Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids Using (*S*,*S*)-Cyclohexane-1,2-diol as a Chiral Auxiliary

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Diastereoselective alkylation of ethyl 2-methyl- and/or 2-ethylacetoacetates using the (*S*,*S*)-cyclohexane-1,2-diol as an acetal chiral auxiliary afforded enol ethers (**2a**−**f** and **5a**−**f**) of 92−>95% de in 31−70% yields. Removal of the cyclohexane-1,2-diol with BF_3−OEt_2 afforded *β*-keto esters (**3** and **6**) bearing a chiral quaternary carbon. The *β*-keto esters could be easily converted into optically active α-methylated and/or α-ethylated α,α-disubstituted amino acids (**12** and **13**) in 21−99% yields using Schmidt rearrangement.

Introduction

α,α-Disubstituted α-amino acids are nonproteinogenic modified amino acids, in which the hydrogen atom at the α-position of natural α-amino acids is replaced with an alkyl substituent.[1] The α-alkyl substituents in α,α-disubstituted amino acids severely restrict the conformational freedom of peptides containing such residues, and these amino acids are used as a probe to investigate the biologically active conformation,[2] to study the secondary structure of peptides,[3] and to search the origin of chirality.[4] The conformational studies of α,α-disubstituted amino acids have concentrated on achiral amino acids, such as α-aminoisobutyric acid (Aib),[3a,5] diethylglycine,[6] and cyclic α,α-disubstituted amino acids[7] because these achiral α,α-disubstituted amino acids could be easily prepared. Recently, peptides containing the chiral α,α-disubstituted amino acids were prepared, and their conformational studies revealed the relationship between the chirality of α,α-disubstituted amino acids and the sense of helicity in the peptides.[8] However, the difficulty in asymmetric synthesis of the chiral α,α-disubstituted amino acids, which bear a chiral quaternary carbon, restricts the available chiral α,α-disubstituted amino acids for the conformational study of peptides containing such residues.[1]

Here, we wish to report practical and facile syntheses of various chiral α,α-disubstituted amino acids, such as α-methylleucine (αMeLeu), α-ethylleucine (αEtLeu), and α-ethylvaline (αEtVal), using the (*S*,*S*)-cyclohexane-1,2-diol as a chiral auxiliary.[9]

Results and Discussion

Synthetic Strategy. We have previously reported the asymmetric alkylation of cyclic *β*-keto esters using the (*S*,*S*)-cycloalkane-1,2-diols as chiral acetal auxiliaries.[9,10]

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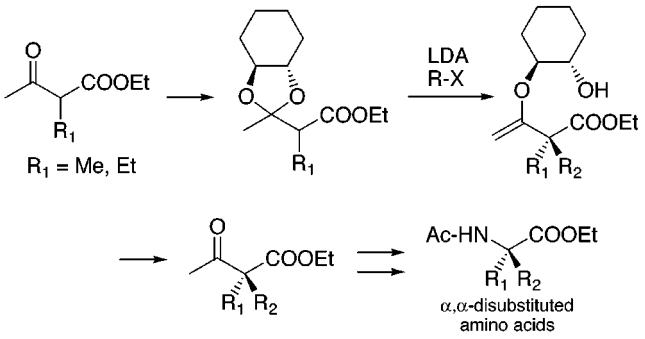

Figure 1. Synthetic strategy for chiral α,α-disubstituted amino acids.

These methods could be applied to acyclic *β*-keto esters, and therefore the chiral quaternary carbons would be efficiently constructed. It was thought that the Beckmann or Schmidt rearrangement from *β*-keto esters bearing a quaternary carbon would afford the chiral α,α-disubstituted α-amino acids. The methyl and ethyl groups were selected as the R_1-substituents because the conformations of α-methylated and α-ethylated α,α-disubstituted amino acids are very different,[8f] and practical methods for synthesis of such chiral α,α-disubstituted amino acids are desired among peptide and medicinal chemists (Figure 1).

Asymmetric Alkylation of Acyclic *β*-Keto Esters. Ethyl 2-methylacetoacetate and ethyl 2-ethylacetoacetate were converted into chiral acetals **1** and **4** in 81% and 56% yields, respectively, by treatment with (*S*,*S*)-cyclohexane-1,2-diol and *p*-toluenesulfonic acid in refluxing benzene. The acetals **1** and **4** were diastereomeric mixtures with regard to the α-methyl and α-ethyl substituents. The ^{1}H NMR spectrum of **1** showed the methine proton signals of the C(2)-position at *δ* 2.82 (q, J = 7.0 Hz) and 2.74 (q, J = 7.0 Hz) in the ratio of 1 to 1, and that of **4** showed the methine signals at *δ* 2.63 (dd, J = 4.0, 11.2 Hz) and 2.54 (dd, J = 3.6, 10.6) in the ratio of 1 to 1. The separation of diastereomers was difficult by column chromatography, but the diastereomeric mixtures could be used for asymmetric alkylation without problem.

The acetal **1** was alkylated into enol ethers **2a**−**f** by treatment with LDA (5 equiv), alkyl halide (5 equiv), and HMPA (5 equiv) in THF (Scheme 1) (Table 1). The alkylated products were obtained in moderate chemical yields (56−64%), except for **2d** and **2e**. The yields of **2d** (32%) and **2e** (42%) were somewhat low because alkyl iodides such as *i*-Pr−I and *i*-Bu−I are less reactive than primary alkyl halides. In these cases (entry 4 and 5), unalkylated product **7**, α,*β*-unsaturated enol ether, was isolated as a major byproduct.

The diastereomer excesses of **2a**−**f** could not be determined at this stage by using ^{1}H NMR spectra or HPLC analysis; therefore, the enol ethers **2** were converted into *β*-keto esters **3** by treatment with BF_3−OEt_2, and the diastereomer excess of **2** was determined as an enantiomeric excess of **3**. The enantiomeric excesses of **3a**−**f** were determined by ^{1}H NMR spectra using a chiral shift reagent (+)-Eu(hfc)$_3$.[11] In the case that the chemical shift of the methyl proton signal in the acetyl function of **3** was shifted from *δ* 2 into *δ* 4 using the shift reagent, the methyl signal equally split away in the racemic *β*-keto esters (±)-**3**, but the signals derived from the enantiomerically enriched **3** appeared in a different ratio or as only one peak. Furthermore, the *β*-keto ester **3e** was converted into (*R*,*R*)-(−)-2,3-butanediol acetal **9**, and the measurement of ^{1}H NMR spectra confirmed the enantiomeric excesses. The enantiomeric excess determined by this method was identical with that measured by the shift reagent methodology. The diastereomer excesses of all products were high (93−>95% de). The absolute configuration of products **3a** and **3f** were determined by comparison of the specific rotations with those of reported values. That is to say, the specific rotation of **3a** was

(11) Eu(hfc)$_3$: Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium(III) derivative.

