organic phases were dried over Na_2SO_4. The organic phases were combined and fractionally distilled under high vacuum. Nitrobenzene (4 g) was obtained, which is a 60% yield. Azo- and azoxybenzene as well as the byproducts were separated by liquid chromatography on silica gel with benzene as eluent. The retention times are as follows: azobenzene 0.66, azoxybenzene 0.50, byproducts 0-0.3.

Analysis. The reactions were followed up by GLC analysis. Dichlorobenzene was used as internal standard. The products were identified by comparison with standards and by gas chromatograph-mass spectra (GCMS) analysis. The column used was 15% OV 101 on Chromosorb W with the following program: 100 °C (3 min), 25 °C/min, 250 °C (10 min). The detector was FID. **Caution!** Avoid contamination with metals. Such contamination may cause rapid decomposition, generation of large quantities of oxygen gas, and high pressures.

Acknowledgment. We are grateful to Abic Ltd. Ramat-Gan for the donation of DDAB.

Registry No. $PhNO_2$, 98-95-3; PhNO=NPh, 495-48-7; $RuCl_3$, 10049-08-8; H_2O_2, 7722-84-1; aniline, 62-53-3; tetraethylammonium bromide, 71-91-0; tetrapropylammonium bromide, 1941-30-6; tetrabutylammonium bromide, 1643-19-2; tetrapentylammonium bromide, 866-97-7; tetrahexylammonium bromide, 4328-13-6; tetraheptylammonium bromide, 4368-51-8; didecyltrimethylammonium bromide, 1119-94-4; didecyldimethylammonium bromide, 2390-68-3; tricaprylmethylammonium bromide, 26305-24-8.

A New and Practical Synthesis of Four Possible Stereoisomers of 3-(2-Furyl)-3-hydroxy-2-methylpropionate

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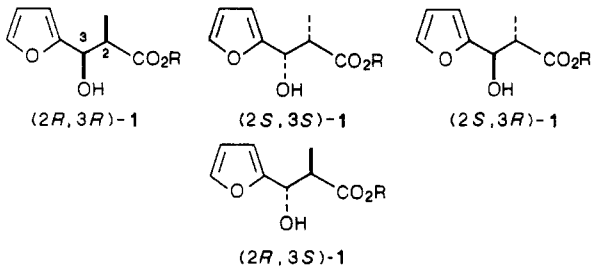
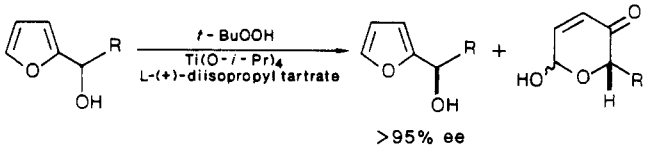
Optically active 3-(2-furyl)-3-hydroxy-2-methylpropionate (1) has been utilized as a key intermediate for the synthesis of several natural compounds,[1] and thus the synthesis of four possible stereoisomers of 1 has attracted much interest in recent years. Procedures currently



available for their preparation include asymmetric aldol reaction of furfural and chiral enolate,[1a,b] asymmetric reduction of 3-(2-furyl)-2-methyl-3-oxopropionate using yeast,[2] and enantioselective enzymatic hydrolysis of the corresponding acetate of 1 using lipase.[3] There is, however, no single methodology that allows the highly stereoselective synthesis of all the four possible stereoisomers of 1.

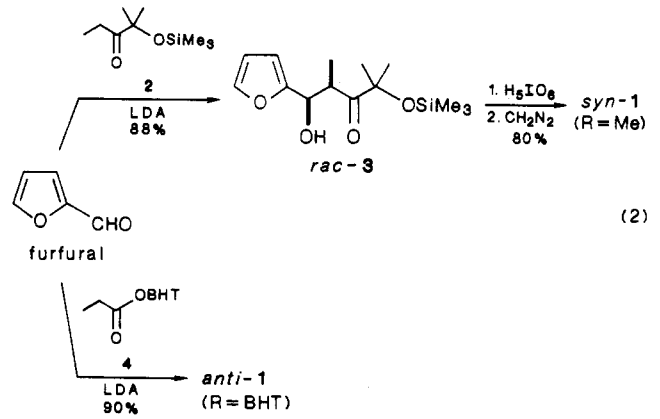
Recently we have reported that the kinetic resolution of 2-furylcarbinols using the Sharpless reagent proceeds highly efficiently to provide a practical method for the synthesis of homochiral 2-furylcarbinols (eq 1).[4] Herein



