Natural Product Synthesis

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Gallium(III)-Catalyzed Cycloisomerization Approach to the Diterpenoid Alkaloids: Construction of the Core Structure for the Hetidines and Hetisines**

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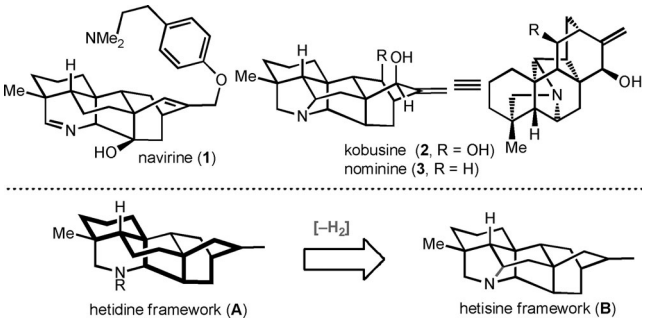
In memory of David Gin

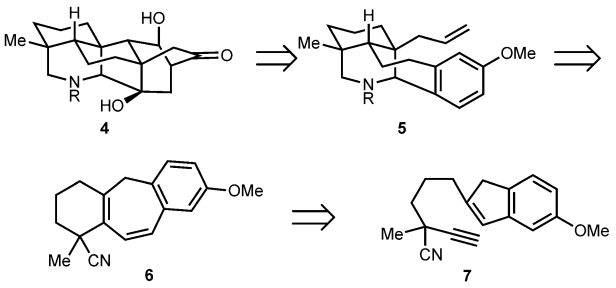
The diterpenoid alkaloids comprise over 1100 natural products of daunting architectural complexity that possess a vast array of hydroxylation patterns.[1] The potent interactions of these molecules with voltage-gated ion channels that lead to a broad spectrum of bioactivity, are well-recognized.[2] Biological activities including acetylcholinesterase inhibition, as well as analgesic, anti-inflammatory, myorelaxant, and anti-arrhythmic properties have been reported for many members of this family.[3] Furthermore, many of the plants that produce diterpenoid alkaloid natural products have various uses, including as sedatives and as fever reducers.[4] As a result of their complex structures, and the emerging interest in their use to address problems in cognitive decline, there has been a veritable renaissance in the chemical syntheses of the diterpenoid alkaloids. Our approach to the construction of these natural products centers on identifying a versatile late-stage intermediate that could be applicable to the syntheses of several members of this family, especially, the hetidines (e.g., navirine, **1**; Scheme 1), for which no syntheses are known. Herein, we report our progress toward this goal, which has resulted in the synthesis of an advanced tetracycle that we believe sets the stage for the syntheses of natural products in the hetidine and hetisine structural classes (e.g., **1**, and kobusine, **2**, respectively).

Although no previous syntheses of molecules in the hetidine structural class have been reported to date, there has been substantial effort dedicated to the synthesis of the hetisine diterpenoid alkaloids. Most of these approaches, which were aimed at the synthesis of a single target,[5] are exemplified by the preparation of nominine (**3**) by Natsume and Muratake in 2004[6] and by the highly efficient synthesis by Gin and Peese, in 2006, using a beautifully orchestrated dipolar cycloaddition/[4+2] cycloaddition strategy.[7] In our analysis of the hetidine and hetisine frameworks, we recognized that a fused 6-7-6 carbocyclic motif (see bolded bonds in **A**, Scheme 1) was conserved and could therefore serve as a common late-stage structure for the construction of these related natural products. We envisioned the hetisine skeleton (see **B**) arising from the hetidine framework (**A**) through a formal dehydrogenative C–N bond-formation reaction. The successful use of the Hoffman–Löffler–Freytag reaction to accomplish an analogous transformation has been previously reported by Okamoto and co-workers, albeit in modest yield.[8]



Scheme 1. Selected hetidine and hetisine diterpenoid alkaloids.

On the basis of the analysis presented above, we selected **4** (Scheme 2) as our initial target. This advanced intermediate, which resembles the hetidine skeleton, has an intermediate oxidation level, thus making it well-suited as a precursor to many hetidine and hetisine diterpenoid alkaloids including navirine (**1**) and kobusine (**2**). The bicyclo[2.2.2] portion of **4** could arise from methoxy arene **5**. To date, the most expedient route to convert methoxybenzene derivatives similar to **5** into the [2.2.2]bicyclic substructure was reported



Scheme 2. Retrosynthetic analysis of common late-stage intermediate **4**.

