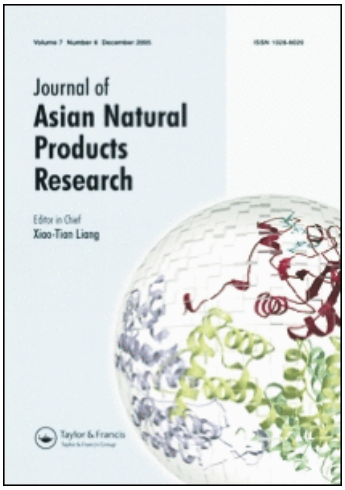

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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To cite this Article Zhang, W. -G. , Lin, J. -G. , Niu, Z. -Y. , Zhao, R. , Liu, D. -L. , Wang, N. -L. and Yao, X. -S.(2007) 'Total synthesis of two new dihydrostilbenes from *Bulbophyllum odoratissimum*', Journal of Asian Natural Products Research, 9: 1, 23 — 28
To link to this Article: DOI: 10.1080/10286020500289543
URL: http://dx.doi.org/10.1080/10286020500289543

Journal of Asian Natural Products Research, Vol. 9, No. 1, January–February 2007, 23–28

Total synthesis of two new dihydrostilbenes from *Bulbophyllum odoratissimum*

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(Received 25 March 2005; revised 21 June 2005; in final form 1 July 2005)

A total synthetic route of two new dihydrostilbenes 5-(2-benzo[1,3]dioxole-5-ylethyl)-6-methoxy benzo[1,3]dioxole-4-ol (**1**) and 5-(2-benzo[1,3]dioxole-5-ylethyl)benzo[1,3]dioxole-4,7-diol (**2**), which were isolated from *Bulbophyllum odoratissimum* Lindl. with significant cytotoxicity toward human cancer cell lines, was developed via Horner reaction etc. The natural products **1** and **2** were obtained in 10.5% and 3.3% overall yield, respectively.

Keywords: Dihydrostilbene; Total synthesis; *Bulbophyllum odoratissimum* Lindl

1. Introduction

Dihydrostilbenes have long been considered as interesting natural products, which had been isolated from many primitive green plants to be used as endogenous growth regulators [1]. Recently, some dihydrostilbenes were found to be tubulin polymerisation inhibitors and to display strong antimitotic activity toward a broad spectrum of human cancer lines [2]. In our effort to search for naturally occurring cancer cell growth inhibitors present in traditional Chinese medicines using the *Pyricularia oryzae* bioassay [3], two new dihydrostilbenes, 5-(2-benzo[1,3]dioxole-5-ylethyl)-6-methoxybenzo[1,3]dioxole-4-ol **1** and 5-(2-benzo[1,3]-dioxole-5-ylethyl)benzo[1,3]dioxole-4,7-diol **2**, were obtained from *Bulbophyllum odoratissimum* Lindl., a folk herbal medicine for the treatment of phthisis and rheumatism in the Chinese community [4]. Both **1** and **2** exhibited significant cytotoxic activities against MCF-7, NCI-H460 and SF-268 human cancer cell lines using the tetrazolium dye reduction assay (MTT assay). Our continued interest in searching for new anti-tumour agents and

