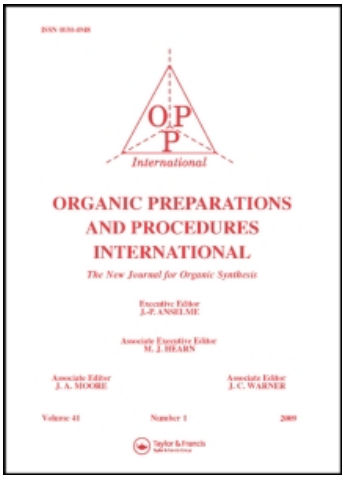

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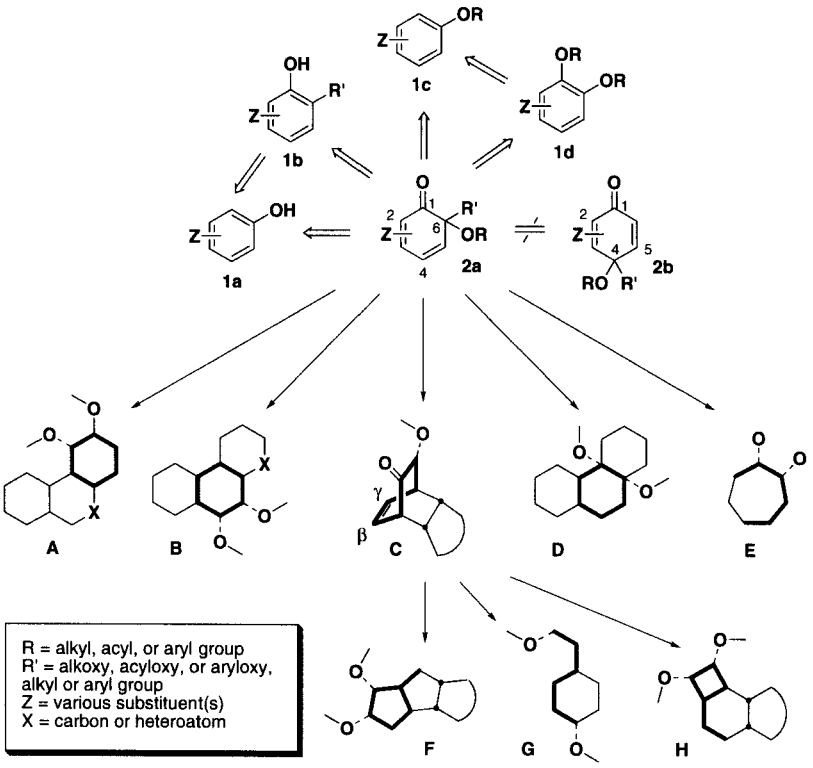
INTRODUCTION

Orthoquinone monoketals **2a**, *i.e.*, 6,6-dioxocyclohexa-2,4-dien-1-one derivatives and their 6-carbo-6-oxocyclohexa-2,4-dien-1-one orthoquinol variants, remain underutilized in preparative organic synthesis, in contrast to their para cyclohexa-2,5-dien-1-one counterparts **2b** whose chemistry has been more extensively studied.[1-3] Paraquinone monoketals **2b** possess a cross-conjugated but relatively stable dienone system which is usually easier to utilize in organic synthesis than the linearly-conjugated but more reactive dienone system of **2a** (*Scheme* 1). Orthoquinone monoketals **2a** would nevertheless constitute valuable electrophilic intermediates in particular because their electronically differing double bonds have the potential of being regioselectively elaborated into various organic motifs. Furthermore, the ketal group permits the differentiation of vicinal oxygen functionalities and at the same time provides monoprotection of the 1,2-dicarbonyl unit of the corresponding benzoquinones. Orthoquinone monoketals, hence sometimes referred to as "masked" benzoquinones,[4] are ideally functionalized for the construction of polyoxygenated carbo- and/or heteropolycyclic skeleta that are featured in numerous natural products (*Scheme* 1). Moreover, the presence of two vicinally oxygenated carbon centers in these potentially versatile synthons should not be overlooked for it is always rather difficult to introduce such functionalities onto a pre-established cyclic hydrocarbon network (*Scheme* 1).[5,6]

Unfortunately, it is often difficult to exploit the reactivity of their linearly conjugated dienone system in a controlled manner because of its propensity to undergo Diels-Alder reactions. The conditions of orthoquinone monoketal preparation must be carefully chosen so as to avoid undesired premature transformations such as Diels-Alder dimerizations and rearomatizing rearrangements.[3] Chemical and electrochemical oxidations of phenol and catechol derivatives **1a-d** are the methods most frequently employed to generate orthoquinone monoketals and their orthoquinol variants (*Scheme* 1). Dearomatisation of phenols **1a/b** is thus achieved by a two-electron process which formally corresponds to a nucleophilic substitution of hydrogen; a nucleophilic two-electron donor attacks a dehydrogenated ($-H^+$, $-2e^-$) phenol. This oxidized phenol intermediate is regioselectively trapped *in situ* by the nucleophile to furnish the orthoquinonoid product **2a**. Phenyl alkyl ethers **1c/d** are usually electrochemically oxidized to orthoquinone bisketals which can then be hydrolyzed down to orthoquinone monoketals (*vide infra*).[1,7] The exact nature of the starting phenol derivatives,

in particular the electronic effect and steric impediment derived from their substituents, the type of oxidizing and nucleophilic agents, the kind of reaction solvent used, the temperature and the reaction time are as many key factors upon which the success of the preparation depends.



Scheme 1

The aim of this review is to provide the reader with information on the different methods available today to make various types of orthoquinone monoketals and orthoquinols, and on the different types of chemistries to which they are susceptible. The review will begin with a presentation of the most commonly used preparation modes. This will be accompanied by elements of mechanistic discussions and followed by a compendium of the most frequently encountered orthoquinone monoketal and orthoquinol reactions. Finally, their most recent and remarkable applications in natural products synthesis will be reviewed.

1. SYNTHESIS OF ORTHOQUINONE MONOKETALS AND THEIR ORTHOQUINOL VARIANTS

The two methods most commonly used to generate orthoquinone monoketals and their orthoquinol variants are (1) chemical oxidative alkoxylation or acyloxylation of phenols, 2-alkoxy- and 2-alkylphenols **1a/b**, and (2) electrochemical anodic oxidation of phenols **1a/b**, as well as phenyl alkyl ethers **1c/d**. In regards to phenyl alkyl ethers **1c/d**, one can here recall Swenton's acid-mediated hydrolysis of electrochemically-generated bisketals derived from methoxy- and dimethoxynaph-

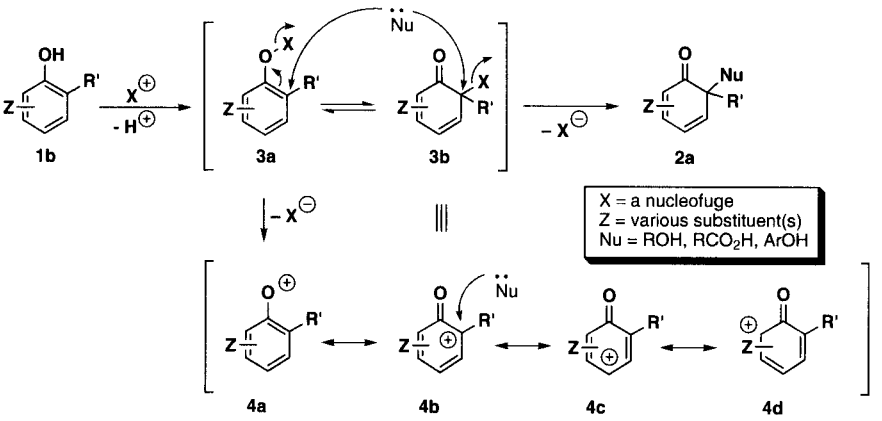
thalenes.[8,9] It is in fact important to note that orthonaphthoquinone monoketals are much less reactive than their simpler orthobenzoquinone analogues. This extra stability is due to the fact that one double bond is part of an aromatic ring in the naphthalenoid series.[1] This factor can be exploited not only to diversify oxidation-mediated uses of naphthyl alkyl ethers and naphthols,[10-12] but also to contemplate further elaboration of the cyclohexa-2,4-dienone moiety of their oxidation products (*Eq.* 26).

Another important factor that controls the chemical reactivity of these cyclohexadienone species is the nature of the substituents at the ketal 6-position. In his work on the behavior of periodate-generated benzenoid orthoquinone monoketals, Andersson had established that 6,6-dialkoxy derivatives are particularly sensitive to Diels-Alder dimerization and cannot generally be isolated as such unless the system is adequately substituted (*vide infra*).[13-15] However, as already alluded to by Swenton[1] on the basis of Wessely's early observations,[16] the corresponding 6,6-diacetoxy- and 6-acetoxy-6-alkoxy compounds are typically less reactive toward dimerization and can be isolated as monomers, albeit usually in moderate yields. Although the substitution pattern of the cyclohexadienone unit must play a role in determining its stability based on steric grounds, it would thus appear that the electronic effect of the 6-substituents is an even more critical factor in the modulation of its stability.

Independently from the type of quinone monoketals or quinols targeted, recent preparations have relied much more on chemical oxidation than anodic oxidation, even though the electrooxidation could be viewed as a cheaper, cleaner and milder alternative to the use of metallic oxidants, often based on toxic metals, such as Pb(IV),[17,18] Tl(III),[19-21] Bi(IV),[22] Mn(IV),[23,24] Ag(I),[25] as well as Fe(III),[21,25,26] Cu(II) or Cu(I),[27] and Ce(IV).[28] Neutral organic oxidants such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[21,23] and tetrachloro-1,2-benzoquinone (*o*-chloranil),[29-31] as well as halogenating agents such as *N*-bromosuccinimide (NBS),[29,32] 2,4,4,6-tetrabromocyclohexa-2,5-dienone,[33] phenyltrimethylammonium tribromide,[34] hypobromite and dihalogens Br_2[32,35,36] or I_2 in the presence of Hg(II) oxide[37] have also been utilized with success.

The utilization of electrophilic halogen sources is a good starting point for discussions on the mechanism(s) of all aforementioned chemical two-electron oxidations used to generate orthoquinone monoketal variants. It has been postulated that such halogenating reactions give rise to "masked" phenoxenium ions of the phenoxide-halide type **3a** and/or of the α-bromo ketone type **3b** as reaction intermediates (*Scheme 2*). An alkoxy, aryloxy, or acyloxy nucleophile would then displace the halide anion (X = Br, I) to furnish the desired cyclohexadienones **2a**. This postulate can be generalized to other oxidative nucleophilic substitution with nucleofugal groups (X) other than halogens such as reducing metallic centers (e.g., X = PbL_3 or TlL_2 with L = ligand) as well as hypervalent iodine(III) (X = IL_3) (*vide infra*). This general mechanism would also encompass the intermediary of free resonating phenoxenium ions of type **4** if departure of the nucleofuge precedes attack of the nucleophile (*Scheme 2*).[38-42] Generation of phenoxenium ions **4** has been evidenced for anodic oxidation of phenols.[43,44] The control of the regiochemistry of nucleophilic attack remains obscur, but it is clear that a small electron-releasing ortho-substituent such as a methoxy group often suffices to orient the attack prefer-

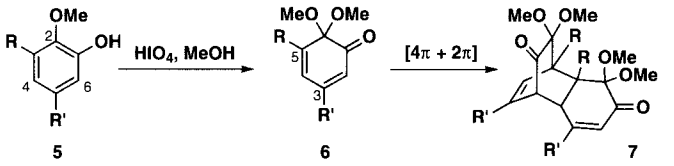
entially at the corresponding substituted carbon center, even when this position is the most sterically hindered one.[38] One can perhaps simply invoke the fact that an electron-donor at an ortho-position make the corresponding resonance forms of type **4b** contribute more to the phenoxenium structure than the unsubstituted para- and ortho-oxocyclohexadienylium cations **4c** and **4d**. Further intramolecular stabilization of **4b** by the nucleofugal group can also be suggested to explain the regiochemical outcome generally observed in this type of reaction (*Scheme* 2). In any event, the pronounced orienting effect of an ortho-methoxy substituent has been corroborated by recent calculations on charge distributions and LUMO coefficients of substituted phenoxenium ions.[38,45] Today, most of the aforementioned reagents are rarely used for the generation of orthoquinone monoketals and ortho-quinol variants because of the development of non-toxic and easy-to-handle oxidizing hypervalent iodine(III)-based reagents which has rendered chemical oxidation the most commonly used technique to make these quinonoid species.[38,39,46-51]



Scheme 2

1. 6,6-Dialkoxy-cyclohexa-2,4-dienones

This class of orthoquinone monoketals, the only ones bearing a genuine ketal functionality, is easily accessible from oxidative alkoxylation of 2-alkoxyphenol. Andersson and Berntsson used methanolic periodic acid to generate 6,6-dimethoxy-cyclohexa-2,4-dienones which rapidly underwent Diels-Alder dimerization.[15] Andersson and co-workers then observed that a small substituent such as a methoxy group at the 3-position of the cyclohexa-2,4-dienone ring significantly retards dimerization,[15] and that the same small substituent at the 5-position is capable of preventing dimerization (*Eq.* 1).[13,14] Isolated yields of 6,6-dialkoxy-cyclohexa-2,4-dienones are often, however, low to moderate (*Eq.*1). Better yields are generally obtained when using 2-alkoxyphenols bearing bulky substituents at their 4- and 6-positions, that is at the 4- and 2-positions of the cyclohexa-2,4-dienone system. A yield of 95% was, for example, reported by Hewitt for the conversion of 2-methoxy-4,6-di-*t*-butylphenol into the corresponding dimethoxy monoketal (not shown).[27]



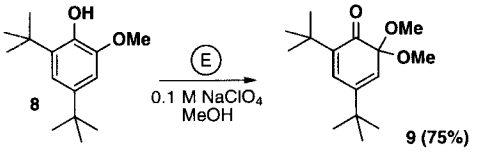
(1)

R	R'	6(yield,%)	7(yield,%)
H	H	0	23
H	OMe	10 [a]	traces
OMe	H	39	0

[a]Full conversion to the Diels-Alder dimer was achieved upon standing at rt for 48 h.

Among other oxidizing systems used to prepare this type of orthoquinone monoketals from phenols, one can here cite Wessely's $Pb(OAc)_4$-mediated oxidation (*i.e.*, LTA = lead tetraacetate),[19] McKillop's $Tl(NO_3)_3$-mediated oxidation (*i.e.*, TTN = thallium trinitrate),[19,20] Hewitt's copper-amine catalyzed autoxidation[27] – all performed in methanol solvent – and the anodic methoxylation that has been thoroughly investigated by, *inter alia*, Ronlán[52] and Swenton.[1] For example, McKillop reported a yield of 25% for **6** (R = OMe, R' = H), but the same oxidation of vanillin, isovanillin and *o*-vanillin rapidly led to Diels-Alder cycloadducts,[20] which is in agreement with Andersson's observations.[13-15]

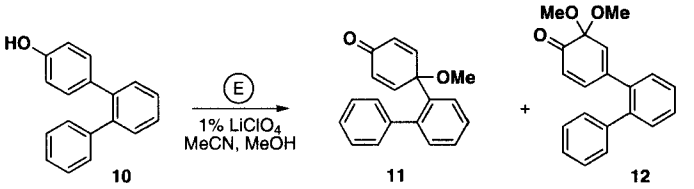
On the electrochemistry front, it is generally considered that electrooxidation of phenols bearing methoxy or small alkyl groups at their *ortho*- or *para*-position follows distinct but characteristic reaction pathways depending upon the electrolysis conditions used. Acidic and basic media tend to favor self-coupling reactions and quinone generation, respectively, whereas the use of neutral electrolyte systems at a low current density seem the most adequate conditions to furnish quinone mono- and bisketals.[43,53] Examples of orthoquinone ketal generation are relatively scarce when compared to those of paraquinone ketals. In addition to the few scattered examples found in Ronlán's[52] and Swenton's[1] early publications, one can here mention Rieker's high yielding preparation of 2,4-di-*t*-butyl-6,6-dimethoxycyclohexa-2,4-dienone **9** from the parent phenol **8** in 0.1M methanolic $NaClO_4$ (Pt anode, +880 mV) (*Eq.* 2)[54] and refer to Yamamura and co-workers' utilization of electrochemically-generated orthoquinone monoketals in natural products synthesis (*Eq.* 51).[55-57]



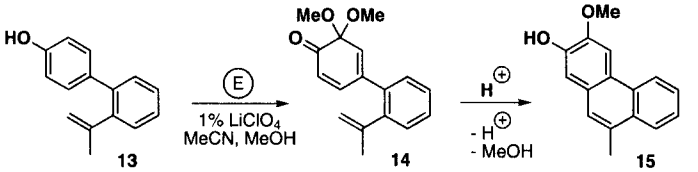
(2)

Morrow and Swenton[44,58] obtained a 1:1 mixture of **11** and the stable orthoquinol monoketal **12** in nearly quantitative yield from the anodic oxidation of 4-(2-biphenyl)phenol **10** in 4:1 MeCN–MeOH containing 1% by wt. of $LiClO_4$ (Pt anode, 0.1 A) (*Eq.* 3). The stability of **12** would be

attributed to the steric impediment confered to the 2,4-dienone system by the biphenyl substituent at the 4-position, again in agreement with Andersson's observations.[13-15] Similarly, phenol **13** gave rise, after silica gel chromatography, to the orthoquinol monoketal **14** in 26% yield, together with the acid-catalyzed cyclization product **15** in 39% yield (*Eq.* 4).[59]

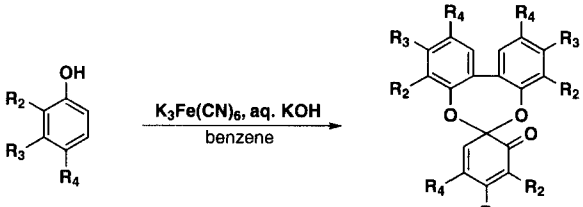


10 **11** **12** (3)



13 **14** **15** (4)

A noteworthy series of chemically-induced oxidative coupling of phenols have been described by several authors to lead to 6,6-diaryloxy-cyclohexa-2,4-dienones of type **17**. For example, treatment of 2,4-diphenylphenol **16a** with alkaline $K_3Fe(CN)_6$ was reported by Becker[26] to furnish, following trimerization via C–C and C–O bond formation, the dioxepin derivative **17a** in good yield (*Eq.* 5). Hewgill and co-workers[25] had earlier described the formation of similar dibenzo[*d,f*]dioxepins from $K_3Fe(CN)_6$-, Ag_2O- and PbO_2-mediated oxidations of various phenols such as **16b-16e** (*Eq.* 5). Mechanisms involving aryloxy radicals have been proposed to account for the initial C–C and C–O coupling reactions, as well as for the spiro-ketalization to the observed trimers,[60] but the involvement of aryloxy anions in two-electron transfers cannot be discounted. In the course of his investigations aimed at elucidating the mechanism of copper-containing enzymes, e.g., laccase and tyrosinase, Hewitt reported an improved yield of 95% for the conversion of **16c** into **17c** (*Eq.* 5) by treating a solution of the starting phenol in MeOH with a catalytic amount of a $CuCl_2$-morpholine complex in the presence of oxygen.[27]

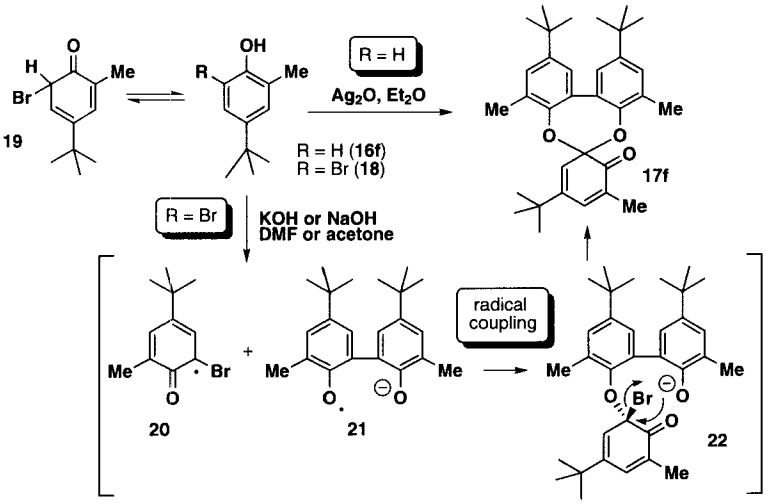


16a : R_2 = Ph, R_3 = H, R_4 = Ph
16b : R_2 = OMe, R_3 = H, R_4 = *t*-Bu
16c : R_2 = H, R_3 = *t*-Bu, R_4 = OMe
16d : R_2 = H, R_3 = *i*-Pr, R_4 = OMe
16e : R_2 = *i*-Pr, R_3 = H, R_4 = OMe

17a (54%)
17b (70%)
17c (47%)
17d (20%)
17e (20%)

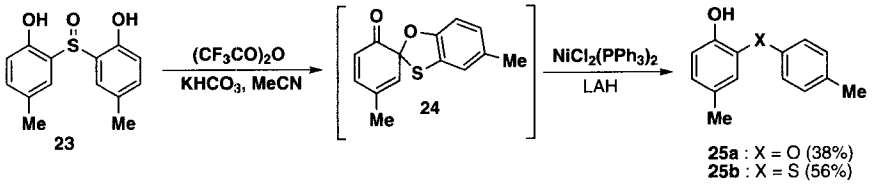
(5)

A rather intriguing variant of this route to dioxepins was also described by Bowman and Hewgill[61] to rely solely on base-induced coupling of 2-bromophenols. For example, the bromocresol **18** consistently gave rise to the dioxepin **17f** in yields higher than 95% when treated with alkali, whereas the corresponding cresol **16f** furnished **17f** in only about 40 % when oxidized with Ag_2O (*Scheme* 3).[61,62] The involvement of aryloxy anions and radicals, as well as ketyl radical anions resulting from one-electron transfer from the phenolate of starting **18** to its keto tautomer **19**, were proposed to rationalize the mechanism of formation of debrominated products;[61] spiro-ketalization was viewed as arising from an intramolecular displacement of a bromide nucleofuge by an attacking aryloxy anion moiety in a preformed trimeric species **22** as depicted in the general *Scheme* 2.



