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A Synthesis of Natural α-Tocopherol Intermediate†

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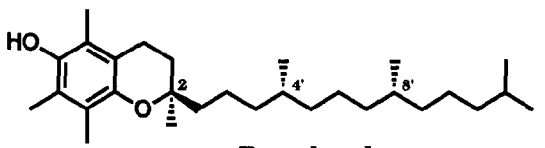
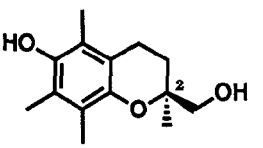
Abstract: (*S*)-(-)-6-Hydroxy-2,5,7,8-tetramethyl-2-chromanmethanol, an intermediate of natural α-tocopherol was synthesized from (*S*)-2-benzyloxy-2-methyl-4-pentenoic acid, which was obtained by the enzymatic hydrolysis of the corresponding racemic methyl ester.

α-Tocopherol (vitamin E) is widely used as the biologically active antioxidant and industrially manufactured by chemical synthesis.[1] 6-Hydroxy-2,5,7,8-tetramethyl-2-chromanmethanol (**1a**) has been developed as an important synthetic intermediate of α-tocopherol. In a recent paper, it has also been reported that this chromanmethanol serves as the starting material for hypolipidemic and hypoglycemic agents.[2] Since it is known that (2*R*)-isomer of α-tocopherol is more bioactive than its (2*S*)-isomer, a number of syntheses of (*S*)-**1a** have been reported so far. In the previous cases, the derivation from chiral natural products,[3] optical resolution of the intermediates,[4,5] and asymmetric syntheses[1,6,7] have been utilized for the introduction of the chiral center of **1a**.

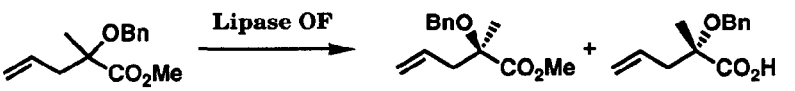


α-Tocopherol



1a

Recently, we reported the preparation of both enantiomers of methyl 2-benzyloxy-2-methyl-4-pentenoate (**2a**) by lipase-catalyzed enantioselective hydrolysis of the corresponding racemate (Scheme 1).[8] Since ester **2a** possesses suitably protected tertiary α-hydroxyacid moiety as well as an allylic side chain, it is expected to have a wide applicability as a new "chiral pool", which has been demonstrated by the synthesis of natural products.[9] Here we report an efficient conversion of (*S*)-**2b** into (*S*)-**1a**.

