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## NEW FURANOCOUMARINS FROM THE FRUITS OF *MELICOPE* *TRIPHYLLA*

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**Abstract** – Four new furanocoumarins (**1–4**) were isolated from the fruits of *Melicope triphylla* (Rutaceae), together with two known coumarins (**5**, **6**), nine flavonoids (**7–15**), two alkaloids (**16**, **17**), and methyl *p*-geranyloxy-*trans*-cinnamate (**18**). The structures of the newly identified compounds were determined by extensive 1D- and 2D-NMR spectroscopic analyses to be linear-types of furanocoumarins bearing a hydroxyl or a hydroperoxy group on the geranyloxy side chain.

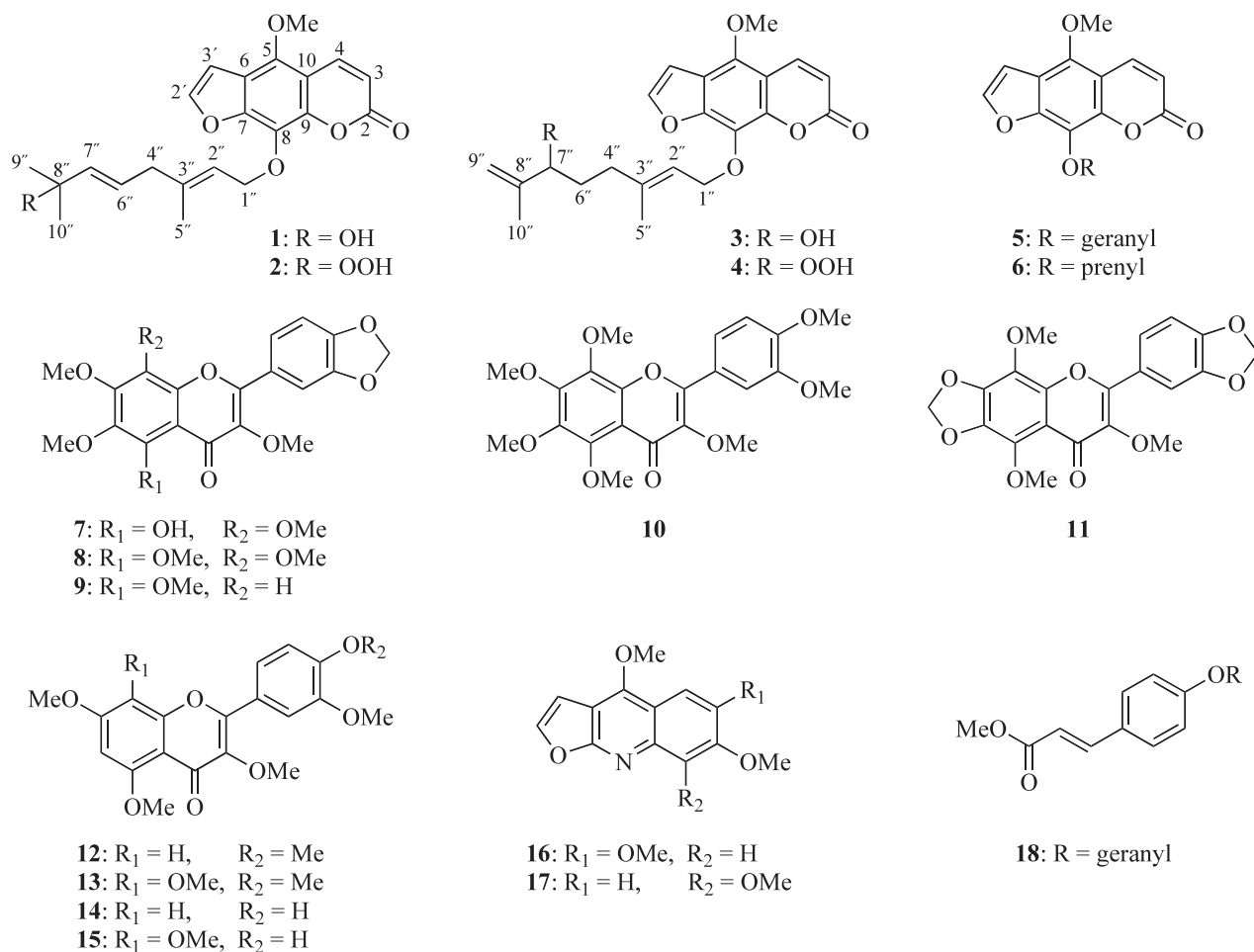
## INTRODUCTION

*Melicope triphylla* (LAM.) MERR. is a rutaceous shrub that grows to 1.5–15 m high, and widely distributed throughout the Pacific islands including the Ryukyus in Japan.<sup>1</sup> Continuous studies by Higa *et al.* have revealed the presence of polymethoxyflavonoids,<sup>2–4</sup> furoquinoline alkaloids,<sup>5</sup> and *p*-coumaric acid derivatives<sup>5</sup> in the leaves of the plant. On the other hand, Wu *et al.* have worked on the root barks and found sesquiterpene lactones.