Scheme 1

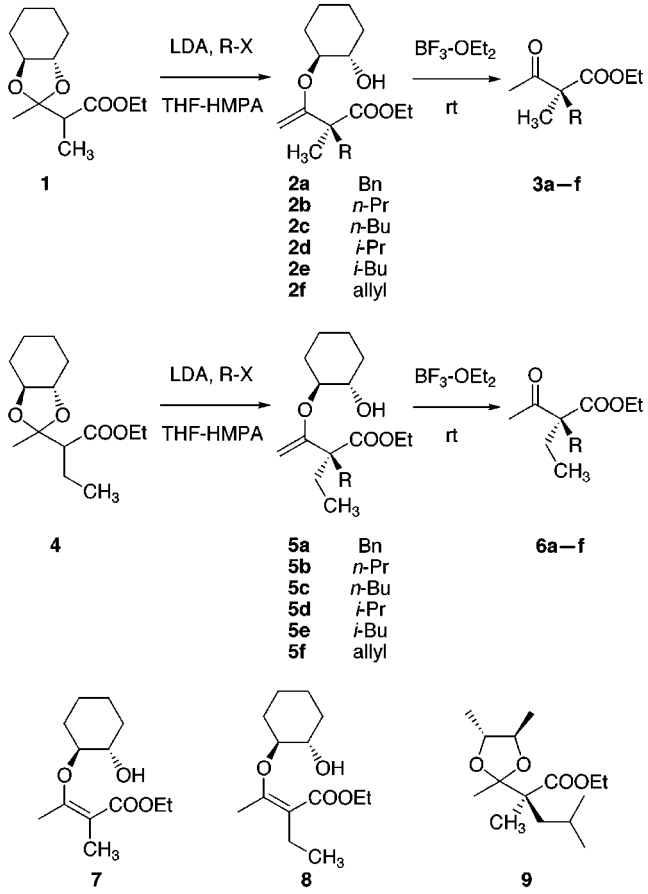

Table 1. Diastereoselective Alkylation of Acetals 1 and 4[a]

			enol ether			*β*-keto ester	
entry	R−X		yield (%)	de (%)[b]		yield (%)	$[\alpha]_D$
1	Bn-Br	**2a**	57	94	**3a**	73	−58.5[c]
2	*n*-Pr−I	**2b**	63	>95	**3b**	79	−9.0
3	*n*-Bu-I	**2c**	56	>95	**3c**	78	−6.4
4	*i*-Pr−I	**2d**	32[d]	93	**3d**	75	+26.8
5	*i*-Bu-I	**2e**	42[d]	95	**3e**	85	−3.1
6	allyl-Br	**2f**	64	>95	**3f**	82	−28.1[c]
7	Bn-Br	**5a**	69	92	**6a**	84	−34.7
8	*n*-Pr−I	**5b**	70	>95	**6b**	76	+3.2
9	*n*-Bu-I	**5c**	58	>95	**6c**	79	+6.6
10	*i*-Pr−I	**5d**	31[d]	>95	**6d**	85	−19.2
11	*i*-Bu-I	**5e**	45[d]	>95	**6e**	85	−9.3
12	allyl-Br	**5f**	66	>95	**6f**	78	−14.1

[a] The reactions were carried out at − 78 °C → − 40 °C using LDA (5 equiv), alkyl halide (5 equiv), and HMPA (5 equiv) in THF. [b] Diastereomer excesses were determined by ^{1}H NMR spectra of *β*-keto esters using (+)-Eu(hfc)$_3$. [c] Literature[12] R = Bn, $[\alpha]_D$ = − 58.2 (92% ee); R = allyl, $[\alpha]_D$ = − 27.9 (94% ee). [d] The reaction was carried out at − 78 °C → room temp.

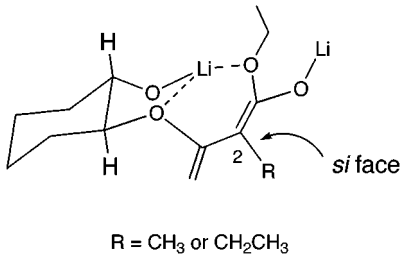

Figure 2. Plausible mechanism of diastereoselection.

−58.5, and the reported value of (*S*)-**3a** was −58.2 (92% ee).[12] Therefore, the absolute stereochemistry of **3a** was unambiguously determined to be *S*; also that of **3f** was determined to be *S*.[12] The absolute configuration of the other products was determined to be *S*, based on the assumption that the same course of stereocontrol occurred in these reactions.

The acetal **4** was also alkylated into enol ethers **5**−**f** under the same reaction conditions. The alkylated products **5** were obtained in moderate chemical yields (58−70%), except for **5d** and **5e**. In the case of **5d** and **5e**, the unalkylated product **8**, which was an α,*β*-unsaturated enol ether, was isolated as a byproduct. The diastereomer excesses of **5a**−**f** were determined after conversion into *β*-keto esters **6** by the ^{1}H NMR spectra in the presence of (+)-Eu(hfc)$_3$. The diastereomer excesses of **5** (92−>95% de) were high enough to use the *β*-keto esters for the preparation of α,α-disubstituted amino acids. The absolute configuration of (+)-**6c** was determined to be (*S*)-**6c** (vide infra) after converting to α,α-disubstituted amino acid. In the case that the (*R*,*R*)-cyclohexane-1,2-diol was used as a chiral auxiliary, the alkylation of *β*-keto ester afforded an enantiomer. For example, the alkylation of **4** bearing an (*S*,*S*)-cyclohexane-1,2-diol with *i*-Bu−I afforded (+)-**5e**, and that of **4** bearing an (*R*,*R*)-diol afforded (−)-**5e**.

The diastereoselection of the alkylation reaction could be explained by the assumption of a chelated intermediate, as shown in Figure 2.[10] In the plausible intermediate, one lithium cation chelated to two oxygens of the chiral auxiliary and to the oxygen of ethyl ester. On the basis of this model, the *re*-face of the C(2)-position might be shielded by the (*S*,*S*)-cyclohexane-1,2-diol moiety, and the electrophiles could exclusively attack the *si*-face of the enolate to afford (2*S*)-products **3** and **6**.

Synthesis of α,α-Disubstituted Amino Acids. The conversion of *β*-keto esters **3** and **6** to the α,α-disubstituted amino acids was first attempted using the Beckmann rearrangement reaction reported by Frutos et al.[13] However, in the case of α-ethylated *β*-keto ester, the yield of the Beckmann rearrangement was very poor. For example, the conversion of oxime **11** into **13a** was only 13% yield. Furthermore, even in the case of α-methylated *β*-keto ester **3a**, the reproducibility in the Beckmann rearrangement of **10** was not good (Scheme 2).

Next, we examined use of the Schmidt rearrangement reported by Georg et al.[12b] The *β*-keto esters **3** and **6** were treated with NaN_3 and methanesulfonic acid in refluxing $CHCl_3$ to afford the α,α-disubstituted amino acids **12** and **13**. The results are summarized in Table 2. The Schmidt

Scheme 2

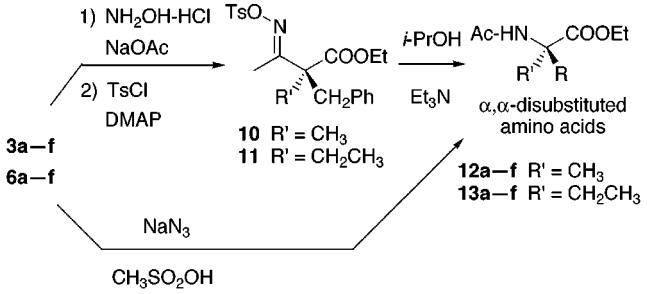

Table 2. Schmidt Rearrangement of *β*-Keto Esters 3 and 6

			α,α-disubstituted amino acid		
entry	*β*-keto ester			yield (%)	$[\alpha]_D$
1	**3a**	Bn	**12a**	95	−63.8[b]
2	**3b**	*n*-Pr	**12b**	99	−12.6
3	**3c**	*n*-Bu	**12c**	89	−14.6
4	**3d**	*i*-Pr	**12d**	50	+2.8
5	**3e**	*i*-Bu	**12e**	80	−29.1
6	**3f**	allyl	**12f**	44	−16.4
7	**6a**	Bn	**13a**	52	−107.1
8	**6b**	*n*-Pr	**13b**	48[a]	−15.6
9	**6c**	*n*-Bu	**13c**	37[a]	−16.4
10	**6d**	*i*-Pr	**13d**	21[a]	−10.5
11	**6e**	*i*-Bu	**13e**	35[a]	−21.2
12	**6f**	allyl	**13f**	−	

