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A Simple Biomimetic Synthesis of *dl*-Chamaejasmine, a Unique 3,3′-Biflavanone

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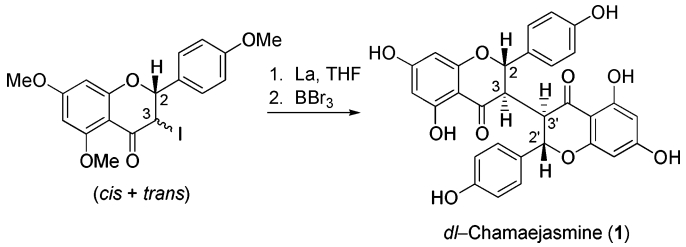
ABSTRACT



The first chemical synthesis of *dl*-chamaejasmine (1), a structurally unique 3,3′-biflavanone natural product, was achieved as shown above, by a two-step sequence starting from trimethyl ether derivatives of 3-iodonaringenin (*cis* + *trans*) involving (i) metallic lanthanum-mediated reductive dimerization in refluxing THF and (ii) global demethylation with BBr_3 in CH_2Cl_2. This synthesis represents a generally applicable biomimetic (reductive) radical dimerization approach to the 3,3′-biflavonoids.

Flavonoids are a diverse group of plant natural products that play important roles in plant growth, development, and self-defense,[1] and their wide ranges of physiological activities have been well recognized.[1] Chamaejasmine (**1**), a structurally unique biflavanone possessing a rare 3/3′ C−C linkage (Figure 1), was first discovered[2] by Huang and Zhang in 1979 from a medicinal plant *Stellera chamaejasmae* L. (known as Langdu in traditional herbal medicine in China) and identified as a C_2-symmetric racemate dimer of naringenin (**3**) at C-3. Many naturally occurring 3,3′-biflavanones have thereafter been isolated[3−10] from Langdu and other plants, including isochamaejasmine (**2**),[3a,b] the meso isomer

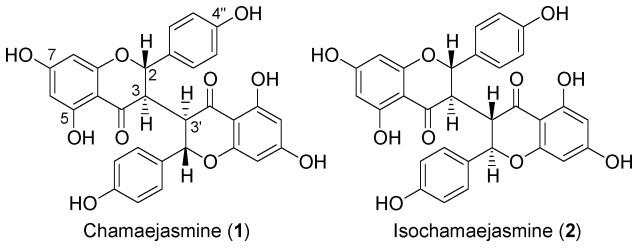


Figure 1. Structures of chamaejasmine (**1**) and its *meso*-isomer **2**.

(1) For reviews, see: (a) Geiger, H.; Quinn, C. In *The Flavonoids: Advances in Research*; Harborne, J. B., Mabry, T. J., Eds.; Chapman & Hall: London, 1982; Chapter 9, pp 505−534. (b) Plant Flavonoids in Biology and Medicine I: Biochemical, Pharmacological and Structure−Activity Relationships. *Progress in Clinical and Biological Research*; Cody, V., Middleton, E., Jr., Harborne, J. B., Eds.; Alan R. Liss, Inc.: New York, 1986; Vol. 213. (c) Plant Flavonoids in Biology and Medicine II: Biochemical, Cellular, and Medicinal Properties. *Progress in Clinical and Biological Research*; Cody, V., Middleton, E., Jr., Harborne, J. B., Beretz, A., Eds.; Alan R. Liss, Inc.: New York, 1988; Vol. 280.

(2) Huang, W.-K.; Zhang, Z.-J. *Kexue Tongbao* **1979**, *24*, 24; *Chem. Abstr.* **1979**, *90*, 135086m. The partial racemate of **1** was isolated later; cf. ref 3b.

