Catalytic Enantioselective Addition of Propionate Units to Imines: An Efficient Synthesis of *anti*-α-Methyl-β-Amino Acid Derivatives

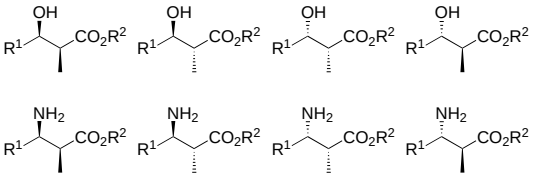
Shū Kobayashi,* Jun Kobayashi, Haruro Ishiani, and Masaharu Ueno[a]

Abstract: Optically active *anti*-α-methyl-β-amino acid derivatives have been prepared based on catalytic enantioselective addition of propionate units to simple and inert imines using a chiral zirconium complex. High reactivity and selectivity with wide substrate scope were attained by using a new chiral ligand, (*R*)-6,6′-bis(pentafluoroethyl)-1,1′-bi-2-naphthol ((*R*)-6,6′-C_2F_5BINOL). The reactions using geometrically isomeric ketene silyl acetals gave excellent *anti*-selectivity with high enantiomeric excess in both cases. Synthetic utility of this reaction has been demonstrated by the preparation of various *anti*-α-methyl-β-amino acid and *trans*-3,4-disubstituted β-lactam derivatives.

Keywords: asymmetric catalysis · β-amino acids · BINOL derivatives · Mannich reactions · zirconium

Introduction

α-Methyl-β-hydroxy units are often observed in biologically important compounds such as macrolides, polyethers, carbohydrates, and several excellent methods for the preparation of these units based on asymmetric catalysis have been developed.[1] On the other hand, the corresponding aza analogues, α-methyl-β-amino units as shown in Scheme 1, are also



Scheme 1. α-Methyl-β-hydroxy units and their aza analogues.

observed in nature such as biologically active peptides of marine origin, for example nodularin,[2] onchidin,[3] majusculamide C.[4] In addition, these units are potentially valuable for preparation of peptidomimetics,[5] and have also successfully been used as intermediates for synthesis of substituted β-lactams,[6] which are candidates for pharmaceutically active compounds. However, examples of catalytic enantioselective methods for the preparation of these units have been limited.[7–12] In this paper, we describe an efficient asymmetric synthesis of α-methyl-β-amino acid derivatives based on catalytic enantioselective Mannich reactions of simple imines with propionate units using a chiral zirconium complex.

[a] Prof. Dr. S. Kobayashi, J. Kobayashi, Dr. H. Ishiani, Dr. M. Ueno
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-0634
E-mail: skobayas@mol.f.u-tokyo.ac.jp

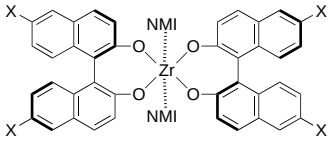
Results and Discussion

We first tested the reaction of aldimine **2a** with ketene silyl acetal **3**(*E*) in the presence of 10 mol% chiral zirconium catalyst **1a**, which was prepared from $Zr(OtBu)_4$, (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol ((*R*)-6,6′-BrBINOL), and *N*-methylimidazole (NMI). The catalyst was known to be effective in similar Mannich reactions of α-unsubstituted, α-alkoxy, and α,α-dialkylsubstituted ketene silyl acetals with imines.[13] The reaction proceeded smoothly in dichloromethane at $-45\,^{\circ}C$ to afford the corresponding α-methyl-β-amino ester **4a** in 94% yield with high *anti*-selectivity; however, the enantiomeric excess of the *anti*-adduct was proven to be less than 50% (Table 1, entry 1). When the reaction was carried out at $-78\,^{\circ}C$, a slight increase in enantioselectivity was observed (66% *ee*), albeit the yield and diastereoselectivity were decreased.

To improve both reactivity and selectivity, we then searched for more efficient ligands in this reaction. In previous investigations, we have revealed that introduction of two halogen atoms at the 6,6′-positions of BINOL derivatives was very effective; namely, Lewis acidity of the zirconium was increased by introducing electron-withdrawing groups at the 6,6′-positions of BINOLs.[13c] As one of the strongest electron-withdrawing groups, we chose a pentafluoroethyl group, so that (*R*)-6,6′-bis(pentafluoroethyl)-1,1′-bi-2-naphthol ((*R*)-6,6′-C_2F_5BINOL) was designed as a new chiral ligand. The

  0947-6539/02/0818-4185 $ 20.00+.50/0

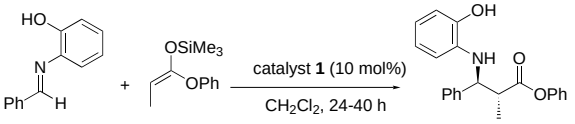
reaction of **2a** with **3**(*E*) was performed using 10 mol% of new catalyst **1b** prepared from $Zr(OtBu)_4$, (*R*)-6,6′-C_2F_5BINOL, and NMI. It was found that catalyst **1b** showed significantly higher enantioselectivity (84% *ee*) at −45 °C compared with catalyst **1a**, and finally, the best result (96% yield, *syn*/*anti* 4:96, *anti* 95% *ee*) was obtained when the



1a: X = Br
1b: X = C_2F_5

reaction was carried out at −78 °C (entry 4).[14] It is noted that the introduction of the pentafluoroethyl group increases not only reactivity but also diastereo- and enantioselectivity of the reaction.[15] In addition, it was interesting from a mechanistic point of view that the reaction using geometrically isomeric ketene silyl acetal **3**(*Z*) also gave excellent *anti*-selectivity, and that the enantiomeric excess of the *anti*-adduct was 83% (entry 5).

Table 1. Catalytic diastereo- and enantioselective Mannich reaction of aldimine **2a** with ketene silyl acetal **3**(*E*).



2a **3**(*E*)[a] **4a**

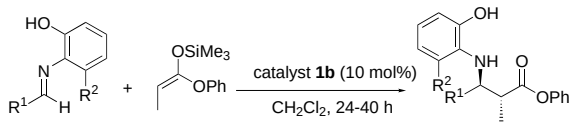
	X	*T* [°C]	Yield [%]	*dr* (*syn*/*anti*)	*ee* (*anti*) [%]
1	Br	−45	94	9/91	47
2	Br	−78	52	13/87	66
3	C_2F_5	−45	92	7/93	84
4	C_2F_5	−78	96	4/96	95
5[b]	C_2F_5	−78	quant.	1/99	83

[a] *E*/*Z* 96:4. [b] **3**(*Z*) (*E*/*Z* 22:78) was used.

We then examined reactions of other aldimines, and the results are summarized in Table 2. In most cases, the reactions proceeded smoothly to give the desired α-methyl-β-amino esters in good yields with high *anti*-selectivity and excellent enantioselectivity.[16] Catalyst **1b** was effective in the reactions of not only aromatic imines but also aliphatic imines. It is noted that in some cases better yields and selectivity were obtained in the presence of 10 mol% of NMI (entries 2, 4, 6–9). In the reactions of aliphatic substrates, aldimines were prepared in situ from the corresponding aldehydes and 2-amino-*m*-cresol instead of 2-aminophenol.[13a] It is also noteworthy that aliphatic substrates gave excellent yields and selectivity in most cases.

Relative and absolute configurations of the Mannich adducts were determined after converting to useful α-methyl-β-amino acid derivatives (Scheme 2). Transesterification of the Mannich adduct **4a** followed by methylation of the phenolic OH and deprotection using catalytic $AgNO_3$ in the presence of excess $(NH_4)_2S_2O_8$[17] gave β-amino ester **6**. The absolute configuration of **6** was determined to be (2*R*,3*S*) by

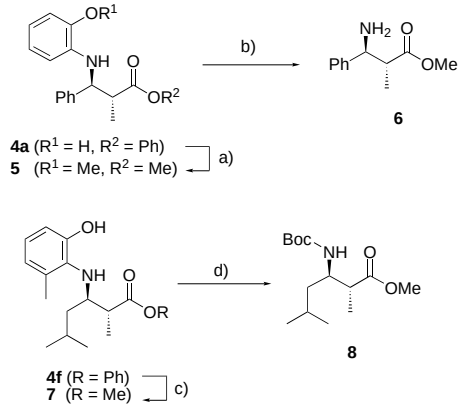
Table 2. Catalytic diastereo- and enantioselective Mannich reactions of various aldimines **2a–i** with ketene silyl acetal **3**(*E*).