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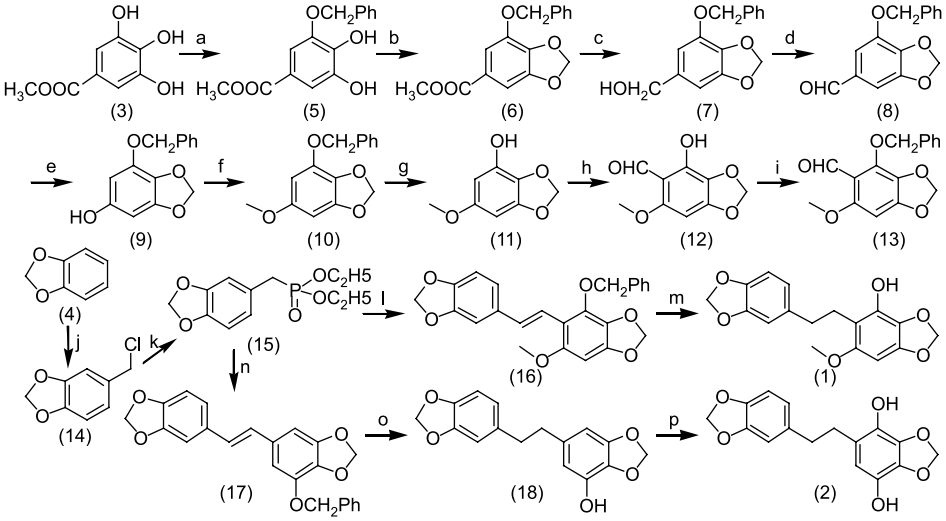
Journal of Asian Natural Products Research
ISSN 1028-6020 print/ISSN 1477-2213 online © 2007 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/10286020500289543

understanding their structure–activity relationships prompted us to develop an efficient total synthetic route for the natural dihydrostilbenes **1** and **2**.

2. Results and discussion

The general approach to the synthesis of **1** and **2** was as described in scheme 1.

Following the reported methodologies [5,6] with only slight modifications, aldehyde **8** was prepared from methyl gallate **3** in 44.0% yield, which was a requisite intermediate for the total synthesis of **2**. The synthesis of aldehyde **13**, a key synthetic intermediate of **1**, was realised in five practical steps from **8**. The Baeyer–Villiger oxidation of **8** with *m*-CPBA in the presence of Na_2HPO_4 gave phenol **9**, which was treated with methyl iodide under alkaline condition to furnish methoxy derivative **10**. To introduce a formyl group to the 5-position of 4- (benzyloxy)-6-methoxybenzo[1,3]dioxole **10** with a satisfactory regio-selectivity was a crucial step of the synthesis of **13**. When we attempted formylation of **10** by Vilsmeier reaction under a variety of conditions, we encountered failure since we could not detect the presence of any 5-formylated product in the reaction mixture. We considered that the poor reactivity should be due chiefly to the steric hindrance of the 4-benzyloxy group, and this assumption was readily proven valid by experiments. The benzyl group of **10** was removed by catalytic hydrogenation to form 4-OH derivative **11**. In our investigation of the synthesis of aldehyde **12**, we found that Vilsmeier reaction of **11** introduced an aldehyde group, –CHO, onto the aromatic ring, mostly *ortho* to the –OH. 4-Hydroxy-6-methoxybenzo[1,3]dioxole-5-carbaldehyde (**12**) was obtained in 78.8% yield while none



Scheme 1. Synthesis of the new dihydrostilbenes **1** and **2**. Reagents and conditions: (a) NaH (80%), B $(OCH_3)_3$, DMF, 10°C, 2 h then $PhCH_2Br$, room temperature (rt), 3 h; followed by 2 N HCl, rt, 0.5 h; (b) CH_2Cl_2, K_2CO_3, DMF, reflux, 4 h, (49.4% from **3**); (c) $LiAlH_4$, THF, 0°C, 1 h (94.2%); (d) MnO_2, 1,2-dichloroethane, rt, ultrasound irradiation, 24 h (94.6%); (e) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0°C then reflux, overnight (80.0%); (f) MeI, K_2CO_3, acetone, reflux, 48 h (92.1%); (g) H_2, 10%Pd-C, EtOAc, rt, overnight (97.2%); (h) $POCl_3$, DMF, rt, 20 min then 75°C, 2 h (78.8%); (i) $PhCH_2Cl$, K_2CO_3, DMF, 50°C, 24 h (90.1%). (j) $(HCHO)_n$, HCl, 25°C, 4 h (82.1%); (k) P $(OC_2H_5)_3$, 140°C, 8 h; (l) aldehyde **13**, NaH, DMF, 0°C, 0.5 h; then rt, 48 h (48.5% from **13**); (m) H_2, Pd-C, EtOAc, rt, overnight (96.9%); (n) aldehyde **8**, NaH, DMF, 0°C, 0.5 h then rt, 36 h (51.1% from **8**); (o) H_2, Pd-C, EtOAc, rt, 48 h (97.0%); (p) $K_2S_2O_8$, KOH, pyridine, rt, 48 h (15.1%).

of 7-formylated product was found in the reaction mixture. Compound **12** was protected again with benzyl group to yield intermediate **13**.