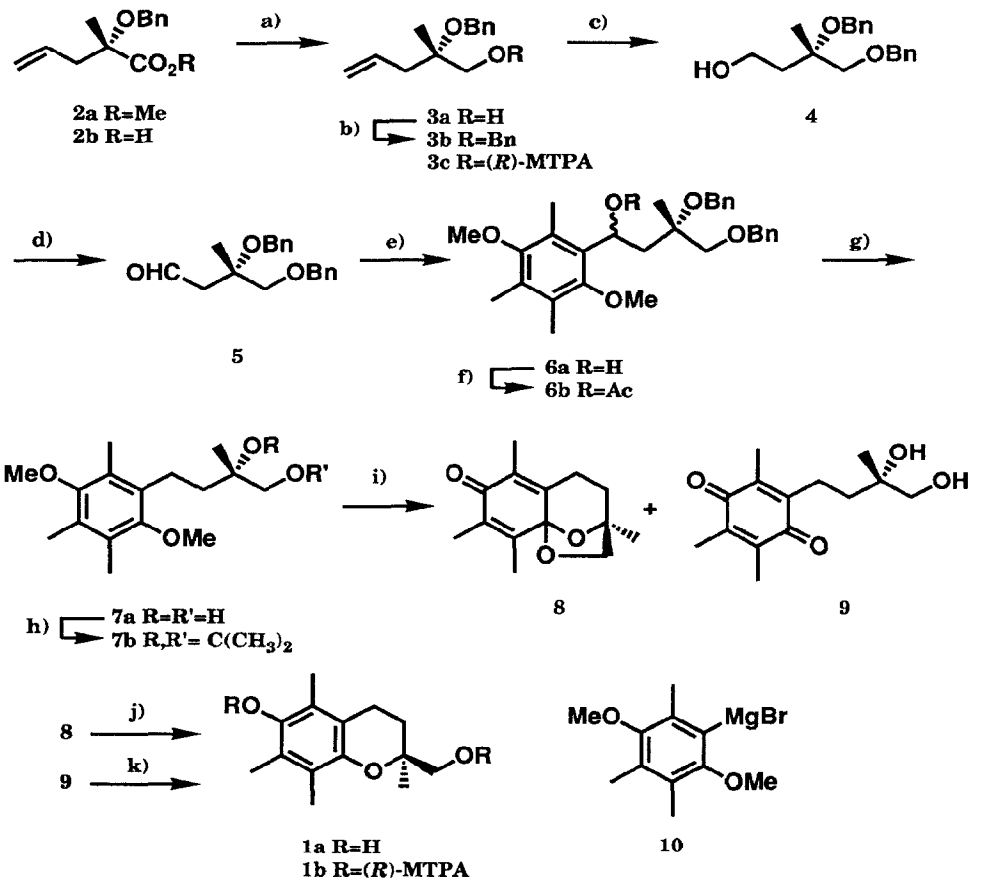


(±)-**2a** (R)-**2a** (S)-**2b**

Scheme 1

† Preparation of Enantiomerically Enriched Compounds by Using Enzymes, Part 12. For Part 11, H. Kakeya, N. Sakai, T. Sugai and H. Ohta, *Agric. Biol. Chem.* in press. The experimental part was taken from the forthcoming M. Sc. thesis of N. W. (March, 1992).

Our synthesis is straightforward as shown in Scheme 2. Methylation of (*S*)-**2b** and subsequent lithium aluminum hydride reduction of resulting (*S*)-**2a** afforded **3a** of 97%*e.e.* (see experimental).[8] The primary hydroxyl group was protected as a benzyl ether to give **3b** (97% from **2a**), so as to make it possible to remove simultaneously both the protective groups for primary and tertiary alcohol at the later step. Direct conversion of **3b** to aldehyde **5** *via* ozonolysis followed by reductive treatment did not afford sufficient yield. Thus the ozonide obtained from **3b** was reduced with sodium borohydride to give alcohol **4** (88%). Aldehyde **5** was obtained in the highest yield by subsequent Swern oxidation. The coupling reaction between components, **5** and Grignard reagent **10**[3] gave disappointing results when carried out in tetrahydrofuran. After some trials, the C-C bond formation was finally successful (93% from **4**) only by using a mixed solvent system, tetrahydrofuran-diethyl ether (1:1).



a) $LiAlH_4$/THF b) NaH, TBAI, BnBr/THF c) O_3/MeOH; $NaBH_4$
d) Swern Oxdn e) 10/THF-ether (1:1), 0°C f) Ac_2O, Et_3N, DMAP/CH_2Cl_2
g) Li/liqNH_3-THF, -35°C h) 2,2-dimethoxypropane, TsOH
i) CAN/MeCN-H_2O then HCl aq/MeOH j) H_2, Pd-C/EtOH
k) H_2, Pd-C/EtOAc then TsOH/benzene

Scheme 2

The remaining part of the route to **1a** involves removal of benzylic hydroxyl group, deprotection of the alcohol moieties and cyclization to the chroman skeleton *via* oxidation of benzene ring to quinone. Catalytic Hydrogenation was first attempted for the deoxygenation of benzylic hydroxyl group as well as the removal of the protective group. The latter smoothly took place, however, the rather sterically hindered alcohol withstood to the reduction. Hydrogenation under acidic conditions resulted in a complex mixture. On the other hand, treatment of the corresponding acetate **6b** with lithium in liquid ammonia worked well to afford a known diol **7a**[1,6,7] (82% from **6a**). As designed in the early stage of the synthesis, reductive elimination of hydroxyl and two benzyl groups could be cleanly performed at the same time.

