A New Synthesis of Pyrocin and Related Compounds*

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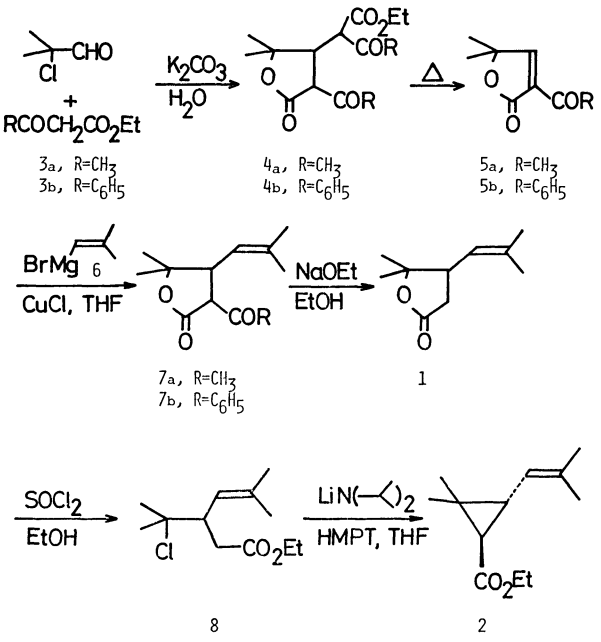
A new synthesis of pyrocin (**1**) and related compounds is described. The reaction of 2-benzoyl-4,4-dimethyl-2-buten-4-olide (**5b**) with 2-methyl-1-propenylmagnesium bromide (**6**) in the presence of CuCl gave α-benzoylpyrocin (**7b**) in 90% yield. The product of **7b** with a specific rotation of +2.43° was obtained when the reaction was carried out in the presence of (−)-sparteine. α-Acetylpyrocin (**7a**) was prepared in the similar manner in 63% yield. The treatment of **7a** and that of **7b** with ethanolic sodium ethoxide gave **1** in 65% and 81% yields, respectively. The reaction of **1** with large excess of $SOCl_2$ in absolute ethanol gave ethyl 3-(1-chloro-1-methylethyl)-5-methyl-4-hexenoate (**8**) in 82% yield. Similar treatment of **7** with $SOCl_2$ gave ethyl 2-substituted-4-(2-methyl-1-propenyl)-5,5-dimethyl-4,5-dihydrofuran-3-carboxylate (**12**). Compound **8** was transformed to ethyl *trans*-(±)-chrysanthemate (**2**) in 75% yield.

Several syntheses of pyrocin (**1**), found in the pyrolysate of pyrethrine and known to possess insecticidal activity,[1a–1d] have been reported.[2a–2k] Recently, we[3] have reported an efficient preparation of 2-acyl-4,4-dimethyl-2-buten-4-olide (**5**) by the thermal decomposition of 2-acyl-3-[benzoyl(ethoxycarbonyl)methyl]-4,4-dimethyl-4-butanolide (**4**), which is readily obtained by the reaction of 2-chloro-2-methylpropanal and ethyl acylacetate (**3**) in aqueous K_2CO_3. In this paper, we wish to report a new synthesis of **1** and ethyl (±)-*trans*-chrysanthemate (**2**) using **5** as a starting material. An attempted synthesis of optically active pyrocin using (−)-sparteine as a chirality-creating reagent also has been described.

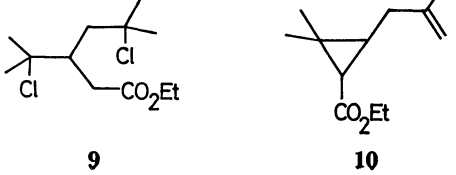
The Michael addition of 2-methyl-1-propenylmagnesium bromide (**6**) to the butenolide **5b** in the presence of CuCl in THF medium afforded α-benzoylpyrocin (**7b**) in 90 % yield. The IR spectrum of **7b** showed strong bands at 1765 and 1685 cm^{-1} due to lactone carbonyl and benzoyl carbonyl, respectively. The NMR spectrum exhibited a multiple splitting doublet at δ 5.03 due to one olefinic proton. α-Acetylpyrocin (**7a**) was obtained similarly from **5a** and **6** in 63% yield.

