CHIRAL SYNTHESIS OF FURANOSESQUITERPENE, (+)-IPOMEAMARONE

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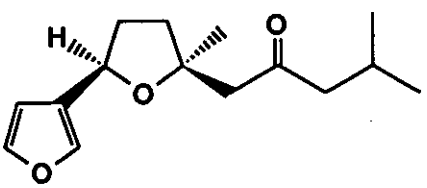
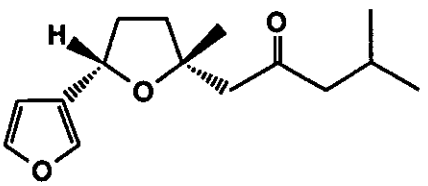
Abstract - (+)-Ipomeamarone, a furanosesquiterpene isolated from mold-damaged sweet potato (*Ipomea batatas*) as one of the phytoalexins, was synthesized starting from (*S*)-lactic acid as the chiral source using Seebach's chiral self-reproduction method.

(+)-Ipomeamarone (**1**) is a furanosesquiterpene isolated from the mold-damaged sweet potato *Ipomea batatas* as one of the first phytoalexins.[1] The structure of ipomeamarone (**1**) was elucidated by Kubota *et al.*[2] and then its absolute stereochemistry was determined by Nakanishi *et al.*[3] in 1983. Interestingly, the (-)-enantiomer of (+)-ipomeamarone (**1**) was also found in nature, and its name is (-)-ngaione (**2**), which was isolated from *Myoporum deserti*.[4]



(+)-Ipomeamarone (1)



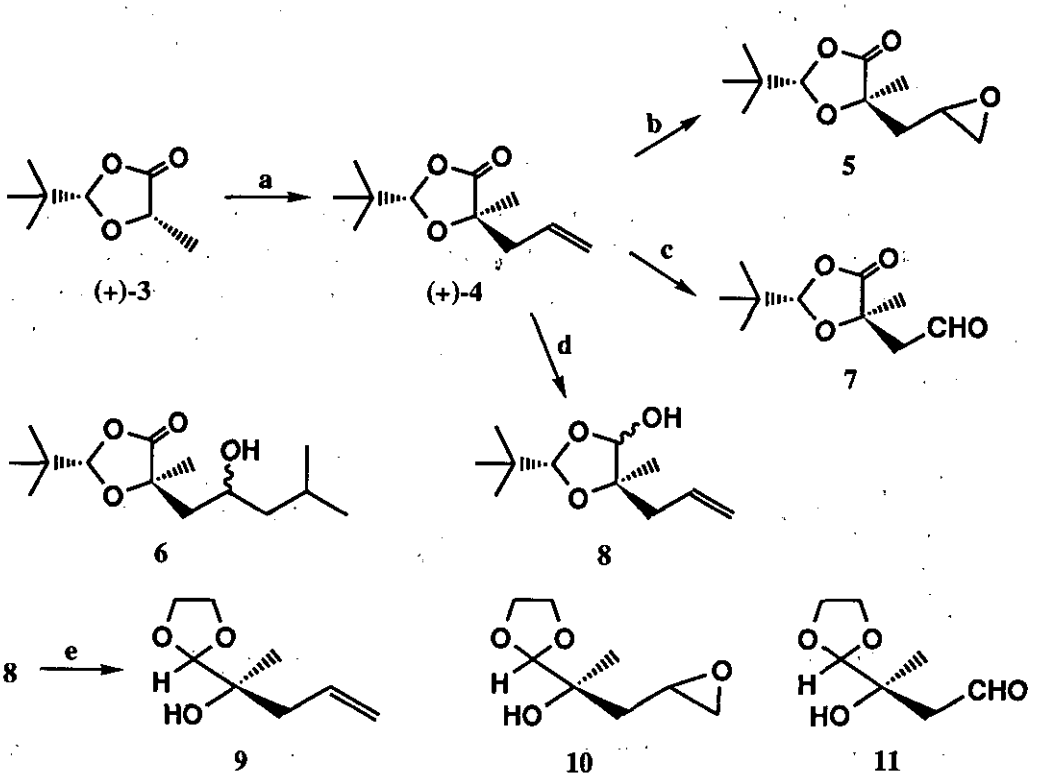
(-)-Ngaione (2)

In the course of our chiral synthetic studies on biologically active natural products, which have a chiral quaternary carbon atom substituted by one oxygen, we have reported the synthesis of (-)-malyngolide and (-)-frontalin starting from D-lactose as a chiral source.[5] Both (+)-ipomeamarone (**1**) and (-)-ngaione (**2**) have a chiral quaternary carbon atom that is substituted by one oxygen atom and possess interesting biological activity worthy of a toxicological study.[6] Therefore, we investigated the method for the synthesis of (+)-**1** as our next synthetic target. Four synthetic papers of racemic **1**[7] and two of (+)-**1**[8] have already been published. One of the synthetic reports of (+)-**1** was published by Tai *et al.*[8a] and they used (2*R*,4*R*)-6-methylheptane-2,4-diol as a starting material. In the other paper by Fukumoto *et al.*,[8b] (2*R*)-2-hydroxymethyl-2-methylcyclobutane was selected as a chiral synthon.

In our synthetic work on (+)-**1**,[9] the dioxolanone derivative ((+)-**4**) was chosen as a starting chiral synthon. Because (+)-**4** possesses one proper chiral center required for (+)-**1**, it was thought to be a

useful compound for the introduction of both the furyl group and the side chain present in the target molecule. Seebach[10] reported the synthesis of dioxolanone ((+)-**4**) in a high optically pure form using the so-called chiral self-reproductive stereospecific allylation of (+)-**3**, which was prepared by the condensation of 2,2-dimethylpropanal and (*S*)-lactic acid in high yield.