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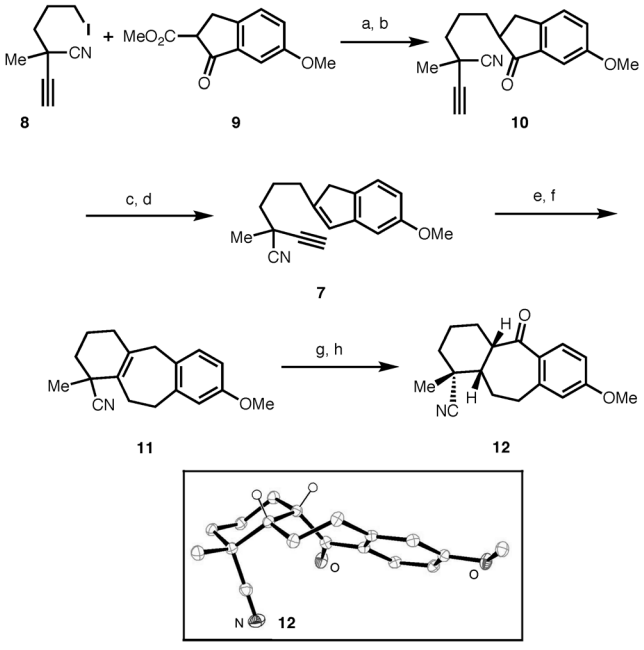
by Gin and Peese,[7] and involves an intramolecular [4+2] cycloaddition. Several recent syntheses of kaurane-type diterpenoids have been achieved by using a similar strategy.[9] As such, we imagined that this tactic or a variant could, in principle, be employed to transform tetracycle **5** into advanced polycycle **4**. The bridged framework of **5** could be simplified to benzannulated cycloheptadiene **6**, which would be formed from indenyl alkyne **7** by a Ga^{III}-catalyzed cycloisomerization transformation, which has been developed in our group[10] and previously used by us in the syntheses of natural products in the icetexane diterpenoid family.[11]

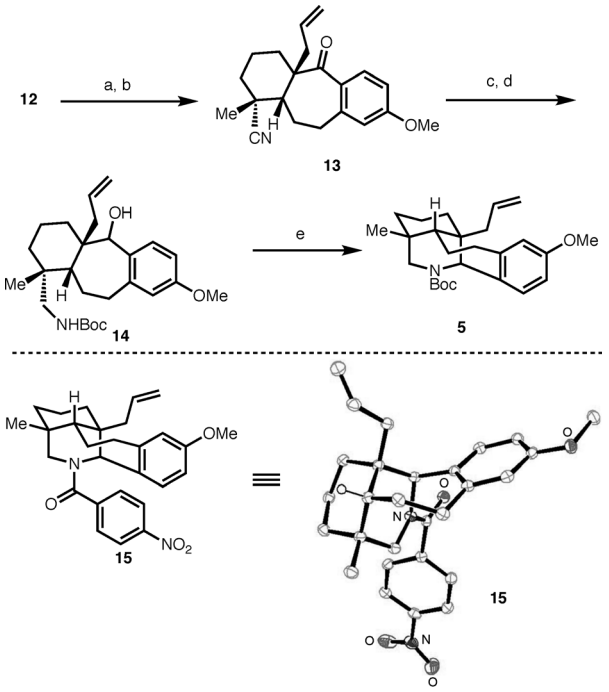
Our synthesis of structures related to **4** began with the preparation of tricycle **12** (Scheme 3) from known iodo alkyne **8**, which can be synthesized in 9 steps from commercially available 3-bromopropan-1-ol,[12] and commercially available β-ketoester **9**.[13,14] A standard alkylation using K_2CO_3 afforded the adduct of **8** and **9**, which, following saponification and decarboxylation, provided indanone **10** in 76% yield over the two steps. Selective reduction of the carbonyl group of **10** proceeded in the presence of the nitrile group, and subsequent elimination of the resulting hydroxy group yielded indene **7**. Cycloisomerization of **7** by using catalytic Ga^{III} iodide under reaction conditions we have previously established, gave benzannulated cycloheptadiene **6** (see Scheme 2), which, following selective reduction of the disubstituted double bond by using diimide, gave **11**. Oxygenation of the doubly activated allylic and benzylic methylene group of **11** was achieved upon brief exposure to cerric ammonium nitrate (CAN) adsorbed on silica to yield an enone (not shown). Hydrogenation of the enone proceeded with high levels of diastereocontrol to give **12**, the structure of which was confirmed by single crystal X-ray analysis (see ORTEP). The remarkable diastereoselectivity of this hydrogenation reaction is not well understood at this time and we are working to gain more insight into the selectivity of this process.[15] Tricycle **12** represents the key 6-7-6 substructure that is common to the hetidine and hetisine diterpenoid alkaloid families (see **A**; Scheme 1).