Deacylation of **7a** and **7b** with ethanolic EtONa at reflux temperature afforded **1** in 65% and 81% yields, respectively. The NMR spectrum of this product was identical with that[5] of the authentic sample. Hirai, *et al.*,[6] have reported a synthesis of optically active pyrocin *via* the asymmetric, catalytic hydrogenation of optically active alcohol esters of 2,2,5,5-tetramethyltetrahydrofurylidene-3-acetic and 2,2,5,5-tetramethyldihydrofuryl-3-acetic acids. We now describe the preparation of optically active **1** by an asymmetric Michael addition of the Grignard reagent **6** to the butenolide **5b**.[7a,7b] The reaction, carried out in the presence of twice molar amount of (−)-sparteine as well as a catalytic amount of CuCl, gave a product of **7b** with $[\alpha]_D^{25}$ +2.43° (ethanol) in 47% synthetic yield. Debenzoylation of this product gave **1** with $[\alpha]_D^{25}$ +1.36° (ethanol), 2.0% optical yield.

Several procedures to transform **1** to the ester **2** have been reported.[1d,2k,8a,8b] They involve the base-catalyzed cyclization of the dichloro ester **9**, which is obtained from **1** by the treatment with $SOCl_2$ in benzene and the subsequent addition of ethanolic HCl. While the isomer **10** is usually produced as an undesirable by-product in these procedures, we are successful to prevent the formation of **10** by using ethyl 3-(1-chloro-1-methylethyl)-5-methyl-4-hexenoate (**8**)[8c] in place of **9** as a starting material. Successive treatments of **1** with large excess of $SOCl_2$ in ethanol, at room temperature for 1 h and then at 60 °C for additional 4 h, yielded the desired ester **8** in 82% yield. The NMR spectrum showed a multiple splitting doublet at δ 4.95 due to one olefinic proton. The treatment of **8** with lithium diisopropylamide in the presence of



Scheme 1.



9 **10**

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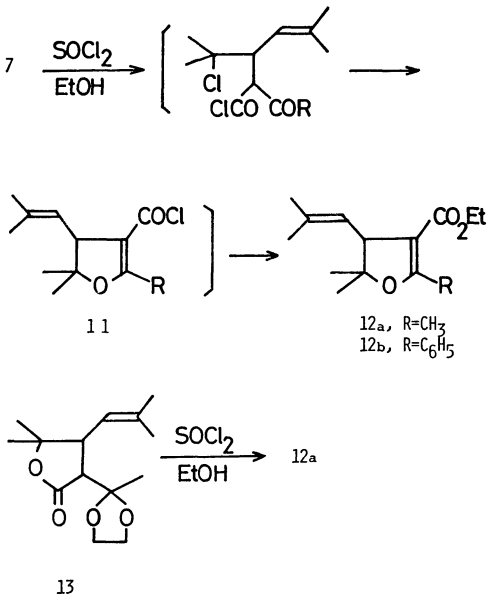
a catalytic amount of hexamethylphosphoric triamide (HMPT) in THF afforded **2** in 75% yield. Its spectral data (IR, NMR, and MS) were identical with those described in the literatures.[9a,9b] The reaction conducted in ethanolic EtONa gave rise to the cyclization of **8** to pyrocin.

Because of the facile formation of dihydrofuran ring, we failed to obtain the α-acyl derivatives of the chloro ester **8**. The reaction of **7** with $SOCl_2$, carried out in the same manner as **1**, gave only ethyl-2-substituted-4-(2-methyl-1-propenyl)-5,5-dimethyl-4,5-dihydrofuran-3-carboxylate (**12**) in good yields (>82%). Ethylene acetal of α-acetylpyrocin (**13**) also underwent the re-cyclization to produce **12**.



Scheme 2.

