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Total Synthesis of A Novel Tetracyclic Alkaloid, Cassiarin F from the Flowers of *Cassia siamea*

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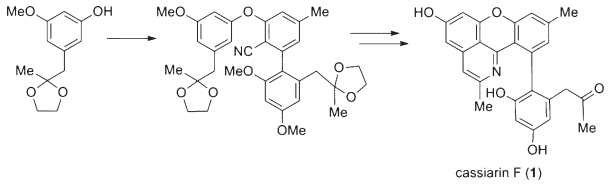
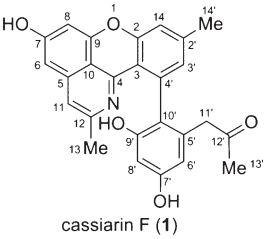
ABSTRACT

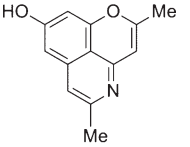


A novel alkaloid, cassiarin F (1), which showed potent antiplasmodial activity against *Plasmodium falciparum* in vitro, was isolated from the flowers of *Cassia siamea*, and its structure was elucidated on the basis of 2D NMR analyses. A total synthesis of 1 was also achieved by employing the Suzuki coupling constructing biaryl unit, nucleophilic aromatic substitution, and Houben–Hoesch type ring construction as key steps.

Cassia siamea Lam. (Leguminosae) has been used widely in traditional medicine, particularly for treatment of periodic fever and malaria in Indonesia.[1] Recently we isolated cassiarin A (**2**),[2] an alkaloid with an unprecedented tricyclic skeleton exhibiting potent antiplasmodial activity, and chrobisiamone A,[3] a bischromone, from the leaves of *C. siamea*.

Owing to the attractive biological activity and the unique structural feature of cassiarin A, which showed *in vivo* antimalarial[4] and vasorelaxant activities,[5] we investigated its total synthesis and succeeded in establishing an efficient synthetic strategy.[6] In 2009 we reported the isolation of new types of dimeric alkaloids, cassiarins D and E from the flowers of *C. siamea*.[7]





Further investigation on extracts from the flowers of *C. siamea* resulted in the isolation of a novel tetracyclic alkaloid, cassiarin F (**1**). In this paper, we would like to

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(1) (a) Mbatchi, S. F.; Mbatchi, B.; Banzouzi, J. T.; Bansimba, T.; Nsonde Ntandou, G. F.; Ouamba, J. M.; Berry, A.; Benoit-Vical, F. *J. Ethnopharmacol.* **2006**, *104*, 168–174. (b) Sanon, S.; Ollivier, E.; Azas, N.; Mahiou, V.; Gasquet, M.; Ouattara, C. T.; Nebie, I.; Traore, A. S.; Esposito, F.; Balansard, G.; Timon-David, P.; Fumoux, F. *J. Ethnopharmacol.* **2003**, *86*, 143–147.

(2) Morita, H.; Oshimi, S.; Hirasawa, Y.; Koyama, K.; Honda, T.; Ekasari, W.; Indrayanto, G.; Zaini, N. C. *Org. Lett.* **2007**, *9*, 3691–3693.

(3) Oshimi, S.; Tomizawa, Y.; Hirasawa, Y.; Honda, T.; Widyawaruyanti, A.; Rudyanto, M.; Ekasari, W.; Indrayanto, G.; Zaini, C. N.; Morita, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3761–3763.

(4) Ekasari, W.; Widyawaruyanti, A.; Zaini, N. C.; Syafruddin, D.; Honda, T.; Morita, H. *Heterocycles* **2009**, *78*, 1831–1836.

(5) Morita, H.; Tomizawa, Y.; Deguchi, J.; Ishikawa, T.; Arai, H.; Zaima, K.; Hosoya, T.; Hirasawa, Y.; Matsumoto, T.; Kamata, K.; Ekasari, W.; Widyawaruyanti, A.; Wahyuni, T. S.; Zaini, N. C.; Honda, T. *Bioorg. Med. Chem.* **2009**, *17*, 8234–8240.

(6) Rudyanto, M.; Tomizawa, Y.; Morita, H.; Honda, T. *Org. Lett.* **2008**, *10*, 1921–1922.

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report the structure elucidation based on spectroscopic analyses and a total synthesis of **1**.

