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Pd-Catalyzed Imine Cyclization: Synthesis of Antimalarial Natural Products Aplidiopsamine A, Marinoquinoline A, and Their Potential Hybrid NCLite-M1

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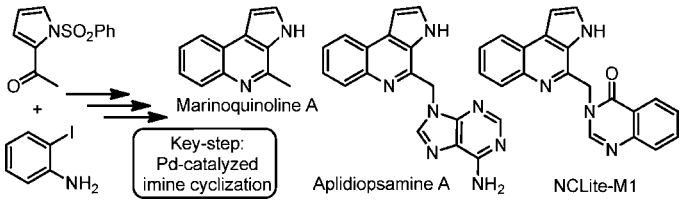
ABSTRACT



Palladium-catalyzed cyclization of imines has been developed to construct the extremely rare 3*H*-pyrrolo[2,3-*c*]quinoline ring system for diversity oriented first total synthesis of antimalarial marine natural product Aplidiopsamine A as well as synthesis of Marinoquinoline A and potential natural product hybrid NCLite-M1.

Alkaloids are an important class of pharmacophores encompassing a wide range of biological properties. Particularly, indole, β-carboline, quinazolinone, or quinoline alkaloids have been demonstrated to possess potent antimalarial activity. Natural products such as febrifugine[1] and quinine[2] alkaloids are well-known antimalarial drugs (Figure 1).

Isolation and bioactivity studies of natural products from plants, bacteria, fungi, and marine organisms in search of novel antimalarial lead structures have led to several drugs and drug candidates.[1,3] However, the malaria parasite develops resistance to drugs owing to its highly adaptive nature; hence alternative drugs with novel structures and diverse mechanisms of action are always needed to treat resistant strains of *Plasmodium*.

Recently, Carroll et al. reported[4] isolation, structure elucidation, and bioactivity studies of an important polyaromatic

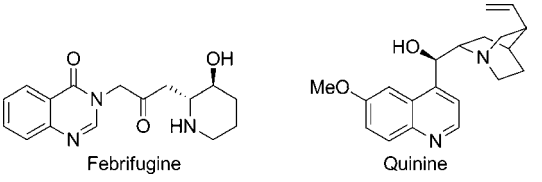


Figure 1. Renowned antimalarial drugs of plant origin.

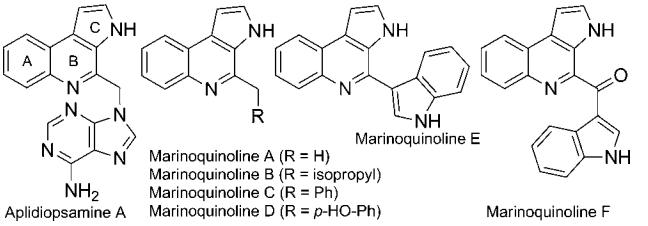


Figure 2. Marine natural products with high antimalarial activity and minimal toxicity.[4–6]

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(2) Kaufman, T. S.; Rfflveda, E. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 854–885.
(3) (a) Sherman, I. W. *Magic Bullets to Conquer Malaria-From Quinine to Qinghaosu*; ASM Press: Washington, D.C., 2010; ISBN 978-1555815431. (b) Kaur, K.; Jain, M.; Kaur, T.; Jain, R. *Bioorg. Med. Chem.* **2009**, *17*, 3229–3256.
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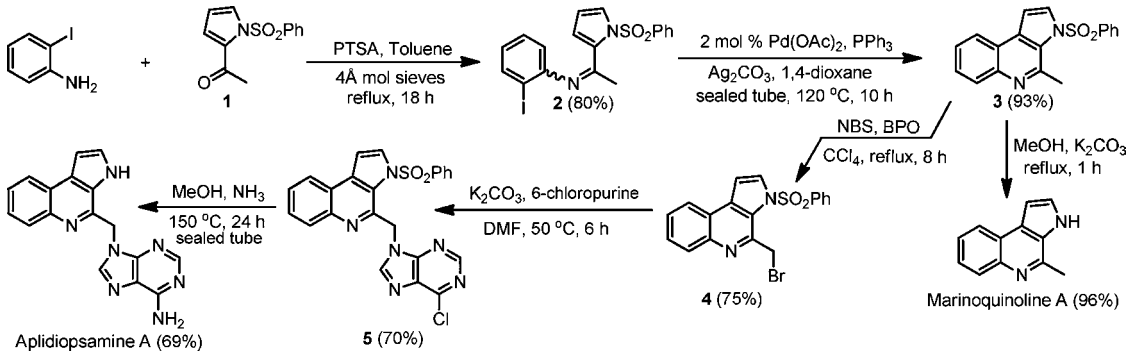
Scheme 1. Total Synthesis of Natural Products Marinoquinoline A and Aplidiopsamine A



