# Cyclohexadienone Ketals and Quinols: Four Building Blocks Potentially Useful for Enantioselective Synthesis

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## *1. Foreword (Applies to Figure 1)*

Cyclohexadienone ketals and quinols are potentially useful building blocks for enantioselective synthesis. Their practical molecular architecture first captivated my interest during a postdoctoral stint in the Danishefsky group. My assignment was to synthesize tricycloillicinone (**1**), a nonracemic sequiterpene isolated by Fukuyama from the evergreen *Illicium tashiroi*.[1] As with all good mentors, continual prodding by Professor Danishefsky's immortal phrase, "Oh, hi ... what's new?" compelled me to complete the synthesis of **1**. We postulated that if the cyclohexadienone **3** could be procured, then the tetracycle **2** could be formed by a series of 5-*exo* radical cyclizations and subsequent radical oxidation triggered by addition of $Mn(OAc)_3/Cu(OAc)_2$ to the masked $\beta$-diketone **3**.

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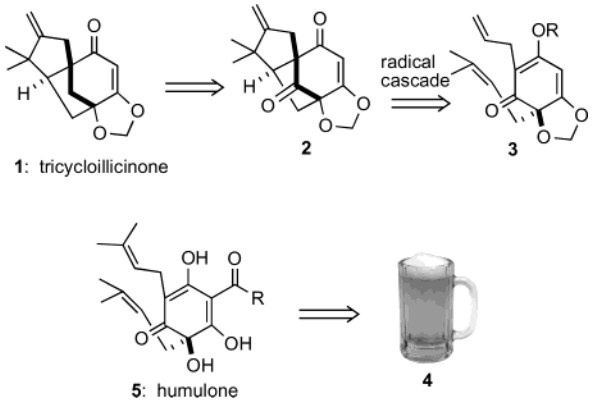


**Figure 1.** Working, drinking, and some thinking about cyclohexadienones.

A new dormitory was being built on the campus of Columbia University on the corner of 114th and Broadway. Every day in route to the laboratory in Havemeyer Hall, I would pass the construction site. I would compare the construction crew's progress with my own. I was determined to complete tricycloillicinone (**1**) before the dormitory was finished. By the time the top floor of the dormitory was fully framed, I began to regret that I had left my previous job in construction. On Friday evenings on the way home, I would stop off at the West-Gate bar and seek consolation in 1−2 beers. Shortly before the lights were installed in the new dorm, I prepared the cyclohexadienone **3**. The radical cascade resulting in **2** succeeded shortly thereafter, and the total synthesis of (±)-tricycloillicinone (**1**) was completed with a week to spare before my departure to UCSB.[2] However, despite considerable thought during 104 Friday nights, I was no closer to imagining an asymmetric method for procuring the key cyclohexadienone intermediate **3**, which would be necessary for an enantioselective synthesis of **1** by this strategy. An ingredient in my amber pint (**4**) posed a similar chiral conundrum that had confounded or at the very least confused chemists for a considerably longer period. Fifty years ago, humulone (**5**) was identified from the fermentation products of hops and shown to display an R configuration at its sole chiral center.[3] Obviously, the cyclohexadienone **3** and the natural product humulone (**5**) display many structural similarities. Furthermore, it is interesting to note that despite knowledge of the absolute configuration of humulone (**5**) for a considerable period, an asym-

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Simon J. Meek was born in Bristol, U.K., in 1980. He received his MSc. from the University of Sheffield, U.K., in 2003. As part of his undergraduate education, he completed a year of study at UCSB, where he worked as an undergraduate researcher in the Pettus laboratory on the addition of chiral ligands to hypervalent iodide reagents for asymmetric dearomatizations of phenols. While attending UCSB, Simon was awarded the prestigious Robert H. DeWolfe summer undergraduate research award for 2002. He is currently working toward his Ph.D. under the supervision of Dr. J. P. A. Harrity at the University of Sheffield.

Dr. Thomas R. R. Pettus was born in Richmond, VA, in 1967. He grew up on a farm in the Piedmont of Virginia near a small town on Hwy-15 called Keysville. After working in construction as a bulldozer operator to build a levy around the town of Scottsville and a sewer main for the town of Stuart, Tom decided to pursue a less challenging career in chemistry. He worked in Professor Hudlicky's laboratory at VPI in Blacksburg, VA, as a summer undergraduate researcher. He earned a Ph.D. with Professor Schlessinger at the University of Rochester in 1996. Tom then joined the laboratories of Professor Danishefsky at Columbia University as a NSF Postdoctoral Fellow. In the fall of 1998, Tom started his independent academic career at the Department of Chemistry and Biochemistry at UCSB. He is the recipient of a Research Corporation Innovation Award and NSF Career award.

metric preparation of this compound has not been forthcoming. The only reported preparation of enantiopure material utilized a resolution. It therefore appears that current asymmetric techniques do not allow for a straightforward preparation of this rather simple tertiary alcohol. One may consequently conclude that the art of organic synthesis is not as mature as declared in recent scientific commentary describing the current state and questionable future of the field of organic chemistry.[4] This and related statements are doing a grave disservice to our community. I often find myself having to defend the pursuit of organic synthesis to my scientific colleagues because of their erroneous belief that organic chemistry, particularly synthesis, is a mature and, therefore, dead field of science. In my opinion, humulone (**5**) and related cyclohexadienones skeletons are proof of the need for organic chemists. This is just one of many classes of molecules for which there are very few enantioselective preparations. These chemical entities along with many yet undiscovered chiral ensembles will surely challenge the acumen and abilities of organic chemists for the near future (by T. Pettus).

## 2. Introduction

Asymmetric methods are becoming of increased financial importance as pharmaceutical companies are exchanging racemic drugs for nonracemic ones to extend the patents on profitable compounds.[5] This financial motivation of the "chiral switch" is partly responsible for the proliferation of enantioselective methods. Processes for reduction of carbonyls, imines, and alkenes; additions to enones, enolate alkylations, aldol reactions, and cycloadditions; as well as sigmatropic rearrangements, such as Claisen, Cope, and others have all been adapted to yield nonracemic products.

Despite these advancements, very few methods have been developed to provide enantiomerically enriched cyclohexadienones or their derivatives. This oversight is surprising because cyclohexadienones are attractive starting points from which to begin total syntheses of numerous natural products. The stereogenic center contained within the six-membered ring of various cyclohexadienones has been elaborated into larger chiral arrays and employed in many total

syntheses. However, despite their intrinsic value, the chemistry of the four types of cyclohexadienones was last reviewed together in 1966.[6]

For this reason, we have decided to summarize the preparation, application, and synthetic uses of cyclohexadienones as well as all the asymmetric methods directed toward their preparation through August of 2002. This review is divided into four sections that relate to the structure of these systems (Figure 2).

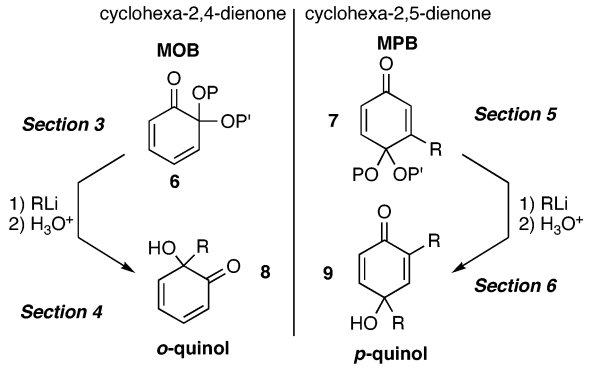
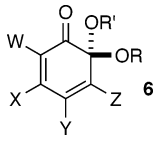



**Figure 2.** The four types of cyclohexadienone building blocks.

Section 3 describes the chemistry of masked *ortho*-benzoquinone ketals (MOBs), **6**. Section 4 summarizes the chemistry of *o*-quinols, such as **8**. The chemistry of these two types of cyclohexa-2,4-dienones is closely related. Indeed, *o*-quinols such as **8** can be derived from MOB ketals such as **6**. The same synthetic relationship proves true for masked *para*-benzoquinone ketals (MPBs) **7** and *p*-quinols **9**, the chemistry of which is outlined in Sections 5 & 6. The aim of this review article is to provide readers with (1) a synopsis of the methods used to prepare each of these classes of cyclohexadienones, (2) a summary of the reactions for these structures, (3) an outline of their specific synthetic applications, and (4) an overview of realized and anticipated enantioselective horizons for these four classes of cyclohexadienones. It is our hope that this review empowers readers to contribute to this area. At the very least, it should (1) persuade readers that the development of methods for fashioning cyclohexadienones in an enantioselective fashion is a worthy goal and (2) enable readers to distinguish new inventions in this regard from old.

## 3. MOB Ketal Building Blocks (6)



Often referred to as a masked-*ortho* benzene (MOB) ketal, this cyclohexadienone nucleus is often prepared by oxidation of a 2-alkoxyphenol, such as **10**. However, different oxidants can lead to different outcomes for similar substrates; therefore, selection of the oxidant is a critical decision. The chemistry of the MOB ketal **6** is dominated by its proclivity toward [4 + 2] dimerization. Fortunately, there are methods to partially suppress this tendency and unlock some of its synthetic potential. Dimerization is less problematic, if (1) the cyclohexadienone ring contains electron-withdrawing groups, (2) oxidation results in a mixed −OAc ketal, and (3) the cyclohexadienone is intercepted in a desired intramolecular [4 + 2] cycloaddition. Stable MOB ketals undergo a wide array of reactions, including 1,2- and 1,4-additions; both normal and inverse-demand Diels−Alder reactions; Michael−Dieckmann reactions; sigmatropic shifts; electrocyclic rearrangements; as well as $S_N2$, $S_N2'$, and bis-allylic displacements. Indeed, MOB building blocks are key intermediates in diastereoselective syntheses of calicheamicinone, ryanodol, forsythide, and colchine. Several of these targets could have been produced in an enantioselective fashion if the starting MOB ketal had been available in an optically enriched form.

### 3.1. Preparation

MOB ketals are usually prepared by one of four methods. The first exposes a mono-protected catechol such as **10** to an oxidant in the presence of a nucleophilic alcohol. The second involves the exposure of a non-*ortho*-substituted phenol, such as **11**, to 2 equiv of an oxidant in the presence of excess alcohol. The third involves ketalization of an *o*-quinone, such as **12**. The fourth procedure involves transketalization of an *o*-quinone ketal, such as **6′**, formed by one of the previous three methods. In the cases involving oxidation, reagents containing $Pb^{iv}$, $I^{iii}$, $Tl^{iii}$, and $Br^+$ have proven successful, as have electron-deficient quinones and electrochemical methods. Each procedure offers subtle differences and often proves superior for specific substrates. For example, phenols lacking a *ortho* substituent, such as **11**, can be oxidized to their respective MOB ketal by $Pb(OAc)_4$. This reagent displays a preference for *ortho* oxidation. Other oxidants [i.e., $I^{iii}$, $Tl^{iii}$, and $Br^+$ reagents, as well as quinones] would have led to *para* functionalization, as will be shown in Section 5.

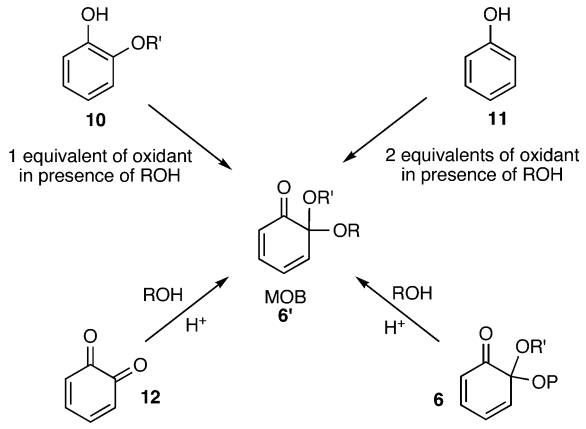



**Figure 3.** Preparations of MOB ketals.

Among $Pb^{iv}$ reagents, lead tetraacetate (LTA) proves to be most popular for oxidation of *o*-substituted phenols. Its use was first popularized by Wessely.[7] LTA displays a strong proclivity for oxidation at the *ortho* position bearing the more electron-rich substituent. Phenol oxidations employing $Pb^{iv}$ reagents

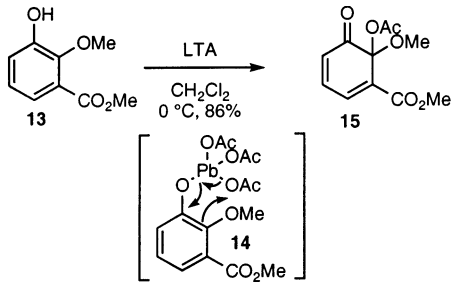



**Figure 4.** LTA oxidations lead to −OAc mixed MOB ketal.

are believed to proceed through a delivery mechanism such as that shown in **14** (Figure 4).[8] The outcome is the installation of a mixed acetate ketal *ortho* to the carbonyl. In a typical procedure, a phenol such as **13** (0.1 M in $CH_2Cl_2$ at RT) is exposed to LTA. As shown in Figure 4, the reaction occurs at the most electron-rich *ortho* position of **13** to afford **15** in 86% yield.[9] Nevertheless, the electronic preference for delivery of the acetate to the *ortho* site can be overridden by steric interactions and reaction conditions.[10] For example, in a sterically encumbered MOB ketal, the allylic acetate is predisposed to allylic transposition, resulting in a *para*-functionalized 2,5-cyclohexadienone product, which is reported to be more thermodynamically stable. Mixed [−OAc] acetals resembling **15** offer several advantages over dialkoxy ketals. The former undergoes $S_N2$, $S_N2'$, and bis-allylic displacements and discourages [4 + 2] dimerization through stereoelectronic effects. Bhatt,[11] Coleman,[12] Hunter,[13] and Pinhey[10] have all extensively investigated the Wessely oxidations of phenols.

Among $I^{iii}$ reagents, $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$ are the most commonly used. The former is sometimes referred to as PIDA, whereas the latter is most often called PIFA. Although the true nature of hypervalent iodine oxidations of phenols remains elusive, the idea of a concerted nucleophilic attack has been dismissed.[14] Electron-rich aromatics are thought to first form a charge-transfer complex upon exposure to the $PhI(ligand)_2$ that permits the transfer of two electrons to the $I^{iii}$ aryl complex, which in turn dissipates negative charge by loss of a ligand. Ligands such as [−OAc] favor a sequential series of SET reactions, whereas ligands such as [$-OCOCF_3$] appear to favor a more anionic mechanism. The substrate also affects the specifics of the mechanism. Protected phenols undergo oxidation through a SET pathway, whereas unprotected phenols tend to oxidize directly through an anionic route. Once a resonance-stabilized cation forms, it undergoes reactions at the site with the greatest LUMO coefficient. However, simple examination of the relative resonance contributors (cf. **16** and **17**, Figure 5) is often satisfactory when making a prediction regarding the site of nucleophile addition. Usually the reaction

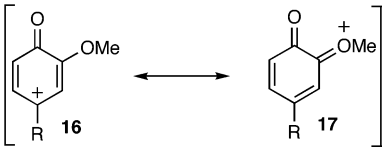



**Figure 5.** Cation coefficients predict reaction site with $I^{iii}$ reagents.

occurs on the carbon atom *para* to the carbonyl as resonance contributors with positive charges at the *ortho* sites are destabilized by their close proximity to the carbonyl group. However, an electron-withdrawing group at the *para* carbon atom or a donating group at an *ortho* carbon atom can reverse the *para* preference and lead to addition of the nucleophile at the *ortho* site to the carbonyl.

In a typical procedure, the $I^{iii}$ reagent is added as a solid to the desired phenol (0.1 M in $CH_2Cl_2$ at 0 °C to RT)[15] while stirring in the presence of 5−10 equiv of the nucleophile. If an intermolecular reaction is intended, $CF_3CH_2OH$ or $(CF_3)_2CHOH$ is often used in place of $CH_2Cl_2$ to prevent competitive addition of the ligand (i.e., OAc) accompanying the $I^{iii}$ reagent.[16] Silylation of the phenol prior to oxidation has been shown to improve the yields in some cases, presumably by lowering the acidity of the reaction upon its completion.[17]

Examples of hypervalent iodine oxidations leading to MOB ketals are shown in Figure 6. Liao reports that oxidation of **18** results in a subsequent [4 + 2] dimerization of the oxidation product **19** at room temperature resulting in **20**. However, installation of a bromine atom at the 4-position (cf. **21**) prevents the occurrence of the dimer almost entirely and enables **22** to be isolated in excellent yield.[18] Mal,[19] Mitchell,[20] and several others have also used $I^{iii}$ reagents to successfully prepare compounds containing a MOB core.

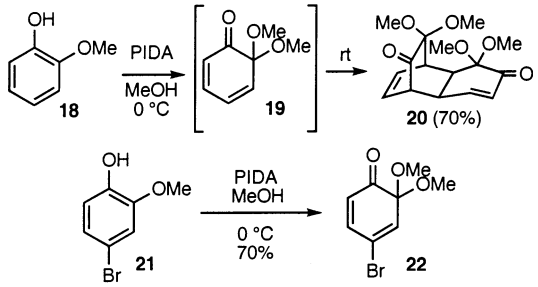



**Figure 6.** $I^{iii}$ oxidations of *o*-methoxyphenols produces MOB ketals.

Among thallium III oxidants, $Tl(NO_3)_3 \cdot 3H_2O$ (TTN) is most commonly used for the preparation of MOB ketals. The initial step is believed to be exchange of the phenol for one of the $NO_3^-$ ligands on the thallium. A series of SET reactions ensues and affords the cation, the reactivity of which has been described above. Nucleophilic addition to this cation is favored *para* to the carbonyl unless overridden by some particular steric or electronic effect. However, TTN is rarely used for intramolecular reactions because the attendant $H_2O$ and $NO_3^-$ are competitive nucleophiles. In the absence of excess nucleophile, substitution with $-ONO_2$ occurs *ortho* to the carbonyl, which suggests a delivery mechanism similar to that reported for LTA.

In a typical procedure, the phenol is dissolved in the intended nucleophile (0.1 M), and the reagent is added while stirring at 0 °C. Horie finds that addition of 2.2 equiv of TTN to **23** results in a double oxidation (Figure 7).[21] Initially, the MPB adduct **24** is produced. However, this adduct undergoes addition of water or

methanol, resulting in **25**, which suffers MeOH elimination, resulting in **26**. Further oxidation with $Tl^{iii}$ produces the MOB ketal **27** and its corresponding MPB ketal tautomer in 85% combined yield. McKillop has demonstrated several other examples of TTN oxidations leading to MOB ketals.[22]

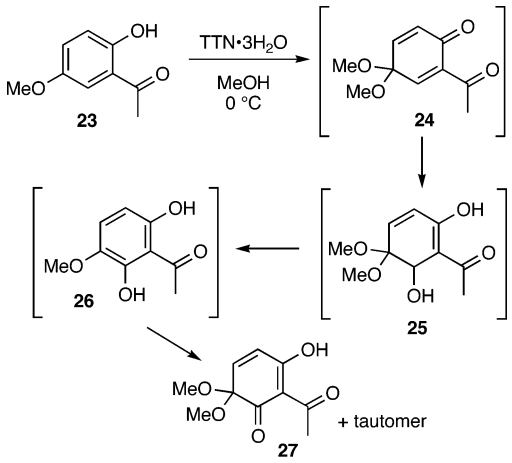



**Figure 7.** $Tl^{III}$ oxidations of properly substituted phenols affords MOB ketals.

In the past, quinones such as DDQ were the oxidizing reagents of choice for the syntheses of MOB ketals from phenols. However, *o*-chloranil can be used in electron-rich systems.[23] A series of SET reactions are thought to produce the cation intermediate. Once formed, the cation again favors *para* substitution in the absence of any overriding steric or electronic effects for the reasons described earlier. A standard procedure involves dissolving the phenol in the intended nucleophile (0.1 M, 0 °C). The quinone is then added while stirring. Barton reports the oxidative dearomatization of 1-methoxy-2-naphthol **28** upon the addition of DDQ in methanol leads to the MOB ketal **29** in excellent yield (Figure 8).[24] This reagent was superior to both $Cu^{II}$/pyridine and *p*-$NO_2$−$BzO_2$/*hν* processes. Girard and Hamel have also investigated the use of other quinones for the preparation of similar MOB ketals.[25]

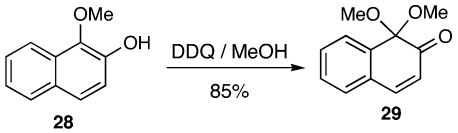



**Figure 8.** DDQ oxidation of *o*-methoxyphenols leads to MOB ketals.

Among electrochemical techniques, implementation of a platinum anode has proven to be the best method for oxidation of phenols. The procedure works well for intramolecular reactions; however, chemical reagents generally prove superior for oxidations involving an intermolecular nucleophilic addition. The reason for this discrepancy resides with the mechanism. Because electrochemical reactions proceed through long-lived radical cation intermediates, poor regioselectivity is often observed for intermolecular processes. For example, Yamamura finds that the electrochemical oxidation of eugenol (**30**) at constant current of 1.5 mA·$cm^{-2}$ at 3 Faraday/mol in dry methanol affords dimers **32** (7%) and **34** (5%) along with the MOB product **33** (68%) and the *p*-quinol product **31** (1.3%) (Figure 9).[26] Barba,[27] Fleury,[28] Ronlan,[29] and Swenton[30] report the use of oxidative electrochemistry to produce other MOB ketals with similar levels of success.

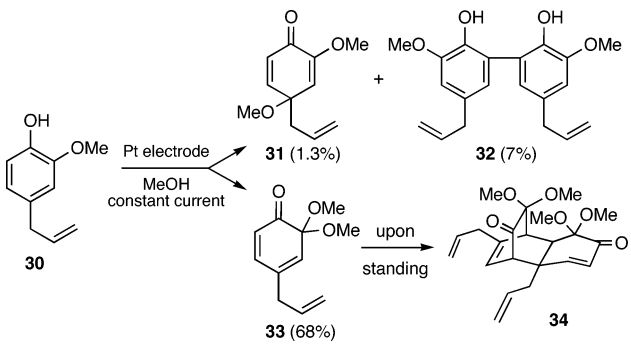



**Figure 9.** Electrochemical oxidation of *o*-methoxyphenols leads to MOB ketals.

## 3.2. Reactions

Undoubtedly, the chemistry of MOB ketals is dominated by their proclivity toward dimerization. However, with proper substitution, MOB ketals prove stable enough to undergo 1,2-ketone additions, 1,4-conjugate additions, intermolecular, and intramolecular [4 + 2] cycloadditions. Michael−Dieckmann reactions, electrocyclizations, sigmatropic shifts, ring-reductions, and photochemically triggered ring openings. In the case of an −OAc mixed ketal, the repertoire of reactions expands to include plethora of allylic transpositions and displacements.

Surprisingly, only a few examples of 1,2-additions to MOB ketals have been reported. Waring finds that organolithium reagents add to the carbonyl in 1,2-fashion.[6] Magnus used a similar ploy during his investigation of the calicheamicinone skeleton and finds that **35** undergoes addition with the lithium acetylide shown to produce the tertiary alcohol **36** in excellent yield (Figure 10).[31]

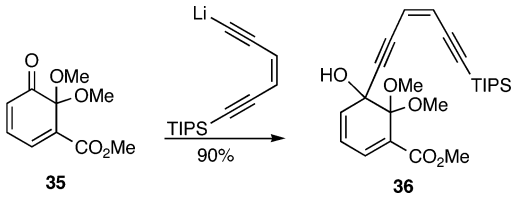



**Figure 10.** 1,2-Addition of a lithium acetylide to a MOB ketal.

Traditional 1,4-conjugate additions of organocuprates to MOB ketals often prove problematic. These organometallic reagents usually transfer electrons to the MOB ketal, resulting in the formation of a radical anion that subsequently undergoes elimination, thereby restoring aromaticity to the six-membered ring. However, softer heteroatom nucleophiles do not lead to reductive rearomatization and participate in a straightforward 1,4-addition. For example, Gammill reports that the phenol **37** undergoes oxidation with TTN in methanol to produce khellinone (**40**) (Figure 11).[32] The transformation is presumed to proceed

through the MOB intermediate **38**, which undergoes a subsequent 1,4-addition to produce **39** and ultimately provides khellinone (**40**) upon MeOH elimination. Both TTN and LTA were equally effective in producing **40** from **37**.

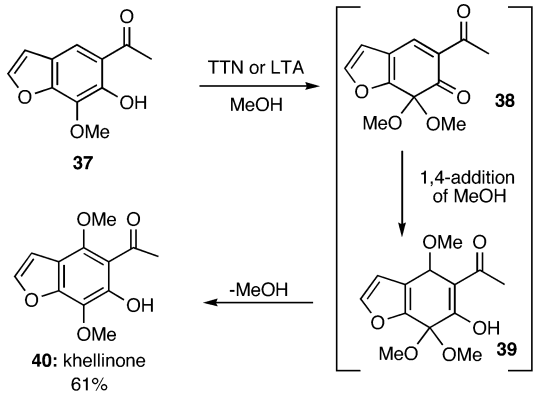



**Figure 11.** 1,4-Addition of methanol to a MOB ketal leading to khellinone.

Mixed −OAc MOB ketals undergo a more extensive list of transformations involving allylic rearrangements. For example, using the LTA product **41**, Quideau devised an intramolecular 1,4-conjugate addition that was triggered by TBAF cleavage of the Tsoc moiety (Figure 12).[33] A 1,4-addition of the amine affords **42**, which undergoes a 1,4-elimination of HOAc to produce the heterocycles **43**. The 6,6-ring system forms in 58% while 6,5-ring systems form in 48% yield. This transformation may prove useful for the construction of α-lycorane alkaloids.

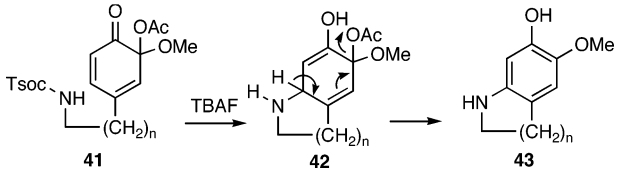



**Figure 12.** 1,4-Amine addition to a MOB ketal leading to α-lycorane alkaloids.

Reductions of the olefins contained within cyclohexadienone ketals and quinols can often prove problematic. In these processes, electron transfer often occurs, which results in reductive rearomatization. A combination of metals with a low ionization potential and cyclohexadienone with electron-rich leaving groups has been shown to minimize this problem. In route to callicarpone, Matsumoto finds that oxidation of **44** with TTN affords the MOB ketal **45** in 85% yield (Figure 13).[34] This material undergoes reduction with $Rh-Al_2O_3$ under an $H_2$ atmosphere in the presence of KOH to give the *cis*-decalin **46** in 41% yield along with minor amounts of diastereomers and the phenol **44**, which results from rearomatization. The configuration of the *i*-Pr residue is likely the result of a post-reductive epimerization. Other hydrogenation catalysts, such as $Pd^0$, applied to **45** led almost exclusively to reductive rearomatization, affording the starting phenol **44**.

With regard to cycloadditions, Coleman reports that the MOB ketal **15** undergoes an intermolecular

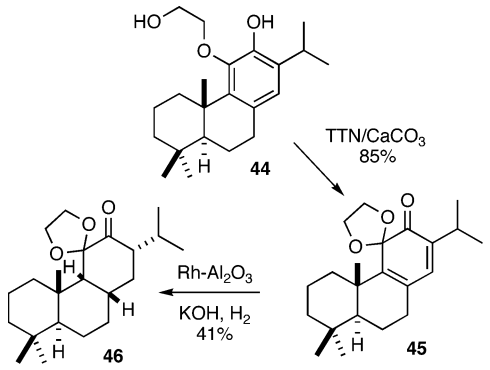



**Figure 13.** Hydrogenation of a MOB ketal.

[4 + 2] cycloaddition with **47** to produce the naphthalene **48** (Figure 14).[12] This process has been employed in the total synthesis of calphostatin.

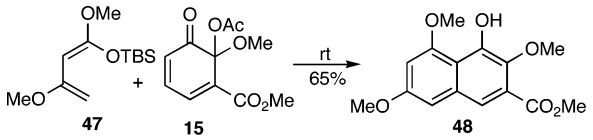



**Figure 14.** [4 + 2] Cycloaddition of a MOB ketal, leading to a naphthol.

Plumet has investigated the reactions of MOB ketals in inverse-demand intermolecular Diels−Alder reactions (Figure 15).[35] The cycloaddition of **50** with enols such as **49** (X = S and O) were highly regioselective, affording the [2.2.2]-bicyclooctene **51** in moderate to excellent yields.

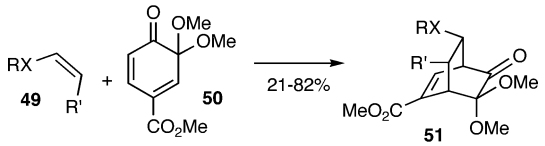



**Figure 15.** Inverse-demand [4 + 2] cycloaddition of a MOB ketal.

Intramolecular cycloadditions have been explored by Rodrigo (Figure 16).[36] These particular reactions involve a concomitant oxidation and [4 + 2] cycloaddition. For example, oxidation of **30** with PIFA in the presence of the dienyl alcohol **52** affords the cyclohexadienone mixed ketal **53**. The butadiene undergoes cycloaddition with an alkene of the MOB ketal (cf. **53a**) from both *exo* and *endo* orientations leading to **54** and **55**. Alternatively, the MOB ketal

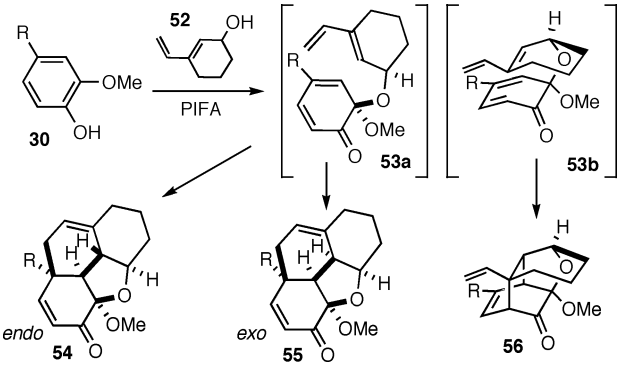



**Figure 16.** Formation and intramolecular [4 + 2] cycloaddition of a MOB ketal.

can serve as a diene (cf. **53b**) and undergo reaction with a single alkene of the dienyl ether to produce the bicyclic adduct **56**.

Wood has implemented a more sophisticated example of this tandem protocol in an approach to the CP-263,114 natural product (Figure 17).[37] The sequence nicely demonstrates the molecular complexity that can be rapidly addressed by a MOB ketal. Oxidation of **57** with PIDA in the presence of propargyl alcohol affords the cycloadduct **59** via the MOB intermediate **58**. Compound **59** is further elaborated by (1) radical-mediated hydrostannylation of the alkyne and (2) bis-ester hydrolysis and cyclization to afford the tertiary alcohol and anhydride moieties contained in the compound **60**.

