A Benzyne-Insertion Approach to Hetisine-Type Diterpenoid Alkaloids: Synthesis of Cossonidine (Davisine)

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Supporting Information Placeholder

ABSTRACT: The hetisine-type natural products exhibit one of the most complex carbon skeletons within the diterpenoid alkaloid family. The use of network analysis has enabled a synthesis strategy to access alkaloids in this class with hydroxylation on the A-ring. Key transformations include a benzyne acyl-alkylation to construct a key fused 6-7-6 tricycle, a chemoselective nitrile reduction, and sequential C–N bond formations using a reductive cyclization and a photochemical hydroamination to construct an embedded azabicycle. Our strategy may enable access to myriad natural and unnatural products within the hetisine-type.

Voltage-gated sodium (Na_v), calcium (Ca_v), and potassium (K_v) channels regulate a wide variety of biophysical responses in the nervous, circulatory, and muscular systems.[1] As a result, the selective targeting of ion channels holds great promise for treating a number of channelopathies, including Alzheimer's disease, epilepsy, and chronic pain.[2] One of the greatest challenges in the discovery of small molecule modulators of ion channels, particularly Na_v channels, is to achieve high selectivity in targeting one isoform over another.[3] For example, targeting $Na_v1.7$ or 1.8 may prove useful in combating chronic pain, but off-target interactions with other isoforms leads to serious cognitive, cardiac, or muscular complications.[3a] The identification, synthesis, and study of isoform-selective ion channel modulators will facilitate a better understanding of the interactions responsible for selectivity.

The diterpenoid alkaloids, a collection of over 1200 natural products isolated from numerous plants in the *Aconitum*, *Delphinium*, and *Consolida* genera, show strong affinities for various Na_v and K_v channels, functioning as either agonists or antagonists.[4] This

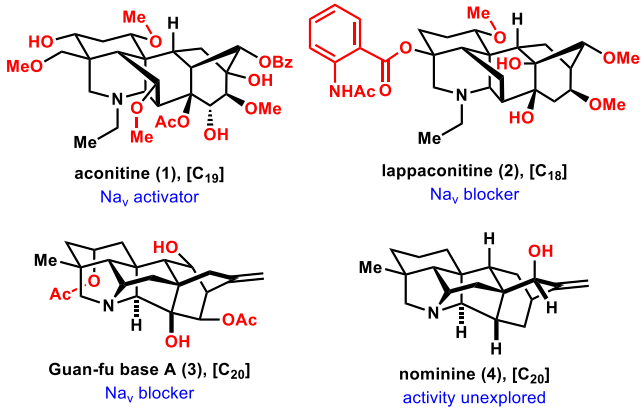


Figure 1. Representative diterpenoid alkaloids.

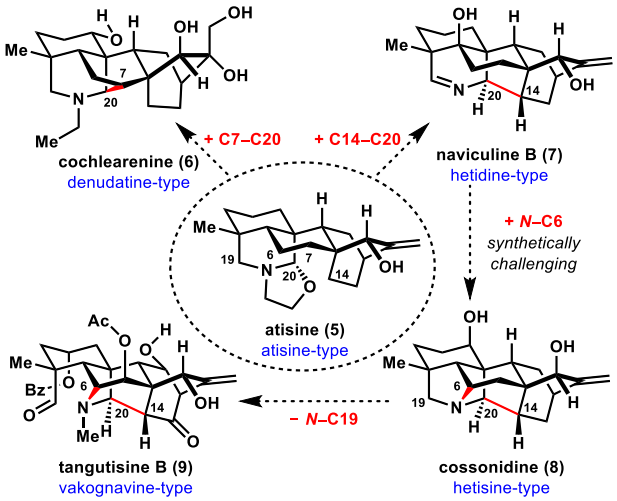
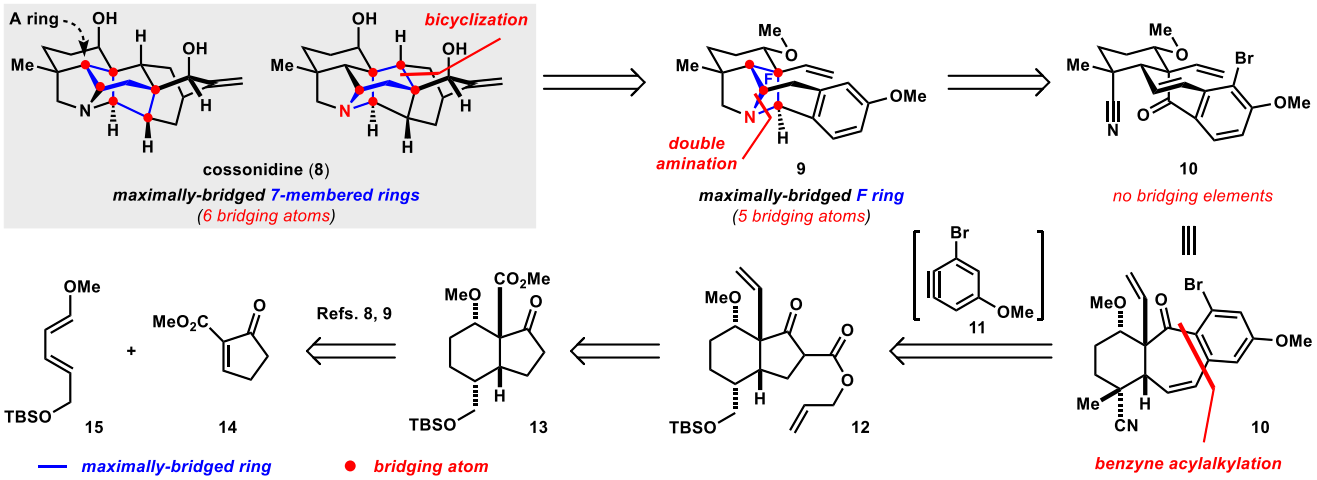


