(c 0.18, $CHCl_3$) {lit.[2b] $[\alpha]^{25}_D = -68.9°$; lit.[2c] $[\alpha]^{19}_D = -107.8°$ (c 1, $CHCl_3$); lit.[6b] $[\alpha]^{23}_D = -77.0°$ (c 0.1, $CHCl_3$)}; IR ($CHCl_3$) 3420, 1686, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, 3 H, J = 6.3 Hz), 1.19 (s, 3 H), 1.35 (s, 3 H), 1.90 (s, 3 H), 1.94 (s, 3 H), 3.79 (q, 1 H, J = 6.3 Hz), 3.80 (s, 3 H), 3.96 (s, 1 H), 5.46 (s, 1 H), 5.87 (s, 1 H), 6.38–6.20 (m, 4 H), 6.49 (dd, 1 H, J = 9.1 and 14.8 Hz), 7.18 (dd, 1 H, J = 11.0 and 15.0 Hz); ^{13}C NMR (50 MHz) δ 8.8, 12.3, 13.4, 17.2, 21.3, 56.1, 77.0, 80.8, 84.7, 85.8, 88.6, 107.8, 118.6, 127.2, 131.1, 134.3, 136.1, 138.6, 140.7, 141.1, 154.6, 163.8, 170.7; HRMS (M^+ + H) 403.2121 calcd for $C_{23}H_{31}O_6$, found 403.2103.

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Supplementary Material Available: $^1H/^{13}C$ NMR spectra for key intermediates (12 pages). Ordering information is given on any current masthead page.

Asymmetric Reduction of Chlorinated 4-Oxopentanoates with Bakers' Yeast. Synthesis of Optically Active γ-Butyrolactones and Useful Chiral Building Blocks

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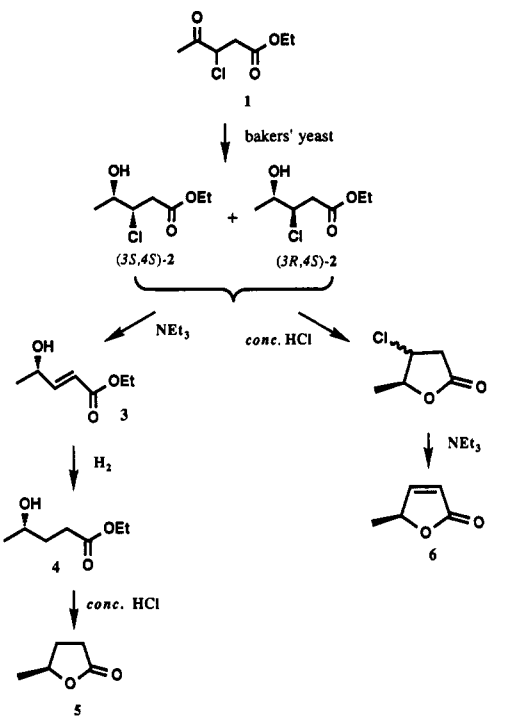
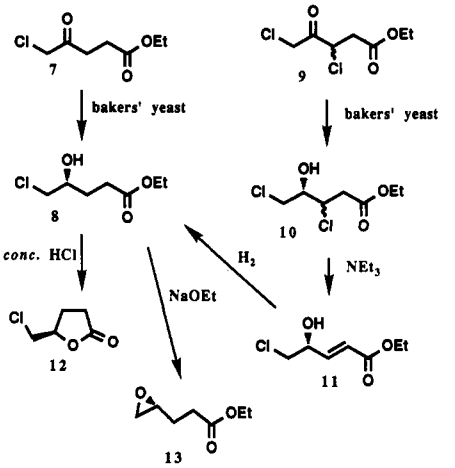
The asymmetric reduction of carbonyl groups by bakers' yeast (Saccharomyces) is a well-known reaction that is widely applied for the preparation of chiral building blocks.[1] It has been published by many groups that α-halo ketones are easily reduced with bakers' yeast to give chiral halo hydrins.[2] Most of these studies are concerned with the reductions of β-keto esters. Recently we reported the syntheses of chiral epoxides, key intermediates of natural products, by the reduction of 3-chloro-2-oxoalkanoates with bakers' yeast.[3,4] Here we describe the results of asymmetric reductions of chlorinated 4-oxopentanoates with bakers' yeast, which gives versatile chiral building blocks. Ethyl 3-chloro-4-oxopentanoate (1) can be easily obtained by the chlorination of ethyl 4-oxopentanoate.[5] Treatment of 1 with bakers' yeast in the presence of glucose for 3 days gave a mixture of ethyl (3*S*,4*S*)-3-chloro-4-hydroxypentanoate (2) and (3*R*,4*S*)-2 with a ratio of 1:1 in 75% yield. Although the isomers could not be separated by any chromatographic procedures, their existence was recognized by ^{13}C NMR analysis. Dehydrochlorination of the mixture of (3*S*,4*S*)-2 and (3*R*,4*S*)-2 with triethylamine gave ethyl (*S*)-(+)-4-hydroxy-2-pentenoate (3) in 71% yield, and the subsequent hydrogenation afforded ethyl (*S*)-4-hydroxypentanoate (4) in 76% yield. Hydrolysis of 4 with concd HCl gave (*S*)-5-methyltetrahydro-2-furanone (5).[6]

