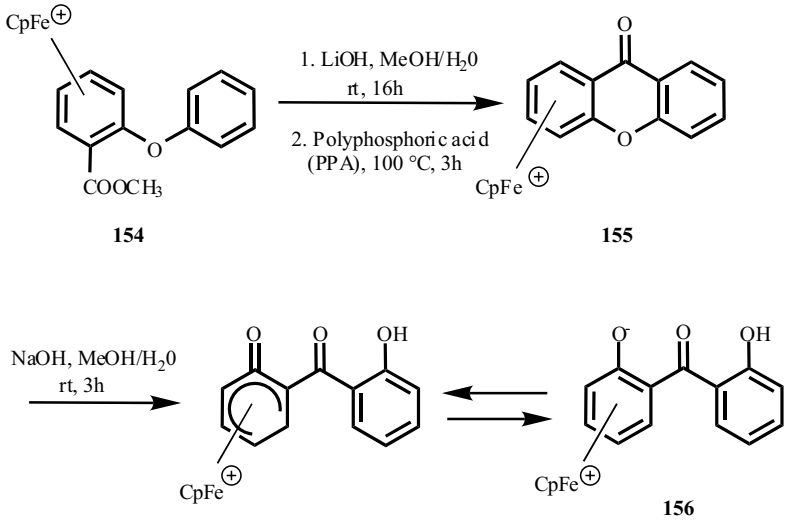
Though, the carbonyl in the xanthone core is known to be susceptible to hydride reduction [46,207] and to nucleophilic attack by alkyl-[208] and aryllithium reagents [209], some studies have documented the stability/low reactivity of the carbonyl in the xanthone nucleus when compared to related ketones [210,211]. Contrary to other aromatic ketones, it was found that the xanthone nucleus was inert to deoxygenation to form a corresponding hydroaromatic derivative in the presence of hydrogen donor solvents at high temperatures [211]. Likewise, an attempted hydrogenation of xanthone by alcohol complexes of tungsten has failed to produce any reaction [210]. The behavior of the xanthone nucleus toward organometallic clusters is exhibited by the formation of the product (**153**) (Fig. (**12**)), in which the endocyclic oxygen of the xanthone is bonded to triosmium clusters [211].



153

Fig. (12).

The xanthone has also found use as an intermediate for the novel synthesis of *o,o'*-disubstituted benzophenones, which involves the multistep construction of a cationic xanthone iron complex (**155**), as illustrated in Scheme **32** [203]. This route is based on nucleophilic substitution and addition reactions, facilitated by transition metal arene complexes accommodated in the xanthone framework. In this synthesis, the η^6-diaryl ether-η^5-cyclopentadienyliron hexafluorophosphate (**154**) as starting material for the synthesis, demonstrated a powerful activation for nucleophilic aromatic substitution induced by the cyclopentadienyl iron moiety. This represents a new approach for a Friedel-Crafts reaction. This methodology has allowed a nucleophilic ring-opening of the xanthone framework (**155**) to furnish the zwitterionic benzophenone (**156**), followed by a one-pot cyanide addition-decomplexation, which is useful for the preparation of *o,o'*-disubstituted benzophenones.

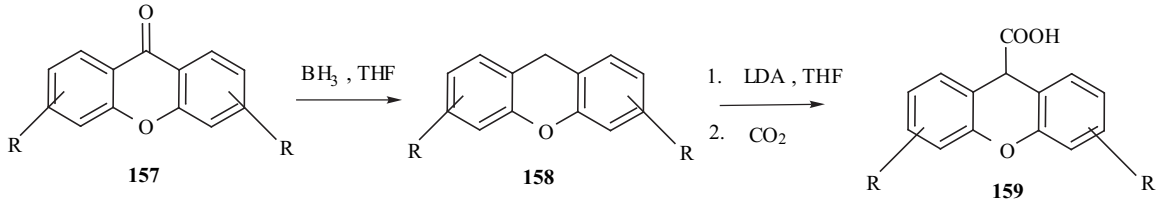


154 **155**

156

$CpFe^+ = \eta^5$-cyclopentadienyliron hexafluorophosphate

Scheme 32.