The diol system of **7a** was temporarily protected as acetonide,[3] then the aromatic ring was oxidized with ceric ammonium nitrate (CAN).[3] Subsequent deprotection with 1N HCl afforded tricyclic acetal **8** (64% from **7a**) as well as an open chain form **9** (30% from **7a**). Reductive transformation[3,5] of both **8** and **9** worked well to give **1a** (62% and 71%, respectively). The *e.e.* of **1a** in both cases was over 99%, since each 400 MHz ^1H NMR spectrum of the corresponding bis-(*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester[10] **1b** showed no detectable signal due to enantiomeric impurity. The recrystallization of the intermediates must resulted in the enantiomeric enhancement.

In conclusion, an important key-intermediate **1a** for natural α-tocopherol was synthesized from (*S*)-**2b** in 12 steps with 31% overall yield.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils and KBr discs for solids on a Jasco IRA-202 spectrometer. ^1H NMR spectra were measured in $CDCl_3$ with TMS as the internal standard at 90 MHz on a JEOL JNM FX-90 spectrometer unless otherwise stated. Optical rotations were recorded on a Jasco DIP 360 polarimeter. Freshly distilled tetrahydrofuran (THF) and Et_2O from sodium-benzophenone ketyl, and distilled CH_2Cl_2 from CaH_2 were employed for anhydrous reaction. Wako Gel B-5F and silica gel 60 K070-WH (70-230 mesh) of Katayama Chemical Co. were used for prep TLC and column chromatography, respectively.

(S)-(-)-4,5-Dibenzyloxy-4-methyl-1-pentene **3b**. Ester **2a** [$[\alpha]_D^{25}$ -3.80 (c=1.63, $CHCl_3$), 2.21 g, 9.45 mmol] was reduced by $LiAlH_4$ in THF in a usual manner. The *e.e.* of resulting diol monobenzyl ether **3a** was determined to be 97% by the NMR measurement of the corresponding (*R*)-MTPA ester **3c**.[8] A soln of crude **3a** in THF (25 ml) was added dropwise to a stirred and ice-cooled suspension of NaH (522 mg, 21.7 mmol, 60% in mineral oil) in THF (7.5 ml) under Ar. To this was added $Bu_4N^+I^-$ (TBAI, 350 mg, 0.10 mmol) and benzyl bromide (2.1 g, 12.3 mmol) in THF (10 ml), and the mixture was stirred under reflux for 1 h. After cooling, the mixture was poured into ice-cooled sat NH_4Cl aq and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 flash column chromatography (200 g). Elution with hexane/EtOAc (50/1) afforded **3b** (2.73 g, 97% from **2a**). Analytical sample: b.p. 205-215°C/2 Torr (bulb-to-bulb distillation); $[\alpha]_D^{25}$ +0.68 (c=1.6, $CHCl_3$); IR νmax 3100-2870, 1500, 1450, 1220, 1100, 1030, 1000, 920, 740, 700 cm^{-1}; ^1H NMR δ 1.25 (3H, s), 2.45 (2H, d, *J*=6 Hz), 3.42 (1H, s), 3.45 (1H, s), 4.55 (4H, s), 4.95-5.20 (2H, m), 5.60-6.10 (1H, m), 7.25-7.40 (10H, m). (Found: C, 81.37; H, 7.76. Calc. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.05%.)

(S)-(+)-3,4-Dibenzyloxy-4-methyl-1-butanol **4**. Ozone was bubbled into a soln of **3b** (2.73 g, 9.21 mmol) in MeOH (150 ml) at -78°C for 2.5 h. To this was added $NaBH_4$ (2.1 g, 55.3 mmol) and the mixture was stirred at room temp overnight. Then 1N HCl was added, and the mixture was concentrated *in vacuo* and extracted with EtOAc. The extract was washed with sat $NaHCO_3$ aq and

brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 flash column chromatography (50 g). Elution with hexane/EtOAc (4/1) afforded **4** (2.44 g, 88%). Analytical sample: b.p. 215-220°C/1 Torr (bulb-to-bulb distillation); $[\alpha]_D^{30}$ +10.1 (c=1.77, $CHCl_3$); IR νmax 3420, 3080-2860, 1500, 1450, 1215, 1100, 1060, 900, 700 cm^{-1}; ^1H NMR (JEOL JNM GX-400, 400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.84 (1H, ddd, *J*=3.9, 7.8, 15.2 Hz), 2.01 (1H, ddd, *J*=3.9, 7.8, 15.2 Hz), 3.49 (1H, d, *J*=9.8 Hz), 3.57 (1H, d, *J*=9.8 Hz), 3.76 (1H, ddd, *J*=3.9, 7.8, 11.5 Hz), 3.86 (1H, ddd, *J*=3.9, 7.8, 11.5 Hz), 4.52 (2H, s), 4.56 (2H, s), 7.20-7.40 (10H, m). An OH signal was not observed due to broadening. (Found: C, 75.80; H, 7.75. Calc. for $C_{19}H_{24}O_3$: C, 75.95; H, 8.05%.)