Allylation of ketone **12** with NaH and allyl bromide (see Scheme 4) resulted in a mixture of O- and C-allyl products, which gave a single diastereomer of the C-allylated compound (**13**) through a Claisen rearrangement upon heating to 160 °C (microwave). Reduction of ketone **13** with lithium aluminium hydride (LAH) yielded an amino alcohol as a single diastereomer,[16] which upon selective Boc protection of the amino group yielded **14**. Exposure of carbamate alcohol **14** to thionyl chloride[17] effected cyclization to form **5**, which contains the piperidine ring.[18] The structure of **5** was unambiguously confirmed by X-ray crystallographic analysis of the corresponding 4-nitrobenzamide derivative (**15**).

Access to **5** set the stage for the exploration of various strategies to install the bicyclo[2.2.2] portion of the hetidines and hetisines; we envisioned that the formation of the

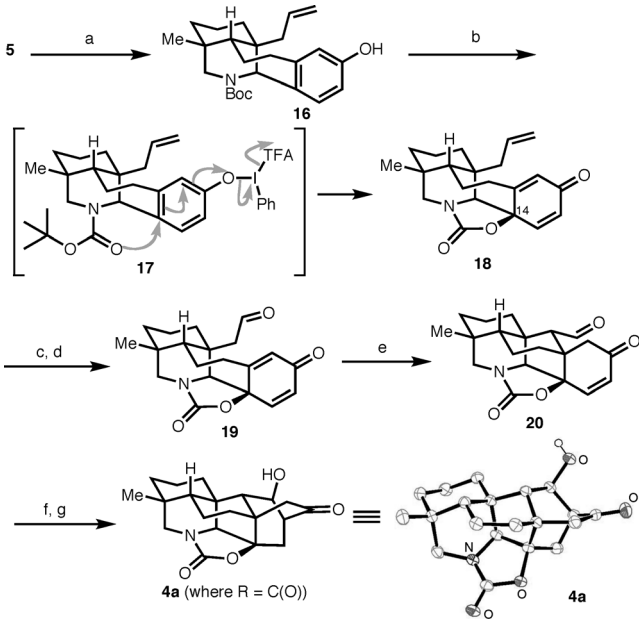


Scheme 3. Synthesis of tricycle **12** and ORTEP representation of **12** with thermal ellipsoids set at 50% probability and most hydrogen atoms omitted for clarity.[21] Reaction conditions: a) K_2CO_3, acetone, 65 °C, 18 h, 76%; b) $LiOH{\cdot}H_2O$, THF/H_2O (4:1), 65 °C, 98%; c) $NaBH_4$, EtOH, 0 °C; d) PPTS, benzene, 80 °C, 70% (over 2 steps); e) GaI_3 (25 mol%), M.S. (4 Å) , toluene, 100 °C, 48 h, 89%; f) Et_3N, $TsNHNH_2$, 1,2-DCE, 65 °C, 83%; g) CAN on silica, CH_2Cl_2/H_2O (4:1), 0 °C, 5 min, 52%; h) H_2 (1 atm), 5 wt% Pd/C, EtOAc, quantitative. CAN = cerric ammonium nitrate, DCE = dichloroethane, M.S. = molecular sieves, PPTS = pyridinium *para*-toluene sulfonate, THF = tetrahydrofuran.



Scheme 4. Synthesis of tetracycle **5** and ORTEP representation of the corresponding 4-nitrobenzamide derivative (**15**) with thermal ellipsoids set at 50% probability and most hydrogen atoms omitted for clarity.[21] Reaction conditions: a) NaH, allyl bromide, DMF, 50 °C, 45 min; b) DMF, 160 °C (microwave), 45 min, 69% (over 2 steps); c) LAH, THF, 65 °C, 4 h; d) Boc_2O, Et_3N, CH_2Cl_2, 23 °C, 92% (over 2 steps); e) $SOCl_2$, CH_2Cl_2, 23 °C, 1 h, 72%. Boc = *tert*-butoxycarbonyl, DMF = dimethylformamide, LAH = lithium aluminum hydride.

bicyclo[2.2.2] portion would involve a dearomatization of the arene moiety. Our early attempts, which proved unfruitful, involved a Birch reduction of methoxybenzene **5**. However, the resulting dihydrobenzene reduction product was unstable and could not be easily advanced. We were ultimately drawn to oxidative dearomatizations, which could site selectively introduce oxygenation at C14 (see **18**, Scheme 5) and would



