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Synthesis of the Active Stilbenoids by Photooxidation Reaction of *trans*-ε-Viniferin

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Two new stilbenoids, *cis*-ε-viniferin (**3**) and 2b,14b-dehydro-bisresveratrol (**4**) were synthesized by photooxidation reaction of *trans*-ε-viniferin (**2**) prepared from *trans*-resveratrol (**1**). Pentamethoxyl *trans*-ε-viniferin (**5**) and pentamethoxyl *cis*-ε-viniferin (**6**) were also obtained by methylation of *trans*-ε-viniferin (**2**) with $(MeO)_2SO_2$. Their structures were elucidated on the basis of spectral evidence. Compounds **3** and **4** showed potent inhibition of TNF-α at concentrations of 10^{-5} mol•L^{-1} with inhibitory ratios of 51.43% and 36.64%, respectively.

Keywords photooxidation, *cis*-ε-viniferin, 2b,14b-dehydro-bisresveratrol, stilbenoid, tumor necrosis factor inhibitory activity

Introduction

It was reported that stilbene monomers showed multi-faced biological activities, such as antioxidation, antimutagen, antibacterial, antifungal activities.[1] Especially, isorhapontigenin and resveratrol showed potent inhibition on biosynthesis of leukotriene and its receptor antagonist.[2] Some oligostilbenes exhibited more potent bioactivities than their monomers.[3] In recent years, a number of oligostilbenes were isolated from natural sources, but a few of studies on their pharmacological activities were hitherto reported due to the scarcity of samples. Therefore, biomimetic synthesis of oligostilbenes is attracting more and more attentions of researchers from all over the world. Recently, some oligomers, such as (+)-hopeaphenol, (+)-vitisin A, ampelopsins A and ampelopsins B,[4,5] have been synthesized successfully. On the other hand, the structure-activity relationship analysis indicated that the *cis* configuration of stilbene unit was the most important factor on combretastatin group for inhibition of cancer cell growth.[6,7] In order to search for strong activity oligostilbenes for various pharmacological screening, our attention was directed toward inducting a *cis* configuration of the olefinic bond of oligostilbene. In 1998, Ito *et al*. converted (+)-*trans*-vitisisn A into its *cis* isomer, (+)-*cis*-vitisin A from *Vitis coignetiae* successfully by photochemical reaction.[8] But more reports on photooxidation of stilbene oligomers were not found in the literatures up to now. As a part of our studies on biomimetic synthesis of active stilbenoids, photooxidation reaction of *trans*-ε-viniferin (**2**) from resveratrol (**1**) has been studied and two new compounds, *cis*-ε-viniferin (**3**) and 2b,14b-dehydro–bisresveratrol (**4**) were synthesized successfully. Two methylated products, pentamethoxyl *trans*-ε-viniferin (**5**) and pentamethoxyl *cis*-ε-viniferin (**6**) were also obtained by methylation of **5**. Compounds **3** and **6** are new stilbene dimers with *cis* configurations of the olefinic bonds, and compound **4** is a new phenanthrene derivative with a dihydrobenzofuran ring cyclized from **3**. The structures of compounds **3**—**6** (Figure 1) were determined on the basis of spectral evidences, and photooxidation reaction mechanism was also discussed. The anti-inflammatory activities of compounds **3**—**6** have been tested. Among them, **3** and **4** showed potent inhibition on tumor necrosis factor (TNF-α).

Results and discussion

Oxidative coupling reaction of **1** in methanol using $FeCl_3$•$6H_2O$ as oxidant afforded compound **2** in 30.2% yield. Irradiation of a solution of **2** in ethanol using ultraviolet light (λ=254 nm) as photosensitive oxidant provided compounds **3** and **4** in 24.2% and 20.0% yield respectively. Methylation of **2** with $(MeO)_2SO_4$ in anhydrous acetone yielded compound **5** and its *cis* isomer **6** in 55.5% and 38.3% yields respectively. The reaction process is shown in Figure 2.

