Published in final edited form as:

Org Lett. 2017 September 01; 19(17): 4632–4635. doi:10.1021/acs.orglett.7b02260.

Magnesiata Addition/Ring-Expansion Strategy To Access the 6-7-6 Tricyclic Core of Hetisine-Type C₂₀-Diterpenoid Alkaloids

Jason J. Pflueger, Louis C. Morrill[†], Justine N. deGruyter, Melecio A. Perea, and Richmond Sarpong^{*}

Department of Chemistry, University of California, Berkeley, California 94720, United States

Abstract

A synthetic strategy to access the fused 6–7–6 tricyclic core of hetisine-type C₂₀-diterpenoid alkaloids is reported. This strategy employs a Diels-Alder cycloaddition to assemble a fused bicyclic anhydride intermediate, which is elaborated to a vinyl lactone-acetal bearing an aromatic ring in five steps. Aromatic iodination is followed by magnesium-halogen exchange with a trialkyl magnesiata species, which undergoes intramolecular cyclization. Subsequent oxidation provides the desired 6–7–6 tricyclic diketoaldehyde, with carbonyl groups at all three positions for eventual C–N bond formation and subsequent elaboration.

Graphical Abstract

Diterpenoid alkaloid natural products have emerged as attractive synthetic targets by virtue of their complex caged skeletons and intriguing biological interactions, particularly with voltage-gated ion channels.¹ Among the many structural classifications that have been established, the hetisine-type C₂₀-diterpenoid alkaloids have emerged as compounds of particular interest. They possess one of the most complex frameworks of any of the diterpenoid alkaloids, with a tertiary amine embedded in a caged heptacyclic core (see nominine (1), Figure 1), and are one of the most prominent diterpenoid alkaloid types, with over 120 known members.² Furthermore, the hetisine-type alkaloid guan-fu base A (3, Scheme 1) is currently in clinical use in China for the treatment of arrhythmia,³ highlighting the therapeutic potential of these natural products. The observed biological effects of guan-fu base A and many other diterpenoid alkaloid natural products are believed to arise from their interactions with voltage-gated ion channels, which are emerging as important therapeutic targets.⁴

The authors declare no competing financial interest.

^{*}Corresponding Author: rsarpong@berkeley.edu.

[†]Present Address School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, U.K.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02260
Experimental details and spectroscopic data (PDF) Compound 10 (CIF)

To date, only a single hetisine-type diterpenoid alkaloid natural product has succumbed to total synthesis: the monohydroxylated alkaloid nominine (1, Figure 1). This molecule was first synthesized by Natsume and Muratake in 2004⁵ and again by Gin in 2006.⁶ Despite these initial successes, the synthesis of more highly oxygenated hetisine-type alkaloids remains elusive, and new strategies to access these secondary metabolites with suitable functional group handles are required. The synthesis of the related hetidine-type core, which lacks the N-C6 bond (Figure 1), has seen more recent success, with routes from our group⁷ as well as the laboratories of Baran⁸ and Qin.⁹ While early work by Okamoto suggested a final N-C6 bond could be formed at a late stage through HLF-type chemistry,¹⁰ this transformation has not been successfully realized by other investigators, suggesting the need for novel strategies that incorporate the formation of this N-C6 bond into the synthetic plan.

Our research group has identified a central fused 6–7–6 tricycle (Scheme 1, highlighted in red) as a key structural motif in the core scaffold of these complex alkaloids. This design choice arises from a network analysis approach to retrosynthesis¹¹ in which the [2.2.2]bicycle is forged late-stage through a [4 + 2] cycloaddition reaction on a derivative of vinyl arene 5. Further disconnection of the C–N bonds leads both the hetidine and hetisine cores back to an all-fused 6–7–6 tricycle (6), the key target for our collective synthetic strategies.

Initial efforts in our group utilized a gallium(In)-catalyzed cycloisomerization reaction to convert alkyne 7 into 6–7–6 tricycle 8.⁷ While this reaction proceeds in a high 89% yield, alkyne 7 takes 13 steps to synthesize (longest linear sequence), and the resulting tricycle is relatively unfunctionalized (Scheme 2). Several steps are then required to introduce key functional groups for both the C–N bond forming reactions and the [4 + 2] cycloaddition. Despite these challenges, the overall strategy was validated with the successful synthesis of the hetidine-type core, which was further elaborated to dihydronavirine (2, Figure 1), the formal hydrogenation product of the natural product navirine.

On the basis of this precedent, we embarked on a streamlined and higher yielding synthesis of a tricycle that would be more ideally functionalized to access the hetisine-type core. We envisioned diketoaldehyde 10 as an ideal precursor, with carbonyl groups at all three carbon atoms that form C–N bonds in the hetisine-type alkaloids (Scheme 3). Intramolecular addition of the aromatic ring moiety in 9 was predicted to enable the synthesis of this desired tricycle. We envisioned a rapid synthesis of this compound from bicyclic anhydride 11, which could be readily accessed through a Diels–Alder cycloaddition from diene 12 and dienophile 13.

