Published in final edited form as:

Angew Chem Int Ed Engl. 2013 April 26; 52(18): . doi:10.1002/anie.201209030.

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

Amy M. Hamlin, Felipe de Jesus Cortez, David Lapointe, and Richmond Sarpong*

Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720 (USA)

Abstract

A versatile core structure has been prepared that should provide a foundation for the syntheses of the hetidine and hetisine type of diterpenoid alkaloids. The synthesis of the caged polycyclic core structure, which features nine contiguous stereocenters, utilizes a Ga(III)-catalyzed cycloisomerization of alkynyl indenenes as well as a Michael/aldol sequence to build the bicyclo-[2.2.2] framework.

Keywords

Diterpenoid alkaloids; Hetidine; Hetisine; catalysis; gallium; oxidative dearomatization

The diterpenoid alkaloids comprise over 1100 natural products of daunting architectural complexity bearing a vast array of hydroxylation patterns.ⁱ The potent interactions of these molecules with voltage-gated ion channels, which lead to a broad spectrum of bioactivity, is well-recognized.ⁱⁱ 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.ⁱⁱⁱ Furthermore, many of the plants that produce diterpenoid alkaloid natural products are used as sedatives and fever reducers, along with many other uses.^{iv} As a result of their complex structures, as well as 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 the goal of 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**, Figure 1), for which no syntheses are known. In this Communication, 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,^v are exemplified by the preparation of nominine (**3**) by Natsume and Muratake in 2004^{vi} and by Gin and Peese's highly efficient synthesis in 2006 using a beautifully orchestrated dipolar cycloaddition/[4+2] cycloaddition strategy.^{vii} In our analysis of the hetidine and hetisine frameworks, we recognized that a fused 6-7-6 carbocyclic motif (see

*Fax: (+1) 510-642-9675, rsarpong@berkeley.edu.

In Memory of Prof. David Gin

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

bolded bonds in **A**, Figure 1) was conserved and could therefore serve productively as a common late stage structure for the construction of these related natural products. In a key chemical transformation that would link these two structural classes, we envisioned the hetisine skeleton (see **B**) arising from the hetidine framework (**A**) using a formally 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 coworkers, albeit in modest yield.^{viii}

On the basis of the analysis presented above, we selected the general structure **4** (Scheme 1) as our initial target. This advanced intermediate, which reflects the hetidine skeleton, is at an intermediate oxidation level that makes 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 related to **5** to the [2.2.2]-bicyclic substructure can be found in the work of Gin and Peese,^{vii} which exploits an intramolecular [4+2] cycloaddition. Several recent syntheses of kaurane type diterpenoids have proceeded along similar lines.^{ix} As such, we imagined that this tactic or a variant could, in principle, be employed to transform tetracycle **5** to advanced polycycle **4**. The bridging framework of **5** could be simplified to benzannulated cycloheptadiene **6**, which would arise from indenyl alkyne **7** using a Ga(III)-catalyzed cycloisomerization transformation that has been developed in our group^x and previously exploited by us in the syntheses of natural products in the icetexane diterpenoid family.^{xi}

Our chemical synthesis of general structures related to **4** began with the preparation of tricycle **12** (Scheme 2) using known iodo-alkyne **8** (9 steps from commercially available 3-bromopropan-1-ol),^{xii} and commercially available α -ketoester **9**.^{xiii, xiv} 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**, which proceeded uneventfully in the presence of the nitrile group, and elimination of the resulting hydroxyl yielded indene **7**. Cycloisomerization of **7** using catalytic Ga(III) iodide under conditions we have previously established gave benzannulated cycloheptadiene **6** (see Scheme 1), which, following selective reduction of the disubstituted double bond using diimide, gave **11**. Oxygenation of the doubly activated allylic and benzylic methylene group of **11** was achieved upon brief exposure to ceric 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.^{xv} Tricycle **12** represents the key 6-7-6 substructure that is conserved in the hetidine and hetisine diterpenoid alkaloid families (see **A**, Figure 1).

