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Concise Total Synthesis of Calothrixins A and B

Takumi Abe,[†] Toshiaki Ikeda,[†] Reiko Yanada,[‡] and Minoru Ishikura*,[†]

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan, and Faculty of Pharmaceutical Sciences, Hiroshima International University, 5-1-1 Hirokoshingai, Kure, Hiroshima 737-0112, Japan

ishikura@hoku-iryo-u.ac.jp

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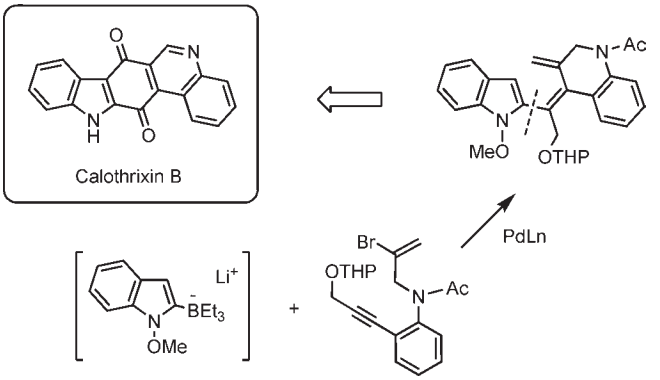
ABSTRACT



The concise total synthesis of calothrixins A and B has been accomplished by utilizing the one-pot formation of hexatriene as a key intermediate via the palladium-catalyzed tandem cyclization/cross-coupling reaction of triethyl(indol-2-yl)borate. In another key transformation, the indolo-[3,2-*j*]phenanthridine core was prepared in high yield via Cu(I)-mediated 6π-electrocyclization.

Calothrixins A (**1**) and B (**2**), first isolated from cyanobacterium of the genus *Calothrix* in 1999,[1] are characterized by a unique indolo[3,2-*j*]phenanthridine core, bearing indole, quinoline, and quinone moieties (Figure 1). Both **1** and **2** inhibit the chloroquinone-resistant strain of malaria parasite *Plasmodium falciparum* and show antiproliferative properties against several cancer cell lines as well as human DNA topoisomerase I poisoning activity.[2] Owing to their intriguing structural features and potential biological activity, **1** and **2** are attractive targets for total synthesis. Beginning with the first total synthesis employing ortholithiation methods by Kelly in 2000,[3] several approaches to synthesizing **1** and **2** have been developed,[4] including the biomimetic total synthesis of **2** reported independently by Hibino's and Moody's groups.[5]

In our ongoing studies of trialkyl(indol-2-yl)borates,[6] we previously found that indolylborates show high reactivity in palladium-catalyzed cross-coupling reactions, such as

[†] Health Sciences University of Hokkaido.
[‡] Hiroshima International University.

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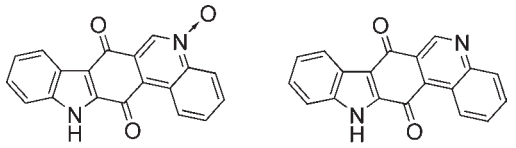
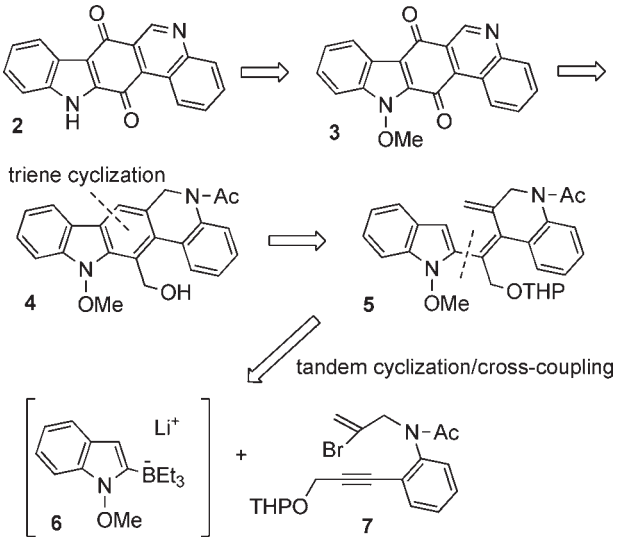


Figure 1. Calothrixins A (**1**) and B (**2**).

carbonylative cross-coupling[7] and tandem cyclization/cross-coupling reactions,[8] although tetravalent organoboron compounds (ate complexes) have proven to be less practical for the palladium-catalyzed cross-coupling reactions.[9] Herein, we describe a new approach to synthesizing **1** and **2** via the palladium-catalyzed tandem cyclization/cross-coupling reaction of triethyl(indol-2-yl)borate; this approach employs one-pot construction of a hexatriene as a key intermediate in building the indolophenanthridine core.

