Sesquiterpenoids and 2-(2-Phenylethyl)-4*H*-chromen-4-one (=2-(2-Phenylethyl)-4*H*-1-benzopyran-4-one) Derivatives from *Aquilaria malaccensis* Agarwood

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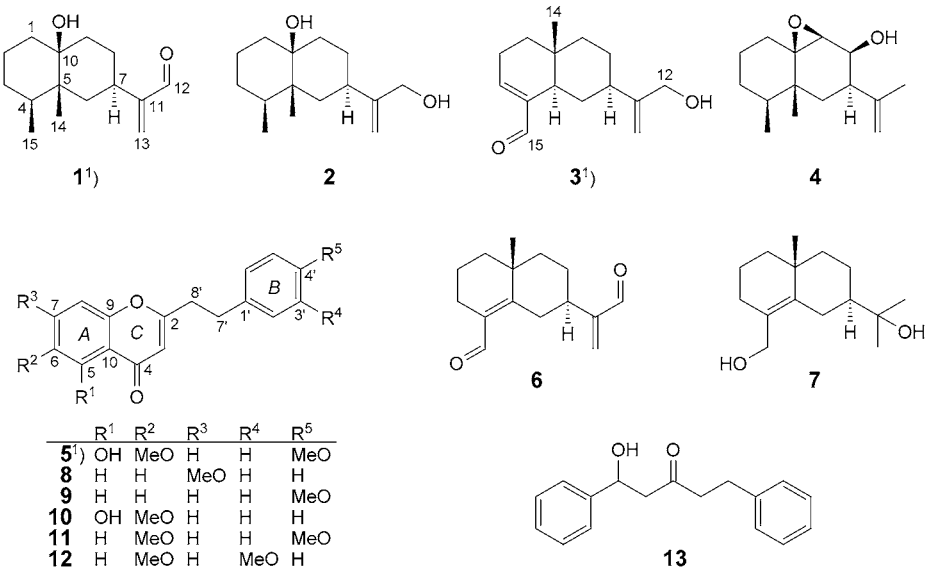
The four new sesquiterpenoids **1**–**4**, and the new 2-(2-phenylethyl)-4*H*-chromen-4-one (=2-(2-phenylethyl)-4*H*-1-benzopyran-4-one) derivative **5**, together with the two known sesquiterpenoids **6** and **7**, the five known chromenones **8**–**12**, and 1-hydroxy-1,5-diphenylpentan-3-one (**13**), were isolated from a 70% MeOH extract of *Aquilaria malaccensis* agarwood chips. Their structures were elucidated on the basis of comprehensive spectral analyses and comparison with literature data.

Introduction. – The *Aquilaria* genus (Thymelaeaceae), consisting of fifteen species of trees, is mainly distributed in rain forests of southeast Asia and New Guinea [1]. Several species of this genus can produce a dark aromatic resin mainly in response to the infection by *Phaeoacremonium parasitica*, a parasitic ascomycetous mould [2]. The resin-deposited heartwood is well known as agarwood, which has long been used as incense, and as sedative, analgesic, and digestive agent in traditional Chinese medicine [3]. Previous phytochemical research on this genus led to the isolation of many (phenylethyl)chromenones [3–8] and sesquiterpenoids [9][10].

As a result of our investigation of the *Aquilaria malaccensis*, the five new compounds **1**–**5** and the eight known compounds **6**–**13** were isolated (*Fig. 1*). Herein, we present the isolation and structure determination of them.

Results and Discussion. – A 70% MeOH extract of *A. malaccensis* agarwood was extracted with Et_2O, BuOH, and H_2O. The Et_2O fraction was then subjected to repeated column chromatographic and preparative HPLC separation to afford thirteen compounds, including **1**–**4** as new sesquiterpenoids and **5** as a new 2-(2-phenylethyl)-4*H*-chromen-4-one (=2-(2-phenylethyl)-4*H*-1-benzopyran-4-one) derivative.

