Wittig Reaction with *N*-Protected 3-(Triphenylphosphonio)alaninates: Synthesis of Optically Active (*E*)-(2-Arylvinyl)glycine Derivatives

Taisuke ITAYA,* Takehiko IIDA, Shigeyuki SHIMIZU, Akemi MIZUTANI, Masatoshi MORISUE, Yasushi SUGIMOTO, and Michiko TACHINAKA

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan.
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(*R*)-[2-Carboxy-2-[(methoxycarbonyl)amino]ethyl]triphenylphosphonium chloride (1) was converted by treatment with anion exchange resin (HCO_3^-) into the inner salt 13h, which gave a better yield (43%) than 1 in the Wittig reaction with benzaldehyde to afford the [*S*-(*E*)]-(2-phenylvinyl)glycine derivative 24. The inner salt 13i bearing an *N*-benzyloxycarbonyl group was prepared by hydrogenolysis of (*R*)-[3-benzyloxy-2-[(benzyloxycarbonyl)amino]-3-oxopropyl]triphenylphosphonium chloride (11e) over palladium on carbon, followed by dehydrochlorination. Hydrogenolysis of 11e over Pearlman's catalyst afforded the unprotected phosphonium chloride 12 (X = Cl). *N*-*tert*-Butoxycarbonylation of 12 followed by dehydrochlorination afforded 13j, which was more efficiently prepared through hydrogenolysis of (*R*)-[3-benzyloxy-2-[(*tert*-butoxycarbonyl)amino]-3-oxopropyl]triphenylphosphonium chloride (11f).

The usefulness of 13h—j as building blocks for the synthesis of configurationally labile (2-arylvinyl)glycine derivatives was exemplified by the Wittig reactions with piperonal, which exclusively afforded the (*E*)-isomers 18h—j with high optical purity in 28—39% yield.

Keywords (*S*)-(2-arylvinyl)glycine; Wittig reaction; (*R*)-3-(triphenylphosphonio)alaninate; β,γ-unsaturated amino acid; stereoselective olefination

There has been considerable interest in β,γ-unsaturated α-amino acids because of their biological importance[1] and use as synthetic intermediates.[2] Nonetheless, chiral synthesis of this class of compounds is still a challenging problem, owing to a marked tendency to racemization and isomerization to the corresponding α,β-dehydro amino acids[3]; only a few general methods of synthesizing optically active β,γ-unsaturated amino acids have been elaborated.[1q,s-v,4-7] We have already achieved syntheses of wybutine (**3**: R = H)[2t,u] and hydroxywybutine (**3**: R = OH),[2v] hypermodified bases of phenylalanine transfer ribonucleic acids, by using the Wittig reaction with **1** as the key step, as shown in Chart 1. The intermediate (*E*)-(2-arylvinyl)glycine derivative **2** was obtained in a completely stereoselective manner in 16% yield. Although complete stereoselectivity was also realized in the Wittig reaction of **1** with benzaldehyde, [*S*-(*E*)]-2-[(methoxycarbonyl)amino]-4-phenyl-3-butenoic acid was obtained as the methyl ester **28** in only 28% yield.[2u] Recently, Elder's[1l] and Sibi's groups[6] attained excellent yields in similar reactions by employing modified reagents **4** and **5**, respectively. However, the reaction with **4** is a racemic synthesis; from **5**, the desired amino acids would be obtained only after hydrolysis of the oxazolidinone ring, followed by oxidation. Although the Wittig reaction with **1** has the merits of straightforwardness, high stereoselectivity, and mild reaction conditions, we felt that **1** should be modified in order to improve the yield. Furthermore, it is necessary to replace the *N*-methoxycarbonyl group of **1** with a better protecting group if this method is to be utilized as a general synthesis of β,γ-unsaturated amino acids. We report herein syntheses of some phosphonium salts and the optical purities of the products obtained in the Wittig reactions using these reagents.