(1)

we report that the kinetic resolution of racemic 1 with syn and anti configuration, both of which can be readily prepared by Heathcock's aldol methodology, provides a convenient access to all the stereoisomers of 1.

The aldol reaction of furfural and α-[(trimethylsilyl)oxy] ketone 2[5] afforded racemic 3 predominantly in 88% yield, which was converted into racemic *syn*-1 (R = Me) in 80% overall yield by oxidative cleavage (H_5IO_6) followed by esterification (CH_2N_2) (eq 2). On the other hand, the reaction of furfural and 2,6-di-*tert*-butyl-4-methylphenyl propionate (BHT propionate, 4)[6] afforded racemic *anti*-1 (R = BHT) predominantly in 90% yield (eq 2).



(2)

The kinetic resolution of *syn*-1 (R = Me) using 0.6 equiv of *tert*-butyl hydroperoxide (TBHP) and a catalytic amount (20 mol %) of Ti(O-*i*-Pr)$_4$/L-(+)-diisopropyl tartrate (L-(+)-DIPT) proceeded highly efficiently to provide (2*R*,3*R*)-1 (R = Me) in 45% yield (based on racemic 1), which can be readily separated from the corresponding oxidation product and L-(+)-DIPT by column chromatography on silica gel (eq 1). The optical purity of (2*R*,3*R*)-1 (R = Me) thus obtained was found to be more than 99% ee by ^{1}H NMR analysis of the corresponding acetate in the presence of (+)-Pr(dppm)$_3$ (dppm = di(perfluoro-2-propoxypropionyl)methanato). Spectral data and optical rotation of (2*R*,3*R*)-1 (R = Me) were in good agreement with the reported values,[1a] $[\alpha]^{25}_D$ +14.7° (*c* 1.64, $CHCl_3$) [lit.[1a] $[\alpha]_D$ +14.75° (*c* 1.8, $CHCl_3$)]. The kinetic resolution of *anti*-1 (R = BHT) under the same reaction conditions also proceeded highly efficiently to afford (2*S*,3*R*)-1 (R = BHT) of more than 99% ee in 49% yield.[7] Needless to say, two other isomers of 1, i.e., (2*S*,3*S*)- and (2*R*,3*S*)-1, can be prepared by the kinetic resolution using D-(−)-DIPT as a chiral source instead of L-(+)-DIPT.

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(7) Compound 3 was found to be a poor kinetic resolution substrate. Thus, the optical purity of the remaining 3 after ca. 60% conversion was only 63% ee.

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In summary, the combination of Heathcock's aldol methodology and the kinetic resolution of 2-furylcarbinols using the Sharpless reagent offers a practical route for the synthesis of all the four possible stereoisomers of **1**.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were measured either on a HITACHI R-40 (90 MHz) or on a JEOL FX-90Q (90 MHz) spectrometer, whereas ^{13}C NMR spectra were recorded on a JEOL FX-90Q instrument. Both ^{1}H and ^{13}C NMR spectra were obtained with CCl_4 or $CDCl_3$ as a solvent, and values are reported in ppm (δ) downfield from tetramethylsilane or residual $CHCl_3$ as an internal standard unless otherwise noted. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet; br s, broad singlet. Infrared (IR) spectra were measured on a JASCO A-100 spectrometer. Optical rotations were measured on a YANACO OR-50 polarimeter using a 20-cm^3 capacity (0.5-dm path length) cell. Elemental analyses were performed by the Research Laboratory of Resources Utilization, Tokyo Institute of Technology.

