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Nine New Norlabdane Diterpenoids from the Leaves of *Austroeupatorium inulifolium*

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Nine new norlabdane diterpenoids were isolated from the leaves of *Austroeupatorium inulifolium* collected in Indonesia. All of them have an acyl-furan unit connected to C(11), and oxygenated functions at C(2) and C(3). The structure elucidations and the assignment of the absolute configurations of the isolated natural products were carried out by extensive spectroscopic analysis and the extended *Mosher* method, as well as chemical correlations. Antimicrobial activities and cytotoxicity against HL-60 cells were determined using bioassays.

Introduction. – *Eupatorium* species (Compositae) [1][2] are widely distributed in the world, especially in South-West Asia, and they have been extensively investigated. *Herout*, *Šorm*, and their co-workers investigated the chemical constituents of *Eupatorium cannabinum* and proposed the structure of eupatoriopicrin [3]. Subsequently, *Kupchan et al.* studied the antileukemic and tumor inhibitory active compounds from *E. cuneifolium* and found several germacranolides [4–6]. Since the report of those compounds, a large number of terpenoids, including hiyodorilactones, have been recorded in the literature [7–10]. Some compounds have been found to exhibit cytotoxic activities against cancer cell lines [11]. Most of the compounds isolated from these species are germacrane-type sesquiterpenoids. *Austroeupatorium inulifolium* has been studied before by *Ferraro et al.* [12], *Herz* and co-workers [13], *Mosquera et al.* [14], and *Triana et al.* [15], who isolated flavonoid compounds and norlabdanes. This plant was previously known as *Eupatorium inulifolium* [16]. Another closely related species, *A. chaparense*, produces labdanes [17]. Benzofuran-type aromatic compounds [18–20] have also been isolated from *Eupatorium* species. We have collected *A. inulifolium* in Indonesia and have studied the chemical constituents, which led to the identification of nine new norlabdane-type diterpenoids, as well as several known compounds. Here, the details of these studies and the biological activities of the compounds are reported.

Results and Discussion. – The leaves and roots of *A. inulifolium* were separately extracted with MeOH. The MeOH extract was directly subjected to silica-gel column chromatography, followed by HPLC, to yield nine new norditerpenoids **1**–**9**, as well as some previously identified compounds, *i.e.*, **10** [14] and austroeupatol (**11**) [15], lupeol, β-amyrin, β-amyrin acetate, caryophyllene oxide, and β-sitosterol.

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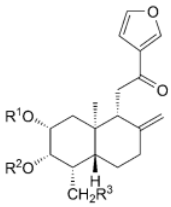
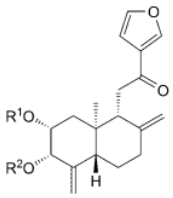


	R^1	R^2	R^3
1	Ac	Ac	OH
2	H	Ac	AcO
3	Ac	Ac	AcO
4	Ac	H	OH
5	H	Ac	OH
6	H	H	AcO
9	H	Ac	H



	R^1	R^2
7	Ac	H
8	H	Ac

Compound **1**, $[\alpha]_D^{21} = -12.6$, showed a molecular-ion peak at *m/z* 418 in the mass spectrum, and its molecular formula was determined as $C_{23}H_{30}O_5$ based on the HR-EI-MS (*m/z* 418.1997). The IR spectrum of compound **1** exhibited absorptions at 3500 and 1730 cm^{-1}, indicating the presence of OH and CO groups. The ^{13}C-NMR spectrum exhibited signals for nine sp^2-C-atoms, including a CO (δ(C) 193.4) and two ester groups (δ(C) 170.0 and 169.6), two O-bearing CH groups (δ(C) 73.8 and 70.1), an O-bearing CH_2 group (δ(C) 60.7), eight sp^3-CH_2/CH groups, and three Me C-atoms (δ(C) 21.3, 21.1 and 16.0) (*Table 1*). The ^{1}H-NMR spectrum indicated the presence of a mono-acyl-substituted furan ring (δ(H) 8.07 (*dd*, *J* = 1.5, 0.7, H–C(16)), 7.45 (*dd*, *J* = 1.8, 1.5, H–C(15)), and 6.77 (*dd*, *J* = 1.8, 0.7, H–C(14))), an exocyclic CH_2 group (δ(H) 4.82 (*s*, 1 H) and 4.40 (*s*, 1 H)), and two AcO groups (δ(H) 2.10 (*s*, 3 H) and 2.07 (*s*, 3 H)) (*Table 1*). Accordingly, the number of C-atoms that constitute the skeleton is 19, considering the presence of two AcO groups. Thus, this compound seems to be a diterpenoid with eight degrees of unsaturation. The connectivities C(1)–C(2)–C(3)–C(4)[–C(19)]–C(5) and C(6)–C(7) were revealed by the ^{1}H,^{1}H-COSY spectrum. The HMBCs of H–C(7) to C(5), H–C(11) to C(8) and C(12), H–C(17) to C(7) and C(9), and H–C(20) to C(1), C(5), C(9), and C(10) indicated that compound **1** has a norlabdane skeleton (*Fig. 1*). Two AcO groups were considered to be at C(2) and C(3), because signals of these CH H-atoms were observed downfield (H–C(2) (δ(H) 5.39) and H–C(3) (δ(H) 5.09)). Therefore, this compound was determined to be a norlabdane derivative with an acyl-furan moiety.

NOE Correlations between the signals of H–C(1) and H–C(3), H–C(1) and H–C(9), H–C(2) and H–C(3), H–C(3) and H–C(4), H–C(3) and H–C(5), and H–C(5) and H–C(9) were observed. Furthermore, correlations between H–C(19) and H–C(20), and between H–C(20) and H–C(11) were observed. These results indicated that the two six-membered rings are *trans*-fused, and that all substituents on the rings (C(2), C(3), C(4), C(9), and C(10)) have the same α-orientation. Thus, the structure of compound **1** was established as depicted in *Fig. 1*, and this compound was named inulifolinone A.