alkaloid Aplidiopsamine A (Figure 2) from the temperate Australian ascidian *Aplidiopsis confluata*. It is the first alkaloid to possess the tricyclic aromatic substructure 3*H*-pyrrolo[2,3-*c*]quinoline conjugated to an adenine and exhibit significant inhibition of growth of chloroquine resistant and sensitive strains of the malaria parasite *Plasmodium falciparum*. The other natural product Marinoquinoline A (Figure 2) isolated from a novel marine gliding bacterium *Rapidithrix thailandica* possessing the unique 3*H*-pyrrolo-[2,3-*c*]quinoline ring system was reported[5] by Plubrukarn et al. Very recently five new natural products, Marinoquinoline B−F (Figure 2), with this unprecedented moiety have been reported.[6]

Total synthesis of Aplidiopsamine A and Marinoquinoline D and F is not known hitherto, whereas the total synthesis of Marinoquinoline A−C and E has been reported[7] very recently. In view of the reported[4−6] high antimalarial activity and minimal toxicity toward human cells, they represent novel lead structures that could be further developed into antimalarial drugs; hence a diversity oriented practical synthetic approach is essential for their SAR studies. This prompted us to initiate studies toward the total synthesis of marine natural products Aplidiopsamine A, Marinoquinoline A−F, and their potential analogues.

These natural products have 3*H*-pyrrolo[2,3-*c*]quinoline core structure. Several attempts using well-known methods starting from a variety of suitable starting materials could not furnish the expected core structure.[8−12] We then designed a diversity oriented synthesis of the core using regioselective metal-catalyzed intramolecular C−C bond formation as a key step. Presented herein is the successful application of this protocol for the first total synthesis of antimalarial marine natural product Aplidiopsamine A as well as synthesis of Marinoquinoline A and their potential natural product hybrid NCLite-M1.

The synthesis (Scheme 1) began with pyrrole, which was converted to ketone **1** in two steps with good yields.[13] The next step, imine formation between 2-iodoaniline and ketone **1**, required several attempts using various reagents and reaction conditions.[14] Finally refluxing iodoaniline, pyrrole **1**, *p*-toluene sulfonic acid, and freshly activated 4 Å molecular sieves in dry toluene with the aid of a Dean−Stark apparatus provided imine **2** in 80% yield.

The novel and key transformation of the planned synthetic route to the above-mentioned natural products is the intramolecular cyclization of imine **2**. Our first attempt (Table 1, entry 1) using a neocuproine-KO^{t}Bu promoted intramolecular cross-coupling[15] reaction gave a trace amount of expected product **3**. Transition-metal-catalyzed inter-/intramolecular cross-coupling reactions have been used in the synthesis of several bioactive natural products and evolved as a powerful tool in organic synthesis;[16] however its application for imine cyclization to furnish natural products has not been reported. The second attempt (Table 1, entry 2) using 10 mol % of $Pd(OAc)_2$ satisfyingly provided the expected product **3** in 51% yield.

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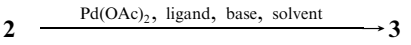
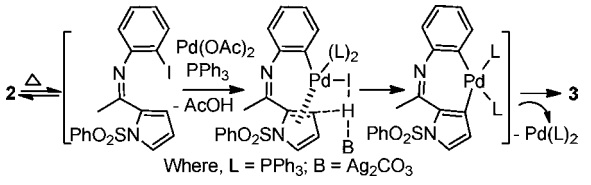
Table 1. Optimization Studies on Cyclization of Iodo-Imine **2** to Pyrroloquinoline **3**[a]