Materials. Methylene chloride was freshly distilled from calcium hydride. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Titanium isopropoxide and L-(+)-DIPT were distilled under high vacuum and stored under an argon atmosphere before use. A stock solution of TBHP in CH_2Cl_2 was prepared and stored as described by Sharpless.[8] The optical purity of the kinetic resolution product was determined by ^{1}H NMR analysis of the corresponding acetate in the presence of (+)-Pr(dppm)$_3$ (Daiichi Pure Chemicals Co., Ltd.).

Preparation of Methyl (2*R,3*R**)-3-(2-Furyl)-3-hydroxy-2-methylpropionate (1 (R = Me)).** To a solution of diisopropylamine (1.42 mL, 10.1 mmol) in THF (15 mL) was added *n*-butyllithium (5.02 mL, 9.20 mmol, 1.83 M in hexane) at 0 °C under argon. After 10 min at 0 °C, the solution was cooled to −78 °C, and 2-methyl-2-[(trimethylsilyl)oxy]-3-pentanone (**2**)[5] (1.50 g, 7.97 mmol) dissolved in THF (1 mL) was added. After 30 min at −78 °C, furfural (0.51 mL, 6.13 mmol) was added. The solution was stirred for 1 min and poured into saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with hexane (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give an oil, which was purified by column chromatography on silica gel to afford **3** (1.53 g, 88%): IR (neat) 3420, 1700, 1180, 1020, 830 cm^{-1}; ^{1}H NMR (CCl_4, D_2O, CH_2Cl_2 as an internal standard) δ 0.04 (s, 9 H), 0.92 (d, J = 7.2 Hz, 3 H), 1.02 and 1.12 (2 s, 6 H), 3.44 (dq, J = 6.0, 7.2 Hz, 1 H), 4.63 (d, J = 6.0 Hz, 1 H), 5.90–6.10 (m, 2 H), 7.03 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 218.4, 154.8, 141.5, 110.1, 106.7, 80.6, 68.9, 44.1, 27.5, 27.1, 12.4, 2.3. Anal. Calcd for $C_{14}H_{24}O_4Si$: C, 59.12; H, 8.50. Found: C, 58.91; H, 8.65.

To a solution of **3** (1.57 g, 5.53 mmol) in MeOH (15 mL) was added H_5IO_6 (6.30 g, 27.6 mmol) dissolved in H_2O (30 mL) at 0 °C. After 3 h at 0 °C, the solution was neutralized by adding saturated aqueous $NaHCO_3$ at room temperature. The solvents were removed in vacuo to leave the crude acid, which was dissolved in ether (10 mL) and treated with diazomethane for 10 min at 0 °C. Concentration of the solution and purification by column chromatography on silica gel afforded (2*R**,3*R**)-**1** (R = Me) (812 mg, 80%): Spectral data (IR, ^{1}H NMR, and ^{13}C NMR) were in good agreement with values reported in the literature.[1a] Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.62; H, 6.62.

Kinetic Resolution of (2*R,3*R**)-1 (R = Me).** To a mixture of crushed 4A molecular sieves (300 mg) and 0.2 equiv of Ti(O-*i*-Pr)$_4$ (0.22 mL, 0.73 mmol) in CH_2Cl_2 (3 mL) was added 0.24 equiv of L-(+)-DIPT (0.18 mL, 0.87 mmol) at −21 °C under argon. The mixture was stirred for 10 min at −21 °C and cooled to −30 °C. To this mixture was added (2*R**,3*R**)-**1** (R = Me) (670 mg, 3.64 mmol) dissolved in CH_2Cl_2 (2 mL), and the mixture was stirred between −30 °C and −20 °C for 30 min. The mixture was again cooled to −30 °C, and 0.6 equiv of TBHP (0.51 mL, 2.19 mmol, 4.32 M in CH_2Cl_2) was slowly added. After the solution was stirred for 20 h at −21 °C, Me_2S (0.16 mL, 2.19 mmol) was added, and the mixture was stirred for 30 min at −21 °C. To this mixture were added 10% aqueous tartaric acid (1 mL), ether (10 mL), and NaF (2 g), and the resulting mixture was vigorously stirred for 2 h at room temperature. The white precipitate was filtered off through a pad of Celite with ether (20 mL). The filtrate was concentrated to give an oil, which was purified by column chromatography on silica gel to afford (2*R*,3*R*)-**1** (R = Me) (302 mg, 45% based on racemic **1**, >99% ee, R_f 0.52 (hexane–AcOEt, 1:1)) and the corresponding oxidation product (350 mg, 48%, R_f 0.35). (2*R*,3*R*)-**1**: $[\alpha]^{25}_D$ +14.7° (*c* 1.64, $CHCl_3$) [lit.[1a] $[\alpha]^{25}_D$ +14.75° (*c* 1.8, $CHCl_3$)]. Spectral data (IR and ^{1}H NMR) of the oxidation product are identical with those reported for its enantiomer.[1a]

