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Synthesis of Methyl-Protected (±)-Chlorizidine A

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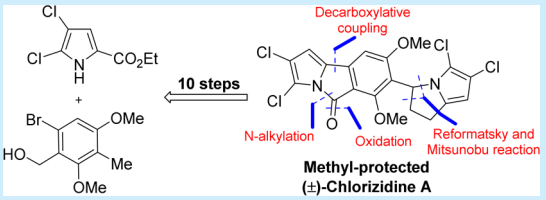
Supporting Information

ABSTRACT: The first total synthesis of the methyl-protected (±)-chlorizidine A has been achieved in 10 steps. Pd-catalyzed decarboxylative coupling and late-stage oxidation were utilized to construct the 5*H*-pyrrolo[2,1-*a*]isoindol-5-one scaffold. Samarium(II) iodide mediated Reformatsky reaction and intramolecular Mitsunobu reactions were efficiently applied for the synthesis of the 2,3-dihydropyrrolizine ring system. Chlorizidine A is highly prone to degradation; hence, methyl-protected (±)-chlorizidine A was prepared.



In recent years, large numbers of pyrrole-containing natural products that possess a unique scaffold in their structure have been isolated from terrestrial as well as marine origins.[1] Most of them exhibit interesting biological activities like antimalarial, antifungal, antibacterial, anticancer, antiprotozoal, etc.[2] The pyrrole unit is also present in the top-selling cholesterol lowering drug atorvastatin A.[3] Pyrrole-containing natural products show a diverse range of applications; therefore, they are under investigation for their structural and biological properties.[1−3] Hughes and co-workers isolated a new pyrrole-containing natural product "chlorizidine A" from *Streptomyces* sp. strain CNH-287 in 2013, which displays notable cytotoxicity against HCT-116 adenocarcinoma cell line with an IC_{50} value 3.2−4.9 μM.[4] Its derivatives were also shown to be potent against various cancer cell lines (Figure 1).[4]

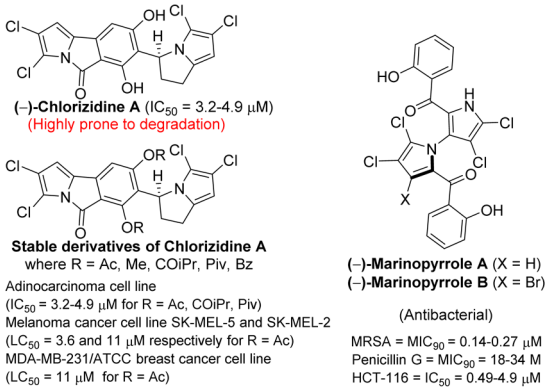
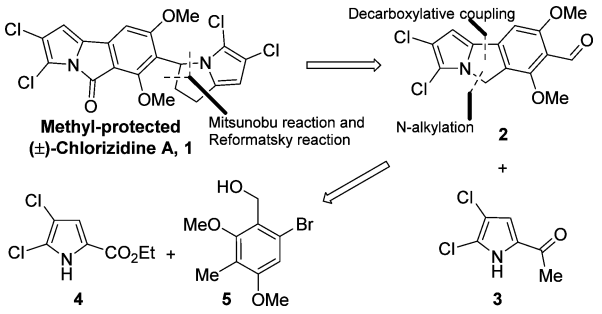


Figure 1. (−)-Chlorizidine A, its derivatives,[4] and (−)-marinopyrroles A and B.[5]

Structurally, chlorizidine A resembles marinopyrrole A,[5] which was also isolated from a *Streptomyces* sp. strain. Chlorizidine A possesses unique features in its structure, such as a 2,3-dihydropyrrolizine ring system attached through the C−C single bond with a 5*H*-pyrrolo[2,1-*a*]isoindol-5-one ring system in the *S*-configuration, wherein pyrrole rings are densely chlorinated (Figure 1). Interestingly, the 5*H*-pyrrolo[2,1-*a*]isoindol-5-one ring system was found for first time in the field of natural products and is probably responsible for the cytotoxicity.[4] The promising biological activity and unique carbon skeleton make it an attractive target for chemical and biological studies.

To date, a chemical synthesis of this molecule has not been reported. Recently, Moore et al. reported biosynthetic logic behind the construction of this rare scaffold using *Streptomyces* sp. CNH-287 based on its biosynthetic gene cluster.[6] Its cytotoxicity was studied by Fenical et al. using combinations of a cellular and molecular method.[7] Studies show that chlorizidine A targets the cytosolic protein GAPDH and ENO1 involved in the glycolytic pathway and is implicated in many diseases like metastatic cancer, autoimmune disorders, neurological disorders, and bacterial infections. Our interest in the synthesis of natural products prompted us to investigate the synthesis of this biologically important and synthetically challenging pyrrole-containing molecule. In this paper, we disclose our synthetic route toward the construction of the methyl derivative of this structurally intriguing molecule for the first time.

