Pergamon

Tetrahedron Vol. 50, No. 40, pp. 11647-11658, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00736-5

Total Syntheses of (+)-Ipomeamarone and (-)-Ngaione via Novel Intramolecular Hydrogen Abstraction

Takashi Sugimura* and Akira Tai*

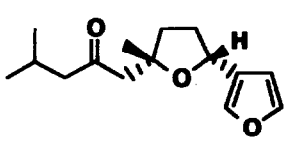
Faculty of Science, Himeji Institute of Technology
Kanaji, Kamigori, Ako-gun, Hyogo 678-12, Japan

Kiyoto Koguro

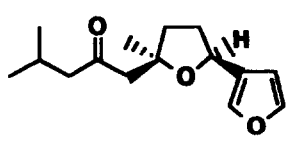
Chemical Research Laboratory, Toyo Kasei Kogyo Co., Ltd.
2900 Sone, Takasago, Hyogo 676, Japan

Abstract: The first total syntheses of enantiomerically pure (+)-ipomeamarone and its enantiomer (-)-ngaione were achieved. From optically pure *sec,sec*-1,3-diol **6** obtained through enantio differentiating hydrogenation, **11a** consisting of *sec,tert*-1,3-diol was prepared using a novel stereocontrolled hydrogen abstraction/olefin addition process. Regiocontrolled *syn* and *anti* hydride additions to optically active bicyclic acetal **5** produced precursors of both (+)-ipomeamarone and (-)-ngaione.

Ipomeamarone (**1**) was isolated from the sweet potato (*ipomea butatas*) under stress conditions such as fungus infection.[1] Independently, its enantiomer **2** named ngaione was isolated from Ellangowan poison bush (*myoporum deserti* A. Cunn.) and later from *eremophia latrobei*.[2] Because those substances are essence of toxins fatal to domestic animals, the toxicology[3] and biosynthesis[4] of **1** and **2** have been extensively studied. Although it had been known that the two toxins were enantiomers of each other, their absolute configurations have only recently been established as 1*R*,4*S* for (+)-**1** and 1*S*,4*R* for (-)-**2** by two independent groups.[5] One of the reasons why the stereochemistries of such well-investigated compounds had not been correctly known is that they had been synthesized only as a racemic compound but not as optically active compounds of known absolute configuration.[6] Here, we report the first total syntheses of optically active (+)-ipomeamarone and (-)-ngaione.[7]

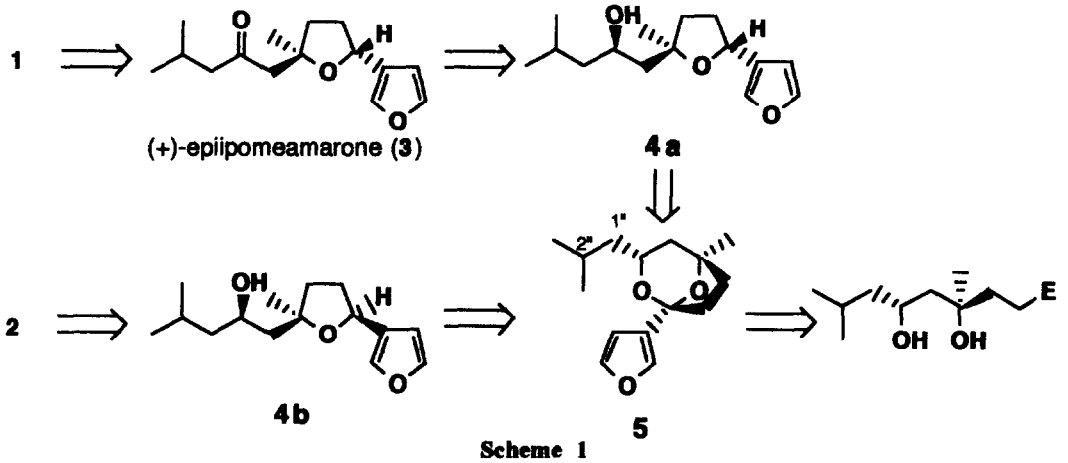


(+)-ipomeamarone (**1**)



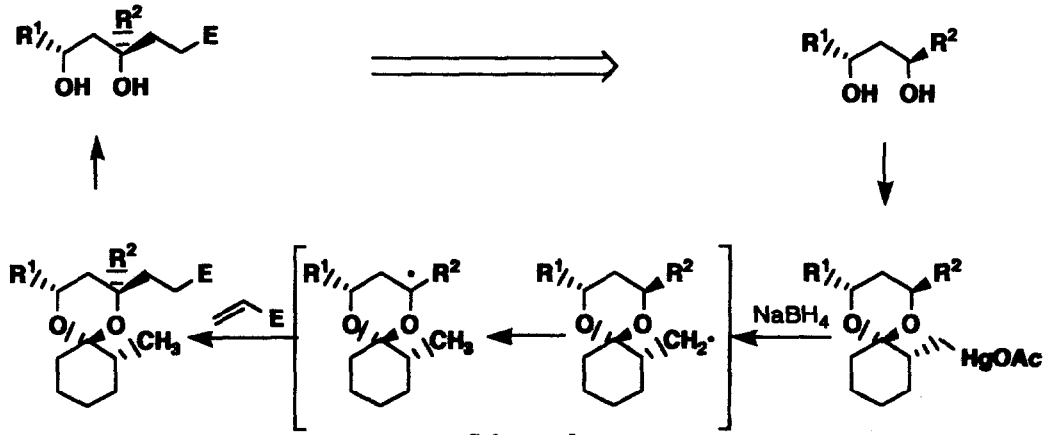
(-)-ngaione (**2**)

The first key point in the present syntheses is that both optically pure (+)-ipomeamarone and (-)-ngaione can be obtained from an optically active bicyclic acetal **5**. That is, regiocontrolled *anti* -hydride addition to the acetal ring in **5** would give **4b**, a precursor of (-)-ngaione (**2**), and *syn* -hydride addition to **5** followed by oxidation and epimerization to give (+)-ipomeamarone (**1**) (Scheme 1). The key intermediate **5** corresponds to the 1",2"-dihydro derivative of (+)-eremoacetal, a constituent of *Eremophila rotundifolia*.[8]

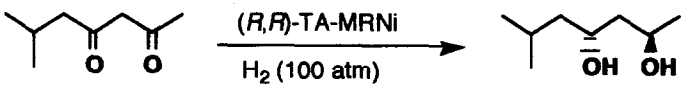


Scheme 1

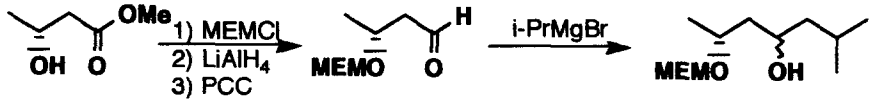
The second key point is the application of a novel intramolecular hydrogen abstraction to construct chiral *sec,tert*-diol from *sec,sec*-1,3-diol (Scheme 2).[9] Optically active *sec,sec*-1,3-diol is transferred to β-mercuro acetal through preparation of cyclohexenyl ether, diastereoface differentiating cyclopropanation, and oxymercuration. Reductive demercuration affords the β-acetal radical, which readily abstracts hydrogen and then adds to the olefin. When $R^1 = R^2 = Me$, the process was fully stereocontrolled giving a single stereoisomer. Although an application of this to the present synthesis (R^1 = iBu and R^2 = Me) might require the separation of the regioisomer, it enables us to obtain *sec,tert*-diol having obvious absolute configuration in high optical purity.



