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Synthesis of cananodine by intramolecular epoxide opening

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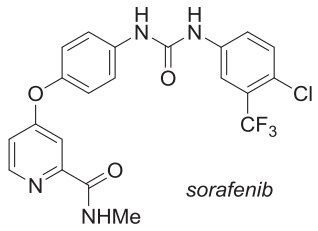
ABSTRACT

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.

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]



sorafenib

Cananodine (**1**) is a guaipyridine alkaloid isolated in small quantities from the fruits of *Cananga odorata* (10 mg from 3.5 kg fruit) (Fig. 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 G_2 and Hep 2,2,15 hepatocarcinoma cell lines, with IC_{50} values of 0.22 and 3.8 μg/mL, respectively.[9] This compares favorably to the in vitro activity of sorafenib against Hep G_2 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 *Artemsia rupestris* (Fig. 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

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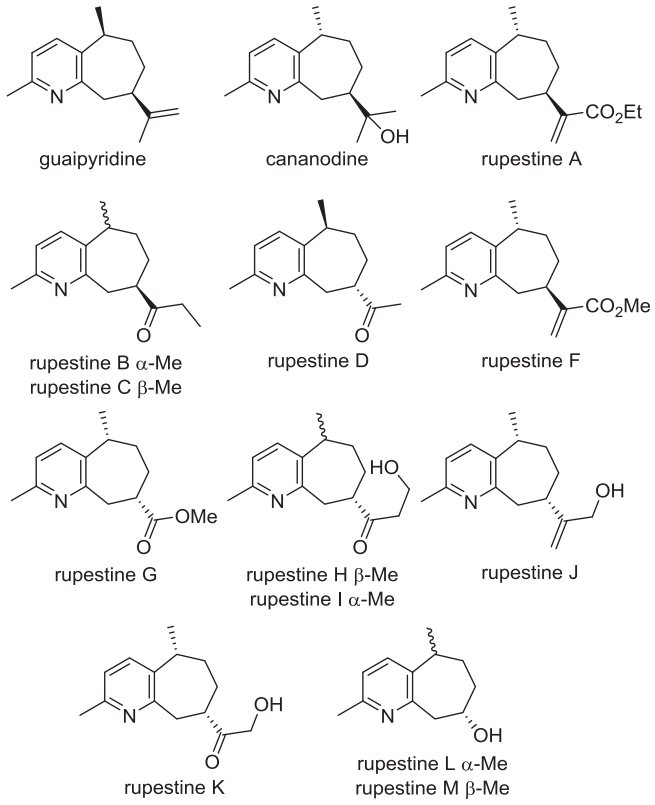
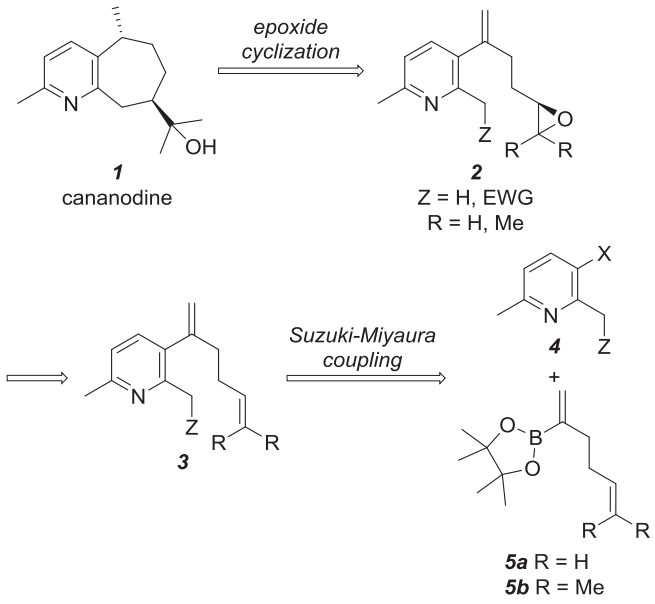


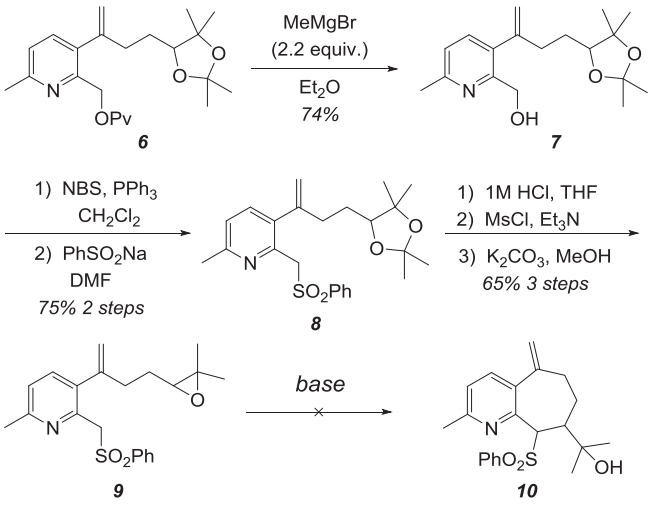
Fig. 1. Guaipyridine alkaloids.



Scheme 1. Retrosynthetic analysis of cananodine.

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



Scheme 2. Initial epoxide opening investigation.

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 elevated temperature, most of the starting epoxide **9** was recovered in each case. Attempts to activate the epoxide after deprotonation (LiBr, $SnCl_2$,[21] $BF_3{\cdot}OEt_2$) 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 procedure[22] 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 closure[23] 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 ^{1}H NMR spectrum of the crude reaction mixture. The oxygenated methine of **14** (δ 3.70 for ^{1}H and δ 72.2 for ^{13}C) 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 Et_2AlCl as a 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 $BF_3{\cdot}OEt_2$ resulted in products arising from rearrangement of the epoxide to the corresponding aldehyde. In no case was the seven-membered product **16** observed by ^{1}H 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