Sesquiterpenoids and Lactone Derivatives from *Ligularia dentata*

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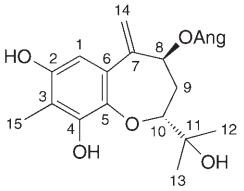
Seven new compounds were isolated from the roots of *Ligularia dentata*, including five bisabolane-type sesquiterpenoids (bisabolane = 1-(1,5-dimethylhexyl)-4-methylcyclohexane), namely (8β,10α)-8-(angeloyloxy)-5,10-epoxybisabola-1,3,5,7(14)-tetraene-2,4,11-triol (**1**), (8β,10α)-8-(angeloyloxy)-5,10-epoxythiazolo[5,4-*a*]bisabola-1,3,5,7(14)-tetraene-4,11-diol (**2**), (1α,2α,3β,5α,6β)-1,5,8-tris(angeloyloxy)-10,11-epoxy-2,3-dihydroxybisabol-7(14)-en-4-one (**3**), (1α,2α,3β,5α,6β)-2,5,8-tris(angeloyloxy)-10,11-epoxy-1,3-dihydroxybisabol-7(14)-en-4-one (**4**), and (1α,2β,3β,5α,6β)-1,8-bis(angeloyloxy)-2,3-epoxy-5,10-dihydroxy-11-methoxybisabol-7(14)-en-4-one (**5**) (angeloyloxy = [(2*Z*)-2-methyl-1-oxobut-2-enyl]oxy), and two lactone derivatives, (2α,3β,5α)-2-(acetyloxy)-9-methoxy-5-(methoxycarbonyl)-2,3-dimethylheptano-5-lactone (**6**), and (2β,4β)-2-ethyl-5-hydroxy-5-(methoxycarbonyl)-4,5-dimethylpentano-4-lactone (**7**) (α/β denote relative configurations), together with (2*E*,4*R*,5*S*)-2-ethylidene-5-(methoxycarbonyl)-4-methylhexano-5-lactone (**8**), a known synthetic compound. Compound **2** is the first sesquiterpenoid derivative containing the uncommon benzothiazole moiety. The structures of **1**–**8** were established by spectroscopic methods, especially 2D-NMR and MS analyses.

Introduction. – *Ligularia dentata* HARA (Compositae) has long been used as a medicinal herb for easing breathing, stimulating blood flow, reducing inflammation, alleviating pain, stopping coughs, and getting rid of phlegm in China [1]. Previous phytochemical investigations of this plant resulted in the isolation of phenolic norsesquiterpenoids [1–3], bisabolane-type sesquiterpenoids [4][5], (bisabolane = 1-(1,5-dimethylhexyl)-4-methylcyclohexane) and pyrrolizidine alkaloids [6]. In continuation of our studies aimed at finding new chemical constituents from the genus *Ligularia* [7], we now report the isolation of the seven new compounds **1**–**7** and of the known synthetic compound **8**.

Results and Discussion. – The Et_2O fraction of a MeOH extract of the roots of *Ligularia dentata* yielded compounds **1**–**8** after repeated silica gel column chromatography and prep. HPLC. Compound **1** was obtained as a colorless oil. The molecular formula of **1** was determined as $C_{20}H_{26}O_6$ based on the HR-EI-MS (*m*/*z* 362.1721 (M^+)). The IR spectrum showed the presence of an OH group (3605, 3383 cm^{-1}), an α,β-unsaturated ester (1708, 1647 cm^{-1}), and an aromatic ring (1630, 1588, 1504 cm^{-1}). The structure of **1** was elucidated as (8β,10α)-8-(angeloyloxy)-5,10-epoxybisabola-1,3,5,7(14)-tetraene-2,4,11-triol[1]) by spectroscopic means. So far, the absolute configuration of **1** could not be determined.



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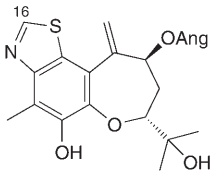

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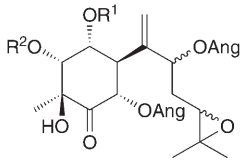
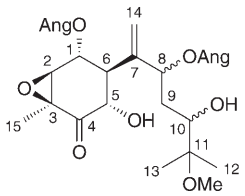


3 R^1 = Ang, R^2 = H
4 R^1 = H, R^2 = Ang



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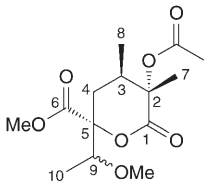

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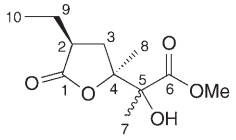

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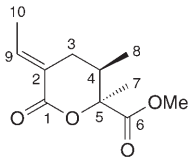

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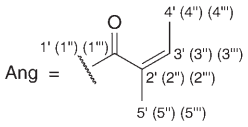

The ^{1}H- and ^{13}C-NMR spectra of **1** in $CDCl_3$ (*Table 1*) exhibited signals due to a substituted i-Pr group (δ(H) 1.26 (*s*), 1.38 (*s*); δ(C) 22.8 (Me), 27.6 (Me), 73.3 (C)), an angeloyloxy (= [(2*Z*)-2-methyl-1-oxobut-2-enyl]oxy) group (δ(H) 1.70 (*dq*, *J* = 1.5, 1.5 Hz), 1.78 (*dq*, *J* = 7.3, 1.5 Hz), 5.99 (*qq*, *J* = 7.3, 1.5 Hz); δ(C) 15.6 (Me), 20.5 (Me), 127.8 (C), 138.2 (CH), 166.7 (C)) [4], one Me group attached to an aromatic ring (δ(H) 2.15 (*s*); δ(C) 8.4 (Me)), a methylidene group (δ(H) 5.30 (*d*, *J* = 1.5 Hz), 5.43 (*d*, *J* = 0.7 Hz); δ(C) 117.5 (CH_2), 145.2 (C)), one CH_2 group (δ(H) 2.16–2.22 (*m*); δ(C) 37.0 (CH_2)), two oxygenated CH groups (δ(H) 3.77 (*dd*, *J* = 10.6, 2.6 Hz), 5.79 (*dd*, *J* = 4.8, 4.8 Hz); δ(C) 73.5 (CH), 84.1 (CH)), and an aromatic ring (δ(H) 6.19 (*s*); δ(C) 105.8 (CH), 110.7 (C), 129.4 (C), 137.4 (C), 147.2 (C), 150.4 (C)). Furthermore, signals at δ(H) 1.83 (br. *s*), 4.56 (br. *s*), and 7.44 (br. *s*) were observed which disappeared by adding D_2O, indicating the presence of OH protons. The ^{1}H,^{1}H-COSY spectrum of **1** (*Fig. 1, a*) implied the connectivities H–C(8)/CH_2(9) and CH_2(9)/H–C(10). The HMBC spectrum (*Fig. 1, a*) showed the correlations H–C(1)/C(2) and C(7), H–C(10)/C(5), Me(12)/C(10), Me(13)/C(10), CH_2(14)/C(6) and C(8), Me(15)/C(2) and C(4), OH–C(2)/C(2), OH–C(4)/C(4), and OH–C(11)/C(10). By considering the chemical shift of H–C(8) (δ(H) 5.79), the linking position of the angeloyloxy group was determined to be C(8). From these data, the constitutional formula of **1** was deduced. The relative configuration at C(8) and C(10) was established as follows (*Fig. 1, b*). The coupling constants *J*(8,9α) and *J*(8,9β) of 4.8 Hz each indicated that the angeloyloxy group at C(8) is β-oriented. Furthermore, *J*(9α,10) = 10.6 Hz and *J*(9β,10) = 2.6 Hz indicated that the side-chain at C(10) is α-oriented.

