Total Synthesis and Stereochemical Confirmation of 2,5-Diaryl-3,4-dimethyltetrahydrofuran Lignans: (+)-Fragransin A_2, (+)-Galbelgin, (+)-Talaumidin, (–)-Saucernetin and (–)-Verrucosin

Stephen Hanessian,* Gone Jayapal Reddy

Department of Chemistry, Université de Montréal, C.P. 6128, Succursale Centre-ville, Montréal, Québec, H3C 3J7, Canada
E-mail: stephen.hanessian@umontreal.ca

Received 25 October 2006

Abstract: A new ring closure to tetrasubstituted tetrahydrofurans from the intramolecular attack of an OMOM ether onto a benzylic mesylate proceeds through a quinonoid intermediate or by direct S_N2 displacement. The synthesis of diastereomeric biologically active natural lignans is described utilizing this general methodology.

Key words: lignans, tetrahydrofurans, quinonoid intermediate, cycloetherification, enantioselective synthesis

Among the multitude of natural products produced by secondary plant metabolites are the lignans.[1] The growing interest in this class of substituted tetrahydrofurans stems from their potent activities against a variety of therapeutically relevant areas such as cancer, infection, inflammation, immunosuppression and their unique antioxidant properties.[2]

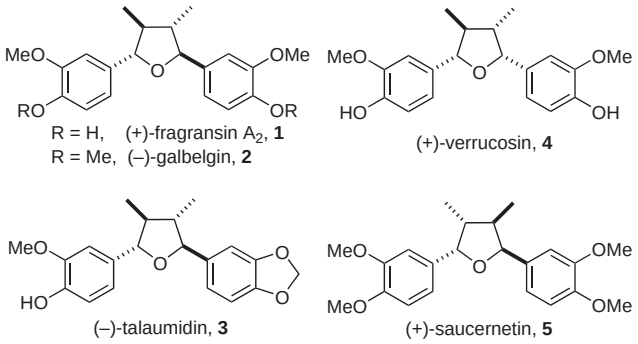


Figure 1 Structures and proposed absolute configurations of representative 2,5-diaryl-3,4-dimethyltetrahydrofurans (lignans).

2,5-Diaryl-3,4-dimethyl-substituted tetrahydrofurans are an important subclass of lignans, with several configurationally distinct members, often varying in the nature of the aromatic ether substituents. They are particularly different with regard to the relative orientations of substituents as illustrated in the proposed structures of fragransin A_2,[3] galbelgin[4] and talaumidin[5] for one group (*anti*/*anti*/*anti*), saucernetin[6] (*syn*/*anti*/*syn*), and verrucosin[3a,7] (*anti*/*anti*/*syn*) for another group (Figure 1).

Lignans are biologically derived from two phenylpropanoid units by oxidative dimerization, and they may be found in either enantiomeric form in nature. Although their biological role in plants is not clear, they may be involved in specific defense mechanisms under hostile stress. In spite of their relatively modest level of structural complexity, lignans are endowed with a host of biological activities. As such they are ideal 'small molecule' natural products for the development of potential chemotherapeutic agents. For example (+)-fragransin A_2 and (–)-galbelgin are inhibitors of NO production,[8] while (–)-talaumidin exhibits neuroprotective activity in the rat.[9]

In most instances only relative configurations have been determined and further studies have relied on spectroscopic and correlation data to assign absolute configurations.[3–7,10] Efforts in enantioselective synthesis of these lignans have been sparse.[11] Often, racemic (or *meso*) mixtures resulting from oxidative coupling of diaryl 1,4-ketones have been obtained,[12] and separated by chiral HPLC.[13] The first enantioselective synthesis of (–)-talaumidin (**3**) was reported only recently.[9]

We report herein a general strategy for the stereocontrolled total synthesis of a series of known lignans or their enantiomers as illustrated in Figure 2. The strategy capitalizes on the utilization of a common intermediate, from which different stereochemical variants can be obtained by varying the nature of a directing *p*-substituent on one of the aromatic moieties, in conjunction with the stereochemistry of the benzylic ether group.

