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# Biomimetic Total Syntheses of Cassiarins A and B

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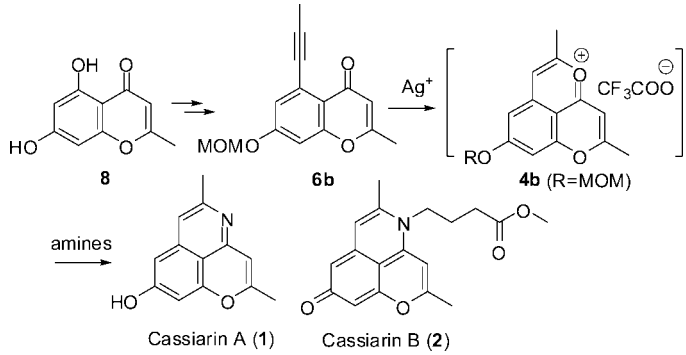


Total syntheses of cassiarins A and B have been efficiently accomplished using a common strategy with biomimetic considerations. Key reactions involved in this synthesis include a Negishi-type coupling, a Ag(I)-promoted formation of the tricyclic 8*H*-pyrano[2,3,4-*de*]chromen-8-one core, and a sequential amine-condensation and cyclization. Three new analogues of cassiarin A bearing different substituents at the C-11 position were synthesized in parallel from the same intermediate. In addition, two other transformations to the key tricyclic cores and cassiarins A and B were achieved from corresponding chemically equivalent precursors.

## Introduction

Development of new antimalarial drugs has been neglected for decades until multiple-drug-resistant strains of malaria parasites were discovered in recent years.[1] The search for new therapeutic agents against malaria is thus pursued from the natural resources and synthetic compounds. Cassiarins A (**1**, 0.0008% isolated yield) and B (**2**, 0.0017% isolated yield, Figure 1) have been isolated by Morita and co-workers in 2007 from the leaves of *Cassia siamea* (Leguminosae), which have been widely used in traditional medicine particularly for the treatment of periodic fever and malaria.[2] Their structures, with an unprecedented tricyclic skeleton (Figure 1A,B), were elucidated and assigned by spectroscopic analysis. Cassiarins A and B exhibit very potent antiplasmodial activity against *Plasmodium falciparum* with an $IC_{50}$ 0.005 and 6.9 $\mu$g/mL, respectively.

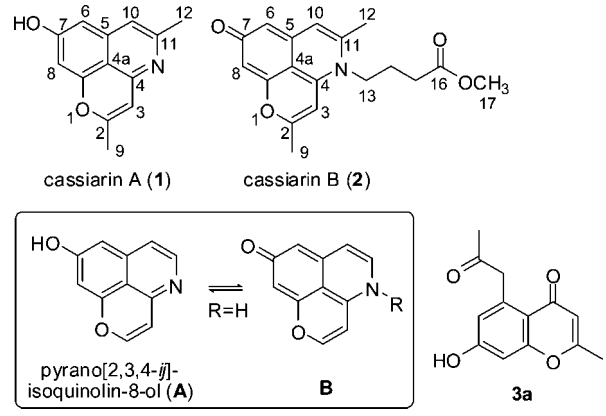


**FIGURE 1.** Structures of cassiarins A (**1**) and B (**2**), their tricyclic cores A and B, and a proposed biogenetic precursor (**3a**).

Thus, these two natural products would be very attractive targets for organic synthesis. Very recently, the first total synthesis of cassiarin A was completed in eight steps from a known compound, methyl 2,4-dihydroxybenzoate, by Honda and Mori-

(1) For recent reviews, see: (a) Schlitzer, M. *Arch. Pharm. (Weinheim)* **2008**, *341*, 149–163. (b) Nosten, F.; White, N. J. *Am. J. Trop. Med. Hyg.* **2007**, *77*, 181–192.

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

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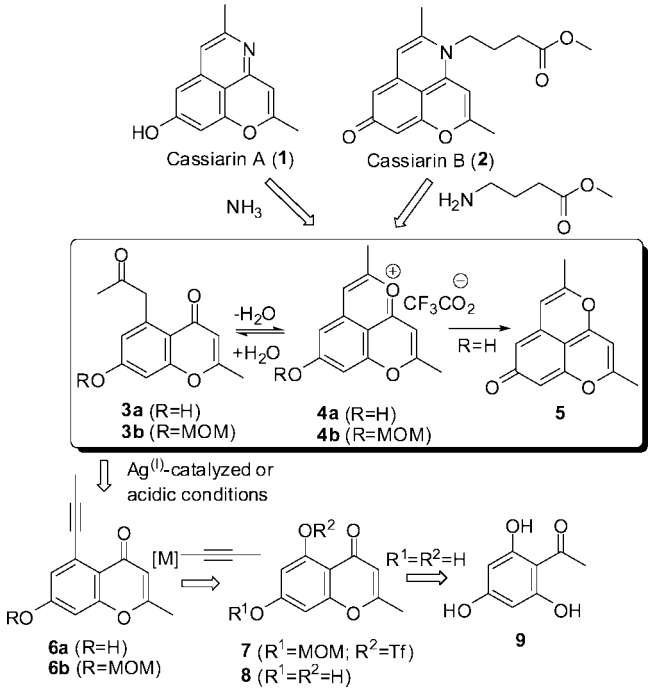



