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Total synthesis of new indolo[2,3-*a*]quinolizine alkaloids sempervirine type, potential pharmaceuticals☆

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Abstract—Total synthesis of the two series of new pentacycilc cycloalk[*g*]indolo[2,3-*a*]quinolizine alkaloids (modified sempervirine possessing the wide range of activity), has been elaborated in five steps from 5-acetyl-3-methylthio-1,2,4-triazine (obtained from the simple acyclic materials). In the two key steps: inverse electron demand Diels–Alder reaction of precursor with cyclic enamines and the following Fischer indolization of 3-acetyl-1-methylthiocycloalka[*c*]pyridines, the AB–DE synthons, has been obtained. The final stages: desulfuration, and formation of the C-ring via the Gribble method have led to the expected zwitterionic alkaloids. Model syntheses of the indolopyridocoline and its methoxy analogue from 2-acetylpyridine have been performed for investigation of the microwave-induced Fischer synthesis of sensitive indoles and for obtaining compounds for comparative study of spectroscopic data.

1. Introduction

In recent years, there has been a growing interest in the synthesis of bioactive molecules and their non-natural analogues in the field of organic chemistry as a result of the new synthetic methods and techniques, which enable creating new medicaments. Sempervirine and other indolo[2,3-*a*]quinolizine alkaloids (alstonine, flavopereirine), were first known as cardiac species,[2] but recently their anticancer[3] (as DNA intercalating agent),[4] immunostimulative[3d,5] and anti-HIV,[3d] sedative and antipsychotic[5a,6] activities have been discovered. Just recently, it has been shown that sempervirine and other indole alkaloids (vinblastine, vincamine, ajmalicine, harmaline) can act as inhibitors of the enzyme CYP2D6 (it might exists as various polymorphic genotypes), giving a wide range of clinical effects, depending on individual organism.[7] Sempervirine, as indolo[2,3-*a*]quinolizinium type of molecule, can exist in acidic and neutral medium as a cation and in alkaline medium it has a conjugated zwitterionic structure, where one neutral canonical structure can be drawn[8,9] (Fig. 1). Since trace amounts of sempervirine exist in a natural resource, the rhizome and roots of *Gelsemium sempervirens*,[10] many methods have already been developed for its total synthesis involving various strategies for construction of the 1,2,3,4-tetrahydrobenz[*g*]indolo[2,3-*a*]quinolizine ring system.[8,11] Among them, the conception of the construction of pentacyclic ring system via a AB–DE synthon was developed,[12,13] as it is shown in Figure 2. This 2-(2-pyridyl)indole-type synthon was obtained by Stevens and co-workers[12] in the Fischer synthesis from 3-acetyl-5,6,7,8-tetrahydroisoquinoline

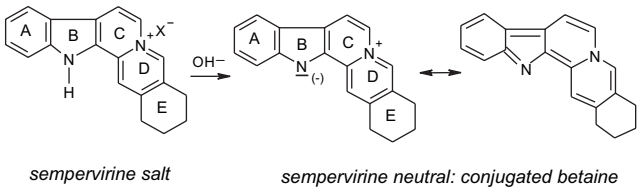

Figure 1.

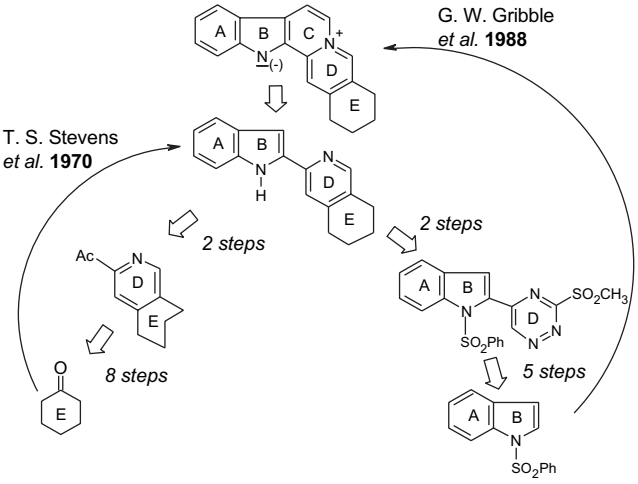

Figure 2.