Table 1. *^{1}H- and ^{13}C-NMR Data for Compounds* **1**–**3** (recorded at 400 and 100 MHz, resp., in $CDCl_3$; δ in ppm, J in Hz)

Position	Inulifolinone A (**1**)		Inulifolinone B (**2**)		Inulifolinone C (**3**)	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	1.98 (*dd*, *J* = 14.6, 3.3, H_a), 1.58 (*dd*, *J* = 14.6, 3.3, H_b)	40.8	2.04 (*dd*, *J* = 14.6, 3.3, H_a), 1.48 (*dd*, *J* = 14.6, 3.3, H_b)	42.5	2.00 (*dd*, *J* = 15.0, 3.3, H_a), 1.57 (*dd*, *J* = 15.0, 3.3, H_b)	40.8
2	5.39 (*q*, *J* = *J* = 3.3)	70.1	4.18 (*q*, *J* = 3.3)	69.5	5.34 (*q*, *J* = 3.3)	70.2
3	5.09 (*dd*, *J* = 6.2, 3.3)	73.8	4.85 (*dd*, *J* = 6.2, 3.3)	75.2	4.96 (*dd*, *J* = 6.6, 3.3)	72.4
4	2.25–2.32 (*m*)	46.4	2.39–2.44 (*m*)	41.7	2.40–2.47 (*m*)	41.9
5	1.90 (*ddd*, *J* = 12.8, 4.4, 3.3)	47.4	1.87 (*ddd*, *J* = 12.8, 4.0, 2.6)	47.0	1.92 (*ddd*, *J* = 12.8, 4.8, 2.6)	47.0
6	1.74 (*qd*, *J* = 12.8, 4.4, H_a), 1.58–1.65 (*m*, H_b)	28.4	1.78 (*qd*, *J* = 12.8, 4.0, H_a), 1.55–1.62 (*m*, H_b)	28.3	1.76 (*qd*, *J* = 12.8, 4.4, H_a), 1.60 (*ddt*, *J* = 12.8, 5.1, 2.6, H_b)	28.2
7	2.44 (*ddd*, *J* = 12.8, 4.4, 2.2, H_a), 2.23 (*td*, *J* = 12.8, 5.1, H_b)	37.0	2.39–2.44 (*m*, H_a), 2.21 (*td*, *J* = 12.8, 5.1, H_b)	37.1	2.40–2.47 (*m*, H_a), 2.22 (*td*, *J* = 12.8, 5.1, H_b)	37.0
8		147.2		147.5		147.2
9	2.61–2.68 (*m*)	50.1	2.64 (br. *d*, *J* = 9.9)	50.3	2.65 (br. *d*, *J* = 10.6)	50.2
10		36.9		37.1		37.0
11	2.98 (*dd*, *J* = 17.2, 10.6, H_a), 2.64 (*dd*, *J* = 17.2, 3.3, H_b)	36.3	3.03 (*dd*, *J* = 16.8, 9.9, H_a), 2.72 (*dd*, *J* = 16.8, 3.3, H_b)	36.3	3.00 (*dd*, *J* = 17.6, 10.6, H_a), 2.64 (*dd*, *J* = 17.6, 2.9, H_b)	36.2
12		193.4		193.8		193.4
13		127.9		128.0		127.9
14	6.77 (*dd*, *J* = 1.8, 0.7)	108.7	6.77 (*dd*, *J* = 1.8, 0.7)	108.7	6.77 (*dd*, *J* = 1.8, 0.7)	108.7
15	7.45 (*dd*, *J* = 1.8, 1.5)	144.2	7.45 (*dd*, *J* = 1.8, 1.5)	144.3	7.45 (*dd*, *J* = 1.8, 1.5)	144.3
16	8.07 (*dd*, *J* = 1.5, 0.7)	146.7	8.09 (*dd*, *J* = 1.5, 0.7)	146.8	8.08 (*dd*, *J* = 1.5, 0.7)	146.7
17	4.82 (*s*, H_a), 4.40 (*s*, H_b)	108.6	4.80 (*s*, H_a), 4.41 (*s*, H_b)	108.2	4.82 (*s*, H_a), 4.40 (*s*, H_b)	108.6
19	4.36 (*dd*, *J* = 11.4, 8.1, H_a), 3.74 (*dd*, *J* = 11.4, 2.6, H_b)	60.7	4.72 (*dd*, *J* = 11.4, 7.3, H_a), 4.34 (*dd*, *J* = 11.4, 3.7, H_b)	62.5	4.68 (*dd*, *J* = 11.7, 6.6, H_a), 4.32 (*dd*, *J* = 11.7, 4.0, H_b)	61.8
20	0.84 (*s*)	16.0	0.96 (*s*)	16.0	0.89 (*s*)	16.0
*Ac*O–C(2)	2.10 (*s*)	170.0, 21.3	–	–	2.12 (*s*)	170.1, 21.4
*Ac*O–C(3)	2.07 (*s*)	169.6, 21.1	2.12 (*s*)	169.9, 21.2	2.05 (*s*)	170.1, 21.1
*Ac*O–C(19)	–	–	2.00 (*s*)	170.8, 21.1	2.01 (*s*)	170.7, 21.0

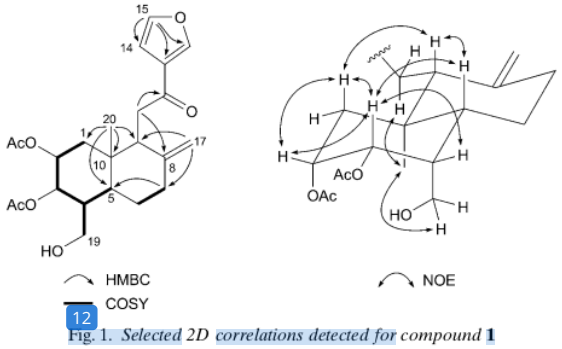


Fig. 1. *Selected 2D correlations detected for compound* **1**

Compound **2**, $[\alpha]_D^{18} = -19.0$, exhibited a molecular-ion peak at *m/z* 418, and the formula was determined to be $C_{23}H_{30}O_7$. The IR spectrum showed absorptions at 3440 and 1728 cm^{-1}, indicating the presence of OH and CO groups. The ^{1}H-NMR spectrum indicated the presence of a Me group (δ(H) 0.96 (*s*)), two AcO groups (δ(H) 2.00, 2.12), three H-atoms due to a furan ring (δ(H) 6.77, 7.45, 8.09), two H-atoms of an *exo*-CH_2 group (δ(H) 4.41, 4.80), as well as four H-atoms attached to O-bearing C-atoms. Both the ^{1}H- and ^{13}C-NMR spectra were very similar to those of compound **1** (*Table 1*). The analysis of the 2D-NMR data established the constitutional formula as shown in *Fig. 2*. The relative configuration was determined by a NOESY spectrum and the structure was established as depicted in *Fig. 2*. This compound was named inulifolinone B.

