Tetrahedron 66 (2010) 2235–2261

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 906

Hypervalent iodine-mediated phenol dearomatization in natural product synthesis

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ARTICLE INFO

Article history:
Received 8 December 2009
Available online 4 January 2010

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1. Introduction

The richness of the chemistry of phenols is quite remarkable when one realizes that it is simply the presence of a hydroxy group on a benzene ring that renders this otherwise quasi-inert aromatic system amenable to so many chemical transformations.[1] In their simplest structural expression (i.e., PhOH), phenols can be viewed as stable enol tautomers that, at least under inert conditions in standard solutions,[2] largely predominate by about 6–10 kcal/mol over their ketonic cyclohexa-2,4- and -2,5-dienone equilibrium counterparts because of the aromaticity of their phenyl ring (Scheme 1).[3] The relatively weak bond dissociation energy of their O–H bond (i.e., 87–90 kcal/mol in the gas phase)[4] opens the door to radical reactions via one-electron dehydrogenative oxidation into delocalized phenoxy radicals (i.e., PhO•, Scheme 1), which notably underly the (bio)synthetic implications of various phenolic precursors in the structural elaboration of numerous complex natural products, including biopolymers such as lignins.[5] This capacity to release homolytically a hydrogen atom is also one of the fundamental processes underlying the acclaimed health-beneficial antioxidant properties of many plant-sourced foods naturally containing phenols (and polyphenols) that are thus, by hydrogen transfer, capable of quenching deleterious free radicals adventitiously generated from biomolecules such as lipids, proteins and oligonucleic acids (i.e., DNA and RNA).[6] Of most relevance to the topic of this report is that phenols first and foremost play the role of

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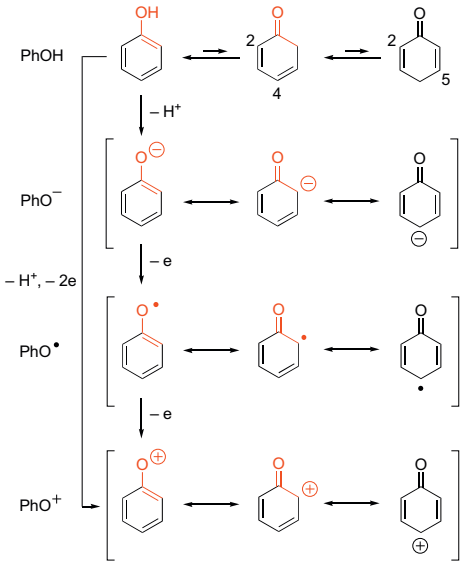
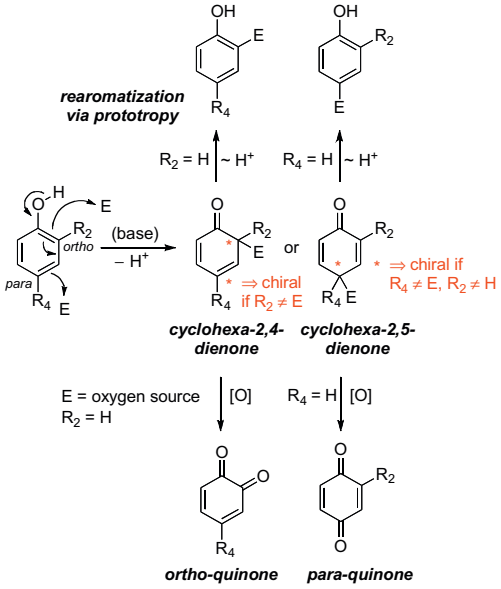
0040-4020/$ – see front matter
doi:10.1016/j.tet.2009.12.046

nucleophiles when enlisted on the ionic reactions stageshow. Phenols indeed share many of their reactivity features with those of any enolic entity, without resort to, at least in principle, any special reaction conditions or activating structural modification to fully express their nucleophilic character. Nevertheless, the stronger organic acidity of the phenolic O–H bond (i.e., pKa≈8–11) relative to that of standard enols derived from monocarbonylated compounds (pKa≈20–25) can be exploited under milder basic conditions to generate phenolate anions (i.e., PhO^-, Scheme 1), which are credited with an enhanced (harder) nucleophilic power. This nucleophilicity can, however, still be bridled for selectively directing reactions at either their oxygen or one of their *ortho*/*para*-carbon centers by making an appropriate choice of reaction conditions (e.g., nature of the countercation, solvent, and electrophilic partner). Acidic conditions can also be used, but, in this case, it is the reactivity of the electrophilic partner that has to be boosted by (catalytic) electrophilic assistance to promote the desired reaction.



Scheme 1.

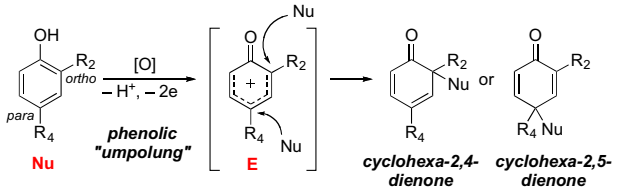
With these considerations in mind, several options are thus available to push nucleophilic phenols toward reaction pathways involving either their oxygen center or one of their *ortho*/*para*-carbon centers. The crucial difference between these two reaction pathways is that any bond-forming event that takes place at one of the *ortho*/*para*-carbon centers does imply a thermodynamically unfavored dearomatized species (Scheme 2). On the one hand, if the targeted carbon center is unsubstituted, such a dearomatization can be limited to an intermediate stage of the reaction, which can then be followed by a prototropic event that will mediate the rearomatization of the construct. Under appropriate (oxidative) reaction conditions, the *ortho*- or *para*-formation of a carbon-heteroatom (e.g., oxygen) bond can still lead to the formation/isolation of a dearomatized product (e.g., *ortho*- or *para*-quinone, Scheme 2), but only if the reactivity/stability of such a product permits. On the other hand, if the targeted carbon already bears a substituent of moderate or poor nucleofugality (e.g., an alkoxy group or a carbon-based substituent), the resulting dearomatized product can be isolated as such. This possibility offers unique strategic opportunities to the synthetic organic chemist, for the starting nucleophilic phenol is thus transformed into an extremely valuable cyclohexa-2,4- or -2,5-dienone synthon, and the six carbon centers of which are, in principle, all amenable to (regioselective) subsequent nucleophilic attacks. Furthermore, the reactivity of the linearly conjugated or cross-conjugated dienone motif of the cyclohexa-2,4- or -2,5-dienone is ideally suited for enabling participation in cycloaddition processes (e.g., Diels–Alder reactions). Another important asset of such a dearomatization of phenols for organic synthesis resides in the fact that one of the sp^2-hybridized carbon centers of a planar achiral starting material is thus transformed into a sp^3-hybridized carbon center and, hence, possibly chiral (Scheme 2). If such a creation of chirality can be enantio- or diastereoselectively controlled, it then offers tremendous opportunities for inducing asymmetry in subsequent reactions.[7]



Scheme 2.

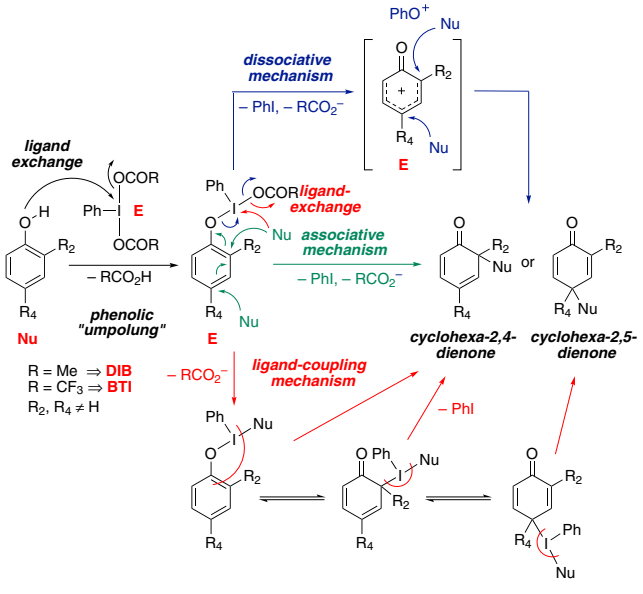
There is probably not much more to add to plead in favor of the value of phenol dearomatization processes in organic synthesis. However, it remains to evoke the different tactics by which such a transformation can be achieved. These tactics have been extensively discussed in several recent review articles.[7–13] Briefly, everything rests on the faculty of the phenolic hydroxyl group to shuttle electrons out of the phenyl ring. In this context, the nucleophilic reactivity of the phenol remains center stage. As depicted in Scheme 2, this reactivity can, for example, be exploited directly to install a desired substituent at an already substituted *ortho*/*para* locus, although the preparative value of such a nucleophilic substitution process usually suffers from a lack of regioselectivity, which is difficult to control with most electrophilic partners and is further impeded by the steric demand of the process.[14] Alternatively, the desired substituent can first be mounted on the phenolic oxygen atom and then transferred on to a substituted *ortho*-carbon center, as long as the inherent reactivity of the oxygen-mounted motif allows it. This is, for example, the case in the classical O-allylation/Claisen rearrangement sequence.[15,16] Another option is to take advantage of the susceptibility of the phenol toward oxidation by electron-transfer processes. For example, under neutral or slightly acidic anodic oxidation conditions, it is possible to convert a phenol (PhOH) into a phenoxenium cation (PhO^+) intermediate (see Scheme 1) that can then be trapped by a nucleophilic species, and this can be achieved in a regioselective manner at substituted *ortho*/*para*-carbons, especially if these bear electron-releasing substituents, to furnish the desired cyclohexadienone products (Scheme 3).[9] In spite of this appealing potential for synthesis, anodic oxidation processes are, unfortunately, not always credited with a high preparative value and often require some special electrochemical apparatus for ensuring selective transformations.[9] However, this tactical option is of fundamental importance, for it conceptually unearths the possibility of oxidatively switching the reactivity of phenols from being nucleophiles into becoming electrophiles (i.e., phenolic 'umpolung', see

Scheme 3). This reactivity switch is the fundamental event hidden behind the utilization of metal-based two-electron oxidants, such as those based on thallium(III), lead(IV) or bismuth(V),[9] to promote the generation of transient phenoxenium species from phenols in ionic reactions, including dearomatizing transformations. Two electrons are thus pulled out of the starting phenol and captured by the so-reduced metallic center. Along the same vein, any reagent capable of (1) expressing a suitable electrophilic character to react at either the oxygen or one of the *ortho*/*para*-carbon centers of a phenol and (2) installing a good leaving group at one of these centers will have the same aptitude as metallic two-electron oxidants at generating a phenoxenium cation or its equivalent.



Scheme 3.

Halogenating and other halogen-based reagents, for example, gather these dual reactivity criteria of electrophilicity and nucleofugality,[11,13] and, among these, hypervalent iodine-based reagents are especially well-suited to induce the desired reactivity switch.[11,13,17–20] In particular, hypervalent iodine(III) reagents (i.e., λ^3-iodanes) such as (diacetoxyiodo)benzene (DIB) and [bis(-trifluoroacetoxy)iodo]benzene (BTI) have, today, since the seminal work of Siegel and Antony,[21] pioneering applications in phenolic coupling-mediated alkaloid syntheses by Szántay,[22] White,[23] and Schwartz,[24] and further ground-breaking developments by Tamura and Kita,[25] Lewis[26] and Pelter,[27] have amply demonstrated their utility in mediating such a phenolic 'umpolung'. The iodine(III) atom first acts as an electrophilic center in a ligand-exchange step, during which one of the carboxylate ligands is substituted by the reacting phenol (Scheme 4). Once the phenoxy group is mounted on to the iodine(III) center, the reaction progress is essentially under the influence of the nucleofugality of the phenyl-λ^3-iodanyl group, which is itself driven by the favorable two-electron reduction of the iodine(III) center with concomitant elimination of a monovalent iodide (i.e., iodobenzene) (Scheme 4).[28]



Scheme 4.

The extent of such an entropically favorable leaving-group ability of a phenyl-λ^3-iodanyl group is extraordinarily high. It has been quantitatively determined by solvolysis experiments for the $Ph(BF_4)I$ unit to be about a million times higher than that of the triflate leaving group.[29] This 'hypernucleofugality' is an argument in favor of a dissociative mechanism by passage via phenoxenium (PhO^+) intermediates in iodine(III)-mediated phenol dearomatization reactions (Scheme 4).[30] The use of coordinative polar solvents such as alcohols and their fluorinated versions (vide infra) can certainly contribute to the stabilization of such cationic intermediates, but other options are conceivable and, perhaps, even favored when using apolar solvents. An associative bimolecular mechanism, during which the departure of the phenyl-λ^3-iodanyl group and the entry of the nucleophile occur in a concerted manner, is one of these options that does not imply any discrete phenoxenium ion intermediate (Scheme 4).[30a,b,31,32] Another possibility is that the initially formed phenoxy-λ^3-iodane species and/or its cyclohexadienonyl-λ^3-iodane (tautomeric) variants suffered a second ligand exchange with an incoming nucleophile to then evolve through reductive elimination of iodobenzene with concomitant bond formation between the other two ligands (i.e., the phenoxy/cyclohexadienonyl unit and the just-installed nucleophilic ligand),[33] by analogy with the *modus operandi* of transition metal-mediated coupling processes (Scheme 4). Of course, if the original iodine(III) ligands display an adequate reactivity in the absence of competing nucleophiles, such concerted ligand-coupling events could directly occur from the initially formed phenoxy-λ^3-iodane species. This could, for example, be the case with an acetate ligand when using DIB in CH_2Cl_2 or a phenyl ligand when using Ph_2ICl in DMF.[34] Such ligand-coupling mechanisms have been proposed to describe various iodine(III)-promoted reactions involving the formation of, *inter alia*, carbon-carbon or carbon-halogen bonds.[28,35,36] The ability to engage in ligand-coupling reaction pathways is, in fact, one of the inherent reactivity criteria that characterize the chemistry of organic hypervalent molecules of main-group elements.[37] This ligand-coupling ability should thus also be considered when describing the manner in which hypervalent iodine(III) reagents mediate the dearomatization of phenols,[33,34b] in much the same way as the related (dearomatizing or not) phenol transformations using, *inter alia*, polyvalent organobismuth(V) and organolead(IV) reagents.[35,38]

All of the above mechanistic descriptions, and even others implying the intervention of free-radical species, have been proposed, investigated and hence partially confirmed or invalidated without, however, reaching any firm conclusion in any case. Needless to say, these mechanistic issues are still the subject of much debate in the literature.[30a,b,31,33,34b,39] It would, of course, be quite utopian to hope for a unique and all-embracing mechanism that could underly the use of hypervalent iodine(III) reagents in phenol dearomatization processes. As for many (if not all) other organic reactions, the mechanistic cursor will move in one direction or another, depending on the reaction conditions used. By reaction conditions, we mean not only the type of solvent used and the physical parameters under which the reaction is performed, but also the nature of the ligands that strongly influences the reactivity at the iodine(III) atom on which they are mounted, as well as the nature of the starting phenol. Both the preference for a mechanistic pathway or another and the (successfully dearomatizing) reaction outcome are highly dependent on the regiochemical and stereoelectronic nature of the substitution pattern of the starting phenol ring. Furthermore, the fact that the desired phenol dearomatizing reaction takes place in an inter- or an intramolecular fashion can also have an impact on both its mechanistic pathway choices and outcomes. We have, so far, deliberately focused this introductory discussion on today's most commonly used hypervalent iodine(III) reagents, in order to expose the relative mechanistic complexity hidden behind

the successful utilization of such reagents in phenol dearomatization processes.

Higher hypervalent iodine reagents can also be used for the same purpose. For example, a λ^5-iodane, 2-iodoxybenzoic acid (IBX), has recently been identified as a powerful reagent to promote, in a strictly *ortho*-regioselective manner, the oxygenating dearomatization of phenols.[40] Phenols with free *ortho*-positions can thus easily be converted into *ortho*-quinones. Phenols bearing an electron-releasing group at one of their *ortho*-positions can conveniently be transformed into 6-hydroxycyclohexa-2,4-dienone derivatives. This IBX-mediated reaction, which we will refer to as the Hydroxylative Phenol Dearomatization (HPD) reaction,[8,41] is particularly useful to convert 2-alkylphenols into 6-alkyl-6-hydroxycyclohexa-2,4-dienones. Some members of this class of trivially named *ortho*-quinols either constitute as such the structural core of certain natural products or can serve as advanced intermediates in the synthesis of others via approaches that can often qualify as biomimetic, as we shall discuss in this report (e.g., see Section 7). Likewise, 2-alkoxyphenols can be regioselectively converted into hemiketalic *ortho*-quinols, which then rapidly collapse with elimination of the alcohol unit to furnish the corresponding *ortho*-quinones. This transformation has, for example, been exploited in the cleavage of *ortho*-phenolic methyl aryl ether bonds with great success by working up reaction mixtures under reductive conditions to convert the *ortho*-quinone products into their corresponding catechols.[40b] Again, the mechanistic details of the implication of IBX (and related λ^5-iodane reagents) in oxygenating phenol dearomatization processes have not yet been fully elucidated. We shall provide an update of the current mechanistic considerations in this report. Finally, another class of polyvalent iodine reagents that had demonstrated early on its utility in oxygenating phenol dearomatization processes is composed of periodic acid and periodates (i.e., Adler oxidation).[42] The success of these reagents also relied on the electrophilic character expressed at their iodine(VII) center and on their capacity to additionally serve as sources of oxygen atoms. Even though hypervalent iodine(III) and iodine(V) compounds are, today, the most commonly used polyvalent iodine reagents in phenol dearomatization reactions, some chemists remain unconditional users of these iodine(VII) reagents, in particular sodium periodate in various applications of the venerable Adler oxidation.

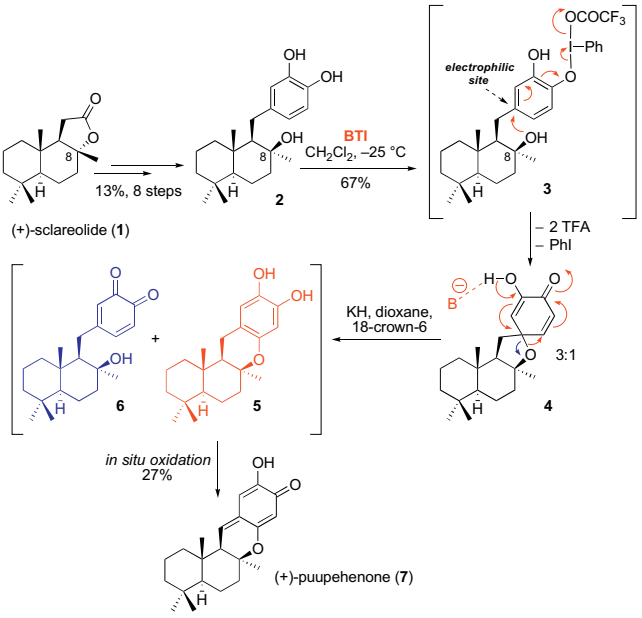
In the following sections of this report are highlighted some applications of hypervalent iodine-mediated phenol dearomatization reactions in natural product synthesis. It is evident from some of the references cited in this introductory section that the dearomatization of a phenol (by any means) is not new to the synthetic organic chemists' community. The main strategic advantage brought about by such a transformation conceptually resides in the fact that a monofunctional planar ring system can be converted into a polyfunctional three-dimensional and possibly chiral ring system, which is then amenable to a variety of subsequent and possibly asymmetric chemical reactions. It is thus not surprising that organic chemists have long perceived the dearomatization of phenolic materials as an attractive tactic in their design of the syntheses of complex natural products of various kinds. Many of the examples that we have selected for this report will illustrate such exploitations of the phenol dearomatization process, after which the phenolic nature of the precursor is hardly recognizable. Alternatively, it is, obviously, also possible to simply take advantage of the dearomatization process to temporarily render the starting phenolic ring susceptible to attack by nucleophiles for substitution, annulation and other functionalization purposes, including phenolic-coupling events. In any case, although several oxidizing systems are capable of promoting such phenolic transformations, as discussed above, the recent developments in the chemistry of hypervalent iodine compounds, notably as metal-free organo-oxidants of low toxicity and of ecologically benign impact, have occasioned a strong reappraisal of their value and utility in this avenue of the chemistry of phenols. Hence, the applications of hypervalent iodine-mediated phenol dearomatization reactions in the synthesis of complex natural products have literally burgeoned over the last ten years or so. The examples selected for this report have been taken from the literature published since 2000 (until May 2009), and are restricted to cases in which only free phenols are involved, and not their simple alkyl ether variants. The most significant other precedents and related applications of this chemistry have been compiled and discussed by us and others in several previous review articles.[7–11,13,19]

2. λ^3-Iodane-mediated dearomatization of phenols into cyclohexa-2,5-dienones

This process can be implemented either intra- or intermolecularly for promoting the formation of various types of bonds depending on the nature of the nucleophilic entity involved in the attack of the *para*-position of the oxidatively activated phenolic species. Examples of applications in natural product synthesis, during which either a C–O, C–N, or C–C, strategic or functional, bond is installed as a result of a λ^3-iodane-mediated dearomatization process, are discussed below.