**FIGURE 2.** Retrosynthetic analysis of cassiarins A (**1**) and B (**2**).

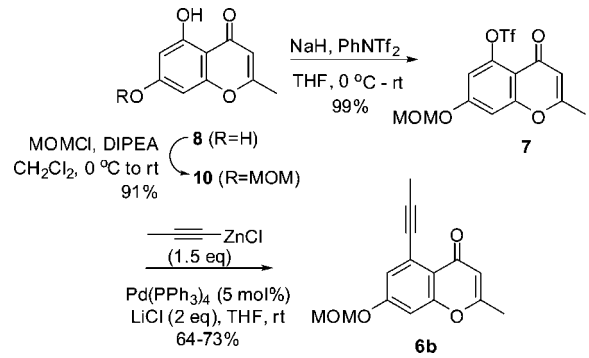
ta.[3] However, their attempts failed to convert cassiarin A to cassiarin B. In this paper, we report highly efficient biomimetic total syntheses of cassiarins A and B, as well as expanded syntheses of three new analogues of cassiarin A with similar chemistries.

**Retrosynthetic Analysis.** As mentioned, cassiarins A and B have a common tricyclic core, pyrano[2,3,4-*ij*]isoquinolin-8-ol (**A**) or its tautomer (**B**) (Figure 1). A biogenetic pathway has been proposed for both of them, starting from a common precursor, 5-acetonyl-7-hydroxy-2-methylchromone (**3a**).[2] With considerations of the plausible biogenetic pathway[2] and our previous experience on isochromenylium salts chemistry,[4] an active salt intermediate **4** and its neutral equivalents **3** and **5** (Figure 2) were therefore regarded as key common intermediate(s) in this synthesis. Salt **4** could be generated in situ from an acetylene precursor **6** using the acidic or Ag(I)-catalyzed reaction conditions,[4,5] and it was supposed to react with the corresponding amines (ammonia and methyl 4-aminobutyrate), affording the desired tricyclic compounds, respectively. Acetylene chromenone **6** could be synthesized from a triflate precursor **7** by cross-coupling with propyne. The further precursor, 5,7-dihydroxy-2-methyl-4*H*-chromen-4-one (**8**), is known and can be easily prepared from a commercially available material, 2,4,6-trihydroxyacetophenone (**9**).

