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TWO NOVEL FLAVONOIDS FROM THE LEAVES OF LINDERA UMBELLATA VAR. LANCEA AND L. UMBELLATA

KAZUHIKO ICHINO, HITOSHI TANAKA, AND KAZUO ITO*

Faculty of Pharmacy, Meijo University,
Tenpaku-ku, Nagoya 468, Japan

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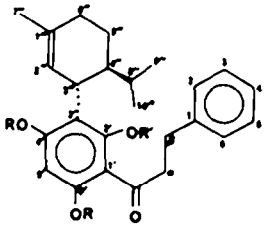
Abstract - Two novel flavonoids, linderatin (1) and linderatone (2), were isolated from the leaves of Lindera umbellata var. membranacea and L. umbellata, and the structures were determined on the basis of chemical and spectroscopic evidence.

The deciduous small tree Lindera umbellata (Japanese name Kuromoji) is known to be rich in terpenoids and widely distributed in Japan. This species is classified into five varieties, L. umbellata, L. umbellata var. lancea, L. umbellata var. membranacea, L. umbellata var. sericea and L. umbellata var. glabrata, but there is no chemical report concerning these varieties except for L. umbellata.[1-10] In this paper, we describe the isolation and structure elucidation of the two novel flavonoids (1 and 2) from the leaves of L. umbellata var. lancea and L. umbellata, and further the synthesis of (±)-1.

From the fresh leaves of L. umbellata var. lancea (Japanese name Himekuromoji), two novel flavonoids named linderatin (1)[11] and linderatone (2) were isolated along with 2',6'-dihydroxy-4'-methoxydihydrochalcone (3) and 2',4',6'-trihydroxydihydrochalcone (4).[12] Linderatone (2) was also isolated[13] from the fresh leaves of L. umbellata together with pinostrobin (5), pinocembrin (6) and 5,6-dehydrokawain (7).

The first compound linderatin (1), $C_{25}H_{30}O_4$, gave a bluish color with ethanolic ferric chloride. The IR spectrum showed absorption bands for hydroxyl, conjugated carbonyl, and benzene ring as follows: $\nu_{max}^{CHCl_3}$ 3580, 1620, 1605, 1495 cm^{-1}. Acetylation of 1 with acetic anhydride in pyridine gave a triacetate (1a) and treatment of 1 with methyl iodide and potassium carbonate gave a dimethyl ether (1b). In the ^1H NMR spectrum of 1, characteristic signals for the 2',4',6'-trihydroxydihydrochalcone (4) were observed at δ 2.92 (2H, t, J=8 Hz, β-H), 3.37 (2H, t, J=8 Hz, α-H), 5.96 (1H, s, 5'-H), 7.20 (5H, br s, Ar-H) and 13.88 (1H, s, OH). In the ^{13}C NMR spectra (Table I) of 1 and 1b, the chemical shifts of the carbon atoms of the dihydrochalcone skeleton, except that of the carbon atom at C-

This article is dedicated to Professor E. C. Taylor on his sixty-fifth birthday.



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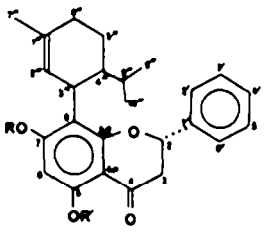
1b R=Me, R'=H



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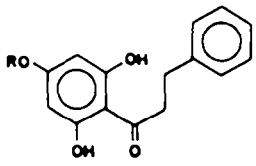
2b R=Me, R'=H



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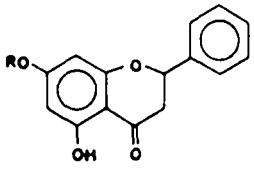

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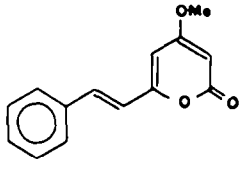
6 R=H



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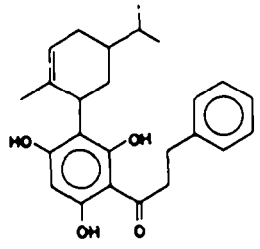

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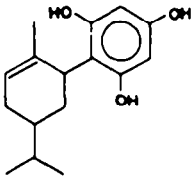

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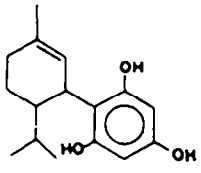