Scheme 1. Retrosynthetic Plan for Methyl-Protected (±)-Chlorizidine A



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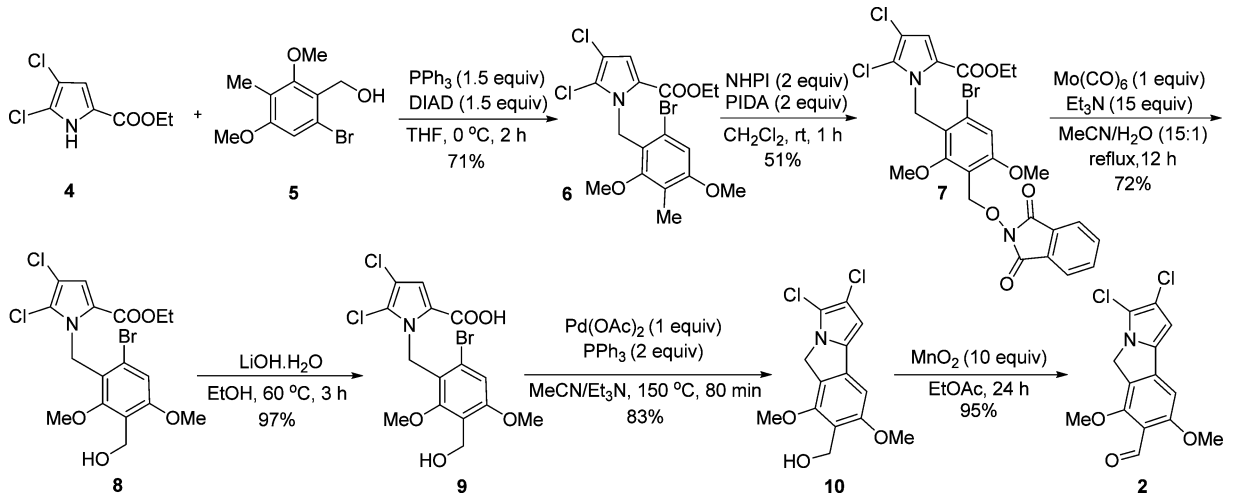
Scheme 2. Synthesis of Precursor 2

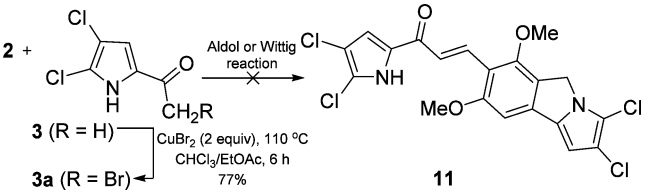


Our retrosynthetic plan for the synthesis of **1** is presented in Scheme 1, where **1** was dissected in two fragments, aldehyde **2** and ketone **3**. Aldehyde **2** can be traced back to compound **4** and **5**. We envisioned that 2,3-dihydropyrrolizine ring could be installed at a later stage using **2** and **3** as the precursor, in which the aldol/Wittig/Reformatsky reaction and intramolecular Mitsunobu reaction could be used. Intermediate **2** could be obtained from **4** and **5** using *N*-alkylation and decarboxylative coupling reactions, respectively.

Our synthesis commenced with the preparation of **4** and **5** (Scheme 2). The dichloro ester **4** was prepared starting from pyrrole 2-carboxylic acid by a known protocol.[8] The alcohol **5** was synthesized starting from commercially available 2,4-dimethoxy 3-methyl benzaldehyde in five steps using reported procedures.[9] The substrates **4** and **5** were coupled using Mitsunobu conditions to furnish **6** in good yield. At this stage, we wanted to oxidize or functionalize both benzylic groups of **6** to facilitate further transformations. For this, we attempted various conditions, but unfortunately, the expected products could not be obtained. Finally, ester **6** was treated with *N*-hydroxyphthalimide under known conditions[10] in the presence of diacetoxyiodobenzene (PIDA) at room temperature to obtain PINO adduct **7** in moderate yield. This protocol was the best and the only condition we have found to activate benzylic methyl group selectively. Reductive cleavage[11] of the PINO adduct **7** using $Mo(CO)_6$ and Et_3N in CH_3CN/H_2O furnished the benzylic alcohol **8** in good yield. Hydrolysis of ester **8** with LiOH in ethanol gave acid **9** in 97% yield. For the construction of the 5*H*-pyrrolo[2,1-*a*]isoindole ring, we tried several Pd-catalyzed decarboxylative coupling reaction conditions; however, expected product was observed in only trace amounts. Interestingly, when the acid **9** was subjected to $Pd(OAc)_2$ (1 equiv)/PPh_3 (2 equiv)[12] in CH_3CN/Et_3N (3:1) at 150 °C, the expected alcohol **10** could be obtained in 83% yield. Treatment of benzyl alcohol **10** with MnO_2 furnished aldehyde **2** in excellent yield.