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Experimental

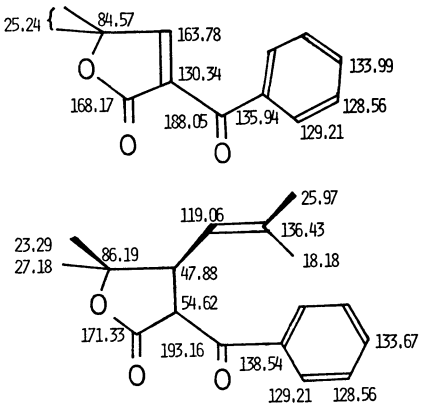
Melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory. Distillations were evaporative bulb-to-bulb distillations using a Büchi Kugelrohrofen at the pressure and oven temperature indicated. Analytical determination and preparative isolation by GLPC were performed on a Hitachi K-53 model gas chromatograph and a Yanagimoto G-80 model gas chromatograph respectively. IR spectra were determined on a Hitachi EPI-S2 model spectrometer. ^1H NMR spectra were taken at 60 MHz on a Hitachi R-24 model spectrometer using TMS as an internal standard. ^{13}C NMR spectra were taken at 25 MHz on a JEOL FX-100 model spectrometer equipped with FT facilities using TMS as an internal standard and $CDCl_3$ as solvent. The pulse width was 6 μs (45° tip) and the FIDs were compiled by using 8 K data points over a spectral width of 6000 Hz. MS spectra were obtained at 70 eV with a Hitachi RMS-4 model mass spectrometer. Optical rotation was measured with a Yanagimoto OR-50 model polarimeter and the cell path length was 0.1 dm. Analytical and preparative TLC were done on a silica gel PF_{254} (E. Merck AG., Darmst.) with layers of 0.25 mm and 1.0 mm thickness respectively. Column chromatography was done on a silica gel, Wakogel C-200 and C-300 (Wako Junyaku Kogyo Co., Ltd.).

Starting materials such as **5a**, **5b**[3] and 1-bromo-2-methyl-propene[10] were prepared by the procedure described in the literatures.

(±)-α-Benzoylpyrocin (7b). To a refluxing mixture of magnesium turnings (0.98 g, 0.04 g-atom), a few drops of ethyl bromide and trace of iodine in 20 ml of THF, was added isobutenyl bromide (5.40 g, 0.04 mol) dropwise. The mixture was refluxed until magnesium turnings were completely dissolved. After cooling to 0 °C and addition of copper(I) chloride (0.2 g, 0.02 mol), the mixture was stirred for 20 min. To the mixture was added the butenolide **5b** (4.32 g, 0.02 mol) in 20 ml of THF dropwise at 0 °C. After being stirred for 2 h at 0 °C, the mixture was allowed to warm to room temperature. To the resulting mixture was added 10 ml of saturated aqueous NH_4Cl and then it was acidified with 10% HCl. An organic layer was extracted with ether and dried over $MgSO_4$. After removal of the solvent, the residual brown oil was obtained and separated by column chromatograph on a silica gel (30 g of Wakogel C-200, hexane : acetone=10 : 1) to give 4.90 g (90% yield) of **7b**. The analytical sample was obtained by one recrystallization from the mixed solvent of benzene and petroleum ether (1 : 1 in v/v): mp 94—95 °C; IR (KBr) 1767 (lactone C=O), 1683 (benzoyl C=O), 1598, 1579 cm^{-1} (benzene C=C); NMR ($CDCl_3$) δ 1.37 (s, 3H, γ-CH_3), 1.49 (s, 3H, γ-CH_3), 1.70 (t, 6H, J=0.1 Hz, $=\langle^{CH_3}_{CH_3}$), 3.37 (dd, 1H, J=11 Hz and 10 Hz, β-H), 4.55 (d, 1H, J=11 Hz, α-H), 5.03 (md, 1H, J=10 Hz, >-H), 7.23—8.18 (m, 5H, C_6H_5); MS *m/e* (rel. intensity) 272 (M^+), 227 (8.0), 214 (4.0), 186 (6.3), 171 (100), 105 ($C_6H_5CO^+$, 97), 77 (C_6H_5, 62).

Found: C, 75.12; H, 7.41%. Calcd for $C_{17}H_{20}O_3$: C, 74.97, H, 7.40%.