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[1]) Trivial or arbitrary atom numbering; for systematic names, see *Exper. Part.* The stereodescriptors α/β denote relative configurations with respect to the mean plane of the structure.

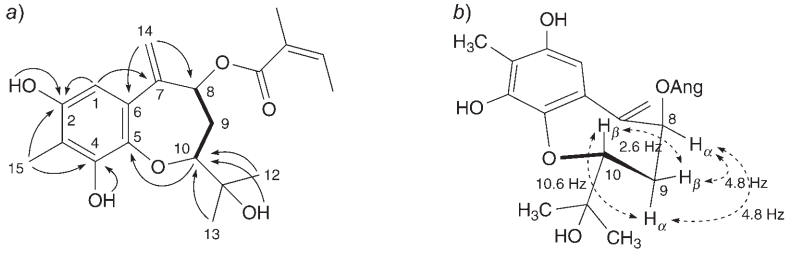

Fig. 1. a) *^{1}H,^{1}H-COSY* (▬) *and HMBC* (→) *Correlations and* b) *selected* J-*values* (←---→) *for* **1**

Table 1. *^{1}H- and ^{13}C-NMR Data of Compounds* **1** *and* **2**[1]). δ in ppm, J in Hz.

	1 ($CDCl_3$)		**1** (CD_3OD)		**2** (CD_3OD)	
	δ(H)[a])	δ(C)[b])	δ(H)[c])	δ(C)[d])	δ(H)[c])	δ(C)[d])
H–C(1) or C(1)	6.19 (*s*)	105.8	6.16 (*s*)	106.4	–	125.8
C(2)	–	150.4	–	152.8	–	150.5
C(3)	–	110.7	–	112.6	–	118.8
C(4)	–	147.2	–	148.2	–	146.8
C(5)	–	137.4	–	138.7	–	144.8
C(6)	–	129.4	–	129.9	–	123.3
C(7)	–	145.2	–	147.7	–	147.8
H–C(8)	5.79 (*dd*, *J* = 4.8, 4.8)	73.5	5.73 (*dd*, *J* = 4.4, 4.4)	75.2	5.85 (*dd*, *J* = 4.1, 4.1)	74.9
CH_2(9)	2.16–2.22 (*m*)	37.0	2.15–2.25 (*m*, 2 H)	38.1	2.27–2.30 (*m*)	37.9
H–C(10)	3.77 (*dd*, *J* = 10.6, 2.6)	84.1	3.72 (*dd*, *J* = 9.8, 3.9)	86.3	3.83 (*dd*, *J* = 9.3, 3.7)	86.4
C(11)	–	73.3	–	73.1	–	73.1
Me(12)	1.26 (*s*)[e])	27.6[f])	1.20 (*s*)[e])	27.0[f])	1.22 (*s*)[e])	26.9[f])
Me(13)	1.38 (*s*)[e])	22.8[f])	1.27 (*s*)[e])	23.0[f])	1.34 (*s*)[e])	22.6[f])
CH_2(14)	5.30 (*d*, *J* = 1.5), 5.43 (*d*, *J* = 0.7)	117.5	5.25 (*d*, *J* = 1.5), 5.36 (*d*, *J* = 0.7)	115.8	5.63 (*d*, *J* = 0.5), 5.80 (*s*)	119.5
Me(15)	2.15 (*s*)	8.4	2.05 (*s*)	8.8	2.58 (*s*)	11.5
H–C(16)	–	–	–	–	9.01 (*s*)	155.1
C(1′)	–	166.7	–	168.1	–	167.9
C(2′)	–	127.8	–	129.1	–	128.8
H–C(3′)	5.99 (*qq*, *J* = 7.3, 1.5)	138.2	6.04 (*qq*, *J* = 7.3, 1.5)	139.0	5.94 (*qq*, *J* = 7.3, 1.5)	139.0
Me(4′)	1.78 (*dq*, *J* = 7.3, 1.5)	15.6	1.76 (*dq*, *J* = 7.3, 1.5)	15.8	1.59 (*dq*, *J* = 7.3, 1.5)	15.6
Me(5′)	1.70 (*dq*, *J* = 1.5, 1.5)	20.5	1.72 (*dq*, *J* = 1.5, 1.5)	20.6	1.54 (*dq*, *J* = 1.5, 1.5)	20.4
OH–C(2)	4.56 (br. *s*)	–	–	–	–	–
OH–C(4)	7.44 (br. *s*)	–	–	–	–	–
OH–C(11)	1.83 (br. *s*)	–	–	–	–	–

[a]) Recorded at 600 MHz. [b]) Recorded at 150 MHz. [c]) Recorded at 400 MHz. [d]) Recorded at 100 MHz. [e]) δ(H) are interchangeable. [f]) δ(C) are interchangeable.

Compound **2** was obtained as a colorless oil. The EI-MS (*m*/*z* 405 (7, $[M+2]^+$), 403 (66, M^+)) indicated the presence of an odd number of N- and of S-atoms [8]. The molecular formula was determined to be $C_{21}H_{25}NO_6S$ by HR-EI-MS (*m*/*z* 403.1448 (M^+)), indicating ten degrees of unsaturation. The structure of **2** was identified by spectroscopic means as (8β,10α)-8-(angeloyloxy)-5,10-epoxythiazolo[5,4-*a*]bisabola-

1,3,5,7(14)-tetraene-4,11-diol[1]), the absolute configuration of which remains to be established.