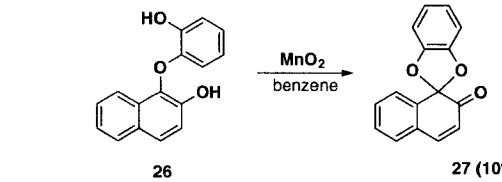
Scheme 3

The structures of this spiroketalic dioxepin **17f** and others were notably confirmed by catalytic hydrogenation to the aryloxybiaryl compound.[62] To our knowledge, this sequence of reaction which enables the conversion of simple phenols into biaryl diaryl ether units has never been exploited in natural product synthesis. In this regard, Michael Jung's report[63] on Pummerer-type rearrangement of an orthohydroxyaryl sulfoxide **23** into an orthoquinone mono(monothioketal) **24**, followed by desulfurization to the diaryl ether **25a** is worth highlighting, even though such a methodology did not so far become a general route to diaryl ethers (*Eq.* 6).

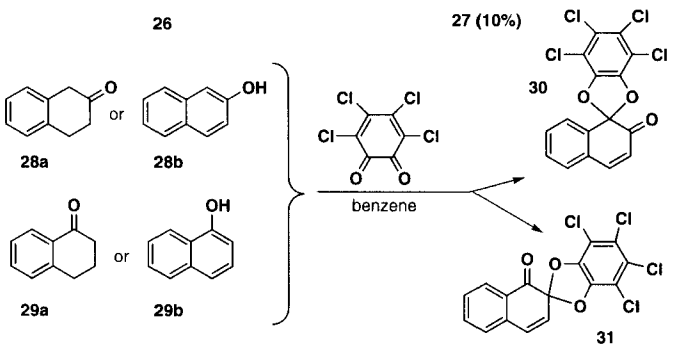


(6)

The related orthoquinone monoketal **27** was proposed by Coutts[23] to arise from MnO_2-mediated oxidation of the 1-(2-hydroxyphenoxy)-2-naphthol **26** (*Eq.* 7). Chlorinated versions of this monoketal have also been prepared from tetrachloro-1,2-benzoquinone treatment of tetralones and naphthols (*Eq.* 8); benzoid and phenanthroid analogues were made by the same dehydrogenative coupling method in moderate to good yields.[30,31]



26 27 (10%) (7)

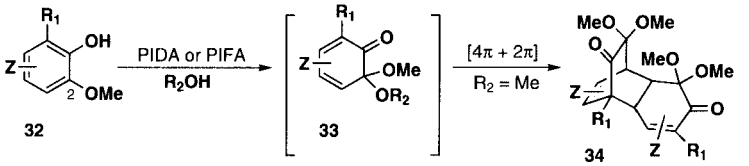


28a 28b 29a 29b 31 (8)

The two hypervalent iodine reagents,[39,46-51] diacetoxyiodobenzene [$PhI(OAc)_2$; also referred to as DAIB, BAIB, or DIB, as well as PIDA standing for phenyliodine(III) diacetoxy] and bis(trifluoroacetoxy)iodobenzene [$PhI(O_2CCF_3)_2$; also referred to as BFIB, BTIB or BTI, as well as PIFA standing for phenyliodine(III) bis(trifluoroacetoxy)], have been the most frequently used two-electron oxidants in recent preparations of orthoquinone monoketals from phenols. This popularity is due to the duality of their iodine(III)-based chemistry— they are good electrophiles but also behave as exceptionally good leaving group by releasing iodobenzene (PhI) — and their lack of toxicity in comparison to traditional metallic oxidants, as well as their operational simplicity. Both reagents are commercially available white microcrystalline solids and removal of PhI and acetic acid or trifluoroacetic acid by-products is conveniently performed by simple drying of crude reaction mixtures. The mechanism of the oxidation process has not yet been clearly established, but putatively occurs via initial formation of an hypervalent iodine arenoxy intermediate of type **3a** (X = I(Ph)OAc or $I(Ph)O_2CCF_3$), which can either fragment to give a transcient phenoxenium ion or directly react with a nucleophile in a concerted fashion to give **2a** (*Scheme* 2).[38-41,50] This mechanism would thus be analogous to the heterolytic pathway also often proposed for metal-based oxidations such as the Wessely oxidation (*Eqs.* 14 and 16)[17] or other polyvalent iodine-based oxidations such as the Adler oxidation.[14,64]

During the last fifteen years, Chun-Chen Liao and co-workers at the National Tsing Hua University in Taiwan have been among the most active chemists in the field of orthoquinone monoketal chemistry. They developed several new synthetic methodologies essentially based on the

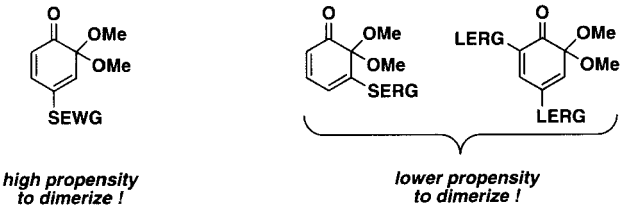
dual Diels-Alder reactivity of these "masked" orthobenzoquinones (*Section* II.1).[4,65] In recent years, their orthoquinone monoketals were generated by PIDA- or PIFA-mediated oxidation of 2-methoxyphenols in some alcoholic solution (*Eq.* 9).



(9)

Z = 4-Me, 4-CO_2Me, 5-CO_2Me
R_1 = H, OMe

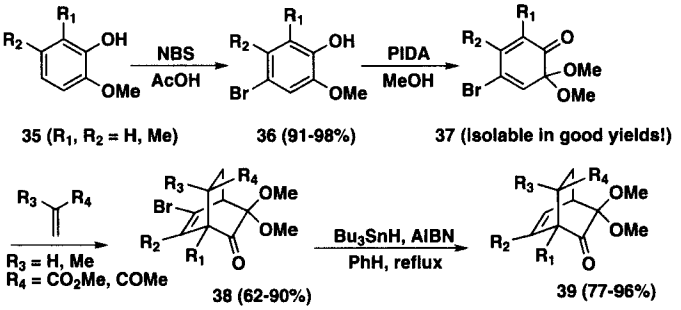
As expected from earlier Andersson's observations,[13-15] 6,6-dimethoxy-cyclohexa-2,4-dienones of type **33** do more or less readily dimerize to furnish **34** (*Eq.* 9), unless they can be trapped *in situ* by reactive π-components to give various bicyclo[2.2.2]octenone derivatives (*Section* II.1).[65-67] Based on both Andersson's[13-15] and Liao's[66] conclusions, a general trend on the propensity of 6,6-dimethoxy-cyclohexa-2,4-dienones to self-dimerize can be suggested. Electron-withdrawing and/or small groups at their 4-position tend to facilitate self-dimerization, whereas electron-releasing and/or large groups at their 2- and/or 4-positions, as well as small electron-releasing groups at their 5-position, have the reverse effect.



SERG = small electron-releasing group
LERG = large electron-releasing group
SEWG = small electron-withdrawing group

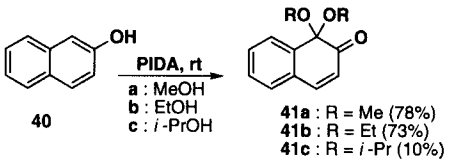
Allylic and homoallylic alcohols have also been used as nucleophilic trapping agents instead of methanol solvent to generate **33** well suited for intramolecular Diels-Alder transformations (*Eq.* 28b).[65,67] It must be said, however, that dimerization can remain an obstacle to bimolecular Diels–Alder exploitation of orthoquinone monoketals of type **33** when the diene or the dienophile used, free or tethered, is not reactive enough.[68]

Liao and co-workers recently offered a solution to this problem by first brominating the starting 2-methoxyphenol at its 4-position (*Scheme* 4).[69] Such a bromine substitution led to ortho-quinone monoketals **37** stable enough to be isolated and used with stoechiometric or slight excess of dienophiles to furnish cycloadducts **38**. Standard debromination led to bicyclo[2.2.2]octenones **39** in overall yields 20 to 40% higher than those obtained in one step (*Eq.* 9).[67] This methodology was recently utilized in a total synthesis of the *cis*-clerodane diterpenic acid **249b** (*Scheme* 26).[68]

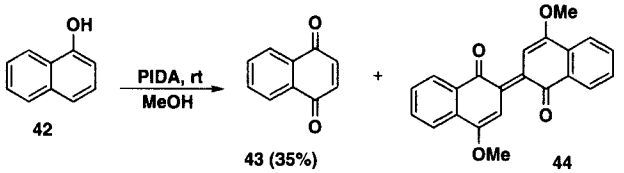


Scheme 4

Mallik and Mallik recently studied similar oxidative alkoxylations of naphthols.[12] PIDA-mediated oxidation of 2-naphthol **40** in alcoholic media gave the corresponding naphthoid 6,6-dialkoxycyclohexa-2,4-dienones **41a-c** in very good yields (*Eq.* 10a). Surprisingly, oxidation of 1-naphthol **42** in MeOH did not afford the expected orthoquinone monoketal, but a mixture of the para-naphthoquinone **43** and a methoxylated C–C coupled product **44** (*Eq.* 10b). Barton and co-workers[10,11] had previously obtained analogous naphthoquinone monoketals using DDQ instead of PIDA, but yields were in general lower. A low yield of **41a** was, for example, obtained when using 2-naphthol **40**, but nearly quantitative conversion of 1-methoxy-2-naphthol into **41a** was however observed upon DDQ oxidation in anhydrous methanol.[10] This lends some support to the hypothesis that the presence of an electron-releasing ortho-substituent would play a significant role in both stabilizing a DDQ-oxidized cationic phenol intermediate of type **4** and in orienting the nucleophilic attack (*Scheme* 2). The fact that higher yields are obtained with PIDA in MeOH could be attributed to a better stabilization of an intermediate of type **3** and to a possible intramolecular delivery of methoxy units from the iodine(III) center.



(10a)

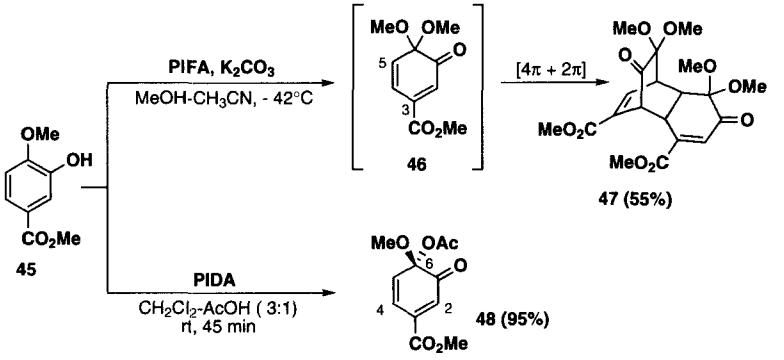


(10b)

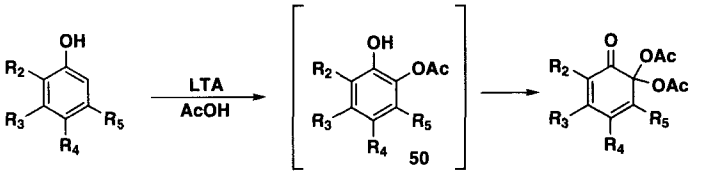
Finally, it is also possible to generate 6,6-dialkoxycyclohexa-2,4-dienone derivatives from their orthoquinone parents via acid-catalyzed ketalization methods. A high-yielding orthoformate-based ketalization protocol was used by Corey and Tramontano[70] in their total synthesis of the quino-protein alcohol dehydrogenase coenzyme (*Eq.* 66).

2. 6,6-Diacetoxy- and 6-Acetoxy-6-alkoxycyclohexa-2,4-dienones

Andersson and Liao established that 6,6-dialkoxycyclohexa-2,4-dienones do not dimerize via Diels-Alder cycloaddition only if appropriately substituted (*vide supra*). Interestingly, however, Wessely and co-workers[71,72] had shown that 6-acetoxy derivatives could be isolated as monomers, whichever was their substitution pattern. These early observations have recently been validated when oxidative methoxylation of **45** with PIFA in MeOH was found to give rise to the crystalline Diels-Alder dimer **47** as the sole isolated product, whereas oxidative acetoxylation of the same 2-methoxyphenol **45**, using our improved iodine(III)-mediated procedure, gave rise to the pure ortho-quinol acetate **48** in *quasi* quantitative yield (*Eq.* 11).[73]



Orthoquinol mono- and diacetates have been traditionaly prepared by the Wessely oxidative acetoxylation of phenols in low to moderate yields in admixture with other acetoxylated products (*Eqs.* 12 and 13).[17,71,74] The effect of the acetoxy substituent on the cyclohexa-2,4-dienone stability remains unexplained. Diacetate formation would result from oxidative acetoxylation of a rearomatized 2-acetoxyphenol intermediate product **50**.

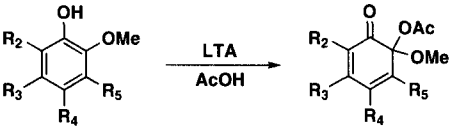


49a : R_2 = H, R_3 = H, R_4 = H, R_5 = H
49b : R_2 = H, R_3 = H, R_4 = Me, R_5 = H
49c : R_2 = H, R_3 = Me, R_4 = Me, R_5 = H
49d : R_2 = Me, R_3 = H, R_4 = Me, R_5 = H
49e : R_2 = Me, R_3 = H, R_4 = *t*-Bu, R_5 = H

51a (2%)
51b (28%)
51c (5%)
51d (12%)
51e (20%)

Methoxylated quinol acetates such as **53a-b** were usually obtained in higher yields,[72,75] again showing the advantage of having a good electron-releasing group at the starting phenol ortho-position for controlling the regiochemical outcome of the reaction (*Eq.* 13). Wessely oxidation of homovanillic acid in CH_2Cl_2 did not give any spiro β-lactone but furnished the decarboxylated product, 6-acetoxy-4-acetoxymethyl-6-methoxycyclohexa-2,4-dienone, in 84% yield (not shown).[76]

Our PIDA-mediated acetoxylation was found to be better than the Wessely procedure in terms of reproductibility and operational facility, not mentioning the fact that no toxic lead salts were generated.[73] The preparative efficacy of these oxidative acetoxylations could be again attributed to the electron-releasing effect of the methoxy group that helps in directing the attack of an acetate anion at the methoxylated position.[72,75] This latter statement, however, assumed an ionic mechanism as in the general mechanistic depiction shown in Scheme 2. A radical-based mechanism involving one-electron oxidation of the starting phenols had initially been proposed by Wessely,[74] but such a proposal was very early on abandoned due to the lack of evidence for free radicals.[17,77]



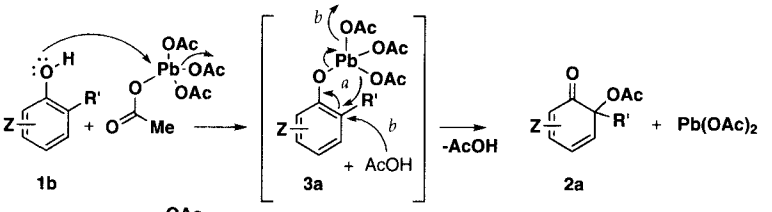
(13)

52a : R_2 = H, R_3 = H, R_4 = CHO, R_5 = H — **53a** (48%)
52b : R_2 = H, R_3 = CHO, R_4 = H, R_5 = H — **53b** (40%)
52c : R_2 = H, R_3 = H, R_4 = COMe, R_5 = H — **53c** (60%)

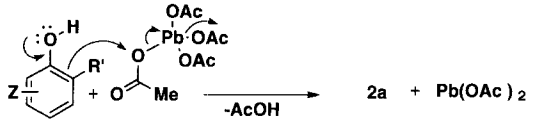
A nucleophilic displacement by an acetate ion with concomitant reduction of lead(IV) into lead(II) thus appeared as a conceivable mechanistic rationale (*Eq.* 14), and both concerted bimolecular and phenoxonium-based unimolecular processes have been invoked, as speculated early on by Criegee[78] and commonly suggested for other oxidative nucleophilic substitutions (*Scheme* 2). The acetate ion could be delivered either intramolecularly (path *a*) from an intermediate species of type **3a** [X = $Pb(OAc)_3$], or intermolecularly (path *b*) from the acetate initially released from $Pb(OAc)_4$ or from the acetic acid reaction solvent (*Eq.* 14).[77] The same can be said of PIDA-mediated oxidative acetoxylation (*Eq.* 16). Bubb and Sternhell[17] had, however, rationalized the Wessely oxidation in terms of an electrophilic substitution at the lead acetate oxygen (*Eq.* 15). The obtention of other acyloxylated or methoxylated analogous products when the reaction was performed in other alcanoic acids or methanol solvents would nevertheless seem to be in favor of nucleophilic displacements, but possible ligand exchange at the lead center does not allow any firm mechanistic conclusion;[17] further discussion on the mode of attack of the acetoxy group and electron transfer still awaits unambiguous experimental demonstration.

Galloyl-derived orthoquinol acetates have recently been synthesized via Wessely oxidation by Feldman and co-workers in the course of their investigation on galloyl C–C biaryl coupling (*Eqs.* 17 an 18).[79,80] Non-dimerizing ketals **55** and **57** were obtained in high yields, and **57** could be dimerized into **58** only upon refluxing in MeOH.[80]

Induction of orthoquinol acetate dimerization via acetoxy-methoxy group exchange is a rather commonly observed phenomenon which confirms the important role played by 6-acetoxy groups in stabilizing quinonoid cyclohexa-2,4-dienone systems.[73] Wessely oxidation of galloyl phenols into orthoquinol acetates was also exploited by Feldman and Hunter in an eminently well designed set of experiments aimed at determining the relative facility of oxidation of the different galloyl ester groups in a model ellagitannin precursor.[81]



(14)



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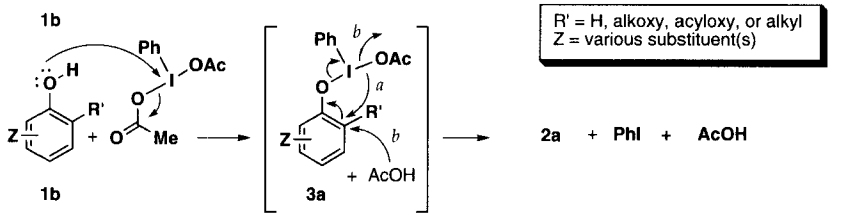
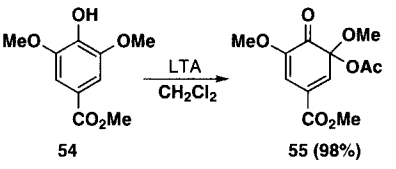
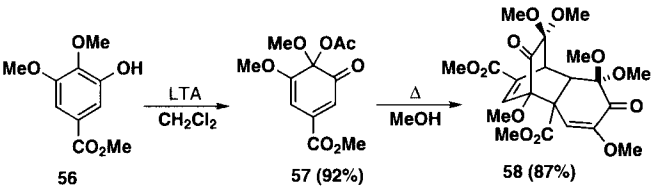


(16)



(17)



(18)

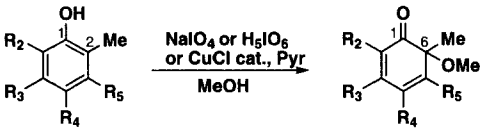
There exist other means to prepare this class of orthoquinone monoketals. Deslongchamps[82] had, for example, used NBS in aqueous acetonitrile[32] to generate the cyclic orthoquinol ester **196** in 95% yield from the sodium carboxylate **195** (*Scheme* 18). Several other *O*-spirodienonelactones have been prepared according to the same methodology by Liao and co-workers.[83] The *O*-spirodienonelactone product **196** is a stable crystalline material that does not dimerize even in refluxing benzene ; both the bulkiness of the compound and the presence of an electron-withdrawing acyl unit in the ketal moiety can be used to explain this stability. It, however, readily undergoes Diels-Alder cycloadditions at room temperature with dienophiles such as vinyl at room temperature (*Scheme* 18).

Orthoquinone monoketals of the orthoquinol ester class are thus usually prepared by adding the carboxylate species to the alkoxylated center, whether this operation is done intra- or intermolecularly (*Eqs.* 14 and 16). To our knowledge, the capability of a 2-acyloxy phenol substituent to direct the attack of an alkoxylate at the 2-position has never been reported. Even though an acetoxy group is seemingly not a regioselector as efficient as a methoxy group to orient an acetate attack (*Eqs.* 11 and 13),

the situation could be improved in the case of an attack by a stronger nucleophile such as an alcohol or an alkoxy anion; this remains to be demonstrated experimentally.