2a-e (R^2 = H) **3**(*E*) **4a-e** (R^2 = H)
2f-i (R^2 = Me) **4f-i** (R^2 = Me)

	R^1	*T* [°C]	Yield [%]	*dr* (*syn*/*anti*)	*ee* (*anti*) [%]
1	Ph (**2a**)	−78	96	4/96	95
2[a]	*p*-ClPh (**2b**)	−78	81	5/95	87
3	*o*-MePh (**2c**)	−45	81	6/94	84
4[a]	1-naphthyl (**2d**)	−78	78	7/93	80
5	2-furyl (**2e**)	−45	91	29/71	85
6[a,b]	iC_4H_9 (**2f**)	−45	88	11/89	96
7[a,b]	nC_5H_{11} (**2g**)	−45	87	8/92	93
8[a,b]	$TBSO(CH_2)_2$ (**2h**)	−45	93	2/98	93
9[a,b]	*c*-C_6H_{11} (**2i**)	−20	54	23/77	90

[a] 10 mol% of NMI was used. [b] The aldimine was prepared from the corresponding aldehyde and 2-amino-*m*-cresol in situ in the presence of $MgSO_4$.



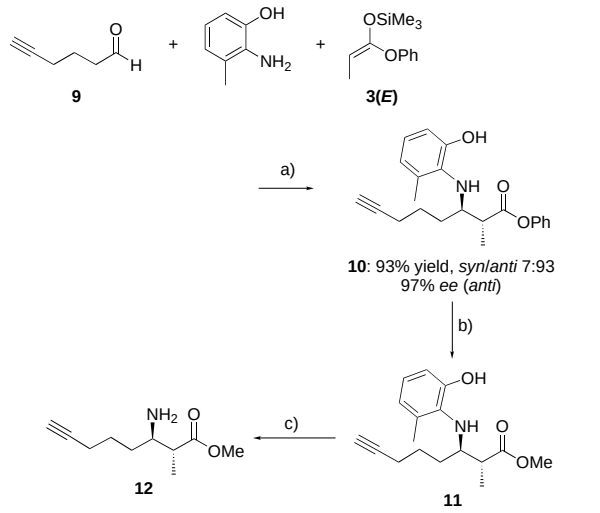
Scheme 2. Conversion of the Mannich adducts to α-methyl-β-amino acid derivatives. a) 1) K_2CO_3, MeOH; 2) K_2CO_3, MeI/acetone, 78% (two steps); b) $AgNO_3$, $(NH_4)_2S_2O_8$, CH_3CN/H_2O, 70%; c) K_2CO_3, MeOH, 95%; d) 1) CAN, CH_3CN/H_2O; 2) Boc_2O, CH_2Cl_2, 44% (two steps).

comparison of the NMR data and the optical rotation with those in the literature.[18] On the other hand, Mannich adduct **4f** was also converted to *N*-Boc-*anti*-α-methyl-β-amino ester **8** by transesterification and deprotection with cerium ammonium nitrate (CAN)[19] followed by Boc protection of the amino group. The absolute stereochemistry was established to be (2*R*,3*R*) by comparison of the NMR data and the optical rotation with those of the authentic sample prepared from Boc-D-leucine.[5b]

Finally, to demonstrate the synthetic utility of this Mannich reaction, we performed asymmetric synthesis of *anti*-α-methyl-β-amino acid and β-lactam derivatives, which are included in biologically important natural products. As shown in Scheme 3, the reaction of the aldimine prepared from 5-hexynal (**9**) and 2-amino-*m*-cresol with ketene silyl acetal **3**(*E*) gave the desired Mannich adduct **10** in 93% yield and high stereoselectivity (*syn*/*anti* 7:93, *anti* 97% *ee*). Transesterification of **10** followed by isolation of a single diastereoisomer and deprotection of the amino group with CAN[19]

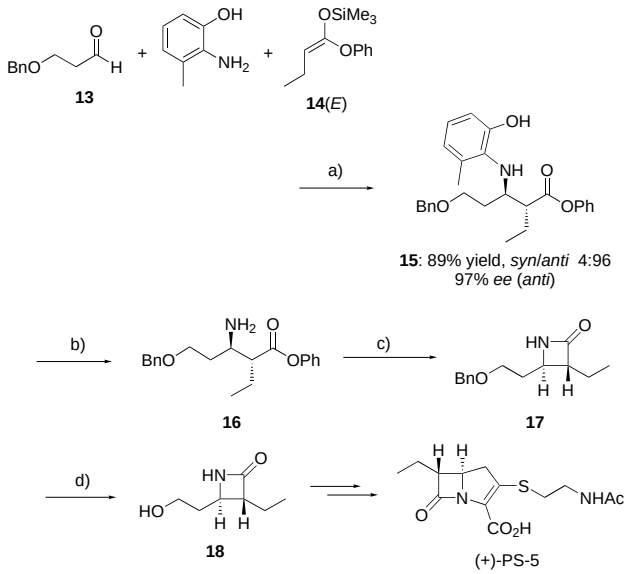
0947-6539/02/0818-4186 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 18

afforded (2*R*,3*R*)-methyl 3-amino-2-methyl-7-octynoate (AMO methyl ester) (**12**).[20] A new β-amino acid, AMO, is one of the units of onchidin,[3] a cytotoxic cyclic depsipeptide from marine mollusc.



Scheme 3. Synthesis of (2*R*,3*R*)-AMO methyl ester. a) catalyst **1b** (10 mol%), $MgSO_4$, CH_2Cl_2, $-45\,^{\circ}C$, 24 h; b) K_2CO_3, MeOH, 91%; c) CAN, CH_3CN/H_2O, 54%.

Furthermore, the Mannich reaction of 3-benzyloxypropanal (**13**), 2-amino-*m*-cresol, and ketene silyl acetal **14**(*E*) derived from phenyl butanoate also proceeded smoothly in high yield and high diastereo- and enantioselectivity (Scheme 4). Deprotection of the Mannich adduct **15** and isolation of an *anti*-isomer gave β-amino ester **16**, which was cyclized smoothly using lithium diisopropylamide (LDA)[21] followed by cleavage of *O*-benzyl bond with $Pd(OH)_2/C$ under hydrogen atmosphere to afford (3*R*,4*R*)-β-lactam **18**.[22] Since **18** has previously been converted to carbapenem antibiotic (+)-PS-5,[23, 24] this method provides a highly efficient asymmetric synthetic route to (+)-PS-5.



Scheme 4. Formal synthesis of the antibiotic (+)-PS-5. a) catalyst **1b** (10 mol%), $MgSO_4$, CH_2Cl_2, $-45\,^{\circ}C$, 24 h; b) CAN, CH_3CN/H_2O, 78%; c) LDA, THF, 55%; d) $Pd(OH)_2/C$, H_2, EtOH, 82%.

Conclusion

In summary, we have developed an efficient method for the preparation of *anti*-α-methyl-β-amino acid derivatives based on highly diastereo- and enantioselective Mannich reactions using a novel chiral zirconium catalyst. This is indeed the first example of catalytic enantioselective Mannich reactions of simple and inert aldimines with propionate units, while many examples of catalytic enantioselective aldol reactions of aldehydes with propionate units have been developed. It is noted that several interesting features have been revealed in this novel aldimine – propionate condensation compared with aldehyde – propionate condensations. Synthetic utility of this reaction has been demonstrated for the preparation of various *anti*-α-methyl-β-amino acid and *trans*-3,4-disubstituted β-lactam derivatives, which are included in biologically important compounds. This procedure will also be applied to synthesis of nitrogen-containing analogues of α-methyl-β-hydroxy units, which are important components of macrolide antibiotics derived from propionyl-CoA.

