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THE FIRST TOTAL SYNTHESES OF (+)-HOSTMANIN A AND (+)-METHYLLINDERATIN

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Abstract – The first total syntheses of (+)-hostmanin A (**1**) and (+)-methyllinderatin (**3**) were achieved in four steps from a known compound, 1-{2,6-dihydroxy-4-methoxy-3-[(1*R*,6*R*)-3-methyl-6-(1-methylethyl)-2-cyclohexen-1-yl]phenyl}ethanone (**6**). The absolute configuration of (+)-methyllinderatin (**3**) was determined. Furthermore, (+)-hostmanin A (**1**), which was isolated as an inseparable mixture of hostmanin A and B, was synthesized as a sole component.

In order to find new antimalarial drugs from plant sources, Fabre and co-workers investigated the *n*-hexane extract of *Piper hostmannianum* (Piperaceae) leaves. As a result, monoterpene-substituted dihydrochalcones, hostmanin A (**1**) and B (**2**), were isolated as an inseparable mixture, as well as a known compound, (-)-methyllinderatin (**3**), in 2007 (Figure 1). (-)-Methyllinderatin (**3**) exhibited antiplasmodial activity against both chloroquine-sensitive and resistant strains of *Plasmodium falciparum* (F32, FcB1) *in vitro*, antimalarial activity against *Plasmodium vinckei petteri* in mice,[1] cytotoxicity towards KB nasopharyngeal carcinoma cells, and antibacterial effects toward *Micrococcus luteus*.[2] (-)-Methyllinderatin (**3**) has also been isolated from leaves of *Piper aduncum* (Piperaceae), whereas (+)-methyllinderatin (**3**) was isolated from leaves of *Lindera umberata* (Lauraceae).[3]

We previously reported the total syntheses of substituted chalcone derivatives, linderol A (**4**)[4,5] and adunctin E (**5**) (Figure 2).[2,6,7] In a continuation of our synthesis of chalcone derivatives, we planned the synthesis of methyllinderatin (**3**) in light of its diverse biological activity. In this paper, we report the first total syntheses of (+)-methyllinderatin (**3**) and (+)-hostmanin A (**1**).

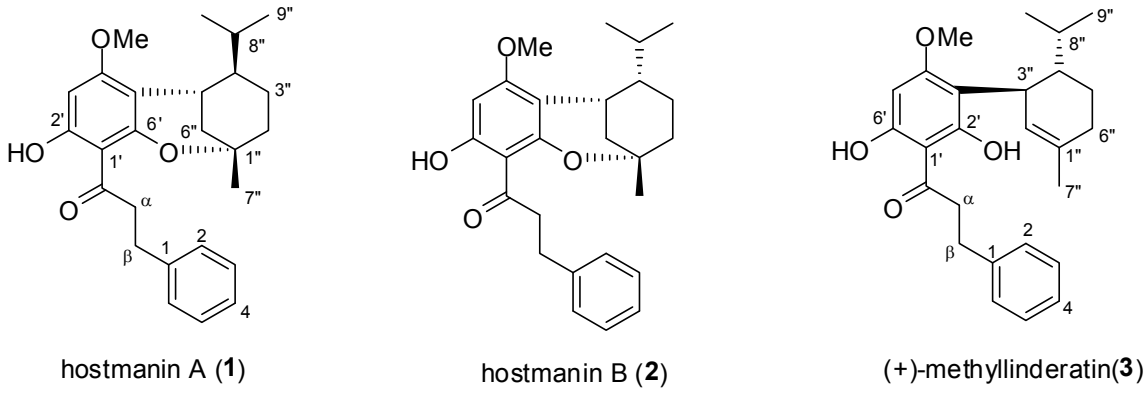


Figure 1. Structures of hostmanin A (**1**), B (**2**), and tentative structure of (+)-methyllinderatin (**3**)

