of the neutral solution with methylene chloride yielded small amounts of dark purple oils whose ^1H NMR spectra indicated extensive decomposition.

Methanol Adduct 1. 4(5)-Nitroso-5(4)-phenylimidazole (100 mg) dissolved in 50 mL of anhydrous methanol was allowed to stand for 1 week. Removal of the solvent by rotary evaporator and overnight drying in a vacuum desiccator over P_2O_5 left a tan solid, mp 80–100 °C dec. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.47. Found: C, 56.60; H, 5.66; N, 20.21.

Isolation of Products from Aqueous Decomposition. 4-(5)-Nitroso-5(4)-phenylimidazole (500 mg) was vigorously stirred in 250 mL of 0.01 M HCl for 1 h, followed by removal of the solvent by lyophilization. A portion of this was subjected to HPLC separation using a Waters C-13 μBondapak reversed-phase preparative column with detection at 254 nm and 40% acetonitrile/60% water as eluting solvent. Solvents were removed from separated samples by rotary evaporation and lyophilization.

Acidity Constant. A solution of 4(5)-nitroso-5(4)-phenylimidazole (200 μM) in 0.002 M NaOH was mixed with an exactly equal volume of various buffers and the absorbance at 364 nm recorded. In the case of solutions with pH <6, extrapolation to zero time was necessary because of the decomposition. The acidity constant K_a was calculated as the average of values of $(A_{acid} - A)[H^+]/(A - A_{base})$ where A_{acid} and A_{base} are absorbances at pH 4 and 11, respectively, and A is the absorbance in the intermediate range pH 6–8.

Kinetics. To 2.5 mL of an equilibrated aqueous solution at 25 °C was added 25 μL of an 0.02 M Me_2SO solution of 4(5)-nitroso-5(4)-phenylimidazole. The absorbance decrease at 365 nm was monitored. Rate constants were calculated by linear regression as the slopes of plots of ln $(A - A_\infty)$ vs. time.

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Regio- and Enantioselective Reduction of α,2-Dioxocycloalkaneacetates with Fermenting Bakers' Yeast. A New Synthesis of (*R*)-(−)-Hexahydromandelic Acid

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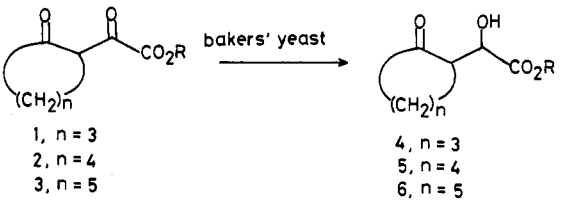
Recently, the use of actively fermenting bakers' yeast for the preparation of optically active building blocks in the synthesis of natural products has increased.[1] It is well-known that the reduction of β-keto esters by actively fermenting bakers' yeast (*Saccharomyces cerevisiae*) affords optically active β-hydroxy esters.[2-5] Although the asymmetric reductions of α-keto esters with fermenting bakers' yeast were reported,[6-8] no attempt has been made for those of α,2-dioxocycloalkaneacetic acid esters **1–3**. This prompted us to investigate the reduction of **1–3** with fermenting bakers' yeast,[9] which would be expected to give optically active α-hydroxy-2-oxocycloalkaneacetic acid esters **4–6**.



α,2-Dioxocycloalkaneacetates **1–3** are readily available from the reaction of the cycloalkanones and oxalic esters in the presence of base.[10] Treatment of **1–3** with fermenting bakers' yeast at 32 °C gave optically active α-hydroxy esters **4–6** as diastereomeric mixtures in fair yield. The chemical yields, the ratios of threo and erythro isomers, and the optical yields are tabulated in Table I.

The reaction proceeded regiospecifically to give only α-hydroxy ester, and even a trace amount of 2-hydroxy-α-oxo ester could not be detected. Diastereomers were separated by either preparative HPLC, GLC, or column chromatography. Determination of the optical purity was established by conversion of each isomer to the corresponding *N*-(3,5-dinitrophenyl)carbamate and then analysis by HPLC using an optically active column and/or by ^1H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$.

