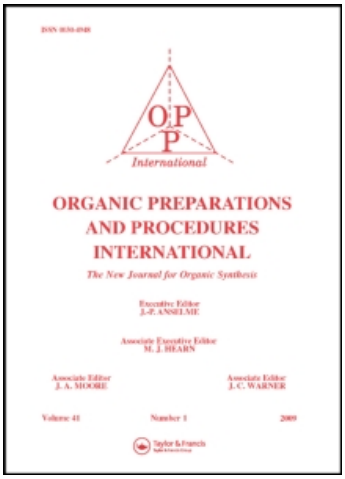

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RECENT PROGRESS IN THE SYNTHESIS OF *p*-QUINONES AND *p*-DIHYDRO-QUINONES THROUGH OXIDATION OF PHENOL DERIVATIVES. A REVIEW

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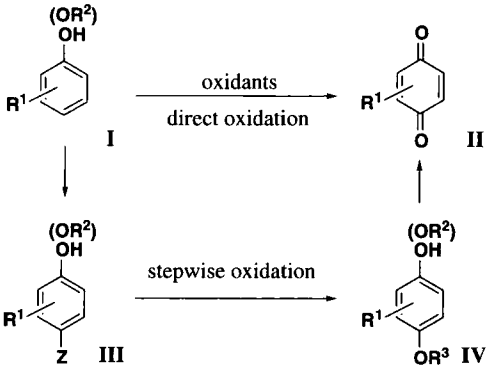
INTRODUCTION

Many naturally occurring compounds having a *p*-quinone or a *p*-dihydroquinone structure show biologically important activities such as antitumor, antibacterial and antiprotozoan activities. Therefore, the development of synthetic methods for *p*-quinone and *p*-dihydroquinone structures has been the subject of long-standing significance in organic synthesis. These works are classified into (i) the synthesis of a carbon skeleton including the *p*-quinone or the *p*-dihydroquinone nucleus and (ii) oxidation or oxygenation of phenols and their derivatives at their *para*-position to afford the *p*-quinones and the *p*-dihydroquinones. Recent progress on the former topic has been covered in several reviews,[1a,b,d,2,3] and some of the latter topic has been mentioned in 1991[1c] and 1995.[2] This review will systematically discuss the recent progress, mostly since 1994, on the latter topic, including our recently developed synthesis of *p*-quinones and *p*-dihydroquinones.

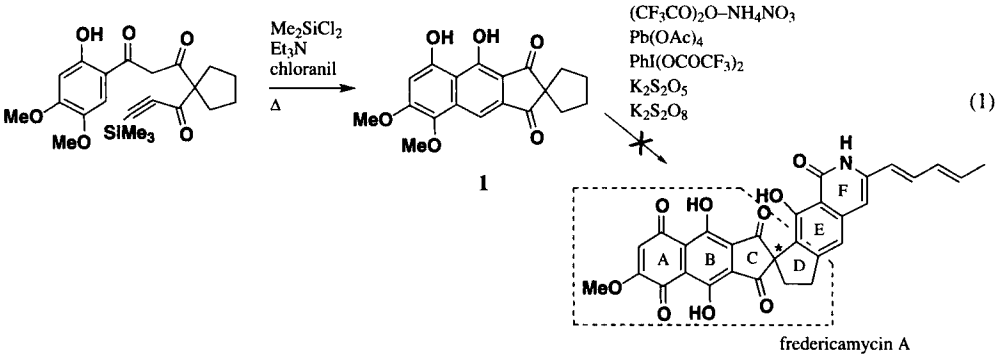
Oxidation of *p*-unsubstituted phenols **I** to *p*-quinones **II** has been achieved by direct oxidation of **I** and by the functionalization of the *para*-position of **I** followed by functional group transformation (**III** → **IV**) (stepwise oxygenation). Dihydroquinones and their protected derivatives **IV** are readily oxidized to **II** under mild conditions. Therefore, **IV** is often used as a convenient equivalent or precursor of **II** (*Scheme 1*).

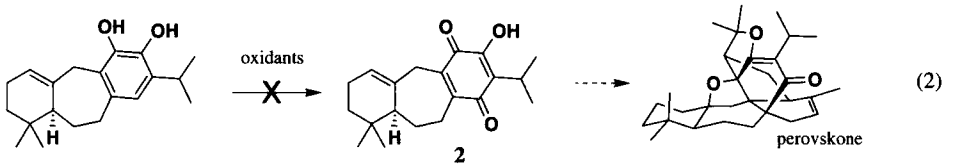


Scheme 1

Although a large number of reports on each reaction (**I** → **II**, **III** → **IV** and **IV** → **II**) have been published in the literature, some problems still remain. For example, direct oxidation sometimes suffers from low reproducibility,[4] *ortho*-oxidation,[5] or other side reactions,[6] and is inefficient for the oxidation of some phenols having electron-withdrawing groups.[7] On the other hand, transformation of

the functional group (Z) of **III** to an oxygen functionality (OR^3) requires fairly harsh reaction conditions including high temperature,[8] strongly basic conditions[9] or oxidation conditions,[10] many of which are incompatible with the presence of other reactive functional groups such as carbonyl groups.[8a,b] In the total synthesis of a complex molecule, the oxidation of a phenol ring to the corresponding *p*-quinone has sometimes been a frustrating step: Examples are found in the oxidation of the B-ring of the ABCD-unit **1** of fredericamycin A (*Eq.* 1)[11] and in the preparation of the quinone **2**, a key precursor of perovskone, from the phenol (*Eq.* 2).[6] Consequently, there has been a continuing need for the development of novel methodologies for the oxidation and/or oxygenation of phenols at their *para*-positions.



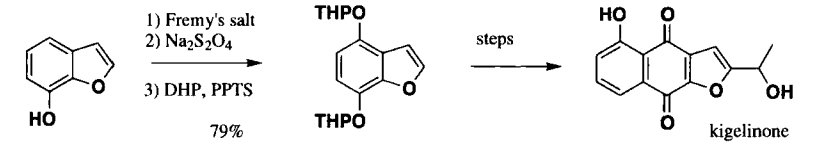


From the point of view of the applicability for the practical synthesis of quinones, this review will focus on (i) recently developed reactions and improvement of conventional methods and (ii) the application for total syntheses of biologically important compounds. The following chapters I–III correspond to each step (**I** → **II**, **III** → **IV** and **IV** → **II**) in *Scheme* 1, respectively. Oxidation of anilines and their derivatives to *p*-quinones and preparation of *p*-quinone imines are also discussed here.

I. DIRECT OXIDATION OF *p*-UNSUBSTITUTED PHENOLS AND THEIR DERIVATIVES

Direct oxidation of *p*-unsubstituted phenols and their derivatives is usually performed by various oxidants including Fremy's salt,[5,12–17] ceric ammonium nitrate (CAN),[18,19] AgO–HNO_3,[20] chromium(VI) salts,[21–23] $Pb(OAc)_4$,[4] thallium(III) salts, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), hypervalent iodine(III) compounds,[24–30] $K_2S_2O_8$,[7a] NH_4NO_3–$(CF_3CO)_2O$,[7b] *N*-bromosuccinimide (NBS)–AcOH,[31] O_2 with salcomine[34] or with other metal catalysts,[35] O_2–base,[32,33] and H_2O_2–hetero polyacid.

