Alkaloid Synthesis

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Synthesis of the C_{18}-Norditerpenoid Alkaloid Neofinaconitine: A Lesson in Convergent Synthesis Planning

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alkaloids · cycloaddition · natural products · terpenoids · total synthesis

In memory of David Y. Gin

Whether you are a seasoned veteran or just entering this fascinating world of molecules, chances are you would be astounded by the architectural intricacy and beauty of the norditerpenoid alkaloids that originate from the *Aconitum* and *Delphinium* species (Figure 1).[1] Indeed, these natural

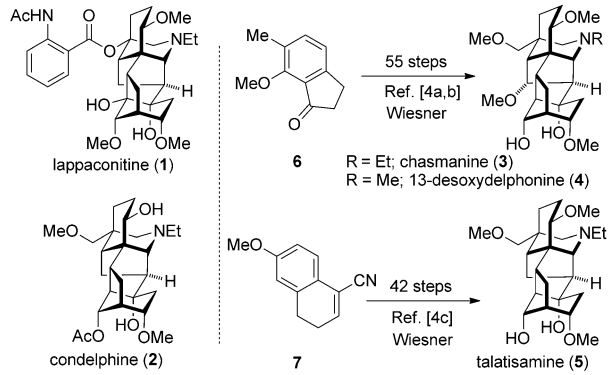

Figure 1. Structures of representative norditerpenoid alkaloids (**1**–**5**) and total syntheses of **3**, **4**, and **5** by Wiesner et al.

products, not to mention their wide spectrum of pharmacological properties and the commercial success of lappaconitine (Allapinin, **1**),[2] represent unprecedented challenges for the synthetic community to rival nature's sophisticated biosynthetic machinery.[3] From both design and execution viewpoints, the unique carbon connectivities and oxygenation pattern within the hexacyclic cage-like scaffold demand innovative synthetic solutions to access the naturally occurring substance in its entirety, or even partial structural domains of this compound. After nearly four decades of synthetic investigations with seminal contributions from Wiesner and co-workers in the 1970s,[4,5] a major milestone was recently achieved by a team of researchers at the Memorial Sloan–Kettering Cancer Institute with a remarkable total synthesis of neofinaconitine (**8**, Scheme 1).[6]

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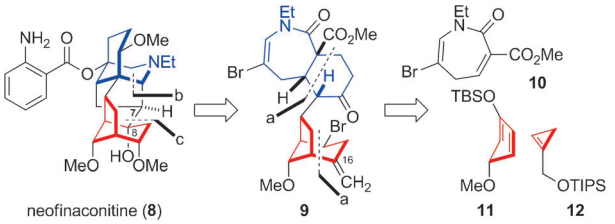
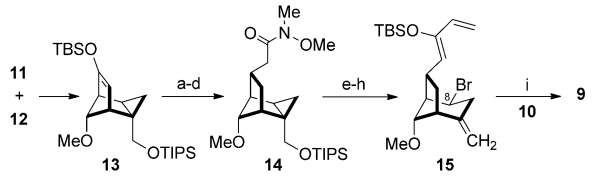


Scheme 1. Retrosynthetic analysis of neofinaconitine (**8**) leading to intermediate **9** and building blocks **10**, **11**, and **12**. a = Diels–Alder reaction, b = Mannich-type *N*-acyliminium cyclization, c = radical cyclization.

Strategically, this synthetic route relied not only on a convergent approach, but also on several cleverly designed bond-forming events with exquisite stereocontrol together with hidden reactivities for the late-stage introduction of functional groups. Two Diels–Alder reactions served to assemble the lower all-carbon [3.2.1] bicyclic system (in red) and to combine it with the upper azepinone **10**; the latter structural motif was converted into the nitrogen-containing [3.3.1] bicycle (in blue) by an intramolecular Mannich-type transformation (Scheme 1). An intramolecular radical addition was envisaged to forge the C7–C8 bond, which completes the formation of the carbon backbone of the target molecule.