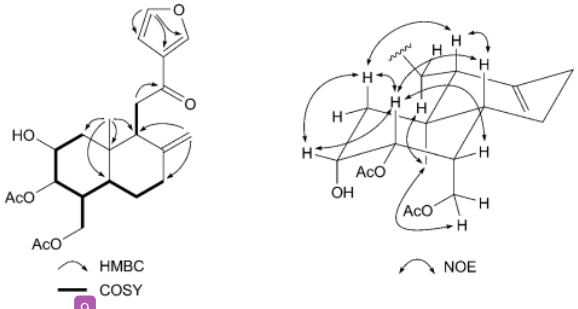


Fig. 2. *Selected 2D correlations detected for compound* **2**

Compound **3**, $[\alpha]_D^{20} = +14$ ($C_{25}H_{33}O_8$, showed absorptions at 1738, 1732, and 1682 cm^{-1} in the IR spectrum. The ^{1}H- and ^{13}C-NMR spectra are very similar to those of compounds **1** and **2**, except for the presence of three AcO groups (δ(H) 2.01, 2.05, and 2.12) in compound **3** (*Table 1*). The 2D-NMR spectra indicated that this compound is a triacetate of either compound **1** or **2**, and the configuration was also the same as

compounds of **1** and **2**. This compound was named inulifolinone C, which was recorded as an *O*-acetylation product of compound **11** (see below) [13].

Compounds **4**, **5**, and **6** had the same molecular formula, $C_{21}H_{28}O_6$, and one AcO group was present in each compound. Otherwise, the NMR spectra were very similar to those of compounds **1** and **2**. Consequently, these compounds appeared to be mono-*O*-acetyl derivatives of either **1** or **2**.

Compound **4** exhibited an AcO resonance at δ(H) 2.[illegible] in the ^{1}H-NMR spectrum, as well as IR absorptions at 3400 and 1728 cm^{-1}. Since the signal of H–C(2) appeared at δ(H) 5.35, that of H–C(3) at δ(H) 4.07, and those of CH_2(19) at δ(H) 3.65 and 4.42, the AcO group should be at C(2) (*Fig. 3* and *Table 2*). The relative configuration is the same as for **1**–**3**. This compound was named inulifolinone D.

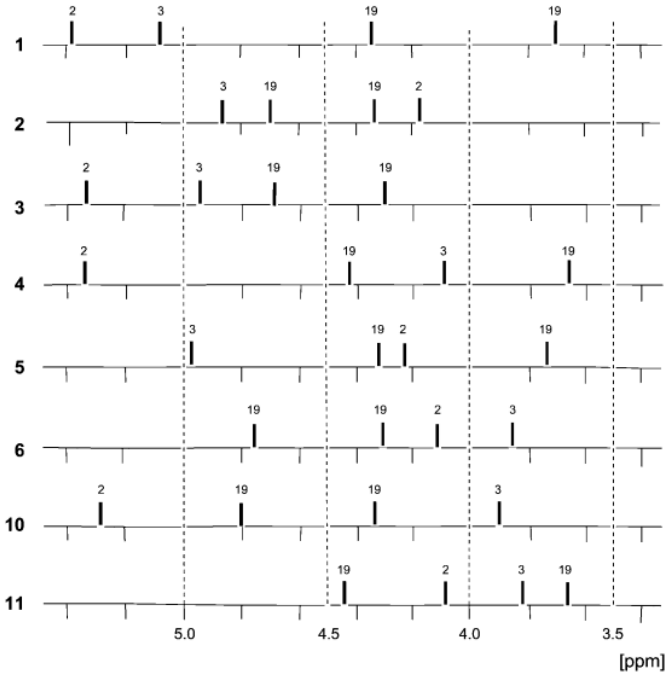


Fig. 3. *Chemical-shift comparison of the H-atoms H–C(2), H–C(3), and CH$_2$(19) for compounds* **1**–**6**, **10**, *and* **11**

The structure elucidation of compound **5** was mainly based on the ^{1}H-NMR spectrum. The H–C(2) resonated at δ(H) 4.21, the H–C(3) at δ(H) 4.97, and the CH_2(19) at δ(H) 3.74 and 4.33, respectively. This observation indicated that this

Table 2. *^{1}H- and ^{13}C-NMR Data for Compounds* **4**–**6** (recorded at 400 and 100 MHz, resp., in $CDCl_3$; δ in ppm, J in Hz)

Position	Inulifolinone D (**4**)		Inulifolinone E (**5**)		Inulifolinone F (**6**)	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	1.98 (*dd*, J = 15.0, 3.3, H_a), 1.54 (*dd*, J = 15.0, 3.3, H_b)	40.8	2.00 (*dd*, J = 14.3, 3.3, H_a), 1.50 (*dd*, J = 14.3, 3.3, H_b)	42.9	2.00 (*dd*, J = 14.6, 3.3, H_a), 1.41 (*dd*, J = 14.6, 3.3, H_b)	42.0
2	5.35 (*q*, J = 3.3)	73.2	4.21 (*q*, J = 3.3)	69.2	4.12 (*q*, J = 3.3)	70.4
3	4.07 (*dd*, J = 5.9, 3.3)	74.2	4.97 (*dd*, J = 6.6, 3.3)	76.1	3.83 (*dd*, J = 6.2, 3.3)	73.0
4	2.28–2.35 (*m*)	47.1	2.27–2.34 (*m*)	45.6	2.12–2.19 (*m*)	45.3
5	1.80 (*ddd*, J = 12.8, 4.8, 3.3)	47.1	1.87 (*ddd*, J = 12.8, 4.8, 2.6)	47.4	1.74–1.81 (*m*)	46.9
6	1.67 (*qd*, J = 12.8, 4.0, H_a), 1.55–1.62 (*m*, H_b)	28.4	1.74 (*qd*, J = 12.8, 4.0, H_a), 1.56 (*ddt*, J = 12.8, 5.1, 2.6, H_b)	28.4	1.81 (*qd*, J = 12.4, 4.0, H_a), 1.53–1.60 (*m*, H_b)	28.4
7	2.43 (*ddd*, J = 12.8, 4.0, 2.6, H_a), 2.22 (*td*, J = 12.8, 5.9, H_b)	37.1	2.42 (*ddd*, J = 12.8, 4.0, 2.6, H_a), 2.22 (br. *td*, J = 12.8, 5.1, H_b)	37.1	2.43 (br. *dd*, J = 12.4, 4.0, H_a), 2.21 (br. *t*, J = 12.4, H_b)	37.0
8		147.5		147.6		147.6
9	2.63 (br. *d*, J = 10.6)	50.2	2.63 (br. *d*, J = 9.5)	50.4	2.62 (*d*, J = 9.5)	50.4
10		36.8		36.8		37.0
11	2.99 (*dd*, J = 17.6, 10.6, H_a), 2.65 (*dd*, J = 17.6, 2.9, H_b)	36.4	3.01 (*dd*, J = 17.2, 9.5, H_a), 2.72 (*dd*, J = 17.2, 3.3, H_b)	36.5	3.03 (*dd*, J = 16.8, 9.5, H_a), 2.74 (*dd*, J = 16.8, 3.3, H_b)	36.3
12		193.6		193.9		194.0
13		128.0		128.0		128.0
14	6.77 (*dd*, J = 1.8, 0.7)	108.7	6.77 (*dd*, J = 1.8, 0.7)	108.7	6.77 (*dd*, J = 1.8, 0.7)	108.7
15	7.45 (*dd*, J = 1.8, 1.5)	144.3	7.45 (*dd*, J = 1.8, 1.5)	144.2	7.45 (*dd*, J = 1.8, 1.5)	144.2
16	8.08 (*dd*, J = 1.5, 0.7)	146.8	8.09 (*dd*, J = 1.5, 0.7)	146.8	8.10 (*dd*, J = 1.5, 0.7)	146.8
17	4.81 (*s*, H_a), 4.39 (*s*, H_b)	108.5	4.80 (*s*, H_a), 4.40 (*s*, H_b)	108.2	4.80 (*s*, H_a), 4.40 (*s*, H_b)	108.0
19	4.42 (*t*, J = 10.6, H_a), 3.65 (br. *d*, J = 10.6, H_b)	61.8	4.33 (*dd*, J = 11.4, 7.3, H_a), 3.74 (*dd*, J = 11.4, 3.3, H_b)	60.4	4.78 (*dd*, J = 11.7, 6.2, H_a), 4.30 (*dd*, J = 11.7, 3.7, H_b)	62.9
20	0.93 (*s*)	16.1	0.93 (*s*)	15.9	0.95 (*s*)	16.0
*Ac*O–C(2)	2.14 (*s*)	171.8, 21.5	–	–	–	–
*Ac*O–C(3)	–	–	2.14 (*s*)	170.0, 21.3	–	–
*Ac*O–C(19)	–	–	–	–	2.05 (*s*)	171.5, 21.3

