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Two novel tetracycles, cassibiphenols A and B from the flowers of *Cassia siamea*

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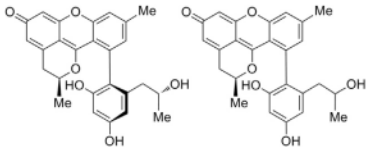
ABSTRACT

Chemical investigation of the flowers of *Cassia siamea* (Leguminosae), resulted in the isolation of two novel tetracycles connecting 5-(2-hydroxypropyl)benzene-1,3-diol, cassibiphenols A (**1**) and B (**2**). The structures were elucidated by analysis of the 1D, 2D NMR, and HRMS spectra. Synthesis of a tetracyclic core of **1** and **2** led to determine the absolute configuration of **1** and C-12 of **2**.

In our screening study on new antiplasmodial agents from plant resources, we have succeeded in the isolation of new various alkaloids,[1] sesquiterpenes,[2] and limonoids.[3] Cassiarin A,[4] an unprecedented tricyclic alkaloid exhibiting potent antimalarial activity against *Plasmodium falciparum* in vitro as well as *Plasmodium berghei* in vivo,[5] was isolated from the leaves of *Cassia siamea* and has attracted attention of synthetic organic chemists[6] as well as pharmacologists.[7] *Cassia siamea* Lam. (Leguminosae), has been used widely in traditional medicine, particularly for treatment of periodic fever and malaria in Indonesia.[8] Recently we isolated cassiarins G, H, J, and K,[9] showing antiplasmodial activity from leaves of *C. siamea*, and achieved total synthesis of a novel tetracyclic alkaloid, cassiarin F isolated from flowers of *C. siamea*.[10] Further isolation work on extracts from the flowers of *C. siamea* has led to purification and structure elucidation of two novel tetracyclic cassibiphenols A (**1**) and B (**2**). In this Letter, we would like to report the structure elucidation based on spectroscopic analyses and partial synthesis of **1** and **2**. The absolute configuration at C-12 was established by the comparison of the CD spectra of tetracyclic core in **1** and **2**.

The flowers of *C. siamea* (1.0 kg) were extracted with MeOH, and the extract was partitioned between EtOAc and 3% aqueous tartaric acid. The aqueous layer was adjusted at pH 9 with saturated Na_2CO_3 aq and extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to a silica gel column, an ODS column, an LH-20 column, and ODS HPLC to give cassibiphenols A (**1**, 0.00002%)[11] and B (**2**, 0.00002%).[12]



cassibiphenol A (**1**) cassibiphenol B (**2**)

Cassibiphenol A (**1**) was obtained as yellowish amorphous solids. **1** showed the molecular formula $C_{26}H_{24}O_6$, which was determined by HRESIMS [*m*/*z* 433.1655 $(M+H)^+$, +0.4 mmu]. The optical activity of **1** was confirmed by the positive and negative Cotton effects at 209 nm and 231 nm of the CD spectrum. IR absorptions implied the presence of hydroxyl (3742 cm^{-1}) and carbonyl (1678 cm^{-1}) functionalities. ^1H and ^{13}C NMR spectra are presented in Table 1. The ^{13}C NMR spectrum revealed 26 carbon signals due to one carbonyl carbon, twelve sp^2 quaternary carbons, six sp^2 and two sp^3 methines, two sp^3 methylenes, and three methyl groups. Among them, five sp^2 quaternary carbons (δ_C 156.7, 158.1, 159.0, 161.5, and 166.8) and two sp^3 methine carbons (δ_C 68.6 and 79.0) were ascribed to those bearing an oxygen atom.