We first converted **1** into the inner salt **13h** by the use of Amberlyst A-26 (HCO_3^-). For a shorter synthesis of **13h**, **10d** was treated with the ion exchanger (HCO_3^-) prior to hydrogenolysis to afford products through β-elimination: benzyl 2-[(methoxycarbonyl)amino]propenoate[8] (40%) and triphenylphosphine (35%). The inner salt structure **13h** is supported by the negative Beilstein test and the appearance of an absorption band at 1630 cm^{-1} due to the carboxylate ion instead of that expected for the carbonate ion at 1750—1770 cm^{-1}. The structural change is also reflected in the difference between the ^{1}H-NMR spectrum of **13h** and that of **1**[9]; the latter resembles those of the esters **10c, d**,[2u] whereas the α- and β-protons of **13h** are more shielded. When the Wittig reaction was conducted with **13h** in a mixture of tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) using two molar equivalents of *n*-butyllithium, the yield of **24** was raised to 43%. Even equimolar use of the base afforded **24**, although

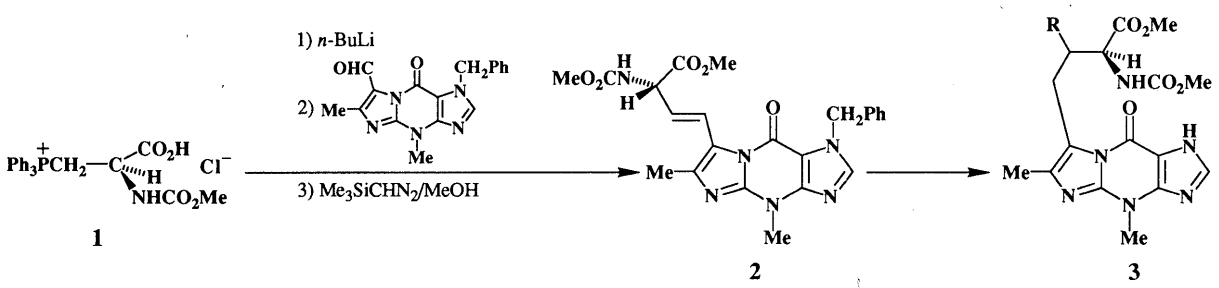
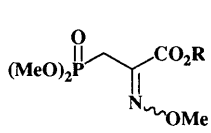


Chart 1



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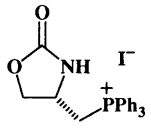

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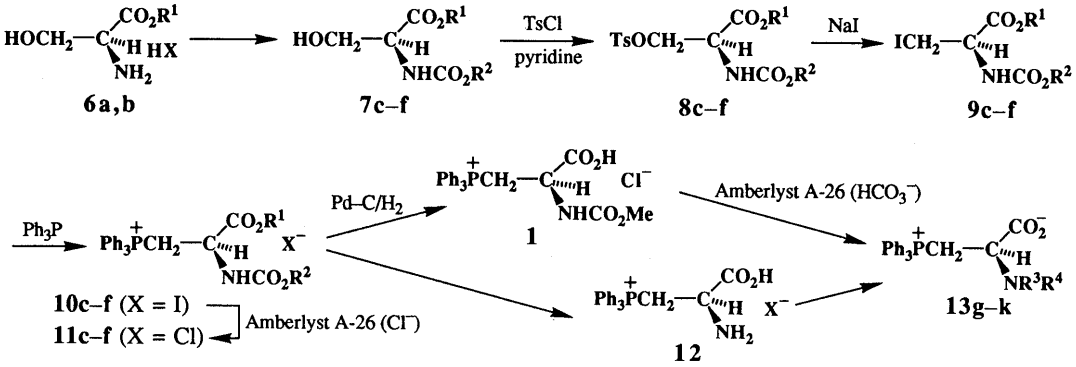
the yield was lowered to 27%. These reactions proved completely (*E*)-selective.

We next attempted to prepare the inner salts bearing better *N*-protecting groups: 2-[(benzyloxycarbonyl)amino]- (**13i**), 2-[(*tert*-butoxycarbonyl)amino]- (**13j**), 2-(phthaloylamino)- (**13k**), and 2-[(9-phenylfluoren-9-yl)amino]-3-(triphenylphosphonio)propanoate (**13l**). Our initial plan for obtaining **13i**—**l** was to modify the amino group of the unprotected phosphonium salt **12** or **13g**. For the preparation of **12**, **10c**[2u] was heated with trimethylsilyl iodide in chloroform.[10] Although smooth removal of one methyl group was observed by NMR spectroscopy upon short treatment, further heating under reflux gave a complex mixture of products. Heating **10c** with trimethylsilyl chloride[11] or trichloromethylsilane[12] in acetonitrile in the presence of sodium iodide did not give better results.

