Synthesis of Wasabidienone A via a Novel Acyl Rearrangement Reaction from Carbon to Oxygen

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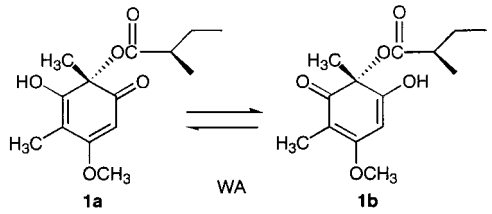
Abstract: Wasabidienone A (WA), a tautomeric mixture of 5-hydroxy-3-methoxy-4,6-dimethyl-(6*S*)-[(2*R*)-2-methylbutyryloxy]-cyclohexa-2,4-dien-1-one (**1a**) and 5-hydroxy-3-methoxy-2,6-dimethyl-(6*R*)-[(2*R*)-2-methylbutyryloxy]cyclohexa-2,4-dien-1-one (**1b**) was synthesized via a novel rearrangement reaction of an acyl group from carbon to the *β*–hydroxy oxygen on the cyclohexadienone ring. This reaction may occur during fermentation of *Phoma wasabiae* to form WA from WB_1.

Key words: wasabidienone A, *Phoma wasabiae*, oxo-enol tautomer, cyclohexadienone, acyl rearrangement

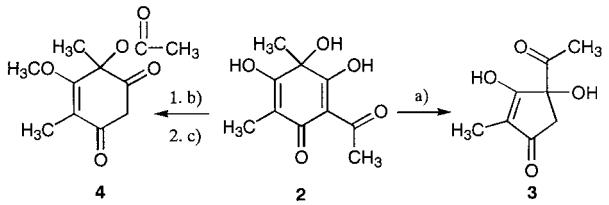
Wasabidienone A (WA), which is a pale yellow pigment having a highly oxidized cyclohexa-2,4-dienone skeleton and exists as a mixture of oxo–enol tautomers, is one of the potato metabolites of *Phoma wasabiae* producing a polyphenol oxidase and a peroxidase.[1]

Since we were interested in the characteristics and biosynthesis of unique pigments which have a chiral carbon on the cyclohexadienone ring and show oxo–enol tautomerism such as pigments of safflower petals,[2] we were also interested in the structure and biosynthesis of WA and undertook its synthesis. Herein, we would like to report the synthesis of WA using a novel acyl rearrangement reaction from carbon to oxygen.



Figure

During the synthesis of WA, it was found that cyclohexa-2,5-dienone **2** isomerized to a five-membered ring **3** under the conditions of deacetylation reaction by refluxing in HCl solution. This isomerization also easily occurred under the conditions of UV light irradiation or alkaline solution, and Soga et al.[1b–d] have also reported that the refluxing of WB_1 in benzene afforded the five-membered ring, WB_0 (see Scheme 3). Because of these reasons, after protection of the C-5 enol hydroxy group of **2** by diazomethane treatment, the deacetylation reaction was then examined (Scheme 1). Under the conditions of refluxing in a 5% Na_2CO_3 aqueous solution and methanol, 5-*O*-methylated **2** was subjected to deacetylation without isomerization and the acetyl group migrated from carbon to the *β*-positioned hydroxy oxygen, providing 4-acetoxy-4,6-dimethyl-5-methoxycyclohex-5-ene-1,3-dione (**4**), which was elucidated in detail by means of spectroscopic analysis.



a) 6N HCl/reflux, 63%; b) CH_2N_2 in EtOAc, 98%; c) 5% Na_2CO_3 aq soln/MeOH (10 : 1), reflux, 1h, 65%

Scheme 1

We employed this novel reaction to the other cyclohexadienone compounds (see Table 1). Even when the bulkier migrating acyl group such as a 3-phenylpropanoyl group (run 8) or the bulkier alkyl group on the *β*-carbon such as *iso*-propyl and 3-methylbut-2-enyl groups (runs 6 and 9) was employed, the rearrangement of an acyl group to the *β*-positioned *tert*-alcohol oxygen proceeded. Surprisingly, the rearrangement of the 2-methylbutanoyl group proceeded in good yield (run 10).

