Recent Advances Towards Syntheses of Diterpenoid Alkaloids

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Dedicated to the 50th anniversary of SYNTHESIS

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Abstract
The diterpenoid alkaloids serve as a rich source of synthetic targets for organic chemists, due to the intriguing structure of the overlapping ring systems, along with biological activities commonly associated with compounds of this group. Fifteen total syntheses and numerous synthetic studies towards construction of ring fragments have been reported since 2010. This review article gives a brief overview of diterpenoid alkaloids and summarizes the recent synthetic efforts.

1 Introduction

1.1 Structural Classification and Biosynthetic Origin

The diterpenoid alkaloids family is generally grouped by key conserved structural features and size of the carbon scaffolds. The smallest of the three main groups are the C18-diterpenoid alkaloids, with over 50 discrete compounds already known.2 These C18-diterpenoid alkaloids can be further subdivided into two distinct types: the lappaconitine-type 1, and the ranaconitine-type 2 (Figure 1) with the major difference being the presence of the additional oxygenation at the C7 position in the ranaconitine core.

1.2 Structure Elucidation of the Aconitum Alkaloids

While researchers worldwide are still discovering new compounds within this class from numerous plant species, these pseudoalkaloids have been traditionally linked to the Aconitum, Consolida, and Delphinium genus of plants, from which they were extracted and used in traditional medicine. However, research into broader applications still continues.4 The most common uses included the treatment of cardiovascular diseases and as an analgesic.

1.3 Total Syntheses

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1.4 Strategies To Synthesize Ring Systems

The C19-diterpenoid alkaloids are the largest of the three groups and represent over 600 fully characterized molecules.6 They are structurally closer to the C18-diterpenoid core, with the variation being an additional carbon at the piperidine ring junction. This group is divided into 6 unique types, with the aconitine- 3 and lycocbarine-type 4 seemingly the most prevalent in Nature (Figure 2). The other

Key words diterpenoids, alkaloids, total synthesis, aconitine, natural products

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Christian Dank (second from right) studied chemistry at the University of Vienna. After receiving the degree Master of Science (M.Sc.) in the group of Prof. Johann Mulzer, during his Ph.D. he worked on syntheses of novel antimalarials, supervised by Dr. Hubert Gstach and Prof. Walther Schmid. In 2016, he joined the medicinal chemistry department of Boehringer Ingelheim in Vienna, working on oncology projects. During his postdoctoral fellowship in the Lautens group, he contributes in his fields of expertise, total synthesis and medicinal chemistry, and explores the field of metal catalysis.

Randy Sanichar (rightmost) completed his Bachelor of Science (B.Sc.) degree in chemistry at the University of Guyana in 2011, graduating with distinction. After working at a local rum distillery as a process chemist for two years, he travelled to Canada to further his education at the University of Alberta. In 2018, he completed his Ph.D. under the supervision of Professor John C. Vederas where he worked on the design and syntheses of probes for the elucidation of biosynthetic pathways of pharmaceutically relevant polyketides; all to facilitate a chemosynthesis production platform. He joined the Lautens group in November 2018, as a postdoctoral researcher, where his current research interests include the total synthesis of novel natural products and the development of new catalytic asymmetric reactions.

Ken-Loon Choo (leftmost) received his B.Sc. degree with honors from the University of Toronto. He then ventured into the oleochemical industry as a research chemist developing a process to synthesize high purity sulfonated fatty acid esters. In 2016, he returned to pursue a graduate degree in the laboratories of Prof. Mark Lautens at the University of Toronto with interest in catalytic asymmetric reactions and total synthesis.

Madeline Olsen (center) enjoyed a thirty-year career in electrical engineering, having been employed at Toronto’s Hospital for Sick Children (1970–1974), Bell Northern Research Ottawa (1975–1978), The National Synchrotron Light Source, Brookhaven National Laboratory (1979–1994), and SLAC National Accelerator Laboratory (1995–1998). A specialist in digital logic design and signal processing, she nonetheless designed and constructed many of the magnet power supplies at the NSLS, ranging from 25 KW to 2.2 MW. She was awarded two United States patents for her work at Bell Northern Research and in 1995, she was invited to CERN Geneva where she gave a lecture to the LEP power supply group outlining the high precision digital power control system she had designed for the NSLS. She enrolled as an undergraduate and having taken the specialist courses offered in organic chemistry, worked in the Lautens lab as a research assistant from 2001–2006. During this time, she worked on the synthesis and ring-opening of novel azabenzonorbornadienes and developed a reaction for the synthesis of dihydronaphthalenes via an aryne Diels–Alder reaction. Additionally, she devised and ran large-scale syntheses for early stage material of a total synthesis project.

Mark Lautens (second from left) was born in Hamilton, Ontario, Canada. He obtained his B.Sc. degree from the University of Guelph followed by doctoral studies at the University of Wisconsin–Madison under the direction of Professor Barry M. Trost where he discovered Mo-catalyzed allylic alkylation and the Pd-catalyzed enyne cycloisomerization. In 1985, he moved to Harvard University where he conducted his NSERC PDF with Professor David A. Evans on studies directed toward the synthesis of bryostatin. He joined the University of Toronto in 1987 as an NSERC University Research Fellow and Assistant Professor. Since 1998 he has held an Endowed Chair, the AstraZeneca Professor of Organic Synthesis, and from 2003–2013 he was named an NSERC/Merck Frosst Industrial Research Chair in New Medicinal Agents via Catalytic Reactions. In 2012, he was appointed as University Professor, the highest rank at the University of Toronto. Most recently he was awarded Officer of the Order of Canada, the highest civilian honor in Canada. His current research interests are in multicatalyst reactions, isomerization reactions, and applications of catalysis in the synthesis of bioactive compounds.
four subgroups are less frequent in occurrence and are comprised of the pyro-type, 7,17-seco-type 5, lactone-type 6, and rearranged-type alkaloids.

Figure 2 C19-type diterpenoid alkaloid skeletons

The C20-diterpenoid alkaloids (Figure 3) are a moderately large group, with over 300 known compounds.2b This group shows the broadest structural diversity of the main groups, and have been categorized into 16 distinct types of diterpenoid alkaloids: atisine 7, denudatine 8, hetidine 9, hetisine 10, cardionidine 11, albovionitine 12, vakognavine 13, veatchine 14, napelline 15, anopterine 16, delnudine 17, kusnezoline 18, actaline 19, racemulosine 20, arcutine 21, and tricalysiamide 22.2b Interestingly, while almost all of the C18- and C19-diterpenoid alkaloids possess a [3.2.1]bicycle in the right side of their scaffolds, the majority of the C20-diterpenoid alkaloids contain a [2.2.2]bicycle.

Despite this vast structural diversity amongst the three groups, these natural products are all derived through biosynthetic insertion of the nitrogen into the mature diterpene scaffolds, which then undergoes further elaborations leading to the final product, as shown in Scheme 1.5 An enzyme-catalyzed cyclization of geranyl-geranyl pyrophosphate affords the ent-copalyl pyrophosphate, which then undergoes a series of transformations, including a critical Wagner–Meerwein rearrangement, affording the ent-kaurane 23 and ent-atisane 24 diterpene skeletons. These scaffolds then undergo amination to form the two main branching points, the veatchines 14 and the atisines 7, notably these can interconvert through a [1,2]-sigmatropic rearrangement.1,2b,5 Through a series of elegant manipulations by Nature, these cores are later transformed into the numerous natural products observed. Some examples of these are the napellines 15 and denudatines 8, which are accessed through C7–C20 bond formation from the veatchines 14 and atisines 7, respectively. In other cases, after the requisite transformations, the scaffold may fragment to access the smaller core, as seen with the denudatines en route to the C19 scaffolds 25 and C18 scaffolds 26.