(1RS,3S)-3,4-Dibenzyloxy-1-(2,5-dimethoxy-3,4,6-trimethylphenyl)-3-methyl-1-butanol **6a**. A soln of DMSO (2.45 g, 31.4 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a stirred and cooled soln of $(COCl)_2$ (1.99 g, 15.7 mmol) in CH_2Cl_2 under Ar at -78°C. To this was added a soln of **4** (2.35 g, 7.84 mmol) in CH_2Cl_2 (50 ml). Then a soln of Et_3N (4.75 g, 47.1 mmol) in CH_2Cl_2 (20 ml) was added dropwise and the temp was raised to -10°C. Water was added and the mixture was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to give crude **5**, ^1H NMR δ 1.38 (3H, s), 2.65 (2H, m), 3.41 (1H, d, *J*=10 Hz), 3.65 (1H, d, *J*=10 Hz), 4.45 (4H, s), 7.30 (10H, s), 9.86 (1H, dd, *J*=3, 5 Hz). This was employed for the next step without further purification.

A soln of crude **5** in Et_2O (50 ml) was added to a stirred and ice-cooled soln of Grignard reagent **10** [prepared from bromotrimethylhydroquinone dimethylether[11] (6.1 g, 23.5 mmol) and Mg (680 mg, 27.4 mg atom)] in THF (50 ml) under Ar. After stirring at the same temp for 15 min, the mixture was poured into ice-cooled sat NH_4Cl aq and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 flash column chromatography (200 g). Elution with hexane/EtOAc (10/1) afforded **6a** (3.47 g, 93% from **4**) as a diastereomeric mixture, IR νmax 3480, 3040-2870, 1450, 1245, 1080, 1020, 1000, 740, 700 cm^{-1}; ^1H NMR δ 1.45 (3H, s), 1.65-2.75 (3H, m), 2.15 (6H, s), 2.35 (3H, s), 3.45-3.75 (2H, m), 3.60 (3H, s), 3.65 (3H, s), 4.55 (2H, s), 4.60 (2H, s), 5.30-5.70 (1H, m), 7.20-7.45 (10H, m).

(1RS,3S)-3,4-Dibenzyloxy-1-(2,5-dimethoxy-3,4,5-trimethylphenyl)-3-methylbutyl acetate **6b**. A mixture of **6a** (3.47 g, 7.30 mmol), Ac_2O (2.99 g, 29.2 mmol), Et_3N (4.42 g, 43.8 mmol) and a catalytic amount of 4-(N,N-dimethylamino)pyridine in CH_2Cl_2 (90 ml) was stirred under Ar at room temp overnight. Then sat $NaHCO_3$ aq was added and the mixture was extracted with CH_2Cl_2 after stirring for 15 min. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 flash column chromatography (200 g). Elution with hexane-EtOAc (8/1) afforded **6b** (3.67 g, 98%) as a diastereomeric mixture, IR νmax 3070-2860, 1740, 1600, 1500, 1450, 1400, 1240, 1080, 1020, 950 cm^{-1}; ^1H NMR δ 1.35 (3H, s), 1.85 (1.5H, s), 1.90 (1.5H, s), 2.15 (6H, s), 2.35 (3H, s), 2.40-2.90 (2H, m), 3.40-3.55 (2H, m), 3.60 (3H, s), 3.75 (3H, s), 4.55 (4H, s), 6.58 (1H, dd, *J*=3 Hz, 9 Hz), 7.25-7.40 (10H, m).