[a] The *β*-keto esters **6** were recovered as starting materials. See Experimental Section. [b] Literature[12] $[\alpha]_D = -47.8°$.

rearrangement of the α-methylated *β*-keto esters **3** required 5−6 h, and the α-methylated α,α-disubstituted amino acids **12** were obtained in good yields (44−99%). The reaction of the α-ethylated *β*-keto esters **6** required long reaction time (20−24 h), and the yields of the α-ethylated α,α-disubstituted amino acids **13** were moderate (21−52%). In some cases, the *β*-keto esters **6** were recovered in 45−58% yields. Taking the recovery of the substrates into account, the conversion yields of **13b**−**e** were 27−83%.

The absolute configuration of products **12** was assumed to be *R*[14] because the Schmidt rearrangement proceeded with retention of stereochemistry at the α-carbon of the carbonyl function. Moreover, the absolute configuration of α-methylated amino acid **12a** was determined to be *R* by comparison of the specific rotation with the reported value.[12b] The absolute configuration of α-ethylated amino acid **13c** was determined to be *R* by comparison of the specific rotation with the material (*S*)-butylethylglycine, which was prepared by another route.[15,16] The absolute configuration of α-ethylated leucine (+)-**13e** prepared using (*R*,*R*)-cyclohexane-1,2-diol was unambiguously determined to be *S* by X-ray crystallographic analysis of its dipeptide with (*S*)-butylethylglycine.[15,17] Judging from these results, we would say that the absolute stereochemistry of the α,α-disubstituted amino acids **12** and **13** prepared using (*S*,*S*)-cyclohexane-1,2-diol is *R*. The enantiomeric excess of **13e** was confirmed to be >95% ee by the ^{1}H NMR spectra in the presence of the chiral

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(14) Conversion of *β*-keto esters into α,α-disubstituted amino acids changes the priority of ligands at the quaternary carbon in the Cahn−Ingold−Prelog system. The stereochemistry of the quaternary carbon was retained.

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(16) Acetylation of (*S*)-(+)-butylethylglycine ethyl ester [(*S*)-Beg-OEt][14] afforded (+)-**13c**; $[\alpha]^{23}_D$ +16.8 (*c* 1.68, $CHCl_3$).

shift reagent (+)-Eu(hfc)$_3$. The ^{1}H NMR spectrum of (±)-**13e** showed the methyl proton signals of ethyl ester at δ 2.43 (t, J = 7.1 Hz) and 2.41 (t, J = 7.1 Hz) in the ratio of 1 to 1, while the corresponding signal from (−)-**13e** and (+)-**13e** showed only one peak (t, J = 7.1 Hz) in the presence of (+)-Eu(hfc)$_3$, respectively. This result means that no epimerization occurred in the Schmidt rearrangement.

Conclusion

A practical procedure for the synthesis of various chiral α,α-disubstituted amino acids has been developed using the cyclohexane-1,2-diol as a chiral auxiliary. Both the optically pure (*S*,*S*)- and (*R*,*R*)-cyclohexane-1,2-diols,[9a] which are easily prepared by the kinetic resolution of racemic diacetate using lipase, can be available on the scale of grams; therefore, these methods would provide both enantiomers of various α,α-disubstituted amino acids. The preparation of peptides containing α,α-disubstituted amino acids described here, and their conformational analysis are currently under way.[6c,d,17,18]

Experimental Section

^{1}H NMR spectra were determined at 270 MHz unless otherwise noted. Benzene was distilled from P_2O_5. THF was purchased from Kanto Chemical Co. and used without distillation. Infrared spectra were recorded on a JASCO A-100 spectrometer (KBr or neat). EIMS, FABMS, and HRMS spectra were taken on a JEOL JMS 610H or JEOL SX102 spectrometer. Elemental analyses were performed in the Analytical Center of the Graduate School of Science at Kyushu University. The other general procedures were followed as described in the previous papers.[10]

Ethyl (2*RS*)-3,3-[(1*S*,2*S*)-Cyclohexane-1,2-dioxy]-2-methylbutanoate (1).[10] A mixture of ethyl 2-methylacetoacate (450 mg, 3.1 mmol), (*S*,*S*)-cyclohexane-1,2-diol (242 mg, 2.1 mmol), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) in benzene (30 mL) was refluxed for 10 h, fixed with Dean−Stark apparatus. After being cooled to room temperature, the mixture was diluted with EtOAc, washed with 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to give **1** (407 mg, 81% based on cyclohexanediol) as a colorless oil: IR (neat) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.19−4.21 (m, 2H), 3.36−3.22 (m, 2H), 2.82 (q, J = 7.0 Hz, 0.5H), 2.74 (q, J = 7.0 Hz, 0.5H), 2.10−2.15 (m, 2H), 1.78−1.85 (m, 2H), 1.47 (s, 1.5H), 1.48 (s, 1.5H), 1.21−1.44 (m, 10H); EIMS *m*/*z* 243 (M^+ + 1, 28), 229 (34), 180 (25), 157 (45), 98 (100).

Ethyl (2*RS*)-3,3-[(1*S*,2*S*)-Cyclohexane-1,2-dioxy]-2-ethylbutanoate (4). Compound **4** was prepared from ethyl 2-ethylacetoacate in a manner similar to that described for the preparation of **1**: 56%; a colorless oil; IR (neat) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.13−4.24 (m, 2H), 3.20−3.39 (m, 2H), 2.63 (dd, J = 4.0, 11.2 Hz, 0.5H), 2.54 (dd, J = 3.6, 10.6 Hz, 0.5H), 2.09−2.17 (m, 2H), 1.63−1.98 (m, 4H), 1.47 (s, 1.5H), 1.46 (s, 1.5H), 1.30 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.6 Hz, 3H); EIMS *m*/*z* 256 (M^+, 80), 214 (27), 188 (42), 126 (38), 61 (100); HRMS calcd for $C_{14}H_{24}O_4$ (M^+) 256.1674, found 256.1671.