Among these reagents, Fremy's salt is one of the most commonly used for the oxidation of electron-rich phenols. Recently, it has often been applied to the synthesis of heteroaromatic-ring-fused *p*-quinones, such as furanoquinones (*Eq.* 3),[12] benzimidazolequinones (*Eq.* 4),[13] carbazolequinones (*Eq.* 5),[14] and indolequinones (*Eq.* 6),[15] having biologically interesting activities. It is also effective for the oxidation of aniline derivatives to the *p*-quinones (*Eq.* 4). However, formation of *o*-quinones as side or even as main products may arise from steric hindrance and electron spin density (*Eq.* 7),[5] and there exists the possibility of explosion.[17]



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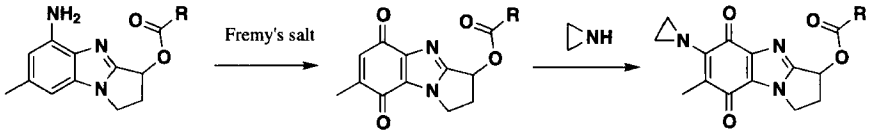
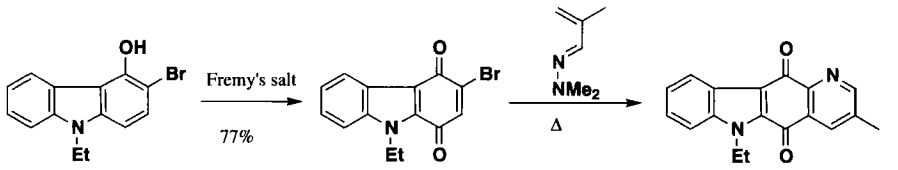


(4)



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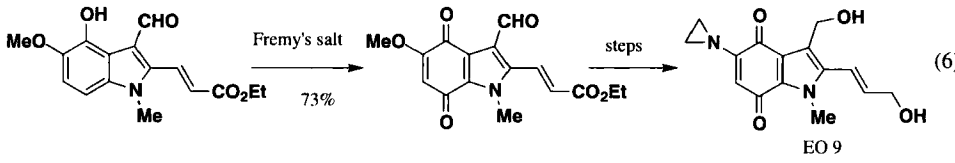
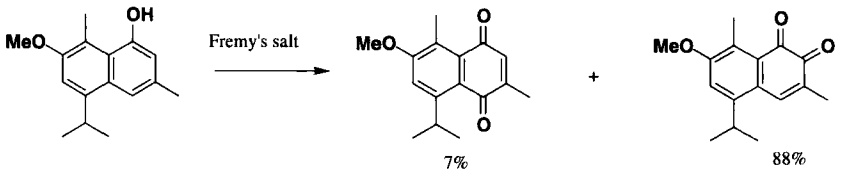
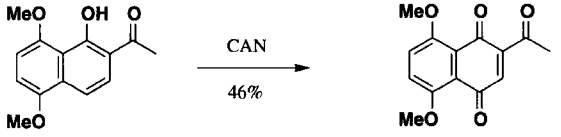


(6)

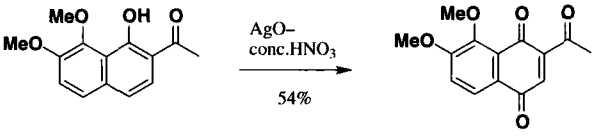


(7)

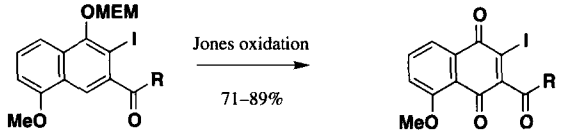
Metal oxidants such as CAN, AgO–HNO_3 and Cr(VI) salts are strong oxidizing reagents and have been used for phenols substituted by electron-withdrawing groups, where oxidation occurs selectively on the phenol rings (*Eqs.* 8,[18] 9,[20] 10[21]). The use of CAN gives a better yield for the reaction in *Eq. 8* than that obtained using Fremy's salt or AgO–HNO_3.



(8)

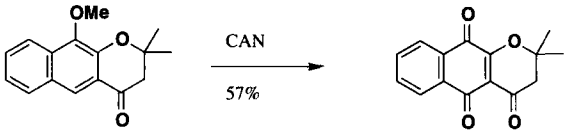


(9)

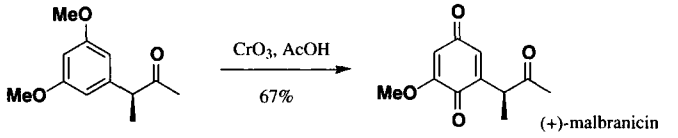


(10)

CAN and CrO_3–AcOH can also oxidize phenol ethers directly to *p*-quinones with cleavage of the ether bond (*Eqs.* 11,[19] 12,[23a] 13[23b]). This approach has been utilized in the total syntheses of (+)-malbranicin and (±)-metachromine A.



(11)



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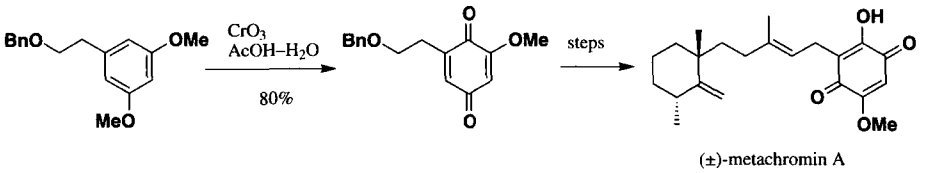
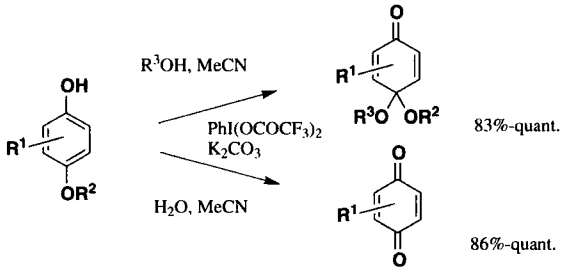


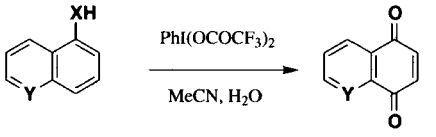
(13)

In contrast to the above-mentioned heavy metal oxidants, non-metallic hypervalent iodine(III) compounds have received increasing attention in the last decade due to their reduced toxicity and strong oxidizing ability. Since our publication of a useful and general oxidative transformation of *p*-alkoxyphenols to *p*-quinone monoacetals[24] and *p*-quinones[25] using $PhI(OCOCF_3)_2$ (*Eq.* 14), various applications of hypervalent iodine(III) compounds for the oxidation of phenols have been reported in rapid succession.



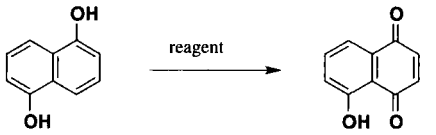
(14)

The oxidation of *p*-unsubstituted phenols and naphthols into *p*-quinones has been reported to proceed in high yields (*Eq.* 15). This oxidation is also effective for anilines (*Eq.* 15).[26] By choosing a highly reactive iodine(III) reagent, the oxidation of 1,5-dihydroxynaphthalene to juglone is attained in a high yield (*Eq.* 16).[27]



	XH = OH	XH = NH_2
Y = CH	73%	57%
Y = N	88%	85%

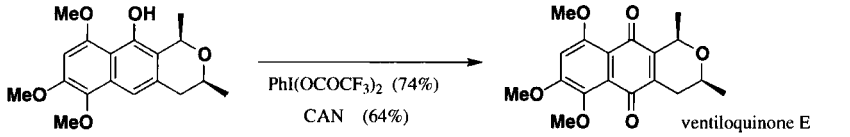
(15)



Reagent	Yield
$PhI(OAc)_2$	26%
$PhI(OCOCF_3)_2$	58%
$C_6F_{13}I(OCOCF_3)_2$	91%

(16)

Oxidation of phenol or aniline derivatives is the key step in syntheses of ventiloquinones,[28] KW-2170,[29] and EO 9,[30] respectively, and is achieved by $PhI(OCOCF_3)_2$ or $PhI(OAc)_2$ (*Eqs.* 17–19). Fremy's salt, CAN and other metal oxidants give lower yields (*Eqs.* 17, 18). It is important to note that the choice of solvents for the reaction of hypervalent iodine(III) reagents is critical for achieving high yields (*Eqs.* 18, 19). It is also noteworthy that the potentially explosive Fremy's salt is replaced by a safer $PhI(OCOCF_3)_2$ for large scale synthesis (*Eq.* 19).