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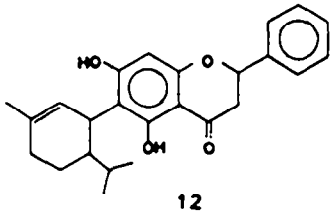

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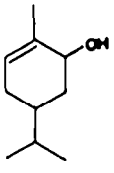

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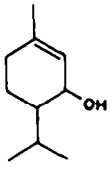

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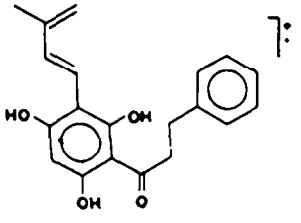

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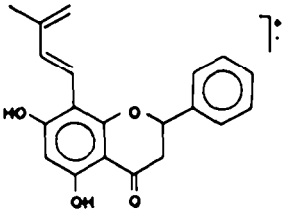
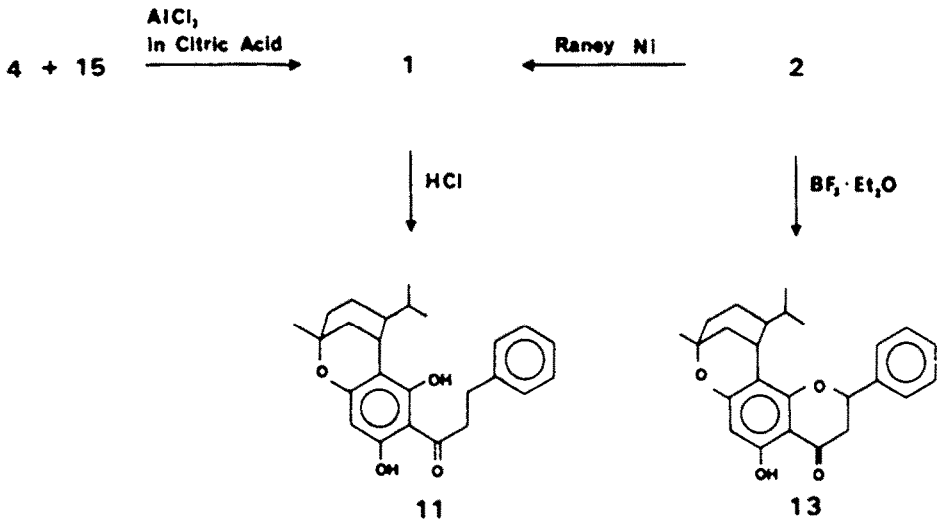


B

Table I. ^{13}C NMR spectral data (25.0 MHz, acetone-d_6)

Carbon	(1)	(1b)	(3)	(4)	(2)	(2b)	(6)[P]	Carbon
C-1	143.2	142.6	143.3	142.9	139.9	140.1	138.0	C-1'
C-2	129.4	129.1	129.6	129.1	129.2	129.5	126.5	C-2'
C-3	129.6	129.2	129.8	129.2	127.1	127.3	128.5	C-3'
C-4	127.1	127.0	127.1	126.5	126.2	126.5	128.5	C-4'
C-5	129.6	129.2	129.8	129.2	127.1	127.3	128.5	C-5'
C-6	129.4	129.1	129.6	129.1	129.2	129.5	126.5	C-6'
C-1'	105.4	106.1	106.2	105.1	103.0	103.6	101.9	C-4a
C-2'	161.4*	162.8*	165.7	165.4	161.7*	162.2*	162.7	C-8a
C-3'	110.5	113.0	94.8	95.8	111.8	113.3	95.1	C-8
C-4'	163.9*	165.4*	167.4	165.4	163.3*	167.4*	166.6	C-7
C-5'	95.8	87.8	94.8	95.8	95.8	92.1	96.1	C-6
C-6'	165.9*	165.3*	165.7	165.4	165.6*	162.6*	163.6	C-5
C=O	205.9	205.6	206.0	205.2	196.7	197.4	195.8	C-4
C=α	46.6	46.7	46.9	46.3	43.7	43.8	42.2	C-3
C=β	31.5	31.5	30.5	31.4	79.7	80.1	78.4	C-2
OMe	-	56.0	56.2	-	-	56.4	-	OMe
	-	56.0	-	-	-	-	-	
C-1"	135.4	131.9	-	-	134.0	132.5	-	C-1"
C-2"	126.9	126.5	-	-	126.2	126.5	-	C-2"
C-3"	36.0†	36.0†	-	-	35.7†	35.9	-	C-3"
C-4"	43.0	42.2	-	-	42.4	42.4	-	C-4"
C-5"	23.7	23.9	-	-	23.6	23.6	-	C-5"
C-6"	31.5	31.5	-	-	31.4	31.5	-	C-6"
C-7"	23.7	23.6	-	-	23.9	23.9	-	C-7"
C-8"	29.1†	29.2†	-	-	29.1†	29.3	-	C-8"
C-9"	16.9	16.7	-	-	16.7	16.7	-	C-9"
C-10"	22.0	21.8	-	-	21.9	21.8	-	C-10"

*, † Assignments may be interchanged.
P Measured in DMSO-d_6.