To circumvent this obstacle, we turned to debenzylation of **10e**, which was obtained from **9e**.[13] Heating **10e** with trichloromethylsilane in acetonitrile in the presence of sodium iodide[12] again afforded a complex mixture of products. Although treatment of **10e** with boron tribromide according to the reported procedure[14] followed by treatment with ion exchange resin afforded crude **13g**, purification of this product was unsuccessful. We then converted the iodide **10e** into the chloride **11e**. When **11e** was hydrogenated over 10% palladium on carbon in ethanol at room temperature under atmospheric pressure, the benzyl group at the carboxylate ester moiety was selectively removed. Purification of the product by chromatography on silica gel was accompanied with dehydrochlorination, to afford the inner salt **13i** [$[\alpha]_D^{23}$ +95° (c=0.46, $CHCl_3$)] in 71% yield. The inner salt structure was supported by the negative Beilstein test, and the IR and ^{1}H-NMR spectral similarities to **13h**. Continuation of the catalytic hydrogenolysis by the addition of perchloric acid afforded **12**·$HClO_4$ (X=Cl or ClO_4) in *ca.* 30% yield. With Pearlman's catalyst, both benzyl groups were removed in the absence of perchloric acid to afford **12** (X=Cl) in 40% yield. Complete deprotection of **10e** or **11e** was achieved more efficiently by heating in 6 N hydrochloric acid at the cost of optical purity (*vide infra*): **12**·HCl (X=Cl) was obtained in 82% yield from **11e**. Treatment of **12**·HCl with Amberlyst A-26 (HCO_3^-) afforded the inner salt **13g** as the sesquihydrate. The IR spectrum of this compound did not show the absorption band due to its carbonate ion structure. This compound did not evolve carbon dioxide on the addition of hydrochloric acid. Its aqueous solution was alkaline (pH 8—9) and negative to the Beilstein test. All these criteria supported the inner salt structure **13g** for this compound.

With the unprotected phosphonium compounds **12** and **13g** in hand, we next tried to prepare **13j**—**l** by protecting the amino group of **12** or **13g**. Before these experiments we carried out benzyloxycarbonylation of **12**·HCl (X=Cl) in order to estimate its optical purity. The specific rotation [$[\alpha]_D^{28}$ +88° (c=0.45, $CHCl_3$)] of **13i**, thus obtained was smaller than that (*vide supra*) of **13i** prepared through hydrogenolysis of **11e**, indicating that the hydrolysis of **11e**



a: R^1 = Me, X = Cl
b: R^1 = $PhCH_2$, X = TsO

c: R^1 = R^2 = Me
d: R^1 = $PhCH_2$, R^2 = Me
e: R^1 = R^2 = $PhCH_2$
f: R^1 = $PhCH_2$, R^2 = Me_3C

g: R^3 = R^4 = H
h: R^3 = H, R^4 = MeOCO
i: R^3 = H, R^4 = $PhCH_2OCO$
j: R^3 = H, R^4 = Me_3COCO
k: R^3R^4 = phthaloyl