2.1. Phenol dearomatization with carbon–oxygen strategic bond formation

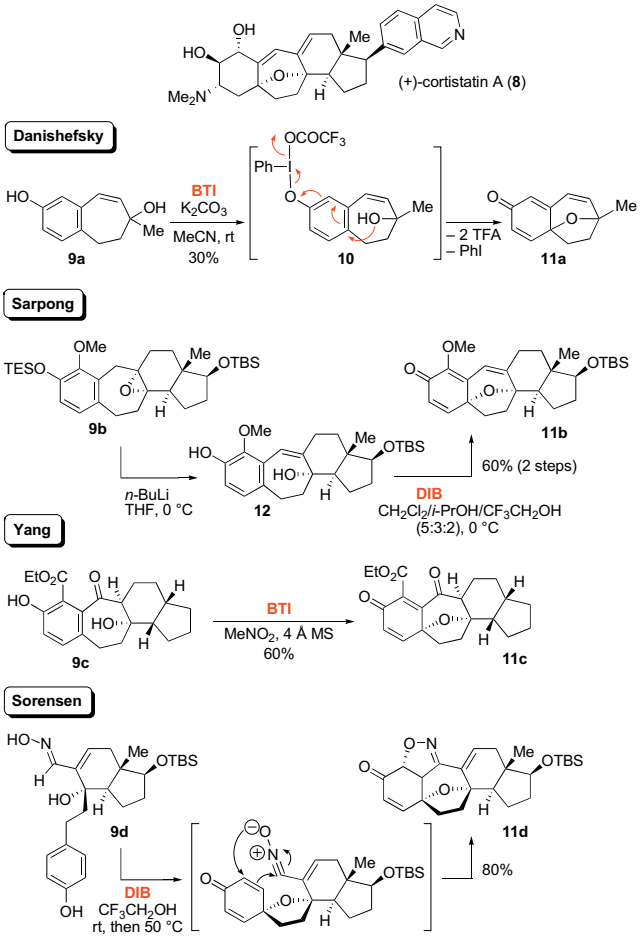
The first synthesis highlighted here is taken from our own work. It illustrates a case of intramolecular formation of a C–O strategic bond, and concerns the total synthesis of the marine quinonoid shikimate-sesquiterpenoid, (+)-puupehenone (**7**),[43] a promising antituberculosis agent, in ten steps starting from the commercially available plant metabolite, (+)-sclareolide (**1**) (Scheme 5).[44] The key feature of this synthesis is the construction of the heterocyclic part of the molecule via an intramolecular nucleophilic attack of the terpenoid C-8 tertiary alcohol on to an oxidatively activated 1,2-dihydroxyphenyl unit. After eight chemical steps from **1**, including the requisite epimerization of the C-8 center, the catechol **2** was treated with the λ^3-iodane BTI reagent at low temperature in dichloromethane to afford (via **3**) the spiro-cyclic advanced intermediate **4** as a 3:1 (unassigned) diastereomeric mixture (Scheme 5). In this transformation, the oxidizing BTI reagent served to promote the umpolung reactivity of the phenolic moiety and, hence, the



Scheme 5.

regioselective development of an electrophilic site at the *para*-carbon center on to which the terpenoid unit is connected. This electrophilic center was then combined with the tertiary alcohol function at C-8 to furnish the spiro-cyclohexa-2,5-dienone **4**, which was subsequently submitted to an anionic rearrangement in anhydrous dioxane in the presence of potassium hydride and 18-crown-6 to generate the rearomatized fused-ring system **5**, presumably together with the ring-opened *ortho*-quinone intermediate **6**. The catechol **5** could not be isolated, for its in situ oxidation, perhaps promoted by the *ortho*-quinone **6**, directly delivered the target (+)-puupehenone (**7**) in 27% yield from the spiro-cycle **4**.[44]

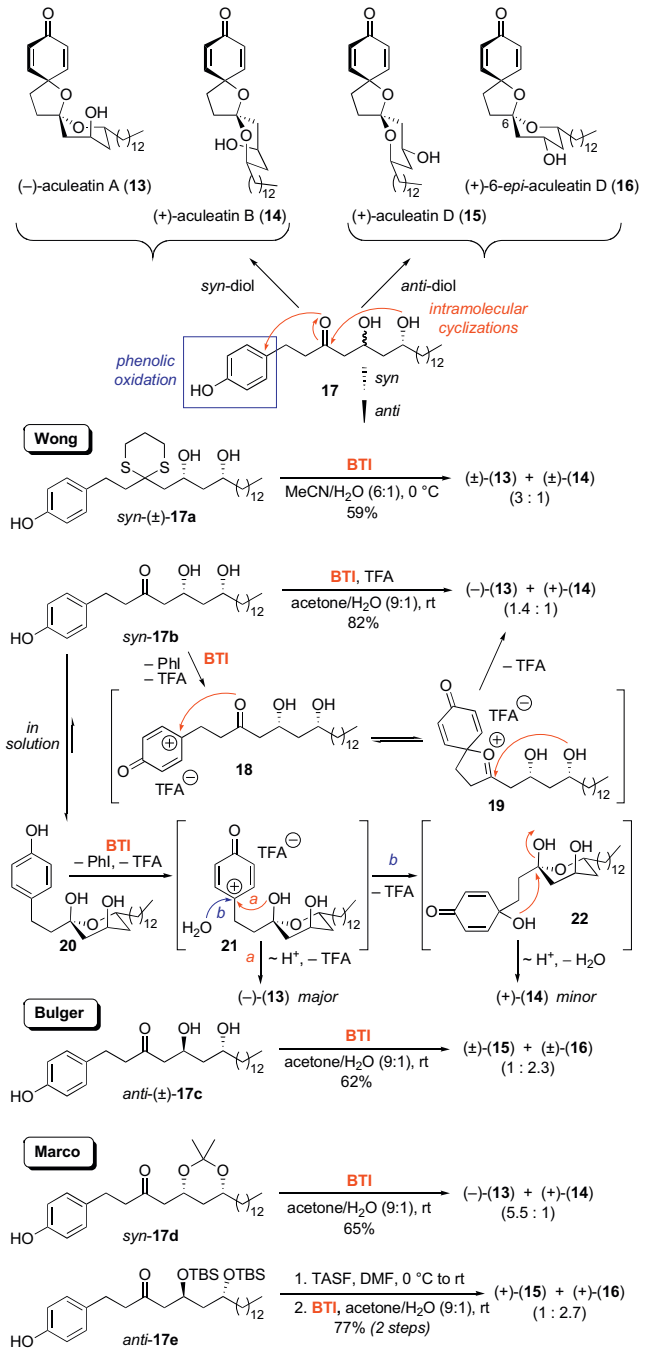
A related dearomatization approach to oxacyclization was recently proposed by Danishefsky's group for the synthesis of the oxabicyclo[3.2.1]octene system of (+)-cortistatin A (**8**), the most potent antiangiogenic member of the cortistatins, a novel class of steroidal alkaloids recently isolated from the marine sponge, *Corticium simplex* (Scheme 6).[45a] Treatment of the phenolic tertiary alcohol **9a** with BTI in the presence of potassium carbonate in acetonitrile at ambient temperature furnished (via **10**) the desired oxatricyclic system **11a** in 30% yield. Although Danishefsky and co-workers did not rely on this transformation in their synthesis of the cortistatin core,[45b] others followed very similar approaches to construct this oxapentacyclic system. Thus, Sarpong and co-workers relied on a DIB-mediated oxidative dearomatization/oxacyclization of the phenolic tertiary alcohol **9b** to generate (via **12**) the oxapentacyclic trienone **11b** in good yield (Scheme 6),[46a] while Yang and co-workers produced the analogous compound **11c** in 60% yield upon treatment of the phenolic tertiary alcohol **9c** with BTI in nitromethane in the presence of 4 Å molecular sieves (Scheme 6).[46b] More recently, Sorensen and co-workers reported the direct and efficient transformation of the phenolic oxime **9d**, using DIB in trifluoroethanol, into diastereomer **11d** by relying on Ciufolini's elegant tandem oxidative cyclizations, comprising (i) an ether ring formation via oxidative dearomatization, (ii) an oxidation of the oxime function to a transient nitrile oxide, and (iii) a final intramolecular [3+2] dipolar cycloaddition (Scheme 6).[47]



Scheme 6.

Another related synthetic venture in which the λ^3-iodane BTI reagent has particularly excelled is that of the synthesis of the aculeatins **13**–**16**. The naturally occurring spiro-ketals **13**–**15**, which were isolated from *Amomum aculeatum* rhizomes, display antiprotozoal activity against some *Plasmodium* and *Trypanosoma* species and feature an unusual 1,7-dioxadispiro[5.1.5.2]pentadecane system, which could arise biosynthetically from two intramolecular cyclizations initiated by a phenolic oxidative activation of a plausible precursor **17** (Scheme 7). This biosynthesis proposal was put to the test in a clever synthesis of racemic aculeatins A (**13**) and B (**14**) reported by Wong,[48] who demonstrated that BTI was the reagent of choice for casting the desired bis-spiro-ketal system. Thus, the phenolic *syn*-1,3-diol **17a** in acetonitrile/water (6:1) was directly converted in 5 min at 0 °C into (±)-**13** and (±)-**14** using BTI, which not only played its role of a phenolic umpolung mediator, but also provoked the cleavage of the 1,3-dithiane protecting group (Scheme 7).[48]

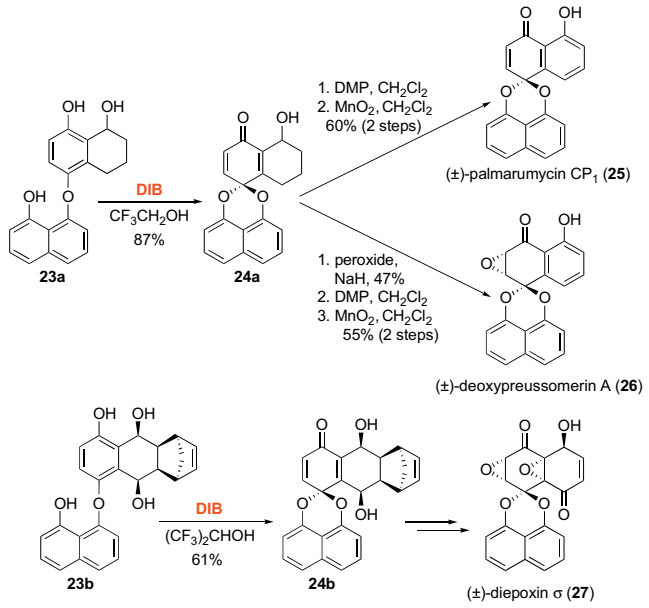
This remarkable biomimetic cascade reaction was later exploited by Bulger and co-workers to achieve the synthesis of racemic aculeatin D (**15**), in which case the *anti*-1,3-diol **17c** was treated with BTI in acetone/water (9:1) at room temperature to furnish (±)-**15** and its non natural 6-epimer (±)-**16** in 19 and 43% yield, respectively (Scheme 7).[49] Marco and co-workers then reported the enantioselective synthesis of (−)-aculeatin A (**13**) and (+)-aculeatin B (**14**) by submitting the optically pure phenolic *syn*-acetonide **17d** to BTI oxidation in acetone/water (9:1) at room temperature for 24 h. Under these conditions, the acetonide unit was hydrolyzed and the oxidative activation of the phenolic moiety engaged the desired spiro-ketalization to afford a 5.5:1 mixture of (−)-**13** and (+)-**14** in a combined yield of 65% (Scheme 7).[50] A similar approach was followed to achieve the enantioselective synthesis of both the natural (+)-aculeatin D (**15**) and the non-natural (+)-6-*epi*-aculeatin D (**16**), for which the bis-silylated *anti*-1,3-diol **17e** was first desilylated using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) prior to BTI oxidation to furnish a 1:2.7 mixture of (+)-**15** and (+)-**16** in 77% yield over two steps (Scheme 7).[50b] More recently, Wong and co-workers have revisited their synthesis and reported significant improvements leading to concise and stereocontrolled syntheses of aculeatins (−)-A (**13**), (+)-B (**14**), (+)-D (**15**) and (+)-6-*epi*-D (**16**).[51] This work notably showed that the yield of the final key phenolic oxidation cascade reaction was increased when carried out in the dark, at higher concentration (0.04 M), and with the addition of 0.4 equivalent of trifluoroacetic acid (TFA). Wong and co-workers reasoned that trifluoroacetate could act as a non-nucleophilic counteranion capable of contributing to the stabilization of cationic phenoxenium intermediates such as **18** or **21**, as well as the spiro-oxocarbenium cation **19** derived from **18** (Scheme 7).[51] Such a passage by phenoxenium species and their derivatives would imply that the BTI-mediated phenolic oxidation follows a dissociative mechanistic pathway (see Section 1, Scheme 4), which is conceivable in the polar protic medium [i.e., acetone/water (9:1)+TFA] in which the reaction occurred. The preferential formation of (−)-A (**13**) over that of (+)-B (**14**) was not easy to rationalize when invoking passage by an intermediate such as **19**, but an open-chain precursor such as **17b** exists in solution as an equilibrium mixture together with its cyclic hemiketal form **20**, which appears to become predominant under acidic conditions.[49,51] Hence, Wong and co-workers proposed that the hemiketal **20**, upon treatment with BTI, would give rise to the phenoxenium cation **21** that can then be trapped by nucleophilic



Scheme 7.

entities according to two pathways, either by intramolecular attack of the hemiketal hydroxyl function (Scheme 7, path *a*) to give (−)-**13**, or through the addition of water (path *b*) and subsequent intramolecular cyclization of the resulting *para*-quinol **22** via an acid-catalyzed displacement of the hemiketal hydroxyl function to afford (+)-**14**.[51] An analogous rationalization was proposed for the preferential formation of (+)-6-*epi*-aculeatin D (**16**) versus (+)-aculeatin D (**15**).[51]

Wipf and co-workers have investigated in great detail the chemistry and synthetic potential of cyclohexa-2,5-dienone derivatives,[10,52] and, in doing so, they also made major contributions to the development of hypervalent iodine-mediated phenol dearomatization processes in natural product synthesis. For example, they relied on the use of the λ^3-iodane DIB reagent in trifluoroethanol to mediate the intramolecular cyclization of the hydroxylated dinaphthyl ether derivative **23a** into the *para*-quinone spiro-monoketal **24a**, which then served as a common intermediate in the racemic synthesis of the fungal naphthoquinone spiro-ketals, palmarumycin CP_1 (**25**) and deoxypreussomerin A (**26**) (Scheme 8).[53] The synthesis of the more highly oxygenated analogue, diepoxin σ (**27**), required additional developments to elaborate its γ-hydroxylated enone moiety. In particular, the enone alkene unit was protected under the form of a cyclopentadiene-derived Diels–Alder adduct throughout the entire synthesis. The key tetrahydroxylated diaryl ether intermediate **23b** was then spiro-cyclized into **24b** in 61% yield by using DIB in hexafluoro-*iso*-propanol (Scheme 8). Five additional steps completed this synthesis of racemic diepoxin σ (**27**).[54]

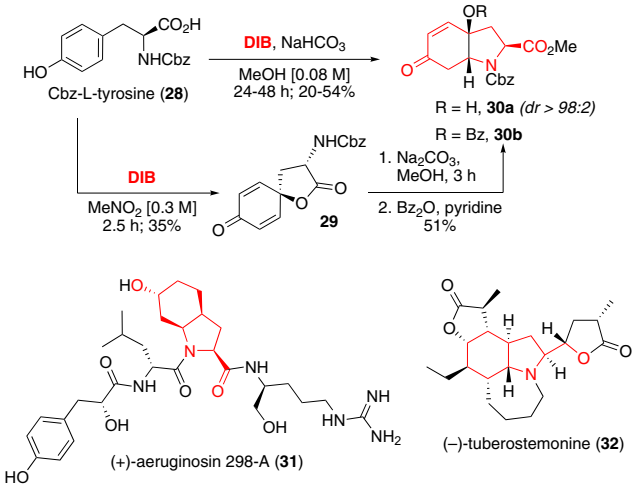


Scheme 8.

2.2. Phenol dearomatization with carbon–nitrogen strategic bond formation

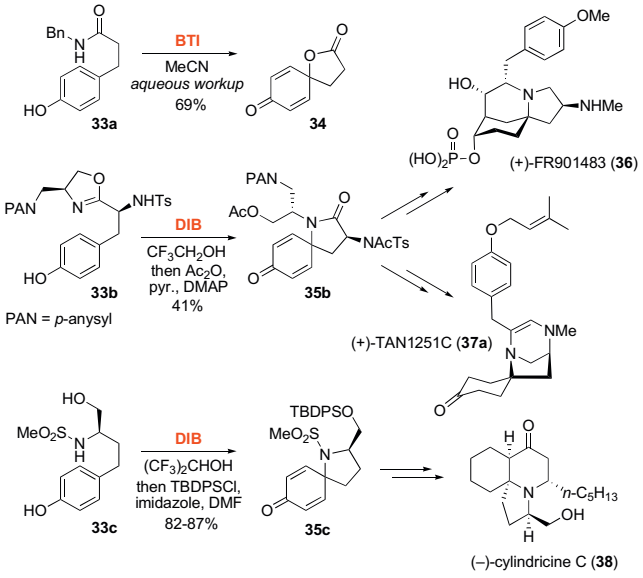
Additional work by the Wipf group will also be highlighted in this section, as they have recently further demonstrated the utility of their λ^3-iodane-mediated tyrosine oxidative spiro-cyclization–rearrangement sequence to access diastereoselectively functionalized hydroindole amino acid derivatives such as **30a**,[55a] from which they had previously achieved the total synthesis of the *Stemona* alkaloid, (−)-stenine.[55b] This tandem process deserves special mention here, for the λ^3-iodane-mediated phenol dearomatization is, in fact, exploited to first install a C–O functional bond, i.e., that of the spiro-lactone intermediate **29** (Scheme 9), which is then opened during the rearrangement event to enable the formation of the C–N strategic bond of the desired azacycle **30a** via an intramolecular Michael process. Thus, Wipf and co-workers also utilized **30a** in the total synthesis of the potent thrombin inhibitor, (+)-aeruginosin 298-A (**31**),[56a] a metabolite isolated from the blue-green freshwater alga, *Microcystis aeruginosa*, and, more recently, in that of the *Stemona* alkaloid, (−)-tuberostemonine (**32**), and its derivatives (Scheme 9).[56b,c] In the course of this remarkable synthesis work, Wipf and co-workers optimized the oxidative spiro-cyclization of L-tyrosine. Carbobenzoxy (Cbz)-*N*-protected L-tyrosine (**28**) was previously dearomatized upon treatment with the λ^3-iodane DIB reagent in methanol (0.08 M) in the presence of

sodium bicarbonate to directly furnish, after 24 to 48 h, the *cis*-indolinone **30a** in yields ranging from 20 to 54%. Scale up of the reaction (100 g vs 500 mg) at a higher concentration (0.3 M) in nitromethane in the absence of base and methanol furnished, after only 2.5 h, the spiro-cyclohexa-2,5-dienone **29** in a still modest, yet reproducible, yield of 35%. This spiro-cycle could then be rearranged using Na_2CO_3 in methanol and benzoylated to afford the *cis*-indolinone **30b** in 51% yield from **29** (Scheme 9).[56c]



Scheme 9.