3' (δ 110.5 and 113.0), were similar to those of the relevant carbon atoms of 3 and 4. These results suggest that linderatin (1) is a 2',4',6'-trihydroxydihydrochalcone with 3'-substituent. The C-3' substituent ($C_{10}H_{17}$) seemed to be a cyclic monoterpene from the ^{1}H NMR spectrum indicating the presence of isopropyl group (δ 0.82, 6H, d, J=7 Hz), an olefinic proton (δ 5.23, 1H, s), and a vinyl methyl group (δ 1.64, 3H, s). Comparisons of the ^{13}C NMR spectrum of 1 with those of the menthane type derivatives[14] revealed that the chemical shifts of the carbon atoms are similar to chemical shifts of the corresponding carbon atoms of p-menthene skeleton. This suggests that the C-3' substituent should be p-menthene. Further, this structure was supported by the mass spectrum. The mass spectrum of 1 exhibited the characteristic fragment ion A at m/z 324 (M^+-C_5H_{10}), which was formed by the retro Diels-Alder reaction[15] of p-menthene portion. Therefore the trihydroxydihydrochalcone moiety in 1 was linked at the C-3" or C-6" carbon atom of p-menthene structure, and the possible structure of linderatin is 1 or 8.

In order to confirm the linking position of the trihydroxydihydrochalcone moiety to the p-menthene group, we next synthesized the two analogous compounds (9 and 10). Condensation of phloroglucinol with a readily available p-menth-1-ene-6-ol (14)[16] or piperitol (15) in 5% citric acid solution for 2 days produced the compounds 9 and 10 respectively.[17] The chemical shifts and coupling constants in the ^{1}H NMR spectrum of 1 were in close agreement with 10, except for those of the dihydrocinnamoyl group in 1. Treatment of 1 with saturated hydrogen chloride afforded the compound 11, whose spectral data showed the presence of a benzopyrane structure and a tert-methyl group.[18]

These data indicate that linderatin (1) contains the partial structure 10 in the molecule. Next, we attempted to synthesize linderatin (1) from 4 and piperitol according to the same method[17] described above but was unsuccessful. Eventually, we found addition of aluminium chloride to the reaction mixture afford linderatin (1). Thus, the alternative structure 8 was eliminated and linderatin was represented by the formula 1. The stereochemistry of the p-menthene portion was deduced from the ^{1}H NMR spectrum of 1. Namely, the coupling constant between the C_3"-H and C_4"-H was 12 Hz, demonstrating that the hydrogens are trans-oriented. Thus the relative stereostructure of linderatin was shown by the formula 1.

The second compound linderatone (2), $C_{25}H_{28}O_4$, gave a bluish color with ethanolic ferric chloride and was positive to the magnesium-hydrochloric acid test and the sodium borohydride test.[19] Acetylation of 2 with acetic anhydride in pyridine afforded a diacetate 2a and treatment of 2 with methyl iodide and potassium carbonate gave a monomethyl ether 2b. The IR spectrum exhibited absorption bands for hydroxyl, conjugated carbonyl, and benzene ring as follows: $\nu_{max}^{CHCl_3}$ 3370, 1635, 1620, 1580, 1450 cm^{-1}. In the ^{1}H NMR spectrum of 2, characteristic signals for 5,7-dihydroxyflavanone pinocembrin (6) were observed at δ 2.77 (1H, dd, J=4, 17 Hz, 3β-H), 3.20 (1H, dd, J=12, 17 Hz, 3α-H), 5.56 (1H, dd, J=4, 12 Hz, 2-H), 6.05 (1H, s, 6-H), 7.4-7.7 (5H, m, Ar-H), 9.15 (1H, br s, 7-OH), and 12.68 (1H, s, 5-OH) along with the signals of terpene-like compound, as seen