Compound **3** was obtained as brown amorphous powder. The molecular formula $C_{28}H_{22}O_6$ was deduced from FABMS *m/z* 454 [M^+], together with ^1H and ^{13}C NMR spectra. The UV-vis spectrum exhibited the absorption bands at λ_{max}^{MeOH} (log ε): 279 (3.68) nm, suggesting the absence of *trans* olefinic bond in the structure. Its ^1H NMR specterum showed the presence of two sets of AA′BB′ system, one set of AB_2 system,

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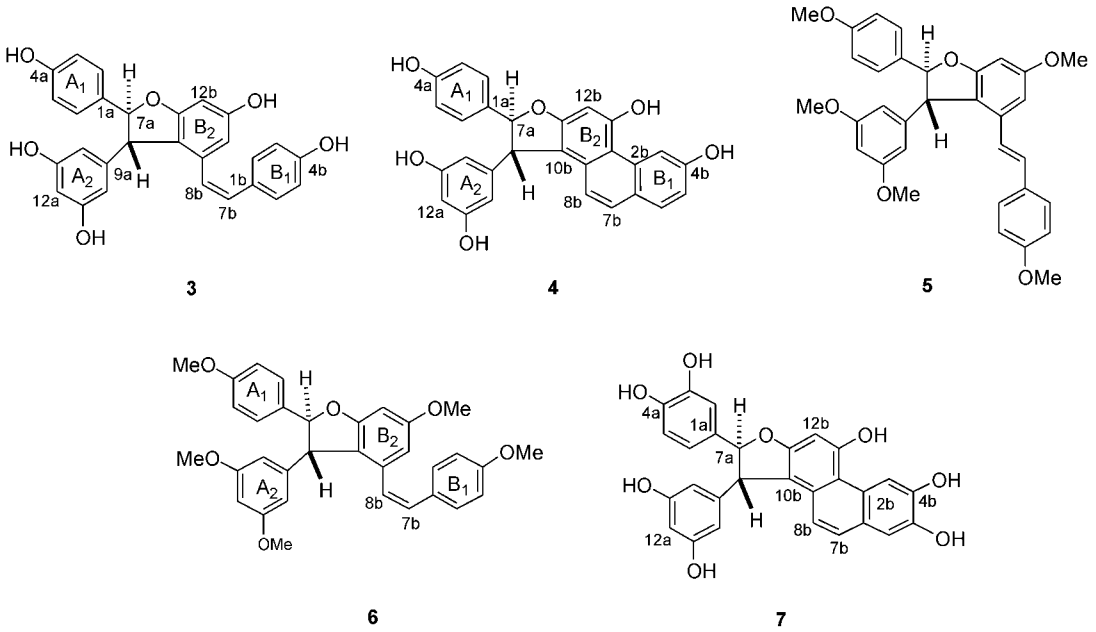

Figure 1 Structures of compounds **3**—**7**.

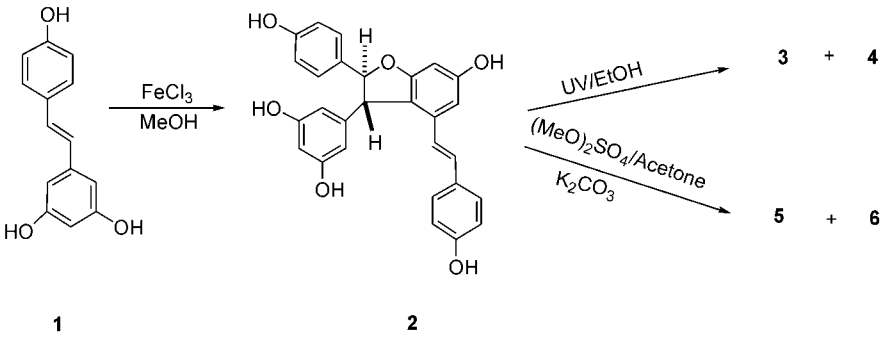

Figure 2 Synthetic routes of stilbenoids.

two *meta*-coupled protons, two *cis* olefinic protons and two coupled aliphatic protons, indicating that compound **3** possessed the similar structure to compound **2** besides two olefinic protons. 7b,8b-protons of **3** resonated at δ 6.24, 6.02 with the coupling constant 12.3 Hz and those of **2** resonated at δ 6.73 and 6.94 with the constant 16.2 Hz in ^{1}H NMR spectra, which indicated that *trans* configuration of the olefinic bond of **2** had been transformed into *cis*-form of **3**. In the NOESY spectum, the interactions between H-7b and H-8b, H-2b or H-6b further confirmed the conclusion. In addition, the correlations between H-7a and H-2(6)a, H-10(14)a, H-8a and H-2(6)a, H-10(14)a indicated a *trans* orientation of H-7a and H-8a. So, the stereostructure of **3** was elucidated as shown in Figure 1.