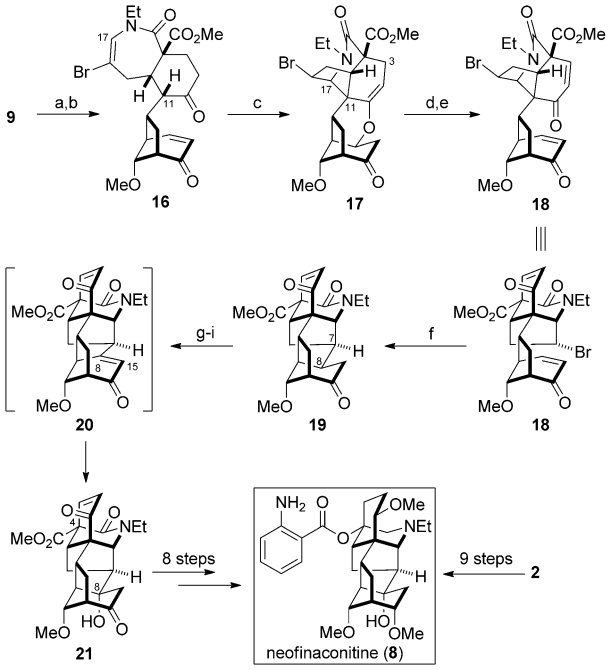
The success of the opening Diels–Alder reaction necessitated the direct introduction of dienophile **12** to the reaction mixture in which diene **11** was generated, to afford **13** as the major regioisomer (1.6:1) and as the diastereomer that originates from a contra-steric approach of the reaction partners (5.6:1; Scheme 2). In a four-step sequence, Diels–Alder product **13** was smoothly converted into Weinreb amide **14**, which was isolated as a single regioisomer. Results of earlier studies suggested that a sterically demanding directing group was essential for the ensuing Diels–Alder reaction with azepinone **10** to proceed diastereoselectively. Therefore, a nucleophilic cyclopropane fragmentation (HBr, AcOH) was employed for the introduction of a sterically demanding bromine atom at the C8 position (neofinaconitine numbering). After conversion of the Weinreb amide into the corresponding silyloxydiene, the much anticipated Diels–Alder reaction between **10** and **15** proceeded with remarkable



Scheme 2. Synthesis of intermediate **9**: a) NaOH, THF/H_2O; b) methyl diethylphosphonoacetate, KHMDS, 0 °C→reflux; c) H_2, Pd/C, EtOAc; d) MeNHOMe·HCl, $AlMe_3$, THF, 39% over six steps (including the generation of **12**); e) TBAF, THF, 99%; f) HBr/AcOH, C_6H_5F, 0 °C, 63%; g) vinylmagnesium bromide, THF, 0 °C; h) TBSOTf, KHMDS, THF, −78 °C, 80% over two steps; i) $SnCl_4$, M.S. (4 Å), CH_3CN, 87%. KHMDS = potassium bis(trimethylsilyl)amide, M.S. = molecular sieves, TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

efficiency (87% yield) to afford cycloadduct **9** as a single diastereoisomer.

In preparation for the intramolecular Mannich-type cyclization to forge the nitrogen-containing [3.3.1] bicycle of neofinaconitine and to prevent the unwanted acid-mediated isomerization of the exocyclic olefin at the C16 position, this functional group was oxidatively cleaved (Scheme 3). Upon elimination of the superfluous C8 bromide, the obtained enone **16** underwent the desired intramolecular Mannich cyclization in an impressive 75% yield with concomitant



Scheme 3. Completion of the total synthesis of neofinaconitine (**8**): 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%. AIBN = 2,2′-azobis(2-methylpropionitrile), CAN = cerium(IV) ammonium nitrate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl, NMO = *N*-methylmorpholine *N*-oxide.

formation of a cyclic enol ether (intermediate **17**). Cleavage of the enol ether proved non-trivial, but ultimately, a creative solution was found by introducing a leaving group (methanesulfonate) at the C3 position; this was followed by an extended double β-elimination to reveal dienone **18**. To complete the carbon framework of neofinaconitine, intramolecular radical cyclization of dienone bromide **18** took place to deliver hexacyclic intermediate **19** in nearly quantitative yield.

Next, the C8 hydroxy group had to be introduced, which called for a formal C–H oxidation at this position. Application of oxidative selenium chemistry first introduced the double bond between the C8 and C15 carbon atoms; the resulting highly strained enone **20** underwent spontaneous nucleophilic attack by water, which installed the tertiary alcohol at the C8 position. With the advanced intermediate **21** in hand, several redox transformations, including decarboxylative hydroxylation at the C4 position[7] and installation of the C4 anthranilate group, finally completed the total synthesis of racemic neofinaconitine (**8**).[8] Furthermore, commercially available condelphine (**2**) was also converted into optically active neofinaconitine (**8**), which confirmed the authenticity of the material that was obtained by total synthesis.[9]

This impressive synthesis of the norditerpenoid alkaloid neofinaconitine (**8**) employed several key transformations in complex molecular settings with remarkable efficiency and a highly modular approach that involves two beautifully conceived and executed Diels–Alder reactions. The development of a successful synthetic strategy, in combination with previous achievements by other groups, has enabled the completion of this efficient and elegant total synthesis, which represents another example of the never ceasing advancement of synthetic organic chemistry.

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[8] Based on intermediates **10** (5 steps, 49% overall yield), **11** (2 steps, 75% overall yield), and **12** (3 steps, 72% overall yield), this synthesis was achieved in 30 linear steps and in 0.027–0.145% overall yield (A higher yield was reported starting from **2** although the same synthetic transformations were employed in both total syntheses; this is presumably due to the greater abundance of the starting material for the relay synthesis). Based on the information publicly available (Ref. [4]), overall yields cannot be established for the total syntheses by Wiesner and co-workers, because reaction yields for several transformations that are part of the overall syntheses were not reported.

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