Figure 3 The 16 categories of the C20-diterpenoid alkaloids
1.2 Structure Elucidation of the Aconitum Alkaloids

The C_{18}- and C_{19}-diterpenoid alkaloids have been of great interest to civilizations since antiquity. Preparations from members of the genera *Aconitum* and *Delphinium* have been used for such diverse applications as traditional Chinese medicine to surreptitious homicide, aconitine (27) being the most toxic; LD_{50} in mice (mg/kg: 0.166, i.v., 0.328 i.p.).\(^6\) However, due to the complexity of these molecules, very little progress beyond isolation was achieved for almost a century. The first published studies into the chemistry of aconitine did not appear until 1894 with additional data published in 1895. Following a 29 year hiatus, three additional papers were published in the German literature (1924–1956).\(^9\) British researchers were also immersed in the aconitine problem, between 1894–1937, twelve papers related to structure determination were published by the Royal Society of Chemistry.\(^10\) In this time period, only one paper was published in the North American literature.\(^11\) Despite much information being obtained about occurrence and activities, little was known about the detailed structure due to the limited capabilities of the classical methods of analysis.

This situation changed with the introduction of UV and IR spectroscopy\(^12\) and later, NMR.\(^13\) Due to their less complex structure, the C_{20} alkaloids were the initial focus of attention. S. W. Pelletier and W. A. Jacobs made many contributions to the structural elucidation, both by chemical and spectroscopic means.\(^14\) A partial synthesis of atisine (28), isoatisine (29), and dihydroatisine (30) was achieved in 1956.\(^15\)

The pioneer in the field of detailed structure determination and total synthesis of the *Delphinium* alkaloids was Karel Wiesner (1919–1986). He arrived at the University of New Brunswick in 1948 determined to clear up the ‘hopeless confusion’ surrounding the structure. However, a review indicated that this had been tried many times in the past to no avail. He thus concluded that the best way to approach the problem would be to solve the structure of the more straightforward C_{20} members of the class.\(^16\) In the period 1948–1975, several total syntheses were achieved, employing 1st through 4th generation methods (Table 1, Figure 4). Some more recent syntheses are included in Table 1. Wiesner published two reviews of his work.\(^17\) Notably, even today, the total synthesis of the fully oxygenated, most complex members of the family, aconitine (27), and beiwutine (31) remain elusive. This article covers advances in total synthesis towards diterpenoid alkaloids from 2010 onwards after excellent coverage of the field by other review articles.\(^5\)\(^,\)\(^18\) Figure 5 depicts structurally unique diterpenoid alkaloids that have been synthesized since 2010, such as salviamine E (32) and F (33);\(^19\) vitezpyroloid A (34) and B...
Table 1  Examples of Significant Total Syntheses by Compound and Year (see Figure 4)

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2  Total Syntheses

2.1  C18-Diterpenoid Alkaloids

2.1.1  Total Synthesis of Neofinaconitine

This convergent total synthesis of neofinaconitine (47) by Shi, Tan, and co-workers in 2013 was designed to begin with an intermolecular Diels–Alder cycloaddition between the in situ generated diene from enone 69 and cyclopropene 70 (Scheme 2).27 To allow for this strategy, the cyclopentenone intermediate 69 was prepared from commercially available furfuryl alcohol,28 while the cyclo-
propene starting material \( \text{70} \) was prepared in 6 steps from methyl acrylate.\(^5\) Notably, due to the rapid Alder–ene dimerization of the cyclopropene intermediate, this compound was isolated and was used immediately in the cycloadition reaction. The Diels–Alder cycloaddition was conducted by addition of intermediate \( \text{70} \) directly to the \textit{in situ} prepared diene from intermediate \( \text{69} \). Importantly, it was reported that attempts at isolating the enolization–silylation product of \( \text{69} \) led to a difficult-to-control mixture of dimerized cyclopentadiene. Nonetheless, this direct addition to the \textit{in situ} prepared diene allowed access to the desired product \( \text{71} \) as an inseparable mixture of diastereomers (1:1.6). Given that the major diastereomer was the desired product, this mixture was taken through the next four steps to access intermediate \( \text{73} \) (39\% over 6 steps). A series of functional group manipulations on intermediate \( \text{73} \) afforded access to diene \( \text{75} \) and set up the second intermolecular Diels–Alder cycloaddition between \( \text{75} \) and \( \text{76} \) catalyzed by \( \text{SnCl}_4\).\(^2\) This is notably an essential step as it afforded a key intermediate \( \text{77} \) as a single diastereomer in excellent yield (87\%). This was then converted into the precursor for the Mannich-type N-acyliminium cyclization by the selective oxidation of the exocyclic olefin to afford a carbonyl and followed by elimination of the \( \beta \)-bromide to form the
enone 78. The Mannich-type N-acyliminium cyclization was achieved by treatment of intermediate 78 with Tf₂NH, thereby forming the C11–C17 bond, but was unfortunately also followed by the formation of the cyclic enol ether to form 79 (75%). To overcome this undesired, but unavoidable, formation of the enol ether, a rather nifty trick was employed, a leaving group was introduced at the C3 position by treatment of 79 with CAN, followed by MsCl/Et₃N in two steps, which was fortunately accompanied by the elimination to afford the dienone 80 (66%, two steps).27 The last of the key steps was completed by an intramolecular radical cyclization of dienone 80 in excellent yield to afford the completed neofinacotine scaffold 81 (99%). Finally, installation of the C8 hydroxyl functionality was achieved via a highly strained enone, allowing for a spontaneous nucleophilic attack by water to give 82 and complete the structural requirements. Over an additional 8 steps, the remaining modifications and tailoring were accomplished to afford the total synthesis of racemic neofinaconitine (47).27

This divergent approach by Shi, Tan, and co-workers was achieved in 30 longest linear steps and afforded racemic neofinaconitine (47) from readily available materials.27 It should be noted that this strategy offers numerous opportunities to access other types of the diterpenoid alkaloids and as such should be exploited for the preparation of derivatives of such natural products.

### 2.1.2 Total Synthesis of Weisaconitine D

The Sarpong group completed the total synthesis of weisaconitine D (48), a ranaconitine-type diterpenoid alkaloid, in 2015 in 30 steps overall (Scheme 3).28 Starting with a Diels–Alder cycloaddition of diene 85 and a cyclopentenone derivative 86, the resulting alkene was reduced to give the basic bicyclic ketone intermediate 87. Preparation of the vinyl triflate by treatment of 87 with LHMDS and phenyl triflimide, followed by Pd(0)-catalyzed cross-coupling with cyanide63 afforded the 1,2-unsaturated nitrile 88. This approach allowed the assembly of the A and F rings, and serves as the substrate for their Rh-catalyzed conjugate addition with the lithium boronate 89 to access 90 in 60% yield. Notably, this guaiacol derivative was installed with high diastereoselectivity. This transformation should be well noted as the aryl ring of 90 after several transformations will eventually be fashioned into the C/D ring and, as such, this is an excellent point to diverge/modify the oxidation patterns around these rings in the final diterpenoid alkaloid simply by use of the appropriately substituted arene. The ester group of 90 was selectively reduced over the nitrile functionality, followed by Dess–Martin oxidation of the resulting primary alcohol to give aldehyde 91. The newly formed aldehyde 91 underwent a Wittig olefination, followed by hydration of the nitrile group64 to provide the carboxamide 92. This carboxamide 92 was then rearranged via a Hofmann rearrangement using (dicycloxyi)benzene [Phi(OAc)]₂, PIDA, and the
Scheme 2  Total synthesis of lappaconitine-type diterpenoid alkaloid neofinaconitine

