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ortho-Quinone methide (*o*-QM): a highly reactive, ephemeral and versatile intermediate in organic synthesis

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Since its first observation in 1907, *ortho*-quinone methide (*o*-QM) has occupied a strategic place within the framework of reactive intermediates in organic synthesis. In recent years, *o*-QM has enhanced its importance as a versatile reactive intermediate, and its applications in organic synthesis, material chemistry, fine chemicals, and pharmaceuticals are increasing rapidly. This critical review summarizes the key concepts behind *o*-QMs and provides an overview of current applications in organic synthesis to provide an appropriate background for synthetic, medicinal and combinatorial developments. This review covers the literature from its origin to the mid of 2014 (112 references).

1. Introduction

ortho-Quinone methides (*o*-QMs) are short-lived, highly reactive and versatile intermediates in organic synthesis, material

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Maya Shankar Singh born in 1960, received his MSc degree in Organic Chemistry from Banaras Hindu University, Varanasi, India in 1981, where he also earned his PhD degree in 1986 working under the tutelage of Professor K. N. Mehrotra. After his postdoctoral work, he joined Vikram University Ujjain in 1990 as Assistant Professor in Organic Chemistry, and moved to Gorakhpur University as Associate Professor in 1998, then to Banaras Hindu University in 2004, where he is currently Professor in Organic Chemistry since 2006. During his sabbatical, he visited the Chemistry Department of the University of Arizona, Tucson, USA; Nagoya Institute of Technology, Nagoya, Japan; Loughborough University, UK and University of Leicester, UK. His research interests are centered on synthetic Organic chemistry with special emphasis in the development of novel building block precursors, new eco-compatible synthetic methods, multicomponent domino/tandem reactions, and structural studies. Fifteen students have completed their PhD degrees under his supervision. He has published 125 research articles and four reviews in journals of high status. Additionally, Prof. Singh has also authored three textbooks in organic chemistry published from Pearson-Education and Wiley-VCH, Weinheim, Germany. He has been elected as a fellow of the Indian Academy of Sciences, India in 2013.

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chemistry, fine chemicals, and pharmaceuticals.[1] The *ortho*-quinone methide (*o*-QM) was first suggested by Fries in 1907 and is generally formed by the reaction of phenol with aldehyde in the presence of an acid or a base. The first direct evidence was given by Gardner in 1963 by trapping it at −100 °C. After 1963, its use as a versatile intermediate in organic synthesis increased enormously, particularly in many tandem [4 + 2] cycloaddition reactions with a variety of dienophiles. However, there are abundant indirect evidences for the *in situ* generation of *ortho*-quinone methides. Most indirect evidence comes from the structural identification of the products that result from dimerization, trimerization, intramolecular and intermolecular [2 + 2] cycloadditions as well as the nucleophilic trapping of *o*-QMs.[2] The chemical behaviour of *o*-QMs resembles that of α, β-unsaturated ketones due to the presence of a 1,3-cyclohexadiene core substituted with a carbonyl and an exo-methylene group. They react very rapidly with nucleophiles and undergo efficient Diels–Alder reactions with electron-rich olefins. Expansive reactivity of the *o*-QM can be used in the linchpin reaction for the construction of various natural products.[3]

Compared to carbocations, carbanions, radicals, carbenes, nitrenes and so forth, *ortho*-quinone methides are relative newcomers to the family of inherently reactive species. Quinone methides exist in three isomeric forms *o*-, *m*-, and *p*-quinone methides (also known as *o*-, *m*-, and *p*-QMs) (Fig. 1). *meta*-Quinone methide is actually a resonance hybrid of two canonical forms, one of which is a zwitterionic form stabilized by aromatic conjugation, increasing its polarity and thus enhancing its reactivity. The importance of *o*- and *p*-quinone methides in organic synthesis and their role in biochemistry have been studied in detail. Unlike benzoquinones, *o*- and *p*-quinone methide derivatives are highly polarized compounds, usually observed with difficulty or postulated as reactive intermediates because of the facile reactions driven by the formation of aromatized phenol derivatives.

ortho-Quinone methides are highly versatile intermediates that have been extensively harnessed by nature (Fig. 2). A variety of plants, animals, and insects capitalize upon these types of compounds as a mean of defence. However, despite general knowledge of *o*-QMs for over a century, these intermediates still lie outside the synthetic mainstream. Pettus and Water[1a] reviewed *o*-QMs, particularly its preparation, the benefits and limitations associated with each method as well as the applications in total synthesis.

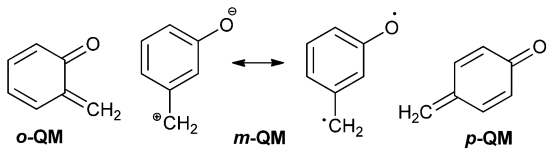

Fig. 1 Isomeric forms of quinone methides.

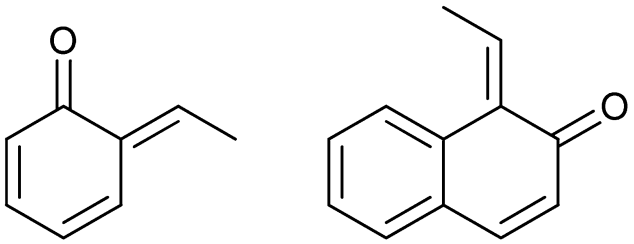

Fig. 2 *ortho*-Quinone methides.

ortho-Quinone methide exists in *E*/*Z* geometric isomers that are fluxional in nature, and behaves as a combination of a charged zwitterionic and biradical structures (Fig. 3). The distribution among these geometric isomers is believed to result from the differences between non-bonded interactions. If from a steric point of view, R^1 substituent is smaller than oxygen, then the *E*-configuration is preferred. However, increasing the size of R^1 substituent can cause the *Z*-configuration to predominate. The *E*/*Z* ratio proves important in governing the diastereoselective outcome for Diels–Alder cycloadditions.

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Sushobhan Chowdhury was born in South 24 Parganas, West Bengal, India, in 1985. He received his B. Sc. degree from the University of Calcutta in 2007 and moved to the Banaras Hindu University, Varanasi for post-graduate studies. There he obtained his M. Sc. degree in 2010 and completed Ph.D. under the supervision of Prof. Maya Shankar Singh in 2014. His doctoral study was mainly themed on the development of synthetic methods based on the dithioester chemistry. Presently, he is working as a postdoctoral fellow at UNIST, Ulsan, South Korea.

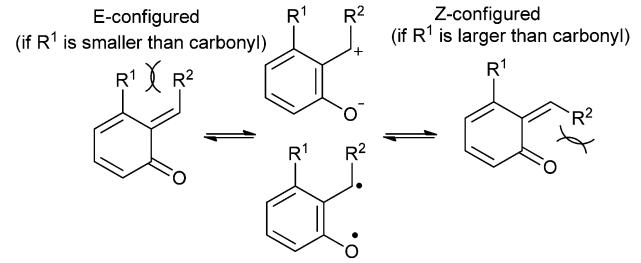


Fig. 3 Geometric, zwitterionic and biradical structures of *o*-QM.

Quinone methides (QMs) are common reactive intermediates in chemistry, as well as in the photochemistry of phenols, attracting considerable attention recently owing to their biological activity.[4] Although the partial zwitterionic character of QMs makes them both electrophilic and nucleophilic, their reactivity with nucleophiles is particularly important in biological systems. It has been demonstrated that QMs react with amino acids[5] and proteins,[6] and inhibit the action of some enzymes. Moreover, they have been implicated as the ultimate cytotoxins responsible for the function of agents such as antitumor drugs, antibiotics, and DNA alkylators in biological chemistry.[7,8] Later on, it was shown that QMs are not the responsible reagents for cross-linking DNA, but they are probably involved in the metabolic formation of formaldehyde.[9] To understand the chemistry of anthracycline antitumor antibiotic, a simple stable *o*-QM has been constructed and entirely characterized. Reaction of quinone methide with nucleophiles, including 2′,3′-isopropylideneadenosine has been examined.[10]

Several important clinical drugs like cisplatin, psoralens, and mitomycin C are known to induce DNA ISC (interstrand cross-links) formation, which can disrupt cell maintenance and replication.[11] Both reductive and oxidative metabolisms form quinone methides and have become a very important topic in drug design and drug safety. Even though *ortho*-quinone methides were investigated in detail 50 years ago, the last few years have brought about a renaissance in their chemistry. This review summarizes the recent developments in this field and highlights key historical contributions.

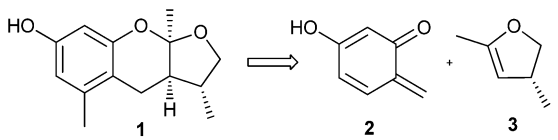
2. Generation of *ortho*-quinone methides

ortho-Quinone methides are highly reactive species that have attracted considerable attention because of their intriguing structure and properties. A number of methods for the generation of *o*-QMs have been developed till date, enabling the straightforward construction of diverse aromatic molecules with successful applications to a number of complete syntheses of complex natural products. In the past decade, the most popular methods were photochemical initiation of *o*-(α-phenyl) substituted phenols or thermal initiation of various substituents on the benzene ring of *ortho*-methyleneacetoxy phenols. Lewis acid, base, and chemical oxidants were also used to generate *o*-QMs. Thus, the method of generation of the *o*-QM becomes intimately linked with the manner in which it is to be utilized.

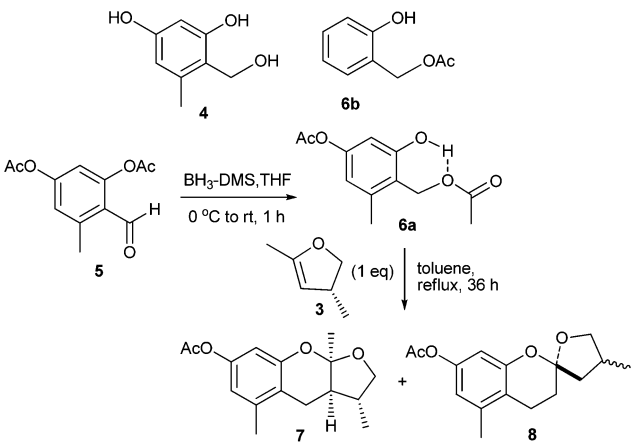
2.1. Thermal generation

Among the used procedures to generate *o*-QMs, the most common ones are thermal and base initiations, in which good to excellent stereoselectivity with excellent yields of the corresponding products have been obtained. Only a limited number of accounts have been reported where acid is used to generate the *o*-QMs. This is mainly due to the low compatibility of acid with the dienophiles, and because of the greater ionic character of the reaction conditions that result in a product with low stereoselectivity. Baldwin and co-workers[12] introduced an efficient method for the generation of *o*-QM from *ortho*-methyleneacetoxy phenols that was used for the biomimetic synthesis of (±)-alboatrin (Scheme 1). Alboatrin **1** is a phytotoxic natural product, and its biosynthesis has been realized through hetero Diels–Alder reaction of an orcinol derived *o*-quinone methide **2** and (*R*)-4,5-dihydro-2,4-dimethylfuran **3**.

Baldwin assumed that dehydration of the corresponding hydroxymethyl orcinol derivative **4** would give *o*-QM. Compound **4** was obtained by the reduction of precursor **6b**, which was found to be unstable and rapidly decomposed under the reaction conditions. Then a diacetate **5** was prepared, which was reduced to its alcohol and consequently underwent transesterification by itself to give an *ortho*-methyleneacetoxy phenol **6a** under thermal conditions (Scheme 2). Subsequently, simple heating of **6a** in the presence of dimethylfuran **3** afforded acetylalboatrin **7** as the major product (63%), acetyl *epi*-alboatrin (5%), and an inseparable mixture of diastereoisomers **8** (25%). Deacylation of **7** yielded the desired (±)-alboatrin, for which



Scheme 1 Retrosynthesis of Alboatrin.



Scheme 2 Synthesis of acetylated (±)-alboatrin (**7**).

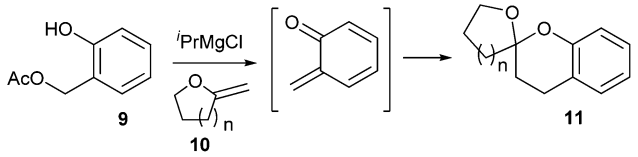
spectral data was found to be identical to the natural (±)-alboatrin. Intramolecular hydrogen bonding might facilitate the elimination of acetic acid upon heating through a six-member transition state, furnishing the *o*-quinone methide.

Christopher D. Bray[13] reported the generation of *o*-QM from deprotonation of *ortho*-hydroxybenzyl acetate **9** with ^{i}PrMgCl under mild anionic reaction conditions, which reacts with *exo*-enol ethers **10** as 2π partners in hetero Diels–Alder (HDA) reactions, furnishing *mono*-benzannelated spiroketals **11** (Scheme 3). This rapid and simple strategy is clearly applicable to the synthesis of a wide range of natural products, including berkelic acid, chaetoquadrin A and cephalostatin.

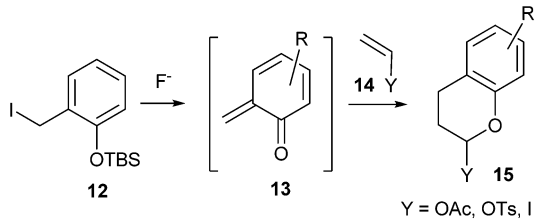
Rosellon and co-workers[14] developed a method for the generation of *ortho*-quinone methides **13** *via* fluoride-induced desilylation of silyl derivatives of *o*-hydroxybenzyl iodides **12** under mild experimental conditions (Scheme 4).

Dolatowska and Wojciechowski[15] reported the thermal extrusion of sulfur dioxide from 1,3-dihydrobenzo[*c*]thiophene-2,2-dioxides **16a** and 1,3-dihydro-2,1-benzisothiazole-2,2-dioxides **16b** to generate the corresponding quinodimethanes **17a** and quinonemethyleneimines **17b**, which undergo Diels–Alder reaction with alkene **18** to give the compound **19** (Scheme 5).

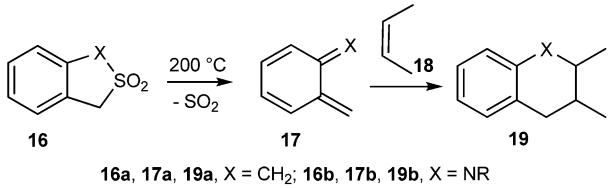
The sultone of 2-hydroxytoluene-α-sulfonic acid **20** after extrusion of SO_2 upon photochemical irradiation gave *o*-quinone methide **21**, which upon reaction with *N*-phenyl maleimides **22** afforded the respective adducts **23** (Scheme 6).



Scheme 3 Generation of *o*-QM using *o*-hydroxybenzyl acetate and ^{i}PrMgCl.



Scheme 4 Formation of *o*-QMs *via* fluoride-induced desilylation.



Scheme 5 Generation of *o*-QMs **17** by thermal extrusion of sulfur dioxide.

Ohwada and co-workers[16] reported a retro-Diels–Alder reaction of 4*H*-1,2-benzoxazines **24** to generate *o*-QMs **25** under the thermal conditions, which undergoes the Diels–Alder reaction with vinyloxy cyclohexane **26** to afford the chroman derivative **27** (Scheme 7). They also presented a mechanistic study of the retro Diels–Alder reaction of benzoxazines **24** with various substituted benzene rings. In general, *o*-QMs are too unstable to be isolated and observed spectroscopically, unless they are trapped with metal complexes such as Cp*Ir. In all the previously reported methods, *o*-QMs were generated *in situ*, and underwent 1,4-conjugate addition with nucleophiles or cycloaddition reaction with suitable dienophiles.

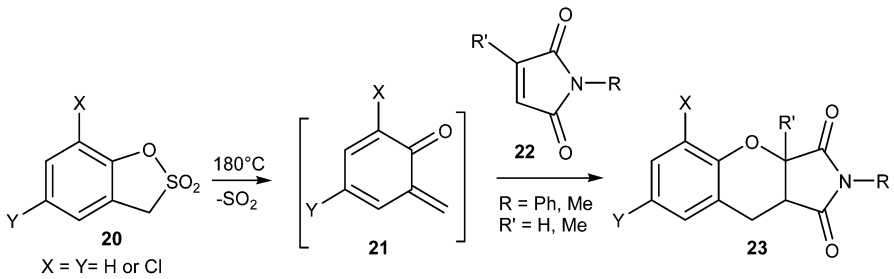
o-QMs may be generated through a diverse range of initiation methodologies (Scheme 8). Perhaps the most commonly encountered method for the generation of *o*-QM is the elimination of a stable molecule, typically a benzylic substituent, to generate the methylene and α-carbonyl functionalities with concomitant dearomatisation. Various precursors have been utilized for the thermolytic generation of *ortho*-quinone methides. It should be noted that all thermal generation techniques preclude the application of nucleophiles that are thermally unstable. With any given precursor, there is a substantial temperature range for initiation that depends upon the substituents. In general, if the process involves significant non-bonded interactions, then the temperature requirements are higher, while extended conjugation or other stabilizing factors lower the overall temperature requirements (Scheme 8).

2.2. Photochemical generation

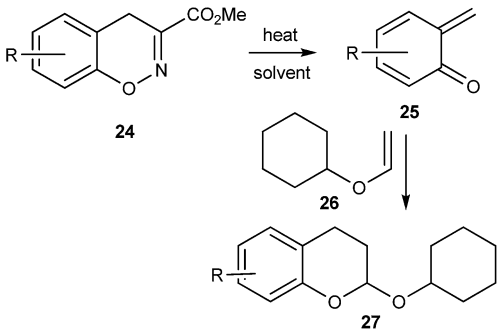
Apart from the thermal generation of *o*-QM intermediates in the presence of different basic or acidic reagents, photochemical energy sources have also been extensively used to generate *o*-QMs. In general, *o*-QM intermediate **29** is generated by light-induced water elimination from *ortho*-hydroxybenzyl alcohols **28** or by excited state intramolecular proton transfer (ESIPT) in *ortho*-hydroxystyrenes **30** (Scheme 9).

The majority of β-cyclodextrin inclusion complexes undergo photohydration of the olefin, preventing the formation of *o*-QM by insertion of a methylene group between the phenol and the olefin moieties. Miranda *et al.*[17] reported the formation of an *o*-QM *via* C–C fragmentation of a zwitterion formed by excited state intramolecular proton transfer (ESIPT) from an *ortho*-allylphenol derivative **31**, for the first time (Scheme 10). The mechanism has been explained in terms of the formation of the zwitterionic intermediate **32A** by the initial ESIPT from the phenolic subunit to the double bond. Thus, subsequent C–C bond formation with concomitant ring opening elucidates the generation of the *o*-QM **32B**, which would be trapped by solvent methanol to give compound **33**. The direct involvement of an *o*-QM intermediate has been confirmed by laser flash photolysis. Use of 266 nm excitation wavelengths in acetonitrile solvent gave a well defined signal with two maxima around 300 and 400 nm.

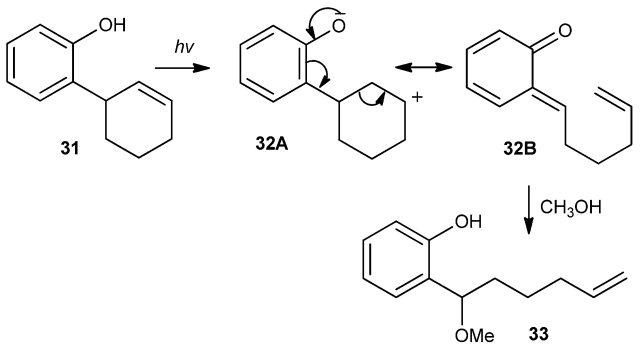
Generation of *o*-QM by flash photolysis of *ortho*-hydroxybenzyl substrates **34** in aqueous solution has also been reported (Scheme 11). Hydrogen-ion catalyzed hydration of *o*-QM



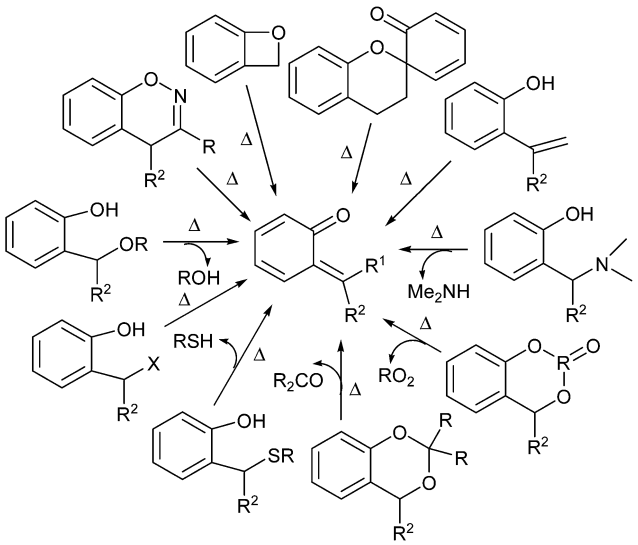
Scheme 6 Generation of *o*-QM from benzosultones.



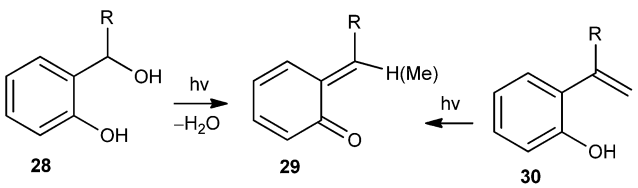
Scheme 7 Formation of *o*-QM *via* retro-Diels–Alder reaction of 4*H*-1,2-benzoxazines **24**.



Scheme 10 Generation of *o*-QM *via* C–C fragmentation of zwitterions.



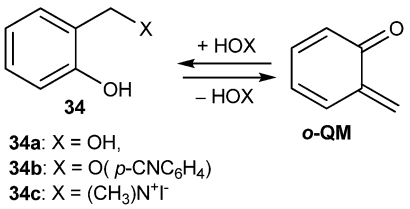
Scheme 8 Thermal generation of *o*-QMs.



Scheme 9 Photochemical generation of *o*-QMs.

furnished back to the *ortho*-hydroxybenzyl alcohol, which was anticipated to ensue through the initial fast equilibrium protonation of the carbonyl oxygen followed by trapping with water. The slower uncatalyzed hydration proceeds through nucleophilic attack of water on the QM methylene group.[18]

o-Quinone α-phenylmethide was produced as a short-lived transient species in aqueous solution by flash photolysis of *ortho*-hydroxy-α-phenylbenzyl alcohol, and its rate of decay was measured in $HClO_4$ and NaOH solutions as well as in CH_3CO_2H, $H_2PO_4^-$, and HCO_3^- buffers. Results showed that the hydration of quinone methide back to its benzyl alcohol precursor occurs by acid-, base-, and un-catalyzed routes. Kresge and co-workers[19] reported the generation of *o*-QMs **35** and **36** by photo-dehydration of the corresponding *ortho*-hydroxybenzyl alcohols **37** and **38**. *ortho*-Hydroxybenzyl-*p*-cyanophenyl ether **39** after photo-cleavage gave *o*-QMs **36** (Fig. 4). Flash photolytic techniques have been used to monitor the progress of the reactions because the reactions of quinone methides are very fast.



Scheme 11 Flash photolysis of *o*-hydroxybenzyl substrate **34** to give *o*-QM.

Lukeman and Wan[20] observed predominate D_2O exchange at the 2′-position irrespective of D_2O (MeOD) content during the study of the photochemical incorporation of deuterium on phenylphenol **40** in D_2O (CH_3OD)–CH_3CN solutions with varying D_2O (CH_3OD) content. Exchange at the 2′-position (but not at the 4′-position) was observed when crystalline samples of compound **40** (deuterated OH *i.e.* OD) were irradiated (Scheme 12).

