Syntheses of Chromenes and Chromanes *via* *o*-Quinone Methide Intermediates

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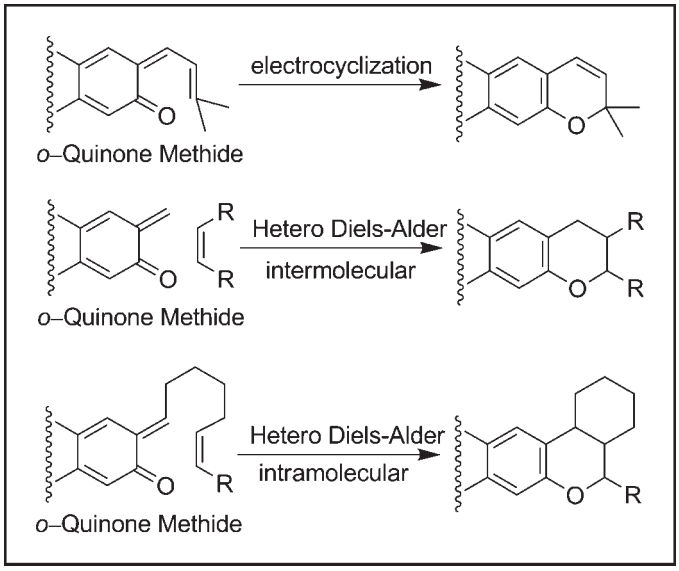

This review intends to explore synthetic methodologies for the preparation of 2*H*-chromenes and their analog chromanes through *ortho*-quinone methide (*o*-QM) intermediates associated with inter and intramolecular hetero-Diels-Alder and electrocyclization reactions.

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INTRODUCTION

Chromane and chromene substructures (Fig. 1) are frequently found in naturally occurring compounds, many of which exhibit useful biological activity [1–3]. Most of the time, the heterocyclic moiety is associated with an aromatic ring, forming 2,3- or 3,4-dihydrobenzopyran systems. From the position of the double bond, the chromene ring can be divided into two classes: 2*H*-chromene and 4*H*-chromene. Chromane is the saturated analog of chromene (Fig. 1).

In general, a number of biologically active chromenes and chromanes have been isolated from several natural sources. These substances have been identified as apoptosis-inducing agents [4], anti-HIV agents [5,6], modulators of the estrogen receptors [7], antibacterials [8], and antifungals [9].

For example, chromenes **1** and **2** (Fig. 2) were isolated from the leaves of *Peperomia serpens* (Sw.) Loudon [10] of genus *Peperomia* (Piperaceae) and presented antifungal activities against *Cladosporium cladosporioides* and *C. sphaerospermum*. Kawahara *et al.* in 1988 [11] isolated 2,2-dialkyl-substituted chromenes **3** and **4**, which exhibited antibacterial activity, from species of the fungi *Crucibulum, Lactarius, Aspergillus silvaticus*, and *Cylindrocarpon* (Fig. 2).

Some other important examples isolated from such diverse natural sources such as fungi, marine organisms, and plants are depicted in Figure 3. Compound **5**, which was isolated from the fungus *Daedalea quercina*, proved to have antioxidant and anti-inflammatory activities [12]. Chromenes with isoprenoid side chains are frequently found in nature [13], being structural analogs of prenylated coumarins, chalcones, and cannabinoids [14,15]. Cordiachromene (**6**) is a chromene with an isoprenoid chain that was isolated from *Cordia alliodora* Ruiz and Pav [16] and marine organisms *Aplidium antillense* [17] and *Aplidium constellatum* [18]. It exhibits antibacterial activity against *Staphylococcus aureus* and anti-inflammatory activity [19].

The most well-known class of naturally occurring 2*H*-chromenes are the precocenes, which are divided in two

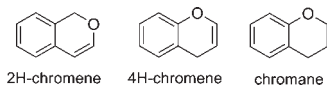


Figure 1. Chemical structures of the systems 2*H*-chromene, 4*H*-chromene, and chromane.

subclasses: precocene I (**7a**) and II (**7b**), also called ageratochromenes. These latter compounds were initially isolated from *Ageratum houstonianum* [2] but later found in several Ageratinae species. They are well known for their insecticidal activity and for inducing precocious metamorphosis [20], meaning they have properties as an antijuvenile hormone by reducing the length of larval life in sensitive species and preventing ovarian development in some adult insects [21].

The chromane moiety is present in other natural products [22–24], such as tocopherols and cannabinoids. α-Tocopherol (**8—**vitamin E) is found in the oil of wheat germ and it is reported that the chromane moiety is responsible for the antiandrogenic properties of vitamin E [25]. 4′-Methoxy-bavachromanol (**9**) was isolated from propolis and was found to be a more powerful antioxidant than lipoxygenases found in soybeans [26]. Among the constituents present in *Cannabis sativa*, tetrahydrocannabinol (**10**) is responsible for the plant's strong hallucinogenic activity (Fig. 4).

Substances that have the chromene or chromane ring fused with *ortho*- or *para*-quinones represent a special class of naturally occurring compounds that are present in many plants, fungi, and insects [27]. Xiloidone, 3,4-dihydro-α-lapachone (**11**) and its isomer, 3,4-dihydro-β-lapachone (**12**), are the most representative substances of the chromene-fused quinone class. These naphthoquinones are minor components in the extract of lapachol (**13**) [28–42]. Rodrigues and coworkers obtained **11** and **12** along with lapachol from *Tabebuia avellanedae* by using supercritical fluid extraction [43]. Gonçalves *et al*. [44,45] reported that xiloidone (**11**) has antibiotic activity against Gram-negative bacteria of the genus *Brucella*. Recently, Kuster *et al*. demonstrated that xiloidone (**11**) has potent antibacterial activity against multiresistant *Staphylococcus aureus* strains [46]. Cho *et al*.

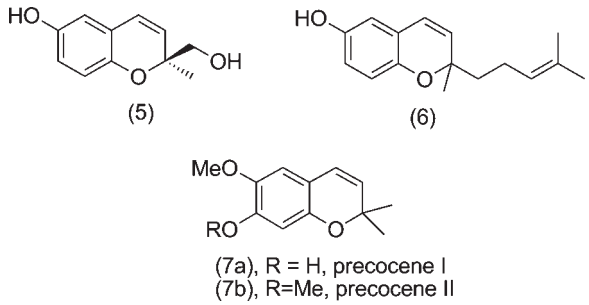


Figure 3. Precocens isolated from different natural sources.

isolated xiloidone (**11**) from *Catalpa ovata* stems and demonstrated it had activity against some plant pathogenic fungi [47].

The biogenetic route to naphthoquinone chromenes seems to have originated from lapachol (**13**) which is very abundant in many plants. D'Albuquerque *et al*. in 1972 and later in 2004 Jassbi *et al*. demonstrated that xiloidone can be obtained by $FeCl_3$ oxidation of lapachol in the presence of pyridine and acetic anhydride [48,49]. Indeed, several pathways for the formation of dihydro-α-lapachone from lapachol involving oxidative dehydrogenation [50] and photoirradiation [51] have been suggested. There are other natural and synthetic, biologically active naphthoquinones derived from lapachol (**13**).

The most important substances of the chromane-fused quinone class are α- (**14**) and β- (**15**) lapachones (Fig. 5). These compounds are the 2H hydrogenated analogs of compounds **11** and **12**. Thus, the development of valuable methods for the preparation of naphthoquinone-2*H*-chromene would also provide access to many analogs and derivatives of these substances.

Briefly, quinones have been the subject of much interest for a number of years due to their various biological activities [52–54]. For example, quinones have been studied for antitumor [55,56], molluscicidal [57–59], leischmanicidal [60], anti-inflammatory [61], antifungal [62], and trypanocidal [63,64] activities. It is described in the literature that the biological profiles of these molecules are centered on its *ortho*- or *para*-quinonoid moiety [65]. This group generally accepts one and/or two

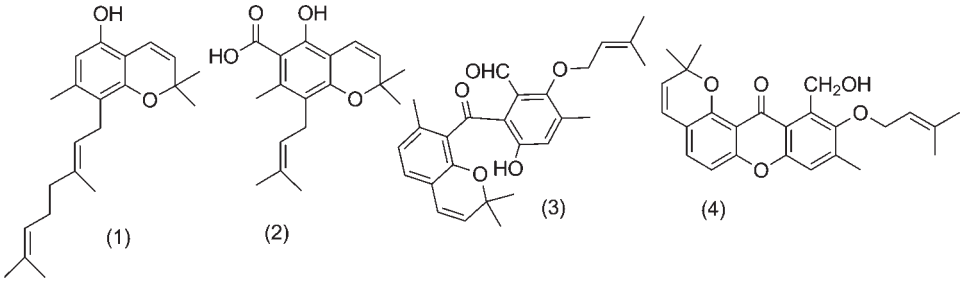


Figure 2. Structures of chromenes isolated from the plant *Peperomia serpens* (**1**–**2**) and from fungi (**3**–**4**).

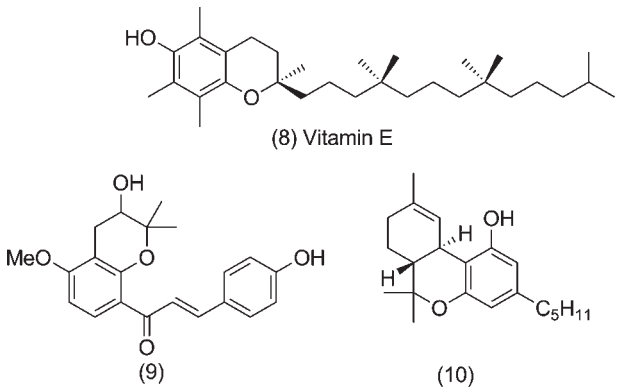


Figure 4. Chromanes isolated from different natural sources.

electrons (redox cycling) [66] to form the corresponding radical anion or dianion species *in situ*. In such way, the semi-quinone radicals accelerate the intracellular hypoxic condition by producing a superoxide anion [67–69]. Because of this mechanism, quinones show cytotoxic activity against cancer cells (and also to normal cells) by interfering with enzymes such as topoisomerases, which are critical for DNA replication [70].

Lapachol (**13**) is a natural naphthoquinone that occurs in the grain of several wooden trees of the Bignoniaceae family and is widely used in American folk medicine for the treatment of several diseases. It was first isolated in 1882 from *Tabebuia Avellanedae* [71], but it occurs in several other species of the genus *Tabebuia* (Tecoma). These trees are commonly known in South America as ''ipês,'' but also as Lapacho, Pau d'Arco, Lapacho roxo, and Taheebo [72,73]. It also occurs in many other families such as Verbenaceae, Proteaceae, Leguminosae, Sapotaceae, Scrophulariaceae, and Malvaceae [68,73]. Since the discovery that lapachol (**13**) [74], a natural naphthoquinone, proved to have antitumor activity against Walker-256 carcinoma, several structural modifications were performed [75,76] in order to find new compounds with other activities [73,77–81].

β-Lapachone (**15**), also known as ARQ501 [82] (Fig. 5), is a natural pyran-*ortho*-naphthoquinone originally obtained from the heartwood of the Lapacho tree, which belongs to the genus *Tabebuia* (Bigoniaceae) and which grows throughout the South America. This compound has been demonstrated to have many different pharmacological effects including promising anticancer activity [70]. Currently, it is undergoing multiple Phase II clinical trials. Several possible mechanisms to explain the cytotoxic effect against cancer cells have been proposed. The most recent proposal suggests that a redox cycle between NAD(P)H and quinone oxireductase 1 (NQO1) enzyme causes the depletion of NAD(P)H and NADH in the cells. This consequently decreases ATP and increases cytochrome C and cytosolic Ca^{+2}, which then affect other pathways in the cell cycle checkpoint resulting in the selective apoptotic cell death of cancer cells. It has also been suggested that the generation of ROS affects the kinases that are involved in cell cycle progression, leading to cell death. β-Lapachone has also been considered as a coadjuvant in killing human cancer cells during radiotherapy treatment. It seems that it inhibits sublethal radiation damage repair. Regarding anticancer activity, it presents significant antineoplasic [83] activity against human cancer cell lines from leukemia [84], prostate [85], malignant glioma [75], hepatoma [86], colon [87], breast [88], ovarian [89], lung [90], and pancreatic [91] tumors, at concentrations in the range of 1–10 μ*M* (IC_{50}). It has also been intensely investigated as a possible drug against the flagellate protozoan *Trypanosoma cruzi*, which is the etiological agent of Chagas disease, in both acute and chronic infections [92–96]. This compound inspired a search for new derivatives with a better therapeutical index. Several heterocyclic derivatives (oxyranes [92(a,b)], oxazoles [64], imidazoles [92(c)], and phenazine [97]) of β-Lapachone (**15**) have been synthesized. Some of them have lower side effects and improved trypanocidal activity.