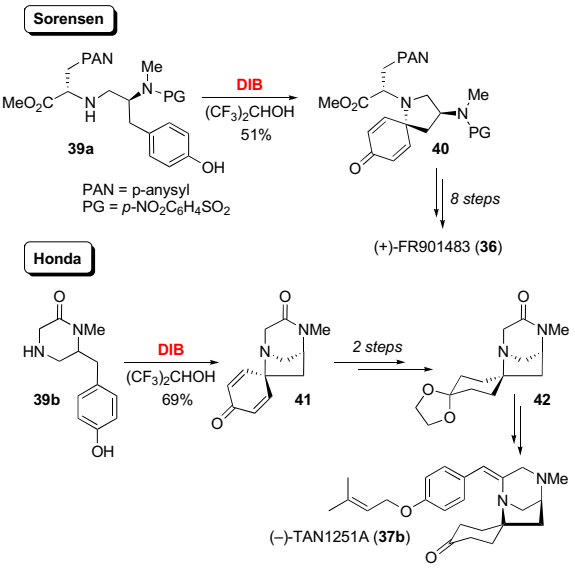
In the context of their synthesis efforts toward tricyclic azaspiranes biosynthetically derived from tyrosine,[57] Ciufolini and co-workers took on the challenge of developing a means to access aza-spiro-cyclic systems from phenols *para*-alkylated with a nitrogen-containing side chain. Initial attempts made by Kita and co-workers using BTI to spiro-cyclize phenolic amides such as **33a** (Scheme 10),[25] as well as *N*-acyltyramines,[58] resulted in products such as **34** only derived from nucleophilic attack of the carbonyl oxygen of the amide groups. Ciufolini and co-workers reasoned that the resonance-promoted electronic displacement from N to O in an amide function would be reversed in an iminoether function, and hence identified oxazolines as amide equivalents adequately suited to express the desired nucleophilic reactivity at the nitrogen



Scheme 10.

center. The synthesis of the cyclohexa-2,5-dienone spiro-lactam **35b** was thus successfully achieved by treating the L-tyrosine-derived oxazoline **33b** with DIB in trifluoroethanol, immediately followed by acetylation (Scheme 10). This spiro-lactam then served as a common intermediate for the synthesis of (+)-FR901483 (**36**)[57c,59] and (+)-TAN1251C (**37a**).[57c] Further investigations on hypervalent iodine-mediated dearomatizing amidation of phenols led Ciufolini and co-workers to work with phenolic sulfonamides that turned out to be much better substrates than oxazolines for aza-spiro-cyclization.[57a,b,60] For example, the sulfonamide **33c** was converted into the cyclohexa-2,5-dienone spiro-cycle **35c** in high yield using DIB at ambient temperature in hexafluoro-*iso*-propanol (Scheme 10). The total synthesis of the ascidian *Clavelina cylindrica* metabolite, (−)-cylindricine C (**38**), was accomplished from this aza-spiro-cyclic intermediate.[60]

In parallel investigations, Sorensen and co-workers also accomplished an enantiospecific synthesis of the potent immunosuppressant, FR901483 (**36**, Scheme 10), by relying on a λ^3-iodane-mediated oxidative phenol dearomatization reaction to cast the azaspirane system (Scheme 11).[61] However, they instead used a phenolic secondary amine **39a**, which they exposed to DIB in hexafluoro-*iso*-propanol at room temperature to generate the azaspiro[4.5]decadienone **40** in 51% yield (Scheme 11). Eight additional transformations furnished the targeted FR901483 (**36**).[61] In a yet similar approach, Honda and co-workers reported an efficient formal synthesis of (−)-TAN1251A (**37b**), for which a DIB-mediated oxidative dearomatization of the phenolic cyclic secondary amine **39b** in hexafluoro-*iso*-propanol at 0 °C was also used to afford the desired spiro-cyclohexa-2,5-dienone **41** in 69% yield. This compound was then transformed in two steps into **42**, a known precursor for the synthesis of (−)-**37b** (Scheme 11).[62]

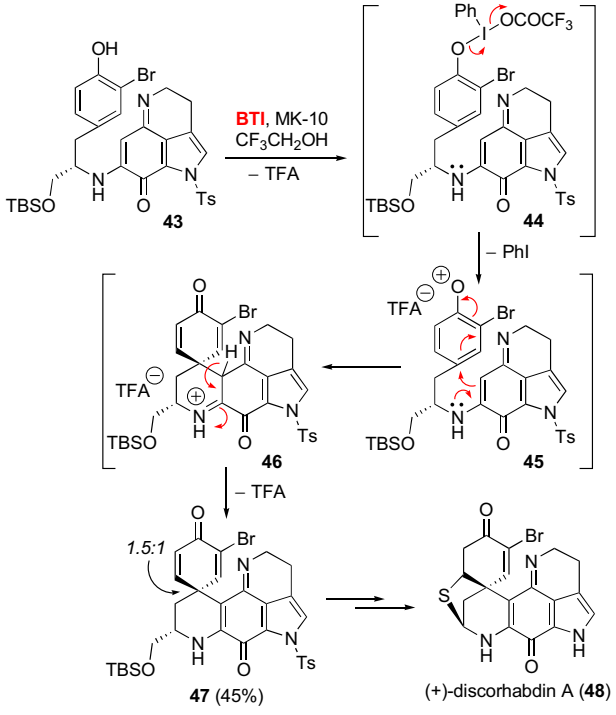


Scheme 11.

2.3. Phenol dearomatization with carbon–carbon strategic bond formation

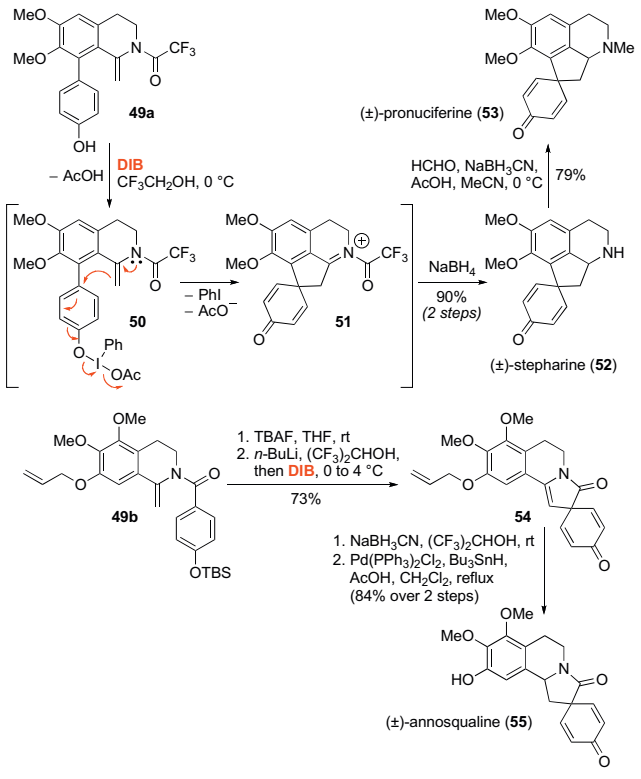
Besides the above formation of C–O and C–N strategic bonds through λ^3-iodane-mediated oxidative dearomatization of phenols into cyclohexa-2,5-dienone species, the construction of C–C-bonded elements of the core architecture of natural products is also possible. Kita and co-workers were among the first to realize the value of the title process. After having contributed in the late 1980s to the development of the utilization of hypervalent iodine

reagents in phenol dearomatization reactions, they remained, over the years, fervent users of this chemistry in their successful efforts toward the synthesis of several natural products. In addition to the work that they previously reported on the synthesis of *Amaryllidaceae* alkaloids using the λ^3-iodane BTI reagent to mediate intramolecular oxidative phenolic C–C-coupling reactions,[63] they implemented a similar tactic to develop a convenient access to the discorhabdins and related pyrroloiminoquinone alkaloids, a series of potent antitumor sponge metabolites.[64] In particular, they described a construction of the unique sulfur-cross linked spiro-cyclic system featured in certain discorhabdins, including discorhabdin A (**48**), of which they recently achieved the first total synthesis.[65] This construction primarily relied on an intramolecular C–C bond-forming cyclization event to convert phenol **43** into the spiro-cyclohexa-2,5-dienone **47** using BTI, which was, in this case, activated with Montmorillonite K-10 (MK-10) in trifluoroethanol (Scheme 12). Kita and co-workers were also the first to introduce the use of fluorinated alcohols such as trifluoroethanol and hexafluoro-*iso*-propanol as solvents in iodine(III)-mediated reactions.[58,66] The highly polar, poorly nucleophilic and slightly acidic (protic) character of these solvents often turned out to be beneficial for enhancing the rate and the yield of these reactions in many instances, and probably also constitutes a key factor in directing reactions more toward dissociative ionic pathways by stabilizing cationic intermediates, such as **45** and **46** (via **44**), in the present case (Scheme 12; see also Scheme 4 in Section 1). Whether the reaction follows such a dissociative pathway or an associative pathway as proposed by Kita and co-workers,[65b] BTI here again served to promote the umpolung reactivity of the phenolic moiety, which hence enabled the intramolecular nucleophilic attack of the enamine unit at the substituted *para*-carbon locus to furnish **47** as a 1.5:1 diastereomeric mixture. This poor diastereomeric ratio was improved (up to 4.8:1) when using a silyl phenyl ether variant of **43**, in which case the spiro-cyclization mechanism is likely to be different and might involve instead an activation of the enamino-imine moiety by BTI with the silylated phenolic unit classically acting as a nucleophilic entity.[65b] Further down the line, the non-brominated enone unit of the resulting cyclohexa-2,5-dienone system **47** played the role of a Michael-type acceptor to forge the sulfur-to-carbon cross linkage of the target, (+)-discorhabdin A (**48**) (Scheme 12).



Scheme 12.

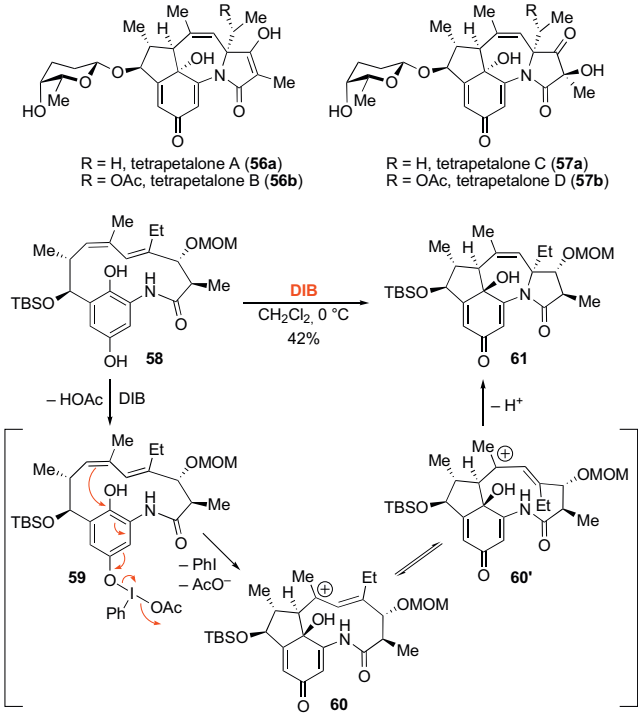
In their total synthesis of (±)-stepharine (**52**) and (±)-pronuciferine (**53**), two proaporphine alkaloids isolated from *Nelumbo nucifera* and *Stephania glabra*, respectively, Honda and co-workers also used DIB in trifluoroethanol at 0 °C to mediate an unprecedented, yet related, C–C bond-forming reaction between the enamide carbon and the phenolic *para*-carbon of the phenolic enamide **49a** (Scheme 13).[67a] Sodium borohydride reduction of the reaction mixture (i.e., **51**, via **50**) proceeded smoothly to directly furnish the desired spiro-cyclohexa-2,5-dienone, (±)-stepharine (**52**), in 90% yield. Subsequent N-methylation of (±)-**52** afforded (±)-pronuciferine (**53**) in 79% yield (Scheme 13).[67a] Honda and co-workers also relied on this DIB-mediated intramolecular enamide-phenol coupling reaction to install the C–C strategic bond of (±)-annosqualine (**55**), a spiro-isoquinoline alkaloid isolated from the stems of *Annona squamosa* (Scheme 13).[67b] Substrate **49b** was first desilylated to unveil the phenolic function, and directly treated with *n*-butyllithium in hexafluoro-*iso*-propanol at 0 to 4 °C to generate the corresponding phenoxide ion. This preliminary formation of the phenoxide ion was found to be essential to the success of the reaction. Addition of DIB to the reaction mixture at below 4 °C rapidly (10 min) led to the expected spiro-cyclohexa-2,5-dienone **54** in 73% yield from **49b**. Reduction of **54** with sodium cyanoborohydride and cleavage of the allyl protecting group completed the synthesis of (±)-annosqualine (**55**) (Scheme 13).[67b]



Scheme 13.

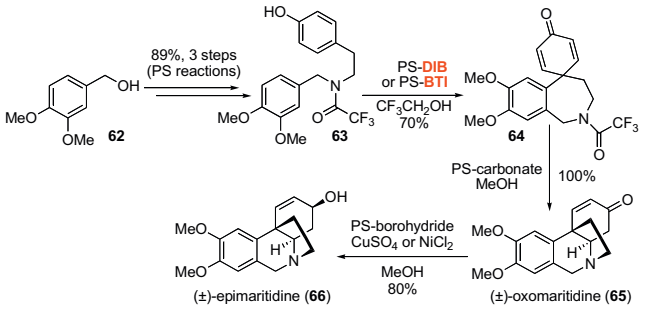
An extremely well thought out and unprecedented exploitation of the use of DIB to mediate the umpolung reactivity of a phenol moiety was recently made by Porco and co-workers in the context of their synthesis efforts toward the soybean lipoxygenase inhibitors, tetrapetalones A to D, **56a**/**b** and **57a**/**b**

(Scheme 14).[68] The macrocyclic hydroquinone **58** was treated with DIB in dichloromethane at 0 °C to promote a diastereoselective transannular [4+3] cyclization into the tetracyclic core of the targeted molecules. Porco proposed that the first step of the reaction, during which the (electron-rich) diene unit of **58** connects with the oxidatively activated hydroquinone moiety (i.e., **59**), is followed by a rotation of the allylic cation part of the resulting *para*-quinol intermediate **60**, hence reaching a conformation **60'** better suited to accommodate the intramolecular nucleophilic attack of the amide nitrogen atom (Scheme 14). The *para*-quinolic tetracycle **61** was thus obtained in 42% yield from **58** via this one-pot process.[68]



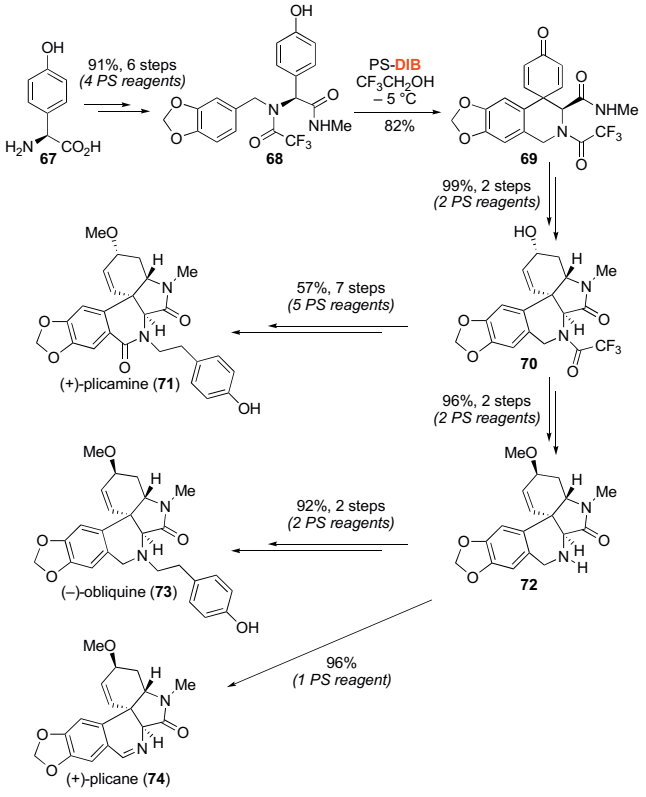
Scheme 14.

Polymer-supported (PS) versions of λ^3-iodanes have also been successfully used in the total syntheses of bioactive natural products. Of most significance in this avenue is the work carried out by Ley's group in the context of their synthesis of several *Amaryllidaceae* alkaloids, during which dearomatizing phenolic coupling routes were also taken to establish strategic C–C connections between phenolic and phenyl alkyl ether moieties within the same molecular entity.[69] Ley and co-workers first demonstrated the usefulness of recyclable PS-DIB or PS-BTI in a total synthesis of both (±)-oxomaritidine (**65**) and (±)-epimaritidine (**66**), using only PS reagents at each individual stage.[70] The amide **63**, prepared from **62**, was cleanly converted into the spiro-cyclohexa-2,5-dienone **64**, which was then treated with PS-carbonate to furnish (±)-**65** via an intramolecular Michael-type 1,4-addition process. Reduction of its ketone group using PS-borohydride afforded (±)-**66**. Overall, the synthesis of (±)-**66** was thus achieved through a linear six-step reaction sequence involving only simple filtration of the spent reagents in a yield of 50% (Scheme 15).[70] This outstanding achievement constitutes the first examples of natural products total syntheses solely relying on a sequence of polymer-supported reagents. Moreover, Ley and co-workers recently adapted this multi-step synthesis of (±)-oxomaritidine (**65**) to flow chemistry, combining seven separate synthetic steps linked into one continuous automated-flow process to produce (±)-**65** with a high level of purity (>90%, as determined by ^{1}H NMR) and in a reproducible overall yield of 40%; PS-BTI was used to generate the seven-membered spiro-tricyclic intermediate **64** (Scheme 15).[71]



Scheme 15.

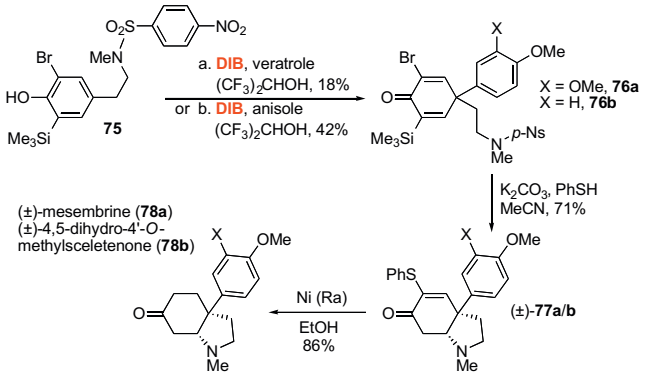
Ley and co-workers also relied on such a polymer-supported approach to achieve the first total synthesis of the *Amaryllidaceae* alkaloid, (+)-plicamine (**71**), in which no less than 13 immobilized systems, including an 82%-yielding PS-DIB-mediated spiro-cyclization of **68** into **69**, were used to produce the target from D-4-hydroxyphenylglycine (**67**) (Scheme 16).[72a,b] The advanced intermediate **70** was also exploited for the synthesis of both (−)-obliquine (**73**) and (+)-plicane (**74**) via the common secondary amine precursor **72** (Scheme 16).[72c]



Scheme 16.

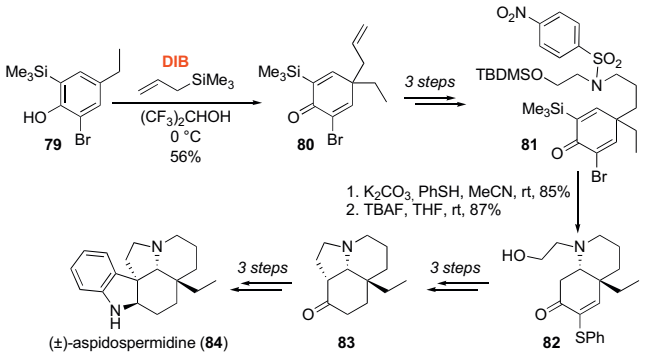
Much rarer are examples in which C–C bonds of natural-product skeleta are made in an intermolecular manner by taking advantage of the umpolung chemistry of phenols upon treatment with hypervalent iodine reagents, yet relevant methodologies have been developed.[32,34b] Nevertheless, interesting cases have recently been reported by Canesi and co-workers, notably in the context of their total synthesis of the *Amaryllidaceae* alkaloids, (±)-mesembrine (**78a**) and (±)-4,5-dihydro-4′-*O*-methylsceletenone (**78b**).[73]

Aromatic carbon-based nucleophiles such as anisole and veratrole were reacted with phenol **75** in the presence of DIB in hexafluoro-*iso*-propanol. The oxidative (umpolung) activation of phenol **75** thus occurred to give rise to the formation of the cyclohexa-2,5-dienones **76a**/**b**, albeit in low-to-moderate yields (Scheme 17). Notwithstanding, these two key compounds were engaged in further transformations during which a Michael-type addition forged the azabicyclic part of the intermediates **77a**/**b**, which were finally treated with Raney nickel to complete the total synthesis of (±)-**78a**/**b** (Scheme 17).[73]



Scheme 17.