Scheme I



Scheme II



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Optical purity of **5** was estimated as 96% ee by comparison of the optical rotation with that of the authentic sample.[7] Hydrolysis of **2** with concd HCl and the subsequent dehydrochlorination with triethylamine gave optically pure β-angelicalactone **6** in 39% overall yield. The absolute configuration of **2** was deduced from the structure of known lactones **5** and **6**.

Asymmetric reduction of ethyl 5-chloro-4-oxopentanoate (**7**) with bakers' yeast yielded ethyl (*R*)-5-chloro-4-hydroxypentanoate (**8**) in 43% yield. The enantiomeric excess was determined to be 63% ee by the ^{1}H NMR analysis of the corresponding methoxy(trifluoromethyl)phenylacetate (MTPA).[8] Ester **8** has never been isolated because of its labile structure to give the γ-butyrolactone. Furthermore, ethyl 3,5-dichloro-4-oxopentanoate (**9**) was treated with bakers' yeast, giving the reduced product **10** as a mixture of two diastereomers with a ratio of 1:1. Dehydrochlorination of **10** with triethylamine afforded ethyl (*R*)-5-chloro-4-hydroxy-2-pentenoate (**11**) with 83% ee, whose structure was confirmed by the hydrogenation to give **8**. Hydrolysis of **8** with hydrochloric acid gave optically active γ-butyrolactone **12** in 36% yield, which can be alternatively prepared in four steps from D-glutamic acid.[9] Treatment of **8** with sodium ethoxide afforded ethyl (*R*)-4,5-epoxypentanoate (**13**) in 21% yield. Compounds **12** and **13** will be useful for chiral building blocks because of their polyfunctionality.

Although ethyl levulinate cannot be reduced by bakers' yeast,[2b] chlorinated levulinates were reduced by bakers' yeast to give chiral halohydrins in moderate yields. Namely, chlorine atoms play a role in the activation of the carbonyl group. For the syntheses of chiral compounds (**3–6** and **11**), the stereochemistry of C-3 in the reduced products **2** and **10** is of no consideration because the chlorine atom bearing at C-3 will be eliminated later. The present paper provides an economical and experimentally simple method for the synthesis of versatile chiral intermediates by reducing chlorinated levulinates with bakers' yeast.

Experimental Section

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano in our laboratory. HPLC analysis was performed with an apparatus fitted with a Yanapak SA-I (6-mm o.d. × 250-mm length) and with a Sumipax OA-3000 (4-mm o.d. × 250-mm length) for determination of enantioselectivity.