Because of the multiple uses and variety of biological activities of chromenes, the synthesis of this heterocyclic substructure has been the subject of intense investigations. Several new synthetic methods and improvements in existing and classical methods have been reported recently. In general, phenols and salicylaldehydes have been used in the preparation of chromenes. Table 1 summarizes some methods. The preparation of chromanes can be achieved by simple hydrogenation of the double bond of the chromenes. Nevertheless, there are several procedures that target the chromane ring directly, such as: (a) sequential [3+3] cyclization and Williamson's reaction [98] from salicylaldehydes [99,100], phenols [101], propargylic phenols [102], and 1,2-benzoxazines [103]; (b) iodine-catalyzed cyclocondensation [104]; (c) ring-closing olefin metathesis [105]; (d) *via* Wittig intermediates [106]; and (e) electrochemistry [107].

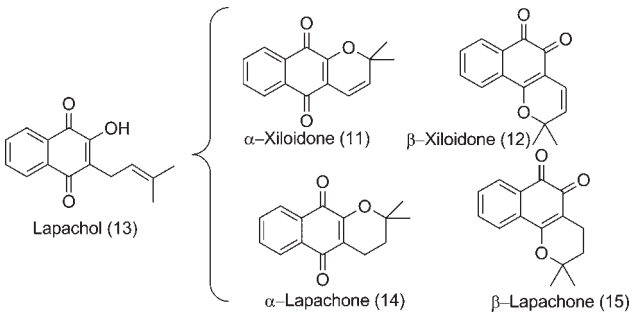
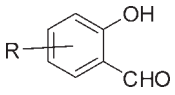
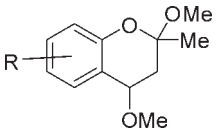
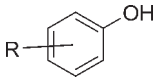
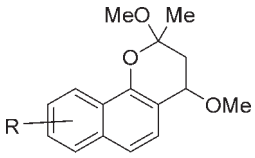
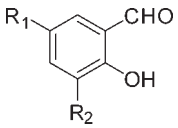
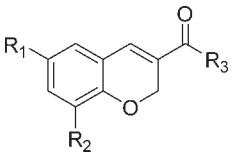
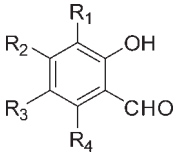
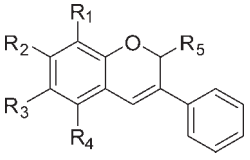
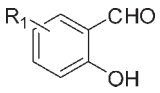
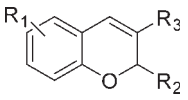
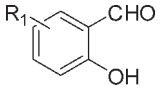
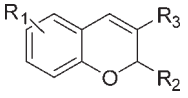
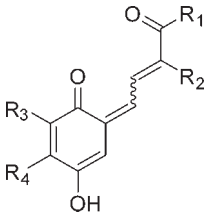
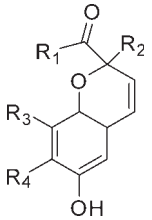
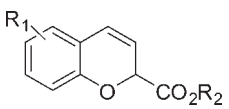
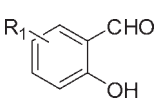


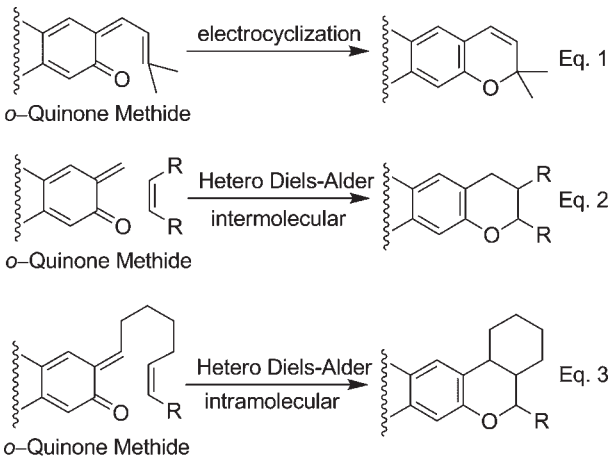
Figure 5. Derivatives of lapachol (**13**) containing rings 2*H*-chromenes and chromanes.

Table 1

Phenols and salicylaldehydes used in preparation of chromenes.

Phenols and salicylaldehydes	Product	Yield (%)	Ref.
		R = H, 90 R = 8-OMe, 86 R = 8-OEt, 82 R = 6-Me, 88 R = 6-Br, 75 R = 6-NO_2, 78	[108]
		R = 4-OMe, 85 R = 3,4-OCH_2O, 87	[108]
		R_1 = R_2 = H; R_3 = Me, 81 R_1 = R_2 = H; R_3 = Et, 83 R_1 = H; R_2 = OMe; R_3 = Me, 79 R_1 = H; R_2 = OEt; R_3 = Me, 84 R_1 = Br; R_2 = H; R_3 = Me, 87 R_1 = Cl; R_2 = H; R_3 = Me, 56	[100]
		R_1 = R_2 = R_3 = R_4 = H; R_5 = morpholinyl, 80 R_1 = OMe; R_2 = R_3 = R_4 = H; R_5 = morpholinyl, 73 R_1 = R_2 = R_3 = R_4 = H; R_5 = piperidinyl, 72 R_1 = R_2 = H; R_3 = NO_2; R_4 = H; R_5 = piperidinyl, 85 R_1 = R_2 = R_3 = R_4 = H; R_5 = pyrrolidinyl, 71 R_1 = R_2 = H; R_3 = Cl; R_4 = H; R_5 = pyrrolidinyl, 79	[104]
		R_1 = 3-OH; R_2 = butyl; R_3 = H, 88 R_1 = 3-OMe; R_2 = butyl; R_3 = H, 91 R_1 = 5-Br; R_2 = butyl; R_3 = H, 90 R_1 = 3,5-dichloro; R_2 = butyl; R_3 = H, 91 R_1 = 3,5-di-*t*-butyl;R_2 = butyl; R_3 = H, 85	[109]
		R_1 = R_2 = R_3 = H, 83 R_1 = 6-Br; R_2 = R_3 = H, 92 R_1 = 7-OMe; R_2 = R_3 = H, 84 R_1 = 6-NO_2; R_2 = R_3 = H, 81 R_1 = 7-$OCH_2CH{=}CH_2$;R_2 = R_3 = H, 90	[105a]
		R_1 = OMe; R_2 = R_3 = R_4 = H, 30 R_1 = R_4 = OMe; R_2 = R_3 = H, 70 R_1 = R_4 = OMe; R_2 = Me; R_3 = H, 63 R_1 = *i*-Pr; R_2 = R_3 = H; R_4 = OMe, 75	[110]
		R_1 = H; R_2 = Et, 85 R_1 = 6-*t*-Bu; R_2 = Et, 99 R_1 = 4-Br; R_2 = Et, 81 R_1 = 4-Me; R_2 = Et, 85 R_1 = H; R_2 = Bn, 87	[111]

Scheme 1



o-QUINONE METHIDES: GENERALITY

In general, *ortho*-quinone methides (*o*-QMs) possess a hexadiene ring with a carbonyl group and a methylene unit in the ring. With these two different functional groups, the molecule becomes highly polarized and is very reactive. With both cationic and anionic centers, the molecule can act either as a nucleophile or electrophile. In addition to quinone methides being excellent partners in Diels-Alder reactions, the structures are also present in many molecules with biological activity. A great variety of plants, animals, and fungus use these substances for defense.

o-QMs have been extensively used for the preparation of 2*H*-chromene and chromane substructures. Chromenes are obtained through electrocyclization reactions [eq. (1), Scheme 1] and chromanes by inter or intramolecular hetero-Diels-Alder reactions [eqs. (2) and (3), Scheme 1]. In both cases, quinone methides are the key intermediates (Fig. 6).

o-QMs are involved in a large number of chemical reactions and biological processes such as enzyme inhibition, reactions with phosphodiesters, DNA alkylation [112], and crosslinking [113,114]. Their electrophilicities towards amines, thiols, water, amino acids, and peptides have also been used for interactions with nucleobases of DNA [115]. Several important clinical anticancer drugs (*e.g.*, cisplatin, psoralens, and mitomycin

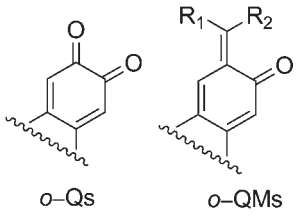
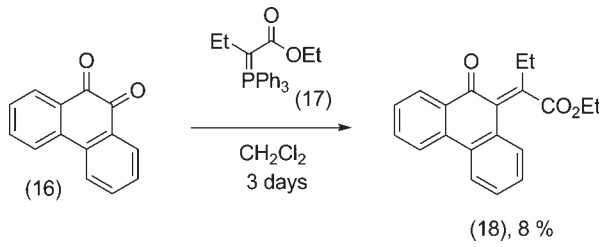


Figure 6. General structure of *o*-quinone methide.

Scheme 2

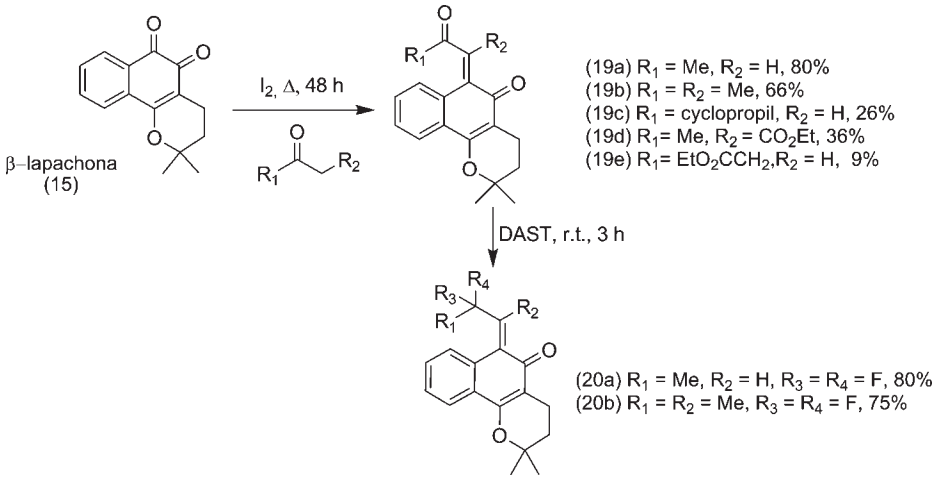


C) are known to induce DNA ISC formation, which can disrupt cell maintenance and replication by a mechanism that involves *o*-QM intermediates. Similarly, *o*-QMs have been detected in daunomycin and have been shown to function as alkylating agents [116]. The formation of *o*-QMs as reactive intermediates in biologically active natural products has been reviewed [117,118]. Apart from their involvement in biological processes, *o*-QMs are also very versatile intermediates in organic synthesis [119–124], but until now they have been less utilized in total syntheses [125]. Since they are ephemeral species [126], they must be generated *in situ* by processes that involve photolysis of *o*-, *m*-, or *p*-hydroxybenzyl alcohols [127], thermal reactions [128,129], thermal extrusion of sulfur dioxide [128] and anionic triggered reactions [130,131]. In this regard, Amouri *et al*. synthesized the first metal-stabilized *o*-QM and found that it is reactive toward alkenes [132,133]. Nevertheless, there are some nonmetal stabilized *o*-QMs that can also be isolated. For example, in 1969, Sullivan *et al.* [134] showed that 9,10-phenanthrenequinone (**16**) reacts with several Wittig reagent (Carbethoxyethylidene) triphenylphosphorane (**17**) reagents to produce *o*-QM derivatives of phenanthrene which were quite stable toward isolation. The authors found that their stabilities were dependent on the electronegativity and bulkiness of the substituents on the *o*-QM moiety. Later on, Nicolaides *et al.* [135] revisited the reaction and prepared other *o*-QMs (*e.g.*, **18**) (Scheme 2).

Very recently, Da Silva *et al.* prepared several stable *o*-QMs (**19a–e, 20a–b**) from β-lapachone (**15**) [136] under conditions that allowed for Aldol condensation with one of the carbonyls (Scheme 3).

The *o*-benzoquinone methide moiety (**21**) is a reactive intermediate that has potential synthetic utility as reported in many articles [137]. In 1976, Heldeweg and Hogeveen showed that *o*-benzoquinone methides prepared by pyrolysis of *o*-hydroxybenzyl alcohols (**22**) at 180°C in the presence of 2 equiv of $[Rh(CO)_2Cl]_2$ afforded 2[3H]-benzofuranone (**23**) in 12% yield [138]. Therefore, it is common that *o*-benzoquinone methides cannot be isolated, even though they can be observed *via* low temperature infrared [139], UV [140] or photoelectron spectroscopy [141] (Scheme 4).

Scheme 3



SYNTHETIC METHODOLOGY FOR PREPARING 2*H*-CHROMENES AND CHROMANES

This review will focus specifically on current strategies involving the construction of chromene and chromane rings *via* *o*-QMs that are mainly coupled with a quinone nucleus (Scheme 1).