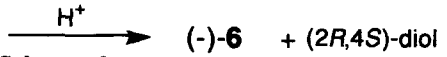
Scheme 2.



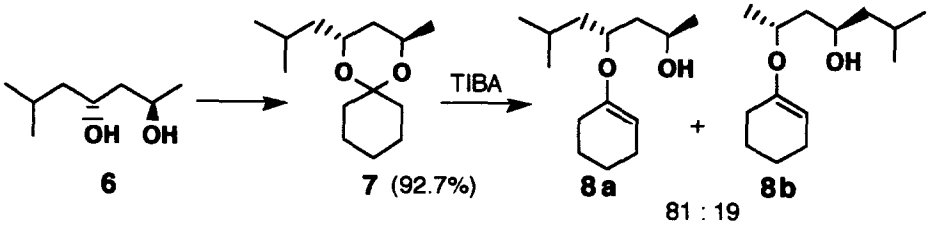
(2*R*,4*R*)-(-)-**6** (31.3%)
(>99% e.e. after recrystallizations)

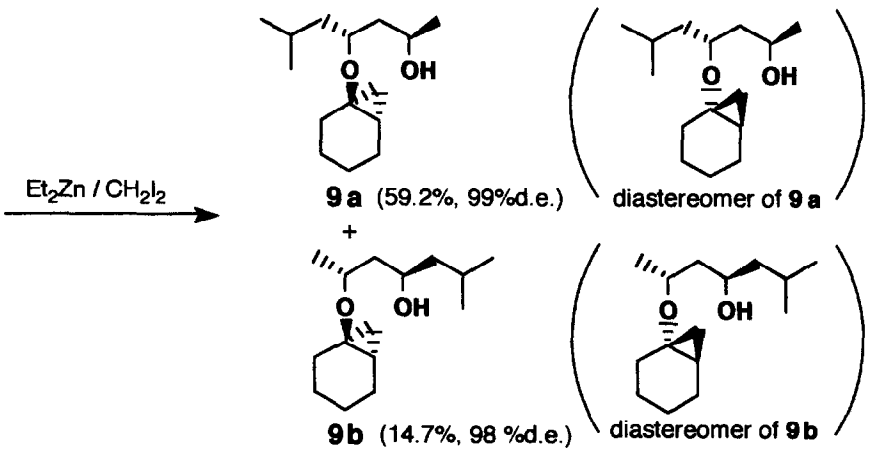


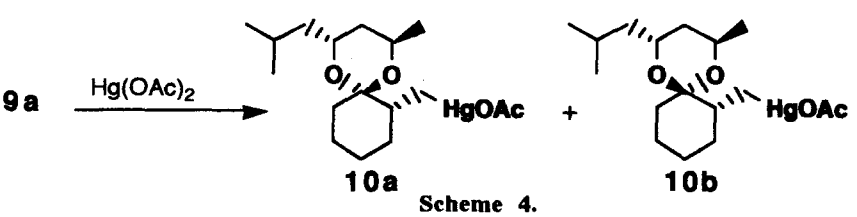
(*R*)-(-)-MHB



Scheme 3.



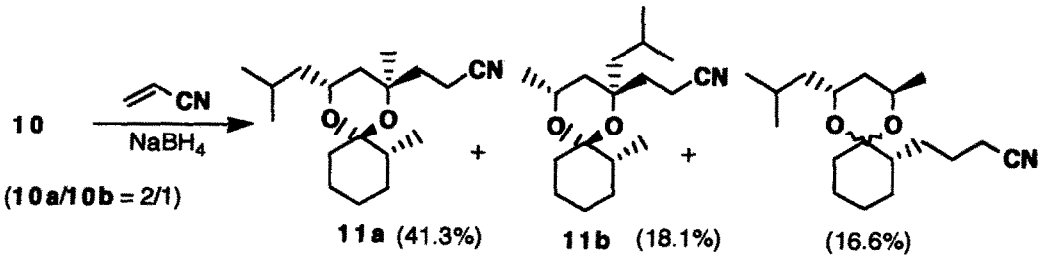


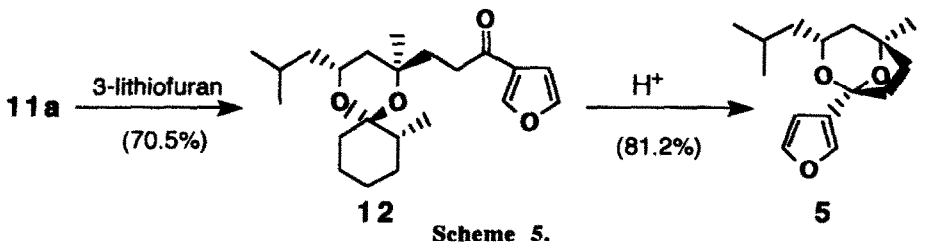


Scheme 4.

Optically pure (2*R*,4*R*)-**6** was obtained in 31% yield by enantio-differentiating hydrogenation of 6-methyl-2,4-heptanedione over (*R*,*R*)-tartaric acid-NaBr-modified ultrasonicated Raney nickel[10] at 100 °C for 43 hours, and four recrystallizations. The enantiomeric purity of **6** was confirmed to be over 99% e.e. by HPLC analysis of its dibenzoate analog on CHIRALPAC-OT(+), and the absolute configuration of (-)-**6** was assigned to be 2*R*,4*R* by chemical correlation with (-)-(*R*)-methyl 3-hydroxybutanoate (MHB) as shown in Scheme 3.