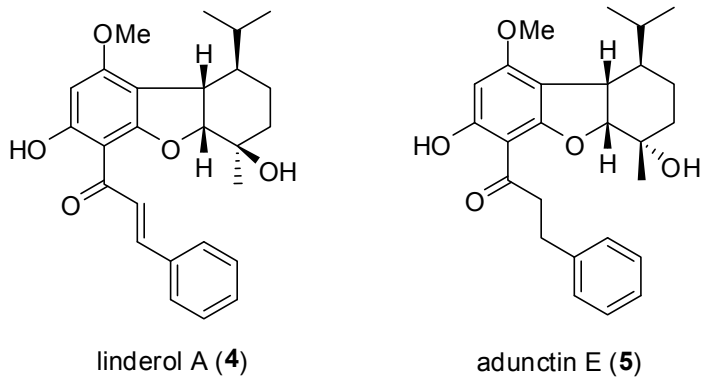
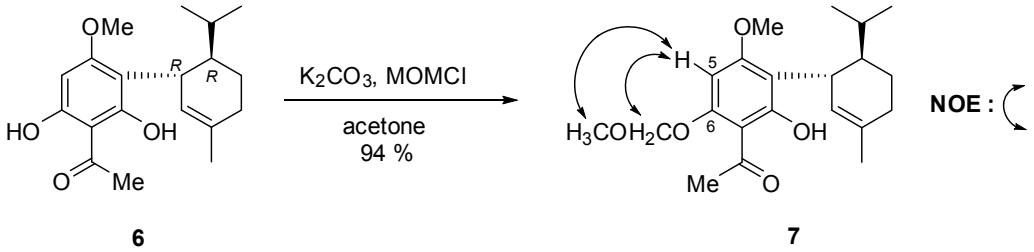


Figure 2. Structure of linderol A (**4**) and proposed structure of adunctin E (**5**)

The starting compound, 1-{2,6-dihydroxy-4-methoxy-3-[(1*R*,6*R*)-3-methyl-6-(1-methylethyl)-2-cyclohexen-1-yl]phenyl}ethanone (**6**), was prepared according to the procedure described in the literature.[8] The direct extension of the acetyl group in **6** to a cinnamoyl group by crossed aldol condensation with benzaldehyde was attempted, but the reaction did not proceed, possibly due to the existence of two hydroxy groups adjacent to the acetyl group. Thus, **6** was treated with MOMCl in the presence of potassium carbonate to protect the less hindered hydroxy group selectively to give **7** in 94% yield. The position of the MOM group was determined by an NOE experiment, which showed relationships between the aromatic hydrogen at the 5-position and the methyl and methylene groups on the MOM group in **7** (Scheme 1).

Crossed aldol condensation of monoprotected **7** with benzaldehyde successfully proceeded in the presence of *tert*-BuOK as a base (Scheme 2).[5] Next, **8** was treated with Et_3SiH in the presence of a catalytic amount of $(Ph_3P)_3RhCl$ to chemoselectively reduce the conjugated carbon-carbon double bond of the cinnamoyl group over the isolated double bond.[9]



Scheme 1. Preparation of **7** and NOE correlations

Finally, the MOM group on **9** was deprotected with 3 N HCl in refluxing methanol for 1.5 h to give two products together with recovery of **9**. The first product was (+)-methyllinderatin (**3**). The structure of the synthetic **3** was confirmed by comparison of the spectral data with those of the natural **3** described in the literature (Tables 1-3).[3]

Table 1. A comparison of the ^{1}H-NMR data of (+)-synthetic **3** with those of (+)-natural **3**