Compound **1** was obtained as colorless oil, and its molecular formula was determined to be $C_{15}H_{24}O_2$ by HR-ESI-MS (*m*/*z* 259.1666, $[M+Na]^+$, $C_{15}H_{24}NaO_2^+$). The signal at δ(C) 194.8 in its ^{13}C-NMR spectrum (*Table 1*) revealed the presence of a carbonyl group, while those at δ(C) 155.1 and 132.8 suggested the existence of an olefinic bond. These two groups accounted for two of the four degrees of unsaturation in **1**, suggesting its bicyclic structure. Two quaternary sp^3 C-atoms resonating at δ(C) 41.4 and 73.2, the latter bearing an O-substituent, together with two CH, six CH_2, and two Me groups were identified through the combinatory analysis of ^{13}C- and



	R^1	R^2	R^3	R^4	R^5
5[1])	OH	MeO	H	H	MeO
8	H	H	MeO	H	H
9	H	H	H	H	MeO
10	OH	MeO	H	H	H
11	H	MeO	H	H	MeO
12	H	MeO	H	MeO	H

Fig. 1. *New and known compounds* **1**–**5** *and* **6**–**13**, *respectively, isolated from* Aquilaria malaccensis *agarwood*

Table 1. *^{13}C-NMR Data* ($CDCl_3$, 125 MHz) *of Compounds* **1**–**4**[1]). δ in ppm.

	1	**2**	**3**	**4**		**1**	**2**	**3**	**4**
C(1)	36.8	36.6	36.5	31.0	C(9)	32.7	32.8	39.7	64.0
C(2)	23.0	22.9	24.5	24.6	C(10)	73.2	73.2	32.2	69.0
C(3)	30.1	30.1	153.0	30.1	C(11)	155.1	153.8	153.8	145.2
C(4)	33.1	33.0	142.3	35.6	C(12)	194.8	65.3	65.3	111.3
C(5)	41.4	41.3	43.6	38.0	C(13)	132.8	108.0	108.2	22.5
C(6)	36.8	37.1	27.3	28.2	C(14)	15.5	15.3	15.7	18.0
C(7)	29.5	34.5	41.8	40.5	C(15)	15.2	15.4	194.9	15.5
C(8)	26.7	27.2	27.0	64.4	C(15)	15.2	15.4	194.9	15.5

HSQC-NMR spectra. Comprehensive consideration of the ^{1}H,^{1}H-COSY and HMBC data enabled the characterization of structural units and connection of them to form an eremophilane-type skeleton for **1** (*Fig. 2*) (eremophilane = decahydro-1,8a-dimethyl-7-(1-methylethyl)naphthalene). Thus, the constitutional formula of **1** was unambiguously established. In the NOESY plot of **1**, a correlation of δ(H) 2.72 (H–C(7)) and 2.03 (H–C(4)) was observed (*Fig. 3*, *Table 2*). Assuming a low-energy chair–chair conformation for this decahydronaphthalene derivative, the observed proximity of these two H-atoms can only be realized when the two rings are *cis*-fused. Besides that, H–C(4) should be located on the same side of the rings as H–C(7) but be *trans* with respect to Me(14) (*Fig. 3*). Therefore, H–C(7), Me(14), and OH–C(10) are α-, β-, and

[1]) Trivial or arbitrary atom numbering; for systematic names, see *Exper. Part.*

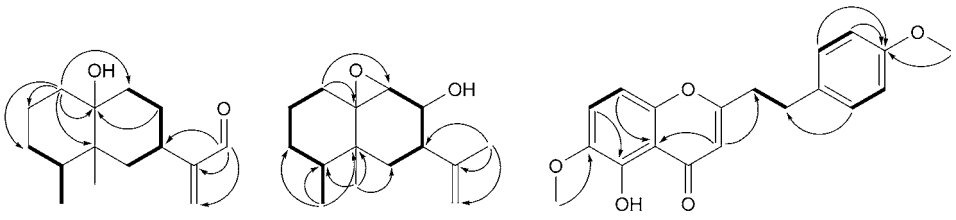


Fig. 2. *Key* $^1H,^1H$*-COSY* (—) *and HMBC* (H → C) *features of* **1**, **4**, *and* **5**