Compound **4** was obtained as brown amorphous powder. The FAB-MS *m/z* 452 (M^+), together with the ^{1}H and ^{13}C NMR spectra prompted the molecular formula $C_{28}H_{20}O_6$, which indicated that **4** was a dimer of resveratrol. Its UV-vis spectrum displayed the absorption bands at λ_{max}^{MeOH} (log ε): 228 (4.50), 263 (4.42), 271 (4.45), 354 (3.58), 372 (3.68) nm, suggesting the presence of strong conjugated system in the molecule. From the ^{1}H NMR spectrum of **4**, it was deduced the existence of a 1,3,5-trisubstituted phenyl group, a 1,4-disubstituted phenyl group, a 1,2,4-trisubstituted phenyl group and a dihydrobenzofuran ring in the molecule. In addition, the signals of 3b-H at δ 8.85 (d, J=3.0 Hz, 1H), together with a pair of doublet signals at δ 6.72 (d, J=8.7 Hz, 1H), 7.12 (d, J=8.7 Hz, 1H) suggested that the stucture of **4** should have a phenanthrene ring. Its ^{13}C NMR spectrum displayed 28 signals representing 28 carbons (13 quaternary carbons with 6 carbons being oxygenated and 15 tertiary carbons). Colligating the above evidences, compound **4** was deduced as a phenanthrene derivative, which had a similar skeleton to cassigarol D (**7**) from *Cassia garrittiana* (Figure 1).[9] In ^{1}H-^{1}H COSY experiment of **4**, the relationships between H-7b and H-8b, H-5b and H-6b further confirmed the assumption. Thus, compound **4** was identified as a new phenanthrene derivative with a dihydrobenzofuran ring. Its ^{1}H and ^{13}C NMR spectral data were assigned by comparison with those of **7** (Table 1 and Table 2). In NOE experiment of **4**, the correlations between H-7a and H-2(6)a, H-10(14)a, H-8a and H-2(6)a, H-10(14)a indicated a *trans* orientation of H-7a and H-8a. Therefore, the stereostructure of **4** was determined as depicted in Figure 1.

Table 1 ^{1}H NMR data (δ) of compounds **3**, **4**, **5**, **6** and **7** [a]

Position	**3**	**4**	**5**	**6**	**7**
	^{1}H	^{1}H	^{1}H	^{1}H	^{1}H
2a	7.05 d, J=8.7	6.88 d, J=7.8	7.26 d, J=8.7	7.07 d, J=8.7	6.72 d, J=1.9
3a	6.80 d, J=8.7	6.48 d, J=7.8	6.85 d, J=8.7	6.82 d, J=8.7	
5a	6.80 d, J=8.7	6.48 d, J=7.8	6.85 d, J=8.7	6.82 d, J=8.7	6.71 d, J=8.5
6a	7.05 d, J=8.7	6.88 d, J=7.8	7.26 d, J=8.7	7.07 d, J=8.7	6.61 dd, J=8.5,1.9
7a	5.27 d, J=5.7	5.12 d, J=6.0	5.52 d, J=6.0	5.32 d, J=6.0	5.32 d, J=4.6
8a	3.98 d, J=5.7	4.34 d, J=6.0	4.61 d, J=6.0	4.00 d, J=6.0	4.55 d, J=4.6
10a	6.03 d, J=2.1	5.79 d, J=2.1	6.42 d, J=2.1	6.12 d, J=2.1	6.01 d, J=1.9
12a	6.20 t, J=2.1	5.86 t, J=2.1	6.33 t, J=2.1	6.28 t, J=2.1	6.05 t, J=1.9
14a	6.03 d, J=2.1	5.79 d, J=2.1	6.42 d, J=2.1	6.12 d, J=2.1	6.01 d, J=1.9
2b	7.01 d, J=8.7		7.21 d, J=8.7	7.00 d, J=8.7	
3b	6.66 d, J=8.7	8.85 d, J=3.0	6.77 d, J=8.7	6.67 d, J=8.7	9.06 s
5b	6.66 d, J=8.7	6.70 dd, J=8.7, 3.0	6.77 d, J=8.7	6.67 d, J=8.7	
6b	7.01 d, J=8.7	7.27 d, J=8.7	7.21 d, J=8.7	7.00 d, J=8.7	7.07 s
7b	6.24 d, J=12.3	7.12 d, J=8.7	6.74 d, J=16.5	6.24 d, J=11.7	7.36 d, J=8.5
8b	6.02 d, J=12.3	6.72 d, J=8.7	6.95 d, J=16.5	6.06 d, J=11.7	6.96 d, J=8.5
12b	6.28 brs	6.46 s	6.75 d, J=3.0	6.37 d, J=2.1	6.77 s
14b	6.28 brs		6.40 d, J=3.0	6.30 d, J=2.1	
OCH_3			3.77—3.67 5×OCH_3	3.73—3.64 5×OCH_3	