Position	Natural **3** (270 MHz, $CDCl_3$)	Synthetic **3** (300 MHz, $CDCl_3$)
9',10'-CH_3	0.81, 0.84 (*d* each, 3H each, *J*=7.4 Hz)	0.81, 0.84 (*d each*, 3H each, *J*=7.0 Hz)
7"-CH_3	1.79 (s, 3H)	1.79 (s, 3H)
α	3.00 (*t*, 2H, *J*=7.4 Hz)	3.00 (*t*, 2H, *J*=7.7 Hz)
β	3.39 (*t*, 2H, *J*=7.4 Hz)	3.39 (*t*, 2H, *J*=7.7 Hz)
OCH_3	3.79 (*s*, 3H)	3.79 (*s*, 3H)
3"-H	3.87 (*br d, J*=10.4 Hz)	3.87 (*br d*, *J*=10.6 Hz)
2"-H	5.46 (*s*)	5.46 (*s*)
5'-H	6.05 (*s*)	6.05 (*s*)
OH (free)	7.05 (*s*)	7.05 (*s*)
Ph	7.27 (*br s*, 5H)	7.14-7.39 (m, 5H)
OH(chelated)	13.71 (*s*)	13.72 (*s*)

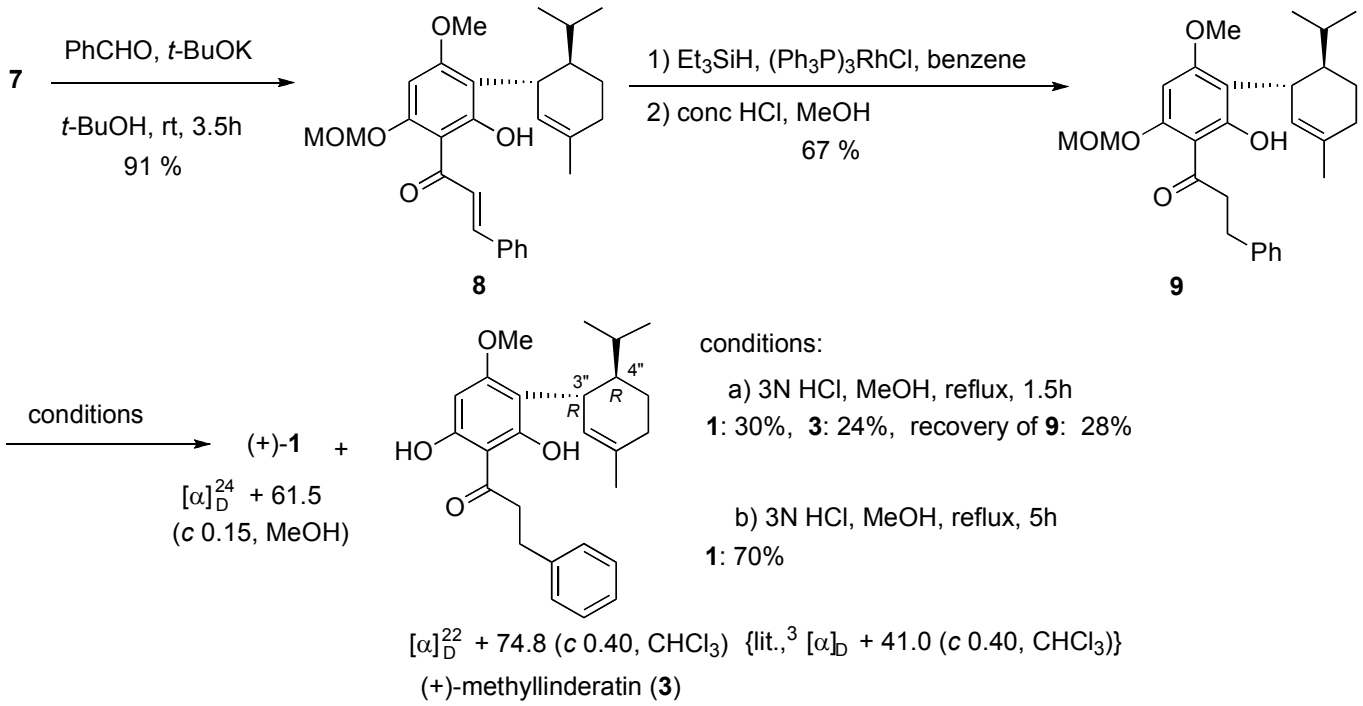
Table 2. A comparison of the ^{13}C-NMR data of (+)-synthetic **3** with those of (+)-natural **3**