(3) For leading references, see: (a) Niwa, M.; Chen, X.-F.; Liu, G.-Q.; Tatematsu, H.; Hirata, Y. *Chem. Lett.* **1984**, 1587. (b) Niwa, M.; Otsuji, S.; Tatematsu, H.; Liu, G.-Q.; Chen, X.-F.; Hirata, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3249. (c) Drewes, S. E.; Hudson, N. A.; Bates, R. B.; Linz, G. S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2809. (d) Castro, O.; Valverde, V. *Phytochemistry* **1985**, *24*, 367. (e) Nyandat, E.; Hassanali, A.; De Vicente, Y.; Multari, G.; Galeffi, C. *Phytochemistry* **1990**, *29*, 2361. (f) Baba, K.; Taniguchi, M.; Kozawa, M. *Phytochemistry* **1994**, *37*, 879. (g) Jiang, Z.-H.; Tanaka, T.; Sakamoto, T.; Kouno, I.; Duan, J.-O.; Zhou, R.-H. *Chem. Pharm. Bull.* **2002**, *50*, 137.

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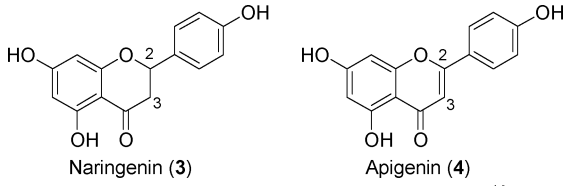
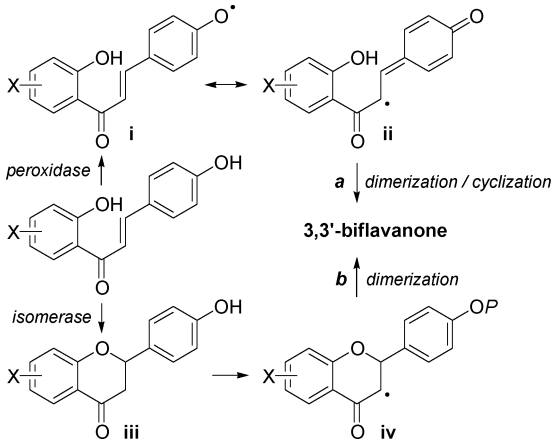
of **1**, other stereoisomers of **1**, and corresponding (ethereal or glycoside) derivatives, as well as other isomeric derivatives (i.e., diphysin[4] and chamaechromone[5]). 3,3′-Biflavonoids have been shown to exhibit a wide range of pharmacological activities, such as antiviral (HIV),[6] antibacterial,[7] and anti-inflammatory,[8] and potential antitumor activities.[9] Moreover, Yamada and Omura et al. have recently shown[10] that ethereal derivatives of **1** are potent antimalarials in vitro ($IC_{50} \approx 0.55$ μg/mL) against the chloroquinine-resistant strain of *Plasmodium falciparum*.

The intriguing structures of these highly oxygenated plant polyphenol substances have emerged as attractive synthetic targets.[11−14] Despite considerable synthetic efforts in the past two decades, including *oxidative* dimerization[11] of naringenin (**3**) or analogous flavanone derivatives, various *reductive* (chemical, photochemical, or electrochemical) dimerizations[12] of apigenin (**4**) or analogous flavone derivatives, hydrogenation[13] of 3,3′-biflavone derivatives, and other attempts,[14] chemical synthesis of **1** is still an unanswered challenge to date.[15] Herein we report the first synthesis of *dl*-**1** by a simple biomimetic approach, which would be generally applicable to the synthesis of 3,3′-biflavanones.



Botta and co-workers have recently realized[16] a direct biotransformation of chalcone substrates to the corresponding 3,3′-biflavanone products as a mixture of racemate and meso isomers, by the action of a purified plant peroxidase. The biosynthetic pathway was thus set forth (Scheme 1, pathway a) in which an initial phenolic radical intermediate **i** was proposed to tautomerize to **ii**, then dimerize at C-3, and subsequently cyclize to give 3,3′-biflavanones. Inspired by these biogenetic investigations,[17] we envisioned a biomimetic synthetic strategy (pathway b) in which a cyclic radical species **iv** derived from flavanone derivative **iii** is anticipated to undergo a biomimetic dimerization, leading to 3,3′-biflavanone in a direct fashion.