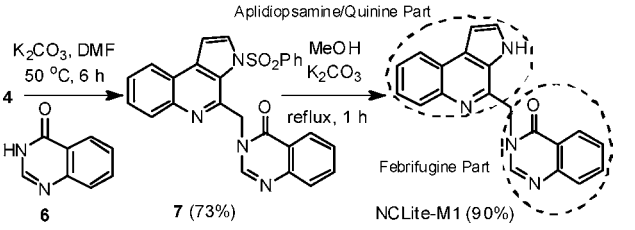
entry	catalyst (equiv)	ligand (equiv)	base (equiv)	solvent	temp	time	yield
01	–	neocuproine (0.50)	KO*t*Bu (2.5)	benzene	100 °C	18 h	trace
02	$Pd(OAc)_2$ (0.10)	PPh_3 (0.20)	Ag_2CO_3 (2.0)	DMF	100 °C	02 h	51%
03	$Pd(OAc)_2$ (0.20)	PPh_3 (0.40)	Ag_2CO_3 (4.0)	DMF	100 °C	02 h	64%
04	$Pd(OAc)_2$ (0.20)	PPh_3 (0.40)	Ag_2CO_3 (2.0)	THF	reflux	04 h	63%
05	**$Pd(OAc)_2$ (0.10)**	**PPh_3 (0.20)**	**Ag_2CO_3 (2.0)**	**1,4-dioxane**	**reflux**	**03 h**	**91%**
06	$Pd(OAc)_2$ (0.04)	PCy_3 (0.08)	Cs_2CO_3 (2.0)	THF	110 °C	24 h	23%
07	$Pd(OAc)_2$ (0.04)	PCy_3 (0.08)	K_2CO_3 (2.0)	DMF	110 °C	24 h	35%
08	$Pd(OAc)_2$ (0.10)	PCy_3 (0.20)	Ag_2CO_3 (2.0)	DMF	110 °C	24 h	31%
09	$Pd(OAc)_2$ (0.05)	PPh_3 (0.10)	Ag_2CO_3 (1.0)	1,4-dioxane	120 °C	07 h	90%
10	$Pd(OAc)_2$ (0.03)	PPh_3 (0.06)	Ag_2CO_3 (0.6)	1,4-dioxane	120 °C	08 h	89%
11	**$Pd(OAc)_2$ (0.02)**	**PPh_3 (0.04)**	**Ag_2CO_3 (0.4)**	**1,4-dioxane**	**120 °C**	**10 h**	**93%**
12	$Pd(OAc)_2$ (0.01)	PPh_3 (0.02)	Ag_2CO_3 (0.2)	1,4-dioxane	120 °C	24 h	72%

[a] Reactions shown in entries 1 and 6–12 were carried out in a sealed tube.

Scheme 2. Proposed Mechanism for Imine Cyclization



Scheme 3. Synthesis of Natural Product Hybrid NCLite-M1



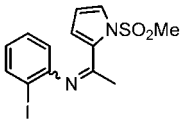
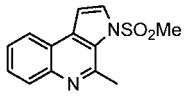
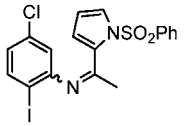
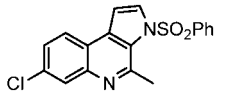
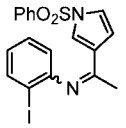
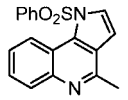
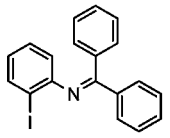
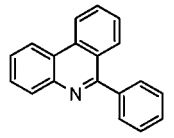
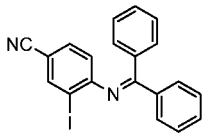
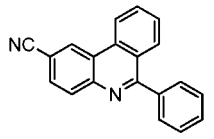
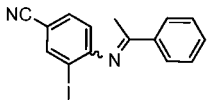
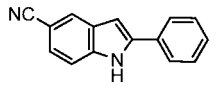
Optimization of the protocol was tried by varying molar ratios, ligand, base, solvent, temperature, and time (Table 1, entries 3–12). Out of several permutations and combinations tried, the reaction conditions shown in Table 1, entry 5 (10 mol % $Pd(OAc)_2$, no sealed tube) and Table 1, entry 11 (2 mol % $Pd(OAc)_2$, using sealed tube) proved to be the best, providing a 91% and 93% yield respectively. Thus, a facile Pd-catalyzed intramolecular C–C bond formation protocol for the construction of pyrroloquinolines was developed. Base-induced deprotection of the phenylsulfonyl moiety from pyrroloquinoline **3** in methanol–K_2CO_3 provided Marinoquinoline A in 96% yield, thus completing its total synthesis in three steps (Scheme 1). A plausible mechanism for Pd-catalyzed imine cyclization is depicted in Scheme 2.

