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Synthesis of (5*S*)-5-Methylfuran-2(5*H*)-one and Its Dihydro Derivative

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Abstract—(5*S*)-5-Methylfuran-2(5*H*)-one and (5*S*)-5-methyltetrahydrofuran-2-one were synthesized starting from L-lactic acid ethyl ester.

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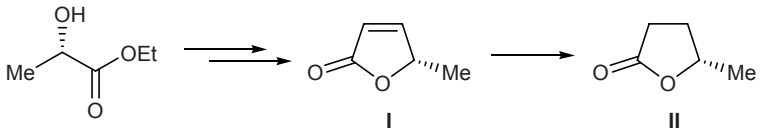
The main application of commercially available low-cost L-lactic acid in organic synthesis is preparation of chiral blocks containing α-methyl-substituted secondary alcohol fragments or their synthetic equivalents. Such fragments are present in molecules of some important natural compounds. In particular, L-lactic acid ethyl ester and (*S*)-(–)-1,2-epoxypropane derived therefrom were used in the synthesis of pheromones [1], Nonactin [2], Brefeldin A [3], Recifeiolide [4], etc. [5]. In the present communication we describe the synthesis of γ-methyl-substituted butenolide **I** from lactic acid ethyl ester (Scheme 1). Compound **I** attracts undoubted interest not only as synthetic equivalent of ω-functionalized secondary methylalkanol (cf. saturated analog **II**) but also as convenient stereodifferentiating Michael acceptor.

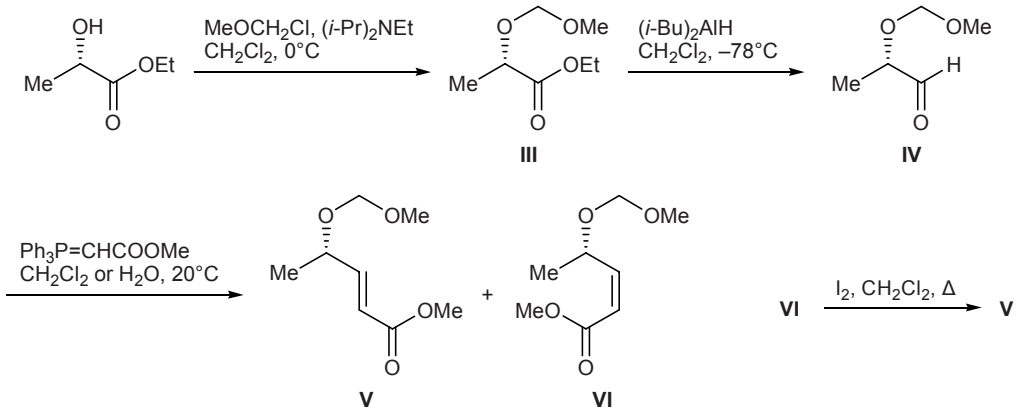
Compounds **I** and **II** were synthesized according to the following scheme. Initially, ethyl (2*S*)-(–)-2-(methoxymethyloxy)propanoate (**III**) [6] was reduced with $(i\text{-Bu})_2$AlH at –78°C to obtain aldehyde **IV** which was treated with methyl (triphenyl-λ^5-phosphanylidene)-acetate in methylene chloride at 20°C. As a result, we isolated a mixture of *E*/*Z*-isomeric unsaturated esters **V** and **VI** at a ratio of 2 : 1 (according to the ^{1}H NMR

Scheme 1.



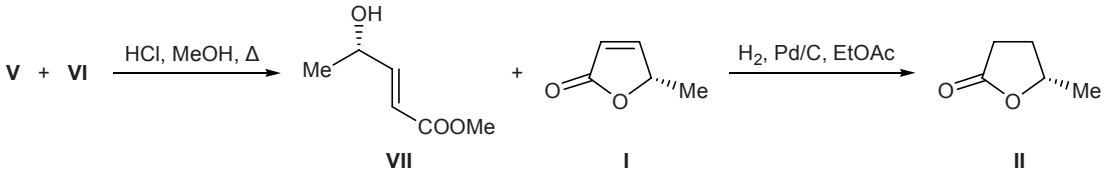
I II

Scheme 2.



III IV V VI

Scheme 3.



data), which cannot be separated by chromatography on silica gel (Scheme 2). Our attempts to convert the isomer mixture into *E* isomer **V** by the action of molecular iodine were unsuccessful. We succeeded only in enriching the isomer mixture with the *E* isomer, so that the ratio **V**:**VI** became 4:1 (^{1}H NMR).

With a view to obtain pure *E* isomer **V**, we tried to use the procedure described in [7] for the olefination of aldehydes with phosphoranes in water. According to [7], the reaction of methyl (triphenyl-λ^5-phosphanylidene)acetate with chiral α-methyl-substituted aldehyde structurally related to compound **IV** was not accompanied by racemization, and the corresponding olefination product was isolated as a mixture of *E* and *Z* isomers at a ratio of 87:13. However, aldehyde **IV** reacted with methyl (triphenyl-λ^5-phosphanylidene)acetate in aqueous medium to produce compounds **V** and **VI** at a ratio of 1:3 (*Z* isomer prevailed), i.e., the stereoselectivity was the opposite to that reported in [7].