Intermediate **6** is readily available in enantiomerically pure form as recently reported in the total synthesis of manassantin A, B and B_1 (Scheme 1).[14] Treatment with 4-benzyloxy-3-methoxyphenylmagnesium bromide in the presence of $CeCl_3$ as an additive[15] gave an epimeric mixture of alcohols, which could be separated into major (**8**) and minor (**9**) compounds as MOM ethers, after removal of the TBS and allyl groups. Oxidation of the mixture of alcohols **7a** and **7b** under Dess–Martin conditions to the ketone, followed by reduction with $NaBH_4$ in the presence of $CeCl_3$[16] gave the *R*-alcohol **7b** as the major product (90:10, Scheme 2). Protection of **7b** as the MOM ether, followed by de-O-silylation gave **10**. Mesylation, resulted in cyclization to the protected lignan **11** in 90% yield, most likely proceeding through a quinonoid intermediate. Deprotection of the allyl and benzyl ethers afforded (+)-fragransin A_2 (**1**),[17] which upon O-methylation led to (+)-

SYNLETT 2007, No. 3, pp 0475–0479
Advanced online publication: 07.02.2007
DOI: 10.1055/s-2007-968019; Art ID: S18006ST

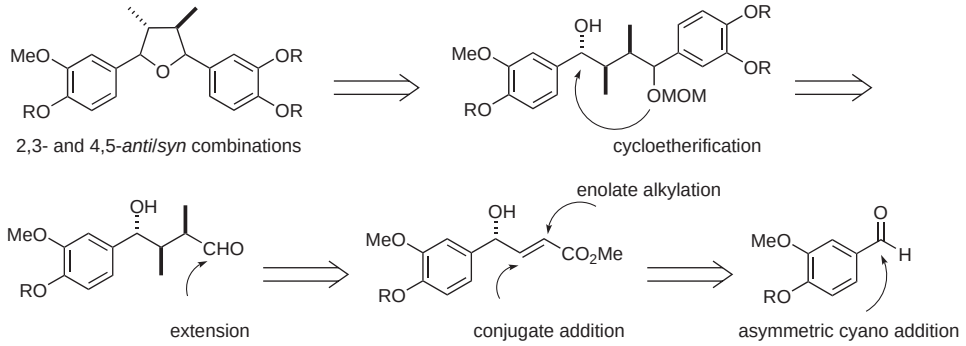
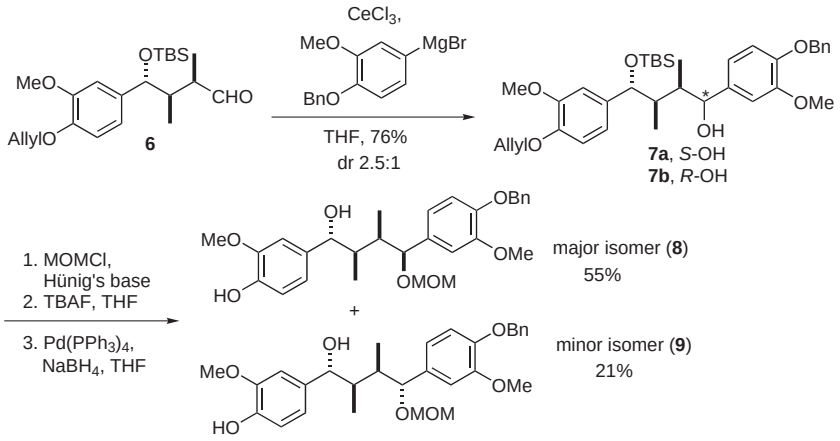


