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Total Synthesis, Relay Synthesis, and Structural Confirmation of the C18-Norditerpenoid Alkaloid Neofinaconitine

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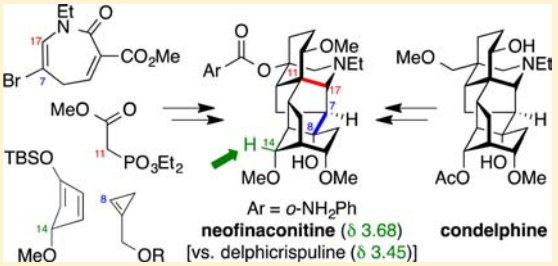
Supporting Information

ABSTRACT: The first total synthesis of the C18-norditerpenoid aconitine alkaloid neofinaconitine and relay syntheses of neofinaconitine and 9-deoxylappaconitine from condelphine are reported. A modular, convergent synthetic approach involves initial Diels–Alder cycloaddition between two unstable components, cyclopropene **10** and cyclopentadiene **11**. A second Diels–Alder reaction features the first use of an azepinone dienophile (**8**), with high diastereofacial selectivity achieved via rational design of siloxydiene component **36** with a sterically demanding bromine substituent. Subsequent Mannich-type *N*-acyliminium and radical cyclizations provide complete hexacyclic skeleton **33** of the aconitine alkaloids. Key endgame transformations include the installation of the C8-hydroxyl group via conjugate addition of water to a putative strained bridgehead enone intermediate **45** and one-carbon oxidative truncation of the C4 side chain to afford racemic neofinaconitine. Complete structural confirmation was provided by a concise relay synthesis of (+)-neofinaconitine and (+)-9-deoxylappaconitine from condelphine, with X-ray crystallographic analysis of the former clarifying the NMR spectral discrepancy between neofinaconitine and delphicrispuline, which were previously assigned identical structures.



INTRODUCTION

Plants from the genera *Aconitum* and *Delphinium* have been used for centuries in traditional Chinese and Japanese folk medicines as antiarrhythmics and analgesics.[1] Although the raw leaves and roots are quite toxic, high-temperature preparations have been applied to reduce their toxicity and render them clinically useful. The long history of these plants as medicines has piqued the interest of natural product chemists, leading to the isolation and characterization of a number of aconitum and delphinium alkaloids.[2] Some of the most biologically active isolates are in the norditerpenoid alkaloid class, which is further subdivided on the basis of the presence [C19-norditerpenoid, e.g., aconitine (**1**)] or absence [C18-norditerpenoid, e.g., lappaconitine (**2**)] of the C18 carbon (Figure 1). The isolation[3] and identification[4] of these alkaloids enabled pharmacological studies that have revealed their roles as ion-channel modulators.[5] Notably, one of these alkaloids, lappaconitine (Allapinin), has been commercialized as an antiarrhythmic drug.[6] The structure of the C19-norditerpenoid alkaloids was first elucidated by Wiesner and co-workers, who also completed the first total synthesis of a member of this group, talatisamine (**4**).[7] They subsequently also achieved the total syntheses of chasmanine (**5**)[8] and 13-deoxydelphonine (**6**)[8b,9] via an alternative strategy that provided improved chemoselectivity at key steps. Despite numerous other attempts,[10] these remain the only published total syntheses of norditerpenoid alkaloids to date. The potent biological activity and absence of a convergent approach to these alkaloids make them attractive targets for synthesis.

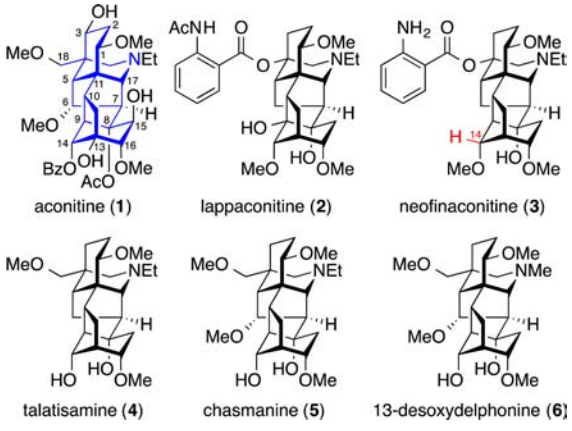


Figure 1. Structures of selected C19- and C18-norditerpenoid alkaloids. Neofinaconitine and delphicrispuline have both been assigned the same structure (**3**) but have distinct chemical shifts reported for the C14 proton (neofinaconitine δ 3.68, delphicrispuline δ 3.45 ppm, $CDCl_3$).[11]

Neofinaconitine (**1**) was chosen as our initial target for total synthesis on the basis of two considerations. First, two groups independently reported the isolation of natural products with the same proposed structure, neofinaconitine (Jiang) and delphicrispuline (Ulubelen).[11] An examination of the reported spectral data revealed a discrepancy in the chemical shift of the

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C14 proton (neofinaconitine δ 3.68, delphicrispuline δ 3.45 ppm, $CDCl_3$). Therefore, the total synthesis of the proposed structure would help elucidate the identity of the natural product (referred to herein as neofinaconitine). Second, biological studies of neofinaconitine have not been reported, primarily because of its scarcity. However, because of its close structural similarity to the natural product lappaconitine, which exhibits intriguing biological activities, such studies are of considerable interest and would be enabled by efficient synthetic access.

