SYNTHESIS OF (+)-*TRANS*-WHISKY LACTONE, (-)-*CIS*-WHISKY LACTONE, (+)-COGNAC LACTONE AND (+)-ELDANOLIDE

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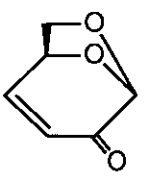
Abstract-------(+)-*trans*-Whisky lactone (**5**) and (-)-*cis*-whisky lactone (**8**), (+)-cognac lactone (**9**) and (+)-eldanolide (**10**) were synthesized starting from levoglucosenone (**1**) in optically pure states.

Levoglucosenone [1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose,(**1**)][1] is widely known as a pyrolytic product of cellulose. It is very useful chiral source for synthesizing natural products[2] because of its highly functionalized structure, which contains essentially one chiral center. For several years, we have reported the synthesis of useful compounds starting from levoglucosenone (**1**), and demonstrated its high availability as a chiral building block.[3]

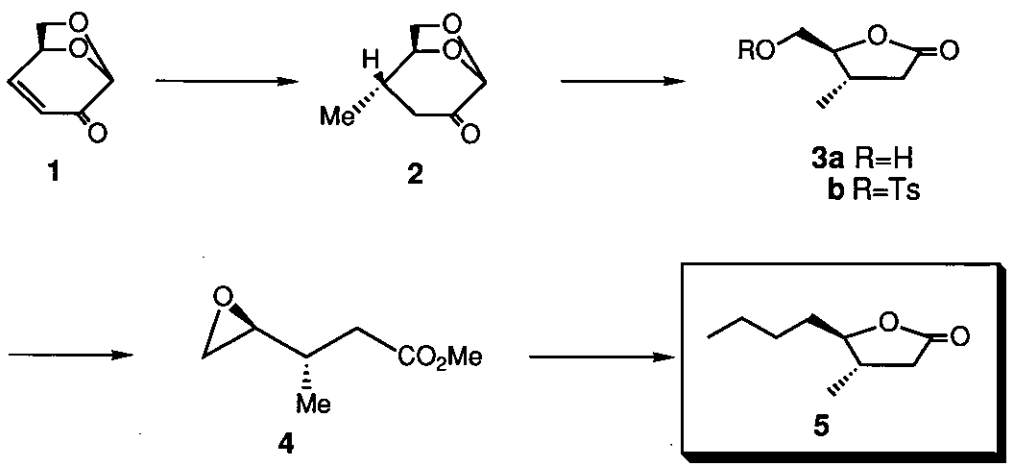


Levoglucosenone (**1**)

In this paper, we report the synthesis of 3,4-disubstituted γ-lactones, which are ubiqitous natural products among insects pheromones and flavor components. In view of the importance of these substances, our interest was directed to their synthesis in optically active form. This paper describes in detail our synthetic approach, which, as a preliminary communication, appeared in 1990.[3b]

Synthesis of *trans* and *cis*-whisky lactone

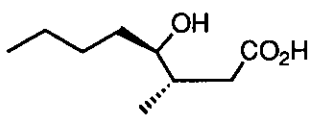
The *trans*- and *cis*-whisky lactones [3-methyloctan-4-olide, (**5** and **8**) respectively] were identified as key aroma components of aged alcoholic beverages such as whisky, brandy and wine.[4] Originally, these two compounds are components of oak used as barrels for alcoholic beverages. These two compounds are extracted slowly from oak barrels into alcoholic beverages for maturing. This is the reason why they are also called 'quercus lactones'. The absolute configurations of natural *trans*- and *cis*-whisky lactones were confirmed to be (3S,4R) and (3S,4S) by Masuda and Nishimura in 1981.[5] Our synthesis is straightforward, as illustrated in Schemes 1 and 2.



