

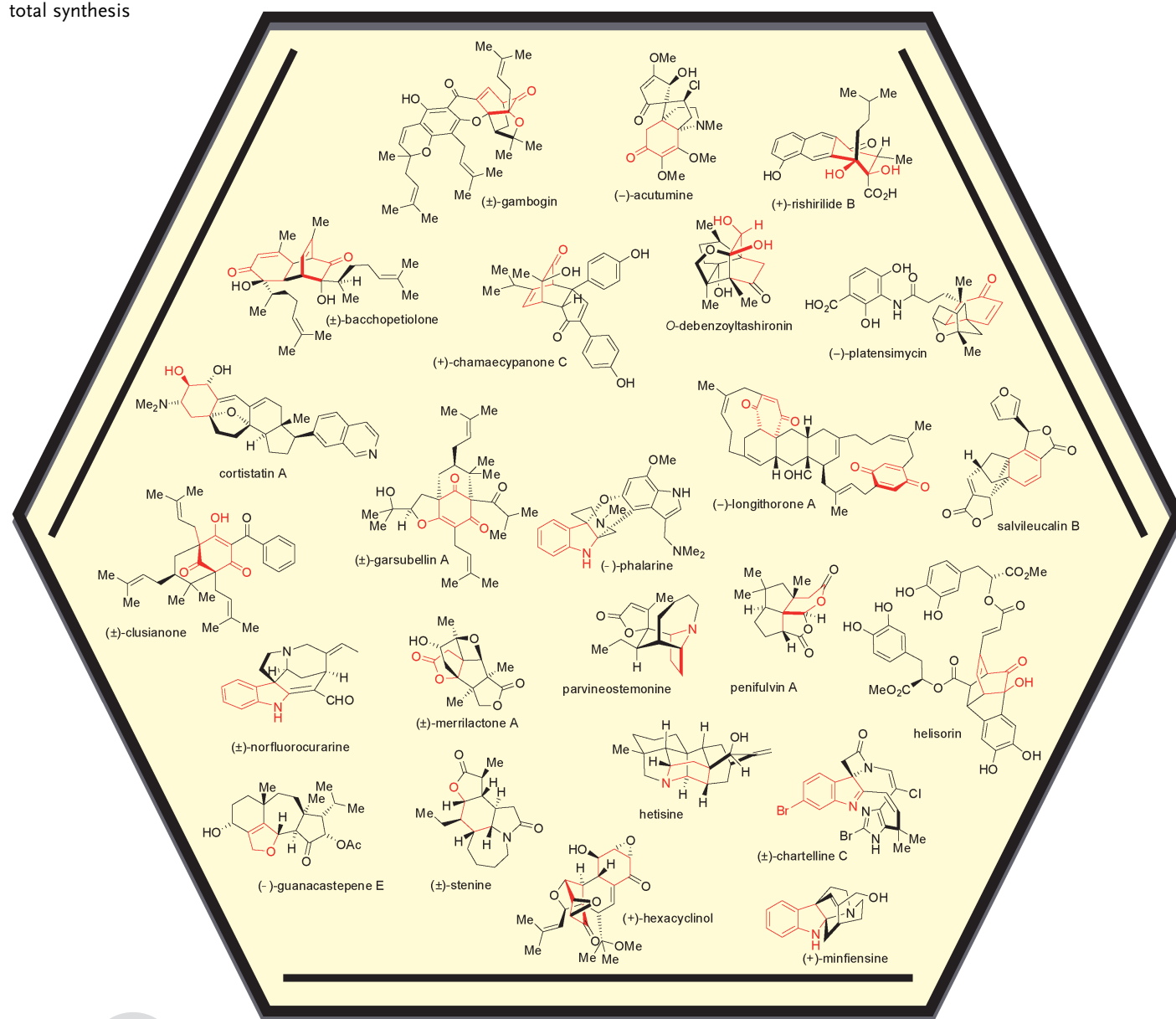
Dearomatization Strategies in the Synthesis of Complex Natural Products

Stéphane P. Roche and John A. Porco Jr.*

Keywords:

arenes · biomimetic synthesis ·
natural products ·
dearomatization ·
total synthesis

Dedicated to Professor Samuel J. Danishefsky



Evolution in the field of the total synthesis of natural products has led to exciting developments over the last decade. Numerous chemo-selective and enantioselective methodologies have emerged from total syntheses, resulting in efficient access to many important natural product targets. This Review highlights recent developments concerning dearomatization, a powerful strategy for the total synthesis of architecturally complex natural products wherein planar, aromatic scaffolds are converted to three-dimensional molecular architectures.

1. Introduction

Since 1865 and the assignment of the benzene structure by the German chemist Friedrich A. Kekulé, suggesting that it is a six-membered ring of carbon atoms with alternating single and double bonds (1,3,5-cyclohexatriene), the physical properties and accurate structure of benzene have been studied in detail. The scientific community has been enthusiastic about the concept of aromaticity owing to a new understanding of benzene stabilization through resonance energy, and hence of all aromatic compounds, which proved to be extremely important for both fundamental and applied chemistry. A quantitative assessment of the degree of aromaticity may be approximated by the value of resonance energy^[1] as well as structural and magnetic criteria.^[2] Despite the high resonance energy of the benzene ring, a number of examples of dearomatization by microorganisms either through oxidation (oxygenases) or reduction (reductases) exist in nature.^[3] Upon dearomatization of aromatic and heteroaromatic derivatives, highly reactive intermediates are generally produced leading to facile formation of carbon–carbon and carbon–heteroatom bonds, spontaneous cycloadditions, and cascade reactions.

As shown in Figure 1, a number of strategies for dearomatization have been utilized by organic chemists during the course of complex total syntheses. Colored in red are aromatic nuclei that have been dearomatized during the course of these synthetic endeavors. In one classical example, Myers and co-workers applied a chemoenzymatic method for arene dearomatization by the dihydroxylation of benzoic acid (**1**) using the bacterium *A. eutrophus* affording 1,2-dihydroxycyclohexadiene **2** with high enantioselectivity (Figure 1 a).^[4] The simple, dearomatized cyclohexadienone **2** was parlayed into a number of useful chiral building blocks (e.g. **3** and **4**) for use in total synthesis and demonstrates the utility of enzymatic dearomatization. In the 1960s, Corey and co-workers employed the alkylative dearomatization of phenols^[5] under basic conditions wherein the phenolate derived from **5** underwent intramolecular *para*-alkylation to access spirocycle **6** (Figure 1 b). Installation of the quaternary center in **6** was crucial to prepare the natural product cedrene (**7**). Schultz and co-workers, pioneers of the diastereoselective Birch reduction/alkylative dearomatization process, reported the first enantioselective synthesis of the alkaloid (+)-cepharamine (**8**; Figure 1 c).^[6] Their route employed a diastereoselective Birch reduction of chiral benzamide **9** to access a chiral enolate intermediate which was alkylated in

situ with iodide **10** to afford 1,4-cyclohexadiene **11** in 95 % yield as a single diastereomer. In two separate studies, Corey and co-workers reported access to enantiopure (–)-trichodimerol,^[7] and Nicolaou and co-workers described the biomimetic synthesis of numerous bisorbicillinoids employing in both cases dearomatization of sorbicillin (**12**; Figure 1 d).^[8] In the Nicolaou work, oxidative dearomatization with lead tetraacetate delivered the desired acetylated *ortho*-acetoxyquinol **13** along with its regioisomer (5:1). Mild and controlled deacetylation generated a highly reactive *ortho*-quinol which underwent different cascade events depending on the reaction conditions. Upon basic treatment, the reactive dearomatized *ortho*-quinol spontaneously dimerized in a Diels–Alder fashion to directly produce the natural product (±)-bisorbicillinol (**14**). In their synthesis of tricycloillicinone (**15**), Danishefsky and co-workers employed an underdeveloped dearomatization strategy involving an *ortho*-Claisen rearrangement (Figure 1 e).^[9] The rearrangement was conducted using the reverse *O*-prenylated derivative **16** to furnish the desired dearomatized cyclohexadienone **17**, a precursor of the natural product. A classical example of indole dearomatization was achieved by Corey and co-workers during the synthesis of the indole alkaloid aspidophytine (**18**; Figure 1 f).^[10] Condensation of tryptamine **19** with enantiopure dialdehyde **20** resulted in intramolecular indole alkylation at C3 generating a dearomatized indolinium that was trapped at C2 by a tethered allylsilane to furnish the aspidophytine core

From the Contents

1. Introduction	4069
2. Dearomatization of Arenes	4070
3. Dearomatization of Phenols and Related Substrates	4071
4. Dearomatization of Electron-Rich Heteroarenes: Furans, Pyrroles, Benzofurans, and Indoles	4081
5. Dearomatization of Electron-Poor Heteroarenes (Pyridinium and Related Compounds)	4085
6. Future Opportunities and Perspectives for Asymmetric Dearomatization	4087
7. Summary	4089

[*] Dr. S. P. Roche, Prof. Dr. J. A. Porco Jr.
Department of Chemistry, Center for Chemical Methodology and Library Development, Boston University
590 Commonwealth Avenue, Boston, MA 02215 (USA)
Fax: (+1) 617-358-2847
E-mail: porco@bu.edu

structure **21**. This dearomatization cascade rapidly assembled the aspidophytine core bearing four stereocenters, two of which are quaternary. Finally, an impressive example of pyridinium dearomatization was reported in the early 1990s by Magnus and co-workers in their total synthesis of the pentacyclic alkaloid nirurine (**22**; Figure 1 g).^[11] Synthesis of the azabicyclo-[2.2.2]octane (isoquinuclidine) core of **22** commenced with the alkylative dearomatization at the C2 position of an acylpyridinium derived from pyridine **23** to introduce an allyl side chain.^[12] Further desilylation generated allenolate intermediate **24** which participated in intramolecular [4+2] cycloaddition to furnish the nirurine core structure in two steps.

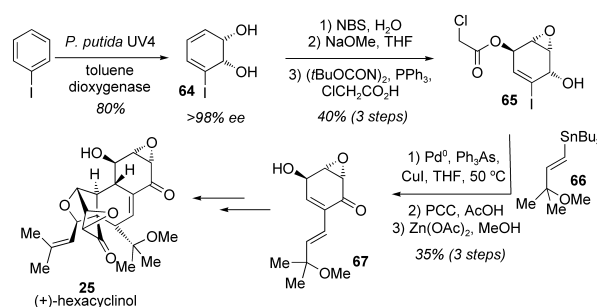
These classical and elaborated examples of dearomatization for the synthesis of complex targets have set the stage for new chemistry to be explored and for novel applications of dearomatization for the construction of complex scaffolds. In the early 1990s, Mander emphasized dearomatization strategies in a review concerning alkylative processes for the synthesis of polycyclic natural products.^[13] Other important reviews have reported methodology developed for dearomatization using transition-metal complexation of simple arenes.^[14] More recently, Pettus and co-workers have exhaustively reviewed the preparation and use of masked *ortho*- and *para*-benzoquinones (MOBs and MPBs) and their derived benzoquinol derivatives.^[15] Quideau and co-workers have also comprehensively reviewed the oxidative dearomatization of phenols and anilines using both iodine(III) and iodine(V) reagents,^[16] culminating in a recent review outlining applications of this chemistry in natural product synthesis.^[17] In this review, we will focus on the dearomatization of arenes, phenols, and heteroarenes as part of total syntheses of complex natural products (cf. **25–63**, Figure 2) from 2002 to the present. Natural product fragments derived from dearomatization are colored in red (Figure 2). In addition to outlining select dearomatization strategies in the context of complex natural product synthesis, we will also describe future perspectives in the field including prospects for the development of enantioselective dearomatization processes.

2. Dearomatization of Arenes

For decades, the dearomatization of arenes has been recognized as a chemical transformation of fundamental

importance and provides a connection between a robust and abundant source of hydrocarbons and the alicyclic frameworks found in many biologically active products.^[13,14] Accordingly, benzene and its derivatives are attractive starting materials with great potential to deliver complex alicyclic building blocks containing unmasked functionality, new carbon–carbon bonds, and stereogenic centers.

Although enzymatic and microbiological techniques are not often emphasized in organic chemistry laboratories, microorganisms are capable of useful transformations on a preparative scale for the production of enantiopure building blocks. For example, the enantiomerically pure cyclohexenediol **64** (>98% ee) was obtained from the enzymatic dihydroxylation of iodobenzene with the toluene dioxygenase *P. putida* UV4 (Scheme 1).^[18] Banwell and co-workers



Scheme 1. Preparation of epoxyquinol synthons by enzymatic dihydroxylation of iodobenzene and elaboration to hexacyclinol (Banwell et al., 2009).^[19]

employed the dearomatized synthon **64** in their synthesis of hexacyclinol (**25**; (Scheme 1).^[19] Bromination of the dearomatized derivative **64** delivered the corresponding bromohydrin which was further converted in two steps to the chiral enantiopure building block **65** in 40% overall yield. The protected epoxydiol **65** was cross-coupled with vinyl stannane **66**, oxidized, and deprotected to deliver the epoxyquinol monomer **67** which was dimerized and deprotected to yield the antiproliferative natural product (+)-hexacyclinol (**25**) in nine steps overall from iodobenzene.

In the early 1990s, Mander and co-workers demonstrated the efficiency of carbene-based methodology for the dearomatization of arenes by means of cyclopropanation (Bucher reaction).^[20] In a recent synthesis of the norcaradiene core



Stéphane P. Roche was born in Thiers (France) in 1979. He received his PhD degree (2006) in chemistry from the Blaise Pascal University under the supervision of Professor D. J. Aitken. He then joined the Institute of Chemical and Engineering Sciences (ICES, @Star) in Singapore, as a research fellow with Professor K. C. Nicolaou (2006–2008). At the end of 2008, he joined the Porco research group at Boston University. His research interests include the development of new “bio-inspired” methodologies and dearomatization strategies and their application to the concise, total syntheses of biologically active natural products.



John A. Porco, Jr. was born in Danbury, Connecticut (USA) in 1963. He received his PhD in 1992 from Harvard University under the direction of Professor Stuart Schreiber. After a period in industry he joined the Department of Chemistry at Boston University in 1999 as Assistant Professor and was promoted to Professor of Chemistry in September 2004. His research is focused in two major areas: the development of new synthetic methodologies for efficient chemical synthesis of complex molecules and the synthesis of complex chemical libraries.

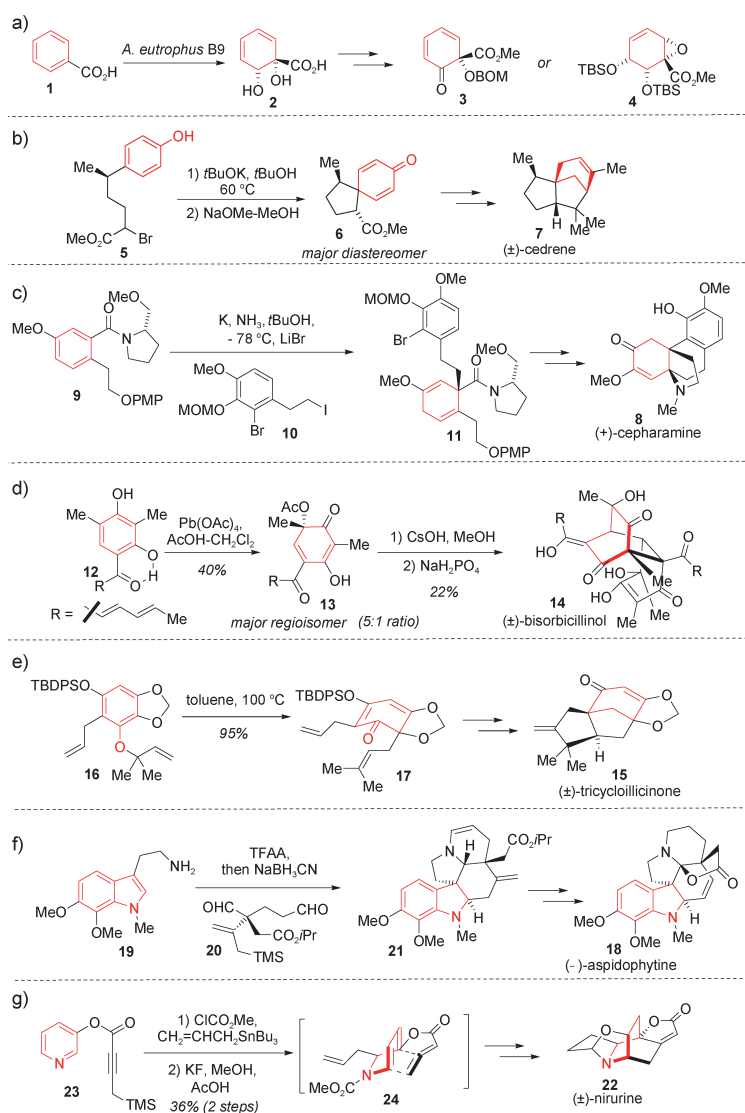


Figure 1. Classical examples of dearomatization in complex synthesis: a) Myers et al.;^[4] b) Corey et al.;^[5] c) Schultz et al.;^[6] d) Nicolaou et al.;^[8] e) Danishefsky et al.;^[9] f) Corey et al.;^[10] g) Magnus et al.^[11] Abbreviations of reagents and protecting groups are defined at the end of the Review.

of salvileucalin B (**26**), Reisman and co-workers also applied the Buchner reaction to assemble the natural product core (Scheme 2).^[21] Exposure of triyne **68** to a catalytic amount of [RuCp(cod)Cl] enabled [2+2+2] cycloaddition leading to the production of indane derivative **69** in 90% yield. After a few manipulations, microwave thermolysis of α -diazo β -ketonitrile **70** in the presence of 10 mol % [Cu(hfacac)₂] led to arene dearomatization to afford the fused cyclopropane **71** in 49% yield (Scheme 2). Late-stage intramolecular cyclopropanation of tricyclic arene **70** thereby provided rapid access to the norcaradiene core of the natural product and demonstrated the feasibility of the proposed route to salvileucalin B (**26**).

Wender's remarkable synthesis of α -cedrene brought the attention of synthetic chemists to the alkene–arene *meta*-photocycloaddition, a formal [3+2] photocycloaddition.^[22] Recently, Mulzer and co-workers highlighted the importance of this seminal work on the photoinduced intramolecular

[3+2] cycloaddition of arenes and olefins in the enantioselective synthesis of the sesquiterpenoid (–)-penifulvin A (**27**; Scheme 3).^[23] The asymmetric synthesis of (–)-**27** was initiated by enantioselective alkylation using the Myers' auxiliary which after several manipulations delivered enantiopure alcohol **72**. Irradiation of arene substrate **72** to the singlet excited state generated excimer **73** which underwent *meta*-photocycloaddition to diradical **74** and produced a mixture of regioisomers **75a** and **75b**. In this example, π -facial stereocontrol is dictated by A^{1,3} strain involving steric interactions between the aryl methyl and the hydroxymethyl group as well as *endo* control in the photocycloaddition.^[22] Final cyclization of diradical **74** delivered the tricyclic core bearing two contiguous quaternary centers as a mixture of constitutional isomers **75a** and **75b**. Final Birch reduction of isomer **75a** afforded the desired triquinane framework **76** which was advanced to (–)-penifulvin A (**27**) using an efficient and innovative oxidative cascade sequence to form the two fused lactone rings in a single operation.

An important approach for arene dearomatization pioneered by Meyers and co-workers involves diastereoselective carbanion addition to aromatic rings.^[24] Clayden and co-workers have further advanced this area and achieved the first enantioselective total synthesis of (–)-isodomoic acid C (**28**) in 15 steps from benzamide **77** (Scheme 4).^[25] Asymmetric deprotonation of *N*-benzyl benzamide **77** using the chiral lithium amide **78** was followed by dearomatizing anionic cyclization to afford bicyclic enone **79** (86% *ee*) after acidic hydrolysis. Further transformations led to ketone **80** which was ultimately advanced to (–)-isodomoic acid C (**28**).