Herein, we report the first total synthesis of neofinaconitine, featuring sequential, convergent cyclopropene/cyclopentadiene and azepinone/siloxydiene Diels–Alder cycloadditions to assemble a key cyclization substrate, followed by successive Mannich-type *N*-acyliminium (Speckamp) and radical cyclizations. Structural insights were used to reengineer the siloxydiene substrate in the azepinone Diels–Alder cycloaddition to achieve improved diastereofacial selectivity. An expedient relay synthesis from commercially available condelphine was also developed to access (+)-neofinaconitine and (+)-9-deoxylappaconitine (**2**), confirming stereochemical assignments in the totally synthetic material. X-ray crystallographic analysis of the relay material unambiguously confirmed the structure of neofinaconitine, thus resolving the NMR spectral discrepancy and indicting that the structure of delphicrispuline requires reconsideration.

RESULTS AND DISCUSSION

Synthesis Strategy. Our overall approach to the synthesis of neofinaconitine (**3**) is outlined in Figure 2. The hexacyclic scaffold of **3** is simplified retrosynthetically by late-stage formation of the C11–C17 and C7–C8 bonds. The [5.4.0]-bicycloazepine ring system in **7** arises from a Diels–Alder cycloaddition[12] between dihydroazepinone **8** and siloxydiene **9**. Although the use of an azepinone such as **8** as a dienophile has not, to our knowledge, been reported in the literature, the convergence of this approach made it an attractive avenue for investigation. Fused cyclopropane **9** is prepared by another unusual Diels–Alder cycloaddition between cyclopentadiene **10** and cyclopropene **11**.[13] Although this approach rapidly

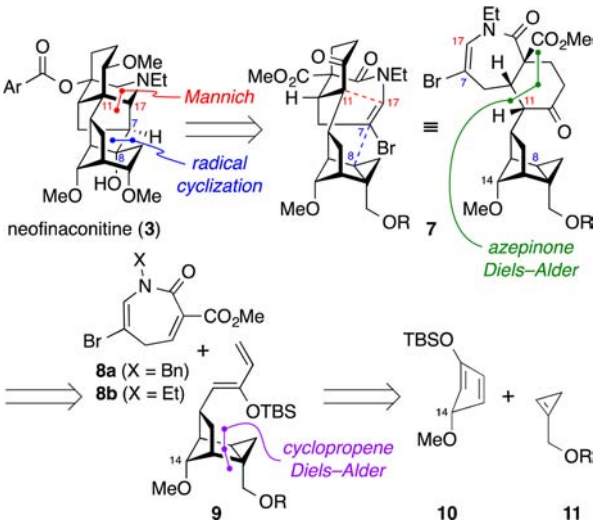

Figure 2. Retrosynthetic analysis of neofinaconitine (**3**) via late-stage formation of the C11–C17 and C7–C8 bonds and sequential Diels–Alder cycloadditions. Ar = 2-aminophenyl; R = TIPS, triisopropylsilyl.

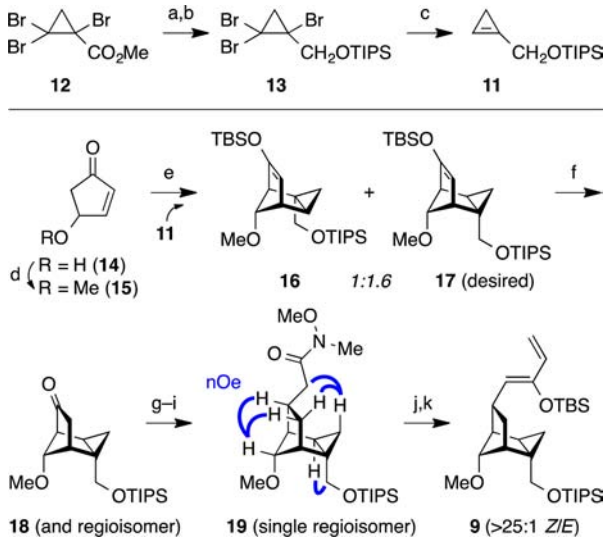

Figure 3. Synthesis of fused tricyclic cyclopropane **9** via cyclopropene Diels–Alder cycloaddition. (a) DIBAL, CH_2Cl_2, −78 to 20 °C. (b) TIPSCl, imidazole, CH_2Cl_2, 72% over two steps. (c) MeLi, THF, −78 °C. (d) MeI, Ag_2O, CH_2Cl_2, 75%. (e) **11**, TBSOTf, Et_3N, 0 °C. (f) NaOH, THF/H_2O. (g) methyl diethylphosphonoacetate, KHMDS 0 to 23 °C, reflux. (h) H_2, Pd/C, EtOAc. (i) *N*,*N*-dimethylhydroxylamine hydrochloride, $AlMe_3$, THF, 39% over six steps from **13** (single isomer). (j) vinylmagnesium bromide, 0 °C. (k) TBSOTf, KHMDS, THF, −78 °C, 77% over two steps. DIBAL is diisobutylaluminum hydride, KHMDS is potassium bis(trimethylsilyl)amide, TBS is *tert*-butyldimethylsilyl, Tf is trifluoromethanesulfonyl, and TIPS is triisopropylsilyl.

builds complexity, it is not without significant challenges. A contra-steric facial approach of dienophile **11** would be required to give the desired stereochemistry at C14. Furthermore, cyclopentadienes are known to dimerize readily and to undergo 1,5-hydrogen shifts,[14] resulting in scrambled substitution patterns. However, a recent example by Gleason and co-workers[15] demonstrated that the presence of a silyl ether significantly retards these hydrogen shifts. Although the dienophiles approach exclusively from the sterically more-accessible face of the diene in that report, contra-steric cycloadditions of heteroatom-substituted cyclopentadienes have been reported elsewhere,[16] and selectivity has been shown to be substrate-dependent.[16c]