Scheme 1. Biomimetic Strategy to 3,3′-Biflavanones



In view of the previous difficulties in generating the C-3 radical species from the corresponding flavanone derivatives by oxidation methods,[11] we decided to explore an alternative reductive approach from readily accessible 3-halogenated flavanone derivatives.[18] Our initial attempts to reductively dimerize 3-iodoflavanone **5** with *n*-Bu_3SnH or $(n\text{-}Bu_3Sn)_2$ as mediators led to the predominate formation of corresponding flavanone and small yields of chalcone and flavone derivatives. After a survey of some metallic single electron

(4) Stermitz, F. R.; Mead, E. W.; Foderaro, T. A.; Castro, O. *Phytochemistry* **1993**, *34*, 287.

(5) (a) Jin, C.; Michetich, R. G.; Daneshtalab, M. *Phytochemistry* **1999**, *50*, 505. (b) Feng, B.-M.; Pei, Y.-H.; Hua, H.-M. *Chinese Chem. Lett.* **2002**, *13*, 738. (c) Tang, S.; Bremner, P.; Kortenkamp, A.; Schlage, C.; Gray, A. I.; Gibbons, S.; Heinrich, M. *Planta Med.* **2003**, *69*, 247.

(6) Ikegawa, T.; Ikegawa, A. JP Patent 08311056; *Chem. Abstr.* **1997**, *126*, 122450.

(7) Castro, O.; Lopez, J.; Vergara, A. *J. Nat. Prod.* **1986**, *49*, 680.

(8) Zeng, Y.-Q.; Recio, M. C.; Manez, S.; Giner, R. M.; Cerda-Nicolas, M.; Rios, J.-L. *Planta Med.* **2003**, *69*, 893.

(9) Fujiki, H.; Horiuchi, T.; Yamashita, K.; Hakii, H.; Suganuma, M.; Nishino, H.; Iwashima, A.; Hirata, Y.; Sugimura, T. *Prog. Clin. Biol. Res.* (*Plant Flavonoids Bio. Med.*) **1986**, *213*, 429.

(10) Nunome, S.; Ishiyama, A.; Kobayashi, M.; Otoguro, K.; Kiyohara, H.; Yamada, H.; Omura, S. *Planta Med.* **2004**, *70*, 76.

(11) For various attempts, see: (a) Molyneux, R. J.; Waiss, A. C., Jr.; Haddon, W. F. *Tetrahedron* **1970**, *26*, 1409. (b) Berge, D. D.; Kale, A. V.; Sharma, T. C. *Chem. Ind.* (London) **1980**, 787. (c) Shivhare, A.; Kale, A. V.; Berge, D. D. *Acta Chim. Hungar.* **1985**, *120*, 107. (d) Li, L.-Z.; Rui, Y.-J. *Beijing Daxue Xuebao* (*Nat. Sci. Ed.*) **1990**, *26*, 421; *Chem. Abstr.* **1991**, *114*, 185079. For relevant studies on the synthesis of brackenin, a 3,3′-bisdihydrochalcone, see: (e) Li, Y.-L.; Zhu, J.-P.; Zhang, F.-J.; Wang, Q. *Chem. J. Chinese Univ.* (Chinese Ed.) **1989**, *10*, 653; *Chem. Abstr.* **1990**, *112*, 197752. (f) Drewes, S. E.; Hogan, C. J.; Kaye, P. T.; Roos, G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1585. Although oxidative homocoupling of ketone enolates (for example, cf.: Frazier, R. H.; Jr.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408 and refs therein) is well-known, this method cannot be applied to 3,3′-biflavanone synthesis, due apparently to the inherent lability of flavanone under strong basic or acidic conditions.