Scheme 4 shows the process from **6** to mercuro acetal **10**. Acetalization of **6** with cyclohexanone and isomerization with triisobutylaluminum[11] afforded **8a** and its regioisomer **8b**. The regioisomeric ratio of **8a** and **8b** was determined to be 81/19 by capillary GLC analysis of those acetyl esters. Without separation, the isomeric mixture of **8** was subjected to cyclopropanation with diethylzinc (5 eq.) and diiodomethane (10 eq.) in THF.[12] The resulting mixture of **9a** and **9b** was separated by MPLC on silica gel (59.2% and 14.7% yields, respectively). The diastereomeric excess of **9a** was 99% and that of **9b** was 98%. Treatment of **9a** with mercuric acetate afforded a mixture of two products, **10a** and **10b**, in a quantitative yield. The ratio (**10a**/**10b**) was affected by the solvent employed and was increased with the use of a more polar solvent; in tetrachloromethane (1/4), in THF (1/3), in dichloromethane (1/2), in acrylonitrile (3/2), and in acetic acid (2/1). However, the use of trifluoroacetic acid or an aqueous solvent resulted in deacetalization of the products. So far, the reaction in acetic acid afforded the best result. The product mixture of **10a** and **10b** was used for the next step without purification.

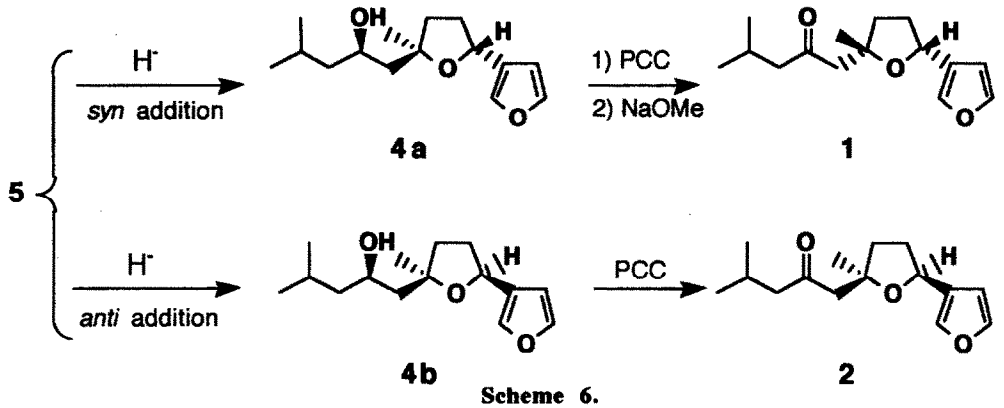




Scheme 5.

The stereocontrolled tandem reaction consisting of reductive radical formation, intramolecular hydrogen abstraction, and addition to acrylonitrile was successively achieved (shown in Scheme 5). Treatment of a mixture of **10a** and **10b** (**10a**/**10b** = 2/1) with aqueous sodium borohydride in dichloromethane in the presence of 3 equivalents of acrylonitrile and separation by MPLC afforded **11a** (41.3%) and **11b** (18.1%) accompanied by a mixture of acrylonitrile adducts without hydrogen abstraction (16.6%). Isolated **11a** was diastereomerically pure determined by capillary GLC analysis. Addition of 3-lithiofuran[13] to **11a** at -25 °C

gave **12** (70.5%) and treatment of this with *p*-toluenesulfonic acid in methanol-benzene (1: 2) resulted in transacetalization and intramolecular reacetalization to give bicyclic acetal **5** (81.4%).

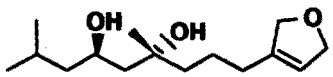


Scheme 6.

Table 1. Hydride addition to **5** under various conditions.

entry	reagents(equivalent)	solvent	temp.	ratio of **4a**/**4b**[a]	yield of **4**
1	DIBAH (6.0)	CH_2Cl_2	0	>99/<1	85
2	DIBAH (6.0)	Et_2O	20	98/2	15
3	$AlBr_2H$ (7.5)	Et_2O	-20	96/4	98
4	$LiAlH_4$ (10) / $BF_3{\cdot}OEt_2$ (7)	Et_2O	reflux	93/7	38
5	$TiCl_4$ (5.0) / Et_3SiH (6.0)	CH_2Cl_2	-78 to r.t.	—	0[c]
6	$TiCl_4$ (3.0) / Et_3SiH (3.0)	CH_2Cl_2	-78 to r.t.	—	0[d]
7	$TiCl_4$ (1.2) / Et_3SiH (4.0)	CH_2Cl_2	-78 to r.t.	63/37	< 2[b]
8	$TiCl_4$ (1.2) / Et_3SiH (5.0)	CH_2Cl_2	-30 to r.t.	41/59	< 2[b]
9	$TiCl_3OiPr$ (1.2) / Et_3SiH (5.0)	CH_2Cl_2	-78 to r.t.	63/37	< 2[b]
10	$BF_3{\cdot}OEt_2$ (2.0) / Et_3SiH (2.0)	CH_2Cl_2	-78 to r.t.	—	0[b]
11	$SnCl_4$ (5.0) / Et_3SiH (5.0)	CH_2Cl_2	-78 to r.t.	—	0[b]
12	TMSOTf (1.2) / $BH_3{\cdot}SMe_2$ (1.2)	CH_2Cl_2	-78 to -15	77/23	95
13	TMSOTf (1.2) / $BH_3{\cdot}SMe_2$ (1.2)	Et_2O	-78 to -5	61/39	70
14	TMSOTf (1.2) / $BH_3{\cdot}SMe_2$ (1.2)	CH_3CN	-40 to 0	56/44	30
15	TMSOTf (1.2) / $BH_3{\cdot}SMe_2$ (1.2)	THF	-78 to -45	53/47	93
16	TMSOTf (1.2) / $BH_3{\cdot}SMe_2$ (1.2)	DME	-78 to -15	59/41	90
17	TMSOTf (1.2) / $BH_3{\cdot}SMe_2$ (1.2)	SMe_2	-78 to 0	53/47	85
18	$TiCl_4$ (1.2) / $BH_3{\cdot}SMe_2$ (1.2)	THF	-35 to r.t.	54/46	60

a) The ratio was determined by capillary GLC.
b) Over 70% of the reactant **5** was recovered.
c) Triply reduced compound **13** was obtained as a sole product.
d) The mixture included **5** and **13** in a ratio of 1:2.