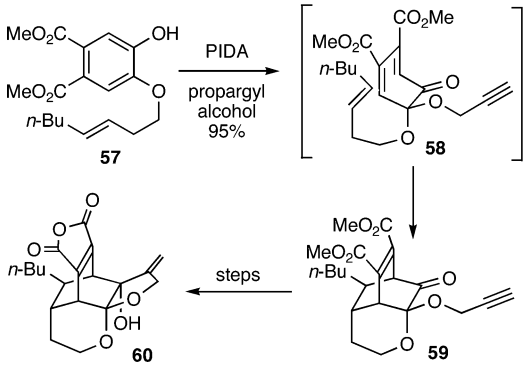



**Figure 17.** Successive oxidation−cycloaddition, leading toward CP-263,114.

Another useful annulation strategy has been reported by Mitchell for the construction of anthraquinones (Figure 18).[20] The cyanophthalide **61** upon deprotonation undergoes a Michael−Dieckmann to the eugenol oxidation product **33** (unpurified to prevent dimerization) to afford the modified alizarin **62** in 92% yield. An analogous sequence with the oxidation product of cresol is reported to proceed in a similar yield. Mal employs the sulfone analogue of **61** for rapid access to hydroxylated benz[*a*]anthraquinones.[19]

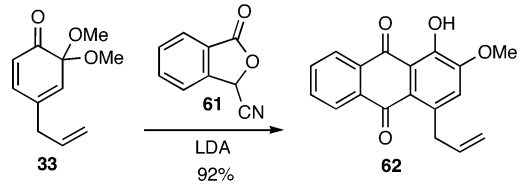



**Figure 18.** A Michael−Dieckmann of a MOB ketal affords an anthraquinone.

Mixed −OAc MOB ketals arising from LTA oxidation of *o*-substituted phenols undergo a variety of $S_N2'$-type reactions. Hoshino reports that oxidation of **63** in $CH_2Cl_2$ with LTA affords the expected mixed acetal **64** (Figure 19).[38] However, upon addition of $CF_3CO_2H$ to **64** or by using $CF_3CO_2H$ as the solvent for the initial LTA oxidation, a mixture of products **65** and **66** arises through various allylic displacement pathways. Meyers used a similar ploy in the synthesis of isopavines.[39]

In a related report, Umezawa finds that oxidation of isomer **67** with LTA affords **68** (Figure 20).[40] This compound, when treated with $CF_3CO_2H$, tautomerizes to **69** and then undergoes a bis-allylic displacement to afford the azabicyclo[3.3.1]nonane **70**. In a synthesis of limousamine, Castedo exploits a related allylic transposition of a LTA adduct.[41]

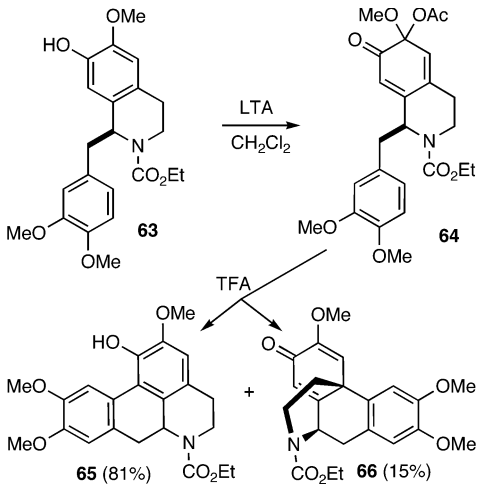



**Figure 19.** $S_N2'$ displacement of an −OAc mixed MOB ketal.

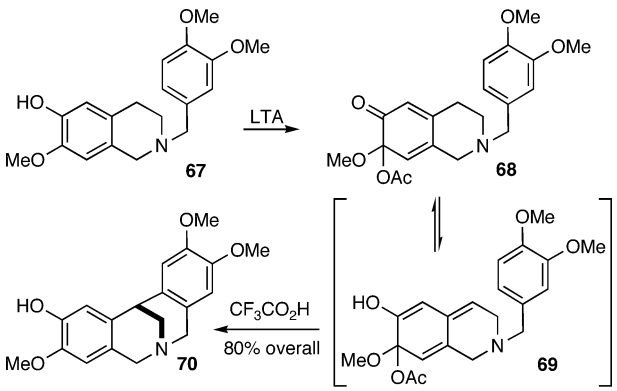



**Figure 20.** Bis-allylic displacement of an −OAc mixed MOB ketal.

With regard to electrocyclizations and sigmatropic shifts involving MOB ketals, Feldman finds that 2 equiv of LTA results in oxidation of both phenol fragments of the stilbene **71**, affording the bis-ketal **72** (Figure 21).[42] Upon refluxing in toluene, **72** undergoes a [1,7]-sigmatropic shift to produce **73**, which then suffers a [1,5]-sigmatropic shift to afford **74**. Compound **74** forms the enol **75**. This intermediate can suffer displacement of one of its tertiary acetates by two different processes. One of these transformations affords the tricycle **76**, while the other leads to the spirocycle **77**. The remaining tertiary acetate in **77** undergoes yet another bis-allylic displacement with chloride, producing **78**.

## 3.3. Synthetic Applications

In addition to the syntheses already mentioned, MOB ketals have played a key role in preeminent syntheses of calicheamicinone, forsythide, and colchicine. For example, Magnus reports the use of a MOB core in the synthesis of calicheamicinone (Figure 22).[43] The reaction of phenol **79** with PIDA in MeOH affords the dimethoxy MOB ketal **80**. 1,2-Addition of a lithium acetylide to the ketone followed by TBAF deprotection of the acetylene and protection of the

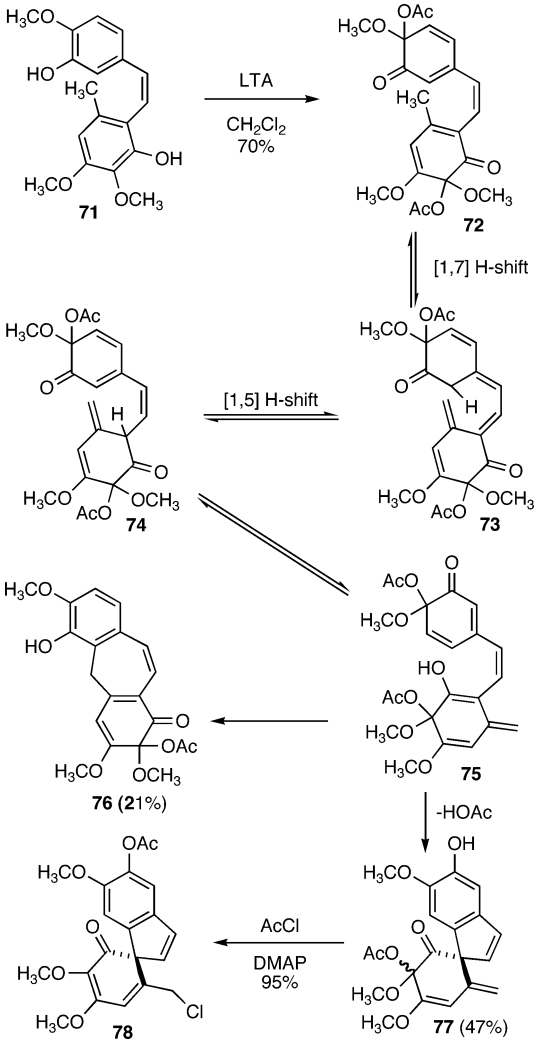



**Figure 21.** Sigmatropic shifts in a MOB ketal.

resulting tertiary alcohol as the TES siloxy ether affords **81** in >60% overall yield. This intermediate can be converted into calicheamicinone (**82**) after several additional steps.

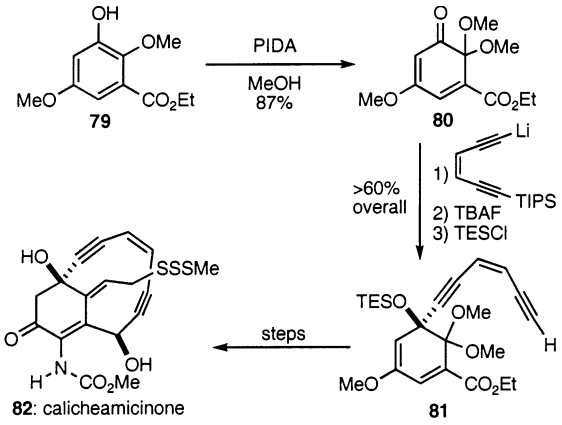



**Figure 22.** Magnus synthesis of calicheamicinone.

Deslongchamp's synthesis of ryanodol is arguably among the best examples of the power of a MOB ketal as a building block for syntheses of complex natural products (Figure 23).[44] Oxidation of **83** was accomplished through NaOH opening of the lactone and reaction of the resulting phenoxide with NBS to

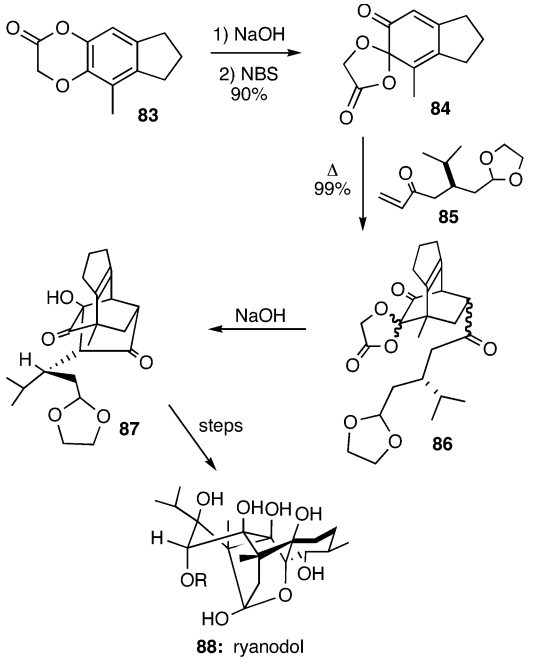



**Figure 23.** Deslongchamp's synthesis of ryanodol.

produce the mixed MOB ketal **84**. Subsequent addition of the chiral dienophile **85** results in a Diels–Alder reaction that produces the [2.2.2]-bicycloadduct **86**. Exposure of **86** to NaOH results in hydrolysis of the mixed ketal and a subsequent aldol reaction producing **87** along with 3 other major side products. This intermediate was eventually transformed into ryanodol (**88**) after a series of transformations.

Liao reported a novel synthesis of the forsythide aglycone dimethyl ester **93**, a derivative of the natural product forsythide (Figure 24).[45] The Diels–Alder reaction of diene **50** with methyl acrylate affords the adduct **89** in >80% yield. A 1,2-ketone transposition produces **90**, which upon photolysis at 300 nm creates the cyclopropane **92** via a Norrish, type I reaction that presumably involves the intermediate **91**. Subsequent conversion of **92** to **93** is accomplished in a straightforward manner.

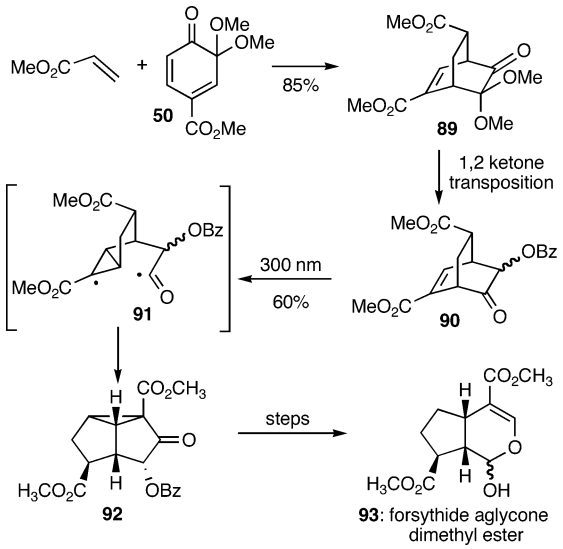



**Figure 24.** Liao synthesis of a forsythide derivative.

Banwell demonstrated the malleability of a MOB ketal in his total synthesis of colchicines (Figure 25).[46]

Addition of trifluoroacetic acid to the MOB ketal **94** generates a phenonium cation that undergoes a Friedel−Crafts alkylation as an electrophile with the tethered trimethoxyaromatic fragment to produce **95**. Oxidation of the aromatic nucleus with TTN in methanol affords the MOB **96** in a 97% yield. Subsequent cyclopropanation results in **97**, which upon treatment with acid yields the tropolone **98**. This compound was eventually converted into colchicine (**99**). Related approaches were used by Banwell in the syntheses of the tropolone isoquinoline alkaloids imerubrine and grandirubrine.[47]

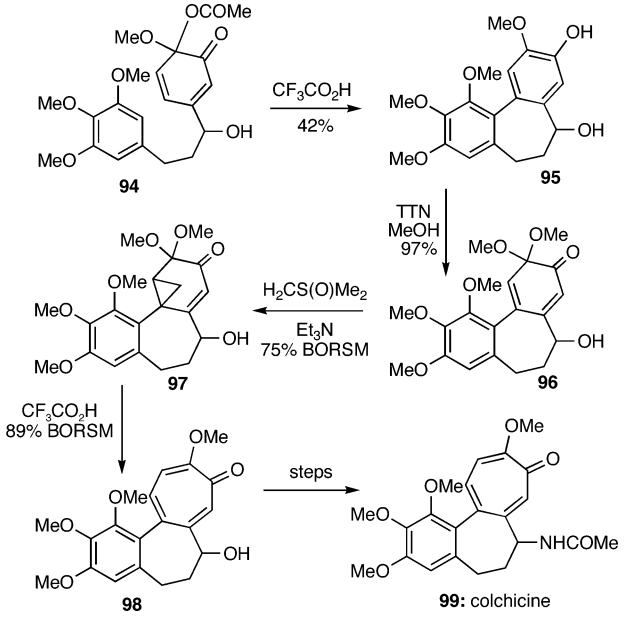



**Figure 25.** Banwell synthesis of colchicine.

## 3.4. Enantioselective Horizons

As evident from the preceding discussions, a method for the enantioselective preparation of a MOB ketal is clearly a worthy goal. If such a chiral entity was accessible in a nonracemic format, and if it enabled stereocontrolled access to the functional groups contained within a cyclohexadienone ring system, then the enantioselective syntheses of calicheamicinone, forsythide, CP-263,114 and ryanodol would be possible (Figure 26).

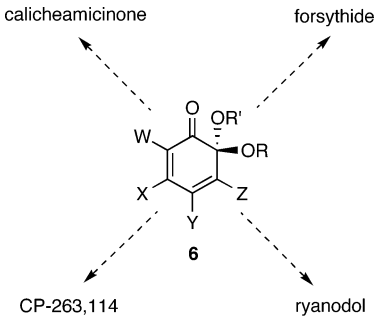



**Figure 26.** Potential of MOB ketals for asymmetric synthesis.

At present, only one researcher has reported findings regarding chiral variants of MOB ketals. Fujioka has constructed the chiral ketal **100** (Figure 27).[48] Reduction of the carbonyl with LAH/LiBr occurs in a diastereoselective fashion to afford the alcohol **102**, which upon hydrogenolysis of the ketal and reduction of the styrene produces the chiral (*R*)-alcohol **104** in 70% *ee*. On the other hand, reduction of **100** with LAH/$MgBr_2$ affords the alcohol **101**, which upon hydrogenolysis of the ketal and reduction of the styrene affords the (*S*)-alcohol **103** in 70% *ee*.

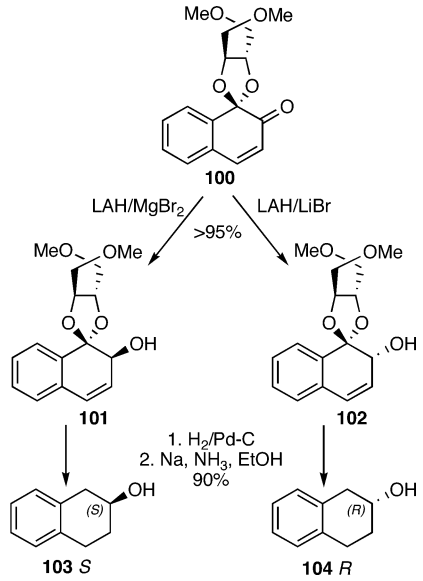
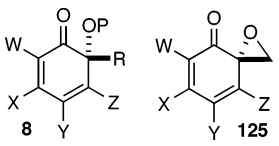



**Figure 27.** Applications of a nonracemic MOB ketal.

Designing an asymmetric preparation of a nonracemic MOB ketal, in which enantioselection occurs during the dearomatization rather than through some postprocessing of the nucleus, such as by transketalization with a chiral diol, remains a challenging task for chemists. The reason lies within the mechanism associated with phenol dearomatization. Hypervalent iodine oxidation leads to a planar cationic intermediate, in which the reagent is far removed from the developing stereocenter. Hence, it is not very feasible to use a chiral $I^{iii}$ oxidant to control the addition of the nucleophile, unless the nucleophile is delivered concomitantly, as with intramolecular mechanisms. In view of this understanding, it is not entirely surprising that the enantiomeric excess afforded by chiral derivatives of PIDA and PIFA in oxidative dearomatizations are modest at best (<30% *ee*).[49] It seems far more plausible to adapt the Wessely oxidation to an enantioselective format since the reaction involves an intramolecular delivery mechanism. Such an asymmetric transformation might make use of a chiral additive that could serve as ligands on the $Pb^{iv}$ to raise its oxidative potential. Recent reports that LTA oxidations are accelerated by the addition of certain amines may suggest a useful course of future research.[50]

## *4. o-Quinol-Derived Building Blocks (8)*




*o*-Quinols, ethers, and their spiroepoxide derivatives are among the least investigated cyclohexadi-

enones among the four types discussed in this review. Like its isoelectronic MOB ketal counterpart, the chemistry is again dominated by a propensity toward dimerization. In addition, *o*-quinols with specific functionality experience a few other problematic reactions. For example, −OAc and −OH *o*-quinols undergo ring opening under basic conditions, whereas the ethers prove to be relatively stable. Wessely,[51] Van Dongen,[52] and Bugg[53] have noted that some unusual products can emerge when *o*-quinols and their corresponding acetates are subjected to basic conditions. Several of these intermediates are believed to resemble those associated with catechol dioxygenase. Natural products, such as humulone (**5**) in Figure 1 and lacinilene (**130**) in Figure 33, as well as wasibidienone are thought to degrade by pathways similar to that shown for the conversion of **105**−**112** (Figure 28).[54]

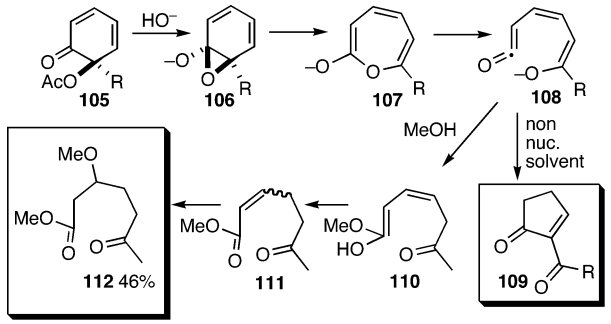



**Figure 28.** Degradative ring opening of an −OAc mixed MOB ketal.

*o*-Quinol spiroepoxides, which have found abundant use in synthesis,[55] rearomatize upon the addition of a variety of nucleophiles. For example, Reiss and Awad find that addition of triethylamine to **113** results in a C−C bond cleavage affording the zwitterion **114**, which then undergoes an intramolecular addition to afford the methylene dioxy compound **115** (Figure 29).[56] Gesson finds that addition of TBSCl result can result in a similar transformation with chloride serving first as the nucleophile and then as the leaving group.[57] Other interesting spiroepoxycyclohexadienone chemistry includes the construction of phenoxanthins, a reaction that has been investigated by Reiss.[58]

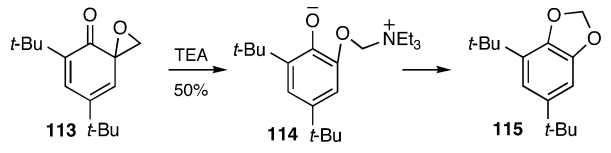



**Figure 29.** Degradative ring opening of an *o*-quinol spiroepoxide.

*o*-Quinol hydroperoxides undergo fragmentation via two pathways. The preparation of hydroperoxides resembling **116** occurs upon exposure of a trisubstituted phenol to a Co(Salpr) catalyst in the presence of molecular oxygen (Figure 30).[59] Nishinaga[60] and Sayre[61] have observed migration of the *o*-alkyl residue in **116** via the epoxide intermediate **117**, which results in the *p*-quinol **118**. Nishinaga reports a rearrangement of the hydroperoxide **116** affords **119** upon attempts to acetylate the hydroperoxide using Schotten−Baumann conditions.[62] The hydroperoxide **119** affords the *syn* epoxy alcohol **120** upon continued exposure to basic conditions. Matsumoto[63] and Wilson[64] note the similarities between these pathways and those of vitamins E and K, respectively.

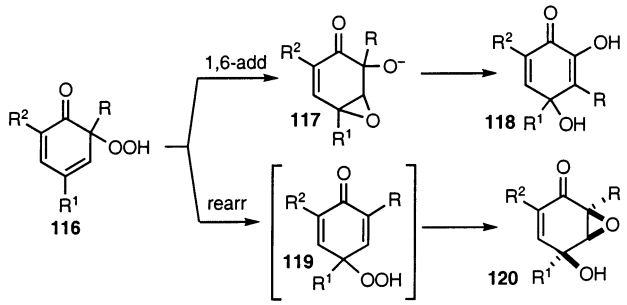



**Figure 30.** Reactions of *o*-quinol hydroperoxides.

## 4.1. Preparation

Mindful of these problematic side reactions, there are several methods for preparing *o*-quinols resembling **8** (Figure 31). These include (1) oxidation of the *ortho*-alkylated phenol **121** in the presence of an oxygen nucleophile; (2) oxidation of the *ortho*-alkoxy phenol **10** in the presence of a carbon nucleophile; (3) [4 + 2] cycloaddition of an oxy-diene to an *o*-quinone methide, such as **123**; (4) single addition of a carbon nucleophile to an *o*-quinone, such as **12**; and (5) rearrangement of an aryl ether **122**. In addition, transition metal carbene-mediated couplings and carbon-insertion processes have been used to a limited extent.[65,66] Among these processes, the prevailing method usually involves oxidation of **121** with intramolecular delivery of a oxygen nucleophile. Pinhey[10] and Thomas[67] have independently investigated the mechanism of the Wessely[68] oxidation of electron-rich *o*-alkylated phenols. Both agree that it involves an intramolecular oxidative delivery of acetate from an intermediary $ArOPb(OAc)_3$ complex. However, when conducted in nucleophilic solvents, such as methanol, the *ortho* delivery can be thwarted. In addition to these preparative methods, the spiroepoxy subset of *o*-quinols **125** can be procured through a Becker−Adler oxidation of an *o*-hydroxybenzyl alcohol, such as **124**.[69] This subset of *o*-quinols, which was recently reviewed,[70] has proven to be of tremendous synthetic importance.[55,56a,69,71]

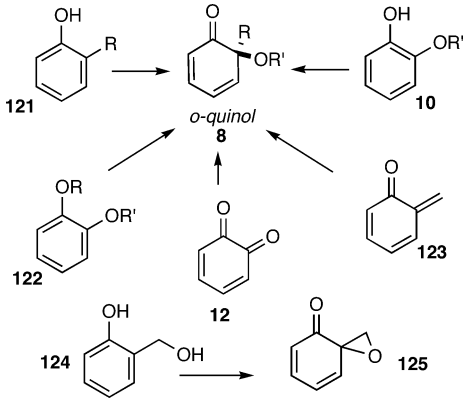



**Figure 31.** Strategies for preparing *o*-quinols and their derivatives.

Bhatt reports that oxidation of **126** with LTA affords the *o*-quinol derivative **127** as the major product (Figure 32). Other products resulting from allylic transposition of the −OAc are also produced. The yield of the *p*-oxidation product increases as the size of the substituent *ortho* to the phenol increases. Replacement of the methyl group with a *t*-butyl substituent leads predominantly to the *p*-quinone product along with minor amounts of the *o*-quinol.[72]

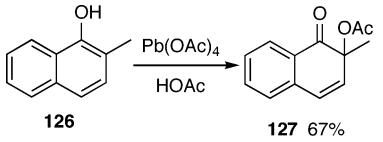



**Figure 32.** Oxidation of an *o*-alkylated phenol with LTA.

Barton has compiled a study on the reactivity of phenols with benzeneseleninic anhydride (BSA).[73] As with LTA, BSA favors an intramolecular *o*-delivery mechanism. Both Meyers[74] and Jeffs[75] apply BSA in the racemic syntheses of the C-7-methyl ether of lacinilene. For example, addition of BSA to **128** affords the selenium ether **129** that ultimately generates **130** (Figure 33).

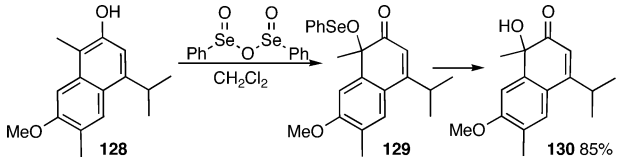



**Figure 33.** Oxidation of an *o*-alkylated phenol with BSA.

Because hypervalent iodide reagents generally favor the formation of *p*-quinol products by an intermolecular mechanism, their application for *o*-quinols has been limited to oxidative cyclizations of molecules containing a tethered functional group. For example, Wood finds that the oxidation of **131** with PIFA affords the transient lactone **132** that undergoes dimerization, affording **133** (Figure 34).[76] Hoshino and Spillings independently report that the *o*-phenolic oxime **134** undergoes an oxidative cyclization, forming **135** upon exposure to PIDA.[77] Bromine substituents were found to improve the overall yield. On the other hand, oxidation of an *o*-hydroxybenzyl alcohol, such as **136** with $NaIO_4$, results in the formation of the spiroepoxycyclohexadienone **113**.[69]

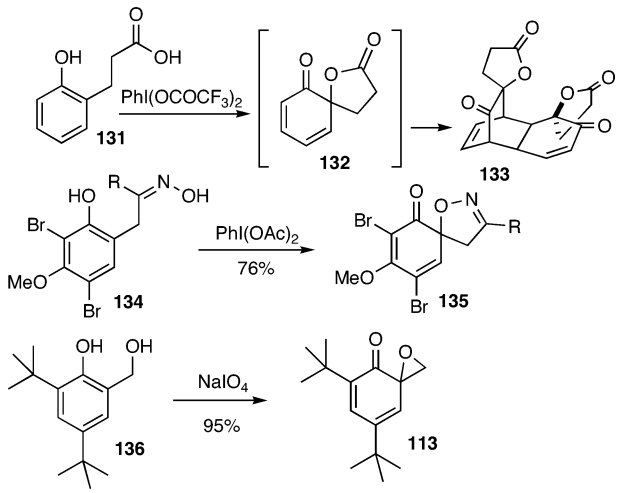



**Figure 34.** Spiro *o*-quinol derivatives formed with hypervalent iodine reagents.

Similarly, DDQ has been used to produce *o*-quinol derivatives from phenols with a nucleophilic tether at the *ortho* position. For example, Giles uses a DDQ-triggered deprotection and oxidation in the synthesis of bikaverin (Figure 35).[78] Upon exposure to DDQ, **137** proceeds to the spirocycle **138** in 61% yield. Kasturi has also utilized DDQ for the preparation of 2,4-cyclohexadienones from 1-(2-hydroxybenzyl)-2-naphthols,[79] and there are reports that $K_3Fe(CN)_6$[80] and KOBr[81] are equally effective with these substrates.

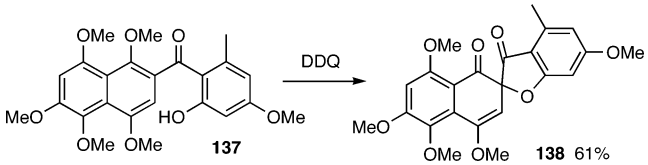



**Figure 35.** DDQ oxidation leading to a spiro *o*-quinol derivative.

*o*-Quinols and their corresponding hydroperoxides are generated from *o*-alkylated phenols upon treatment with bases in the presence of oxygen, a hydroperoxide, or $KO_2$.[63a,b,82] Among these reactions, *tert*-butyl hydroperoxide (TBHP) has the most success as an oxidant and is usually employed in combination with a transition metal. For instance, Krohn reports that Zr, Ti, and Mo species can catalyze the formation of naphthols **140** and **141** from **139** in the presence of stoichiometric TBHP (Figure 36).[83] The ratio of **140**/**141** depends on the metal species chosen.

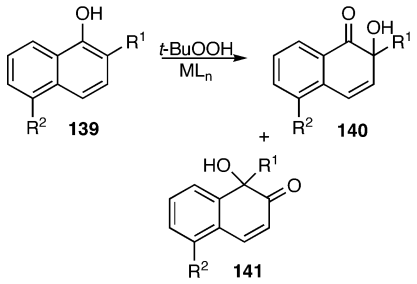



**Figure 36.** Metal-catalyzed hydroperoxide oxidation leading to *o*-quinols.

With regard to the introduction of an alkyl residue during the oxidative dearomatization, this is accomplished by either an intermolecular process initiated with an $I^{iii}$ reagent, or in an intramolecular reaction with a $Pb^{iv}$ or $Bi^{iii}$ reagent. For example, Quideau reports that oxidation of **142** with $PhI(OCOCF_3)_2$ in the presence of an allylsilane results in the formation of **144** in 69% yield (Figure 37).[33,84] The reaction most

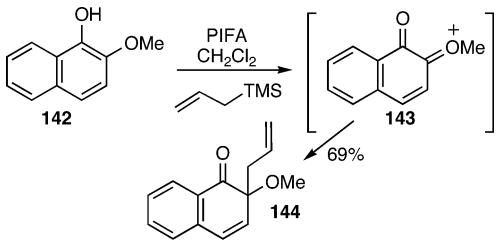



**Figure 37.** Nucleophile addition during PIFA oxidation of an *o*-alkoxyphenol.

likely proceeds via the cationic intermediate **143**.

Pinhey demonstrated the alternative delivery method, in which the carbon substituent is delivered in an intramolecular fashion.[85] For example, when an alkyl $Pb^{iv}$ reagent is mixed with the phenol **142**, a ligand exchange occurs to afford intermediate **145**, which then undergoes oxidative alkyl delivery. The $Pb^{iv}$ is simultaneously reduced to $Pb^{ii}$ as the cyclohexadienone **146** forms (Figure 38).

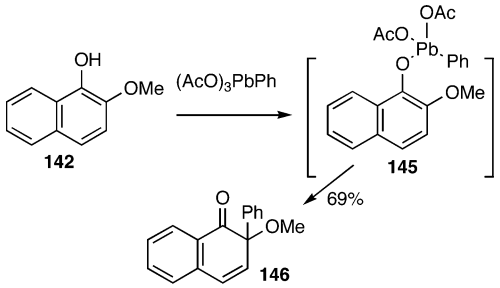



**Figure 38.** $Pb^{iv}$ ligand delivery during oxidation of an *o*-alkoxyphenol.

Yamamura has investigated the electrochemical oxidation of *o*-alkoxyphenols in the presence of assorted enol ethers (Figure 39).[86] Oxidation of **147** at a Pt anode in the presence of ethyl vinyl ether **148** affords a mixture of cyclohexadienone **149** and **150.** The *o*-quinol product **150** and its corresponding diethyl acetal are the major products. This result is somewhat surprising in view of a similar study by Pattenden, which found that electrochemical oxidation of *o*-alkoxyphenols in the presence of carbon nucleophiles favors *p*-quinols, whereas $Pb^{iv}$ organometallic reagents afford *o*-quinols through intramolecular delivery mechanisms.[87]

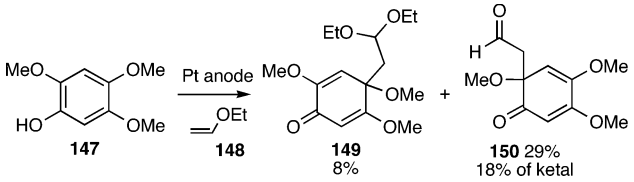



**Figure 39.** Nucleophile addition during anodic oxidation of an *o*-alkoxyphenol.

Barton finds that dichlorocarbene can be used to produce an *o*-quinol system, which ultimately furnishes a tropolone skeleton (Figure 40).[88] For example, addition of dichlorocarbene to phenol **151** affords the *o*-quinol ether **152**. Subsequent radical

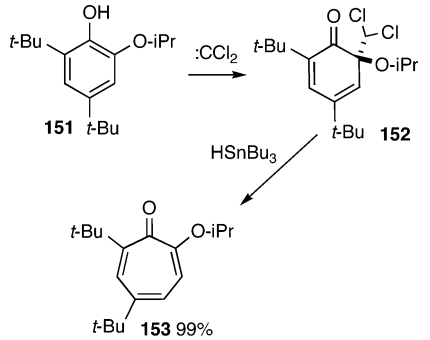



**Figure 40.** Oxidation of an *o*-alkoxyphenol with dichlorocarbene followed by ring expansion.

reduction of dichloride **152** with $Bu_3SnH$/AIBN affords the tropolone **153** in nearly quantitative yield.

