

Recent Advances Towards Syntheses of Diterpenoid Alkaloids

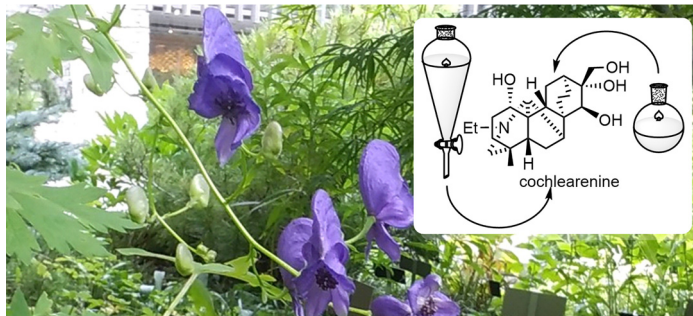
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Abstract The diterpenoid alkaloids serve as a rich source of synthetic targets for organic chemists, due to the intriguing structure of the overlapping ring systems, along with biological activities commonly associated with compounds of this group. 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.

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

While researchers worldwide are still discovering new compounds within this class from numerous plant species, these pseudoalkaloids have been traditionally linked to the *Aconitum*, *Consolidum*, 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.

1.1 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.^{2b} 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.

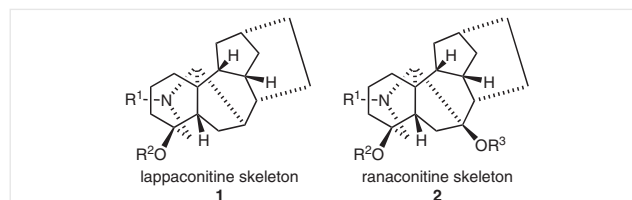


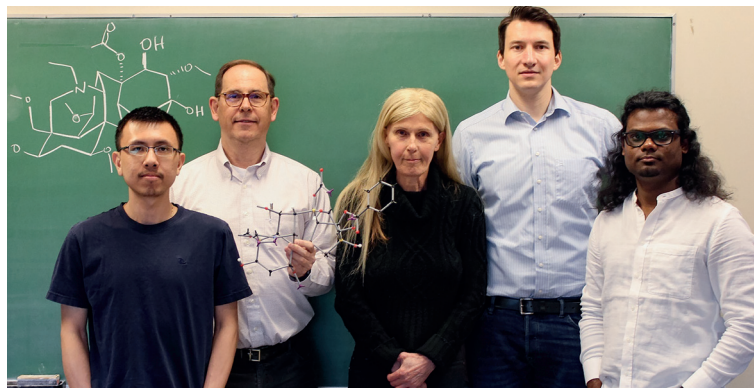
Figure 1 C₁₈-type diterpenoid alkaloid skeletons

1 Introduction

The diterpenoid alkaloids (C₁₈, C₁₉, and C₂₀) are a group of chemically and structurally complex natural products that possess a long list of pharmaceutical properties.¹ This list includes, but is not limited to, anti-inflammatory, analgesic, and antiarrhythmic properties.² Most of these properties are reported to be derived from interactions between the natural products and voltage-gated ion channels, particularly potassium and sodium channels.³

The C₁₉-diterpenoid alkaloids are the largest of the three groups and represent over 600 fully characterized molecules.^{1c} 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 lycoctonine-type **4** seemingly the most prevalent in Nature (Figure 2). The other

Biographical Sketches



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 chemobiosynthetic 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-open-

ing 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.

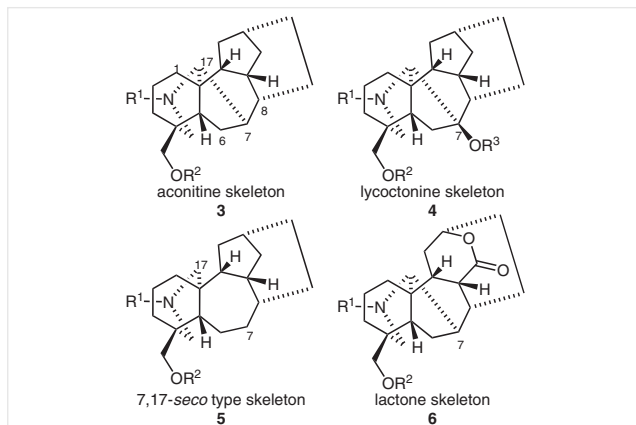


Figure 2 C_{19} -type diterpenoid alkaloid skeletons

The C_{20} -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**, albiovionidine **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 C_{18} - and C_{19} -diterpenoid alkaloids possess a [3.2.1]bicycle in the right side of their scaffolds, the majority of the C_{20} -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 C_{19} scaffolds **25** and C_{18} scaffolds **26**.

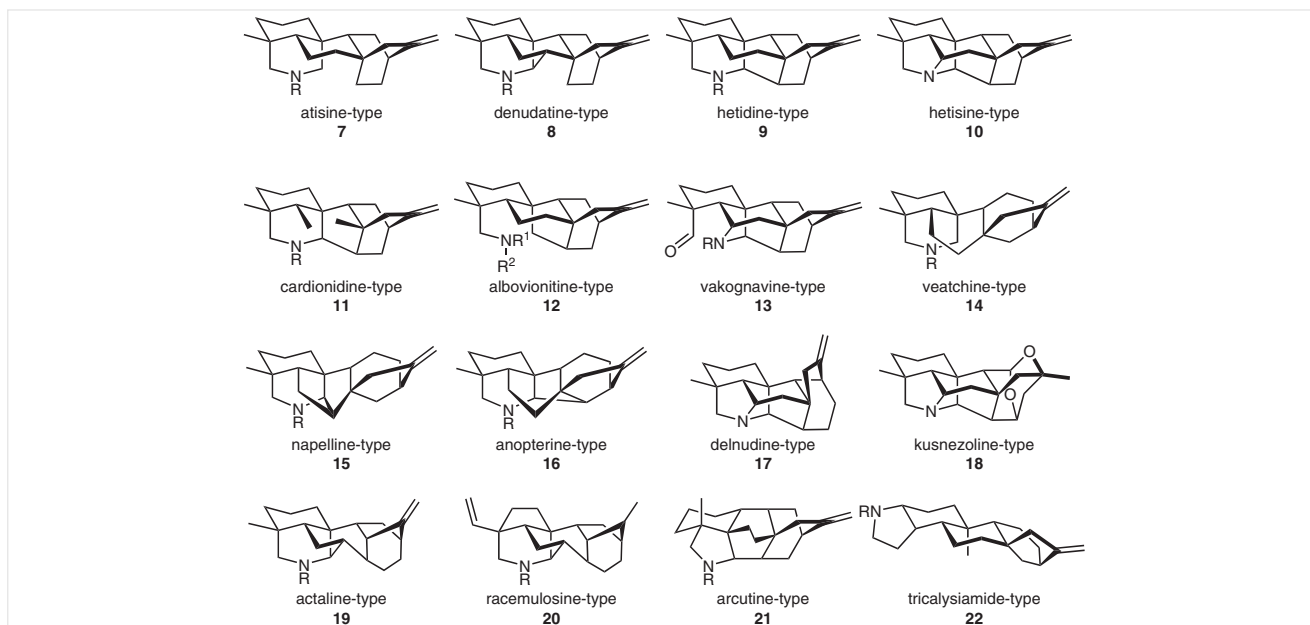


Figure 3 The 16 categories of the C_{20} -diterpenoid alkaloids

Table 1 Examples of Significant Total Syntheses by Compound and Year (see Figure 4)

Compound	1960s	1970s	1980s	1990s	2000s	2010s
C ₁₈ neofinaconitine (47)						2013 ²⁷
weisaconitine D (48)						2015 ²⁸
C ₁₉ talatisamine (49)		1974 ²⁹ 1975 ³⁰				
chasmanine (50)		1977 ³¹ 1978 ³² 1979 ³³				
13-desoxydelphonine (51)		1978 ³² 1979 ³³				
liljestrandinine (52)						2015 ²⁸
(–)-cardiopetaline (53)						2017 ³⁴
C ₂₀ atisine (28)	1963 ³⁵ 1964 ³⁶ 1966 ³⁷ 1967 ³⁸		1988 ³⁹	1990 ⁴⁰		2012 ⁴¹
garryine (54)	1964 ⁴² 1967 ⁴³					
veatchine (55)	1964 ⁴² 1967 ⁴³ 1968 ⁴⁴					
napelline (56)		1974 ⁴⁵	1980 ⁴⁶			
nominine (57)					2004 ⁴⁷ 2006 ⁴⁸ 2008 ⁴⁹	
(–)-isoatisine (29)						2014 ⁵⁰
lepenine (58)						2014 ⁵¹
cochlearenine (59)						2016 ⁵²
dihydroajaconine (60)						2016 ^{53,54}
N-ethyl-1 α -hydroxy-17-veratroyldictyzine (61)						2016 ⁵²
gymnandine (62)						2016 ⁵³
paniculamine (63)						2016 ⁵²
(\pm)-spiramine C (64)						2016 ⁵⁴
(\pm)-spiramine D (65)						2016 ⁵⁴
azitine (66)						2018 ⁵⁵
cossonidine (67)						2018 ⁵⁶
septedine (68)						2018 ⁵⁷

(**35**);²⁰ paspaline (**36**);²¹ paspalinine (**37**);²² ileabethoxazole (**38**), pseudopteroxazole (**39**), and *seco*-pseudopteroxazole (**40**);²³ (–)-anominine (**41**), (\pm)-terpendole E (**42**);²⁴ aflavazole (**43**) and 14-hydroxyaflavinine (**44**);²⁵ chamobtusin A (**45**);²⁶ and emindole PB (**46**).^{21b} However, these diterpenoids are not from the *Aconitum/Delphinium* family. Thus, the total syntheses of these natural products are not covered in detail in this review article.

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,⁵⁸ while the cyclo-

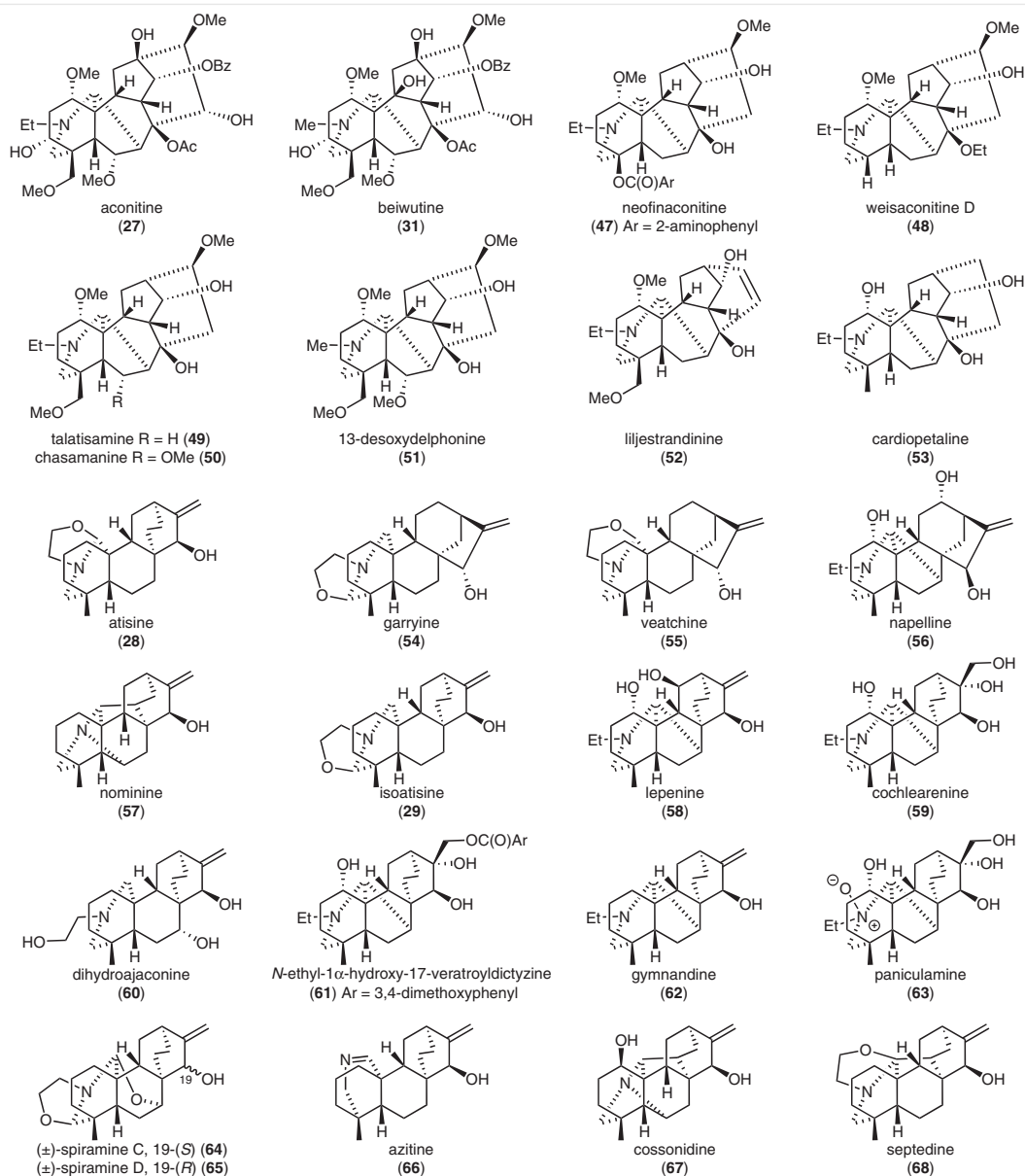


Figure 4 Structures of aconitine, beiwutine, and targets of total syntheses, listed in Table 1

propene starting material **70** was prepared in 6 steps from methyl acrylate.⁵⁹ Notably, due to the rapid Alder–ene dimerization of the cyclopropene intermediate, this compound was isolated and was used immediately in the cycloaddition reaction. The Diels–Alder cycloaddition was conducted by addition of intermediate **70** directly to the *in situ* prepared diene from intermediate **69**. Importantly, it was reported that attempts at isolating the enolization–silylation⁶⁰ product of **69** led to a difficult-to-control mixture of dimerized cyclopentadiene. Nonetheless, this direct addition to the *in situ* prepared diene allowed access to the desired product **71** as an inseparable mixture of diastereo-

mers (1:1.6). Given that the major diastereomer was the desired product, this mixture was taken through the next four steps to access intermediate **73** (39% over 6 steps). A series of functional group manipulations on intermediate **73** afforded access to diene **75** and set up the second intermolecular Diels–Alder cycloaddition between **75** and **76** catalyzed by SnCl₄.²⁷ This is notably an essential step as it afforded a key intermediate **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 β -bromide to form the