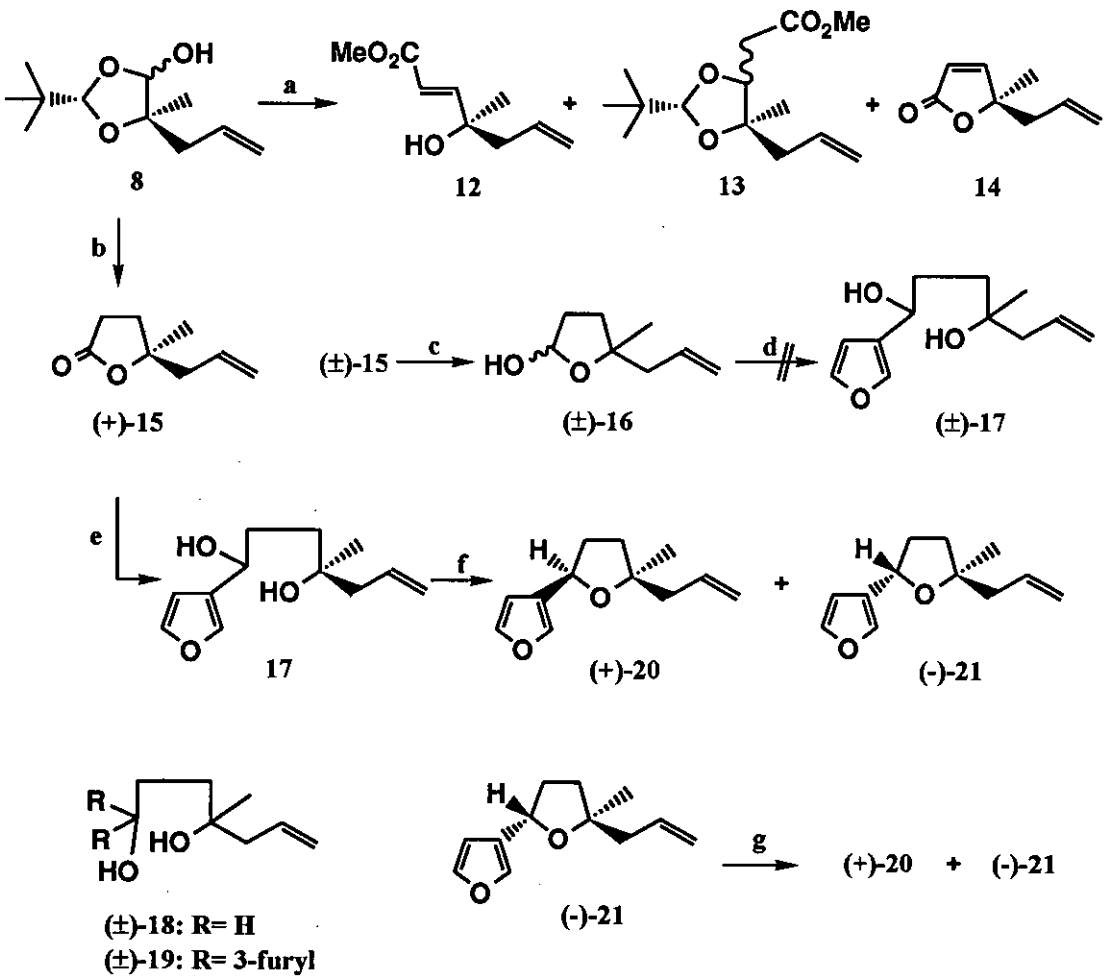
For the construction of the side chain of (+)-**1**, (+)-**4** was oxidized with *m*-chloroperbenzoic acid (MCPBA) to form the epoxide (**5**) in 63% yield. Treatment of **5** with isopropylmagnesium bromide in THF in the presence of CuI[11] or boron trifluoride diethyl etherate[12] failed to give the alcohol (**6**) and resulted in the formation of a complex mixture. Although an aldehyde (**7**), prepared in 36% yield by OsO_4-$NaIO_4$ oxidation of (+)-**4**, reacted with isobutylmagnesium bromide, the desired alcohol (**6**) was not isolated. Grignard-type reaction with the epoxide (**10**) and the aldehyde (**11**), similarly prepared from **9**[13] as previously shown, were carried out, but with unsuccessful results.



Scheme 1. *Reagents and conditions*: a. Ref. 10; b. MCPBA, $NaHCO_3$ in $CHCl_3$; c. OsO_4-$NaIO_4$ in THF-H_2O; d. DIBAL-H in CH_2Cl_2; e. ethylene glycol, *p*-TsOH.

We changed the initial approach and then tried to construct the tetrahydrofuran ring before the side chain introduction. The lactone ((+)-**15**) was thought to be a convenient intermediate for the introduction of the furan ring and the construction of the tetrahydrofuran moiety. Treatment of the hemiacetal (**8**), which was obtained by reduction of (+)-**4** with diisobutylaluminum hydride (DIBAL-H), with trimethyl phosphonoacetate in the presence of NaH in THF gave a mixture of the conjugate ester (**12**), the saturated ester (**13**)

and the conjugate lactone (**14**) in 26, 21 and 19% yields, respectively. It was thought possible to convert **12** and **14** to the desired saturated lactone ((+)-**15**) by selective conjugate reduction of each compound and successive acidic workup. But it should be hard to transform the saturated ester (**13**), which was formed through intramolecular conjugate addition of the intermediate via the Wittig-Horner reaction, to the lactone ((+)-**15**). Therefore, the selective reduction of the conjugate double bond must be



Scheme 2. *Reagents and conditions* : a. $(MeO)_2P(O)CH_2CO_2Me$, NaH in THF; b. i) $(MeO)_2P(O)CH_2CO_2Me$, NaH in THF, ii) K-Selectride in THF; 10% NaOH, 30% H_2O_2, iii) 10% HCl; c. DIBAL-H in CH_2Cl_2; d. 3-furyllithium in ether; e. i) 3-furyllithium in ether, ii) $LiAlH_4$ in ether; f. i) *p*-TsCl, pyridine, ii) SiO_2 column separation; g. *p*-TsOH in CH_2Cl_2.

performed immediately after the Wittig-Horner reaction to diminish the formation of **13** . Thus, the successive reactions of **8** including the Wittig-Horner reaction, conjugate reduction with potassium tri-*sec*-butylborohydride (K-Selectride),[14] oxidative workup, and the final treatment of the product with acid gave the lactone ((+)-**15**) in 47% overall yield from **8**.

With the lactone ((+)-**15**) finally synthesized, we next examined the introduction of the furyl group using (±)-**15**.[15] When 3-furyllithium[16] was treated with the lactol ((±)-**16**), which was obtained by DIBAL-H reduction of (±)-**15** in 78% yield, the expected diol ((±)-**17**) was not obtained and the lactol ((±)-**16**) was recovered. A similar unreactivity of the lactol with 3-furyllithium during the synthesis of a diterpene portulal has been encountered.[17] In that case, we overcame the difficulty by the reaction of the lactone with 3-furyllithium and then reduction of the formed ketone to the alcohol.[17, 18] When 2.9 eq of 3-furyllithium was added to the ether solution of (±)-**15** at -20 °C and stirred for 2 h, and then sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) was added to the reaction mixture and stirred for 1 h at the same temperature, the desired diol ((±)-**17**) and 1,1-bis(3-furyl)-4-methyl-6-heptene-1,4-diol ((±)-**19**) were isolated in 34 and 36% yields, respectively. Treatment of (±)-**15** with 2.0 eq of 3-furyllithium at -78 °C for 5.5 h and successive reduction of the product with $LiAlH_4$ at -78 °C gave (±)-**17** and 4-methyl-6-heptene-1,4-diol ((±)-**18**), the latter of which was the reduction product of (±)-**15**, in 46 and 20% yields, respectively.

