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Synthesis of (±)-rupestines B and C by intramolecular Mizoroki-Heck cyclization

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ABSTRACT

The total synthesis of rupestines B and C, two guaipyridine sesquiterpene alkaloids, is reported. These compounds are isolated from *Artemisia rupestris* L. and have structural similarities to that of cananodine, a guaipyridine alkaloid with activity against two liver cancer cell lines. The synthesis of rupestines B and C was accomplished in six steps using an intramolecular Mizoroki-Heck cyclization as the key-step to form the seven-membered carbocycle of the targets.

The guaipyridine alkaloids (Chart 1) are a small family of sesquiterpenoid natural products. One member of the family is cananodine, isolated in small quantities from the fruits of *Cananga odorata* [1]. Cananodine is active against Hep G2 and Hep 2,2,15 hepatocellular carcinoma (HCC) cell lines with IC_{50} values of 0.22 and 3.8 μg/mL, respectively, while the in vitro IC_{50} of the current first-line HCC treatment, sorafenib, is 2.1 μg/mL against Hep G2 [2]. HCC is responsible for more than 12,000 deaths a year in the U.S. and diagnosed cases in the U.S. has tripled over the last four decades. Outside the U.S. the problem is much more severe, where HCC results in 700,000 deaths each year [3,4]. Curative treatments may be administered to the approximately one-third of patients diagnosed with HCC in the early stages of the disease. The 5-year survival rate for those diagnosed early is 31%, but once the disease has spread to surrounding tissues, this survival rate drops to 11%. For patients that have undergone liver resection, the 5-year survival rate is 25–50% with a high rate of recurrence [5,6]. Only 10–15% of patients are candidates for surgery due to their decrease in liver function [7]. Survival time for those who are not candidates for curative treatments can be as low as six weeks. Two total syntheses of cananodine have been reported to date, the first by Craig and Henry in 2006 [8] and the second from our lab in 2017 [9]. Rupestine G was recently synthesized by Huang and co-workers in ten steps from 5-bromo-2-methylpyridine and produced the seven-membered carbocycle using ring-closing metathesis. The target compound and its stereoisomers were produced as a mixture that was separated by chiral HPLC. This was recently extended

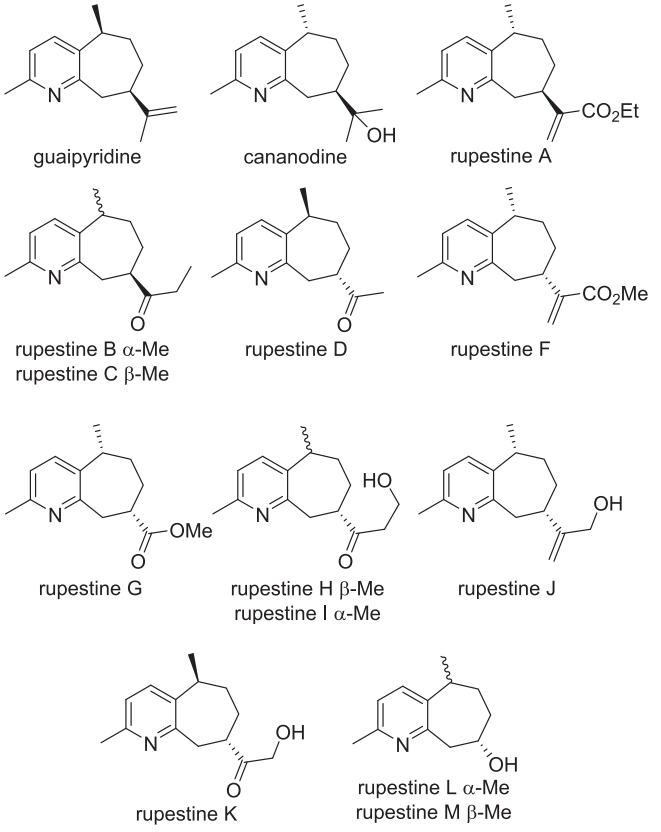

Chart 1. Guaipyridine alkaloids.

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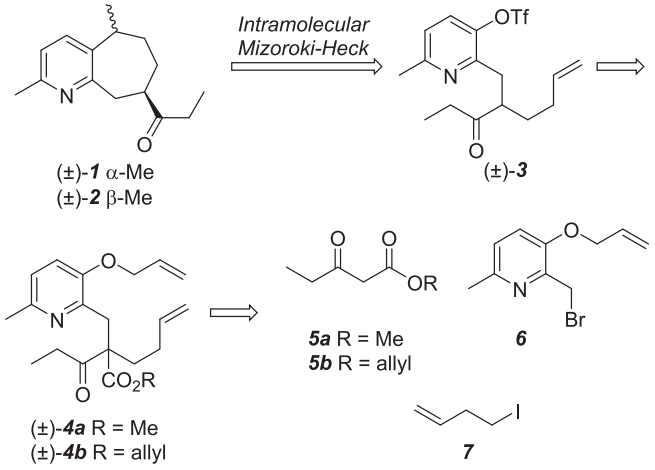
to a synthesis of cananodine as reported in a Chinese patent [10,11].