Figure 2. Biosynthetic relationships between selected C_{20}-diterpenoid alkaloids.

broad range of activity and selectivity arises from relatively subtle changes on scaffolds consisting of 18, 19, and 20 carbon atoms. For example, despite their overwhelming similarities, the C_{19}-diterpenoid alkaloid aconitine (**1**, Figure 1) is a potent Na_v channel activator, whereas the related C_{18}-diterpenoid alkaloid lappaconitine (**2**) is a Na_v channel blocker.[5] The C_{20}-diterpenoid alkaloid Guan-fu base A (**3**), another Na_v channel blocker, is approved and marketed in China for the treatment of arrhythmia.[6] Within this family, there exist other oxygenated congeners with unexplored activity.[7] Therefore, the ability to access myriad oxygenated diterpenoid alkaloid natural products and their associated derivatives would enable studies to deepen our understanding of the structure-activity relationships across all classes and types.

Our group's interest in this class of molecules has culminated in the syntheses of several C_{18}- and C_{19}-aconitine-type, as well as C_{20}-denudatine-type natural products.[8,9] Within the C_{20} family, the hetisine-type molecules are the most prevalent, with more than 120 known members, including **3**.[10] Of the biosynthetically related atisine-, denudatine-, hetidine-, hetisine- and vakognavine-type natural products (Figure 2), the carbon framework of the hetisine-type diterpenoid alkaloids (exemplified by cossonidine (**8**)) is considered to be the most complex, featuring a C14–C20 bond and an *N*–C6 bond, which results in a tertiary amine embedded within a heptacyclic skeleton. Strategies for the syntheses of atisine- and hetidine-type diterpenoid alkaloids have been advanced;[11–15] however, to date, only a single hetisine-type alkaloid—the monohydroxy-

Scheme 1. Network-Analysis-Guided Retrosynthesis of Cossonidine



lated nominine (**4**)—has been accessed through total synthesis by Muratake and Natsume[16] as well as by Gin and Peese.[17] The relatively low number of hetisine syntheses can, in part, be attributed to the challenge in forming the N-C6 bond at a late stage through chemical synthesis.[11a,13]