Scheme 3  Total synthesis of ranaconitine-type diterpenoid alkaloid weisaconitine D
intermediate isocyanate was trapped with methanol, followed by deprotection to the tert-butyldimethylsilyl group with TBAF to give 93. The primary hydroxyl group was then activated by mesylation and treated with KOt-Bu to form the C19–N bond, thereby fashioning the piperidiny1 ring of 94. This key step allowed completion of the A, E, and F rings for the C18-diterpenoid alkaloids. In order to set construction of the B, C, and D rings, the MOM protecting group of 94 was cleaved, and the phenol was then subjected to an oxidative dearomatization to afford the dienone 95. By merely heating intermediate 95, it underwent an intramolecular Diels–Alder cycloaddition forming 96. This step effectively allowed access to the C20 core framework of the denudatine-type diterpenoid alkaloids. As such, this pathway can be viewed as an equally effective route to the denudatine-type diterpenoid alkaloids.

To effect the transformation of the bicyclo[2.2.2] structural motif to the bicyclo[3.2.1] core, the ketone functionality of 96 was stereoselectively reduced. It was postulated that this selectivity is as a result of torsional strain from the β-disposed methoxy group of the dimethyl ketal. The ketal protecting group was then hydrolyzed to afford 97. Intermediate 97 was then treated with MOMCl to protect the free secondary hydroxyl group, followed by the diastereoselective reduction of the ketone group to provide alcohol 98. The triflation of alcohol 98, followed by treatment with DBU and DMSO at 120 °C led to a Wagner–Meerwein-type rearrangement and thus completed the B, C, and D rings in 99. While several strategies were explored for a formal hydro-methoxilation of the C15–C16 double bond of 99, it was found that this was best achieved via an epoxide intermediate. They employed a hydroxyl-directed epoxidation from the β-face using m-CPBA, followed by alklylation of the tertiary hydroxyl to provide 100. The epoxide was regio-selectively opened (95) to provide a β-disposed secondary alcohol group that was methylated to furnish 101 and thus completed the D-ring of weisaconitine D. The methoxy carbonyl protecting group was removed, the nitrogen was acylated, and the acetamide was reduced using LiAlH4. Finally, removal of the MOM protecting by acid treatment of afforded the final product weisaconitine D (52) in 9 steps.

This successful total synthesis of weisaconitine D (48) by the Sarpong group28 should be viewed as a direct opening to other members of the C18-ranaconitine class of diterpenoid alkaloids as well as the C20-denudatine types. Importantly, their synthetic plan shows great promise in allowing for the preparation of any number of unnatural analogues of this natural product.

### 2.2 C19-Diterpenoid Alkaloids

In contrast to the numerous reports of total syntheses of C20-diterpenoid alkaloids, there are only a handful of recent total syntheses of C19 norditerpenoid alkaloids. The total syntheses of liljestrandinine (52)28 and (−)-cardioptetaline (53)67 have been reported by the Sarpong group and Fukuyama, Yokoshima, and co-workers, respectively. The total synthesis of aconitine (27) can be considered a holy grail in organic synthesis due to its intricate, highly oxygenated caged framework. The synthesis of this molecule has remained elusive, and the most recent attempt was reported by Qin, Zhang, and co-workers.56 Several groups have made strategic efforts towards the construction of the C19 cores and the reported methodologies will be covered here.

#### 2.2.1 Total Synthesis of Liljestrandinine

The synthesis of liljestrandinine (52)28 starting from synthon 93 is shown in Scheme 4; dienone 104 was prepared in 7 steps in a similar fashion to the synthesis of weisaconitine D (48). At this point, the stage is set for an intramolecular Diels–Alder reaction. The ketone moiety of the Diels–Alder adduct was then reduced to give the hexacyclic alcohol 105, which was converted into the C19-diterpenoid alkaloid liljestrandinine (52) in 9 steps.

In a unifying approach to the C18-, C19-, and C20-diterpenoid alkaloids, the Sarpong group accomplished the preparations of weisaconitine D (48), liljestrandinine (52), as well as the denudatine-type compounds cochlearenine (59), N-ethyl-1α-17-veratryldictyzine (61), and paniculamine (63).46 The advanced intermediate 93 is common to all of these natural product syntheses.

#### 2.2.2 Total Synthesis of (−)-Cardioptetaline

Fukuyama, Yokoshima, and co-workers disclosed a novel Wagner–Meerwein rearrangement of a sulfonloyloxirane to construct the aconitine skeleton (Scheme 5).67 Sulfonloyloxirane 114 was synthesized from synthetic intermediate 108 en route to their previous reported total synthesis of lepinene.51 Protection of the hydroxy group of 108 followed by removal of the methoxy groups under reductive conditions with SmI2 furnished ketone 109. Hydrogenation of the olefin was achieved using Pd(OH)2 on carbon to afford ketone 110, which was then converted into α-phenylsulfanyl ketone 111 via a silyl enolate intermediate. Stereoselective reduction gave a secondary alcohol, which was subsequently acylated to yield 112. The sulfide group was oxidized into a sulfone using Oxone and then base-mediated elimination of the acetate group furnished the vinyl sulfone 113. Stereoselective epoxidation was then carried out with tert-butyl hydroperoxide (TBHP) to give sulfonloyloxirane 114 with the appropriate stereoconfiguration for a Wagner–Meerwein rearrangement.

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Surprising stability was observed with the sulfonyloxirane 114 where the intended rearrangement was not observed even under harsh acidic or thermal conditions. The desired rearrangement was finally realized by applying microwave irradiation at 150 °C in methanol. An alkyl shift first occurred to cleave the oxirane to give alcohol 116. The resulting carbocation was trapped by methanol followed by the extrusion of benzenesulfonic acid to form hexacyclic ketone 117. Reduction of the ketone was carried out immediately due to its instability to give alcohol 118. The total synthesis of (−)-cardiopetaline (53) was completed with heating in aqueous sulfuric acid to unmask the alcohol groups.
In 2017, Fukuyama, Yokoshima, and co-workers published another variant (shown in Scheme 6) of the (−)-cardiopetaline (53) synthesis, which does not require pre-activation of the pivotal hydroxy group.34 The requisite diol 120 was also synthesized from intermediate 108.51 The ketone in TBS-protected 119 was stereoselectively reduced to alcohol 120 using alane with pyridine as an additive to prevent damage to the ketal moiety; hydrolysis of the ketal followed by exhaustive hydrogenation afforded diol 120, which was the target for the Wagner–Meerwein rearrangement. A number of reaction conditions were tested to initiate the rearrangement, but it was finally found that p-toluenesulfonic acid produced the desired rearranged product mixture 123. Pivalic acid was crucial for the suppression of the undesired acylation of the diol substrate. Hydrolysis was then carried out to liberate the alcohol groups to give (−)-cardiopetaline (53).