Cyclopropene/Cyclopentadiene Diels–Alder Cycloaddition. Synthesis of the cyclopropene component commenced with known tribromocyclopropane **12**, available in three steps from methyl acrylate[17] (Figure 3). Ester reduction with DIBAL followed by silyl protection provided cyclopropene precursor **13**. Lithium–halogen exchange of **13** with 2 equiv of MeLi followed by an aqueous quench of the resulting vinyl anion gave cyclopropene **11**, which could be isolated and was used immediately because of rapid Alder–ene dimerization. The cyclopentadiene component was prepared from the known cyclopentenone **14**,[18] available in one step from furfuryl alcohol. Methylation of the allylic alcohol[19] (Ag_2O, MeI) provided ether **15**. Enolization–silylation[19] (TBSOTf, Et_3N) of **15** with aqueous workup provided an intractable mixture of cyclopentadiene dimers. However, when cyclopropene **11** was introduced directly into the cyclopentadiene reaction mixture prior to workup, desired cycloadduct **17** was obtained as an inseparable 1.6:1 mixture with undesired regioisomer **16**, along with small amounts of other isomers.[20,21] Notably, this reaction

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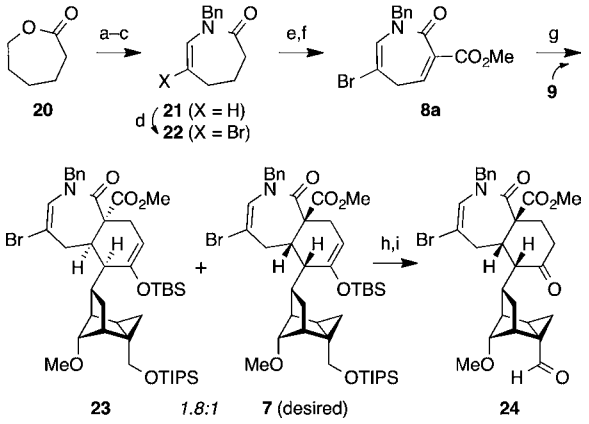

Figure 4. Synthesis of cyclopropane carboxaldehyde **24** via azepinone Diels–Alder cycloaddition. (a) $BnNH_2$, 120 °C, 78%. (b) SO_3·pyridine, Et_3N, CH_2Cl_2/DMSO, 93%. (c) TsOH, toluene, 110 °C, 77%. (d) Br_2, Et_3N, CH_2Cl_2, 0 °C, 86%. (e) LiHMDS, $ClCO_2Me$, PhSeCl, −78 to 20 °C. (f) H_2O_2, CH_2Cl_2, 0 °C, 99% over two steps. (g) **10**, $Sc(OTf)_3$, PhMe, 69%. (h) TBAF, THF, 77%. (i) IBX, CH_3CN, sonication, 87% combined yield from **23** and **7**, 31% isolated yield of **24**. LiHMDS is lithium bis(trimethylsilyl)amide, and Ts is *p*-toluenesulfonyl.

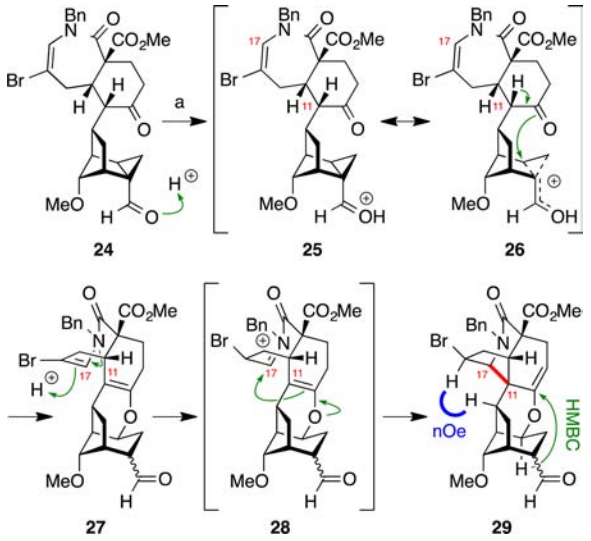

Figure 5. Mannich-type *N*-acyliminium cyclization of **24** to form the key C11–C17 bond in **29**. (a) Tf_2NH, CH_2Cl_2, 0 °C, 71%.

favored the contra-steric approach of the cyclopropene dienophile to the cyclopentadiene (5.6:1).[21,22] Attempts to improve the regioisomeric ratio through the use of a methyl enoate derived directly from ester **12** provided only a complex mixture of products with no indication of successful cycloaddition. Therefore, the mixture of **16** and **17** was taken on via a four-step route involving NaOH hydrolysis of the silyl ether to form ketone **18**, Horner–Wadsworth–Emmons olefination,[23] Pd-catalyzed stereoselective hydrogenation, and $AlMe_3$-mediated Weinreb amide formation.[24] At this point, desired Weinreb amide **19** could be separated from the regioisomeric mixture obtained from the cyclopropene/cyclopentadiene Diels–Alder reaction. Treatment with vinylmagnesium bromide[25] then KHMDS and TBSOTf[26] provided *Z*-siloxydiene **9**, the 4π component for the second key Diels–Alder cycloaddition below.