Acid hydrolysis of isomer mixture **V**/**VI** gave a difficultly separable mixture of *trans*-alcohol **VII** and lactone **I** (Scheme 3). Obviously, the latter was formed from the hydrolysis product of *Z* isomer **VI**, and the isomer ratio was conserved. Unsaturated lactone **I** was quantitatively converted into saturated analog **II** under standard hydrogenation conditions. Taking into account published data [8], the optical rotation of **II** corresponded to almost 100% enantiomeric purity.

EXPERIMENTAL

The IR spectra were recorded from thin films on a UR-20 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal reference. Analytical thin-layer chromatography was performed on Silufol plates. The optical rotations were determined on a Perkin–Elmer 241-MC polarimeter.

Ethyl (2*S*)-(–)-2-(methoxymethyloxy)propanoate (III). A solution of 15 g (0.127 mol) of (*S*)-(–)-lactic acid ethyl ester in 50 ml of anhydrous methylene chloride was cooled to 0°C, 14.58 g (0.195 mol) of chloromethyl methyl ether and 34.83 g (0.285 mol) of ethyl(diisopropyl)amine were added under stirring, and the mixture was stirred for 12 h at 20°C, adjusted to pH 2 by adding hydrochloric acid, and extracted with methylene chloride (3×100 ml). The extracts were combined, washed with water until neutral reaction, and dried over Na_2SO_4, the solvent was distilled off, and the residue was distilled at 178–180°C. Yield 18.54 g (90%), colorless liquid. IR spectrum, ν, cm^{-1}: 1734, 1273, 1159, 1124. ^{1}H NMR spectrum, δ, ppm: 1.26 t (3H, CH_3, J = 7 Hz), 1.39 d (3H, CH_3, J = 6.9 Hz), 3.35 s (3H, OCH_2), 4.15 q (3H, 4-H, J = 7.1 Hz), 4.65 s (2H, OCH_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.99 (CH_3), 18.39 (CH_3), 55.64 (OCH_3), 60.71 (OCH_2CH_3), 95.69 (OCH_2O), 172.87 (C=O).

(2*S*)-(–)-2-(Methoxymethyloxy)propanal (IV). A solution of 4.26 g (30 mmol) of (*i*-Bu)$_2$AlH in 50 ml of anhydrous methylene chloride was added dropwise over a period of 10 min to a solution of 4.0 g (25 mmol) of ester **III** in 200 ml of anhydrous methylene chloride, cooled to –78°C. The mixture was allowed to warm up to –40°C over a period of 2 h and then to 5°C, and 5 ml of water was slowly added dropwise under vigorous stirring to avoid self-heating. The mixture was stirred for 2 h at room temperature, and the resulting gel-like material was filtered and washed with water and hot methylene chloride. The organic phase was separated, the aqueous phase was extracted with methylene chloride (3×50 ml), and the extracts were combined with the organic phase, washed with a saturated solution of sodium chloride, and dried over $MgSO_4$. The solvent was carefully evaporated to obtain 3.1 g of a pale green liquid residue which was purified by column chromatography on silica gel using hexane–Et_2O (1:1) as eluent. Yield 2.6 g (90%). IR spectrum, ν, cm^{-1}: 2721, 1734, 1240, 1030. ^{1}H NMR spectrum, δ, ppm: 1.37 d (3H, CH_3, J = 7.2 Hz), 3.40 s (3H, OCH_3), 4.03 d.d (1H, J = 7.2, 1.4 Hz), 4.73 s (2H, OCH_2O), 9.70 d (1H, CHO, J = 1.4 Hz).

Methyl (2*E*,4*S*)-4-(methoxymethyloxy)pent-2-enoate (V) and methyl (2*Z*,4*S*)-4-(methoxymethyloxy)-pent-2-enoate (VI). *a*. Aldehyde **IV**, 1 g (8.5 mmol), was dissolved in 20 ml of anhydrous methylene

chloride, 3.2 g (9.5 mmol) of methyl (triphenyl-λ^5-phosphanylidene)acetate was added, and the mixture was stirred for 1 h. The solvent was removed, and the residue was subjected to chromatography on silica gel using hexane–ethyl acetate (3:1) as eluent to isolate 1.3 g (88%) of isomer mixture **V**/**VI** (2:1, ^{1}H NMR) as an oily material.

b. Aldehyde **IV**, 1 g (8.5 mmol), was dissolved in 20 ml of distilled water, 3.2 g (9.5 mmol) of methyl (triphenyl-λ^5-phosphanylidene)acetate was added, and the mixture was stirred for 2 h. The precipitate of triphenylphosphine oxide was separated by decanting, the aqueous phase was extracted with methylene chloride (3×50 ml), the extracts were combined and dried over $MgSO_4$, the solvent was removed, and the residue was subjected to chromatography on silica gel using hexane–ethyl acetate (3:1) as eluent to isolate 1.25 g (85%) of isomer mixture **V**/**VI** (1:3, ^{1}H NMR) as an oily material.