Scheme 5. Synthesis of **4a**, a common late-stage intermediate for the hetidines and hetisines, and ORTEP representation of **4a** with thermal ellipsoids set at 50% probability and most hydrogen atoms omitted for clarity.[21] Reaction conditions: a) NaH, EtSH, DMF, 180°C (microwave), 15 min), 85%; b) PIFA (1.5 equiv), $MeCN/CF_3CH_2OH$ (1:1), 0°C, 54%; c) cat. OsO_4, NMO, $THF:H_2O$ (2:1), 23°C, 5 days; d) $NaIO_4$ on silica, CH_2Cl_2, 23°C, 30 min, 59% (over 2 steps); e) SiO_2, CH_2Cl_2, 36 h, 80%; f) H_2, 5 wt% Rh/Al_2O_3 (50 wt%), benzene, 24 h; g) K_2CO_3 (10 equiv), MeOH: CH_2Cl_2 (9:1), 4 h, 43% (over 2 steps). MeCN = acetonitrile, NMO = *N*-methylmorpholine *N*-oxide, PIFA = phenyliodine bis(trifluoroacetate).

be advantageous for the synthesis of navirine (**1**) and related alkaloids. Thus, cleavage of the methyl ether in **5** afforded phenol **16** in 85% yield. Oxidative dearomatization of **16** with phenyliodine bistrifluoroacetate (PIFA; [bis(trifluoroacetoxy)iodo]benzene) gave cyclohexadienone **18**, in 54% yield, via the presumed intermediacy of **17**.[19] To the best of our knowledge, this is the first example of the use of a Boc carbamate as a nucleophile in an oxidative dearomatization reaction. Dihydroxylation/periodate cleavage[20] of the allyl group in **18** yielded aldehyde **19**, which upon stirring with silica gel gave the Michael addition product **20**. At this stage, reduction of the enone double bond and treatment of the resulting ketone aldehyde with K_2CO_3 in methanol led to aldol cyclization to provide **4a**. The structure of **4a** was unambiguously determined by X-ray crystallographic analysis.

The synthesis of **4a** addresses many of the significant challenges inherent in the synthesis of the hetidine and hetisine diterpenoid alkaloids. These challenges include the introduction of nine contiguous stereocenters (3 of which are quaternary) and the construction of a highly caged, bridged ring system. Our approach reinforces the significance of our recognition of the 6-7-6 ring system as an important starting point for the synthesis of the diterpenoid alkaloids. Key to the success of our outlined plan thus far is the use of a Ga^{III}-catalyzed cycloisomerization reaction for the synthesis of the 6-7-6 tricycle, a remarkably diastereoselective hydrogenation that effectively distinguishes between a methyl and nitrile group, and an unusual oxidative dearomatization reaction involving a Boc carbamate to initiate the construction of the bicyclo[2.2.2] framework. Despite these advances, several challenges, including the selective manipulation of the bicyclo[2.2.2] framework (i.e., removing the hydroxy group or converting the ketone group into an *exo*-methylene moiety) remain. Studies to implement these planned synthetic steps, as well as related efforts to use **4a** in the syntheses of hetidine and hetisine alkaloids, including navirine and kobusine, are the focus of our current studies.

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[1] a) F.-P. Wang, X.-T. Liang in *The Alkaloids: Chemistry and Biology*, *Vol. 59* (Ed.: G. A. Cordell), Elsevier Science, New York, **2002**, pp. 1–280; b) F.-P. Wang, Q.-H. Chen, X.-Y. Liu, *Nat. Prod. Rep.* **2010**, *27*, 529–570.

[2] a) A. Ameri, *Prog. Neurobiol.* **1998**, *56*, 211–235; b) J. Friese, J. Gleitz, U. T. Gutser, J. F. Heubach, T. Matthiesen, B. Wilffert, N. Selve, *Eur. J. Pharmacol.* **1997**, *337*, 165–174; c) D. J. Triggle, M. Gopalakrishnan, D. Rampe, W. Zheng in *Voltage-Gated Ion Channels as Drug Targets*, *Vol. 29*, Wiley-VCH, Weinheim, **2006**, pp. 1–479.

[3] For a description of the bioactivities of these compounds, see Ref. [1].

[4] a) T. Anger, D. J. Madge, M. Mulla, D. Riddall, *J. Med. Chem.* **2001**, *44*, 115–137; Ref. [1b] provides an excellent summary of these medicinal applications.

