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Lawsone in Organic Synthesis

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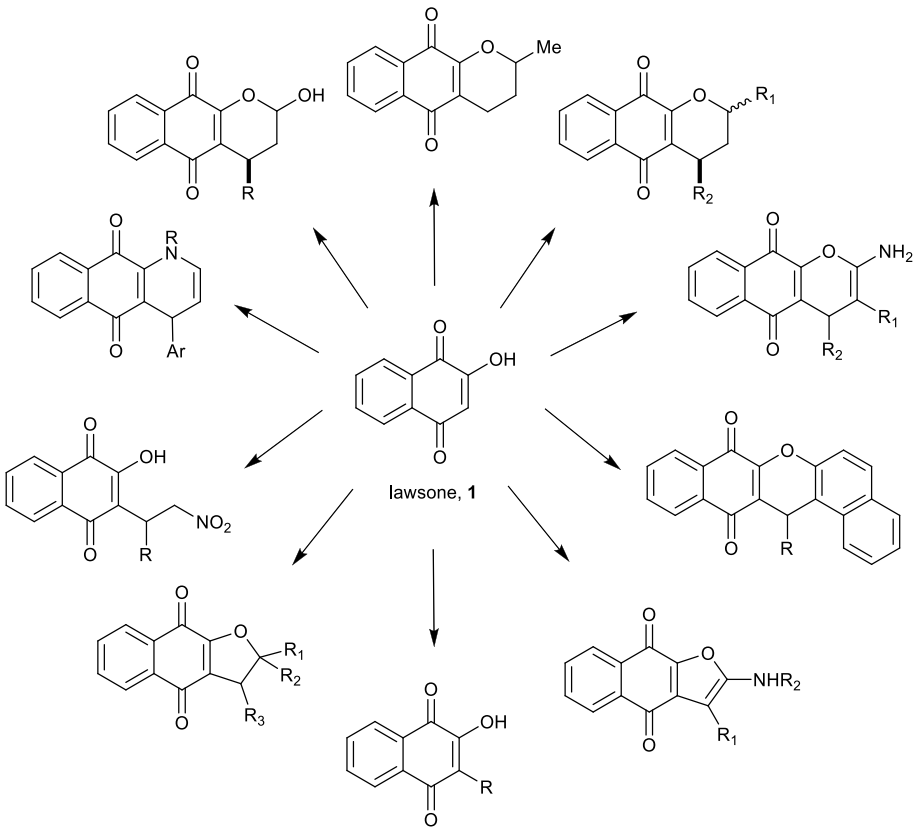
Lawsone (**1**) is a special naphthoquinone that is useful for many applications in various scientific and technological fields. For over 100 years, it has been used as the starting material for the synthesis of a variety of biologically active compounds and materials with interesting properties. In organic synthesis, it has been used in many reactions. This review aims to address the various aspects of its use in organic synthesis.



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1. Introduction

Quinones are widely distributed in nature, and several of its synthetic and natural products are very important in many diverse areas of chemistry and biochemistry.[1] They play a fundamental role in several living cells as electron carriers in the respiratory chain, as well as in blood coagulation and carboxylation of glutamates. Due to the intimate relationship between quinones and the biochemical processes of cells, these compounds have been extensively explored in the synthesis[2] of several bioactive compounds with antitumor,[3-5] molluscicidal,[6,7] antiparasitic,[8-10] leishmanicidal,[11] antiinflammatory,[12] antifungal,[13] antimicrobial[14] and trypanocidal[15-17] activities. Various reports note that the biological activities of these molecules stem from their *ortho* or *para*-quinonoid group that accepts one and/or two electrons (redox cycling) to form the corresponding radical anion or dianion species *in situ*.[18,19] Thus, the semi-quinone radicals accelerate the creation of intracellular hypoxic conditions by producing superoxide anions.[20,21] Through this mechanism, quinones may present cytotoxicity in mammalian cells, possibly by affecting enzymes such as topoisomerases, a group of enzymes that are critical for DNA replication in cells.[22]

The quinone class includes several important synthetic and natural compounds bearing a hydroxy group on the quinone ring. Specifically, the lawsone (**1**) motif and that of its isomeric form 4-hydroxy-1,2-naphthoquinone are common subunits of compounds with a number of valuable biological activities,[23] examples of which are illustrated in Fig. 1: lapachol (**2**), atovaquone (**3**), parvaquone (**4**), NQ1 (**5**),[24] β-lapachone (**6**) and α-lapachone (**7**).

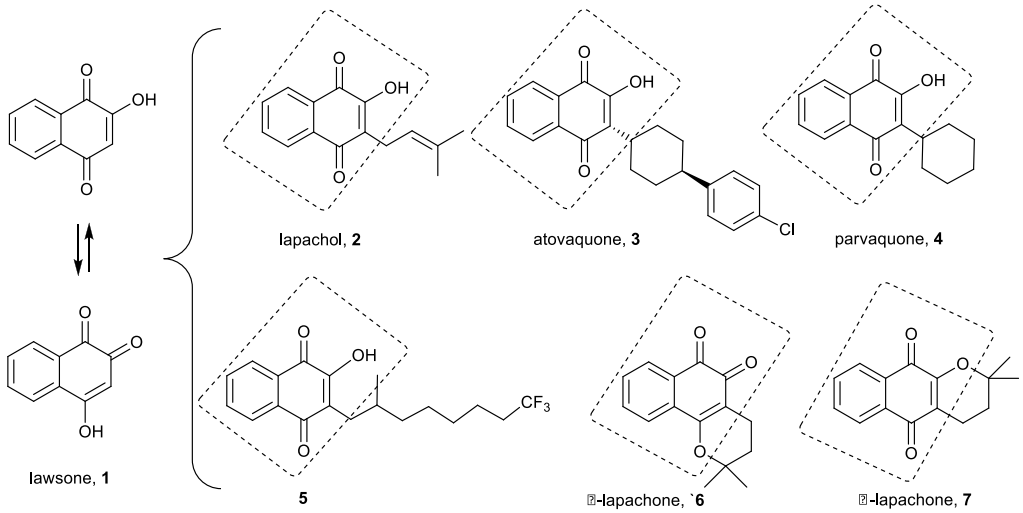


Fig. 1 Natural and synthetic bioactive naphthoquinones containing the lawsone fragment.

2- Hydroxy-1,4-naphthoquinone (**1**), or lawsone, or hennotannic acid, is one of the simplest naturally occurring naphthoquinones. This red-orange pigment, classified as Natural Orange 6 (C.I. 75480), can be obtained from the extract of dried powdered leaves of henna (*Lawsonia* spp., family Lythraceae), a branched shrub or small tree with grayish-brown bark. The most common species are *Lawsonia alba, Lawsonia spinosa* and *Lawsonia inermis* Linn. (mignonette tree)[25,26] that contain approximately 0.5-1.5% of **1**.[27,28] This compound is also found in the jewelweed *Impatiens balsamina*[29] and in *Juglans regia* (or walnut).[30] An important isomer of **1** is 5-hydroxy-1,4-naphthoquinone or juglone, which is also a natural 1,4-naphthoquinone found in several species of the Juglandaceae family, such as *Juglans nigra*, *J. cinerea*, and *J. regia*. The position of the hydroxyl group in these compounds is crucial to their biological activities as it affects their redox potentials and prooxidant activities.[31-34]

Lawsone (**1**) is responsible for the red dye properties of henna, which is traditionally used for coloring hair and dying nails and skin,[35-37] and served as an inspiration for the development of new bioactive compounds.[38] This dye has been used since the most ancient times by the Egyptians and Indians. Presently, henna extracts are still commercialized for skin,[39] wool[40] and cotton[41] dyeing purposes in several countries from Asia and Africa, with the Pali district of Rajasthan in India being the area with the highest production of henna extract, mainly from *L. inermis* Linn.[42,43]

Extracts of henna are widely used in folk medicine, especially in developing countries,[44,45] to treat burn wounds infected by microorganisms[46] such as *Mycobaterium tuberculosis*,[47] *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Fusarium oxosporum*, *Aspergillus niger* and *Candida albicans*, due to its antibacterial properties,[48] as well as headaches, lumbago, bronchitis, ophthalmia, syphilitis, sores and amenorrhoea.[43] In several countries, henna is a sacred plant that is widely used in religious ceremonies, and it symbolizes prosperity, fertility and happiness. Despite its long history of use, the toxicity of henna extracts has only been investigated in recent decades.[49] According to these studies, extracts of henna and **1** are highly toxic, causing hemolytic anemia and renal tubular necrosis when administered orally to rats,[50] as well as hypersensitivity with urticaria, rhinitis and bronchial asthma.[51] Recently, this compound was evaluated by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers of the European Community,[52] which concluded that it is moderately toxic on acute ingestion, with mortalities occurring at 300 mg/kg and above. In addition, two 13-week studies have shown clear signs of toxicity in the haemopoietic system,[53] kidneys, forestomach and liver, but when compound **1** was used on the skin, most of it remained there with only low absorption levels by the fluids.[54] McMillan *et al.* found that henna ingestion can induce severe hemolytic anemia and that administration of **1** to

rats induces a hemolytic response that is associated with oxidative damage to erythrocytes.[55] Several deaths of children to whom henna was administered during joyous, celebratory events have been reported.[56,57]

Because **1** is easily obtained from natural sources and is currently commercially available in bulk from Yucca Enterprises (India) and Sigma-Aldrich, it is not surprising that its activity against various microorganisms including fungi, bacteria and viruses has been investigated.[58-60]

Marzin and Kirkland found that **1**, obtained from the natural dye of henna, is non-genotoxic in the mouse bone marrow micronucleus test and does not produce oxidative DNA damage in Chinese hamster ovary cells, and they therefore concluded that **1** poses no or negligible genotoxic risk.[61] Recently, Klotz and co-workers studied the oxidative damage and stress signaling pathway in HaCaT human keratinocytes induced by several 1,4-naphthoquinones and stated that neither lawsone (**1**) nor-lapachol (**2**) (up to 100 μM) were active in any of these assays, but they discovered that these compounds induce phosphorylation of the epidermal growth factor receptor (EGFR) and the related ErbB2 receptor tyrosine kinases.[62] In a report published in 2005, the Norwegian Scientific Committee for Food Safety was of the opinion that "if **1** is considered as an *in vivo* mutagen and using an estimated systemic exposure dose based on a worst case use situation, the possible cancer risk associated with the use of Henna products for hair-dyeing containing **1** would be negligible."[63]

Besides its cosmetic applications, lawsone (**1**) has several other uses. A literature search reveals a long list of applications, including skin protection from ultraviolet radiation,[64,65] cloth dyeing, antiaging additive to vulcanized natural rubber,[66] corrosion inhibition for steel,[67,68] and oxidation of chlorinated compounds.[69,70] Furthermore, it reacts with the amino acids of latent fingermark deposits on paper surfaces to yield a clean purple-brown detailed impression that is also photoluminescent.[71] Recently, it was demonstrated that **1** is a sensitive colorimetric and electrochemical sensor for anions, such as cyanide, acetate, fluoride and dihydrogen phosphate (DHP) in acetonitrile. These anions cause a color change of the solution of **1** from yellow to orange-red, which is not observed in the presence of other anions, such as chloride, bromide, iodide or perchlorate.[72]

The complexation reactions of **1** have been investigated for various purposes, and a number of metal compounds exhibiting a variety of structures have been described in the literature, examples of which are illustrated in Fig. 2.[73-76] Potentially, **1** and analogous compounds can bind to metal ions in three different oxidation states (Fig. 2), quinone, semiquinone (the one-electron reduced form of quinone)[77] and catechol (the two-electron reduced form), and this binding ability is, in part, believed to be responsible for the important role of quinones in biological systems.[78] Hence, iron complexes

of **1** have been studied in an attempt to mimic the iron-quinone couple found in bacterial reaction centers,[79-82] whereas copper complexes of **1** have been investigated mainly to understand metal-quinone interactions and to mimic the structural and functional models of copper-containing enzymes.[83] Metals can also play an important role in modifying the pharmacological properties of known drugs. In this way, metal complexes of **1** (Fig. 2) were also evaluated for their potential cytoxicity against cancer cells, and the copper(II) complex **9** was found to induce apoptosis in HepG2 human cancer cells by a mechanism that involves activation of caspases and modulation of apoptotic related proteins.[84] Last but not least, the ruthenium(III) lawsonate complex **10a** has been shown to oxidize primary and secondary alcohols to aldehydes and ketones, respectively, in the presence of *N*-methylmorpholine-*N*-oxide as co-oxidant.[85] The catalytic cycle of the oxidation is activated by the metal center that undergoes oxidation and is capable of stabilizing the coordinated semiquinone (II) and catechol (III) forms of the naphthoquinone.

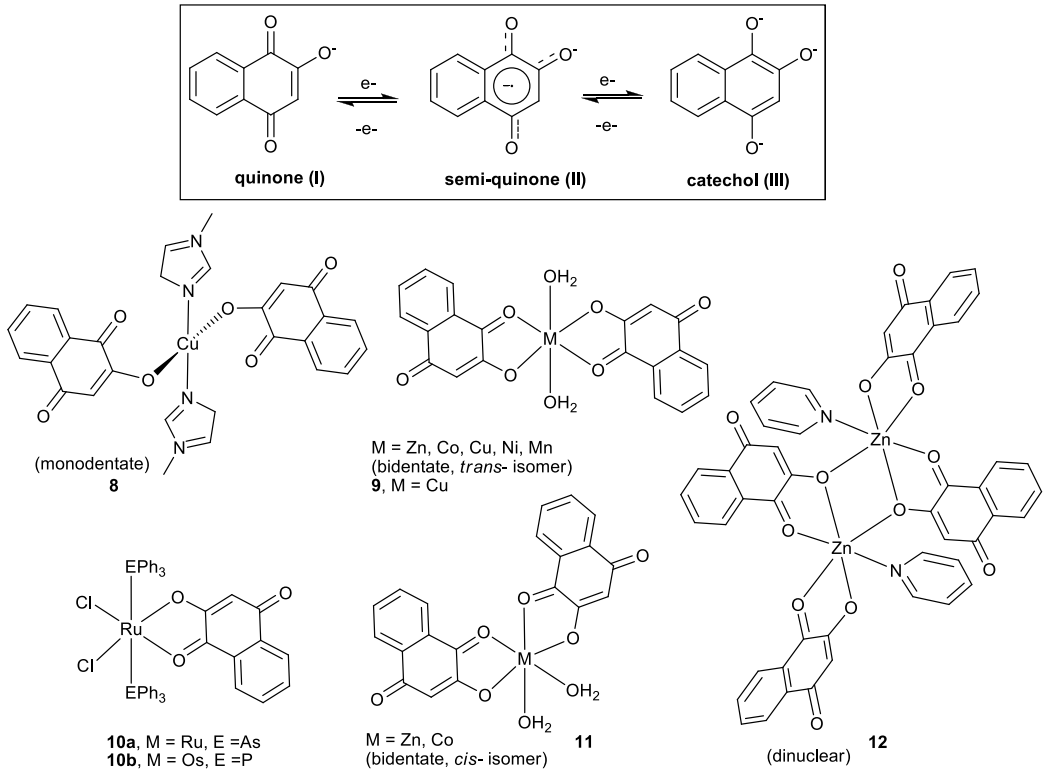


Fig. 2 Redox forms of the lawsone anion and schematic structure of some of its metal(II) complexes.

If controversy exists over the use of **1** as a hair and skin dye because of its toxicological and biological effects,[86-89] the same does not exist for its use as a starting material in organic synthesis. Hydroxyquinone moieties[90] are present in a number of natural products with interesting biological

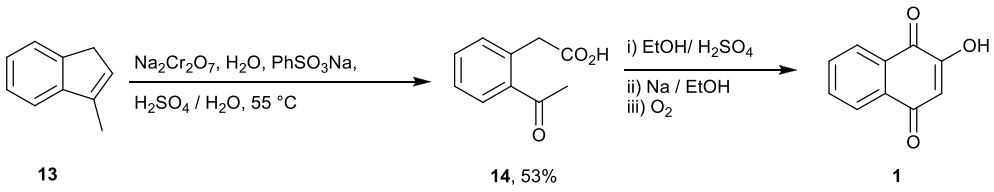
activities, but this review will only focus on the use of 2-hydroxy-1,4-naphthoquinone (**1**) in organic synthesis.

2. Methods for the preparation of lawsone (1)

Several methods have been reported in the literature for the synthesis of **1,** which are based on either the *de novo* construction of the naphthoquinone system or the use of naphthalene derivatives as starting materials. In some cases, the two methods are complementary.