2.2.3 Attempted Total Synthesis of Aconitine

The most recent attempt at the total synthesis of aconitine (27) in 2019 was reported by Qin, Zhang, and co-workers (Scheme 7).66 The synthesis commenced with the decarboxylation of (−)-(R)-carvone (124) to install the desired substituents on the A ring. Nitrone 126 was generated in situ from 125. DDQ, Et3N, DCM/H2O (10:1) provided the desired product 127 in 67% yield. The synthesis proceeded with further elaboration to install the desired substituents on the A ring.
glyoxylate 125 when treated with N-PMB-hydroxylamine, which then induced an intramolecular [3+2] cycloaddition to give isoxazolidine 127 as a single diastereomer.

Deprotection of the N-PMB group followed by oxidation was achieved using DDQ to give imine 128. Hydrolysis, followed by Krapcho decarboxylation, and selective methylation afforded β-hydroxynitrile 129. Subsequent steps, including functional group manipulations and an intramolecular Mannich reaction, were carried out to build the E ring giving aldehyde 130. Addition of the alkyn fragment 131 provided propargyl alcohol 132. Further manipulations provided xanthate 133, which was the substrate required to carry out the key radical cascade for the formation of the BD ring systems. The planned cascade first generates a radical at C11 that subsequently cyclizes on to the C10 acceptor and is finally trapped by the alkyn moiety. Various radical initiating conditions were tested, but only decomposition of the substrate was observed without the formation of the desired cyclized product 135. The success of the cascade may be hampered by the premature interference of the alkyn moiety, the acceptor at C10 may be too distant, as well as the possibility of the formation of nitrogen-centered radicals on the tertiary amine. The final key transformation in the proposed route utilized an aza-Prins cascade to furnish the F ring of aconitine (27). Overall, the reported route achieved the synthesis of the fully functionalized AE ring systems of aconitine (27) in 27 steps with an overall yield of 1.64% from (–)-(R)-carvone (124).

2.3 C_{20}-Diterpenoid Alkaloids

2.3.1 Total Synthesis of Septedine

The first and asymmetric total synthesis of septedine (68) was reported in 2018 by Li and co-workers. Septedine (68) is a hetidine type C_{20}-diterpenoid alkaloid bearing an oxygenated heptacyclic scaffold. Highlights of the total synthesis are shown in Scheme 8. Starting from Weinreb
amide 136, aryldiene 141 was accessible in 5 steps. Iridium-catalyzed polyene cyclization using the conditions of Carreira gave tricyclic intermediate 143. Intermediate 146 was prepared in order to perform a Diels–Alder reaction. Surprisingly, treatment of 146 with LHMDS gave cyclized product 147. In a sequence of five steps, the protected secondary alcohol was transformed into a ketone, and several manipulations on C-15 and C-16 led to intermediate 149. C–H activation of C-7 via Sanford’s oxidation conditions and conversion of the vinyl group, via an epoxide, into an aldehyde gave 151. The natural product septedine (68) was obtained through a methylation, ester hydrolysis, and reductive amination which occurred under concomitant condensation. In order to investigate the final steps (reductive amination and N,O-ketalization), 7-deoxyseptedine was prepared from a model substrate (not shown).

### 2.3.2 Total Synthesis of Azitine

A unified approach to assemble atisine-and hetidine-type diterpenoid alkaloids was presented by Liu and Ma. The total syntheses of azitine (66) and the reported structure of navirine C (156) are shown in Scheme 9. Both syntheses contain a common sequence from nitrile 157 to tetra cyclic dinitrile 152 in 10 steps (Scheme 10). Reduction of 152 with LiAlH₄ and Li/NH₃ (liq.) led to the formation of imine 153. The final steps towards natural product azitine (66) were a deprotection, olefination, and subsequent allylic oxidation. The other synthesis accomplished from tetracyclic dinitrile 152 started with the formation of the bond between C–20 and C–14 under Shenvi’s conditions to give cyclized product 154. A further six steps were required to obtain a structure that was reported to be the natural product navirine C (156), but the spectroscopic data differed from the reported data after isolation.

### 2.3.3 Formal Synthesis of (±)-Atisine

A formal synthesis of (±)-atisine (28), utilizing a cascade of oxidative dearomatization/intramolecular Diels–Alder cycloaddition, was reported by Wang, Chen, and co-workers in 2012. As shown in Scheme 11, aldehyde 167 was accessible from commercially available ethyl 2-oxocyclohexanecarboxylate (165) in 9 steps. Wittig olefination gave styrene.
which was transformed into phenol in five steps. Oxidative dearomatization and intramolecular Diels–Alder cycloaddition was followed by hydrogenation, olefination, and cleavage of an acetal group to give enone. This intermediate was previously used by Pelletier and co-workers, and therefore this constitutes a formal synthesis of (±)-atisine.

2.3.4 Synthesis of the Hetidine Scaffold and Total Synthesis of Dihydroajaconine and Gymnandine

A bioinspired synthetic approach to the skeleton of the C20-diterpenoid alkaloid type hetidine was presented by Qin, Liu, and co-workers; Scheme 12 outlines the synthetic path. Starting from alkene was obtained in 5 steps. Then, a Corey–Seebach reaction followed by the well-established oxidative dearomatization and intramolecular Diels–Alder cascade were performed to obtain intermediate. The synthesis of this intermediate also concluded the synthesis of the pentacyclic atisine skeleton.

Intermediate was treated with MeMgBr, the dithiane moiety was removed by reaction with Dess–Martin periodinane, and the resulting ketone was reduced to give diol. Deacetylation and subsequent amide formation gave intermediate, featuring the requisite C-7 hydroxy group and an o-aminobenzamide moiety. Aminal was obtained after reaction with NaNO2, CuCl, and HCl/Et2O reported by Weinreb and co-workers. A radical mechanism was postulated that proceeds via diazotization and a 1,5-H shift to form intermediate, which has the ajaconine skeleton. Cyclization to give the desired hetidine-type product was achieved by an aza-Prins reaction. Throughout the investigations, additional unwanted heptacyclic products were prepared (not shown).
Pentacyclic intermediate 177 was also used by Qin, Liu, and co-workers as starting point for the syntheses of dihydroajaconine (60) and gymnandine (62) (Scheme 13).1 As precursor 186 was subjected to the method developed by Weinreb and co-workers.70 Hemiaminal 187 was then successfully transformed into the atisine-type alkaloid diterpenoid dihydroajaconine (60) in 4 steps.

Simultaneous cleavage of the amide C–N bond and the aminal C–O bond of aminal 188 gave cyclic imine 191 in excellent yield. Oxidation of the secondary alcohol, as described by Iwabuchi and co-workers,71 and cyclization promoted by SmI2 and subsequent N-acetylation gave the hexacyclic intermediate 192 featuring the denudatine core. After construction of the carbon skeleton, natural product gymnandine (62) was obtained after six additional synthetic steps.