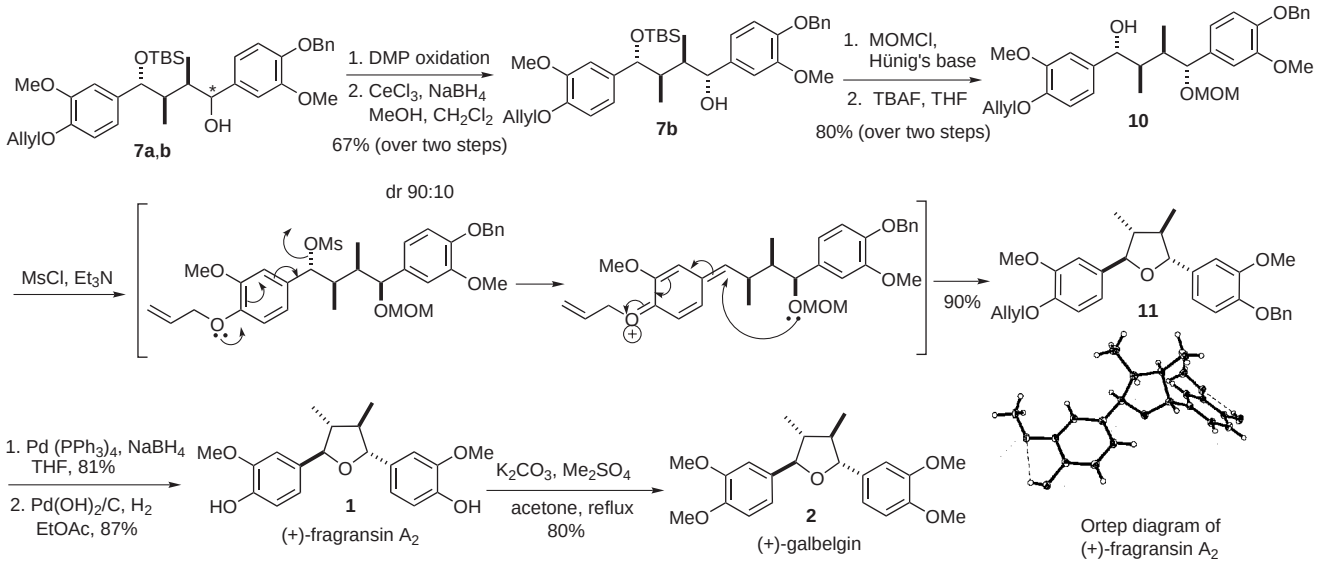
Figure 2 Disconnective analysis.



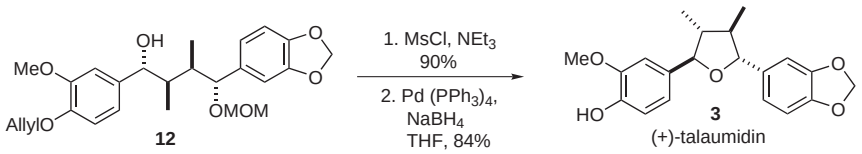
Scheme 1 Synthesis of compound **8** and **9**.

galbelgin (**2**).[18] The assigned structures and configurations were confirmed by a single crystal X-ray analysis of synthetic (+)-fragransin A_2 (**1**). Although the optical rotation of **1** is in accord with the reported value, the absolute configuration should be revised. Thus, our synthetic sequence establishes the correct absolute configuration of (+)-fragransin A_2 (**1**) as shown in Scheme 2 and relates it to (+)-galbelgin (**2**; rather than to its enantiomer as originally assumed,[3] Scheme 1).

The synthesis of (+)-talaumidin was completed in the same manner from the 3,4-methylenedioxyaryl intermediate **12**, obtained from **6** as described in Scheme 1 and Scheme 2. Intramolecular displacement of the mesylate also took place in a highly face selective attack on a



Scheme 2 Total synthesis of (+)-fragransin A_2 (**1**) and (+)-galbelgin (**2**). Revised absolute configuration of (+)-fragransin A_2.