Scheme 1

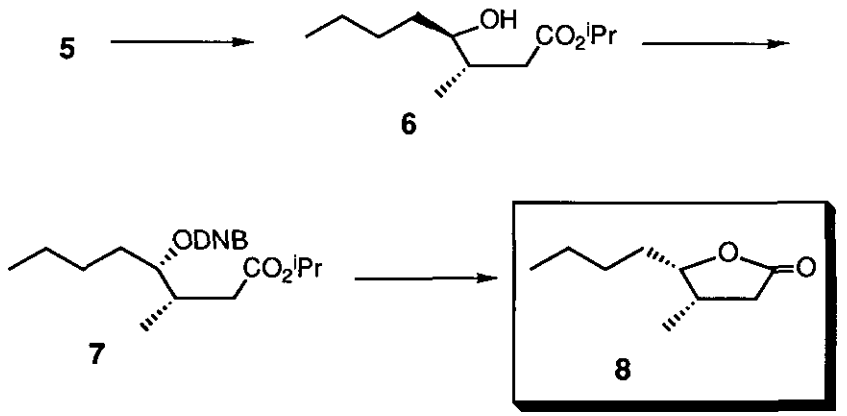
Treatment of levoglucosenone (**1**) with Me_2CuLi gave **2**, which was shown to be 100 % diastereomerically pure when analyzed by glc and ^1H nmr. Ketone (**2**) was oxidized with AcOOH[3a] to give **3a** in 86.0 % yield. **3a** was converted to the corresponding tosylate (**3b**) in 85.5 % yield in a usual manner. Tosylate (**3b**) was treated with K_2CO_3 in MeOH to give epoxide (**4**) in 77.7 % yield. Finally, treatment of **4** with *n*-Pr_2CuLi gave *trans*-whisky lactone (**5**) in 76.2 % yield {$[\alpha]_D^{23}$ +79.5° (MeOH), lit.,[6b] $[\alpha]_D^{20}$ +72.8° (MeOH)}.

The conversion of *trans*-whisky lactone (**5**) into *cis*-whisky lactone (**8**) was examined next. At first we investigated the intramolecular inversion of hydroxy carboxylic acid (**A**) under several conditions.



(A)

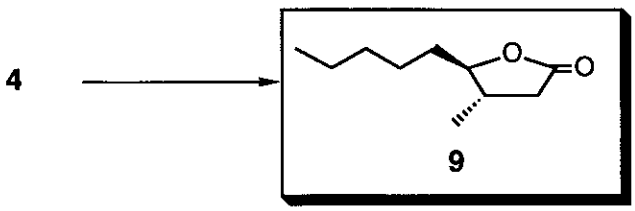
But unfortunately, almost 1:1 mixture of **5** and **8** was obtained, due to the ease of cyclization of compound (**A**). Thus we chose the intermolecular inversion method for this purpose. That is, *trans*-whisky lactone (**5**) was hydrolyzed with KOH solution and subsequently treated with ^{i}PrBr to give **6**. Ester (**6**) was treated with 3,5-dinitrobenzoic acid in the presence of DEAD and Ph_3P under Mitsunobu procedure[7] to give **7** in 76.5 % yield. Finally, diester (**7**) was hydrolyzed with NaOH solution and then acidified to give *cis*-whisky lactone (**8**) in 84.1 % yield {$[\alpha]_D^{23}$ -75.3° (MeOH), lit.,[8a] $[\alpha]_D^{20}$ -78° (MeOH)}. The overall yield of *trans*-whisky lactone (**5**) from **1** was 37.4 % in 5 steps, while that of *cis*-whisky lactone (**8**) from **1** was 24.1 % in 8 steps. Although *trans*- and *cis*-whisky lactones (**5** and **8**) have been prepared by other groups,[6,8] both syntheses of **5** and **8**, described above, require the shortest synthetic steps and give the best overall yield up to date.



Scheme 2

Synthesis of cognac lactone

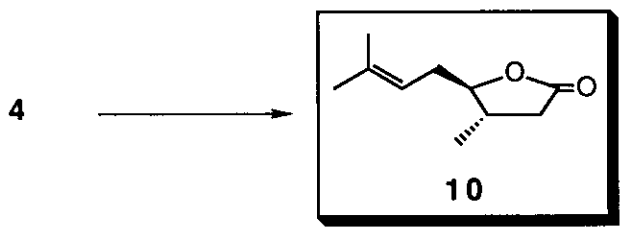
Recently, 3-methylnonan-4-olide (**9**) was detected in cognac and named 'cognac lactone', whose configuration was presumed to be *trans*.[9] Due to the scarcity of the natural cognac lactone, its absolute configuration remaines unknown. We became interested in synthesizing optically active cognac lactone stereoselectively in order to clarify its absolute stereochemistry. The synthesis of (3S,4R)- cognac lactone (**9**) was easily accomplished (Scheme 3). Treatment of **4** with *n*-Bu_2CuLi gave cognac lactone (**9**) in 78.3 % yield {$[\alpha]_D^{23}$ +79.5° (CH_2Cl_2), lit.,[10] $[\alpha]_D^{15}$ +48.3° (CH_2Cl_2)}. The overall yield of (3S,4R)-**9** from **1** was 38.5 % in 5 steps. Direct comparison of our synthetic (3S,4R)-cognac lactone (**9**) with the natural cognac lactone was not possible. Consequently, the absolute configuration of the natural cognac lactone is still unknown.



