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Convenient Syntheses of Optically Active Abscisic Acid and Xanthoxin

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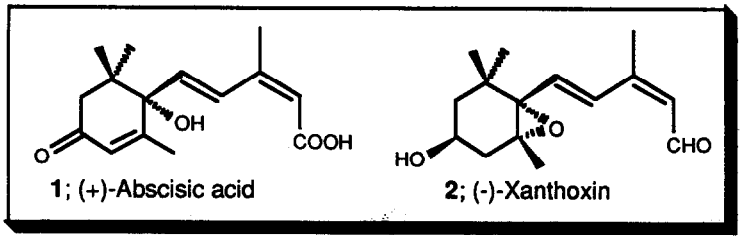
Abstract: *The Reformatsky reaction of 3-(bromomethyl)crotonate with an optically active epoxycyclohexane aldehyde derivative (3), followed by dehydration, gave the chiral dienoic acid (6)stereospecifically. The product was derived to optically active abscisic acid (1) and xanthoxin (2) successfully.*

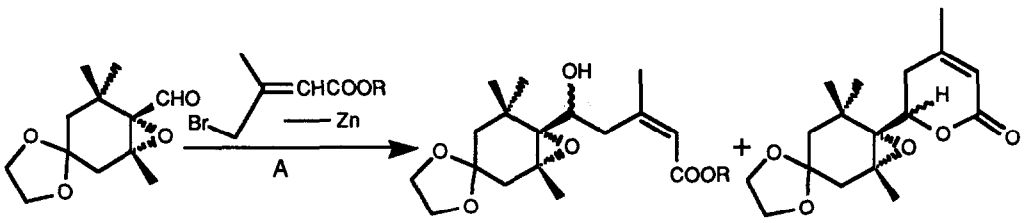
Although, abscisic acid (**1**) (ABA) was recognized to have important activities as a plant hormone,[1] the agricultural application was not yet developped.[2] The poor availability of **1** was claimed as one of plausible reasons. Moreover, xanthoxin (**2**),[3] which has analogous hormonal activities in a plant and was shown to be a precursor of abscisic acid (ABA) in a plant,[4] was hard to obtain. The structural characteristic of both **1** and **2** is to have a side chain with (2Z,4E)-diene structure, of which the isomerization to (2E,4E)-configuration means the loss of its hormonal activity.[1]



1; (+)-Abscisic acid **2**; (-)-Xanthoxin

In a series of synthetic works of abscisic acid (**1**),[5-7] the stereospecific formation of (2Z,4E)-diene structure of the side chain has been the principal matter. For one of the purpose, the Reformatsky reaction method was used conveniently for the stereospecific formation of the (2Z,4E)-diene system as shown by Gedye[8] Constantino[5f] or Kienzle.[6e] Although the (2Z,4E)- side chain was constructed with a high stereospecificity from 3-(halomethyl)crotonate with cyclohexenealdehyde structure, the reaction had not been applied to the epoxy aldehyde derivative such as **3**, because the Reformatsky reaction was known to react with

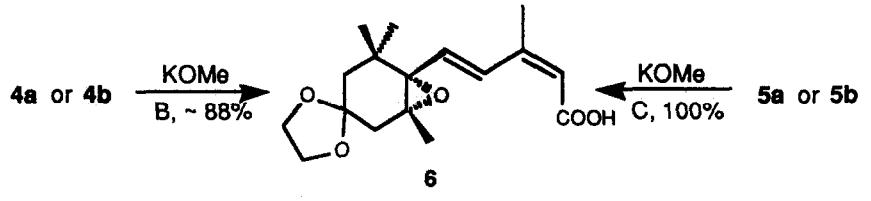
cyclic ring epoxides principally to give ring contruction products.[9] On the other hand, when the well-known Wittig-Horner reaction was applied to the epoxy aldehyde such as **3**, the stereospecificity was lost to give (2E,4E)-isomer as the major product.[10,6f] However, we considered that the sterically crowded circumstance around the epoxide ring of the epoxy aldehyde (**3**), in which all positions were substituted with bulky groups, should require severe conditions to contribute reactions at the epoxide ring for its steric hindrance. Thus Reformatsky conditions should react at the aldehyde group without disturbing the epoxy ring. We here report the synthesis of optically active ABA (**1**) and xanthoxin (**2**) employing the stereoselective formation of (2Z,3E)-side cahin by the Reformatsky reaction to the optically active epoxide (**3**) as a key step.



(+)-**3** R = **Me** **4a** + **4b** 19% + trace **5a** + **5b** 18% + 28%
R = **Et** **4a** + **4b** 22% + 5% **5a** + **5b** 12% + 17%

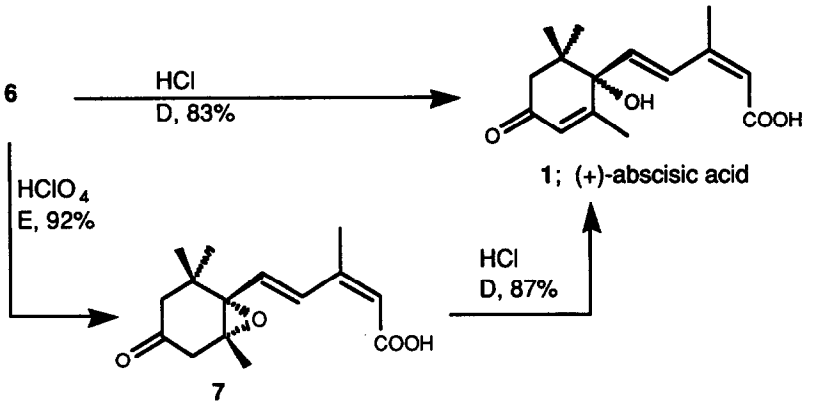
A, 2eqiv $BrCH_2(CH_3)C{=}CHCOOR$, 4eqiv Zn powder, I_2 cat / THF, rt, 30min