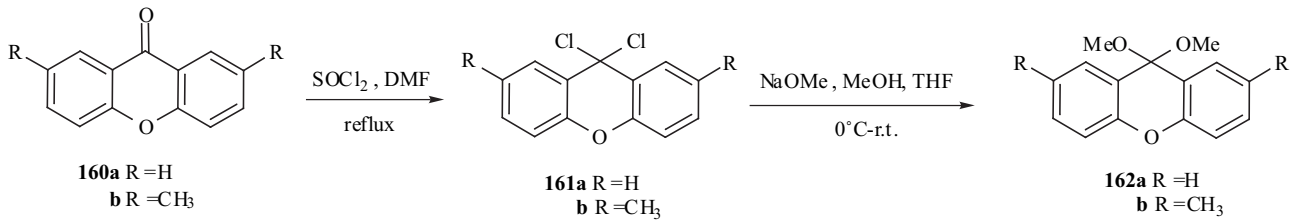
Scheme 33.

Xanthones, being 9*H*-xanthen-9-ones, are important intermediates for the synthesis of biologically active xanthenes. Thus, a series of xanthene-9-carboxylic acids (**159**) was synthesized through lithiation followed by carboxylation of suitably substituted xanthenes (**158**) (Scheme **33**) to give carboxamide derivatives of 5'-amino-2',5'-dideoxy-5-ethyluridine for their investigation as inhibitors of *Herpes simplex* virus thymidine kinase [198]. The xanthonic intermediates (**157**) obtained *via* Ullmann reaction were reduced by BH_3 in tetrahydrofuran to furnish the xanthenes (**158**) (Scheme **33**).

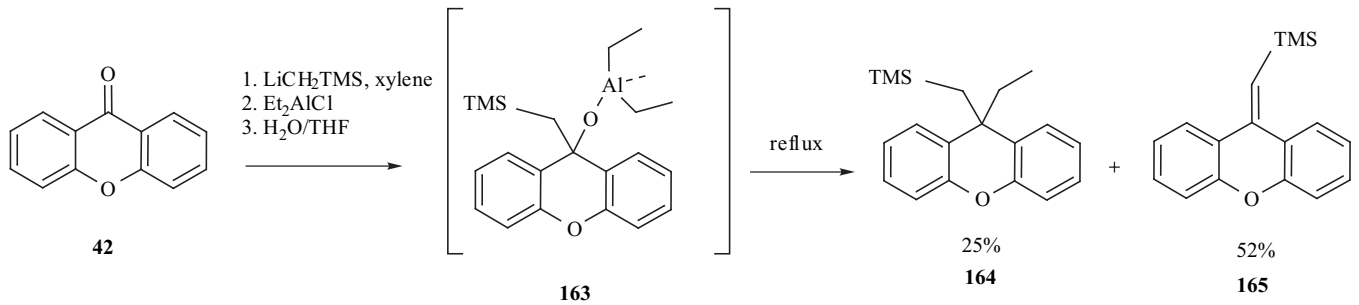
Investigations on xanthen-9-ylidene as protecting groups in glycerol chemistry have led to the preparation of 1,2-*O*-(xanthen-9-ylidene)glycerol and 1,2-*O*-(2,7-dimethylxanthen-9-ylidene)glycerol [202]. The key reagents required for the preparation of 1,2-*O*-(xanthen-9-ylidene) and 1,2-*O*-(2,7-dimethylxanthen-9-ylidene derivatives (Scheme **34**) were 9,9-dimethoxyxanthenes (**162a**, **162b**). The latter (**162**) were prepared by heating, under reflux, the corresponding xanthones (**160**) with thionyl dichloride, in the presence of a catalytic amount of dimethylformamide, to afford 9,9-dichloroxanthenes (**161**), followed by treatment with sodium methoxide in methanol–tetrahydrofuran (Scheme **34**).