Ethyl (2*S*)-2-Benzyl-2-methyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (2a). *n*-BuLi (1.4 mL, 2.25 mmol, 1.5 M in hexane) was added dropwise to the stirred solution of diisopropylamine (223 mg, 2.25 mmol) in THF (8 mL) at −78 °C, the solution was warmed to 0 °C, and then stirred for 30 min at 0 °C. The solution was cooled to −78 °C, HMPA (403 mg, 2.25 mmol) was added, and then **1** (120 mg, 0.45 mmol) in THF (2 mL) was added dropwisely. The solution was stirred at −78 °C for 30 min, and then benzyl bromide (450 mg, 2.25 mmol) was added dropwise to the stirred solution. The solution was stirred at −78 °C for 3 h, −40 °C for 2 h, and diluted with saturated aqueous NH_4Cl. The whole was extracted with EtOAc and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane gave enol ether **2a** (84 mg, 51%) as a colorless oil: $[\alpha]^{22}_D$ +58.8 (*c* 1.50, $CHCl_3$); IR (neat) 3500 (br), 1730, 1660, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10−7.26 (m, 5H), 4.15−4.27 (m, 2H), 4.14 (d, J = 3.0 Hz, 1H), 3.90 (d, J = 3.0 Hz, 1H), 3.84 (m, 1H), 3.59 (m, 1H), 3.29 (s, 1H), 3.27 (d, J = 14.0 Hz, 1H), 3.00 (d, J = 14.0 Hz, 1H), 2.04−2.24 (m, 2H), 1.73−1.82 (m, 2H), 1.20−1.41 (m, 4H), 1.28 (t, J = 7.0 Hz, 3H), 1.21 (s, 3H); FAB(+) HRMS calcd for $C_{20}H_{29}O_4$ (M^+ + H) 333.2066, found 333.2065.

Ethyl (2*S*)-2-Methyl-2-propyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (2b). Compound **2b** was prepared from **1** in a manner similar to that described for the preparation of **2a**: 63%; a colorless oil; $[\alpha]^{23}_D$ +50.8 (*c* 1.30, $CHCl_3$); IR (neat) 3480 (br), 1720, 1640, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.08−4.21 (m, 2H), 4.16 (d, J = 3.0 Hz, 1H), 4.12 (d, J = 3.0 Hz, 1H), 3.78 (m, 1H), 3.51 (m, 1H), 3.12 (br s, 1H), 2.01−2.11 (m, 2H), 1.60−1.88 (m, 4H), 1.14−1.41 (m, 4H), 1.31 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H); FAB(+) HRMS calcd for $C_{16}H_{29}O_4$ (M^+ + H) 285.2066, found 285.2060.

Ethyl (2*S*)-2-Butyl-2-methyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (2c). Compound **2c** was prepared from **1** in a manner similar to that described for the preparation of **2a**: 56%; a colorless oil; $[\alpha]^{23}_D$ +49.3 (*c* 1.30, $CHCl_3$); IR (neat) 3500 (br), 1730, 1650, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.16 (d, J = 2.3 Hz, 1H), 4.12 (d, J = 2.3 Hz, 1H), 4.08−4.21 (m, 2H), 3.78 (m, 1H), 3.54 (m, 1H), 3.12 (br s, 1H), 2.01−2.11 (m, 2H), 1.61−1.90 (m, 4H), 1.09−1.41 (m, 8H), 1.30 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); FAB(+) HRMS calcd for $C_{17}H_{31}O_4$ (M^+ + H) 299.2222, found 299.2225.

Ethyl (2*S*)-2-Isopropyl-2-methyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (2d). Compound **2d** was prepared from **1** in a manner similar to that described for the preparation of **2a**: 32%; a colorless oil; $[\alpha]^{20}_D$ +95.1 (*c* 1.00, $CHCl_3$); IR (neat) 3500 (br), 1720, 1650, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.10−4.18 (m, 4H), 3.70 (m, 1H), 3.55 (m, 1H), 3.54 (br s, 1H), 2.62 (septet, J = 7.0 Hz, 1H), 2.02−2.17 (m, 2H), 1.70−1.76 (m, 2H), 1.16−1.36 (m, 4H), 1.27 (t, J = 7.0 Hz, 3H), 1.21 (s, 3H), 0.87 (d, J = 7.0 Hz, 6H); FAB(+) HRMS calcd for $C_{16}H_{29}O_4$ (M^+ + H) 285.2066, found 285.2061.

Ethyl (2*S*)-2-Isobutyl-2-methyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (2e). Compound **2e** was prepared from **1** in a manner similar to that described for the preparation of **2a**: 42%; a colorless oil; $[\alpha]^{26}_D$ +61.5 (*c* 0.70, $CHCl_3$); IR (neat) 3500 (br), 1720, 1645, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.07−4.21 (m, 4H), 3.77 (m, 1H), 3.52 (m, 1H), 3.32 (br s, 1H), 2.02−2.12 (m, 2H), 1.83 (m, 1H), 1.59−1.73 (m, 4H), 1.16−1.36 (m, 4H), 1.35 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H); FAB(+) HRMS calcd for $C_{17}H_{31}O_4$ (M^+ + H) 299.2222, found 299.2220.

Ethyl (2*S*)-2-Allyl-2-methyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (2f). Compound **2f** was prepared from **1** in a manner similar to that described for the preparation of **2a**: 64%; a colorless oil; $[\alpha]^{22}_D$ +68.8 (*c* 1.10, $CHCl_3$); IR (neat) 3500 (br), 1730, 1650, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.68 (m, 1H), 5.03−5.09 (m, 2H), 4.09−4.21 (m, 2H), 4.17 (d, J = 3.3 Hz, 1H), 4.10 (d, J = 3.3 Hz, 1H), 3.78 (m, 1H), 3.53 (m, 1H), 3.07 (br s, 1H), 2.65 (dd, J = 6.1, 13.6 Hz, 1H), 2.42 (dd, J = 8.3, 13.6 Hz, 1H), 2.01−2.11 (m, 2H), 1.69−1.72 (m,

(17) Dipeptide CF_3CO-αEtLeu-(*S*)-Beg-OEt was prepared by using solution phase methods, and the X-ray analysis revealed that the configuration of (+)-**13e** prepared using (*R*,*R*)-cyclohexane-1,2-diol was *S*. Crystal data of CF_3CO-αEtLeu-(*S*)-Beg-OEt: solvent of recryst. = MeOH, $C_{20}H_{35}O_4N_2F_3$, M_r = 424.50, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 11.301, b = 11.318, c = 19.284 Å, V = 2466.5 Å^3, Z = 4, D_{calcd} = 1.143 gcm^{-3}, μ (Mo-Kα) = 0.093 cm^{-1}, no. of observation = 1829 ($I > 2.0\ \sigma(I)$), R = 0.075, R_w = 0.103. The synthesis and conformational analysis of peptides will be published elsewhere.

(18) While we were preparing the manuscript, Maruoka et al. reported the enantioselective synthesis of α-allylated and α-methylated α-amino acids using chiral phase-transfer catalyst. See: Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

2H), 1.29 (s, 3H), 1.25 (t, J = 7.3 Hz, 3H), 1.15−1.45 (m, 4H); FAB(+) HRMS calcd for $C_{16}H_{27}O_4$ (M^+ + H) 283.1909, found 283.1913.

Ethyl (2*S*)-2-Benzyl-2-ethyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (5a). Compound **5a** was prepared from **4** in a manner similar to that described for the preparation of **2a**: 69%; a colorless oil; $[\alpha]^{23}_D$ +45.7 (*c* 1.40, $CHCl_3$); IR (neat) 3500 (br), 1725, 1650, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08−7.34 (m, 5H), 4.02−4.35 (m, 2H), 4.25 (d, J = 3.3 Hz, 1H), 3.88 (d, J = 3.3 Hz, 1H), 3.82 (m, 1H), 3.58 (m, 1H), 3.20 (d, J = 13.5 Hz, 1H), 3.09 (d, J = 13.5 Hz, 1H), 2.70 (br, 1H), 2.22 (m, 1H), 2.03 (m, 1H), 1.53−1.81 (m, 4H), 1.20−1.45 (m, 4H), 1.31 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.0 Hz, 3H); FAB(+) HRMS calcd for $C_{21}H_{31}O_4$ (M^+ + H) 347.2222, found 347.2226.