The synthesis begins with the construction of maleic anhydride dienophile 13 (Scheme 4) following a sequence used to synthesize a related compound by Wood and co-workers.¹² In this route, benzyl protection of commercially available 3-butyne-1-ol (14) is followed by a palladium-catalyzed dicarboxylation reaction to access diester 16 in 65% yield over two steps after optimization. Saponification of the diester enabled a dehydrative cyclization reaction in the presence of acetic anhydride to give dienophile 13 in four steps. Diels–Alder cycloaddition with known diene 12¹³ then affords Diels–Alder adduct 11 in 72% yield as a single diastereomer.

After exploring a wide range of nucleophiles, we discovered benzylic ester 17 (readily synthesized through esterification of 3-methoxyphenylacetic acid) adds with complete chemo-selectivity into the desired carbonyl group (Scheme 5). Treatment of the resulting adduct with HCl then cleaves the silyl ether, and the resulting primary hydroxyl group spontaneously cyclizes to form lactone acetal 18. A Krapcho- type decarboxylation with lithium chloride¹⁴ facilitates removal of the methyl ester, after which a one-pot alkene hydrogenation/benzyl ether hydrogenolysis provides primary alcohol 19. A Grieco elimination completes the installation of the vinyl group needed for eventual formation of the [2.2.2]bicycle, affording 9. This sequence proceeds in only five steps and 52% overall yield from Diels—Alder adduct 11, allowing rapid access to the cyclization precursor.

We initially explored using a direct Friedel—Crafts cyclization to forge the desired C—C bond. Despite screening a variety of Lewis acids, cyclization was not observed, with most attempts simply leading to recovery of starting material. We then turned to the formation of a discrete aromatic nucleophile via metal—halogen exchange of an aryl iodide. An investigation of electrophilic iodination conditions, including iodine monochloride and NIS, with and without Bronsted or Lewis acid additives, identified an indium(III) triflate-catalyzed protocol developed by Romo and co-workers as the most effective,¹⁵ producing the desired aryl iodide (21), along with its ortho- positioned isomer (20), in a roughly 1:1 mixture (Scheme 6). These isomers were readily separated, and the undesired isomer could be recycled through metal—halogen exchange to regenerate vinyl lactone—acetal 9 (see the Supporting Information for details). Ultimately, a 65% yield of desired aryl iodide 21 (based on recovered starting material) could be obtained.

With aryl iodide 21 in hand, conditions for metal—halogen exchange were then investigated. Lithium-halogen exchange¹⁶ proved to be too reactive, leading only to nonspecific decomposition products. Direct Grignard formation with magnesium turnings was likewise unsuccessful, returning only starting material. Classic magnesium-halogen exchange¹⁷ with *iso*-propyl magnesium chloride or with the Turbo Grignard reagent¹⁸ likewise proved to be too unreactive to lead to product formation. Lithium trialkylmagnesiates, developed by Oshima and co-workers,¹⁹ gratifyingly facilitated magnesium—halogen exchange as well as a subsequent 1,2-addition of the resulting magnesiate into the lactone carbonyl. The resulting adduct exists as an equilibrium of hemiacetal structures; as such, the crude reaction mixture was directly oxidized with Dess—Martin periodinane following a modified protocol reported by Nicolaou,²⁰ providing diketoaldehyde 10, the structure of which was confirmed by an X-ray crystallographic study of a single crystal. This sequence proceeds in 59% yield over two steps and can be readily performed on gram-scale, allowing for rapid material throughput.

This route to diketoaldehyde 10 represents the next step in our group's evolving strategy to rapidly access the 6—7—6-fused tricyclic core of hetidine- and hetisine-type diterpenoid alkaloid natural products. Building upon our previous synthetic studies, we have now designed an efficient route to a highly functionalized 6—7—6 tricycle. This route features a highly diastereoselective Diels—Alder cycloaddition, chemoselective addition of a benzyl enolate nucleophile, and a finely tuned magnesiate addition/ring-expansion/oxidation sequence to access the desired tricycle. This tricycle possesses key functional groups at

strategic locations, with carbonyl groups at all three carbon atoms bearing C—N bonds in the hetisine-type alkaloids, as well as the aromatic ring and vinyl group required for the eventual [4 + 2] cycloaddition reaction. Further studies will focus on the selective derivatization and elaboration of this tricycle into the hetisine-type core, selected natural products, and structural derivatives for biological evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We are grateful to the NIH (NIGMS R01 GM084906) for financial support. We thank the NSF and Eli Lilly for graduate fellowships to J.J.P. and the Amgen Scholars Program for summer fellowships to J.N.D. and M.A.P. We also thank A. DiPasquale (UC Berkeley) for solving the crystal structure of 10 (displayed with CYLView), supported by the NIH Shared Instrumentation Grant (S10-RR027172).