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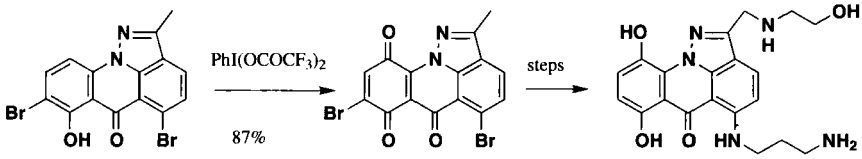
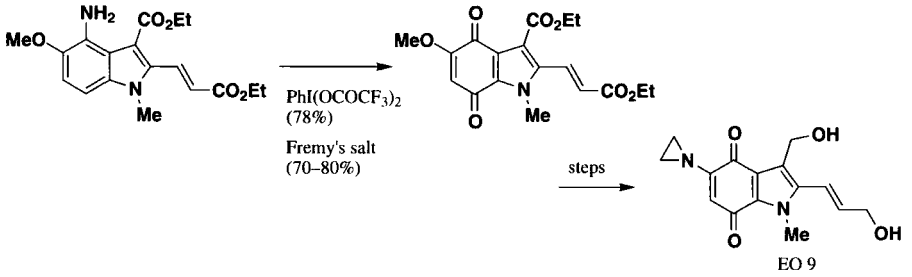
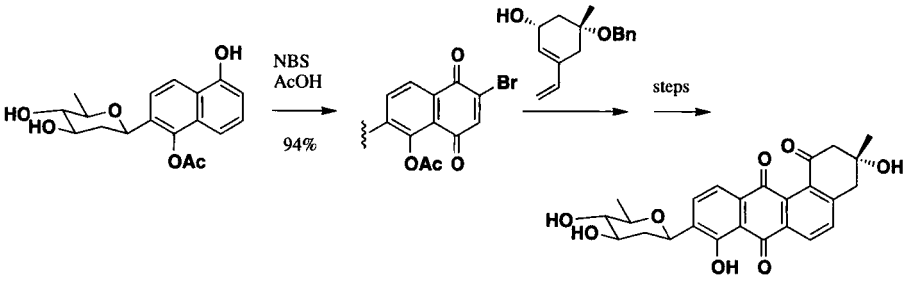


(18)



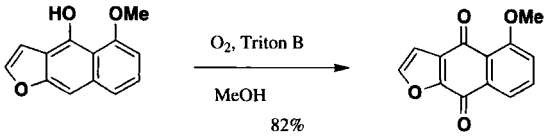
(19)

The use of NBS in AcOH provides a direct and regioselective preparation of 2-bromo-1,4-naphthoquinones from 1-naphthols. These products have been employed in the Diels–Alder reaction as dienophiles, which has led to the synthesis of urdamycinone B and related compounds (*Eq.* 20).[31]



(20)

Another important route to quinones involves the use of molecular oxygen, which oxidizes some electron-rich phenols under basic conditions (*Eqs.* 21,[32] 22[33]) (see also Chapter V–1. *Scheme* 12 for auto-oxidation under neutral conditions).



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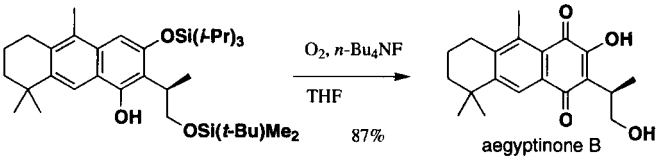
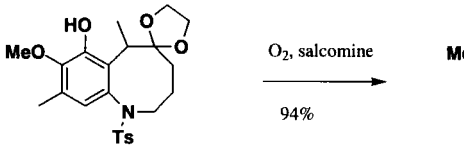


(22)

Salcomine-catalyzed air oxidation provides *p*-quinones under neutral conditions by a simple procedure. This method is useful for substrates having base- or acid-sensitive functional groups (*Eqs.* 23,[34a] 24,[34b] 25[34c]).



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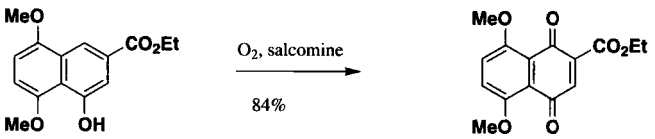
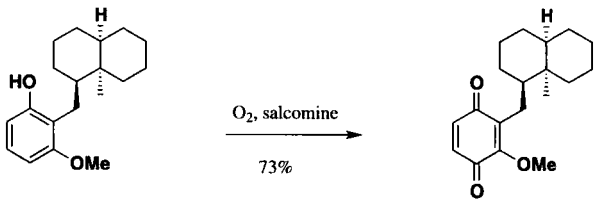
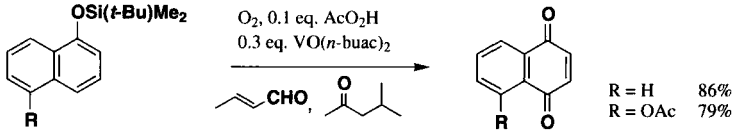


(24)



(25)

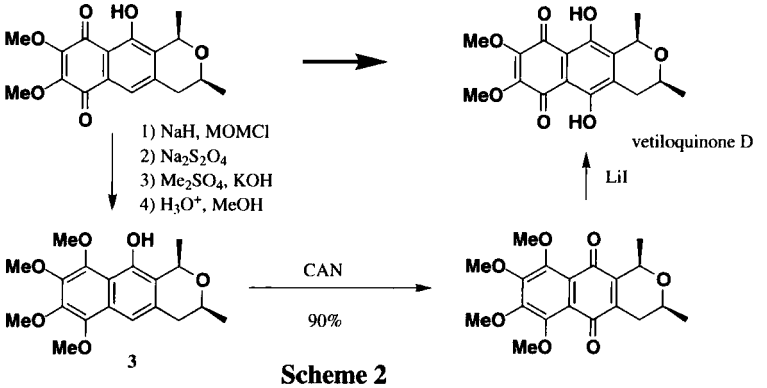
Air oxidation catalyzed by an oxovanadium(VI) complex provides juglone derivatives from 1-naphthyl *tert*-butyldimethylsilyl ethers (*Eq.* 26).[35,36]



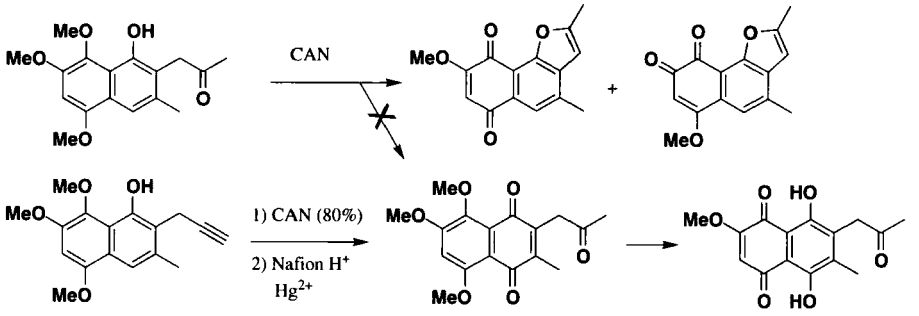
(26)

A similar oxidation of phenols and their methyl ethers to *p*-benzoquinones can be accomplished by the combined use of dimethyl dioxirane–acid[37] or H_2O_2–ketone.[38]

Generally, oxidation of *p*-unsubstituted phenols is greatly influenced by the steric and electronic nature of the substituents on the phenol ring. A typical example of this issue is the oxidation of a phenol next to a *p*-quinone, in which a detour is taken through oxidation of the *p*-dihydroquinone ether **3** in 6 steps (*Scheme* 2).[28] An adjacent functional group can also disturb the desired reaction (*Scheme* 3).[39]



Scheme 2



Scheme 3

II. *ipso*-OXYGENATION OF *p*-FUNCTIONALIZED PHENOLS AND THEIR DERIVATIVES

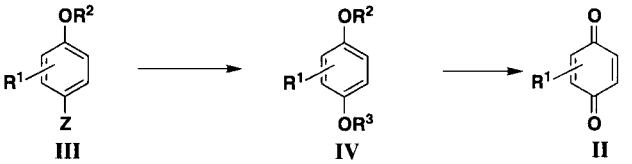
Transformation of the *p*-functional group Z of the phenol **III** to an oxygen functional group is an alternative method for the synthesis of *p*-quinones **II**, because the oxidation of the resultant *p*-dihydroquinone derivatives **IV** proceeds readily under mild conditions to give **II** (see Chapter III). This route is especially useful when the direct oxidation of the corresponding *p*-unsubstituted phenols is difficult.[32,40] Dihydroquinones are often employed as masked quinones in the total synthesis of

complex molecules. Diaryl ethers **IV** (R^3 = aryl) are also found in biologically active compounds. Therefore, numerous efforts have been devoted to this transformation over several decades.