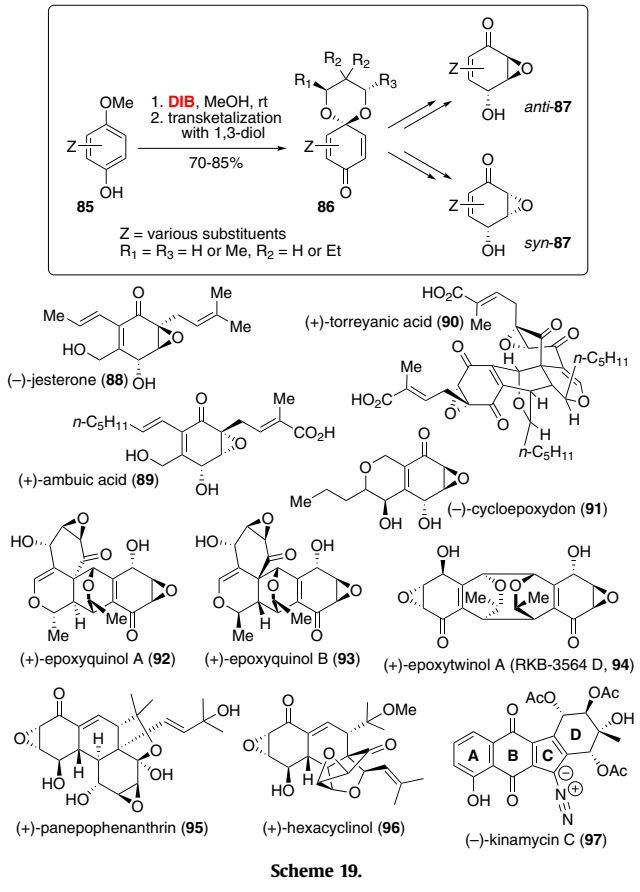
Canesi and co-workers followed a similar approach in their total synthesis of the *Aspidosperma* alkaloid, (±)-aspidospermidine (**84**) (Scheme 18).[74] DIB-mediated oxidative activation of phenol **79** in hexafluoro-*iso*-propanol using, this time, allyltrimethylsilane as a carbon-based nucleophile[32] afforded the cyclohexa-2,5-dienone **80** in 56% yield (Scheme 18). Three additional steps were implemented to reach the sulfonamide **81**, which then successively suffered, under Fukayama's conditions in the presence of thiophenolate, deprotection of its amino group, substitution of its bromide by a phenylthio ether, and complete desilylation with concomitant azacyclization via a Michael process to furnish **82**. This bicyclic compound was next converted into the known tricycle **83**, en route to (±)-**84** via a Fischer indole synthesis (Scheme 18).[74]



Scheme 18.

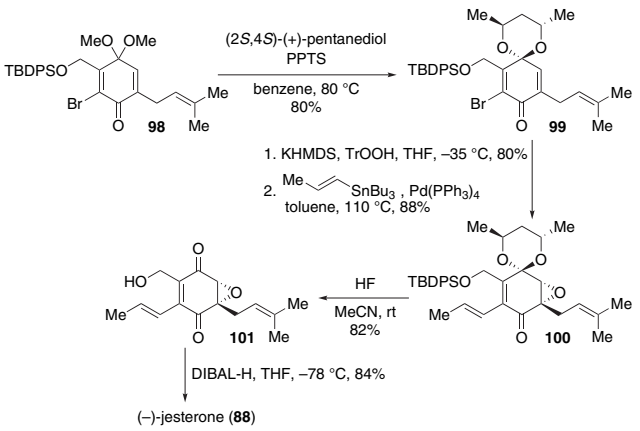
2.4. Phenol dearomatization with carbon–oxygen functional bond formation

Besides the above examples of rather elaborated and intramolecular applications of BTI/DIB-mediated dearomatizations of phenols into cyclohexa-2,5-dienones, one can take advantage of more elementary applications of this chemistry to rapidly access oxygenated cyclohexenone motifs after converting simple (methoxylated) phenols into *para*-quinone dimethyl monoketal synthons.[25,27] Such 6,6-dimethoxycyclohexa-2,5-dienones are ideally suited for the incorporation of chiral moieties by transketalization reactions, and subsequent asymmetric oxygenation of their olefinic double bond(s).[75] The Porco group has recently reported several applications and variations of these transformations in an outstanding series of syntheses of complex naturally occurring epoxyquinoid systems. Oxidative methoxylation reactions were performed on differently substituted *para*-methoxyphenols of the type **85** using DIB in methanol to generate the corresponding 6,6-dimethoxy-cyclohexa-2,5-dienones. These ketals were subsequently transketalized with chiral or achiral 1,3-diols to afford *para*-quinone cyclic monoketals of the type **86**, which were found to be much better substrates for nucleophilic epoxidation reactions. These monoketals were then further transformed by either substrate- or reagent-controlled stereoselective epoxidation, and cleavage of the cyclic ketal unit before or after regio/stereoselective ketone reduction to access epoxyquinols of the type **87**, with either *anti* or *syn* stereochemistry (Scheme 19).



Scheme 19.

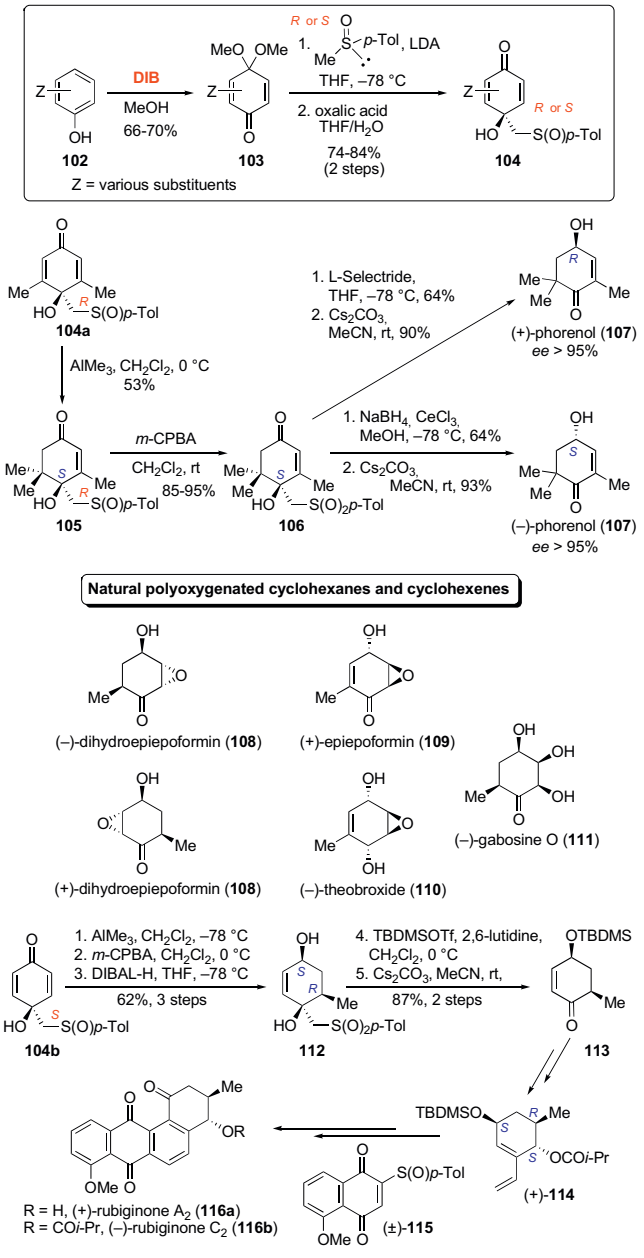
For example, this approach was successfully applied to the total synthesis of the potent antifungal agent, (−)-jesterone (**88**, *anti*-**87** type).[76] The dimethylketal **98** was transketalized with (2*S*,4*S*)-pentanediol to afford the chiral quinone monoketal **99**, which was then diastereoselectively epoxidized using Ph_3COOH, and propenylated under Stille conditions to give **100**. Subsequent desilylation afforded the epoxyquinone **101**, the α-hydroxymethylated ketone function of which was finally regio/stereoselectively reduced to furnish the *anti*-epoxyquinol target **88** (Scheme 20).



Scheme 20.

Its *syn*-epoxyquinol congener, (+)-ambuic acid (**89**, *syn*-**87** type), and the related epoxyquinone-derived 2*H*-pyran [4+2] cyclodimer, (+)-torreyanic acid (**90**), were both synthesized by similar approaches, but relying on the use of an achiral quinone monoketal of the type **86** and on the implementation of a reagent-controlled, tartrate-mediated nucleophilic epoxidation reaction.[77] The same enantioselective epoxidation had, in fact, first been used for the synthesis of the NF-kB inhibitor, (−)-cycloepoxydon (**91**, *anti*-**87** type),[78a] and, later on, for the synthesis of the *anti*-**87** type epoxyquinol-derived 2*H*-pyran [4+2] cyclodimers and angiogenesis inhibitors, (+)-epoxyquinols A (**92**) and B (**93**),[78b,c] as well as their related *anti*-epoxyquinol-derived 2*H*-pyran [4+4] dimeric congener, (+)-epoxytwinol A (RKB-3564 D, **94**).[78c,d] Diels–Alder dimerizations of other *anti*-epoxyquinol monomers generated in the same manner from achiral *para*-quinone cyclic monoketals of the type **86** led to the successful synthesis of the fungal metabolite and ubiquitin-activating enzyme inhibitor, (+)-panepophenanthrin (**95**),[78e] as well as to that of its antiproliferative congener, (+)-hexacyclinol (**96**).[78f] This abundant flow of natural product syntheses accomplished by Porco and co-workers does not stop there, as they also reported the first enantioselective total synthesis of the unusual diazobenzofluorene antibiotic, (−)-kinamycin C (**97**), by taking advantage again of the preparation of a *syn*-epoxyquinol intermediate of the type **87** to establish the desired stereochemistry of the highly oxygenated cyclohexene D-ring subunit of (−)-**97** (Scheme 19).[78g]

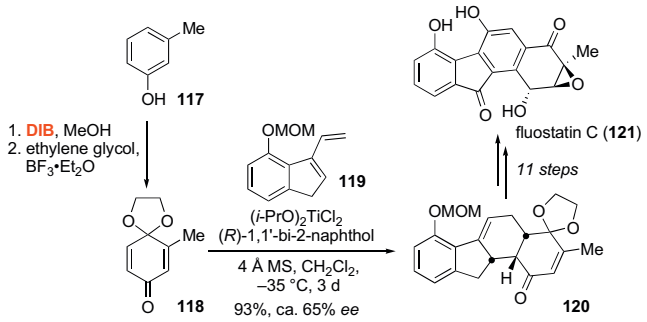
Carreño and co-workers also exploited the facile DIB-mediated conversion of simple phenols into *para*-quinone dimethyl monoketals of the type **103** to generate [(*para*-tolylsulfinyl)methyl]-*para*-quinols of the type **104** as starting materials for the asymmetric synthesis of natural products. The preparation of **104** thus started with the oxidative methoxylation of phenol **102** using DIB in methanol to furnish the 6,6-dimethoxycyclohexa-2,5-dienone **103**, and was followed by nucleophilic addition of the α-lithio-methylsulfinyl carbanion derived from enantiomerically pure methyl *para*-tolylsulfoxide on to the ketone function of **103** to furnish **104** in good overall yields of 74–84% after removal of the dimethylketal function (Scheme 21).[79a] Interestingly, conjugate addition of organoaluminum reagents (e.g., $AlMe_3$ in CH_2Cl_2) to **104** occurred in a highly π-facial diastereoselective manner, that is directed by the quinol hydroxyl group, while efficiently promoting the desymmetrization of the cyclohexa-2,5-dienone moiety (e.g., **104a**→**105**).[79b] Furthermore, oxidation of the sulfoxide group with *m*-CPBA (e.g., **105**→**106**) and elimination of the resulting sulfone upon treatment with a weak base (e.g., Cs_2CO_3 in MeCN) allowed the timely liberation of the ketone functionality. These transformations were first put to work in the synthesis of both enantiomers of **107**, known as phorenol, a useful intermediate in the synthesis of several natural products (Scheme 21).[80] This chemistry proved to be very fruitful in that it enabled Carreño's group to accomplish the asymmetric synthesis of several polyoxygenated cyclohexane-based natural products such as the two enantiomers of dihydroepiepoformin (**108**), (+)-epiepoformin (**109**), (−)-theobroxide (**110**), and (−)-gabosine O (**111**) (Scheme 21).[81] The enantioselective total synthesis of the angucyclinone-type antibiotics, rubiginones A_2 [(+)-**116a**] and C_2 [(−)-**116b**], was also achieved via a Diels–Alder reaction between the enantiopure vinylcyclohexene (+)-**114** and the racemic sulfinylnaphthoquinone (±)-**115** (Scheme 21).[82] Access to (+)-**114** was again secured by employing the chemo- and stereoselective addition of trimethylaluminum to (*S*)-[(*para*-tolylsulfinyl)methyl]-*para*-quinol **104b** and elimination of the chiral sulfoxide as methyl *para*-tolylsulfone as the key steps (i.e., **104b**→**112**, and **112**→**113**, respectively; Scheme 21).[82]



Scheme 21.

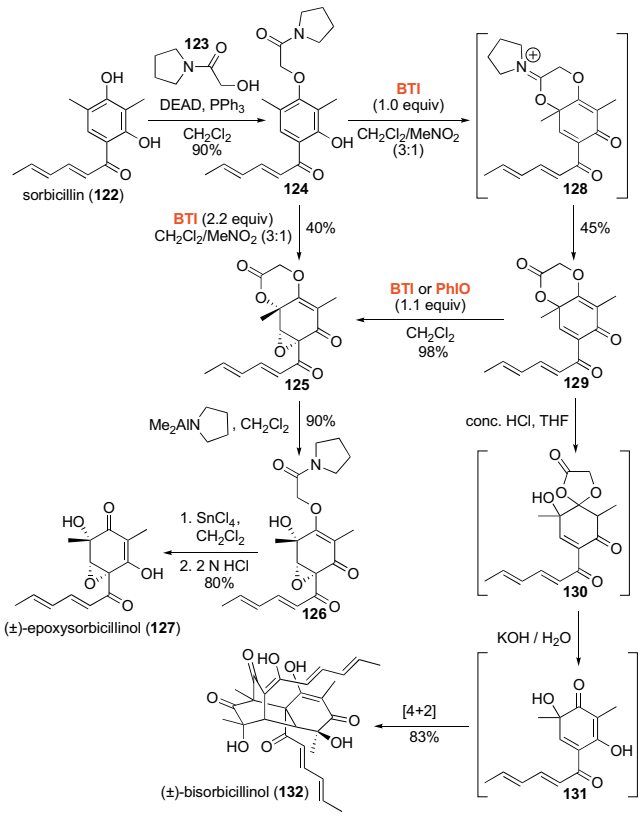
A classical use of cyclohexa-2,5-dienones of the *para*-quinone monoketal type in synthesis is their participation as dienophiles in

Diels–Alder processes. In their straightforward synthesis of fluostatin C (**121**), a member of the larger family of antibiotic and antitumor fluostatins recently isolated from the fermentation broth of *Streptomyces* strain Acta 1383, Danishefsky and co-workers relied on a highly regioselective Diels–Alder reaction between the substituted vinylindene diene **119** and the cyclohexa-2,5-dienone monoketal **118** (Scheme 22).[83] This key reaction was performed under the Lewis acid-mediated Mikami–Corey catalytic protocols,[84] and furnished the fluostatin tetracyclic system **120** in 93% yield and ca. 65% ee (Scheme 22). The *p*-quinone monoketal dienophile **118** had been prepared by oxidative methoxylation of 3-methylphenol (**117**) using DIB in methanol, followed by $BF_3{\cdot}Et_2O$-catalyzed transketalization with ethylene glycol (Scheme 22).[83]



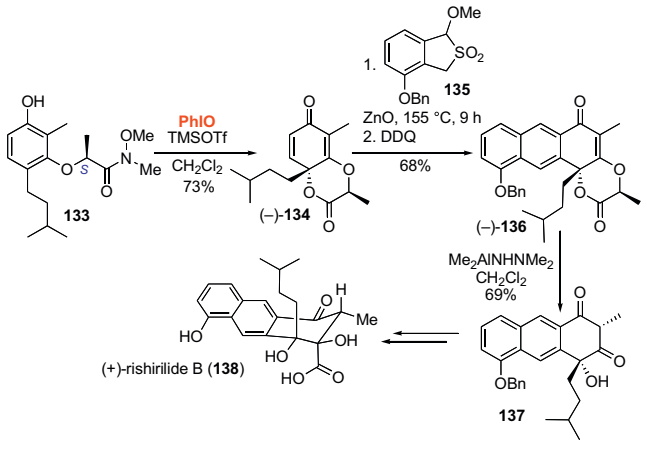
Scheme 22.

The Pettus group has also made major contributions to the development of hypervalent iodine-mediated phenol dearomatization processes in natural product synthesis. As part of their continuing research efforts on oxygenative dearomatization of resorcinol derivatives, Pettus and co-workers have reported an interesting synthesis of the vertinoid polyketide, (±)-epoxysorbicillinol (**127**), from its putative precursor, sorbicillin (**122**) (Scheme 23).[85a] After coupling **122** with the α-hydroxy amide **123** under Mitsunobu conditions, the oxygenative dearomatization of the resorcinol core was accomplished by using a first equivalent of the λ^3-iodane BTI reagent in $CH_2Cl_2/MeNO_2$ to generate the lactonic cyclohexa-2,5-dienone intermediate **129** in 45% yield. As discussed above (see Section 2.2), the amide group served as the oxygenating function during this intramolecular cyclization with the oxidatively activated resorcinol core. The resulting iminium species **128** was then hydrolyzed during the work up to furnish the desired δ-lactone system **129** (Scheme 23).[85b,c] This cyclohexa-2,5-dienone could then be regioselectively epoxidized in almost quantitative yield by using either a second equivalent of BTI or one equivalent of the λ^3-iodane, iodosylbenzene (PhIO), to furnish the epoxide **125**. Although the epoxidizing capacity of PhIO is known,[86] that of BTI constitutes an intriguing aspect of this synthesis, which was tentatively explained by the possibility of having BTI in equilibrium with PhIO in CH_2Cl_2.[85a] In any event, the use of two equivalents of BTI directly and exclusively converted **124** into the desired epoxide **125** as the sole diastereomer isolated in 40% yield. This epoxide was next submitted to a Weinreb-amidation procedure[87] to liberate the tertiary alcohol function in the amide **126**, which was finally treated with $SnCl_4$/2 N HCl to furnish (±)-**127** (Scheme 23).[85a] In parallel, the dimeric (±)-bisorbicillinol (**132**) was also synthesized by treating **129** with concentrated HCl in tetrahydrofuran to contract its δ-lactone unit into the presumed *O*-spiro-γ-lactonic ketal **130**. This ketal was then hydrolytically cleaved under alkaline conditions and worked up under acidic conditions to probably unleash the fleeting *ortho*-quinolic cyclohexa-2,4-dienone **131** that spontaneously underwent a [4+2] cycloaddition to afford (±)-**132** in 83% yield.[85a]



Scheme 23.

Further investigations along the same lines by the same group led to a concise synthesis of (+)-rishirilide B (**138**), an oxygenated dearomatized anthracene entity isolated from *Streptomyces rishiriensis* OFR-1056 that inhibits α_2-macroglobulin and glutathione *S*-transferase.[88a] For this synthesis, Pettus and co-workers implemented their diastereoselective dearomatization route to resorcinol-derived cyclohexa-2,5-dienones[85c] and installed a chiral amide tether on one of the phenolic hydroxyl groups of the starting resorcinol derivative (Scheme 24). The resulting enantiomerically pure precursor **133** was then dearomatized via oxidative activation

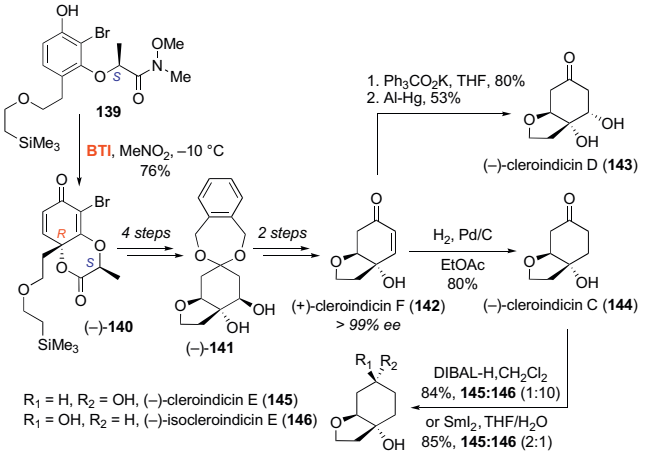


Scheme 24.

of its free phenolic function using this time a combination of PhIO and TMSOTf in dichloromethane. The addition of TMSOTf probably enhanced the reactivity of PhIO by causing the in situ generation of the λ^3-iodane, PhI(OTMS)OTf. This combination of reagents turned

out to be better suited than BTI or DIB to mediate the desired transformation of **133** into (−)-**134**, which was thus obtained in 73% yield (Scheme 24).[88a] This *para*-quinol derivative was then engaged in a [4+2] cycloaddition reaction with the *ortho*-quinone dimethide precursor **135** to deliver the anthracyclic ring system (−)-**136**.[88b,c] Opening of the lactone was here achieved under Benderly's conditions[89] using a dimethylaluminum hydrazide, which also promoted the complete expulsion of this chiral directing and protecting group to afford the hydroxy dione **137**, en route to the first synthesis of (+)-rishirilide B (**138**, Scheme 24).[88a]

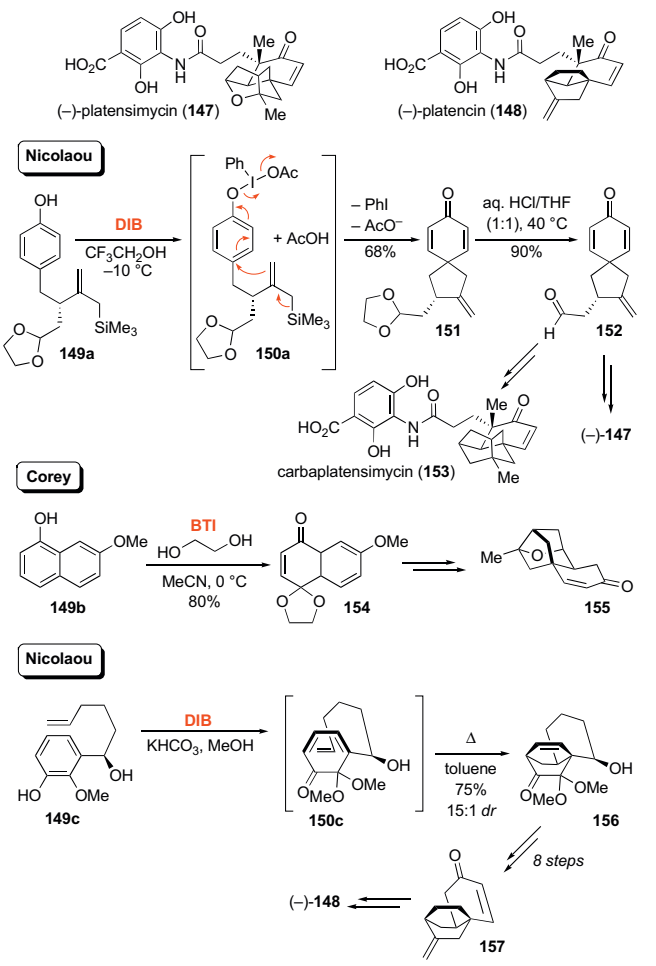
A similar approach was recently reported by the same group for their total synthesis of natural oxidized cyclohexanones, referred to as cleroindicins, that were isolated from the *Clerodendrum indicum*, *C. japonicum* and *C. bungei* plant species (Scheme 25).[90] In this case, the λ^3-iodane BTI reagent served the intended purpose and the δ-lactone **140** was generated as a single diastereomer in 76% yield from the chirally appended phenol **139** in nitromethane at −10 °C. The δ-lactone (−)-**140** was further submitted to a stereoselective *anti*-reduction, followed by a TMSI-induced debromidation-desilylation-cyclization sequence, a ketalization of the ketone function, and a final two-step removal of the chiral auxiliary (Scheme 25).[90] The resulting *trans*-diol (−)-**141** was then easily converted into *inter alia* (+)-cleroindicin F (**142**) via a tosylation-hydrogenolysis sequence (Scheme 25). The cyclohexenone (+)-**142** was next used as an intermediate to access (−)-cleroindicin D (**143**) and (−)-cleroindicin C (**144**) (Scheme 25). (−)-cleroindicin E (**145**) and its isomer **146** were finally prepared from (−)-**144** in a ratio of 1:10 or 2:1 upon treatment with either DIBAL-H or samarium diiodide, respectively (Scheme 25).[90]



Scheme 25.