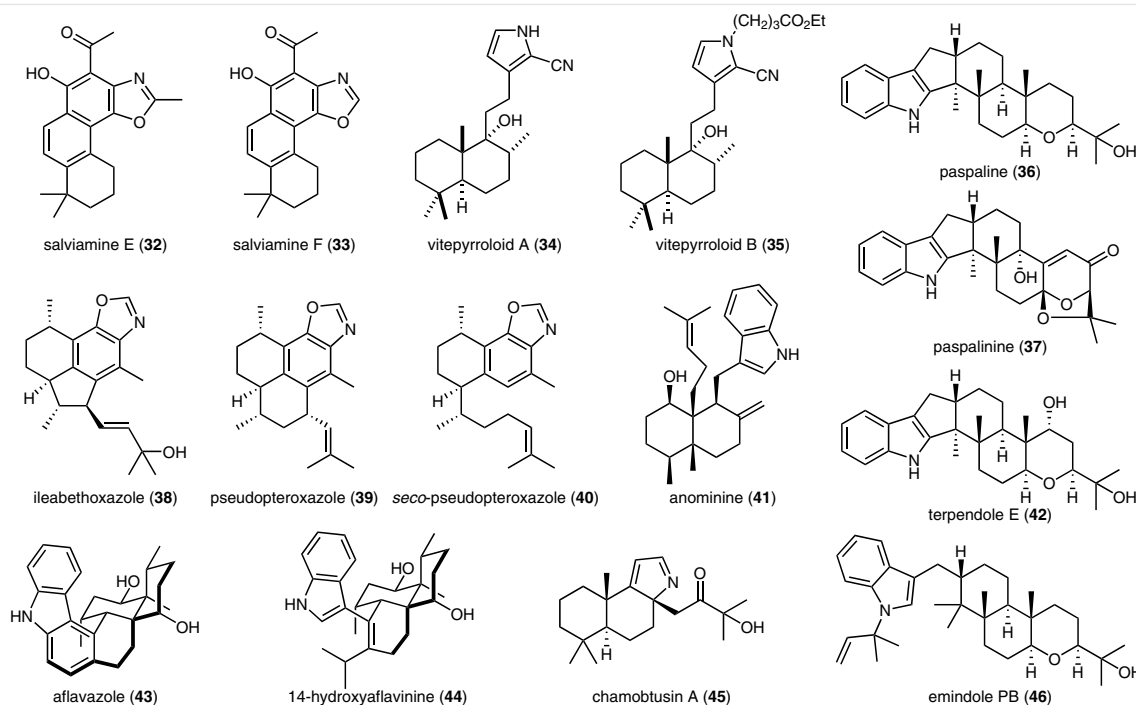


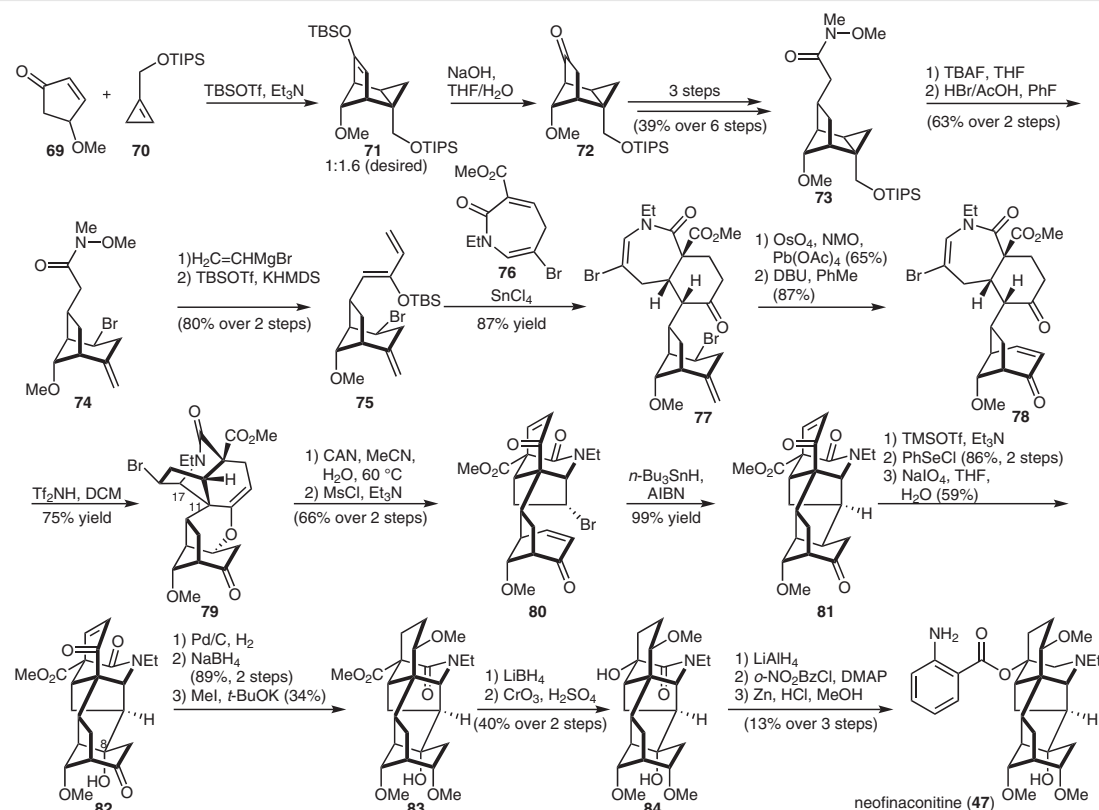
Figure 5 Recently synthesized structurally unique diterpenoid alkaloids

enone **78**. The Mannich-type *N*-acyliminium cyclization was achieved by treatment of intermediate **78** with TiF_2NH , 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 $\text{MsCl}/\text{Et}_3\text{N}$ 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 neofinaconitine 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

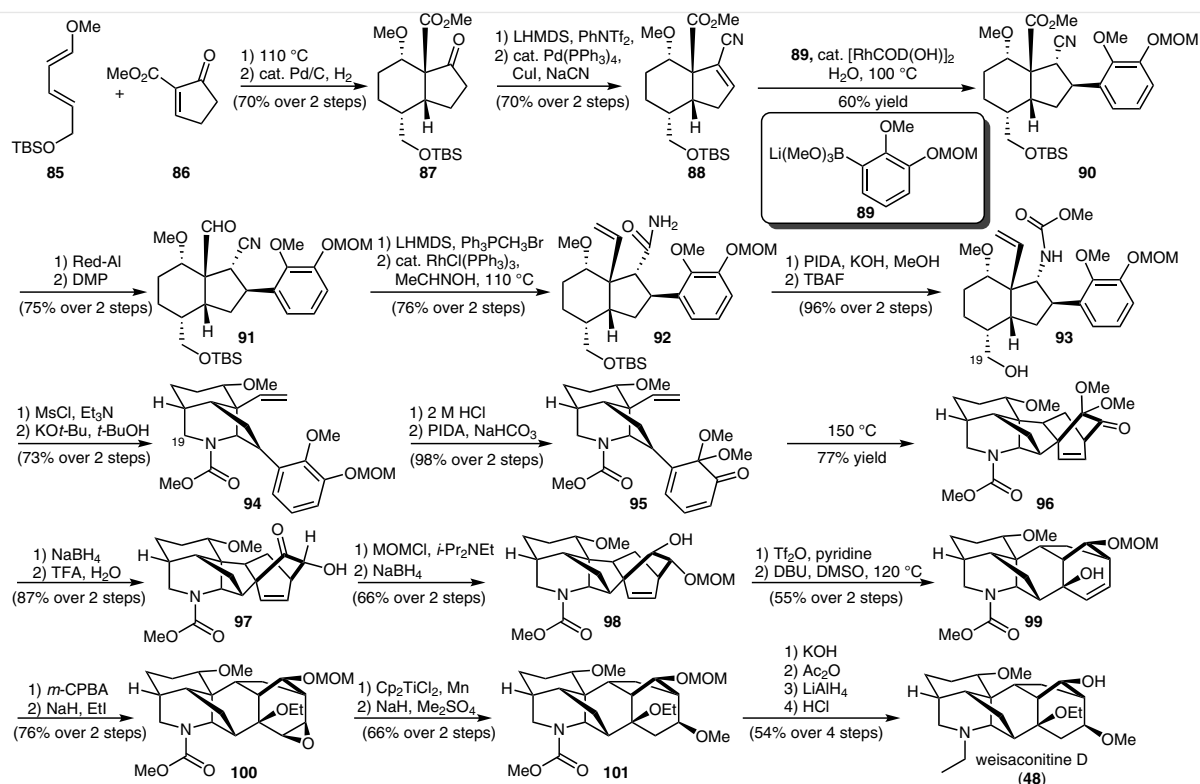
This divergent approach by Shi, Tan, and co-workers was achieved in 30 longest linear steps and afforded racemic neofinaconitine (**47**) from readily available materials.²⁷ It should be noted that this strategy offers numerous opportunities to access other types of the diterpenoid alkaloids and as such 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**⁶¹ and a cyclopentenone derivative **86**,⁶² 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 $\text{Pd}(0)$ -catalyzed cross-coupling with cyanide⁶³ afforded the α,β -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 (diacetoxyiodo)benzene [$\text{PhI}(\text{OAc})_2$, 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 KO*t*-Bu to form the C19–N bond, thereby fashioning the piperidinyl 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**.⁶ While several strategies were explored for a formal hydro-methoxylation 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 alkylation of the tertiary hydroxyl to provide **100**.²⁸ The epoxide was regioselectively opened⁶⁵ to give a β -disposed secondary alcohol group that was methylated to furnish **101** and thus this completed the D-ring of weisaconitine D. The methoxycarbonyl protecting group was removed, the nitrogen was acylated, and the acetamide was reduced using LiAlH₄. Finally, removal of the MOM protecting by acid treatment afforded the final product weisaconitine D (**48**) in a total of 30 steps.²⁸

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 (–)-cardiopetaline (**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.⁶⁶ Several groups have made strategic efforts towards the construction of the C₁₉ cores and the reported methodologies will be covered here.

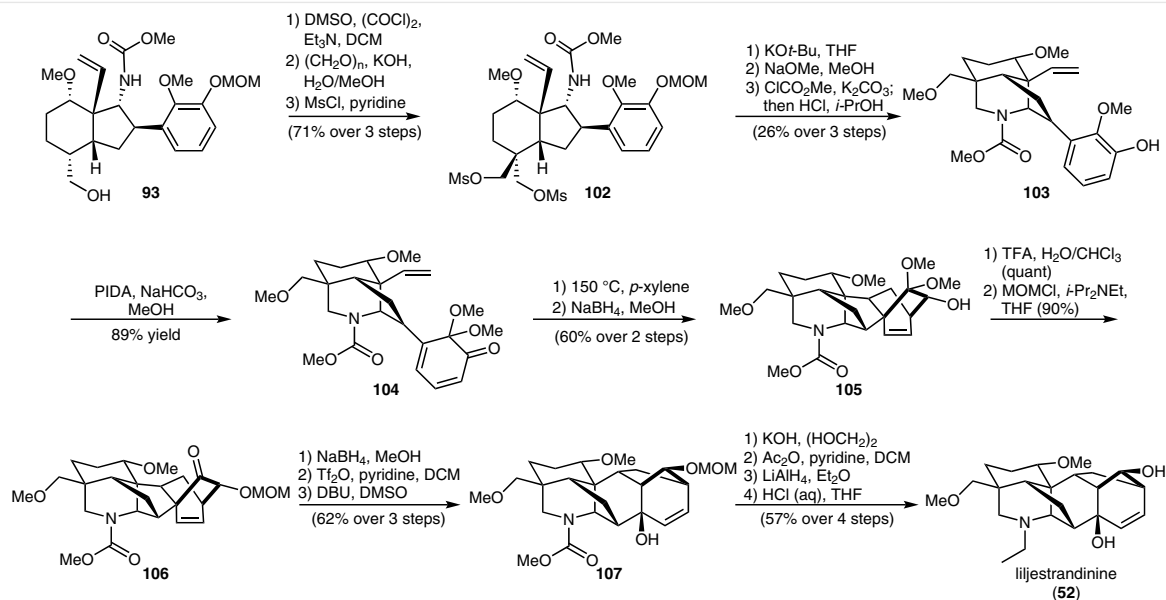
2.2.1 Total Synthesis of Liljestrandinine

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.