3. 6-Acetoxy-6-alkyl- and 6-Alkoxy-6-alkylcyclohexa-2,4-dienones

It is possible to introduce regioselectively various oxygen-bearing functionalities including hydroxy, alkoxy and acetoxy groups at the 2- or 4-positions of 2-alkyl- or 4-alkylphenols to furnish various ortho- and paraquinol derivatives. For example, 6-hydroxy-6-alkyl-cyclohexa-2,4-dienones can be generated by the Adler's periodate-based oxidation performed in aqueous solvents[13,84] or by the benzeneselenic anhydride-based Barton oxidation[85,86] of alkylphenols, which can both be followed by derivatization to orthoquinol ethers or esters. Before the emergence of iodine(III)-based reagents, the two oxidizing systems that have been most commonly used to prepare the title orthoquinols directly from 2-alkylphenols were again the Wessely oxidative acetoxylation (*Eq.* 14, R' = alkyl)[17] and the Adler periodate-based oxidation performed in anhydrous alcoholic solvents (*Eq.* 19).[14,64]



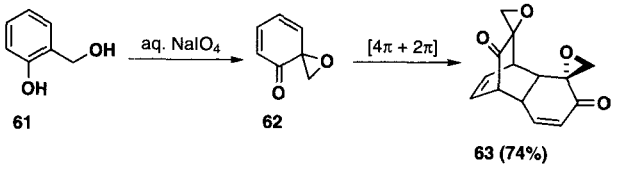
(19)

59a : R_2 = H, R_3 = H, R_4 = H, R_5 = Me — **60a** (12%)
59b : R_2 = Me, R_3 = H, R_4 = H, R_5 = Me — **60b** (17%)
59c : R_2 = H, R_3 = H, R_4 = H, R_5 = OMe — **60c** (17%)
59d : R_2 = *t*-Bu, R_3 = H, R_4 = Tr, R_5 = H — **60d** (74%)
59e : R_2 = *t*-Bu, R_3 = H, R_4 = *t*-Bu, R_5 = H — **60e** (95%)

Numerous examples of conversions of 2-methylphenols into 6-methoxy-6-methyl-cyclohexa-2,4-dienones have been reported by Adler, Andersson, Becker and their colleagues at the Swedish University of Göteborg during the seventies. These orthoquinol ethers species chemically behave like 6,6-dialkoxycyclohexa-2,4-dienones, and easily dimerize unless appropriately substituted. Their Diels-Alder dimerization is indeed generally prevented by the same type of substitution pattern as for their 6,6-dialkoxy analogues. A small substituent at the 5-position (Me or OMe) or at least one bulky substituent at the 2- or 4-position is required to stabilise these compounds (*Eq.* 19).[13,14,64] These stabilized systems do not even dimerize upon heating. Interestingly, steric hindrance at the 2- and 4-positions also help controlling the regiochemistry of nucleophilic addition, hence the overall yield of the reaction; the least hindered reactive site of 2-methylphenol substrates being the most accessible to a nucleophile entry (*Eq.* 19, **60d**[64] and **60e**). The high yield of the orthoquinol methyl ether **60e** was obtained via the oxidative copper-amine catalysis developed by Hewitt.[27] Oxidative introduction of a methoxy group into 2-alkylphenols can also be achieved via the $Pb(OAc)_4$-mediated Wessely oxidation performed in methanol solvent.[77]

A classical intramolecular variant of the Adler oxidation is the conversion of salicyl alcohol **61** into the spiroepoxy-cyclohexa-2,4-dienone **62**, which rapidly dimerizes to furnish stereoselectively the Diels-Alder *endo*-adduct **63** (*Eq.* 20).[84,87,88] As alluded to above, this dimerization is prevented if the ortho-dienone system bears bulky substituents at the 2- and/or 4-positions (*Eq.* 21).[89] Here, again, the mechanism of the Adler oxidation is the object of several proposals based on either concerted or

stepwise pathways, and involving passage via periodic esters or phenoxonium ions. All proposals invoke two-electron transfers to iodine, but mention either (1) initial coordination between the phenolic hydroxyl group and the iodine followed by nucleophilic attack of the alcoholate species onto the preformed periodic ester or its corresponding phenoxonium ion, or (2) carbon-based nucleophilic attack of the phenol onto the alkoxide oxygen of a preformed periodic ester,[64,90-92] in a manner similar to the mechanism proposed by Bubb and Sternhell for the Wessely oxidation (*Eq.* 15).[17]



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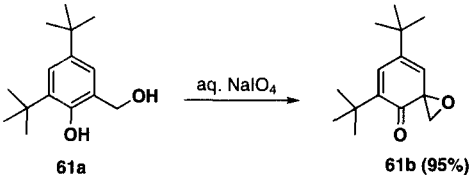
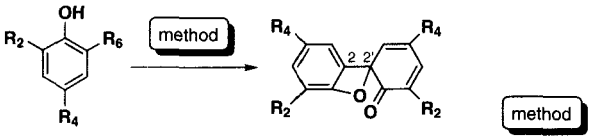


(21)

Hewitt's copper-amine catalyzed autoxidation can also be used to generate 6-aryloxy-6-aryl-cyclohexa-2,4-dienones of benzoxet type such as **65** in high yield (*Eq.* 22). A monophenol or its 2,2'-biphenol coupling product can be converted into a dimeric benzoxet via intramolecular addition of one phenol unit onto the oxidatively activated second unit. Yields up to 95% were obtained using $CuCl_2$ in pyridine–MeOH or its morpholine complex in CH_3CN–MeOH (*Eq.* 22).[27,93] Alkali treatment of the halogenated phenols **64b** also gave rise to the benzoxet **65** in high yield (*Eq.* 22 and *Scheme* 3).[61]



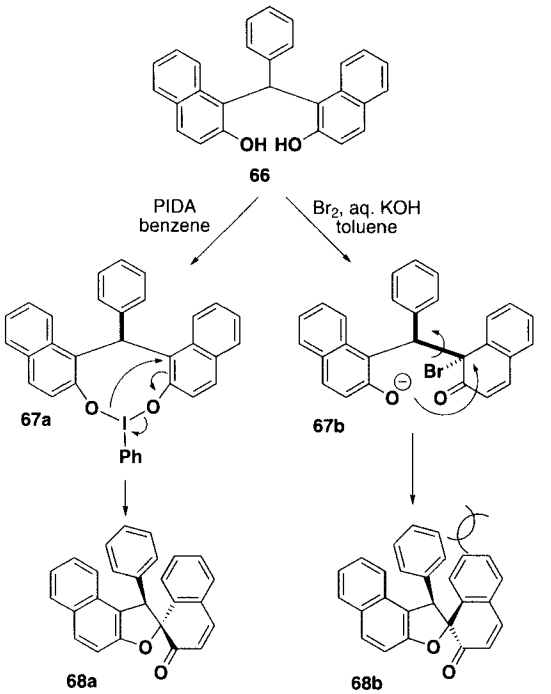
(22)

64a : R_2 = *t*-Bu, R_4 = *t*-Bu, R_6 = H — **65** (95%) — $CuCl_2$–morpholine, CH_3CN–MeOH
64b : R_2 = *t*-Bu, R_4 = *t*-Bu, R_6 = Br or I — (90%) — $CuCl_2$, KOH, Pyr–MeOH
(90%) — KOH, acetone or DMF

Another related cyclization of phenols leading to orthoquinol aryl ethers is the oxidation of bisnaphthols **66** into spirans **68** (*Scheme* 5). Dean and co-workers have investigated the effect of various oxidants on the stereochemical outcome of such cyclizations.[36] Most one-electron oxidants commonly used for phenolic coupling, including alkaline $K_3Fe(CN)_6$, copper-amine complexes, and peroxidase had not stereochemical effect. Interestingly, PIDA and hypobromite (Br_2 + aq. KOH) gave rise to two different spiran diastereomers **68a** and **68b**, respectively (*Scheme* 5). On the one hand, a cyclic intermediate of type **67a** was postulated for the PIDA-mediated oxidation. This phenyliodine(III) diaryloxy species then would collapse to release the sterically favored spiran **68a**.

On the other hand, an intramolecular SN_2 inversion of a preformed sterically favored α-bromo ketone **67b** (*Scheme* 2, **3b**) would force formation of the sterically unfavored spiran **68b**. It is worth noting that stereocontrol of these oxidative bond formation would rely on intramolecular substitution reactions rather than on radical coupling processes.[36]

The formation of similar chiral spirans from *p-tert*-butylcalix[n]arenols using alkaline $K_3Fe(CN)_6$ or brominating phenyltrimethylammonium tribromide have more recently been described by Biali and coworkers (*Eq.* 23).[34,94] For example, *p-tert*-butylcalix[4]arenols were transformed into the diastereomeric bis(spirodienone) derivatives **70a/71a** and **72a**.

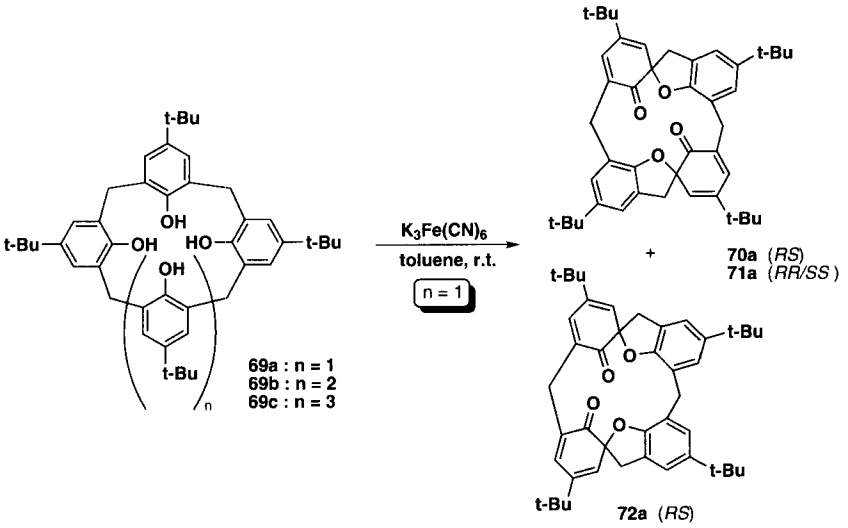


Scheme 5

In contrast to the above 6-alkoxy-6-alkyl-cyclohexa-2,4-dienones that do not spontaneously dimerize only if appropriately substituted, 6-acyloxy-6-alkyl-cyclohexa-2,4-dienones such as **74** are stable at room temperature (*Eq.* 24). Heating is necessary to induce Diels-Alder cycloaddition.[84,95,96] The dimerization is both regio- and stereoselective giving always adducts derived from attack on the face of both the diene and the dienophile bearing the acetoxy group.[97] This type of orthoquinol acetates have been prepared by treating the parent phenol with sodium periodate or sodium bismuthate in aqueous acetic acid,[22] or via Wessely oxidative acetoxylation in acetic acid [16,17,71,84,98] or benzene solvent.[77]

Finally, an interesting set of data was gathered by Rieker and co-workers in the course of their investigation on anodically-generated phenoxenium ions.[43] The hindered phenols **76** were submitted to two-electron oxidation conditions via electrolysis (Pt/Ir anode, + 1200 mV) to produce

the corresponding phenoxenium ions **77**. These were quenched by addition of Z-protected glycine, alanine and aminoisobutyric acid to give both ortho-**78** and para-**78** quinol esters in varying ratio depending upon the nature of the substituent at the 4-position of **76**, and on steric encumbrance at the amino acid α-position (*Eq.* 25). The electronically conjugating phenyl group at the 4-position appeared to favor attack at the ortho-position, but increasing steric bulk at the amino acid α-position nullifies this effect to favor attack at the para-position.



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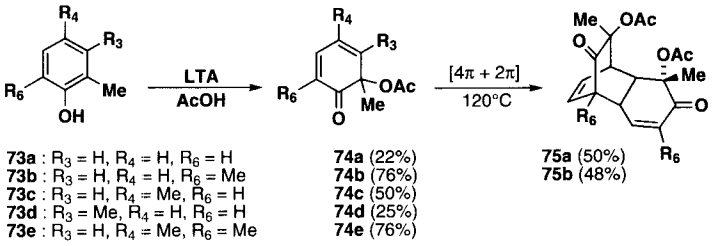
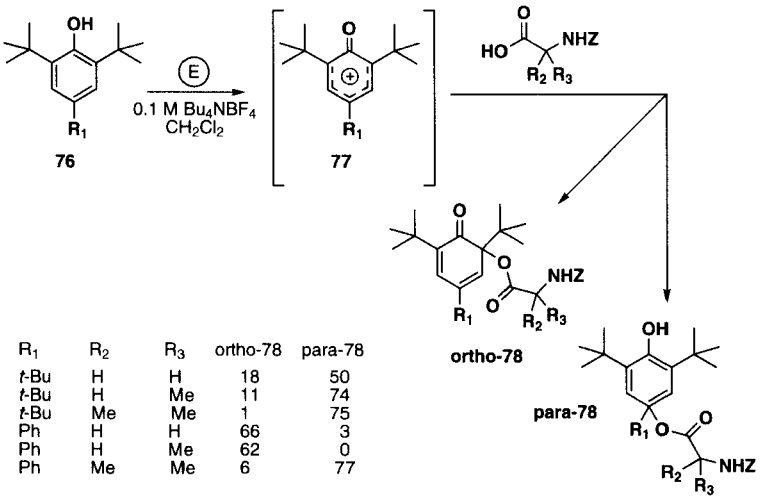


(24)

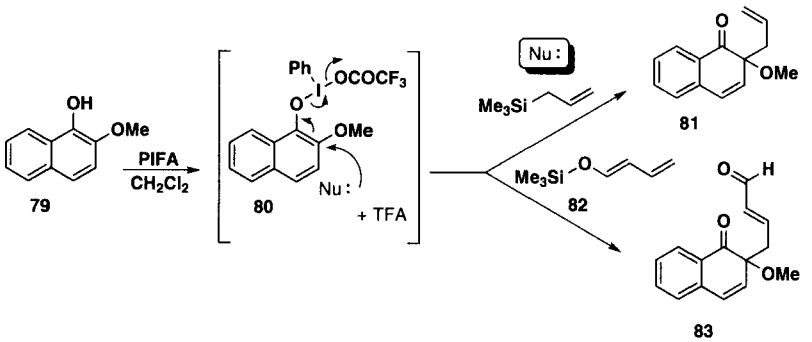
Preparations of 6-oxo-6-alkyl-cyclohexa-2,4-dienones are thus usually based on the regioselective introduction of an oxygen-based nucleophile onto a carbon-substituted center of an oxidized phenol intermediate. Two known alternative routes to this type of orthoquinols are (1) direct addition of a carbon nucleophile to one of the two carbonyls of a preformed orthoquinone,[99] and (2) base-induced phenol alkylation at an ortho-oxygenated center.[100] Another synthetically valuable strategy could rely on (3) the regioselective attack of carbon-based nucleophiles at an oxygen-substituted center of an oxidized phenol intermediate.



R_1	R_2	R_3	ortho-78	para-78
t-Bu	H	H	18	50
t-Bu	H	Me	11	74
t-Bu	Me	Me	1	75
Ph	H	H	66	3
Ph	H	Me	62	0
Ph	Me	Me	6	77

(25)

Exploratory studies have been initiated toward the development of bimolecular reactions based on this third alternative (3),[101] in which phenols are oxidized to become strong electrophiles instead of deprotonated to enhance their inherent nucleophilicity. Thus, treatment of 2-methoxynaphthols with PIFA in the presence of allyl silane or the silyl enol ether **82** furnished, via a timely domino reaction sequence, the highly functionalized naphthoid orthoquinol ethers **81** and **83** in moderate to good yields (*Eq.* 26).[101] Optimization and synthetic application studies of this remarkable C–C bond forming reaction are currently in progress.



(26)

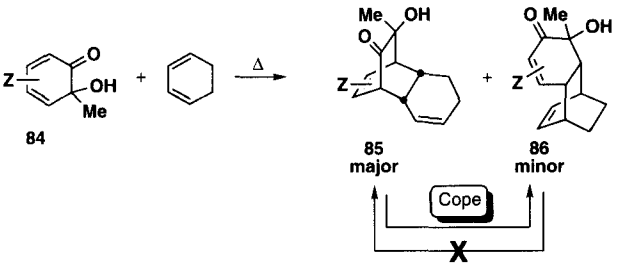
II. REACTIONS OF ORTHOQUINONE MONOKETALS AND THEIR ORTHOQUINOL VARIANTS

In comparison to the multitude of reactions that has been performed and well documented on paraquinone ketals,[1-3,7,102] a relatively limited number of reaction types has been investigated for orthoquinone monoketals and their orthoquinol variants, despite their remarkable synthetic potential principally based on (1) their monoprotected 1,2-dicarbonyl function, (2) electrophilic reactivity, and (3) differentially activated double bonds.

1. Diels-Alder Cycloadditions

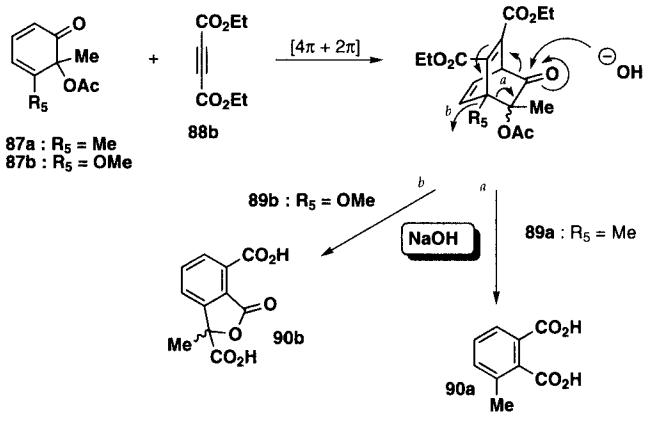
The capability of the cyclohexa-2,4-dienone unit of orthoquinone monoketals and orthoquinol variants to react as either a diene or a dienophile component in [4π + 2π] cycloadditions is their principal virtue in organic synthesis, and paradoxally is also the principal reason why it is often difficult to exploit orthoquinone monoketals in synthesis; they often dimerize faster than they can combine with another π-system partner. Nonetheless, the ketal moiety can be considered (1) as a stabilizing protecting group; unprotected orthoquinone derivatives are usually even less stable than orthoquinone monoketals, and (2) as a regio- and stereoselecting group in Diels-Alder reactions with unsymmetrical dienophiles.[82] To date, most utilizations of orthoquinone monoketals and orthoquinol variants in Diels–Alder reactions have been as 4π components perhaps because highly activated 2π dienophiles were simply more readily accessible than 4π dienes electron-rich enough to trap quinonoid 2π dienones before they dimerize. This seemingly more common 4π behavior of quinonoid dienones would then correspond to an inverse electron-demand for the cycloaddition reaction. Nevertheless, an increasing number of reports are today describing the use of the title ketals as 2π dienones with electron-rich 4π dienes (*vide infra*).[65,103-106] In their investigation aimed at understanding this apparent mechanistic dichotomy, Singh and co-workers[107] initially observed that orthoquinols of type **84** would preferentially behave as 4π dienones with 2π cyclopentadiene, cyclohexadiene, and cycloheptatriene. Cycloadducts **86** apparently resulting from thermally-induced 2π dienone + 4π combinations could also be isolated when using cyclohexadiene and cycloheptatriene. However, thermally-allowed [3,3]-sigmatropic Cope rearrangements readily converted adducts of type **85** into adducts of type **86**, but not the reverse (*Eq.* 27). These observations led the authors to conclude that orthoquinols of type **84** would primarily follow the inverse electron-demand Diels–Alder cycloaddition mode.[107]

One of the earliest synthetic applications of orthoquinol acetates was the utilization of 6-acetoxy-5,6-dimethylcyclohexa-2,4-dienone **87a** as a diene in its transformation into the phthalic acid **90a** via an initial Diels-Alder cycloaddition with the acetylenedicarboxylate **88b**, which was followed by an alkali treatment (*Scheme* 6, path *a*). Interestingly, the 6-methoxy analogue **87b** furnished cycloadduct **89b** from which elimination of the methoxide anion instead led to the benzannulated γ-lactone **90b** (*Scheme* 6, path *b*).[108]



(27)

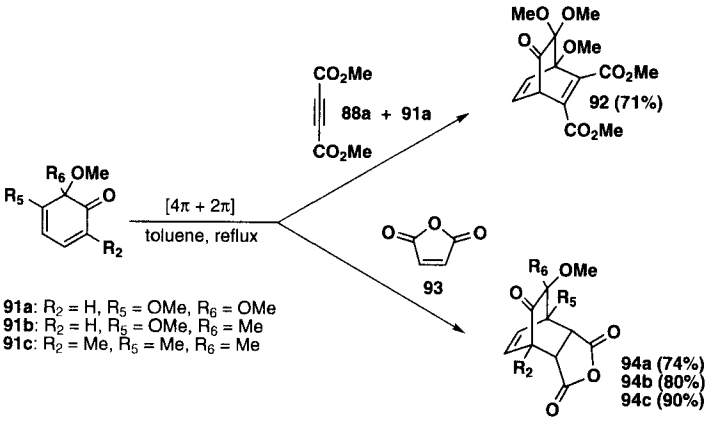
Other Diels-Alder reactions between 6-acetoxy-6-methyl or 6-acetoxy-6-phenyl analogues of **87** and maleic anhydride, butadiene and cyclopentadiene had also been investigated by Wessely and co-workers.[109]



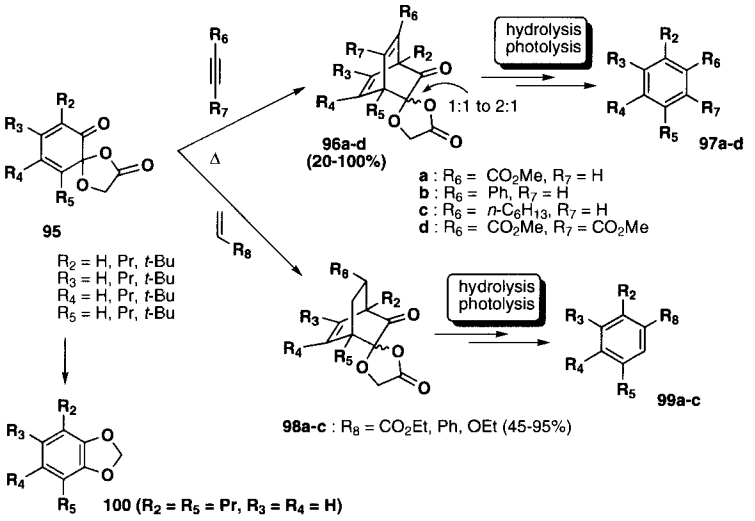
Scheme 6

Andersson investigated further the Diels-Alder behavior of non-dimerizing 5-substituted orthoquinone monoketals and orthoquinol methyl ethers such as **91a-c**, and found that they do undergo [4π + 2π] cycloadditions with reactive dienophiles such as the acetylenedicarboxylate **88a** or maleic anhydride **93** in refluxing toluene (*Scheme* 7); the stereochemical outcome of the reactions with maleic anhydride (*i.e.*, *endo*-orientation at the ring fusion and configuration at the geminally substituted bridge center) was assumed analogous to that found in dimerization adducts (*Eqs.* 18, 20 and 24).[14]

The dienic reactivity of orthoquinol esters of the *O*-spirolactone type **95** towards acetylenes have been investigated by Liao and co-workers (*Scheme* 8).[110,111] Moderate to excellent yields of Diels-Alder cycloadducts **96** were obtained regioselectively by reacting the *O*-spirodienonelactones **95** with neat mono- or disubstituted acetylene derivatives **a-d** in a sealed tube at temperature ranging from 80°C to 130°C (*Scheme* 8). These catechol-derived bicyclo[2.2.2]octadienone adducts could be readily hydrolyzed into the corresponding diketones, then decarbonylated into tetrasubstituted benzene derivatives **97** via photolysis.