Chart 2

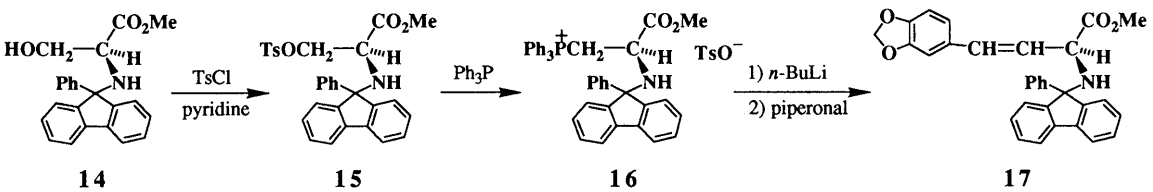


Chart 3

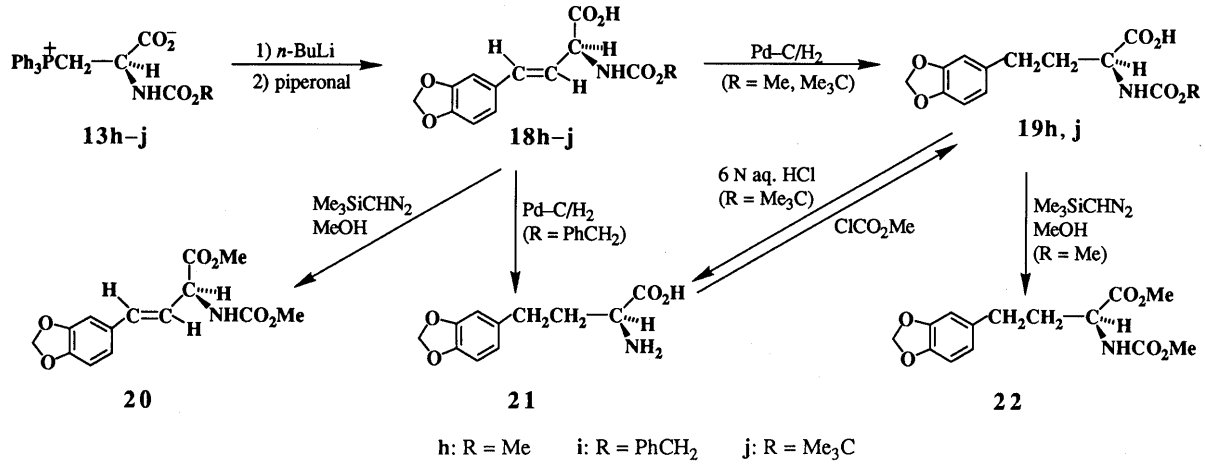
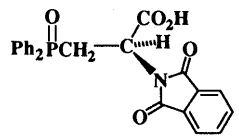


Chart 4

with hydrochloric acid had been accompanied with partial racemization. Treatment of **12** (X=Cl) with di-*tert*-butyl dicarbonate[15] followed by dehydrochlorination afforded **13j**. Alternatively, **13j** was synthesized by hydrogenolysis of **11f**, which was prepared from **6b** as shown in Chart 2. Compound **13k** was prepared from **12**·HCl according to the procedure reported for the *N*-phthaloylation.[16] Compound **13l**, however, was not obtained by *N*-alkylation of either **12** or **13g** with 9-bromo-9-phenylfluorene.[17] We then attempted to prepare **13l** *via* its methyl ester **16**. For the synthesis of **16**, **14**[18] was treated with *p*-toluenesulfonyl chloride in pyridine to afford **15** in 90% yield. Heating **15** with triphenylphosphine in toluene at 80 °C afforded **16** in 47% yield. The tosylate **15** was treated with sodium iodide in acetone to provide the more reactive iodide, affording a complex mixture of products. Selective removal of the methyl group from **16** by treatment with boron tribromide[14] was unsuccessful: the 9-phenylfluoren-9-yl group was also lost during this treatment.

In order to evaluate the usefulness of the new phosphonium salts **13i—k** and **16** as the Wittig reagents, we compared the reactions of these compounds with that of **13h** using piperonal as the carbonyl component. The Wittig reactions with **13h—j** were initiated at −70 °C by using two molar equivalents of *n*-butyllithium in THF–HMPA, then the reaction temperature was allowed to rise to 0 °C. Each reaction afforded the corresponding (*E*)-olefin **18** exclusively. The yields of **18h** and **18i** were nearly the same (38% and 39%); **18j** was obtained in 28% yield. When the reaction of **13k** with piperonal was similarly performed



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using one molar equivalent of *n*-butyllithium, we merely obtained degradation products of **13k** [compound **23**[19] (18%), phthalimide (42%), and triphenylphosphine oxide (7%)] besides piperonal (82%). On the other hand, the reaction with **16** in THF using one molar equivalent of *n*-butyllithium afforded a mixture of equal amounts of the (*E*)- and (*Z*)-olefins **17** in 12% yield, although no successful Wittig reaction with a phosphonium salt bearing an alkoxycarbonyl group at the *β*-position had been reported owing to the lability toward *β*-elimination.[2t,u] The unusual stability of **16** to *β*-elimination is probably due to the *N*-protecting group, which prevents deprotonation at the asymmetric center.[17]

Having established that **13h—j** were useful for the stereoselective synthesis of (*E*)-(2-arylvinyl)glycine derivatives, we next focused our attention on determination of the optical purities of the products **18h—j**. We first attempted to establish a method of determining the optical purity of **24**,[2u] because this compound should be easily correlated to commercially available **26**. As shown in Chart 5, (±)-**25** and (±)-**29** were prepared from (±)-**26**. Attempts to discriminate the enantiomers of (±)-**25** or (±)-**29** by means of ^{1}H-NMR spectroscopy using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) were