Reduction of ethyl α,2-dioxocyclopentaneacetate (**1**) yielded optically active ethyl α-hydroxy-2-oxocyclopentaneacetate (**4**) in 74% yield as a diastereomeric mixture of threo (α*R*,1*S*) and erythro (α*R*,1*R*) isomers (2/3). Reduction of ethyl α,2-dioxocyclohexaneacetates (**2b**) showed better diastereoselectivity (threo/erythro = 9/1) than that in the case of methyl ester **2a**. To get the best reaction conditions, the relative amount of bakers' yeast to the substrate **2b** was varied, and the results are tabulated in Table II.

The chemical yield and threo selectivity increased as the ratio of the amount of yeast to **2b** decreased. Although immobilized bakers' yeast improved enantiomeric excess in the reduction of some α-keto esters,[11a] we found no notable improvement in chemical yield and diastereoselectivity using immobilized yeast. Reduction of ethyl α,2-dioxocycloheptaneacetate (**3**) with bakers' yeast gave the reduced product **6** in low diastereo- and enantioselectivity.

The stereochemistry of the reduced products was determined by analyzing the NMR spectra with reference to the literature.[12] In ^1H NMR spectra, the α-proton of a threo isomer generally appeared at higher field than that of the erythro one. In the ^{13}C NMR spectrum of ethyl

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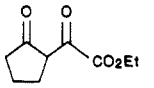
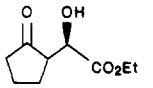
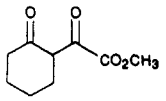
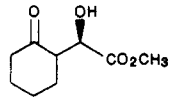
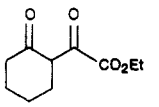
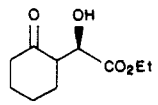
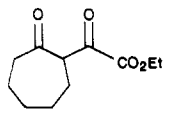
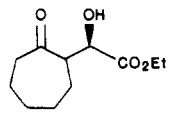
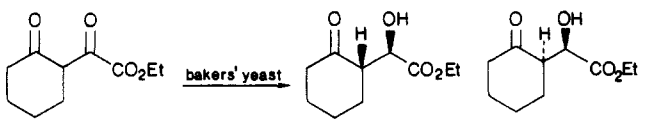
0022-3263/87/1952-1359$01.50/0

Table I. Asymmetric Reduction of α,2-Dioxocycloalkaneacetic Acid Esters 1–3 with Fermenting Bakers' Yeast

ketone	product	yield,[a] %	(αR,1S)/(αR,1R) (threo/erythro)	ee (αR,1S)	ee (αR,1R)
 1	 4	74	2/3	76	88
 2a	 5a	51	3/1	>95	>95
 2b	 5b	57	9/1	99	99
 3	 6	34	3/2	12	60

[a] Isolated yield.

Table II. Reduction of 2b with Bakers' Yeast



2b (αR,1S)-5b (αR,1R)-5b

yeast/2b, g/g	time, h	yield, %	5b[a] (αR,1S)/(αR,1R)
5.5	40	29	82/18
2.5	45	50	89/11
1.2	50	57	90/10
4[b]	30	36	89/11

[a] Both isomers were optically pure by ^{1}H NMR analysis [Eu(hfc)$_3$]. [b] Immobilized bakers' yeast in carrageenan was used. See ref 11b.

α-hydroxy-2-oxocyclohexaneacetate (**5b**), the signal (27.0 ppm) due to C-6 of an erythro isomer appeared at higher field than that (30.1 ppm) of the threo because of the steric hindrance between a C-6 methylene and an ester group. For that reason, it is presumably suggested that the free rotation of the C_α–C_1 bond is restricted by an intramolecular hydrogen bond.[13]

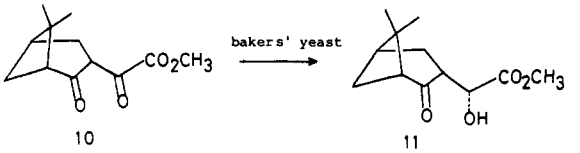
The absolute configuration of the α-carbon of **5** was definitely determined by conversion to (*R*)-(−)-hexahydromandelic acid (**8**). Treatment of ethyl α-hydroxy-

5b 7, R = Et 8, R = H

2-oxocyclohexaneacetate (**5b**) with Zn–HCl at 0 °C gave optically active ethyl (*R*)-α-hydroxycyclohexaneacetate (**7**) in 78% yield, which was hydrolyzed with 1 M KOH to afford **8** in 59% yield. The optical purity was estimated to be 99% ee by comparison of the optical rotation with that of an authentic sample.[14] Usually enantioselective reductions of α-oxo esters with fermenting bakers' yeast afford (*R*)-α-hydroxy esters.[7,8] Therefore, the absolute configuration of the α-carbon of other products (**4**, **5a**, **6**) can be presumed to be *R*.