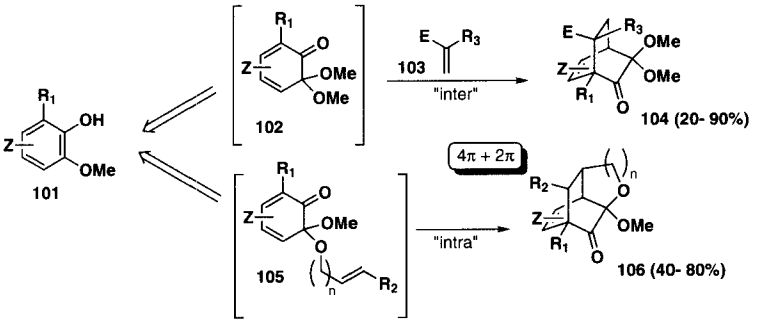
Scheme 7



Scheme 8

Unactivated acetylenes such as hex-3-yne did not act as dienophile; a methylenedioxylated benzene derivative **100** was instead formed in 50-65% yield.[110,112] Diels-Alder reactions between the same type of *O*-spirolactones **95** and olefinic dienophiles were also reported to yield bicyclo[2.2.2]octenones of type **98** in a regio- and stereoselective fashion.[113,114] Hydrolysis and photolysis afforded the corresponding cyclohexa-1,3-diene derivatives **99**.

Liao's research group[65-67] also recently reported on the exploitation of the diene reactivity of 6,6-dimethoxycyclohexa-2,4-dienones by trapping them with various olefinic dienophiles **103** to furnish bicyclo[2.2.2]oct-5-en-2-one derivatives **104** (*Eq.* 28a). Again, these cycloadditions were both regioselective and stereoselective, giving only products derived from *endo*-addition; the electron-withdrawing group E is adjacent (*ortho*) and *anti* to the octenone carbonyl function. These reaction controls have been tentatively rationalized in terms of the Frontier Molecular Orbital theory on the basis of *ab initio* calculations of HOMO and LUMO energie gaps and coefficients.[66]

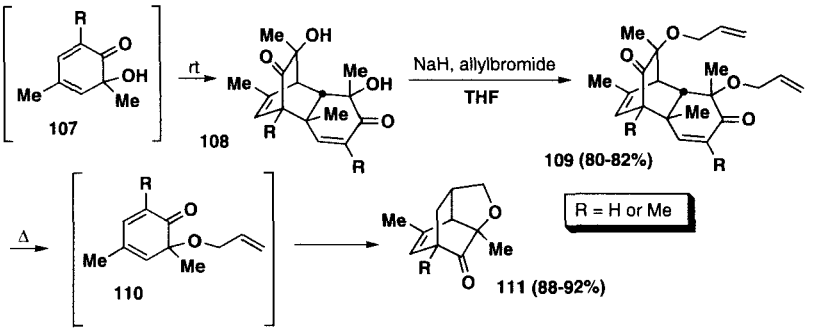


(28a)

(28b)

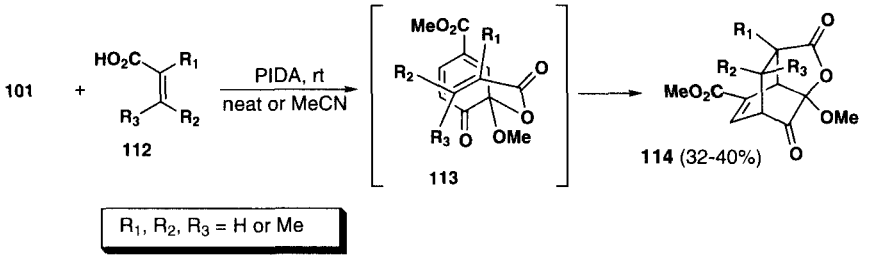
Tethered allylic and homoallylic units were sufficiently dienophilic to permit intramolecular [4π + 2π] cycloadditions.[115] Oxatricyclic compounds of type **106** were thus obtained (*Eq.* 28b). It is worth noting that these species **106** can be viewed as *meta/syn* cycloadduct equivalents, hitherto never obtained by the bimolecular reaction. Monoketal intermediates **105** were produced from **101** via PIDA-mediated oxidation using the corresponding allylic or homoallylic alcohol in CH_2Cl_2 solvent in the presence of $NaHCO_3$.[67] Even the unsubstituted starting 2-methoxyphenol guaiacol (Z = R_1 = H) led to oxatricycles **106** in 30 to 72% yields.[115] An application of this methodology to the synthesis of a *cis*-clerodane diterpenic acid is described in *Scheme* 25.[116]

An indirect route comprising two different orthoquinols was recently used by Singh and co-workers[117] to access bridged heterotricycles of type **106**. Diols **108**, readily available from "domino" Adler oxidation/Diels–Alder dimerization of their monomeric phenol parents **107**,[91] were allylated, then submitted to retro-Diels–Alder reaction conditions to afford **111** via *in situ* intramolecular Diels-Alder reaction (*Scheme* 9).



Scheme 9

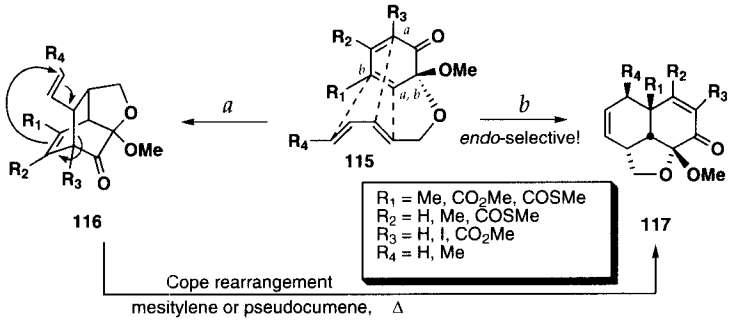
Alkenoic acids have also been used in place of alkenols. The PIDA-mediated oxidation of methyl vanillate **101** (Z = 4-CO_2Me, R_1 = H) in the presence of acrylic acid **112** or derivatives thereof gave rise to the formation of tricyclic lactones **114** in moderate yields (*Eq.* 29).[115] Similar reactions had previously been performed on 2-methylphenols by Yates and co-workers (*vide infra*).[118,119]



(29)

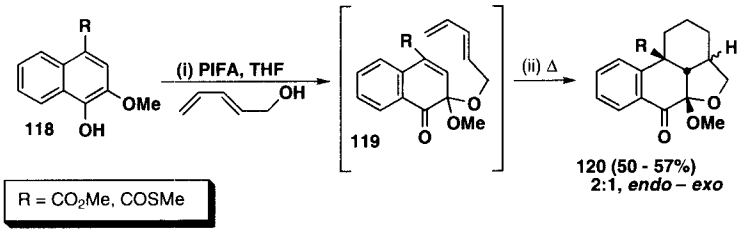
A remarkable extension of this "domino" oxidative phenol ketalization–intramolecular Diels-Alder reaction allowed the stereocontrolled preparation of highly functionalized *cis*-decalins. By

replacing simple allylic alcohols by 2,4-dienols, the cyclohexa-2,4-dienone moiety behaved both as a diene (path *a*) and as a *dienophile* (path *b*) to give mixtures of bicyclo[2.2.2]octenones of type **116** and *cis*-decalins **117**, respectively, in good yield and varying ratios (*Eq.* 30).[65,105,106] The dienophile character of the Δ^4 double bond of the 2,4-dienone of **115** increased with an electron-withdrawing group at the 4-position (e.g., $R_1 = CO_2Me$).



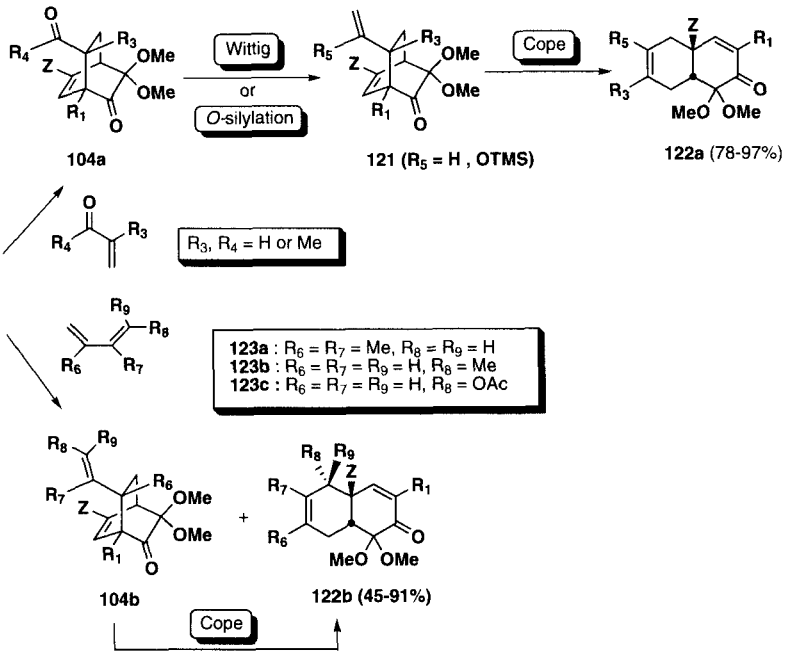
(30)

Furthermore, the bicyclo[2.2.2]octenones **116** smoothly underwent Cope rearrangements to furnish the *cis*-decalins **117**, making this set of reactions a potentially very short stereocontrolled route to decalin-containing natural products.[65,105,106] Naphthoid and anthracenoid compounds have also been used as substrates, notably with the aim of making orthoquinone monoketals whose Δ^4 dienophilic reactivity would be more pronounced because of the involvement of Δ^2 double bond into a fused aromatic ring. Moderate to good yields of cycloadducts were thus obtained but as *endo–exo* mixtures (*Eq.* 31). This is in contrast to the use of more reactive benzoid compounds that only led to *endo*-addition products.[105]



(31)

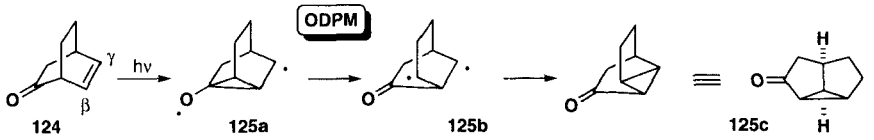
A series of formyl- and acetylbicyclo[2.2.2]octenones **121** have been prepared from **102** and acrolein- or vinyl ketone-type dienophiles, then, respectively, converted to their vinyl homologues and silyl enol ethers to undergo Cope rearrangements to the *cis*-decalins of type **122a** via **104a** (*Eq.* 32).[120] Alternatively, it was also unprecedently found that **102** can behave as a dienophile in intermolecular Diels–Alder reactions with various unactivated butadienes **123** to give **122b** and **104b** in moderate to good yields (*Eq.* 33) and varying ratios.[104] Again, an electron-withdrawing group at the 4-position of **102** (e.g., Z = 4-CO_2Me) favors its dienophilic behavior to furnish higher amount of **122b**. Bicyclo[2.2.2]octenones **104b** readily underwent Cope rearrangements to afford *cis*-decalins **122b** in high yields.[104]



(32)

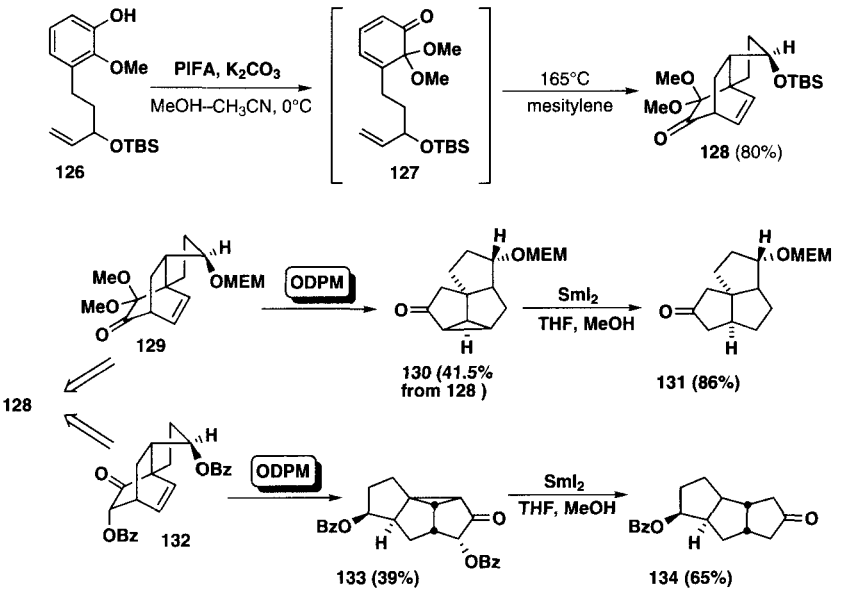
(33)

Several other 2-methoxyphenol-derived bicyclo[2.2.2]octenones of type **104** and their octenolic Grignard reaction products had also been previously transformed via anionic oxy-Cope [3,3] and [1,3] rearrangements into *cis*-decalins of type **122**, *i.e.*, bicyclo[4.4.0]octenones, as well as expanded bicyclo[4.2.2]decenone derivatives (not shown).[121] Bicyclo[2.2.2]oct-5-en-2-ones constitute synthetically useful systems that can be transformed into a variety of different structural skeleta.[66,115] In addition to Cope and related sigmatropic shift reactions, these bridged β,γ-unsaturated ketones have been subjected to oxa-di-π-methane (ODPM)[122] rearrangements upon triplet excitation for the construction of, *inter alia*, polycyclopentanoid systems (*Eq.* 34).



(34)

Orthoquinone monoketal chemistry have thus become important in that area of organic synthesis since they can furnish bicyclo[2.2.2]octenones in a regio- and stereocontrolled manner thanks to the Diels-Alder cycloaddition (*vide supra*). Hwang and Liao[123] managed to prepare both linearly and angularly fused triquinanes from a common orthoquinone monoketal intermediate **127**. Intramolecular Diels-Alder cycloaddition gave the tricyclic octenone derivative **128** in 80% yield (*Scheme* 10). This species was transformed into the ODPM rearrangement products **130** or **133**. Samarium-induced reductive opening of their three-membered ring gave rise to the triquinanes **131** and **134**, respectively.

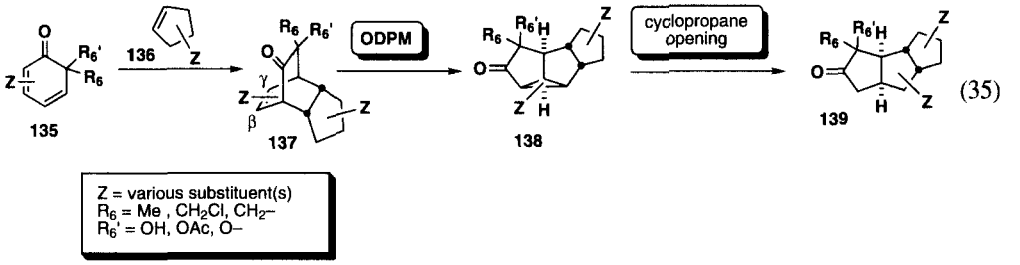


Scheme 10

Another somewhat simpler route to linear triquinanes, again based on the ODPM rearrangement of bicyclo[2.2.2]oct-5-en-2-ones but derived from intermolecular combination of 6,6-dimethoxycyclohexa-2,4-dienones and cyclopentadiene, has recently been described by Liao and co-workers.[124] Hence, these authors proposed their orthoquinone monoketal-based methodology as an alternative to Wender's arene-alkene *meta* photoaddition strategy and Singh's own related ODPM rearrangement approach to naturally occurring *cis*:*anti*:*cis* triquinane systems (*vide infra*).

Singh's group at the Indian Institute of Technology in Bombay have, during the last fifteen years, extensively studied the various possibilities of photochemically rearranging phenol-derived bicyclo[2.2.2]octenones into complex polycyclic systems,[125] and in particular, linearly fused tricyclopentanoids or triquinanes,[126-128] as well as angularly and linearly fused tetraquinanes.[129] They notably utilized a wide variety of orthoquinol acetates and ethers **135** with appropriate cyclopentenic dienophiles **136** to build various bicyclo[2.2.2]octenones **137** via inverse electron-demand [4π + 2π] cycloadditions. Orthoquinols were usually generated via Adler oxidation (*Eqs.* 19 and 20). ODPM rearrangements of *endo*-annulated bicyclo[2.2.2]octenones led to stereospecific formation of cyclopropane-containing tricyclopentanoids **138**. Their three-membered ring units were then opened via electrophile-assisted or reductive cleavage to furnish *cis*:*anti*:*cis* triquinanes (*Eq.* 35). Applications of this general methodology to the synthesis of various naturally occurring polyquinanes such as coriolin **225** and capnellene **230** have been reported (*Schemes* 22 and 23).[130-132]

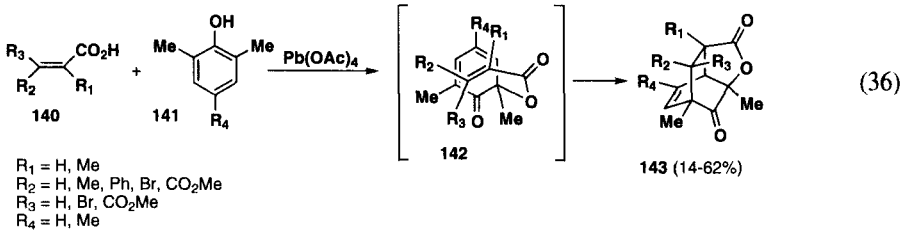
As alluded to above, Yates and co-workers prepared a series of 2-methylphenol-derived bicyclo[2.2.2]octenones via a Wessely-type acyloxylation/intramolecular Diels–Alder reaction. Various alkenoic acids **140** were used in place of acetic acid in the $Pb(OAc)_4$-mediated oxidation to give orthoquinol esters of type **142** which are then thermally converted into tricyclic lactones **143** in



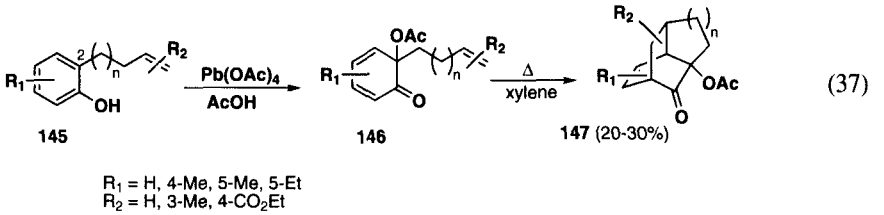
(35)

14-62% yields (*Eq.* 36).[118,119] Bridged xanthenes have been produced from 4-methylxanthen-3-ol by the same methodology (not shown).[133]

An all-carbon version of this "domino" reaction relied on the standard Wessely acetoxylation for making orthoquinol acetates **146** from olefinic phenols **145**. This variation permitted to access, albeit in relatively low yields but in a very concise manner, tricarbocycles of the isotwistane family (*Eq.* 37, **147**, n = 1).[134,135]



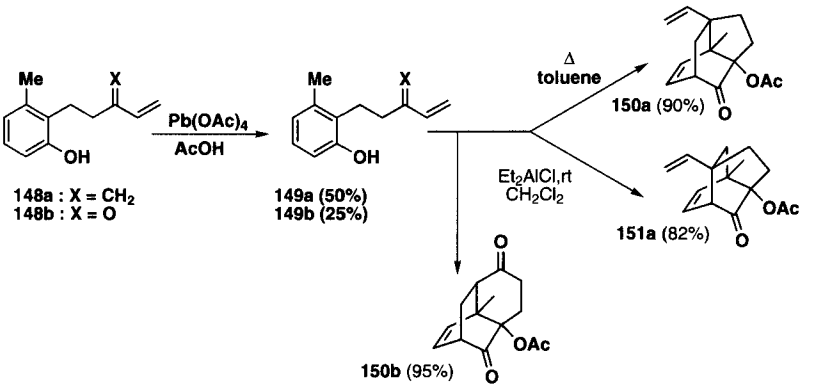
(36)



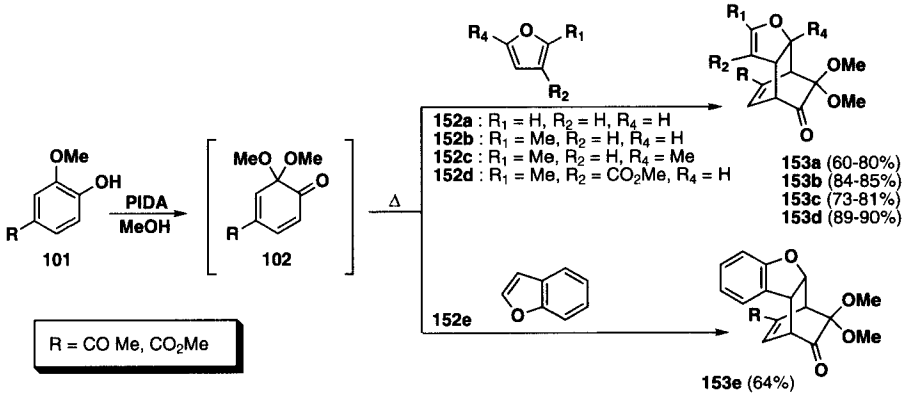
(37)

More recently, Yates and co-workers extended this methodology to the synthesis of homotwistane derivatives (*Eq.* 37, **147**, n = 2).[136] For example, the α,β-enone **148b** gave the deacetylated homoisotwist-5-en-2-one **150b** in high yield (*Scheme* 11). Interestingly, the diene analogue **148a** did not lead to any homotwistane, but to the regioisomeric twistanes **150a** and **151a** depending upon whether the reaction was induced thermally or by Lewis acid catalysis.