1. Conventional Methods and their Improvements

Hydrolysis of diazonium salts (Z = N_2^+), Ullmann reaction (Z = halogen), Baeyer–Villiger (Z = COR) or Dakin reaction (Z = CHO), and the reaction of the organometallic compounds derived from **III** (Z = halogen) with oxygen or its equivalents are all well-studied. Some recent examples of these reactions are listed in Table 1. However, most of them require fairly high temperatures, strongly basic conditions or harsh oxidative conditions and, therefore, are inconsistent with other reactive functional groups such as carbonyls.

Table 1.

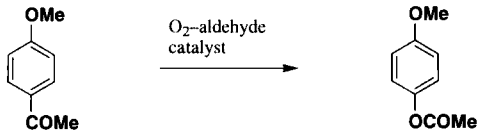


III, Z =	Reaction Conditions	**IV**, R^3 =	Ref.
$N_2^+ \cdot BF_4^-$	TfOH, Δ or hν	Tf	41
halogen	Cu(I), $R^3O^-M^+$ DMF, 90°	alkyl	8c
	Cu(I) or Cu(II), R^3OH, K_2CO_3 or NaH pyridine or collidine 130-185°	aryl	42
halogen	1) alkyllithium, 2) $B(OMe)_3$, 3) H_2O_2	H	9
CHO	1) H_2O_2, areneselenic acid, 2) KOH	H	43
CHO	Na_2CO_3 $1.5H_2O_2$	H	44
$COCF_3$	H_2O_2, aq. NaOH	*a*	32, 40
I^+-Ar $\cdot BF_4^-$	Ar'OH, Cu, Et_3N	Ar'	45
$SiMe_2SiMe_3$	1) Bu_4NF, 2) H_2O_2, $KHCO_3$	H	10

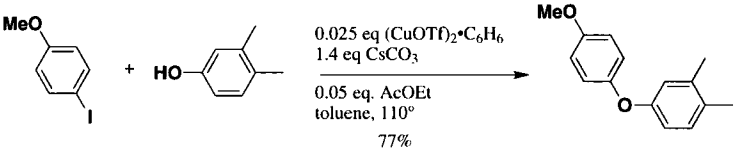
a Quinones **II** are directly obtained.

Recently, the *ipso*-substitution reaction of an iodonium salt (Z = I^+Ar) with phenols and the conversion of the *p*-disilanyl group of phenol ethers into a hydroxy group have been reported (Table 1). Some improved methods for the Baeyer–Villiger reaction have also been disclosed which involve the combined use of molecular oxygen (oxidant) and an aldehyde (reductant) in the presence of metal catalysts or hydrotalcite catalysts (Table 2). Additionaly, the Ullmann reaction has been shown to proceed in a nonpolar solvent such as toluene with the use of a catalytic amount of copper(I) salt and the weak base $CsCO_3$ (*Eq.* 27).[49] However, the application of these methods for complex molecules having various functional groups awaits further investigation.

Table 2.

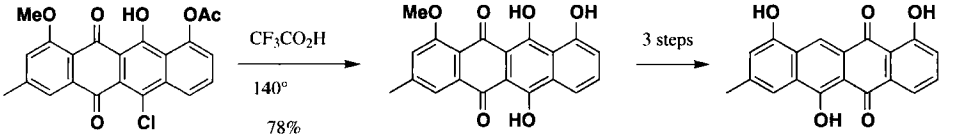


Reaction Conditions	Yield	Ref.
0.01 eq. $Ni(dpm)_2$, *i*-BuCHO, $ClCH_2CH_2Cl$, rt	76%	35b, 46
0.01 eq. Fe_2O_3, PhCHO, C_6H_6, rt	80%	47
cat. $Mg_{10}Al_2(OH)_{24}CO_3$, PhCHO, $ClCH_2CH_2Cl$, 40°	≥94%	48



(27)

In the total synthesis of SS-228R, replacement of the chloro group in the tetracyclic quinone by a hydroxy group has been achieved by treatment with CF_3CO_2H at 140° (*Eq.* 28).[50]

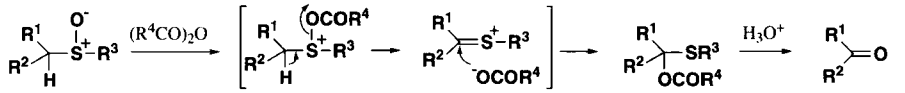


(28)

SS-228R

2. Novel *ipso*-Substitution of *p*-Sulfinylphenols through Aromatic Pummerer-type Reaction

Based on the following speculation, a novel synthesis of *p*-quinones has been developed utilizing the aromatic version of the Pummerer reaction: The treatment of aliphatic sulfoxides with acid anhydrides produces α-acyloxysulfides *via* the Pummerer rearrangement. This sequence offers a convenient method for the transformation of sulfinyl groups into carbonyl groups through hydrolysis of the α-acyloxysulfides (*Eq.* 29). If a similar sequence of reactions occurs with *p*-sulfinylphenols **4**, this could provide the α-acyloxysulfide **C** through intermediates **A** and **B**, where the electron-donating hydroxyl group at the *para*-position should strongly accelerate the S–O bond fission in **A**. An appropriate hydrolysis of **C** would give the desired *p*-quinone (*Eq.* 30).



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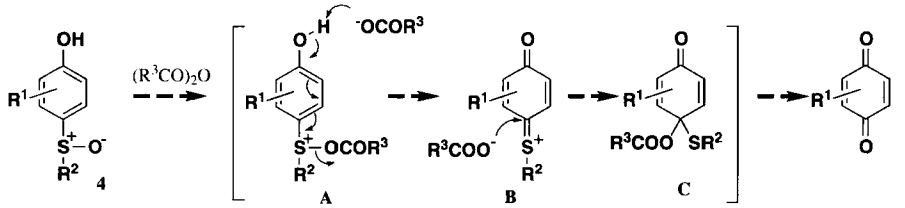
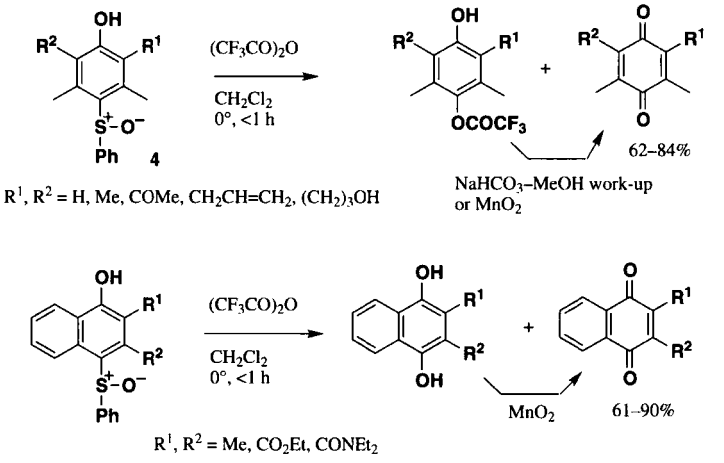


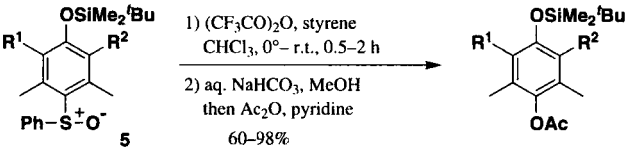
(30)

Indeed, the reaction of *p*-sulfinylphenols **4** with trifluoroacetic anhydride in CH_2Cl_2 is complete within 1 h at 0° to give a 1:1 mixture of the *p*-dihydroquinone mono trifluoroacetates and the *p*-quinones almost quantitatively. Work up of these crude products with $NaHCO_3$ in MeOH or by treatment with MnO_2 readily converts the dihydroquinones to the quinones, affording high yields of the benzoquinones. The same treatment of 4-sulfinyl-1-naphthols provides naphthoquinones. This protocol is compatible with various functional groups including ketone, ester, amide, allyl and primary hydroxy groups. Although the oxidation of phenols bearing electron-withdrawing group is often troublesome, this method is useful even for such substrates (*Scheme* 4).[51,52]