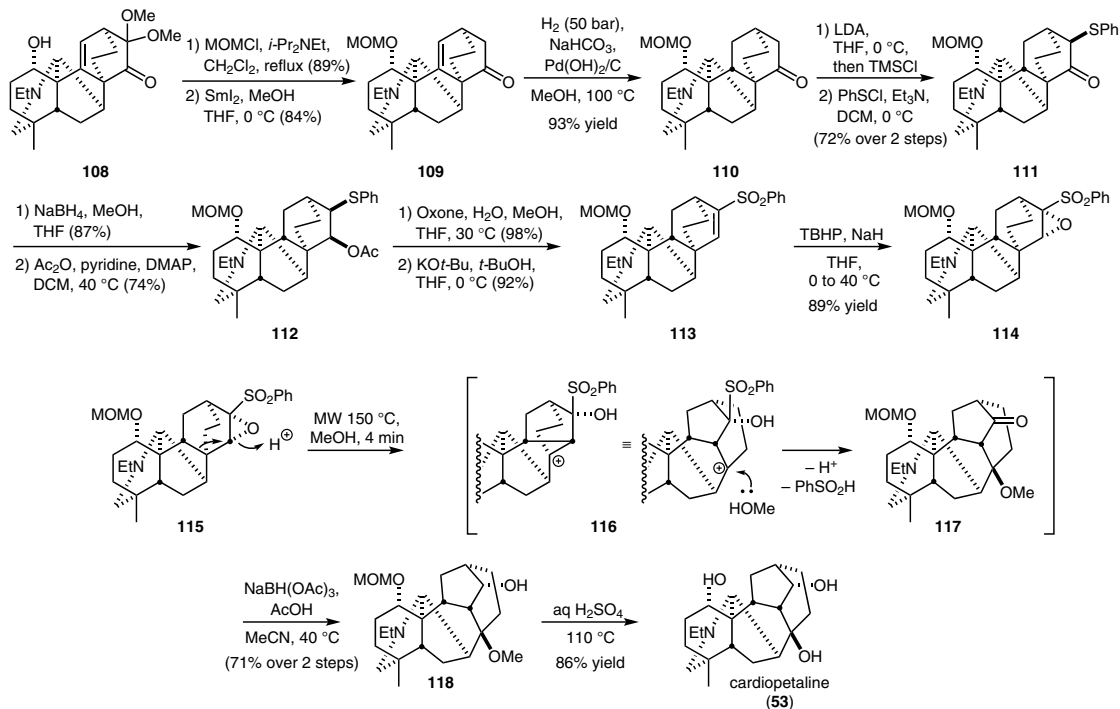
In a unifying approach to the C₁₈-, C₁₉-, and C₂₀-diterpenoid alkaloids, the Sarpong group accomplished the preparations of weisaconitine D (**48**), liljestrandinine (**52**), as well as the denudatine-type compounds cochlearenine (**59**), *N*-ethyl-1 α -17-veratrolydictyzine (**61**), and paniculamine (**63**).^{4a} The advanced intermediate **93** is common to all of these natural product syntheses.

2.2.2 Total Synthesis of (–)-Cardiopetaline

Fukuyama, Yokoshima, and co-workers disclosed a novel Wagner–Meerwein rearrangement of a sulfonyloxirane to construct the aconitine skeleton (Scheme 5).⁶⁷ Sulfonyloxirane **114** was synthesized from synthetic intermediate **108** en route to their previous reported total synthesis of lepenine.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 sulfonyloxirane **114** with the appropriate stereoconfiguration for a Wagner–Meerwein rearrangement.



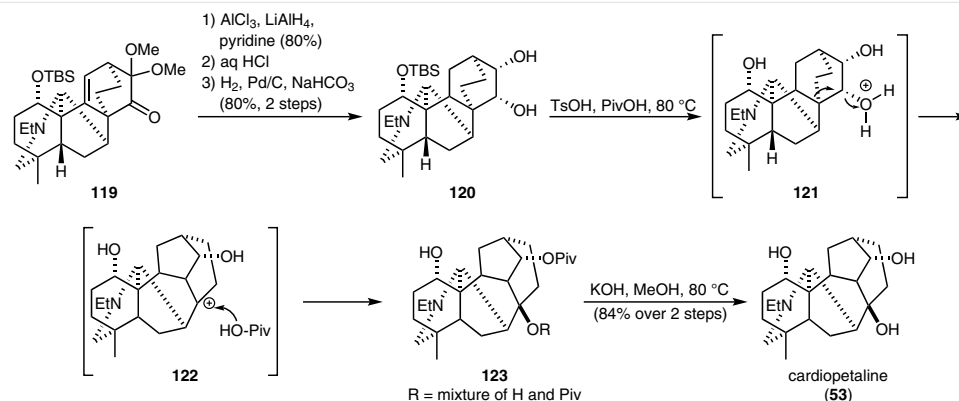
Scheme 4 Total synthesis of liljestrandinine



Scheme 5 Total synthesis of (–)-cardiopetaline via the Wagner-Meerwein rearrangement of a sulfonyloxirane

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.



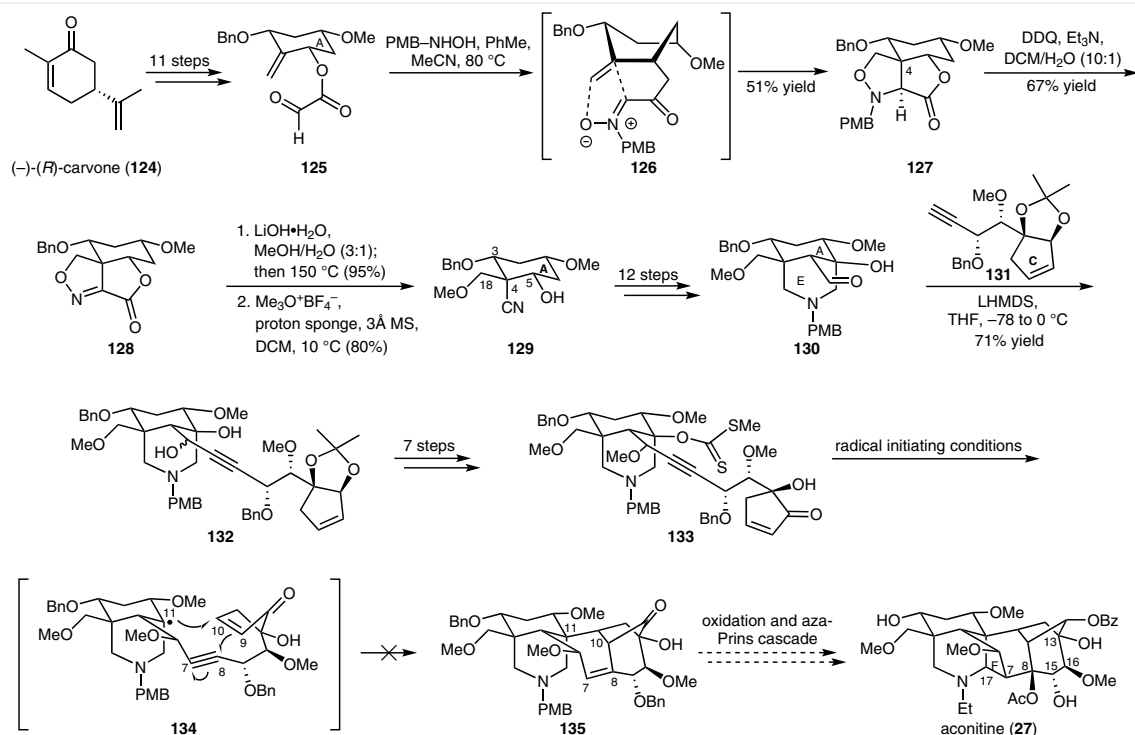
Scheme 6 Total synthesis of (–)-cardiopetaline via the Wagner–Meerwein rearrangement of a diol without pre-activation

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. Nitron **126** was generated *in situ* from



Scheme 7 Progress towards the total synthesis of aconitine

glyoxylate **125** when treated with *N*-PMB-hydroxylamine, which then induced an intramolecular [3+2] cycloaddition to give isoxazolidine **127** as a single diastereomer.

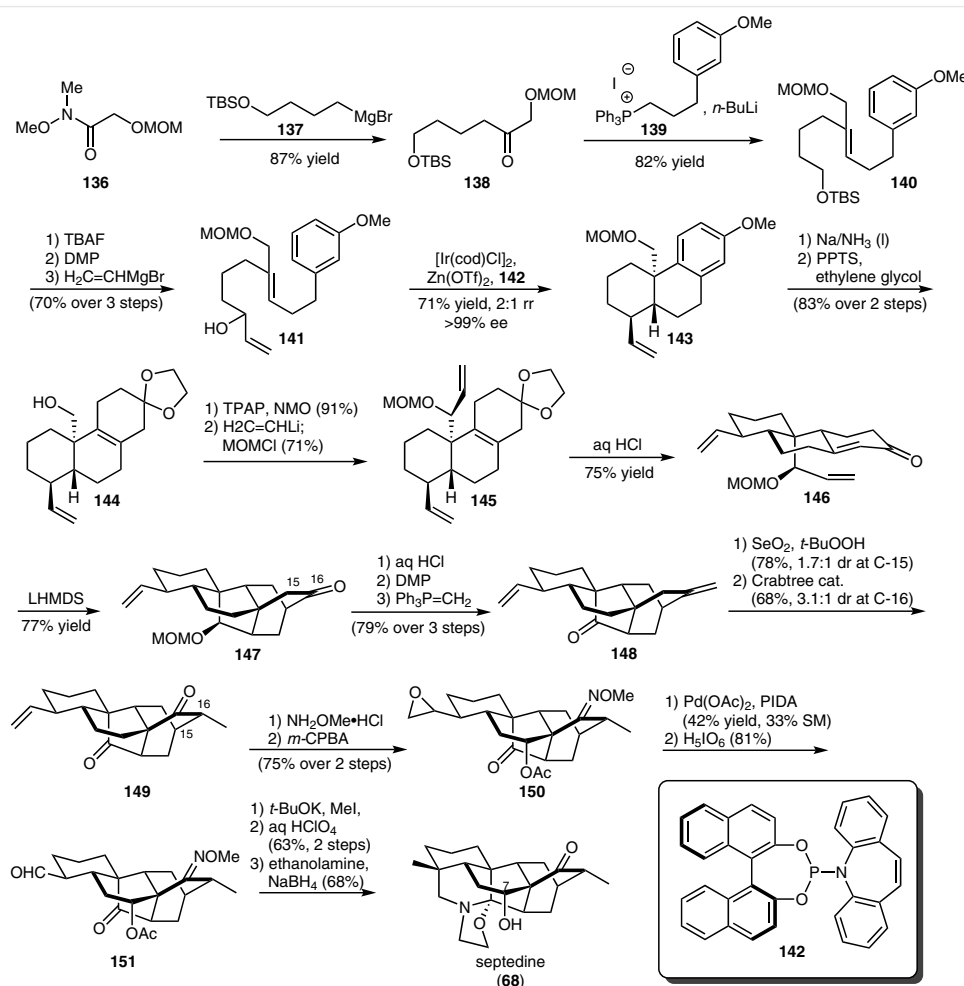
Deprotection of the *N*-PMB group followed by oxidation was achieved using DDQ to give imine **128**. Hydrolysis, followed by Krapcho decarboxylation, and selective methylation afforded β -hydroxynitrile **129**. Subsequent steps, including functional group manipulations and an intramolecular Mannich reaction, were carried out to build the E ring giving aldehyde **130**. Addition of the alkyne 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 alkyne 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 alkyne 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 C₂₀-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.⁵⁷ Septedine (**68**) is a hetidine type C₂₀-diterpenoid alkaloid bearing an oxygenated heptacyclic scaffold. Highlights of the total synthesis are shown in Scheme 8. Starting from Weinreb

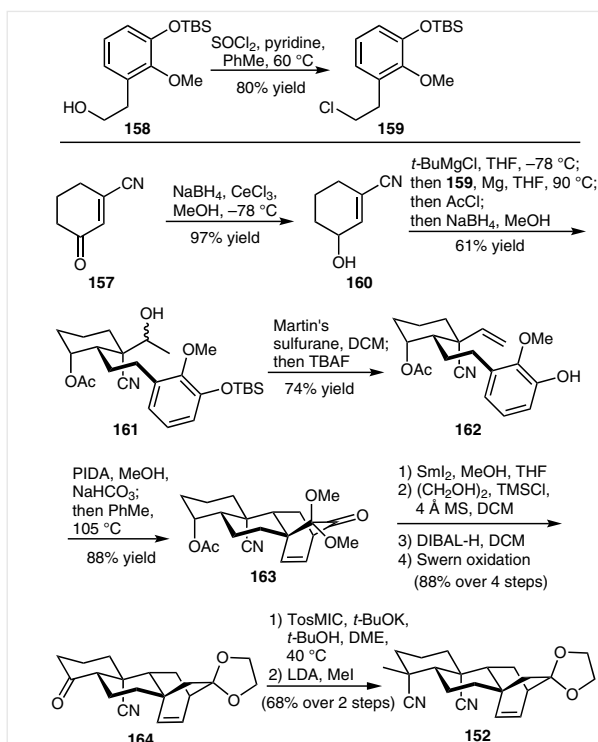


Scheme 8 Total synthesis of septedine

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

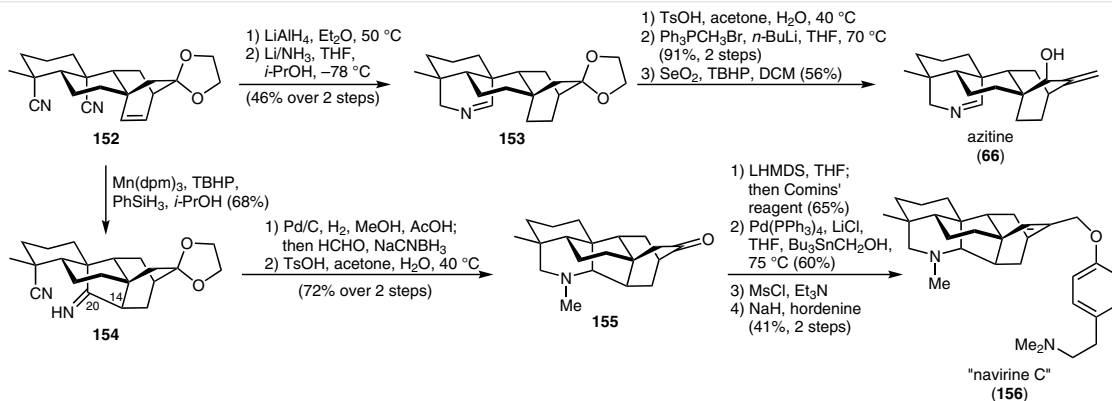
A unified approach to assemble atisine- and hetidine-type diterpenoid alkaloids was presented by Liu and Ma.⁵⁵ The total syntheses of azitine (**66**) and the reported structure of navirine C (**156**) are shown in Scheme 9. Both syntheses contain a common sequence from nitrile **157** to tetracyclic dinitrile **152** in 10 steps (Scheme 10). Reduction of **152** with LiAlH_4 and Li/NH_3 (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.