<sup>6,7</sup> However, no phytochemical studies of the fruits have been achieved. Herein we described on the structure elucidation of four new furanocoumarins, as well as fourteen known compounds, isolated from the fruits of *M. triphylla*.

## RESULTS AND DISCUSSION

A new coumarin, named melicotriphyllin A (**1**), was obtained as yellow oil with absorption maxima at 312 and 270 nm in the UV spectrum. The HR-ESIMS gave an [M+Na]<sup>+</sup> ion peak at *m/z* 407.1458, which established the quasi-molecular formula as C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>Na (calc. 407.1465). The <sup>1</sup>H-NMR spectrum

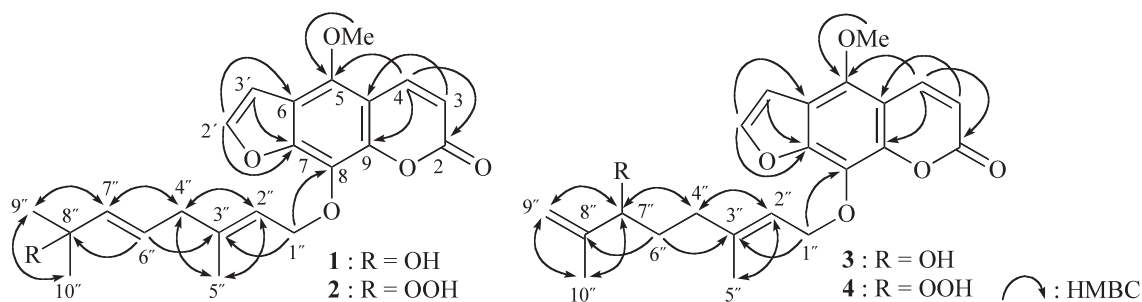
showed two pairs of mutually coupled doublets at  $\delta_{\text{H}}$  6.26, 8.11 (1H each, d,  $J = 9.7$  Hz) and  $\delta_{\text{H}}$  7.01, 7.63 (1H each, d,  $J = 2.4$  Hz); the former protons were assignable to H-3 and H-4 in a coumarin skeleton, while the latter were regarded as H-2' and H-3' on a furan ring. A three-proton singlet resonated at  $\delta_{\text{H}}$  4.18 to be identified as a methoxy group that exhibited essential NOEs toward H-4 and H-3' in the NOESY spectrum. Therefore, **1** was considered to be a linear furanocoumarin having a methoxy group at C-5.