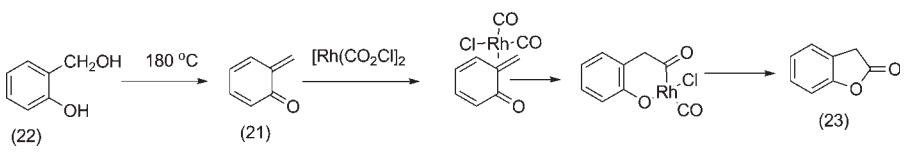
SYNTHESIS OF 2*H*-CHROMENES AND CHROMANES BY TRAPPING OF *o*-QMS *VIA* ELECTROCYCLIZATION

In 1969, Dudley and Chiang [50] reported a one-step synthesis of 2,2-dimethyl-2*H*-chromenes by exposing isolapachol (**24**) to an equimolar quantity of DDQ in benzene, resulting in oxidative cyclization to a mixture of the dehydro-α and -β-lapachones (**11** and **12**, Fig. 5). Consideration of the possible mechanisms by which chromenes **11** and **12** might arise led to the postulate that the isomeric *o*-quinone methide intermediates **25** and **26** might undergo a 6π-electrocyclic reaction. This simple procedure proved to be a facile entry into the lapachone series and was further simplified by the observation that **12** can be converted to **11** by treatment with acid. The authors proposed that the two isomeric *o*-QMs are involved as the key intermediates in the reaction mechanism and that their electrocyclization leads to the formation of the chromene moiety (Scheme 5).

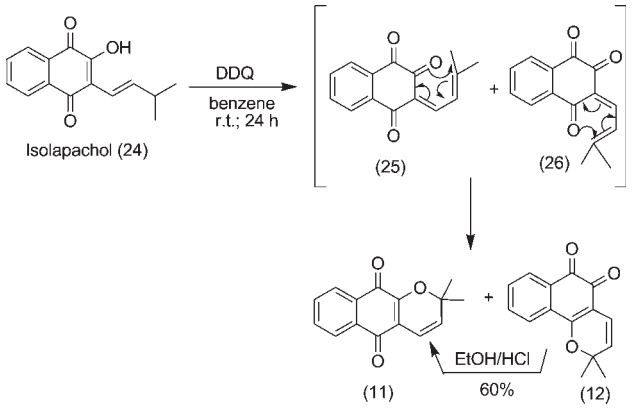
A new route for introducing the chromene moiety, based on the formation of an *o*-QM intermediate (**27**) through a tandem Knoevenagel-electrocyclic reaction, was reported by Ferreira *et al*. in 1980 [142]. The reaction of lawsone (**28**) with α,β-unsaturated aldehydes exclusively produced α-dehydrolapachones (**29–31**) in an average yield of 33%. The same synthetic route and conditions were used by De Oliveira *et al*. [143] for the preparation of the naturally occurring dihydro-α-caryopterone (**32**) and its isomer, 6-hydroxy-dehydro-α-lapachone (**33**) (Scheme 6).

Recently, the reaction of lawsone (**28**) with 3-methyl-2-butenal (**34**) utilizing several bases and Lewis acid catalysts was reinvestigated in order to improve the yield of dehydro-α-lapachone (**11**) [144]. This study found that indium (III) chloride (10 mmol %) and ytterbium (III) triflate (10 mol %) catalysts in acetonitrile produced the desired compound in very low yields. However, by using $Yb(OTf)_3$ in DMF at 100°C, the desired compound was produced in higher yield (55%). By using pyridine as a catalyst and solvent, the product was formed in 54% yield. The best condition found was with ethylenediamine diacetate (10 mol %) as the catalyst in MeOH (75%) or benzene (80%) (Scheme 7) [145]. As previously observed by Ferreira *et al*. in 1980, only the dehydro-α-lapachones were formed under these reaction conditions (Scheme 6).

Scheme 4



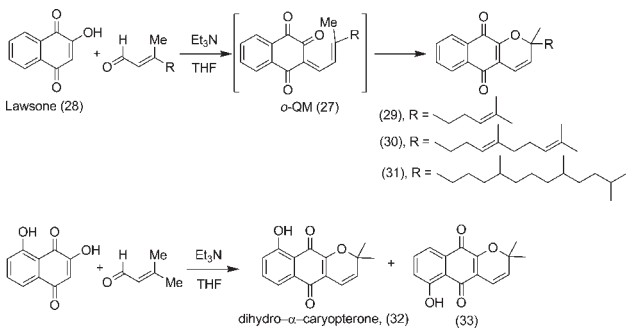
Scheme 5



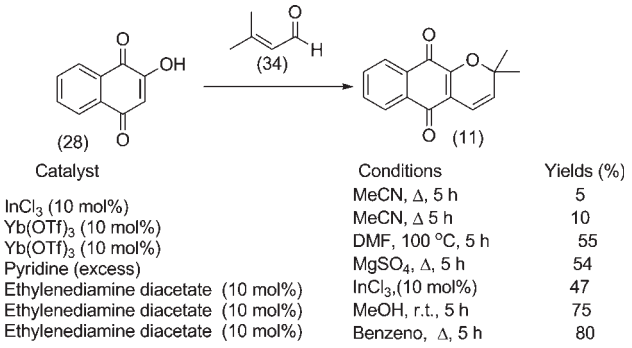
Although the aforementioned tandem-Knoevenagel-electrocyclic reaction with α,β-unsaturated aldehydes exclusively produced dehydro-α-lapachones quite successfully, Hayashi *et al*. found that in sharp contrast, the reaction of lawsone (**28**) with acrolein (**35**) does not even undergo cycloaddition [146]. Instead, two products were formed. The major isolated compound was *o*-QM (**36**), which is very stable. These products arose from two different possible condensations between acrolein and lawsone, a Claisen-Schmidt reaction and a Michael reaction, leading to **36** or **37**, respectively, after acetalization. Tournaire *et al*. [147] revisited this condensation under several acidic conditions and isolated **36** and **37**, as previously reported, along with some other products. When the reaction was performed in the presence of an excess of hydrochloric acid, **39** was isolated in less than 10% yield. Compound **39** is presumably produced *via* the formation of *o*-QM (**38**), followed by chlorination of a double bond (Scheme 8).

Other research groups soon became attracted to the opportunities presented by these tandem Knoevenagel-electrocyclic reactions. For instance, Hua *et al*. reported the condensation of various 6-substituted 4-hydroxypyrones with 1-cyclohexenecarboxaldehydes in the presence of L-proline in ethyl acetate gave high yields of substituted 1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-

Scheme 6



Scheme 7

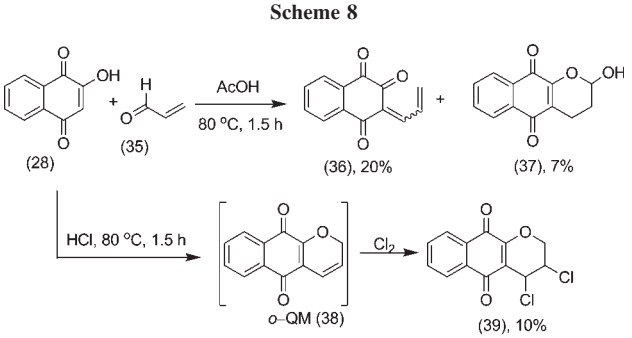


b][1]benzopyrans [148]. And the next advance was disclosed by Snieckus and coworkers. They reported a facile procedure for preparing 2*H*-chromenes (*e.g*., **40**, Scheme 9) by coupling commercially available phenols (**41**) and naphthols (*e.g*., **42**) with α,β-unsaturated aldehydes (**43**) under the influence of phenylboronic acid [149]. This reaction protocol was extended to a synthesis of β-lapachone (**15**) [150,151], which illustrates the rapid access to these types of molecules by this method.

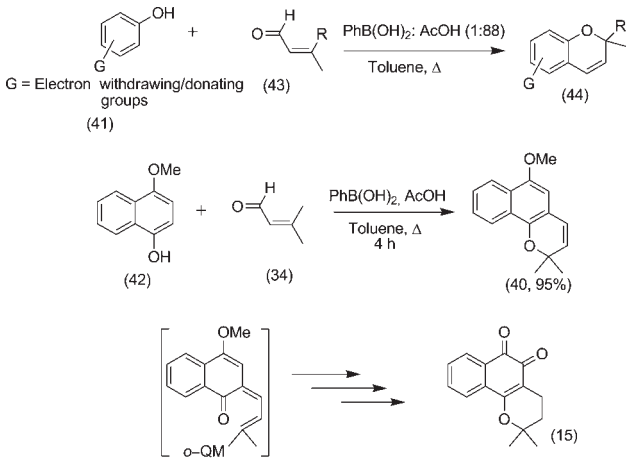
An interesting strategy for the synthesis of epoxynaphthopyranoquinone (**45**), a xiloidone derivative, was reported by Tapia and coworkers [152]. The authors synthesized benzopyran quinone (**46**) using the tandem Knoevenagel-electrocyclic protocol *via* an *o*-QM intermediate (**47**). Their synthetic route started from 2,5-dimethoxyphenol (**48**) that had its phenolic group protected as a tetrahydropyranyl (THP). This intermediate was transformed to *o*-hydroxy-γ,γ-dimethyl allyl alcohol (**49**) by reaction of **50** with 3-methyl-2-butenal (**34**) under basic conditions. The mild hydrolysis of the THP protecting group and dehydration of **50** led to formation of the *o*-QM intermediate, which upon intramolecular electrocyclization, formed benzopyrane (**46**). The latter compound was transformed in three steps to epoxynaphthopyanoquinone (**45**) (Scheme 10).

More recently, Dintzner and coworkers [153] reported for the first time a direct condensation of phenols with α,β-unsaturated aldehydes catalyzed by clays. The reaction between 3-methyl-2-butenal (**34**) and sesamol (**51**)

Scheme 8



Scheme 9

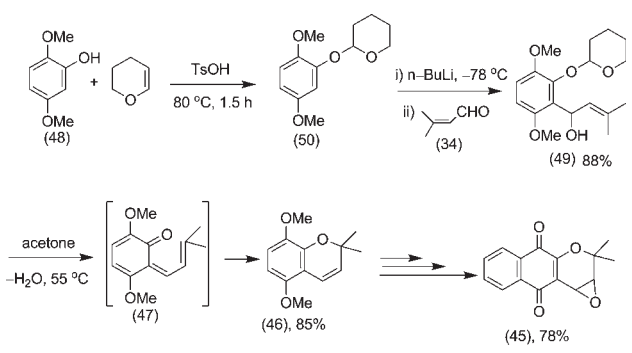


was used as the model reaction in order to prepare methylenedioxyprecocene (**52**), which as mentioned previously, exhibited antijuvenile hormone activity in some insects. Acidic montmorillonite K10 clay promoted the electrophilic aromatic addition yielding the desired 2*H*-chromene (**52**) through an *o*-QM intermediate (**53**). The optimal conditions for this process involved the reaction of the substrate on basic clay (K10–K^+) at 110°C, without solvent, under microwave irradiation (Scheme 11).

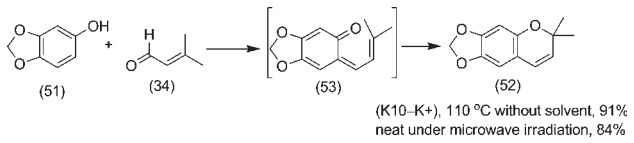
Parker and Mindt developed a very useful one-step procedure for synthesizing chromenes (**54a–c**) by a thermally induced 6π-electrocyclization of the enolizable vinyl quinone (**55**) *via* an intermediate quinone methide (**56**). The enolizable vinyl quinones are the products of Stille coupling. Application of this method led to the total synthesis of an *Ageratum* juvenile hormone (Scheme 12) [110].

Very recently, Da Silva and coworkers [154] developed a new general methodology that involves the reaction of *ortho*-naphthoquinones with allyltriphenylphosphonium salts **58a** and **58b** in the presence of an aqueous solution of NaOH and chloroform. The reaction proceeded *via in situ* formation of an ylide, and subsequent reaction with an *ortho*-naphthoquinone to produce *o*-QM intermediate **59**, which cyclizes to a 2*H*-chromene, as outlined in Scheme 13. With this selective and general one-pot synthesis, several 2*H*-chromene derivatives (**60**, **61,** and **62**) were obtained from the appropriate *ortho*-naphthoquinones and allyltriphenylphosphonium in yields ranging from 47 to 85%. It should be noted that the attack of the phosphorus ylide occurred exclusively at the more reactive 1- or α-position of the carbonyl carbon of the *ortho*-naphthoquinone. No products were detected from attack at the 2- or β-carbonyl.

Scheme 10



Scheme 11



SYNTHESIS OF 2*H*-CHROMENES AND CHROMANES *VIA* *o*-QMS HETERO-DIELS-ALDER REACTIONS

The unique feature of the Diels-Alder reaction of constructing up to four new stereogenic centers in one step has made this reaction one of the most important tools in the field of organic synthesis. It is not surprising, considering its scope, that Diels-Alder reaction continues to be important for constructing polycyclic ring systems of complex natural product targets [155]. Its broad reaction possibilities have led to an enormous number of variations, both intermolecular and intramolecular [156,157], with high levels of stereocontrol, as summarized in several review articles [158].