Scheme 10 Synthesis of the common intermediate for the total syntheses of azitine and the proposed structure of navirine C

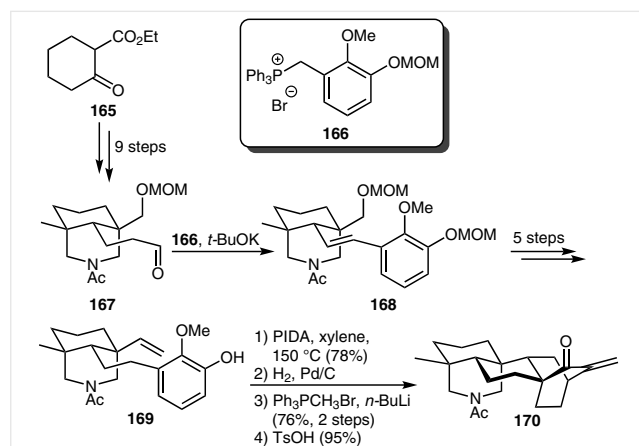
2.3.3 Formal Synthesis of (±)-Atisine

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 2012.⁴¹ As shown in Scheme 11, aldehyde **167** was accessible from commercially available ethyl 2-oxocyclohexanecarboxylate (**165**) in 9 steps. Wittig olefination gave styrene



Scheme 9 Total syntheses of azitine and the proposed structure of navirine C

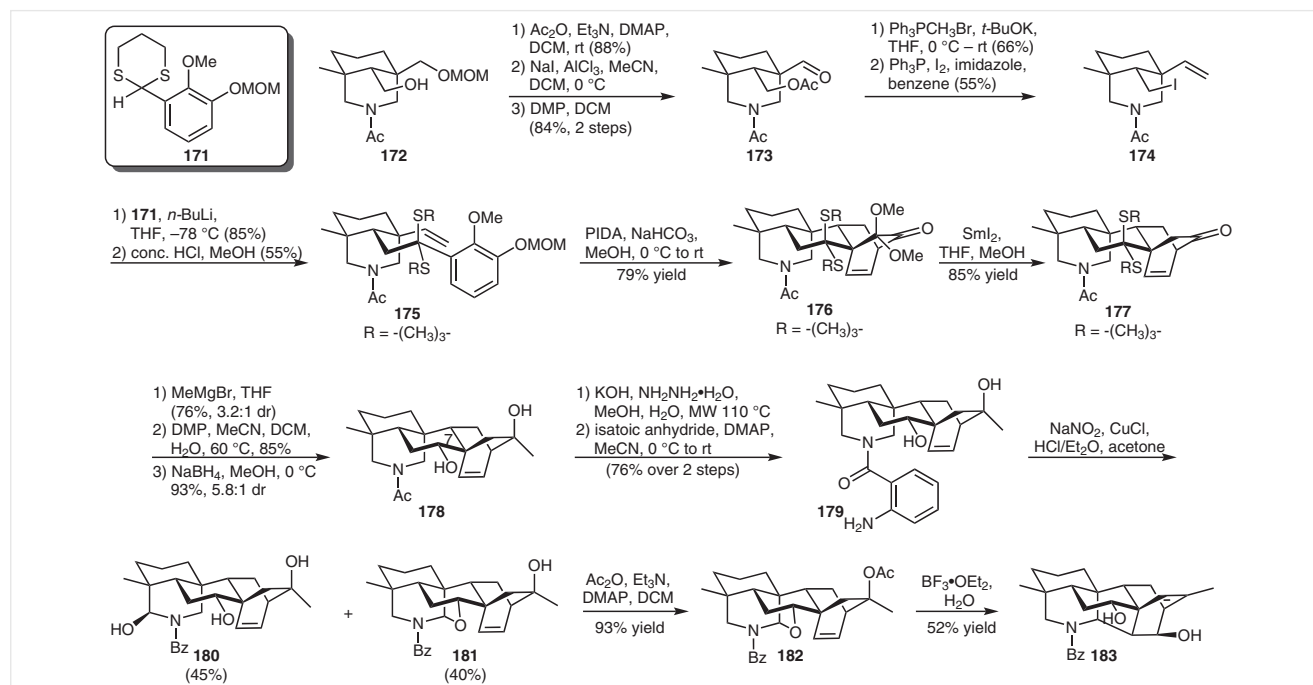
168, which was transformed into phenol **169** in five steps. Oxidative dearomatization and intramolecular Diels–Alder cycloaddition was followed by hydrogenation, olefination, and cleavage of an acetal group to give enone **170**. This intermediate was previously used by Pelletier and co-workers, and therefore this constitutes a formal synthesis of (\pm)-atisine (**28**).^{15,68}



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;^{53,69} Scheme 12 outlines the synthetic path. Starting from **172**,^{39,40} alkene **174** 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 **176**. The synthesis of this intermediate also concluded the synthesis of the pentacyclic atisine skeleton.

Intermediate **177** was treated with MeMgBr, the dithiane moiety was removed by reaction with Dess–Martin periodinane, and the resulting ketone was reduced to give diol **178**. Deacetylation and subsequent amide formation gave intermediate **179**, featuring the requisite C-7 hydroxy group and an *o*-aminobenzamide moiety. Aminal **181** was obtained after reaction with NaNO₂, CuCl, and HCl/Et₂O reported by Weinreb and co-workers.⁷⁰ A radical mechanism was postulated that proceeds *via* diazotization and a 1,5-H shift to form intermediate **181**, which has the ajaconine skeleton. Cyclization to give the desired hetidine-type product **183** was achieved by an aza-Prins reaction. Throughout the investigations, additional unwanted heptacyclic products were prepared (not shown).



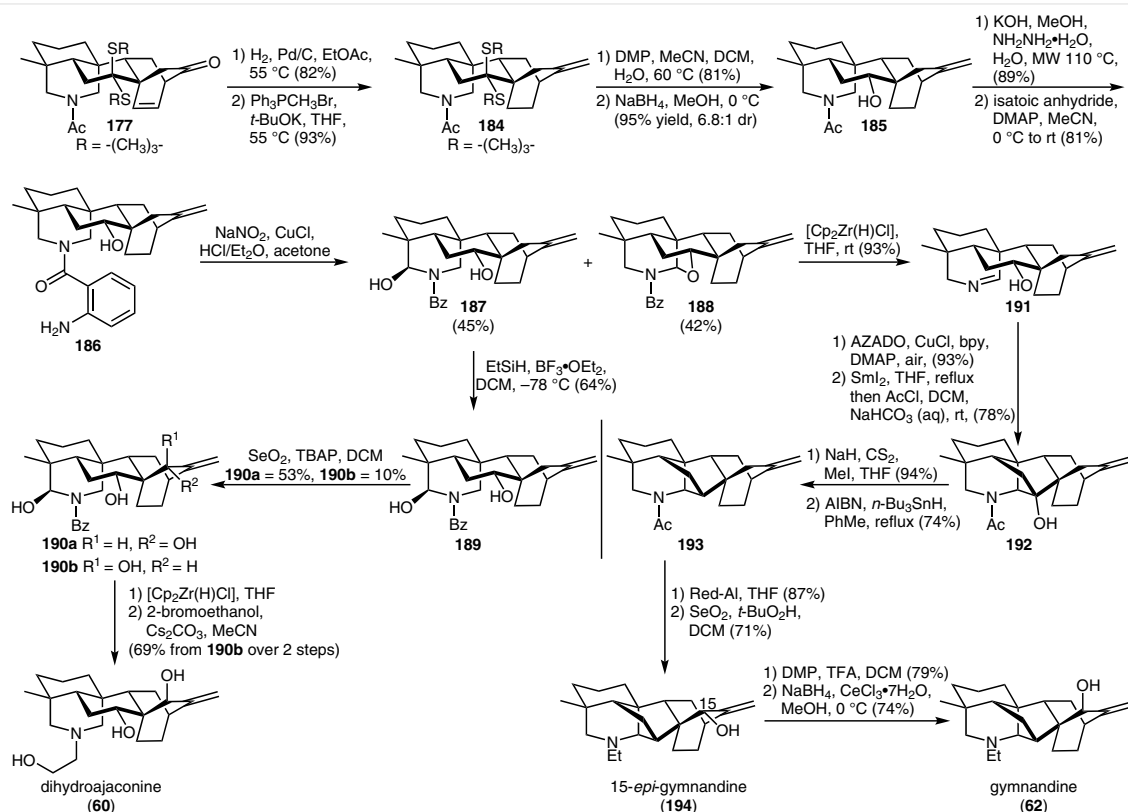
Pentacyclic intermediate **177** was also used by Qin, Liu, and co-workers as starting point for the syntheses of dihydroajaconine (**60**) and gymnandine (**62**) (Scheme 13).⁵³ Precursor **186** was subjected to the method developed by Weinreb and co-workers.⁷⁰ Hemiaminal **187** was then successfully transformed into the atisine-type alkaloid diterpenoid dihydroajaconine (**60**) in 4 steps.

Simultaneous cleavage of the amide C–N bond and the amination C–O bond of amination **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 Sml_2 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.

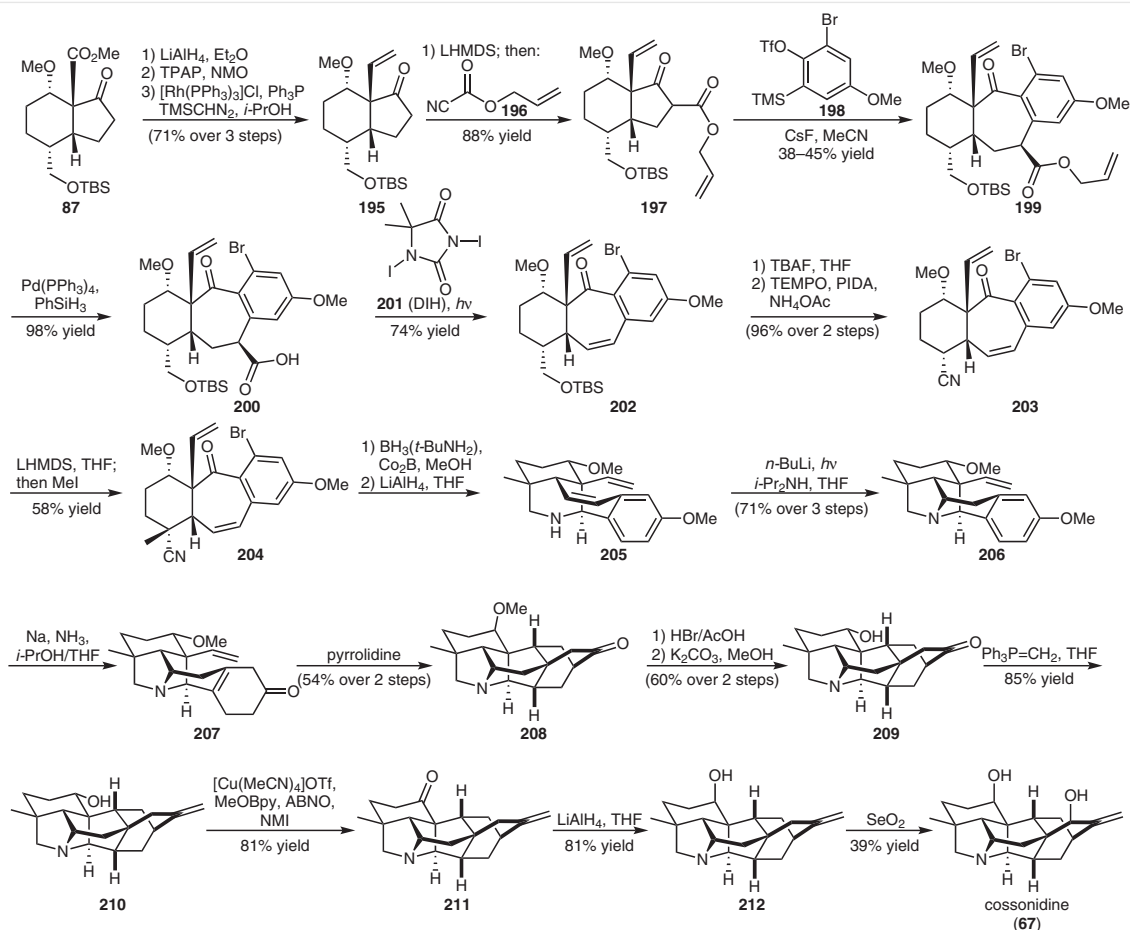
2.3.5 Total Synthesis of Cossonidine

The Sarpong group chose the hydrindanone **87**^{4a,28,52} as the entry point to their synthetic strategy (Scheme 14). They had previously enjoyed success towards the C_{18} -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