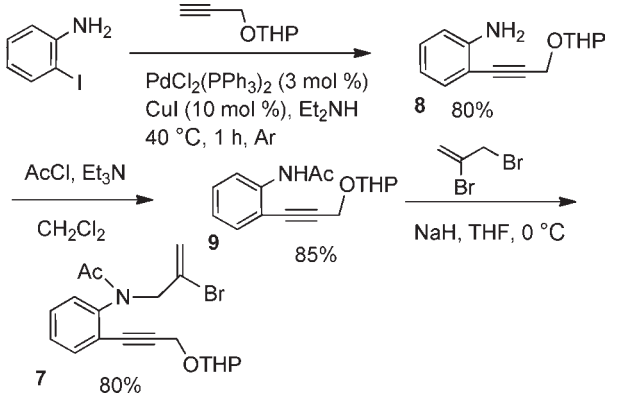
The retrosynthetic analysis of **2** is shown in Scheme 1. We envisioned that the palladium-catalyzed cyclization/cross-coupling reaction of indolylborate **6** (generated in situ from the corresponding indole) with bromide **7** could be used to generate hexatriene **5** in a one-pot procedure, and that **5** could then be easily transformed into the indolophenanthridine **4** through 6π-elecrocyclization. Subsequently, **4** would be converted into calothrixin B (**2**) through quinone **3**.

Scheme 1. Retrosynthetic Analysis of Calothrixin B (**2**)



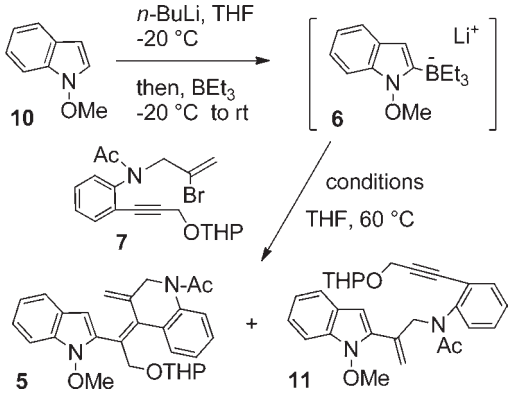
The preparation of the requisite bromide **7** is outlined in Scheme 2. The Sonogashira coupling reaction of

Scheme 2. Prepation of Vinyl Bromide **7**



2-iodoaniline with 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran in the presence of $PdCl_2(PPh_3)_2$ (3 mol %) and CuI (10 mol %) in Et_2NH at 40 °C for 1 h easily produced **8** in 80% yield. *N*-Acetylation of **8** with AcCl in CH_2Cl_2 afforded amide **9** in 85% yield, and the subsequent

Table 1. Palladium-Catalyzed Tandem Cyclization/Cross-Coupling Reaction of **6** with **7**



		yield (%)[b]	
entry	conditions[a]	**5**	**11**
1	$Pd(OAc)_2$ (5 mol %), 0.5 h	42	5
2	$Pd(OAc)_2$ (5 mol %), P(*o*-tol)$_3$ (10 mol %), 0.5 h	55	8
3	$PdCl_2[P(o\text{-tol})_3]_2$ (5 mol %), 0.5 h	60	8
4	$PdCl_2(PPh_3)_2$ (5 mol %), 2 h	20	7
5	$Pd_2(dba)_3$•$CHCl_3$ (2.5 mol %)	50	6
6	$Pd_2(dba)_3$•$CHCl_3$ (2.5 mol %), PPh_3 (10 mol %), 0.5 h	18	7
7	$Pd_2(dba)_3$•$CHCl_3$ (2.5 mol %), P(*o*-tol)$_3$ (10 mol %), 0.5 h	68	5

[a] Borate **6** [derived in situ from **10** (2 mmol), *n*-BuLi (2.4 mmol), and BEt_3 (2.4 mmol) in THF under an argon atmosphere] was treated with bromide **7** (1 mmol) in the presence of a Pd complex (5 mol %). [b] Isolated yield based on **7**.

