DOI 10.5012/bkcs.2010.31.10.3027

Concise Synthesis of Stemofurans A, C, and Derivatives

Hee Jin Lee, Sung Hong Kim,[§] Yong Rok Lee,[*] Xue Wang,[†] and Won Seok Lyoo[‡]

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea
[*]E-mail: yrlee@yu.ac.kr
[†]School of Chemical Engineering & Food Science, Xiangfan University, Hubei 441053, China
[‡]School of Textiles, Yeungnam University, Gyeongsan 712-749, Korea
[§]Analysis Research Division, Daegu Center, Korea Basic Science Institute, Daegu 702-701, Korea
Received August 21, 2010, Accepted August 30, 2010

Key Words: Stemofurans A and C, Suzuki coupling, Pyrano-2-arylbenzofurans

Stemofurans A-F (**1-6**) are isolated from *Stemona collinsae*, *S. tuberose*, and *S. peirrei*, which are mainly distributed in southeast Asia (Fig. 1).[1] These plants have been used in traditional Asian medical practices for the treatment of inflammatory-related diseases.[2] The dried root tuber of these plants, "baibu", is listed in the Chinese pharmacopoeia and used to relieve cough.[3] These plants are also used as antiasthmatics in Vietnamese folk medicine.[4] Furthermore, compounds isolated from these plants have shown to possess antifungal[1a] and antibacterial activities,[5] as well as inhibition properties of leukotriene formation.[1b] These important biological activities and properties have led to the development of new synthetic approaches to such natural products. The first synthesis of stemofuran A (**1**) was reported by Pasturel *et al.* starting from 2-hydroxybenzaldehyde through transformations involving hydroxyl protection and deprotection.[6] Another total synthesis of stemofuran A (**1**) was accomplished from phenylboronic acid *via* a [3,3]-sigmatropic rearrangement as the key step in four steps.[7] Nevertheless, there is still a demand for a more concise and efficient method for synthesizing the biologically interesting stemofurans A - F. In particular, no total synthesis of natural stemofuran C (**3**) has been reported thus far.

This lab reported the total synthesis of naturally occurring (+)-machaeriol B (**8**) using stemofuran A (**1**) as a key intermediate, which was prepared from commercially available *O*-phenylhydroxylamine (**7**) in 3 steps according to the known method shown in Scheme 1.[8] As part of an ongoing study for the development of new synthetic routes to stemofurans A - F, we describe herein a concise synthesis of stemofurans A and C, and its application to give benzofuran molecules with benzopyranyl rings.

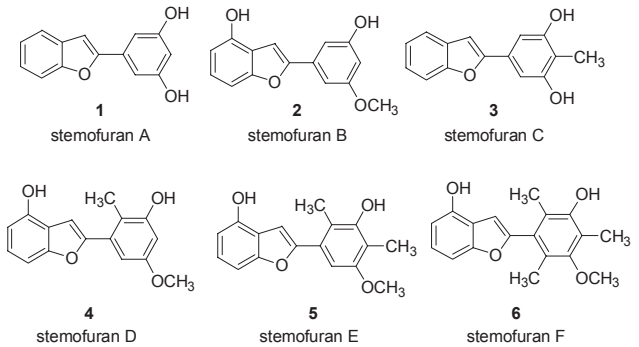
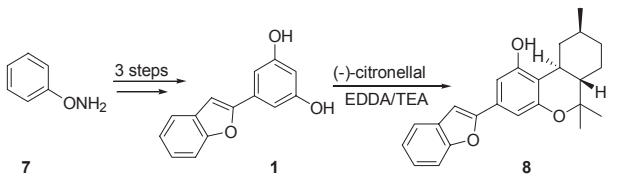


Figure 1. Naturally occurring stemofurans A-F (**1-6**) isolated from *Stemona collinsae*.