Allylation of ketone **12** using NaH and allyl bromide (see Scheme 3) resulted in a mixture of O- and C-allyl products which converged to a single diastereomer of the C-allylated compound (**13**) via a Claisen rearrangement upon heating to 160 °C (microwave). Reduction of ketone **13** with LAH yielded an amino alcohol as a single diastereomer,^{xvi} which upon selective Boc-protection of the amino group yielded **14**. Exposure of carbamate alcohol **14** to thionyl chloride^{xvii} effected cyclization to form **5**, where the piperidine ring has been installed.^{xviii} 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 tactics to install the bicyclo-[2.2.2] portion of the hetidines and hetisines, which we envisioned would involve a dearomatization

of the arene moiety. Our early attempts, which proved unfruitful, sought to proceed by the 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 4) and would 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** using phenyliodine bistrifluoroacetate (PIFA; a.k.a. [bis(trifluoroacetoxy)iodo]benzene) yielded cyclohexadienone **18** in 54% yield via the presumed intermediacy of **17**.^{xix} To the best of our knowledge, this is the first example of enlisting a Boc carbamate as a nucleophile in an oxidative dearomatization reaction. Dihydroxylation/periodate cleavage^{xx} 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 K₂CO₃ in methanol led to aldol cyclization to provide **4a**. The structure of **4a** was unambiguously secured 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. This includes 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 to an exo-methylene) lie ahead. Studies to implement these planned synthetic steps, as well as related efforts to apply **4a** to the syntheses of hetidine and hetisine alkaloids including navirine and kobusine are the focus of our current studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The work was supported by a grant from the NIH USA (NIGMS RO1 084906). FJC is grateful to the NIH USA for a graduate award (F31 GM089139) and DL thanks the FQNRT Canada for a postdoctoral fellowship. RS is a Camille-Dreyfus Teacher Scholar, Alfred P. Sloan Fellow and acknowledges unrestricted support from Abbott, Eli Lilly, Astra Zeneca and Aldrich.

References

- i. (a) Wang F-P, Liang X-T. *Alkaloids*. 2002; 59:1–280. [PubMed: 12561418] (b) Wang F-P, Chen Q-H, Liu X-Y. *Nat. Prod. Rep.* 2010; 27:529–570. [PubMed: 20336236]
- ii. (a) Ameri A. *Prog. Neurobiol.* 1998; 56:211–235. [PubMed: 9760702] (b) Friesen J, Gleitz J, Gutser UT, Heubach JF, Matthiesen T, Wilffert B, Selve N. *Eur. J. Pharmacol.* 1997; 337:165–174. [PubMed: 9430411] (c) Triggie, DJ.; Gopalakrishnan, M.; Rampe, D.; Zheng, W. *Voltage-Gated Ion Channels as Drug Targets*. Vol. vol. 29. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA; 2006. p. 1-479.
- iii. For a description of the bioactivities of these compounds, see Ref. i.

