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Syntheses of Denudatine Diterpenoid Alkaloids: Cochlearenine, *N*-Ethyl-1α-hydroxy-17-veratroyldictyzine, and Paniculamine

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Supporting Information

ABSTRACT: The denudatine-type diterpenoid alkaloids cochlearenine, *N*-ethyl-1α-hydroxy-17-veratroyldictyzine, and paniculamine have been synthesized for the first time (25, 26, and 26 steps from **16**, respectively). These syntheses take advantage of a common intermediate (**8**) that we have previously employed in preparing aconitine-type natural products. The syntheses reported herein complete the realization of a unified strategy for the preparation of C_{20}, C_{19}, and C_{18} diterpenoid alkaloids.

Syntheses of architecturally complex secondary metabolites are not easily accomplished using an iterative approach where a particular bond construction method (e.g., aldol reaction, cross-coupling, etc.) features prominently.[1−5] For topologically complex frameworks, the strategy that is adopted for synthesis takes on added significance. Many highly complex, bioactive, secondary metabolites often co-occur in the producing organism with congeners that also possess interesting and desirable bioactivity. For these reasons, unified strategies using a versatile intermediate often provide the most efficient approach to these topologically complex, structurally related, compounds.[6] The diterpenoid alkaloids (Figure 1 and Scheme 1) are a family

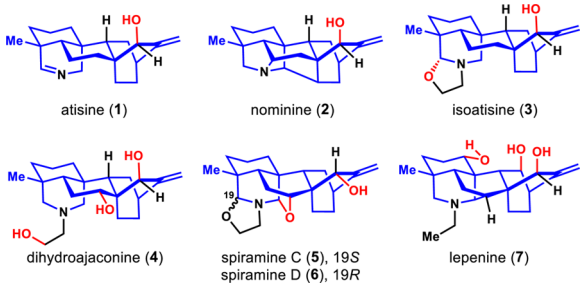
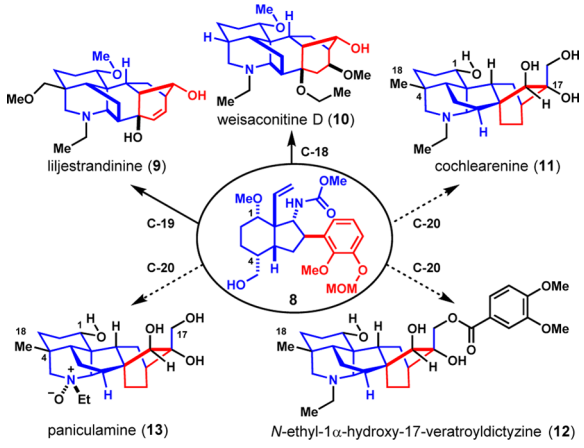


Figure 1. Examples of C_{20} diterpenoid alkaloids.

of compounds for which this context is highly pertinent. These secondary metabolites are isolated from the *Aconitum*, *Consolidum*, and *Delphinium* genera of plants, which are used in traditional medicine (e.g., in China) for the treatment of pain and cardiovascular diseases.[7−9] Importantly, these natural products are noted for their potential to modulate Na^+ and/or K^+ ion channels[10] and in some cases may be subtype-specific.[11] This characteristic may allow specific targeting of particular ion channel isoforms implicated in channelopathies and, thus, may provide new opportunities for developing therapeutics where side effects are minimized.[12]

Scheme 1. A Unified Strategy to the C_{20}, C_{19}, and C_{18} Diterpenoid Alkaloids



The over 1200 known diterpenoid alkaloids are categorized into C_{20}, C_{19}, and C_{18} families depending on the number of contiguous carbon atoms comprising the framework.[13−15] These nitrogen-containing diterpenoids have attracted significant attention from the synthetic community as a result of their diverse biological activity and structural complexity.[16] The earliest synthetic efforts focused on the C_{20} alkaloids, resulting in syntheses of atisine (**1**),[17,18] garryine,[19,20] veatchine,[20,21] napelline,[22] and nominine (**2**).[23] Baran et al. demonstrated a unified approach to (−)-methyl atisenoate, its alkaloidal counterpart (−)-isoatisine (**3**), and the hetidine skeleton.[24] Similarly, Xu et al. reported the syntheses of atisine-type dihydroajaconine (**4**) as well as spiramines C (**5**) and D (**6**), along with the biosynthetically related diterpenes spiramilactone B and spiraminol, all arising from a common, advanced intermediate.[25] Fukuyama and co-workers were the first to complete a synthesis of a denudatine-type alkaloid, lepenine (**7**).[26]