The ^{1}H- and ^{13}C-NMR spectra of **2** in CD_3OD (*Table 1*) were very similar to those of **1**, except for a fully substituted benzene ring (δ(C) 118.8 (C(3)), 123.3 (C(6)), 125.8 (C(1)), 144.8 (C(5)), 146.8 (C(4)), 150.5 (C(2))) and an additional CH group (δ(H) 9.01 (*s*, H–C(16)); δ(C) 155.1 (C(16))). The proton resonating at δ(H) 9.01, which appeared to be at a C-atom situated between two heteroatoms according to the chemical shift of the C-atom (δ(C) 155.1) and a one-bond C,H coupling (J(C,H) = 215 Hz) [9], showed long-range coupling to C(1) (δ 125.8) and C(2) (δ 150.5) in the HMBC plot. After subtraction of the unsaturations due to an angeloyl group, a benzene ring, an exocyclic C=C and a seven-membered ring, we concluded that **2** comprises a thiazole ring fused to C(1) and C(2). The orientation was deduced by comparison of the δ(C)s with those of known benzothiazoles [10].

Compound **3** was obtained as a colorless oil. The molecular formula of **3** was determined as $C_{30}H_{42}O_{10}$ based on the HR-EI-MS (*m*/*z* 562.2785 (M^+)). The IR spectrum showed the presence of an OH group (3482 cm^{-1}), a six-membered ring ketone (1716 cm^{-1}), and an α,β-unsaturated ester (1716, 1647 cm^{-1}). The structure of **3** was determined to be (1α,2α,3β,5α,6β)-1,5,8-tris(angeloyloxy)-10,11-epoxy-2,3-dihydroxybisabol-7(14)-en-4-one[1]). The absolute and relative configurations at C(8) and C(10) remain to be established.

The ^{1}H- and ^{13}C-NMR spectra of **3** in $CDCl_3$ (*Table 2*) exhibited signals due to three Me groups (δ(H) 1.22 (*s*), 1.24 (*s*), 1.48 (*s*); δ(C) 18.8 (Me), 20.2 (Me), 24.6 (Me)), three angeloyl groups (δ(H) 1.89 (*dq*, *J* = 1.5, 1.5 Hz), 1.901 (*dq*, *J* = 1.5, 1.5 Hz), 1.904 (*dq*, *J* = 1.5, 1.5 Hz), 1.97 (*dq*, *J* = 7.3, 1.5 Hz), 1.98 (*dq*, *J* = 7.3, 1.5 Hz), 2.00 (*dq*, *J* = 7.3, 1.5 Hz), 6.11 (*qq*, *J* = 7.3, 1.5 Hz, 3 H); δ(C) 15.8 (Me), 15.9 (Me), 16.0 (Me), 20.5 (Me), 20.55 (Me), 20.57 (Me), 126.9 (C), 127.0 (C), 127.4 (C), 139.1 (CH), 139.6 (CH), 140.3 (CH), 166.11 (C), 166.15 (C), 166.8 (C)), a methylidene group (δ(H) 5.41 (*s*), 5.47 (*s*); δ(C) 114.6 (CH_2), 144.7 (C)), one CH_2 group (δ(H) 1.83 – 1.87 (*m*), 2.01 – 2.04 (*m*); δ(C) 33.2 (CH_2)), one CH group (δ(H) 3.22 (*dd*, *J* = 12.1, 11.4 Hz); δ(C) 44.1 (CH)), an epoxide moiety (δ(H) 2.80 (*dd*, *J* = 5.9, 5.9 Hz); δ(C) 58.1 (C), 60.9 (CH)), four oxygenated CH groups (δ(H) 4.13 (br. *d*, *J* = 2.6 Hz), 5.56 (*dd*, *J* = 8.8, 3.3 Hz), 5.94 (*dd*, *J* = 11.4, 2.6 Hz), 6.09 (*d*, *J* = 12.1 Hz); δ(C) 71.8 (CH), 72.9 (CH), 74.0 (CH), 76.2 (CH)), an oxygenated quaternary sp^3 C-atom (δ(C) 76.9 (C)), and a C=O group (δ(C) 201.8). Furthermore, signals at δ(H) 2.16 (br. *s*) and 3.28 (br. *s*) were observed which disappeared by adding D_2O, indicating the presence of OH protons. To accommodate ten degrees of unsaturation, compound **3** was proposed to have a monocyclic sesquiterpene skeleton, with three angeloyl groups, an epoxy group, a keto group, and an exocyclic C=C bond. The ^{1}H,^{1}H-COSY of **3** (*Fig. 2, a*) implied the connectivities

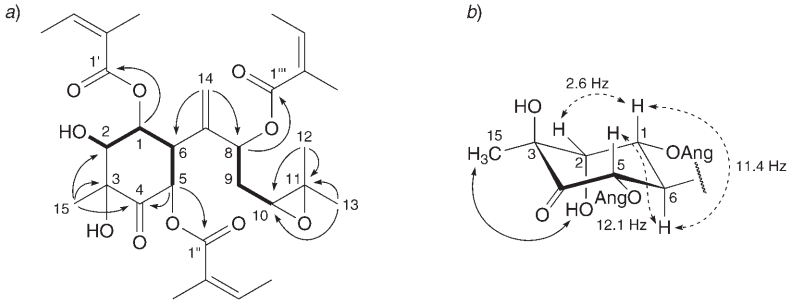

Fig. 2. a) *^{1}H,^{1}H-COSY* (▬) *and HMBC* (→) *Correlations and* b) *selected* J*-values* (←---→) *and NOEs* (↔) *for* **3**

Table 2. *^{1}H- and ^{13}C-NMR Data ($CDCl_3$) of Compounds* **3**–**5**[1]). δ in ppm, J in Hz.

