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Magnesiate Addition/Ring-Expansion Strategy To Access the 6−7−6 Tricyclic Core of Hetisine-Type C_{20}-Diterpenoid Alkaloids

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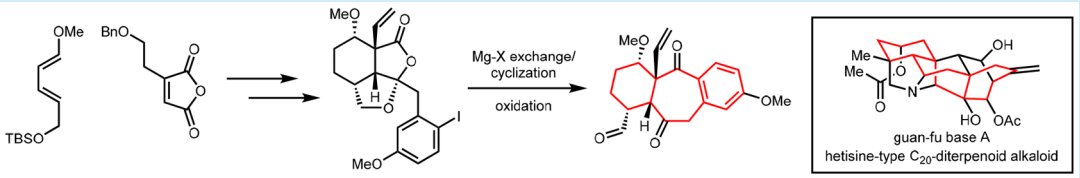
Supporting Information



ABSTRACT: A synthetic strategy to access the fused 6−7−6 tricyclic core of hetisine-type C_{20}-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 magnesiate 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.

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 C_{20}-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

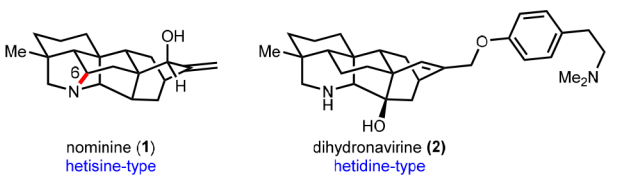
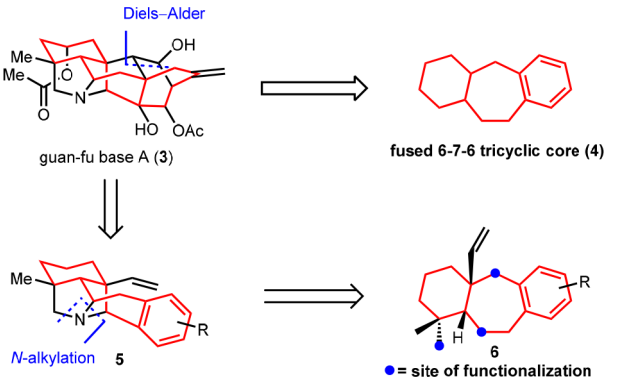


Figure 1. Hetisine- and hetidine-type diterpenoid alkaloids.

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]

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

Scheme 1. Synthetic Strategy toward the Hetisine Core



2004[5] 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 group[7] as well as the laboratories of Baran[8] 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.

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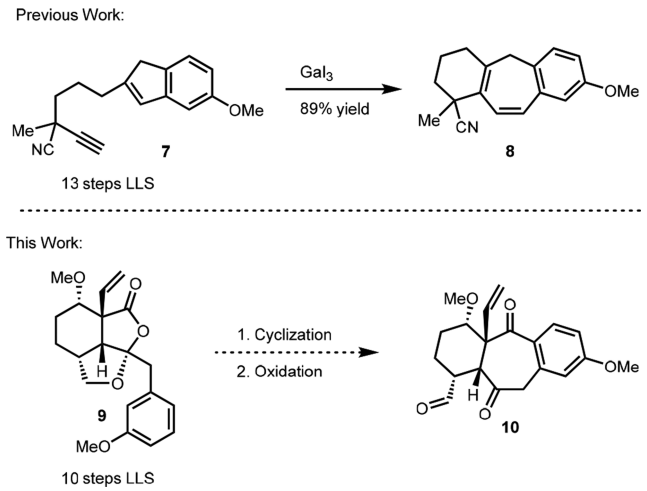
Our research group has identified a central fused 6−7−6 tricycle (Scheme 1, highlighted in red) as a key structural motif in the core scaffold of these complex alkaloids. This design choice arises from a network analysis approach to retrosynthesis[11] in which the [2.2.2]bicycle is forged late-stage 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(III)-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.