Table 1. Reaction of (±)-**15** with 3-furyllithium

run[a]	3-furyllithium (mol)[b]	stirring time (h)	reducing agent (mol)[c]	temp. (°C) stirring time (h)	yield (%) (±)-**17**	(±)-**18**	(±)-**19**
1	2.9	2.0	Red-Al 2.7 X 2	-20 1	34	—	36
2	2.0	5.5	$LiAlH_4$ 1.0	-78 → rt[d] 16	46	20	—
3	1.5	2.5	$LiAlH_4$ 1.0	-78 → rt[d] 17	84	—	—
4	1.0	3.0	$LiAlH_4$ 1.2	-78 → rt[d] overnight	74	15	—

a) An ether solution of 3-furyllithium was added to an ether solution of (±)-**15** in the case of runs 1 and 2. An ether solution of (±)-**15** was added to an ether solution of 3-furyllithium in the case of runs 2 ~4.
b) Molar ratio of 3-furyllithium against (±)-**15**.
c) Molar ratio of reducing agent against (±)-**15**.
d) Room temperature.

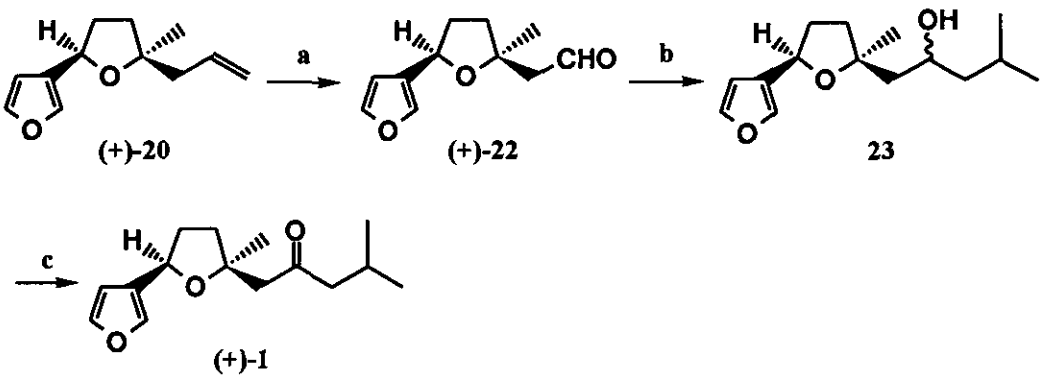
But when the ether solution of (±)-**15** was added to the ether solution of 3-furyllithium (1.5 eq) at -78 °C and stirred for 2.5 h, and the subsequent $LiAlH_4$ reduction was carried out, the desired diol ((±)-**17**) was obtained in 84% yield and no byproduct was detected. Reduction of the amount of 3-furyllithium to 1.0 eq resulted in decreasing the yield of (±)-**17** to 74% and formation of the byproduct ((±)-**18**) in 15% yield. These results are summarized in Table 1.

Tosylation of (±)-**17** with *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine gave a mixture of the desired cyclization product ((±)-**20**) and its epimer ((±)-**21**) in 93% yield. The mixture was separeted by

preparative SiO_2 thin layer chromatography (ptlc) and the ratio of (±)-**20** and (±)-**21** was 17:19. The stereochemistry of (±)-**20** was determined by observation of the NOE between the tertiary methyl group (δ:1.27 ppm) and the methine proton (δ: 4.94 ppm) on the tetrahydrofuran ring. On the other hand, such NOE was not observed in (±)-**21**.

Now, as the route to (±)-**20** from (±)-**15** was established, these successive reactions were carried out starting from (+)-**15**, and (+)-**20** and (-)-**21** were synthesized in overall yields of 25 and 37% from (+)-**15**, respectively, after SiO_2 column chromatography purification. Fortunately, treatment of (-)-**21** with *p*-TsOH in dichloromethane under reflux gave a mixture of (+)-**20** and (-)-**21** in a ratio of about 3:2.[8b] This result suggests that (-)-**21** is also useful for the synthesis of (+)-**1**.

The preparation of the side chain of (+)-**1** was carried out by a three-step reaction sequence from (+)-**20**. Oxidation[19] of (+)-**20** with OsO_4-$NaIO_4$ in THF-H_2O gave the aldehyde ((+)-**22**) in 25% yield. But OsO_4-*N*-methylmorpholine *N*-oxide (NMO) oxidation of (+)-**20** in acetonitrile-H_2O and the subsequent $NaIO_4$ oxidation of the diol formed in THF-H_2O and keeping the reaction mixture neutral by the addition of 1 M $NaHCO_3$ aqueous solution gave (+)-**22** in 72% yield.[20] The Grignard reaction of (+)-**22** with isobutylmagnesium bromide in THF furnished the isomeric mixture of alcohols (**23**) in 91% yield. The mixture was finally oxidized with pyridinium chlorochromate (PCC)-Celite in the presence of

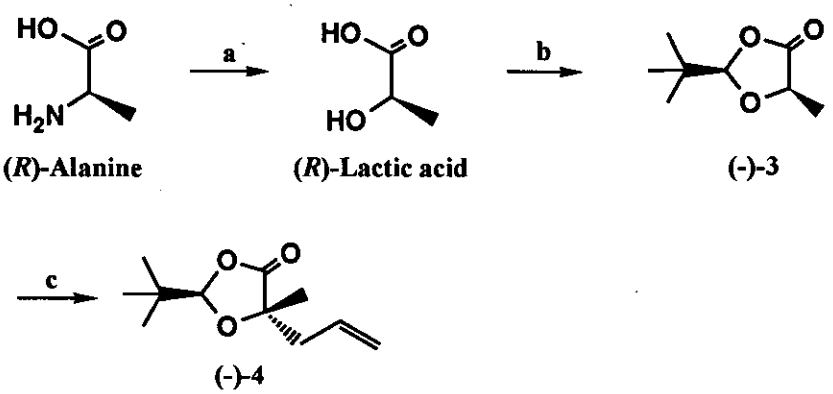


Scheme 3. *Reagents and conditions*: a. i) OsO_4-NMO in CH_3CN-H_2O, ii) $NaIO_4$, 1 M $NaHCO_3$ in THF-H_2O; b. isobutylmagnesium bromide in THF; c. PCC-Celite, NaOAc in CH_2Cl_2.

anhydrous sodium acetate in dichloromethane to give (+)-ipomeamarone (**1**) in 86% yield; $[\alpha]_D^{25}$ +23.5° (*c*=4.9, EtOH)[lit.,[3] $[\alpha]_D$ +27° (*c*=4.7, EtOH)]. The ir and ^{1}H-nmr spectral data of the synthesized (+)-**1** are identical to those of the natural one.[3, 8] Thus, (+)-ipomeamarone (**1**) was synthesized in 16% overall yield starting from the known (+)-dioxolanone (**4**).