Once aldehyde **2** was in hand, we focused on the installation of the 2,3-dihydropyrrolizine ring system (Scheme 3). Initially, our plan was to synthesize α,β-unsaturated ketone using aldehyde **2** and ketone **3** by aldol condensation. Various acidic and basic conditions could not furnish the expected product **11** (Scheme 3). Next, we thought of using Wittig olefination reaction in which α,β-unsaturated ketone could be synthesized

Scheme 3. Attempts for Aldol or Wittig Reaction



and later cyclized using an intramolecular Michael addition reaction. Hence, ketone **3** was brominated[13] using $CuBr_2$ in $CHCl_3$/EtOAc to obtain **3a** in good yield. Various conditions were attempted for Wittig olefination, but we could not observe the expected chalcone **11**.

Hence, we planned to use the Reformatsky reaction (Scheme 4). Initially, we attmpted the zinc-mediated Reformatsky reaction conditions, wherein a trace amount of product was observed. A literature survey revealed that samarium iodide mediated Reformatsky reaction was efficiently used for the synthesis of β-hydroxy ketone.[14] Aldehyde **2** and bromoketone **3a** were then subjected to the Reformatsky reaction using SmI_2 (0.1 M) in THF at refluxing temperature. Pleasingly, we observed 58% yield of the expected product **12** in the first attempt. Further optimization of the reaction condition enhanced the yield up to 70%. β-Hydroxy ketone **12** was then subjected to intramolecular Mitsunobu conditions using PPh_3/DIAD at room temperature to obtain cyclized ketone **13**. The next goal was to oxidize the benzylic methyl of pyrroloisoindole; therefore, **13** was subjected to series of oxidation reagents and reaction conditions, but we always ended up with either no reaction or complex product formation. Reaction with $KMnO_4$ and benzyl triethylammonium chloride (BTAC) in CH_2Cl_2[15] showed the formation of only a trace amount of the expected product. Hence, we postponed this transformation at a later stage. Compound **13** was subjected to ketone reduction[16] in the presence of ZnI_2 and $NaCNBH_4$ to provide **14** in moderate yield. This completed the synthesis of dihydropyrrolizine ring system. To oxidize the benzylic methyl, we tried several oxidation reactions but met with failure; hence, we applied the $KMnO_4$–BTAC conditions.[15] Under these conditions, the compound **1** was obtained in low yield, but this is the only condition we found where we obtained the expected compound. We observed

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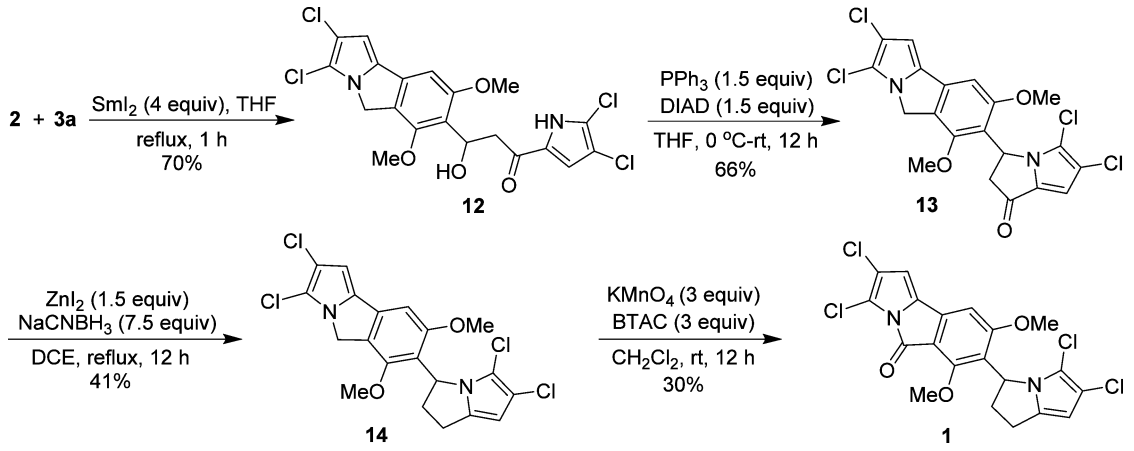
Scheme 4. Completion of Synthesis



mixture atropisomers in the ^{1}H and ^{13}C NMR spectra of compounds **13**, **14**, and **1**.

Further, as expected, the conversion of **1** to chlorizidine A using various conditions for deprotection of the methoxy group did not work because of the instability of the product as reported by Hughes et al. in the isolation paper.[4] The spectral and analytical data of the synthesized methyl-protected chlorizidine A are in complete agreement with the reported data,[4] which confirms the structure of the isolated natural product chlorizidine A.

In conclusion, we have achieved the first total synthesis of methyl-protected (±)-chlorizidine A. By this route, the Pd-mediated decarboxylative coupling, Mitsunobu reaction, and samarium iodide mediated Reformatsky reaction were efficiently applied to construct the rare 5*H*-pyrrolo[2,1-*a*]isoindol-5-one ring and 2,3-dihydropyrrolizine ring systems. Further functional group manipulation completes the synthesis. The designed synthetic route paves a way to synthesize other potential analogues for structure−activity relationship studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01090.

Experimental procedures and ^{1}H and ^{13}CNMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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