The use of optically active hexahydromandelic acid has become increasingly important in organic syntheses. For example, Masamune et al. have utilized **8** for the total synthesis of macrolides.[15] Compound **8** has been so far prepared by the hydrogenation of optically active mandelic acid in the presence of rhodium catalyst.[16] Therefore, the present process offers a practical and economical method for the preparation of **8**.

Application of the present reduction to ethyl α,2-dioxocyclooctaneacetate (**9**) resulted in the recovery of the starting material. However, methyl (1*R*,5*R*)-α-(6,6-dimethyl-2-oxobicyclo[3.1.1]hept-3-yl)-α-oxoacetate (**10**) gave optically active α-hydroxy acetate **11** as a diastereomeric mixture of (αR,1S) and (αR,1R) isomers (7/2) in 32% yield.[17]



10 11

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(17) Reduction of **10** with bakers' yeast (32 °C, 7.5 days) gave **11** in 32% yield. (αR,1S)-**11**: ^{1}H NMR (CCl_4) δ 0.85–2.80 (m, 13 H), 3.78 (s, 3 H), 4.73 (d, *J* = 2.5 Hz, 1 H). (αR,1R)-**11**: ^{1}H NMR (CCl_4) δ 0.85–2.80 (m, 13 H), 3.78 (s, 3 H), 4.88 (d, *J* = 2.0 Hz, 1 H). Compound **11** may be useful for the synthesis of thromboxane A_2 antagonist: Wilson, N. H.; Peesapati, V.; Johns, R. L.; Hamilton, K. *J. Med. Chem.* **1982**, *25*, 495.

The enol might play a role in either enhancing or diminishing the potential for substrates to be reduced by yeast.[18] Proton NMR analysis showed that more than 95% of keto esters 1–3 exists as an enol form in a mixture with water. On the other hand, in yeast reduction solution, which contains inorganic materials and glucose, more than 95% of keto esters 1 and 3 is enolyzed but compound 2 is enolyzed only 65%. This fact may be related to the high enantioselectivity of 5 because the carbonyl group will be reduced by the hydride anion of enzymes of yeast although the accurate mechanism cannot be predicted.[19]

In conclusion, reduction of α,2-dioxocycloalkaneacetates with fermenting bakers' yeast afforded chiral α-hydroxy-2-oxocycloalkaneacetates exclusively, which were useful for the synthesis of natural products[20] because the reaction conditions are mild and the procedures are simple and economically feasible.

Experimental Section

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Eiichiro Amano in our laboratory. Analytical spectra were obtained with the following instruments: IR, Jasco Model A-102; ^{1}H NMR (60 MHz), JEOL JNM-PMX60SI apparatus; ^{1}H NMR (100 MHz) and ^{13}C NMR (25 MHz), JEOL JNM-FX100 apparatus. Optical rotations were measured on a Jasco DIP-4 spectrometer. HPLC analysis was performed with a Yanagimoto liquid chromatograph L-2000 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 the determination of enantioselectivity.

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

Ethyl α,2-dioxocyclopentaneacetate (1) was prepared from cyclopentanone and ethyl oxalate in the presence of sodium ethoxide in 82% yield by adaptation of the method described in the literature;[10] bp 129–30 °C (7 mm).

Methyl α,2-dioxocyclohexaneacetate (**2a**) and ethyl α,2-dioxocyclohexaneacetate (**2b**) were prepared by the method described in the literature.[10]

Ethyl α,2-dioxocycloheptaneacetate (3) was prepared from cycloheptanone and ethyl oxalate in the presence of sodium ethoxide by the method described in the literature: 37% yield; IR (neat) 1740 (ester C=O), 1700 (C=O), 1620 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.32 (t, J = 6 Hz, 3 H), 1.70 (br s, 8 H), 2.20–2.75 (m, 3 H), 4.24 (q, J = 6 Hz, 2 H), 3.9–4.4 (m, 0.2 H), 15.50 (s, 0.8 H). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.06; H, 7.65.

Reduction of ketones with bakers' yeast is shown below representatively.