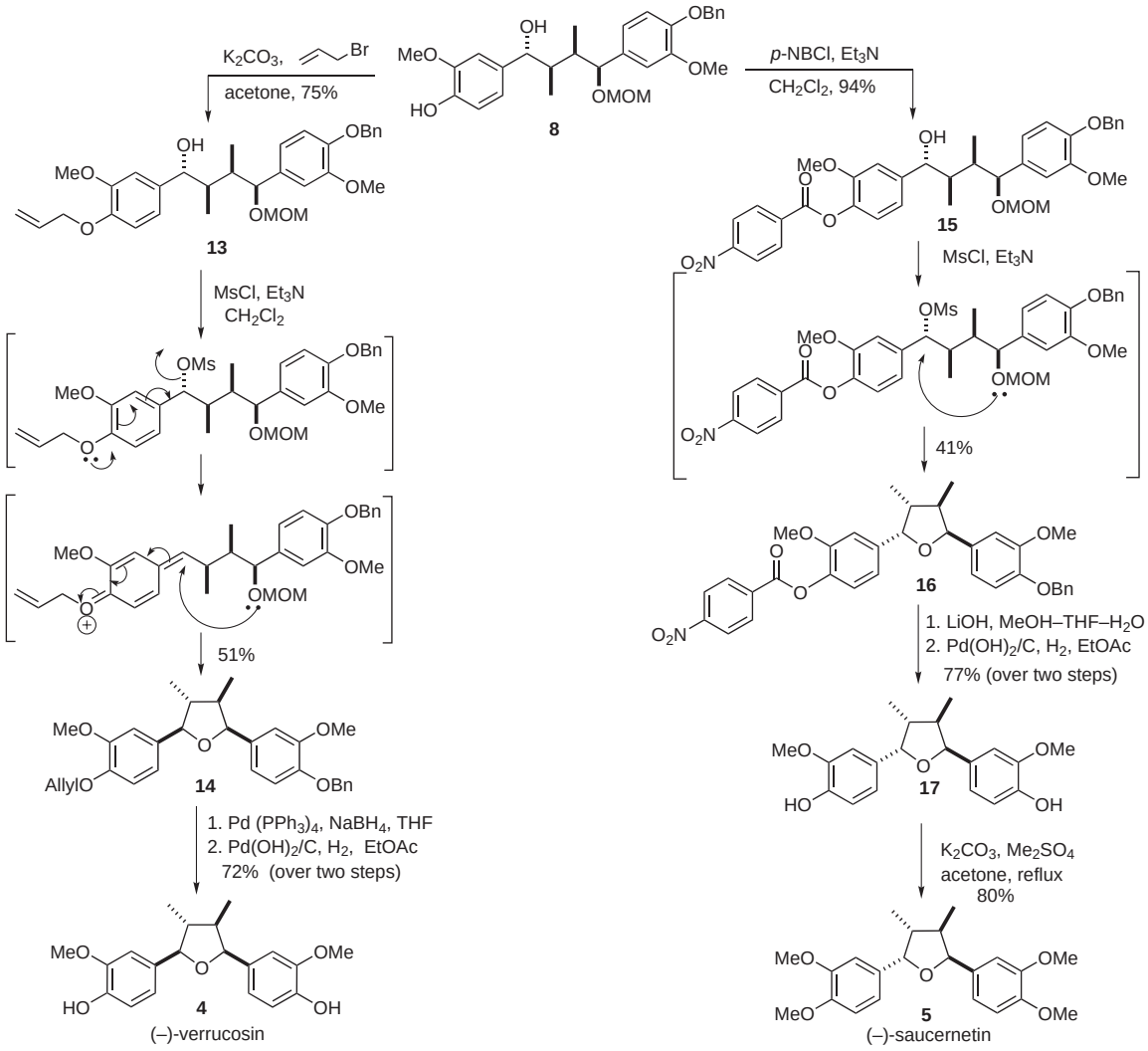
Scheme 3 Total synthesis of (+)-talaumidin (**3**).

quinonid intermediate to give, after allyl deprotection, (+)-talaumidin (**3**) in excellent overall yield (16 steps, 12.7% overall yield, Scheme 3).[19]

The authors of the recent paper,[9] describing the synthesis of natural (–)-talaumidin, utilize Evans aldol chemistry[20] to set up an *anti*-aldol intermediate, which is followed by a series of functional group adjustments and extensions that comprise three oxidations, a Tebbe olefination, and a Brown hydroboration leading to a lactone intermediate, before the second aryl group is introduced. Nevertheless, (–)-talaumidin was obtained in 16 steps and 10.7% overall yield.[9]

The synthesis of (–)-verrucosin (**4**) was initiated with the epimeric benzylic alcohol **13**, available as the major isomer in the original Grignard addition (Scheme 4). Again mesylation led directly to the tetrahydrofuran **14** which upon deprotection gave (–)-verrucosin (**4**).[21] The intramolecular cyclization of **13** to **14** was less efficient (51% yield compared to 90% for **10** to **11**), although only one diastereomer was formed. Presumably, the trajectory of attack on the quinonoid oxonium ion intermediate in the case of **11** (oxonium ion **A**), is more favorable compared to that leading to **14** (oxonium ion **B**) as illustrated in Figure 3.

