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ARTICLE

Dearomative Logic in Natural Product Total Synthesis

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The natural world is a prolific source of some of the most interesting, rare, and complex molecules known, harnessing sophisticated biosynthetic machinery evolved over billions of years for their production. Many of these natural products represent high-value targets of total synthesis, either for their desirable biological activities or for their beautiful structures outright; yet, the high sp^3-character often present in nature's molecules imparts significant topological complexity that pushes the limits of contemporary synthetic technology. Dearomatization is a foundational strategy for generating such intricacy from simple materials that has undergone considerable maturation in recent years. This review highlights the recent achievements in the field of dearomative methodology, with a focus on natural product total synthesis and retrosynthetic analysis. Disconnection guidelines and a three-phase dearomative logic are described, and a spotlight is given to nature's use of dearomatization in the biosynthesis of various classes of natural products. Synthetic studies from 2011 to 2021 are reviewed, and 425 references are cited.

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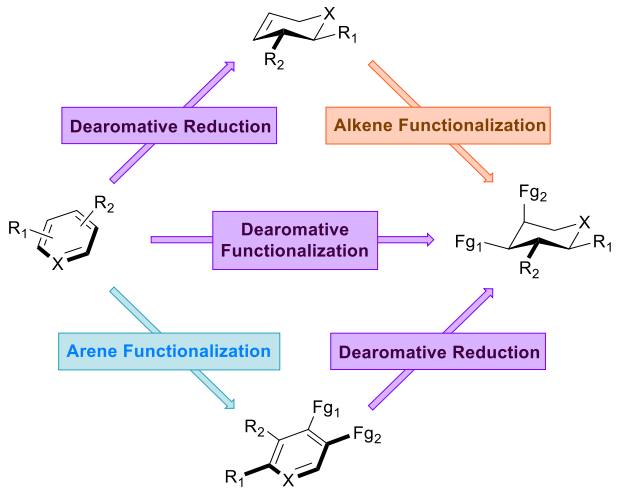


Figure 1. Dearomatization as a means to generate complex carbocycles.

Introduction

Although once fixated on complex molecule structure elucidation and the exploration of synthetic feasibility, the objectives of natural product total synthesis have evolved recently under increased pressure for utility, efficiency, and novel reactivity.[1-4] Simultaneously, organic synthesis has infiltrated other fields such as chemical biology, drug development, agriculture, food science, cosmetics and fragrances, alternative energy, microelectronics, and materials science, providing crucial support and molecular tools for interdisciplinary research with extraordinary societal impact.[5] The need for practical and scalable approaches to complex molecules is apparent,[6] both in support of these other areas as well as in its own right as the field of organic synthesis continues to mature.[7]

Questions of structure and reactivity notwithstanding, today's synthetic chemists are primarily concerned with the assembly of molecules possessing desirable properties and functions,[8] which, in the area of natural product total synthesis, lie almost exclusively within the vast realm of molecular recognition and its influence upon a biological system. The well-established correlation between structural complexity and biological activity demands synthetic chemists to construct highly saturated molecular architectures that encompass intricate systems of fused or caged rings, numerous and often contiguous stereogenic centers, and a diverse assortment of correctly placed functional groups.[9,10] Although history has shown that synthetic chemists can access such intricate structures quite well, doing so in a practical and efficient manner remains a challenge. The continuous development of modern methods has fueled the emergence of distinct strategies that can address these limitations.[11] The aim of the present review is to reiterate the value of disconnections-based retrosynthetic analysis[12] through the widening lens of dearomative chemistry, a powerful, complexity-generating tactic that has gained traction in recent years due to significant advancements in methodology.[13-18]

Dearomative Logic in Retrosynthetic Analysis

Given the ubiquity of cyclic motifs within natural products, drugs, and other fine chemicals, the case for dearomative strategy in total synthesis can be stated quite clearly: it is often much easier and more efficient to acquire, manipulate, and then dearomatize arenes than it is to selectively functionalize cyclohexane derivatives or build them *de novo* (Figure 1). Simple aromatics are produced on hundred-million-ton scales annually and are some of the most inexpensive and abundant feedstock chemicals accessible; the robust methods available for their elaboration—including nucleophilic and electrophilic aromatic substitutions, condensations, directed *ortho*- metalation, aryne functionalizations, and cross-couplings—are considered to be so classical that they constitute the largest sections of organic chemistry textbooks as well as the bulk of synthetic research published to date.[19] Arene functionalization is so well-developed as to make possible the synthesis of nearly every conceivable substitution pattern on a benzene ring.

Furthermore, the chemistry used to modify aromatic rings is often orthogonal to that used for saturated systems. Sufficiently advanced sp^3 C–H activation methods may someday trivialize the construction and functionalization of saturated natural product scaffolds, and many admirable efforts have been made in this field,[20-25] but until such technology reaches its pinnacle, synthetic chemists must rely upon the use of pre-functionalized building blocks to forge the requisite bonds of a particular natural product. By their very nature, arenes have embedded within them considerable synthetic potential; with benzene derivatives, for example, a chemist can perform up to three separate transformations and bond-forming events *en route* to a decorated cyclohexane ring—provided that the first encompass an olefin-like

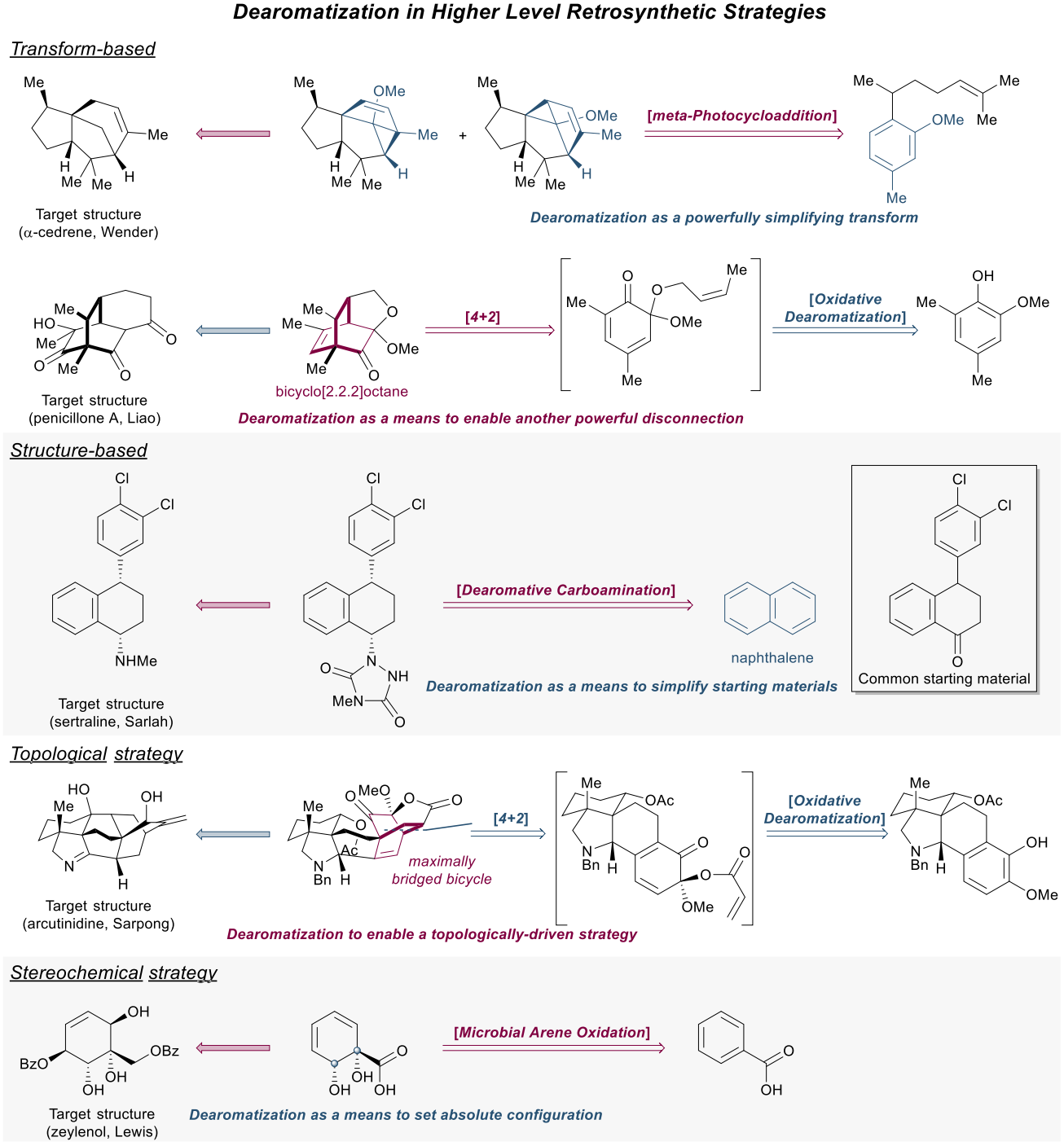


Figure 2. Applications of dearomative logic in high-level retrosynthetic strategies.

dearomatization. In asymmetric dearomative processes, aromatic rings provide an exponentially greater number of potential chiral compounds than any other class of prochiral substrates. Recently, tremendous advancements have been made in dearomative methodology, increasing the scope and sophistication of building blocks available from feedstock arenes. The rapid generation of complexity from simplicity through dearomative strategies allows us to postulate that this approach will find increased usage as chemists continue to place greater emphasis on efficiency and practicality in total synthesis.[26]

Disconnection Guidelines

Dearomative logic can be used to complement most retrosynthetic strategies (Figure 2).[12] Within transform-based approaches, dearomatization itself can function as powerfully simplifying transform when associated with concomitant C–C or C–X bond disconnection, exemplified by Wender's use of the arene-alkene meta-photocycloaddition in his total synthesis of α–cedrene.[27] Dearomatization can also serve as a means to obtain the precursors for other powerful complexity-generating transformations, such as cyclohexenones for conjugate addition or cyclohexa-1,3-dienes for subsequent [4+2] cycloaddition. Liao's synthesis of penicillone A[28] serves to illustrate nicely this tactic that has been used quite frequently in the construction of the bicyclo[2.2.2]octane scaffold. In structure-goal strategies, dearomative transforms can quickly simplify dense, three-dimensional structures into cheap and readily available aromatic compounds, desirable starting materials with the proper carbon count. In Sarlah's synthesis of the blockbuster antidepressant sertraline, an asymmetric dearomative carboamination imprints all necessary functionality, with proper stereochemistry, directly onto the feedstock chemical naphthalene.[29] Topological and network-guided analyses of intricate polycyclic and caged ring systems often dictate strategic bond disconnections that generate retrons for dearomative transforms, simplifying that particular ring even further.[30] This approach is showcased in Sarpong's syntheses of diterpenoid alkaloids like arcutinidine.[31] Finally, dearomative transformations can be used to great advantage in stereochemical strategies, both to control relative stereochemistry, such as the use of arene hydrogenation to obtain an all-*cis* relationship for substituents within a cyclohexane ring, as well as to establish absolute stereochemistry (e.g., through asymmetric hydrogenation of heteroarenes[32] or microbial arene oxidations,[33] as in Lewis's synthesis of zeylenol[34]).

Within the framework of a dearomative retrosynthetic logic, there are three fundamental stages in which the decoupled chemistries of aromatics and aliphatics and the practicality of dearomatization can be put to good use (Figure 3). The first phase (denoted in orange) requires the application of any transform on a cyclic system that produces either a full or partial dearomative retron. In many cases this may simply entail a hydrogenation; when possible, however, it is highly strategic to disconnect C–C and C–X bonds that can be formed from the unsaturation left behind after the dearomative event. Typical examples

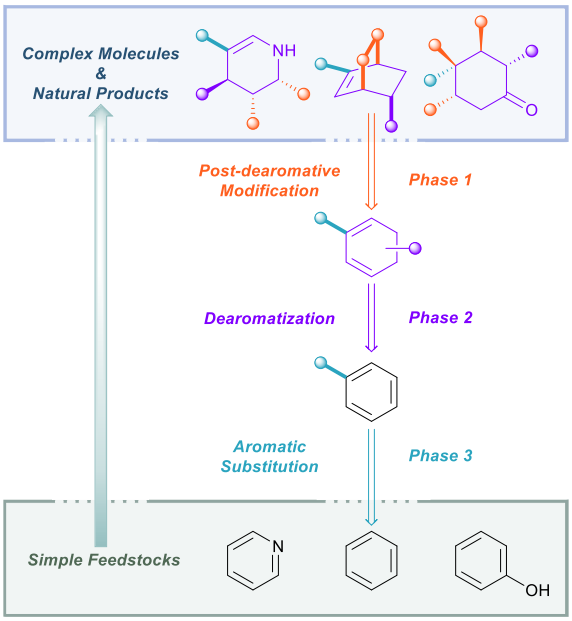


Figure 3. Three phases of dearomative retrosynthetic logic.

of this include olefin functionalizations, β-functionalization of cyclohexenones through conjugate addition, and cycloadditions. When intramolecular, the latter two transformations can often be achieved concurrently with dearomatization, resulting in dramatic cascade reactions or one-pot processes.[35] In this context, one may also consider conformational changes brought on through dearomatization that may facilitate other intramolecular processes (e.g., lactamization in Stoltz's jorumycin synthesis, *vide infra*).

The second stage of dearomative analysis, depicted in purple, concerns the dearomative event itself. This of course depends entirely upon the retron generated during the first phase. There may arise situations in which several dearomative retrons could be generated from a single intermediate, and therefore several dearomative processes may be possible. In these cases, one must judge the dearomative and post-dearomative transformations and prioritize the route with the most structurally simplifying disconnection, whether this encompasses the formation of an important C–C bond or the establishment of a critical stereoenter.

Dearomative transforms bridge the gap between the orthogonal realms of arene chemistry and aliphatic/olefin chemistry. Thus, the third and final stage of dearomative logic (marked in light blue) regards those bonds that may be easily formed on an aromatic precursor, but which would be extremely challenging to install directly on an aliphatic system. This tactic is especially useful for constructing C–C and

C–X bonds attached to sp^3 carbons that are distal to other functional groups in the target structure. In this phase, it is important to keep in mind the availability and cost of variously substituted aromatic starting materials so that a balance may be struck between substituents that are more efficient to "buy" and those that are more practical to build through EAS or cross coupling.

The remainder of this review is devoted to the exhibition of outstanding applications of dearomative logic in the total synthesis of natural products. We have restrained ourselves to showcase examples primarily from the past decade, as an excellent review on this topic was published in 2011.[36] Readers interested in earlier cases of dearomatization in total synthesis are highly encouraged to see this work, as well as others.[37-40]

Applications of Dearomative Logic in Natural Product Total Synthesis

Terpenes

***ent*-Kaurene diterpenoids:** Leaves and extracts from the *Isodon* (mint) family of plants were prized in ancient Chinese and Japanese folk medicine for their antibacterial, anticancer, anthelmintic, stomachic, and anti-inflammatory properties.[41-43] Many of these herbal remedies are still in use today. Modern isolation studies revealed that many of these plants are prodigious sources of biologically active terpenoids; their *ent*-kaurene diterpenoids, in particular, possess excellent antibacterial and antitumor pharmacological profiles (Figure 4a). Notable examples include the potent, gram-positive antibiotic platensimycin (**1**), first reported by Merck in 2006, which inhibits type II bacterial fatty acid synthesis and shows no cross-resistance to any other strains of antibiotic-resistant bacteria,[44-46] as well as oridonin (**2**), the major component of *Rabdosia rubescens* (donglingcao), a Chinese anti-inflammatory herbal remedy.[47-49] Compound **2** has shown great promise for the treatment of a variety of cancers, and its analogue HAO472 (not shown) has recently entered a phase I clinical trial in China for acute myeloid leukemia.[50] With their characteristic bicyclo[3.2.1]octene core embedded within a precisely oxidized hydrocarbon skeleton, the *ent*-kaurene diterpenoids pose a significant challenge for synthetic chemists, and at present only a handful of these natural products have succumbed to total synthesis.[42,51,52] Nonetheless, the incipient medicinal properties of furnished *ent*-kaurene diterpenoids such as **2-4,** and of their even further decorated seco-*ent*-kaurenoids like **1**, **5**, and **6**, have in

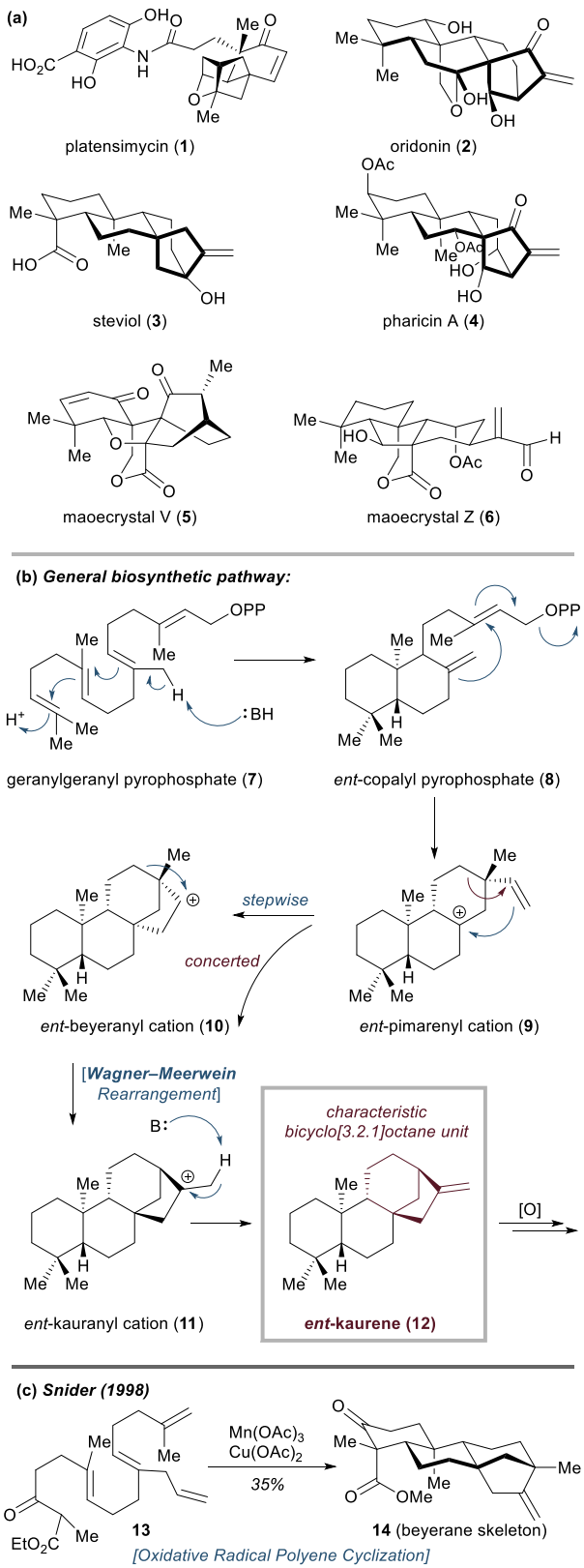


Figure 4. Structures, biosynthesis, and early synthetic work on *ent*-kaurenes.

recent years renewed interest within the synthetic community to take on these formidable targets.

ent-Kaurene biosynthesis proceeds first through protonation and conversion of geranylgeranyl pyrophosphate (**7**) to *ent*-copalyl pyrophosphate (**8**), followed by loss of the diphosphate group and 6-*exo*-trig cyclization (**8** → **9**), and finally a series of carbocation rearrangements (**9** → **12**) catalyzed by the *ent*-kaurene synthase enzyme (Figure 4b).[42,53] The intermediacy of secondary carbocations (e.g., **10**) in this mechanism has been questioned in recent years, and a computational study from Tantillo and coworkers strongly supports a mechanism with direct conversion of the *ent*-pimarenyl cation (**9**) to the *ent*-kaurenyl cation (**11**) through a concerted cyclization and alkyl shift.[54] Without the use of an enzyme catalyst, this precisely orchestrated cascade of C–C bond formations and 1,2-rearrangements would seem an edifice beyond the reach of synthetic chemistry, and indeed such a polyene cyclization has never been reproduced in a laboratory setting. In their total synthesis of isosteviol (not shown), Snider and coworkers reported an impressive Mn(III)/Cu(II) oxidative radical polyene cyclization of **13** that could reliably deliver the isomeric beyerene carbon skeleton **14** (Figure 4c); however, such strategies are not easily adaptable towards the synthesis of the *ent*-kaurenoids given the requisite alkyl shift.[55] With the possibility of polyene cyclization precluded, multistep routes to the bicyclo[3.2.1]octane have continued to dominate synthetic efforts towards the *ent*-kaurenes.

Early work from Ireland and Ziegler established two classic dearomative strategies used to construct the C8 quaternary center and bridged ring system, both relying upon Birch reduction of fused phenyl ethers (Figure 5).[56-61] Ireland's synthesis of (±)-kaurene (**12**) proceeds through a Saucy–Marbet enol ether Claisen rearrangement, followed by intramolecular aldol reaction (**15** → **16**),[56-59] a strategy later used by the Hong group in their total synthesis of cafestol (not shown).[62] Pioneering efforts from Ziegler and Kloek established the [2+2] cycloaddition with allene (generating **17**) as a powerful tool for the construction of the bicyclo[3.2.1]octane motif in steviol methyl ester (**18**).[60,61] Despite the low yield of the ring expansion (**17** → **18**), the allene [2+2] has endured as a highly effective way to forge a C–C bond at C8; later, more efficient methods were utilized to trigger fragmentation of the methylenecyclobutane, such as ozonolysis, used in Corey's synthesis of neotripterifordin (not shown).[63] This allene [2+2] and ozonolysis sequence was also applied in Baran's recent synthesis of steviol (**3**).[64] It is worth noting that in all of these examples, the authors built the most complex

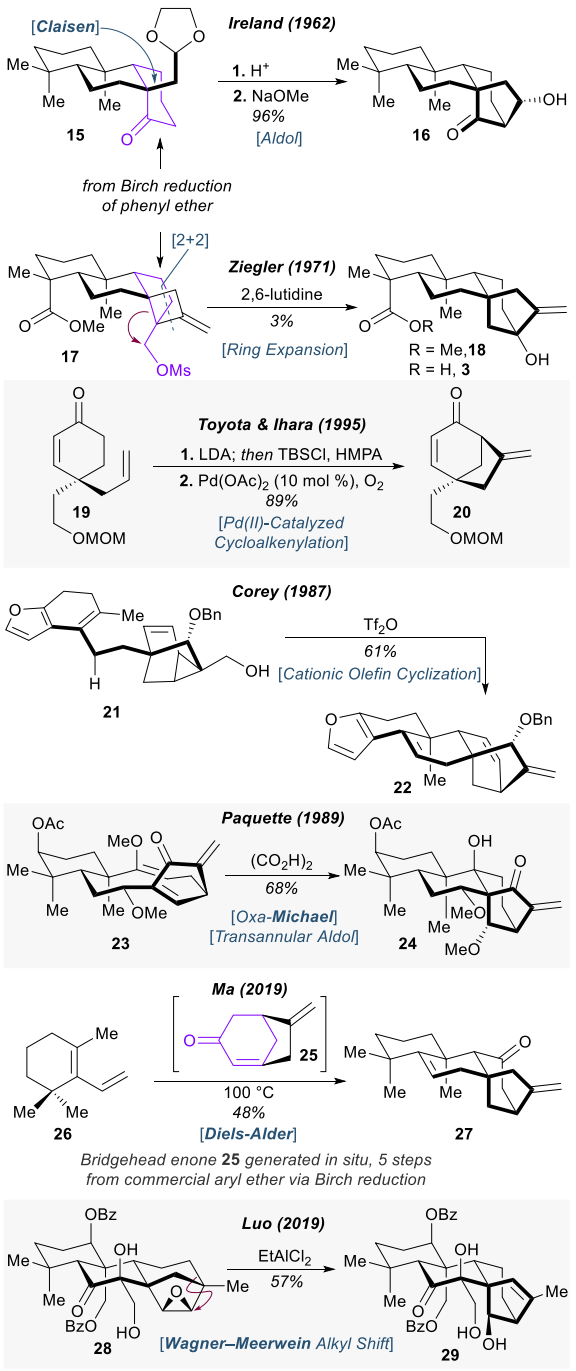


Figure 5. Selected approaches towards the bicyclo[3.2.1]octane motif of the *ent*-kaurenes.

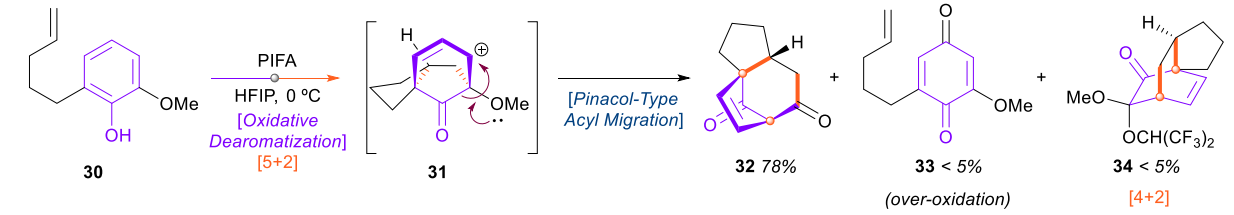
and three-dimensional portion of the molecule from what had originally been a flat aromatic ring, leveraging its synthetic potential through dearomatization.

One of the most widely-adopted methods for construction of the bicyclo[3.2.1]octane is the palladium-catalyzed cycloalkenylation (**19** → **20**) first reported by Toyota and Ihara in 1994[65,66] and later used in their total syntheses of the *ent*-kaurenoids

(±)-methyl atis-16-en-19-oate[67] and (–)-methyl kaurenoate,[68] as well as for a number of other terpenoids.[69] Toyota and Ihara's oxidative cyclization reaction would later serve as a key step in Reisman's syntheses of (–)-trichorabdal A and (–)-longikaurin E,[70] and most recently has been used in Ma's convergent asymmetric syntheses of lungshengenin D and 1α,6α-diacteoxy-*ent*-kaura-9(11),16-dien-12,15-dione.[71]

Beyond these canonical approaches, the architectural complexity of the *ent*-kaurene scaffold has inspired some interesting alternative strategies. During his synthesis of cafestol, Corey showcased the viability of the cyclopropyl methyl cation to trigger polyolefin cyclization, closing the final ring of the natural product (**21** → **22**).[72] A dramatic cascade reaction incorporating enol ether hydrolysis, hemiacetal formation, oxa-Michael addition, and finally a transannular aldol reaction back into the original ketone served as the final step in Paquette's synthesis of dimethylshikoccidin (**23** → **24**).[73] Although requiring preinstallation of the bicyclo[3.2.1]octane motif (via radical cyclization), Ma has demonstrated that Diels–Alder cycloaddition with transiently generated bridgehead enone **25** is a powerful tactic to rapidly construct the *ent*-kaurene skeleton in a convergent fashion (**26** → **27**).[74] This method was applied in the total syntheses of 11β-hydroxy-16-kaurene, 11α-hydroxy-16-kaurene, liangshanin G, and gesneroidin B. Biomimetic conversion of the beyerene skeleton to the kaurene skeleton through 1,2-alkyl shift (**28** → **29**) was recently achieved by Luo and coworkers, using Lewis acid-promoted epoxide opening to trigger the rearrangement.[75] This synthesis is also notable for its application of an interesting interrupted Nazarov cyclization. While impressive, all of these approaches towards the tetracyclic, *ent*-kaurene scaffold either proceed from complex, advanced intermediates acquired through multistep syntheses, or suffer from a lack of generality.

A fundamentally new, dearomative approach towards the bicyclo[3.2.1]octane structure was reported by Ding and coworkers in 2017 (Figure 6).[76] They found that, on mono-protected catechols with a pendent alkene side chain (e.g., **30**), an oxidative dearomatization-induced [5+2] cycloaddition yielded cedrene-like cationic intermediates **31** with a proximal bridgehead methoxy group, which readily promoted a



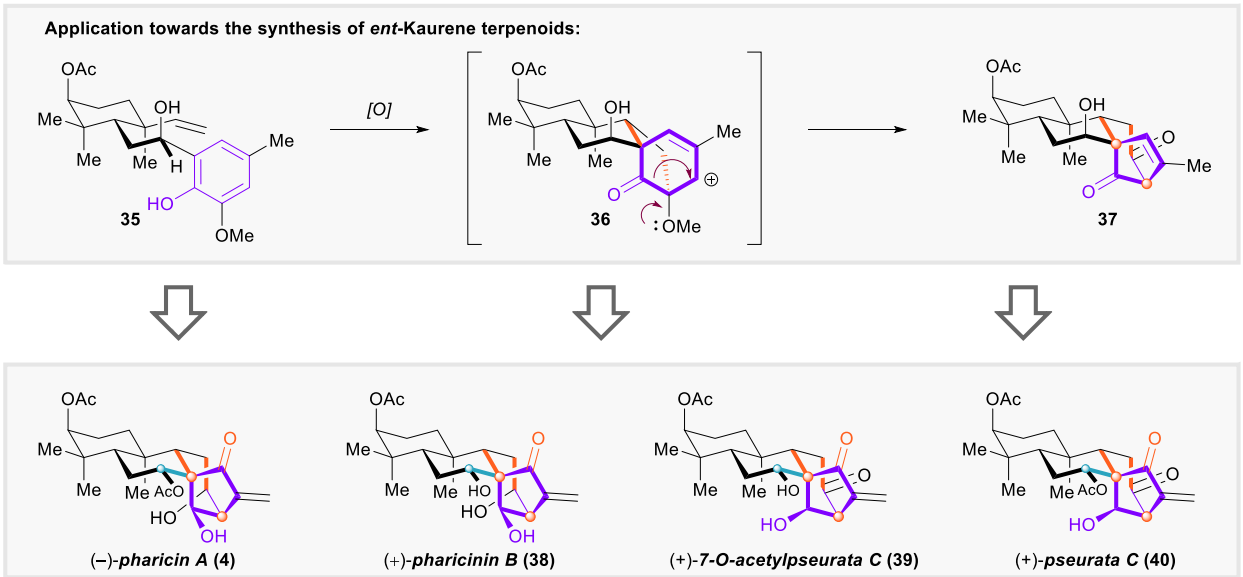


Figure 6. Ding's oxidative dearomatization-induced [5+2] cycloaddition, and application towards *ent*-kaurenes.

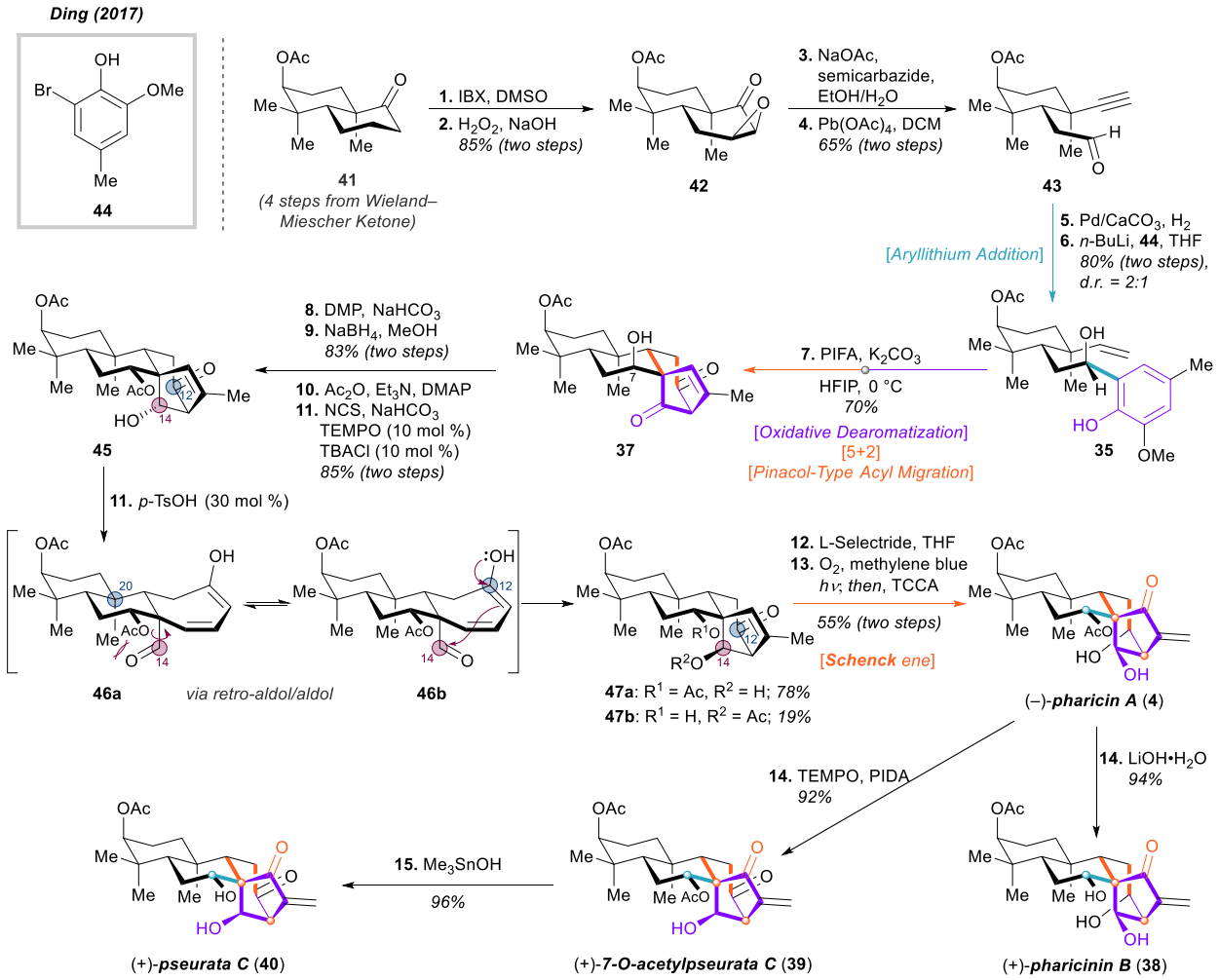


Figure 7. Ding's total syntheses of (–)-pharicin A (**4**), (+)-pharicinin B (**38**), (+)-7-*O*-acetylpseurata C (**39**), and (+)-pseurata C (**40**).

pinacol-type 1,2-acyl migration to reveal the bicyclo[3.2.1]octene framework of the *ent*-kaurenoids (**32**). A screen of solvents and oxidants was sufficient to optimize the yield of the desired product while minimizing the production of byproducts **33** and **34** from overoxidation or addition of solvent and [4+2] cycloaddition.

The dearomative [5+2] cycloaddition/pinacol shift is an attractive strategy for the synthesis of *ent*-kaurenoids (**35** → **36** → **37**). It generates considerable topological complexity within a single step, and it proceeds from relatively simple starting materials that can likely be derivatized and interchanged in a modular fashion, leaving open the possibility that this approach might be general. Ding and coworkers aptly demonstrated the utility of this method by completing the first asymmetric total syntheses of four *ent*-kaurenoids: (–)-pharicin A (**4**), (+)-pharicinin B (**38**), (+)-7-*O*-acetylpseurata C (**39**), and (+)-psuerata C (**40**) (Figure 7).[76]

Starting from known bicyclic ketone **41**, made in four steps from commercially available Wieland–Miescher ketone, a Nicolaou oxidation followed by nucleophilic epoxidation delivered epoxy ketone **42** in 85% overall yield, which was then subjected to a modified Eschenmoser–Tanabe fragmentation (**42** → **43**). Likely due to the steric hindrance of this ketone, modified conditions for the fragmentation were required, using the more nucleophilic semicarbazide followed by lead tetraacetate oxidation and fragmentation.[77] Lindlar reduction of the alkyne and nucleophilic addition of the aryllithium derived from aryl bromide **44** furnished **35**, the requisite precursor for the dearomative cycloaddition. Treatment of **35** with PIFA in HFIP smoothly promoted the oxidative dearomatization-induced [5+2] cycloaddition, followed by pinacol-type 1,2-acyl shift, building two new rings

and completely assembling the bicyclo[3.2.1]octene motif of **37** in a single step. Notably, the full tetracyclic *ent*-kaurene framework was completed in only seven steps.

The endgame of Ding's total synthesis required selective reduction of both ketones, and inversion of the stereocenter at C7. The latter task was accomplished through DMP oxidation and subsequent reduction with sodium borohydride; however, during this sequence it became apparent that hydride reductions consistently reduced the ketone at C14 from the undesired face, despite a screen of reductants and attempts to use the free hydroxyl groups at C7 and C12 for assistance. Thus, an alternative strategy was envisioned involving a retro-aldol/aldol sequence, an approach Ding and coworkers had used in their recent synthesis of steenkrotin A.[78] Preparation for this key manipulation required monoacetylation at C7 with acetic anhydride, and selective oxidation at C12 with catalytic TEMPO and NCS to give β-hydroxy ketone **45**. The envisioned retro-aldol proceeded readily under acidic conditions to generate a transient, freely rotating aldehyde **46** at C14. Ding rationalizes the selectivity of the subsequent aldol reaction as the result of an unfavorable 1,3-diaxial interaction between this aldehyde and the C20 bridgehead methyl substituent, the aldehyde reacting preferably from rotamer **46b** in which it points away from the ring, resulting in an apparent inversion of stereochemistry of the hydroxyl at C14. Partial acetyl transfer occurred during this process, generating **47a** and **47b**. Finally, the synthesis of (–)-pharicin A (**4**) was completed after reduction with L-Selectride and Shenck ene reaction with subsequent Kornblum–DeLaMare fragmentation. Simple protecting and functional group manipulations allowed Ding to elaborate (–)-pharicin A to three additional *ent*-kaurene terpenoids **38**-**40**. Additionally, the authors later applied this transformation in a total synthesis of (–)-rhodomollanol A.[79]

Maoecrystal V: Upon its structural elucidation in 2004,[80] maoecrystal V (**5**) immediately captivated the imaginations of chemists around the globe and inspired over a decade of synthetic studies (Figure 8).[81] Valiant efforts from the groups of Baran,[82] Yang,[83] Danishefsky,[84,85] Singh,[86] Trauner,[87] Thomson,[88,89] Zakarian,[90] Nicolaou and Chen,[91,92] Chisholm,[93] May,[94] Njardarson,[95] Christie,[96] and Sorenson[97-99] brought to light the immense challenges awaiting those undertaking the synthesis of this unusual molecule. The crux of the synthetic problem imposed by the fascinating structure of maoecrystal V is the construction of two vicinal quaternary centers, adjacent to a tertiary alcohol, linking a cyclohexene subunit with a bicyclo[2.2.2]octan-2-one. A bridging δ-valerolactone and strained oxolane ring amplify this problem considerably. Additionally, **5** was reported to have remarkably selective and potent antiproliferative effects against the HeLa cervical cancer cell line, thus

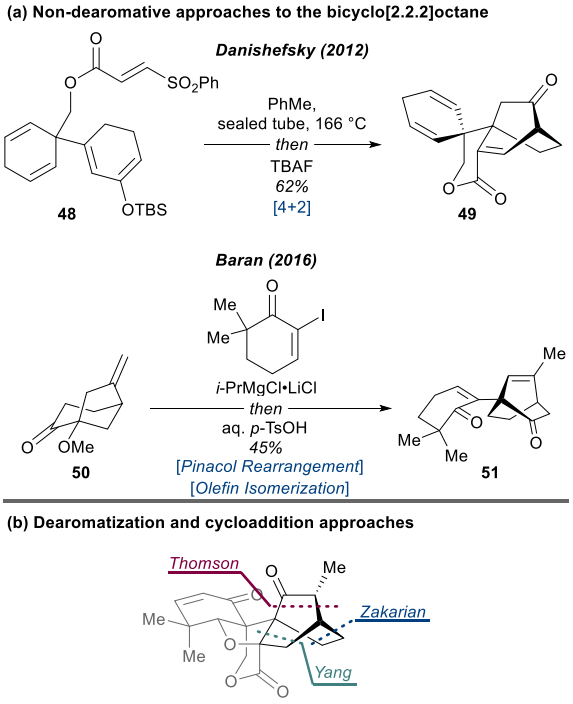


Figure 8. Key disconnections for dearomative and non-dearomative syntheses of maoecrystal V (**5**).

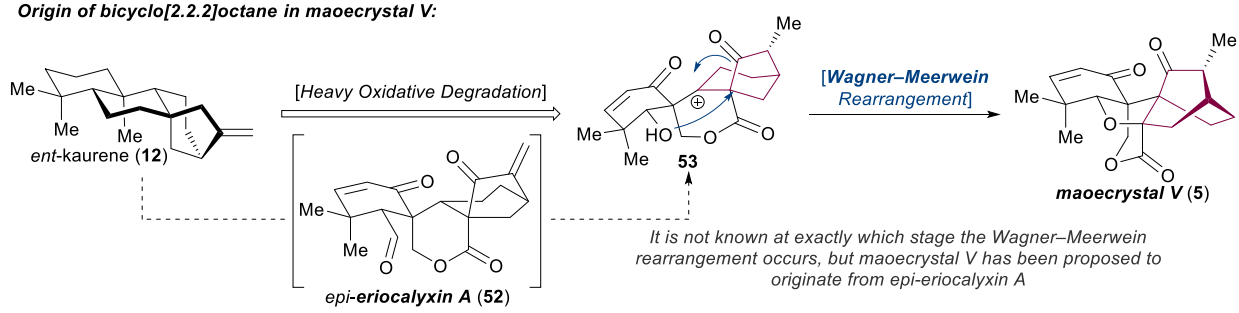


Figure 9. Proposed biosynthetic mechanism for the conversion of [3.2.1]-bicycle to [2.2.2].

presenting a highly attractive synthetic target despite—indeed because of—its difficult structure.

Five research groups have now completed the total synthesis of maoecrystal V: racemic approaches were reported by Yang in 2010,[100] Danishefsky in 2012,[101] and Zakarian in 2013.[102] Asymmetric syntheses were disclosed from Thomson in 2014,[103] a collaborative effort from Zakarian and Davies also in 2014,[104] Yang in 2015,[105] and most recently from Baran in 2017.[106] Notably, the total synthesis completed in the Baran laboratory produced enough of the natural product to reproduce the biological assays, with the surprising result that maoecrystal V possessed no anticancer activity whatsoever.

In a retrosynthetic analysis of maoecrystal V, the utility of the Diels–Alder transform to disconnect the bicyclo[2.2.2]octane is apparent; indeed, ten of the synthetic studies and four out of the five completed total syntheses leverage this robust method (e.g., **48** → **49** in Danishefsky's approach, Figure 8a). The lone alternative strategy, reported from the Baran laboratory, successfully applies a biomimetic pinacol-type shift of **50** → **51**, inspired by the proposed conversion of *epi*-eriocalyxin A (**52**) to maoecrystal V (**5**) through a cationic intermediate such as **53** (Figure 9). When the cycloaddition tactic is applied in conjunction with dearomative disconnections, some attractive synthetic designs emerge (Figure 8b). The Yang, Zakarian/Davies, and Thomson syntheses all incorporate the oxidative dearomatization of a phenol and a [4+2] cycloaddition to assemble the bridging ring. Despite sharing this basic disconnection, the three approaches are quite distinct, each incidentally breaking the bicyclo[2.2.2]octane at a different location, with associated advantages and disadvantages.

Yang's strategy adopts the most structurally simplifying of the three possible [4+2] cycloadditions—a powerful transformation—but one that necessarily proceeds from a fairly complex intermediate (**54**, Figure 10). The synthetic route addresses the problem of assembling one of the quaternary centers immediately, employing arylplumbane **56** in a high-yielding oxidative arylation of β-ketoester **57**.[107] The electron-rich phenol might have played an unexpected yet critical role in the following stage. Requiring diastereoselective ketone reduction from the more hindered face of the cyclohexenone to give alcohol **59a**, Yang and coworkers found that many conventional hydride reducing agents were highly selective for the undesired isomer **59b**. Some of the failed reductants include $LiAlH_4$, DIBAL-H, $NaBH_4$ with a Lewis acid

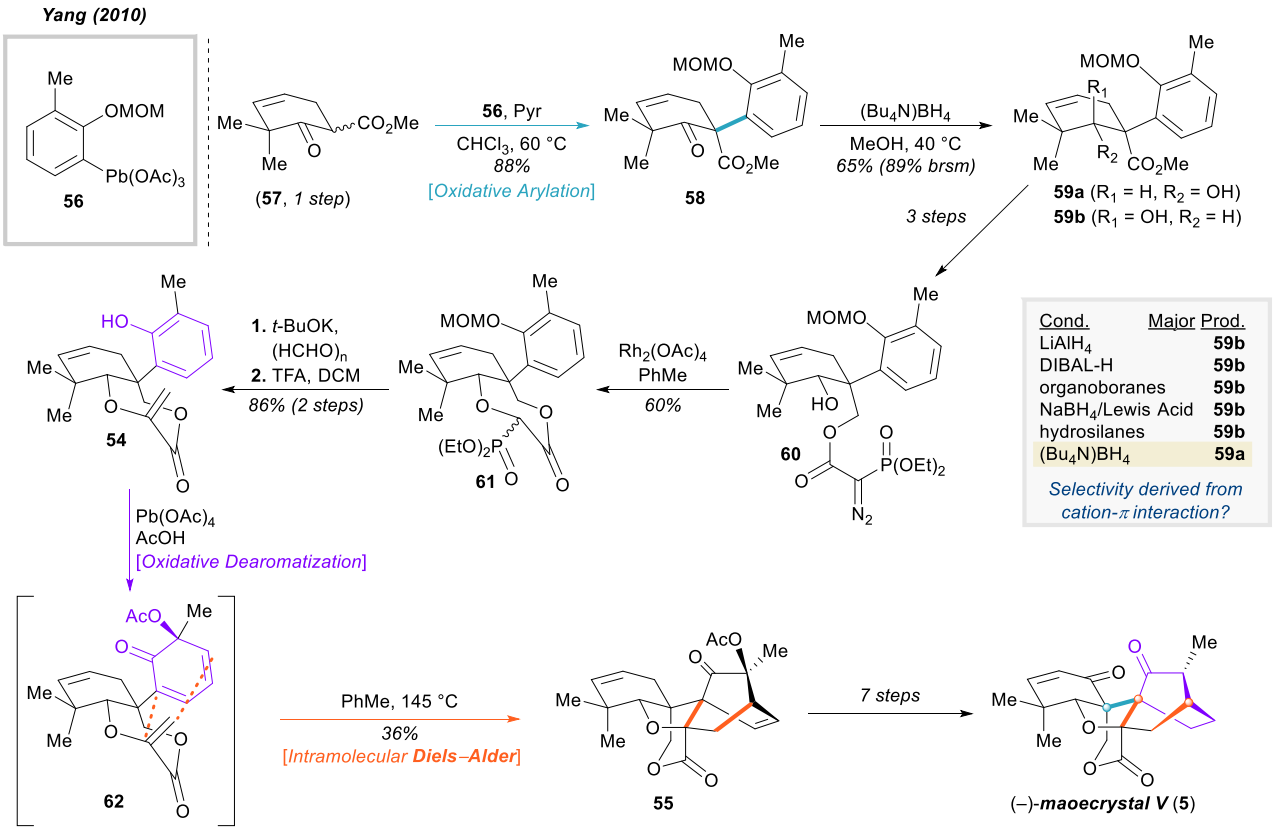


Figure 10. Yang's synthesis of maoecrystal V (**5**).