- iv. Anger T, Madge DJ, Mulla M, Riddall D. *J. Med. Chem.* 2001; 44:115–137. [PubMed: 11170622]
(b) Ref. 1b provides an excellent summary of these medicinal applications.
- v. (a) Somei M, Okamoto T. *Chem. Pharm. Bull.* 1970; 18:2135–2138.(b) van der Baan JL, Bickelhaupt F. *Recl. Trav. Chim. Pays-Bas.* 1975; 94:109–112.(c) Shibamura Y, Okamoto T. *Chem. Pharm. Bull.* 1985; 33:3187–3194.(d) Kwak Y, Winkler JD. *J. Am. Chem. Soc.* 2001; 123:7429–7430. [PubMed: 11472177] (e) Muratake H, Natsume M. *Tetrahedron Lett.* 2002; 43:2913–2917.(f) Williams CM, Mander LN. *Org. Lett.* 2003; 5:3499–3502. [PubMed: 12967309] (g) Peese KM, Gin DY. *Org. Lett.* 2005; 7:3323–3325. [PubMed: 16018651] (h) Williams CM, Mander LN, Bernhardt PV, Willis AC. *Tetrahedron.* 2005; 61:3759–3769.(i) Hutt OE, Mander LN. *J. Org. Chem.* 2007; 72:10130–10140. [PubMed: 18027969]
- vi. (a) Muratake H, Natsume M. *Angew. Chem. Int. Ed.* 2004; 43:4646–4649.(b) Muratake H, Natsume M. *Tetrahedron.* 2007; 62:7056–7070.(c) Muratake H, Natsume M. *Tetrahedron.* 2007; 62:7071–7092.(d) Muratake H, Natsume M. *Tetrahedron.* 2007; 62:7093–7112.
- vii. (a) Peese KM, Gin DY. *J. Am. Chem. Soc.* 2006; 128:8734–8735. [PubMed: 16819859] (b) Peese KM, Gin DY. *Chem. Eur. J.* 2008; 14:1654–1665. [PubMed: 18046691]
- viii. Yatsunami T, Isono T, Hayakawa I, Okamoto T. *Chem. Pharm. Bull.* 1975; 23:3030–3032.
- ix. (a) Gong J, Lin G, Sun W, Li C-C, Yang Z. *J. Am. Chem. Soc.* 2010; 132:16745–16746. [PubMed: 21049937] (b) Liu X-Y, Cheng H, Li X-H, Chen Q-H, Xu L, Wang F-P. *Org. Biomol. Chem.* 2012; 10:1411–1417. [PubMed: 22193953]
- x. Simmons EM, Sarpong R. *Org. Lett.* 2006; 8:2883–2886. [PubMed: 16774281]
- xi. (a) Simmons EM, Yen JR, Sarpong R. *Org. Lett.* 2007; 9:2705–2708. [PubMed: 17559223] (b) de J. Cortez F, Sarpong R. *Org. Lett.* 2010; 12:1428–1431. [PubMed: 20192209]
- xii. See Ref. (Jesse's paper)
- xiii. House HO, Hudson CB. *J. Org. Chem.* 1970; 35:647–651.
- xiv. Of note, the lone stereocenter in **8** may be introduced in enantioenriched form using the enantioselective Rh-catalyzed conjugate addition protocol of Ito (Sawamura M, Hamashima H, Ito Y. *Tetrahedron.* 1994; 50:4439–4454. Sawamura M, Hamashima G, Shinoto H, Ito Y. *Tetrahedron Lett.* 1995; 36:6479–6482.) which will set the stage for an enantioselective synthesis of our targets by employing subsequent diastereoselective processes.
- xv. The observed diastereoselectivity may be rationalized by torsional steering. For a review, see: Houk KN, Tucker JA, Dorigo AE. *Acc. Chem. Res.* 1990; 23:107–113.
- xvi. The sense of diastereoselectivity, which is inconsequential, was not determined.
- xvii. Xu F, Simmons B, Reamer RA, Corley E, Murry J, Tschaen D. *J. Org. Chem.* 2008; 73:312–315. [PubMed: 18052293]
- xviii. The efficiency of this step may be attributed to the possible formation of a stabilized benzylic carbocation intermediate.
- xix. For pertinent reviews on dearomatization processes see: Roche SP, Porco JA Jr. *Angew. Chem. Int. Ed.* 2011; 50:4068–4094. Magdziak D, Meek SJ, Pettus TRR. *Chem. Rev.* 2004; 104:1383–1429. [PubMed: 15008626]
- xx. Zhong Y-L, Shing TKM. *J. Org. Chem.* 1997; 62:2622–2624. [PubMed: 11671605]

Figure 1.
Selected hetidine and hetisine diterpenoid alkaloids

Scheme 1.
Retrosynthetic analysis of common late-stage intermediate general structure **4**

Scheme 2.

Synthesis of tricycle **12**: a) K_2CO_3 , acetone, 65 °C, 18 h 76%; b) $\text{LiOH}\cdot\text{H}_2\text{O}$, 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%), 4 Å MS, 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.

THF = tetrahydrofuran, PPTS = pyridinium *para*-toluene sulfonate, MS = molecular sieves, DCE = dichloroethane, CAN = ceric ammonium nitrate.

Scheme 3.

Synthesis of tetracycle **5**: 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) Boc₂O, Et₃N, CH₂Cl₂, 23 °C, 92% (over 2 steps); e) SOCl₂, CH₂Cl₂, 23 °C, 1 h, 72%. DMF = dimethylformamide, LAH = lithium aluminum hydride, Boc = *tert*-butoxy carbonyl.

Scheme 4.

Synthesis of **4a**, a common late-stage intermediate for the hetidines and hetisines: a) NaH, EtSH, DMF, 180 °C (microwave), 15 min, 85%; b) PIFA (1.5 equiv), MeCN: CF₃CH₂OH (1:1), 0 °C, 54%; c) cat. OsO₄, NMO, THF:H₂O (2:1), 23 °C, 5 days; d) NaIO₄ on silica, CH₂Cl₂, 23 °C, 30 min, 59% (over 2 steps); e) SiO₂, CH₂Cl₂, 36 h, 80%; f) H₂, 5 wt% Rh/Al₂O₃ (50 wt%), benzene, 24 h; g) K₂CO₃ (10 equiv), MeOH: CH₂Cl₂ (9:1), 4 h, 43% (over 2 steps). DMF = dimethylformamide, PIFA = phenyliodine bis(trifluoroacetate), MeCN = acetonitrile, NMO = *N*-methylmorpholine *N*-oxide.