Fermentation was carried out in a thermostated bath at 32 ± 2 °C by using industrial bakers' yeast purchased from Oriental Yeast Co., Ltd. All glasswares were sterilized by boiling water before use.

Ethyl 3-chloro-4-oxopentanoate (**1**) was prepared by the chlorination of ethyl 4-oxopentanoate with sulfuryl chloride:[10] bp 67–77 °C (4 mm). Crude product was purified by column chromatography (SiO_2, hexane/ether, 10/1–3/1): TLC (hexane/ether, 1/1), R_f 0.51.

Ethyl (3*S*,4*S*)- and (3*R*,4*S*)-3-Chloro-4-hydroxypentanoate (2). To a mixture of KH_2PO_4 (0.6 g), $NH_4H_2PO_4$ (0.6 g), $MgSO_4$ (0.3 g), $CaCO_3$ (1.5 g), glucose (18 g), and boiling water (300 ml) was added 17 g of bakers' yeast at 35 °C. After bubbles formed (ca. 30 min), 2.21 g (12.4 mmol) of **1** was added and then the mixture was stirred at 32 ● 2 °C. After 12 h, 18 g of glucose was added. After 2 days, the organic materials were extracted with ether, washed with water, dried over $MgSO_4$, and concentrated. The residual oil (2.25 g) was chromatographed on SiO_2 [hexane/ethyl acetate (10/1–2/1)] to give 1.67 g (75%) of **2**: $[\alpha]^{22}_D$ +10.1° (*c* 3.21, $CHCl_3$); IR (neat) 3480, 3000, 2900, 1740, 1380, 1280, 1130, 955, 870 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.25 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.23 (d, *J* = 6 Hz, 3 H, $CH(OH)CH_3$), 2.60–3.00 (m, 3 H, OH, CH_2CO_2Et), 3.60–4.30 (m, 2 H, CH(OH), CHCl), 4.08 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$)[11] δ 14.2 (q), 19.2 (q), 20.0 (q), 39.0 (t), 39.9 (t), 61.1 (t), 62.7 (d), 63.1 (d), 69.5 (d), 70.4 (d), 170.5 (s), 170.7 (s). Anal. Calcd for $C_7H_{13}ClO_3$: C, 46.55;, H, 7.25. Found: C, 46.75; H, 7.13.

Ethyl (*S*)-(+)-(*E*)-4-Hydroxy-2-pentenoate (3). To a solution of 1.40 g (7.76 mmol) of **2** in dry ether (14 mL) was added 1.29 mL (936 mg, 92.7 mmol) of triethylamine. The mixture was stirred for 4 days at room temperature and then poured into ice water. The organic materials were extracted with CH_2Cl_2. The usual workup followed by column chromatography over SiO_2 [hexane/ethyl acetate (10/1–2/1)] gave 725 mg (71% from consumed **2**) of **3**: TLC [hexane/ethyl acetate (1/1)] R_f 0.50; $[\alpha]^{22}_D$ +22.8° (*c* 3.46, $CHCl_3$); IR (neat) 3460, 3000, 1720, 1658, 1300, 1270, 1180, 1045 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.28 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.30 (d, *J* = 6 Hz, 3 H, $CH_3CH(OH)$), 2.85 (br s, 1 H, OH), 4.41 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 4.41 (m, 1 H, CHOH), 5.86 (dd, *J* = 1 and 15 Hz, 1 H, $=CHCO_2$) 6.85 (dq, *J* = 6 and 15 Hz, 1 H, $CH_3CH=$). Spectral data were identical with those of the racemate.[12]