Ethyl (2*S*)-2-Ethyl-2-propyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (5b). Compound **5b** was prepared from **4** in a manner similar to that described for the preparation of **2a**: 70%; a colorless oil; $[\alpha]^{20}_D$ +60.5 (*c* 1.00, $CHCl_3$); IR (neat) 3500 (br), 1720, 1650, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.05−4.23 (m, 2H), 4.19 (d, J = 3.3 Hz, 1H), 4.12 (d, J = 3.3 Hz, 1H), 3.77 (m, 1H), 3.51 (m, 1H), 2.75 (br s, 1H), 2.00−2.22 (m, 2H), 1.62−1.88 (m, 6H), 1.00−1.40 (m, 6H), 1.27 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H), 0.83 (t, J = 7.0 Hz, 3H); FAB(+) HRMS calcd for $C_{17}H_{31}O_4$ (M^+ + H) 299.2222, found 299.2224.

Ethyl (2*S*)-2-Butyl-2-ethyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (5c). Compound **5c** was prepared from **4** in a manner similar to that described for the preparation of **2a**: 58%; a colorless oil; $[\alpha]^{30}_D$ +34.0 (*c* 0.50, $CHCl_3$); IR (neat) 3450 (br), 1730, 1650, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02−4.25 (m, 2H), 4.22 (d, J = 3.3 Hz, 1H), 4.14 (d, J = 3.3 Hz, 1H), 3.78 (m, 1H), 3.54 (m, 1H), 2.72 (br s, 1H), 1.98−2.15 (m, 2H), 1.64−1.89 (m, 6H), 1.00−1.40 (m, 8H), 1.28 (t, J = 7.6 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3H), 0.83 (t, J = 7.6 Hz, 3H); FAB(+) HRMS calcd for $C_{18}H_{33}O_4$ (M^+ + H) 313.2379, found 313.2384.

Ethyl (2*S*)-2-Ethyl-2-isopropyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (5d). Compound **5d** was prepared from **4** in a manner similar to that described for the preparation of **2a**: 31%; a colorless oil; $[\alpha]^{28}_D$ +43.1 (*c* 1.10, $CHCl_3$); IR (neat) 3500 (br), 1715, 1640, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10−4.28 (m, 3H), 4.03 (d, J = 3.3 Hz, 1H), 3.76 (m, 1H), 3.53 (br s, 1H), 3.51 (m, 1H), 2.02−2.25 (m, 2H), 1.66−1.93 (m, 5H), 1.22−1.37 (m, 4H), 1.28 (t, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.84 (t, J = 7.0 Hz, 3H); FAB(+) HRMS calcd for $C_{17}H_{31}O_4$ (M^+ + H) 299.2222, found 299.2225.

Ethyl (2*S*)-2-Ethyl-2-isobutyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (5e). Compound **5e** was prepared from **4** in a manner similar to that described for the preparation of **2a**: 45%; a colorless oil; $[\alpha]^{26}_D$ +49.3 (*c* 0.90, $CHCl_3$); IR (neat) 3500 (br), 1730, 1645, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03−4.24 (m, 4H), 3.77 (m, 1H), 3.50 (m, 1H), 2.87 (br s, 1H), 2.00−2.23 (m, 2H), 1.55−1.90 (m, 7H), 1.13−1.36 (m, 4H), 1.24 (t, J = 7.0 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); FAB(+) HRMS calcd for $C_{18}H_{33}O_4$ (M^+ + H) 313.2379, found 313.2381. The alkylation using (*R*,*R*)-cyclohexane-1,2-diol gave (2*R*)-(−)-**5e**; $[\alpha]^{28}_D$ −47.7 (*c* 0.98, $CHCl_3$).

Ethyl (2*S*)-2-Allyl-2-ethyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]-3-butenoate (5f). Compound **5f** was prepared from **4** in a manner similar to that described for the preparation of **2a**: 66%; a colorless oil; $[\alpha]^{19}_D$ +65.0 (*c* 0.70, $CHCl_3$); IR (neat) 3500 (br), 1730, 1645, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.65 (m, 1H), 5.02−5.11 (m, 2H), 4.10−4.24 (m, 4H), 3.79 (m, 1H), 3.55 (m, 1H), 2.72 (br s, 1H), 2.61 (dd, J = 6.6, 13.9 Hz, 1H), 2.50 (dd, J = 8.1, 13.9 Hz, 1H), 2.01−2.13 (m, 2H), 1.68−1.85 (m, 4H), 1.18−1.37 (m, 4H), 1.29 (t, J = 7.3 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H); FAB(+) HRMS calcd for $C_{17}H_{29}O_4$ (M^+ + H) 297.2066, found 297.2068.

Ethyl (*S*)-2-Benzyl-2-methylacetoacetate (3a). BF_3−OEt_2 (1 mL, 8 mmol) was added dropwise to the stirred solution of **2a** (132 mg, 0.40 mmol) in EtOH (8 mL) and H_2O (1 mL) at room temperature. After being stirred for 3 h, the solution was diluted with brine, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (3% EtOAc in hexane) to give β-keto ester **3a** (68 mg, 73%) as a colorless oil: $[\alpha]^{27}_D$ −58.5 (*c* 1.30, $CHCl_3$), lit.[12] $[\alpha]_D$ −58.2 (92% ee); IR (neat) 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03−7.28 (m,5H), 4.14−4.25 (m, 2H), 3.29 (d, J = 14.0 Hz, 1H), 3.04 (d, J = 14.0 Hz, 1H), 2.17 (s, 3H), 1.28 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); FAB(+) HRMS calcd for $C_{14}H_{19}O_3$ (M^+ + H) 235.1334, found 235.1331.

Ethyl (*S*)-2-Methyl-2-propylacetoacetate (3b). Compound **3b** was prepared from **2b** in a manner similar to that described for the preparation of **3a**: 79%; a colorless oil; $[\alpha]^{24}_D$ −9.1 (*c* 1.30, $CHCl_3$); IR (neat) 1720, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (q, J = 7.3 Hz, 2H), 2.16 (s, 3H), 1.67−1.92 (m, 2H), 1.32 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.12−1.30 (m, 2H), 0.95 (t, J = 6.9 Hz, 3H); FAB(+) HRMS calcd for $C_{10}H_{19}O_3$ (M^+ + H) 187.1334, found 187.1330.

Ethyl (*S*)-2-Butyl-2-methylacetoacetate (3c). Compound **3c** was prepared from **2c** in a manner similar to that described for the preparation of **3a**: 78%; a colorless oil; $[\alpha]^{24}_D$ −5.4 (*c* 1.24, $CHCl_3$); IR (neat) 1720 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (q, J = 7.3 Hz, 2H), 2.14 (s, 3H), 1.67−1.94 (m, 2H), 1.32 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H), 1.10−1.37 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); FAB(+) HRMS calcd for $C_{11}H_{21}O_3$ (M^+ + H) 201.1491, found 201.1495.