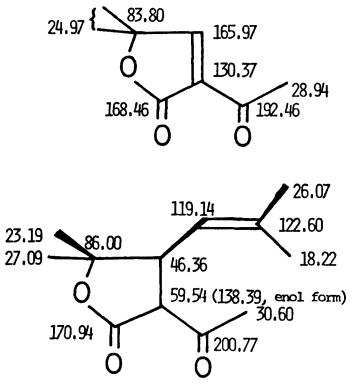
The natural abundance ^{13}C NMR spectra of **5b** and **7b** are summarized in the following structure.



(±)-α-Acetylpyrocin (7a). The mixture of butenolide **5a** (3.08 g, 0.02 mol), 2-methyl-1-propenylmagnesium bromide (0.04 mol), and 0.02 g of copper(I) chloride in 40 ml of THF was reacted and worked up in the same manner as the foregoing experiment to give 2.62 g (63% yield) of **7a**: IR (neat) 1760 (lactone C=O), 1717 (acetyl C=O), 1645 cm^{-1} (C=C); NMR (CCl_4) δ 1.22 (s, 3H, γ-CH_3), 1.38 (s, 3H, γ-CH_3), 1.73 (sharp m, 6H, $=\langle^{CH_3}_{CH_3}$), 2.32 (s, 3H, $COCH_3$), 3.29 (d, 1H, J=16 Hz, α-H), 3.50 (dd, 1H, J=16 Hz and 11 Hz, β-H), 4.83 (m, 1H, >-H); MS *m/e* (rel. intensity) 210 (M^+), 195 ($M-CH_3$, 0.3), 177 (0.4), 167 ($M-COCH_3$), 152 (5), 137 (4), 124 (11), 108 (100).

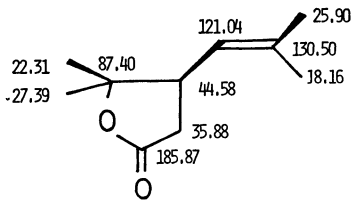
Found: C, 68.66; H, 8.42%. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63%.

The natural abundance ^{13}C NMR spectra of **5a** and **7a** are summarized in the following structure. Off-resonance decoupling was used to support the assignments in each case.



(±)-Pyrocin (1) (Debenzoylation of 7b). To a stirried mixture of EtONa (4.76 g, 0.07 mol) in 100 ml of ethanol was added **7b** (3.82 g, 0.014 mol) dissolved in 50 ml of ethanol. The resulting mixture was refluxed for 42 h. After evaporation of ethanol under reduced pressure, the residue was acidified with 10% HCl, and then extracted with ether. The ether extract was washed with aqueous $NaHCO_3$ to remove benzoic acid and dried over $MgSO_4$. After removal of the solvent 2.0 g of crude pyrocin was obtained. The purification by column chromatograph on a silica gel (15 g of Wakogel C-200, hexane : acetone=10 : 1) gave 1.90 g of pyrocin, 81% yield: mp 58—58.5 °C (lit,[4] 59—60 °C); IR (KBr) 1761 cm^{-1} (lactone C=O); NMR (CCl_4) δ 1.20 (s, 3H, γ-CH_3), 1.36 (s, 3H, γ-CH_3), 1.68 (d, 3H, J=0.2 Hz, $\gtrless$-CH_3), 1.75 (d, 3H, J=0.2 Hz, $\gtrless$-CH_3), 1.95—2.45 (m, 2H, α-H_2, ABX), 2.60—3.35 (m, 1H, β-H, ABX), 5.01 (md, 1H, J=10 Hz, $\gtrless$-H).[5]

The natural abundance ^{13}C NMR spectrum of **1** is summarized in the following structure. Off-resonance decoupling was used to support the assignment.



Deacetylation of **7a** (343 mg, 1.63 mmol) with EtONa gave 177 mg of **1**, 65% yield.