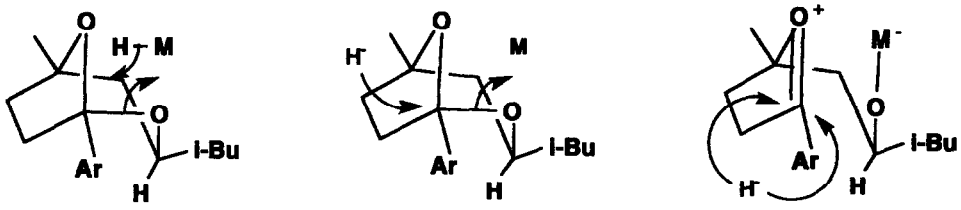
13

Hydride addition to **5** resulted in C—O bond fission under various reaction conditions. The results are summarized in Table 1. *Syn*-hydride addition to **5** with DIBAH[14] at 0 °C in dichloromethane produced over 99% diastereomerically pure **4a** in good yield (entry 1). Oxidation of **4a** afforded (+)-epiipomeamarone (**3**), which was converted into a 1:1 mixture of (+)-ipomeamarone (**1**) and **3** by treatment with sodium methoxide.[15] Optically pure (+)-ipomeamarone (**1**) was completely separated from **3** by HPLC on a preparative ODS column.

Spectra and optical rotation of the synthetic toxin were fully identical with those of reported natural ipomeamarone.[1]

On the other hand, the *anti* -hydride adduct (**4b**) could not be obtained preferentially. The reduction of **5** with triethylsilane and titanium tetrachloride[16] did not proceed below -30 °C. When the reaction was carried out at room temperature, over reduced compound **13** was obtained as a sole product (entries 5 and 6). The reaction with a slight excess of Lewis acid and excess triethylsilane afforded a trace amount of **4**, which included both diastereomers (entries 7, 8, and 9). Hydride addition to **5** with borane dimethylsulfide and trimethysilyl trifluoromethanesulphonate[17] went smoothly, resulting in a good yield of **4**. The ratio of **4a** and **4b** was somewhat affected by the solvent used. The best result so far obtained was a 1 to 1 mixture of **4a** and **4b** by the reaction in THF (entry 15). Oxidation of the mixture of **4b** and **4a** gave (-)-ngaione (**2**) and (+)-**3** in the same ratio (65% in two steps). Isolated (-)-ngaione by HPLC had the same spectra as the reported compound and those of (+)-ipomeamarone except for levorotatory optical rotation.

It should be noted that, through all types of hydride addition studied herein, the product having a perhydrooxepine ring (seven membered cyclic ether) was not detected, so that cleavage of the C—O bond in bicyclic acetal of **5** was highly regiocontrolled.[18] High yield and high stereodifferentiation in the reaction with DIBAH suggested that, in an SN-i-like reaction,[14] the substrate **5** allowed hydride attack without steric or electronic problems. Slow reaction and poor yield in the reaction with Lewis acid and silane could be attributed to steric hindrance in an SN-2-like reaction.[16] The reagents' combination of strong Lewis acid and weakly nucleophilic borane tended to react through an SN-1-like mechanism[19] and resulted in poor selectivity but good yield, because the hydride reagent attack was free from the steric hindrance.



Acknowledgment: We thank Dr. Kazuo Yoshihara of the Suntory Institute for Bioorganic Research (SUNBOR), Osaka, Japan for supplying spectra of natural ipomeamarone. We also thank Daicel Chemical Industries, Ltd., for the gift of the chiral HPLC column, CHIROPAC-OT(+).

Experimental

All melting points are uncorrected. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) were recorded on a JEOL GX-400 spectrometer in $CDCl_3$ as a solvent and as an internal standard (7.26 ppm and 77.1 ppm). IR spectra were obtained on a JASCO IR-810 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 243B polarimeter. Analytical GLC was conducted with a Hitachi G-3000. MPLC was carried out using a FMI pump (10 ml min^{-1}) and a Lobar column (Merck Si-60, type B). HPLC was conducted with Hitachi L-

6200 and L-3000. Dry diethyl ether and THF were distilled from sodium-benzophenone ketyl and the other dry solvents were distilled from calcium hydride. All reactions were carried out under dry nitrogen atmosphere.

Preparation of (2*R*,4*R*)-6-methyl-2,4-heptanediol (**6**)

In an autoclave (1000 ml capacity) were introduced 6-methyl-2,4-heptanedione (49.8 g), THF (200 ml), acetic acid (1 ml), and (*R*,*R*)-TA-NaBr-RNi-U prepared from 38 g of Raney nickel alloy (see ref. 10 for the preparation method of TA-NaBr-RNi-U). The autoclave was charged with hydrogen to a pressure of 100 kg cm^{-2} and the mixture in the autoclave was kept at 100 °C for 43 hours with shaking. After cooling the autoclave and evacuation of hydrogen, the contents of the autoclave were taken out and filtered. A small portion of the mixture was taken out and purified by MPLC to determine the optical purity. Evaporation of a major portion and four recrystallizations from a mixture of ether and hexane (2:1) gave 16.1 g of **6** as colorless prisms (31.3% yield). m.p. = 67.0—67.6 °C. $[\alpha]_D^{20}$ = -25.5 (c 1.0, methanol). ^{1}H-NMR ($CDCl_3$) δ 4.16 (q like, *J* = 6.4 Hz, 1H), 4.03 (m, 1H), 2.21 (brs, 2H, -OH), 1.74 (m, 1H), 1.61—1.57 (m, 2H), 1.54—1.45 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H). IR (KBr, cm^{-1}) 3320, 2840, 1350, 1150, 1130, 1060, 1040, 1020, 920. Anal. Calcd for $C_8H_{18}O_2$: C: 65.71, H: 12.41, Found: C: 65.45, H: 12.51.

HPLC analysis of the optical purity of **6**

The dibenzoate derived from **6** was purified by preparative TLC and subjected to HPLC analysis on a CHIRALPAC OT(+) column (Daicel Chemical Industries, Ltd., Japan) with a mixture of methanol-ethanol (1:2) as an eluent (0.5 ml min^{-1}, at 5 °C). The dibenzoate of (2*R*,4*R*)-**6** had a longer retention time (15.0 min) than that of (2*S*,4*S*)-**6** (12.3 min). Enantiomeric excess of **6** isolated by MPLC from the reaction mixture was 72%, and that by four recrystallizations was over 99%.

Determination of the stereochemistry of **6**.