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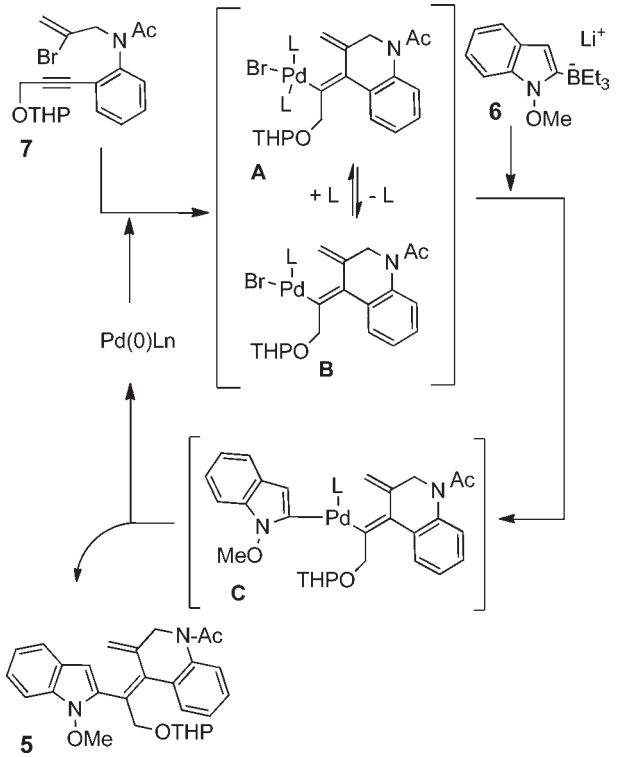
treatment of **9** with NaH and 2,3-dibromopropene in THF gave bromide **7** in 80% yield.

The synthesis of **2** began with the palladium-catalyzed tandem cyclization/cross-coupling reaction of indolylborate **6** with **7**.

The treatment of **6** [generated *in situ* from 1-methoxyindole (**10**) and *n*-BuLi in THF, followed by treatment with BEt_3] with **7** in the presence of a palladium complex (5 mol %) in THF at 60 °C under an argon atmosphere produced triene **5** and a small amount of vinyl indole **11** (Table 1).