No deuterium exchange was observed in case of compounds **49–52**, whereas 2,2′-biphenol **48** underwent similar photo-exchange reaction as compound **40** (Fig. 5).

Wan and co-workers[21] reported the generation of quinone methide **54** by ESIPT, in which naphthyl group acts as the proton acceptor (Scheme 13). The reaction has been carried out in a variety of solvents, as well as in the solid state, illustrating that the proton transfer is intrinsic (proton transfer does not require water).

Zhan and co-workers[22] have reported the generation of *o*-thioquinone methide **59** by flash photolysis of benzothiete **58** in aqueous medium (Scheme 14). The hydration rates of the quinone methide **59** to *ortho*-mercaptobenzyl alcohol **60** were measured in perchloric acid solution using H_2O and D_2O as the solvent in acetic acid in the presence of tris(hydroxymethyl) methylammonium ion buffers.

The solvent isotope effects on hydronium-ion catalysis of hydration for the two substrates are different. Solvent isotopic

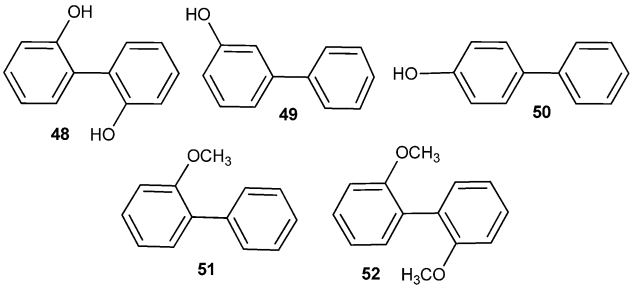
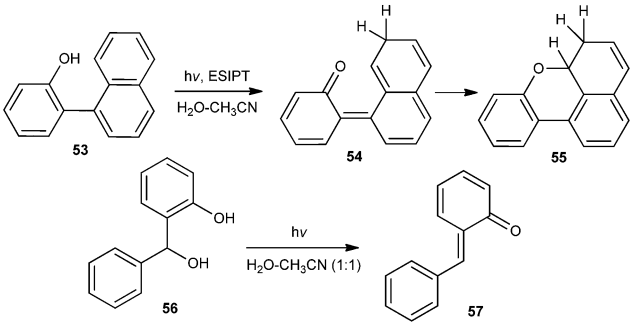


Fig. 5 Structure of compounds which do not undergo deuterium exchange.



Scheme 13 Generation of *o*-QM by ESIPT.

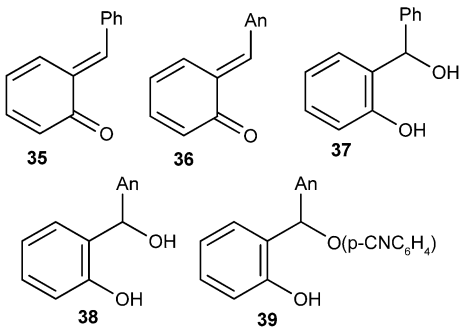
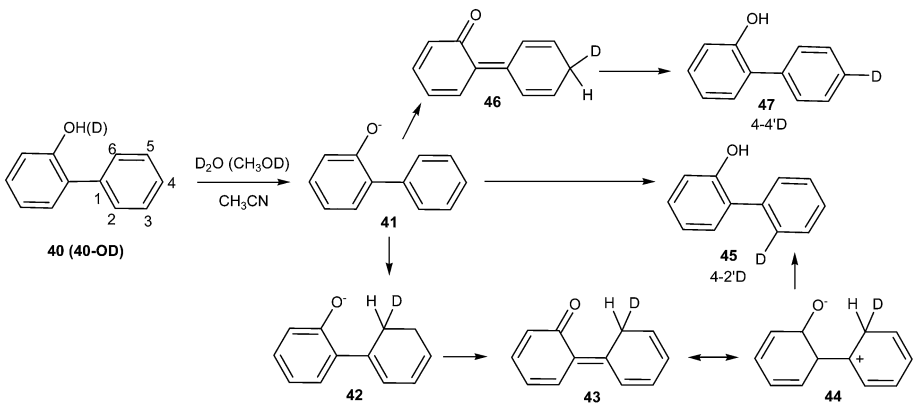


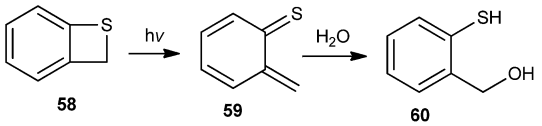
Fig. 4 Structures of *o*-hydroxybenzyl alcohols and their photo-dehydrated *o*-QMs.

effect for the oxygen quinone methide **61** is $k_H/k_D = 0.42$, whereas for the sulfur substrate **59** is $k_H/k_D = 1.66$. The inverse isotope effect ($k_H/k_D < 1$) in the oxygen containing system specifies pre-equilibrium proton-transfer reaction mechanism by which protonation of the substrate on its oxygen atom being fast and reversible, and capture of the benzyl-type carbocationic intermediate is observed. On the other hand, the normal isotope effect ($k_H/k_D > 1$) in the sulfur system indicates that the protonation of the substrate on its sulfur atom is rate-determining and carbocation capture is fast (Scheme 15).

Matsumoto and co-workers[23] reported that the thermal and photochemical generation of *o*-QM was accelerated by the presence of water molecules in the reaction solvents *via* the



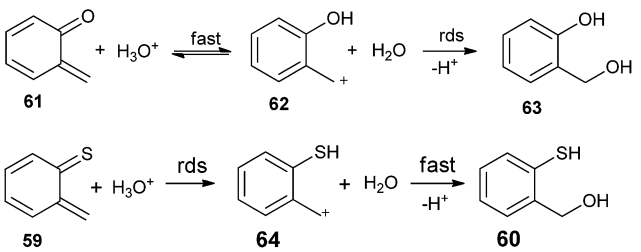
Scheme 12 Photochemical incorporation of deuterium on phenylphenol.



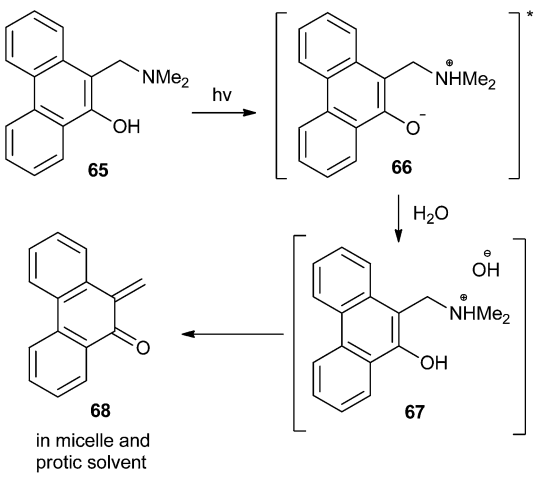
Scheme 14 Generation of *o*-thioquinone methide **59**.

formation of anionic micelles and vesicles. According to their report, amino phenanthrol **65** and their naphthalene analogues act as precursors and transforms to QM **68** in the presence of light (Scheme 16).

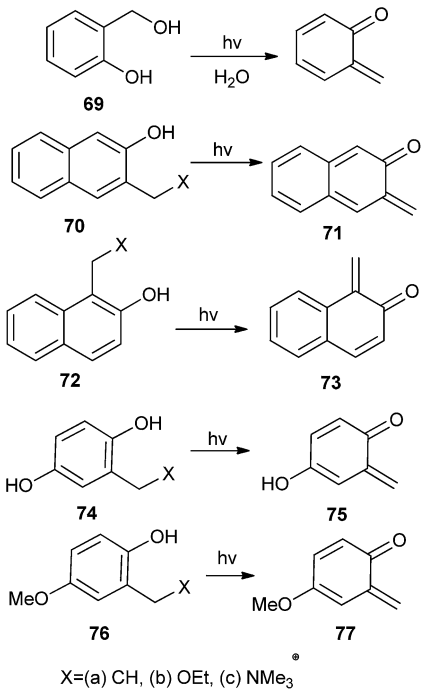
Popik and Arumugam[24] reported the efficient generation of quinone methide from 2-hydroxymethyl phenol **69**. Isomeric 3-hydroxy-2-naphthalenemethanol **70** and 2-hydroxy-1-naphthalenemethanol **72** resulted the respective naphthaquinone methides, 2,3-naphthoquinone-3-methide **71** and 1,2-naphthoquinone-1-methide **73** (Scheme 17). During the generation of *ortho*-naphthaquinone methides (*o*-NQMs) **71** and **73** in the flash photolysis of ammonium precursors **70c** and **72c** ensues within the duration of a laser pulse, irradiation of **70a** and **72a** as well as their ethoxy derivatives **70b** and **71b** provides evidence for the detection of a kinetic precursor to *o*-NQMs. The rate of formation of *o*-NQMs does not depend on the pH of the solution. Furthermore, the generation of cyclohexadienone **75**



Scheme 15 Solvent isotope effects on *o*-QM and *o*-thioquinone methide.



Scheme 16 Generation of QMs by the formation of anionic micelle and vesicle.

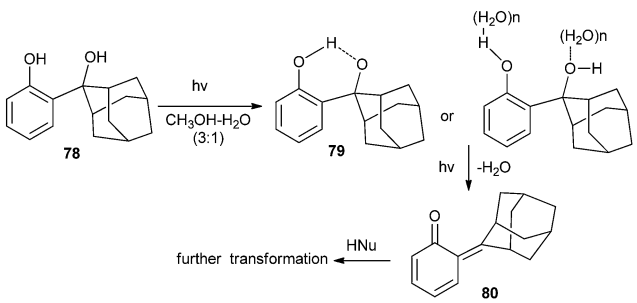


Scheme 17 Generation of *o*-QM by using phenolic derivatives.

and **76** by the photochemical irradiation of three different precursors **74a–c** and **76a–c** have been reported (Scheme 17).

Wan and co-workers[25] tactically substituted the hydroxymethyl phenols with 2-hydroxy-2-adamantyl moiety and explored their photochemical reactivity. Upon the excitation of AdPh derivative **78** to its singlet excited state, it undergoes a intramolecular proton transfer at first, followed by the loss of H_2O to give quinone methide **80**, which has been detected by laser flash photolysis (CH_3CN–H_2O 1 : 1, $\tau = 0.55$ s) and UV-vis spectroscopy (Scheme 18). The quantum yield of QM formation has been increased by three fold, and the lifetime is enhanced by the introduction of the adamantyl substituent on the *ortho*-hydroxymethyl phenol moiety.

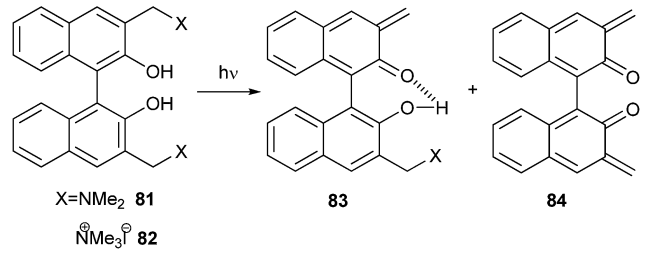
Freccero and co-workers[26] reported the photogeneration of new Binol quinone methides **83** and **84**. They also explored mono- and bisalkylation of free nucleophiles by product distribution analysis and laser flash photolysis in water solution using Binol quaternary ammonium derivatives **81** and **82** as photoactivated precursors (Scheme 19).



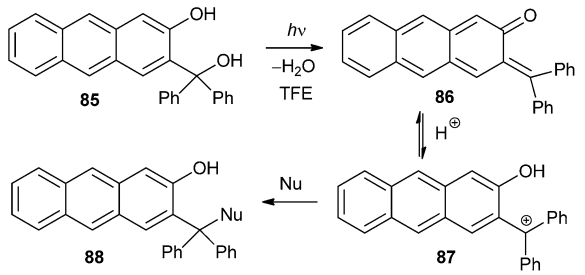
Scheme 18 Formation of adamantyl substituted *o*-QM **80**.

Excitation of anthracene derivative **85** to S_1 initiates photodehydration giving the corresponding quinone methide **86** that was detected by laser flash photolysis (LFP) in 2,2,2-trifluoroethanol.[27] The QM decays by protonation giving a cation **87**, which subsequently reacts with nucleophiles to give compound **88** (Scheme 20). QMs of the anthrol series is important for its potential use in biological systems because the chromophore absorbs at wavelengths > 400 nm. Anti-proliferative investigations conducted with 2-anthrol derivative **85** on three human cancer cell lines showed higher activity for irradiated cells.

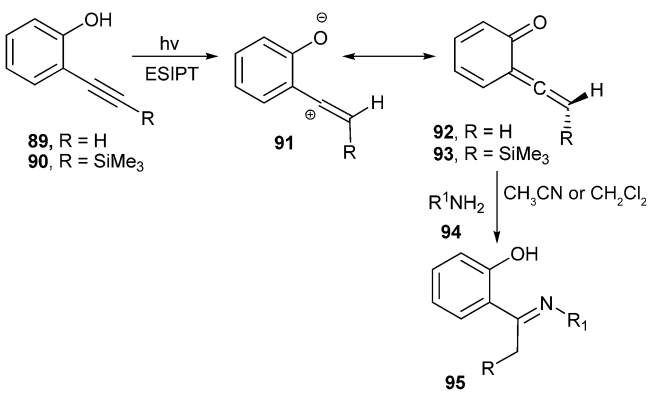
The vinylidene-quinone methides **92** and **93** were generated by irradiation of 2-alkynylphenols **89** and **90**, respectively, which were detected by laser flash photolysis in organic solvents and aqueous acetonitrile (Scheme 21).[28] It was also shown that the UV-vis properties and the electrophilicity are enhanced by a β-silicon effect and solvent polarity.



Scheme 19 Photochemical generation of binol quinone methide.



Scheme 20 Formation of QM by photodehydration of hydroxylated anthracene.



Scheme 21 Photochemical generation of vinylidene-QMs.

3. Reactions of *ortho*-quinone methides

The transient nature of *ortho*-quinone methides is due to their propensity to undergo rapid rearomatisation, either by the Michael addition of nucleophiles or often more usefully by the cycloaddition with 2π partners or *via* oxa-6π-electrocyclisation. Surprisingly, this rapid reactivity was historically seen as a deterent to synthetic development in the field, with the potential for dimerisation and trimerisation sometimes being major stumbling block. To avert this, it is common to employ an excess of the nucleophilic or dieneophilic components and the localized *o*-QM concentration is often kept low.

o-QMs, being labile intermediates, have been stabilized by metal coordination. The examples of simple isolated quinone methides are rare. In fact, in condensed phases, the parent compound has only been characterized spectroscopically at lower temperatures because it is extremely reactive. Spectroscopic evidence of the zwitterionic form of the *o*-QM derived from vitamin E has only been possible at −78 °C, through the stabilization by interaction with *N*-methylmorpholine *N*-oxide. These results show how difficult it is to isolate quinone methides. *para*-Quinone methides have been discussed as intermediates in the chemistry of lignins and have been used in organic synthesis as electrophiles or electron acceptors. Because the parent *o*-QM molecule is unstable, NMR spectroscopic data are not available. Therefore, the metalated parent *ortho*-quinone methide complex was examined using two-dimensional NMR spectroscopic techniques to understand its structure and reactivity. *o*-QMs are also believed to be key intermediates in the action of several antitumor and antibiotic drugs.

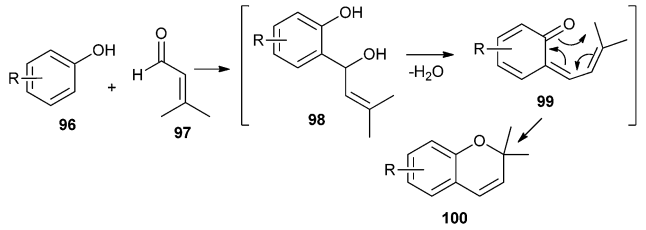
3.1. Electrocyclisation and cycloadditions

3.1.1. [4 + 2] electrocyclisation and cycloadditions. Baldwin and Adler[29] have reported a proficient process for the synthesis of 2,2-dimethyl-2*H*-chromenes in a single step from the corresponding phenol and 3-methyl-2-butenal *via* microwave irradiation in $CDCl_3$. These reactions generated a transient *o*-QM intermediate **99**, which upon *in situ* electrocyclization gave the final bicyclic chromenes **100** in good yields (Scheme 22).

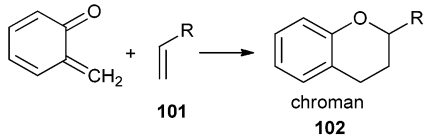
ortho-Quinone methides are versatile intermediates involving a minimum of seven carbon atoms, which are mainly involved in 1,4-Michael type additions as well as aza-Michael reactions with various nucleophiles. *o*-QMs also give Diels–Alder and hetero-Diels–Alder cycloaddition products (Scheme 23). *o*-QM especially derived from 4-hydroxycoumarin undergo [4 + 2] cycloaddition reaction with penta-fulvenes to afford pyranocoumarin and pyranopyrone.[30]

Ploypradith *et al.*[31] reported the generation of *o*-QMs by the reaction of compound **103** with *p*-TsOH on silica. Hetero Diels–Alder (HDA) reaction of *in situ* generated *o*-QMs **104** with styrenes **105** and **106** gave the corresponding arylchromans **107** and **108** in good yields (Scheme 24).

Sajiki and co-workers[32] established a $FeCl_3$-catalyzed method for the synthesis of 1-naphthoquinone-2-methides **112a** from dihydronaphthalenes **109** and further transformation of the



Scheme 22 Synthesis of chromenes *via* electrocyclization of *o*-QMs.

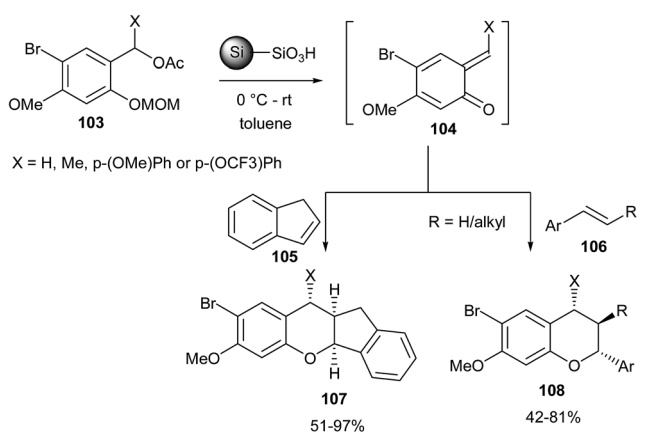


Scheme 23 Reactivity of *ortho*-quinone methide with alkenes.

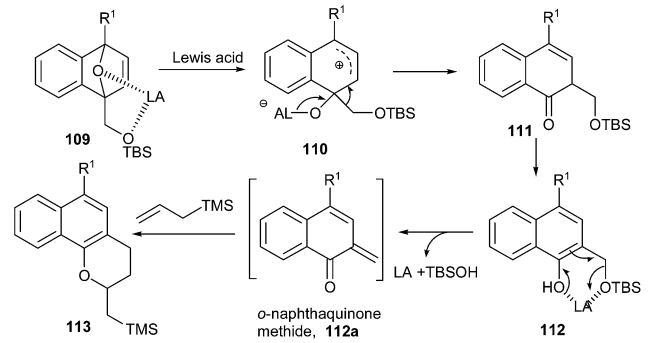
products in an annulation reaction with various allyl silanes to afford biologically useful dihydronaphthopyran derivatives. The annulation can proceed *via* an *o*-NQM intermediate. The site-selective cleavage of one C=O bond is promoted by the coordination of the two oxygen atoms of **109** to the Lewis acid to give a five-member ring, which is then cleaved to give the zwitterionic intermediate **110**. Subsequent migration of the siloxymethyl group (–CH_2OTBS) and aromatization provides the 2-siloxymethyl-1-naphthol **112**. Further, Lewis acid induced elimination of the silanol (TBSOH) leads to an *o*-NQM **112a**, which undergoes annulation with allyl-TMS through a hetero-Diels–Alder reaction to furnish **113** (Scheme 25).

Lindsley *et al.*[33] reported the total synthesis of polemannones B **114** and C **115**, which are highly oxygenated benzoxanthenones derived from *Polemannia montana*, by employing a catalytic Cu(II)/sparteine oxidant system for β,β-phenolic couplings and cascade Diels–Alder reaction by tandem inverse-electron demand, producing 75–90% yield (Fig. 6).

The polemannones are unique because there is an extra electron donating ether moiety. Compounds containing



Scheme 24 Acid-catalysed generation of *o*-QMs and their HDA reaction with styrenes.



Scheme 25 $FeCl_3$-catalyzed synthesis of 1-naphthoquinone-2-methides.

electron-donating ether moieties *para* to the phenol, such as **116**, stabilize the *o*-QM intermediate and provide the 'push' in the inverse-electron demand in the Diels–Alder reaction during the synthesis of **118** *via* *o*-QM **117** (Scheme 26). If two electron-donating ether moieties are present, the second one is always located at *meta* to the phenol.

But exceptionally, it is interesting that the *o*-methoxy group, as in **119**, equally stabilizes the *o*-QM intermediate and provides the 'push' in the inverse electron demand in the Diels–Alder reaction to provide the unnatural benzoxanthenone **121** (Scheme 27).

Jha and co-workers[34] reported the synthesis of naphthopyrans **133** from 2-naphthol **129**, a secondary amine **124**, and 3-hydroxy-2,2-dialkylpropanal **122** in the presence of a catalytic amount of *p*-toluenesulfonic acid. This reaction is a one-pot

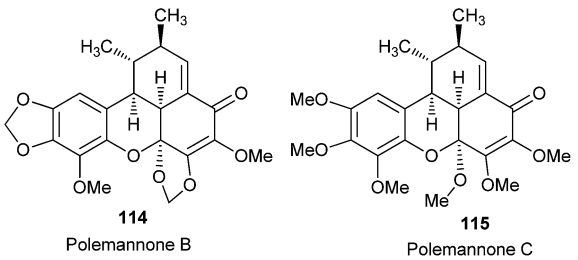
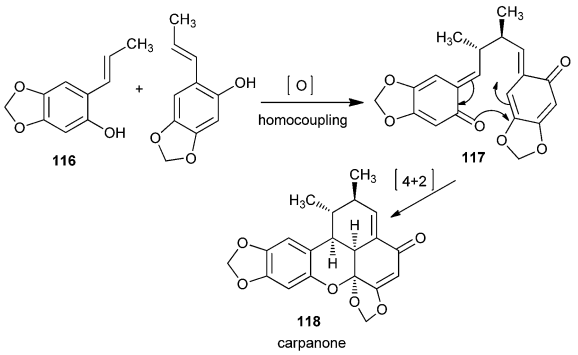


Fig. 6 Structure of polemannones.



Scheme 26 Synthesis of carpanone *via* electrocyclization of *o*-QM **117**.

retro–aldol disintegration of 3-hydroxy-2,2-dialkylpropanal followed by formation of a Mannich base intermediate **130** from 2-naphthol, a secondary amine, and formaldehyde (retro–aldol product). The Mannich base undergoes disproportionation to give a QM intermediate **132** and a secondary amine. Compound **125** reacts with amine **124** to generate enamine **128**. QM intermediate undergoes electrocyclization with enamines to generate the final product **133** (Scheme 28).

3,3-Dialkyl-2-morpholino-3,4-dihydro-2*H*-naphtho[1,2-*b*]-pyrans **137** were synthesized by the reaction of 1-naphthol **134**, morpholine **135** and compound **136** in the presence of a catalytic amount of *p*-TSA (Scheme 29).