LiAlH_4 , 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 methylenation⁷⁴ was employed. Acylation of intermediate **195** was accomplished using allyl cyanofornate (**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 performed⁷⁶ using catalytic $\text{Pd}(\text{PPh}_3)_4$ and PhSiH_3 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 piperidiny ring. Treatment of **204** with a cobalt boride (Co_2B) and borane-*tert*-butylamine complex,⁷⁸ followed by treatment with LiAlH_4 to reduce the ketone and facilitate protodebromination, was accompanied by a serendipitous direct cyclization to form the N–C20 bond, thus accessing intermediate **205**. Photochemical



Scheme 13 Syntheses of dihydroajaconine and gymnandine; AZADO = 2-azaadamantane-*N*-oxyl



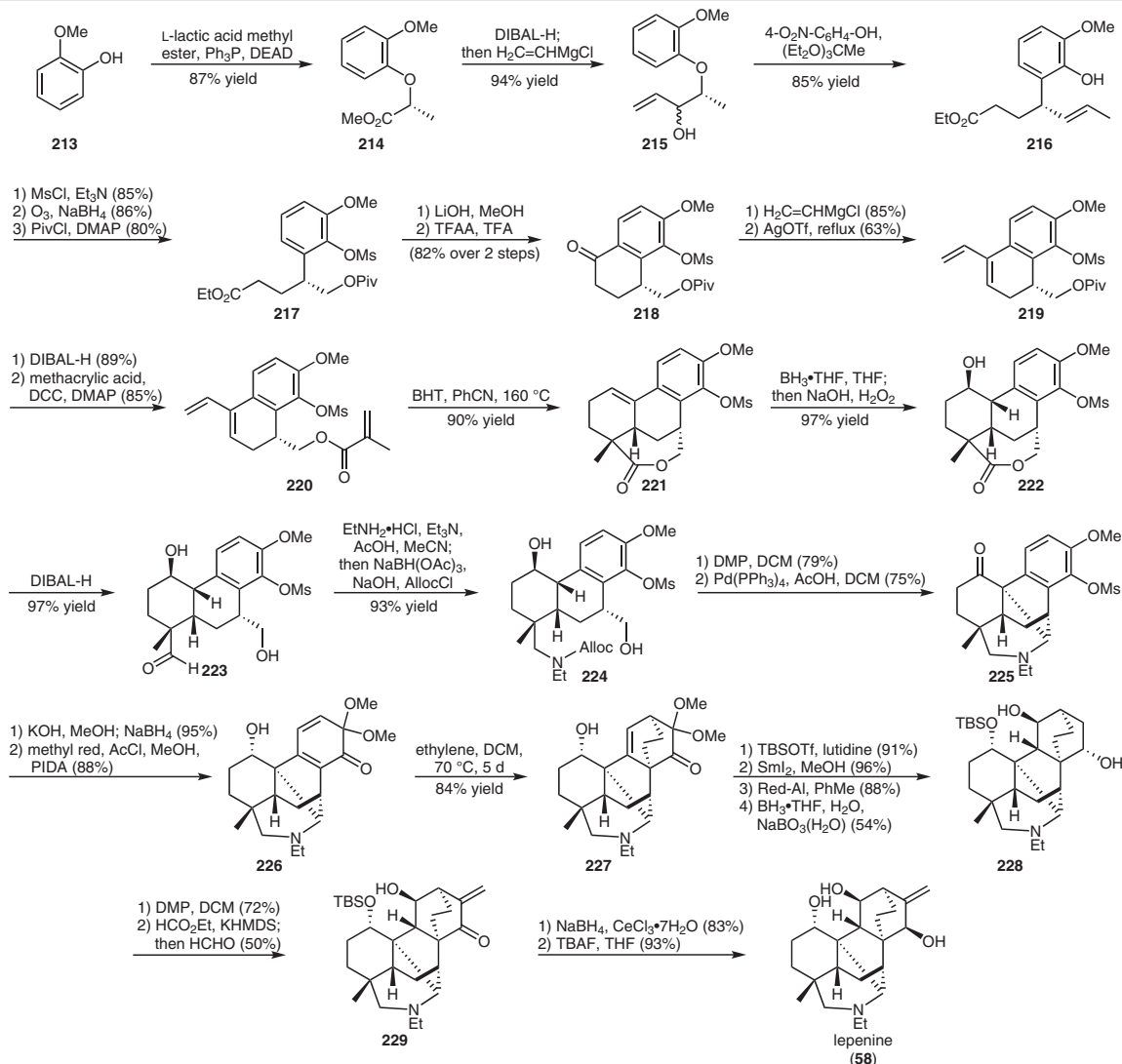
Scheme 14 Total synthesis of hetisine-type diterpenoid alkaloid cossonidine

hydroamination⁷⁹ afforded the tertiary amine **206**. The formation of the bicyclo[2.2.2] rings was effected through a Birch reduction/intramolecular Diels–Alder sequence⁸⁰ to give the structural core **208**. The selective cleavage of the C1 methyl ether was carried out using HBr/AcOH, followed by treatment with K₂CO₃ in methanol to yield the free alcohol **209**. Next, a standard Wittig methylenation was carried out to convert the ketone of **209** into an exocyclic methylene **210**, and thus completing the C₂₀ carbon scaffold for the hetisine-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**).⁵⁶

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).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(PPh₃)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–



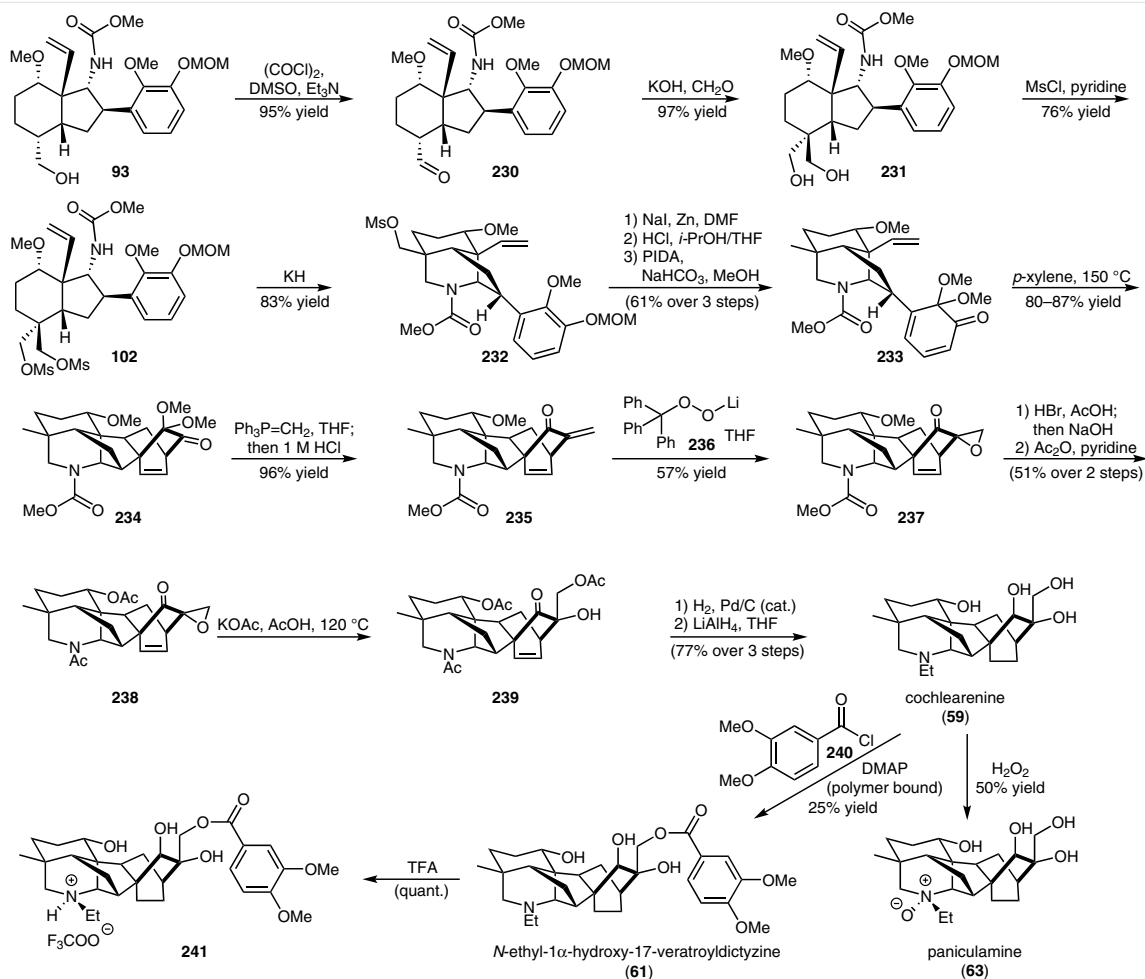
Scheme 15 Total synthesis of denudatine-type diterpenoid alkaloid lepenine

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-1 α -hydroxy-17-veratrolydictyzine, 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 **230** via a Swern oxidation. An aldol–Cannizzaro sequence on **230** afforded the diol **231**, which was then converted into the dimesylate **102** (76%). Intermediate **102** was treated with KH to effect the cyclization yielding **232** as the sole product. Next, the methylene *O*-mesylate group of **232** 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 **233**. This dienone was then heated to 150 °C to allow formation of the intramolecular Diels–Alder cycloaddition product **234**, thus forming

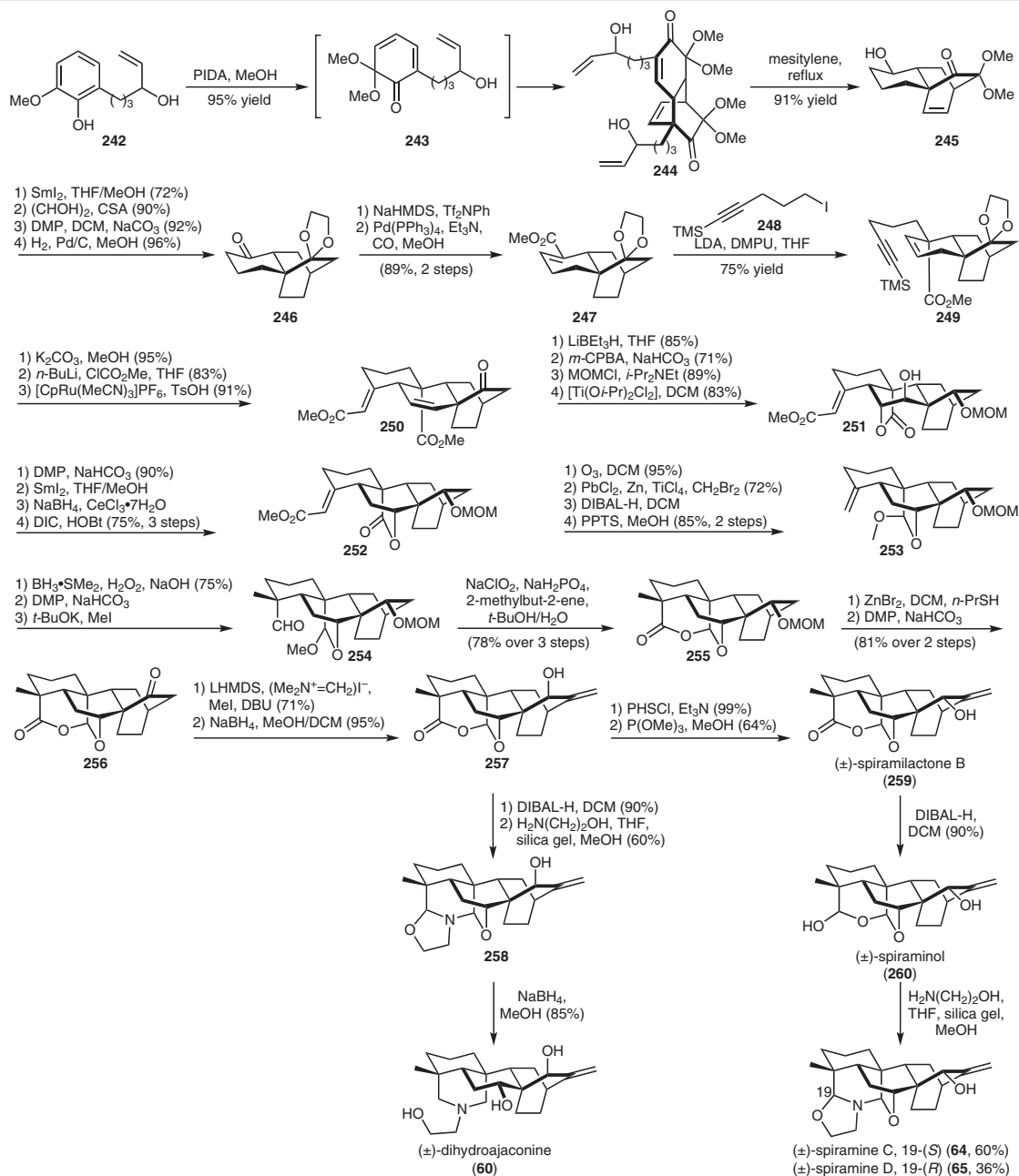


Scheme 16 Total synthesis of denudatine-type diterpenoid alkaloids cochlearenine, *N*-ethyl-1 α -hydroxy-17-veratroldictyzine, and paniculamine

all the requisite rings for the C_{20} 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 epoxidation⁸¹ to install an α -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 Ac_2O 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 α -hydroxy-17-veratroldictyzine (**61**) in 25% yield, and its protonated TFA salt form **241** upon treatment with TFA. Finally, treatment of **59** with H_2O_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[6.2.2.0^{1,6}] structure **245** was then taken through a series of functional group transformations to afford intermediate **246**, which was converted into the α,β -unsaturated methyl ester **247**. This key scaffold **247** was alkylated⁸⁴ at C10 by treatment with lithium diisopropylamide and 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) followed by addition of the electrophile **248** to give **249**