(S)-(+)-2-Methyl-4-(2,5-dimethoxy-3,4,5-trimethylphenyl)butane-1,2-diol **7a**. Li wire (3.25 g, 0.47 g atom) was added portionwise to stirred and cooled liq NH_3 (*ca.* 600 ml) at -35°C. To this was added a soln of **6b** (3.69 g, 7.12 mmol) in THF (50 ml). After stirring at the same temp for 1 h, powdered NH_4Cl was added until the deep blue color discharged and then NH_3 was evaporated at room temp. To the residue was added brine and the mixture was extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 flash column chromatography (80 g). Elution with hexane/EtOAc (1/1) followed by recrystallization from hexane/EtOAc afforded **7a** as colorless needles (1.37 g, 65%), m.p. 85-86.5°C; $[\alpha]_D^{25}$ +2.9 (c=1.15, CH_2Cl_2) [lit.[1] $[\alpha]_D^{25}$ +2.79 (c=2, $CHCl_3$); lit.[6] $[\alpha]_D$ +3.1 (c=1.14, CH_2Cl_2); lit.[7] $[\alpha]_D^{20}$ +3.07 (c=2.2, CH_2Cl_2)]; IR νmax 3400, 3000-2840, 1460, 1400, 1280, 1250, 1200, 1080, 1040, 1000 cm^{-1}; ^1H NMR δ 1.25 (3H, s), 1.50-1.80 (2H, m), 2.15 (6H, s), 2.25 (3H, s), 2.40-2.80 (4H, m), 3.48 (1H, br.s), 3.52 (1H, br.s), 3.65 (3H, s), 3.70 (3H, s). Its NMR spectrum was identical with that reported previously.[6]

(S)-4-[2-(2,5-Dimethoxy-3,4,6-trimethylphenyl)ethyl]-2,2,4-trimethyl-1,3-dioxorane **7b**. A mixture of **7a** (464 mg, 1.58 mmol), 2,2-dimethoxypropane (5 ml) and a catalytic amount of TsOH was stirred at room temp for 15 min. To this was added sat $NaHCO_3$ aq and the mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 flash column chromatography (25 g). Elution with hexane/EtOAc (10/1) afforded **7b** (530 mg, quant). Analytical sample: b.p. 180-190°C/3 Torr (bulb-to-bulb distillation); $[\alpha]_D^{27}$ +4.6 (c=0.44, $CHCl_3$) [lit.[3] $[\alpha]_D$ +4.5 (c=2.2, $CHCl_3$)]; IR νmax 3000-2850, 1460, 1410, 1250, 1220, 1150, 1100, 1070, 1020, 990 cm^{-1}; ^1H NMR δ 1.30 (3H, s), 1.50 (6H, s), 1.70-2.70 (4H, m), 2.20 (6H, s), 2.30 (3H, s), 3.50 (3H, s), 3.55 (3H, s), 3.60-3.90 (2H, m). Its IR and NMR spectra were identical with those reported previously.[3]

(3S,9aR)-(-)-3,6,8,9-Tetramethyl-3,9a-epoxy-2,3,4,5,7,9a-hexahydro-1-benzoxepin-1-one **8** *and (S)-(+)-2-methyl-4-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)butane-1,2-diol* **9**. A soln of $Ce(NH_4)_2(NO_3)_6$ (1.71 g, 3.1 mmol) in water (15 ml) was added to a stirred and ice-cooled soln of **7b** (522 mg, 1.56 mmol) in MeCN (15 ml). After stirring at the same temp for 2 h, the mixture was poured into sat $NaHCO_3$ aq and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in a mixture of MeOH (15 ml) and 1N HCl aq (4 ml). After stirring at room temp for 19 h, sat $NaHCO_3$ aq was added to the mixture. The resulting mixture was concentrated *in vacuo* and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 flash column chromatography (25 g). Elution with hexane-EtOAc (4/1) afforded **8** (236 mg, 64% from **7b**). This was recrystallized from hexane to give **8** as colorless needles (175 mg, 47%), m.p. 102.5-103°C (lit.[3] m.p. 99-100°C); $[\alpha]_D^{26}$ -55.1 (c=0.70, benzene) [lit.[3] $[\alpha]_D$ -58.4 (c=0.7, benzene)]; IR νmax 3000-2900, 1680, 1630, 1450, 1260, 1160, 1110, 1050, 1000, 950 cm^{-1}; ^1H NMR δ 1.25 (3H, s), 1.75 (3H, s), 1.75-2.00 (2H, m), 1.85 (3H, s), 1.90 (3H, s), 2.55-2.80 (2H, m), 3.65 (1H, d, *J*=6 Hz), 4.15 (1H, d, *J*=6 Hz). Its IR and NMR spectra were identical with those reported previously.[3]