(12) (a) Kirrstetter, R. G. H.; Vagt, U. *Chem. Ber.* **1981**, *114*, 630. (b) Li, Y.-L.; Zhang, F.-J.; Wang, Q. *Chinese J. Chem.* **1992**, *10*, 359; *Chem. Abstr.* **1993**, *119*, 95266. (c) Lu, K.-K.; Tan, Z.; Li, Y.-L.; Wang, X. *Chinese Chem. Lett.* **1995**, *6*, 143; *Chem. Abstr.* **1995**, *122*, 290497. (d) Chen, A.-H.; Cheng, C.-Y.; Chen, C. W. *J. Chinese Chem. Soc.* (Taipei) **2002**, *49*, 1105. (e) Yokoe, I.; Taguchi, M.; Shirataki, Y.; Komatsu, M. *J. Chem. Soc., Chem. Commun.* **1979**, 333. (f) Chen, C.-F.; Zhu, Y.; Liu, Y.-C.; Xu, J.-X. *Tetrahedron Lett.* **1995**, *36*, 2835. (g) Chen, A.-H.; Kuo, W.-B.; Chen, C.-W. *J. Chinese Chem. Soc.* (Taipei) **2003**, *50*, 123.

(13) (a) Zhu, J.-P.; Wang, Q.; Li, Y.-L. *J. Chem. Soc., Chem. Commun.* **1988**, 1549. (b) Wang, Q.; Zhu, J.-P.; Li, Y.-L. *Chinese Sci. Bull.* **1990**, *35*, 744; *Chem. Abstr.* **1991**, *114*, 6071. Further studies were unfruitful due to the reproducibility of these results (personal communications with Y.-L. Li).

(14) (a) Khan, M. S. Y.; Khan, M. H.; Javed, K. *Indian J. Chem.* **1990**, *29B*, 1101. (b) Lin, G.-Q.; Hong, R. *J. Org. Chem.* **2001**, *66*, 2877.

(15) Although a few earlier reports (cf.: refs 11b,c, 13b, and ref 10 of ref 11a) had described the preparation of some 3,3′-biflavanone derivatives, there are no conceivable spectroscopic evidences to support these claims.

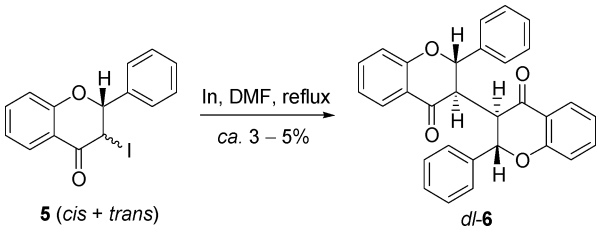
(16) (a) Botta, B.; Ricciardi, P.; Vitali, A.; Vinciguerra, V.; Garcia, C.; Delle-Monache, G. *Heterocycles* **1999**, *50*, 757. (b) Vitali, A.; Botta, B.; Delle-Monache, G.; Zappitelli, S.; Ricciardi, P.; Melino, S.; Petruzzelli, R.; Giardina, B. *Biochem. J.* **1998**, *331*, 513. (c) Botta, B.; Vinciguerra, V.; De Rosa, M. C.; Scurria, R.; Carbonetti, A.; Ferrari, F.; Delle-Monache, G.; Misiti, D. *Heterocycles* **1989**, *29*, 2175.

(17) Cf. also: Pelter, A.; Bradshaw, J.; Warren, R. F. *Phytochemistry* **1971**, *10*, 835.

(18) 3-Iodoflavanone derivatives are superior substrates comparing to the corresponding 3-bromo analogues. 3-Halogenated flavanone derivatives are selectively synthesized by either SeO_2-I_2 in refluxing CH_3CN, NIS in refluxing CCl_4, or $CuBr_2$ in refluxing ethyl acetate−chloroform (3:2, v/v) as a chromatographically separable mixture of *cis* and *trans* isomers in a ratio of ca. ∼4−5:1; see the Supporting Information for details.

reductants, we found that a racemate dimeric product **6** (mp 199−201 °C) was produced in a small yield (3∼5%) from 3-iodoflavanone **5** (mixture of cis and trans isomers), by the action of metallic indium in refluxing DMF,[19] along with the corresponding flavone (20%), chalcone (25%), and flavanone (5%) in the product mixture (Scheme 2). The identity of 3,3′-biflavanone *dl*-**6** was fully confirmed spectroscopically.

