Enzymatic Preparation of Enantiomerically Enriched Tertiary α-Benzyloxy Acid Esters. Application to the Synthesis of (S)-(−)-Frontalin[1]

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Enzymatic preparation of enantiomerically enriched tertiary α-benzyloxy acid esters is described. Enantioselective hydrolysis of the racemic esters of the formula [R-C(CH_3)(OCH_2Ph)CO_2CH_3] by lipase OF (from *Candida cylindracea*, Meito Sangyo Co.) was successfully carried out on a preparative scale. With the asymmetric carbon atom possessing a tertiary benzyloxy group, (*S*)-(−)-frontalin, a component of the aggregation pheromone of the southern pine beetle, was efficiently synthesized.

Optically active tertiary α-hydroxy acids and esters are a useful class of compounds as starting materials or synthetic intermediates for pyrrolizidine alkaloids,[2] insect pheromones,[3] α-tocopherol,[4] bioactive metabolite of vitamin D_3,[5] synthetic prostaglandin analogues,[6] and other chiral natural products. These enantiomerically pure compounds are rather less abundant than the secondary ones in natural sources. The most readily available is citramalic acid (1), which is far more expensive (ca. $100/g) than malic (ca. $0.30/g) or tartaric acid (ca. $0.04/g). The tertiary α-hydroxy acids, unlike the secondary, are difficult to prepare starting from α-amino acids via stereoselective deamination. Thus, a classical optical resolution process was developed for the large-scale preparation of enantiomerically pure tertiary α-hydroxy acid lactone **2**, for the synthesis of frontalin (**3**, Figure 1).[7] However, it suffered from tedious multiple recrystallizations of diastereomeric amine salts.

On the other hand, those compounds have been the challenging targets for asymmetric synthesis. A number of methods have been developed for the asymmetric nucleophilic addition of alkyl groups to α-oxo esters.[8-10]

Recent studies from our laboratory showed that enantioselective enzymatic hydrolysis of racemic tertiary α-acetoxy nitriles (ketone cyanohydrin acetates) using a microorganism, *Pichia miso* IAM 4682, yielded enantiomerically enriched tertiary α-acetoxy nitriles (Figure 2).[11] Subsequent chemical hydrolysis of the unhydrolyzed starting materials constitutes a preparation of optically active tertiary α-hydroxy acid esters. However, direct hydrolysis of racemic α-hydroxy acid ester derivatives would be still more convenient for the preparation of both enantiomers, if the racemic substrates are readily available and the stereoselectivity of enzymatic hydrolysis is satisfactory. For example, the preparation of enantiomerically enriched glyceric acid analogues possessing a tertiary α-hydroxy group has been reported.[12] In this paper, we report the enantioselective enzymatic hydrolysis of racemic tertiary α-benzyloxy esters.

Table I. Results of the Hydrolysis of Tertiary (±)-α-Benzyloxy Esters

		(+)-4		5		
compd	cult., h	recovery, %	ee, %	recovery, %	ee, %	E^a
4a	96	41	81[b]	54	60[c]	10
4b	72	40	95[b]	18	70[c]	20
4c	72	40	>99[d]	52	82[e]	52
4d	72	38	>99[b]	35	67[c]	25
4e	72	40	94[f]	38	67[f]	17
4f	72	76	0[g]	3	–	–

[a] *E* value[14] [E(S) = ln [(1 − *c*)[1 − ee(S)]]/ln[(1 − c)[1 + ee(S)]]] was calculated on the basis of the ee of **4** and conversion [*c* = [ee(S) + ee_0]/[ee(S) + ee(P)]]. [b] Determined by ^{1}H NMR (400 MHz) in the presence of Eu(hfc)$_3$. [c] Determined by ^{1}H NMR (400 MHz) in the presence of Eu(hfc)$_3$, after conversion to the corresponding methyl ester. [d] Determined by ^{1}H NMR (400 MHz) in the presence of tris[3-(trifluoromethylhydroxymethylene)-(−)-camphorato]europium(III). [Eu(tfc)$_3$]. [e] Determined by ^{1}H NMR (400 MHz) in the presence of Eu(tfc)$_3$, after conversion to the corresponding methyl ester. [f] Determined by HPLC analysis, after reduction with $LiAlH_4$ and conversion to the corresponding MTPA ester. [g] Showed no specific rotation ($CHCl_3$).

Several years ago, we reported a preparation of optically active secondary α-benzyloxy acid esters using enantioselective hydrolysis of the corresponding racemates by a microorganism, *Corynebacterium equi* IFO 3730 (Figure 2).[13] Because the enantioselectivities are high and the benzyl protective group is readily removable by hydrogenolysis, this method is very effective for the preparation of corresponding enantiomerically enriched secondary α-hydroxy esters. However, only one enantiomer (unaffected ester) could be obtained after workup, because the other enantiomer was apparently further degraded in the metabolic system of the microorganism. In the present study, tertiary α-benzyloxy acid ester **4a** (R = CH_3CH_2) was chosen as the first candidate substrate. Initially, 15 kinds of microorganisms, including *C. equi* and commercially available lipases, were used for a screening test for efficiency of hydrolysis.

