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Total Synthesis of (±)-Marinopyrrole A via Copper-Mediated N-Arylation

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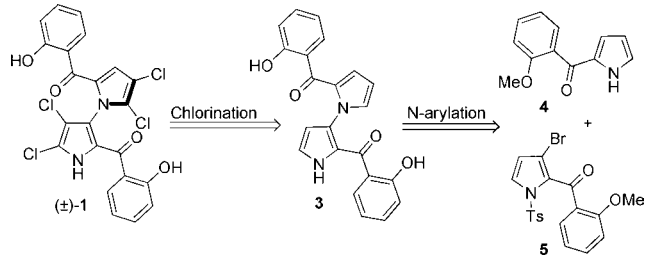
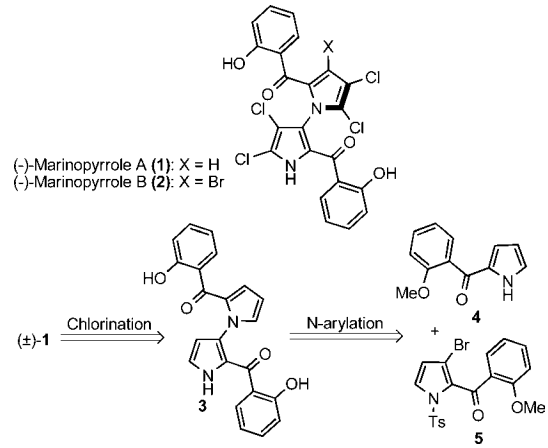
ABSTRACT



The total synthesis of the racemic form of the marine alkaloid marinopyrrole A is described. The characteristic 1,3′-bipyrrole core was constructed by a copper-mediated N-arylation process under microwave irradiation.

Resistance to currently available antibiotics is an increasing public health problem.[1] To address the urgent need for novel antibiotics to treat infections, current research efforts are refocused on identifying novel antibiotics from natural sources.[2] Natural products and their derivatives have played an important role in antibiotic drug discovery. Thus, many medicines in the market are of natural origin, being based on compounds originally isolated from plants and microbes such as penicillin, cephalosporin, vancomycin, fosfomycin, etc. Marinopyrroles A (**1**) and B (**2**) were extracted as single atropo-enantiomers in 2008 from the marine *Streptomyces* strain CNQ-418 (Scheme 1).[3] Interestingly, when screened for biological activity, marinopyrroles exhibited antibacterial activity against *methicillin-resistant Staphylococcus aureus* (MRSA) and cytotoxicity against human cancer cells. Soon after their isolation and preliminary activity studies, efforts to uncover the molecular mechanism of action of marinopyrroles began with the synthesis of derivatives labeled with an immunoaffinity fluorescent tag (IAF). Subsequent immunoprecipitation studies, conducted on cells and cell lysates treated with the IAF probes, identified actin as a molecular target of marinopyrroles.[4]

Scheme 1



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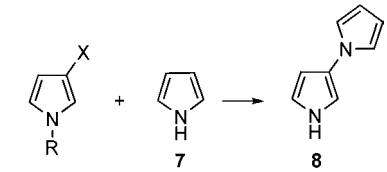
Axially chiral compounds are common scaffolds in many natural products that exhibit promising biological activities.[5] The marinopyrroles represent the first naturally occurring axially halogenated chiral 1,3′-bipyrroles. Fenical reported that marinopyrrole A exists as a single *M*-atropoisomer, is stable at room temperature, and can be racemized in toluene at 120 °C to give the non-natural (*P*)-(+)-marinopyrrole A. The fact that the marinopyrroles were isolated as single atropo-enantiomers suggests that their biosynthesis probably involves an enzyme-mediated critical pyrrole coupling.[3] Inspired by this idea, we envisaged to construct the 1,3′-bipyrrole core via an Ullmann-type coupling reaction for the C(pyrrolyl)−N bond formation (Scheme 1). During the course of our studies, Fenical's group tried to synthesize marinopyrrole A in a similar synthetic approach but without success.[6] Thus, they synthesized bipyrrole derivatives by the Paal−Knorr reaction which involved the condensation of a diketo compound onto 3-aminopyrrole. Li and co-workers followed the same method to prepare a small library of marinopyrrole analogues to study further the anticancer and antibiotic activities of this novel class of bioactive compounds.[7]

Ullmann and Goldberg first reported the coupling of C−C and C−N bonds by copper complexes more than a century ago.[8] Thereafter, improvements and novel applications of C−N bond-forming reactions continually appeared in the literature.[9] Among them, the N-arylation of nitrogen-containing heterocycles has recently received particular attention. A variety of procedures are available for the N-arylation of pyrroles including the coupling of pyrroles with aryl halides in the presence of Pd,[10] Cu,[11] and Fe[12] or coupling of pyrroles with arylboronic acids.[13] Herein, we describe an easy access to the 1,3′-bipyrrole template by a copper-mediated N-arylation protocol. An example of the application of this methodology was demonstrated in the total synthesis of the natural product (±)-marinopyrrole A.