Ethyl α-Hydroxy-2-oxocyclopentaneacetate (4).[21] To a mixture of KH_2PO_4 (2 g), $NH_4H_2PO_4$ (2 g), $MgSO_4$ (1 g), $CaCO_3$ (5 g), glucose (150 g), and boiled water (1 L) was added 20 g of bakers' yeast (Oriental Yeast Co.) at 32 °C. After bubbles formed (ca. 20 min), 10 g (0.0543 mol) of 1 was added and then the mixture was allowed to stand at 32 °C for 4 days. The organic layer was extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated to give 7.4 g (74%) of 4:[21] $[\alpha]^{13}_D$ +67.9° (c 4.77, $CHCl_3$);[22] IR (neat) 3500 (OH), 2980, 1735 (C=O), 1260, 1220, 1140, 1020 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.29 (t, J = 6.5 Hz, 3 H, CH_3), 1.62–2.8 (m, 6 H, 3 CH_2), 3.16 (d, J, = 4.5 Hz, 1 H, OH), 4.0–4.42 (m, 3 H, $CO_2CH_2CH_3$ and COC*H*), 4.50 (dd, J = 2 and 4.5 Hz, 1 H, C*H*OH). HPLC analysis [SA-I; hexane/ethanol/ethyl acetate (20/1/1), 1.5 mL/min] showed two peaks at 10.3 and 10.7 min with the intensity ratio of 55/45 due to erythro (α*R*,1*R*) and threo (α*R*,1*S*) isomers. Both peaks, which could not be separated, were collected by preparative HPLC: $[\alpha]^{29}_D$ +50.7° (c 11.8, $CHCl_3$). Analytical GLC [column, 10% silicone SE-30 on Chromosorb W (3-mm o.d. × 1-m length); 150 °C; carrier gas, N_2 (0.5 kg/cm^2)] showed two peaks at R_t 3.75 and 4.30 min with the intensity ratio of 2/3 due to threo and erythro isomers. Two fractions were collected by preparative GLC (column, 10% Apiezone Grease L on Chromosorb W (3-mm o.d. × 1-m length); 150 °C; carrier gas, He, 30 mL/min). First fraction: (α*R*,1*S*)/(α*R*,1*R*) = 60:40; $[\alpha]^{31}_D$ +6.2° (c 4.0, $CHCl_3$). Last fraction: (α*R*,1*S*)/(α*R*,1*R*) = 33:67; $[\alpha]^{32}_D$ +44.1° (c 2.0, $CHCl_3$). ^{13}C NMR data were assigned tentatively. (α*R*,1*S*)-4: ^{13}C NMR ($CDCl_3$) δ 14.0 (q, CH_3), 20.7 (t, C-4), 25.8 (t, C-5), 38.5 (t, C-3), 51.9 (d, C-1), 62.0 (t, CH_2CH_3), 69.6 (d, C-α), 174.0 (s, CO_2), 217.7 (s, C=O). (α*R*,1*R*)-4: ^{13}C NMR ($CDCl_3$) δ 14.1 (q, CH_3), 20.5 (t, C-4), 22.3 (t, C-5), 38.3 (t, C-3), 51.5 (d, C-1), 62.0 (t, CH_2CH_3), 68.8 (d, C-α), 174.0 (s, CO_2), 217.7 (s, C=O).

Determination of Enantiomeric Excess of 4. To a mixture of 4 (15 mg, 0.09 mmol), dry toluene (1 mL), and 3,5-dinitrophenyl isocyanate (30 mg, 0.16 mmol) was added 0.5 mL of dry pyridine. The mixture was heated at 60–70 °C for] h and cooled. The precipitate was filtered off and washed with ether. Concentration of the filtrate gave 18 mg of crude ethyl α-[[(3,5-dinitrophenyl)carbamoyl]oxy]-2-oxocyclopentaneacetate, which was analyzed with HPLC [Sumipax OA-3000; hexane/ethyl acetate/ethanol (20/1/1); 0.8 mL/min]. Peaks, retention times (min), and percentages of the integrated peak area except the peak of 3,5-dinitrophenyl isocyanate were as follows: 1, 7.2, 47%; 2, 7.8, 3%; 3, 8.2, 44%; 4, 8.6, 6%. Peaks 1 and 2: (α*R*,1*R*)-4; 88% ee. Peaks 3 and 4: (α*R*,1*S*)-4; 76% ee.

