Short syntheses of the tricyclic indole alkaloids cimitrypazepine and fargesine.

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Abstract

A short synthetic sequence leading to the tricyclic alkaloids cimitryptazepine and fargesine is reported. An intramolecular Heck reaction and a palladium catalyzed reductive *N*-heterocyclization are key steps in the synthesis.

Introduction Naturally occurring azepino[5,4,3-*cd*]indoles have been isolated from diverse natural sources (Figure 1). This group of alkaloids include aurantioclavine (as a mixture of diastereomers) isolated from the fungus *Penicillium aurantiovirens*,¹ clavicipitic acid from the fungus *Claviceps fusiformis*,² the diastereomeric alkaloids hyrtireticuline C and D from the marine sponge *Hyrtios reticulatus*,³ and fargesine from the roots and stems of *Evodia fargesii*.⁴ In addition, cimitrypazepine was identified in the roots and rhizomes of black cohosh (*Cimicifuga racemosa*).⁵

Figure 1. Naturally occurring azepino[5,4,3-*cd*]indoles.

A variety of synthetic strategies have been used to prepare the azepino[5,4,3-*cd*]indole ring system and the most prevalent are functional group manipulations of 3,4-disubstituted indoles to form the azepine ring. Formation of the azepine ring via the carbon-nitrogen bond **b** is the most commonly used approach in total synthesis^{6,7} although, the formation of carbon-nitrogen bond **c**⁸ and carbon-carbon bonds **a**^{5,9} and **d**¹⁰ have been employed (Figure 2). The assembly of both the pyrrole and azepine rings onto a functionalized benzene ring is more unusual but sequential **f-e-b**,¹¹ **b** then **f**,¹² and **e** then **f**¹³ bond formations have been described. The latter methodologies offers perhaps more flexible routes to a variety of functionalized analogs compared to the use of a preassembled indole ring as the starting material.

Figure 2. Ring disconnections employed in syntheses of naturally occurring azepino[5,4,3-*cd*]indoles.

The tricyclic *N*-oxide alkaloid fargesine was isolated from the roots and stems of *Evodia fargesii* in 2006⁴ and a total synthesis was reported by Jia *et al.*¹³ The fruits of the plant have been used in Chinese folk medicine as an analgesic and cough suppressant. The closely related non-oxidized alkaloid named cimitryptazepine was later identified in Black cohosh (*Cimicifuga racemosa*), a flowering plant native to eastern North America.⁵ A synthesis was reported by the authors wherein a Pictet-Spengler type cyclization of *N*-methylserotonin and formaldehyde, forming the **a**-bond, was used as the key azepine ring-forming step. While this methodology

developed by Somei et al¹⁴ is simple, it usually affords mixtures of azepino[5,4,3-*cd*]indoles and 1,2,3,4-tetrahydro- β -carbolines employing aliphatic aldehydes.¹⁵ In addition, the formation of azepino[5,4,3-*cd*]indoles is limited to 5-hydroxytryptamines. Black cohosh has traditionally been used by Native Americans for treating colds, rheumatism, and for alleviating menopausal symptoms such as hot flashes. Herein is reported a linear total synthesis of cimitrypazepine and fargesine *via* first formation of the azepine ring by an intramolecular Heck reaction followed by the pyrrole ring by a palladium catalyzed reductive *N*-heterocyclization (bonds **e** then **f**, in Figure 2).¹⁶ Carbon monoxide serves as the ultimate reducing agent in the latter reaction forming carbon dioxide as the only byproduct. The synthesis discussed below is flexible and opens the possibility for the preparation of a number of cimitrypazepine analogs and other naturally occurring azepino[5,4,3-*cd*]indoles.

Results and Discussion

6-Hydroxy-2-iodo-3-nitrobenzaldehyde (**1**),¹⁷ readily prepared from commercially available 4-hydroxy-2-iodo-1-nitrobenzene, served as the starting point for the synthesis of both cimitrypazepine and fargesine (Scheme 1). Reductive amination of **1** using 4-amino-1-butene (**2**) and sodium borohydride afforded the expected product **3**. Both the hydroxy and the amino group in **3** were protected by reaction with di-*t*-butyldicarbonate ((Boc)₂O) in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP). The starting material (**3**) was cleanly converted into a single new compound (by TLC). The anticipated di-protected compound **4** was the only aromatic compound seen in the ¹H NMR spectrum of the crude reaction mixture. However, upon purification by chromatography on silica gel, the *O*-deprotected compound **5** was isolated as the major product, in addition to **4**. The *N*-Boc group was intended to serve a dual purpose, lowering

the coordination ability of the nitrogen, at times a problem in intramolecular Heck reactions, and as a source of the azepine *N*-methyl group after reduction. In our case, protection of the amine was crucial for the Heck reaction to occur.¹⁸ Treatment of compound **3** using a palladium diacetate – tri(*o*-tolyl)phosphine catalyst system in triethylamine as the solvent (125 °C), typical Heck conditions, did not furnish any observable amount of the anticipated bicyclic product.