**Figure 1.** Structure of the compounds **1–18** isolated from the fruits of *M. triphylla*

The double quantum filtered COSY (DQF-COSY) spectrum inferred two segments [ $\delta_{\text{H}}$  4.86 (2H, d,  $J = 7.2$  Hz), 5.60 (1H, br t,  $J = 7.2$  Hz) for  $-\text{OCH}_2\text{CH}=\text{}$ ;  $\delta_{\text{H}}$  2.68 (2H, d,  $J = 6.6$  Hz), 5.50 (1H, dt,  $J = 15.9, 6.6$  Hz), 5.59 (1H, d,  $J = 15.9$  Hz) for  $-\text{CH}_2\text{CH}=\text{CH}-$ ] and three methyl groups [ $\delta_{\text{H}}$  1.29 (6H, s, overlapping) and 1.64 (3H, s)]. The HMBC spectrum showed a side chain as  $-\text{OCH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2\text{CH}=\text{CHC}(\text{CH}_3)_2\text{OH}$  formed from a geranyl or a neryl group by the following correlations: H<sub>2</sub>-1''/C-3''; H-2''/C-4'', C-5''; H<sub>2</sub>-4''/C-7''; H-6''/C-3'', C-8''; and H-7''/C-9''(10'') (Figure 2). In the EIMS, the base ion peak at  $m/z$  233 generated after the loss of C<sub>10</sub>H<sub>16</sub>O from the molecular ion also supported the presence of the side chain. In the NOESY spectrum, the key NOEs were observed

between H<sub>2</sub>-1''/H<sub>3</sub>-5'', H-2''/H<sub>2</sub>-4'' and H<sub>2</sub>-4''/H-7'', which indicated that the C<sub>10</sub> side chain was originated from a geranyl group and the configurations were 2''*E* and 6''*E*. The C-8 substitution was demonstrated by a HMBC correlation between H<sub>2</sub>-1'' (δ<sub>H</sub> 4.86) and C-8 (δ<sub>C</sub> 126.5). Thus, the structure of melicotriphyllin A was established as **1** (Figure 1).



**Figure 2.** Selected HMBC correlations in **1–4**

**Table 1.** <sup>1</sup>H-NMR (400 MHz) data of compounds **1–4** in CDCl<sub>3</sub>

No.	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
3	6.26 (1H, d, 9.7)	6.28 (1H, d, 9.7)	6.27 (1H, d, 9.7)	6.28 (1H, d, 9.7)
4	8.11 (1H, d, 9.7)	8.13 (1H, d, 9.7)	8.12 (1H, d, 9.7)	8.12 (1H, d, 9.7)
2'	7.63 (1H, d, 2.4)	7.63 (1H, d, 2.4)	7.63 (1H, d, 2.4)	7.63 (1H, d, 2.4)
3'	7.01 (1H, d, 2.4)	7.00 (1H, d, 2.4)	7.00 (1H, d, 2.4)	7.00 (1H, d, 2.4)
1''	4.86 (2H, d, 7.2)	4.87 (2H, d, 7.2)	4.87 (2H, m)	4.87 (2H, d, 7.0)
2''	5.60 (1H, br t, 7.2)	5.65 (1H, m)	5.62 (1H, br t, 7.2)	5.62 (1H, br t, 7.0)
4''	2.68 (2H, d, 6.6)	2.73 (2H, d, 5.5)	2.03 (2H, m)	2.04 (2H, br t, 7.2)
5''	1.64 (3H, s)	1.63 (3H, s)	1.67 (3H, s)	1.67 (3H, s)
6''	5.50 (1H, dt, 15.9, 6.6)	5.56 (1H, dt, 15.9, 5.5)	1.58 (2H, m)	1.51 (1H, m)
				1.64 (1H, m)
7''	5.59 (1H, d, 15.9)	5.55 (1H, d, 15.9)	3.93 (1H, t, 6.8)	4.23 (1H, t, 6.8)
9''	1.29 (3H, s) <sup>a</sup>	1.31 (3H, s) <sup>b</sup>	4.94 (1H, br s)	4.94 (1H, br s)
			4.99 (1H, br s)	4.99 (1H, t, 1.5)
10''	1.29 (3H, s) <sup>a</sup>	1.31 (3H, s) <sup>b</sup>	1.71 (3H, s)	1.71 (3H, s)
5-OMe	4.18 (3H, s)	4.19 (3H, s)	4.15 (3H, s)	4.18 (3H, s)

δ<sub>H</sub> in ppm, *J* in Hz. <sup>a, b</sup> overlapping signals.