Cassarin F (**1**)[8] was obtained as a yellow amorphous solid, and its molecular formula was established to be $C_{26}H_{21}NO_5$ by HRESITOFMS analysis. In addition to ^1H and ^{13}C NMR data (Table 1), 2D NMR correlations indicated that **1** had a cassiarin A type skeleton with a biaryl moiety, which is the first example of *Cassia* alkaloid (Figure 1). The biaryl moiety of **1** was considered to be racemic from its small optical rotation value and CD spectrum, in which no Cotton effect was observed. Cassiarin F (**1**) showed potent antiplasmodial activity against the chloroquine-sensitive *P. falciparum* strain 3D7 (IC_{50} 3.3 μM), while showing no cytotoxicity against human blood premyelocytic leukemia (HL-60, > 50 μM).

Table 1. ^1H [δ_H (J, Hz)] and ^{13}C NMR Data [δ_C] of Cassiarin F (**1**) in Pyridine-d_5 at 300 K

Position		
2		155.7
3		119.1
4		148.3
5		139.9
6	6.91 (1H, d, 2.2)	101.2
7		161.8
8	6.98 (1H, d, 2.2)	100.1
9		154.1
10		111.6
11	6.89 (1H, s)	114.2
12		153.1
13	2.26 (3H, s)	24.6
14	7.01 (1H, d, 1.0)	117.0
2′		141.2
3′	7.09 (1H, d, 1.0)	130.5
4′		138.0
5′		134.0
6′	6.99 (1H, d, 2.4)	108.6
7′		158.7
8′	7.08 (1H, d, 2.4)	102.6
9′		157.2
10′		120.0
11′a	3.60 (1H, d, 13.3)	49.8
11′b	3.65 (1H, d, 13.3)	
12′		206.0
13′	1.97 (3H, s)	29.2
14′	2.20 (3H, s)	21.0

In order to confirm its unique tetracyclic structure, a total synthesis of cassiarin F (**1**) was undertaken. Our retrosynthetic analysis of **1** is outlined in Figure 2. In this approach, the two heterocyclic rings would be constructed at a late stage in the synthesis, because of their susceptibility to acidic and basic reaction conditions.

(7) Oshimi, S.; Deguchi, J.; Hirasawa, Y.; Ekasari, W.; Widyawaruyanti, A.; Wahyuni, T. S.; Zaini, N. C.; Shirota, O.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 1899–1901.

(8) Cassiarin F (**1**): yellow amorphous solid; IR (KBr) ν_{max} 3430, 3270, 1710, and 1600 cm^{-1}; UV (MeOH) λ_{max} 202 (ε 13000), 245 (ε 3200) and 290 (ε 1400) nm; ^1H and ^{13}C NMR (Table 1); ESIMS (pos.) m/z 428 $(M + H)^+$; HRESITOFMS m/z 428.1473 $(M + H)^+$, calcd for $C_{26}H_{22}NO_5$ 428.1498.

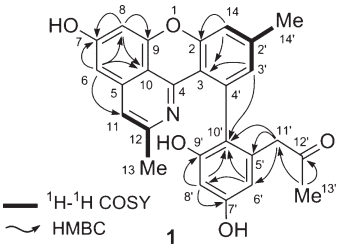


Figure 1. Selected 2D NMR correlations for cassiarin F (**1**) in pyridine-d_5.

Making the two disconnections shown to **1** led to **3** as the key intermediate for the Houben–Hoesch type ring closure. Two further disconnections generated the three building blocks (phenol **4**, benzonitrile **5**, and boronic acid **6**) needed for the assembly of **3** (Figure 2). It was envisaged that a Suzuki coupling of **5** with **6** would lead to formation of the desired biphenyl unit.[9] Then selective nucleophilic aromatic substitution of the resulting halogenated biaryl derivative with **4** would give the key intermediate **3**.

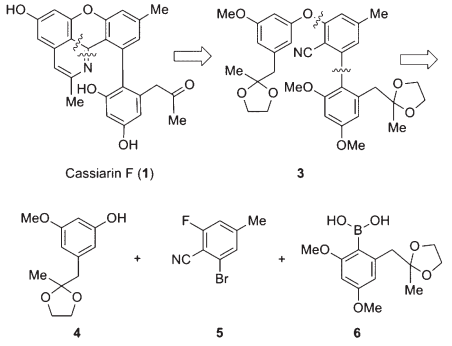


Figure 2. Retrosynthetic analysis for cassiarin F (**1**).