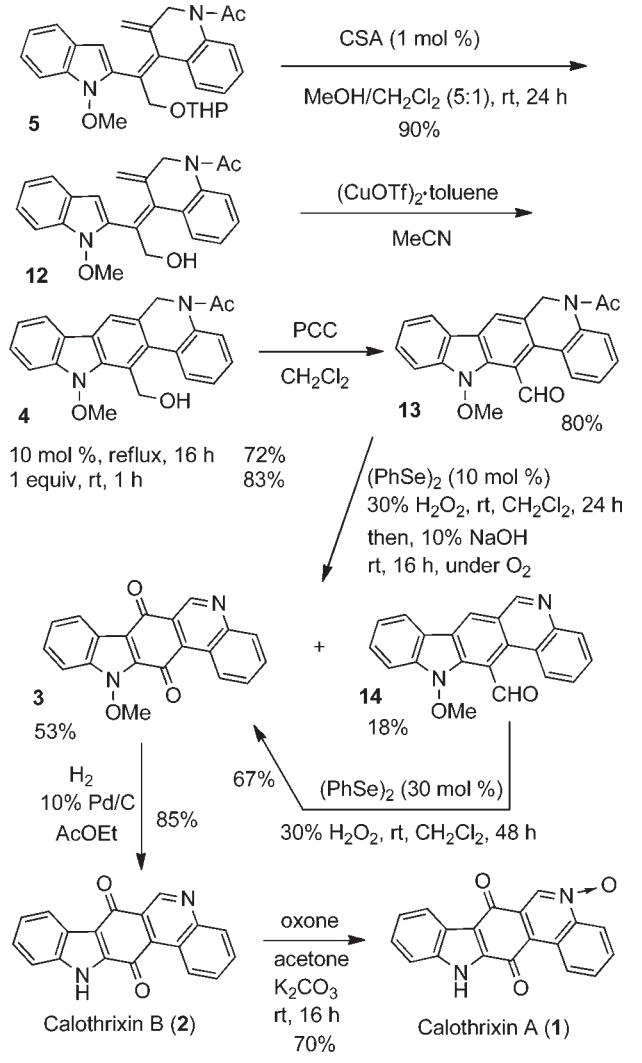
Scheme 3. Catalytic Cycle



Catalyst evaluation revealed that the presence of a bulky P(*o*-tol)$_3$ ligand was important for the successful Pd-catalyzed cross-coupling reaction of **6** with **7**. When the reaction was carried out using $Pd(OAc)_2$ (5 mol %), **5** was obtained in 42% yield along with a small amount of **11** (5%) (entry 1). The combination of $Pd(OAc)_2$ with 2P(*o*-tol)$_3$ increased the yield of **5** to 55% (entry 2). As compared with the reaction using $PdCl_2[P(o\text{-tol})_3]_2$ that produced **5** in 60% yield, the reaction using $PdCl_2(PPh_3)_2$ was slower and produced **5** in a low yield of 20% (entries 3 and 4). The reaction using $Pd_2(dba)_3$•$CHCl_3$ (2.5 mol %) in conjunction with P(*o*-tol)$_3$ (10 mol %) resulted in the highest yield of **5** (68%) along with a small amount of **11** (5%) (entry 7); **5** was obtained in 18% and 50% yields in the presence of $Pd_2(dba)_3$•$CHCl_3$ (2.5 mol %) with and without PPh_3, respectively (entries 5 and 6).

The proposed catalytic cycle is shown in Scheme 3. The coordination of the bulky P(*o*-tol)$_3$ ligand to Pd shifts the equilibrium between tetracoordinate complex **A** and tricoordinate complex **B** toward the less crowded complex **B**.[10] The transfer of the indole ring from indolylborate **6** to the Pd of complex **B** promptly occurs, leading to **5** via complex **C**.

Scheme 4. Total Synthesis of Calothrixins A (**1**) and B (**2**)



After removal of the *O*-THP group of **5** with CSA (camphorsulfonic acid) in $MeOH/CH_2Cl_2$ (5:1), the construction of indolophenanthridine **4** via cyclization of hexatriene **12** was investigated (Scheme 4). As our previous work in this area indicated that **12** should photochemically cyclize to **4**, the irradiation of **12** with a high-pressure mercury lamp in benzene was first carried out.[11] However, the reaction produced only a complex mixture. In addition, the thermal reaction was attempted to convert **12** to **4**,

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without success. Although many examples of 6π-electrocyclization have been reported,[12] we sought out the feasibility of the Lewis acid mediated cyclization sequence.[13] After screening various Lewis acids such as $In(OTf)_3$, $[IrCpCl_2]_2$, $ZnBr_2$, and $TiCl_4$, we found that a $(CuOTf)_2$•toluene complex was effective in promoting the proposed cyclization. Treating **12** with the $(CuOTf)_2$•toluene complex (1 equiv) in MeCN at room temperature for 1 h produced **4** in 83% yield. Moreover, the reaction worked well using a catalytic amount of the $(CuOTf)_2$•toluene complex (10 mol %) in MeCN under reflux for 16 h, giving **4** in 72% yield. Although there are some examples of CuOTf-mediated olefin photocycloaddition reactions,[14] to our knowledge, use of Cu(OTf) as a mediator for 6π-electrocyclization is unprecedented.

With pentacycle **4** in hand, the subsequent conversion of **4** to calothrixin B (**2**) was achieved in a three-step sequence (Scheme 4). The oxidation of the primary alcohol of **4** with PCC in CH_2Cl_2 readily gave aldehyde **13** in 80% yield. At this stage, we found that Dakin oxidation[15] of **13** [30% H_2O_2, $(PhSe)_2$ (10 mol %), and then 10% NaOH under O_2] led to the one-pot production of quinone **3** in 53% yield and aldehyde **14** in 18% yield, accompanied by in situ *N*-Ac deprotection and oxidation. Aldehyde **14** was transformed into **3** in 67% yield by oxidation with $(PhSe)_2$ (30 mol %) and 30% H_2O_2 in CH_2Cl_2 at room temperature for 48 h. Finally, the *N*-OMe group of **3** was easily removed by catalytic hydrogenation over 10% Pd/C in AcOEt, providing calothrixin B (**2**) in 85% yield. Furthermore, the oxidation of **2** by treatment with dimethyl dioxirane,[16] prepared in situ from oxone and acetone in the presence of K_2CO_3, at room temperature for 16 h gave calothrixin A (**1**) in 70% yield.

In summary, we have demonstrated a new approach to synthesizing calothrixins A (**1**) and B (**2**) through the palladium-catalyzed tandem cyclization/cross-coupling reaction of indolylborate **6** by taking advantage of the one-pot generation of the key intermediate **5** for constructing indolophenanthridine **4**. In addition, the unprecedented use of CuOTf for the 6π-elecrocyclization of **12** to **4** was developed. Further synthetic studies of this cross-coupling protocol are in progress.

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Supporting Information Available. Experimental procedures and characterization data for products and isolated intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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