Applying the same strategy to a *p*-nitrobenzoyl substituent, readily available from **8**, resulted in the direct formation of the *syn*/*anti*/*syn*-tetrahydrofuran **16** through an S_N2-type reaction (Scheme 4).



Scheme 4 Total synthesis of (–)-verrucosin (**4**) and (–)-saucernetin (**5**).

Deprotection of the ester and benzyl ether groups gave **17** which was O-methylated to (–)-saucernetin (**5**).[22] Our synthesis confirms the proposed structure (Figure 1), however, the reported[6c] sign of optical rotation should be reversed.

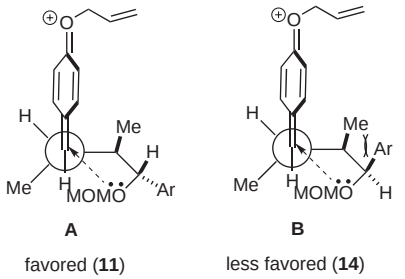


Figure 3 Favored (A) and less favored (B) transition states of quinonoid oxonium ions.

In conclusion, we have described a general method for the intramolecular cyclization of suitably disposed and functionally differentiated 1,4-benzylic alcohols as a 1,4-diaryl-2,4-dimethyl acyclic framework, to the corresponding tetrasubstituted tetrahydrofurans. A *p-O*-allyl ether group assists in the facile departure of a benzylic mesylate through the formation of quinonoid oxonium ion intermediate which in turn is attacked in an intramolecular face selective fashion by the ether oxygen of a MOM ether. When an ester group (*p*-NB) replaces the allyl group, tetrahydrofuran formation proceeds in an S_N2-type manner. Thus, by selecting the aromatic substituents, and the configuration of the OMOM-substituted benzylic carbon, it is possible to access a diverse set of configurationally distinct 2,5-diaryl-3,4-dimethyl-substituted tetrahydrofuran lignans of natural origins, as well as their enantiomers.

Acknowledgment

We thank NSERC for financial assistance, and Navjot Chahal for assisting in the preparation of some intermediate compounds. We also thank Michel Simard for X-ray crystal structure analysis.

References and Notes

(1) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183; and earlier reviews in this series.

(2) (a) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, *22*, 696. See also: (b) Li, G.; Ju, H. K.; Chang, H. W.; Jahng, Y.; Lee, S.-H.; Son, J.-K. *Biol. Pharm. Bull.* **2003**, *26*, 1039. (c) Lopes, N. P.; Kato, M. J.; Yoshida, M. *Phytochemistry* **1999**, *51*, 29. (d) Kraft, C.; Jenett-Siems, K.; Kohler, I.; Tofern-Reblin, B.; Siems, K.; Bienzle, U.; Eich, E. *Phytochemistry* **2002**, *60*, 167. (e) Zhai, H.; Inoue, T.; Moriyama, M.; Esumi, T.; Mitsumoto, Y.; Fukuyama, Y. *Biol. Pharm. Bull.* **2005**, *28*, 289. (f) Zhai, H.; Nakatsukasa, M.; Mitsumoto, Y.; Fukuyama, Y. *Planta Med.* **2004**, *70*, 598.

(3) (a) Hattori, M.; Hada, S.; Kawata, Y.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Chem. Pharm. Bull.* **1987**, *35*, 3315. (b) Kasahara, H.; Miyazawa, M.; Kameoka, H. *Phytochemistry* **1996**, *43*, 111.