We first examined various intermolecular amination procedures for the coupling of 3-bromo-*N*-tosyl-pyrrole **6a**[14] with pyrrole as the model substrate for optimization of the reaction conditions (Table 1). Our initial attempts focused on the Fukuyama modification[15] of the Ullmann−Goldberg reaction, which has been applied to the synthesis of highly functionalized nitrogen heterocycles.[16] Fukuyama and co-workers used a combination of CuI (2.0 equiv) and CsOAc providing a mild intramolecular aryl amination of aryl halides. Building on these studies, You et al. presented an efficient CuI-catalyzed N-arylation protocol for N-containing heterocycles including pyrrole with aryl and heteroaryl bromides or chlorides.[17] We, therefore, chose to focus our initial studies on the cross-couplings of pyrrole through the use of CuI and Cs_2CO_3 without the assistance of an additional chelating ligand in DMF. Under these conditions, the coupling reaction did not proceed in refluxing DMF, while deprotection of the tosyl group from compound **6a** was observed. The same results were obtained when the coupling was tested in the presence of diamine ligands according to Buchwald[18] or the Hartwig procedure with $Pd(OAc)_2$ and DPPF and the Chan−Evans−Lam-Modified Ullmann condensation between boronic acid **6d**[19] and pyrrole.

For this reason, we decided to attempt the N-arylation using microwave heating. The use of microwave irradiation proved

Table 1. Cu-Mediated N-Arylation of Pyrrole **7**



6a: R = Ts, X = Br
6b: R = TIPS, X = Br
6c: R = BOC, X = Br
6d: R = TIPS, X = $B(OH)_2$

entry	conditions	yield (%)[a]
1	**6a** (1.5 equiv), **7** (1 equiv), Cs_2CO_3 (2 equiv), DMF, 200 °C, (MW), 2 h	–
2	**6a** or **6b** or **6c** (1.5 equiv), **7** (1 equiv), CuI (2 equiv), Cs_2CO_3 (3 equiv), DMF, 200 °C, (MW), 2 h	85−90
3	**6a** (1.5 equiv), **7** (1 equiv), CuI (0.1 equiv), Cs_2CO_3 (1.5 equiv), DMF, 200 °C, (MW), 2 h	22
4	**6a** (1.5 equiv), **7** (1 equiv), $Cu(PPh_3)_3Br$ (1 equiv), Cs_2CO_3 (2 equiv), DMF, 200 °C, (MW), 2 h	2
5	**6d** (1 equiv), **7** (1 equiv), $Cu(OAc)_2$, Et_3N, CH_2Cl_2, 5 mol %, MS 4 Å, rt, 24 h	–

[a] Isolated yield of purified product.

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particularly effective for this transformation, and the desired amination product was obtained at 200 °C in 86% yield (Table 1). A catalytic version of this reaction did not work satisfyingly since attempts to decrease the amount of copper catalyst caused a significant decrease of yields (entry 3, Table 1). In an effort to examine the protecting group compatibility, 3-bromo-*N*-triisopropylsilyl-pyrrole and 3-bromo-*N*-Boc-pyrrole were used under the same coupling conditions. In both cases, N-deprotection occurred, and 1,3′-bipyrrole **8** was the only isolated product. We further tested the soluble [$Cu(PPh_3)_3Br$] catalyst according to the procedure of Venkataraman[20] under conventional heating or microwave irradiation. Compound **8** was produced in small amounts, while large quantities of starting materials remained unconsumed.