Position	Natural **3** (25 MHz, acetone-d_6)	Synthetic **3** (75 MHz, acetone-d_6)	Position	Natural **3** (25 MHz, acetone-d_6)	Synthetic **3** (75 MHz, acetone-d_6)
C-1	142.8	142.9	C-α	46.7	46.8
C-2	129.1	129.1	C-β	31.4	31.3
C-3	129.2	129.3	OMe	55.8	55.8
C-4	126.7	126.9	C-1"	133.9	133.7
C-5	129.2	129.3	C-2"	126.5	126.6
C-6	129.1	129.1	C-3"	35.9	35.9
C-1'	105.5	105.5	C-4"	42.6	42.6
C-2'	162.1	162.0	C-5"	23.6	23.6
C-3'	111.5	111.5	C-6"	31.4	31.4
C-4'	163.7	163.9	C-7"	23.6	23.6
C-5'	91.7	91.8	C-8"	29.1	29.1
C-6'	165.2	165.2	C-9"	16.7	16.6
C=O	205.7	205.8	C-10"	21.9	21.8

Table 3. A comparison of the other data of (+)-synthetic **3** with those of (+)-natural **3**

Data	Natural **3**	Synthetic **3**
IR ($CHCl_3$, cm^{-1})	3360, 1630, 1590.	3356, 1624, 1585.
LRMS *m/z*	408 (M^+), 338, 323.	408 (M^+), 338, 323.
HRMS *m/z*	408.2306 (M^+, calcd for $C_{26}H_{32}O_4$: 408.2299)	408.2294 (M^+, calcd for $C_{26}H_{32}O_4$: 408.2300)
Specific rotation	$[\alpha]_D$ + 41.0 (*c* 0.40, $CHCl_3$)	$[\alpha]_D^{22}$ + 74.8 (*c* 0.40, $CHCl_3$)

Ichino assigned the relative configuration at the 3”- and 4”-positions of (+)-**3** as 3”*S*, 4”*S* as shown in Figure 1, and Sticher *et al*. and Fabre *et al*. showed those of (-)-**3** as 3”*R*, 4”*R* based on Ichino’s representation.[1,2] The present total synthesis of (+)-**3** indicated the absolute configuration at the 3”- and 4”-positions to be 3”*R*, 4”*R* as shown in Scheme 2.



Scheme 2. Syntheses of (+)-hostmanin A (**1**) and (+)-methyllinderatin (**3**)

The second product was an unexpected byproduct. The byproduct was found to correspond to $C_{26}H_{32}O_4$ by high resolution mass spectrometry (M^+; 408.2294). Disappearance of the proton signals on the double bond and one proton signal from the two phenolic hydroxy groups was observed by comparison of the H^1-NMR spectra of **3** and the byproduct. The byproduct was determined to be (+)-hostmanin A (**1**) on the basis of spectral data, which were consistent with the spectral data of natural hostmanin A (**1**)

(Tables 4-6).[1,10] A longer reaction time improved the yield of (+)-**1** to 70% without the formation of (+)-**3**.