Also, in the synthesis of vinylsilanes (**165**) (Scheme **35**), the xanthone (**42**) was used as the starting material in one-pot procedure involving the addition of (trimethylsilylmethyl)lithium into the ketone group followed by addition of diethylaluminum chloride and then a small amount of water [199]. This procedure employed an organoalane to mediate the E1-like vinylsilane formation with the β-silyl group providing additional stabilization of a carbocation intermediate (Scheme **35**).

In a study to evaluate the potential of spiro[dithiolane-fluorene] analogs as molecular switching elements in information storage devices, a chiral spiro[(4-*N*,*N*-dimethyldithiocarbamato)-(2-*N*,*N*- dimethylimino)-1,3-dithiolane-5,9'-xanthene] (**168**) was obtained [201]. The general synthesis is represented in Scheme **36**: lithiation of a methylene(bisdimethyldithiocarbamate) (**166**) was followed by quenching with xanthone (**42**) to yield the tertiary alcohol (**167**). Subsequent dehydration and cyclization promoted by strong acids followed by anion exchange using KPF_6 gave the required compound (**168**). The reductive coupling of the xanthone (**42**) was easily achieved in tetrahydrofuran and saturated aqueous ammonium chloride in the presence of zinc, to afford the corresponding pinacolic alcohol (**169**) in high yields (Fig. (**13**)). This constitutes an important

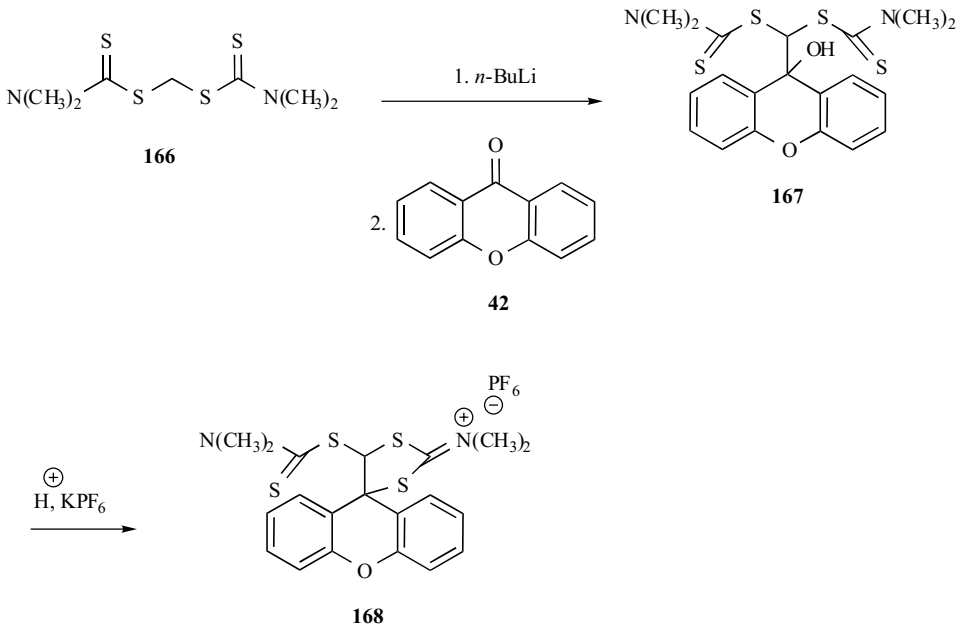


Scheme 34.



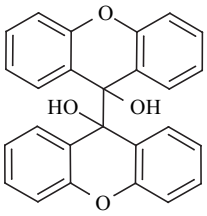
TMS = trimethylsilyl

Scheme 35.



Scheme 36.

method for the formation of vicinally functionalized carbon-carbon bonds [204].