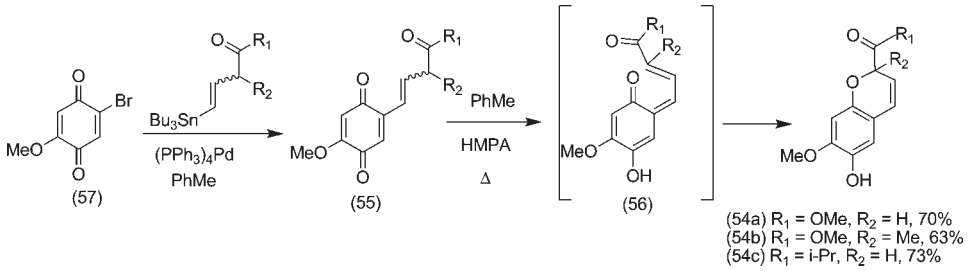
A very important variation of the typical Diels-Alder reaction is the hetero-Diels-Alder reaction. In this variation, heteroatoms, such as a carbonyl group, replace a carbon–carbon double bond in either the diene or dienophile [159–162].

o-QMs are hetero-dienes suitable for [4 + 2] cycloadditions with a wide range of dienophiles in either inter or intramolecular processes (Fig. 7). This reaction would lead directly to the chromane substructures. However, the intermolecular process has two major problems that must be overcome (among others): the fast dimerization of the *o*-QMs to spiro compounds [163,164] and that *o*-QMs generation and trapping must be done *in situ*.

SYNTHESIS OF 2*H*-CHROMENES AND CHROMANES *VIA* *o*-QMS AND INTERMOLECULAR HETERO-DIELS-ALDER REACTIONS

The first example that generated and made use of an *o*-QM in an intermolecular hetero-Diels-Alder reaction

Scheme 12

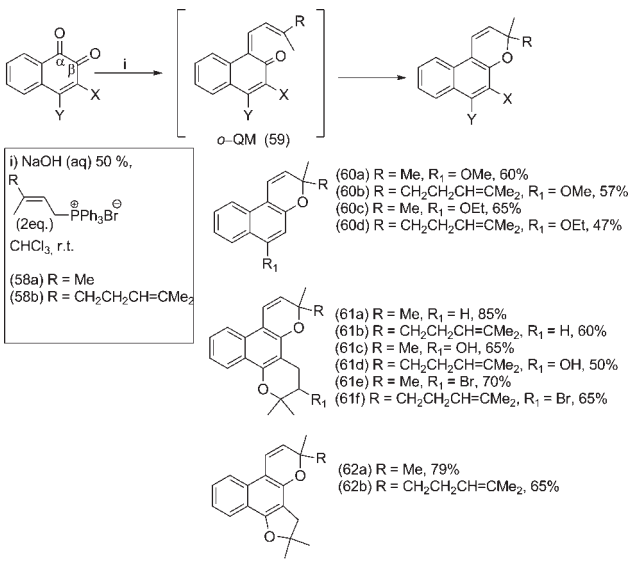


was reported by Brougidou and Christol [165,166], who reacted *o*-QMs with butadiene (**63**) to obtain 2-vinylchromans (**64**) as the only reaction product. Chapman and Mcintosh in 1971 (Scheme 14) [167] demonstrated that the dimerization of *o*-QMs could be a useful methodology to prepare natural products. In this regard, they produced an *o*-QM by photodecarbonylation of the unsaturated lactone (**65**), which was then efficiently trapped with 1,l-dimethoxyethylene (**66**) producing an *ortho*-lactone (**67**) with high yield (>90%). Very recently, this reaction was reinvestigated, but the generation of *o*-QM (**68**) and subsequent hetero-Diels-Alder reactions was under mild, anionic conditions to prepare benzopyrans (**69a–d**) [168].

Baldwin and coworkers developed a biomimetic synthesis of Lucidene (**71**) based upon the fact that both this compound and humulene (**72**) were isolated from the root bark of *Uvaria lucida ssp. lucida* and **71** could be formed as the products of a double Diels-Alder reaction with two molecules of *o*-benzoquinone methide [169]. In a subsequent work, the same group synthesized pycnidione and epolone B using an *o*-QM derived from benzotropolone (**73**) *via* a hetero-Diels-Alder reaction with humulene [170]. More recently, they reported a biomimetic hetero-Diels-Alder reaction between humulene and a novel tropolone *o*-QM (**74**) to give a deoxy analog of epolone B (**75**) (Scheme 15) [171].

The search for new *in situ* methods to generate *o*-QM intermediates without side reactions or with long reaction times and at low temperatures continues to be desired. In this regard, Baldwin and coworkers explored reductive transesterification with an aldehyde (**76**) to produce *o*-methyleneacetoxy-phenol (**77**), which under thermal conditions generated an *o*-quinone methide that cyclized (**78**). They applied this methodology to the synthesis of (±)-alboatrin (**79**) [172] and (±)-lucidene (**71**) (Scheme 16) [173].

Scheme 13



SYNTHESIS OF 2*H*-CHROMENES AND CHROMANES *VIA* *o*-QMS AND INTRAMOLECULAR HETERO-DIELS-ALDER REACTIONS

Chapman and coworkers demonstrated that palladium chloride induced dimerization of *o*-vinylphenol (**80**) to generate an *o*-QM (**81**), which undergoes intramolecular hetero-Diels-Alder cyclization. They applied this useful methodology to prepare the natural product carpanone (**82**) in one step following a biomimetic pathway (Scheme 17) [174].

Much research has been focused on developing new and better methods for generating *o*-QM intermediates that can be trapped by an intramolecular Diels-Alder reaction. Hug and coworkers [175] reported that thermal dehydration of *o*-hydroxybenzyl alcohol (**83**) led to three products that could only be produced through an intermediate *o*-QM (**84**) generated *in situ*, followed by an intramolecular Diels-Alder cycloaddition. The authors proposed that the formation of the *o*-QM (**84**) occurs by an initial dehydration and concerted [1,5]-hydrogen shift, which is followed by a [4 + 2] cycloaddition to produce the product (**85**, **86**, and **61**) in 69% yield. Later, Boekelheide and Mao [176] performed flash

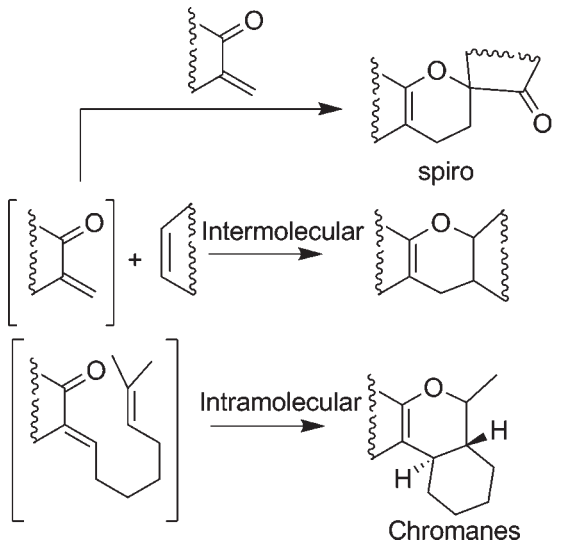


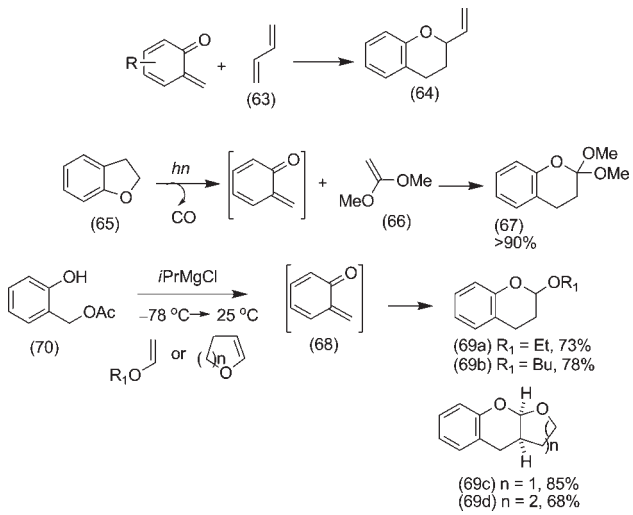
Figure 7. *o*-QMs as hetero-dienes for the construction of chromanes.

pyrolysis experiments of **84** at 700°C and found only product **85**, but in only 12% yield (Scheme 18).

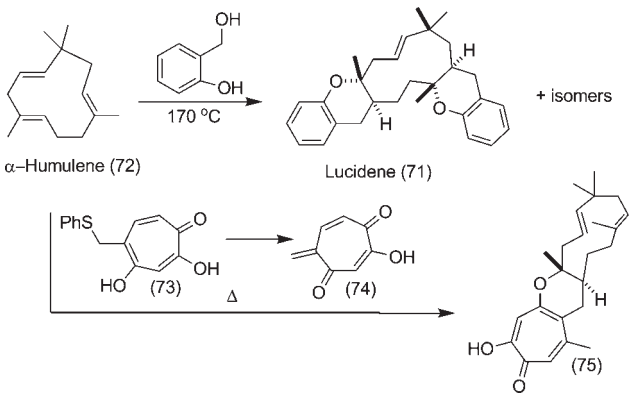
Tietze and coworkers described the intramolecular Diels-Alder reaction between 1,3-cyclohexadione (**88**) and citronellal (**89**). They obtained tricyclic dihydropyran (**90**) with trans stereochemistry *via* an *exo-E-anti* transition state [177–179]. It is worthy to note that this structure was proved by X-ray structure analysis. The investigation into the conformation of the transition state was extended to benzylidenepyrazolones and benzylideneisoxazolones. The same *exo-E-anti* stereochemistry was also observed for these products (Scheme 19) [180,181].

Ferreira and Pinto [182] in 1980 reported a novel preparation of tetracyclic α- and β-pyranaphthoquinones using an *o*-QM intermediate, generated *in situ*, followed

Scheme 14



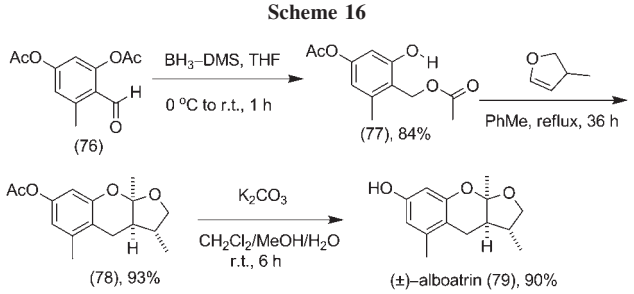
Scheme 15



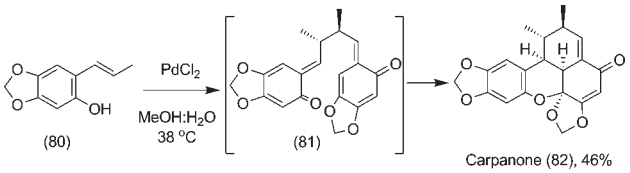
by a tandem Knoevenagel/hetero-Diels-Alder reaction. The authors, instead of reacting natural α,β-unsaturated aldehydes with lawsone (**28**) (*e.g.*, citral) [142], reacted lawsone with an aldehyde bearing a remote double bond (*e.g.*, citronellal—**89**). In the later case, the *o*-QMs (**91** and **92**) underwent an intramolecular hetero-Diels-Alder reaction with the double bond to form tetracyclic α- and β-pyranaphthoquinones (**93** and **94**) in 70% yield. In order to obtain β-pyranaphthoquinone (**94**), a tetracyclic derivative of β-lapachone, the mixture was treated with H_2SO_4 (Scheme 20). Recently, Jiménez-Alonso and coworkers performed the asymmetric version of this reaction with (*s*)-(-)-citronellal, producing compounds **93** and **94** in a 1:1 ratio with 94% overall yield [183]. By using Yadav's methodology [184], they extended this reaction to other prenylated aromatic aldehydes with the double bond at an appropriate distance to generate new naphthoquinones. It should be noted that aromatic aldehydes furnished only *cis* adducts due to an *endo-E-syn* transition state. For instance, compounds **95** and **96** were obtained in 72% at a 1:1 ratio (Scheme 20).

Other research groups soon became attracted to the opportunities presented by these aforementioned thermal dehydrations of *o*-hydroxybenzyl alcohols that gave products that could only be produced through an *o*-QM intermediate followed by an intramolecular Diels-Alder cycloaddition. In 1985, Talley [185] studied this reaction both thermally and photochemically, starting with (*R*)-

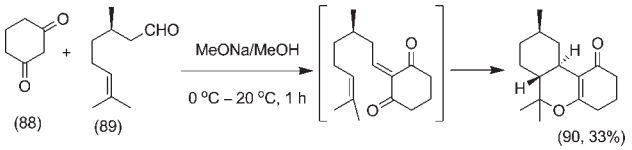
Scheme 16



Scheme 17



Scheme 19



citronellal (**89**), in order to obtain informations about the transition state of the cycloaddition. The reactions were very successful in the generation of substituted *o*-QMs by the thermal dehydration of *o*-hydroxybenzyl alcohol derivatives (**97**) and subsequent intramolecular Diels-Alder reaction. The dehydration of *o*-hydroxybenzyl alcohol followed by intramolecular Diels-Alder reaction proceeded with excellent regio and stereospecificity. The presence of a chiral center on the alkyl side chain resulted in a high degree of stereocontrol during the cycloaddition reaction. The *trans* stereochemistry was the same as observed by Pinto and Ferreira and is thought to proceed *via* a pseudoequatorial conformation adopted by the chair-like exo transition state during the intramolecular Diels-Alder cycloaddition (Scheme 21).