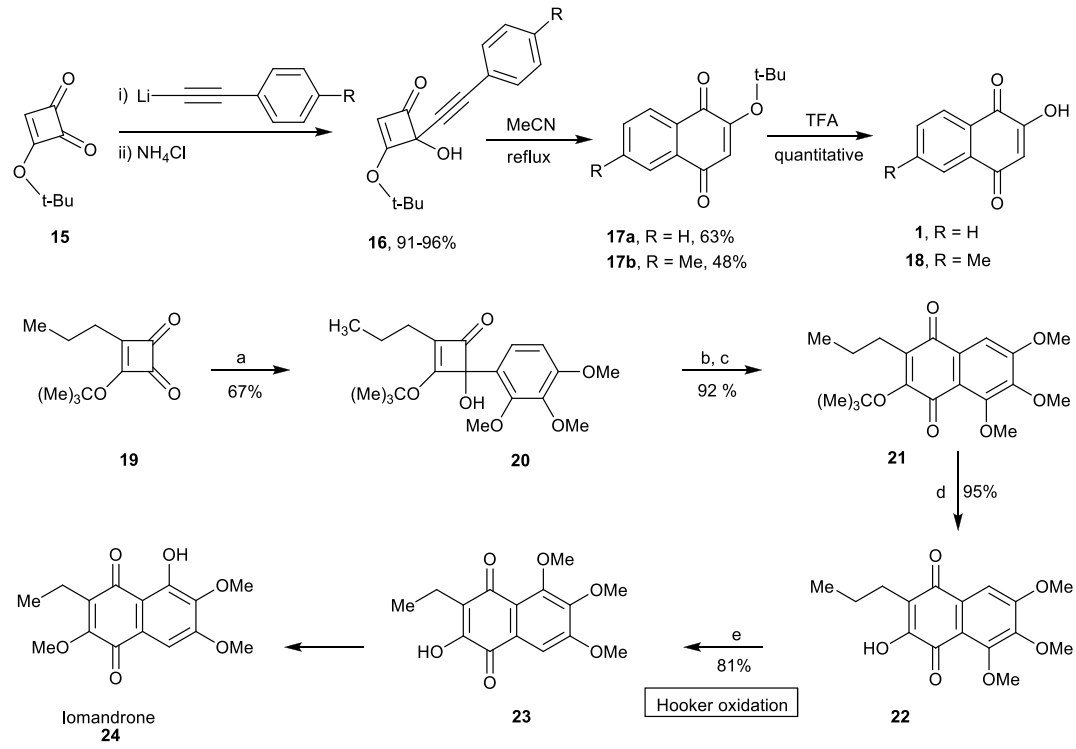
2.1 Preparation of lawsone (1) by ring constructing methods

Hooker described the first synthesis of **1** in 1892 *via* construction of the naphthalene core from 3-methyl-1*H*-indane **13**. This compound was oxidized and cleaved with sodium dichromate to phenylacetic acid **14**, which upon cyclization and oxidation produced **1** (Scheme 1).[91,92]



Scheme 1

A short route to **1** and other similar naphthoquinones was described by Heerding and Moore from 4-alkynyl-3-*tert*-butoxy-4-hydroxycyclobutenones **16** as illustrated in Scheme 2. Addition of the alkynyllithium reagent to 3-*tert*-butoxycyclobutene-l,2-dione **15** gave the cyclobutenones in excellent (91-96%) yields. Thermolysis to promote ring expansion, performed in refluxing acetonitrile, provided naphthoquinones **17a** and **17b** in 63 and 48% yields, respectively. Deprotection of the *tert*-butoxy quinones led to lawsone (**1**) and quinone **18** in quantitative yields (Scheme 2).[93] The same research group used a variation of this ring expansion method to produce hydroxynaphthoquinone **22** from 3-*t*-butoxy-4-aryl-4-hydroxycyclobutenone **20**. Hooker oxidation of **22** yields **23**, which can be used to prepare the natural naphthoquinone lomandrone (**24**).[94] This synthetic sequence was employed to prepare two analogues of parvaquone (**4**) in good yields, starting from diisopropyl squarate, by addition of the appropriate aryl lithium compounds and ring expansion-cyclization induced by microwave irradiation.[95]



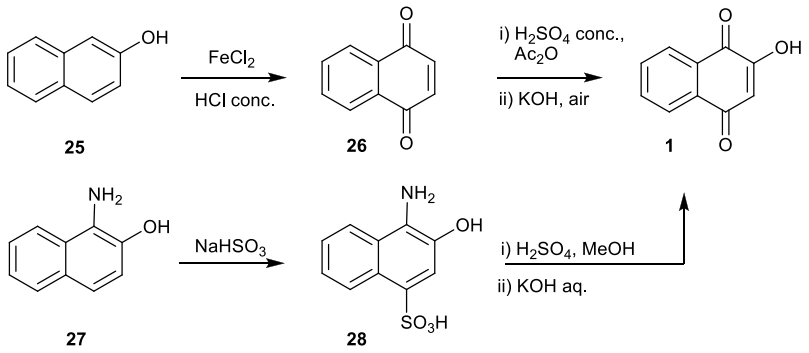
a) (1)-Lithio-2,3,4-trimethoxybenzene/hexanes, -78 °C; b) toluene, 110 °C, 2 h; c) Ag_2O; d) TFA, 0 °C; e) $KMnO_4/OH^-$

Scheme 2

2.2 Preparation of lawsone (1) from naphthalene derivatives

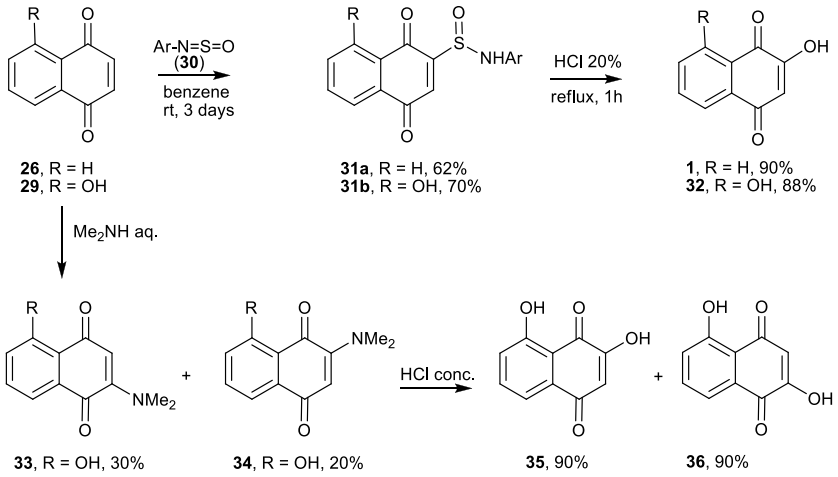
Because several naphthol derivatives are easily obtained from naphthalene, these are the most convenient starting materials for the preparation of **1**. Indeed, the most efficient methods used to prepare **1** involve the oxidation of naphthoquinones, 1- or 2-naphthols, dihydroxy naphthalenes, aminonaphthols and tetralones. The variety of existing methods for the preparation of **1**[96] is a good indication of its importance as a starting material in organic synthesis.

2-Naphthol **25** can be converted into 1,4-naphthoquinone **26** by reaction with a solution of ferric chloride hexahydrate in concentrated hydrochloric acid.[97] Compound **26** reacts with acetic anhydride-sulfuric acid to give 1,2,4-trihydroxynaphthalene triacetate, which is hydrolyzed and oxidized to **1**.[98] 1-Amino-2-naphthol (**27**)[99] has been used an alternative starting material for the synthesis of **1**. Its reaction with sodium bisulfite in aqueous 6 N sodium hydroxide[100] produces 1-amino-2-naphthol-4-sulfonic acid (**28**), which upon hydrolysis with concentrated sulfuric acid in methanol leads to 2-methoxy-lawsone. Hydrolysis of the methoxy group in aqueous sodium hydroxide solution gives **1**.[101] By using this sequence starting from β-naphthol, **1** can be obtained in 82-84% overall yields (Scheme 3).



Scheme 3

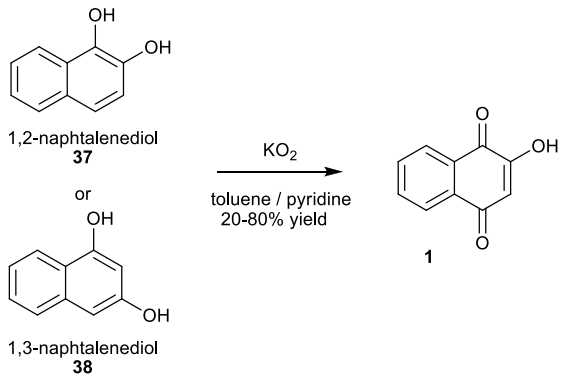
The hydroxyl group can be introduced in position 2 of 1,4-naphthoquinones by several procedures. For instance, 2 + 2 cycloaddition of the N=S bond of *N*-sulfinylarylamines (**30**) with 1,4-naphthoquinone, followed by a 1,3-H sigmatropic shift, produces 2-(*N*-arylsulfinamoyl)-1,4-naphthoquinones **31a-b**. Hydrolysis of the latter compounds in aqueous HCl gives **1** (Scheme 4).[102] By adding amines into the 1,4-unsaturated system **29** (R = OH), Oliveira *et al*. obtained the necessary intermediate for the preparation of the natural product α-caryopterone.[103]



Scheme 4

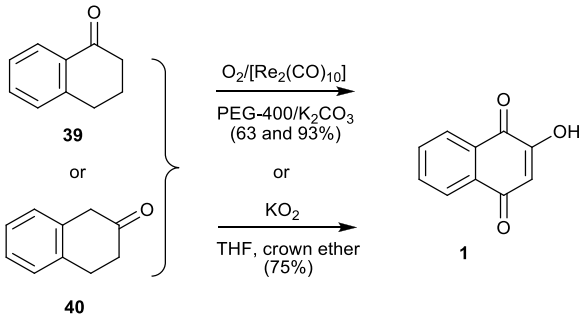
With the emergence of green chemistry as a response to the need to minimize the environmental impact of the classic chemical processes, many alternative, more sustainable and profitable methods have been developed. Thus, Yan *et al.* selectively converted 2-naphthol into **1** in high yield (62%) and selectivity (100%) by reaction with molecular oxygen under air pressure in an alkaline solution over iron porphyrin catalysts, such as Fe-porphyrin (TMOPPFeCl),[104] 5,10,15,20-tetra (4-methoxylphenyl) porphyrin iron chloride,[105] or by cobalt porphyrins immobilized on polymer

microspheres (80%).[106] These methods are relatively cheap and use an environmentally benign oxidant. Naphthalene diols are also competent substrates for the oxidation to **1**. The performance of the oxidation depends on the relative position of the hydroxy groups on the naphthalene. Maurette and co-workers[107,108] developed a method to produce **1** involving the oxidation of dihydroxynaphthalenes **37** or **38** with potassium superoxide (KO_2) in a heterogeneous aprotic medium (Scheme 5). Other options for the oxidation of naphthalene diols to **1** include tetraethylammonium superoxide for the oxidation of 1,2-naphthalene diols (56% yield)[109] and the use of supported metallated phthalocyanine on montmorillonite K10 or zirconium phosphate ($ZrPO_4$) as the oxidation catalysts (80% yield).[110]



Scheme 5

Tetralones **39** or **40** also can be oxidized to **1** by oxygen, potassium hydroxide, potassium carbonate, and catalytic amounts of rhenium carbonyl, $[Re_2(CO)_{l0}]$, and polyethylene glycol (PEG-400)[111] with potassium superoxide in THF with crown ether in good yields,[112] or by Thomson´s method of autoxidation with O_2/t-BuOK/t-BuOH.[113,114] Ullas[115] prepared ^{14}C-labelled **1** ([phenyl-^{14}C(U)] 2-hydroxy-1,4-naphthoquinone) from [^{14}C(U)]benzene. The last step of the synthesis involved oxidation of [phenyl-^{14}C(U)]α-tetralone to [phenyl-14C(U)] **1** in 40% by Thomson´s method. Likewise, Ashwell *et al.*[116] used Thomson's oxidation method to transform substituted α-tetralones into hydroxy-naphthoquinones in the total synthesis of β-lapachones substituted on the aromatic ring (Scheme 6).



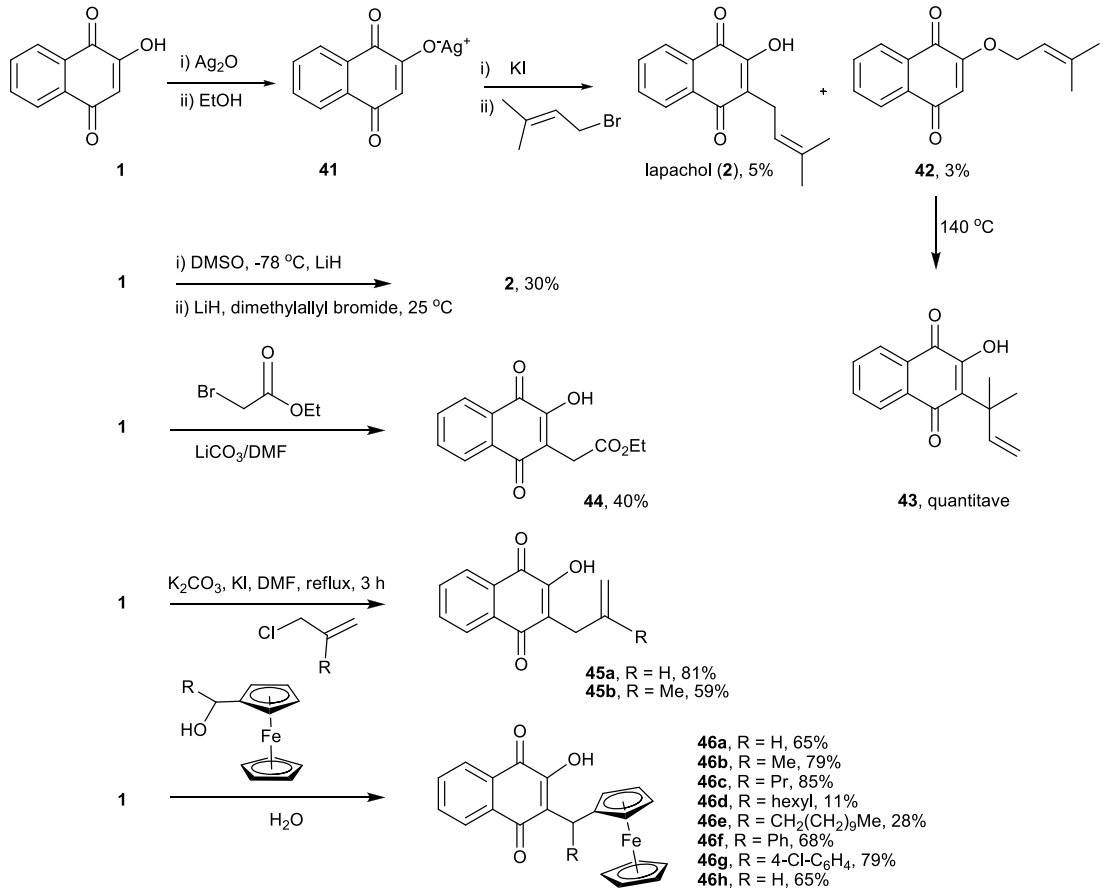
Scheme 6

3. Lawsone (1) as a starting reagent in organic synthesis

3.1 *C*-Alkylation and *O*-alkylation of lawsone

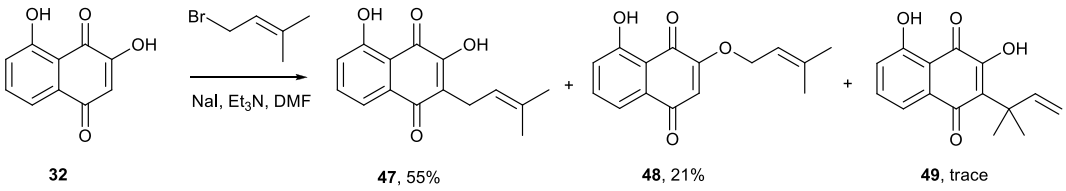
Lawsone (**1**) can be considered as the stable enol form of a β-diketone and can therefore be alkylated either at the oxygen (*O*-alkylation) or at the carbon (*C*-alkylation). The first attempt to alkylate **1** was described in 1927 by Fieser, who reported a preparation for lapachol (**2**) by reacting the silver salt of **1** with isoprenyl bromide, as shown in Scheme 7. However, the yields of both *C*-alkylated **2** (5%)[117-119] and *O*-alkylated **42** (3%) products were very low. Interestingly, upon heating, the *O*-alkylated product **42** underwent a Claisen rearrangement, resulting in the *C*-alkylated natural product **43** in quantitative yield,[120] whose carbon connectivity is different from that of the product obtained from direct *C*-alkylation, **2**. This latter strategy is another alternative for the *C*-alkylation of **1**, which was subsequently rearranged and used in the synthesis of the dunnione pigment.[121,122] Recently, Frydman and co-workers developed an improved method for the alkylation of **1** by reacting its lithium salt in DMSO with dimethylallyl bromide to produce lapachol (**2**) in 30% yield.[123] Direct *C*-alkylation of **1** was employed for the synthesis of an important intermediate used for the preparation of compounds, which were found to be active against various cancer cell lines. The reactions of **1** with α-bromoacetate ethyl ester or allyl halide in DMF catalyzed by carbonate salts resulted in *C*-alkylated products **44** and **45a-b**,[124] respectively, in moderate yields. A mild procedure for the *O*-alkylation of 2-hydroxynaphthoquinones using phase-transfer catalysts was developed recently. In spite of being selective for the *O*-alkylation of **1,** this procedure gave only 20% of the desired product.[125] The examples presented above indicate that, in general, direct *C*-alkylation of **1** is not a good route to *C*-alkylated products. However, when the reactions of **1** with ferrocenemethanol derivatives are carried out in water, in the absence of a catalyst and at moderate temperatures, the alkylated products **46a-h**

are obtained in moderate to high yields. These naphthoquinones have shown *in vitro* antiplasmodial activity against chloroquine-sensitive and resistant *Plasmodium falciparum* strains.[126]



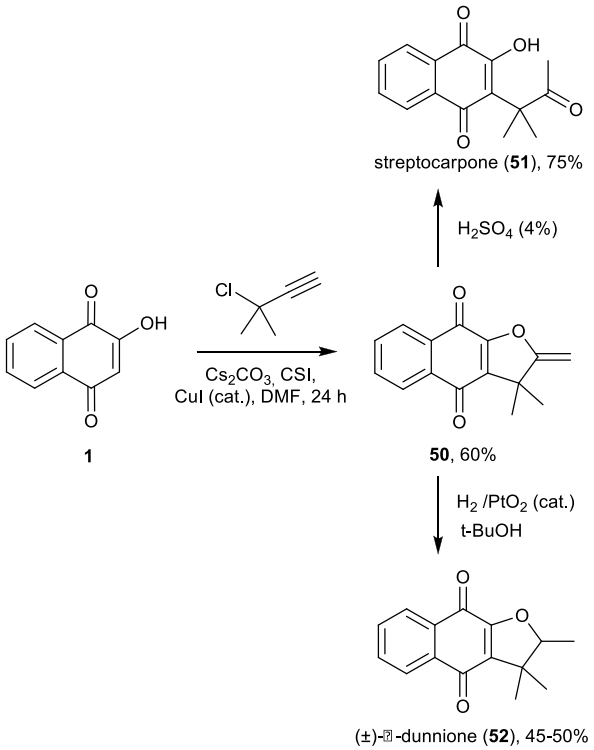
Scheme 7

Other similar 1,4-naphthoquinones undergo *C*-alkylation with higher degrees of regioselectivity than **1**. For example, recently Padrón and coworkers developed a synthetic route to 5-hydroxylapachol (**47**) through alkylation of 2-hydroxyjuglone (**32**) with 1-bromo-3-methyl-2-butene. The desired product **47** was formed in moderate yields with side products **48** and **49**. Thus, the *C*-alkylation of (**32**) gave better results than the analogous reaction of **1** (Scheme 8).[127]