Ethyl (*S*)-2-Isopropyl-2-methylacetoacetate (3d). Compound **3d** was prepared from **2d** in a manner similar to that described for the preparation of **3a**: 78%; a colorless oil; $[\alpha]^{18}_D$ +26.8 (*c* 1.00, $CHCl_3$); IR (neat) 1735, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.22 (q, J = 7.2 Hz, 2H), 2.64 (septet, J = 6.9 Hz, 1H), 2.16 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.24 (s, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H); FAB(+) HRMS calcd for $C_{10}H_{19}O_3$ (M^+ + H) 187.1334, found 187.1331.

Ethyl (*S*)-2-Isobutyl-2-methylacetoacetate (3e). Compound **3e** was prepared from **2e** in a manner similar to that described for the preparation of **3a**: 85%; a colorless oil; $[\alpha]^{31}_D$ −3.1 (*c* 1.50, $CHCl_3$); IR (neat) 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.22 (q, J = 7.3 Hz, 2H), 2.15 (s, 3H), 1.93 (dd, J = 14.2, 6.9 Hz, 1H), 1.77 (dd, J = 14.2, 5.6 Hz, 1H), 1.64 (m, 1H), 1.35 (s, 3H), 1.26 (t, J = 7.3 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6H); FAB(+) HRMS calcd for $C_{11}H_{21}O_3$ (M^+ + H) 201.1491, found 201.1494.

Ethyl (*S*)-2-Allyl-2-methylacetoacetate (3f). Compound **3f** was prepared from **2f** in a manner similar to that described for the preparation of **3a**: 82%; a colorless oil; $[\alpha]^{19}_D$ −28.1 (*c* 0.80, $CHCl_3$); IR (neat) 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.65 (m, 1H), 5.06−5.13 (m, 2H), 4.23 (q, J = 7.2 Hz, 2H), 2.68 (dd, J = 7.0, 14.2 Hz, 1H), 2.54 (dd, J = 7.6, 14.2 Hz, 1H), 2.15 (s, 3H), 1.33 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); FAB(+) HRMS calcd for $C_{10}H_{17}O_3$ (M^+ + H) 185.1178, found 185.1181.

Ethyl (*S*)-2-Benzyl-2-ethylacetoacetate (6a). Compound **6a** was prepared from **5a** in a manner similar to that described for the preparation of **3a**: 84%; a colorless oil; $[\alpha]^{20}_D$ −34.7 (*c* 1.10, $CHCl_3$); IR (neat) 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.50−5.66 (m, 5H), 4.10−4.23 (m, 2H), 3.24 (d, J = 14.1 Hz, 1H), 3.14 (d, J = 14.1 Hz, 1H), 2.10 (s, 3H), 1.90 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H); FAB(+) HRMS calcd for $C_{15}H_{21}O_3$ (M^+ + H) 249.1491, found 249.1495.

Ethyl (*S*)-2-Ethyl-2-propylacetoacetate (6b). Compound **6b** was prepared from **5b** in a manner similar to that described for the preparation of **3a**: 76%; a colorless oil; $[\alpha]^{25}_D$ +3.20 (*c* 0.30, $CHCl_3$); IR (neat) 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (q, J = 7.3 Hz, 2H), 2.11 (s, 3H), 1.71−1.98 (m, 4H), 1.28 (t, J = 7.3 Hz, 3H), 1.03−1.16 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H), 0.79 (t, J = 7.6 Hz, 3H); FAB(+) HRMS calcd for $C_{11}H_{21}O_3$ (M^+ + H) 201.1491, found 201.1489.

Ethyl (*S*)-2-Butyl-2-ethylacetoacetate (6c). Compound **6c** was prepared from **5c** in a manner similar to that described for the preparation of **3a**: 79%; a colorless oil; $[\alpha]^{26}_D$ +6.60 (*c* 1.10, $CHCl_3$); IR (neat) 1735, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (q, J = 7.3 Hz, 2H), 2.11 (s, 3H), 1.79−1.98 (m, 4H), 1.23−1.36 (m, 2H), 1.28 (t, J = 7.3 Hz, 3H), 1.01−1.11 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H), 0.79 (t, J = 7.3 Hz, 3H); FAB(+) HRMS calcd for $C_{12}H_{23}O_3$ (M^+ + H) 215.1647, found 215.1645.

Ethyl (*S*)-2-Ethyl-2-isopropylacetoacetate (6d). Compound **6d** was prepared from **5d** in a manner similar to that described for the preparation of **3a**: 85%; a colorless oil; $[\alpha]^{26}_D$ −19.2 (*c* 1.20, $CHCl_3$); IR (neat) 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.26 (q, J = 7.3 Hz, 2H), 2.43 (septet, J = 6.9 Hz, 1H), 2.16 (s, 3H), 1.82−2.03 (m, 2H), 1.31 (t, J = 7.3 Hz, 3H), 0.93 (d, J = 6.9 Hz, 6H), 0.81 (t, J = 7.6 Hz, 3H); FAB(+) HRMS calcd for $C_{11}H_{21}O_3$ (M^+ + H) 201.1491, found 201.1493.

Ethyl (*S*)-2-Ethyl-2-isobutylacetoacetate (6e). Compound **6e** was prepared from (+)-**5e** in a manner similar to that described for the preparation of **3a**: 85%; a colorless oil; $[\alpha]^{31}_D$ −9.30 (*c* 1.50, $CHCl_3$); IR (neat) 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.22 (q, J = 7.0 Hz, 2H), 2.12 (s, 3H), 1.92−2.50 (m, 2H), 1.78−1.90 (m, 2H), 1.55 (m, 1H), 1.26 (t, J = 7.0 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 7.6 Hz, 3H); FAB(+) HRMS calcd for $C_{12}H_{23}O_3$ (M^+ + H) 215.1647, found 215.1645. The specific rotation of **6e** prepared using (*R*,*R*)-cyclohexane-1,2-diol showed $[\alpha]^{26}_D$ +9.17 (*c* 1.15, $CHCl_3$).

Ethyl (*S*)-2-Allyl-2-ethylacetoacetate (6f). Compound **6f** was prepared from **5f** in a manner similar to that described for the preparation of **3a**: 78%; a colorless oil; $[\alpha]^{19}_D$ −14.1 (*c* 0.90, $CHCl_3$); IR (neat) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.58 (m, 1H), 5.04−5.13 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 2.53−2.65 (m, 2H), 2.13 (s, 3H), 1.99 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.81 (t, J = 7.6 Hz, 3H); FAB(+) HRMS calcd for $C_{11}H_{19}O_3$ (M^+ + H) 199.1334, found 199.1331.

Ethyl 3-[(1*S*,2*S*)-2-Hydroxycyclohexyloxy]-2-methylbut-2-enoate (7): a colorless oil; IR (neat) 3410 (br), 1700, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12−4.28 (m, 2H), 3.60 (m, 1H), 2.80 (m, 1H), 2.17 (br s, 3H), 1.92 (br s, 3H), 1.11−2.20 (m, 12H); FAB(+) HRMS calcd for $C_{13}H_{23}O_4$ (M^+ + H) 243.1596, found 243.1592.

Ethyl 2-Ethyl-3-[(1*S*,2*S*)-2-hydroxycyclohexyloxy]but-2-enoate (8): a colorless oil; IR (neat) 3420 (br), 1695, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.30 (br s, 1H), 4.10−4.30 (m, 2H), 3.52−3.68 (m, 2H), 1.90−2.35 (m, 4H), 1.98 (s, 3H), 1.65−1.80 (m. 2H), 1.29 (t, J = 7.3 Hz, 3H), 1.20−1.50 (m, 4H), 1.00 (t, J = 7.4 Hz, 3H),; FAB(+) HRMS calcd for $C_{14}H_{25}O_4$ (M^+ + H) 257.1753, found 257.1758.

