



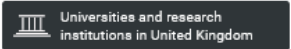
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Tetrahedron Letters

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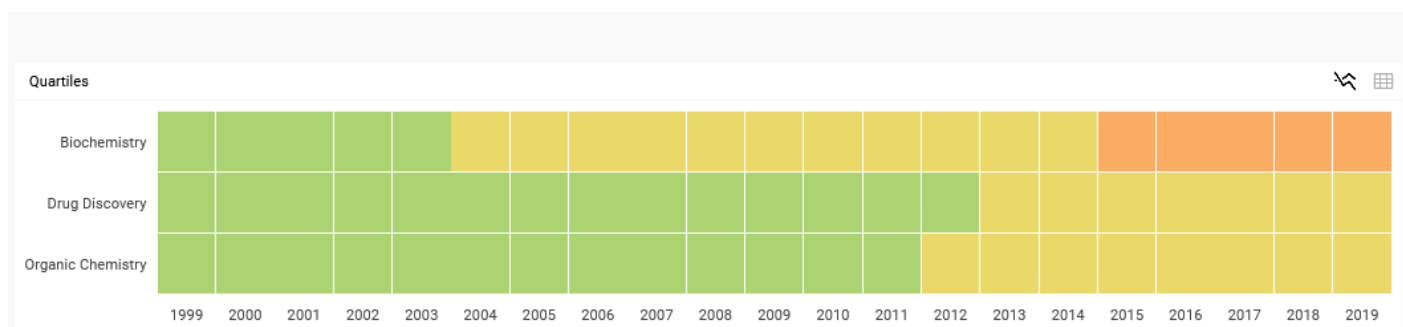
Tetrahedron Letters

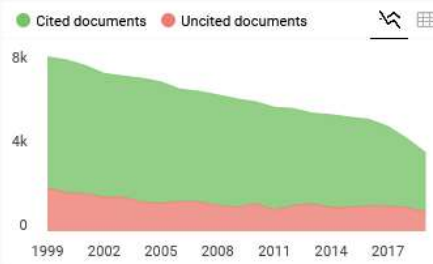
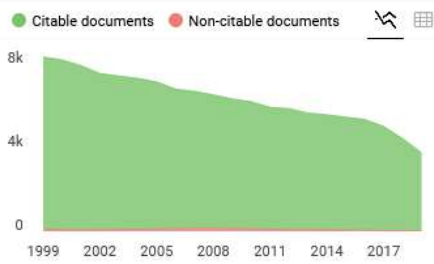
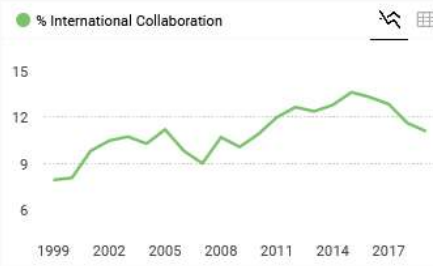
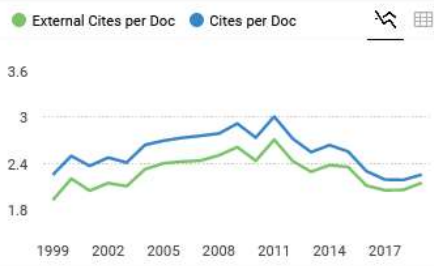
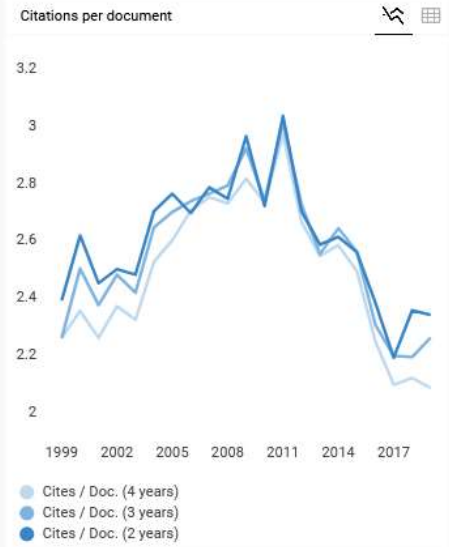
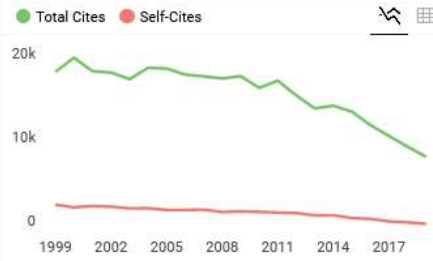
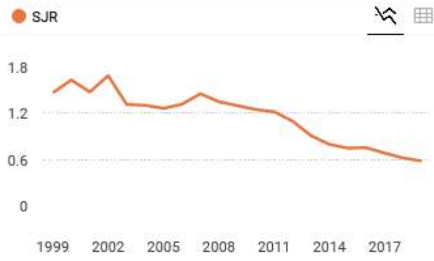
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SCOPE