A mixture of enantiomerically pure methyl (R)-3-hydroxybutanoate (1.66 g), 2-methoxyethoxymethyl-chloride (MEMCl, 2.4 ml), and N,N-diisopropylethylamine (5.0 ml) in dichloromethane (120 ml) was stirred over night at room temperature. The mixture was washed with water, dried over sodium sulfate, and concentrated to give 2.83 g of crude MEM ether (98% crude yield). A part of this was purified by MPLC on silica gel (elution with 50% ethyl acetate in hexane) to give colorless oil. $[\alpha]_D^{20}$ = -15.7 (c 1.0, benzene). ^{1}H-NMR ($CDCl_3$) δ 4.76 (d, *J* = 7.4 Hz, 1H), 4.74 (d, *J* = 7.4 Hz, 1H), 4.19 (m, 1H), 3.68 (m, 2H), 3.67 (s, 3H), 3.55 (m, 2H), 3.39 (s, 3H), 2.59 (dd, *J* = 15.1, 7.6 Hz, 1H), 2.43 (dd, *J* = 15.1, 5.4 Hz, 1H), 1.24 (s, 3H). IR (neat, cm^{-1}) 2930, 2870, 1738, 1438, 1384, 1200, 1108, 1040. High resolution MS, Calcd for $C_9H_{18}O_5$: 206.1154, Found: 206.1103. A solution of crude MEM ether (1.90 g) in dry ether (10 ml) was added to a suspension of lithium alminum hydride (350 mg) in dry ether (40 ml) at 0 °C. The mixture was stirred for 1 hour at the same temperature and quenched with water. Extraction with ether (three times), drying over sodium sulfate, and evaporation afforded 1.30 g of the crude alcohol (79% crude yield). To a solution of the crude alcohol (600 mg) in dry dichloromethane (50 ml) was added a molecular sieves (3A, powder, 6.0 g) and pyridinium chlorochromate (1.13 g), and the mixture was stirred for 3 hours at room temperature. After the usual work-up and MPLC purification on silica gel (elution with 50% ethyl acetate in hexane), 467 mg of the corresponding aldehyde was obtained as a colorless oil (78% yield). $[\alpha]_D^{20}$= -26.1 (c 1.0, dichloromethane).

^{1}H-NMR ($CDCl_3$) δ 9.78 (s, 1H), 4.79 (d, J = 7.3 Hz, 1H), 4.73 (d, J = 7.3 Hz, 1H), 4.28 (m, 1H), 3.73—3.66 (m, 2H), 3.56—3.54 (m, 2H), 3.39 (s, 3H), 2.67 (ddd, J = 16.4, 7.6, 1.7 Hz, 1H), 2.51 (ddd, J = 16.4, 7.6, 1.7 Hz, 1H), 1.27 (d, J = 6.1 Hz, 3H). IR (neat, cm^{-1}) 2970, 2930, 2880, 1728, 1460, 1380, 1120, 1040. This was treated with an excess amount of isobutylmagnesium bromide in dry ether (5 ml) to give 400 mg of the adduct (67.5%), which was stirred with 35% perchloric acid in THF. The diastereomer ratio of (2*R*,4*R*)-**6** and (2*R*,4*S*)-**6** was determined to be 98/2 by capillary GLC analysis (TC-WAX, 60 m, 150 °C), and (2*R*,4*R*)-**6** isolated by MPLC on silica gel (elution with 50% ethyl acetate in hexane, 15% yield) had an optical rotation of -20 (c 0.2, methanol).

Preparation of acetal **7**

A solution of **6** (2.66 g), cyclohexanone (2.18 g), and a catalytic amount of *p*-toluenesulfonic acid in benzene (150 ml) was dehydrated using a Dean-Stark trap under reflux conditions. After 20 hours, the solution was washed with sodium bicarbonate, dried over magnesium sulfate, and purified by column chromatography on silica gel (elution with 6% ethyl acetate in hexane) to give 3.87 g of **7** as a colorless oil (92.7% yield). $[\alpha]_D^{20}$ = -5.96 (c 1.3, methanol), ^{1}H-NMR ($CDCl_3$) δ 3.97 (m, 1H), 3.88 (m, 1H), 1.82—1.69 (m, 3H), 1.63—1.41 (m, 11H), 1.34 (m, 1H), 1.18 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H). IR (neat, cm^{-1}) 2940, 2860, 1450, 1380, 1370, 1280, 1240, 1160, 1100, 1000, 970. Anal. Calcd for $C_{14}H_{26}O_2$, C: 74.28, H: 11.58, Found, C: 73.99, H: 11.80.

Preparation of cyclopropyl ether **9a**

To a solution of **7** (3.87 g) in dry dichloromethane (250 ml) was added a solution of triisobutylaluminum (1M in hexane, 91 ml) at 0°C. After 3 hours, the mixture was poured into 1N aqueous sodium hydroxide (450 ml) and extracted with dichloromethane (three times). After drying over potassium carbonate and evaporation, a mixture of **8a** and **8b** (4.21 g) was obtained (108% crude yield). A small portion of the mixture was treated with acetic anhydride in pyridine and subjected to capillary GLC analysis (PEG-20M, 50 m, 140 °C). The major isomer **8a** had a shorter retention time (31.3 min) than that of **8b** (33.8 min), and the ratio was 81/19. A major portion of **8** (3.87 g) was dissolved in dry THF (120 ml) and cooled to 0 °C. To this was added diethylzinc (85 ml, 1.01 M in hexane) and then diiodomethane (13.8 ml), and the mixture was allowed to stand for 2.5 hours at the same temperature and for 4 hours at room temperature. This was poured into a saturated aqueous ammonium chloride solution (900 ml) and extracted with ether three times. After MPLC purification on silica gel (elution with 10% ethyl acetate in hexane), **9a** (2.18 g, 59.2%) and **9b** (0.765 g, 14.7%) were obtained. The diastereomeric purities of **9a** and **9b** were determined to be 99% and 98%, respectively, by capillary GLC (PEG-20M, 50 m, 160 °C). **9a**: colorless oil, $[\alpha]_D^{20}$ = -25.7 (c 1.0, methanol). ^{1}H-NMR ($CDCl_3$) δ 4.08 (m, 1H), 3.89 (m, 1H), 2.11 (m, 1H), 2.04—1.93 (m, 2H), 1.74 (m, 1H), 1.57—1.48 (m, 4H), 1.47—1.34 (m, 2H), 1.27—1.20 (m, 4H), 1.15 (d, J = 6.1 Hz, 3H), 1.07 (m, 1H), 0.90 (d, J = 5.4 Hz, 3H), 0.89 (d, J = 5.1 Hz, 3H), 0.85 (m, 1H), 0.28 (dd, J = 5.4, 5.4 Hz, 1H). IR (neat, cm^{-1}) 3450, 2940, 2860, 1475, 1455, 1375, 1205, 1110, 1090, 1025, 990, 950. High resolution MS (*m/z*) Calcd for $C_{15}H_{28}O_2$: 240.2089, Found: 240.2045. **9b**: colorless oil, ^{1}H-NMR ($CDCl_3$) δ 4.09 (m, 1H), 3.94 (m, 1H), 2.10 (m, 1H), 1.96 (m, 1H), 1.75 (m, 1H), 1.61—1.47 (m, 4H), 1.46—1.37 (m, 2H), 1.26—1.22 (m, 2H), 1.20 (d, J = 6.4 Hz, 3H), 1.17 (m, 1H), 1.12 (m, 1H), 1.05 (m, 1H), 0.91 (d, J = 5.2 Hz, 3H), 0.90 (J=5.2

Hz, 3H), 0.87 (m, 1H), 0.28 (dd, J = 5.4, 5.4 Hz, 1H). IR (neat, cm^{-1}) 3450, 2940, 2860, 1200, 1150, 1130, 1100, 1080, 1045. High resolution MS (m/z) Calcd for $C_{15}H_{28}O_2$: 240.2089, Found: 240.2035.