	3		**4**		**5**	
	δ(H)[a])	δ(C)[b])	δ(H)[c])	δ(C)[d])	δ(H)[a])	δ(C)[b])
H–C(1)	5.94 (*dd*, *J* = 11.4, 2.6)	72.9	4.65 (*dd*, *J* = 10.1, 2.5)	71.7	5.43 (*d*, *J* = 9.2)	70.5
H–C(2)	4.13 (br. *d*, *J* = 2.6)	76.2	5.58 (*d*, *J* = 2.5)	77.2	3.45 (*s*)	66.8
C(3)	–	76.9	–	76.1	–	60.7
C(4)	–	201.8	–	202.1	–	205.8
H–C(5)	6.09 (*d*, *J* = 12.1)	74.0	6.08 (*d*, *J* = 12.2)	73.2	4.78 (*dd*, *J* = 12.1, 4.4)	70.1
H–C(6)	3.22 (*dd*, *J* = 12.1, 11.4)	44.1	2.79 (*dd*, *J* = 12.2, 10.1)	47.3	2.76 (*dd*, *J* = 12.1, 9.2)	54.3
C(7)	–	144.7	–	146.8	–	146.4
H–C(8)	5.56 (*dd*, *J* = 8.8, 3.3)	71.8	5.11 (*dd*, *J* = 8.2, 4.0)	75.6	5.48 (*dd*, *J* = 9.9, 1.8)	72.1
CH_2(9)	1.83–1.87, 2.01–2.04 (*m*)	33.2	n.d.[e])	32.7	1.67–1.77 (*m*)	36.6
H–C(10)	2.80 (*dd*, *J* = 5.9, 5.9)	60.9	2.83 (*dd*, *J* = 6.3, 6.3)	60.7	3.51 (*ddd*, *J* = 10.3, 3.7, 1.8)	73.2
C(11)	–	58.1	–	58.4	–	76.8
Me(12)	1.22 (*s*)[f])	18.8[g])	1.25 (*s*)[f])	18.9[g])	1.09 (*s*)[f])	19.2[g])
Me(13)	1.24 (*s*)[f])	24.6[g])	1.30 (*s*)[f])	24.6[g])	1.11 (*s*)[f])	20.5[g])
CH_2(14)	5.41, 5.47 (2*s*)	114.6	5.32 (br. *s*)	111.4	5.26, 5.40 (2*s*)	114.6
Me(15)	1.48 (*s*)	20.2	1.36 (*s*)	19.9	1.54 (*s*)	14.5
C(1′)	–	166.11	–	167.8	–	166.5
C(1″)	–	166.8	–	167.0	–	167.2
C(1‴)	–	166.15	–	166.4	–	
C(2′)	–	126.9	–	127.2	–	126.9
C(2″)	–	127.0	–	127.2	–	127.5
C(2‴)	–	127.4	–	127.2	–	–
H–C(3′)	6.11 (*qq*, *J* = 7.3, 1.5)	139.1	6.15 (*qq*, *J* = 7.3, 1.5)	139.3	6.10 (*qq*, *J* = 7.3, 1.5)	139.2
H–C(3″)	6.11 (*qq*, *J* = 7.3, 1.5)	139.6	6.15 (*qq*, *J* = 7.3, 1.5)	139.5	6.17 (*qq*, *J* = 7.3, 1.5)	140.6
H–C(3‴)	6.11 (*qq*, *J* = 7.3, 1.5)	140.3	6.15 (*qq*, *J* = 7.3, 1.5)	141.1	–	–
Me(4′)	1.97 (*dq*, *J* = 7.3, 1.5)	15.8	1.94 (*dq*, *J* = 7.3, 1.5)	15.8	1.97 (*dq*, *J* = 7.3, 1.5)	15.8
Me(4″)	1.98 (*dq*, *J* = 7.3, 1.5)	15.9	1.96 (*dq*, *J* = 7.3, 1.5)	15.9	2.02 (*dq*, *J* = 7.3, 1.5)	16.0
Me(4‴)	2.00 (*dq*, *J* = 7.3, 1.5)	16.0	2.00 (*dq*, *J* = 7.3, 1.5)	16.0	–	–
Me(5′)	1.89 (*dq*, *J* = 1.5, 1.5)	20.5	1.86 (*dq*, *J* = 1.5, 1.5)	20.5	1.89 (*dq*, *J* = 1.5, 1.5)	20.5
Me(5″)	1.901 (*dq*, *J* = 1.5, 1.5)	20.55	1.88 (*dq*, *J* = 1.5, 1.5)	20.6	1.92 (*dq*, *J* = 1.5, 1.5)	20.6
Me(5‴)	1.904 (*dq*, *J* = 1.5, 1.5)	20.57	1.89 (*dq*, *J* = 1.5, 1.5)	20.5	–	–
OH–C(1)	–	–	4.68 (br. *s*)	–	–	–
OH–C(2)	2.16 (br. *s*)	–	–	–	–	–
OH–C(3)	3.28 (br. *s*)	–	2.85 (br. *s*)	–	–	–
OH–C(5)	–	–	–	–	3.64 (*d*, *J* = 4.4)	–
OH–C(10)	–	–	–	–	2.57 (*d*, *J* = 3.7)	–
MeO–C(11)	–	–	–	–	3.21 (*s*)	49.1

[a]) Recorded at 600 MHz. [b]) Recorded at 150 MHz. [c]) Recorded at 270 MHz. [d]) Recorded at 67.8 MHz. [e]) Not determined. [f]) δ(H) are interchangeable. [g]) δ(C) are interchangeable.

H–C(1)/H–C(2), H–C(1)/H–C(6), H–C(2)/OH–C(2), H–C(5)/H–C(6), H–C(8)/CH_2(9), and CH_2(9)/H–C(10). The HMBC (*Fig. 2, a*) showed the correlations H–C(1)/C(1′), H–C(5)/C(4) and C(1″), H–C(8)/C(1‴), Me(12)/C(10) and C(11), Me(13)/C(10) and C(11), CH_2(14)/C(6) and C(8), and Me(15)/C(2), C(3), and C(4). From these data, the constitution of **3** was deduced. The relative configuration of the substituents at the cyclohexenone ring was determined as follows. The coupling constants for H–C(6) (J(1,6) = 11.4 Hz, J(5,6) = 12.1 Hz) suggested that the angeloyloxy groups at C(1) and C(5) are both α-equatorially oriented, and the side chain at C(6) is β-equatorially oriented

(*Fig. 2, b*). The coupling constant for H–C(2) ($J(1,2) = 2.6$ Hz) suggested that the OH group at C(2) is α-axially oriented (*Fig. 2, b*). The NOE correlation between OH–C(2) and Me(15) in the NOESY plot confirmed that the OH group at C(3) is β-axially oriented.

Compound **4** was obtained as a colorless oil. The molecular formula of **4** was determined as $C_{30}H_{42}O_{10}$ based on the HR-EI-MS (*m/z* 562.2795 (M^+)). The ^{1}H- and ^{13}C-NMR spectra of **4** (*Table 2*) were analogous to those of **3**. The structure of **4** was deduced as (1α,2α,3β,5α,6β)-2,5,8-tris(angeloyloxy)-10,11-epoxy-1,3-dihydroxybisabol-7(14)-en-4-one[1]). The absolute and relative configurations at C(8) and C(10) remain to be established.

The one significant difference in the ^{1}H-NMR spectrum of **4**, compared with that of **3**, was that a *d* occurred at δ(H) 5.58 ($J = 2.5$ Hz). Moreover, the *dd* of **3** at δ(H) 5.94 (H–C(1)) was shifted to δ(H) 4.65. The foregoing results clearly indicated that **4** was a constitutional isomer of **3**. The correlation peak between H–C(2) and C(1′) (δ 167.8) in the HMBC of **4** also supported the proposed structure.