Ethyl (*S*)-4-Hydroxypentanoate (4). A mixture of **3** (524 mg, 3.66 mmol), Pd/C (140 mg), and dry ethanol (8 mL) was stirred for 6 days under 1 atm of hydrogen and then filtered. Concentration of the solvent gave the crude product (442 mg), which was purified with column chromatography [SiO_2, hexane/ethyl acetate (10/1–1/1)] to give 401 mg (76%) of **4**: $[\alpha]^{26}_D$ +10.98° (*c* 3.15, $CHCl_3$): IR (neat) 3500, 3000, 1740, 1380, 1280, 1160, 1030 cm^{-1}: ^{1}H NMR (CCl_4) δ 1.27 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.35 (d, *J* = 6 Hz, 3 H, $CH(OH)CH_3$), 2.35 (t, *J* = 7 Hz, 2 H, CH_2CO_2), 2.75 (m, 2 H, $CH_2CH_2CO_2$), 3.75 (m, 1 H, CHOH), 4.12 (q, *J* = 7 Hz, 2 H, CH_2CH_3). Spectral data were identical with those of the racemate prepared by the reduction of ethyl levulinate with $NaBH_4$.[13]

(*S*)-5-Methyltetrahydro-2-furanone (5). A mixture of **4** (117 mg, 0.648 mmol), concd HCl (0.5 mL), and water (0.5 mL) was heated at 95 °C for 8 h. The organic materials were extracted with ether. The usual workup followed by concentration of the solvent gave 31.3 mg (36%) of **5**: TLC (SiO_2, hexane/ethyl acetate, 1/1) R_f 0.32; $[\alpha]^{26}_D$ −28.6° (*c* 1.79, CH_2Cl_2) (lit.[7] $[\alpha]^{23}_D$ −29.6° (*c* 1.29, CH_2Cl_2)); IR (neat) 3550, 3000, 1780, 1175, 1042, 920, 740 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.9–2.7 (m, 4 H, CH_2CH_2COO), 3.67 (d, *J* = 5 Hz, 2 H, CH_2Cl), 4.70 (m, 1 H, $ClCH_2CHO$). Spectral data were identical with those of the authentic sample.[7]

(*S*)-(+)-5-Methyl-2(5*H*)-furanone (β-Angelicalactone, 6). A mixture of **2** (1.74 g, 9.64 mmol), concd HCl (8 mL), and water (8 mL) was heated at 50 °C for 25 h and then cooled. The organic materials were extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. The crude product (1.01 g) was chromatographed on SiO_2 [hexane/ethyl acetate (10/1–2/1)] to give a mixture (878 mg) of 4-chloro-5-methyltetrahydro-2-furanone and **6** (1/1 by ^{1}H NMR). To the solution of this mixture in dry ether (4 mL) was added triethylamine (0.40 mL, 2.87 mmol), and the mixture was stirred for 4 days at room temperature and then poured into water. The organic materials were extracted with ether. The usual workup followed by column chromatography over SiO_2 gave 365 mg (39%) of **6**:[14] $[\alpha]^{21}_D$ +117° (*c* 3.60, $CHCl_3$) [lit.[14] $[\alpha]_D$ −107.0° (*c* 1.61, $CHCl_3$) for (*R*)-(−)-**6**]; IR (neat) 1785, 1760, 1605 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.42 (d, *J* = 7 Hz, 3 H, CH_3), 5.08 (br q, *J* = 7 Hz, 1 H, C_γ-H), 5.98 (dd, *J* = 2 and 7 Hz, 1 H, C_α-H), 7.50 (dd, *J* = 2 and 7 Hz, 1 H, C_β-H).

Ethyl 5-chloro-4-oxopentanoate (7) was prepared in 55% yield by the reaction of 3-(ethoxycarbonyl)propanoyl chloride with diazomethane as described in the literature.[15] Spectral data were obtained newly: IR (neat) 1730, 1185, 1090, 860, 775 cm^{-1}; ^{1}H

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NMR (CCl_4) δ 1.24 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 2.40–2.90 (m, 4 H, CH_2CH_2), 4.02 (s, 2 H, $COCH_2Cl$), 4.06 (q, J = 7 Hz, 2 H, CO_2CH_2).