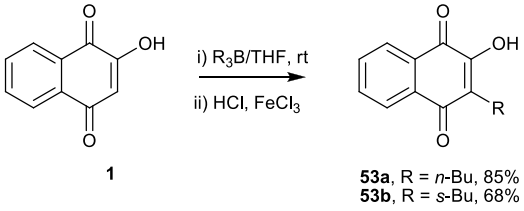
Scheme 8

A very interesting copper-catalyzed regioselective *C*-alkylation of **1** was carried out with 3-chloro-3-methyl-1-butyne (Scheme 9), and this method was used for the preparation of the related natural isoprenylated naphthoquinone pigments streptocarpone (**51**) and (±)-α-dunnione (**52**). The major product of this one-pot formal [3+2] cyclization is the furanonaphthoquinone **50,** which, upon acid treatment, is converted into streptocarpone (**51**) or, upon hydrogenation, into (±)-α-dunnione (**52**).[128]



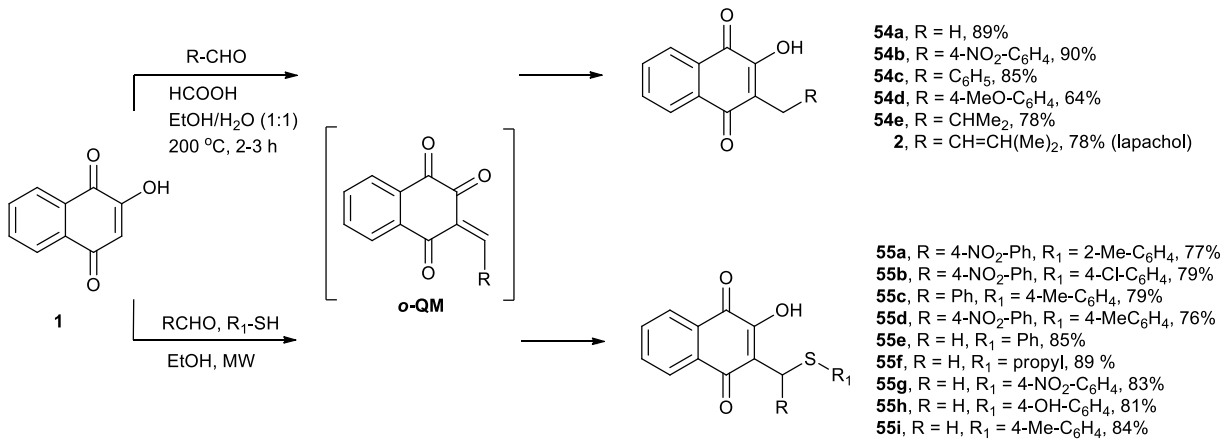
Scheme 9

Bieber and co-workers[129] developed a direct regioselective alkylation of **1** using trialkylboranes. The initially formed product, a reduced boranequinone complex, was oxidatively hydrolyzed to 3-alkyl-lawsones **53a** and **53b**, which are the only two reported examples (Scheme 10).



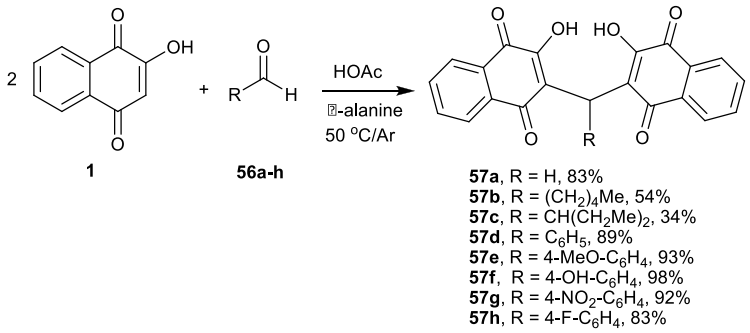
Scheme 10

Ferreira and co-workers have developed a method for the *C*-alkylation of **1** by reacting it with various aldehydes in ethanol-water (1:1), forming *in situ* *o*-quinone methide (*o*-QM) intermediates that are immediately reduced by formic acid. Using this protocol, they prepared several 3-alkyl derivatives of 2-hydroxy-1,4-naphthoquinone **54a-e**, including lapachol (**2**), in moderate to excellent yields. This one-pot reaction was used to prepare **54a**, a commercial product known as phthiocol that possesses molluscicidal activity (Scheme 11).[130] The same research group developed a new three-component process for the *C*-alkylation of **1** with simultaneous thiol addition. With this method, a series of new *C*-alkyl or *C*-arylsulfanylmethyl-[1,4]-naphthoquinones **55a-i** were synthesized in good to high yields (Scheme 11). The reaction involved *in situ* generation of *o*-quinone methide intermediates (*o*-QM), which are formed *via* Knoevenagel condensation and react with thiols through 1,4-addition reactions. The compounds synthesized by this method showed moderate to good activity against the human malaria parasite *Plasmodium falciparum* (3D7)[131] and *Leishmania (L.) infantum*.[132] Very recently, Dmitrenok *et al.* used the same protocol to produce a series of *N*-acetyl-*S*-[(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl]-*L*-cysteine conjugates in good yields. Based on the products of this reaction, fibrostatins B, C, and D were synthesized.[133]



Scheme 11

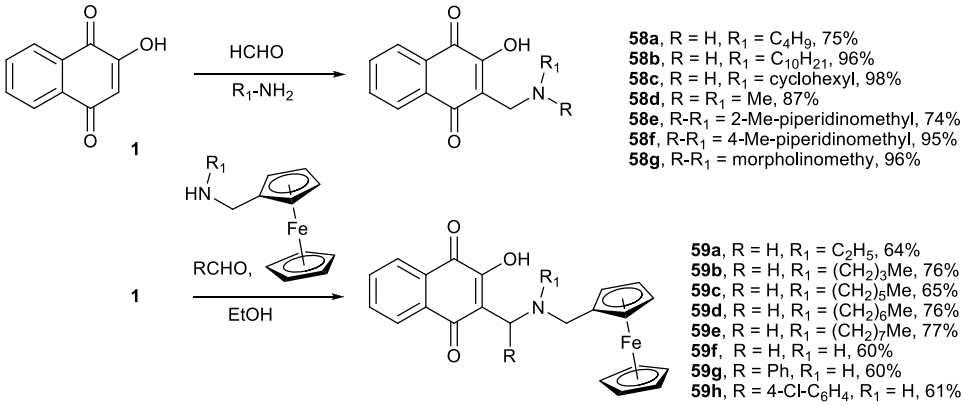
Alexandre-Moreira and co-workers[134] have studied the synthesis of a series of 3,3'-(R-methylene)bis-2-hydroxy-1,4-naphthoquinone derivatives **57a-h** that were prepared in high yields through the condensation of **1** with aromatic and aliphatic aldehydes **56a-h** under mild acidic conditions (β-alanine/AcOH) (Scheme 12). The compounds were evaluated *in vitro* against *Leishmania amazonensis* and *Leishmania braziliensis* promastigotes. Some compounds showed good activity without significant toxic effects, and the compound with the highest activity (**57a**) was used for an *in vivo* assay with *Leishmania amazonensis*.



Scheme 12

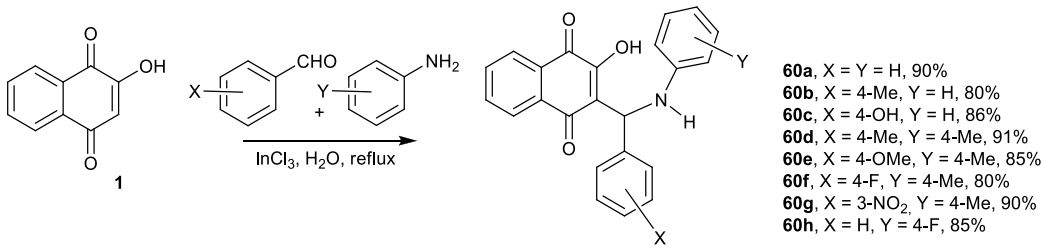
The Mannich reaction is a very useful one-pot *C*-aminoalkylation adjacent to a carbonyl functional group. The final product is a β-amino-carbonyl compound that is also known as a Mannich base. In this reaction, nucleophilic addition of an amine to a carbonyl group, followed by dehydration, forms a Schiff base that reacts in a second step with nuclophiles, such as enol or enone derivatives, to form an amino *C*-alkylated adduct (Scheme 13). This easy-to-perform three-component reaction of **1** (an enone) with aldehydes and amines produces the amino *C*-alkylated adduct in high yields and high atom economy. This reaction is therefore ideal for the preparation of a library of compounds for biological screening.

During their search for 3-alkyl-1,4-naphthoquinones with antimalarial activity, Leffler and Hathaway were the first to investigate this reaction.[135] By using **1**, formaldehyde and several amines, they produced a series of compounds **58a-g** containing an aminomethyl side chain in high yields (Scheme 13 for R^1 = H). Afterward, Dalgliesh reinvestigated this reaction and produced other Mannich bases derived from **1**.[136] He also proposed a mechanism to explain the formation of 3,3'-(R-methylene)*bis*-2-hydroxy-1,4-naphthoquinones (Scheme 13) from the reactions with bulky secondary amines instead of the Mannich bases that are obtained in excellent yields from the reactions with primary amines. Various 2-hydroxy-3-alkyl-1,4-naphthoquinones thus synthesized showed significant molluscicidal activity against the *Biomphalaria glabrata* snail, which is the intermediate host of *Schistosoma mansoni*.[137] Following the same methodology, Brocard and co-workers synthesized a number of Mannich bases of **1** from ferrocenylmethylamines. The ferrocenyl aminohydroxynaphthoquinones **59a-g** containing aliphatic chains with 6-8 carbon atoms were found to be significantly active against the atovaquone (**3**)-resistant strain of *Toxoplasma gondii*.[138]



Scheme 13

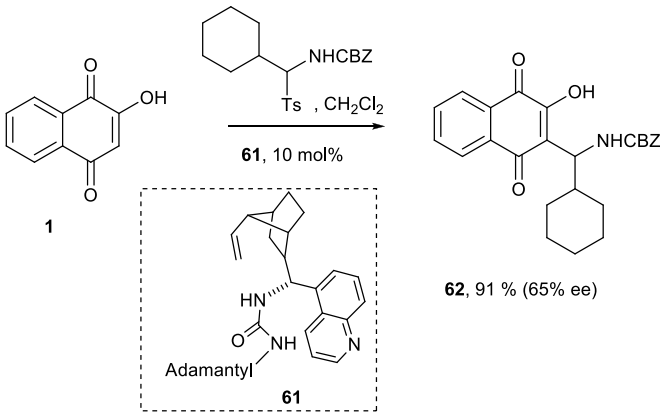
Recently, Greco and co-workers showed that the one-pot, three-component reactions of **1** with aromatic aldehydes and the secondary amine pyrrrolidine or 4-nitroaniline occur in the presence of catalytic amounts of *p*-TsOH at room temperature to give the respective Mannich bases in good yields.[139] Bazgir and coworkers investigated the synthesis of Mannich bases derived from **1**, aromatic aldehydes and heterocyclic or carbocyclic amines to form fluorescent hydroxyl naphthalene-1,4-dione derivatives **60a-h**. They used catalytic amounts of $InCl_3$ in refluxing water, which makes this process very simple, green and highly atom-economic. The authors speculated that the Lewis acid interacts with the nitrogen of the Schiff base intermediate, increasing its eletrophilicity. The reaction works very well for aromatic aldehydes containing both electron-withdrawing and electron-donating substituents as well as with heterocyclic amines. The products were fluorescent in solution and emitted in the green part of the spectrum (546-560 nm) (Scheme **14**).[140] The use of environmentally friendly ionic liquids as solvents in the condensation reactions of **1** with aromatic aldehydes and aromatic amines was also investigated, and similar Mannich bases were obtained in high yields.[141]



Scheme 14

Ayaz and Westermann also have attempted the nucleophilic addition of **1** to imines under organocatalytic conditions. In this particular case, several commonly used organocatalysts were screened to give Mannich bases in excellent yields but with moderate enantioselectivities. The use of

catalyst **61**, an analogue of Takemoto's catalyst, gave the best enantioselectivity for compound **62** (Scheme 15).[142]



Scheme 15

The 1,4-naphthoquinone Mannich bases derived from **1** can coordinate to several metal ions, thus potentially generating new molecules with improved biological activities.[143] Within this context, Vargas and coworkers were the first research group to report metal complexes of Mannich bases derived from **1**, benzaldehydes or pyridinecarboxaldehyde, and a variety of amines. The copper(II) complexes **63**, for example,[144] (Scheme 16) were easily prepared but showed less antimicrobial activity than the free Mannich bases, which was attributed to their low solubility. The same group demonstrated that the coordinating ability of the Mannich bases can be controlled by judicious choice of the amine and the aldehyde.[145] Thus, from the bases derived from aminomethyl pyridine, and by slight variation of the complexation reaction conditions, different dinuclear copper(II) complexes were synthesized.[146] Furthermore, they also synthesized a series of platinum(IV)[147] and platinum(II)[148] complexes of the Mannich bases derived from pyridinecarboxaldehyde, the latter of which was structurally related to picoplatin, and evaluated their cytotoxicity against various cancer cell lines[149] and studied their mechanism of action.[150] Complex **66**, for instance, is responsible for the formation of mono-adducts with 5′-GMP, suggesting that it can interact similarly with DNA (Fig. 3).

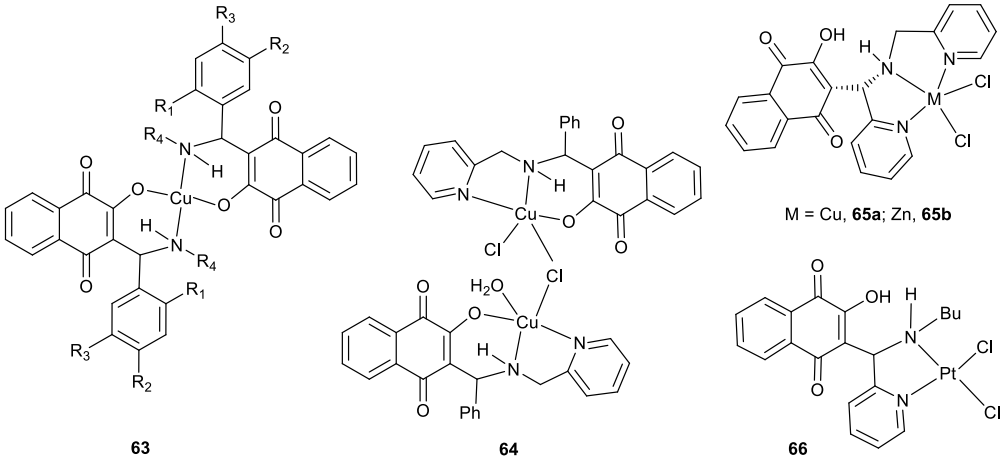
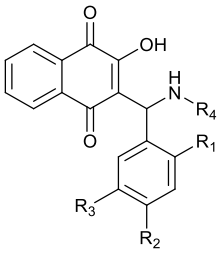


Fig. 3 Examples of metal complexes formed from Mannich bases derived from **1**.

Paixão and co-authors[151] evaluated the antiviral potential of several of the Mannich bases described above against Bovine herpesvirus type 5 (BoHV-5), the etiologic agent of meningoencephalitis in cattle. The most potent compound of the **67** series (Fig. 4) is a selective inhibitor of this virus and exhibits better CC_{50} and EC_{50} values than acyclovir.



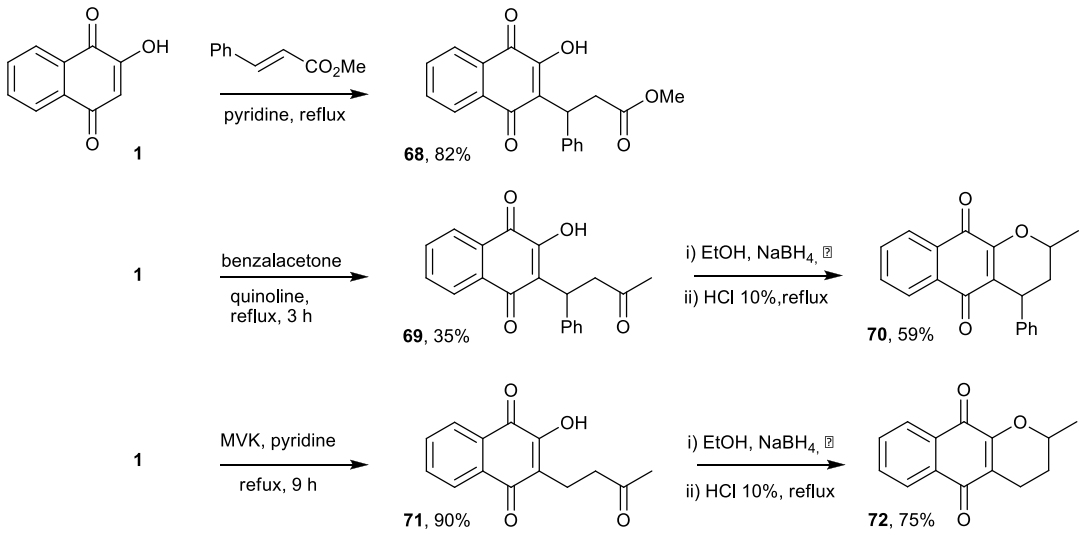
	CC_{50} (μM)	EC_{50} (μM)	Selectivity index (SI)
67a, $R_1 = R_2 = Cl$; $R_3 = H$; R_4 = n-Bu	31 ± 2.5	3.2 ± 1.0	**9.7**
67b, $R_1 = R_2 = Cl$; $R_3 = H$; R_4 = Bn	36 ± 3.5	3.2 ± 0.9	**11**
67c, $R_1 = R_2 = H$; $R_3 = NO_2$; R_4 = Bn	1867 ± 8.3	3.8 ± 1.2	**491**
67d, $R_1 = R_2 = H$; $R_3 = NO_2$; R_4 = n-Bu	985 ± 4.6	not assayed	-
Acyclovir	989 ± 2	166 ± 2	**6.0**

Fig. 4 Antiviral evaluation of selected aminomethylnaphthoquinones against BoHV-5.