pound is a *C(3)*-AcO derivative (*Fig. 3* and *Table 2*). These results were supported by the 2D-NMR spectra, and this compound was named inulifolinone E.

The 2D-NMR spectra of compound **6**, $[\alpha]_D^{20} = +34.9$, indicated the same skeleton and substitution patterns as of **1**–**5**. Since the H–C(2) resonated at δ(H) 4.12, the H–C(3) at δ(H) 3.83, and the CH_2(19) at δ(H) 4.30 and 4.78, the AcO group was determined to be at C(19) (*Fig. 4* and *Table 2*). The relative configuration was determined to be the same as in **1**–**5**, as established by its NOESY spectrum. This compound was named inulifolinone F.

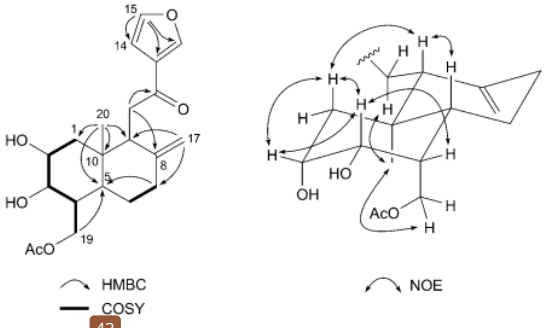


Fig. 4. *Selected 2D correlations detected for compound* **6**

The chemical shifts for H–C(2), H–C(3), and CH_2(19) of compounds **1**–**6**, as well as of the known compounds **10** and **11**, were compared with each other (*Fig. 3*). The differences of the chemical shifts between the HO–CH group and its acetate are evident. However, the chemical shifts of the CH_2(19) were rather distinct for each compound due to an intramolecular H-bond. That is why these H-atoms display very different chemical shifts.

Compounds **7** and **8** did not display signals of the O-bearing CH_2 group, C(19), in the ^{1}H- and ^{13}C-NMR spectra, while the other signals were quite similar to those of other compounds mentioned above. However, compounds **7** and **8** showed additional two *singlets* at δ(H) 5.22 and 4.85, and δ(H) 4.98 and 4.81, respectively, in the ^{1}H-NMR spectrum, suggesting that both compounds contain a second exocyclic CH_2 group at C(4) (*Table 3*). This was confirmed by correlations from H–C(19) to C(3), C(4), and C(5) in the HMBC spectrum (*Fig. 5*). An AcO group is connected to C(2) in compound **7**, whereas the AcO group is at C(3) in compound **8**. These compounds were named inulifolinones G and H, respectively.

Compound **9** showed one more Me signal (δ(H) 1.10 (*d*, *J* = 8.1, Me(19)) and δ(C) 11.1) in its NMR spectra. The position of this Me group was determined as C(4) based on the COSY spectrum. The configuration of this Me group is α, based on an NOE between H–C(3) and H–C(4) (*Fig. 6* and *Table 3*). Accordingly, its structure was established as depicted in *Fig. 6*. This compound was named inulifolinone I.

Table 3. *^{1}H- and ^{13}C-NMR Data for Compounds* **7**–**9** (recorded at 400 and 100 MHz, resp., in $CDCl_3$; δ in ppm, J in Hz)