Experimental Section

General: Melting points were uncorrected. Optical rotations were recorded on a JASCO P-1010 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-610 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^1H NMR, and $CDCl_3$ was used internal standard ($\delta = 77.0$) for ^{13}C NMR. High performance liquid chromatography (HPLC) was carried out using following apparatuses: liquid chromatograph SHIMADZU LC-10AT, UV-VIS detector SHIMADZU SPD-10A, and chromatopac SHIMADZU C-R6A or C-R8A. Column chromatography was performed on Silica gel 60 (Merck) and preparative thin-layer chromatography was carried out using Wakogel B-5F. Dichloromethane was distilled from P_2O_5, then from CaH_2, and dried over MS 4 Å. Aldimines of aromatic aldehydes and heteroaromatic aldehydes were prepared from the corresponding aldehyde and 2-aminophenol by usual methods. The crude aldimines were recrystallized from ethanol to give the pure materials. Ketene silyl acetals **3**(*E*),[25] **3**(*Z*),[26] and **14**(*E*)[25] were prepared according to the literature. All other solvents and chemical compounds were purified based on standard procedures.

Diastereo- and enantioselective Mannich reactions of aromatic imines with ketene silyl acetals using a chiral zirconium catalyst: A typical experimental procedure is described for the reaction of aldimine **2a** with ketene silyl acetal **3**(*E*). $Zr(OtBu)_4$ (0.04 mmol) in dichloromethane (0.25 mL) and *N*-methylimidazole (0.08 mmol) in dichloromethane (0.25 mL) were added at room temperature to a solution of (*R*)-6,6′-bis(pentafluoroethyl)-1,1′-bi-2-naphthol (0.088 mmol) in dichloromethane (0.5 mL). The mixture was stirred for 1 h at the same temperature and then cooled to $-78\,^{\circ}C$. Dichloromethane solutions (1.5 mL) of **2a** (0.4 mmol) and **3**(*E*) (0.48 mmol) were successively added. The mixture was stirred for 24 h, and saturated aqueous $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with dichloromethane, and the crude adduct was treated with THF/1N HCl (10:1) at $0\,^{\circ}C$ for 30 min. After a usual work-up, the crude product was chromatographed on silica gel to give the desired adduct **4a**. The diastereomer ratio was determined by ^1H NMR analysis, and the optical purity was determined by HPLC analysis using a chiral column (see below).

Diastereo- and enantioselective Mannich reactions of aliphatic imines with ketene silyl acetals using a chiral zirconium catalyst: A typical experimental procedure is described for the reaction of aldimine **2f** with ketene silyl acetal **3**(*E*). Isovaleraldehyde (0.48 mmol) in dichloromethane (0.4 mL) was added at room temperature to a mixture of 2-amino-*m*-cresol (0.40 mmol) and $MgSO_4$ (200 mg) in dichloromethane (0.2 mL). The

mixture was stirred for 20 min at the same temperature and then cooled to −45 °C. A dichloromethane solution (1.0 mL) of catalyst **1b** (0.04 mmol) prepared by the same procedure described above and dichloromethane solution (0.4 mL) of **3**(*E*) (0.48 mmol) were successively added. The mixture was stirred for 24 h, and saturated aqueous $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with dichloromethane, and the crude product was chromatographed on silica gel to give the desired adduct **4f**. The diastereomer ratio was determined by ^{1}H NMR analysis, and the optical purity was determined by HPLC analysis using a chiral column (see below).

(*R*)-6,6′-Bis(pentafluoroethyl)-1,1′-bi-2-naphthol ((*R*)-6,6′-C_2F_5BINOL): We previously reported that (*R*)-2,2′-bis(methoxymethyloxy)-6,6′-bis(pentafluoroethyl)-1,1′-binaphthyl (MOM-(*R*)-6,6′-C_2F_5BINOL) was prepared from (*R*)-2,2′-bis(methoxymethyloxy)-6,6′-diiodo-1,1′-binaphthyl (MOM-(*R*)-6,6′-IBINOL).[15b] A saturated HCl methanolic solution (8.0 mL) was added at 0 °C to a solution of MOM-(*R*)-6,6′-C_2F_5BINOL (3.50 g, 5.7 mmol) in CH_2Cl_2 (5.0 mL). After 30 min the resulting solution was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with water and sat. aq. $NaHCO_3$, and dried over Na_2SO_4. After evaporation of the solvents the residue was purified by chromatography on silica gel (hexane/CH_2Cl_2 1:2) to afford (*R*)-6,6′-C_2F_5BINOL (2.87 g, 96 %). $[\alpha]_D^{19} = -23.2$ ($c = 1.05$, $CHCl_3$); M.p. 87–89 °C; IR (KBr): $\tilde{\nu} = 3460$, 1613, 1478, 1208, 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 5.28$ (s, 2H), 7.21 (d, $J =$ 8.8 Hz, 2H), 7.43 (d, $J = 9.1$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 8.06 (d, $J =$ 9.1 Hz, 2H), 8.19 (s, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 110.6$, 113.6 (tq, $J = 38.3$, 253.5 Hz), 119.2 (tq, $J = 39.6$, 285.9 Hz), 119.3, 124.2 (t, $J = 5.7$ Hz), 124.5 (t, $J = 24.3$ Hz), 124.9, 127.8 (t, $J = 6.7$ Hz), 128.4, 132.6, 135.0, 154.6; ^{19}F NMR (283 MHz, CF_3COOH: $\delta = -76.5$, $CDCl_3$): $\delta = -114.5$ (4F), −84.85 (6F); elemental analysis calcd (%) for $C_{24}H_{12}F_{10}O_2$: C 55.19, H 2.32; found: C 55.09, H 2.55.

Phenyl 3-(2-hydroxyphenyl)amino-2-methyl-3-phenylpropanoate (4a) (*syn*/*anti* 4:96): IR (neat): $\tilde{\nu} = 3420$, 3053, 1739, 1604, 1517, 742, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 1.24$ (d, $J = 7.0$ Hz, 3H), 3.12 (dq, $J = 7.0$, 8.7 Hz, 1H), 4.55 (d, $J = 8.7$ Hz, 1H), 6.44–6.69 (m, 4H), 6.98–7.00 (m, 2H), 7.13–7.44 (m, 8H); ***syn***: $\delta = 1.36$ (d, $J = 7.1$ Hz, 3H), 3.24 (dq, $J = 6.0$, 7.1 Hz, 1H), 4.89 (d, $J = 6.0$ Hz, 1H), 6.44–6.69 (m, 4H), 6.81–6.83 (m, 2H), 7.13–7.44 (m, 8H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = 15.2$, 47.0, 61.7, 114.5, 114.9, 118.8, 120.9, 121.5, 126.0, 127.1, 127.7, 128.6, 129.4, 135.0, 140.6, 144.9, 150.5, 174.6; ***syn***: $\delta = 12.4$, 46.7, 60.7, 113.2, 114.3, 117.8, 121.2, 121.4, 125.9, 127.1, 127.5, 128.6, 129.3, 135.7, 140.6, 143.7, 150.4, 173.2; HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH 19:1, flow rate = 0.75 mL min^{-1}): ***anti***: $t_R =$ 18.0 min (minor = 2*S*,3*R*), $t_R = 35.4$ min (major = 2*R*,3*S*); ***syn***: $t_R = 23.3$ min (minor = 2*R*,3*R*), $t_R = 44.9$ min (major = 2*S*,3*S*); elemental analysis calcd (%) for $C_{22}H_{21}NO_3$: C 76.06, H 6.09, N 4.03; found: C 76.14, H 6.27, N 3.98.