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Table 1
^{1}H NMR data [δ_H (J, Hz)] and ^{13}C NMR Data [δ_C] of cassibiphenols A (**1**) and B (**2**) in CD_3OD at 300 K

Position	Cassibiphenol A (**1**)		Cassibiphenol B (**2**)	
	δ_H	δ_C	δ_H	δ_C
2		158.1		157.7
3		113.5		113.3
4		166.8		166.8
5		137.5		137.7
6	6.41 (1H, s)	123.1	6.41 (1H, s)	123.2
7		186.0		185.9
8	6.32 (1H, s)	103.3	6.32 (1H, d, 1.4)	103.3
9		161.5		161.7
10		103.3		103.3
11a	2.82 (1H, dd, 16.3, 16.3)	34.3	2.79 (1H, dd, 16.6, 13.4)	34.5
11b	3.01 (1H, d, 16.3)		3.01 (1H, dd, 16.6, 2.9)	
12	4.41 (1H, m)	79.0	4.45 (1H, m)	79.5
13	1.16 (3H, d, 6.1)	20.2	1.16 (3H, d, 6.3)	20.2
14	7.44 (1H, s)	117.7	7.44 (1H, s)	117.7
2′		148.5		148.2
3′	7.08 (1H, s)	131.9	7.06 (1H, s)	132.4
4′		139.0		139.2
5′		138.3		139.3
6′	6.34 (1H, s)	109.4	6.34 (1H, d, 2.0)	109.1
7′		159.0		158.9
8′	6.26 (1H, s)	101.6	6.28 (1H, d, 2.0)	101.3
9′		156.7		156.5
10′		122.0		121.8
11′a	2.21 (1H, dd, 13.0, 5.4)	44.3	2.30 (1H, dd, 13.6, 6.2)	44.1
11′b	2.71 (1H, dd, 13.0, 5.4)		2.49 (1H, dd, 13.6, 6.2)	
12′	3.58 (1H, m)	68.6	3.76 (1H, m)	68.9
13′	1.01 (3H, d, 5.9)	22.9	0.95 (3H, d, 6.1)	22.9
14′	2.55 (3H, s)	22.0	2.54 (3H, s)	22.0

The gross structure of **1** was classified into two units, 3-methyl-3*H*-isochromen-6(4*H*)-one (C-4 to C-13) and a biphenyl unit (C-2, C-3, C-14, and C-2′ to C-14′), which were deduced from extensive analysis of HMBC spectrum in CD_3OD (Fig. 1).

Three partial structures, **a** (C-11 to C-13), **b** (C-14, C-2′, C-3′, and C-14′), and **c** (C-11′ to C-13′) were deduced from analysis of the ^{1}H–^{1}H COSY spectrum. Connection between partial structure **a** and the dienone ring, which form 3-methyl-3*H*-isochromen-6(4*H*)-one, could be assigned by HMBC correlations of H-6 (δ_H 6.41) to C-8 (δ_C 103.3), C-10 (δ_C 103.3), and C-11 (δ_C 34.3) and H-8 (δ_H 6.32) to C-7 (δ_C 186.0), C-9 (δ_C 161.5), and C-10, and a four bond HMBC correlation to C-4 (δ_C 166.8), and H-11a (δ_H 3.01) to C-5 (δ_C 137.5) and C-10 (δ_C 103.3). Partial structure **b** in the benzene ring, which connected with C-2 and C-3 through C-4′ was indicated by HMBC correlations of H-14 (δ_H 7.44) to C-2 (δ_C 158.1) and C-3 (δ_C 113.5) and H-3′ (δ_H 7.08) to C-3 and C-4′ (δ_C 139.0). The ether linkage between C-2 and C-9 could be assigned by the both down-field shifts of ^{13}C NMR data; δ_C 161.5 and δ_C 158.1. The connection of C-3 and C-4 was deduced by the ^{13}C NMR chemical data of quaternary sp^2 carbons; δ_C 113.5 and δ_C 166.8. The presence of 5-(2-hydroxypropyl)benzene-1,3-diol was supported by ^{1}H and ^{13}C NMR data (δ_H 3.58, 6.26, and 6.34; δ_C 68.6, 101.6, 109.4, 122.0, 138.3, 156.7, and 159.0) and HMBC correlations of H-11′a (δ_H 2.21) to C-5′ (δ_C 138.3), C-6′ (δ_C 109.4), and C-10′ (δ_C 122.0) indicating the connection of partial structure **c** and C-5′. The connectivity of C-4′ and C-10′ was assigned by a HMBC correlation of H-3′ (δ_H 7.08) to C-10′.