The further crossover experiment was carried out. A mixture of the substrates of runs 2 and 4, and runs 6 and 8 (1:1) gave only the corresponding intramolecular-rearrangement products respectively, and none of the intermolecular-rearrangement product. From the above result, it is suggested that this rearrangement reaction proceeds intramolecularly. The mechanism of this rearrangement reaction can be explained as follows: the alkoxy anion generated under alkaline conditions attaches to the *β*-acyl carbonyl carbon, giving the rearrangement product of an acyl group to the *β*-positioned hydroxy oxygen.[3]

We then attempted the synthesis of WA using this rearrangement reaction as the key step (Scheme 2). The Friedel–Crafts acylation of 1,3,4,5-benzenetetrol[14] with racemic 2-methylbutanoic acid in the presence of BF_3•OEt_2 at 80 °C gave a monoacylated product **5** in 77.5% yield. The bis-*C*-methylation of **5** with methyl iodide in the presence of sodium hydride followed by *O*-methylation with diazomethane provided 5-methoxycyclohexa-2,5-dienone **7** as diastereomixtures in 56% yield. Since **7** was inseparable, the condensation of **7** with an *N*-carbobenzyloxy (Cbz)-L-valine was performed to afford **8a** and **8b** as a 1:1 mixture retaining the chirality on the cyclohexadienone ring in a total of 97% yield, which

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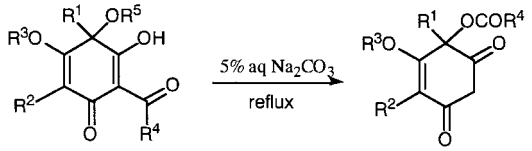
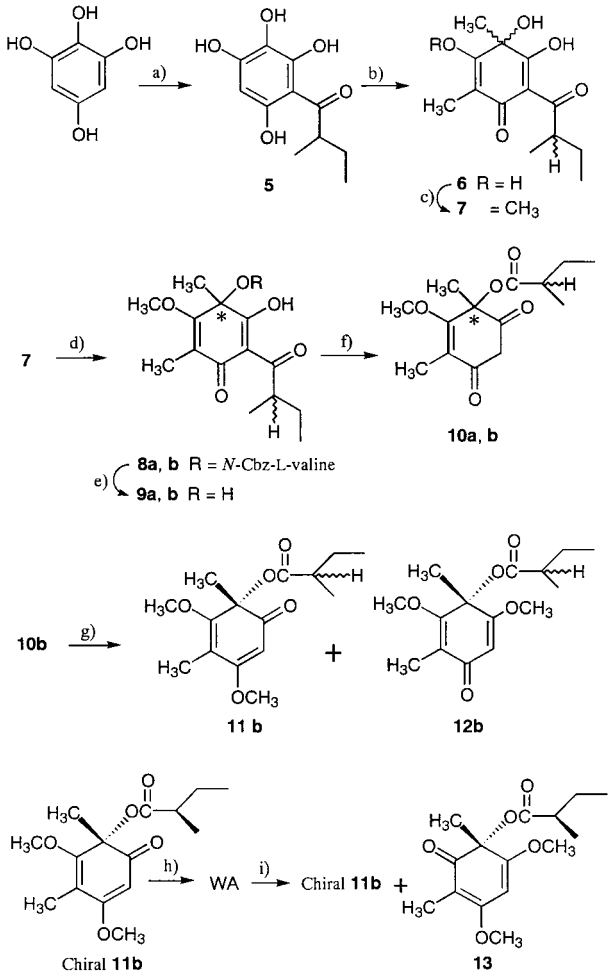
Table. Acyl Rearrangement Reaction of Cyclohexadienone