Melicotriphyllin B (**2**), yellow oil, exhibited absorption bands at 313 and 269 nm in the UV spectrum. The quasi-molecular formula of **2** was confirmed to be C<sub>22</sub>H<sub>24</sub>O<sub>7</sub>Na (calc. 423.1414) based on the [M+Na]<sup>+</sup> ion peak at *m/z* 423.1434 in the HR-ESIMS. This compound, then, bears one more oxygen atom than **1**. The <sup>1</sup>H-NMR spectrum of **2** was superimposed to that of **1**, which implied that **2** was the similar furanocoumarin as **1** (Table 1). Comparison with both <sup>13</sup>C-NMR spectral data, however, showed a significant downfield shift of the carbon signal at C-8'' from δ<sub>C</sub> 70.4 (**1**) to δ<sub>C</sub> 82.0 (**2**) (Table 2), indicating that the hydroxyl group attaching to C-8'' in **1** was converted into the hydroperoxy group in **2**.

The reduction of **2** with triphenylphosphine in MeOH at room temperature produced a compound identical to **1**.<sup>8</sup> Accordingly, the structure of melicotriphyllin B was determined as **2**.

**Table 2.** <sup>13</sup>C-NMR (100 MHz) data of compounds **1–4** in CDCl<sub>3</sub>

No.	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
2	160.5	160.7	160.5	160.7
3	112.5	112.7	112.8	112.7
4	139.4	139.5	139.4	139.5
5	144.3	144.4	144.4 <sup>c)</sup>	144.3
6	114.3	114.4	114.5	114.5
7	150.8	150.9	150.9	150.8
8	126.5	126.6	126.7	126.6
9	144.4	144.5	144.4 <sup>c)</sup>	144.4
10	107.3	107.4	107.5	107.5
2'	145.0	145.1	145.1	145.1
3'	105.0	105.1	105.1	105.1
1''	70.1	70.2	70.2	70.2
2''	120.2	120.6	119.9	120.3
3''	141.5	141.2	147.4	142.1
4''	41.9	42.2	35.4	35.3
5''	16.4	16.6	16.4	16.3
6''	123.8	128.5	32.7	28.6
7''	140.1	135.6	75.1	88.8
8''	70.4	82.0	142.6	143.6
9''	29.6 <sup>a)</sup>	24.2 <sup>b)</sup>	111.0	114.2
10''	29.6 <sup>a)</sup>	24.2 <sup>b)</sup>	17.6	17.0
5-OMe	60.6	60.7	60.7	60.7

$\delta_c$  in ppm. <sup>a-c)</sup> overlapping signals.

Melicotriphyllin C (**3**), obtained as optically inactive yellow oil, showed the same quasi-molecular formula for C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>Na (calc. 407.1465) as **1** in the HR-ESIMS ([M+Na]<sup>+</sup> at *m/z* 407.1488). The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra had identifiable signals for a linear furanocoumarin framework (Tables 1 and 2). The location of a methoxy group was confirmed at C-5 by the NOESY correlations from MeO [ $\delta_H$  4.15 (3H, s)] to H-4 [ $\delta_H$  8.12 (1H, d, *J* = 9.7 Hz)] and H-3' [ $\delta_H$  7.00 (1H, d, *J* = 2.4 Hz)]. Therefore, the structural difference between **1** and **3** was due to the geranyl-derived side chain. The <sup>1</sup>H-NMR and DQF-COSY spectra exhibited a –OCH<sub>2</sub>CH= moiety [ $\delta_H$  4.87 (2H, m), 5.62 (1H, br t, *J* = 7.2 Hz)], a –CH<sub>2</sub>CH<sub>2</sub>CH(O)– moiety [ $\delta_H$  2.03 (2H, m), 1.58 (2H, m), 3.93 (1H, t, *J* = 6.8 Hz)], two methyl groups [ $\delta_H$  1.67, 1.71 (3H each, s)], and an olefinic methylene group [ $\delta_H$  4.94, 4.99 (1H each, br s)]. The side chain was established as –OCH<sub>2</sub>CH=C(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH(OH)C(CH<sub>3</sub>)=CH<sub>2</sub> by the following HMBC correlations: H<sub>2</sub>-1''/C-3''; H-2''/C-4'', C-5''; H<sub>2</sub>-4''/C-7''; H<sub>2</sub>-6''/C-3'', C-8''; and H-7''/C-9'', C-10'' (Figure