Compound **5** was obtained as a colorless oil. The molecular formula of **5** was determined as $C_{26}H_{38}O_9$ based on the HR-EI-MS (*m/z* 494.2509 (M^+)). The IR spectrum showed the presence of an OH group (3503 cm^{-1}), a six-membered-ring ketone (1719 cm^{-1}), and an α,β-unsaturated ester (1719, 1646 cm^{-1}). The structure of **5** was determined to be (1α,2β,3β,5α,6β)-1,8-bis(angeloyloxy)-2,3-epoxy-5,10-dihydroxy-11-methoxybisabol-7(14)-en-4-one[1]). The absolute and relative configurations at C(8) and C(10) remain to be established.

The ^{1}H- and ^{13}C-NMR spectra of **5** in $CDCl_3$ (*Table 2*) exhibited signals due to three Me groups (δ(H) 1.09 (*s*), 1.11 (*s*), 1.54 (*s*); δ(C) 14.5 (Me), 19.2 (Me), 20.5 (Me)), one MeO group (δ(H) 3.21 (*s*); δ(C) 49.1 (MeO)), two angeloyl groups (δ(H) 1.89 (*dq*, $J = 1.5$, 1.5 Hz), 1.92 (*dq*, $J = 1.5$, 1.5 Hz), 1.97 (*dq*, $J = 7.3$, 1.5 Hz), 2.02 (*dq*, $J = 7.3$, 1.5 Hz), 6.10 (*qq*, $J = 7.3$, 1.5 Hz), 6.17 (*qq*, $J = 7.3$, 1.5 Hz); δ(C) 15.8 (Me), 16.0 (Me), 20.5 (Me), 20.6 (Me), 126.9 (C), 127.5 (C), 139.2 (CH), 140.6 (CH), 166.5 (C), 167.2 (C)), a methylidene group (δ(H) 5.26 (*s*), 5.40 (*s*); δ(C) 114.6 (CH_2), 146.4 (C)), one CH_2 group (δ(H) 1.67–1.77 (*m*); δ(C) 36.6 (CH_2)), one CH group (δ(H) 2.76 (*dd*, $J = 12.1$, 9.2 Hz); δ(C) 54.3 (CH)), an epoxide moiety (δ(H) 3.45 (*s*); δ(C) 60.7 (C), 66.8 (CH)), four oxygenated CH groups (δ(H) 3.51 (*ddd*, $J = 10.3$, 3.7, 1.8 Hz), 4.78 (*dd*, $J = 12.1$, 4.4 Hz), 5.43 (*d*, $J = 9.2$ Hz), 5.48 (*dd*, $J = 9.9$, 1.8 Hz); δ(C) 70.1 (CH), 70.5 (CH), 72.1 (CH), 73.2 (CH)), an oxygenated quaternary sp^3 C-atom (δ(C) 76.8 (C)), and a C=O group (δ(C) 205.8). Furthermore, signals at δ(H) 2.57 (*d*, $J = 3.7$ Hz) and 3.64 (*d*, $J =$ 4.4 Hz) were observed which disappeared by adding D_2O, indicating the presence of OH protons. To accommodate eight degrees of unsaturation, compound **5** was proposed to have a monocyclic sesquiterpene skeleton, with two angeloyl, an epoxy, and a keto group, and an exocyclic C=C bond. The ^{1}H,^{1}H-COSY of **5** (*Fig. 3, a*) implied the connectivities H–C(1)/H–C(6), H–C(6)/H–C(5), H–C(5)/OH–C(5), H–C(8)/CH_2(9), CH_2(9)/H–C(10), and H–C(10)/OH–C(10). The HMBC (*Fig. 3, a*) showed the correlations H–C(1)/C(1′), H–C(1)/C(2), H–C(8)/C(1″), Me(12)/C(10) and C(11), Me(13)/C(10) and C(11), CH_2(14)/C(6) and C(8), Me(15)/C(2), C(3), and C(4), and MeO(11)/C(11). From these data, the constitution of **5** was deduced. The relative configuration of the substituents at the cyclohexenone ring was determined by the NOE correlations H–C(1)/H–C(5) in the NOESY and the coupling constants for H–C(6) ($J(1,6) = 9.2$ Hz, $J(5,6) = 12.1$ Hz) which suggested that the angeloyloxy group at C(1) and the OH group at C(5) are both α-equatorially oriented, and the side chain at C(6) is β-equatorially oriented (*Fig. 3, b*). The epoxy group at C(2)–C(3) must be β-oriented because the coupling constant of H–C(1) with H–C(2) was almost zero so their dihedral angle must be *ca.* 90° which results from the β-oriented epoxy group [11]. The epoxy configuration was supported by a NOESY cross-peak between H–C(2) and Me(15) (*Fig. 3, b*).

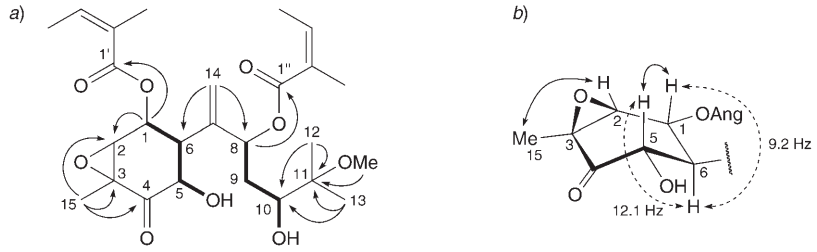

Fig. 3. a) *$^1H,^1H$-COSY* (▬) *and HMBC* (→) *Correlations and* b) *selected* J*-values* (←---→) *and NOEs* (↔) *for* **5**

Compound **6** was obtained as a colorless oil. The molecular formula of **6** was determined as $C_{14}H_{22}O_7$ based on the HR-EI-MS (*m/z* 302.1368 (M^+)). The structure of **6** was determined to be (2*α*,3*β*,5*α*)-2-(acetyloxy)-9-methoxy-5-(methoxycarbonyl)-2,3-dimethylheptano-5-lactone[1]). The absolute and relative configurations at C(9) remain to be established.