in the spectrum of 1, at δ 0.85, 0.88 (6H, 2 x d, J=7 Hz), 1.67 (3H, br s), 3.87 (1H, br d, J=10 Hz) and 5.23 (1H, br s). The mass spectrum of 1 showed a molecular ion at m/z 392 which indicate the lack of two protons from linderatin (1). This spectrum also had a characteristic fragment ion B at m/z 322 ($M^+-C_5H_{10}$) which was formed by a retro Diels-Alder reaction[15] of a p-menthene unit, as in 1. Comparison of the ^{13}C NMR spectrum of 2 with those of 1 and 6 showed the following fact. All chemical shifts of the carbon atoms of 2, except C-2 (δ 79.7) in 2 and C-β (δ 31.5) in 1, are similar to those of the relevant carbon atoms of 1. The chemical shifts of the carbon atoms of the dihydroxyflavanone skeleton, except that of C-6 or C-8, are also similar to those of the relevant carbon atoms of pinocembrin (6). These results suggest that linderatone may be a cyclization product of 1 and it was further supported as follows. Hydrogenation of 2 with Raney Nickel (W-3) in EtOH at room temperature for 4 h provided the optically active product (1) in 25 % yield which was identical with linderatin (1) in all respects. Two possible structures 2 and 12 are now depicted for linderatone. The former structure was supported as follows. Linderatone was negative to the Gibbs test[20] and showed the bathochromic shift ($\lambda_{max}^{MeOH+AlCl_3}$ nm: 315 and 361) in the UV spectrum on addition of aluminium chloride. It is known[21] that the aluminium chloride-induced shift in the UV spectra of 5-hydroxyflavanones occurs only in the absence of an alkyl substituent at C-6. Consequently, the structure 12 is eliminated and linderatone is represented by the formula 2. Finally, the CD spectrum of 2 exhibits the characteristic Cotton effects for 2S flavanones[22] and the flavanone ling of 2 is fixed to 2S configuration.

This is the second example[23] of a new class of compound in which a $C_6-C_3-C_6$ unit (flavonoid) is linked with a cyclic monoterpene. But linderatin (1) and linderatone (2) are first flavonoids which have a p-menthene substituent and they are biogenetically very interesting compounds.

EXPERIMENTAL

Extraction and separation of the compounds. The fresh leaves (7.3Kg) of Lindera umbellata Thunb. var. lancea Momiyama, collected at Asuke, Aichi prefecture, Japan, in July 1983, were extracted with MeOH. The MeOH extract was divided into the n-hexane and EtOAc soluble fractions. The n-hexane soluble fraction (150g) was chromatographed on florisil column. Elution with benzene gave geranyl acetate (25mg), linderatin (1) (336mg), and linderatone (2) (100mg). The EtOAc soluble fraction (58g) was chromatographed on silica gel. Elution with $CHCl_3$ furnished 2',6'-dihydroxy-4'-methoxydihydrochalcone (3) (804mg) and 2',4',6'-trihydroxydihydrochalcone (4) (510mg).

The fresh leaves (12.0 Kg) of L. umbellata Thunb., collected at Shirakawa-mura, Gifu prefecture, Japan, in July 1984, were extracted with MeOH. The MeOH extract was divided into the n-hexane and $CHCl_3$ soluble fractions. The n-hexane soluble fraction (55 g) was chromatographed on florisil column. Elution with benzene gave linderatone (2)(270 mg) and pinostrobin (5)(1085 mg). Following elution with

benzene-$CHCl_3$ (5:1) gave pinocembrin (6)(410 mg) and 5,6-dehydrokawain (7)(260 mg). The $CHCl_3$ soluble fraction was chromatographed on florisil column. Following elution with benzene-$CHCl_3$ (1:1) gave pinostrobin (5)(10 mg), pinocembrin (6)(226 mg), and 5,6-dehydrokawain (7)(80 mg).

Linderatin (1). Viscous oil; $[\alpha]_D^{20}$ +19.1° ($CHCl_3$; c 0.45); HRMS m/z: 394.2116 $[M]^+$ (calc. for $C_{25}H_{30}O_4$: 394.2142); MS m/z: 394 $[M]^+$, 351, 324, 309, 271; UV λ_{max}^{EtOH} nm (log ε): 225 (sh, 4.11), 290 (4.15), 338 (sh, 3.44); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3350, 1620, 1605, 1495; ^1H NMR (acetone-d_6): δ 0.82 (6H, d, J=7 Hz, 2 x 8"-Me), 1.64 (3H, br s, 1"-Me), 2.92 (2H, t, J=8 Hz, β-H), 3.37 (2H, t, J=8 Hz, α-H), 3.84 (1H, br d, J=12 Hz, 3"-H), 5.23 (1H, br s, 2"-H), 5.96 (1H, s, 5'-H), 7.20 (5H, br s, Ar-H), 13.88 (1H, s, OH); ^{13}C NMR (Table I).