While previously reported synthesis strategies target either one diterpenoid alkaloid or several biogenetically related natural products within the C_{20} family, we have focused on a strategy that would provide access to C_{20}, C_{19}, and C_{18} congeners. We recently disclosed a successful approach to the C_{19} and C_{18} secondary metabolites liljestrandinine (**9**) and weisaconitine D (**10**) using

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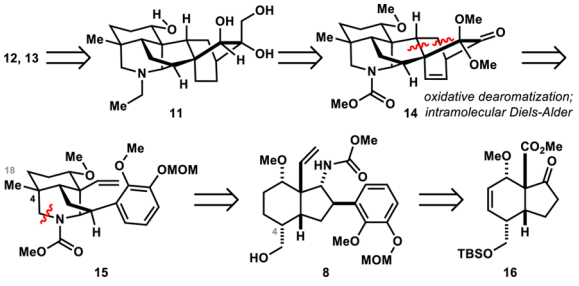
hydrindane derivative **8** as a common intermediate.[27] Herein, we demonstrate the extension of this strategy to the syntheses of the C_{20} denudatine-type alkaloids cochlearenine (**11**),[28,29] *N*-ethyl-1α-hydroxy-17-veratroyldictyzine (**12**),[30] and paniculamine (**13**)[31] (Scheme 1). The seemingly "simpler" framework of **11**, **12**, and **13** (relative to **9** and **10**) belies the challenge that is inherent in their syntheses. This challenge includes the installation of the C18 methyl group and the orchestration of synthetic steps to achieve the desired hydroxylation pattern on the bicyclo[2.2.2] structural motif. From a function standpoint, cochlearenine (**11**) is especially interesting because it exhibits a dose-dependent bradycardic effect in guinea pig atria at doses between 0.1 and 1.0 mg/mL.[32] The biological functions of veratroylated derivative **12** and *N*-oxide **13** have not been evaluated; we anticipate that their structural similarities to cochlearenine (**11**) would yield insight into the structure–activity relationships of the denudatines.

Retrosynthetically, we envisioned **11**, **12**, and **13** arising from **14** by late-stage manipulation of the functional groups on the [2.2.2] bicycle (Scheme 2). This bicyclic moiety would be forged

Scheme 2. Retrosynthesis of 11, 12, and 13

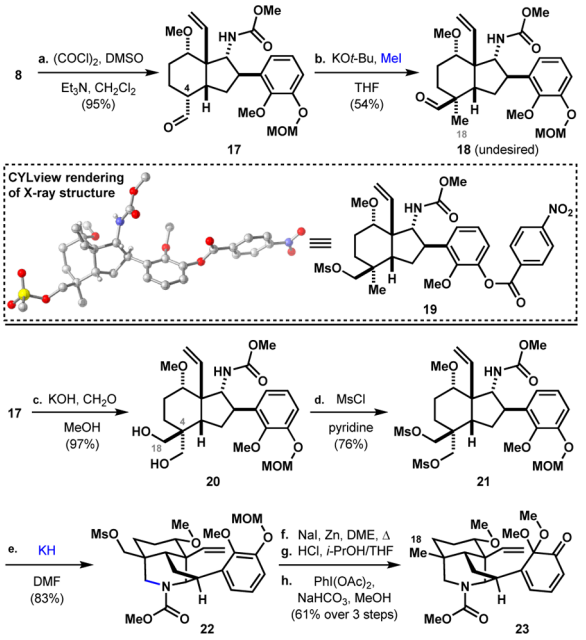


by intramolecular Diels–Alder cycloaddition of tricycle **15**, which can be assembled from **8** by a sequence involving methylation at C4 to install the C18 methyl group and piperidine ring formation. In turn, **8** could be obtained in 10 steps (25% overall yield) from **16** using an improved version of our previously established sequence (see SI for details).[27]

With **8** in hand, we focused on installing the C18 methyl group (Scheme 3). In preparation for this functionalization, **8** was converted to aldehyde **17** in 95% yield using a Swern oxidation. It was our expectation that generation of an enolate from **17** (with accompanying deprotonation of the methyl carbamate) and treatment with a methyl electrophile would result in α-methylation of the enolate from the convex face of the bicycle.[33] However, in our hands only the C4 epimer **18**, which is unambiguously supported by an X-ray crystallography study of its derivative, **19**, was obtained. Presumably, approach of the electrophile from the convex face of the bicycle is disfavored in this case due to steric crowding imposed by the axially disposed vinyl group at the ring junction through a developing *syn*-pentane interaction between the electrophile and angular vinyl group (see Supporting Information for details). To overcome this challenge, we sought to install an electrophile at C4 that would obviate the undesired diastereoselectivity that we observe. Inspired by the studies of Wiesner,[34,35] we have shown in our previous studies[27] that an aldol–Cannizzaro sequence on **17** produces diol **20** (97% yield), which was activated to give dimesylate **21** in 76% yield.