Position	Inulifolinone G (**7**)		Inulifolinone H (**8**)		Inulifolinone I (**9**)	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	2.09 (*dd*, J = 14.6, 3.3, H_a), 1.65 (*dd*, J = 14.6, 3.3, H_b)	40.5	2.01 (*dd*, J = 14.3, 2.9, H_a), 1.57–1.69 (*m*, H_b)	42.7	2.04 (*dd*, J = 14.6, 3.3, H_a), 1.48 (*dd*, J = 14.6, 3.3, H_b)	42.6
2	5.23 (*q*, J = 3.3)	74.3	4.21 (*q*, J = 2.9)	70.2	4.18 (*q*, J = 3.3)	70.0
3	4.21 (br. *s*)	72.7	5.31 (*d*, J = 2.9)	76.3	4.85 (*dd*, J = 6.4, 3.3)	77.6
4	–	147.5	–	143.4	2.19–2.27 (*m*)	36.3
5	2.08–2.15 (*m*)	49.6	2.17–2.23 (*m*)	50.1	1.71–1.83 (*m*)	47.5
6	1.72 (*ddt*, J = 12.8, 5.1, 2.6, H_a), 1.57 (*qd*, J = 12.8, 4.0, H_b)	25.8	1.70 (*ddt*, J = 12.8, 5.1, 2.6, H_a), 1.51–1.65 (*m*, H_b)	25.7	1.71–1.83 (*m*, H_a), 1.38–1.45 (*m*, H_b)	28.5
7	2.44 (*ddd*, J = 13.2, 4.0, 2.6, H_a), 2.21 (br. *td*, J = 13.2, 5.1, H_b)	36.4	2.42 (*ddd*, J = 13.2, 4.0, 2.6, H_a), 2.23 (br. *td*, J = 13.2, 5.1, H_b)	36.3	2.42 (br. *d*, J = 11.4, H_a), 2.19–2.27 (*m*, H_b)	37.1
8		147.3		147.3		148.1
9	2.79 (br. *d*, J = 10.6)	49.0	2.78–2.84 (*m*)	49.2	2.61 (br. *d*, J = 9.5)	50.9
10		39.9		40.2		37.3
11	2.99 (*dd*, J = 16.8, 10.6, H_a), 2.70 (*dd*, J = 16.8, 3.3, H_b)	36.8	3.02 (*dd*, J = 17.9, 10.6, H_a), 2.78 (*dd*, J = 17.9, 3.3, H_b)	37.0	3.02 (*dd*, J = 16.8, 9.5, H_a), 2.74 (*dd*, J = 16.8, 3.3, H_b)	36.3
12		193.6		193.8		194.0
13		127.9		128.0		128.1
14	6.78 (*dd*, J = 1.8, 0.7)	108.6	6.78 (*dd*, J = 1.8, 0.7)	108.7	6.78 (*dd*, J = 1.8, 0.7)	108.7
15	7.45 (*dd*, J = 1.8, 1.5)	144.2	7.45 (*dd*, J = 1.8, 1.5)	144.3	7.44 (*dd*, J = 1.8, 1.5)	144.2
16	8.08 (*dd*, J = 1.5, 0.7)	146.8	8.09 (*dd*, J = 1.5, 0.7)	146.8	8.08 (*dd*, J = 1.5, 0.7)	146.7
17	4.84 (*s*, H_a), 4.40 (*s*, H_b)	108.7	4.84 (*s*, H_a), 4.42 (*s*, H_b)	108.7	4.79 (*s*, H_a), 4.40 (*s*, H_b)	107.8
19	5.22 (*s*, H_a), 4.85 (*s*, H_b)	106.8	4.98 (*s*, H_a), 4.81 (*s*, H_b)	107.3	1.10 (*d*, J = 8.1, H_a)	11.1
20	0.71 (*s*)	14.7	0.83 (*s*)	15.2	1.06 (*s*)	16.5
*Ac*O–C(2)	2.06 (*s*)	171.1, 21.3	–	–	–	–
*Ac*O–C(3)	–	–	2.19 (*s*)	169.4, 21.0	2.14 (*s*)	169.9, 21.2

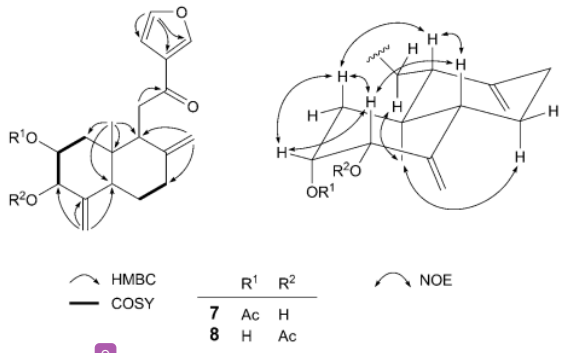


Fig. 5. *Selected 2D correlations detected for compounds* **7** *and* **8**

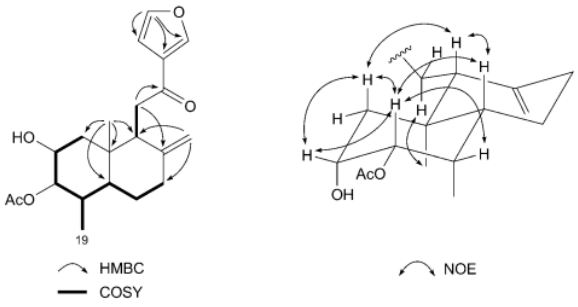


Fig. 6. *Selected 2D correlations detected for compound* **9**

In summary, compounds **1** and **2** are *O*-diacetates, compound **3** *O*-triacetate, and compounds **4**, **5**, and **6** *O*-monoacetates, all with the same norlabdane skeleton. The known compounds, diacetate **10** [14] and triol **11** [15], were also isolated. However, because the absolute configurations of these known compounds have not been determined yet, we prepared MTPA (=α-methoxy-α-(trifluoromethyl)phenylacetic acid) esters of compound **10** [14]. The results depicted in *Fig. 7* established the absolute configuration of this compound as shown [21]. To correlate the absolute configurations of other molecules, each compound was acetylated and converted to triacetate **3**, $[\alpha]_D = +14.3$ ($CHCl_3$). The specific rotation of the triacetate derived from the known compound **10** was $[\alpha]_D = +13.2$ (EtOH), and those derived from compounds **1**, **2**, and **6** showed similar values, establishing the same absolute configurations for these norditerpenoids. From these results, we assume that the other new compounds, **4**, **5**, **7**, **8**, and **9** also have the same absolute configuration.

The antioxidant activities of compounds **1**, **2**, **6**, **10**, and **11** were tested. Only compound **2** showed a weak activity (3.5 unit/ml of SOD) compared with catechin (91.1

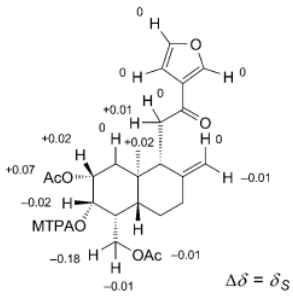


Fig. 7. *Chemical-shift differences for the MTPA esters derived from compound* **10**

unit/ml), whereas compounds **1**, **6**, **10**, and **11** had no activity. The antimicrobial activities were also tested for compound **11** (*Table 4*); however, its activity turned out to be very weak. To test the cytotoxicity against HL-60 cells, we prepared several derivatives, *i.e.*, **12**–**14**. Compound **12** [13] was derived from inulifolinone A (**1**), and compounds **13** and **14**[1]) were prepared from austroeupatol (**11**). The NMR data of compounds **12**–**14** are shown in *Table 5*, and the results of the cytotoxicity test are compiled in *Table 6*. These compounds showed only weak activities against HL-60 cells.