2). The configuration at C-2'' was indicated to be *E* by the NOEs between H<sub>2</sub>-1''/H<sub>3</sub>-5'' and H-2''/H<sub>2</sub>-4''. Consequently, the structure of melicotriphyllin C was confirmed as **3**.

Melicotriphyllin D (**4**) was obtained as optically inactive yellow oil. The quasi-molecular formula was established as C<sub>22</sub>H<sub>24</sub>O<sub>7</sub>Na (calc. 423.1414) by an [M+Na]<sup>+</sup> ion peak observed at *m/z* 423.1380 in the HR-ESIMS. Then, the structure relationship between **3** and **4** seemed identical to that between **1** and **2**. The significant downfield shifts observed in the proton and carbon signals at C-7'' from δ<sub>H</sub> 3.93 and δ<sub>C</sub> 75.1 (**3**) to δ<sub>H</sub> 4.23 and δ<sub>C</sub> 88.8 (**4**) demonstrated that a hydroperoxy group was substituted at C-7'' in **4** instead of a hydroxyl group in **3**. The idea was corroborated by the chemical conversion of **4** to **3** upon treatment with triphenylphosphine in the same manner as **2**. Thus, the structure of melicotriphyllin D was determined to be **4**. Since **3** and **4** were optically inactive, both were suggested to exist as racemic mixtures.

In addition, 8-geranyloxy-5-methoxypsoralen (**5**),<sup>9</sup> phellopterin (**6**),<sup>10</sup> 5-demethylmelibentin (**7**),<sup>3,11</sup> melibentin (**8**),<sup>11,12</sup> melisimlexin (**9**),<sup>12,13</sup> 3,5,6,7,8,3',4'-heptamethoxyflavone (**10**),<sup>14</sup> 3,5,8-trimethoxy-6,7:3',4'-bis(methylenedioxy)flavone (**11**),<sup>2,12</sup> quercetin pentamethyl ether (**12**),<sup>3</sup> gossypetin hexamethyl ether (**13**),<sup>3</sup> 4'-hydroxy-3,5,7,3'-tetramethoxyflavone (**14**),<sup>2</sup> 4'-hydroxy-3,5,7,8,3'-pentamethoxyflavone (**15**),<sup>3</sup> kokusaginine (**16**),<sup>15</sup> skimmianine (**17**),<sup>16</sup> and methyl *p*-geranyloxy-*trans*-cinnamate (**18**)<sup>5</sup> were isolated and identified by comparisons with the literatures.

All new compounds (**1–4**) were oxidative metabolites of **5** that was rarely found in natural sources and a characteristic component in the fruits of *M. triphylla*, although **6** was isolated from several rutaceous and apiaceous plants and common in every parts of this plant. And, geranyloxycompounds possessing a hydroperoxy group such as **2** and **4** were yet discovered in genera of *Phebalium*<sup>17</sup> and *Clausena*<sup>18</sup> (Rutaceae). We also revealed that the fruits of *M. triphylla* abundantly contained **5**, **8**, **11**, **17** and **18**. Higa *et al.* have reported the presence of **18** in the leaves, however, the compound was apparently major in the fruits rather than the leaves based on our TLC analysis. From the chemotaxonomic standpoint of view,<sup>19–21</sup> the genus *Melicope* may involve two chemical races depending on whether the primary components are polymethoxyflavones or prenyl acetophenones. Considering the previous and the present studies, *M. triphylla* would be a specimen classified into the polymethoxyflavone-rich race in the genus.