### 2.3.5 Total Synthesis of Cossonidine

The Sarpong group chose the hydrindanone 87 as the entry point to their synthetic strategy (Scheme 14). They had previously enjoyed success towards the C18-diterpenoid alkaloids scaffold, as well as the preparation of the 6-7-6 fused tricyclic core72 of the hetidine- and hetisine-types using this compound as a starting point.56 In order to convert the ester into an aldehyde, 87 was treated with LiAlH4, which led to the reduction of both the ester and ketone functionalities; Ley oxidation73 furnished the ketoaldehyde intermediate, which was immediately transformed into the olefin 195. Notably, the standard Wittig conditions were observed to give poor yields, so Lebel’s Rh-catalyzed methylation74 was employed. Acylation of intermediate 195 was accomplished using allyl cyanofomrate (196)75 to afford the β-keto ester 197, which was followed by an aryne insertion assisted by CsF to provide intermediate 199. So as to later functionalize the C6 position, a deallylation reaction was performed10 using catalytic Pd[PPh3]4 and PhSiH3 to afford the carboxylic acid 200, which was then treated with 1,3-diiodo-5,5-dimethylhydantoin (DIH, 201) under photochemical conditions to achieve oxidative decarboxylation,77 and thus leave the C6 carbon as an internal olefin. The methyl group at C4 was installed by deprotection of the primary alcohol, followed by oxidation, then direct conversion into nitrile 203, which then directed the diastereoselective methylation of 203 leading to intermediate 204. This key intermediate bearing handles at C6 and C20 was now set up for formation of the piperidinyl ring. Treatment of 204 with a cobalt boride (Co2B) and borane–tert-butylamine complex,78 followed by treatment with LiAlH4 to reduce the ketone and facilitate protodebromination, was accompanied by a serendipitous direct cyclization to form the N–C20 bond, thus accessing intermediate 205.

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hydroamination\(^\text{79}\) afforded the tertiary amine 206. The formation of the bicyclo[2.2.2] rings was effected through a Birch reduction/intramolecular Diels–Alder sequence\(^\text{80}\) to give the structural core 208. The selective cleavage of the C1 methyl ether was carried out using HBr/AcOH, followed by treatment with K\(_2\)CO\(_3\) in methanol to yield the free alcohol 209. Next, a standard Wittig methylation was carried out to convert the ketone of 209 into an exocyclic methylene 210, and thus completing the C20 carbon scaffold for the hetidine-type skeleton. A sequence of oxidation/reduction was then utilized to invert the stereochemistry at the C1 position affording 212, which simply left a selenium dioxide oxidation to furnish the allylic alcohol and the final product cossonidine (67).

### 2.3.6 Total Synthesis of Lepenine

The strategy employed by Fukuyama and co-workers in 2014 focused on expanding from the scaffold of tetralone 218, which was accessed over 8 steps starting from L-lactic acid methyl ester and guaiacol (213) in excellent yields (Scheme 15).\(^\text{51}\) Having established a successful route to the tetralone, the ketone was then transformed into the diene 219 through a Grignard addition to the ketone followed by silver triflate mediated dehydration. Deprotection of the pivaloyl group in 219 was then followed by coupling to a methacrylic group to afford a key intermediate, triene 220. This intermediate is now set up for the intramolecular Diels–Alder cycloaddition reaction, and upon heating in the presence of a radical scavenger (BHT), it afforded the tetracyclic lactone 221. Hydroboration–oxygenation of the internal alkene in 221 followed by a half reduction of the lactone 222 with DIBAL-H allowed access to the aldehyde 223, which was then converted into a secondary amine by reductive amination and protected with AllocCl to yield 224. This intermediate was then treated with DMP to afford a ketoaldehyde that was treated with Pd(PPh\(_3\))\(_4\) catalyst and acetic acid to remove the Alloc group and resulted in an intramolecular Mannich reaction. This sequence of manipulations provided the polycyclic system 225 and sets up the framework for the formation of the bicyclo[2.2.2] structural core. Two steps of functional group transformations accessed the ortho-quinone monoketal 226 that was treated with ethylene at 70 °C resulting in an intermolecular Diels–
Alder reaction to give the bicyclo[2.2.2] 227; functional group manipulations and final deprotection of protecting groups gave lepenine (58).51

2.3.7 Total Syntheses of Cochlearenine, N-Ethyl-1α-hydroxy-17-veratroyldictyzine, and Paniculamine

The Sarpong group embarked on the mammoth task to design a route that was suitably amenable to modifications at the latest possible stage and yet still access 59, 63, and 61/241; three denudatine-type diterpenoid alkaloids (Scheme 16).52 This was achieved by designing a route to intermediate cochlearenine (59); from 59, following a few late-stage manipulations of the functional groups on the bicyclo[2.2.2] structural element, each of the intended targets was successfully accessed. Starting from 93, which the Sarpong group had previously designed and accessed in 10 steps (25% overall yield),28 the primary alcohol was converted into the corresponding aldehyde via a Swern oxidation. An aldol–Cannizzaro sequence on afforded the diol, which was then converted into the dimesylate (76%). Intermediate was treated with KH to effect the cyclization yielding as the sole product. Next, the methylene O-mesylate group of was transformed into a methyl group via reduction with the combination of NaI/Zn. This was a key step in the strategy, as stereoselective installation of the methyl group, which is present in all the C20 alkaloids, was achieved. Following the removal of the MOM protecting group, oxidative dearomatization of the resulting phenol afforded the dienone. This dienone was then heated to 150 °C to allow formation of the intramolecular Diels–Alder cycloaddition product 234, thus forming.
all the requisite rings for the C20 scaffold. The addition of the carbon atom on the bicyclo[2.2.2] structure of 234 was achieved by Wittig methylenation and ketal hydrolysis to afford 235 and a modified Weitz–Scheffer epoxidation 81 to install an \( \alpha \)-epoxide thus forming 237. The epoxy ketone 237 was then treated with a solution of HBr/AcOH at 110 °C effectively cleaving the methyl carbamate and the methyl group on the C1 hydroxyl; the reaction mixture was quenched with NaOH, then treated with Ac2O and pyridine to form intermediate 238. Functional group manipulations of 238 gave cochlearenine (59) which was coupled with veratroyl chloride to produce N-ethyl-1\( \alpha \)-hydroxy-17-veratroyldictyzine (61) in 25% yield, and its protonated TFA salt form 241 upon treatment with TFA. Finally, treatment of 59 with \( \text{H}_2\text{O}_2 \) gave paniculamine (63) in 50% yield.52

2.3.8 Total Syntheses of (\( \pm \))-Spiramilactone B, (\( \pm \))-Spiraminol, (\( \pm \))-Dihydroajaconine, and (\( \pm \))-Spiramines C and D

The strategy employed by Xu and co-workers in 2016 focused on targeting 242 as the entry point into this multi-target synthesis (Scheme 17).54 This tricyclic intermediate 245 was accessed in large quantities, over two steps, as a single diastereomer, in excellent yields.82,83 This tricyclo[6.2.2.01,6] structure 245 was then taken through a series of functional group transformations to afford intermediate 246, which was converted into 247 at C10 by treatment with lithium diisopropylamide and 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1\( \text{H} \))-one (DMPU) followed by addition of the electrophile 248 to give 249.