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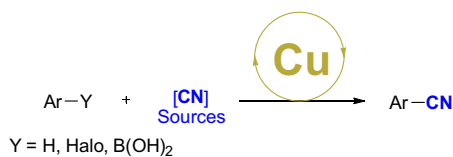
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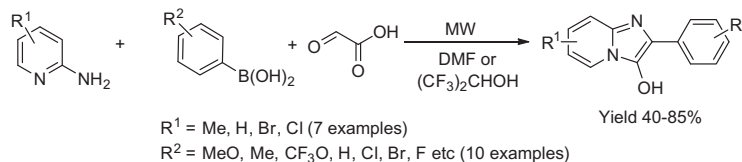


COMMUNICATIONS

An expeditious approach to access 2-arylimidazo[1,2-a]pyridin-3-ol from 2-amino pyridine through a novel Petasis based cascade reaction

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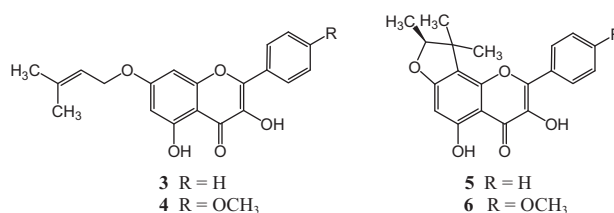
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Further prenylated flavonols from *Platanus acerifolia*'s unripe buds

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Mourad Kaouadji*

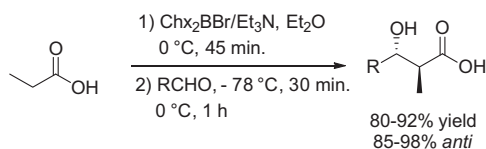


The toluene extract of defatted *Platanus acerifolia*'s fresh unripe buds afforded 8 metabolites. In all, prenylated flavonols 3–6 are reported for the first time in the plant kingdom.

anti-Selective enolboration–aldolization of propanoic acid

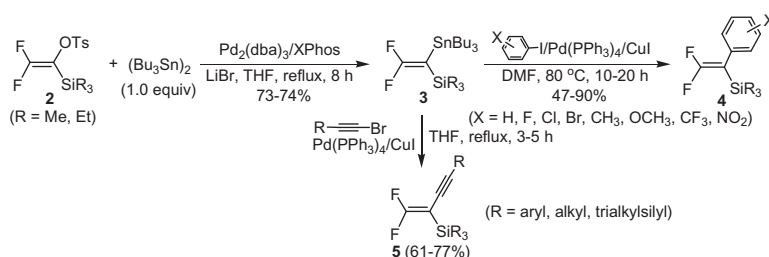
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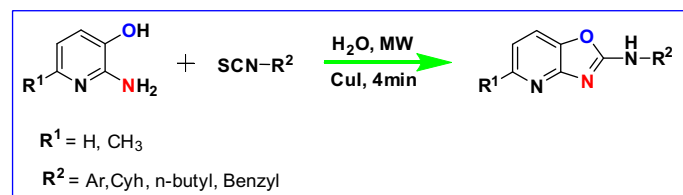
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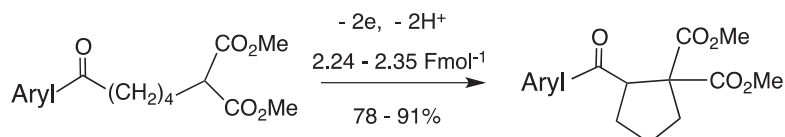
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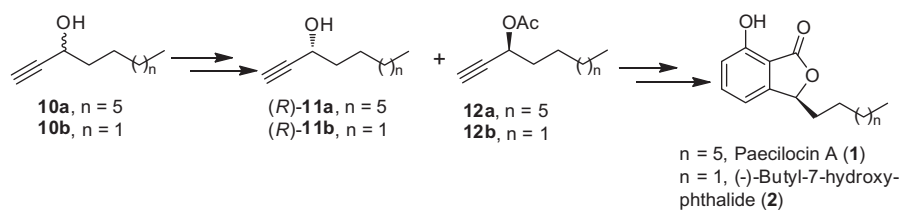
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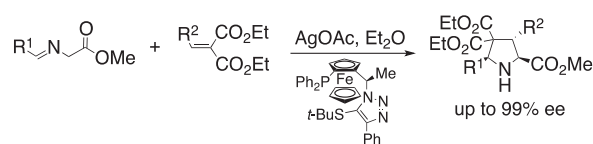
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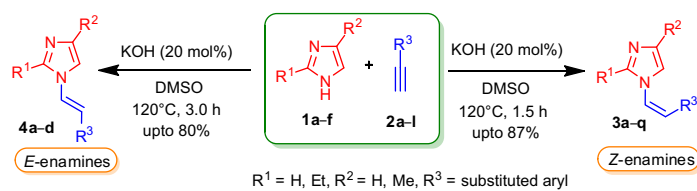
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Monika Patel, Rakesh K. Saunthawal, Akhilesh K. Verma*