Scheme 17 Total synthesis of atisine-type diterpenoid alkaloids spiramillactone B, spiraminol, dihydrojaconine, spiramine C, and spiramine D

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 LiEt₃H, the C6–C7 olefin was epoxidized using *m*-CPBA, and the free hydroxyl group was protected; regioselective epoxide opening catalyzed by [Ti(O*i*-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;⁸⁵ 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 oxidation⁸⁶ of **254** and completed the

core skeleton of spiramylactone B (**259**). At this point only a few tailoring steps were required to access the specific diterpenoids of the atisine type.⁵⁴

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

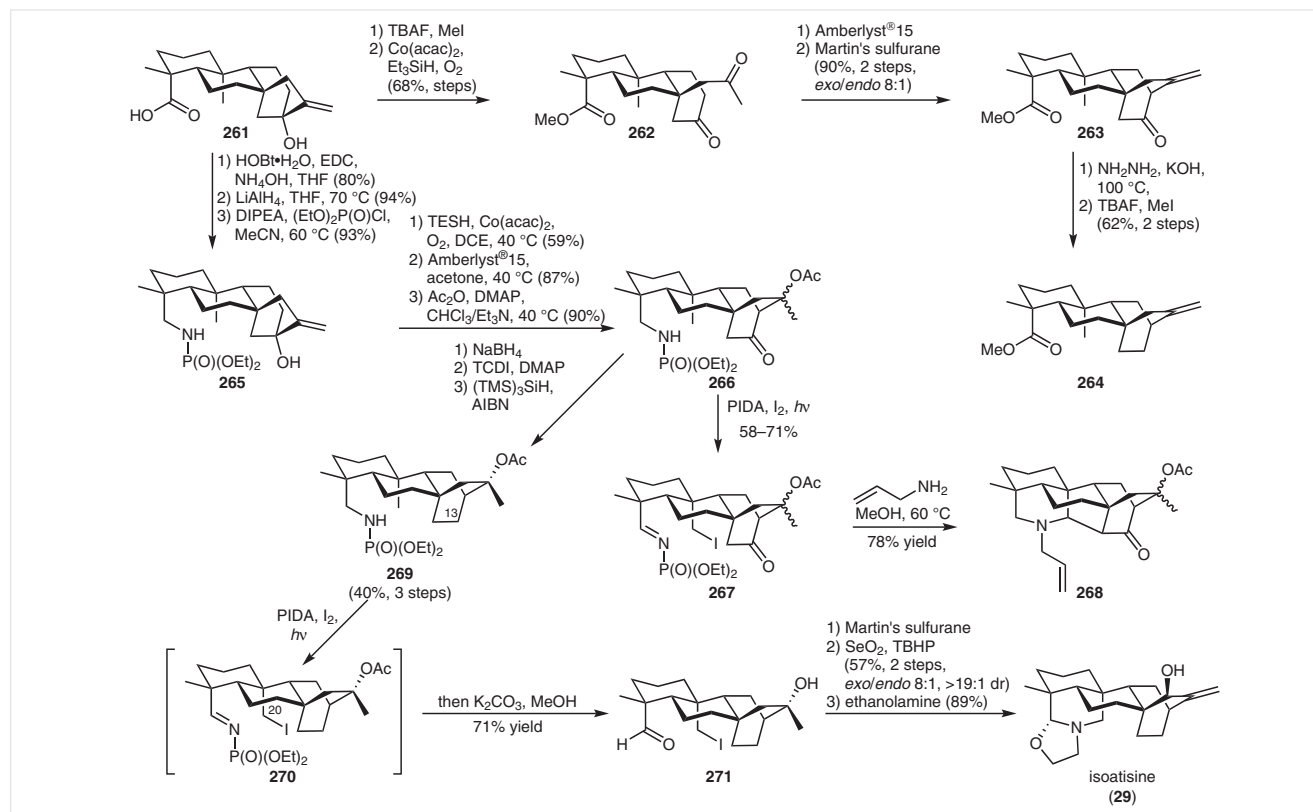
The Baran group developed a unified approach to *ent*-atisane diterpenoids and related alkaloids.⁵⁰ As illustrated in Scheme 18, (–)-methyl atisenoate (**264**), (–)-isoatisine (**29**), and also **268**, a hetidine skeleton, were synthesized starting from (–)-steviol (**261**). The synthesis of *ent*-atisane 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–Freitag 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**).

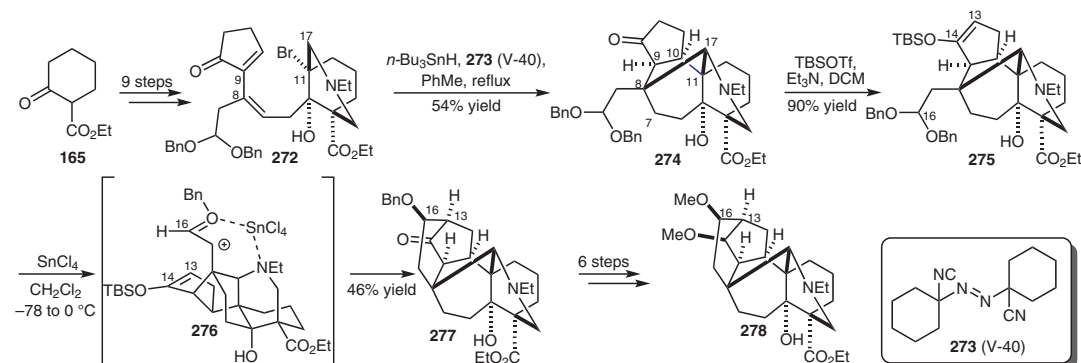
3 Strategies to Synthesize Ring Systems

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** (V-40) 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**



Scheme 18 Synthesis of (–)-methyl atisenoate, (–)-isoatisine, and hetidine derivative from the common precursor (–)-steviol



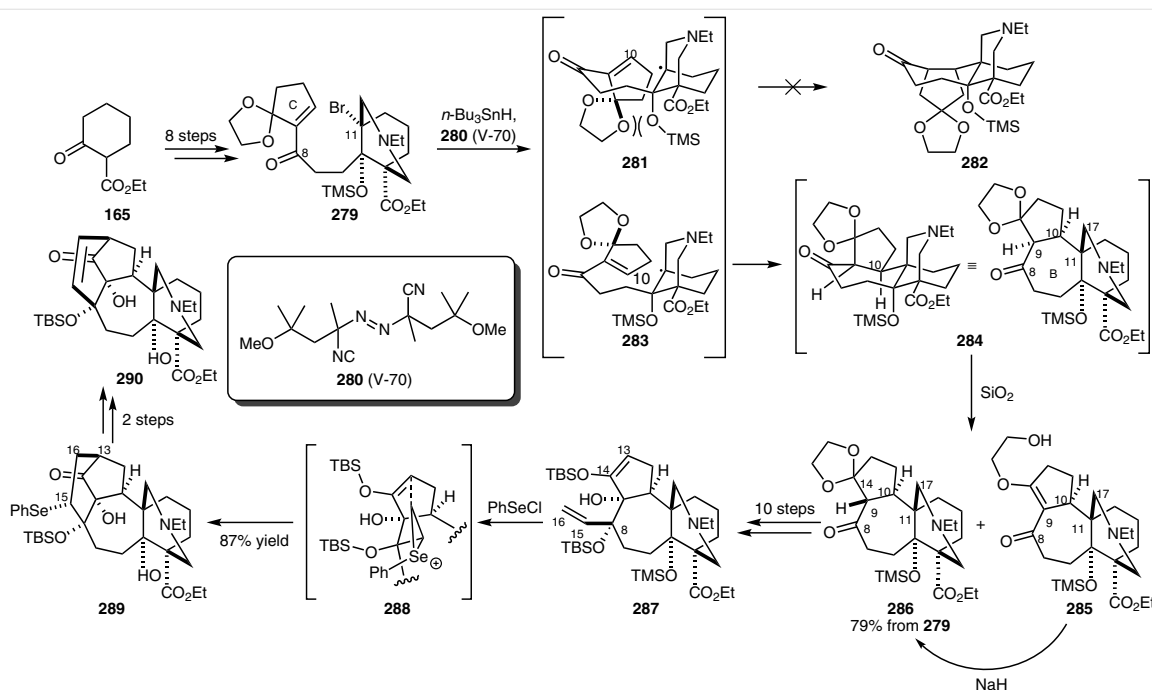
Scheme 19 Radical-based cyclization/translocation/cyclization process followed by an aldol reaction for the synthesis of the fused hexacycle of pu-beruline C

with TBSOTf to give the silyl enol ether **275**, variety of Lewis acids were screened for the intramolecular Mukaiyama aldol reaction of **275**; this reaction was realized using SnCl₄ 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 SnCl₄ between the oxygen and nitrogen atoms in **276** which dictates the nucleophilic attack of the silyl enol ether on to the *si*-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).⁸⁹ Treating **279** with *n*-Bu₃SnH and **280** (V-70) resulted in the formation of a stereochemi-

cally fixed C11 bridgehead radical **283** that underwent stereo- and regioselective 7-*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**.

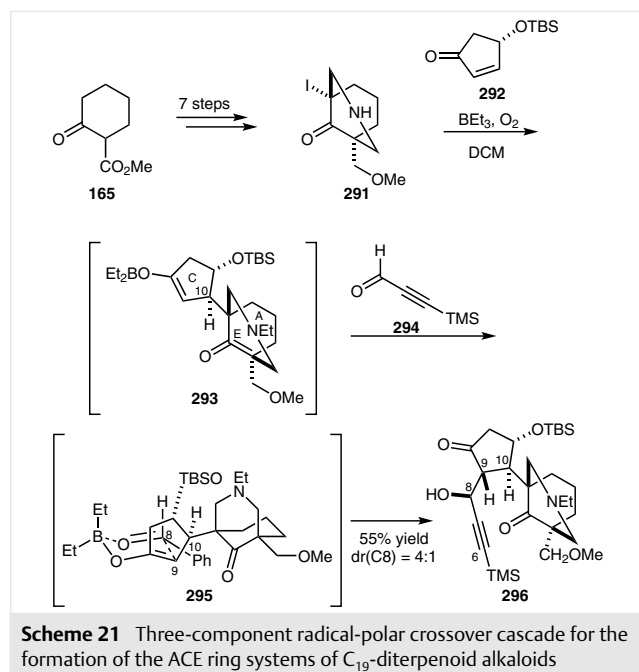
Purification of **284** with silica gel caused C14-oxygen β -elimination and C9 epimerization to form enone **285** and *trans*-fused **286** from the initial *cis*-fused **284**, respectively. Treatment of **285** with NaH yields **286** in a 79% combined yield from **279**. Pentacycle **286** was then converted into **287** in ten steps which were required to carry out a 6-*endo* cationic cyclization to install the D ring. The C15–C16 double bond was activated with PhSeCl, allowing attack by the TBS



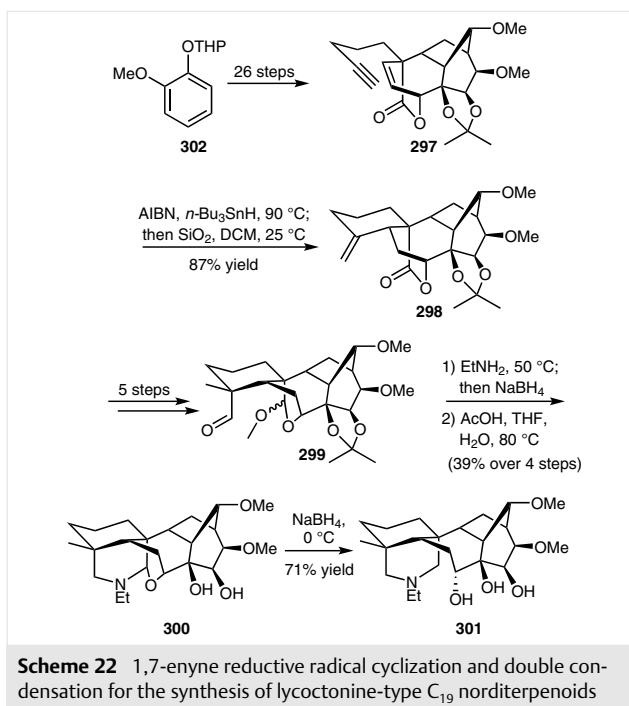
Scheme 20 Radical and cationic cyclizations for the formation of the pentacyclic core of talatisamine

enol ether to afford pentacycle **289**. Finally, oxidation of selenide **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.