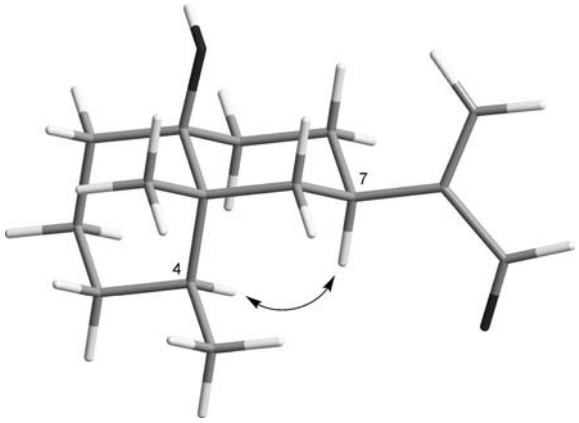


Fig. 3. *Configuration-diagnostic NOESY* (↔) *correlation in compound* **1**

β-oriented, respectively, when an α-configuration of H–C(4) is assumed. Based on all the information given above, the structure of **1**, apart from its absolute configuration, was elucidated as shown in *Fig. 1*.

Comparative analysis of the ^{1}H- and ^{13}C-NMR spectra of **1** and **2** (*Tables 2* and *1*) indicated a close structural similarity between them, except for the presence of a CH_2OH group linked to C(11) in **2** instead of CHO in **1**. The relative configuration of **2** was the same as that of **1**, as suggested by the NOESY cross-peak δ(C) 2.20 (H–C(7))/ δ(H) 1.94 (H–C(4)).

Compound **3** was isolated as a pale yellow oil, and its molecular formula $C_{15}H_{22}O_2$ was deduced from the HR-ESI-MS (*m*/*z* 235.1685, $[M+H]^+$, $C_{15}H_{23}O_2^+$). According to the spectral data, its structure closely resembled that of (−)-selina-3,11-dien-14-al (=(4a*S*,7*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-4a-methyl-7-(1-methylethenyl)naphthalene-1-carboxaldehyde) reported by *Ishihara et al.* [10], with the only difference that a CH_2OH group rather than a Me group was attached to C(11). Since both of these two compounds were isolated from the *Aquilaria* genus, considering the biosynthetic aspect, their relative configurations were assumed to be the same. Thus, the structure of **3** was determined as depicted in *Fig. 1*.

Compound **4** was obtained as colorless oil and assigned a molecular formula $C_{15}H_{24}O_2$ by HR-ESI-MS (*m*/*z* 237.1841, $[M+H]^+$, $C_{15}H_{25}O_2^+$). Its ^{13}C- and DEPT-

Table 2. *^{1}H-NMR Data* ($CDCl_3$, 500 MHz) *of Compounds* **1**–**4**[1]). δ in ppm, J in Hz)

	1	**2**	**3**	**4**
CH_2(1)	1.72 (*td*, J = 13.1, 4.8), 1.62–1.44 (*m*)	1.71 (*td*, J = 13.2, 4.8), 1.37–1.36 (*m*)	1.45 (*dd*, J = 12.4, 5.3), 1.36–1.30 (*m*)	2.05 (*td*, J = 13.4, 4.4), 1.07 (*dd*, J = 13.4, 2.3)
CH_2(2)	1.62–1.44 (*m*)	1.57–1.55, 1.46–1.45 (2*m*)	2.44–2.40, 2.38–2.36 (2*m*)	1.78–1.76, 1.37–1.37 (2*m*)
CH_2(3)	1.43–1.25 (*m*)	1.42–1.27 (*m*)	6.69–6.68 (*m*)	1.53–1.49, 1.34–1.34 (2*m*)
H–C(4)	2.06–1.99 (*m*)	1.97–1.92 (*m*)		1.72–1.68 (*m*)
H–C(5)	–	–	2.23–2.20 (*m*)	–
CH_2(6)	1.43–1.25 (*m*)	1.54–1.51, 1.42–1.40 (2*m*)	2.77 (br. *d*, J = 13.3), 1.09–1.08 (*m*)	1.32–1.32 (*m*)
H–C(7)	2.75–2.69 (*m*)	2.23–2.17 (*m*)	2.13–2.06 (*m*)	2.14 (*dt*, J = 11.7, 4.1)
CH_2(8) or H–C(8)	1.61–1.58 (*m*)	1.62–1.61 (*m*)	1.64–1.63 (*m*), 1.60 (*dd*, J = 12.5, 4.0)	4.19–4.16 (*m*)
CH_2(9) or H–C(9)	2.30–2.24, 1.43–1.25 (2*m*)	2.23–2.17, 1.30–1.27 (2*m*)	1.52 (*dt*, J = 13.4, 3.4), 1.25–1.22 (*m*)	3.23 (*d*, J = 5.3)
H–C(12), CH_2(12), or Me(12)	9.50 (*s*)	4.10 (br. *s*)	4.14 (*s*)	1.81 (*s*)
CH_2(13)	6.25, 5.94 (2 br. *s*)	5.00, 4.90 (2 br. *s*)	5.02 (*d*, J = 1.1), 4.91 (br. *s*)	4.88 (br. *s*), 4.71 (br. *s*)
Me(14)	0.82 (*s*)	0.82 (*s*)	0.80 (*s*)	0.98 (*s*)
Me(15) or H–C(15)	0.83 (*d*, J = 7.3)	0.77 (*d*, J = 6.8)	9.39 (*s*)	0.82 (*d*, J = 6.8)