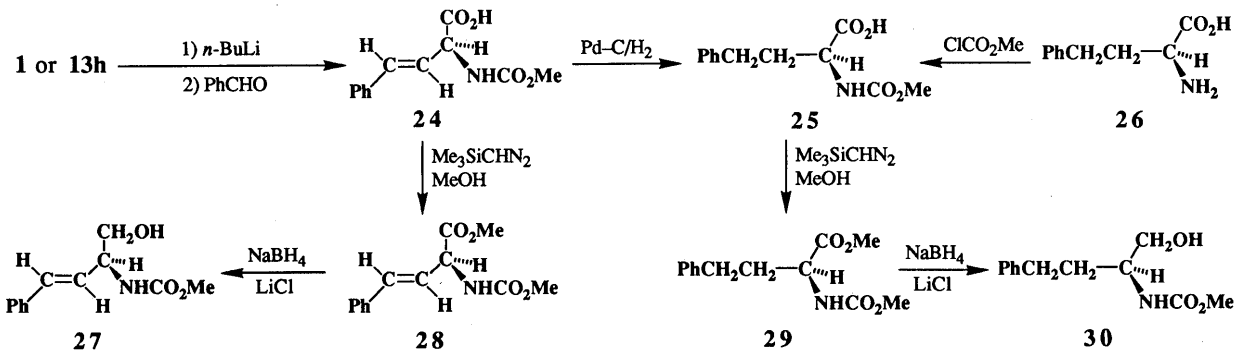


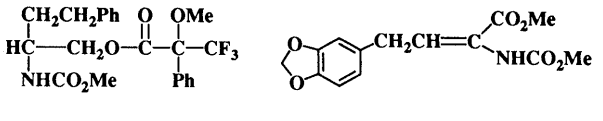
Chart 5

unsuccessful. Assuming that amino acids bearing an *N*-(alkoxycarbonyl) group stereospecifically undergo enzymatic digestion at the carbamate moiety, the reaction can be used for determining the optical purity of compounds of this type. *N*-(Methoxycarbonyl)-L-alanine indeed underwent hydrolysis catalyzed by Acylase I in 0.1 M phosphate buffer (pH 7.0) at 38 °C, as had been reported,[20] whereas the D-isomer was inert under the same conditions. Unfortunately, when (±)-**25** was the substrate, the stereospecificity of hydrolysis catalyzed by this enzyme was not high enough for estimating the optical purity of **25**.

We next converted (±)-**29** into a diastereomeric mixture **31** by borohydride reduction followed by esterification with (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[21] Although the diastereomers **31** could not be distinguished from each other by ^{1}H-NMR spectroscopy, they could be separated by HPLC. Thus, we found that [*R*-(*R**,*S**)]-**31** prepared from **26** was pure, whereas the isomer ratio of **31** prepared from **24** through **25** was *ca.* 96:4. We supposed that racemization to the extent of 8% had occurred during the work-up procedure after the Wittig reaction: we had heated **24** at 80—90 °C to remove HMPA by evaporation. When the double bond of **24** was saturated without removal of HMPA and the resulting **25** was transformed into [*R*-(*R**,*S**)]-**31**, the amount of the isomer in this sample of **31** was indeed reduced to *ca.* 1%. We finally determined the optical purity of **29** (*ca.* 98% ee) more conveniently, using an optically active column (Sumichiral OA-4600). For similar analysis of the 3,4-methylenedioxy compound **22**, (±)-**22** is necessary. This compound was prepared through racemization of **20** followed by catalytic hydrogenation; on treatment with triethylamine in methanol, **20** underwent rapid racemization and slow isomerization to **32**. Compound (±)-**22** thus obtained, was cleanly resolved by using the same optically active column. According to this HPLC analysis, **22** was optically pure unless it had been derived from heated **18h**, showing that **18h** was configurationally more stable than **24**. We similarly examined the optical purity of **18i,j** by transforming them into **22** as illustrated in Chart 4. Both samples of **22** were of *ca.* 99% ee.