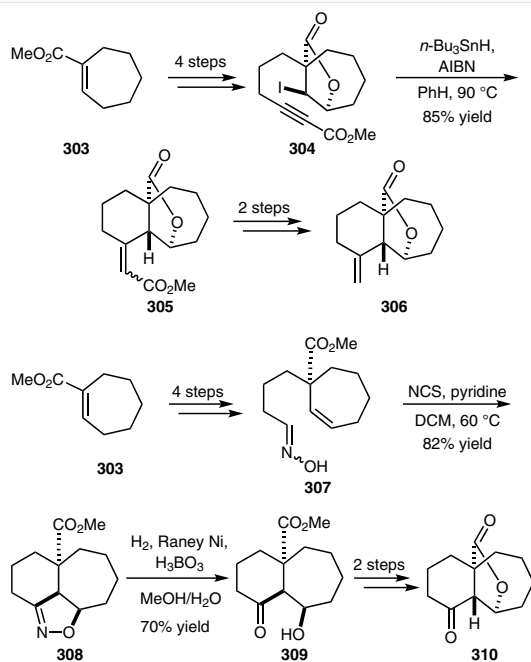
Wang, Xu, and co-workers utilized, in 2018, a 1,7-enyne reductive radical cyclization and double condensation for the synthesis of lycotinine-type C₁₉-norditerpenoid alkaloid (Scheme 22).⁹¹ 1,7-Enyne **297**, which was prepared from a previously reported intermediate,⁹² underwent a reductive cyclization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



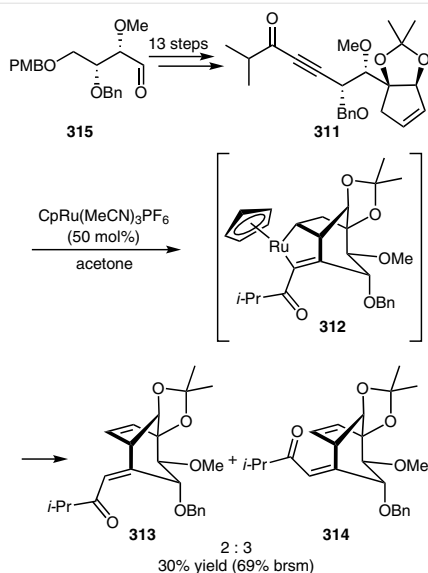
Another radical-based cyclization was adopted by Xu and co-workers in the synthesis of the BCD ring systems of 7,17-*seco*-type C₁₉-norditerpenoid alkaloids (Scheme 23).⁹³ It was shown that similar ring systems can be accessed via a [3+2] cycloaddition of a nitrile oxide. Bicyclic iodide **304** participated 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 ruthenacycle **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.



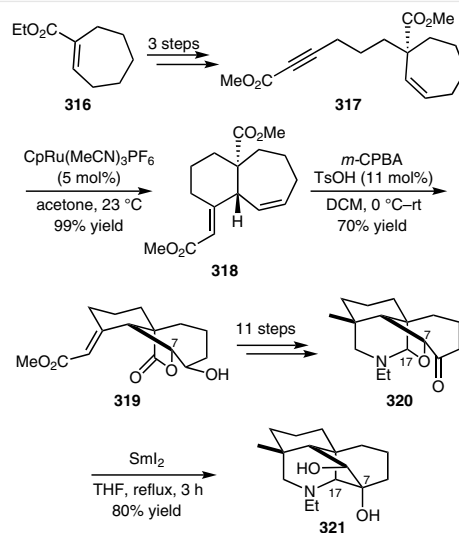
Scheme 23 Radical cyclization and [3+2] cycloaddition for the formation of the BCD ring system of 7,17-*seco*-type C_{19} norditerpenoids



Scheme 24 Ruthenium-mediated enyne cycloisomerization for the construction of CD ring systems of aconitine

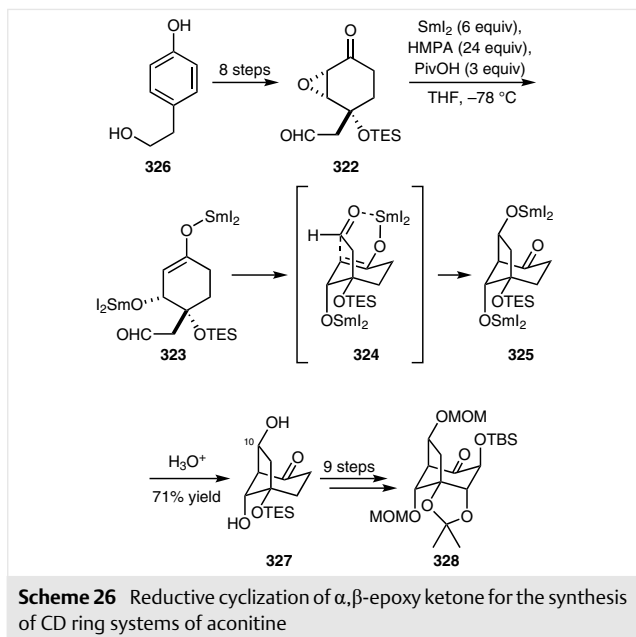
3.3 Reductive Coupling

In 2014, Xu and co-workers reported the synthesis of ABEF ring systems of lycoctonine-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 Trost⁹⁴ (Scheme 25).⁹⁶ Treatment of bicycle **318** with *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 *N,O*-acetal in **320** was accomplished using SmI_2 to form tetracycle **321** bearing the ABEF ring systems of *Lycoctonine*-type and 7,17-*seco*-type C_{19} -norditerpenoid alkaloids.



Scheme 25 Construction of the ABEF ring system with ruthenium-catalyzed enyne cycloisomerization and SmI_2 -induced reductive coupling

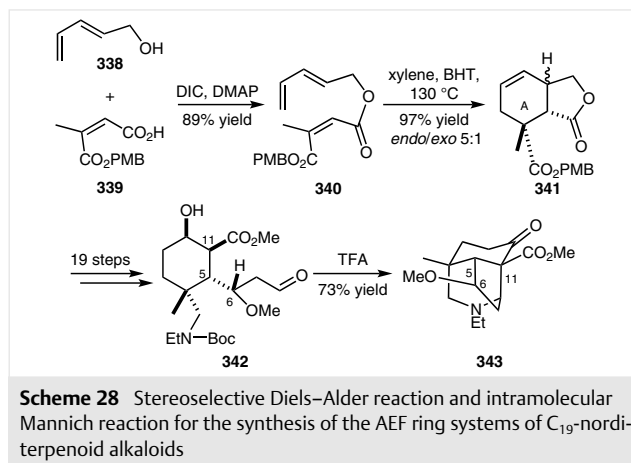
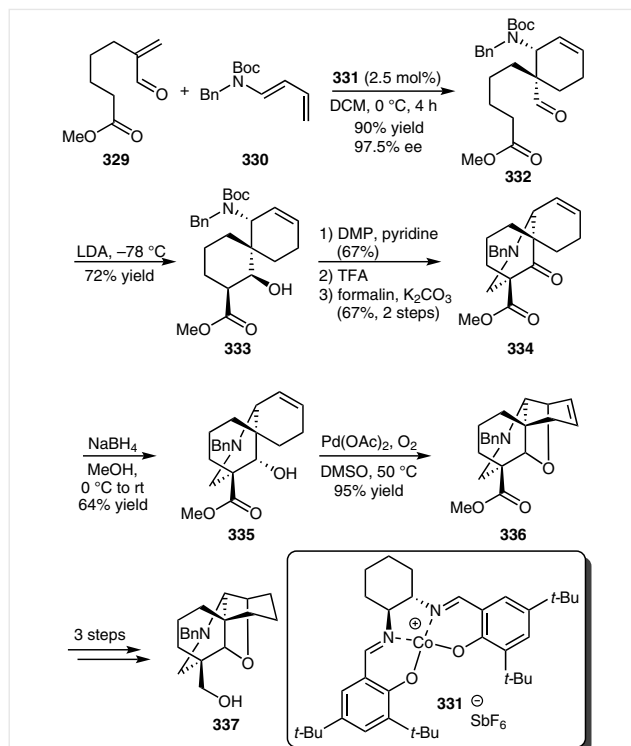
Sugita and co-workers reported a reductive cyclization strategy of α,β -epoxy ketone **322** to synthesize the CD ring system of aconitine (**27**) (Scheme 26).⁹⁷ SmI_2 initiates the formation of samarium enolate **323** that subsequently underwent an intramolecular aldol cyclization with the pendant 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_2 (6 equiv) and HMPA (24 equiv) furnished the desired product **327** in 71% yield.



3.4 Diels–Alder Reactions

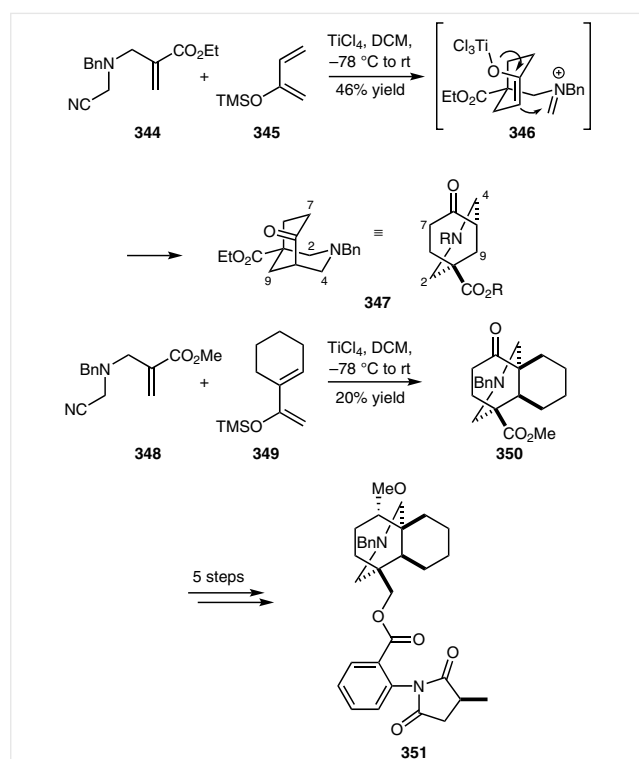
Brimble and co-workers reported the enantioselective synthesis of the ABEF ring systems of methyllycaconitine analogues (Scheme 27).⁹⁸ The elegant approach utilized sequential Diels–Alder reaction, aldol, Mannich, and Wacker-type cyclizations to furnish the tetracyclic scaffold **337**. The enantioselective 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 ABE tricyclic 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 and ABE ring systems of *Delphinium* alkaloids (Scheme 29).¹⁰¹ A titanium-mediated [4+2] cycloaddition was carried out between the α -[(cyanomethyl)amino]methylacrylate **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 majusine A (**360**) were amongst the presented examples, as well as their *N*-benzyl analogues **364–368**.

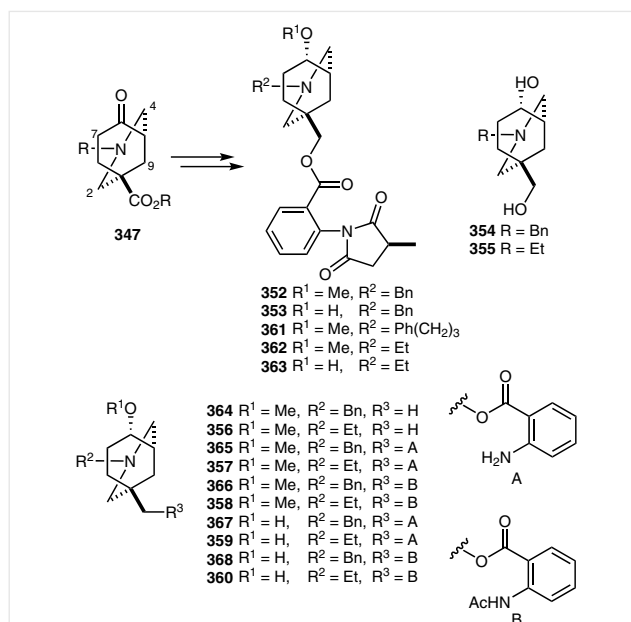


Scheme 29 Tandem titanium-mediated Diels–Alder/Mannich reaction for the construction of the ABE ring systems of *Delphinium* alkaloids

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.¹⁰²

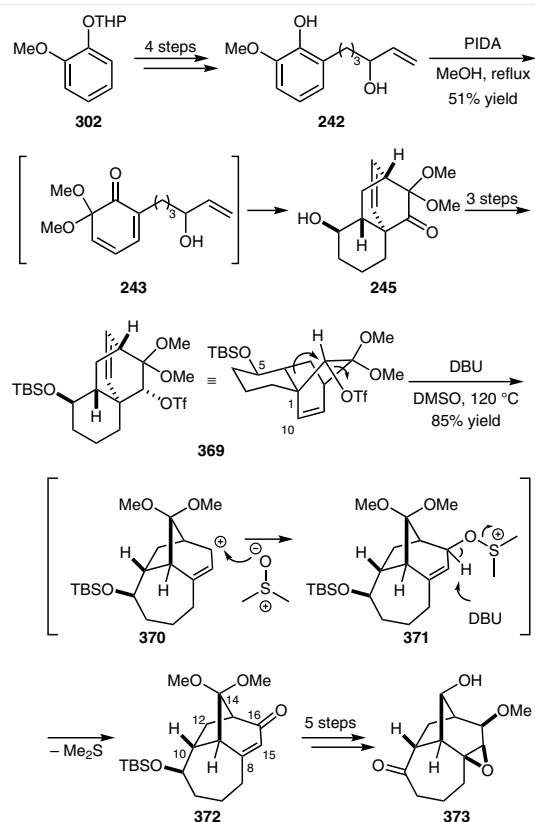
Xu, Wang, and co-workers also demonstrated the synthetic versatility of the Diels–Alder reaction by applying it to the synthesis of the BCD ring systems of *C*₁₉-norditer-



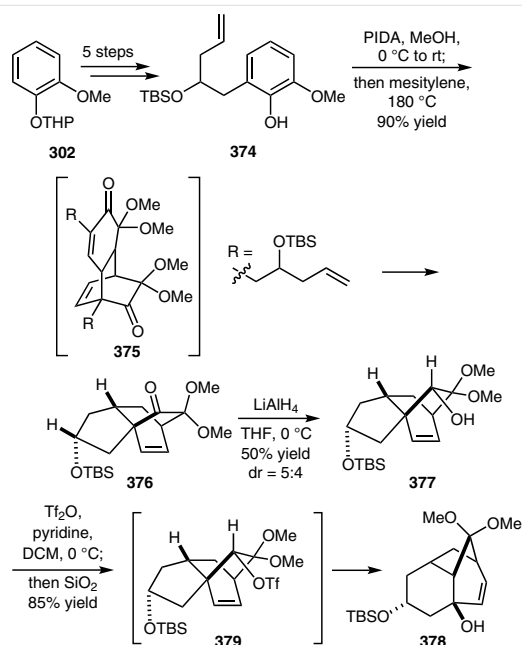
Scheme 30 Derivatization of a bicyclic ketone to furnish various synthons for *Delphinium* and *Aconitum* alkaloids

penoid alkaloids (Scheme 31).⁹² An intramolecular Diels–Alder reaction of a masked *o*-benzoquinone **243** developed by Liao and co-workers was applied to synthesize the tetracyclic ketone **245**.⁸² 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 triflate **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.