The diastereotopic methylene protons (H_2-11) at δ_H 2.82 and 3.01 were vicinally coupled with H-12 with respective J values of H-11a (dd, J = 16.3, 16.3 Hz) and H-11b (d, J = 16.3 Hz), which indicated that the former proton was pseudoaxial and the latter was assignable to pseudoequatorial position. The relative configuration of **1** was deduced through inspection of a molecular model as well as the ROESY spectrum (Fig. 2), with ROESY correlations between H-3′/H-11′b, H-11′a/H_3-13′, and H_3-13′/H_3-13 indicating a biphenyl bond at C-4′ and C-10′ was *S**-configuration and a secondary hydroxyl group at C-12′ was *R**-configuration, and a methyl group at C-12 was *S**-configuration as shown in Figure 2. Therefore, Cassibiphenol A (**1**) was concluded to be a novel tetracycle connecting 5-(2-hydroxypropyl)benzene-1,3-diol.

Cassibiphenol B (**2**) was obtained as yellowish amorphous solid. **2** showed the similar CD curve and the same molecular formula as **1**, $C_{26}H_{24}O_6$, which was determined by HRESIMS [m/z 433.1653 $(M+H)^+$, +0.2 mmu]. ^{1}H and ^{13}C NMR spectra are presented in Table 1. The gross structure of **2** was deduced from extensive analysis of the HMBC spectrum in CD_3OD and revealed **2** had the same planar structure as **1** (Fig. 1). According to the similar CD data of **1** and **2**, they were deduced to have the same absolute configuration at C-12 and/or biphenyl configuration. The two possible relative configurations of **2** were deduced through the difference of the ^{1}H NMR chemical shifts from H-11′ to H-13′ of **2** and **1** and ROESY correlations between H-3′/H-11′a, and H-11′a/H_3-13′ indicating **2** was a steroisomer at C-12′ or a rotational isomer of **1** (Fig. 3). The stereochemistry of the secondary hydroxyl group of **1** and **2** could be assigned by applying the Mosher method.[13] However, the limited amount of **1** and **2** prohibited the further investigation by the chemical means.

Plausible biogenetic pathways for **1** and **2** were proposed as shown in Scheme 1. **1** and **2** might be derived through a Michael addition of 5-acetonyl-7-hydroxy-2-methylchromone[14] producing chrobisiamone A,[15] followed by cleavage of an ether bond, cyclization with the α,β-unsaturated ketone, and finally acid-promoted ring disclosure[16] to produce an isochromen part as shown in Scheme 1.

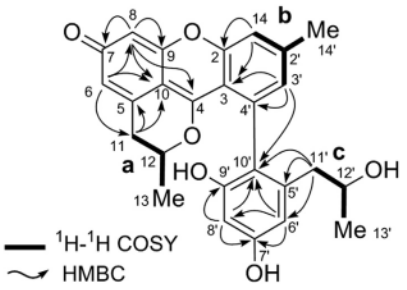


Figure 1. Selected 2D NMR correlations for cassibiphenol A (**1**) and B (**2**).

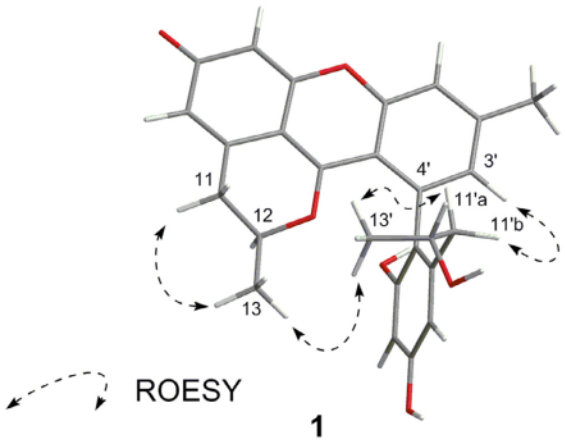


Figure 2. Selected ROESY correlations for cassibiphenol A (**1**).