The preparation of optically active (+)-**3** was known to be obtainable easily starting from mesityl oxide and ethyl acetoacetate[11] in five steps *via* chiral induction by the Sharpless epoxidation.[6f] The key reaction of the epoxy aldehyde (**3**) with 3-(bromomethyl)crotonates (E : Z = 1 : 1, R = Me or Et) in the presence of zinc powder under the usual conditions[12] gave a mixture of four products and they were isolated by column chromatography. They were identified as two hydroxy esters (**4a** and **4b**), and cyclized lactones (**5a** and **5b**) without further assignment of the configuration of hydroxy groups in (**4a** and **4b**) and the oxygens in lactone ring in (**5a** and **5b**). The lactones (**5a** and **5b**) were already isolated in racemic forms[5f] as the intermediates in the synthesis of (±)-ABA by Constantino.[5f] The hydroxy esters (**4a** and **4b**) were assigned for the first time as intermediates in the synthesis of ABA. All of these four intermediates gave the single diene product (**6**) by a treatment with alkoxide in high yields, respectively.



B, 2.5eqiv KOMe / MeOH, 60°C, 2h: C, 2.5eqiv KOMe / MeOH, rt, 18h

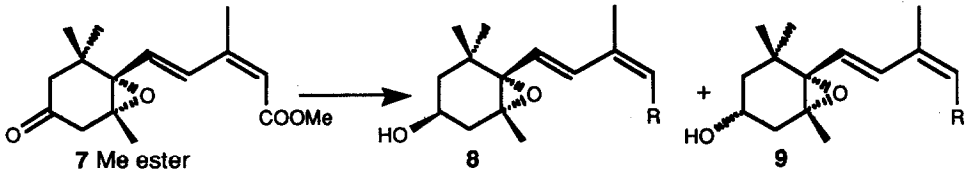
For the synthetic purpose, separation of the reaction products was not neccessary and the treatment of the mixture (**4a, 4b, 5a,** and **5b**) with methoxide gave the diene (**6**) in 92% yield also. The stereochemistry of the side chain in **6** was confirmed by NOE measurement between 3-methyl group and 2-olefinic proton and by the coupling constant between 4- and 5-olefinic protons (J = 16.0 Hz) to be (2Z,4E) configuration.



D, 0.2M HCl / MeOH-H $_2$O (4:1), rt, 18h: E, 10% $HClO_4$ / THF-H_2O (1:1) ice-cooled, 2min

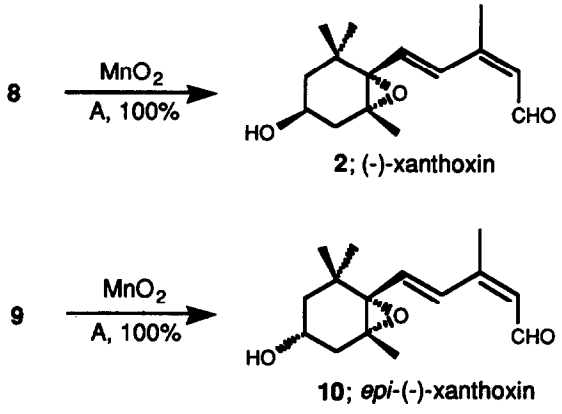
The conversion of the diene (**6**) to (+)-ABA (**1**) was performed in one-pot conveniently by treatment with a dilute hydrochloric acid to do deacetalization followed by the spontaneous enone formation by epoxy ring opening in high efficiency. For the synthesis of the optically acive ABA, the route would be a practically useful method to be able to obtain (+)-ABA in oveall up to 43% yield in three steps from the epoxide (**3**). It is also possible to afford antipodal (-)-ABA by choosing the enantiomer of the epoxy aldehyde, (-)-**3**, at the stage of Sharpless epoxidation. The control of the acid treatment conditions using dilute perchloric acid[11b] gave the deaceatalized product (**7**) exclusively in 92% yield and gave (+)-ABA also by a following treatment with dilute hydrochloric acid. The product (**7**), relatively stable under neutral conditions, was used as an intermediate for the synthesis of optically active xanthoxin (**2**).

Table 1



	reaction conditions	R in **8** and **9**	**8** / **9** ratio	yield, %
1	$LiAlH_4$, THF, -25 C	R = CH_2OH	49 : 51	94
2	DIBAL, toluene, -78 C	R = CH_2OH	56 : 44	70
3	$NaBH_4$, THF, -78 C	R = COOMe	36 : 64	67
4	$NaBH_4$, THF, -78 C	R = COOMe	29 : 71	75
5	K-Selectride, THF, -78 C	R = COOMe	77 : 23	54
6	L- Selectride, THF, -78 C	R = COOMe	82 : 18	30

Reduction of the ring carbonyl group to hydroxy group was examined under several conditions as summarized in Table 1. The lithium aluminum hydride and diisobutylaluminum hydride did not revealed the stereoselectivity, sodium borohydride-ceric chloride system gave an α-OH rich product and K- or L-Selectride^R provided β-OH rich product even in low yields. In the case of sodium borohydride-ceric chloride system, the formation of α-OH by the attack of the hydride from the crowded β-side is estimated that the bulky ceric chloride coordinate to the ring carbonyl from the less hindered α-side and hydride had to attack from the hindered β-side. The attack of the bulky Selectrides^R favored from the α-side to give β-OH product with even low yields as estimated to be decomposed by a high basicity of the reagents. The diols were separable as the diacetates. The stereochemical assignment of ring OH group in **8** and **9** was confirmed by the NOE observation of the diacetate derived from **9** between the methyl group at C-2 positiona and the proton at OAc group attached carbon and no measurement of the NOE of the diacetate derived from **8** The β-OH isomer and α-OH isomer were derived to (-)-xanthoxin (**2**) and epi-(-)-xanthoxin (**10**) by the treatment with MnO_2.