REFERENCES

- (1). (a) Liu X-Y; Qin Y *Asian J. Org. Chem* 2015, 4, 1010–1019. (b) Ameri A *Prog. Neurobiol* 1998, 56, 211–235. [PubMed: 9760702]
- (2). (a) Wang F-P; Liang X-T *C2o-Diterpenoid Alkaloids In The Alkaloids: Chemistry and Biology*; Cordell GA, Ed.; Elsevier: Amsterdam, Netherlands, 2002; Vol. 59, pp 1–280. [PubMed: 12561418] (b) Wang F-P; Chen Q-H; Liu X-Y *Nat. Prod. Rep.* 2010, 27, 529–570. [PubMed: 20336236]
- (3). Jin S-S; Guo Q; Xu J; Yu P; Liu J-H; Tang, Chin Y-Q. *J. Nat. Med.* 2015, 13, 361–367.
- (4). (a) Catterall WA; Cestele S; Yarov-Yarovoy V; Yu FH; Konoki K; Scheuer T *Toxicon* 2007, 49, 124–141. [PubMed: 17239913] (b) Camerino DC; Tricarico D; Desaphy J-F *Neurotherapeutics* 2007, 4, 184–198. [PubMed: 17395128] (c) Ahuja S; et al. *Science* 2015, 350, aac5464. [PubMed: 26680203]
- (5). Muratake H; Natsume M *Angew. Chem. Int. Ed.* 2004, 43, 4646–4649.
- (6). (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]
- (7). Hamlin AM; Lapointe D; Owens K; Sarpong R *J. Org. Chem.* 2014, 79, 6783–6800. [PubMed: 25004408]
- (8). Cherney EC; Lopchuk JM; Green JC; Baran PS *J. Am. Chem. Soc.* 2014, 136, 12592–12595. [PubMed: 25159015]
- (9). Li X-H; Zhu M; Wang Z-X; Liu X-Y; Song H; Zhang D; Wang F-P; Qin Y *Angew. Chem. Int. Ed.* 2016, 55, 15667–15671.
- (10). (a) Yatsunami T; Isono T; Hayakawa I; Okamoto T *Chem. Pharm. Bull.* 1975, 23, 3030–3032. (b) Yatsunami T; Furuya S; Okamoto T *Chem. Pharm. Bull.* 1978, 26, 3199–3207.
- (11). (a) Corey EJ; Howe WJ; Orf HW; Pensak DA; Petersson G *J. Am. Chem. Soc.* 1975, 97, 6116–6124. (b) Heathcock CH *Angew. Chem. Int. Ed.* 1992, 31, 665–681.
- (12). Spiegel DA; Njardarson JT; Wood JL *Tetrahedron* 2002, 58, 6545–6554.
- (13). (a) Marth CJ; Gallego GM; Lee JC; Lebold TP; Kulyk S; Kou KGM; Qin J; Lilien R; Sarpong R *Nature* 2015, 528, 493–498. [PubMed: 26675722] (b) Kou KGM; Li BX; Lee JC; Gallego GM; Lebold TP; DiPasquale A; Sarpong R *J. Am. Chem. Soc.* 2016, 138, 10830–10833. [PubMed: 27525345]
- (14). Krapcho AP; Weimaster JF; Eldridge JM; Jahngen EGE; Lovey AJ; Stephens WP *J. Org. Chem.* 1978, 43, 138–147.
- (15). Zhou C-Y; Li J; Peddibhotla S; Romo D *Org. Lett.* 2010, 12, 2104–2107. [PubMed: 20387852]
- (16). Bailey WF; Patricia JJ *J. Organomet. Chem.* 1988, 352, 1–46.

- (17). Knochel P; Dohle W; Gommermann N; Kneisel FF; Kopp F; Korn T; Sapountzis I; Vu VA *Angew. Chem. Int. Ed.* 2003, 42, 4302–4320.
- (18). Krasovskiy A; Knochel P *Angew. Chem. Int. Ed.* 2004, 43, 3333–3336.
- (19). Inoue A; Kitagawa K; Shinokubo H; Oshima K *J. Org. Chem.* 2001, 66, 4333–4339. [PubMed: 11397172]
- (20). Nicolaou KC; Baran PS; Zhong Y-L; Fong KC; Choi H-S *J. Am. Chem. Soc.* 2002, 124, 2190–2201. [PubMed: 11878973]

Figure 1.
Hetisine- and hetidine-type diterpenoid alkaloids.

Scheme 1.
Synthetic Strategy toward the Hetisine Core

Previous Work:

This Work:

Scheme 2.

Efforts toward the Central 6—7—6 Tricycle

Scheme 3.
Retrosynthesis

Scheme 4.
Dienophile Synthesis and Diels—Alder Cycloaddition

Scheme 5.
Elaboration to Vinyl Lactone—Acetal

Scheme 6.
Completion of the Desired 6—7—6 Tricycle