We then extended our studies toward the coupling of pyrrole esters under the above standard conditions (Scheme 2). Generally, substituents in the ortho position to the site

Scheme 2

of bond formation are expected to prevent the coupling due to steric hindrance. Yu has demonstrated that 2-ketopyrroles are suitable substrates for N-arylation with aryl boronic acids, and the 2-keto group has an accelerating effect in the reaction course, probably through the chelation of copper with the amino and keto groups.[13] In our case, the reaction took place at higher temperatures compared with the unsubstituted pyrrole (240 °C, MW). At these conditions, the substrates decomposed, and ester hydrolysis, subsequent decarboxylation, and *N*-tosyl deprotection took place. As a result, products **11** and **8** were isolated from the reaction mixture in 20 and 30% yield, respectively. The copper-mediated decarboxylation has been previously described for a wide range of aliphatic and aromatic carboxylic acids.[21] Furthermore, carboxylic acids decarboxylate in the presence of copper to give arylmetal species that may serve as the nucleophilic components in a cross-coupling reaction with aryl halides.[22] Nevertheless, we were not able to isolate coupling products from this reaction path that should give access to the 1,2′-bipyrrole system. To increase the reaction yield, other conditions were tested, such as CuI/pyridine or CuI/$Pd(Ph_3P)_4$, but proved unsuccessful. Similarly, bipyrrole **8** was isolated from the reaction of methyl pyrrole-2-carboxylate **9** with 3-bromo-*N*-tosyl-pyrrole **6a**.

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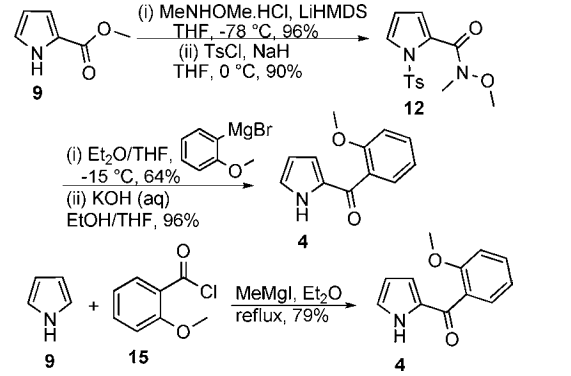
Following up our initial retrosynthesis toward marinopyrrole A, monomers **4** and **5** were synthesized (Scheme 1). Methyl pyrrole-2-carboxylate **9** was treated with MeNHOMe•HCl in the presence of LiHMDS at −78 °C to give the corresponding Weinreb amide, whose N−H group was then protected with a tosyl group to give sulfonamide **12** (Scheme 3). Next, dechloropyoluteorin **4** was prepared in a two-step

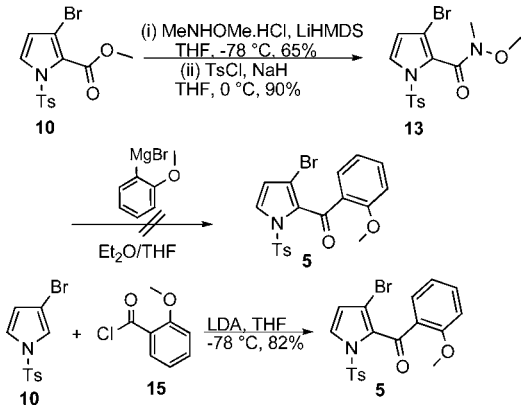
Scheme 3



sequence involving the reaction of Weinreb amide precursor **12** with anisoyl magnesium bromide and subsequent tosyl group deprotection. More conveniently, dechloropyoluteorin **4** was synthesized in a one-step procedure from the reaction of pyrrolylmagnesium and anisoyl chloride in 79% yield.

The synthesis of compound **5** was accomplished in an analogous fashion as depicted in Scheme 4. Initially, Weinreb

Scheme 4

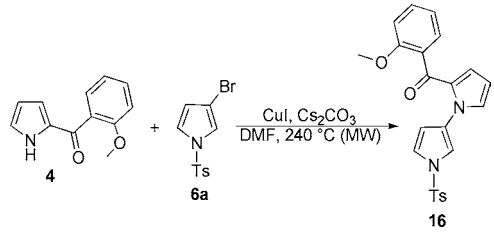


amide **13** was synthesized from ester **10**, prepared from *N*-tosyl-pyrrole according to Iwao.[23] Then, the reaction of Weinreb amide **13** with anisoyl magnesium bromide was tested as described previously. In this case, the reaction needs higher temperature and large excess of Grignard reactant to proceed, providing a complicated reaction mixture of products. To overcome this problem, compound **5** was synthesized by selective deprotonation of 3-bromo-*N*-tosyl-pyrrole **6a** with

LDA and addition of anisoyl chloride at −78 °C. A related study based on the directed lithiation of N-protected pyrroles and the reaction of the generated C-2 lithio species with various electrophiles has been published recently by Iwao.[24]