NMR spectra revealed fifteen C-atom signals arising from three Me, five CH_2, and four CH groups and from three quaternary C-atoms. Among them, the two signals at δ(C) 145.2 and 111.3 indicated the presence of an olefinic bond (*Table 1*). Cross-peaks in the HSQC spectrum permitted the assignment of the H-atoms to their directly connected C-atoms (*Table 2*). Partial structures of **4** were identified with the assistance of ^{1}H,^{1}H-COSY and HMBC data (*Fig. 2*) and assembled to form an eremophilane-type framework. Three signals at δ(C) 64.4, 64.0, and 69.0 were assigned to the oxygenated C(8), C(9), and C(10), respectively. The molecular formula of **4** and the upfield shift of its C(10) signal (δ(C) 69.0) relative to that of **1** (δ(C) 73.2) suggested the location of an epoxy group between C(9) and C(10). Similarly to **1**, the NOESY correlation δ(H) 2.14/δ(H) 1.70 indicated the α-, β-, and β-configuration of H–C(7), Me(14), and the O-atom at C(10), respectively, if H–C(4) is assumed to be α-oriented. The H–C(8) should also be positioned on the α-face, because its signal at δ(H) 4.18 coupled with the signal of the axial H–C(7) at δ(H) 2.14 in the NOESY plot. Therefore, the structure of **4** was established as shown in *Fig. 1*.

The absolute configurations of compounds **1**–**4** were not determined due to the scarcity of the samples.

Compound **5** was obtained as pale yellow amorphous powder. Its HR-ESI-MS spectrum exhibited a molecular-ion peak at *m/z* 327.1228 ($[M+H]^+$, $C_{19}H_{19}O_5^+$), in accordance with the molecular formula $C_{19}H_{18}O_5$. In the aromatic region of its ^{1}H-NMR spectrum (*Table 3*), two *d* at δ(H) 7.19 ($J = 9.0$ Hz, 1 H) and 6.84 ($J = 9.0$ Hz, 1 H) and two *d* at δ(H) 7.08 ($J = 8.5$ Hz, 2 H) and 6.81 ($J = 8.5$ Hz, 2 H) were attributable to a tetrasubstituted and a *para*-disubstituted benzene ring, respectively. Besides that, a comprehensive analysis of the ^{1}H- and ^{13}C-NMR data (*Table 3*) revealed the presence of one carbonyl, one olefinic CH, two CH_2, one OH, and two MeO groups. The above findings suggested a (phenylethyl)chromenone skeleton for **5**, which was further confirmed by HMBC data (*Fig. 2*). The three signals at δ(C) 158.3, 149.5, and 143.3 in the ^{13}C-NMR spectrum, arising from O-bearing aromatic C-atoms, were ascribed to C(4′), C(5), and C(6), respectively, on the basis of relevant HMBC cross-peaks and comparison with a structurally similar known compound [8]. The two MeO groups were determined to be located at C(6) and C(4′), respectively, based on HMBC cross-peaks between the Me H-atoms and the corresponding C-atoms. Thus, the OH group should be linked to the last open position, namely to C(5). Consequently, the structure of **5** was elucidated as shown in *Fig. 1*.

Table 3. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$, 500 and 125 MHz, resp.) *of Compound* **5**[1]). δ in ppm, J in Hz.