Experimental

General procedure

Melting points were determined with a YANACO MP-3 micro melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded with a JASCO A-202 instrument. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz with a Bruker AM-400 spectrometer, using $CDCl_3$ as solvent. Chemical shifts are recorded in δ value using TMS as internal standard and coupling constants are given in Hz. Low resolution mass spectra were obtained with a Hitachi RMU-6MG instrument and high resolution mass spectra were measured with a Hitachi M-80A mass spectrometer. Optical rotation were measured with a Horiba SEPA-200 automatic digital polarimeter. Enantiomeric excess was obtained by HPLC using a DAICEL CHIRALCEL OD column.

4,4-Ethylenedioxy-2,6,6-trimethyl-1,2-oxocyclohexanmethanol[6f]

In a stirred mixture of diethyl D-(-)-tartrate (39 μL, 15 mol%), titanium (IV) isopropoxide (43 μL, 10 mol%), and powdered Molecular Sieves^R 3A (80 mg) in dichloromethane (8.0 mL) under an argon atmosphere, added

2.4M solution of *tert*-butyl hydroperoxide (378 μL, 1.63 mmol) in isooctane slowly at -20°C. After 45 min, added 4,4-ethylenedioxy-2,6,6-trimethyl-1-cyclohexenmethanol (314 mg, 1.48 mmol) in dichloromethane (0.5 mL) and stirred at the same temperature for 1 h. The solution was treated with water (0.9 mL) and then 10% sodium hydroxide in saturated brine (1.5 mL) by stirring for 1 h, followed by extraction with dichloromethane, washing the organic layer with water and drying over sodium sulfate. The crude product (351 mg) after removal of the solvent was purified by column chromatography on silica gel to give pure 4,4-ethylenedioxy-2,6,6-trimethyl-1,2-oxocyclohexanemethanol (252 mg, 75% yield) as an oil with 90% ee as estimated by NMR in the presence of Eu(tfc)3 shift reagent: ^{1}H NMR δ 1.09 (s, 3 H), 1.17 (s, 3 H), 1.32 (dd, 1 H, J = 2.3, 13.8 Hz), 1.41 (s, 3 H), 1.63 (d, 1 H, J = 13.8 Hz), 1.87 (t, 1 H, J = 3.1 Hz), 2.00 (dd, 1 H, J = 2.3, 15.6 Hz), 2.25 (d, 1 H, J = 15.6 Hz), 3.71 (dd, 1 H, J = 4.9, 11.3 Hz), 3.77 - 3.81 (m, 5 H); MS m/z 229 (M^+ + 1), 213 (M^+ - CH_3); HRMS m/z calcd. for $C_{11}H_{17}O_4$ (M^+ - CH_3) 213.1126, found 213.1147; $[\alpha]_D$ + 19.5° (c 0.84, $CHCl_3$). (lit.,[6f] +22.9° (c 0.8, $CHCl_3$)).

4,4-Ethylenedioxy-1,2-oxo-2,6,6-trimethylcyclohexanecarboxaldehyde (3)

Oxalyl chloride (140 μL, 1.59 mmol) and dimethyl sulfoxide (225 μL, 3.13 mmol) were mixed in dichloromethane (7 mL) under an argon atmosphere at 0°C. To this was added 4,4-ethylenedioxy-1,2-oxo-2,6,6-trimethylcyclohexanemethanol (329 mg, 1.44 mmol) in dichlormethane (2 mL) slowly. After 20 min, added triethylamine (1.5 mL, 10.8 mmol) and stirred at the same temperature for 10 min. Added water and the mixture was extracted with dichloromethane, and the organic layer was washed with water and dried over sodium sulfate. By removal of the solvent **3** was obtained purely (322 mg, 99% yield) as an oil: ^{1}H NMR δ 1.08 (s, 3 H), 1.31 (s, 3 H), 1.32 (dd, 1 H, J = 1.9, 13.8 Hz), 1.46 (s, 3 H), 1.71 (d, 1 H, J = 13.8 Hz), 2.09 (dd, 1 H, J = 1.9, 15.8 Hz), 2.30 (d, 1 H, J = 15.8 Hz), 3.82 - 3.90 (m, 2H), 3.91 - 3.95 (m, 2H), 9.78 (s, 1H); MS m/z 226 (M^+), 211 (M^+ - CH_3) 197 (M^+ - CHO); HRMS m/z calcd. for $C_{12}H_{18}O_4$ 226.1206, found 226.1200; [α]$_D$ -56.7° (c 0.98, $CHCl_3$) (lit.,[6f] -57°, (c 0.86, $CHCl_3$)).