Furans, despite their aromaticity, can be used as Diels–Alder reaction components. This utilization is essentially limited to their role as dienes. Of particular note is their recently described involvement as dienophiles in cycloadditions with orthoquinone monoketals (*Scheme* 12).[137] Furans **152** bearing either electron-releasing or -withdrawing groups all act as dienophiles when combined with 6,6-dimethoxycyclohexa-2,4-dienone derivatives **102** to furnish in good to high yields *endo*-annulated bicyclo[2.2.2]octenones **153**. Even highly aromatic benzofuran **152e** led to bridged cycloadducts in good yields.[137]



Scheme 11



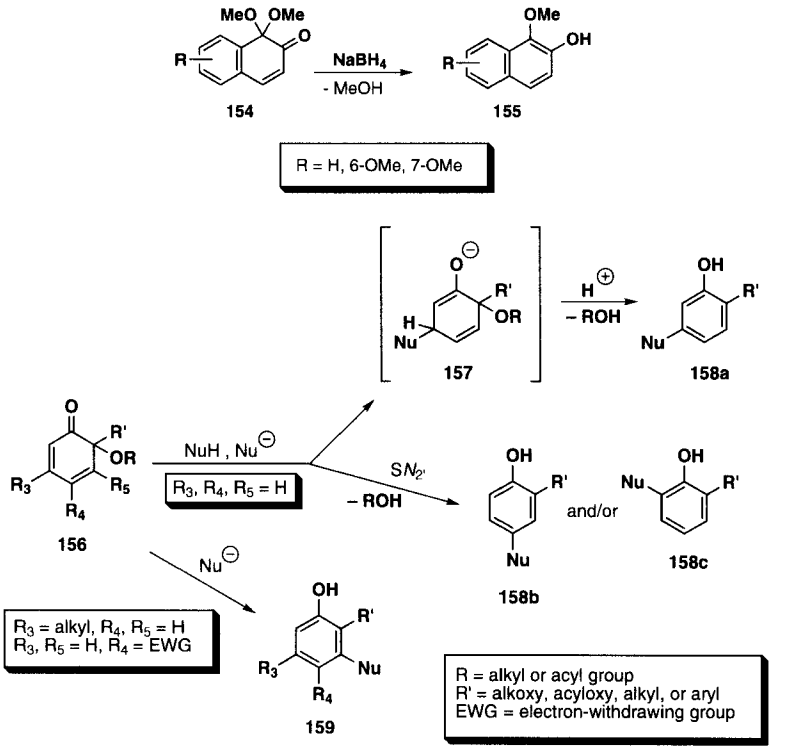
Scheme 12

2. Nucleophilic Additions

Orthoquinone monoketals (*i.e.*, 6,6-dioxocyclohexa-2,4-dienones) are monoprotected versions of orthoquinones, but their chemical reactivity still strongly relies on their electrophilic character. Orthoquinols (*i.e.*, 6-oxo-6-alkylcyclohexa-2,4-dienones) also behave as good electrophiles in various types of nucleophilic additions. The electrophilicity of numerous 6-oxo-cyclohexa-2,4-dienone derivatives of the orthoquinol acetate type vis-à-vis various nucleophilic species including carbon-based nucleophiles (enolates, Grignard and organolithium reagents, Wittig reagents, cyanide), hydroxide and alkoxide anions, amines, sulfinic acids, thiols and thiolates, and phosphonates has been reviewed by Miller.[3]

Products **158a** and **159** resulting from both conjugate 1,4- and 1-6-additions to the dienone moiety are normally encountered with most nucleophiles (*Scheme* 13), although direct carbonyl addition is also possible. For example, Dolson and Swenton had proven the structures of electrochemically-generated naphthoid orthoquinone monoketals of type **154** by hydride-mediated reduction of the quinonoid carbonyl followed by *in situ* rearomatization via elimination of methanol (e.g., *Eq.* 38).[8] More recently, both Danishefsky's and Magnus' groups successfully performed chemoselective

enediynyl anion addition to the carbonyl group of orthoquinol derivatives in their synthesis of calicheamicinone (*Schemes* 33 and 34).[138,139]



(38)

Scheme 13

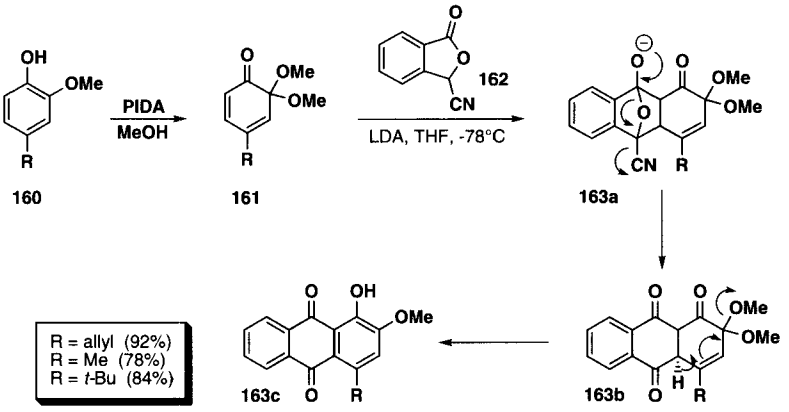
a) Carbon-carbon Bond-forming Reactions

Carbon-based nucleophiles generally attack orthoquinone monoketals and orthoquinol variants at their 3-position via a conjugate 1,4-addition path to the enone moiety unless the 3-position is already substituted or the 4-position bears a conjugated electron-withdrawing group (*Scheme* 13), in which case a corresponding conjugate 1,6-addition would be the next preferred reaction path. After the addition, elimination of acetic acid, in the case of orthoquinol acetates, or alcohol, in the case of 6,6-dialkoxycyclohexadienone derivatives (e.g., **157** →**158a**), readily takes place to furnish rearomatized substitution products of the type **158a** or **159** (*Scheme* 13).[3]

Phenol products of type **158b** that resulted from deacetylation of orthoquinol acetates via nucleophilic attack at the 4-position of **156** (*Scheme* 13), have often been observed when using electron-rich Grignard reagents (SN_2'-like reaction).[140,141] Cyanoacetate have also been reported to behave similarly in its reaction with **156** (R_4 = Me) to furnish a phenol of type **158c**.[3]

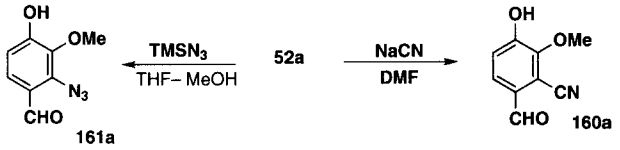
The propensity of orthoquinone monoketals to undergo 1,4-addition with carbon nucleophiles was exploited by Russel and Mitchell[142,143] in their synthesis of anthraquinones. Eugenol (**160**, R = allyl) and creosol (**160**, R = Me) were oxidized with PIDA in MeOH to yield ketals **161** which were immediatly trapped *in situ* with the anion of 3-cyanophthalide **162** to furnish the anthraquinone

products **163c** in high yields (*Scheme* 14). It was also noted that the 4-*t*-Butylated 2-methoxyphenol **160** gave rise to a particularly stable non-dimerizing orthoquinone monoketal **161** (R = *t*-Bu) that could be isolated in 43% yield.[142] This two-step preparation of anthraquinones can be viewed as a convenient alternative to classical Diels-Alder approaches which often relies on the use of unstable dienes.[144]

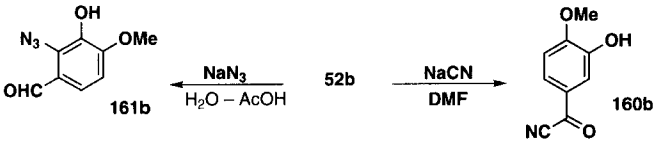


Scheme 14

Wessely and co-workers were the first to demonstrate the importance of the positioning and electronic nature of substituents on the outcome of nucleophilic additions to orthoquinone monoketals.[3] For example, they evidenced a divergence in reactivity between the vanillin- and isovanillin-derived orthoquinol acetates **53a** and **53b** by subjecting them to cyanide attack.[72] Conjugate 1,4-addition to the α,β-unsaturated aldehyde moiety was observed with **53a** in dimethylformamide (DMF), whereas direct addition to the more reactive aldehyde group of the conjugated keto-aldehydic unit of **53b** was observed in the same solvent (*Eqs.* 39 and 40).[3] In contrast, a conjugate 1,4-addition to this aldehyde of **53b** was observed when using the azide anion (*Eq.* 40) (*vide infra*).[145]



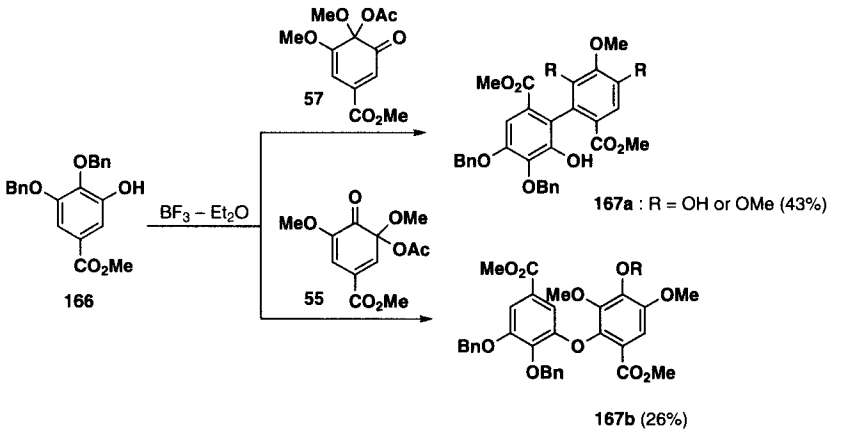
(39)



(40)

A rather puzzling change of chemoselectivity is observed in the addition reaction of the monophenolic gallate **166** with orthoquinol acetate **55** *versus* **57**. Upon Lewis acid-mediation, **57** behaved as a carbon-based nucleophile with **166** to furnish biaryl **167a** in 43% yield via SN_2-like

reaction pathways (*Eq.* 41), whereas it behaved as an oxygen-based nucleophile with **55** to furnish diaryl ether **167b** as the sole adduct, albeit in low yield, via conjugate 1,4- or 1,6-addition (*Eq.* 42).[79]



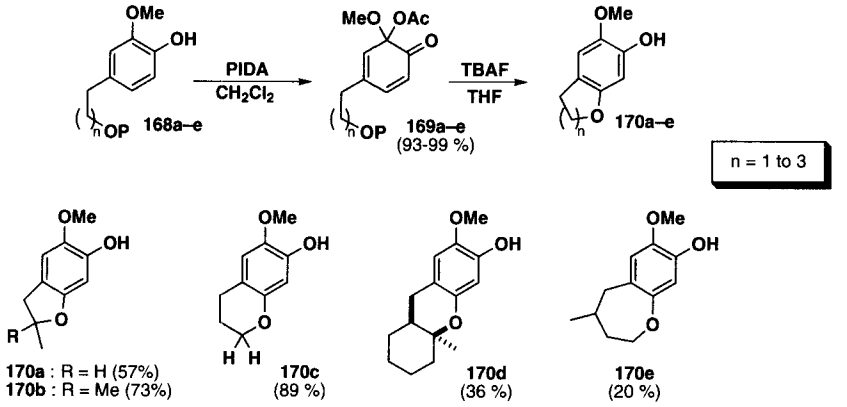
(41)

(42)

b) Heteroatom-carbon Bond-forming Reactions

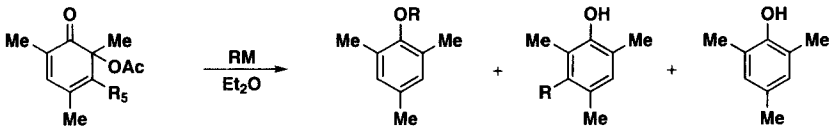
Most heteroatomic nucleophiles follow the same general trend as carbon-based nucleophiles do in their attack to orthoquinone monoketals, and in particular to orthoquinol acetates.[3] Conjugate 1,4- and 1,6-additions to the dienone moiety do usually take place (e.g., *Eqs.* 42 and 43) unless substitution blocks the corresponding cyclohexyl positions (*vide supra*). Some known exceptions are here worth recalling (see also *Scheme* 12). Addition of the azide ion to the vanillin-derived orthoquinol acetate **53a** expectedly furnished the azidophenol **165a** in 60% yield (*Eq.* 39), but use of the isovanillin-derived orthoquinol acetate **53b** led to the formation of **165b** in 95% yield (*Eq.* 40). In both cases, product formation can be explained by a conjugate 1,4-addition to the α,β-unsaturated aldehyde moiety followed by rearomatizing acetate elimination. This is in contrast to the observation made when using the cyanide anion whose nucleophilicity better matched the stronger electrophilicity of the aldehyde group of **53b** (*Eq.* 40).[145] Another rather intriguing combination of orthoquinol acetates and heteroatomic species is the one concerning thiols that systematically target the 2- and 4-positions of the cyclohexadienone unit to produce phenols of type **158b** and **158c** (*Scheme* 13), even when the starting quinone ketal is unsubstituted at the 3- and 5-position. The capability of thiols to generate rather stable free radical species has been invoked in mechanistic suggestions concerning this peculiar behavior.[3]

A recent exploitation of the Michael-type electrophilicity of orthoquinol acetates led to regioselective heterocyclizations for the production of benzannnulated ether rings of various sizes. Phenols of type **168** were transformed into stable and isolable orthoquinol acetates **169** via PIDA-mediated oxidation in CH_2Cl_2. These silyloxy derivatives were then treated with TBAF to engender cyclization with concomitant rearomatization to furnish the corresponding 5- to 7-membered ether rings **170a-e** (*Eq.* 43). Such cyclizations could follow either a conjugate 1,4- or 1,6-addition route to the dienone system, but only *exo-trig* attack at the least sterically congested center did occur, *i.e.*, 1,4-addition (*Eq.* 43).[203]



(43)

Finally, one must also recall this remarkable heteroatom-carbon bond-forming addition reaction first discovered by Wessely and Kotlan[146] and based on the addition of certain Grignard and organolithium reagents at the *oxygen* center of orthoquinol acetates to furnish aryl ethers.[3] Miller extended the study of this reaction to orthoquinol monoacetates and found that the better the electron-releasing ability of the Grignard reagent is, the higher the yield of aryl ethers **172a** (*Eq.* 44).[140,141] Radical-based C–O coupling mechanisms have been proposed to rationalize this behavior of orthoquinonoid species.[140] Varying amounts of "normal" conjugate addition products **172b** and reduced compounds **172c** were also observed (*Eq.* 44),[140] as well as SN_2'-reaction products of type **158b** (*Scheme* 13) when using substrates unsubstituted at their 4-position.[141] This possibility of performing oxophilic additions at quinonoid carbonyls has been utilized for the preparation of simple diaryl ether species.[147]



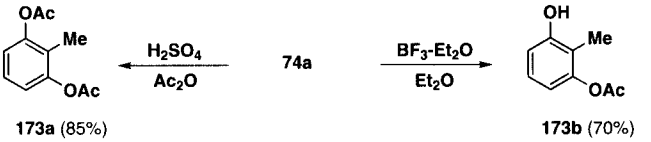
(44)

RM	172a : 172b : 172c (%)
MeMgBr	< 0.1:39:4
sec-BuMgBr	67:16:17
t-BuMgBr	28:< 0.1:72
t-BuLi	15:< 0.1:85
BnMgBr	91:< 0.2:9

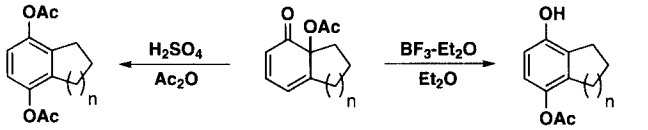
3. Rearrangements

Orthoquinone monoketals and orthoquinols are cyclohexa-2,4-dienones that can be considered as "blocked" aromatic species; the presence of a single quaternary sp^3 center prevents them from attaining aromaticity.[3] Nevertheless, they remain particularly prone to aromatizing rearrangements such as those related to the acid-mediated phenol-dienone rearrangement.

The aromatizing rearrangement of numerous orthoquinol acetates such as **74a-e** (*Eq.* 24), using either acetic anhydride in the presence of H_2SO_4 (the Thiele reaction) or BF_3-etherate in ether have been investigated by Wessely and co-workers,[71,148] as well as Goodwin and Witkop,[149] and well reviewed by Miller in 1968.[3] Several types of apparent acetate migrations have been observed including 1,2-, and 1,3-shifts. For example, the orthoquinol acetate **74a** gave rise to the phenol **173b** in 70% yield upon treatment with BF_3-etherate (*Eq.* 45), whereas a 1,3-migration predominates when the 5-position of the cyclohexa-2,4-dienone ring is substituted such as in the conversion of **174** and **175** into **176** and **177** (*Eq.* 46).[71,98]

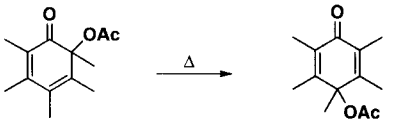


173a (85%) **173b** (70%) (45)

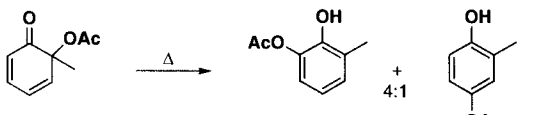


176a (n = 1; 85%)
177a (n = 2; 80%)
174 (n = 1)
175 (n = 2)
176b (n = 1; 40%)
177b (n = 2; 60%) (46)

Other orthoquinol acetates and diacetates such as 6-acetoxy-6-alkoxy- and 6,6-diacetoxycyclohexa-2,4-dienones have also been submitted to a variety of acetoxy migrations either under the conditions of the Thiele reaction or in the presence of BF_3-etherate.[3] Thermal rearrangements have also been performed.[3] A noteworthy example is the rearrangement of the permethylated orthoquinol acetate **178a** into its para-counterpart **178b** (*Eq.* 47).[150] Although this shift cannot be driven by aromatization, it would corroborate the higher stability of paraquinols over that of π-conjugated orthoquinols. The same regioisomerization has also been catalyzed by BF_3-etherate.[150] Interestingly, when an ortho-position is unsubstituted, thermal rearrangement of the acetoxy is preferentially to the ortho- rather than to the para-position; a 4:1 ratio of phenols **180a** and **180b** was, for example, observed for the rearrangement of the orthoquinol acetate **179** (*Eq.* 48).[151]

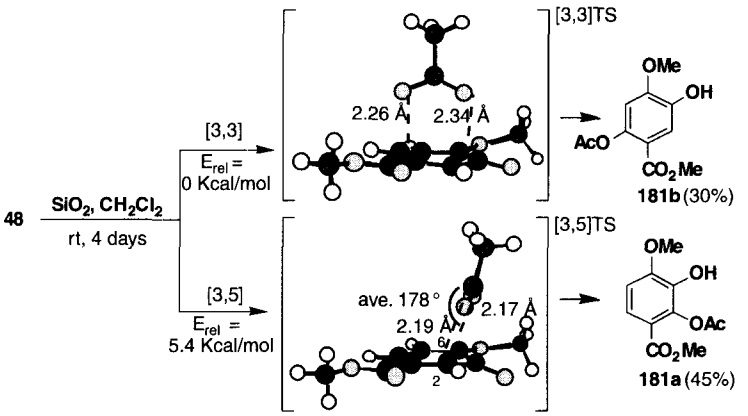


178a **178b** (47)



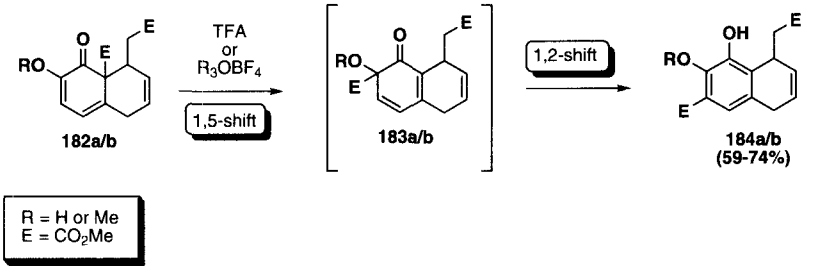
179 **[3,5]-180a** **[3,3]-180b** (48)

Several mechanisms involving either concerted sigmatropic shifts, radical dissociation–recombination, and successive cationic 1,2-shifts have been proposed to rationalize these 1,3-acetoxy migrations.[3,152] Sigmatropic shifts were dismissed early on by consideration of Woodward and Hoffmann's rules of orbital symmetry conservation. It has, however, recently been calculated that such acetate rearrangements can conceivably derived from concerted [3,5] and [3,3] sigmatropic shifts.[153] Furthermore, density functional theory calculations indicated that the [3,5] shift that furnishes **181a** from **48** is *pseudopericyclic*, has a remarkably low activation energy of *ca.* 20 Kcal/mol, and is favored by *ca.* 5 Kcal/mol over the pericyclic [3,3] shift that leads to **181b** (*Scheme* 15).[73] These calculations on energy barriers were in qualitative agreement with our experimental observations on mild acid catalysis of this orthoquinol acetate rearrangement.[73]



Scheme 15

Orthoquinols were recently proposed as intermediates in acid-mediated rearrangements of cyclohexa-2,4-dienones.[154] Upon treatment with TFA or trialkyloxonium tetrafluoroborate in CH_2Cl_2, esters **182a/b** would undergo 1,5-shifts of their carboxymethyl group to furnish orthoquinols **183a/b** which would then rearranged into phenols **184a/b** via 1,2-shifts (*Eq.* 49).

