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PREPARATION OF BIOACTIVE ISORHAPONTIGENIN DIMERS THROUGH CHEMICAL TRANSFORMATION OF BISISORHAPONTIGENIN A

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Abstract –Two new stilbene dimers, bisisorhapontigenin E (**2**) and bisisorhapontigenin F (**3**), and two novel cyclooligostilbenes, bisisorhapontigenin G (**4**) and 13b-methoxyl bisisorhapontigenin G (**5**) were prepared through isomerization reaction of bisisorhapontigenin A with sulfuric acid as a catalyst. Their structures and relative stereochemistry were elucidated on the basis of spectral analysis and their possible formation mechanisms were proposed. The pharmacological activities on anti-inflammation and anti-oxidant of **2-4** have been tested. All of them exhibited potent anti-oxidant activities.

INTRODUCTION

In the past few years, our research group has been engaged in some mimic biosynthesis of oligostilbenes by oxidative coupling reaction using $FeCl_3 \cdot 6H_2O$, Ag_2O etc as oxidants.[1,2,3,4] Among them, most of the products have a benzofuran-type skeleton. Recently, Takaya *et al.* reported that acidic isomerization of (+)-ε-viniferin could produce various types of stilbene dimers.[5] In order to obtain various stilbene

oligomers with special skeletons for pharmacological screening, we picked out bisisorhapontigenin A (**1**), which was synthesized from isorhapontigenins,[3] to achieve a chemical transformation catalyzed by sulfuric acid. Two new cyclooligostilbenes, bisisorhapontigenin E (**2**), bisisorhapontigenin F (**3**), and two novel stilbene dimers, bisisorhapontigenin G (**4**) and 13b-methoxyl bisisorhapontigenin G (**5**) (Figure 1) have been obtained. In this paper, we describe the preparation, structural elucidation, plausible formation mechanisms and activities of these new cyclooligostilbenes.

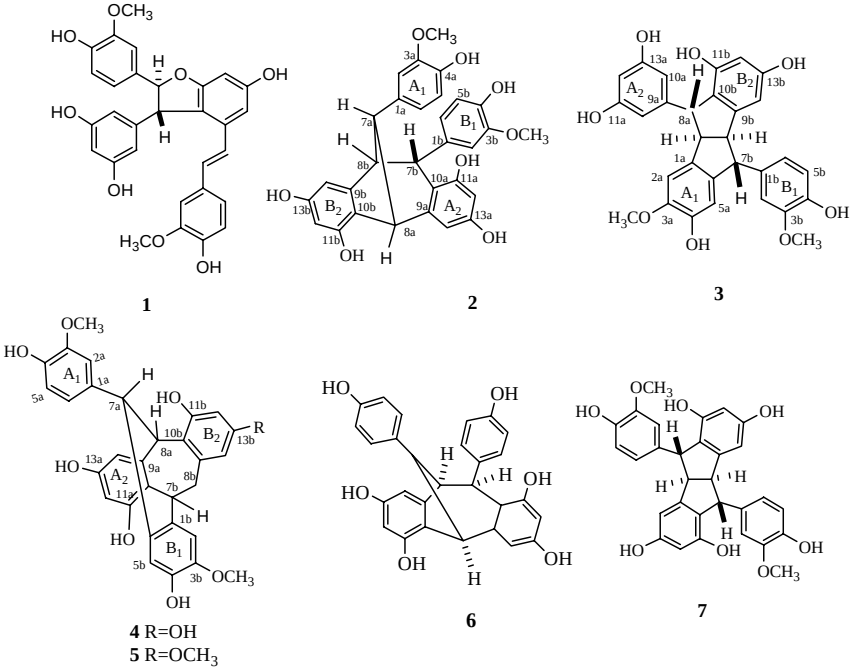

Figure 1. Structures of Compounds (**1**-**7**)

RESULTS AND DISCUSSION

Isomerization of **1** in methanol catalyzed by sulfuric acid afforded four new cyclooligostilbenes, (**2**), (**3**), (**4**) and (**5**) in 4.3%, 6.2%, 12.6% and 2.0% yields, after purification on Rp-18 column chromatography.