For the synthesis of (-)-ngaione (**2**), the promising starting material, (-)-dioxolanone (**4**) was prepared as follows. (*R*)-Lactic acid prepared from (*R*)-alanine in 82% yield[21] was reacted with 2,2-dimethylpropanal to form the (-)-dioxolanone (**3**) ($[\alpha]_D^{22}$ -44.67°, *c*=1.94, $CHCl_3$) in 38% yield, after repeated recrystallization at low temperature. Allylation of (-)-**3** with allyl bromide in the presence of lithium

diisopropylamide (LDA) in THF using a chiral self-reproduction technique afforded the (-)-dioxolanone (**4**) ($[\alpha]_D^{23}$ -52.76°, *c*=1.82, $CHCl_3$) in 62% yield. (-)-Ngaione (**2**) might be synthesized starting from (-)-**4** using the same reaction sequences employed for (+)-ipomeamarone (**1**).



Scheme 4. *Reagents and conditions*: a. $NaNO_2$, 1 N H_2SO_4; b. 2,2-dimethylpropanal, *p*-TsOH, conc. H_2SO_4 in pentane; c. LDA, allyl bromide in THF.

EXPERIMENTAL SECTION

Unless otherwise stated the following procedures were adopted. Melting points were determined using a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. Ir spectra were measured with a Hitachi 260-30 infrared spectrophotometer. ^{1}H-Nmr spectra were recorded on a JEOL JNM-GSX270 (270 MHz) spectrometer using tetramethylsilane as the internal standard. High-resolution mass spectra (HRms) were measured with a JEOL JMS-HX100 instrument at 70 eV. Optical rotations were recorded on a JASCO DIP-370 polarimeter.

(2*S*,4*RS*,5*R*)-5-Allyl-2-(*t*-butyl)-5-methyl-1,3-dioxolan-4-ol (8)

A solution of DIBAL-H in toluene (1.5 M solution, 29.9 ml, 44.9 mmol) was added dropwise to a stirred solution of (+)-4[10] (6.0 g, 34.8 mmol) in dry dichloromethane (66.6 ml) by syringe at -78 °C and the mixture was stirred for 20 min at the same temperature. After methanol was added at the same temperature, the mixture was warmed to room temperature and stirred for 30 min. The mixture was filtered through Celite pad and the filtrate was concentrated under reduced pressure to give a yellow oil (5.956 g). The oil was purified by SiO_2 column chromatography (benzene) to furnish **8** (5.854 g, 97%). Ir (neat): 3450, 1640, 1100, 975 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.84 and 0.86 (9H in total, each s, $C(CH_3)_3$), 1.14 and 1.19 (3H in total, each s, CCH_3), 2.10~2.80 (4H, m, $CC\underline{H}_2CH=CH_2$, O<u>H</u>), 4.66 and 4.86 (1H in total, each s, OCHO), 4.97~5.10 (3H, m, $CH=C\underline{H}_2$, $OC\underline{H}OH$), 5.65~5.90 (1H, m, $CC\underline{H}=CH_2$). Ms (*m*/*z*): 143, 97, 85, 69, 57.

2-((1*R*)-1-Hydroxy-1-methyl-3-butenyl)-1,3-dioxolane (9)

A solution of **8** (1.00 g, 5.7 mmol), *p*-TsOH (123 mg) and ethylene glycol (0.71 ml, 12.7 mmol) in chloroform (123 ml) was refluxed for 30 min. Chloroform (100 ml) was added to the reaction mixture and the whole was heated to give 100 ml of distillate. The solution was washed with saturated $NaHCO_3$ solution, H_2O and brine, successively and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave **9** as an yellow oil (754 mg, 83%). Ir (neat): 3440, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.18 (3H, s, CCH_3), 2.00 (1H, s, OH), 2.21~2.41 (2H, m, $CC\underline{H}_2CH=CH_2$), 3.90~4.05 (4H, m, OCH_2CH_2O), 4.71 (1H, s, OCHO), 5.08~5.17 (2H, m, $CH=C\underline{H}_2$), 5.83~5.99 (1H, m, $CC\underline{H}=CH_2$).

(4*R*)-Methyl 4-hydroxy-4-methyl-2,6-heptadienoate (12), (2*R*,4*R*,5*RS*)-2-*t*-Butyl-5-methoxycarbonylmethyl-4-methyl-4-(2-propenyl)-1,3-dioxolane (13) and (4*R*)-4-Methyl-4-(2-propenyl)-2-buten-4-olide (14)

A solution of trimethyl phosphonoacetate (0.82 ml, 4.96 mmol) in dry THF (3 ml) was added dropwise to a stirred suspension of NaH (216 mg, 5.40 mmol, 60% in a mineral oil) in dry THF (34 ml) under N_2 atmosphere at room temperature and the mixture was stirred for 1 h at room temperature. A solution of **8** (456 mg, 2.28 mmol) in dry THF (3 ml) was added to the above mixture and the whole was stirred for 4 h at room temperature. After removal of the solvent under reduced pressure, the residue was dissolved in H_2O. The solution was acidified with 10% HCl until pH 3 and then extracted with ether. The combined extract was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil, which was separated by SiO_2 column chromatography (ether : *n*-hexane = 1 : 1) into a mixture (190 mg) of **12** and **14**, and the crude **13**. The mixture of **12** and **14** (168 mg) was purified by SiO_2 preparative tlc (benzene : ethyl acetate = 6 : 1) to furnish pure **12** (89 mg, 26%) and **14** (52 mg, 19%) as colorless oils, respectively. The crude **13** was purified by SiO_2 column chromatography (ether : *n*-hexane = 1 : 5) to afford pure **13** (125 mg, 21%) as a colorless oil. **12**: Ir (neat): 3410, 1710, 1660, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.34 (3H, s, CCH_3), 1.90 (1H, s, OH), 2.26~2.46 (2H, m, $CC\underline{H}_2CH=CH_2$), 3.75 (3H, s, CO_2CH_3), 5.11~5.23 (2H, m, $CH=C\underline{H}_2$), 5.75 (1H, dddd, *J*=17, 10, 8, 6.5 Hz, $CH_2C\underline{H}=CH_2$), 6.04 (1H, d, *J*=15.5 Hz, $CH=C\underline{H}CO_2CH_3$), 6.985 (1H, d, *J*=15.5 Hz, $CC\underline{H}=CHCO_2CH_3$). **13**: Ir (neat): 1735, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.89, 0.895 and 0.91 (9H in total, each s, $C(CH_3)_3$), 1.07~1.26 (3H, m, CH_3), 2.26~2.67 (4H, m, $CC\underline{H}_2CH=CH_2$, $CHC\underline{H}_2CO_2CH_3$), 3.70~3.74 (3H, m, CO_2CH_3), 4.03, 4.12 and 4.225 (1H in total, dd, dt, dd, *J*=5, 9 Hz, *J*=4.5, 9 Hz, *J*=5, 9 Hz, $OC\underline{H}CH_2CO_2CH_3$), 4.585, 4.61 and 4.705 (1H in total, each s, OCHO), 5.03~5.17 (2H, m, $CH=C\underline{H}_2$), 5.74~5.98 (1H, m, $CH_2C\underline{H}=CH_2$). **14**: Ir (neat): 1760, 1640, 1605 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.47 (3H, s, CCH_3), 2.505 (2H, d, *J*=7 Hz, $CC\underline{H}_2CH=CH_2$), 5.09~5.20 (2H, m, $CH=CH_2$), 5.68 (1H, tdd, *J*=16.5, 10.5, 7 Hz, $CH_2C\underline{H}=CH_2$), 6.03 (1H, d, *J*=5.5 Hz, $CH=C\underline{H}CO$), 7.365 (1H, d, *J*=5.5 Hz, $CC\underline{H}=CHCO$).