## EXPERIMENTAL

**General.** <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were measured on a JEOL JNM-AL-400 spectrometer equipped with a field gradient system (<sup>1</sup>H at 400 MHz and <sup>13</sup>C at 100 MHz). Chemical shifts are given in δ values (ppm) relative to tetramethylsilane as an internal standard. EIMS (at 30 eV) and HR-ESIMS were obtained using a JEOL JMS-700T and a Shimadzu LCMS-IT-TOF spectrometers, respectively. UV

spectra were recorded using a Shimadzu UV-3100 spectrophotometer (in MeOH solution). Optical rotations were recorded using a Jasco P-1020 polarimeter (in MeOH solution). Silica gel 60 (70–230 mesh, Merck) and Sephadex LH-20 (GE Healthcare) were used for column chromatography (CC). Vacuum liquid chromatography (VLC) was performed using silica gel 60H (Merck), while TLC analysis was performed using silica gel 60F<sub>254</sub> (Merck) and silica gel RP-18F<sub>254S</sub> (Merck). Semi-preparative HPLC was performed on a Shimadzu LC-6AD liquid chromatography system equipped with a SCL-10A system controller, SIL-10A autoinjector, CTO-10A column oven, and SPD-10A UV-Vis detector, SPM-10Avp diode array detector, with the aid of Shiseido Capcell Pak C<sub>18</sub> UG120 5 μm (10 mm i.d. x 250 mm).

**Plant Material.** The fruits of *M. triphylla* (1.7 Kg, dried weight) were collected at Ishigaki-jima in the Ryukyu Islands, Japan, in August 2009. A voucher specimen was deposited at Gifu Pharmaceutical University, Gifu, Japan.

**Extraction and Isolation.** The fruits were extracted with a 1:1 mixture of CHCl<sub>3</sub> and MeOH at room temperature. The extract (220 g) was subjected to silica gel CC (Si CC) to afford 16 main fractions: Frs. 1, 2 (eluted with *n*-hexane–acetone, 20:1), Frs. 3, 4 (15:1), Fr. 5 (10:1), Fr. 6 (8:1), Frs. 7, 8 (6:1), Frs. 9, 10 (4:1), Frs. 11, 12 (2:1), Frs. 13, 14 (1:1), Frs. 15, 16 (0:1). Fr. 2 was separated by Si CC (*n*-hexane–EtOAc, 40:1 to 20:1) to yield **18** (746.3 mg). Fr. 4 was purified repetitively using Sephadex LH-20 CC (CHCl<sub>3</sub>–MeOH, 1:2), Sep-Pak tC<sub>18</sub> cartridge (MeOH–H<sub>2</sub>O, 9:1), Si CC (CHCl<sub>3</sub>), and preparative HPLC (48% MeCN–H<sub>2</sub>O) to afford **2** (35.0 mg), **3** (12.9 mg), **4** (27.0 mg), and **5** (1.26 g). Fr. 5 was purified by Si CC (benzene–EtOAc, 7:2) and Sep-Pak tC<sub>18</sub> cartridge (MeOH–H<sub>2</sub>O, 9:1) to yield **1** (23.4 mg), **6** (387.6 mg), and **7** (114.0 mg). Fr. 7 was dissolved in acetone to crystallize **8** (4.29 g). Fr. 9 was separated with the aid of Sephadex LH-20 CC (acetone), Sep-Pak tC<sub>18</sub> cartridge (MeOH–H<sub>2</sub>O, 1:1), Si CC (*c*-hexane–EtOH, 5:1; benzene–EtOAc, 6:1), and VLC (benzene–acetone, 15:1) to provide **9** (143.4 mg), **10** (50.0 mg), and **16** (50.0 mg). Frs. 10 and 12 were dissolved in acetone to give **11** (1.57 g) and **17** (2.07 g) in crystal forms, respectively. Fr. 16 was separated by Si CC (CHCl<sub>3</sub>) and successive crystallization in EtOH to afford **12** (149.4 mg), **13** (26.2 mg), **14** (390.3 mg), and **15** (71.0 mg).