Preparation of 2,6-Di-*tert*-butyl-4-methylphenyl (2*S,3*R**)-3-(2-Furyl)-3-hydroxy-2-methylpropionate (1 (R = BHT)).** To a solution of diisopropylamine (1.35 mL, 9.66 mmol) in THF (15 mL) was added *n*-butyllithium (5.39 mL, 9.05 mmol, 1.68 M in hexane) at 0 °C under argon. After 10 min at 0 °C, the solution was cooled to −78 °C and BHT propionate (**4**)[6] (2.17 g, 7.85 mmol) dissolved in THF (5 mL) was added. After 45 min at −78 °C, furfural (0.5 mL, 6.04 mmol) was added. The solution was stirred for 1 min at −78 °C and poured into saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give an oil, which was purified by column chromatography on silica gel to afford (2*S**,3*R**)-**1** (R = BHT) (2.03 g, 90%) as a white solid: mp 101–102 °C (recrystallized from hexane); IR (Nujol) 3460, 1730, 725 cm^{-1}; ^{1}H NMR (CCl_4, D_2O) δ 1.16–1.35 (m, 21 H), 2.18 (s, 3 H), 3.07 (qui, J = 7.8 Hz, 1 H), 4.68 (d, J = 7.8 Hz, 1 H), 6.10 (br s, 2 H), 6.88 (s, 2 H), 7.15 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 175.5, 153.7, 142.0, 141.9, 134.7, 127.2, 126.8, 110.1, 108.0, 69.5, 45.5, 35.2, 31.4, 21.3, 13.3. Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.27; H, 8.48.

Kinetic Resolution of (2*S,3*R**)-1 (R = BHT).** The reaction was run as described above for the kinetic resolution of (2*R**,3*R**)-**1** (R = Me) using (2*S**,3*R**)-**1** (R = BHT) (1.66 g, 4.46 mmol), Ti(O-*i*-Pr)$_4$ (0.27 mL, 0.89 mmol), L-(+)-DIPT (0.23 mL, 1.1 mmol), 4A molecular sieves (500 mg), TBHP (0.62 mL, 2.7 mmol, 4.32 M in CH_2Cl_2), and CH_2Cl_2 (3 mL) for 48 h. Workup as described above and purification by column chromatography on silica gel afforded (2*S*,3*R*)-**1** (R = BHT) (812 mg, 49% yield based on racemic **1**, >99% ee, R_f 0.49 (hexane–ether, 2:1)) as a white solid and the corresponding oxidation product (R_f 0.23) as an inseparable mixture with L-(+)-DIPT (1.12 g). The yield of the oxidation product was estimated to be 50% based on ^{1}H NMR analysis of the crude reaction mixture. (2*S*,3*R*)-**1** (R = BHT): mp 80–81 °C (recrystallized from hexane); $[\alpha]^{25}_D$ +9.52° (*c* 1.39, $CHCl_3$).

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Stereospecific Synthesis of Leukotriene Antagonists

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Leukotrienes C_4, D_4, and E_4 comprise a family of arachidonic acid metabolites that have been implicated in a variety of immediate hypersensitivity diseases, including allergic asthma.[1] It was recently noted that 2-nor-leu-

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