Compound (**2**) was obtained as a brown amorphous powder. Its high resolution FAB-MS *m/z* 514.1640 (514.1628 calcd for $C_{30}H_{26}O_8$) agreed with a molecular formula of $C_{30}H_{26}O_8$, indicating that **2** was an isorhapontigenin dimer. The UV absorption bands at λ_{max} (log ε) 226 (4.72), 283 (4.17) nm suggested the absence of *trans* olefinic bond in **2**. Its IR spectrum exhibited absorptions of hydroxyl (3400 cm^{-1}) and aromatic group (1614, 1514, 1464 cm^{-1}). The ^1H NMR spectrum showed the presence of two methoxyls at δ 3.78 (3H, s), 3.63 (3H, s), two sets of ABX system for ring A_1 and ring B_1 at δ 6.96 (1H, d, *J*=1.5 Hz); 6.75 (1H, d, *J*=8.7 Hz), 6.67 (1H, dd, *J*=8.7, 1.5 Hz) and 6.61 (1H, d, *J*=1.5 Hz), 6.57 (1H, d, *J*=8.7 Hz), 6.41 (1H, dd, *J*=8.7, 1.5 Hz), and two sets of *meta*-coupled protons for ring A_2 and ring B_2 at δ 6.02 (1H, d, *J*=1.5 Hz), 6.55 (1H, d, *J*=1.5 Hz) and 6.16 (1H, d, *J*=1.5 Hz), 6.44 (1H, d, *J*=1.5 Hz). In addition, four coupled aliphatic methines at δ 4.21 (1H, brs), 3.44 (1H, brs), 3.69 (1H, brs) and 4.14 (1H, brs) ppm in the ^1H NMR spectrum of **2**, in combination with the corresponding carbon signals at δ 47.4, 57.6, 51.0

and 50.2 ppm in its ^{13}C NMR spectrum suggested that **2** possessed a similar bicyclo[3.2.1]octane skeleton as the natural compound (+)-ampelopsin F (**6**).[5] The difference between them was that the former was an isorhapontigenin dimer, while the latter was a resveratrol dimer. In the HMBC spectrum (Figure 2, **a**), correlations between H-7a/C-2a, C-6a; H-7b/C-6b, C-9b, C-10a, C-11a; and H-8b/C-1b, C-10b, C-14b, C-10a confirmed the connection pattern of the two isorhapontigenins. Thus, the planar structure of **2** was elucidated as depicted in structure (**2**) (Figure 1).

The stereochemistry of **2** was established on the basis of NOE experiments (Figure 2, **b**). Irradiation of the H-7a signals enhanced the signals of H-2a, H-6a, H-8a, illustrating a *cis* orientation of H-7a and H-8a; The NOE enhancements between H-7b with H-2b, H-6b, H-2a, H-6a indicated a *cis* orientation of H-7b, and ring A_1; while NOE interactions between H-8b and H-2b, H-6b, H-7b, H-14b suggested an adjacent relationship of H-8b, H-7b and ring B_1. Thus, the relative stereochemistry of **2** was determined as shown in structure **2** (Figure 1).