4,4-Ethylenedioxy-1-(4-alkoxycarbonyl-1-hydroxy-3-methyl-3-buten-1-yl)-1,2-oxo-2,6,6-trimethylcyclohexanes (4a, b) and 4,4-ethylenedioxy-1-(5,6-dihydro-2H-4-methyl-2-oxopyran-6-yl)-1,2-oxo-2,6,6-trimethylcyclohexanes (5a, b)

To a mixture of activated zinc powder (200 mg, 4.0 equiv), iodine (10 mg) in tetrahydrofuran (1.5 mL) under an argon atmosphere at 0°C, added 3-(bromomethyl)crotonic acid methyl ester (E : Z = 4 : 5) (313 mg, 1.58 mmol). After 10 min, the aldehyde **3** (178 mg, 0.79 mmol) in tetrahydrofuran (1.5 mL) was added slowly and stirred for 30 min. The solution was treated first with saturated ammonium chloride (5 mL) and then extracted with ether, and the organic layer was washed with saturated brine and dried over sodium sulfate. The crude product mixture (303 mg) was separated by column chromatography on silica gel (hexane / ethyl acetate = 6 / 1) to give a mixture of **4a** and **4b** (as methyl esters) (51 mg, 19%), lactone **5a**[5f] (44 mg, 18%), and lactone **5b**[5f] (68 mg, 28%). Under the same reaction conditions starting from 3-(bromomethyl)crotonic acid ethyl ester (E / Z = 1 / 1) (106 mg, 1.62 mmol) and **3** (136 mg, 0.6 mmol), a mixture of **4a** (ethyl ester) (46 mg, 22%), **4b** (ethyl ester) (11 mg, 5%), **5a** (22mg, 12%), and **5b** (31 mg, 17%) was obtained: **4a** (methyl ester) (oil) ^{1}H NMR δ 1.08 (s, 3 H), 1.20 (s, 3 H), 1.31 (dd, 1 H, J = 2.5, 14.0 Hz), 1.52 (s, 3 H), 1.60 (d, 1 H, J = 14.0 Hz), 1.97 (d, 1 H, J = 16.0 Hz), 2.19 (dd, 1 H, J = 2.5, 16.0 Hz), 2.28 (d, 3 H, J = 1.3 Hz), 2.41 - 2.51 (m, 2 H), 2.59 (s, 1 H), 3.69 (s, 3 H), 3.82 - 3.94 (m, 4 H), 4.25 (m, 1 H), 5.80 (dd, 1 H, J = 1.1, 2.4 Hz); MS m/z 341 (M^+ + 1), 339 (M^+ - 1), 325 (M^+ - CH_3), 309 (M^+ - OCH_3); HRMS calcd. for $C_{17}H_{25}O_6$ ((M^+ - 325.1650, found 325.1658; $[\alpha]_D$ +35.7° (c 0.83, $CHCl_3$): **4a** (ethyl ester) (oil) ^{1}H NMR δ 1.09 (s, 3 H), 1.21

(s, 3 H), 1.28 (t, 3 H, J = 7.1 Hz), 1.31 (dd, 1 H, J = 2.4, 14.0 Hz), 1.52 (s, 3 H), 1.61 (d, 1 H, J = 14.0 Hz), 1.97 (dd, 1 H, J = 2.4, 16.0 Hz), 2.19 (d, 1 H, J = 16.0 Hz), 2.27 (d, 3 H, J = 1.3 Hz), 2.40 - 2.50 (m, 2 H), 2.60 (bs, 1 H), 3.87 - 3.96 (m, 4 H), 4.15 (q, 2 H, J = 7.1 Hz), 4.27 (m, 1 H), 5.79 (m, 1 H); $[\alpha]_D$ +33.7° (c 0.52, $CHCl_3$): **4b** (ethyl ester) (oil) ^1H NMR δ 1.05 (s, 3 H), 1.28 (t, 3 H, J = 7.1 Hz), 1.33 (s, 3 H), 1.47 (s, 3 H), 1.65 (d, 1 H, J = 14.0 Hz), 2.03 (dd, 1 H, J = 2.1, 16.0 Hz), 2.20 (d, 1 H, J = 16.0 Hz), 2.23 (d, 3 H, J = 1.2 Hz), 2.33 (d, 2 H, J = 6.5 Hz), 3.81 - 3.95 (m, 4 H), 4.15 (q, 2 H, J = 7.1 Hz), 4.40 (t, 1 H, J = 6.5 Hz), 5.76 (d, 1 H, J = 1.2 Hz); $[\alpha]_D$ - 5.6° (c 1.00, $CHCl_3$): **5a** mp 157.5 - 161.0°C (lit.,[5f] racemic 163 - 164°C); ^1H NMR δ 1.00 (s, 3 H), 1.30 (dd, 1 H, J = 2.0, 14.0 Hz), 1.31 (s, 3 H), 1.42 (s, 3 H), 1.67 (d, 1 H, J = 14.0 Hz), 1.99 (dd, 1 H, J = 4.7, 19.0 Hz), 1.99 (s, 3 H), 2.07 (dd, 1 H, J = 2.0, 16.0 Hz), 2.21 (d, 1 H, J = 16.0 Hz), 2.62 (ddd, 1 H, J = 1.2, 14.0, 19.0 Hz), 3.78 - 3.96 (m, 4 H), 5.04 (dd, 1 H, J = 4.7, 14.0 Hz), 5.79 (d, 1 H, J = 1.2 Hz); MS m/z 308 (M^+), 293 (M^+ - CH_3); HRMS calcd. for $C_{17}H_{24}O_5$ 308.1622, found 308.1632; $[\alpha]_D$ - 57.9° (c 1.02, $CHCl_3$): **5b** (amorphous) (lit.,[5f] racemic mp 96 - 98°C); ^1H NMR δ 1.21 (s, 3 H), 1.34 (dd, 1 H, J = 1.6, 14.0 Hz), 1.35 (s, 3 H), 1.44 (s, 3 H), 1.69 (d, 1 H, J = 14.0 Hz), 2.02 (t, 3 H, J = 1.2 Hz), 2.10 (dd, 1 H, J = 1.6, 16.0 Hz), 2.24 (d, 1 H, J = 16.0 Hz), 2.36 (dd, 1 H, J = 3.7, 18.0 Hz), 2.87 (ddd, 1 H, J = 1.4, 14.0, 18.0 Hz), 3.83 - 3.93 (m 4 H), 4.52 (dd, 1 H, J = 3.7, 14.0 Hz), 5.81 (dd, 1 H, J = 1.4, 2.3 Hz); MS m/z 308 (M^+), 293 (M^+ - CH_3); HRMS calcd. for $C_{17}H_{24}O_5$ 308.1622, found 308.1624; $[\alpha]_D$ +52.3° (c 0.99, $CHCl_3$).