Azepinone/Siloxydiene Diels–Alder Cycloaddition. Synthesis of the azepinone 2π component began with commercially available ε-caprolactone **20** (Figure 4). Lactone aminolysis[27] ($BnNH_2$, neat, 120 °C) was followed by Parikh–Doering oxidation[28] of the resulting primary alcohol and acid-catalyzed intramolecular enamine formation to afford **21**. Halogenation with bromine then provided vinyl bromide **22** (Br_2, Et_3N). Sequential treatment of the lithium enolate of **22** with $ClCO_2Me$ and PhSeCl followed by selenide oxidation/elimination (H_2O_2)[29] then furnished azepinone dienophile **8a**.

At this juncture, both the 4π and 2π components (**9** and **8a**) were in hand for the convergent Diels–Alder cycloaddition to produce the [5.4.0]-bicycloazepine ring system. Notably, the use of a dihydroazepine as a dienophile was without literature precedent, so the expected regio-, *endo*/*exo*-, and facial selectivity of this transformation was unclear, especially in the setting of a complex polycyclic diene such as **9**. After extensive experimentation with thermal and Lewis acid catalysis in a variety of solvents, we found that when a solution of dienophile **8** and diene **9** in toluene was treated with $Sc(OTf)_3$ the Diels–Alder cycloaddition provided complete regioselectivity and *endo* selectivity. However, the product was obtained as an inseparable 1.8:1 mixture of undesired stereofacial cycloadduct **23** and desired cycloadduct **7** in 69% combined yield.[21] Silyl deprotection (TBAF, THF) followed by oxidation (IBX, CH_3CN, sonication) and separation of the diastereomers provided aldehyde **24** in 31% yield, along with 56% of the undesired diastereomer (not shown). Although this sequence favored the undesired distereomer, the rapid increase in complexity provided by this approach enabled exploration of the installation of the remaining C11–C17 and C7–C8 bonds.

C11–C17 Bond Formation by Mannich-Type *N*-Acyliminium Cyclization. Next, the C11–C17 bond was formed via Mannich-type acid-catalyzed nucleophilic attack of an enol at C11 onto an *N*-acyliminium at C17 (Figure 5). When cyclopropane carboxaldehyde **24** was treated with any of a number of Lewis or Brønsted acids, cyclic enol ether **27** formed quickly and could be recovered from the reaction mixture. Presumably, this product is formed via activation of the aldehyde as cyclopropylcarbinyl oxocarbenium **25** and its resonance form **26**. The regioselective intramolecular attack by the ketone oxygen upon this cation then forms observed cyclic enol ether **27**.[21] Ultimately, the use of the much stronger acid Tf_2NH not only effected this cyclopropane rupture but also catalyzed the formation of the key C11–C17 bond through protonation of the enamide in **27** to give putative *N*-acyliminium intermediate **28**, which then underwent nucleophilic attack by the C11 enol to provide enol ether **29**. The structure of **29** was confirmed by extensive 1D NOE and 2D NMR analyses.[21]

C7–C8 Bond Formation by Radical Cyclization. To complete the synthesis of the hexacyclic skeleton of the norditerpenoid alkaloids, the cyclic enol ether in **29** needed to be cleaved. However, this enol ether proved to be quite robust, withstanding standard aqueous acidic conditions even at elevated temperature. More extreme conditions (12 N HCl, 60 °C) resulted in the hydrolysis of both the methyl ester and methyl ether, but no products were detected in which the enol ether had been cleaved. Interestingly, the vinyl proton in **29** appeared at 5.4 ppm in the ^1H NMR spectrum. This unusually downfield vinyl ether signal could arise from poor orbital overlap of the oxygen lone pair and the π system of the alkene and suggested that hydrolysis would continue to be a challenge.

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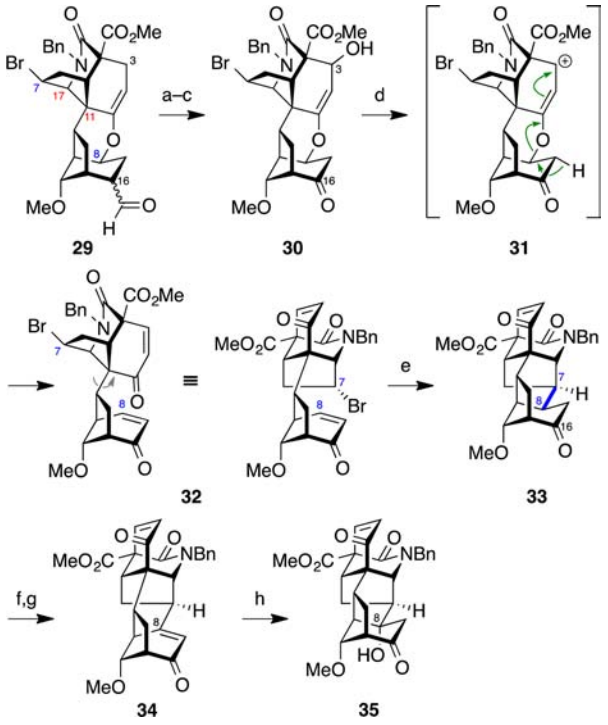

Figure 6. Intramolecular radical conjugate addition of **32** to form the key C7–C8 bond in **33** and completion of the carbon skeleton of C19-norditerpenoid alkaloids **35**. (a) TBSOTf, Et_3N, CH_2Cl_2, 86%. (b) OsO_4, $PhI(OAc)_2$, 2,6-lutidine, THF/H_2O, 74%. (c) $Ce(NH_4)_2(NO_3)_6$, $CH_3CN/CH_2Cl_2/H_2O$, 50 °C. (d) MsCl, Et_3N, CH_2Cl_2, 50 °C, 57% over two steps. (e) Bu_3SnH, AIBN, PhH, 80 °C, 86%. (f) LiHMDS, PhSeCl, THF, −78 °C, 75%. (g) H_2O_2, CH_2Cl_2, 0 °C, 90%. (h) AcOH, THF, H_2O, 77%. AIBN is 2,2′-azobis(2-methylpropionitrile), and Ms is methanesulfonyl.