[a] Measured in CD_3COCD_3 at 300 MHz and J in Hz.

Table 2 ^{13}C NMR data (δ) of compounds **3**, **4**, **5**, **6** and **7** [a]

Position	**3**	**4**	**5**	**6**	**7**
	^{13}C	^{13}C	^{13}C	^{13}C	^{13}C
1a	136.4	133.6s	135.5	136.3	132.8
2a	127.6	127.7d	128.0	127.3	112.6
3a	115.1	115.8d	114.2	113.7	145.3
4a	157.5	159.3s	159.9	129.8	145.2
5a	115.1	115.8d	114.2	113.7	115.3
6a	127.6	127.7d	128.0	127.3	116.8
7a	93.5	94.2d	93.0	93.0	92.8
8a	56.3	57.4d	56.5	56.7	56.2
9a	146.4	147.8s	146.5	145.9	146.2
10a	106.1	106.5d	106.2	105.8	105.2
11a	158.9	159.5s	161.7	161.3	158.5
12a	101.1	101.8d	102.3	106.6	100.9
13a	158.9	159.5s	161.7	161.3	158.5
14a	106.1	106.5d	106.2	105.8	105.2
1b	128.7	132.3s	130.2	128.9	125.1
2b	130.3	133.7s	127.2	130.1	129.5
3b	115.4	112.8d	114.1	113.9	112.4
4b	157.0	159.1s	159.9	159.3	145.6

Continued

Position	**3**	**4**	**5**	**6**	**7**
	^{13}C	^{13}C	^{13}C	^{13}C	^{13}C
5b	115.4	115.2d	114.1	113.9	144.1
6b	130.3	130.0d	127.2	130.1	111.9
7b	130.5	128.9d	129.6	130.6	127.3
8b	125.4	120.4d	133.3	125.9	119.4
9b	132.9	125.6s	130.2	131.4	125.1
10b	119.3	114.4s	120.4	120.2	113.1
11b	161.8	156.9s	161.7	161.9	156.8
12b	95.9	97.1d	95.1	94.8	95.8
13b	158.7	158.0s	161.7	161.3	157.3
14b	107.7	114.6s	98.6	98.4	113.5
OCH_3			56.5—54.9	56.8—54.8	

[a] Measurede in CD_3COCD_3 at 75 MHz and J in Hz.

Compound **5** was obtained as colourless oil. Its similar spectral feature to *trans*-ε-viniferin in ^{1}H NMR, ^{13}C NMR and UV-vis spectra indicated that **5** possessed the same skeleton with that of **2**. The signals at δ 3.83—3.67 (15H, 5×OCH_3) in ^{1}H NMR spectrum and signals at δ 56.5—54.5 (5×OCH_3) in ^{13}C NMR, together with the ion peak at m/z 524 (M^+) in FABMS suggested that **5** was pentamethoxyl *trans*-ε-viniferin as showed in Figure 1.