Intramolecular Heck reactions were attempted using both **4** and **5** in order to evaluate the need for *O*-protection. Diprotected compound **4** was completely consumed after 3.5 h as observed by TLC. Work up and careful purification by chromatography gave four different products. Two 2-benzazepines, the di-*O,N*-Boc protected compound **6** and the *N*-Boc protected compound **7**, were isolated as the major products. In addition, minor amounts of two 2-benzazocines (**8** and **9**) differing in the position of the unsaturation in the eight-membered ring were also obtained. The latter two compounds had lost the *O*-Boc group during the reaction or upon purification of the crude reaction mixture. Intramolecular Heck reactions affording mixtures of 2-benzazepines and 2-benzazocines have previously been reported.¹⁹ It should be noted that the Heck reaction of **4** was unpredictable and varying ratios and yields of products were obtained from seemingly identical reaction conditions and concentrations. The result shown in Scheme 1 represents the highest isolated yield of **6/7** obtained in several cyclizations of **4**. In comparison to the reaction of **4**, cyclization of **5** was more consistent but gave a slightly lower isolated yield of the 2-benzazepine product **7** (relative to **6+7**, 66%) and a slightly higher yield of 2-benzazocine **8** (Scheme 1).

Scheme 1. Synthesis of 2-benzazepines **6** and **7** and benazocines **8** and **9**.

Palladium catalyzed reductive *N*-heterocyclization of **6** using a bis(dibenzylideneacetone)palladium-1,3-bis(diphenylphosphino)propane-1,10-phenanthroline catalyst system in the presence of carbon monoxide (pCO=6 atm, 120 °C) in *N,N*-dimethylformamide, furnished the di-*N,O*-protected azepino[5,4,3-*cd*]indole **10** in addition to the *N*-protected analogue **11** in 79% total yield (Scheme 2). Treatment of compound **7** using the same reagents and reaction conditions also gave **11** in a somewhat lower isolated yield. Finally, upon treatment of **10** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene at reflux, the *O*-Boc group was removed and the *N*-Boc group was reduced to a methyl group affording **12** (cimitryptazepine). Alkaloid **12** was also isolated in excellent yield from Red-Al reduction of **11**. All analytical data including ^1H and ^{13}C NMR, IR, HRMS, and melting point of synthetic cimitryptazepine were identical to the literature values of the compound isolated and synthesized by Nikolic *et al.*⁵

Scheme 2. N-Heterocyclization and reduction to give cimitryptazepine (**12**).

Direct oxidation of the azepine-nitrogen of **12** using *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane²⁰ or hydrogen peroxide – ammonium hydrogen carbonate in water did not furnish fargesine; instead intractable mixtures were obtained in all attempted reactions. It is plausible, based on results from oxidations of 5-hydroxyindoles, that a quinone imine was formed followed by decomposition.²¹ In place of a direct oxidation of **12** to fargesine, we decided to intercept an intermediate reported in the previous synthesis of fargesine. Thus, cimitryptazepine (**12**) was *O*-Boc-protected to give **13** in excellent yield. This compound has previously been oxidized and deprotected using *m*-CPBA and sodium hydroxide, respectively, to afford **14** (fargesine).

Scheme 3. Synthesis of fargesine (**14**).

In summary, a linear total syntheses of the naturally occurring azepino[5,4,3-*cd*]indoles, cimitryptazepine and fargesine has been completed. The key steps are an intramolecular Heck reaction forming the azepine ring and a palladium catalyzed reductive N-heterocyclization

building the pyrrole ring of the indole. This sequence of steps is flexible and opens the possibility for the synthesis of a number of cimitryptazepine analogs by the use of substituted aminoalkenes related to **2**.

Supporting data

Supplementary data associated with this article including experimental procedures and ^1H NMR and ^{13}C NMR spectra can be found in the online version, at <http://dx.doi.org/10.1016/j.bmc.2012.04.011>

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Graphical Abstract for:

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