In 2008, Procter and co-workers reported thionium activation of aryl α -ketoamide substrates resulting in arene dearomatization (Scheme 5).^[26] Specifically, thionium ion **81**, generated by addition of thiols ($R^F = \text{CH}_2\text{CH}_2\text{C}_8\text{F}_{17}$) to *N*-benzylglyoxamide derivative **82**, underwent an unprecedented dearomatizing spirocyclization. The highly activated thionium species participated in diastereoselective spirocyclization; steric interactions between the *ortho*-methoxy group and the thionium moiety favored the *anti* transition state **81**, leading to 2-azaspiro[4.5]decane **83** as a single diastereomer. This flexible methodology was applied to several substrates leading to simultaneous formation of carbon–carbon and carbon–sulfur bonds with two new stereocenters. This creative strategy may be applied in the future to the synthesis of spirocyclic alkaloids including spirostaphylotrichin A (**29**).

3. Dearomatization of Phenols and Related Substrates

Phenols are by far the most frequently utilized substrates for dearomatization en route to complex natural products.

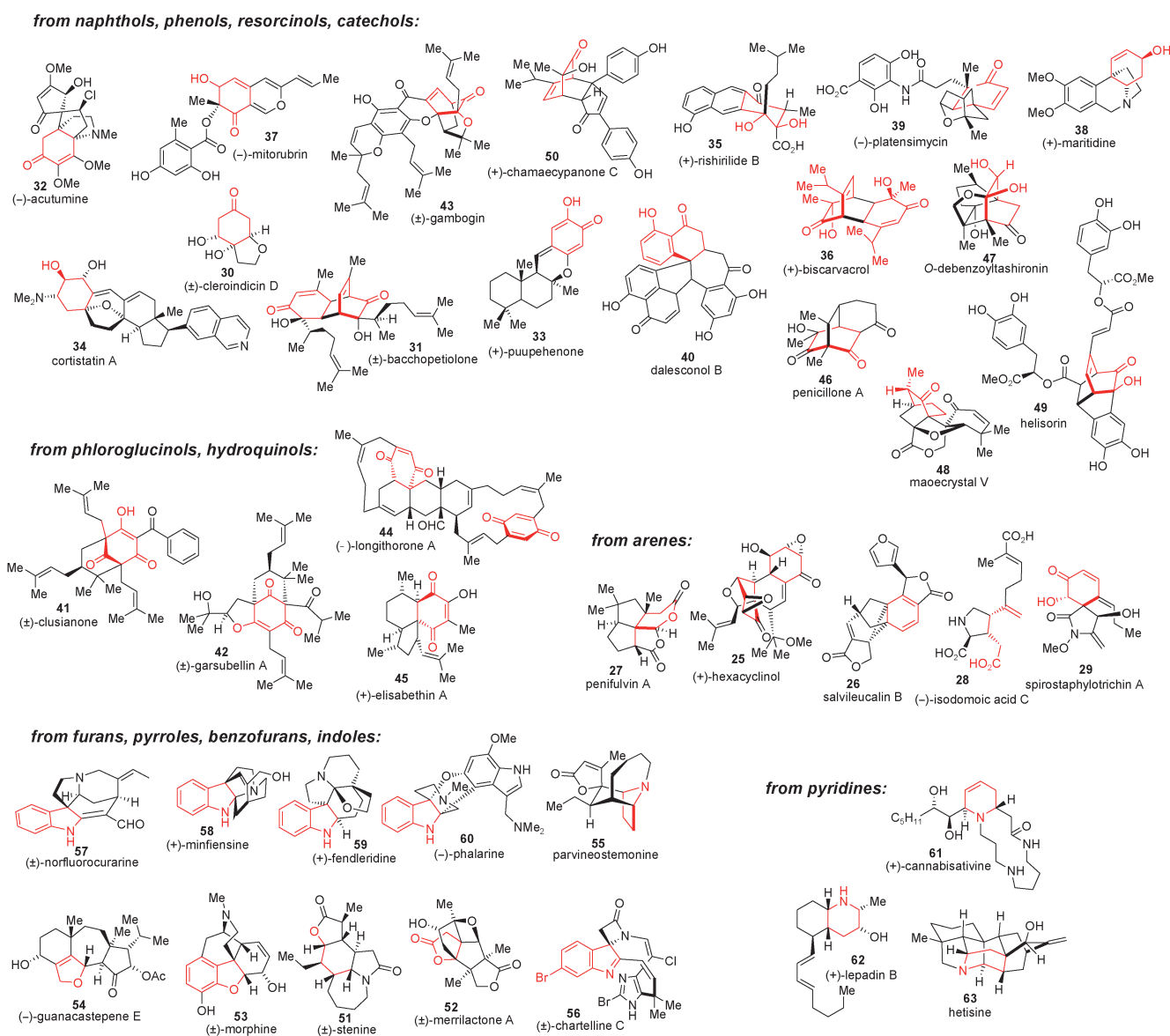
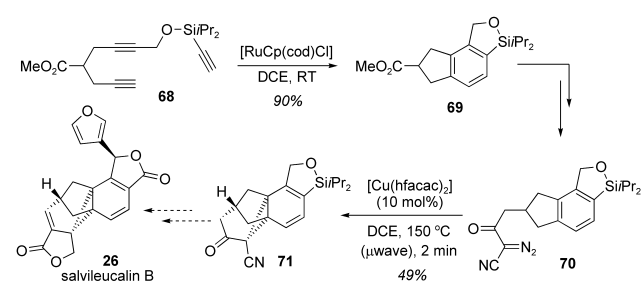
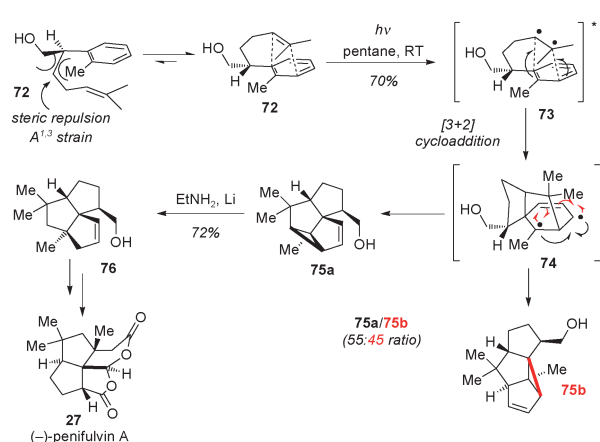


Figure 2. Recent work highlighting syntheses of complex natural products using dearomatization strategies (2002–2010).

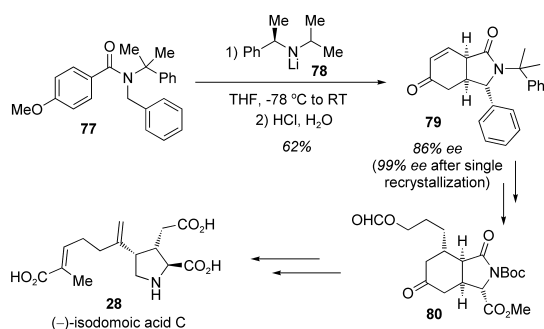


Scheme 2. Approach to salvileucalin B: Preparation of the pentacyclic framework by Buchner dearomatization (Reisman et al., 2010).^[21]

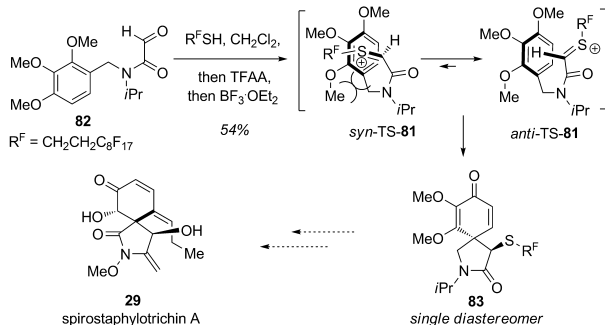
The following section will be devoted to an overview of phenol dearomatization through the formation of C–X and C–C bonds. Catechol, resorcinol, and hydroquinone derivatives have been dearomatized to cyclohexadienones, whose



Scheme 3. Total synthesis of penifulvin A using photoinduced [3+2] cycloaddition (Mulzer et al., 2009).^[23]



Scheme 4. Enantioselective synthesis of (–)-isodomoic acid C by dearomatizing anionic cyclization (Clayden et al., 2005).^[25]

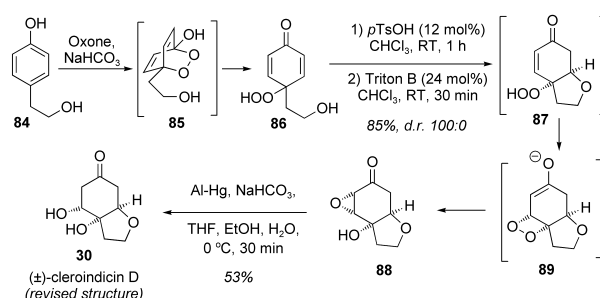


Scheme 5. Alkylative dearomatization by thionium activation (Procter et al., 2008).^[26]

reactivity varies depending on their intrinsic electronic stabilization. The resulting dearomatized cyclohexadienone intermediates generally react spontaneously or upon chemical activation to generate complex polycyclic frameworks. In addition, alkylative dearomatization of phenolate anions and sigmatropic, dearomatizing reactions will be presented along with oxidative dearomatization/Diels–Alder cascade strategies.

3.1. Oxidative Dearomatization of Phenols by O-Alkylation

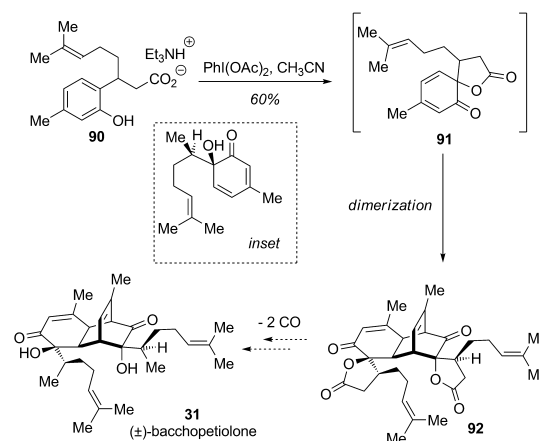
In general, dearomatization of phenols with oxygen-centered nucleophiles involves activation with hypervalent iodine or other oxidants resulting in either *ortho*-dearomatization (*ortho*-quinol or masked *ortho*-benzoquinone (MOBs)) or *para*-dearomatization (*para*-quinol or *para*-benzoquinone). Carreño and Urbano developed an efficient method for the selective oxidative dearomatization of *para*-alkyl phenols to access *para*-peroxyquinols and *para*-quinols using Oxone as a source of singlet oxygen.^[27] This proved to be an attractive method for the synthesis of (±)-cleroindicin D (**30**; Scheme 6).^[28] Dearomatization of *para*-(2-hydroxyethyl)phenol **84** with Oxone afforded the cyclic endoperoxide **85** which was readily ring-opened to the corresponding *para*-peroxyquinol **86**. The resulting prochiral *para*-peroxyquinol **86** was treated sequentially with *p*TsOH and Triton-B to afford the cyclic peroxyenone **87** which rearranged diastereospecifically to the desired tricyclic epoxide **88** via



Scheme 6. Total synthesis of cleroindicin using oxidative dearomatization with Oxone (Carreño/Urbano et al., 2007).^[28]

proposed dioxetane intermediate **89**. In this sequence, oxidative dearomatization and consecutive acidic/basic treatments efficiently created two new rings with four contiguous stereogenic centers in a diastereoselective manner. This methodology allowed for the synthesis and stereochemical assignment of (±)-cleroindicin D (**30**).

An underdeveloped oxidative dearomatization methodology involves oxidative spirolactonization with iodine(III) reagents.^[29] This approach is exemplified by work conducted by Wood and co-workers en route to the natural product (±)-bacchopetiolone (**31**; Scheme 7).^[29c] Indeed, bacchopetiolone

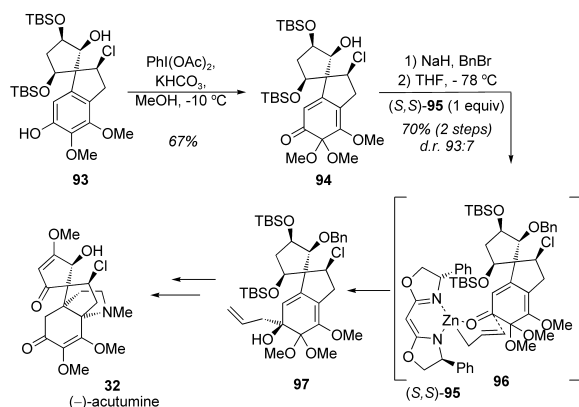


Scheme 7. Approach to bacchopetiolone employing oxidative spirolactonization/dearomatization (Wood et al., 2006).^[29c]

may be derived from biosynthetic [4+2] dimerization of a bisabolene monomer (Scheme 7, see inset). The authors envisioned oxidative spirolactonization of the carboxylic salt **90** to access the monomeric subunit **91**, a surrogate for the bisabolene monomer, which spontaneously dimerized to furnish the complex natural product framework **92** in a single step. Wood and co-workers also extensively examined lactone opening and Suárez fragmentation of the advanced intermediate **92**.^[29c] Further studies are underway targeting the removal of two carbon monoxide units to complete the synthesis of (±)-bacchopetiolone (**31**).

In the first total synthesis of (–)-acutumine (**32**), Castle and co-workers outlined the utility of the oxidative dearoma-

tization of chiral chloroindane **93** to the corresponding MOB derivative **94** (Scheme 8).^[30] Late-stage phenolic oxidation of phenol **93** was accomplished using bis(acetoxy)iodobenzene

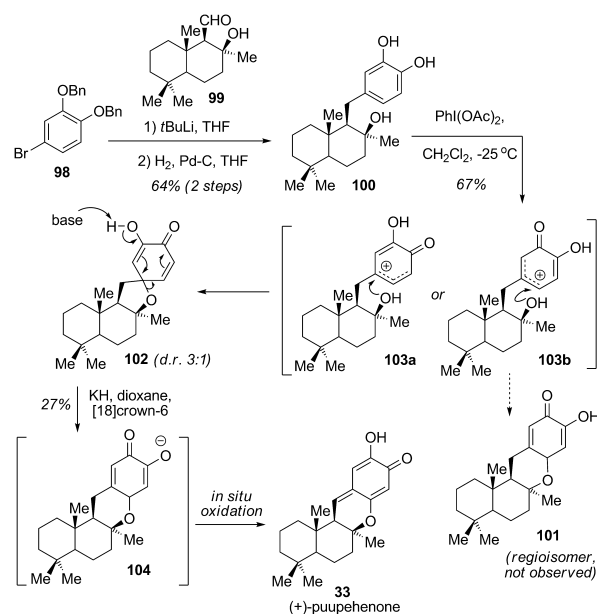


Scheme 8. Total synthesis of acutumine including late-stage dearomatization (Castle et al., 2009).^[30]

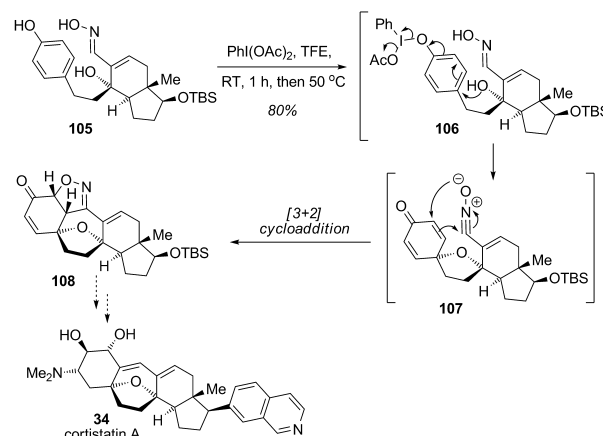
(PIDA) in 67% yield. This result highlights the utility of iodine(III) reagents for the oxidative dearomatization of highly complex substrates. Allylation of a protected form of ketone **94** was examined, first with allylmagnesium bromide, which showed modest diastereoselection (d.r. 7:3), and finally using Nakamura's chiral allylzinc reagent (*S,S*)-**95**. Catalyst control in the latter instance led to allyl addition via the proposed transition state **96** to yield the desired allylic alcohol **97** (d.r. 93:7). Further manipulations, including an anionic oxy-Cope rearrangement, led to an elegant asymmetric synthesis of (–)-acutumine (**32**).

Quideau and co-workers reported the biomimetic synthesis of (+)-puupehenone (**33**), a drimane sesquiterpene appended with a shikimate-derived hydroxyquinone fragment (Scheme 9).^[31] In this interesting study, the authors examined the regioselectivity of the oxidative dearomatization of an unsymmetrical catechol. Addition of the anion of protected bromocatechol **98** to enantiopure aldehyde **99** produced catechol **100** in 64% overall yield after hydrogenolysis. The key regioselective oxidative activation of catechol **100** using hypervalent iodine (PIDA) did not afford the desired tetracyclic fused-ring system **101** but led instead to spirocycle **102** (d.r. 3:1). Accordingly, the authors proposed that the drimane framework exhibits an electron-releasing effect stabilizing the more substituted carbocation intermediate **103a** versus **103b** thereby triggering exclusive 5-*exo*-trig spiroannulation. Further rearrangement under basic conditions permitted a 1,2-oxyalkyl shift to the fused heterocyclic intermediate **104**, which spontaneously oxidized in situ to furnish synthetic (+)-puupehenone (**33**) in 27% yield.

Recently, a cascade process triggered by intramolecular oxidative dearomatization was reported by Sorensen and co-workers for construction of the pentacyclic core of cortistatin A (**34**; Scheme 10).^[32] This elegant sequence illustrates the power of oxidative dearomatization in complex settings employing tandem intramolecular oxidative *para*-dearomatization/intramolecular dipolar cycloaddition. Exposure of the



Scheme 9. Total synthesis of (+)-puupehenone involving the regioselective oxidative dearomatization of a catechol (Quideau et al., 2002).^[31]

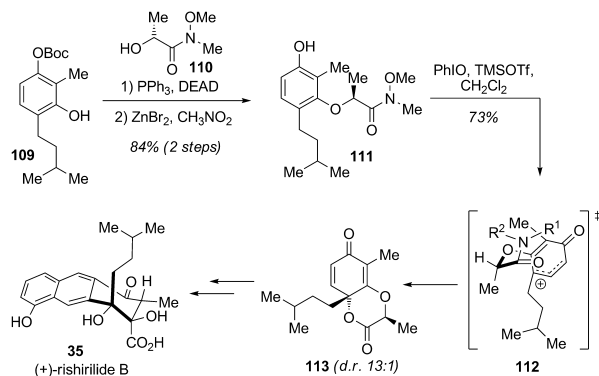


Scheme 10. Approach to the cortistatin A framework through tandem oxidative dearomatization/[3+2] cycloaddition (Sorensen et al., 2010).^[32]

advanced phenol **105** to PIDA led to phenol activation followed by nucleophilic attack of the proximate tertiary alcohol via intermediate **106**. Further oxidation of the oxime to a nitrile oxide generated both reaction partners for intramolecular [3+2] dipolar cycloaddition of substrate **107**.^[33] These two successive transformations carried out in the same reaction vessel produced the hexacyclic product **108** as a single diastereomer, a compound presenting the pentacyclic core architecture of cortistatin A (**34**).