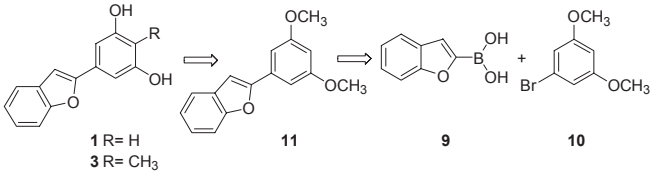
Scheme 2 shows the retrosynthetic analysis for stemofurans A (**1**) and C (**3**). Stemofuran A (**1**) can be readily prepared by demethylation of compound **11**, generated from commercially available 2-benzofuranboronic acid (**9**) and 3,5-dimethoxybromobenzene (**10**) through a Suzuki coupling reaction. In addition, stemofuran C (**3**) can be prepared from compound **11** by alkylation and demethylation reactions.

Scheme 3 shows a concise synthetic approach to natural stemofurans A (**1**) and C (**3**). First, the synthesis of compound **11** as a key intermediate was attempted using the well-known Suzuki coupling reaction.[9] Reaction of 2-benzofuranboronic acid (**9**) with 3,5-dimethoxybromobenzene (**10**) in the presence of $Pd(PPh_3)_4$ in refluxing aqueous THF for 8 h gave **11** in 66% yield. Demethylation of **11** with BBr_3 in methylene chloride at 0 °C for 5 h afforded stemofuran A (**1**) in 91% yield. Next, treatment of **11** with *n*-BuLi, followed by addition of methyl iodide, gave **12** in 76% yield, which was readily converted into stemofuran C (**3**) in 92% yield by treatment with BBr_3. The spectroscopic data of synthetic compounds **1** and **3** are in good agreement with the reported data for the natural products.[1a]

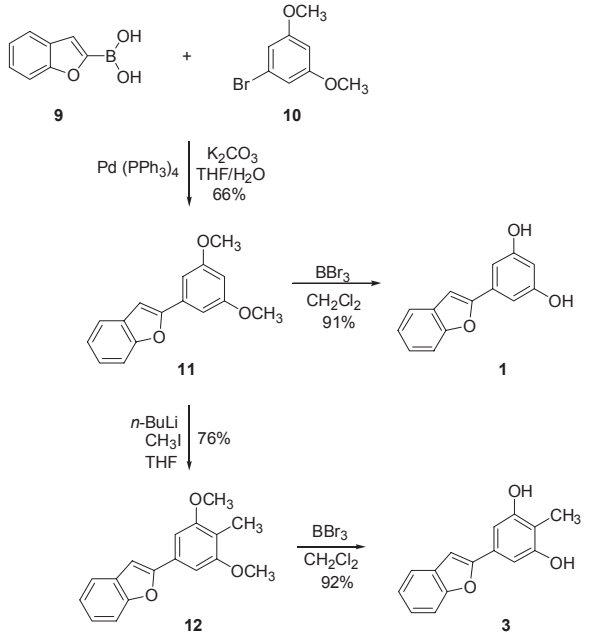
As an application for usefulness of the synthesized stemofuran



Scheme 1. Reported synthesis of (+)-machaeriol B (**8**) from stemofuran A (**1**)



Scheme 2. Retrosynthetic analysis for the synthesis of stemofurans A (**1**) and C (**3**)



Scheme 3

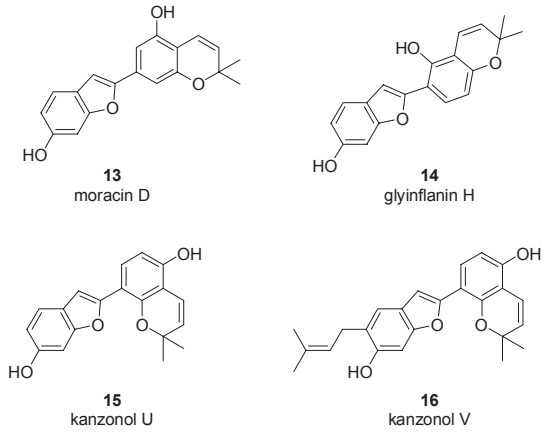
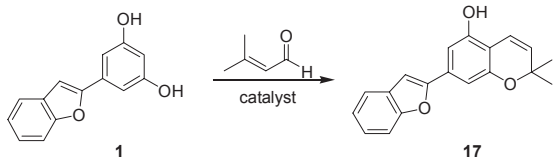


Figure 2. Selected naturally occurring pyrano-2-arylbenzofurans **13-16**.