Compound **6** was obtained as colourless oil. Its FAB-MS *m/z* 524 (M^+), together with its ^1H and ^{13}C NMR spectra gave the molecular formula $C_{33}H_{32}O_6$. The UV-vis spectrum suggested the absence of *trans* olefinic bond. Its ^1H NMR spectrum showed the occurrence of two sets of AA'BB' system, a set of AB_2 system, two coupled *cis* olefinic protons (J=11.7 Hz), two coupled *meta*-protons, two coupled aliphatic protons and 15 methoxyl protons. The ^{13}C NMR spectrum of **6** displayed 24 signals representing 33 carbons (11 quarternary carbons with 6 carbons being oxygenated, 17 tertiary carbons and 5 methoxy carbons). These spectral data suggested that **6** had the same skeleton to compound **3** except that 5 methoxyls in **6** replaced 5 hydroxyls in **3**. Thus, compound **6** was determined as shown in structure **6** (Figure 1).

The possible formation mechanism of compounds **3** and **4** by photooxidation of *trans*-ε-viniferin in ethanol may be rationalized as follows. It is reported that isoeugenol can generate radicals $\mathbf{R_4}\cdot$ and $\mathbf{R_5}\cdot$ by photooxidation as shown in Figure 3.[10] Accordingly, **2** may be converted into its *cis*-isomer **3** in EtOH under irradiation of ultraviolet light (λ=254 nm), then the phenolic hydrogen was abstracted by photosensitive oxidant to afford the radical $\mathbf{RO}\cdot$, which exhibited the other resonance hybrids of $\mathbf{R_{14b}}\cdot$. Finally, intramolecular cyclization of the radical led to the generation of compound **4** through the intermediate **8** (Figure 4). Achievement of compounds **3** and **4** in this reaction further confirmed the assumption.

On the other hand, the rotation optical values zero for compounds **2**, **3**, **4**, **5** and **6** showed that all of them were racemoid. Because the oxidative coupling of **1** was a non-stereospecific radical reaction, product **2** was indeed a pair of racemic products. In the course of photooxidation and methylation, the configurations of substrates were not changed. These results were closely in agreement with the formation mechanisms mentioned above.

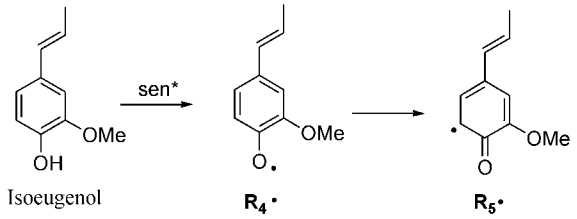

Figure 3 Possible free radicals in the photooxidation of isoeugenol.

Biological activities

The pharmacological activities of compounds **3**, **4**, **5** and **6** have been tested. The inhibitory ratios of tumour necrosis factor-α (TNF-α) for compounds **3**, **4**, **5** and **6** at concentrations of 10^{-5} mol•L^{-1} were 51.43% ($P<0.05$), 36.64% ($P<0.05$) −12.73% and −7.81% ($P>0.05$), respectively. It suggested that compounds **3** and **4** possessed potent inhibition activity, but **5** and **6** were inactive on TNF-α. These results indicated that the hydroxyls and *cis* olefinic bond should be very important in expressing this activity. When hydroxyls were completely situated by methoxyls, the stilbenoids were found to be inactive (such as **3**, **5** and **6**). Moreover, the inhibitory ratio of **4** was less than that of **3**, which may be due to the absence of *cis* olefinic bond in the structure of **4**. Nevertheless, the *cis* olefinic bond seems not to be indispensable because **6** is inactive at all. However, these structure-activity considerations should be confirmed by further biological testing of other oligostilbenes.