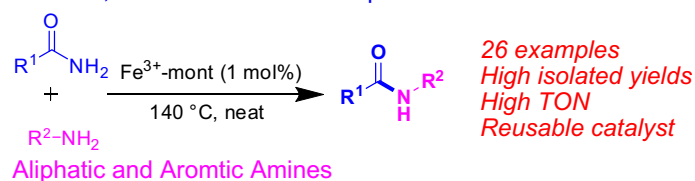


An efficient transition-metal free approach for the regio- and stereoselective addition of imidazoles **1a-f** onto alkynes **2a-l** to provide the *Z*- and *E* isomers of imidazolyl enamines **3a-q** and **4a-d** using catalytic amount of KOH is described. Stereoselectivity of the addition products (*Z* and *E* isomer) was found to be dependent upon time. Competitive experiments show that imidazole is less reactive than pyrrole and more reactive than aniline toward hydroamination.

**Fe³⁺-exchanged clay catalyzed transamidation of amides with amines under solvent-free condition**

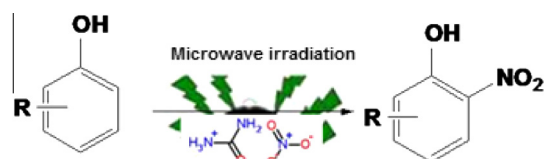
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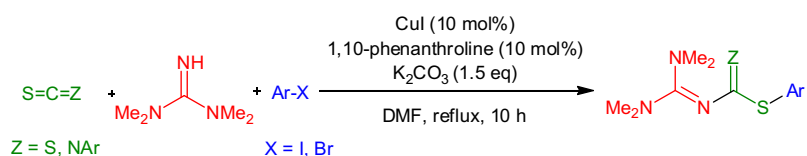
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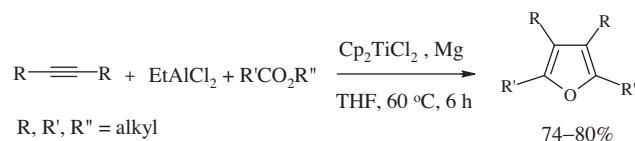
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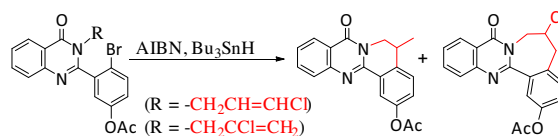
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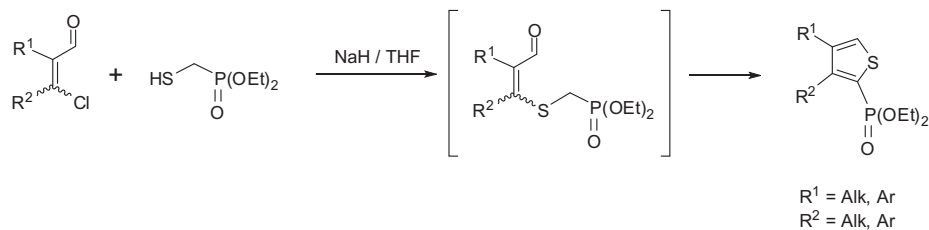
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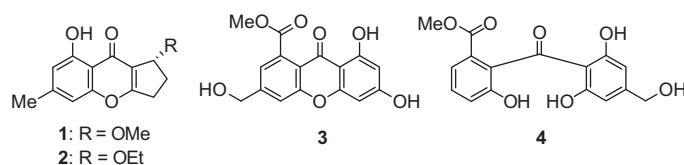
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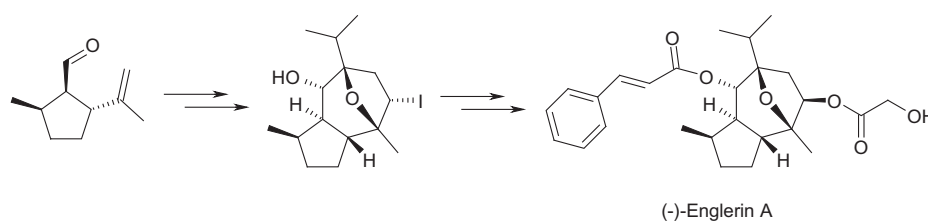
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**Total synthesis of (-)-Englerin A**