4,4-Ethylenedioxy-1-(4-carboxyl-3-methyl-1,3-butadien-1-yl)-1,2-oxo-2,6,6-trimethylcyclohexane (6) from 4a

Added **4a** (ethyl ester) (146 mg, 0.411 mmol) in absolute methanol (8 mL) to a solution of pottasium methoxide (75 mg, 1.3 mmol) in methanol (2 mL) under an argon atmosphere. Heated at 60°C for 2 h, then added saturated ammonium chloride solution, extracted with ether, and the organic layer was washed with saturated brine. The solvent was removed after drying over sodium sulfate to give **6** (111 mg, 88% yield). It was purified by recrystallization from chloroform: mp 171-172°C; ^1H NMR δ 1.00 (s, 3H), 1.21 (s, 3H), 1.25 (s, 3H), 1.35 (dd, 1H, J = 2.0, 13.7 Hz), 1.74 (d, 1H, J = 13.7 Hz), 2.05 (d, 3H, J = 1.2 Hz), 2.05 (dd, 1H, J = 2.0, 15.7 Hz), 2.28 (d, 1H, J = 15.7 Hz), 3.82 - 3.96 (m, 4H), 5.72 (d, 1H, J = 1.2 Hz), 6.34 (dd, 1H, J = 0.6, 16.0 Hz), 7.63 (dd, 1H, J = 0.6, 16.0 Hz); MS m/z 308 (M^+), 222 (M^+ - $C_4H_6O_2$), 207 (M^+ - $C_4H_6O_2$ - CH_3); HRMS m/z calcd. for $C_{17}H_{24}O_5$ 308.1622, found 308.1636; $[\alpha]_D$ +19.9° (c 1.01, $CHCl_3$); **6** gave methyl ester quantitatively by a treatment with diazomethane: **6** methyl ester (oil) ^1H NMR δ 1.00 (s, 3H), 1.22 (s, 3H), 1.25 (s, 3H), 1.34 (dd, 1H, J = 2.2, 13.7 Hz), 1.74 (d, 1H, J = 13.7 Hz), 2.01 (s, 3H) 2.04 (dd, 1H, J = 2.2, 15.7 Hz), 2.28 (d, 1H, J = 15.7 Hz), 3.70 (s, 3H), 3.82 - 3.95 (m, 4H), 5.72 (bs, 1H), 6.28 (d, 1H, J = 16.0), 7.62 (d, 1H, J = 16.0 Hz); MS m/z 322 (M^+), 291 (M^+ - OCH_3), 263 (M^+ - $COOCH_3$), 236 (M^+ - $C_4H_6O_2$); HRMS calcd. for $C_{18}H_{26}O_5$ 322.1779, found 322.1773.; $[\alpha]_D$ +52.9° (c 0.84, $CHCl_3$)

6 from 4b (ethyl ester)

From **4b** (ethyl ester) (27 mg, 0.076 mmol) and pottasium methoxide (11 mg, 0.19 mmol), **6** (21 mg, 90% yield) was obtained by the treatment as shown above.

6 from 5a

To a solution of pottasium methoxide (11 mg, 0 19 mmol) in absolute methanol (4.0 mL) under an argon atmosphere added **5a** (22 mg, 0.071 mmol) in methanol (1.0 mL) at room temperature and stirred at the same

temperature for 18 h. The reaction mixture was extracted with ether after addition of saturated ammonium chloride solution, and the organic layer was washed with saturated brine and dried over sodium sulfate. By removal of the solvent **6** (22 mg, 100% yield) was obtained.

6 from 5b

From **5b** (25 mg, 0.081 mmol) and pottasium methoxide (12 mg, 0.20 mmol), **6** (24 mg, quantitative yield) was obtained by the treatment as shown above.

6 from a mixture of 4a, 4b, 5a, and 5b (methyl ester)

A mixture of the Reformatsky reaction product (765 mg) in absolute methanol (10 mL) was treated with pottasium methoxide (716 mg, 12.3 mmol) as shown above heating at 60°C for 2 h, to give **6** (688 mg, 92% yield).