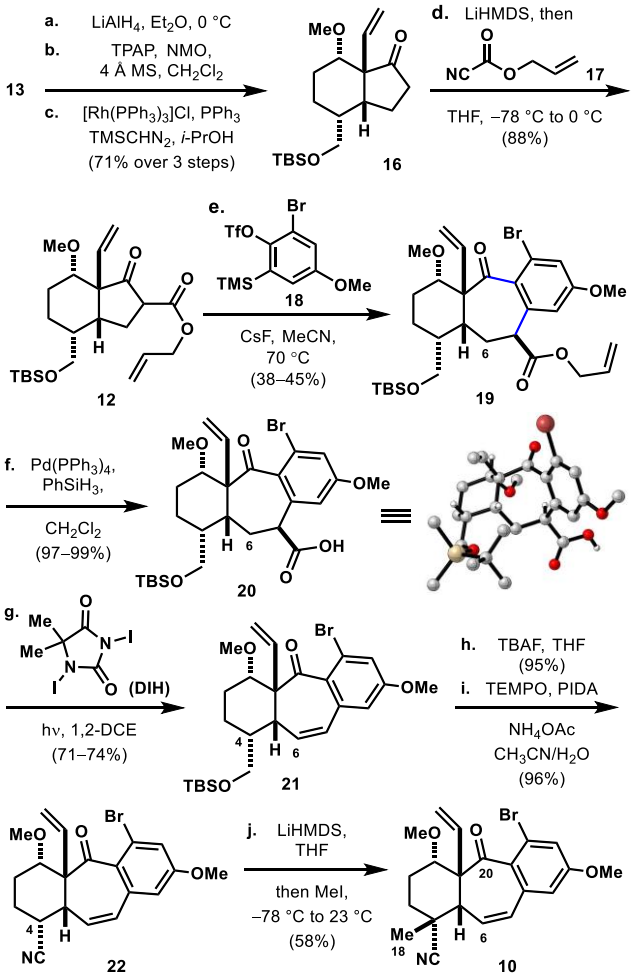
Cognizant of the fact that most hetisine-type diterpenoid alkaloids, including the medicinally relevant Guan-fu base A (**3**), possess additional oxygenation on the A ring, our group set out to develop a synthesis route to the hetisine framework that would introduce A ring oxygenation, while obviating the challenge associated with a late-stage installation of the N-C6 bond. In this Communication, we report a validation of our approach, which has resulted in the first synthesis of cossonidine (**8**), a hetisine-type alkaloid isolated independently in 1996 by de la Fuente[7b] and Pelletier[7c] (who termed this natural product davisine).

By constraining our analysis to a maximum ring size of seven in our network-analysis of cossonidine (**8**),[18,19] we identified two maximally-bridged ring systems: a carbocyclic 7-membered ring and a nitrogen-containing 7-membered ring (highlighted in blue, Scheme 1), both of which contain 6 bridging atoms. To achieve maximal simplification of the highlighted bridged ring systems, we envisioned a bicyclization transform that would alleviate bridging atoms in both ring systems, thus leading back to pentacycle **9** containing an alkene and arene functional groups. Network analysis of **9** revealed the F ring to be maximally-bridged, with 5 bridging atoms. Disconnecting the two C–N bonds in **9** using two amination transforms effectively simplified the target structure to fused tricycle **10**, which exhibits no bridging elements. Forging the seven-membered ring motif in **10** was envisioned to occur through an acyl-alkylation annulation between functionalized benzyne derivative **11** and β-ketoester **12**, which in turn could arise from literature-reported hydrindanone **13**.[8,9]

Hydrindanone **13**, prepared on multi-gram scale in two steps from dienophile **14** and diene **15** according to our previously reported procedures,[8,9] served as the starting point for our studies (see Scheme 2). $LiAlH_4$-mediated reduction of both the ester and ketone groups in **13**, followed by Ley oxidation[20] provided a ketoaldehyde intermediate (not shown). While olefination of the aldehyde under standard Wittig conditions led to poor yields of the desired alkene, application of Lebel's Rh-catalyzed methylenation[21] effected selective formation of terminal alkene **16** in 71% yield over 3 steps. Acylation using allyl cyanoformate (**17**)[22] proceeded in 88% yield to provide β-ketoester **12**, the substrate for the aryne insertion reaction. Following the precedent of Stoltz and coworkers,[23] treatment of a mixture of β-ketoester **12** and aryne precursor **18**[24] with CsF in MeCN at 70 °C provided tricycle **19** in 38–45% yields. The bromine atom on the aryne was required to obtain high regioselectivity in the acyl-alkylation process, in accordance with studies by Garg and Houk.[25] This transformation represents one of the most complex applications of the benzyne acyl-alkylation reaction reported to date.[26]