E Isomer **V**. IR spectrum: ν 1300 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 1.25 d (3H, CH_3, J = 6.9 Hz), 3.32 s (3H, OCH_3), 3.70 s (3H, OCH_3), 4.20 m (1H, 4-H), 4.70 s (2H, OCH_2O), 5.95 d.d (1H, 4-H, J = 1.4, 15.7 Hz), 6.82 d.d (1H, 3-H, J = 5.8, 15.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.38 (CH_3), 51.41 (OCH_3), 52.20 (OCH_3), 70.20 (C^4), 94.00 (OCH_2O), 120.32 (C^2), 148.98 (C^3), 165.94 (C=O).

Z Isomer **VI**. IR spectrum: ν 1400 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 1.20 d (3H, CH_3, J = 6.6 Hz), 3.31 s (3H, OCH_3), 3.67 s (3H, OCH_3), 4.15m (1H, 4-H), 4.58 s (2H, OCH_2O), 5.75 d.d (1H, 2-H, J = 2.3, 11.7 Hz), 6.15 d.d (1H, 3-H, J = 8.2, 11.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.38 (CH_3), 51.16 (OCH_3), 69.45 (C^4), 94.96 (OCH_2O), 118.90 (C^2), 151.75 (C^3), 165.93 (C=O).

Isomerization of mixture V/VI. Isomer mixture **V**/**VI**, 100 mg (0.57 mmol), was dissolved in 5 ml of methylene chloride, a solution of 20 mg of iodine in 5 ml of methylene chloride was added, and the mixture was heated for 2 h under reflux. The mixture was treated with a solution of $Na_2S_2O_3$, filtered, and extracted with methylene chloride (3×10 ml). The combined extracts were washed with water and dried over $MgSO_4$, and the solvent was removed to obtain 95 mg of isomer mixture **V**/**VI** at a ratio of 4:1 (^{1}H NMR) as an oily material.

Acid hydrolysis of isomer mixture V/VI. Isomer mixture **V**/**VI**, 1.2 g (6.8 mmol), was dissolved in 5 ml of boiling moist methanol, 0.1 ml of concentrated hydrochloric acid was added, and the mixture was heated for 1 h under reflux. The mixture was then adjusted to pH 5 by adding an aqueous solution of $NaHCO_3$, and the aqueous phase was saturated with solid sodium chloride and extracted with ethyl acetate (3×50 ml). The extracts were combined, washed with water, and dried over $MgSO_4$, and the solvent was distilled off to obtain 0.9 g of a yellow oily liquid which was additionally purified by column chromatography on silica gel using $CHCl_3$–MeOH (40:1) as eluent.

Methyl (2*E*,4*S*)-4-hydroxypent-2-enoate (VII). IR spectrum, ν, cm^{-1}: 3435, 1718, 1305, 1274. ^{1}H NMR spectrum, δ, ppm: 1.28 d (3H, CH_3, J = 6.8 Hz), 1.60 br.s (1H, OH), 3.65 s (3H, OCH_3), 4.40 m (1H, 4-H), 5.95 d.d (1H, 2-H, J = 1.7, 15.7 Hz), 6.90 d.d (1H, 3-H, J = 4.6, 15.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.52 (CH_3), 51.50 (OCH_3), 66.87 (C^4), 118.88 (C^2), 151.43 (C^3), 167.08 (C=O).

(5*S*)-5-Methylfuran-2(5*H*)-one (I). Yellow oily liquid, $[\alpha]_D^{20}$ = +26.2° (c = 0.6, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1757, 1600. ^{1}H NMR spectrum, δ, ppm: 1.38 d (3H, CH_3, J = 6.6 Hz), 5.05 m (1H, 5-H), 6.03 d.d (1H, 3-H, J = 1.9, 5.7 Hz), 7.38 d.d (1H, 4-H, J = 1.4, 5.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.63 (CH_3), 79.64 (C^5), 121.09 (C^3), 157.44 (C^4), 173.18 (C^2).

(5*S*)-5-Methyltetrahydrofuran-2-one (II). Compound **I**, 100 mg (1.02 mmol), was dissolved in 5 ml of ethyl acetate, 0.02 g of Pd/C was added, and the mixture was stirred for 5 h under hydrogen. When the initial compound disappeared (TLC), the mixture was filtered, and the filtrate was evaporated. Yield 99 mg, oily liquid, $[\alpha]_D^{20}$ = –39° (c = 1, CH_2Cl_2); published data [8]: $[\alpha]_D^{20}$ = –36.8° (c = 1.44, CH_2Cl_2, *ee* 99.5%). IR spectrum: ν 1790 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 1.37 d (3H, CH_3, J = 7 Hz), 2.4 m (4H, 3-H, 4-H), 4.58 m (1H, 5-H).

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