	δ(H)	δ(C)		δ(H)	δ(C)
C(2)		170.2	C(1′)		131.5
H–C(3)	5.99 (*s*)	107.9	H–C(2′)	7.08 (*d*, $J = 8.5$)	129.2
C(4)		184.0	H–C(3′)	6.81 (*d*, $J = 8.5$)	114.1
C(5)		149.5	C(4′)		158.3
C(6)		143.3	H–C(5′)	6.81 (*d*, $J = 8.5$)	114.1
H–C(7)	7.19 (*d*, $J = 9.0$)	119.1	H–C(6′)	7.08 (*d*, $J = 8.5$)	129.2
H–C(8)	6.84 (*d*, $J = 9.0$)	105.7	CH_2(7′)	2.98–2.95 (*m*)	32.0
C(9)		150.5	CH_2(8′)	2.87–2.84 (*m*)	36.4
C(10)		110.8	*Me*O–C(6)	3.91 (*s*)	57.0
			*Me*O–C(4)	3.76 (*s*)	55.2

The known compounds isolated were identified as selina-4,11-diene-12,15-dial (**6**) [11][12], eudesm-4-ene-11,15-diol (**7**) [13], 7-methoxy-2-(2-phenylethyl)-4*H*-chromen-4-one (**8**) [14][15], 2-[2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one (**9**) [6], 5-hydroxy-6-methoxy-2-(2-phenylethyl)-4*H*-chromen-4-one (**10**) [8], 6-methoxy-2-[2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one (**11**) [6], 6-methoxy-2-[2-(3-methoxyphenyl)ethyl]-4*H*-chromen-4-one (**12**) [5], and 1-hydroxy-1,5-diphenylpentan-3-one (**13**) [16] by comparing their spectroscopic data with those reported in the above references. To the best of our knowledge, **8** was isolated from a natural source for the first time, **7** was first obtained from a plant, **6** was first isolated from the *Aquilaria* genus, and **9**–**11** were first obtained from *A. malaccensis* species.

Experimental Part

General. Column chromatography (CC): silica gel (*Kieselgel 60*, No. *7734*, 70–230 mesh; *Kieselgel 60*, No. *9385*, 230–400 mesh; *Merck*) and *Sephadex*™ *LH-20* (*GE Healthcare*, Sweden). Anal. TLC: silica gel *60* F_{254} glass plates 20 × 20 cm (*Merck*). Semi-prep. HPLC: *Hitachi* instrument (pump *L-7100*, UV detector *L-7420*); *Waters-SunFire*™*-Prep-C18-OBD*™ column (19 × 150 mm, 5 μm); t_R in min. Optical rotations: *Jasco-P-1020* polarimeter (Japan). UV Spectra: *Hitachi-U-3010* spectrophotometer (Japan); λ_{max} (log ε) in nm. IR Spectra: *Jasco-FT/IR-4200* spectrometer (Japan); in cm^{-1}. NMR Spectra: *Bruker-Avance-500* FT-NMR spectrometer (Germany); δ in ppm rel. to the residual solvent signal of $CDCl_3$. MS: *Bruker-micrOTOF-Q-II* mass spectrometer (Germany); in *m*/*z*.

Plant Material. The agarwood chips of *A. malaccensis* were purchased from *Industrial Plantation Co.*, Vientiane, Laos, in January, 2010. The voucher specimen was deposited with the Herbarium of the Natural Product Research Institute, Seoul National University.

Extraction and Isolation. Air-dried *A. malaccensis* agarwood chips (450 g) were crushed and exhaustively refluxed with 70% MeOH. The extract was concentrated to give a residue of 68.2 g, which was successively partitioned with Et_2O, BuOH, and H_2O. The Et_2O fraction (21.5 g) was subjected to CC (SiO_2, hexane/AcOEt 40:1 → 1:1): *Fractions E1–E14*. Further purification of *Fr. E11* by CC (SiO_2, $CHCl_3$) yielded **3** (8.9 mg). By using semi-prep. HPLC (mobile phase: $A = H_2O$, B = MeCN; flow rate 5 ml/min; monitor wavelength 203 nm), **4** (2.8 mg, with 60% B; t_R 26.20) and **6** (3.3 mg, with 70% B; t_R 30.50) were isolated from *Fr. E6*, **1** (4.9 mg, with 65% B; t_R 19.25) and **13** (10.7 mg, with 65% B; t_R 6.12) from *Fr. E7*, **9** (1.9 mg, with 50% B; t_R 37.30) and **10** (10.7 mg, with 60% B; t_R 31.25) from *Fr. E9*, **5** (9.1 mg, with 60% B; t_R 28.50) and **8** (4.7 mg, with 50% B; t_R 39.75) from *Fr. E12*, and **2** (12.6 mg, with 55% B; t_R 15.05), **7** (10.4 mg, with 55% B; t_R 23.00), and **11**/**12** (26.1 mg, with 55% B; t_R 31.10) from *Fr. E13*.