Linderatone (2). Viscous oil; $[\alpha]_D^{20}$ -25.6° ($CHCl_3$; c 0.5); CD (MeOH; c 0.023): $[\theta]_{312}$ +2.30 x 10^3, $[\theta]_{295}$ -1.36 x 10^4, $[\theta]_{256}$ +2.39 x 10^3, $[\theta]_{247}$ +3.41 x 10^2, $[\theta]_{238}$ +8.52 x 10^3; HRMS m/z: 392.1963 $[M]^+$ (calc. for $C_{25}H_{28}O_4$: 392.1986); MS m/z: 392 $[M]^+$, 349, 322, 307, 270; UV λ_{max}^{MeOH} nm (log ε): 234 (sh, 4.06), 292 (4.06), 331 (sh, 3.45); UV $\lambda_{max}^{MeOH+AlCl_3}$ nm: 220, 315, 361; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370, 1635, 1620, 1580, 1450; ^1H NMR (acetone-d_6): δ 0.85, 0.88 (6H, each d, J=7 Hz, 2 x 8"-H), 1.67 (3H, br s, 1"-H), 2.77 (1H, dd, J=4, 17 Hz, 3β-H), 3.20 (1H, dd, J=12, 17 Hz, 3α-H), 3,87 (1H, br d, J=10 Hz, 3"-H), 5.23 (1H, br s, 2"-H), 5.56 (1H, dd, J=4, 12 Hz, 2-H), 6.05 (1H, s, 6-H), 7.4-7.7 (5H, m, Ar-H), 9.15 (1H, br s, 7-OH), 12.68 (1H, s, 5-OH); ^{13}C NMR (Table I).

2'6'-Dihydroxy-4'-methoxydihydrochalcone (3). Colourless plates; mp 174-175° (from CH_2Cl_2), lit. 175° [25]; HRMS m/z: 272.1188 $[M]^+$ (calc. for $C_{16}H_{16}O_4$: 272.1048); MS m/z: 272 $[M]^+$, 255, 253, 177, 167; UV λ_{max}^{EtOH} nm (log ε): 225 (4.15), 284 (4.23), 323 (sh, 3.50); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 1630; ^1H NMR (acetone-d_6): δ 2.97 (2H, t, J=8 Hz, β-H), 3.42 (2H, t, J=8 Hz, α-H), 3.78 (3H, s, OMe), 6.00 (2H, s, 3'-H and 5'-H), 7.26 (5H, s, Ar-H); ^{13}C NMR (Table I).

2',4',6'-Trihydroxydihydrochalcone (4). Colourless prisms; mp 134-135° (from C_6H_6), lit. 138-139° [26]; MS m/z: 258 $[M]^+$, 240, 214, 153, 126, 123; UV λ_{max}^{EtOH} nm (log ε): 222 (4.12), 286 (4.20), 326 (sh, 3.57); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1630; ^1H NMR (acetone-d_6): δ 2.96 (2H, t, J=8 Hz, β-H), 3.40 (2H, t, J=8 Hz, α-H), 4.24 (3H, br s, 3 x OH), 6.00 (2H, s, 3'-H and 5'-H), 7.24 (5H, s, Ar-H); ^{13}C NMR (Table I).

Pinostrobin (5). Colourless plates; mp 103-104° (from MeOH), lit. 100° [27]; $[\alpha]_D^{20}$ -1.6° ($CHCl_3$; c 0.45); HRMS m/z: 270.0904 $[M]^+$ (calc. for $C_{16}H_{14}O_4$: 270.0891); MS m/z: 270 $[M]^+$, 252, 193, 166; UV λ_{max}^{MeOH} nm: 224 (sh), 287, 324 (sh); UV $\lambda_{max}^{EtOH+AlCl_3}$ nm: 308, 378; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3250 (br), 3210, 1640, 1630, 1570; ^1H NMR ($CDCl_3$): δ 2.81 (1H, dd, J=4, 18 Hz, 3β-H), 3.12 (1H, dd, J=12, 18 Hz, 3α-H), 3.82 (3H, s, OMe), 5.44 (1H, dd, J=4, 12 Hz, 2-H), 6.07 (2H, s, 6-H and 8-H), 7.43 (5H, br s, Ar-H), 12.09 (1H, s, 5-OH).