Run	R^1	R^2	R^3	R^4	R^5	Reflux time (h)	Isolated yield (%)
1	Me	H	Me	Me	H	0.75	18 (30[a])
2	Et	Et	Me	Me	H	1	30[b] (33[a])
3	Me	Me	Me	Me	Me	>3	–[c]
4	Me	Me	Me	Et	H	0.72	53 (7[a])
5	Me	Me	Me	Et	Me	>3	–[c]
6	*i*-Pr	*i*-Pr	Me	Me	H	2.17	40 (39[a])
7	H	H	*i*-Pr	Et	H	1.5	37 (24[a])
8	Me	Me	Me	$PhCH_2CH_2$	H	0.80	57[d] (8[a])
9	3-methyl-but-2-enyl	3-methyl-but-2-enyl	Me	*i*-Bu	H	5.16	20 (23[a])
10	Me	Me	Me	Et(Me)CH	H	1	90 (5[a])

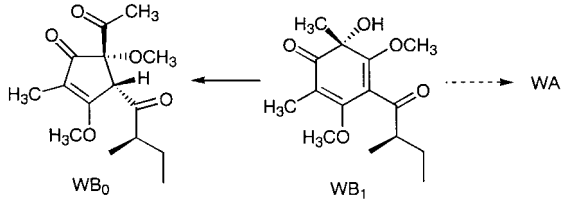
All compounds gave satisfactory spectroscopic data and microanalyses.
[a] Recovery.
[b] 50 and [d]17% of them were their de-*O*-acylated products, respectively.
[c] No reaction.

could be easily separated by silica gel column chromatography (silica gel TLC, EtOAc/hexane = 2:1, **8a**; R_f = 0.6 and **8**b; 0.4).[5] Each diastereomixture **8a** and **8b** had a valine moiety removed by sodium methoxide to yield **9a** and **9b** respectively in 74 % yield, each of which was a racemic mixture in the 2-methylbutanoyl moiety. Next, the crucial rearrangement reactions by refluxing of **9a** and **9b** in a 5 % Na_2CO_3 aqueous solution and methanol (12:1) produced the rearrangement products **10a** and **10b** in 90% yield respectively. As the optical activity of diastereomer **10b** showed the same positive sign as that of the natural WA's methyl ether,[1b–d] subsequent diazomethane treatment of **10b** was carried out, yielding methyl ether **11b** and its regioisomer **12b** in total of 79% yield (ratio 1:1.5). The ^{1}H NMR spectrum of **11b** was similar to that of one of the two methyl ethers derived from the natural WA.[6] Upon further HPLC analytic comparison of the diastereomeric mixture **11b** and the natural one (silica column, hexane/EtOAc = 80:20, 1 mL/min, retention time; 14.1 and 15.7 min, ratio 1.2:1), the retention time of the first eluate of **11b** was identical with that of the natural methyl ether. Their specific rotations were also identical. Finally, regioselective de-*O*-methylation of the C-5 methoxy group of the chiral first eluate of **11b** which was separated by preparative HPLC, was performed by using aluminum chloride and ethanethiol in CH_2Cl_2 affording the desired chiral WA in 67% yield. The synthetic WA was unstable and identical with the natural metabolite in silica gel TLC, mass, IR and ^{1}H NMR spectra, and further diazomethane treatment of WA provided two regioisomeric methyl ethers **11b** and **13** (1:1), as well as natural one.[1b–d] Thus, it was confirmed that WA derived from the chiral **11b** was identical with the natural specimen. It can be assumed that natural WA was also produced from the other metabolite, WB_1 via rearrangement reaction of the 2-methylbutanoyl group to the β-hydroxy group, during fermentation of *Phoma wasabiae*, as well as WB_0 being produced from WB_1 (Scheme 3).[1b–e]



a) *dl*-2-methylbutanoic acid/$BF_3 \cdot OEt_2$, 80°C, 1 h, 77.5%; b) CH_3I/NaH, 57%; c) CH_2N_2, >95%; d) Cbz-L-valine/DCC/DMAP, 97%; e) NaOMe/MeOH, r.t., 1 h, 74%; f) 5% Na_2CO_3 aq soln/MeOH (12 : 1), reflux, 1 h, 90%; g) CH_2N_2 in EtOAc, 79% (1 : 1.5); h) $AlCl_3$ (9 equiv)/EtSH (11 equiv), r.t., 18 h, 69%; i) CH_2N_2, 76% (**11b** : **13** = 1 : 1)