(4) (a) Takaoka, D.; Watanabe, K.; Hiroi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3564. (b) Lopes, N. P.; Blumenthal, E. E. A.; Cavalheiro, A. J.; Kato, M. J.; Yoshida, M. *Phytochemistry* **1996**, *43*, 1089. (c) Parmar, V. S.; Jain, S. C.; Gupta, S.; Talwar, S.; Rajwanshi, V. K.; Kumar, R.; Azim, A.; Malhotra, S.; Kumar, N.; Jain, R.; Sharma, N. K.; Tyagi, O. M.; Lawrie, S. J.; Errington, W.; Howarth, O. W.; Olsen, C. E.; Singh, S. K.; Wengel, J. *Phytochemistry* **1998**, *49*, 1069.

(5) Vieira, L. M.; Kijjoa, A.; Silva, A. H. S.; Mondranondra, I.-O.; Herz, W. *Phytochemistry* **1998**, *48*, 1079.

(6) (a) Rao, K. V.; Alvarez, F. M. *Tetrahedron Lett.* **1983**, *24*, 4947. (b) Rao, K. V.; Oruganty, R. S. *J. Liq. Chromatogr. Relat. Technol.* **1997**, *20*, 3121. (c) Hwang, B. Y.; Lee, J.-H.; Nam, J. B.; Hong, Y.-S.; Lee, J. J. *Phytochemistry* **2003**, *64*, 765.

(7) (a) Hossain, C. F.; Kim, Y.-P.; Baerson, S. R.; Zhang, L.; Bruick, R. K.; Mohammed, K. A.; Agarwal, A. K.; Nagle, D. G.; Zhou, Y.-D. *Biochem. Biophys. Res. Commun.* **2005**, *333*, 1026. (b) Giang, P. M.; Son, P. T.; Matsunami, K.; Otsuka, H. *Chem. Pharm. Bull.* **2006**, *54*, 383.

(8) Konishi, T.; Konoshima, T.; Daikonya, A.; Kitanaka, S. *Chem. Pharm. Bull.* **2005**, *53*, 121.

(9) Esumi, T.; Hojyo, D.; Zhai, H.; Fukuyama, Y. *Tetrahedron Lett.* **2006**, *47*, 3979.

(10) Fonseca, S. F.; Barata, L. E. S.; Ruveda, E. A. *Can. J. Chem.* **1979**, *57*, 441.

(11) (a) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (b) Jahn, U.; Rudakov, D. *Org. Lett.* **2006**, *8*, 4481; and references cited therein.

(12) (a) Biftu, T.; Gamble, N. F.; Doebber, T.; Hwang, S. B.; Shen, T. Y.; Snyder, J.; Springer, J. P.; Stevenson, R. *J. Med. Chem.* **1986**, *29*, 1917. (b) Stevenson, R.; Williams, J. R. *Tetrahedron* **1997**, *33*, 285.

(13) Moinuddin, S. G. A.; Hishiyama, S.; Cho, M.-H.; Davin, L. B.; Lewis, N. G. *Org. Biomol. Chem.* **2003**, *1*, 2307.

(14) Hanessian, S.; Reddy, G. J.; Chahal, N. *Org. Lett.* **2006**, *8*, 5477.

(15) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(16) (a) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (b) See also: Llu, C.; Burnell, D. J. *Tetrahedron Lett.* **1997**, *38*, 6573.

(17) **Data of (+)-Fragransin A_2 (1).**
Mp 198–200 °C (Lit.[3a] 200–202 °C); $[\alpha]_D$ +77.7 (*c* 1.0, $CHCl_3$) [Lit.[3a] +79.0 (*c* 0.84, $CHCl_3$)]. IR (thin film): 3428, 2957, 2926, 1515, 1272, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85–6.98 (m, 6 H), 5.58 (s, 2 H), 4.65 (d, 2 H, *J* = 9.2 Hz), 3.94 (s, 6 H), 1.76–1.82 (m, 2 H), 1.06 (d, 6 H, *J* = 6.0 Hz) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 146.2, 144.7, 134.0, 119.0, 113.6, 108.0, 88.0, 55.6, 50.6, 13.47 ppm. HRMS: *m/z* calcd for $C_{20}H_{25}O_5$ $[M + H]^+$: 345.1698; found: 345.1696.