(**1**), benzopyran formation reactions were next investigated. Benzofuran molecules with benzopyranyl rings (pyrano-2-arylbenzofurans) are widely found in nature[10] and posses interesting biological activities (Fig. 2).[11] This range of biological activities and properties has stimulated further research into the synthesis of pyrano-2-arylbenzofuran derivatives.

Recently, we reported a new methodology for synthesizing a variety of benzopyrans by ethylenediamine diacetate-catalyzed reactions of resorcinols with α,β-unsaturated aldehydes.[12] Further work and new methodologies for the synthesis of benzofuran molecules with benzopyranyl rings were attempted. Reaction of stemofuran A (**1**) with 3-methyl-2-butenal was investigated under several catalysts (Table 1). Both indium (III) chloride (20 mol %) and ytterbium (III) triflate (20 mol %), as Lewis acid catalysts in refluxing acetonitrile, gave no adducts. Treatment of **1** with 3-methyl-2-butenal in the presence of 20 mol % $Ca(OH)_2$, according to Shigemasa conditions,[13] gave

Table 1. Reaction of **1** with 3-methyl-2-butenal under several catalysts



condition		Yield (%)
$InCl_3$ (20 mol %)	acetonitrile, reflux, 12 h	0
$Yb(OTf)_3$ (20 mol %)	acetonitrile, reflux, 12 h	0
$Ca(OH)_2$ (20 mol%)	methanol, reflux, 12 h	0
pyridine (excess)	140 °C, 24 h	0
EDDA (20 mol %)	xylene, reflux, 24 h	30
EDDA (20 mol %)	benzene, reflux, 24 h	52

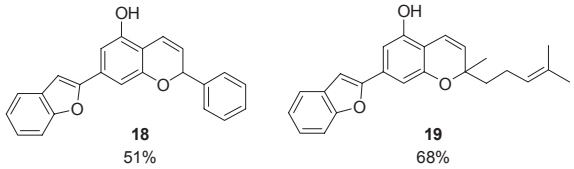


Figure 3

no products. With pyridine as a reactant and solvent, no products were obtained. With ethylenediamine diacetate (20 mol %) as a catalyst, adduct **17**, having a skeleton of the naturally occurring moracin D (**13**), was produced. The best yield (52%) was obtained in refluxing benzene for 24 h.

Additional reactions of **1** with α,β-unsaturated aldehydes such as *trans*-cinnamaldehyde and citral were carried out in the presence of ethylenediamine diacetate (20 mol %). Reaction of **1** with *trans*-cinnamaldehyde in refluxing benzene for 24 h afforded adduct **18** in 51% yield, whereas with citral, **19** was afforded in 68% yield (Fig. 3). These reactions provide a rapid route for the synthesis of pyrano-2-arylbenzofuran derivatives.

In conclusion, concise syntheses of biologically interesting stemofurans A (**1**) and C (**3**) were carried out starting from 2-benzofuranboronic acid (**9**) and 3,5-dimethoxybromobenzene (**10**) in the presence of $Pd(PPh_3)_4$. The key strategy in the syntheses was the Suzuki coupling reaction. Stemofuran A (**1**) was readily converted into benzofuran derivatives with benzopyranyl rings. These synthetic routes are expected to be widely used in the synthesis of natural products, including a benzofuran skeleton with benzopyranyl rings.

Experimental Section

All experiments were carried out in a nitrogen atmosphere. Merck, pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$, CD_3OD, and acetone-d_6 as the solvent chemical shift. All IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS and MS spectra were carried out at the Korea Basic Science

Institute.