Table 4. A comparison of the ^{1}H-NMR data of (+)-synthetic **1** with those of natural **1**

Position	Natural **1** (500 MHz, $CDCl_3$)[a)]	Synthetic **1** (300 MHz, $CDCl_3$)
Dihydrochalcone moiety		
2-H to 6-H	7.21-7.29 (m, 5H)	7.18-7.29 (m, 5H)
α-H	3.49 (m, 2H)	3.46 (t, 2H, *J*=7.8 Hz)
α-H	3.06 (t, 2H, *J*=8.0 Hz)	3.03 (t, 2H, *J*=7.8 Hz)
3'-H	6.02 (s)	5.99 (s)
OH (chelated)	13.90 (s)	13.88 (s)
4-OCH_3	3.83 (s, 3H)	3.80 (s, 3H)
Monoterpene moiety		
2"-H_a	1.74 (m)	1.71 (ddd, *J*=13.8, 2.4, 2.4 Hz)
2"-H_b	1.61 (m)	1.58 (ddd, *J*=13.8, 13.4, 4.5 Hz)
3"-H	1.53 (m, 2H)	1.40-1.52 (m, 2H)
4"-H_a	1.21 (m)	1.14-1.23 (m)
5"-H_b	3.39. (m)	3.29-3.39 (m)
6"-H_a	1.91 (dd, *J*=13.4, 3.4 Hz)	1.87 (dd, *J*=13.8, 2.7 Hz)
6"-H_b	1.51 (dd, *J*=13.4, 5.3 Hz)	1.47 (dd, *J*=13.8, 4.5 Hz)
7"-CH_3	1.36 (s, 3H)	1.33 (s, 3H)
8"-H	1.78 (m)	1.79 (qqd, *J*=6.6, 6.6, 11.1, Hz)
9"-CH_3	1.08 (d, 3H, *J*=6.8Hz)	1.04 (d, 3H, *J*=6.6 Hz)
10"-CH_3	0.97 (d, 3H, *J*=6.8Hz)	0.94 (d, 3H, *J*=6.6 Hz)

a) Multiplicity patterns were unclear due to signal overlapping of hostmanin A (**1**) and B (**2**). The ratio of **1** and **2** was 55 to 45.

Table 5. A comparison of the ^{13}C-NMR data of (+)-synthetic **1** with those of natural **1**

Position	Natural **1** (125 MHz, $CHCl_3$)	Synthetic **1** (75 MHz, $CHCl_3$)	Position	Natural **1** (125 MHz, $CHCl_3$)	Synthetic **1** (75 MHz, $CHCl_3$)
C-1	141.8	141.7	C-α	45.5	45.3
C-2	128.3	128.3	C-β	30.7	30.6
C-3	128.4	128.3	OMe	55.7	55.8
C-4	125.8	125.8	C-1"	77.9 [a)]	76.9
C-5	128.4	128.3	C-2"	35.3	35.2
C-6	128.3	128.3	C-3"	20.5	20.5
C-1'	104.7	104.6	C-4"	44.0	44.0
C-2'	165.4	165.3	C-5"	27.2	27.1
C-3'	91.2	91.2	C-6"	30.1	30.1
C-4'	162.3	162.1	C-7"	29.2	29.1
C-5'	106.8	106.8	C-8"	26.3	26.2
C-6'	158.9	158.9	C-9"	20.9	20.9
C=O	204.9	204.8	C-10"	22.1	22.1

a) The C-1" position of hostmanin B (**2**) was assigned as 76.7 ppm.

In conclusion, the first total syntheses of (+)-methyllinderatin (**3**) and (+)-hostmanin A (**1**) were achieved in four steps from the optically pure compound (**6**). The absolute configuration of (+)-**3** was determined by this synthesis. Furthermore, (+)-hostmanin A (**1**), which was isolated as an inseparable mixture,

could be prepared as one component. The formation of (+)-**1** would suggest that (+)-**3** would be the precursor of **1** in biosynthesis. Efforts to increase the yield of (+)-**3** are currently in progress.