Pinocembrin (6). Colourless prisms; mp 201-203 (from MeOH), lit. 201-203° [28]; $[\alpha]_D^{20}$ -3.4° (MeOH; c 0.5); HRMS m/z: 256.0711 $[M]^+$ (calc. for $C_{15}H_{12}O_4$: 256.0734); MS m/z: 256 $[M]^+$, 238, 179, 152; UV λ_{max}^{MeOH} nm: 224 (sh), 288, 324 (sh); UV $\lambda_{max}^{MeOH+AlCl_3}$ nm: 309, 375; IR ν_{max}^{KBr} cm^{-1}: 3020 (br), 1630, 1600, 1580; ^1H NMR (acetone-d_6): δ 2.77 (1H, dd, J=4, 17 Hz, 3β-H), 3.16 (1H, dd, J=12,

17 Hz, 3α-H), 5.57 (1H, dd, J=4, 12 Hz, 2-H), 6.01 (2H, s, 6-H and 8-H), 7.34-7.64 (5H, m, Ar-H), 12.18 (1H, s, 5-OH); ^{13}C NMR (Table I).

5,6-Dehydrokawain (7). Pale yellow needles; mp 137-138° (from EtOH), lit. 138-140° [29]; HRMS m/z: 228.0816 [M]$^+$ (calc. for $C_{14}H_{12}O_3$: 228.0786); MS m/z: 228 [M]$^+$, 200, 157, 125, 103; UV λ_{max}^{EtOH} nm: 233, 255, 343; IR ν_{max}^{KBr} cm^{-1}: 1720, 1635, 1605, 1550, 1445; ^{1}H NMR ($CDCl_3$): δ 3.80 (3H, s, OMe), 5.45, 5.88 (2H, 2 x d, J=2 Hz, 5-H and 3-H), 6.50, 7.42 (2H, 2 x d, J=16 Hz, -CH=CH-), 7.34 (5H, m, Ar-H).

Acetylation of linderatin. A mixture of linderatin (1)(4 mg) in Ac_2O (0.5 ml) and pyridine (0.5 ml) was heated at 60° for 4 hr. After work-up, the reaction product was purified by preparative TLC on silica gel ($CHCl_3$) to give a triacetate (1a)(3.5 mg). Viscous oil; $C_{31}H_{36}O_7$. $[\alpha]_D^{20}$ +37.8° ($CHCl_3$; c 0.80); MS m/z: 520 [M]$^+$, 478, 477, 436, 435, 394, 393; UV λ_{max}^{MeOH} nm: 270; UV $\lambda_{max}^{MeOH+AlCl_3}$ nm: 289, 380; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1640, 1600, 1495; ^{1}H NMR ($CDCl_3$): δ 0.83, 0.90 (6H, each d, J=7 Hz, 2 x 8"-Me), 1.62 (3H, br s, 1"-Me), 2.00, 2.04, 2.15 (9H, each s, 3 x OAc), 2.95 (4H, m, α-H and β-H), 5.00 (1H, br s, 2"-H), 6.82 (1H, s, 5'-H), 7.14 (5H, br s, Ar-H).

Methylation of linderatin. A mixture of linderatin (1)(20 mg), K_2CO_3 (56 mg), and MeI (144 mg) in acetone (5 ml) was heated under reflux for 3 hr. The reaction mixture was filtered off and the filtrate was evaporated to dryness. The residue was purified by preparative TLC on silica gel ($CHCl_3$) to give a dimethyl ether (1b)(9 mg). This compound gave a dark green colour with the Gibbs test.[20] Viscous oil; $C_{27}H_{34}O_4$. $[\alpha]_D^{20}$ +97.7° ($CHCl_3$; c 1.75); MS m/z: 422 [M]$^+$, 407, 352, 337; UV λ_{max}^{MeOH} nm: 225 (sh), 290; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (br), 1615, 1595, 1495; ^{1}H NMR (acetone-d_6): δ 0.80, 0.84 (6H, each d, J=7 Hz, 2 x 8"-Me), 1.63 (3H, br s, 1"-Me), 2.92 (2H, t, J=8 Hz, β-H), 3.32 (2H, t, J=8 Hz, α-H), 3.85, 3.93 (6H, each s, 2 x OMe), 5.02 (1H, br s, 2"-H), 6.16 (1H, s, 5'-H), 7.17 (5H, br s, Ar-H), 13.98 (1H, s, OH); ^{13}C NMR (Table I).