2.5. Synthesis of platensimycin and platencin—a case of reliance on λ^3-iodane-mediated phenol dearomatization

(−)-Platensimycin (**147**) and (−)-platencin (**148**), two compounds initially discovered in 2006 in the course of the Merck screening program, have become highly competitive synthetic targets, due to their promising antibiotic activity and their unusual complex molecular architecture (Scheme 26).[91] These natural compounds were isolated from strains of *Streptomyces platensis* and are characterized by a conserved polar aromatic group coupled through an amide linkage to a variable ketolide core. Among the numerous approaches so far reported to achieve the synthesis, either total or formal, of these novel antibiotics,[91] a few relied on hypervalent iodine-mediated oxidative phenol dearomatization tactics at various stages for various purposes. For example, in their racemic-to-asymmetric variation of the total synthesis of



Scheme 26.

platensimycin (**147**), Nicolaou and co-workers reported the conversion of the non-racemic phenol **149a** bearing a pendent allylsilane group into the spiro-cyclohexa-2,5-dienone **151** in 68% yield (via **150a**) upon exposure to DIB in trifluoroethanol at −10 °C (Scheme 26).[92] This strategic C–C bond-forming reaction is reminiscent of that developed by the present authors using allylsilane or vinylogous silyl enol ethers as non-aromatic carbon-centered nucleophiles in BTI-promoted naphthol dearomatization reactions in the intermolecular mode.[32,93] The acetal protection of the spirocyclic dienone **151** was removed under acidic conditions to furnish the enantiomerically enriched aldehyde **152**, which was then converted into (−)-**147**, as well as its non-natural bioactive analogue, carbaplatensimycin (**153**) (Scheme 26).[92,94] In parallel investigations, Corey's group developed an efficient enantiocontrolled synthetic pathway to access the platensimycin ketolide core **155** (Scheme 26).[95] The point of departure for the construction of **155** was the methoxy α-naphthol **149b**, which was oxidatively ketalized using BTI and ethylene glycol in acetonitrile at 0 °C to furnish the *para*-naphthoquinone monoketal **154** in 80% yield (Scheme 26).[95] Nicolaou and co-workers also recently reported an expedient asymmetric synthesis of the tricyclic cyclohexenone **157**, a known intermediate in the synthesis of (−)-platencin (**148**) (Scheme 26).[96] Inspired by the work of Liao and co-workers (see Section 3.1), an intramolecular Diels–Alder reaction of the 6,6-dimethoxycyclohexa-2,4-dienone **150c**, generated by oxidative methoxylation of the olefinic 2-methoxyphenol **149c** using DIB in methanol, was performed in refluxing toluene to furnish in one step the tricyclic motif **156** in 75% yield and with a diastereomeric ratio of 15:1

(Scheme 26). This Diels–Alder adduct was converted into the platencin intermediate **157** in eight steps (Scheme 26).[96]

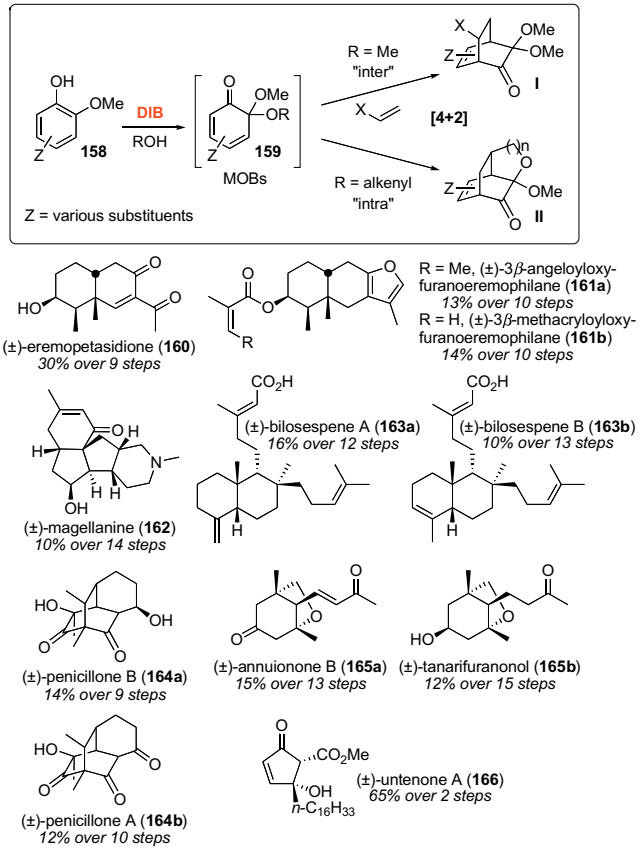
3. λ^3-Iodane-mediated dearomatization of phenols into quinonoid cyclohexa-2,4-dienones

In the last example of the previous section, Nicolaou and co-workers relied on the use of DIB in methanol to install a ketalic C–O bond via dearomatization of a 2-methoxyphenol. The resulting 6,6-dimethoxycyclohexa-2,4-dienone unit then acted as a diene in an intramolecular Diels–Alder process. Such 6,6-dialkoxycyclohexa-2,4-dienones, trivially referred to as *ortho*-quinone monoketals, constitute remarkably useful systems for synthesis,[11,13] and are indeed particularly well-suited to participate in [4+2] cycloaddition reactions, due to the propensity of their conjugated dienone to behave either as a diene or as a dienophile.[97]

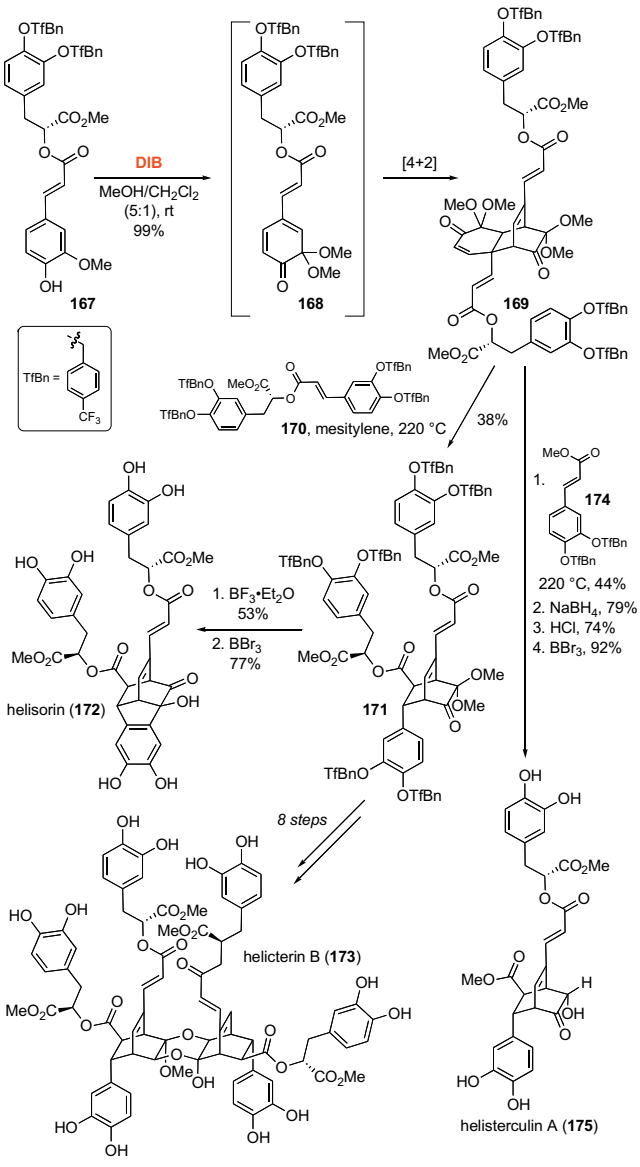
3.1. 6,6-Dialkoxycyclohexa-2,4-dienones in Diels–Alder reactions

The Diels–Alder chemistry of 6,6-dialkoxycyclohexa-2,4-dienones (**159**) has been extensively studied and exploited in synthesis by Liao and co-workers, who referred to these compounds as masked *ortho*-benzoquinones (MOBs).[98] In particular, they developed convenient and general approaches to diverse and complex structural frameworks via inter- or intramolecular Diels–Alder reactions, leading to bicyclo[2.2.2]octenone intermediates of the types **I** and **II**, respectively (Scheme 27). The 6,6-dialkoxycyclohexa-2,4-dienones, which served as diene components in these [4+2] cycloaddition processes, were generated in situ by oxidative alkoxylation of adequately substituted 2-methoxyphenols (**158**) using the λ^3-iodane DIB reagent (Scheme 27). Liao's group has successfully exploited this key two-step/one-pot sequence in numerous total syntheses of natural products over the years. Among the most recent examples are the syntheses of the polyfunctionalized *cis*-decalins, (±)-eremopetasidione (**160**),[99a] (±)-3β-angeloyloxyfuranoeremophilane (**161a**), and (±)-3β-methacryloyloxyfuranoeremophilane (**161b**),[99b] as well as the sesterpenic acids, (±)-bilosespenes A (**163a**) and B (**163b**),[99c] the tetracyclic *Lycopodium* alkaloid, (±)-magellanine (**162**),[99d] the tricyclo[5.3.1.0^{3,8}]undecane derivatives, (±)-penicillones B (**164a**) and A (**164b**),[99e] and the 6-oxabicyclo[3.2.1]octane derivatives, (±)-annuionone B (**165a**) and (±)-tanarifuranonol (**165b**)[99f] (Scheme 27).

The facility with which 6,6-dimethoxycyclohexa-2,4-dienones of the type **159** undergo Diels–Alder cycloaddition reactions was recently exploited by Snyder and co-workers in their concise total syntheses of helisorin (**172**), helicterin B (**173**) and helisterculin A (**175**), three neolignans isolated from the Indonesian plant, *Helicteres isora*, that possess mild inhibitory activity against the avian myeloblastosis virus (Scheme 28).[100] The 2-methoxyphenolic rosmarinic acid derivative **167** was oxidized upon treatment with DIB in methanol/dichloromethane (5:1) to give the corresponding 6,6-dimethoxycyclohexa-2,4-dienone **168** that



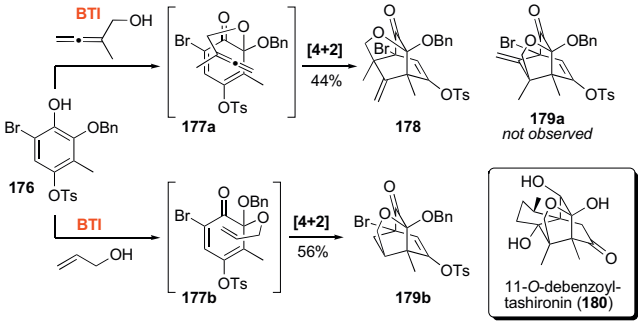
Scheme 27.



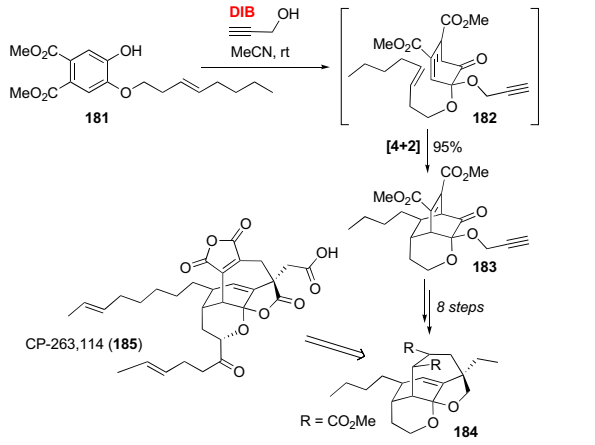
Scheme 28.

underwent a spontaneous Diels–Alder cyclodimerization to afford the homodimer **169** in nearly quantitative yield (Scheme 28). Next, a retro Diels–Alder/Diels–Alder sequence using the dienophile **170** in excess in refluxing mesitylene led to the bicyclo[2.2.2]octenone **171**, which then served as a common intermediate for the synthesis of both helisorin (**172**) and helicterin B (**173**), respectively (Scheme 28).[100] In addition, the homodimer **169** was engaged in a similar retro Diels–Alder/Diels–Alder sequence using the dienophile **174** to reach helisterculin A (**175**) in four additional steps (Scheme 28).[100]

Liao's oxidative phenol dearomatization/intramolecular Diels–Alder cascade reaction using alkenyl alcohols as trapping nucleophiles and dienophiles (Scheme 27), which corresponds to a hypervalent iodine-promoted variant of the reaction developed in the 1970s by Yates using lead tetraacetate (i.e., Wessely oxidation) and alkenyl carboxylic acids,[101] was recently exploited by Danishefsky and co-workers during their investigations on the synthesis of 11-*O*-debenzoyltashironin (**180**), a potentially valuable lead candidate in the development of a neutrophic agent (Scheme 29).[102] Phenol **176** was thus oxidatively activated with BTI in the presence of an allenyl or allyl alcohol to furnish, respectively, the cyclohexa-2,4-dienones **177a** or **177b** that underwent spontaneous intramolecular [4+2] cycloaddition. The regioselectivity of this Diels–Alder process was completely switched by changing the dienophile. Trapping of the allenyl alcohol during this annelating oxidative dearomatization sequence unfortunately gave rise to the undesired six-membered ketal product **178** (instead of **179a**), whereas trapping of allylic alcohol afforded the five-membered ketal ring system **179b** of the tashironin core (Scheme 29).[102]



Scheme 29.

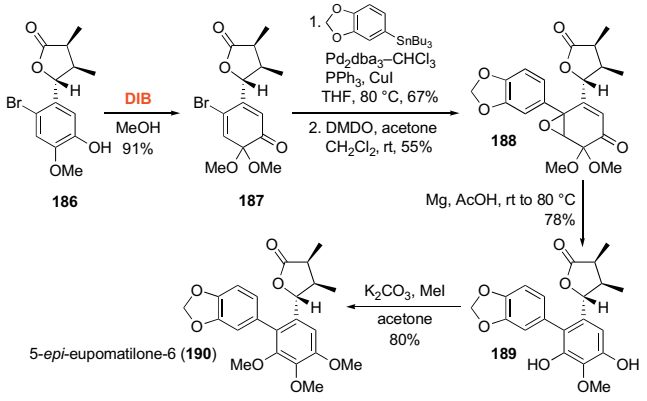


Scheme 30.

A variant of this tandem hypervalent iodine-mediated oxidative phenol dearomatization/intramolecular Diels–Alder sequence was earlier used by Wood and co-workers to achieve the assembly of the carbocyclic core of CP-263,114 (**185**, phomoidride B) (Scheme 30).[103] DIB-mediated oxidation of the olefinic phenol **181** in acetonitrile, in the presence of propargyl alcohol as the trapping/dearomatizing nucleophile, afforded in 95% yield, via the cyclohexa-2,4-dienone **182**, the desired cycloadduct **183**, which was further functionalized in a short and efficient synthesis to obtain the isotwistane ring system **184** needed for the synthesis of the phomoidride (Scheme 30).[103]

3.2. Other recent utilizations of λ^3-iodane-generated quinonoid cyclohexa-2,4-dienones

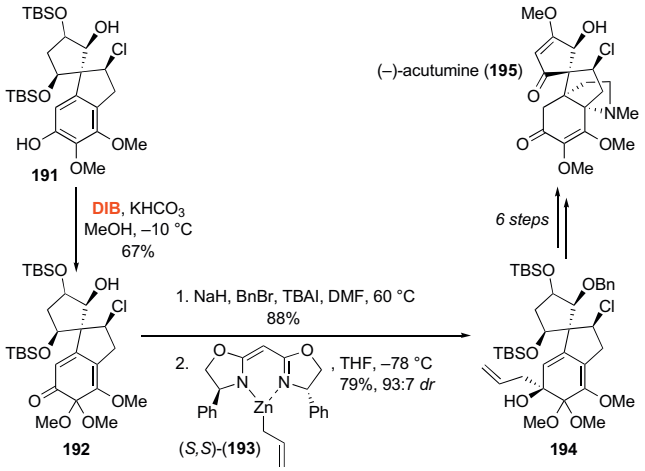
The chemistry of *ortho*-quinonoid cyclohexa-2,4-dienones does not, of course, stop at their exploitation in [4+2] cycloaddition processes. In principle, the six carbons of their cyclic skeleton are all electrophilic centers. Featuring three conjugated double bonds and two adjacent oxygenated functions, i.e., a ketone and either a ketal or a tertiary alcohol in the case of *ortho*-quinol variants (see Sections 6 and 7), these cyclohexadienones are amenable to various selective transformations relying on the reactivity of their double bonds and based on olefin oxygenation, as well as direct or conjugate nucleophilic addition and substitution reactions. For example, in the context of their synthesis efforts toward the eupomatilones, a family of unusual lignans isolated from the Australian shrub, *Eupomatia bennettii*, McIntosh and Hong reported a synthesis of 5-*epi*-eupomatilone-6 (**190**), for which they converted the 4-bromo-2-methoxyphenolic lactone **186** into the 6,6-dimethoxycyclohexa-2,4-dienone **187** in a yield of 91% (Scheme 31).[104] Stille coupling of this *ortho*-quinone monoketal with piperonyltributylstannane, followed by regioselective epoxidation of the dienone unit with dimethyldioxirane (DMDO), afforded the epoxide **188** (Scheme 31). A reductive ring opening of the epoxide **188** engaged rearomatization of the phenolic ring to give **189**, which was then dimethylated to complete the synthesis of **190** as a 1:1 mixture of atropisomers (Scheme 31).[104]



Scheme 31.

