Published in final edited form as:

Tetrahedron Lett. 2017 August ; 58(35): 3478–3481. doi:10.1016/j.tetlet.2017.07.080.

Synthesis of cananodine by intramolecular epoxide opening

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Abstract

Cananodine is a guaipyridine alkaloid with activity against liver cancer. Cananodine was synthesized using a remarkable intramolecular opening of a trisubstituted epoxide as the key step in construction of the seven-membered carbocycle of the target. The epoxide opening strategy allows all four stereoisomers of cananodine to be prepared.

Graphical abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with an estimated 750,000 new cases each year leading to nearly as many deaths.¹ Although HCC is particularly prevalent in Asia, the incidence of HCC in the U.S. has increased dramatically over the last two decades, to an estimated 27,000 new cases per year,² probably as a result of the increase in chronic hepatitis C virus (HCV) infections in this country, which has resulted in the age-related incidence of HCC shifting to younger people.^{1,3} The prognosis for patients diagnosed with HCC is grave. The primary treatment and only proven curative therapy is liver resection or transplant, and although the 5-year survival rate for these surgical patients is 25–50%, there is a high rate of recurrence.^{4,5} Worse, only 10–15% of HCC patients are surgical candidates due to decreased liver function or metastasis of the tumor.^{5,6} A variety of anticancer drugs have been tried as systemic HCC treatments, but exceedingly few have proven effective. Currently the only approved drug for HCC is sorafenib (Nexavar®), a multi-kinase inhibitor containing a pyridine head group and diaryl urea tail that was introduced in 2007.⁷ Sorafenib improved overall survival time in patients with advanced HCC from 7.9 to 10.7 months.^{7a} Clearly there is room for progress.⁸

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Supporting Information

Experimental procedures, compound characterization data, and copies of NMR spectra (PDF).

Cananodine (**1**) is a guaipyridine alkaloid isolated in small quantities from the fruits of *Cananga odorata* (10 mg from 3.5 kg fruit) (Figure 1).⁹ *C. odorata* is a member of the Annonaceae family and commonly known as “ylang-ylang,” since steam distillation of the flowers provides fragrant ylang-ylang oil. Moreover, *C. odorata* is known to be rich in alkaloids,¹⁰ and has been used in traditional folk medicine in Southeast Asia.^{11,12} Cananodine was also recently isolated from *Cyperus scariosus*.¹³ Most importantly, cananodine (**1**) has activity against both the Hep G₂ and Hep 2,2,15 hepatocarcinoma cell lines, with IC₅₀ values of 0.22 and 3.8 µg/mL, respectively.⁹ This compares favorably to the in vitro activity of sorafenib against Hep G₂ of 2.0 µg/mL.¹⁴ Among natural sesquiterpene pyridine alkaloids, the guaipyridine skeleton is rare.¹⁵ Recently discovered guaipyridine alkaloids include the rupestines, isolated from *Artemisia rupestris* (Figure 1).¹⁶ No biological activity for the rupestines has been reported yet.

Despite the anticancer activity and unusual structure of cananodine, only one synthetic investigation has been reported to date, a total synthesis reported by Craig and Henry, which raised a question about the optical rotation of the natural product.¹⁷ The only other synthetic approaches to guaipyridines in the literature are best described as regio- and/or stereo-random, and all of them began with an intact seven-membered carbocycle.¹⁸ Herein we report the synthesis of optically active cananodine, its enantiomer and their diastereomers.

In our retrosynthesis of cananodine (**1**), we desired a strategy that would allow for the preparation of either enantiomer of the natural product. Thus, we planned to form the seven-membered ring through intramolecular attack of a picolyl anion on an optically active epoxide **2** (Scheme 1).¹⁹ The ‘Z’ group in **2** was intended to be electron withdrawing to make the α-protons at C-2 of the pyridine ring more acidic than the protons on the C-6 methyl group, thereby allowing for selective deprotonation to promote the intramolecular reaction. The epoxide **2** would be prepared from pyridyl diene **3**, which in turn is formed by Suzuki-Miyaura coupling of pyridyl halide/triflate **4** and alkenyl boronate **5**.²⁰

Our first investigation involved use of a sulfone as the aforementioned directing group. Thus, cleavage of the pivaloate group in **6**²⁰ gave primary alcohol **7** which was converted to sulfone **8** in a two-step process (Scheme 2). Cleavage of the acetonide followed by conversion of the resulting diol to the trisubstituted epoxide via the mesylate yielded **9**. Treatment of sulfone epoxide **9** with various bases (*t*-BuOK, LDA, *n*-BuLi) produced the

orange-red color of the substituted picolyl anion,¹⁹ but no cyclized product **10** was obtained. Even with prolonged reaction times, and in some cases elevated temperature, most of the starting epoxide **9** was recovered in each case. Attempts to activate the epoxide after deprotonation (LiBr, SnCl₂,²¹ BF₃•OEt₂) were unsuccessful in producing cyclized products also, again returning mostly unreacted **9**. The highly delocalized anion that is produced upon deprotonation of the activated methylene in **9** is apparently not nucleophilic enough to open the relatively hindered epoxide.

To see if reducing steric demands of the epoxide would facilitate cyclization, we next examined a monosubstituted epoxide with a single picolyl position to eliminate the need for a group to direct deprotonation. Chemoselective asymmetric dihydroxylation of the monosubstituted olefin of **11**²⁰ produced diol **12** in good yield (Scheme 3). A portion of the diol was converted to the corresponding acetonide for analysis by chiral GC, which showed an enantiomeric excess of 76%. Sharpless' one pot procedure²² was used to convert the diol to epoxide **13** in a relatively low yield, but provided sufficient material to study the cyclization.