Thus, alternative methods to cleave the enol ether were investigated, and oxidative elimination of the enol ether ultimately proved to be an effective route (Figure 6). The C16 aldehyde side chain in **29** was subjected to a two-step, one-carbon truncation[30] (TBSOTf, Et_3N and then OsO_4, $PhI(OAc)_2$, 2,6-lutidine) followed by C3 allylic oxidation adjacent to the enol ether (CAN, CH_3CN/H_2O) to provide keto-alcohol **30**. Activation of the allylic alcohol as a mesylate (MsCl, Et_3N) then generated bis-enone **32**, presumably by elimination of the enol-ether oxygen via allyl cation **31**. Site-selective intramolecular radical conjugate addition of a bromide-derived radical at C7 into the enone at C8 (Bu_3SnH, AIBN) provided the desired hexacycle **33**.

Completion of the Hexacyclic Skeleton of the C19-Norditerpenoid Alkaloids. Finally, we sought to install the requisite C8-hydroxyl group found in the aconitine alkaloids. The paucity of precedents for this formal C–H oxidation led us to pursue an unconventional strategy that exploited the inherent reactivity embedded within the molecular framework. A three-step sequence involving α-selenylation of the C16-ketone (LiHMDS, PhSeCl), selenoxide elimination (H_2O_2) to give highly strained bridgehead enone **34**, and immediate trapping with water (aq THF, AcOH) provided tertiary alcohol **35** comprising the complete hexacyclic skeleton of the C19-norditerpenoid alkaloids. The structure was confirmed by extensive 2D NMR analysis.[21]

Completion of the hexacyclic skeleton of the norditerpenoid alkaloids was a welcome achievement. However, the exploration

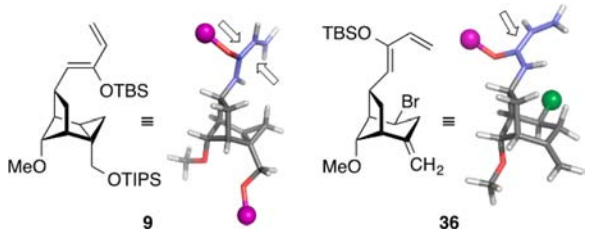

Figure 7. Three-dimensional models of original cyclopropane-containing siloxydiene **9** and bromine-containing siloxydiene **36** suggesting improved diastereofacial selectivity in the Diels–Alder cycloaddition of **36**. Dienes are shown in blue, bromine is shown as a green sphere, and silyl groups are abbreviated as purple spheres for simplicity.

of the installation of the remaining functional groups was hampered by low material throughput resulting primarily from the poor diastereoselectivity of the azepinone/siloxydiene Diels–Alder cycloaddition between **8** and **9** (Figure 4). Therefore, we embarked upon a second-generation synthesis to enable the total synthesis of neofinaconitine.

Enhanced Azepinone/Siloxydiene Diels–Alder Diastereoselectivity through Rational Substrate Reengineering. To improve the diastereofacial selectivity of the azepinone/siloxydiene Diels–Alder cycloaddition, we envisioned alternative siloxydiene **36** (Figure 7). On the basis of molecular modeling studies, we hypothesized that a sterically demanding bromine atom would restrict rotation and block the "back" face of the diene, thus favoring the desired facial approach of the dienophile from the "front" face. It was unclear, however, whether such reengineering of the diene would erode the excellent regioselectivity and *endo* selectivity observed previously.

To test this hypothesis, siloxydiene **36** was prepared from Weinreb amide **19** (Figure 8). Silyl deprotection (TBAF) was followed by acid-catalyzed nucleophilic cyclopropane fragmentation of the resulting cyclopropyl carbinyl alcohol to provide bromide **37**. This transformation proved to be nontrivial because competing intramolecular trapping of the putative cyclopropylcarbinyl carbocation by the amide led to various side products. Ultimately, we found that treatment with HBr/AcOH in fluorobenzene promoted the desired fragmentation with mimimal side reactions and concomitant installation of the equatorial bromide. Siloxydiene **36** was then prepared through a two-step procedure (vinylmagnesium bromide, THF, then TBSOTf, KHMDS, −78 °C).[26] The requisite *N*-ethyl azepinone dienophile **8b** was synthesized from ϵ-caprolactone (cf. Figure 4).[21] We were then in a position to test whether the equatorial bromide in siloxydiene **36** would provide the desired facial control in the key Diels–Alder cycloaddition.