An *ortho*-quinone dimethyl monoketal was also very recently used by Castle and co-workers in their total synthesis of (−)-acutumine (**195**), a tetracyclic alkaloid originally isolated from the Asian vine, *Menispermum dauricum*, and that possesses selective T-cell cytotoxicity and *anti*-amnesic properties (Scheme 32).[105a] Upon oxidative methoxylation using DIB in the presence of potassium bicarbonate in methanol at −10 °C, phenol **191** was efficiently dearomatized into its corresponding 6,6-dimethoxycyclohexa-2,4-dienone **192** in a yield of 67% (Scheme 32).[105] This species was

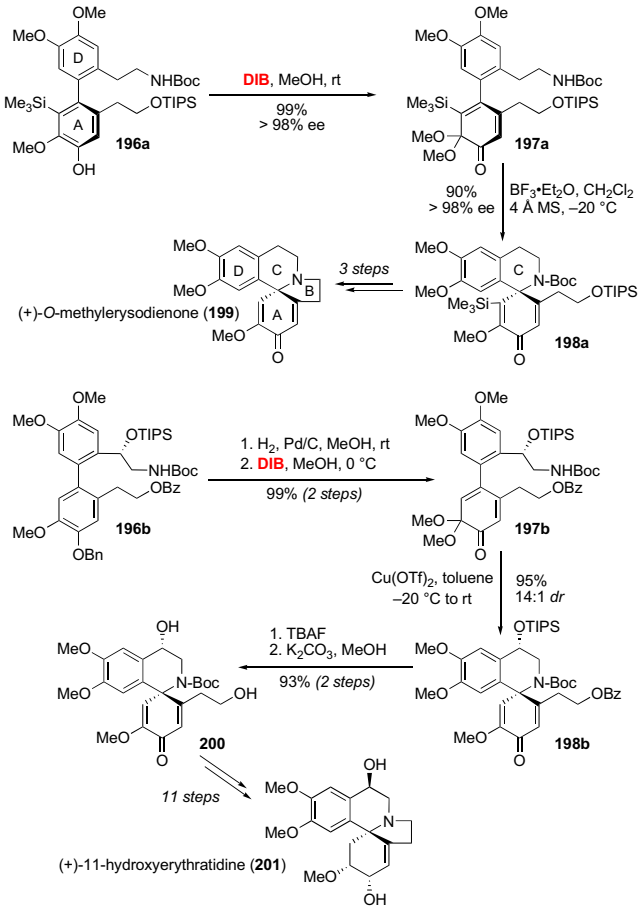
sufficiently stable to be first benzylated at its secondary alcohol function prior to allylation of its ketone using Nakamura's chiral allylzinc reagent (*S*,*S*)-**193** to furnish the cyclohexa-2,4-dienol **194** in a yield of 79% with a dr of 93:7 (Scheme 32). The synthesis of (−)-**195** was then completed in six steps from **194**, including an anionic oxy-Cope rearrangement of the allyl substituent that preceded the formation of the fourth cycle of the target (Scheme 32).[105a]



Scheme 32.

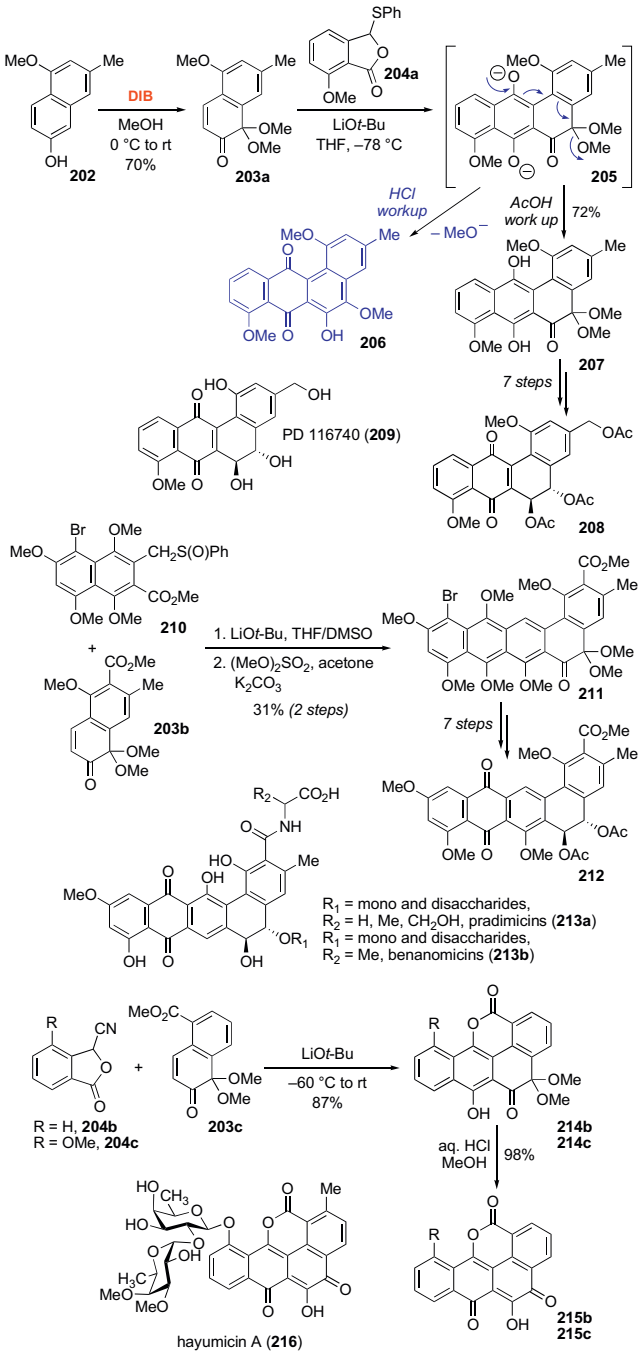
Matsumoto and co-workers also relied on 6,6-dimethoxycyclohexa-2,4-dienone derivatives as key intermediates in the synthesis of the erythrinan skeleton, i.e., an indolo[7a,1-*a*]isoquinoline core, of alkaloids isolated from many plant species of the *Erythrina* family. These unique tetracyclic amino structures were shown to exhibit curare-like, sedative, hypotensive and central nervous system-depressant activities. The atropisomerically pure biphenylic phenol **196a** was successfully dearomatized into the desired *ortho*-quinone monoketal **197a** upon treatment with DIB in methanol at room temperature (Scheme 33).[106a] Subsequent Lewis acid-promoted aza-spiro-cyclization of **197a** into **198a** was achieved in 90% yield using boron trifluoride etherate in dichloromethane at −20 °C (Scheme 33). Both the starting cyclohexa-2,4-dienone **197a** and the spiro-isoquinoline product **198a** proved to be enantiomerically pure, hence showing the efficacious transmission of the axial chirality of the biphenyl **196a** to the sp^3-central chirality of the spiro-cycle **198a** during this focal S_N2'-type reaction of the synthesis (Scheme 33).[106a] The total synthesis of (+)-*O*-methylerysodienone (**199**) was next completed through three additional steps previously set up for the synthesis of the racemate (±)-**199** (Scheme 33).[106b] More recently, this strategy was also followed by the same group to achieve the total synthesis of (+)-11-hydroxyerythratidine (**201**), a C-11 oxygenated erythrinan alkaloid (Scheme 33).[106c] The biphenyl **196b** was debenzylated and then dearomatized using DIB in methanol to prepare the 6,6-dimethoxycyclohexa-2,4-dienone **197b** in nearly quantitative yield (Scheme 33). In this case, copper(II) trifluoromethanesulfonate [$Cu(OTf)_2$] in toluene was found to deliver the desired aza-spirocycle **198b** in a yield of 95% with a excellent 14:1 diastereomeric ratio (Scheme 33).[106c] Further desilylation and debenzoylation afforded the advanced intermediate **200**, en route to (+)-**201** (Scheme 33).[106c]

λ^3-Iodane-generated 6,6-dimethoxycyclohexa-2,4-dienone motifs have also been successfully used as Michael acceptors in Hauser annulation reactions.[107] Hauser and co-workers reported the first racemic synthesis of a methylated derivative of PD 116740 (**209**), one of the rare angucyclines featuring a 5,6-



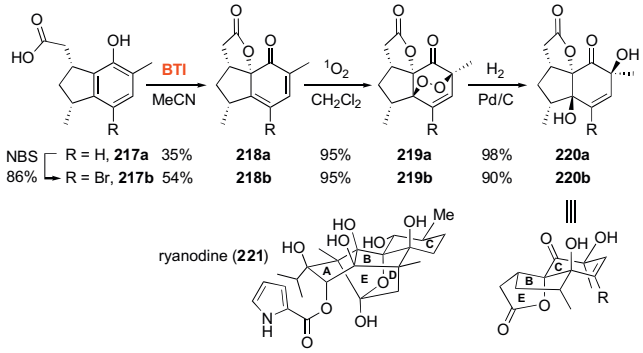
Scheme 33.

dihydroxylation (Scheme 34).[108a] DIB-mediated oxidative dearomatization of phenol **202** in methanol afforded the *ortho*-quinone dimethyl monoketal **203a**, which was next condensed with the anion of the phthalide sulfide **204a** to undergo the Hauser–Kraus annulation via **205** (Scheme 34). When the work up was performed with a strong acid such as hydrochloric acid, the annulation cascade does not stop at the expected product, but progresses to the anthraquinone **206**; however, when the reaction was quenched with acetic acid, exclusive formation of **207** was achieved in 72% yield (Scheme 34).[108a] This tetracyclic compound was further transformed to furnish the peracetylated *O*-methyl derivative **208** of PD 116740 (Scheme 34). Hauser and co-workers extended their strategy for the synthesis of an analogue of the potent antifungal metabolites, pradimicins/benanomicins **213a**/**b** (Scheme 34).[108b] Condensation of the anion of the sulfoxide **210** with the DIB-generated *ortho*-quinone monoketal **203b** was performed in a tetrahydrofuran/dimethylsulfoxide solvent mixture, and subsequent methylation gave the pentacycle **211** in a 31% overall yield. Further transformations led to the pentacyclic analogue **212** (Scheme 34).[108b] Mal and co-workers also recently applied the Hauser–Kraus annulation in their synthesis of benzonaphthopyranone cores of the glycosidic polyketide antibiotics, chartreusin, chrymutasins and hayumicins.[109] The DIB-generated *ortho*-quinone monoketal **203c** was successfully condensed with the anion of the cyanophthalides **204b**/**c** to afford the pentacycles **214b**/**c** in good yields. Final acid-mediated ketal hydrolysis provided motifs **215b**/**c**, which feature all of the important structural components of the hayumicin A (**216**) aglycon (Scheme 34).[109]



Scheme 34.

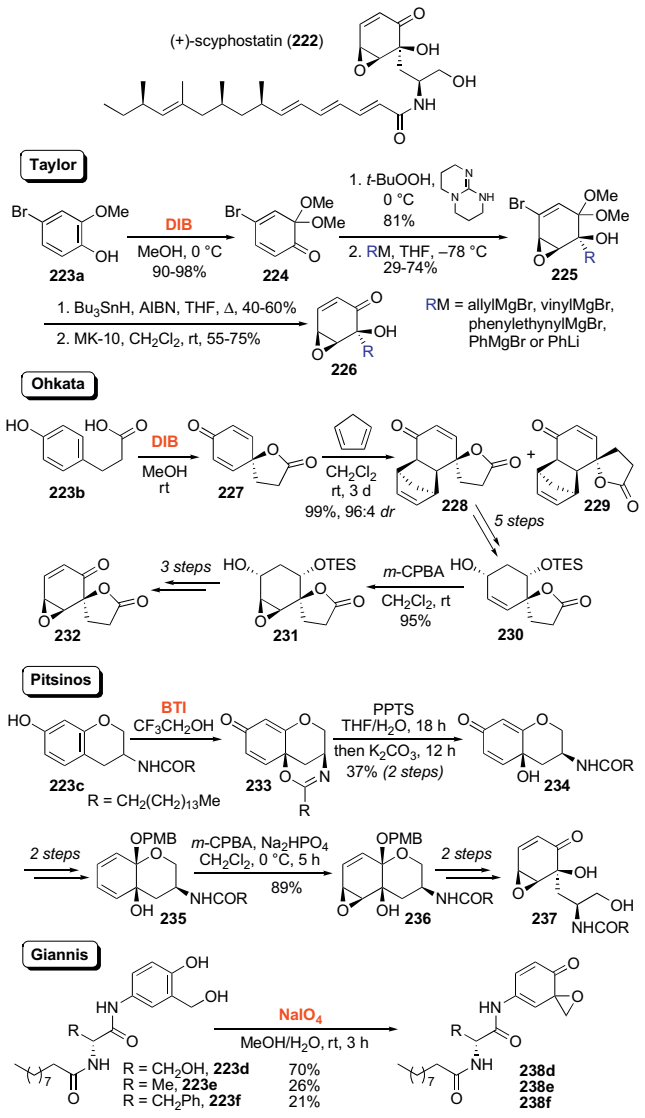
In a different exploitation of the chemistry of *ortho*-quinone dimethyl monoketals, Liao and co-workers recently accomplished a short synthesis of (±)-untenone A (**166**), an antiproliferative natural 4-hydroxycyclopenten-2-one. In this case, a DIB-generated 6,6-dimethoxycyclohexa-2,4-dienone derived from 4-hexadecyl-2-methoxyphenol was submitted to a photooxygenation that promoted a ring-contracting event, leading to the natural cyclopentenone (±)-**166** (see Scheme 27).[110] In a related exploitation of this photooxygenating chemistry, Wood and co-workers implemented an elegant intramolecular variation of λ^3-iodane-mediated dearomatization of a phenol into a cyclohexa-2,4-dienone species of the *ortho*-quinol class. This was accomplished in the context of their synthesis of the BCE-ring system of ryanodine (**221**), a metabolite isolated from the insecticidal plant, *Ryania speciosa* Vahl (Scheme 35).[111] BTI-mediated oxidative dearomatization of the carboxylic acid-tethered phenol **217a** afforded, in a moderate yield of 35%, the cyclohexa-2,4-dienone **218a**, which was next oxygenated with singlet oxygen to afford a single diastereomeric *endo*-peroxide **219a** in an excellent yield of 95% (Scheme 35). A standard hydrogenolysis of **219a** then furnished the diol **220a** in 98% yield (Scheme 35).[111] It is worth noting that the yield of the BTI-mediated dearomatizing phenolic oxidation reaction was improved to 54% when using the *para*-brominated phenol **217b**, and that the whole sequence of reactions (i.e., **218b**→**219b**, and **219b**→**220b**) constitutes a fast and efficient approach to the synthesis of *trans*-fused bridgehead-oxygenated [4.3.0]-bicyclic systems similar to that found in ryanodine (**221**) (Scheme 35).[111] Two additional recent utilizations of λ^3-iodane-generated quinonoid cyclohexa-2,4-dienones are highlighted in the section concerning the synthesis of naturally occurring *ortho*-quinol-derived [4+2] cyclodimers (see Section 7).



Scheme 35.

4. Synthetic studies toward the functionalized polar core of scyphostatin—another case of reliance on λ^3-iodane-mediated phenol dearomatization

(+)-Scyphostatin (**222**) was first isolated from a mycelial extract of the microorganism, *Dasyscyphus mollissimus* SANK-13892, and exhibits selective inhibitory activity against neutral sphingomyelinase (*N*-SMase), an enzyme involved in inflammatory processes. Taylor and co-workers targeted the highly functionalized epoxycyclohexenone nucleus of (+)-**222** and synthesized a series of analogues **226** (Scheme 36).[112] DIB-mediated oxidative dearomatization of 4-bromoguaiacol (**223a**) in methanol afforded the cyclohexa-2,4-dienone dimethylketal **224** in 90–98% yield, and subsequent epoxidation upon treatment with *tert*-butyl hydroperoxide and 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine gave rise to a key bromo-epoxide intermediate, which was submitted to a range of organometallic reagents (Scheme 36). The resulting *syn* epoxy-alcohols **225** were then successfully debrominated by the slow addition of tributyltin hydride, and ketal hydrolysis proceeded smoothly using Montmorillonite K-10 (MK-10) to give the scyphostatin analogues **226** (Scheme 36).[112] Another analogue bearing a spiro-lactone was reported by Ohkata and co-workers (Scheme 36).[113] The spiro-lactonic cyclohexa-2,5-dienone **227** was obtained by an intramolecular DIB-mediated oxidative dearomatization of phenol **223b**, and was engaged in a Diels–Alder reaction with cyclopentadiene that proceeded with high π-facial selectivity to furnish the compounds **228** and **229** in 99% yield and 96:4 dr (Scheme 36). Further chemical transformations of **228**, including a retro-Diels–Alder reaction by heating at 230 °C in the presence of maleic anhydride, led to the intermediate **230**, which was then expoxidized efficiently using *meta*-chloroperbenzoic acid

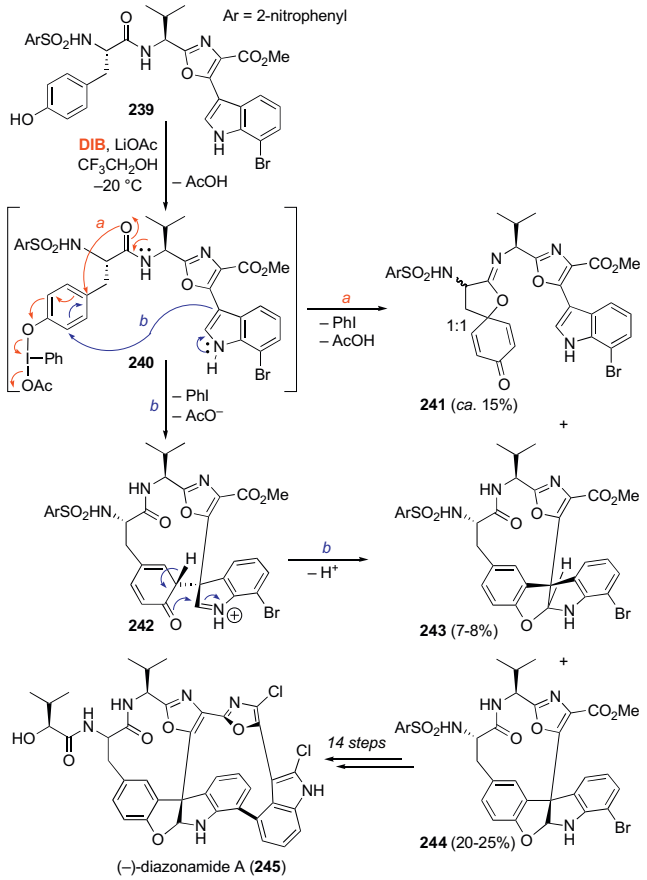


Scheme 36.

(*m*-CPBA) to give **231** in 95% yield, en route to the hydrophilic scyphostatin analogue **232** (Scheme 36).[113] More recently, Pitsinos and Cruz reported a short and efficient route to the fully functionalized polar core of (+)-scyphostatin (**222**) (Scheme 36).[114] Conversion of the phenolic benzopyran amide **223c** into the cyclohexa-2,5-dienone **233** was performed upon treatment with BTI in trifluoroethanol, and subsequent hydrolysis of the resulting oxazine ring furnished the *para*-quinol **234** in 37% yield over two steps (Scheme 36). Five additional steps, including a regio- and diastereoslective epoxidation of **235** into **236** in 89% yield using a slight excess of *m*-CPBA in the presence of Na_2HPO_4 at 0 °C, completed the synthesis of the fully functionalized polar core **237** of (+)-scyphostatin (**222**) (Scheme 36).[114] In addition, Giannis and co-workers reported the synthesis of **238d**, a cyclohexa-2,4-dienone analogue of scyphostatin featuring a reactive spiro-epoxide group at the C-6 center in place of the original epoxy-*ortho*-quinol system.[115] For the preparation of such an analogue, the Giannis group relied on an Adler oxidation (see Section 8) using sodium periodate in aqueous methanol at room temperature to convert the phenolic benzylic alcohol **223d** into the desired epoxide **238d** in 70% yield (Scheme 36). Similar experimental conditions were used to prepare the analogues **238e** and **238f** from the phenols **223e** and **223f** in yields of 26 and 21%, respectively (Scheme 36).[116] Irreversible inhibition of N-SMase by these three spiro-epoxides was found to be 88, 33, and 23%, repectively.[116]

5. λ³-Iodane-mediated transient dearomatization in phenolic-coupling reactions

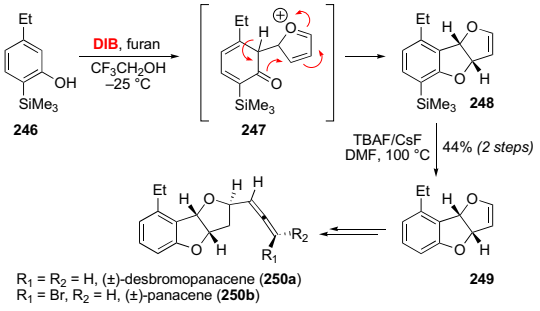
As alluded to in the introduction of this report, the reversal of polarity imposed on a phenol upon treatment with a hypervalent iodine reagent can, of course, also be exploited to promote the attack of a nucleophile on to an unsubstituted position of the starting phenol, in which case its dearomatization is only temporary and rapidly followed by a rearomatizing prototropic event. This process underlies the possibility of using hypervalent iodine reagents in phenolic-coupling reactions leading to biaryl constructs, and can be more generally exploited to install C–C-linked units on to phenolic entities. Moreover, with an adequate choice of carbon-based nucleophilic partners, such a process can further lead to the formation of benzannulated oxocyclic systems by taking advantage of the nucleophilic character recovered at the phenolic oxygen locus upon rearomatization. For example, interesting applications of this chemistry were recently made by Harran and co-workers, in the course of their synthesis of the antimitotic natural product, (−)-diazonamide A (**245**). These authors submitted the advanced phenolic/indolic amide intermediate **239** to DIB in the presence of lithium acetate in trifluoroethanol at −20 °C (Scheme 37).[117] This treatment gave rise to the formation of the undesired dearomatized and spiro-annulated cyclohexa-2,5-dienone product **241** in ca. 15% yield (Scheme 37, path *a*), as a consequence of the previously mentioned propensity of amides to participate in spiro-annulating events through their oxygen atom in related settings (see Section 2.2). Nevertheless, the two diastereomeric macrolactams **243** and



Scheme 37.