There are several examples in which an *o*-quinone methide participates in a Diels−Alder reaction to generate an *o*-quinol derivative. For instance, Suzuki finds that generation of the *o*-quinone methide **154** leads to a Diels−Alder reaction producing the dimer **155** in 86% yield (Figure 41).[89] If an excess of another alkene is present, then the *o*-quinol dimer does not form. Kasturi,[90] McNelis,[91] Solomon,[92] and Habicher[93] have reported similar observations.

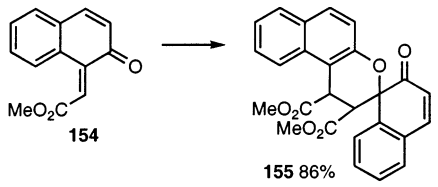



**Figure 41.** [4 + 2] Dimerization of an *o*-quinone methide affords *o*-quinol derivative.

*o*-Quinones produce *o*-quinols upon [4 + 2], [3 + 2], and [2 + 2] cycloadditions as well as by 1,2-additions involving one of the carbonyl functionalities. For example, Fillion reports that the 2-azadiene **157** undergoes a cycloaddition with the *o*-quinone **156** to afford the intermediate spirocycle **158**, which hydrolyzes to form the *o*-quinol **159** in 70% yield (Figure 42).[94] Surprisingly, if the diene **157** is replaced with a less nucleophilic diene, then the [4 + 2] reaction proceeds with the enone olefin rather than the carbonyl residue. Desimoni finds similar *o*-quinones undergo related [4 + 2] cyloadditions.[95]

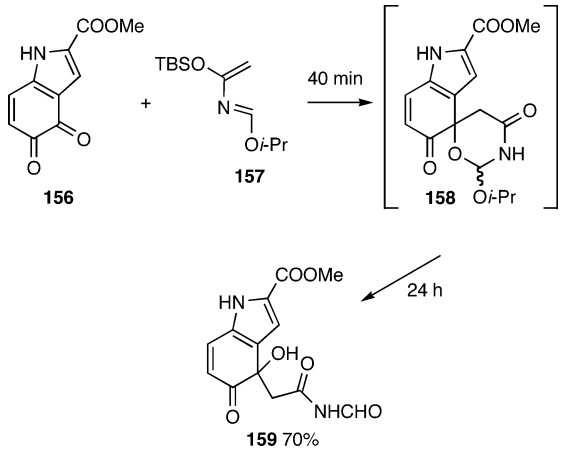



**Figure 42.** [4 + 2] Cycloaddition of an *o*-quinone carbonyl provides an *o*-quinol.

Nair and others find that *o*-quinones participate in [3 + 2] cycloadditions.[96] For instance, the ylide **161** to the *o*-quinone **160** results in the formation of the [3.2.1]-bicycloadduct **162** in 76% yield (Figure 43). Other examples involve the addition of an initiator, such as cyclohexyl isocyanide or $PPh_3$, to dimethyl acetylene dicarboxylate, followed by a [3 + 2] cycloaddition with a carbonyl of an *o*-quinone.[97]

Kim and others have used a Paterno−Buchi [2 + 2] cycloaddition for the construction of *o*-quinol derivatives.[98] The oxabutane products are of interest because of their spectroscopic properties. Kim reports that the phenanthraquinone **163** and diene **164**

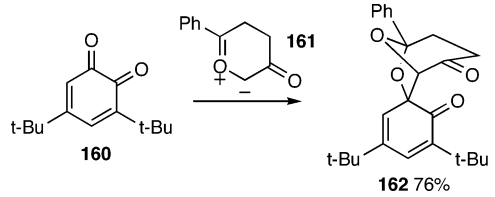



**Figure 43.** [3 + 2] Cycloaddition onto carbonyl of an *o*-quinone affords *o*-quinol derivative.

afford the cycloadduct **165** in 68% yield (Figure 44). The regioselectivity of this and related [2 + 2] cycloadditions is often rationalized with regard to the stability of a hypothetical biradical intermediate. Enols procured from 1,3-diketones undergo related [2 + 2] cycloadditions with *o*-quinones;[99] however, in some instances, a [4 + 2] cycloaddition occurs instead to produce the corresponding dihydrodioxane.[100]

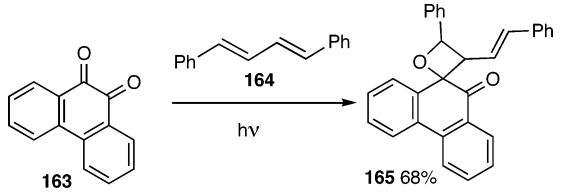



**Figure 44.** [2 + 2] Cycloaddition onto carbonyl of an *o*-quinone affords *o*-quinol derivative.

Not surprisingly, the 1,2-addition of nucleophiles to *o*-quinones is a powerful tool for the construction of *o*-quinols. For instance, Moore finds that the *o*-quinone **166** undergoes a 1,2-addition with lithioacetylide **167**, resulting in adduct **168** (Figure 45).[101] Similar 1,2-additions have been reported with allyl indium and tin species[102] and *t*-BuMgCl,[103] as well as aluminum, cadmium, and zinc reagents.[104]

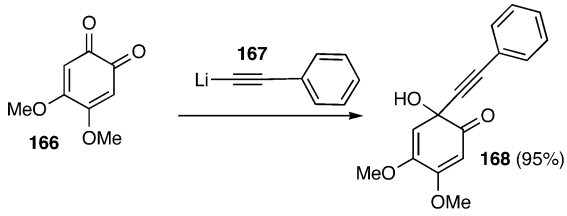



**Figure 45.** 1,2-Addition of a carbon nucleophile to an *o*-quinone affords an *o*-quinol.

In a related 1,2-addition, Lee finds that upon chromatography, the *o*-quinone **169** undergoes an aldol reaction with acetone to produce the *o*-quinol **170** (Figure 46).[105] This reversible transformation is thought to be critical in the role of some *o*-quinone

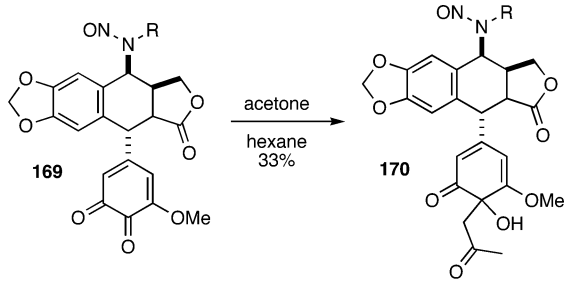



**Figure 46.** Aldol addition to an *o*-quinone affords an *o*-quinol.

cofactors, such as methozatin, which acts as a dehydrogenase.[106]

Suzuki reports a novel Darzens reaction between a carbonyl of the symmetric *o*-quinone **163** and the α-bromo ketone **171**. The reaction affords the quinol epoxide **172** (Figure 47).[107] In a related reaction, the trifluoromethyl anion was found to undergo reaction with the *o*-quinone phenanthraquinone to give a TES-protected *o*-quinol bearing a trifluoromethyl residue.[108]

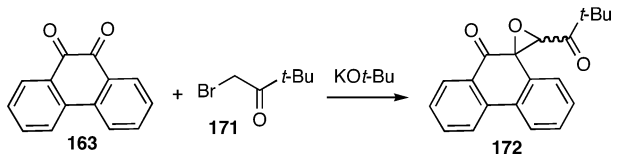



**Figure 47.** Darzens reaction with an *o*-quinone affords an *o*-quinol spiroepoxide.

A rarely used procedure for preparing *o*-quinols involves the addition between an electrophile and an electron rich phenol. In general, the process is only useful if the aromatic nucleophile contains at least three hydroxy residues. For example, Sato reports that deprotonation of the tetraphenol **173** with NaH in the presence of MeI affords the *o*-quinol **174** (Figure 48).[109] This compound serves as an intermediate in the synthesis of the carthamin model **175**.

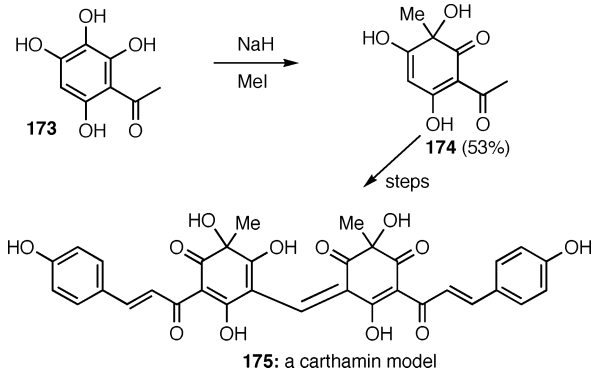



**Figure 48.** C-Alkylation of a catechol leads to an *o*-quinol.

In some cases, [3,3]-, [2,3]-, and [1,3]-rearrangements proceed to the corresponding *o*-quinol products; however, the aromatic nucleus usually contains several electron-donating residues. For example, Danishefsky reports that the highly oxygenated aromatic compound **176** undergoes a Claisen rearrangement (Figure 49).[2,110] Because of steric restrictions, the *o*-quinol product **3** does not undergo the anticipated Cope rearrangement to restore aromaticity. Instead, **3** undergoes a Snider radical cascade with $Mn(OAc)_3/Cu(OAc)_2$ to ultimately provide tricycloillicinone (**1**).

Yamauchi reports that the reaction of phenol **177** in the presence of the electrophilic Corey−Kim reagent **178** generates the intermediate **179**. This species then undergoes a [2,3]-sigmatropic rearrangement to give the methyl sulfide **180** in 90% yield, as shown in Figure 50.[111] The same product is obtained when **177** is treated with a mixture of DMSO, pyridine, and $SO_3$.[112]

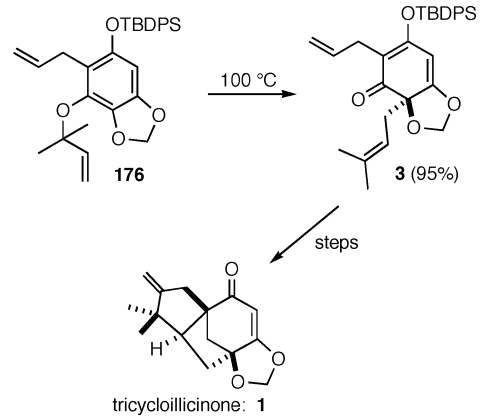



**Figure 49.** [3,3]-Sigmatropic rearrangement within a bis-etherificated catechol affords an *o*-quinol.

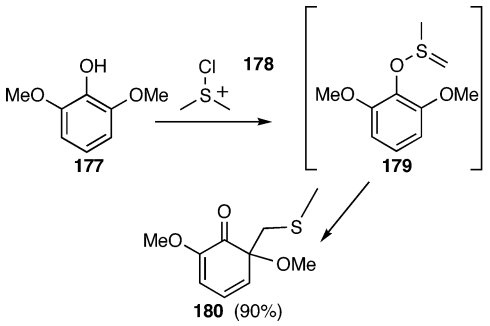



**Figure 50.** [2,3]-Sigmatropic rearrangement leads to an *o*-quinol.

Sutherland finds that the zwitterion **182**, produced by addition of allyl bromide to **181**, undergoes an initial [2,3]-rearrangement to give the transient species **183**, which then suffers a rapid [1,5]-shift, resulting in **184** (Figure 51).[113]

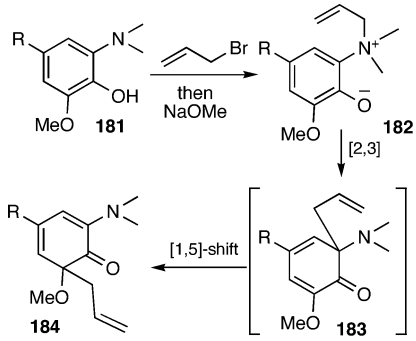



**Figure 51.** A [1,5]-shift within an appropriately substituted phenoxide affords an *o*-quinol.

A surprisingly facile [1,3]-sigmatropic resulting in dearomatization has been observed by Bolton under mild conditions (Figure 52).[114] Mild heating of the benzyl-protected phenol **185** triggers an intramolecular migration of the benzyl group and produces the cyclohexadienone **186** in high yield.

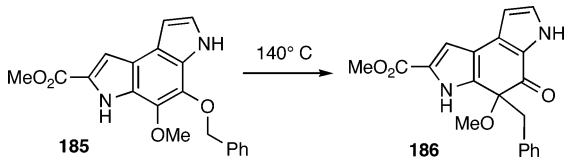



**Figure 52.** Thermal-induced [1,3]-sigmatropic shift within a bis-etherificated catechol affords an *o*-quinol.

## 4.2. Reactions

*o*-Quinol derivatives undergo an array of transformations, including acid-catalyzed rearrangements and nucleophilic displacements that result in rearomatization. In addition, *o*-quinols undergo diastereoselective 1,2-additions, epoxidations, dihydroxylations, Diels−Alder reactions, and a variety of photochemical transformations. Despite these many uses, the implementation of *o*-quinols and their derivatives in total synthesis has been limited, perhaps due to their propensity toward dimerization.

With regard to acid-catalyzed rearrangements of *o*-quinols, Van Dongen reports that exposure of **187** to $HSbCl_6$ affords the rearomatized product **188** through acetoxy migration (Figure 53).[52b] Pattenden observes a similar rearrangement with TFA.[87] However, if the substrate **187** is treated with 50% sulfuric acid, both acetoxy and methyl migrations transpire to deliver compounds **189** and **190** after ester hydrolysis.[52b] Because of its substitution, Moore finds that **168** participates in a Ferrier-type of rearrangement upon treatment with acid to afford the cation **191**, which hydrolyzes to produce **192**.[101]

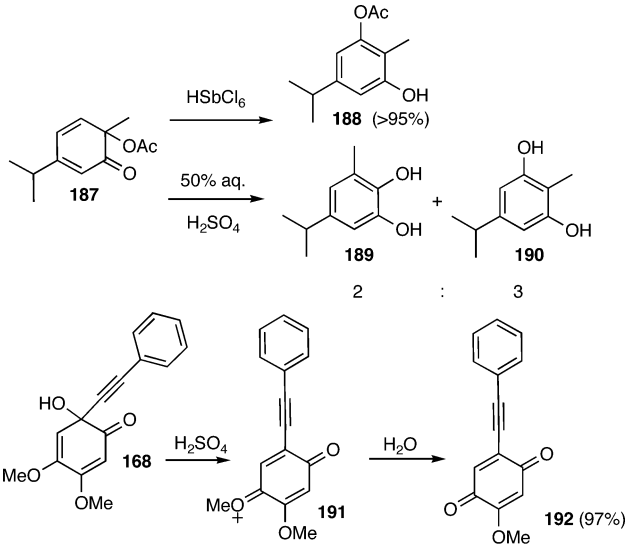



**Figure 53.** Acid-catalyzed dienone rearrangement results in rearomatization.

For the synthesis of illicinone, Danishefsky reports that a diastereoselective 1,2-reduction of **3** with L-selectride occurs to afford **193** upon acetylation (Figure 54).[2,110] This diene suffers elimination affording illicinone (**194**) in 65% yield upon sequential treatment with TBAF and DBU.

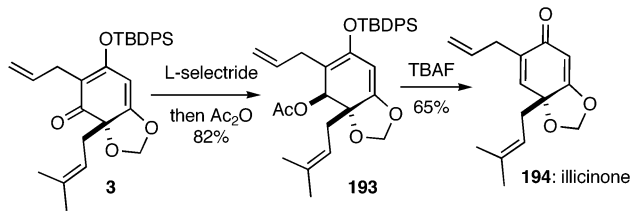



**Figure 54.** 1,2-Additiion of hydride to an *o*-quinol ether.

Carbon nucleophiles also participate in diastereoselective 1,2-additions with the carbonyl of *o*-quinol compounds. Danishefsky reports that addition of the

lithium amide to the aldehyde **195** masks this aldehyde functional group and allows the subsequent treatment with lithiodiacetylide, which results in the tertiary alcohol **196** upon workup (Figure 55).[115] This reaction proved useful for the total synthesis of calicheamicinone.[116]

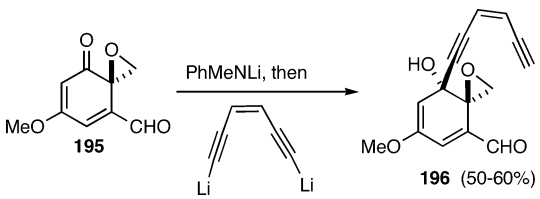



**Figure 55.** 1,2-Addition of organolithium to an *o*-quinol derivative.

In stark contrast to other *o*-quinol derivatives, *o*-quinol acetates undergo 1,4- and 1,6-additions with Grignard reagents. Wessely reports that this reactivity can be harnessed to produce phenols with various alkyl groups in the meta position (Figure 56).[67b−e,117] For example, the 1,4-addition of PhMgBr to **197** proceeds to magnesium enolate **198**, which furnishes **199** upon acidic workup. Miller subsequently investigated the reactions and found that transformation was limited to aryl- and secondary alkyl Grignard reagents.[118]

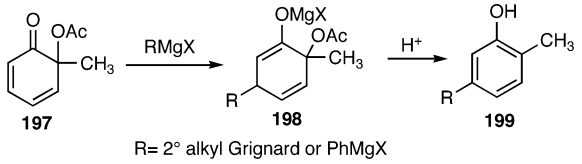



**Figure 56.** 1,4-Addition of a Grignard reagent to an −OAc *o*-quinol derivative.

There are several examples in which a tertiary *o*-quinol acetate appears to participate in a $S_N2$ reaction. For instance, the intermediate acetate **200**, which is produced by Wessely oxidation of the corresponding phenol, undergoes a $S_N2$ like displacement resulting in the lactone **201** in a 74% yield (Figure 57).[119] Compound **201** was ultimately converted into the core of lactonamycin. This intermediate was subsequently converted into the core of lactonamycin.

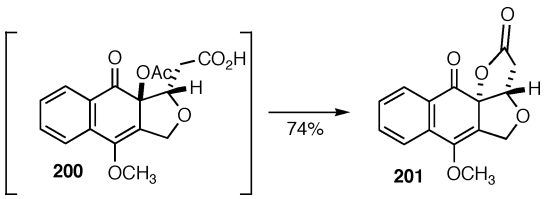



**Figure 57.** $S_N2$-like displacement of an acetylated *o*-quinol.

A similar $S_N2$ displacement occurs with strained oxetane *o*-quinol derivatives (Figure 58).[120] In this example, the initial *o*-quinol derivative **202** undergoes ring opening with a primary amine to produce the *o*-quinamine **203**. The amine moiety then adds the adjacent carbonyl, forming the aziridine **204**, which then undergoes fragmentation to produce **205** and ultimately the azopinone **206** upon protonation.

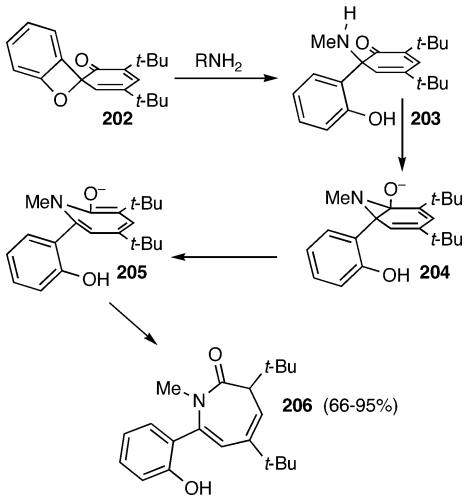



**Figure 58.** $S_N2$-like displacement of a strained *o*-quinol ether, leading to an azopinone.

Ponpipom reports what appears to be an allylic displacement of a 1:1 epimeric ratio of *o*-quinol acetates **208α** and **209*β***, formed by *ortho* oxidation of **208** with LTA (Figure 59).[121] The 1:1 ratio observed in this reaction with products **210α**/**211*β*** supports the idea that initial *ortho* oxidation of **207** by LTA is not diastereoselective, whereas the subsequent allylic displacement of the two acetates **208α**/**209*β*** probable proceeds in stereospecific fashion. Interestingly, oxidation of **207** with other reagents that favor *para* oxidation proceed in a stereoselectivity fashion. Bis-allylic displacements of related dienyl acetates with nitrogen and sulfur nucleophiles have been reported that result in similar aromatic materials.[122]

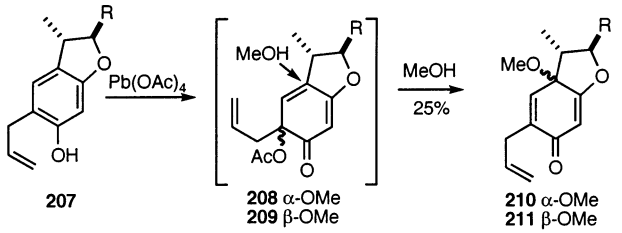



**Figure 59.** $S_N2'$ and bis-allylic acetate displacements of an acetylated *o*-quinol.

Moore finds that the *o*-quinol **168** undergoes bis-allylic displacement upon the addition of thionyl chloride, resulting in the chlorinated phenol **212** (Figure 60).[101]

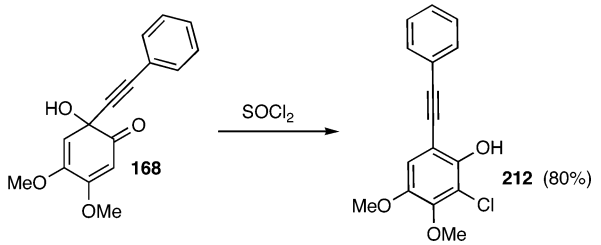



**Figure 60.** Bis-allylic displacements of an *o*-quinol with chloride.

Kurosawa finds that the 3-(2-hydroxyphenyl)coumarin **213** participates in a related displacement (Figure 61).[123] Oxidation of **213** with LTA affords **214**

in 16% yield. When this product is warmed, it undergoes a Nazarov-type reaction to furnishing **215** in 22% yield.

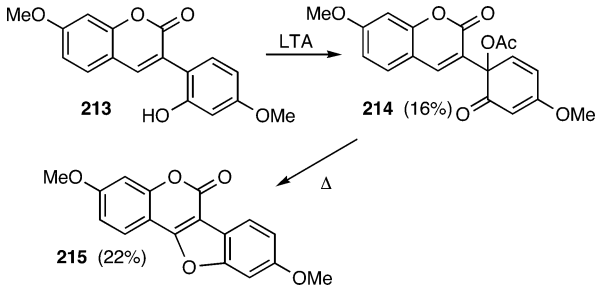



**Figure 61.** An allylic displacement of an acetylated *o*-quinol, leading to a furan derivative.

In regard to diastereoselective epoxidations, Danishefsky demonstrated an elegant example while exploring the synthesis of the lactonamycin core.[119] Subjection of quinol derivative **201** to dimethyldioxirane affords the expected alcohol **216** with undesired stereochemistry (Figure 62). Epoxidation of the quinol **217** with trifluoroperacetic acid, however, occurs via intramolecular delivery in Henbest format to produce the desired stereoisomer **218** in a 20:1 mixture. Similar diastereoselective epoxidations of naphthoquinols have also been reported.[124]

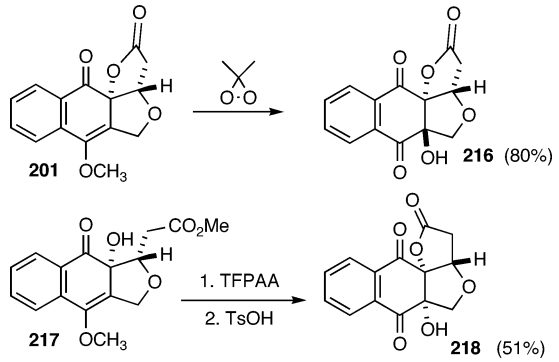



**Figure 62.** Diastereoselective epoxidation of an *o*-quinol and its spirocyclic acetylated derivative.

*o*-Quinols participate in dihydroxylation reactions. However, the *o*-quinol acetate **219** upon dihydroxylation with osmium tetroxide affords a 1:1 mixture of **220** and **221** (Figure 63).[125]

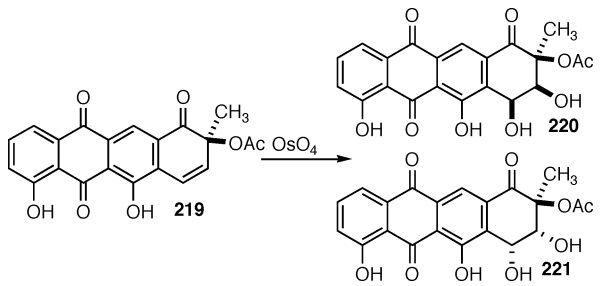



**Figure 63.** Dihydroxylation reaction of an *o*-quinol acetate.

Intermolecular Diels−Alder reactions have been observed with several *o*-quinol derivatives; however, it is important that the dienophile be present upon formation of the *o*-quinol to avoid its dimerization. For instance, if the highly reactive dienone **180** is generated in the presence of a dienophile [EWGCH=$CH_2$], then the [2.2.2]-bicycloadduct **222** arises (Figure 64).[111] Photochemical treatment of **222** with a Pyrex filter affords the cyclopropane product **224**, presumably through the intermediary cyclobutanone **223**.

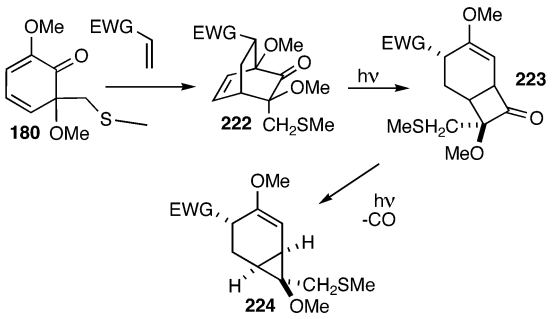



**Figure 64.** A diastereoselective Diels−Alder reaction of an *o*-quinol ether.

Van Dongen reports that *o*-quinol acetate derivatives are far less prone to dimerization. Moreover, ring substituents, particularly $\beta$ to the carbonyl, further decrease the reactivity of these −OAc *o*-quinol derivatives.[52b] For example, vigorous conditions are required for the union of maleic anhydride **225** with diene **187** (Figure 65). The cycloaddition requires 28 days of refluxing in a mixture of chloroform and ethanol to yield **226**. Singh and Farina have noted similar results with cyclopentadiene **229**.[122,126]

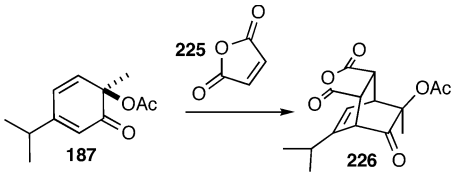



**Figure 65.** A diastereoselective Diels−Alder reaction of an *o*-quinol acetate.

Spiroepoxy cyclohexadienones undergo [4 + 2] reactions as either dienophiles or dienes. The product emerging from the reaction often depends on the nature of the other reacting component (Figure 66).[56a,127] For example, the spiroepoxide **125** undergoes reaction as a diene with excess ethyl vinyl ether **148** to furnish adduct **227** in 22% yield along with the dimer **228**. A similar outcome is noted when electron-rich ketene acetals are used in place of EVE (**148**).[128] With cyclopentadiene **229**, however, **125** participates as the 2$\pi$ component to afford **230** in a

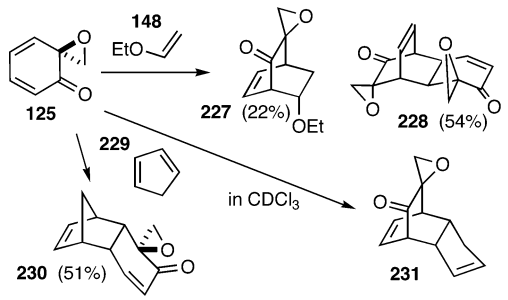



**Figure 66.** Diastereoselective normal and inverse-demand Diels−Alder reactions of *o*-quinol spiroepoxides.

51% yield. Interestingly, in $CDCl_3$, compound **231** arises from combination of **125** and **229**.

Yates reports another example of this bimodal reactivity of *o*-quinol derivatives in tandem Wessely oxidation/Diels−Alder processes, leading to the construction of twistanes, isotwistanes, and homoisotwistanes (Figure 67).[129] Treatment of phenol **232** and **233** with LTA affords the *o*-quinol acetates **234** and **235**, respectively. These adducts readily undergo [4 + 2]-cycloadditions in refluxing toluene to produce compounds **236** when X = O and **237** when X = 2H.

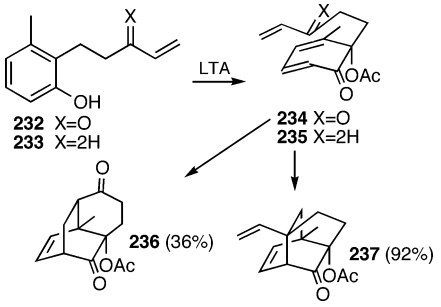



**Figure 67.** Successive formation and intramolecular [4 + 2] cycloadditions of *o*-quinol acetates.

With regard to useful photochemical applications, *o*-quinol derivatives can serve as a precursor to $\epsilon$-ketoesters (Figure 68). Schultz was among the first to investigate this ring opening.[130] For example, photolysis of **105** at 340 nm results in the ketene **238**, which is intercepted by methanol to produce **239**. Snider used this sequence quite effectively in a synthesis of xestin A and B.[131] Subsequent acetate cleavage with methoxide produces the enone **240.** Quinkert has used a similar sequence for intramolecular lactonization in a synthesis of (+)-aspicilin[132] and has developed the complementary photolactamization strategy.[133]

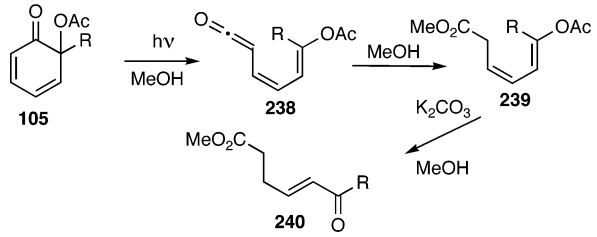



**Figure 68.** Photolytic opening of *o*-quinol acetates in alcoholic solvent.

Sugawara has also investigated the photochemical reactivity of the spirocycle *o*-quinol derivative **241** (Figure 69).[134] Irradiation of **241** affords the transient triene **242**, which undergoes an electrocyclization with loss of $CO_2$ to produce the benzofuran **243**.

## 4.3. Synthetic Applications

Although only a few natural products have been constructed exploiting *o*-quinol derivatives, the diversity among these structures is quite impressive. Examples include calicheamicinone, ovalicin, the sorbicillinoids, and aerothionin.

Danishefsky reported the total synthesis of calicheamicinone (**82**) (Figure 70).[135] The synthesis commences with a Becker−Adler oxidation of **244**, followed by oxidation of the remaining alcohol with Dess−Martin reagent to afford the spiroepoxide **245**. After masking the aldehyde with a lithioamide, the ketone undergoes a diastereoselective intramolecular 1,2-addition of a lithium acetylide to generate **246**. This intermediate is then transformed through a short series of steps into calicheamicinone (**82**).