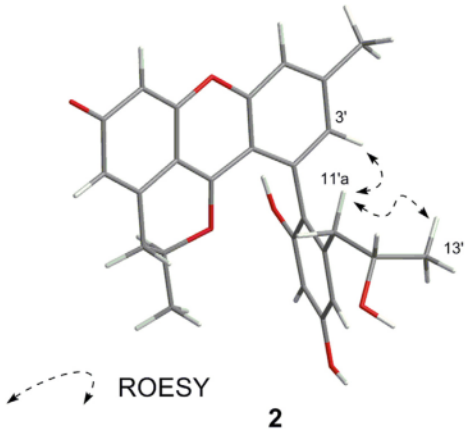
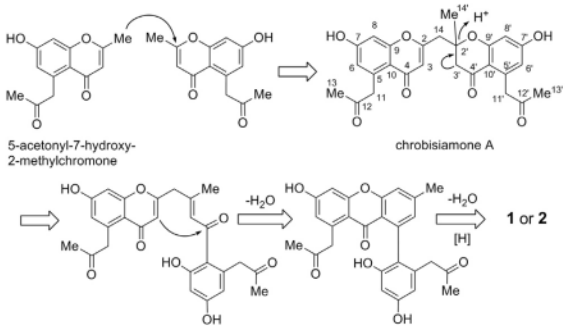
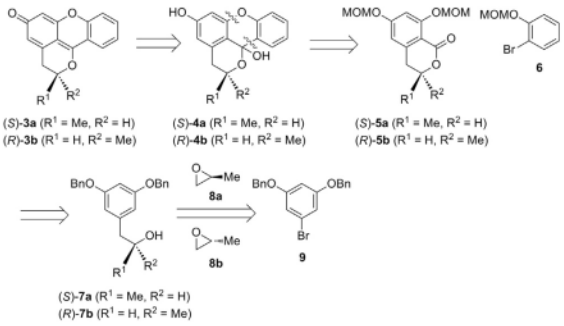


Figure 3. Selected ROESY correlations for cassibiphenol B (**2**).

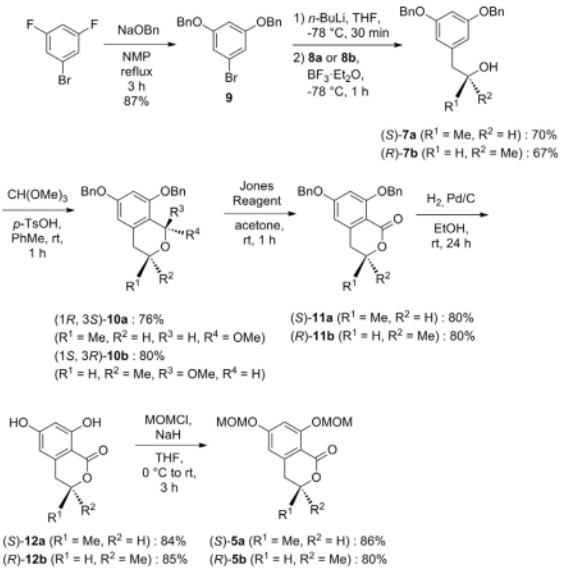


Scheme 1. Plausible biogenetic pathway for cassibiphenols A (**1**) and B (**2**).



Scheme 2. Retrosynthetic analysis for tetracyclic core of **1** and **2**.