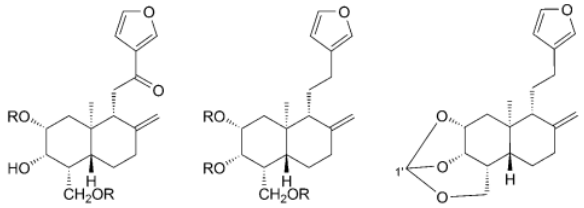


Table 4. *The Antimicrobial Activity of Compound* **11** (given as the diameter of inhibition in mm)

	Compound **11**	Erythromycin
Staphylococcus aureus 209P	9	31
Bacillus subtils PCI219	8.5	29
Escherichia coli NIHJ	10	33

Conclusions. – We have isolated nine new norlabdane diterpenoids and established their structures including the absolute configuration. They comprise one triacetate, two diacetates, three monoacetates, two monoacetate with exocyclic CH_2 groups, and one

[1]) The reason of formation of compound **14** in this reaction is not clear. However, it is presumably derived from DMF used as a solvent.

Table 5. *^{1}H- and ^{13}C-NMR Data for Compounds* **12** – **14** (recorded at 400 and 100 MHz, resp., in $CDCl_3$; δ in ppm, J in Hz)

Position	**12**		**13**		**14**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	1.99 (*dd*, *J* = 14.3, 2.9, H_a), 1.39 (*dd*, *J* = 14.3, 2.9, H_b)	44.1	2.25 (*dd*, *J* = 14.6, 2.9, H_a), 0.93 (*dd*, *J* = 14.6, 2.9, H_b)	38.0	2.38 (*dd*, *J* = 15.0, 2.9, H_a), 1.27 (*dd*, *J* = 14.6, 2.9, H_b)	39.0
2	4.07 (*q*, *J* = 2.9)	72.3	3.70 (*q*, *J* = 2.9)	78.3	4.08 (*dt*, *J* = 4.4, 2.9)	72.3
3	3.81 (*dd*, *J* = 6.2, 2.9)	75.6	3.28 (*dd*, *J* = 4.8, 2.9)	82.5	4.46 (*dd*, *J* = 9.5, 4.4)	71.1
4	2.11 – 2.17 (*m*)	48.7	2.19 – 2.26 (*m*)	43.2	2.52 – 2.58 (*m*)	39.3
5	1.75 – 1.82 (*m*)	48.8	1.52 (*ddd*, *J* = 12.8, 7.0, 2.9)	48.0	1.46 (*ddd*, *J* = 12.8, 4.0, 2.9)	45.2
6	1.72 (*qd*, *J* = 12.8, 4.0, H_a), 1.51 – 1.58 (*m*, H_b)	29.9	1.81 (*qd*, *J* = 12.8, 4.4, H_a), 1.53 – 1.60 (*m*, H_b)	29.3	1.63 (*qd*, *J* = 12.8, 4.4, H_a), 1.24 – 1.32 (*m*, H_b)	28.5
7	2.40 (*ddd*, *J* = 12.8, 4.0, 2.6, H_a), 2.17 (*td*, *J* = 12.8, 5.5, H_b)	38.5	2.43 (*ddd*, *J* = 12.8, 4.4, 1.8, H_a), 2.02 (*td*, *J* = 12.8, 5.1, H_b)	38.1	2.43 (*ddd*, *J* = 12.8, 4.4, 2.2, H_a), 2.04 (*td*, *J* = 12.8, 5.1, H_b)	37.6
8		149.7		147.3		146.6
9	2.54 (br. *d*, *J* = 10.3)	52.3	1.56 – 1.61 (*m*)	55.8	1.54 – 1.59 (*m*)	55.6
10		38.2		38.5		36.3
11	3.13 (*dd*, *J* = 17.2, 10.3, H_a), 2.80 (*dd*, *J* = 17.2, 3.3, H_b)	37.5	1.62 – 1.72 (*m*, 2 H)	24.5	1.67 – 1.77 (*m*, 2 H)	24.2
12		196.9	2.57 (*ddd*, *J* = 14.6, 7.7, 5.1, H_a), 2.24 (*dt*, *J* = 14.6, 7.3, H_b)	23.5	2.58 (*dt*, *J* = 14.6, 6.6, H_a), 2.26 (*dt*, *J* = 14.6, 8.4, H_b)	23.3
13		129.3		125.3		125.2
14	6.77 (*dd*, *J* = 1.8, 0.7)	109.3	6.27 (br. *s*)	110.9	6.27 (br. *s*)	110.9
15	7.59 (*dd*, *J* = 1.8, 1.5)	145.9	7.35 (*t*, *J* =	142.7	7.36 (*t*, *J* = 1.5)	142.8
16	8.45 (*dd*, *J* = 1.5, 0.7)	149.7	7.20 (br. *s*)	138.7	7.20 (br. *s*)	138.8
17	4.74 (*s*, H_a), 4.41 (*s*, H_b)	108.3	4.93 (*s*, H_a), 4.60 (*s*, H_b)	107.6	4.97 (*s*, H_a), 4.65 (*s*, H_b)	108.3
19	4.44 (*dd*, *J* = 10.6, 8.8, H_a), 3.65 (*dd*, *J* = 10.6, 3.7, H_b)	62.1	3.76 (*dd*, *J* = 10.3, 3.7, H_a), 3.55 (*dd*, *J* = 10.3, 5.1, H_b)	70.1	3.66 (*dd*, *J* = 11.0, 8.8, H_a), 3.59 (*dd*, *J* = 11.0, 1.8, H_b)	55.0
20	0.92 (*s*)	16.7	0.84 (*s*)	14.6	1.00 (*s*)	13.1
*Me*O–C(2)	–	–	3.33 (*s*)	57.0	–	–
*Me*O–C(3)	–	–	3.42 (*s*)	56.5	–	–
*Me*O–C(19)	–	–	3.27 (*s*)	58.3	–	–
1′	–	–	–	–	6.03 (*s*)	110.8

Table 6. *Antiproliferative Activity for HL-60 Cell Induced by Norlabdane-Type Diterpenoids*

Compound	IC_{50} [mM]	Compound	IC_{50} [mM]
1	34.3	**9**	43.9
2	36.5	**10**	52.5
3	54.0	**11**	27.5
6	92.7	**12**	159.7
7	48.8	**13**	41.9
8	55	**14**	59.3

reduced form of a monoacetate. Although the *ent*-form was presumed so far for known compounds [13–15], there was no evidence. Sometimes the absolute configuration for labdanes and clerodanes are controversial. It is very important to determine their absolute configuration unambiguously. We have achieved to confirm the absolute configuration as *ent*-form. There was no germacrane-type compounds in this plant, and the previous report as well as the present work support the phylogenic study of classification [16].