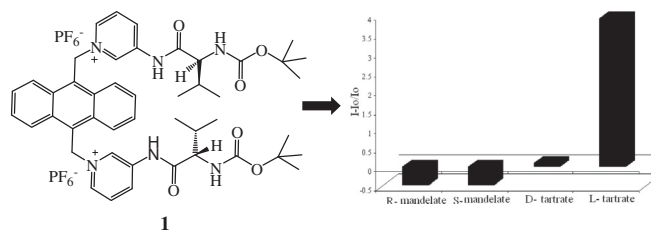
Jinghua Zhang, Shuyan Zheng, Wei Peng, Zhengwu Shen*

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**Anthracene-labeled pyridinium-based symmetrical chiral chemosensor for enantioselective recognition of L-tartrate**

Kumaresh Ghosh*, Tanmay Sarkar

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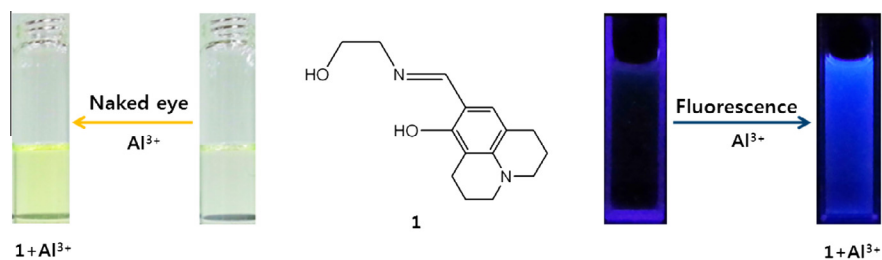
A new anthracene-based chiral chemosensor **1** has been designed and synthesized. L-Valine has been used as the chiral source in the design. The chemosensor **1** has been established as an efficient enantioselective sensor for L-tartrate over D-tartrate. The enantiomeric fluorescence difference ratio (*ef*) has been determined to be 29.38.



A fluorescent and colorimetric chemosensor for selective detection of aluminum in aqueous solution

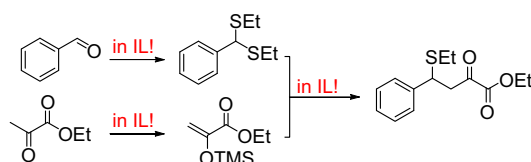
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Kyung Beom Kim, Dong Min You, Jun Hwi Jeon, Yo Han Yeon, Jong Ha Kim, Cheal Kim*

**Synthesis in ionic liquids only: access to α -oxo- γ -thio-esters via Mukaiyama coupling**

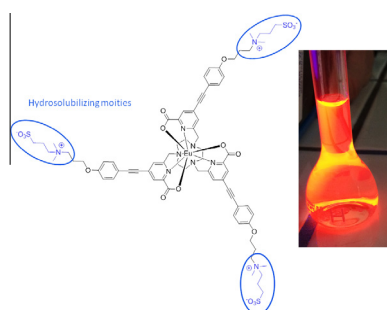
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Khoulood Jebri, Marie-Rose Mazières, Stéphanie Ballereau, Taicir Ben Ayed, Jean-Christophe Plaquevent, Michel Baltas*, Frédéric Guillen*

**Design and synthesis of europium luminescent bio-probes featuring sulfobetaine moieties**

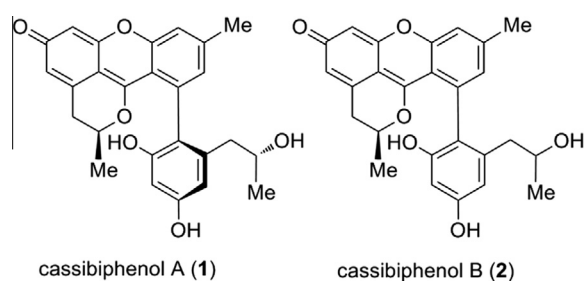
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Virginie Placide, Delphine Pitrat, Alexei Grichine, Alain Duperray, Chantal Andraud, Olivier Maury*