Extensive experimentation revealed that the Diels–Alder cycloaddition between siloxydiene **36** and dienophile **8b** could be executed under $SnCl_4$ catalysis to provide cycloadduct **38** as a single isomer with the desired stereochemical configuration, as confirmed by X-ray crystallography. All other Lewis acids tested gave lower yields or selectivities (e.g., $Yb(OTf)_3$, $Sc(OTf)_3$, $ZnCl_2$). The excellent stereoselectivity is thought to arise from effective blocking of the undesired "back" face by the bulky bromine atom, favoring dienophile approach from the desired "front" face (Figure 7). We then attempted Mannich-type *N*-acyliminium cyclization to install the C11–C17 bond as in Figure 5. Although the treatment of **38** with Tf_2NH did effect the desired cyclization, isomerization of the exocyclic

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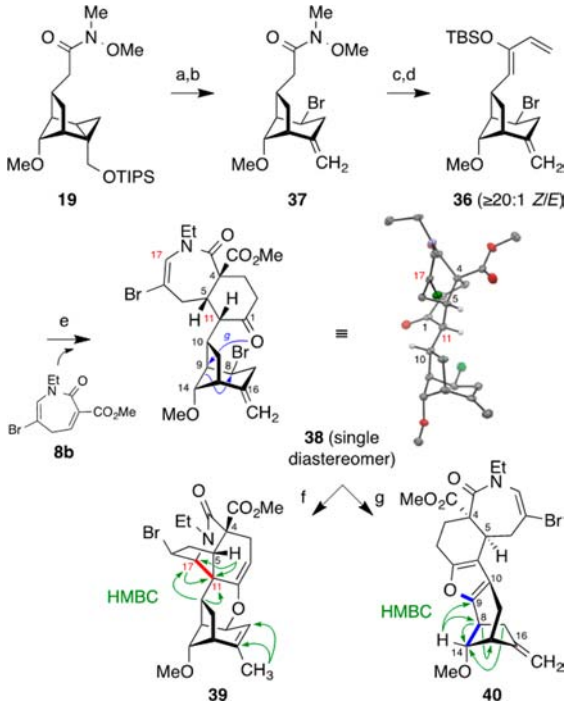

Figure 8. Diastereoselective Diels–Alder cycloaddition of bromide-containing siloxydiene **36**. (a) TBAF, THF, 99%. (b) HBr/AcOH, C_6H_5F, 0 °C, 63%. (c) vinylmagnesium bromide, THF, 0 °C. (d) TBSOTf, KHMDS, THF, −78 °C, 80% over two steps. (e) **8b**, $SnCl_4$, 4 Å molecular sieves, CH_3CN, 87%. (f) Tf_2NH, CH_2Cl_2, 46%. (g) AgO_2CCF_3, CH_2Cl_2, 60%.

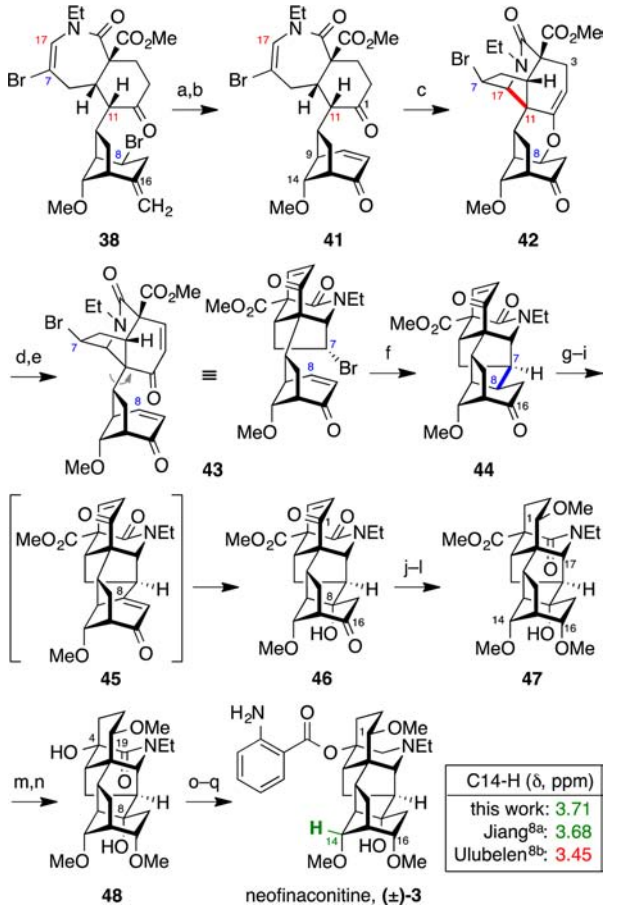

Figure 9. Completion of the total synthesis of neofinaconitine via C11–C17 Mannich-type *N*-acyliminium cyclization and C7–C8 radical cyclization; diagnostic ^1H NMR peaks for neofinaconitine[11a] and delphicrispuline[11b] ($CDCl_3$). (a) OsO_4, NMO, THF, H_2O, then $Pb(OAc)_4$, 65%. (b) DBU, toluene, 87%. (c) Tf_2NH, CH_2Cl_2, 75%. (d) CAN, CH_3CN, H_2O, 60 °C. (e) MsCl, Et_3N, CH_2Cl_2, 50 °C, 66% over two steps. (f) Bu_3SnH, AIBN, PhH, 80 °C, 99%. (g) TMSOTf, Et_3N, THF, 0 °C. (h) PhSeCl, CH_2Cl_2, 0 °C 86% over two steps. (i) $NaIO_4$, THF, H_2O, 59%. (j) Pd/C, H_2, EtOAc. (k) $NaBH_4$, MeOH, 0 °C, 89% over two steps. (l) MeI, *t*-BuOK, THF, 0 °C, 34%. (m) $LiBH_4$, THF. (n) CrO_3, 0.5 N H_2SO_4, 40% over two steps. (o) $LiAlH_4$, THF, 85 °C. (p) *o*-NO_2BzCl, DMAP, Et_3N, C_6H_6, 80 °C. (q) Zn, HCl, MeOH, H_2O, 13% over three steps.