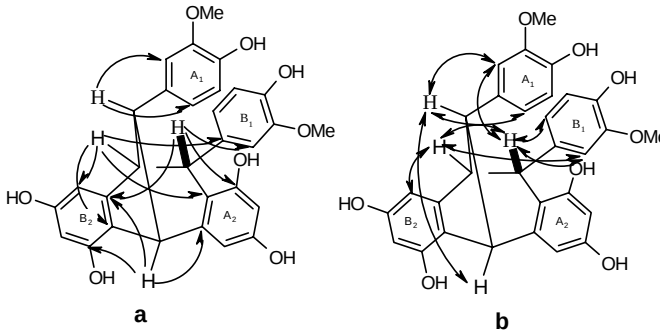

Figure 2. Key HMBC (a) and NOE (b) Interactions of **2**

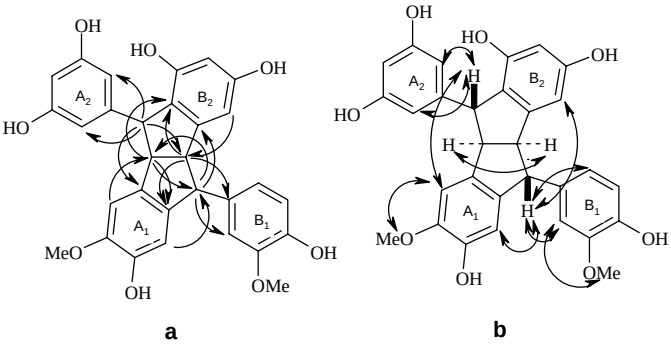

Figure 3. Key HMBC (a) and NOE (b) Correlations of **3**

Compound (**3**) was obtained as a brown amorphous powder. The FAB-MS *m/z* 514 and HR-FAB-MS *m/z* 514.1635 (514.1628 calcd for $C_{30}H_{26}O_8$) gave the molecular formula $C_{30}H_{26}O_8$, which in combination with ^{1}H NMR spectrum suggested that **3** was an isorhapontigenin dimer. Its UV spectrum [λ_{max} (log ε): 226 (4.43), 283 (3.94) nm] was similar to that of **2,** indicating the absence of a *trans* olefinic bond in **3**. The ^{1}H NMR spectrum of **3** showed one set of ABX system attributed to ring B_1 at δ 6.80 (1H, d, *J*=1.8 Hz), 6.72 (1H, d, *J*=8.7 Hz), 6.52 (1H, dd, *J*=8.7, 1.8 Hz), one set of AB_2 system assigned to ring A_2 at δ 6.18 (2H, d, *J*=2.1 Hz), 6.14 (1H, t, *J*=2.1 Hz), one pair of *meta*-coupled protons due to ring B_2 at δ 6.18 (1H, d, *J*=2.1 Hz), 6.55 (brs), and two uncoupled singlets due to ring A_1 at δ 7.16 (1H, s), 6.50 (1H, s). In addition to two methoxyl signals at δ 3.78 (3H, s), 3.90 (3H, s), four coupled aliphatic methine protons at δ 3.89 (2H, m), 4.47 (1H, brs), 4.39 (1H, brs) due to two fused five membered-ring, combined with the corresponding four aliphatic carbon signals at δ 55.2, 58.4, 60.3 (2×C) implicated that the structure of **3** was similar to that of gneafricanin F (**7**),[7] having a bicyclo[3.3.0]octane skeleton. The difference between **3** and **7** was that in the former the two isorhapontigenins were connected by head to head, while in the latter the two units were connected by head to tail. In the HMBC spectrum of **3** (Figure 3, **a**), long range

couplings were observed between H-8a with C-1a, C-7a, C-10(14)a, C-8b, C-10b, and H-7b with C-2b, C-6b, C-8b, C-9b, C-6a, C-7a, indicating that ring A_2 should be attached to C-8a and ring B_2 to C-7b. Thus, the planar structure of **3** was concluded as shown in Figure 1.

Table 1. ^{1}H- and ^{13}C-NMR Data for **2** and **3** (δ in ppm and *J* in Hz)*

Position	**2**		**3**	
	δ_H	δ_C	δ_H	δ_C
1a		139.0		137.6
2a	6.96 d, 1.5	112.9	7.16 s	107.9
3a		147.6		148.2
4a		145.3		147.3
5a	6.75 d, 8.7	115.1	6.50 s	112.1
6a	6.67 dd, 8.7, 1.5	121.3		138.6
7a	4.21 d, 1.5	47.4	3.89 m	60.3
8a	3.44 brs	57.6	4.47 brs	55.2
9a		147.9		149.6
10a		127.7	6.18 d, 2.1	106.7
11a		153.1		159.3
12a	6.02 d, 1.5	101.7	6.14 t, 2.1	101.0
13a		158.6		159.3
14a	6.55 d, 1.5	104.1	6.18 d, 2.1	106.7
1b		136.1		139.3
2b	6.61 d, 1.5	112.2	6.80 d, 1.8	111.8
3b		147.6		148.3
4b		145.4		145.5
5b	6.57 d, 8.7	115.1	6.72 d, 8.7	115.7
6b	6.41 dd, 8.7, 1.5	120.8	6.52 dd, 8.7, 1.8	120.3
7b	3.69 s	51.0	4.39 brs	58.4
8b	4.14 brs	50.2	3.89 m	60.3
9b		147.8		150.7
10b		113.3		122.7
11b		157.1		159.3
12b	6.16 d, 1.5	101.6	6.18 d, 2.1	102.4
13b		157.9		155.5
14b	6.44 d, 1.5	105.6	6.55 brs	103.2
OCH_3	3.78 s	56.2	3.90 s	56.4
OCH_3	3.63 s	55.9	3.78 s	56.2

* Measured in CD_3COCD_3 at 500 MHz for ^{1}H NMR, and 125 MHz for ^{13}C NMR, repectively.