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).¹⁰³ Treatment of phenol **374** with PIDA in the presence of methanol resulted in the dimer **375**. Fortunately, the desired cycloadduct **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**.

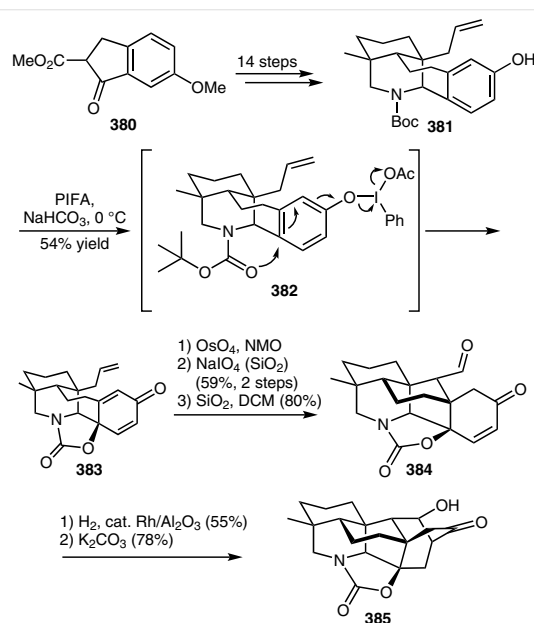


Scheme 31 Intramolecular Diels-Alder reaction and a Wagner-Meerwein rearrangement for the construction of the BCD ring systems of C_{19} -norditerpenoid alkaloids

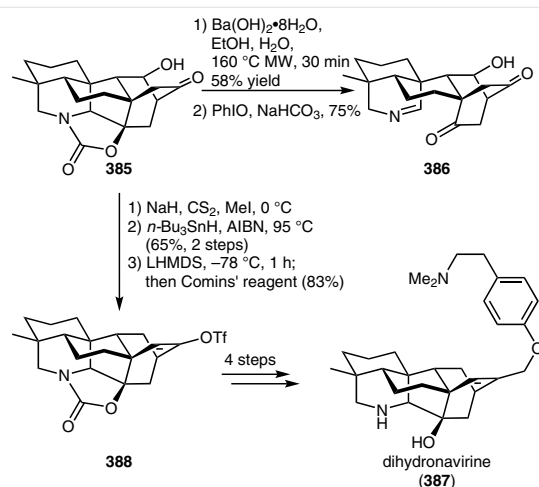


Scheme 32 PIDA-promoted oxidative cyclization and a Wagner-Meerwein rearrangement to furnish the BCD rings systems of aconitine

The Sarpong group presented studies in 2014 on C_{20} -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 **382**. A sequence of dihydroxylation, periodate cleavage, and Michael addition, promoted by simple stirring with silica gel in dichloromethane, gave aldehyde **384**. Hydrogenation and aldol reaction gave synthon **385** (Scheme 33).



Scheme 33 Synthesis of a versatile intermediate for the hetidine framework



Scheme 34 Construction of atisine and hetidine frameworks

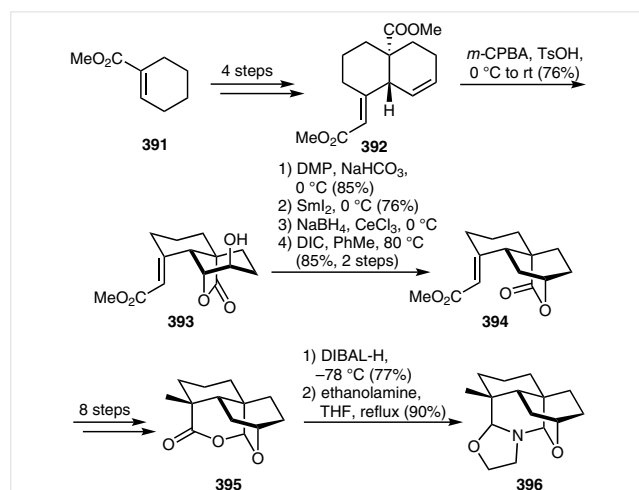
The versatile synthon **385** was used to synthesize compound **386** having the atisine carbon skeleton in 2 steps (Scheme 34). The same synthon was also used to synthesize dihydronavirine (**387**), which unfortunately could not be converted into the natural product navirine.

In a methodological study, Chen and Wang presented an efficient synthesis of the C/D rings (Scheme 35) of atisine-type C_{20} -diterpenoid alkaloids.¹⁰⁵ The synthesis also relies on the oxidative dearomatization/intramolecular Diels-Alder strategy.



Scheme 35 Synthesis of the C/D rings of atisine-type C_{20} -diterpenoid alkaloids

Xu and co-workers accessed the core ring systems of *Spiraea* 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**).

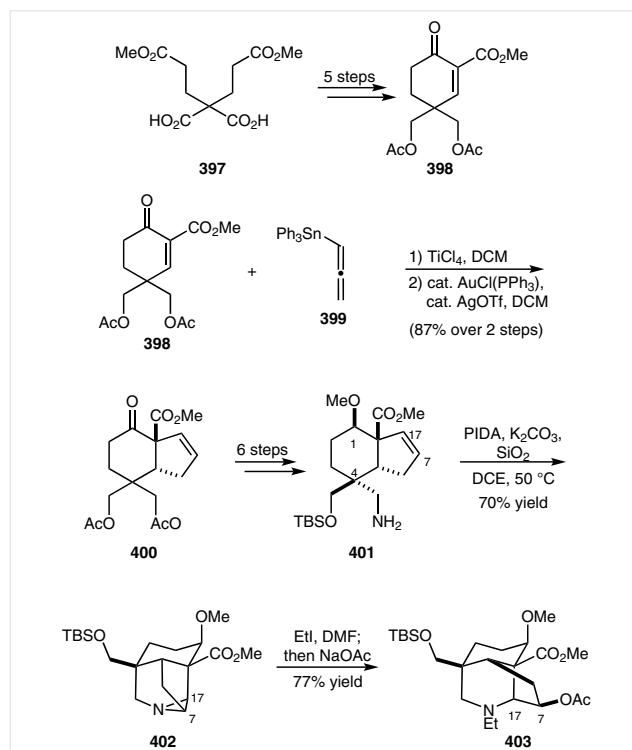


Scheme 36 Biomimetic synthesis of the ABEFG pentacyclic amine of *Spiraea* atisine-type diterpenoid alkaloids

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 C_{19} -nordi-

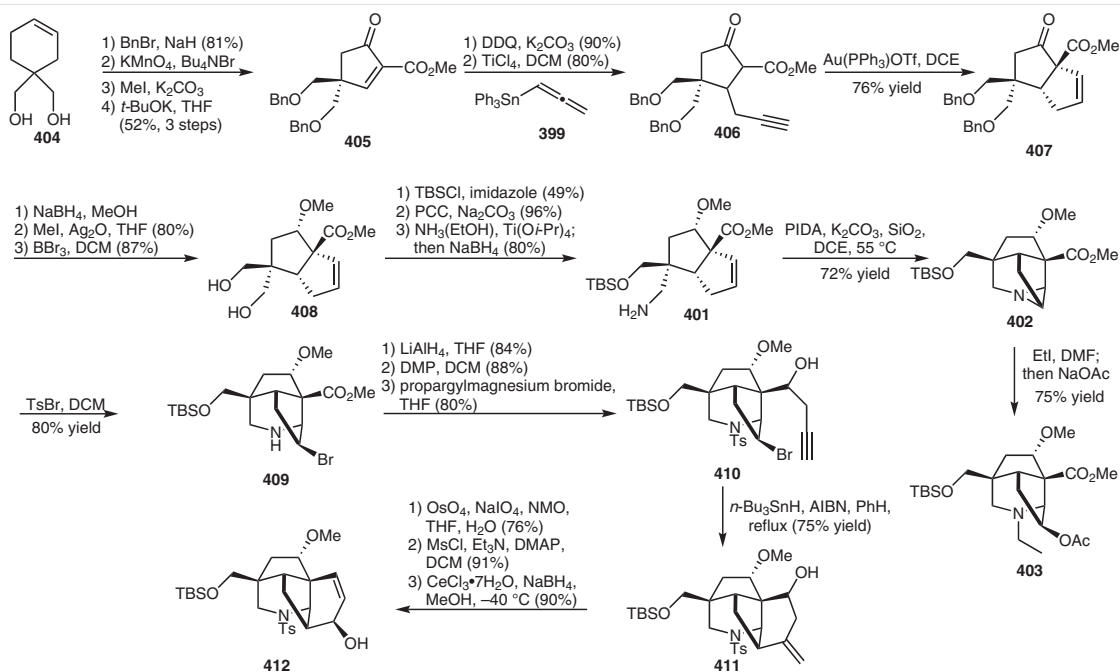
terpenoid alkaloids (Scheme 37).¹⁰⁷ Starting from symmetric **397**, intermediate **398** was obtained in 5 steps. β -Keto acrylate **398** was subjected to $TiCl_4$ -mediated conjugate propargylation¹⁰⁸ followed by a gold(I)-catalyzed cyclization¹⁰⁹ to afford the β -keto ester **400**. Subsequent transformations 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 C_{19} -nordi-terpenoid alkaloids.



Scheme 37 PIDA-promoted intramolecular transannular aziridination followed by regioselective ring cleavage to deliver the AEF ring systems of lycoctonine-type C_{19} -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[3.3.2.0^{4,8}]decane skeleton 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



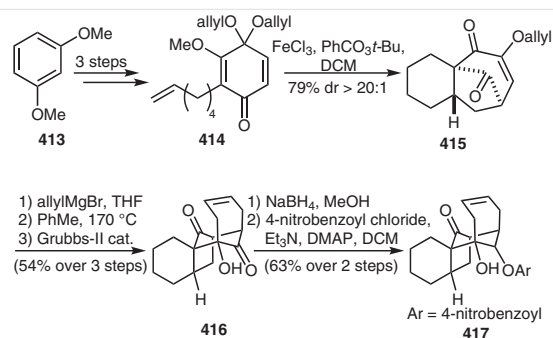
Scheme 38 Synthetic studies towards racemulsonine

protected and then converted into the β -keto ester **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 MeI 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-azatricyclo[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**.¹¹¹ 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 ABEF core was completed, and with minor tailor-

ing, 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 racemulsonine core.

3.7 Intramolecular [5+2] Cycloaddition

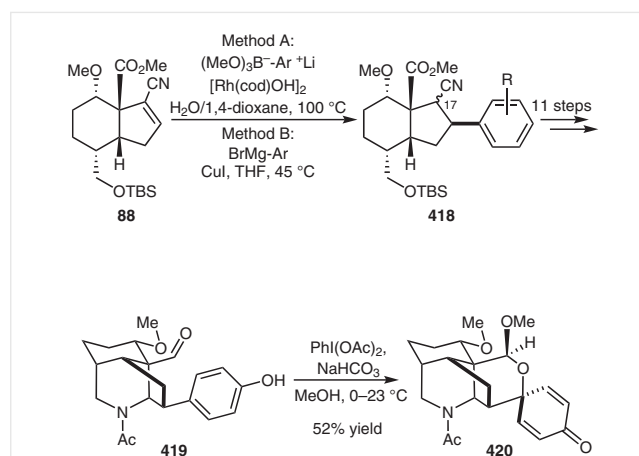
The synthesis of a 6/5/6/7 ring system (Scheme 39) matching parts of the skeleton of C₁₈/C₁₉-diterpenoid alkaloids was reported by Liu and co-workers in 2018.¹¹⁴ The synthesis features an iron-catalyzed intramolecular [5+2] cycloaddition that they had reported earlier.¹¹⁵ Cycloaddition adduct **415** was transformed into tetracyclic synthon **416** in 3 steps. It was also demonstrated that the chemoselective reduction of a ketone moiety is feasible. The result-

Scheme 39 Synthesis of the tetracyclic 6/5/6/7 core skeleton of C₁₈/C₁₉-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 vinyl nitrile **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 dearomatized spirocycle **420**.

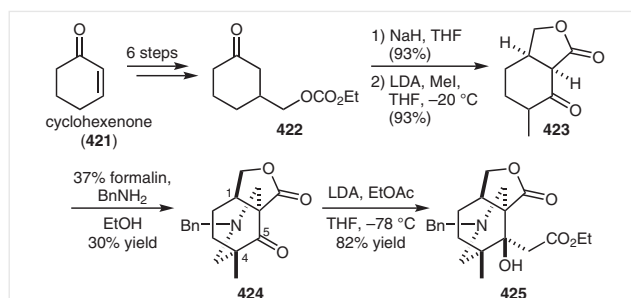


Scheme 40 Conjugate arylation of vinyl nitrile to study the structural activity relationship for aconitine

An expedient synthesis of the AE ring systems bearing a 5β-hydroxyl 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-hydroxyl 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, dis-



Scheme 41 Sequential intramolecular Claisen condensation, double Mannich reaction and stereoselective aldol addition for the formation of the AE ring systems bearing a 5β-hydroxyl group for C₁₉-norditerpenoid alkaloids

cussing 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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