Rapid racemization of *N*-protected (2-arylvinyl)glycine esters under basic conditions observed with **20** was also realized in the borohydride reduction of **28**: the almost racemized alcohol **27** was obtained in good yield, showing that **28** underwent racemization much faster than isomerization to the α,β-unsaturated compound under basic conditions. Such configurational lability of **28** might be caused by the enhanced acidity of the α-methine: the conjugate base **33** should be stabilized by resonance, as depicted in Chart 6. The β,γ-unsaturation should stabilize the enolate form **34** and the phenyl group at the γ-position might be an extra factor stabilizing the enolate. On the other hand, thermal racemization of the free acid **24** probably takes place through acid-catalyzed enolation to **36**, which should be stabilized by conjugation with the styrene moiety. If this is the case, the electronic structure of the aromatic moiety of **24** should affect the rate of racemization, because it concerns the acidity of the α-methine of **24**·H$^+$. We can thus rationalize the fact that **18h** bearing an electron-rich aryl group undergoes racemization more slowly than **24**.

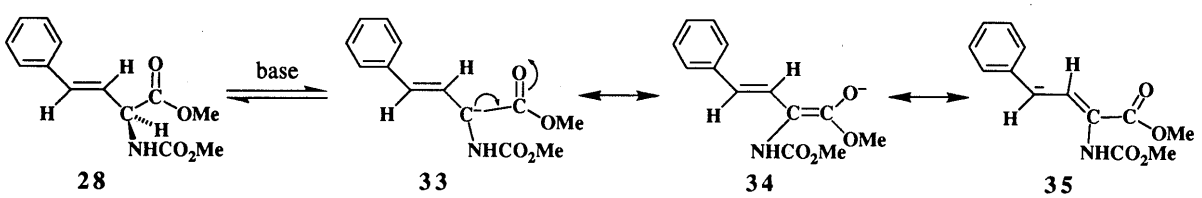
In conclusion, we have prepared 2-[(alkoxycarbonyl)-amino]-3-(triphenylphosphonio)propanoates (**13h—j**) from (*S*)-serine through **11d—f** as shown in Chart 2. In the Wittig reactions with piperonal, these phosphonium salts **13h—j** afforded **18h—j** with high optical purities in a completely stereoselective manner. The present method is useful for syntheses of configurationally labile (*E*)-(2-arylvinyl)glycine derivatives. Syntheses of 3-β-D-ribofuranosides of **3** and related compounds according to this method are in progress.



31 **32**

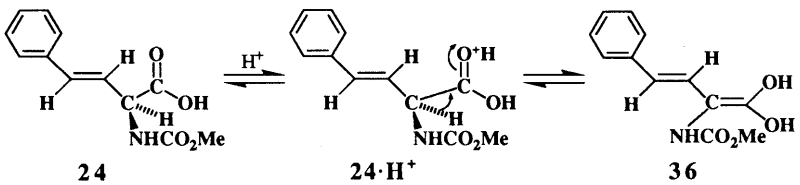
Experimental

General Notes All melting points were taken on a Yamato MP-1 or a Büchi 530 capillary melting point apparatus and are corrected. IR spectra and mass spectra (MS) were recorded on a JASCO A-202 IR spectrophotometer and a Hitachi M-80 mass spectrometer. NMR spectra were measured with JEOL JNM-PMX-60 (at 35 °C), JEOL JNM-FX-100 (at 25 °C), JEOL JNM-EX-270 (at 23—27.5 °C), and JEOL JNM-GSX-500 (27 °C) NMR spectrometers with tetramethylsilane as an internal standard; unless otherwise stated, they were recorded at 100 MHz. Optical rotations were measured with a JASCO DIP-181 polarimeter using a 1-dm sample tube. The liquid chromatographic system was a Waters model 204 ALC which included a 6000A pump, a U6K injector, and a model 440 absorbance detector operating at 254 nm. Microanalyses were conducted by Mr. Y. Itatani and his associates at Kanazawa University. Pre-coated silica gel plates (0.25 mm) with a fluorescent indicator (Merck) were used for



28 **33** **34** **35**

Chart 6



24 **24**·H$^+$ **36**

Chart 7

analytical thin-layer chromatography (TLC). Flash chromatography was performed on silica gel according to the reported procedure.[22] The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-doublets-of-doublets, dddd = doublet-of-doublets-of-doublets-of-doublets, dt = doublet-of-triplets, m = multiplet, q = quartet, s = singlet, t = triplet.