Scheme 16  Total synthesis of denudatine-type diterpenoid alkaloids cochlearenine, N-ethyl-1\( \alpha \)-hydroxy-17-veratroyldictyzine, and paniculamine
The alkynyl-substituted ester 249 was desilylated and acylated, and then subjected to Ru-catalyzed cycloisomerization to give tetracyclic ketone 250 as a single diastereomeric product. To set up for the bridged core structure, intermediate 250 was treated with LiBEt₃H, the C₆–C₇ olefin was epoxidized using m-CPBA, and the free hydroxyl group was protected; regioselective epoxide opening catalyzed by [Ti(O₂i-Pr)₂Cl₂] afforded the formation of hydroxy γ-lactone 251, thereby completing the pentacyclic core structure. This γ-lactone 251 was rearranged to the δ-lactone 252 over a few synthetic manipulations. Treatment of 252 with ozone gave the ketone which was converted into a terminal olefin by Takai olefination; this lactone was then partially reduced to the aldolactol, followed by condensation with MeOH to afford 253. A hydroboration–oxidation reaction on the olefin of 253 allowed access to the primary alcohol, which was converted into the aldehyde, thus allowing for selective alkylation on treatment with potassium tert-butoxide and methyl iodide. The lactone 255 was directly accessed by a Pinnick oxidation of 254 and completed the
core skeleton of spiramilactone B \( (259) \). At this point only a few tailoring steps were required to access the specific diterpenoids of the atisine type.\(^5\)

### 2.3.9 Total Syntheses of \((-\))-Methyl Atisenoate, \((-\))-Isoatisine, and a Hetidine Derivative

The Baran group developed a unified approach to ent-atisane diterpenoids and related alkaloids.\(^5\) As illustrated in Scheme 18, \((-\))-methyl atisenoate \((264)\), \((-\))-isoatisine \((29)\), and also \(268\), a hetidine skeleton, were synthesized starting from \((-\))-steviol \((261)\). The synthesis of ent-atisane started by methylation of \(261\) followed by treatment with Mukaiyama’s conditions,\(^87\) which led directly to diketone \(262\). Cyclization of \(262\) was realized by Amberlyst-15 promoted aldol reaction and then dehydration reaction with Martin's sulfurane gave exomethylene \(263\), which underwent Wolff–Kishner reduction and re-esterification to complete the synthesis of \((-\))-methyl atisenoate \((264)\). Intermediate \(266\) was obtained from \((-\))-steviol \((261)\) in 6 steps. Neopentyl iodide \(267\) was obtained after a Hoffmann–Löffler–Freytag reaction. Condensation with allylamine led to Mannich-type reaction cyclization and thus formed the hetidine skeleton \(268\) in good yield. The synthesis of the other diterpenoid alkaloid presented, \((-\))-isoatisine \((29)\), was also synthesized starting from intermediate \(266\). The ketone moiety on C13 was removed in 3 steps to give \(269\), C–H activation led to neopentyl iodide \(270\), which was subsequently transformed into alcohol \(271\). Installation of an exomethylene group into \(271\), followed by allylic oxidation and the subsequent condensation with ethanolamine gave \((-\))-isoatisine \((29)\).

### 3 Strategies to Synthesize Ring Systems

#### 3.1 Radical-Based Cyclizations

In 2016, Inoue and co-workers disclosed the use of a radical-based cyclization/translocation/cyclization process followed by an aldol cyclization for the synthesis of the fused hexacycle of puberuline C \((278)\) (Scheme 19).\(^88\) Treatment of tricycle \(272\) with \(n\)-Bu3SnH and \(273\) under refluxed conditions initiated a 7-endo cyclization from C11 to C10, followed by a 1,5-hydrogen abstraction from C7 to C17, and finally resulting in a transannular 6-exo cyclization from C17 to C8. The efficiency of this cascade is remarkable as five stereocenters (C8, C9, C10, C11, and C17) are introduced with the desired stereoconfiguration despite the moderate yield of \(274\) (54%). After treatment of \(274\)
with TBSOTf to give the silyl enol ether 275, variety of Lewis acids were screen for the intramolecular Mukaiyama aldol reaction of 275; this reaction was realized using \( \text{SnCl}_4 \) to activate the acetal moiety for the formation of the D ring in 277. The stereoconfiguration of C16 can be explained by the binding of \( \text{SnCl}_4 \) between the oxygen and nitrogen atoms in 276 which dictates the nucleophilic attack of the silyl enol ether on to the \( \text{silyl} \) face of the oxocarbenium ion. Subsequent steps installed the stereocenter at C14 of the hexacyclic core of puberuline C.

In 2016, Inoue and co-workers detailed the formation of the pentacyclic core of talatisamine (49) via radical and cationic cyclizations (Scheme 20).\(^9\) Treating 279 with \( \text{n-Bu}_3\text{SnH} \) and 280 (V-70) resulted in the formation of a stereochemically fixed C11 bridgehead radical 283 that underwent stereo- and regioselective 7-\( \text{endo} \) cyclization on to C10 to form the B ring in 284. Steric repulsion between the C5-TMS ether and C14-acetal moieties favored the transition state 283 over 281.

Purification of 284 with silica gel caused C14-oxygen \( \beta \)-elimination and C9 epimerization to form enone 285 and trans-fused 286 from the initial cis-fused 284, respectively. Treatment of 285 with NaH yields 286 in a 79% combined yield from 279. Pentacycle 286 was then converted into 287 in ten steps which were required to carry out a 6-\( \text{endo} \) cationic cyclization to install the D ring. The C15–C16 double bond was activated with PhSeCl, allowing attack by the TBS
enol ether to afford pentacycle 289. Finally, oxidation of selene 289 triggers a selenoxide elimination to give the pentacyclic core 290 of talatisamine (49).

In 2017, Inoue and co-workers disclosed a three-component coupling approach to append the AE ring systems to the C ring of C19-diterpenoid alkaloids in an expedient manner (Scheme 21).90 The strategy utilized a radical-polar crossover cascade initiated with Et3B/O2 and iodide 291 to form a bridgehead radical that first underwent conjugate addition with enone 292 on the opposite side of the OTBS substituent. The boron enolate intermediate 293 then underwent an aldol addition with alkynal 294 via the six-membered transition state 295 to form the coupled product 296. High chemoselectivity was demonstrated as no addition to the alkyne was observed. The simultaneous generation of three new stereocenters in a single step under mild reaction conditions proved to be an efficient method to provide the advanced intermediate for the synthesis of C19-diterpenoid alkaloids.

Another radical-based cyclization was adopted by Xu and co-workers in the synthesis of the BCD ring systems of 7,17-seco-type C19-norditerpenoid alkaloids (Scheme 23).93 It was shown that similar ring systems can be accessed via a [3+2] cycloaddition of a nitrile oxide. Bicyclic iodide 304 participated in a radical cyclization when treated with n-Bu3SnH and AIBN to form tricyclic lactone 305 which can then be transformed into 306, a key intermediate to the ABEF ring system of C19-norditerpenoids. The alternative approach utilized an intramolecular [3+2] nitrile oxide cycloaddition to form the tricyclic system. Oxime 307 was oxidized into the nitrile oxide upon treatment with NCS, and this nitrile oxide underwent an intramolecular cycloaddition to form tricycle 308. Cleavage of the N–O bond was achieved under hydrogenolysis conditions with Raney nickel to afford β-hydroxy ketone 309, which can then be transformed into the key tricyclic core 310.

### 3.2 Ruthenium-Mediated Enyne Cycloisomerization

Song, Qin, and co-workers drew inspiration from Trost’s ruthenium-mediated enyne cycloisomerization94 for the synthesis of the CD ring systems of aconitine (27) (Scheme 24).95 Chiral enyne 311 was treated with 50 mol% Cp-Ru(MeCN)3PF6 to give the five-membered ruthenacene 312 which then underwent β-hydride elimination followed by reductive elimination to give stereoisomers 313 and 314 in 2:3 ratio. Initial attempts were made with palladium catalysts, but they did not give cyclized products.