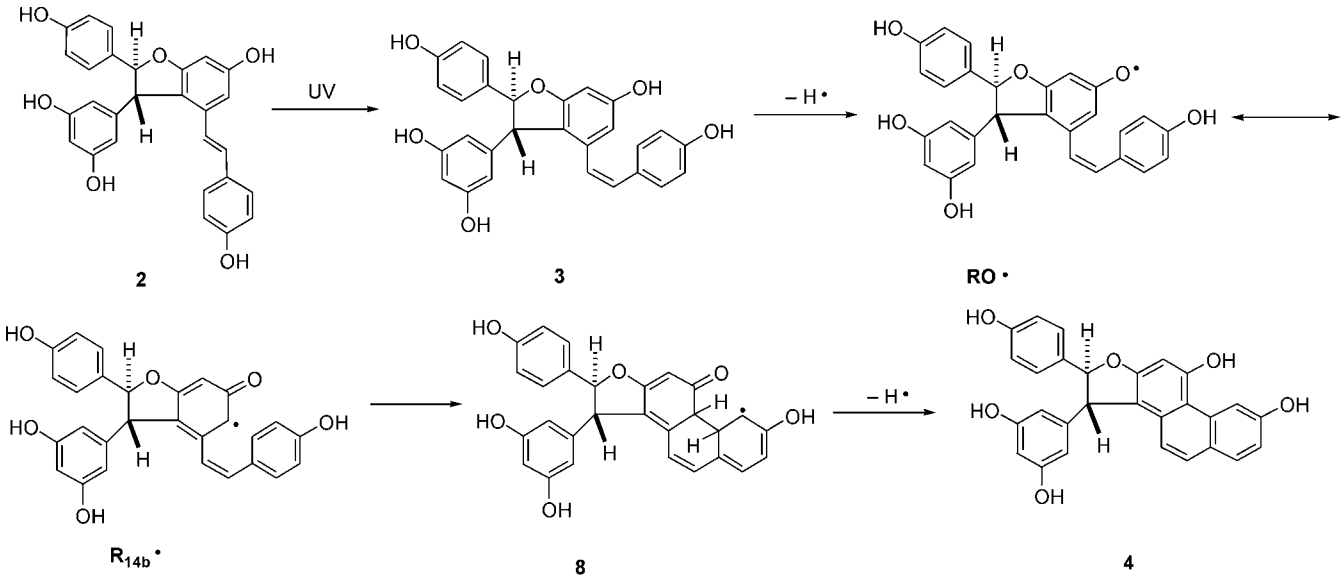

Figure 4 Possible formation mechanism of **3** and **4**.

Experimental

General

IR spectra were run on a Perkin Elmer 683 infrared spectrometer in KBr pellets. UV-vis spectra were taken on a Shimadzu UV-260 spectrophotometer. NMR spectra were carried out on a Mucury 300 spectrometer using TMS as internal standard. FAB-MS data were taken on an autospec-ultima-Tof mass spectrometer and HPLC was performed on Waters 411. TLC was conducted on silica gel GF254 (Qingdao Haiyang Chemical Group Co.), and fluorescence generated by a 200-W medium-pressure Hanovia Hg Lamp with wavelength 254 nm.

Preparation of compound 2 from compound 1

A solution of $FeCl_3$•$6H_2O$ (1.24 g, 4.58 mmol) in water (8 mL) was added dropwise to a solution of **1** (1.03 g, 4.52 mmol) in methanol (10 mL) under stirring. The mixture was kept at room temperature for 49 h. After removal of the methanol *in vacuo*, the residue was diluted with water and extracted with EtOAc three times. Then the combined organic layer was evaporated to dryness (1.66 g), which was subjected to chromatography on silica gel column eluted with cyclohexane acetone (3∶1—2∶1) to provide compound **2** (310 mg, 30.2%) and unreacted compound **1** (408 mg), respectively.

***Trans*-ε-viniferin (2)**: Grey amorphous powder, ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.21 (d, J=8.7 Hz, 2H, 2a-H, 6a-H), 7.19 (d, J=8.4 Hz, 2H, 2b-H, 6b-H), 6.85 (d, J=8.7 Hz, 2H, 3a-H, 5a-H), 6.75 (d, J=8.4 Hz, 2H, 3b-H, 5b-H), 6.94 (d, J=16.2 Hz, 1H, 8b-H), 6.73 (d, J=16.2 Hz, 1H, 7b-H), 6.75 (brs, 2H, 12b-H, 14b-H), 6.34 (t, J=2.2 Hz, 1H, 12a-H), 6.26 (d, J=2.2 Hz, 2H, 10a-H, 14a-H), 5.44 (d, J=5.1 Hz, 1H, 7a-H), 4.46 (d, J=5.1 Hz, 1H, 8a-H); EI-MS *m/z*: 454 [M^+].