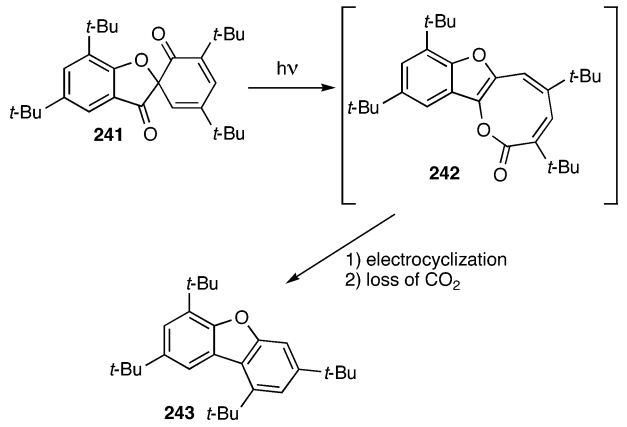



**Figure 69.** Photolysis of a spirocycle *o*-quinol derivative.

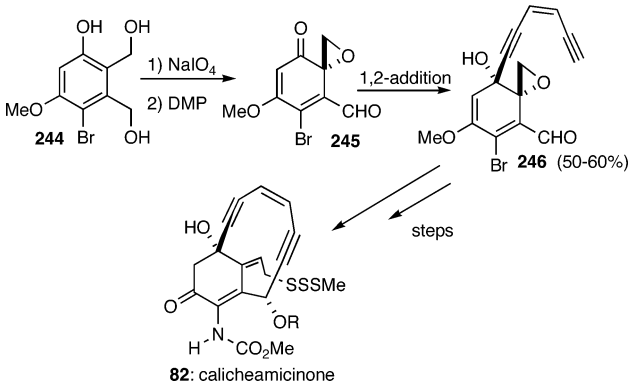



**Figure 70.** Danishefsky synthesis of calicheamicinone.

The Corey synthesis of ovalicin also demonstrates the synthetic power of the spiroepoxide *o*-quinol derivatives (Figure 71).[136] Subjecting compound **247** to $NaIO_4$ generates the spirocyclohexadienone **248** in 61% yield. Reduction of **248** with diimide overcomes the reductive rearomatizations that often plague these types of systems and affords the desired epoxide **249** in 77% yield. Addition of an unusual vinyllithium reagent to the carbonyl group occurs in a diastereoselective fashion, resulting in **250**. Subsequent functional group manipulations provide ovalicin (**251**).

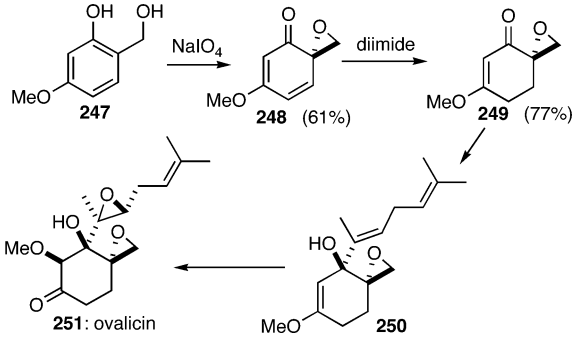



**Figure 71.** Corey synthesis of ovalicin.

Spilling completed a formal synthesis of aerothionin (**254**) and homoaerothionin (**255**) by using a polymer-supported (diacetoxyiodo)benzene (PSDIB) reagent for oxidation of the phenol **252** (Figure 72).[77b] The polymer-supported reagent proves beneficial because the dienone **253** readily degrades upon chromatography. Polymer-supported reagents simplify chromatographic purification, which others have noted as problematic, and are required when nonpolymeric oxidants are applied to **252**.[137]

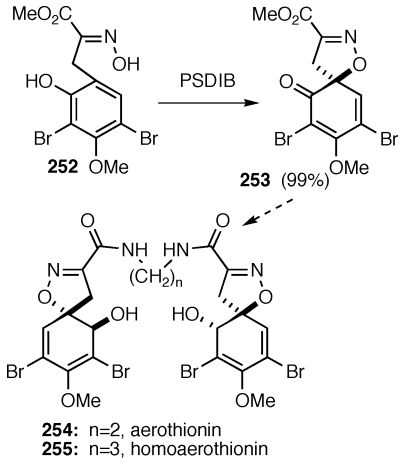



**Figure 72.** Spilling synthesis of aerothionin and homoaerothionin.

Trichodimerol (**262**), an α-TNF inhibitor, has been synthesized by Abe,[138] Corey,[139] and Nicolaou (Figure 73).[140] The key transformation in the latter two routes is oxidation of the more acidic phenol in **256** with LTA, resulting in the *o*-quinol acetate derivative **257**. Both Corey and Nicolaou find that hydrolysis of **257** under near neutral conditions affords **262**, presumably through a series of conjugate additions involving intermediate **260**, which results in the bis-Michael adduct **261**, which in turn undergoes two hemiketalizations. The Nicolaou group has also reported a synthesis of bisorbicillinol **259** by hydrolysis of **257**, followed by subsequent acidification. Under these conditions, a [4 + 2] cycloaddition ensues between the tautomers shown in **258**.[140] In view of these findings and the work of Abe, it appears that neither **259** nor **262** is a natural product, but probably emerges during isolation of the *o*-quinol sorbicillinol.[142]

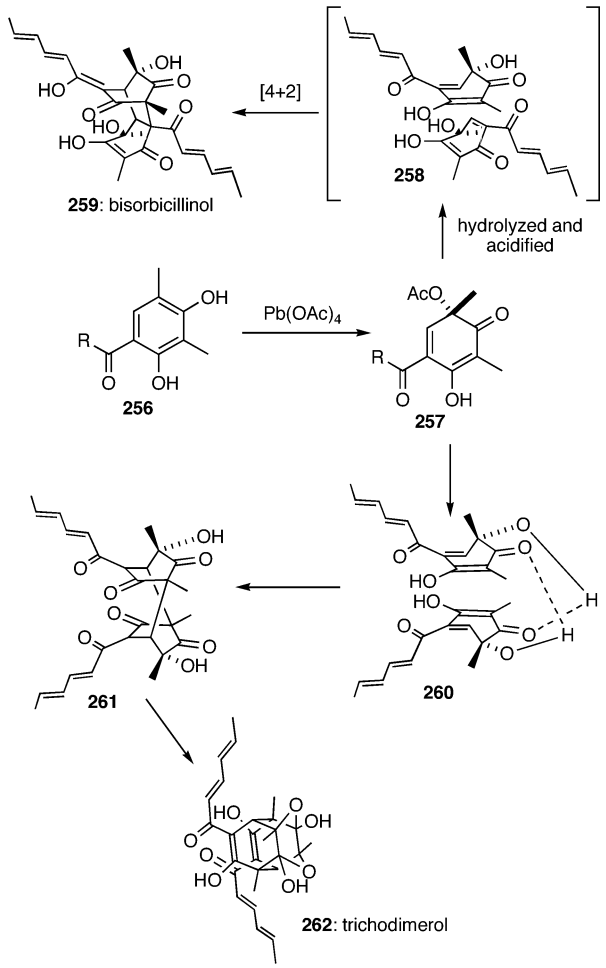



**Figure 73.** Nicolaou synthesis of trichodimerol and bisorbicillinol.

Danishefsky reports an interesting radical cascade starting from the *o*-quinol derivative in the synthesis of tricycloillicinone (Figure 74).[2] Specifically, treatment of the *o*-quinol derivative **3** with $Mn(OAc)_3$/$Cu(OAc)_2$ affords the tetracycle **2** in 80% yield. This material was ultimately converted into tricycloillicinone **1** by erasure of the carbonyl group through reduction and subsequent Barton deoxygenation.

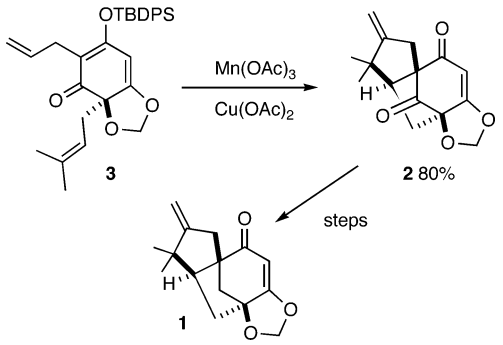



**Figure 74.** Danishefsky synthesis of tricycloillicinone.

## 4.4. Enantioselective Horizons

Currently, there are only a few methods available for either diastereoselective or enantioselective preparation of *o*-quinol building blocks, such as **8**. However, in view of the many racemic syntheses that have utilized these intermediates, enantioselective access to *o*-quinol derivatives would be tantamount to enantioselective syntheses of many important natural products (see Figure 75).

With regard to the preparation of *o*-quinols by fermentation or enzymatic processes, two methods have been described. Using an unspecified soil bacterium, Breitmaier reports that the oxidation of 2,6-xylenol **263** results in the Diels−Alder adduct **265** ($[\alpha_D] = +39$); a dimer of the presumed *o*-quinol intermediate **264** (Figure 76).[141] Coincidently, Pettus finds that treatment of **263** with IBX affords **265** in racemic fashion.[142]

Myers demonstrated an enantioselective route to *o*-quinol derivatives (Figure 77).[143] He reports that benzoic acid **266** undergoes a 1,2-dihydroxylation

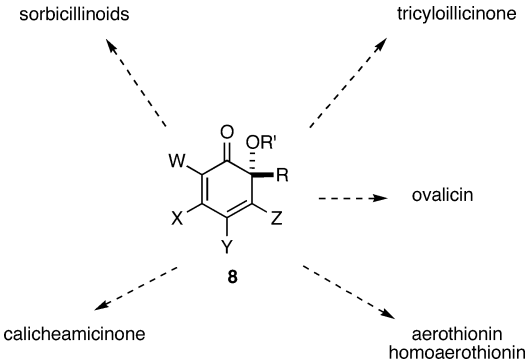



**Figure 75.** Potential of *o*-quinol derivatives for asymmetric synthesis.

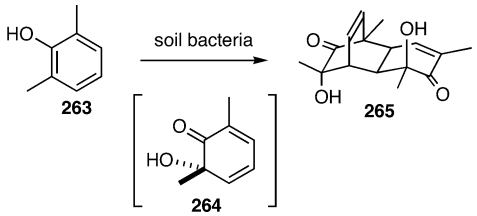



**Figure 76.** Enzymatic oxidation of an *o*-alkylated phenol leading to an *o*-quinol derivative.

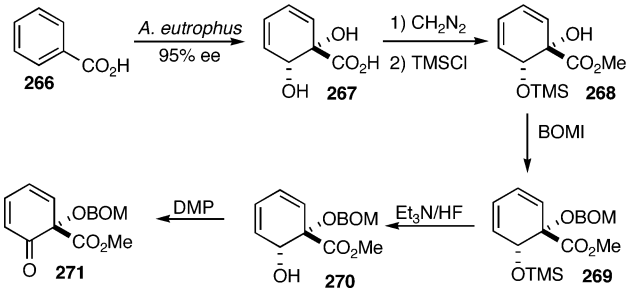



**Figure 77.** Enzymatic dihydroxylation following five-step synthetic sequence leads to *o*-quinol derivative.

with *Alcaligenes eutrophus*-B9 to create diol **267**. Methylation and silylation affords **268**. The tertiary alcohol is protected with BOMI to produce **269**. The silyl residue is then cleaved with buffered HF to afford **270**. Oxidation with Dess−Martin reagent converts this material into the *o*-quinol derivative **271** in 95% *ee*.

Tius reports a diastereoselective formation of a spiroepoxide through the Becker−Adler reaction (Figure 78).[71b] Treatment of differently substituted naphthols **272**−**275** with $NaIO_4$ affords the corresponding diastereomeric spiroepoxides in varying yields. Compounds **279**−**281** are the major diastereomers and **276**−**278** are the minor ones. As the size of the R substituent increases, the yields and the diastereoselectivity decrease. Compound **279** (R = −Me) undergoes addition of methyllithium to furnish compound **282**, which undergoes a Payne rearrangement to produce **283**.

Another example of a diastereoselective oxidative dearomatization is seen in the oxidation of naphthol **284** with PIDA (Figure 79).[144] The spirocycle **285** forms as the sole product in 85% yield. However, when HOBr is used as the oxidant, the opposite diastereomer **287** is produced. This reversal is attributed to a change in mechanism. For the first transformation, it is suggested that the iodine atom

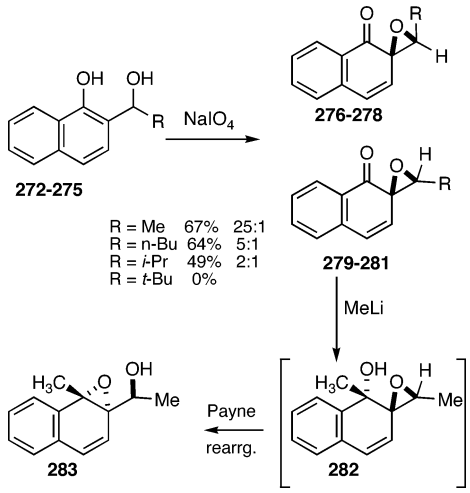



**Figure 78.** Diastereoselective 1,2-addition of an organolithium to an *o*-quinol spiroepoxide.

in PIDA coordinates to the two-hydroxyl groups of the substrate, and a phenol then dissociates and adds to the neighboring cation with least motion. In the case of the hypobromite oxidation, the bromine atom appears to add through an intramolecular delivery to create **286**. Subsequent $S_N2$ displacement delivers **287** in 98% yield.

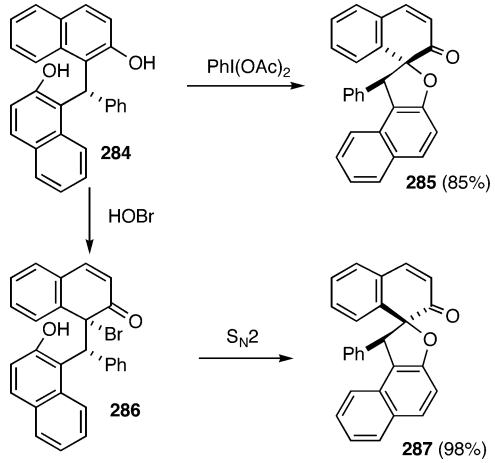



**Figure 79.** Diastereoselective oxidative dearomatizations leading to *o*-quinol derivatives.

To the best of our knowledge, there is only one example in which a chiral auxiliary is employed in an oxidative cyclization reaction to produce an enantiomerically enriched product (Figure 80).[77d] The strategy entails use of a chiral ester to control the diastereoselectivity of an intramolecular cyclization. Treatment of oxime **288** with one of several hypervalent iodine reagents affords the spiroisooxazoline **289**. It is interesting to note that the conditions had such a surprising effect on the diastereoselectivity of the reaction. The greatest *de* is observed with a mixture of PhIO/(−)-CSA.

It should be evident that developing a reliable enantioselective method for preparing nonracemic *o*-quinol derivatives is a challenging task. However, from the preceding discussion, the problem appears solvable and obviously has many ramifications within the context of enantioselective total syntheses.

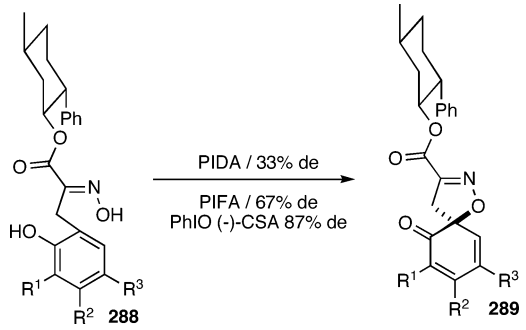
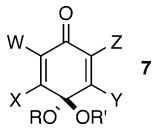



**Figure 80.** Asymmetric oxidative dearomatization of an oxime leading to a *o*-quinol derivative.

### 5. MPB Ketal Building Blocks (7)




Of the four types of cyclohexadienones that contain a heteroatom at the $sp^3$-hybridized site within the six-membered ring system, the MPB ketal (**7**) is undoubtedly the best studied and most exploited. Masked *para* benzoquinone ketals are usually prepared by oxidative dearomatization with hypervalent iodide reagents or by ketalization of *p*-quinones. The subsequent chemistry of MPB ketals is dominated by 1,2- and 1,4-addition reactions, which include carbonyl olefination and enone cyclopropanation. However, additions of some organometallic reagents result in an undesired reductive aromatization via a single electron transfer (SET) mechanism. MPB ketals undergo a variety of desirable annulation reactions, including Michael−Dieckmann, and Diels−Alder reactions, as well [3 + 2]- and [5 + 2]-cycloadditions. As building blocks, these six-membered rings have been successfully applied in the construction of antheridic acid, *C*-glycosides, calicheamicinone, illudine M, members of the manumycin family, miroestrol, and torreyanic acid, as well as for derivatives of abscisic acid, huperzine, and palmarumycin. Their asymmetric potential as nonracemic building blocks has been partially demonstrated by enantioselective syntheses of diepoxin, (*S*)-4-hydroxycyclohexenone, jesterone, and members of the manumycin family, as well as preussomerins.

#### 5.1. Preparation

Several strategies lead to a MPB ketal **7** (Figure 81). These include oxidation of the monoalkoxy material **290** in an alcoholic solvent; double oxidation of the phenol **11** in an alcoholic solvent;[145] oxidation of the *p*-hydroquinone derivative **292** to the bis-ketal **293**,[146] followed by hydrolysis of just one ketal;[147] ketalization of the *p*-quinone **291**;[213a] or transketalization of one MPB ketal **7** for another.[148] Among these, the most popular method is indisputably oxidation of **290** in the presence of a nucleophilic alcohol, such as MeOH. Metal salts, such as $Mn^{ii}$,[149] $Ag^{i}$,[150] and $Ce^{iii}$,[151] as well as electrochemical oxidations[152] afford the desired nucleus with sporadic consistency. Their success largely depends on the structure of the starting phenol. $Tl^{iii}$ salts, especially thallium nitrate (TTN), were among the first reliable oxidants.[22] Büchi subsequently pioneered the implementation of DDQ and $Fe^{iii}$.[153] More recently, Pelter popularized the nontoxic hypervalent iodide reagent $PhI(OAc)_2$ as a reliable replacement for TTN,[154] and Kita demonstrated the superiority of $PhI(OCOCF_3)_2$.[155]

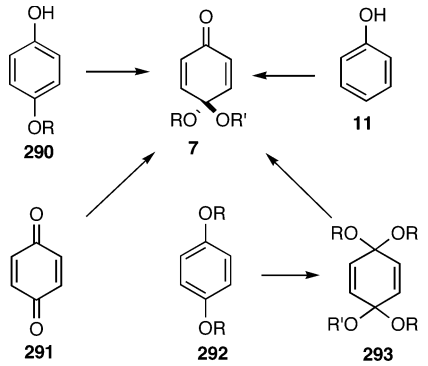



**Figure 81.** Strategies for the preparation of MPB ketal (*7*).

#### 5.2. Reactions

The carbonyl of the MPB ketals undergoes 1,2-additions with a variety of nucleophiles, including organolithium and organocerium reagents, phosphonium ylides, lithium enolates, borohydrides, and amines. The enol functionality of MPB ketals undergoes 1,4-additions with active methylene compounds as well as a variety of other soft nucleophiles. Moreover, organolithiums and Grignard reagents add in 1,4-fashion when the carbonyl first undergoes precomplexation with a bulky Lewis acid, such as methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD). However, all of these 1,2- and 1,4-addition processes are overshadowed by the inclination of the MPB ketal to undergo reductive aromatization. Indeed, Liotta has proposed that MPB ketals are excellent indicators of SET phenomena that readily undergo reductive aromatization upon thermal and Lewis acid treatment.[156]

Swenton has extensively investigated the 1,2-addition of organolithium reagents to dialkoxy *p*-benzoquinone ketals, such as **7**,[30,157] and monosilyloxy ketals, such as **294** (Figure 82).[158] Compound **294** is prepared by selective hydrolysis of the corresponding bis-ketal formed by electrolysis of a 4-trialkylsiloxyanisole in methanol.[159] Organolithium species add smoothly to **294** and produce the corresponding tertiary alcohol **295**, which upon treatment with fluoride leads to the ketone **296**. Although the diastereoselectivity of this 1,2-addition has not been determined, addition on the least hindered face of the

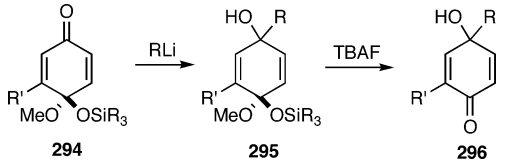



**Figure 82.** 1,2-Addition of an organolithium to a −OTBS mixed MPB ketal.

carbonyl opposite the siloxy substituent is expected. This sequence of events avoids a potential complication that can be imagined with dialkoxy MPB ketals, namely, the dienone rearrangement occurring when dialkoxy MPB ketals are treated with acid.

Morrow finds that the MPB ketal **7** (R = −Me) undergoes addition with the aryllithium **297** to afford the tertiary alcohol **298** (Figure 83).[160] Subsequent treatment with $BF_3 \cdot Et_2O$ results in displacement of an alkoxy substituent of the ketal and produces the phenanthrene **299**.

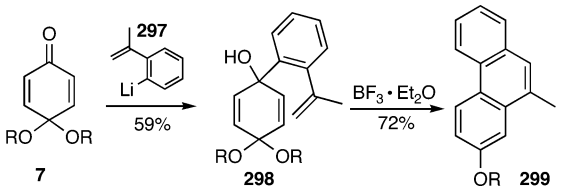



**Figure 83.** 1,2-Addition of an *o*-lithiated styrene to a MPB ketal resulting in a phenanthrene.

Parker reports that the carbonyl of the MPB ketal **7** (R = −Me) suffers 1,2-addition of the vinyllithium **300** to produce the alcohol **301** (Figure 84).[161] When this alcohol is treated with 2 equiv of DIBAL, followed by the addition of $POCl_3$, rearomatization affords **302**, a key intermediate in the construction of the *C*-aryl glycoside **303**.

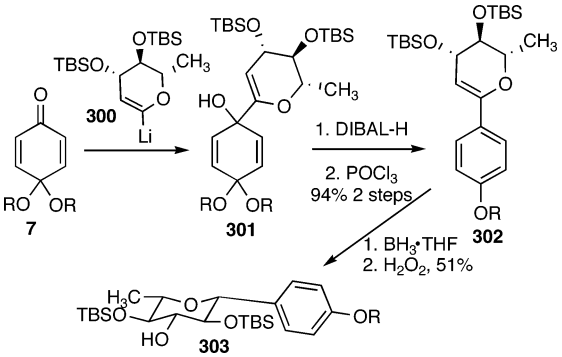



**Figure 84.** 1,2-Addition of an organolithium to MPB ketal resulting in a *C*-aryl glycoside.

Abrams reported a synthesis of an abscisic acid analogue by way of 1,2-addition of an organolithium reagent the carbonyl of a MPB ketal (Figure 85).[162] Oxidation of phenol **193** with 2 equiv of PIDA in the presence of ethylene glycol affords the ketal **304**. Addition of the alkynyllithium alkoxide **305** produces the tertiary alcohol **306**. Subsequent Red-Al reduction of the alkyne affords the (*E*)-olefin **307**. A two-step oxidation produces the ester **308**, which then undergoes hydrolysis in another two-step process to form the *p*-quinol **309**, an analogue of abscisic acid.

Many other researchers have investigated 1,2-additions of organometallic reagents. Langlois has developed a process for the addition of a trifluoromethyl residue to a carbonyl of a MPB ketal in a 1,2-fashion;[163] however, many examples are not without some problems. Semmelhack noted that the addition of hindered organolithiums, such as **311**, as well as thiazolium salts to **310** results in aromatization,

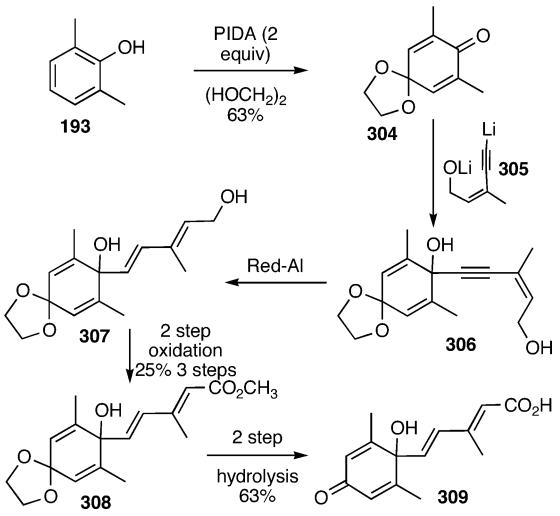



**Figure 85.** 1,2-Addition of an organolithium to MPB ketal, followed by deketalization resulting in a *p*-quinol.

leading to naphthalene **312**, presumably through a reductive SET mechanism (Figure 86).[164]

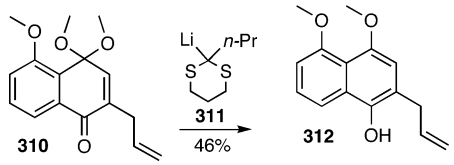



**Figure 86.** Addition of a bulky organolithium to a MPB ketal leads to reductive rearomatization.

Similarly, Imamoto finds that while smaller organocerium reagents add to the carbonyl of **304** in 1,2-fashion affording **313**, bulky organocerium reagents (R = *i*-Pr, *n*-Bu) result in significant amounts of the reductive aromatization product **314** (Figure 87).[151]

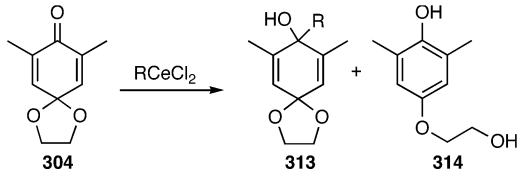



**Figure 87.** Organocerium reagents afford both 1,2-addition and rearomatization products.

Evans investigated the addition of the lithium enolate **315** to the MPB ketal **7** (Figure 88).[165] This

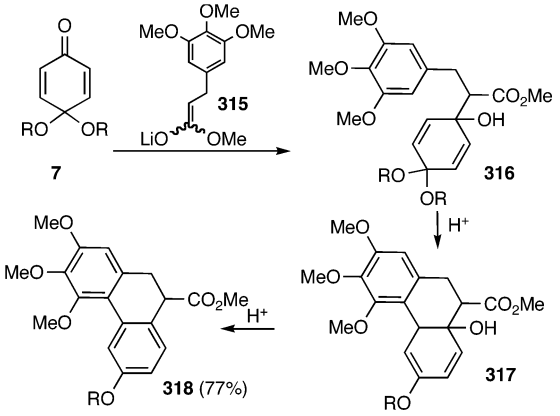



**Figure 88.** 1,2-Addition of an enolate to a MPB ketal.

combination affords the tertiary alcohol **316**, which upon treatment with acid produces the tricycle **317** that undergoes further elimination to produce the aromatic **318**.

The carbonyl of MPB ketals can participate in Wittig and related olefination reactions (Figure 89).[166] Addition of the lithium phenoxide ylide **319** to **7** affords the triene **320**. Subsequent treatment with $BF_3{\cdot}Et_2O$ affords **321**, a precursor to the natural product cherylline. In other work, Pelter uses Wittig couplings of MPB ketals to produce an assortment of useful organometallic ligands.[167]

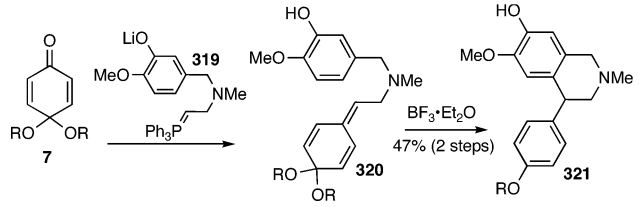



**Figure 89.** Wittig reaction of a MPB ketal.

With regard to the 1,2-addition of other nucleophiles, Omura reports that the sterically hindered ketal **323**, produced by $PbO_2$ oxidation of **322** in MeOH, undergoes reduction with $NaBH_4$ to produce the stable alcohol **324** (Figure 90).[168]

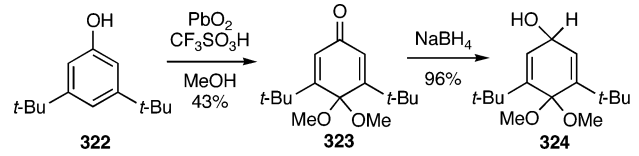



**Figure 90.** 1,2-Addition of hydride to a MPB ketal.

Swenton reports a method for the construction of imines from the carbonyl of various MPB ketals (Figure 91).[169] The trifluoroamide of the bis-ketal **325** is cleaved by mildly basic conditions, resulting in the corresponding amine, whereupon the ketal closest to the amine functionality hydrolyzes upon treatment with acid, resulting in **326**. The regiospecificity among ketals is probably a result of the vinylogous ester, which assists in hydrolysis. Once formed, **326** undergoes immediate cyclization to produce imine **327**.

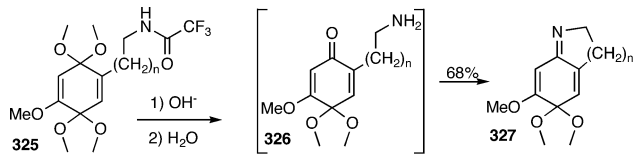



**Figure 91.** Formation an imine from a MPB ketal.

With regard to 1,4-conjugate additions, Parker has examined the reactivity of MPB ketals with dimethyl malonate,[170] and Torii has studied the reactivity of MPB ketals with $\beta$-ketoesters (Figure 92).[171] Under basic conditions, the anion of **328** adds efficiently to **7** to generate **329** in 93% yield. However, when **330** is deprotonated under electrochemical conditions and added to **7**, the bicycle **331** emerges in a nearly quantitative 98% yield.

Wheeler examined the 1,4-conjugate addition of malonitrile and the application of the arising adduct

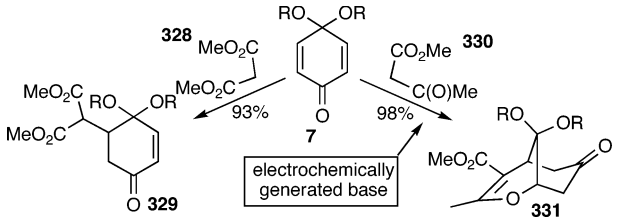



**Figure 92.** 1,4-Additions of stabilized anions to a MPB ketal.

in the synthesis of the AB ring of podocarpate (Figure 93).[172] The Michael reaction between **333** and **332** affords the epimeric mixture of **334**. Addition of methyl iodide and acrylonitrile under basic conditions affords the methylated adduct **335** as a single diastereomer. Thorpe−Ziegler condensation provides the *trans*-decalin **336**.

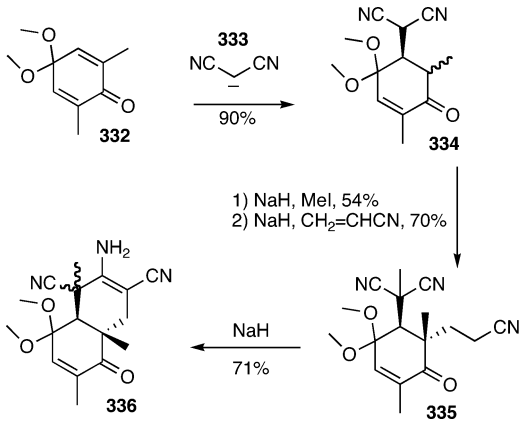



**Figure 93.** 1,4-Additions of a stabilized nitrile anion and synthesis of the AB ring system of podocarpate.

Semmelhack reports that the MPB ketal **310** undergoes 1,4-conjugate addition with the nitrolate **337** to produce a diastereomeric mixture of **338** in combined 95% yield (Figure 94).[164] Furthermore, Semmelhack finds that a related ketal **339** undergoes addition of the organonickel complex **340** and subsequent allylation with allyl iodide **341** to afford **342** in 82% yield.