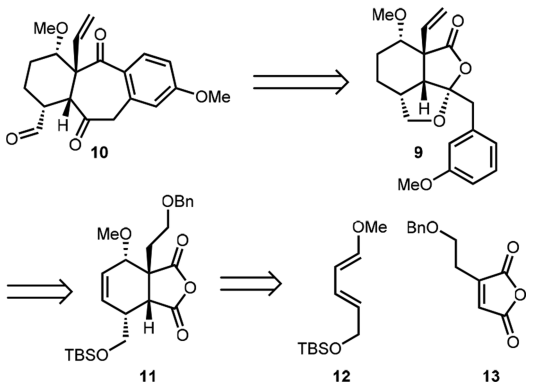
Scheme 2. Efforts toward the Central 6−7−6 Tricycle



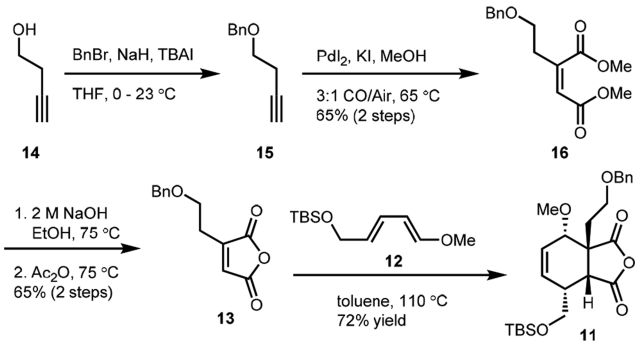
On the basis of this precedent, we embarked on a streamlined and higher yielding synthesis of a tricycle that would be more ideally functionalized to access the hetisine-type core. We envisioned diketoaldehyde **10** as an ideal precursor, with carbonyl groups at all three carbon atoms that form C−N 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 coworkers.[12] In this route, benzyl protection of commercially available 3-butyn-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 **12**[13] then affords Diels−Alder adduct **11** in 72% yield as a single diastereomer.

Scheme 3. Retrosynthesis

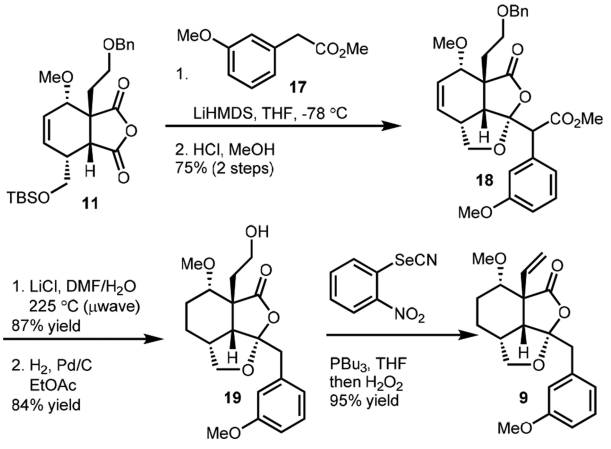


Scheme 4. Dienophile Synthesis and Diels−Alder Cycloaddition



After exploring a wide range of nucleophiles, we discovered benzylic ester **17** (readily synthesized through esterification of 3-methoxyphenylacetic acid) adds with complete chemoselectivity into the desired carbonyl group (Scheme 5).

Scheme 5. Elaboration to Vinyl Lactone−Acetal



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 chloride[14] 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%

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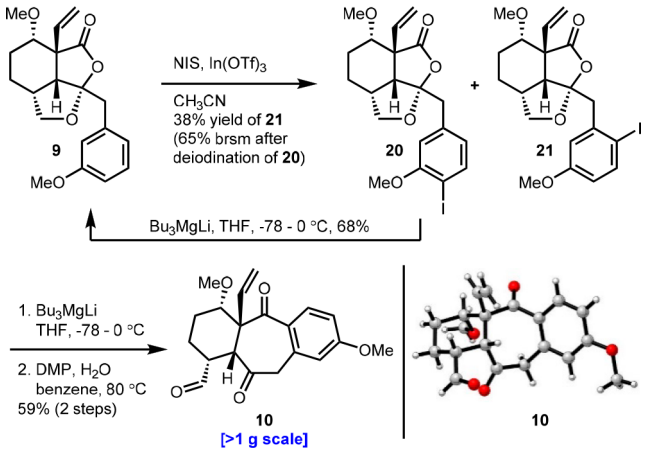
overall yield from Diels–Alder adduct **11**, allowing rapid access to the cyclization precursor.

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).

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



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 exchange[16] 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 exchange[17] with *iso*-propyl magnesium chloride or with the Turbo Grignard reagent[18] 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.

■ 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)

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Notes

The authors declare no competing financial interest.

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