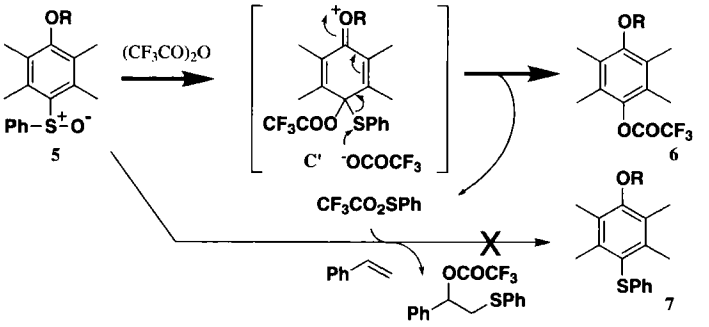
Scheme 4

Similarly, the reaction of the corresponding phenol ethers **5** provides the protected *p*-dihydroquinones **6** (*Scheme 5*). This reaction is thought to proceed *via* a cationic intermediate **C'**, where the counter anion attacks the sulfur atom selectively to give **6**. Although preliminary reaction employing the same conditions developed for quinone synthesis resulted in the formation of a mixture of the desired product **6** and a sulfide **7**, addition of olefins such as styrene and 2,2-dimethylbutene depressed the formation of **7** to give **6** quantitatively. This additive effect serves to capture CF_3CO_2SPh, which is generated from the Pummerer-type reaction and reduces the sulfoxides (*Scheme* 5). Electron-rich phenol derivatives such as *tert*-butyldimethylsilyl ethers and methyl ethers are applicable to this reaction, while the corresponding acetate is less reactive. This reaction proceeds between 0° to room temperature within 2 h and is compatible with allyl, *tert*-butyldimethylsilyl ether, acetoxy, hydroxy and formyl groups (*Eq.* 31).[52,53]



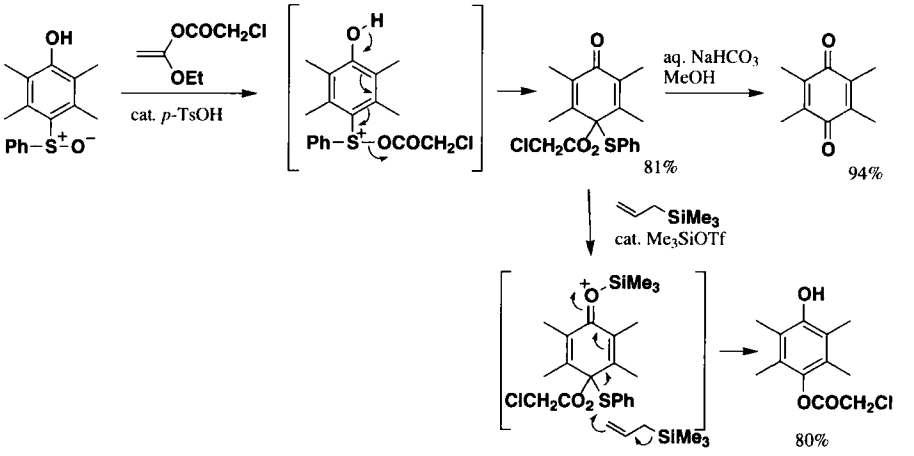
(31)

R1, R2 = *n*-Pr, allyl, $(CH_2)_3OSiMe_2(t\text{-Bu})$, $(CH_2)_3OAc$, $(CH_2)_3OH$, $(CH_2)_2CHO$



Scheme 5

Although the formation of the quinone mono *O,S*-acetals **C**, **C'** was expected in the above reactions, they were never isolated. However, the use of 1-ethoxyvinyl chloroacetate instead of trifluoroacetic anhydride led to the isolation of the quinone monoacetals in good yields. Conversion of these intermediates to both quinones and dihydroquinones also proceeds selectively (*Scheme* 6).[54]

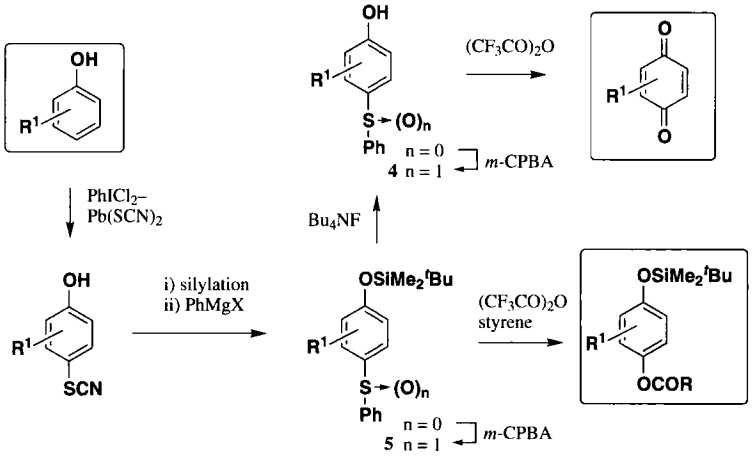


Scheme 6

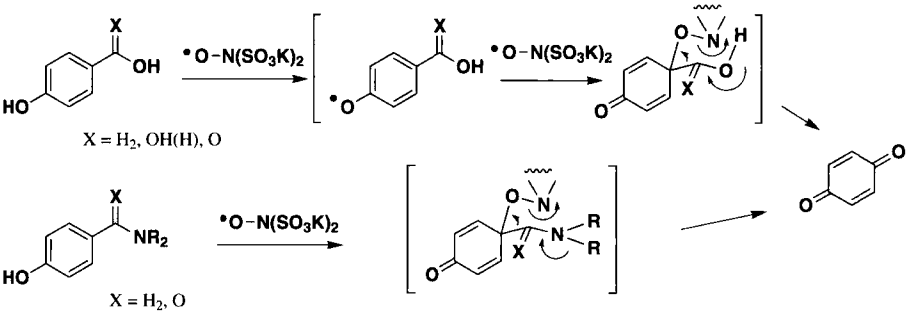
Preparation of the *p*-sulfinylphenols **4** and their ethers **5** has been achieved through regiospecific introduction of a thiocyanato group at the *para*-position of the phenols[55] followed by functional group manipulation to the sulfinyl groups (*Scheme* 7).[52]

3. Oxidative Degradation Approach to *p*-Quinones

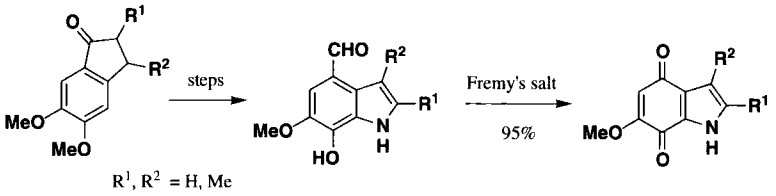
A unique synthesis of *p*-quinones involves the Fremy's salt-mediated oxidative degradation of phenols with carbon substituents at their *para*-position. This reaction is believed to proceed *via* cyclic intermediates leading directly to the *p*-quinones. Carboxyl, formyl, hydroxymethyl, aminomethyl and carbamoyl groups can be employed as the *p*-substituents of the phenols, although the reaction is limited to compounds whose redox potentials are lower than that of Fremy's salt (*Scheme* 8).[56] Of these substrates, the conversion of *p*-formylphenol derivatives to *p*-quinones (*Eq.* 32)[57] is noteworthy as an alternative to the conventional Dakin reaction (see Chapter II–1.) followed by oxidation.



Scheme 7

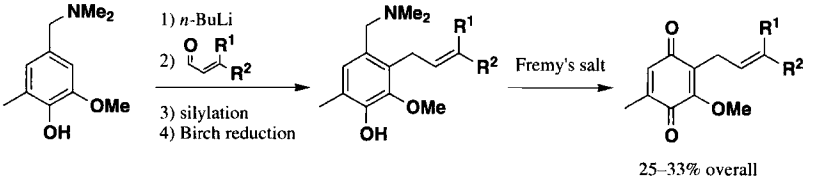


Scheme 8



(32)

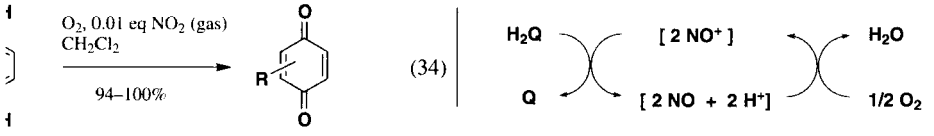
Combination of the above-mentioned method with the directed *o*-lithiation protocol provides a useful synthesis of functionalized *p*-quinones, which has been applied to the preparation of *p*-quinones having prenyl side chains (*Eq.* 33).[58]



(33)

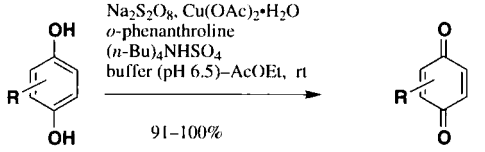
III. OXIDATION OF *p*-DIHYDROQUINONES AND THEIR PROTECTED DERIVATIVES

p-Dihydroquinones are usually oxidized to *p*-quinones by CAN, $FeCl_3$,[59] nitric acid, AgO, Cr(VI) salts, MnO_2, hypervalent iodine(III) compounds,[26c,60] and so on.[61] However, these methods require more than stoichiometric amounts of the reagents, some of which are expensive and/or require strongly acidic conditions, and tedious workup and purification procedures. On the other hand, auto-oxidation proceeds under neutral conditions and is successful for some *p*-dihydroquinones,[62] although it is not always effective. The use of a catalytic amount of gaseous NO_2 for the auto-oxidation provides an inexpensive and convenient method which allows isolation of *p*-quinones merely by concentration of the reaction mixture (*Eq.* 34).[63] The NO^+-catalyzed oxidation mechanism is proposed (*Scheme 9*), which starts with the disproportionation of NO_2 giving $NO^+NO_3^-$.