Experimental Part

General. Column chromatography (CC): silica gel *BW-127ZH* (SiO_2; 100–270 mesh; *Fuji Silysia*). TLC: silica gel *60* F_{254} plates (*Merck*). The absorbance was measured with a *SPECTRAmax® 340PC* microplate spectrophotometer (*Molecular Devices Corporation*). HPLC (*JASCO pump system*): *Chemcopak Nucleosil 50-5*. Optical rotations: *JASCO DIP-140*. IR Spectra: *JASCO FT/IR-5300* spectrophotometer. ^{1}H-, ^{13}C-, and 2D-NMR spectra: *Varian Unity 600* (600 MHz) or *JEOL ECP-400* (400 MHz) spectrometer. MS and HR-MS: *JEOL JMS AX-500* spectrometer.

Plant Material. Austroeupatorium inulifolium was collected from the Klecko forest, Nongkojajar, Pasuruan, East Java, Indonesia on August 2, 2004, and was identified by Mr. *Wardaya* from the Purwodadi Botanical Garden, East Java, Indonesia. A voucher specimen has been deposited with the herbarium of the Purwodadi Botanical Garden (Number: P.2004.1119).

Extraction and Isolation. The dried and powdered leaves of *A. inulifolium* (446 g) were exhaustively extracted with MeOH (3 × 2 l) for 24 h at r.t. Removal of the solvent *in vacuo* yielded a dark green viscous fluid. The same procedure was also applied to the dried powdered stem of *A. inulifolium* (668 g). The MeOH extract (20.3 g) of the aerial parts of *A. inulifolium* was subjected to CC (SiO_2; hexane/AcOEt gradient) and then to HPLC (*Nucleosil 50-5*; hexane/AcOEt or $CHCl_3$/AcOEt) to afford nine new norlabdane-type diterpene compounds: **1** (388.4 mg), **2** (121.7 mg), **3** (6.4 mg), **4** (1.8 mg), **5** (7.2 mg), **6** (83.3 mg), **7** (5.6 mg), **8** (3.2 mg), and **9** (2.1 mg), as well as two known compounds, **10** (223.7 mg) and **11** (3653.4 mg).

Inulifolinone A (=*(1*R,*2*S,*3*R,*4a*R,*5*R,*8a*R*)-5-[2-(Furan-3-yl)-2-oxoethyl]decahydro-1-(hydroxymethyl)-4a-methyl-6-methylidenenaphthalene-2,3-diyl Diacetate*; **1**). Oil. $[\alpha]_D^{21} = -12.6$ ($c = 1.03$, $CHCl_3$). IR (KBr): 3500, 1730. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 418 (M^+), 188, 178, 158, 105, 95 (100). HR-EI-MS: 418.1997 (M^+, $C_{23}H_{30}O_7^+$; calc. 418.1991).

Inulifolinone B (=*{(1*R,*2*S,*3*R,*4a*R,*5*R,*8a*R*)-2-(Acetyloxy)-5-[2-(furan-3-yl)-2-oxoethyl]decahydro-3-hydroxy-4a-methyl-6-methylidenenaphthalen-1-yl}methyl Acetate*; **2**). Oil. $[\alpha]_D^{18} = -19.0$ ($c = 0.40$, $CHCl_3$). IR (KBr): 3440, 1728. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 418 (M^+), 298, 188, 170, 135, 95 (100). HR-EI-MS: 418.1992 (M^+, $C_{23}H_{30}O_7^+$; calc. 418.1991).

Inulifolinone C (=*(1*R,*2*S,*3*R,*4a*R,*5*R,*8a*R*)-1-[(Acetyloxy)methyl]-5-[2-(furan-3-yl)-2-oxoethyl]decahydro-4a-methyl-6-methylidenenaphthalene-2,3-diyl Diacetate*; **3**). Oil. $[\alpha]_D^{20} = +14.3$ ($c = 0.57$, $CHCl_3$). IR (KBr): 1738, 1732, 1682, 1254. ^{1}H- and ^{13}C-NMR: see *Table 1*. CI-MS: 461 (100, $[M+H]^+$), 401, 341. HR-CI-MS: 461.2180 ($[M+H]^+$, $C_{25}H_{33}O_8^+$; calc. 461.2173).

Inulifolinone D (=*(2*R*,3*S*,4*R*,4a*R*,8*R*,8a*R*)-8-[2-(Furan-3-yl)-2-oxoethyl]decahydro-3-hydroxy-4-(hydroxymethyl)-8a-methyl-7-methylidenenaphthalen-2-yl Acetate*; **4**). Oil. $[\alpha]_D^{19} = -14.8$ ($c = 0.18$, EtOH). IR (KBr): 3400, 1728, 1672. ^{1}H- and ^{13}C-NMR: see *Table 2*. CI-MS: 377 ($[M+H]^+$), 359, 317 (100), 299. HR-CI-MS: 377.1965 ($[M+H]^+$, $C_{21}H_{29}O_6^+$; calc. 377.1962).

Inulifolinone E (=*(1*R*,2*S*,3*R*,4a*R*,5*R*,8a*R*)-5-[2-(Furan-3-yl)-2-oxoethyl]decahydro-3-hydroxy-1-(hydroxymethyl)-4a-methyl-6-methylidenenaphthalen-2-yl Acetate*; **5**). Oil. $[\alpha]_D^{20} = +1.4$ ($c = 0.43$, EtOH). IR (KBr): 3416, 1715, 1666. ^{1}H- and ^{13}C-NMR: see *Table 2*. CI-MS: 377 (100, $[M+H]^+$), 359, 317, 299. HR-CI-MS: 377.1961 ($[M+H]^+$, $C_{21}H_{29}O_6^+$; calc. 377.1962).

Inulifolinone F (=*{(1*R*,2*S*,3*R*,4a*R*,5*R*,8a*R*)-5-[2-(Furan-3-yl)-2-oxoethyl]decahydro-2,3-dihydroxy-4a-methyl-6-methylidenenaphthalen-1-yl}methyl Acetate*; **6**). Solid. $[\alpha]_D^{20} = +34.9$ ($c = 0.20$, $CHCl_3$). IR (KBr): 3350, 1728. ^{1}H- and ^{13}C-NMR: see *Table 2*. EI-MS: 376 (M^+), 188, 170, 135, 95 (100). HR-EI-MS: 376.1877 (M^+, $C_{21}H_{28}O_6^+$; calc. 376.1885).