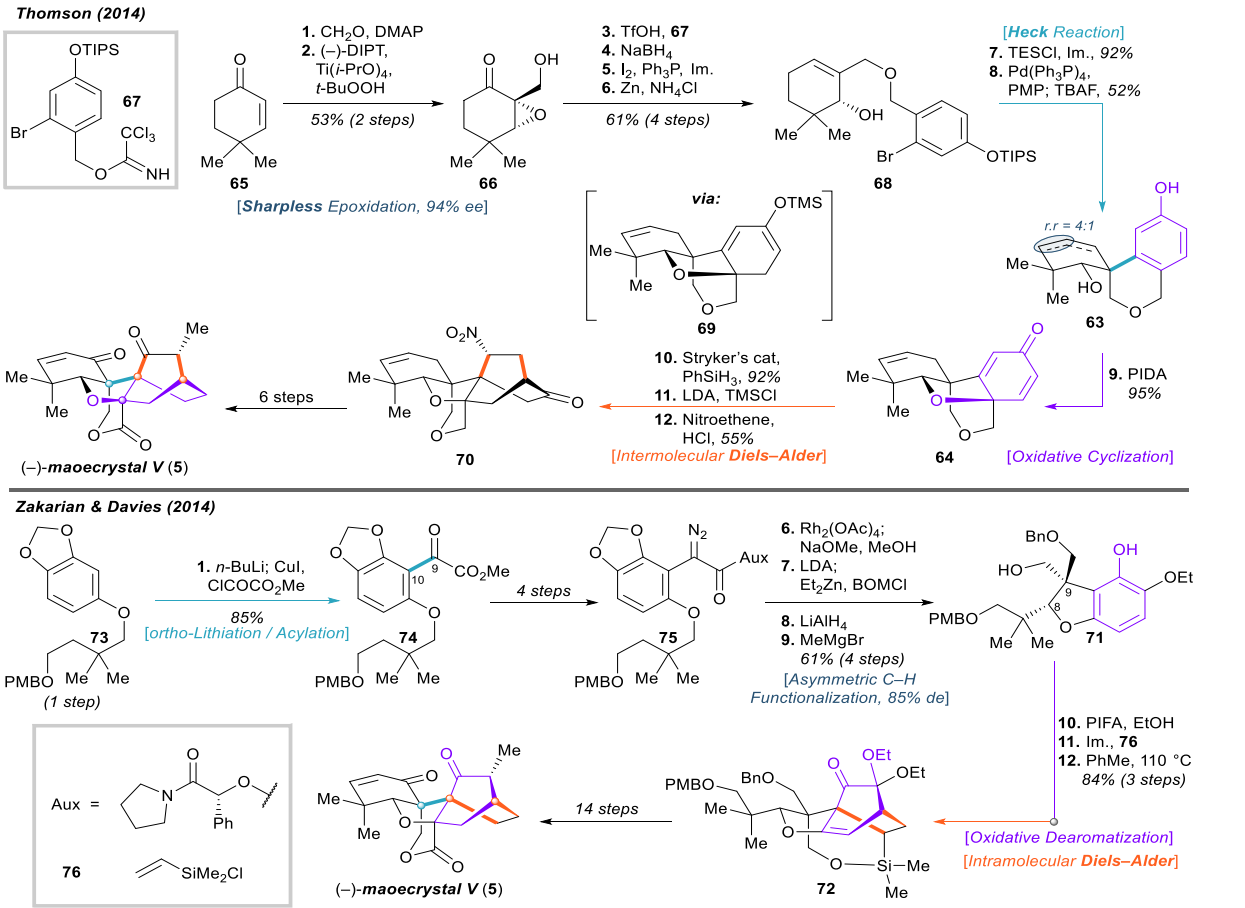


Figure 11. The Thomson and Zakarian/Davies syntheses of maoecrystal V (**5**).

additive, organoboranes, and hydrosilanes. Strikingly, the use of $(Bu_4N)BH_4$ effected a complete reversal in diasteroselectivity, producing alcohol **59a** as a single isomer. The authors ascribe this unusual outcome to accelerating and directing effects that may result from a noncovalent cation-π interaction between the ammonium salt and the electron-rich phenol, to deliver the hydride *syn* to the arene. However, this rationale is speculative, and several examples of highly *cis*-selective reductions of related β-ketoesters lacking aromatic groups have been reported.[108]

After a three-step sequence of ester reduction, acylation, and diazo transfer (**59a** → **60**), Yang's team was able to quickly prepare a suitable substrate **54** for the oxidative dearomatization and [4+2] cycloaddition cascade. Rhodium-catalyzed intramolecular O–H insertion (**60** → **61**),[109] deprotection of the phenol, and Wittig olefination furnished dioxepane **54**. Notably, this process also created the precursors for the *δ*-lactone and oxolane rings; thus, upon Wessely oxidation and reflux in toluene, the envisioned dearomative cascade reaction occurred (via **62**), simultaneously forging three rings as well as the second of the challenging vicinal quaternary centers. Although quite an impressive transformation, a drawback of this disconnection is the lack of diastereoselectivity, generating a mixture of three products and only 36% yield of the desired isomer **55**. With the intricate skeletal framework completed, Yang and associates were able to complete the first total synthesis of maoecrystal V after seven additional redox maneuvers.[100]

Thomson's strategy is unique among the Diels–Alder approaches in that its [4+2] cycloaddition is intermolecular and unrelated to the dearomative step, allowing instead for an oxidative phenol dearomatization to close the strained oxolane ring and establish the tertiary alcohol (**63** → **64**, Figure 11). Freeing the dienophile from a tether, the authors employed an elegantly streamlined sequence to swiftly assemble the complex framework from a simple intermediate, albeit at the cost of some late-stage functional group manipulations to access the optically pure precursor.

The route to this precursor commences with a Baylis–Hilman reaction of enone **65** with

formaldehyde. High optical purity (94% ee) was established with a Sharpless asymmetric epoxidation, and the remaining alcohol **66** was benzylated with trichloroimidate **67**. Reductive fragmentation of the epoxide was achieved in a three-step sequence to reveal allylic alcohol **68**, which was subsequently protected as the triethylsilyl ether.

In the first of a series of key steps, the C9 quaternary center was constructed with ease through an intramolecular Heck reaction with the arene, generating **63**. The phenol was then immediately subjected to oxidative dearomatization with hypervalent iodine, closing the oxolane ring through intramolecular attack from the allylic alcohol. The resultant cyclohexadienone **64** was arranged for the impending Diels–Alder through conjugate reduction of the more exposed olefin and conversion to the unstable silyl dienol ether **69**. Without purification, **69** was applied directly in a [4+2] cycloaddition with nitroethene as the active dienophile. Hydrolysis of the silyl enol ether was achieved upon acidic workup. Despite the missing and misplaced functionality of this complex intermediate **70**, Thomson and coworkers were able to complete the synthesis of (–)-maoecrystal V in six additional steps.[103]

The [4+2] detachment that Zakarian and Davies chose (**71** → **72**)—arguably the most difficult of the three possibilities—may at first appear unorthodox, as it seems to require an ethylene equivalent as its dienophile. However, this disconnection highly advantageous because it unravels the complicated polycyclic system into simple benzofuran derivative **71**. This judicious choice allowed the authors to address the construction of the strained oxolane ring early in the synthesis, the difficulty of which either presented significant problems in or arrested entirely numerous

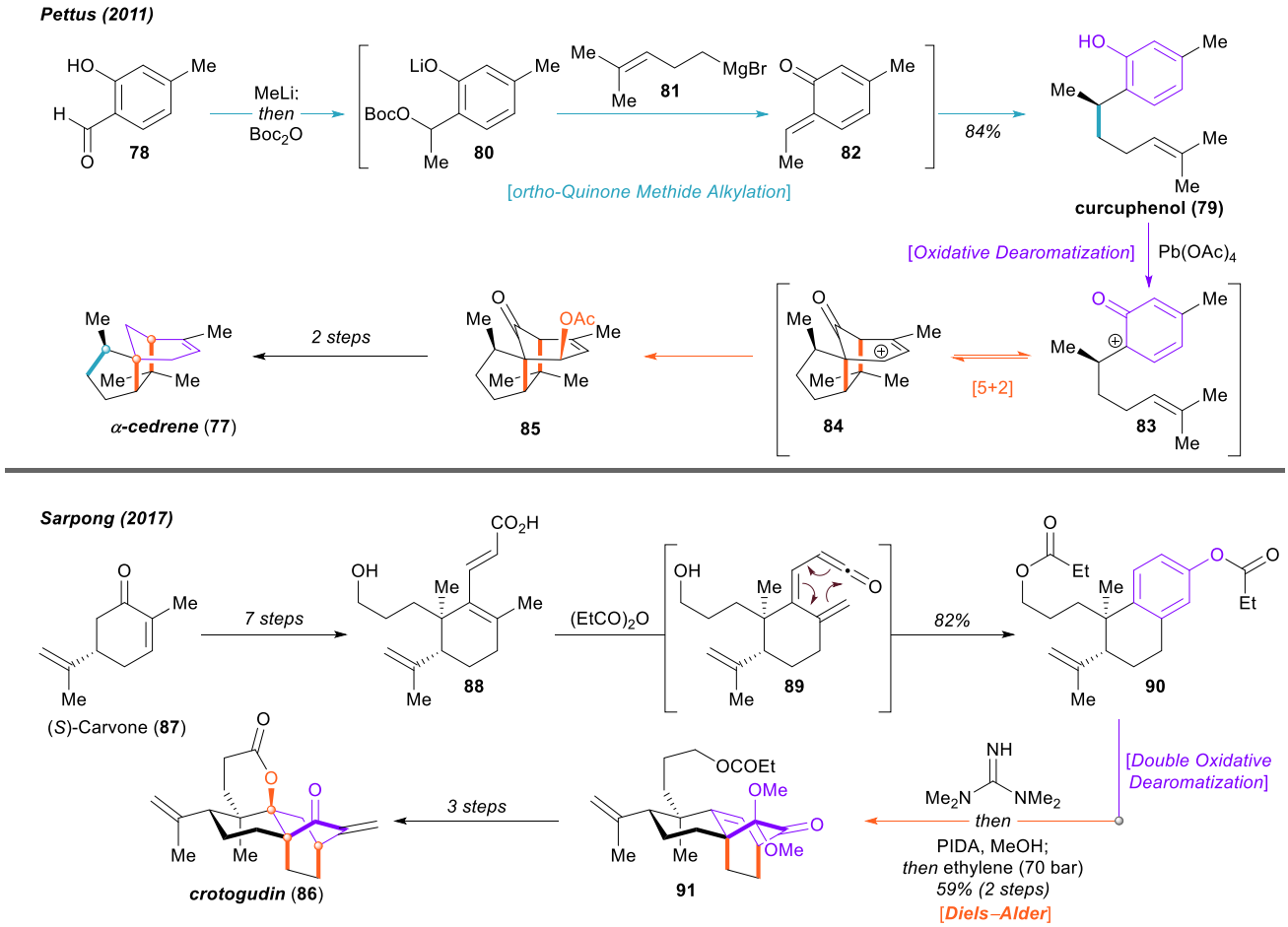


Figure 12. Pettus synthesis of cedrene (**77**) and Sarpong synthesis of crotogudin (**86**).

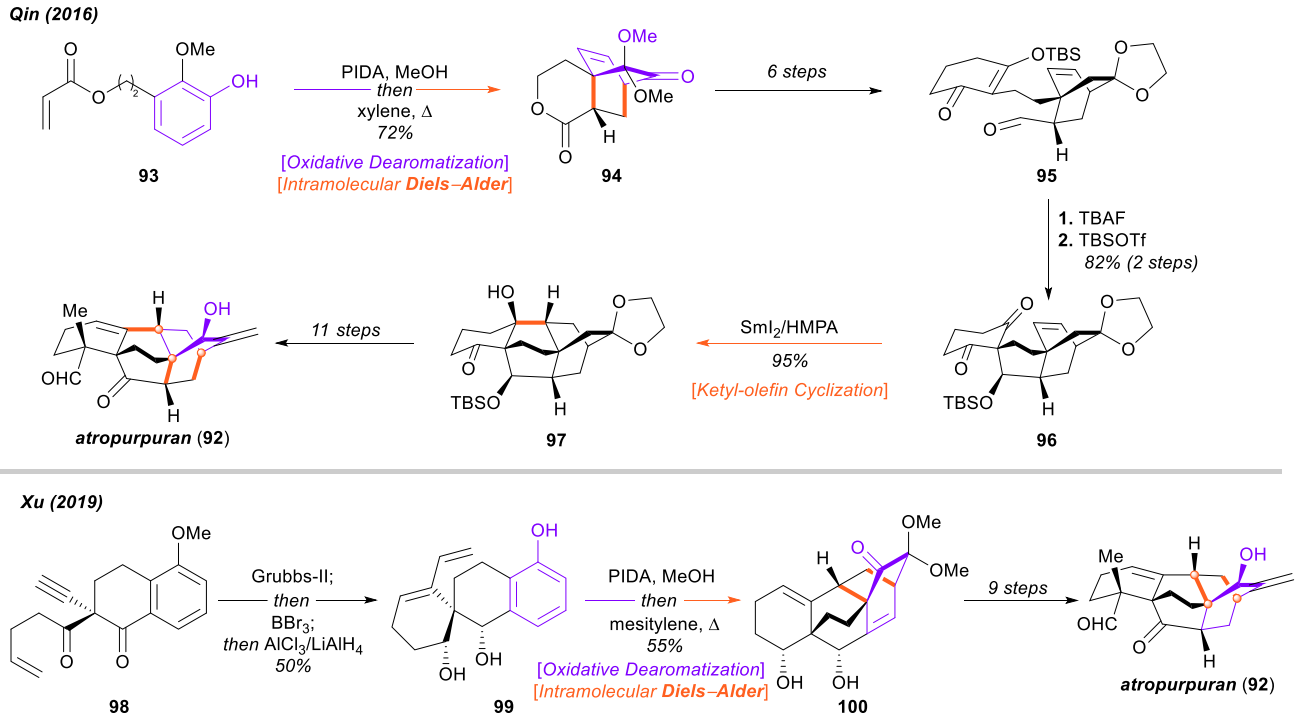


Figure 13. Qin and Xu syntheses of atropurpuran (**92**).

synthetic attempts requiring late-stage ring closure.[81-85,88,89,93] The benzofuran intermediate **71** is also a strategic target for an asymmetric synthesis, as it could be generated through a catalytic, enantioselective C–H insertion of a rhodium carbenoid, a process previously reported by and heavily studied in the Davies laboratory.[110] The solution the authors found for the Diels–Alder was to use a silicon-tethered olefin in an intramolecular reaction, which could be desilylated after the cycloaddition. The use of these two critical steps in concert to construct the oxolane and bicyclo[2.2.2]octane is tactful; however, the necessary intermediates are quite complex, and the strategy does little to accommodate the synthesis of the cyclohexenone, which required several functional-group transformations to assemble.

Aryl ether **73** was synthesized in one step through a Mitsunobu reaction of sesamol and the corresponding monoprotected, neopentylic diol. Regioselective *ortho*-lithiation, transmetalation to zinc, and acylation with methyl chloroxoacetate furnished α-keto ester **74**. At this early stage, classical arene chemistry was used to forge the incumbent C9–C10 bond, a vital connection that would be extremely difficult to make on the bicyclo[2.2.2]octane after dearomatization. Intermediate **75** was equipped for the enantioselective C–H insertion via a four-step sequence to install the diazo group and attach a mandelic acid-derived chiral auxiliary. The auxiliary was employed only after an exhaustive screen of chiral ligands and reaction conditions suffered from low diastereoselectivity at the C8 position. High enantioselectivity at C9 could be obtained with chiral ligands on rhodium; however, as C9 is immediately epimerized to provide the thermodynamically favored isomer, the poor diastereoselectivity of the C–H insertion effectively rendered the overall process racemic.

With the chiral auxiliary in place, rhodium-catalyzed C–H insertion proceeded in good yield and 84% diastereomeric excess. Cleavage of the auxiliary and epimerization at C9 to the *trans*-isomer was accomplished with sodium methoxide. This methyl ester was alkylated with benzyl chloromethyl ether and reduced with lithium aluminum hydride. Dioxolane cleavage with methylmagnesium bromide furnished benzofuran **71**. The bicyclo[2.2.2]octane foundation **72** was assembled by a three-step sequence incorporating oxidative dearomatization with bis(trifluoroacetoxy)iodobenzene, silylation of the free alcohol with dimethylvinylchlorosilane (**76**), and reflux in toluene. With the construction of the A-ring cyclohexenone and the δ-lactone remaining, the authors achieved the total synthesis of (–)-maoecrystal V in fourteen steps from siloxacycle **72**.[104]

Miscellaneous Terpenoids: The oxidative dearomatization-induced [5+2] cycloaddition has been of great utility in a number of synthetic approaches to

terpenes that feature bridged ring structures as well. A notable example was reported by Pettus and coworkers in their 2011 total synthesis of α-cedrene (**77**), *sec*-cedrenol, and α-pipitzol (Figure 12).[111] Effective dearomative logic is used throughout the synthesis, beginning with the transformation of salicylaldehyde **78** into curcuphenol (**79**). Two equivalents of methyllithium facilitate 1,2-addition into the aldehyde and deprotonation of the phenol, followed by monocarbonylation of the dianion with di-*tert*-butyl dicarbonate (**78** → **80**). In the same pot, treatment with the homoprenylmagnesium bromide reagent **81** promotes carbonate elimination from the magnesium phenoxide and generates *ortho*-quinone methide **82**, into which the magnesium reagent adds to furnish curcuphenol (**79**) in 84% yield overall. The authors report an asymmetric approach to this compound as well, via inverse electron demand hetero Diels–Alder reaction of *ortho*-quinone methide **82** with a vinyl ether bearing a chiral auxiliary and subsequent fragmentation of the resultant chroman ketal. The key oxidative dearomatization-induced [5+2] cycloaddition (**79** → **83** → **84** → **85**) failed with a variety of hypervalent iodine oxidants; however, the use of lead tetraacetate uniquely promoted clean formation of the cedrene scaffold **85** in 61% yield. From this intermediate, Pettus and coworkers were able to complete the syntheses of α-cedrene (**77**), *sec*-cedrenol, and α-pipitzol in a rapid fashion.

In 2017, the Sarpong group reported an interesting approach to crotogudin (**86**) through a benzannulation of (*S*)-carvone (**87**) and an unusual, regioselective double oxidative dearomatization and intramolecular [4+2] cycloaddition cascade.[112] Seven steps were required to convert (*S*)-carvone into precursor **88**. Heating this compound in solvent quantities of propionic anhydride resulted in the formation of ketene **89**, and subsequent 6π-electrocyclization delivered the benzannulated derivative **90**. Cleavage of the phenyl propionate with tetramethylguanidine, followed by regioselective iodine(III)-mediated oxidative dearomatization generated a dienone acetal that was carried through a high-pressure Diels–Alder reaction with ethylene to construct the bicyclo[2.2.2]octenone **91**, bearing the full carbon skeleton of crotogudin (**86**). The authors were able to complete the synthesis of this natural product in an additional three steps.

Diels–Alder cycloadditions triggered by the oxidative dearomatization of phenols continue to find wide application in the synthesis of topologically complex, caged terpenoid structures. One natural product of particular interest, given its possible biosynthetic relationship[113] to the enigmatic arcutane-type diterpenoid alkaloids (*vide infra*), is atropurpuran (**92**, Figure 13). Bearing a unique tetracyclo[5.3.3.0.^{4,9}.0^{4,12}]tridecane framework with two adjacent bicyclo[2.2.2] octane ring systems, atropurpuran has been the subject of numerous syntheses[114-117] since its initial isolation in 2009.[118] Two successful campaigns, from the groups of Qin[119] and Xu[120] in 2016 and 2019, respectively, both make use of the dearomatization/cycloaddition tactic in the construction of either one or both of the [2.2.2] bicyclic motifs .

Qin's approach carries out this operation at the outset, building tricyclic intermediate **94** from **93** in the first step under standard conditions. This was advanced to **95** in six steps, after which an intramolecular aldol reaction (**95** → **96**) followed by SmI_2-promoted ketyl-olefin cyclization assembled the remaining bicyclo[2.2.2]octane system **97** and completed the synthesis of the complex carbon framework. Qin and coworkers were able to complete the first synthesis of atropurpuran (**92**) in an additional eleven steps.[119]

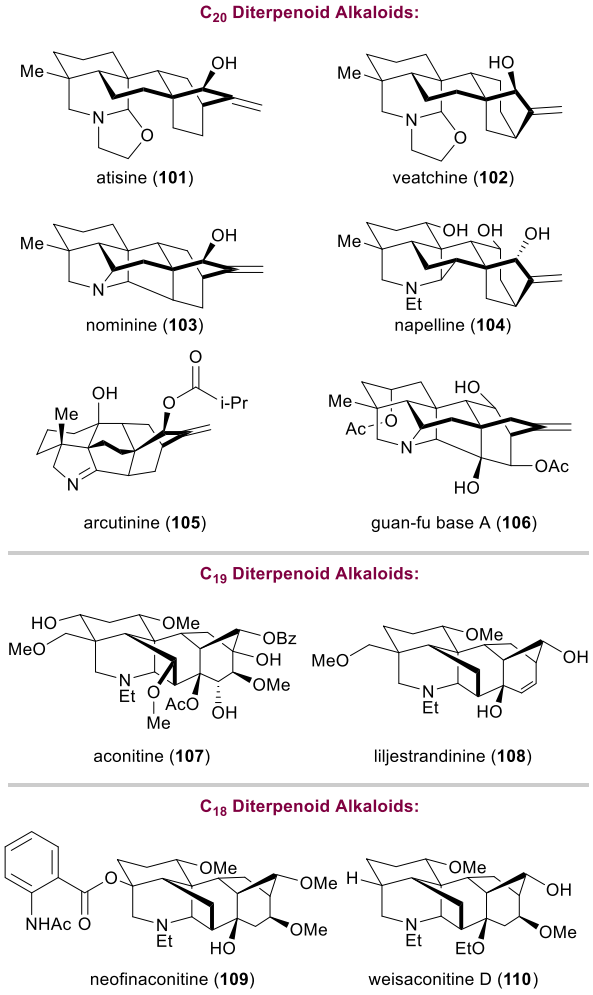


Figure 14. Structures of selected diterpenoid alkaloids.

Xu's 13-step 2019 approach began with the preparation of enyne **98** from commercially available 5-methoxytetralone in two steps. Extremely rapid assembly of the full tetracyclo[5.3.3.0.^{4,9}.0^{4,12}]tridecane scaffold was achieved through two subsequent C–C bond-forming events. Intramolecular ring-closing enyne metathesis with subsequent methyl ether deprotection and reduction of the 1,3-dicarbonyl delivered spirocycle **99**, which was subject to a regioselective double oxidative dearomatization/intramolecular [4+2] cycloaddition cascade that notably builds both [2.2.2] bicycles in **100** in a single step. Following this impressive sequence, Xu and coworkers completed the total synthesis of atropurpuran (**92**) in nine additional steps.[120]

Diterpenoid Alkaloids: Few molecular architectures have captivated the imaginations of synthetic organic chemists more than the diterpenoid alkaloids of the *Aconitum*, *Delphinium*, and *Consolidum* genera of plants (e.g., **101**–**110**, Figure 14). These highly complex nitrogenous terpenoids are more appropriately classified as pseudo- or crypto-alkaloids with respect to their biosynthetic origins (*vide infra*) and are included in this section as such.[121] As the main agents responsible for the toxic effects of *Aconitum* plants (monkshood/wolfsbane), some diterpenoid alkaloids have gained notoriety as poisons used in hunting, warfare, and a number of high-profile murders, and also feature prominently in the novels of Agatha Christie.[122-127] Nonetheless, their strong affinity for voltage-gated Na^+ and K^+ ion channels lends these natural products powerful analgesic, antiarrhythmic, and other desirable medicinal properties, and herbal remedies containing aconite alkaloids continue to find use in traditional medicinal practices in China and Slovenia.[128] Lappaconitine (not shown) is approved for the treatment of arrhythmia and pain in Russia and China, and the guan-fu base A (**106**) has been approved by the Chinese Food and Drug Administration for paroxysmol supraventricular tachycardia in 2005, and is currently in stage IV postclinical trials in China for similar indications.[129-131,137] Several diterpenoid alkaloids have high channel subtype specificity and demonstrate potential therapeutic value in a variety of channelopathies.[121,132-134]

The chemistry and biology of the diterpenoid alkaloids have been reviewed extensively, most notably by Wang and coworkers,[121] who have segregated them by their carbon backbones into the C_{18},[135] C_{19},[136] and C_{20}[137] diterpenoid alkaloid families. The C_{20} diterpenoid alkaloids can be further classified into a variety of skeletal frameworks of increasing topological complexity. Unlike true amino acid-derived alkaloids, crypto-alkaloids are generated from the structurally related atisane and *ent*-kaurane diterpenoids via oxidation and subsequent amination with L-serine (Figure 15).[137] A series of Wagner–Meerwein shifts and C–C bond forming events gives rise to a constellation of elaborate molecular architectures. Further rearrangement and excision of the exocyclic methylene group furnishes the C_{19} family of natural products,[136] while cleavage of the remaining C4 methyl group delivers the C_{18} diterpenoid

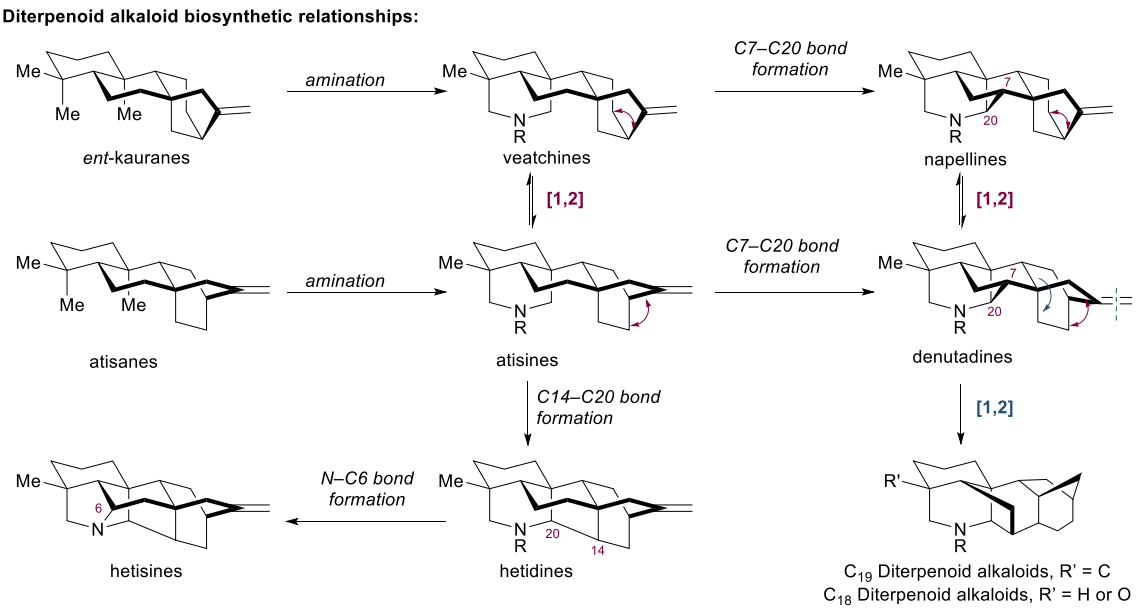


Figure 15. Biosynthetic relationships among the diterpenoids alkaloids as well as with other diterpenes.

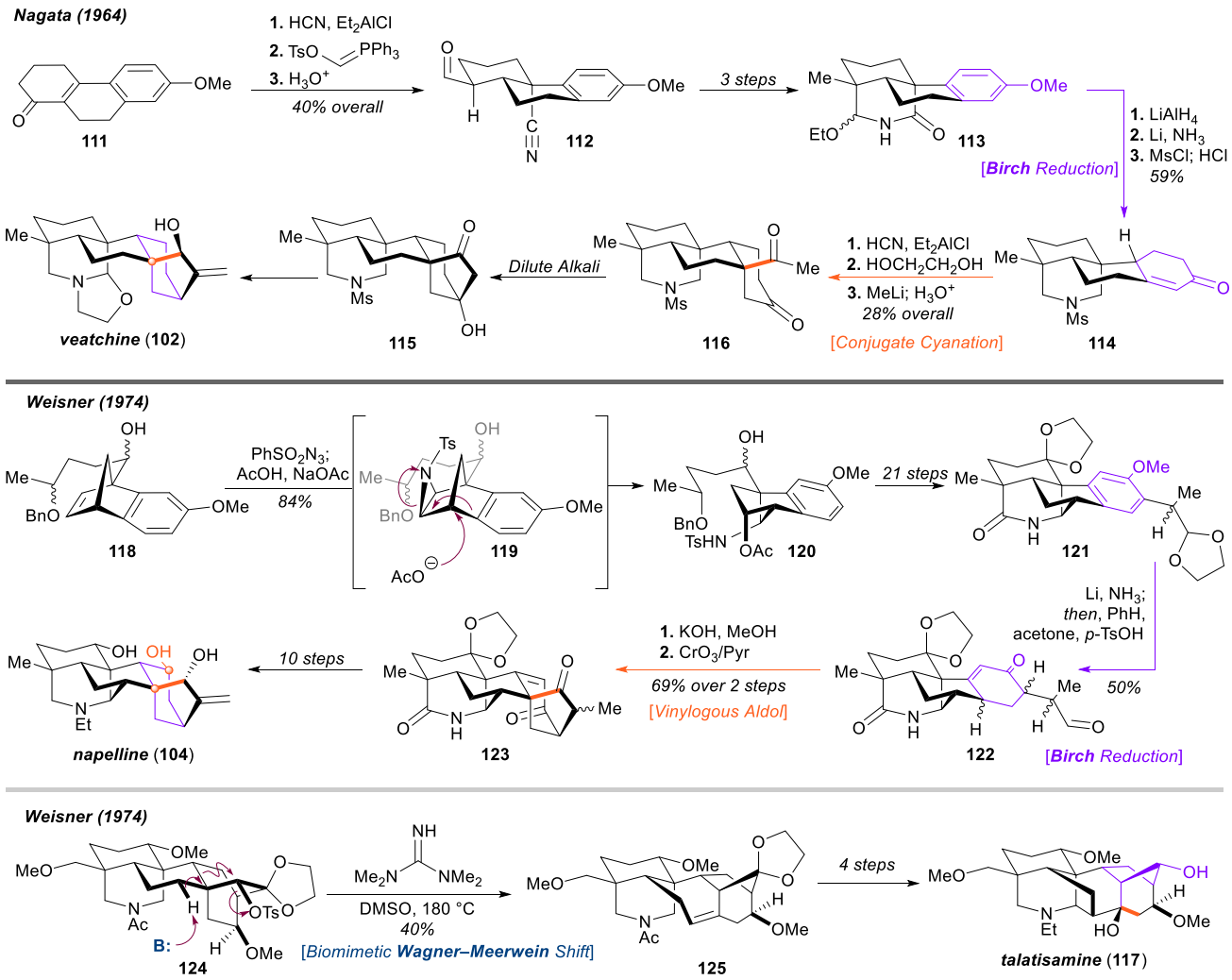


Figure 16. Landmark early syntheses of the diterpenoid alkaloids.

alkaloids.[135] In addition to their daunting skeletal complexity, many diterpenoid alkaloids are heavily oxidized, providing the rich structural and functional diversity responsible for their myriad downstream biological effects.

Pioneering spectroscopic and degradative structural studies from Pelletier,[138-140] Weisner and Büchi,[141-143] and others[144-146] revealed the alluring topologies and rich oxidative decor of the aconite alkaloids by the mid 1950s; however, such architectural features characteristic of these remarkable structures have proven so challenging to construct that efficient synthesis of diterpenoid alkaloids remains an active and difficult area of research even today, nearly seventy years later. In fact, despite landmark initial synthetic accomplishments from Nagata,[147,148] Masamune,[149-153] and Weisner[154-160] in the 1960s and 1970s, perhaps only within the last decade has the state-of-the-art of diterpenoid alkaloid synthesis advanced significantly. This growing renaissance in aconite alkaloid synthesis can be attributed in large part to emerging strategies that place great emphasis on dearomative C–C bond-forming events that construct bridging rings within caged polycyclic frameworks.[161] In these strategies, as was the case with the parent atisane and *ent*-kaurene diterpenoid families, it is pertinent to note that the maximally bridged and most topologically complex portions of diterpenoid alkaloid scaffolds most often germinate from flat, aromatic building blocks through the use of dearomative chemistry.

This concept is not new—indeed, it lays the groundwork for nearly all successful diterpenoid alkaloid syntheses reported to date, including the seminal efforts from Nagata, Masamune, and Weisner (Figure 16). The two principal synthetic problems posed by all of the diterpenoid alkaloids is the installation of nitrogen during the construction of the

azabicyclo[3.3.1]octane subunit, and the assembly of the highly caged polycyclic ring systems found in the eastern hemisphere of the molecules. Additional challenges are to be found on a case-by-case basis as more C–C and C–N bonds are made to form additional bridging rings.

In Nagata's classical approach to both atisine (**101**)[147] and veatchine (**102**),[148] a conjugate hydrocyanation of enone **111** served as a key step to affix the axial bridgehead methyl group as well as to bring in the nitrogen functionality preinstalled for subsequent closure of the azabicyclo[3.3.1]octane system. Wittig homologation delivered aldehyde **112**, which successfully underwent ring closure after a sequence incorporating methylation and reduction of the nitrile (**112** → **113**). Treatment with lithium aluminum hydride and reductive dearomatization of the phenyl ether and resulting bis-hemiaminal under Birch conditions furnished enone **114**, which could be used to construct the [3.2.1] bicycle **115** following another conjugate cyanation and generation of the methyl ketone (**114** → **116**), and intramolecular aldol reaction. This intermediate could be advanced to veatchine after several additional steps.[148]

Along with their groundbreaking structural studies[141] and early total syntheses of atisine (**101**)[156] and veatchine (**102**),[155] the substantial synthetic accomplishments of Wiesner's group included their successful pursuit of several members of more challenging diterpenoid alkaloid structural classes, including napelline (**104**)[157-160] and the C_{19} norditerpenoid alkaloids talatisamine (**117**) and 13-desoxydelphonine.[162,163] Paramount to Wiesner's approach to napelline (**104**) was the establishment of a C7–C20 bond during the assembly of the azabicyclo[3.3.1]octane system, which was achieved through Diels–Alder cycloaddition of benzeindene to construct benzonorbornene **118**. Aziridination, acetolysis, and rearrangement (via **119**) delivered sulfonamide **120**, which could be advanced to the polycyclic scaffold **121** in 21 steps. Construction of the requisite bicyclo[3.2.1]octane motif **123** was accomplished through dearomative Birch reduction of the methyl phenyl ether and acetal deprotection (**121** → **122**), and vinylogous intramolecular aldol reaction. Diketone **123** was carried forward to the natural product napelline (**104**) in 10 steps.[160] In another landmark effort from 1974, Wiesner and coworkers reported the first total synthesis of the C_{19} diterpenoid alkaloid talatisamine (**117**) through the use of a biomimetic Wagner–Meerwein rearrangement of the atisine-type [2.2.2] bicyclic system **124** to the bicyclo[3.2.1]heptane **125** characteristic of the aconitine alkaloids.[162]

Adoption of the powerful oxidative dearomatization/Diels–Alder cascade in aconite alkaloid synthesis can be traced to Wang's 2012 formal synthesis of atisine (**101**) (Figure 17).[164] This highly efficient approach served to inspire many subsequent synthetic efforts, and now constitutes one of the most fundamental strategies in the area of diterpenoid alkaloid synthesis.[161] In Wang's report, commercial β-ketoester **126** was transformed into azabicyclo[3.3.1]octane **127** in two steps through methylation and a double Mannich reaction with benzylamine. This intermediate was converted to cycloaddition precursor **128** in 13 steps. Oxidative dearomatization with PIDA and subsequent intramolecular [4+2] cycloaddition established the full atisine core in a very expedient fashion, and **129** could be advanced to atisine along Pelletier's route,[138] thus completing the formal synthesis.

Similar oxidative dearomatization/intramolecular Diels–Alder sequences (e.g., **130** → **131**, **132** → **133**, and **134** → **135**) have served as the backbone of numerous other synthetic approaches, such as Ma's 2018 total synthesis of azitine (**136**),[165] Liu and Qin's synthesis of gymnandine (**137**),[166] and Xu's 2016 synthesis of spiramine C (**138**).[167] An interesting variant on this strategy was reported by Fukuyama in 2014, using ethylene as the dienophile in an intermolecular cycloaddition to build the core of lepenine (**139**).[168] Rapid construction of the caged polycyclic scaffold was achieved through back-to-back tandem reactions. Palladium-catalyzed deprotection of allyl carbamate **140** triggered intramolecular Mannich condensation to forge both challenging N–C20 and C10–C20 bonds in a single step (**141** → **142** → **143**). An intervening mesyl deprotection and hydride reduction then set the stage for oxidative dearomatization and high-pressure [4+2] cycloaddition (**143** → **144** → **145**) with ethylene to finish the synthesis of the denudatine core, which was advanced to the natural alkaloid lepenine (**139**) in eight steps.

Some of the most substantial recent contributions to diterpenoid alkaloid synthesis come from Sarpong, who has espoused the virtues of chemical network analysis in the deconstruction of topologically complex polycyclic scaffolds (Figure 18). In an early approach towards the hetidine family of natural products, Sarpong and coworkers utilized a gallium(III)-catalyzed cycloisomerization of enyne **146** to provide quick access to the key 6-7-6 tricyclic intermediate **147**.[169] Due to the lack of significant functionality, seven steps were required to convert **147** to benzylic alcohol **148**. Treatment with thionyl chloride afforded piperidine ring closure, and the methyl phenyl ether was deprotected with sodium ethanethiolate under

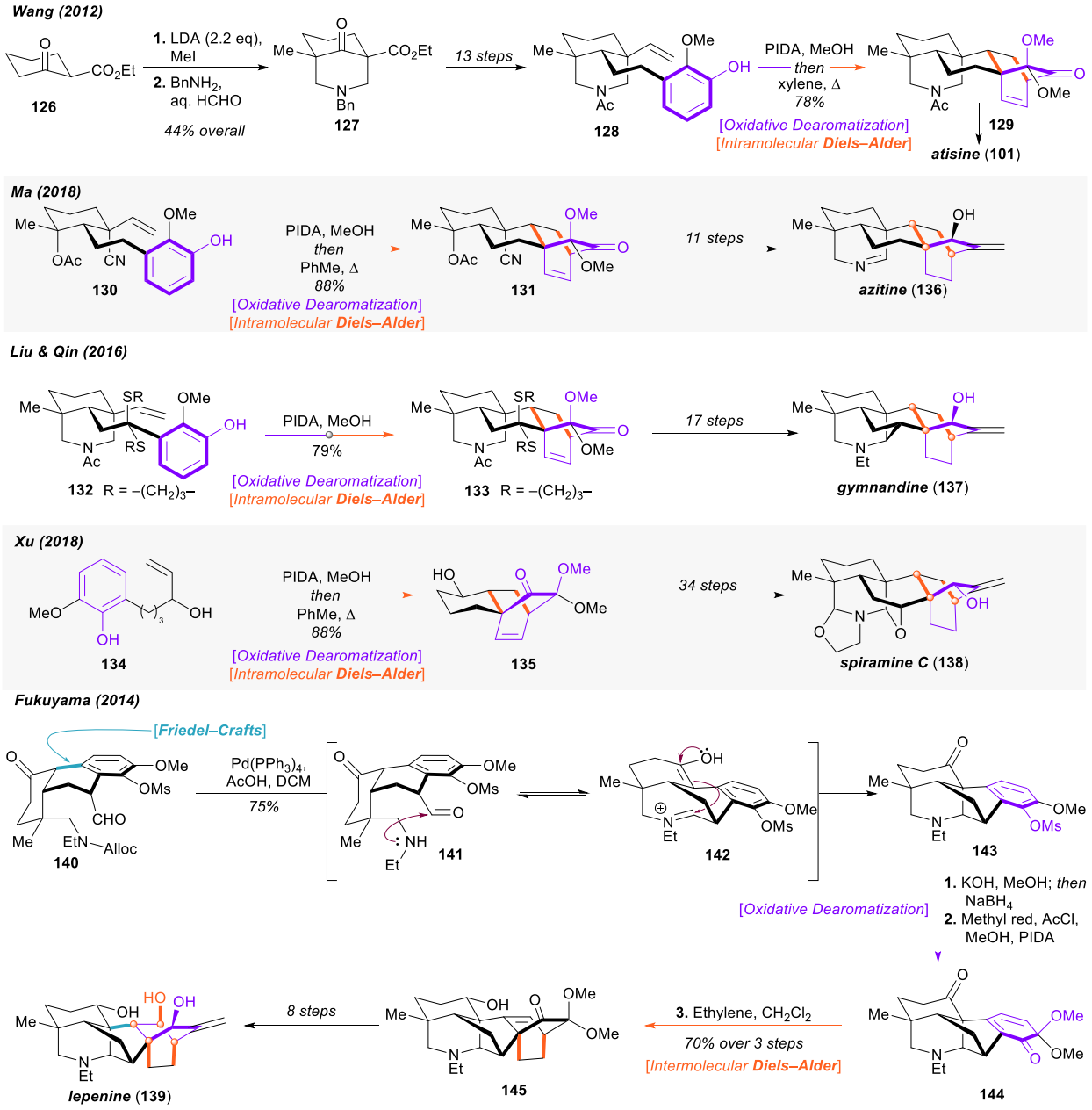


Figure 17. Selected total syntheses of diterpenoid alkaloids using the oxidative dearomatization/intramolecular Diels–Alder approach.

microwave irradiation, revealing **149**. Hypervalent iodine-induced oxidative dearomatization *para* to the phenol occurred through intramolecular nucleophilic attack of the Boc-carbamate, installing requisite C14 oxygenation as well as generating a reactive enone to be used in the final ring-closure sequence. This process was achieved, after Johnson–Lemieux oxidation of the allyl group, via silica-mediated conjugate addition of the resultant aldehyde **150** into the enone, followed by rhodium/alumina-catalyzed hydrogenation and subsequent intramolecular aldol reaction to close the final ring of the hetidine skeleton. Compound **151** was advanced to the natural product dihydronavirine (**152**) in seven steps.