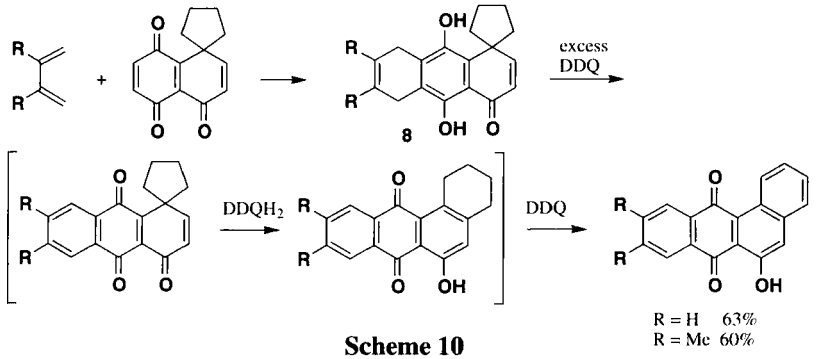
Scheme 9

The use of sodium persulfate in the presence of a copper(II) ion also provides a mild and efficient oxidation of *p*-dihydroquinones (*Eq.* 35).[61]



(35)

The reaction of spiroanthracenones **8**, prepared by Diels–Alder reaction of the spiro-naphthoquinone and dienes, with excess DDQ in refluxing benzene gives benz[*a*]anthraquinones directly (*Scheme* 10). The strongly acidic 2,3-dichloro-5,6-dicyano-1,4-dihydrobenzoquinone ($DDQH_2$), generated in the redox reaction, induces the dienone–phenol rearrangement.[64]

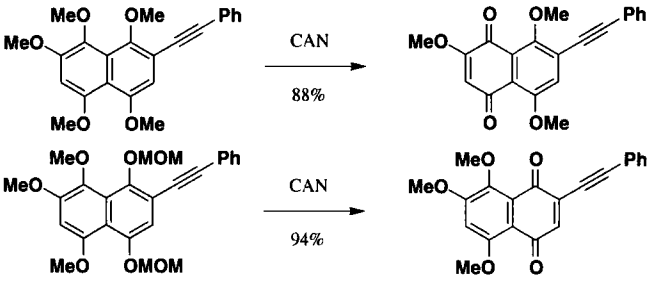


Scheme 10

On the other hand, the ethers of *p*-dihydroquinones are readily and directly oxidized to *p*-quinones by CAN,[14b,65–68] HNO_3,[69] and AgO–HNO_3.[70,71] While methyl ethers are the typical

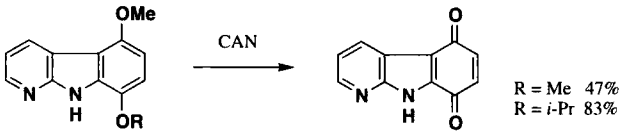
protecting group, the use of other protecting groups can sometimes be crucial as the following two examples illustrate.

A proper choice of Me and methoxymethyl (MOM) groups allows the regioselective oxidation of each ring of the pentaalkoxy naphthalene (*Scheme* 11).[66]



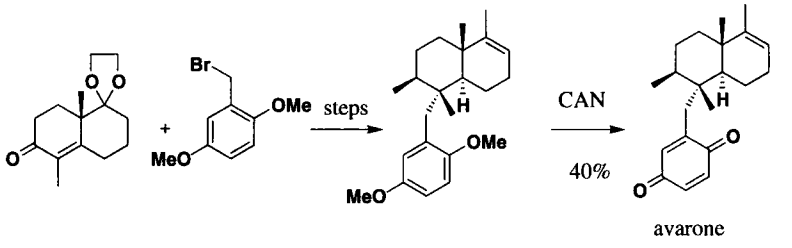
Scheme 11

The use of an *i*-Pr ether gives a better yield of the *p*-quinone than does the use of a Me ether. This may be due to a greater stabilization of the intermediate oxonium ion radical by the *i*-Pr group compared to the Me group (*Eq.* 36).[14b]



(36)

Some recent examples of the oxidation of *p*-dihydroquinone ethers are found in the total syntheses of avarone,[67] C104,[68] and hongconin[71] (*Eqs.* 37–39).



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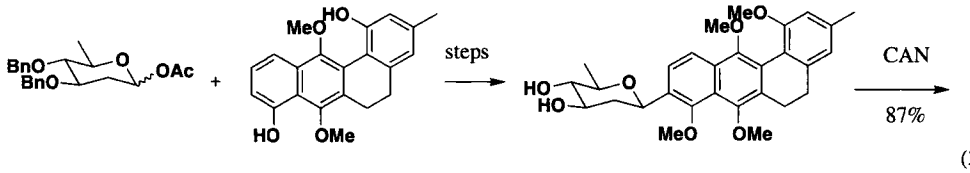

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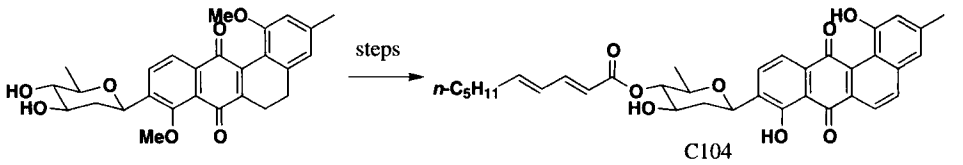
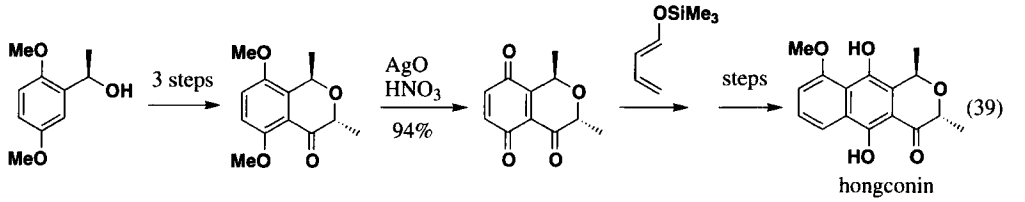
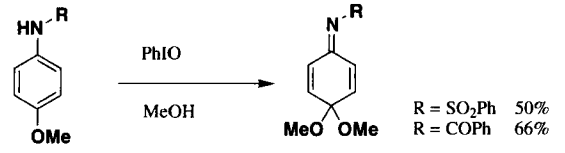




IV. SYNTHESIS OF *p*-QUINONE IMINES AND THEIR DERIVATIVES

Quinone imines and their acetals have been proposed as intermediates in a number of biological processes. They are also found in the structure of recently isolated marine alkaloids such as cystodytins, isobatzellines and discorhabdins.

In addition to intramolecular imine formation of *p*-quinones, *p*-quinone imines are also obtained from *p*-alkoxyaniline derivatives by anodic oxidation,[72] or by treatment with a hypervalent iodine(III) compound (*Eq.* 40)[73] or MnO_2 (*Eq.* 41).[74] Oxidation of an *p*-unsubstituted anilide by iodoxybenzene (*Eq.* 42)[75] and an aniline derivative by Fremy's salt under neutral conditions (*Eq.* 43)[13] afford the *p*-quinone imines, although oxidation of anilines usually affords complex mixtures.