Phenyl 3-(4-chlorophenyl)-3-(2-hydroxyphenyl)amino-2-methylpropanoate (4b) (*syn*/*anti* 5:95): IR (neat): $\tilde{\nu} = 3419$, 3055, 1739, 1611, 1589, 1515, 740, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 1.26$ (d, $J = 7.1$ Hz, 3H), 3.08 (dq, $J = 7.1$, 8.4 Hz, 1H), 4.53 (d, $J = 8.4$ Hz, 1H), 6.39–6.67 (m, 4H), 6.98–7.01 (m, 2H), 7.14–7.35 (m, 7H); ***syn***: $\delta = 1.32$ (d, $J = 6.9$ Hz, 3H), 3.19 (dq, $J = 6.0$, 6.9 Hz, 1H), 4.88 (d, $J = 6.0$ Hz, 1H), 6.39–6.67 (m, 4H), 6.83–6.86 (m, 2H), 7.14–7.35 (m, 7H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = 15.1$, 46.8, 61.0, 114.6, 114.7, 119.0, 121.0, 121.4, 126.0, 128.3, 128.8, 129.4, 133.3, 134.7, 139.2, 144.7, 150.4, 174.2; ***syn***: $\delta = 12.2$, 46.4, 59.5, 114.3, 114.7, 118.0, 121.0, 121.3, 126.0, 128.3, 128.7, 129.4, 133.2, 135.3, 139.1, 143.5, 150.3, 172.9; HPLC (Daicel Chiralcel OD, hexane/*i*PrOH 19:1, flow rate = 1.0 mL min^{-1}): ***anti***: $t_R = 19.2$ min (minor = 2*S*,3*R*), $t_R = 35.4$ min (major = 2*R*,3*S*); ***syn***: $t_R = 22.8$ min (minor = 2*R*,3*R*), $t_R = 44.0$ min (major = 2*S*,3*S*); elemental analysis calcd (%) for $C_{22}H_{20}ClNO_3$: C 69.20, H 5.28, N 3.67; found: C 69.35, H 5.51, N 3.57.

Phenyl 3-(2-hydroxyphenyl)amino-2-methyl-3-(2-methylphenyl)propanoate (4c) (*syn*/*anti* 6:94): IR (neat): $\tilde{\nu} = 3417$, 1735, 1604, 1517, 1425, 741, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 1.28$ (d, $J = 7.1$ Hz, 3H), 2.34 (s, 3H), 3.15 (dq, $J = 7.1$, 8.8 Hz, 1H), 4.81 (d, $J = 8.8$ Hz, 1H), 6.31–6.66 (m, 4H), 6.98–7.00 (m, 2H), 7.11–7.35 (m, 7H); ***syn***: $\delta = 1.33$ (d, $J = 7.0$ Hz, 3H), 2.49 (s, 3H), 3.20 (dq, $J = 5.3$, 7.0 Hz, 1H), 5.20 (d, $J = 5.3$ Hz, 1H), 6.31–6.66 (m, 4H), 6.80–6.82 (m, 2H), 7.11–7.35 (m, 7H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = 15.1$, 19.5, 46.6, 57.5, 114.6, 115.6, 119.5, 120.7, 121.5, 125.4, 126.0, 126.7, 127.2, 129.4, 130.5, 134.7, 136.0, 139.1, 145.6, 150.4, 174.9; ***syn***: $\delta = 11.6$, 19.2, 44.8, 56.2, 114.4, 115.4, 119.5, 121.2, 121.4, 125.8, 126.2, 126.5, 127.2, 129.3, 130.8, 135.2, 135.7, 138.7, 145.6, 150.5, 173.5; HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH 19:1, flow rate = 0.75 mL min^{-1}): ***anti***: $t_R = 15.5$ min (minor = 2*S*,3*R*), $t_R = 29.8$ min (major = 2*R*,3*S*); ***syn***: $t_R = 17.8$ min (minor = 2*R*,3*R*), $t_R = 42.9$ min (major = 2*S*,3*S*); elemental analysis calcd (%) for $C_{23}H_{23}NO_3$: C 76.43, H 6.41, N 3.88; found: C 76.19, H 6.71, N 3.78.

Phenyl 3-(2-hydroxyphenyl)amino-2-methyl-3-(1-naphthyl)propanoate (4d) (*syn*/*anti* 3:97): IR (neat): $\tilde{\nu} = 3420$, 3056, 1737, 1610, 1589, 1514, 738, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 1.38$ (d, $J = 6.8$ Hz, 3H), 3.39 (dq, $J = 6.8$, 7.1 Hz, 1H), 5.47 (d, $J = 7.1$ Hz, 1H), 6.30–6.63 (m, 4H), 6.87–7.87 (m, 11H), 8.22 (d, $J = 8.3$ Hz, 1H); ***syn***: $\delta = 1.21$ (d, $J = 7.1$ Hz, 3H), 3.52 (dq, $J = 4.1$, 7.1 Hz, 1H), 5.84 (d, $J = 4.1$ Hz, 1H), 6.30–6.63 (m, 4H), 6.87–7.87 (m, 11H), 8.35 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta =$ 15.7, 46.6, 56.4, 113.2, 114.3, 117.9, 121.0, 121.5, 122.2, 123.7, 125.5, 125.7, 125.9, 126.4, 128.1, 129.3, 129.3, 131.5, 133.9, 135.4, 136.7, 144.1, 150.3, 174.5; ***syn***: $\delta = 10.2$, 44.3, 55.5, 113.0, 114.3, 117.7, 121.1, 121.6, 122.3, 124.4, 125.5, 125.6, 125.9, 126.6, 128.1, 129.3, 129.4, 130.6, 134.1, 135.6, 136.7, 143.5, 150.7, 173.4; HPLC (Daicel Chiralpak AD, hexane/*i*PrOH 19:1, flow rate = 1.0 mL min^{-1}): ***anti***: $t_R = 43.7$ min (minor = 2*S*,3*R*), $t_R = 53.4$ min (major = 2*R*,3*S*); ***syn***: $t_R = 28.3$ min (minor = 2*R*,3*R*), $t_R = 32.2$ min (major = 2*S*,3*S*); elemental analysis calcd (%) for $C_{26}H_{23}NO_3$: C 78.57, H 5.83, N 3.52; found: C 78.28, H 6.12, N 3.42.

Phenyl 3-(2-furyl)-3-(2-hydroxyphenyl)amino-2-methylpropanoate (4e) (*syn*/*anti* 29:71): IR (neat): $\tilde{\nu} = 3412$, 1737, 1603, 1515, 1445, 741, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 1.26$ (d, $J = 7.1$ Hz, 3H), 3.31 (dq, $J = 7.1$, 9.0 Hz, 1H), 4.56 (d, $J = 9.0$ Hz, 1H), 6.15–6.76 (m, 6H), 7.06–7.09 (m, 2H), 7.30–7.40 (m, 4H); ***syn***: $\delta = 1.39$ (d, $J = 7.1$ Hz, 3H), 3.36 (dq, $J =$ 5.9, 7.1 Hz, 1H), 4.96 (d, $J = 5.9$ Hz, 1H), 6.15–6.76 (m, 6H), 6.93–6.96 (m, 2H), 7.30–7.40 (m, 4H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = 14.2$, 44.4, 56.1, 108.2, 110.1, 114.6, 114.8, 116.9, 120.5, 121.4, 125.9, 129.4, 134.1, 142.1, 146.4, 150.5, 152.7, 174.3; ***syn***: $\delta = 12.6$, 44.2, 54.8, 107.4, 110.2, 114.2, 115.2, 119.0, 121.0, 121.4, 125.8, 129.3, 135.2, 141.9, 144.6, 150.5, 153.7, 173.0; HPLC (Daicel Chiralpak AD (double), hexane/*i*PrOH 9:1, flow rate = 0.80 mL min^{-1}): ***anti***: $t_R = 33.4$ min (major = 2*R*,3*S*), $t_R = 39.2$ min (minor = 2*S*,3*R*); ***syn***: $t_R = 31.4$ min (major = 2*S*,3*S*), $t_R = 44.8$ min (minor = 2*R*,3*R*); elemental analysis calcd (%) for $C_{20}H_{19}NO_4$: C 71.20, H 5.68, N 4.15; found: C 70.91, H 5.98, N 4.09.