The next task of converting 1,3-benzodioxole to the desired phosphonate **15** was achieved in a very simple two-step reaction sequence. Thus, the Blanc chloromethylation of 1,3-benzodioxole (**4**) with paraformaldehyde and hydrogen chloride provided benzyl chloride (**14**). Further, Michaelis–Arbuzov reaction of **14** with triethyl phosphite provided **15**, which could be used directly in the next step.

Having accomplished the preparations of aldehydes **13**, **8** and phosphonate **15**, attention was focused on the synthesis of the target molecules **1** and **2**. Compound **15** was treated with NaH in DMF, followed by the addition of **13** to give *trans*-stilbene **16** in 48.5%. Catalytic hydrogenation of **16** over palladium on carbon provided the target dihydrostilbene **1** in 96.9% yield, resulting from removal of the benzyl-protecting group and reduction of the double bond. Similarly, Horner reaction of **15** with **13** afforded the *trans*-stilbene **17** in 51.1%, which was hydrogenated to yield dihydrostilbene **18**. Elbs persulfate oxidation was employed in the introduction of a –OH group to the 4-position of **18** to give the natural product **2** in 15.1% yield. The synthetic materials **1** and **2** were identical in ^{1}H NMR, ^{13}C NMR and MS with the samples of the natural products.

In summary, the first total synthesis of two new natural dihydrostilbenes, 5-(2-benzo[1,3]-dioxole-5-ylethyl)-6-methoxybenzo[1,3]dioxole-4-ol (**1**) and 5-(2-benzo[1,3]dioxole-5-ylethyl)benzo[1,3]dioxole-4,7-diol (**2**), had thus been achieved in 10.5% and 3.3% overall yield, respectively. In addition, it was confirmed that Vilsmeier reaction of phenol **11** could provide the 5-formylated product **12** in a good yield. Although Elbs persulfate oxidation suffered from the major drawback of an unsatisfactory yield, this method allowed us to obtain the desired compound **2** with a high regio-selectivity. Application of this methodology toward the analogues of the natural products **1** and **2** for their structure–activity relationships is currently in progress.

3. Experimental

3.1 General experimental procedures

^{1}H NMR and ^{13}C NMR spectra were taken in $CDCl_3$ or 6d-DMSO solution on Bruker AVANCE-400, Bruker ARX-300 or Bruker ARX-600 spectrometers with TMS as the internal reference. MS spectra were obtained using Bruker Esquire 2000, JMS-DX300 or Shimadzu GCMS-QP5050A spectrometers. TLC was carried out on silica gel (GF_{254}). Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals. Compounds **5**, **6**, **7** and **8** were prepared according to the procedures reported by Brayer et al. [5,6].

3.2 Preparation

3.2.1 Compound 9. To a suspension of **8** (6.0 g, 23.4 mmol) and Na_2HPO_4 (6.0 g, 50.0 mmol) in CH_2Cl_2 (25 ml) was added portionwise *m*-CPBA (5.33 g, 30.9 mmol) at 0°C and then the mixture was stirred at room temperature for 1 h. The resulting mixture was refluxed overnight, then poured into ice-water, extracted with EtOAc, and worked up as usual. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 3:1)

to give **9** (4.57 g, 80.0%) as a white solid, mp 70.6–72.1°C (from EtOAc, *n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.90 (1H, br s, –OH), 5.12 (2H, s, $-OCH_2Ph$), 5.88 (2H, s, H-2), 6.04 (1H, d, $J = 2.3$ Hz, H-6), 6.09 (1H, d, $J = 2.3$ Hz, H-4), 7.30–7.41 (5H, m, aromatic H). EI-MS *m/z*: 244 (M^+).