3.2 *C*-Alkylation *via* the Michael addition reaction

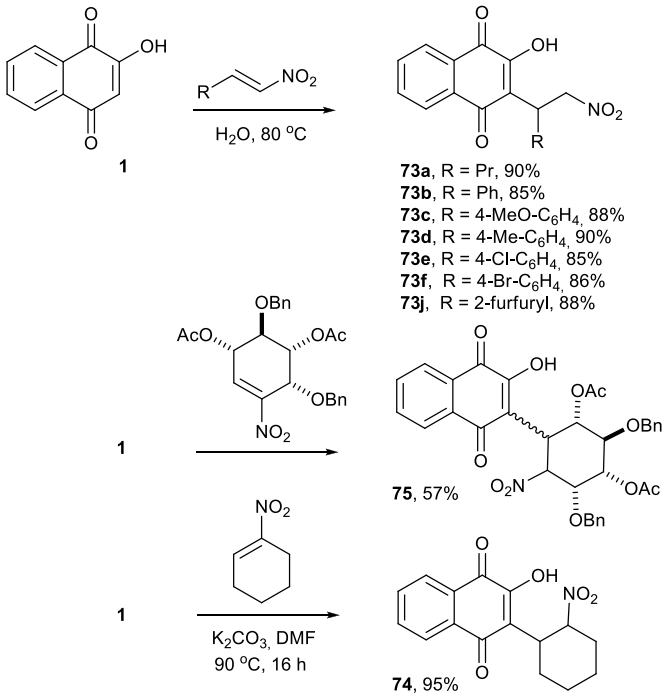
The Michael addition reaction represents one of the most important and general methods for the construction of a carbon-carbon bonds in organic synthesis. Thus, direct alkylation of **1** by Michael addition to α,β-unsaturated carbonyl compounds occurs selectively at position 3 and was initially explored by Zaugg for the production of pyranonaphthoquinones (see compound **50** in Scheme 9).[152] Tapia and co-workers used this strategy to perform the *C*-alkylation of **1** and transform the Michael

adducts into pyranonaphthoquinones with potential biological activities. The Michael adducts **69** and **71** were reduced with sodium borohydride and cyclized under acid conditions to form the pyranaphthoquinones **70** and **72** in 64-75% yields (Scheme 16).[153,154]



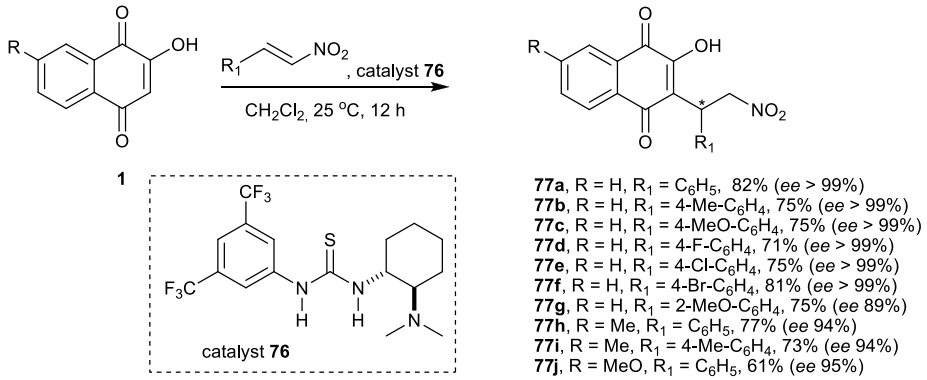
Scheme 16

Nitroolefins are very versatile building blocks in organic synthesis due to their ready availability and ease of transformation into a wide variety of functionalities.[155,156] *C*-Alkylations through Michael additions of **1** to various nitroolefins were easily performed in good yields under aqueous conditions.[157] The mechanism of these reactions can be explained on the basis of dual activation of the nitroalkene and **1** *via* hydrogen bonding. *C*-Alkylation of 2-hydroxy-1,4-naphthoquinone (**1**) was controlled by electronic factors. This reaction has attractive features, such as operational simplicity, high product yields (85-90%), high atom economy, versatility with respect to the β-nitrostyrenes and being environmentally benign (Scheme 17). Recently, Otero and coworkers reported the Michael addition of **1** to nitrocyclohexene, producing **74** in 95% yield, and to a chiral nitrocyclohexene, producing a diastereoisomeric mixture of **75** in moderate yields (Scheme 17).[158]



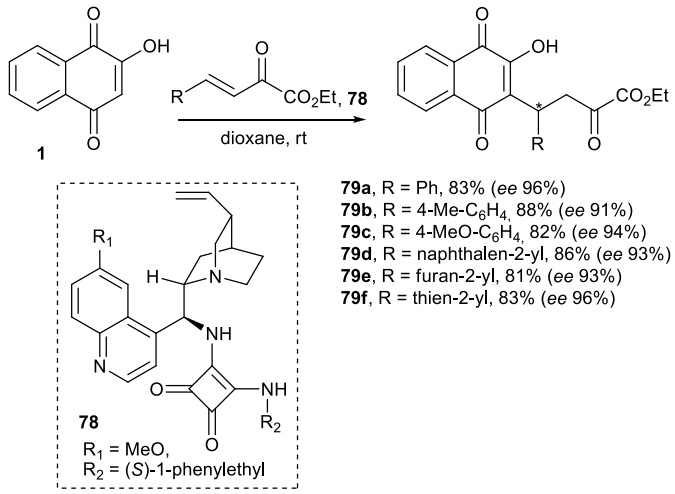
Scheme 17

Organocatalysis has been applied to various asymmetric reactions. This methodology is ideal for the *C*-alkylation of **1** (described above in Schemes 16 and 17) because it generates a chiral center. Thus, enantioselective Michael addition of **1** to nitroolefins was first studied by Du and co-workers who reported good yields of the products **77** with excellent enantioselectivities (up to > 99% *ee*) and high atom economy. This first report of an organocatalytic asymmetric Michael addition of **1** showed that it is possible to produce these optically active compounds and that the presence of electron-rich substituents on the 7-position of the 2-hydroxy-1,4-naphthoquinone does not affect the efficiency of the reaction (Scheme 18).[159]



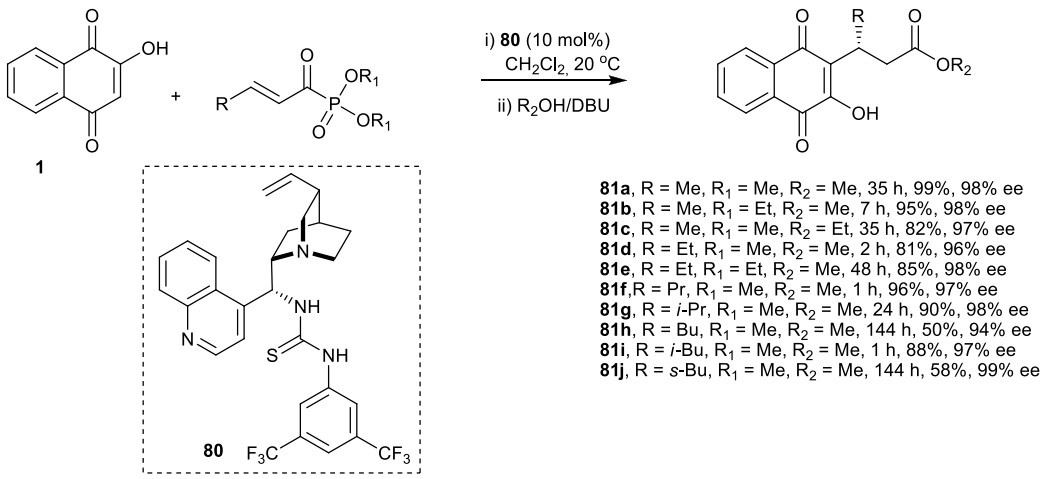
Scheme 18

Wang and co-workers[160] have studied the analogous reaction with β,γ-unsaturated α-oxo esters and bifunctional chiral amine-derived squaramides (**78**) as catalysts that function through a hydrogen-bond mediated activation mechanism, and they obtained the chiral adducts in high yields and excellent enantioselectivities under mild conditions. This organocatalytic asymmetric Michael addition provides an efficient route to optically active functionalized naphthoquinones **79a-f** (Scheme 19).



Scheme 19

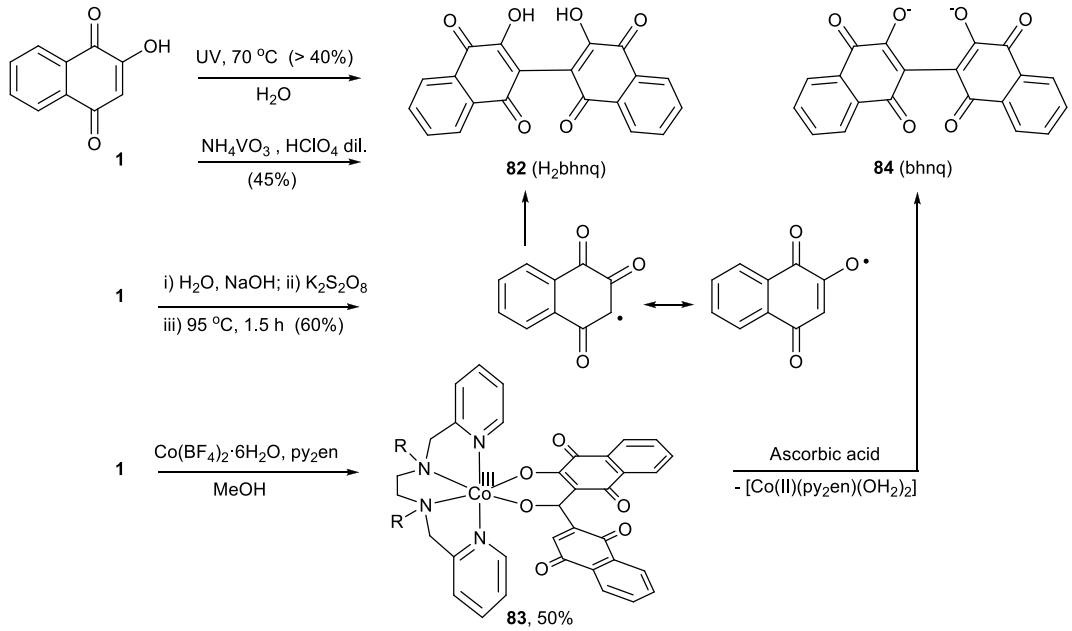
Tang and co-workers developed an organocatalytic Michael addition process to synthesize some novel optically active β,γ-unsaturated α- derivatives of **1** by employing a cinchonine-based thiourea catalyst (Scheme 20). This process produced the desired ketophosphonate adducts of **1** with high enantioselectivity. The chiral ketophosphonates were then transformed into the corresponding β-substituted carboxylates **81a-j** in excellent yields and with high levels of enantioselectivities upon treatment with DBU in MeOH.[161]



Scheme 20

3.3 Dimerization of lawsone (1)

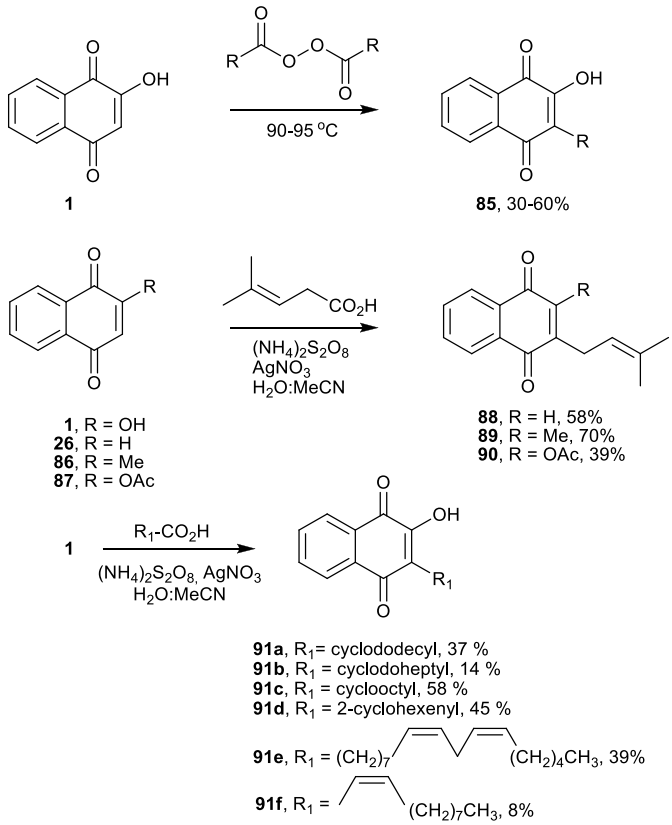
In the 1890s, Hooker and co-workers[162] noted that aqueous solutions of **1** deposited the dimeric compound 2,2'-bis(3-hydroxy-1,4-naphthoquinone) **82** when left exposed for long periods of time. Later, they showed that this compound could be prepared in yields over 40% by exposing a hot aqueous solution of **1** to ultraviolet light (Scheme 21). This reaction was reinvestigated by Chandrasenan and Thomson,[163] who speculated that the dimerization process occurred *via* a radical coupling reaction and, therefore, carried out the persulfate oxidation of **1**, producing **82** in *ca* 60% yield. In this case, only the coupling at C-3 was observed. This reaction is also promoted by ammonium metavanadate in the presence of diluted perchloric acid[164] as well as by $FeCl_3$; however, the principal products in the latter case are the iron complexes of the dimer.[165] Recently Lanznaster and coworkers reported the dimerization of **1** upon reaction with $Co(BF_4)_2 \cdot 6H_2O$ and *N*,*N*′-bis(pyridin-2-ylmethyl)ethylenediamine (py_2en) in the presence of Et_3N. The product from this reaction is the metal complex **83** that contains the deprotonated form of **84**, (bhnq),[166] and dissociation of this dianion was promoted by reduction with ascorbic acid. Coordination of two lawsonate molecules to Co(II) was shown to be a necessary step prior to dimerization.[167] The anticancer[168] and antimycobacterial[169] activities among others of **82** have been investigated, but the main interest lies in the complexing capability of its dianion, a flexible hingelike ligand that has been used for the construction of metal organic frameworks (Scheme 21).[170]



Scheme 21

3.4 Free radical alkylation of lawsone (1)

Free radical reactions have proved to be especially useful for numerous cascade or domino sequences because they offer many advantages when compared with ionic or organometallic reactions.[171,172] The reaction of **1** with radical species was one of the first radical methods employed to obtain *C*-alkylated lawsone derivatives. The method, developed by Fieser and co-workers in 1945, involved the alkylation of hydroxynaphthoquinones by heating them with diacyl peroxide (Scheme 22). This general one-step alkylation process gives moderate to good yields and pure products that can be readily isolated from the reaction mixture by acid-base extraction. The diacyl peroxides used in this reaction can be obtained from the reaction of a carboxylic acid with an acyl chloride. The yields of the alkylation process are generally in the range of 30-60%, with some sharp decreases in yield with high-molecular-weight compounds. One limitation of this peroxide alkylation reaction is poor yields (1-20%) when using peroxides obtained from α-branched acids and cycloalkane carboxylic acids (Scheme 22).[173,174] Jacobsen and Torssell improved this reaction by replacing diacyl peroxide for carboxylic acids in a radical process generated by decarboxylation with ammonium peroxodisulfate and catalytic amounts of silver nitrate.[175,176] The reaction is widely applicable to the synthesis of 2-*C*-alkylated-2 hydroxynaphthoquinones and 1,4-quinones (Scheme 22).[177,178] In this regard, Liu and co-workers synthesized several plastoquinone derivatives with ω-substituted alkyl side chains,[179] and Tauraité synthesized lipophilic 1,4-naphthoquinone derivatives with redox properties.[180] Boehm and co-workers have also used this procedure to prepare a series of naphthoquinones that were evaluated *in vitro* against the causative agent of the cattle disease East Coast Fever or *Theileria parva* infection.[181] Recently, the same methodology was used for the synthesis of novel naphthoquinones from lipids, which were assayed against the infective bloodstream form of *Tripanosoma cruzi* (Scheme 22). Among the compounds, **91e** exhibited excellent ability to inhibit the growth of the microorganism with an IC_{50} of 7.8 μM.[182] It is worth noting that the use of acylated lawsone gives better yields of *C*-alkylated products by peroxysulfate-mediated radical decarboxylation.[121]

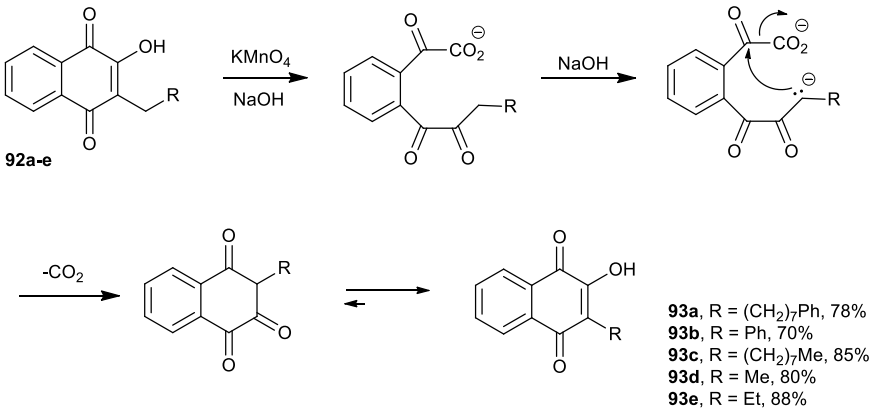


Scheme 22

3.5 *C*-alkylated derivatives of 1 by the Hooker oxidation method

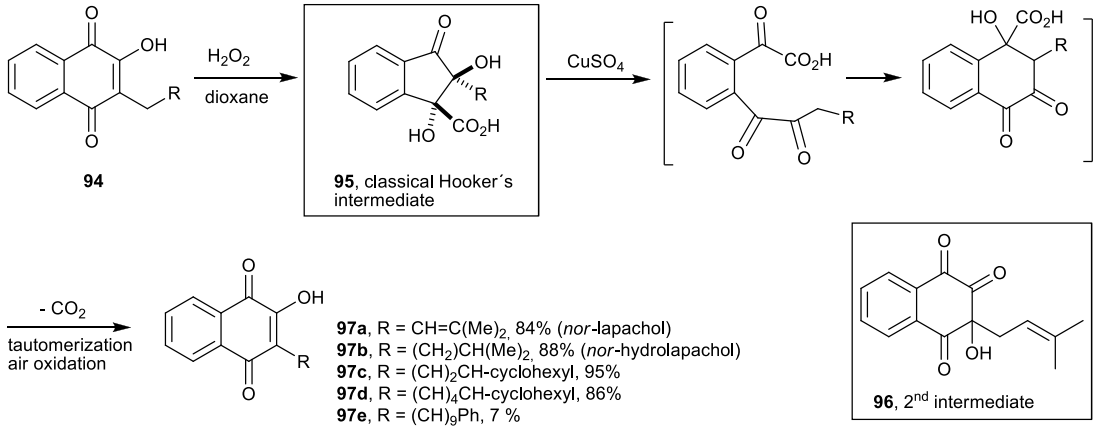
Lapachol (**2**) stands out among the natural naphthoquinones and may be considered one of the main representatives of the group of natural quinones. First isolated from *Tabebuia avellanedae* (Bignoniaceae) by E. Paternò, in 1882,[183] it was later isolated also from other plants, *e.g.,* of the Verbenaceae and Proteaceae families. Paternò also proposed a structure for it, but with the double bond of the side chain in the wrong position.[184,185] Hooker assigned its structure correctly and also made several derivatives of this molecule between 1889-1896.[186,187] When studying the degradation reactions of lapachol (**2**) with potassium permanganate in alkaline medium, he found a remarkable degradation reaction, which was of general scope and could transform 3-alkyl-2-hydroxy-1,4-naphthoquinones into other 3-alkyl-2-hydroxy-1,4-naphthoquinones with one less CH_2 in the side chain.[185,188] This reaction has been used for the synthesis of a number of new naphthoquinones.[189-192] Fieser wrote the following in his memoir published in 1964: "A second reaction which proved to be extremely useful is a remarkable one discovered by Dr. Hooker in retirement and known as the Hooker oxidation. On reaction of M-1926 (R = $(CH_2)_9CH_3$ in Scheme 23) with alkaline potassium permanganate in the cold, a CH_2 unit mysteriously disappear from the side chain"[193] Some examples of this methodology are illustrated in Scheme 23. Hooker's proposed mechanism for this reaction

was that oxidation would occur by cleavage of the 3-alkyl-2-hydroxy-naphthoquinone **92** ring by the permanganate ion, followed by cyclization with release of one CO_2 molecule, and subsequent tautomeric equilibrium, resulting in the lower homologue of the 3-alkyl-2-hydroxy-1,4-naphthoquinone **93**.