Optically Active α-Benzoylpyrocin and Pyrocin. To a stirred solution of 2-methyl-1-propenylmagnesium bromide (10.4 mmol) in 15 ml of THF prepared by the same procedure as **7b**, were added copper(I) chloride (100 mg, 1.0 mmol) and (−)-sparteine (5.0 g, 20.8 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C. To the mixture, a solution of **5b** (2.25 g, 10.4 mmol) in 15 ml of THF was added slowly. The stirring was continued for 7 h at 0 °C and for additional 12 h at room temperature. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl. It was then acidified with 10% HCl. An organic layer was extracted with ether and dried over $MgSO_4$. After removal of the solvent, 2.77 g of brown oil was obtained. After separation by column chromatograph on a silica gel (40 g of Wakogel C-200, hexane : acetone=10 : 1), 0.98 g of **5b** and 1.36 g of (+)-α-benzoylpyrocin were obtained, 47% synthetic yield. An analytical sample was obtained after one recrystallization from the mixed solvent of benzene and petroleum ether (1 : 1 in v/v): mp 94—95 °C; $[\alpha]_D^{25}$ +2.43° (*c* 4.12 g, ethanol). Its NMR and IR spectra were completely identical with those of **7b**.

(+)-Pyrocin was obtained from this product of (+)-α-benzoylpyrocin in the same manner as described in the foregoing section: $[\alpha]_D^{25}$ +1.36° (*c* 1.21 g, ethanol), optical yield 2%. Its IR and NMR spectra were identical with those of authentic sample of **1**.

Ethyl 3-(1-chloro-1-methylethyl)-5-methyl-4-hexenoate (8). To a stirred solution of **1** (750 mg, 4.46 mmol) in 40 ml of ethanol was added thionyl chloride (3.8 ml, 44.6 mmol) with caution at room temperature. The stirring was continued for 1 h at room temperature and then for additional 4 h at 60 °C. After removal of the solvent and low boiling materials, 1.41 g of dark brown oil was obtained. It was separated by column chromatograph on a silica gel (30 g of Wakogel C-300, hexane) to afford 852 mg of **8**, 82% yield. The analytical sample was obtained by bulb-to-bulb distillation: bp 90 °C (0.06 Torr); IR (neat) 1734 cm^{-1} (C=O); NMR (CCl_4) δ 1.19 (t, 3H, J=7 Hz, ester CH_3), 1.44 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.65 (d, 3H, J=2 Hz, $\gtrless$-CH_3), 1.70 (d, 3H, J=2 Hz, $\gtrless$-CH_3), 1.8—3.2 (m, 3H, α-H_2 and β-H), 3.99 (q, 2H, J=7 Hz, ester CH_2), 4.95 (md, 1H, J=10 Hz, $\gtrless$-H); MS *m/e* (rel. intensity) 196 (M^+—HCl, 20), 181 (6), 155 (42), 109 (100), 123 (32), 77 (75).

Found. C, 62.10; H, 8.88%. Calcd for $C_{12}H_{21}O_2Cl$: C, 61.92; H, 9.10%.

Ethyl (±)-trans-Chrysanthemate (2). To a solution of diisopropylamine (0.39 ml, 3.0 mmol) in 3 ml of THF was added dropwise the solution of butyllithium (3.6 mmol) in 3 ml of ether at 0 °C. After the mixture was stirred for 30 min at 0 °C, 0.25 ml of HMPT was added dropwise. After being stirred for additional 30 min at 0 °C, was added the solution of the chloroester **8** (225 mg, 0.97 mmol) in 2 ml of THF. The mixture was stirred for 40 min at 0 °C and then allowed to react for overnight at room temperature. The resulting mixture was poured into a large exess of 10% HCl and extracted with ether, dried over $MgSO_4$. After removal of the solvent, an yellow oil was obtained. It was separated by column chromatograph on a silica gel (7 g of Wakogel C-200, hexane : acetone=10 : 1) to afford 114 mg of **2**, 75% yield. The analytical sample was obtained by preparative GLPC[11] and identified by comparison of its IR and NMR spectra with those of authentic sample.[9]