3.2.2 Compound 10. A mixture of **9** (4.5 g, 18.4 mmol), MeI (2.25 ml, 51.5 mmol) and anhydrous K_2CO_3 (4.5 g, 32.7 mmol) in anhydrous acetone (20 ml) was refluxed for 48 h. After filtration, the filtrate was acidified with 1 N HCl and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 5:1) to give **10** (4.37 g, 92.1%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.71 (3H, s, $-OCH_3$), 5.17 (2H, s, $-OCH_2Ph$), 5.90 (2H, s, H-2), 6.12 (1H, d, $J = 2.1$ Hz, H-6), 6.18 (1H, d, $J = 2.1$ Hz, H-4), 7.31–7.44 (5H, m, aromatic H). EI-MS *m/z*: 258 (M^+), 200, 182, 165, 150.

3.2.3 Compound 11. A solution of **10** (4.0 g, 15.5 mmol) in EtOAc (20 ml) was stirred under a hydrogen atmosphere in the presence of 10% Pd-C (0.2 g) at room temperature overnight. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo* to give **11** (2.53 g, 97.2%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.72 (3H, s, $-OCH_3$), 4.81 (1H, br s, –OH), 5.90 (2H, s, H-2), 6.05 (1H, d, $J = 2.0$ Hz, H-6), 6.14 (1H, d, $J = 2.0$ Hz, H-4). EI-MS *m/z*: 168 (M^+), 153, 123.

3.2.4 Compound 12. $POCl_3$ (5.5 ml, 59.5 mmol) was added dropwise to DMF (10 ml, 129.4 mmol) over 15 min at 5°C. The mixture was stirred at room temperature for 20 min. **11** (2.5 g, 14.9 mmol) was added in one portion, and the mixture was slowly heated to 75°C and then stirred at this temperature for 2 h. The resulting mixture was cooled to 5°C and poured into water (50 ml). After filtration, the filter cake was purified by column chromatography (*n*-hexane/EtOAc = 4:1) to give **12** (2.3 g, 78.8%) as a white solid, mp 158.1–159.0°C (from EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.85 (3H, s, $-OCH_3$), 6.01 (2H, s, H-2), 6.07 (1H, s, H-7), 10.13 (1H, s, –CHO), 12.11 (1H, s, –OH). ^{13}C NMR ($CDCl_3$) δ (ppm): 56.3 ($-OCH_3$), 85.6 (C-7), 102.5 (C-2), 107.1 (C-5), 127.4 (C-3a), 146.4 (C-4), 156.1 (C-7a), 160.7 (C-6), 192.8 (–CHO). ESI-MS *m/z*: 197 ($[M + H]^+$).

3.2.5 Compound 13. A mixture of benzyl chloride (1.42 g, 11.2 mmol), K_2CO_3 (2.25 g, 16.4 mmol) and **12** (2 g, 10.2 mmol) in DMF (10 ml) was stirred at 50°C for 24 h. The reaction mixture was poured into water and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 3:1) to give **13** (2.48 g, 90.1%) as a light yellow solid, mp 92.2–94.1°C (from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.84 (3H, s, $-OCH_3$), 5.35 (2H, s, $-OCH_2Ph$), 5.97 (2H, s, H-2), 6.27 (1H, s, H-7), 7.33-7.43 (5H, m, aromatic H), 10.33 (1H, s, –CHO). EI-MS *m/z*: 270 (M^+).

3.2.6 Compound 14. To a mixture of 1,3-benzodioxole **4** (6.1 g, 50.0 mmol) and paraformaldehyde (4.5 g, 150.0 mmol), conc. HCl (12.9 ml, 150.0 mmol) was added

dropwise at 20–25°C. The reaction mixture was stirred at the same temperature for 4 h and then cooled to 15°C. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the crude product of **14** (7.0 g, 82.1%) was obtained as a yellow oil.