Phenyl 2,5-dimethyl-3-(2-hydroxy-6-methylphenyl)aminohexanoate (4f) (*syn*/*anti* 9:91): IR (neat): $\tilde{\nu} = 3369$, 2953, 2868, 1740, 1590, 1492, 740, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 0.85$ (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J =$ 6.3 Hz, 3H), 1.38 (d, $J = 7.1$ Hz, 3H), 1.40–1.49 (m, 1H), 1.62–1.76 (m, 1H), 2.29 (s, 3H), 2.85 (dq, $J = 5.7$, 7.1 Hz, 1H), 3.77 (dt, $J = 5.7$, 7.3 Hz, 1H), 6.66–7.39 (m, 8H); ***syn***: $\delta = 0.88$ (d, $J = 6.3$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 1.34 (d, $J = 7.3$ Hz, 3H), 1.40–1.49 (m, 1H), 1.62–1.76 (m, 1H), 2.28 (s, 3H), 2.93 (dq, $J = 2.8$, 7.3 Hz, 1H), 3.69 (dt, $J = 2.8$, 6.8 Hz, 1H), 6.66–7.39 (m, 8H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = 13.2$, 18.4, 22.4, 23.2, 25.1, 43.3, 44.2, 56.0, 113.4, 121.4, 122.5, 123.1, 125.9, 129.4, 130.7, 132.5, 149.8, 150.5, 175.0; ***syn***: $\delta = 10.9$, 18.2, 22.5, 22.9, 25.1, 41.1, 41.8, 56.1, 113.6, 121.4, 122.2, 124.1, 126.0, 129.4, 131.4, 132.4, 150.5, 151.4, 174.7; HPLC (Daicel Chiralpak AD (double), hexane/*i*PrOH 9:1, flow rate = 0.80 mL min^{-1}): ***anti***: $t_R = 17.9$ min (minor = 2*S*,3*S*), $t_R = 19.2$ min (major = 2*R*,3*R*); ***syn***: $t_R = 20.5$ min (major = 2*S*,3*R*), $t_R = 31.8$ min (minor = 2*R*,3*S*); elemental analysis calcd (%) for $C_{21}H_{27}NO_3$: C 73.87, H 7.97, N 4.10; found: C 74.10, H 7.78, N 4.26.

Phenyl 3-(2-hydroxy-6-methylphenyl)amino-2-methyloctanoate (4g) (*syn*/*anti* 9:91): IR (neat): $\tilde{\nu} = 3368$, 2930, 2857, 1742, 1590, 1492, 741, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 0.86$ (t, $J = 6.8$ Hz, 3H), 1.17–1.58 (m, 8H), 1.40 (d, $J = 7.1$ Hz, 3H), 2.27 (s, 3H), 2.88 (dq, $J = 6.8$, 7.1 Hz, 1H), 3.55–3.61 (m, 1H), 6.66–7.39 (m, 8H); ***syn***: $\delta = 0.86$ (t, $J = 6.8$ Hz, 3H), 1.17–1.58 (m, 8H), 1.36 (d, $J = 7.3$ Hz, 3H), 2.28 (s, 3H), 2.97 (dq, $J = 2.9$, 7.3 Hz, 1H), 3.55–3.61 (m, 1H), 6.66–7.39 (m, 8H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta =$ 13.9, 14.2, 18.2, 22.5, 24.7, 32.0, 32.0, 43.6, 58.2, 113.6, 115.3, 121.4, 122.2, 123.5, 125.9, 129.4, 131.0, 132.3, 150.5, 175.6; ***syn***: $\delta = 10.7$, 13.9, 18.1, 22.5, 26.4, 31.7, 31.8, 41.6, 58.3, 113.4, 117.5, 121.4, 122.1, 124.3, 126.0, 129.4, 131.3, 132.6, 151.7, 174.7; HPLC (Daicel Chiralcel OD-H (double), hexane/*i*PrOH 19:1, flow rate = 0.40 mL min^{-1}): ***anti***: $t_R = 41.7$ min (major = 2*R*,3*R*), $t_R =$ 45.0 min (minor = 2*S*,3*S*); ***syn***: $t_R = 38.8$ min (major = 2*S*,3*R*), $t_R = 48.1$ min (minor = 2*R*,3*S*); elemental analysis calcd (%) for $C_{22}H_{29}NO_3$: C 74.33, H 8.22, N 3.94; found: C 74.13, H 8.49, N 4.16.

Phenyl 5-*tert*-butyldimethylsiloxy-3-(2-hydroxy-6-methylphenyl)amino-2-methylpentanoate (4h) (*syn*/*anti* 2:98): IR (neat): $\tilde{\nu} = 3369$, 2936, 2863, 1746, 1590, 1469 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 0.08$ (s, 3H), 0.09 (s,

0947-6539/02/0818-4188 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 18

3H), 0.91 (s, 9H), 1.37 (d, $J = 7.1$ Hz, 3H), 1.63–1.71 (m, 1H), 1.84–1.92 (m, 1H), 2.30 (s, 3H), 2.92 (dq, $J = 5.7$, 7.1 Hz, 1H), 3.78–3.83 (m, 1H), 3.86–3.96 (m, 2H), 6.65–7.38 (m, 8H); ***syn***: $\delta = 0.10$ (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.30 (d, $J = 7.3$ Hz, 3H), 1.69–1.76 (m, 1H), 1.84–1.92 (m, 1H), 2.30 (s, 3H), 2.99 (dq, $J = 2.7$, 7.3 Hz, 1H), 3.78–3.83 (m, 1H), 3.93–4.03 (m, 2H), 6.65–7.38 (m, 8H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = -5.5$, -5.4, 13.4, 18.3, 18.4, 25.9, 34.1, 43.7, 55.4, 60.4, 114.0, 121.4, 122.1, 123.3, 125.8, 129.3, 130.9, 132.4, 150.4, 150.5, 174.7; ***syn***: $\delta = -5.4$, -5.4, 12.8, 18.3, 18.3, 25.9, 33.2, 42.4, 56.6, 60.7, 113.9, 121.4, 121.9, 123.9, 126.0, 129.4, 131.7, 132.1, 150.4, 150.4, 174.0; HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH 100:1, flow rate = 1.0 mL min^{-1}): ***anti***: $t_R = 24.2$ min (minor = 2*S*,3*S*), $t_R = 30.3$ min (major = 2*R*,3*R*); ***syn***: $t_R = 17.9$ min (major = 2*S*,3*R*), $t_R = 33.2$ min (minor = 2*R*,3*S*); elemental analysis calcd (%) for $C_{25}H_{37}NO_4Si$: C 67.68, H 8.41, N 3.16; found: C 67.64, H 8.49, N 3.19.

Phenyl 3-cyclohexyl-3-(2-hydroxy-6-methylphenyl)amino-2-methylpropanoate (4i) (*syn*/*anti* 27:73): IR (neat): $\tilde{\nu} = 3378$, 2923, 2851, 1738, 1590, 1492, 745, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 1.07–1.90$ (m, 11H), 1.37 (d, $J = 7.1$ Hz, 3H), 2.29 (s, 3H), 2.92 (dq, $J = 7.1$, 8.3 Hz, 1H), 3.74 (dd, $J = 3.3$, 8.3 Hz, 1H), 6.65–6.82 (m, 3H), 7.00–7.03 (m, 2H), 7.19–7.36 (m, 3H); ***syn***: $\delta = 1.07–1.90$ (m, 11H), 1.36 (d, $J = 7.2$ Hz, 3H), 2.28 (s, 3H), 3.00 (dq, $J = 3.1$, 7.2 Hz, 1H), 3.70 (dd, $J = 3.1$, 5.1 Hz, 1H) 6.65–6.82 (m, 3H), 6.90–6.93 (m, 2H), 7.19–7.36 (m, 3H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = 15.5$, 18.6, 26.5, 26.6, 26.7, 28.3, 29.6, 41.1, 43.2, 61.7, 114.8, 121.4, 122.1, 122.6, 126.0, 128.9, 129.4, 133.7, 149.1, 150.5, 176.6; ***syn***: δ 11.9, 18.6, 26.3, 26.5, 26.6, 30.2, 30.7, 41.2, 42.4, 61.6, 114.4, 121.4, 122.5, 122.8, 125.9, 129.4, 130.2, 133.3, 149.5, 150.8, 175.3; HPLC (Daicel Chiralcel OD-H (double), hexane/*i*PrOH 24:1, flow rate = 0.60 mL min^{-1}): ***anti***: $t_R = 35.4$ min (major = 2*R*,3*R*), $t_R = 44.3$ min (minor = 2*S*,3*S*); ***syn***: $t_R = 33.2$ min (major = 2*S*,3*R*), $t_R = 40.5$ min (minor = 2*R*,3*S*); elemental analysis calcd (%) for $C_{23}H_{29}NO_3$: C 75.17, H 7.95, N 3.81; found: C 75.20, H 8.15, N 3.84.