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

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Jun Deguchi, Tadahiro Sasaki, Yusuke Hirasawa, Toshio Kaneda, Idha Kusumawati, Osamu Shiota, Hiroshi Morita*



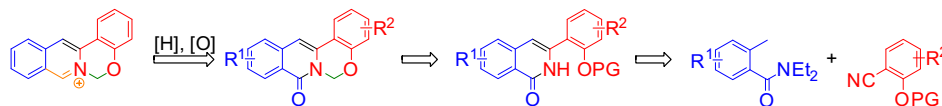
Chemical investigation of the flowers of *Cassia siamea* (Leguminosae), resulted in the isolation of two novel tetracycles connecting 5-(2-hydroxypropyl)benzene-1,3-diol, cassibiphenols A (1) and B (2). The structures were elucidated by analysis of the 1D, 2D NMR, and HRMS spectra. Synthesis of a tetracyclic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



Synthesis of novel 5-oxaprotoberberines as bioisosteres of protoberberines

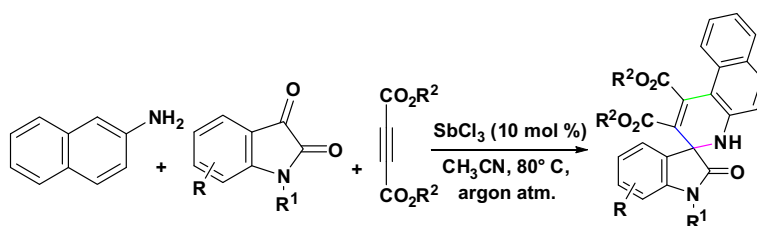
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Yifeng Jin, Daulat Bikram Khadka, Su Hui Yang, Chao Zhao, Won-Jea Cho*

**One-pot three-component reaction for the synthesis of biologically important spiro[benzo[f]quinoline-3,3'-indoline] derivatives**

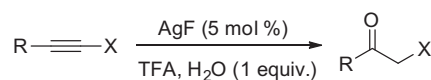
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Rajiv Karmakar, Utpal Kayal, Biswajit Bhattacharya, Gourhari Maiti*

**AgF/TFA-promoted highly efficient synthesis of α -haloketones from haloalkynes**

pp 1373–1375

Zheng-Wang Chen*, Dong-Nai Ye, Min Ye, Zhong-Gao Zhou, Shen-Huan Li, Liang-Xian Liu*



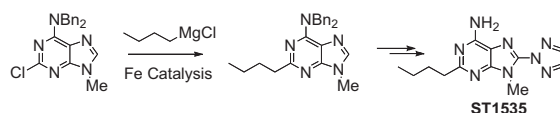
R = aryl, X = Cl, Br up to 95% yield

A AgF/TFA-promoted highly efficient synthesis of a wide range of α -haloketones from haloalkynes is described. The reactions are conducted under convenient conditions and provide products in moderate to excellent yields, with broad substrate scope, including a variety of aromatic chloroalkynes and bromoalkynes.

**Development of a practical and sustainable strategy for the synthesis of ST1535 by an iron-catalyzed Kumada cross-coupling reaction**

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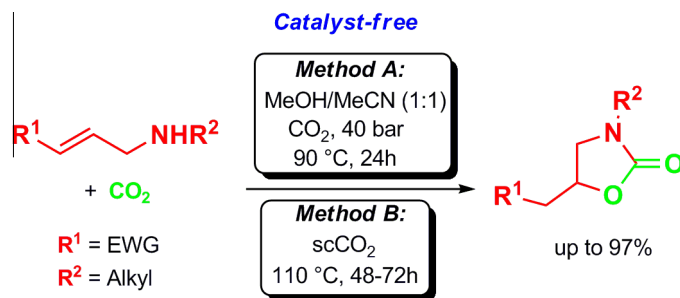
Francesca Bartocchini, Giovanni Piersanti*, Silvia Armaroli, Alberto Cerri, Walter Cabri*



A novel one-pot synthesis of oxazolidinones through direct introduction of CO₂ into allylamine derivatives