Scheme 2



Scheme 3

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Mps were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Mass spectra were recorded on a JEOL JMS-AX505HA spectrometer and HRMS were recorded on a HX-110 spectrometer (The Analytical Center of the Graduate School of Science at Tohoku University). Electron spectra were recorded on a Hitachi 228A spectrometer. IR spectra were recorded on a Horiba FT-200 IR spectrometer as KBr pellets or neat on NaCl cell. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 270, a Varian Mercury 200 and a Varian INOVA 500 spectrometers with TMS as an internal standard. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter using a 0.5 dm cell. Analytical TLC was performed on Merck silica gel 60 F_{254} plates. Flash column chromatography was carried out with Merck silica gel 60 (230–400 mesh). HPLC was performed on a Hitachi L-7100 and L-4200H system using the following conditions; column: GL Sciences Inc., Inertsil SIL 100-5 column (5 × 150 mm), solvent: hexane: EtOAc = 80:20, flow rate: 1 mL/min, wave length: UV254 or 250 nm. Preparative HPLC; Inertsil SIL 100-5, 10 × 250 mm, hexane:EtOAc = 75:25, 5 mL/min, UV254 nm.

2-Acetyl-3,4,5-trihydroxy-4,6-dimethylcyclohexa-2,5-dien-1-one ***(2)***: colorless prisms, mp 153–154 °C (lit.[7] 150.5–151.5 °C).
EIMS: *m/z* = 212(M^+).
UV(EtOH): λ_{max}(logε) = 229(4.18), 321(4.09), 358(4.01) nm.
IR(KBr): ν = 3384, 3181, 2985, 1664, 1533, 1479, 1279 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.57 and 1.87 (each 3H, s, CH_3 × 2), 2.57 (3H, s, Ac), 18.74 (1H, s, chelated OH).

Anal. ($C_{10}H_{12}O_5$): Calc. C, 56.60; H, 5.70. Found C, 56.56; H, 5.74.
4-Acetyl-3,4-dihydroxy-2-methylcyclopent-2-en-1-one **(3)**: colorless prisms, mp 152–154 °C.
EIMS: *m/z* = 170(M^+).
UV(EtOH): λ_{max}(logε) = 207 (3.51), 254 (4.12) nm.
IR(KBr) ν = 3481, 2935, 1718, 1560, 1410, 1361, 1265 cm^{-1}.
1H NMR (DMSO-d_6): δ = 1.49 (3H, s, CH_3), 2.20 (3H, s, Ac), 2.30 and 2.80 (each 1H, d, *J*=17Hz, CH_2), 6.2 (br s, OH).
^{13}C NMR (DMSO-d_6): δ = 208.9(s), 192.8(s), 190.6(s), 111.3(s), 84.0(s), 43.3(t), 26.0(q), 6.3(q).
Anal. ($C_8H_{10}O_4$): Calc. C, 56.47; H, 5.92. Found C, 56.35; H, 5.94.

4-Acetoxy-5-methoxy-4,6-dimethylcyclohex-5-ene-1,3-dione (**4**): pale yellow prisms, mp 146 °C.
EIMS: *m/z* = 226(M^+).
UV(EtOH): λ_{max}(logε) = 247(4.06), 297(sh, 3.65), 347(sh, 3.43) nm.
^{1}H NMR($CDCl_3$): δ = 1.64 and 1.94 (each 3H, s, CH_3 × 2), 2.13 (3H, s, OAc), 3.57 (2H, s, $COCH_2CO$, disappeared with D_2O), 3.92 (3H, s, OCH_3).
^{13}C NMR($CDCl_3$): δ = 198.2(s), 191.3(s), 170.1(s), 169.5(s), 119.1(s), 80.1(s), 61.8(q), 50.2(t), 23.4(q), 20.3(q), 10.1(q).
Anal. ($C_{11}H_{14}O_5$): Calc. C, 58.40; H, 6.24. Found C, 58.51; H, 6.43.