(4*S*)-(+)-4-Methyl-4-(2-propenyl)butan-4-olide (15)

Trimethyl phosphonoacetate (14 ml, 84.76 mmol) was added by syringe to a stirred suspension of NaH (3.389 g, 84.73 mmol, 60% in mineral oil) in dry THF (570 ml) under N_2 atmosphere at room temperature. After the mixture was stirred for 1 h, a solution of **8** (7.713 g, 38.51 mmol) in dry THF (45 ml) was added and the whole was stirred for 3 h at room temperatre. 10% HCl was added to make the

mixture acidic until pH 2 under ice cooling and THF was distilled off under reduced pressure. The residue was extracted with ether and the combined extract was washed with brine. After drying over anhydrous Na_2SO_4, the solution was concentrated under reduced pressure to give an oil (13.453 g). K-Selectride (47.0 ml, 47.0 mmol, 1.0 M THF solution) was added by syringe to a solution of the above oil in dry THF (77 ml) under N_2 atmosphere at -78 °C. After the mixture was stirred at -78 °C for 2.5 h, more K-Selectride (47.0 ml, 47.0 mmol, 1.0 M THF solution) was added and the whole was stirred at -78 °C for 2.5 h. To the reaction mixture were added 10% NaOH aqueous solution (162 ml) and 30% H_2O_2 aqueous solution (116 ml) under ice cooling and the whole was stirred for 13 h at room temperature. The reaction mixture was acidified by addition of 10% HCl until pH 2 and the whole was stirred at 50 °C for 30 min. The organic layer was separated and the water layer was extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, successively, and dried over anhydrous Na_2SO_4. Removal of the solvent gave an oil, which was purified by SiO_2 column chromatography (ethyl acetate : chloroform : benzene = 1 : 5 : 4) to give (+)-**15** (2.559 g, 47%) as a colorless oil. bp 73 °C (0.4 Torr). $[\alpha]_D^{17}$ +3.33° (*c*=1.27, MeOH). Ir (neat): 1760, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.40 (3H, s, CCH_3), 1.96 and 2.16 (each 1H, each ddd, *J*=13, 9, 7 Hz, *J*=13, 9, 8 Hz, $CC\underline{H}_2CH_2CO$), 2.42 (2H, d, *J*=7 Hz, $CC\underline{H}_2CH{=}CH_2$), 2.59 and 2.60 (2H in total, each dd, *J*=9, 7 Hz, *J*=9, 8 Hz, $CH_2C\underline{H}_2CO$), 5.12~5.22 (2H, m, $CH{=}C\underline{H}_2$), 5.79 (1H, tdd, *J*=16, 11, 7 Hz, $CH_2C\underline{H}{=}CH_2$). HRms (*m/z*): Calcd for $C_8H_{12}O_2$: 140.0810. Found: 140.0837.

(±)-5-Hydroxy-2-methyl-2-(2-propenyl)oxolane (16)

DIBAL-H (11.5 ml, 17.25 mmol, 1.5 M toluene solution) was added to a stirred solution of (±)-**15** (2.003 g, 14.29 mmol) in dry dichloromethane (31 ml) by syringe under N_2 atmosphere at -78°C. After the reaction mixture was stirred for 3.5 h, additional DIBAL-H (9.0 ml, 13.5 mmol) was added and the whole was stirred for 30 min. Methanol was added to the reaction mixture to stop the reaction and then the precipitates formed were removed by filtration. The filtrate was concentrated under reduced pressure to give (±)-**16** (1.581 g, 78%) as a pale yellow oil. Ir (neat): 3370, 1635 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.16 and 1.38 (3H in total, each s, CCH_3), 1.59~2.12 (4H, m, $CHC\underline{H}_2C\underline{H}_2C$), 2.18~2.23 and 2.39~2.45 (each 1H, each m, $CC\underline{H}_2CH{=}CH_2$), 3.21 and 3.36 (1H in total, each br s, OH), 5.02~5.14 (2H, m, $CH{=}C\underline{H}_2$), 5.47~5.53 (1H, m, $C\underline{H}OH$), 5.71~5.96 (1H, m, $CH_2C\underline{H}{=}CH_2$).

Attempted Reaction of (±)-16 with 3-Furyllithium

n-BuLi (2.9 ml, 4.64 mmol, 1.6 mol *n*-hexane solution) was added to a stirred solution of 3-furyl bromide (0.35 ml. 3.78 mmol) by syringe at -78 °C and the mixture was stirred for 1 h. A solution of (±)-**16** (506 mg, 3.56 mmol) was added to the above reaction mixture and the whole was warmed to 0°C. The mixture was stirred at 0°C for 30 min. and at room temperature for 1 h. After addition of saturated ammonium chloride solution, the mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave starting (±)-**16** (472 mg, 93% recovery).