Our synthesis began with preparation of the boronic acid **6**, which was readily accessible from known propanone **7**.[10]

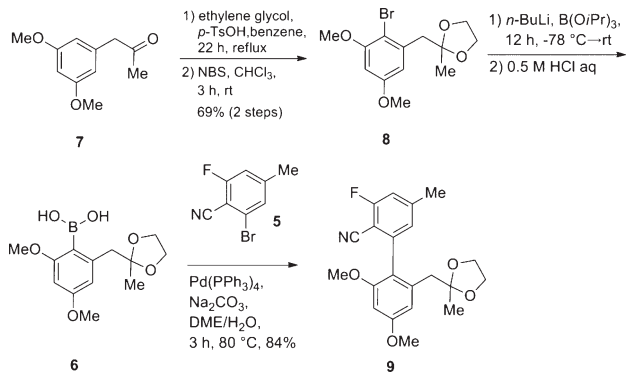
Ketalization of **7** with ethylene glycol and subsequent bromination with *N*-bromosuccinimide (NBS) gave bromide **8** in good yield. The boronic ester was obtained by halogen–metal interchange with *n*-butyllithium and trapping the generated compound with triisopropyl borate. The desired boronic acid **6** was obtained by hydrolysis of the ester with hydrochloric acid. Suzuki coupling of **6** with **5**[11] was carried out in the usual manner to provide the biaryl **9** in 84% yield (Scheme 1).

(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

(10) Bringmann, G.; Gulder, T.; Reichert, M.; Meyer, F. *Org. Lett.* **2006**, *8*, 1037–1040.

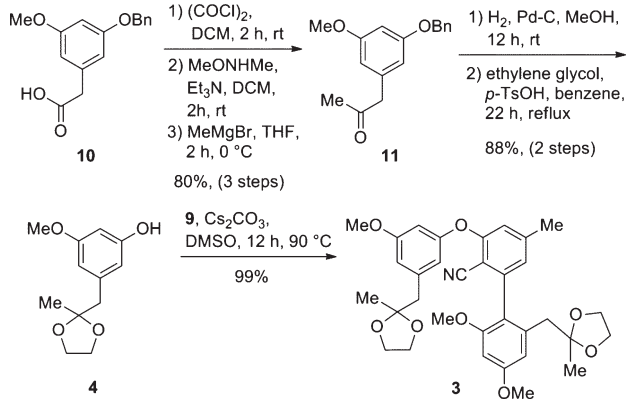
(11) Kristensen, J. L. *Tetrahedron Lett.* **2008**, *49*, 2351–2354.

Scheme 1. Synthesis of Key Biaryl Intermediate **9**



The phenol **4** was readily accessed in a five-step process from the known carboxylic acid **10**.[12] Treatment of **10** with oxalyl chloride provided the corresponding acyl chloride, which was directly reacted with *N*,*O*-dimethylhydroxylamine in the presence of triethylamine to give the Weinreb amide. The resulting Weinreb amide was treated with MeMgBr to generate the desired methyl ketone **11** in 80% yield from **10**. Debenzylation of **11** via Pd-catalyzed hydrogenation, followed by ketalization of carbonyl group with ethylene glycol, gave the desired phenol **4**. Selective nucleophilic aromatic substitution of **9** with **4** in the presence of cesium carbonate in DMSO gave **3** in excellent yield (Scheme 2).

Scheme 2. Synthesis of Key Intermediate **3** for Houben–Hoesch Type Ring Closure

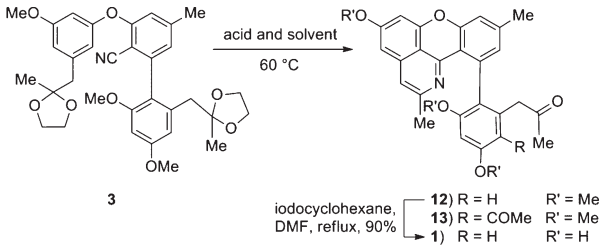


Having the desired cyano compound in hand, our attention was focused on construction of the two heterocyclic rings as follows. It has been recognized that both a Brønsted acid and Lewis acid generate ketimine species from the corresponding nitriles in a Houben–Hoesch type cyclization.[13] Therefore, treatment of **3** with acid could lead to the formation of two heterocyclic rings, simultaneously.