We have previously found that subjecting **21** to KO*t*-Bu to effect cyclization to piperidine **22** results in low yields.[27] A closer examination of this reaction revealed that piperidine **22** is formed in only 30% yield and a significant amount of the mass balance

Scheme 3. Installing the C18 Methyl Group[a]



[a]Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2C1_2, −78 °C, then Et_3N, −78 to 23 °C, 95%; (b) KO*t*-Bu, MeI, 0 °C, 54%; (c) KOH, formalin, MeOH, 97%; (d) MsCl, pyridine, 0–23 °C, 76%; (e) KH, DMF, 23 °C, 83%; (f) NaI, Zn, DME, 105 °C; (g) HCl, THF/*i*-PrOH, 23 °C; (h) $PhI(OAc)_2$, $NaHCO_3$, MeOH, 23 °C, 61% over three steps.

(39%) is accounted for by KO*t*-Bu mediated decarbamoylation[36] to the corresponding deprotected amine that does not cyclize under the reaction conditions (see SI for details). This challenge was overcome by using KH as the base. This modification affords piperidine **22** as the major product (62% yield) along with minor amounts of side products lacking the mesyl group (16%, see SI) when conducted in THF as the solvent. Using KH and DMF as the solvent, cyclization of **21** occurs to give **22** as the exclusive product in 83% yield. The methylene *O*-mesylate group of **22** was reduced to the corresponding methyl group using a combination of NaI/Zn. In this way, the methyl group that is present in all of the C_{20} alkaloids can be stereoselectively introduced. Removal of the MOM group and oxidative dearomatization of the resulting phenol with $PhI(OAc)_2$ in MeOH yields dienone **23** in 61% yield over three steps and sets the stage for an intramolecular Diels–Alder cycloaddition.

Heating dienone **23** in *p*-xylene effects clean conversion to hexacycle **14** in 80–87% yield (Scheme 4). To complete the C_{20} framework of the denudatine natural products, an additional carbon atom is required on the [2.2.2] bicycle (see **26**). To this end, we first investigated a Corey–Chaykovsky epoxidation.[37] Using dimethylsulfonium ylide in THF/DMSO at 0 °C resulted in exclusive formation of epoxide **24**, which was the undesired diastereomer in the context of our target molecules. The diastereomer of epoxide **24** (i.e., **26**) was easily obtained from **14** using a Wittig methylenation (and ketal hydrolysis to give **25**; 96% yield) and Weitz–Scheffer epoxidation[38] to install an α-epoxide. Of note, the use of hydrogen peroxide or *tert*-butyl hydroperoxide led to poor conversions and to mixtures of epoxide diastereomers, whereas the use of trityl peroxide[39] generated epoxy-ketone **26** as a single diastereomer in 57% yield.

Drawing inspiration from an observation made by Wang and co-workers,[40] epoxy-ketone **26** was subjected to a solution of

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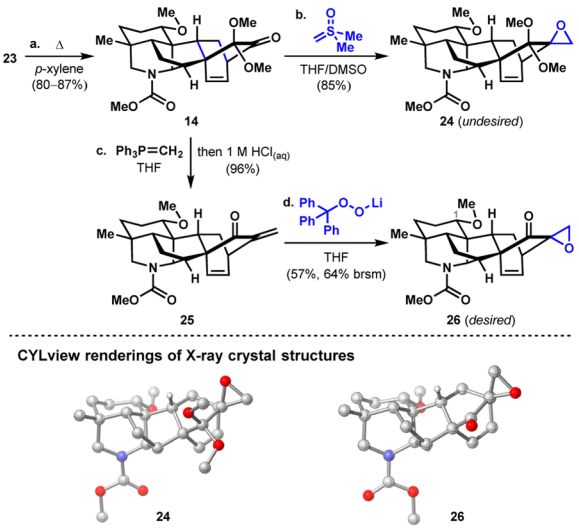
Scheme 4. Complementary Epoxide Formations[a]