Ethyl 2-Methyl-4-(2-methyl-1-propenyl)-5,5-dimethyl-4,5-dihydrofuran-3-carboxylate (12a). To a stirred solution of lactone **7a** (331 mg, 1.58 mmol) in 15 ml of ethanol was added thionyl chloride (1.16 ml, 15.8 mmol) dropwise at room temperature. During the addition a vigorous exothermic reaction occurred. The resulting solution was stirred for 6 h at 70 °C. After removal of the solvent and low boiling materials under reduced pressure, there was obtained a residual dark brown oil. It was separated by column chromatograph on a silica gel (Wakogel C-200, hexane : acetone=10 : 1) to give 308 mg of crude **12a**, 82% yield. The analytical sample was obtained by preparative TLC on a silica gel (hexane : acetone=4 : 1) followed by bulb-to-bulb distillation: bp 110 °C (5 Torr); IR (neat) 1695 (conjugated ester C=O), 1648 cm^{-1} (C=C); NMR (CCl_4) δ 1.17 (t, 3H, J=7 Hz, ester CH_3), 1.17 (s, 3H, 5-CH_3), 1.28 (s, 3H, 5-CH_3), 1.64 (d, 3H, J=1 Hz, $\gtrless$-CH_3), 1.69 (d, 3H, J=1 Hz, $\gtrless$-CH_3), 2.08 (d, 3H, J=0.2 Hz, 2-CH_3), 3.45 (d, 1H, J=10 Hz, 4-H), 4.01 (q, 2H, J=7 Hz, ester CH_2), 4.91 (md, 1H, J=10 Hz, $\gtrless$-H); MS *m/e* (rel. intensity) 238 (M^+), 223 (M−CH_3), 183 (32), 177 (12), 149 (14), 119 (14), 1.0

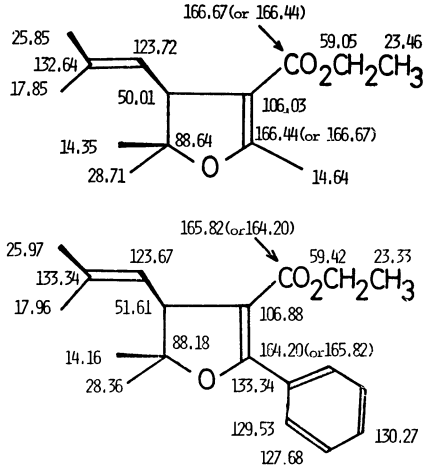
(14), 107 (27), 91 (32), 79 (17), 67 (20), 43 (100).

Found: C, 70.77; H, 9.35%. Calcd for $C_{14}H_{20}O_3$: C, 70.56; H, 9.30%.

Ethyl 2-Phenyl-4-(2-methyl-1-propenyl)-5,5-dimethyl-4,5-dihydrofuran-3-carboxylate (**12b**). The reaction of α-benzoylpyrocin (971 mg, 3.57 mmol) with thionyl chloride (3.04 ml, 35.7 mmol) in 20 ml of ethanol was carried out in the same manner as the foregoing experiment to give 940 mg of **12b**, 87% yield. The analytical sample was obtained by preparative TLC on a silica gel (hexane : acetone=4 : 1): IR (neat) 1685—1690 (conjugated ester C=O), 1622 (C=C), 1597—1580 cm^{-1} (phenyl C=C); NMR (CCl_4) δ 1.17 (t, 3H, J=8 Hz, ester CH_3), 1.25 (s, 3H, 5-CH_3), 1.35 (s, 3H, 5-CH_3), 1.68 (d, 3H, J=1 Hz, $\gtrless$-CH_3), 1.70 (d, 3H, J=1 Hz, $\gtrless$-CH_3), 3.66 (d, 1H, J=10 Hz, 4-H), 3.97 (q, 2H, J=8 Hz, ester CH_2), 5.05 (md, 1H, J=10 Hz, $\gtrless$-H), 7.2—7.8 (m, 5H, C_6H_5); MS *m/e* 300 (M^+), 285 ($M-CH_3$), 227 ($M-CO_2Et$).

Found: C, 76.11; H, 8.16%. Calcd for $C_{19}H_{23}O_3$: C, 75.97; H, 8.05%.