Scheme 23

The Hooker oxidation works very well in the 1-2 g scale, but reaction with larger quantities results in the formation of undesirable overoxidation products. Fieser *et al.* solved this problem by developing a two-step process that used peroxide and copper sulfate and gave the desired products in 85-90% yields. By treating the appropriate 2-hydroxy-3-alkyl-1,4-naphthoquinone **94** with hydrogen peroxide in a dioxane-soda solution, he obtained the colorless acid known as Hooker´s intermediate **95**[194] that was converted by the action of copper sulfate and alkali into the corresponding 2-hydroxyl-3-*nor*-alkylnaphthoquinone **97** in very high overall yields.[195] By using this modified Hooker oxidation methodology, Cram synthesized a series of lipophilic naphthoquinones in high yields.[196] Fieser proposed a structure for the Hooker´s intermediate obtained from lapachol (**2**) (1,2-dihydroxy-2-(3-methylbut-2-enyl)-3-oxo-2,3-dihydro-1*H*-indene-1-carboxylic acid, **95**), which was later confirmed by ^{13}C-labeling studies[197] and, recently, by an X-ray diffraction analysis (Scheme 24).[198] In a recent study, however, evidence was presented for the formation of another intermediate (**96**) before the classical Hooker´s intermediate (Scheme 24).[199]

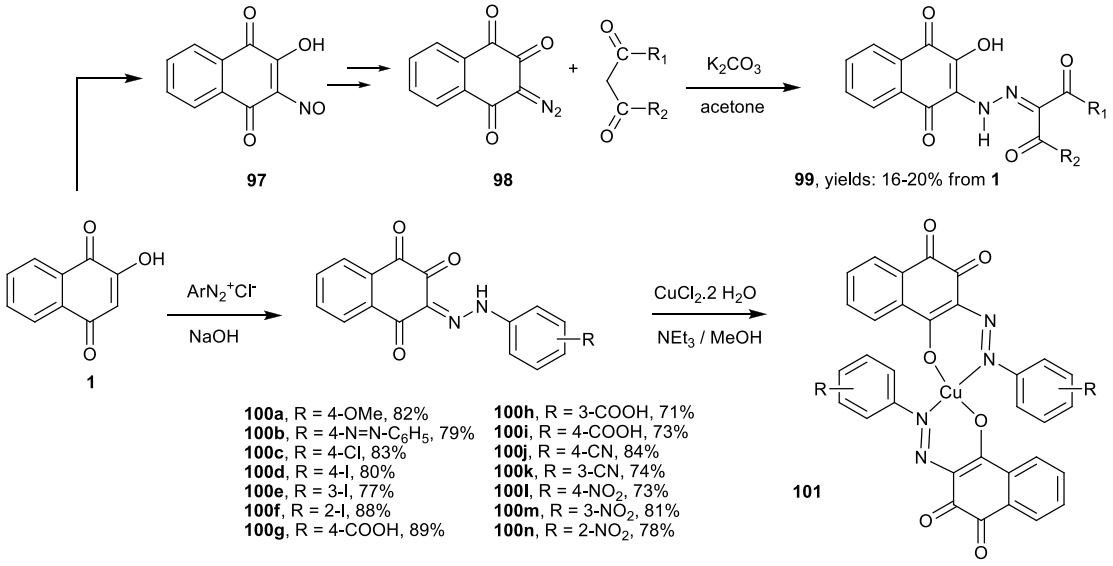


Scheme 24

Schwalbe *et al*. have synthesized various 2-hydroxy-3-alkyl-1,4-naphthoquinones containing a variety of alkyl side chains, some of which were obtained using the Hooker oxidation method. The compounds were tested as inhibitors against the membrane-embedded protein quinol/fumarate reductase (QFR) from *Wolinella succinogenes*, which is a target related to QFRs from the human pathogens *Helicobacter pylori* and *Campylobacter jejuni*. Several naphthoquinones showed IC_{50} values in the low micromolar range. Systematic elongation of the alkyl side chain in the hydroxyl series resulted in increased inhibition. Furthermore, the presence of the hydroxyl group was proved crucial for the activity.[200]

3.6 One further step in the chemistry of lawsone (1)

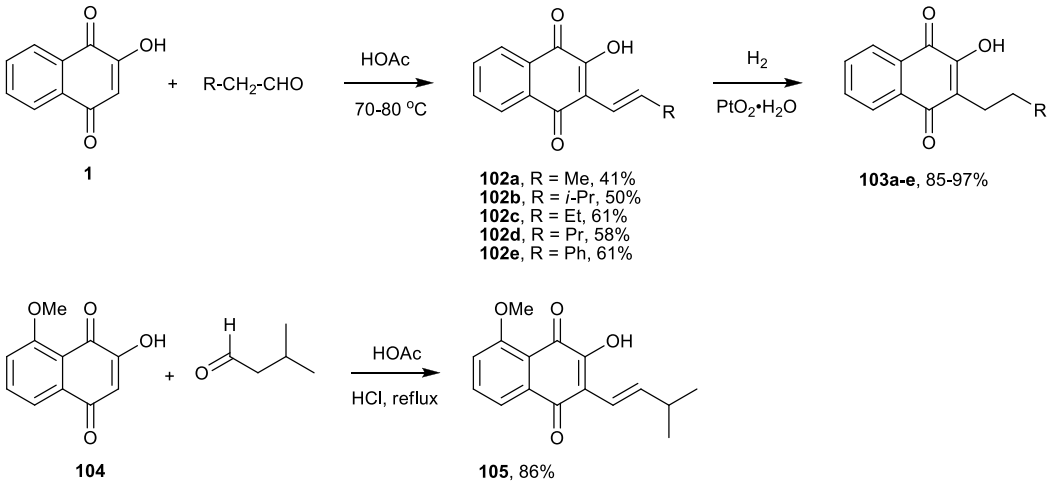
As discussed above, the C-3 position of **1**, next to the hydroxy group, is very reactive toward electrophiles. Thus, the reactions with, *e.g.*, halogens, nitro derivatives[201] and diazonium salts[202] are easily performed in one step and yield important derivatives of **1** that can be used as starting reagents for the synthesis of other compounds (Scheme 25). For example, a series of 3-hydroxy-2-hydrazino-1,4-naphthoquinones **99** were synthesized from the nitroso derivative (**97**) by reduction with $NaBH_4$/MeOH, followed by diazotization of the resulting 3-amine-2-hydroxy-1,4-naphthoquinone with sodium nitrite in hydrochloric acid, and then by reaction of the 3-diazo-naphthalene-1,2,4-trione (**98**) with 1,3-dicarbonyl enolates in the presence of K_2CO_3 in acetone. Overall yields of **99** from **1** varied from 16 to 20%. From the reactions of **1** with diazonium salts, various 3-(2-R-phenylhydrazono)-naphthalene-1,2,4-triones **100a-n** were isolated in good yields. Their copper(II) complexes **101** showed improved antimalarial activity[203] and anticancer properties[204] compared to the free ligands.



Scheme 25

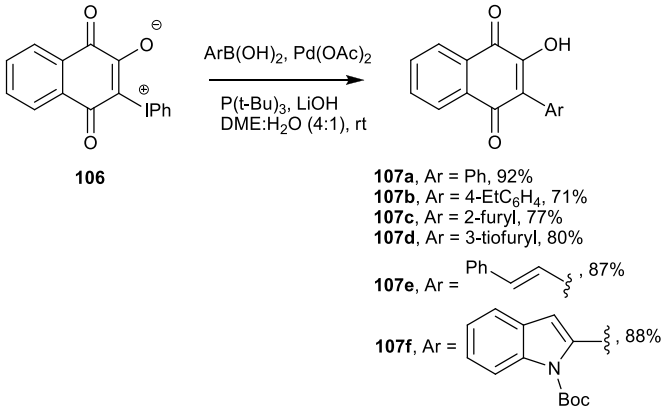
In this part of the review, emphasis will be given to useful compounds synthesized from the reactions of **1** with electrophiles and their further reactions to produce novel derivatives.

Before the discovery of cross coupling reactions, $C(sp^2)$-$C(sp^2)$ coupling at position 3 of **1** was achieved through the condensation with aldehydes. Indeed, the Knoevenagel condensation of **1** with aldehydes forms the reactive *o*-quinone methides that, depending upon the experimental conditions and the structure of the aldehyde, can follow several reaction pathways. Fieser[117] and Hooker[205] used this reaction to produce alkenyl derivatives, as illustrated in Scheme 26 (compounds **102a-e**). For instance, the reaction of **1** with isovaleraldehyde resulted in the formation of isolapachol (**105**). In a subsequent step, hydrogenation of the newly formed double bond of the side chain can lead to *C*-alkylated compounds (**103a-e**). These two reactions are generally applicable to the preparation of derivatives of **1** containing the corresponding *C*-alkenyl and *C*-alkyl groups at the quinone ring next to the hydroxyl group. Giles *et al*. also used this reaction for the preparation of the alkenyl derivative (**105**) as the key step in the total synthesis of dihydro-2*H*-benzo[*g*]chromene-5,10-dione *via* condensation of naphthoquinone (**104**) with 3-methyl butanal in good yield.[206] In search of compounds with pesticidal properties, Jacobsen *et al.* prepared several molecules similar to the series **102a-e** and **105** in Scheme 26, but using triethylamine to catalyze the condensation of **1** with aldehydes. These reaction conditions gave much poorer yields of the compounds.[207]



Scheme 26

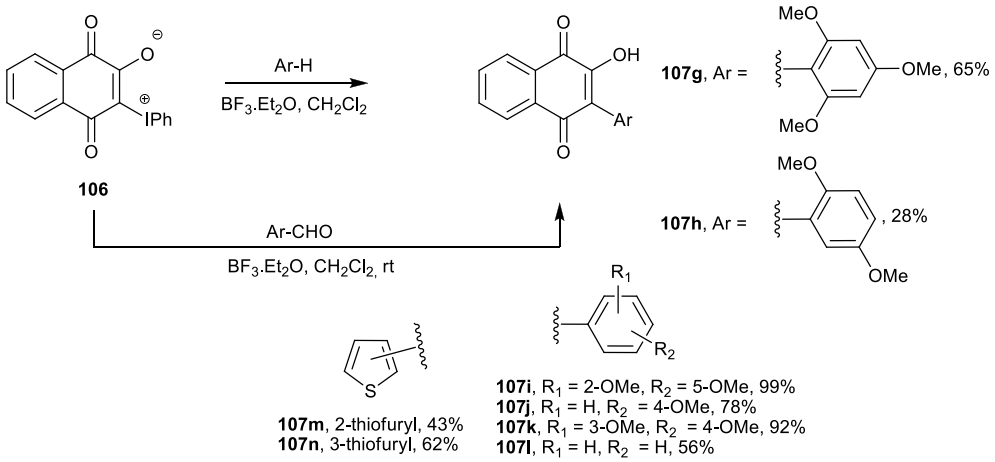
Advances in cross coupling reactions have made formation of $C(sp^2)$-$C(sp^2)$ bonds involving **1** easier and more accessible than they have been in the past. The zwitterionic iodonium 3-phenyliodonium ylide (**106**) is easily obtained from **1** upon reaction with diacetoxyiodobenzene and other diacetoxyiodoarenes.[208,209] This hypervalent iodine ylide is a suitable starting material for *C*-arylation and *C*-alkenylation reactions. It was used in Stille[210,211] and Suzuki-type couplings. For instance, the Suzuki-type coupling of this ylide with aryl- and heteroarylboronates in DME/H_2O produced *C*-aryl and *C*-alkenyl 2-hydroxy-naphthoquinones (**107a-f**) in fair to good yields (Scheme 27).[212]



Scheme 27

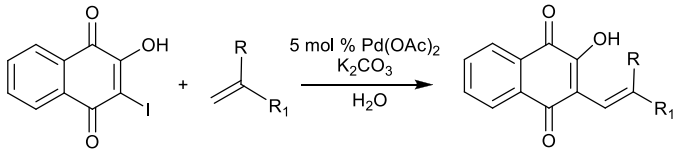
Ylide **106** also reacts with electron-rich arenes in the presence of $BF_3.Et_2O$ as catalyst to afford the corresponding Suzuki-type *C*-arylated 1,4-naphthoquinones (**107g-n**).[213] Furthermore, it also undergoes an unusual *C*-arylation-deformylation reaction with aromatic aldehydes activated by

$BF_3.Et_2O$ that also leads to Suzuki type 2-aryl-3-hydroxy-1,4-naphthoquinones (**107g-n**). This reaction is very useful because aromatic aldehydes are cheap and readily available (Scheme 28).



Scheme 28

Another efficient $C(sp^2)$-$C(sp^2)$ coupling involving **1** is the Heck reaction of 2-hydroxy-3-iodo-naphthoquinone (**108**) with electron-deficient alkenes (unsaturated acids and amides). Perez and coworkers[214] described it as a simple methodology and with facile work-up to produce *C*-alkenyl products (**109**) in good to excellent yields (Scheme 29). It is worth noting that 2-hydroxy-3-bromo-1,4-naphthoquinone can be easily obtained from **1** by using several different reaction conditions such as morpholine/iodine,[215] chloroform/H_2SO_4/H_2O_2/Br_2 (92%), Br_2/CH_3CN,[216] and NH_4Br/oxone (99%).[217]



Scheme 29

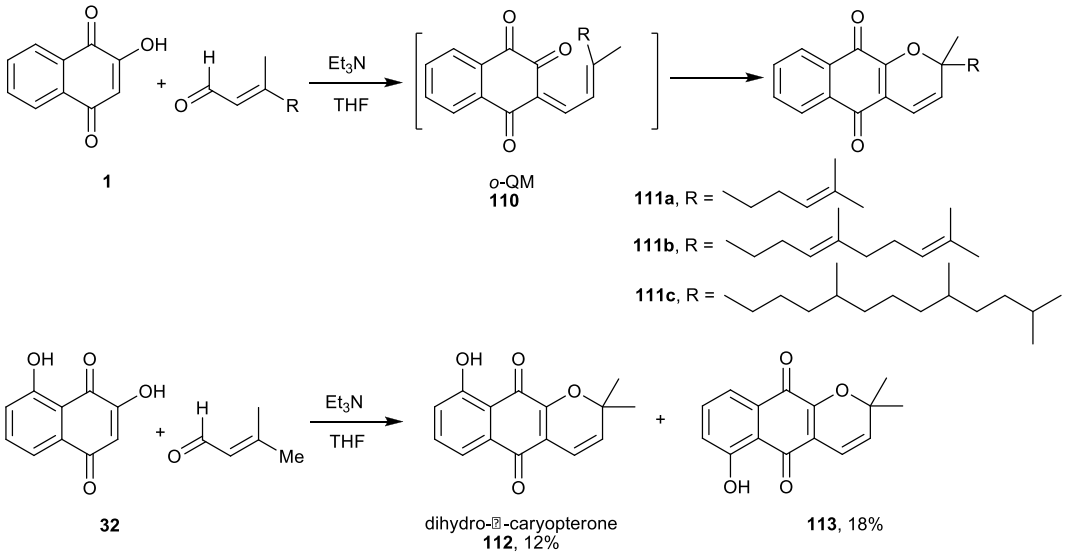
3.7 Synthesis of 2*H*-chromene- and chromane-fused naphthoquinones

A number of natural and synthetic heterocyclic naphthoquinones have important biological activities, and in the past few years, several research programs have been directed towards the synthesis of these compounds. Heterocycles are of great importance because many of the biochemical materials

essential to life belong to this class of compounds, *e.g.,* drugs, vitamins and active metabolites in plants and marine organisms. In this regard, numerous heterocyclic rings containing the naphthoquinone moiety have been synthesized, among which those bearing a chromene or a chromane ring fused with *ortho*- and *para*-quinones must be highlighted. They represent a special class of naturally occurring molecules present in many plants, fungi and insects.[218] The most important substances of the chromane-fused-quinone class are α- (**6**) and β- (**7**) lapachones (Fig. 1). Thus, the development of reliable methods for the preparation 2*H*-chromene- and chromane-naphthoquinones will be valuable to access analogues and derivatives of these compounds.