2-(dl-2-Methylbutanoyl)benzene-1,3,4,5-tetrol (5):
A mixture of benzenetetrol (35.2 mmol, 5.00 g), *dl*-2-methylbutanoic acid (70.4 mmol, 7.68 mL), BF_3•OEt_2 (84.5 mmol, 10.4 mL) and powdered molecular sieves 4Å (1 g) was heated at 80 °C under Ar for 1h. After cooling, the mixture was poured into ice-water and then extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the residual reddish brown syrup was purified by column chromatography (EtOAc/hexane) to give **5** (6.17 g, 77.5%) as a pale brown oil.
EIMS: *m/z* = 226(M^+).
IR(neat): ν = 3377, 2968, 1645, 1456, 1379, 1226 cm^{-1}.
^{1}H NMR (DMSO-d_6): δ = 0.83(3H, t, *J*=7.4Hz, CH_2CH_3), 1.05(3H, d, *J*=6.6Hz, >$CHCH_3$), 1.31 and 1.70 (each 1H, m, CH_2CH_3), 3.78 (1H, m, >$CHCH_3$), 5.87 (1H, s, ArH), 7.88 (1H, br s, OH), 10.09, 11.24 and 12.27 (each 1H, s, OH × 3).

3,4,5-Trihydroxy-4,6-dimethyl-2-(2-methylbutanoyl)cyclohexa-2,5-dien-1-one (6):
To a solution of **5** (22.1 mmol, 5.00 g) in anhyd DMSO (10 mL) a suspension of NaH (55.3 mmol, 1.33 g) in anhyd toluene was added under N_2. After stirring until the end of the evolution of H_2 (for ca. 0.5h), MeI (55.3 mmol, 7.85 g) was added slowly to the mixture and then stirred at r.t. for 2h. The mixture was quenched by adding an ice cold 2M HCl solution and extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine and dried (Na_2SO_4), and then evaporated. The residual product was purified by column chromatography (EtOAc/hexane) to give **6** as a pale brown oil (3.20 g, 57%).
EIMS: *m/z* = 254(M^+).

3,4-Dihydroxy-5-methoxy-4,6-dimethyl-2-(2-methylbutanoyl)cyclohexa-2,5-dien-1-one (7):
To a solution of **6** (11.8 mmol, 3.00 g) in EtOAc a solution of diazomethane in Et_2O was added dropwise in an ice bath until the disappearance of the material on silica gel TLC monitoring. After evaporating of the solvent, the residual syrup was purified by column chromatography (EtOAc/hexane) to give **7** (3.07 g, 97.0%) as a pale yellow oil.
EIMS: *m/z* = 268(M^+).

4-O-(*N*-Benzyloxycarbonyl-L-valyl)-3-hydroxy-4,6-dimethyl-2-(*dl*-2-methylbutanoyl)-5-methoxy-(4*R*- and 4*S*)cyclohexa-2,5-dien-1-one (8a and 8b):
To a solution of **7** (9.47 mmol, 2.54 g) and *N*-Cbz-L-valine (10.4 mmol, 3.54 g) in anhyd CH_2Cl_2 (3 mL) DCC (13.46 mmol, 2.78 g) and DMAP (1.28 mmol, 156 mg) were added in an ice bath under Ar. After stirring at r.t. for 5h, EtOAc (10 mL) was added to the mixture and then the precipitates were filtered through a pad of Celite. The filtrate was evaporated and separated by column chromatography (toluene/EtOAc/HOAc) to give **8a** (2.26 g, 47.6%) and **8b** (2.31 g, 48.8%) as a colorless syrup, $[\alpha]_D^{22}$ –231 (*c* = 1.24, $CHCl_3$).

8a: FABMS : *m/z* = 502(M^++H).
IR (neat): ν = 3344, 2968, 1716, 1531, 1456 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 0.86–1.19 (12H, m, CH_3 × 4), 1.39 (1H, m, CH_2CH_3), 1.69 (3H, each s, CH_3), 1.71 (1H, m, CH_2CH_3), 1.95 (3H, s, CH_3), 2.41 (lH, m, $CH(CH_3)_2$), 3.74 (lH, m, $CH(CH_3)CH_2CH_3$), 3.86 (3H, each s, CH_3), 4.40 (1H, dd, *J*=3.9 and 9.3Hz, >CHNH), 5.08 (2H, s, CH_2Ph), 7.33 (5H, m, ArH), 19.27 and 19.26 (1H, each s, chelated OH).