Reaction of (±)-15 with 3-Furyllithium (Table 1. run 1)

A solution of 3-furyl bromide (0.97 ml, 10.47 mmol) in dry ether (20 ml) was added to *n*-BuLi (7.8 ml, 12.48 mmol, 1.6 M *n*-hexane solution) under N_2 atmosphere and stirring at -78 °C and the mixture was stirred for 1 h. Thus prepared 3-furyllithium solution was added to a stirred solution of (±)-**15** (498 mg, 3.55 mmol) in dry ether (25 ml) by siringe under N_2 atmosphere at -20 °C and the mixture was stirred for 2 h. Red-Al (2.8 ml, 9.52 mmol, 3.4 M toluene solution) was added to the reaction mixture and the whole was stirred for 30 min. Additional Red-Al (2.8 ml, 9.52 mmol) was added and then the mixture was stirred for more 30 min. After addition of water, the mixture was extracted with ether. The extract was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil (1.009 g), 104 mg of which were purified by ptlc (acetone - *n*-hexane = 1 : 2) to afford (±)-**17** (26 mg, 34%) and (±)-**19** (36 mg, 36%) as yellow oils. (±)-**17**: Ir (neat): 3370, 1645, 1600, 1505 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.185 (3H, s, CCH_3), 1.45~1.71 (2H, m, $CHCH_2C\underline{H}_2C$), 1.80~1.91 (2H, m, $CHC\underline{H}_2CH_2$), 2.10 and 2.78 (each 1H, each br s, OH x 2), 2.24 (2H, d, *J*=7.5 Hz, $CC\underline{H}_2CH{=}CH_2$), 4.65 and 4.67 (1H in total, dd and t, *J*=7, 5 Hz, *J*=6 Hz, C<u>H</u>OH), 5.06~5.18 (2H, m, C<u>H</u>=CH_2), 5.835~5.845 (1H in total, each tdd, *J*=16.5, 10.5, 7.5 Hz, $CH_2C\underline{H}{=}CH_2$), 6.385~6.41 (1H, m, CCH=C<u>H</u>), 7.38 and 7.39 (2H in total, each s, =C<u>H</u>OC<u>H</u>=). (±)-**19**: ^{1}H-Nmr ($CDCl_3$) δ: 1.16 (3H, s, CCH_3), 1.48~1.56 (2H, m, $CCH_2C\underline{H}_2C$), 2.11~2.19 (2H, m, $CC\underline{H}_2CH_2C$), 2.21 (2H, d, *J*=7.5 Hz, $CC\underline{H}_2CH{=}CH_2$), 5.00~5.16 (2H, m, CH=C<u>H</u>$_2$), 5.79 (1H, tdd, *J*=17, 10, 7.5 Hz, $CH_2C\underline{H}{=}CH_2$), 6.30~6.38 (2H, m, OCH=C<u>H</u> x 2), 7.31~7.40 (4H, C<u>H</u>OC<u>H</u> x 2).

Reaction of (±)-15 with 3-Furyllithium (Table 1. run 2)

3-Furyllithium (prepared from 3-furyl bromide (0.495 ml, 5.34 mmol) and *n*-BuLi (3.8 ml, 6.08 mmol, 1.6 M *n*-hexane solution) as above) was added to a stirred solution of (±)-**15** (502 mg, 3.58 mmol) in dry ether (15 ml) by syringe under N_2 atmosphere at -78 °C and the mixture was stirred for 5.5 h. $LiAlH_4$ (140 mg, 3.69 mmol) was added to the reaction mixture and the whole was warmed to room temperature and stirred for 16 h. After addition of water, the precipitates formed were removed by filtration and the filtrate was extracted with ether. The combined extract was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil, which was purified by SiO_2 column chromatography (ethyl acetate) to give (±)-**17** (244 mg, 46%) and (±)-**18** (101 mg, 20%) as yellow oils. (±)-**18**: Ir (neat): 3320, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) d: 1.20 (3H, s, CCH_3), 1.53~1.75 (4H, m, CH_2 x 2), 2.26 (2H, d, *J*=7.5 Hz, $CC\underline{H}_2CH{=}CH_2$), 2.47 (2H, br s, OH x 2), 3.66 (2H, t, *J*=6 Hz, $CH_2C\underline{H}_2OH$), 5.07~5.18 (2H, m, CH=C<u>H</u>$_2$), 5.86 (1H, tdd, *J*=16.5, 10.5, 7.5 Hz, $CH_2C\underline{H}{=}CH_2$).

Reaction of (±)-15 with 3-Furyllithium (Table 1. run 3)

A solution of (±)-**15** (500 mg, 3.57 mmol) in dry ether (2 ml) was added to the stirred 3-furyllithium solution (prepared from 3-furyl bromide (0.495 ml, 5.34 mmol, dry ether (25 ml) solution) and *n*-BuLi (3.8 ml, 6.08 mmol, 1.6 M *n*-hexane solution) as above) under N_2 atmosphere at -78 °C and the whole was stirred for 2.5 h. $LiAlH_4$ (138 mg, 3.64 mmol) was added to the reaction mixture and the whole was warmed to room temperature and stirred for 17 h. After addition of water, the precipitatates were removed by filtration and the filtrate was extracted with ether. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil, which

was purified by SiO_2 column chromatography (acetone : *n*-hexane =1 : 2) to give (±)-**17** (629 mg, 84%) as a pale yellow oil.

Reaction of (±)-15 with 3-Furyllithium (Table 1. run 4)

A solution of (±)-**15** (3.825 g, 27.29 mmol) in dry ether (7 ml) was added to the stirred 3-furyllithium solution (prepared from 3-furyl bromide (2.6 ml, 28.05 mmol) and *n*-BuLi (20 ml, 32 mmol, 1.6 M *n*-hexane solution) in dry ether (200 ml) as above) under N_2 atmosphere at -78 °C and the whole was stirred for 3 h. $LiAlH_4$ (1.245 g, 32.81 mmol) was added to the reaction mixture and the reaction mixture was warmed to room temperature and stirred overnight. After addition of water, the precipitates formed were removed by filtration and the filtrate was extracted with ether. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil, which was purified by SiO_2 column chromatography (ethyl acetate) to give (±)-**17** (4.222 g, 74%) and (±)-**18** (593 mg, 15%) as pale yellow and yellow oils, respectively.