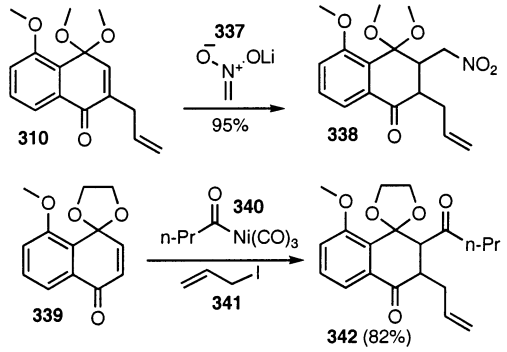



**Figure 94.** 1,4-Additions of a nitroenolate and acylcarbene to MPB ketals.

Chan, no doubt intending a [4 + 2] cycloaddition, finds that the MPB ketal **7** participates in a 1,4-conjugate addition with 2,5-bis(siloxyfuran) **343**, resulting in **344** (Figure 95).[173] This material readily decomposes.

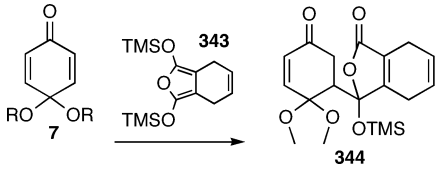



**Figure 95.** 1,4-Additions of a ketene acetal to a MPB ketal.

Complexation of the carbonyl of the MPB ketal with the bulky Lewis acid, such as MAD, can override the innate preference for 1,2-addition to the carbonyl (Figure 96). For example, addition of MAD to **345** followed by the treatment with organolithium reagents or Grignard reagents leads to derivatives of **346** in varying yields.[174] Vinyl and alkynyl nucleophiles proceed in excellent yield; however, alkyl and hydride additions are less efficient. Hart uses MAD in combination with a substituted phenyllithium reagent and a cyclohexadienone MOB ketal in the synthesis of defucogilvocarcin M and V.[175]

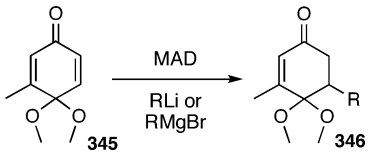



**Figure 96.** 1,4-Additions of RLi and RMgX reagents to MPB ketals promoted by MAD.

MPB ketals are highly reactive in acidic conditions. Winterfeldt reports that addition of HCl to the enone **347** affords the chlorobenzene **348** (Figure 97).[146b]

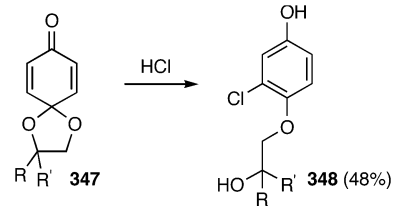



**Figure 97.** $H^+$-promoted 1,4-addition of [$Cl^-$] to a MPB ketal.

Foster has extensively investigated the 1,4-additions of heteroatom nucleophiles to MPB ketals, such as **7** (Figure 98).[176] For example, the addition of LiOMe to **7** produces **349**, whereas the thermal addition of morpholine **352** to **7** affords **353**. The addition of phenylthiol, on the other hand, results in a double addition, producing **350**. de March finds

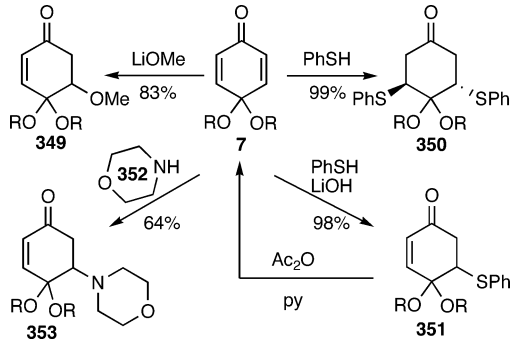



**Figure 98.** 1,4-Additions of heteroatom nucleophiles to a MPB ketal.

that PhSH and catalytic LiOH results in the monoadduct **351**.[177] Because treatment of the $\beta$-thioether resembling **351** with pyridine and $Ac_2O$ results in elimination, this latter method amounts to temporary protection of enone functionality.

Parker utilized a consecutive 1,4-conjugate addition/base-triggered aromatization sequence in the synthesis of mimosamycin (Figure 99).[178] 1,4-Addition of KCN to **354** in the presence of 18-crown-6 (**355**) affords the arylnitrile **356** directly in a 60% yield.

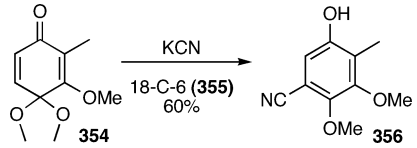



**Figure 99.** 1,4-Additions of cyanide to a MPB ketal.

With regard to annulation protocols, Taylor has developed several epoxidation procedures for use in the synthesis of palmarumycin and deoxypreussomerin[179] and aranorosin[180] (Figure 100). Treatment of the ketal **357** with the guanidine (**358**) and *t*-BuOOH affords the epoxide **359**. Reaction of this material with $NaBH_4$ results in a diastereoselective reduction that affords the *syn*-epoxy alcohol **360**. Wipf has studied similar epoxidation strategies on related targets.[181]

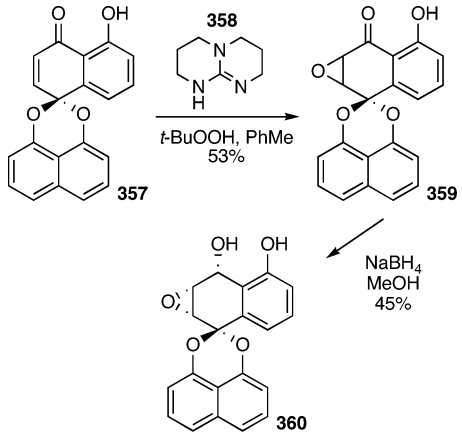



**Figure 100.** Epoxidation and reduction of a MPB ketal.

Meinwald finds that MPB ketals undergo cyclopropanation with Corey's sulfonium reagent (Figure 101).[182] For example, ketalization of the *p*-quinone **361** proceeds with the more accessible carbonyl and produces **304**. Addition of the ylide to this material affords the cyclopropane **362**, which undergoes a 1,4-conjugate addition with L-selectride in the presence of $Tf_2NPh$ to produce the triflate **363**. The preference for 1,4-addition of the hydride in lieu of 1,2-addition is the result of a severe steric interaction associated with the 1,2-approach. The triflate **363** smoothly couples with the vinyl cuprate **364** to afford diene **365**. This material participates in diastereoselective [4 + 2]-cycloaddition with *p*-quinone **366** to produce **367**.

With regard to annulation of MPB ketals such as **7**, in order to construct ring systems, Mitchell utilizes the cyanophthalide **61** in combination with **7** for construction of anthraquinones (Figure 102).[20] Low-

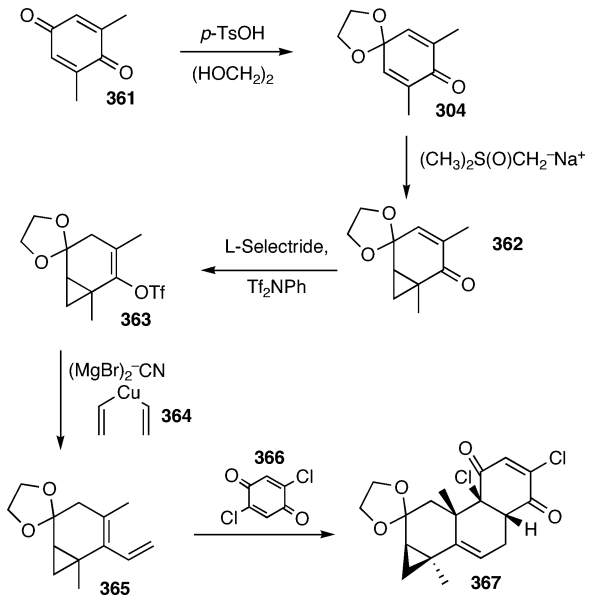



**Figure 101.** Cyclopropanation and other manipulation of a MPB ketal.

temperature addition affords the intermediate oxabicycle **368**, which collapses to the dienone **369** before undergoing a $\beta$-elimination to produce **370**. Monneret has used a very similar process to complete the synthesis of other anthraquinones.[183] Paredes has used the sulfone counterpart to **61** developed by Hauser and applied it toward the daunomycin problem.[184,185] Swenton reports application of a related Michael−Dieckmann strategy for the preparation of analogues of adriamycin.[186]

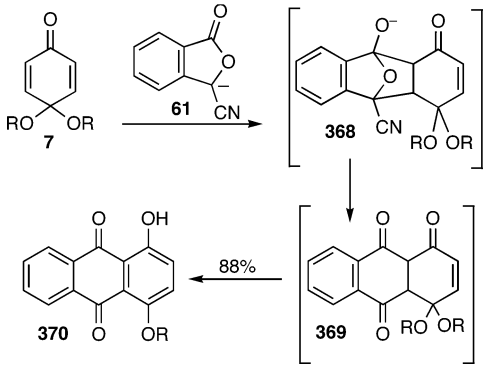



**Figure 102.** A Michael−Dieckman reaction of a MPB ketal.

In addition, Swenton has developed a related annulation strategy using the enolate of the diester **371** (Figure 103).[187] The sodium enolate of **371** adds in 1,4-fashion to the least substituted enone of the cyclohexadienone **345**, and the resulting enolate participates in a Dieckmann condensation with the

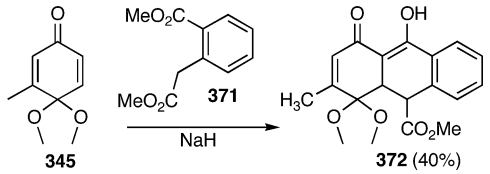



**Figure 103.** A Michael−Dieckman reaction of a MPB ketal.

benzoate ester to afford the tricyclic compound **372** in 40% yield.

A Barco annulation strategy has been developed for use with MPB ketals (Figure 104).[188] A 1,4-conjugate addition of the amine **374** to the more accessible enone in **373** results in the adduct **375**. The secondary amine is then protected as its corresponding methyl carbamate, and the allylic alcohol oxidizes with PDC to produce **376**. An intramolecular 1,4-conjugate addition to the newly formed unsaturated aldehyde initiated by DBU affords the pyrrolidine **377** as the predominate diastereomer.

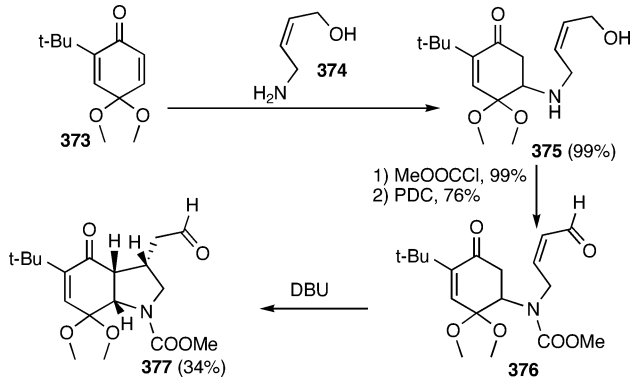



**Figure 104.** 1,4-Additions of an amine to a MPB ketal.

Coates has reported an expeditious synthesis of the highly substituted phenol **383** (Figure 105).[189] The route begins by a conjugate addition to the enone **378**. The nucleophilic dienolate **379** undergoes reaction at its most accessible α-carbon atom. This addition resulting in **380** is followed by another conjugate addition of the amine moiety onto the vinylogous ester, which affords the rather unusual [3.3.1] adduct **381**. A regio- and diastereoselective α-methylation of the ketone directed by the tertiary methoxy residue produces **382**, which affords the indole **383** upon treatment with acid.

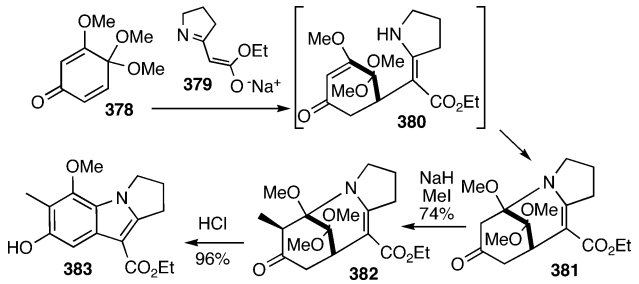



**Figure 105.** 1,4-Additions of an enolate to a MPB ketal.

Because of their inherent instability toward Lewis acids and thermal conditions, [4 + 2] cycloadditions of MPB ketals can be problematic. Warrener and Russell report that cycloadditions of **345** and **7** with the substituted isobenzofuran **384** are highly selective, resulting in adducts **386** and **385**, respectively (Figure 106).[190]

Liao has devised several tandem oxidative dearomatization/intramolecular Diels−Alder reactions of MPB ketals (Figure 107). For example, dearomatization of **387** in methanol produces the *endo* and *exo* products **388** and **389**, respectively. This tandem process enables rapid synthesis of highly function-

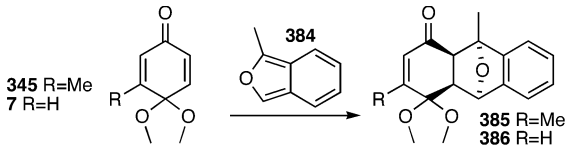



**Figure 106.** [4 + 2] Intermolecular cycloaddition of a MPB ketal.

alized *cis*-decalins.[191] Morrow has also explored a similar sequence that reverses the overall order of addition.[192]

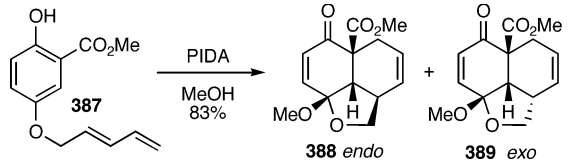



**Figure 107.** Successive oxidation and intramolecular [4 + 2] cycloaddition of a MPB ketal.

MPB ketals undergo [3 + 2] cycloadditions with nitrones (Figure 108); however, de March finds that a double addition occurs with symmetric MPB ketals.[177] For example, **347** undergoes a [3 + 2] cycloaddition with **390** to produce a mixture of **391** and **392**. Masking one enone by mono addition of a thiophenyl residue and subsequent elimination of that residue after a single [3 + 2] cycloaddition allows for the selective construction of **391** in good yields.

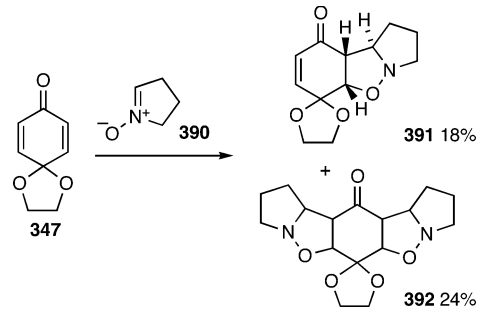



**Figure 108.** [3 + 2] Cycloadditions of a MPB ketal.

Ghera and Hassner have devised a general synthesis of cis-5,6 fused-ring systems from MPB ketals (Figure 109).[193] For example, treatment of the MPB ketal **7** with the anion of **393** affords the cis-fused 5,6-adduct **394** in 65% yield.

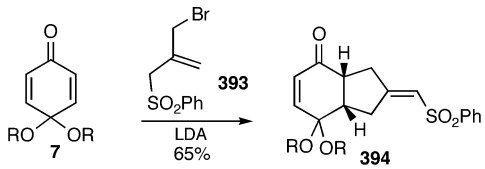



**Figure 109.** A [3 + 2] cyclopentanation of a MPB ketal.

Another interesting annulation role demonstrated with MPB ketals are [5 + 2] cycloaddition processes, in which the dienone core effectively serves as a 5-atom (4$\pi$) component (Figure 110). For example, Grieco reports that treatment of **395** with TMSOTf in $LiClO_4$/EtOAc effectively promotes an intramolecular [5 + 2] cycloaddition, affording the dione adduct **397** via the probable cation intermediate **396**.[194] Similar reactions have been demonstrated by Yamamura[195] and Büchi.[196]

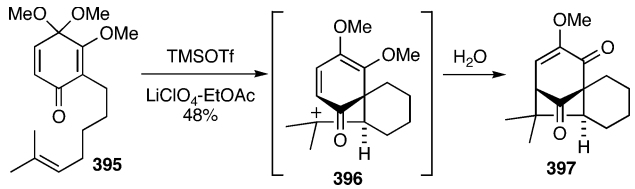



**Figure 110.** [5 + 2] Intramolecular cycloaddition of a MPB ketal.

MPB ketals undergo several types of $S_N2'$ displacements. Swenton has utilized this reactivity to make thiobenzohydrofurans (Figure 111).[197] In the presence of acid, addition of the vinyl thiol **398** to **7** proceeds to the cation intermediate **399**, which tautomerizes to **400** and then undergoes cyclization to provide the thiobenzohydrofuran **401**.

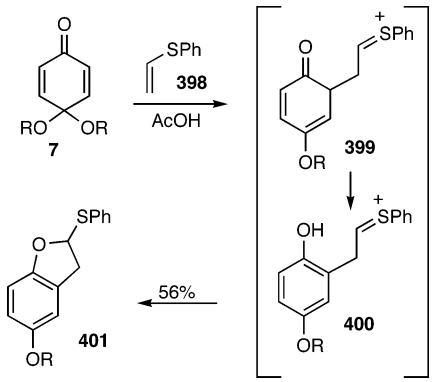



**Figure 111.** Acid-promoted allylic displacement of a MPB ketal.

Coutts finds that upon oxidation of **402** with $MnO_2$, the MPB ketal **403** forms (Figure 112). This material undergoes an $S_N2'$ displacement with MeMgI to afford the phenol **404**.[198] The success of this reaction, in regard to a competitive 1,2-addition to the carbonyl, is most likely a consequence of the aryl ketal and the stability of the resulting magnesium phenoxide.

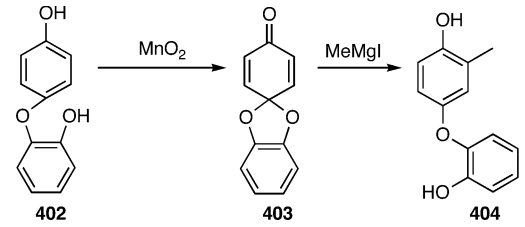



**Figure 112.** Allylic displacement of a catechol derived MPB ketal.

Other examples of $S_N2'$ reactivity have been demonstrated by Sartori (Figure 113).[199] For example, when the MPB ketal **7** is treated with a Lewis acid

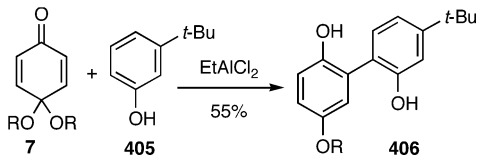



**Figure 113.** Lewis acid-promoted allylic displacement of a MPB ketal.

in the presence of the phenol **405**, a Friedel−Crafts alkylation occurs *ortho* to the phenol functionality to produce the biphenyl **406**. $EtAlCl_2$ is among the most efficient Lewis acids for this transformation.

With regard to the inherent stability of MPB ketals and the likelihood for them to undergo aromatization, Swenton reports a difference in thermal stability for acyclic and cyclic ketals (Figure 114). For example, the ethylene glycol derivative **347** survived for a prolonged period at 180 °C, but the dimethyl ketal **7** (R= −Me) rapidly decomposes to **290**, presumably through its tautomer **407**.[200]

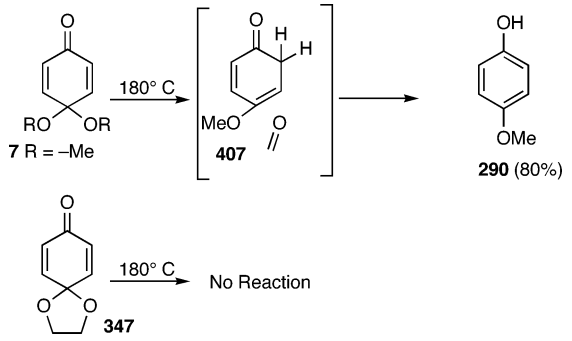



**Figure 114.** Thermal-promoted rearomatization of MPB ketals.

The reduction of MPB building blocks with $Pd/H_2$ has often been problematic, resulting in aromatization rather than enone reduction. However, Ohta has used this inherent reactivity to an advantage in the synthesis of α-tocopherol analogues (Figure 115).[201] For example, oxidation of the dimethoxyhydroquinone **408** with cerium ammonium nitrate (CAN) affords the quinone **409**, which upon treatment with acid affords the MPB ketal **410**. Addition of $Pd/H_2$ generates **411** via SET-triggered elimination of the alkoxy substituent that is disposed in the most pseudoaxial orientation and displaying the best overlap with the adjacent π-orbitals. Achiwa has used a similar ploy.[202]

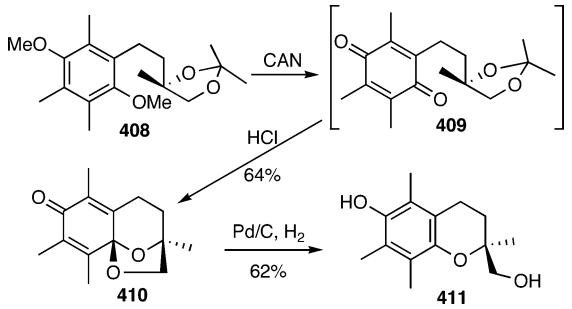



**Figure 115.** Hydrogenation-promoted rearomatization of a MPB ketal.

Swenton finds the mixed siloxyketal **294** to be better behaved in heterogeneous reductions (Figure 116).[158] For example, the hydrogenation proceeds easily with palladium to afford the cyclohexanone **412,** whereupon the carbonyl can be erased using Wolff−Kishner conditions to furnish the mixed ketal **413**.

With regard to other reductions of the enone functionality, Morrow has investigated the complexation of MPB-ketals with a stoichiometric amount of

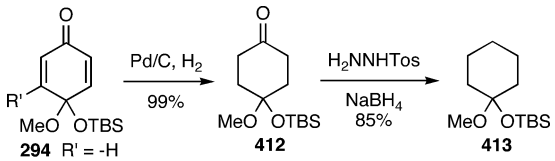



**Figure 116.** Hydrogenation of an −OTBS mixed MPB ketal.

the Lewis acid MAD, followed by the addition of L-selectride (Figure 117).[203] Substituted compounds, such as **414**, participate in mono 1,4-reductions to produce **415** in good yields. Unsubstituted MPB ketals, such as **7**, however, tend to undergo 1,4-reduction, and the resulting enolate of **416** undergoes intermolecular 1,4-additions with remaining enone functionality.

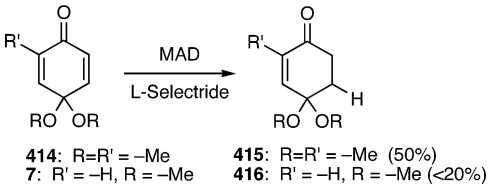



**Figure 117.** 1,4-Additions of hydride to MPB ketals.

The photochemistry of MPB ketals has been examined, and the outcome appears to largely depend on the substituents about the ring system and the solvent employed in the reaction (Figure 118).[204] For example, photolysis of **417** ($R^1 = R^6 = H$, $R^2 = R^5 =$ alkyl) in a nonnucleophilic solvent results in ho-

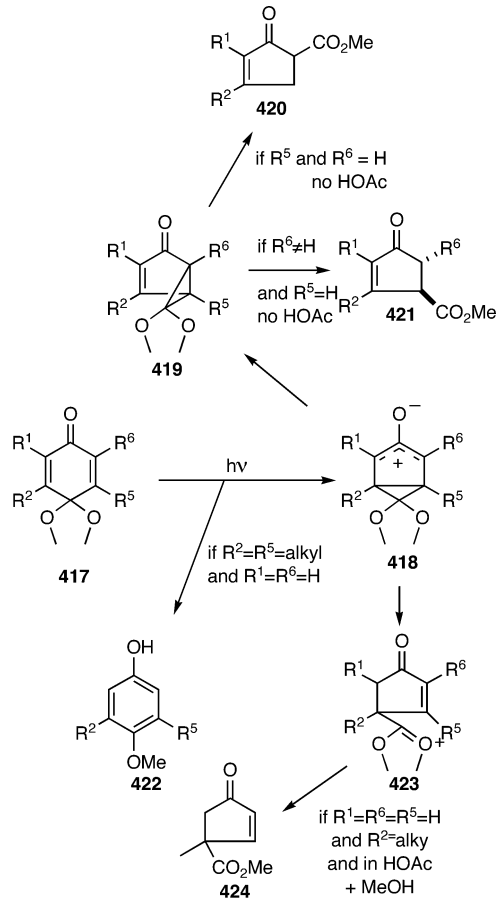



**Figure 118.** Photochemical-promoted rearrangement of MPB ketals.

molytic cleavage of the ketal and affords the phenol **422**. In polar conditions, however, several cyclopentenone products can emerge. Photolysis proceeds to a long-lived cyclopropyl zwitterion **418** and continues on to **424** via intermediate **423** when $R^1 = R^6 = R^5 =$ H and the solvent is HOAc/MeOH. Alternatively, when HOAc is absent, the zwitterion **418** proceeds to the cyclopropane **419**. The subsequent fragmentation proves to be substituent-dependent and leads to either **420** or **421**.

## 5.3. Synthetic Applications

The MPB ketal has served as the key building block in the total syntheses of five natural product families: the manumycins, huperizes, torreyanoids, diepoxins, and illudines. For example, Wipf's synthesis of nisamycin, a member of the manumycin family of antibiotics, begins with the *N*-alloc-protected aniline **425** (Figure 119).[205] Its oxidation with PIDA in MeOH affords the bis-ketal **426**, which undergoes a single hydrolysis with HCl to give the MPB ketal **427**. The more electron-deficient enone undergoes epoxidation with a mixture of TBHP and DBU with concomitant cleavage of the Alloc group to produce the epoxidized vinylogous amide **428**. Acylation of the vinylamine with the acid chloride **429** affords the amide **430**. This compound undergoes a diastereoselective 1,2-addition of the organolithium **431** to produce the vinyl bromide **432** after tin−bromide exchange. Nisamycin (**433**) is obtained by a vinylic coupling and ketal deprotection.

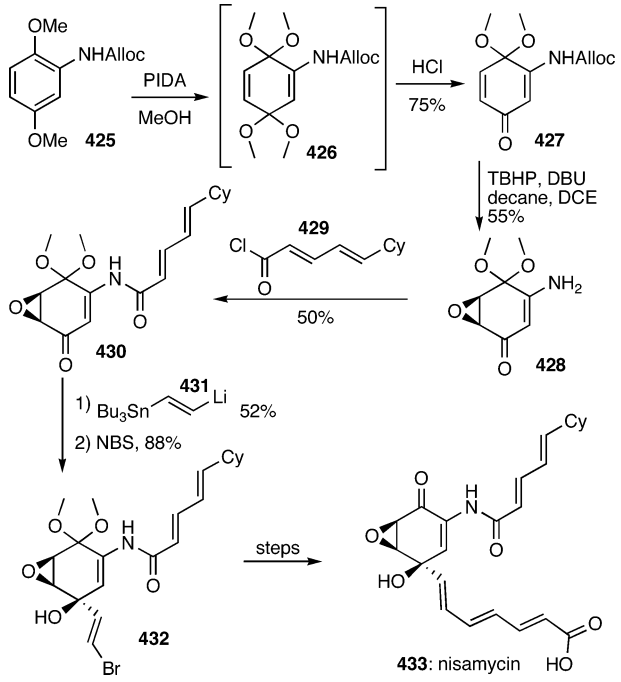



**Figure 119.** Wipf synthesis of nisamycin.

Using a similar epoxidation strategy, Taylor completed a total synthesis of (+)-manumycin A **436** (Figure 120).[206] Intermediate **435**, which is realized from **434** in a fashion similar to the above scheme, was subjected to a Stille coupling utilizing Negishi's catalyst [$PdCl_2$−($PPh_3$)$_2$, DIBAL-H] and produced (+)-manumycin A (**438**).

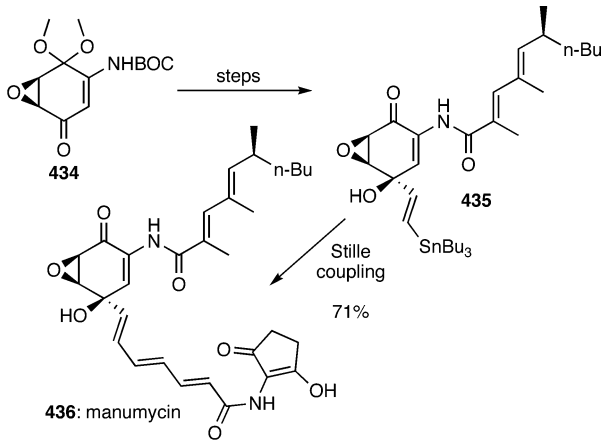



**Figure 120.** Taylor synthesis of manumycin.

Mulzer reports a synthesis of a des-amino huperzine analogue using a MPB ketal as the key building block (Figure 121).[207] The synthesis commences with a series of base-triggered Michael additions between the MPB ketal **347** and the ketoester **437**. Under basic conditions, a hydrolysis of the nonconjugated ester of **438** ensues. A decarboxylation then occurs upon protic workup, producing **439** in 77% yield. This intermediate is eventually converted into **440**.

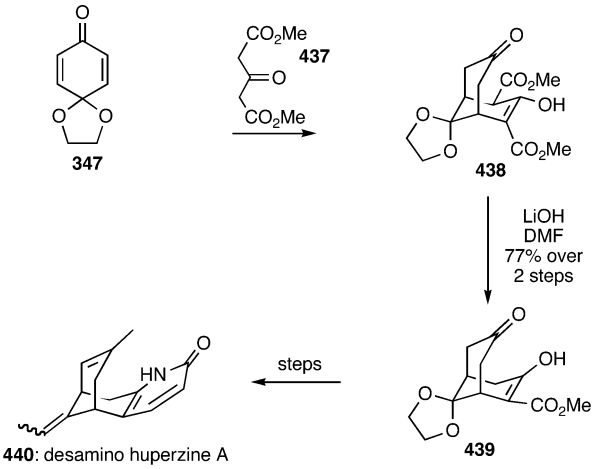



**Figure 121.** Mulzer synthesis of desamino huperzine A.

Porco completed the total synthesis of torreyanic acid (**445**) (Figure 122).[208] This quinone epoxide dimer is cytotoxic to cells that are sensitive to protein kinase C agonists. Its construction begins with the oxidation of **441** with PIDA in the presence of MeOH, which results in the MPB ketal **442**. This adduct is then transketalized to give the more stable MPB ketal **443**. Epoxidation was accomplished with freshly prepared anhydrous $Ph_3COOH$ deprotonated with KHMDS. These conditions afford the epoxide **444**. Subsequent Stille coupling with the vinyl bromide and deprotection under acidic conditions results in an immediate [4 + 2] dimerization, which upon oxidation with DMP furnishes **445**.

A key diepoxin derivative has been synthesized by Wipf using the MPB building block (Figure 123).[181] Starting from MPB ketal **446**, addition of hydrogen peroxide in the presence of base affords the bis-epoxide **447** as a single diastereomer.