In their studies, the Quideau and Pettus research groups have developed significant oxidative methods involving *ortho*-dearomatization^[34] of catechols and *para*-dearomatization^[35] of resorcinols (Scheme 11 and Scheme 12). A concise asymmetric synthesis of (+)-rishirilide B (**35**) reported by

Pettus and co-workers highlights two highly efficient methods: 1) coupling of *ortho*-quinone methides and 2) diastereoselective dearomatization of resorcinols providing access to densely functionalized bicyclic enones (Scheme 11).^[36] Resor-

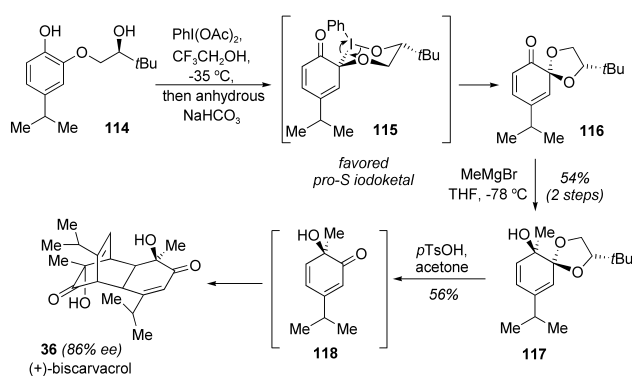


Scheme 11. Total synthesis of (+)-rishirilide B by means of the diastereoselective *para*-oxidative dearomatization of a resorcinol substrate (Pettus et al., 2006).^[36]

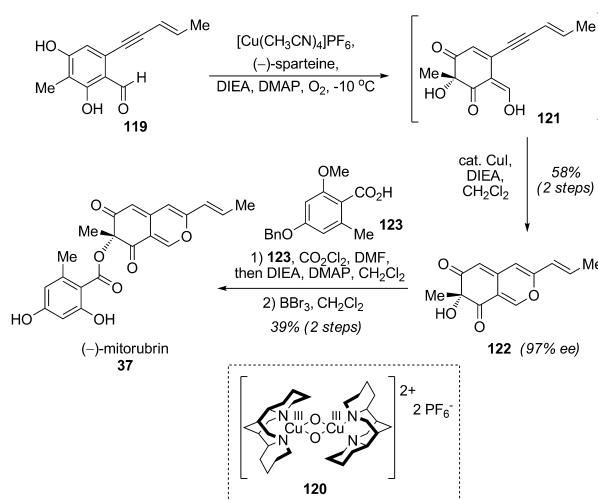
cinol **109** was coupled through a Mitsunobu reaction to lactate derivative **110** to afford substrate **111** after deprotection. Diastereoselective oxidative dearomatization of **111** using in situ generated $\text{PhI}[\text{OTMS}]\text{OTf}$ ^[35] presumably proceeded via the chairlike transition state **112** and led to chirality transfer from the chiral auxiliary to afford 1,4-dioxan-2-one **113** in high diastereoselectivity. Further transformations of **113** completed an efficient asymmetric total synthesis of (+)-rishirilide B (**35**) in 15 steps and 12.5 % overall yield.

Quideau and co-workers developed an efficient route to masked *ortho*-benzoquinones (MOBs) in chiral, nonracemic form through the λ 3-iodane (PIDA)-mediated *ortho*-oxidative dearomatization of catechols. The methodology was successfully applied to the asymmetric total synthesis of the bis(monoterpene) (+)-biscarvacrol (**36**; Scheme 12).^[37] During this synthesis, the authors demonstrated the utility of a chiral tether for the diastereoselective spiroketalization of resorcinol **114**. A chairlike iodine(III) intermediate **115**, which may be stabilized by orbital interactions between the iodine and spiro-carbon atom, was proposed to explain the stereochemical outcome of the reaction and production of (*S,S*)-MOB diastereomer **116**. The addition of methyl Grignard to ketone **116** from the less hindered face was found to be highly diastereoselective (d.r. >95:5) and afforded alcohol **117** in 54 % yield over two steps. The ketal auxiliary was finally removed under acidic conditions which initiated spontaneous and regioselective cyclodimerization of *ortho*-quinol intermediate **118** to furnish (+)-biscarvacrol (**36**) as the major stereoisomer (86 % *ee*).

Porco and co-workers described the synthesis of (–)-mitorubrin (**37**) and related azaphilone natural products employing enantioselective oxidative dearomatization of resorcinols (Scheme 13).^[38] Dearomatization of the resorcinol aldehyde **119** using the $[(\text{–})\text{-sparteine}]_2\text{Cu}_2\text{O}_2$ complex **120** was achieved in a regioselective manner with high enantioselectivity to afford vinylogous acid **121**. Enyne **121** was



Scheme 12. Total synthesis of (+)-biscarvacrol using a tethered chiral auxiliary for *ortho*-oxidative dearomatization (Quideau et al., 2008).^[37]



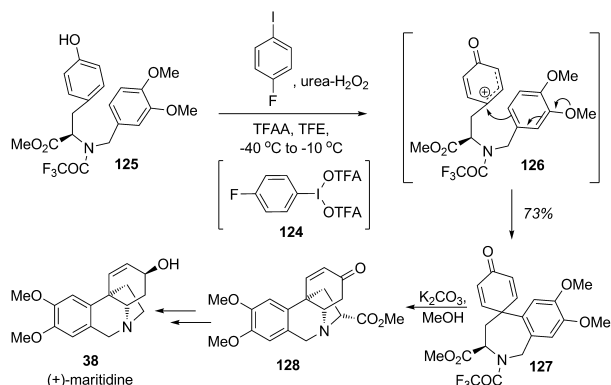
Scheme 13. Total synthesis of (–)-mitorubrin employing enantioselective *ortho*-oxidative dearomatization (Porco, Jr. et al., 2006).^[38]

subjected to Cu^{I} -catalyzed cycloisomerization to afford the mitorubrin core structure **122** (58 % for two steps, 97 % *ee*). Further esterification with acid **123** and final deprotection afforded the desired azaphilone (–)-mitorubrin (**37**). This convergent synthesis featured the highly enantioselective oxidative dearomatization of resorcinol aldehyde **119** using a readily accessible chiral bis- μ -oxo copper complex.

3.2. Oxidative and Alkylative Dearomatization of Phenols with Concomitant C–C Bond Formation

As highlighted in the previous section, many oxidative dearomatizations involve the introduction of soft heteroatomic nucleophiles.^[39] Despite a few sparse examples, C–C bond formation during oxidative dearomatization is of significant interest in complex natural product synthesis.^[40] Recently, Kita and co-workers have developed catalytic processes for iodoarene-catalyzed C–C bond formations of phenols.^[41] Use of the novel and recyclable iodine(III) reagent (bisacetoxo)iodozo(4-fluoro)benzene **124** (prepared in situ from 1-fluoro-4-iodobenzene and urea- H_2O_2 (UHP)

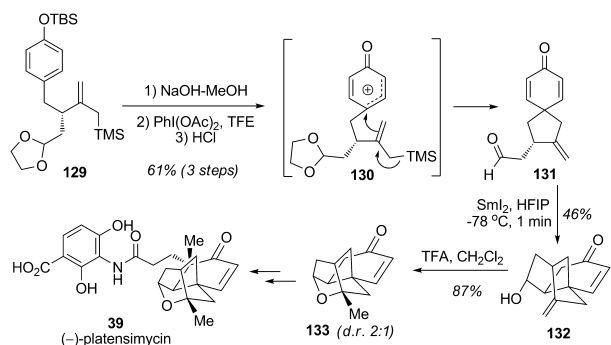
with trifluoroacetic anhydride (TFAA)) should allow new possibilities for oxidative dearomatization (Scheme 14).^[41] In fact, the highly reactive iodine(III) reagent **124** can be



Scheme 14. Formal synthesis of (+)-maritidine employing oxidative dearomatization/C-arylation (Kita et al., 2008).^[41]

produced catalytically and was shown to react with phenolic substrate **125** to produce the discrete carbocation intermediate **126** which was selectively trapped by the pendant aromatic ring to afford the desired spirocyclic amino ester **127**. After trifluoroacetamide removal, further cyclization to **128** was accomplished completing a formal synthesis of (+)-maritidine (**38**).

An important example of the oxidative dearomatization of a phenolic substrate with concomitant C–C bond formation in the context of complex total synthesis was reported by Nicolaou and co-workers in their enantioselective synthesis of (–)-platensimycin (**39**; Scheme 15).^[42] The authors employed

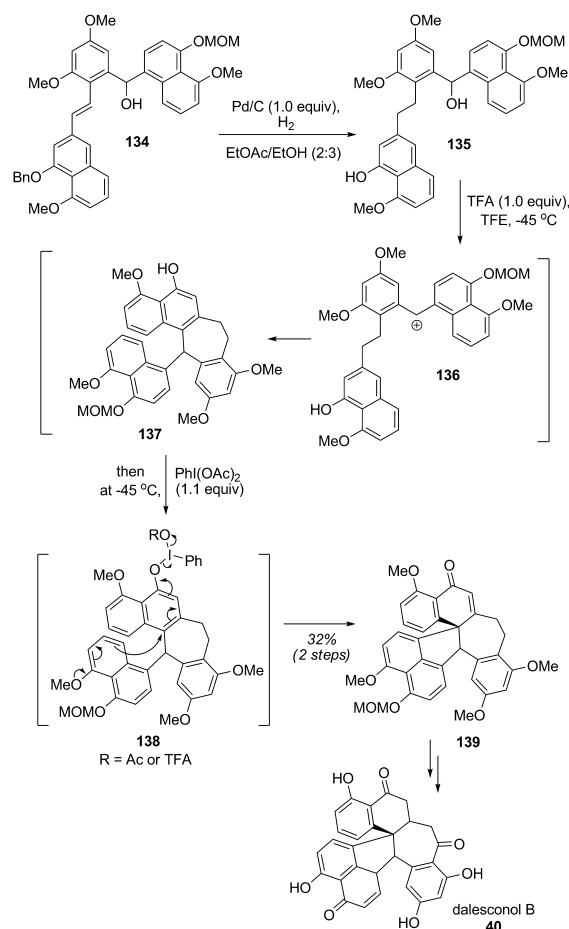


Scheme 15. Total synthesis of (–)-platensimycin involving an oxidative *para*-spiroannulation strategy (Nicolaou et al., 2007).^[42]

oxidative dearomatization with intramolecular *para*-spiroannulation of a pendant allylsilane^[43] using hypervalent iodine activation to assemble the first two rings of the natural product. Allylsilane **129** was prepared enantioselectively using the Myers' auxiliary for asymmetric alkylation. After silyl deprotection under basic conditions, the key spirocyclization/dearomatization was then investigated using iodine(III) reagents. Only few examples of nonaromatic carbon-

centered nucleophiles in iodine(III)-mediated oxidative dearomatizations have been reported. Activation of the free phenol moiety by PIDA in a polar solvent (TFE) afforded the activated intermediate **130** bearing a delocalized carbocation which reacted internally with the allylsilane to furnish the desired spirocyclic dienone. Subsequent removal of the ethylene acetal group led to the free aldehyde substrate **131** in 61% overall yield. Further radical-mediated cyclization using samarium diiodide furnished tricyclic product **132** which underwent acid-mediated etherification to efficiently produce the tetracyclic core of platensimycin **133**.

In a recent synthesis of the immunosuppressive polyketide dalesconol B (**40**), Snyder and co-workers employed oxidative dearomatization as part of a clever tandem process (Scheme 16).^[44] In this sequence, finetuning of the two phenol

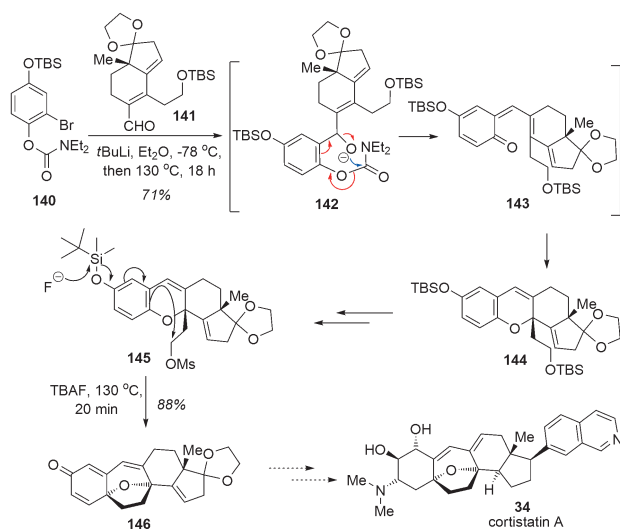


Scheme 16. Total synthesis of dalesconol B employing a Friedel–Crafts/oxidative *para*-cyclization tandem sequence (Snyder et al., 2010).^[44]

protecting groups and the acid sources were required for the sequence of Friedel–Crafts cyclizations. Indeed, in such complex syntheses of polyphenolic structures, stabilized carbocations from retro-Friedel–Crafts or skeletal rearrangements may occur and generate multiple polycyclic structures. Hydrogenation of substrate **134** delivered the isolable free phenol **135**. The latter compound was first treated with TFA producing carbocation **136** thereby triggering intramolecular

Friedel–Crafts alkylation to **137** in a controlled manner. Subsequent oxidation of naphthol **137** in the same reaction vessel using PIDA afforded **138** which initiated oxidative dearomatization and assembly of the polycyclic dalesconol precursor **139** in 32 % overall yield. This remarkable access to the complex heptacyclic core structure through tandem Friedel–Crafts/oxidative dearomatization paved the way for the total synthesis of dalesconol B after a few additional steps.

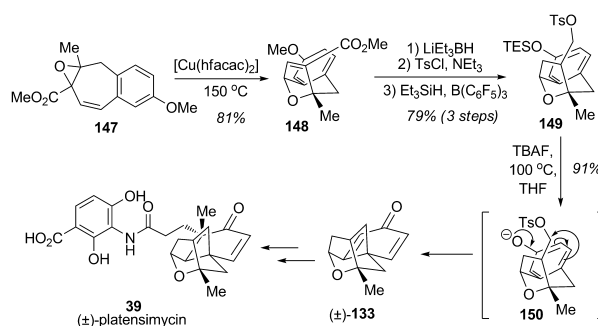
Other useful methodologies have emerged for the construction of polycyclic frameworks involving *para*-alkylation of phenols under basic conditions.^[45] Danishefsky and co-workers recently reported their efforts toward cortistatin A (**34**) using a cascade sequence involving electrocyclization followed by alkylative *para*-dearomatization of a phenol (Scheme 17).^[46] Addition of the aryllithium derived from aryl



Scheme 17. Approach to cortistatin A by means of *para*-alkylative phenol dearomatization (Danishefsky et al., 2008).^[46]

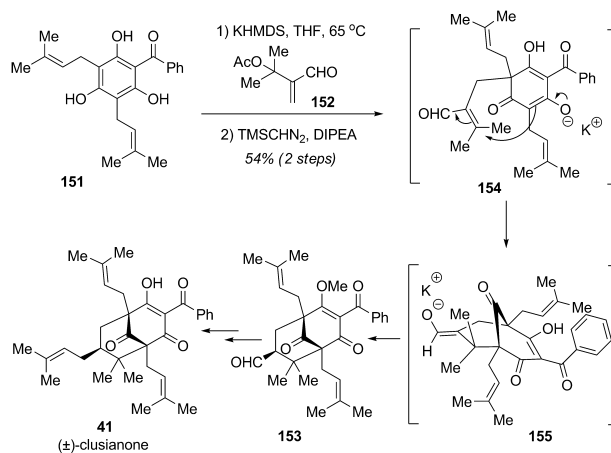
bromide **140** to aldehyde **141** initiated a cascade process involving acyl transfer, elimination to *ortho*-quinone methide **143**, and 6π -electrocyclization leading to isolation of dihydropyran **144** in 71 % yield. After protecting group manipulations, alkylative dearomatization of substrate **145** was accomplished using a fluoride source at elevated temperature to promote regioselective spirocyclization and form the last ether ring of the cortistatin core **146** (88 % yield).

Utilizing a similar *para*-alkylation of a phenolate, Njardarson and co-workers developed a short route to dienone (\pm)-**133**, a key intermediate in the synthesis of platensimycin (**39**; Scheme 18).^[47] For this purpose, the vinyl oxirane substrate **147** was subjected to ring-expansion catalyzed by a copper(II) catalyst to effect rearrangement to the desired bicyclo[2.3.1] ether **148** in 81 % yield. Further reduction of **148**, followed by tosylation of the primary alcohol and silylation, afforded silyl ether **149**. Treatment of the protected phenol **149** with a fluoride source under thermal conditions promoted smooth spirocyclization via **150** which generated the tetracyclic framework and the crucial quaternary stereocenter of the platensimycin core **133** (91 % yield).



Scheme 18. Approach to (\pm)-platensimycin using intramolecular *para*-alkylative phenol dearomatization (Njardarson et al., 2009).^[47]

Porco and co-workers reported efforts towards the synthesis of the bicyclo[3.3.1] framework of the polycyclic polyprenylated acylphloroglucinol (PPAP) (\pm)-clusianone (**41**; Scheme 19).^[48] The convergent strategy involved a three-

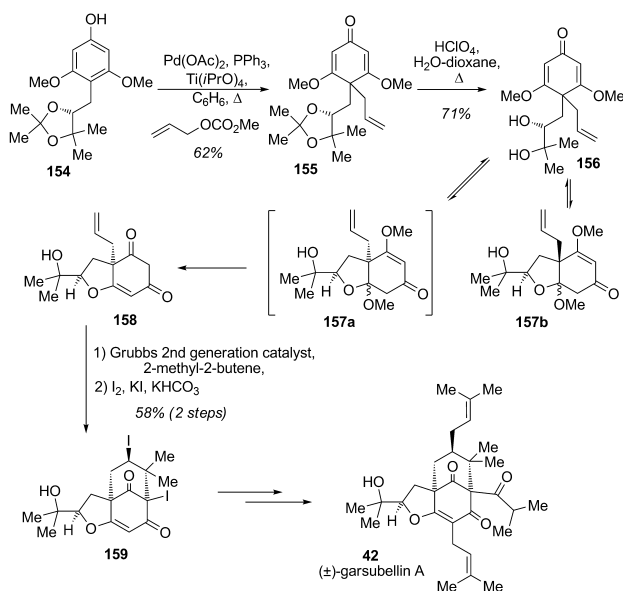


Scheme 19. Total synthesis of (\pm)-clusianone using a MEM sequence (Porco, Jr. et al., 2007).^[48]

step cascade sequence involving Michael addition/elimination/Michael addition (MEM) of the readily accessible and naturally occurring acylphloroglucinol clusiaphenone B (**151**). This proposed biomimetic approach delivered the bicyclic framework of the natural product in a single step. In the dearomatization event, treatment of **151** with KHMDS followed by addition of α -acetoxymethyl acrylate **152** led to an efficient and highly diastereoselective MEM cascade sequence to produce the desired product **153** after methyl enol formation (54 % overall yield). This MEM cascade entails three steps: 1) Michael addition of the phenolate derived from phloroglucinol **151** to α,β -unsaturated aldehyde **152**, 2) elimination of the tertiary acetate to afford intermediate **154**, and 3) a second Michael addition and annulation to core structure **155** with the formation of two contiguous quaternary centers. Final diastereoselective reprotonation of enolate **155** was found to be under thermodynamic control and yielded exclusively aldehyde **153**. Extension of the aldehyde to a prenyl group and final deprotection afforded

(\pm)-clusianone (**41**) in seven steps overall. The authors separately reported an efficient method for the dearomatization of phloroglucinol derivatives through alkylation of allylic bromides and primary alkyl triflates.^[49]

Another strategy for alkylative dearomatization with concomitant C–C bond formation is based on [3,3]-sigmatropic rearrangement. In 2006, Danishefsky and co-workers reported the construction of the triterpene (\pm)-garsubellin A (**42**; Scheme 20).^[50] The bicyclo[3.3.1]nonane framework is



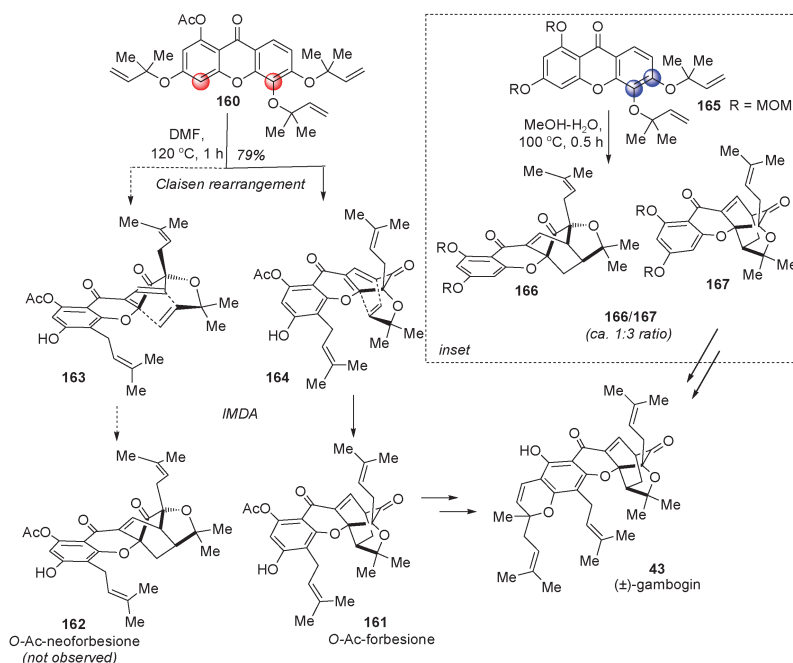
Scheme 20. Total synthesis of (\pm)-garsubellin A by means of *para*-alkylative dearomatization of a phloroglucinol (Danishefsky et al., 2006).^[50]

present in numerous natural products exhibiting important biological properties including neurotrophic activity. One of the challenges to access the core structure of (\pm)-garsubellin A (**42**) is the generation of a *para*-dearomatized product from phloroglucinol derivative **154**. To address this issue, Danishefsky and co-workers explored an unusual dearomatizing strategy through allylation of phenol **154** at the *para* position, which may proceed either by direct *para* C-allylation or via O-allylation followed by tandem Claisen–Cope rearrangements under Lewis acidic conditions.^[51] This sequence delivered the desired dienone **155** in 62% yield. Further treatment of acetonide **155** under acidic conditions led to diol **156** which spontaneously cyclized to give a mixture of Michael-type products **157a** and **157b**. Longer reaction times promoted an additional step of the cascade with the transformation of intermediate **157a** to the corresponding ketone **158** (71% overall yield). After installation of the isoprene side chain via cross metathesis, Danishefsky and co-workers achieved carbocyclization using an iodonium intermediate

under basic conditions to produce the desired bicyclo[3.3.1]nonane framework **159**. Further synthetic manipulations completed an impressive synthesis of (\pm)-garsubellin A (**42**).