(2*S,5*R**)-5-(3-Furyl)-2-methyl-2-(2-propenyl)oxolane (20) and (2*S**,5*S**)-5-(3-Furyl)-2-methyl-2-(2-propenyl)oxolane (21)**

p-TsCl (5.089 g, 25.89 mmol) was added to a stirred solution of (±)-**17** (5.179 g, 24.63 mmol) in dry pyridine (36 ml) under ice cooling and the reaction mixture was stirred at 0 °C for 30 min and at room temperature for 14.5 h. After addition of chloroform (180 ml), the mixture was washed with water (90 ml), 5% HCl (360 ml), 10% HCl (180 ml) and water (180 ml), successively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a mixture (4.385 g, 93%) of (±)-**20** and (±)-**21** as a yellow oil. The mixture (54 mg) was separated by ptlc (ethyl acetate : *n*-hexane =1 : 9) into pure (±)-**20** (17 mg, more polar) and (±)-**21** (19 mg, less polar). (±)-**20**: Ir (neat): 1645, 1600, 1500 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.265 (3H, s, CCH_3), 1.69~2.03 and 2.16~2.27 (4H in total, each m, $ArCHC\underline{H}_2C\underline{H}_2C$), 2.33 (2H, d, *J*=7 Hz, $CC\underline{H}_2CH=CH_2$), 4.94 (1H, dd, *J*=8, 6 Hz, $ArC\underline{H}CH_2$), 5.03~5.14 (2H, m, $CH=C\underline{H}_2$), 5.875 (1H, tdd, *J*=18, 9.5, 7 Hz, $CH_2C\underline{H}=CH_2$), 6.37~6.40 (1H, m, $OCH=C\underline{H}$), 7.35~7.40 (2H, m, $C\underline{H}OC\underline{H}$). (±)-**21**: Ir (neat): 1645, 1600, 1500 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.275 (3H, s, CCH_3), 1.70~1.85, 1.87~2.03 and 2.15~2.27 (4H in total, each m, $ArCHC\underline{H}_2C\underline{H}_2$), 2.30~2.36 (2H, m, $CC\underline{H}_2CH=CH_2$), 4.905 (1H, dd, *J*=8, 6 Hz, $ArC\underline{H}CH_2$), 5.04~5.14 (2H, m, $CH=C\underline{H}_2$), 5.87 (1H, tdd, *J*=18, 9.5, 7 Hz, $CH_2C\underline{H}=CH_2$), 6.37~6.39 (1H, m, $OCH=C\underline{H}$), 7.36~7.39 (2H, m, $C\underline{H}OC\underline{H}$).

(2*S*,5*R*)-(+)-5-(3-Furyl)-2-methyl-2-(2-propenyl)oxolane (20) and (2*S*,5*S*)-(-)-5-(3-Furyl)-2-methyl-2-(2-propenyl)oxolane (21) from (+)-15

n-BuLi (17.5 ml, 28.0 mmol, 1.6 M *n*-hexane solution) was added to a stirred solution of 3-furyl bromide (2.25 ml, 24.28 mmol) in dry ether (113 ml) by syringe at -78 °C under N_2 atmosphere and the reaction mixture was stirred for 1 h. A solution of (+)-**15** (2.268 g, 16.18 mmol) in dry ether (9 ml) was added to the reaction mixture and the whole was stirred at -78 °C for 2.5 h. $LiAlH_4$ (615 mg, 16.21 mmol) was added and the reaction mixture was warmed gradually and stirred at room temperature for 17 h. Water was added and the precipitates formed were separated by filtration. The filtrate was extracted with ether and the

combined extract was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the crude **17** (4.44 g). *p*-TsCl (2.233 g, 11.36 mmol) was added to the stirred solution of the crude **17** (2.968 g) under ice cooling and the mixture was stirred at 0 °C for 30 min and at room temperature for 16.5 h. Chloroform (80 ml) was added and the obtained solution was washed with water (40 ml), 5% HCl (160 ml), 10% HCl (80 ml) and water (80 ml), successively. After drying over anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure, the residual oil was purified by SiO_2 column chromatography (ethyl acetate : *n*-hexane = 1 : 29) to give (+)-**20** (524 mg, 25%) and (-)-**21** (774 mg, 37%) as colorless oils, respectively. (+)-**20**: $[\alpha]_D^{24}$ +11.78° (*c*=1.14, MeOH). HRms (*m/z*): Calcd for $C_{12}H_{16}O_2$: 192.1151. Found: 192.1123. (-)-**21**: $[\alpha]_D^{24}$ -14.14° (*c*=1.24, MeOH).

Isomerization of (-)-21

A solution of (-)-**21** (127 mg, 0.661 mmol) and *p*-TsOH (84 mg, 0.488 mmol) in dry dichloromethane (20 ml) was refluxed for 3 h. After removal of the solvent under reduced pressure, the residue was purified by ptlc (ethyl acetate : *n*-hexane =1 : 9) to furnish (+)-**20** (42 mg, 33%) and (-)-**21** (28 mg, 22%) as colorless oils, respectively.

(2*S*,5*R*)-(+)-2-Formylmethyl-5-(3-furyl)-2-methyloxolane (22)

NMO (745 mg, 6.17 mmol) and 2% OsO_4 aqueous solution (1.80 ml, 0.142 mmol) were added to a solution of (+)-**20** (593 mg, 3.08 mmol) in acetonitrile (36 ml) and water (16 ml) under N_2 atmosphere at room temperature and the reaction mixture was stirred for 3 h. Saturated Na_2SO_3 aqueous solution (12 ml) was added and the mixture was stirred for 30 min. After addition of NaCl, the mixture was extracted with ethyl acetate. The combined extract was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a crude oil (790 mg), which was dissolved in a mixture of THF (50 ml) and water (19 ml). $NaIO_4$ (1.325 g, 6.19 mmol) was added portionwise to the stirred above mixture, during the addition (70 min), 1 M $NaHCO_3$ aqueous solution was added dropwise to keep the reaction mixture neutral at room temperature. After the reaction mixture was stirred for 1 h, the precipitates formed were removed by filtration and the filtrate was concentrated under reduced pressure. After addition of NaCl, the residue was extracted with ethyl acetate and the extract was dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil, which was purified by SiO_2 column chromatography (acetone : *n*-hexane = 2 : 3) to furnish (+)-**22** (434 mg, 72%) as a colorless oil. Ir (neat): 1720, 1600, 1500 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.405 (3H, s, CCH_3), 1.90~2.08 and 2.24~2.36 (3H and 1H, each m, ArCHC$\underline{H}_2$C$\underline{H}_2$), 2.64 (2H, d, *J*=2.5 Hz, CC$\underline{H}_2$CHO), 4.96~5.03 (1H, m, ArCH), 6.35~6.37 (1H, m, OCH=C$\underline{H}$), 7.36~7.40 (2H, m, C$\underline{H}$OC$\underline{H}$), 9.845 (1H, t, *J*=2.5 Hz, $CH_2C\underline{H}O$). Ms (*m/z*): 194 (M^+), 151, 95, 43. $[\alpha]_D^{25}$ +12.48° (*c*=1.28, MeOH).