2-(3,5-Dimethoxyphenyl)benzofuran (11): To a mixture 2-benzofuranboronic acid (0.486 g, 3.0 mmol), 3,5-dimethoxybromobenzene (0.651 g, 3.0 mmol), and K_2CO_3 (0.806 g, 4.2 mmol) in THF/H_2O (1:1) (30 mL) was added $Pd(PPh_3)_4$ (0.175 g, 0.15 mmol) under N_2 and the mixture was heated under reflux for 8 h. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with water (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel using hexane/ethyl acetate (5:1) afforded **11** (0.503 g, 66%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.61 (2H, m), 7.42-7.30 (2H, m), 7.12 (2H, s), 7.09 (1H, s), 6.57 (1H, br s), 3.95 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 155.7, 154.8, 132.2, 129.1, 124.3, 122.9, 120.9, 111.1, 103.0, 101.8, 101.0, 55.4 ; IR (neat) 3063, 2952, 1605, 1459, 1354, 1250, 1202, 1158, 1067, 944, 843, 747 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{16}H_{14}O_3$: 254.0943. Found: 254.0945.

Stemofuran A (1): To a solution of boron tribromide (2.4 mL, 1.0 M in CH_2Cl_2, 2.4 mmol) in methylene chloride (30 mL) was added compound **11** (0.51 g, 2.0 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 5 h. Addition of ice water (30 mL), the mixture was extracted with methylene chloride (3 × 30 mL), washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (3:1) gave **1** (0.412 g, 91%) as a solid. mp 181 - 182 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (1H, d, *J* = 8.0 Hz), 7.38 (1H, d, *J* = 8.0 Hz), 7.18-7.06 (2H, m), 6.93 (1H, d, *J* = 1.5 Hz), 6.74 (2H, dd, *J* = 1.5, 1.5 Hz), 6.20 (1H, s), 4.78 (2H, br s); ^{13}C NMR (75 MHz, CD_3OD) δ 160.0, 157.4, 156.1, 133.4, 130.5, 125.3, 124.0, 121.9, 111.8, 104.5, 104.1, 102.3; IR (KBr) 3331, 1620, 1579, 1449, 1358, 1246, 1148, 999, 953, 853, 833, 801, 748 cm^{-1}; EIMS *m*/*z* (%) 226 (M^+, 100), 197 (11), 181 (2), 169 (3), 152 (4), 151 (3), 150 (4), 141 (4), 139 (3), 115 (5), 113 (5); HRMS *m*/*z* (M^+) calcd for $C_{14}H_{10}O_3$: 226.0630. Found: 226.0631.

2-(3,5-Dimethoxy-4-methylphenyl)benzofuran (12): *n*-BuLi (0.36 mL, 2.5 M in hexane, 0.9 mmol) was added at 0 °C to a solution of **11** (0.181 g, 0.8 mmol) in THF (20 mL) and the resulting solution was stirred at 0 °C for 2 h. Methyl iodide (0.128 g, 0.9 mmol) was added dropwise to the reaction mixture at 0 °C, which was stirred at room temperature for 10 h. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with water (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel using hexane/ethyl acetate (5:1) afforded **12** (0.163 g, 76%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.44 (2H, m), 7.23-7.12 (2H, m), 6.97 (2H, s), 6.92 (1H, br s), 3.85 (6H, s), 2.06 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 156.7, 154.9, 129.2, 128.6, 124.1, 122.9, 120.7, 115.0, 111.1, 100.9, 100.4, 55.8, 8.4; HRMS *m*/*z* (M^+) calcd for $C_{17}H_{16}O_3$: 268.1099. Found: 268.1096.

Stemofuran C (3): To a solution of boron tribromide (0.6 mL, 1.0 M in CH_2Cl_2, 0.6 mmol) in methylene chloride (10 mL) was added compound **12** (0.134 g, 0.5 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 10 h. Addition of ice water (20 mL), the mixture was extracted with methylene chloride (3 × 30 mL), washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (3:1) gave **3** (0.111 g, 92%) as a solid. mp 195 - 196 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.59 (1H, d, *J* = 8.1 Hz), 7.50 (1H, d, *J* = 8.1 Hz), 7.27-7.22 (2H, m), 7.03 (1H, s), 6.99 (2H, s), 2.14 (3H, s); ^{13}C NMR (75MHz, acetone-d_6) δ 157.5, 157.3, 155.5, 100.1, 129.1, 124.9, 123.8, 121.7, 113.0, 111.5, 104.1, 101.4, 8.7; IR (KBr) 3597, 2926, 2855, 1623, 1601, 1577, 1522, 1510, 1453, 1421, 1377, 1365, 1351, 1299, 1257, 1185, 1157, 1144, 1108, 1081, 1007, 961, 937, 867 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{15}H_{12}O_3$: 240.0786. Found: 240.0788.