(*S*)-*N*-(Benzyloxycarbonyl)serine Benzyl Ester (7e) Compound **6b**[23] (5.34 g, 14.5 mmol) was dissolved in a solution of sodium bicarbonate (3.65 g, 43.4 mmol) in water (43 ml). Benzyl chloroformate (2.97 g, 17.4 mmol) was added to the solution under cooling in ice water. The mixture was then stirred at room temperature for 2 h. After neutralization with 10% hydrochloric acid, the resulting mixture was extracted with benzene (2 × 50 ml). The organic phases were combined, washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated *in vacuo* to afford **7e** (4.42 g, 92%) as a colorless solid, mp 74—81 °C. Recrystallization of crude **7e** from diethyl ether afforded an analytical sample of **7e** as colorless needles, mp 82—83 °C (lit.[24] mp 84—85 °C); $[\alpha]_D^{21}$ +6.14° (c=4.10, $CHCl_3$) [lit.[24] $[\alpha]_D$ +5.7° (c=4, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 2.21 (1H, br t, J=4 Hz, OH), 3.94 (2H, br, $C\underline{H}_2CH$), 4.47 (1H, dt, J=7, 4 Hz, $CH_2C\underline{H}$), 5.11 (2H, s, $PhC\underline{H}_2$ of the carbamate ester), 5.20 (2H, s, $PhC\underline{H}_2$ of the carboxylate ester), 5.72 (1H, d, J=7 Hz, NH), 7.34 (10H, s, two Ph's). *Anal.* Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.54; H, 5.73; N, 4.20.

(*S*)-*N*-(*tert*-Butoxycarbonyl)serine Benzyl Ester (7f) Sodium bicarbonate (59.5 g, 708 mmol) and **6b**,[23] which was prepared from (*S*)-serine (24.82 g, 23.6 mmol), were dissolved in a mixture of dioxane (450 ml) and water (450 ml). Di-*tert*-butyl dicarbonate (56.7 g, 26 mmol) was added to the cold solution, and the whole was stirred at room temperature for 2 h. The resulting solution was concentrated *in vacuo* to *ca.* 600 ml, and extracted with benzene (2 × 300 ml). The organic layers were combined, washed with water (4 × 150 ml), dried over magnesium sulfate, and concentrated *in vacuo* to leave a slightly yellow syrup. This was crystallized by treating it with hexane (50 ml). The resulting precipitate was collected by filtration to afford **7f** (65.14 g, 93% based on serine) as a colorless solid, mp 56—64 °C. Recrystallization from hexane–ether (2 : 1, v/v) afforded an analytical sample of **7f** as colorless needles, mp 66.5—68 °C (lit.[25] mp 69—70 °C); $[\alpha]_D^{26}$ −18.4° (c=2.01, MeOH) [lit.[25] $[\alpha]_D^{23}$ −18.9° (c=2, MeOH); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s, CMe_3), 2.08 (br, OH), 3.91 (1H, dd, J=11.2, 3.5 Hz) and 3.98 (1H, dd, J=11.2, 4.0 Hz), ($C\underline{H}_2CH$), 4.42 (1H, br, $CH_2C\underline{H}$), 5.21 and 5.22 (1H each, d, J=12.5 Hz, $PhC\underline{H}_2$), 5.46 (1H, br, NH), 7.36 (5H, s, Ph). *Anal.* Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.07; H, 7.52; N, 4.76.

(*S*)-*N*-(Benzyloxycarbonyl)-*O*-(*p*-toluenesulfonyl)serine Benzyl Ester (8e) This compound was prepared from **7e** according to the reported procedure[26] in 81% yield, mp 72.5—75.5 °C. Recrystallization from ethanol afforded an analytical sample of **8e** as colorless needles, mp 75.5—77.5 °C (lit.[26] mp 75.5—77 °C); $[\alpha]_D^{27}$ −6.33° (c=2.02, DMF) [lit.[26] $[\alpha]_D^{24}$ −7.41° (c=2, DMF)]; ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, Me), 4.34 and 4.44 (1H each, dd, J=10, 3 Hz, $C\underline{H}_2CH$), 4.58 (1H, ddd, J=3, 3, 7 Hz, $CH_2C\underline{H}$), 5.07 (2H, s, $PhC\underline{H}_2$ of the carbamate ester), 5.09 and 5.18 (1H each, d, J=12 Hz, $PhC\underline{H}_2$ of the carboxylate ester), 5.56 (1H, d, J=7 Hz, NH), 7.29 (2H, m, phenyl protons *meta* to the sulfonyl group), 7.34 (10H, s, two Ph's), 7.70 (2H, m, phenyl protons *ortho* to the sulfonyl group). *Anal.* Calcd for $C_{25}H_{25}NO_7S$: C, 62.10; H, 5.21; N, 2.90. Found: C, 61.98; H, 4.99; N, 2.72.