Ethyl (*R*)-(+)-5-Chloro-4-hydroxypentanoate (8). To a mixture of boiled water (450 mL), glucose (30 g), $NH_4H_2PO_4$ (0.9 g), KH_2PO_4, $MgSO_4$ (0.45 g), and $CaCO_3$ (2.25 g) was added 20 g of bakers' yeast at 35 °C. After the mixture was stirred for 30 min, 2.76 g (15.5 mmol) of 7 was added and the mixture was stirred at 32 °C. Every 2 days bakers' yeast (10 g) and glucose (10 g) were added. After 13 days the mixture was extracted with ethyl acetate. The usual workup gave the crude product (1.73 g), which was chromatographed on SiO_2 [hexane/ethyl acetate (30/1)] to give 1.20 g (43%) of 8: $[\alpha]^{24}_D$ +2.93° (*c* 4.23, $CHCl_3$); 63% ee (estimated by the ^1H NMR analysis for the corresponding MTPA ester in the presence of Eu(hfc)$_3$): IR (neat) 3450, 1730, 1180, 1095 cm^{-1}; ^1H NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.60–1.95 (m, 2 H, CH_2CO_2), 2.30–2.55 (m, 2 H, $CHOHCH_2$), 2.98 (br s, 1 H, OH), 3.40–4.00 (m, 3 H, $CHOHCH_2Cl$), 4.08 (q, J = 7 Hz, 2 H, CH_2CH_3). Anal. Calcd for $C_7H_{13}ClO_3$: C, 46.55; H, 7.25. Found: C, 46.34; H, 7.11.

MTPA ester of 8 was prepared by the method described in the literature.[8] A mixture of 8 (77.7 mg, 0.430 mmol), pyridine (3 mL), and (−)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride (122 mg, 0.483 mmol) was stirred for 24 h at room temperature and then poured into ice water. The organic materials were extracted with ether, and the ethereal extracts were washed with dilute HCl, water, and dried over $MgSO_4$. Evaporation of the solvent gave the crude product, which was purified by preparative TLC [hexane/ethyl acetate (2/1)] to give 60.5 mg (35%) of the MTPA ester of 8: R_f 0.41; IR (neat) 1745, 1260, 1180, 1020 cm^{-1}; ^1H NMR (CCl_4) δ 1.23 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.90–2.50 (m, 4 H, CH_2CH_2), 3.40–3.80 (m, 5 H, CH_2Cl, OCH_3), 4.07 (q, J = 7 Hz, CH_2CH_3), 5.20 (m, 1 H, CHO), 7.18–7.60 (m, 5 H, C_6H_5). Anal. Calcd for $C_{17}H_{20}O_5ClF_3$: C, 51.46; H, 5.08. Found: C, 51.49; H, 5.19.

Ethyl 3,5-Dichloro-4-oxopentanoate (9). To a solution of levulinic acid (10.7 g, 92.1 mmol) in chloroform (7 mL) was introduced chlorine gas at room temperature for 1 h. The mixture was stirred overnight, and chlorine gas was again introduced for 26 h at 35 °C. Air was bubbled into the mixture for 20 h and the precipitates were filtered off to give 4.87 g (28.6%) of 3,5-dichloro-4-oxopentanoic acid (14): IR (KBr) 3000, 1735, 1705, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.01–3.02 (m, 2 H, CH_2CO_2H), 4.41 (s, 2 H, $ClCH_2CO$), 4.80 (t, J = 6 Hz, 1 H, $CHClCH_2$), 10.2 (br s, 1 H, CO_2H). Concentration of the filtrate gave 13.7 g (81%) of 3,5-dichloro-4-oxopentanoic acid. The mixture of 14 (3.03 g, 16.4 mmol), dry ethanol (30 ml), and *p*-toluenesulfonic acid (100 mg) was heated at the reflux temperature for 13 h. After the mixture was concentrated, the organic materials were extracted with ether, washed with aqueous $NaHCO_3$ and water, and dried over $MgSO_4$. Evaporation of the solvent gave 2.95 g (85%) of 9: TLC [hexane/ethyl acetate (1/1)] R_f 0.57; IR (neat) 1730, 1205, 1020, 790 cm^{-1}; ^1H NMR (CCl_4) δ 1.24 (t, J = 7 Hz, 3 H, CH_2CH_3), 2.88–3.08 (m, 2 H, CH_2CO_2), 4.09 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.38 (s, 2 H, $ClCH_2CO$), 4.77 (t, J = 7 Hz, 1 H, $CHClCH_2$). Anal. Calcd for $C_7H_{10}Cl_2O_3$: C, 39.46; H, 4.73. Found: C, 39.48; H, 4.61.