General Procedure for the synthesis of compounds 17-19. Ethylenediamine diacetate (18 mg, 0.1 mmol) was added to a solution of stemofuran A (**1**) (0.5 mmol) and α,β-unsaturated aldehydes (1.0 mmol) in benzene (10 mL). The reaction mixture was refluxed for 24 h and the removal of the solvent left an oily residue, which was purified by column chromatography on silica gel to give the products.

Compound 17: A reaction of **1** (0.113 g, 0.5 mmol) with 3-methyl-2-butenal (0.084 g, 1.0 mmol) in refluxing benzene (10 mL) for 24 h afforded compound **17** (0.076 g, 52%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (1H, dd, *J* = 7.5, 1.5 Hz), 7.64 (1H, d, *J* = 7.5 Hz), 7.47-7.36 (2H, m), 7.11 (1H, s), 7.10 (1H, s), 7.04 (1H, d, *J* = 1.5 Hz), 6.83 (1H, d, *J* = 9.9 Hz), 5.82 (1H, d, *J* = 9.9 Hz), 5.32 (1H, br s), 1.64 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 154.7, 154.2, 151.6, 130.9, 129.7, 129.1, 124.3, 122.9, 120.9, 116.3, 111.0, 110.1, 105.9, 104.4, 101.6, 76.3, 27.8; IR (neat) 3467, 2974, 2930, 1618, 1562, 1450, 1423, 1370, 1251, 1120, 1069, 962, 900, 849, 803 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{16}O_3$: 292.1099. Found: 292.1097.

Compound 18: A reaction of **1** (0.113 g, 0.5 mmol) with *trans*-cinnamaldehyde (0.132 g, 1.0 mmol) in refluxing benzene (10 mL) for 24 h afforded compound **18** (0.087 g, 51%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.06 (9H, m), 7.80 (1H, d, *J* = 10.8 Hz), 6.77 (1H, s), 6.76 (1H, s), 5.79 (1H, d, *J* = 3.6 Hz), 5.71 (1H, dd, *J* = 10.8, 3.6 Hz), 5.21 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 154.7, 154.3, 151.6, 140.4, 131.3, 129.0, 128.7, 128.4, 127.1, 124.4, 123.6, 122.9, 120.9, 118.1, 111.0, 110.2, 105.6, 104.7, 101.9, 76.9; IR (neat) 2923, 2855, 1626, 1569, 1450, 1357, 1257, 1079, 803, 747 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{23}H_{16}O_3$: 340.1099. Found: 340.1096.

Compound 19: A reaction of **1** (0.113 g, 0.5 mmol) with citral (0.152 g, 1.0 mmol) in refluxing benzene (10 mL) for 24 h afforded compound **19** (0.123 g, 68%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* = 7.0 Hz), 7.38 (1H, d, *J* = 7.5 Hz), 7.20-7.12 (2H, m), 6.84 (2H, s), 6.76 (1H, s), 6.61 (1H, d, *J* = 9.9 Hz), 5.52 (1H, d, *J* = 9.9 Hz), 5.03 (1H, t, *J* = 6.6 Hz), 2.12-2.01 (2H, m), 1.78-1.60 (2H, m), 1.58 (3H, s), 1.51 (3H, s), 1.34 (3H, s); ^{13}C NMR (75MHz, $CDCl_3$) δ 155.3, 154.6, 154.4, 151.6, 131.7, 130.8, 129.1, 128.7, 124.2, 124.0, 122.8, 120.8, 116.7, 111.0, 110.0, 105.7, 104.3, 101.6, 78.6, 41.0, 26.2, 25.6, 22.7, 17.6; IR (neat) 3410, 3061, 2969, 2823, 1618, 1562, 1449, 1357, 1253, 1157, 1085, 962, 908, 849, 801, 747 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{24}H_{24}O_3$: 360.1725. Found: 360.1727.