Baldwin's rules for ring closure²³ do not address medium ring cases. Although the tendency for epoxides to undergo nucleophilic attack at the less substituted position under basic conditions is well-established for acyclic cases and in the formation of small rings, we predicted that the transannular strain in the incipient 8-membered ring would disfavor the 8-*endo* cyclization and make the 7-*exo* mode more likely.²⁴ Treatment of **13** with LDA, however, produced only the 8-membered product **14** along with a significant amount of recovered starting material. No **16** was detected in the ¹H NMR spectrum of the crude reaction mixture. The oxygenated methine of **14** (δ 3.70 for ¹H and δ 72.2 for ¹³C) was the key to assigning the 8-membered ring structure to the product, along with the splitting pattern of the benzylic protons at 3.06 and 2.95 ppm (each a ddd). The use of Et₂AlCl Lewis acid to coordinate to the epoxide and in an attempt to alter the regioselectivity of the cyclization was unsuccessful, instead producing the chloride **15** after conversion of the initially produced chlorohydrin to the acetate ester to aid in purification and characterization. Use of BF₃•OEt₂ resulted in products arising from rearrangement of the epoxide to the corresponding aldehyde. In no case was the seven-membered product **16** observed by ¹H NMR analysis of the crude products.

Despite the fact that our earlier investigation of the intermolecular reaction of a picolyl anion with a trisubstituted epoxide gave relatively low-yields,¹⁹ we proceeded to prepare a trisubstituted epoxide cyclization precursor expecting that the intramolecular reaction would be more successful than the intermolecular case. (Scheme 4). Pd-catalyzed cross coupling of pyridyl iodide **17** with dienylboronate **5b**²⁰ in the presence of Ag₂O²⁵ was found to be the most efficient method to obtain **18** in high yield. Asymmetric dihydroxylation of the more electron rich olefin of **18** gave diol **19** in moderate yield.²⁶ Conversion of the diol to the corresponding epoxide via the intermediate mesylate²⁷ provided epoxide **20**, which was determined to have an enantiomeric excess of 96% by chiral GC analysis. Treatment of **20** with butyllithium resulted in deprotonation at the picolyl positions and 7-*exo* opening of the epoxide to produce **21** in modest yield. Although this reaction is intramolecular, deprotonation of the picolyl positions is non-selective and deprotonation at C6 is

unproductive in terms of opening the epoxide, making the maximum yield 50% assuming irreversible deprotonation.

The last step in the synthesis was hydrogenation of the exo methylene group of **21**. We were hopeful that the tertiary alcohol of **21** would provide a handle for hydroxyl-directed hydrogenation.²⁸ Crabtree's catalyst²⁹ was ineffective, both at 1 atm or 50 psi of hydrogen. Wilkinson's catalyst³⁰ accomplished the transformation under elevated hydrogen pressure, but with poor diastereoselectivity, producing cananodine (**1**) and its epimer in 49% yield as a 1:1 mixture. Either the tertiary hydroxyl group is too hindered to effectively coordinate to the metal, or the dominant conformation of the seven-membered ring does not bring the group sufficiently close to the olefin. Molecular modeling supports the latter. Unfortunately, we were unable to separate the diastereomers with either normal or reverse phase chromatography. Resonances belonging to cananodine (**1**) were easily assigned in the ¹H and ¹³C NMR spectra of the mixture, however, and matched those previously reported.¹⁷

For the sake of completeness, we also prepared the enantiomeric series of intermediates (Scheme 5). Diene **18** was converted to the epoxide **24** via diol **23** in good yield and high enantiomeric excess. Cyclization of epoxide **24** proceeded in a yield consistent with previous results to produce **25**. Hydrogenation with Wilkinson's catalyst as before led to the diastereomeric mixture of *ent*-cananodine (**26**) and its epimer **27**.

In summary, an intramolecular epoxide opening strategy successfully produces the bicyclic guaipyridine core. Both enantiomers of the epoxide substrate are accessible through asymmetric dihydroxylation in the preparation of the epoxide substrate. Following the remarkable epoxide cyclization, hydrogenation of the exo-methylene in the penultimate intermediate was not diastereoselective, however. Cananodine was prepared in six steps from 3-iodo-2,6-dimethylpyridine in 4% overall yield as a mixture with its diastereomer. Cananodine's enantiomer was prepared in 3% overall yield as a diastereomeric mixture. Thus, all four stereoisomers of the target compound were prepared from a common intermediate. Current efforts are aimed at more efficient construction of the guaipyridine core and enantioselective hydrogenation of the exo-methylene in the late stages of the synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Cancer Institute, National Institutes of Health (R15 CA122084) and the Western Washington University Fund for the Enhancement of Graduate Research. We thank Prof. Donald Craig for ¹H and ¹³C NMR spectra of cananodine.

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Highlights

- Guaipyridine alkaloid cananodine was synthesized in 6 steps
- 7-membered carbocycle was constructed using a remarkable intramolecular opening of a trisubstituted epoxide
- Opening of a similar monosubstituted epoxide produced an 8-membered carbocycle
- Epoxide opening strategy resulted in the synthesis of all four diastereomers of the target

Figure 1.
Guaipyridine alkaloids.

Scheme 1.
Retrosynthetic analysis of cananodine.

Scheme 2.
Initial epoxide opening investigation.

Scheme 3.
Cyclization of a monosubstituted epoxide.

Scheme 4.
Synthesis of cananodine and its epimer.

Scheme 5.
Synthesis of *ent*-cananodine and its epimer.