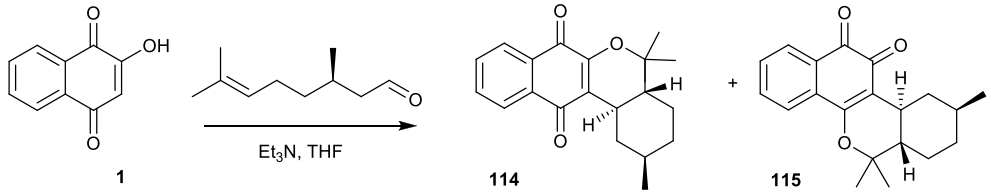
β-Lapachone (**6**) is a natural pyran-*ortho*-naphthoquinone originally obtained from the heartwood of various Lapacho trees that belong to the genus *Tabebuia* (Bigoniaceae) and that grow throughout South America. This compound has been demonstrated to exhibit many different biological activities, including a promising anticancer activity.[219] Indeed, it presents significant antineoplastic[220] activity against various human cancer cell lines from leukemia,[221] prostate,[222] malignant glioma,[223] hepatoma,[224] colon,[225] breast,[226] ovarian,[227] lung[228] and pancreatic[229] tumors. Moreover, it has been intensely investigated as a possible prototype compound against *Trypanosoma cruzi*, the etiological agent of Chagas disease, in both acute and chronic infections.[230-233] This compound inspired several researchers in search of new derivatives with better therapeutical index. Several heterocyclic derivatives, such as oxyranes,[234,235] oxazoles,[236] imidazoles[237] and phenazines,[238] have been synthesized from **6,** and some have shown fewer side effects and improved trypanocidal activity.

A very useful route to new analogues of **6** involves the construction of 2*H*-chromene or chromane moieties adjacent to naphthoquinone **1**, by using the *o*-quinone methide (*o*-QMs) intermediate (**110**, Scheme 30)[239] that undergoes a Knoevenagel condensation, followed by an electrocyclization process or a hetero Diels-Alder reaction to form the heterocyclic rings, respectively. Ferreira and coworkers[240] reported the first reaction of **1** with α,β-unsaturated aldehydes producing exclusively chromene-naphthoquinones (**111a-c**) in 33-35% yield by the Knoevenagel reaction, followed by an intramolecular eletrocyclization. The same synthetic route and conditions were used by Oliveira and coworkers[241] for the preparation of the naturally occurring dihydro-α-caryopterone (**112**) and its isomer 6-hydroxy-dehydro-α-lapachone (**113**) from naphthoquinone (**32**).



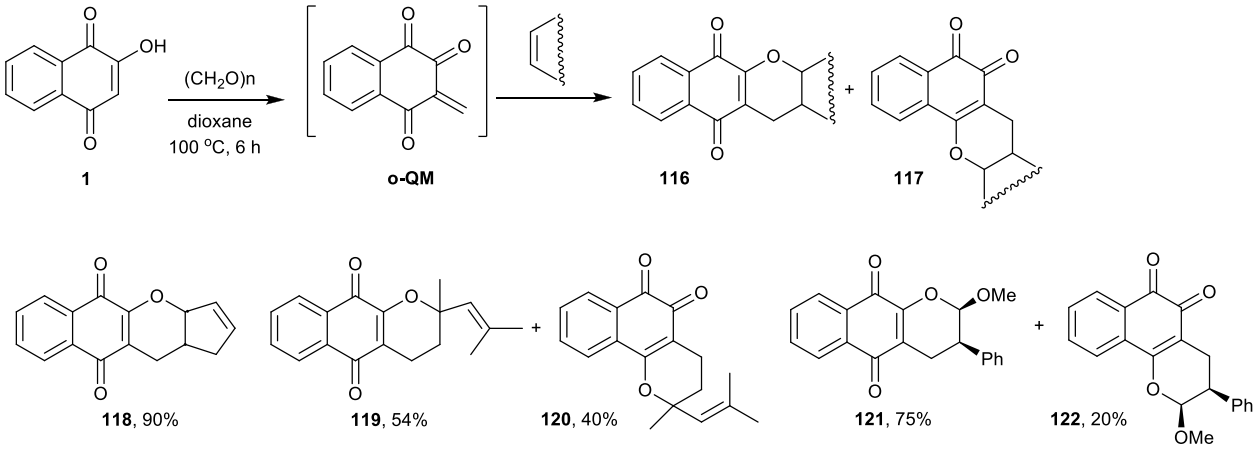
Scheme 30

The same research group has also developed a novel preparation of the tetracyclic α- and β-pyran naphthoquinones (**114** and **115**), obtained in 70% overall yield by the reaction of citronellal,[240] an aldehyde bearing a remote double bond, with **1**, *via* the *o*-QM intermediate generated *in situ* (Scheme 31). Estévez-Braun and co-workers have performed the asymmetric version of this reaction with (*S*)-(-)-citronellal, producing compounds **114** and **115** in a 1:1 ratio and 94% overall yield.[242]



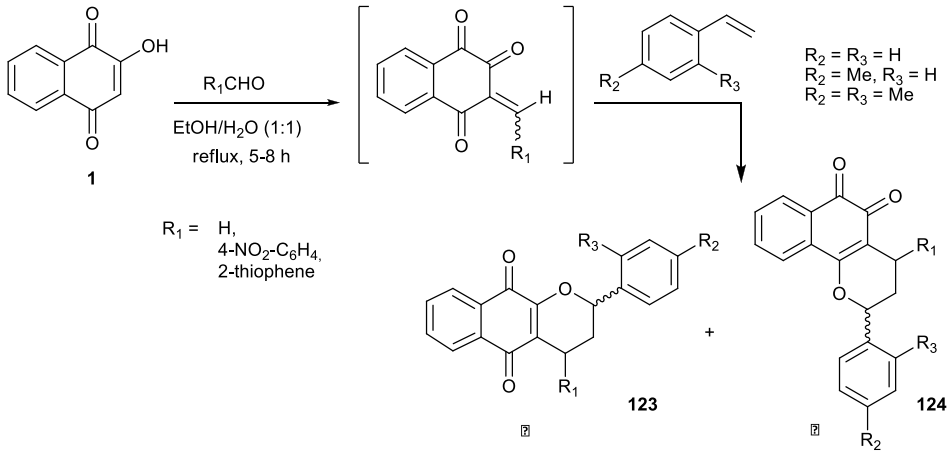
Scheme 31

Nair and Treesa improved the later methodology by using an *o*-QM[243] generated *in situ* from **1** and formaldehyde to perform the one-pot intermolecular Diels-Alder reaction with olefins. This new three-component protocol overcame the limitation regarding the use of appropriately substituted aldehydes in the Tanden-Knoevenagel/intramolecular hetero Diels-Alder cycloaddition methodology. By this reaction, and using several different olefins, they prepared a wide variety of α- and β-lapachone derivatives (chromane-naphthoquinones) in moderate to good yields, examples of which are shown in Scheme 32.



Scheme 32

Despite the good performance achieved in the reactions with formaldehyde described above, the same reaction with aromatic aldehydes did not work. Nonetheless, by investigating solvent effects, Ferreira and coworkers found that the reaction was accelerated in ethanol/water (1:1) at reflux, leading to new substituted chromane-naphthoquinones.[244] With this improved method, β-pyranonaphthoquinones were obtained more selectively, in better yields, with shorter reaction times and, most importantly, from any type of aldehyde, as illustrated in Scheme 33 and Table 1 (entries 1-8).

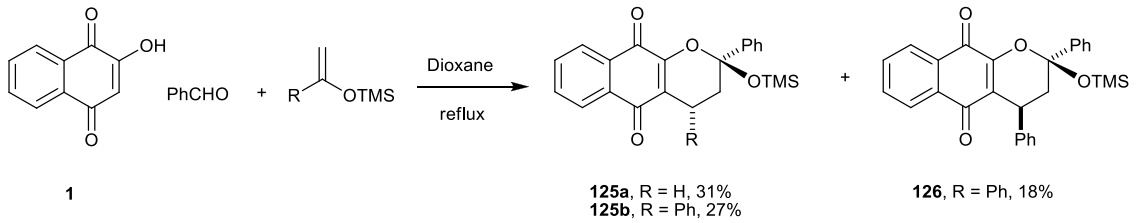


Scheme 33

Table 1 Synthesis of chromane-naphthoquinones **123** and **124** by hetero Diels-Alder reaction with *o*-QM

Entry	R_1	R_2	R_3	Conditions	Time (h)	Yield (%)	Ratio α/β (**123**:**124**)	α (*syn*:*anti*)	β (*syn*:*anti*)
1	H	H	H	EtOH/H_2O (1:1)	6	94	3.1	-	-
2	H	Me	H	EtOH/H_2O (1:1)	6	95	3.8	-	-
3	H	Me	Me	EtOH/H_2O (1:1)	6	97	4.7	-	-
4	4-NO_2-C_6H_4	Me	H	EtOH/H_2O (1:1)	5	50	1.4	37:63	18:82
5	2-thiophene	Me	H	EtOH/H_2O (1:1)	8	60	0.8	54:46	0:100
6	Ph	Me	H	EtOH/H_2O (1:1)	8	52	0.6	20:80	12:88
7	H	H	H	dioxane/HOAc	4	96	2.2	-	-
8	4-NO_2-C_6H_4	Me	H	dioxane/HOAc	5	55	1.1	35:65	17:83

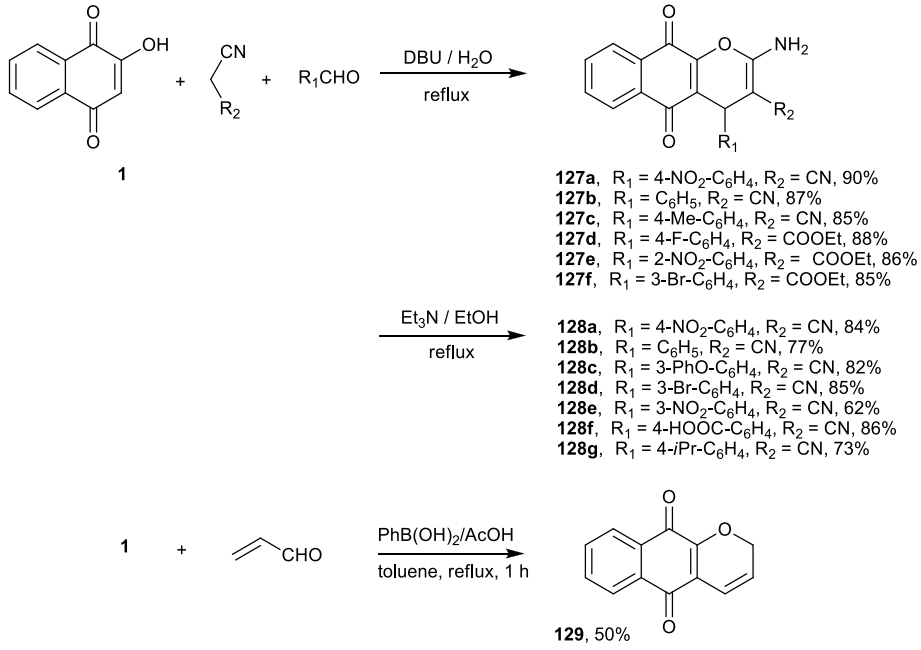
This reaction protocol also allows the use of electron-rich olefins, such as silyl enol ethers, in the preparation of chromane-naphthoquinones (Scheme 34).[245] In this way, a series of siloxy-containing naphtho[2,3-*b*]pyran-5,10-dione derivatives were obtained in moderate to high yields, with the reactions giving α-lapachone derivatives regioselectively.



Scheme 34

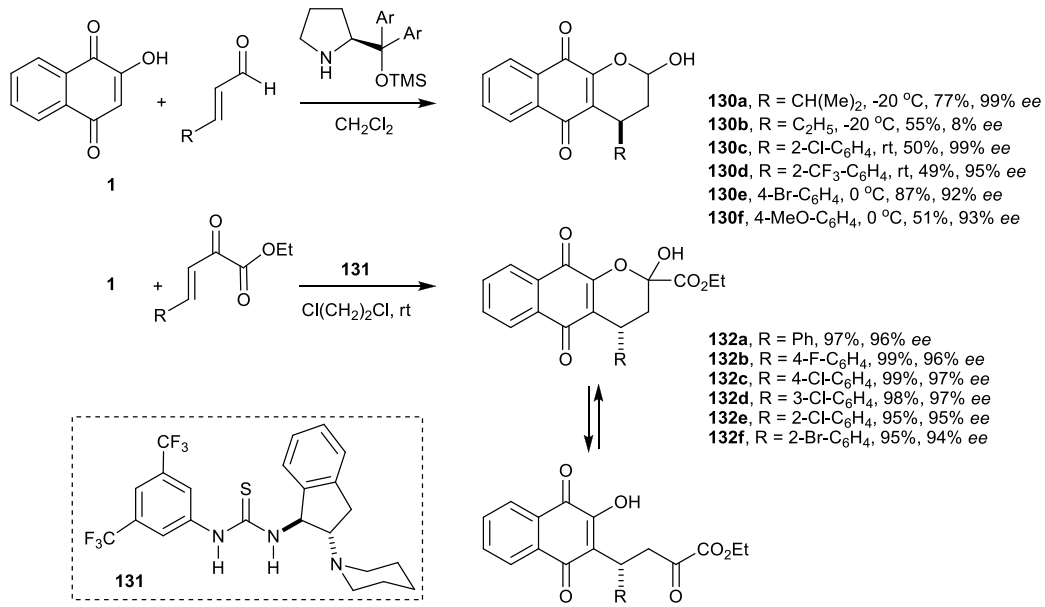
A new three-component route for the synthesis of 4*H*-chromene-naphthoquinones was developed by Saluja and coworkers[246] involving the cyclo-condensation reaction of **1** with an aldehyde and malononitrile or ethyl cyanoacetate. The reaction produced excellent yields of chromene-naphthoquinones (**127a-f** and **128a-g**) with a high atom economy (Scheme 35). The reaction with malononitrile and aromatic aldehydes was reinvestigated by Magedov *et al.* Their theoretical analysis using semiempirical and DFT calculations indicated that the formation of 1,4-naphthoquinones is favored over the 1,2-products both thermodynamically and kinetically. The antiproliferative properties of a number of chromene-naphthoquinones thus synthesized were investigated against a panel of cancer cell lines, and the apoptosis-inducing effects of the 3-substituted phenyl derivative (**127b**) was found to rival those of clinically relevant α-lapachone.[247] An interesting one-pot

preparation of 3*H*-chromene (**129**) was developed by Costa and coworkers[248] that adapted the synthesis of chromenes from phenols developed by Snieckus *et al.*



Scheme 35

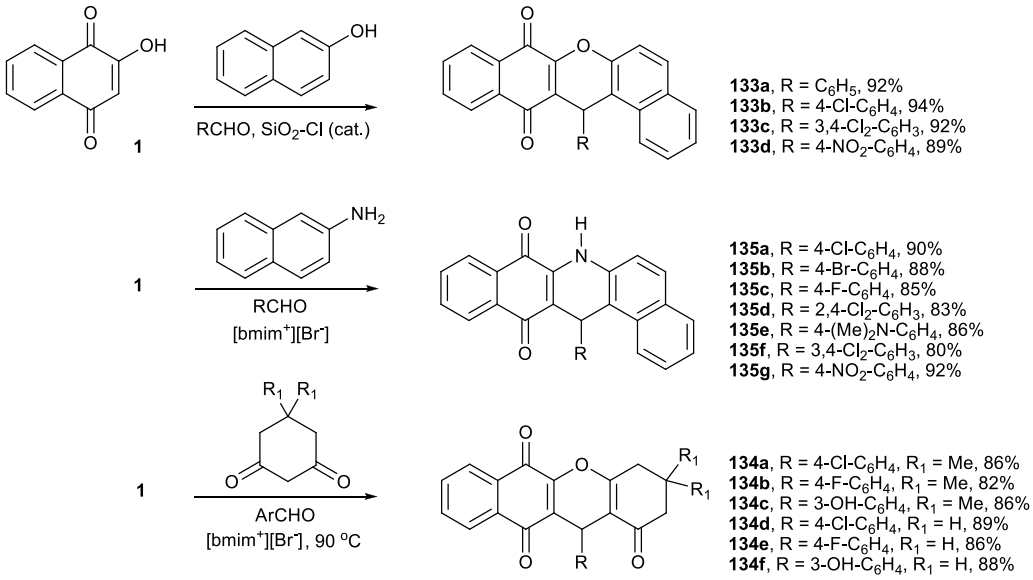
The reaction of **1** with α,β-unsaturated aldehydes usually leads to 2*H*-chromenes *via* tandem Knoevenagel electrocyclization. Under organocatalysis conditions, however, efficient, enantioselective cascade 1,4-addition/cyclization reactions take place (Scheme 36)[249] and provide valuable chromane-naphthoquinones with aliphatic and aromatic α,β-unsaturated aldehydes in good yields and with excellent enantioselectivities (90-99% *ee*). Recently, Wang and coworkers studied a similar organocatalyzed reaction between **1** and β-unsaturated α-keto esters [(*E*)-ethyl 2-oxo-4-aryllbut-3-enoates] (Scheme 36).[250] The most effective chiral organocatalyst for this reaction was a *trans*-indane thiourea (**131**), which allowed for quick construction of diversely functionalized naphthoquinones under mild reaction conditions, with excellent yields and high enantioselectivities.