In order to clarify the stereochemistry of **3**, the NOE difference experiment (Figure 3, **b**) was carried out. Irradiation of the H-7a signal enhanced the signal of H-8b, suggesting a *cis* orientation of H-7a and H-8b; irradiation of the H-8a signal showed enhancements of H-2a, H-10(14)a signals, suggesting a *trans* orientation of H-7a and H-8a; as well as H-7b and H-8b. Therefore, the relative stereochemistry of **3** was assigned as depicted in Figure 1.

Compound (**4**) was obtained as a brown amorphous powder. It was found to have the molecular formula of $C_{30}H_{26}O_8$ by HR-FAB-MS *m/z* 514.1632 (514.1628 calcd for $C_{30}H_{26}O_8$), suggesting that **4** should be an isorhapontigenin dimer with 18 degrees of unsaturation. The ^{1}H NMR spectrum of **4** showed the presence of one set of ABX system due to ring A_1 at δ 6.08 (1H, d, *J*=2.1 Hz), 6.57 (1H, d, *J*=8.1 Hz), 6.46 (1H, dd, *J*=8.1, 2.1 Hz), two pairs of *meta*-coupled aromatic protons due to ring A_2 and ring B_2 at δ 6.30 (1H, d,

Table 2. ^{1}H- and ^{13}C-NMR Data for **4** and **5** (δ in ppm and *J* in Hz)*

Position	**4**			**5**	
	δ_H	δ_C	HMBC	δ_H	δ_C
1a		139.3			139.1
2a	6.08 d, 2.1	113.6	C-1a, 3a, 4a, 6a	6.06 s	113.6
3a		147.3			147.3
4a		145.5			145.5
5a	6.57 d, 8.1,	114.6	C-1a, 3a, 4a	6.57 d, 8.1	114.6
6a	6.46 dd, 8.1, 2.1	122.0	C-5a, 5a, 8a	6.46 brd, 8.1	121.9
7a	4.71 d, 4.2	49.8	C-8a, 9a, 10a, 1b, 10b	4.70 d, 3.9	49.8
8a	4.41 d, 4.2	56.2	C-1a, 7a,9a,6b	4.39 d, 3.9	55.0
9a		143.7			143.4
10a		123.2			123.1
11a		154.2			158.9
12a	6.30 d, 2.4	101.1	C-10a,11a,13a,14a	6.35 d, 3.0	101.5
13a		156.1			154.3
14a	5.64 d, 2.4	110.7		5.62 d, 2.0	110.6
1b		134.4			134.3
2b	6.91 s	114.4	C-1b, 6b, 4b	6.91 brs	114.4
3b		146.5			146.6
4b		145.1			145.1
5b	6.26 s	120.1	C-3b, 4b, 6b	6.25 s	120.1
6b		132.1			131.9
7b	4.93 t, 4.2	40.8	C-9a,10a,11a,1b,2b, 6b, 8b, 9b	4.94 t, 3.9	40.7
8bα	3.20 dd, 4.2, 7.0	44.0	C-10a, 6b, 7b, 9b, 10b, 14b	3.23 m	44.3
8bβ	3.20 dd, 4.2, 7.0				
9b		140.8			140.8
10b		119.2			120.5
11b		156.5			156.2
12b	6.23 d,2.4	101.4	C-11b,13b,14b	6.23 d, 2.1	100.0
13b		156.5			156.5
14b	5.98 d, 2.4	109.8	C-10b,12b,13b	6.02 d, 2.4	107.6
OCH_3	3.44 s	56.0		3.43 s	56.0
OCH_3	3.84 s	56.1	C-10a, 12a, 13a	3.84 s	56.1
OCH_3				3.60 s	56.1

* Measured in CD_3COCD_3 at 500 MHz for ^{1}H NMR, and 125 MHz for ^{13}C NMR, repectively.