(2*R*,3*S*)-Methyl 3-(2-methoxyphenyl)amino-2-methyl-3-phenylpropanoate (5): K_2CO_3 (166 mg, 1.20 mmol) was added at room temperature to a solution of **4a** (*syn*/*anti* 2:98, *anti* = 92% *ee*) (210 mg, 0.60 mmol) in MeOH (8.0 mL). After being stirred for 20 min, the reaction mixture was quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2 and dried over Na_2SO_4. Filtration and removal of the solvents afforded methyl 3-(2-hydroxyphenyl)amino-2-methyl-3-phenylpropanoate, a crude sample of which was dissolved in a MeI/acetone (1:5) solution (8.0 mL), followed by addition of K_2CO_3 (332 mg, 2.40 mmol) at room temperature. After the mixture was stirred for 8 h, sat. aq. NH_4Cl was added to quench the reaction. After a usual work-up, the crude product was chromatographed on silica gel to give **5** (131 mg, 78%) as a pure *anti*-isomer. $[\alpha]_D^{18} = -16.0$ ($c = 1.34$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3414$, 2944, 1733, 1603, 1513, 1456, 736, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.14$ (d, $J = 7.0$ Hz, 3H), 2.88 (dq, $J = 7.0$, 7.7 Hz, 1H), 3.63 (s, 3H), 3.85 (s, 3H), 4.51 (d, $J = 7.7$ Hz, 1H), 6.39–6.73 (m, 4H), 7.17–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 15.0$, 46.7, 51.7, 55.5, 60.4, 109.4, 110.9, 116.4, 121.0, 126.9, 127.3, 128.4, 136.7, 141.2, 146.8, 175.3.

(2*R*,3*S*)-Methyl 3-amino-2-methyl-3-phenylpropanoate (6):[18] A catalytic amount of $AgNO_3$ (14 mg, 0.08 mmol) was added at 60 °C to a solution of **5** (50 mg, 0.17 mmol) in a CH_3CN/H_2O (2:1) solution (2.8 mL), followed by portionwise addition of excess $(NH_4)_2S_2O_8$[17] (306 mg, 1.34 mmol) for 20 min. After being stirred for 4 h, the reaction mixture was cooled at room temperature, diluted with water, treated with K_2CO_3 to a pH of over 7, and extracted with EtOAc. After a usual work-up, the crude product was chromatographed on silica gel to afford the desired β-amino ester **6** (23 mg, 70%). $[\alpha]_D^{22} = -30.8$ ($c = 1.12$, $CHCl_3$) (lit.:[18] $[\alpha]_D^{25} = -29.2$ ($c = 1.00$, $CHCl_3$)); IR (neat): $\tilde{\nu} = 3379$, 2944, 1736, 1454, 766, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.95$ (d, $J = 7.1$ Hz, 3H), 1.86 (br s, 2H), 2.71 (dq, $J = 7.1$, 9.5 Hz, 1H), 3.73 (s, 3H), 4.02 (d, $J = 9.5$ Hz, 1H), 7.25–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 15.3$, 47.9, 51.7, 59.1, 127.0, 127.5, 128.6, 143.4, 176.4.

(2*R*,3*R*)-Methyl 2,5-dimethyl-3-(2-hydroxy-6-methylphenyl)aminohexanoate (7): K_2CO_3 (102 mg, 0.74 mmol) was added at room temperature to a solution of **4f** (*syn*/*anti* 9:91, *anti* 92% *ee*) (127 mg, 0.37 mmol) in MeOH (5.0 mL). After being stirred for 20 min, the reaction mixture was quenched with sat. aq. NH_4Cl. After a usual work-up, the crude product was chromatographed on silica gel to afford **7** (98 mg, 95%) as a pure *anti*-isomer. $[\alpha]_D^{17} = +5.2$ ($c = 1.10$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3367$, 2954, 2863, 1711, 1588, 1461 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.79$ (d, $J = 6.3$ Hz, 6H), 1.24 (d, $J = 7.1$ Hz, 3H), 1.31–1.36 (m, 2H), 1.54–1.64 (m, 1H), 2.25 (s, 3H), 2.59 (dq, $J = 7.0$, 7.1 Hz, 1H), 3.57–3.62 (m, 1H), 3.69 (s, 3H), 6.63–6.80 (m, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 13.8$, 18.3, 22.2, 23.2, 25.0, 43.8, 44.6, 51.8, 55.8, 113.6, 122.3, 122.8, 130.3, 132.7, 149.8, 177.2.

(2*R*,3*R*)-Methyl 3-(*tert*-butoxycarbonyl)amino-2,5-dimethylhexanoate (8):[5b] Cerium ammonium nitrate (CAN)[19] (459 mg, 0.84 mmol) was added at 0 °C to a solution of **7** (78 mg, 0.28 mmol) in a CH_3CN/H_2O (4:1) solution (3.5 mL). After being stirred for 20 min, the reaction mixture was diluted with water and EtOAc, treated with K_2CO_3 to a pH of over 7. Insoluble inorganic materials were filtered through a pad of celite and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with 10% aq. Na_2CO_3, 10% aq. Na_2SO_3 and brine, and dried over Na_2SO_4. Filtration and evaporation of solvents afforded (2*R*,3*R*)-methyl 3-amino-2,5-dimethylhexanoate as a crude mixture, which was dissolved in CH_2Cl_2 (3.0 mL), followed by addition of Boc_2O (183 mg, 0.84 mmol) in CH_2Cl_2 (0.8 mL) at room temperature. After 4 h, solvents were removed under reduced pressure and the crude product was chromatographed on silica gel to afford *N*-Boc-β-amino ester **8** (34 mg, 44%). $[\alpha]_D^{23} = +23.4$ ($c = 1.42$, $CHCl_3$) (authentic sample of **8**[5b] prepared according to the literature: $[\alpha]_D^{21} = +25.7$ ($c = 1.43$, $CHCl_3$)); IR (neat): $\tilde{\nu} = 3374$, 2959, 2883, 1718, 1508, 1366, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.90$ (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.3$ Hz, 3H), 1.14–1.21 (m, 1H), 1.20 (d, $J = 7.1$ Hz, 3H), 1.31–1.38 (m, 1H), 1.44 (s, 8H, rotamer), 1.47 (s, 1H, rotamer), 1.60–1.70 (m, 1H), 2.59–2.69 (m, 1H), 3.68 (s, 3H), 3.80–3.87 (m, 1H), 4.72 (d, $J = 10.7$ Hz, 0.1H, rotamer), 5.04 (d, $J = 10.0$ Hz, 0.9H, rotamer); ^{13}C NMR ($CDCl_3$): $\delta = 14.3$, 22.0, 23.1, 24.9, 28.3, 43.0, 43.2, 50.6, 51.5, 78.9, 155.9, 175.8.