Lipase OF from *Candida cylindracea* (Meito Sangyo Co., Japan) was chosen as the most effective enzyme. A preparative scale hydrolysis of (±)-**4a** (Figure 3, see the

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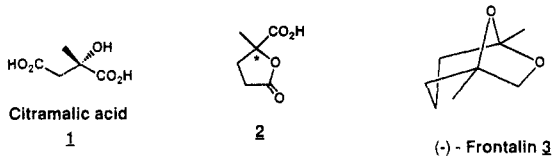

Figure 1.

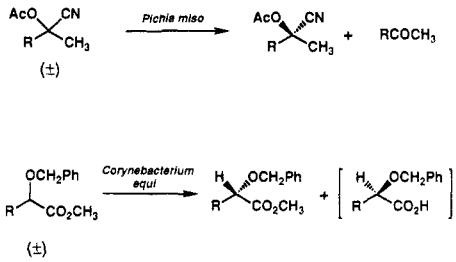

Figure 2. Previous examples of hydrolysis.

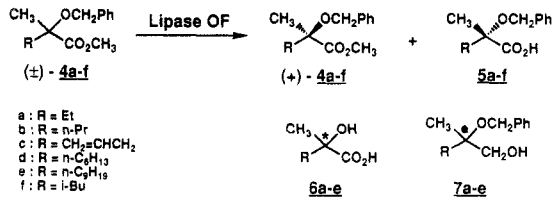

Figure 3. Enzymatic hydrolysis of tertiary (±)-α-benzyloxy esters.

Experimental Section) gave (+)-**4a** (41% yield) and the corresponding carboxylic acid **5a** (54% yield). The enantiomeric excess (ee) of (+)-**4a** was determined to be 81% from the 400-MHz ^{1}H NMR spectrum in the presence of tris[(3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$]. Acid **5a** was methylated to give (-)-**4a** and determined to be 60% ee as above. The *E* value of the present hydrolysis was estimated to be 10.[14] Then, acid **5a** was hydrogenated to give (+)-2-hydroxy-2-methylbutyric acid **6a**. The absolute configuration of acid **6a** [=(-)-**4a**] was determined to be *S* by comparing the sign of optical rotation with that of an authentic (*R*)-(-)-**6a**.[15] In this way, enantiomerically enriched **6a**, a structural component of the natural products, glaucarubin[16] and clerodendrin A,[17] can be prepared in a satisfactory ee.

Several substrates possessing a different side chain were tested in our hydrolytic system (Figure 3). The results are summarized in Table I. The reaction proceeded well for substrates with a straight alkyl chain. The ester (+)-**4c** was selectively hydrogenated to (+)-**4b** and coincided with the one derived from the hydrolysis of racemic **4b**. As all of the signs of rotations of recovered (unreacted) esters were revealed to be (+), the absolute configurations are tentatively assigned to be *R*. In the case of **4f**, a substrate possessing a branched side chain, the hydrolysis was very slow compared to the other substrates.

Because the ester **4c** possessing an allyl group as the side chain is considered to be a synthetic precursor of **1** and **2**, the preparation of both enantiomers on a larger scale was investigated. Racemic **4c** (10 g) was hydrolyzed with lipase OF for a prolonged reaction period (30 °C, 96 h) to give (+)-**4c** (4.0 g, 40%) in an enantiomerically pure state as judged from the 400-MHz ^{1}H NMR spectrum of the

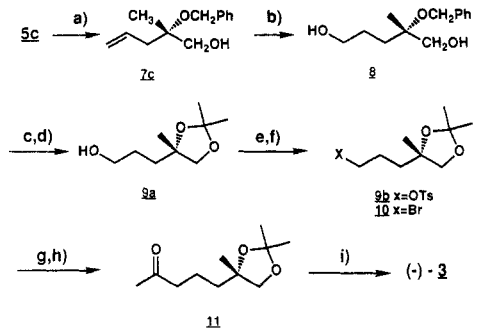

Figure 4. Synthesis of (-)-frontalin. (a) $LiAlH_4$/THF; (b) BH_3/THF, H_2O_2; (c) H_2, Pd-C; (d) TsOH, 2,2-dimethoxypropane/acetone; (e) TsCl/C_5H_5N; (f) LiBr, $NaHCO_3$/acetone; (g) Mg/THF; CH_3CHO; (h) PCC, molecular sieves 3A/CH_2Cl_2; (i) aqueous HCl.

corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)[18] ester derivative **7b**. On the other hand, resulting acid **5c** (52% yield) was methylated to (-)-**4c** and was revealed to be 82% ee. The *E* value in this case was ca. 52. The hydrolysis was repeated on the enriched ester (-)-**4c** to make the ee still higher.[19] A second incubation for a shorter period (24 h) gave ester **4c** (27% yield) and acid **5c** (68% yield). The acid **5c** was obtained enantiomerically pure as determined above, leaving behind (-)-**4c** in as low ee as 20%. In this way, both enantiomers of **4c** have become available on a preparative scale. Next, the application of (-)-**4c** as the starting material for natural product synthesis was developed.