Preparation of **11a**

A solution of **9a** (2.12 g) in acetic acid (36 ml) was treated with mercuric acetate (2.81 g) for 1 hour at room temperature. Acetic acid was removed from the mixture under vacuo and the residue was dissolved in dichloromethane and filtered. Concentration of the filtrate gave a mixture of **10a** and **10b** (2:1, 5.16 g), which was used for the next step without further purification.

To a solution of **10** (5.16 g) and acrylonitrile (1.40 g) in dichloromethane (100 ml) was added a saturated aqueous solution of sodium borohydride (ca. 5 ml) dropwise for 15 minutes at room temperature under vigorous stirring. Extraction with ether and MPLC purification on silica gel (elution with 3% ethyl acetate in hexane) afforded 1.07 g of **11a** (41.3% yield for two steps), 470 mg of **11b** (18.1% yield for two steps), and a diastereomeric mixture of adducts without hydrogen abstraction (430 mg, 16.6% yield). **11a**: colorless prisms, m.p. = 43—49 °C. $[\alpha]_D^{20}$ = 15.1 (c 0.7, methanol). ^{1}H-NMR ($CDCl_3$) δ 3.88 (m, 1H), 2.52 (m, 1H), 2.39 (m, 1H), 2.31—2.22 (m, 2H), 1.86 (m, 1H), 1.68 (m, 1H), 1.59—1.11 (m, 12H), 1.13 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.1 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 120.6, 100.2, 71.1, 62.0, 45.8, 42.2, 41.7, 36.6, 34.3, 31.3, 29.3, 25.7, 24.0, 23.67, 23.65, 22.2, 14.3, 12.0. IR (neat, cm^{-1}) 2930, 2850, 2240, 1445, 1370, 1360, 1275, 1145, 1130, 1085, 970. High resolution MS (m/z) Calcd for $C_{18}H_{31}NO_2$: 293.2356, Found: 293.2330. **11b**: colorless prisms, m.p. = 51.8—52.4 °C. $[\alpha]_D^{20}$ = 5.5 (c 0.9, methanol). ^{1}H-NMR ($CDCl_3$) δ 3.95(m, 1H), 2.56—2.03 (m, 6H), 1.85—1.17 (m, 12H), 1.17 (d, J = 6.1 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H). IR (neat, cm^{-1}) 2930, 2860, 2250, 1448, 1280, 1158, 1140, 1108. High resolution MS (m/z) Calcd for $C_{18}H_{31}NO_2$: 293.2356, Found: 293.2342.

Preparation of **12**

A solution of 3-bromofuran (1.35 ml) in dry ether (50 ml) was treated with butyllithium (1.61 N, 9.27 ml) at -78 °C and stirred for 1 hour. To this solution was added **11a** (880.5 mg in 25 ml of dry ether), and the mixture was warmed to -25 °C for 5 hours. The mixture was quenched with aqueous ammonium chloride, extracted, and purified by MPLC on silica gel (elution with 6% ethyl acetate in hexane) to give **12** (766.9 mg) as colorless prisms (70.5% yield). m.p. = 64—67 °C. $[\alpha]_D^{25}$ = 21.3 (c 1.2, methanol). ^{1}H-NMR ($CDCl_3$) δ 8.06 (m, 1H), 7.44 (m, 1H), 6.78 (m, 1H), 3.95 (m, 1H), 3.00—2.86 (m, 2H), 2.41—2.33 (m, 2H), 1.86 (m, 1H), 1.63 (m, 1H), 1.53—1.10 (m, 12H), 1.18 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H). IR (neat, cm^{-1}) 3150, 2910, 2850, 1670, 1160, 1105, 1095, 980, 875. High resolution MS (m/z) Calcd for $C_{22}H_{34}O_4$: 362.2457, Found: 362.2445.

Preparation of **5**

A solution of **12** (761 mg) and a catalytic amount of pyridinium *p*-toluenesulfonate in benzene (60 ml) and methanol (30 ml) was stirred for 4 hours under reflux. The mixture was extracted with ether, washed with water, saturated aqueous sodium bicarbonate, and then brine. After drying over sodium sulfate and evaporation, the crude product was purified by MPLC on silica gel (elution with 3% ethyl acetate in hexane) to yield **5** (427.8 mg) as a colorless oil (81.4% yield). $[\alpha]_D^{25}$ = 17.2 (c 0.7, methanol). ^{1}H-NMR ($CDCl_3$) δ

7.50 (m, 1H), 7.34 (m, 1H), 6.45 (m, 1H), 4.01 (m, 1H), 2.35 (m, 1H), 2.22 (m, 1H), 1.93 (m, 1H), 1.86—1.77 (m, 2H), 1.60—1.50 (m, 3H), 1.40 (s, 3H), 1.26 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 142.9, 139.8, 127.6, 108.6, 103.5, 81.0, 67.8, 45.4, 43.2, 37.5, 35.1, 26.2, 24.3, 23.1, 22.6. IR (neat, cm^{-1}) 2955, 2940, 2870, 1510, 1475, 1155, 1080, 1035, 940, 880. Anal. Calcd for $C_{15}H_{22}O_3$, C: 71.97, H: 8.86, Found, C: 71.08, H: 8.84.

Reduction of **5** with DIBAH (Table 1, entry 1)

To a solution of **5** (9.4 mg) in dry dichloromethane (2 ml) was added DIBAH (1.0 M solution in hexane, 0.23 ml) at 0 °C. After 5 hours, the reaction mixture was quenched with dilute hydrochloric acid, extracted, and purified by MPLC on silica gel (elution with 6% ethyl acetate in hexane) to give 8.6 mg of **4a** (colorless oil, 85% yield). $[\alpha]_D^{20}$ = 17.9 (c 1.4, methanol). IR(neat, cm^{-1}), 3430, 2960, 2875, 1475, 1380, 1162, 1142, 1100, 1030, 908, 880, 800. ^{1}H-NMR ($CDCl_3$) δ 7.38—7.37 (m, 2H), 6.37 (m, 1H), 4.98 (m, 1H), 4.02 (m, 1H), 2.28—2.00 (m, 3H), 1.84—1.71 (m, 3H), 1.66 (m, 1H), 1.48 (m, 1H), 1.28 (s, 3H), 1.17 (m, 1H), 0,94 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C-NMR δ 143.57, 139.47, 127.51, 108.84, 84.67, 74.59, 66.54, 47.18, 47.12, 36.28, 33.45, 29.97, 24.53, 23.49, 22.56. High resolution MS (m/z) Calcd for $C_{15}H_{24}O_3$: 252.1725, Found: 252.1688.