(*R*,*R*)-2,3-Butanediol Acetal of 3e (9). A mixture of β-keto ester **3e** (30 mg, 1.15 mmol), (*R*,*R*)-(−)-2,3-butanediol (18 mg, 0.2 mmol), and *p*-toluenesulfonic acid monohydrate (3 mg) in benzene (10 mL) was refluxed for 3 h, fixed with Dean−Stark apparatus. After being cooled to room temperature, the mixture was diluted with ether, washed with 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent, the residue was briefly purified by column chromatography on silica gel to afford **9** as a colorless oil. The 500 MHz ^1H NMR spectrum of acetal **9** derived from the β-keto ester (±)-**3e** showed the methyl proton signals at δ 1.37 (s, 1.5H) and 1.35 (s, 1.5H) in the ratio of 1 to 1, while the corresponding signal from (−)-**3e** alkylated by our methods was observed at δ 1.35 (s, 3H), only.

Ethyl (2*S*)-2-Benzyl-2-methyl-3-(*N*-*p*-toluenesulfonyloxyimino)butanoate (10).[13] ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.13−7.35 (m, 3H), 6.90−6.95 (m, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.19 (d, J = 13.5 Hz, 1H), 3.02 (d, J = 13.5 Hz, 1H), 2.44 (s, 3H), 1.90 (s, 3H), 1.23 (s, 3H)., 1.18 (t, J = 7.0 Hz, 3H).

Ethyl (2*S*)-2-Benzyl-2-ethyl-3-(*N*-*p*-toluenesulfonylimino)butanoate (11). A mixture of **6a** (315 mg, 1.27 mmol), NaOAc (26 mg, 0.32 mmol), and NH_2OH−HCl (176 mg, 2.54 mmol) in EtOH (6 mL) was stirred at 50 °C for 8 h. The mixture was diluted with saturated aqueous NH_4Cl, extracted with $CHCl_3$, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (3% EtOAc in hexane) to afford oxime (216 mg, 65%): colorless crystals; $[\alpha]^{20}_D$ −20.8 (*c* 0.50, $CHCl_3$); IR (KBr) 3450 (br), 3300 (br), 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.32 (br, 1H), 7.03−7.27 (m, 5H), 4.08−4.22 (m, 2H), 3.25 (d, J = 13.9 Hz, 1H), 3.13 (d, J = 13.9 Hz, 1H), 1.79 (s, 3H), 1.64−1.82 (m, 2H), 1.27 (t, J = 7.3 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H); FABMS *m*/*z* 263 (M^+ + H). A mixture of oxime (155 mg, 0.59 mmol), 4-DMAP (7 mg), and *p*-TsCl (228 mg, 1.20 mmol) in pyridine (5 mL) was stirred at 60 °C for 10 h. The mixture was diluted with brine, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 2% EtOAc in hexane gave **11** (197 mg, 80%) as a colorless oil: $[\alpha]^{22}_D$ −42.4 (*c* 2.00, $CHCl_3$); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.10−7.20 (m, 3H), 6.90−6.95 (m, 2H), 4.00−4.20 (m, 2H), 3.16 (d, J = 14.2 Hz, 1H), 3.02 (d, J = 14.2 Hz, 1H), 2.44 (s, 3H), 1.61−1.87 (m, 2H), 1.82 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H), 0.75 (t, J = 7.6 Hz, 3H); FAB(+) HRMS calcd for $C_{22}H_{28}N_1O_5S_1$ (M^+ + H) 418.1688, found 418.1691.

(*R*)-*N*-Acetyl-α-methylphenylalanine Ethyl Ester (12a).[12b] Methansulfonic acid (0.73 mL, 10.0 mmol) was added dropwise to the stirred solution of β-keto ester **3a** (234 mg, 1.00 mmol) in $CHCl_3$ (5 mL) at 0 °C, and then NaN_3 (325 mg, 5.0 mmol) was added. After being refluxing for 6 h, the reaction mixture was cooled to room temperature, diluted with H_2O, neutralized with diluted aqueous NH_3, extracted with ether, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (10% EtOAc in hexane) to give **12a** (237 mg, 95%) as a colorless oil: $[\alpha]^{28}_D$ −63.8 (*c* 1.10, $CHCl_3$), lit.[12b] $[\alpha]_D$ −47.8 (>95% ee); IR (neat) 3300 (br), 1720, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18−7.30 (m, 3H), 7.02−7.08 (m, 2H), 6.09 (br s, 1H), 4.29 (m, 2H), 3.60 (d, J = 13.5 Hz, 1H), 3.21 (d, J = 13.5 Hz, 1H), 1.96 (s, 3H), 1.66 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.9, 169.5, 136.6, 129.8, 128.2, 126.8, 61.8, 61.2, 41.0, 24.0, 23.4, 14.1; FABMS *m*/*z* 250 (M^+ + H).

(*R*)-*N*-Acetyl-α-methylpropylglycine Ethyl Ester (12b). Compound **12b** was prepared from **3b** in a manner similar to that described for the preparation of **12a**: 99%; colorless crystals; mp 74−75 °C; $[\alpha]^{23}_D$ −12.6 (*c* 1.10, $CHCl_3$); IR (KBr) 3300 (br), 1740, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (br s, 1H), 4.22 (q, J = 7.3 Hz, 2H), 2.28 (ddd, J = 1.6, 11.9, 13.5 Hz, 1H), 1.97 (s, 3H), 1.73 (ddd, J = 4.6, 11.9, 13.5 Hz, 1H), 1.56 (s, 3H), 1.27 (t, J = 7.3 Hz, 3H), 0.95−1.22 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 169.0, 61.2, 60.0, 38.6, 23.5, 22.7, 17.2, 13.9, 13.8; FABMS *m*/*z* 202 (M^+ + H). Anal. Calcd for $C_{10}H_{19}N_1O_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.53; H, 9.44; N, 7.30.

(*R*)-*N*-Acetyl-α-butylmethylglycine Ethyl Ester (12c). Compound **12c** was prepared from **3c** in a manner similar to that described for the preparation of **12a**: 89%; colorless crystals; mp 70−71 °C (recryst. from hexane); $[\alpha]^{23}_D$ −14.6 (*c* 1.10, $CHCl_3$); IR (KBr) 3300 (br), 1735, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (br s, 1H), 4.21 (q, J = 7.3 Hz, 2H), 2.26 (m, 1H), 1.99 (s, 3H0, 1.79 (m, 1H), 1.58 (s, 3H), 0.93−1.36 (m, 4H), 1.28 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.6, 169.0, 61.4, 60.3, 36.0, 26.3, 23.8, 22.9, 22.5, 14.0, 13.8; FABMS *m*/*z* 216 (M^+ + H). Anal. Calcd for $C_{11}H_{21}N_1O_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.32; H, 9.83; N, 6.54.

(*R*)-*N*-Acetyl-α-methylvaline Ethyl Ester (12d). Compound **12d** was prepared from **3d** in a manner similar to that described for the preparation of **12a**: 50%; a colorless oil; $[\alpha]^{24}_D$ +2.80 (*c* 0.58, $CHCl_3$); IR (neat) 3300 (br), 1735, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.03 (br s, 1H), 4.20 (q, J = 6.9 Hz, 2H), 2.27 (septet, J = 6.9 Hz, 1H), 1.98 (s, 3H), 1.57 (s, 3H), 1.28 (t, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H); FAB(+) HRMS calcd for $C_{10}H_{20}N_1O_3$ (M^+ + H) 202.1443, found 202.1445.