Using the same reaction sequence Marinoquinoline B–F and their analogues can be prepared from related ketones.[13] For the synthesis of Aplidiopsamine A our initial attempts to brominate pyrroloquinoline **3** using NBS and radical initiators such as AIBN, ABCN, etc. provided a maximum 30% yield of bromide **4**, but it could be improved to 75% by BPO-catayzed NBS bromination. The reaction of bromide **4** with adenine in DMF–K_2CO_3 at 50 °C provided a complex reaction mixture; however treatment with 6-chloropurine under the same conditions provided **5** in 70% yield. Treatment of pyrroloquinoline **5** in a saturated methanolic solution of ammonia in a sealed tube at 150 °C provided Aplidiopsamine A in 69% yield, thus, completing its first total synthesis (Scheme 1). The spectral and analytical data of the synthesized Aplidiopsamine A and Marinoquinoline A were in complete agreement with the reported data.[4,5] Synthesis of Marinoquinoline B–D should be also possible by reacting the appropriate Grignard reagent with bromide **4**.

Application of the diversity oriented intermediate **4** for the synthesis of potential analogues was exemplified by the synthesis of a natural product hybrid analogue named NCLite-M1. It was synthesized (Scheme 3) in two steps from the intermediate **4**. Thus, treatment of quinazolinone (**6**) with compound **4** in the presence of K_2CO_3 gave quinazolinone **7** in 73% yield. Deprotection of **7** using methanol and K_2CO_3 furnished NCLite-M1 in 90% yield. Likewise, several other nucleophiles can be reacted with the intermediate **4** to generate combinatorial libraries for SAR studies in search of novel drug entities.

The Pd-catalyzed imine cyclization protocol developed herein was applied on various imines (Table 2, entries 1–6). Entry 1 provides methylsulfonyl protected derivative of Marinoquinoline A, and entry 2 provides an efficient access to a chlorinated analogue of Marinoquinoline A. Entry 3 is intersting since it provides a positional isomer of phenylsulfonyl protected Marinoquinoline A. Entires 4 and 5 smoothly provide phenanthridine alkaloids in good

Table 2. Generalization Studies of the Optimized Pd-Catalyzed Intramolecular Imine Cyclization Protocol[a]

entry	imine substrate	product	time	yield
01			08 h	82%
02			10 h	70%
03			05 h	62%
04			10 h	90%
05			10 h	85%
06			24 h	51%

[a] Reaction condition: imine substrate (1 equiv), $Pd(OAc)_2$ (0.02 equiv), PPh_3 (0.04 equiv), Ag_2CO_3 (0.4 equiv), 1,4-dioxane, sealed tube, 120 °C.

yields. Interestingly during these investigations a methodology on Pd-catalyzed C−H activation/C−C bond formation to construct phenanthridines was reported[17] by Li et al. The C−C bond cyclization in the case of entry 6 followed a different path and furnished the indole alkaloid probably via an enamine intermediate.[18]

In conclusion, we have demonstrated a diversity oriented practical approach for the first total synthesis of Aplidiopsamine A as well as synthesis of Marinoquinoline A and the potential natural product hybrid analogue NCLite-M1. An efficient regioselective intramolecular Pd-catalyzed C−C bond forming reaction was developed to construct a 3*H*-pyrrolo[2,3-*c*]quinoline core structure. Application of the protocol to other imines also provided interesting alkaloids as well as analogues of Marinoquinoline A. Total synthesis of Marinoquinoline B−F and synthesis of Aplidiopsamine A and NCLite-M1 analogues in search of novel antimalarial drug candidates are underway.

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Supporting Information Available. Experimental details, analytical and spectral data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.