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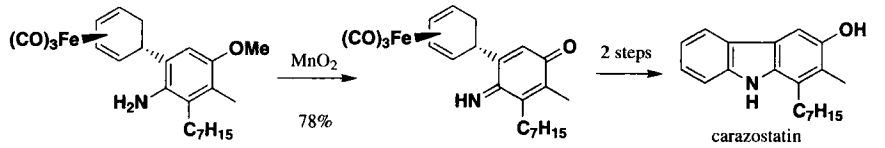

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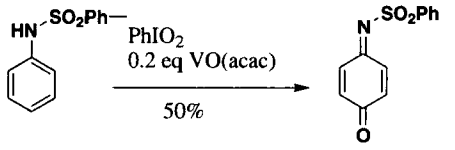

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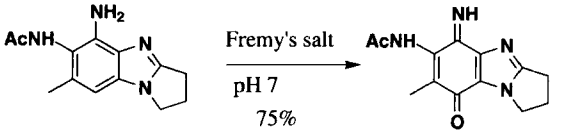
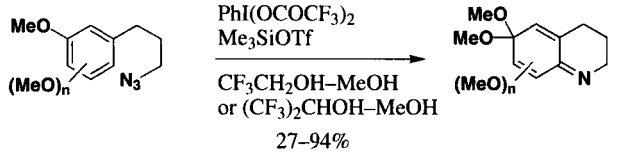


(43)

Oxidative imine formation of *p*-unsubstituted phenol derivatives has been attained by the intramolecular reaction of phenol ethers having alkyl azido sidechains in the presence of $PhI(OCOCF_3)_2$ and Me_3SiOTf. The use of polar and poorly nucleophilic solvents such as CF_3CH_2OH and $(CF_3)_2CHOH$ is essential for this reaction, which is proposed to proceed *via* a radical cation intermediate. The azido group can be successfully employed as a nitrogen-nucleophile, while amino and amide groups cannot be used due to their rapid reaction with hypervalent iodine species (*Eqs.* 44,[76] 45[77]).



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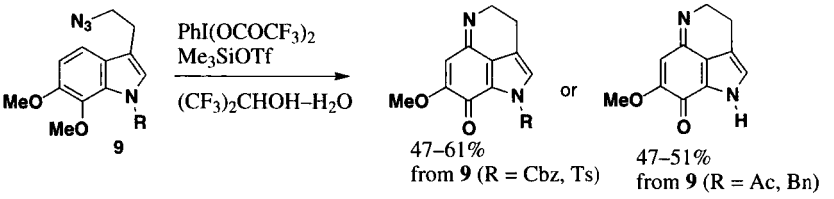
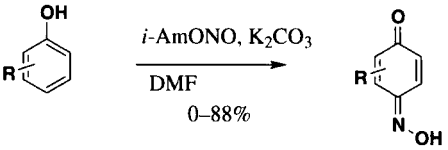


(45)

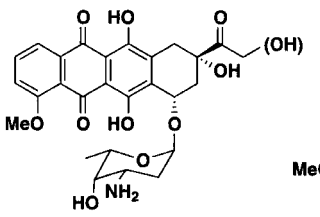
In contrast to the standard aromatic nitrosation reaction, which proceeds in aqueous acidic media and leads predominantly to *ortho*-nitrosated products for some phenols, nitrosation under basic, non-aqueous conditions occurs at the *para*-position selectively to produce *p*-quinone monooximes (*Eq.* 46).[78] These results have been rationalized by MO calculations which show the highest electron density in the HOMOs of protonated phenols exist at the *ortho*-position while those of deprotonated ones exist at the *para*-position.



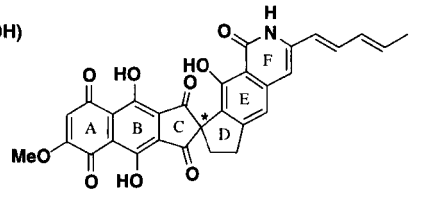
(46)

V. APPLICATION FOR THE SYNTHESES OF *peri*-HYDROXY POLYCYCLIC QUINONE COMPOUNDS

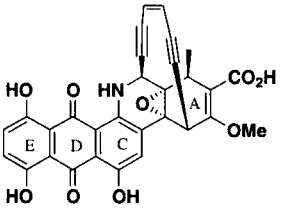
Polycyclic quinones bearing many oxygen functional groups at the *peri*-positions are found in the structures of natural products such as anthracyclines, pyranonaphthoquinones, fredericamycin A and dynemicin A. These compounds have important biological activities such as antibiotic and anti-tumor activities, and their total syntheses have been the target of intense study. Many of these syntheses involve the oxidative formation of the *p*-quinone structure as a key step.[79] Since these compounds have a variety of functional groups, the use of mild reaction conditions is imperative. This chapter examines the efforts to synthesize two quinone-natural products, dynemicin A and fredericamycin A and will focus on the quinone formation steps.



anthracyclines



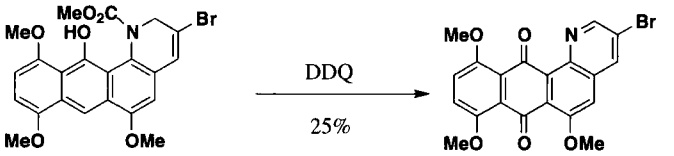
fredericamycin A



dynemicin A

1. Dynemicin A

In model studies for the syntheses of tetracyclic quinone cores, suitably functionalized phenol precursors have been oxidized to the quinones with standard oxidants such as DDQ,[80] Jones reagent,[81] and CAN[82] (*Eqs.* 47–49).



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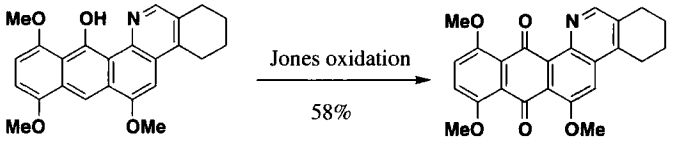

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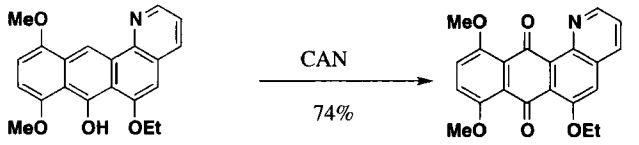
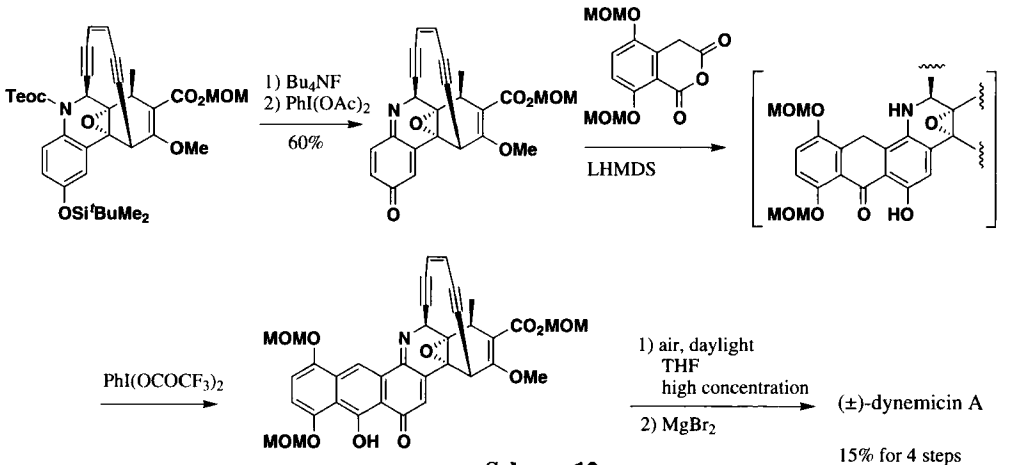