Phenyl 3-(2-hydroxy-6-methylphenyl)amino-2-methyl-7-octynoate (10) (*syn*/*anti* 7:93): IR (neat): $\tilde{\nu} = 3366$, 3299, 2942, 2863, 1739, 1489, 1458, 1190, 1161, 744, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 1.41$ (d, $J = 7.2$ Hz, 3H), 1.60–1.75 (m, 4H), 1.94 (t, $J = 2.6$ Hz, 1H), 2.14–2.19 (m, 2H), 2.28 (s, 3H), 2.88 (dq, $J = 7.0$, 7.2 Hz, 1H), 3.61–3.67 (m, 1H), 6.66–6.93 (m, 3H), 7.06–7.40 (m, 5H); ***syn***: $\delta = 1.38$ (d, $J = 7.3$ Hz, 3H), 1.60–1.75 (m, 4H), 1.95 (t, $J = 2.7$ Hz, 1H), 2.14–2.19 (m, 2H), 2.26 (s, 3H), 2.97 (dq, $J = 3.0$, 7.3 Hz, 1H), 3.61–3.67 (m, 1H), 6.66–6.93 (m, 3H), 7.06–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = 14.0$, 18.4, 18.5, 24.3, 31.5, 43.8, 57.7, 68.9, 83.7, 113.7, 121.4, 122.4, 123.3, 125.9, 129.4, 130.8, 132.2, 150.0, 150.4, 175.3; ***syn***: $\delta = 10.9$, 18.2, 18.4, 25.6, 30.8, 41.9, 58.0, 68.9, 83.6, 113.6, 121.4, 122.3, 124.3, 126.0, 129.4, 131.2, 132.4, 150.4, 151.3, 174.5; HPLC (Daicel Chiralcel OD-H (double), hexane/*i*PrOH 19:1, flow rate = 0.50 mL min^{-1}) ***anti***: $t_R = 54.0$ min (major = 2*R*,3*R*), $t_R = 63.6$ min (minor = 2*S*,3*S*); ***syn***: $t_R = 49.6$ min (major = 2*S*,3*R*), $t_R = 67.6$ min (minor = 2*R*,3*S*); elemental analysis calcd (%) for $C_{22}H_{25}NO_3$: C 75.19, H 7.17, N 3.99; found: C 74.92, H 7.35, N 3.97.

(2*R*,3*R*)-Methyl 3-(2-hydroxy-6-methylphenyl)amino-2-methyl-7-octynoate (11): According to the same procedure for **7** from **4f**, Mannich adduct **10** (*syn*/*anti* 7:93, *anti* 97% *ee*) (285 mg, 0.81 mmol) was converted to the corresponding methyl ester and isolated as a pure *anti*-isomer **11** (214 mg, 91%). ^{1}H NMR ($CDCl_3$): $\delta = 1.27$ (d, $J = 7.2$ Hz, 3H), 1.47–1.65 (m, 4H), 1.93 (t, $J = 2.7$ Hz, 1H), 2.11–2.17 (m, 2H), 2.25 (s, 3H), 2.63 (dq, $J = 7.2$, 7.9 Hz, 1H), 3.47–3.53 (m, 1H), 3.73 (s, 3H), 6.63–6.85 (m, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 14.7$, 18.3, 18.5, 24.1, 31.7, 44.1, 52.0, 57.6, 68.8, 83.6, 113.9, 122.1, 123.4, 130.6, 132.3, 150.4, 177.5.

(2*R*,3*R*)-Methyl 3-amino-2-methyl-7-octynoate (AMO methyl ester) (12):[20] According to the same conversion of **7** to **8**, the amino group of **11** (40 mg, 0.14 mmol) was deprotected to afford the desired β-amino ester **12** (14 mg, 54%). $[\alpha]_D^{22} = -9.6$ ($c = 0.14$, $CHCl_3$) (lit.:[20] $[\alpha]_D = -6.0$ ($c = 0.40$, $CHCl_3$)); ^{1}H NMR ($CDCl_3$): $\delta = 1.19$ (d, $J = 7.0$ Hz, 3H), 1.37–1.80 (m, 6H), 1.96 (t, $J = 2.7$ Hz, 1H), 2.20–2.25 (m, 2H), 2.49 (dq, $J = 6.8$, 7.0 Hz, 1H), 2.91 (m, 1H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 14.2$, 18.3, 25.0, 33.7, 46.0, 51.6, 53.6, 68.6, 84.1, 175.8.

Phenyl 5-benzyloxy-2-ethyl-3-(2-hydroxy-6-methylphenyl)aminopentanoate (15) (*syn*/*anti* 4:96): IR (neat): $\tilde{\nu} = 3365$, 2932, 2870, 1746, 1590, 1490, 1452, 1195, 1159, 745, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$): ***anti***: $\delta = 1.01$ (t, $J = 7.6$ Hz, 3H), 1.50–2.08 (m, 4H), 2.25 (s, 3H), 2.67–2.74 (m, 1H), 3.56–3.72 (m, 2H), 3.84–3.89 (m, 1H), 4.48 (d, $J = 11.8$ Hz, 1H), 4.52 (d, $J = 11.8$ Hz, 1H), 6.64–6.89 (m, 3H), 7.01–7.40 (m, 10H); ***syn***: $\delta = 0.97$ (t, $J = 7.3$ Hz, 3H), 1.50–2.08 (m, 4H), 2.30 (s, 3H), 2.67–2.74 (m, 1H), 3.56–3.72 (m, 2H), 3.84–3.89 (m, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.59 (d, $J = 12.0$ Hz, 1H), 6.64–6.89 (m, 3H), 7.01–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$): ***anti***: $\delta = 12.2$, 18.3, 22.4, 32.0, 51.9, 54.7, 66.7, 73.2, 114.4, 121.5, 122.3, 123.1, 125.9, 127.8, 128.0, 128.4, 129.4, 130.1, 132.6, 137.5, 150.1, 150.4, 174.6; ***syn***: δ 12.4, 18.1, 21.9, 30.8, 50.8, 56.3, 67.4, 73.1, 114.0, 121.4, 122.1, 124.1, 126.0, 127.8, 128.0, 128.4, 129.5, 132.2, 132.6, 137.4, 150.3, 151.4, 173.2; HPLC (Daicel

Chiralpak AD (double), hexane/*i*PrOH 19:1, flow rate = 1.0 mL min^{-1}): ***anti***: t_R = 38.1 min (major = 2*R*,3*R*), t_R = 44.1 min (minor = 2*S*,3*S*); ***syn***: t_R = 41.4 min (major = 2*S*,3*R*), t_R = 53.3 min (minor = 2*R*,3*S*); elemental analysis calcd (%) for $C_{27}H_{31}NO_4$: C 74.80, H 7.21, N 3.23; found: C 74.66, H 7.32, N 3.24.

(2*R*,3*R*)-Phenyl 3-amino-5-benzyloxy-2-ethylpentanoate (16): The amino group of **15** (113 mg, 0.26 mmol) was also deprotected with CAN under the similar condition described above and diastereoisomers of the product were separated to give the desired pure *anti*-isomer **16** (66 mg, 78%). ^{1}H NMR ($CDCl_3$): δ = 1.05 (t, *J* = 7.3 Hz, 3H), 1.60–2.28 (m, 6H), 2.51–2.62 (m, 1H), 3.22–3.46 (m, 2H), 3.64–3.69 (m, 1H), 4.52 (s, 2H), 7.06–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 12.0, 22.7, 35.2, 51.0, 53.4, 67.7, 73.1, 121.6, 125.8, 126.9, 127.6, 128.4, 129.4, 138.2, 150.5, 173.5.

(3*R*,4*R*)-4-(2-Benzyloxyethyl)-3-ethylazetidin-2-one (17): *n*BuLi (1.58 M hexane solution, 0.30 mL, 0.47 mmol) was added at 0 °C to a THF solution (0.5 mL) of diisopropylamine (47 mg, 0.47 mmol). After stirred for 10 min, the mixture was cooled to −78 °C. β-Amino ester **16** (51 mg, 0.16 mmol) in THF (1.7 mL) was added and the mixture was stirred for 24 h at the same temperature.[21] Water was added to quench the reaction and after a usual work-up, the crude product was chromatographed on silica gel to afford β-lactam **17** (20 mg, 55%). ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, *J* = 7.4 Hz, 3H), 1.59–1.84 (m, 2H), 1.92 (dt, *J* = 4.5, 6.6 Hz, 2H), 2.76 (dddd, *J* = 1.3, 2.2, 6.2, 8.3 Hz, 1H), 3.44 (dt, *J* = 2.2, 6.6 Hz, 1H), 3.54–3.60 (m, 2H), 4.49 (s, 2H), 5.88 (br s, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 11.4, 21.4, 34.9, 53.0, 58.5, 68.1, 73.2, 127.6, 127.8, 128.5, 138.0, 170.7.