Cyclization of linderatin. A solution of linderatin (1)(20 mg) in saturated HCl-$CHCl_3$ (3 ml) was stirred at room temperature for 2 hr. The reaction mixture was evaporated to dryness and the residue was purified by preparative TLC on silica gel ($CHCl_3$-acetone, 40:1) to yield a cyclolinderatin (11)(12 mg). Colourless prisms; mp 128-130° (from $CHCl_3$); $[\alpha]_D^{20}$ +59.8° ($CHCl_3$; c 2.9); HRMS m/z: 394.2102 [M]$^+$ (calc. for $C_{25}H_{30}O_4$: 394.2142); MS m/z: 394 [M]$^+$, 324, 309; UV λ_{max}^{MeOH} nm: 225 (sh), 288; UV $\lambda_{max}^{MeOH+AlCl_3}$ nm: 271, 310 (sh), 348; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3250, 1620, 1610, 1500; ^{1}H NMR ($CDCl_3$): δ 0.94, 1.05 (6H, each d, J=7 Hz, 2 x 8"-Me), 1.33 (3H, s, 1"-Me), 3.00 (2H, t, J=8 Hz, β-H), 3.40 (2H, t, J=8 Hz, α-H), 5.83 (1H, s, 5'-H), 7.18 (5H, br s, Ar-H).

5-Isopropyl-2-methylcyclohex-2-enylphloroglucinol (9). A suspension of phloroglucinol (1.0 g) and p-menth-1-ene-6-ol (14)(0.421 g) in 5% citric acid (20 ml) was stirred at room temperature for 2 days. The reaction mixture was extracted with ether and then extracted twice with AcOEt. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to give a residual oil. The oil was purified by repeated preparative TLC on silica gel ($CHCl_3$-acetone, 5:1) to afford (9)(11 mg). Viscous oil; HRMS m/z: 262.1534 [M]$^+$ (calc. for $C_{16}H_{22}O_3$:

262.1567); MS m/z: 262 $[M]^+$, 219, 177; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3380, 1630, 1605, 1510; ^1H NMR (acetone-d_6): δ 0.86, 0.88 (6H, each d, J=7 Hz, 2 x 8"-Me), 1.67 (3H, br s, 1'-Me), 3.83 (1H, br s, 6'-H), 5.68-5.84 (1H, m, 2'-H), 5.90 (2H, s, 3-H and 5-H).

Piperityl phloroglucinol (10). A solution of piperitol (15)(0.61 g) in Et_2O (2 ml) was added to a suspension of phloroglucinol (1.0 g) in 5% citric acid (30 ml) and stirred at room temperature for 2 days. The reaction mixture was extracted with ether and then extracted twice with AcOEt. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The resulting residue was purified by preparative TLC on silica gel ($CHCl_3$-acetone, 10:1) to give piperityl phloroglucinol (10)(20 mg). Viscous oil; HRMS m/z: 262.1578 $[M]^+$ (calc. for $C_{16}H_{22}O_3$: 262.1567); MS m/z: 262 $[M]^+$, 192, 177; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3420, 1630, 1605, 1510; ^1H NMR (acetone-d_6): δ 0.83 (6H, each d, J=7 Hz, 2 x 8'-Me), 1.69 (3H, br s, 1'-Me), 3.80 (1H, br d, 3'-H), 5.34 (1H, br s, 2'-H), 5.91 (2H, s, 3-H and 5-H).

Synthesis of (±) linderatin (1). (±)-Piperitol (15)(50 mg) was added to a suspension of 2',4',6'-trihydroxydihydrochalcone (4)(100 mg) and $AlCl_3$ (50 mg) in 5% citric acid (3 ml) and stirred at room temperature for 2 days. The reaction mixture was extracted with $CHCl_3$. And the organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by preparative TLC on silica gel ($CHCl_3$-acetone, 40:1) to yield a racemic linderatin (1)(11 mg). Spectra (MS, UV, IR, and ^1H NMR) of this synthetic product were superimposable on those of a natural linderatin (1).