## Results and Discussion

**Synthesis of Common Precursor 6b.** The common alkyne precursor **6b** was synthesized as shown in Scheme 1. Under

**SCHEME 1. Synthesis of the Common Acetylene Intermediate 6b**



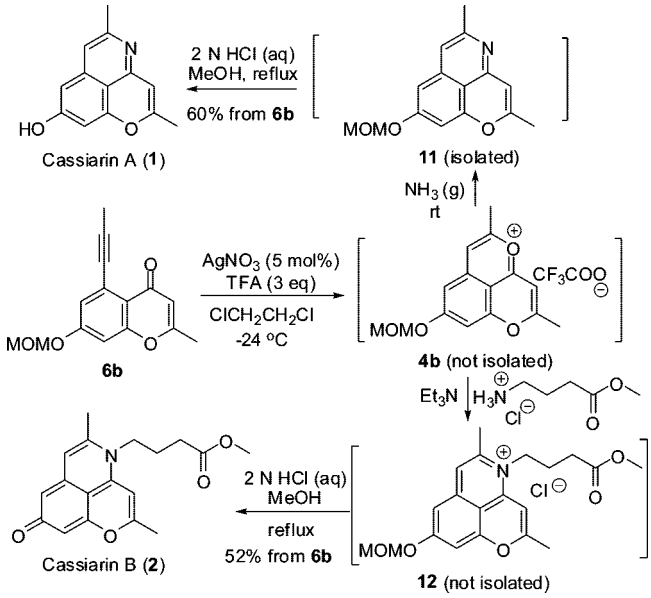

the literature conditions,[6] 5,7-dihydroxy-2-methyl-4*H*-chromen-4-one (**8**) was prepared in a large scale from the commercially available material 2,4,6-trihydroxyacetophenone (**9**). With assistance of the intramolecular H-bonding between C-5 hydroxyl and C-4 ketone carbonyl,[7] selective protection of C-7 hydroxyl group of chromenone **8** was achieved using MOMCl and DIPEA in $CH_2Cl_2$, and gave MOM ether **10** in 91% yield. Then, the remaining phenol hydroxyl of chromenone **10** was converted to the corresponding triflate **7**. Initially, attempts to prepare triflate **7** all failed using combinations of $Tf_2O$ with different bases. Finally, treatment of **10** with $PhN(Tf)_2$ in the presence of NaH[8] at 0 °C gave the desired triflate **7** in 99% yield. Negishi-type coupling of triflate **7** with commercially available 1-propynylmagnesium bromide (1 M, THF solution) was accomplished in the presence of $ZnCl_2$ (1 equiv) and $Pd(PPh_3)_4$ (5 mol %),[9] affording acetylene **6b** in up to 73% yield.

**Total Syntheses.** With acetylene **6b** in hand, elaboration to the tricyclic salt intermediate **4b** was then explored (Scheme 2). This reaction worked very well in 1,2-dichloroethane at −24 °C with a catalytic amount of $AgNO_3$ and 3 equiv of TFA. However, our attempts to separate and characterize salt **4b** failed. Finally, a successive operation was adopted. Directly bubbling dry ammonia into the dichloroethane solution of the previous reaction containing crude salt **4b** afforded a tricyclic compound **11**, which was isolated and its structure was confirmed by $^1H$ NMR and MS. Further treatment of **11** with 2 M aqueous HCl in MeOH under reflux gave cassiarin A (**1**) (60% overall yield from **6b**). In parallel, cassiarin B (**2**, 52% yield from **6b**) was synthesized from the same precursor **6b** using methyl 4-aminobutyrate (to replace ammonia in the previous case).

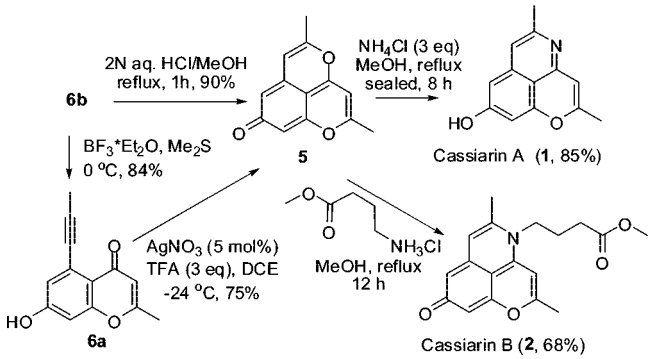
According to our previous retroanalysis (Figure 2), other two pathways to cassiarins were also explored using chemical equivalents of salt **4**. One is based on the neutral tricyclic compound **5**, which is chemically equal to salt **4a** (R = H, Figure 2) and offers another potential entrance to cassiarins. Compound **5** could be easily prepared from the acetylene **6b** using either a one-step procedure (2 N aq HCl, MeOH, reflux) or a two-step alternative (Lewis acid based deprotection followed by $Ag^+$-catalyzed cyclization) (Scheme 3). Exactly as previously proposed, reaction of **5** with 3 equiv of $NH_4Cl$ in MeOH under reflux (sealed tube) for 8 h gave cassiarin A (**1**)

(3) Rudyanto, M.; Tomizawa, Y.; Morita, H.; Honda, T. *Org. Lett.* **2008**, *10*, 1921–1922.
(4) (a) Wei, W. G.; Yao, Z. J. *J. Org. Chem.* **2005**, *70*, 4585–4590. (b) WeiW.-G.; Qian, W.-J.; Zhang, Y.-X.; Yao, Z.-J. *Tetrahedron Lett.* **2006**, *47*, 4171–4174. (c) Qian, W.-J.; Wei, W.-G.; Zhang, Y.-X.; Yao, Z.-J. *J. Am. Chem. Soc.* **2007**, *129*, 6400–6401.
(5) (a) Zhu, J. L.; Grigoriadis, N. P.; Lee, J. P.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2005**, *127*, 9342–9343. (b) Zhu, J. L.; Germain, A. R.; Porco, J. A., Jr *Angew. Chem., Int. Ed.* **2004**, *43*, 1239–1243. (c) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499–6504.
(6) Murti, S. *Proc. Indian Acad. Sci. Sect. A* **1949**, *30*, 107–112.
(7) Kelly, T. R.; Kim, M. H. *J. Org. Chem.* **1992**, *57*, 1593–1597.
(8) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, 446–448. (b) Zhong, B. F.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 3617–3620.
(9) (a) King, A. O.; Okukado, N.; Negishi, E.-i. *J. Chem. Soc., Chem. Commun.* **1977**, 683–684. (b) Negishi, E.-i.; Kotora, M.; Xu, C. D. *J. Org. Chem.* **1997**, *62*, 8957–8960. (c) Wang, K. K.; Wang, Z. G.; Gannett, P. *J. Am. Chem. Soc.* **1996**, *118*, 10783–10791.