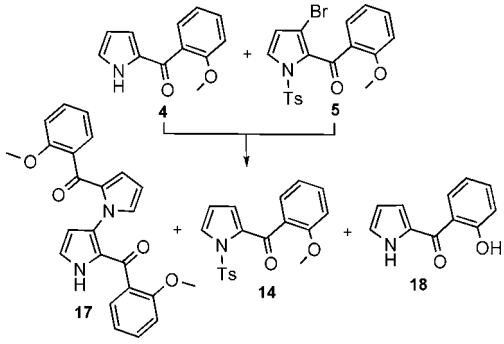
We further investigated the applicability of 2-keto pyrrolo derivative **4** as a substrate for the N-arylation with bromide **6a** under the optimal conditions. As shown in Scheme 5,

Scheme 5



the coupling reaction proceeded at 200 °C under microwave irradiation to afford the desired tosyl-bipyrrole **16** in 20% isolated yield (60% based on recovered **4**) along with appreciable amounts of unreacted starting material. Prolonged reaction time did not improve the reaction yield.

Table 2. Cu-Mediated N-Arylation of **4** and **5**



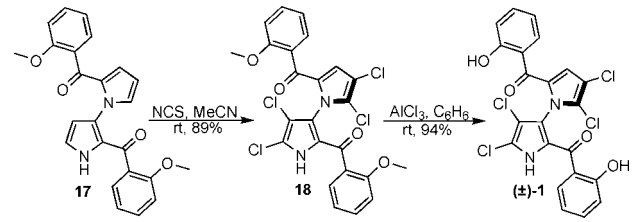
entry	conditions	yield (%)[a] **17**
1	Cs_2CO_3 (2 equiv), CuI (1 equiv), DMF, 200 °C, (MW), 2 h	24[b]
2	Cs_2CO_3 (2 equiv), CuI (0.2 equiv), 1,10-phenanthroline (0.4 equiv), DMF, 200 °C, (MW), 2 h	traces
3	Cs_2CO_3 (2 equiv), CuI (0.1 equiv), *N*,*N*′-dimethylethane-1,2-diamine (0.2 equiv), DMF, 200 °C, (MW), 2 h	0[c]
4	K_3PO_4 (2 equiv), CuI (0.2 equiv), proline (0.4 equiv), DMF, 200 °C, (MW), 2 h	traces
5	$Cu(OAc)_2$ (1 equiv), DBU (2 equiv), DMF, 200 °C, (MW), 2 h	43[d]

[a] Isolated yields. [b] Compound **14** was isolated in 19% yield. [c] Compound **18** was isolated in 86% yield. [d] Compound **14** was isolated in 19% yield.

Then, the assembly of the building blocks **4** and **5** was examined (Table 2). When CuI was used as a catalyst and Cs_2CO_3 as a base in DMF, the desired bipyrrole **17** was isolated in a poor yield of 24%, and the yield was not improved even after prolonged reaction times or elevated temperatures. The coupling was tested in different solvents, bases, catalysts, reaction temperatures, and time. Demethylation was proved an additional problem when *N*,*N*′-dimethylethane-1,2-diamine was used as a ligand (entry 3, Table 2). After careful experimentation, we were pleased to synthesize 1,3′-bipyrrole **17** in 43% isolated yield (based on starting material **5**), by using $Cu(OAc)_2$ and DBU as a base in DMF.[25] The use of the $Cu(OAc)_2$ catalyst effected a very clean transformation, but large quantities of starting materials remained unconsumed. Prolonged reaction time did not improve the yield of the desired product. Additionally, the outcome of the reaction was dependent on the nature of the solvent and on the base. For example, when the reaction was carried out in DMSO,no coupling product could be isolated.

Having in hand precursor **17**, we proceeded toward the completion of the total synthesis of marinopyrrole A (Scheme 6). Regioselective chlorination with NCS in MeCN leads to

Scheme 6



incorporation of four chlorine atoms into the pyrrole rings and provided the tetrachloro bipyrrole **18** in 89% yield. In the last step, demethylation of phenolic methyl ethers with $AlCl_3$ in benzene resulted in the production of (±)-marinopyrrole A in 94% yield.[26] The spectroscopic properties (IR, ^1H and ^{13}C NMR, HRMS) of the synthetic sample (±)-**1** were identical with those of the natural product (−)-**1**.

In summary, we synthesized the racemic form of the marine alkaloid marinopyrrole A by a copper-mediated coupling of two pyrrole units. In comparison, Li reported the first total synthesis of (±)-marinopyrrole A via a nine-step procedure in an overall yield of 30%.[7] Our synthesis requires a total of six steps and proceeds in 22% overall yield.

Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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