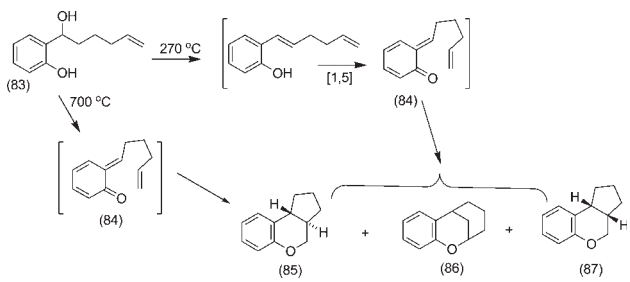
Given the success of the preliminary results [152,186], Tapia's group [187] showed an interesting approach to obtain 2*H*-benzopyrans by using a Tandem Knoevenagel hetero-Diels-Alder reaction with citral (α,β-unsaturated aldehyde) instead of a Tandem Knoevenagel electrocyclization. Their protocol involved the addition of a suitably protected aryl lithium derivative of citral, followed by deprotection and cyclization *via* an *o*-QM to produce the chromane (**100**) [188]. In two more steps, the latter compound was transformed to an α-lapachone derivative (**101**). It is also clear from their results that the cis stereochemistry of **101** is opposite of that found by Hug [175], Ferreira [182] and Talley [185]. This is likely because of the endo transition state is favored due to conjugated double bond with *o*-QM moiety (Scheme 22).

o-Quinone methides (**106**) can also be efficiently produced by photoirradiation of phenolic Mannich bases (**107**) in aqueous solvents at neutral pH, by irradiation with >300 nm light and rapid trapping by ethyl vinyl ether (**108**) *via* an intermolecular hetero-Diels-Alder reaction [189]. This strategy has been used to prepare a series of chromane derivatives such as compounds **109** and **110** in Scheme 23. This procedure was also applied to the formation and trapping of bisquinone methide (**111**), although in low yield (Scheme 23).

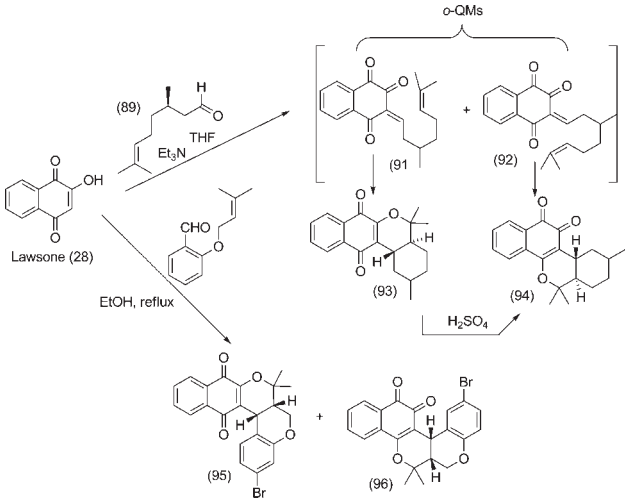
Ye and coworkers conveniently developed an interesting protocol for the synthesis of 5-one heterocyclic systems *via* heterocyclic quinone methides. A wide variety of pyrano[3,2-c]quinolines (**114a–d**) possessing different functional groups have been prepared successfully by the tandem Knoevenagel condensation of 4-Hydroxyquinolin-2(1H)-ones (**115**) with aldehydes (**116**). The formation of the products was rationalized by an initial Aldol condensation, to form the methide intermediate (**117**). This then undergoes a Michael-type-1,4-addition of the enolate anion followed by an intramolecular cyclization (Scheme 24) [190].

Similarly, Nair and coworkers reported a series of articles exploring the reactivity profile of *o*-QMs [191] generated *in situ* from lawsone (**28**), 4-hydroxycoumarin (**118**) and 4-hydroxyquinoline (**119**) and their subsequent intermolecular Diels-Alder reaction. This protocol overcomes the limitation regarding the use of appropriately substituted aldehydes in the tandem Knoevenagel/intramolecular hetero-Diels-Alder cycloaddition methodology.

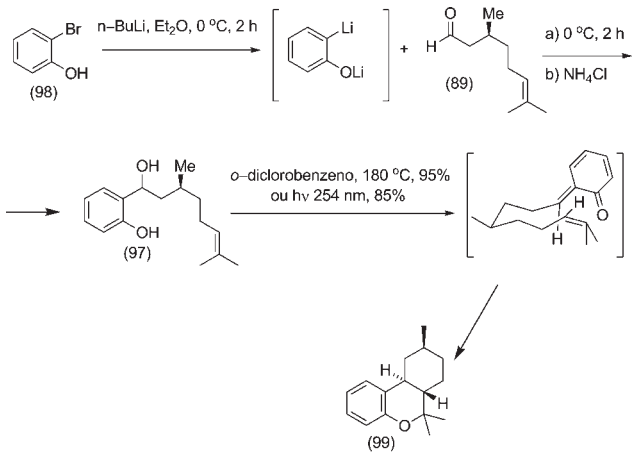
Scheme 18



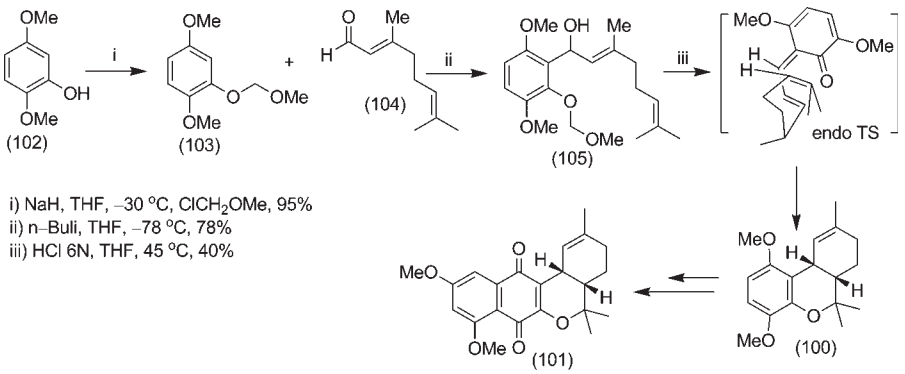
Scheme 20



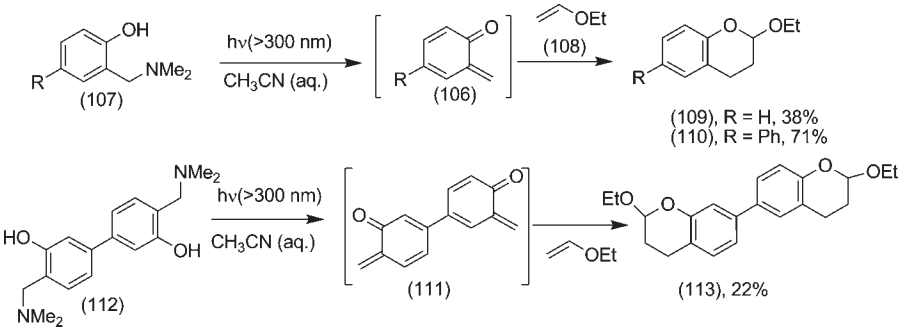
Scheme 21



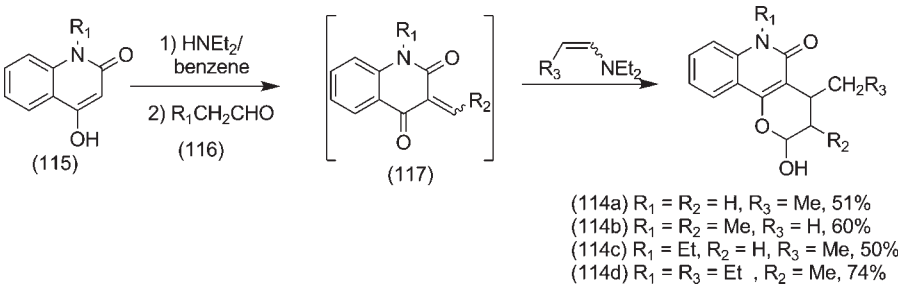
Scheme 22



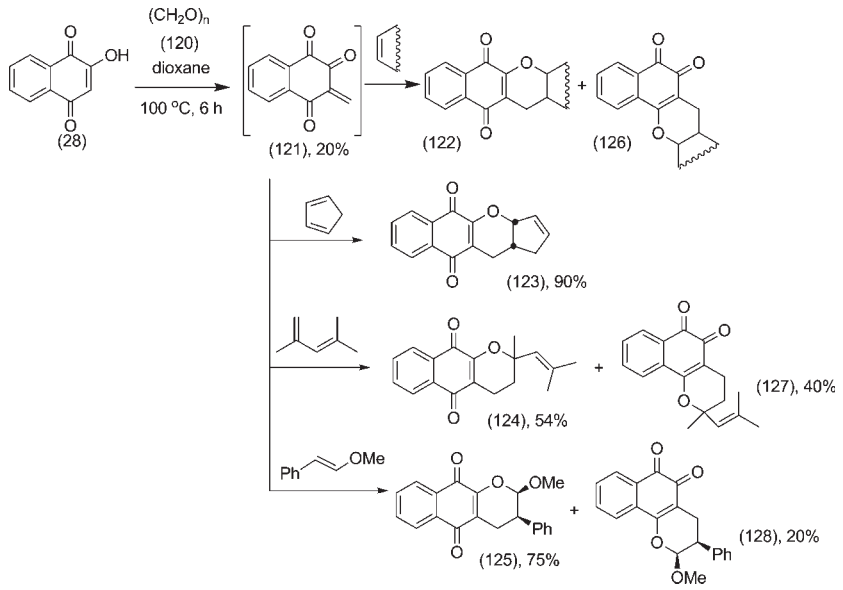
Scheme 23



Scheme 24



Scheme 25



Scheme 26

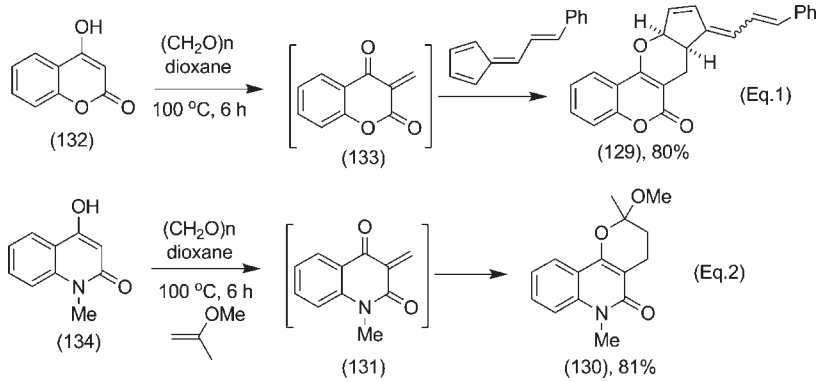
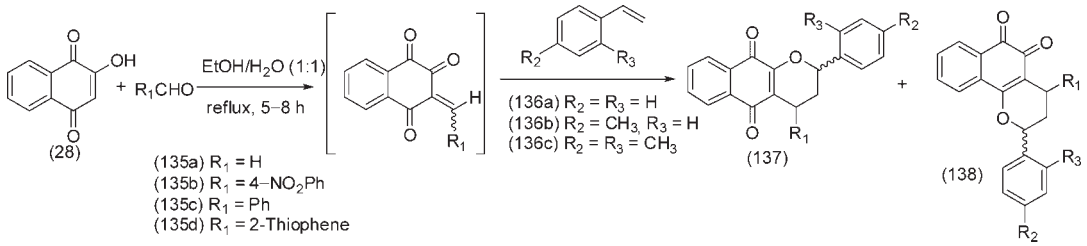


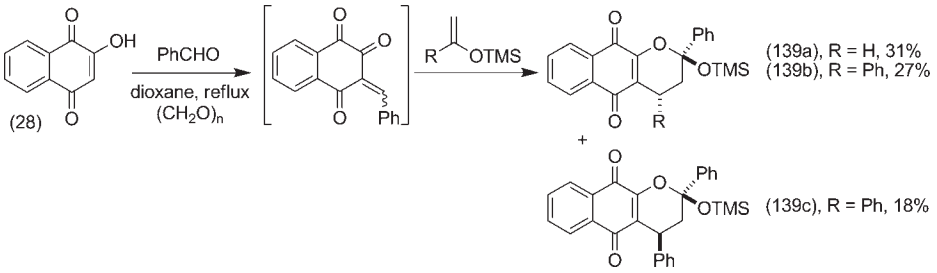
Table 2

Intermolecular hetero Diels-Alder to obtain α- and β-pyranaphthoquinones.