8b: $[\alpha]_D^{22}$ +l28 (*c* = 1.59, $CHCl_3$).
FABMS: *m/z* = 502(M^++H).
IR (neat): ν = 3340, 2968, 1716, 1527, 1456 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 0.86–l.19 (12H, m, CH_3 × 4), 1.42 (1H, m, CH_2CH_3), 1.55 and 1.56 (3H, each s, CH_3), 1.72 (1H, m, CH_2CH_3), 1.97 (3H, s, CH_3), 2.26 (1H, m, $CH(CH_3)_2$), 3.78 (1H, m, $CH(CH_3)CH_2CH_3$), 4.35 (1H, dd, *J*=3.9 and 9.3Hz, >CHNH), 5.12 (2H, s, CH_2Ph), 7.26 (5H, m, ArH), 19.25 and 19.26 (1H, each s, chelated OH).

3,4-Dihydroxy-4,6-dimethyl-5-methoxy-2-(*dl*-2-methylbutanoyl)-(4*R*- and 4*S*)-cyclohexa-2,5-dien-1-one (9a and 9b):
To a stirred solution of **8a** (4.107 mmol, 2.058 g) in anhyd MeOH (5 mL) 28% NaOMe (13 mmol, 2.51 g) was added and then stirred at r.t. under Ar for 2h. The mixture was poured into the ice cold 2M HCl solution (30 mL) and extracted with EtOAc (2 × 20 mL). The combined extracts were washed with brine and dried (Na_2SO_4) and then evaporated. The residual syrup was purified by column chromatography (EtOAc/hexane) to give **9a** (0.814 g, 74.0%) as a colorless syrup. **9b** (0.812 g, 73.8%).
EI MS: *m/z* = 268(M^+). **9a**; $[\alpha]_D^{23}$ –5.07 (*c* = 1.10, $CHCl_3$), **9b**; $[\alpha]_D^{22}$ +4.38 (*c* = 1.09, $CHCl_3$).

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4,5-Dimethyl-5-methoxy-(4*R* and 4*S*)-4-(2-methylbutyryloxy)cyclohex-5-ene-1,3-dione (10a and 10b):
Compound **9a** or **9b** (3.32 mmol, 890 mg) was added to a mixture of a 5% Na_2CO_3 aqueous solution (21 mL) and MeOH (1.6 mL), and the mixture was then refluxed for 1h. The mixture was cooled and poured into an ice cold 1M HCl solution and then extracted with EtOAc (2 × 20 mL). The combined extracts were washed with brine and dried (Na_2SO_4), then evaporated. The residual syrup was purified by column chromatography (EtOAc/hexane) to give **10a** (800 mg, 90%) as a colorless prisms and recovered **9a** (22 mg, 2.5%). **10b** (90%), **9b** (2.4%).

10a: HPLC: retention time (R_t) = 17.6 and 18.6 min (1:1). $[\alpha]_D^{23}$ –180 (c = 0.96, $CHCl_3$).
10b: colorless prisms. mp 122 °C.

HPLC: Rt = 17.4 and 18.2 min (1:1). $[\alpha]_D^{23}$ +155 (c = 1.09, $CHCl_3$).
EIMS: *m/z* = 268(M^+).
^{1}H NMR (DMSO-d_6): δ = 0.89 (3H, t, J=7.4Hz, CH_2CH_3), 1.06 and 1.08 (3H, each d (1:1.2), J = 6.9 Hz, $CHCH_3$), 1.36–1.65 (2H, m, CH_2), 1.76 and 1.77 (3H, each s (1:1.2), CH_3), 2.40 (1H, m, >CH), 3.74 and 3.75 (3H, each s (1:1.2), OCH_3), 5.32 (1H, s, olefinic H).
Anal. ($C_{11}H_{14}O_5$): Calc. C, 62.67; H, 7.51. Found C, 62.40; H, 7.63.