Methyl (α*R*)-α-Hydroxy-2-oxocyclohexaneacetate (5a).[21] In the same manner as shown for 4, compound **2a** (0.459 g, 2.3 mmol) was treated with bakers' yeast (4.3 g) at 32 °C for 43 h, and 0.374 g of crude **5a** was obtained. HPLC analysis [SA-I; hexane/ethyl acetate/ethanol (20/1/1)] showed four peaks. Peaks, retention times (min), and percentages of the integrated peak area are as follows: 1, 5.8, 33%; 2, 11.9, 45%; 3, 13.8, 14%; 4, 24.6; 8%. Each component was separated by preparative HPLC. Peak 2: (α*R*,1*S*)-**5a**; 39% yield; $[\alpha]^{32.5}_D$ −50.6° (c 3.88, $CHCl_3$); 95% ee, determined by ^{1}H NMR in the presence of 85% Eu(hfc)$_3$, a single peak at δ 18.4 (C*H*OH); IR (neat) 3520 (OH), 1740 (ester C=O), 1710 (C=O) cm^{-1}; ^{1}H NMR (CCl_4) δ 1.4–3.4 (m, 10 H, OH, >CHCO), 3.70 (s, 3 H, CH_3), 3.39 (d, 1 H, C*H*OH). Peak 3: (α*R*,1*R*)-**5a**; 12% yield; $[\alpha]^{34}_D$ −34.2° (c 0.59, $CHCl_3$); 95% ee, determined by ^{1}H NMR in the presence of 64% Eu(hfc)$_3$, a single peak at δ 16.3 (C*H*OH); IR (neat) 3500 (OH), 1740 (ester C=O), 1710 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.5–3.2 (m, 10 H, 4 CH_2, OH, COCH<), 3.72 (s, 3 H, CH_3), 4.43 (d, J = 3.2 Hz, C*H*OH).

Ethyl (α*R*)-α-Hydroxy-2-oxocyclohexaneacetate (5b).[21] Compound **2b** (4.9 g, 24.7 mmol) was treated with 6 g of bakers' yeast in 500 mL of boiled water that contained glucose (75 g), KH_2PO_4 (1 g), $NH_4H_2PO_4$ (1 g), $MgSO_4$ (0.5 g), and $CaCO_3$ (2.5 g). Experimental details and spectral data were described in the previous paper.[9]

Determination of Optical Purity of 5b. The ^{1}H NMR spectrum of (α*R*,1*R*)-**5b**, which was obtained by preparative HPLC, in the presence of Eu(hfc)$_3$ showed no trace of paired signals, indicating that it is optically pure. Treatment of (α*R*,1*S*)-**5b** with 3,5-dinitrophenyl isocyanate by the same procedure as described for 4 gave (α*R*,1*S*)-α-[[(3,5-dinitrophenyl)carbamoyl]oxy]-2-oxocyclohexaneacetate: HPLC analysis [Sumipax OA-3000; hexane/ethyl acetate/ethanol (20/1/1); 1.0 mL/min], single peak at R_t 5.3 min; IR (neat) 3000 (NH), 2960,

(18) Indicated by a reviewer.

(19) The reviewer pointed out that it is not certain that the reverse reaction, i.e. oxidation of the alcohols by oxidoreductase, would occur; therefore, we checked this point by the treatment of chiral alcohol 4 with fermenting bakers' yeast as follows: Compound 4 [2.1 g, 11.3 mmol; $[\alpha]^{25}_D$ +67.8° (c 1.25, $CHCl_3$)] was treated with 10 g of bakers' yeast in 250 mL of boiled water for 47 h as described in the preparation of 4, and the purification of the crude product (1.83 g) with column chromatography gave 1.59 g (75.7%) of 4: $[\alpha]^{25}_D$ +63.9° (c, 2.00, $CHCl_3$). Therefore, this fact shows that the reverse reaction described above did not occur.