Lee *et al.*[35] have reported an efficient one-pot approach for the synthesis of benzopyranobenzo pyrans and naphthopyranobenzo pyrans. Resorcinol and naphthols undergo a domino aldol type reaction followed by a hetero Diels–Alder reaction with the benzaldehyde. The reaction of compound **139** with resorcinol **140** in the presence of ethylenediamine diacetate (EDDA)/TEA first gives intermediate **141** as an aldol-type product. TEA promoted the dehydration of intermediate **141** to form quinone methides **142a** and **142b**. Because of a sp^2-geminal effect, the endo-transition structure **142b** may be more favourable than the *exo*-transition structure **142a** due to the 1,3-allylic strain. The regiospecificity is attributed to the products **143a** and **143b** due to possibility of hydrogen bonding between the hydroxyl group and carbonyl group (Scheme 30).

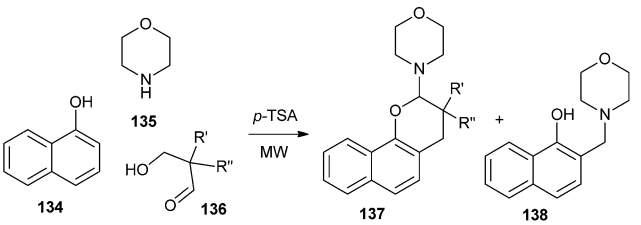
ortho-Quinone methide **147** arising from a formal [2 + 2] cycloaddition between aryne **144** and DMF was found to undergo a [4 + 2] cycloaddition with ester enolate **148** or ketenimine anion to produce diverse coumarins **150** (Scheme 31).[36]

Silver oxide-mediated oxidation of phenol substrates **151** for the synthesis of *o*-QMs **152** has been developed by Lei *et al.*[37] for the biomimetic syntheses of novel trimeric natural products, (±)-schefflone and tocopherol trimers **153** (Scheme 32).

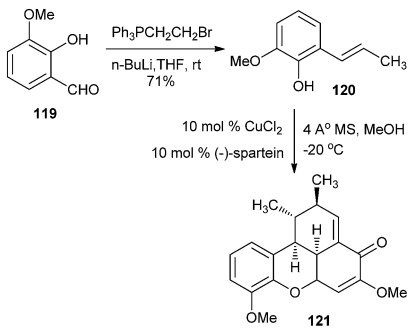
Bharate and Singh[38] have reported the synthesis of antimalarial robustadials A and B **159** starting from the commercially accessible phloroglucinol. A biomimetic three-component reaction that involves the *in situ* generation of an *o*-QM *via* the Knoevenagel condensation followed by the Diels–Alder cycloaddition with (−)-β-pinene **157** gave robustadials A and B. A retrosynthetic pathway is shown in Scheme 33.

Robustadials A and B have been anticipated to be formed biogenetically from the Diels–Alder cycloaddition of *o*-QM **158** with (−)-β-pinene **157**. The key intermediate *o*-QM **158** could be generated by the oxidation of diformylated synthon **154** or by the coupling of phenol **155** and aldehyde **156** *via* a Knoevenagel condensation (Scheme 34).

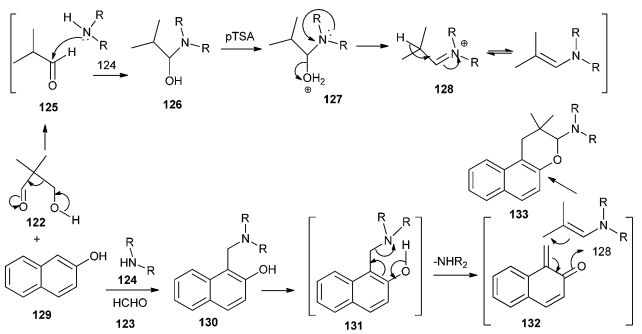
The treatment of **155** with **156** and (−)-β-pinene **157** in the presence of sodium acetate in acetic acid under microwave irradiation (1000 W) for 4 min resulted in the formation of the



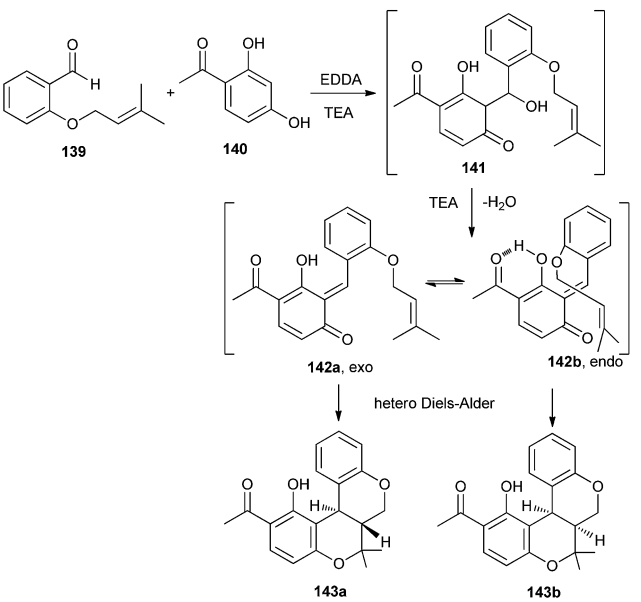
Scheme 29 Synthesis of naphtho fused pyrans *via* *o*-QM.



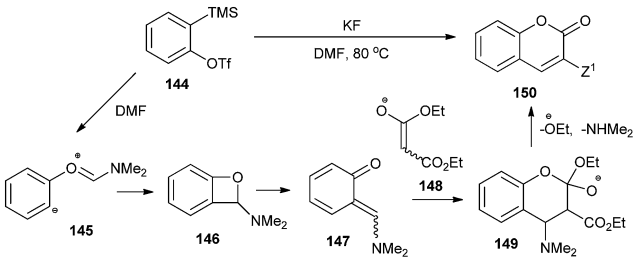
Scheme 27 Synthesis of benzoxanthenone **121**.



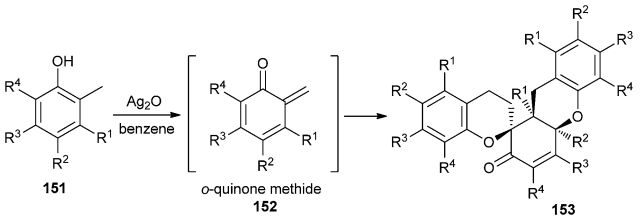
Scheme 28 Synthesis of naphtha pyrans **133** *via* electrocyclization of *o*-QM with enamines.



Scheme 30 Synthesis of benzopyranobenzo pyrans and naphthopyranobenzo pyrans.



Scheme 31 [4 + 2] Cycloaddition of *o*-QM with ester enolate.

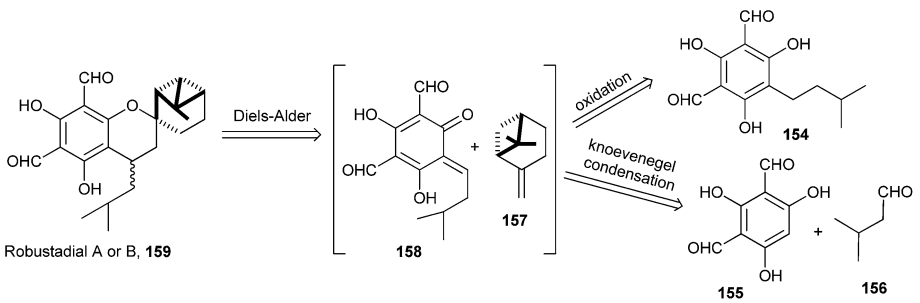


Scheme 32 Silver oxide-mediated generation of *o*-QM for the synthesis of tocopherol trimers.

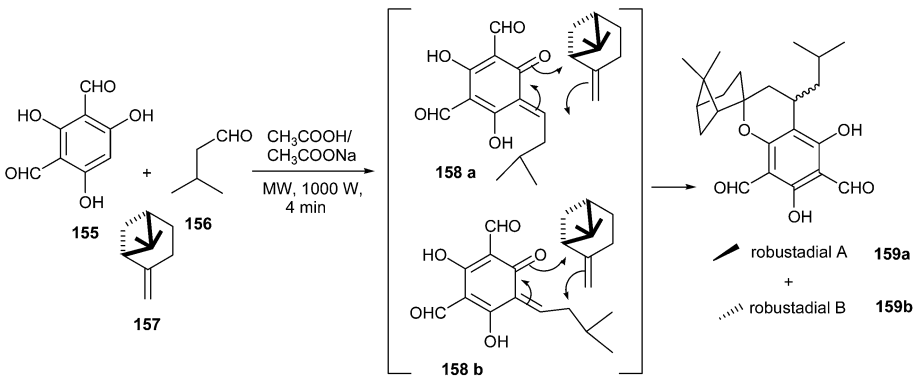
desired products in a combined yield of 68% (Scheme 34). Similar results were obtained when the reaction was carried out under conventional heating at 80 °C for 2 h. The *o*-QM **158** is produced *in situ* by the addition of phloroglucinol **155** with isovaleraldehyde **156** followed by dehydration (Knoevenagel-like condensation). Then **157** can undergo the cycloaddition reaction with *o*-QM **158a** and **158b** *via* two different orientations, and each can lead to two pairs of diastereoisomers **159a** and **159b**. The formation of two isomers is attributed to the attack of the oxygen of the QM only to the more substituted terminus of the pinene double bond (Scheme 34).

The biosynthesis of the meroterpenoid guajadial **163** has been achieved *via* the hetero-Diels–Alder reaction between caryophyllene **160** and an *o*-QM.[39] Biomimetic synthesis of guajadial **163** and psidial A **164** involved a three-component coupling reaction between caryophyllene **160**, benzaldehyde **161**, and diformylphloroglucinol **162** in an aqueous medium (Scheme 35). It has been envisaged that the relative stereochemistry of guajadial **163** would be partly controlled by the conformation of caryophyllene **160** during the hetero-Diels–Alder reaction. The essential *o*-QM **165** could be derived retrosynthetically from a simple Knoevenagel condensation between diformylphloroglucinol **162** and benzaldehyde **161**. Consequently, a domino three-component one-pot reaction between diformylphloroglucinol **162**, benzaldehyde **161**, and caryophyllene **160** constituted a simple biomimetic synthesis of guajadial **163**.

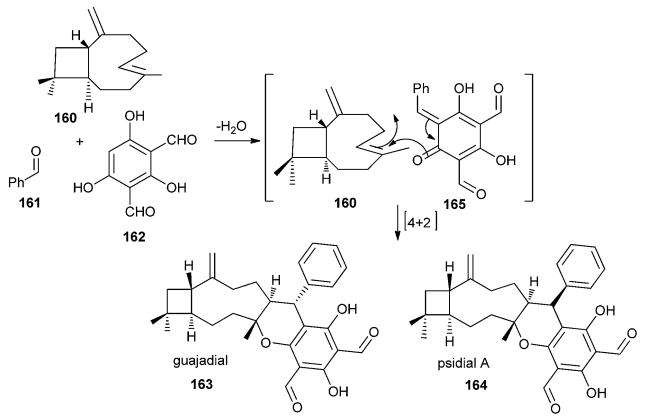
The intermolecular Diels–Alder reactions between *o*-QMs and double bonds that are not electron-rich are known to be difficult to achieve due to the easy dimerization of the *o*-QMs, which in turn accounts for the novelty and efficiency of the protocol. Caryophyllene **160** possesses a certain degree of conformational mobility; therefore, it was not certain how this flexibility would influence the facial bias in the *in vitro* hetero-Diels–Alder reaction. And from ^{13}C NMR studies and molecular mechanics calculations, we came to know that caryophyllene



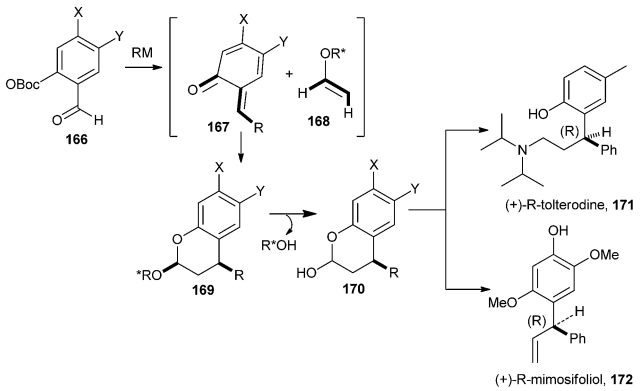
Scheme 33 Retro-synthesis of Robustadials A and B.



Scheme 34 Synthesis of Robustadials A and B.



Scheme 35 Synthesis of the guajadial and psidial A.



Scheme 37 Synthesis of (+)-mimosifoliol.

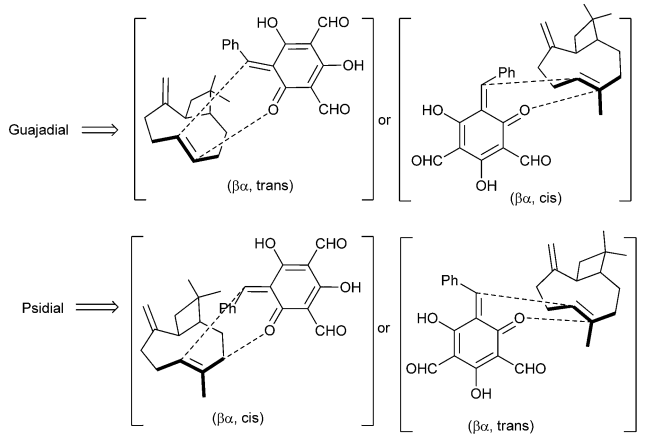
has four possible conformations (ααo αβo βα, ββ), which vary according to the relative nature of the exocyclic methylene and olefinic methyl groups. It has been considered that the proposed biogenetic hetero-Diels–Alder reaction must involve the βα conformer (the most stable conformer) of caryophyllene **160** with proposed transition states (Scheme 36). The stereo chemical upshot of the hetero-Diels–Alder reaction was mainly controlled by the local conformation and intrinsic chirality of caryophyllene **160**.

An enantioselective cycloaddition of an *o*-QM **167** with a chiral enol ether **168** was reported for the first time by Selenski and Pettus,[40] and it has been portrayed along with the formal synthesis of (+)-tolterodine **171** and the total synthesis of (+)-mimosifoliol **172**, as shown in Scheme 37. These syntheses demonstrate a three-component one-pot benzopyran approach for the construction of chiral benzylic junctions. A low-temperature anionic method for *o*-QM generation was achieved in high *endo*/*exo* ratios for ensuing cycloadditions.[41]

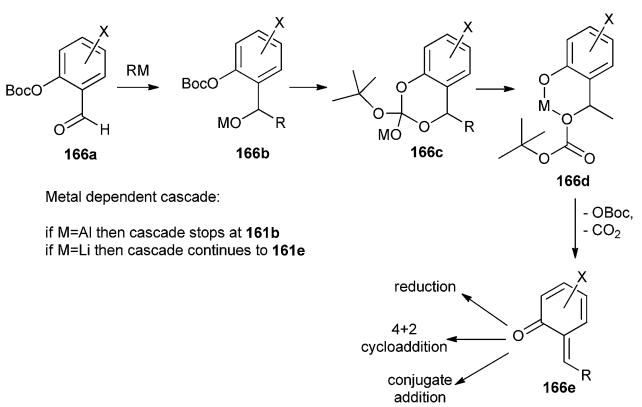
o-QM generation results from a series of events called the *o*-QM cascade. The cascade began with the nucleophilic addition of an organometallic reagent to an OBoc salicylaldehyde **166a**. The consequential benzyloxy anion **166b** attacks the OBoc carbonate to form a cyclic intermediate **166c**, which then disintegrates to form a more stable phenoxide **166d**. Within particular conditions, the β-elimination of the OBoc residue generates an *o*-QM **166e**, as shown in Scheme 38. The cascade invasion is both metal and temperature dependent and presumably represents the strength of the oxygen-metal bond and the electrophilicity of the metal cation, like an aluminium reagent proceeds to intermediate **166b**, whereas a lithium reagent leads to intermediate **166d** and a Mg reagent assists the ultimate conversion to **166e**. The consequential geometry of the *o*-QM olefin is *E*, except for a large group that is situated at the 6-position of the salicylaldehyde.

o-QM in the presence of chiral enol ether addicted in a diastereoselective [4 + 2] cycloaddition. The facial selectivities of enol ethers **173** and **174** through cycloaddition are shown in Scheme 39.

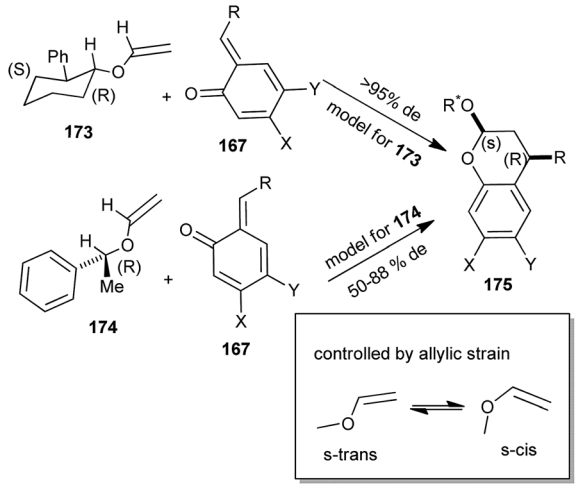
The *syn* affiliation flanked by the phenyl residue of the benzopyran and the oxygen substituent of the acetal results from an *endo* transition state. By taking pseudoallylic strain and Houk's calculation into vindication, the enol ether reacts in the *s-trans* conformation. The *o*-QM endures reaction opposite the methyl residue of enol ether **173** and opposite the phenyl residue of enol ether **174**. The *S*-stereocenter of **173** and the 2*R*-stereocenter of **174** induce the *S*-configuration of the resulting benzyl junction of compound **175** (Scheme 39). The absolute configuration of the chiral enol ether determines the



Scheme 36 Possible conformations of guajadial and psidial A.



Scheme 38 Generation of *o*-QM using anionic method.



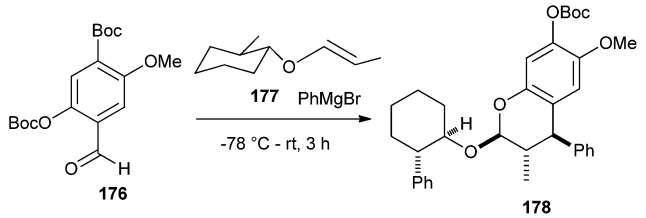
Scheme 39 Cycloaddition reaction of *o*-QM with chiral enol ether.

absolute configuration of the resulting benzopyran. The diastereoselectivity of *trans*-2*S*-phenyl-1*R*-cyclohexanol vinyl ether **174** was outstanding for all the *o*-QMs that ultimately created *R*-mimosifoliol and *R*-tolterodine.[40]

The substituted enol ether **177** should also undergo a diastereoselective cycloaddition. Addition of phenyl Grignard reagent to aldehyde **176** in the presence of enol ether **177** affords benzopyran **178** creating three chiral centers with a 60% yield and 95% de (Scheme 40).

Singh and co-workers[42] have reported the biomimetic synthesis of *S*-Euglobals and their antileishmanial, antimalarial, and antimicrobial activities. Compound **179** was treated with formaldehyde and different terpenes like (+)-2-carene (**182**), (1*R*)-(−)-myrtenol (**183**), and (1*R*)-(−)-nopol (**184**) in the presence of NaOAc in CH_3COOH, resulted in the development of respective pairs of regioisomers, **185** and **186** from 2-carene, **187** and **188** from myrtenol, and **189** and **190** from nopol in good yields. Similarly, treatment of **180** and **181** with formaldehyde and different terpenes in the presence of sodium acetate in acetic acid resulted in the formation of the desired cycloadducts, **191–193** and **194–196**, respectively (Scheme 41).

Singh and co-workers[43] also described the synthesis of new analogues of euglobals **200–203** by a biomimetic approach (Scheme 42). These synthetic compounds differ from natural euglobals in the nature of monoterpene and acyl functionality. Oxidative addition of phloroglucinol-terpene with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in nitromethane gave the corresponding *o*-QM, which further undergoes



Scheme 40 Diastereoselective synthesis of compound **178**.

intermolecular cycloadditions with monoterpenes such as β-pinene **157**, α-pinene **197**, (+)-3-carene **198** and (−)-camphene **199**.

Kucklaendera *et al.*[44] reported 1,4,9,10-anthradiquinone as a precursor for antitumor compounds, according to which the naphtho-condensed indoles **206** were obtained by the reactions of unsubstituted 1,4-anthraquinone **204** with enamines **205** *via* the normal Nenitzescu method. Indoles **206** were converted to Mannich bases followed by dimerization through the Diels–Alder reaction of *o*-QM intermediate **207** to give the compound **208** (Scheme 43). These synthesized heterocyclic compounds were appraised for their anticancer properties in the NCI's human disease oriented *in vitro* anticancer screen.

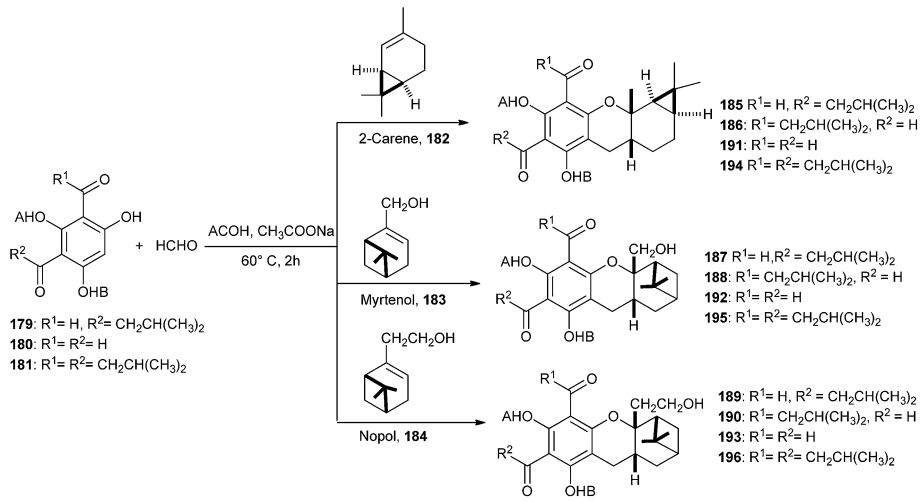
Generation of *o*-QMs by the photolysis of carboxylate derivatives **209** in aqueous acetonitrile was reported by Steinmetz and Chen.[45] The carboxylate leaving groups are swiftly eliminated by photolysis of the 1,4-benzoquinone **209** to produce an *o*-QM intermediate **211** that is trapped by [4 + 2] cycloaddition with unreacted starting material **209** and generated photoadduct **212**. The carboxylate leaving groups are easily expelled upon photocyclisation to benzoxazolines **210** under aqueous conditions (Scheme 44).

Photolysis of 0.02 M solution of compound **209** in a mixture of 30% D_2O and 70% CD_3CN with a 120 W sunlamp formed benzoic acid in 58% yield with a 100% conversion rate, according to ^{1}H NMR spectroscopy. The other photoproduct **212** was formed in 36% yield, which was isolated by chromatography and identified as a 1 : 1 mixture of diastereomers by ^{1}H and ^{13}C NMR spectroscopy.