Table 6. A comparison of the other data of (+)-synthetic **1** with those of natural **1** and **2**

Data	Natural **1** and **2**[a)]	Synthetic **1**
IR ($CHCl_3$,cm^{-1})	3425 (chelated OH), 1616, 1585	3550-3000 (chelated OH), 1618, 1587
LRMS *m/z*	407 $(M - H)^+$	408 (M^+)
HRMS *m/z*	407.2242 ($[M - H]^+$, calcd for $C_{26}H_{32}O_4$: 407.2222)	408.2294 (M^+, calcd for $C_{26}H_{32}O_4$: 408.2300)
Specific rotation	$[\alpha]_D^{25}$ - 31.0 (*c* 0.15, MeOH)	$[\alpha]_D^{24}$ + 61.5 (*c* 0.15, MeOH)

a) The ratio of hostmanin A (**1**) and B (**2**) was 55 to 45.

EXPERIMENTAL

NMR spectra were measured on a JEOL AL-300 (^{1}H; 300 MHz, ^{13}C; 75.5 MHz) and a Varian INOVA 400NB (^{1}H; 400 MHz) for an NOE experiment. IR spectra were taken with a Shimadzu FTIR-8400 spectrophotometer. A JEOL JMS-GC mate spectrometer and a Shimadzu GCMS-QP5050A spectrometer were used for low-resolution electron ionization MS (MS) and a JEOL JMS-GC mate spectrometer was used for high-resolution electron ionization MS (HRMS). Specific rotation was measued on a JASCO P-2200 polarimeter. All extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure in the usual work-up procedure. Silica gel 60 (grade 7734, 60 – 230 mesh, Merck) for column chromatography and Silica Gel 60 PF_{254} (5 – 50 μm, Nacalai tesque) for preparative TLC were used.

2-Hydroxy-4-methoxy-6-methoxymethoxy-3-[(1*R*,6*R*)-3-methyl-6-(1-methylethyl)-2-cyclohexen-1-yl]acetophenone (7)

To a solution of **6** (400 mg, 1.26 mmol) and MOMCl (303 mg, 3.76 mmol) in distilled acetone (40 mL) was added K_2CO_3 (469 mg, 3.39 mmol), and the whole was refluxed for 0.5 h under N_2 atmosphere. After filtration of the K_2CO_3, the filtrate was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 3) to give **7** (428 mg, 94 %). Pale yellow oil. $[\alpha]_D^{24}$ + 96.46 (*c* 1.00, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.77, 0.82 [d each, 3H each, J = 7.0 Hz, $(C\underline{H}_3)_2CH$-], 1.18–1.50 [m, 2H, $(CH_3)_2CH$-CH-$C\underline{H}_2$-], 1.65 [s, 3H, $C\underline{H}_3$], 1.69-1.79 [m, 1H, $(CH_3)_2CH$-$C\underline{H}$-], 1.91-2.23 [m, 3H, $(CH_3)_2CH$-CH-CH_2-$C\underline{H}_2$- and $(CH_3)_2C\underline{H}$-], 2.65 [s, 3H, $C\underline{H}_3$-C(=O)-], 3.53 [s, 3H, $C\underline{H}_3$-O-CH_2-O-], 3.80 [s, 3H, Ar-$OC\underline{H}_3$], 3.82-3.90 [m, 1H, Ar-$C\underline{H}$-], 5.12 [s, 1H,

Ar-CH-C<u>H</u>-], 5.27 [s, 2H, CH_3-O-C<u>H</u>$_2$-O-], 6.21 [s, 1H, Ar-<u>H</u>], 13.82 [s, 1H, Ar-O<u>H</u>]. ^{13}C-NMR ($CDCl_3$) δ: 16.2, 21.6, 22.9, 23.4, 28.5, 30.9, 33.2, 35.3, 41.2, 55.5, 56.5, 88.9, 94.4, 106.2, 113.7, 125.8, 132.0, 159.3, 164.3, 164.3, 203.3. IR ($CHCl_3$) cm^{-1}: 3500 - 3000 (chelated OH), 2932, 1612 (-C=O), 1597. HRMS (EI) *m/z*: 362.2100 (Calcd for $C_{21}H_{30}O_5$: 362.2093). LRMS (EI) *m/z* (rel. int. %): 45 (100), 195 (19), 247 (30), 292 (17), 317 (25), 362 (M$^+$, 9).