Scheme 2. Reductive Dimerization of **5** Mediated by In



Interestingly, a *dehalogenated* dimeric product, likely to be 3,3′-biflavanone **6**, was distinctly observed (Figure 2, *m*/*z* 447.1596) in the FT-ICR (SIMS) HR mass spectrometry analysis of iodide **5**, which implies a ready homolysis of the C−I bond and subsequent radical dimerization may have taken place during the collisional activation.[20]

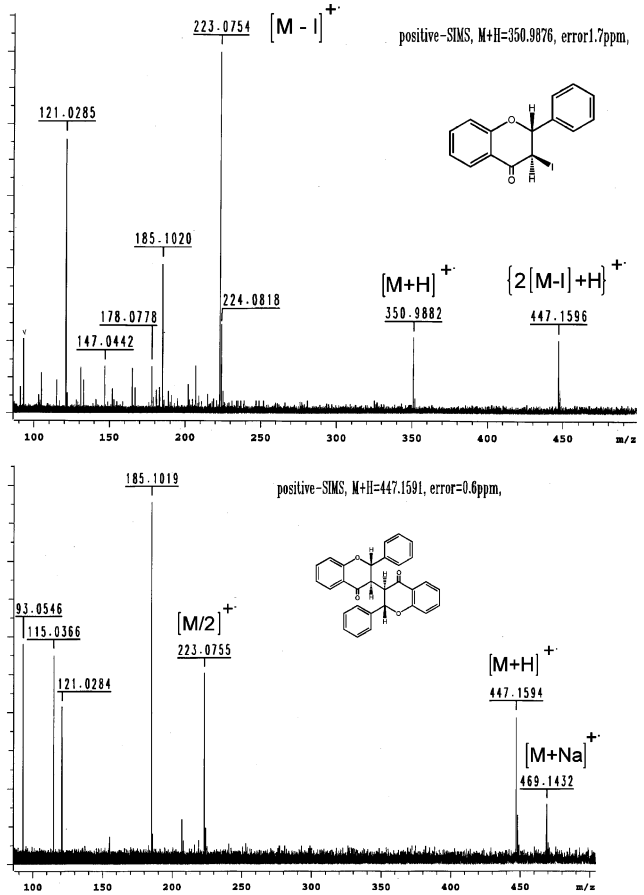
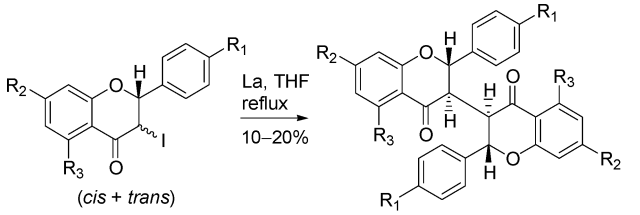


Figure 2. HRMS (SIMS) spectra of **5** (above) and **6** recorded on a Bruker Daltonics APEX II 47e FT-ICR mass spectrometer.

Encouraged by these initial results, we next examined metallic lanthanoids as reducing agents in view of their recent use[21] in reductive homocoupling of alkyl halides. Among available lanthanoid metals we screened,[22] lanthanum turned out to be the most effective reductant for the reductive dimerization of 3-iodoflavanone derivatives in refluxing THF. Thus, racemate dimers **6**, **10**, and **11** were obtained in an average isolated yield of 15−20% from the corresponding 3-iodoflavanones **5**, **7**, and **8** respectively, after preparative TLC purification (Scheme 3). Other major isolable products include the corresponding flavanone (5%), chalcone (25%), and flavone (15%) derivatives, which are recyclable to the starting 3-iodoflavanone derivatives in principle. Remarkably, all dimerization products were obtained solely as racemates[23] regardless of the stereochemistry (cis or trans) of the starting 3-iodoflavanone derivatives employed.