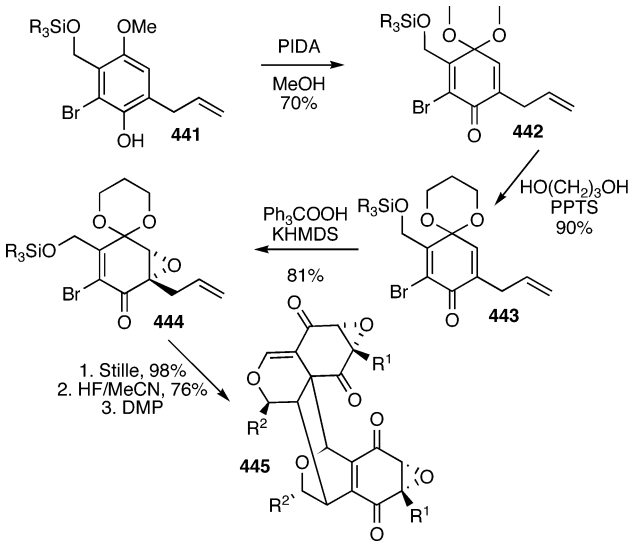



**Figure 122.** Porco synthesis of torreyanic acid.

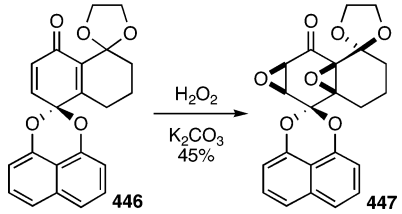



**Figure 123.** Wipf synthesis of diepoxin derivative.

Franck-Neumann reports an interesting synthesis of 2,3-dehydro illudine M from a MPB ketal (Figure 124).[209] The route begins by ketalization of the more accessible carbonyl of the *p*-quinone **361** with the diol **450**. This material undergoes reduction with $Pd/H_2$ to produce **448**. Presumably, the glycol ketal **304** is resistant toward reductive aromatization with $Pd/H_2$, as compared to MPB ketals earlier discussed. In any event, the hydrogenation product **448** serves as a controllable platform from which to complete a diastereoselective synthesis of 2,3-dehydro illudine M (**449**).

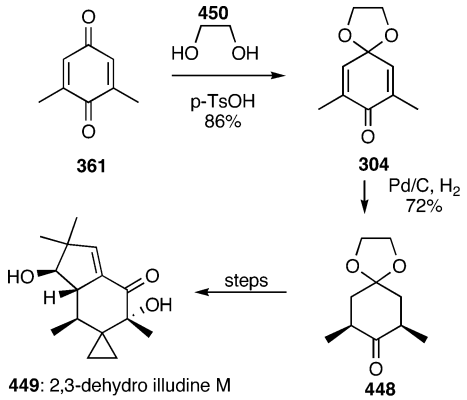



**Figure 124.** Franck−Neumann synthesis of 2,3-dehydroilludine M.

## 5.4. Enantioselective Horizons

Among the four types of cyclohexadienones, which are substituted at their $sp^3$ site with a heteroatom, the enantioselective potential of the MPB ketal **7** is undoubtedly the most developed. Nonracemic MPB

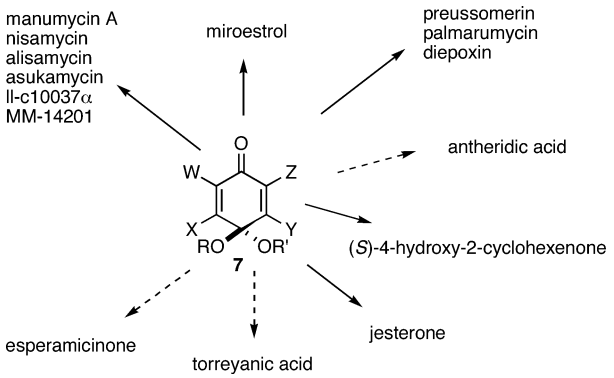



**Figure 125.** Potential of MPB ketals for enantioselective synthesis.

ketals and their derivative have led to enantioselective syntheses of many members of the manumycin family of antibiotics, the estrogenic phenol miroesterol, the naphthaquinone ketals preussomerin and diepoxin, and the epoxy-quinoid jesterone, as well as (*S*)-4-hydroxy-2-cyclohexenone. In principle, enantioselective syntheses of antheridic acid, torreyanic acid, and esperamicinone could be achieved from the current level of technology.

There are several processes for conversion of a MPB ketal into a chiral building block for subsequent use in diastereoselective syntheses. One approach avoids the issue of creating stereocenters within the ring. Instead, a chiral group is introduced temporarily to either a ketone or olefin. The stereocenters within the introduced functional group are then used to direct subsequent transformations within the remaining functional groups contained within the 2,5-cyclohexadienone. The chiral directing group is then cleaved, thereby fulfilling the definition of a chiral auxiliary. Although this type of process has been the most utilized, diastereoselective control has often been moderate at best. However, since the subsequent reaction leads to diastereomers rather than enantiomers, the product can be readily purified. A more efficient variation of this strategy makes use of a catalyzed asymmetric reaction to install the temporary directing group. It requires the same number of overall transformations as the preceding chiral auxiliary approach; however, it uses less material from the chiral pool, since only a chiral catalyst is need. Yet another strategy involves the use of a chiral reagent for temporary desymmetrization of the cyclohexadienone core. Once adulterated, however, only a few types of subsequent synthetic alterations can be made to the remainder of the core structure before the directing group is cleaved. Desymmetrization reactions include reduction of a carbonyl residue in nonsymmetric cyclohexadienone systems or epoxidation, 1,4-conjugate addition, and [4 + 2]-cycloaddition of the enone functionality in symmetric cyclohexadienone systems.

With regard to these processes, Corey demonstrated the first chiral auxiliary approach in the synthesis of miroestrol **461** (Figure 126).[210] Oxidation of the bromophenol **451** with PIDA in the presence of methanol afforded the cyclohexadienone **452** in 98% yield. Transketalization with (*R,R*)-**453** affords the chiral cyclic ketal **454** in 90%. Conformer **455** is

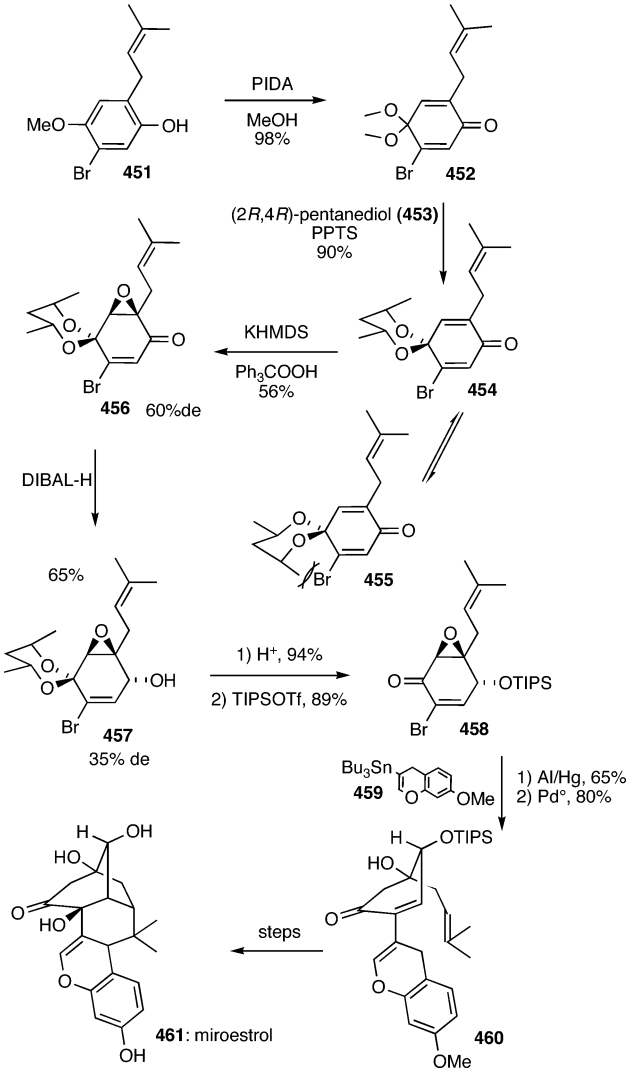



**Figure 126.** Corey diastereoselective epoxidation of chiral MPB ketal for the synthesis of miroestrol.

*not* produced because of the steric interaction between the methyl and bromo-substituents as shown. Epoxidation provides **456** in 60% *de*. The $Ph_3COO^-$ adds in 1,4-fashion to the more accessible $\beta$-site and face of the enone opposite the axial methyl residue in the ketal **454**. Reduction of the ketone **456** provides **457** with 35% *de*. However, the isomers are easily separable, and the desired compound **457** is isolated in a 65% yield. The chiral ketal is then cleaved, and the diol **453** is recovered for reuse. The secondary alcohol is then protected to afford the silyloxyether **458**. Reductive opening of the epoxide with aluminum amalgam followed by a palladium-mediated coupling of stannane **459** affords the enone **460**. This material is converted in subsequent steps to miroestrol (**461**).

Wipf used a similar strategy in the enantioselective synthesis of LL-C10037$\alpha$ (Figure 127).[211] The chiral ketal **462** is favored over its conformer **463** and undergoes epoxidation with $K_2CO_3$ and $H_2O_2$ to afford **464**:**465** in 63% *de*. As in the Corey example, reaction at the olefin occurs on the face opposite the axial methyl residue of the preferred conformer **462**. After ketal hydrolysis, addition of an organolithium reagent takes place at the most reactive carbonyl in a diastereoselective 1,2-fashion, but the epoxide does *not* offer very good diastereocontrol for this addition.

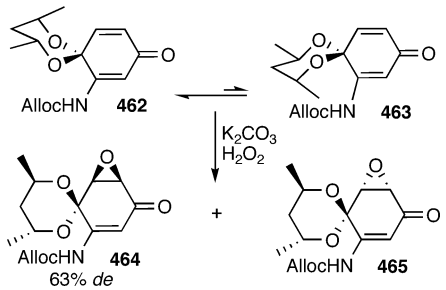



**Figure 127.** Wipf diastereoselective epoxidation of chiral MPB ketal for the synthesis of LL-C10037$\alpha$.

Porco has also applied this chiral auxiliary protocol in the synthesis of (−)-jesterone (**470**), a structure related to torreyanic acid (Figure 128).[212] Oxidation of **466** with PIDA affords the ketal **467**, which upon transketalization with the (*S*,*S*)-**453** furnishes the chiral ketal **468,** and as before, it exists predominately in one chair conformer. Epoxidation with $Ph_3$-COOH at −35 °C affords **469** in 80% isolated yield. None of the undesired diastereomer is observed. A palladium-mediated Stille coupling, followed by deprotection of the ketal and silyl residue and reduction of the least encumbered ketone, furnishes **470**. Presumably, a similar strategy could be used for preparation of torreyanic acid.

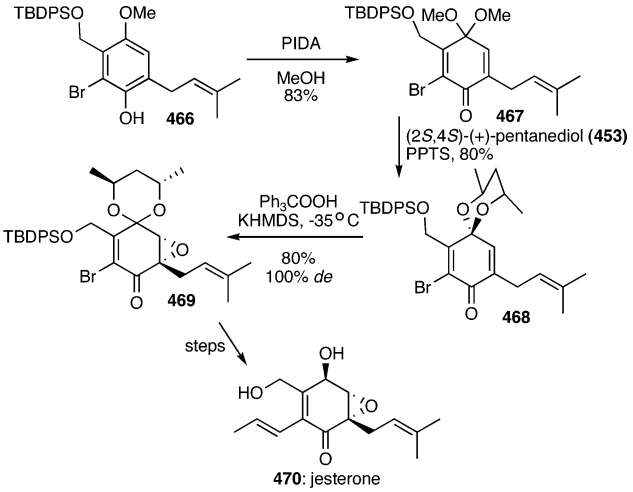



**Figure 128.** Porco diastereoselective epoxidation of chiral MPB ketal for the synthesis of jesterone.

A related strategy leading to a five-membered chiral ketal has been developed by de March and Figueredo (Figure 129).[213] They report using diols **471** and **472** for the preparation of the 1,2-diphenyl and dimethyl monoketals **473** and **474** from benzoquinone **291**. The phenyl derivative **474** undergoes partial hydrogenation with Wilkinson catalyst to produce **475** in a >75% yield. Other catalysts afford complex mixtures of products. Reduction of the carbonyl group in **475** with $NaBH_4$ followed by hydrolysis of the ketal affords **476** in 60% *ee*. Crystallization permits isolation of enantiopure material in 67% yield. On the other hand, a Diels−Alder reaction of **474** with the cyclopentadiene **229** affords adducts **478** and **477** in a 2:1 ratio in 97% yield based on recovered starting material.

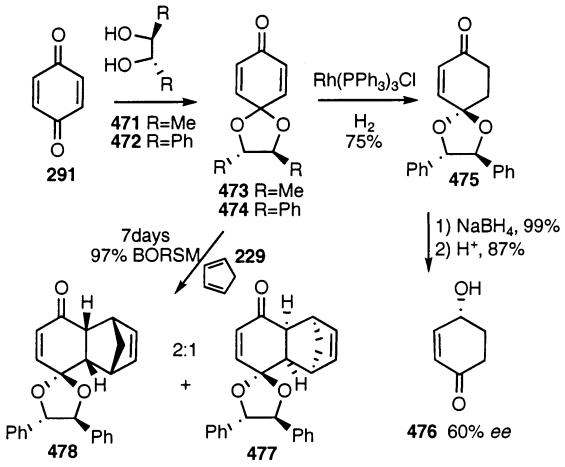



**Figure 129.** de March diastereoselective cycloaddition of chiral MPB ketal.

Wipf reports some rather unusual long-range directing effects with regard to trifluoromethyl-substituted MPB ketals (Figure 130).[214] As in the prior example, two conformations, **479** and **480**, are plausible; however, for obvious reasons, **479** is preferred. Addition of MeMgBr to **479** affords **481** in a 2:1 ratio with **482**. This observation was incorporated in a synthetic exploration of the palmarumycin skeleton as addition of MeMgBr to **483** afforded the tertiary alcohol **484** as a single diastereomer. Subsequent hydrolysis of the chiral ketal afforded the *p*-quinol **485**.

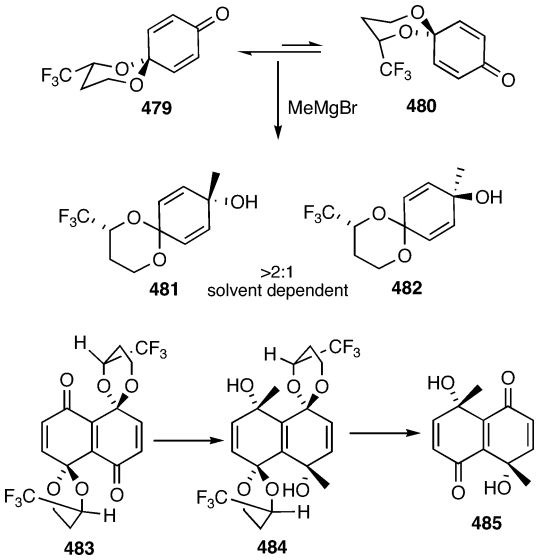



**Figure 130.** Diastereoselective 1,2-addition in other chiral MPB ketals.

Winterfeldt has developed a conceptually related strategy (Figure 131).[215] A chiral diene undergoes a [4 + 2] cycloaddition with a prochiral MPB ketal. The resulting chiral adduct directs subsequent stereochemical manipulations in the remaining functionality. Eventually, the substrate is subjected to retro-Diels−Alder to furnish a chiral cyclohexadienone derivative and the nonracemic diene for reuse. For example, ketal **347** undergoes a [4 + 2] cycloaddition with the chiral diene **486** at 6.5 kbar to produce adduct **487**. The remaining enone in **487** can then be derivatized by epoxidation or cyclopropanation. In this case, however, the enone is reduced in 1,4-fashion with an admixture of Zn and $NiCl_2$. The resulting enolate is then allylated in a diastereoselective manner to produce **488**. Reduction of the ketone **488** with LAH affords **489** as a single diastereomer. The ketal hydrolyzes to produce **490.** Upon heating at reduced pressure, this material undergoes a retro [4 + 2] cycloaddition and affords the enone **491**.

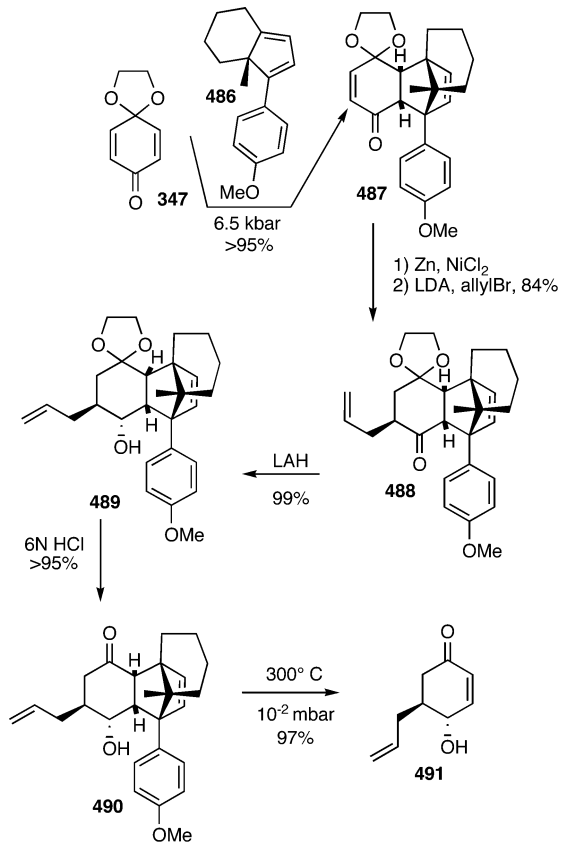



**Figure 131.** Winterfeldt enantioselective desymmetrization of prochiral MPB ketal by cycloaddition.

Another method, developed by Carreno, employs a chiral sulfoxide (Figure 132).[216] Addition of the lithiated chiral sulfoxide **492** to the MPB ketal **7** affords the *p*-quinol **493** after hydrolysis. This material undergoes a somewhat diastereoselective [4 + 2] cycloaddition with cyclopentadiene **229**, affording **494** in 50% *de* to **495**.

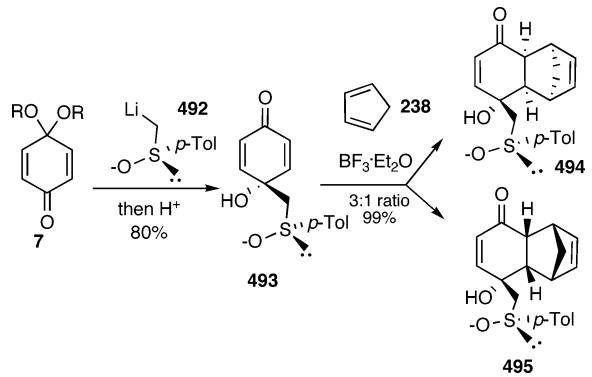



**Figure 132.** Carreno enantioselective desymmetrization of a prochiral MPB ketal by 1,2-addition.

Wipf has developed a more efficient approach than the preceding strategies that makes use of a chiral catalyst to introduce a temporary group that can be used to direct reactions in a diastereoselective fashion. This process has been used in the synthesis of diepoxin (Figure 133).[217] For example, the chiral ligand **497** affects an asymmetric Diels−Alder reaction between cyclopentadiene **229** and the enone **496,** which results in **498**. Depending upon the R substituent in the biphenyl ligand, the reaction proceeds in 94% *ee*. Reduction of **498** with $NaBH_4$ proceeds in a highly diastereoselective fashion and affords the triol **499**. This compound then undergoes a copper-mediated coupling with the iodide **500**, followed by demethylation with $Ph_2PLi$ to afford **501**. Oxidation with PIDA generates the ketal **502**, which upon silylation of the more accessible alcohol and subsequent oxidation affords ketone **503**. A bis epoxidation occurs at the most electron-deficient olefin opposite to the siloxy residue, and then the second epoxidation is directed in a diastereoselective sense to the convex side of the tricycle, affording **504**. A retro-Diels−Alder reaction ensues to form diepoxin (**505**).

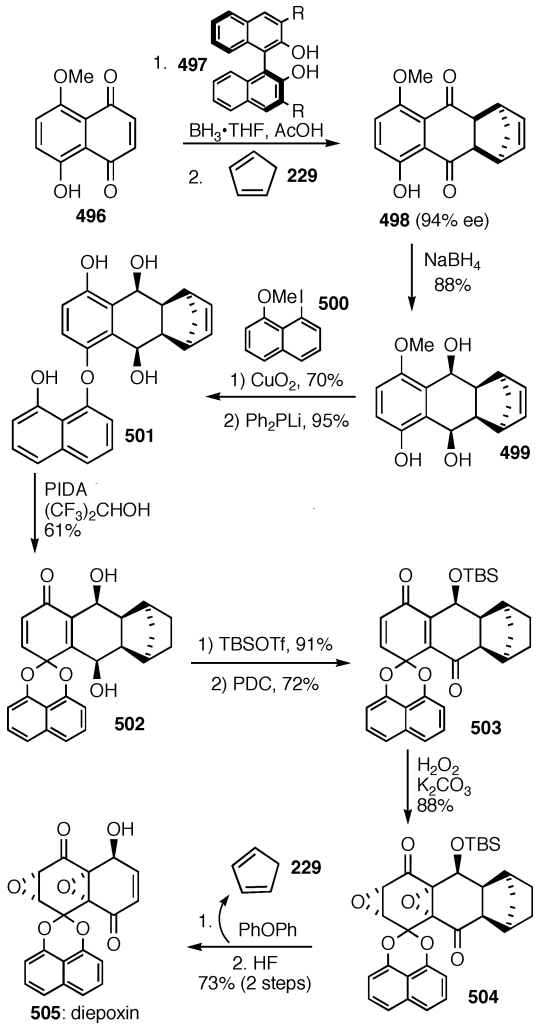



**Figure 133.** Wipf enantioselective desymmetrization of a prochiral MPB ketal by cycloaddition and use in the synthesis of diepoxin.

With regard to the application of chiral reagents to derivatives of MPB ketals, Corey reports a method in an enantioselective approach toward antheridic acid (Figure 134). Rh−C/$H_2$ is shown to be effective for reduction of the most accessible olefin in **506**, whereupon enone **507** is produced.[218] This material undergoes an asymmetric reduction with CBS reagent to produce the allylic alcohol **508** in 92% *ee*. This material can then be transformed into the enone **509** and, ultimately, the advanced intermediate **510** after a few simple transformations.

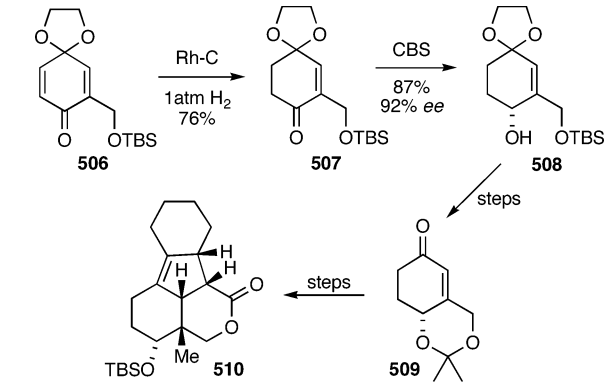



**Figure 134.** Corey enantioselective derivatization of a MPB ketal through reduction used in the synthesis of antheridic acid.

Nicolaou devised an approach toward esperamicin using a derivative of MPB ketal (Figure 135).[219] The ketal **511** undergoes oxidation with CAN in ethylene glycol to produce **512**. Epoxidation of the allyl alcohol using Sharpless conditions affords the epoxide **513**. This material upon addition of the isocyanate **514** affords the carbamate **515**, which when treated with $BF_3$•$Et_2O$ affords the carbonate **516** by an $S_N2$-like process. The latter is proposed as a possible advanced intermediate in the synthesis of esperamicinone.

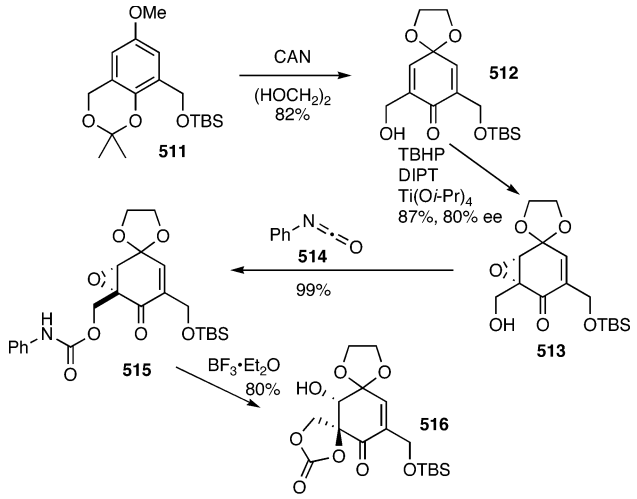



**Figure 135.** Nicolaou enantioselective derivatization of a MPB ketal through catalytic epoxidation for use toward esperamicin.

Taylor developed an asymmetric epoxidation reaction for application to a MPB ketal (Figure 136).[220] For example, exposure of the prochiral ketal **517** to a combination of TBHP and the chiral amine **518** affords **434** in 35% *ee*. In another communication, Taylor reports that much higher enantioselectivity is realized in **434** when the reaction is conducted in

the presence of the chiral amine **519**.[221] Taylor uses this enantioselective epoxidation process for an enantioselective synthesis of manumycin.

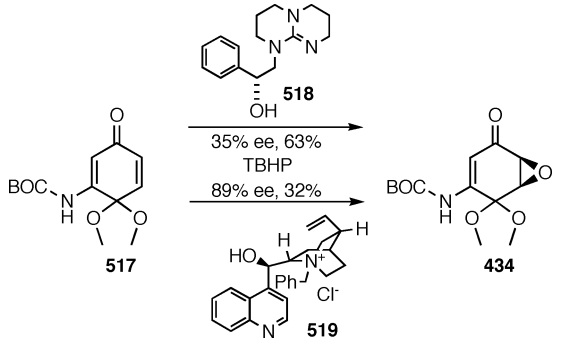



**Figure 136.** Taylor enantioselective desymmetrization of prochiral MPB ketal by epoxidation.

Feringa has reported a catalytic enantioselective addition of organozinc reagents to MPB ketals (Figure 137).[222] For example, the cyclohexadienone **7** undergoes an enantioselective conjugate addition with diethyl zinc in the presence of the chiral phosphoramide ligand **520** to afford the enone **521** in 85−99% *ee*. The specific enantiomeric excess depends on the R substituent.

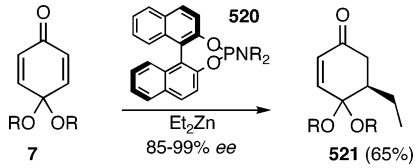



**Figure 137.** Feringa enantioselective desymmetrization of prochiral MPB ketal by conjugate addition.

Corey reports that MPB ketals undergo asymmetric Diels−Alder reactions in the presence of chiral binaphthyl titanium catalysts (Figure 138).[223] For example, ketal **522** undergoes both a regio- and enantioselective [4 + 2] reaction with the butadiene **523** in the presence of catalyst **524** to afford the *cis*-decalin **525** in 97% *ee*. Lower enantioselectivities were observed as the size of the R and R′ residues increased on the starting MPB ketal.

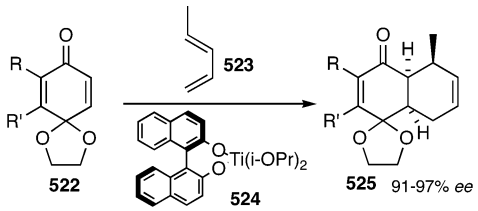



**Figure 138.** Corey enantioselective desymmetrization of prochiral MPB ketal by cycloaddition.

Despite all of these previous studies and efforts, there have been no reports describing the creation of an $sp^3$ stereocenter during the dearomatization process itself. As explained in sections 4.4 and 5.4, most enantioselective processes involve derivatization of the cyclohexadienone product in an asymmetric manner rather than forming this material in an enantioselective fashion upon dearomatization. The problem rests with the mechanism associated with dearomatization that involves a planar cation intermediate. Perhaps the first step toward designing such an asymmetric process would be to develop an understanding of the steric and electronic effects guiding the subsequent reactions of the intended chiral product. For example, Farina finds that the chiral ketal **526** affords modest diastereoselective control in a subsequent Diels−Alder reaction with **527**, resulting in the formation of adducts **528** and **529** in a 1:3 ratio (Figure 139).[224]

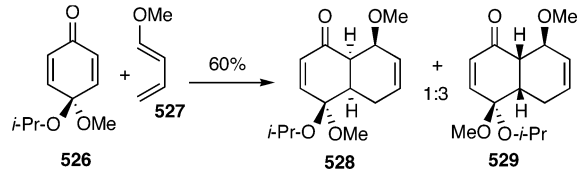



**Figure 139.** Diastereoselective cycloaddition of a chiral MPB ketal.

Wipf reports that preussomerin G (**530**) undergoes reactions with thiols in a highly diastereoselective fashion to give the C-3′adduct **531** in nearly quantitative yield (Figure 140).[181]

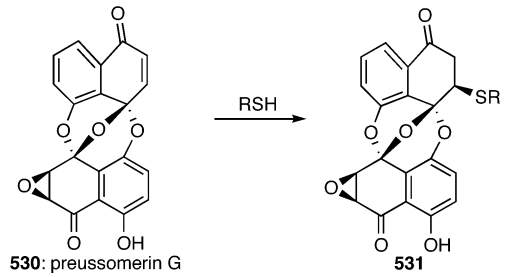



**Figure 140.** Diastereoselective 1,4-addition of a chiral MPB ketal.

Pelter and Ward have recorded several diastereoselective reactions that result from directing effects afforded by remote stereocenters (Figure 141).[225] For example, oxidation of the phenol **532** affords a greater

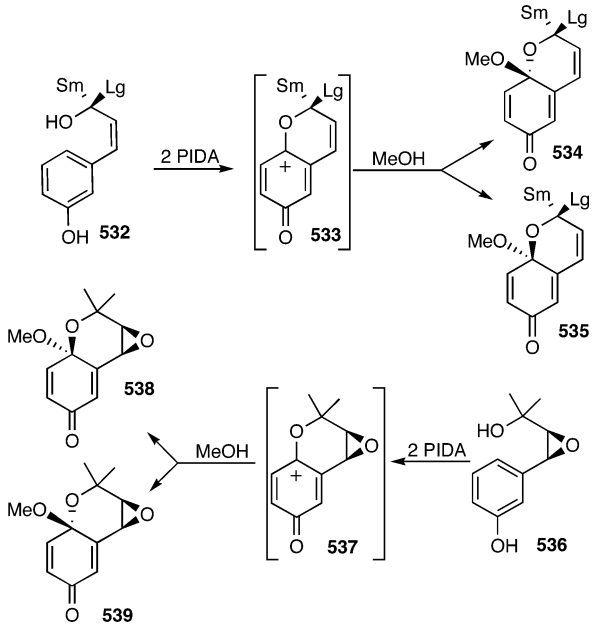
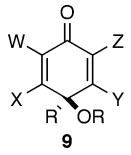



**Figure 141.** Diastereoselective formation of a chiral MPB ketal.

amount of **535** than **534**. Presumably, addition to the cation **533** occurs preferentially from the more accessible face opposite the large residue. Similarly, oxidation of the phenol **536** affords **538** in diastereomeric preference to **539**, which can be understood on similar grounds with respect to cation **537**.

Clearly, further investigations might uncover better methods for preparing these useful entities, perhaps using an intramolecular diastereoselective dearomatization involving some chiral tether that can be eventually cleaved from the cyclohexadienone core.