Dearomatization by means of a Claisen rearrangement has been sparsely used in total synthesis.^[52] The most impressive examples are presented in Scheme 21 wherein Theodorakis et al.^[53] and Nicolaou et al.^[54] independently demonstrated the validity of a biomimetic process^[55] through Claisen rearrangement/dearomatization to access the natural product (\pm)-gambogin (**43**). In the Theodorakis synthesis, exposure of acetylated xanthone **160** bearing reverse *O*-prenylated side chains to thermal conditions in polar protic solvents led to a remarkable Claisen dearomatization/Diels–Alder (CDDA) cascade. In this study, the authors evaluated the impact of different xanthone protecting groups and determined that electronic factors govern the regioselectivity of the Claisen rearrangement. Using an acetate protecting group, the authors were able to exclusively produce the desired CDDA isomer *O*-Ac-forbesione **161** in 79% yield in which case the constitutional isomer *O*-Ac-neoforbesione **162** was not observed. Regioselective dearomatization of xanthone **160** by means of two Claisen rearrangements presumably delivered intermediate **164** which underwent intramolecular Diels–Alder (IMDA) cycloaddition. Final deprotection and condensation with citral concluded an efficient biomimetic synthesis of (\pm)-gambogin (**43**).

In their study, Nicolaou and co-workers observed that a related cascade sequence could be conducted in polar protic solvents (methanol–water) leading to a remarkable rate acceleration (see inset in Scheme 21). Reaction of xanthone **165** afforded in this case the pentacyclic structural isomers **166** and **167** in a 1:3 ratio and 100% yield. Unfortunately, use of

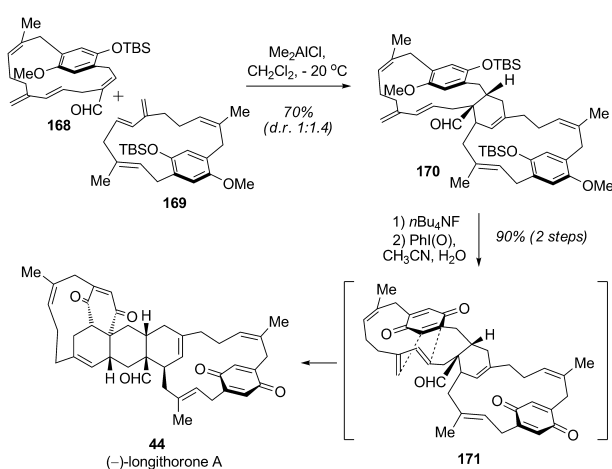


Scheme 21. Total syntheses of gambogin involving Claisen rearrangement/dearomatization (Theodorakis et al., 2004; Nicolaou et al., 2005).^[53,54]

the MOM-protected xanthone **165** revealed poor electronic differentiation of the two prenyl groups and afforded a mixture of both isomers **166** and **167**. Further DFT studies from the authors in collaboration with Houk and co-workers revealed that in the CDDA cascade, the Claisen rearrangement is reversible and relatively unselective, while the Diels–Alder cycloaddition dictates regioselectivity favoring formation of the five-membered-ring ether.^[56] Further deprotections, prenyl installation, and cyclization led to the second total synthesis of (±)-gambogin (**43**).

3.3. Oxidative Dearomatization of Phenol Triggering Diels–Alder Cycloaddition

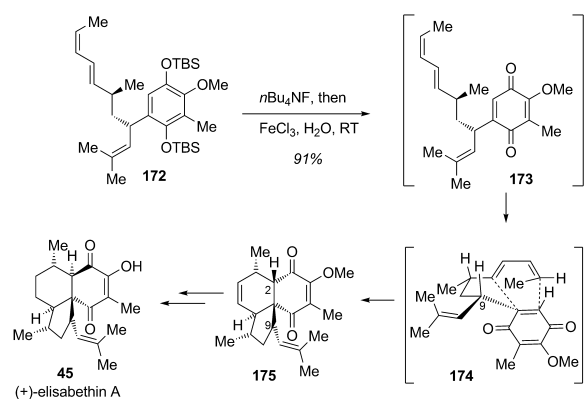
Studies regarding Diels–Alder cycloadditions in nature have been of great interest to the organic chemistry community. Few examples of spontaneous Diels–Alder reactions in biosyntheses and some examples of enzymatically promoted Diels–Alder reactions have been reported.^[57] According to this concept, Schmitz and co-workers proposed a biosynthesis of (–)-longithorone A (**44**) involving consecutive inter- and intramolecular Diels–Alder cycloadditions.^[58] A few years later, Shair and co-workers disclosed an elegant biomimetic synthesis of (–)-longithorone A (**44**) involving an intermolecular Diels–Alder cycloaddition between [12]paracyclophanes **168** and **169** promoted by a Lewis acid to generate cyclohexene derivative **170** in 70% yield (d.r. 1:1.4; Scheme 22).^[59] Further oxidation of both hydroquinone



Scheme 22. Total synthesis of (–)-longithorone A through oxidation with a hypervalent iodine reagent and Diels–Alder cycloaddition (Shair et al., 2002).^[59]

moieties led to the corresponding dearomatized bis(*para*-benzoquinone) intermediate **171** which spontaneously underwent transannular Diels–Alder cycloaddition to simultaneously forge the last three rings of the natural product (90% yield). This synthesis was highlighted by two consecutive key transformations first constructing the cyclohexene ring by [4+2] cycloaddition and then assembling the last three rings in a single oxidative dearomatization/Diels–Alder cycloaddition sequence.

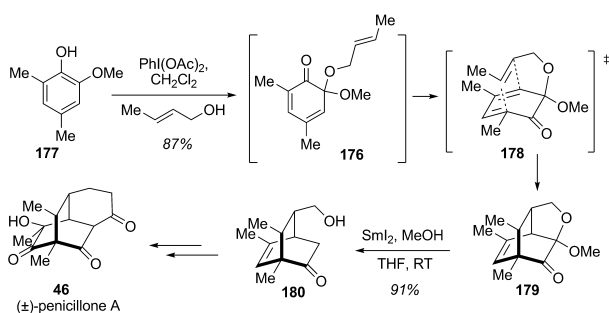
In 2001, Nicolaou and co-workers reported a concise construction of colombiasin A using the intrinsic reactivity of a dearomatized quinone to participate in an efficient IMDA cycloaddition to produce the natural product core.^[60] Other elegant examples of this approach were reported separately in the total syntheses of (+)-elisabethin A (**45**) by the Mulzer group^[61a] and elisapterosin B by the Rawal group,^[61b] both employing oxidative dearomatization/IMDA cycloaddition cascade sequences (Scheme 23). In the first synthesis by



Scheme 23. Total synthesis of (+)-elisabethin A through oxidative dearomatization/intramolecular Diels–Alder cycloaddition (Mulzer et al., 2003).^[61a]

Mulzer and co-workers, bis(silyl) hydroquinone **172** was cleanly deprotected by tetrabutylammonium fluoride to give the corresponding hydroquinone which was subject to the dearomatization-IMDA cascade under the action of iron trichloride. This “one-pot” procedure generated in situ the desired trisubstituted *para*-benzoquinone **173** which spontaneously cyclized via *exo*-transition state **174** to produce the desired tricyclic product **175** in 91% yield. This late-stage oxidative dearomatization/IMDA cascade relied on the *Z* configuration of the terminal olefin to induce the desired stereochemistry. The facial selectivity of the diene–quinone cycloaddition is presumably dictated by the minimization of allylic strain between the substituents at C9 and the quinone carbonyl moiety in *endo* transition state **174** such that cycloadduct **175** is produced as a single diastereoisomer. Required chemoselective removal of the endocyclic alkene, epimerization at C2, and deprotection afforded elisabethin A in an elegant manner.

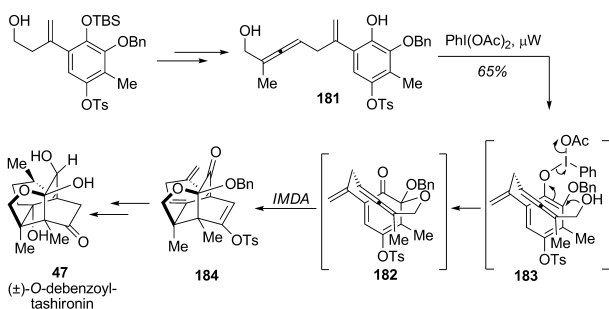
The *ortho*-oxidative dearomatization of phenols has also provided opportunities for the construction of complex scaffolds using Diels–Alder cycloaddition. Liao and co-workers have conducted extensive studies regarding sequential oxidative dearomatization/Diels–Alder cycloaddition.^[62] A recent example from this group is shown in Scheme 24 and illustrates the formation of a highly functionalized bicyclo-[2.2.2]octane ring system in a single operation en route to (±)-penicillone A (**46**; Scheme 24).^[63] Masked *ortho*-benzoquinone (MOB) derivative **176** was prepared by regioselective *ortho*-oxidative dearomatization of phenol **177** with PIDA and *trans*-crotyl alcohol. The highly reactive, dearom-



Scheme 24. Total synthesis of (±)-penicillone A using an *ortho*-oxidative dearomatization/IMDA cascade (Liao et al., 2007).^[63]

atized intermediate **176** readily reacted in an IMDA cycloaddition at room temperature via the presumed *endo* transition state **178**. The reactivity of MOB **176** as a diene allowed the formation of bicyclo[2.2.2]octane **179** in a single step in 87 % yield. Further reduction of the cyclic ketal with samarium iodide provided alcohol **180** which was elaborated in six steps to the natural product (±)-penicillone A (**46**).

(±)-11-*O*-Debenzoyletashironin (**47**) is a tetracyclic caged structure possessing three quaternary centers, two of which are positioned at junctions of the [2.2.2]bicyclic framework (Scheme 25). The strategy proposed by Danishefsky and co-

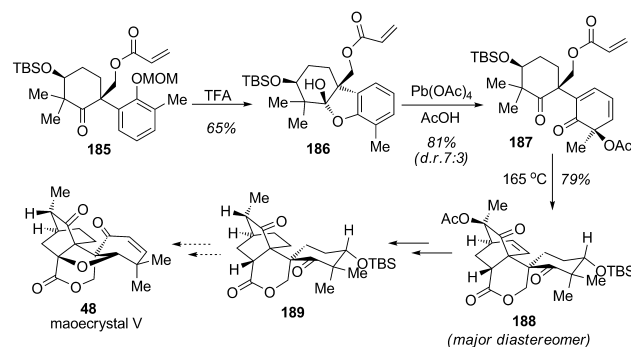


Scheme 25. Total synthesis of (±)-*O*-debenzoyletashironin through oxidative dearomatization/Diels–Alder cycloaddition (Danishefsky et al., 2006).^[64]

workers to access 11-*O*-debenzoyletashironin (**47**) featured an original *ortho*-oxidative dearomatization/IMDA cycloaddition sequence (Scheme 25).^[64] Allenic substrate **181** was prepared from the corresponding homoallylic alcohol in 60 % yield over five steps. Regioselective *ortho*-oxidative dearomatization of phenol **181** delivered a highly reactive MOB **182** via activated intermediate **183** leading to transannular Diels–Alder cycloaddition upon heating to produce the desired tetracyclic adduct **184** in 65 % yield. This remarkable transformation employed an allene fragment as a dienophile for a transannular cycloaddition cascade which produced all four rings of this highly congested and challenging molecule.

In an early approach to maeocrystal V (**48**), Baran and co-workers also executed an *ortho*-oxidative dearomatization/IMDA sequence to create the core of the natural product

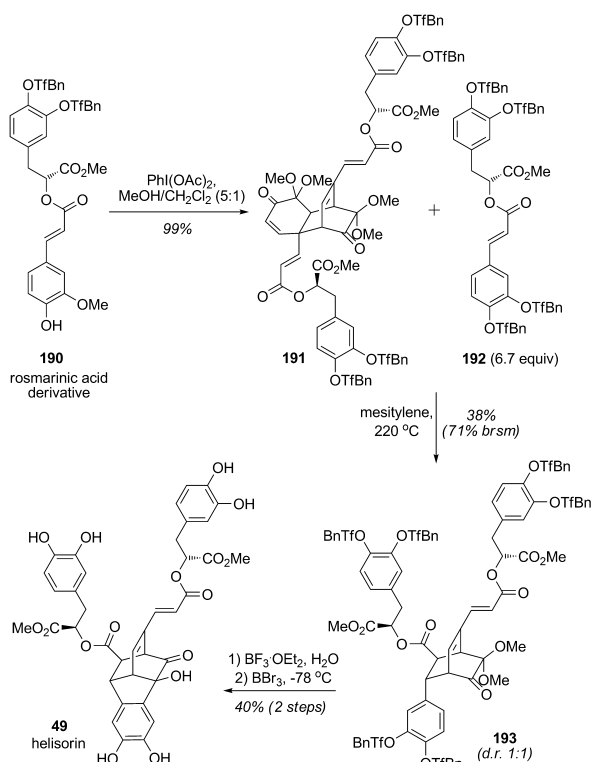
(Scheme 26).^[65] Treatment of the advanced aryl ketone **185** with TFA simultaneously removed the ether protecting group and induced cyclization to afford hemiketal **186** in 65 % yield.



Scheme 26. Approach to maeocrystal V using oxidative *ortho*-dearomatization/IMDA cycloaddition (Baran et al., 2009).^[65]

Wessely oxidation^[66] of **186** employing Pb(OAc)₄ led to *ortho*-oxidative dearomatization with modest diastereoselectivity (d.r. 7:3), thereby generating the dearomatized *ortho*-quinol derivative **187** in 81 % yield. Diels–Alder cycloaddition was successfully conducted at high temperature to deliver both *endo* cycloadducts (major diastereomer **188** shown). Further hydrogenation and cleavage of the α -acetoxyketone and diastereoselective reprotonation (d.r. 17:3) yielded the tricyclic product **189**, a compound bearing the carbon skeleton of maeocrystal V (**48**).

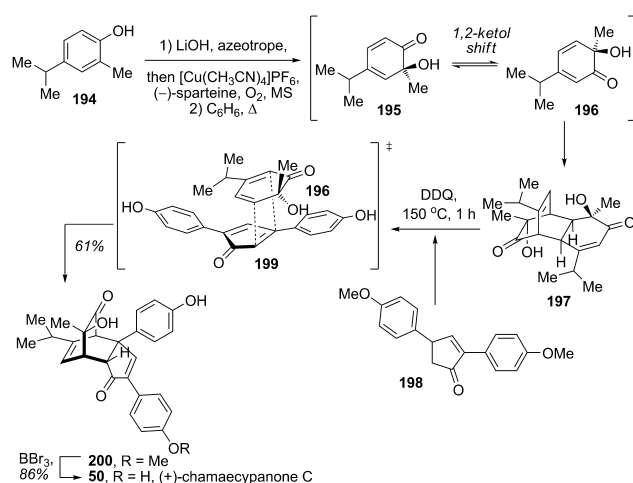
Flavonoids, polyphenols, and heteroarenes present in nature are sources of a significant number of complex dearomatized metabolites. Indeed, the propensity for dearomatization of polyphenols through single electron transfer (SET) and oxidative dearomatization has led to the generation of a number of highly complex structures. In this regard, Snyder and co-workers examined biomimetic access to helisorin and related neolignan natural products from rosmarinic acid (Scheme 27).^[67] Oxidative homodimerization of the rosmarinic methyl ester derivative **190** using PIDA by Diels–Alder cycloaddition yielded the tricyclic product **191**. In this type of *ortho*-oxidative dearomatization with substrates lacking stabilizing substituents at the *para* position, the resulting MOB intermediates are well known to spontaneously dimerize.^[68] Dimer **191** was engaged in a retro-Diels–Alder/Diels–Alder sequence at elevated temperature with a large excess of the dienophile partner **192** which afforded the desired Diels–Alder heteroadduct **193** in 38 % yield (d.r. 1:1). This example illustrates that the remote stereocenter of rosmarinic derivative **192** did not induce high stereoselectivity during the Diels–Alder cycloaddition. Nevertheless, chromatographic separation of the cycloadduct diastereomers afforded pure bicyclo[2.2.2]octenone **193** which was next treated with BF₃·OEt₂ to achieve intramolecular Friedel–Crafts reaction and deliver the tetracyclic core of helisorin. Controlled exposure to BBr₃ at low temperature resulted in the full deprotection of the *para*-(CF₃)-benzyl ethers providing helisorin (**49**) in 40 % yield (two steps). This elegant synthesis of helisorin (**49**) not only emphasizes a common



Scheme 27. Total synthesis of helisorin with an *ortho*-oxidative dearomatization and a retro-Diels–Alder/Diels–Alder sequence (Snyder et al., 2009).^[67]

biomimetic pathway towards several neolignan natural products, but also the careful handling required to access the highly oxygenated and sensitive intermediates.

Porco and co-workers recently demonstrated the utility of related *ortho*-quinol derivatives in an enantioselective synthesis of (+)-chamaecypanone C (**50**; Scheme 28).^[69] In this study, the authors outlined use of chiral, nonracemic *ortho*-quinols obtained by enantioselective *ortho*-oxidative dearomatization of lithium phenolates with a copper bis(oxo)



Scheme 28. Total synthesis of (+)-chamaecypanone C by means of enantioselective copper-mediated oxidative dearomatization/[4+2] cycloaddition (Porco, Jr. et al., 2009).^[69]

complex derived from (–)-sparteine. This chiral copper complex mediated the chemoselective *ortho*-dearomatization of 2,4-disubstituted phenol **194** to afford *ortho*-quinol **195** which equilibrated by means of a [1,2]-ketol shift to isomer **196**. *ortho*-Quinol **196** spontaneously underwent Diels–Alder dimerization to generate bicyclo[2.2.2]octenone **197** in 80 % overall yield

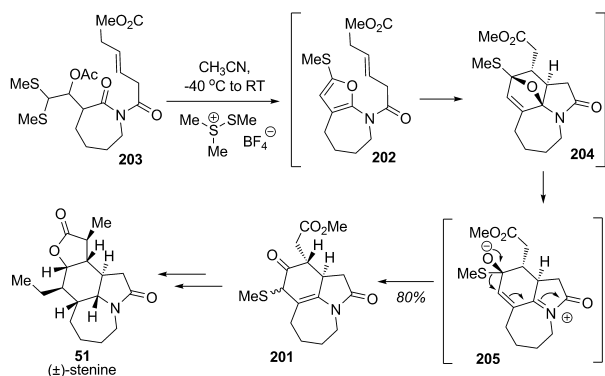
(>99 % *ee*). The dimeric chiral *ortho*-quinol **197** underwent retro-Diels–Alder cycloaddition upon exposure to elevated temperature and was further reacted through Diels–Alder cycloaddition with the in situ generated diarylcyclopentadienone **198**. This three-step cascade thus involved 1) thermolytic generation of chiral *ortho*-quinol **196**, 2) oxidation of cyclopentenone **198** to a highly reactive 2,4-diarylcyclopentadienone **199** and 3) their union through an *endo*- and face-selective Diels–Alder cycloaddition to afford the desired enantiopure cycloadduct **200** in 61 % yield. Final, demethylation of **200** using BBr_3 afforded (+)-chamaecypanone C (**48**) in 86 % yield.