Scheme 3. Biomimetic Synthesis of *dl*-Chamaejasmine (**1**)



5, $R_1 = R_2 = R_3$ = H
7, R_1 = OMe, $R_2 = R_3$ = H
8, $R_1 = R_2$ = OMe, R_3 = H
9, $R_1 = R_2 = R_3$ = OMe

dl-**6**, $R_1 = R_2 = R_3$ = H
dl-**10**, R_1 = OMe, $R_2 = R_3$ = H
dl-**11**, $R_1 = R_2$ = OMe, R_3 = H
dl-**12**, $R_1 = R_2 = R_3$ = OMe (*ca.*10%)
dl-**13**, $R_1 = R_2$ = OMe, R_3 = OH
dl-**1**, $R_1 = R_2 = R_3$ = OH

a: BBr_3, CH_2Cl_2, −78 °C to r.t., 24 h (70%)

The reductive dimerization of 3-iodonaringenin trimethyl ether **9** proceeded smoothly under the above conditions (La, THF, refluxing) to give *dl*-chamaejasmine hexamethyl ether **12** (from petroleum ether−EtOAc, mp 185−187 °C)[24] in 10% isolated yield.[25] Global demethylation of *dl*-**12** was achieved by exposure to excess BBr_3 (10 equiv) in CH_2Cl_2 (−78 °C to rt, 24 h) to give fully demethylated *dl*-**1** (from acetone, mp 293−295 °C)[26] in 70% isolated yield. The synthetic *dl*-**1** was identical in every respect (TLC mobility,

(19) Cf.: Ranu, B. C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* **1998**, *39*, 9557. Slow reductive dehalogenation occurred at lower reaction temperature. For a recent review on the use of indium in organic synthesis, see: Podlech, J.; Maier, T. C. *Synlett* **2003**, 633.

(20) This phenomenon cannot be observed by other ionization methods (i.e., EI, ESI, or FAB). Substituted 3-iodoflavanone derivatives **7**−**9** behave similarly; see Table 2 of the Supporting Information (file 1).

(21) Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 966.

(22) Use of other metals, i.e., Ce, Nd, Sm, Yb, Lu, etc., gave mainly or exclusively a product mixture of the corresponding chalcone and flavone.

(23) Mesomeric dimers were not detectable by ^{1}H NMR analysis of the crude reaction products. As one reviewer pointed out, we cannot rule out the possibility that the meso dimer undergoes a rapid homo cleavage at C-3/C-3′. We are currently working on the asymmetric synthesis of chiral naringenin derivatives (i.e., **9**) and hope to test this possibility in our subsequent work.

IR, MS, and NMR spectroscopic properties) via direct comparison with an authentic sample of chamaejasmine racemate isolated by Huang and Zhang. A partially demethylated tetramethyl ether *dl*-**13** (trihydrate from petroleum ether−acetone, mp 118−120 °C) was obtained when the above demethylation reaction was quenched in 1 h, and its stereostructure was verified by a single-crystal X-ray diffraction analysis (Figure 3).[27]

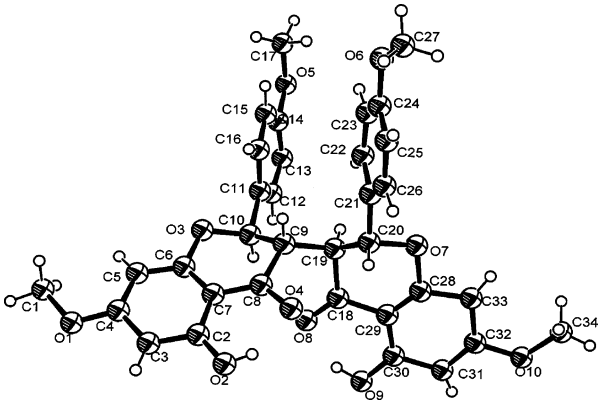
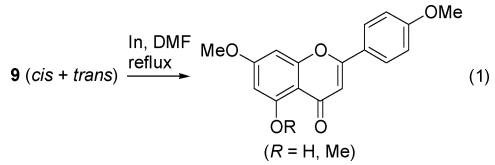


Figure 3. X-ray crystal structure of **13**.