(18) **Data of (+)-Galbelgin (2).**
Mp 140–142 °C (Lit.[4c] 141–142 °C); $[\alpha]_D$ +83.4 (*c* 0.47, $CHCl_3$) [Lit.[4c] –85.1 (*c* 0.047, $CHCl_3$) for (–)-galbelgin]. IR (thin film): 2957, 2929, 1515, 1263, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.84–7.01 (m, 6 H), 4.68 (d, 2 H, *J* = 9.2 Hz), 3.93 (s, 6 H), 3.90 (s, 6 H), 1.78–1.87 (m, 2 H), 1.07 (d, 6 H, *J* = 5.6 Hz) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 148.6, 148.0, 134.5, 118.2, 110.4, 108.7, 88.0, 55.54, 55.52, 50.6, 13.5 ppm. HRMS: *m/z* calcd for $C_{22}H_{29}O_5$ $[M + H]^+$: 373.2009; found: 373.2014.

(19) **Data of (+)-Talaumidin (3).**
Colorless oil; $[\alpha]_D$ +76.0 (*c* 0.5, $CHCl_3$) [Lit.[9] –81.8 (*c* 0.43, $CHCl_3$) for (–)-talaumidin]. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.77–6.97 (m, 6 H), 5.96 (s, 2 H), 5.57 (br s, 1 H), 4.63 (d, 2 H, *J* = 8.8 Hz), 3.93 (s, 6 H), 1.74–1.82 (m, 2 H), 1.05

(d, 3 H, *J* = 5.6 Hz), 1.04 (d, 3 H, *J* = 6.0 Hz) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 147.4, 146.6, 146.2, 144.7, 136.2, 133.7, 119.3, 119.0, 113.6, 108.1, 107.6, 106.2, 100.6, 88.1, 87.8, 55.6, 50.8, 50.5, 13.45, 13.43 ppm. HRMS: *m/z* calcd for $C_{20}H_{23}O_5$ $[M + H]^+$: 343.1540; found: 343.1553.

(20) Evans, D. A.; Rieger, D. L.; Biodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

(21) **Data of (–)-Verrucosin (4).**
Colorless oil; $[\alpha]_D$ –16.14 (*c* 0.96, $CHCl_3$) [Lit.[3a] +14.8 (*c* 1.38, $CHCl_3$) for (+)-verrucosin]. IR (thin film): 3435, 2937, 2963, 1510, 1266, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81–7.07 (m, 6 H), 5.62 (s, 1 H), 5.56 (s, 1 H), 5.14 (d, 1 H, *J* = 8.6 Hz), 4.42 (d, 1 H, *J* = 9.3 Hz), 3.94 (s, 3 H), 3.88 (s, 3 H), 2.19–2.31 (m, 1 H), 1.76–1.86 (m, 1 H), 1.08 (d, 3 H, *J* = 6.5 Hz), 0.68 (d, 3 H, *J* = 7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 145.8, 144.8, 144.2, 132.9, 132.4, 119.5, 118.9, 113.8, 113.5, 109.4, 109.3, 87.0, 82.8, 55.50, 55.46, 47.3, 45.6, 14.6, 14.5 ppm. HRMS: *m/z* calcd for $C_{20}H_{25}O_5$ $[M + H]^+$: 345.1698; found: 345.1693.

(22) **Data of (–)-Saucernetin (5).**
Mp 77–79 °C (Lit.[6c] 78–80 °C); $[\alpha]_D$ –44.2 (*c* 0.5, $CHCl_3$) [lit.[6c] +48.1 (*c* 0.5, $CHCl_3$)]. IR (thin film): 2957, 2926, 1515, 1272, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85–6.90 (m, 6 H), 5.47 (d, 2 H, *J* = 6.0 Hz), 3.92 (s, 6 H), 3.90 (s, 6 H), 2.25–2.32 (m, 2 H), 0.71 (d, 6 H, *J* = 6.4 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 148.2, 147.5, 133.6, 118.0, 110.3, 109.1, 83.1, 55.5, 43.7, 14.4 ppm. HRMS: *m/z* calcd for $C_{22}H_{29}O_5$ $[M + H]^+$: 373.2009; found: 373.2014.