3,5-Dimethoxy-4,6-dimethyl-(6*R*)-6-[(2*R*)-2-methylbutyryloxy]-cyclohexa-2,4-dien-1-one (11b): and 2,4-Dimethyl-3,5-dimethoxy-(4*S*)-4-[(2*R* and 2*S*)-2-methylbutyryloxy]cyclohexa-2,5-diene-1-one (12b, 12b*):
To a solution of **9b** (2.63 mmol, 705 mg) in EtOAc a solution of diazomethane in Et_2O was added dropwise in an ice bath until the disappearance of the material on silica gel TLC monitoring. After evaporating of the solvent, the residual syrup was purified by column chromatography (EtOAc/hexane = 1:2) to give **11b** (236 mg, 31.8%) as a pale yellow oil and **12b** (354 mg, 47.7%) as colorless prisms.

11b: (The first eluate on HPLC: R_t = 14.1 min): pale yellow oil. $[\alpha]_D^{23}$ +65.3 (c = 2.10, $CHCl_3$), (natural **11b**: +65.1, lit.[1b–d] +63.6).
EIMS: *m/z* = 282(M^+).
UV(EtOH): λ_{max}(logε) = 215(4.20), 319(3.54) nm.
^{1}H NMR ($CDCl_3$): δ = 0.979 (3H, t, J=7.4 Hz, CH_2CH_3), 1.166 (3H, d, J=7.1Hz, $CHCH_3$), 1.505 (3H, s, CH_3), 1.496 and 1.753 (each 1H, m, CH_2), 1.861 (3H, s, CH_3), 2.482 (1H, m, >CH), 3.764 (3H, s, OCH_3), 3.794 (3H, s, OCH_3), 5.446 (1H, s, olefinic H).
^{13}C NMR($CDCl_3$): δ = 195.40(s), 175.52(s), 172.70(s), 163.24(s), 112.68(s), 95.99(d), 79.16(s), 61.22(q), 56.20(q), 40.00(d), 26.56(t), 23.97(q), 16.28(q), 11.26(q), 9.48(q).
HRMS: *m/z* = calc. for $C_{15}H_{22}O_5$ 282.1467, found 282.1465.

3,5-Dimethoxy-4,6-dimethyl-(6*R*)-6-[(2*S*)-2-methylbutyryloxy]-cyclohexa-2,4-dien-1-one (11b*):
(The latter eluate on HPLC: R_t = 15.7 min). pale yellow oil. $[\alpha]_D^{23}$ +79.5 (c = 1.22, $CHCl_3$).
^{1}H NMR($CDCl_3$): δ = 0.960 (3H, t, J=7.4 Hz, CH_2CH_3), 1.476 (3H, d, J=7.1Hz, $CHCH_3$), 1.507 (3H, s, CH_3), 1.476 and 1.758 (each 1H, m, CH_2), 1.863 (3H, s, CH_3), 2.456 (1H, m, >CH), 3.775 (3H, s, OCH_3), 3.792 (3H, s, OCH_3), 5.446 (1H, s, olefinic H).
^{13}C NMR($CDCl_3$): δ = 195.54(s), 175.47(s), 172.89(s), 163.45(s), 112.53(s), 96.04(d), 79.16(s), 61.32(q), 56.28(q), 40.47(d), 26.43(t), 24.11(q), 16.39(q), 11.62(q), 9.58(q).