Reduction of **5** with triethylsilane and titanium tetrachloride (Table 1, entry 5)

To a solution of **5** (7.5 mg) in dry dichloromethane (2 ml) was added titanium tetrachloride (1.0 M solution in dichloromethane, 150 μl) at -78 °C. After stirring 10 minuets, triethylsilane (28.8 μl) was added to this at the same temperature. The mixture was allowed to stand for 1 hour and then warmed gradually to 0 °C. Extraction and purification by column chromatography on silica gel (elution with 40% ethyl acetate in hexane) afforded 5 mg of **13** as a colorless oil (60% yield). ^{1}H-NMR ($CDCl_3$) δ 5.50 (m, 1H), 4.65—4.52 (m, 2H), 4.54—4.52 (m, 2H), 4.05 (m, 1H), 2.89 (s, 1H), 2.14—2.04 (m, 2H), 1.71 (m, 1H), 1.66—1.53 (m, 6H), 1.49—1.39 (m, 2H), 1.21 (m, 1H), 1.20 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 140.2, 119.3, 77.1, 76.1, 73.5, 67.5, 47.9, 47.1, 40.3, 28.9, 27.7, 24.5, 23.3, 22.7, 22.5. High resolution MS (m/z) Calcd. for $C_{15}H_{28}O_3$: 256.2039, Found: 256.1996.

Reduction of **5** with TMSOTf and BH_3·SMe_2 (Table 1, entry 15)

To a solution of **5** (427.8 mg) in dry THF (30 ml) was added trimethylsilyl trifluoromethanesulfonate (396.3 ml) at -78 °C and then borane dimethylsulfide (1.0 M in dichloromethane, 2.05 ml). The solution was warm to -45 °C for 3 hours. Extraction and purification by column chromatography on silica gel (elution with 10% ethyl acetate in hexane) gave a mixture of **4a** and **4b** (358.2 mg, 83.1% yield, **4a/4b** = 53/47). The mixture was oxidized without separation.

Reduction of **5** by the other methods

Reactions were carried out with 10–15 mg of **5**. Dibromoaluminum hydride was prepared from lithium aluminum hydride and aluminum bromide in ether at 0 °C (Table 1, entry 3). The reaction conditions of entries 6–11 in Table 1 were same as that of entry 5 except for the reagents.

Preparation of epiipomeamarone (**3**)

To a solution of **4a** (46.7 mg) in dry dichloromethane (9 ml) was added a powdered molecular sieve (3A, 467 mg) and pyridinium chlorochromate (102.5 mg) at room temperature. After 3 hours, the mixture was extracted and purified by MPLC on silica gel (elution with pentane/ether = 6/1) to give 30.2 mg of **3** (65%yield). **3**: colorless oil, $[\alpha]_D^{20} = 3.1$ (c 1.6, ethanol) (lit.[2] for enantiomer of **3** (epingaione) $[\alpha]_D$ = -7.3 (10%, ethanol)). ^{1}H-NMR ($CDCl_3$) δ 7.38—7.37 (m, 2H), 6.36 (m, 1H), 4.98 (m, 1H), 2.70 (d, *J* = 15.0 Hz, 1H), 2.69 (d, *J* = 15.0 Hz, 1H), 2.36 (d, *J* = 7.1 Hz, 2H), 2.19 (m, 1H), 2.15—2.07 (m, 2H), 2.00—2.07 (m, 2H), 2.00—1.90 (m, 2H), 1.33 (s, 3H), 0.91 (d, *J* = 6.6 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 209.7, 143.4, 139.3, 127.4, 108.7, 81.8, 73.6, 53.7, 53.5, 37.3, 33.5, 28.0, 24.5, 22.6 (double). IR (neat, cm^{-1}) 3150, 2965, 2940, 2880, 1720, 1035, 880. High resolution MS (*m/z*) Calcd for $C_{15}H_{22}O_3$: 250.1569, Found: 250.1602.

Preparation of ipomeamarone (**1**)

To a solution of sodium methoxide in methanol (prepared from 700 mg of sodium and 16 ml of dry methanol) was added **3** (17.6 mg). After refluxing for 1.5 hours, the solution was extracted with ether and concentrated to give 14.4 mg of a mixutre of **1** and **3** (**1**/**3** = 51/49). Purification by HPLC on ODS column (elution with 35% water in methanol) yielded 3.4 mg of **1** and 1.0 mg of **3**. **1**: colorless oil, $[\alpha]_D^{20} = 27.8$ (c 0.3, ethanol) (lit.[1] $[\alpha]_D^{27} = 27$ (c 4.7, ethanol). ^{1}H-NMR ($CDCl_3$) δ 7.38—7.37 (m, 2H), 6.37 (m, 1H), 4.92 (m, 1H), 2.71 (d, *J* = 14.9 Hz, 1H), 2.64 (d, *J* = 14.9 Hz, 1H), 2.32 (dd, *J* = 12.0, 2.2 Hz, 1H), 2.32 (dd, *J* = 12.0, 1.5 Hz, 1H), 2.26 (m, 1H), 2.15—2.07 (m, 2H), 1.95—1.88 (m, 2H), 1.33 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H). IR (neat, cm^{-1}) 2965, 2940, 2880, 2860, 1715, 1510, 1475, 1370, 1165, 1030, 920, 880. Anal. Calcd for $C_{15}H_{22}O_3$, C: 71.97, H: 8.86, Found, C: 71.50, H: 8.83.