Frontalin (**3**) is a component of the aggregation pheromone of females of the southern pine bark beetle, *Dendroctonus frontalis*, and of males of western pine bark beetle, *Dendroctonus brevicomis*.[20] It is well established that only the 1*S*,5*R* isomer is physiologically active.[21] A number of syntheses of frontalin have been reported.[22] The present synthesis of (-)-frontalin is straightforward (Figure 4). Lithium aluminum hydride reduction of acid **5c** gave alcohol **7c** in 97% yield. Hydroboration–oxidation of **7c** yielded diol **8** in 88% yield. The known acetonide alcohol **9a**[7] was obtained from **8** via catalytic hydrogenation, followed by acetal formation in 94% yield. The acetonide alcohol was converted to bromide **10** via tosylate **9b** in 94% yield. The reaction of the corresponding Grignard reagent with acetaldehyde, followed by oxidation, afforded acetonide ketone **11** in 66% yield. Finally, (-)-frontalin (**3**) was obtained by acidic hydrolysis of the acetonide and intramolecular acetalization in 82% yield. It was revealed to be enantiomerically pure by 400-MHz ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$.[11] The absolute configuration of (-)-**4c** was confirmed to be *S*.

In conclusion, lipase OF catalyzed enantioselective hydrolysis gave various enantiomerically enriched tertiary α-benzyloxy esters [R-C(CH_3)(OCH_2Ph)CO_2CH_3]. The racemic substrates are readily obtainable, the operation of the hydrolytic reaction is very easy, and furthermore the functional group of the product is suitably protected. From the chiral carboxylic acid **5c** obtained above, (-)-frontalin was efficiently synthesized in nine steps and 41% total yield, demonstrating the utility of this method.

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Further application of (+)- and (−)-**4c** as starting material for natural product synthesis is now under investigation.

Experimental Section

General Procedures. All boiling and melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ at 90 or 400 MHz. Optical rotations were measured in $CHCl_3$ unless otherwise stated. Mass spectra were recorded at 70 eV. TLC analyses were performed with Merck Kieselgel 60 F_{254} (Art 5715). Wako Gel B-5F and silica gel 60 K070-WH (70–230 mesh) of Katayama Chemical Co. were used for preparative TLC and column chromatography, respectively. Lipase OF was purchased from Meito Sangyo Co., Japan.

Preparation of the Substrates 4a, 4b, 4d, 4e, and 4f. These were prepared from the corresponding ketones via cyanohydrin formation, hydrolysis, methylation,[11] and benzylation in the usual manner.

4a: bp 105–109 °C (1.0 mm); ^1H NMR δ 0.95 (t, J = 7.5 Hz, 3 H), 1.50 (s, 3 H), 1.87 (q, J = 7.5 Hz, 2 H), 3.72 (s, 3 H), 4.48 (s, 2 H), 7.27–7.50 (m, 5 H); IR (film) 1730, 1495, 1130, 735, 695 cm^{-1}; MS m/e (rel intensity) 163 [3, $(M^+ + 1) - CH_4, CO_2$], 116 [18, $(M^+ + 1) - CH_4, C_7H_7$], 91 (100, $C_7H_7^+$). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 69.47; H, 7.76.

4b: bp 155–160 °C (1.5 mm); ^1H NMR δ 0.90 (t, J = 7.0 Hz, 3 H), 1.18–1.58 (m, 2 H), 1.48 (s, 3 H), 1.62–1.90 (m, 2 H), 3.73 (s, 3 H), 4.46 (s, 2 H), 7.24–7.40 (m, 5 H); MS m/e (rel intensity) 177 [4, $(M^+ - 1) - CH_4, CO_2$], 130 [14, $(M^+ + 1) - CH_4, C_7H_7$], 91 (100, $C_7H_7^+$). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.65; H, 8.26.

4d: bp 215–220 °C (1.6 mm); ^1H NMR δ 0.87 (t, J = 7.0 Hz, 3 H), 1.10–1.55 (m, 8 H), 1.48 (s, 3 H), 1.65–1.90 (m, 2 H), 3.75 (s, 3 H), 4.46 (s, 2 H), 7.26–7.50 (m, 5 H); MS m/e (rel intensity) 172 [11, $(M^+ - 1) - CH_4, C_7H_7$], 91 (100, $C_7H_7^+$). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.59; H, 9.21.

4e: bp 195–200 °C (1.0 mm); ^1H NMR[23] δ 0.75–1.00 (deformed t, 3 H), 1.18–1.58 (m, 14 H), 1.48 (s, 3 H), 1.65–1.90 (m, 2 H), 3.74 (s, 3 H), 4.46 (s, 2 H), 7.15–7.40 (m, 5 H); MS m/e (rel intensity) 261 [3, $(M^+ + 1) - CH_4, CO_2$], 216 [14, $(M^+ + 1) - CH_4, C_7H_7$], 91 (100, $C_7H_7^+$).