In 2015, the Sarpong group reported an impressive hybrid application of dearomative logic and chemical network analysis that enabled the development of a general strategy towards C_{18}, C_{19}, and C_{20} diterpenoid alkaloids, and they demonstrated its efficacy by

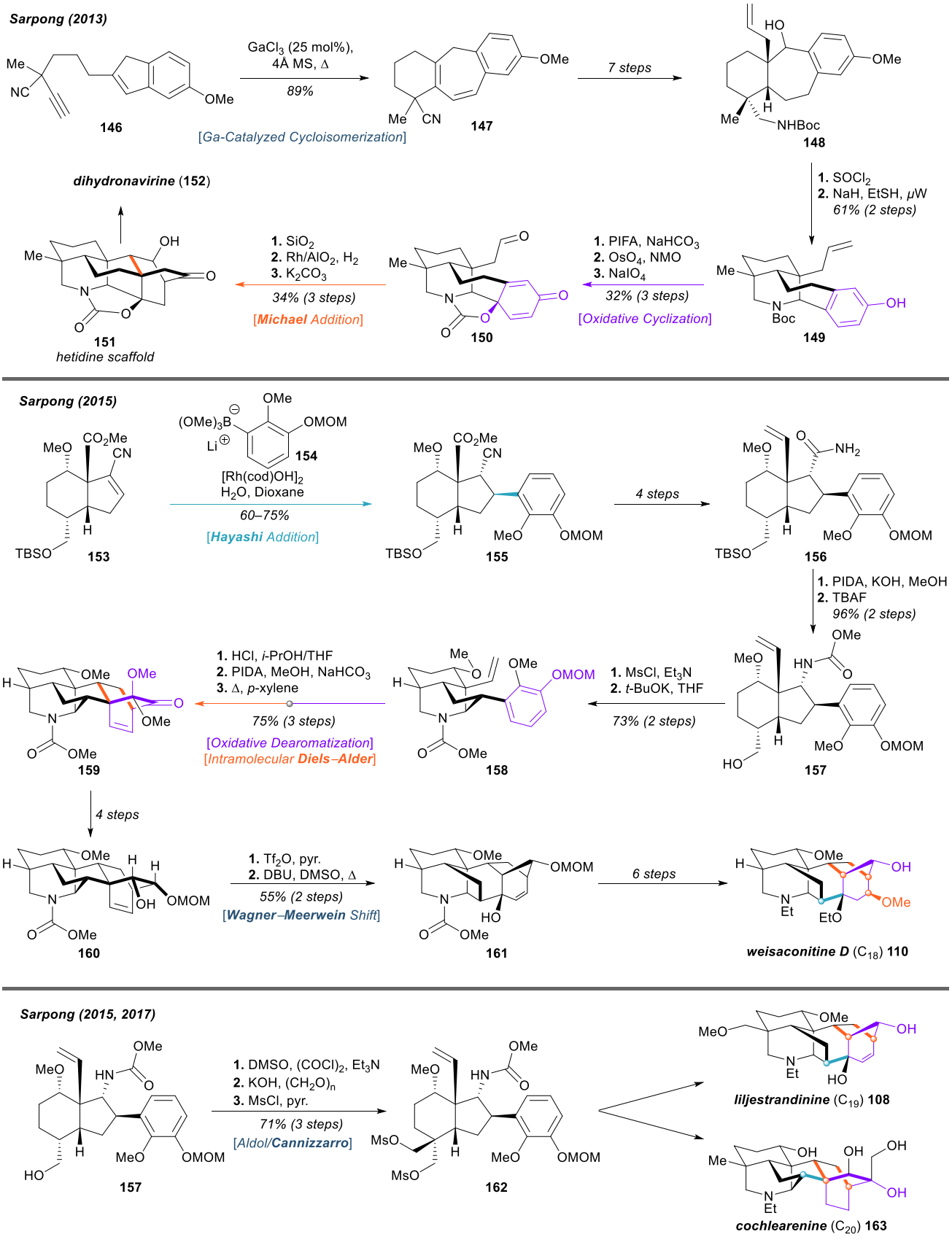


Figure 18. General approaches to C_{20}, C_{19}, and C_{18} diterpenoid alkaloids from the Sarpong group, using oxidative dearomatization and chemical network analysis.

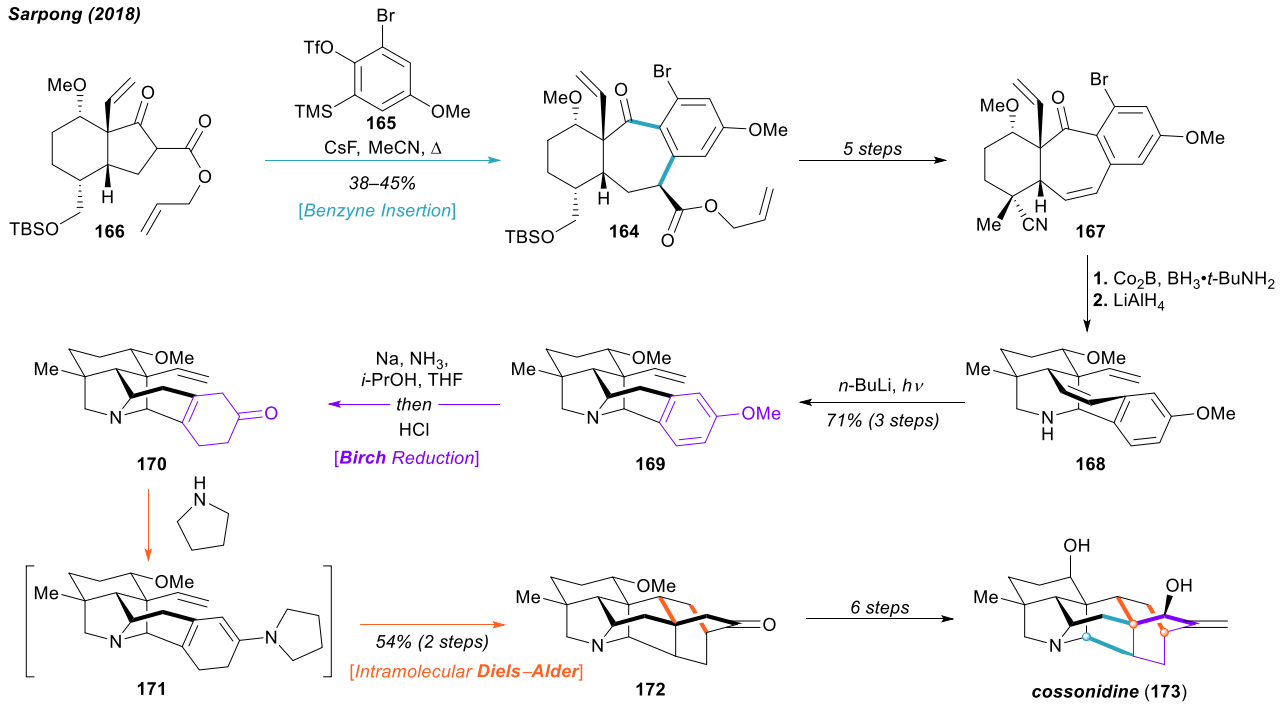


Figure 19. Sarpong's synthesis of cossonidine (**173**) using reductive dearomatization and chemical network analysis.

completing the first total syntheses of weisaconitine D (**110**) and liljestrandinine (**108**).[170] Highly functionalized hydrindane **153** was obtained in four steps through Diels–Alder cycloaddition. Hayashi addition of lithium boronate **154** served as a key step to install the guaiacol motif that is later dearomatized. β-cyanoester **155** was converted in four steps to primary amide **156**, which was then subject to a series of critical C–C and C–N bond-forming events that rapidly allow a denudatine-type core structure to take shape. PIDA-promoted Hofmann rearrangement of the amide and deprotection of the primary silyl ether with TBAF delivered methyl carbamate **157**, which underwent ring-closure to form the crucial piperidine moiety of **158** upon treatment with methanesulfonyl chloride and potassium *tert*-butoxide. Cleavage of the MOM ester allowed for subsequent oxidative phenol dearomatization and intramolecular [4+2] cycloaddition to fabricate the remainder of a denudatine-like core framework **159**, merely lacking the C4 methyl substituent. Four steps were required to prepare this scaffold for a biomimetic Wagner–Meerwein rearrangement (á la **124** → **125**, Figure 16) to the C_{18} diterpenoid alkaloid core, which was achieved by triflation of the free hydroxyl group in **160** and heating in DMSO with concomitant addition of DBU. The resulting [3.2.1] bicyclic system **161** could be advanced to the natural product weisaconitine D (**110**) in eight additional steps.

In this and a follow up report in 2017,[171] Sarpong and coworkers demonstrated an aldol/Cannizzaro sequence on an early intermediate from the weisaconitine D synthesis (**157** → **162**), enabling functionalization at the C4 position and extension of the synthetic strategy to both the C_{19} diterpenoid alkaloids as well as the denudatine-type C_{20} diterpenoid alkaloids. The generality of this approach was validated through the total synthesis of C_{19} diterpenoid alkaloids liljestrandinine (**108**),[170] and later of three C_{20} diterpenoid alkaloids, including cochlearenine (**163**), paniculamine (not pictured), and *N*-ethyl-1α-hydroxy-17-veratroyldictyzine (not pictured).[171]

In addition to their oxidatively dearomative strategies, the Sarpong group has recently reported an excellent joint application of reductively dearomative logic and chemical network analysis in a second-generation approach to the hetidine and hetisine scaffolds (Figure 19).[172] Taking advantage of recent developments in aryne chemistry from Stoltz,[173] Sarpong and coworkers were able to streamline their route to highly functionalized key 6-7-6 tricycle **164**—reminiscent of intermediate **148** in their earlier synthesis of dihydronavirine (**152**)—through aryne insertion of **165** into β-ketoester **166**, obtained in four steps from the common hydrindane precursor **153** in their previous routes. Notably, the aryl bromide was required to achieve proper regioselectivity in the aryne

insertion.[174] A five-step sequence (**164** → **167**) encompassing the removal of the allyl ester, conversion of the silyl ether to a nitrile, and installation of the necessary C4 methyl group of the C_{20} diterpenoid alkaloids delivered **167**, an important precursor compound for a series of highly productive C–C and C–N bond-forming events that swiftly build up the hetisine core scaffold in analogy to prior strategies from the Sarpong group. Chemoselective reduction of the nitrile with cobalt boride and borane *tert*-butylamine complex, followed by treatment with lithium aluminum hydride afforded ketone reduction, protodebromination, and direct cyclization to forge the N–C20 bond of **168**. Photochemical hydroamination (**168** → **169**) formed the challenging N–C6 bond, and a Birch reduction/intramolecular Diels–Alder sequence (**169** → **170** → **171** → **172**) similar to that used by Gin in the synthesis of nominine (**103**)[175] established the complete hetisine framework **172**. With this advanced intermediate in hand, Sarpong and coworkers were able to complete the synthesis of cossonidine (**173**) in six steps.

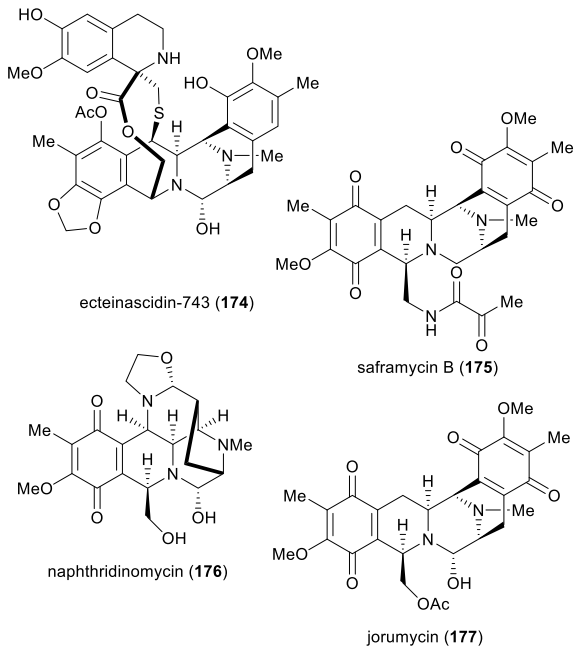


Figure 20. Structures of selected bis-tetrahydroisoquinoline alkaloids.

Alkaloids

bis-Tetrahydroisoquinoline Alkaloids: The remarkable story of the bis-tetrahydroisoquinoline (bis-THIQ) antitumor antibiotics begins in 1969 with the first reports of potent *in vivo* antitumor activity of crude extracts of the colonial sea squirt *Ecteinascidia turbinate* (e.g., **174**–**177**, Figure 20).[176] It would be another 21 years until the structure of ecteinascidin-743 (**174**), the agent responsible for this activity, was reported simultaneously by Rinehart[177] and Wright,[178] but the isolation of numerous other tetrahydroisoquinoline natural products captured the attention of researchers and catalyzed more than 40 years of study into their synthesis, structural elucidation, and chemical biology.[179] Landmark efforts from Fukuyama,[180,-186] Kubo,[187-201] Myers,[202-204] Corey,[205-209] Williams,[210-217] and others[218-224] have enabled synthetic access to many structurally complex bis-THIQ natural products, and have codified general strategies that build individual piperidine rings in a stepwise fashion via Pictet–Spengler, Bischler–Napieralski, and Pomeranz–Fritsch cyclizations[179,225] Two classic approaches from Fukuyama[181] and Myers[202] towards saframycin A (**178**) are depicted in Figure 21, both of which serve to illustrate the critical role of electron-rich arenes in facilitating electrophilic aromatic substitution chemistry to construct each of the piperidine rings (e.g., **179** → **180**, **181** → **182**, **185** → **186**, **187** → **188**, **188** → **189**).

Ecteinascidin-743 (**174**) has achieved iconic status as the first marine natural product approved for the treatment of cancer (trabectin), and as one of the most structurally complex drugs produced through chemical synthesis to date.[226] Although Corey's total synthesis[206] was able to supply enough material for clinical trials, industrial production required PharmaMar's development of a scalable semisynthetic route from cyanosafracin B,[222] averting the difficult construction of the functionalized bis-THIQ scaffold but also restricting the scope of analogues that could be generated for further medicinal chemistry endeavors. The biochemical profile of bis-THIQ natural products is very broad;[179] thus, significant effort has been put towards the identification and synthesis of simpler bis-THIQ natural products or analogues that retain these desirable properties, but which are more synthetically tractable.[204,207,209,212-214,216]

One such compound is jorumycin (**177**), first isolated in 2000 from the Pacific nudibranch *Jorunna funebris*, an antitumor bis-THIQ of nearly equivalent potency as ecteinascidin-743 (**174**), but with a stripped-down core scaffold.[227] An enantioselective synthesis of (–)-jorumycin was reported by Williams in 2005,[228] followed by several others,[229-231] all of which leverage biomimetic Pictet–Spengler reactions to construct both THIQ rings. One of the major synthetic challenges in the bis-THIQ natural products is the all-*cis* stereochemistry of sp^3 C–C bonds relative to the central piperazine ring, which has plagued a significant number of bis-THIQ synthetic efforts and demanded subsequent

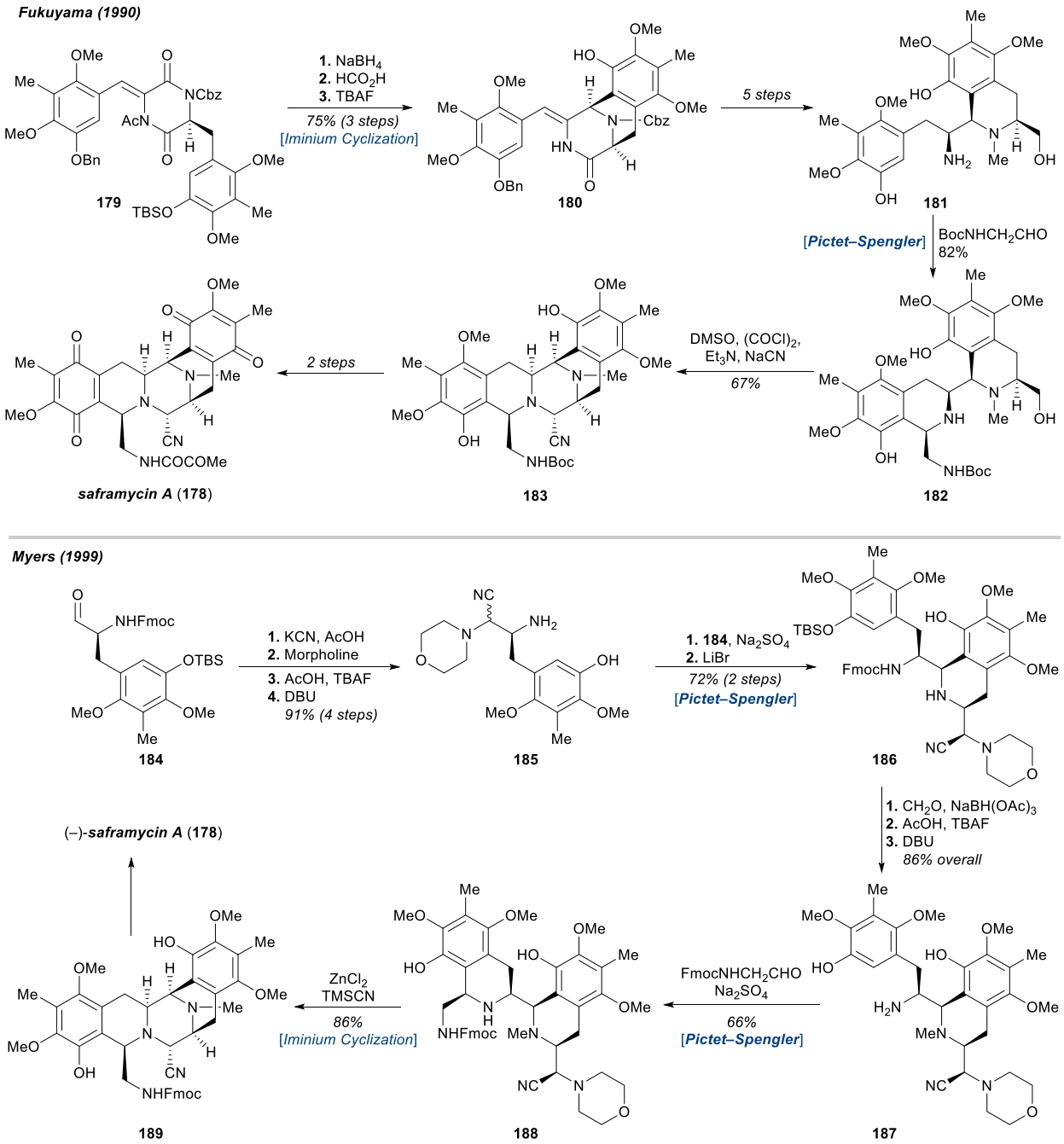


Figure 21. Fukuyama's and Myers's total syntheses of saframycin A (**178**), leveraging classical ring-forming reactions.

epimerization after the Pictet–Spengler or similar cyclization.[232]

In a beautiful application of dearomative logic, the Stoltz group reported in 2019 the asymmetric synthesis of (–)-jorumycin (**177**) by a fundamentally different strategy, exploiting the all-*cis* stereochemical relationships through the use of a catalytic asymmetric hydrogenation of a simple bis-isoquinoline (**190**, Figure 22).[233] The retrosynthetic application of late-stage quinone oxidation is the key transform that simplifies the structure of (–)-jorumycin to bis-THIQ **191**, in which two retrons for the asymmetric hydrogenation of isoquinoline can now be readily identified. **191** can be

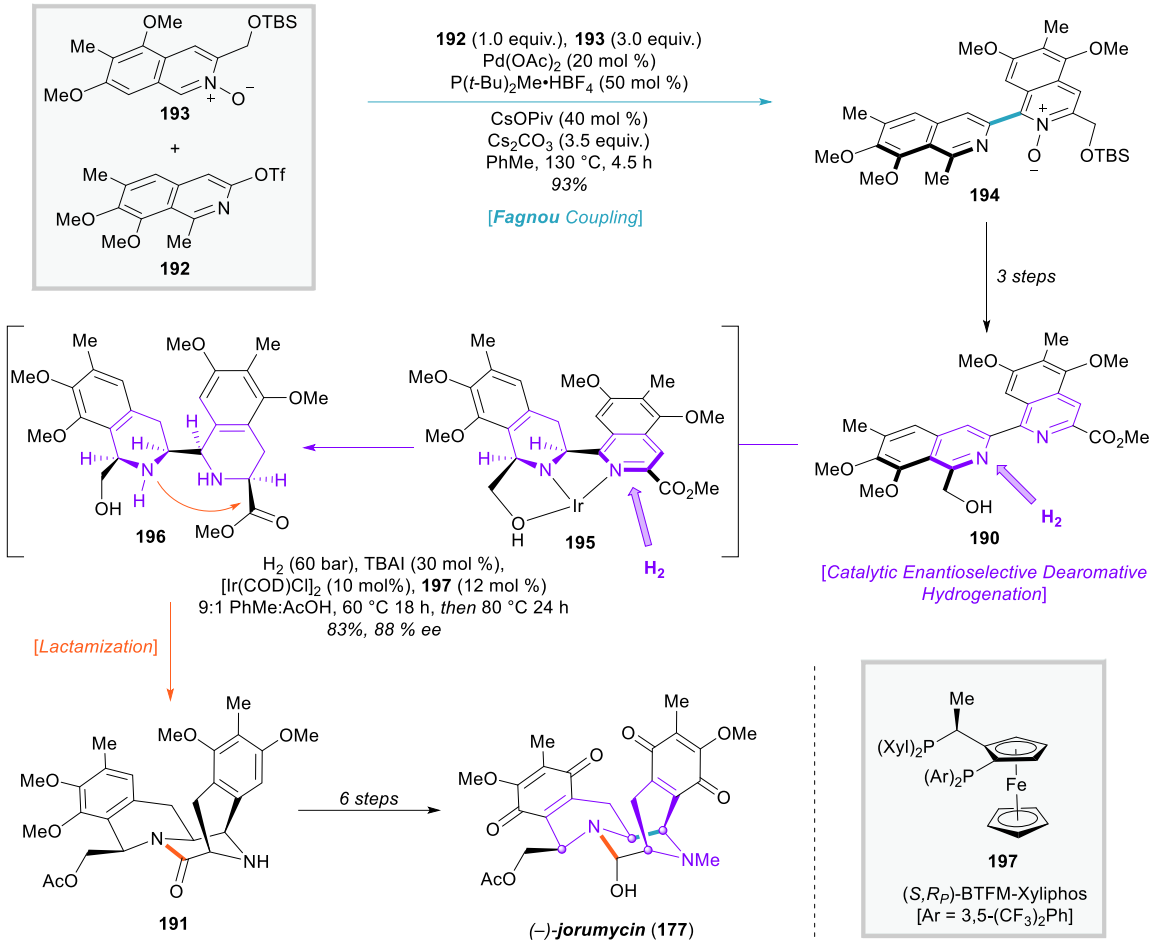


Figure 22. Stoltz's synthesis of jorumycin (**178**), using enantioselective hydrogenation of isoquinolines.

traced back to **190** through hydrogenation and lactamization, and this bis-isoquinoline can easily be disconnected through arene coupling chemistry.

This synthesis utilizes all three phases of dearomative logic to rapidly establish the core scaffold of the bis-THIQ natural products. Isoquinoline monomer **192** was synthesized in two steps using in-house aryne chemistry developed by the Stoltz group,[234] while isoquinoline *N*-oxide **193** was synthesized in two steps through a silver(I)-catalyzed cyclization of an alkynylbenzaldoxime. Direct cross-coupling of these arenes under Fagnou's conditions[235] forged a critical bond in **194** as a pre-dearomative event. Several redox adjustments of **194** were necessary to deliver gram-quantities of the dearomative hydrogenation substrate **190**. Notably, this cross-coupling strategy is unaffected by the electronics of the arenes, allowing for the synthesis of unnatural analogues with electron-withdrawing groups that would not be accessible through the conventional strategies based on electrophilic aromatic substitution.

Unlike most nitrogen-based heteroarenes, isoquinolines are very challenging substrates for enantioselective hydrogenation, and only a handful of examples have been reported.[32] The Stoltz team planned to use the unprotected hydroxymethyl substituent in concert with the isoquinoline nitrogens to chelate a transition-metal catalyst and direct the hydrogenation to the B-ring first. They reasoned that the addition of two molar equivalents of hydrogen to **190** would force the second isoquinoline into a pseudoaxial conformation (**195**) on the newly-formed piperidine ring, providing substrate-reinforced diastereoselectivity for a second dearomative hydrogenation from the same face, and leaving compound **196** poised for rapid post-dearomative lactamization to construct the final ring of the pentacyclic core. After substantial screening, a catalytic system was developed that could achieve this remarkable transformation in 83% yield, >20:1 d.r., and 88% ee. This powerful dearomative event set four stereocenters and closed the fifth ring of the bis-THIQ in a single step. After lactamization, the Stoltz group

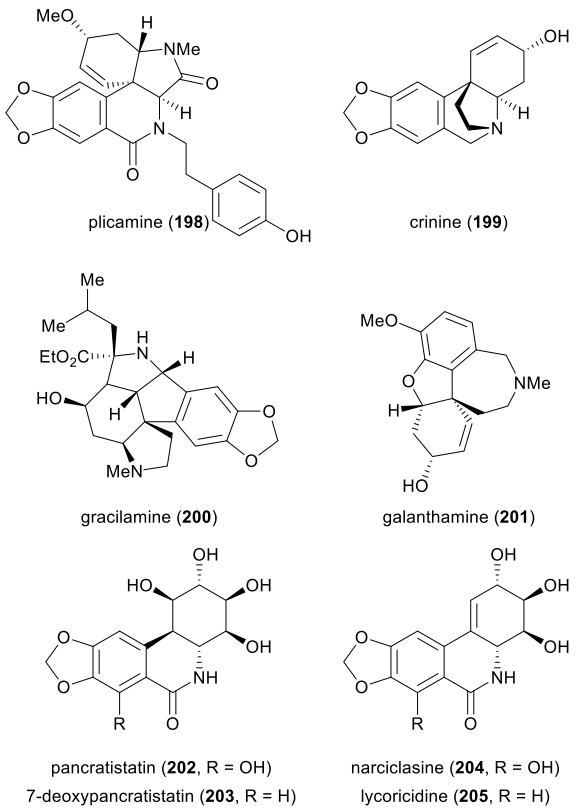


Figure 23. Structures of selected amaryllidaceae alkaloids.

was able to complete the synthesis of (–)-jorumycin (**177**) in six additional steps, intercepting the bis-THIQ natural product (–)-jorunnamycin *en route*. Using this non-biomimetic strategy, they prepared four unnatural analogues of **177** and investigated their cytotoxic effects through preliminary structure–activity relationship studies in collaboration with the Slamon group.

Amaryllidaceae Alkaloids: The Amaryllidaceae alkaloids and isocarbostyril constituents (e.g., **198–205**) have long served as benchmark compounds for synthetic chemists to test new methods and strategies but stand as important targets in their own right for their wide range of medicinal properties (Figure 23). Most notable are their potent antitumor and cholinesterase (AChE and BuChE) inhibitory activities, but these diverse natural products from the daffodil family have also demonstrated analgesic, antibacterial, antifungal, antimalarial, antiviral, anti-inflammatory, and even antidiabetic and anti-obesity effects.[236] The alkaloid galanthamine (**201**) has been approved by the FDA for the treatment of mild to moderate dementia and Alzheimer's disease due to its strong inhibition of acetylcholinesterase.[237]

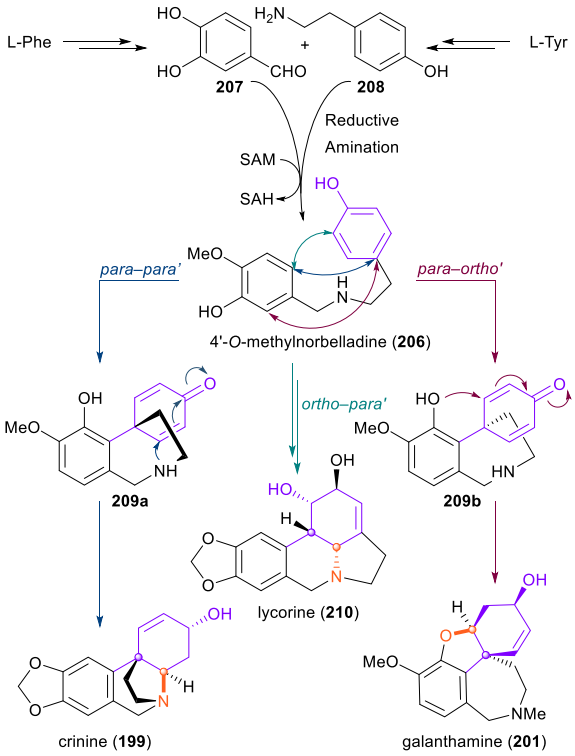


Figure 24. Different oxidative phenol couplings in Amaryllidaceae alkaloid biosynthesis generate diverse scaffolds.

Tyrosine-derived alkaloids such as **198–201** and isocarbostyril constituents **202–205** are particularly appropriate subjects for dearomative analysis because this is how nature makes them;[238] different oxidative phenol couplings of 4'-*O*-methylnorbelladine (**206**), generated from L-phenylalanine and L-tyrosine via reductive amination of **207** and **208**, give rise to three primary alkaloid scaffolds (**199**, **201**, **210**), which in turn may convert to several other major alkaloid families through bond cleavage and oxidative transformations (Figure 24).[236] Indeed, numerous early synthetic reports of dearomative routes to the lycorine (**210**),[239,240] galanthamine (**201**),[241-253] plicamine (**198**),[254-256] and crinine (**199**)[257-268] families of alkaloids have demonstrated the efficiency of this biomimetic strategy. Dearomative approaches towards the phenanthridine isocarbostyrils **202–205** through microbial arene oxidation have also been quite successful,[269-271] with notably strong work in this area from Hudlicky and coworkers.[272-280] Although non-biomimetic, these strategies showcase the power of dearomative logic in the construction of densely functionalized carbocyles.

The crinine scaffold in particular has been the subject of intense dearomative study. The requisite *para–para'* oxidative coupling has been achieved photolytically,[257] electrochemically,[258] and with

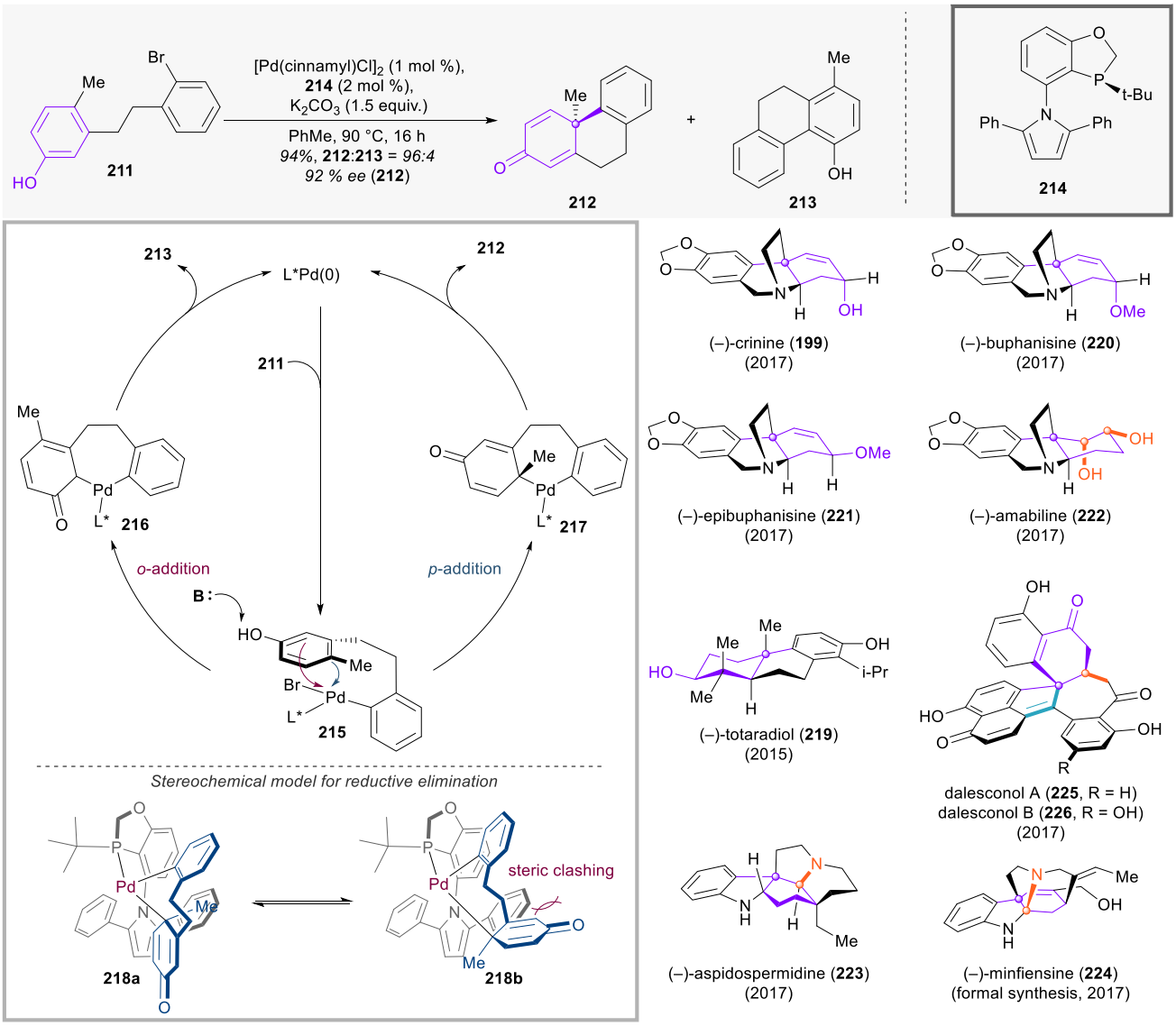


Figure 25. Palladium-catalyzed enantioselective dearomatization of phenols, and structures of natural products synthesized by the Tang group using this method.

stoichiometric oxidants such as $VOCl_3$,[259] $Tl(TFA)_2$,[260-262] $[Fe(DMF)_3Cl_2][FeCl_4]$,[263,264] VOF_3–TFA/TFAA,[265] and hypervalent iodine reagents.[266-268] In addition to the use of a stoichiometric (and often toxic) oxidant, a major drawback of these methods is their lack of enantioselectivity, although a limited number of asymmetric syntheses have been reported using chiral controller groups that require subsequent removal.[262,263]

Building off strong preliminary work from Buchwald[281-283] and You,[284] Tang and coworkers reported a dramatic advance in this coupling methodology in 2015 (Figure 25).[285] They found that, under palladium catalysis, dihydrostilbenoids containing a *para*-substituted phenol and an aryl bromide (e.g., **211**) could engage in a dearomative intramolecular Heck-type coupling to build a quaternary center and assemble the phenanthrenone skeleton **212**. Bulky chiral phosphine ligand **214** enables profound catalyst discrimination between the two enantiotopic faces of the phenol, and the product is generated in very high (up to 99%) enantiomeric excess. Although similar in appearance to previously reported oxidative phenol couplings, this method is actually isohypsic, thereby exchanging the use of stoichiometric oxidants for the requirement of an aryl bromide substrate.

The Tang group proposes the following mechanism: Oxidative addition of the palladium(0) catalyst to the aryl bromide **211** yields the palladium(II) complex **215**. The phenol may then undergo nucleophilic addition to the palladium(II) complex from either the *ortho* (**215** →

216) or the *para* (**215** → **217**) positions, leading to products **213** and **212**, respectively. Although **213** is the thermodynamically favored product, Tang proposes that palladacycle **217** is formed preferentially for kinetic reasons. Reductive elimination forges a new C–C bond, a quaternary stereocenter, and regenerates the palladium(0) catalyst.

This catalytic enantioselective dearomative cyclization holds enormous potential for application in the total synthesis of natural products, and the Tang group has done a fine job demonstrating this. In addition to disclosing the method, their initial publication included streamlined routes to a key chiral intermediate used in kaurene synthesis, the full skeleton of the anabolic steroid boldenone, and the terpenoid natural product (–)-totaradiol (**219**). This work was followed up in 2017 with highly efficient, biomimetic asymmetric total syntheses of several crinine-type alkaloids, including (–)-buphanisine (**220**), (–)-epibuphanisine (**221**), (–)-amabiline (**222**), and (–)-crinine (**199**) itself.[286] The same report also described the enantioselective syntheses of the *strychnos* alkaloids (–)-aspidospermidine (**223**, *vide infra*) and (–)-minfiensine (**224**), and a later publication describes the enantioselective syntheses of the complex aromatic polyketides dalesconol A and B (**225** and **226**, *vide infra*).[287]

The plicamine isocarbostyrils, first isolated in 1999,[288] have received considerably less attention than the crinine alkaloids but are in fact susceptible to the identical dearomative analysis, as they biosynthetically derive from crinine via ring cleavage and amination with tyramine. Thus, they contain the same dearomatized phenol and fused pyrrolidine, a fact that Ley and coworkers used to great advantage when they reported the first and only asymmetric total synthesis of (+)-plicamine (**198**) in 2002.[254,255] In addition to its biomimetic oxidative phenol dearomatization, this 16-step sequence is notable for using almost entirely solid-supported reagents and scavengers, requiring no chromatography. This strategy was later applied to the total syntheses of (–)-obliquine and (+)-plicane as well.[256]

A very interesting adaptation of Ley's route was reported by Miranda and Mijangos in 2016 (Figure 26).[289] The authors cleverly noticed that Ley's key intermediate **227** prior to dearomatization could essentially be synthesized in a single step through an Ugi four-component condensation of *p*-hydroxybenzaldehyde (**228**), piperonylamine (**229**), formic acid (**230**), and methylisocyanide (**231**) (the only difference being a formate-protected amine vs. Ley's trifluoroacetamide). This reaction was optimized and found to proceed best under microwave irradiation.

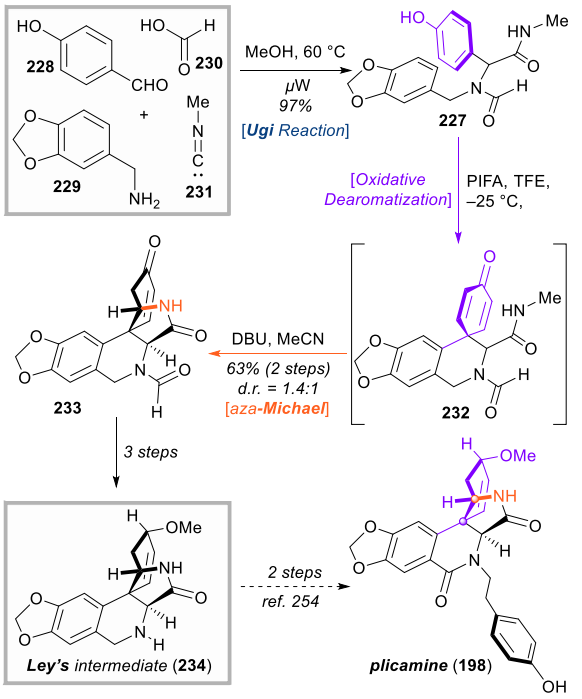


Figure 26. Miranda and Mijangos's approach to plicamine, featuring a four-component Ugi reaction and oxidative dearomatization.

The Ugi adducts **227** were immediately subject to hypervalent iodine-mediated oxidative dearomatization (**227** → **232**), and the authors were able to develop a one-pot sequence incorporating this dearomative cyclization with base-promoted aza-Michael addition (**232** → **233**) to fully assemble the plicamine scaffold in just three steps from very simple precursors. Given the modularity of the Ugi reaction, a library of seventeen plicamine-type analogues were readily synthesized by changing the carboxylic acid and isocyanide components. Finally, they demonstrated the applicability of this method by intercepting a late-stage intermediate (**234**) from Ley's route, completing an 8-step formal synthesis of (±)-plicamine (**198**). Although the synthesis is racemic, Miranda's use of the Ugi four- component reaction reduces the step count by half and provides nearly endless opportunities for analogue synthesis.

Although only a recent addition to the family of Amaryllidaceae alkaloids, the rare pentacyclic dinitrogenous base gracilamine (**200**)—isolated in 2005— has been the subject of no fewer than eight

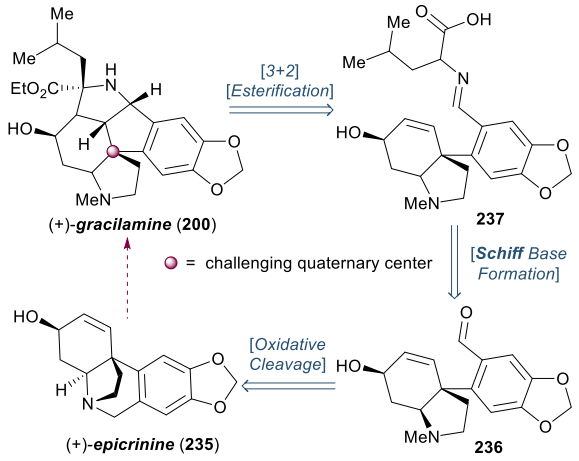


Figure 27. Proposed biosynthetic pathway from crinine to gracilamine.

synthetic efforts within the past ten years.[290-298] The intriguing structure of gracilamine is proposed to derive biosynthetically from (+)-epicrinine (**235**, Figure 27). Oxidative cleavage of the B-ring and condensation of aldehyde **236** with L-leucine generates imine **237**. Intramolecular 1,3-dipolar cycloaddition completes the pentacyclic core and, followed by esterification, furnishes (+)-graciliamine (**200**).[236] In addition to a complex ring system containing two basic amines, a major challenge in the synthesis of gracilamine is the construction of the highly congested all-carbon quaternary stereocenter embedded within the polycyclic scaffold at the junction of three rings. This quaternary center is established through oxidative dearomative cyclization in the biosynthesis of crinine, which suggests that this motif may be amenable to dearomative retrosynthetic logic; however, the majority of synthetic efforts towards gracilamine have avoided this approach.[290]

The first total synthesis, reported by Ma in 2012, actually did construct the quaternary carbon via oxidative dearomatization, but carried symmetric achiral intermediates most of the way through the route, finally establishing it as a stereocenter with a biomimetic 1,3-dipolar cycloaddition (**238** → **239**) in good d.r. (5.8:1, Figure 28).[291] Gao's 2014 synthesis forged this critical asymmetric carbon center through photo-Nazarov cyclization (**240** → **241**),[292] while a 2016 formal synthesis from Snyder utilized an intramolecular [4+2]/*retro*-[4+2] cycloaddition of a pyrone (**242** → **243**).[293] More exotic strategies from Yu (formal synthesis, 2016),[294] Pandey (2017),[295] and Banwell (2017)[296] construct this stereocenter through Rh-catalyzed [3+2+1] cycloaddition (**244** → **245**), ring opening of an aza-norbornene derivative (**246** → **247**), and Pd-catalyzed intramolecular Alder-ene reaction (**248** → **249**), respectively. In 2017, Zhou and Xie

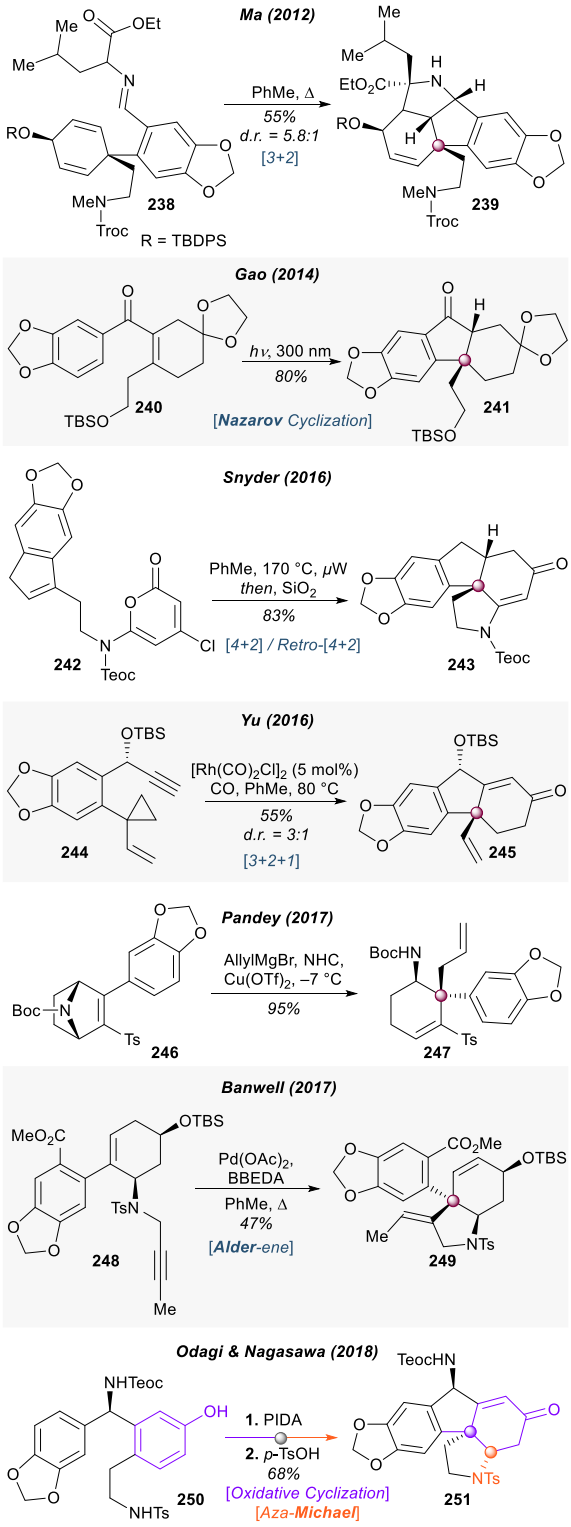


Figure 28. Key steps forming the congested quaternary center in several gracilamine total syntheses.

published a notable semisynthesis of (+)-gracilamine from a crinine derivative that proceeds through oxidative cleavage, Schiff-base formation with

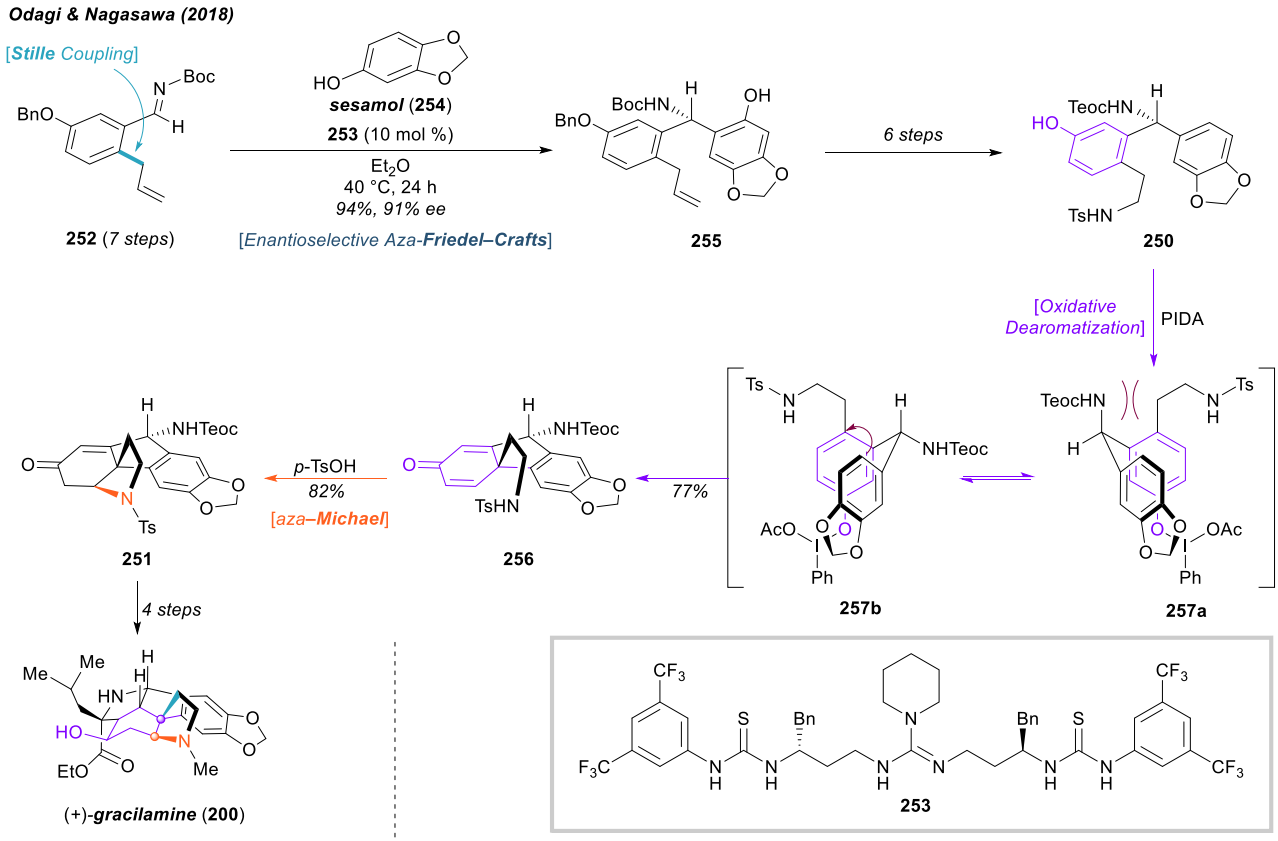


Figure 29. Total synthesis of gracilamine from Odagi and Nagasawa.