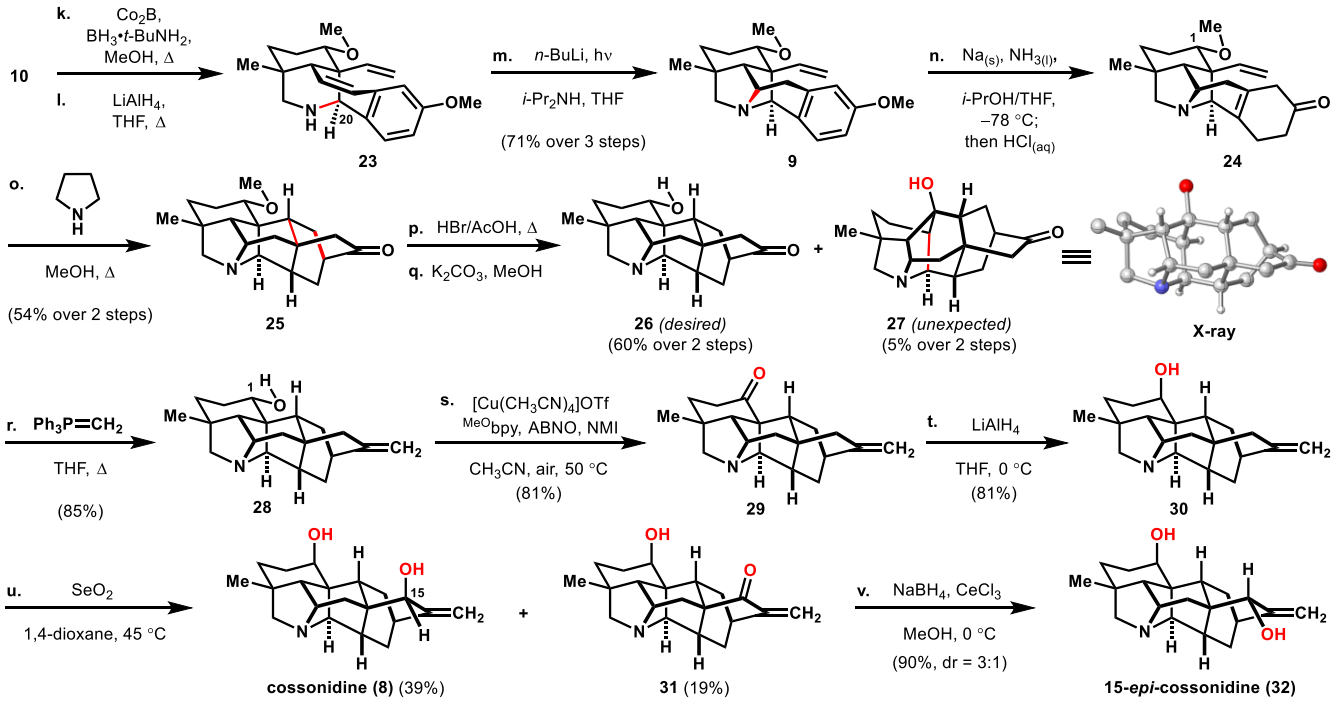
We next sought to install a functional handle in the form of an alkene group at C6 to aid in the formation of the *N*–C6 bond at a

Scheme 2. Synthesis and Elaboration of the 6-7-6 Tricycle



TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, 4 Å MS = 4 Å molecular sieves, DIH = 1,3-diiodo-5,5-dimethylhydantoin, TBAF = tetrabuylammonium fluoride; TEMPO = 2,2,6,6-tetramethylpiperidin-1-yl)oxyl, PIDA = phenyliodonium diacetate.

Scheme 3. Assembly of the Heptacyclic Core of the Hetisine-type Alkaloids and Completion of Cossonidine



MeObpy = 4,4'-dimethoxy-2,2'-bipyridine, ABNO = 9-azabicyclo[3.3.1]nonane-*N*-oxyl, NMI = *N*-methylimidazole.

later stage of the synthesis. Thus, deallylation using catalytic $Pd(PPh_3)_4$ and $PhSiH_3$ provided carboxylic acid **20** in 97–99% yield,[27] which was characterized by X-ray crystallography. Subsequent treatment with 1,3-diiodo-5,5-dimethylhydantoin (DIH) under photochemical conditions effected oxidative decarboxylation[28] to furnish styrenyl derivative **21** in 71–74% yield.

The next challenge was to introduce the methyl group (C18) at the C4-position, which is present not only in the hetisine-type, but in all the C_{20}-diterpenoid alkaloid natural products. Efforts to introduce this methyl group at earlier stages in the synthesis were unsuccessful, resulting in recovered starting material or nonspecific decomposition. Ultimately, the primary hydroxyl resulting from TBAF-mediated desilylation of **21** (95% yield) was directly converted into nitrile **22** in 96% yield,[29] and diastereoselective methylation of **22** was accomplished in 58% yield by deprotonation with LiHMDS followed by addition of methyl iodide. Access to tricyclic intermediate **10**, bearing functional handles at C6 and C20, set the stage for the subsequent C–N bond-forming reactions.