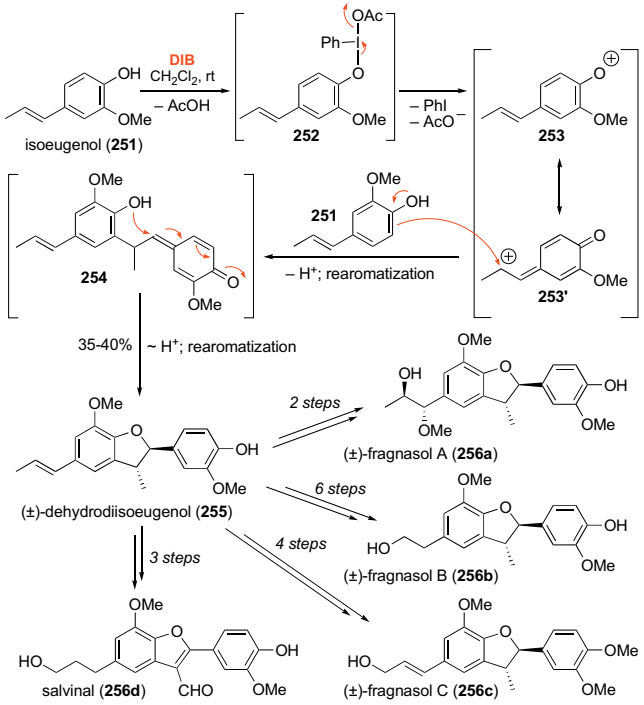
244 were fortunately also produced in a 1:3 ratio (ca. 30% yield) according to the proposed path *b*, through which the transient intermediate **240** (or a discrete phenoxenium form generated after departure of its λ^3-iodanyl unit) is intramolecularly trapped by the nucleophilic indolic moiety, followed by rearomatization of the resulting cyclohexa-2,4-dienone intermediate **242** with a concerted oxocyclization on to its iminium unit leading to the observed benzofuran products (Scheme 37). Alternatively, the possibility of having, instead, an initial DIB-mediated oxidative activation of the indolic enamine moiety, in which case the phenolic unit would classically act as a nucleophilic partner in the reaction, remains to be further investigated.[117] This alternative could also apply to the case of the BTI-mediated intramolecular phenolic enamino-imine-coupling reaction involved in Kita's synthesis of (+)-discorhabdin A (**48**) (see Section 2.3, Scheme 12). In any event, the major benzofuran compound **244** was further transformed to afford (−)-diazonamide A (**245**) after 14 additional steps (Scheme 37).[117]

Canesi and co-workers used furan as an aromatic carbon-based nucleophile in a related, but intermolecular, case of phenol oxidative activation, which they referred to as 'aromatic ring umpolung'.[118] DIB was also used in trifluoroethanol at −25 °C to activate 2-trimethylsilyl-5-ethylphenol (**246**), which was then regioselectively trapped by furan from which a C–C strategic bond was thus established at the unsubstituted phenolic *ortho*-position (Scheme 38). Hence, rearomatization occurred and provoked the concerted attack of the phenolic oxygen on to the cationic furan-derived moiety of the presumed intermediate **247** to furnish the benzofuranoid *cis*-dioxabicyclo[3.3.0]octane derivative **248**. This formal [3+2] cycloaddition product was then further elaborated to achieve the total synthesis of the natural allenic products, (±)-desbromopanacene (**250a**) and (±)-panacene (**250b**), via **249** (Scheme 38).[118]



Scheme 38.

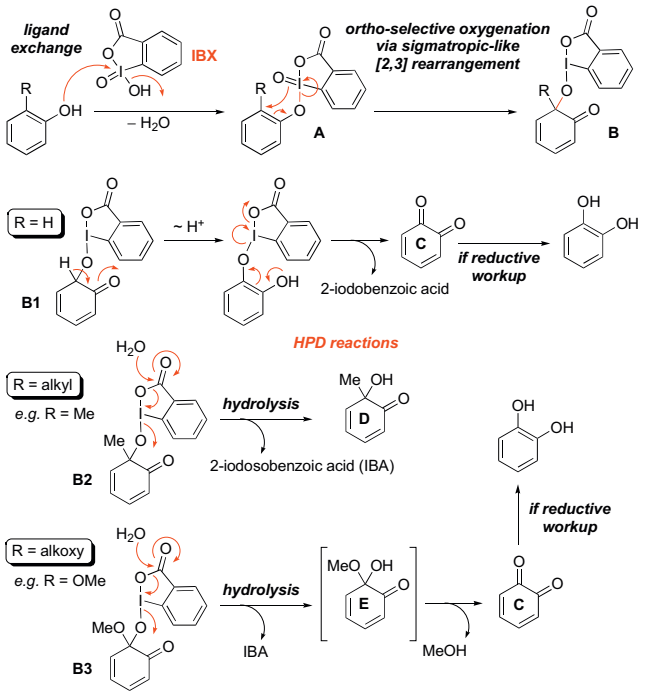
A related exploitation of such a λ^3-iodane-mediated phenolic umpolung, during which the dearomatization of the starting phenol is only transient, was earlier made by Antus and co-workers in the context of a classical phenolic-coupling dimerization. These authors reported in 2000 a simple synthesis of benzofuranoid neolignans isolated from *Myristica fragrans*, starting from isoeugenol (**251**) that was activated into **252** using DIB in dichloromethane (Scheme 39).[119] They proposed a dissociative-type mechanism (see Scheme 4) leading to the partial formation of a proposed phenoxenium ion intermediate **253**/**253′**, which is then trapped by some intact (and nucleophilic) isoeugenol (**251**) to forge the requisite C–C bond of the 2,3-dihydrobenzo[*b*]furan skeleton (Scheme 39). The resulting *para*-quinone methide dimeric intermediate **254** (or its protonated cationic form) then undergoes a rearomatizing intramolecular nucleophilic addition with the remaining phenolic function to furnish (±)-dehydrodiisoeugenol (**255**) in 35–40% yield (Scheme 39). In addition, (±)-**255** was used as a precursor for the synthesis of the natural neolignans, (±)-fragnasols A (**256a**), B (**256b**) and C (**256c**), in two, six and four steps, respectively (Scheme 39).[119] Kuo and co-workers recently applied the same hypervalent iodine-based tactic in their total synthesis of salvinal (**256d**), a neolignan firstly isolated from the Chinese medicinal plant, *Salvia mitorrhiza* Burge (Scheme 39).[120]



Scheme 39.

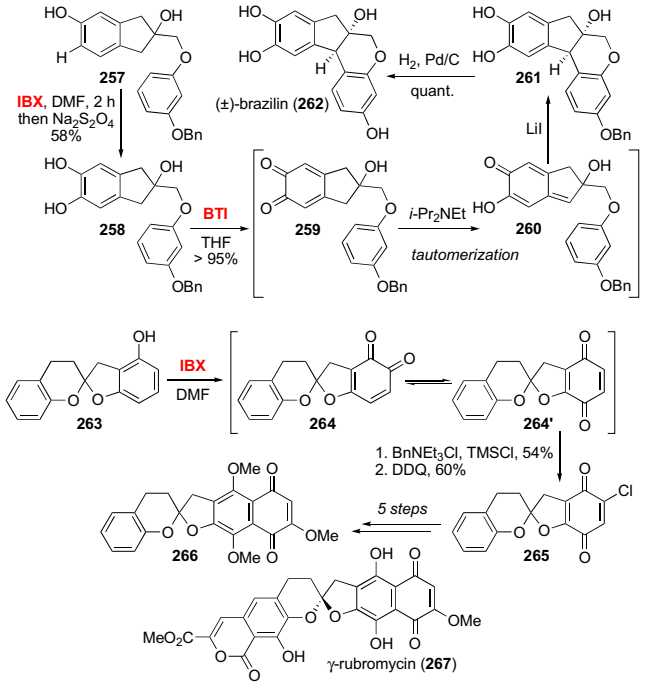
6. λ^5-Iodane-mediated *ortho*-oxygenative phenol dearomatization reactions

Pettus and co-workers were the first to report on the remarkable capability of the λ^5-iodane IBX reagent to deliver *ortho*-selectively an oxygen atom during phenol dearomatization processes (Scheme 40).[40] Indeed, a phenol can react with IBX, presumably through an initial ligand-exchange step with elimination of water, to give rise to a phenyloxy-λ^5-iodane of the type **A**. This species can then rearrange in a 2,3-sigmatropic-like fashion by forming regioselectively a single oxygen-carbon bond at one of the *ortho*-carbon centers of the phenyloxy unit, with concomitant two-electron reduction of the iodine(V) atom leading to a λ^3-iodanyl species of the type **B**. This species can evolve differently depending on the substitution pattern of the starting phenol. For example, if the *ortho*-position does not bear any substituent (i.e., R=H, Scheme 40), it can be argued that **B1** will first rearomatize by prototropy before reductive elimination of the λ^3-iodanyl moiety drives the reaction toward the generation of an *ortho*-quinone product **C**. If an alkyl substituent occupies the *ortho*-position that has been oxygenated (i.e., R=Me, Scheme 40), the λ^3-iodanyl moiety of **B2** can be slowly released by hydrolysis to give 2-iodosobenzoic acid (IBA) and an *ortho*-quinol product **D**. We refer to this transformation as the Hydroxylative Phenol Dearomatization (HPD) reaction (vide infra).[8,41] The outcome of such an HPD reaction is different when the *ortho*-position bears an alkoxy group (i.e., R=OMe, Scheme 40), in which case the hemiketal product **E**, obtained from **B3**, eliminates methanol to furnish an *ortho*-quinone product **C**. Nevertheless, this transformation constitutes a valuable means to cleave *ortho*-phenolic methyl phenyl ether bonds[40b] that has found pertinent applications in natural product synthesis (vide infra).



Scheme 40.

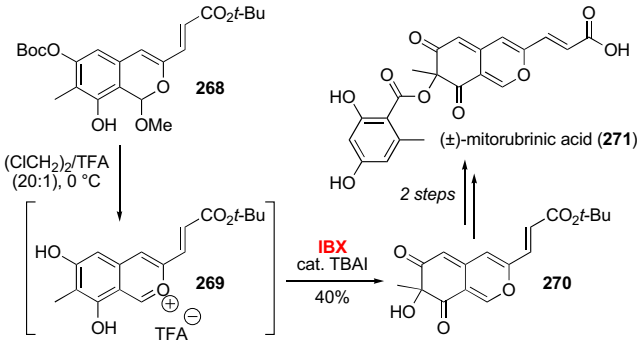
Pettus and co-workers exploited the *ortho*-selective oxygenating capability of IBX to convert phenols into *ortho*-quinones and catechols,[40a] and, later, they used this methodology in their racemic synthesis of the natural pigment and telomerase inhibitor, brazilin (**262**) (Scheme 41).[121a] Treatment of the phenolic material **257** with IBX, followed by reductive work up using $Na_2S_2O_4$,[40b] afforded the catechol **258**, which was oxidized back to the *ortho*-quinone **259** using BTI. Upon base-promoted tautomerization, this quinone was transformed into the *para*-quinone methide **260**, which then cyclized in the presence of lithium iodide to produce



Scheme 41.

the benzylated brazilin **261** (Scheme 41).[121a] IBX was also used by the Pettus group to convert phenol **263** into *ortho*-quinone **264** in the context of a model study related to the synthesis of rubromycins such as **267**, a 5,6-aryloxy spiro-ketal antibiotic species isolated from cultures of *Streptomyces* (Scheme 41). The *ortho*-quinone **264** was found to be unstable and slowly rearranged into the more stable *para*-quinone **264′**, which was then further elaborated (via **265**) into the naphthoquinoid rubromycin model compound **266** (Scheme 41).[121b]

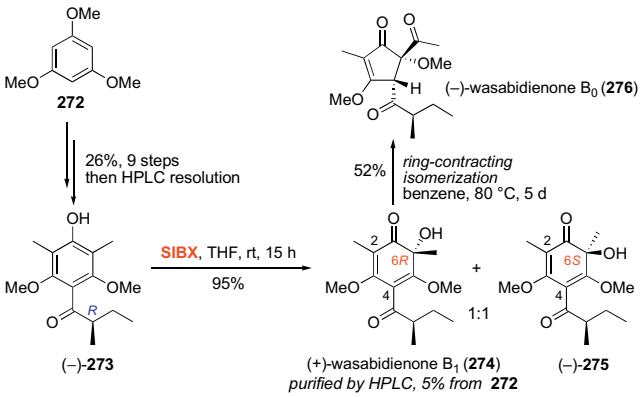
In their synthesis of the azaphilone fungal metabolite, (±)-mitorubrinic acid (**271**), Pettus and co-workers used IBX to perform an HPD reaction.[122] A key step of this synthesis was the preliminary conversion of the isocoumarin-derived *O*-Boc monoprotected phenolic ketal **268** into the benzopyrilium salt **269** upon treatment with TFA in 1,2-dichloroethane. Indeed, the HPD of **268** using IBX in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI) failed, but that of **269** under the same conditions delivered the desired azaphilone **270** that was then successfully converted in two steps into (±)-mitorubrinic acid (**271**) (Scheme 42). These conditions of conversion of benzopyrilium salts into azaphilones had been earlier described by the Porco group in a report on the synthesis of several unnatural azaphilones.[123] The addition of TBAI, acting both as a phase-transfer catalyst and probable activator of IBX, proved to be crucial to the success of these HPD reactions.



Scheme 42.

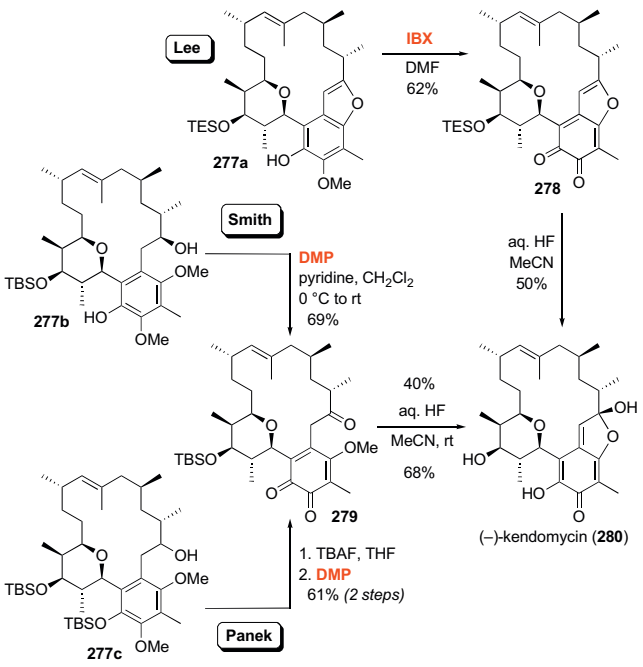
Our own development of the stabilized (non-explosive) formulation of IBX, called SIBX, and its application in the oxidation of alcohols and the hydroxylative demethoxylation of 2-methoxyphenols (see Scheme 40)[40b] also led us to contemplate its use in HPD reactions of 2-alkylphenols to access 6-alkyl-6-hydroxycyclohexa-2,4-dienone derivatives, trivially referred to as *ortho*-quinols.[41,124] The first total synthesis of the natural non-dimerizing *ortho*-quinol, (+)-wasabidienone B_1 (**274**), a fungal polyketide isolated from a potato culture of *Phoma wasabiae* Yokogi,[125] was thus accomplished.[126] The commercially available 1,3,5-trimethoxybenzene (**272**) was converted into the adequately symmetrically substituted 2,6-dimethylphenol **273** in nine chemical steps and in a 26% overall yield; subsequent HPLC resolution afforded the desired phenol (*R*)-**273** (Scheme 43). Its HPD transformation was performed using SIBX in THF at room temperature and afforded a 1:1 mixture of (+)-**274** and its 6-epimer (−)-**275** in an excellent yield of 95%. Semi-preparative HPLC separation of this diastereomeric mixture then furnished pure (+)-**274**, which was additionally converted into its congener, (−)-wasabidienone B_0 (**276**), in a 52% yield via a thermally induced ring-contracting isomerization reaction (Scheme 43).[126]

The previously mentioned capacity of IBX to release *ortho*-phenolic methyl phenyl ether bonds via hydroxylative demethoxylation (see Scheme 40)[40b] was recently exploited by Lee and co-workers in their first synthesis of kendomycin (**280**), also known as (−)-TAN



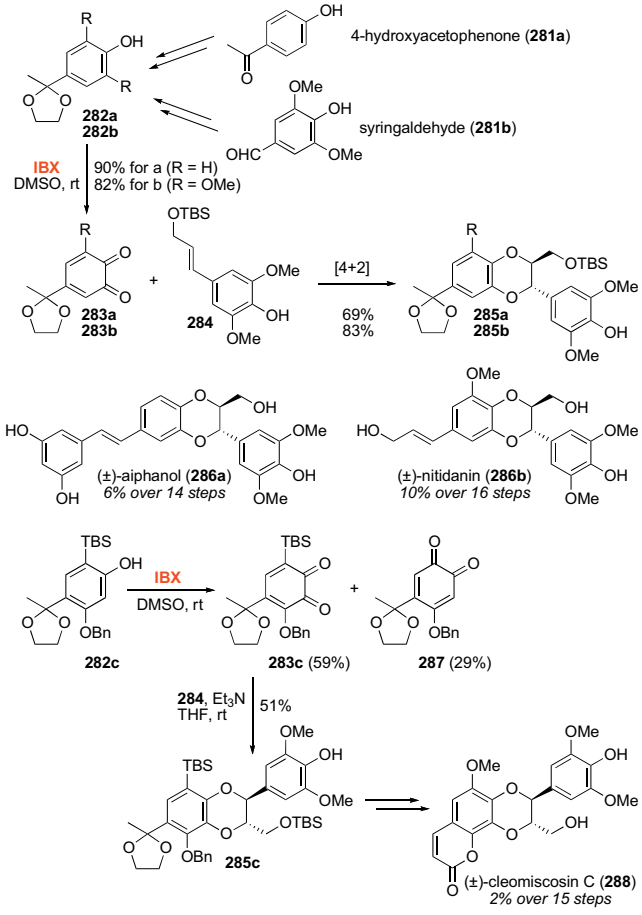
Scheme 43.

2161, a bacterial antibiotic metabolite that was originally isolated from *Streptomyces violaceuber* and that was shown to possess potent activity as both an endothelin receptor antagonist and a calcinotin receptor agonist.[127] In fact, the construction of this polyketide macrocycle led to the development of several synthesis approaches, but all of the so-far reported total syntheses were completed using a key λ^5-iodane-mediated phenol dearomatization step. Thus, Lee and co-workers relied on a macroglycosidation approach to elaborate the macrocylic core of the target, and a subsequent IBX-mediated hydroxylative demethoxylation of the resulting 2-methoxyphenolic advanced intermediate **277a** afforded the *ortho*-quinone **278** in 62% yield (Schemes 40 and 44).[127] Removal of the TES group and hydration of the *ortho*-quinone by the action of aqueous hydrogen fluoride (50% yield) completed the synthesis of (−)-**280** (Scheme 44).[127] In their version of the total synthesis of the same target, Smith and co-workers exploited a Petasis–Ferrier rearrangement and a ring-closing olefin metathesis to prepare the phenolic macrocycle **277b**.[128] The λ^5-iodane Dess–Martin periodinane (DMP) reagent was used instead of IBX to convert the 2-methoxyphenol **277b** into the *ortho*-quinone **279** in a yield of 69% (Scheme 44).[128] More recently, Panek and co-workers reported the elaboration of the macrocycle **277c** through an organosilane-based [4+2]-annulation strategy and a samarium(II) iodide-assisted cyclization (i.e., an intramolecular Barbier-type reaction).[129] The silylated 2-methoxyphenol moiety of **277c** was next deprotected and subsequently dearomatized into the *ortho*-quinone **279**, again using DMP (Scheme 44).[129] In both syntheses, a final treatment of the *ortho*-quinone **279** with aqueous hydrogen fluoride afforded (−)-kendomycin (**280**) in 40 and 68% yield, respectively (Scheme 44).[128,129]



Scheme 44.