**SCHEME 2. Total Syntheses of Cassiarins A and B via Salt Intermediate 4**




**SCHEME 3. Total Syntheses of Cassiarins A (1) and B (2) via Neutral Intermediate 5**




in 85% yield. The other parallel reaction of **5** with methyl 4-aminobutyrate hydrochloride in MeOH under reflux for 12 h afforded cassiarin B (**2**) in 68% yield.

5-Acetonyl-7-hydroxy-2-methylchromone (**3a**, Figure 2) is one more potential biogenetic precursor for both cassiarins.[2] Hydrolysis of salt **4b** (prepared from **6b**, Scheme 2) with aqueous NaOAc afforded diketone **3b** (70%). Further acidic deprotection of MOM ether **3b** gave the desired diketone **3a** (78%). To our delight, both diketones **3b** and **3a** could be converted to cassiarins A (**1**, 52%) and B (**2**, 65%) after their reactions with $NH_4Cl$ and methyl 4-aminobutyrate hydrochloride, respectively (Scheme 4).

**Confirmation of Structures.** The synthesized cassiarin A (**1**) is in full agreement with all aspects of natural product.[2] Surprisingly, synthetic cassiarin B (**2**) shows significant differences in both $^1H$ NMR and $^{13}C$ NMR ($CD_3OD-CDCl_3$, 1:1) by comparison with those spectra of natural product, though it gives similar peak patterns. Our further H−H COSY, HMBC, and NOESY studies confirmed that both synthetic cassiarins have correct structures as proposed (Table 1).[2] In order to explain the causes of spectral difference, extensive studies were conducted. At first, the chemical shifts of lower field protons of cassiarin B (especially for H-6, H-8, H-3, H-10) were found to be very sensitive to the ratio of the mixed solvent ($CD_3OD-CDCl_3$) used for NMR experiments. We initially

**SCHEME 4. Total Syntheses of Cassiarins A and B via Diketone Intermediates 3a and 3b**

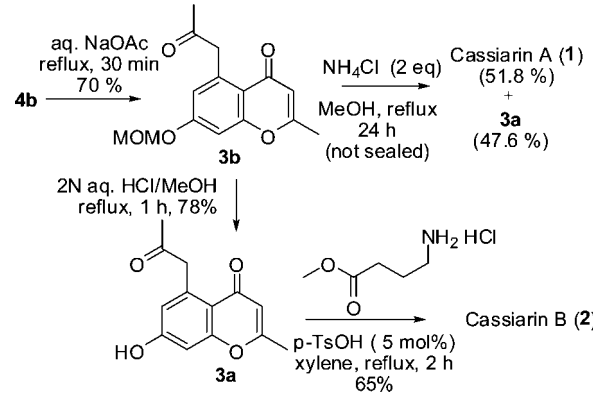
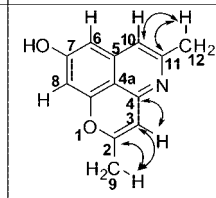
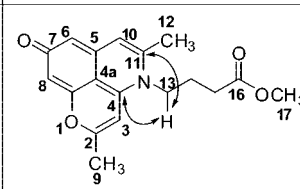
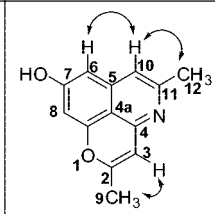
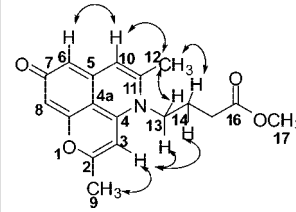



**TABLE 1. Summary of Key Information from NOESY and HMBC Experiments of Synthesized Cassiarins**[a]

| | cassiarin A | cassiarin B |
|---|---|---|
| HMBC |  |  |
| NOESY |  |  |

[a] 2D NMR experiments were performed in $CD_3OD-CDCl_3$ (1:1).