Entry	R_1	R_2	R_3	Conditions	Time (h)	Yield %	Ratio α/β (139:140)	α (cis:trans)	β (cis:trans)
1	H	H	H	$EtOH/H_2O$ (1:1)	6	94	3.1	–	–
2	H	CH_3	H	$EtOH/H_2O$ (1:1)	6	95	3.8	–	–
3	H	CH_3	Me	$EtOH/H_2O$ (1:1)	6	97	4.7	–	–
4	4-NO_2Ph	CH_3	H	$EtOH/H_2O$ (1:1)	5	50	1.4	37:63	18:82
5	2-Thiophene	CH_3	H	$EtOH/H_2O$ (1:1)	8	60	0.8	54:46	0:100
6	Ph	CH_3	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_2Ph	CH_3	H	Dioxane/HOAc	5	55	1.1	35:65	17:83

Scheme 27



In the first approach, Nair and Treesa [192] described a new, general three-component reaction for the synthesis of a wide variety of derivatives of α- and β-lapachone and other heterocyclic compounds. The reaction involved the Knoevenagel condensation between lawsone reagent (**28**) and paraformaldehyde (**120**) leading to the *o*-QM (**121**), which reacts *in situ* with several possible olefins to generate products in moderate to good yields. The latter methodology offers several alternative approaches for the syntheses of α- (**122, 123, 124,** and **125**) and β-lapachone (**126, 127,** and **128**) derivatives as illustrated in the selected examples shown in the Scheme 25.

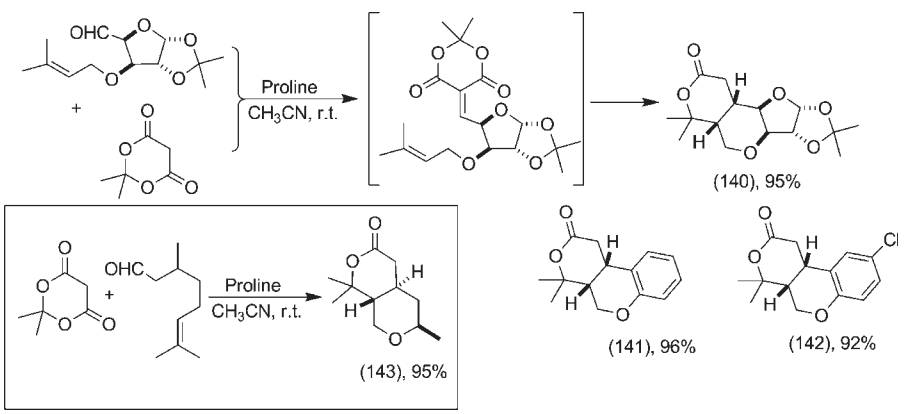
In related studies, the same group extended this three component methodology for the preparation of pyranopyrone derivatives (**129**) [Scheme 26, eq. (1)] [193]. They also demonstrated the potential of this protocol by applying it to the synthesis of pyranquinolines (*e.g.*, **130**) *via* quinoline quinone methide (**131**) as the key intermediate [Scheme 26, eq. (2)] [191].

Despite the good yields achieved in previous reactions with formaldehyde, aromatic aldehydes did not work even at reflux for periods exceeding 48 h. Aiming to improve the scope of this reaction and thus, to obtain various derivatives of lapachones, Ferreira and coworkers investigated the effect of solvents and found that reaction was accelerated in ethanol/water (1:1) at reflux [194]. With this improved methodology, it was possible to obtain β-pyranaphthoquinones more selectively, in better yields and with lower reaction times. Additionally, this methodology allowed the use of other aldehydes, not just formaldehyde (Table 2).

This reaction protocol was extended to the synthesis of silyl enol ethers to give a series of siloxy-containing naphtho[2,3-b]pyran-5,10-dione derivatives (**139a–c**) in moderate to high yields (Scheme 27) [195]. As expected, the reaction regioselectively produced α-lapachone derivatives. The authors rationalized these results by calculating the parameters of the frontier molecular orbital. This indicated that interaction of the *o*-QM with the silyl enol ether is a more energetically favorable pathway.

A very interesting variation of the protocol for *in situ* formation of *o*-QMs followed by Diels-Alder cycloaddition was reported by Sabitha *et al.* [196,197]. In this work, it was shown that the reaction of *O*-prenyl and *N*-prenyl aldehydes with Meldrum's acid led to cis-fused lactones (**140–142**) in excellent yields. Aliphatic aldehydes, such as citral, could also be used in this reaction, but as expected, the product **143** is trans (Scheme 28).

Scheme 28



CONCLUSIONS AND OUTLOOK

This review has given ample evidence that *o*-QM intermediates have developed into a useful synthetic tool for preparing chromene and chromane rings over recent years. Major progress has been made in terms of substrate scope and the development of efficient procedures for their preparation. All these developments have led to extensive use of *o*-QM intermediates in inter and intramolecular hetero-Diels-Alder and electrocyclization reactions in the field of total synthesis. The reaction even turned out to be a key tool for the preparation of pyran naphthoquinones. However, these reactions still have some drawbacks. For example, intermolecular reactions with *o*-QMs are, by far, more difficult to achieve, which is often due to reaction reversibility. Despite the improved methods for generation of *o*-QMs, their use with aldehydes has been difficult. Only very recently has this problem been partly addressed by modifying the conditions in the tandem processes. There is still a need for even more general reaction protocols, especially in the areas of intermolecular reactions and enantioselectivity.

REFERENCES AND NOTES

[1] Ellis, G. P. In Chemistry of Heterocyclic Compounds; Wiley: New York, 1977.

[2] Bowers, R. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. Science 1976, 193, 542.

[3] Katrikzy, A. R.; Rees, C. W.; Scriven, E. F. V.; McKillop, A., Eds. Comprehensive Heterocyclic Chemistry II; Elsevier: Amsterdam, 1996.

[4] (a) Kemnitzer, W.; Kasibhatla, S.; Jiang, S. C.; Zhang, H.; Zhao, J. H.; Jia, S. J.; Xu, L. F.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labrecque, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. Bioorg Med Chem 2005, 15, 4745; (b) Afantitis, A.; Melagraki, G.; Sarimveis, H.; Koutentis, P. A.; Markopoulos, J.; Igglessi-Markopoulou, O. Bioorg Med Chem 2006, 14, 6686.

[5] Engler, T. A.; LaTessa, K. O.; Iyengar, R.; Chai, W. Y.; Agrios, K. Bioorg Med Chem 1996, 4, 1755.

[6] Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K. H. Tetrahedron 2001, 57, 1559.

[7] (a) Kaltenbach, R. F.; Robinson, S. P.; Trainor, G. L. PCT U.S. Pat. 20,050,267,183 (2005); (b) Zhang, X.; Sui, Z. PCT U.S. Pat. 20,060,020,018 (2006).

[8] (a) Kidwai, M.; Saxena, S.; Khan, M. K. R.; Thukral, S. S. Bioorg Med Chem Lett 2005, 15, 4295; (b) Khafagy, M. M.; Abd El-Wahab, A. H. F.; Eid, F. A.; El-Agrody, A. M. IL Farmaco 2002, 57, 715.

[9] Lago, J. H. G.; Ramos, C. S.; Casanova, D. C. C.; Morandim, A. D.; Bergamo, D. C. B.; Cavalheiro, A. J.; Bolzani, V. S.; Furlan, M.; Guimarães, E. F.; Young, M. C. M.; Kato, M. J. J Nat Prod 2004, 67, 1783.

[10] Kitamura, R. O. S.; Romoff, P.; Young, M. C. M.; Kato, M. J.; Lago, J. H. G. Phytochemistry 2006, 67, 2398.

[11] Kawahara, N.; Nozawa, K.; Nakajima, S.; Kawai, K. J Chem Soc Perkin Trans 1 1988, 907.

[12] Gebhardt, P.; Dornberger, K.; Gollmick, F. A.; Grafe, U.; Hartl, A.; Gorls, H.; Schlegel, B.; Hertweck, C. Bioorg Med Chem 2007, 17, 2558.

[13] Odinokov, V. N.; Spivak, A. Y.; Emelyanova, G. A.; Kutepov, B. I. Russ Chem Bull Int Ed 2002, 51, 526.

[14] Cardillo, G.; Merlini, L.; Mondelli, R. Tetrahedron 1968, 24, 497.

[15] Clarke, D. G.; Crombie, L.; Whiting, D. A. J Chem Soc Perkin Trans 1 1974, 1007.

[16] Manners, G. D.; Jurd, L. J Chem Soc Perkin Trans 1 1977, 405.

[17] Benslimane, A. F.; Pouchus, Y. F.; Leboterff, J.; Verbist, J. F.; Roussakis, C.; Monniot, F. J Nat Prod 1988, 51, 582.

[18] Targett, N. M.; Keeran, W. S. J Nat Prod 1984, 47, 556.

[19] Benslimane, A. F.; Pouchus, Y. F.; Verbist, J. F.; Petit, J. Y.; Brion, J. D.; Welin, L. J Clin Pharmacol 1995, 35, 298.

[20] Pratt, G. E.; Jennings, R. C.; Hamnett, A. F.; Brooks, G. T. Nature 1980, 284, 320.

[21] Khafagi, W. E.; Hegazi, E. M. Biocontrol 2004, 49, 517.

[22] Seo, E. K.; Wani, M. C.; Wall, M. E.; Navarro, H.; Mukherjee, R.; Farnsworth, N. R.; Kinghorn, A. D. Phytochemistry 2000, 55, 35.

[23] Ali, S.; Goundar, R.; Sotheeswaran, S.; Beaulieu, C.; Spino, C. Phytochemistry 2000, 53, 281.

[24] Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. J Nat Prod 2001, 64, 208.

[25] Thompson, T. A.; Wilding, G. PCT Int Appl W 2,005, 011,658 (2005).

[26] Kumazava, S.; Suzuki, S.; Ahn, M.; Kamihira, M.; Udagawa, Y.; Bang, K.; Nakayama, T. Food Sci Technol Res 2006, 12, 67.

[27] Oliveira, A. B.; Raslan, D. S.; Miraglia, M. C. M.; Mesquita, A. A. L.; Zani, C. L.; Ferreira, D. T.; Maia, J. G. S. Quim Nova 1990, 13, 302.

[28] Jain, S.; Chauhan, P.; Singh, P. J Indian Chem Soc 2002, 79, 946.

[29] Hannedouche, S.; Souchard, J. P.; Jacquemond-Collet, I.; Moulis, C. Fitoterapia 2002, 73, 520.

[30] Bracho, J. C. Bol Soc Quim Peru 2000, 66, 198.

[31] Oliveira, M. E.; Lemos, T. L. G.; Braz-Filho, R. Rev Bras Farm 1999, 80, 46.

[32] Jacome, R. L. R. P.; De Oliveira, A. B.; Raslan, D. S.; Muller, A.; Wagner, H. Quim Nova 1999, 22, 175.

[33] Villegas, J. R.; Amato, S.; Castro, I.; Castro, O.; Jacobson, U. Fitoterapia 1995, 66, 281.

[34] Houghton, P.; Pandey, R.; Hawkes, J. E. Phytochemistry 1994, 35, 1602.

[35] Grazziotin, J. D.; Schapoval, E. E. S.; Chaves, C. G.; Gleye, J.; Henriques, A. T. J Ethnopharmacology 1992, 36, 249.

[36] Singh, P.; Jain, S.; Bhargava, S. Phytochemistry 1989, 28, 1258.

[37] Girard, M.; Kindack, D.; Dawson, B. A.; Ethier, J. C.; Awang, D. V. C. J Nat Prod 1988, 51, 1023.

[38] Ghogomu-Tih, R.; Nyasse, B.; Tsamo, E.; Sondengam, B. L. Planta Med 1986, 52, 342.

[39] Joshi, K. C.; Sharma, A. K.; Singh, P. Planta Med 1986, 52, 71.

[40] Inoue, K.; Chen, C. C.; Inouye, H.; Kuriyama, K. J Chem Soc Perkin Trans 1 1981, 2764.

[41] Ueda, S.; Inoue, K.; Shiobara, Y.; Kimura, I.; Inouye, H. Planta Med 1980, 40, 168.

[42] Joshi, K. C.; Singh, P.; Pardasani, R. T.; Singh, G. Planta Med 1979, 37, 60.

[43] Viana, L. M.; Freitas, M. R.; Rodrigues, S. V.; Baumann, W. Braz. J Chem Eng 2003, 20, 317.

[44] Gonçalves, O. L.; D'Albuquerque, I. L.; Borba, M. A. P.; Mello, J. F. Rev Inst Antibiot Univ Recife 1966, 6, 23.

[45] Gonçalves, O. L.; D'Albuquerque, I. L.; Lima, C. G.; Maia, M. H. D. Rev Inst Antibiot Univ Recife 1972, 12, 317.

[46] Machado, T. B.; Pinto, A. V.; Pinto, M. C. F. R.; Leal, I. C. R.; Silva, M. G.; Amaral, A. C. F.; Kuster, R. M.; Netto-dos Sa, K. R. Int J Antimicrob Agents 2003, 21, 279.

[47] Cho, J. Y.; Kim, H. Y.; Choi, G. J.; Jang, K. S.; Lim, H. K.; Lim, C. H.; Cho, K. Y.; Kim, J. C. Pest Manage Sci 2006, 62, 414.