Scheme 3

Synthesis of eldanolide

Eldanolide [3,7-dimethyl-6-octen-4-olide,(**10**)] was isolated from the male wing glands of the African sugar cane bore Eldana saccharina (Wlk) as a sex pheromone.[11] This insect is a major pest on sugar-cane and maize in many African countries. The absolute configuration of the natural eldanolide was confirmed to be (3S,4R) by Vigneron *et al.* in 1984.[12a] Synthesis of eldanolide (**10**) was also accomplished easily (Scheme 4) as follows. Treatment of **4** with $Me_2C{=}CHMgBr$ in the presence of CuBr gave eldanolide (**10**) in 73.8 % yield {$[\alpha]_D^{23}$ +57.8° (EtOH), lit.,[12b] $[\alpha]_D^{21}$ +55.9° (EtOH)}. Although eldanolide (**10**) has been prepared by other groups,[12] the synthesis described is superior, since the overall yield is 36.3 % in 5 steps from levoglucosenone (**1**), the best yield reported till now.



Scheme 4

In summary, (+)-*trans*- and (-)-*cis*-whisky lactones (**5** and **8**), (+)-cognac lactone (**9**) and (+)-eldanolide (**10**) were synthesized in optically pure forms starting from levoglucosenone (**1**), stereoselectively. The present work proved the utility of levoglucosenone (**1**) in chiral synthesis of 3,4-disubstituted γ-lactonic compounds.

EXPERIMENTAL

All bps and mps were uncorrected. Ir spectra were measured with a Jasco FT/IR 5000 spectrophotometer, and ^{1}H nmr spectra were recorded at 300 MHz and ^{13}C nmr at 75 MHz, with TMS as an internal standard on a Brucker AC-300P spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Glc analyses were performed on a Shimadzu GC-14A gas chromatograph.

(3S,4S)-5-Hydroxy-3-methylpentan-4-olide (**3a**).

To a solution of **2** (5 g, 35.2 mmol) in acetic acid (37 ml), peracetic acid (6.7 ml, 40 % in acetic acid) was added dropwise slowly at 20°-30°C. The mixture was stirred overnight at room temperature. Then dimethyl sulfide (2.4 g, 38.7 mmol) was added to the mixture. After stirring for 30 min at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in methanol (30 ml) and then ten drops of conc. HCl were added to this solution. After stirring for 6 h at 50°C, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Fuji Davison BW-820 MH, 30 g). Elution with *n*-hexane-ethyl acetate (1:1-1:3) yielded **3a** which was purified by distillation to give 3.94 g (86.0 %) of **3a**, bp 104-105°C / 0.05 mm Hg, $[\alpha]_D^{27}$ +79.0° (c 1.0, $CHCl_3$); ir (film) 3400 (brs), 2970 (s), 2938 (s), 2882 (m), 1775 (s), 1214 (s), 1162 (s), 1098 (s), 1035 (s), 934 (s), ^{1}H-nmr ($CDCl_3$) δ: 1.18 (3H, d, *J*=6.7 Hz), 2.23 (1H, dd, *J*=8.7 and 17.3 Hz), 2.45-2.62 (1H, m), 2.76 (1H, dd, *J*=8.6 and 17.3 Hz), 2.81 (1H, s), 3.61-3.74 (1H, m), 3.85-3.96 (1H, m), 4.09-4.19 (1H, m). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.04; H, 7.70.

(3S, 4S)-3-Methyl-5-tosyloxypentan-4-olide (**3b**).