Inulifolinone G (=*(2*R*,3*S*,4a*S*,8*R*,8a*S*)-8-[2-(Furan-3-yl)-2-oxoethyl]decahydro-3-hydroxy-8a-methyl-4,7-dimethylidenenaphthalen-2-yl Acetate*; **7**). Oil. $[\alpha]_D^{22} = -6.1$ ($c = 0.56$, $CHCl_3$). IR (KBr): 3477, 1730, 1672. ^{1}H- and ^{13}C-NMR: see *Table 3*. CI-MS: 359 ($[M+H]^+$), 299 (100). HR-CI-MS: 359.1852 ($[M+H]^+$, $C_{21}H_{27}O_5^+$; calc. 359.1857).

Inulifolinone H (=*(2*S*,3*R*,4a*S*,5*R*,8a*S*)-5-[2-(Furan-3-yl)-2-oxoethyl]decahydro-3-hydroxy-4a-methyl-1,6-dimethylidenenaphthalen-2-yl Acetate*; **8**). Oil. $[\alpha]_D^{21} = +5.1$ ($c = 0.32$, $CHCl_3$). IR (KBr): 3493, 1730. ^{1}H- and ^{13}C-NMR: see *Table 3*. CI-MS: 359 ($[M+H]^+$), 299, 281 (100). HR-CI-MS: 359.1849 ($[M+H]^+$, $C_{21}H_{27}O_5^+$; calc. 359.1857).

Inulifolinone I (=*(1*S*,2*S*,3*R*,4a*R*,5*R*,8a*R*)-5-[2-(furan-3-yl)-2-oxoethyl]decahydro-3-hydroxy-1,4a-dimethyl-6-methylidenenaphthalen-2-yl Acetate*; **9**). Solid. $[\alpha]_D^{19} = +7.7$ ($c = 0.21$, $CHCl_3$). IR (KBr): 3489, 1728, 1668. ^{1}H- and ^{13}C-NMR: see *Table 3*. CI-MS: 361 (100, $[M+H]^+$), 301, 283. HR-CI-MS: 361.2016 ($[M+H]^+$, $C_{21}H_{29}O_5^+$; calc. 361.2013).

*{(1*R*,2*S*,3*R*,4a*R*,5*R*,8a*R*)-3-(Acetyloxy)-5-[2-(furan-3-yl)-2-oxoethyl]decahydro-2-hydroxy-4a-methyl-6-methylidenenaphthalen-1-yl}methyl Acetate* (**10**). Oil. $[\alpha]_D^{21} = +1.4$ ($c = 1.60$, $CHCl_3$). IR (KBr): 3480, 1727. EI-MS: 418 (M^+), 188, 170, 135, 95 (100). HR-EI-MS: 418.1992 (M^+, $C_{23}H_{30}O_7^+$; calc. 418.1991).

Austroeupatol (=*(1*R*,2*S*,3*R*,4a*R*,5*R*,8a*R*)-5-[2-(Furan-3-yl)ethyl]decahydro-1-(hydroxymethyl)-4a-methyl-6-methylidenenaphthalene-2,3-diol*; **11**). Solid. $[\alpha]_D^{20} = -36.5$ ($c = 1.28$, $CHCl_3$). IR (KBr): 3360. EI-MS: 320 (M^+), 135, 105, 81 (100). HR-EI-MS: 320.1966 (M^+, $C_{19}H_{28}O_4^+$; calc. 320.1988).

Preparation of Triol **12** (=*2-[(1*R*,4a*R*,5*R*,6*S*,7*R*,8a*R*)-Decahydro-6,7-dihydroxy-5-(hydroxymethyl)-4a-methyl-2-methylidenenaphthalen-1-yl]-1-(furan-3-yl)ethanone*). To a stirred soln. of **1** (39.5 mg) in MeOH (1.0 ml) was added MeONa (28% in MeOH, 200 µl, 11.0 equiv.) at 0°, and the mixture was stirred for 1.5 h. H_2O was added, and the mixture was extracted with AcOEt three times. The org. layer was washed with brine, and the solvent was evaporated to afford a residue. The residue was purified by SiO_2 CC to give triol **12** (17.9 mg, 57%).

Acetylation of **1**, **2**, *and* **6**. The compound was dissolved in pyridine, and Ac_2O was added dropwise at r.t. The mixture was stirred overnight, then MeOH was added. The mixture was extracted with H_2O. The org. layer was washed with brine, and the solvent was evaporated to afford a residue. The residue was purified by SiO_2 CC to give the corresponding acetate.

Methylation of Austroeupatol (**11**). To a stirred soln. of **11** (41.2 mg) in DMF (1.0 ml) was added NaH (60%, 65.4 mg, 12.7 equiv.) at 0°. The mixture was stirred for 30 min, and MeI (90 µl) was added. The mixture was warmed at 60° for 3 d. H_2O was added, and the mixture was extracted with AcOEt three times. The org. layer was washed with brine, and the solvent was evaporated to afford a residue. The residue was purified by SiO_2 CC to give **13** (16.9 mg, 36%; *3-[2-[(1*R*,4a*R*,5*R*,6*S*,7*R*,8a*R*)-decahydro-6,7-dimethoxy-5-(methoxymethyl)-8a-methyl-2-methylidenenaphthalen-1-yl]ethyl]furan*) and **14** (2.6 mg, 6%; *(4a*S*,5*R*,6a*R*,7*R*,10a*R*,10b*R*)-7-[2-(furan-3-yl)ethyl]decahydro-6a-methyl-8-methylidene-1*H*-3,5-epoxynaphtho[2,1-d][1,3]dioxine*).

Bioassays (Paper Disc Method). A soln. (20 µl) of samples (10 mg) in DMSO (1 ml) was sintered in a paper disc (8 mm; 0.2 mg/disc) and applied to *Escherichia*, *Bacillus*, and *Staphylococcus*. The diameter of inhibition was measured after 24 h.

MTT Assay. HL-60 Cells were seeded into 96-well plates at a density of 2×10^4 cells/well in *RPMI 1640* medium with 10% fetal bovine serum and cultured for 2 h, followed by the addition of various concentrations of each of the test compounds and incubated at 37° for 24 h. The cells were then mixed with MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) at a final concentration of 0.5 mg/ml. After 4 h of incubation at 37°, a 10% SDS soln. in 0.01M HCl was added to each well, and the plate was further incubated overnight. The absorbance ($A_{570}-A_{630}$) of each mixture was measured with a microplate spectrophotometer. The percentage absorbance of tested cells as compared with cells that were cultured without a test compound was calculated.

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