(*E*)-1-{2-Hydroxy-4-methoxy-6-methoxymethoxy-3-[(1*R*,6*R*)-3-methyl-6-(1-methylethyl)-2-cyclohexen-1-yl]phenyl}-3-phenylprop-2-en-1-one (8)

To a solution of **7** (312 mg, 0.86 mmol) and PhCHO (137 mg, 1.29 mmol) in distilled *t*-BuOH (12 mL) was added *t*-BuOK (193 mg, 1.72 mmol), and the whole was stirred at rt for 3.5 h under N_2 atmosphere. After addition of saturated aqueous NH_4Cl solution, the whole was extracted with AcOEt (three times). The combined organic layers were washed, dried, and evaporated. The crude product was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 3) to give **8** (352 mg, 91 %). Orange-yellowish oil. $[\alpha]_D^{25}$ + 100.56 (*c* 1.00, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.78, 0.83 [d each, 3H each, *J* = 6.8 Hz, (C<u>H</u>$_3$)$_2$CH-], 1.28–1.52 [m, 2H, (CH_3)$_2$CH-CH-C<u>H</u>$_2$-], 1.66 [s, 3H, C<u>H</u>$_3$], 1.71-1.81 [m, 1H, (CH_3)$_2$CH-C<u>H</u>-], 1.91-2.22 [m, 3H, (CH_3)$_2$CH-CH-CH_2-C<u>H</u>$_2$- and (CH_3)$_2$C<u>H</u>-], 3.54 [s, 3H, C<u>H</u>$_3$-O-CH_2-O-], 3.82 [s, 3H, Ar-OC<u>H</u>$_3$], 3.84-3.94 [m, 1H, Ar-C<u>H</u>-], 5.15 [s, 1H, Ar-CH-C<u>H</u>-], 5.29 [s, 2H, CH_3-O-C<u>H</u>$_2$-O-], 6.22 [s, 1H, Ar-<u>H</u>], 7.33-7.47 [m, 3H, Ph], 7.50-7.66 [m, 2H,Ph], 7.74, 7.87 [d each, 1H each, *J* = 15.7 Hz, Ar-C(=O)-C<u>H</u>=C<u>H</u>-], 13.65 [s, 1H, Ar-O<u>H</u>]. ^{13}C-NMR ($CDCl_3$) δ: 16.3, 21.6, 21.7, 23.0, 23.5, 28.5, 30.9, 35.4, 55.6, 56.7, 89.8, 95.2, 114.1, 125.6, 125.8, 127.9, 128.0, 128.1, 128.2, 128.9(2C), 129.9, 132.2, 135.6, 141.6, 158.7, 164.5, 193.2. IR ($CHCl_3$) cm^{-1}: 3500 - 3000 (chelated OH), 2930, 1630 (-C=O), 1611, 1572. HRMS (EI) *m/z*: 450.2399 (Calcd for $C_{28}H_{34}O_5$: 450.2406). LRMS (EI) *m/z* (rel. int. %): 45 (100), 103 (29), 131(63), 179 (23), 335 (19), 405 (37), 450 (M$^+$, 21).

1-{2-Hydroxy-4-methoxy-6-methoxymethoxy-3-[(1*R*,6*R*)-3-methyl-6-(1-methylethyl)-2-cyclohexen-1-yl]phenyl}-3-phenylpropan-1-one (9)

