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Alkenes with antioxidative activities from *Murraya koenigii* (L.) Spreng

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ABSTRACT

Four new alkenes (**1**–**4**), and six known alkenes (**5**–**12**) were isolated from *Murraya koenigii* (L.) Spreng. Their structures were elucidated on the basis of spectroscopic analyses and references. Compounds (**1**–**12**) were evaluated for antioxidative activities. Among them, compounds **1**, **2**, **4**, and **7** exhibited significant antioxidative activities using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay with IC_{50} = 21.4–49.5 μM. The known compounds (**5**–**12**) were isolated from this plant for the first time.

Murraya koenigii (L.) Spreng has been known as a spice in Southeast Asia areas for a long time, which is mainly distributed the tropical and subtropical areas in the world. In fork, *M. koenigii* is not only used as condiment, but also herb. Previous phytochemical investigation of this plant reported the presence of various compounds such as alkaloids,[1] coumarins,[2,3] and volatile oils.[4–6] Modern pharmacology revealed that *M. koenigii* exhibited many pharmacological activities such as antidiarrhoeal,[7] antimicrobial,[8] hepatoprotective,[9] radical-scavenging,[10] hypoglycemic,[11] and immunomodulatory[12] activities. The biological importance of *M. koenigii* encouraged us to undertake a phytochemical study of this plant. According to references, the bioactivities of alkenes from *M. koenigii* were previously little chemically studied. Consequently, we described here the bio-guided isolation and structure elucidation of four new alkenes (**1**–**4**), together with six known alkenes (**5**–**12**) from the EtOAc-soluble fraction of *M. koenigii*. Meanwhile, all the compounds (**1**–**12**) (Fig. 1) were evaluated for their antioxidative activities, compounds **1**, **2**, **6**, and **7** exhibited significant antioxidative activities using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay with IC_{50} = 21.4–49.5 μM (Table 3).

Compound **1** was isolated as a colorless amorphous powder and its molecular formula was determined to be $C_{21}H_{36}O_8$ by HR-ESI-MS data (*m*/*z* 439.2310 $[M+Na]^+$, calcd. for 439.2302) elucidating four degrees of unsaturation. The UV spectrum showed at λ_{max} 201, 233 nm. The IR spectrum indicated the presence of hydroxyl (3370.5 cm^{-1}), methyl (2921.5, 1376.5 cm^{-1}) functionalities.

The ^1H NMR spectrum of compound **1** exhibited a typical terminal double bond[13] at δ_H 6.00 (1H, dd, *J* = 17.1, 6.3 Hz, H-11), 5.23 (1H, d, *J* = 6.3 Hz, H-12a), 5.05 (1H, d, *J* = 17.1 Hz, H-12b), two trans double bonds at δ_H 5.77 (1H, t, *J* = 15.9, 6.3 Hz, H-4), 6.19 (1H, d, *J* = 15.9 Hz, H-5), and an alkene hydrogen at δ_H 5.59 (1H, m, H-7) in the low field. Furthermore, in the middle field of the ^1H NMR spectrum, there were four methyl signals according to the data of ^1H NMR and ^{13}C NMR (Table 1). In addition, a characteristic doublet at δ_H 4.45 (1H, d, *J* = 7.5 Hz, H-1′) was ascribed to the anomeric proton of the glucosyl unit, corresponding to δ_C 106.4 (C-1′) of the ^{13}C NMR and HSQC spectra, which indicated the presence of the glucose in compound **1** (Table 1). In the HMBC spectrum of **1**, correlations of H-3/C-1′, C-2; H-4/C-3, C-5; H-5/C-4, C-6; H-7/C-6, C-9; H-8/C-6; H-9/C-10; H-11/C-10; H-12/C-10, C-11; H-1′/C-3, C-3′ (Fig. 2) indicating the planar construction of **1**. Moreover, the relative configuration of compound **1** was determined by the 2D-NOESY correlations of H-1′/H-3; H-4/H-3, H-5 (Fig. 2).