12b: (The first eluate on HPLC: R_t – 16.5 min): $[\alpha]_D^{22}$ +36.3 (c = 1.19, $CHCl_3$). Colorless prisms. mp 37–39 °C.
EIMS: *m/z* = 282(M^+).
UV(EtOH): λ_{max}(logε) = 203(3.92), 249(4.23), 291(3.64) nm.
IR(KBr): ν = 2968, 2941, 1739, 1666, 1622, 1456, 1375, 1361, 1232 cm^{-1}.
^{1}H NMR($CDCl_3$): δ = 0.942 (3H, t, J=7.3 Hz, CH_3), 1.066 (3H, d, J=9.4Hz), 1.450 (1H, m, CH_2), 1.613 (3H, s, CH_3), 1.713 (1H, m, CH_2), 1.916 (3H, s, CH_3), 2.396 (1H, m, >CH), 3.705 (3H, s, OCH_3), 3.850 (3H, s, OCH_3), 5.530 (1H, s, olefinic H).
^{13}C NMR($CDCl_3$): δ = 187.60, 174.84, 170.97, 167.13, 116.90, 100.45, 75.17, 61.40, 56.04, 41.00, 26.43, 25.36, 16.79, 11.62, 9.55.
Anal. ($C_{15}H_{22}O_5$): Calc. C, 63.8l; H, 7.85. Found C, 63.51; H, 7.77.
12b* (The latter eluate on HPLC: R_t = 17.3 min): $[\alpha]_D^{22}$ +69.5 (c = 1.05, $CHCl_3$).
^{1}H NMR ($CDCl_3$): δ = 0.930 (3H, t, J=7.4 Hz, CH_3), 1.149 (3H, d, J=7.1Hz), 1.483 (1H, m, CH_2), 1.614 (3H, s, CH_3), 1.688 (1H, m, CH_2), 1.911 (3H, s, CH_3), 2.438 (1H, m, >CH), 3.702 (3H, s, OCH_3), 3.839 (3H, s, OCH_3), 5.529 (1H, s, olefinic H).
^{13}C NMR($CDCl_3$): δ = 187.57, 175.00, 171.02, 167.04, 117.14, 100.39, 75.23, 61.38, 55.96, 40.56, 26.65, 25.33, 16.56, 11.28, 9.51.

Wasabidienone A: 5-Hydroxy-3-methoxy-4,6-dimethyl-(6*R*)-[(2*R*)-2-methylbutyryloxy]cyclohexa-2,4-dien-1-one (1a) and 5-Hydroxy-3-methoxy-2,6-dimethyl-(6*S*)-[(2*R*)-2-methylbutyryloxy]-cyclohexa-2,4-dien-1-one (1b):
To a stirred solution of the chiral first eluate of **11b** (127 mg, 0.45 mmol) and EtSH (365 μL, 4.95 mmol) in CH_2Cl_2 (2 mL), $AlCl_3$ (540 mg, 4.05 mmol) was added at 0°C under Ar and the mixture was stirred for 18 h at r.t. The mixture was poured into an ice 1M HCl mixture and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine and dried (Na_2SO_4), and then evaporated. The residue was purified by column chromatography (hexane/EtOAc = 2:1) to give WA (84 mg, 69%) as a pale yellow oil.
EIMS: *m/z* = 268(M^+).
IR(neat): ν = 3450–3200, 2972, 2939, 2879, 1732, 1668, 1614 cm^{-1}, natural WA : lit.[1b–d] (CCl_4) : ν = 3450–3200, 1735, 1675, 1620 cm^{-1}.

3,5-Dimethoxy-2,6-dimethyl-(6*R*)-6-[(2*R*)-2-methylbutyryloxy]-cyclohexa-2,4-dien-1-one (13):
A diazomethane treatment of the WA and a subsequent purification were carried out in a same manner as the synthesis of **11b** and **12b**, pale yellow crystals, $[\alpha]_D^{24}$ +93 (c = 0.27, $CHCl_3$), natural : lit.[1b–d] +140 (c = 2.0).
HPLC: R_t = 11.3 min.
EIMS: *m/z* = 282(M^+).
UV(EtOH): λ_{max}(logε) = 221(4.16), 366(3.55) nm.
IR(neat): ν = 2968, 2937, 1734, 1653, 1637, 1558, 1373, 1217, 1091 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 0.923 (3H, t, J= 7.4 Hz, CH_3), 1.15 (3H, d, J=7.1Hz), 1.49 (3H, s, CH_3), 1.50 and 1.69 (each 1H, m, CH_2), 1.78 (3H, s, CH_3), 2.48 (1H, m, >CH), 3.74 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 5.48 (1H, s, olefinic H).
^{13}C NMR($CDCl_3$): δ = 194.6(s), 175.2(s), 169.2(s), 167.8(s), 106.8(s), 86.1(d), 77.9(s), 55.9(q), 55.8(q), 40.1(d), 26.7(t), 24.9(q), 16.4(q), 11.3(q), 7.3(q).
HRMS: calc. for $C_{15}H_{22}O_5$ 282.1467, found 282.1472.

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