A solution of **8** (200 mg, 0.44 mmol), Et_3SiH (206 mg, 1.77 mmol), and $(Ph_3P)_3RhCl$ (40 mg) in benzene (8 mL) was refluxed for 12 h under N_2 atmosphere. After cooling, a solution of concd HCl (25 drops) in MeOH (5 mL) was added to the reaction mixture at rt, and the whole was stirred for additional 2 h. After addition of saturated aqueous $NaHCO_3$ solution and Et_2O, the whole was extracted with Et_2O (three times). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried, and evaporated. The crude product was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 3) to give **9** (134 mg, 67 %). Pale yellow oil. $[\alpha]_D^{23}$ + 84.45 (*c* 1.00, MeOH). ^{1}H-NMR ($CDCl_3$)

δ: 0.77, 0.83 [d each, 3H each, J = 6.8 Hz, $(C\underline{H}_3)_2CH$-], 1.28–1.50 [m, 2H, $(CH_3)_2CH$-CH-$C\underline{H}_2$-], 1.65 [s, 3H, $C\underline{H}_3$], 1.70-1.79 [m, 1H, $(CH_3)_2CH$-$C\underline{H}$-], 1.90-2.22 [m, 3H, $(CH_3)_2CH$-CH-CH_2-$C\underline{H}_2$- and $(CH_3)_2C\underline{H}$-], 3.02 [t, 2H, J = 7.8 Hz, Ph-$C\underline{H}_2$-], 3.35 [t, 2H, J = 7.8 Hz, Ph-CH_2-$C\underline{H}_2$-], 3.47 [s, 3H, $C\underline{H}_3$-O-CH_2-O-], 3.79 [s, 3H, Ar-$OC\underline{H}_3$], 3.82-3.92 [m, 1H, Ar-$C\underline{H}$-], 5.12 [s, 1H, Ar-CH-$C\underline{H}$-], 5.24 [s, 2H, CH_3-O-$C\underline{H}_2$-O-], 6.22 [s, 1H, Ar-$\underline{H}$], 7.11-7.36 [m, 5H, Ph], 13.77 [s, 1H, Ar-$O\underline{H}$]. ^{13}C-NMR ($CDCl_3$) δ: 16.3, 21.5, 22.9, 23.4, 28.5, 30.8, 35.4, 41.2, 45.9, 55.4, 55.5, 56.5, 89.0, 94.3, 94.5, 94.7, 106.0, 113.8, 125.6, 125.9, 128.4(2C), 132.1, 141.7, 159.1, 164.1, 164.3, 204.7. IR ($CHCl_3$) cm^{-1}: 3500 - 3000 (chelated OH), 2932, 1610 (-C=O), 1599. HRMS (EI) *m/z*: 452.2568 (Calcd for $C_{28}H_{36}O_5$: 452.2563). LRMS (EI) *m/z* (rel. int. %): 45 (100), 91 (54), 105(24), 218(21), 337 (22), 407 (43), 452 (M^+, 15).

(2*S*,5*R*,6*S*)-3,4,5,6-Tetrahydro-9-hydroxy-7-methoxy-2-methyl-5-(1-methylethyl)-2,6-methano-2*H*-1-benzoxocin (1) [(+)-Hostmanin A] and {2,6-Dihydroxy-4-methoxy-3-[(1*R*,6*R*)-3-methyl-6-(1-methylethyl)-2-cyclohexen-1-yl]phenyl}-3-phenylpropan-1-one (3) [(+)-Methyllinderatin]

To a solution of **9** (40 mg, 0.09 mmol) in MeOH (0.5 mL) added 3N HCl (1.0 mL), and the whole was heated at 100°C for 1.5 h. The reaction mixture was extracted with AcOEt (three times). The combined organic layers were washed, dried, and evaporated. The crude product was purified by preparative TLC (AcOEt : *n*-hexane = 1 : 3) to give **1** (11 mg, 30 %) as pale yellow oil, **3** (9 mg, 24 %) as pale yellow oil, and recovery of **9** (11 mg, 28 %).

(+)-Hostmanin A (1)

When the reaction time was prolonged 1.5 h to 5 h at 100°C, only (+)-hostmanin A (**1**) was obtained in 70% yield.

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