According to the biosynthesis pathway and literature[14] of compound **1**, the absolute configuration of C-10 was identified as 10*R*. In addition, the absolute configuration of C-3 was determined by the CD method. The 10-OH of compound **1** was protected by *tert*-butyldimethylsilyl chloride (TBSCl),[15] and obtained ramification

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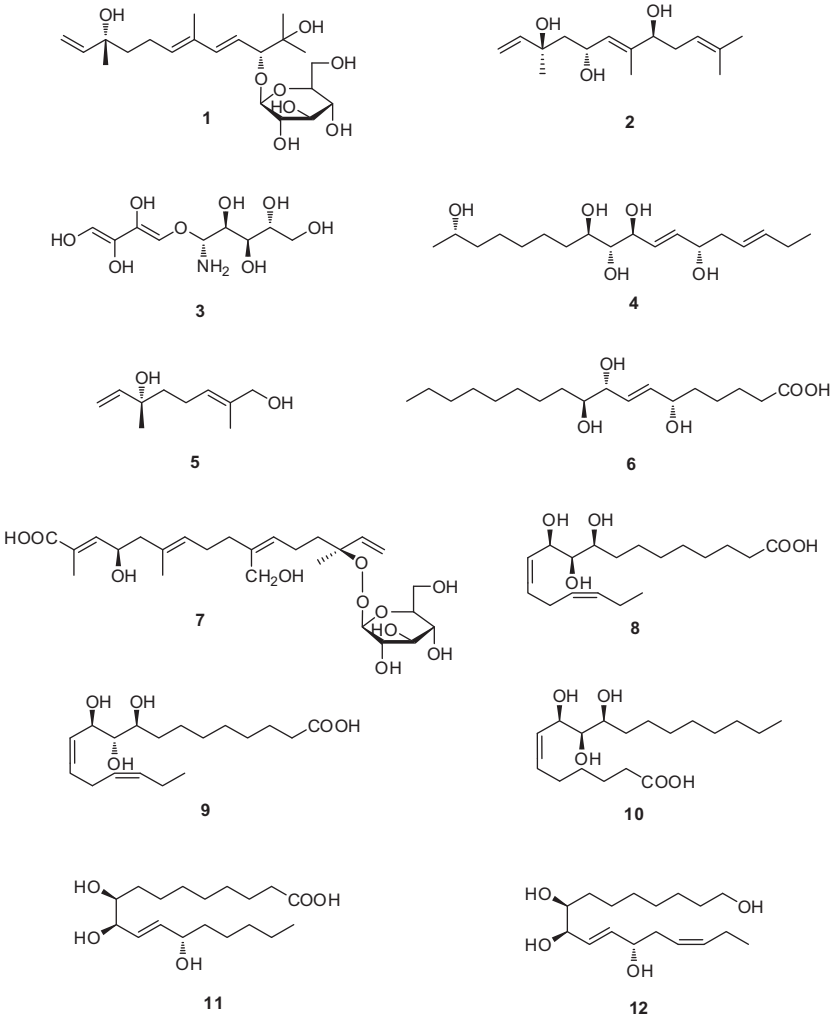

Figure 1. Structures of compounds (**1**–**12**).

1a. Compound **1a** was a TBS ether which its 10-OH was protected by TBSCl, then its CD spectrum was recorded on a JASCO J-815 CD spectrometer. From the CD spectrum of compound **1a**, it was found that the positive cotton effect at 285 ($\Delta\varepsilon$ +0.08) nm and the negative cotton effect at 228 ($\Delta\varepsilon$ −0.85) nm, which was induced by reagent of $MO_2(OAC)_4$. According to the spiral rule and literature,[13] compound **1** was identified as (3*S*,4*E*,6*E*,10*R*)-2,10-dihydroxy-2-hydroxy-2-methylethyl-6,10-di-methyl-4,6,11-sencolaninic-3-β-D-glucopyranoside.