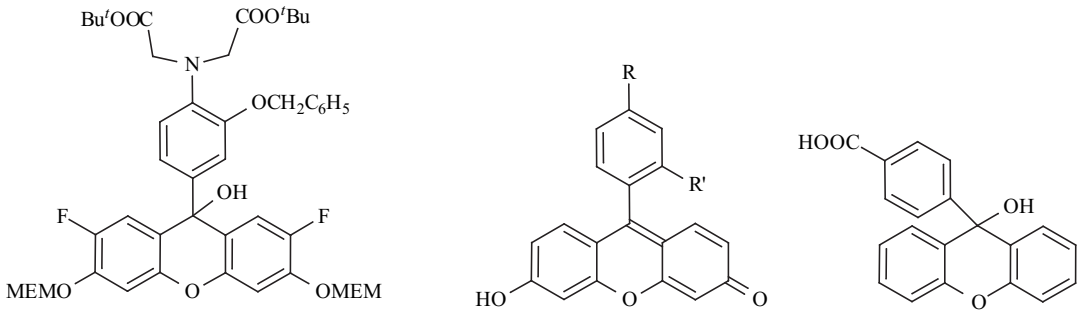
169

Fig. (13).

The reactivity of the carbonyl group was also exploited in the synthesis of fluorescence probes with a xanthenyl (**170**) [196] or a fluorone moiety (**171**) (Fig. (**14**)) [197]. The advantage of this synthesis of the fluorone probes through the Grignard coupling of substituted bromobenzenes and xanthone is that it gives a single desired fluorone product, instead of two isomers normally obtained by the condensation of phthalic anhydride and resorcinol [197]. Similarly, the synthesis of 9-hydroxy-9-(4-carboxyphenyl) xanthene (**172**), a new linker for the solid phase synthesis of peptide amides, was achieved in good yield by treatment of xanthone with 4-bromotoluene in a Grignard reaction (Fig. (**14**)) [200].

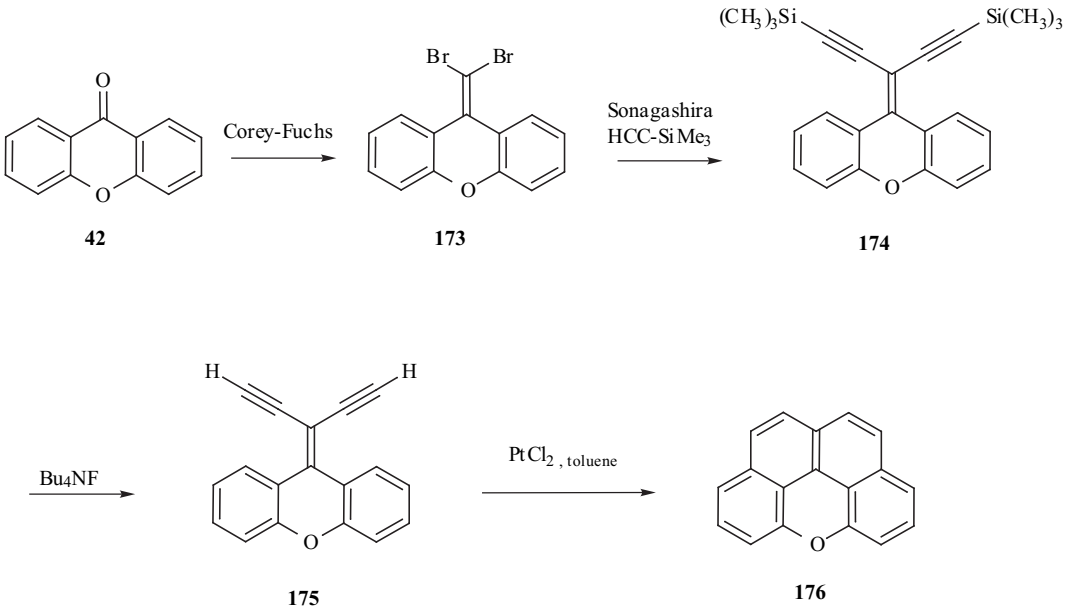
Moreover, the xanthone framework (**42**) was also applied to the synthesis of fused naphthalenes (**176**) [205]. Scheme **37** illustrates the four steps used to accomplish the overall naphthoannulation. As xanthone (**42**) was sluggish in the Corey-Fuchs olefination it was first converted to dibromoalkene (**173**), which subsequently furnished the corresponding 1,1-bis(trimethylsilylethynyl) alkene (**174**). Desilylation of compound (**174**) gave the parent diyne (**175**). A transition metal-catalyzed double ring closure of the 1,1-diaryl-2,2-diethynylethylene (**175**) resulted, although in low yields, in a naphthalene ring system (**176**) embedded in a larger polycyclic network.