## 6. *p*-Quinol-Derived Building Blocks (9)




**9**

The reactivity of *p*-quinols such as **9** closely parallels that reported for MPB ketals and includes a myriad of reactions, such as 1,2-additions to the carbonyl functionality, as well as 1,4-additions and annulations of the enone functionality. All of these reactions, however, are overshadowed by the proclivity of *p*-quinols toward aromatization through reductive single electron-transfer processes as well as the dienone rearrangement triggered by acidic conditions.

### 6.1. Preparation

By far the most common method for preparing *p*-quinols involves the oxidation of a 4-substituted phenol, such as **542** (Figure 142). Singlet oxygen has been used extensively for this purpose. In some instances, these reactions can be adapted to metal ion catalysis with hydroperoxide as the sacrificial oxidant. Lead tetraacetate, which usually proceeds through an *ortho* delivery mechanism, can be used in certain instances to prepare *p*-quinols from **542**, as can hypervalent $I^{iii}$ oxidants and $Tl^{iii}$ reagents. Benzene selenenic anhydride (BSA) has found limited use for this oxidation. In addition, some oxidants both deprotect and oxidize aryl ethers, such as **541**. Moreover, there are a few examples of oxidants that cleave an aryl or alkyl group from the aromatic substrate during the oxidation. Such a transformation would be required with compound **540**. In addition to oxidative methods outlined above, various 1,2-addition reactions and [4 + 2] cycloadditions to the carbonyl of *p*-quinone, such as **291**, lead to *p*-quinol derivatives.

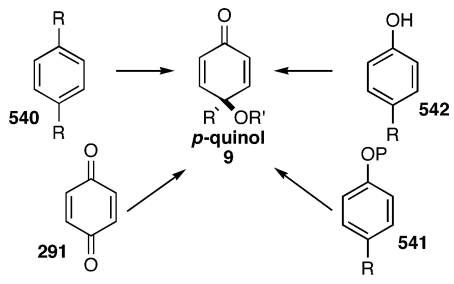



**Figure 142.** Strategies for the preparation of *p*-quinols.

Singlet oxygen has proven to be a very effective oxidant for producing *p*-quinols (Figure 143). *Endo* prepared rengyoside (**546**) by this method. Photooxygenation of the phenol **543** affords the *p*-quinol hydroperoxide **544**, which upon addition of dimethyl sulfide (DMS) undergoes rapid reduction of the peroxide to produce the tertiary alcohol **544**, followed by continued reduction in the presence of hydrogen gas and Pd/C to rengyoside (**546**).[226] Breton used a similar ploy in the synthesis of hallerone, halleridone, and rengyol.[227] Futamura and Saito report that 9,-10-dicyanoanthracene (DCA) accelerates photooxygenation by acting as a sensitizer.[228] Wasserman implemented a photooxygenation strategy to prepare a *p*-quinol intermediate in the synthesis of tetracyclin.[229] Fujioka has used the photooxygenation strategy in an approach to the avermectins.[230] In addition to the normal protocols, there are several other processes for the construction of the corresponding hydroperoxide. For example, Kharasch[231] has noted that the oxidation of a *p*-substituted phenol with oxygen in alkaline solution generates the corresponding hydroperoxide. In a related example, Pinhey[232] disclosed the autoxidation of a α-naphthol into its corresponding hydroperoxide compound. Pryor reports the oxidation of 2,6-di-*tert*-butyl-4-cresol (BHT) with ozone to generate the corresponding *p*-quinol hydroperoxide.[233] Metal complexes, on the other hand, containing $Cr^{vi}$,[234] $Co^{ii}$,[59a,235] $Mo^{v}$,[236] $Ti^{iv}$,[237] $Ru^{iii}$,[238,239] and $I^{iii}$,[240] are known to catalyze the formation of the *p*-quinol hydroperoxides. In contrast, $Cu^{i}$,[241] $Fe^{iii}$,[242] and $Co^{iii}$(salpr)(OH)[243] are known to convert the phenol directly into the *o*-quinols without a separate reduction with $PPh_3$, DMS or $H_2$−Pd/C.

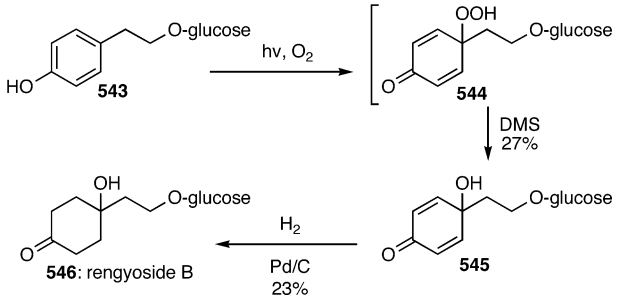



**Figure 143.** Generation of *p*-quinol hydroperoxides with $O_2$.

With regard to chemical oxidants, LTA can be used if it is added in the presence of a vast excess of HOAc (Figure 144). For example, Umezawa reports that treatment of phenol **67** in HOAc with LTA affords the *p*-quinol **547**.[40] Similarly, Bhatt finds that the addition of a polar solvent such as acetonitrile generates more of the *p*-quinol derivative.[11] In addition to solvent overriding the preference of LTA

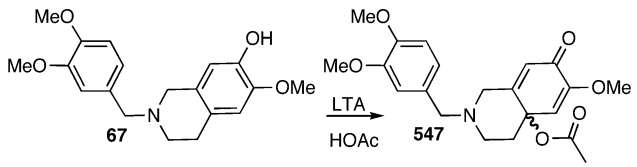



**Figure 144.** LTA/HOAc oxidation leads to a *p*-quinol product.

toward *o*-oxidation, if the starting phenol is substituted at the *o*- and *p*-positions, then the initial *o*-quinol product can undergo rearrangement to the thermodynamically more stable *p*-quinol product.

$I^{iii}$ oxidants have become the reagent of choice for the preparation of *p*-quinols. PIDA has been utilized extensively by Lewis,[244] Wipf,[245] Young,[246] and Pelter[154,247] for the preparation of *p*-quinols and their corresponding acetates. PIFA, although more expensive than PIDA, is often better behaved. An explanation is thought to reside with the more ionic nature of the PIFA mechanism, as compared with PIDA. The latter is believed to proceed through a SET mechanism. On many occasions, Kita,[16,155,248] Taylor,[16] Jacquesy,[249] and others have demonstrated the effectiveness of PIFA for oxidative dearomatization of phenols. For example, Hoshino reports that addition of a more than 3-fold excess of PIDA to **548**, followed by the addition of chloride ion results in the formation of the dichloro-*p*-quinol acetate **549** (Figure 145).[250] The transformation is presumed to involve the intermediate **550**. Togo,[251] Ley,[15] and Giannis[252] have developed polymeric derivatives that simplify workup procedures.

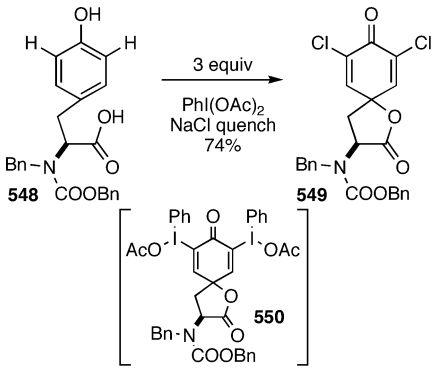



**Figure 145.** $I^{iii}$ oxidations result in *p*-oxidation and *o*-chlorination.

Before the advent of $I^{iii}$ reagents, $Tl^{iii}$ was the oxidant of choice for the preparation of *p*-quinols. For example, Schwartz reports that oxidation of phenol **551** with thallium trifluoroacetate results in the formation of quinol iminium intermediate **552** via an intramolecular oxidative pathway (Figure 146).[253] This iminium intermediate then undergoes hydrolysis on addition of $H_2O$, and the resulting amine adds in 1,4-fashion to afford the 4,5-hydroindolenone nucleus **553**. This technology could be of potential use in the synthesis of the lycorine alkaloid. Interestingly, if R′ = H on the nitrogen atom, then the starting material is recovered along with isolation of a complex mixture of products. In other $Tl^{iii}$ work, Nakano reports the oxidation of methyl podocarpate with thallium perchlorate in perchloric acid.[254] Kita finds that the oxidation of the amide **551** with $I^{iii}$ reagents also affords the pyrrolidine **553** in higher yields.[255] The cation **552** is postulated as the key intermediate that undergoes hydrolysis upon workup, resulting in a secondary amine, which adds to an enone in an intramolecular 1,4-addition.

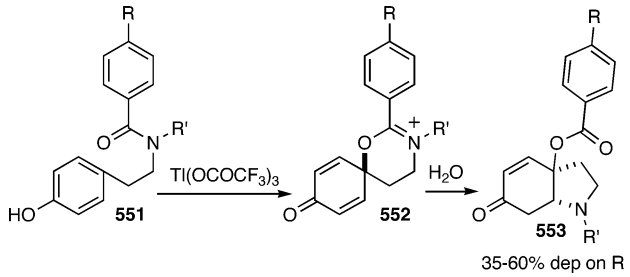



**Figure 146.** $Tl^{iii}$ oxidations successful for intramolecular additions.

There are a few examples in which benzeneseleninic anhydride (BSA) has been used for the preparation of *p*-quinols (Figure 147). Although the reagent usually favors *o*-delivery, the initial selenoxide adduct can be induced to undergo a [2,3]-rearrangement. For example, Cambie[256] reports that oxidation of totarol **554** with BSA initially affords **555**, but this selenoxide undergoes a [2,3]-rearrangement with subsequent cleavage of the PhSe−OR bond to produce the tertiary alcohol **556**. Barton has also investigated the formation of *p*-quinols with BSA.[257]

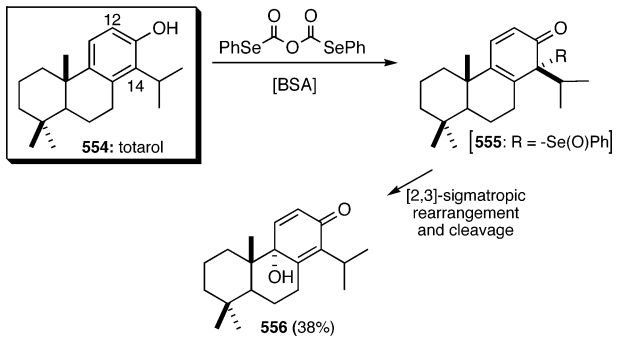



**Figure 147.** BSA oxidation and rearrangement affords a *p*-quinol.

With regard to electrochemical oxidations, Swenton has studied extensively the oxidations of phenols at platinum anodes and finds the electrochemical dearomatization method to be useful for the preparation of many *p*-quinols in both intermolecular and intramolecular formats.[30,158,258] However, in general, electrochemical methods provide products in lower yields than chemical oxidants. For example, Rieker investigated the electrochemical oxidation of tyrosine derivatives, such as **557** (Figure 148).[259] Anodic oxidation with graphite affords the lactone **558** in 44% yield. However, oxidation of **557** with NBS produces **558** in 97% yield. Similarly, PIFA oxidation of an analogue of **557** (*t*-Bu = H and Ac = BOC) proceeds to the corresponding lactone in a 76% yield. Nishiyama reports using a similar electrochemical process for the construction of spiroethers from 4-alkylated phenols.[260]

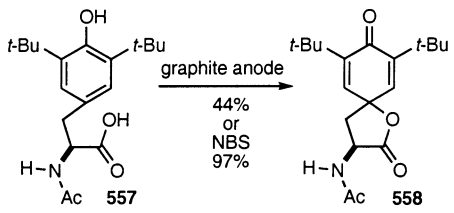



**Figure 148.** Electrochemical anodic oxidation.

A variety of other common oxidants can be used to generate *p*-quinols from 4-alkylated phenols. Benjamin observes *p*-quinone formation upon oxidation of BHT with $KMnO_4$ on Celite.[261] Milic reports that a combination of *m*-CPBA, $Bz_2O$, and light can be used to produce *p*-quinols from 4-alkylated phenols.[262] However, one of the more interesting mechanisms was reported by Yang (Figure 149).[263] It involves generation of a dioxirane from a carbonyl within the molecule and subsequent delivery of oxygen to the electron-rich aryl ring. For example, when compound **559** is exposed to oxone, the dioxirane **560** is thought to form. This intermediate delivers the oxygen atom producing epoxide **561**. Subsequent ring opening produces hemiketal **562**, which is isolated in 26% yield. This compound may undergo a second oxidation to form the dioxirane **563**. This reactive intermediate in turn epoxidizes the remaining olefin by an intramolecular delivery. Subsequent hemiketalization affords **564** in 22% yield.

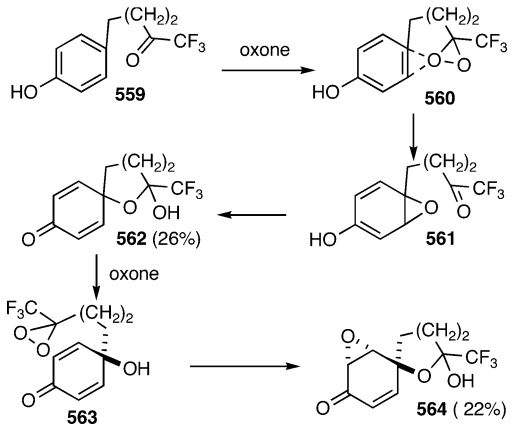



**Figure 149.** Oxone-initiated dearomatization of a phenol.

Several transition metal oxidants provide *p*-quinols. $Fe^{iii}$ in ferricyanide is the most prevalent. For example, Krauss reports that an intramolecular oxidative coupling occurs upon exposure of the diphenolic substrate **565** to $Fe(CN)_6^{3-}$ and results in the *p*-quinol derivative **566** (Figure 150).[264] Other groups have recounted similar reactivity of $Fe^{iii}$ reagents.[265]

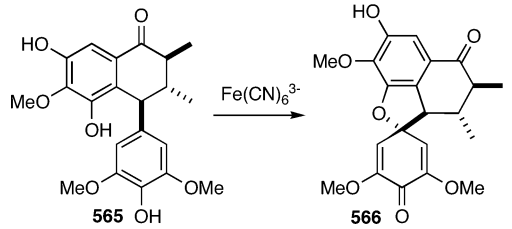



**Figure 150.** Ferricyanide oxidation and subsequent cyclization.

Triarylaminium salts have been used for oxidative dearomatizations (Figure 151).[266] For example, Tobinaga reports that exposure of **567** to Weitz's tris-(4-bromophenyl)aminium hexachloroantimonate salt (BAHA) results in oxidative cyclization and affords the *p*-quinol derivative **568** in 53% yield.

Cerium$^{iv}$ reagents work equally well; however, these reagents are particularly destructive and can

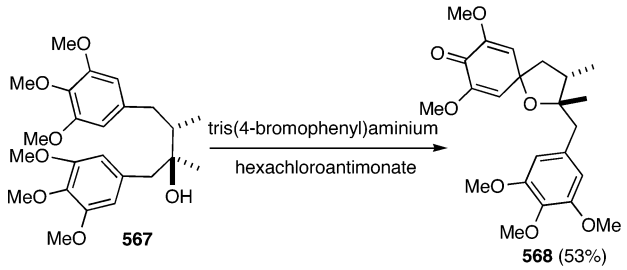



**Figure 151.** BAHA-initiated oxidation.

cleave an attached group during the oxidative dearomatization. For instance, Bhatt observed that treatment of the bis-phenyl naphthalene **569** with cerium ammonium sulfate affords the *p*-quinol **570** in 52% yield (Figure 152).[267]

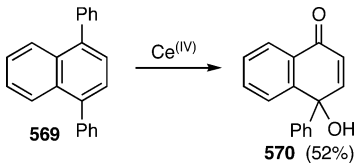



**Figure 152.** $Ce^{IV}$ oxidation and phenyl cleavage.

In addition to oxidation reactions, there are several strategies for preparing *p*-quinols from *p*-quinones. Among these, 1,2-additions and cycloadditions are of greatest importance. These reactions alleviate the need to install the oxygen atom *para* to the phenol and instead focus on the installation of a carbon atom. However, it is often difficult to stop the process after addition to one carbonyl of a *p*-quinone, but there are a few cases. For instance, Nair finds that dimethyl acetylene dicarboxylate (DMAD) can be induced to add to the most electron-deficient carbonyl of various benzoquinones in the presence of some nucleophilic initiator, such as $PPh_3$ or an isonitrile (Figure 153).[97a,b] In particular, the benzoquinone **571** undergoes cyclization in the presence of cyclohexyl isocyanide and DMAD to afford the iminolactone **572** in 92% yield. In related work, Engler has observed a [3 + 2] addition of silyl allenes to *p*-quinones promoted by $Ti^{iv}$,[268] and Pirrung has shown that the carbonyl ylides, generated by a rhodium-catalyzed decomposition of diazoketones, add to a carbonyl of *p*-quinones.[269]

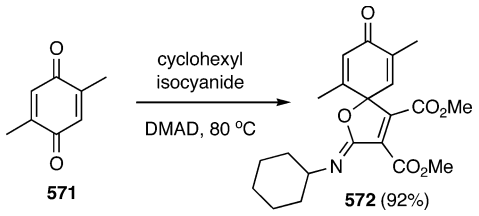



**Figure 153.** Ylide addition to *p*-quinones.

The Paterno−Buchi reaction between an alkene and a *p*-quinone carbonyl group has been shown to lead to *p*-quinol derivatives. Kochi,[270] Chrisl,[271] Takeshita,[272] Oshima,[273] Adam,[100c,274] Xu,[275] and Kim,[276] have investigated this reaction; however, Gilbert[277] determined the factors that influence the regiochemistry of the spirooxetane formation. For example, photolysis of **291** in the presence of ethyl

vinyl ether **148** furnishes **573** (Figure 154). It is proposed that a radical-ion pair charge-transfer exciplex forms leading to a biradical intermediate.

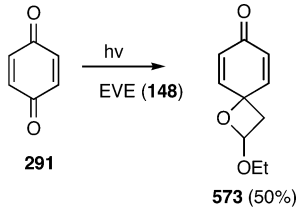



**Figure 154.** Paterno−Buchi reaction of *p*-quinones.

*p*-Quinones also undergo hetero-Diels−Alder reactions under thermal and photochemical conditions. For example, Hudlicky demonstrated that photolysis of **291** in the presence of diene **574** affords the [4 + 2] adduct **575** (Figure 155).[278] Kochi extensively studied the related thermal reactions with *o*-quinone dimethanes serving as the corresponding diene.[279]

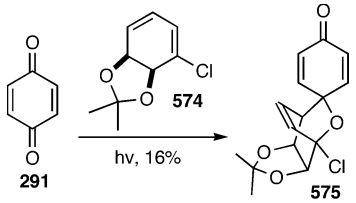



**Figure 155.** Hetero [4 + 2] reaction of *p*-quinones.

The most widely accepted method for producing *p*-quinols from *p*-quinones involves the 1,2-addition of a nucleophile to one of the carbonyls of a *p*-quinone. Chamberlin,[280] Evans,[281] Fischer,[282] Liotta,[283] Mukaiyama,[284] and Zwanenburg[285] have demonstrated this strategy in conjunction with organolithiums, Grignard reagents, and metalloenolates. In addition, organo-cerium,[286] -indium,[287] and -cadmium[288] nucleophiles have been reported. Triethyl(trifluoromethyl)silane undergoes a reaction with *p*-quinone to give a dienone bearing a geminal trifluoromethyl-protected triethylsilyl alcohol.[108] Cyanation reactions of *p*-quinones, which have been reported by Evans,[281] Onaka,[289] and Turner,[290] can be grouped in this category, as well. Hegedus reports that a cobalt complex transfers acyl residues to *p*-quinones.[291] With regard to the synthesis of unique molecular ensembles, Hibino combined methyllithium with a *p*-quinone in the total synthesis of carbazomycin G.[292] In addition, spirolactones can be constructed by the addition of *ortho*-lithiated oxazoles to *p*-quinones;[293] however, none of these transformations proves to be either enantioselective or diastereoselective. Corey reports a 1,2-addition to a *p*-quinone involving the zirconium enolate of **576**. This species adds to the *p*-quinone **577** to give **578** in 83% yield in a ratio of 1.3:1.0 (Figure 156).[294] This substrate was subsequently used in a synthesis of miroestrol.

## 6.2. Reactions

The synthetic chemistry of the *p*-quinol building block is overshadowed by its propensity toward aromatization via the dienone−phenol rearrangement when encountering acidic conditions and formation of a *p*-quinone methide under basic conditions. This leaves a small window for productive diastereoselective reactions. Nevertheless, *p*-quinols undergo 1,2- and 1,4-addition reactions, epoxidations, rearrangements and photochemical transformations.

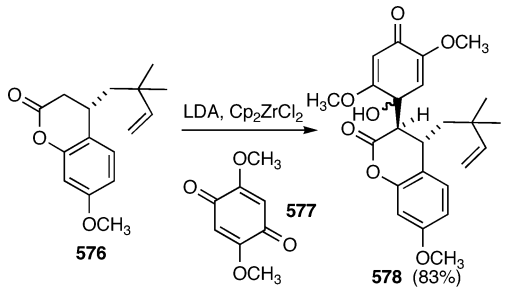



**Figure 156.** 1,2-Addition of a zirconium enolate to a *p*-quinone.

As shown in Figure 157, the dienone-phenol rearrangement of unsymmetrical cyclohexa-2,5-dienones such as **579** can lead to four potential aromatic products (**580**−**583**), and these transformations are of some use in synthetic aromatic chemistry. In most instances, because of the electron-donating properties of the OP group, the geminal R residue migrates to the most electron-deficient adjacent unsubstituted carbon; however, there are exceptions to this rule. For example, Suzuki finds that perfluoroalkyl residues impede the rearrangement of the R residue and instead result in OP migration.[295]

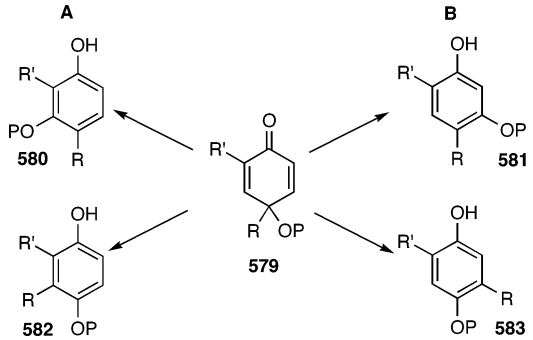



**Figure 157.** Dienone−phenol rearrangement pathways.

A nice example that demonstrates some of these effects has been reported by Swenton (Figure 158).[296] Treatment of **584** with the Lewis acid $TiCl_4$ triggers an aryl migration and affords **585** in yields ranging from 65 to 75%.

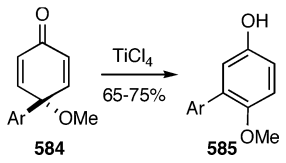



**Figure 158.** Lewis acid-mediated dienone rearrangement.

Woodgate has investigated the reactions of *p*-quinols under a variety of protic conditions (Figure 159).[297] Compound **586** proves unique in that the dienone−phenol rearrangement does not occur. Instead, treatment with $Ac_2O/H_2SO_4$ affords a mixture of **587** and **588**. The yields vary according with temperature and time. Under vigorous acidic condi-

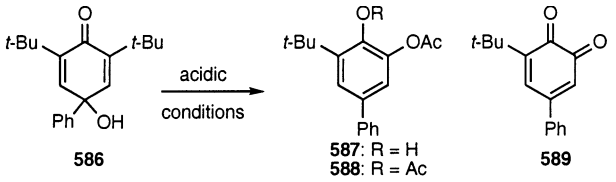



**Figure 159.** Protic acid-catalyzed rearrangements.

tions ($HClO_4$, $CF_3SO_3H$), the only products observed are the phenol **587** and the *o*-quinone **589**.

It was initially suspected that a dienone−phenol rearrangement explained the formation of **596** from **590** in 39% yield (Figure 160).[298] However, when conducted with the corresponding 8-deuterio *p*-quinol acetate, the regiochemistry of the substituents in the product could not be explained by the dienone−phenol rearrangement. Hoshino proposes the mechanism below, which involves intermediates **591**−**595** and includes several rearrangements and a Pictet−Spengler reaction.

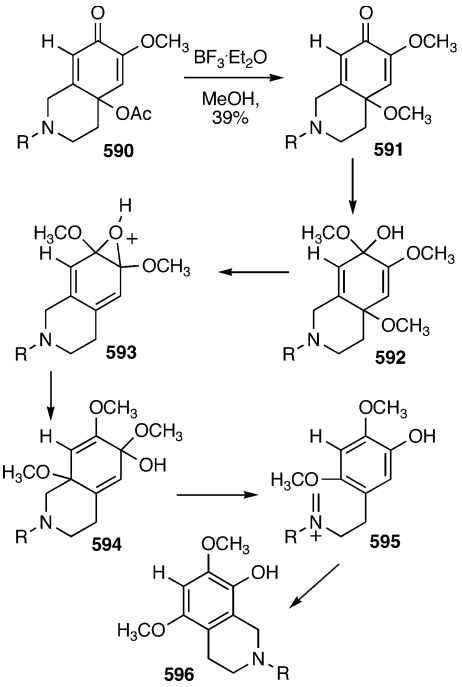



**Figure 160.** Boron trifluoride-induced rearrangement.

The sequence appears related to another rearomatization reported by Hoshino (Figure 161).[299] Treatment of *p*-quinol derivative **597** with $BF_3$·$Et_2O$/MeOH leads to the presumed ketal intermediate **598**, which undergoes an $S_N2'$ displacement to produce the intermediate **599**, which then eliminates the most electron-deficient group to produce compound **600**. This one-pot protocol is an efficient method for constructing resorcinol analogues of tyrosine.

With regard to reductive aromatizations, Swenton has shown that the treatment of *p*-quinol **601** with Zn/Cu results in the formation of the aromatic compound **602** (Figure 162).[258] This process most likely involves a SET to the *p*-quinol derivative resulting in a radical anion that suffers an elimination of the oxygen residue as its corresponding zincate.

Zwanenburg reports that depending upon the substitution on the 4-alkyl side chains, some *p*-quinols can serve as precursors to *p*-quinone methides.[285] He has incorporated this observation in efficient syntheses of several *p*-hydroxyphenylglycine derivatives (Figure 163). For example, treatment of **603** with DBU affords the intermediate *p*-quinone methide **604**, which undergoes addition of benzylamine to produce **605**. Umezawa, on the other hand, has used acidic conditions to generate *p*-quinone methides.[40a] For example, treatment of the *p*-quinol acetate **547** with $CF_3CO_2H$ affords the intermediate *p*-quinone methide **606**, which suffers addition of the electron-rich aryl ring to afford the azabicyclo[3.3.1]-nonane **607**. *p*-Quinone methides have also been generated from *p*-quinol hydroperoxides.[300]

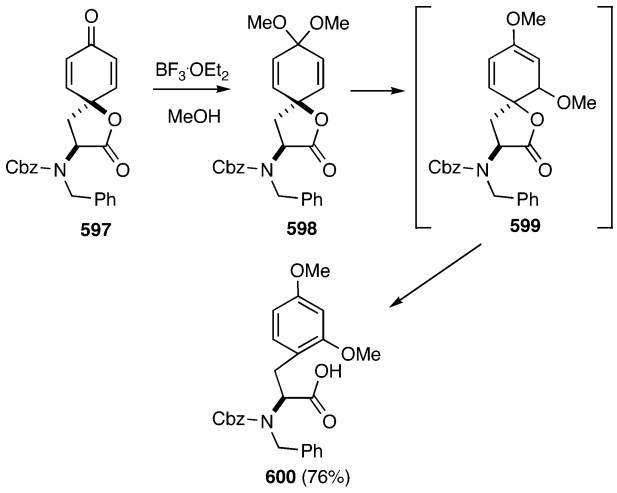



**Figure 161.** Ketalization and allylic displacement leading to a resorcinol.

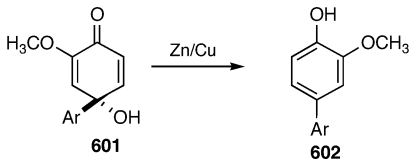



**Figure 162.** Zn/Cu reductive rearomatization of *p*-quinols.

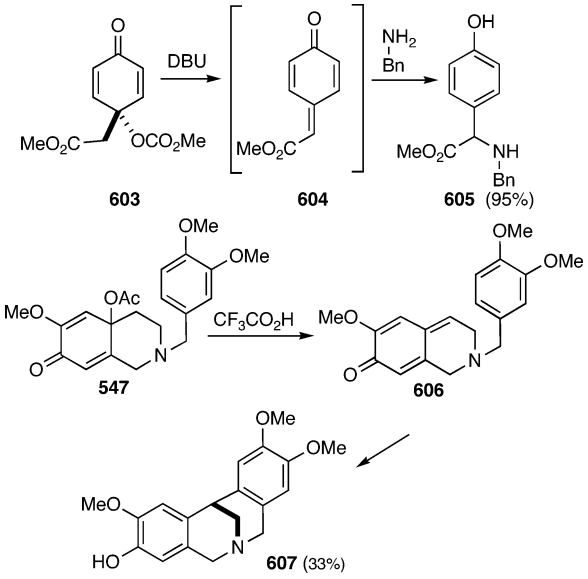



**Figure 163.** *p*-Quinone methides formation and reaction.

With regard to reactions of *p*-quinol derivatives resulting in stereochemical ramifications, such as 1,2-

addition to the carbonyl, there is strong evidence that facial selectivity observed in these reactions is often due to dipolar effects,[301] as in the addition of hard nucleophiles, such as cyanide.[302] For example, Fischer finds that the alkoxide **608** undergoes a diastereoselective 1,2-addition of methyllithium to afford the *syn* adduct **610** in preference to the *anti* adduct **611** (Figure 164).[282,303] Wipf reports similar facial selectivity in related systems.[301] The reaction of the ether **609** in the presence of methyllithium affords compounds **612** and **613** in a 3:1 ratio, respectively, in a 77% combined yield. Moore observes a *syn* preference upon the addition of lithium acetylides to other *p*-quinols.[101a]

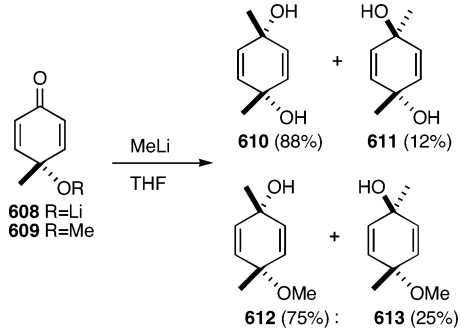



**Figure 164.** 1,2-Addition of alkyllithiums to *p*-quinols.

Traditionally, organolithium reagents favor 1,2-addition to the carbonyl moiety of a *p*-quinol derivative. However, upon the addition of bulky Lewis acid, such as MAD, this preference is overridden in favor of 1,4-addition addition. For example, precomplexation of ketone **584** with MAD and addition of R′MgBr produces **614** (Figure 165).[304]

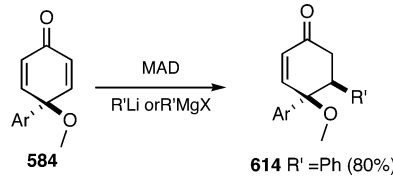



**Figure 165.** MAD complexation and 1,4-addition.

Unprotected *p*-quinol derivatives undergo diastereoselective 1,4-conjugate additions (Figure 166). Liotta finds that unprotected *p*-quinols undergo chelation-assisted nucleophilic addition reactions with Grignard and aluminum reagents.[283] For example, the reaction of **615** (R = −Bu) with MeMgBr affords **616**, whereas the addition of DIBAL-H to **608** (R= −Me) affords **617**. The corresponding protected derivatives are reported to afford an ∼1:1 diastereomeric ratio upon intermolecular 1,4-conjugate additions with malonitrile[305] and amines.[306]

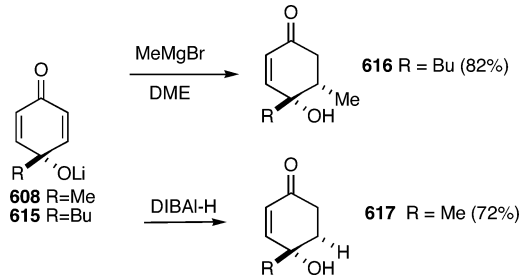



**Figure 166.** Directed 1,4-addition to *p*-quinols.

Wipf has investigated the intramolecular 1,4-additions of amines, and he finds the reaction to be highly diastereoselective. For example, PIDA oxidation of the amine **618** in methanol affords the *p*-quinol derivative **619** (Figure 167).[307] Subsequent treatment with base yields the pyrrolidine **620** by a subsequent 1,4-addition of the amine.