4. Dearomatization of Electron-Rich Heteroarenes: Furans, Pyrroles, Benzofurans, and Indoles

Dearomatization of electron-rich arenes has often been employed as a key part of complex total synthesis endeavors. For instance, furans have been extensively used in intramolecular Diels–Alder (IMDA)^[70] cycloadditions and the hetero-Diels–Alder (HDA)^[71] counterpart to generate complex ring structures. Other applications, including vinylogous aldol reactions, are prominent for 2-silyloxyfurans to forge C–C bonds and introduce butenolide fragments in a single step.^[72] In this section, we outline a number of representative examples in total synthesis involving the dearomatization of furans, pyrroles, indoles, and related heterocycles. In addition, examples of modern diastereo- and enantioselective dearomatization of electron-rich heteroarenes to build complex chiral frameworks will be presented.

4.1. Dearomatization of Furans, Pyrroles, and Benzofurans in Total Synthesis

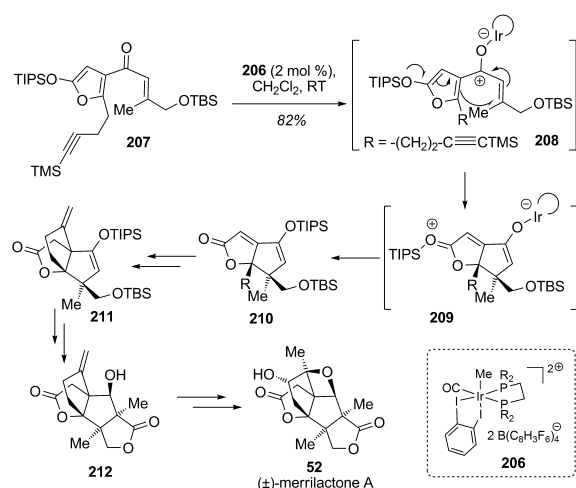
The hydroxindole core skeleton of stenine (**51**) contains seven contiguous stereocenters and is a structural motif shared by several members of the *Stemona* alkaloids (Scheme 29). During their studies, Padwa and co-workers demonstrated the feasibility of a domino amido-Pummerer/Diels–Alder sequence which provided access to complex hetrocycles in a single step with concomitant formation of three new rings.^[73] Extensive studies showed that 2,5-disubstituted furans bearing heteroatoms have a great propensity for dearomatization, especially through cascade reactions initiated by IMDA cycloadditions.^[74] In their recent campaign toward the total synthesis of (±)-stenine (**51**), Padwa and Ginn found the IMDA/*N*-acyliminium strategy to be of great utility for construction of the highly functionalized hydroxindole core **201** (Scheme 29).^[75] The requisite 2-methylthio-5-amidofuran **202** necessary for the intramolecular [4+2]



Scheme 29. Total synthesis of (±)-stenine through dearomatization of a 2-thiomethylfuran (Padwa et al., 2002).^[75]

cycloaddition was prepared by cyclization of imidodithioacetal **203** using dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF). The 2-methylthio-5-amidofuran intermediate **202** could not be isolated^[75] and participated directly in intramolecular [4+2] cycloaddition to afford the dearomatized, cyclic hemiaminal **204**. Ring opening of hemiaminal **204** led to the production of the *N*-acyliminium intermediate **205** which further rearranged by a 1,2-shift to afford azepinoinole **201** in 80% overall yield (d.r. 1:1). The total synthesis of (±)-stenine (**51**) was subsequently accomplished in sixteen steps and 2.1% overall yield from ϵ -caprolactam.

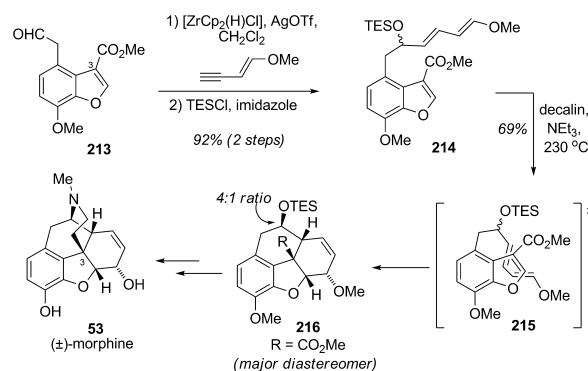
Frontier and co-workers reported the stereoselective total synthesis of the pentacyclic sesquiterpene dilactone (±)-merrillactone A (**52**) featuring the catalytic Nazarov cyclization of 2-silyloxyfurans (Scheme 30).^[76] Recently, catalytic Nazarov cyclizations have been reported employing a wide range of transition-metal complexes and have demonstrated that dienones with high electron density at one terminus of the pentadienyl cation intermediate exhibit high cyclization reactivity. In this context, Frontier and co-workers employed iridium complex **206** to catalyze the Nazarov cyclization of



Scheme 30. Total synthesis of (±)-merrillactone A: catalytic Nazarov cyclization using the dearomatization of a 2-silyloxyfuran (Frontier et al., 2008).^[76]

trialkyl-2-silyloxyfuranyl enone **207** (Scheme 30). Indeed, the authors suggested that iridium(III) complex **206** or a Lewis acidic silicon species could be involved in the dearomatization of silyloxyfuran via **208** and activation of the enone moiety leading to the bicyclic framework **209** which may be followed by silyl transfer to produce bicyclic enone product **210** in 82% yield. This approach for catalytic enone activation triggered the dearomatization of the 2-silyloxyfuran and afforded the desired trisubstituted Nazarov product **210** bearing two adjacent, highly crowded stereocenters. The third ring was installed by radical cyclization to access scaffold **211** in a few steps. Finally, generation of an ether from the exocyclic alkene in **212** to install the angular oxetane concluded an elegant synthesis of (±)-merrillactone A (**52**).

In the case of the morphine alkaloids, a key structural challenge involves the construction of four rings sharing the same carbon atom C3 having a high propensity for skeletal rearrangement. A number of research groups have devoted significant efforts to studying the Diels–Alder reactions of indoles and benzofurans,^[77] which proved to be fruitful for the formal synthesis of morphine by Stork and co-workers (Scheme 31).^[78] A Suzuki reaction sequence involving hydro-

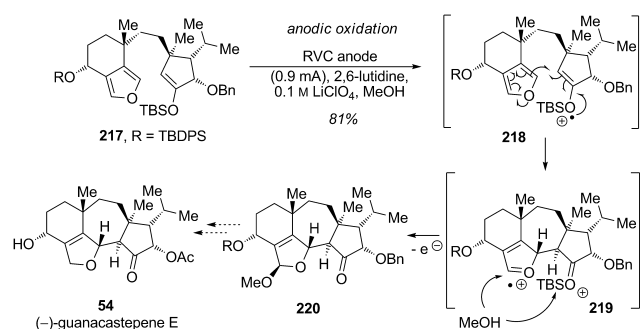


Scheme 31. Formal synthesis of (±)-morphine highlighted by an IMDA dearomatization of a benzofuran (Stork et al., 2009).^[78]

zirconation and in situ addition to benzofuranacetaldehyde **213** produced silyl ether **214** in 95% yield. IMDA cycloaddition of **214** occurred via *endo* transition state **215** affording control of five contiguous asymmetric stereocenters of tetracyclic product **216**. Specifically, cycloaddition in decalin at elevated temperature afforded a 69% yield of cycloadduct **216** (d.r. 4:1) along with recovered starting material. This *endo* intramolecular Diels–Alder cycloaddition installed four of the five required stereocenters of morphine (**53**) and greatly facilitated final manipulations including construction of the tertiary amine bridge to afford after a few additional steps the natural product (±)-codeine, a precursor to the alkaloid (±)-morphine (**53**).

Several research groups have studied and demonstrated the utility of electrochemical, oxidative furan dearomatization with enol ether partners.^[79] Indeed, electrochemical oxidation of the silyl enol ether should occur preferentially as determined by cyclic voltammetry studies (TMS enol ether $E_{ox} = 0.87$ V (vs. Ag/Ag^+) when monosubstituted furan $E_{ox} =$

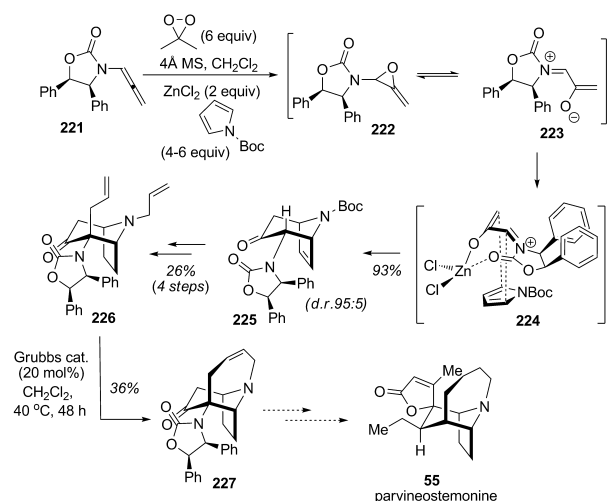
1.31 V (vs. Ag/Ag⁺)). In their approach toward the guanacastepene family of natural products ((-)-guanacastepene E (**54**)), Trauner and co-workers established that an oxidative radical cation cascade could be accomplished in a complex setting (Scheme 32).^[80] Late-stage anodic oxidation of poly-



Scheme 32. Synthetic approach toward (-)-guanacastepene E: oxidative radical annulation by means of furan dearomatization (Trauner et al., 2005).^[80]

cyclic substrate **217** presumably generated the radical cation **218** which was then trapped by the pendant bicyclic furan to forge a new C–C bond and generate intermediate **219**. Quenching of the oxonium ion **219** with methanol, followed by a second oxidation and desilylation, generated acetal **220** in 81 % overall yield. This radical cation cascade triggered the dearomatization of furan through “umpolung-like” reactivity allowing two nucleophiles to enter successively at the C2 and C4 positions of the furan moiety and elegantly afforded the highly functionalized tetracyclic guanacastepene core **220**.

[4+3] Cycloaddition of furans and pyrroles is a powerful dearomatizing reaction for the construction of bridged bicyclic frameworks.^[81] Highly stereoselective [4+3] cycloadditions of *N*-substituted pyrroles with allenamide-derived, nitrogen-stabilized chiral oxyallyl cations were reported by Hsung and co-workers (Scheme 33).^[82] This diastereoselective methodology provides an efficient means for construction of the chiral tropinone alkaloid parvineostemonine (**55**). Reaction of allenamide **221** with dimethyldioxirane in the presence of *N*-Boc-pyrrole afforded the allene oxide intermediate **222** which subsequently tautomerized to the highly reactive oxyallyl cation species **223**. First, the Seebach chiral auxiliary (not shown)^[83] was found to perform well and induce high diastereoselection (81 % yield, d.r. 95:5). The stereochemical outcome obtained upon use of allenamide **221** derived from the (1*R*,2*S*)-diphenyloxazolidinone auxiliary can be rationalized from proposed transition state **224**, wherein the bottom face of the zinc-chelated oxyallyl cation is open for [4+3] cycloaddition to afford bicyclic derivative **225** (93 % yield, d.r. 95:5). After hydrogenation, protecting group removal, and allyl group installation, the bicyclic piperidine derivative **226** was obtained in 26 % yield over four steps. Transannular ring-closing metathesis of substrate **226** delivered the tricyclic core **227** of the natural product parvineostemonine in 36 % yield.

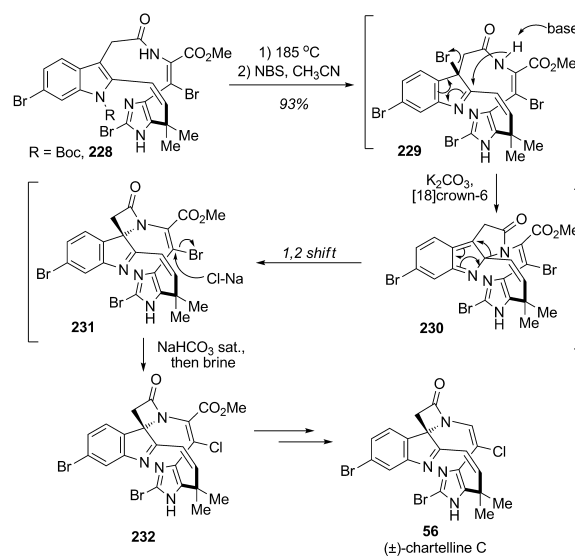


Scheme 33. Approach to parvineostemonine employing asymmetric oxyallyl cation [4+3] cycloaddition for pyrrole dearomatization (Hsung et al., 2007).^[82]

4.2. Indole Dearomatization in Total Synthesis

As outlined in the introduction of this Review, many indolic alkaloid frameworks can be accessed from either Diels–Alder cycloaddition or stepwise nucleophilic dearomatization at C3 followed by successive trapping at C2. In this regard, impressive examples of indole dearomatization have emerged and will be summarized in the following section.

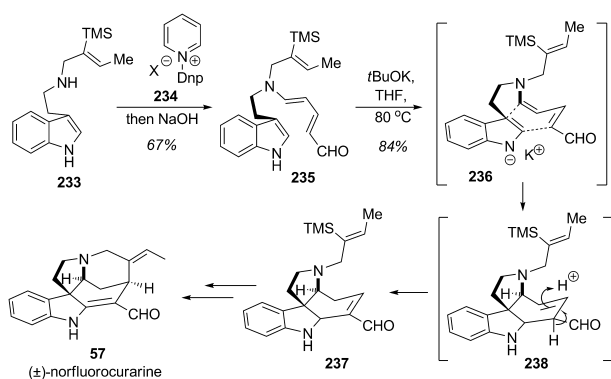
Recently, Baran and co-workers reported several total syntheses in which indolic cores were efficiently dearomatized.^[84] In the synthesis of (±)-chartelline C (**56**), Baran and co-workers developed a biomimetic strategy involving brominative dearomatization followed by amide trapping (Scheme 34).^[85] Initial carbamate deprotection under thermal



Scheme 34. Total synthesis of chartelline C by brominative indole dearomatization/amide trapping (Baran et al., 2006).^[85]

conditions was followed by a cascade process promoted by *N*-bromosuccinimide (NBS). Bromoindolenine **229** was presumably formed upon exposure of macrocycle **228** to NBS with base and trapped at the C2 position by the proximate amide nitrogen to afford pyrroloindoline **230** which underwent ring contraction to produce the β -lactam **231**. Aqueous workup resulted in bromine displacement to afford the chloroenamide **232** in 93% overall yield. Further ester hydrolysis and thermolytic decarboxylation concluded an elegant synthesis of (\pm)-chartelline C (**56**).

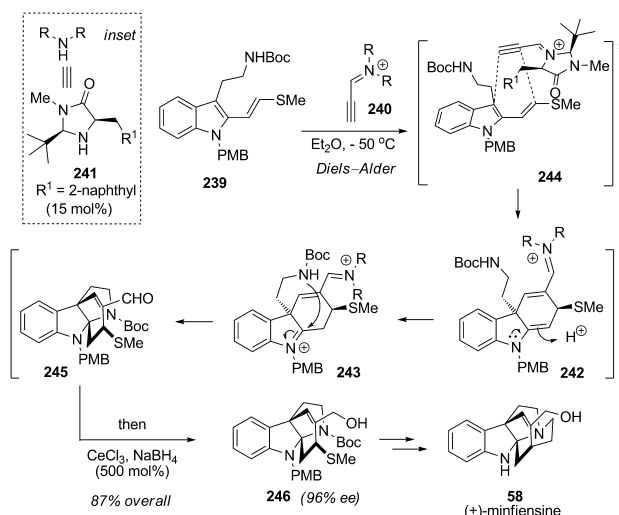
In a recent synthesis of the *Strychnos* alkaloid (\pm)-norfluorocurarine (**57**), Vanderwal and co-workers manipulated the indole nucleus without employing protecting groups to implement IMDA cycloaddition leading to rapid construction of the functionalized tetracyclic ring system (Scheme 35).^[86] The secondary amine substrate **233** (readily



Scheme 35. Total synthesis of (\pm)-norfluorocurarine using IMDA indolic dearomatization (Vanderwal et al., 2009).^[86]

obtained from tryptamine) was condensed with the dinitrophenylpyridinium salt **234** using the Zincke protocol to produce the corresponding dienamine aldehyde **235** after ring-opening of the pyridinium salt intermediate.^[87] As reported earlier by Marko and co-workers,^[88] bis-cyclization of indole anion **236** was achieved by treatment of indole derivative **235** with *t*BuOK in THF at 80 °C in a sealed tube to afford the tetracyclic alkaloid structure **237** as a single diastereomer in 84% yield through formal Diels–Alder cycloaddition and olefin isomerization of aldehyde **238**. Even though a stepwise or concerted mechanism for this dearomatization cascade has not yet been elucidated, this spectacular dearomatization through the anionic bicyclization of **235** established, in a single dearomatization step, the tetracyclic core of the *Strychnos*-type alkaloids. Installation of the iodine onto the vinylsilane and final Heck cyclization completed the total synthesis of (\pm)-norfluorocurarine (**57**) in 16% overall yield (nine steps in the longest linear sequence).

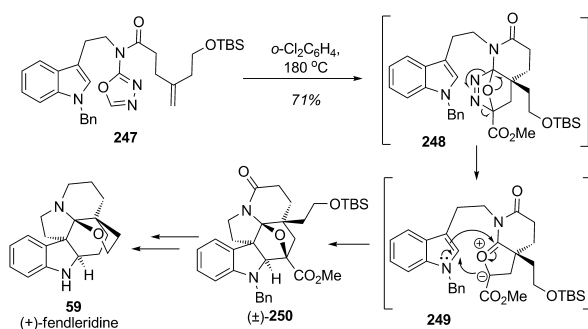
The total synthesis of (+)-minfiensine (**58**) has been reported several times prior to 2009. However, the organocatalytic enantioselective cascade underlined by indole dearomatization by means of Diels–Alder cycloaddition is a major achievement in modern alkaloid synthesis (Scheme 36).^[89] MacMillan and co-workers reported a remarkable synthesis



Scheme 36. Total synthesis of (+)-minfiensine: enantioselective iminium-catalyzed Diels–Alder dearomatization of indoles (MacMillan et al., 2009).^[89]

with the following key features: 1) an organocatalytic [4+2] cycloaddition coupled with hemiaminal isomerization/cyclization to allow rapid access to the desired tetracyclic framework and 2) a second radical cyclization to install the last ring of the alkaloid. In the first event, protected tryptamine **239** participated in a dearomatization cascade by means of a catalytic Diels–Alder reaction with propyne 4-imidazolodinium **240** (from imidazolidinone catalyst **241**) to generate the enamine intermediate **242** which underwent isomerization to indolinium **243**. Further cyclization of the pendant protected amine in a 5-*exo*-trig manner furnished pyrroloindoline **245**. The authors proposed a specific arrangement for the Diels–Alder cycloaddition wherein the acetylenic group of the iminium intermediate **244** may be positioned away from the *tert*-butyl substituent of catalyst **241**, thereby facilitating *endo* selectivity during the cycloaddition (cf. **244**) and establishing the C3 stereocenter of indoline intermediate **242**. Reductive workup in the same pot delivered product **246** in 87% yield and 96% *ee*. This organocatalytic cascade and tandem reduction sequence allowed MacMillan and co-workers to produce the tetracyclic core of minfiensine **246** in a single step with high enantioselectivity and diastereocontrol. Further transformations (with a 6-*exo*-dig radical cyclization) completed an efficient nine-step total synthesis of (+)-minfiensine (**58**).