(20) For example, oxidation of 4 with *m*-chloroperbenzoic acid ($CHCl_3$, 61 °C, 30 h) gave the optically active δ-lactone (ethyl α-hydroxy-α-(5-pentanolid-5-yl)acetate (**13**): $[\alpha]^{34}_D$ −1.27° (c 3.14, $CHCl_3$); IR (neat) 3500, 1740 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.30 (t, J = 6 Hz, 3 H), 1.5–2.7 (m, 6 H), 3.4 (br s, 1 H), 4.0–4.8 (m, 4 H). Lactone **13** may be useful for asymmetric synthesis of the insect pheromone *erythro*-6-acetoxy-5-hexadecanolide: Laurence, B. R.; Pickett, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 59.

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(22) After 5 months, it became $[\alpha]^{17}_D$ +50.7° (c 11.8, $CHCl_3$).

1730 (ester C=O), 1603 (phenyl), 1540 (NHCO), 1350, 1205, 730 cm^{-1}.

Ethyl α-Hydroxy-2-oxocycloheptaneacetate (6). Compound **3** (2.09 g, 9.77 mmol) was treated with bakers' yeast (20 g) at 32 °C for 70 h. Flash column chromatography of the crude products afforded 1.75 g of crude **6**. Purification by preparative HPLC [SA-I; hexane/ethyl acetate/ethanol (20/1/1)] gave two components. The first fraction gave 0.430 g (20.6%) of (αR,1S)-**6**: R_t 8.8 min; $[\alpha]^{26}_D$ -58.20° (*c* 1.62, $CHCl_3$); IR (neat) 3400 (OH), 1740 (ester C=O), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, *J* = 6 Hz, 3 H, CH_3), 1.2-2.2 (m, 8 H, 4 CH_2), 2.3-3.2 (m, 4 H, CH_2COCH, OH), 4.00 (d, *J* = 3.5 Hz, 1 H, CHOH), 4.20 (q, *J* = 6 Hz, 2 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 24.0 (t), 28.1 (t), 29.2 (t), 29.9 (t), 44.1 (t), 55.1 (d), 61.7 (t), 73.6 (d), 173.5 (s), 214.9 (s). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.69; H, 8.33.

The second fraction gave 0.287 g (13.7%) of (αR,1R)-**6**: R_t 9.4 min; $[\alpha]^{26}_D$ +48.61° (*c* 1.44, $CHCl_3$); IR (neat) 3400 (OH), 1740 (ester C=O), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, *J* = 6 Hz, 3 H, CH_3), 1.2-2.2 (m, 8 H, 4 CH_2), 2.3-3.2 (m, 4 H, CH_2COCH, OH), 4.20 (q, *J* = 6 Hz, 2 H, $CO_2CH_2CH_3$), 4.36 (d, *J* = 3 Hz, 1 H, CHOH); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 24.2 (t), 25.7 (t), 29.1 (t), 29.9 (t), 43.9 (t), 55.3 (d), 61.8 (t), 72.1 (d), 173.6 (s), 214.5 (s). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66, H, 8.47. Found: C, 61.68; H, 8.41.

Determination of Enantiomeric Excess of 6. (a) In the same manner as shown in **4**, (αR,1S)-**6** (34 mg, 0.159 mmol) was treated with 3,5-dinitrophenyl isocyanate (40 mg, 0.19 mmol) to give 58 mg (85.6%) of ethyl (αR,1S)-α-[[(3,5-dinitrophenyl)carbamoyl]oxy]-2-oxocycloheptaneacetate: ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 6 Hz, 3 H, CH_3), 1.3-2.2 (m, 8 H, 4 CH_2), 2.3-3.2 (m, 4 H, CH_2COCH, NH), 4.20 (apparent s, 1 H, CHOCONH), 4.25 (q, *J* = 6 Hz, 2 H, $CO_2CH_2CH_3$), 7.7-8.8 (m, 3 H, $C_6H_3(NO_2)_2$). HPLC analysis [Sumipax OA-3000; hexane/ethyl acetate (20/1/1), 1.0 mL/min] showed two peaks at 4.0 and 4.3 min (intensity ratio 56/44), 12% ee.

(b) In the same manner, (αR,1R)-**6** (25 mg, 0.12 mmol) gave 43 mg (87%) of ethyl (αR,1R)-α-[[(3,5-dinitrophenyl)carbamoyl]oxy]-2-oxocycloheptaneacetate: ^1H NMR ($CDCl_3$) δ 1.25 (t, *J* = 6 Hz, 3 H, CH_3), 1.3-2.2 (m, 8 H, 4 CH_2), 2.3-3.2 (m, 4 H, CH_2COCH, NH), 4.25 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 4.56 (d, *J* = 3 Hz, 1 H, CHOCONH), 7.7-8.8 (m, 3 H, $C_6H_3(NO_2)_2$). HPLC analysis [Sumipax OA-3000; hexane/ethyl acetate (20/1/1); 0.7 mL/min] showed two peaks at 5.6 and 6.2 min (intensity ratio 80/20); 60% ee.