The rupestines are isolated from *Artemisia rupestris* (Chart 1) [12,13]. This plant has been used in traditional Chinese medicine and has reported antitumor, antibacterial, and antiviral activities, as well as reported protection of the liver from various maladies. Like cananodine, the rupestines are only isolated from their source plant in small quantities, making the total synthesis of these guaipyridine alkaloids of particular interest. Herein we report the first synthesis of guaipyridine alkaloids rupestine B and C.

In our retrosynthetic analysis of rupestines B (**1**) and C (**2**) (Scheme 1) we planned to form the target compounds as a mixture of diastereomers that we would separate in the final step. The final step was to be a hydrogenation of the conjugated 1,1-disubstituted alkene formed in the intramolecular Mizoroki-Heck reaction of triflate **3**. Triflate **3** would arise from double deprotection of intermediate **4** that would also result in the decarboxylation of the beta-keto acid. Intermediate **4** would be prepared from beta-keto ester **5** and picolyl bromide **6** [14] through simple alkylation, followed by alkylation of that intermediate with 4-iodo-1-butene (**7**).

We began by alkylating commercially available methyl 3-oxopentanoate (**5a**) with picolyl bromide **6** to give **8** in nearly quantitative yield (Scheme 2). A number of bases were explored:



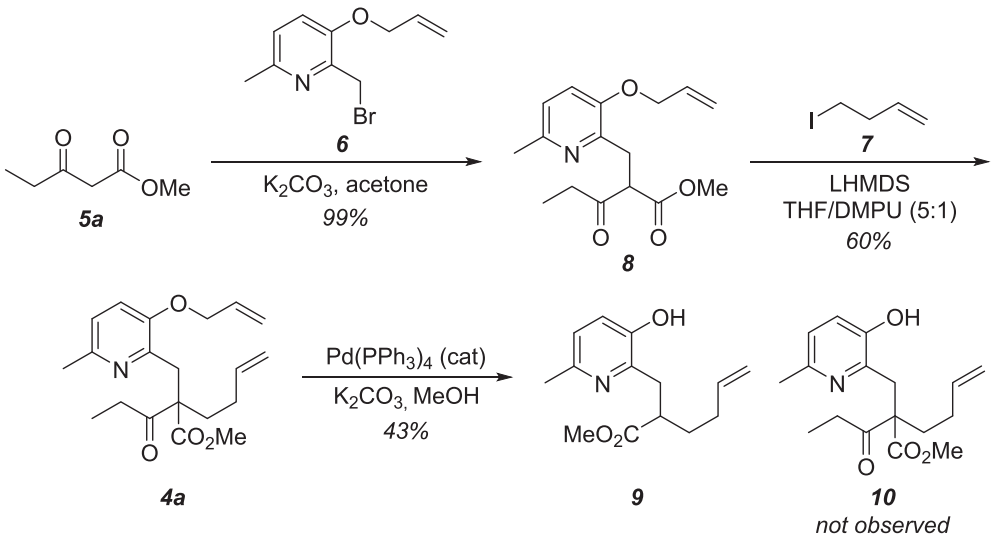
Scheme 1. Retrosynthetic analysis of rupestines B and C.

NaOMe, LHMDS, KO^{t}Bu, and NaH. Excess K_2CO_3 was found to be superior to the other conditions. A second alkylation using 4-iodo-1-butene (**7**) provided the substituted product **4a**. This second alkylation step proved rather difficult due to the steric hindrance involved in creating the quaternary carbon center. We tried a number of conditions, changing the base (K_2CO_3, KO^{t}Bu, LHMDS), reaction temperature (0 °C to reflux) and solvent (acetone, *t*-BuOH, THF). The yield of **4a** ranged from 20 to 60%, with most of the unreacted **8** being recovered through flash column chromatography. The most successful alkylation conditions proved to be LHMDS as base in a solvent mixture of 5:1 THF:DMPU [15].

We then planned to cleave the allyl ether group to reveal the phenolic hydroxyl of **10**, which would then be converted to the corresponding aryl triflate, setting the stage for an intramolecular Mizoroki-Heck reaction [16–18]. Unfortunately, when allyl ether **4a** was exposed to palladium(0) in methanolic potassium carbonate, the ethyl ketone was cleaved as well, producing a complex mixture containing **9**. Keto ester **10** was not observed in the ^{1}H NMR spectrum of the crude product mixture [19,20].