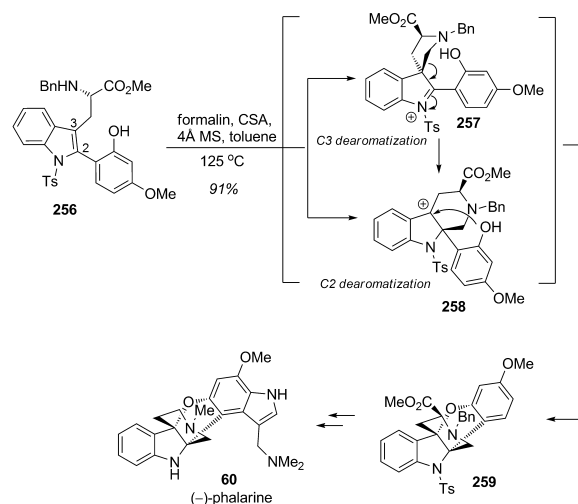
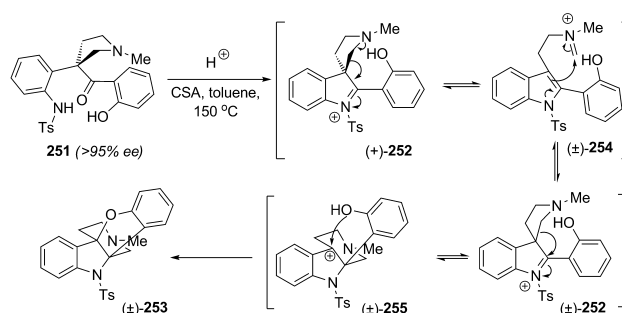
As described in the introduction, approaches to the tricyclic ring system containing the angular tertiary amine of the *Aspidosperma* alkaloids have been a central objective for the synthesis of various indole alkaloids. Boger and co-workers have developed an impressive methodology to create such a ring system in a single step involving [4+2]/[3+2] cycloaddition of an 1,3,4-oxadiazole substrate.^[90] In their recent synthesis of (+)-fendleridine (**59**; Scheme 37),^[91] the Boger group reported an elegant reaction cascade from tryptamine derivative **247** (prepared in four steps from *N*-benzyltryptamine) by means of the intramolecular and regioselective [4+2] cycloaddition of the 1,3,4-oxadiazole



Scheme 37. Total synthesis of (+)-fendleridine using tandem [4+2]/[3+2] cycloadditions of 1,3,4-oxadiazoles with indole dearomatization (Boger et al., 2010).^[91]

moiety with the tethered 1,1-disubstituted alkene. Diels–Alder cycloadduct **248** spontaneously extruded nitrogen to provide 1,3-dipole intermediate **249** which is stabilized by substitution at the dipole termini. 1,3-Dipole intermediate **249** subsequently triggered indole dearomatization through regio- and diastereoselective [3+2] cycloaddition to produce the hexacyclic alkaloid structure **250** as a racemate in 71 % yield. The intrinsic regioselectivity of the ensuing 1,3-dipolar cycloaddition is reinforced by the linking tether and the relative stereochemistry dictated by *endo* cycloaddition wherein the dipolarophile is sterically directed to the opposite face of the newly formed fused lactam. In total, four C–C bonds, three rings, five relative stereogenic centers including the C19 N,O-ketal and the complete natural product skeleton are assembled in a single step affording product **250**. It is noteworthy that the use of a 1,1-disubstituted alkene as the dienophile in the inverse-demand [4+2] cycloaddition allowed the formation of the crucial quaternary stereocenter. Subsequent modifications of the N,O-ketal moiety, redox adjustments, and separation of the enantiomers by HPLC finalized the synthesis of (+)-fendleridine (**59**).

In their quest to synthesize the alkaloid (–)-phalarine (**60**), Danishefsky and co-workers developed a new pathway involving the interception of a Pictet–Spengler intermediate with a tethered nucleophile (Scheme 38).^[92] In their approach, the enantiopure aniline derivative **251** (>95 % ee) was subjected to acid to initiate cyclization to the chiral, non-racemic spirocyclic indolinium (+)-**252**. As proposed by the authors, a possible pathway for the production of the pentacyclic core of phalarine **253** may involve a Wagner–Meerwein-type 1,2-shift. This structural rearrangement is expected to proceed in a suprafacial, diastereoselective fashion and deliver product (+)-**253** with preservation of enantiomeric integrity. Unfortunately, Danishefsky and co-workers obtained the desired core of phalarine (±)-**253** in racemic form which suggested that racemization occurred, most likely by means of a retro-Mannich reaction leading to the achiral aromatized tryptamine iminium **254**. This aromatic intermediate was set for dearomatization (Pictet–Spengler reaction) and regeneration of spirocyclic indolinium intermediate (±)-**252** as racemate. A subsequent 1,2-shift created benzylic carbocation (±)-**255** which was trapped by the proximate phenol to give the racemic pentacyclic structure



Scheme 38. Total synthesis of (–)-phalarine through indole dearomatization: Pictet–Spengler cyclization and intramolecular carbocation trapping (Danishefsky et al., 2010).^[92c]

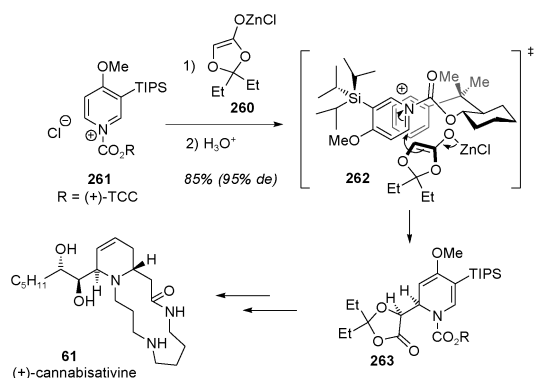
(±)-**253** in 52 % yield. To solve this problem, Danishefsky and co-workers conducted a diastereoselective Pictet–Spengler reaction using the enantiopure tryptophan derivative **256**.^[92c] Accordingly, dearomatization was conducted using iminium chemistry either at C2 or C3 (via intermediates **257** or **258**, respectively) to afford pentacycle **259** as a single diastereomer in 91 % yield. Both pathways via iminium **257** or stabilized carbocation **258** are plausible and provide a good handle for chirality transfer at both the C2 and C3 positions during the dearomatization. The total synthesis of (–)-phalarine (**60**) was further completed with reductive decarboxylation and installation of the tryptamine portion by means of the Gassman oxindole synthesis. In these studies, the authors demonstrated the versatility of dearomatization using the Pictet–Spengler reaction coupled with nucleophilic trapping to generate the desired core structure of the natural product in a single step.

5. Dearomatization of Electron-Poor Heteroarenes (Pyridinium and Related Compounds)

Pyridines and their activated pyridinium counterparts provide a class of interesting substrates for dearomatization chemistry and syntheses of complex piperidine, quinoline, and alkaloidal structures. Pyridinium compounds present high electronic deficiency at both the C2 and C4 positions leading

to two possible regioselective dearomatization pathways.^[93] It is noteworthy that only few methodologies for the alkylative dearomatization of pyridinium/isoquinolinium compounds have been reported in a catalytic, enantioselective context.^[94]

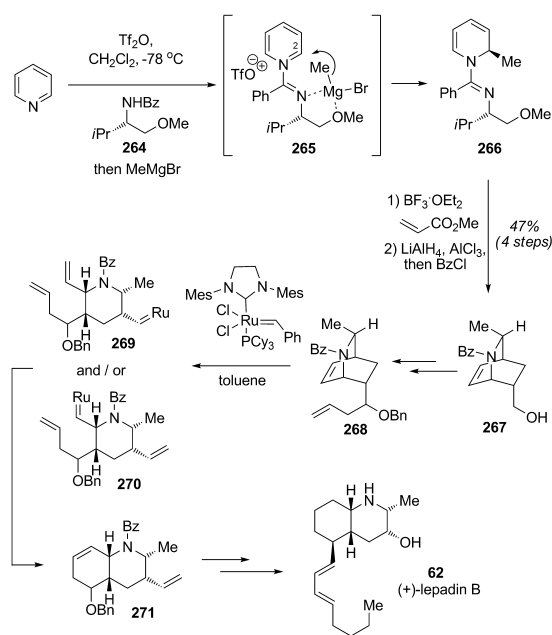
For chirality control in the dearomatization of pyridinium compounds, most methodologies reported up to date are diastereoselective. In the early stage of the stereoselective synthesis of (+)-cannabisativine (**61**), Comins and co-workers demonstrated the high selectivity of their alkylative methodology with the addition of the prochiral zinc enolate **260** to pyridinium electrophile **261** (Scheme 39).^[95] The preformed *E*



Scheme 39. Total synthesis of (+)-cannabisativine using the diastereoselective C2-alkylation of pyridiniums (Comins et al., 2004).^[95]

zinc enolate **260** added stereoselectively to pyridinium **261**, thereby differentiating the diastereotopic faces created by the *trans*-2-(*R*)-cumylcyclohexyl chiral auxiliary ((+)-TCC) through proposed transition state **262**^[96] to afford dihydropyridone **263** as the major diastereomer (95% *de*) in 85% yield. In this case, the authors presumed involvement of acyclic transition state **262** with a synclinal orientation wherein the TCC auxiliary blocks the back face of pyridinium **261**. Further manipulations were used to generate the dihydroxylated side chain of the natural product followed by macrocyclization to achieve an elegant synthesis of (+)-cannabisativine (**61**).

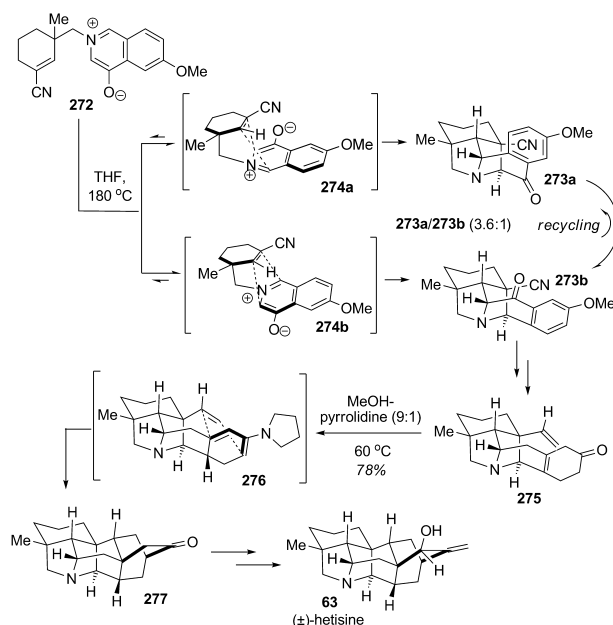
Recently, Charette and co-workers relied on a similar diastereoselective dearomatization strategy based on the alkylation of a pyridinium species for the synthesis of the alkaloid (+)-lepadin B (**62**; Scheme 40).^[97] Reaction of pyridine with the triflic amidate of L-(OMe)-valinol **264** generated amidinium **265** which underwent regio- and diastereoselective alkylation at C2.^[98] In fact, the bulky phenyl group discouraged nucleophilic attack at C4 by chelation of the valinol auxiliary with organomagnesium or zincate reagents leading to dearomatization (shown for methyl Grignard) to afford the amidine product **266**. *endo*-Selective Diels–Alder cycloaddition and further reduction/protection afforded the isoquinoline skeleton **267** in 47% overall yield (three steps) and 84% *ee*. After few manipulations, the derived isoquinoline substrate **268** was successfully subjected to tandem metathesis (ROM–RCM) which proceeded via a presumed mixture of intermediates **269/270** to furnish the desired *cis*-fused decahydroquinoline **271** having the framework of the natural product. This stereoselective total synthesis of (+)-



Scheme 40. Total synthesis of (+)-lepadin B using the diastereoselective alkylation of a pyridinium (Charette et al., 2008).^[97]

lepadin B (**62**) represents a key strategy for the synthesis of fused piperidines by combining diastereoselective alkylative dearomatization/Diels–Alder cycloaddition and tandem ROM–RCM.

1,3-Dipolar cycloadditions involving oxidopyridinium betaines have previously been used in alkaloid synthesis.^[99] Gin and co-workers fully illustrated the value of this dearomatization approach in a complex setting during their elegant synthesis of (±)-hetisine (**63**; Scheme 41).^[100] In this



Scheme 41. Total synthesis of (±)-hetisine employing the intramolecular 1,3-dipolar cycloaddition of oxidoisoquinolinium betaines (Gin et al., 2006).^[100]

work, the authors reported dearomatization of oxidoisoquinolinium betaine **272** at 180 °C through intramolecular 1,3-dipolar cycloaddition to provide pyrrolidines **273a** and **273b** (constitutional isomers, 3.6:1 ratio). The two constitutional isomers arose from the different facial approaches of the dipolarophile partner in arrangements **274a** and **274b**. The authors confirmed that the 1,3-dipolar cycloaddition was reversible and under thermodynamic control which enabled the recycling of the undesired isomer **273a** to increase the production of the desired pentacyclic core **273b**. After a few steps, the β,γ -unsaturated cyclohexenone **275** was obtained and transformed upon exposure to pyrrolidine into dienamine **276** which readily underwent intramolecular Diels–Alder cycloaddition to afford the desired heptacyclic core structure **277** in 78 % yield. (\pm)-Hetisine (**63**) was ultimately prepared in 15 steps from commercially available starting materials, underscoring the utility of the dearomatization of oxidoisoquinolinium betaine through 1,3-dipolar cycloaddition for the construction of complex alkaloids.

6. Future Opportunities and Perspectives for Asymmetric Dearomatization

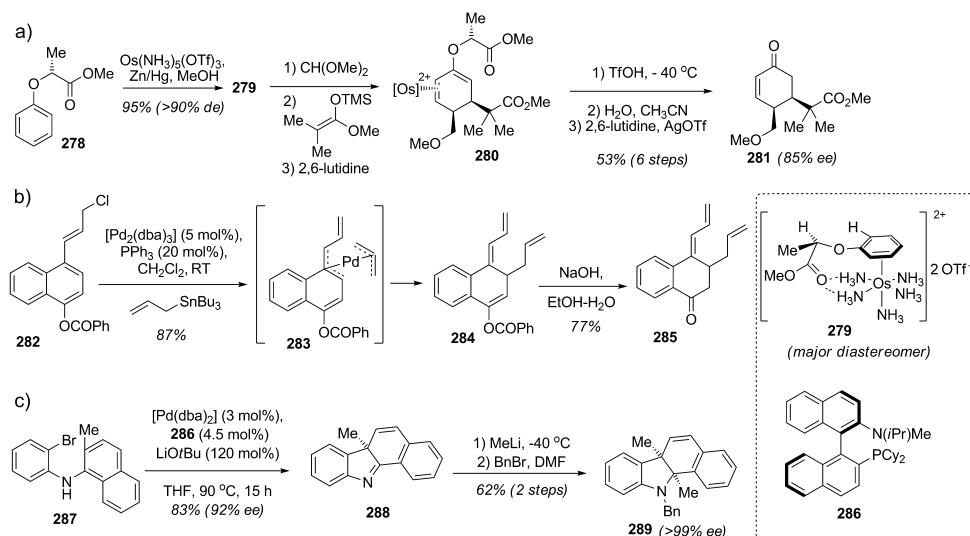
As described in this Review (Section 2), the dearomatization of arenes is a highly important chemical transformation for the preparation of polycyclic frameworks of many biologically active natural products. Transition-metal-catalyzed dearomatization has been developed in the past few years employing arene coordination (Scheme 42).^[101] For instance, Harman and co-workers have developed a useful approach to arene dearomatization. Simple coordination of arenes to a transition metal, in particular, π -basic transition-metal complexes, has been found to disrupt aromatic stabilization through η^2 coordination (Scheme 42a).^[102] Such coordination between the chiral enantiopure phenol ether **278** and osmium could be made in a well-defined complex

such as **279** (>90 % *de*) which promotes diastereoselective addition toward electrophiles (e.g. formate) followed by addition of a silyl ketene acetal to afford the highly substituted cyclohexadiene **280**. Further acidic treatment promoting auxiliary removal and decomplexation of the transition metal furnished the useful cyclohexenone building block **281** in 53 % overall yield and 85 % *ee*. In another study concerning π -allyl reactivity, Yamamoto and co-workers discovered the unexpected reactivity of benzyl chlorides and naphthalene allyl chlorides such as **282** (Scheme 42b).^[103] Indeed, both systems when treated with catalytic palladium(0) reacted via π -allyl species to deliver different dearomatized products. In the case of the naphthalene allyl chloride derivative **282**, the authors believe that the original bis(η^3 -allyl)palladium intermediate may isomerize to the more stable η^3 -benzylpalladium complex **283**, which after reductive elimination regenerates the original palladium(0) catalyst and delivers the dearomatized compound **284** possessing both butadiene and allyl moieties. Final deprotection of the carbonate moiety delivers the cyclohexenone fragment **285**. This chemistry highlights the possibility of synthesizing fused six-membered-ring systems from simple naphthalenes or phenanthrenes by means of extremely mild palladium-catalyzed allylative dearomatization reactions with allyltributylstannane. Recently, Rawal and co-workers also reported a palladium-mediated alkylative dearomatization of numerous indolic substrates at C3 position using allyl methylcarbonate.^[104]

Asymmetric dearomatization methods are underdeveloped and significant potential for chemical synthesis. Therefore, the development of new catalytic and enantioselective dearomatization methods such as that recently reported by Buchwald and co-workers will set the bar for further applications in the total synthesis of complex molecules (Scheme 42c).^[105] The authors found that a palladium(0) complex bearing the chiral P,N ligand **286** catalyzed asymmetric, intramolecular dearomatization of naphthalene derivatives such as **287** to produce

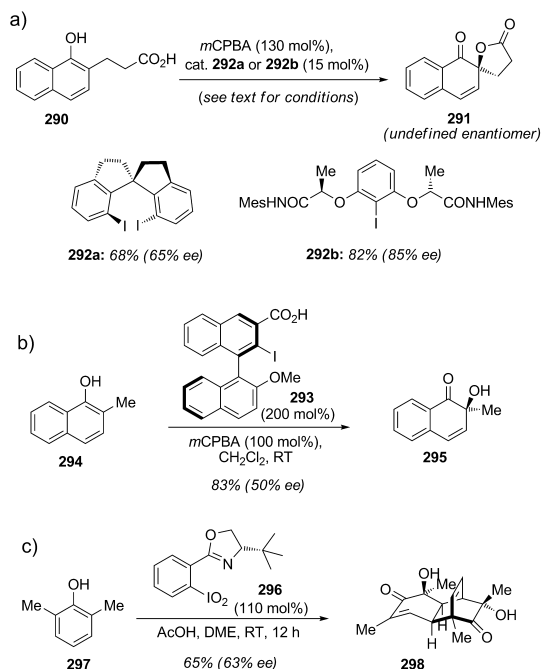
the fused tetracyclic indolenine **288** (83 % yield, 92 % *ee*) which contains two contiguous nonaromatic rings proximal to a quaternary stereocenter. Indolenine **288** was further functionalized at C2 by highly diastereoselective addition of methyl-lithium (d.r. 9:1) and directly protected on the indoline nitrogen to deliver tetracyclic product **289** in 62 % overall yield and 99 % *ee*. This elegant work should inspire future studies in the area of transition-metal-catalyzed, enantioselective dearomatization.