L-leucine, and intramolecular 1,3-dipolar cycloaddition, lending strong support to the proposed biosynthesis.[297]

An elegant approach to (+)-gracilamine (**200**) was reported by Odagi and Nagasawa in 2018, utilizing a *non-biomimetic* oxidative dearomative phenol coupling (**250** → **251**) to first assemble the somewhat strained 6-5-6 core ring system, after which the periphery rings could be installed stepwise (Figure 29).[298] Eschewing the biomimetic 1,3-dipolar cycloaddition strategy used by Ma, Pandey, Zhou and Xie, and Banwell to build the E-ring, Odagi and Nagasawa opted to disconnect this motif through the *retro*-Mannich transformation first reported by Gao and used in the formal syntheses of Snyder and Yu. A logical aza-Michael transform unveils a catechol-bound derivative that could be disconnected in a number of different ways; in this context the authors chose to use an organocatalytic enantioselective aza-Friedel–Crafts reaction that had been previously developed in their laboratory.[299]

All three phases of dearomative logic were applied during the construction of the quaternary stereocenter and the adjacent pyrrolidine ring. Benzaldimine **252** was synthesized from 3-hydroxybenzoic acid in seven steps, using standard EAS to brominate *para* to the phenol. Subsequent cross coupling with allyltributylstannane installed the pendent allyl substituent, which would later be transformed to an amine. In the presence of chiral guanidine–bisthiourea bifunctional organocatalyst **253**, the enantioselective aza-Friedel–Crafts reaction with sesamol (**254**) proceeded smoothly, delivering benzhydrylamine **255** in 94% yield and 91% ee. This compound was converted to the dearomative cyclization precursor through a six-step sequence (**255** → **250**) incorporating triflation of the phenol, reductive ozonolysis and nucleophilic azidation of the allyl group, and catalytic hydrogenation to cleave the triflate and reduce the azide to the amine. The amine was protected as a toluenesulfonylamide, and the Boc was exchanged for a Teoc group due to solubility issues.

Oxidative dearomatization of **250** with phenyliodine(III) diacetate closed the B-ring of gracilamine, forming the central quaternary center of **256** with good yield and as a single isomer. The authors propose that this excellent diastereoselectivity derives from the configuration of the carbamate set during the aza-Friedel–Crafts reaction, driving a conformational preference (**257a** → **257b**) in the transition state to avoid steric interactions between the bulky protected amines and yielding exclusively the *trans*-isomer **256**. The resulting cyclohexadienone was used immediately to build the pyrrolidine ring in **251** through an acid-

catalyzed aza-Michael addition. Having essentially arrived at Gao's intermediate,[292] Odagi and Nagasawa were able to complete the total synthesis of (+)-gracilamine (**200**) in four steps encompassing hydrogenation of the enone, condensation of an α–ketoester with subsequent Mannich annulation, hydride reduction of the ketone, and removal of protecting groups. Notably, this enantioselective dearomative route enabled the authors to synthesize enough material to determine its absolute configuration, a characteristic that had remained a mystery for thirteen years.

Isocarbostyril Alkaloids: The *Amaryllidaceae* constituents that have attracted by far the most interest from the synthetic community are the isocarbostyrils narciclasine (**204**), lycoricidine (**205**), pancratistatin (**202**), and 7-deoxypancratistatin (**203**, Figure 23). The potent antitumor effects of crude daffodil extracts were known to ancient Greek physicians by the time of Hippocrates and have found applications in various medicinal practices throughout the world for over two thousand years.[300] The identification of the isocarbostyrils **202**–**205** as the specific metabolites responsible for this activity stimulated intense research efforts aimed to develop these auspicious compounds into modern anticancer treatments through natural product total synthesis, analogue development, and structure–activity relationship studies.[301]

To address the difficulties encountered in their isolation, particularly regarding the low yield of the pancratistatins **202** and **203**, dozens of total syntheses of the isocarbostyril alkaloids have been reported; however, the densely packed functionality decorating their compact aminocyclitol cores poses a daunting challenge for practical and efficient total synthesis, and despite the brevity and elegance of many approaches, until recently, only milligram quantities of the isocarbostyril alkaloids have been prepared. Several excellent reviews summarizing the state of *Amaryllidaceae* isocarbostyril alkaloid synthesis have been published[300,302] and thus only one particularly strong pioneering example will be discussed here.

In 1995, Hudlicky and coworkers published the first asymmetric total synthesis of (+)-pancratistatin (**202**), leveraging the power of dearomative microbial oxidation of bromobenzene (**258**) to acquire optically pure, *cis*-dihydrodiol **259** (Figure 30).[274] This highly strategic starting material, with the necessary asymmetry and vicinal *syn*-diol, possesses two sterically and electronically differentiated olefins suitable for further elaboration to the full aminocyclitol core through a series of olefin and functional-group

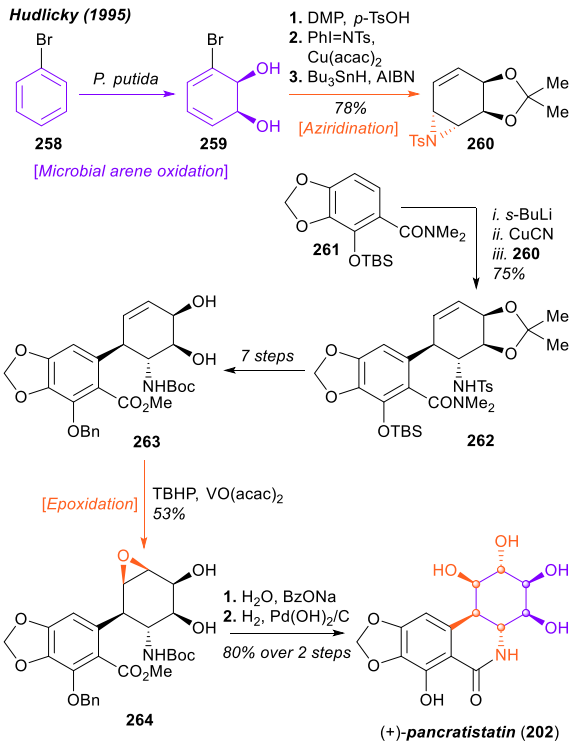


Figure 30. Hudlicky's total synthesis of pancratistatin.

manipulations. Acetonide protection of the diol was followed by aziridination to install a C–N bond, and the vinyl bromide—no longer necessary to maintain asymmetry—was removed via radical dehalogenation (**259** → **260**). Vinylaziridine ring opening with the higher-order aryl cuprate derived from arene **261** cleanly produced tosylamide **262** in 75% yield, bearing four requisite components of the hexafunctionalized aminocyclitol core. At this stage, seven steps were required to adjust the functionality and protecting groups from **262** to **263** to prepare for the final olefin functionalization and δ-lactam closure. The final *trans*-diol **264** was synthesized through a Sharpless directed epoxidation and benzoate-catalyzed epoxide opening, with concomitant cleavage of the Boc group and cyclization of the lactam. Although some debenzylation was observed in the previous step, the authors reported a more efficient deprotection via hydrogenolysis that delivered (+)-pancratistatin (**202**) in 80% yield.

With modern developments in dearomative methods, Sarlah and coworkers reported rapid strategies towards the isocarbostyril alkaloids in 2017 and 2019 (Figure 31).[303,304] Using the arenophile-mediated asymmetric dearomative *anti*-carboamination, a catalytic desymmetrization of benzene (**265**) with MTAD (**266**) was achieved in 98:2

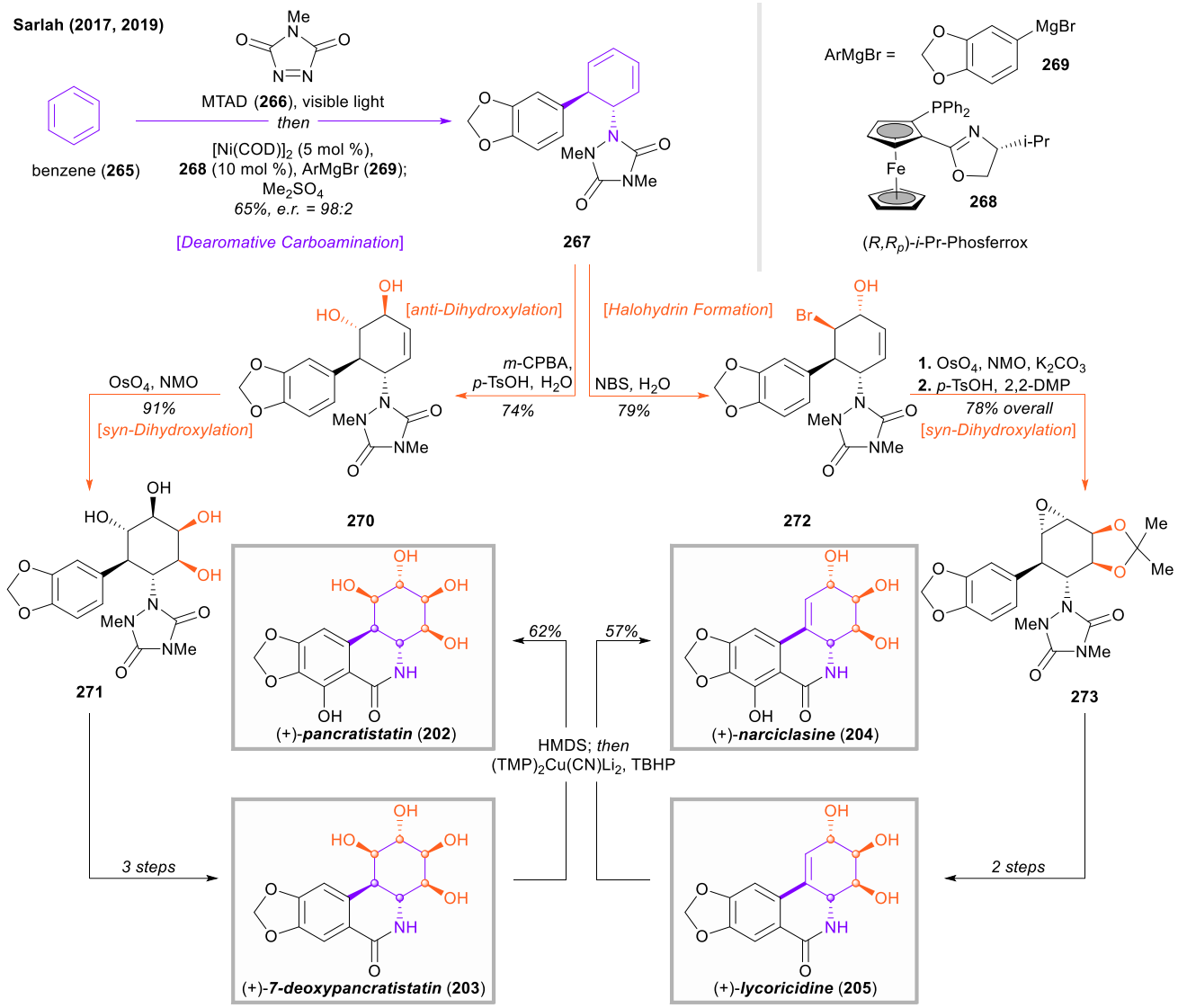


Figure 231. Sarlah's catalytic desymmetrization of benzene and application to the total synthesis of pancratistatin, 7-deoxypancaratistatin, narciclasine, and lycoricidine.

er. The product, critical diene intermediate **267**, could easily be elaborated to the full aminocyclitol core of the pancratistatins in just two steps, consisting of an *anti*-dihydroxylation followed by a *syn*-dihydroxylation (**267** → **270** → **271**). Notably, all six components of the aminocyclitol core were installed in just three steps, treating benzene as a surrogate for 1,3,5-cyclohexatriene subjected to three subsequent olefin difunctionalization reactions. This intermediate was carried forward to complete the synthesis of (+)-7-deoxypancratistatin (**203**) in just three steps. Alternatively, diene **267** underwent a bromohydrin reaction with concomitant aryl bromination with NBS in water. Upjohn dihydroxylation of **272** was followed by treatment with potassium carbonate to facilitate epoxide closure, and the diol was protected as the acetonide **273**. This intermediate was readily advanced to the natural product (+)-lycoricidine (**205**) in three steps. Although the syntheses of the hydroxylated isocarbostyrils pancratistatin (**202**) and narciclasine (**204**) could be completed through analogous routes that incorporated an appropriately oxidized Grignard reagent in the dearomative carboamination, Sarlah's strategy towards these natural products is unique in that it provides the first direct access from their deoxygenated congeners. After global silylation of the free hydroxyl moieties of **203** and **205** with HMDS, a novel, amide-directed arylcupration, developed by Uchiyama and coworkers,[305] allowed for the direct oxidation with TBHP to complete the syntheses of both (+)-pancratistatin (**202**) and (+)-narciclasine (**204**) in a total of seven steps from benzene.

Morphinan and Hasuban Alkaloids: Given their potent analgesic activity and therapeutic applications, morphinan (**274**)-based opioid narcotics such as morphine (**275**), codeine (**276**), hydrocodone (**277**), and oxycodone (**278**) have been the subject of extensive studies (Figure 32).[306] Morphinan biosynthesis begins with the condensation of two tyrosine derivatives, dopamine (**279**) and 4-hydroxyphenylacetaldehyde (**280**). Multiple methyl transfers, hydroxylation of C4, and epimerization at C9 furnishes the key biosynthetic precursor (*R*)-reticuline (**281**). Salutaridinol (**282**), the first promorphinan alkaloid, is produced via cytochrome P450 (SalSyn)-catalyzed intramolecular phenol coupling. Ketone C7 reduction catalyzed by NADPH-dependent reductase (Sal) is followed by acetyl transfer to deliver intermediate **283**. Spontaneous rearrangement occurs, yielding thebaine (**284**), the first pentacyclic morphinan alkaloid. Several additional biocatalytic steps are required for conversion of thebaine into various morphinans such as morphine (**275**) and codeine (**276**).

The exceptional medicinal importance of the morphinan alkaloids stimulated copious synthetic studies since the early 1950s.[307,308] More than 30 total and formal syntheses have been reported to date (Figure 33). Construction of the quaternary stereocenter at C13, buried within the caged structure, might be considered to be the most significant obstacle *en route* to morphinans. Informed by the biosynthetic hypothesis, researchers have often incorporated dearomative cyclization as a key transform in their retrosynthesis. Indeed, dearomative logic in the context of morphinan synthesis has proven quite fruitful, as the corresponding reticuline-like aromatic precursors such as **285** can be easily synthesized from simple building blocks (e.g., via Bischler–Napieralski reaction of **286** and **287**).

The first practical synthesis, reported by Rice in 1980, is a milestone in the field of morphinan alkaloids (Figure 33).[309] The key C12/C13 bond formation is secured by Grewe-type cyclization under strong acidic conditions. The requisite precursor **288** was obtained *via* Birch reduction of the corresponding methoxy-substituted aromatic compound, and a bromine atom was used as a blocking group on the arene to achieve necessary site-selectivity during Grewe cyclization (**288** → **289**). Thus, in this case dearomative cyclization is separated into two distinct chemical operations. Compound **289** was further elaborated to (±)-dihydrothebaione, a precursor for morphine (**275**), codeine (**276**) and thebainone, in only six steps from commercial material with 37% overall yield. Another classical approach is a direct *ortho-para* phenolic coupling (**290** → **291**). Notably, this biomimetic

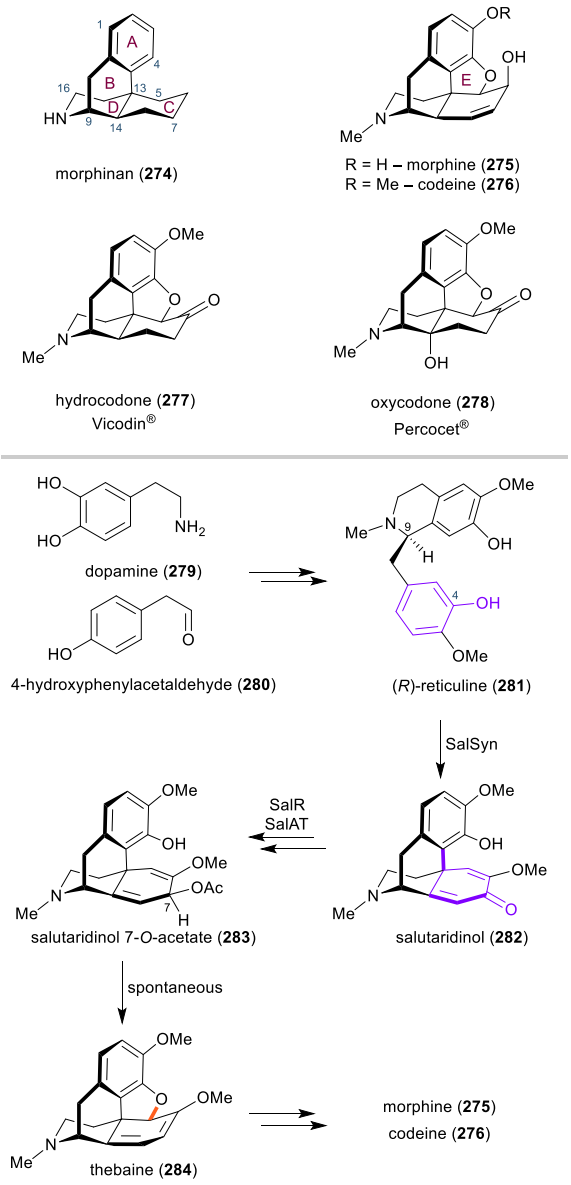


Figure 32. Structures of selected morphinan alkaloids and proposed biosynthetic pathway.

transformation is challenging to reproduce in a flask, as four potential constitutional isomers can be expected. Significant efforts were needed to identify effective conditions, since inherent reaction selectivity lies towards undesired 8,6´- and 4a,6´-isomers.[310] In 1983, White and coworkers published a synthesis of (–)-codeine employing a bromine substituent at the 6´-position to overcome this intrinsic bias and furnish the desired scaffold of the natural product in 21% yield.[311] In 1993, Overman applied a Heck cyclization (**292** → **293**) in his enantioselective synthesis of dihydrocodeinone and morphine.[312] This approach would become canonical in the field. Of note, even though dearomatization is not involved in the key

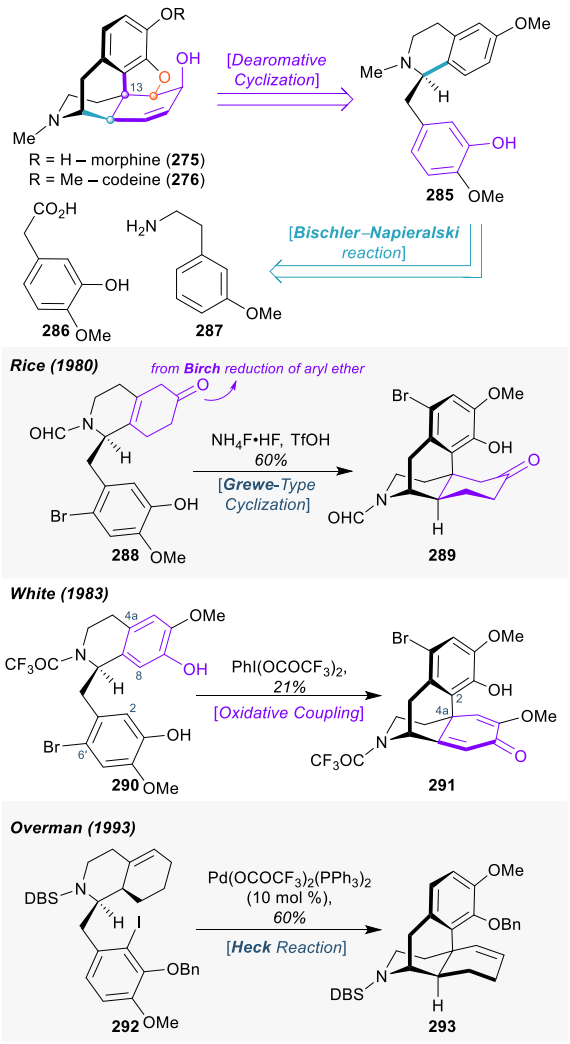


Figure 33. Classical approaches for the synthesis of morphinan alkaloids.

transformation, substrates like **292** are often synthesized from corresponding aromatic counterparts. While other elegant strategies towards morphinans have emerged over the years,[313-316] considering the tremendous success of dearomative methods, it is not surprising that, even after 35 years, these approaches still dominate the field.

During last decade, significant progress was made to increase the selectivity and efficiency of phenolic oxidative couplings (Figure 34). To avoid regioselectivity issues in his formal synthesis of (–)-morphine, Gaunt used substrate **294** for oxidative coupling, the structure of which significantly differs from biosynthetic precursor **281**.[317] The existing stereocenter at C16 serves as a controlling element in the following Michael addition (**295** → **296**). The overall process delivers the desired product in 48% yield and furnishes three new stereocenters with exclusive diastereoselectivity. Downstream intermediate **297** was subjected to a sequence comprising Luche reduction, treatment with acid, and subsequent reductive amination in order to rearrange the core into the morphinan scaffold (**298** → **299** → **300**).

Another demonstration of the unique ability of dearomative approaches to convert easily accessible arenes into three-dimensional complex structures is formal synthesis of (–)-thebaine (**284**) completed by Opatz and coworkers.[310] In the quest to overcome the undesired regioselectivity of the oxidative coupling, substrate **301** with a symmetrically oxygenated aromatic B-ring was employed. Anodic oxidation (**301** → **302**) in an undivided cell reliably affords the cyclized product in good yield. A six-step sequence allows for orthogonal deprotection, deoxygenation of C5′ and E-ring formation. Ultimately, the phenolic coupling strategy can be rightfully considered to be one of the most powerful for the synthesis of morphinan alkaloids. However, further improvements are desirable, such as exclusion of excessive substitution in aromatic precursors, which inevitably hampers efficiency of the synthesis.

Tandem dearomatization/Heck cyclization is a remarkably effective tactic for construction of the morphinan scaffold (Figure 35). For that reason, this approach has been widely implemented in key retrosynthetic disconnections. Chen and coworkers applied oxidative dearomatization of the arene **304** with singlet oxygen.[318] Desymmetrization (**305** → **306**), catalyzed by chiral phosphoric acid **307**, followed by hydrogenation and fragmentation, afforded intermediate **308**. Pd-catalyzed cyclization yielded key ABC-ring system **309** in 69% yield. Finally, Ueno–Stork cyclization served for construction of the C13 stereocenter within tetracyclic fragment **310**. Seven additional steps were required to complete total synthesis of *ent*-oxycodone (**278**).

The use of enzymatic arene oxidation in the context of the dearomatization/Heck-based strategy towards morphinans was explored by Hudlicky and coworkers.[319] Phenethylacetate **311** was subjected to microbial dihydroxylation in whole-cell fermentation with *E.coli* JM109(pDTG601A) to furnish **312** in 5 g/L yield. Semireduction of the diene followed by protection (**312** → **313**) and Mitsunobu substitution with phenol **314** afforded intermediate **315**. Thus, only four steps including the key dearomatization of a simple arene were necessary to bring significant complexity that would otherwise be hard to achieve. Heck cyclization (**315** → **316**) forged the AEC-ring system of oxycodone with concomitant formation of the stereocenter at C13 in 89% yield. Four distinct approaches were developed by the group to complete

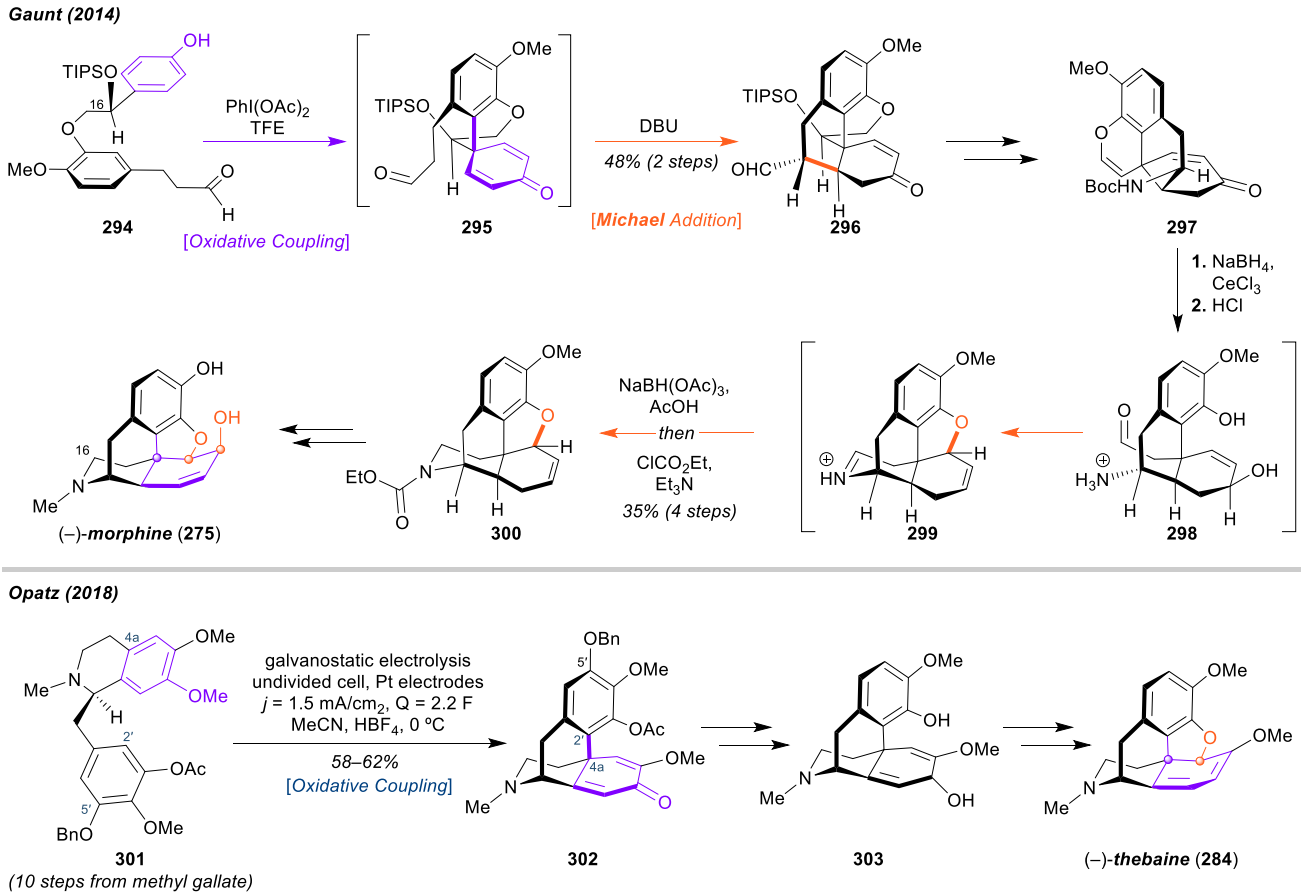


Figure 34. Modern syntheses of morphine and thebaine with improved oxidative coupling conditions.

the total synthesis of *ent*-oxycodone with the most efficient comprising only five steps from **316**.[320]

Besides evolution of the classical approaches towards morphinans, new tactics have emerged over the years. For example, Hudlicky reported the total synthesis of *ent*-hydromorphone (**317**) using a double dearomatization/cycloaddition strategy.[321] Commencing with an analogous microbial dearomatization of phenethylbromide (**318** → **319**), compound **320** was attained through a nine-step synthetic sequence. Lead-mediated oxidative dearomatization (**320** → **321**) of the phenol followed by *in situ* Diels–Alder cycloaddition (**321** → **322**) proceeded in 50% yield. The simultaneous formation of the ABCE-ring system of morphine along with quaternary and tertiary stereocenters in the course of a single operation demonstrates a good suitability of such dearomative logic. *ent*-Hydromorphone (**317**) was obtained after five additional steps. Notably, only the unnatural series of morphinans can be synthesized using the chemoenzymatic approaches shown in Figure 35 due to the inability to switch the sense of enantioinduction during microbial oxidation.

The hasubanan (**323**) alkaloids are closely related natural products to morphinans but with a rearranged [4.4.3]-propellane core (Figure 36).[322] They are mostly produced by plants of genus *Stephania*. Comparatively little is known regarding their biosynthesis as well as medicinal potential. In 2011, the Herzon[323] and Reisman[324] laboratories published enantioselective total syntheses of the hasubanan alkaloids (–)-runanine (**324**) and (–)-8-demethoxyrunanine (**325**) employing very similar strategies (Figure 37): the sequence of 1,2-addition to a quinone derivative followed by Friedel–Crafts cyclization was utilized in order to furnish the desired scaffold. Interestingly, in both instances easily accessible arenes were used as starting materials, following a structure-based retrosynthetic strategy. Of note, even though dearomatization is not involved in the key bond-forming events, the assortment of functional groups available after the dearomative process and their orthogonal reactivities are crucial for expedient elaboration of the synthetic precursors.

In Herzon's synthesis, substituted pyrogallol **327** was oxidized to the corresponding quinone.[323] Regio- and enantioselective cycloaddition with 5-

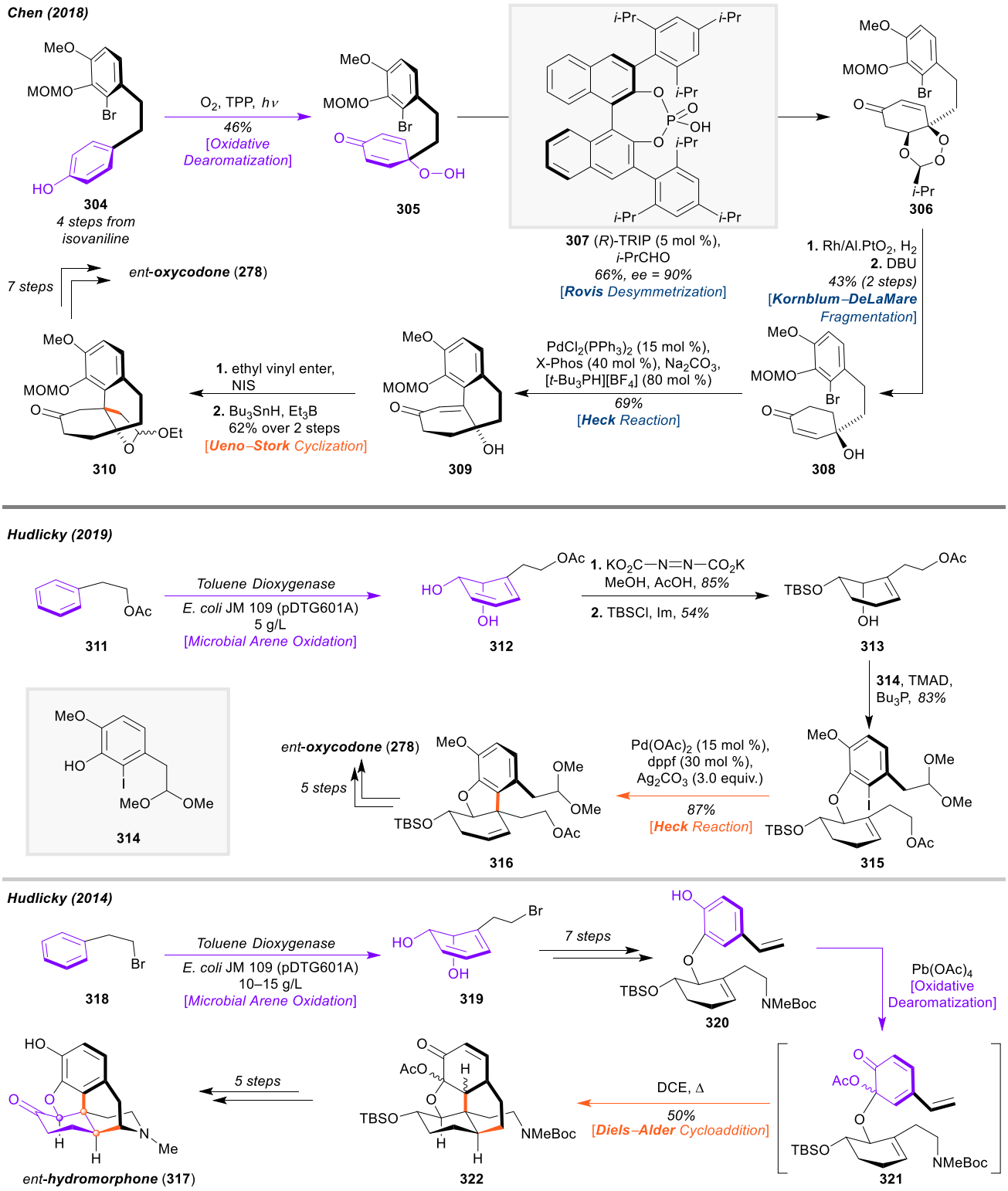


Figure 35. Approaches to morphinan alkaloids using dearomatization/Heck sequences.

trimethylsilylcyclopentadiene was exploited to mask the quinone motif, prevent tautomerization in the following steps, and render the synthesis enantioselective. Compound **328** was obtained in 78% yield and 93% ee. Staudinger reduction, methylation of the resulting imine, and addition of alkynyl lithium reagent **331** into the iminium cation produced **332** in 62% yield. Once the new C–C bond was formed at C14,

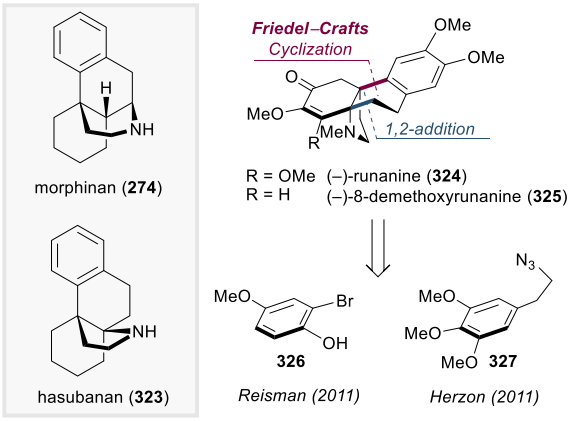


Figure 36. Comparison of morphinan and hasubanan alkaloid scaffolds, and summary of Herzon's and Reisman's synthetic approaches.

the masked olefin was revealed *via* thermal retro-cycloaddition. Semireduction of the alkyne followed by triflic acid-mediated intramolecular Friedel–Crafts alkylation and the final reduction of the *cis*-olefin furnished natural product (–)-runanine (**324**) in eight steps and 7.6% overall yield.

Analogously, in Reisman's synthesis, substituted phenol **326** was oxidized to the dimethyl acetal of quinone.[324] Chiral imine **334** was formed upon condensation with Ellman's auxiliary. Diastereoselective addition of Grignard reagent **335**, followed by methylation, furnished intermediate **336** with a properly installed stereocenter at C14. In order to form the D-ring, two-carbon building block **337** was merged with vinyl bromide **336** *via* Stille cross-coupling. Treatment of **338** with acid promotes cleavage of the sulfonamide with concomitant condensation to form the indolone motif. Chemoselective reduction followed by similar Friedel–Crafts cyclization yielded key intermediate **339**. Finally,

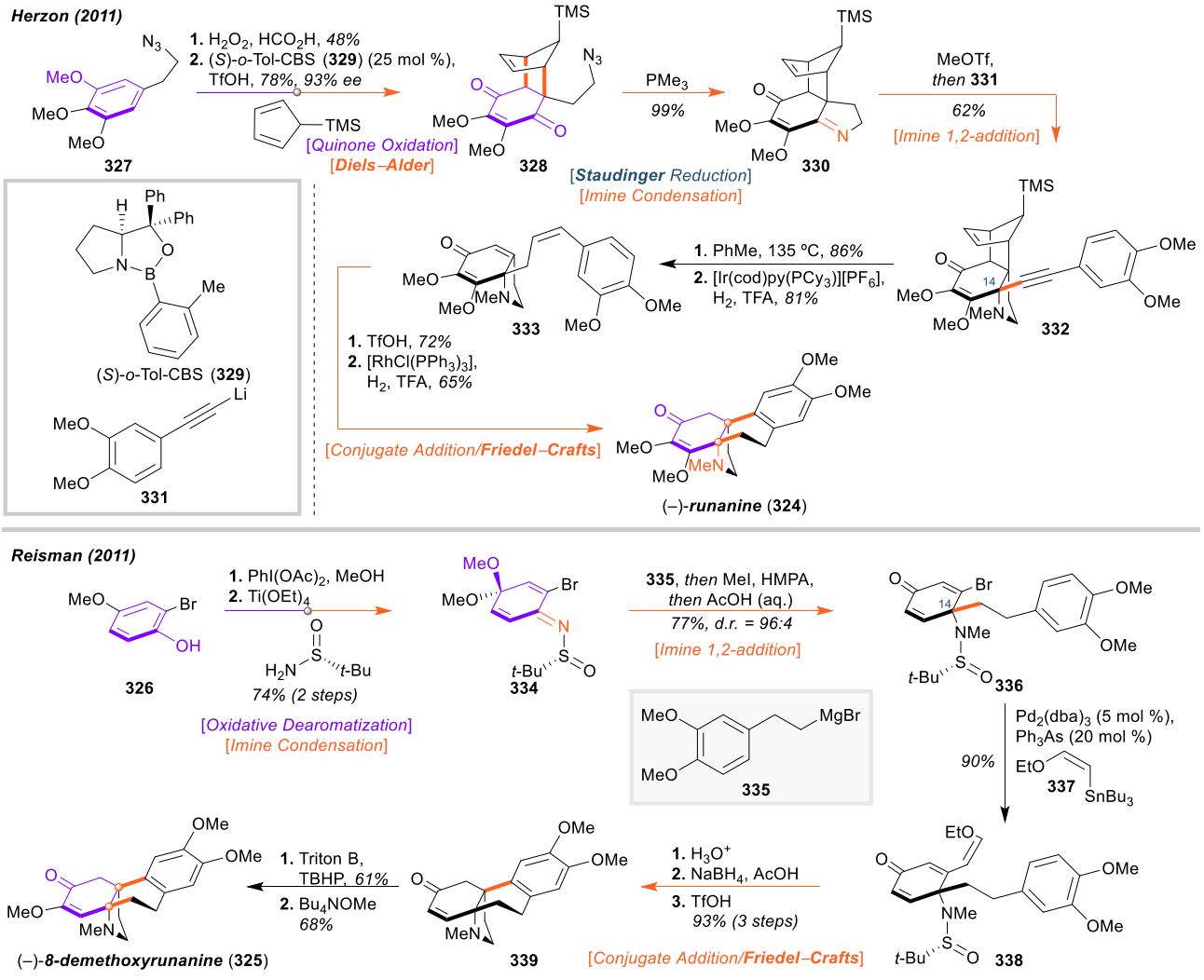
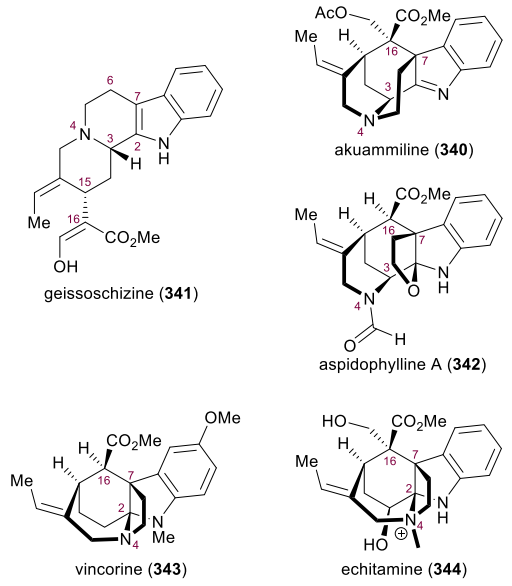


Figure 37. Herzon's and Reisman's total syntheses of hasubanan alkaloids.

sequential epoxidation, nucleophilic opening, and elimination afforded the natural product (–)-8-demethoxyrunanine (**325**) in nine steps and 19% overall yield.

Akuammiline Alkaloids: Akuammiline alkaloids are plant-derived monoterpenoid indole natural products (e.g., **340–344**, Figure 38).[325-330] Their namesake compound, akuammilline (**340**), was isolated in 1932 from seeds of *Picralima klaineana*.[331] However, some of its other members have been known over 145 years. Biosynthetically, these alkaloids derive from cyclization of geissoschizine (**341**), forming a bond between C7 and C16.[332,333] Some members, including akuammiline itself or aspidophylline A (**342**), possess N4-C3 connectivity, whereas others such as vincorine **343** or echitamine **344** feature N4-C2 connectivity instead. Further oxidative modifications bring wide diversity to the akuammiline alkaloid family with more than 100 members being isolated to date. Importantly, while some hypotheses regarding their biosynthetic origin have been offered, the exact mechanism is yet to be determined. A broad range of biological properties have been reported for the akuammiline alkaloids, such as anticancer, antimicrobial, anti-inflammatory, and analgesic activities.[334-339] Aspidophylline A has demonstrated the ability to reverse drug resistance in KB cells.[340] Picraline has displayed selective activity towards renal cortex membraine protein SGLT2, which regulates glucose reabsorption and represents a potential target for type-II diabetes intervention.[341,342] Of note, due to minute isolation yields, most of these alkaloids have not been studied in depth and their full medicinal potential remains underexplored.



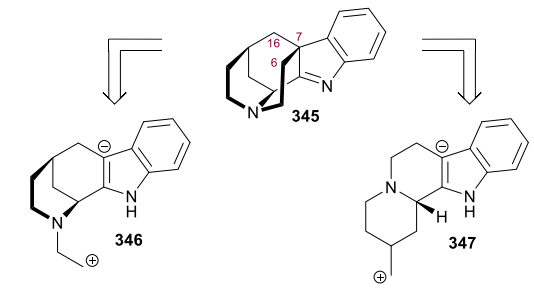


Figure 38. Structures of selected akuammiline alkaloids and proposed biosynthetic synthons.

Early synthetic studies towards akuammiline alkaloids suggested the densely substituted 6-membered ring with several quaternary stereocenters, including one at C7, to be the most problematic structural feature of these natural products.[343] Given the substitution pattern and oxidation state of the core (**345**), it became evident that dearomatization of the indole motif—perhaps through intramolecular alkylation of synthons **346** or **347**—would be the most productive maneuver for the assembly of the caged scaffold. Consequentially, this dearomative logic has been incorporated in a variety of elegant total syntheses and approaches. Even though the first isolation report of an akuammiline alkaloid is dated to 1875, only during the last decade have these molecules capitulated to total synthesis campaigns. This surge can be attributed to the development of new technologies suitable for dearomative construction of the C7 stereocenter, such as transition-metal catalyzed cyclizations and oxidative coupling. Of note, dearomative construction of the C7 quaternary stereocenter is typically performed at the final stage of the synthesis, demanding a robust and highly effective process.