3.2.7 Compounds 15 and 16. A mixture of **14** (3.8 g, 22.3 mmol) and triethyl phosphite (7.6 g, 45.7 mmol) was refluxed at 140°C for 8 h, then residual triethyl phosphite was removed *in vacuo* to give compound **15** (6.0 g, 22.0 mmol). To a suspension of 92% NaH (0.3 g, 11.7 mmol) in dry DMF (5 ml) was added **15** (1.50 g, 5.85 mmol) in dry DMF (10 ml) dropwise at 0°C under nitrogen atmosphere. The resulted solution was stirred at room temperature for 3 h, to which aldehyde **3** (1.58 g, 5.85 mmol) in dry DMF (5 ml) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 48 h, then was poured into ice-water (100 ml). After filtration and washing with H_2O, the crude product was purified by column chromatography (*n*-hexane/EtOAc = 3:1) to give the *trans*-stilbene **16** (1.1 g, 48.5% from **4**) as a white powder, mp 112.6–114.1°C (from EtOAc, *n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.80 (1H, s, $-OCH_3$), 5.25 (2H, s, $-OCH_2Ph$), 5.89 (2H, s, H-2′), 5.93 (2H, s, H-2), 6.31 (1H, s, H-7), 6.74 (1H, d, $J = 8.0$ Hz, H-7′), 6.8 (1H, dd, $J = 8.0$ Hz, $J = 1.5$ Hz, H-6), 6.99 (1H, d, $J = 1.5$ Hz, H-4′), 7.12-7.47 (7H, m, aromatic H and $-CH=CH-$). EI-MS *m/z*: 388 (M^+).

3.2.8 Compound 1. A mixture of **2** (1.0 g, 2.58 mmol) and EtOAc (25 ml) in the presence of 10% Pd-C (0.05 g) was stirred overnight under a hydrogen atmosphere. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo* to give **1** (0.79 g, 96.9%) as a white powder, mp 94.6–96.1°C (from EtOAc, *n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.69 (2H, m, $-CH_2-$), 2.83 (2H, m, $-CH_2-$), 3.72 (3H, s, $-OCH_3$), 4.80 (1H, br s, $-OH$), 5.87 (2H, s, H-2′), 5.91 (2H, s, H-2), 6.18 (1H, s, H-7), 6.60 (1H, d, $J = 7.9$ Hz, H-6′), 6.72 (1H, d, $J = 7.9$ Hz, H-7′), 6.73 (1H, s, H-4′). ^{13}C NMR ($CDCl_3$) δ (ppm): 25.7 ($-CH_2-$), 35.4 ($-CH_2-$), 56.4 ($-OCH_3$), 87.7 (C-7), 100.7 (C-2′), 101.0 (C-2), 108.1 (C-7′), 109.1 (C-4′), 111.2 (C-5), 121.1 (C-6′), 128.4 (C-5′), 136.6 (C-3a), 137.9 (C-4), 145.5 (C-7′a), 146.2 (C-7a), 147.4 (C-3′a), 153.1 (C-6). HRFAB-MS *m/z*: 317.1030 (calcd for $C_{17}H_{17}O_6$, 317.1025 $[M + H]^+$).