As described in Section 3 of this Review, three main



Scheme 42. New strategies for arene dearomatization using transition-metal catalysis (Harman,^[102] Y. Yamamoto,^[103] Buchwald^[105] et al., 2008–2010).

challenges remain in the development of oxidative dearomatization processes of phenols induced by hypervalent iodine reagents: 1) addition of carbon-centered nucleophiles, 2) development of catalytic processes for dearomatization, and finally 3) improvement of catalytic, enantioselective dearomatization methods (Scheme 43). A number of research

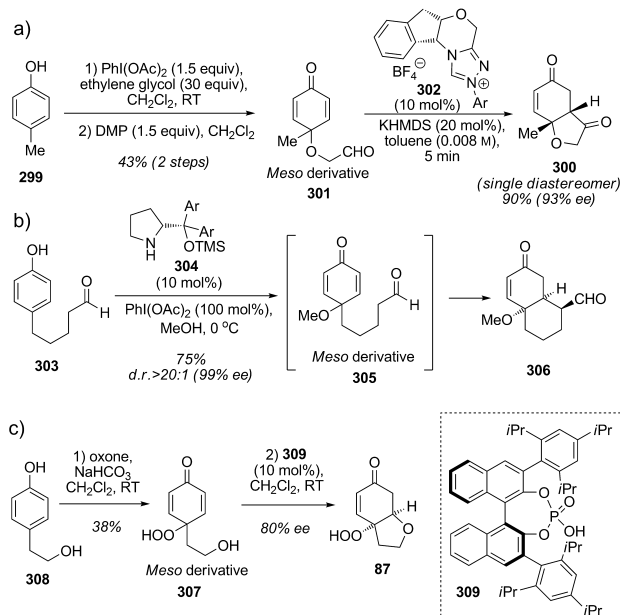


Scheme 43. Enantioselective and catalytic oxidative dearomatization methodologies (Kita,^[106] Ishihara,^[107] Quideau,^[108] Birman^[110] et al., 2008–2010).

groups are currently working in the area of enantioselective oxidative dearomatization employing hypervalent iodine reagents. A recent example by Kita and co-workers described the first catalytic enantioselective oxidative dearomatization of naphthol **290** to produce chiral *ortho*-spirolactone **291** (Scheme 43a).^[106] In this study, the authors evaluated the activity of a new chiral spirocyclic organoiodine(III) reagent formed in situ from **292a** and the effect of polar solvents on the yield and enantioselectivity of the dearomatization. Indeed, particular conditions were needed to avoid formation of a discrete carbocation that may result in diminished enantioselectivity and the spirolactone **291** was obtained in 68% yield and 65% ee. Dichloromethane or chloroform were found to be suitable solvents for this reaction in the presence of stoichiometric amounts of acetic and *meta*-chloroperbenzoic acid to regenerate the iodine(III) catalyst from reagent **292a**. At the beginning of 2010, Ishihara and co-workers examined the same reaction using a new catalytic C₂-symmetric iodine source **292b** and were able to isolate the desired spirolactone **291** in 82% yield and increased 85% ee.^[107] Reactions were optimized using dichloromethane/nitromethane as the solvent mixture without any acid additive leading to high levels of enantioselectivity in the intramolecular oxidative dearomatization of naphthols. Pre-

viously, Quideau and co-workers developed the iodine reagent **293** based on a binaphthyl framework (Scheme 43b).^[108] To date, this approach has not been successfully applied to the enantioselective dearomatization of naphthol **294** in a catalytic fashion, but showed promising results for enantioselective, intermolecular dearomatization to access α -hydroxy ketone **295** in 83% yield and 50% ee. New iodine(V) reagents have also been developed notably by Zhdankin and co-workers^[109] and IBX derivatives have been successfully used for the dearomatization of phenols. Additionally, Birman and co-workers have explored the potential of new chiral organoiodine(V) reagents (Scheme 43c).^[110] Indeed, the *ortho*-substituted iodoxybenzene derivatives **296** possessing chiral oxazoline groups were utilized for the enantioselective oxidative dearomatization of *ortho*-alkyl phenols. The authors were able to dearomatize phenolic substrates such as 2,6-disubstituted phenol **297** with a stoichiometric amount of a chiral hypervalent iodine(V) reagent and acetic acid to deliver an *ortho*-quinol that spontaneously dimerized to produce enantioenriched tricyclic products such as **298** in 29–68% yield (62–77% ee).

Another promising area for oxidative dearomatization relies on the desymmetrization of derived *meso* dienones to afford chiral enantiopure polycyclic building blocks (Scheme 44).^[111] Rovis and co-workers reported a three-step



Scheme 44. Organocatalytic desymmetrization of *meso* dienones obtained through oxidative dearomatization (Rovis,^[112] Gaunt,^[113] You^[114] et al., 2006–2010).

sequence involving dearomatization, oxidation, and Stetter condensation starting from *para*-alkylphenol **299** to deliver in high diastereo- and enantioselectivity various complex lactones **300** (Scheme 44a).^[112] This strategy involved *para*-oxidative dearomatization of phenols **299** with ethylene glycol to generate after oxidation with Dess–Martin periodinane (DMP) the *meso*-cyclohexadienone aldehydes **301** (20–50%

yield), thereby establishing a powerful maneuver for further enantioselective desymmetrization using the Stetter reaction. Next, the key asymmetric intramolecular Stetter reaction using a chiral enantiopure N-heterocyclic carbene (NHC) catalyst (triazolium **302**) afforded hydrobenzofuranone **300** in good yield as a single diastereomer with excellent enantioselectivity (93 % *ee*). Gaunt and co-workers also reported their efforts for the direct conversion of *para*-substituted phenols **303** to highly functionalized chiral building blocks by means of *para*-oxidative dearomatization with methanol and other protic/soft nucleophiles followed by proline-catalyzed enantioselective desymmetrization (Scheme 44b).^[113] This creative transformation demonstrated the possibility of cascade sequences using hypervalent iodine with an organocatalyst. In the presence of proline catalyst **304**, *meso*-cyclohexadieneone **305** cyclized via enamine chemistry to yield bi- or tricyclic frameworks such as **306** in 75 % yield with high diastereo- and enantioselectivity. Finally, a recent example from You and co-workers, based on the previous work of Urbano and Carreño,^[27] demonstrated the possibility for desymmetrization of *meso*-peroxyquinol **307** through an enantioselective oxa-Michael addition (Scheme 44c).^[114] Dearomatization of *para*-alkylphenol **308** with Oxone delivered *meso para*-peroxyquinol **307** which was subsequently desymmetrized in a presumed thermodynamic oxa-Michael process catalyzed by the chiral Brønsted acid **309** to deliver the enantioenriched bicyclic ether **310** in 80 % *ee*.

7. Summary

This Review has illustrated a number of examples and possibilities for the dearomatization of arenes, phenols, and heteroaromatic compounds which in the appropriate setting may be used to generate complex natural product frameworks in a stereocontrolled fashion. Further understanding of aromaticity and thus dearomatization will continue to evolve and provide new opportunities for methodology development and applications in total synthesis. As outlined in this Review, oxidative, but also reductive and alkylative dearomatization methodologies may be further developed as powerful tools for chemical synthesis. In addition, examples of reagent-controlled and catalytic enantioselective dearomatization of arenes, indoles, and pyridines are somewhat limited to date. Future research and emphasis in this area should lead to additional strategies and methods for the construction of polycyclic scaffolds which should be of great value to the field of natural products total synthesis.

Abbreviations

Ac	acyl
acac	acetylacetonate
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
brsm	based on recovered starting material
CDDA	Claisen dearomatization/Diels–Alder
cod	cyclooctadiene

Cp	cyclopentadienyl
Cy	cyclohexyl
CSA	camphorsulfonic acid
dba	<i>trans,trans</i> -dibenzylideneacetone
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMP	Dess–Martin periodinane
Dnp	3,5-dinitrophenyl
hfacac	hexafluoroacetylacetonate
HFIP	hexafluoroisopropanol
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels–Alder
KHMDS	potassium hexamethyldisilazide
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
MES	mesitylene
MOB	masked <i>ortho</i> -benzoquinone
MOM	methoxymethyl ether
MS	molecular sieves
NBS	<i>N</i> -bromosuccinimide
PCC	pyridinium chlorochromate
PIDA	bis(acetoxy)iodobenzene
Piv	pivaloyl
PMB	<i>para</i> -methoxybenzyl
PMP	<i>para</i> -methoxyphenyl
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl, SO ₂ CF ₃
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
Ts	tosyl, toluenesulfonyl
TS	transition state

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- [1] J. L. Franklin, *J. Am. Chem. Soc.* **1950**, 72, 4278–4280.
- [2] a) T. M. Krygowski, M. K. Cyrański, *Chem. Rev.* **2001**, 101, 1385–1419; b) A. T. Balaban, D. C. Oniciu, A. R. Katritzky, *Chem. Rev.* **2004**, 104, 2777–2812; c) Z. Chen, C. S. Wannere, C. Corminboeuf, R. Puchta, P. von R. Schleyer, *Chem. Rev.* **2005**, 105, 3842–3888.

- [3] a) M. Boll, *J. Mol. Microbiol. Biotechnol.* **2005**, *10*, 132–142; b) B. Thiele, O. Rieder, B. T. Golding, M. Müller, M. Boll, *J. Am. Chem. Soc.* **2008**, *130*, 14050–14051; c) J. W. Kung, S. Baumann, M. Von Bergen, M. Müller, P.-L. Hagedoorn, W. R. Hagen, M. Boll, *J. Am. Chem. Soc.* **2010**, *132*, 9850–9856.
- [4] a) A. G. Myers, D. R. Siegel, D. J. Buzard, M. G. Charest, *Org. Lett.* **2001**, *3*, 2923–2926; For a recent example, see: b) M. D. Mihovilovic, H. G. Leisch, K. Mereiter, *Tetrahedron Lett.* **2004**, *45*, 7087–7090.
- [5] E. J. Corey, N. N. Girotra, C. T. Mathew, *J. Am. Chem. Soc.* **1969**, *91*, 1557–1559.
- [6] a) A. G. Schultz, A. Wang, *J. Am. Chem. Soc.* **1998**, *120*, 8259–8260; For review on asymmetric Birch reduction, see: b) A. G. Schultz, *Chem. Commun.* **1999**, 1263–1271.
- [7] D. Barnes-Seeman, E. J. Corey, *Org. Lett.* **1999**, *1*, 1503–1504.
- [8] a) K. C. Nicolaou, K. B. Simonsen, G. Vassilikogiannakis, P. S. Baran, V. P. Vidali, E. N. Pitsinos, E. A. Couladouros, *Angew. Chem.* **1999**, *111*, 3762–3766; *Angew. Chem. Int. Ed.* **1999**, *38*, 3555–3559; b) K. C. Nicolaou, G. Vassilikogiannakis, K. B. Simonsen, P. S. Baran, Y.-L. Zhong, V. P. Vidali, E. N. Pitsinos, E. A. Couladouros, *J. Am. Chem. Soc.* **2000**, *122*, 3071–3079.
- [9] a) T. R. R. Pettus, X.-T. Chen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1998**, *120*, 12684–12685; b) T. R. R. Pettus, M. Inoue, X.-T. Chen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2000**, *122*, 6160–6168; for new developments of prenylic dearomatization, see: c) X. Lei, M. Dai, Z. Hua, S. J. Danishefsky, *Tetrahedron Lett.* **2008**, *49*, 6383–6385.
- [10] F. He, Y. Bo, J. D. Altom, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.
- [11] a) P. Magnus, J. Rodríguez-López, K. Mulholland, I. Matthewst, *J. Am. Chem. Soc.* **1992**, *114*, 382–383; b) P. Magnus, J. Rodríguez-López, K. Mulholland, I. Matthews, *Tetrahedron* **1993**, *49*, 8059–8072.
- [12] R. Yamaguchi, M. Moriyasu, M. Yoshioka, M. Kawanisi, *J. Org. Chem.* **1988**, *53*, 3507–3512.
- [13] L. N. Mander, *Synlett* **1991**, 134–144.
- [14] a) A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917–2940; b) P. L. Smith, M. D. Chordia, W. D. Harman, *Tetrahedron* **2001**, *57*, 8203–8225; c) E. P. Kündig, A. Pape, *Top. Organomet. Chem.* **2004**, *7*, 71–94; d) J. M. Keane, W. D. Harman, *Organometallics* **2005**, *24*, 1786–1798; e) F. López Ortiz, M. J. Iglesias, I. Fernández, C. M. Andújar Sánchez, G. R. Gómez, *Chem. Rev.* **2007**, *107*, 1580–1691.
- [15] D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* **2004**, *104*, 1383–1429.
- [16] a) S. Quideau, L. Pouységu, *Org. Prep. Proced. Int.* **1999**, *31*, 617–680; b) S. Quideau, L. Pouységu, D. Deffieux, *Synlett* **2008**, 467–495.
- [17] L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235–2261.
- [18] a) D. R. Boyd, N. D. Sharma, B. Byrne, M. V. Hand, J. F. Malone, G. N. Sheldrake, J. Blacker, H. Dalton, *J. Chem. Soc. Perkin Trans. I* **1998**, 1935–1943. For reviews on biocatalysis for oxidative enantioselective dearomatization, see: b) T. Hudlicky, D. Gonzalez, D. T. Gibson, *Aldrichimica Acta* **1999**, *32*, 35–62; c) T. Hudlicky, J. W. Reed, *Synlett* **2009**, 685–702.
- [19] D. M. Pinkerton, M. G. Banwell, A. C. Willis, *Org. Lett.* **2009**, *11*, 4290–4293.
- [20] a) L. N. Mander, S. G. Pyne, *J. Am. Chem. Soc.* **1979**, *101*, 3373–3375; b) L. N. Mander, *Acc. Chem. Res.* **1983**, *16*, 48–54; c) G. R. King, L. N. Mander, N. J. T. Monck, J. C. Morris, H. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3828–3829; d) B. Frey, A. P. Wells, D. H. Rogers, L. N. Mander, *J. Am. Chem. Soc.* **1998**, *120*, 1914–1915.
- [21] S. Levin, R. R. Nani, S. E. Reisman, *Org. Lett.* **2010**, *12*, 780–783.
- [22] a) P. A. Wender, J. J. Howbert, *J. Am. Chem. Soc.* **1981**, *103*, 688–690. For reviews about the dearomatizing cycloaddition of arenes, see: b) J. Cornélisse, *Chem. Rev.* **1993**, *93*, 615–669; c) N. Hoffmann, *Synthesis* **2004**, 481–495; d) D. Chappell, A. T. Russell, *Org. Biomol. Chem.* **2006**, *4*, 4409–4430; e) J. Mattay, *Angew. Chem.* **2007**, *119*, 674–677; *Angew. Chem. Int. Ed.* **2007**, *46*, 663–665.
- [23] a) T. Gaich, J. Mulzer, *J. Am. Chem. Soc.* **2009**, *131*, 452–453; b) T. Gaich, J. Mulzer, *Org. Lett.* **2010**, *12*, 272–275.
- [24] a) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356–363; b) A. I. Meyers, K. Higashiyama, *J. Org. Chem.* **1987**, *52*, 4592–4597; c) R. C. Andrews, S. J. Teague, A. I. Meyers, *J. Am. Chem. Soc.* **1988**, *110*, 7854–7858; d) A. J. Robichaud, A. I. Meyers, *J. Org. Chem.* **1991**, *56*, 2607–2609.
- [25] a) J. Clayden, F. E. Knowles, I. R. Baldwin, *J. Am. Chem. Soc.* **2005**, *127*, 2412–2413; For a review on intramolecular dearomatization through alkylation with nucleophilic anions, see: b) J. Clayden, M. N. Kenworthy, *Synthesis* **2004**, 1721–1736.
- [26] C. Ovens, N. G. Martin, D. J. Procter, *Org. Lett.* **2008**, *10*, 1441–1444.
- [27] M. C. Carreño, M. González-López, A. Urbano, *Angew. Chem.* **2006**, *118*, 2803–2807; *Angew. Chem. Int. Ed.* **2006**, *45*, 2737–2741.
- [28] S. Barradas, M. C. Carreño, M. González-López, A. Latorre, A. Urbano, *Org. Lett.* **2007**, *9*, 5019–5022.
- [29] a) C. Cox, S. J. Danishefsky, *Org. Lett.* **2000**, *2*, 3493–3496; b) J. L. Wood, J. K. Graeber, J. T. Njardarson, *Tetrahedron* **2003**, *59*, 8855–8858; c) A. Bérubé, I. Drutu, J. L. Wood, *Org. Lett.* **2006**, *8*, 5421–5424; d) J. G. M. Morton, L. D. Kwon, J. D. Freeman, J. T. Njardarson, *Synlett* **2009**, 23–27.
- [30] F. Li, S. S. Tartakoff, S. L. Castle, *J. Am. Chem. Soc.* **2009**, *131*, 6674–6675.
- [31] S. Quideau, M. Lebon, A.-M. Lamidey, *Org. Lett.* **2002**, *4*, 3975–3978.
- [32] J. L. Frie, C. S. Jeffrey, E. J. Sorensen, *Org. Lett.* **2010**, *12*, 5394–5397.
- [33] a) B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh, M. A. Ciufolini, *Org. Lett.* **2009**, *11*, 1539–1542; b) B. A. Mendelsohn, M. A. Ciufolini, *Org. Lett.* **2009**, *11*, 4736–4739.
- [34] S. Quideau, I. Fabre, D. Deffieux, *Org. Lett.* **2004**, *6*, 4571–4573.
- [35] a) R. W. Van De Water, C. Hoarau, T. R. R. Pettus, *Tetrahedron Lett.* **2003**, *44*, 5109–5113; b) L. H. Mejorado, C. Hoarau, T. R. R. Pettus, *Org. Lett.* **2004**, *6*, 1535–1538; c) C. Hoarau, T. R. R. Pettus, *Org. Lett.* **2006**, *8*, 2843–2846; d) T. A. Wenderski, S. Huang, T. R. R. Pettus, *J. Org. Chem.* **2009**, *74*, 4104–4109.
- [36] L. H. Mejorado, T. R. R. Pettus, *J. Am. Chem. Soc.* **2006**, *128*, 15625–15631.
- [37] L. Pouységu, S. Chassaing, D. Dejugnac, A.-M. Lamidey, K. Miqueu, J.-M. Sotiropoulos, S. Quideau, *Angew. Chem.* **2008**, *120*, 3608–3611; *Angew. Chem. Int. Ed.* **2008**, *47*, 3552–3555.
- [38] a) J. Zhu, N. P. Grigoriadis, J. P. Lee, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 9342–9343; b) J. Zhu, J. A. Porco, Jr., *Org. Lett.* **2006**, *8*, 5169–5171.
- [39] For select examples of soft nucleophiles used in oxidative dearomatization, see: a) M. Ousmer, N. A. Braun, M. A. Ciufolini, *Org. Lett.* **2001**, *3*, 765–767; b) See also Ref. [33b]; c) H. Liang, M. A. Ciufolini, *Org. Lett.* **2010**, *12*, 1760–1763; For a review of nitrogen nucleophiles in oxidative dearomatization, see: d) M. A. Ciufolini, N. A. Braun, S. Canesi, M. Ousmer, J. Chang, D. Chai, *Synthesis* **2007**, 3759–3772.
- [40] For recent examples of oxidative dearomatization with C–C bond formation, see: a) J. S. Swenton, A. Callinan, Y. Chen, J. J. Rohde, M. L. Kearns, G. W. Morrow, *J. Org. Chem.* **1996**, *61*, 1267–1274; b) H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, Y. Kiyono, M. Egi, Y. Kita, *J. Am. Chem. Soc.* **2003**, *125*,