☆ See Ref. 1.
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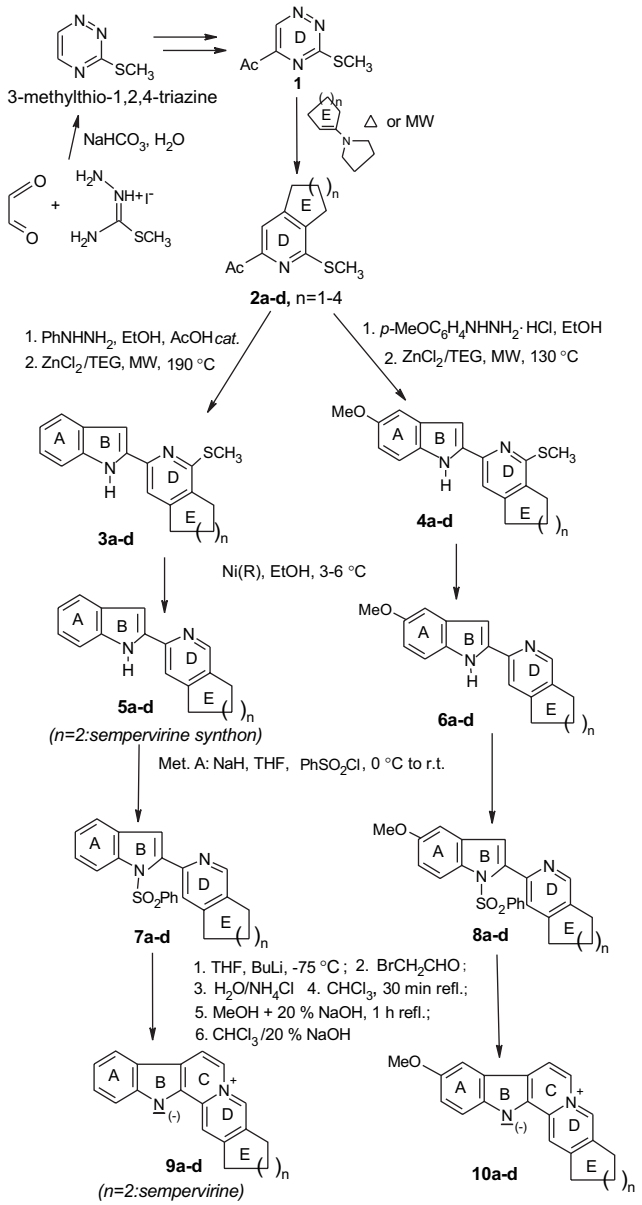
prepared in eight steps from cyclohexanone. The second synthesis by Gribble and co-workers[13] formed the AB–CD synthon in eight steps from *N*-phenylsulfonylindole, which was functionalized in C2 position for construction of the 1,2,4-triazine ring, next transformed by Diels–Alder reaction with the 1-(1-pyrrolidine)cyclohexene. The latter investigators successfully formed the middle C-ring via the indole *N*-protection, direct metalation and reaction with bromoacetaldehyde as a 1,2-dielectrophile. We took some advantage of these two developments and elaborated a novel total synthesis strategy, not only to improve the yield of sempervirine, but also to gain access to its new analogues for biological evaluation.

In present paper, we describe the scope and limitations of our method (see Scheme 1) and, report the full experimental details after optimization of its key steps and give the characterization data of the intermediates and final products.



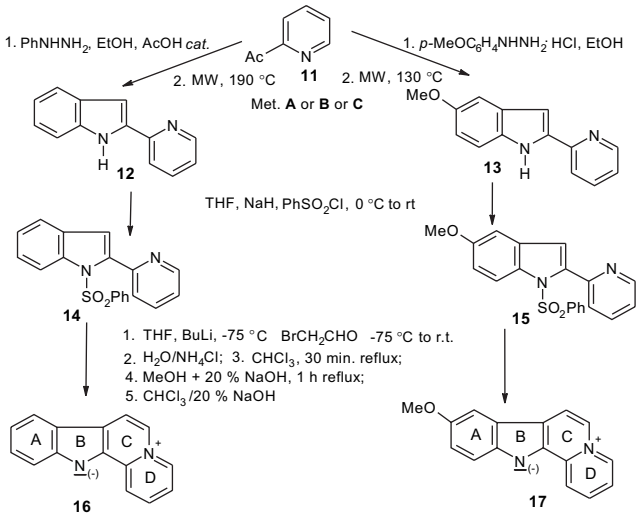
Scheme 1. Synthesis of the two series of modified sempervirine.

2. Results and discussion

2.1. Synthetic strategy

Our total synthesis strategy is based on the availability of the 5-acetyl-3-methylthio-1,2,4-triazine **1**[14] and the possibility of its transformation into 3-acetyl-1-methylthiocycloalka[*c*]pyridines **2a–d** by the Diels–Alder reaction with cyclic enamines.[15] Thus, we envisioned and discovered that the AB–DE sempervirine synthon **5b**[14b] as well as other 2-(2-pyridyl)indoles could be constructed in the Fischer indolization, thanks to the presence of the acetyl group in the molecules **2a–d** (see Scheme 1). With this perspective in mind, we planned the synthesis of **3a–d**[15b] and **4a–d**,[16] and next the AB–CD synthons **5a–d** and **6a–d**. The latter can be transformed into pentacyclic indolo[2,3-*a*]quinolizine alkaloids via the Gribble method.[13]

The starting material, 5-acetyl-3-methylthio-1,2,4-triazine **1**, was prepared in 40% yield in two-step synthesis[14] from 3-methylthio-1,2,4-triazine,[17] which can be obtained on a large laboratory-scale (up to 100 g) from the glioxal and *S*-methylthiosemicarbazide hydroiodide. Syntheses of **2a–d** via inverse electron demand Diels–Alder reaction of the **1** with cyclic enamines have been optimized recently.[18] The acetyl group remains in compounds **2a–d**, which gives access to the construction of the indole moiety via the Fischer synthesis. Initially, we obtained **3b** in conventional conditions;[14b] in a medium of excess molten zinc chloride and methylnaphthalene at temperature 200–220 °C, according to the Steven's method.[12] We chose this procedure from the two classic methods for performing the difficult Fischer synthesis. However, this procedure was inconvenient and non-ecological and gave rather low and non-reproducible 25–55% yield. The second method for performing difficult Fischer synthesis, described as efficient for transformation of 2-acetylpyridine **11** into 2-(2-pyridyl)indole **12** (see Scheme 2), involves using the polyphosphoric acid as a reaction medium.[19] However, we observed that this procedure gave the overall degradation of more complicated molecules like the **2a–d** phenylhydrazones. Having observed this, we had to search for another, more efficient



Scheme 2. Model synthesis of the indolopyridocoline **16** and its methoxy analogue **17**.