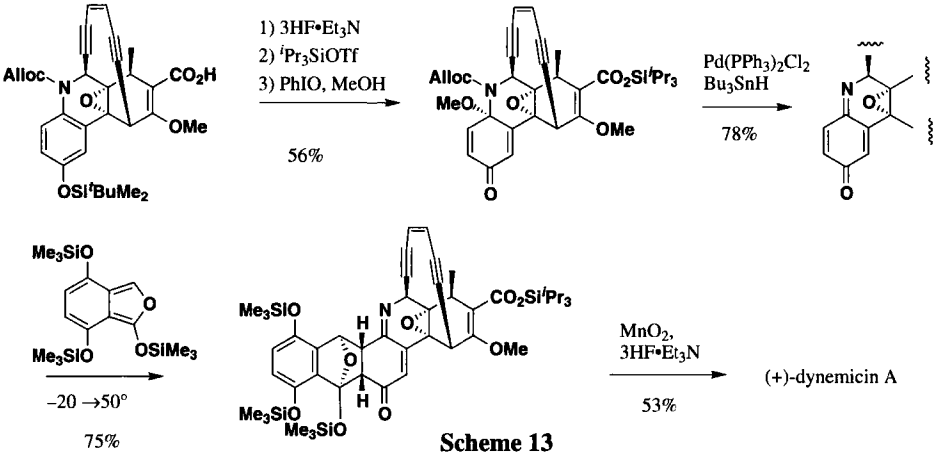
(49)

Recently total syntheses of dynemicin A have been achieved by both Danishefsky's group and Myers' group, in which the quinone imine formation and the quinone formation are successively executed in the final stages. The quinone imine formation is attained through the oxidation of *p*-aminophenol derivatives by hypervalent iodine(III) compounds in both cases, while the following oxidation of the D-ring of the fully functionalized molecules required especially delicate conditions. After screening numerous unsuccessful oxidation protocols, Danishefsky's group accomplished the first total synthesis of the racemic form by exposure of the precursor to daylight under aerobic conditions followed by deprotection (*Scheme* 12).[83] In Myers' synthesis, a careful procedure involving the



Scheme 12

combined use of $3HF•Et_3N$ and activated MnO_2 followed by quick purification provides the optically active (+)-dynemicin A (*Scheme* 13).[84]



Scheme 13

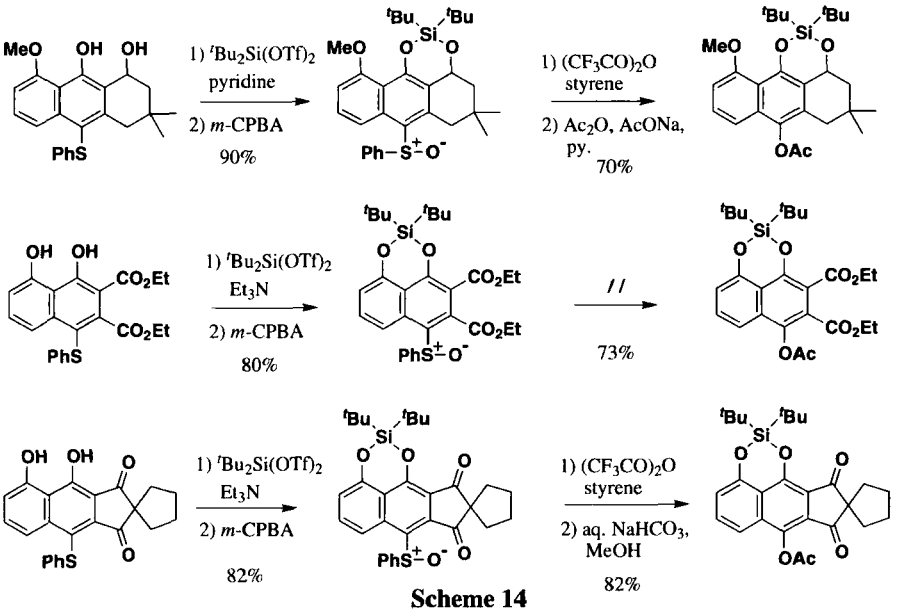
2. Fredericamycin A

Although the total synthesis of fredericamycin A has been achieved by 6 groups, five of these are syntheses of the racemic form. In one synthesis, the optically pure form has been attained by the separation of the racemic product by HPLC (see footnotes of ref. 11b). On the other hand, we have been approaching the asymmetric total synthesis of fredericamycin A through the intramolecular [4+2]cycloaddition of the silylene-protected styrene derivatives, which is expected to provide the chiral spiro framework with accurate absolute stereochemistry. However, as mentioned before (see *Eq.* 1), the introduction of another hydroxy group at the B-ring of the tetracyclic adduct was an issue which remained to be resolved.

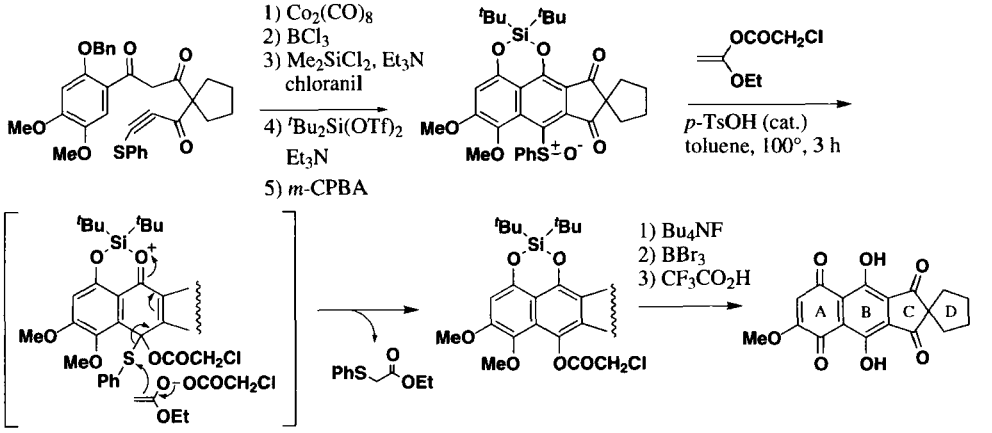
A successful application of the aromatic Pummerer-type reaction, mentioned in Chapter II–2, to synthesis of the *peri*-hydroxy polycyclic quinone structures related to anthracyclines and fredericamycin A has been accomplished in high overall yields. In these reactions, silylene protection of two neighboring hydroxy groups of the *peri*-hydroxy aromatic sulfides is essential for the Pummerer-type reaction (*Scheme* 14).[85]

Combination of this protocol with the above-mentioned intramolecular [4+2]cycloaddition methodology has provided a synthesis of the ABCD-ring of fredericamycin A (*Scheme* 15).[11b,86]

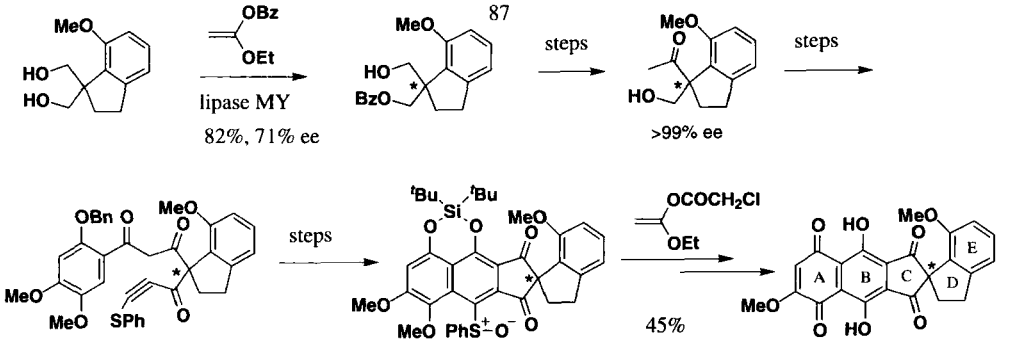
Very recently, this method was successfully applied to the synthesis of the optically pure ABCDE-ring of fredericamycin A (*Scheme* 16).[86]



Scheme 14



Scheme 15



Scheme 16

VI. CONCLUSION

This review has shown the characteristics of each reaction in *Scheme* 1 and has described their applications to a number of total syntheses of biologically important compounds. It has also highlighted the recent advances in oxidative *p*-quinone synthesis. In particular, the stepwise oxygenation strategy (Chapter 2) has been shown to have great potential as an alternative to direct oxidation since (i) some of the functional groups Z in the precursor **III** are stable under a wide range of reaction conditions and (ii) their transformation into the oxygen functional groups can be run under specific conditions which are compatible with a variety of functional groups. However, in order to make these methodologies more practical, further investigations into the flexible and efficient introduction of the group Z to a phenol ring are necessary. Another important area for future work in this field should involve extending the use of molecular oxygen, since it will supply milder and more economical protocols for quinone formation.

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