Ethyl (4*S*)-(+)-3,5-Dichloro-4-hydroxypentanoate (10). To a mixture of boiled water (300 mL), glucose (6 g), $NH_4H_2PO_4$ (0.6 g), KH_2PO_4 (0.6 g), $MgSO_4$ (0.3 g), and $CaCO_3$ (1.5 g) was added bakers' yeast (10 g) at 35 °C. After 30 min, 1.78 g (8.36 mmol) of 9 was added and the mixture was stirred for 5 days at 35 °C. The organic materials were extracted with ethyl acetate. The usual workup followed by column chromatography over SiO_2 [hexane/ethyl acetate (10/1–1/1)] gave 0.862 g (48%) of 10: $[\alpha]^{25}_D$ +5.46° (*c* 5.02, $CHCl_3$); IR (neat) 3450, 1730, 1160, 1100, 950 cm^{-1}; ^1H NMR (CCl_4) δ 1.27 (t, J = 7 Hz, 3 H, CH_2CH_3), 2.70–3.25 (m, 3 H, CH_2CO_2, OH), 3.80–4.40 (m, 4 H, $ClCH_2CH(OH)CHCl$), 4.13 (q, J = 7 Hz, 2 H, CH_2CH_3). Anal. Calcd for $C_7H_{12}Cl_2O_3$: C, 39.09; H, 5.63. Found: C, 39.43; H, 5.57.

Ethyl (*R*)-(+)-(*E*)-5-Chloro-4-hydroxy-2-pentenoate (11). A mixture of 10 (862 mg, 4.01 mmol), dry ether (8 mL), and triethylamine (1.35 mL, 8.82 mmol) was stirred for 98 h at room temperature and then poured into ice water. After the mixture was acidified with dilute HCl, the organic materials were extracted with ethyl acetate. After the usual workup, the crude product (556 mg) was chromatographed on SiO_2 [hexane/ethyl acetate (10/1–1/1)] to give 306 mg (43%) of 11: $[\alpha]^{26}_D$ +6.30° (*c* 3.65, $CHCl_3$); 83% ee by the ^1H NMR analysis in the presence of Eu(hfc)$_3$; IR (neat) 3500, 1720, 1665, 1300, 1275, 1180 cm^{-1}; ^1H NMR (CCl_4) δ 1.27 (t, J = 7 Hz, 3 H, CH_2CH_3), 3.45 (br s, 1 H, OH), 3.52 (d, J = 7 Hz, 2 H, CH_2Cl), 4.11 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.30 (m, 1 H, CH(OH)), 5.99 (dd, J = 1.2 and 15 Hz, 1 H, $=CHCO_2$), 6.77 (dd, J = 4.4 and 15 Hz, 1 H, $CHOHCH=$). Anal. Calcd for $C_7H_{11}ClO_3$: C, 47.07; H, 6.21. Found: C, 47.11; H, 6.35.