The ^{1}H- and ^{13}C-NMR spectra of **6** in $CDCl_3$ (*Table 3*) exhibited signals due to three Me groups (δ(H) 1.00 (*d*, *J* = 6.8 Hz), 1.13 (*d*, *J* = 6.4 Hz), 1.46 (*s*); δ(C) 13.9 (Me), 14.6 (Me), 18.9 (Me)), one AcO group (δ(H) 2.07 (*s*); δ(C) 21.0 (Me), 169.7 (C)), two MeO groups (δ(H) 3.42 (*s*), 3.86 (*s*); δ(C) 53.1 (MeO), 58.6 (MeO)), one CH_2 group (δ(H) 1.89 (*dd*, *J* = 14.3, 13.5 Hz), 2.33 (*dd*, *J* = 14.3, 3.6 Hz); δ(C) 30.1 (CH_2)), one CH group (δ(H) 2.75–2.82 (*m*); δ(C) 30.2 (CH)), an oxygenated CH group (δ(H) 3.64

Table 3. *^1H-* (600 MHz) *and ^{13}C-NMR* (150 MHz) *Data of Compounds* **6**–**8**[1]) *in $CDCl_3$.* δ in ppm, *J* in Hz.

	6		**7**		**8**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
C(1)	–	170.5	–	178.8	–	165.6
C(2) or H–C(2)	–	78.8	2.70–2.76 (*m*)	42.6	–	125.4
H–C(3) or CH_2(3)	2.75–2.82 (*m*)	30.2	1.61 (*dd*, *J* = 13.6, 8.8), 2.63 (*dd*, *J* = 13.6, 10.6)	36.0	2.00 (*ddd*, *J* = 16.9, 14.3, 1.8), 2.57 (*dd*, *J* = 16.9, 5.1)	29.3
CH_2(4), C(4) or H–C(4)	1.89 (*dd*, *J* = 14.3, 13.5, H_α), 2.33 (*dd*, *J* = 14.3, 3.6, H_β)	30.1	–	86.0	2.08–2.15 (*m*)	36.5
C(5)	–	88.4	–	79.0	–	85.1
C(6)	–	170.3	–	175.0	–	171.2
Me(7)	1.46 (*s*)	18.9	1.48 (*s*)	20.6	1.64 (*s*)	23.7
Me(8)	1.00 (*d*, *J* = 6.8)	14.6	1.49 (*s*)	24.9	1.14 (*d*, *J* = 7.0)	16.0
H–C(9) or CH_2(9)	3.64 (*q*, *J* = 6.4)	79.6	1.50–1.53 (*m*), 1.87–1.90 (*m*)	25.3	7.17 (*qdd*, *J* = 7.3, 1.8, 1.8)	141.0
Me(10)	1.13 (*d*, *J* = 6.4)	13.9	0.98 (*t*, *J* = 7.3)	11.5	1.79 (*dd*, *J* = 7.3, 1.1)	14.1
OH–C(5)	–	–	3.34 (*s*)	–	–	–
MeO–C(6)	3.86 (*s*)	53.1	3.84 (*s*)	53.4	3.76 (*s*)	52.6
MeO–C(9)	3.42 (*s*)	58.6	–	–	–	–
AcO	2.07 (*s*)	21.0	–	–	–	–
	–	169.7	–	–	–	–

(q, $J = 6.4$ Hz); δ(C) 79.6 (CH)), two oxygenated quaternary sp^3 C-atoms (δ(C) 78.8 (C), 88.4 (C)), and two C=O groups (δ(C) 170.3, 170.5). The ^{1}H,^{1}H-COSY of **6** (*Fig. 4, a*) implied the connectivities H–C(3)/CH$_2$(4), H–C(3)/Me(8), and H–C(9)/Me(10). The HMBC (*Fig. 4, a*) showed the correlations CH$_2$(4)/C(5) and C(9), Me(7)/C(1) and C(2), Me(8)/C(2), Me(10)/C(5), MeO–C(6)/C(6), and MeO–C(9)/C(9). According to the molecular formula, there were four degrees of unsaturation in the molecule. One AcO group and two C=O groups accounted for three of those. The remaining degree of unsaturation was assumed to be due to a δ-lactone ring formed between C(1) and C(5) on the basis of the ^{13}C-NMR data (δ(C) 88.4 (C(5)), 170.5 (C(1))) and the IR absorption (1736 cm^{-1}). The presence of the AcO group at C(2) was indicated by the NOESY plot, in which a cross-peak was observed between the AcO group and Me(7) (*Fig. 4, a*). From these data, the constitution of **6** was deduced. The relative configuration of **6** was determined as follows. The coupling constants $J(3,4\alpha) = 3.7$ Hz and $J(3,4\beta) =$ 13.6 Hz suggested that H–C(3)/H$_\alpha$–C(4) and H–C(3)/H$_\beta$–C(4) are *gauche* and *anti* arranged, respectively (*Fig. 4, b*). The NOESY cross-peak Me(7)/Me(8) and Me(8)/Me(10) implied that Me–C(2) and Me–C(3) are on the same face (β) of the ring system, and that AcO–C(2) and MeOOC–C(5) are both on the α side (*Fig. 4, b*).

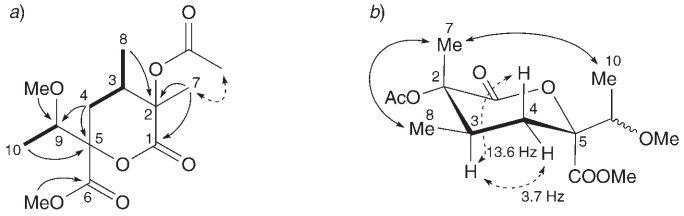

Fig. 4. a) *^{1}H,^{1}H-COSY* (▬), *HMBC* (→), and *NOESY* (⇠⇢) *Correlations and* b) *selected* J*-values* (⇠⇢) *and NOEs* (↔) *for* **6**

Compound **7** was obtained as a colorless oil. The molecular formula of **7** was determined as $C_{11}H_{18}O_5$ based on HR-EI-MS (*m/z* 230.1163 (M^+)). The structure of **7** was determined to be (2β,4β)-2-ethyl-5-hydroxy-5-(methoxycarbonyl)-4,5-dimethylpentano-4-lactone[1]). The absolute and relative configurations at C(5) remain to be established.