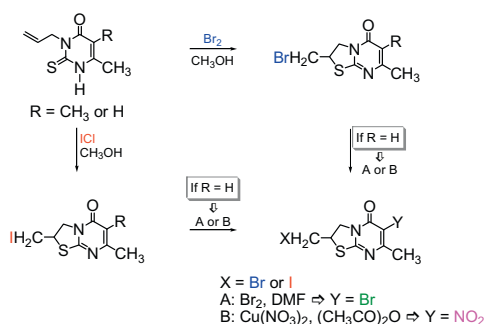
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Laura Soldi, Chiara Massera, Mirco Costa, Nicola Della Ca*

A facile synthesis of the novel thiazolo[3,2-*a*]pyrimidine derivatives

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Renata Studzińska*, Marcin Wróblewski, Aleksandra Karczmarzka-Wódzka, Renata Kołodziejka



*Corresponding author

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



Jun Deguchi^a, Tadahiro Sasaki^a, Yusuke Hirasawa^a, Toshio Kaneda^a, Idha Kusumawati^b, Osamu Shiota^c, Hiroshi Morita^{a,*}

^a Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

^b Faculty of Pharmacy, Airlangga University, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia

^c Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, 1314-1 Shido, Sanuki City, Kagawa 769-2193, Japan

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ABSTRACT

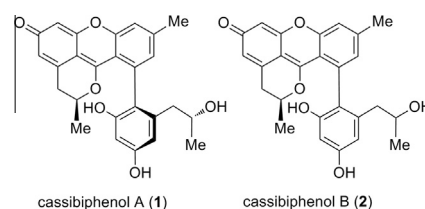
Chemical investigation of the flowers of *Cassia siamea* (Leguminosae), resulted in the isolation of two novel tetracycles connecting 5-(2-hydroxypropyl)benzene-1,3-diol, cassibiphenols A (**1**) and B (**2**). The structures were elucidated by analysis of the 1D, 2D NMR, and HRMS spectra. Synthesis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

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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 chemists⁶ 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 Na₂CO₃ aq and extracted with CHCl₃. CHCl₃-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**) was obtained as yellowish amorphous solids. **1** showed the molecular formula C₂₆H₂₄O₆, 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 ¹³C NMR spectra are presented in Table 1. The ¹³C NMR spectrum revealed 26 carbon signals due to one carbonyl carbon, twelve sp² quaternary carbons, six sp² and two sp³ methines, two sp³ methylenes, and three methyl groups. Among them, five sp² quaternary carbons (δ_C 156.7, 158.1, 159.0, 161.5, and 166.8) and two sp³ methine carbons (δ_C 68.6 and 79.0) were ascribed to those bearing an oxygen atom.

* Corresponding author. Tel./fax: +81 354985778.

E-mail address: moritah@hoshi.ac.jp (H. Morita).

Table 1
 ^1H NMR data [δ_{H} (J, Hz)] and ^{13}C NMR Data [δ_{C}] of cassibiphenols **1** and **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 ^1H - ^1H 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}

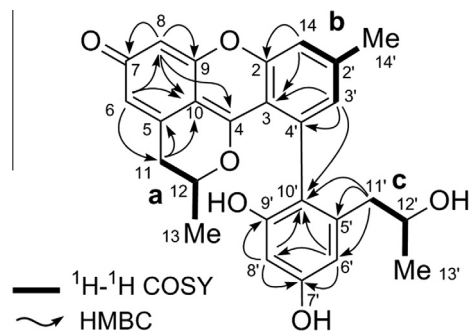


Figure 1. Selected 2D NMR correlations for cassibiphenol A (**1**) and B (**2**).

166.8. The presence of 5-(2-hydroxypropyl)benzene-1,3-diol was supported by ^1H 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 (H₂-11) 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/H₃-13', and H₃-13'/H₃-13 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**, $\text{C}_{26}\text{H}_{24}\text{O}_6$, which was determined by HRESIMS [*m/z* 433.1653 (*M*+*H*)⁺, +0.2 mmu]. ^1H 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 ^1H 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/H₃-13' indicating **2** was a stereoisomer 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-methylchromone¹⁴ producing chrobisiamone A,¹⁵ followed by cleavage of an ether bond, cyclization with the α,β -unsaturated ketone, and finally acid-promoted ring disclosure¹⁶ to produce an isochromen part as shown in Scheme 1.