The conformation revealed[28] by the unique C_2-symmetric X-ray crystal structure of *dl*-**13** may suggest a preferable transition conformational alignment (Figure 4) for this highly stereoselective radical homocoupling process, in which a $\pi-\pi$ stacking interaction (see arrows) might be responsible for directing the predominate *Re*−*Re* (or *Si*−*Si*) facial-selective radical dimerization.[29]

(24) A melting point of 117−119 °C (from *n*-hexane) was recorded for a partial racemate of hexamethyl ether derivative of (2*S*,3*R*)-chamaejasmine (enantiomeric ratio of ca. 2:1) by Galeffi et al. (ref 3e).

(25) It is evident that 5-methoxylated 3-iodoflavanone derivatives gave a relatively lower yield of dimerization products, due probably to the formation of a more delocalized metal-chelated radical species, while metallic indium could not induce the desired C-3 radical dimerization of 5-methoxylated 3-iodoflavanone derivatives, led to the formation of the corresponding dehydrohalogenatated and demethylated flavone products instead (eq 1):



(1)

(26) A melting point of 309 °C (uncorrected, recrystallized from ethanol) for racemate chamaejasmine was recorded by Huang and Zhang (ref 2).

(27) See the Supporting Information for detailed X-ray crystallographic data.

(28) Cf.: Jiang, R.-W.; Ye, W.-C.; Woo, K.-Y.; Du, J.; Che, C.-T.; But, P. P.-H.; Mak, T. C. W. *J. Mol. Struct.* **2002**, *642*, 77.

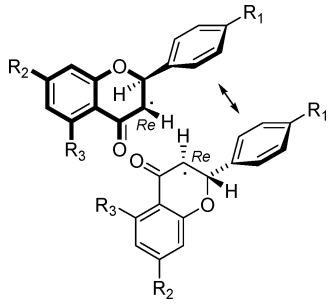


Figure 4. Possible transition assembly of radical dimerization.

In summary, a simple and general approach based on a biomimetic (reductive) radical dimerization strategy[30] was developed for the stereoselective synthesis of 3,3′-biflavanones, by which the first chemical synthesis of *dl*-chamaejasmine (**1**) was achieved. This method would facilitate further evaluation of 3,3′-biflavanones as potential chemotherapeutical agents or a novel type of C_2-symmetric ligand[31] in asymmetric catalysis. Further investigations along these lines are underway in our laboratory.[23]

Acknowledgment. This paper is dedicated in memory of the late Wen-Kui Huang, the discoverer of chamaejasmine. We are grateful to Dr. Xin-Ping Yang for mass spectrometry and Mr. Li-Xiang Cai for X-ray crystallographic analysis assistance, respectively. We thank the National Natural Science Foundation of China (Distinguished Youth Fund 29925204 and Group Fund 20021001) for financial support. The Cheung Kong Scholars program is gratefully acknowledged.

Supporting Information Available: Detailed experimental procedures, spectral data and spectrum of compounds **1** and **5**−**13**. X-ray crystallographic data of compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) For a recent *oxidative* radical dimerization strategy in natural product synthesis, see: Nicolaou, K. C.; Gray, D. L. F. *J. Am. Chem. Soc.* **2004**, *126*, 607; *Angew. Chem., Int. Ed.* **2001**, *40*, 761. In contrast, plant peroxidase-catalyzed biotransformation of chalcone derivatives gave the corresponding 3,3′-biflavanones as a mixture of racemate and *meso* isomers (cf.: ref 16), and *reductive* dimerization of flavone derivatives produced a mixture of racemic and *meso* isomers of 2,2′-biflavanones (cf. ref 12).

(30) For other representative examples of this *biomimetic* radical dimerization strategy in natural product synthesis, see: (a) Scott, A. I.; McCapra, F.; Hall, E. S. *J. Am. Chem. Soc.* **1964**, *86*, 302. (b) Hendrickson, J. B.; Goschke, R.; Rees, R. *Tetrahedron* **1964**, *20*, 565. (c) Barton, D. H. R.; Deflorin, A. M.; Edwards, O. E. *J. Chem. Soc. 1956*, 530.

(31) An asymmetric synthesis of 3,3′-biflavanones based on this approach can be envisioned starting from optically pure flavanones.