[48] D'Albuquerque, I. L.; De Araujo, M. C. M.; Maciel, M. C. M.; Maciel, G. M. B.; Lacerda, A. L.; Martins, D. G. Rev Inst Antibiot Univ Recife 1972, 12, 25.

[49] Jassbi, A. R.; Singh, P.; Jain, S.; Tahara, S. Helv Chim Acta 2004, 87, 820.

[50] Dudley, K. H.; Chiang, R. W. J Org Chem 1968, 34, 120.

[51] Ettlinger, M. G. J Am Chem Soc 1950, 72, 3666.

[52] Hassani, M.; Cai W.; Holley, D. C.; Lineswala, J. P.; Maharjan, B. R.; Ebrahimian, G. R.; Seradj, H; Stocksdale, M. G.; Mohammadi, F; Marvin, C. C.; Gerdes, J; Beall, H. D.; Behforouz, M. J Med Chem 2005, 48, 7733.

[53] Lee, J. H.; Cheong, J. H.; Park, Y. M.; Choi, Y. H. Pharmacol Res 2005, 51, 553.

[54] Skibo, E. B.; Xing, C. J Med Chem 2001, 44, 3545.

[55] Liu, K. C.; Li, J.; Sakya, S. Mini Rev Med Chem 2004, 4, 1105.

[56] Asche, C. Mini Rev Med Chem 2006, 5, 449.

[57] Santos, A. F.; Ferraz, P. A. L.; Pinto, A. V.; Pinto, M. C. F. R.; Goulart, M. O. F.; Sant'Ana, A. E. G. Int J Parasitol 2000, 30, 1199.

[58] Dos Santos, A. F.; Ferraz, P. A. L.; de Abreu, F. C.; Chiari, E.; Goulart, M. D. F.; Sant'Ana, A. E. G. Planta Med 2001, 67, 92.

[59] Barbosa, T. P.; Camara, C. A.; Silva, T. M. S.; Martins, R. M.; Pinto, A. C.; Vargas, M. D. Bioorg Med Chem 2005, 13, 6464.

[60] Teixeira, M. J.; Almeida, Y. M.; Viana, J. R.; Holanda Filha, J. G.; Rodrigues, T. P.; Prata, J. R. C., Jr.; Coelho, I. C. B.; Rao, V. S.; Pompeu, M. M. L. Phytoterapy Res 2001, 15, 44.

[61] Almeida, E. R. J Ethnopharmacol 1990, 29, 239.

[62] Garnier, S.; Wolfender, J. L.; Nianga, M.; Stoeckli-Evans, H.; Hostettmann, K. Phytochemistry 1996, 42, 1315.

[63] Pinto, C. N.; Dantas, A. P.; De Moura, K. C. G.; Emery, F. S.; Polequevitch, P. F.; Pinto, M. C. F. R.; De Castro, S. L.; Pinto, A.V. Arzneim Forsc (Drug Res) 2000, 50, 1120.

[64] De Moura, K C. G. F.; Emery, S.; Neves-Pinto, C.; Pinto, M. C. F. R.; Dantas, A. P.; Salomão, K.; De Castro, S. L.; Pinto, A. V. J Braz Chem Soc 2001, 12, 325.

[65] Monks, T. J.; Hanzlik, R. P.; Cohen, G. M.; Ross, D.; Graham, D. G. Toxicol App Pharmacol 1992, 112, 2.

[66] (a) Kappus, H. Biochem Pharmacol 1986, 35, 1; (b) De Abreu, F. C.; Ferraz, P. A. L.; Goulart, M. O. F. J Braz Chem Soc 2002, 13, 19.

[67] Santos, E. V. M.; Carneiro, J. W. M.; Ferreira, V. F. Bioorg Med Chem 2004, 12, 87.

[68] Da Silva, M. N.; Ferreira, V. F.; de Souza, M. C. B. V. Quim Nova 2003, 26, 407.

[69] (a) Rover, L., Jr.; Höehr, N. F.; Vellasco, E. A. P.; Kubota, L.T. Quim Nova 2001, 24, 112; and references therein; (b) Muniz, M. Ciência Hoje 1995, 115, 70; (c) Fridovisc, I. J Exp Biol 1998, 201, 1203.

[70] Pardee, A. B.; Li, Y. Z.; Li, C. J. Curr Cancer Drug Targets 2002, 2, 227.

[71] Paternó, E. Gazz Chim Ital 1882, 12, 337.

[72] Fonseca, S. G. C.; Braga, R. M. C.; Santana, D. P. Rev Bras Farm 2003, 84, 9.

[73] Hussain, H.; Krohn, K.; Ahmad, V. U.; Miana, G. A.; Green, I. R. Arkivoc 2007, ii, 145; and referenced therein.

[74] Rao, K. V.; McBride, T. J.; Oleson, J. J Cancer Res 1968, 28, 1952.

[75] Weller, M.; Winter, S.; Schmidt, C.; Esser, P.; Fontana, A.; Dichgans, J.; Groscurth, P. Int J Cancer 1997, 73, 707.

[76] Afrasiabi, Z.; Sinn, E.; Chen, J.; Ma, Y.; Rheingold, A. L.; Zakharov, L. N.; Rath, N.; Padhye, S. Inorg Chim Acta 2004, 357, 271.

[77] Pérez-Sacau, E.; Díaz-Peñate, R. G.; Estévez-Braun, A.; Ravelo, A. G.; Garcia-Castellano, J. M.; Pardo, L.; Campillo, M. J Med Chem 2007, 50, 696.

[78] Pinto, A. V.; Menna-Barreto, R. F. S.; de Castro, S. L. Recent Progress in Medicinal Plants; Studium Press: Houston, 2006.

[79] Lin, R.; Connolly, P. J.; Huang, S.; Wetter, S. K.; Lu, Y.; Murray, W. V.; Emanuel, S. L.; Gruninger, R. H.; Fuentes-Pesquera, A. R.; Rugg, C. A.; Middleton, S. A.; Jolliffe, L. K. J Med Chem 2005, 48, 4208.

[80] Zhang, Q.; Peng, Y.; Wang, X. I.; Keenan, S. M.; Arora, S.; Welsh, W. J. J Med Chem 2007, 50, 749.

[81] Silva, T. M. S.; Camara, C. A.; Barbosa, T. P.; Soares, A. Z.; da Cunha, L. C.; Pinto, A. C.; Vargas, M. D. Bioorg Med Chem 2005, 13, 193.

[82] Miao, X. S.; Song, P.; Savage, R. E.; Yang, R. Y.; Kizer, D.; Wu, H.; Volckova, E.; Ashwell, M. A.; Chan, T. C. K. Drug Metab Dispos 2008, 36, 641.

[83] Da Silva Júnior, E. N.; De Souza, M. C. B. V.; Pinto, A. V.; Pinto, M. C. F. R.; Goulart, M. O. F.; Pessoa, C.; Costa-Lotufo, L.; Montenegro, R. C.; Moraes, M. O.; Ferreira, V. F. Bioorg Med Chem 2007, 15, 7035.

[84] Planchon, S. M.; Wuerzberger, S.; Frydman, B.; Witiak, D. T.; Hutson, P.; Church, D. R.; Wilding, G.; Boothman, D. A. Cancer Res 1996, 55, 3706.

[85] Li, C. L.; Wang, C.; Pardee, A. B. Cancer Res 1995, 55, 3712.

[86] Lai, C. C.; Liu, T. J.; Ho, L. K.; Don, M. J.; Chau, Y. P. Histol Histopathol 1998, 13, 89.

[87] Woo, H. J.; Park, K. Y.; Rhu, C. H.; Lee, W. H.; Choi, B. T.; Kim, G. Y.; Park, Y. M.; Choi, Y. H. J Med Food 2006, 9, 161.

[88] Wuerzberger, S. M.; Pink, J. J.; Planchon, S. M.; Byers, K. L.; Bornmann, W. G.; Boothman, D. A. Cancer Res 1998, 58, 1876.

[89] Li, C. J.; Li, Y. Z.; Pinto, A. V.; Pardee, A. B. Proc Natl Acad Sci USA 1999, 96, 13369.

[90] Bey, E. A.; Bentle, M. S.; Reinicke, K. E.; Dong, Y.; Yang, C. R.; Girard, L.; Minna, J. D.; Bornmann, W. G.; Gao, J.; Boothman, D. A. Proc Natl Acad Sci USA 2007, 104, 11832.

[91] Li, Y. Z.; Li, C. J.; Yu, D. H.; Pardee, A. B. Mol Med 2000, 6, 1008.

[92] (a) Ferreira, V. F.; Jorqueira, A.; Souza, A. M. T.; Da Silva, M. N.; De Souza, M. C. B. V.; Gouvêa, R. M.; Rodrigues, C. R.; Pinto, A. V.; Castro, H. C.; Santos, D. O.; Araújo, H. P.; Bourguignon, S. C. Bioorg Med Chem 2006, 14, 5459; (b) Jorqueira, A.; Gouvêa, R. M.; Ferreira, V. F.; Da Silva, M. N.; De Souza, M. C. B. V.; Zuma, A. A.; Cavalcanti, D. F. B.; Araújo, H. P.; Bourguignon, S. C. Parasitol Res 2006, 9, 429; (c) De Moura, K. C. G.; Salomão, K.; Menna-Barreto, R. F. S.; Emery, F. S.; Pinto, M. D. F. R.; Pinto, A. V.; Castro, S. L. Eur J Med Chem 2004, 39, 639.

[93] Dubin, M.; Fernadez Villamil, S. H.; Stoppani, A. O. Medicina 2001, 61, 343.

[94] Ravelo, A. G.; Estévez-Braun, A.; Chávez-Orellana, H.; Pérez-Sacau, E.; Mesa-Siverio, D. Curr Top Chem 2004, 4, 241.

[95] Marr, J. J.; Docampo, R. Rev Infect Dis 1986, 8, 884.

[96] Goijman, S. G.; Stoppani, A. O. M. Arch Biochem Biophys 1985, 240, 273.

[97] Neves-Pinto, C.; Malta, V. R. S.; Pinto, M. D.; Santos, R. H. A.; De Castro, S. L.; Pinto, A.V. J Med Chem 2002, 45, 2112.

[98] Nguyen, V. T. H.; Appel, B.; Langer, P. Tetrahedron 2006, 62, 7674.

[99] (a) Yadav, J. S.; Reddy, B. V. S.; Hashim, S. R. J Chem Soc Perkin Trans 1 2000, 3082; (b) DeBoer, C. D. J Org Chem 1974, 39, 2426; (c) Balalaie, S.; Sheikh-Ahmadi, M.; Bararjanian, M. Catal Commun 2007, 8, 1724; (d) Liu, F.; Evans, T.; Das, B. C. Tetrahedron Lett 2008, 49, 1578.

[100] Kaye, P. T.; Nocanda, X. W. J Chem Soc Perkin Trans 1 2000, 1331.

[101] (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J Chem Soc Chem Commun 1979, 836; (b) March, P. D.; Moreno-Manas, M.; Casado, J.; Pleixats, R.; Roca, J. L.; Trius, A. J Heterocycl Chem 1984, 21, 85; (c) Moreno-Manas, M.; Papell, E.; Pleixats, R.; Ribas, J.; Virgili, A. J Heterocycl Chem 1986, 23, 413; (d) Cervera, M.; Moreno-Manas, M.; Pleixats, R. Tetrahedron 1990, 46, 7885.

[102] (a) Hlubeck, J.; Ritchie, E.; Taylor, W. C. Tetrahedron Lett 1969, 10, 1369; (b) Kahn, P. H.; Cossy, J. Tetrahedron Lett 1999, 40, 8113; (c) Kenny, R. S.; Mashelkar, U. C.; Rane, D. M.; Bezawada, D. K. Tetrahedron 2006, 62, 9280; (d) Prado, S.; Janin, Y. L.; Bost, P. E. J Heterocycl Chem 2005, 43, 1605.

[103] (a) Yato, M.; Ohwada, T.; Shudo, K. J Am Chem Soc 1990, 112, 5341; (b) Nakamura, S.; Uchiyama, M.; Ohwada, T. J Am Chem Soc 2003, 125, 5282.

[104] Varma, R. S.; Dahiya, R. J Org Chem 1998, 63, 8038.

[105] (a) Chang, S.; Grubbs, R. H. J Org Chem 1998, 63, 864; (b) Van Otterlo, W. A. L.; Ngidi, E. L.; Kuzvidza, S.; Morgans, G. L.; Moleele, S. S.; de Koning, C. B. Tetrahedron 2005, 61, 9996.

[106] (a) Schweizer, E. E.; Minami, T.; Anderson, S. E. J Org Chem 1974, 39, 3038; (b) Hanamoto, T.; Shindo, K.; Matsuoka, M.; Kiguchi, Y.; Kondo, M. J Chem Soc Perkin Trans 1 2000, 103; (c) Bestmann, H. J.; Tömösközi, I. Tetrahedron 1968, 24, 3299; (d) Bestmann, H. J.; Kloeters, W. Tetrahedron Lett 1977, 18, 79.

[107] (a) Jinno, M.; Kitano, Y.; Tada, M.; Chiba, K. Org Lett 1999, 1, 435; (b) Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. Chem Commun 1999, 8, 691.