Ethyl (*R*)-(-)-Hexahydromandelate (7). Dry hydrogen chloride was introduced into 13 mL of ether at -15 °C. After addition of **5b** (0.12 g, 0.6 mmol), 0.78 g (0.012 mol) of zinc powder was added with several portions. The mixture was stirred for 2 h at -5 °C and then poured into ice-water and extracted with ether. The extract was washed with dilute sodium hydrogen carbonate and water and dried ($MgSO_4$). Removal of the solvent gave 88 mg (78%) of **7**: $[\alpha]^{30.5}_D$ -6.92° (*c* 39.6, $CHCl_3$); IR (neat) 3500 (OH), 1740 (C=O), 1450, 1260, 1120 cm^{-1}; ^1H NMR (CCl_4) δ 1.35 (t, *J* = 6 Hz, 3 H, CH_3), 1.5-2.2 (m, 11 H, cyclohexyl) 4.25 (q, *J* = 6 Hz, 2 H, $CO_2CH_2CH_3$). This was used for the next step without further purification.

(*R*)-(-)-Hexahydromandelic Acid (8). A mixture of 1.1 g (6.0 mmol) of **7**, 0.5 g (8.91 mmol) of KOH, and 9 mL of water was stirred at room temperature. After 8 h, the mixture was acidified with 10% HCl and extracted with ether. The ether layer was washed with water and dried ($MgSO_4$). The solvent was evaporated to give 0.569 g (59%) of **8**: mp 127-129 °C (from benzene) (lit.[16a] mp 129 °C); $[\alpha]^{33}_D$ -12.0° (*c* 2.0, EtOH) [lit.[14] $[\alpha]^{25}_D$ +12.0° (*c* 2.0, EtOH)], $[\alpha]^{22}_D$ -25.3° (*c* 1.0, HOAc) [lit.[16a] $[\alpha]^{20}_D$ -25.5° (*c* 1.0, HOAc)].

Methyl (1*R*,5*R*)-α-[6,6-Dimethylbicyclo[3.1.1]hept-3-yl]-2,α-dioxoacetate (10). In a same manner as shown in **3**, a solution of 3.31 g (0.024 mol) of nopinone[23] and 2.83 g (0.024 mol) of dimethyl oxalate in 20 mL of THF was treated with 1.30 g (0.024 mol) of sodium methoxide. The crude product was chromatographed on silica gel (hexane/ethyl acetate, 10/1) to give 3.59 g (81.4%) of **10**: IR (neat) 1730 (ester C=O), 1700 (C=O), 1630, 1585 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (s, 3 H), 1.35 (s, 3 H), 1.5-2.7 (m, 4 H), 2.85 (d, *J* = 2.5 Hz, 2 H), 3.80 (s, 3 H), 14.1 (br s, 1 H). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.08; H, 7.29.

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Trifluoroacetylation of Amines and Amino Acids by Polymer-Bound Trifluoroacetylation Reagents

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Trifluoroacetylation of amino acids[1-6] and amines[7] with trifluoroacetic anhydride, *S*-ethyl trifluorothioacetate,[8] or alkyl trifluoroacetates[9-11] is a useful method for the reversible protection of the amino group, but all of these methods have certain limitations and drawbacks. Our interests in solid-phase syntheses[12,13] and protection of amino groups[7] have led us to develop an exceedingly attractive and simple method for N-trifluoroacetylation using polymer-bound *S*-benzyl trifluorothioacetate (**2a**) or polymer-bound benzyl trifluoroacetate (**2b**). Incorporation of an *S*-benzyl (instead of the *S*-ethyl group of *S*-ethyl trifluorothioacetate) on a polymer support ensures that the potentially odiferous mercaptan liberated on reaction of **2a** with amines remains attached to the insoluble support and is hence nonvolatile.

Polymer-bound benzyl thioalcohol (**1a**)[14,15] and polymer-bound benzyl alcohol (**1b**)[15,16] can be readily converted

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