The first total synthesis of an akuammiline alkaloid was reported by Qin in 2009 (Figure 39).[344] The key complexity-generating event was a tandem transformation consisting of intramolecular dearomative cyclopropanation (**348** → **349**) and fragmentation of the donor-acceptor cyclopropane to iminium **350**, followed by aminocyclization to form pyrrolidine **351**. Thus, nearly the entire framework of (±)-vincorine (**343**) was assembled from a simple starting material in a single step. This precedent set the stage for application of dearomative methods for future syntheses of akuammiline natural products. MacMillan[345] and Yang[346] developed unique approaches employing catalytic enantioselective methods for dearomatization of the indole moiety based on sequential Diels–Alder cycloaddition/amination (**352** → **353**) and Ir-catalyzed allylic substitution reaction (**355** → **356**), respectively.

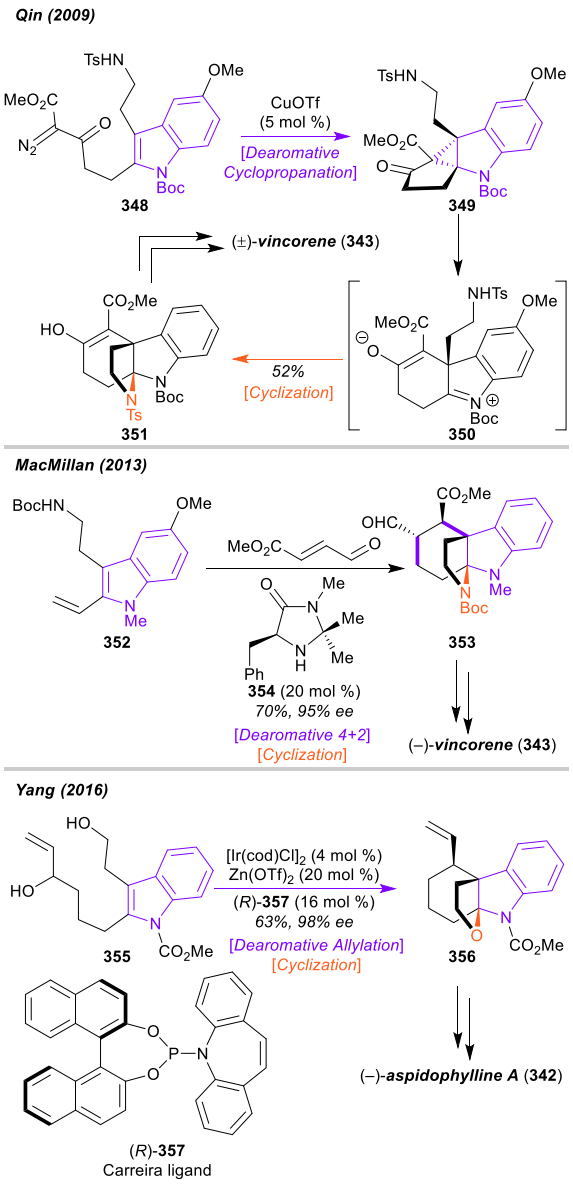


Figure 39. Qin, MacMillan, and Yang syntheses of akuammiline alkaloids.

Both syntheses are discussed in greater details in a previous review.[347]

C6–C7 formation and assembly of the intricate skeleton of akuammiline alkaloids based on dearomative alkylation (formally through **346**) was one of the first successful strategies applied (Figure 40). It has been shown that not all substrates are suitable for this cyclization due to high strain energy associated with the corresponding products,[343] and harsh conditions (high temperature, strong base, etc.) are often necessary. Nevertheless, this approach proved to be quite effective. For instance, Smith and coworkers completed first total synthesis of (+)-scholarisine A (**358**) in 2012 using this strategy.[348] Readily available bicycle **359** was subjected to heterogeneous nitrile reduction followed by spontaneous nucleophilic opening of epoxide. Protection of the newly revealed secondary amine and oxidation of the alcohol delivers substrate **360** for Fischer indole synthesis. The use of 1-benzyl-1-phenylhydrazine (**361**) proved to be critical for successful annulation. The resultant indole **362** possesses the majority of the structural features of the natural product. Redox adjustments, protecting group manipulations, and incorporation of a one-carbon synthon at C5 were required to furnish precursor **363** for the final key step. With the aid of the strong base BTPP (**364**), dearomative alkylation resulted in the formation of the final ring of **365** and a quaternary stereocenter in good yield. Only deprotection and oxidation of the secondary amine were required to complete total synthesis of (+)-scholarisine A (**358**).

Ang Li and coworkers employed a Toste cyclization and dearomative alkylation as key C–C bond forming reaction in the first and asymmetric total syntheses of aspidodasycarpine (**366**) and lonicerine.[349] Towards this end, tricyclic ketone **367** was converted to the silyl enol ether, which was subjected to a gold-catalyzed cycloisomerization reaction (**367** → **369**). After several functional group manipulations, tetracyclic intermediate **369** was converted to **370**, the precursor for a dearomative cyclization. Reaction with lithium *tert*-butoxide furnished the quaternary stereocenter in 73% yield with exclusive diastereoselectivity, and subsequent deprotection afforded key intermediate **371**. Only five additional steps were required for adjustment of oxidation states (**371** → **372**) and global deprotection (**372** → **366**) to deliver the natural product. In 2019, this approach was applied by the same group in the syntheses of seven other alkaloids including akuammiline (**340**), echitamine (**344**), and rhazicine.[350]

Arboridinine (**373**) was isolated in 2015 from the bark of the Malayan *Kopsia arborea* tree.[351] While this alkaloid bears the features of akuammiline alkaloids, it has an unusual connectivity pattern. Yun Li and coworkers reported an elegant enantioselective total synthesis of (+)-arboridinine in 2019.[352] Their first key complexity-generating transformation was a double Mannich cyclization (**374** → **376**) under Brimble conditions. Bridged bicycle **376** was produced in 60% yield with three of the requisite stereocenters. The indole motif was incorporated via Fischer reaction, and a few additional chemical operations led to the key intermediate **377**. An ethylene linchpin between N4 and C7 was introduced over three steps to form the final ring and quaternary stereocenter of **378** in 21% overall yield. Hydrolysis of the ester, followed by an

ambitious decarboxylative acetoxylation, delivered the

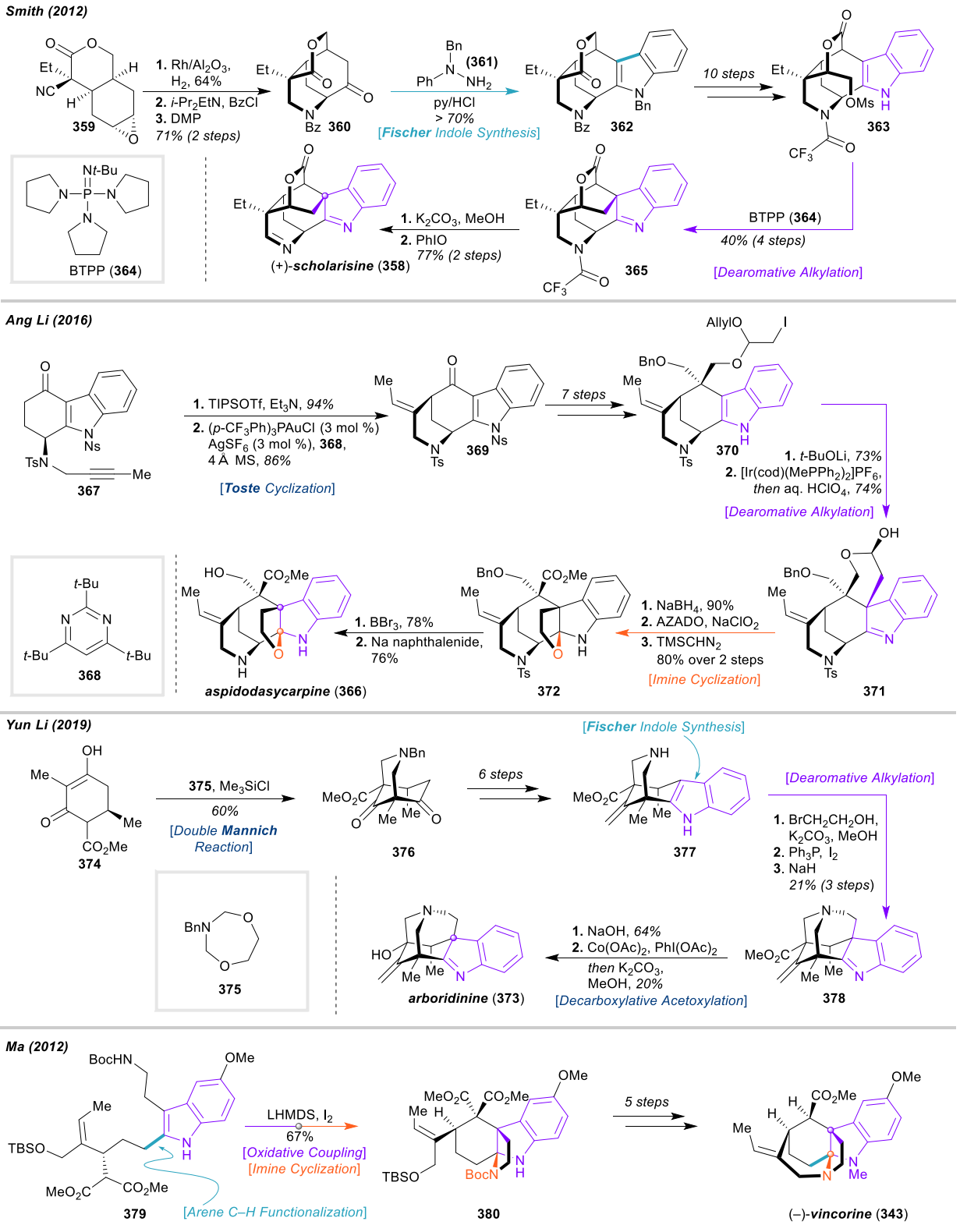


Figure 40. Smith's, Ang Li's, Yun Li's, and Ma's syntheses of akuammiline alkaloids.

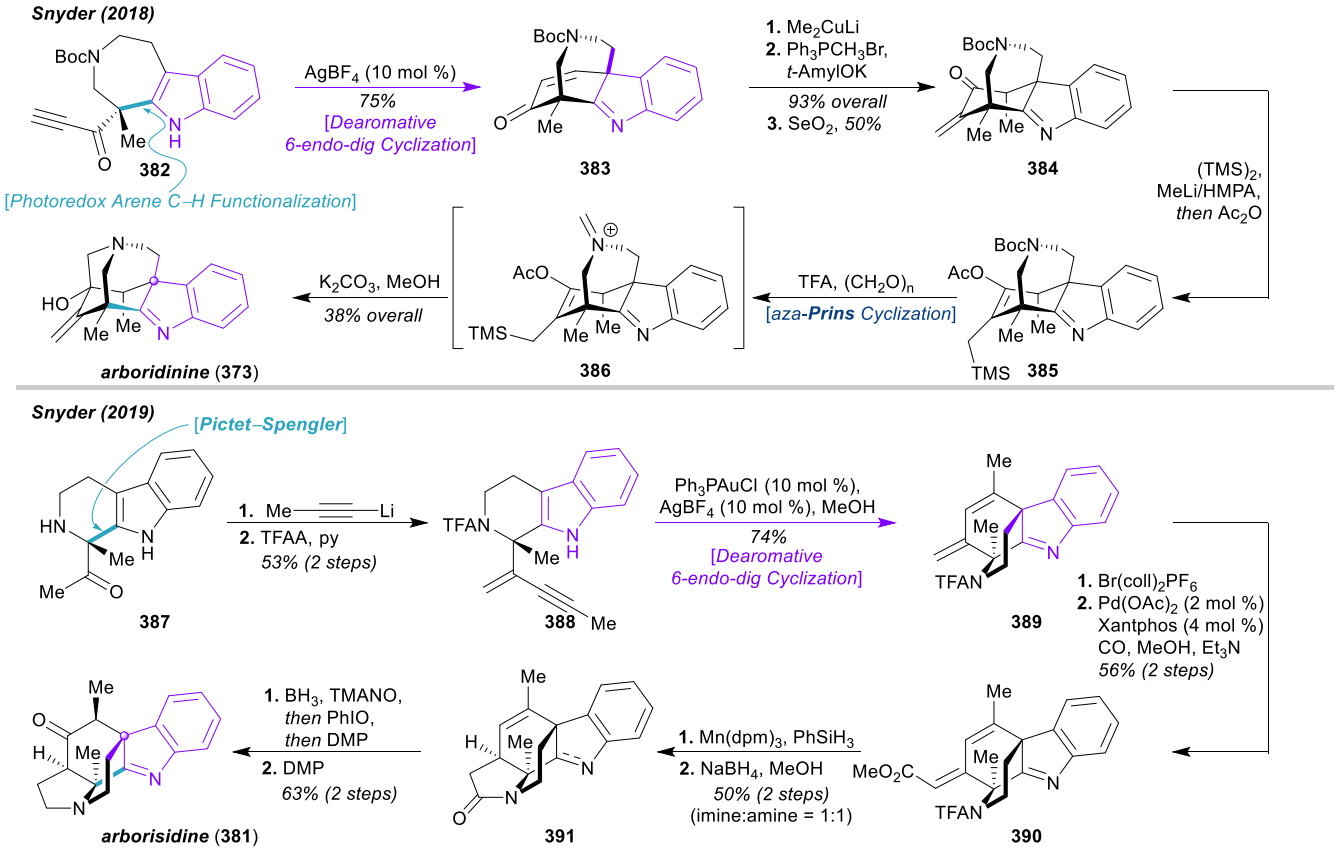


Figure 41. Snyder's total syntheses of arboridine and arborisidine.

natural product. These selected examples demonstrate the utility of dearomative alkylation as a reliable and straightforward method for the synthesis of various arduously caged alkaloids.

A conceptually distinct approach was disclosed by the Ma group in their total synthesis of (–)-vincorene (**343**).[353] Instead of the C7–C6 disconnection used in the dearomative alkylation strategy, the key quaternary stereocenter and basic framework of the natural product was assembled via formation of the C7–C16 bond (synthon **347**). This disconnection was realized by intramolecular oxidative coupling between indole and malonate motifs. The key precursor **379**, with a single stereocenter, was prepared from 5-methoxytryptamine. Sequential oxidative coupling/aminal formation (**379** → **380**) were carried out under basic conditions in presence of iodine as an oxidant with 67% yield and exclusive diastereoselectivity. Thus, a single dearomative operation allowed for formation of the complex polycyclic structure and two quaternary stereocenters, enabling rapid access to the akuammiline alkaloid. Only five additional steps were required to complete the synthesis. Notably, this design has been extended further to the total synthesis of (±)-aspidophylline (**342**) reported in 2014.[354]

Alternatively, C7–C16 bond formation can be accomplished *via* 6-*endo*-dig cyclization between the indole and an alkyne. Pioneering studies by Wang and coworkers (not shown) demonstrated the feasibility of this dearomative approach towards akuammiline alkaloid scaffold using gold catalysis.[355] Inspired by these initial results, the Snyder group elaborated upon this strategy and completed total syntheses of strictamine (**402**, Figure 41),[356] arboridinine (**373**),[357] and arborisidine (**381**).[358]

The first total synthesis of aboridinine leveraged a 6-*endo*-dig cyclization of the compound **382**, accessible from tryptamine.[359] The authors discovered that a silver catalyst is sufficient for high conversion, affording key intermediate **383** in 75% yield. Addition of Gilman's reagent followed by methylenation and allylic oxidation delivered compound **384** in 46% yield over three steps. This α,β–unsaturated enone was converted into allylsilane **385**. Under acidic conditions in presence of paraformaldehyde, the Boc-protected

amine was converted to iminium cation **386**, which underwent *aza*-Prins cyclization to close the final ring and set a quaternary stereocenter at C15. *In situ* hydrolysis of the acetate furnished arboridinine (**373**) in 38% yield from **385**.[357]

An analogous dearomative cyclization was employed in the first total synthesis of (+)-arborisidine (**381**) (Figure 41).[358] First, the acetyl group of readily synthesized compound **387** was converted into enyne **388**. A rapid increase of complexity was attained via gold-catalyzed cycloisomerization (**388** → **389**) in 74% yield. Only formation of the pyrrolidine ring and adjustment of oxidation states were required to complete the synthesis. Towards this end, diene **389** was converted to the dienyl bromide, followed by palladium-catalyzed carboxylation. Sequential HAT-type reduction of α,β,γ,δ–unsaturated ester **390** and deprotection of secondary amine resulted in formation of pyrrolidinone **391** in 50% yield. Partial undesired but inconsequential reduction of the imine was observed during this process. Reduction of the lactam, formation of the ketone at C15, and reestablishment of the imine functionality was achieved in two steps, affording (+)-arborisidine (**381**) in 63% from **391**.

It is important to acknowledge that not only dearomative strategies have been successful in the past. Construction of the crucial structural element—the C7 quaternary stereocenter—was realized through a C7–C8 disconnection as well (Figure 42). A series of alkaloids have been prepared by Garg and coworkers, exploiting the interrupted Fischer indolization methodology developed in their laboratory.[359-364] Azabicyclo[3.3.1]-nonane precursor **393** was quickly accessed via Heck cyclization of **392**. Closure of the δ–lactone during a multistep sequence from **393** to **395** provided additional rigidity to the system. **395** was treated with phenylhydrazine in presence of TFA, and the generated intermediate **396** was trapped with a hydroxyl unit released *in situ* via basic hydrolysis. Thus, compound **397** with a furoindole core and the C7 stereocenter was synthesized in 70% yield. Functional group swap at N4 delivered racemic aspidophylline A

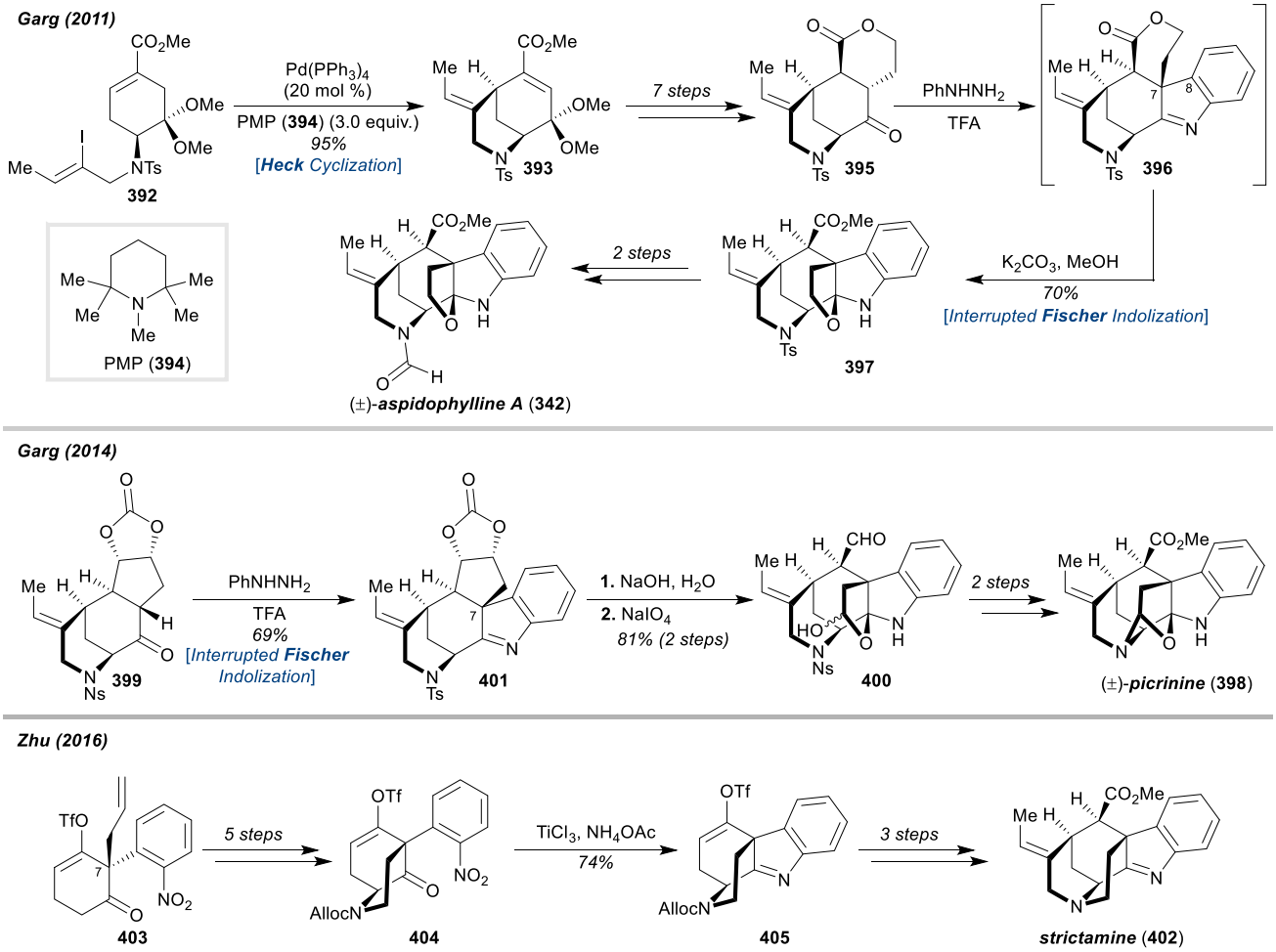


Figure 42. Non-dearomative approaches to akuammiline alkaloids from Garg and Zhu.

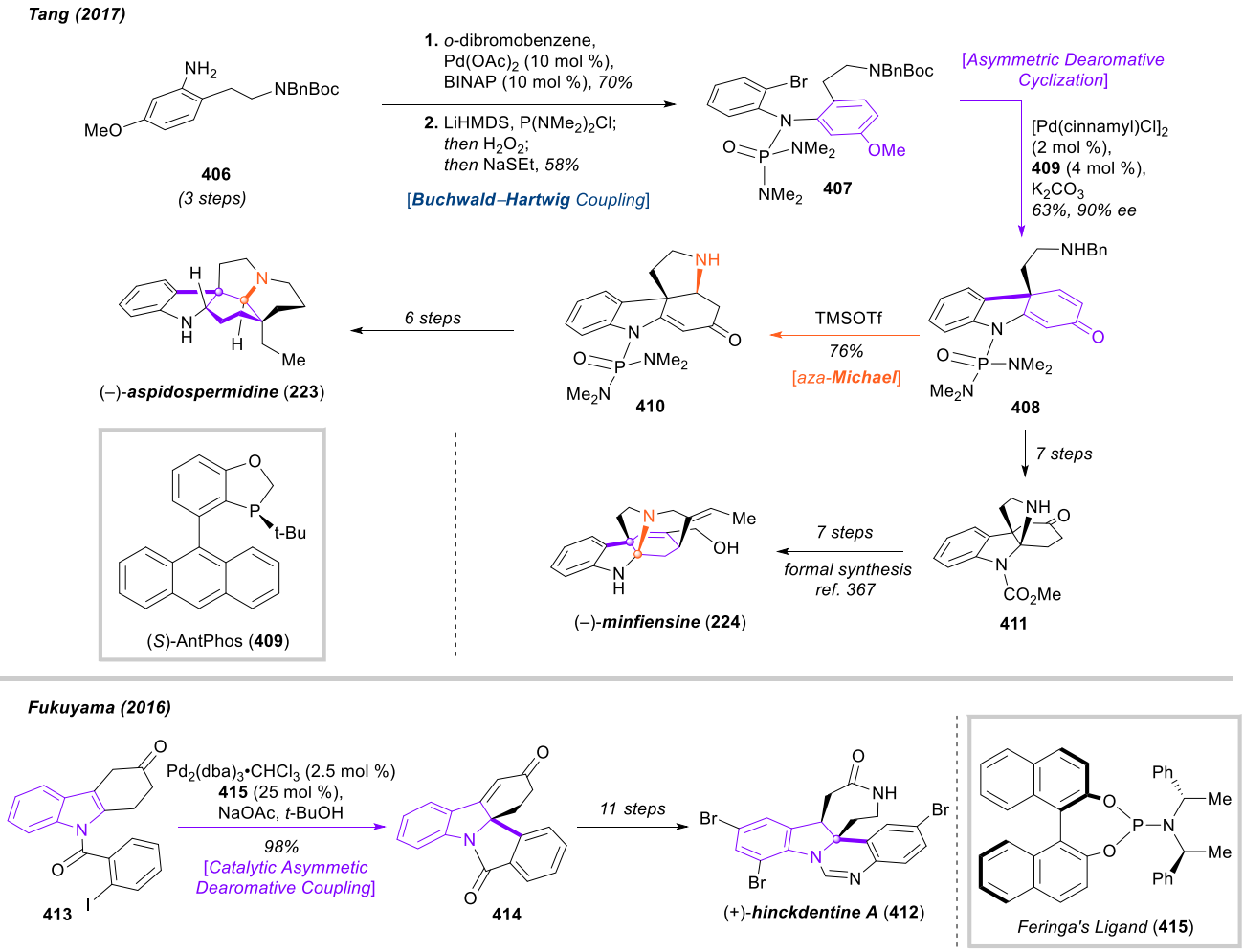


Figure 43. Tang's synthesis of aspidospermidine and formal synthesis of minfiensine, using enantioselective palladium-catalyzed dearomatization of phenols. Fukuyama's synthesis of hinckdentine A using a catalytic asymmetric dearomative coupling.

(**342**).[359] The Garg group applied a similar strategy for the first synthesis of picrinine (**398**) in 2014.[361] In this case 5-membered protected diol **399** was incorporated to induce necessary rigidity, which was oxidatively cleaved to aldehyde **400** directly after indolization (**399** → **401**). Zhu and coworkers completed a total synthesis of strictamine (**402**) in 2016, utilizing sequential functionalization of a 1,3-cyclohexanedione to assemble the C7 stereocenter of **403**.[365] Reduction of the nitro group in the elaborated synthetic intermediate **404** was followed by simultaneous condensation to afford indole **405** in 74% yield, which was advanced to strictamine (**402**) in three steps.

Miscellaneous Alkaloids: The total synthesis of *Strychnos* and *Aspidosperma* alkaloids using indole dearomatization is a rich field of study, and numerous examples have been reported within the last decade; however, they will not be discussed here and instead the reader is referred to an excellent review that has been recently published on this topic.[366] Although the dearomatization of tryptamine derivatives has been the most widely adopted approach to these indole alkaloid natural products, several alternative and efficient dearomative strategies have been disclosed that deviate from this paradigm.

A noteworthy example that proceeds through *phenol* dearomatization is Tang's 2017 total synthesis of aspidospermidine (**223**) (Figure 43),[286] utilizing their previously developed catalytic asymmetric dearomative cyclization methodology (*vide supra*).[285] Effective use of dearomative logic enabled swift assembly of a tetracyclic scaffold bearing appropriate functionality for further elaboration, using the natural reactivity of the intermediates. Buchwald–Hartwig coupling of *ortho*-dibromobenzene and aniline **406**, prepared in three steps from a commercially available nitrated phenethylamine, forged a critical Csp^2–N

bond. Protection of nitrogen as the phosphoramide **407** set the stage for a key, palladium-catalyzed dearomative asymmetric cyclization (**407** → **408**) to establish the indoline system and an all- carbon quaternary center. An additional benefit of this transformation was the generation of a reactive cyclohexadienone perfectly set up for an aza-Michael addition to close the pyrrolidine ring of **410**, following deprotection of the benzylamine. From this intermediate, the authors completed the total synthesis of (–)-aspidospermidine (**223**) in six steps. Additionally, intermediate **408** could be taken forward in seven steps to intercept Overman's intermediate **411**,[367] thus completing a formal asymmetric synthesis of (–)-minfiensine (**224**) as well.

Another powerful catalytic asymmetric dearomatization was reported by Fukuyama in 2016, during the total synthesis of the unusual indole alkaloid (+)-hinckdentine A (**412**).[368] Tetrahydrocarbazole **413**, with a pendent aryl iodide, proved a competent substrate for dearomative Heck-type cyclization (**413** → **414**) to establish an all-carbon quaternary center at C2 of the indole. This process was rendered asymmetric with the use of Feringa's ligand **415**, and the Fukuyama team was able to complete the total synthesis of (+)-hinckdentine A (**412**) after eleven steps.

Related catalytic asymmetric dearomatization (CADA) reactions of indoles, such as those pioneered by MacMillan,[369-374] You,[375-380] Reisman,[381-383] and Knowles[384] have been utilized with great success in the synthesis of numerous other indole alkaloids during the past decade.[366] For more examples and an in-depth discussion of CADA reactions of indoles in total synthesis, the reader is referred to a recent review from You on the subject.[347]

Polyketides and Meroterpenoids

Dalesconols: The Snyder group has completed a large and impressive body of work relating to the synthesis of oligomeric, resveratrol-based natural products, leveraging unique and divergent reactivity modes of unnatural biaryl alcohol building blocks similar to **416** (Figure 44).[385-387] In 2010, they reported an extension of this methodology towards the synthesis of the potent immunosuppressant polyphenolic natural products dalesconol A (**225**) and dalesconol B (**226**),[388] featuring a powerful dearomative cascade sequence in which carbon 19 served as both a nucleophile and electrophile to forge the quaternary center embedded in the center of the molecules. Assembly of **416** from phosphonate ester **417** was achieved in two steps via Horner–Wadsworth–Emmons olefination with **418**, followed by lithium-halogen exchange and aryllithium addition into naphthaldehyde derivative **419**. Debenzylation and hydrogenation of the stilbene delivered biaryl alcohol **420**, which underwent immediate Friedel–Crafts cyclization (**420** → **421**) upon treatment with TFA, and oxidative dearomatization and cyclization with PIDA (**421** → **422**) to furnish the entire heptacyclic scaffold of the dalesconols in a single operation. Snyder and coworkers were able to complete the synthesis of dalesconol B (**226**) in another seven steps, as well as a synthesis of dalesconol A (**225**) in nine steps LLS following an analogous strategy.

In 2017, the Tang group reported an alternative approach towards the dalesconol natural products, utilizing their palladium-catalyzed dearomative cyclization (**423** → **424**) to construct the central quaternary center. This method allowed them to complete asymmetric syntheses of both dalesconols in nine steps LLS.[287]

Anthracyclines: The anthracycline polyketides have provided some of the most effective chemotherapeutics and antibiotics used in the clinic for over 50 years.[389] These drugs possess well-characterized, cumulative dose-dependent cardiotoxicity,[390] the severity of which has fueled decades of research into the synthesis and identification of suitable analogues that maintain their desirable potency but with reduced harmful side effects.[391] The vast canon of synthetic approaches consists entirely of convergent strategies that utilize annulation processes to generate at least one of the four carbocyclic rings.

Sarlah and coworkers disclosed a fundamentally different, non-annulative strategy towards the idarubicin aglycone (**425**) in 2019, via global functionalization of a polynuclear arene already in possession of the full tetracyclic scaffold (Figure 44).[392] Starting from tetracene (**426**), two sequential, selective C–H oxidation events delivered protected tetracenequinone **427**. An arenophile-mediated, dearomative hydroboration, developed specifically for this synthesis, furnished boronic ester **428**, which was subject to Zweifel olefination (**428** → **429**) to forge the remaining C–C bond to the pendent acetyl group. β-elimination and methylation of the urazole (**429** → **430**) set the stage for the completion of the synthesis, which required three steps for the installation of two hydroxyl groups and deprotection of the hydroquinone. Notably, this novel, "functionality-imprinting" approach resulted in the shortest synthesis of idarubicinone (**425**) to date.

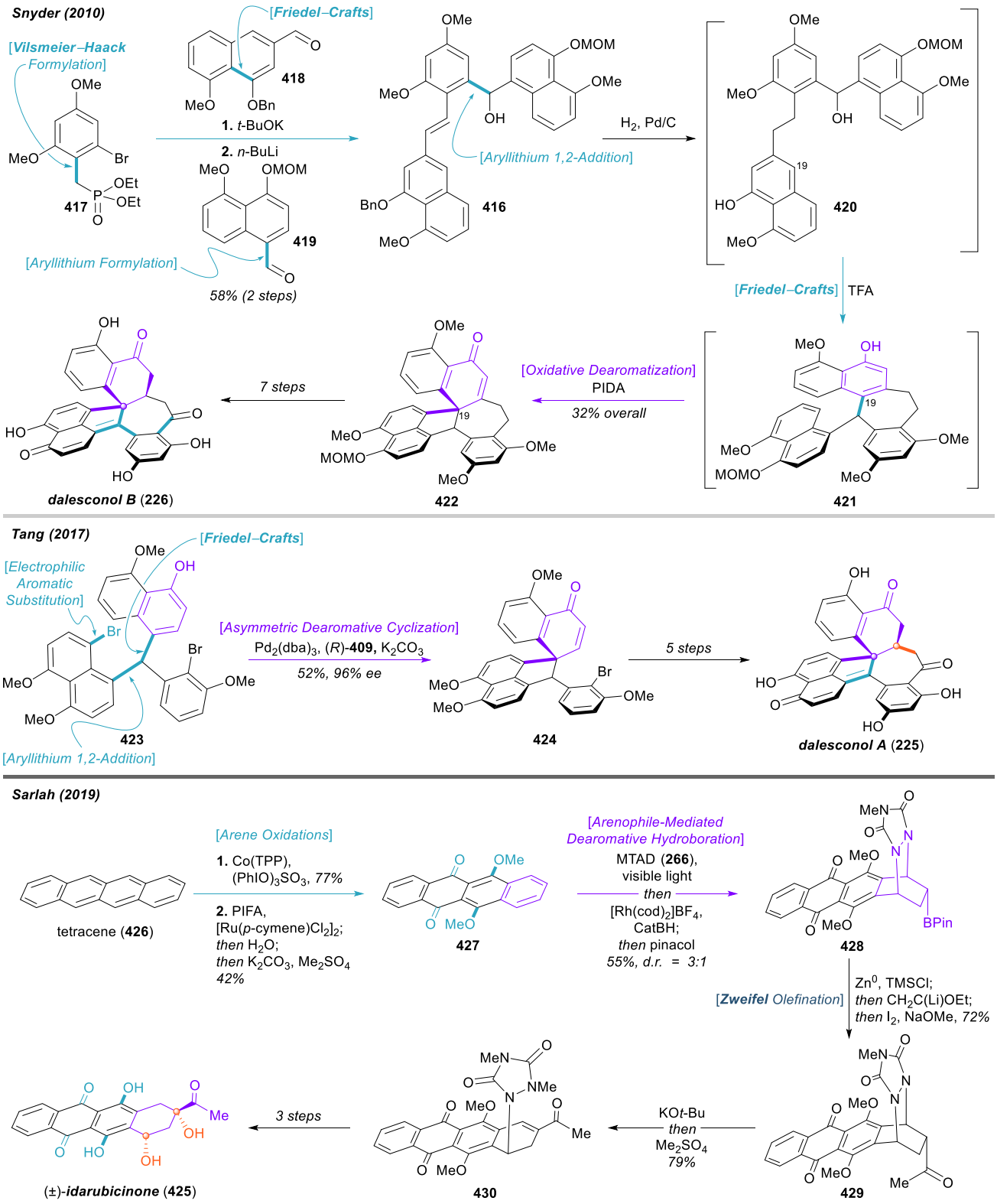


Figure 44. Snyder and Tang's syntheses of dalesconals, and Sarlah's synthesis of idarubicinone from tetracene.

Azaphilones: So named for their characteristic affinity for ammonia, the azaphilones comprise a small family of fungal pigments bearing a dearomatized pyranoquinone bicyclic core with a chiral tertiary alcohol (Figure 45).[393] Their propensity to alkylate nitrogenous biomolecules via substitution reactions

that form vinylogous γ–pyridones lends them numerous desirable properties including antifungal, antimicrobial, antiviral, and cytotoxic activities.[394] As attractive targets for total synthesis, several successful approaches have emerged, most commonly employing oxidative dearomatization of appropriately functionalized resorcinol derivatives.[393] However, as both (*R*)- and (*S*)-configurations of the C7 quaternary center have been observed in nature, the enantioselective synthesis of azaphilones has been hampered by the relative dearth of methods available for asymmetric oxidative dearomatization.

A major breakthrough in this area was disclosed by Porco in 2006, during the total synthesis of (–)-mitorubrin (**431**, Figure 45).[395] Using copper-oxo (–)-sparteine complex **432**, the asymmetric oxidative dearomatization of alkynylbenzaldehyde **433** was carried out to establish the (*R*)-configured quaternary center in 98% ee. A copper(I)-catalyzed cycloisomerization then furnished the remainder of the pyranoquinone framework (**435**), which was advanced to (–)-mitorubrin (**431**) in two additional steps. With the (+)-sparteine enantiomer not readily available, this method was initially unsuitable to be used for the

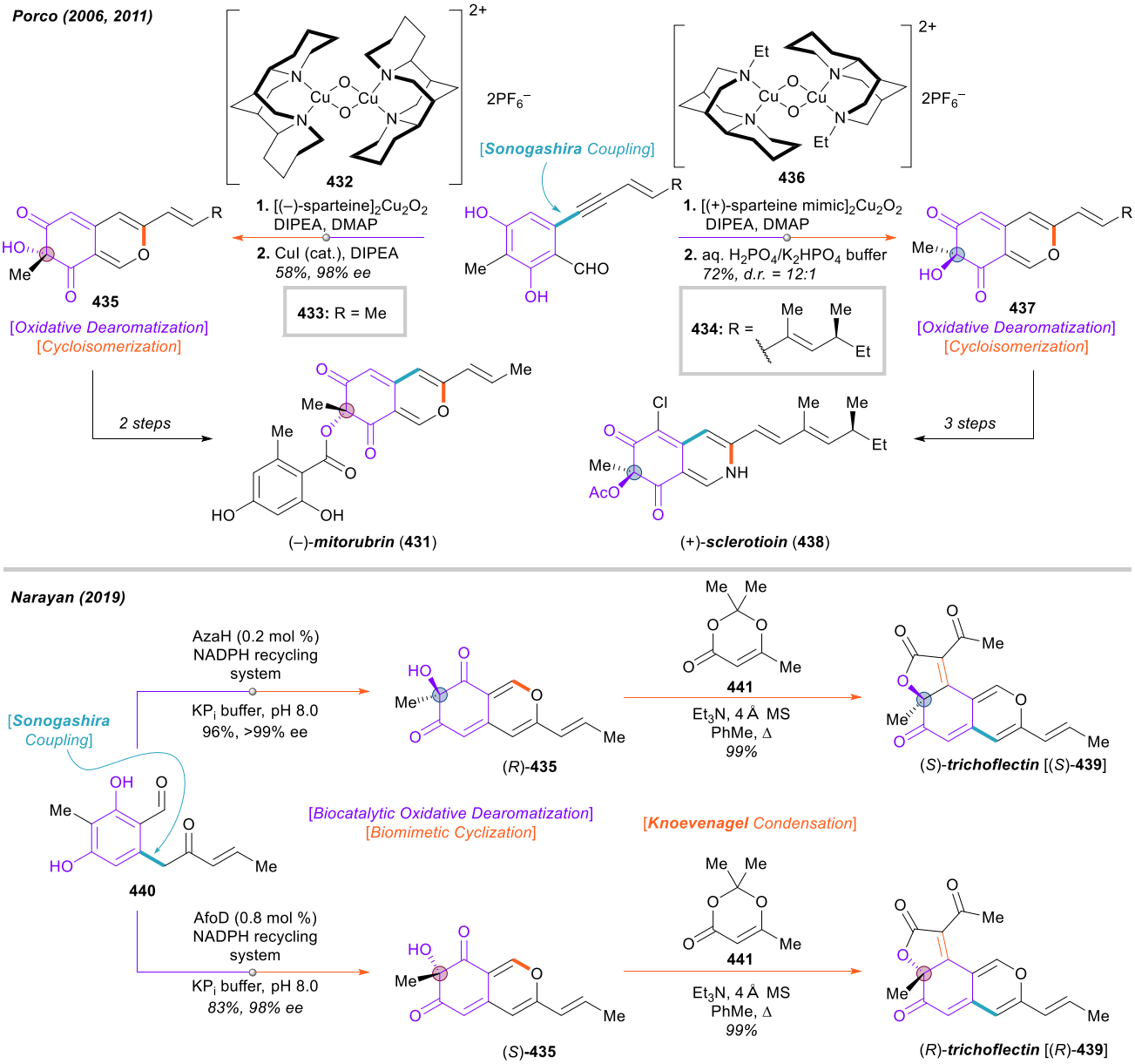


Figure 45. Porco's enantiodivergent oxidative dearomatization of resorcinols, applied within the total syntheses of mitorubrin and sclerotioin, and Narayan's enantiodivergent chemoenzymatic syntheses of trichoflectins.

synthesis of the (*S*)-series of azaphilones; however, Porco and coworkers screened a variety of surrogates that might be used for this transformation, and they reported in 2011 the successful application of a copper-oxo complex with O'Brian's *N*-ethyl-(+)-sparteine mimic (**436**) to promote the (*S*)-selective oxidative dearomatization (**434** → **437**) of alkynylbenzaldehydes.[396] The Porco group then used this modified approach to access a number of (S)-configured azaphilone natural products including (+)-sclerotiorin (**438**) and (+)-8-*O*-methylsclerotiorinamine.

With the exception of microbial arene oxidations providing access to *cis*-dihydrodiols,[397,398] the use of biocatalysis in dearomative synthesis remains an emerging field. In a rare example of enantiodivergent dearomative biocatalysis, Narayan and coworkers reported in 2019 the chemoenzymatic total synthesis of both (*R*)- and (*S*)-trichoflectin [(*S*)-**439** & (*R*)-**439**], alongside a series of epimeric azaphilones including deflectin-1a and lunatoic acid A.[399,400] Their syntheses hinged on the curious observation that both C7 epimers of certain azaphilones occur in nature, but are produced in different fungal species (i.e., not as a racemate). At the time, all flavin-dependent monooxygenases, such as AzaH, known to perform the requisite asymmetric oxidative dearomatization only produced the (*R*) enantiomer. Since azaphilones with the (*S*)-configuration were known, the authors postulated that enzymes capable of assuring this stereochemical outcome might be discovered via bioinformatic analysis. A sequence similarity network of flavin-dependent monooxygenases was assembled, from which several distinct clusters of related proteins emerged. Representative sequences from these clusters were selected for their proximity in the network to previously reported monooxygenases that carry out oxidative dearomatization of resorcinols; these were expressed in *E. coli* and screened for this desired reactivity, revealing a set of enzymes indeed able to catalyze the oxidative dearomatization of resorcinols with (*S*)-configuration. With these powerful tools in hand, Narayan and coworkers embarked upon the total synthesis of (*S*)-trichoflectin [(*S*)-**439**]. Enone **440** was obtained in a 5-step sequence from methyl atratate. Oxidative dearomatization [**440** → (*R*)-**435**] with AzaH proceeded in 96% yield and >99% ee. Esterification with the acylketene of **441** and *in situ* Knoevenagel condensation quickly delivered the natural product, whose optical rotation was of the opposite sign to that reported in the literature. Chemoenzymatic synthesis of (*R*)-trichoflectin [(*R*)-**439**)], exploiting the newly discovered (*S*)-selective oxidative dearomatization with AfoD, confirmed the misassignment of absolute configuration in the original isolation report.

Bisorbicillinoids: Gulder's 2017 synthesis of bisorbicillinoid natural products stands as another exceptional case of biocatalytic, asymmetric oxidative dearomatization with flavin-dependent monooxygenases (Figure 46).[401] Many sorbicillinoids, including bisorbicillinol (**442**), are effective radical scavengers with powerful antioxidant properties. Several of these fungal secondary metabolites also possess admirable anticancer [e.g., trichodimerol (**443**) and bisorbicilinbutenolide (**444**)], antiviral, and antimicrobial [e.g., bisorbicillinol (**442**)] activities as well. Their complex, cage-like architectures arise biosynthetically through spontaneous homodimerization of the cyclohexadienone sorbicillinol (**445**), itself derived from the namesake aromatic compound sorbicillin (**446**) via precise, enzymatic oxidative dearomatization of its resorcinol motif.[402] The brevity and simplifying power of the biosynthetic approach presents an attractive strategy for total synthesis; indeed, several biomimetic total syntheses of bisorbicillinoids have been reported from Corey,[403] Nicolaou,[404,405] Pettus,[406] and Deng,[407] exploiting the spontaneous homodimerization of sorbicillinol derivatives. While Deng's route successfully constructs the monomeric building block in enantioselective fashion through a nine-step sequence, Corey's, Nicolaou's, and Pettus's expedient approaches proceed with poor or no stereoselectivity during oxidative dearomatization, greatly diminishing the yield and efficiency of this process.