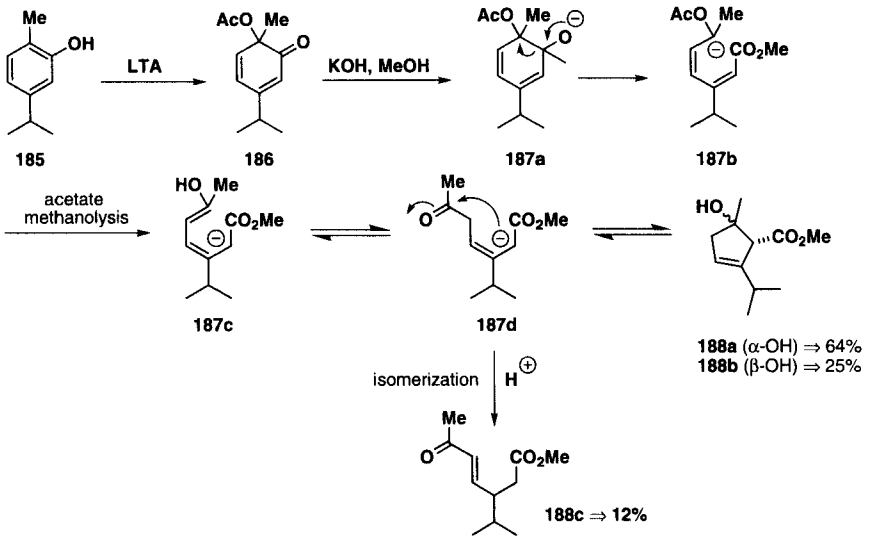


(49)

Alkali-induced rearrangements of orthoquinol acetates have been evidenced notably by Carman and co-workers during their work on the synthesis of carvacrol-derived diterpenoids (*vide*

infra). Treatment of the acetate **186** with methanolic KOH gave the two diastereomeric ring contraction products **188a** and **188b**, and the open-chain keto-ester **188c**. These products result from *direct* attack of the methoxide anion at the cyclohexadienone carbonyl as depicted below (*Scheme* 16).[155]

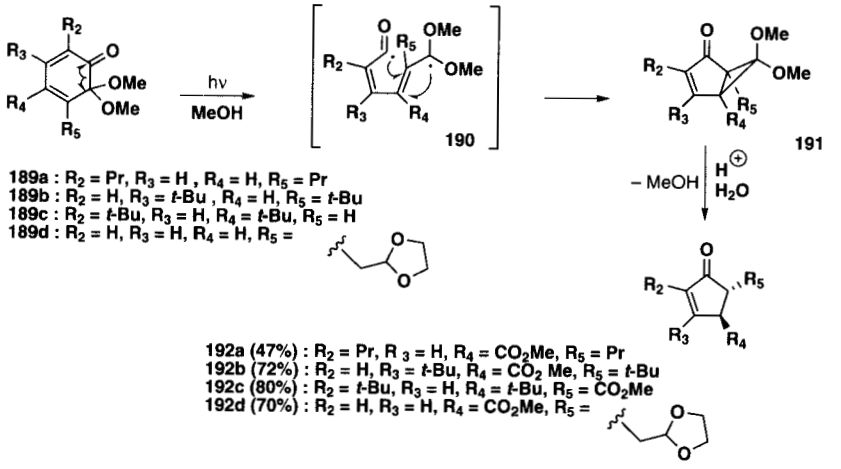
Transformations of cyclohexa-2,4-dienone rings into either open-chain or ring contracted products can also be performed via light irradiation.[152,156] The enone moiety of cyclohexa-2,4-dienones render them particularly sensitive to photochemically-induced chemistry. Orthoquinone monoketals and orthoquinol variants are no exception, and can rearrange under photochemical conditions.[152]



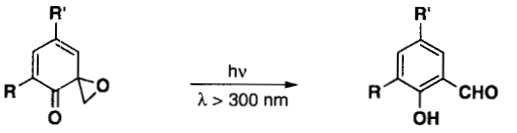
Scheme 16

A novel entry into cyclopentenones was recently proposed by Liao and Wei,[112] who reported the photochemically-induced conversion of non-dimerizing orthoquinone monoketals **189a-d** into bicyclo[3.1.0]hexenones **191**. This transformation was followed by acid-catalyzed opening of the cyclopropyl unit to furnish diastereoselectively substituted cyclopentenones **192a-d** in 30% to 80% (*Scheme* 17). Orthoquinol esters of the *O*-spirolactone type were also used as substrates but with less preparative efficiency due to premature opening of the lactone ring.[112] The 2- and 3-unsubstituted cyclopentenone **192d** were generated in CF_3CH_2OH in order to limit the formation of open-chain by-products from ketene intervention.[150,156] This species could constitute a valuable intermediate for prostaglandin synthesis. A recent application of photolytic ring opening of an orthoquinol[152] for the synthesis of a natural product is depicted in *Scheme* 32.[157]

Thermally-stable spiroepoxy-cyclohexa-2,4-dienones such as **194a-d**, accessible from Adler oxidation of the corresponding salicyl alcohols, readily photoisomerize into the salicyl aldehydes **195a-d** (*Eq.* 50).[89]



Scheme 17



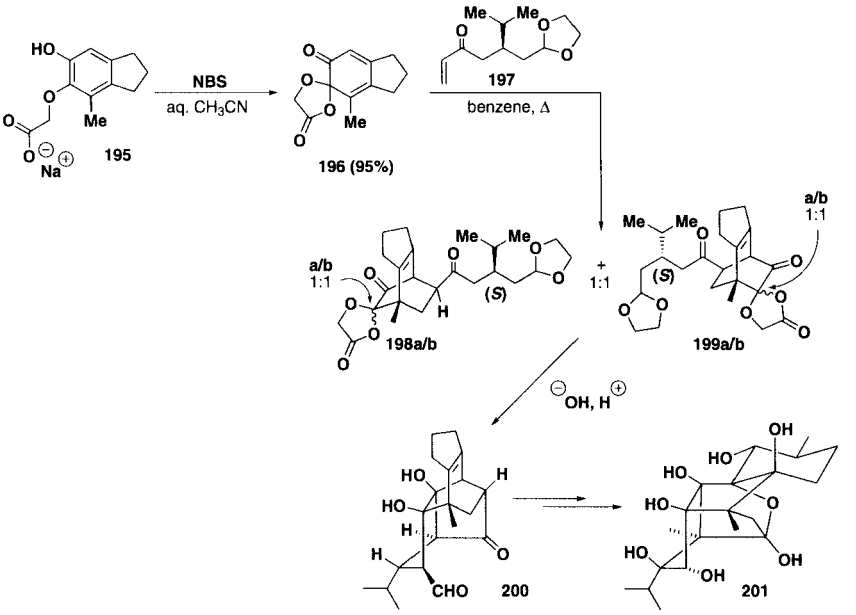
(50)

R = t-Bu, R' = t-Bu (**193a**) — **194a** (90%)
R = C_6H_{11}, R' = CH_3 (**193 b**) — **194b** (94%)
R = CH_2OH, R' = t-Bu (**193c**) — **194c** (88%)
R = H, R' = t-Bu (**193d**) — **194d** (73%)

III. APPLICATIONS IN NATURAL PRODUCT SYNTHESIS AND BIO-ORGANIC STUDIES

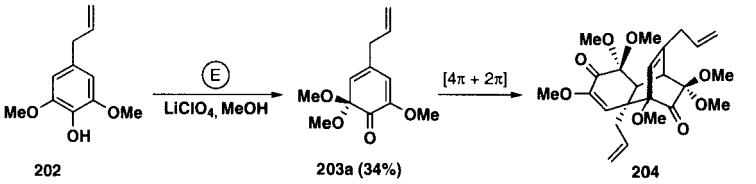
One of the earliest elaborate example of the utilization of an orthoquinone monoketal in natural product synthesis is the one reported by Deslongchamps and co-workers[82,158] for the synthesis of the diterpene (+)-ryanodol **201** (*Scheme* 18). The racemic *O*-spirolactone **196** was used as a diene component in a Diels-Alder reaction with the optically active (+)-isopropyl vinylketone acetal **197** to furnish a 1:1 mixture of the diastereomeric adducts **198a/b** and **199a/b** in quantitative yield. Two successive intramolecular aldol reactions then led to the formation of the dihydroxyketoaldehyde **200**, which was eventually tranformed into (+)-ryanodol **201**. Extensive model studies had been performed to identify the best *O*-spirolactone diene and vinylketone dienophile for the most convergent route to **201**; this work was recently reviewed by Deslongchamps himself.[159,160]

Phenol anodic oxidation was applied by Yamamura and co-workers as a key step in the synthesis of several bioactive natural products.[55-57,161] The asatone group of neolignans was first targeted (*Eq. 51*). Allyl-phenol **202** was electrolyzed at a constant current (5 mA) using $LiClO_4$ as a supporting electrolyte to afford the orthoquinone monoketal **203a** (34% yield). This compound was then transformed into asatone **204** via a [4π + 2 π] cyclodimerization.

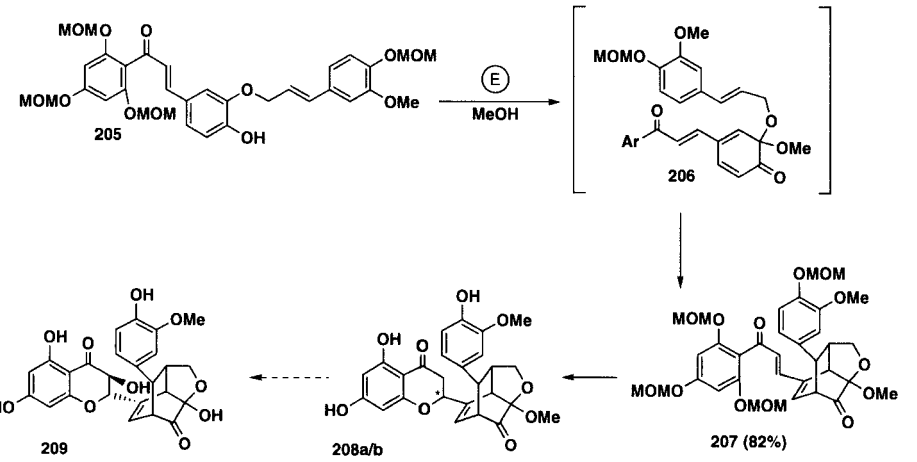


Scheme 18

Yamamura and co-workers also accomplished a facile synthesis of diastereoisomers **208a/b** which both possess the 9-oxaisotwist-8-en-2-one structure of silydianin **209** (an antihepatotoxic agent isolated from the fruits of *Silybum marianum* G.) (*Scheme* 19). This electrochemical method gave



(51)

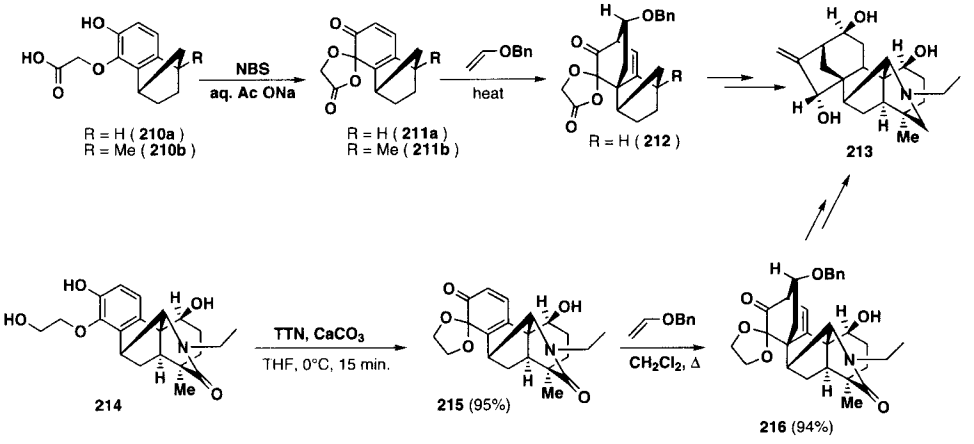


Scheme 19

better results than Yates' approach to isotwistenones.[135] (82% *vs.* 20-30%, *Eq.* 37) which was based on Wessely oxidation. Furthermore, the acidic conditions of the Wessely oxidation are incompatible with the use of acid sensitive protecting groups such as the methoxymethyl (MOM) ether group.

Construction of the CD ring sytem of denadutine-type alkaloids targeted by Wiesner and co-workers was based on the addition of a dienophile to an orthoquionone monoketal of the *O*-spirolactone dienone type.[162-164] Two different routes were developed. In the first one, the phenolic acid **210a/b** was oxidized to the *O*-spirolactone **211a/b** with NBS.[82] The cyclic orthoquinol ester **211a** was evaporated to dryness and immediatly treated with an excess of dienophile (benzyl vinyl ether, methyl vinyl ether, or ethyl vinyl sulfide ether) (*Scheme* 20). The resulting nordenudatine-type intermediate **212** was then modified in a few stereospecific steps to the napelline **213**. The second synthesis used intermediate **214** which was submitted to a McKillop oxidation to furnish crystalline **215** in 95% yield; a Diels-Alder reaction similar to the one leading to **212** enabled the preparation of the advanced napelline precursor **216** (*Scheme* 20).

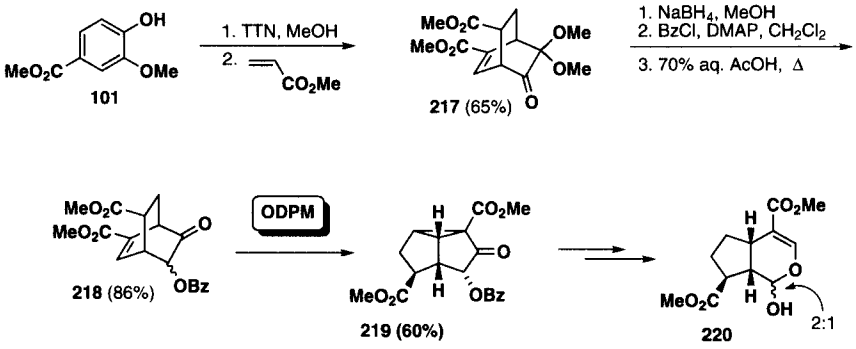
The possibility of generating bicyclo[2.2.2]octenones from Diels–Alder reactions of ortho-quinone monoketals with dienophiles was also utilized by Liao and Wei in their 1989's racemic synthesis of the the iridoid aglycone of (±)-forsythide, as its dimethyl ester **220** (*Scheme* 21).[165] McKillop oxidation of phenol **101** followed by a Diels–Alder reaction with methyl propenoate furnished the bicyclic octenone **217**. Transposition of the carbonyl group of **217** into **218** was achieved in three steps. The bicyclic ketone **218** was then subjected to light irradiation to undergo a key ODPM rearrangement into **219** in good yield. This tricycle was then converted into an epimeric mixture of the target **220** over five steps.



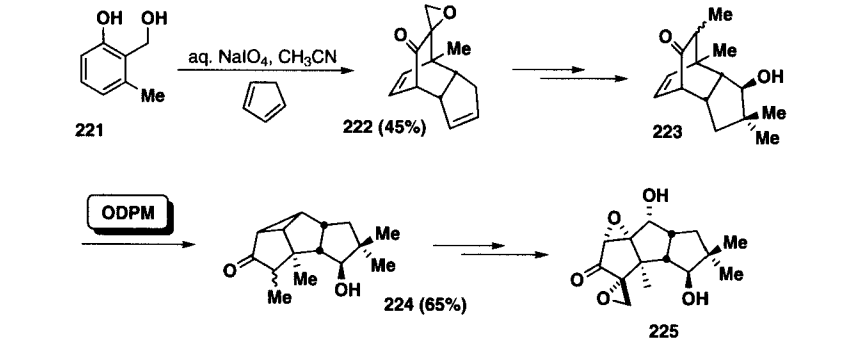
Scheme 20

The ODPM rearrangement of *endo*-annulated bicyclo[2.2.2]octenones have been utilized by Singh's group in their synthesis of sesquiterpenoid triquinanes.[126,127] A formal total synthesis of coriolin **225** was, for example, derived from Adler oxidation of 6-methylsaligenin **221** with cyclopentadiene (*Scheme* 22).[131] The resulting bicyclo[2.2.2]octenone **222** underwent a 1,2-acyl shift via an

ODPM rearrangement which afforded the tetracycle **224** in good yield. This was further elaborated into a known advanced intermediate for the synthesis of coriolin **225**.[131]

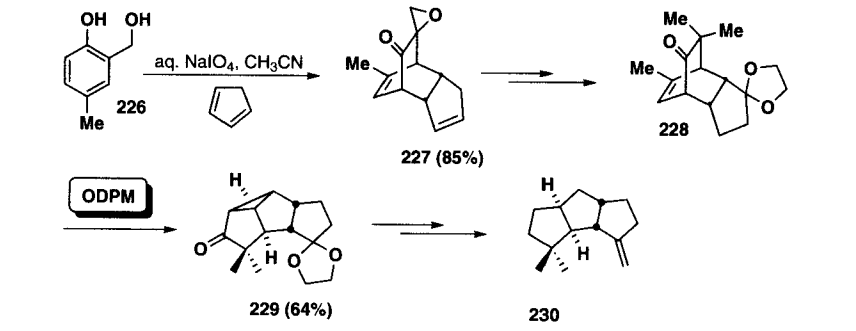


Scheme 21



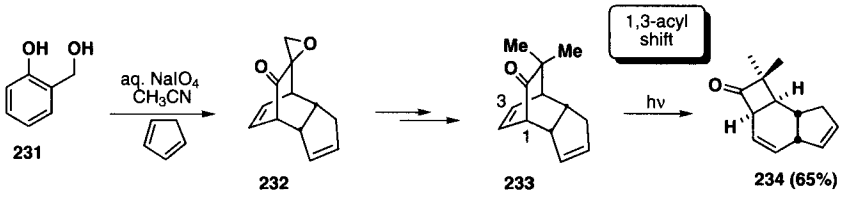
Scheme 22

A similar strategy was used by the same group for a total synthesis of the sesquiterpene capnellene **230** in racemic form.[132] Here, a *para*-cresol derivative **226** was used as the starting phenol which was submitted to an Adler oxidation in the presence of cyclopentadiene. The *endo*-annulated bicyclic ketone **227** was obtained in 85% yield, and converted into the target **230** in 3% yield over 14 steps (*Scheme* 23).[132] Advanced precursors to oxygenated capnellanes have also been synthesized by the same route.[130]



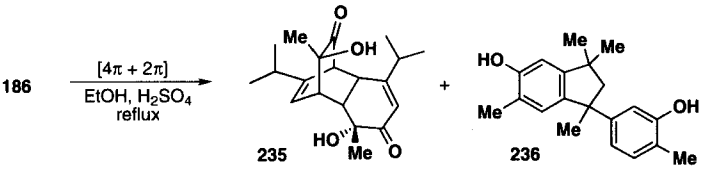
Scheme 23

Bicyclo[2.2.2]octenones, annelated with cyclopentenyl moiety, have also been reported to undergo sigmatropic 1,3-acyl shifts in singlet excited state to furnish protoilludanoid systems such as in the transformation of salicyl alcohol **231** into the cyclobutanone **234** (*Eq.* 52).[166]

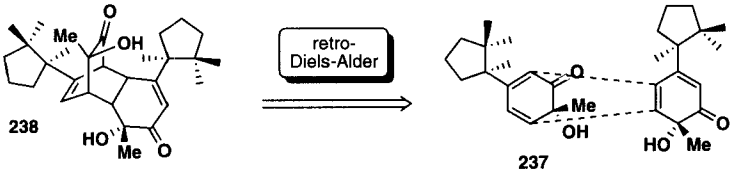


(52)

Carman and co-workers[167] synthesized the racemate of the *Callitris macleayana* carvacrol-derived diterpene **235** in *ca.* 30% yield by acid-catalyzed Diels-Alder dimerization of the orthoquinol acetate **186** (*Scheme* 16) under the reaction conditions used by Metlesics and Wessely (*Eq.* 53).[96] Deacetylation occurred *in situ*, and the indan **236** was also produced via acid-catalyzed cationic dimerization of deacetylated **186**.[168] Interestingly, a novel bis-sesquiterpene, aquaticol **238**, has recently been isolated from the traditional Chinese medicine *Veronica anagallis-aquatica*. It was postulated to derive biosynthetically from a Diels-Alder dimerization of the naturally occurring sesquiterpenoid orthoquinol **237** (*Eq.* 54).[169] This judicious proposal now awaits demonstration by total synthesis.