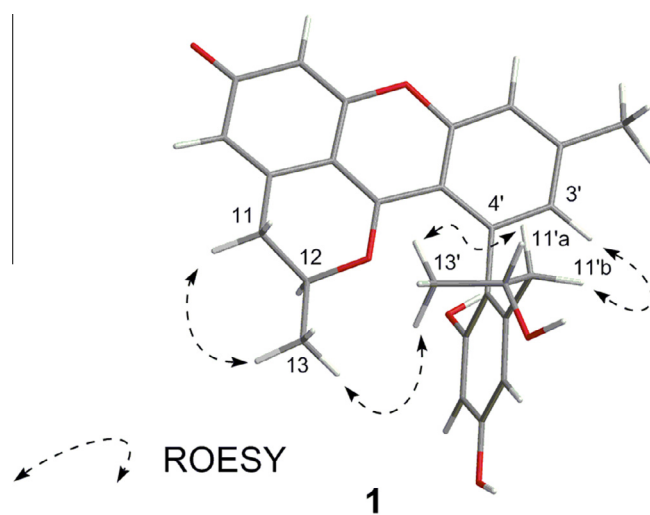


Figure 2. Selected ROESY correlations for cassibiphenol A (**1**).

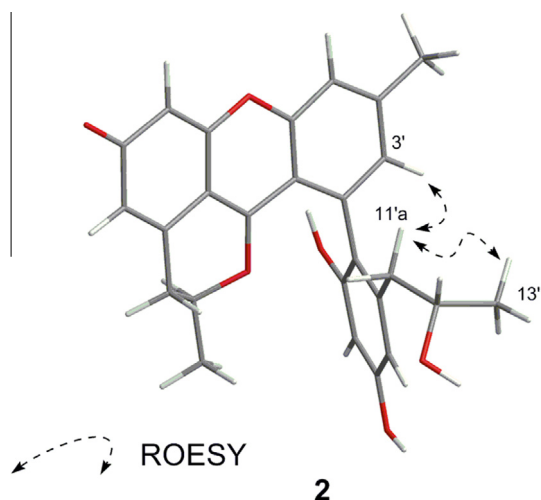
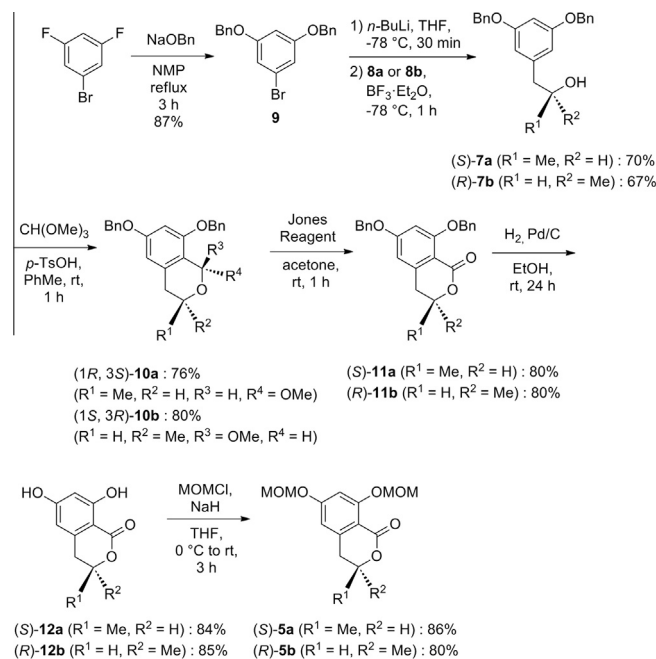


Figure 3. Selected ROESY correlations for cassibiphenol B (2).



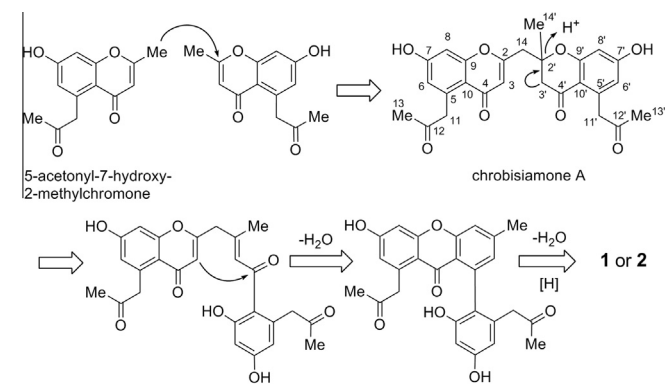
Scheme 3. Synthesis of enantiopure 3,4-dihydroisocoumarins, **5a** and **5b**.

nol **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 cyclization¹⁸ and Jones oxidation.¹⁹