double bond also occurred (**39**). Attempted activation with Ag(TFA) resulted in skeletal rearrangement of the bicyclo[3.2.1] ring system (**40**), whose structure was assigned on the basis of 2D NMR analysis.[21]

Completion of the Total Synthesis of Neofinaconitine. To overcome the above undesired reactions, we reasoned that an alternative enone substrate **41** (Figure 9) would allow the orchestration of the desired Mannich-type *N*-acyliminium cyclization by obviating the olefin migration in **39** and by precluding the skeletal rearrangement in **40** as a result of poor stereoelectronic overlap between the C9–C14 bond and the enone π system. Thus, chemoselective oxidative cleavage of the C16 exocyclic olefin in **38** (OsO_4, NMO then $Pb(OAc)_4$) followed by bromine elimination with DBU provided enone **41**. As predicted, the treatment of **41** with Tf_2NH then provided desired cyclization product **42**, presumably via acid-catalyzed conjugate addition of the C1 ketone oxygen to the enone, followed by Mannich-type *N*-acyliminium cyclization to furnish the C11–C17 bond.

Construction of the aconitine skeleton was then completed via a series of transformations similar to those in Figure 6. Allylic oxidation at C3 of enol ether **42** (CAN)[31] followed by activation of the resulting allylic alcohol as the mesylate with ensuing elimination (MsCl, Et_3N) provided bis-enone **43**. Conjugate addition of the radical generated from the secondary C7 bromide (Bu_3SnH, AIBN) to the enone at C8 then afforded hexacyclic skeleton **44**. Installation of the C8-hydroxyl was achieved by a three-step sequence involving silylenolation of the C16 ketone (TMSOTf, Et_3N), α-selenylation (PhSeCl), and selenoxide elimination with concomitant chemoselective conjugate addition of water at C8 of the putative highly strained bridgehead olefin intermediate **45** ($NaIO_4$) to afford tertiary alcohol **46**.

The C1 enone in **46** was then transformed to a C1 methyl ether in **47** by enone hydrogenation (H_2, Pd/C), $NaBH_4$ reduction of both the C1 and C16 ketones, and selective methylation of the C1 and C16 secondary alcohols in the presence of the C8 tertiary alcohol (MeI, *t*-BuOK). The remainder of the material consisted of a mixture of C1-*O* and C16-*O* monomethylated products. An alternative, improved approach involving the selective demethylation of a tris(methyl ether) was developed subsequently (vide infra). Notably, the $NaBH_4$ reduction step gave a single diastereomer with two newly generated stereocenters at C1 and C16. Although the stereochemical configurations at C1 and C16 remained formally unassigned at this stage, axial attack by borohydride was presumed, and the material was carried forward for later verification of the configurations at these centers.

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The endgame was then advanced by one-carbon oxidative truncation of the C4 methyl ester in **47** to the tertiary alcohol in **48** ($LiBH_4$ then CrO_3).[32] Amide reduction at C19 in **48** ($LiAlH_4$) then revealed the requisite tertiary amine. The remaining formidable task was selective acylation of the C4 tertiary alcohol in the presence of the C8 tertiary alcohol. The scarcity of literature precedents for such a hindered acylation with anthranilic acid[33] prompted us to develop a two-step procedure via the corresponding *o*-nitrobenzoate (*o*-NO_2BzCl, then Zn, HCl) to provide racemic neofinaconitine, (±)-**3**. The observed site selectivity for C4 presumably arises from steric shielding of the C8 alcohol by the C14- and C16-methoxy groups.

The ^{1}H NMR spectrum of this synthetic material was consistent with the reported spectral data for neofinaconitine.[11a,21] Unfortunately, we were unable to obtain an authentic sample for direct comparison, and efforts to prepare an X-ray-quality crystal with this material were unsuccessful.

Relay Synthesis of Neofinaconitine and 9-Deoxylappaconitine from Condelphine and Structural Confirmation. Although the spectral agreement above confirmed that our synthetic material was identical to the natural product, the lack of stereochemical confirmation at C1 and C16 in our total synthesis and the spectral discrepancy between neofinaconitine and delphicrispuline[11] at the C14 proton prompted us to develop a relay synthesis of neofinaconitine starting from a commercially available aconitine alkaloid that provided well-established stereochemistry and bond connectivity. The convergence of spectral data for the relay synthetic material, our fully synthetic material, and the natural product would then further corroborate the assigned structure of neofinaconitine.

After a careful evaluation of commercially available alkaloids from the aconitine family, condelphine (**49**) was chosen as the starting point for relay synthesis because it possesses all of the required substitutions and stereochemistry at C1, C8, C14, and C16 (Figure 10). However, a method needed to be developed for the truncation of the C4-methoxymethyl group to the requisite C4-hydroxyl.