- 11235–11240; c) A. Ozanne-Beaudenon, S. Quideau, *Angew. Chem.* **2005**, *117*, 7227–7231; *Angew. Chem. Int. Ed.* **2005**, *44*, 7065–7069; d) T. Honda, H. Shigehisa, *Org. Lett.* **2006**, *8*, 657–659; e) H. Shigehisa, J. Takayama, T. Honda, *Tetrahedron Lett.* **2006**, *47*, 7301–7306; f) K. C. Nicolaou, U. Majumder, S. P. Roche, D. Y.-K. Chen, *Angew. Chem.* **2007**, *119*, 4799–4802; *Angew. Chem. Int. Ed.* **2007**, *46*, 4715–4718; g) K. C. Guérard, C. Sabot, L. Racicot, S. J. Canesi, *J. Org. Chem.* **2009**, *74*, 2039–2045; h) K. Eastman, P. S. Baran, *Tetrahedron* **2009**, *65*, 3149–3154.
- [41] T. Dohi, Y. Minamitsuji, A. Maruyama, S. Hirose, Y. Kita, *Org. Lett.* **2008**, *10*, 3559–3562.
- [42] K. C. Nicolaou, D. J. Edmonds, A. Li, G. S. Tria, *Angew. Chem.* **2007**, *119*, 4016–4019; *Angew. Chem. Int. Ed.* **2007**, *46*, 3942–3945.
- [43] a) S. Quideau, M. A. Looney, L. Pouységu, *Org. Lett.* **1999**, *1*, 1651–1654; b) S. Quideau, L. Pouységu, M. Oxoby, M. A. Looney, *Tetrahedron* **2001**, *57*, 319–329; c) C. Sabot, B. Commare, M.-A. Duceppe, S. Nahi, K. C. Guérard, S. Canesi, *Synlett* **2008**, 3226–3230; d) C. Sabot, K. C. Guérard, S. Canesi, *Chem. Commun.* **2009**, 2941–2943.
- [44] S. A. Snyder, T. C. Sherwood, A. G. Ross, *Angew. Chem.* **2010**, *122*, 5272–5276; *Angew. Chem. Int. Ed.* **2010**, *49*, 5146–5150.
- [45] a) S. Masamune, *J. Am. Chem. Soc.* **1961**, *83*, 1009–1010; b) D. L. Boger, K. Machiya, *J. Am. Chem. Soc.* **1992**, *114*, 10056–10058; c) G. Lalic, E. J. Corey, *Org. Lett.* **2007**, *9*, 4921–4923.
- [46] M. Dai, S. J. Danishefsky, *Tetrahedron Lett.* **2008**, *49*, 6610–6612.
- [47] N. A. McGrath, E. S. Bartlett, S. Sittihan, J. T. Njardarson, *Angew. Chem.* **2009**, *121*, 8695–8698; *Angew. Chem. Int. Ed.* **2009**, *48*, 8543–8546.
- [48] J. Qi, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 12682–12683.
- [49] B. Mitasev, J. A. Porco, Jr., *Org. Lett.* **2009**, *11*, 2285–2288.
- [50] D. R. Siegel, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 1048–1049.
- [51] a) J. Borgulya, H. J. Hansen, R. Barner, H. Schmid, *Helv. Chim. Acta* **1963**, *46*, 2444–2445; b) T. Satoh, M. Ikeda, M. Miura, M. Nomura, *J. Org. Chem.* **1997**, *62*, 4877–4879.
- [52] a) E. J. Tisdale, C. Chowdhury, B. G. Vong, H. Li, E. A. Theodorakis, *Org. Lett.* **2002**, *4*, 909–912; b) E. J. Tisdale, B. G. Vong, H. Li, S. H. Kim, C. Chowdhury, E. A. Theodorakis, *Tetrahedron* **2003**, *59*, 6873–6887; c) E. J. Tisdale, I. Slobodov, E. A. Theodorakis, *Org. Biomol. Chem.* **2003**, *1*, 4418–4422; d) For review on caged *Garcinia xanthones*, see: O. Chantarasriwong, A. Batova, W. Chavasiri, E. A. Theodorakis, *Chem. Eur. J.* **2010**, *16*, 9944–9962.
- [53] E. J. Tisdale, I. Slobodov, E. A. Theodorakis, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12030–12035.
- [54] K. C. Nicolaou, X. Hao, M. Wartmann, *Angew. Chem.* **2005**, *117*, 766–771; *Angew. Chem. Int. Ed.* **2005**, *44*, 756–761.
- [55] a) D. Hilvert, K. D. Nared, *J. Am. Chem. Soc.* **1988**, *110*, 5593–5594; b) V. E. Gouverneur, K. N. Houk, B. de Pascual-Teresa, B. Beno, K. D. Janda, R. A. Lerner, *Science* **1993**, *262*, 204–208; c) Y. M. Chook, J. V. Gray, H. Ke, W. N. Lipscomb, *J. Mol. Biol.* **1994**, *240*, 476–500; d) A. Y. Lee, P. A. Karplus, B. Ganem, J. Clardy, *J. Am. Chem. Soc.* **1995**, *117*, 3627–3628.
- [56] A. E. Hayden, X. Hao, K. C. Nicolaou, K. N. Houk, *Org. Lett.* **2006**, *8*, 2989–2992.
- [57] a) E. M. Stocking, R. M. Williams, *Angew. Chem.* **2003**, *115*, 3186–3223; *Angew. Chem. Int. Ed.* **2003**, *42*, 3078–3115; b) T. Ose, K. Watanabe, T. Mie, M. Honma, H. Watanabe, M. Yao, H. Oikawa, I. Tanaka, *Nature* **2003**, *422*, 185–189; c) K. Auclair, A. Sutherland, J. Kennedy, D. J. Witter, J. P. Van den Heever, C. R. Hutchinson, J. C. Vederas, *J. Am. Chem. Soc.* **2000**, *122*, 11519–11520; d) H. Oikawa, T. Kobayashi, K. Katayama, Y. Suzuki, A. Ichihara, *J. Org. Chem.* **1998**, *63*, 8748–8756; For a review on biomimetic Diels–Alder reaction, see: e) U. Pindur, G. H. Schneider, *Chem. Soc. Rev.* **1994**, *23*, 409–415.
- [58] a) X. Fu, M. B. Hossain, F. J. Schmitz, D. van der Helm, *J. Org. Chem.* **1997**, *62*, 3810–3819; b) X. Fu, M. B. Hossain, D. Van der Helm, F. J. Schmitz, *J. Am. Chem. Soc.* **1994**, *116*, 12125–12126.
- [59] a) M. E. Layton, C. A. Morales, M. D. Shair, *J. Am. Chem. Soc.* **2002**, *124*, 773–775; b) C. A. Morales, M. E. Layton, M. D. Shair, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12036–12041.
- [60] K. C. Nicolaou, G. Vassilikogiannakis, W. Mägerlein, R. Kranich, *Angew. Chem.* **2001**, *113*, 2543–2547; *Angew. Chem. Int. Ed.* **2001**, *40*, 2482–2486.
- [61] a) T. J. Heckrodt, J. Mulzer, *J. Am. Chem. Soc.* **2003**, *125*, 4680–4681; For similar strategy using a different oxidative dearomatization, see b) N. Waizumi, A. R. Stankovic, V. H. Rawal, *J. Am. Chem. Soc.* **2003**, *125*, 13022–13023.
- [62] For a review concerning oxidative dearomatization/IMDA cascade sequences, see: a) C.-C. Liao, R. K. Peddiniti, *Acc. Chem. Res.* **2002**, *35*, 856–866; b) C.-C. Liao, *Pure Appl. Chem.* **2005**, *77*, 1221–1234.
- [63] D.-S. Hsu, C.-C. Liao, *Org. Lett.* **2007**, *9*, 4563–4565.
- [64] S. P. Cook, A. Polara, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 16440–16441.
- [65] P. J. Krawczuk, N. Schöne, P. S. Baran, *Org. Lett.* **2009**, *11*, 4774–4776.
- [66] For recent examples of the Wessely oxidation, see: G. Mehta, P. Maity, *Tetrahedron Lett.* **2007**, *48*, 8865–8868; also see references [7] and [28a].
- [67] S. A. Snyder, F. Kontes, *J. Am. Chem. Soc.* **2009**, *131*, 1745–1752.
- [68] J. Gagnepain, R. Méreau, D. Dejugnac, J.-M. Léger, F. Castet, D. Deffieux, L. Pouységu, S. Quideau, *Tetrahedron* **2007**, *63*, 6493–6505.
- [69] S. Dong, E. Hamel, R. Bai, D. G. Covell, J. A. Beutler, J. A. Porco, Jr., *Angew. Chem.* **2009**, *121*, 1522–1525; *Angew. Chem. Int. Ed.* **2009**, *48*, 1494–1497.
- [70] For select recent examples of furan dearomatization through Diels–Alder cycloaddition, see: a) T. Matsumoto, T. Sohma, H. Yamaguchi, S. Kurata, K. Suzuki, *Synlett* **1995**, 263–265; b) D. E. Kaelin, Jr., O. D. Lopez, S. F. Martin, *J. Am. Chem. Soc.* **2001**, *123*, 6937–6938; c) A. Toró, P. Deslongchamps, *J. Org. Chem.* **2003**, *68*, 6847–6852; d) M. Dadwal, M. K. Kesharwani, V. Danayak, B. Ganguly, S. M. Mobin, R. Murganatham, I. N. N. Namboothiri, *Eur. J. Org. Chem.* **2008**, 6106–6118; e) F. I. Zubkov, J. D. Ershova, A. A. Orlova, V. P. Zaytsev, E. V. Nikitina, A. S. Peregudov, A. V. Gurbanov, R. S. Borisov, V. N. Khrustalev, A. M. Maharramov, A. V. Varlamov, *Tetrahedron* **2009**, *65*, 3789–3803; f) P. Magnus, R. Littich, *Org. Lett.* **2009**, *11*, 3938–3941.
- [71] For recent examples of the photoxidative dearomatization of furan in total synthesis, see: a) G. Vassilikogiannakis, M. Stratakis, *Angew. Chem.* **2003**, *115*, 5623–5626; *Angew. Chem. Int. Ed.* **2003**, *42*, 5465–5468; b) G. Vassilikogiannakis, I. Margaros, T. Montagnon, *Org. Lett.* **2004**, *6*, 2039–2042; c) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, K. Tanino, *Science* **2004**, *305*, 495–499; d) F. Yoshimura, M. Sasaki, I. Hattori, K. Komatsu, M. Sakai, K. Tanino, M. Miyashita, *Chem. Eur. J.* **2009**, *15*, 6626–6644.
- [72] For recent examples of the dearomatization of 2-silyloxyfuran to generate butenolides, see: a) J. Burghart, R. Brückner, *Angew. Chem.* **2008**, *120*, 7777–7782; *Angew. Chem. Int. Ed.* **2008**, *47*, 7664–7668; b) B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem.* **2009**, *121*, 4413–4417; *Angew. Chem. Int. Ed.* **2009**, *48*, 4349–4353.
- [73] For a review on Pummerer/Diels–Alder cascade reactions highlighting furan dearomatization, see: a) A. Padwa, *Chem.*

- Commun.* **1998**, 1417–1424; b) S. K. Bur, A. Padwa, *Chem. Rev.* **2004**, *104*, 2401–2432.
- [74] a) J. D. Ginn, S. M. Lynch, A. Padwa, *Tetrahedron Lett.* **2000**, *41*, 9387–9391; b) S. K. Bur, S. M. Lynch, A. Padwa, *Org. Lett.* **2002**, *4*, 473–476; c) H. Zhang, J. Boonsombat, A. Padwa, *Org. Lett.* **2007**, *9*, 279–282.
- [75] J. D. Ginn, A. Padwa, *Org. Lett.* **2002**, *4*, 1515–1517.
- [76] W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2008**, *130*, 300–308.
- [77] For recent examples of benzofuran dearomatization using Diels–Alder cycloaddition, see: a) C.-H. Chen, P. D. Rao, C.-C. Liao, *J. Am. Chem. Soc.* **1998**, *120*, 13254–13255; b) A. Marrocchi, L. Minuti, A. Taticchi, H. W. Scheeren, *Tetrahedron* **2001**, *57*, 4959–4965; c) S. France, J. Boonsombat, C. A. Leverett, A. Padwa, *J. Org. Chem.* **2008**, *73*, 8120–8123; For recent examples of indole dearomatization using Diels–Alder cycloaddition, see: d) S. Kobayashi, T. Ueda, T. Fukuyama, *Synlett* **2000**, 883–886; e) S. L. Crawley, R. L. Funk, *Org. Lett.* **2003**, *5*, 3169–3171; For the catalytic enantioselective dearomatization of indole through the Diels–Alder cycloaddition, see: f) C. Gioia, L. Bernardi, A. Ricci, *Synthesis* **2010**, 161–170.
- [78] G. Stork, A. Yamashita, J. Adams, G. R. Schulte, R. Chesworth, Y. Miyazaki, J. J. Farne, *J. Am. Chem. Soc.* **2009**, *131*, 11402–11406.
- [79] For review on the electrochemistry of furans, see: a) J. B. Sperry, D. L. Wright, *Chem. Soc. Rev.* **2006**, *35*, 605–621; b) K. D. Moeller, *Synlett* **2009**, 1208–1218.
- [80] C. C. Hughes, A. K. Miller, D. Trauner, *Org. Lett.* **2005**, *7*, 3425–3428.
- [81] For use of nitrogen-stabilized oxyallyl cations in [4+3] cycloadditions, see: a) M. A. Walters, H. R. Arcand, *J. Org. Chem.* **1996**, *61*, 1478–1486; b) D. I. MaGee, E. Godineau, P. D. Thornton, M. A. Walters, D. J. Sponholtz, *Eur. J. Org. Chem.* **2006**, 3667–3680; For the use of oxyallyl cations in stereoselective [4+3] cycloadditions, see: c) M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058–2059; d) J. Huang, R. P. Hsung, *J. Am. Chem. Soc.* **2005**, *127*, 50–51.
- [82] J. E. Antoline, R. P. Hsung, J. Huang, Z. Song, G. Li, *Org. Lett.* **2007**, *9*, 1275–1278.
- [83] a) T. Hintermann, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 2093–2121; b) C. Gaul, D. Seebach, *Org. Lett.* **2000**, *2*, 1501–1504.
- [84] a) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2004**, *126*, 7450–7451; b) P. S. Baran, C. A. Guerrero, B. D. Hafenstein, N. B. Ambhaikar, *Angew. Chem.* **2005**, *117*, 3960–3963; *Angew. Chem. Int. Ed.* **2005**, *44*, 3892–3895; c) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404–408.
- [85] a) P. S. Baran, R. A. Shenvi, C. A. Mitsos, *Angew. Chem.* **2005**, *117*, 3780–3783; *Angew. Chem. Int. Ed.* **2005**, *44*, 3714–3717; b) P. S. Baran, R. A. Shenvi, *J. Am. Chem. Soc.* **2006**, *128*, 14028–14029.
- [86] D. B. C. Martin, C. D. Vanderwal, *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.
- [87] For a recent example of the ring-opening of a pyridinium with a secondary amine, see: S. E. Steinhardt, J. S. Silverston, C. D. Vanderwal, *J. Am. Chem. Soc.* **2008**, *130*, 7560–7561.
- [88] a) L. Turet, I. E. Markó, B. Tinant, J.-P. Declercq, R. Touillaux, *Tetrahedron Lett.* **2002**, *43*, 6591–6595; b) N. Heureux, J. Wouters, I. E. Markó, *Org. Lett.* **2005**, *7*, 5245–5248.
- [89] S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606–13607.
- [90] a) G. D. Wilkie, G. I. Elliott, B. S. J. Blagg, S. E. Wolkenberg, D. R. Soenen, M. M. Miller, S. Pollack, D. L. Boger, *J. Am. Chem. Soc.* **2002**, *124*, 11292–11294; b) G. I. Elliott, J. R. Fuchs, B. S. J. Blagg, H. Ishikawa, H. Tao, Z.-Q. Yuan, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 10589–10595; c) D. Kato, Y. Sasaki, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 3685–3687; For a review on the HDA reaction showing the utility of nitrogen extrusion, see: d) D. L. Boger, *Chem. Rev.* **1986**, *86*, 781–793; For seminal work on HDA reactions with indole triggering nitrogen extrusion, see: e) S. C. Benson, L. Lee, L. Yang, J. K. Snyder, *Tetrahedron* **2000**, *56*, 1165–1180.
- [91] E. L. Campbell, A. M. Zuhl, C. M. Liu, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 3009–3012.
- [92] a) C. Li, C. Chan, A. C. Heimann, S. J. Danishefsky, *Angew. Chem.* **2007**, *119*, 1466–1469; *Angew. Chem. Int. Ed.* **2007**, *46*, 1444–1447; b) C. Li, C. Chan, A. C. Heimann, S. J. Danishefsky, *Angew. Chem.* **2007**, *119*, 1470–1472; *Angew. Chem. Int. Ed.* **2007**, *46*, 1448–1450; c) J. D. Trzuppek, D. Lee, B. M. Crowley, V. M. Marathias, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 8506–8512.
- [93] For a recent example of pyridinium dearomatization, see: a) C. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2003**, *125*, 6360–6361; b) G. Arnott, H. Brice, J. Clayden, E. Blaney, *Org. Lett.* **2008**, *10*, 3089–3092; c) G. Barbe, G. Pelletier, A. B. Charette, *Org. Lett.* **2009**, *11*, 3398–3401; d) J. J. Mousseau, A. Fortier, A. B. Charette, *Org. Lett.* **2010**, *12*, 516–519; For reviews about pyridinium dearomatization, see: e) R. Lavilla, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1141–1156; f) D. L. Comins, *J. Heterocycl. Chem.* **1999**, *36*, 1491–1500.
- [94] For example of enantioselective pyridinium/isoquinolinium dearomatization, see: a) K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 6212–6217; *Angew. Chem. Int. Ed.* **2005**, *44*, 6058–6063; b) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 6858–6862; *Angew. Chem. Int. Ed.* **2005**, *44*, 6700–6704; c) Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, *129*, 6686–6687.
- [95] J. T. Kuethe, D. L. Comins, *J. Org. Chem.* **2004**, *69*, 5219–5231.
- [96] a) D. L. Comins, H. Hong, *J. Am. Chem. Soc.* **1993**, *115*, 8851–8852; b) D. L. Comins, H. Hong, *J. Org. Chem.* **1993**, *58*, 5035–5036; c) D. L. Comins, J. T. Kuethe, H. Hong, F. J. Lakner, *J. Am. Chem. Soc.* **1999**, *121*, 2651–2652; d) D. L. Comins, J. J. Sahn, *Org. Lett.* **2005**, *7*, 5227–5228.
- [97] G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 13873–13875.
- [98] a) A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf, J. Martel, *J. Am. Chem. Soc.* **2001**, *123*, 11829–11830; b) A. Lemire, M. Grenon, M. Pourashraf, A. B. Charette, *Org. Lett.* **2004**, *6*, 3517–3520; c) T. Focken, A. B. Charette, *Org. Lett.* **2006**, *8*, 2985–2988.
- [99] a) A. P. Kozikowski, G. L. Araldi, R. G. Ball, *J. Org. Chem.* **1997**, *62*, 503–509; b) M. J. Sung, H. I. Lee, Y. Chong, J. K. Cha, *Org. Lett.* **1999**, *1*, 2017–2019; For a review on oxidopyridinium dearomatization, see: c) K. V. Radhakrishnan, *Top. Heterocycl. Chem.* **2008**, *13*, 71–98.
- [100] a) K. M. Peese, D. Y. Gin, *Org. Lett.* **2005**, *7*, 3323–3325; b) K. M. Peese, D. Y. Gin, *J. Am. Chem. Soc.* **2006**, *128*, 8734–8735.
- [101] For recent and innovative examples of transition-metal-catalyzed dearomatization, see: a) F. C. Pigge, J. J. Coniglio, R. Dalvi, *J. Am. Chem. Soc.* **2006**, *128*, 3498–3499; b) S. Lavy, A. Pérez-Luna, E. P. Kündig, *Synlett* **2008**, 2621–2624; c) Y. Lian, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 440–441; d) M. R. Fructos, E. Álvarez, M. M. Díaz-Requejo, P. J. Pérez, *J. Am. Chem. Soc.* **2010**, *132*, 4600–4607.
- [102] For selected examples of π -basic dearomatizing agents, see: a) M. D. Chordia, W. D. Harman, *J. Am. Chem. Soc.* **2000**, *122*, 2725–2736; b) S. M. Stokes, Jr., F. Ding, P. L. Smith, J. M. Keane, M. E. Kopach, R. Jarvis, M. Sabat, W. D. Harman, *Organometallics* **2003**, *22*, 4170–4171; c) E. C. Lis, Jr., R. J. Salomon, M. Sabat, W. H. Myers, W. D. Harman, *J. Am. Chem. Soc.* **2008**, *130*, 12472–12476; For a recent review on this topic, see: d) For a recent review on this topic, see Ref. [14d].

- [103] a) M. Bao, H. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 759–760; b) S. Lu, Z. Xu, M. Bao, Y. Yamamoto, *Angew. Chem.* **2008**, *120*, 4438–4441; *Angew. Chem. Int. Ed.* **2008**, *47*, 4366–4369; For DFT calculations on palladium-catalyzed dearomatization, see: c) A. Ariafard, Z. Lin, *J. Am. Chem. Soc.* **2006**, *128*, 13010–13016.
- [104] N. Kagawa, J. P. Malerich, V. H. Rawal, *Org. Lett.* **2008**, *10*, 2381–2384.
- [105] J. García-Fortanet, F. Kessler, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 6676–6677.
- [106] T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, *Angew. Chem.* **2008**, *120*, 3847–3850; *Angew. Chem. Int. Ed.* **2008**, *47*, 3787–3790.
- [107] M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem.* **2010**, *122*, 2221–2223; *Angew. Chem. Int. Ed.* **2010**, *49*, 2175–2177.
- [108] S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénédé, *Angew. Chem.* **2009**, *121*, 4675–4679; *Angew. Chem. Int. Ed.* **2009**, *48*, 4605–4609.
- [109] a) U. Ladziata, A. Y. Kuposov, K. Y. Lo, J. Willging, V. N. Nemykin, V. V. Zhdankin, *Angew. Chem.* **2005**, *117*, 7289–7293; *Angew. Chem. Int. Ed.* **2005**, *44*, 7127–7131; b) U. Ladziata, J. Willging, V. V. Zhdankin, *Org. Lett.* **2006**, *8*, 167–170.
- [110] J. K. Boppisetti, V. B. Birman, *Org. Lett.* **2009**, *11*, 1221–1223.
- [111] a) M. Breuning, E. J. Corey, *Org. Lett.* **2001**, *3*, 1559–1562; b) R. Imbos, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 184–185.
- [112] a) Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553; b) Q. Liu, T. Rovis, *Org. Process Res. Dev.* **2007**, *11*, 598–604.
- [113] N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404–405.
- [114] Q. Gu, Z.-Q. Rong, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 4056–4057.
-