4f: bp 195–200 °C (2.8 mm); ^1H NMR δ 0.92 (d, J = 5.7 Hz, 6 H), 1.51 (s, 3 H), 1.70–1.90 (m, 3 H), 3.74 (s, 3 H), 4.49 (s, 2 H), 7.22–7.60 (m, 5 H); MS m/e (rel intensity) 191 [6, $(M^+ + 1) - CH_4, CO_2$], 144 [16, $(M^+ + 1) - CH_4, C_7H_7$], 91 (100, $C_7H_7^+$). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.34; H, 8.68. The IR spectra of **4b,d–f** were almost identical with that of **4a**.

Methyl 2-(Benzyloxy)-2-methyl-4-pentenoate (4c). This was prepared according to a reported procedure with a slight modification.[24] To a solution of methyl pyruvate (10.0 g, 97.9 mmol) in dry CH_2Cl_2 (200 mL) was added successively $TiCl_4$ (10.7 mL, 97.9 mmol) and allyltrimethylsilane (16.1 g, 127 mmol) with stirring at −78 °C under Ar. After 1 h the reaction was quenched by addition of saturated $NaHCO_3$ solution with ice cooling, before being warmed to room temperature. The mixture was filtered through a pad of Celite, and the filtrate was dried (Na_2SO_4) and concentrated in vacuo. The residue was used for the next step without further purification because of the volatility.

To a suspension of NaH (4.8 g, 60% in mineral oil, 121 mmol) in dry THF (50 mL) was added a solution of the crude alcohol obtained above in dry THF (100 mL) at 0 °C under Ar. The mixture was stirred at room temperature for 1.5 h, and a solution of benzyl bromide (16.7 mL, 141 mmol) in dry THF (100 mL) and $Bu_4N^+I^-$ (2.5 g, 10 mol %) were added at 0 °C. Stirring was continued at room temperature for 2 h, and then the mixture was heated under reflux for 2 h. After cooling, the mixture was quenched by the addition of saturated NH_4Cl solution and extracted with ether. The extract was washed with 10% $Na_2S_2O_3$ solution and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was distilled to give (±)-**4c** (16.4 g, 72%): bp 105–108 °C (0.6 mm); ^1H NMR ($CDCl_3$) δ 1.49 (s, 3 H), 2.60 (d, J = 7.0 Hz, 2 H), 3.75 (s, 3 H), 4.49 (s, 2 H), 5.01–5.21 (m, 2 H), 5.36–6.10 (m, 1 H), 7.27–7.43 (m, 5 H); IR (film) 3000, 2950, 1740, 1450, 1215, 1155, 1110, 1020, 920, 735, 700 cm^{-1}; MS m/e (rel intensity) 177 [4, $(M^+ + 1) - CH_4, CO_2$], 130 [14, $(M^+ + 1) - CH_4, C_7H_7$], 91 (100, $C_7H_7^+$). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.69. Found: C, 71.74; H, 7.57. ^1H NMR [1.5 equiv of Eu(tfc)$_3$, C_6D_6]: δ 1.67, (s, 1.5 H), 1.70 (s, 1.5 H), 3.45 (s, 1.5 H), 3.47 (s, 1.5 H). A small amount of this sample was reduced with $LiAlH_4$ and treated with (+)-MTPA-Cl in pyridine to give the MTPA ester of (±)-**7c**: ^1H NMR δ 1.26 [s, 1.5 H, C(CH_3)(OBn)], 1.28 [s, 1.5 H, C(CH_3)(OBn)], 2.40 (m, 2 H), 3.52 (s, 3 H), 4.25 (d, J = 11.2 Hz, 0.5 H, C*H*HOMTPA), 4.30 (d, J = 11.2 Hz, 0.5 H, C*H*HOMTPA), 4.34 (d, J = 11.2 Hz, 0.5 H, CH*H*OMTPA), 4.39 (d, J = 11.2 Hz, 0.5 H, CH*H*OMTPA), 4.46 (s, 2 H), 5.10 (m, 2 H), 5.82 (m, 1 H), 7.25–7.53 (m, 10 H).

General Procedure for Hydrolysis Using Lipase OF. The substrate (ca. 100 mg) and lipase OF (100–150 mg) were shaken in phosphate buffer (0.1 M, pH 7, 50 mL) for 72–96 h at 30 °C. The mixture was extracted with ethyl acetate after acidification. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography to yield ester **4** and acid **5**. In the case of **4a**, the scale was about 20 times larger than described above, and the products were separated by silica gel column chromatography.

4a: substrate, 2.00 g (9.00 mmol). (+)-**4a**: 828 mg (41%); $[\alpha]^{24}_D$ +4.2° (*c* 2.4). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 69.78; H, 7.57. ^1H NMR [0.5 equiv of Eu(hfc)$_3$, C_6D_6]: δ 4.09, (s, 0.28 H), 4.15 (s, 2.72 H); 81% ee. **5a**: 1.01 g (54.0%). This was converted to (−)-**4a** with ethereal diazomethane solution, $[\alpha]^{25}_D$ −2.6° (*c* 1.3). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 69.87; H, 7.61. ^1H NMR [0.5 equiv of Eu(hfc)$_3$, C_6D_6]: δ 4.09, (s, 2.40 H), 4.15 (s, 0.60 H); 60% ee.