In order to determine the absolute stereochemistry of C-12, a synthesis of a tetracyclic core of cassibiphenols A (**1**) and B (**2**), **3a** and **3b** was undertaken. Our retrosynthetic analysis of **3** is outlined in Scheme 2. To construct the 3-methyl-3*H*-isochromen-6(4*H*)-one, left half of the tetracyclic core, **4a** and **4b** were regarded as synthetic precursors, which converted to **3** through dehydration of a tertially alcohol as the similar conversion of barakol to anhydrobarakol.[16] Making the two disconnections generated the three building blocks (methoxymethyl (MOM)-protected *S*- or *R*-6-hydroxymellein[17] **5a** and **5b**, and MOM protected 2-bromophenol **6**) needed for assembly of **4a** and **4b**. Enantiomerically pure **5a** and **5b** were obtained from **9** by inserting proper stereochemistry from the chiral reagent *S*- or *R*-propylene oxide (**8a** and **8b**). In addition, the δ-valerolactone could be synthesized through oxa-Pictet–Spengler cyclization[18] and Jones oxidation.[19]

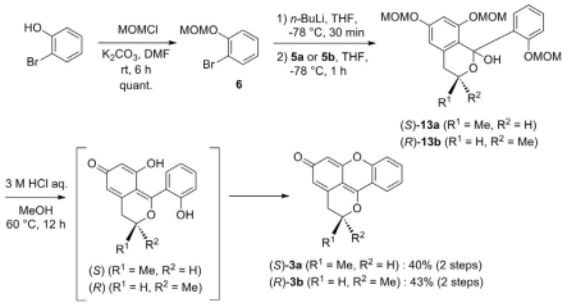


Scheme 3. Synthesis of enantiopure 3,4-dihydroisocoumarins, **5a** and **5b**.

Our synthesis began with preparation of two enantiomerically pure MOM-protected *S*- or *R*-6-hydroxymellein (**5a** and **5b**), which was readily accessible from a known bromobenzene **9**[20] synthesized from commercially available 1-bromo-3,5-difluorobenzene. Regioselective boron trifluoride diethyl etherate promoted ring opening of **8a** and **8b** with an aryl anion of **9** to afford the phenyl-2-propanol **7a** and **7b** in 70% and 67% yields, respectively. Condensation of **7a** and **7b** with trimethyl orthoformate under *p*-TsOH condition yielded the isochroman acetal **10a** and **10b** in 76% and 80% yields, respectively, which were characterized to be single diastereomers of *trans*-pyran.[21] Jones oxidation of **10a** and **10b** led to the formation of lactones **11a** and **11b**, which were converted to the natural product, *S*- or *R*-6-hydroxymellein **12a** and **12b** by removal of both aromatic benzyl ether functions under hydrogenation. Finally, **5a** and **5b** were obtained by re-protection of two phenolic alcohols as MOM ethers in 86% and 80% yields, respectively (Scheme 3).

Assessment of the enantiomeric excess by HPLC analysis of **11a** and **11b** confirmed >99% enantiomeric excess (see the Supplementary data), and the each positive and negative specific optical rotation of **12a** ($[\alpha]_D^{20}$ +54 (*c* 0.12, MeOH)) and **12b** ($[\alpha]_D^{20}$ −53 (*c* 0.35, MeOH) {lit.[22] $[\alpha]_D^{18}$ −51 (*c* 0.10, MeOH)}) and the characteristic Cotton effects of *S*-6-hydroxymellein, **12a** (CD (MeOH) λ_{max} (nm)/$\Delta\varepsilon$: 234 (+9.5) and 268 (+7.1) {lit.[23] CD (MeOH) λ_{max} (nm)/$\Delta\varepsilon$: 233 (+10.4) and 268 (+6.7)}, and *R*-6-hydroxymellein, **12b** (CD (MeOH) λ_{max} (nm)/$\Delta\varepsilon$: 233 (−9.7) and 268 (−7.0) {lit.[23] CD (MeOH) λ_{max} (nm)/$\Delta\varepsilon$: 233 (−9.0) and 268 (−8.1)) confirmed the absolute configuration.

MOM-protected 2-bromophenol **6**, which was produced from commercially available 2-bromophenol in quantitative yield, was treated with *n*-BuLi and allowed to react with **5a** and **5b** to give hemiketals **13a** and **13b** as a mixture of two diastereomers. The phenolic MOM groups of **13a** and **13b** were removed by 3 M HCl aq in MeOH, which occurred through a dehydration of tertially



Scheme 4. Construction of the tetracyclic core, **3a** and **3b**.