The relay synthesis began with basic hydrolysis of the C14 acetate of condelphine (**49**) (aq NaOH),[34] followed by permethylation (NaH, MeI) to give a pentamethyl ether that was subjected directly to $KMnO_4$ oxidation of the tertiary amine to afford C19 amide **50**.[32] This seemingly superfluous C19 oxidation served two vital purposes. First, it enabled selective demethylation of the C18-methoxy group (BBr_3), presumably because of boron precoordination to the C19 carbonyl enabling the selective activation of C18 oxygen. Second, it promoted the oxidative cleavage of the C18 alcohol (CrO_3) to deliver the requisite C4 tertiary alcohol (−)-**48**, in which the C8-methoxy group had also been cleaved (H_2SO_4, 80 °C). This formal C8-*O*-demethylation may proceed through the intermediacy of the C8 tertiary carbocation, which is trapped with water. Finally, (−)-**48** was advanced to enantiomerically pure neofinaconitine, (+)-**3**, as in the total synthesis route (cf. Figure 9).

The spectroscopic data of the relay synthetic neofinaconitine matched those of the total synthesis material, confirming the identity of the latter and the stereochemical configurations at C1 and C16. In addition, the acetylation of neofinaconitine (Ac_2O, pyridine) afforded 9-deoxylappaconitine, (+)-**51**, the spectral data of which was also consistent with literature data.[11a,21] Furthermore, X-ray crystallographic analysis of the relay synthetic neofinaconitine provided unambiguous confirmation of the structure of the relay synthetic material and, by extension, the structures of the fully synthetic and natural neofinaconitine. Variation of the concentration did not modulate the ^{1}H NMR chemical shift of the C14 proton, and the addition of 1 equiv of HCl resulted in precipitation from $CDCl_3$. Accordingly, because of the significant discrepancy in the reported chemical shift of the C14 proton of delphicrispuline (Figure 9), its structural assignment as identical to neofinaconitine merits reevaluation.

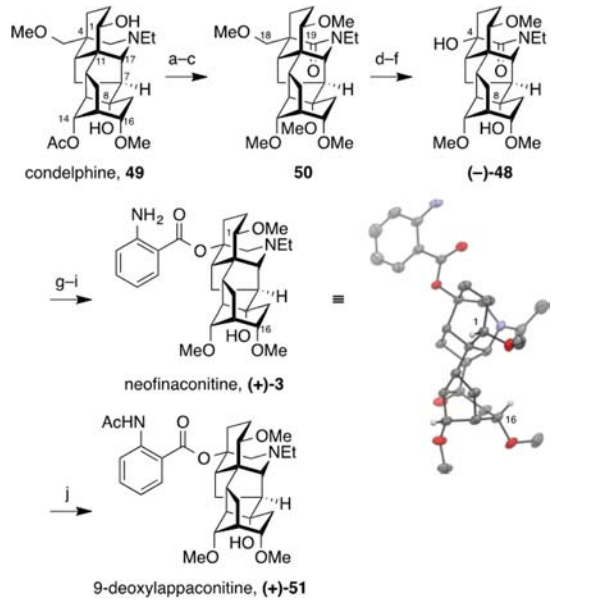

Figure 10. Relay synthesis of neofinaconitine and 9-deoxylappaconitine from condelphine. (a) NaOH, H_2O, EtOH. (b) NaH, MeI, THF, 100 °C. (c) $KMnO_4$, H_2O, CH_2Cl_2, 54% over three steps. (d) $BBr_3 \cdot SMe_2$, CH_2Cl_2, −78 °C. (e) CrO_3, 0.5 N H_2SO_4. (f) 0.5 N H_2SO_4, 80 °C, 46% over three steps. (g) $LiAlH_4$, THF, 80 °C. (h) *o*-NO_2BzCl, DMAP, Et_3N, C_6H_6, 80 °C. (i) Zn, HCl, MeOH, H_2O, 70% over three steps. (j) Ac_2O, pyridine, 91%.

■ CONCLUSIONS

A novel, modular, and convergent synthetic strategy for the norditerpenoid alkaloids has been developed, culminating in the first total synthesis of neofinaconitine. An unusual Diels–Alder cycloaddition between unstable cyclopentadiene **10** and cyclopropene **11** proved successful with no scrambling of cyclopentadiene substituents observed. Azepinones **8** were also established as competent Diels–Alder dienophiles that allowed the rapid construction of the [5.4.0]-bicycloazepine ring system in key cyclization precursors **7** and **38**. Although the Mannich-type *N*-acyliminium cyclization of **24** afforded cyclic enol ether **29** that proved recalcitrant to hydrolysis, this obstacle was overcome using an oxidative elimination approach (**30** → **32**). The poor diastereoselectivity of the key azepinone/siloxydiene Diels–Alder cycloaddition was improved by substrate reengineering with a sterically demanding bromine substituent. Moreover, a concise, 10-step relay synthesis of neofinaconitine and 9-deoxylappaconitine from condelphine was developed, confirming the structure of the neofinaconitine natural product by X-ray crystallographic analysis. The determination of the true structure of delphicrispuline will require further studies. Synthetic access to neofinaconitine analogues will enable full biological evaluation and the elucidation of mechanisms of ion channel modulation by the norditerpenoid alkaloids.

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■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and analytical data for key new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Regiochemistry in **17** was assigned by COSY analysis of the subsequent ketone **18**, and stereochemical configurations were assigned on the basis of 1D-NOE analysis of subsequent Weinreb amide **19**.

(21) See Supporting Information for complete details.

(22) Diels−Alder cycloaddition of 2,5-bis(*t*-butyldimethylsiloxy) cyclopentadiene with cyclopropene **11** also favored a contra-steric approach (≥10:1). In contrast, reaction with benzophenone as the dienophile proceeded almost exclusively from the sterically less-hindered face of this diene (1:15).

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