J=2.4 Hz), 5.64 (1H, d, *J*=2.4 Hz), and 6.23 (1H, d, *J*=2.4 Hz), 5.98 (1H, d, *J*=2.4 Hz), two uncoupled singlets at δ 6.91 (1H, s), 6.26 (1H, s) due to ring B_1, and two methoxyl signals at δ 3.44 (3H, s), 3.84 (3H, s), as shown in Table 3. Moreover, five coupled aliphatic proton signals at δ 4.71 (1H, d, *J*=4.2 Hz), 4.41

(1H, d, *J*=4.2 Hz), 4.93 (1H, t, *J*=4.2 Hz) and 3.20 (2H, dd, *J*=4.2, 7.0 Hz), in combination with the corresponding carbon signals at δ 49.8, 56.2, 40.8 and 44.0 indicated that **4** has a bicyclo[3.3.2]decane skeleton. By comparing the ^{1}H NMR signal patterns with those of bisisorhapontigenin A,[3] two uncoupled singlets in **4** instead of the ABX system in bisisorhapontigenin A and the absence of dihydrobenzofuran signals in **4** implicated that C-7a was connected with ring B_1 forming an eight membered-ring. This conjection was further confirmed by the following evidence. As shown in Figure 4, correlations between H-7a and C-8a, C-9a, C-1b, C-10b, H-8a and C-1a, C-6b, H-7b and C-9a, C-10a, C-11a, C-2b, C-6b, C-8b, C-9b, H-8b (α, β) and C-10a, C-10b, C-14b were observed in the HMBC spectrum (Figure 4, **a**). Consequently, the structure of **4** should be characterized as shown in Figure 1.

The stereochemistry of **4** was established on the basis of NOE difference experiments (Figure 4, **b**). Irradiation of the H-7a doublet enhanced the signals of H-2a, H-6a, H-8a and H-5b, suggesting a *cis* orientation of H-7a and H-8a; Irradiation of the H-8bα and H-8bβ signals enhanced the signals of H-7b and H-14b but no enhancement of the signals for H-2a and H-6a was observed, suggesting a *cis* orientation of ring A_1 and ring A_2. Therefore, the relative configuration of **4** could tentatively be assigned as structure (**4**) (Figure 1).

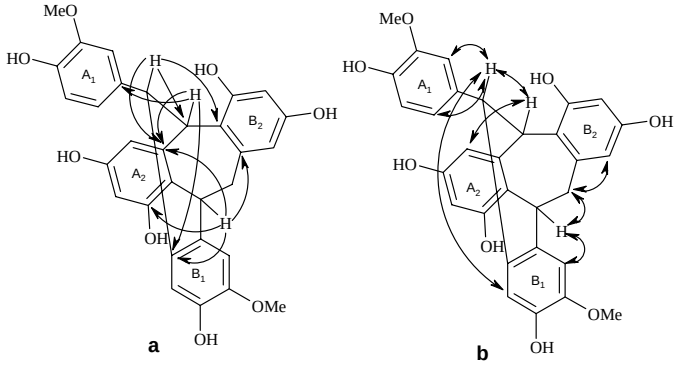

Figure 4. Significant HMBC (**a**) and NOE (**b**) Interactions of **4**

Compound (**5**) was obtained as a light brown amorphous powder. Its UV, IR, ^{1}H NMR and ^{13}C NMR spectra resembled closely to those of **4**, suggesting that they have the similar skeletons. The HR-FAB-MS *m/z* 528.1780 (528.1784 calcd for $C_{31}H_{28}O_8$) suggested the molecular formula of $C_{31}H_{28}O_8$, which indicated that the structure of **5** have one methyl more than that of **4**. A singlet at δ 3.60 ppm for a methoxyl in the ^{1}H NMR spectrum of **5**, together with the corresponding carbon signal at δ 56.0 ppm further confirmed the above assumption. In the NOE difference experiments, irradiation of the methoxyl signals at δ 3.60 ppm showed enhancement of the H-12b, H-14b signals, suggesting that the methoxyl should be located at C-13b. The relative configuration of **5** (Figure 1) was identical to that of **4**. Accordingly, the relative configuration of **5** was determined as shown in Figure 1. Both **4** and **5** belong to a new type of oligostilbenes with a bicyclo[3.3.2]decane skeleton.

According to the isomerization reaction mechanisms of ε-viniferin,[5] the possible formation mechanisms of compounds (**2**), (**3**), (**4**) and (**5**) may be rationalized as follows (Figure 5). The difference of the products is apparently due to the difference of the position of the protonation at the initial stage of the reaction. In the case of path a, the reaction started with protonation of the double bond, followed by cyclization to form the intermediate (**A**). Subsequently, an acidic protonation of the oxygen atom on the

dihydrofuran ring, followed by nucleophilic attack of ring C yielded compound (**4**); afterwards, a hydroxyl of **4** was connected to a methoxyl by acidic methanol forming compound (**5**). In the case of path b, an acidic protonation of the oxygen atom on the dihydrofuran ring, followed by nucleophilic attack of the double bond, formed a intermediate (**B** or **C**). In the case of **B** or **C**, second nucleophilic attack of ring B or ring A and subsequent deprotonation gives product (**2**) or (**3**).