suspected that the reported solvent ratio ($CDCl_3-CD_3OD$, 1:1) for NMR measurements might not be very accurate. Thus, a number of mixed solvents with different ratios around 1:1 ($CDCl_3$ vs $CD_3OD$, in ratios of 40:60, 45:55, 48:52, 50:50, 52:48, 55:45, 60:40) were examined by $^1H$ NMR experiments of our synthesized cassiarin B (**2**). Unfortunately, that $^1H$ NMR spectrum reported for natural cassiarin B could not be reproduced, and the closest one is that measured in $CD_3OD-CDCl_3$ (1:1). Even in a single solvent $CD_3OD$, both the $^1H$ and $^{13}C$ NMRs of synthetic cassiarin B could not match the standard spectra of natural sample (its concentration unknown).[10]

These results suggested to us that such irreproducibility of NMR spectra might be caused by some unusual solution behaviors, which are usually sensitive to the sample concentrations. With such suspicion, $^1H$ NMRs of synthetic cassiarin B (in $CD_3OD$) were examined using samples within different concentrations. Tuning sample concentrations of cassiarin B resulted in slow movement of the chemical shifts of some protons (Table 2). As sample concentration increases, chemical shifts of protons H-6, H-8, H-3, and H-10 move to the higher fields, and other protons H-17, H-15, H-12, and H-9 are

(10) The $^1H$ and $^{13}C$ NMR spectra of natural cassiarins A and B ($CD_3OD$, 400 MHz) were recorded and provided by Prof. Hiroshi Morita on April 3, 2008 (see the Supporting Information).

**TABLE 2. Summary for $^1$H NMR Comparison of Synthetic Cassiarin B (2) in $CD_3OD$**

| no. | sample wt[a] | chemical shifts (ppm) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | H-10 | H-3 | H-8 | H-6 | H-13 | H-17 | H-15 | H-12 | H-9 | H-14 |
| 1 | 0.5 mg | 6.90 | 6.83 | 6.61 | 6.49 | 4.17 | 3.72 | 2.60 | 2.54 | 2.45 | 2.01 |
| 2 | 1.0 mg | 6.89 | 6.82 | 6.59 | 6.47 | 4.16 | 3.72 | 2.60 | 2.54 | 2.45 | 2.01 |
| 3 | 1.5 mg | 6.88 | 6.81 | 6.58 | 6.46 | 4.15 | 3.72 | 2.60 | 2.53 | 2.44 | 2.01 |
| 4 | 2.0 mg | 6.86 | 6.80 | 6.57 | 6.45 | 4.14 | 3.72 | 2.60 | 2.53 | 2.44 | 2.00 |
| 5 | 4.0 mg | 6.82 | 6.76 | 6.53 | 6.41 | 4.11 | 3.72 | 2.59 | 2.52 | 2.43 | 1.99 |
| 6 | 6.0 mg | 6.80 | 6.74 | 6.50 | 6.38 | 4.11 | 3.72 | 2.59 | 2.51 | 2.42 | 1.95 |
| 7 | 10.0 mg | 6.75 | 6.70 | 6.45 | 6.33 | 4.06 | 3.72 | 2.59 | 2.49 | 2.41 | 1.96 |
| 8 | no. 4 + no. 6 | 6.83 | 6.76 | 6.53 | 6.41 | 4.12 | 3.72 | 2.60 | 2.52 | 2.43 | 1.99 |
| 9[b] | natural | 6.89 | 6.83 | 6.61 | 6.50 | 4.15 | 3.72 | 2.60 | 2.53 | 2.45 | 2.01 |

[a] Samples 1−7 were dissolved in 0.4 mL of $CD_3OD$ (see the Supporting Information for the recorded spectra). [b] The $^1$H NMR spectrum of natural cassiarin B in $CD_3OD$ was recorded and provided by Prof. H. Morita on April 3, 2008, and its concentration is unknown.

relatively not very sensitive to such changes. For example, the spectra of samples 4 (2 mg of **2** in 0.4 mL $CD_3OD$, Table 2), 5 (4 mg of **2** in 0.4 mL $CD_3OD$), and 6 (6 mg of **2** in 0.4 mL $CD_3OD$) are quite different from each other. However, an additional experiment by mixing samples 4 and 6 afforded the same spectrum as sample 5. The above information proposes that the densely conjugated benzoquinone moiety in cassiarin B might be responsible for the supramolecular interactions in solution observed in NMR studies. We believe supramolecular interactions of cassiarin B in solution are more complicated, and further investigation will be needed for a full explanation. To our delight, a very dilute sample (0.5 mg of synthetic cassiarin B in 0.4 mL of $CD_3OD$) finally gave an $^1$H NMR spectrum identical to that of the natural product.[10]