Hydrogenation of 11. A mixture of 11 (296 mg, 1.66 mmol), dry ethanol (3 mL), and palladium on charcoal (66 mg) was stirred for 45 h under 1 atm of hydrogen. After filtration, concentration of the solvent left 214 mg of an oil, which was chromatographed on SiO_2 [hexane/ethyl acetate (20/1–5/1)] to give 117 mg (39%) of 8: $[\alpha]^{26}_D$ +5.26° (*c* 2.93, $CHCl_3$); TLC [hexane/ethyl acetate (1/1)] R_f 0.48. The spectral data were identical with those of the sample prepared from 7.

(*R*)-5-(Chloromethyl)tetrahydro-2-furanone (12). A mixture of 8 (117 mg, 0.648 mmol), concd HCl (0.5 mL), and water (0.5 mL) was stirred for 8 h at 95 °C. The organic materials were extracted with ether and worked up as usual. Evaporation of the solvent gave 32 mg (36%) of 12: $[\alpha]^{26}_D$ −7.18° (*c* 2.20, $CHCl_3$) (lit.[9] $[\alpha]^{27}_D$ −12.9° (*c* 3.03, $CHCl_3$)); IR (neat) 1780, 1175, 1040, 920 cm^{-1}; ^1H NMR (CCl_4) δ 1.90–2.72 (m, 4 H, $(CH_2)_2$), 3.67 (d, J = 5 Hz, 2 H, CH_2Cl), 4.70 (m, 1 H, CHO). Spectral data were identical with those of the authentic sample.[9]

Ethyl (*R*)-4,5-Epoxypentanoate (13). Sodium (85 mg, 3.7 mmol) was dissolved in dry ethanol (6 mL), and 8 (552 mg, 3.06 mmol) was added at 0 °C with stirring. The mixture was stirred for 5 h, poured into ice water, and acidified with dilute HCl. The organic materials were extracted with CH_2Cl_2. The usual workup followed by column chromatography [SiO_2, hexane/ethyl acetate (20/1–1/1)] gave 92 mg (21%) of 13: $[\alpha]^{24}_D$ +4.10° (*c* 3.32, $CHCl_3$); IR (neat) 1740, 1260, 930, 880 cm^{-1}; ^1H NMR (CCl_4) δ 1.23 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.78 (m, 2 H, $CH_2CH_2CO_2$), 2.20–3.00 (m, 5 H, CH_2OCH and CH_2CO_2), 4.06 (q, J = 7 Hz, 2 H, CO_2CH_2). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.14; H, 8.14.

Registry No. 1, 136576-72-2; (3*R*,4*S*)-2, 136576-80-2; (3*S*,4*S*)-2, 136576-73-3; 3, 132341-85-6; 4, 112789-84-1; 5, 19041-15-7; 6, 92694-51-4; 7, 14594-24-2; 8, 136576-74-4; 8 MTPA ester, 136599-73-0; 9, 136576-75-5; (3*R*,4*S*)-10, 136576-76-6; (3*S*,4*S*)-10, 136576-82-4; 11, 136576-77-7; 12, 52813-64-6; 13, 136576-78-8; 14, 136576-79-9; 4-chloro-5-methyltetrahydro-2-furanone, 136576-81-3; 3-(ethoxycarbonyl)propanoyl chloride, 14794-31-1; levulinic acid, 123-76-2.

Attempted de Novo Design, Synthesis, and Evaluation of a Ligand for the Allosteric Site of Phosphofructokinase

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The design of small-molecule ligands for protein binding sites has traditionally focused on enzyme inhibitors, using strategies that depend on knowledge of enzymatic mechanism or modification of lead structures. With the increasing availability of structural information through X-ray crystallography and NMR methods have come attempts to design ligands directly, using a combination of intuition and automated methods to invent completely new molecules to complement the geometric and electronic characteristics of a binding site. The possibility of devising ligands for noncatalytic sites, such as receptor or allosteric sites, can now be addressed as well. This report describes our attempt to design a ligand for the allosteric effector site of phosphofructokinase (PFK).

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