4b: substrate, 108 mg (0.46 mmol). (+)-**4b**: 42.8 mg (40%); $[\alpha]^{28}_D$ +2.6° (*c* 1.2). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.10; H, 8.36. ^1H NMR [1.0 equiv of Eu(hfc)$_3$, C_6D_6]: δ 3.88, (s, 0.07 H, CO_2CH_3), 3.93 (s, 2.93 H, CO_2CH_3); 95% ee. **5b**: 18.3 mg (18.0%). This was converted to (−)-**4b**, $[\alpha]^{28}_D$ −1.9° (*c* 1.3). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.14; H, 8.09. ^1H NMR [1.0 equiv of Eu(hfc)$_3$, C_6D_6]: δ 3.88 (s, 2.55 H, CO_2CH_3), 3.93 (s, 0.45 H, CO_2CH_3); 70% ee.

4d: substrate, 104 mg (0.37 mmol). (+)-**4d**: 39.4 mg (38%); $[\alpha]^{22}_D$ +1.4° (*c* 0.85). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 74.09; H, 9.35. ^1H NMR [0.5 equiv of Eu(hfc)$_3$, C_6D_6]: δ 0.91, (t, 3 H, CH_2CH_3); >99% ee. **5d**: 34.4 mg (35%). This was converted to (−)-**4d**, $[\alpha]^{24}_D$ −0.94° (*c* 1.1). Anal. Calcd for $C_{17}H_{26}O_3$: C, 72.93; H, 8.93. Found: C, 73.59; H, 9.21. ^1H NMR [0.5 equiv of Eu(hfc)$_3$, C_6D_6]: δ 0.90, (t, 2.50 H, CH_2CH_3), 0.91 (t, 0.50 H, CH_2CH_3); 67% ee.

4e: substrate, 95.6 mg (0.30 mmol). (+)-**4e**: 37.8 mg (40%); $[\alpha]^{22}_D$ +0.63° (*c* 0.94). This was converted to the MTPA ester of **7e** as above. HPLC analysis [column, Zorbax Sil (4.6 mm × 250 mm); eluent, hexane/ethyl acetate, 100/1; flow rate, 0.5 mL/min] t_R (min): 40.4 (97.0%), 44.5 (3.0%); 94% ee. **5e**: 35.0 mg (38%). This was converted to the corresponding MTPA ester via **4e**. HPLC analysis (under the same condition) t_R (min): 40.4 (16.6%), 44.5 (83.4%); 67% ee.

In all cases, IR and NMR spectra of the esters obtained above were identical with those of racemic samples.

Determination of Absolute Configuration of 5a. A mixture of **5a** obtained above (500 mg, 2.4 mmol, 60% ee) and Pd–C (10%, 100 mg) in ethanol (30 mL) was vigorously stirred overnight at room temperature under H_2. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by recrystallization from toluene–hexane to give (+)-**6a** (191 mg, 67%) as needles: mp 68–71 °C (lit.[15] mp 78–79 °C); $[\alpha]^{25}_D$ +4.6° (*c* 3.1) [lit.[15] $[\alpha]^{25}_D$ −8.9° (*c* 3) for the *R* isomer]. From the sign of rotation, the absolute configuration of the sample was determined to be *S*.

Large-Scale Hydrolysis of 4c. First Hydrolysis. The substrate **4c** (10 g, 42.7 mmol) and lipase OF (10 g) were shaken in phosphate buffer (0.1 M, pH 7, 1000 mL) for 96 h at 30 °C. The mixture was extracted with ethyl acetate after acidification. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane/ethyl acetate (15/1) gave (+)-**4c** (4.0 g, 40%) as an oil: bp 160–170 °C (0.9 mm); $[\alpha]^{25}_D$

(23) The NMR spectrum is available for the proof of the purity of these compounds.

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+3.80° (c 1.63); ^{1}H NMR [1.5 equiv of Eu(tfc)$_3$, C_6D_6] δ 1.67, [s, 3 H, C(CH_3)(OBn)], 3.47 (s, 3 H, CO_2CH_3) and the signal due to other enantiomer could not be detected. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.69. Found: C, 71.88; H, 7.50. IR and NMR spectra were identical with those of (±)-**4c**. This was converted into the MTPA ester of **7c** as above: ^{1}H NMR δ 1.28 [s, 3 H, C(CH_3)(OBn)], 4.30 (d, J = 11.2 Hz, 1 H, C*H*HOMTPA), 4.34 (d, J = 11.2 Hz, 1 H, CH*H*OMTPA) and no contamination of the other diastereomer was confirmed.