Phytooxidation of compound 2 in ethanol

A solution of **2** (100 mg) in anhydrous ethanol (20 mL) was irradiated with a 200-W medium-pressure Hanovia Hg lamp (λ=254 nm) for 1 h under stirring. After removal of the solvent *in vacuo*, the residue (105 mg) was purified by column chromatography on RP-18 eluted with a mixture of methanol-water (4∶6—5∶5) to give two products: compound **3** (24.2 mg, 24.2%) and compound **4** (20 mg, 20%), together with the starting material compound **2** (8.2 mg).

Compound 3: Brown amorphous powder; UV-vis (MeOH) λ_{max} (log ε) 279 (3.68) nm; IR (KBr) ν_{max}: 3346, 2924, 2854, 1697, 1655, 1608, 1514, 1444, 1338, 1238, 1120, 999, 833, 750, 690 cm^{-1}; ^{1}H NMR and ^{13}C NMR see Table 1 and Table 2 respectively. FAB-MS *m/z*: 454 (M^+); HR FAB-MS calcd for $C_{28}H_{22}O_6$ 454.1416, found 454.1420.

Compound 4: Brown amorphous powder; UV-vis (MeOH) λ_{max} (log ε): 228 (4.50), 263 (4.42), 271 (4.45), 354 (3.58), 372 (3.68) nm; IR (KBr) ν_{max}: 3350, 2922, 2850, 1699, 1608, 1516, 1456, 1336, 1215, 1161, 1111, 1005, 833, 690 cm^{-1}. ^{1}H NMR and ^{13}C NMR see Table 1 and Table 2 respectively. FAB-MS *m/z*: 452 (M^+); HR FAB-MS calcd for $C_{28}H_{20}O_6$ 452.1260, found 452.1269.

Preparation of compound 5 and compound 6 from compound 2

$(MeO)_2SO_4$ (138 mg, 1.095 mmol) was added dropwise to a well stirred suspension of compound **2** (100 mg, 0.220 mmol) in anhydrous acetone with K_2CO_3, and the reaction solution was filtered after stirring for 6 h under refluxing, which was evaporated to dryness *in vacuo*. Then the residue (250 mg) was subjected to chromatography on silica gel column (petrol ether-acetone, 40∶1, *V*∶*V*) to afford compounds **5** (64 mg, 55.5%) and **6** (44 mg, 38.3%), respectively.

Compound 5: Colourless oil; UV-vis (MeOH λ_{max} (log ε): 321 (4.23), 225 (sh) (4.56) nm; IR (KBr) ν_{max}: 2929, 1606, 1580, 1512, 1462, 1304, 1248, 1132, 1034, 960, 829 cm^{-1}; ^{1}H NMR and ^{13}C NMR see Table 1 and Table 2 respectively; FAB-MS *m/z*: 524 (M^+); HR FAB-MS calcd for $C_{33}H_{32}O_6$: 524.2199, found 524.2132.

Compound 6: Colourless oil; UV-vis (MeOH) λ_{max} (log ε): 225 (sh) (3.76), 276 (3.22) nm; IR (KBr) ν_{max}: 2954, 2923, 2854, 1660, 1608, 1512, 1464, 1377, 1254, 1132, 1070, 831, 721 cm^{-1}. ^{1}H NMR and ^{13}C NMR see Table 1 and Table 2 respectively; FAB-MS *m/z*: 524 (M^+); HR FAB-MS calcd for $C_{33}H_{32}O_6$ 524.2199, found 524.2191.

Biological assays

Adherent macrophages were harvested from male mice after the injection of brewer thioglycollate medium and were seeded in 48 well cell culture cluster (Costar) at a cell density of 1.1×10^6 cell/mL in RPMI medium 1640 supplemented with 5% (*V*/*V*) newborn calf serum, 100 units/mL penicillin and 100 mg/mL streptomycin. Macrophages that have been incubated with test compound for 1 h were stimulated with lipopolysaccharide (1 μg/mL) for 24 h. The concentration of TNF-α in supernatants was measured as described.[11] The inhibitory effect was expressed as the cytotoxicity of L929 cells. Dexamethasone was used as a positive control with an IC_{50} at 10^{-6} mol•L^{-1}.

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