[5] For selected recent approaches, see: a) M. Somei, T. Okamoto, *Chem. Pharm. Bull.* **1970**, *18*, 2135–2138; b) J. L. van der Baan, F. Bickelhaupt, *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 109–112; c) Y. Shibanuma, T. Okamoto, *Chem. Pharm. Bull.* **1985**, *33*, 3187–3194; d) Y.-S. Kwak, J. D. Winkler, *J. Am. Chem. Soc.* **2001**, *123*, 7429–7430; e) H. Muratake, M. Natsume, *Tetrahedron Lett.* **2002**, *43*, 2913–2917; f) C. M. Williams, L. N. Mander, *Org. Lett.* **2003**, *5*, 3499–3502; g) K. M. Peese, D. Y. Gin, *Org. Lett.* **2005**, *7*, 3323–3325; h) C. M. Williams, L. N. Mander, P. V. Bernhardt, A. C. Willis, *Tetrahedron* **2005**, *61*, 3759- 3769; i) O. E. Hutt, L. N. Mander, *J. Org. Chem.* **2007**, *72*, 10130–10140.

[6] a) H. Muratake, M. Natsume, *Angew. Chem.* **2004**, *116*, 4746–4749; *Angew. Chem. Int. Ed.* **2004**, *43*, 4646–4649; b) H. Muratake, M. Natsume, *Tetrahedron* **2006**, *62*, 7056–7070; c) H. Muratake, M. Natsume, *Tetrahedron* **2006**, *62*, 7071–7092; d) H. Muratake, M. Natsume, *Tetrahedron* **2006**, *62*, 7093–7112.

[7] a) K. M. Peese, D. Y. Gin, *J. Am. Chem. Soc.* **2006**, *128*, 8734 – 8735; b) K. M. Peese, D. Y. Gin, *Chem. Eur. J.* **2008**, *14*, 1654 – 1665.
[8] T. Yatsunami, T. Isono, I. Hayakawa, T. Okamoto, *Chem. Pharm. Bull.* **1975**, *23*, 3030 – 3032.
[9] a) J. Gong, G. Lin, W. Sun, C.-C. Li, Z. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 16745 – 16746; b) X.-Y. Liu, H. Cheng, X.-H. Li, Q.-H. Chen, L. Xu, F.-P. Wang, *Org. Biomol. Chem.* **2012**, *10*, 1411 – 1417.
[10] E. M. Simmons, R. Sarpong, *Org. Lett.* **2006**, *8*, 2883 – 2886.
[11] a) E. M. Simmons, J. R. Yen, R. Sarpong, *Org. Lett.* **2007**, *9*, 2705 – 2708; b) F. de J. Cortez, R. Sarpong, *Org. Lett.* **2010**, *12*, 1428 – 1431.
[12] See Ref. [11b].
[13] H. O. House, C. B. Hudson, *J. Org. Chem.* **1970**, *35*, 647 – 651.
[14] Of note, the lone stereocenter in **8** may be introduced in enantioenriched form by using the enantioselective Rh-catalyzed conjugate addition protocol of Ito, which will set the stage for an enantioselective synthesis of our targets by employing subsequent diastereoselective processes. For the protocol of Ito, see: a) M. Sawamura, H. Hamashima, Y. Ito, *Tetrahedron* **1994**, *50*, 4439 – 4454; b) M. Sawamura, H. Hamashima, H. Shinoto, Y. Ito, *Tetrahedron Lett.* **1995**, *36*, 6479 – 6482.
[15] The observed diastereoselectivity may be rationalized by torsional steering. For a review, see: K. N. Houk, J. A. Tucker, A. E. Dorigo, *Acc. Chem. Res.* **1990**, *23*, 107 – 113.
[16] A major diastereomer was obtained. However, it was not unambiguously characterized.
[17] F. Xu, B. Simmons, R. A. Reamer, E. Corley, J. Murry, D. Tschaen, *J. Org. Chem.* **2008**, *73*, 312 – 315.
[18] The efficiency of this step may be attributed to the possible formation of a stabilized benzylic carbocation intermediate.
[19] For pertinent reviews on dearomatization processes, see: a) S. P. Roche, J. A. Porco, Jr., *Angew. Chem.* **2011**, *123*, 4154 – 4179; *Angew. Chem. Int. Ed.* **2011**, *50*, 4068 – 4093; b) D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* **2004**, *104*, 1383 – 1430.
[20] Y.-L. Zhong, T. K. M. Shing, *J. Org. Chem.* **1997**, *62*, 2622 – 2624.
[21] CCDC 923055 (**4a**), CCDC 923053 (**12**), and 923054 (**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