3.2.9 Compound 17. To a suspension of 92% NaH (1.2 g, 46.8 mmol) in dry DMF (25 ml) was added compound **15** (6.0 g, 22.0 mmol) in dry DMF (50 ml) dropwise at 0°C under nitrogen atmosphere. The resulted solution was stirred at room temperature for 3 h, to which aldehyde **8** (5.2 g, 20.3 mmol) in dry DMF (25 ml) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 48 h, and then was poured into ice-water (500 ml). After filtration and washing with H_2O, the crude product was purified by column chromatography (*n*-hexane/EtOAc = 5:1) to give the *trans*-stilbene **17** (3.88 g, 51.1% from **14**) as a white powder, mp 124.0–126.1°C (from EtOAc, *n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.21 (2H, s, $-OCH_2Ph$), 5.97 (2H, s, H-2′), 5.98 (2H, s, H-2), 6.69 (1H, d, $J = 16.4$ Hz, $-CH=$), 6.70 (1H, d, $J = 16.4$ Hz, $=CH-$), 6.78 (1H, d, $J = 8.1$ Hz, H-7′), 6.80 (1H, s, H-6), 6.81 (1H, s, H-4), 6.89 (1H, d, $J = 8.1$ Hz, H-6′), 7.01 (1H, s, H-4′), 7.33–7.47 (5H, m, aromatic H). EI-MS *m/z*: 374 (M^+).

3.2.10 Compound 18. A solution of the *trans*-stilbene **17** (4 g, 10.6 mmol) in EtOAc (50 ml) was stirred in the presence of 10% Pd-C (0.2 g) under a hydrogen atmosphere at room temperature for 12 h. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo* to give dihydrostilbene **18** (2.94 g, 97.0%) as a slight yellow powder, mp 150.1–152.0°C (from EtOAc, *n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.76 (4H, br s, $-CH_2-$), 4.70 (1H, br s, $-OH$), 5.92 (2H, s, H-2′), 5.93 (2H, s, H-2), 6.30 (1H, s, H-6), 6.31 (1H, s, H-4), 6.60 (1H, d, $J = 7.9$ Hz, H-6′), 6.65 (1H, s, H-4′), 6.71 (1H, d, $J = 7.9$ Hz, H-7′). EI-MS *m/z*: 286 (M^+).

3.2.11 Compound 2. Compound **18** (1.0 g, 3.5 mmol) in pyridine (20 ml) and 8% aqueous solution of KOH (12 ml) was oxidised by slow addition of $K_2S_2O_8$ (1.0 g, 5.2 mmol) in H_2O (20 ml) at room temperature over 2 h. After stirring at room temperature for 48 h, the reaction mixture was acidified to pH 2.0 with dilute HCl, filtered and extracted with Et_2O. Additional conc. HCl (20 ml) was added to the aqueous layer, which was refluxed for 1 h and then extracted with $CHCl_3$, washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (*n*-hexane/EtOAc = 1:1) to give **2** (0.15 g, 15.1%) as colourless crystals, mp 178.0–172.2°C (from EtOAc, *n*-hexane). ^{1}H NMR (600 MHz, 6d-DMSO) δ (ppm): 2.63 (4H, m, $-CH_2-$), 5.86 (2H, s, H-2′), 5.94 (2H, s, H-2), 6.11 (1H, s, H-6), 6.62 (1H, dd, $J = 7.9$ Hz, $J = 1.2$ Hz, H-6′), 6.77 (1H, d, $J = 1.2$ Hz, H-4′), 6.78 (1H, d, $J = 7.9$ Hz, H-7′), 8.47 (1H, s, $-OH$), 8.82 (1H, s, $-OH$). ^{13}C NMR (DMSO-d_6) δ (ppm): 32.3 ($-CH_2-$), 36.1 ($-CH_2-$), 100.8 (C-2′), 101.0 (C-2), 108.1 (C-7′), 109.2 (C-4′), 111.4 (C-6), 121.5 (C-6′), 124.4 (C-5), 131.7 (C-5′), 133.4 (C-7a), 134.0 (C-4), 136.3 (C-3a), 136.7 (C-7), 145.6 (C-7′a), 147.4 (C-3′a). HRFAB-MS *m/z*: 303.0881 (calcd for $C_{16}H_{15}O_6$, 303.0869 $[M + H]^+$).

Acknowledgements

We gratefully acknowledge Professor Mao-sheng Cheng and Professor Ying-liang Wu, Shenyang Pharmaceutical University, for valuable discussion.

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