Compound **2** was obtained as a colorless amorphous powder. Its molecular formula, $C_{15}H_{26}O_3$, with three degrees of unsaturation, was based on HR-ESI-MS data (*m*/*z* 277.1776 $[M+Na]^+$, calcd. for 277.1774). The UV spectrum showed at λ_{max} 202, 230 nm. The IR spectrum indicated the presence of hydroxyl (3423.3 cm^{-1}), methyl (2973.0, 1372.3 cm^{-1}) functionalities. The UV and IR data of compound **2** were similar to those of compound **1**. So, compounds 1 and 2 were both alkeno-derivatives.

The ^1H NMR spectrum of **2** (Table 1) revealed the presence of a typical terminal double bond[13] at δ_H 5.20 (1H, dd, *J* = 12.0, 2.0 Hz, H-1a), 4.96 (1H, dd, *J* = 6.0, 2.0 Hz, H-1b), 5.93 (1H, dd, *J* = 12.0, 2.0 Hz, H-2) and two protons of alkene at δ_H 5.21 (1H, d, *J* = 15.5 Hz, H-6), 5.66 (1H, m, H-10) in the middle field. Furthermore, four methyl signals were observed in the ^1H NMR and ^{13}C NMR spectra of compound **2** (Table 1). The planar construction of compound **2** was determined by the HMBC correlations of H-1/C-2, C-3; H-2/C-3; H-4/C-2, C-3, C-6; H-6/C-4, C-8; H-9/C-11; H-10/C-8, C-11 (Fig. 2). According to the correlations of H-2/3-CH_3; H-10/8-OH of 2D-NOESY spectrum, the relative configuration was identified. The 3-OH of compound **2** was protected by *tert*-butyldimethylsilyl chloride (TBSCl),[15] and obtained ramification **2a**. Compound **2a** was also a TBS ether which the 3-OH was protected by TBSCl. The ramification **2a** was measured by the CD method. The CD spectrum of compound **2a** showed that the positive cotton effect at 218 ($\Delta\varepsilon$ +0.56) nm, which was induced by reagent of $Rh_2(OCOCF_3)_4$. Consequently, compound **2** was identified as (3*R*,5*S*,6*E*,8*S*,10*E*)-3,7,11-trimethyl-1,6,10-dodecatriene-3,5,8-triol according to the spiral rule and reference.[13]

Compound **3** was isolated as a colorless powder, its molecular formula was determined to be $C_9H_{17}NO_8$ by HR-ESI-MS data (*m*/*z* 290.0853 $[M+Na]^+$, calcd. for 290.0846) with two degrees of unsaturation. The UV spectrum showed at λ_{max} 206, 260 nm. The IR absorption at 3332.3 cm^{-1} suggested the presence of amino group in compound **3**.

In the ^1H NMR spectrum of compound **3**, there were two single peaks of at δ_H 8.19 (1H, s, H-1), 8.32 (1H, s, H-4) in the aromatic field, it can be concluded two alkene hydrogens by the degrees of unsaturation of compound **3**. Moreover, a double-peak of single proton at δ_H 5.97 (1H, d, *J* = 6.3 Hz, H-5) in the middle field which indicated that the fragment of $-NH_2$ was in compound **3** according to Ref. 16. The ^{13}C NMR spectrum (Table 2) of compound **3** showed

Table 1
^{1}H NMR, ^{13}C NMR, and HMBC correlations of compound (**1**–**2**)