[108] Hanamoto, T.; Shindo, K.; Matsuoka, M.; Kiguchi, Y.; Kondo, M. J Chem Soc Perkin Trans 1 2000, 103.

[109] Wang, Q.; Finn, M. G. Org Lett 2000, 2, 4063.

[110] Parker, K. A.; Mindt, T. L. Org Lett 2001, 3, 3875.

[111] Ye, L. W.; Sun, X. L.; Zhu, C. Y.; Tang, Y. Org Lett 2006, 8, 3853.

[112] Zhou, Q. B.; Rokita, S. E. Proc Natl Acad Sci USA 2003, 100, 15452.

[113] Freccero, M. Mini Rev Org Chem 2004, 1, 403.

[114] Wang, P.; Song, Y.; Zhang, L. X.; He, H. P.; Zhou, X. Curr Med Chem 2005, 12, 2893.

[115] Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M. J Org Chem 2003, 68, 6411.

[116] Alves, R. B.; Oliveira, R. B. Quim Nova 2002, 25, 976.

[117] Wakselman, M. New J Chem 1983, 7, 439.

[118] Chiang, Y.; Kresge, A. J.; Zhu, Y. J Am Chem Soc 2002, 124, 6349.

[119] Katada, T.; Eguchi, S.; Esaki, T.; Sasaki, T. J Chem Soc Perkin Trans 1 1984, 2649.

[120] Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. Can J Chem 1996, 74, 465.

[121] Wan, P.; Brousmiche, D. W.; Chen, C. Z.; Cole, J.; Lukeman, M.; Xu, M. Pure Appl Chem 2001, 73, 529.

[122] Ezcurra, J. E.; Karabelas, K.; Moore, H. W. Tetrahedron 2005, 61, 275.

[123] Chiang, Y.; Kresge, A. J.; Zhu, Y. Pure Appl Chem 2000, 72, 2299.

[124] El Kain, L.; Grimaud, L.; Oble, J. Org Biomol Chem 2006, 4, 3410.

[125] Van De Water, R. W.; Pettus, T. R. R. Tetrahedron 2002, 58, 5367.

[126] Wang, H.; Wang, Y.; Han, K. L.; Peng, X. J. J Org Chem 2005, 70, 4910.

[127] Brousmiche, D. W.; Wan, P. J. Photochem Photobiol A Chem 2002, 149, 71.

[128] Wojciechowski, K.; Dolatowska, K. Tetrahedron 2005, 61, 8419.

[129] Dorrestijn, E.; Pugin, R.; Nogales, M. V. C.; Mulder, P. J Org Chem 1997, 62, 4804.

[130] Kiselyov, A. S. Tetrahedron Lett 2001, 42, 3053.

[131] Jones, R. M.; Van Der Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. J Org Chem 2001, 66, 3435.

[132] (a) Amouri, H.; Vaissermann, J.; Rager, M. N.; Grotjahn, D. B. Organometallics 2000, 19, 5143; (b) Amouri, H.; Vaissermann, J.; Rager, M. N.; Grotjahn, D. B. Organometallics 2000, 19, 1740.

[133] Amouri, H.; Le Bras, J. Acc Chem Res 2002, 35, 501.

[134] Sullivan, W. W.; Ullman, D.; Shechter, H. Tetrahedron Lett 1969, 10, 457.

[135] Nicolaides, D. N.; Litinas, K. E.; Lefkaditis, D. A.; Adamopoulos, S. G.; Raptopoulou, C. P.; Terzis, A. J Chem Soc Perkin Trans 1 1994, 2107.

[136] Da Silva, M. N.; Ferreira, S. B.; Jorqueira, A.; De Souza, M. C. B. V.; Pinto, A. V.; Kaiser, C. R.; Ferreira, V. F. Tetrahedron Lett 2007, 48, 6171.

[137] (a) Saul, S. J.; Sugumaran, M. FEBS Lett 1991, 279, 145; (b) Sugumaran, M. Pigment Cell Res 1995, 8, 250; (c) Nematollahi, D; Tammari, E. Electrochim Acta 2005, 50, 3648; (d) Majetich, G.; Zou, G. Org Lett 2008, 10, 81.

[138] Heldeweg, R. F.; Hogeveen, H. J Am Chem Soc 1976, 98, 6040.

[139] Mcintosh, C. L.; Chapman, O. L. J Chem Soc Chem Commun 1971, 771.

[140] Letulle, M.; Guenot, P.; Ripoll, J. L. Tetrahedron Lett 1991, 32, 2013.

[141] Eck, V.; Schweig, A.; Vermeer, H. Tetrahedron Lett 1978, 19, 2433.

[142] Ferreira, V. F.; Pinto, A. V.; Coutada, L. C. M. An Acad Bras Cienc 1980, 52, 478.

[143] De Oliveira, A. B.; Ferreira, D. T.; Raslan, D. S. Tetrahedron Lett 1988, 29, 155.

[144] Lee, Y. R.; Lee, W. K. Synth Commun 2004, 34, 4537.

[145] Lee, R.; Choi, J. H.; Trinh, D. T. L.; Kim, N. W. Synthesis 2005, 3026.

[146] Hayashi, T.; Smith, F. T.; Lee, K. H. J Med Chem 1987, 30, 2005.

[147] Tournaire, C.; Caujolle, R.; Payard, M.; Commenges, G.; Bessikes, M. H.; Bories, C.; Loiseau, P. M.; Gayral, P. Eur J Med Chem 1996, 31, 507.

[148] Hua, D. H.; Chen, Y.; Sin, H. S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J. P.; Chiang, P. K. J Org Chem 1997, 62, 6888.

[149] Chauder, B. A.; Lopes, C. C.; Lopes, R. S. C.; Da Silva, A. J. M.; Snieckus, V. Synthesis 1998, 279.

[150] Alves, G. B. C.; Lopes, R. S. C.; Lopes, C. C.; Snieckus, V. Synthesis 1999, 1875.

[151] Brandão, M. A. F.; Oliveira, A. B.; Snieckus, V. Tetrahedron Lett 1993, 34, 2437.

[152] Tapia, R. A.; Lizama, C.; López, C.; Valderrama, J. A. Synth Commun 2001, 31, 601.

[153] Dintzner, M. R.; Lyons, T. W.; Akroush, M. H.; Wucka, P.; Rzepka, A. T. Synlett 2005, 785.

[154] Da Silva, F. C.; Jorqueira, A.; Gouvêa, R. M.; De Souza, M. C. B. V.; Howie, R. A.; Wardell, J. L.; Wardell, S. M. S. V.; Ferreira, V. F. Synlett 2007, 3123.

[155] Suzuki, T.; Tanaka, N.; Matsumura, T.; Hosoya, Y.; Nakada, M. Tetrahedron Lett 2006, 47, 1593.

[156] Funk, R. L.; Vollhardt, K. P. C. Chem Soc Rev 1980, 9, 41.

[157] Taber, D. F. Intramolecular Diels-Alder Reactions and Alder Ene Reactions; Springer Verlag: New York, 1984.

[158] (a) Martin, J. G.; Hill, R. K. Chem Rev 1961, 61, 537; (b) Dewar, M. J. S.; Pierini, A. B. J Am Chem Soc 1984, 106, 203; (c) Houk, K. N.; Li, Y.; Evanseck, J. D. Angew Chem Int Ed Engl 1992, 31, 682; (d) Oppolzer, W. Angew Chem Int Ed Engl 1984, 23, 876; (e) Ghosez, L. In Adventure in Cycloaddition Reaction—Past, Present and Future in Stereocontrolled Organic Synthesis; Trost, B. M., Ed.; Blackwell: Melbourne, 1994, 193; (f) Craig, D. Chem Soc Rev 1987, 16, 187; (g) Dias, L. C. J Braz Chem Soc 1997, 8, 289; (h) Ciganek, E. Org Reactions 1984, 32, 1; (i) Deslongchamps, P. Aldrichim Acta 1991, 24, 43.

[159] Desimoni, G.; Tacconi, G. Chem Rev 1975, 75, 651.

[160] Schmidt, R. R. Acc Chem Res 1986, 19, 250.

[161] Boger, D.; Weinreb, S. Hetero Diels-Alder Methodology in Organic Synthesis; Academic Press: San Diego, 1987.

[162] Rowland, G. B.; Rowland, E. B.; Zhang, Q.; Antilla, J. C. Curr Org Chem 2006, 10, 981.

[163] Santos, J. S.; Ferrioli-Filho, F.; Kanesiro, M. M.; Ferreira, V. F.; Santos, S. C.; Pinto, C. N.; Fonseca, J. L.; Mizrahy, H. E.; Gilbert, B.; Pinto, M. C. F. R.; Ribeiro, F. W.; Pinto, A. V. Mem Inst Oswaldo Cruz 1992, 87, 345.

[164] Cacioli, P.; Mackay, M. F.; Reiss, J. A. Tetrahedron Lett 1980, 21, 4973.

[165] Brougidou, J.; Christol, H. C. R. Acad Sci Ser C 1963, 257, 3149.

[166] Brougidou, J.; Christol, H. C. R. Acad Sci Ser C 1963, 257, 3323.

[167] Chapman, O. L.; Mcintosh, C. L. J Chem Soc Chem Commun 1971, 383.

[168] Bray, C. D. Org Biomol Chem 2008, 6, 2815.

[169] Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Williams, A. J.; Watkin, D. J. Org Lett 1999, 1, 1937.

[170] Baldwin, J. E.; Mayweg, A. V. W.; Neumann, K.; Pritchard, G. J. Org Lett 1999, 1, 1933.

[171] Adlington, R. M.; Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J. Org Lett 2002, 4, 3009.

[172] Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. Org Lett 2004, 6, 3617.

[173] Rodriguez, R.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. Org Biomol Chem 2005, 3, 3488.

[174] Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. J Am Chem Soc 1971, 93, 6696.

[175] Hug, R.; Hansen, H. J.; Schmid, H. Helv Chim Acta 1972, 55, 1675.

[176] Mao, Y. L.; Boekelheide, V. Proc Natl Acad Sci USA 1980, 77, 1732.

[177] Tietze, L. F.; Kiedrowski, G. V.; Harms, K.; Clegg, W.; Sheldrick, G. Angew Chem Int Ed Engl 1980, 19, 134.

[178] Tietze, L. F.; Vonkiedrowski, G. Tetrahedron Lett 1981, 22, 219.

[179] Tietze, L. F.; Bratz, M.; Machinek, R.; Vonkiedrowski, G. J Org Chem 1987, 52, 1638.

[180] Tietze, L. F.; Brumby, T.; Pretor, M.; Remberg, G. J Org Chem 1988, 53, 810.

[181] Tietze, L. F.; Brand, S.; Brumby, T.; Fennen, J. Angew Chem Int Ed Engl 1990, 29, 665.

[182] Ferreira, V. F.; Coutada, L. C.; Pinto, M. C. F. R.; Pinto, A.V. Synth Commun 1982, 12, 195.

[183] Jiménez-Alonso, S.; Orellana, H. C.; Estévez-Braun, A.; Ravelo, A. G.; Pérez-Sacau, E.; Machín, F. J Med Chem 2008, 51, 6761.

[184] Sabitha, G.; Reddy, E. V.; Fatima, N.; Yadav, J. S; Ramakrishna, K. V. S. R.; Kunwar, A. C. Synthesis 2004, 1150.

[185] Talley, J. J. J Org Chem 1985, 50, 1695.

[186] Zuloaga, F.; Tapia, R.; Quintanar, C. J Chem Soc Perkin Trans 2 1995, 939.

[187] Tapia, R. A.; Alegria, L.; Valderrama, J. A.; Cortes, M.; Pautet, F.; Fillion, H. Tetrahedron Lett 2001, 42, 887.

[188] Cruz-Almanza, R.; Pérez-Flores, F.; Lemini, C. Heterocycles 1994, 37, 759.

[189] Nakatani, K.; Higashida, N.; Saito, I. Tetrahedron Lett 1997, 38, 5005.

[190] Ye, J. H.; Ling, K. Q.; Zhang, Y.; Li, N.; Xu, J. H. J Chem Soc Perkin Trans 1 1999, 2017.

[191] Nair, V.; Mathew, B.; Rath, N. P.; Vairamani, M; Prabhakar, S. Tetrahedron 2001, 57, 8349.

[192] Nair, V.; Treesa, P. M. Tetrahedron Lett 2001, 42, 4549.

[193] Nair, V.; Jayan, C. N.; Radhakrishnan, K. V. Tetrahedron 2001, 57, 5807.

[194] Da Silva, F. C.; Ferreira, S. B.; Kaiser, C. R.; Pinto, A. C.; Ferreira, V. F. J Braz Chem Soc 2009, 20, 1478.

[195] Peng, D. Q.; Liu, Y.; Lu, Z. F.; Shen, Y. M.; Xu, J. H. Synthesis 2008, 1182.

[196] Sabitha, G.; Kumar, M. R.; Reddy, M. S. K; Yadav, J. S.; Krishna, K. V. R. S.; Kunwar, A. C. Tetrahedron Lett 2005, 46, 1659.

[197] Sabitha, G.; Fatima, N.; Reddy, E. V.; Yadav, J. S. Adv Synth Catal 2005, 347, 1353.