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**Scheme 22** 1,7-enyne reductive radical cyclization and double condensation for the synthesis of lycoctonine-type C19-norditerpenoids

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Wang, Xu, and co-workers utilized, in 2018, a 1,7-enyne reductive radical cyclization and double condensation for the synthesis of lycoctonine-type C19-norditerpenoid alkaloid (Scheme 22).91 1,7-Enyne 297, which was prepared from a previously reported intermediate,92 underwent a reductive cyclization to form the A ring of pentacyclic intermediate 298 when treated with n-Bu3SnH and AIBN. Double reductive amination of 299 with ethylenamine followed by an acetonide removal furnished the hexacycle 300 which was the precursor to the pentacyclic core of methyllycaconitine (301).
3.3 Reductive Coupling

In 2014, Xu and co-workers reported the synthesis of ABEF ring systems of lycocotonine-type and 7,17-seco-type C_{19}-norditerpenoid alkaloids starting from the trans-fused 6,7-bicycle 318 formed from a ruthenium-catalyzed diastereoselective enyne cycloisomerization protocol developed by Trost\textsuperscript{94} (Scheme 25). Treatment of bicycle 318 with \textit{m}-CPBA in the presence of catalytic TsOH resulted in the stereoselective epoxidation of the olefin with concurrent ring-opening by the ester group to give tricyclic lactone 319. A series of transformations on 319 afforded tetracycle 320. Finally, reductive coupling between the ketone and \textit{N},\textit{O}-acetal in 320 was accomplished using SmI\textsubscript{2} to form tetracycle 321 bearing the ABEF ring systems of Lycocotonine-type and 7,17-seco-type C_{19}-norditerpenoid alkaloids.

Sugita and co-workers reported a reductive cyclization strategy of \textalpha,\textbeta-epoxy ketone 322 to synthesize the CD ring system of aconitine (27) (Scheme 26).\textsuperscript{97} SmI\textsubscript{2} initiates the formation of samarium enolate 323 that subsequently underwent an intramolecular aldol cyclization with the pendant aldehyde. The reaction was expected to proceed through cyclic transition state 324. Initial reaction conditions either gave low yields of bicyclic ketone 325 or side products from premature protonation of 324 or with observed TES group migration. Optimized conditions with SmI\textsubscript{2} (6 equiv) and HMPA (24 equiv) furnished the desired product 327 in 71% yield.
3.4 Diels–Alder Reactions

Brimble and co-workers reported the enantioselective synthesis of the ABEF ring systems of methyllycaconitine analogues (Scheme 27).98 The elegant approach utilized sequential Diels–Alder reaction, aldol, Mannich, and Wacker-type cyclizations to furnish the tetracyclic scaffold 337. The enantioselective synthesis commenced with a cobalt(III)–salen complex 331 catalyzed Diels–Alder reaction between enal 329 and diene 330 to give the endo-adduct 332 in excellent yield and enantioselectivity; the benzyl group on the amine was necessary to affect high enantioselectivity. The endo-adduct 332 was then treated with LDA to promote intramolecular aldol cyclization between the ester and the aldehyde to give β-hydroxy ester 333. A three-step sequence ending with an intramolecular Mannich reaction was used to construct the ABEF ring system 334. Reduction of the ketone in 334 gave alcohol 335, which underwent an intramolecular Wacker-type oxidative cyclization to install the F ring of the tetracycle 336. Subsequent transformations provided alcohol 337, representing the ABEF scaffold of methyllycaconitine analogues.

Xu, Wang, and co-workers initiated the synthesis of the AEF ring systems of C_{19}-norditerpenoid alkaloids with a stereoselective intramolecular Diels–Alder reaction (Scheme 28).99 The cycloadduct furnished the bicyclic lactone 341 with 5:1 endo selectivity thus establishing the A ring of the target. Subsequent transformations provided the N-protected aminoaldehyde 342. Deprotection of the Boc group in 342 under acidic conditions was followed by intramolecular Mannich reaction to furnish the tricyclic ketone 343, thus completing the synthesis of the AEF ring systems.

Barker and co-workers drew inspiration from the work of Yang and co-workers100 by applying a tandem Diels–Alder/Mannich reaction for the construction of the AE ring systems of Delphinium alkaloids (Scheme 29).101 A titanium-mediated [4+2] cycloaddition was carried out between the α-[[[(cyanomethyl)amino]methyl]acrylate 344 and diene 345 to form cyclic enolate intermediate 346. This enolate intermediate then underwent an intramolecular Mannich reaction with the unmasked iminium ion to give bicyclic ketone 347, which mapped on to the AE ring...
systems of *Delphinium* alkaloids. Similarly, using the diene-containing a cyclohexene moiety 349 resulted in the formation of tricyclic ketone 350, which maps on to the ABE ring systems. Installation of the succinimide-bearing benzoyl group furnished the methyllycaconitine analogue 351. It was also shown that various derivatizations of the bicyclic core 347 could be used to give a wide variety of possible precursors of *Delphinium* and *Aconitum* alkaloids analogues (Scheme 30). Substitution patterns of methyllycaconitine (352), grandiflorine (353), talatisamine (354), delcosine (355), eldeline (356), inuline (357), ajacine (358), delvestine (359), and mahuim Sulfonylation of the alcohol in 371 with PIDA in the presence of methanol gave enone 372 thus constructing the BCD ring systems of C_{19}′′′norditerpenoid alkaloids. A similar PIDA-promoted oxidative cyclization strategy was applied by Xu, Wang, and co-workers to furnish the BCD ring systems of aconitine (27) (Scheme 32). Treatment of phenol 374 with PIDA in the presence of methanol resulted in the dimer 375. Fortunately, the desired cycloduct 376 was formed under thermodynamic conditions to induce a retro-[4+2]/intramolecular Diels–Alder reaction from 375; reduction of the ketone in 376 provided alcohol 377. Sulfonylation of the alcohol in 377 on exposure to triflic anhydride initiated the Wagner–Meerwein rearrangement to form tricyclic alcohol 378, containing the BCD ring systems of aconitine (27), from intermediate 379.

3.5 Oxidative Dearomatization/Diels–Alder Sequence

One of the extensively used strategies in syntheses of diterpenoid alkaloids and related diterpenes is the oxidative dearomatization/Diels–Alder cycloaddition cascade. Xu, Wang, and co-workers also demonstrated the synthetic versatility of the Diels–Alder reaction by applying it to the synthesis of the BCD ring systems of C_{19}′′′norditerpenoid alkaloids (Scheme 31). An intramolecular Diels–Alder reaction of a masked o-benzoquinone 243 developed by Liao and co-workers was applied to synthesize the tetra cyclic ketone 245. PIDA-mediated oxidative dearomatization of phenol 242 in the presence of methanol gave diene 243 that underwent an intramolecular [4+2] cycloaddition to give 245. Subsequent transformations of 245 formed trflate 369, which underwent Wagner–Meerwein rearrangement, an alkyl shift with extrusion of the triflate group, in the presence of DBU and DMSO to form carbocation 370 that was trapped by DMSO giving 371. Elimination of dimethyl sulfide from 371 gave enone 372 thus constructing the BCD ring systems of C_{19}′′′norditerpenoid alkaloids.

Scheme 29 Tandem titanium-mediated Diels–Alder/Mannich reaction for the construction of the ABE ring systems of *Delphinium* alkaloids.