The Pettus IBX-mediated preparation of *ortho*-quinones from phenols[40a] and our related hydroxylative demethoxylation of phenolic methyl phenyl ethers[40b] were also implemented by Kuboki, Ohira and co-workers to develop a convenient approach to 1,4-benzodioxane ring systems such as **285** via a [4+2] cycloaddition of *ortho*-quinones **283** and the silylated cinnamyl alcohol **284** (Scheme 45).[130] Thus, regioselective oxidation of phenols **282a**/**b**, prepared from **281a**/**b**, with IBX in DMSO at room temperature afforded the *ortho*-quinones **283a**/**b** in very good yields of 90 and 82%, respectively (Scheme 45). Subsequent [4+2] cycloadditions between these *ortho*-quinones **283a**/**b** and dienophile **284** furnished 1,4-benzodioxanes **285a**/**b** in yields of 69 and 83%, respectively. This key two-step sequence has been successfully applied to the racemic total synthesis of the stilbenolignans (±)-aiphanol (**286a**),[130a] a metabolite isolated from the seeds of *Aiphanes aculeata* Willd that possesses significant inhibitory activity against cyclooxygenases, and (±)-nitidanin (**286b**),[130b] an antimalarial agent isolated from the wood of *Xanthoxylum nitidum* D.C. as a racemate and from the heartwood of Indian *Santalum album* L. as a pure enantiomer (Scheme 45). In their mechanistic studies, Kuboki, Ohira and co-workers also demonstrated that the regiochemistry of the [4+2] cycloaddition was reversed when an



Scheme 45.

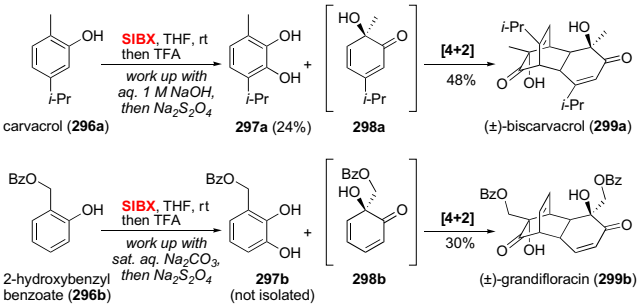
alkoxy substituent is present *meta*, instead of *ortho*, to the starting phenol function (i.e., **282c**).[130c] This finding was successfully applied to the total synthesis of (±)-cleomiscosin C (**288**), a bioactive coumarinolignan, also named aquillochin, via preparation of the precursor **285c** from the *ortho*-quinone **283c**, which was obtained with concomitant *ortho*-quinone **287** (Scheme 45).[130d]

7. Iodane-mediated (biomimetic) *ortho*-oxygenative phenol dearomatization/Diels–Alder cyclodimerization reactions

Wasabidienone B_1 (**274**) is, in fact, one of the relatively rare examples of naturally occurring *ortho*-quinols. In most cases, the high propensity of their hydroxydienone unit to participate in [4+2] Diels–Alder reactions causes them to spontaneously dimerize via such cycloaddition processes. This propensity is the characteristic reactivity feature of such cyclohexa-2,4-dienones, as well as their *ortho*-quinone monoketal variants, and can only be bypassed if the cyclohexa-2,4-dienone core bears blocking substituents at key positions. For example, a small alkyl or alkoxy group at the carbon-5 position,[131] a bromine atom at the carbon-4 position[132] or an acetate protection of the 6-hydroxy group[34a,97d,133] is usually enough to prevent dimerization. Following the tracks left early on by Wessely and Andersson,[131,133a,134] Liao's group and ourselves more recently spent much effort to delineate not only the reasons underlying these blocking effects, but also, and most importantly, the extraordinary level of regio-, site-, and stereoselectivities observed when [4+2] cyclodimerizations are allowed to proceed.[97a-c,135] This understanding is of most fundamental importance, for numerous natural products of various biosynthetic origins are derived from the dimerization of *ortho*-quinols, which are probably themselves biogenerated by a regioselective oxygenative (hydroxylative) dearomatization of a corresponding phenolic precursor.[97a] Hence, iodane-mediated HPD reactions offer a particularly appropriate and biomimetic means to rapidly access these natural products by chemical synthesis.

Our synthesis of (+)-aquaticol (**295**), a bis(sesquiterpene) isolated from *Veronica anagallis-aquatica*, a plant used in traditional Chinese medicine,[136] illustrates this strategy. (±)-Cuparene (**289**) was hydroxylated through a three-step procedure to furnish (±)-hydroxycuparene (**290**) in an overall yield of 57%. This racemic 2-methylphenol was then resolved by chiral HPLC separation, and the dextrorotatory *R*-enantiomer was submitted to HPD reaction conditions using SIBX (Scheme 46).[137] This reaction directly furnished a 1:1 mixture of (+)-aquaticol (**295**) and the 'all *R*' dimer (+)-**294** in a yield of 50%, together with the 1,2-dihydroxycuparene (+)-**293** as a result of unavoidable oxygenation at the free *ortho*-position of the starting phenol (+)-**290** (Scheme 46). Although no stereocontrol could be imposed at the *ortho*-quinolic C-6 center by this IBX-mediated HPD reaction, the two diastereomeric *ortho*-quinols **291** and **292** 'recognized' each other and exclusively self-reacted according to the regio-, site-, and stereoselectivity controls that we demonstrated for Diels–Alder cyclodimerizations of *ortho*-quinonoid cyclohexadienones (Scheme 46).[97a,137]

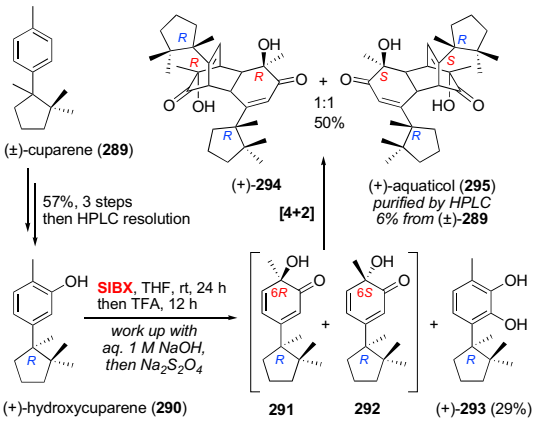
The above SIBX-mediated tandem HPD/Diels–Alder cyclodimerization sequence was also employed to achieve a simpler racemic synthesis of other natural *ortho*-quinol-based [4+2] cyclodimers. (±)-Biscarvacrol (**299a**), a carvacrol-derived dimer isolated from the heartwood of *Callitris macleayana*,[138] and (±)-grandifloracin (**299b**) that was isolated from the plant *Uvaria grandiflora*[139] were thus cleanly prepared in one step from carvacrol (**296a**) and 2-hydroxybenzyl benzoate (**296b**) in yields of 48 and 30%, respectively, via *ortho*-quinols **298a**/**b** sometimes obtained with concomitant catechols **297a**/**b** (Scheme 47).[41]



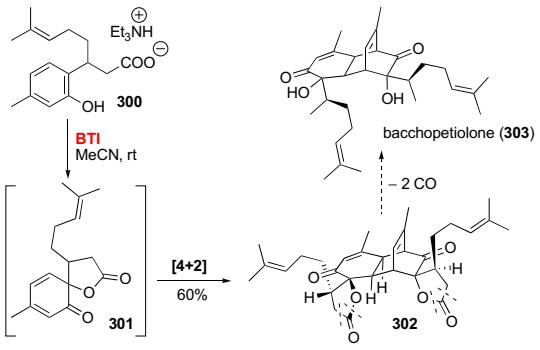
Scheme 47.

In the same vein, Wood and co-workers also envisaged a tandem hypervalent iodine-mediated oxygenative phenol dearomatization/Diels–Alder cyclodimerization sequence to synthesize the carbocyclic core of bacchopetiolone (**303**), a dimeric sesquiterpene isolated from the Chilean shrub, *Baccaris petiolata* (Scheme 48).[140] Treatment of the phenolic triethylammonium carboxylate **300** with BTI in acetonitrile resulted in a smooth oxidative dearomatization into the spiro-lactone **301**, which underwent spontaneous [4+2] cyclodimerization to provide the dimer **302** as a single diastereomer in 60% yield (Scheme 48). Although the synthesis has not yet been completed from **302**, it must be emphasized that this advanced intermediate features the entirely functionalized tricyclic skeleton of bacchopetiolone (**303**) with the correct relative stereochemistry and that only two carbonyl units are to be removed to reach the target (Scheme 48).[140]

Although IBX, stabilized or not, is particularly efficient at promoting (biomimetic) HPD reactions in a strictly *ortho*-selective manner, it lacks the possibility to control the configuration of the aromatic carbon center undergoing the sp^2-to-sp^3 geometry

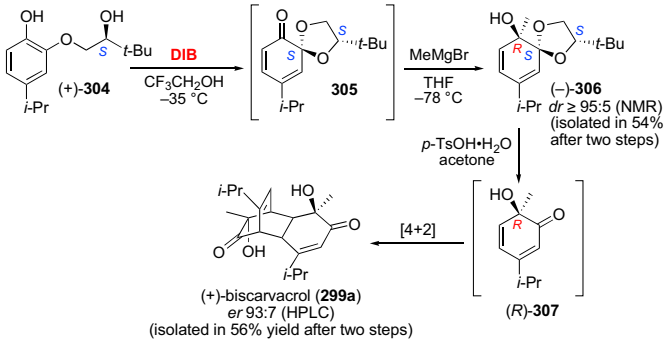


Scheme 46.



Scheme 48.

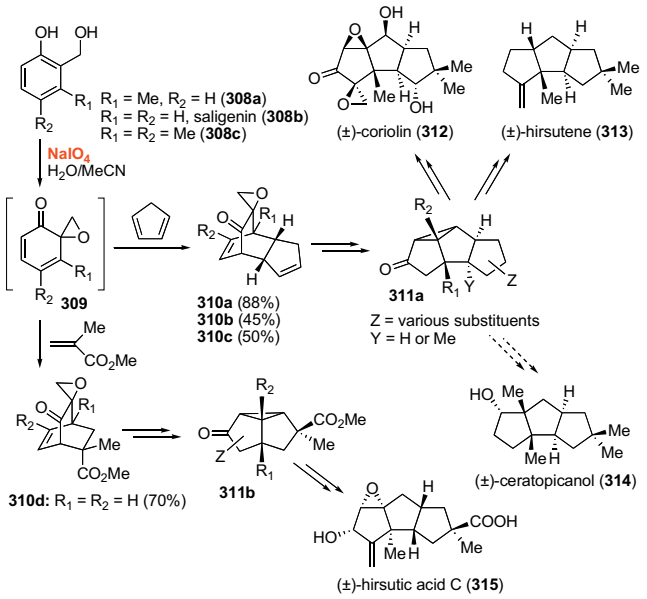
change. This drawback initially led us to explore substrate-controlled routes to *ortho*-quinoid cyclohexadienones in a non-racemic format.[33,141] Again, reliance on hypervalent iodine chemistry offered a satisfactory solution, which was then implemented for the enantioselective synthesis of the bis(monoterpene), (+)-biscarvacrol (**299a**).[33] The optically active phenol (+)-**304** was treated with the λ^3-iodane DIB reagent in trifluoroethanol at −35 °C to generate the requisite *ortho*-quinone spiro-ketal (*S*,*S*)-**305**. This compound was immediately treated with a methylating Grignard reagent to furnish the tertiary alcohol (−)-**306** with a remarkably high level of diastereoselectivity (Scheme 49). Cleavage of the ketal function gave the enantioenriched *ortho*-quinol (*R*)-**307**, which spontaneously cyclodimerized to afford (+)-**299a** as the major and crystallizable stereoisomer (Scheme 49).[33]



Scheme 49.

8. λ^7-Iodane-mediated spiro-epoxydative phenol dearomatization/Diels–Alder reactions

In their research program aimed at developing a unified strategy for the synthesis of polyquinanes and protoilludanes, Singh and co-workers relied on [4+2] cycloaddition reactions of in situ-generated spiro-epoxycyclohexa-2,4-dienones **309** to rapidly build complex annulated bicyclo[2.2.2]octenones such as **310a–c** (Scheme 50).[142a,b] Further chemical and photochemical transformations of these polycycles were investigated and led to the development of new routes to diquinane, triquinane, tetraquinane, protoilludane and oxa-sterpurane frameworks.[142a,c] For example, the formal synthesis of (±)-coriolin (**312**),[143a,b] the total synthesis of (±)-hirsutene (**313**),[143c] the formal synthesis of (±)-hirsutic acid C (**315**)[143d] and ongoing work toward the synthesis of (±)-ceratopicanol (**314**)[143e] exemplify the utility and value of Singh's strategy toward natural *cis*,*anti*,*cis*-triquinanes (Scheme 50). In all of these syntheses, the founding event of such a remarkable elaboration of molecular complexity from simple phenolic precursors is an application of the Adler oxidation.[42] Thus, upon treatment with the λ^7-iodane sodium periodate reagent in aqueous acetonitrile, the phenolic benzyl alcohols, 6-methylsaligenin (**308a**), saligenin (**308b**), and 2-hydroxymethyl-3,4-dimethylphenol (**308c**), were dearomatized into their corresponding spiro-epoxycyclohexa-2,4-dienones **309**, which were immediately intercepted by cyclopentadiene to furnish, respectively, **310a**, **310b** and **310c** in moderate-to-high yields (Scheme 50). In the case of the synthesis of **315**, methyl methacrylate was used as the dienophile in this Diels–Alder reaction with **309** to afford **310d** (Scheme 50). Further manipulations of these systems, including a photochemically induced 1,2-acyl shift to generate the pivotal cyclopropane-bearing tetracyclic or tricyclic core system **311a**/**b**, gave access to the triquinane targets **312–315** or their advanced intermediates (Scheme 50).



Scheme 50.

9. Conclusions and future challenges

The large amount of literature data published during the last ten years or so on the applications of hypervalent iodine-mediated phenol dearomatizations in natural product synthesis constitutes a remarkable ensemble of successful results that unarguably demonstrates the value and utility of such a process in modern organic synthesis. From the seminal work of Siegel and Antony in 1955[21] to today's most advanced implementations in the synthesis of complex natural products, this tactical use of iodane reagents in phenol dearomatizing transformations has obviously benefited from the impressive development that the chemistry of hypervalent iodine in general has been submitted to in recent years,[17,144] a development that has paralleled an urge to replace the use of toxic heavy metals in phenol dearomatization processes. Surely, one can soon expect further progress in this chemistry, so appealing to the synthetic organic chemist's mind is the concept of rapidly transforming an achiral flat aromatic ring like that of a phenol into a chiral (or pro-chiral) polyfunctionalized three-dimensional system like that of a cyclohexadienone molecule. The first fruits of currently ongoing efforts in several laboratories have begun to appear in the literature. For example, Gaunt and co-workers have reported an enantioselective organocatalytic oxidative dearomatization reaction sequence based on a DIB-mediated conversion of a *para*-substituted phenol into a prochiral cyclohexa-2,5-dienone, followed in situ by a chiral amine-catalyzed desymmetrizing intramolecular Michael reaction.[145] The long-standing challenge of developing chiral iodane reagents capable of controlling the configuration of the carbon center undergoing the sp^2-to-sp^3 geometry change during dearomatization of phenols into *ortho*-quinoid cyclohexa-2,4-dienones is also starting to be overcome. For example, Kita and co-workers have described such a chiral λ^3-iodane reagent, a bis(λ^3-iodane) spiro-biindane-based reagent, capable of promoting the intramolecular dearomatization of naphthols into spiro-lactonic cyclohexa-2,4-dienones with enantiomeric excesses of up to 86%.[31] Boppisetti and Birman have designed a chiral oxazoline-containing λ^5-iodane reagent capable of promoting asymmetric HPD reactions of 2-methylphenols with enantiomeric excesses of up to 77%.[146] Organocatalytic versions of hypervalent iodine-mediated reactions have also made their entry into the scene,[147] and some researchers, including ourselves, were not long

to apply this alternative to the dearomatization of phenols. Using a catalytic amount of an iodoarene and *m*-CPBA as a terminal co-oxidant, Kita and co-workers thus implemented a solution to the challenging C–N bond-forming spiro-cyclization of phenolic amides, which was discussed in Section 2.2.[148] They also proposed a catalytic version of the use of their new chiral bis(λ^3-iodane) reagent by oxidizing in situ its bis(iodoarene) precursor with *m*-CPBA to deliver spiro-lactonic cyclohexa-2,4-dienone products with enantiomeric excesses of up to 69%.[31] In our case, we developed an asymmetric HPD reaction using a chiral iodobiarene, which, when used as an organocatalyst in concert with excess *m*-CPBA, enables subsequent regio- and diastereoselective epoxidation of the cyclohexa-2,4-dienone system, whereas stoichiometric amounts of both the chiral iodobiarene and *m*-CPBA enable strict HPD reactions with enantiomeric excesses of up to 50%.[149] Moreover, such an in situ generation of iodanes from iodoarenes and *m*-CPBA (catalytic or not) turned out to be a convenient alternative to the often difficult ex situ oxidation of iodoarenes into iodanes.[149] Despite all of these promising advances, needless to say that there is still a lot of room left for improvement, in particular in the asymmetric variants corner. Furthermore, the mechanistic knowledge of these reactions is still today in its infancy, gathering several working hypotheses rather than firm elucidations of reaction pathways. Progress will have to continue in this area with the help of additional physical organic investigations and theoretical calculations, especially in view of the recent developments on in situ generation of iodanes from iodoarenes.[149] A sound knowledge of the mechanistic intricacies of iodane-mediated phenol dearomatization processes will undoubtedly help the design of new and efficient (chiral) reagents to be used in the synthesis of natural products, as well as useful building blocks for organic synthesis.

Acknowledgements

Financial support from the Institut Universitaire de France (IUF), the Ministère de la Recherche, the Centre National de la Recherche Scientifique (ATIP 'Jeunes Chercheurs' 2005–2007), the Association Nationale de la Recherche et de la Technologie (CIFRE Grants N° 301/2002 and N° 457/2005), the Conseil Régional d'Aquitaine (Grant N° 990209003), Simafex and GlaxoSmithKline is gratefully acknowledged.

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Biographical sketch

Laurent Pouységu was born in Dax, France, in 1971. He received his PhD degree from the University of Bordeaux in 1997 for his work on structural determination in carbohydrate chemistry under the supervision of Prof. Bernard De Jéso. He then joined the research group of Prof. Stéphane Quideau at Texas Tech University, USA, for one year as a postdoctoral fellow, where he contributed to the development of *ortho*-quinol acetate chemistry and oxocyclization reactions. In 1998, he moved back to Bordeaux where he obtained a position as Maître de Conférences in Organic Chemistry in Prof. Stéphane Quideau's group. His research interests include hypervalent iodine chemistry and oxidative dearomatization of phenols for the total synthesis of bioactive natural products.

Denis Deffieux was born in Bordeaux, France, in 1965. He received his PhD degree in September 1993 from the University of Bordeaux for his work on electrochemical silylation of polyhalogenated aromatic compounds under the supervision of Prof. Biran and Prof. Bordeau in Dr. Dunoguès' Laboratory. In October 1993, he joined the group of Prof. George Olah in Los Angeles, USA, as a postdoctoral fellow. In 1996, he moved back to Bordeaux where he obtained a position as Maître de Conférences in Organic Chemistry at the University of Bordeaux, and joined Prof. Stéphane Quideau's group in 1999. His research interests include the development of electrochemical methodologies based on anodic oxidation of oxygenated aryl compounds for total synthesis of bioactive natural products.

Stéphane Quideau was born in Lannilis, France, in 1966. He received his PhD degree in natural products chemistry from the University of Wisconsin-Madison, USA, in 1994 under the supervision of Prof. John Ralph. After a postdoctoral stint at The Pennsylvania State University in State College (USA) under the guidance of Prof. K. S. Feldman, he moved to Texas Tech University in Lubbock (USA) as an Assistant Professor. In 1999, he moved back to France as an Associate Professor at Bordeaux 1 University. He joined the European Institute of Chemistry and Biology (IECB) as a Group Leader in 2002. He was nominated as a Junior Member of the 'Institut Universitaire de France' (IUF) in 2004. His team received the Young Investigators Award (ATIP) from the CNRS in 2005, and he was promoted to the rank of Full Professor in 2005. His current fields of interest encompass structural, synthetic and biomechanistic studies of bioactive natural products, including plant polyphenols, terpenoids, alkaloids and angucycline antibiotics, the development of synthetic methodologies based on hypervalent iodine-mediated dearomatization of phenols, and the rational design of antigenic peptidomimetics as immunotherapeutic agents for the development of anticancer vaccines. In 2006, he received the Acros Prize from the French Chemical Society and the Dr. and Mme Henri Labbé Prize from the French Academy of Sciences. In 2008, he received the Scientific Prize of the 'Groupe Polyphénols' Society, and was elected President of this Society for the following four years.