No.	**1**			**2**		
	δ_H	δ_C	HMBC (^{1}H–^{13}C)	δ_H	δ_C	HMBC (^{1}H–^{13}C)
1a	1.20(s)	24.5	—	5.20(d,12.0,2.0)	111.3	C-2,C-3
1b	1.20(s)	24.5	—	4.96(dd,6.0,2.0)	111.3	C-2,C-3
2	—	74.7	—	5.93(dd,12.0,2.0)	146.9	C-3
3	3.49(m)	90.4	C-1′,C-2	—	72.8	—
4	5.77(t,15.9,6.3)	129.9	C-3,C-5	2.22(d,6.0)	46.4	C-2,C-3,C-6
5	6.19(d,15.9)	139.3	C-4,C-6	3.79(dt,13.0,6.5)	86.3	—
6	—	134.9	—	5.21(d,15.5)	139.8	C-4,C-8
7	5.59(m)	123.2	C-6,C-9	—	140.8	—
8a	2.48(m)	31.4	C-6	3.57(dd,14.0,7.0)	83.3	—
8b	2.25(m)	31.4	C-6	3.57(dd,14.0,7.0)	83.3	—
9a	2.33(m)	46.9	C-10	1.83(m)	38.3	C-11
9b	2.33(m)	46.9	C-10	1.64(m)	38.3	C-11
10	—	73.9	—	5.66(m)	123.7	C-8,C-11
11	6.00(dd,17.1,6.3)	146.4	C-10	—	139.8	—
12a	5.23(d,6.3)	111.9	C-10,C-11	1.12(s)	26.7	—
12b	5.05(d,17.1)	111.9	C-10,C-11	1.12(s)	26.7	—
1′	4.45(d,7.5)	106.4	C-3,C-3′	—	—	—
2′	3.27(m)	75.9	—	—	—	—
3′	3.36(m)	78.3	—	—	—	—
4′	3.24(m)	71.6	—	—	—	—
5′	3.34(m)	77.8	—	—	—	—
6′a	3.89(dd,11.8,5.9)	62.8	—	—	—	—
6′b	3.74(dd,11.8,4.8)	62.8	—	—	—	—
2-CH_3	1.22(s)	26.3	—	—	—	—
3-CH_3	—	—	—	1.19(s)	26.9	—
6-CH_3	1.74(s)	12.9	—	—	—	—
7-CH_3	—	—	—	1.26(s)	27.6	—
10-CH_3	1.24(s)	27.1	—	—	—	—
11-CH_3	—	—	—	1.09(s)	26.3	—

1 1H NMR (300 MHz, CD_3OD), ^{13}C NMR (125 MHz, CD_3OD).
2 ^{1}H NMR (300 MHz, CD_3COCD_3), ^{13}C NMR (125 MHz, CD_3COCD_3).

nine carbons except for two double bonds. Consequently, five saturated carbons was left, which indicated the fragment of –CHOHCHOHCHOHCH$_2$OH was in compound **3** according to its molecular formula. The planar configuration of compound **3** was determined by the HMBC correlations of H-1/C-2, C-3; H-4/C-3; H-5/C-4, C-6; H-6/C-5, C-8; H-7/C-5, C-8, C-9; H-8/C-7; H-9/C-7, C-8 (Fig. 2). Moreover, the relative configuration of compound **3** was determined by the 2D-NOESY spectrum correlations of H-4/H-5, H-6/H-8, H-7/H-9 (Fig. 2).

The absolute configuration of compound **3** was determined by circular dichroism (CD) method. According to the spiral rule and literature,[16] the CD spectrum of compound **3a** showed that the positive cotton effect at 230 ($\Delta\varepsilon$ +0.21), 311 ($\Delta\varepsilon$ +0.01) nm and the negative cotton effect at 267 ($\Delta\varepsilon$ −0.84) nm, which was induced by reagent of $MO_2(OAC)_4$. Therefore, compound **3** was identified as (5*S*,6*R*,7*S*,8*R*)-5-amino-(2*Z*,4*Z*)-1,2,3-trihydroxybuta-2,4-dienyloxy-pentane-6,7,8,9-tetraol.

Compound **4** was obtained as a colorless powder, its molecular formula was determined to be $C_{18}H_{34}O_5$ with by HR-ESI-MS data (*m*/*z* 353.2303 [M+Na]$^+$, calcd. for 353.2298) elucidating two degrees of unsaturation. The UV spectrum showed at λ_{max} 203 nm. The IR absorption at hydroxyl (3332.0 cm^{-1}), methyl (2926.6, 1407.4 cm^{-1}) functionalities.