Acknowledgments. This study was supported by grant No. RTI04-01-04 from the Regional Technology Innovation Pro-

gram of the Ministry of Knowledge Economy (MKE).

References

1. (a) Pacher, T.; Segar, C.; Engelmeier, D.; Vajrodaya, S.; Hofer, O.; Greger, H. *J. Nat. Prod*. **2002**, *65*, 820. (b) Adams, M.; Pacher, T.; Greger, H.; Bauer, R. *J. Nat. Prod*. **2005**, *68*, 83.
2. (a) Bauer, R. In *Bioassay Methods in Natural Product and Drug Development*; Bohlin, L., Bruhn, J. C., Eds.; Kluwer Academic Publishers: Dorrecht, 1999; p 119. (b) Adams, M.; Kunert, O.; Bauer, R. *Planta Med.* **2004**, *70*, 904.
3. *Pharmacopoeia of the Peoples Republic of China*; Chemical Industry Press: Beijing, 2000; Vol. 1, p 199.
4. Do, T. L. *Vietnamese Traditional Medicinal Plants and Drugs*, 3rd ed.; Publishing House of Medicine: Hanoi, 2001; p 162.
5. Zhao, W. M.; Qin, G. W.; Ye, Y.; Xu, R. S.; Le, X. F. *Phytochemistry* **1995**, *38*, 711.
6. Pasturel, J. Y.; Solladie, G.; Maignan, J. Fr. Demande FR 2833259, 2003; *Chem. Abstr*. **2003**, *139*, 36375.
7. (a) Miyata, O.; Takeda, N.; Naito, T. *Org. Lett*. **2004**, *6*, 1761. (b) Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem*. **2007**, 1491.
8. Lee, H. J.; Lee, Y. R.; Kim, S. H. *Helv. Chim. Acta* **2009**, *92*, 1404.
9. (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002.
10. (a) Takasugi, M.; Nagao, S.; Ueno, S.; Masamune, T.; Shirata, A.; Takahashi, K. *Chem. Lett.* **1978**, 1239. (b) Fukai, T.; Nomura, T. *Phytochemistry* **1995**, *38*, 759. (c) Fukai, T.; Sheng, C.-B.; Horikoshi, T.; Nomura, T. *Pyotochemistry* **1996**, *43*, 1119.
11. Na, M.; Hoang, D. M.; Njamen, D.; Mbafor, J. T.; Fomum, Z. T.; Thuong, P. T.; Ahn, J. S.; Oh, W. K. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 3868.
12. (a) Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett*. **2005**, *46*, 7539. (b) Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853. (c) Lee, Y. R.; Kim D. H. *Synthesis* **2006**, 603. (d) Lee, Y. R.; Kim, J. H. *Synlett* **2007**, 2232. (e) Wang, X.; Lee, Y. R. *Tetrahedron Lett*. **2007**, *48*, 6275. (f) Wang, X.; Lee, Y. R. *Synthesis* **2007**, 3044. (g) Lee, Y. R.; Xia, L. *Synthesis* **2007**, 3240. (h) Lee, Y. R.; Kim, Y. M. *Helv. Chim. Acta* **2007**, *90*, 2401. (i) Lee, Y. R.; Li, X.; Kim, J. H.; *J. Org. Chem*. **2008**, *73*, 4313. (j) Xia, L.; Lee, Y. R. *Synlett* **2008**, 1643. (k) Lee, Y. R.; Hung, T. V. *Tetrahedron* **2008**, *64*, 7338. (l) Lee, Y. R.; Xia, L. *Tetrahedron Lett*. **2008**, *49*, 3283. (m) Lee, Y. R.; Wang, X. *Tetrahedron* **2009**, *65*, 10125. (n) Lee, Y. R.; Kim, Y. M.; Kim. S. H. *Tetrahedron* **2009**, *65*, 101. (o) Jung, D, H.; Lee, Y. R.; Kim, S. H. *Helv. Chim. Acta* **2010**, *93*, 635.
13. Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem*. **1996**, *61*, 6768.