TsCl (15.1 g, 79.0 mmol) was added to a solution of **3a** (7.9 g, 60.8 mmol) in dry pyridine (60 ml) with stirring and ice-cooling. Stirring was continued overnight at room temperature before the mixture was poured into ice-cooled diluted HCl solution and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Fuji Davison BW-820 MH, 300 g). Elution with *n*-hexane-ethyl acetate (5:1-1:2) gave 16.1 g of **3b**. This was crystallized from *n*-hexane-ethyl acetate to give 14.8 g (85.5 %) of pure **3b**, mp 53-54°C, $[\alpha]_D^{22}$ +55.8° (c 1.0, $CHCl_3$); ir (KBr) 2972 (m), 2910 (m), 2882 (m), 1773 (s), 1599 (m), 1365 (s), 1176 (s), 963 (s), ^{1}H-nmr ($CDCl_3$) δ: 1.16 (3H, d, *J*=6.8 Hz), 2.19 (1H, dd, *J*=8.1 and 17.4 Hz), 2.35-2.56 (4H, m, containing 3H, s at 2.46), 2.72 (1H, dd, *J*=8.6 and 17.4 Hz), 4.10-4.25 (3H, m), 7.39 (2H, d, *J*=8.5 Hz), 7.78 (2H, d, *J*=8.5 Hz). Anal. Calcd for $C_{13}H_{16}O_5S$: C, 54.93; H, 5.67. Found: C, 54.67; H, 5.93.

Methyl (3S, 4S)-4,5-epoxy-3-methylpentanoate (4).

Powdered anhydrous potassium carbonate (7.91 g, 57.3 mmol) was added to a stirred solution of **3b** (14.8 g, 52.1 mmol) in methanol (60 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with *n*-hexane (100 ml) and ether (150 ml), and the filtrate was concentrated under atmospheric pressure. The residue was distilled to give 5.83 g (77.7 %) of **4**, bp 93-95°C / 26 mm Hg, n_D^{23} 1.4278, $[\alpha]_D^{23}$ -1.73° (c 1.22, dioxane); ir (film) 2960 (m), 1738 (s), 1437 (m), 1259 (m), 1164 (m), 934 (m), ^{1}H-nmr ($CDCl_3$) δ: 1.05 (3H, d, *J*=6.9 Hz), 1.59-1.95 (1H, m), 2.29 (1H, dd, *J*=8.3 and 15.2 Hz), 2.50-2.60 (2H, m), 2.75-2.84 (2H, m), 3.70 (3H, s). Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.19; H, 8.44.

(3S, 4R)-3-Methyl-4-octanolide (*trans*-Whisky lactone,5).

A solution of propyllithium (1.0 N, 20.8 ml, 20.8 mmol) was added dropwise to a suspension of CuI (1.98 g, 10.4 mmol) in dry ether (20 ml) at -50°C under Ar. To a stirred and cooled solution of **4** (1.0 g, 6.94 mmol) in dry ether (25 ml), this mixture was added dropwise at -60°C under Ar. The reaction temperature was gradually raised to -20°C during 3 h. The reaction mixture was poured into a mixture of saturated NH_4Cl solution and ice, and stirred for 30 min and filtered to remove the insoluble material. The filtrate was extracted with ether. The ethereal solution was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in methanol (20 ml) and 10 % aqueous sodium hydroxide solution (20 ml). This was stirred for 3 h at room temperature and then concentrated *in vacuo*. The residue was diluted with water and washed with ether to remove neutral impurities. The aqueous layer was acidified with diluted HCl to pH<1 and extracted with ether. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Fuji Davison BW-820 MH, 20 g). Elution with *n*-hexane-ethyl acetate (10:1-5:1) yielded **5** which was purified by distillation to give 823 mg (76.2 %) of **5**, bp 123-125°C / 16 mm Hg, n_D^{23} 1.4402, $[\alpha]_D^{23}$ +79.5° (c 1.0, MeOH); ir (film) 2964 (s), 2938 (s), 2876 (m), 1783 (s), 1462 (m), 1427 (m), 1383 (m), 1359 (m), 1334 (m), 1284 (m), 1257 (m), 1214 (s), 1174 (s), 1125 (m), 1079 (s), 986 (s), 944 (m), 928 (m), 857 (w), 785 (w), 735 (w), ^{1}H-nmr ($CDCl_3$) δ: 0.92 (3H, t, *J*=7.2 Hz), 1.14 (3H, d, *J*=6.4 Hz), 1.30-1.75 (6H, m), 2.12-2.31 (2H, m), 2.60-2.75 (1H, m), 4.01 (1H, dt, *J*=4.0 and 7.7 Hz); ^{13}C-nmr ($CDCl_3$) δ: 13.69, 17.26, 22.28, 27.65, 33.49, 35.87, 36.91, 87.24, 176.39; glc:[column, DB-1 0.25mm x 30m; temperature, 100-150°C (2.5°C/min); Carrier gas, He, 1.0 kg/cm^2]; t_R 11.6 min (single); hrms Calcd for $C_9H_{16}O_2$ (M^+): 156.1150. Found: 156.1149.