(53)

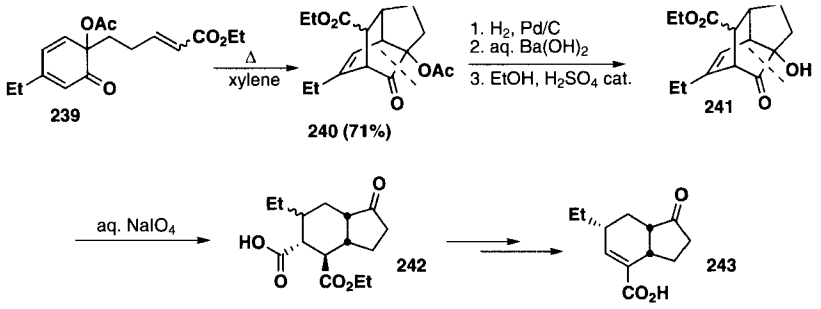


(54)

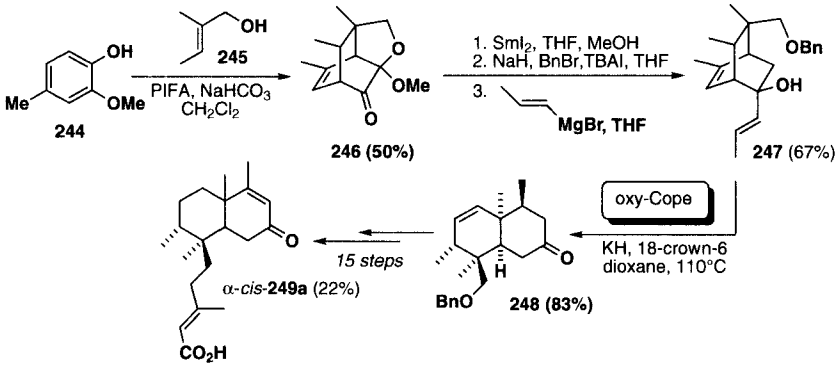
Peter Yates and co-workers successfully and efficiently utilized their Wessely oxidation/intramolecular Diels–Alder route to isotwistenones in a total synthesis of (±)-coronafacic acid **243**. A yield of 71% was reported for the key "domino" reaction.[170,171] The special sensitivity of the vicinally-oxygenated unit of **241** toward oxidative cleavage was then exploited to furnish the keto ester **242** which was subsequently converted into **243** in about 39% yield from **240** (*Scheme* 24).[170]

Liao and co-workers have applied their orthoquinone monoketal-based route to bicyclo[2.2.2]octenones in the syntheses of two diastereomeric but naturally occurring *cis*-clerodane diterpenic acids **249a** (*Eperua purpurea*) and **249b** (*Aristolochia brasiliensis*) in racemic forms (*Schemes* 25 and 26). The first synthesis[116] featured the oxidative ketalization of the 2-methoxyphenol

244 with the allyl alcohol **245** followed *in situ* by an intramolecular Diels–Alder reaction to furnish the oxatricyclic ketone **246** in 50% yield. This compound was then transformed into the dienol **247** for a subsequent anionic oxy-Cope rearrangement into the *cis*-decalin **248**. Further elaboration led to the α-*cis*-clerodane diterpenic acid **249a**.

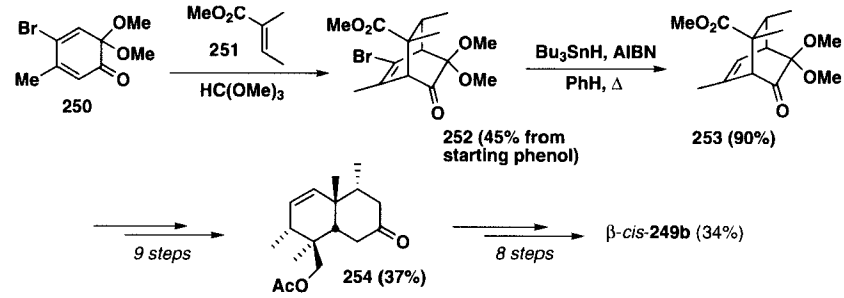


Scheme 24



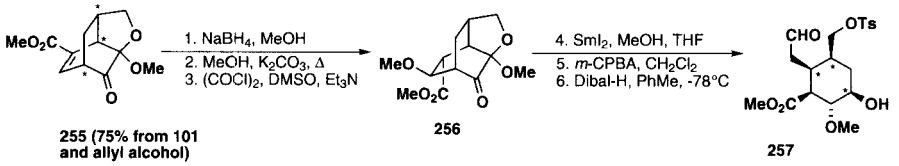
Scheme 25

The second synthesis[68] made use of the improved intermolecular Diels-Alder reaction of dimerizing orthoquinone monoketals depicted in *Scheme* 4.[69] Thus, 6,6-dimethoxy-4-bromo-3-methylcyclohexa-2,4-dienone **250** was combined with the dienophile ester **251** to furnish the *ortholanti* cycloadduct **252** in 45% yield. Standard reductive debromination led to **253** which was then converted in several steps to the targeted β-*cis*-clerodane diterpenic acid **249b** (*Scheme* 26).



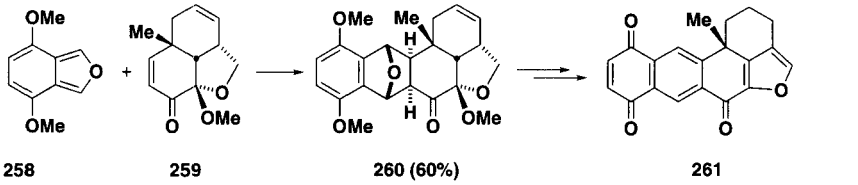
Scheme 26

A formal synthesis of the alkaloid (±)-reserpine was claimed by Liao and co-workers on the basis of the preparation of the cyclohexane derivative **257** which was a key intermediate in Stork's synthesis of reserpine. Methyl vanillate **101** was transformed into the oxatricyclic enone **255** in the usual fashion (*Eq.* 28b).[67] The relative configuration of three out of the five stereocenters of **257** were thus already set at this stage. Ketone reduction, Michael addition of methanol to the α,β-unsaturated methyl ester, Swern oxidation, samarium iodide-induced reduction of the ketal group, tosylation of the unveiled primary alcohol, regioselective Baeyer–Villiger lactonization, and low-temperature Dibal-H reduction of the lactone thus furnished the desired aldehyde in 18% overall yield from **255** (*Eq.* 55).[172]

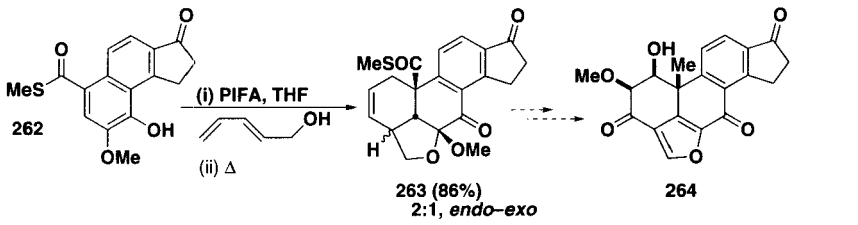


255 (75% from 101 and allyl alcohol) 256 257 (55)

Rodrigo and co-workers reported the synthesis of the marine sponge metabolite (±)-xestoquinone **261** from 4,7-dimethoxyisobenzofuran **258** and the *cis*-decalin **259** (*Eq.* 56).[105] The latter species was generated via an oxidative ketalization of 2-methoxy-4-methylphenol with (*E*)-2,4-pentadienol and an *endo*-selective intramolecular Diels–Alder reaction in concert with a Cope rearrangement (*Eq.* 30). An advanced intermediate **263** for the synthesis of viridin **264** was also produced from the tricyclic benzindanone **262** in good yield (*Eq.* 57).

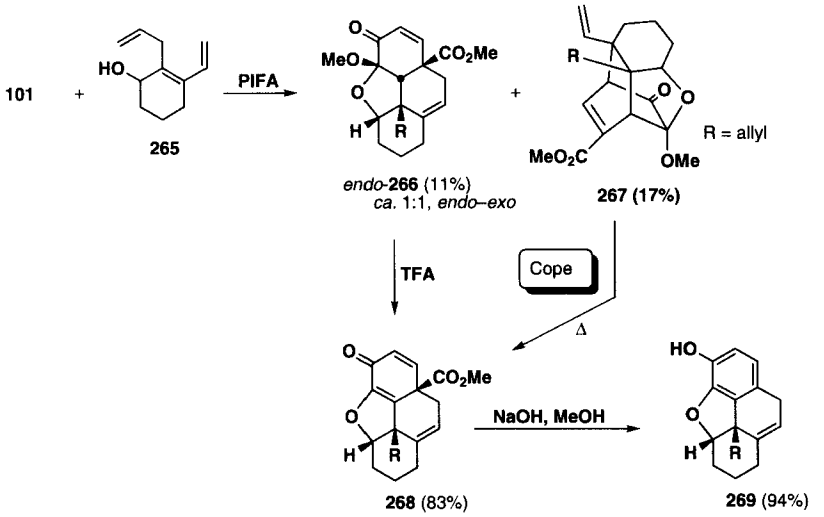


258 259 260 (60%) 261 (56)



262 263 (86%) 2:1, *endo–exo* 264 (57)

Complex furophenanthroid species such as **269** which are potentially well suited for the synthesis of the ABCE ring systems of morphinan alkaloids have been prepared in three steps from methyl vanillate **101** and the 2-allylcyclohexenol **265** according to the same Diels-Alder/Cope methodology (*Eqs.* 30, 56 and 57). Elimination of methanol to produce **268** occurred either via a brief exposure to TFA in the case of the *endo*-adduct **266** or concommitantly with the Cope rearrangement of the bicylo[2.2.2]octenone Diels–Alder product **267**.[106]

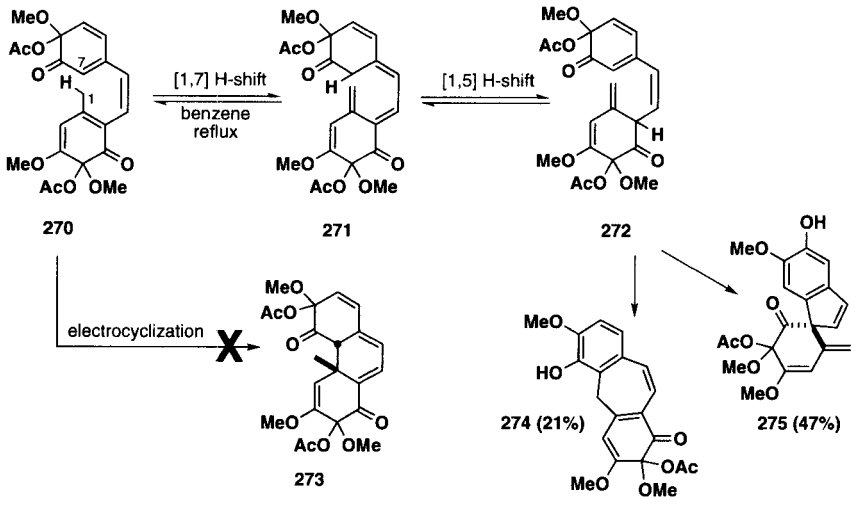


Scheme 27

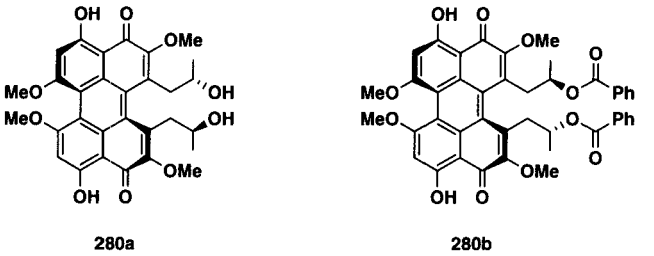
Another orthoquinone monoketal-based strategy has been attempted to construct the phenanthrene skeleton of morphinan alkaloids (*Scheme* 28). The 6π electron electrocyclization of the bis(orthoquinone monoketal) **270**, generated in good yield from its parent bisphenol, was contemplated to lead to the substituted phenanthrene **273**. Thermal induction of hydrogen shifts followed by two distinct SN_2'-like ring closures instead gave rise to **274** and **275**.[173]

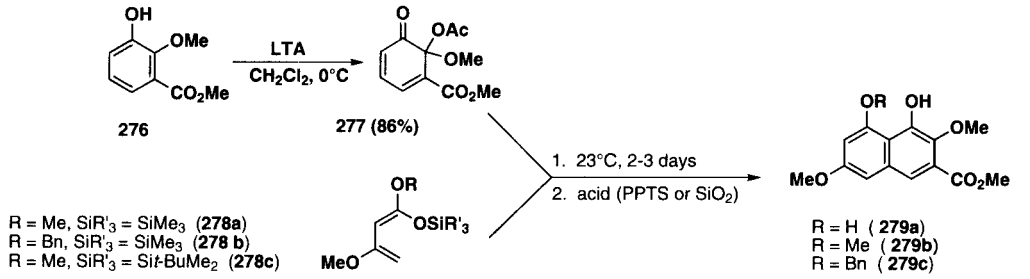
A novel access to perylenequinone natural antibiotics such as phleichrome **280a** and calphostin A **280b** has been described by Coleman and co-workers.[103,174] This new and efficient route is based on the regioselective construction of differentially protected polyoxygenated naphtalene subunits. Diels-Alder reactions between the orthoquinol acetate **277** – prepared in 86% yield by Wessely oxidative acetoxylation of phenol **276** – and 1,1,3-trioxygenated butadienes **278a-c**, followed by selective acid-promoted elimination of R_3SiOH and AcOH, directly afforded naphtalenes **279a-c** (*Scheme* 29). Such naphthalene subunits were further elaborated and submitted to atrop-diastereoselectively biaryl syntheses to furnish both **280a** and **280b** with excellent control of absolute stereochemistry.

The conversion of phenols into electrophilic orthoquinone monoketals have also been used to activate benzylic phenols for carbon-carbon bond formation. For example, Meyers and co-workers[175] at Colorado State University completed an asymmetric synthesis of the isopavine alkaloids (-)-desmethyl-*O*-methylthalisopavine **283a** and (-)-reframoline **283b** by treating the 1-benzyl-1,2,3,4-tetrahydroisoquinolines **281a/b** with LTA in CH_2Cl_2. The resulting crude orthoquinol acetates **282a/b** were then cyclized with acid (*i.e.*, conc. HCl) to furnish the desired seven-membered ring alkaloids via aryl/benzyl C–C bond formation (*Eq.* 58, path *a*). Intriguingly, Umezawa and co-workers hadearlier used the same Wessely oxidation-based protocol to induce biaryl synthesis in the same starting tetrahydroisoquinolines for the preparation of aporphine alkaloids.[176] Thus, by treating **282a** and **282b**



Scheme 28

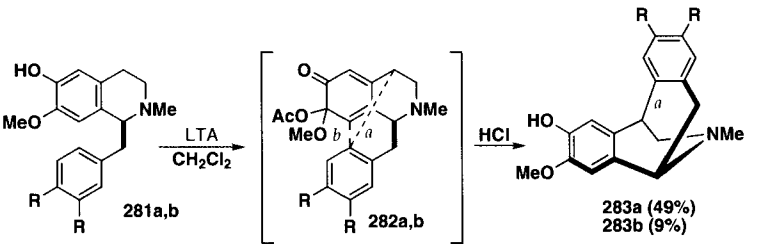




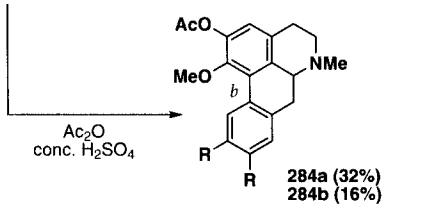
Scheme 29

with Ac_2O-conc. H_2SO_4, (±)-*O*-acetylpredicentrine **284a** and (±)-*O*-acetylisodomesticine **284b** were obtained in 32% and 16%, respectively (*Eq.* 59, path *b*).[176] The reason for this change in C–C bond formation chemoselectivity remains obscur. Cyclizations to **284a/b** can be rationalized in terms of a direct 1,6-conjugate addition to the 2,4-dienone moiety of **282a/b**, but one cannot dismiss the possibility of an initial SN_2-like substitution at the allylic acetate unit – a 5-*exo-trig* cyclization mode – followed by an aromatizing 1,2-aryl shift.

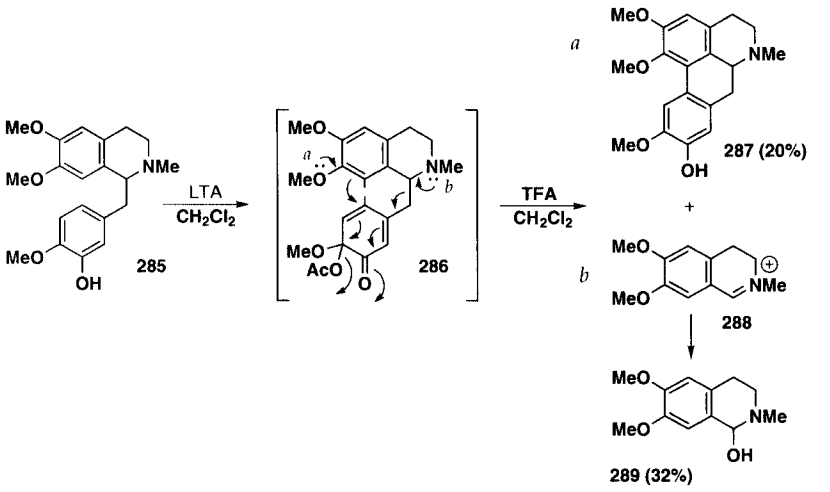
An analogous biaryl bond formation was also obtained by Umezawa and co-workers in their synthesis of another hydroxyaporphine alkaloid, (±)-*N*-methyllaurotetanine **287** (*Eq.* 60).[177] In this case, however, elaboration of an orthoquinol acetate unit was implemented at the phenolic 1-benzyl substituent of **285** with the aim of directing intramolecular bond formation toward biaryl synthesis via an SN_2'-like substitution at the allylic acetate unit (path *a*). A vinylogous retro-Mannich side-reaction (path *b*) was identified to hamper the preparative value of the desired biaryl synthesis by giving rise to the formation of the 1-hydroxy-1,2,3,4-tetrahydroisoquinoline **289**.



(58)



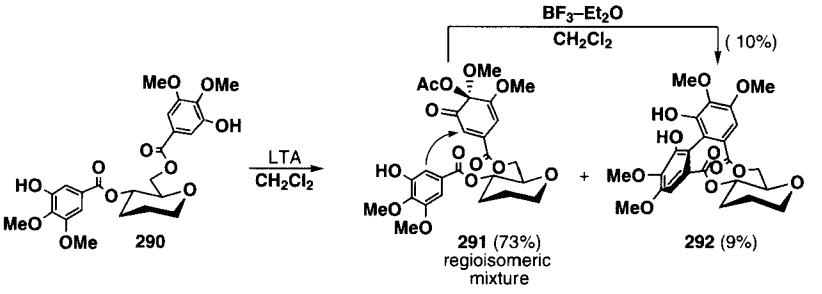
(59)



(60)

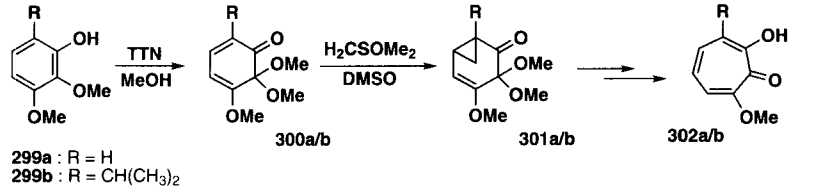
Similar biaryl coupling reactions were investigated by Feldman and co-workers in their synthetic studies toward ellagitannin natural products.[79,80] Wessely oxidation of model ellagitannin substrate **290** furnished the regioisomeric orthoquinol acetates **291** in admixture with a small amount of the desired biaryl product **292** (*Eq.* 61). This cyclized product could have resulted from either (1)

adventitious direct intramolecular trapping of one galloyl group as a phenoxenium-like species by the second phenolic galloyl group, or (2) an SN_2'-like substitution at the vinylogous allylic acetate unit of **291**. Attempts to cyclize **291** into **292** by Lewis acid mediation were unproductive, but high-yielding biaryl galloyl couplings were later obtained by simply increasing steric bulk at the galloyl ether functions to favor direct intramolecular trapping of oxidized galloyl intermediates.[79,80]



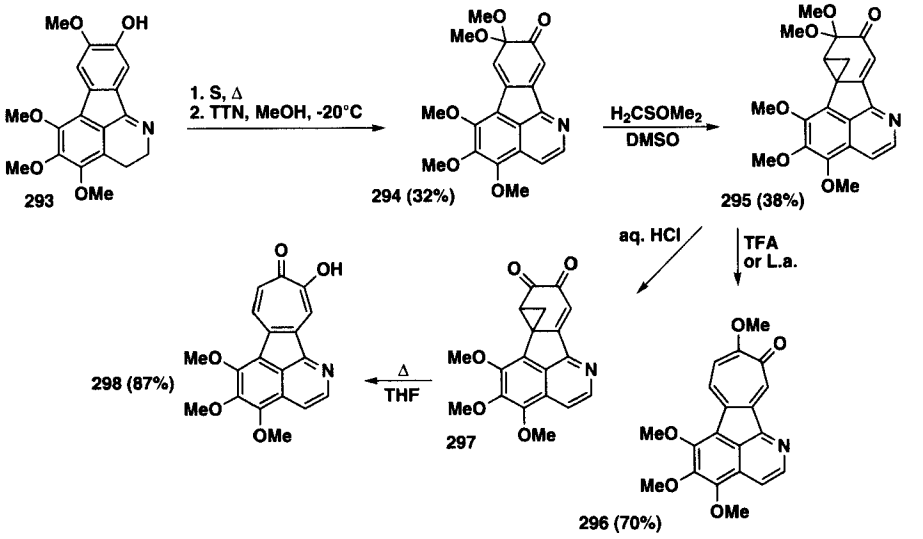
(61)

The first total synthesis of a tropoloisoquinoline alkaloid also made use of the chemistry of orthoquinone monoketal. In their synthesis of imerubrine **296**, Banwell and Ireland[178] performed a McKillop oxidative methoxylation of the azafluoranthene **293**, followed by a regioselective cyclopropanation of the Δ^4 double bond of the resulting 6,6-dimethoxycyclohexa-2,4-dienone **294** (*Scheme* 30). Acid-catalyzed ring expansion of the σ-homo-orthobenzoquinone monoketal **295** afforded **296** in 70% yield. Alternatively, hydrolysis of **295** straightforwardly afforded grandirubine **298**.[179] This methodology had been previously used by the same group for the synthesis of α-tropolone derivatives, including the simpler naturally occurring MY3-469 **302a**, isopygmaein **302b**, and colchicine **308** (*Eq.* 62).[180,181]