Xanthone derivatives were also used as key intermediates in the synthesis of isoquinolines (**177**) and related frameworks (**178-180**) (Fig. (**15**)) [111,115,195,206]. [1]Benzopyrano [2,3,4-*i*,*j*] isoquinolines (**177**) (Scheme **38**)



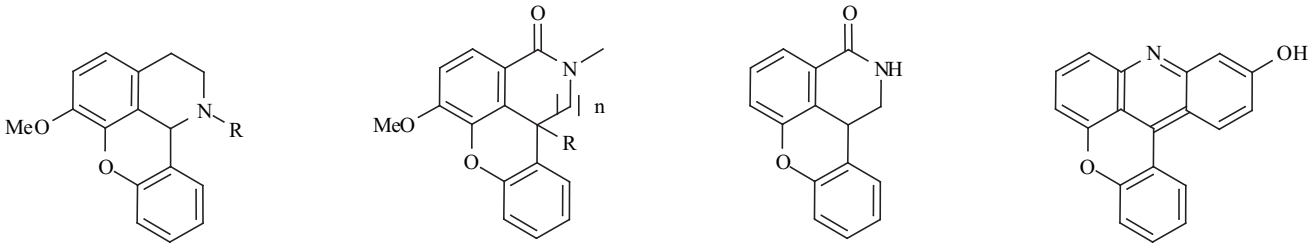
170 **171** **172**

Fig (14). Fluorescence probes for protein kinase C (**170**) and galactosidase (**171**) activity and a linker for solid phase peptide syntheses (**172**).



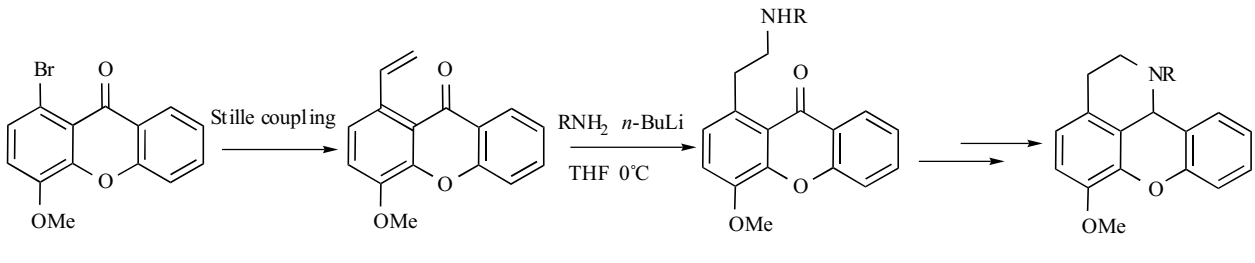
42 **173** **174** **175** **176**

Scheme 37.