Further elution with EtOAc afforded **9** (120 mg, 30% from **7b**). This was recrystallized from hexane/EtOAc to give **9** as yellow needles (97 mg, 24%), m.p. 111-113°C (lit.[3] m.p. 111-112°C); $[\alpha]_D^{26}$ +5.4 (c=0.82, $CHCl_3$) [lit.[3] $[\alpha]_D$ +6.1 (c=1.5, $CHCl_3$); IR νmax 3100, 3000-2800, 1640, 1620, 1300, 1280, 1210, 1060, 1010, 920 cm^{-1}; ^1H NMR δ 1.25 (3H, s), 1.40-1.65 (2H, m), 2.00 (6H, s), 2.05 (3H, s), 2.30 (2H, s), 2.40-2.70 (2H, m), 3.50 (2H, s). Its IR and NMR spectra were identical with those reported previously.[3]

(S)-(-)-6-Hydroxy-2,5,7,8-tetramethyl-2-chromanmethanol **1a**. From **8**. A mixture of **8** (123 mg, 0.53 mmol) and a catalytic amount of 5% Pd-C in EtOH (25 ml) was vigorously stirred under H_2 for 20 min at room temp. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (hexane/EtOAc, 2/1) to give **1a** (77 mg, 62%). This was recrystallized from hexane-CH_2Cl_2 to give colorless plates (65 mg, 52%), m.p. 130-131°C (lit.[3] m.p. 127-128°C); $[\alpha]_D^{27}$ -2.36 (c=1.49, CH_2Cl_2) [lit.[3] $[\alpha]_D$ -2.88 (c=0.52, CH_2Cl_2)]; IR νmax 3500, 3000-2940, 1460, 1420, 1300, 1280, 1250, 1170, 1120, 1090 cm^{-1}; ^1H NMR δ 1.25 (3H, s), 1.60-2.00 (2H, m), 2.10 (6H, s), 2.15 (3H, s), 2.55-2.80 (2H, s), 3.55 (2H, s). (Found: C, 70.97; H, 8.62. Calc. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%.) Its IR and NMR spectra were identical with those reported previously.[3] This was converted into bisMTPA ester **1b** in a usual manner.[10] ^1H NMR (JEOL JNM GX-400, 400 MHz, $CDCl_3$) δ 3.53 (3H, s), 3.67 (3H, s), 4.23 (1H, d, *J*=11.3 Hz), 4.48 (1H, d, *J*=11.3 Hz). An authentic specimen **1b** prepared from (±)-**1a**: δ 3.53 (1.5H, s), 3.55 (1.5H, s), 3.67 (3H, s), 4.23 (0.5H, d, *J*=11.3 Hz), 4.25 (0.5H, d, *J*=11.3 Hz), 4.42 (0.5H, d, *J*=11.3 Hz), 4.48 (0.5H, d, *J*=11.3 Hz). Therefore (*S*)-(-)-**1a** was revealed to be over 99% *e.e.*

From **9**. A mixture of **9** (19 mg, 0.075 mmol) and a catalytic amount of 10% Pd-C in EtOAc (2 ml) was vigorously stirred under H_2 for 4 h at room temp. The solvent was carefully removed *in vacuo* to avoid the contact with air, and the residue was dissolved in degassed benzene (7 ml), and a catalytic amount of TsOH was added. The resulting mixture was stirred under reflux for 30 min under Ar. After cooling, the mixture was poured into sat $NaHCO_3$ aq and extracted with EtOAc. The extract was washed

with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC (hexane/EtOAc, 2/1) to give **1a** (13 mg, 71% from **9**). This was recrystallized from hexane/CH_2Cl_2 to give colorless plates (8 mg, 44%), $[\alpha]_D^{27}$ -2.38 (c=0.42, CH_2Cl_2). Its IR and NMR spectra were identical with those obtained as above. The *e.e.* of this sample was confirmed to be over 99% in the same manner as already described.

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