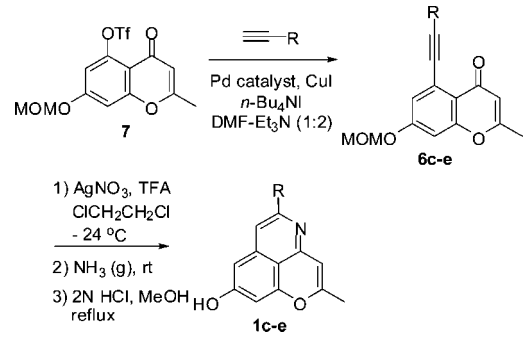
**Synthesis of New Analogues.** Because of the highly potent antiplasmodial activity exhibited by cassiarin A, structural expansion upon its unique tricyclic core is of extreme importance. As one advantage of our developed protocols, such a task could be easily achieved by simply following the steps in Scheme 2. Three new analogues of cassiarin A (**1c**, **1d**, and **1e**) bearing different substituents at the C-11 position were prepared in parallel, commonly starting from the same triflate **7** (Table 3).

## Conclusion

In summary, the efficient biomimetic total syntheses of cassiarins A (**1**) and B (**2**) have been accomplished in four operations from 5,7-dihydroxy-2-methyl-4*H*-chromen-4-one (**8**) in 39% and 34% overall yield, respectively, according to the first route (Schemes 1 and 2). A Negishi-type coupling, a Ag(I)-catalyzed formation of key salt intermediate **4b**, and an aminolysis of salt **4** and following condensations successfully served as key steps in these syntheses. Conversions of other two precursors **3** and **5** to cassiarins A and B were also achieved. Both the synthesized cassiarins were confirmed by their 1D NMR and 2D NMR experiments, as well as corresponding spectral comparisons. A preliminary structural expansion based on tricyclic core of cassiarin A was explored, and three new analogues of cassiarin A were prepared from the same intermediate **7**. Further applications of the developed chemistry and biological study of new cassiarin analogues are underway and will be reported in due course.

(11) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron* **2001**, *42*, 5275–5278.

**TABLE 3. Parallel Syntheses of New Analogues of Cassiarin A**




| entry | R | Pd catalyst | **6** (yield) | **1**[c] (yield) |
|---|---|---|---|---|
| 1 | Ph | $Pd(PPh_3)_4$[a] | **6c** (94%) | **1c** (50%) |
| 2 |  | $Pd(PPh_3)_4$ | **6d** (88%) | **1d** (61%) |
| 3 | n-$C_5H_{11}$ | $Pd(PPh_3)_2Cl_2$[b] | **6e** (71%) | **1e** (46%) |

[a] The cross coupling was carried out with 10 mol % of $Pd(PPh_3)_4$, 30 mol % of CuI, and 150 mol % of *n*-$Bu_4NI$ in DMF/$Et_3N$ (1/2, v/v) under $N_2$ at rt.[11] [b] $Pd(PPh_3)_2Cl_2$ was used to replace $Pd(PPh_3)_4$. [c] All reactions were carried out under the same conditions as described in Scheme 2.

## Experimental Section

**5-Hydroxy-7-(methoxymethoxy)-2-methyl-4*H*-chromen-4-one (10).** To a stirred solution of 5,7-dihydroxy-2-methyl-chromen-4-one (**8**, 2.70 g, 14.0 mmol) in $CH_2Cl_2$ (40 mL) was added DIPEA (1.3 mL, 17.0 mmol) at 0 °C under $N_2$. After the solution was stirred for 10 min, MOMCl (1.27 mL, 17.0 mmol) was added at the same temperature. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h until completion of the reaction (TLC). The reaction was quenched with satd aq $NaHCO_3$. The solvent was removed under reduced pressure and water was added and then extracted with ethyl acetate. The combined organic phases were successively washed with 1 M HCl, water, and brine, dried with anhydrous $Na_2SO_4$, and concentrated in vacuo. Purification with column chromatography (petroleum ether/ethyl acetate = 2/1) gave a pale yellow solid (**10**, 3.07 g, 91%): mp 109−111 °C; IR 1668, 1625, 1594, 1338, 1158, 1020 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.67 (s, 1H), 6.53 (d, $J$ = 2.4 Hz, 1H), 6.45 (d, $J$ = 2.1 Hz, 1H), 6.04 (s, 1H), 5.22 (s, 2H), 3.49 (s, 3H), 2.35 (s, 3H); ESI-MS (*m*/*z*) 237 ($M + H^+$), 259 ($M + Na^+$). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.68; H, 5.09.