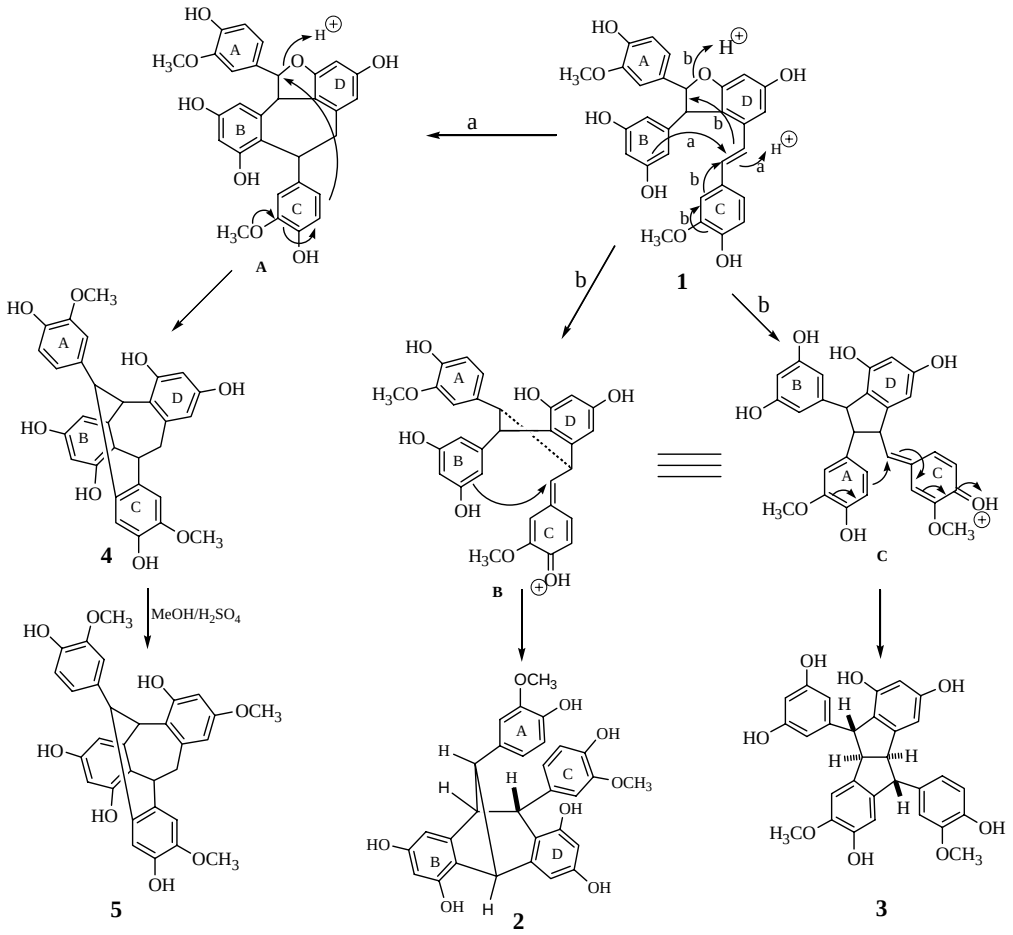

Figure 5. Plausible Formation Mechanisms of Compounds (**2**), (**3**), (**4**) and (**5**)

Table 3. Inhibitory activities on TNFα and MDA of **2**, **3** and **4** *

	TNFα inhibitory rates (%)	MDA inhibitory rates(%)		
	1×10^{-5}M	1×10^{-4}M	1×10^{-5}M	1×10^{-6}M
2	-12.70	99.57	93.27	87.42
3	-12.83	97.83	91.97	87.63
4	-9.96	99.78	94.14	58.78

* Dexamethasone was used as a positive control for TNFα with IC_{50} of 1×10^{-6} M, and Vit E was used for MDA with IC_{50} of 1×10^{-6} M.