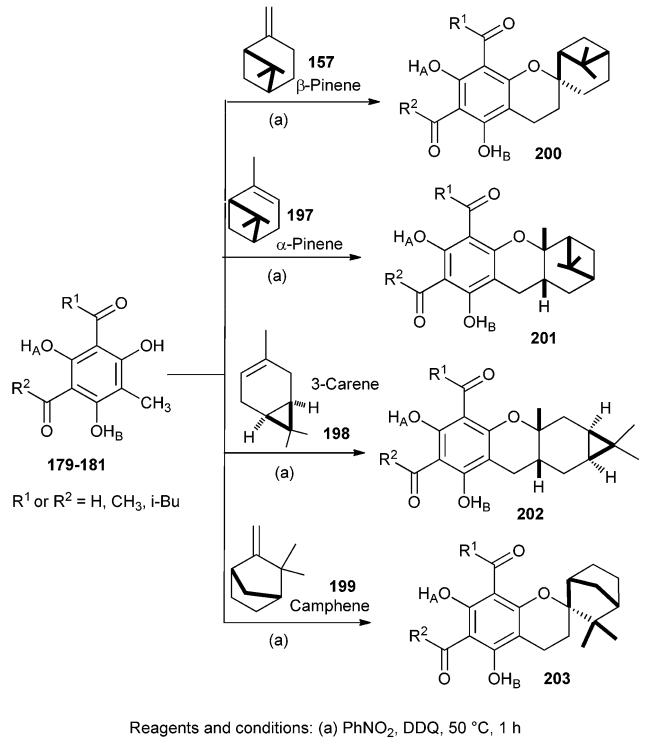
The *o*-QM intermediate **211** has been photolysed with various alkenes. Irradiation of compound **210** (10^{-2} M) with compound **213** (0.1 M) in 30% aqueous CH_3CN produced the cycloadduct **214**. The cycloadduct **214** was produced in 79–87% yields at 100% conversion rates of the reactants (Scheme 45). Other alkene trapping reagents, such as dihydropyran, ethyl vinyl ether, methyl trimethylsilyl dimethylketene acetal, and diethyl fumarate, were inadequately reactive in trapping the *o*-QM, which was deactivated by multiple electron-releasing substituents.

The immediate precursor in the photocyclization to benzoxazoline **210** is zwitterionic in character in ground state as with structure **216**. From photochemistry of α-keto amides it has been shown that intermediates analogous to **216** can cyclize as well as expel phenolate or carboxylate leaving groups (Scheme 46). The mechanism for elimination of carboxylate leaving groups to form *o*-QM **211** is uncertain, because the elimination is possible either from **216** or **210**. No evidence could be obtained to support the direct elimination of carboxylate leaving groups from **216** using nanosecond laser flash photolysis methods.

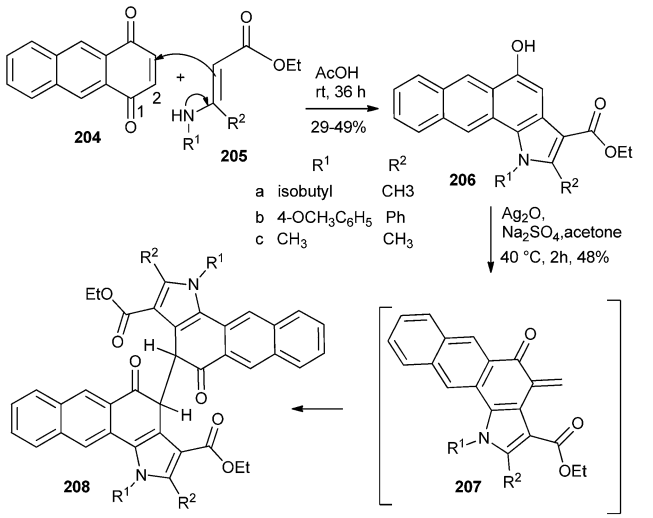
Barrero and co-workers[46] reported the synthesis of bioactive pupehedione derivatives involving a hetero Diels–Alder cycloaddition of *o*-QM, which was generated by the fluoride-induced desilylation of silyl derivatives of *o*-hydroxybenzyl iodides. In this protocol, two variations were investigated. At first, the compound **218** was reacted with dienophiles **219** and **221**, and it was found that the reaction proceeded *via* the formation of **220** and **222**. It has also been revealed that *o*-QMs undergo [4 + 2] cycloadditions with ethers **219** and **221**,



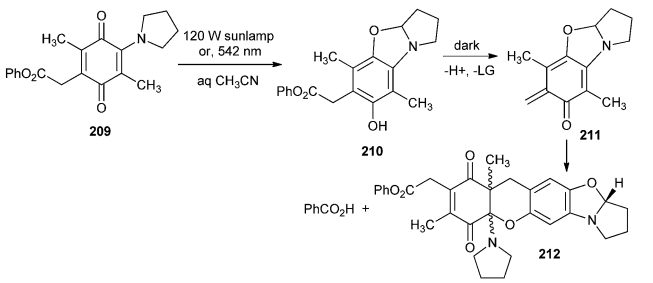
Scheme 41 Biomimetic synthesis of *S*-euglobals.



Scheme 42 Biomimetic synthesis of *S*-euglobals analogues.



Scheme 43 Synthesis of naphtho-condensed indoles.

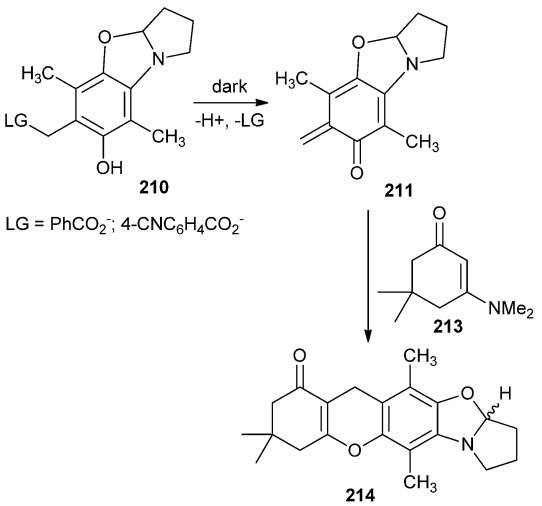


Scheme 44 Synthesis of compound **212** *via* photogenerated *o*-QM.

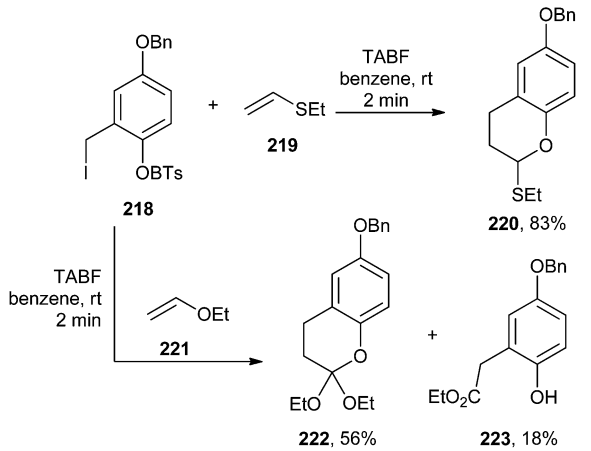
acting as dienophiles during the course of the reaction (Scheme 47).

In the second attempt, variations were introduced to explore the scope of this procedure by using different oxadienic moieties. Thus, *ortho*-silyloxybenzyl iodide, **226** was obtained from commercial 2-hydroxybenzaldehyde **224.** When this compound was treated with ethyl vinyl ether, the reaction proceeded in a similar fashion to give chroman **227** exclusively (Scheme 48).

The unstable 3-methylenepyridin-4-one intermediate **233** has been developed by Baldwin and co-workers[47] by heating the di-Boc-pyridin-4-one derivative **232.** The intermediate **233** undergoes rearomatization followed by the Diels–Alder cycloaddition with activated alkenes to give substituted pyrano[3,2-*c*]-pyridines **234.** The precursor **231** for the synthesis of **234** was obtained from commercially available 4-methoxypyridine **228.** Formylation of **228** gives **229,** which after reduction furnished compound **230** (Scheme 49).



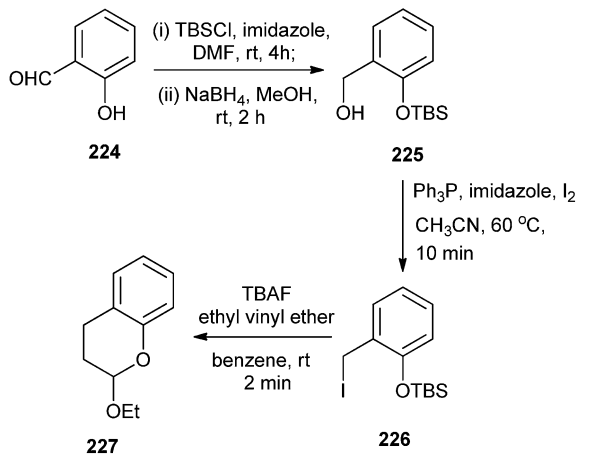
Scheme 45 Photolysis of *o*-QM **211** with alkene.



Scheme 47 [4 + 2] Cycloadditions of *o*-QM with ethers.

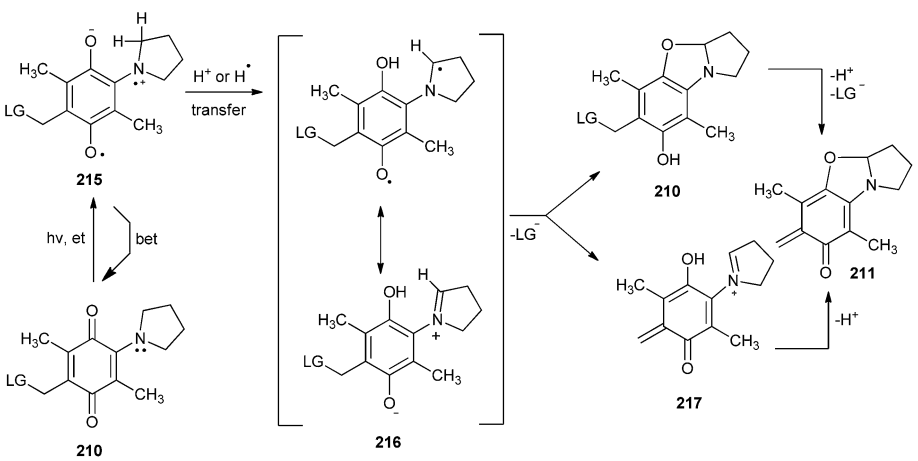
Unusual hetero Diels–Alder reactions between various electron-rich oxazoles and *o*-QMs have been achieved by Lindsey and Pettus.[48] In this case, the *o*-QM intermediate has been generated by deprotonation of either of the *ortho*-OBoc hydroxymethyl aromatic compounds (**240** or **241**, 0.1 M in Et_2O or THF) with *tert*-butyl magnesium bromide, which led to the migration of -OBoc and subsequent β-elimination (Scheme 50). Even though these *o*-QM species are extremely reactive, 4-methyl-oxazole **235** proved futile as a nucleophile. Instead, the *o*-QM intermediate undergoes self-destruction *via* known manifolds such as Diels–Alder dimerization and trimerization. The generation of *o*-QM **243** from compound **241** in the presence of oxazole **237** led to two adducts in a 62% combined yield. In this case, the 1,4-addition product prevails in the mixture and the [4 + 2] cycloadduct **245** arises in small amounts (**1 : 10**, **245 : 246**), as shown in Scheme 50.

Surprisingly, silylated 4-hydroxymethyl oxazole **247** undergoes reaction with *o*-QM **242** to afford a 66% combined yield with a 3 : 1 mixture, favouring the [4 + 2] adduct **249** over the 1,4-conjugate addition product **250**. In addition, the

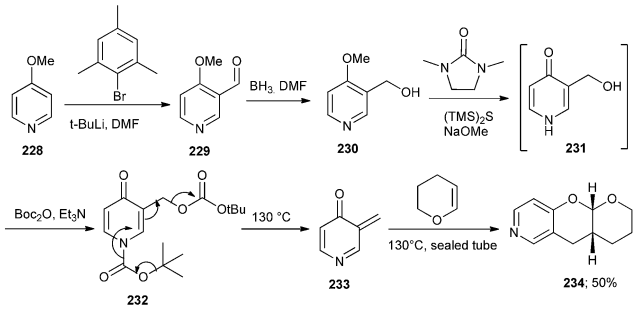


Scheme 48 Synthesis of chroman by the reaction of *o*-QM and ethyl vinyl ether.

carbonate protected 4-hydroxymethyl oxazole **248** undergoes cycloaddition with *o*-QM **243**, affording benzopyran **251** in a 46% yield as the only identifiable product (Scheme 51).



Scheme 46 Mechanistic analysis for the generation of *o*-QM **211**.



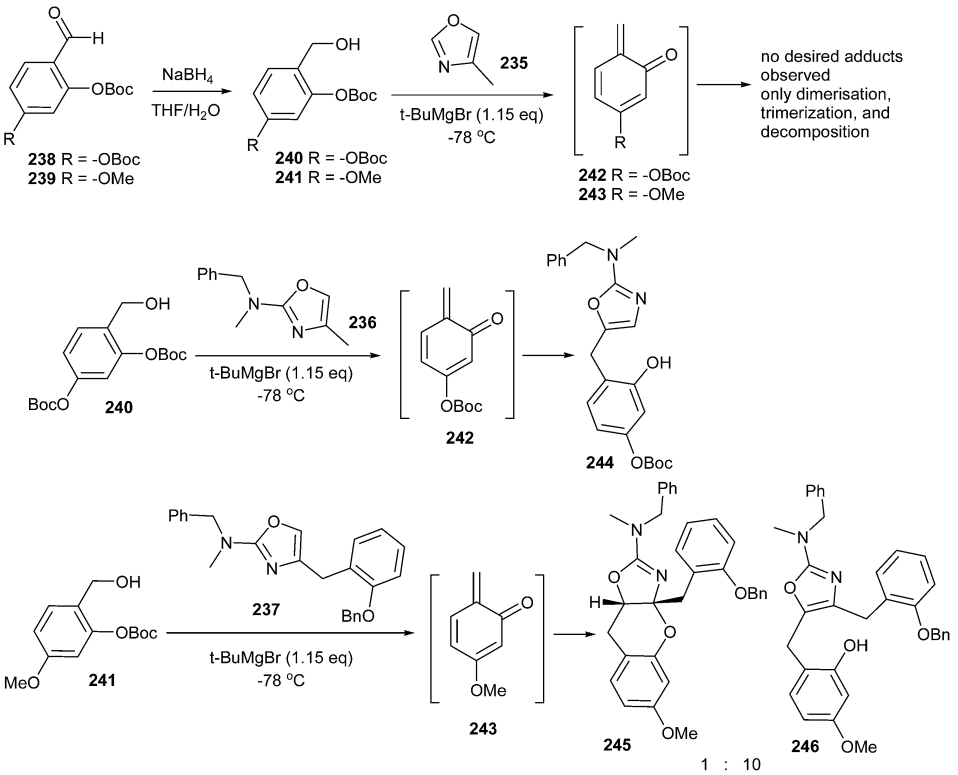
Scheme 49 Diels–Alder cycloaddition of *o*-QM with activated alkenes.

The 2-amino oxazoles displaying an electron-rich substituent at the 4-position (R = H, Bn) underwent highly asynchronous reactions, leading to 1,4-conjugate addition adducts, whereas the oxazoles displaying an electron-withdrawing substituent at the 4-position (R = –OTBS, –OCO_2Et) underwent a synchronous reaction, affording the [4 + 2]cycloadduct (Scheme 52).

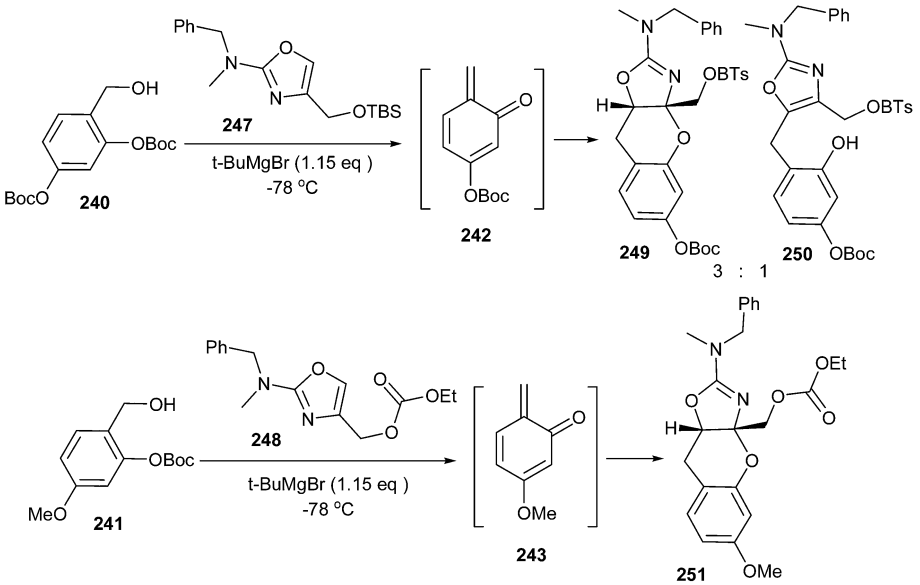
Moreover, the *o*-QM derived from tocopherol was trapped with DNMM (4-methyl-3,4-dihydro-2*H*-[1,4]oxazine) **256** *via* the hetero-Diels–Alder reaction with inverse electron demand, and confirmed that compound **256** occurs as a degradation product of *N*-methylmorpholine-*N*-oxide.[49] As dehydro-NMM is an electron-rich olefin and *o*-QM is electron deficient, the hetero-Diels–Alder reaction of *o*-QM with ethyl vinyl ether proceeds regioselectively in a particular way, so that the α-carbon of the vinyl reacts with the oxygen and the vinylic β-carbon reacts with the methylene carbon of the QM.[49b] But in the case of DNMM **256**, the situation was less unequivocal, as the compound contains both a vinyl ether and an enamine; hence, two directions of addition with *o*-QMs **254** and **255** took place, leading to tetracycles **257–260**. Computations on the DFT level was performed on the shortened model compounds **255**, **258**, and **260**, possessing a methyl group instead of the isoprenoid side chain that predicted **260** to be 12.6 kJ mol^{-1} more stable than **258** (Scheme 53).

A mechanistically interesting enantioselective [4 + 2] cycloaddition of *o*-QM with silyl ketene acetals by catalytic pathway is well described in a previously reported method,[50] and was initiated by a chiral cinchona alkaloid-derived ammonium fluoride "precatalyst" complex to afford a variety of alkyl- and aryl-substituted 3,4-dihydrocoumarin products in excellent yields with good enantioselectivity. The electron-rich *o*-QM **261** was first generated by Jurd in 1977 by the reaction of sesamol and 4-methoxybenzyl alcohol under the mild Friedel–Crafts conditions followed by Ag_2O oxidation. Then, the newly generated *o*-QM **261** was treated with butyryl chloride, thermodynamic Hunig's base, which generates stable enolate and kinetic base/chiral catalyst benzoylquinidine (BQd) **262**. It has been found that the high electron density on *o*-QM was not compatible with the mild nucleophilic zwitterionic ketene enolate **262**; therefore, silyl ketene acetal **263** was used as the ketene enolate precursor to synthesize the compound **267** (Schemes 54 and 55).

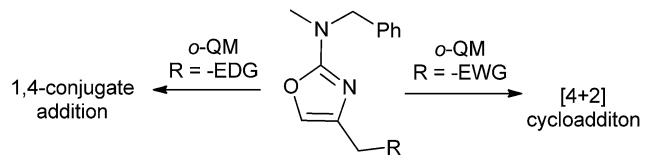
Next, reaction of *o*-QM **261** with **263** in the presence of catalytic tetrabutylammonium fluoride (TBAF) in THF afforded



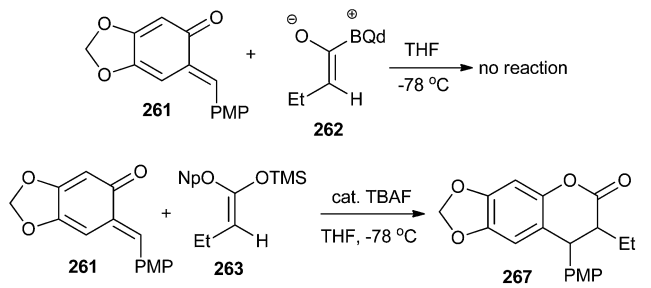
Scheme 50 Hetero-Diels–Alder reactions between various electron-rich oxazoles and *o*-QMs.



Scheme 51 Reaction of substituted oxazoles with *o*-QM.



Scheme 52 [4 + 2] Cycloadduct of oxazole derivatives.

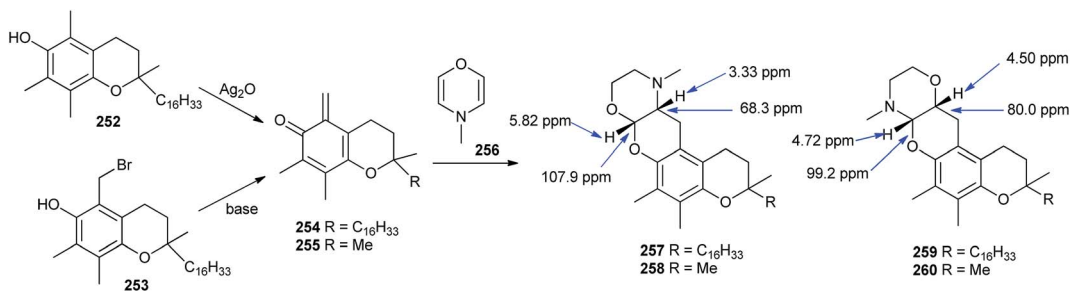


Scheme 54 Synthesis of compound **267** utilizing silyl ketene acetal **263** and *o*-QM **261**.

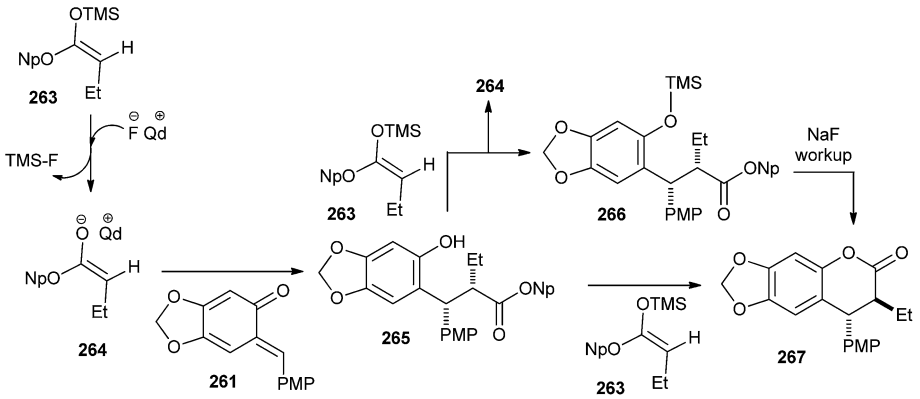
the cycloaddition product **267** with 80% ee. Thus, it shows that the precatalyst's effect on the enantioselectivity of the reaction was not dictated by steric bulk, but rather by electronic effects (Scheme 55).

A variety of chroman spiroketals have been synthesized by Pettus and co-workers[51] *via* inverse-demand [4 + 2] cycloaddition of enol ethers with *o*-QMs. At low temperature, *in situ* generation of *o*-QM allows the kinetic diastereoselective construction of these motifs, providing entry to a number of unusual chroman spiroketals. When benzyl alcohol **269** (0.1 M in toluene, −78 °C) and 2–4 equivalents of the 1,3-dihydroisobenzofuran enol ether **268** were treated with *t*-BuMgCl, an endo-selective cycloaddition took place as the reaction mixture slowly increases to room temperature (Scheme 56). The reaction cleanly produced the chroman spiroketal **270** in 60% isolated yield (>8 : 1 dr).