The ^{1}H NMR spectrum of compound **4** (Table 2) revealed the presence of two trans double bonds at δ_H 5.44 (1H, d, *J* = 15.9 Hz, H-3), 5.46 (1H, d, *J* = 15.9 Hz, H-4) and 5.68 (1H, d, *J* = 16.0 Hz,

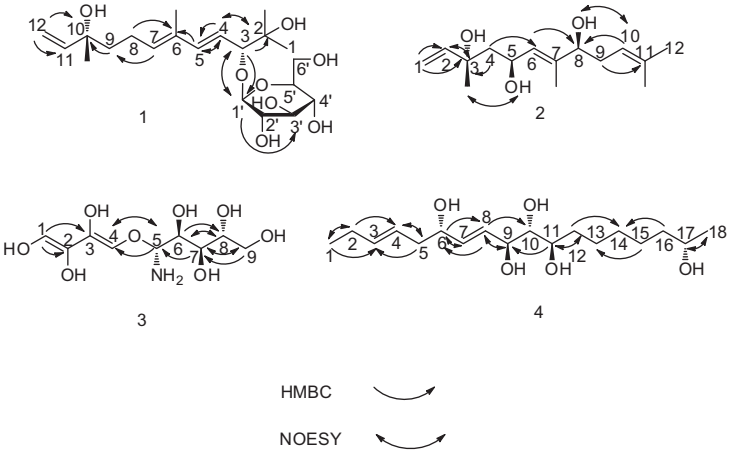

Figure 2. Key HMBC (H → C) and NOESY correlations of (**1**–**4**).

Table 2
^{1}H NMR (300 MHz, CD_3OD), ^{13}C NMR (125 MHz, CD_3OD), and HMBC correlations of compounds (**3**–**4**)

No.	**3**			**4**		
	δ_H	δ_C	HMBC (^{1}H–^{13}C)	δ_H	δ_C	HMBC (^{1}H–^{13}C)
1	8.19(s)	153.5	C-2,C-3	0.97(t,15.0,7.5)	14.6	C-2,C-3
2	—	157.6	—	2.07(m)	21.7	C-1,C-3,C-4
3	—	150.0	—	5.44(d,15.9)	134.3	C-1,C-5
4	8.32(s)	142.0	C-3	5.46(d,15.9)	126.4	C-2
5a	5.97(d,6.3)	91.3	C-4,C-6	2.36(m)	31.6	C-3,C-4,C-6
5b	5.97(d,6.3)	91.3	C-4,C-6	2.14(m)	31.6	C-3,C-4,C-6
6	4.75(t,12.0,6.0)	75.5	C-5,C-8	3.46(m)	75.9	C-4,C-5,C-8
7	4.34(m)	72.7	C-5,C-8,C-9	5.68(d,16.0)	136.5	C-8
8	4.18(m)	88.2	C-7	5.75(d,16.0)	131.1	C-6,C-10
9a	3.92(dd,12.6,2.7)	63.5	C-7,C-8	3.96(m)	75.8	C-7,C-8
9b	3.77(dd,12.6,2.7)	63.5	C-7,C-8	3.96(m)	75.8	C-7,C-8
10	—	—	—	4.06(m)	73.0	C-8
11	—	—	—	3.93(m)	76.5	C-9
12	—	—	—	1.32(m)	30.6	C-14
13	—	—	—	1.33(m)	30.3	—
14	—	—	—	1.34(m)	30.4	C-15
15	—	—	—	1.60(m)	26.5	C-13
16	—	—	—	1.52(m)	38.3	C-14,C-15
17	—	—	—	3.65(m)	71.4	—
18	—	—	—	1.34(d,7.2)	26.4	—