2-[(2β,4aβ,8β,8aβ)-Decahydro-4a-hydroxy-8,8a-dimethylnaphthalen-2-yl]prop-2-enal (=*2β,4aβ,8β,8aβ)-Decahydro-4a-hydroxy-8,8a-dimethyl-α-methylenenaphthalene-2-autaldehyde*; **1**): Colorless oil. $[\alpha]_D^{25} = 56.0$ ($c = 0.191$, MeOH). UV (MeOH): 219 (4.07), 199 (3.90). IR (film): 3473, 2926, 2862, 1690, 1449, 1379, 1247, 1174, 1008. ^{1}H- and ^{13}C-NMR: *Tables 2* and *1*. HR-ESI-MS (pos.): 259.1666 ($[M + Na]^+$, $C_{15}H_{24}NaO_2^+$; calc. 259.1669).

*(1β,4aβ,7β,8aβ)-Octahydro-7-[1-(hydroxymethyl)ethenyl]-1,8a-dimethylnaphthalen-4a(2*H*)-ol* (=*1β,4aβ,7β,8aβ)-Decahydro-4a-hydroxy-8,8a-dimethyl-α-methylidenenaphthalene-2-ethanol*; **2**): Colorless oil. $[\alpha]_D^{25} = +30.2$ ($c = 0.159$, MeOH). UV (MeOH): 247 (3.39), 203 (3.56). IR (film): 3403, 2924, 2863, 1653, 1449, 1380, 1053, 1033. ^{1}H- and ^{13}C-NMR*: Tables 2* and *1*. HR-ESI-MS (pos.): 261.1803 ($[M + Na]^+$, $C_{15}H_{26}NaO_2^+$; calc. 261.1825), 221.1892 ($[M - OH]^+$, $C_{15}H_{25}O^+$; calc. 221.1900).

(4aβ,7β,8aβ)-3,4,4a,5,6,7,8,8a-Octahydro-7-[1-(hydroxymethyl)ethenyl]-4a-methylnaphthalene-1-carboxaldehyde (**3**): Pale yellow oil. $[\alpha]_D^{25} = -12.3$ ($c = 0.280$, MeOH). UV (MeOH): 203 (3.64). IR (film): 3387, 2948, 2837, 1654, 1451, 1415, 1114, 1026. ^{1}H- and ^{13}C-NMR*: Tables 2* and *1*. HR-ESI-MS (pos.): 235.1685 ($[M + H]^+$, $C_{15}H_{23}O_2^+$; calc. 235.1693).

*(1aβ,2β,3β,4aβ,5β,8aβ)-Octahydro-4a,5-dimethyl-3-(1-methylethenyl)-3*H*-naphth[1,8a-*b*]oxiren-2-ol* (**4**): Colorless oil. $[\alpha]_D^{25} = -60.6$ ($c = 0.145$, MeOH). UV (MeOH): 246 (2.46), 204 (3.01). IR (film): 3503, 2934, 2861, 1746, 1647, 1542, 1449, 1374, 1135, 1046. ^{1}H- and ^{13}C-NMR*: Tables 2* and *1*. HR-ESI-MS (pos.): 237.1841 ($[M + H]^+$, $C_{15}H_{25}O_2^+$; calc. 237.1849).

*5-Hydroxy-6-methoxy-2-[2-(4-methoxyphenyl)ethyl]-4*H*-1-benzopyran-4-one* (**5**): Pale yellow amorphous powder. UV (MeOH): 342 (3.38), 230 (4.22), 203 (4.23). IR (film): 3375, 2919, 2836, 1734, 1651, 1627, 1579, 1513, 1478, 1453, 1398, 1271, 1243, 1230, 1157, 1051, 1031. ^{1}H- and ^{13}C-NMR*: Table 3*. HR-ESI-MS (pos.): 327.1228 ($[M + H]^+$, $C_{19}H_{19}O_5^+$; calc. 327.1227).

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Received October 20, 2011