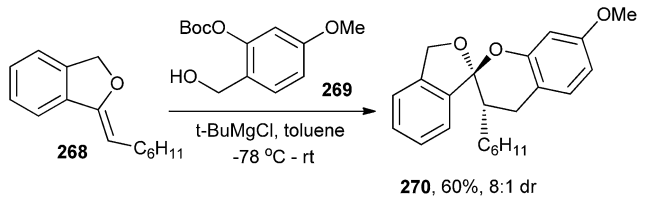
The simple *exo*-enol ethers readily equilibrate with their *endo*-isomers under acidic and sometimes also thermal conditions. The major product was the expected benzopyran **273**, and the mono-benzannulated spiroketal **274** (as a mixture of diastereomers) was observed in a 25% yield during the reaction of compound **271** with *endo*-enol ether **272**. Apparently, this was the result of the cycloaddition of the intermediate *o*-QM with 4,5-dihydro-2,4-dimethylfuran (Scheme 57).[12,13]



Scheme 53 Reaction of *o*-QM (derived from tocopherol) with oxazine.



Scheme 55 Enantioselective synthesis of compound **267**.

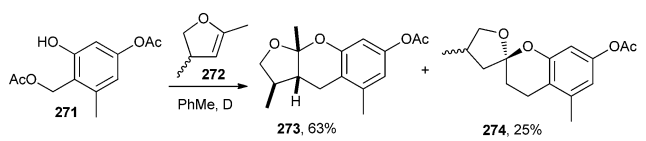


Scheme 56 Synthesis of chroman spiroketal.

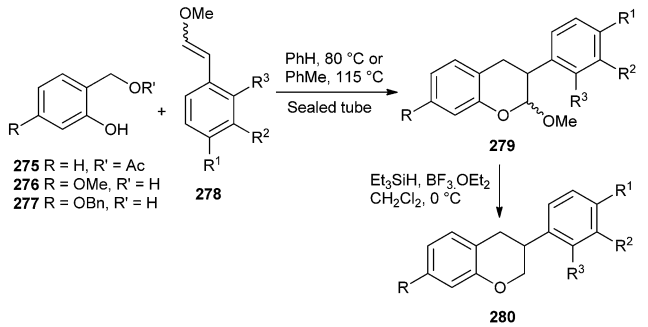
The intermediacy of *o*-QM has been employed to develop a concise strategy for the synthesis of isoflavans *via* the Diels–Alder reaction between *o*-QM and aryl-substituted enol ethers **278** followed by the reductive cleavage of the acetal group.[52] The method is extended toward the total syntheses of equol, 3′-hydroxyequol, and vestitol. A reductive removal of the methoxy group from acetal **279** was achieved by using $BF_3 \cdot OEt_2$ and triethylsilane to give isoflavan **280** (Scheme 58).

It has been envisioned that the Lewis acid should be able to catalyze both the [4 + 2] cycloaddition and the reductive removal of the methoxy group of the acetal moiety in a one-pot transformation. In this course, the reaction of phenol **277** and enol ether **278a** with $BF_3 \cdot OEt_2$ in CH_2Cl_2 at 0 °C in the presence of triethylsilane in the same pot gave isoflavan **280a** in a 34% yield (Scheme 59).

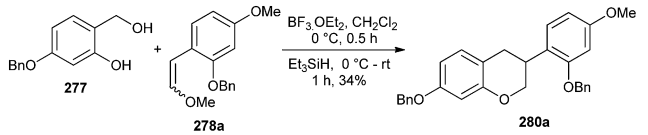
3.1.2. [4 + 4] Cycloaddition. A one-pot [4 + 4] cyclization pathway for the generation of eight-membered sultams *via in situ* generated *o*-QM was reported by Hanson and co-workers.[53] They examined the pairing of ambiphilic synthons in a complementary fashion, whereby *o*-fluorobenzenesulfonamides **281** were merged with *in situ* generated *o*-QM **283** (from compound **282**) in a formal [4 + 4] cyclization pathway to afford dibenzooxathiazocine dioxides **284** under microwave (MW)



Scheme 57 Synthesis of benzopyran **273** and mono-benzannulated spiroketal **274**.



Scheme 58 Synthesis of isoflavan **280** *via* intermediacy of *o*-QM.



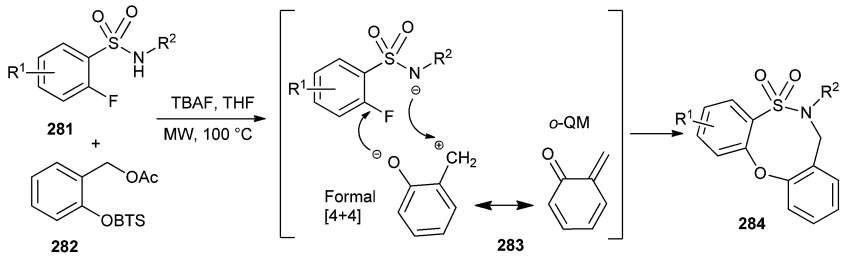
Scheme 59 [4 + 2] Cycloaddition reaction of substituted phenol with enol ether **278a**.

conditions (Scheme 60). This is the first report representing the use of an *o*-QM in a formal hetero [4 + 4] cyclization.

3.1.3. [5 + 2] Cycloaddition (phenoxonium analogous to *o*-QM). Green and Pettus[54] have synthesised α-Cedrene, α-Pipitzol, and *sec*-Cedrenol by the oxidative dearomatization-induced [5 + 2] cycloaddition. Phenols with various *ortho*-(pent-4-enyl) substitutions were directly prepared from salicylaldehydes by low temperature *o*-QM generation and consumption. The key conversion attributed to the oxidative dearomatization of an *ortho*-(pent-4-enyl)-phenol **285**, followed by an intramolecular [5 + 2] cycloaddition of the respective phenoxonium intermediates **287** across the attached olefin, affords the respective derivatives of skeleton **289** (Scheme 61).

3.2. Addition of nucleophiles

Bromination of α-tocopherol **290** for the formation of **294** is not possible by simple bromination because an ethano-dimer of



Scheme 60 Synthesis of 5,2,1-dibenzooxathiazocine-2,2-dioxides by hetero [4 + 4] cyclization.

α-tocopherol **290** after bromination affords pyrano-spirodimer of α-tocopherol **291** in > 95% yields. Compound **290** and **291** constitute a largely reversible redox pair.[55] Bromine oxidizes one α-tocopherol **290** to an *ortho*-quinone methide (*o*-QM) intermediate **292**, which is immediately attacked by the phenolic OH group of the tocopherol. It is evidently favoured over the 1,4-addition of evolving HBr by a pre-organizational effect, as the ethano-bridge keeps the two reacting moieties in close distance. This acid facilitates the opening of **291** to regenerate the *o*-QM **292.**[56] Thus, the OH group was protected by TMS, which continuously traps a small percentage of the *o*-QM intermediate present and cannot react back to give compound **291.** In this way, **291** is eventually completely converted into **293** (Scheme 62). Further reaction of **293** with elemental bromine followed by desilylation provided the target bisbromide **294**.

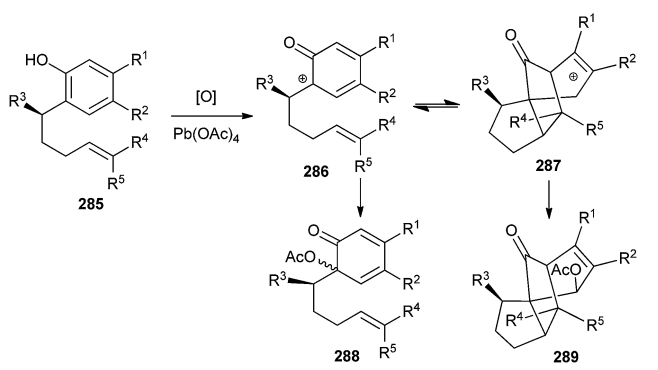
The pseudo three-component condensation reaction of 2-naphthol with aldehydes in the presence of various catalysts to form xanthenes has been widely studied. The reaction proceeds through the *in situ* formation of *o*-QMs with 2-naphthol acting as a nucleophile. However, the three-component condensation reactions of 2-naphthol and aldehydes with other nucleophiles are rarely reported in previously studied reports. Singh and co-workers[57] generated substituted xanthenes **297** by one-pot condensation of 2-naphthol with aliphatic/aromatic aldehydes **295** in the presence of P_2O_5 or $InCl_3$ as catalysts under solvent-free conditions. They also reported a one-pot synthesis of tetrahydrobenzoxanthenone **299** and diazabenzoanthracenedione **300** in the presence of an Indium(III) chloride catalyst by a three-component cyclocondensation of aldehydes **295,** β-naphthol **296** and cyclic 1,3-dicarbonyl compounds **298** under solvent-free conditions in high yields. This transformation has also been effectively carried out by using P_2O_5 as a catalyst. The use of aldehyde **295,** β-naphthol **296,** and 3-oxo-3-phenyldithiopropionic acid methyl ester **301** in equimolar amounts in the presence of $InCl_3$ produces benzo[*f*]chromene **302** in good yields (Scheme 63).

The nucleophilic addition of β-naphthol **296** to aldehyde **295** in the presence of $InCl_3$ gives naphthoquinone methide intermediate **303**, which then reacts with the nucleophile like 1,3-dicarbonyl compound **298** followed by the addition of the phenolic hydroxyl moiety to the carbonyl of ketone, providing cyclic hemiketal, which on dehydration afforded **299** (Scheme 64).

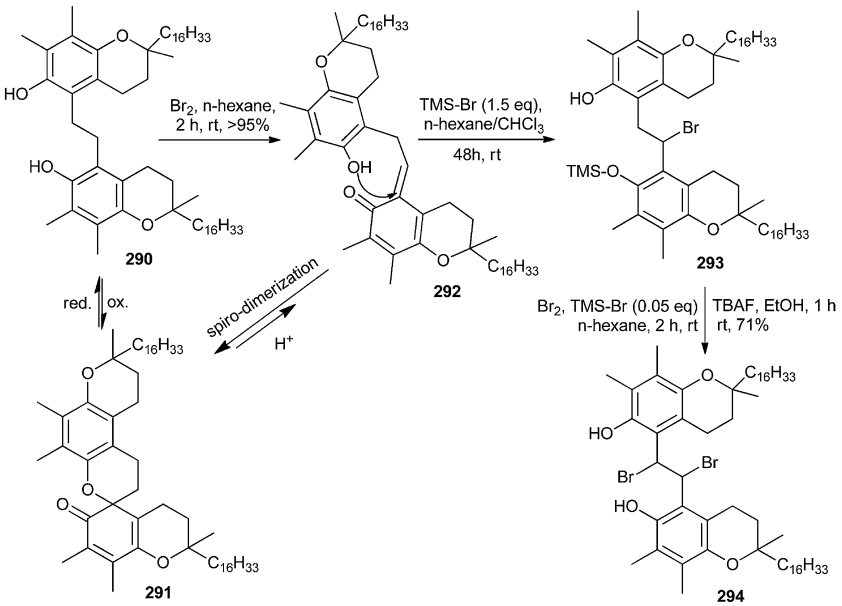
The *in situ* formation of *o*-QM intermediates in the presence of solid silica chloride under sonication followed by the nucleophilic attack of amide has been reported to lead to the formation of amidoalkyl-2-naphthol.[58] Due to the collapse of the cavitation bubbles near the surface of the catalyst, the oxygen of the carbonyl group might have easily replaced the chlorine atom present on the catalyst silica chloride to give the activated aldehyde, which could be attacked by β-naphthol to give *o*-QM **307**. Thus, the *in situ* generated *o*-QM **307** upon reaction with amide **308** furnished the envisioned amidoalkyl naphthol **309** (Scheme 65). This reaction was previously reported under the influence of P_2O_5, which acts as a catalyst as well as a water scavenger.[59]

Nagawade and Shinde[60] reported the rapid synthesis of biologically significant amidoalkyl naphthols using a catalytic amount of iodine. Chlorinated solvents (dichloroethane > dichloromethane > chloroform) gave the highest yields. The yields of the end products depend on the polarity of the solvent used, and after a through screening, 1,2-dichloroethane was found to be the best solvent for the protocol. *o*-QM has also been generated by the treatment of β-naphthol, aryl aldehyde and ureas or amides in the presence of catalytic amounts of *p*-TSA at 125 °C.[61] In addition to that hafnium(IV) bis(perfluorooctanesulfonyl)imide complex,[62] $(Hf(NPf_2)4)$, $NaHSO_4 \cdot H_2O$[63] and $H_3PW_{12}O_{40}$ have also been shown to be effective catalysts for the same reaction, with respect to reaction times and yields in the molten salt media.[64]

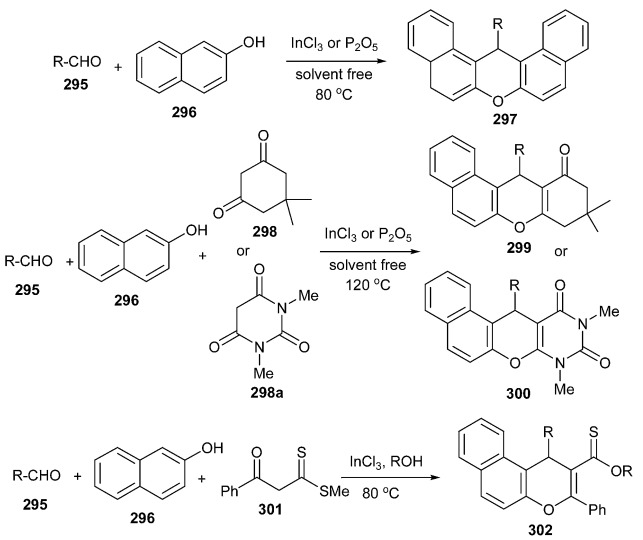
2′-Aminobenzothiazolomethyl naphthols or 5-(2′-aminobenzothiazolomethyl)-6-hydroxyquinolines **313** was prepared by the reaction of *o*-QM **312,** and 2-aminobenzothiazole. *o*-QM was generated *in situ* from the reaction of β-naphthol or 6-hydroxyquinoline and aldehyde **311** (Scheme 66).[65]



Scheme 61 Intramolecular [5 + 2] cycloaddition of phenoxonium intermediates.



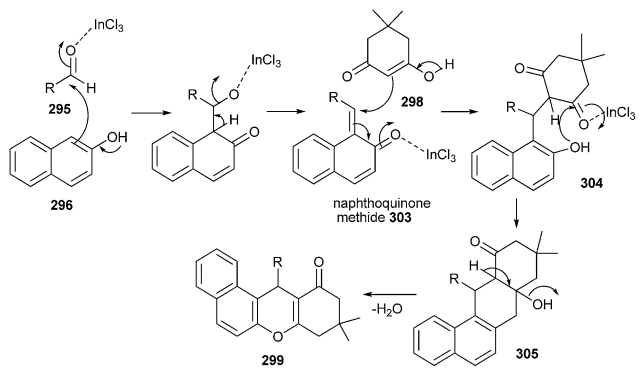
Scheme 62 Bis-bromination of ethano-dimer of α-tocopherol.



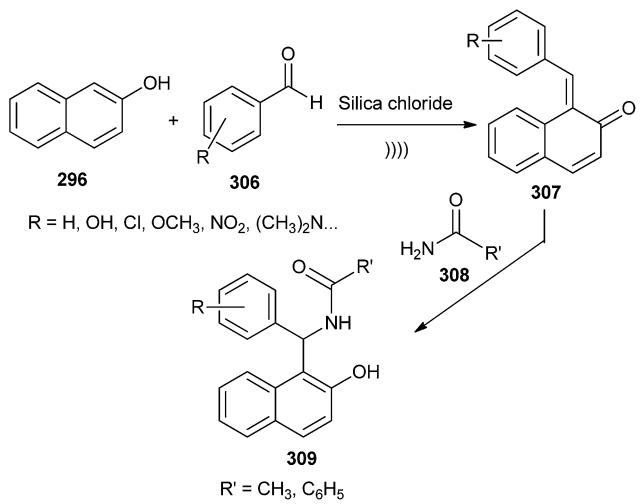
Scheme 63 Cyclocondensation reaction *via* *o*-QMs intermediates.

1,2-Dihydronaphtho[2,1-*b*]furans and 2,3-dihydrobenzofurans **316** substituted at C-2 by an acyl or aryl group were prepared in a diastereoselective manner. The reaction goes through the formation of the *o*-quinone methide intermediate followed by a Michael-type addition of the ylide **315** to the *o*-QM with a consequent intramolecular nucleophilic substitution. The reaction is applicable to a range of Mannich bases and pyridinium salts with a variety of versatile functional groups (Scheme 67).[66]

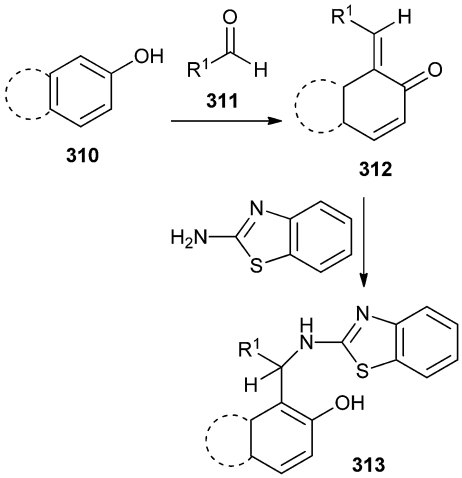
Salvadoria and co-workers[67] reported the oxidation of α-tocopherol **317** leading to *o*-QM species **318**, which when reacted with bromide as a nucleophile from hydrogen bromide, affords the benzylic brominated product **319** (Scheme 68).



Scheme 64 Nucleophilic addition of β-naphthol to aldehyde *via* *o*-QM intermediacy.



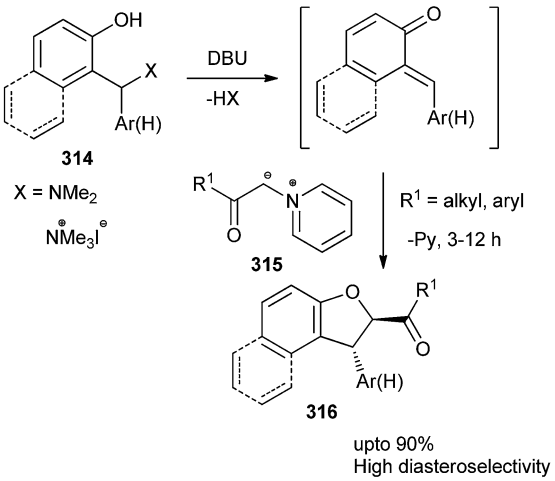
Scheme 65 Synthesis of amidoalkyl naphthols.



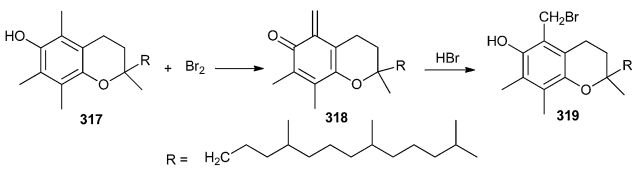
Scheme 66 Synthesis of 2′-aminobenzothiazolomethyl naphthols.

The bromo-α-tocopherols **317** and **320** after treating with nucleophilic triphenyl phosphene followed by acylation gives the furotocooherols **325** & **326** (Scheme 69).[68]

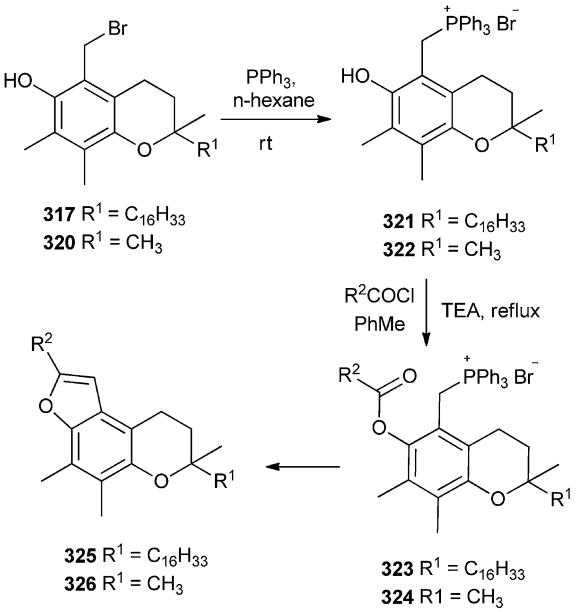
Chen and co-workers[69] reported the stereoselective synthesis of *trans*-dihydrobenzofurans **332** by the reaction of *o*-QM **328** and sulfur ylides **329.** This gave intermediate **330,** which undergoes *trans*-elimination–cyclization to afford **332.** *o*-QM intermediates have been generated from 2-tosylalkylphenols **327** under mild basic conditions (Scheme 70).



Scheme 67 Diastereoselective synthesis of naphthofurans and benzofurans.



Scheme 68 Bromination of α-tocopherol.

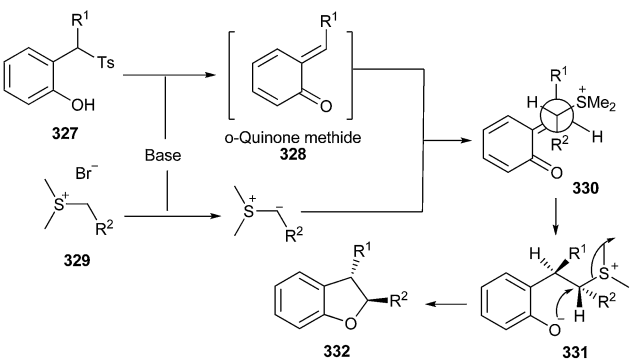


Scheme 69 Synthesis of urotocooherols from bromo-α-tocopherols.

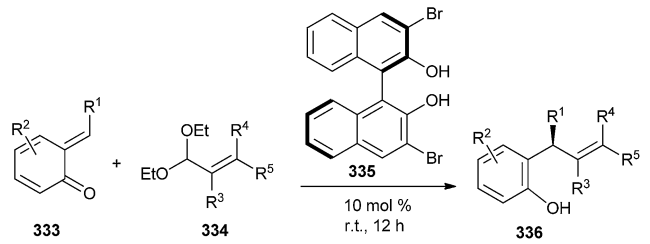
Chiral biphenols were found to catalyze the enantioselective asymmetric addition of aryl- or alkenylboronates to *o*-QMs **333.** Thus, substituted 2-styrylphenols **336** were obtained in high yields (up to 95%) with high enantiomeric ratios (up to 98 : 2) in the presence of 10 mol% of 3,3′-Br_2-BINOL **335** (Scheme 71).[70]

Kumar and co-workers[2,71] have developed an efficient and catalyst-free approach for C–H hydroarylation of *in situ* generated *o*-QM **339** with electron-rich arenes (*tert*-aryl amines **340**) in a glycerol medium. A number of 3-substituted 4-hydroxycoumarin **341** and 4-hydroxypyrone derivatives were obtained in good to excellent yields. The reaction takes place in water without any catalyst, and is highly regioselective (Scheme 72). They have used coumarins, indole, and 4-hydroxypyrone derivatives to generate corresponding *o*-QMs. It is noteworthy that in all the cases, *para* substituted products were exclusively obtained. The reason of regioselectivity is the steric hindrance of *N*-alkyl group and *ortho* hydrogen of *N*,*N*-dialkylanilines, which provides the *para* selectivity.