**7-(Methoxymethoxy)-2-methyl-4-oxo-4*H*-chromen-5-yl Trifluoromethanesulfonate (7).** To a stirred solution of **10** (5.00 g, 21.2 mmol) in THF (90 mL) was added NaH (60%, 0.97 g, 24.3 mmol) by portions at 0 °C under $N_2$. The suspended yellow solution was stirring for 10 min, and then a solution of $PhNTf_2$ (9.08 g, 25.4 mmol) in THF (25 mL) was added. The resulting mixture was allowed to warm to room temperature after it became clear. After being stirred for an additional 1 h, the reaction was quenched with satd aq $NH_4Cl$. THF was evaporated, and the residue was diluted with water and extracted with ethyl acetate three times. The combined organic phases were washed with water and brine, dried over anhydrous $Na_2SO_4$, and concentrated. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate =

3/1) to give **7** (7.30 g, 99%): mp 109−110 °C; IR 1668, 1623, 1425, 1389, 1214, 1138, 1024 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.11 (d, $J$ = 2.1 Hz, 1H), 6.85 (d, $J$ = 1.8 Hz, 1H), 6.10 (s, 1H), 5.27 (s, 2H), 3.51 (s, 3H), 2.35 (s, 3H); ESI-MS (*m*/*z*) 369 [M + $H^+$], 391 (M + $Na^+$). Anal. Calcd for $C_{13}H_{11}F_3O_7S$: C, 42.40; H, 3.01. Found: C, 42.18; H, 3.07.

**7-(Methoxymethoxy)-2-methyl-5-(prop-1-ynyl)-4*H*-chromen-4-one (6b).** To a 50 mL flask were added **7** (2.00 g, 5.40 mmol), $Pd(PPh_3)_4$ (314 mg, 0.27 mmol), and LiCl (420 mg, 10.8 mmol). The mixture was degassed and kept under nitrogen atmosphere at room temperature, and then 15 mL of freshly distilled THF was added. In the other flask, 1-propynylzinc chloride was prepared by treatment of 1-propynylmagnesium bromide (0.5 M in THF, 16.2 mL) with a solution of anhydrous $ZnCl_2$ in THF (1.0 M, 8.1 mL) at rt. The prepared solution of 1-propynylzinc chloride was transferred via syringe into the first flask at room temperature. The resulting red solution was stirred for 20 h until water was added to quench the reaction. THF was evaporated, and the residue was diluted with water and extracted with ethyl acetate. The combined organic phases were successively washed with water and brine, dried over anhydrous $Na_2SO_4$, and concentrated. Purification by flash chromatography (petroleum ether/ethyl acetate = 4/1) gave **6b** (0.97 g, 75% based on 93% conversion of starting material): mp 109−110 °C; IR 1654, 1601, 1391, 1338, 1156, 1078 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.08 (d, $J$ = 1.8 Hz, 1H), 6.93 (d, $J$ = 2.1 Hz, 1H), 6.03 (s, 1H), 5.21 (s, 2H), 3.47 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 5.0, 20.0, 56.4, 78.6, 92.6, 94.3, 103.3, 111.2, 118.6, 120.7, 124.3, 158.5, 159.7, 164.2, 177.1; ESI-MS (*m*/*z*) 259 [M + $H^+$]. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.41; H, 5.52.

**Cassiarin A (1) (from 6b).** To a solution of **6b** (105 mg, 0.415 mmol) and $AgNO_3$ (3.5 mg, 5 mol %) in $(CH_2Cl)_2$ (5 mL) was added dropwise TFA (92 $\mu$L, 1.25 mmol) at −24 °C under nitrogen atmosphere. The resulting orange solution was stirred for 1 h at this temperature. After removal of the cooling bath, anhydrous ammonia was bubbled into the reaction mixture for 20−30 min, and the whole mixture was stirred overnight at room temperature. The solvent was removed, and 2 N aq HCl (3 mL) and MeOH (7 mL) were added. The mixture was refluxed for 30 min. The reaction was cooled to room temperature, and MeOH was removed in vacuo. The aqueous layer was adjusted to pH 9 with 2 N aq $Na_2CO_3$ and then extracted with a mixture of $CH_2Cl_2$ and MeOH (20/1). The combined organic phases were washed with water and brine, dried over anhydrous $Na_2SO_4$, and concentrated. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH = 30/1) to give **1** (52 mg, 60%): mp 280−282 °C; IR 1663, 1618, 1567, 1394, 1189, 1170 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3/CD_3OD$ = 1/1) $\delta$ 6.71 (s, 1H), 6.48 (d, $J$ = 1.9 Hz, 1H), 6.46 (d, $J$ = 1.9 Hz, 1H), 6.03 (s, 1H), 2.35 (s, 3H), 2.20 (s, 3H); $^1H$ NMR ($CD_3OD$, 500 MHz) $\delta$ 6.79 (s, 1H), 6.50 (s, 2H), 6.09 (d, $J$ = 1.0 Hz, 1H), 2.38 (s, 3H), 2.25 (d, $J$ = 1.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3/CD_3OD$ = 1/1) $\delta$ 20.0, 22.9, 100.8, 102.9, 103.9, 111.7, 113.7, 139.0, 149.9, 150.8, 156.4, 161.4, 164.6; $^{13}C$ NMR ($CD_3OD$, 125 MHz) $\delta$ 20.8, 23.6, 102.0, 104.3, 105.0, 112.8, 115.0, 140.7, 151.4, 152.2, 157.9, 163.4, 166.4. ESI-MS (*m*/*z*) 214 [M + $H^+$]; HRMS (ESI) calcd for $C_{13}H_{12}NO_2$ [M + $H^+$] 214.0863, found 214.0867.