(+)-Abscisic acid (1) from 6

A solution of **6** (525 mg, 1.70 mmol) in methanol (16 mL) was treated with 1M hydrochloric acid (3.6 mL) at room temperature for 19 h. Added saturated brine, extracted with dichloromethane, and the organic layer was washed with water and dried over sodium sulfate. From the crude product after removal of the solvent, **1** was purely obtained by recrystallization from hexane - chloroform (372 mg, 83% yield) with 97% ee as determined by HPLC (DAICEL CHIRALCEL OD 25 x 0.46 cm; hexane :i-propanol = 9 : 1, 0.5 mL/min; (+)-ABA 13.0 min, (-)-ABA 20.9 min) : mp 161.5 - 162.0°C (lit.,[6e] 161 - 163°C); ^{1}H NMR δ 1.03 (s, 3H), 1.12 (s, 3H), 1.93 (d, 3H, J = 1.3 Hz), 2.05 (d, 3H, J = 1.2 Hz), 2.30 (d, 1H, J = 17.2 Hz), 2.49 (d, 1H, J = 17.2 Hz), 5.78 (bs, 1H), 5.97 (bs, 1H), 6.18 (d, 1H, J = 16.1 Hz), 7.81 (d, 1H, J = 16.1 Hz); MS m/z 264 (M^+), 246 (M^+ - H_2O), 208 (M^+ - C_4H_8); HRMS m/z calcd. for $C_{15}H_{20}O_4$ 264.1360, found 264.1390; $[\alpha]_D$ +383.7° (c 1.02, EtOH) (lit.,[6e] +411° (c 1, EtOH)).

4-{4-(Carboxy)-3-methyl-1,3-butadien-1-yl}-3,4-oxo-3,5,5-trimethylcyclohexan-1-one (7)

In a perchloric acid solution (0.1 mL) {prepared from 70% perchloric acid (1.7 mL), water (1.3 mL), and tetrahydrofuran (2.0 mL)}, **6** (11 mg) was dissloved at 4°C, and after 2 min the solution was neutralized with saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was washed with water and dried over sodium sulfate. By removal of the solvent under reduced pressure **7** was obtained as an oil (8.7 mg, 92% yield): ^{1}H MNR δ 1.08 (s, 3H), 1.16 (s, 3H), 1.27 (s, 3H), 1.98 (d, 1H, J = 15.4 Hz), 2.20 (d, 3H, J = 1.3 Hz), 2.60 (d, 1H, J = 19.9 Hz), 2.63 (d, 1H, J = 15.4 Hz), 2.87 (d, 1H, J = 19.9 Hz), 5.78 (bs, 1H), 6.32 (d, 1H, J = 16.0 Hz), 7.72 (d, 1H, J = 16.0 Hz); IR (KBr) νmax 3450, 2980, 1718, 1676, 1246 cm^{-1}; MS m/z 264(M^+), 246 (M^+ - H_2O), 231 (246 - CH_3), 207 (M^+ - C_2HO_2),190 (207 - OH),162 (190 - CO); $[\alpha]_D$ +115.8° (c 0.81, $CHCl_3$).

7 methyl ester from 6 methyl ester

It was obtained by the same treatment with perchloric acid as shown above as an oil in 86% yield: ^{1}H NMR δ 1.07 (s, 3H), 1.15 (s, 3H,), 1.27 (s, 3H), 1.97 (d, 1H, J = 15.5 Hz), 2.04 (d, 3H, J = 1.2 Hz), 2.59 (d, 1H, J = 19.9 Hz), 2.63 (d, 1H, J = 15.5 Hz), 2.86 (d, 1H, J = 19.9 Hz), 3.71 (s, 3H), 5.75 (bs, 1H), 6.26 (dd, 1H, J = 0.6, 16.1 Hz), 7.74 (dd, 1H, J = 0.7, 16.1 Hz); MS m/z 278 (M^+), 263 (M^+ - CH_3), 260 (M^+ - H_2O), 246 (M^+ - CH_4O), 236 (M^+ - C_2H_2O), 221 (260 - C_3H_3), 205 (236 - CH_3O); $[\alpha]_D$ +196.4° (c 1.00, $CHCl_3$).

(+)-1 from 7

To a solution of **7** (8.7 mg, 0.033 mmol) in methanol (2.0 mL) added 1M hydrochloric acid (0.5 mL) and stirred 1 h at room temperature. Then, to this was added saturated brine solution, extracted with dichloromethane, and the organic layer was washed with water and dried over sodium sulfate. The crude

product after removal of the solvent was purified by column chromatogaphy on silica gel (hexane / ethyl acetate = 4 / 1) to give (+)-**1** (7.5 mg, 87% yield).

4-Hydroxy-1-{4-substituted-3-methyl-1,3-butadien-1-yl}-1,2-oxo-2,6,6-trimethylcyclohexane (8 and 9)

With lithium aluminum hydride: To a suspension of lithium aluminum hydride (46 mg, 1.2 mmol) in tetrahydrofuran (8 mL) under an argon atmosphere at -25°C, added **7** methyl ester (225 mg, 0.810 mmol) in tetrahydrofuran (2 mL) and stirred for 2 h at room temperature. Added water (46 μL), 15% sodium hydroxide solution (46 μL), and water (138 μL), and filtered off the solid suspension after stirring for 1 h. The organic layer was dried over sodium sulfate and the solvent was removed. The crude product was purified by column chromatography on silica gel (hexane / ethyl acetate = 4 / 1) to give a mixture of **8** and **9** (R = CH_2OH) (192 mg, 94% yield) in a ratio of 49 : 51 as estimated by HPLC. They were separable partially by column chromatography and obtained sufficient amounts of pure samples to measure NMR and MS spectra: **8** (amorphous) (lit.,[6e] mp 88 - 89°C); ^1H NMR δ 0.98 (s, 3H), 1.14 (s, 3H), 1.19 (s, 3H), 1.24 - 1.27 (m, 2H), 1.60 - 1.66 (m, 1H), 1.87 (d, 3H, J = 1.0 Hz), 2.38 (ddd, 1H, J = 1.8, 5.1, 14.2 Hz), 3.87 - 3.94 (m, 1H), 4.29 - 4.34 (m, 2H), 5.57 (t, 1H, J = 6.8 Hz), 5.96 (d, 1H, J = 15.5 Hz), 6.56 (dd, 1H, J = 0.6, 15.5 Hz); MS m/z 252 (M^+); HRMS m/z calcd. for $C_{15}H_{24}O_3$ 252.1724, found 252.1714 ; $[\alpha]_D$ -45.9° (c 1.0, $CHCl_3$) (lit.,[6e] -66.2° (c 1, $CHCl_3$): **9** (amorphous) (lit.[6e] mp 69 - 70°C);^1H NMR δ 1.01 (s, 3H), 1.15 (s, 3H), 1.19 (s, 3H), 1.36 (ddd, 1H, J = 1.4, 3.9, 12.7 Hz), 1.87 (s, 3H),1.89 (dd, 1H, J = 8.5, 14.9 Hz), 2.20 (ddd, 1H, J = 1.4, 6.7, 14.9 Hz), 3.84 - 3.91 (m, 1H), 4.31 (d, 2H, J = 6.7 Hz), 5.58 (t, 1H, J = 6.9 Hz), 5.90 (d, 1H, J = 15.6 Hz), 6.57 (dd, 1H, J = 0.6, 15.6 Hz); MS m/z 252 (M^+); HRMS m/z calcd. for $C_{15}H_{24}O_3$ 252.1724, found 252.1736.