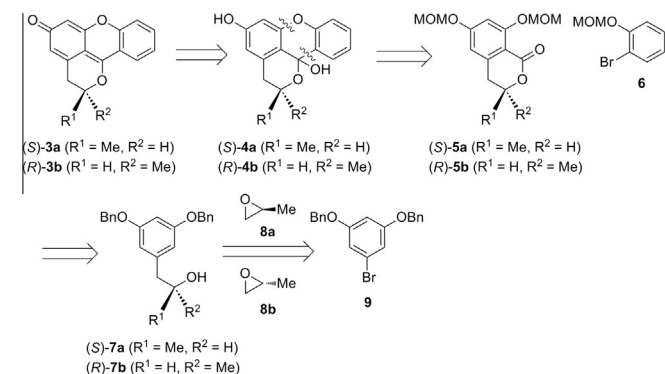
Our synthesis began with preparation of two enantiomerically pure MOM-protected *S*- or *R*-6-hydroxymellein (**5a** and **5b**), which was readily accessible from a known bromobenzene **9**²⁰ synthesized from commercially available 1-bromo-3,5-difluorobenzene. Regioselective boron trifluoride diethyl 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)/ $\Delta\epsilon$: 234 (+9.5) and 268 (+7.1)) {lit.²³ CD (MeOH) λ_{\max} (nm)/ $\Delta\epsilon$: 233 (+10.4) and 268 (+6.7)}, and *R*-6-hydroxymellein, **12b** (CD (MeOH) λ_{\max} (nm)/ $\Delta\epsilon$: 233 (-9.7) and 268 (-7.0)) {lit.²³ CD (MeOH) λ_{\max} (nm)/ $\Delta\epsilon$: 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

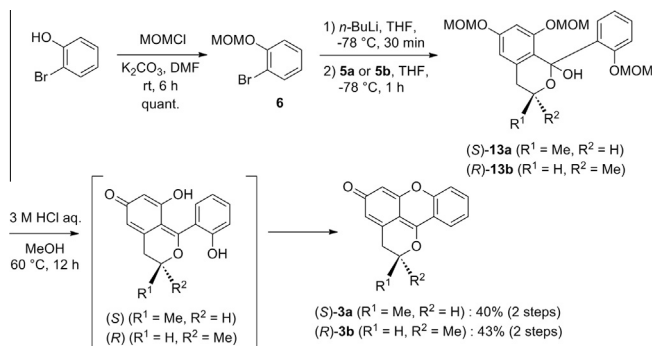


Scheme 1. Plausible biogenetic pathway for cassibiphenols A (1) and B (2).



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-hydroxymellein¹⁷ **5a** and **5b**, and MOM protected 2-bromophe-



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

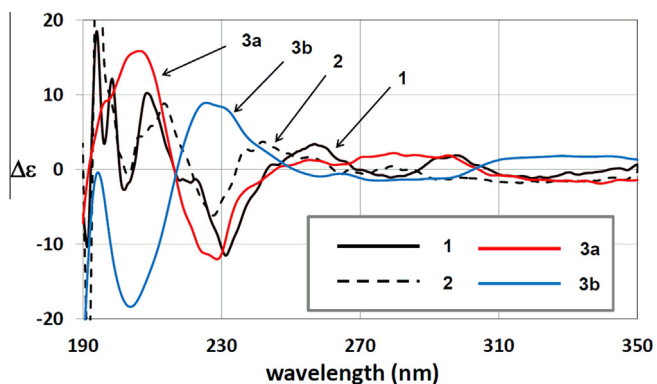


Figure 4. Comparison of CD spectra of **1**, **2**, **3a**, and **3b**.

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 1*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.

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Supplementary data

Supplementary data (experimental details, scanned copies of NMR spectra including ^1H NMR, ^{13}C NMR, ^1H – ^1H 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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- 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} ($\Delta\epsilon$) 202 (–2.7), 209 (+10.3), 231 (–11.5), and 257 (+3.4) nm; ^1H and ^{13}C NMR (Table 1); ESIMS (pos.) m/z 433 (M+H) $^+$; HRESIMS m/z 433.1655 (M+H) $^+$, calcd for $\text{C}_{26}\text{H}_{25}\text{O}_6$ 433.1651.
- 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} ($\Delta\epsilon$) 203 (–0.7), 214 (+8.8), 228 (–6.1), and 242 (+3.7) nm; ^1H and ^{13}C NMR (Table 1); ESIMS (pos.) m/z 433 (M+H) $^+$; HRESIMS m/z 433.1653 (M+H) $^+$, calcd for $\text{C}_{26}\text{H}_{25}\text{O}_6$ 433.1651.
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