Further elution with hexane/ethyl acetate (9/1–1/1) gave **5c** (4.7 g, 52.0%): IR (film) 3100, 3050, 3000, 2950, 1710, 1640, 1500, 1455, 1390, 1280, 1160, 1120, 1030, 920, 740, 700 cm^{-1}. This was immediately treated with acidic methanol to give (−)-**4c** in quantitative yield: bp 160–170 °C (0.9 mm); $[\alpha]^{23}_D$ −2.61° (c 0.98); ^{1}H NMR [1.5 equiv of Eu(tfc)$_3$, C_6D_6] δ 1.67, [s, 0.27 H, C(CH_3)(OBn)], 1.70, [s, 2.73 H, C(CH_3)(OBn)]; 82% ee. IR and NMR spectra were identical with those of (±)-**4c**.

Second Hydrolysis. The substrate (−)-**4c** (5.9 g, 25.2 mmol) and lipase OF (6.0 g) were shaken in phosphate buffer (0.1 M, pH 7, 600 mL) for 24 h at 30 °C. After workup in the same manner as above, (−)-**4c** (1.6 g, 27%) and **5c** (3.8 g, 68%) were obtained. (−)-**4c**: $[\alpha]^{25}_D$ −0.74° (c 2.1). This was estimated to be ca. 20% ee, comparing its optical rotation with that of an authentic sample obtained above. **5c** was converted to (−)-**4c** as above: bp 160–170 °C; $[\alpha]^{26}_D$ −3.7° (c, 1.4). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.69. Found: C, 72.10; H, 7.41. IR and NMR spectra were identical with those of (±)-**4c**. This was converted into the MTPA ester of **7c** as above: ^{1}H NMR δ 1.26 [s, 3 H, C(CH_3)(OBn)], 4.25 (d, J = 11.2 Hz, 1 H, C*H*HOMTPA), 4.39 (d, J = 11.2 Hz, 1 H, CH*H*OMTPA); and no contamination of the other diastereomer was confirmed.

Conversion of (+)-4c to (+)-4b. A mixture of (+)-**4c** [$[\alpha]^{23}_D$ +4.1° (c 1.3), 37.0 mg, 0.16 mmol] and a catalytic amount of $(Ph_3P)_3RhCl$ in dry benzene (3.5 mL) was vigorously stirred overnight at room temperature under H_2. Then the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (developed with hexane/ethyl acetate, 9/1) to give (+)-**4b** (34.0 mg, 91%): $[\alpha]^{23}_D$ +2.9° (c 1.3). IR and NMR spectra were identical with those of (±)-**4b**.

(*S*)-(−)-2-(Benzyloxy)-2-methyl-4-penten-1-ol (7c). The carboxylic acid **5c** (1.57 g, 7.13 mmol) was reduced by $LiAlH_4$ (606 mg, 16.0 mmol) in dry THF in the usual manner to give **7c** (1.43 g, 97%) as an oil after chromatographic purification: $[\alpha]^{22}_D$ −3.5° (c 0.85); ^{1}H NMR[23] δ 1.25 (s, 3 H), 1.84–1.98 (m, 1 H), 2.41 (d, J = 7.0 Hz, 2 H), 3.53 (d, J = 6.2 Hz, 2 H), 4.48 (s, 2 H), 4.95–5.24 (m, 2 H), 5.65–6.00 (m, 1 H), 7.23–7.32 (m, 5 H); IR (film) 3450, 3000, 2950, 2900, 1640, 1455, 1380, 1050, 920, 880, 740, 700 cm^{-1}; MS m/e (rel intensity) 175 [33, (M^+ + 1) − CH_3OH], 91 (100, $C_7H_7^+$).

(*S*)-2-(Benzyloxy)-2-methylpentane-1,5-diol (8). A solution of BH_3 in THF (0.82 M, 12.4 mL, 10.2 mmol) was added dropwise to a stirred and ice-cooled solution of **7c** in THF (10 ml) under Ar. Stirring was continued for 15 min at room temperature. The mixture was quenched by the successive addition of methanol (0.3 mL), 3 N NaOH solution (H_2O/methanol, 1/1, 3 mL), and 35% H_2O_2 (3 mL) at 0 °C. After stirring for 1.5 h at room temperature, the mixture was extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent hexane/ethyl acetate, 1/2) to give 8 (1.33 g, 88%) as an oil: $[\alpha]^{22}_D$ +1.1° (c 0.72); ^{1}H NMR[23] δ 1.27 (s, 3 H), 1.63–1.72 (m, 2 H), 1.70–2.04 (m, 2 H), 3.56 (d, J = 6.2 Hz, 2 H), 3.60–3.75 (m, 2 H), 4.46 (s, 2 H), 7.33 (br s, 5 H); MS m/e (rel intensity) 193 [25, (M^+ + 1) − CH_3OH], 91 (100, $C_7H_7^+$).