Diacetates of 8 and 9

A mixture of **8** and **9** (R = CH_2OH) (49 mg) was dissolved in pyridine (1.0 mL) under an argon atmosphere. To this was added acetic anhydride (73 mL, 4.0 equiv) at 0°C. After 3 h, added saturated sodium bicarbonate solution, extracted with ether,and the organic layer was washed with sodium bicarbonate solution and saturated brine, and dried over sodium sulfate. Crude product after removal of the solvent was separated by column chromatography on silca gel (hexane / ether = 10 / 1) to give **8** diacetate (29 mg) and **9** diacetate (27 mg): ^1H NMR **8** diacetate δ 0.99 (s, 3H), 1.16 (s, 3H), 1.19 (s, 3H), 1.37 (dd, 1H, J = 8.7, 13.4 Hz), 1.67 (ddd, 1H, J = 1.2, 3.5, 13.4 Hz), 1.78 (dd, 1H, J = 6.9, 14.9 Hz), 1.89 (d, 3H, J = 1.1 Hz), 2.02 (s, 3H), 2.05 (s, 3H), 2.40 (ddd, 1H, 1.1, 5.7, 14.9 Hz), 4.72 (dd, 2H, J = 0.6, 7.2 Hz), 4.93 (dddd, 1H, J = 3.5, 5.7, 6.9, 8.7 Hz),5.51 (d, 1H, J = 7.2 Hz), 5.99 (d, 1H, J = 15.5 Hz), 6.58 (dd, 1H, J = 0.6, 15.5 Hz); MS m/z 292(M^+ - C_2H_4O), 276 (M^+ - $C_2H_4O_2$), 261 (276 - CH_3), 260 (276 - H), 220 (276 - C_3H_4O); $[\alpha]_D$ -12.23 (c 0.64, $CHCl_3$); **9** diacetate δ 0.99 (s, 3H), 1.17 (s, 3H), 1.21 (s, 3H), 1.35 (ddd, 1H, J = 1.5, 4.2, 12.4 Hz), 1.68 (dd, 1H, J = 11.9, 12.4 Hz), 1.87 (dd, 1H, J = 9.5, 14.8 Hz), 1.89 (d, 3H, J = 1.0 Hz), 2.02 (s, 3H), 2.05 (s, 3H), 2.32 (ddd, 1H, J = 1.5, 7.6, 14.8 Hz), 4.71 (dd, 1H, J = 0.7, 7.2 Hz), 4.91 (dddd, 1H, J = 4.2, 7.6, 9.5, 11.9 Hz), 5.51 (d, 1H, J = 7.2 Hz), 5.92 (d, 1H, J = 15.6 Hz), 6.57 (dd, 1H, J = 0.7, 15.6 Hz); MS m/z 276 (M^+ - $C_2H_4O_2$), 220 (276 - C_3H_4O), 217 (276 - $C_2H_3O_2$), 216 (217 - H), 161 (220 - $C_2H_3O_2$), 160 (161 - H), 135 (160 - C_2H_3);. $[\alpha]_D$ +29.0° (c 1.07, $CHCl_3$).

With diisobutylaluminum hydride: To a solution of **7** methyl ester (77 mg, 0.28 mmol) in toluene (8 mL) under an argon atmosphere at -78°C, was added diisobutylaluminum hydride hexane solution (1.0 M) (1.38 mL, 5.0 equiv). After 2 h, the mixture was quenched with a small amount of methanol, added saturated ammonium chloride, then extacted with ether. The organic layer was washed with saturated brine, dried over sodium sulfate, and removed the solvent. The crude product was purified by column chromatography on silica

gel (hexane / ethyl acetate = 4 / 1), to afford a mixture of **8** and **9** (R = CH_2OH) (49 mg, 70% yield) in a ratio of 56 : 44.