(*R*)-*N*-Acetyl-α-methylleucine Ethyl Ester (12e). Compound **12e** was prepared from **3e** in a manner similar to that described for the preparation of **12a**: 80%; colorless crystals; mp 54−55 °C (recryst. from hexane); $[\alpha]^{27}_D$ −29.1 (*c* 1.10, $CHCl_3$); IR (KBr) 3300 (br), 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.56 (br s, 1H), 4.22 (q, J = 7.3 Hz, 2H), 2.37 (dd, J = 5.0, 13.9 Hz, 1H), 1.99 (s, 3H), 1.52−1.72 (m, 2H), 1.59 (s, 3H), 1.30 (t, J = 7.3 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.3, 168.9, 61.5, 59.9, 44.2, 24.6, 24.0, 23.9, 23.6, 22.8, 13.9; FABMS *m*/*z* 216 (M^+ + H). Anal. Calcd for $C_{11}H_{21}N_1O_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.25; H, 9.77; N, 6.56.

(*R*)-*N*-Acetyl-α-allylmethylglycine Ethyl Ester (12f). Compound **12f** was prepared from **3f** in a manner similar to that described for the preparation of **12a**: 44%; a colorless oil; $[\alpha]^{23}_D$ −16.4 (*c* 1.09, $CHCl_3$); IR (neat) 3300 (br), 1730, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.23 (br s, 1H), 5.65 (m, 1H), 5.13 (br s, 1H), 5.08 (m, 1H), 4.21 (q, J = 7.3 Hz, 2H), 2.99 (dd, J = 7.3, 13.9 Hz, 1H), 2.55 (dd, J = 7.6, 13.9 Hz, 1H), 1.98 (s, 3H), 1.59 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H); FAB(+) HRMS calcd for $C_{10}H_{18}N_1O_3$ (M^+ + H) 200.1287, found 200.1290.

(*R*)-*N*-Acetyl-α-ethylphenylalanine Ethyl Ester (13a). Compound **13a** was prepared from **6a** in a manner similar to that described for the preparation of **12a**: 52%; a colorless oil; $[\alpha]^{30}_D$ −107.2 (*c* 1.40, $CHCl_3$); IR (neat) 3400 (br), 3300 (br), 1725, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18−7.30 (m, 3H), 7.02−7.08 (m, 2H), 6.17 (br s, 1H), 4.17−4.34 (m, 2H), 3.79 (d, J = 13.5 Hz, 1H), 3.11 (d, J = 13.5 Hz, 1H), 2.71 (m, 1H), 1.98 (s, 3H), 1.93 (m, 1H), 1.37 (t, J = 7.0 Hz, 3H), 0.81 (t, J = 7.0 Hz, 3H); FAB(+) HRMS calcd for $C_{14}H_{20}N_1O_3$ (M^+ + H) 250.1443, found 250.1448.

(*R*)-*N*-Acetyl-α-ethylpropylglycine Ethyl Ester (13b). Compound **13b** was prepared from **6b** in a manner similar to that described for the preparation of **12a**. **13b**: 48%. Compound **6b** was recovered in 42%. **13b**: colorless crystals; mp 44−45 °C (recryst. from hexane); $[\alpha]^{27}_D$ −15.6 (c 2.00, $CHCl_3$); IR (KBr) 3400 (br), 3300 (br), 1715, 1640 cm^{-1}; 1H NMR ($CDCl_3$) δ 6.40 (br s, 1H), 4.23 (q, J = 7.3 Hz, 2H), 2.41−2.60 (m, 2H), 2.01 (s, 3H), 1.60−1.82 (m, 2H), 1.29 (m, 1H), 1.30 (t, J = 7.3 Hz, 3H), 0.98 (m, 1H), 0.87 (t, J = 7.0 Hz, 3H), 0.73 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.4, 168.8, 65.5, 61.7, 37.2, 28.1, 24.1, 17.6, 14.2, 13.9, 8.3; FABMS *m*/*z* 216 (M^+ + H). Anal. Calcd for $C_{11}H_{21}N_1O_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.49; H, 9.84; N, 6.59.

(*R*)-*N*-Acetyl-α-butylethylglycine Ethyl Ester (13c). Compound **13c** was prepared from **6c** in a manner similar to that described for the preparation of **12a**: **13c**: 37%. Compound **6c** was recovered in 50%. **13c**: a colorless oil; $[\alpha]^{25}_D$ −16.37 (*c* 0.63, $CHCl_3$); IR (neat) 3330 (br), 1740, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (br s, 1H), 4.24 (q, J = 7.2 Hz, 2H), 2.42−2.54 (m, 2H), 2.01 (s, 3H), 1.66−1.80 (m, 2H), 1.19−1.32 (m, 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.88 (m, 1H), 0.86 (t, J = 7.0 Hz, 3H), 0.73 (t, J = 7.0 Hz, 3H); FAB(+) HRMS calcd for $C_{12}H_{24}N_1O_3$ (M^+ + H) 230.1756, found 230.1756.

(*R*)-*N*-Acetyl-α-ethylvaline Ethyl Ester (13d). Compound **13d** was prepared from **6d** in a manner similar to that described for the preparation of **12a**: **13d**: 21%. Coumpound **6d** was recovered in 21%. **13d**: a colorless oil; $[\alpha]^{24}_D$ −10.5 (*c* 0.71, $CHCl_3$); IR (neat) 3400, 3300 (br), 1715, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.47 (br s, 1H), 4.25 (q, J = 6.9 Hz, 2H), 2.63 (septet, J = 6.9 Hz, 2H), 2.02 (s, 3H), 1.97 (septet, J = 7.3 Hz, 1H), 1.31 (t, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.73 (t, J = 7.3 Hz, 3H); FAB(+) HRMS calcd for $C_{11}H_{22}N_1O_3$ (M^+ + H) 216.1600, found 216.1603.

(*R*)-*N*-Acetyl-α-ethylleucine Ethyl Ester (13e). Compound **13e** was prepared from **6e** in a manner similar to that described for the preparation of **12a**. **13e**: 35%. Compound **6e** was recovered in 40%. **13e**: colorless crystals; mp 42−43 °C (recryst. from hexane); $[\alpha]^{27}_D$ −21.2 (*c* 1.00, $CHCl_3$); IR (KBr) 3400 (br), 3300 (br), 1720, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.53 (br s, 1H), 4.17−4.28 (m, 2H), 2.46−2.57 (m, 2H), 2.02 (s, 3H), 1.52−1.73 (m, 3H), 1.31 (t, J = 7.1 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H), 0.70 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1, 168.8, 64.9, 61.7, 43.5, 29.1, 24.9, 24.2, 23.8, 22.7, 14.1, 8.1; FABMS *m*/*z* 230 (M^+ + H). Anal. Calcd for $C_{12}H_{23}N_1O_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.43; H, 10.01; N, 6.33. The specific rotation of **13e** prepared using (*R*,*R*)-cyclohexane-1,2-diol showed $[\alpha]^{25}_D$ +21.2 (*c* 1.09, $CHCl_3$).

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Supporting Information Available: Copies of the ^1H NMR spectra of all new compounds, and some ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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