(*S*)-(−)-3-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)propan-1-ol (9a). A mixture of 8 (1.25 g, 5.57 mmol) and 10% Pd–C (300 mg) in ethanol (75 mL) was vigorously stirred under H_2 for 2 days at room temperature. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in a mixture of dry acetone (8 mL) and 2,2-dimethoxypropane (1.74 g, 16.7 mmol), followed by the addition of a catalytic amount of *p*-toluenesulfonic acid. The resulting solution was stirred for 5 h at room temperature and then concentrated in vacuo. After addition of saturated $NaHCO_3$ solution, the mixture was extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent hexane/ethyl acetate, 2/1) to give **9a** (911 mg, 94% from 8) as an oil: $[\alpha]^{24}_D$ −2.1° (c 0.85) [lit.[7] $[\alpha]^{23}_D$ −0.5° (c 2.25, acetone)]; ^{1}H NMR δ 1.30 (s, 3 H), 1.39 (s, 6 H), 1.58–1.66 (m, 2 H), 1.87–1.98 (m, 2 H), 3.55–3.85 (m, 2 H), 3.76 (s, 2 H); IR (film) 3450, 1245, 1215, 1120, 1060 cm^{-1}; MS m/e (rel intensity) 159 [47, (M^+ + 1) − CH_4], 115 (56), 99 (76), 81 (21), 72 (60), 59 (32), 57 (38), 43 (100).

(*S*)-3-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)propan-1-ol *p*-Toluenesulfonate (9b). According to the reported procedure,[7] alcohol **9a** (900 mg, 5.17 mmol) was converted to the corresponding tosylate **9b** (1.59 g, 94%) as an oil: $[\alpha]^{22}_D$ −2.0° (c 0.91); ^{1}H NMR δ 1.23 (s, 3 H), 1.33 (s, 3 H), 1.36 (s, 3 H), 1.56–2.10 (m, 4 H), 2.45 (s, 3 H), 3.70 (broad s, 2 H), 4.06 (t, J = 5.7 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H). The IR spectral data are identical with those reported previously.[7] This compound was employed in the next step without further purification.

(*S*)-4-(3-Bromopropyl)-2,2,4-trimethyl-1,3-dioxolane (10). To a solution of **9b** (1.57 g, 4.78 mmol) in acetone (30 mL) was added LiBr (622 mg, 7.17 mmol) and $NaHCO_3$ (643 mg, 7.65 mmol). The mixture was stirred for 3.5 h under reflux. After cooling, the mixture was concentrated in vacuo. The residue was diluted with saturated $NaHCO_3$ solution and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ solution and brine, dried (K_2CO_3), and concentrated in vacuo. The residue was distilled in the presence of K_2CO_3 to give **10** (1.06 g, 94%): bp 100–110 °C (2.0 mm, bulb-to-bulb distillation); ^{1}H NMR[23] δ 1.29 (s, 3 H), 1.39 (s, 6 H), 1.60–2.08 (m, 4 H), 3.44 (t, J = 6.2 Hz, 2 H), 3.70 (d, J = 7.0 Hz, 1 H), 3.80 (d, J = 7.0 Hz, 1 H); IR (film) 1250, 1215 cm^{-1}; MS m/e (rel intensity) 223 [100, (M^+ + 1) − CH_4], 221 [97, (M^+ + 1) − CH_4], 72 (50), 43 (69).

(*S*)-5-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)pentan-2-one (11). A solution of **10** (500 mg, 2.1 mmol) in THF (1.5 mL) was added to Mg (179 mg, 7.4 mmol) in THF (2 mL) under Ar. To this was added a small piece of solid I_2, and the mixture was stirred under ultrasonic vibration for 30 min. After the mixture was cooled to 0 °C, a solution of acetaldehyde (1.0 g, 22.7 mmol) in THF (1.5 mL) was added. After being stirred for 1.5 h at room temperature, the mixture was quenched by the addition of NH_4Cl solution and filtered. The filtrate was extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent hexane/ethyl acetate, 7/1–3/1) to give a crude acetonide alcohol as an oil.

To a suspension of PCC (1.12 g, 5.2 mmol) and powdered molecular sieves 3A (2.5 g) in dichloromethane (10 mL) was added dropwise a solution of the crude acetonide alcohol obtained above in dichloromethane (5 mL) stirring in an ice–water bath. The mixture was stirred for 2 h at room temperature. Florisil (5 g) and ether (50 mL) were added to the mixture, which was filtered through a pad of Celite and Florisil, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent hexane/ethyl acetate, 10/1) to give **11** (277 mg, 66% from **10**) as an oil: ^{1}H NMR[23] δ 1.27 (s, 3 H), 1.37 (s, 6 H), 1.56–2.00 (m, 4 H), 2.12 (s, 3 H), 2.30–2.60 (m, 2 H), 3.75 (seemingly d, 2 H); IR (film) 1720, 1245, 1210, 1115, 1060, 980, 910, 860 cm^{-1}; MS m/e (rel intensity) 185 [68, (M^+ + 1) − CH_4], 125 (64), 115 (53), 107 (17), 72 (46), 43 (100).