To avoid the decarbonylation of the ketone, we changed our starting material such that the decarboxylation of the ester would be favored (Scheme 3). Alkylation of allyl 3-oxopentanoate (**5b**), prepared from **5a** through transesterification with allyl alcohol [21], with bromide **6** provided intermediate **11** in excellent yield. Alkylation of **11** with 4-iodo-1-butene (**7**) as described above gave keto ester **4b** in modest yield. Treatment of **4b** with palladium(0) in basic methanol resulted in the cleavage of both allyl groups and *in situ* decarboxylation of the intermediate keto acid to provide **12**. Triflation of the phenolic hydroxyl of **12** gave the cyclization substrate **3** without incident. Exposure of **3** to palladium(0) in hot, basic dioxane resulted in an intramolecular Mizoroki-Heck reaction that formed the seven-membered carbocycle of **13** in satisfactory yield. Finally, hydrogenation of the exocyclic alkene gave racemic rupestines B (**1**) and C (**2**) in quantitative yield as a 1:2 mixture of stereoisomers. While these diastereomers were not separable using normal phase flash column or radial chromatography, we were able to separate them using reverse phase MPLC. The ^{1}H and ^{13}C spectra for each diastereomer were easily assigned and matched the data reported in the isolation of the natural products [12].

In summary, an intramolecular Mizoroki-Heck cyclization strategy produced the carbocyclic core of the guaipyridines. While the hydrogenation step was not highly stereoselective, the



Scheme 2. Preliminary investigation of enolate alkylations.

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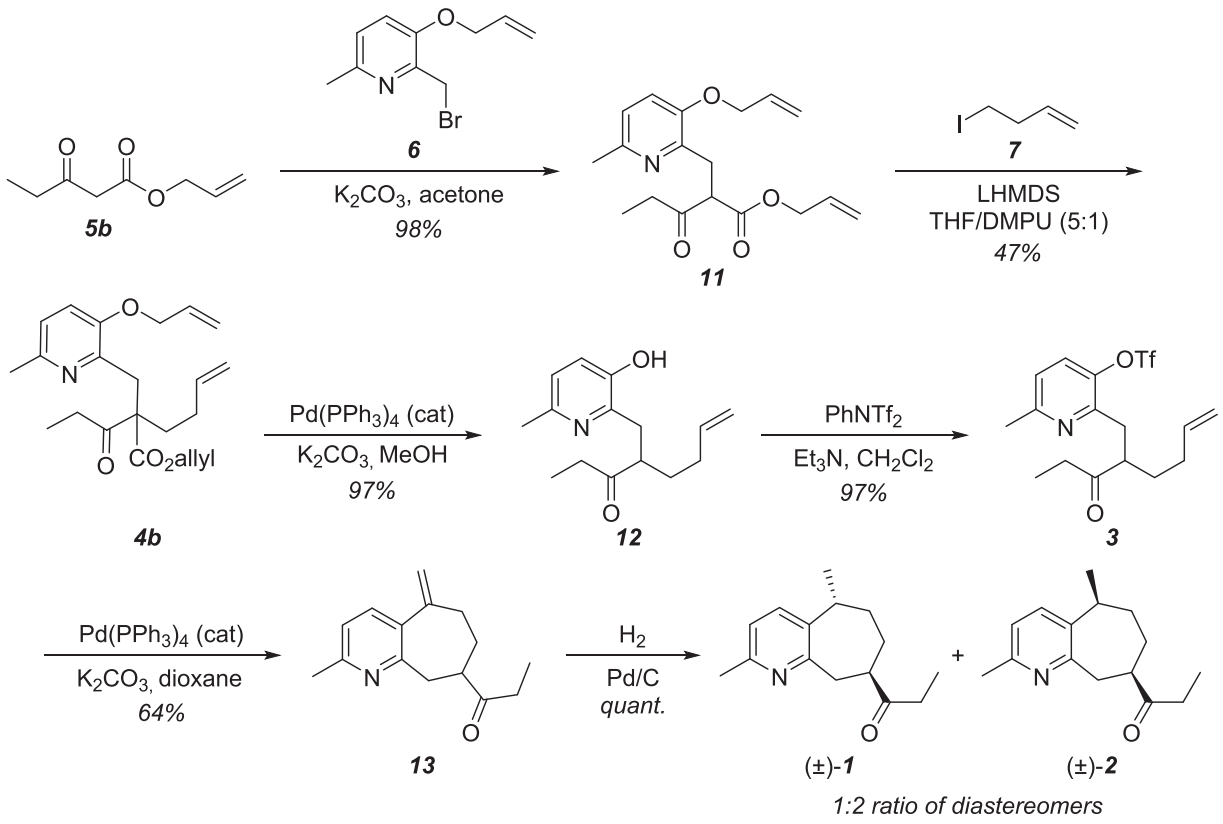

Scheme 3. Synthesis of rupestines B and C.

diastereomers were separable by reverse-phase chromatography. Racemic rupestines B (**1**) and C (**2**) were prepared in six steps from allyl 3-oxopentanoate (**5b**) in yields of 9% and 18%, respectively.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data (full experimental details and copies of ^{1}H and ^{13}C NMR spectra are provided.) to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151837.

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