(3*R*,4*R*)-3-Ethyl-4-(2-hydroxyethyl)azetidin-2-one (18):[22] The mixture of **17** (20 mg, 0.085 mmol) and 20% $Pd(OH)_2$/C (13 mg) in EtOH (1.0 mL) was stirred under hydrogen at room temperature for 14 h. After filtration and evaporation, the crude product was purified by chromatography on silica gel to afford **18** (10 mg, 82%). $[\alpha]_D^{22}$ = +20.9 (*c* = 0.40, $CHCl_3$) (lit.:[22d] $[\alpha]_D^{21}$ = +21.6 (*c* = 0.35, $CHCl_3$)); ^{1}H NMR ($CDCl_3$): δ = 1.03 (t, *J* = 7.4 Hz, 3H), 1.63–1.95 (m, 4H), 2.78 (ddd, *J* = 2.1, 6.3, 8.3 Hz, 1H), 3.47 (ddd, *J* = 2.1, 5.1, 7.8 Hz, 1H), 3.72–3.83 (m, 2H), 6.25 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ = 11.4, 21.4, 37.3, 52.8, 58.5, 60.6, 171.1.

Acknowledgement

This work was partially supported by CREST and SORST, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Science.

[1] The catalytic asymmetric aldol reaction is one of the most powerful methods: E. M. Carreira in *Comprehensive Asymmetric Catalysis*, *Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 998.

[2] K. L. Rinehart, K. Harada, M. Namikoshi, C. Chen, C. A. Harvis, M. H. G. Munro, J. W. Blunt, P. E. Mulligan, V. R. Beasley, A. M. Dahlem, W. W. Carmichael, *J. Am. Chem. Soc.* **1988**, *110*, 8557.

[3] J. Rodríguez, R. Fernández, E. Quiñoá, R. Riguera, C. Debitus, P. Bouchet, *Tetrahedron Lett.* **1994**, *35*, 9239.

[4] D. C. Carter, R. E. Moore, J. S. Mynderse, W. P. Niemczura, J. S. Todd, *J. Org. Chem.* **1984**, *49*, 236.

[5] a) J. Xie, J.-M. Soleilhac, C. Schmidt, J. Peyroux, B. P. Roques, M.-C. Fournié-Zaluski, *J. Med. Chem.* **1989**, *32*, 1497; b) D. Seebach, S. Abele, K. Gademann, G. Guichard, T. Hintermann, B. Jaun, J. L. Matthews, J. V. Schreiber, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1998**, *81*, 932.

[6] W.-B. Wang, E. J. Roskamp, *J. Am. Chem. Soc.* **1993**, *115*, 9417 and references therein.

[7] Reviews on asymmetric synthesis of β-amino acids and α-substituted β-amino acids: a) *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), VCH, Weinheim, **1997**; b) E. Juaristi, D. Quintana, J. Escalante, *Aldrichim. Acta* **1994**, *27*, 3; c) D. C. Cole, *Tetrahedron* **1994**, *50*, 9517; d) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1996**, 117.

[8] Examples of asymmetric synthesis of α-alkyl-β-amino carbonyl compounds based on diastereoselective enolate-imine condensations: a) D. J. Hart, C.-S. Lee, W. H. Pirkle, M. H. Hyon, A. Tsipouras, *J. Am. Chem. Soc.* **1986**, *108*, 6054; b) C. Gennari, I. Venturini, G. Gislon, G. Schimperna, *Tetrahedron Lett.* **1987**, *28*, 227; c) T. Yamada, H. Suzuki, T. Mukaiyama, *Chem. Lett.* **1987**, 293; d) D. A. Evans, F. Urpí, T. C. Sommers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, *112*, 8215; e) E. J. Corey, C. P. Decicco, R. C. Newbold, *Tetrahedron Lett.* **1991**, *32*, 5287; f) K. Hattori, M. Miyata, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 1151; g) D. Enders, D. Ward, J. Adam, G. Raabe, *Angew. Chem.* **1996**, *108*, 1059; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 981; h) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060.

[9] Catalytic diastereo- and enantioselective synthesis of α-alkyl-β-amino units derived from α-imino esters: D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury III, L. Ryzhkov, A. E. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 67.

[10] Catalytic asymmetric direct Mannich reactions were recently reported: a) S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron* **1999**, *55*, 8857; b) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083; *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2995; c) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827.

[11] Some methods using diastereoselective hydrogenation and kinetic resolution of α-(α-aminoalkyl)acrylates were also reported: a) J. M. Brown, A. P. James, L. M. Prior, *Tetrahedron Lett.* **1987**, *28*, 2179; b) M. Takagi, K. Yamamoto, *Tetrahedron* **1991**, *47*, 8869.

[12] For asymmetric synthesis of α-methyl-β-amino units using catalytic enantioselective Mannich reactions of simple imines with enolate components, only one example was reported to the best of our knowledge, but regioselectivity was moderate (see ref. [10c]).

[13] a) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153; b) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431; c) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8180; d) S. Kobayashi, H. Ishitani, Y. Yamashita, M. Ueno, H. Shimizu, *Tetrahedron* **2001**, *57*, 861.

[14] Ketene silyl acetals derived from alkyl esters gave lower selectivity.

[15] Similar effects of the pentafluoroethyl group has been observed in a different catalyst system: a) Y. Yamashita, S. Saito, H. Ishitani, S. Kobayashi, *Org. Lett.* **2002**, *4*, 1221; b) Y. Yamashita, H. Ishitani, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 3292.

[16] *anti*-Selectivity was remarkable because *syn*- and *anti*-selectivity was observed in the reactions of α-*tert*-butyldimethylsilyloxy and α-benzyloxy ketene silyl acetals, respectively. It was reported in aldol reactions that *syn*-selectivity was obtained in the reactions of propionate components and α-*tert*-butyldimethylsilyloxy ketene silyl acetals, while only α-benzyloxy ketene silyl acetals gave *anti*-adducts: T. Mukaiyama, I. Shiina, H. Uchiro, S. Kobayashi, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708.

[17] K. Bhattarai, G. Cainelli, M. Panunzio, *Synlett* **1990**, 229.

[18] S. G. Davies, I. A. S. Walters, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1129.

[19] D. R. Kronenthal, C. Y. Han, M. K. Taylor, *J. Org. Chem.* **1982**, *47*, 2765.

[20] M. Fernández-Suárez, L. Muñoz, R. Fernández, R. Riguera, *Tetrahedron: Asymmetry* **1997**, *8*, 1847.

[21] K. Ikeda, Y. Terao, M. Sekiya, *Chem. Pharm. Bull.* **1981**, *29*, 1747.

[22] a) D. Tanner, P. Somfai, *Tetrahedron* **1988**, *44*, 619; b) C. Gennari, P. G. Cozzi, *J. Org. Chem.* **1988**, *53*, 4015; c) C. Mukai, O. Kataoka, M. Hanaoka, *J. Chem. Soc. Perkin Trans. 1* **1993**, 563; d) Y. Kita, N, Shibata, N. Kawano, T. Tohjo, C. Fujimori, K. Matsumoto, S. Fujita, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2405.

[23] D. Favara, A. Omodei-Salè, P. Consonni, A. Depaoli, *Tetrahedron Lett.* **1982**, *23*, 3105.

[24] Recent reports of asymmetric synthesis of (+)-PS-5: a) H. Ishibashi, K. Kodama, C. Kameoka, H. Kawanami, M. Ikeda, *Tetrahedron* **1996**, *52*, 13867; b) O. Miyata, Y. Fujiwara, I. Ninomiya, T. Naito, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2167; c) N. Kise, N. Ueda, *Org. Lett.* **1999**, *1*, 1803.

[25] R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868.

[26] H. Emde, G. Simchen, *Liebigs Ann. Chem.* **1983**, 816.

Received: May 21, 2002 [F4108]