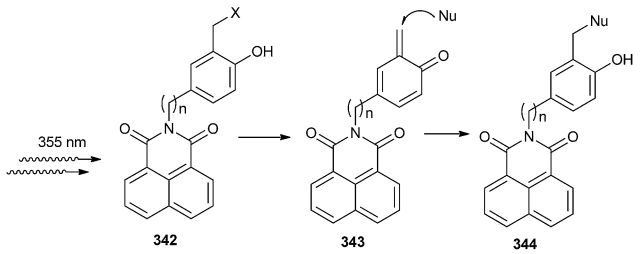
Antonio and Freccero[72] have reported the synthesis and the unexpected photochemical reactivity of a new class of



Scheme 70 Stereoselective synthesis of *trans*-dihydrobenzofurans.



Scheme 71 Enantioselective addition of aryl- or alkenylboronates to *o*-QMs.



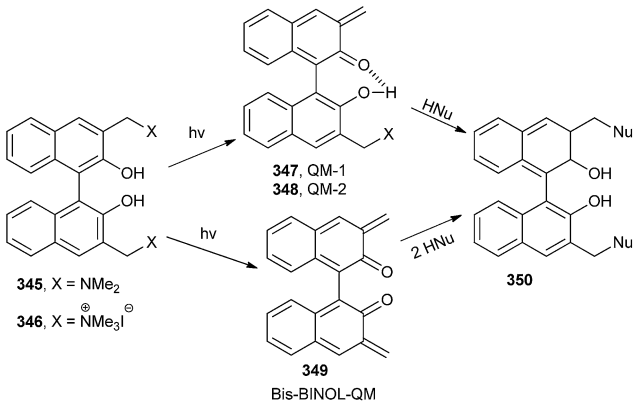
Scheme 73 Phototriggering of QMs *via* photoinduced electron transfer (PET).

naphthalimide derivatives (NIs) **342** bearing quinone methide precursor (QMPs) at the imide moiety by irradiation of the NI core (Scheme 73). Photogeneration of the transient QM **343** through a PET mechanism between the phenolic precursors and the NI core was rationalized. Such reactivity represents the first case of non-direct phototriggering of QMs *via* photoinduced electron transfer (PET) involving a tethered peripheral moiety.

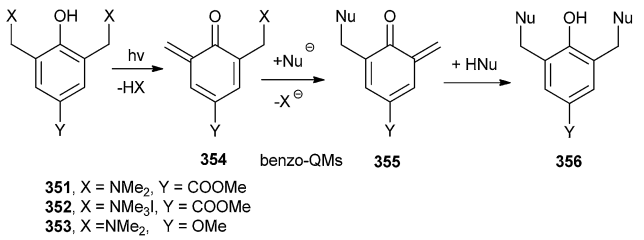
Freccero and co-workers[26] have reported the photoinduced generation of new binol quinone methides **349**, which undergo mono- and bisalkylation of free nucleophiles by product distribution analysis and laser flash photolysis in water solution using binol quaternary ammonium derivatives **346** and **352** as photoactivated precursors (Schemes 74 and 75). *N* and *S* nucleophiles are powerfully competitive in alkylation with the hydration reaction.

The DNA cross-linking potency of the water-soluble binol quaternary ammonium salt **346** was investigated as a pH function and compared to that of other quaternary ammonium salts proficient for photogenerated benzo-QM by gel electrophoresis. DFT calculations in the gas phase and in water bulk on the binol and benzo quaternary ammonium salts **346** and **352** evidence structural and electrostatic features of the binol derivative, which might offer a validation of its promising high photo-cross-linking efficiency.

o-QM **358** (NDI-QM) has been generated by activation of suitable quinone methide precursors (QMPs) **357** under biocompatible conditions such as mild thermal digestion (40 °C), UV-Vis irradiation and mild mono-electronic reduction (Scheme 76).[73] The conjugated NDI-QMPs might have been acting as a hybrid ligand-alkylating structures selectively targeting G-4 folding oligonucleotides.



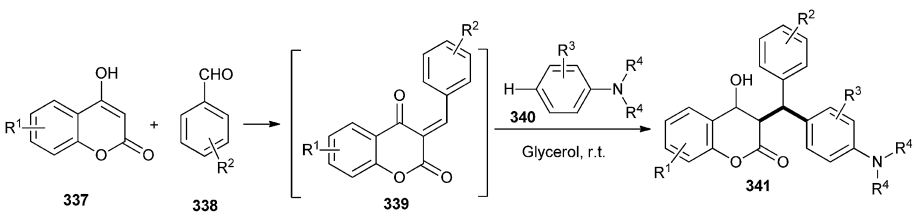
Scheme 74 Addition of nucleophiles on binol quinone methides.



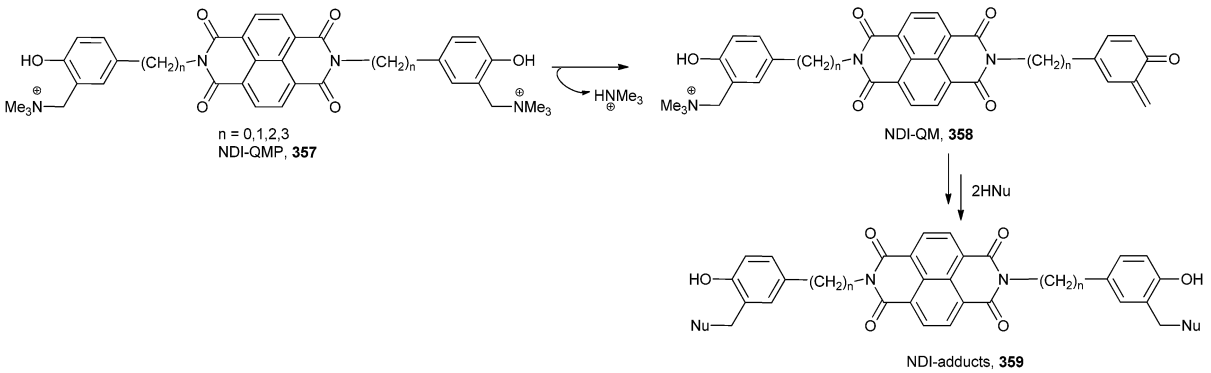
Scheme 75 Bis-alkylation of photoinduced *o*-QM **354** and **355**.

3.3. Alkylation on *o*-QM: DNA alkylation

The formation of QMs depends on the strength of the leaving group attached to the benzylic position of *o*-QM **360** in the presence of biological nucleophiles (dN).[74,75] The formation and reaction of QMs are also highly responsive to the presence of electron-withdrawing and electron-donating groups. The observed trends of reactivity are consistent with the electron-deficient nature of the QM intermediate. Electron-donating groups greatly facilitate initial QM generation and its subsequent regeneration from adducts formed by the nucleophiles of



Scheme 72 C–H hydroarylation of *in situ* generated *o*-QM.



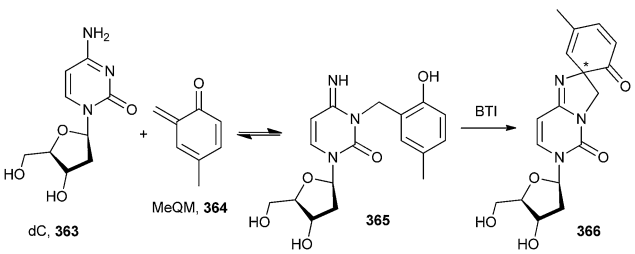
Scheme 76 Addition of nucleophile on NDI-QM **358**.

deoxynucleosides (dN) that also function as good leaving groups. Conversely, electron-withdrawing groups greatly suppress initial formation of QM and its regeneration from the reversible deoxynucleoside adducts **362** (Scheme 77). The stability of *o*-QM is mainly influenced by the electronic perturbation over it, and the kinetics of the product formation is also altered by the reaction with deoxynucleosides.[76] Electron-rich QMs react considerably more slowly but selectively with nucleophiles than the electron-poor QMs. These fundamental characteristics provide the basis for explaining the product profiles observed after DNA has been exposed to various QMs.[77] These characteristics are used to fine-tune the stability and reactivity of QM conjugates for target-promoted and gene-specific alkylation.[78]

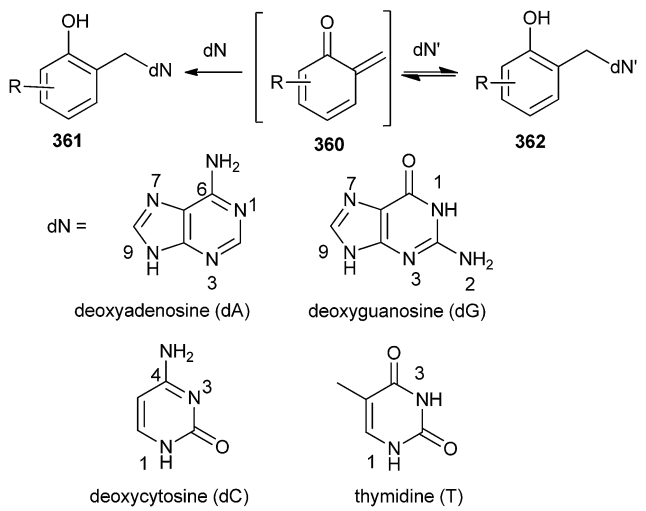
Rokita and co-workers[79] reported the formation of the reversible quenching adducts **366** under physiological conditions between *o*-QM **364** and deoxycytidine **363** by selective oxidation using bis[(trifluoroacetoxy)iodo]benzene (BTI), which induces a surprising rearrangement driven by over oxidation of a derivative lacking an alkyl substituent at the 4-position of the QM (Scheme 78).

The rates of alkylation of 2′-deoxyguanosine **369** and guanosine **370** with *o*-quinone α-(*p*-anisyl)methide **368** (Scheme 79) were studied by flash photolysis in a series of aqueous sodium hydroxide solutions and bicarbonate ion, *t*-butylhydrogenphosphonate ion as well as in biphosphate ion buffers.[80] Rate constants showed the reaction of *o*-quinone α-(*p*-anisyl)-methide **368** with guanosine and deoxyguanosine to be quite a fast process. Even it was considerably faster than the biologically wasteful reaction of the quinone methide with water, which is the ubiquitous medium in biological systems, and hence makes the quinone methide a potent guanosine and deoxyguanosine alkylator.

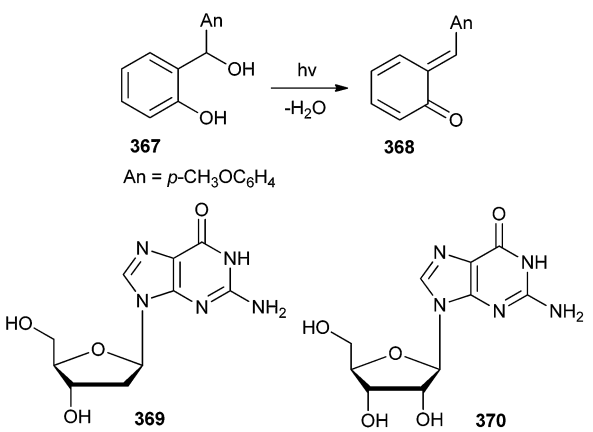
The selenide derivatives **371** can generate covalent interstrand cross-linking with its complementary strand through the



Scheme 78 Reaction of *o*-QM with deoxycytidine **363**.



Scheme 77 Generation of deoxynucleoside and *o*-QM adducts.



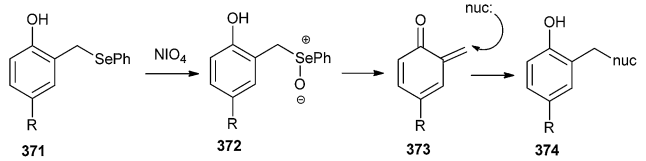
Scheme 79 Alkylation of 2′-deoxyguanosine and guanosine on *o*-quinone α-(*p*-anisyl)methide.

formation of *o*-QM intermediate **373**, induced by periodate oxidation.[81] It has been evidenced by hydroxyl radical footprinting experiments that the quinone appendage specifically alkylated the cytosine base (nuc) extending the duplex formed between the conjugate and the target strand (Scheme 80).

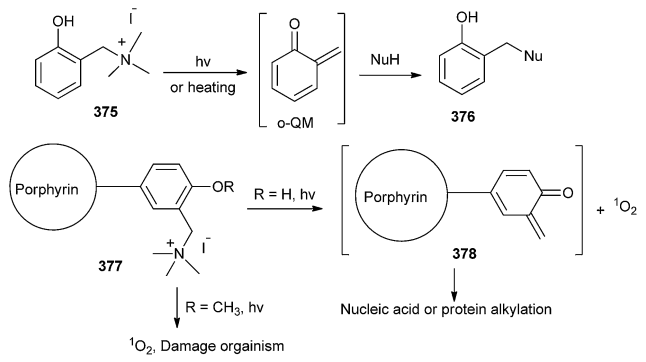
It is well known that cation on porphyrin can increase both selective binding affinity to nucleic acid or protein and solubility in aqueous conditions. Hence, with photoinducing, *o*-QM intermediate and singlet oxygen could be formed and they may play an important role for both alkylation and oxidative damage to nucleic acids or proteins. In all probability, porphyrin **377** was photochemically activated and induced to form both singlet oxygen and *o*-QM intermediate **378**, which led to both oxidative damage and the alkylation of the organism in the bacterial system (Scheme 81).[82]

Song and co-workers[83] reported three water-soluble DNA cross-linking phenol quaternary ammonium derivatives, which could inhibit the transcription *in vitro* by photo-activation. The cross-linking agent **379** could be a significant reason for the late apoptosis of tumour cells. The twisted form and two quaternary ammonium groups could anchor DNA strands and facilitate the binding of DNA strands and the cross-linking between strands can then proceed through a bis(quinone methide) intermediate **380**. The *in situ* formed *o*-QM has also been trapped by *t*-BuNH$_2$ (Scheme 82).

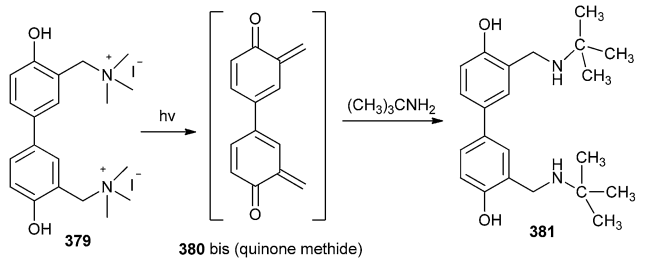
Quinolinyl QM **387** was designed through the fluoride-induced QM generation by desilylation and elimination of acetate group from compound **386** (Scheme 83). The incorporation of the quinolinyl substitute was designed to enhance the potential interactions with DNA through possible partial intercalation and charges of the quinoline moiety and also for the investigation of the steric effect on the reactivity of QMs.



Scheme 80 Alkylation of *o*-QM by using cytosine base (nuc).



Scheme 81 Binding of nucleic acid or protein on *o*-QM having porphyrin unit.



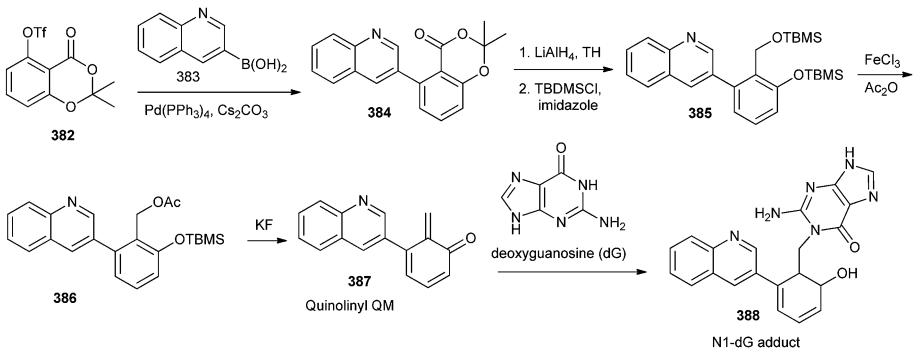
Scheme 82 Trapping of bis(quinone methide) intermediate by *t*-BuNH$_2$.

Authors have reported that the N1-dG adduct **388** was selectively formed with quinolinyl QM as a favored dG adduct in 30% aqueous DMF and 10 mM phosphate buffer (pH 7.0).[84]

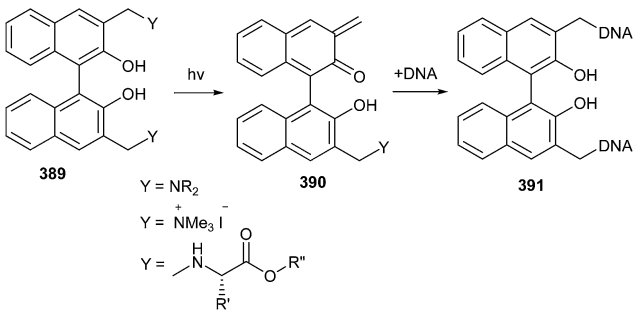
A novel G-quadruplex (G-4), ligand/alkylating hybrid structures **391** tethering the naphthalene diimide moieties to quaternary ammonium salts of Mannich bases, as quinone-methide precursors **389**, was activated by mild thermal digestion (40 °C).[85] The bis-substituted naphthalene diimides were capably synthesized and their reactivity as activatable bis-alkylating agents was explored in the presence of thiols and amines in aqueous buffered solutions (Scheme 84). During alkylation, it has been found that the reversible process is a precondition to DNA alkylation, which in turn strengthens the G-quadruplex structural reorganization.

Freccero and co-workers[86] also reported a photoactivation of new BINOL-amino acid and BINOL-amino ester conjugates acquiesced alkylating and DNA cross-linking agents with high photoefficiency and superior cytotoxicity. While using nucleosides as nucleophiles, only the conjugate adducts with deoxycytidine at the N3 (dC-N3), deoxyadenosine at both N1 and NH$_2$ (dA-N1 and dA-NH$_2$), and deoxyguanosine at NH$_2$ (dG-NH$_2$) are stable in water solution. Conversely, the alkylation adducts at N7 of both dG and dA are thermodynamically unstable, because the reversal of the alkylation becomes a competitive process.

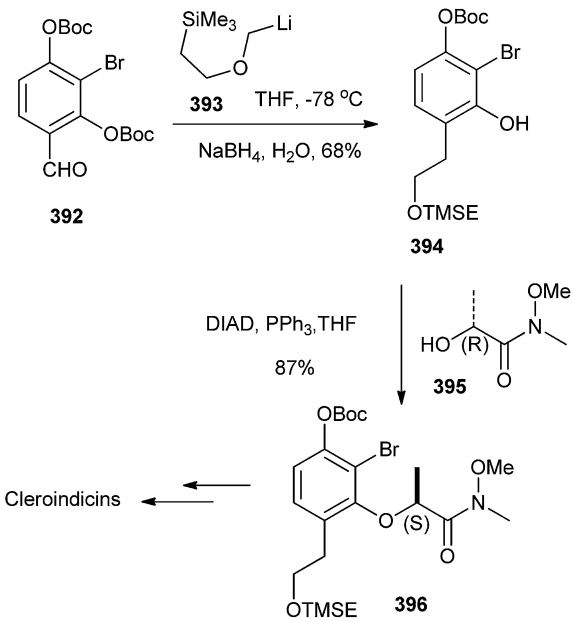
The alkylation reaction of 9-methyladenine and 9-methylguanine (as prototype substrates of deoxyadenosine and deoxyguanosine) with the parent *o*-QM have been studied by using DFT at the B3LYP/6-311+G(d,p) level.[87] The guanine oxygen atom (O^6) (ΔG_q gas, 5.6 kcal mol^{-1}) followed by the adenine N1 (ΔG_q gas, 10.3 kcal mol^{-1}) are more nucleophilic, whereas other centres have comparatively lower nucleophilicity. But water as a solvent diminishes the nucleophilicity of both 9-methyladenine N1 (DG_q solv, 14.5 kcal mol^{-1}) and 9-methylguanine O6 (ΔG_q solv, 17.0 kcal mol^{-1}), and as a consequence it reverts the purine base nucleophilicity. Regarding the product stability, calculations predict that only two adducts of *o*-QM with 9-methyladenine at NH$_2$ and N1 positions, are in lower energy than reactants, in the gas and water phases. However, adduct at N1 can easily be dissociated in water. In particular, the oxygen alkylation adduct becomes slightly unstable in water ($¢G_{solv}$, +1.4 kcal mol^{-1}), and the N7 alkylation product remains only moderately more stable than free reactants ($¢G_{solv}$, −2.8 kcal mol^{-1}).



Scheme 83 Synthesis of N1-dG adduct using quinolinyl QM and deoxyguanosine.



Scheme 84 DNA alkylation *o*-QM precursors to generate G-quadruplex.



Scheme 85 Synthesis of chiral Cleroindicins from the substituted benzaldehyde **392**.

Pettus *et al.*[88] have reported the total synthesis of all of the known chiral Cleroindicins from the known substituted benzaldehyde **392**, which has been treated with [(2-(trimethylsilyl)ethoxy)methyl]lithium **393** resulted in Boc migration, and afforded an intermediate phenoxide. This phenoxide generated the *o*-QM by *in situ* elimination, which then underwent succeeding *in situ* 1,4-reduction with sodium borohydride to produce the phenol **394** in a 68% yield. Mitsunobu coupling of compound **394** with amide **395** afforded the inverted amide **396** in an 85% yield and >99% ee (Scheme 85).

3.4. Coupling reactions

The coupling of *o*-QM has been done by redox reactions of vitamin E in 1,2-dichloroethane with oxidants in water/1,2-dichloroethane interface.[89] Here, the oxidation reaction of α-tocopherol (TOH) with MnO_4^- in DCE has been explained by a series of reactions (eqn (1)–(3)). After the formation of α-TD in hexane and *o*-QM of α-TOH produced during the oxidation of α-TOH dimerizes easily to α-TD, as shown in Scheme 86.

$$3\alpha\text{-TOH}_{DCE} + 2MnO_{4DCE}^- + 4H_2O_{DCE} \rightarrow 2MnO_{2DCE} + 3\alpha\text{-TO}_{DCE} + 5OH_{DCE}^- \quad (1)$$

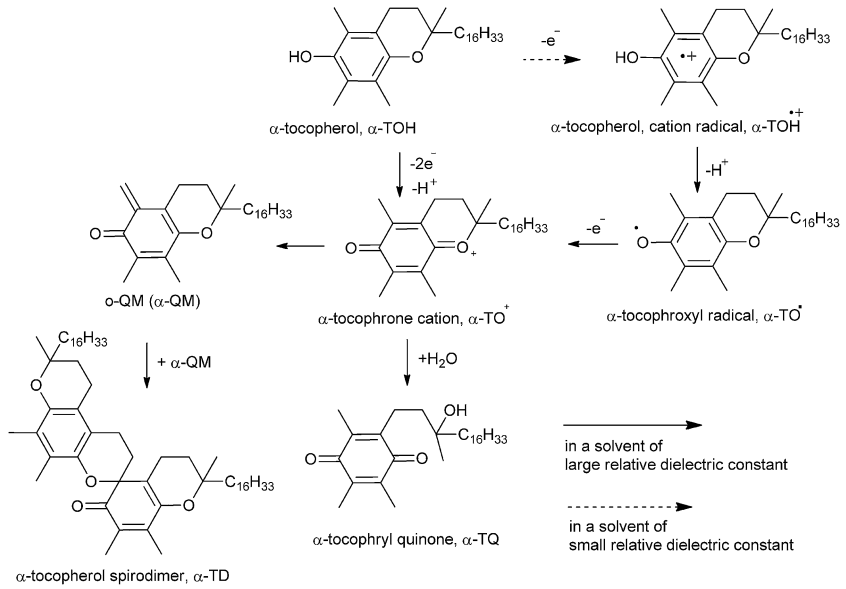
$$\alpha\text{-TO}_{DCE}^+ + OH_{DCE}^- \rightarrow \alpha\text{-QM}_{DCE} + H_2O_{DCE} \quad (2)$$

$$2\alpha\text{-QM}_{DCE} \rightarrow \alpha\text{-TD}_{DCE} \quad (3)$$

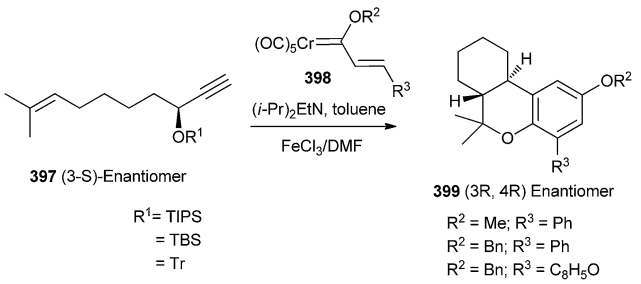
3.5. Complex formation with metals

Korthals and Wulff[90] reported that the reactions of Chromium carbene complexes of type **398** with enynyl propargyl ethers **397** in the presence of a base would generate hexahydrodibenzopyrans **399** after an oxidative workup. The involvement of a [4 + 2] cycloaddition of a Cr complexed *o*-QM intermediate was inferred from the observed high asymmetric induction (Scheme 87).