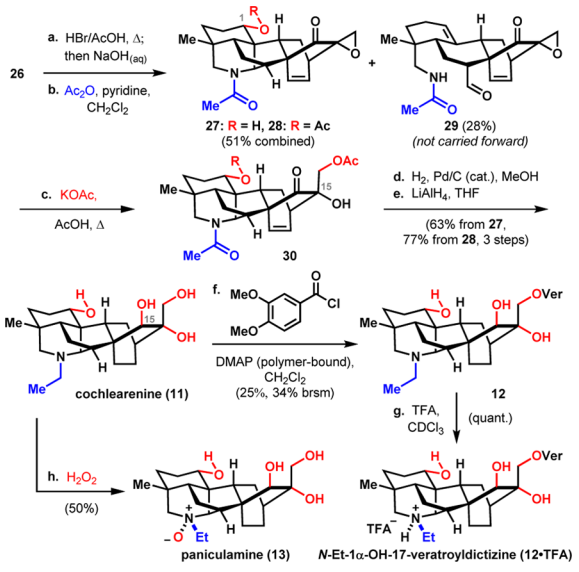


[a]Reagents and conditions: (a) *p*-xylene, 150 °C, 80−87%; (b) Corey−Chaykovsky reagent, THF/DMSO, 0−21 °C, 85%; (c) $Ph_3P{=}CH_2$ (from Ph_3PMeBr, LiHMDS, 70 °C), 0−40 °C, then 1 M $HCl_{(aq)}$, 96%; (d) Ph_3CO_2Li (from Ph_3CO_2H, MeLi), THF, 0−40 °C, 57% (64% brsm).

HBr/AcOH at 110 °C, which resulted in cleavage of the methyl carbamate and the methyl group on the C1 hydroxyl (Scheme 5). The desired *N*-acetylated products **27** and **28**, along with fragmentation product **29**, were formed in a combined 79% yield upon quenching with NaOH and treating the crude mixture with Ac_2O and pyridine.[41]

Mono- and diacetylated epoxy-ketones **27** and **28** (51% combined yield from **26**) were independently advanced to **11**, from which **12** and **13** were synthesized. This sequence commenced with epoxide opening using KOAc. The strained alkene group was hydrogenated using Pd/C as catalyst, and a final, global reduction with $LiAlH_4$ produced cochlearenine (**11**) in 63−77% yield over the three steps. While the spectroscopic data obtained for the material prepared by us is not consistent with those reported in the initial isolation disclosure,[28] it is consistent with the data reported in a subsequent isolation study,[29] with the exception of a single ^{13}C resonance (see SI for details). Using density functional theory (DFT), we confirmed that the predicted ^1H and ^{13}C NMR data for cochlearenine (**11**) agree most closely with our experimental data and fully support the assignment of the reported structure.[42] Coupling **11** with veratroyl chloride produces *N*-ethyl-1α-hydroxy-17-veratroyldictyzine (**12**) in 25% yield. The literature data[30] reported for this natural product are inconsistent with the ^1H and ^{13}C NMR data for the neutral form of the synthetic material. However, the isolation data are fully consistent with the protonated form (**31**) that is generated upon treatment with TFA. Finally, treating **11** with H_2O_2 affords paniculamine (**13**) in 50% yield.

Scheme 5. Accessing Denudatine Natural Products[a]



[a]Reagents and conditions: (a) HBr, AcOH, microwave (110 °C), 50 min, then 2 M $NaOH_{(aq)}$; (b) Ac_2O, pyridine, CH_2Cl_2, 0−23 °C, 22% **27** + 29% **28** + 28% **29**, two steps (79% combined yield); (c) KOAc, AcOH, 120 °C; (d) H_2 (100 psi), MeOH, 23 °C; (e) $LiAlH_4$, THF, 0−23 °C, three steps (63% from **27**, 77% from **28**); (f) veratroyl chloride, polymer-supported DMAP, CH_2Cl_2, 0−23 °C (25%); (g) TFA, $CDCl_3$; (h) H_2O_2, MeOH/H_2O, 60 °C (50%).

In summary, the first total syntheses of cochlearenine (**11**), *N*-ethyl-1α-hydroxy-17-veratroyldictyzine (**12**), and paniculamine (**13**) in racemic form have been accomplished. These syntheses were achieved in 25, 26, and 26 steps, respectively, from hydrindenone **16**. This readily available bicycle is prepared in 30 g in a single pass. Importantly, we have previously reported an enantioselective route to **16**,[27] and so our racemic syntheses of **11**, **12**, and **13** may be rendered enantioselective. From a broader perspective, the completion of the syntheses of these denudatine-type alkaloids represents a realization of a unified synthetic strategy to the C_{20}, C_{19}, and C_{18} diterpenoid alkaloids when placed in the context of our previously reported syntheses of liljestrandinine and weisaconitine D. Keys to success in preparing **11**, **12**, and **13** include a stereoselective installation of the C18 methyl group via dimesylate **21**, identifying optimal conditions for the piperidine ring formation, and demethylation of the 1-methoxy group under acidic conditions. Our syntheses of **11** and **12** should enable a study of the effect of veratroylation as well as of other acylations on the biological activity of the C_{20} denudatine-type diterpenoid alkaloids.[10,43] Furthermore, access to **13** should facilitate an evaluation of the importance of the basic tertiary amine to the biological activity of the denudatine-type alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07268.

Crystallographic data (CIF, CIF, CIF, CIF, CIF)
Procedures, DFT calculations, single crystal X-ray data, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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