The ^{1}H- and ^{13}C-NMR spectra of **7** in $CDCl_3$ (*Table 3*) exhibited signals due to three Me groups (δ(H) 0.98 (*t*, $J = 7.3$ Hz), 1.48 (*s*), 1.49 (*s*); δ(C) 11.5 (Me), 20.6 (Me), 24.9 (Me)), one MeO group (δ(H) 3.84 (*s*); δ(C) 53.4 (MeO)), two CH$_2$ groups (δ(H) 1.50–1.53 (*m*), 1.61 (*dd*, $J = 13.6$, 8.8 Hz), 1.87–1.90 (*m*), 2.63 (*dd*, $J = 13.6$, 10.6 Hz); δ(C) 25.3 (CH$_2$), 36.0 (CH$_2$)), one CH group (δ(H) 2.70–2.76 (*m*); δ(C) 42.6 (CH)), two oxygenated quaternary sp^3 C-atoms (δ(C) 79.0 (C), 86.0 (C)), and two C=O groups (δ(C) 175.0, 178.8). Furthermore, a signal at δ(H) 3.34 (*s*) was observed which disappeared by adding D_2O, indicating the presence of an OH proton. The ^{1}H,^{1}H-COSY of **7** (*Fig. 5*) implied the connectivities H–C(2)/CH$_2$(3), H–C(2)/CH$_2$(9), and CH$_2$(9)/Me(10). The HMBC (*Fig. 5*) showed the correlations CH$_2$(3)/C(1), Me(7)/C(4), C(5), and C(6), Me(8)/C(3), C(4), and C(5), MeO–C(6)/C(6), and OH–C(5)/C(5) and C(6). There were three degrees of unsaturation in the

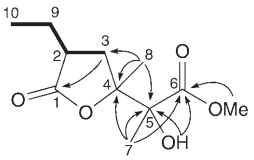

Fig. 5. *^{1}H,^{1}H-COSY* (–) *and HMBC* (→) *Correlations for* **7**

molecule according to the molecular formula. Two C=O groups accounted for two of those. The remaining degree of unsaturation was assumed to be due to a γ-lactone ring formed between C(1) and C(4) on the basis of the ^{13}C-NMR data (δ(C) 86.0 (C(4)), 178.8 (C(1))) and the IR absorption (1765 cm^{-1}). From these data, the constitution of **7** was deduced. The NOESY cross-peak H–C(2)/Me(8) implied that the Et group at C(2) and the Me group at C(4) have β and α orientations, respectively.

Compound **8** was obtained as a colorless oil. The molecular formula of **8** was determined as $C_{11}H_{16}O_4$ based on HR-EI-MS (*m/z* 212.1055 (M^+)). The IR spectrum showed the presence of an ester (1740 cm^{-1}) and an α,β-unsaturated ester (1716, 1640 cm^{-1}). The ^{1}H- and ^{13}C-NMR data (*Table 3*), analyzed with the aid of ^{1}H,^{1}H-COSY, NOESY, HMQC, and HMBC experiments, and the optical rotation value of **8** were in accord with those of (2*E*,4*R*,5*S*)-2-ethylidene-5-(methoxycarbonyl)-4-methylhexano-5-lactone[1]) [12]. Compound **8** was isolated from a natural source for the first time, although **8** has already been synthesized by *Niwa et al.* [12].

We are grateful to Mr. *S. Satoh* and Mr. *T. Matsuki* for NMR and MS measurements.

Experimental Part

General. Column chromatography (CC): silica gel (230–400 mesh; *Merck*). Prep. HPLC: *CCPD* pump (*Tosoh*); *TSKgel ODS-120T* column (300 × 7.8 mm, *Tosoh*); *RI-8010* detector (*Tosoh*). Optical rotations: *Jasco DIP-360* digital polarimeter. UV Spectra: *Beckman DU-64* spectrophotometer. IR Spectra: *Perkin-Elmer Spectrum-One-FT-IR* spectrometer. NMR Spectra: *Jeol JNM-LA-600* (^{1}H, 600 MHz; ^{13}C, 150 MHz), *Jeol JNM-LA-400* (^{1}H, 400 MHz; ^{13}C, 100 MHz), and *Jeol JNM-EX-270* (^{1}H, 270 MHz; ^{13}C, 67.8 MHz) spectrometers; chemical shifts δ in ppm, rel. to the residual signals of $CDCl_3$ (δ(H) 7.27, δ(C) 77.0) and CD_3OD (δ(H) 3.31, δ(C) 49.0). MS: *Jeol JMS-DX-303* and *Jeol JMS-700* mass spectrometers; in *m/z* (rel. %).

Plant Material. The roots of *Ligularia dentata* were collected in Sendai City, Miyagi Prefecture, Japan, in May 2004. A voucher specimen (LDB-2004-01) was deposited at the Laboratory of Molecular Structural Analysis, Tohoku Pharmaceutical University.

Extraction and Isolation. The roots of *Ligularia dentata* (2.3 kg) were extracted three times (14 days each time) with MeOH at r.t. and filtered. The MeOH extract was concentrated under reduced pressure, and the residue (138 g) was suspended in a small excess of H_2O. This suspension was extracted with Et_2O. The Et_2O-soluble fraction was concentrated under atmospheric pressure to afford a residue (16.6 g), which was subjected to CC (silica gel, hexane/AcOEt 4:1 → 1:4, AcOEt, $CHCl_3$/MeOH 4:1 → 1:1, and MeOH): *Fractions 1–44*, according to TLC. *Fr. 18*, on prep. HPLC (MeOH/H_2O 2:1, 1.0 ml/min), gave 0.5 mg of **8** (t_R 14.4 min), 0.8 mg of **1** (t_R 21.3 min), and 1.1 mg of **2** (t_R 37.8 min). *Fr. 19*, on prep. HPLC (MeOH/H_2O 2:1, 1.0 ml/min), gave **6**/**7** (t_R 15.0 min) and 2.3 mg of **4** (t_R 96.6 min). The mixture **6**/**7**, on prep. HPLC (MeOH/H_2O 1:1, 1.0 ml/min), gave 1.1 mg of **7** (t_R 22.5 min) and 0.8 mg of **6** (t_R 27.0 min). *Fr. 20*, on prep. HPLC (MeOH/H_2O 2:1, 1.0 ml/min), gave 0.6 mg of **5** (t_R 49.2 min) and 1.4 mg of **3** (t_R 77.4 min).

(8β,10α)-8-(Angeloyloxy)-5,10-epoxybisabola-1,3,5,7(14)-tetraene-2,4,11-triol (=*(2Z)-2-Methylbut-2-enoic Acid* rel-*(2*R,*4*S*)-2,3,4,5-Tetrahydro-7,9-dihydroxy-2-(1-hydroxy-1-methylethyl)-8-methyl-5-methylene-1-benzoxepin-4-yl Ester*; **1**): Colorless oil. $[\alpha]_D^{21} = +12.0$ ($c = 0.08$, MeOH). UV (MeOH): 214 (4.4), 248 (sh, 3.8), 295 (3.3). IR ($CHCl_3$): 3605, 3383, 1708, 1647, 1630, 1588, 1504. ^{1}H- and ^{13}C-NMR: *Table 1*. EI-MS: 362 (39, M^+), 344 (2), 304 (2), 262 (52), 244 (16), 229 (28), 204 (34), 191 (100). HR-EI-MS: 362.1721 (M^+, $C_{20}H_{26}O_6^+$; calc. 362.1729).