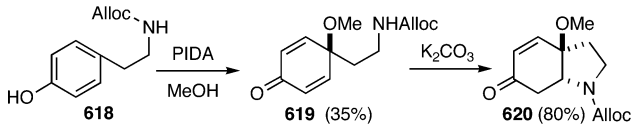



**Figure 167.** Intramolecular 1,4-addition of an amine.

Related conjugate additions of oxygen nucleophiles have also been reported (Figure 168). For example, upon sequential treatment with base and acid, Swenton[296] reports that the spirolactone **621** affords the lactone **622** in 54% yield.

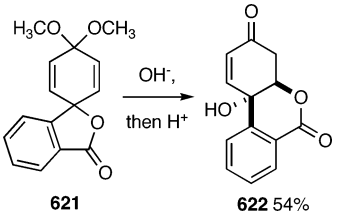



**Figure 168.** Saponification and intramolecular conjugate addition of RC(O)O−.

Several epoxidation reactions have been investigated in conjunction with *p*-quinols and their derivatives. For example, the *p*-quinol **623** undergoes epoxidation in the presence of *t*-BuOOH and VO(acac)$_2$ to give a 1:1 mixture of the *syn* epoxy alcohols **624** and **625**, as shown in Figure 169.[308] Some regiochemical selectivity was observed when VO(acac)$_2$ was replaced with Ti(O*i*-Pr)$_4$. The *dr* of **624** and **625** was found to be 69:31 and is presumably a consequence of olefin accessibility.

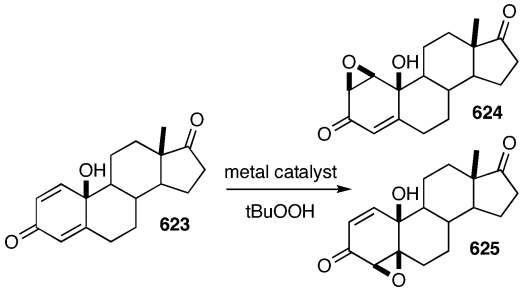



**Figure 169.** *Syn* epoxidation.

Dowd,[309] Wilson,[64] and Carnduff[310] have extensively investigated the chemistry of *p*-quinol hydroperoxides resembling the biochemistry of vitamin K (Figure 170). Compound **626** emerges from the pho-

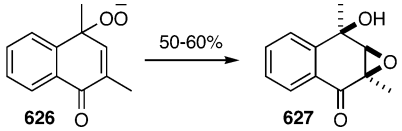



**Figure 170.** Hydroperoxides afford *syn* epoxy alcohols.

tooxygenation of the corresponding 4-substituted naphthol and then serves as an internal oxidant to produce the *syn* epoxy alcohol **627**.

A combination of [$Bn^+NMe_3$ −OH and $H_2O_2$] proves effective for diastereoselective epoxidation of *p*-quinols derivatives. Addition generally occurs on the face opposite the 4-alkyl substituent. Without dissimilar enones, the epoxidation occurs twice, resulting in a bis-epoxide. Neef utilized this reaction in the epoxidation of **628**, which provides **629** in 87% yield (Figure 171).[311]

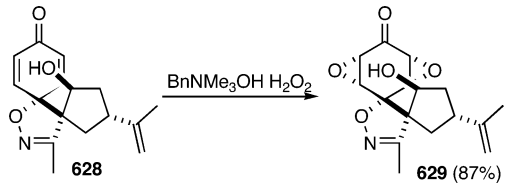



**Figure 171.** Other diastereoselective epoxidations.

With regard to annulation reactions leading to carbon ring frameworks, Camps reports that *p*-quinol derivative **630** undergoes a diastereoselective conjugate addition reaction with dimethyl 1,3-acetonedicarboxylate **437** on the face opposite the polar C−OMe bond (Figure 172).[312] Subsequent hydrolysis of the two esters and a bis-decarboxylation provides **631** in 44% yield.

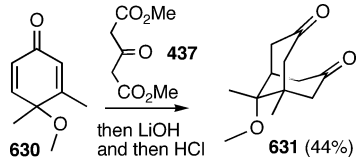



**Figure 172.** Sequential conjugate additions.

Anthraquinones are readily accessible from *p*-quinol derivatives via a Michael−Dieckmann sequence (Figure 173). For example, Mal[19] and Mitchell[20] report that the *p*-quinol derivative **632** undergoes a Michael−Dieckmann reaction with **61** to produce the anthraquinone **633** in a respectable 85% yield.

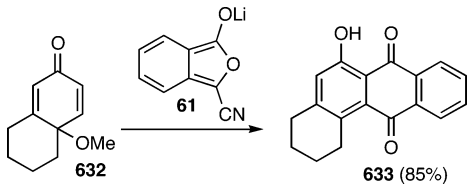



**Figure 173.** Michael−Dieckmann annulation.

The phenonium cations generated from *p*-quinol derivatives also undergo [5 + 2] cycloaddition reactions (Figure 174). For example, Thomas finds that exposure of the *p*-quinol **634** to methanesulfonyl chloride/triethylamine results in a cycloaddition with a styrene to form [3.2.1]-cycloadduct **635**.[313]

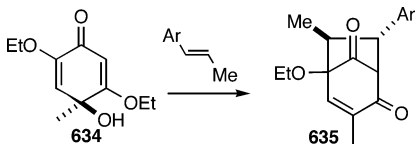



**Figure 174.** [5 + 2]-Cycloaddition reaction.

A rather unusual rearrangement has been observed with cyclic vinyl ethers that are derived from *p*-quinol spirolactones (Figure 175).[314] For example, upon heating, Swenton finds that the cyclic vinyl ether **636** proceeds to the ketone **637**. However, acyclic systems do not undergo this transformation. Instead, addition of [$(C_8H_{12})Ir(PMePh_2)_2$]$PF_6$ to the allyl ether **638** affords the vinyl ether **639**, which undergoes a Claisen rearrangement, affording **640**. This intermediate undergoes a cyclization and loss of $H_2O$ to give the benzofuran product **641**.

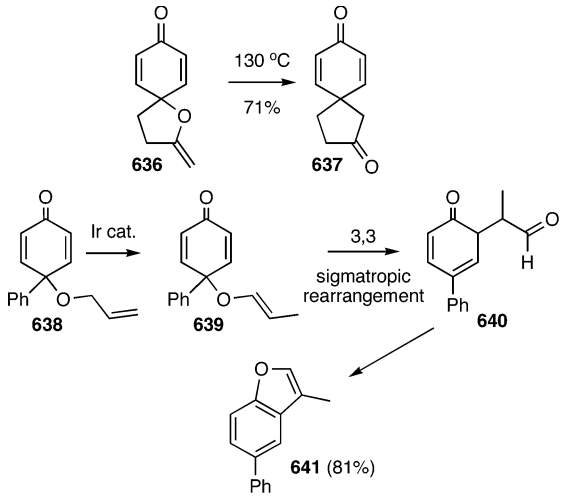



**Figure 175.** Rearrangements of *p*-quinol-derived vinyl ethers.

With regard to other reactions of *p*-quinol derivatives resembling $S_N2$ and $S_N2'$ transformations, Hoshino reports that **642** in the presence of TFA at 0 °C produces **65** and **66** (Figure 176).[38]

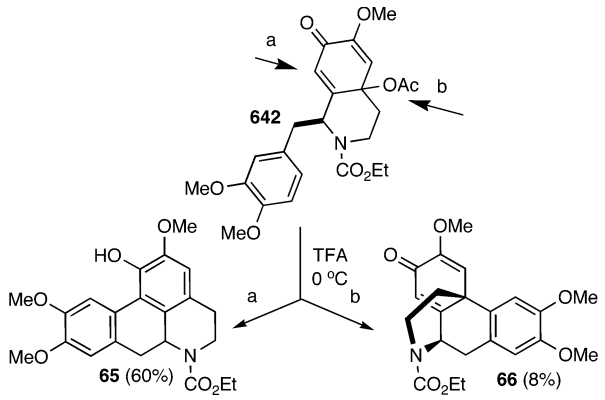



**Figure 176.** Intramolecular $S_N2'$ and $S_N2$ reactions.

Kurihara has devised an intermolecular variant of this process for the synthesis of biaryl compounds (Figure 177).[315] Treatment of the *p*-quinol **644** with a Lewis acid in the presence of various benzene derivatives affords the biaryl derivative **643**. Kuri-

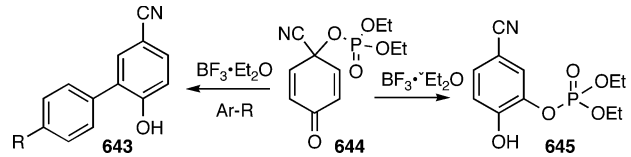



**Figure 177.** Intermolecular and intramolecular $S_N2'$ reactions

hara has also observed a 1,3-allyl transposition of diethyl phosphate, resulting in the conversion of the *p*-quinol derivative **644** into the *o*-hydroquinone derivative **645**.

As with MPB-ketals, *p*-quinols readily undergo reductive rearomatization under a variety of conditions. Parker reports that treatment of the *p*-quinol **646** with sodium dithionite in wet THF results in the formation of the phenol **647** in an 83% yield (Figure 178).[316]

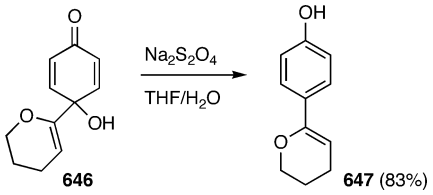



**Figure 178.** Reduction.

*p*-Quinols undergo many of the photochemical transformations resembling those of MPB ketals (Figure 179). Product distribution again is dependent upon the nature of the substituents and the reaction conditions.[317] For example, Taveras reports that photolysis of **648** (X = Br; R = *t*-Bu; $R^1$=OMe) affords the cyclopropane **653**, presumably through the biradicals **649** and **650**. On the other hand, photolysis of **648** (X = H; R = *t*-Bu; $R^1$=OMe) in methanol affords the ketal **652**, presumably via formation of the oxonium **651** from **650**. Schultz has further demonstrated that the cyclopropane **653** further degrades to the corresponding diradical **654**, which could also be viewed as the zwitterion **665**. The latter is intercepted via an intramolecular [3 + 4] cycloaddition to produce **656**.[130a]

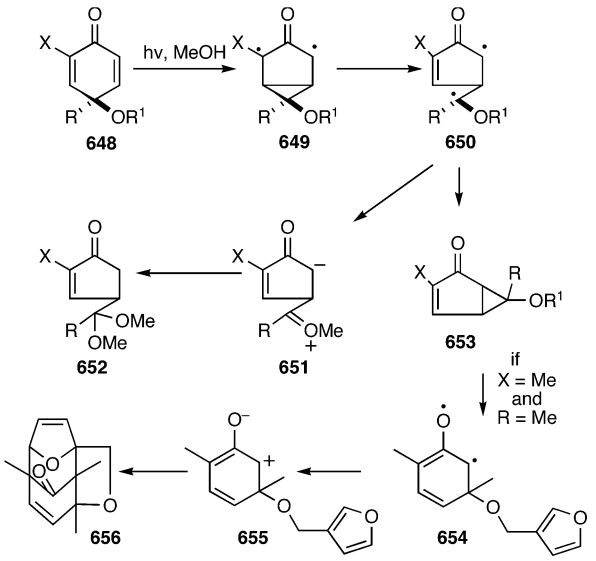



**Figure 179.** Photochemical reactions.

## 6.3. Synthetic Applications

In view of the many diastereoselective reactions that *p*-quinol derivatives undergo, it is very surprising that this class of tertiary alcohols has rarely been used as an intermediate in total synthesis. To the best of our knowledge, only the griseofulvinoids, futoquinoids, sorbicillinoids and ananorosinoids have been constructed from this class of cyclohexadienones.

Previous work on griseofulvin (**659**) and its dehydro counterpart **658** testify to the difficulties surrounding the development of an enantioselective route to the *p*-quinol nucleus and its innovative use in diastereoselective synthesis. For example, the absolute configuration of the tertiary alcohol of (+)-dehydrogriseofulvin (**658**) and (+)-griseofulvin (**659**) were established in 1959.[318] Although both molecules have been constructed in a racemic fashion by dearomatization of **657** (Figure 180),[319−322] neither has been formulated via an enantioselective dearomatization. However, Danishefsky[323] and Taub[320] have found that the enone **658** undergoes a diastereoselective hydrogenation with hydrogen adding from the less congested face of the enone to afford **659**.

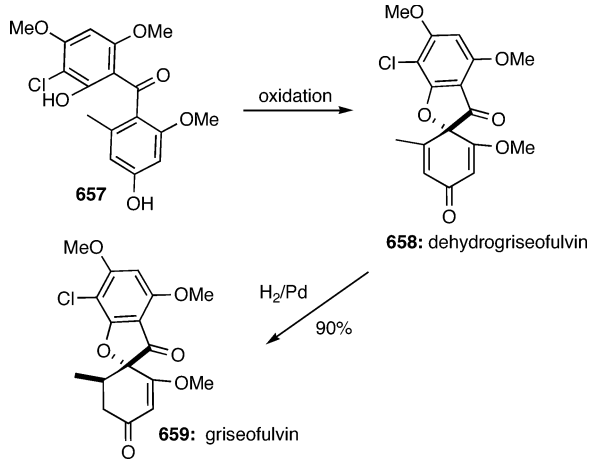



**Figure 180.** Synthesis of griseofulvin.

Yamamura has constructed several members of the futoquinoids family of natural products by an electrochemical oxidation in methanol (Figure 181).[324] For example, the electrochemical oxidation of phenol **660** produces isodihydrofutoquinol A (**661**) in a diastereoselective manner along with a 1:1 epimeric mixture of the *o*-quinols **662**. The mixture within **662** suggests that these *o*-quinol products are the result of *ortho* addition to the phenonium cation rather than by the reaction of the *p*-quinol adduct **661** with

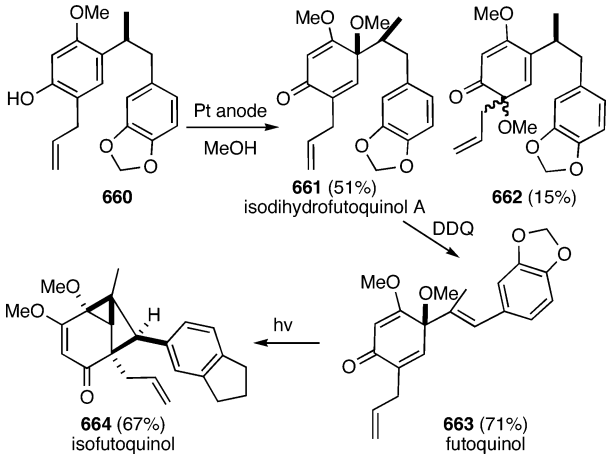



**Figure 181.** Yamamura synthesis of the futoquinoids.

methanol. In addition, Yamamura find that subjecting **661** to dehydrogenation with DDQ affords futoquinol (**663**). When this material is further subjected to photolysis, the unique carbon skeleton of isofutoquinol (**664**) forms.

Wipf,[325] McKillop,[326] and Hoshino[327] have reported syntheses of aranorosin using related *p*-quinol derivatives. Wipf reports that a PIDA oxidation of phenol **665** generates the *p*-quinol **666** in 40% yield (Figure 182). After protecting the nitrogen atom with a second Cbz residue, as shown in **667**, 1,2-addition of [(benzyloxy)methyl]lithium to the carbonyl provides **668** in a 5:1 mixture of diastereomers (major diastereomer shown). The allyl alcohol **668** is then subjected to a directed epoxidation and a few other transformations to install the side-chain and furnish aranorosin (**669**).

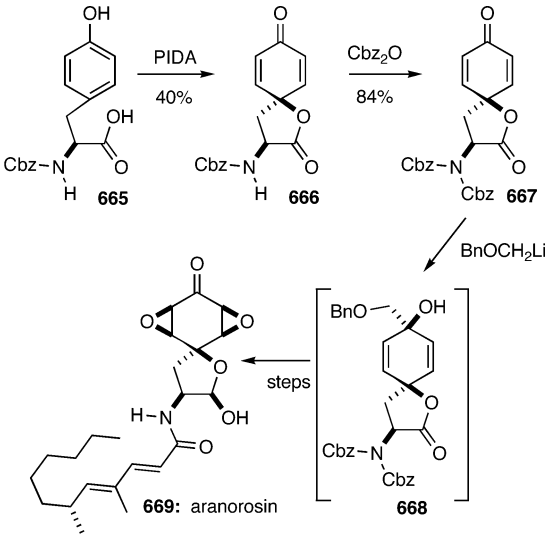



**Figure 182.** Wipf synthesis of aranorosin.

Pettus reports synthesizing both epoxysorbicillinol (**676**) and bisorbicillinol (**259**) from the same *p*-quinol intermediate **671** (Figure 183).[328] Oxidation of the phenol **670** furnishes the novel *p*-quinol derivative **671** in 63% yield. Treatment with PhIO affords the epoxide **672** as a single diastereomer. The sorbic side chain emerges unscathed from this epoxidation procedure. When the aluminum species **674** is added to the lactone **672**, the amide **675** arises in almost quantitative yield. Treatment of the vinylogous ester with $SnCl_4$ furnishes epoxysorbicillinol (**676**) upon protonation. In the case of bisorbicillinol (**259**), an acid-promoted rearrangement of **671** affords the spiroketal **673**. Successive treatment of this material with KOH and HCl affords **259** by way of a Diels–Alder cycloaddition of a $\beta$-diketone intermediate.

## 6.4. Enantioselective Horizons

Even though *p*-quinols and their derivatives have been used in relatively few syntheses of natural products, their unrealized potential for future enantioselective syntheses is outstanding. However, one obstacle remains: very few avenues permit the nonracemic creation of *p*-quinols. Only aranorosin has been synthesized in enantioselective manner. This achievement was because it could be derived

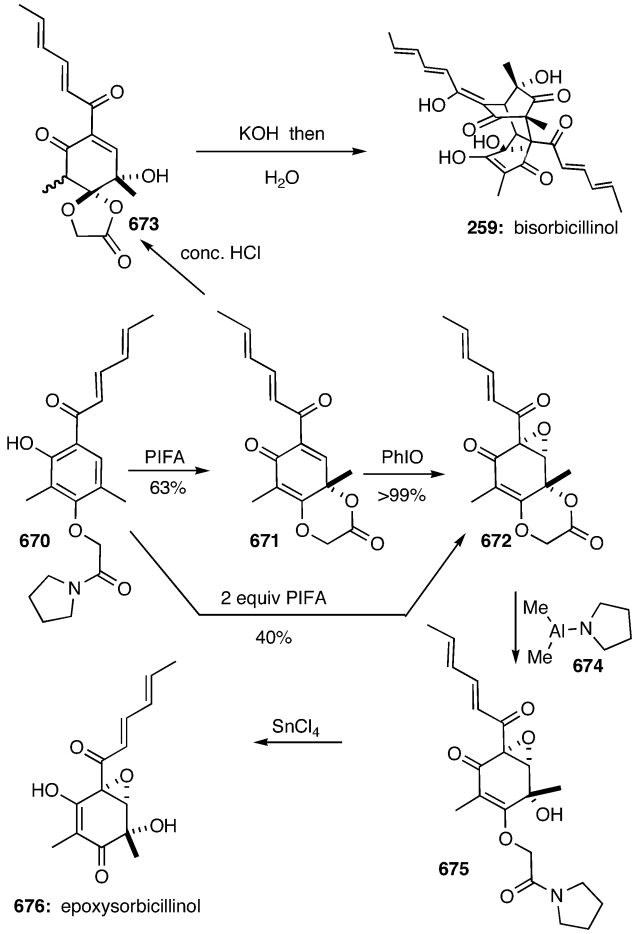



**Figure 183.** Pettus synthesis of epoxysorbicillinol and bisorbicillinol.

from L-tyrosine, a readily available amino acid available in the chiral pool. If other methods could be developed that address nonracemic *p*-quinol derivatives, then a plethora of natural products would be accessible in an enantioselective manner (Figure 184). The following figures and texts describe the preliminary research in this area.

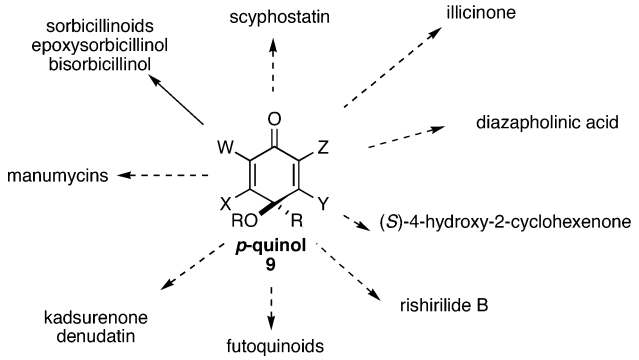



**Figure 184.** Plausible enantioselective syntheses from *p*-quinol intermediates.

Ponpipom completed a diastereoselective synthesis of kadsurenone (**211**) with $Tl(NO_3)_3$ (Figure 185).[121] Interestingly, oxidative dearomatization of the identical benzohydrofuran **207** with LTA affords a 1:1 mixture of kadsurenone (**211**) and its diastereomer denudatin (**210**). Presumably, the LTA oxidation proceeds by *ortho*-oxidation, which would be expected

to be stereo-indiscriminate along with the subsequent $S_N2'$ displacement of the tertiary acetate intermediate by methanol. On the other hand, the $Tl(NO_3)_3$ oxidation delivers the *p*-quinol product **211** directly. This latter mechanism permits the chiral methyl residue to exert diastereocontrol during the addition of methanol to the intermediate phenonium cation.

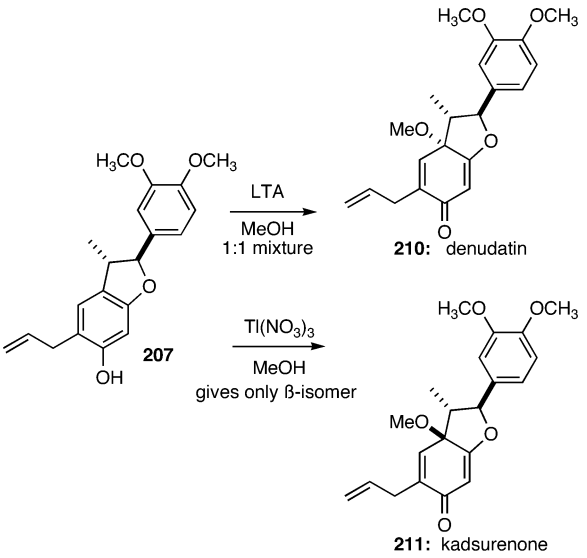



**Figure 185.** Syntheses of denudatin and kadsurenone.

Pettus reports a diastereoselective oxidative dearomatization of **677** using (*S*)-lactic amide to control the formation of the *p*-quinol product (Figure 186).[328] For example, oxidation of **677** with PIFA afforded **679** and **678** in a *dr* of 76:24. This crude material, when carried forward to (+)-bisorbicillinol (**259**) provided the natural product with 51% *ee*. Chromatographic separation of **679** leads to **259** in >99% *ee*.

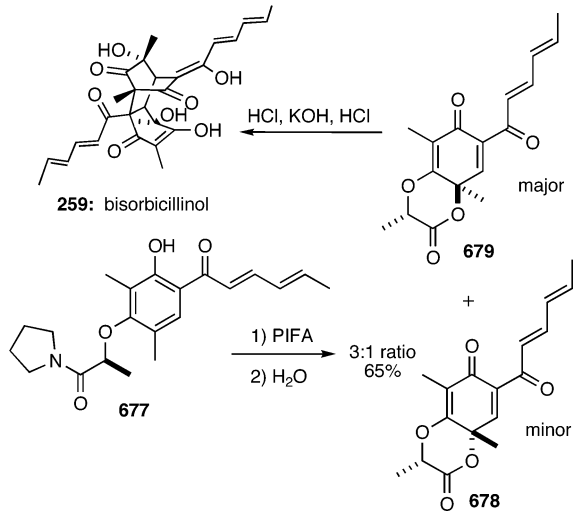



**Figure 186.** Diastereoselective oxidative dearomatization reaction.

More recently, Pettus has greatly improved upon this lactic amide directed dearomatization (Figure 187).[329] Provided the starting resorcinol derivative expresses a bromine atom between the two oxygen atoms, the *N*-methoxy-*N*-methylamide **680** affords dramatically improved diastereoselectivities. Oxidation of **680** with PIFA followed by the addition of $H_2O$ affords **681** with >15:1 diastereoselectivity. Subsequent reduction and elimination of the directing group provides the chiral cyclohexanol **682** in >99.1% *ee*.

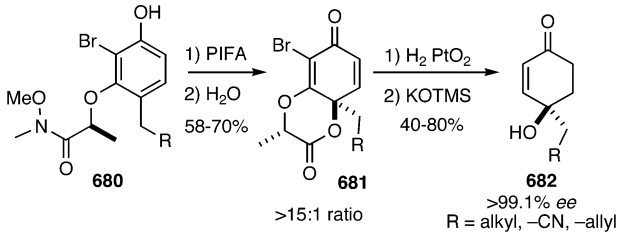



**Figure 187.** Diastereoselective dearomatization of 4-alkyl resorcinols.

Nishiyama has investigated the synthesis of various spirodienones and their subsequent conversion into benzopyran (Figure 188).[260] Electrochemical oxidation of **683** affords **684** and **685** in a 1:1 *dr*. Remarkably, treatment of **684** with $BF_3 \cdot Et_2O$ affords **686**, but treatment of its diastereomer **685** under similar conditions results in the formation of **687**. Both regioisomers are the result of a Lewis acid-promoted dienone−phenol rearrangement.

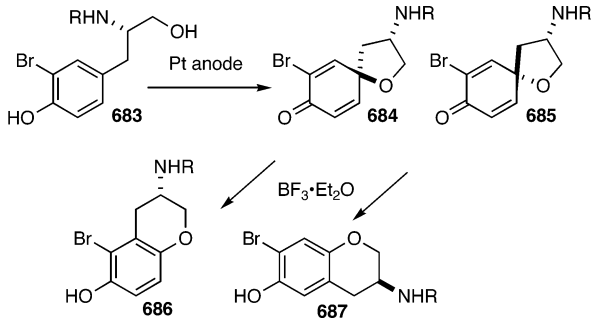



**Figure 188.** Nondiastereoselective dearomatization of chiral phenols.

Biosynthetic transformations have been utilized for the preparation of *p*-quinol derivatives (Figure 189).[330] For example, oxidation of **688** with a stable cell line isolated from the Chinese herbal plant *Tripterygium wilfordii* (coded as TRP4a) afforded **689** and **690** via an apparent "epoxidase" enzyme.

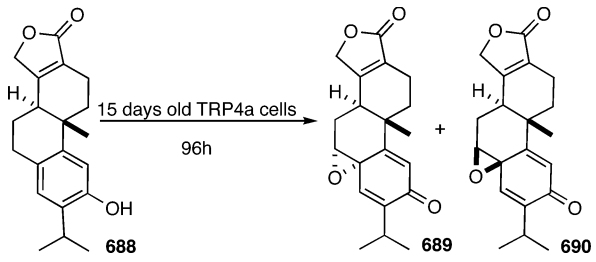



**Figure 189.** Enzymatic oxidation and epoxidation.

Another example of a diastereoselective Diels−Alder involving the chiral cyclopentadiene **486** applies it to the *p*-quinol derivative **691**.[216] The reaction of **691** with **486** under 6.5 kbar of pressure produces **692** as the sole adduct in 92% yield (Figure 190).

Feringa reports that chiral phosphoroamidite ligands catalyze the enantioselective 1,4-additions of dialkylzinc reagents to *p*-quinol derivatives when

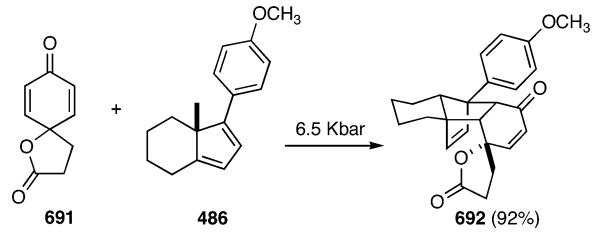



**Figure 190.** Enantioselective desymmetrization of prochiral MPB ketal by cycloaddition.

$Cu(OTf)_2$ is added (Figure 191).[222a] For instance, under these conditions, addition of diethylzinc to **609** affords **693** with a dr of 90:10 and in an *ee* of 97%.

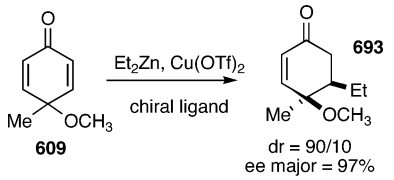



**Figure 191.** Enantioselective desymmetrization of prochiral MPB ketal by conjugate addition.

Renaud has investigated a related desymmetrization strategy of *p*-quinol derivatives via the formation of carbon−carbon bonds by the Ueno−Stork radical cyclization (Figure 192).[331] For example, the intramolecular radical cyclization of the ketal **694** initiated with $Et_3B/O_2$ affords **695** in a 74% yield and >98% *dr*.

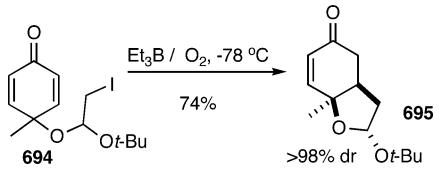



**Figure 192.** Diastereoselective radical initiated desymmetrization.

Clearly, the tools leading to the enantiomeric preparation of *p*-quinols and their derivatives are being sought. The methods mentioned above represent the first steps in the ability to control the diastereoselectivity and the enantioselectivity of these useful intermediates. Much of this work has already delineated the steric factors controlling the enantioselective preparation of *p*-quinol derivatives. It is only a matter of time before *p*-quinols and their derivatives are implemented in efficient enantioselective preparations of structurally diverse natural products.

## 7. Conclusion

The objective of this review article has been to present an overview of the preparations and applications of MOB-ketals, *o*-quinols, MPB-ketals, and *p*-quinols. We hope that readers have gleaned the unrealized potential of cyclohexadienones for enantioselective syntheses. The diastereoselective syntheses testify to the usefulness of these compounds as intermediates. Chiral auxiliaries and derivatizations, such as those shown in Figures 27, 80, 126−128, 131, 186, 187, 190, and 191 have been used with success for the production of these types of nonracemic cyclohexadienones. The more recent asymmetric catalytic methods shown in Figures 133 and 138 bode well for future enantioselective applications. We hope that readers choose to build upon some of these recent observations and design efficient enantioselective syntheses of biologically useful natural products using these systems as key intermediates. We consider the area to be an especially fertile frontier from which the chemical community should expect many more achievements.

## 8. Acknowledgment

We thank Dr. P. Wipf for taking the time to review this manuscript. His work has undoubtedly left a lasting impression on future chemistry of *p*-quinols, MPB-ketals, *o*-quinols, and MOB-ketals, and his diligence and helpfulness within the community are traits to which fellow academicians should all aspire.

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