The natural abundance ^{13}C NMR spectra of **12a** and **12b** are summarized in the following structures. Off-resonance decoupling was used to support the assignment of **12a.**



2-(1,1-Ethylenedioxyethyl)-3-(2-methyl-1-propenyl)-4,4-dimethyl-4-butanolide (**13**). A mixture of α-acetylpyrocin **7a** (840 mg, 4 mmol), ethylene glycol (248 mg, 4 mmol), and *p*-toluenesulfonic acid (3 mg, 0.02 mmol) in 5 ml of benzene was refluxed for 6.5 h with continuous removing of water as a benzene azeotrope. After cooling, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine. An organic layer was separated and dried over $MgSO_4$. The removal of the solvent left 840 mg of the crude acetal **13**, 82% yield. The analytical sample was obtained as a clean oil by column chromatograph on a silica gel (7 g of Wakogel C-200, hexane : acetone=10 : 1): IR (neat) 1766 cm^{-1} (lactone C=O); NMR (CCl_4) δ 1.16 (s, 3H, γ-CH_3), 1.32 (s, 6H, γ-CH_3 and CH_3- ), 1.68 (d, 3H, J=0.1 Hz, $\gtrless$-CH_3), 1.74 (d, 3H, J=0.1 Hz, $\gtrless$-CH_3), 2.68 (d, 1H, J=11 Hz, α-H), 3.04 (dd, 1H, J=11 Hz and 9 Hz, β-H), 3.83 (m, 4H, O-CH_2CH_2-O), 5.06 (md, 1H, J=9 Hz, $\gtrless$-H).

Reaction of 2-(1,1-Ethylenedioxyethyl)-3-(2-methyl-1-propenyl)-4,4-dimethyl-4-butanolide with Thionyl Chloride in Ethanol. To a stirred solution of acetal **13** (372 mg, 1.47 mmol) in 15 ml of ethanol was added thionyl chloride (1.17 ml, 14.7 mmol) slowly at room temperature and allowed to react for additional 3 h at 60 °C. The removal of the solvent and low boiling materials left a dark brown oil. Filtration through a silica gel column (3 g of Wakogel C-200, hexane : acetone=10 : 1) helped to remove dark brown impurities. Evaporation of the solvent yielded 240 mg of an yellow oil. The GLPC analysis of the oil[12] showed two peaks at the retention times of 1.5 and 3.4 min in the ratio of 54 : 46. Each fraction was collected by preparative GLPC. The component with the retention time of 1.5 min was identified as dihydrofuran **12a** (20% yield estimated by GLPC) and the other as **7a**.

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7) (a) R. A. Kretchmer, *J. Org. Chem.*, **37**, 2744 (1972); (b) J. S. Zweig, J. L. Luche, E. Rarreiro, and P. Crabbe, *Tetrahedron Lett.*, **1975**, 2355. These authors have found that (−)-sparteine causes asymmetric Michael addition of organometallic reagents to $\Delta^{\alpha,\beta}$-unsaturated carbonyl compounds. It has been suggested in these literatures that this chiral diamine acts as a bindetate ligand which creates a chiral environment around the metal atom, and this chirality is reflected in the stereochemistry of the addition product. It also has been suggested that the synthetic yield is reduced, due to the formation of bulky and hindered metal complex of **6** and (−)-sparteine.

8) (a) M. Julia, S. Julia, and M. Langlois, *C. R. Acad. Sci.*, **256**, 436 (1963); (b) M. Julia, S. Julia, and M. Langlois, *Bull. Soc. Chim. Fr.*, **1965**, 1014; (c) M. Julia, Fr. Patent 1269127 (1961); *Chem. Abstr.*, **57**, 2096g (1962). The synthetic method of **2** *via* the ester **8** has been patented by M. Julia. It involves the preparation of **8** by the treatment of **1** with $SOCl_2$ in $CHCl_3$ followed by the addition of ethanolic HCl. There has been given any scientific datum of **8** supporting its structure neither in the patent record nor in other publications.

9) (a) J. L. Pierre, R. Perraud, and P. Arnaud, *Bull. Soc. Chim. Fr.*, **1970**, 1540; (b) G. Pattenden, L. Crombie, and P. Hemesley, *Org. Mass Spectrom.*, **7**, 719 (1973).

10) E. A. Bauole and E. A. Evans, *J. Chem. Soc.*, **1955**, 3324.

11) 10% Apiezone Grease L on Chromosolb W; oven temperature 170 °C, N_2 1000 ml/min.

12) Carbo Wax 20 M on Celite 545; oven temperature 180 °C, N_2 1000 ml/min.