177 **178** **179** **180**

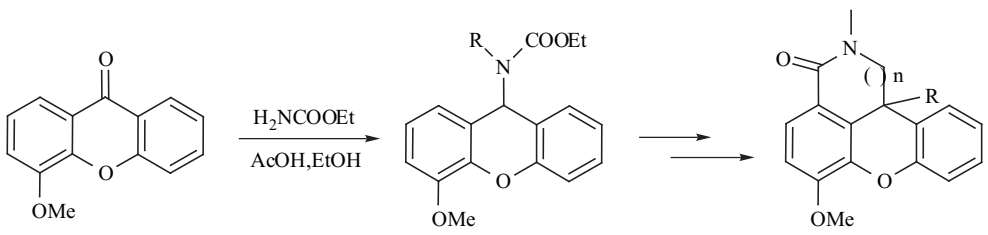
Fig. (15).



181 **182** **183** **177**

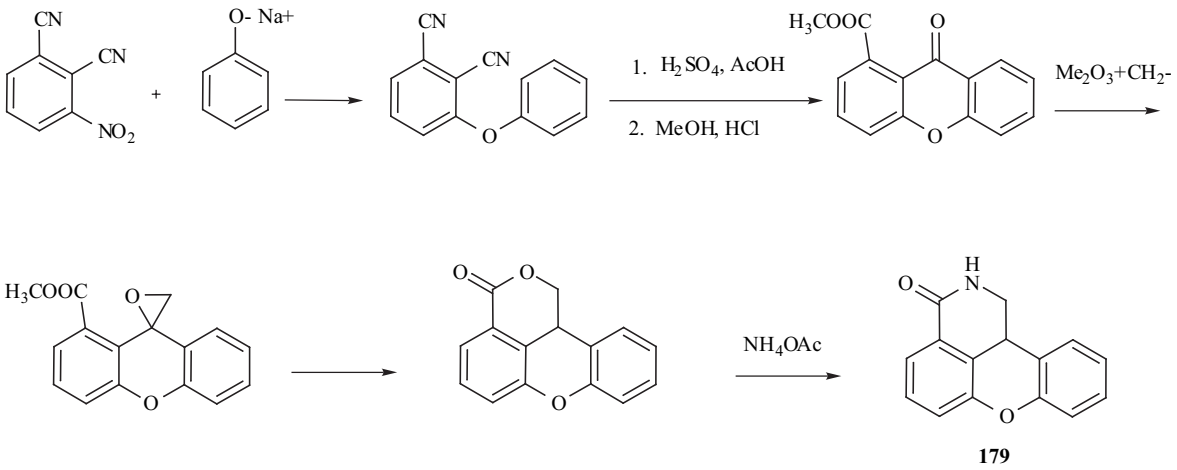
Scheme 38.

were synthesized from 1-bromo-4-methoxyxanthone (**181**) by assembly of the isoquinoline ring in three steps: *peri*-carbonyl vinylation to give compound (**182**), hydroamination with the lithium salt of a primary amine and ring-closing reduction of the xanthone carbonyl of derivatives (**183**) with $NaBH_4$/glacial acetic acid to furnish



184 **185** **178**

Scheme 39.



Scheme 40.

isoquinolines (**177**) (Scheme **38**) [115]. It is interesting to note that in the same study, the reduction of the carbonyl group of 4-methoxyxanthone (**184**) with zinc powder/alkaline ethanol was accomplished in excellent yields.

The total synthesis of chromeno[4,3,2-*cd*]isoindolin-2-ones and chromeno[4,3,2-*de*]isoquinolin-3-ones (**178**) from 4-methoxyxanthone (**184**) was recently achieved as illustrated in Scheme **39** [195]. The construction of the nitrogenated ring was accomplished by both intramolecular electrophilic and anionic cyclizations of the corresponding carbamate precursors (**185**), although, for isoindolinones only anionic cyclization was possible.

In a totaly different approach, GPI6150 (**179**), a poly ADP-ribose polymerase inhibitor was synthesized as outlined in Scheme **40** [206].

The xanthone framework serves also as a key-intermediate for the synthesis of [1]benzopyrano[2,3,4-*kl*]acridine (**180**) derivatives (Fig. (**15**)) [111]. The key compound 1-(3'-methoxyanilino)-xanthone was obtained from 1-aminoxanthone (Table **1**).

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