Acetylation of linderatone. A mixture of linderatone (2)(5 mg) and Ac_2O (0.1 ml) in pyridine (0.1 ml) was stirred at room temperature overnight. After work-up, the reaction product was purified by preparative TLC on silica gel ($CHCl_3$) to give a diacetate (2a)(5 mg). Viscous oil; $C_{29}H_{32}O_6$; $[\alpha]_D^{20}$ +21.2° ($CHCl_3$, c 1.75); MS m/z: 476 $[M]^+$, 434, 433, 392, 391, 365, 364, 323, 322; UV λ_{max}^{MeOH} nm: 228, 258, 321; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1690, 1615, 1570, 1455; ^1H NMR ($CDCl_3$): δ 0.81, 0.87 (6H, 2 x d, J=7 Hz, 2 x 8"-Me), 1.70 (3H, br s, 1"-Me), 2.24, 2.34 (6H, 2 x s, 2 x OAc), 2.74 (1H, dd, J=4, 17 Hz, 3β-H), 3.11 (1H, dd, J=13, 17 Hz, 3α-H), 3.56 (1H, br d, J=9 Hz, 3"-H), 5.20 (1H, br s, 2"-H), 5.54 (1H, dd, J=4, 13 Hz, 2-H), 6.79 (1H, s, 6-H), 7.50 (5H, s, Ar-H).

Methylation of linderatone. A mixture of linderatone (2)(20 mg) in saturated CH_2N_2-Et_2O (5 ml) was stirred for 5 hr at room temperature. The reaction mixture was evaporated, and the residue was purified by preparative TLC on silica gel ($CHCl_3$) to give a monomethyl ether (2b)(11 mg). Viscous oil; $[\alpha]_D^{20}$ +51.1° ($CHCl_3$; c 0.36); HRMS m/z: 406.2093 $[M]^+$ (calc. for $C_{26}H_{30}O_4$: 406.2142); MS m/z: 406 $[M]^+$, 363, 336, 321; UV λ_{max}^{MeOH} nm: 232 (sh), 292, 341; UV $\lambda_{max}^{MeOH+AlCl_3}$ nm: 315, 354; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1630, 1570, 1495; ^1H NMR ($CDCl_3$): δ 0.79, 0.84 (6H, d x 2, J=7 Hz, 2 x 8"-Me), 1.66 (3H, br s, 1"-Me), 2.76 (1H, dd, J=4, 17 Hz, 3β-H), 3.10 (1H, dd, J=13, 17 Hz, 3α-H), 3.77 (3H, s, 7-OMe), 5.16 (1H, br s, 2"-H), 5.43 (1H, dd, J=4, 13 Hz, 2-H), 6.08 (1H, s, 6-H), 7.44 (5H, s, Ar-H), 12.34 (1H, s, OH); ^{13}C NMR (Table I).

Cyclization of linderatone. $BF_3 \cdot Et_2O$ (3 drops) was added to a solution of

linderatone (2)(35 mg) in $CHCl_3$ (1 ml) at 0° and the mixture was stirred for 30 min. at room temperature. After cooling, the reaction mixture was washed with H_2O and the $CHCl_3$ layer was dried over Na_2SO_4 and evaporated. The residue was purified by preparative TLC on silica gel (n-hexane-ether 3:1) to give a cyclolinderatone (13)(10 mg). Viscous oil; $[\alpha]_D^{20}$ -28.7° ($CHCl_3$; c 0.3); HRMS m/z 392.1974 $[M]^+$ (calc. for $C_{25}H_{28}O_4$: 392.1985); MS m/z: 392 $[M]^+$, 377, 349, 322, 307; UV λ_{max}^{MeOH} nm: 296, 324 (sh); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (br), 1640, 1625, 1575, 1495; ^1H NMR ($CDCl_3$): δ 0.93, 1.07 (6H, 2 x d, J=7 Hz, 2 x 8"-Me), 1.32 (3H, s, 1"-Me), 2.73 (1H, dd, J=4, 17 Hz, 3β-H), 3.04 (1H, dd, J=12, 17 Hz, 3α-H), 3.40 (1H, br s, 3"-H), 5.41 (1H, dd, J=4, 12 Hz, 2-H), 5.98 (1H, s, 6-H), 7.43 (5H, s, Ar-H), 12.31 (1H, s, OH).

Hydrogenolysis of linderatone. A mixture of linderatone (2)(16 mg) and Raney Ni (W-3) in EtOH (5 ml) was stirred for 4 hr at room temperature under the hydrogen atomosphere. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by preparative TLC on silica gel ($CHCl_3$-acetone, 40:1) to give a optically active linderatin (1)(4 mg). This compound was indistinguishable from natural linderatin (1) by optical rotation and all spectra (MS, UV, IR, and ^1H NMR).

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