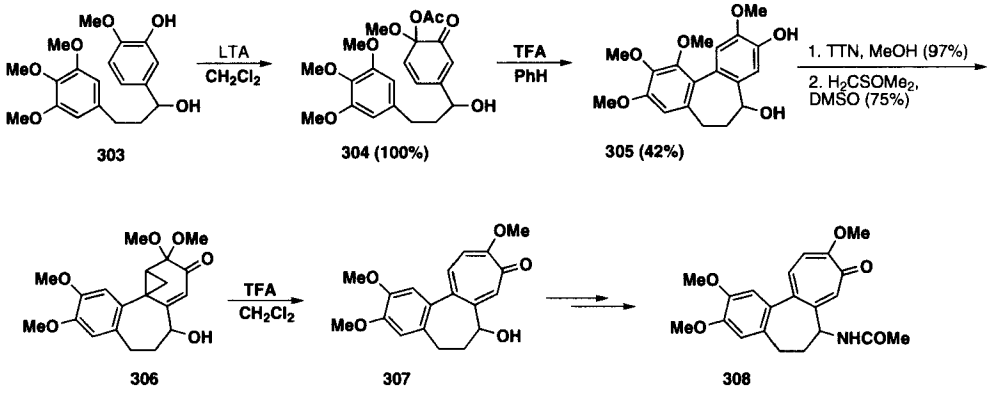


(62)

Their total synthesis of (±)-colchicine **308** is particularly remarkable, for it is fully regiocontrolled and illustrates two synthetic applications of orthoquinone moketal chemistry (*Scheme* 31). Phenol **303** was subjected to Wessely oxidative acetoxylation to give quantitatively the orthoquinol acetate **304**, which was then cyclized as *per* Uzemawa's protocol (*vide supra*). The resulting phenolic seven-membered ring **305** was then subjected to McKillop's oxidative methoxylation, nucleophilic cyclopropanation, and ring expansion to the α-tropolone derivative **307** en route to (±)-**308**.[181]



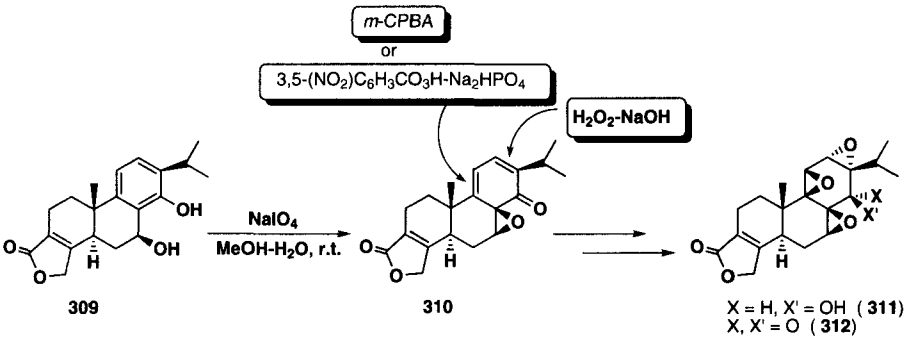
Scheme 30



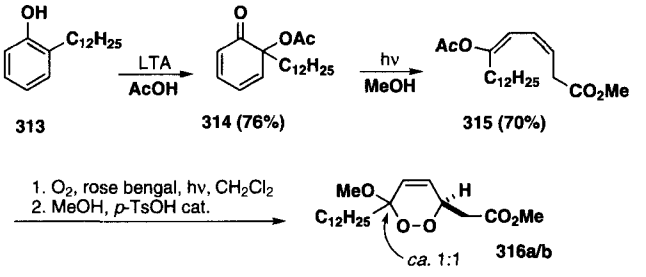
Scheme 31

Both van Tamelen's[182] and Berchtold's[183,184] group chose a spiroepoxy-cyclohexa-2,4-dienone intermediate for their total synthesis of the diterpenoid triptolide **311** and triptonide **312**. These biologically active agents were prepared from the advanced butenolide precursor **309** which was submitted to the Adler oxidation.[89] The resulting epoxy dienone **310** was then selectively functionalized by using appropriate epoxidation agents: *m*-CPBA, 3,5-dinitroperbenzoic acid, or alkaline hydrogen peroxide (*Eq.* 63).

The capability of photochemically inducing ring opening of cyclohexa-2,4-dienone derivatives[152] was recently exploited by Snider and Shi[157] in their synthesis of naturally occuring antitumor cyclic peroxy ketals and analogues **316a/b**. A Wessely oxidation of starting phenol **313** furnished the orthoquinol acetate **314** for photochemical cleavage and oxygenation to a 1.1:1 mixture of the diasteromers **316a/b** (*Scheme* 32).



(63)



Scheme 32

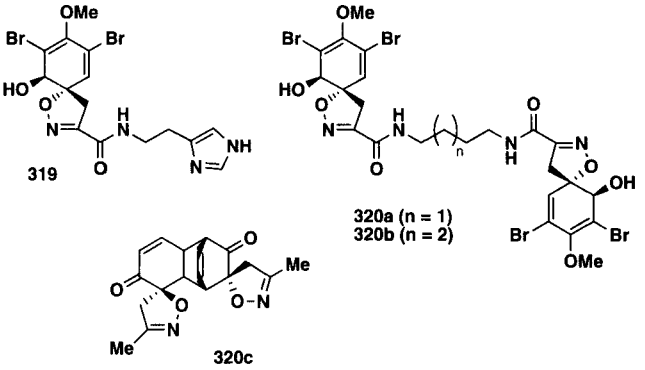
The spirocyclohexadienylisoxazoline unit **318** is featured in numerous marine metabolites derived from dibrominated tyrosine and exemplified here by aerophobin 1 **319**, aerothionin **320a**, and homoaerothionin **320b**. This unit can, in principle, be obtained from oxidative spirocyclization of tyrosine-derived 4-hydroxy- or 2-hydroxyphenylketoximes. Synthetic strategies can thus call for the formation of para- or orthoquinol derivatives, respectively.[185] Various oxidants, as well as brominating agents, have been tried to achieve these transformations with more or less preparative efficiency (*Eq.* 64).[33,186-188] Nishiyama and Yamamura first accomplished the synthesis of both **320a** and **320b** in racemic forms using a TTN-mediated oxidation of **317b** into **318b** (*Eq.* 65). Reduction with $Zn(BH_4)_2$ followed by diamidation with either 1,4-diaminobutane or 1,5-diaminobutane afforded **320a** and **320b**, respectively (*Eq.* 65).[188]

(64)

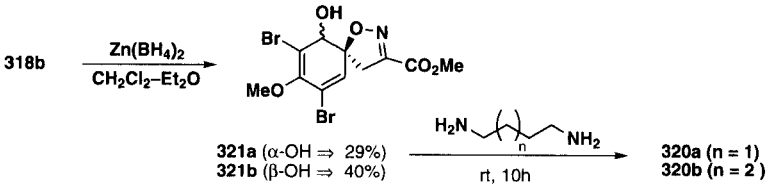
	reagent	
317a : R_1 = 3,5-diBr, 4-OMe, R_2 = $CONHCH_2CH_2]_2$	TBCD	**318a** (64%)[187]
317b : R_1 = 3,5-diBr, 4-OMe, R_2 = CO_2Me	TTN, TFA	**318b** (27%)[188]
317c : R_1 = H, R_2 = Me	PIFA	**318c** (45%)[185]
317b : R_1 = 3,5-diBr, 4-OMe, R_2 = CO_2Me	PIDA	**318b** (76%)[189]
317d : R_1 = 3,5-diBr, 4-OMe, R_2 = (-)-8-phenylmenthyl	PIDA	**318d** (31%; d.e., 33%)[189]
	PIFA	**318d** (88%; d.e., 67%)[189]
	PhIO/(-)-CSA	**318d** (87%; d.e., 82%)[189]

TBCD = 2,4,4,6-tetrabromocyclohexa-2,5-dienone
317a = *cis-cis*-aerothionin

McKillop's PIFA-mediated attempt at generating an orthoquinol derivative of type **318** (R_1 = H) resulted in the formation of the Diels-Alder adduct **320c**.[185] This result was not unexpected when considering the lack of substituents on the cyclohexadienone moiety of **317** (R_1 = H). Hoshino and co-workers[189,190] reported the formation of several spirocyclohexadienylisoxazolines **318** in moderate to good yields using different hypervalent iodine-based reagents, and observed significant asymmetric induction at the spiro center using the chiral oxime ester **317d** (*Eq.* 64).



Construction of the key bicyclo[7.3.1]enediyne core structure of the potent antitumor agent aglycon (±)-calicheamicinone **326** has been accomplished using two different oxidized phenol intermediates: a spiroepoxy- and a dimethoxy-cyclohexa-2,4-dienone. Danishefsky and co-workers utilized **323**.[138,191,192] This spiroepoxy-cyclohexa-dienone was obtained by Adler oxidation of **322**, followed by Dess-Martin oxidation. Introduction of the (*Z*)-silyl enediyne **324** and cyclization gave rise to the desired core structure which was then properly functionalized in several steps to obtain **326** (*Scheme* 33).

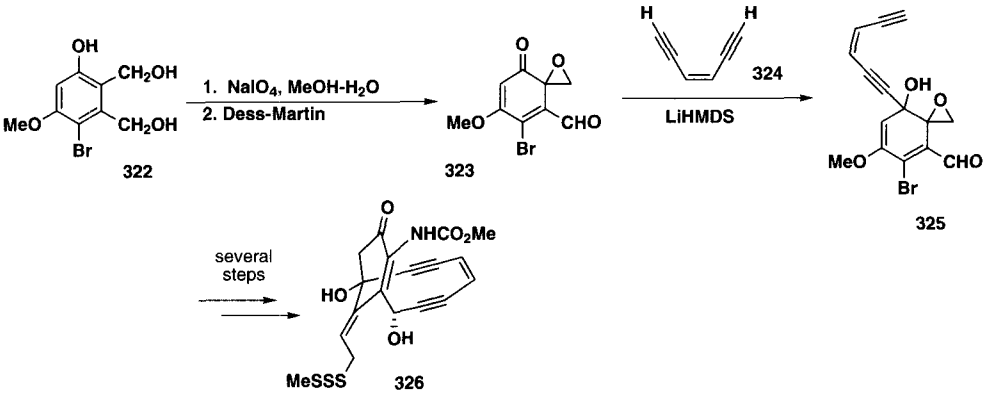


(65)

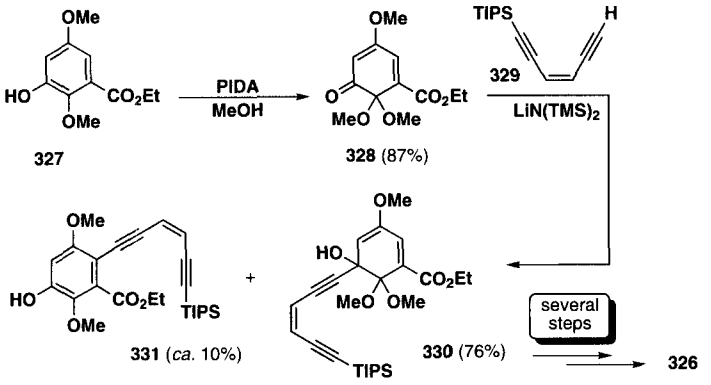
Magnus and co-workers recently applied an orthoquinone monoketal-based strategy to access **326**.[139,193] Oxidation of phenol **327** with PIDA in MeOH gave **328** in 87% yield (*Scheme* 34); the choice of this 6,6-dimethoxycyclohexa-2,4-dienone derivative enabled Magnus' group to achieve the total synthesis of **326** in a slightly more concise manner than Danishefsky's group (*Scheme* 33).

A short biomimetic synthesis of neolignans based on cationic annulation between the ortho-quinone monoketal **203b** and propylbenzenes **332*E*** and **332*Z*** has been reported by Horne and co-

workers.[194] Ketal **203b** was obtained in 90% yield via McKillop oxidation and, then, treated with stannic chloride to afford several neolignan targets **333-334** (*Scheme* 35).



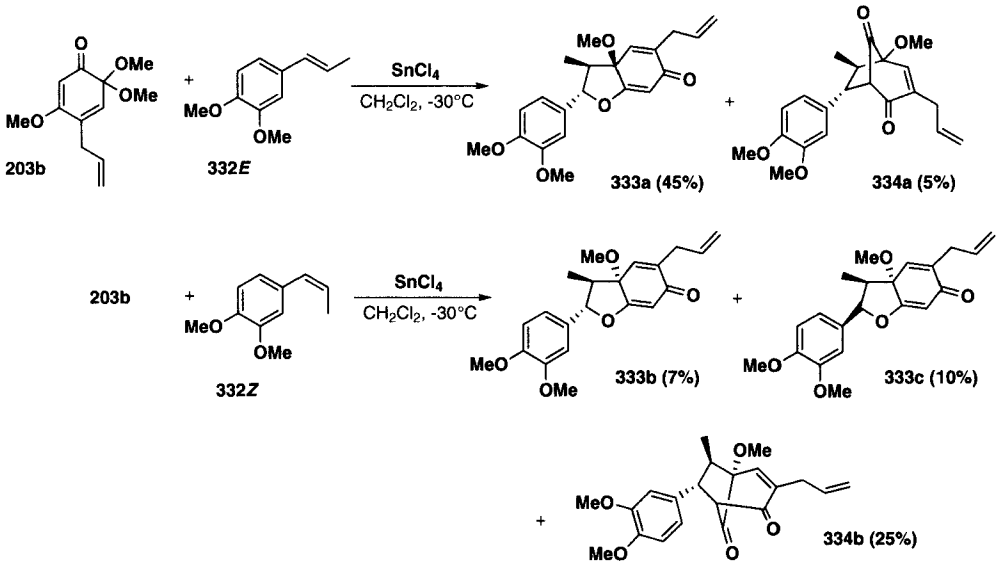
Scheme 33



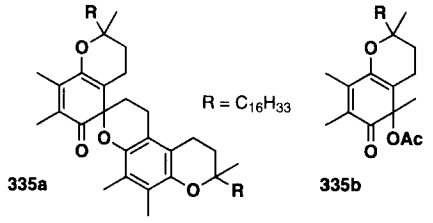
Scheme 34

Finally, despite the importance of phenol oxidation processes in nature, orthoquinone monoketals and orthoquinol derivatives are relatively seldom proposed to be involved in biological systems. Here are a few worthnoting applications of orthoquinone monoketal and orthoquinol chemistry in bio-organic chemical studies that demonstrated the possible biological significance of these quinonoid species. For example, Hewgill had proposed the formation of orthoquinol aryl ethers such as **335a** in the mammalian metabolism of α-tocopherol; such metabolites would originate from oxidative dimerization via both C–O and benzylic C–C coupling.

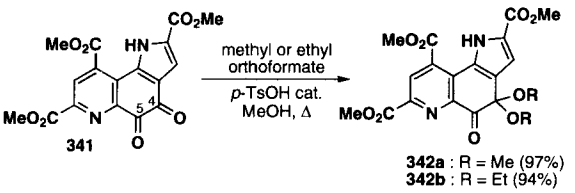
This dimerization has been previously evidenced chemically using alkaline $K_3Fe(CN)_6$.[195] Dürckheimer and Cohen[29] had observed the formation of the analogous 5-acetoxy-α-tocopherone **335b** by treating α-tocopherol with NBS[32] in the presence of tetramethylammonium acetate in anhydrous CH_3CN.



Scheme 35

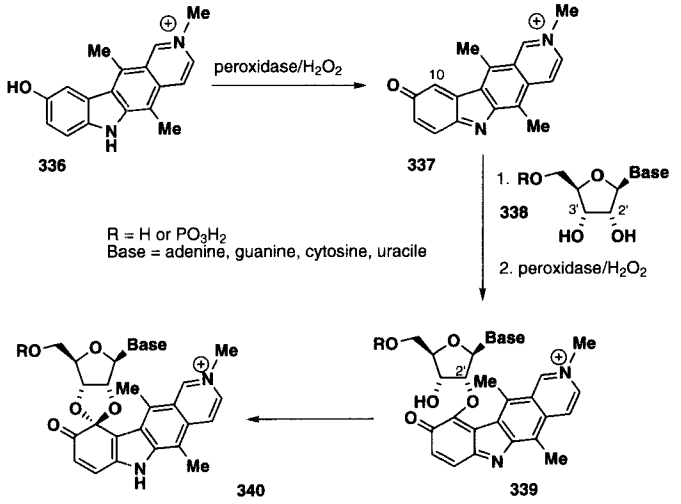


The formation of stable "aromatic" orthoquinone monoketals have been proposed to be involved in the biomechanism of certain therapeutic agents such as *N*-2-Methyl-9-hydroxyellipticinium (NMHE) acetate **336**. This antitumor ion drug would behave not only as an intercalating agent but would also give rise to purine and pyrimidine nucleotide monoketal adducts. Oxidative bioconversion of the NMHE phenol unit into electrophilic quinone imine moieties followed by two successive conjugate nucleophilic additions of the 2'- and 3'-hydroxy groups of RNA ribose units onto the NMHE 10-carbon would give rise to stable orthoquinonoid monoketals of type **340** (*Scheme* 36). Such a covalent modification of RNA molecules could conceivably cause the inhibition of protein synthesis. Various synthetic model adducts have been prepared in moderate to good yields according to the aforementioned mechanism via either the Wessely lead(IV)-mediated oxidation or the Hewitt's copper-catalyzed autoxidation, as well as via peroxidase-catalyzed oxidation (*Scheme* 36)[196-200] The first addition always involved the 2'-hydroxy groups of the ribose and the spirocyclization is stereoselective.[197]



(66)

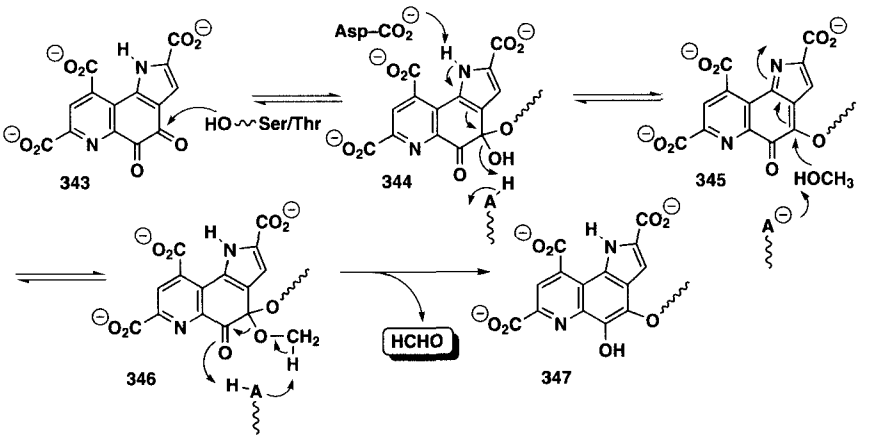
The participation of orthoquinone monoketals has also been postulated for the mechanism of quinoprotein alcohol dehydrogenases. In their studies on the role of pyrroloquinolinequinone (PQQ) co-factor **343**, also referred to as methoxatin, Itoh and co-workers[201] prepared a series of orthoquinone monoketals from PQQ models and derivatives. For example, the trimethyl ester of PQQ **341** was converted into the 6,6-dimethoxy- and the 6,6-diethoxycyclohexa-2,4-dienone derivatives **342a** and **342b** by using Corey's orthoformate-based ketalization (*Eq.* 66).[70] Ketal **342a** was also obtained by simply refluxing **341** in methanol under acidic conditions, albeit in low yield.[201]



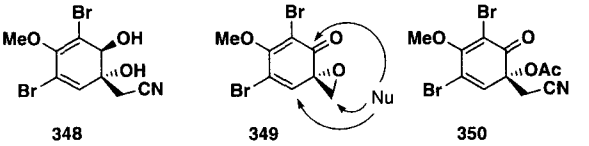
Scheme 36

The biological significance of this C-4 PQQ ketalization reaction was expressed in a putative mechanistic depiction of quinoprotein alcohol dehydrogenase-catalyzed oxidation of alcohols (*Scheme* 37).[201] It is worth noting that intermediary of orthoquinone monoketals are entailed in both the total synthesis[70] and the biological role of the PQQ coenzyme.[201]

The possibility of forming orthoquinol derivatives from adequately substituted phenols have been recently exploited by Waldmann and Herrlich[202] in their search for less hydrophilic and more active analogues of the marine aeroplysinin **348**, a promising lead inhibitor of receptor tyrosine kinases. The orthoquinol spiroepoxide **349** was one of these analogues made by Adler oxidation of the parent phenol.[202] Epoxide **349** was opened by cyanide attack and acetylated to furnish the orthoquinol derivative **350**. The electrophilic reactivity of both cyclohexa-2,4-dienones could underly their enhanced activity over that of the cyclohexa-1,3-diene **348**.



Scheme 37



IV. CONCLUSION

This review has presented the most important advances in the chemistry of orthoquinone monoketals and orthoquinol variants. The different modes of their preparations – from the classical and still used metallic and anodic oxidation methods to modern methods relying on hypervalent iodine chemistry – have been reviewed. Subtle electronic and steric effects from the substitution pattern of their parent phenols are often the keys to their high-yielding formation and stability. These monoprotected orthoquinonoid species remain today among the most potentially useful intermediates that can be used to generate quickly molecular complexity from simple phenol-derived aromatic molecules. Highly remarkable and recent examples of such utilizations have been described. In particular, the propensity of such quinonoid dienones to undergo Diels-Alder reactions has been exploited many times to construct regio- and stereoselectively bicyclo[2.2.2]oct-5-en-2-one systems; these are extremelly valuable in synthesis as they provide access to complex organic skeleta with excellent selectivities *via* thermal and photochemical rearrangements. Polyoxygenated carbo- and heteropolycycles of various sizes including *cis:trans:cis* triquinanes, *cis*-decalins, α-tropolones, and benzannulated ether rings are accessible from orthoquinone monoketals or their orthoquinol variants. It is expected that numerous other synthetic uses, notably based on their electrophilicity and differentially activated double bonds, will be found as the manipulation of these attractive synthons is mastered.

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