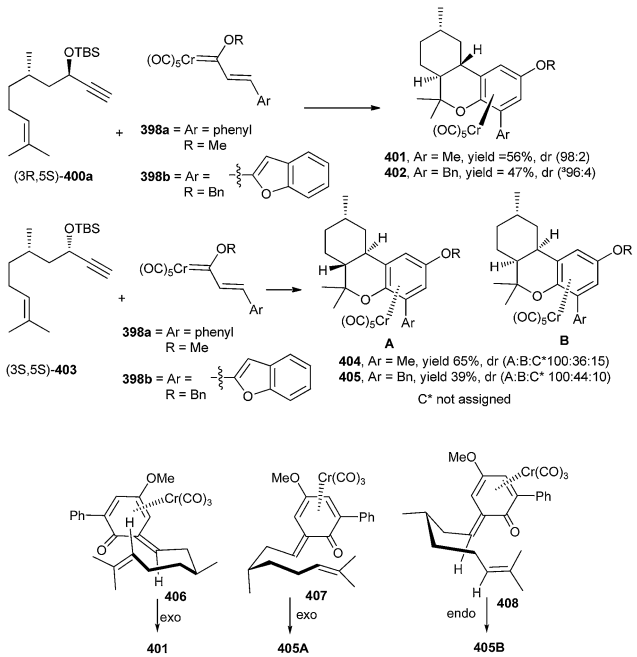
Compound **401** was prepared through the Diels–Alder reaction of the *o*-QM intermediate **406**. The methyl group at the C-9 position of *o*-QM **406** puts into effect the formation of a single diastereomer from the Diels–Alder reaction possessing a chair transition state in an *exo*-cycloaddition where the CH_3 is in an equatorial position. Such a chair transition state is possible in **406**, where the cycloaddition occurs *anti* to the chromium. But in the case of diastereomer **407**, the Cr is on the opposite face of the *o*-QM, where the chair transition state for the *exo*-cycloaddition *anti* to the metal has an axial methyl. The (3*S*,5*S*)-enyne



Scheme 86 Formation and dimerization of α-TD.



Scheme 87 [4 + 2] Cycloaddition of a Cr complexed *o*-QM with enynyl propargyl ethers.

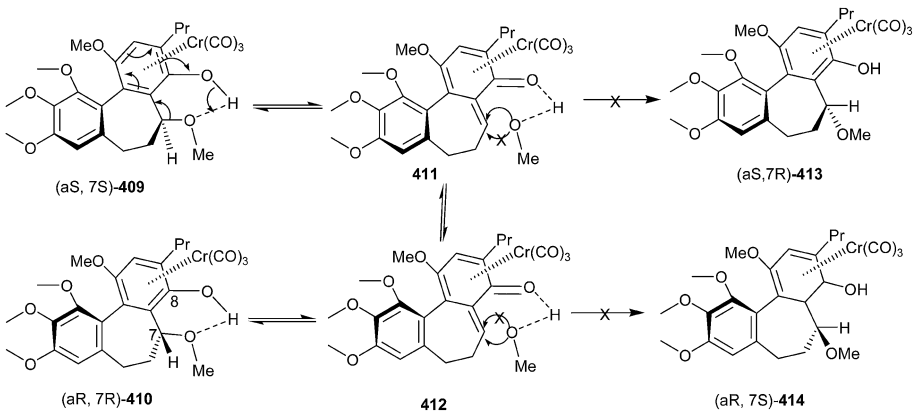


Scheme 88 Diastereoselactive synthesis of hexahydrodibenzopyrans *via* a chair transition state of a Cr complexed *o*-QM.

403 is an incompatible case and gives a mixture of diastereomers, the two most predominate of which are formed *via* an *exo* cycloaddition with a chair transition state with an axial methyl **407** and an *endo*-cycloaddition with a chair transition state with an equatorial methyl **408** (Scheme 88).

Wulff and co-workers[91] also disclosed the synthesis of allocolchicinoids that involves the benzannulation reaction of the Fischer chromium carbene complexes and alkynes with high to moderate diastereoselectivity. One of the diastereomer **409** was recemized, but not the other **413**. The intermediacy of an *o*-quinone methide chromium tricarbonyl complexes **411** & **412** and the intramolecular hydrogen bonding assist the reversible dissociation of methanol in compound (aS, 7S) **409** to give (aR, 7R) **410**. Due to the intramolecular H-bonding, it only becomes possible in diastereomer **409**, whereas the opposite diastereomer **413** would not participate, and thus retains its enantiomeric purity (Scheme 89).

QMs could be stabilized by the steric bulk or by coordination to electron-rich transition metal complexes. The mechanism of an enantioselective palladium-catalyzed alkene difunctionalization reaction gives evidence of rapid ligand exchange between palladium and copper, as well as a correlation between ligand electronic nature and enantioselectivity.[92] A substrate having an alkene with an adjacent *ortho*-phenol and a linked nucleophile **415** was used. *ortho*-Phenol not only coordinates the Pd(II) intermediate **416**, preventing hydride elimination, but it also allows for the *in situ* formation of an electrophilic quinone methide **418**, necessary for the second functionalization (Scheme 90). So this approach contrasts with others in the oxidation of the substrate, because the Pd centre does not promote the addition of the second nucleophile.

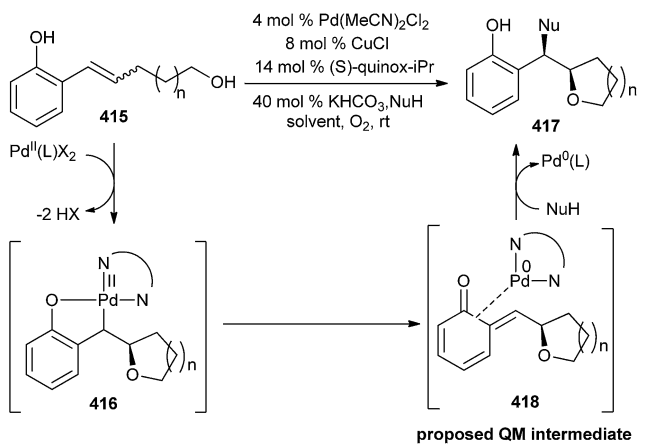


Scheme 89 Synthesis of allocolchicinoids involving Fischer chromium carbene complex and alkynes.

Pd(II) catalyzes the aerobic reductive coupling reactions of organometallic reagents and styrenes through *o*-QM intermediates.[93] Compound A initially oxidizes the alcoholic solvent to generate the Pd-hydride intermediate B, which coordinates with alkene **419** to give cationic complex C. The alkene inserts into the Pd-hydride yielding D and D′. As the consequence of formation of the benzylic addition product only, it has been emphasized that intermediate D′ proceeds to product *via* formation of *o*-QM E, with concomitant reduction of Pd(II) to Pd(0) and generation of **420**. Subsequently, ethanol reacts with the *o*-QM E to liberate the ether product **420** and the Pd(0) F, which has been reoxidized by $CuCl_2$ or O_2 (Scheme 91).

Phenols when bound to pentaammine osmium(II) **424**, readily react with aldehydes **425** to generate the complexes of *o*-QMs **427**. While these complexes are remarkably stable, when exposed to air or dissolved in water, treatment with CAN oxidizes the metal and releases the intact QM ligand, which can be trapped by a suitable dienophile **428** to give the compound **429** (Scheme 92).[94]

Whenever the phenol complex was treated with acetaldehyde, it gave the *o*-QM **430** with small amounts of acetaldehyde complex $[Os(NH_3)_5(acetaldehyde)]^{2+}$. The reaction of complex **430** with an excess of 3,4-dihydropyran and 1.5 equiv of CAN in acetonitrile provided tetrahydropyranochromene **431** (Scheme 93).



Scheme 90 Enantioselective palladium-catalyzed difunctionalization of alkene.

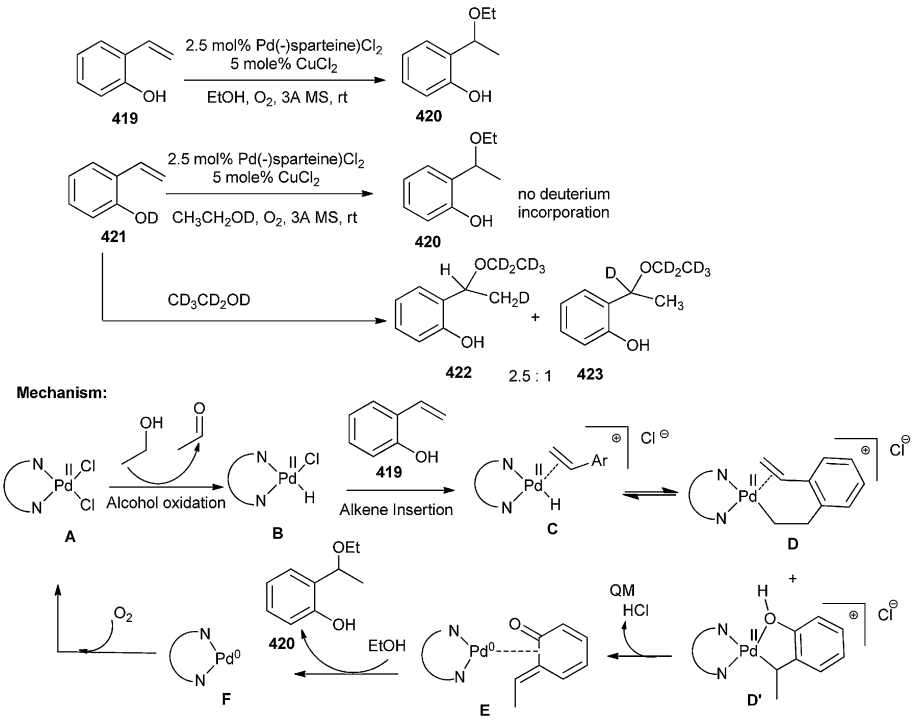
The intramolecular Diels–Alder reaction was accomplished by using the *o*-QM **432**, which was formed by treatment of the phenol complex **424** with (*R*)-citronellal and pyridine. Compound **432**, after treatment with CAN, leads to the demetallation and cycloaddition to form the benzo[*c*]chromene **433** in 52% yield as a single diastereomer (Scheme 94).

Cycloaddition reactions of activated olefins and styrenes **435** with *o*-quinine methides **436** in the presence of $PtCl_4$ and $AuCl_3$ gave a wide range of 2-alkyl or 2-aryl chromans **437**. Good diastereoselectivity (up to >99 : 1) of the chromans was obtained (Scheme 95).[95]

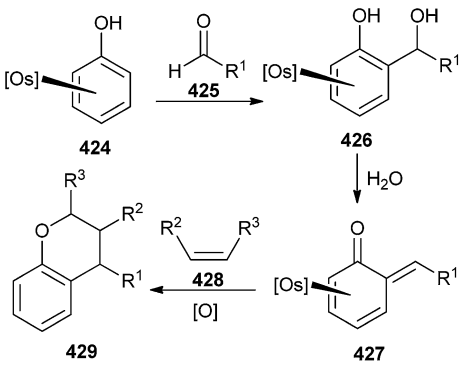
The reactivity[96] of an *o*-QM can be understood from M^{III} resonance form in which the carbon can be viewed as bearing a negative charge (Scheme 96). It has been emphasized that the stabilisation of *o*-QM could be correlated to the degree of deviation of the carbonyl/alkene segment of the *o*-QM from planarity with the coordinated diene segment, which is a consequence of metal back-bonding into the aromatic system.

Metal stabilised *o*-QM showed a complete reverse effect; the methylene carbon became nucleophilic upon transition metal coordination. For example, in Cp*Ir(*o*-QM) **442** the exocyclic carbon undergoes nucleophilic substitution reactions, *e.g.* with iodine or methyl propiolate, and [3 + 2] dipolar cycloadditions, as in the case of the electron-poor dienophile *N*-methylmaleimide **443** (Scheme 97). The partial charge and hinge angle follow the order Ru < Co < Rh < Ir. The Ru and Co complexes predicted high reactivity. Mono substituted nucleophilic metal complexes were isolated to establish the importance to the application of this chemistry for the stereoselective synthesis.

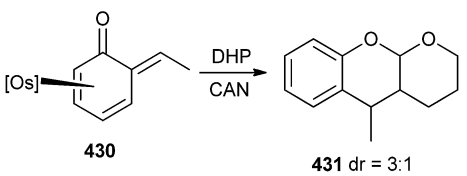
Knoevenagel reaction of 2-hydroxy-1,4-naphthoquinone, 4-hydroxycoumarin, and 4-hydroxy-6-methylcoumarin with paraformaldehyde generated respective quinone methides **447**, **448** and **449**. They applied these *in situ* generated intermediate in the hetero-Diels–Alder reaction with β-vinyl-*meso* tetraphenylporphyrinatozinc(II) **446**, leading to macrocycles containing 5,10-dioxobenzo[*g*]chromene, 5,6-dioxobenzo[*h*]-chromene **450**, pyrano[3,2-*c*]coumarin **451**, and benzopyran **452** motifs at the β-position (Scheme 98).[97]



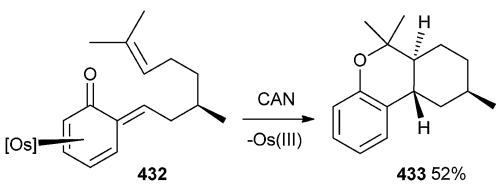
Scheme 91 Pd(II) catalyzed reductive coupling of organometallic reagents and styrenes *via* *o*-QM intermediate.



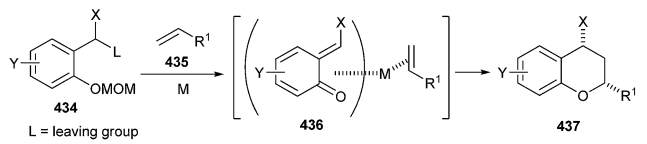
Scheme 92 Trapping of Os-complexed *o*-QM by different alkenes.



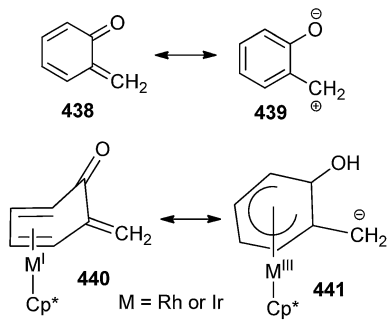
Scheme 93 Reaction of Os-complexed *o*-QM with 3,4-dihydropyran.



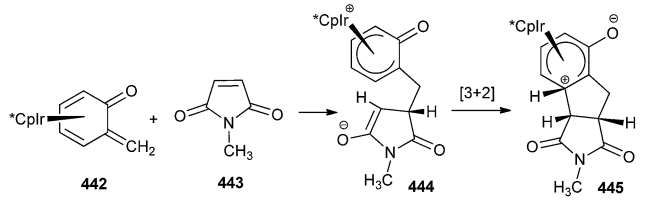
Scheme 94 Diastereoselective synthesis of benzo[*c*]chromene.



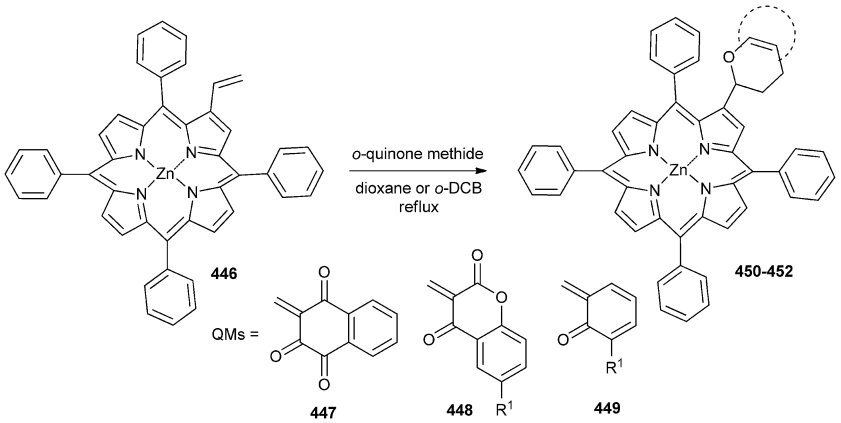
Scheme 95 Cycloaddition reactions of activated olefins with *o*-QM.



Scheme 96 Resonating forms of metal *o*-QM complex.



Scheme 97 Cycloaddition reaction of Cp*Ir(*o*-QM) with *N*-methylmaleimide.



Scheme 98 Hetero-Diels–Alder reaction of *o*-OMs with β-vinyl-*meso* tetraphenylporphyrinatozinc(II).

3.6. Rearrangement reactions

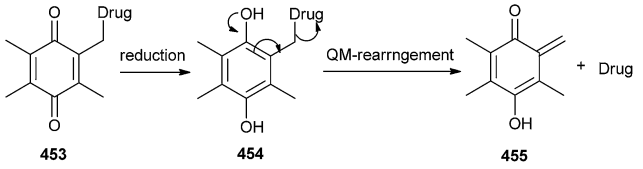
The chemical transformation of fluorogenic BCC triggered by thiols proceeds through a tandem benzoquinone reduction and QM type rearrangement reactions, which are spontaneous and irreversible at physiological temperatures in aqueous media.[98] In general, the intracellular reduction of the quinone moiety **453** produces the corresponding hydroquinone **454** that instinctively releases the deactivated drug and gives compound **455** *via* a QM-type rearrangement (Scheme 99).

QM-type rearrangement reaction sequence has been employed as part of the fluorescence releasing mechanism for latent fluorophores or the drugs release mechanism of the prodrugs, as shown in Scheme 100.

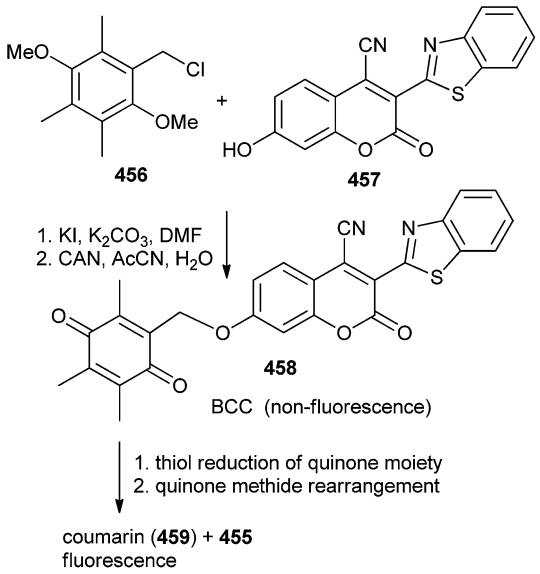
Silva and Bozzelli[99] have reported that *o*-QM, a 6-methylene-2,4-cyclohexadiene-1-one is an important intermediate in lignin and alkyl benzene combustion, and so the thermal decomposition of *o*-QM is pertinent to the combustion of transportation fuels (containing toluene) and of biomass and low-rank coals (containing lignin). A potential pathway leading to *o*-QM **463** formation has been demonstrated by the reaction of the benzyl radical **464** with O_2, which would also be important in toluene combustion (Scheme 101).

The formation of tropone *via* a hydroxyphenylcarbene intermediate **467** from *o*-QM undergoes an intramolecular hydrogen shift to produce 2-hydroxphenylycarbene **467** in a concerted process (Scheme 102).

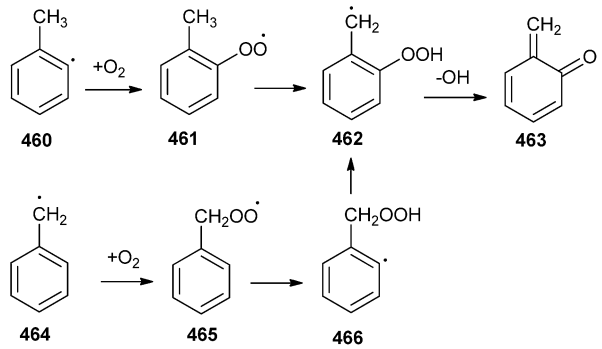
Eventually, the mechanism for fulvene (+CO) formation has been considered. The ring opened product **470** cyclises to the bicyclic intermediate bicyclo[3.2.0]hepta-3,5-dien-1-one **471**, which rearranges to yield spiro[2.4]hepta-4,6-dien-1-one (**472**).



Scheme 99 Generation of deactivated drug *via* QM-type rearrangement.



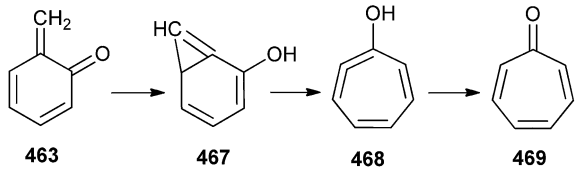
Scheme 100 Drugs release mechanism of the prodrugs.



Scheme 101 Combustion of toluene.

This intermediate subsequently dissociates to fulvene **473** and CO (Scheme 103).

It has been assumed[100] that the structure obtained after proton transfer is a resonance hybrid of two possible forms,

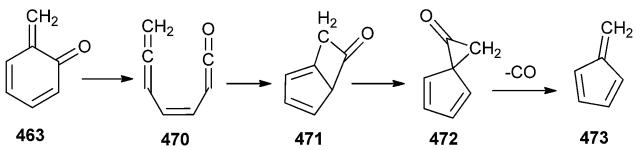


Scheme 102 Synthesis of tropone from *o*-QM.

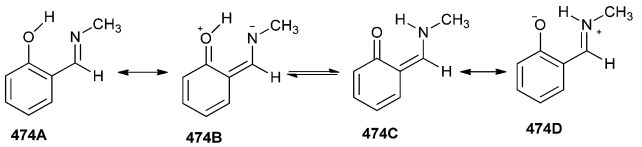
zwitterionic (*ortho*-quinoid, **474B**) and keto enes (*ortho*-quinoid, **474C**), as shown in Scheme 104. The wave function of the real structure is a linear combination of the wave functions of two resonance forms. The results demonstrate that not only resonance enhances the strength of hydrogen bonds, but also that the formation of intramolecular hydrogen bonds leads to more efficient resonance. The value of this stabilization can be estimated as a difference in energy between the proton transfer state and the open one, which is about 5 kcal mol^{-1} in *N*-methyl-2-hydroxybenzylideneamine.