(−)-Frontalin (3). According to the reported procedure,[11] ketone **11** (375 mg, 1.87 mmol) was converted into **3** (219 mg, 82%). In the present case, the solvent for the reaction was changed from *n*-pentane to ether: bp 95–100 °C (100 mmHg, bulb-to-bulb distillation) $[\alpha]^{22}_D$ −52.8° (c 1.64, ether) [lit.[25] $[\alpha]^{23}_D$ −54.4° (c 1.33, ether)]; ^{1}H NMR δ 1.33 (s, 3 H), 1.44 (s, 3 H), 1.50–1.67 (m, 2 H), 1.86–2.03 (m, 2 H), 3.46 (dd, J = 2.0, 6.8 Hz, 2 H), 3.92 (d, J = 6.8 Hz, 2 H); IR (film) 2980, 2940, 2880, 1740, 1650, 1450, 1390, 1380, 1260, 1240, 1200, 1170, 1120, 1060, 1020, 930, 890, 845, 820 cm^{-1}; IR and NMR spectra were identical with those reported previously.[11] MS m/e (rel intensity) 143 (19, M^+ + 1), 142 (18, M^+), 112 (14), 100 (44), 85 (8), 72 (69), 71 (23), 43 (100); high-resolution mass spectra, calcd for $C_8H_{14}O_2$ m/e 142.0992, found (M) 142.0966. Anal. Calcd for $C_8H_{14}O_2$: C, 64.40; H, 8.93. Found: C, 64.32; H, 8.93. ^{1}H NMR [1 equiv of Eu(hfc)$_3$, C_6D_6]: δ 2.77,

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[single signal, C(1)-CH_3] and no signal due to the other enantiomer could be detected; corresponding racemate[11] 2.70 [C(1)-CH_3, 1.5 H], 2.77 [C(1)-CH_3, 1.5 H]. Thus, the product was concluded to be enantiomerically pure within the sensitivity limits of 400-MHz NMR spectroscopy.

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Supplementary Material Available: ^1H NMR spectra for compounds **4e**, **7c**, **8**, **10**, and **11** (5 pages). Ordering information is given on any current masthead page.

Lanthanide-Induced Shift Investigation of α-Alkoxy Aldehydes. A Spectroscopic Search for Evidence of Chelation in the Lewis Acid Catalyzed Hetero Diels–Alder Reaction

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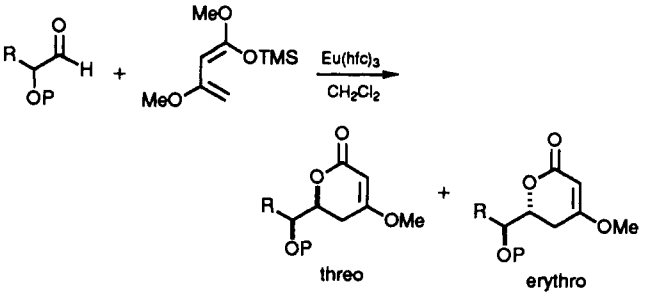
Lanthanide-induced shift studies were performed using a chiral lanthanide shift reagent Eu(hfc)$_3$. Simple ethers exhibited little complexation to the shift reagent. Simple aldehydes produced large lanthanide-induced shifts. The α-alkoxy aldehydes gave lanthanide-induced shifts consistent with contributions from a "chelated" species. The degree of chelation was dependent on the steric bulk of the alkyl side chain.

Lanthanide shift reagents (LSRs) have found extensive use in organic chemistry. Since the first reported use of lanthanide shift reagents,[1] the most common application has been in the area of structure determination through nuclear magnetic resonance spectroscopy.[2] Less common is the use of LSRs as a reagent in synthetic applications. Results from ours[3] and other laboratories[4] have demonstrated that LSRs will promote cycloaddition reactions of carbonyl compounds with activated dienes.

We have found that the chiral LSR tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Eu(hfc)$_3$) catalyzes the cycloadditions of α-alkoxy aldehydes with 1,3-dimethoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene (Brassard's diene[5]). The degree of diastereoselectivity observed in the lactone products is dependent on the alkyl side chain and the protecting group of the alkoxy group (Table I).[6,7] Initially, the observed selectivity was rationalized by a "chelation-control" model of addition.[8] When this presumed chelation is diminished by the use of a bulky protecting group (TBDMS), there is little selectivity observed in the product.[9]

Table I. Selectivity of Cycloaddition Reactions Catalyzed by Eu(hfc)$_3$



aldehyde	% yield	threo:erythro
1a	80	92:8
1b	75	78:22
1c	85	50:50

Table II. Slopes[a] of the Observed LIS vs LSR/Substrate for Simple Aldehydes

aldehyde	Ha	Hb
3a	4.5	3.2
3b	2.5	2.1
3c	1.8	1.4

[a] Values are derived from the best fit (linear regression) line for a set of data; units are in ppm·mol % LSR^{-1}.

Of interest, however, was the fact that when protecting groups such as benzyl were used, the selectivity of cycloaddition was dependent on the size of the alkyl side chain. As the steric bulk of the side chain was increased from *n*-butyl to *tert*-butyl, the degree of diastereoselectivity decreased. This result was opposite of that predicted by a simple chelation-control model. In the chelation-control mode, an increase in size of the alkyl group should increase the facial selectivity by directing the diene to the least hindered face of the chelated complex. In an effort to better understand the mechanism of cycloaddition, we

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