Scheme 36

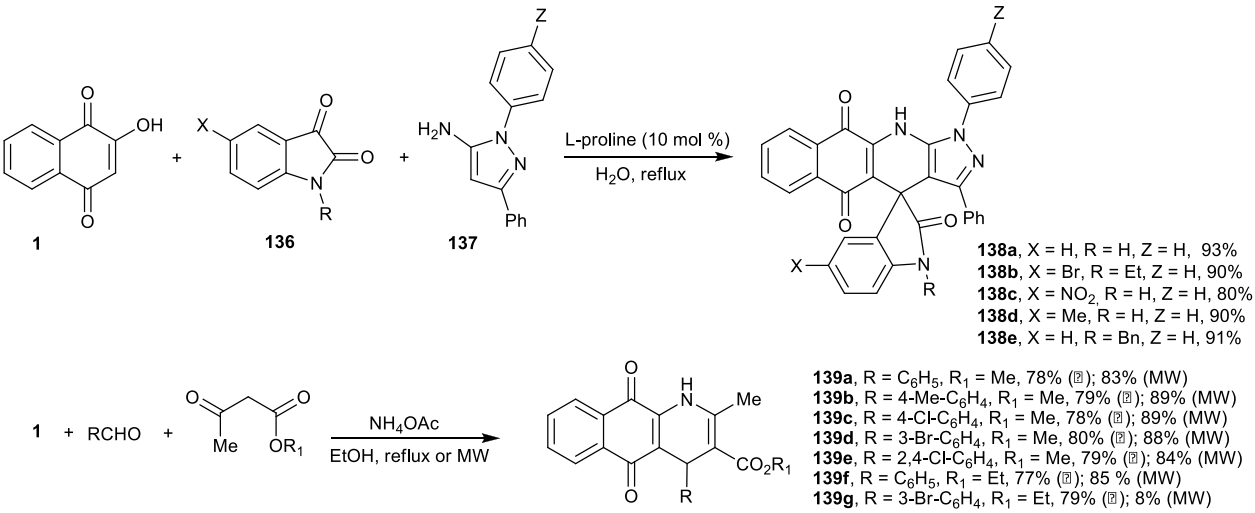
When the chromane-naphthoquinones are fused with a second naphthoquinone or with an aromatic ring, they belong to the class of xanthenes and benzoxanthenes, respectively. These compounds are of great interest because of their wide range of biological and pharmaceutical properties, such as antiviral[251] and antibacterial properties.[252] Several methods for their preparation have been described in the literature.

The one pot solvent-free condensation of **1** with β-naphthol and aromatic aldehydes in the presence of the heterogenous catalyst silica chloride affords the aryl-14*H*-dibenzo-xanthenes (**133a-d**) in short reaction times and excellent yields (Scheme 37).[253,254] Recently, Du *et al.*[255] performed this reaction to prepare xanthene derivatives from **1** and aromatic aldehydes, and by using 1,3-dicarbonyl compounds, they also produced a series of benzo-xanthenes derivatives (**134a-f**). The reactions are performed at 90 °C, in the ionic liquid [bmim$^+$][Br$^-$] that can be recycled and reused (Scheme 37). Similarly, Rahmati described the synthesis of various xanthenes from the condensation reactions of β-naphthol or dimedone with various aldehydes in the presence of trifluoroacetic acid as a catalyst in an ionic liquid.[256] Li *et al.*[257] also described a similar reaction, using β-naphthylamine instead of β-naphthol in [bmim$^+$][BF$_4^-$] as solvent, from which they produced dibenzo-acridines (**135a-g**) in good yields (Scheme 37). These reactions were also studied by other research groups in the presence of various catalysts[258-260] and ionic liquids.[261]



Scheme 37

The dibenzo-acridines can also be prepared by the recently described multicomponent reactions[262] developed by Dabiri *et al*., who reported the reactions of **1** with indoles, in place of aldehydes, and 1-*H*-pyrazol-5-amines in the presence of L-proline as catalyst. Several new spiro-oxindoles (**138a-e**) were obtained in good yields (Scheme 38).[263] Perumal and coworkers developed a four-component domino reaction of **1**, aromatic aldehydes, methyl or ethyl acetoacetate and ammonium acetate in ethanol, under heating or microwave irradiation, to produce tetrahydrobenzo[*g*]quinoline-5,10-diones (**139a-g**) in good yields (Scheme 38). This transformation probably proceeds *via o*-QM, followed by Michael addition of the enol of the methyl or ethyl acetoacetate and intramolecular regioselective annulation with ammonia available from the dissociation of ammonium acetate (Scheme 38).[264]



Scheme 38

3.8 Synthesis of xanthenes *via o*-quinone methide

9*H*-xanthenes (**140**, Fig. 5) constitute a general class of natural and synthetic heterocyclic compounds[265-267] with many applications, such as in biological targets and fluorescent dyes.[268] In the biological field, these heterocyclic compounds exhibit a broad spectrum of activities, such as trypanothione reductase inhibition,[269] antiviral,[270] antibacterial,[271,272] antiplasmodial,[273,274] anticancer,[275-278] antimalarial,[279] antifungal,[280] antiinflammatory,[281] and antihypertensive[282] activities, which have been investigated for photodynamic therapy.[283] Because of all of these biological properties, many methods for the preparation of 9*H*-xanthene derivatives have been described in the literature,[284-287] mainly related to the two- or three-component reaction of β-naphthol and aldehydes.[253,254,256,288-296]

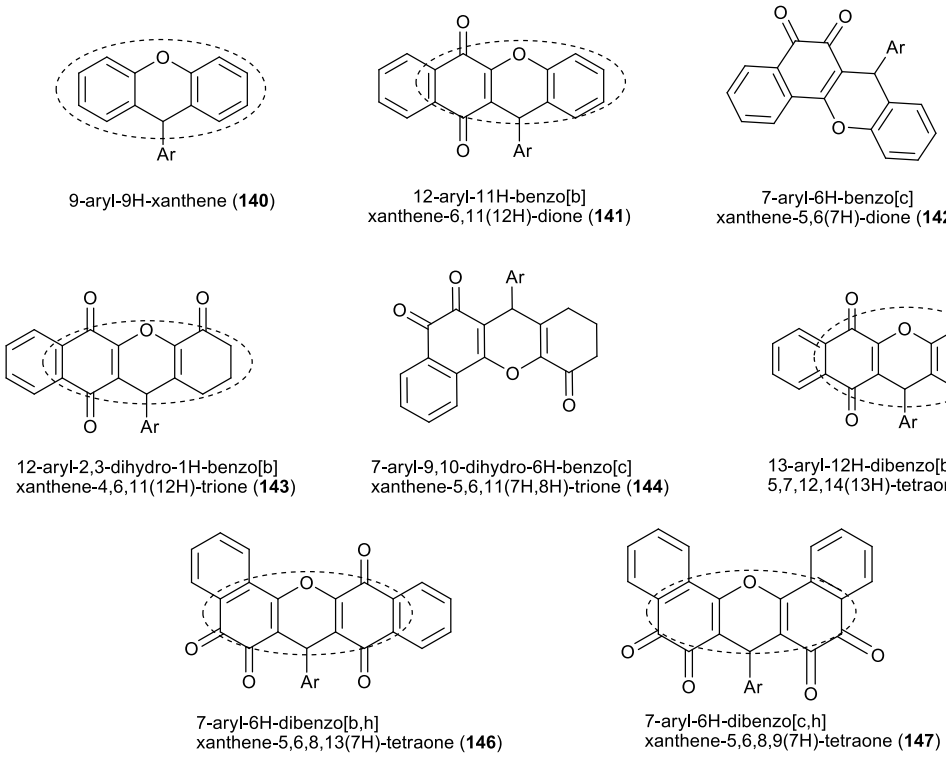
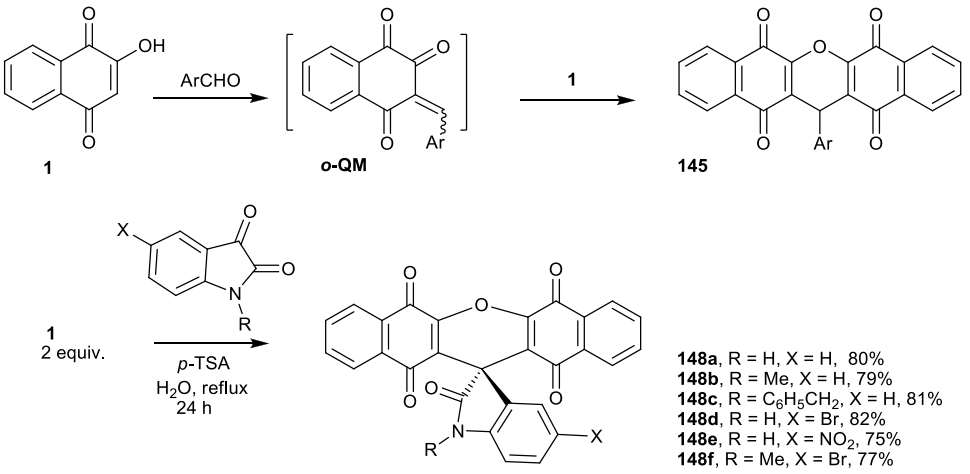


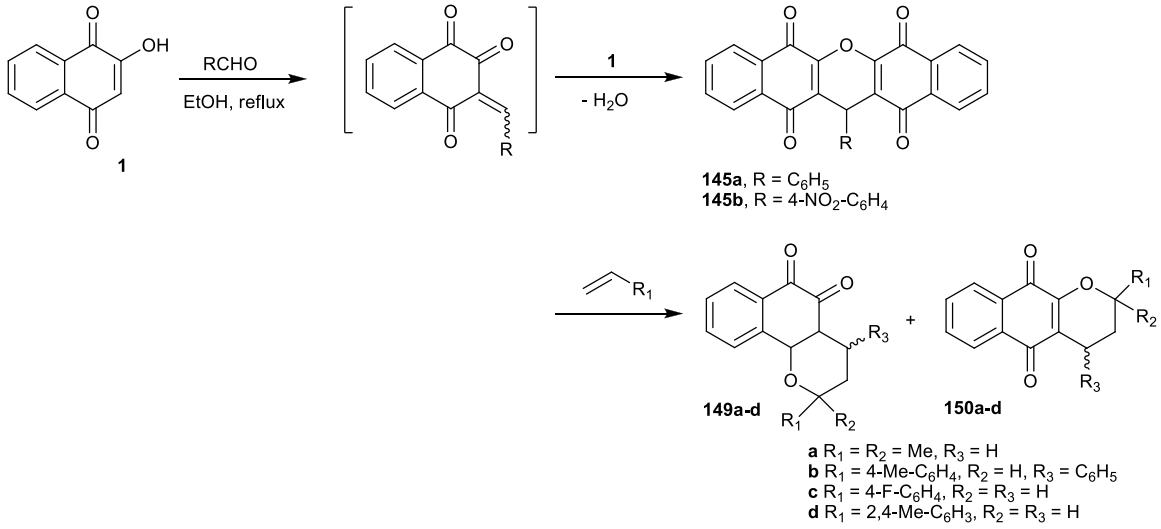
Fig. 5 Naphthoquinones fused with xanthenes.

The preparations of various naphthoquinones fused with xanthene rings (Fig. 5) have been reported, *e.g.*, benzoxanthenes with one naphthoquinone moiety and represented by compound **141** and its isomer **142**; benzoxanthenetrione **143** and its isomer **144**;[255,297-303] and dibenzoxanthenes containing two naphthoquinone moieties attached to the central pyran ring and that can exist as one of the three isomers **145**, **146** and **147**. Tisseh *et al.* reported the first simple and efficient method for the preparation of dibenzo[*b,i*]xanthene derivatives **145** under solvent-free conditions *(p*-toluene sulfonic acid 10 mol%), but with very basic spectroscopic characterization (Scheme 39). In general, this *o*-quinone methide protocol works very well in the absence of an additional nucleophile, which allows another equivalent of **1** to add to the *o*-QM intermediate formed *in situ*, giving the desired product after cyclization with loss of a water molecule.[304] Reactive carbonyl compounds, such as isatins, have also been used in this reaction in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA). The reactions proceeded smoothly in water, at reflux, for 24 h, to produce spiro[dibenzo[*b,i*]-xanthenes **148a-f** adducts in good yields (Scheme 39).[305]



Scheme 39

Ferreira and co-workers[306] have described the syntheses of various pyranaphthoquinones by reacting **1** with an aldehyde (formaldehyde or arylaldehydes) that results in the *in situ* generation of the *o*-QM, which then undergoes hetero Diels-Alder reactions with the appropriate dienophiles. Xanthenes **149a-d** and **150a-d** were produced by nucleophilic addition of **1** on the *o*-QM intermediate, followed by dehydration. Some selected examples are shown in Scheme 40. All compounds were tested as inhibitors of the ATPase activity of the viral NS3 enzyme in *in vitro* assays and the replication of dengue virus in cultured cells. Two 1,4-pyranaphthoquinones inhibited dengue virus replication in mammal cells by 99.0%, and three others reduced the dengue virus ATPase activity of NS3.

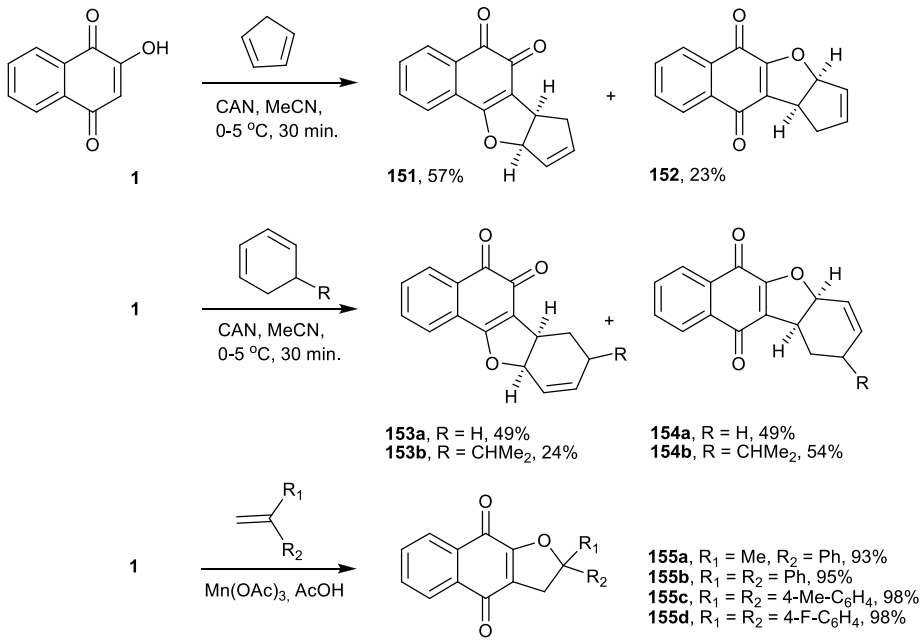


Scheme 40

3.9 Synthesis of other heterocycles from lawsone (1)

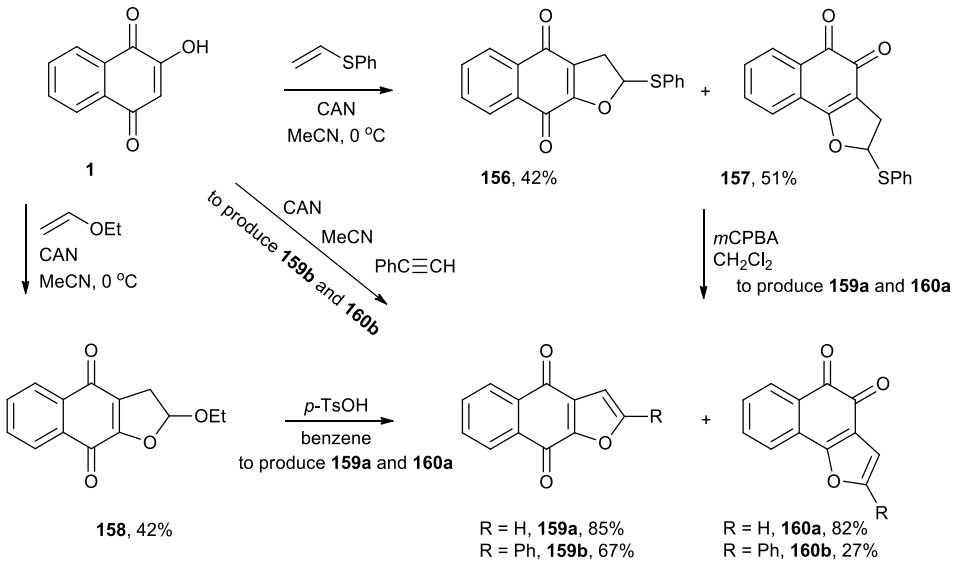
Furonaphthoquinones constitute another important class of naturally occurring or synthetic five-membered heterocyclic fused naphthoquinones. Several synthetic routes to this class of compounds have been described in the literature, some of which use **1** as the starting material.