Reaction of guaiazulene[101] **475** with 2-methoxybenzaldehyde **476** in methanol in the presence of hexafluorophosphoric acid at 25 °C gives (3-guaiazulenyl)(2-methoxyphenyl)methylium hexafluorophosphate **477** with 93% yield. Similarly, reaction of **475** with 3-methoxybenzaldehyde under the same reaction conditions affords (3-guaiazulenyl)(3-methoxyphenyl)-methylium hexafluorophosphate **478** (91% yield) or with 4-methoxybenzaldehyde gives (3-guaiazulenyl)(4-methoxyphenyl) methylium hexafluorophosphate **479** (97% yield). The crystal structures of these monocarbenium-ion compounds, possessing interesting resonance forms, are stabilized by the 3-guaiazulenyl and anisyl (2-, 3-, or 4-methoxyphenyl) groups (Scheme 105).

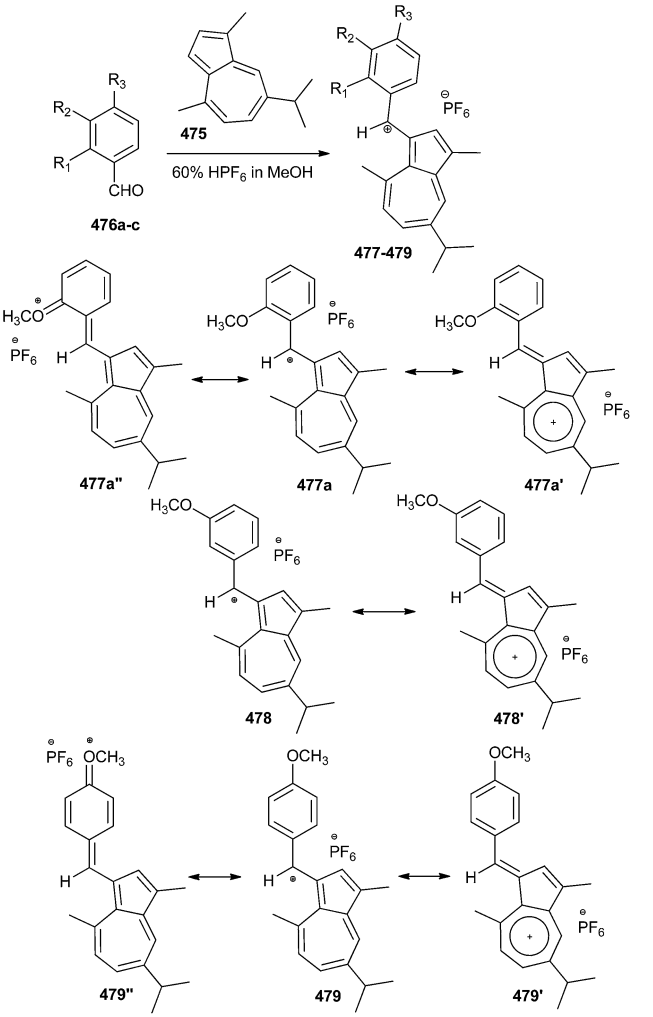
The regiochemical product of Pictet–Spengler cyclization reactions, focussed toward the preparation of the pentacyclic core of the ecteinascidin class of antitumor antibiotics, has been explored on two different phenolic substrates.[102] The reduction of the β-lactam unit in compound **480** proceeds through the coordinated lithium complex **481**, which also prevents the over-reduction of the corresponding aldehyde group. Following aqueous quench with NH_4Cl, condensation of



Scheme 103 Synthesis of fulvene.



Scheme 104 Resonating structures of zwitterions (*ortho*-quinoid, and keto enes).



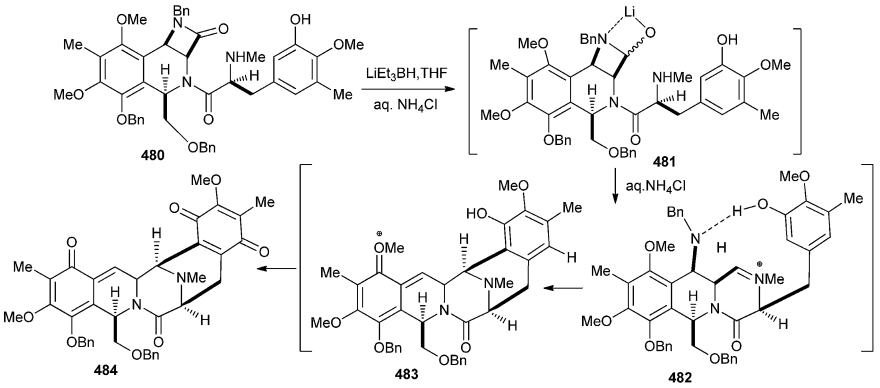
Scheme 105 Reaction of guaiazulene with methoxybenzaldehyde and resonating structure of products **477–479**.

the secondary amine group onto the hemi-aminal unit **481** led to the key iminium ion intermediate **482**. The expected hydrogen bonding between the C-4 benzylic amine and the E-ring phenolic residue directs the Pictet–Spengler cyclization *ortho* to the phenol. Finally, spontaneous elimination of the C-4 benzylamine group occurs through the intermediacy of *o*-QM **483** to afford the C3–C4 unsaturated pentacyclic compound **484** as the major product (Scheme 106).

3.7. Tautomerism

After oxidation, quercetin **485** exists in the four tautomeric forms **486–489**, one *o*-quinone isomer **486** and three quinone methide isomers **487**, **488** and **489**.[103] Due to the relatively high abundance of the quinone methide isomers, glutathionyl adduct formation occurs at positions C6 and C8 of the quercetin A ring to give 6-GSQ **490** and 8-GSQ **491** (Scheme 107).

Depending on the orientation of the indole rings around the single bond, it has been predicted that the pairs of *syn*-periplanar (sp) and *anti*-periplanar (ap) rotamers for the *o*-quinone, quinone methide, and quinonimine tautomers of dimers **493–**

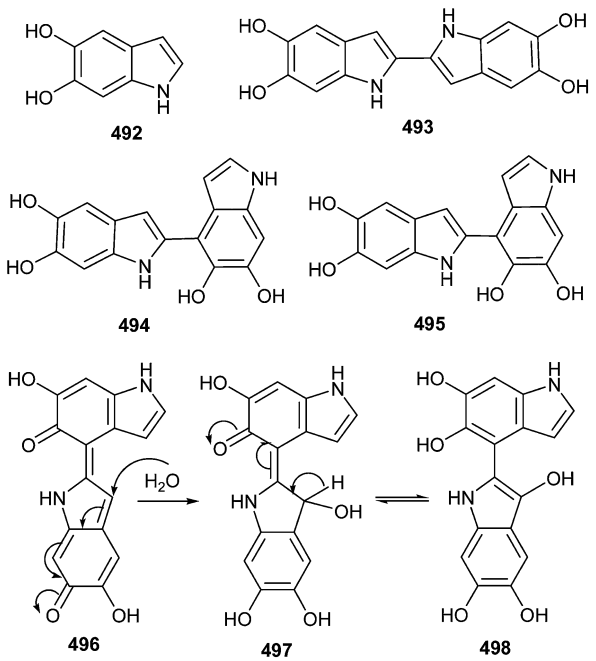


Scheme 106 Pictet–Spengler cyclization reaction for the synthesis of C3–C4 unsaturated pentacyclic compound **484**.

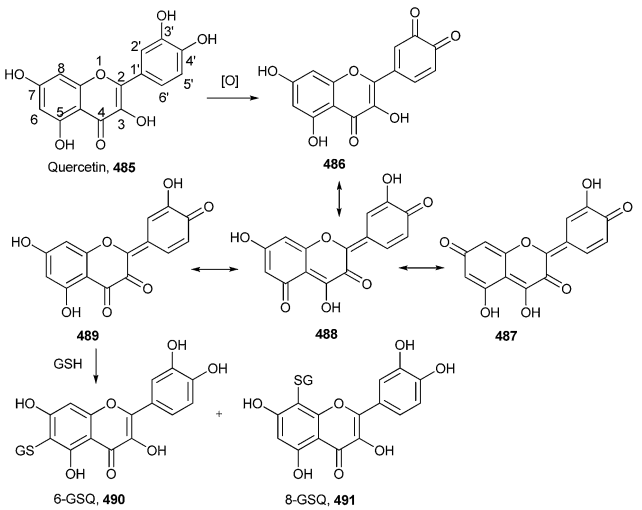
495, two geometrical isomers (*E* and *Z*) are possible for the extended forms.[104] In order to resolve a reasonable entrant among these structures for the observed two-electron oxidation products of the dimers, all tautomeric quinones of dimers **493–495** were geometry-optimized in vacuum at the PBE 0/6-31+G(d,p) level of theory. The pentahydroxybiindolyl **498** was isolated from unprecedented hydroxylated indole derivative by oxidation of dimer **494** (Scheme 108).

Pestacin occurs naturally as a racemic mixture of (S) **499** and (R) **501** enantiomers.[105] This racemization probably occurs post-biosynthetically as enzyme mediated reactions with stereo-specificity. A racemization mechanism proceeds through a cationic intermediate **500**, which has the desirable feature of being stabilized by different resonating structures. These intermediates are further stabilized by their ability to tautomerize into the three neutral *o*-QMs **501–503** (Scheme 109).

It has been identified that certain aryl quinones experience a tautomeric isomerization to an intermediate QM because of the low barriers of rotation about central aryl-quinone C–C bond, which brings significant implications to consider in the design of synthetic routes leading to natural aryl quinones such as



Scheme 108 Structures of dimers of indole and hydroxybiindolyl.

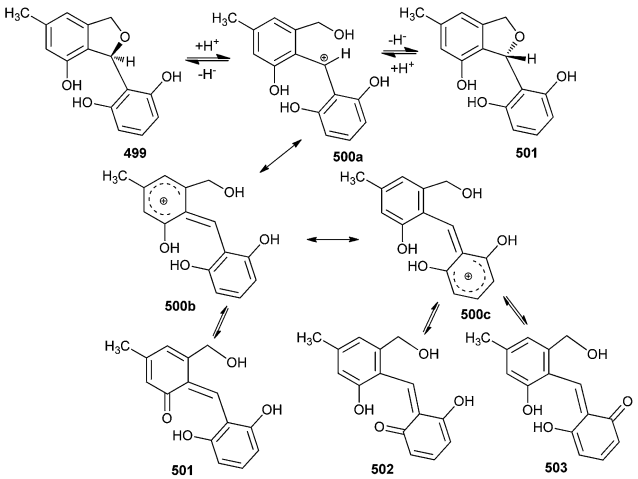


Scheme 107 Glutathionyl adduct formation at the quercetin ring.

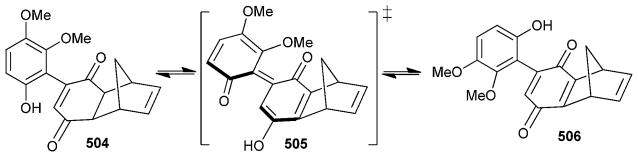
hibarimicin B.[106] The rotational barrier of phenol is significantly lowered due to the stabilization of the transition state structure, leading to the interconversion of **504** and **506** by tautomerization to intermediate QM **505** (Scheme 110).

3.8. Photochemical reactions

The photochemistry of a number of *p*-biphenyls and terphenyls substituted with hydroxyl and hydroxymethyl groups in aqueous solutions has been studied in detail by Wan and co-workers.[107] They reported that the simple hydroxyl group can strongly and appropriately activate substituted benzenes or biphenyls towards dehydroxylation due to its strongly electron-donating nature, as well as for being carrier of an acidic proton. The intermediates formed are the corresponding quinone methides (QMs) or biphenyl quinone methides (BQM, **508** & **511**), as shown in Scheme 111.



Scheme 109 Resonating structures of Pestacin.

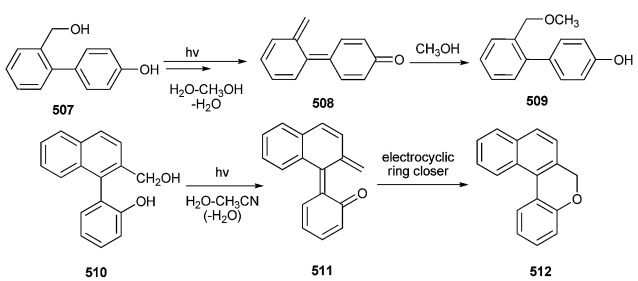


Scheme 110 Tautomerization in quinone methide.

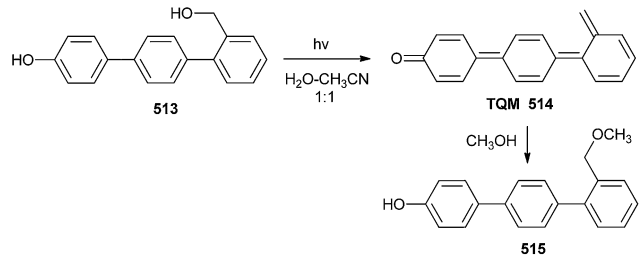
There was no pH effect on the photosolvolysis quantum yield of the hydroxyterphenyls **513** in the pH 4–12 region, so the most probable mechanism for photosolvolysis is the formation of excited state phenolate followed by dehydroxylation to give terphenyl quinone methides (TQM, **514**), which after reaction with methanol gives compound **515** (Scheme 112).[107a]

Compound **516** with competing photosolvolytic reaction generated compound **517** by the ESIPT process, with or without water.[108] At higher water contents, an intermediate **518** (with one or more water molecules) underwent the loss of hydroxide ions from the benzylic position with the assistance of the hydronium ion to generate quinone methide **519**, and finally over all solvolysis (attack by CH_3OH at the terminal quinone methide position) gave compound **520** (Scheme 113).

The compound 9-(2′-hydroxyphenyl) anthracene **521** undergoes proficient photoaddition of water and alcohols at the 9- and 10-positions of the anthracene moiety to give isolable



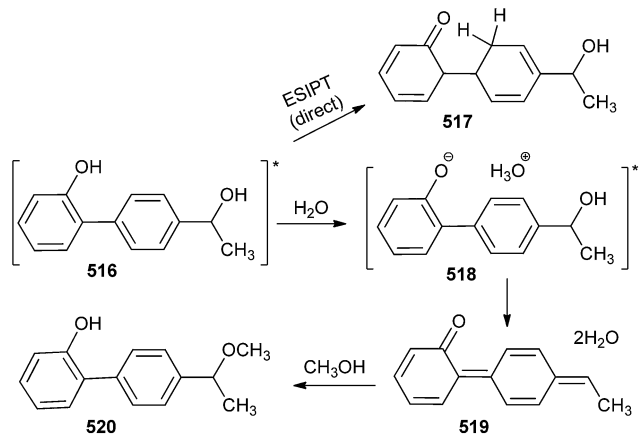
Scheme 111 Photochemical synthesis of compounds **509** and **512**.



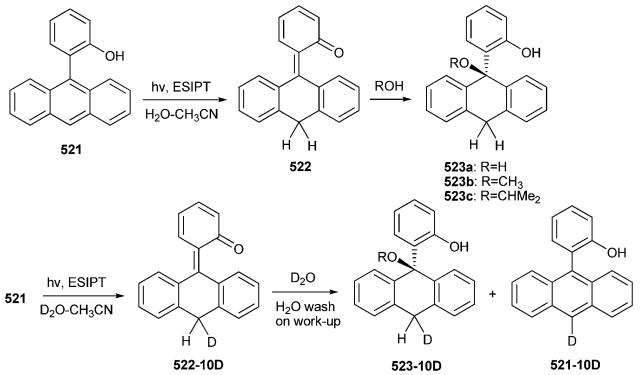
Scheme 112 Reaction of methanol with terphenyl quinone methide **514**.

triphenylmethanol or triphenylmethyl ether type of products.[21] The reaction is supposed to ensue *via* water-mediated formal excited state an intramolecular proton transfer (ESIPT) from the phenolic OH to the 10-position of the anthracene ring, generating an *o*-QM intermediate that is observable by nanosecond laser flash photolysis, and is trappable with nucleophiles. Irradiation in deuterated solvents led to incorporation of one deuterium atom at the methylene position in the photoaddition product, and partial deuterium exchange of the 10-position of recovered starting material, which is reliable with the proposed formal excited state proton transfer mechanism (Scheme 114). The deuterium exchange and the photoaddition have got maximum quantum efficiency in 5 M water (in CH_3CN or CH_3OH), and no reaction was observed in the absence of a hydroxylic solvent, thus representing the sensitivity of this type of ESIPT to solvent composition. Once formed, QM **522** is transformed to **523** (hydration product) or returns to **521** *via* enolization. These two reaction pathways from **522** are not really astonishing apart from the isolation of the stable anthracene hydrates and alcohol adducts (Scheme 114).

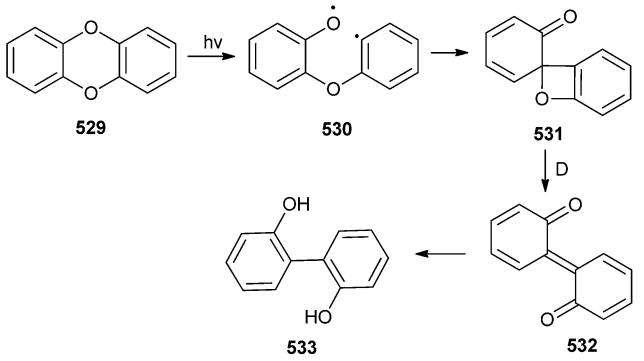
In general, caged carbonyl compounds[109] are prepared by their acetalization with (2,5-dimethoxyphenyl)ethylene glycol followed by oxidative demethylation to produce the corresponding (1,3-dioxolane-4-yl)-1,4-benzoquinones. (2,5-Dihydroxyphenyl) ethylene glycol acetals of aldehydes and ketones **524a–e** upon irradiation (at 300 nm) resulted in their efficient



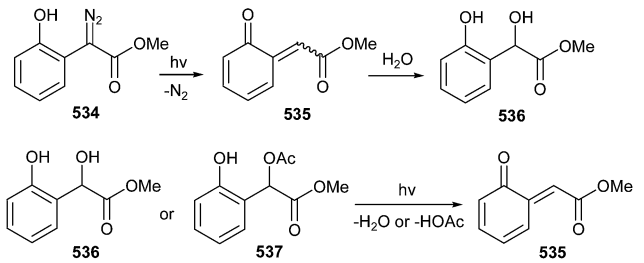
Scheme 113 Photosolvolytic reaction of quinone methide **519**.



Scheme 114 Photoaddition of hydroxylic solvents at 10-position of the anthracene.



Scheme 116 Photochemical aryl-ether bond homolysis of dibenzo-[1,4]dioxin.



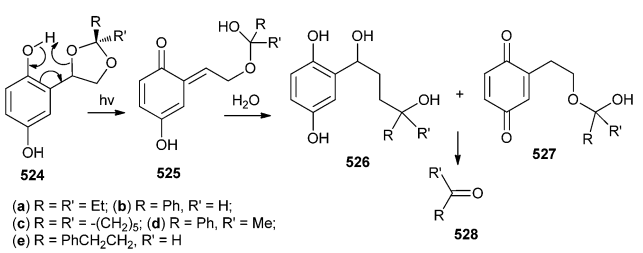
Scheme 117 Photolysis of methyl 2-hydroxyphenyl diazoacetate.

cleavage and in the regeneration of the carbonyl compound. This proceeds *via* photoinduced transfer of the phenolic proton to the dioxolane oxygen in the 3-position accompanied by the C–O bond cleavage and the formation of an intermediate *o*-QM **525**. *o*-QM is very reactive and could undergo rapid hydration or tautomerization to form corresponding unstable hemiacetals **526** and/or **527**. The hydrolysis of **526** and **527** liberates the carbonyl compound **528** (Scheme 115).

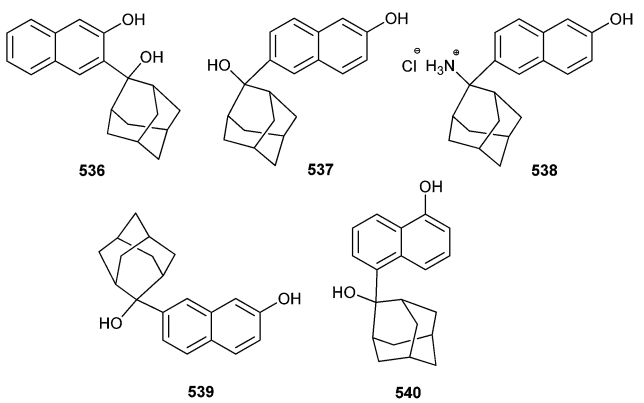
The dibenzo[1,4]dioxins **529** underwent a photochemical aryl–ether bond homolysis to generate reactive 2-spiro-6-cyclohexa-2,4-dienone **531** and subsequent biphenylquinone intermediates.[110] Under steady-state irradiation, the 2,2′-biphenylquinones **532** undergo an excited state hydrogen abstraction from the organic solvent to give the corresponding 2,2-dihydroxybiphenyls **533** (Scheme 116).

The flash photolysis of methyl 2-hydroxyphenyldiazoacetate **534** in dilute aqueous perchloric acid solution and acetic acid and biphosphate ion buffers generated a transient species that was identified as *o*-quinone-α-carbomethoxymethide **535** (Scheme 117).[111] This structural assignment is based on the solvent isotope effects, the form of buffer catalysis, UV absorption maxima, and the identity of decay rate constants with those determined for the transient, obtained by flash photolysis of other more conventional quinone methide precursors such as the benzyl alcohol methyl 2-hydroxy mandelate **536** and its acetate, 2-acetoxy-2-hydroxyphenylacetate **537**.

New (2-adamantyl)naphthol derivatives **536–540**, quinone methide precursors (QMP, Scheme 118) were synthesized and their photochemical reactivity was investigated by preparative photolyses, fluorescence spectroscopy, and laser flash photolysis (LFP). All derivatives undergo photosolvolysis *via* QM intermediates. Presence of adamantly moiety results in different reactivity pattern compared to the non-substituted structure. They also investigated the anti-proliferative activity of the QMPs on three human cancer cell lines: HCT 116 (colon), MCF-7 (breast), and H 460 (lung). Exposure of cells treated with 5 to 300 nm of irradiation led to enhanced anti-proliferative effect on MCF-7 cell line, classifying 5 (or QM5) as a potential lead for further anti-proliferative studies.[112]



Scheme 115 Regeneration of the carbonyl compound by irradiation of ethylene glycol acetals.



Scheme 118 Quinone methide precursors of (2-adamantyl)naphthol derivatives.

4. Concluding remarks

In this review, we present the power and diversity of applications of *ortho*-quinone methides (*o*-QMs), which have become powerful, fascinating, and highly efficient intermediates in organic synthesis. Recent advances toward the generation, reactivity and application of *o*-QMs in organic synthesis offer a bright future for the development of novel methodologies for the synthesis of natural and man-made compounds. The cases cited in this review have been selected to highlight the most promising applications of *o*-QMs in organic synthesis. It can be seen that many well-established different methodologies were successfully applied to *o*-QMs by worldwide laboratories to more environmentally benign approaches. This area is clearly expanding in several aspects and will reveal spectacular applications in the near future, ranging from organic synthesis, material chemistry, fine chemicals, and pharmaceuticals to the synthesis of natural products. Definitely, much more remains to be done in this field, and in the next few years, we will see many new, exciting findings in *o*-QMs chemistry. Moreover, it will lead to the serendipitous discovery of many more new reactions, for as much as we may know, chemistry always has new and intriguing surprises in store. Therefore, we sincerely hope that this overview will be of interest for the synthetic community as well as for the general readers. Despite the flurry of recent interest in this species, it is unlikely that we have seen a peak, and it is probable that in future years *o*-QMs will be viewed in the same light as radicals, carbenes, benzynes or similar reactive intermediates.

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