With sodium borohydride; Added **7** methyl ester (23 mg, 0.083 mmol) in tetrahydrofuran (1.5 mL) to a suspension of sodium borohydride (3.2 mg, 0.083 mmol) in tetrahydrofuran (1.0 mL) under an argon atmosphere at -78°C, and stirred for 2 h. Quenched with water, extracted with ether, and the organic layer was washed with saturated brine and dried over sodium sulfate. The crude product was purified by columnchromatography on silica gel affording a mixture of **8** and **9** (R = COOMe) (14 mg, 67% yield) in a ratio of 36 : 64: ^{1}H NMR **8** (R = COOMe) δ 1.01 (s, 3H), 1.15 (s, 3H), 1.22 (s, 3H), 1.0 - 1.66 (m, 1H), 2.01 (d, 3H, J = 1.2 Hz), 2.38 (ddd, 1H, J = 1.7, 5.0, 14.1 Hz), 3.70 (s, 3H), 3.59 - 3.64 (m, 1H), 5.70 (bs, 1H), 6.27 (d, 1H, J = 16.0 Hz), 7.60 (d, 1H, J = 16.0 Hz); MS m/z 280 (M^+), 265 (M^+ - CH_3), 263 (M^+ - OH), 248 (M^+ - CH_4O); HRMS m/z calcd. for $C_{16}H_{24}O_4$ 280.1672, found 280.1668; $[\alpha]_D$ +16.30 (c 0.65, $CHCl_3$); **9** (R = COOMe) δ 1.04 (s, 3H), 1.16 (s, 3H), 1.22 (s, 3H), 1.36 (ddd, 1H, J = 1.5, 3.9, 13.0 Hz), 1.90 (dd, 1H, J = 8.4, 15.0 Hz), 2.01 (s, 3H), 2,20 (ddd, 1H, J = 1.3, 6.7, 15.0 Hz), 3.70 (s, 3H), 3.72 - 3.77 (m, 1H), 5.71 (bs, 1H), 6.20 (d, 1H, J = 16.0 Hz), 7.62 (d, 1H, J = 16.0 Hz); MS m/z 280 (M^+), 265 (M^+ - CH_3), 263 (M^+ - OH), 248 (M^+ - CH_4O), 221 (248 - C_2H_3); $[\alpha]_D$ +54.81° (c 0.54, $CHCl_3$).

With sodium borohydride-ceric chloride system: A mixture of ceric chloride (35 mg, 0.14 mmol) and **7** methyl ester (46 mg, 0.14 mmol) in tetrahydrofuran (1.5 mL) was stirred at -78°C under an argon atmosphere for 30 min. To this was added sodium borohydride (6.0 mg, 0.16 mmol) and continued stirring at the same temperature for 16 h. Added water, extracted with ether, and the organic layer was washed with saturated brine and dried over sodium sulfate. Crude product was purified by column chromatography on silica gel to give a mixture of **8** and **9** (R = COOMe) (30 mg, 75% yield) in a ratio of 29 : 71.

With K-Selectride^R: To a solution of **7** methyl ester (60 mg, 0.22 mmol) in tetrahydrofuran (0.6 mL) under an argon atmosphere at -78°C, added K-Selectride^R solution (0.5 M) (0.43 mL, 0.22 mmol) slowly and allowed to react for 30 min. Added saturated ammonium chloride at the same temperature, extracted with ether, and the organic layer was washed with saturated brine and dried over sodium sulfate. The crude product was purified by column chromatography on silica gel to afford a mixture of **8** and **9** (R = COOMe) (30 mg, 54% yield) in a ratio of 77 : 23.

With L-Selectride^R: From **7** methyl ester (60 mg, 0.22 mmol) and L-Selectride^R (1.0 M) (0.22 mL, 0.22 mmol) by the same treatment as shown above, **8** and **9** (R = COOMe) (14 mg, 30% yield) in a ratio of 82 : 18 was obtained.

(-)-Xanthoxin (2)

A mixture of **8** (R = CH_2OH) (7.0 mg, 0.024 mmol) and active manganese dioxide (42 mg, Ca. 20 equiv) in dichloromethane (1.0 mL) was stirred at room temperature for 2 h. From the organic layer after filtration, **2** (6.8 mg, 100% yield) was obtained by removal of the solvent as an amorphous solid (lit.,[6e] mp 85 - 86°C): ^{1}H NMR δ 1.00 (s, 3H), 1.19 (s, 3H), 1.21 (s, 3H), 1.25 - 1.28 (m, 1H), 1.58 - 1.67 (m, 1H), 1.66 (dd, 1H, J = 8.9, 14.4 Hz), 2.12 (bs, 3H), 2.40 (ddd, 1H, J = 1.7, 5.1, 14.4 Hz), 3.87 - 3.96 (m, 1H), 5.88 (d, 1H, J = 8.2 Hz), 6.38 (d, 1H, J = 15.4 Hz), 7.21 (d, 1H, J = 15.4 Hz), 10.20 (d, 1H, J = 8.2 Hz); $[\alpha]_D$ -38° (c 0.87, $CHCl_3$) (lit.,[6e] -56° (c 1, $CHCl_3$)).

Epi-(-)-xanthoxin (10)

From **9** (R = CH_2OH), **10** was available also in quantative yield by the same treatment shown as above as an amorphous solid (lit.,[6e] mp 85 - 86°C): ^{1}H NMR δ 1.03 (s, 3H), 1.20 (s, 3H), 1.21 (s, 3H), 1.38 (ddd, 1H, J =

1.5, 3.8, 12.7 Hz), 1.58 - 1.67 (m, 1H), 1.99 (dd, 1H, J = 8.8, 14.9 Hz), 2.12 (bs, 3H), 2.24 (ddd, 1H, J = 1.4, 6.7, 14.9 Hz), 3.86 - 3.95 (m, 1H), 5.89 (d, 1H, J = 8.1 Hz), 6.39 (d, 1H, J = 15.4 Hz), 7.21 (d, 1H, J = 15.4 Hz), 10.18 (d, 1H, J = 8.1 Hz); [α[D +21.2° (c 0.59, CHCl3) (lit.,[6e] enantiomer -25.1° (c 1, CHCl3)).

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