Gulder and coworkers reported an elegant solution to this problem using biocatalytic oxidative dearomatization with SorbC, the native enzyme responsible for this key step in the biosynthesis of bisorbicillinoids.[401] Like AzaH and AfoD, SorbC is a flavin-dependent oxidoreductase able to catalyze the oxidative dearomatization of resorcinols, but it does so with complementary site-selectivity. A convenient *in vitro* protocol with NADH in pH 8 phosphate buffer and acetone was developed, facilitating efficient conversion of sorbicillin (**446**) to sorbicillinol (**445**) in >99.5% ee, the structure of which was confirmed after trapping with acetyl chloride. Perhaps counterintuitively, **445** was quite stable in the aqueous system, but the authors were able to leverage some remarkable solvent effects to deliberatively promote three different dimerization mechanisms and assemble diverse bisorbicillinoid scaffolds. Whereas quenching the biocatalytic reaction with DCM resulted in smooth core/core Diels–Alder reaction, furnishing bisorbicillinol (**442**) in 27% yield, the use of DMF as

cosolvent was sufficient to alter the prevailing mechanism to double Michael addition/ketalization, such that trichodimerol (**443**) became the major product in 27% yield, with an additional 20% of bisorbicillinol. Furthermore, the authors found that heating the extract of the DMF reaction with pyridine allowed for the addition of sorbiquinol (**447**) to the product distribution, the result of core/side-chain [4+2] cycloaddition. Simple conversions of bisorbincillinol (**442**) to bisorbibutenolide (**444**) and bisorbicillinolide (**448**) have previously been reported by Nicolaou[405] and Deng,[407] respectively; therefore, Gulder's biocatalytic approach to bisorbicillinol constitutes formal, chemoenzymatic syntheses of these natural products as well. Overall, the enzymatic oxidative dearomatization of sorbicillin (**446**) enables the first truly enantioselective, biomimetic syntheses of numerous polyketides within the bisorbicillinoid family of natural products.

PPAPs: The polycyclic polyprenylated acylphloroglucinols (PPAPs) comprise a large family of natural products primarily isolated from the plants of the *Hypericum* and *Garcinia* genera (Figure 47).[408] More than 500 members of this family are known, most of which can be separated into two major types: type A features a characteristic bicycle[3.3.1]nonane core with an α-acyl-β-hydroxyenone motif, while the type B PPAPs bear that acyl group in the bridgehead position instead. Beyond their intriguing structures, these natural products also possess important biological properties. For example, although not isolated or characterized until 1971, hyperforin (**449**) has been used since the time of ancient Greece as the major component of St. John's wort, a well-known plant with antidepressant properties. In the modern era, hyperforin has become a popular treatment for anxiety and mild depression. It has been suggested that PPAP natural products may activate cation channels such as TRPC6,[409] leading to an influx of Na^+ and Ca^{2+} and diminished membrane electrochemical gradient, thus indirectly inhibiting synaptosomal reuptake of various neurotransmitters. Nemorosone (**450**) and clusianone (**451**) display antimicrobial and anti-HIV activities, along with chemopreventive properties.[410] Garsubellin A (**452**) was identified as a potent inducer of choline acyltransferase, which is a key enzyme in the biosynthesis of the essential neurotransmitter acetylcholine.[411] Low concentrations of this neurotransmitter are associated with the development of neuorodegenerative diseases such as Alzheimer's disease.

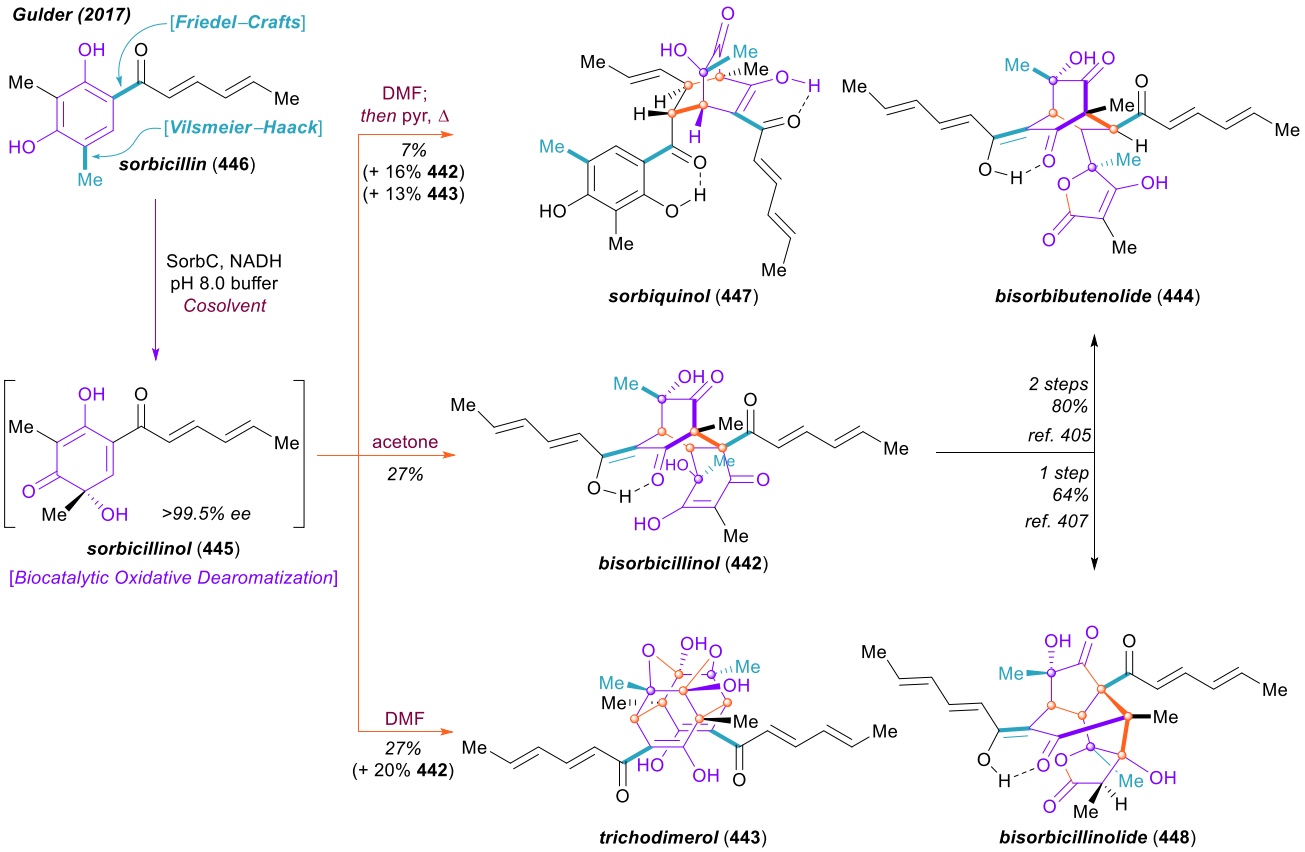


Figure 46. Gulder's chemoenzymatic synthesis of bisorbicillinoids.

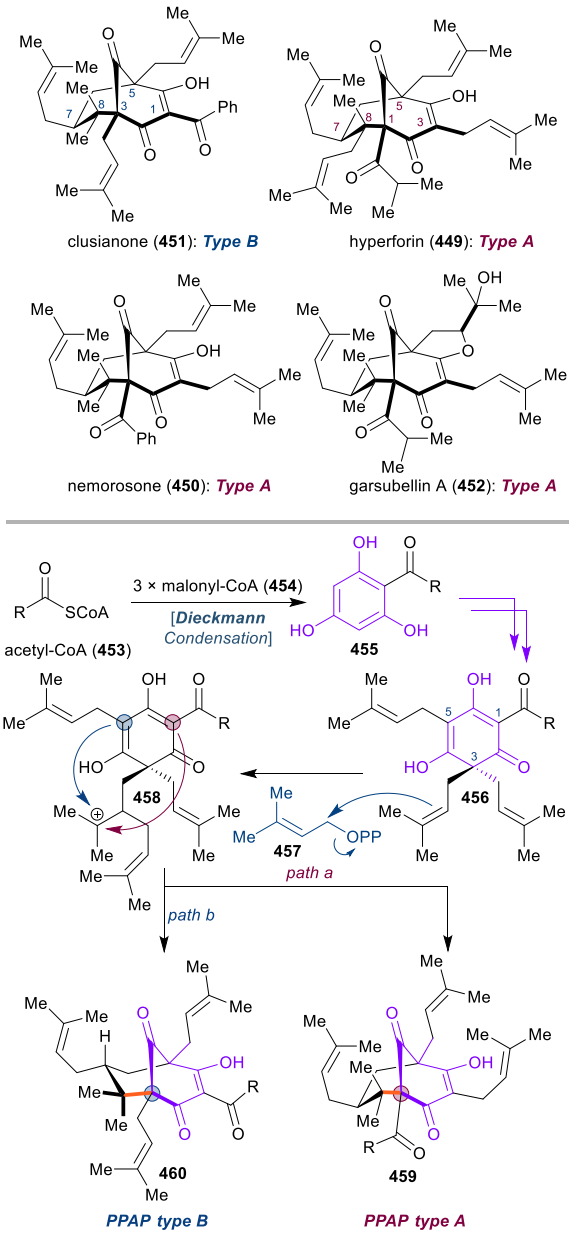


Figure 47. Structures of selected PPAPs and proposed biosynthetic pathways to type A and type B scaffolds.

The biosynthesis of PPAPs begins with condensation of one molecule of acetyl-CoA (**453**) and three molecules of malonyl-CoA (**454**), as was elucidated by labeling and enzymology studies.[408] The resulting tetraketide **455** undergoes Dieckman condensation followed by dearomative alkylation of phloroglucinol moiety (**455** → **456**). One of the geminal prenyl groups in intermediate **456** is further alkylated by another molecule of prenyl pyrophosphate (**457**), furnishing tertiary carbocation **458**. From this divergent point, two pathways for additional cyclization are possible: cyclization at C1 leads to the type A PPAPs (**459**), whereas type B PPAPs (**460**) are constructed after cyclization at C5. Additional cyclizations may occur, which endow this family of natural products with great diversity [e.g., garsubellin A (**452**)]. Accordingly, several attempts have been made to implement such a powerful transformation into synthetic approaches towards PPAPs in a laboratory setting. Although modified substrates successfully engaged in biomimetic cationic cyclizations, the fully decorated core was not susceptible to the desired transformation. This phenomenon was ascribed to the substantial buildup of strain in the transition-state as well as steric interactions associated with formation of two vicinal quaternary stereocenters. Thus, the most significant synthetic challenge posed by these molecules is the assembly of the bicycle[3.3.1]nonane core structure with quaternary stereocenters at the bridgehead positions.

The intricate architectures of the PPAPs coupled with their important biological properties have galvanized significant synthetic endeavors, and a variety of approaches and completed total syntheses have been published to date. Due to specific features of the basic scaffold (**461**), several common themes and disconnections can be unearthed within these synthetic studies. In 2006, Simpkins and coworkers disclosed the total synthesis of (±)-clusianone (**451**, Figure 48).[412] The key feature of their synthesis was a regioselective and highly efficient lithiation of the bicycle[3.3.1]nonane core (**462**) to install a requisite quaternary stereocenter. Thus, compound **463** was obtained in 91% yield by direct alkylation of **462** at the C5 bridgehead position with prenyl bromide (**464**). Acylation of C1 and hydrolysis then furnished the natural product (**461**) in a concise manner. This approach, where substituents R_3 and R_4 (Figure 46) are installed via directed metalation, has been widely adopted and this tactic constitutes the endgame in the majority of PPAP syntheses. Another quite widespread strategy for construction of the bicycle[3.3.1]nonane core relies on sequential α,α'-functionalization of the C6 carbonyl motif of cyclohexanones like **465** with an appropriate substitution pattern, followed by a ring-closing event. For example, Plietker employed sequential double alkylation (**465** → **466**) and Dieckman condensation (**466** → **467**) to forge desired core **467** with both quaternary stereocenters in place.[413] The modularity and robust nature of this approach allowed for the synthesis of four different type B PPAPs in only 7 steps and good overall yield.

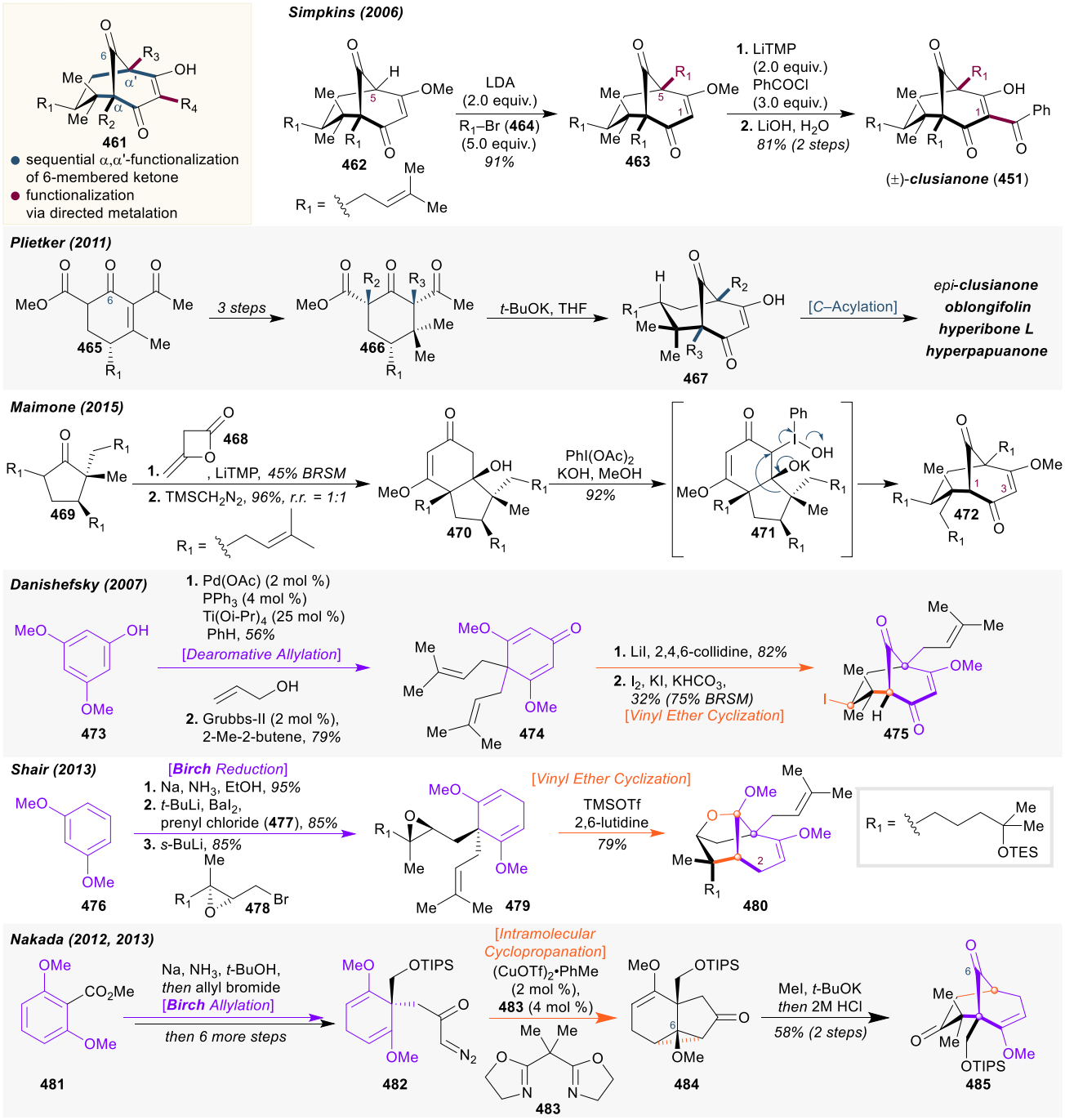


Figure 48. Synthetic considerations and summary of non-dearomative and dearomative approaches to type B PPAPs.

Several alternative strategies for accessing the bicyclic core of PPAPs have emerged recently. Maimone and coworkers completed the enantioselective total synthesis of hyperforin (**449**), employing several unorthodox transformations.[414] First, a newly developed annulation method with diketene (**468**) was performed on ketone **469** to generate a bicyclic 1,3-diketone, after which methylation gave β–methoxyenone **470**. This compound was subjected to oxidative fragmentation with PIDA (**470** → **471** → **472**), leading to a 1,2-alkyl shift in high yield. From bicyclo[3.3.1]nonane **472**, Maimone and coworkers were able to complete the synthesis of hyperforin (**449**) after four additional steps. As noted above, functionalization of C1 and C3 still relies on the Simpkins direct metalation strategy.

The arrangement of three carbonyl groups within one 6-membered ring of the bicycle[3.3.1]nonane core

suggests that dearomatization of phloroglucinol derivatives would be a powerful disconnection, in line with the biosynthetic hypothesis; indeed, this biomimetic strategy was recognized and resulted in total syntheses of various members of PPAP family. The earliest example of such approach can be found in Danishefsky's total synthesis of garsubellin A (**452**), which has been extensively covered elsewhere. An analogous approach was used for the synthesis of nemorosone (**450**) and clusianone (**451**) by the same group.[415] Towards this end, Pd-catalyzed dearomative alkylation of phloroglucinol derivative **473** with allyl alcohol, followed by cross-metathesis with 2-methyl-2-butene, led to bisprenylated precursor **474**. Of note, conversion of the allyl to prenyl group via cross metathesis is a standard way to circumvent an otherwise rather challenging α–selective prenylation. Demethylation followed by cyclization of electron-rich vinyl ether onto the appended olefin activated *via* formation of iodonium ion (**474** → **475**) led to the formation of the bicyclic core in moderate yield. In 2013, Shair and coworkers described an enantioselective total synthesis of hyperforin (**449**) using a similar disconnection between the vinyl ether as post-dearomative handle and an electrophilic site on the appended side-chain.[416] Reductive dearomatization of dimethyl resorcinol (**476**) followed by double alkylation with prenyl chloride (**477**) and bromoepoxide **478** afforded the precursor **479** for the ring-forming event. TMSOTf was employed as a Lewis acid to facilitate ring-opening of the trisubstituted epoxide by the vinyl ether, resulting in a highly diastereoselective cyclization. Product **480** was formed in 79% yield and contains the desired scaffold with the quaternary stereocenter incorporated at the bridgehead position. The residual carbonyl functionality at C2 was installed via allylic C–H oxidation. Nakada and coworkers completed the total synthesis of nemorosone (**450**) in 2012,[417] and garsubellin A (**452**) in the following year,[418] using intramolecular cyclopropanation as a key step. To prepare the precursor, an alkylative Birch reduction of **481** was conducted, followed by several functional group interconversions to reach compound **482**. Cu-catalyzed cyclopropanation reaction between the diazo motif and the aforementioned vinyl ether as post-dearomative handle in compound **482** yielded the overbred intermediate **484**. Subsequent dimethylation of C6 and cyclopropane fragmentation delivered the core of PPAPs **485** in 58% yield, which was elaborated further into corresponding natural products **450** and **452**.

Natural products such as plukenetione A (**486**) and hyperibon K (**487**), representing type A and type B PPAPs, respectively, feature an unusual adamantane core (Figure 49). This structure derives from an additional cyclization within the more common bicyclo[3.3.1]nonane (bond formation between C10 and C3/C1). Porco and coworkers rationalized that application of a synthon such as **488**, that could form three bonds and the entire framework from simple aromatic compound **489** in a single operation, would be highly beneficial for synthetic efficiency. The authors identified enals of type **490** as likely synthetic equivalents of **488**. Based on their previous work,[419] an enantioselective, alkylative dearomatization/annulation process (**489** → **491**) was realized through phase-transfer catalysis.[420] During this process, clusiaphenone B (**489**, accessible in one step from acylphloglucinol via direct aromatic prenylation) undergoes sequential Michael addition/elimination with **490**, followed by Michael addition/aldol reaction. Judicious optimization of catalyst structure (**492**) allowed for the transformation to proceed in high yield, enantioselectivity, and exclusive chemo- and diastereoselectivity, delivering the core of the type B PPAPs (**491**). A subsequent retro-aldol and 1,2-addition process with vinylmagnesium bromide **493** delivered a mixture of isomeric allylic alcohols **494**, which upon treatment with Lewis acid in nitromethane as a cation-stabilizing solvent, ionized and cyclized to form hyperibon K (**487**) in 50% overall yield.

In order to swing the chemoselectivity of the annulation process towards the core of type A PPAPs, a blocking strategy was applied.[421] The C4 phenolic group of **495** was protected as a methyl ether and the previously developed conditions were applied (**495** → **497**). In contrast to the cascade reaction observed with free acylphloroglucinol **498**, the Michael reaction of **496** with methyl-protected **495** forged a single C–C bond, perhaps the result of rapid reversibility during the second Michael addition. Acid-mediated demethylation/cyclization of **497** delivered adamantane core **498**. A retro-aldol/alkylation (**498** → **499**), analogous to that used in the synthesis of hyperibon K (**487**), was followed by methylation to afford compound **500**. The moderate yield of the sequence is ascribed to the nonselective methylation of the unsymmetrical 1,3-diketone **499**. Ionization/cyclization and subsequent cross metathesis leads to (±)-plukenetione A (**486**). The same strategy was applied to the total synthesis of 7-*epi*-nemorosone (**503**).[422] Intermediate **499** was used as a point of divergency. Its 1,3-dicarbonyl motif was protected as pivaloyl ester and the allylic alcohol was acylated (**499** → **501**). Pd-catalyzed reduction (**501** → **502**), followed by cross metathesis and hydrolysis (**502** → **487**), furnished the natural product. Overall, the alkylative

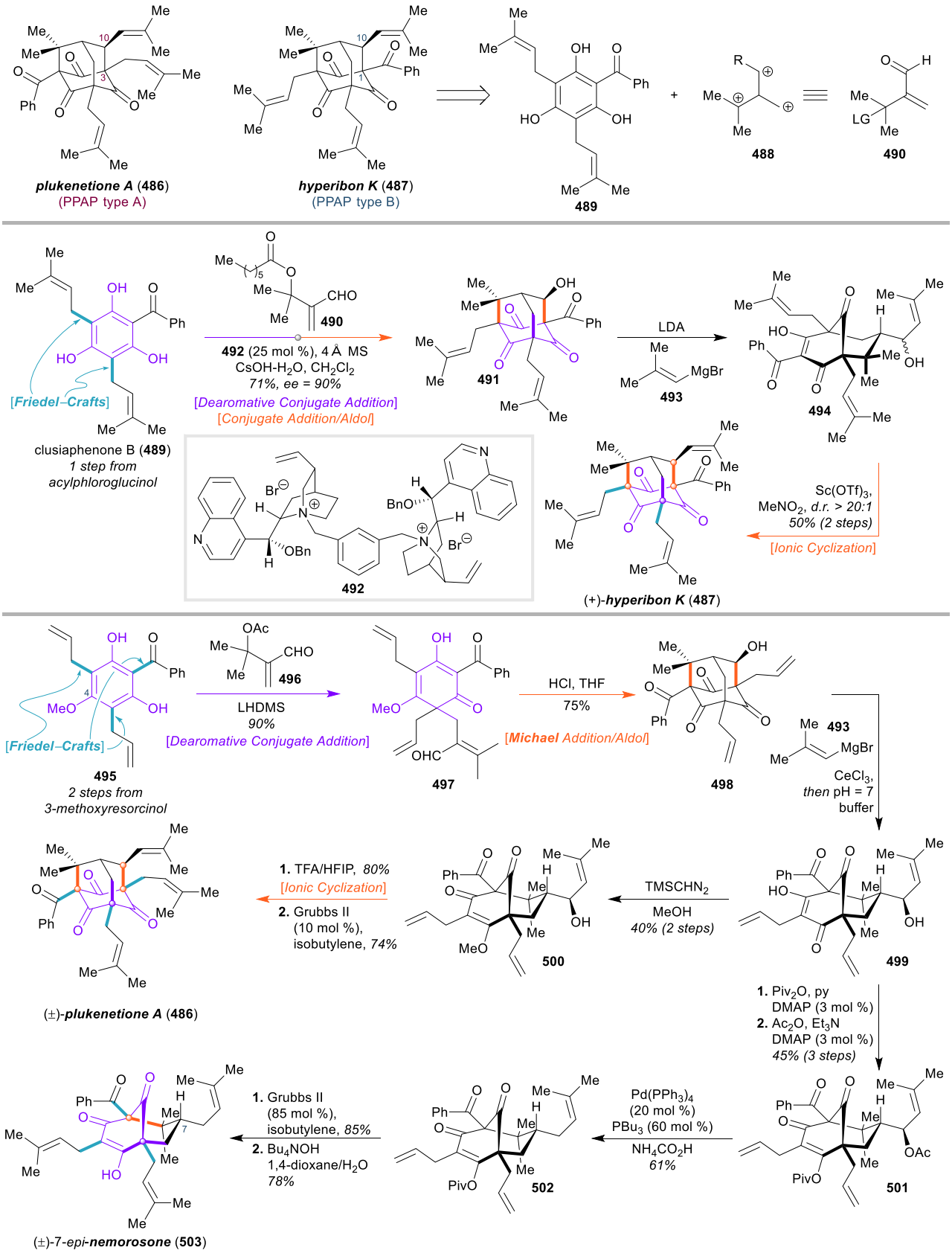


Figure 49. Porco's synthetic approaches to type A and B PPAPs.

dearomatization/annulation strategy has proven to be

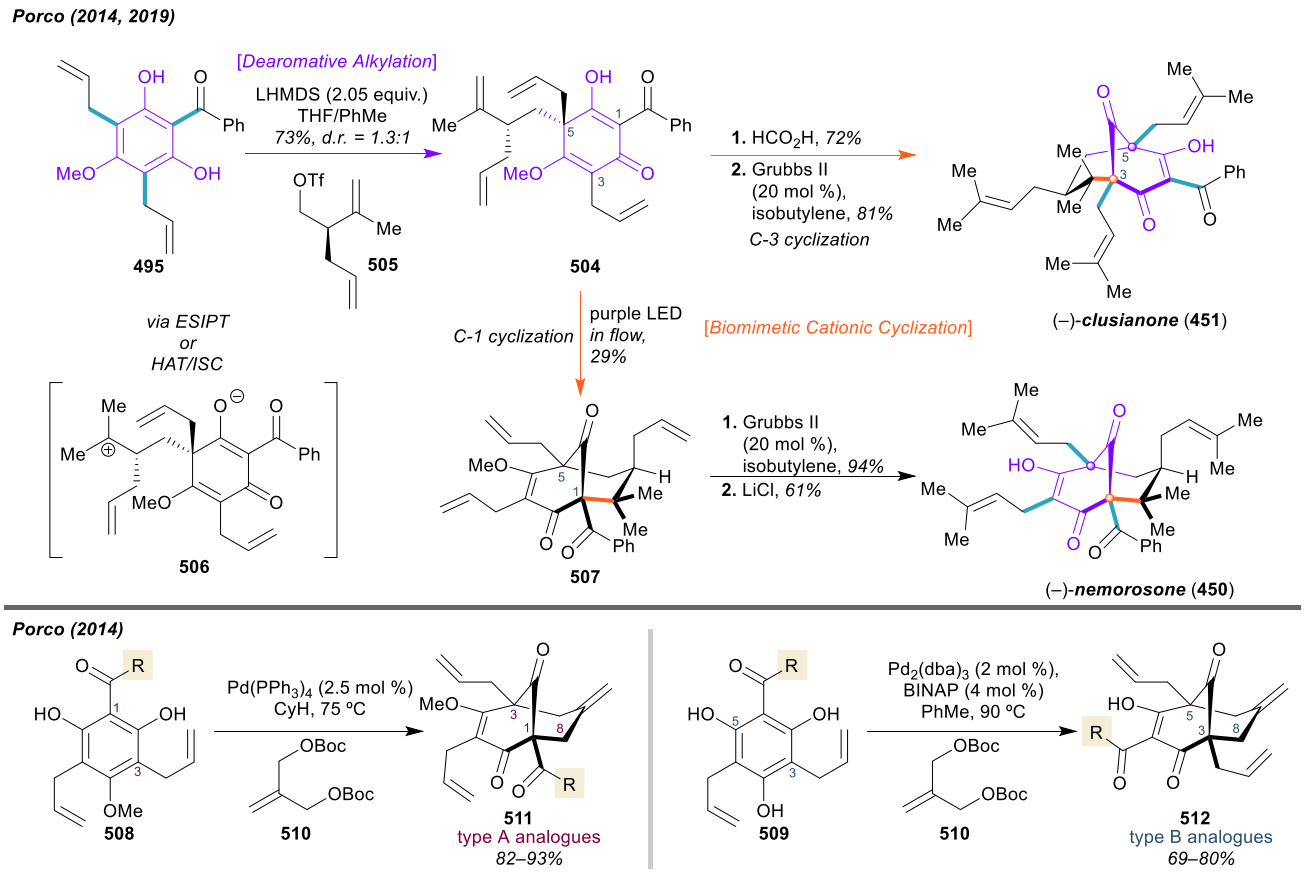


Figure 50. Porco's second-generation strategy towards the PPAPs, using a biomimetic cationic cyclization.

a powerful tool for the synthesis of bicyclo[3.3.1]nonane-containing natural products. However, introduction of the stereocenter at C8 remains rather challenging.

Inspired by the biosynthesis of PPAPs, several years later Porco and coworkers developed a second-generation strategy realizing the biomimetic cationic cyclization (Figure 50).[423] The previously exploited persubstituted compound **495** was competent for dearomative alkylation (**495** → **504**) with enantiopure triflate **505** in 72% yield but with little diastereoselectivity. After extensive screening for an optimal promoter, Porco's team discovered that formic acid induces formation of a tertiary carbocation from the 1,1-disubstituted olefin of **504**. The following electrophilic cyclization delivers the core of type A PPAPs with high chemoselectivity in 72% yield. Ordinary cross-metathesis yields (–)-clusianone (**451**). The brevity of this approach allows for expedient synthesis of the natural product in only six steps from commercial methoxyresorcinol. In order to manipulate the relative reactivity of C1 vs. C3 and as a result render this biomimetic strategy divergent, an alternative mode of cyclization was investigated. It was found that upon irradiation with purple LEDs, intermediate **504** underwent excited-state intramolecular proton transfer (ESIPT) to form zwitterion **506**.[424] Since, under these conditions, C1 is more activated for cyclization than C3, the core of type B PPAPs is selectively assembled to give **507**. Cross metathesis followed by deprotection delivers (–)-nemorosone (**450**) in seven steps from commercial material, which represents the shortest synthesis of this natural product reported to date. Ultimately, this biomimetic strategy may provide access to a large variety of biologically important PPAP natural products, and stereoisomers thereof, in a concise manner from readily available commercial materials. However, more studies are needed to address yet unresolved challenges in this field. For example, a diastereoselective dearomative alkylation, which could avoid significant loss in reaction output and tedious separation of stereoisomers, would be highly beneficial for such an approach.

Finally, it is noteworthy to mention another dearomative strategy towards bicyclo[3.3.1]nonane scaffold developed in Porco's laboratory.[425] Pd-catalyzed conjunctive allylic annulation of substrates like **508** and **509** with TMM precursor **510** can yield

bicyclic structures like **511** and **512**, with both quaternary stereocenters at bridgehead position in place. Using their previous results,[421] a similar blocking strategy was utilized to achieve divergent access to the frameworks of both families of natural products. Thus, depending on the substitution pattern of the aromatic precursor (**508** vs. **509**), both type A and type B cores are accessible in high yields. Although this approach cannot be used for synthesis of PPAP natural products, due to the missing substitution at C8 that comes from TMM-precursor **510**, it provides expedient access to valuable analogues for medicinal chemistry studies.

Summary and Conclusions

The complex, saturated architectures underlying natural products continue to challenge chemists and defy existing strategies and tactics within the synthetic canon. Dearomatization offers a strategic means of egress from the established chemistry of aromatic feedstocks into natural product scaffolds. Recent progress in dearomative methodology has initiated a paradigm shift in the way chemists disconnect molecules and has enabled groundbreaking achievements in the construction of such molecules. A three-phase dearomative logic encompassing arene substitution, dearomative reduction or functionalization, and alkene transformation provides myriad opportunities to decorate intermediates in demanding positions en route to ornate natural products. The presently insurmountable challenges posed by many natural products have stimulated intense study within the synthetic community, and novel developments in dearomative chemistry continue to nourish the blossoming field of natural product total synthesis with increased practicality and efficiency. This review presents powerful advances in dearomative methods from the past decade that have streamlined the synthesis of complex natural products, as well as modern approaches showcasing classical transformations in a new light. As nascent dearomative technology continues to mature and more chemists are exposed to the advantages of dearomative logic, we expect these approaches to see increased adoption among chemists seeking pragmatic solutions to complex synthetic problems. We hope the present review will serve to advance this movement.

ARTICLE

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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References

1 J. I. Seeman, On the Relationship between Classical Structure Determination and Retrosynthetic Analysis/Total Synthesis, *Isr. J. Chem.,* 2018, **58**, 28–44.
2 K. C. Nicolaou, C. R. H. Hale, The endeavor of total synthesis and its impact on chemistry, biology and medicine, *Natl. Sci. Rev.*, 2014, **1**, 233–252.
3 T. Gaich, P. S. Baran, Aiming for the ideal synthesis, *J. Org. Chem.*, 2010, **75**, 4657–4673.
4 A. M. Armaly, Y. C. Deporre, E. J. Groso, P. S. Riehl, C. S. Schindler, Discovery of Novel Synthetic Methodologies and Reagents during Natural Product Synthesis in the Post-Palytoxin Era, *Chem. Rev*., 2015, **115**, 9232–9276.
5 K. C. Nicolaou, Organic synthesis: the art and science of replicating the molecules of living nature and creating others like them in the laboratory, *Proc. R. Soc. A Math. Phys. Eng. Sci.*, 2014, **470**: 20130690.
6 C. A. Kuttruff, M. D. Eastgate, P. S. Baran, Natural product synthesis in the age of scalability, *Nat. Prod. Rep*., 2014, **31**, 403–606.
7 K. C. Nicolaou, The Emergence and Evolution of Organic Synthesis and Why It is Important to Sustain It as an Advancing Art and Science for Its Own Sake, *Isr. J. Chem*., 2018, **58**, 104–113.
8 C.H. Heathcock, Panel Discussion I. As We Head Into the 21st Century, is There Still Value in Total Synthesis of Natural Products as a Research Endeavor?, in *Chemical synthesis: gnosis to prognosis*, eds. C. Chatgilialoglu and V. Snieckus, Kluwer Academic, Dordrecht, 1996, pp. 223–244.
9 F. Lovering, J. Bikker, C. Humblet, Escape from flatland: Increasing saturation as an approach to improving clinical success, *J. Med. Chem*., 2009, **52**, 6752–6756.
10 F. Lovering, Escape from Flatland 2: complexity and promiscuity, *Med. Chem. Commun*. 2013, **4**, 515–519.
11 M. D. Eastgate, M. A. Schmidt, K. R. Fandrick, On the design of complex drug candidate syntheses in the pharmaceutical industry, *Nat. Rev. Chem*., 2017, **1**, 1–16.
12 E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, John Wiley & Sons, Inc., New York. 1995.
13 C. J. Huck, D. Sarlah, Shaping Molecular Landscapes: Recent Advances, Opportunities, and Challenges in Dearomatization, *Chem*., 2020, **6**, 1589–1603.
14 W. C. Wertjes, E. H. Southgate, D. Sarlah, Recent advances in chemical dearomatization of nonactivated arenes, *Chem. Soc. Rev.*, 2018, **48**, 7996–8017.
15 M. P. Wiesenfeldt, Z. Nairoukh, T. Dalton, F. Glorius, Selective Arene Hydrogenation for Direct Access to Saturated Carbo- and Heterocycles, *Angew. Chem. Int. Ed*., 2019, **58**, 10460–10476.
16 B. K. Liebov, W. D. Harman, Group 6 Dihapto-Coordinate Dearomatization Agents for Organic Synthesis, *Chem. Rev*., 2017, **117**, 13721–13755.
17 A. R. Pape, K. P. Kaliappan, E. P. Kündig, Transition-Metal-Mediated Dearomatization Reactions, *Chem. Rev*., 2000, **100**, 2917–2940.
18 F. L. Ortiz, M. J. Iglesias, I. Fernández, C. M. A. Sánchez, G. R. Gómez, Nucleophilic dearomatizing (DNAr) reactions of aromatic C,H-Systems. A mature paradigm in organic synthesis, *Chem. Rev*., 2007, **107**, 1580–1691.
19 V. Snieckus, Directed Aromatic Metalation: A Continuing Education in Flatland Chemistry, in *Chemical synthesis: gnosis to prognosis*, eds. C. Chatgilialoglu and V. Snieckus, Kluwer Academic, Dordrecht, 1996, pp. 191–222.
20 W. R. Gutekunst, P. S. Baran, C–H functionalization logic in total synthesis, *Chem. Soc. Rev*., 2011, **40**, 1976–1991.
21 J. F. Hartwig, M. A. Larsen, Undirected, homogeneous C-H bond functionalization: Challenges and opportunities, *ACS Cent. Sci*., 2016, **2**, 281–292.
22 M. C. White, J. Zhao, Aliphatic C-H Oxidations for Late-Stage Functionalization, *J. Am. Chem. Soc*., 2018, **140**, 13988–14009.
23 J. F. Hartwig, Catalyst-controlled site-selective bond activation, *Acc. Chem. Res*., 2017, **50**, 549–555.
24 S. R. Neufeldt, M. S. Sanford, Controlling site selectivity in palladium-catalyzed C-H bond functionalization, *Acc. Chem. Res*., 2012, **45**, 936–946.
25 J. He, M. Wasa, K. S. L. Chan, Q. Shao, J. Q. Yu, Palladium-Catalyzed Transformations of Alkyl C-H Bonds, *Chem. Rev*., 2017, **117**, 8754–8786.
26 P. S. Baran, Natural Product Total Synthesis: As Exciting as Ever and Here To Stay, *J. Am. Chem. Soc*., 2018, **140**, 4751–4755.
27 P. A. Wender, J. J. Howbert, Synthetic studies on arene-olefin cycloadditions: total synthesis of (±)-α-cedrene, *J. Am. Chem. Soc*., 1981, **103**, 688–690.
28 D.-S. Hsu, C.-C. Liao, First Total Syntheses of (±)-Penicillones A and B, *Org. Lett*., 2007, **9**, 4563–4565.
29 C. Tang, M. Okumura, Y. Zhu, A. R. Hooper, Y. Zhou, Y. H. Lee, D. Sarlah, Palladium-Catalyzed Dearomative syn-1,4-Carboamination with Grignard Reagents. *Angew. Chem. Int. Ed*., 2019, **58**, 10245–10249.
30 E. J. Corey, W. J. Howe, H. W. Orf, D. A. Pensak, G. Petersson, General methods of synthetic analysis. Strategic bond

disconnections for bridged polycyclic structures, *J. Am. Chem. Soc*., 1975, **97**, 6116–6124.
31 K. R. Owens, S. V McCowen, K. A. Blackford, S. Ueno, Y. Hirooka, M. Weber, R. Sarpong, Total Synthesis of the Diterpenoid Alkaloid Arcutinidine Using a Strategy Inspired by Chemical Network Analysis, *J. Am. Chem. Soc*., 2019, **141**, 13713–13717.
32 D. S. Wang, Q. A. Chen, S. M. Lu, Y. G. Zhou, Asymmetric Hydrogenation of Heteroarenes and Arenes, *Chem. Rev*., 2011, **112**, 2557–2590.
33 S. E. Lewis, Applications of biocatalytic arene ipso,ortho cis-dihydroxylation in synthesis, *Chem. Commun*., 2014, **50**, 2821–2830.
34 M. J. Palframan, G. Kociok-Köhn, S. E. Lewis, Photooxygenation of a microbial arene oxidation product and regioselective Kornblum-DeLamare rearrangement: Total synthesis of zeylenols and zeylenones, *Chem. Eur. J.*, 2012, **18**, 4766–4774.
35 K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, Cascade reactions in total synthesis. *Angew. Chem. Int. Ed*., 2006, **45**, 7134–7186.
36 S. P. Roche, J. A. Porco, Dearomatization strategies in the synthesis of complex natural products, *Angew. Chem. Int. Ed*., 2011, **50**, 4068–4093.
37 L. N. Mander, Exploitation of Aryl Synthons in the Synthesis of Polycyclic Natural Products, *Synlett*, 1991, 134–144.
38 L. Pouységu, D. Deffieux, S. Quideau, Hypervalent iodine-mediated phenol dearomatization in natural product synthesis, *Tetrahedron*, 2010, **66**, 2235–2261.
39 M. Heravi, M. Fard, Z. Faghihi, Recent Applications of Birch Reduction in Total Synthesis of Natural Products, *Curr. Org. Chem*., 2015, **19**, 1491–1525.
40 J. H. George, Biomimetic Dearomatization Strategies in the Total Synthesis of Meroterpenoid Natural Products, *Acc. Chem. Res*., 2021, **54**, 1843–1855.
41 H.-D. Sun, S.-X. Huang, Q.-B. Han, Diterpenoids from Isodon species and their biological activities. *Nat. Prod. Rep*., 2006, **23**, 673–698.
42 Y. Ding, H. Chen, J. Zhou, Chemistry and Bioactivity of Ent-Kaurene Diterpenoids. *Studies in Natural Product Chemistry*, 2017, **54**, 141–197.
43 M. Liu, W.-G Wang, H.-D. Sun and J.-X. Pu, Diterpenoids from Isodon species: an update. *Nat. Prod. Rep*., 2017, **34**, 1090–1140.
44 J. Wang, S. M. Soisson, K. Young, W. Shoop, S. Kodali, A. Galgoci, R. Painter, G. Parthasarathy, Y. S. Tang, R. Cummings, S. Ha, K. Dorso, M. Motyl, H. Jayasuriya, J. Ondeyka, K. Herath, C. Zhang, L. Hernandez, J. Allocco, ngela Basilio, J. R. Tormo, O. Genilloud, F. Vicente, F. Pelaez, L. Colwell, S. Ho Lee, B. Michael, T. Felcetto, C. Gill, L. L. Silver, J. D. Hermes, K. Bartizal, J. Barrett, D. Schmatz, J. W. Becker, D. Cully, S. B. Singh, Platensimycin is a selective FabF inhibitor with potent antibiotic properties, *Nature*, 2006, **441**, 358–361.
45 E. Martens, A. L. Demain, Platensimycin and platencin: Promising antibiotics for future application in human medicine. *J. Antibiot. (Tokyo)*., 2011, **64**, 705–710.
46 R. Shang, J. Liang, Y. Yi, Y. Liu, J. Wang, Review of Platensimycin and Platencin: Inhibitors of β-Ketoacyl-acyl Carrier Protein (ACP) Synthase III (FabH). *Molecules*, 2015, **20**, 16127–16141.
47 Z. Zhao, Y. Chen, Oridonin, a Promising Antitumor Natural Product in the Chemotherapy of Hematological Malignancies. *Curr. Pharm. Biotechnol*., 2014, **15**, 1083–1092.
48 X. Liu, J. Xu, J. Zhou, Q. Shen, Oridonin and its derivatives for cancer treatment and overcoming therapeutic resistance. *Genes & Diseases*, 2021, **8**, 448–462.
49 J. Xu, E. Wold, Y. Ding, Q. Shen, J. Zhou, Therapeutic Potential of Oridonin and Its Analogs: From Anticancer and Antiinflammation to Neuroprotection. *Molecules*, 2018, **23**, 474–490.
50 CTR20150246; http://www.chinadrugtrials.org.cn
51 P. S. Riehl, Y. C. DePorre, A. M. Armaly, E. J. Groso and C. S. Schindler, New avenues for the synthesis of ent-kaurene diterpenoids, *Tetrahedron*, 2015, **71**, 6629–6650.
52 K. E. Lazarski, B. J. Moritz and R. J. Thomson, *Angew. Chem., Int. Ed*., 2014, **53**, 10588–10599.
53 R. M. Coates, P. L. Cavender, Stereochemistry of the Enzymatic Cyclization of Copalyl Pyrophosphate to Kaurene in Enzyme Preparations from Marah macrocarpus, *J. Am. Chem. Soc*., 1980, **102**, 6358–6359.
54 Y. J. Hong, D. J. Tantillo, Formation of beyerene, kaurene, trachylobane, and atiserene diterpenes by rearrangements that avoid secondary carbocations, *J. Am. Chem. Soc*., 2010, **132**, 5375–5386.
55 B. B. Snider, J. Y. Kiselgof, B. M. Foxman, Total Syntheses of (±)-Isosteviol and (±)-Beyer-15-ene-3β,19-diol by Manganese(III)-Based Oxidative Quadruple Free-Radical Cyclization, *J. Org. Chem*., 1998, **63**, 7945–7952.
56 R. F. Church, R. E. Ireland, J. A. Marshall, Experiments Directed toward the Total Synthesis of Terpenes. VII. The Synthesis of (±)-8β-Carbomethoxy-13-oxopodocarpanone, a Degradation Product of Phyllocladene, *J. Org. Chem*., 1966, **31**, 2526–2530.
57 R. A. Bell, R. E. Ireland, R. A. Partyka, Experiments Directed toward the Total Synthesis of Terpenes. VIII. The Total Synthesis of (±)-Kaurene and (±)-Atisirene, *J. Org. Chem*., 1966, **31**, 2530–2536.
58 R. F. Church, R. E. Ireland, J. A. Marshall, The stereospecific total synthesis of d1-8β-carbomethoxy-13-oxopodocarpane, a degradation product of phyllocladane, *Tetrahedron Lett*., 1960, **1**, 1–4.
59 R. A. Bell, R. E. Ireland, R. A. Partyka, The Total Synthesis of dl-Kaurene. *J. Org. Chem*., 1962, **27**, 3741–3744.
60 F. E. Ziegler, J. A. Kloek, 1-Hydroxy-7-methylene bicyclo[3.2.1]octane: a gibbane-steviol c/d ring model. *Tetrahedron Lett*., 1971, **12**, 2201–2203.
61 F. E. Ziegler, J. A. Kloek, The stereocontrolled photoaddition of allene to cyclopent-1-ene-1-carboxaldehydes. A total synthesis of (±) steviol methyl ester and isosteviol methyl ester. *Tetrahedron*, 1977, **33**, 373–380.
62 L. Zhu, J. Luo, R. Hong, Total synthesis of (±)-cafestol: A late-stage construction of the furan ring inspired by a biosynthesis strategy. *Org. Lett*., 2014, **16**, 2162–2165.
63 E. J. Corey, K. Liu, Enantioselective total synthesis of the potent Anti-HIV agent neotripterifordin. Reassignment of stereochemistry at C(16). *J. Am. Chem. Soc*., 1997, **119**, 9929–9930.
64 E. C. Cherney, J. C. Green, P. S. Baran, Synthesis of ent -Kaurane and Beyerane Diterpenoids by Controlled Fragmentations of Overbred Intermediates. *Angew. Chemie Int. Ed*., 2013, **52**, 9019–9022.
65 M. Toyota, T. Wada, Y. Nishikawa, K. Yanai, K. Fukumoto, Pd2+ -Promoted Cyclization in Gibberellin Synthesis - A New Strategy for C20 Gibberellin Synthesis. *Synlett*, 1994, 597–598.
66 M. Toyota, T. Wada, Y. Nishikawa, K. Yanai, K. Fukumoto, C. Kabuto, Simple design for the construction of complex gibberellin framework-Stereoselective synthesis of a possible key intermediate to GA12 via Pd2+-promoted cycloalkenylation reaction. *Tetrahedron*, 1995, **51**, 6927–6940.
67 M. Toyota, T. Wada, M. Ihara, Total syntheses of (–)-methyl atis-16-en-19-oate, (–)-methyl kaur-16-en-19-oate, and (–)-methyl trachyloban-19-oate by a combination of palladium-catalyzed cycloalkenylation and homoallyl-homoallyl radical rearrangement. *J. Org. Chem*., 2000, **65**, 4565–4570.