The pharmacological activities of anti-oxidant and anti-inflammatory of compounds (**2**-**4**) have been evaluated. As shown in Table 3, none of them were found to be active on TNF-α. Nevertheless, the inhibitory rates of malondialdehyde (MDA) for compounds (**2**), (**3**) and (**4**) at a concentration of $1x10^{-6}$ M

were 87.42%, 87.63% and 58.78% (as a positive control, the inhibitory rate of MDA for vitamin E at concentration of 1×10^{-6} M was 50.60%) respectively. The results suggested that **2**, **3** and **4** have potent anti-oxydant activity.

EXPERIMENTAL

General

IR spectra were run on a Perkin Elmer 683 infrared spectrometer in KBr pellets. UV spectrum were taken on a Shimadzu UV-300 spectrophotometer. NMR spectra were carried out on AM 500 using TMS as internal standard. FAB-MS were obtained by using an Autospec-Ulma-Tof mass spectrometer and HPLC on Waters 411. Bisisorhapontigenin A (500 mg) was synthesized in previous paper.[3]

Biomimetic Synthesis of 2-5

Bisisorhapontigenin A (**1**, 500 mg) from isorhapontigenin was dissolved in 50 ml anhydrous methanol containing 2.5 ml sulfuric acid. The solvent was refluxed 72 h under stirring, then much water was added. The mixture was extracted with EtOAc three times, the extract was combined and concentrated *in vacuo* to afford a residue (495 mg), which was subjected to column chromatography on RP-18 using MeOH-H_2O (3:7-4:6) as eluent yielding compounds (**2**) (21.3 mg, 4.3%), (**3**) (31 mg, 6.2%), (**4)** (63 mg, 12.6%) and (**5**) (10 mg, 2.0%) respectively.

Bisisorhapontigenin E (2): A brown amorphous powder; mp 256-268 °C; $[\alpha]_D^{25}$ 0° (*c*=0.10, MeOH); FAB-MS: *m/z* 514 (M^+); HR-FAB-MS: *m/z* 514.1640 (514.1628 calcd for $C_{30}H_{26}O_8$); UV λ_{max} (MeOH) (logε) nm: 226 (4.72), 283 (4.17); IR ν_{max} (KBr) 3400, 1614, 1514, 1464, 1336, 1269, 1146, 1032, 845 cm^{-1}. ^{1}H- and ^{13}C-NMR (acetone-d_6) see Table 1.

Bisisorhapontigenin F (3): A brown amorphous powder; mp 189-191 °C; $[\alpha]_D^{25}$ 0° (*c*=0.10, MeOH); FAB-MS: *m/z* 514 (M^+); HR-FAB-MS: *m/z* 514.1635 (514.1628 calcd for $C_{30}H_{26}O_8$); UV λ_{max} (MeOH) (logε) nm: 226 (4.43), 283 (3.94); IR ν_{max} (KBr) 3400, 1604, 1514, 1502, 1464, 1323, 1259, 1128, 1032, 995, 847, 688 cm^{-1}; ^{1}H- and ^{13}C-NMR (acetone-d_6) see Table 1.

Bisisorhapontigenin G (4): A brown amorphous powder; mp 232-234 °C; $[\alpha]_D^{25}$ 0° (*c*=0.10, MeOH); FAB-MS: *m/z* 514 (M^+); HR-FAB-MS: *m/z* 514.1632 (514.1628 calcd for $C_{30}H_{26}O_8$); UV λ_{max} (MeOH) (log ε) nm: 226 (4.45), 283 (3.95); IR ν_{max} (KBr) 3300, 1612, 1514, 1448, 1348, 1273, 1144, 1053, 1007, 854, 746 cm^{-1}; ^{1}H- and ^{13}C-NMR (acetone-d_6) see Table 2.

13b-Methoxyl bisisorhapontigenin E (5): A brown amorphous powder; mp 202-204 °C; $[\alpha]_D^{25}$ 0° (*c*=0.10, MeOH); FAB-MS: *m/z* 528 (M^+); HR-FAB-MS: *m/z* 528.1780 (528.1784 calcd for $C_{31}H_{28}O_8$); UV λ_{max} (MeOH) (log ε) nm: 226 (3.97), 282 (3.53); IR ν_{max} (KBr) 3400, 2924, 2852, 1647, 1612, 1514, 1464, 1354, 1273, 1146, 1124, 1053, 1007, 849, 669 cm^{-1}; ^1H NMR and ^{13}C NMR see Table 2.

Anti-inflammation and Anti-oxidant Activity Tests were carried out in accord with the methods discussed in the literature.[8,9]

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