(12) Pearson, A. J.; Belmont, P. O. *Tetrahedron Lett*. **2000**, *41*, 1671–1675.

Our first trial, starting from **3** in concentrated sulfuric acid, expectedly only led to extensive decomposition. Fortunately, treatment of **3** with sulfuric acid in acetic acid produced the tetracyclic core **12**. Trials with different combinations of acids or solvents are summarized (Scheme 3). The best result was obtained with the reaction conditions of entry 5. Thus a 30% yield of the tetracyclic core **12** with a side product **13**[14] was obtained using sulfuric acid and acetic acid in a ratio of 1:1.

Scheme 3. Construction of the Tetracyclic Core of Cassiarin F (**1**) via a Houben–Hoesch Type Ring Closure[a]



entry	acid or Lewis acid	solvent	ratio[a]	time (*h*)	yield (%)[b]	
					12	**13**
1	H_2SO_4	AcOH	1:4	12	12	0
2	H_2SO_4	CH_2Cl_2	1:1	1	12	0
3	H_2SO_4	AcOH	2:1	1	23	17
4	TfOH	AcOH	2:1	1	17	19
5	H_2SO_4	AcOH	1:1	1	30	10
6	H_2SO_4	AcOH	9:10	1	26	7
7	$BF_3{\cdot}OEt_2$ (1 equiv)	CH_2Cl_2		3	0	0
8	$TiCl_4$ (1 equiv)	CH_2Cl_2		3	0	0

[a] Concentration; 1 mL for 10 mg of **3**. [b] Isolated yields.

The tris-*O*-demethylation of aryl methyl ether **12** was achieved by treatment of iodocyclohexane in DMF.[15]

Spectroscopic data (^{1}H and ^{13}C NMR, MS, and IR) and TLC behavior of the synthesized compound were identical to those of the authentic sample of isolated compound.

In summary, we have isolated a novel alkaloid, cassiarin F (**1**), a hybrid compound consisting of cassiarin A and a biphenyl unit with an acetonyl moiety. The occurrence of a tetracyclic polysubstituted skeleton with a biaryl unit is very rare. Cassiarin F (**1**) might be biosynthetically produced by a transformation of a

(13) (a) Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I.; Hunt, D. E. *Aust. J. Chem*. **1982**, *35*, 1451–1468. (b) Auricchio, S.; Antonella, B.; Pastormerlo, E.; Ricca, A.; Truscello, A. M. *Tetrahedron* **1994**, *50*, 7589–7596. (c) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc*. **1995**, *117*, 3037–3043. (d) Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc*. **1991**, *113*, 691–692. (e) Amer, M. I.; Booth, B. L.; Noori, G. F. M.; Proenca, M. F. J. R. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1075–1081.

(14) **13** should be produced by the Friedel–Crafts type reaction with acetic acid. **13** was obtained in the way we predicted by the treatment of **12** with sulfuric acid in acetic acid. The position of methyl ketone of **13** was determined by NOESY correlations.

(15) (a) Zuo, L.; Yao, S.; Wang, W.; Duan, W. *Tetrahedron Lett*. **2008**, *49*, 4054–4056. (b) Since **12** has a labile functionality, methyl ketone, acidic conditions utilizing Lewis acids such as BBr_3 cannnot be applied for this purpose. The use of Lewis acids led to significant decomposition of the material.

bischromone, chrobisiamone A. We have also achieved the total synthesis of cassiarin F (**1**) (8 steps, 10% overall yield) by combination of the Suzuki coupling reaction, nucleophilic aromatic substitution, and a Houben–Hoesch type ring construction as key reactions. As such we have confirmed its structure; the strategy with a Houben–Hoesch type ring construction seems to be an innovative approach to the synthesis of the tetracyclic core of **1.**

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Supporting Information Available. Experimental procedures for isolation of cassiarin F; preparation of compounds **1**, **3**, **4**, **6**, **8**, **9**, **11**, **12**, and **S1**; copies of ^{1}H, ^{13}C NMR, and 2D spectral data for natural cassiarin F; and ^{1}H and ^{13}C NMR spectral data for compounds **1**, **3**, **4**, **8**, **9**, **11**, **12**, **13**, and **S1**. This material is available free of charge via the Internet at http://pubs.acs.org.