To construct the azabicycle moiety, we sought to first form the *N*–C20 bond through a global reduction of **10**, which we envisioned would convert the nitrile to a primary amine, the ketone to a hydroxyl group, and effect removal of the bromine atom. At this stage, displacement of the C20-hydroxyl group by the resultant primary amine through a Mitsunobu reaction or via an intermediate alkyl chloride was expected to forge the piperidine ring (the N–C20 bond).[12b] Treatment of **10** with $LiAlH_4$, however, resulted in a complex mixture of products, presumably due to incomplete reduction of the nitrile group. We posited that a potential solution would be to first chemoselectively reduce the nitrile group in the presence of the ketone carbonyl and two alkene groups. This was achieved with cobalt boride (Co_2B) and borane *t*-butylamine complex (Scheme 3).[30] Gratifyingly, upon subjecting the resulting primary amine to $LiAlH_4$ in THF at reflux, ketone reduction, protodebromination, and cyclization to form the N–C20 bond occurred to deliver directly secondary amine **23**. A photochemical hydroamination furnished tertiary amine **9** in 71% yield over 3 steps.[31]

At this stage, formation of the [2.2.2] bicycle was explored following the Birch reduction/intramolecular Diels–Alder sequence utilized in the Gin synthesis of nominine.[17] Notably, while the cycloaddition performed by Gin and coworker (on an intermediate analogous to **24** but lacking the C1-methoxy substituent) proceeded in high yield at only 60 °C, the cycloaddition of **24** required significantly elevated temperatures. The best results were achieved using microwave irradiation at 110 °C in 9:1 MeOH/pyrrolidine for 2 h, forging the heptacyclic product (**25**) after hydrolysis in 54% yield over 2 steps. We postulate that the steric influence of the equatorial C1-methoxy substituent in **24** preferentially orients the vinyl group away from the diene, a penalty which is avoided in the Gin substrate lacking the methoxy group.

With the heptacyclic core assembled, we investigated reaction conditions for selective cleavage of the C1 methyl ether. While an evaluation of standard Lewis acid-mediated conditions for the cleavage of aliphatic methyl ethers proved unsuccessful, exposure of ether **25** to HBr in AcOH,[9,32] and ensuing treatment with K_2CO_3 in methanol provided secondary alcohol **26** in 60% yield over 2 steps. Under these conditions, a Wagner-Meerwein rearrangement product (**27**), which was umambiguously characterized by X-ray crystallography, is also form in 5% yield over 2 steps (see the SI for details). Wittig methylenation converted the ketone group of **26** into the terminal alkene (**28**) in 85% yield, thereby introducing the final carbon atom of the hetisine-type skeleton. An oxidation/reduction sequence was then explored to invert the C1-stereocenter. Application of Stahl's aerobic oxidation conditions[33] gave the ketone **29** in 81% yield. In a reversal of the typical stereoselectivity trend observed in cyclohexanone reductions,[34] reacting this ketone with $LiAlH_4$ resulted in a diastereoselective reduction (6.6:1 dr) in favor of the desired alcohol (**30**) with the axially-disposed hydroxyl group, which was isolated in 81% yield. Subjecting **30** to selenium dioxide produced cossonidine (**8**) and enone **31** in 39% and 19% yields, respectively. Reduction of enone **31** under Luche conditions resulted in 90% yield of a 3:1 mixture of diastereomers favoring 15-*epi*-cossonidine (**32**).

In summary, our work has provided access to the complete hetisine-type skeleton bearing key functional group handles on both the A ring and the [2.2.2] bicycle for further derivatization. This

route proceeds in 21 steps from known hydrindanone **13** and features a benzyne acyl-alkylation ring expansion, a chemoselective nitrile reduction, a light-mediated hydroamination, and an intramolecular Diels–Alder cycloaddition as key steps. With the complex hetisine skeleton assembled, future studies will be directed toward generating more highly oxygenated congeners.[7] Furthermore, by starting with enantioenriched hydrindanone **13**, which was recently reported by our group,[8,9] this synthesis should be readily rendered enantioselective.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge on the ACS Publications Website at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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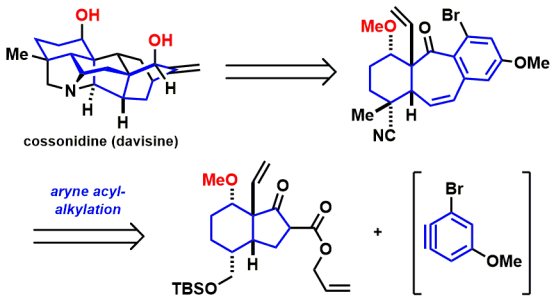
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