**Cassiarin B (2) (from 6b).** To a solution of **6b** (117 mg, 0.426 mmol) and $AgNO_3$ (3.6 mg, 5 mol %) in $(CH_2Cl)_2$ (4 mL) was dropwise added TFA (100 $\mu$L, 1.35 mmol) at −24 °C under nitrogen atmosphere. The orange solution was stirred for 1 h at same temperature. After the cooling bath was removed, methyl $\gamma$-aminobutyrate hydrochloride (85 mg, 0.54 mmol) and $Et_3N$ (0.3 mL, 2.25 mmol) were added. The resulting mixture was stirred overnight at room temperature. After removal of solvent, 2 N aq HCl (3 mL) and MeOH (7 mL) were added. The mixture was refluxed for 30 min before cooling to room temperature. Solvent was removed, and water was added. The aqueous layer was adjusted to pH 9 with 2 N aq $Na_2CO_3$ and extracted with $CHCl_3$. The organic phase was washed with water and brine, dried over anhydrous $Na_2SO_4$, and concentrated. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH = 10/1) to give **2** (74 mg, 52%): mp 80 °C dec; IR 1733, 1654, 1597, 1457, 1437, 1197, 1170 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3/CD_3OD$ = 1/1) $\delta$ 6.78 (s, 1H), 6.73 (s, 1H), 6.61 (d, $J$ = 1.8 Hz, 1H), 6.46 (d, $J$ = 1.8 Hz, 1H), 4.14 (t, $J$ = 8.5 Hz, 2H), 3.81 (s, 3H), 2.65 (t, $J$ = 6.4 Hz, 2H), 2.56 (s, 3H), 2.49 (s, 3H), 2.05 (m, 2H); $^1H$ NMR (0.5 mg in 0.4 mL $CD_3OD$, 300 MHz) $\delta$ 6.90 (s, 1H), 6.83 (s, 1H), 6.61 (d, $J$ = 1.8 Hz, 1H), 6.49 (d, $J$ = 1.8 Hz, 1H), 4.17 (t, $J$ = 8.1 Hz, 2H), 3.72 (s, 3H), 2.60 (t, $J$ = 6.6 Hz, 2H), 2.54 (s, 3H), 2.45 (s, 3H), 1.99−2.05 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3/CD_3OD$ = 1/1) $\delta$ 20.4, 21.3, 24.2, 30.5, 47.9, 52.6, 97.0, 106.2, 108.7, 109.0, 116.8, 136.4, 140.9, 148.2, 157.0, 167.4, 174.5, 177.9; $^{13}C$ NMR (10.0 mg in 0.4 mL $CD_3OD$, 100 MHz) $\delta$ 20.1, 20.8, 24.1, 30.6, 48.3, 52.3, 97.5, 105.6, 108.5, 109.1, 116.9, 137.0, 142.1, 148.8, 157.2, 168.0, 174.9, 176.8; ESI-MS (*m*/*z*) 314 [M + $H^+$]; HRMS (ESI) calcd for $C_{18}H_{20}NO_4$ [M + $H^+$] 314.1387, found 314.1389.

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**Supporting Information Available:** Experimental procedures and characterization data; $^1H$ NMR and $^{13}C$ NMR spectra of compounds **6b**, **6a**, **5**, **3b**, **3a**, **6c**, **1c**, **1d**, **6e**, **1e**, **1**, and **2**; $^1H$ NMR spectra of compounds **10**, **11**, **7**, and **6d**; NOESY, HMBC, HMQC, and H−H COSY spectra of synthetic cassiarin A (**1**); NOESY and HMBC spectra of synthetic cassiarin B (**2**); and $^1H$ NMR spectral comparison of cassiarin B (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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