*(8β,10α)-8-(Angeloyloxy)-5,10-epoxythiazolo[5,4-*a*]bisabola-1,3,5,7(14)-tetraene-4,11-diol* (=*(2Z)-2-Methylbut-2-enoic Acid* rel-*(7*R,*9*S*)-7,8,9,10-Tetrahydro-5-hydroxy-7-(1-hydroxy-1-methylethyl)-4-methyl-10-methyleneoxepino[2,3-*g*]benzothiazol-9-yl Ester*; **2**): Colorless oil. $[\alpha]_D^{24} = -27.3$ ($c = 0.11$, MeOH). UV (MeOH): 212 (4.4), 260 (4.0), 313 (3.5). ^{1}H- and ^{13}C-NMR: *Table 1*. EI-MS: 405 (7,

$[M+2]^+$), 403 (66, M^+), 303 (100), 285 (41), 270 (37), 245 (40), 232 (82). HR-EI-MS: 403.1448 (M^+, $C_{21}H_{25}NO_6S^+$; calc. 403.1453).

(1α,2α,3β,5α,6β)-1,5,8-Tris(angeloyloxy)-10,11-epoxy-2,3-dihydroxybisabol-7(14)-en-4-one (=*(2Z,2′Z)-2-Methylbut-2-enoic Acid* rel-*(1R,2S,3S,4S,5R)-2-{3-(3,3-Dimethyloxiranyl)-1-methylene-2-{[(2Z)-2-methyl-1-oxobut-2-enyl]oxy}propyl}-4,5-dihydroxy-5-methyl-6-oxocyclohexane-1,3-diyl Ester*; **3**): Colorless oil. $[\alpha]_D^{20} = +7.4$ ($c = 0.14$, MeOH). IR ($CHCl_3$): 3482, 1716, 1647. ^{1}H- and ^{13}C-NMR: *Table 2*. EI-MS: 562 (2, M^+), 544 (1), 462 (3), 444 (2), 362 (5), 344 (5), 262 (9), 244 (6), 83 (100). HR-EI-MS: 562.2785 (M^+, $C_{30}H_{42}O_{10}^+$; calc. 562.2778).

(1α,2α,3β,5α,6β)-2,5,8-Tris(angeloyloxy)-10,11-epoxy-1,3-dihydroxybisabol-7(14)-en-4-one (=*(2Z,2′Z)-2-Methylbut-2-enoic Acid* rel-*(1R,2S,4S,5R,6R)-5-{3-(3,3-Dimethyloxiranyl)-1-methylene-2-{[(2Z)-2-methyl-1-oxobut-2-enyl]oxy}propyl}-2,6-dihydroxy-2-methyl-3-oxocyclohexane-1,4-diyl Ester*; **4**): Colorless oil. $[\alpha]_D^{20} = +4.4$ ($c = 0.23$, MeOH). ^{1}H- and ^{13}C-NMR: *Table 2*. EI-MS: 562 (1, M^+), 462 (1), 362 (2), 262 (2), 83 (100). HR-EI-MS: 562.2795 (M^+, $C_{30}H_{42}O_{10}^+$; calc. 562.2778).

(1α,2β,3β,5α,6β)-1,8-Bis(angeloyloxy)-2,3-epoxy-5,10-dihydroxy-11-methoxybisabol-7(14)-en-4-one (=*(2Z)-2-Methylbut-2-enoic Acid* rel-*(1R,2S,3R,4R,6R)-4-Hydroxy-3-{4-hydroxy-5-methoxy-5-methyl-1-methylene-2-{[(2Z)-2-methyl-1-oxobut-2-enyl]oxy}hexyl}-6-methyl-5-oxo-7-oxabicyclo[4.1.0]hept-2-yl Ester*; **5**): Colorless oil. $[\alpha]_D^{19} = +17.5$ ($c = 0.06$, MeOH). IR ($CHCl_3$): 3503, 1719, 1646. ^{1}H- and ^{13}C-NMR: *Table 2*. EI-MS: 494 (1, M^+), 462 (1), 421 (11), 394 (1), 362 (2), 321 (37), 294 (2), 262 (2), 221 (7), 83 (77), 73 (100). HR-EI-MS: 494.2509 (M^+, $C_{26}H_{38}O_9^+$; calc. 494.2516).

(2α,3β,5α)-2-(Acetyloxy)-9-methoxy-5-(methoxycarbonyl)-2,3-dimethylheptano-5-lactone (=rel-*(2R,4R,5S)-5-(Acetyloxy)tetrahydro-2-(1-methoxyethyl)-4,5-dimethyl-6-oxo-2H-pyran-2-caroxylic Acid Methyl Ester;* **6**): Colorless oil. $[\alpha]_D^{25} = +11.9$ ($c = 0.08$, MeOH). IR ($CHCl_3$): 1736. ^{1}H- and ^{13}C-NMR: *Table 3*. EI-MS: 302 (1, M^+), 244 (100), 216 (4), 202 (5), 184 (15), 174 (52), 156 (16), 141 (9), 113 (10), 59 (61). HR-EI-MS: 302.1368 (M^+, $C_{14}H_{22}O_7^+$; calc. 302.1365).

(2β,4β)-2-Ethyl-5-hydroxy-5-(methoxycarbonyl)-4,5-dimethylpentano-4-lactone (=rel-*(2R,4R)-4-Ethyltetrahydro-α-hydroxy-α,2-dimethyl-5-oxofuran-2-acetic Acid Methyl Ester*; **7**): Colorless oil. $[\alpha]_D^{26} = -18.9$ ($c = 0.11$, MeOH). IR ($CHCl_3$): 3527, 1765, 1728. ^{1}H- and ^{13}C-NMR: *Table 3*. EI-MS: 230 (1, M^+), 171 (11), 153 (4), 127 (100), 99 (15), 43 (39). HR-EI-MS: 230.1163 (M^+, $C_{11}H_{18}O_5^+$; calc. 230.1154).

(2E,4R,5S)-2-Ethylidene-5-(methoxycarbonyl)-4-methylhexano-5-lactone (=*(2S,3R,5E)-5-Ethylidenetetrahydro-2,3-dimethyl-6-oxo-2H-pyran-2-carboxylic Acid Methyl Ester*; **8**): Colorless oil. $[\alpha]_D^{22} = +20.4$ ($c = 0.05$, MeOH). UV (MeOH): 221 (3.8). IR ($CHCl_3$): 1740, 1716, 1640. ^{1}H- and ^{13}C-NMR: *Table 3*. EI-MS: 212 (7, M^+), 153 (100), 134 (10), 125 (16), 107 (11), 81 (17), 43 (47). HR-EI-MS: 212.1055 (M^+, $C_{11}H_{16}O_4^+$; calc. 212.1049).

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