68 M. Toyota, T. Wada, K. Fukumoto, M. Ihara, Total synthesis of (±)-methyl atis-16-en-19-oate via homoallyl- homoallyl radical rearrangement. *J. Am. Chem. Soc*., 1998, **120**, 4916–4925.
69 M. Toyota, T. Wada, K. Fukumoto, INOC reaction in gibberellin synthesis-a practical synthesis of the key intermediate for gibberellin A12, *Heterocycles*, 1995, **41**, 1135–1138.
70 J. T. S. Yeoman, V. W. Mak, S. E. Reisman, A unified strategy to ent -kauranoid natural products: Total syntheses of (–)-trichorabdal A and (–)-longikaurin e. *J. Am. Chem. Soc*., 2013, **135**, 11764–11767.
71 X. Zhao, W. Li, J. Wang, D. Ma, Convergent Route to ent-Kaurane Diterpenoids: Total Synthesis of Lungshengenin D and 1α,6α-Diacetoxy-ent-kaura-9(11),16-dien12,15-dione. *J. Am. Chem. Soc*., 2017, **139**, 2932-2935.
72 E. J. Corey, G. Wess, Y. Bin Xiang, A. K. Singh, Stereospecific Total Synthesis of (±)-cafestol. *J. Am. Chem. Soc*., 1987, **109**, 4717–4718.
73 D. Backhaus, L. A. Paquette, Synthetic entry into the ent-kaurene framework. Application of an unprecedented transannular cyclization for forming the central bond common to the B and C rings. *Tetrahedron Lett*., 1997, **38**, 29–32.
74 J. Wang, D. Ma, 6-Methylenebicyclo[3.2.1]oct-1-en-3-one: A Twisted Olefin as Diels–Alder Dienophile for Expedited Syntheses of Four Kaurane Diterpenoids. *Angew. Chemie Int. Ed*., 2019, **58**, 15731–15735.
75 L. Kong, F. Su, H. Yu, Z. Jiang, Y. Lu, T. Luo, Total Synthesis of (−)-Oridonin: An Interrupted Nazarov Approach, *J. Am. Chem. Soc.*, 2019, **141**, 20048–20052.
76 C. He, J. Hu, Y. Wu, H. Ding, Total Syntheses of Highly Oxidized ent-Kaurenoids Pharicin A, Pharicinin B, 7-O-Acetylpseurata C, and Pseurata C: A [5+2] Cascade Approach, *J. Am. Chem. Soc*., 2017, **139**, 6098–6101.
77 G. A. Macalpine, J. Warkentin, Thermolysis of Δ3-1,3,4-oxadiazolin-2-ones and 2-phenylimino- Δ3-1,3,4-oxadiazolines derived from α,β-epoxyketones. An alternative method for the conversion of a α,β-epoxyketones to alkynones and alkynals, *Can. J. Chem*., 1978, **56**, 308–315.
78 S. Pan, J. Xuan, B. Gao, A. Zhu, H. Ding, Total Synthesis of Diterpenoid Steenkrotin A. *Angew. Chemie Int. Ed*., 2015, **54**, 6905–6908.
79 J. Gao, P. Rao, K. Xu, S. Wang, Y. Wu, C. He, H. Ding, Total Synthesis of (−)-Rhodomollanol A. *J. Am. Chem. Soc*., 2020, **142**, 4592–4597.
80 S.-H. Li, J. Wang, X.-M. Niu, Y.-H. Shen, H.-J. Zhang, H.-D. Sun, M.-L. Li, Q.-E. Tian, Y. Lu, P. Cao, Q.-T. Zheng, Maoecrystal V, Cytotoxic Diterpenoid with a Novel C19 Skeleton from Isodon eriocalyx (Dunn.) Hara. *Org. Lett*., 2004, **6**, 4327–4330.
81 B. R. Smith, J. T. Njardarson, Review of synthetic approaches toward maoecrystal V. *Org. Biomol. Chem*., 2018, **16**, 4210–4222.
82 P. J. Krawczuk, N. Schone and P. S. Baran, A synthesis of the carbon skeleton of maoecrystal V, *Org. Lett*., 2009, **11**, 4774–4776.
83 J. Gong, G. Lin, C. Li and Z. Yang, Synthetic study toward the total synthesis of maoecrystal V, *Org. Lett*., 2009, **11**, 4770–4773.
84 F. Peng, M. Yu and S. J. Danishefsky, Synthetic Studies towards Maoecrystal V, *Tetrahedron Lett*., 2009, **50**, 6586–6587.
85 F. Peng and S. J. Danishefsky, Toward the total synthesis of maoecrystal V: an intramolecular Diels-Alder route to the maoecrystal V pentacyclic core with the appropriate relative stereochemistry, *Tetrahedron Lett*., 2011, **52**, 2104–2106.
86 V. Singh, P. Bhalerao and S. M. Movin, A tandem oxidative dearomatization/intramolecular Diels–Alder reaction: a short and efficient entry into tricyclic system of maoecrystal V, *Tetrahedron Lett*., 2010, **51**, 3337–3339.
87 I. Baitinger, P. Mayer and D. Trauner, Toward the total synthesis of maoecrystal V: establishment of contiguous quaternary stereocenters, *Org. Lett*., 2010, **12**, 5656–5659.
88 K. E. Lazarski, D. X. Hu, C. L. Stern and R. J. Thomson, A synthesis of the carbocyclic core of maoecrystal V, *Org. Lett*., 2010, **12**, 3010–3013.
89 K. E. Lazarski, B. Akpinar and R. J. Thomson, Evaluation of 'east-to-west' ether-forming strategies for the total synthesis of maoecrystal V, *Tetrahedron Lett*., 2013, **54**, 635–637.
90 Z. Gu and A. Zakarian, Studies toward the synthesis of maoecrystal V, *Org. Lett*., 2011, **13**, 1080–1082.
91 K. C. Nicolaou, L. Dong, L. Deng, A. C. Talbot and D. Y.-K. Chen, Synthesis of functionalized maoecrystal V core structures, *Chem. Commun*., 2010, **46**, 70–72.
92 L. Dong, L. Deng, Y.-H. Lim, G. Y. C. Leung and D. Y.-K. Chen, Synthesis of an advanced maoecrystal V core structure, *Chem. – Eur. J*., 2011, **17**, 5778–5781.
93 P. Carberry, D. R. Viernes, L. B. Choi, M. W. Fegley and J. D. Chisholm, An unusual intramolecular Diels–Alder approach toward maoecrystal V, *Tetrahedron Lett*., 2013, **54**, 1734–1737.
94 S. Jansone-Popova and J. A. May, Stereoelectronic factors in bridgehead C–H bond insertion: studies toward the total synthesis of maoecrystal V, *Tetrahedron*, 2016, **72**, 3734–3747.
95 B. R. Smith and J. T. Njardarson, Double-Diels-Alder Approach to Maoecrystal V. Unexpected C-C Bond-Forming Fragmentations of the [2.2.2]-Bicyclic Core, *Org. Lett*., 2017, **19**, 5316–5319.
96 T. M. Chang, PhD Dissertation, University of Arizona, 2012.
97 D. D. McLeod, PhD Dissertation, Princeton University, 2010.
98 M. J. Smith, PhD Dissertation, Princeton University, 2013.
99 M. R. Naylor, PhD Dissertation, Princeton University, 2014.
100 J. Gong, G. Lin, W. Sun, C.-C. Li and Z. Yang, Total synthesis of (±) maoecrystal V, *J. Am. Chem. Soc*., 2010, **132**, 16745–16746.
101 F. Peng and S. J. Danishefsky, Total synthesis of (±)-maoecrystal V, *J. Am. Chem. Soc*., 2012, **134**, 18860–18867.
102 P. Lu, Z. Gu and A. Zakarian, Total synthesis of maoecrystal V: early-stage C-H functionalization and lactone assembly by radical cyclization, *J. Am. Chem. Soc*., 2013, **135**, 14552–14555.
103 C. Zheng, I. Dubovyk, K. E. Lazarski and R. J. Thomson, Enantioselective total synthesis of (–)-maoecrystal V, *J. Am. Chem. Soc*., 2014, **136**, 17750–17756.
104 P. Lu, A. Mailyan, Z. Gu, D. M. Guptill, H. Wang, H. M. L. Davies and A. Zakarian, Enantioselective synthesis of (–)-maoecrystal V by enantiodetermining C-H functionalization, *J. Am. Chem. Soc*., 2014, **136**, 17738–17749.
105 W.-B. Zhang, W.-B. Shao, F.-Z. Li, J.-X. Gong and Z. Yang, Asymmetric Total Synthesis of (–)-Maoecrystal V, *Chem. – Asian J.,* 2015, **10**, 1874–1880.
106 A. Cernijenko, R. Risgaard and P. S. Baran, 11-Step Total Synthesis of (–)-Maoecrystal V, *J. Am. Chem. Soc*., 2016, **138**, 9425–9428.
107 J. T. Pinhey and B. A. Rowe, The chemistry of aryllead(IV) tricarboxylates. Reaction with β-keto esters: a convenient route to α-arylated ketones, *Aust. J. Chem*., 1980, **33**, 113–120.
108 C. A. M. Fraga, L. H. P. Teixeira, C. M. de S. Menezes, C. M. R. Sant'Anna, M. da C. K. V. Ramos, F. R. de Aquino Neto, E. J. Barreiro, Studies on diastereoselective reduction of cyclic β-ketoesters with boron hydrides. Part 4: The reductive profile of functionalized cyclohexanone derivatives, *Tetrahedron*, 2004, **60**, 2745–2755.
109 R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert, Ph. Teyssié, Transition metal catalysed reactions of

diazocompounds - II insertion in the hydroxylic bond, *Tetrahedron Lett*., 1973, **14**, 2233–2236.

110 H. M. L. Davies, M. V. A. Grazini, and E. Aouad, Asymmetric Intramolecular C−H Insertions of Aryldiazoacetates, *Org. Lett*. 2001, **3**, 1475–1477.

111 J. C. Green, T. R. R. Pettus, An oxidative dearomatization-induced [5 + 2] cascade enabling the syntheses of α-cedrene, α-pipitzol, and sec -cedrenol. *J. Am. Chem. Soc*., 2011, **133**, 1603–1608.

112 P. Finkbeiner, K. Murai, M. Röpke, R. Sarpong, Total Synthesis of Terpenoids Employing a "Benzannulation of Carvone" Strategy: Synthesis of (−)-Crotogoudin. *J. Am. Chem. Soc.*, 2017, **139**, 11349–11352.

113 M. Weber, K. Owens, R. Sarpong, Atropurpuran—missing biosynthetic link leading to the hetidine and arcutine C20-diterpenoid alkaloids or an oxidative degradation product? *Tetrahedron Lett*., 2015, **56**, 3600–3603.

114 T. Suzuki, A. Sasaki, N. Egashira, & S. Kobayashi, S. A synthetic study of atropurpuran: construction of a pentacyclic framework by an intramolecular reverse-electron-demand Diels–Alder reaction. *Angew. Chem. Int. Ed*., 2011, **50**, 9177–9179.

115 R. Hayashi, Z. X. Ma, & R. P. Hsung, A tandem 1,3-H-shift–6pi- electrocyclization–cyclic 2-amido-diene intramolecular Diels–Alder cycloaddition approach to BCD-ring of atropurpuran. *Org. Lett.*, 2012, **14**, 252–255.

116 H. Chen, D. Zhang, F. Xue, & Y. Qin, Synthesis of the atropurpuran A-ring via an organocatalytic asymmetric intramolecular Michael addition. *Tetrahedron*, 2013, **69**, 3141–3148.

117 H. Chen, X.-H. Li, J. Gong, H. Song, X.-Y. Liu, & Y. Qin, Synthetic approach to the functionalized tricyclic core of atropurpuran. *Tetrahedron*, 2016, **72**, 347–353.

118 P. Tang, Q. H. Chen, F. P. Wang, Atropurpuran, a novel diterpene with an unprecedented pentacyclic cage skeleton, from Aconitum hemsleyanum var. atropurpureum, *Tetrahedron Lett*., 2009, **50**, 460–462.

119 J. Gong, H. Chen, X.-Y. Liu, Z.-X. Wang, W. Nie, Y. Qin, Total synthesis of atropurpuran. *Nat. Commun*., 2016, **7**, 12183.

120 S. Xie, G. Chen, H. Yan, J. Hou, Y. He, T. Zhao, J. Xu, 13-Step Total Synthesis of Atropurpuran. *J. Am. Chem. Soc*., 2019, **141**, 3435−3439.

121 F.-P. Wang, Q. H. Chen, X.-Y. Liu, Diterpenoid alkaloids. *Nat. Prod. Rep.*, 2010, **27**, 529–570.

122 K. Wada, H. Yamashita, Cytotoxic Effects of Diterpenoid Alkaloids Against Human Cancer Cells. *Molecules*, 2019, **24**, 2317.

123 Y. Ohno, The Experimental Approach to the Murder Case of Aconite Poisoning. *J. Tox.: Tox. Rev*., 2009, **17**, 1–11.

124 A. A. Van Landeghem, E. A. De Letter, W. E. Lambert, C. H. Van Peteghem, M. H. A. Piette. Aconitine involvement in an unusual homicide case. *Int. J. Legal Med*,. 2007, **121**, 214–219.

125 M. L. Colomboa, C. Bugattib, F. Davanzoc, A. Persicob, C. Ballabiob, P. Restanib, Analytical Aspects of Diterpene Alkaloid Poisoning with Monkshood. *Nat. Prod. Comm*., 2009, **4**, 1551–1552.

126 H. Miyaguchi, H. Sekine, Homicide involving Aconitum tuberous root: LC-MS-MS analysis of Aconitum alkaloids and their hydrolysates in formalin-fixed tissues. *Forensic. Toxicol*., 2010, **28**, 47–51.

127 K. B. Bonnici, D. Stanworth, M. S. J. Simmonds, E. Mukherjee, R. E. Ferner, Flowers of evil. *The Lancet*, 2010, **376**, 1616.

128 M. Povšnar, G. Koželj, S. Kreft, M. Lumpert, Rare tradition of the folk medicinal use of Aconitum spp. is kept alive in Solčavsko, Slovenia. *J. Enthobiol. Enthomed*., 2017, **13**, 45.

129 X. Huang, Y. Yang, J. Zhu, Y. Dai, J. Pu, The Effects of a Novel Anti-arrhythmic Drug, Acehytisine Hydrochloride, on the Human Ether-a-go-go Related Gene K+ Channel and Its Trafficking. *Basic Clin. Pharmacol. Toxicol*., 2008, **104**, 145–154.

130 X. Gao, J. Zhu, Y. M. Yang, J. D. Li, Z. M. Yang, J. H. Liu, Acehytisine Hydrochloride Injection Phase II Clinic Trial Group Investigators, Efficacy of intravenous Acehytisine Hydrochloride versus propafenone on terminating paroxysmal supraventricular tachycardia: a double-blinded, randomized multi-center study. *Zhonghua Xin Xue Guan Bing Za Zhi,* 2007, **35**, 151–154. In Chinese.

131 Y. M. Yang, J. Zhu, X. Gao, Y. L. Yin, Y. X. Hao, J. H. Liu, Guanfu Base A Hydrochloride Injection Phase II Clinic Trial Group Investigators, Effect of Guanfu Base A in patients with ventricular arrhythmias. *Zhonghua Xin Xue Guan Bing Za Zhi,* 2006, **34**, 329–332. In Chinese.

132 M. Stevens, S. Peigneur, J. Tytgat, Neurotoxins and their binding areas on voltage-gated sodium channels. *Front Pharmacol*., 2011, **2**, 71.

133 T. Anger, D. J. Madge, M. Mulla, D. Riddall, Medicinal Chemistry of Neuronal Voltage-Gated Sodium Channel Blockers. *J. Med. Chem*., 2001, **44**, 115–137.

134 S.-Y. Wang, G. K. Wang, Voltage-gated sodium channels as primary targets of diverse lipid-soluble neurotoxins. *Cell. Signal*., 2003, **15**, 151–159.

135 F.-P. Wang, Q. H. Chen, X.-T. Liang, The C18-diterpenoid alkaloids. *Alkaloids Chem Biol*., 2009, **67**, 1–78.

136 F.-P. Wang, Q. H. Chen, The C19-diterpenoid alkaloids. *Alkaloids Chem. Biol*., 2010, **69**, 1–577.

137 F. P. Wang, X.-T. Liang, C20 diterpenoid alkaloids, *Alkaloids Chem. Biol*. 2002, **59**, 1–280.

138 S. W. Pelletier, P. C. Parthasarathy, The Diterpene Alkaloids: A Partial Synthesis of Atisine. *Tetrahedron Lett*., 1963, **4**, 205–208.

139 S. W. Pelletier, W. A. Jacobs, The aconite alkaloids. XXVII. The structure of atisine, *J. Am. Chem. Soc*., 1954, **76**, 4496–4497.

140 N. V. Mody, S. W. Pelletier. 13C nuclear magnetic resonance spectroscopy of atisine and veatchine-type C20-diterpenoid alkaloids from aconitum and garrya species. *Tetrahedron*, 1978, **34**, 2421–2431.

141 K. Wiesner, J. A. Edwards, The basicity and steric configuration of the diterpene alkaloids veatchine and atisine, *Experientia*, 1955, **11**, 255–259.

142 K. Wiesner, F. Bickelhaupt, D. R. Babin, M. Gotz, The structure of delphinine, *Tetrahedron Lett*., 1959, **1**, 3, 11–14.

143 K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown, G. Büchi, The structure of aconitine, *Tetrahedron Lett.*, 1959, **1**, 2, 15–24.

144 O. E. Edwards, T. Singh, Atsine: The heterocyclic ring and functional groups, *Can. J. Chem*., 1954, **32**, 465–473.

145 O. E. Edwards, T. Singh, Atsine: The functional groups, *Can. J. Chem*., 1955, **33**, 448–451.

146 W. A. Jacobs, The Aconite Alkaloids. XXIV. The Degradation of Atisine and Isoatisine, *J. Org. Chem*., 1951, **16**, 1593–1602.

147 W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, Y. Hayase, Stereospecific Total Synthesis of dl-Atisine. *J. Am. Chem. Soc*., 1963, **85**, 2342–2343.

148 W. Nagata, M. Narisada, T. Wakabayashi, T. Sugasawa, Total Synthesis of dl-garryine and dl-veatchine. *J. Am. Chem. Soc*., 1964, **85**, 929–930.

149 S. Masamune, Synthesis of 4a,6-ethano-5.6 7,8-tetrahydro- 2(4a)-naphthalenone. *J. Am. Chem. Soc*., 1961, **83**, 1009–1010.

150 S. Masamune, Total Syntheses of Diterpenes and Diterpene Alkaloids. II. A Tetracyclic Common Intermediate. *J. Am. Chem. Soc*., 1964, **86**, 288–289.

151 S. Masamune, Total Syntheses of Diterpenes and Diterpene Alkaloids. III. Kaurene. *J. Am. Chem. Soc*., 1964, **86**, 289–290.
152 S. Masamune, Total Syntheses of Diterpenes and Diterpene Alkaloids. IV. Garryine. *J. Am. Chem. Soc*., 1964, **86**, 290–291.
153 S. Masamune, Total Syntheses of Diterpenes and Diterpene Alkaloids. V. Atisine. *J. Am. Chem. Soc*., 1964, **86**, 291–292.
154 Z. Valenta, K. Wiesner, C. H. Wang, Synthesis in the diterpene alkaloid series - II. A total synthesis of the garrya alkaloids. *Tetrahedron Lett*., 1964, **5**, 2437–2442.
155 R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta, K, Wiesner, The total synthesis of the Garrya veatchii alkaloids. *Collect. Czech. Chem. Commun*., 1966, **31**, 602–621.
156 R. W. Guthrie, Z. Valenta, K. Wiesner, Synthesis in the series of diterpene alkaloids VI. A simple synthesis of atisine. *Tetrahedron Lett*., 1966, **7**, 4645–4654.
157 K. Wiesner, P.-T. Ho, D. Chang, Y. K. Lam, C. S. J. Pan, W. Y. Ren, The Synthesis of Songorine: A Simplified Synthesis of the Aromatic Intermediate. *Can. J. Chem*., 1973, **51**, 3978–3988.
158 K. Wiesner, P. Ho, C. S. J. (Pan) Tsai, The Total Synthesis of a Hexacyclic Relay for the Alkaloid Napelline. *Can. J. Chem*., 1974, **52**, 2353–2355.
159 K. Wiesner, P. Ho, C. S. J. (Pan) Tsai, Y. K. Lam, The Total Synthesis of Racemic Napelline. *Can. J. Chem*., 1974, **52**, 2355–2357.
160 S. P. Sethi, K. S. Atwal, R. M. Marini-Bettolo, T. Y. R. Tsai, K. Wiesner, A stereospecific synthesis of napelline. *Can. J. Chem*., 1980, **58**, 1889–1891.
161 X.-Y. Liu, Y. Qin, Enabling syntheses of diterpenoid alkaloids and related diterpenes by an oxidative dearomatization/Diels–Alder cycloaddition strategy. *Nat. Prod. Rep*., 2017, **34**, 1044–1050.
162 K. Weisner, T. Y. R. Tsai, K. Huber, S. E. Bolton, R. Vlahov, Total synthesis of talatisamine, a delphinine type alkaloid, *J. Am. Chem. Soc.,* 1974, **96**, 4990–4992.
163 K. Wiesner, T. Y. R. Tsai, K. P. Nambiar, A new stereospecific total synthesis of chasmanine and 13-desoxydelphonine, *Can. J. Chem*., 2011, **56**, 1451–1454.
164 X.-Y. Liu, H. Cheng, X.-H. Li, Q.-H. Chen, L. Xu, F.-P. Wang, Oxidative dearomatization/intramolecular Diels-Alder cycloaddition cascade for the syntheses of (±)-atisine and (±)-isoazitine, *Org. Biomol. Chem*., 2012, **10**, 1411–1417.
165 J. Liu, D. Ma, A Unified Approach for the Assembly of Atisine- and Hetidine-type Diterpenoid Alkaloids: Total Syntheses of Azitine and the Proposed Structure of Navirine C, *Angew. Chem. Int. Ed*., 2018, **57**, 6676–6680.
166 X.-H. Li, M. Zhu, Z.-X. Wang, X.-Y. Liu, H. Song, D. Zhang, F.-P. Wang, Y. Qin, Synthesis of Atisine, Ajaconine, Denudatine, and Hetidine Diterpenoid Alkaloids by a Bioinspired Approach, *Angew. Chem. Int. Ed.*, 2016, **55**, 15667–15671.
167 H. Cheng, F.-H. Zeng, X. Yang, Y.-J. Meng, L. Xu, F.-P. Wang, Collective Total Syntheses of Atisane-Type Diterpenes and Atisine-Type Diterpenoid Alkaloids: (±)-Spiramilactone B, (±)-Spiraminol, (±)-Dihydroajaconine, and (±)-Spiramines C and D, *Angew. Chem. Int. Ed*., 2016, **55**, 392–396.
168 Y. Nishiyama, Y. Han-Ya, S. Yokoshima, T. Fukuyama, Total Synthesis of (−)-Lepenine, *J. Am. Chem. Soc*., 2014, **136**, 6598−6601.
169 A. M. Hamlin, F. de Jesus Cortez, D. Lapointe, R. Sarpong, Gallium(III)-Catalyzed Cycloisomerization Approach to the Diterpenoid Alkaloids: Construction of the Core Structure for the Hetidines and Hetisines, *Angew. Chem. Int. Ed*., 2013, **52**, 4854–4857.
170 C. J. Marth, G. M. Gallego, J. C. Lee, T. P. Lebold, S. Kulyk, K. G. M Kou, J. Qin, R. Lilien, R. Sarpong, Network-analysis-guided synthesis of weisaconitine D and liljestrandinine, *Nature*, 2015, **528**, 493–498.
171 K. G. M. Kou, S. Kulyk, C. J. Marth, J. C. Lee, N. A. Doering, B. X. Li, G. M. Gallego, T. P. Lebold, R. Sarpong, A Unifying Synthesis Approach to the C 18-, C 19-, and C 20-Diterpenoid Alkaloids, *J. Am. Chem. Soc*., 2017, **139**, 13882−13896.
172 K. G. M. Kou, J. J. Pflueger, T. Kiho, L. C. Morrill, E. L. Fisher, K. Clagg, T. P. Lebold, J. K. Kisunzu, R. Sarpong, A Benzyne Insertion Approach to Hetisine-Type Diterpenoid Alkaloids: Synthesis of Cossonidine (Davisine), *J. Am. Chem. Soc*., 2018, **140**, 8105−8109.
173 U. K. Tambar, B. M. Stoltz, The direct acyl-alkylation of arynes, *J. Am. Chem. Soc*., 2005, **127**, 5340–5341.
174 J. M. Medina, J. L. MacKey, N. K. Garg, K. N. Houk, The role of aryne distortions, steric effects, and charges in regioselectivities of aryne reactions*, J. Am. Chem. Soc.*, 2014, **136**, 15798–15805.
175 K. M. Peese, D. Y. Gin, Efficient Synthetic Access to the Hetisine C20-Diterpenoid Alkaloids. A Concise Synthesis of Nominine via Oxidoisoquinolinium-1,3-Dipolar and Dienamine-Diels-Alder Cycloadditions, *J. Am. Chem. Soc*., 2006, **128**, 8734–8735.
176 M. M. Sigel, L. L. Wellham, W. Lichter, L. E. Dudeck, J. L. Gargus, and L. H. Lucas, "Anticellular and antitumor activity of extracts from tropical marine invertebrates." *Food-Drugs From the Sea: Proceedings*, 1969; ed. H. W. Youngken, Jr., Marine Technology Society, Washington DC, 1970, 281–294.
177 K. L. Rinehart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li and D. G. Martin, Ecteinascidins 729, 743, 745, 759A, 759B, and 770: potent antitumor agents from the Caribbean tunicate Ecteinascidia turbinate. *J. Org. Chem*., 1990, **55**, 4512– 4515; K. L. Rinehart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li and D. G. Martin, Ecteinascidins 729, 743, 745, 759A, 759B, and 770: potent antitumor agents from the Caribbean tunicate Ecteinascidia turbinata [Erratum to document cited in CA113(9):75189d]. *J. Org. Chem.,* 1991, **56**, 1676.
178 A. E. Wright, D. A. Forleo, P. G. Gunawardana, S. P. Gunasekera, F. E. Koehn and O. J. McConnell, Antitumor tetrahydroisoquinoline alkaloids from the colonial ascidian Ecteinascidia turbinate. *J. Org. Chem.*, 1990, **55**, 4508–4512.
179 J. D. Scott, R. D. Williams, Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev*. 2002, **102**, 1669–1730.
180 T. Fukuyama, R. A. Sachleben, Stereocontrolled Total Synthesis of (±)-saframycin B. *J. Am. Chem. Soc*., 1982, **104**, 4957–4958.
181 T. Fukuyama, L. Yang, K. L. Ajeck, R. A. Sachleben, Total Synthesis of (±)-saframycin A. *J. Am. Chem. Soc*., 1990, **112**, 3712–3713.
182 T. Fukuyama, S. D. Linton, M. M. Tun, A stereocontrolled total synthesis of (±)-renieramycin A. *Tetrahedron Lett*., 1990, **31**, 5989–5992.
183 A. Endo, T. Kann, T. Fukuyama, Synthetic Study on Ecteinascidin 743 Starting from d-Glucose. *Synlett*, 1999, **7**, 1103–1105.
184 T. Fukuyama, A. A. Laird, Synthetic approaches toward naphthyridinomycin. I. Stereoselective synthesis of a tetracyclic intermediate. *Tetrahedron Lett*., 1986, **27**, 6173–6176.
185 T. Fukuyama, L. Li, A. A. Laird, R. K. Frank, Stereocontrolled total synthesis of (±)-cyanocycline A. *J. Am. Chem. Soc*., 1987, **109**, 1587–1589.
186 T. Fukuyama, J. J. Nunes, Stereocontrolled total synthesis of (±)-quinocarcin. *J. Am. Chem. Soc*., 1988, **110**, 5196–5198.
187 A. Kubo, N. Saito, R. Yamauchi, S. Sakai, Synthesis of Saframycins. I Total Synthesis of (±)-Saframycin B and its Congeners. *Chem. Pharm. Bull.*, 1987, **35**, 2158–2161.

188 A. Kubo, N. Saito, H. Yamato, Y. Kawakami, Preparations and Reactions of (Z)-3-Arylidene-6-arylmethyl-2,5-piperazinediones Having Highly Oxygenated Benzene Rings. *Chem. Pharm. Bull*., 1987, **35**, 2525–2532.

189 A. Kubo, N. Saito, M. Nakamura, K. Ogata, S. Sakai, A Promising Cyclization of the 3-Arylidene-6-arylmethyl-2,5-piperazinedione to Construct Tricyclic Lactam as an Intermediate to Saframycin Synthesis. *Heterocycles*, 1987, **26**, 1765–1770.

190 A. Kubo, N. Saito, H. Yamato, R. Yamauchi, K. Hiruma, S. Inoue, Synthesis of Saframycins. II.: Preparations and Reactions of N-Methyl-2,5-piperazinediones. *Chem. Pharm. Bull.*, 1988, **36**, 2607–2614.

191 A. Kubo, N. Saito, H. Yamato, K. Masubuchi, M. Nakamura, Stereoselective Total Synthesis of (±)-saframycin B. *J. Org. Chem*., 1988, **53**, 4295–4310.

192 N. Saito, Y. Ohira, A. Kubo, Synthesis of Saframycins. IV.: Selenium Oxide Oxidation of 4-oxo-hexahydro-1,5-imino-3-benzazocin-7,10-dione; Promising Method to Construct Saframycins C and D from Saframycin B. *Chem. Pharm. Bull*., 1990, **38**, 821–823.

193 N. Saito, Y. Ohira, N. Wada, A. Kubo, A. Synthesis of saframycins. V. Selenium oxide oxidation of hexahydro-1,5-imino-3-benzazocin-7,10-dione; a useful method for constructing saframycins C and D from saframycin B. *Tetrahedron*, 1990, **46**, 7711–7728.

194 N. Saito, S. Harada, M. Nishida, I. Inouye, A. Kubo, Synthesis of Saframycins. X. Transformation of (–)-Saframycin A to (-)-Saframycin Mx Type Compound with the Structure Proposed for Saframycin E. *Chem. Pharm. Bull*., 1995, **43**, 777–782.

195 N. Saito, M. Nishida, A. Kubo, Synthesis of Saframycins. VI. The Useful Transformation of (–)-saframycin A to (–)-saframycin Mx Type Compound. *Chem. Pharm. Bull*., 1991, **39**, 1343–1345.

196 N. Saito, S. Harada, I. Inouye, K. Yamaguchi, A. Kubo, Synthesis of saframycins. XII. 1 total synthesis of (–)-N-acetylsaframycin Mx 2 and Its epi-(+)-enantiomer. *Tetrahedron*, 1995, **51**, 8231–8246.

197 N. Saito, M. Tanitsu, T. Betsui, R. Suzuki, A. Kubo, Synthesis of Novel Octahydro-1,5-imino-3-benzazocin-4,7,10-trione Derivatives Having a Methyl Group at the C-2 Position as ABC Ring Models of Saframycins. *Chem. Pharm. Bull*., 1997, **45**, 1120–1129.

198 N. Saito, R. Yamauchi, A. Kubo, Synthesis of Saframycins. VII. The Synthesis of Novel Renieramycin Congeners. *Heterocycles*, 1991, **32**, 1203–1214.

199 N Saito, M. Tachi, R. Seki, H. Kamayachi, A. Kubo, A Practical Synthesis of the ABC Ring Model of Ecteinascidins. *Chem. Pharm. Bull*., 2000, **48**, 1549–1557.

200 N. Saito, H. Kamayachi, M. Tachi, A. Kubo, An Improved Synthesis of the ABC Ring Model of Ecteinascidins. *Heterocycles*, 1999, **51**, 9–12.

201 N. Saito, K. Tashiro, Y. Maru, K. Yamaguchi, A. Kubo, Synthetic approaches toward ecteinascidins. Part 1. Preparation of an (E)-2-arylidene-3-benzyl-1,5-imino-3-benzazocin-4-one having a protected phenol in the E-ring. *J. Chem. Soc., Perkin Trans. 1*, 1997, 53–70.

202 A. G. Myers, D. W. Kung, A Concise, Stereocontrolled Synthesis of (−)-Saframycin A by the Directed Condensation of α-Amino Aldehyde Precursors. *J. Am. Chem. Soc*., 1999, **121**, 10828–10829.

203 A. G. Myers, D. W. Kung, One-Step Construction of the Pentacyclic Skeleton of Saframycin A from a "Trimer" of α-Amino Aldehydes. *Org. Lett*., 2000, **2**, 3019–3022.

204 A. G. Myers, A. T. Plowright, Synthesis and Evaluation of Bishydroquinone Derivatives of (−)-Saframycin A: Identification of a Versatile Molecular Template Imparting Potent Antiproliferative Activity. *J. Am. Chem. Soc*., 2001, **123**, 5114–5115.

205 E. J. Martinez, E. J. Corey, Enantioselective Synthesis of Saframycin A and Evaluation of Antitumor Activity Relative to Ecteinascidin/Saframycin Hybrids. *Org. Lett*., 1999, **1**, 75–78.

206 E. J. Corey, D. Y. Gin, R. S. Kania, Enantioselective Total Synthesis of Ecteinascidin 743. *J. Am. Chem. Soc*., 1996, **118**, 9202–9203.

207 E. J. Martinez, E. J. Corey, A New, More Efficient, and Effective Process for the Synthesis of a Key Pentacyclic Intermediate for Production of Ecteinascidin and Phthalascidin Antitumor Agents. *Org. Lett*., 2000, **2**, 993–996.

208 E. J. Corey, D. Y. Gin, A convergent enantioselective synthesis of the tetrahydroisoquinoline unit in the spiro ring of ecteinascidin 743. *Tetrahedron Lett*., 1996, **37**, 7163–7166.

209 E. J. Martinez, T. Owa, S. L. Schreiber, E. J. Corey, Phthalascidin, a synthetic antitumor agent with potency and mode of action comparable to ecteinascidin 743. *Proc. Natl. Acad. Sci*., 1999, 96, 3496–3501.

210 B. Herberich, M. Kinugawa, A. Vazquez, R. M. Williams, Sequential Staudinger/Pictet–Spengler cyclization strategy for the construction of tetrahydroisoquinolines of the bioxalomycin and ecteinascidin family of alkaloids. *Tetrahedron Lett*., 2001, **42**, 543–546.

211 M. E. Flanagan, R. M. Williams, Synthetic Studies on Quinocarcin: Total Synthesis of (±)-Quinocarcinamide via Dipole Cycloaddition of an Azomethine Ylide Generated by NBS Oxidation. *J. Org. Chem*., 1995, **60**, 6791–6797.

212 R. M. Williams, T. Glinka, R. Gallegos, P. P. Ehrlich, M. E. Flanagan, H. Coffman, G. Park, Synthesis, conformation, crystal structures and DNA cleavage abilities of tetracyclic analogs of quinocarcin. *Tetrahedron*, 1991, **47**, 2629–2642.

213 M. E. Flanagan, S. B. Rollins, R. M. Williams, Netropsin and spermine conjugates of a water-soluble quinocarcin analog: analysis of sequence-specific DNA interactions. *Chem. Biol*., 1995, **2**, 147–146.

214 B. Herberich, J. D. Scott, R. M. Williams, Synthesis of a netropsin conjugate of a water-soluble epi-quinocarcin analogue: the importance of stereochemistry at nitrogen. *Bioorg. Med. Chem*., 2000, **8**, 523–532.

215 J. D. Scott, R. M. Williams, Total Synthesis of (−)-Tetrazomine and Determination of Its Stereochemistry. *Angew. Chem*. 2001, **40**, 1463–1465.

216 J. D. Scott, R. M. Williams, Total Synthesis of (−)-Tetrazomine. Determination of the Stereochemistry of Tetrazomine and the Synthesis and Biological Activity of Tetrazomine Analogues. *J. Am. Chem. Soc*., 2002, **124**, 2951–2956.

217 J. D. Scott, R. M. Williams, Synthetic studies on tetrazomine: lipase PS resolution of racemic cis-β-hydroxypipecolic acid. *Tetrahedron Lett*., 2000, **41**, 8413–8416.

218 B. Zhou, S. Edmondson, J. Padron, S. J. Danishefsky, Synthetic explorations in the saframycin-ecteinascidin series: construction of major chiral subunits through catalytic asymmetric induction. *Tetrahedron Lett*., 2000, **41**, 2039–2042.

219 B. Zhou, J. Guo, S. J. Danishefsky, A novel face specific Mannich closure providing access to the saframycin-ecteinascidin series of piperazine based alkaloids. *Tetrahedron Lett*., 2000, **41**, 2043–2046.

220 S. J. Danishefsky, P. J. Harrison, R. R. Webb II, B. T. O'Neil, Total synthesis of quinocarcinol methyl ester. *J. Am. Chem. Soc*., 1985, **107**, 1421–1423.

221 T. T. Shawe, L. S. Liebeskind, Saframycin synthetic studies. *Tetrahedron*, 1991, **47**, 5643–5666.

222 C. Cuevas, M. Pérez, M. J. Martín, J. L. Chicharro, C. Fernádez-Rivas, M. Flores, A. Francesch, P. Gallego, M.

Zarzuelo, F. de la Calle, J. García, C. Polanco, I. Rodríguez, I. Manzanares, Synthesis of Ecteinascidin ET-743 and Phthalascidin Pt-650 from Cyanosafracin B. *Org. Lett*., 2000, **2**, 2545–2548.

223 D. A. Evans, S. A. Biller, The total synthesis of (±)-naphthyridinomycin. I. Preparation of a key tricyclic lactam intermediate. *Tetrahedron Lett*., 1985, **26**, 1907–1910.

224 D. A. Evans, S. A. Biller, The total synthesis of (±)-naphthyridinomycin. II. Construction of the pentacyclic carbon skeleton. *Tetrahedron Lett*., 1985, **26**, 1911–1914.

225 M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, Asymmetric Synthesis of Isoquinoline Alkaloids: 2004−2015. *Chem. Rev*., 2016, **116**, 12369−12465.

226 D. J. Newman, G. M. Cragg, Drugs and Drug Candidates from Marine Sources: An Assessment of the Current "State of Play." *Planta Med*., 2016, **82**, 775–789.

227 A. Fontana, P. Cavaliere, S. Wahidulla, C. G. Naik, G. Cimino, A New Antitumor Isoquinoline Alkaloid from the Marine Nudibranch Jorunna funebris. *Tetrahedron*, 2000, **56**, 7305–7308.

228 J. W. Lane, Y. Chen, R. M. Williams, Asymmetric Total Syntheses of (–)-Jorumycin, (–)-Renieramycin G, 3-epi-Jorumycin, and 3-epi-Renieramycin G. *J. Am. Chem. Soc*., 2005, **127**, 12684–12690.

229 Y.-C. Wu, J. Zhu, Asymmetric Total Syntheses of (–)-Renieramycin M and G and (–)-Jorumycin Using Aziridine as a Lynchpin. *Org Lett*., 2009, **11**, 5558–5561.

230 W. Liu, X. Liao, W. Dong, Z. Yan, N. Wang, Z. Liu, Total synthesis and cytotoxicity of (–)-jorumycin and its analogues. *Tetrahedron*, 2012, **68**, 2759–2764.

231 R. Chen, H. Liu, X. Chen, Asymmetric Total Synthesis of (−)-Jorunnamycins A and C and (−)-Jorumycin from L-Tyrosine. *J. Nat. Prod*., 2013, **76**, 1789−1795.

232 Ong, C. W.; Lee, H. C. A Rapid Synthesis of 2,3,11,11a-Tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-diones Through an Amido Iminium Ion Cyclization. *Aust. J. Chem*., 1990, **43**, 773–775.

233 E. R. Welin, A. Ngamnithiporn, M. Klatte, G. Lapointe, G. M. Pototschnig, M. S. J. McDermott, D. Conklin, C. D. Gilmore, P. M. Tadross, C. K. Haley, K. Negoro, E. Glibstrup, C. U. Grünanger, K. M. Allan, S. C. Virgil, D. J. Slamon, B. M. Stoltz, Concise total syntheses of (–)-jorunnamycin A and (–)-jorumycin enabled by asymmetric catalysis. *Science*, 2019, **363**, 270–275.

234 K. M. Allan, B. D. Hong, B. M. Stoltz, Expedient synthesis of 3-hydroxyisoquinolines and 2-hydroxy-1,4-naphthoquinones via one-pot aryne acyl-alkylation/condensation. *Org. Biomol. Chem*., 2009, **7**, 4960–4964.

235 L.-C. Campeau, D. J. Schipper, K. Fagnou, Site-Selective sp2 and Benzylic sp3 Palladium-Catalyzed Direct Arylation. *J. Am. Chem. Soc*., 2008, **130**, 3266–3267.

236 Z. Jin, G. Yao, Amaryllidaceae and Sceletium alkaloids. *Nat. Prod. Rep*. 2019, **36**, 1462-1488.

237 L. J. Scott, K. L. Goa, Galantamine: a review of its use in Alzheimer's disease. *Drugs*., 2000, **60**, 1095–1122.

238 P. M. Dewick, in *Medicinal Natural Products: A Biosynthetic Approach*, John Wiley & Sons Ltd, West Sussex, 2nd edn, 2002, ch. 6, pp. 291–404.

239 A. G. Schultz, M. A. Holoboski, M. S. Smyth, The first asymmetric synthesis of a lycorine alkaloid. Total synthesis of (+)-1-deoxylycorine. *J. Am. Chem. Soc.*, 1993, **115**, 7904–7905.

240 A. G. Schultz, M. A. Holoboski, M. S. Smyth, The First Asymmetric Total Syntheses of (+)-Lycorine and (+)-1-Deoxylycorine. *J. Am. Chem. Soc*., 1996, **118**, 6210–6219.

241 T. Kametani, K. Shishido, E. Hayashi, C. Seino, T. Kohno, S. Shibuya, K. Fukumoto, Synthesis of heterocyclic compounds CCCXCVI. Alternative total synthesis of (±)-galanthamine. *J. Org. Chem*., 1971, **36**, 1295–1297.

242 T. Kametani, K. Yarnaki, T. Terui, S. Shibuya, K. Fukumoto, Studies on the syntheses of heterocyclic compounds. Part CDLXVI. Synthesis of narwedine-type enones by photochemical cyclisation. *J. Chem. Soc. Perkin Trans. 1*, 1972, 1513–1516.

243 T. Kametani, K. Yamaki, T. Terui, Studies on the syntheses of heterocyclic compounds. Part DVII. A synthesis of (±)-N-norgalanthamine. *J. Heterocyclic Chem*., 1973, **10**, 35–37.

244 K. Shimizu, K. Tomioka, S.-I. Yamada, K. Koga, A Biogenetic-type Asymmetric Synthesis of Optically Active Amaryllidaceae Alkaloids: (+)- and (-)-Galanthamine from L-Tyrosine. *Heterocycles*, 1977, **8**, 277–282.

245 K. Shimizu, K. Tomioka, S.-I. Yamada, K. Koga, Stereochemical Studies. LIV. A Biogenetic-type Asymmetric Synthesis of optically Active Galanthamine from L-Tyrosine. *Chem. Pharm. Bull*., 1978, **26**, 3765–3771.