Scheme 30 Derivatization of a bicyclic ketone to furnish various syn thons for *Delphinium* and *Aconitum* alkaloids.
The Sarpong group presented studies in 2014 on C20-diterpenoid alkaloids, showing the synthesis of hetidine framework and its conversion into the atisine core structure.104 Starting from commercially available β-keto ester 380, advanced intermediate 381 was obtained in 14 steps. Treatment of 381 with the hypervalent iodide reagent [bis(trifluoroacetoxy)iodo]benzene (PIFA) facilitated oxidative dearomatization to give cyclic carbamate 383. A sequence of dihydroxylation, periodate cleavage, and Michael addition, promoted by simple stirring with silica gel in dichloromethane, gave aldehyde 384. Hydrogenation and aldehyde reaction gave synthon 385 (Scheme 33).
The versatile synthons 385 were used to synthesize compound 386 having the atisine carbon skeleton in 2 steps (Scheme 34). The same synthon was also used to synthesize dihydronavirine (387), which unfortunately could not be converted into the natural product navirine.

In a methodological study, Chen and Wang presented an efficient synthesis of the C/D rings (Scheme 35) of atisine-type C20-diterpenoid alkaloids.105 The synthesis also relies on the oxidative dearomatization/intramolecular Diels–Alder strategy. Xu and co-workers accessed the core ring systems of Spiraeea atisine-type diterpenoid alkaloids through a bio-inspired synthetic route.106 A four-step process led from commercially available methyl cyclohex-1-enecarboxylate (391) to trans-decalin 392 (Scheme 36). Epoxidation of 392 in the presence of catalytic amounts of TsOH gave γ-lactone 393. Intermediate 393 was converted into δ-lactone 394 in 4 steps; a further 8 transformations led to tetracyclic lactone 395. This synthon was successfully converted into pentacyclic target 396, featuring the ABEFG rings of spiramine C (64) and D (65).

### 3.6 Transannular Aziridination

Xu and co-workers reported a PIDA-promoted intramolecular transannular aziridination strategy for the formation of the AEF ring systems of lycoctonine-type C19-norditerpenoid alkaloids (Scheme 37).107 Starting from symmetric 397, intermediate 398 was obtained in 5 steps. β-Keto acrylate 399 was subjected to TiCl4-mediated conjugate propargylation108 followed by a gold(I)-catalyzed cyclization109 to afford the β-keto ester 400. Subsequent transformations of 400 furnished the amine 401 ready for intramolecular transannular aziridination. Initial conditions developed by Nagata and co-workers using lead(IV) acetate did not provide the desired product.110 It was found that using PIDA together with silica gel as an additive gave the optimal yield of the aziridine 402. Finally, regioselective ring cleavage was achieved with ethyl iodide and DMF followed by treatment with NaOAc to give the tricyclic amine 403 that models the AEF ring systems of lycoctonine-type C19-norditerpenoid alkaloids.

The racemulsonine family has been an evasive core in terms of successful attempts at its total synthesis. However, work by Wang and co-workers has made it significantly easier to access the 10-azatricyclo[3.3.2.04,8]decane precursor towards the final product (Scheme 38).111 The strategy employed towards this synthesis of the cage-like azatricyclic skeleton was fashioned after the intramolecular aziridination reaction by Nagata and co-workers,110 transforming the unsaturated primary amine 409 to afford the bridged aziridine 410 that will later be transformed into 415. Starting with diol 404, it was globally...
protected and then converted into the β-ketoester 405 in four steps. This diprotected diol 405 was then treated with DDQ to provide the conjugated enone,112 which underwent conjugate propargylation with allenyltriphenylstannane yielding 406. A Au(I)-catalyzed annulation via a modified Toste conditions109 accessed the cis-fused cyclopentene scaffold 407 as a single diastereomer, thus completing the A/F ring core. Reduction of the ketone in 407 and protection with Mel installed the final C3–OMe group, and this was followed by deprotection of the benzyl protecting groups and monoprotection with TBSCl to afford the product as a mixture of the desired and undesired isomers (1.2:1); the alcohol was transformed into the primary amine 401. A modification of the method by Nagata and co-workers using 401 with PIDA and K₂CO₃ in 1,2-dichloroethane at 55 °C gave the optimized yields of 402. The selective aziridine ring cleavage was then achieved by treatment of 402 with acetic anhydride, yielding the 10-azaatricyclo[3.3.2.0^4,8]decane core (OAc analogue of 409) as a single regio- and stereoisomer in an excellent 90% yield. Notably, the direct introduction of the N-ethyl group to form the tricyclic amine was achieved by treatment of 402 with ethyl iodide followed by NaOAc to give N-ethyl tricyclic amine 403.113 This work was expanded in 2016113 by using exo-cyclization under radical conditions to furnish the B ring, thus expanding the scaffold. With just a few tailoring steps they were able to access 410 from compound 409, and cyclization occurred upon treatment of 410 with n-Bu₃SnH and AIBN under reflux conditions in benzene to give 411 in 75% yield. At this stage, the ABF core was completed, and with minor tailoring, the scaffold was further functionalized to give 412 which allows for further elaborations. This was an important development as this synthesis brought the work of Xu and co-workers much closer to the final racemulosine core.

### 3.7 Intramolecular [5+2] Cycloaddition

The synthesis of a 6/5/6/7 ring system (Scheme 39) matching parts of the skeleton of C_{18}/C_{19}-diterpenoid alkaloids was reported by Liu and co-workers in 2018.114 The synthesis features an iron-catalyzed intramolecular [5+2] cycloaddition that they had reported earlier.115 Cycloaddition adduct 415 was transformed into tetracyclic synthon 416 in 3 steps. It was also demonstrated that the chemoselective reduction of a ketone moiety is feasible.

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**Scheme 38** Synthetic studies towards racemulosine

**Scheme 39** Synthesis of the tetracyclic 6/5/6/7 core skeleton of C_{18}/C_{19}-diterpenoid alkaloids
ing synthon 417 features the A, B, and F rings and the precursor of the C/D ring system of the diterpenoid alkaloid skeletons.

3.8 Miscellaneous

The Sarpong group aimed to study the structural activity relationship of aconitine (27) and the variation of substituents on the D ring while maintaining the structure of the AEF ring systems (Scheme 40).116 Starting with vinylnitrile 88, aryl nucleophiles with different substitution pattern were appended in a conjugate fashion under Hayashi-type Rh-catalysis117 or with the Cu-mediated strategy to give conjugate addition product 418. Subsequent elaborations on the products afforded tetracycle 419 or the dearmatized spirocycle 420.

An expedient synthesis of the AE ring systems bearing a 5β-hydroxy group for C19-norditerpenoid alkaloids was reported by Wang and co-workers utilizing a series of intramolecular Claisen condensation, double Mannich reaction, and stereoselective aldol addition (Scheme 41).118 Starting with keto carbonate 422, Claisen condensation followed by methylation furnished the bicyclic β-keto lactone 423. Double Mannich reaction with benzylamine in the presence of formaldehyde installed the E ring to give 424. Finally, stereoselective addition of a carbonyl group dictated by the 1β-substituent formed the 5β-hydroxy group in 425.

4 Conclusion

The diterpenoid alkaloids have proven to be an intriguing and challenging target to researchers worldwide. A century following their discovery, synthetic strategies towards diterpenoid alkaloids have continuously expanded. Herein, we summarized synthetic efforts over the past decade, discussing successful total syntheses and pioneering work towards future attempts of total syntheses. The current success can be viewed as an open door towards accessing unnatural derivatives of these diterpenoid alkaloids in an effort to tune the prevalent biological activities.

Despite the great successes reported, there are still challenging targets left to synthesize, which is especially true for the C19-diterpenoid alkaloids with aconitine (27) as the most popular representative. Further, it can be expected that natural product isolation will yield additional structurally challenging compounds with interesting biological activities.

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