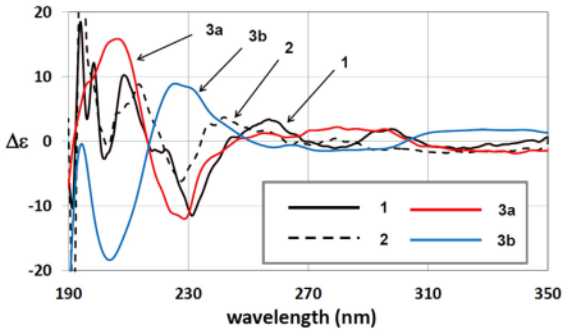


Figure 4. Comparison of CD spectra of **1**, **2**, **3a**, and **3b**.

alcohol forming isochromen skeleton and an intramolecular dehydrate cyclization to give desired **3a** and **3b** in 40% and 43% yields, respectively (Scheme 4).

In the CD spectra of **3a** and **3b**, two Cotton effects were observed in methanol. The bands of negative and positive sign around 230 and 210 nm could be assigned to the $\pi \rightarrow \pi^*$ transition of 3*H*-xanthen-3-one chromophore and the helicity of the pyran ring. Comparison of the CD spectra for **1**, **2**, **3a**, and **3b** indicated the absolute configuration at C-12 of **1** and **2** were *S* configuration as in **3a** (Fig. 4). According to the relative configuration of **1**, we came to the conclusion of the absolute configuration of **1** as 12*S*,4′*S*,12′*R*.

In conclusion, structure elucidation of cassibiphenols A (**1**) and B (**2**) consisting of a novel tetracyclic skeleton and a biphenyl unit was reported and synthesis of a tetracyclic core of **1** and **2** (11% overall yield for **3a** and **3b** in 8 steps) for determination of the absolute configuration of **1** and C-12 of **2** was described. The strategy with two sequences of dehydrate aromatic ring construction seems to be an innovative approach to the synthesis of the tetracyclic core of **1** and **2**, which would be potentially useful in the total synthesis and determination of the absolute configuration of **2**. Studies in this direction are underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, scanned copies of NMR spectra including ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, HSQC, HMBC, ROESY, and chiral HPLC spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.023.

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11. *Cassibiphenol A* (**1**): yellow amorphous solid; IR (Zn-Se) ν_{max} 3742, 3366, 2923, 1678, 1604, and 1558 cm^{-1}; UV (MeOH) λ_{max} 204 (ε 30860), 231 (ε 23410), 268 (ε 12220), 366 (ε 6050), and 423 (ε 11240) nm; CD (MeOH, 0.00046 M) λ_{max} ($\Delta\varepsilon$) 202 (−2.7), 209 (+10.3), 231 (−11.5), and 257 (+3.4) nm; ^{1}H and ^{13}C NMR (Table 1); ESIMS (pos.) *m*/*z* 433 (M+H)$^+$; HRESIMS *m*/*z* 433.1655 (M+H)$^+$, calcd for $C_{26}H_{25}O_6$ 433.1651.
12. *Cassibiphenol B* (**2**): yellow amorphous solid; IR (Zn-Se) ν_{max} 3730, 3260, 2952, 1683, 1597, and 1544 cm^{-1}; UV (MeOH) λ_{max} 203 (ε 31688), 231 (ε 23117), 270 (ε 12554), 359 (ε 5931), and 423 (ε 12943) nm; CD (MeOH, 0.00046 M) λ_{max} ($\Delta\varepsilon$) 203 (−0.7), 214 (+8.8), 228 (−6.1), and 242 (+3.7) nm; ^{1}H and ^{13}C NMR (Table 1); ESIMS (pos.) *m*/*z* 433 (M+H)$^+$; HRESIMS *m*/*z* 433.1653 (M+H)$^+$, calcd for $C_{26}H_{25}O_6$ 433.1651.
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