246 J. Szewczyk, A. H. Lewin, F. I. Carroll, An improved synthesis of galanthamine. *J. Heterocyclic Chem*., 1988, **25**, 1809–1811.

247 J. Szewczyk, J. W. Wilson, A. H. Lewin, F. I. Carroll, Facile synthesis of (±)-, (+)-, and (–)-galanthamine. *J. Heterocyclic Chem*., 1995, **32**, 195–199.

248 R. A. Holton, M. P. Sibi, W. S. Murphy, Palladium-mediated biomimetic synthesis of narwedine. *J. Am. Chem. Soc*., 1988, **110**, 314–366.

249 W. P. Malachowski, T. Paul, S. Phounsavath, The Enantioselective Synthesis of (−)-Lycoramine with the Birch−Cope Sequence. *J. Org. Chem.*, 2007, **72**, 6792–6796.

250 L. Czollner, M. Treu, J. Froehlich, B. Kueenburg, U. Jordis, Synthesis of galanthamine. *ARKIVOC*, 2001, **2**, 191–200.

251 A. H. Lewin, J. Szewczyk, J. W. Wilson, F. I. Carroll, Galanthamine analogs: 6H-benzofuro[3a,3,2,-e,f][1]benzazepine and 6H-benzofuro[3a,3,2-e,f][3]benzazepine. *Tetrahedron,* 2005, **61**, 7144–7152.

252 M. Node, S. Kodama, Y. Hamashima, T. Baba, N. Hamamichi, An Efficient Synthesis of (±)-Narwedine and (±)-Galanthamine by an Improved Phenolic Oxidative Coupling. K. Nishide, *Angew Chem., Int. Ed*. 2001, **40**, 3060–3062.

253 S. Kodama, Y. Hamashima, K. Nishide, M. Node, Total Synthesis of (–)-Galanthamine by Remote Asymmetric Induction. *Angew. Chem., Int. Ed*. 2004, **43**, 2659–2661.

254 I. R. Baxendale, S. V. Ley, C. Piutti, Total Synthesis of the Amaryllidaceae Alkaloid (+)-Plicamine and Its Unnatural Enantiomer by Using Solid-Supported Reagents and Scavengers in a Multistep Sequence of Reactions. *Angew. Chem., Int. Ed*. 2002, **41**, 2194–2197.

255 I. R. Baxendale, S. V. Ley, M. Nessi, C. Piutti, Total synthesis of the amaryllidaceae alkaloid (+)-plicamine using solid-supported reagents. *Tetrahedron*, 2002, **58**, 6285–6304.

256 I. R. Baxendale and S. V. Ley, Synthesis of the Alkaloid Natural Products (+)-Plicane and (−)-Obliquine, Using Polymer-Supported Reagents and Scavengers. *Ind. Eng. Chem. Res*., 2005, **44**, 8588–8592.

257 T. Kametani, T. Kohno, S. Shibuya, K. Fukumoto, Studies on the syntheses of heterocyclic compounds-CDXXXVI: Photolytic synthesis of the crinine ring system-formal total synthesis of (±)-maritidine. *Tetrahedron*, 1971, **27**, 5441–5444.

258 E. Kotani, N. Takeuchi, S. Tobinaga, Total synthesis of the alkloids (±)-oxocrinine and (±)-oxomaritidine via anodic oxidation. *J. Chem. Soc. Chem. Commun*., 1973, 550–551.

259 M. A. Schwartz, R. A. Holton, Intramolecular oxidative phenol coupling. II. Biogenetic-type synthesis of (±)-maritidine. *J. Am. Chem. Soc*., 1970, **92**, 1090–1092.

260 M. A. Schwartz, B. F. Rose, B. Vishnuvajjala, Intramolecular oxidative phenol coupling. III. Two-electron oxidation with

thallium(III) trifluoroacetate. *J. Am. Chem. Soc*., 1973, **95**, 612–613.

261 M. A. Schwartz, B. F. Rose, R. A. Holton, S. W. Scott, B. Vishnuvajjala, Intramolecular oxidative coupling of diphenolic, monophenolic, and nonphenolic substrates. *J. Am. Chem. Soc*., 1977, **99**, 2571–2578.

262 K. Tomioka, K. Koga, S.-I. Yamada, Stereochemical Studies. XLIX. A Biogenetic-type Total Synthesis of Natural (+)-Maritidine from L-Tyrosine using highly Specific Asymmetric Cyclization. *Chem. Pharm. Bull*., 1977, **25**, 2681–2688.

263 S.-I. Yamada, K. Tomioka, K. Koga, A biogenetic-type asymmetric synthesis of natural (+)-maritidine from L-tyrosine. *Tetrahedron Lett*., 1976, **17**, 57–60.

264 E. Kotani, N. Takeuchi, S. Tobinaga, Biogenetic-type synthesis of (±)-oxomaritidine by the catalytic oxidation with [Fe(dmf)3Cl2][FeCl4]. *Tetrahedron Lett*., 1973, 2735–2736.

265 S. M. Kupchan, O. P. Dhingra, C.-K. Kim, Efficient intramolecular monophenol oxidative coupling. *J. Org. Chem*., 1978, **43**, 4076–4081.

266 J. D. White, W. K. M. Chong, K. Thirring, Phenolic oxidative coupling with hypervalent iodine. A synthesis of 6a-epipretazettine. *J. Org. Chem*., 1983, **48**, 2300–2302.

267 Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk, J. Eichhorn, An Oxidative Intramolecular Phenolic Coupling Reaction for the Synthesis of Amaryllidaceae Alkaloids Using a Hypervalent Iodine(III) Reagent. *J. Org. Chem*., 1991, **61**, 5857–5864.

268 S. Kodama, H. Takita, T. Kajimoto, K. Nishide, M. Node, Synthesis of Amaryllidaceae alkaloids, siculine, oxocrinine, epicrinine, and buflavine. *Tetrahedron*, 2004, **60**, 4901–4907.

269 S. Elango, T.-H. Yan, A Short Synthesis of (+)-Lycoricidine. *Tetrahedron*, 2002, **58**, 7335–7338.

270 S. Elango, T.-H. Yan, A Short Synthesis of (+)-Narciclasine via a Strategy Derived from Stereocontrolled Epoxide Formation and SnCl4-Catalyzed Arene-Epoxide Coupling. *J. Org. Chem*., 2002, **67**, 6954–6959.

271 A. N. Phung, M. T. Zannetti, G. Whited, W.-D. Fessner, Stereospecific Biocatalytic Synthesis of Pancratistatin Analogues. *Angew. Chem. Int. Ed*., 2003, **42**, 4821–4824.

272 T. Hudlicky, H. F. Olivo, A short synthesis of (+)-lycoricidine. *J. Am. Chem. Soc*., 1992, **114**, 9694–9696.

273 X. Tian, R. Maruya, K. Konigsberger, T. Hudlicky, Asymmetric Total Synthesis of (+)-7-Deoxypancratistatin. *Synlett*, 1995, 1125–1126.

274 X. Tian, T. Hudlicky, K. Konigsberger, First Total Synthesis of (+)-Pancratistatin: An Unusual Set of Problems. *J. Am. Chem. Soc.*, 1995, **117**, 3643–3644.

275 T. Hudlicky, X. Tian, K. Konigsberger, R. Maurya, J. Rouden, B. Fan, Toluene Dioxygenase-Mediated cis-Dihydroxylation of Aromatics in Enantioselective Synthesis. Asymmetric Total Syntheses of Pancratistatin and 7-Deoxypancratistatin, Promising Antitumor Agents. *J. Am. Chem. Soc*., 1996, **118**, 10752–10765.

276 T. Hudlicky, U. Rinner, D. Gonzalez, H. Akgun, S. Schilling, P. Siengalewicz, T. A. Martinot, G. R. Pettit, Total Synthesis and Biological Evaluation of Amaryllidaceae Alkaloids: Narciclasine, ent-7-Deoxypancratistatin, Regioisomer of 7-Deoxypancratistatin, 10b-epi-Deoxypancratistatin, and Truncated Derivatives. *J. Org. Chem.*, 2002, **67**, 8726–8743.

277 H. Akgün, T. Hudlicky, Total syntheses of ent-conduramine A and ent-7-deoxypancratistatin. *Tetrahedron Lett*., 1999, **40**, 3081–3084.

278 U. Rinner, P. Siengalwicz, T. Hudlicky, Total Synthesis of epi-7-Deoxypancratistatin via Aza-Payne Rearrangement and Intramolecular Cyclization. *Org. Lett*., 2001, **4**, 115–117.

279 U. Rinner, H. Hillebrenner, D. R. Adams, T. Hudlicky, G. R. Pettit, Synthesis and biological activity of some structural modifications of pancratistatin. *Bioorg. Med. Chem. Lett*., 2004, **14**, 2911–2915.

280 U. Rinner, T. Hudlicky, H. Gordon, G. R. Pettit, A β-Carboline-1-one Mimic of the Anticancer Amaryllidaceae Constituent Pancratistatin: Synthesis and Biological Evaluation. *Angew. Chem. Int. Ed*., 2004, **43**, 5342–5346.

281 J. García-Fortanet, F. Kessler, S. L. Buchwald, Palladium-catalyzed asymmetric dearomatization of naphthalene derivatives, *J. Am. Chem. Soc*., 2009, **131**, 6676–6677.

282 S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, Palladium(0)-catalyzed arylative dearomatization of phenols, *J. Am. Chem. Soc*., 2011, **133**, 9282–9285.

283 P. J. Milner, T. J. Maimone, M. Su, J. Chen, P. Müller, S. L. Buchwald, Investigating the dearomative rearrangement of biaryl phosphine-ligated Pd(II) complexes, *J. Am. Chem. Soc.*, 2012, **134**, 19922–19934.

284 R. Q. Xu, Q. Gu, W. T. Wu, Z. A. Zhao, S. L. You, Construction of erythrinane skeleton via pd(0)-catalyzed intramolecular dearomatization of para -aminophenols, *J. Am. Chem. Soc.*, 2014, **136**, 15469–15472.

285 K. Du, P. Guo, Y. Chen, Z. Cao, Z. Wang, W. Tang, Enantioselective Palladium-Catalyzed Dearomative Cyclization for the Efficient Synthesis of Terpenes and Steroids. *Angew. Chem. Int. Ed*., 2015, **54**, 3033 –3037.

286 K. Du, H. Yang, P. Guo, L. Feng, G. Xu, Q. Zhou, B. Lung, W. Chung, W. Tang, Efficient syntheses of (–)-crinine and (–)-aspidospermidine, and the formal synthesis of (–)-minfiensine by enantioselective intramolecular dearomative cyclization, *Chem. Sci*., 2017, **8**, 6247–6256.

287 G. Zhao, G. Xu, C. Qian, W. Tang. Efficient Enantioselective Syntheses of (+)-Dalesconol A and B. *J. Am. Chem. Soc*., 2017, **139**, 3360–3363.

288 N. Ünver, T. Gözler, N. Walch, B. Gözler, M. Hesse, Two novel dinitrogenous alkaloids from Galanthus plicatus subsp. byzantinus (Amaryllidaceae), *Phytochemistry*, 1999, **50**, 1255–1261.

289 M. V. Mijangos, L. D. Miranda, Multicomponent access to indolo[3,3a-c]-isoquinolin-3,6-diones: formal synthesis of (±)-plicamine, *Org. Biomol. Chem*., 2016, **14**, 3677.

290 Y. Shi, H. He, S. Gao, Recent advances in the total synthesis of gracilamine, *Chem. Commun*., 2018, **54**, 12905–12913.

291 S. Tian, W. Zi, D. Ma, Potentially Biomimetic Total Synthesis and Relative Stereochemical Assignment of (±)-Gracilamine, *Angew. Chem. Int. Ed*., 2012, **51**, 10141–10144.

292 Y. Shi, B. Yang, S. Cai, S. Gao, Total Synthesis of Gracilamine, *Angew. Chem. Int. Ed*., 2014, **53**, 9539–9543.

293 P. Gan, M. W. Smith, N. R. Braffman, S. A. Snyder, Pyrone Diels-Alder Routes to Indolines and Hydroindolines: Syntheses of Gracilamine, Mesembrine, and Δ7 -Mesembrenone, *Angew. Chem. Int. Ed*., 2016, **55**, 3625–3630.

294 S. Bose, J. Yang, Z.-X. Yu, Formal Synthesis of Gracilamine Using Rh(I)-Catalyzed [3 + 2 + 1] Cycloaddition of 1-Yne−Vinylcyclopropanes and CO, *J. Org. Chem*., 2016, **81**, 6757–6765.

295 A. Chandra, P. Verma, A. Negel, G. Pandey, Asymmetric Total Synthesis of (–)-Gracilamine Using a Bioinspired Approach, *Eur. J. Org. Chem*., 2017, 6788–6792.

296 N. Gao, M. G. Banwell, A. C. Willis, Biomimetic Total Synthesis of the Pentacyclic Amaryllidaceae Alkaloid Derivative Gracilamine, *Org. Lett*., 2017, **19**, 162–165.

297 X. Zuo, S. Guo, R. Yang, J. Xie, Q. Zhou, Asymmetric Total Synthesis of Gracilamine and Determination of Its Absolute Configuration, *Org. Lett*., 2017, **19**, 5240–5243.

298 M. Odagi, Y. Yamamoto, K. Nagasawa, Total Synthesis of (+)-Gracilamine Based on an Oxidative Phenolic Coupling Reaction and Determination of Its Absolute Configuration, *Angew. Chem. Int. Ed*., 2018, **57**, 2229–2232.

299 M. Kato, S. Hirao, K. Nakano, M. Sato, M. Yamanaka, Y. Sohtome, K. Nagasawa, Entropy-Driven 1,2-Type Friedel–Crafts Reaction of Phenols with N-tert-Butoxycarbonyl Aldimines, *Chem. Eur. J.*, 2015, **21**, 18606–18612.
300 A. Kornienko, A. Evidente, Chemistry, Biology, and Medicinal Potential of Narciclasine and its Congeners, *Chem. Rev.*, 2008, **108**, 1982–2014.
301 L. Ingrassia, F. Lefranc, V. Mathieu, F. Darro, R. Kiss, Amaryllidaceae Isocarbostyril Alkaloids and Their Derivatives as Promising Antitumor Agents, *Transl. Oncol.*, 2008, **1**, 1–13.
302 W. A. L. Van Otterlo, I. R. Green, A Review on Recent Syntheses of Amaryllidaceae Alkaloids and Isocarbostyrils (Time period mid-2016 to 2017), *Nat. Prod. Commun.*, 2018, **13**, 255–277.
303 L. W. Hernandez, J. Pospech, U. Klöckner, T. W. Bingham, D. Sarlah, Synthesis of (+)-Pancratistatins via Catalytic Desymmetrization of Benzene, *J. Am. Chem. Soc.*, 2017, **139**, 15656–15659.
304 T. W. Bingham, L. W. Hernandez, D. G. Olson, R. L. Svec, P. J. Hergenrother, D. Sarlah, Enantioselective Synthesis of Isocarbostyril Alkaloids and Analogs Using Catalytic Dearomative Functionalization of Benzene, *J. Am. Chem. Soc.*, 2019, **141**, 657−670.
305 N. Tezuka, K. Shimojo, K. Hirano, S. Komagawa, K. Yoshida, C. Wang, K. Miyamoto, T. Saito, R. Takita, M. Uchiyama, Direct Hydroxylation and Amination of Arenes via Deprotonative Cupration, *J. Am. Chem. Soc.*, 2016, **138**, 9166–9171.
306 A. Onoyovwe, J. M. Hagel, X. Chen, M. F. Khan, D. C. Schriemer, P. J. Facchini, Morphine Biosynthesis in Opium Poppy Involves Two Cell Types: Sieve Elements and Laticifers, *Plant Cell*, 2013, **25**, 4110–4122.
307 M. Gates, G. Tschudi, The synthesis of morphine, *J. Am. Chem. Soc.*, 1952, **74**, 1109–1110.
308 M. Gates, G. Tschudi, The synthesis of morphine, *J. Am. Chem. Soc.*, 1956, **78**, 1380–1393.
309 K. C. Rice, Synthetic opium alkaloids and derivatives, A short total synthesis of (±)-dihydrothebainone, (±)-dihydrocodeinone, and (±)-nordihydrocodeinone as an approach to a practical synthesis of morphine, codeine, and congeners, *J. Org. Chem*. 1980, **45**, 3135–3137.
310 A. Lipp, D. Ferenc, C. Gütz, M. Geffe, N. Vierengel, D. Schollmeyer, H. J. Schäfer, S. R. Waldvogel, T. Opatz A Regio- and Diastereoselective Anodic Aryl–Aryl Coupling in the Biomimetic Total Synthesis of (–)-Thebaine, *Angew. Chem. Int. Ed*. 2018, **57**, 11055–11059.
311 J. D. White, G. Caravatti, T. B. Kline, E. Edstrom, K. C. Rice, A. Brossi, Biomimetic total synthesis of (−)-codeine, *Tetrahedron*, 1983, **39**, 2393–2397.
312 C. Y. Hong, N. Kado, L. E. Overman, Asymmetric synthesis of either enantiomer of opium alkaloids and morphinans, Total synthesis of (-)- and (+)-dihydrocodeinone and (-)- and (+)-morphine, *J. Am. Chem. Soc.*, 1993, **115**, 11028–11029.
313 J. Brousseau, A. Xolin, L. Barriault, A Nine-Step Formal Synthesis of (±)-Morphine, *Org. Lett.*, 2019, **21**, 1347–1349.
314 S. Chu, N. Münster, T. Balan, M. D. Smith, A Cascade Strategy Enables a Total Synthesis of (±)-Morphine, *Angew. Chem. Int. Ed.*, 2016, **55**, 14306–14309.
315 H. Umihara, S. Yokoshima, M. Inoue, T. Fukuyama, Total Synthesis of (–)-Morphine, *Chem. Eur. J.*, 2017, **23**, 6993–6995.
316 B. M. Trost, W. Tang, Enantioselective Synthesis of (–)-Codeine and (–)-Morphine, *J. Am. Chem. Soc.*, 2002, **124**, 14542–14543.
317 M. Tissot, R. J. Phipps, C. Lucas, R. M. Leon, R. D. M. Pace, T. Ngouansavanh, M. J. Gaunt, Gram-Scale Enantioselective Formal Synthesis of Morphine through an Ortho–Para Oxidative Phenolic Coupling Strategy., *Angew. Chem. Int. Ed.*, 2014, **53**, 13498–13501.
318 K. H. Park, D. Y.-K. Chen, A Desymmetrization-Based Approach to Morphinans: Application in the Total Synthesis of Oxycodone, *Chem. Commun.*, 2018, **54**, 13018–13021.
319 J. W. Reed, T. Hudlicky, The Quest for a Practical Synthesis of Morphine Alkaloids and Their Derivatives by Chemoenzymatic Methods, *Acc. Chem. Res.*, 2015, **48**, 674–687.
320 M. Makarova, M. A. A. Endoma-Arias, H. E. Dela Paz, R. Simionescu, T. Hudlicky, Chemoenzymatic Total Synthesis of Ent-Oxycodone: Second-, Third-, and Fourth-Generation Strategies, *J. Am. Chem. Soc.*, 2019, **141**, 10883–10904.
321 V. Varghese, T. Hudlicky, Short Chemoenzymatic Total Synthesis of Ent-Hydromorphone: An Oxidative Dearomatization/Intramolecular [4+2] Cycloaddition/Amination Sequence, *Angew. Chem. Int. Ed.*, 2014, **53**, 4355–4358.
322 S. M. King, S. B. Herzon, Chapter Three – The Hasubanan and Acutumine Alkaloids, *The Alkaloids: Chemistry and Biology*, 2014, **73**, 161–222.
323 S. B. Herzon, N. A. Calandra, S. M. King, Efficient Entry to the Hasubanan Alkaloids: First Enantioselective Total Syntheses of (−)-Hasubanonine, (−)-Runanine, (−)-Delavayine, and (+)-Periglaucine B, *Angew. Chem. Int. Ed.*, 2011, **50**, 8863–8866.
324 K. V. Chuang, R. Navarro, S. E. Reisman, Short, Enantioselective Total Syntheses of (−)-8-Demethoxyrunanine and (−)-Cepharatines A, C, and D, *Angew. Chem. Int. Ed.*, 2011, **50**, 9447–9451.
325 A. Ramirez, S. Garcia-Rubio, Current Progress in the Chemistry and Pharmacology of Akuammiline Alkaloids, *Curr. Med. Chem.*, 2003, **10**, 1891–1915.
326 T. S. Kam, Alkaloids: *Chem. Biol. Perspect.*, 1999, **14**, 285.
327 H. Arai, Y. Hirasawa, A. Rahman, I. Kusumawati, N. C. Zaini, S. Sato, C. Aoyama, J. Takeo, H. Morita, Alstiphyllanines E–H, picraline and ajmaline-type alkaloids from Alstonia macrophylla inhibiting sodium glucose cotransporter, *Bioorg. Med. Chem.*, 2010, **18**, 2152–2158.
328 H. L. Pearce, in *The Alkaloids*, Vol. 37 (Eds.: A. Brossi, M. Suffness), Academic Press, San Diego, 1990, p. 145.
329 R. Eckermann, T. Gaich, The Akuammiline Alkaloids; Origin and Synthesis, *Synthesis*, 2013, **45**, 2813–2823.
330 J. M. Smith, J. Moreno, B. W. Boal, N. K. Garg, Cascade Reactions: A Driving Force in Akuammiline Alkaloid Total Synthesis, *Angew. Chem. Int. Ed.*, 2015, **54**, 400–412.
331 J. A. Goodson, Echitamine, *J. Chem. Soc.*, 1932, 2759−2768.
332 G. F. Smith, Echitamine: hypothetical biogenetic scheme, *Chem. Ind.*, 1961, **29**, 1120.
333 E. Wenkert, B. J. Wickberg, General methods of synthesis of indole alkaloids. IV. A synthesis of dl-eburnamonine, *J. Am. Chem. Soc.*, 1965, **87**, 1580−1589.
334 P. Leewanich, M. Tohda, K. Matsumoto, S. Subhadhirasakul, H. Takayama, H. Watanabe, Behavioral Studies on Alkaloids Extracted from the Leaves of Hunteria zeylanica, *Biol. Pharm. Bull.*, 1996, **19**, 394–399.
335 V. Saraswathi, S. Subramanian, N. Ramamoorthy, V. Mathuram, S. Govindasamy, In vitro cytotoxicity of echitamine chloride and adriamycin on Ehrlich ascites carcinoma cell cultures, *Med. Sci. Res.*, 1997, **25**, 167–170.
336 A. Maier, C. Maul, M Zerlin, S. Grabley, R. Thiericke, A Novel Screening Approach for the Discovery of Biologically Active Secondary Metabolites, *J. Antibiot.*, 1999, **52**, 952–959.
337 M. S. Baliga, G. C. Jagetia, J. N. Ulloor, M. P. Baliga, P. Venkatesh, R. Reddy, K. V. N. M. Rao, B. S. Baliga, S. Devi, S. K. Raju, V. Veeresh, T. K. Reddy, K. L. Bairy, The evaluation of the acute toxicity and long term safety of hydroalcoholic extract of Sapthaparna (Alstonia scholaris) in mice and rats, *Toxicol. Lett.*, 2004, **151**, 317–326.

338 P. Kamarajan, N. Sekar, V. Mathuram, S. Govindasamy, Antitumor effect of echitamine chloride on methylcholonthrene induced fibrosarcoma in rats, *Biochem. Int*., 1991, **25**, 491–498.

339 M. Duwiejua, E. Woode, D. D. Obiri, Pseudo-akuammigine, an alkaloid from Picralima nitida seeds, has anti-inflammatory and analgesic actions in rats, *J. Ethnopharmacol*., 2002, **81**, 73–79.

340 G. Subramaniam, O. Hiraku, M. Hayashi, T. Koyano, K. Komiyama, T.-S. Kam, Biologically Active Aspidofractinine, Rhazinilam, Akuammiline, and Vincorine Alkaloids from Kopsia, *J. Nat. Prod*., 2007, **70**, 1783–1789.

341 H. Arai, Y. Hirasawa, A. Rahman, I. Kusumawati, N. C. Zaini, S. Sato, C. Aoyama, J. Takeo, H. Morita, Alstiphyllanines E–H, picraline and ajmaline-type alkaloids from Alstonia macrophylla inhibiting sodium glucose cotransporter, *Bioorg. Med. Chem*., 2010, **18**, 2152−2158.

342 W. Meng, B. A. Ellsworth, A. A. Nirschl, P. J. McCann, M. Patel, R. Girotra, G. Wu, P. M. Sher, E. P. Morrison, S. A. Biller, R. Zahler, P. P. Deshpande, A. Pullockaran, D. L.Hagan, N. Morgan, J. R. Taylor, M. T. Obermeier, W. G. Humphreys, A. Khanna, L Discenza, J. G. Robertson, A. Wang, S. Han, J. R. Wetterau, E. B. Janovitz, O. P. Flint, J. M. Whaley, W. N. Washburn, Discovery of Dapagliflozin: A Potent, Selective Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes, *J. Med. Chem*., 2008, **51**, 1145−1149.

343 G. Adams, A. B. Smith III, The Chemistry of the Akuammiline Alkaloids. in *The Alkaloids*; Knolker, H.-J., Ed.; Elsevier: New York, 2016; Vol. 76, pp 171−257.

344 M. Zhang, X. Huang, L. Shen, Y. Qin, Total Synthesis of the Akuammiline Alkaloid (±)-Vincorine, *J. Am. Chem. Soc*., 2009, **131**, 6013–6020.

345 D. W. C. MacMillan, Nine-Step Enantioselective Total Synthesis of (−)-Vincorine, *J. Am. Chem. Soc*., 2013, **135**, 6442–6445.

346 S.-Z. Jiang, X.-Y. Zeng, X. Liang, T. Lei, K. Wei, Y.-R. Yang, Iridium-Catalyzed Enantioselective Indole Cyclization: Application to the Total Synthesis and Absolute Stereochemical Assignment of (–)-Aspidophylline A, *Angew. Chem. Int. Ed*., 2016, **55**, 4044–4048.

347 C. Zheng, S.-L. You, Catalytic asymmetric dearomatization (CADA) reaction-enabled total synthesis of indole-based natural products, *Nat. Prod. Rep*., 2019, **36**, 1589–1605.

348 G. L. Adams, P. J. Carroll, A. B. Smith, Total Synthesis of (+)-Scholarisine A, *J. Am. Chem. Soc*., 2012, **134**, 4037–4040.

349 Y. Li, S. Zhu, J. Li, A. Li, Asymmetric Total Syntheses of Aspidodasycarpine, Lonicerine, and the Proposed Structure of Lanciferine, *J. Am. Chem. Soc*., 2016, **138**, 3982–3985.

350 X. Zhang, B. N. Kakde, R. Guo, S. Yadav, Y. Gu, A. Li, Total Syntheses of Echitamine, Akuammiline, Rhazicine, and Pseudoakuammigine, *Angew. Chem. Int. Ed*., 2019, **58**, 6053–6058.

351 S. P. Wong, C. Y. Gan, K. H. Lim, K. N. Ting, Y. Y. Low, T. S. Kam, Arboridinine, a Pentacyclic Indole Alkaloid with a New Cage Carbon-Nitrogen Skeleton Derived from a Pericine Precursor, *Org. Lett*., 2015, **17**, 3628−3631.

352 Z. Zhang, S. Xie, B. Cheng, H. Zhai, Y. Li, Enantioselective Total Synthesis of (+)-Arboridinine, *J. Am. Chem. Soc*., 2019, **141**, 7147–7154.

353 W. Zi, W. Xie, D. Ma, Total Synthesis of Akuammiline Alkaloid (−)-Vincorine via Intramolecular Oxidative Coupling, *J. Am. Chem. Soc*., 2012, **134**, 9126–9129.

354 M. Teng, W. Zi, D. Ma, Total Synthesis of the Monoterpenoid Indole Alkaloid (±)-Aspidophylline A, *Angew. Chem. Int. Ed*., 2014, **53**, 1814–1817.

355 W. Xu, W. Wang, X. Wang, Gold-Catalyzed Cyclization Leads to a Bridged Tetracyclic Indolenine that Represses β-Lactam Resistance, *Angew. Chem. Int. Ed*., 2015, **54**, 9546–9549.

356 M. W. Smith, Z. Zhou, A. X. Gao, T. Shimbayashi, S. A. Snyder, A 7-Step Formal Asymmetric Total Synthesis of Strictamine via an Asymmetric Propargylation and Metal-Mediated Cyclization, *Org. Lett*., 2017, **19**, 1004–1007.

357 P. Gan, J. Pitzen, P. Qu, S. A. Snyder, Total Synthesis of the Caged Indole Alkaloid Arboridinine Enabled by aza-Prins and Metal-Mediated Cyclizations, *J. Am. Chem. Soc*., 2018, **140**, 919–925.

358 Z. Zhou, A. X. Gao, S. A. Snyder, Total Synthesis of (+)-Arborisidine, *J. Am. Chem. Soc*., 2019, **141**, 7715–7720.

359 L. Zu, B. W. Boal, N. K. Garg, Total Synthesis of (±)-Aspidophylline A, *J. Am. Chem. Soc*., 2011, **133**, 8877–8879.

360 B. J. Simmons, M. Hoffmann, P. A. Champagne, E. Picazo, K. Yamakawa, L. A. Morrill, K. N. Houk, N. K. Garg, Understanding and Interrupting the Fischer Azaindolization Reaction, *J. Am. Chem. Soc*., 2017, **139**, 14833–14836.

361 J. M. Smith, J. Moreno, B. W. Boal, N. K. Garg, Total Synthesis of the Akuammiline Alkaloid Picrinine, *J. Am. Chem. Soc*., 2014, **136**, 4504–4507.

362 J. M. Smith, J. Moreno, B. W. Boal, N. K. Garg, Fischer Indolizations as a Strategic Platform for the Total Synthesis of Picrinine, *J. Org. Chem*., 2015, **80**, 8954–8967.

363 J. Moreno, E. Picazo, L. A. Morrill, J. M. Smith, N. K. Garg, Enantioselective Total Syntheses of Akuammiline Alkaloids (+)-Strictamine, (−)-2(S)-Cathafoline, and (−)-Aspidophylline A, *J. Am. Chem. Soc*., 2016, **138**, 1162–1165.

364 E. Picazo, L. A. Morrill, R. B. Susick, J. Moreno, J. M. Smith, N. K. Garg, Enantioselective Total Syntheses of Methanoquinolizidine-Containing Akuammiline Alkaloids and Related Studies, *J. Am. Chem. Soc*., 2018, **140**, 6483–6492.

365 W. Ren, Q. Wang, J. Zhu, Total Synthesis of (±)-Strictamine, *Angew. Chem. Int. Ed*., 2016, **55**, 3500–3503.

366 J. M. Saya, E. Ruijter, R. V. A. Orru, Total Synthesis of Aspidosperma and Strychnos Alkaloids through Indole Dearomatization, *Chem. Eur. J*., 2019, **25**, 8916–8935.

367 A. B. Dounay, P. G. Humphreys, L. E. Overman and A. D. Wrobleski, Total Synthesis of the Strychnos Alkaloid (+)-Minfiensine: Tandem Enantioselective Intramolecular Heck−Iminium Ion Cyclization, *J. Am. Chem. Soc*., 2008, **130**, 5368.

368 K. Douki, H. Ono, T. Taniguchi, J. Shimokawa, M. Kitamura, and T. Fukuyama, Enantioselective Total Synthesis of (+)-Hinckdentine A via a Catalytic Dearomatization Approach, *J. Am. Chem. Soc*., 2016, **138**, 14578–14581.

369 J. F. Austin, S. G. Kim, C. J. Sinz, W. J. Xiao, D. W. C. MacMillan, Enantioselective organocatalytic construction of pyrroloindolines by a cascade addition-cyclization strategy: Synthesis of (-)-flustramine B, *Proc. Natl. Acad. Sci. U. S. A*., 2004, **101**, 5482–5487.

370 S. B. Jones, B. Simmons, D. W. C. MacMillan, Nine-step enantioselective total synthesis of (+)-minfiensine, *J. Am. Chem. Soc.*, 2009, **131**, 13606–13607.

371 S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, Collective synthesis of natural products by means of organocascade catalysis, *Nature*, 2011, **475**, 183–188.

372 R. R. Knowles, J. Carpenter, S. B. Blakey, A. Kayano, I. K. Mangion, C. J. Sinz, D. W. C. MacMillan, Total synthesis of diazonamide A, *Chem. Sci*., 2011, **2**, 308–311.

373 S. Zhu, D. W. C. MacMillan, Enantioselective copper-catalyzed construction of aryl pyrroloindolines via an arylation-cyclization cascade, *J. Am. Chem. Soc.*, 2012, **134**, 10815–10818.

374 R. Jiang, L. Ding, C. Zheng, S.- L. You, Iridium-catalyzed Z-retentive asymmetric allylic substitution reactions, *Science*, 2021, **371**, 380–386.

375 Q.- F. Wu, H. He, W.- B. Liu, S.- L. You, Enantioselective construction of spiroindolenines by Ir-catalyzed allylic alkylation reactions, *J. Am. Chem. Soc*., 2010, **132**, 11418–11419.
376 C. Liu, W. Zhang, L.- X. Dai, S.- L. You, Copper(I)-catalyzed cascade dearomatization of 2-substituted tryptophols with arylidonium salts, *Org. Lett*., 2012, **14**, 4525–4527.
377 Q.-F. Wu, C. Zheng, S.- L. You, Enantioselective Synthesis of Spiro Cyclopentane-1,3'-indoles and 2,3,4,9-Tetrahydro-1H-carbazoles by Iridium-Catalyzed Allylic Dearomatization and Stereospecific Migration, *Angew. Chem. Int. Ed*., 2012, **51**, 1680–1683.
378 C. Liu, J.- C. Yi, Z.- B. Zheng, Y. Tang, L.- X. Dai, S.- L. You, Enantioselective Synthesis of 3a-Amino-Pyrroloindolines by Copper-Catalyzed Direct Asymmetric Dearomative Amination of Tryptamines, *Angew. Chem. Int. Ed*., 2016, **55**, 751–754.
379 H.- F. Tu, X. Zhang, C. Zheng, M. Zhu, S.- L. You, Enantioselective dearomative prenylation of indole derivatives. *Nat. Catal*., 2018, **1**, 601–608.
380 X.- J. Liu, C. Zheng, Y.- H. Yang, S. Jin, S.- L. You, Iridium-Catalyzed Asymmetric Allylic Aromatization Reaction, *Angew. Chem. Int. Ed*., 2019, **58**, 10493–10499.
381 M. E. Kieffer, K. V. Chuang, S. E. Reisman, A copper-catalyzed arylation of tryptamines for the direct synthesis of aryl pyrroloindolines, *Chem. Sci.*, 2012, **3**, 3170–3174.
382 M. E. Kieffer, K. V. Chuang, S. E. Reisman, Copper-catalyzed diastereoselective arylation of tryptophan derivatives: Total synthesis of (+)-naseseazines A and B, *J. Am. Chem. Soc*., 2013, **135**, 5557–5560.
383 H. Wang, S. E. Reisman, Enantioselective Total Synthesis of (−)-Lansai B and (+)-Nocardioazines A and B, *Angew. Chem. Int. Ed*., 2014, **53**, 6206–6210.
384 E. C. Gentry, L. J. Rono, M. E. Hale, R. Matsuura, R. R. Knowles, Enantioselective Synthesis of Pyrroloindolines via Noncovalent Stabilization of Indole Radical Cations and Applications to the Synthesis of Alkaloid Natural Products, *J. Am. Chem. Soc*., 2018, **140**, 3394–3402.
385 S. A. Snyder, A. L. Zografos, Y. Lin. Total Synthesis of Resveratrol-Based Natural Products: A Chemoselective Solution. *Angew. Chem. Int. Ed*., 2007, **46**, 8186 –8191.
386 S. A. Snyder, A. Gollner, M. I. Chiriac. Regioselective Reactions for Programmable Resveratrol Oligomer Synthesis, *Nature*, 2011, **474**, 461–466.
387 S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos. Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block, *J. Am. Chem. Soc*., 2009, **131**, 1753–1765.
388 S. A. Snyder, T. C. Sherwood, A. G. Ross. Total Syntheses of Dalesconol A and B, *Angew. Chem. Int. Ed*., 2010, **49**, 5146–5150.
389 M. B. Hulst, T. Grocholski, J. J. C. Neefjes, G. P. van Wezel, M. Metsä-Ketalä, Anthracyclines: biosynthesis, engineering and clinical applications, *Nat. Prod. Rep*., 2022, **39**, 814–841.
390 R. Zucchi, R. Danesi. Cardiac Toxicity of Antineoplastic Anthracyclines, *Curr. Med. Chem.: Anti-Cancer Agents*, 2003, **3**, 151−171.
391 M. Binaschi, M. Bigioni, A. Cipollone, C. Rossi, C. Goso, C. A. Maggi, G. Capranico, F. Animati. Anthracyclines: Selected New Developments, *Curr. Med. Chem.: Anti-Cancer Agents*, 2001, **1**, 113−130.
392 D. G. Dennis, M. Okumura, D. Sarlah. Synthesis of (±)-Idarubicinone via Global Functionalization of Tetracene, *J. Am. Chem. Soc*., 2019, **141**, 10193−10198.
393 J.-M. Gao, S.-X. Yang, J.-C. Qin. Azaphilones: Chemistry and Biology, *Chem. Rev*., 2013, **113**, 4755–4811.
394 N. Osmanova, W. Schultze, N. Ayoub. Azaphilones: a class of fungal metabolites with diverse biological activities, *Phytochem. Rev*., 2010, **9**, 315–342.
395 J. Zhu, J. A. Porco. Asymmetric Syntheses of (−)-Mitorubrin and Related Azaphilone Natural Products, *Org. Lett*., 2006, **8**, 5169–5171.
396 A. R. Germain, D. M. Bruggemeyer, J. Zhu, C. Genet, P. O'Brien, J. A. Porco, Synthesis of the Azaphilones (+)-Sclerotiorin and (+)-8- O -Methylsclerotiorinamine Utilizing (+)-Sparteine Surrogates in Copper-Mediated Oxidative Dearomatization, *J. Org. Chem*., 2011, **76**, 2577–2584.
397 R. A. Johnson. Microbial Arene Oxidations. In Organic Reactions; American Cancer Society, 2004; pp 118–264.
398 S. E. Lewis. Asymmetric Dearomatization Under Dearomative Conditions. In Asymmetric Dearomatization Reactions; Wiley-VCH Verlag GmbH & Co. KGaA., 2016; pp 279–346.
399 J. B. Pyser, S. A. Baker Dockrey, A. R. Benítez, L. A. Joyce, R. A. Wiscons, J. L. Smith, A. R. H. Narayan, Stereodivergent, Chemoenzymatic Synthesis of Azaphilone Natural Products, *J. Am. Chem. Soc.*, 2019, **141**, 18551–18559.
400 S. Chakrabarty, E. O. Romero, J. B. Pyser, J. A. Yazarians, A. R. H. Narayan, Chemoenzymatic Total Synthesis of Natural Products. *Acc. Chem. Res*., 2021, **54**, 50.
401 A. Sib, T. A. M. Gulder, Stereoselective Total Synthesis of Bisorbicillinoid Natural Products by Enzymatic Oxidative Dearomatization/Dimerization, *Angew. Chemie Int. Ed*., 2017, **56**, 12888–12891.
402 L. Kahlert, E. F. Bassiony, R. J. Cox, E. J. Skellam, Diels–Alder Reactions During the Biosynthesis of Sorbicillinoids., *Angew. Chemie Int. Ed*., 2020, **59**, 5816–5822.
403 D. Barnes-Seeman, E. J. Corey, A Two-Step Total Synthesis of the Natural Pentacycle Trichodimerol, a Novel Inhibitor of TNF-α Production, *Org. Lett*., 1999, **1**, 1503–1504.
404 K. C. Nicolaou, R. Jautelat, G. Vassilikogiannakis, P. S. Baran, K. B. Simonsen, Studies towards Trichodimerol: Novel Cascade Reactions and Polycyclic Frameworks, *Chem. Eur. J*., 1999, **5**, 3651–3665.
405 K. C. Nicolaou, G. Vassilikogiannakis, K. B. Simonsen, P. S. Baran, Y.- L. Zhong, V. P. Vidali, E. N. Pitsinos, E. A. Couladouros, Biomimetic Total Synthesis of Bisorbicillinol, Bisorbibutenolide, Trichodimerol, and Designed Analogues of the Bisorbicillinoids, *J. Am. Chem. Soc*., 2000, **122**, 3071–3079.
406 L. H. Pettus, R. W. Van De Water, T. R. R. Pettus, Synthesis of (±)-Epoxysorbicillinol Using a Novel Cyclohexa-2,5-dienone with Synthetic Applications to Other Sorbicillin Derivatives, *Org. Lett*., 2001, **3**, 905–908.
407 R. Hong, Y. Chen, L. Deng, Catalytic Enantioselective Total Syntheses of Bisorbicillinolide, Bisorbicillinol, and Bisorbibutenolide, *Angew. Chem. Int. Ed*., 2005, **44**, 3478–3481.
408 R. Ciochina, R. B. Grossman, Polycyclic Polyprenylated Acylphloroglucinols, *Chem. Rev*., 2006, **106**, 3963–3986.
409 K. Leuner, V. Kazanksi, M. Müller, K. Essin, B. Henke, M. Gollasch, C. Harteneck, W. E. Müller, Hyperforin—a key constituent of St. John's wort specifically activates TRPC6 channels, *FASEB J*., 2007, **21**, 4101–4111.
410 O. Cuesta-Rubio, H. Velez-Castro, B. A. Frontana-Uribe, J. Cárdenas, Nemorosone, the major constituent of floral resins of Clusia rosea, *Phytochemistry*, 2001, **57**, 279–283.
411 Y. Fukuyama, H. Minami, A. Kuwayama, Garsubellins, polyisoprenylated phloroglucinol derivatives from Garcinia subelliptica, *Phytochemistry*, 1998, **49**, 853–857.
412 V. Rodeschini, N. A. Ahmad, N. S. Simpkins, Synthesis of (±)-Clusianone: High-Yielding Bridgehead and Diketone Substitutions by Regioselective Lithiation of Enol Ether Derivatives of Bicyclo[3.3.1]nonane-2,4,9-triones, *Org. Lett*., 2006, **8**, 5283−5285.
413 N. Biber, K. Möws, B. Plitker, The total synthesis of hyperpapuanone, hyperibone L, epi-clusianone and oblongifolin A, *Nat. Chem*., 2011, **3**, 938–942.

414 C. P. Ting, T. J. Maimone, Total Synthesis of Hyperforin, *J. Am. Chem. Soc*., 2015, **137**, 10516–10519.

415 C. Tsukano, D. R. Siegel, S. J. Danishefsky, Differentiation of Nonconventional "Carbanions"—The Total Synthesis of Nemorosone and Clusianone, *Angew. Chem. Int. Ed*., 2007, **46**, 8840–8844.

416 B. A. Sparling, D. C. Moebius, M. D. Shair, Enantioselective Total Synthesis of Hyperforin, *J. Am. Chem. Soc*., 2013, **135**, 644–647.

417 M. Uwamori, A. Saito, M. Nakada, Stereoselective Total Synthesis of Nemorosone, *J. Org. Chem*., 2012, **77**, 5098–5107.

418 M. Uwamori, M. Nakada, Stereoselective total synthesis of garsubellin A, *J. Antibiot*., 2013, **66**, 141–145.

419 J. Qi, J. A. Porco Jr., Rapid Access to Polyprenylated Phloroglucinols via Alkylative Dearomatization−Annulation: Total Synthesis of (±)-Clusianone, *J. Am. Chem. Soc*., 2007, **129**, 12682–12683.

420 J. Qi, A. B. Beeler, Q. Zhang, J. A. Porco Jr., Catalytic Enantioselective Alkylative Dearomatization−Annulation: Total Synthesis and Absolute Configuration Assignment of Hyperibone K, *J. Am. Chem. Soc*., 2010, **132**, 13642–13644.

421 Q. Zhang, B. Mitasev, J. Qi, J. A. Porco Jr., Total Synthesis of Plukenetione A, *J. Am. Chem. Soc*., 2010, **132**, 14212–14215.

422 Q. Zhang, J. A. Porco Jr., Total Synthesis of (±)-7-epi-Nemorosone, *Org. Lett*., 2012, **14**, 1796−1799.

423 J. B. Boyce, J. A. Porco Jr., Asymmetric, Stereodivergent Synthesis of (−)-Clusianone Utilizing a Biomimetic Cationic Cyclization, *Angew. Chem. Int. Ed*., 2014, **53**, 7832–7837.

424 S. Wen, J. H. Boyce, S. K. Kandappa, J. Sivaguru, J. A Porco Jr., Regiodivergent Photocyclization of Dearomatized Acylphloroglucinols: Asymmetric Syntheses of (−)-Nemorosone and (−)-6-epi-Garcimultiflorone A, *J. Am. Chem. Soc*., 2019, **141**, 11315–11321.

425 A. J. Grenning, J. H. Boyce, J. A. Porco Jr., Rapid Synthesis of Polyprenylated Acylphloroglucinol Analogs via Dearomative Conjunctive Allylic Annulation, *J. Am. Chem. Soc.*, 2014, **136**, 11799–11804.