Preparation of ngaione (**2**)

To a solution of a mixture of **4a** and **4b** (341.4 mg, **4a**/**4b** = 53/47) in dry dichloromethane (60 ml) were added a powdered molecular sieve (3A, 3.41 g) and pyridinium chlorochromate (729 mg) at room temperature. After 3 hours, the mixture was extracted and purified by MPLC on silica gel (elution with 6% ethyl acetate in hexane) to give 246.8 mg of a mixture of **2** and **3** (72.9% yield, **2**/**3** = 48/52). The obtained isomeric mixture was separated by HPLC on ODS column (elution with 35% water in methanol) to afforded 63.1 mg of **2** and 17.9 mg of **3**. **2**: colorless oil, $[\alpha]_D^{20} = -32.2$ (C 0.9, ethanol) (lit.[5] $[\alpha]_D$ = -27 (neat)). IR (neat, cm^{-1}) 2860, 2940, 2880, 1715, 1510, 1475, 1370, 1160, 1030, 920, 880, 795. ^{1}H-NMR ($CDCl_3$) δ 7.38—7.37 (m, 2H), 6.36 (m, 1H), 4.92 (m, 1H), 2.71 (d, *J* = 15.0 Hz, 1H), 2.64 (d, *J* = 15.0 Hz, 1H), 2.33 (dd, *J* = 12.0, 2.2 Hz, 1H), 2.32 (dd, *J* = 12.0, 1.5 Hz, 1H), 2.26 (m, 1H), 2.17—2.05 (m, 2H), 1.95—1.85 (m, 2H), 1.33 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 209.5, 143.4, 139.3, 127.3, 108.9, 81.8, 72.6, 54.3, 53.8, 37.1, 33.2, 26.8, 24.5, 22.6 (double). Anal. Calcd for $C_{15}H_{22}O_3$, C: 71.97, H: 8.86, Found, C: 71.36, H: 8.81.

References

1. Hiura, M., *Rep. Gifu. Agric. Coll.* **1943**, *50*, 1. Kubota, T.; Matsuura, T., *Chem. Ind. (London)*, **1956**, 521. Uritani, I.; Uritani, M.; Yamada, H., *Phytopathology* **1960**, *50*, 10. Kim, W. K.; Uritani,

I., *Plant Cell Physiol.* **1974**, *15*, 1093. Oba, K.; Tatematsu, H.; Yamashita, K.; Uritani, I., *Plant Physiol.* **1976**, *58*, 51.

2. Birch, A. J.; Massay-Westropp, R.; Wright, S. E., *Aust. J. Chem.* **1953**, *6*, 385. Hegarty, B. F.; Kelly, J. R.; Park, R. J.; Sutherland, M. D., *Aust. J. Chem.* **1970**, *23*, 107. Hamilton, W. D.; Park, R. J.; Perry, R. J.; Sutherland, M. D., *Aust. J. Chem.* **1973**, *26*, 375.
3. Burka, L. T.; Kuhnert, L.; Wilson, B. J.; Harris, T. M., *J. Am. Chem. Soc.* **1977**, *99*, 2302. Denz, F. A.; Hanger, W. G. *J. Path. Bat.* **1961**, *81*, 91. Uritani, I.; Oba, K.; Takeuchi, A.; Sato, K.; Inoue, H.; Ito, R.; Ito, I., in Antinutrients and Natural Toxicants in Foods' (Ed. R. L. Ory) p. 1 (Food and Nutrition Press: Westport, CT 1981).
4. Akazawa, T.; Uritani, I., *Agr. Biol. Chem.* **1962**, *26*, 131. Oba, K.; Uritani, I., *Plant Cell Pysiol.* **1979**, *20*, 819. Inoue, H.; Uritani, I., *Plant Cell physiol.* **1979**, *20*, 1307. Burka, L. T.; Felica, L. J.; Jackson, S. W., *Phytochemistry* **1981**, *20*, 647. Schneider, J.; Lee, J.; Yoshhara, K.; Mizukawa, K.; Nakanishi, K., *J. Chem. Soc., Chem. Commun.* **1984**, 372.
5. (a) Russell, C. A.; Sutherland, M. D., *Aust. J. Chem.* **1982**, *35*, 1881. (b) Schneider, J. A.; Yoshihara, K.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 352.
6. Total synthesis of racemic ipomeamarone (ngaione): Burka, L. T.; Wilson, B. J., *J. Org. Chem.* **1974**, *39*, 2212. Kondo, K.; Matsumoto, M. *Tetrahedron Lett.* **1976**, 4363.
7. Preliminary report has been published: Sugimura, T.; Koguro, K.; Tai, A., *Tetrahedron Lett.* **1993**, *34*, 509.
8. Dimitriadis, E.; Massy-Westropp, R. A., *Aust. J. Chem.* **1979**, *32*, 2003.
9. Sugimura, T.; Goto, S.; Koguro, K.; Futagawa, T.; Misaki, S.; Morimoto, Y.; Yasuoka, N.; Tai, A.,,*Tetrahedron Lett.* **1993**, *34*, 505.
10. Tai, A.; Kikukawa, T.; Sugimura, T.; Inoue, Y.; Osawa, T.; Fujii, S., *J. Chem. Soc., Chem. Commun.* **1991**, 795. Tai, A.; Ito, K.; Harada, T., *Bull. Chem. Soc. Jpn.* **1981**, *54*, 223.
11. Naruse, Y.; Yamamoto, H., *Tetrahedron* **1988**, *44*, 6021. *idem*, *Tetrahedron Lett.* **1986**, *27*, 1363.
12. Sugimura, T.; Futagawa, T.; Tai, A., *Tetrahedron Lett.* **1988**, *29*, 5775. Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A., *Tetrahedron Lett.* **1989**, *30*, 3807. Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A., *Tetrahedron* **1990**, *46*, 5955.
13. Haarmann, H.; Eberbach, W., *Tetrahedron Lett.* **1991**,*32*, 903.
14. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H., *Tetrahedron Lett.* **1983**, *24*, 4581. *idem*, *J. Organomet. Chem.* **1985**, *285*, 83.
15. Hailton, W. D.; Park, R. J.;Sutherland, M. D., *Aust. J. Chem.* **1973**. *26*, 375.
16. Bartlett, P. A.; Johnson, W. S.; Elliott, J. D., *J. Am. Chem. Soc.* **1983**, *105*, 2088. Ishihara, K.; Mori, A.; Yamamoto, H., *Tetrahedron Lett.* **1986**, *27*, 983. Mori, A.; Ishihara, K.; Yamamoto, H., *ibid.* **1986**, *27*, 987. *idem*, *Tetrahedron* **1987**, *43*, 755.
17. Hunter, R.; Bartels, B.; Michael, J. P., *Tetrahedron Lett.* **1991**, *32*, 1095.
18. Kotsuki, H.; Ushio, Y.; Katoda, I.; Ochi, M., *J. Org. Chem.* **1989**, *54*, 5153. Ishihara, K.; Mori, A.; Yamamoto, H., *Tetrahedron* **1990**, *46*, 4595.
19. Yamamoto, Y.; Nishii, S.; Yamada, J., *J. Am. Chem. Soc.* **1986**, *108*, 7116. Denmark, S. E.; Almstead, N. G., *J. Am. Chem. Soc.* **1991**, *113*, 8089.

(*Received in Japan* 15 *July* 1994; *accepted* 13 *August* 1994)