H-7), 5.75 (1H, d, J = 16.0 Hz, H-8) in the middle field. Moreover, there were two methyl signals at δ_H 0.97 (3H, t, J = 15.0, 7.5 Hz, H-1), 1.34 (3H, d, J = 7.2 Hz, H-18) in the ^{1}H NMR of compound **4** (Table 2). Based above spectral data, the skeleton of compound **4** was concluded to be alkene by the degrees of unsaturation of compound **4**. In the HMBC spectrum of compound **4**, correlations of H-1/C-2, C-3; H-2/C-1, C-3, C-4; H-3/C-1, C-5; H-4/C-2; H-5/C-3, C-4, C-6; H-6/C-4, C-5, C-8; H-7/C-8; H-8/C-6, C-10; H-9/C-7, C-8; H-10/C-8; H-11/C-9; H-12/C-14; H-14/C-15; H-15/C-13; H-16/C-14, C-15 (Fig. 2) indicating the planar construction of compound **4**. According to the correlations of H-1/H-2; H-4/H-5; H-6/H-7; H-8/H-9; H-11/H-12; H-17/18-CH_3 of 2D-NOESY spectrum, the relative configuration of compound **4** was identified. The absolute configuration of compound **4** was established by Mosher's method. Two aliquots (1.0 mg) of pure compound were treated with (+)-(*R*)-MTPA-Cl and (−)-(*S*)-MTPA-Cl (MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl), respectively. Assignment of the H-atoms vicinal to CH–OH groups of the two diasterotopic diesters was obtained by related spectra.[17] According to above spectral data and reference,[16] the structure of compound **4** was identified as (3*E*,6*S*,7*E*,9*R*,10*S*,11*S*,17*R*)-octadeca-3,7-diene-6,9,10,11,17-pentaol.

Additionally, eight known compounds (**5**–**12**) belonging to alkenes, which were isolated and identified as (2*E*,6*R*)-2,6-dimethyl-2,7-octadiene-1,6-diol (**5**),[18] (6*R*,7*E*,9*S*,10*R*)-6,9,10-trihydroxy-7-octadecenoic acid (**6**),[19] capsianoside V (**7**),[20] (9*S*,10*R*,11*R*,12*Z*,15*Z*)-9,10,11-trihydroxy-octadeca-12,15-dienoic acid (**8**),[21] oxylipin (**9**),[20] (8*R*,9*R*,10*S*,6*Z*)-trihydroxyoctadec-6-enoic acid (**10**),[21] (9*S*,10*R*,11*E*,13*S*)-9,10,13-trihydroxyoctadec-11-enoic acid (**11**),[17] (8*S*,9*R*,10*E*,12*S*,14*Z*)-heptadeca-10,14-diene-1,8,9,12-tetraol (**12**)[17] by comparison of their physical and spectroscopic data with those reported in the references. To the best of our knowledge, the known compounds (**5**–**12**) were isolated from this plant for the first time.

Compounds (**1**–**12**) were evaluated for their antioxidative activities using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, and the chlorogenic acid was included for comparison.[22,23] According the screening results of all the compounds (**1**–**12**), we found that some compounds exhibited significant antioxidative activities using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay with IC_{50} = 21.4–49.5 μM. Moreover, the chlorogenic acid was served as the reference compound (IC_{50} = 56.4 μM) in the DPPH assay (Table 3), and its IC_{50} value was greater than those of selective compounds. Among them, compounds **2** and **4** showed the strongest antioxidative activities with IC_{50} values of 23.5 and 25.4 μM, respectively. Compounds **1** and **7** with IC_{50} values of 38.4 and 40.2 μM, which showed moderate antioxidative activities. However, the other compounds exhibited no antioxidative activities. Based the chemical structures and bioactivities of the active compounds, the fact showed that the active compounds contained terminal alkenyl and trans double bonds played positive roles in the mediating their antioxidative activities. Moreover, the antioxidative activities would decrease if the active compounds contained the glucosyl unit. The study of Structure-Activity Relationship of the active compounds from *M. koenigii* which needed further research.

Table 3
Antioxidative activities of selective compounds

Compound	IC_{50} (μM)
1	38.4
2	23.5
4	25.4
7	40.2
Chlorogenic acid	56.4

In conclusion, we had isolated and identified four new alkenes (**1**–**4**) and eight known alkenes (**5**–**12**) from *M. koenigii*. The known compounds (**5**–**12**) were isolated from this plant for the first time. Meanwhile, we had evaluated the antioxidative activities of compounds (**1**–**12**). Among them, compounds **1**, **2**, **4**, and **7** exhibited significant antioxidative activities using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay with IC_{50} = 21.4–49.5 μM.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.12.091.

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