**Melicotriphyllin A** (4-methoxy-9-[[*(2E,5E)*-7-hydroxy-3,7-dimethyl-2,5-octadien-1-yl]oxy]-7*H*-furo[3,2-*g*][1]benzopyran-7-one) (**1**): Yellow oil. UV (log ε, MeOH): 270 (4.19), 312 (4.00). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) and <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz): see Tables 1 and 2, respectively. HR-ESIMS (pos.): 407.1458 ([M+Na]<sup>+</sup>, C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>Na<sup>+</sup>; calc. 407.1465). EIMS (%): 233 ([M+H-C<sub>10</sub>H<sub>16</sub>O]<sup>+</sup>, 100), 217 (94), 189 (43), 161 (21), 134 (54), 119 (46).

**Melicotriphyllin B** (4-methoxy-9-[[*(2E,5E)*-7-hydroperoxy-3,7-dimethyl-2,5-octadien-1-yl]oxy]-7H-furo[3,2-g][1]benzopyran-7-one) (**2**): Yellow oil. UV (log  $\epsilon$ , MeOH): 269 (4.58), 313 (4.39).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz) and  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 100 MHz): see Tables 1 and 2, respectively. HR-ESIMS (pos.): 423.1434 ( $[\text{M}+\text{Na}]^+$ ,  $\text{C}_{22}\text{H}_{24}\text{O}_7\text{Na}^+$ ; calc. 423.1414). EIMS (%): 232 ( $[\text{M}-\text{C}_{10}\text{H}_{16}\text{O}]^+$ , 100), 217 (93), 189 (49), 161 (24), 135 (55), 134 (49), 119 (23).

**Melicotriphyllin C** (4-methoxy-9-[[*(2E)*-6-hydroxy-3,7-dimethyl-2,7-octadien-1-yl]oxy]-7H-furo[3,2-g][1]benzopyran-7-one) (**3**): Yellow oil.  $[\alpha]_{\text{D}}^{20}$  ( $c$  0.1, MeOH). UV (log  $\epsilon$ , MeOH): 271 (4.09), 313 (3.91).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz) and  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 100 MHz): see Tables 1 and 2, respectively. HR-ESIMS (pos.): 407.1488 ( $[\text{M}+\text{Na}]^+$ ,  $\text{C}_{22}\text{H}_{24}\text{O}_6\text{Na}^+$ ; calc. 407.1465). EIMS (%): 232 ( $[\text{M}-\text{C}_{10}\text{H}_{16}\text{O}]^+$ , 100), 217 (100), 189 (52), 161 (26).

**Melicotriphyllin D** (4-methoxy-9-[[*(2E)*-6-hydroperoxy-3,7-dimethyl-2,7-octadien-1-yl]oxy]-7H-furo[3,2-g][1]benzopyran-7-one) (**4**): Yellow oil.  $[\alpha]_{\text{D}}^{20}$  ( $c$  0.1, MeOH). UV (log  $\epsilon$ , MeOH): 269 (4.11), 313 (3.92).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz) and  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 100 MHz): see Tables 1 and 2, respectively. HR-ESIMS (pos.): 423.1380 ( $[\text{M}+\text{Na}]^+$ ,  $\text{C}_{22}\text{H}_{24}\text{O}_7\text{Na}^+$ ; calc. 423.1414). EIMS (%): 233 ( $[\text{M}+\text{H}-\text{C}_{10}\text{H}_{16}\text{O}]^+$ , 100), 217 (100), 189 (60), 161 (28).

**Reduction of 2 and 4 with triphenylphosphine.** **2** (13.2 mg) was dissolved in MeOH (10 mL), and triphenylphosphine (13.3 mg) was added to the solution. The mixture was stirred for 4 hrs at room temperature, and then the solvent was evaporated off. The residue was purified by Sep-Pak  $\text{tC}_{18}$  cartridge (75% MeOH– $\text{H}_2\text{O}$ ) to give **1** (7.6 mg). Equally, **4** (11.2 mg) and triphenylphosphine (11.3 mg) was treated as above. After purification, **3** (8.4 mg) was obtained.

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