Isopropyl (3S, 4S)-4-hydroxy-3-methyloctanoate (6).

To a stirred and ice-cooled solution of **5** (1.07 g, 6.86 mmol) in methanol (7 ml) and water (1.4 ml) was added potassium hydroxide (491 mg, 7.54 mmol). The ice bath was removed, the mixture was stirred for 5 h at room temperature and then concentrated *in vacuo*. The residue was diluted with ether and concentrated *in vacuo*. The residue was dried over KOH for 6 h. It was then suspended in dry DMF (10 ml). ^{i}Propyl bromide (1.69 g, 13.7 mmol) was added to this suspension with stirring at room temperature. The mixture was stirred overnight at room temperature, poured into water (30 ml) and extracted with ether. The ethereal solution was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 1.60 g of crude **6**, ir (film) 3500 (br), 2962 (s), 2934 (s), 2876 (s), 1729 (s), 1715 (s), 1465 (m), 1377 (s), 1270(s), 1178(s), 1108 (s), 975 (s), 899 (m). This was employed in the next step without further purification.

Isopropyl (3S, 4S)-4-(3',5'-dinitrobenzoyloxy)-3-methyloctanoate (7).

To a stirred and ice-cooled solution of crude **6** (1.60 g) in dry tetrahydrofuran (12 ml) were added Ph_3P (2.70 g, 10.3 mmol), 3,5-dinitrobenzoic acid (2.18 g, 10.3 mmol) and diethyl azodicarboxylate (1.79 g, 10.3 mmol). The ice-bath was removed, the mixture was stirred for 3 days at room temperature. Then it was poured into ice-water and extracted with ether. The ethereal solution was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Fuji Davison BW-820MH, 50 g). Elution with *n*-hexane-ether (10:1-5:1) gave 2.15 g (76.5 % from **5**) of **7**, n_D^{23} 1.5034, $[\alpha]_D^{23}$ -1.47° (c 1.02, $CHCl_3$); ir (film) 3108 (m), 2966 (m), 2940 (m), 2878 (m), 1729 (s), 1549 (s), 1348 (s), 1280 (s), 1172 (m), 1110 (m), 731 (m), 721 (m), ^{1}H-nmr ($CDCl_3$) δ: 0.90 (3H, t, *J*=6.9 Hz), 1.09 (3H, d, *J*=6.8 Hz), 1.21 (3H, d, *J*=6.2 Hz), 1.23 (3H, d, *J*=6.2 Hz), 1.26-1.40 (4H, m), 1.62-1.85 (2H, m), 2.13-2.25 (1H, m), 2.35-2.50 (2H, m), 5.01 (1H, m), 5.23-5.30 (1H, m), 9.11-9.18 (2H, m), 9.21-9.25 (1H, m). Anal. Calcd for $C_{19}H_{26}O_8N_2$: C, 55.60; H, 6.39; N, 6.83. Found: C, 55.51; H, 6.51; N,6.91.

(3S, 4S)-3-Methyl-4-octanolide (*cis*-Whisky lactone,**8**).

To a stirred and ice-cooled solution of **7** (380 mg, 0.93 mmol) in methanol (5 ml) was added dropwise 2 % aqueous sodium hydroxide solution (10 ml, 5 mmol). The reaction mixture was stirred overnight at room temperature. This was acidified with 1N HCl to pH<1 and extracted with ether. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Fuji Davison BW-820MH, 10 g). Elution with *n*-hexane-ether (10:1-2:1) yielded **8** which was purified by distillation to give 122 mg (84.1 %)