One important and direct method for synthesizing furonaphthoquinones is the one-electron oxidation of **1** with ceric ammonium nitrate (CAN) and C-C bond formation with olefins. CAN, a well know one-electron oxidant,[307,308] easily handled and soluble in various solvents, is very useful in many reactions.[309-311] For instance, the reaction of **1** with CAN and cyclodienes in acetonitrile resulted in the formation of 1,4- and 1,2-furonaphthoquinones (**151-154**), as presented in Scheme 41.[312] Additionally, manganese(III) acetate dihydrate can promote the radical cyclization of **1** with alkenes, leading selectively to 1,4-furonaphthoquinones (**155a-d**) in excellent yields (Scheme 41).[313]



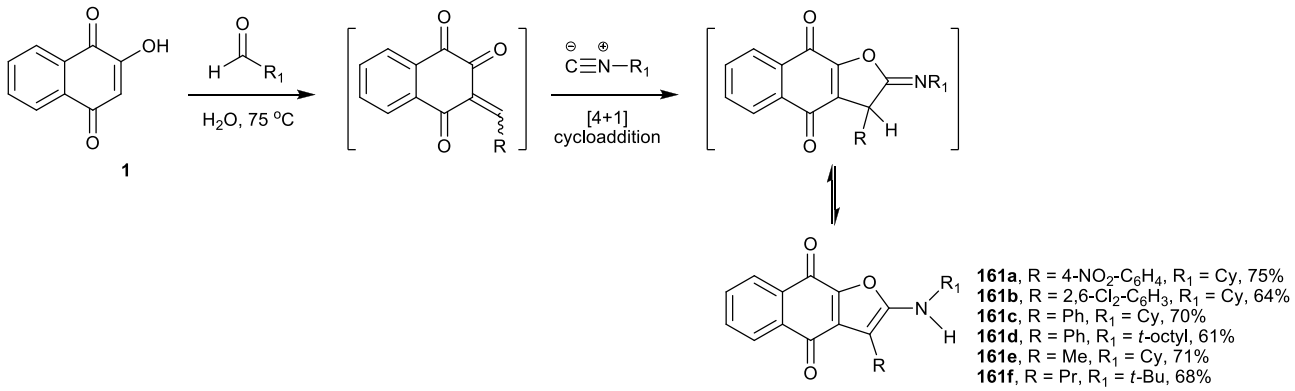
Scheme 41

CAN also promotes the formation of a radical of **1** that adds to phenyl vinyl sulfide and ethyl vinyl ether, followed by intramolecular cyclization, producing dihydrofuronaphthoquinones (**156**, **157** and **158**). These dihydrofurans can be transformed into furan tethered to 1,2- and 1,4-naphthoquinones (**159a** and **160a**).[314] It is worth noting that 1,4-furonaphthoquinone (**159a**) is a natural product isolated from *Avicennia marina*.[315] Kobayashi and co-workers studied the same reaction between 2-hydroxy-1,4-naphthoquinone and phenylacetylene that yielded **159b** and **160b** (Scheme 42).[316]



Scheme 42

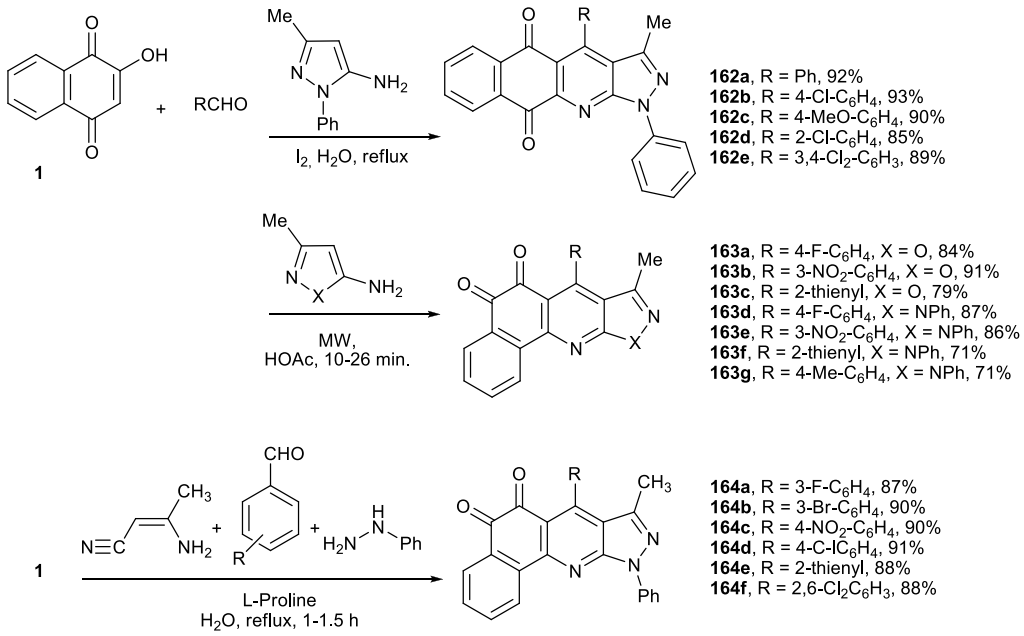
Teimouri and coworkers[317] have developed an efficient and green method for the preparation of highly substituted linear naphtho[2,3-*b*]-furan-4,9-dione derivatives starting from **1**, alkyl isocyanides and a variety of aldehydes. This one-step method furnishes regioselectively the linear 1,4-naphthoquinones (**161a-f**) in good yields (Scheme 43).



Scheme 43

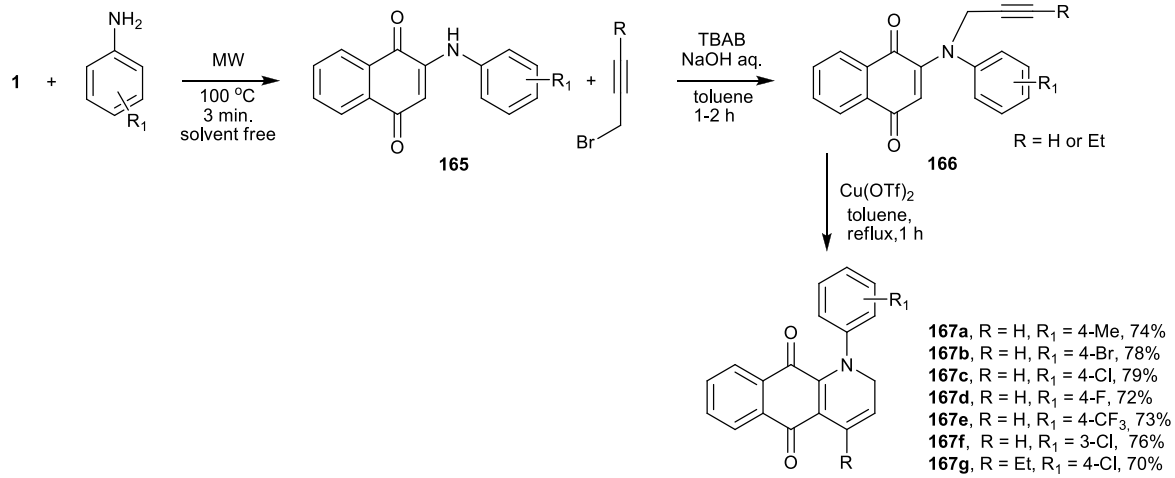
Wu and co-workers have described an efficient multicomponent method for the synthesis of benzo[*h*]pyrazolo[3,4-*b*]quinolines tethered to the 1,4-naphthoquinone nucleus. The syntheses were performed by condensation of **1** with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and various benzaldehydes using molecular iodine as catalyst in water. The most plausible mechanism involves a cascade sequence starting with Knoevenagel condensation to form the *o*-QM, followed by Michael addition of the amino-pyrazole, intramolecular nucleophilic cyclization and, finally, dehydration.

This method is experimentally simple, uses inexpensive and readily available reagents and catalysts, and the products, 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones (**162a-e**), are formed in good yields and high atom economy (Scheme 44).[318] The same multicomponent domino annulation reaction was studied by Li and coworkers under modified experimental conditions. Upon treatment with acetic acid under microwave irradiation, the benzo[*h*] isoxazolo[3,4-*b*]quinolines (**163a-g**) were formed regioselectivily, in which the β-isomer of the naphthoquinone is tethered to benzo[*h*]pyrazolo[3,4-*b*]quinolines (Scheme 44).[319] Recently, another multi-component protocol was described for the synthesis of novel polyheterocyclic systems containing a benzo[*h*]quinoline-5,6-dione nucleus (**164a-f**) from **1** in aqueous medium. In this four-component process, L-proline catalyses the Michael addition of phenylhydrazine to 3-aminocrotononitrile with annulation *via* the elimination of ammonia to give 3-methyl-1-phenyl-1*H*-pyrazol-5-amine *in situ*, as well as the Knoevenagel reaction of the aldehyde and **1** (Scheme 44).[320]



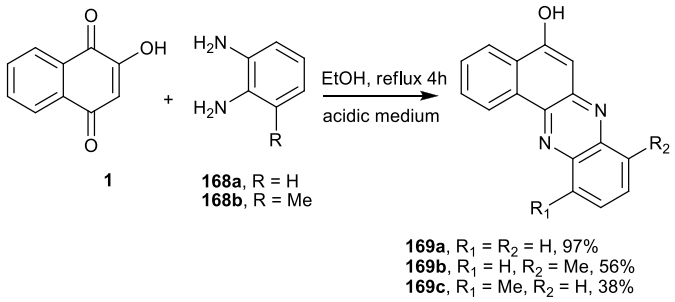
Scheme 44

Perumal *et al.* reported a very interesting three-component one-pot synthetic sequence to prepare quinolines fused with the naphthoquinone moiety. In the first step, **1** reacts with the appropriate aniline, replacing the hydroxyl group to give product **165**, which reacts with propargyl bromides furnishing *N*-propargylaminonaphthoquinones **166**. Intramolecular 6-endo-dig cyclization catalyzed by copper(II) triflate furnishes the naphthoquinone-quinolines (**167a-g**) in good yields (Scheme 45).[321]



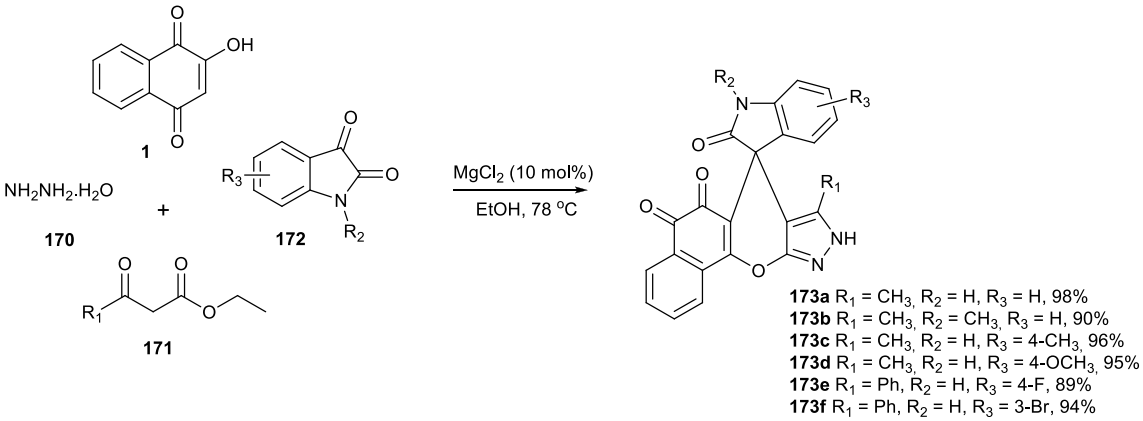
Scheme 45

Recently, Jain *et al.*[322] performed the reaction of **1** with 1,2-diaminobenzenes **168a-b** and obtained the corresponding tetracyclic phenazine derivative (**169a**), whereas the reaction with 2,3-diaminotoluene gave a mixture of the regioisomers (**169b**) and (**169c**) (Scheme 46).



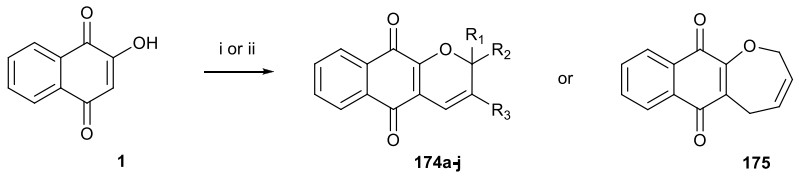
Scheme 46

Song and coworkers[323] have described an efficient one-pot synthesis of 5*H*-spiro[benzo[7,8]chromeno[2,3-*c*]pyrazole-7,30-indoline]-20,5,6(9*H*)-trione derivatives *via* a four-component reaction of hydrazine hydrate, β-keto esters, isatins and lawsone catalyzed by $MgCl_2$ in ethanol. This reaction provides the advantages of excellent yields, environmentally friendly solvent, simple workup procedure and short reaction times (Scheme 47).



Scheme 47

Very recently, Ferreira and co-workers[324] reported the synthesis of α-xyloidones **174a-j** and oxepine **175** in moderate to good yields *via* the Knoevenagel condensation-electrocyclization reaction between **1** and α,β-unsaturated aldehydes in the presence of formic acid at reflux or microwave irradiation. Given the difficulty involved with synthesizing other xyloidone derivatives, such as **174i** and **174j**, an alternative synthetic method was investigated, involving the *O*- and *C*-alkylation of **1**, followed by cyclization using ring-closing metathesis (RCM, Scheme 48).



i) $R_1R_2C=CR_3CHO$, $EtOH/H_2O$, HCOOH 1 %, reflux or MW
ii) Three steps (a or b, c then d)
a) $(CH_3)_2CH_2CHO$, TsOH, $PhCH_3$, reflux or b) AllBr, DMF, K_2CO_3, MW.
c) AllBr or propargyl bromide, acetone, K_2CO_3
d) CH_2Cl_2, Grubbs catalyst, reflux

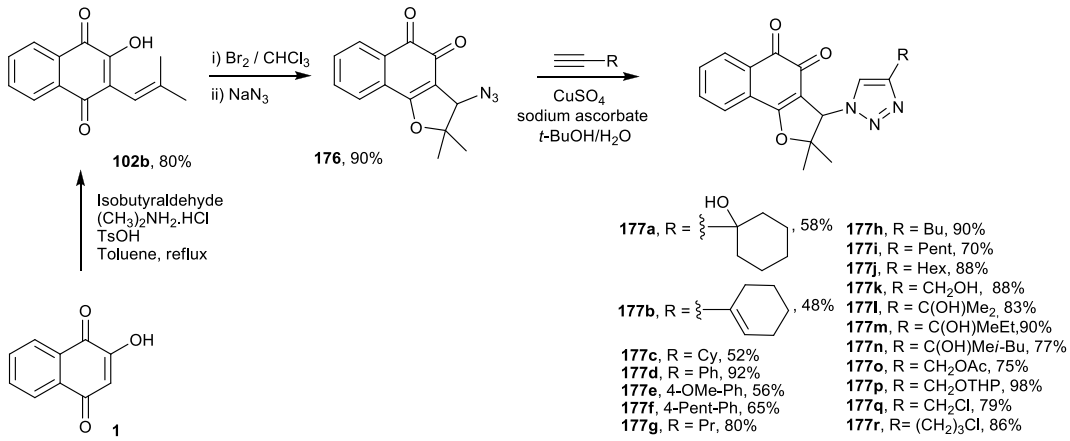
Scheme 48

Table 1 α-xyloidones **174a-j** and oxepine **175** by Knoevenagel condensation-electrocyclization reaction

Entry	Product	Δ	MW	Method
1	**174a**, R_1= R_2=Me, R_3= H	65 % (1 h)	73 % (1.5 h, 80 °C)	(i)
2	**174b**, R_1=Me, R_2=CH_2-Prenyl, R_3=H	8 % (1 h)	70 % (5.5 h, 80 °C)	(i)
3	**174c**, R_1= R_2=H, R_3= Me	26 % (6 h)	70 % (1.2 h, 80 °C)	(i)
4	**174d**, R^1=Me, R_2= R_3=H	14 % (1 h)	54 % (55 min., 80 °C)	(i)
5	**174e**, R_1= R_3= H, R_2= Pr	6 % (1 h)	46 % (1.5 h, 80 °C)	(i)
6	**174f**, R_1=R_3= H, R_2= Furyl	3 % (1 h)	Degraded	(i)
7	**174g**, R_1=R_3= H, R_2= phenyl	-	10 % (2 h, 80 °C)	(i)
8	**174h**, R_1= R_2 = R_3= H	-	-	(i)

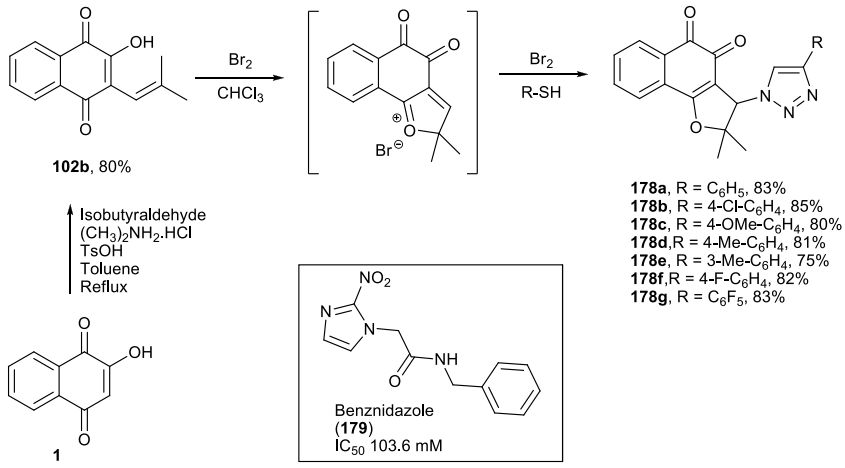
Entry	Product	Steps			
		a or b	c	d	
9	**174i**, R_1= R_2 = R_3= H	80 % (a)	66 %	73 %	(ii)
10	**174j**, R_1= R_2 = H, R_3= CH=$(CH_3)_2$	80 % (a)	45 %	88 %	(ii)
11	**175**	55 % (b)	40 %	54 %	(ii)

Ferreira and co-workers have also synthesized 18 new 1,2-furanonaphthoquinones tethered to 1,2,3-1*H*-triazoles from *nor*-lapacol (**120b**) and evaluated their activity against four different leukemia cell lines. Compounds **177q** and **177r** showed better results than the classical therapeutic drugs doxorubicin and *cisplatin*, with IC_{50} values for lymphoid cells (MOLT4) of 0.48 μM and 0.05 μM, respectively (Scheme 49).[325]



Scheme 49

The same research group has also reported the synthesis of new *nor*-β-lapachones containing phenylthio groups at position 3 of the furan ring (**178a-g**, Scheme 50). These compounds were screened against bloodstream trypomastigotes of *Trypanosoma cruzi* and showed a broad range of activities (IC_{50}/24 h from 9.2 to 182.7 μM). The derivative **178b** was 11 times more active than the standard drug, benznidazole (**179**).[326]



Scheme 50

4. Conclusions

In spite of the controversy over the use of **1** as a hair and skin dye, due to its toxicological and biological side effects, there is no doubt that this molecule is an extremely useful starting material for organic synthesis. The reactions of lawsone (**1**), described in hundreds of publications, have allowed the preparation of a variety of biologically active compounds that are potentially useful for the treatment of several diseases. Thus, the chemistry of this molecule is sufficiently useful to justify it being reviewed.

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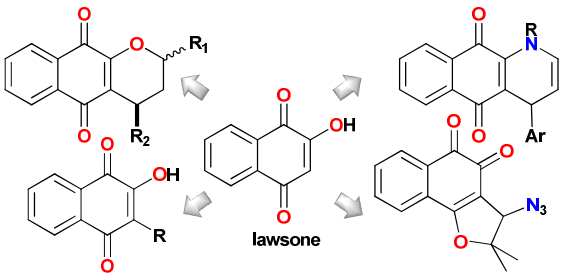
Table of contents

Lawsone in Organic Synthesis



Lawsone has been used as the starting material for the synthesis of a variety of biologically active compounds and materials.