(2*S*,5*R*)-4-(3-Furyl)-2-((2*RS*)-2-hydroxy-4-methylpentyl)-2-methyloxolane (23)

A solution of (+)-**22** (386 mg, 1.99 mmol) in dry THF (18 ml) was added dropwise to a stirred solution of isobutylmagnesium bromide (prepared from isobutyl bromide (1.30 ml, 11.95 mmol) and magnesium (291 mg, 11.91 mmol) in dry ether (5 ml) in the presence of catalytic amount of iodine) in ether under ice

cooling. The reaction mixture was stirred under ice cooling for 2 h. After addition of half saturated ammonium chloride solution and NaCl, the reaction mixture was extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give an oil, which was purified by SiO_2 column chromatography (ethyl acetate : benzene = 1 : 6) to afford an isomeric mixture of **23** (455 mg, 91%) as a colorless oil. Ir (neat): 3470, 1505, 1230 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.91 and 0.93 (6H in total, dd and d, *J*=6.5, 1.2 Hz and *J*=6.5 Hz, $CH(C\underline{H}_3)_2$), 1.06~1.21 and 1.37~2.38 (1H and 8H, each m, $CHC\underline{H}_2C\underline{H}(CH_3)_2$), $CC\underline{H}_2CHOH$), $CHC\underline{H}_2C\underline{H}_2C$), 1.31 and 1.365 (total 3H, each s, CCH_3), 3.835 and 4.065 (1H in total, each s, OH), 3.93~4.14 (1H, m, C<u>H</u>OH), 4.90~5.01 (1H, m, ArCH), 6.385~6.405 and 6.415~6.44 (1H in total, each m, OCH=C<u>H</u>), 7.34~7.42 (2H, m, C<u>H</u>OC<u>H</u>).

(+)-Ipomeamarone (1)

A solution of **23** (244 mg, 0.967 mmol) in dry dichloromethane (4 ml) was added dropwise to a stirred mixture of PCC (826 mg, 3.755 mmol), anhydrous sodium acetate (67 mg, 0.817 mmol) and dry Celite (1.011 g) in dry dichloromethane (6 ml) at room temperature and the whole was stirred for 5 h. Celite was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was passed through SiO_2 short column (ether) and then purified by SiO_2 column chromatography (ethyl acetate : benzene = 1 : 6) to give (+)-**1** (209 mg, 86%) as an colorless oil. $[\alpha]_D^{25}$ +23.53° (*c*=4.85, EtOH); lit., [3] $[\alpha]_D$ +27°(*c*=4.7, EtOH). Ir (neat) : 1705, 1500, 1450, 1365, 1160, 1040, 1020, 920, 875, 790, 600 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 and 0.89 (each 3H, d, *J*=6.5 Hz, $CH(C\underline{H}_3)_2$), 1.33 (3H, s, CH_3), 1.85~1.98 and 2.02~2.29 (2H and 3H, each m, $CH_2C\underline{H}(CH_3)_2$, $CHC\underline{H}_2C\underline{H}_2C$), 2.325 and 2.33 (2H in total, each d, *J*=6.5 Hz and *J*=7.5 Hz, $COC\underline{H}_2CH(CH_3)_2$), 2.63 and 2.73 (each 1H, each d, each *J*=15 Hz, CCH_2CO), 4.885~4.95 (1H, m, ArCH), 6.35~7.37 (1H, m, OCH=C<u>H</u>), 7.36~7.385 (2H, m, C<u>H</u>OC<u>H</u>). HRms (*m/z*) : Calcd for $C_{15}H_{22}O_3$: 250.1569. Found: 250.1581. *Anal.* Calcd for $C_{15}H_{22}O_3 \cdot 1/10\ H_2O$: C, 71.45; H, 8.87. Found: C, 71.33; H, 8.69.

(2*S*,5*R*)-(-)-2-*t*-Butyl-5-methyl-1,3-dioxolan-4-one (3)

A mixture of (*R*)-lactic acid (34.9 g, 0.387 mol), 2,2-dimethylpropanal (85.2 ml, 0.784 mol), *p*-TsOH (787 mg), 8 drops of conc. H_2SO_4 and *n*-pentane (317 ml) was refluxed with azeotropic removal of the water formed for 10 h. The mixture was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residure, which was crystallized from *n*-pentane at -78 °C. Recrystallization at low temperature was repeated three times. Distillation gave (-)-**3** (23.252 g, 38%) as a colorless oil. Bp 85~87 °C (33 Torr). $[\alpha]_D^{22}$ -44.74° (*c*=1.89, $CHCl_3$) [lit.,[10] for (+)-**3**: $[\alpha]_D^{20}$ +44.8° (*c*=1.83, $CHCl_3$)]. Ir (neat): 1800, 1200, 1110 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.98 (9H, s, $C(CH_3)_3$), 1.48 (3H, d, *J*=6.5 Hz, $CHC\underline{H}_3$), 4.36 (1H, dq, *J*=6.5, 1 Hz, OCHCO), 5.15 (1H, d, *J*=1 Hz, OCHO).

(2*R*,5*S*)-(-)-2-*t*-Butyl-5-methyl-5-(2-propenyl)dioxolan-4-one (4)

A solution of (-)-**3** (4.920 g, 31.10 mmol) in dry THF (4 ml) was added dropwise to an LDA solution (prepared from diisopropylamine (5.5 ml, 39.24 mmol), *n*-BuLi (23.0 ml, 1.6 M *n*-hexane solution) and dry THF (210 ml)) at -78 °C and the reaction mixture was stirrd for 45 min. Allyl bromide (4.0 ml, 46.22

mmol) was added to the reaction mixture and the cooling bath was removed. The mixture was stirred for 20.5 h. Half saturated ammonium chloride solution (150 ml) was added and the mixture was extracted with ether . The combined extract was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil, which was purified by SiO_2 column chromatography (benzene) to afford (-)-**4** (3.800 g, 62%). $[\alpha]_D^{23}$ -52.76° (*c*=1.82, $CHCl_3$) [lit.,[10] for (+)-**4**: $[\alpha]_D^{26}$ +52.9° (*c*=2.23, $CHCl_3$)]. Ir (neat): 1800, 1640, 1240, 1200, 1140, 1080, 1030 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.95 (9H, s, $C(CH_3)_3$), 1.44 (3H, s, CCH_3), 2.39~2.59 (2H, m, $CC\underline{H_2}CH=CH_2$), 5.16~5.27 (3H, m, OCHO, $CH=C\underline{H_2}$), 5.74~5.92 (1H, $CH_2C\underline{H}=CH_2$). Ms (*m/z*): 169, 157, 141, 113, 87, 69, 57, 43.

ACKNOWLEDGMENTS

We thank Dr. Kazuo Yoshihara of SUNBOR, Osaka, Japan, and Dr. Takashi Sugimura of Himeji Institute of Technology, Hyogo, Japan, for supplying spectra of the natural and synthetic ipomeamarones, respectively.

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Received, 14th March, 1996