of **8**, bp 124-126°C / 17 mm Hg, n_D^{23} 1.4458, $[\alpha]_D^{23}$ -75.3° (c 1.35, MeOH); ir (film) 2962 (s), 2938 (s), 2876 (s), 1779 (s), 1466 (m), 1425 (m), 1383 (m), 1338 (m), 1296 (m), 1259 (w), 1212 (s), 1172 (s), 1093 (m), 1081 (m), 996 (m), 975 (s), 928 (s), 855 (w), 785 (w), 735 (w), ^{1}H-nmr ($CDCl_3$) δ: 0.92 (3H, t, *J*=7.0 Hz), 1.02 (3H, d, *J*=6.9 Hz), 1.20-1.75 (6H, m), 2.20 (1H, dd, *J*=3.8 and 16.8 Hz), 2.51-2.64 (1H, m), 2.70 (1H, dd, *J*=7.8 and 16.8 Hz), 4.40-4.48 (1H, m); ^{13}C-nmr ($CDCl_3$) δ: 13.76, 13.85, 22.45, 27.95, 29.50, 32.94, 37.49, 83.62, 176.86; glc:[column, DB-1 0.25mm x 30m; temperature, 100-150°C (2.5°C/min); Carrier gas, He, 1.0 kg/cm^2]; t_R 12.7 min (single); hrms Calcd for $C_9H_{16}O_2$: 156.1150. Found: 156.1139.

(3S, 4R)-3-Methyl-4-nonanolide (Cognac lactone,**9**).

In the same manner, except for using lithium dibutylcuprate insted of lithium dipropylcuprate, **4** (500 mg, 3.47 mmol) gave 421 mg (71.4 %) of **9**, bp 101-103°C / 6 mm Hg, n_D^{23} 1.4431, $[\alpha]_D^{23}$ +83.2° (c 0.69, MeOH); ir (film) 2962 (s), 2936 (s), 2866 (m), 1779 (s), 1462 (m), 1212 (s), 1172 (s), 1004 (m), 938 (m), 862 (w), ^{1}H-nmr ($CDCl_3$) δ: 0.90 (3H, t, *J*=6.8 Hz), 1.14 (3H, d, *J*=6.3 Hz), 1.26-1.75 (8H, m), 2.12-2.30 (2H, m), 2.60-2.75 (1H, m), 4.01 (1H, dt, *J*=4.0 and 7.7 Hz); ^{13}C-nmr ($CDCl_3$) δ: 13.89, 17.40, 22.41, 25.33, 31.50, 33.91, 36.00, 37.06, 87.40, 176.54. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.32; H, 10.67.

(3S, 4R)-3,7-Dimethyl-6-octen-4-olide (Eldanolide,**10**).

Cuprous bromide (49.8 mg, 0.35 mmol) was added to a solution of **4** (500 mg, 3.47 mmol) in dry tetrahydrofuran (10 ml) under Ar. A Grignard solution was prepared separately from 2-methylpropenyl bromide (2.34 g, 17.4 mmol), magnesium (842 mg, 34.7 mmol) and tetrahydrofuran (40 ml) in the usual manner. This Grignard solution was added dropwise slowly to the stirred and cooled solution of **4** containing cuprous bromide at -20°C until the disappearance of the starting material **4** as checked by glc. Then the mixture was poured into saturated ammonium chloride solution and extracted with ether. The ethereal solution was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in methanol (10 ml) and 10 % aqueous sodium hydroxide solution (10 ml). This was stirred for 3 h at room temperature and then concentrated *in vacuo*. The residue was diluted with water and washed with ether to remove neutral impurities. The aqueous layer was acidified with diluted HCl to pH<1 and extracted with ether. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Fuji Davison BW-820MH, 10 g). Elution with *n*-hexane-ethyl acetate (10:1-5:1) yielded **10** which was purified by distillation to give 430 mg

(73.8 %) of **10**, bp 115-117°C / 21 mm Hg, n_D^{23} 1.4606, $[\alpha]_D^{23}$ +52.4° (c 0.86, MeOH); ir (film) 2972 (s), 2920 (s), 1783 (s), 1456 (m), 1425 (m), 1383 (m), 1214 (m), 1195 (m), 1158 (m), 1033 (s), 1004 (m), 924 (m), ^{1}H-nmr ($CDCl_3$) δ: 1.14 (3H, d, *J*=6.5 Hz), 1.64 (3H, s), 1.73 (3H, s), 2.10-2.50 (4H, m), 2.68 (1H, dd, *J*=7.5 and 16.6 Hz), 4.06 (1H, dd, *J*=6.5 and 12.2 Hz), 5.10-5.22 (1H, m); ^{13}C-nmr ($CDCl_3$) δ: 17.63, 17.86, 25.70, 32.07, 35.00, 36.98, 87.07, 117.86, 135.36, 176.57; hrms Calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1133.

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