(*S*)-*N*-(*tert*-Butoxycarbonyl)-*O*-(*p*-toluenesulfonyl)serine Benzyl Ester (8f) Compound **8f**[27] (7.69 g, 98%) was prepared from **7f** (5.13 g, 17.4 mmol) as a colorless solid, mp 87—89 °C, in a manner similar to that reported for the synthesis of **8d**.[2u] Recrystallization of crude **8f** from isopropanol afforded an analytical sample of **8f** as colorless needles, mp 92.5—93.5 °C, $[\alpha]_{365}^{17}$ +2.1° (c=1.00, MeOH); ^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s, CMe_3), 2.43 (3H, s, $\underline{Me}Ph$), 4.20—4.62 (3H, m, CH_2CH), 5.09 and 5.18 (1H each, d, J=12 Hz, $PhC\underline{H}_2$), 5.31 (1H, d, J=8 Hz, NH), 7.31 (2H, d, J=10 Hz, phenyl protons *meta* to the sulfonyl group), 7.33 (5H, s, $\underline{Ph}CH_2$), 7.71 (2H, d, J=10 Hz, phenyl protons *ortho* to the sulfonyl group). *Anal.* Calcd for $C_{22}H_{27}NO_7S$: C, 58.78; H, 6.05; N, 3.12. Found: C, 58.55; H, 6.12; N, 3.08.

(*R*)-*N*-(Benzyloxycarbonyl)-3-iodoalanine Benzyl Ester (9e) This compound was prepared from **8e** according to the reported procedure[28] in 97% yield, mp 75—77 °C. Recrystallization of crude **9e** from methanol afforded an analytical sample as colorless needles, mp 78.5—80 °C (lit.[28] 76—77 °C); $[\alpha]_{546}^{24}$ −24.9° (c=2.00, DMF) [lit.[28] $[\alpha]_{546}^{25}$ −24.6° (c=2.03, DMF)]; ^{1}H-NMR ($CDCl_3$) δ: 3.59 (2H, d, J=4 Hz, ICH_2), 4.60 (1H, dt, J=4, 7 Hz, CH), 5.13 (2H, s, $PhC\underline{H}_2$ of the carbamate ester), 5.21 (2H, s, $PhC\underline{H}_2$ of the carboxylate ester), 5.63 (1H, d, J=7 Hz, NH), 7.36 (10H, m, two Ph's). *Anal.* Calcd for $C_{18}H_{18}INO_4$: C, 49.22; H, 4.13; N, 3.19. Found: C, 49.17; H, 3.99; N, 3.01.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-3-iodoalanine Benzyl Ester (9f) Compound **9f**[29] (7.79 g, 96%) was prepared as a yellow solid, mp 77—79 °C, in a manner similar to that reported for the synthesis of **9d**.[2u] Recrystallization from methanol afforded an analytical sample of **9f** as colorless needles, mp 79—79.5 °C; $[\alpha]_D^{19}$ −20.5° (c=1.00, MeOH); ^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s, CMe_3), 3.56 (2H, d, J=4 Hz, $C\underline{H}_2CH$), 4.52 (1H, m, CH), 5.19 (2H, s, $PhC\underline{H}_2$), 5.32 (1H, br, NH), 7.35 (5H, s, Ph). *Anal.* Calcd for $C_{15}H_{20}INO_4$: C, 44.46; H, 4.97; N, 3.46. Found: C, 44.52; H, 5.04; N, 3.37.

(*R*)-[3-Benzyloxy-2-[(benzyloxycarbonyl)amino]-3-oxopropyl]triphenylphosphonium Iodide (10e) A solution of **9e** (5.09 g, 11.6 mmol) and triphenylphosphine (3.35 g, 12.8 mmol) in dry toluene (42 ml) was kept at 35 °C for 7 d. The resulting oil was collected by decantation, washed with toluene (5 × 3 ml), and dried by suction to afford **10e** (2.39 g) as a colorless foam. The mother liquor and the washings were combined and concentrated to *ca.* 20 ml. The solution was kept at 35 °C for a further 7 d, and the resulting precipitate was treated in the same way as described for obtaining the first crop to afford a second crop (5.44 g; the total yield was 96%) of **10e** as an almost colorless foam. Crude **10e** thus obtained was suitable for use as an intermediate, although it was found by TLC to contain traces of other substances. A portion (2.72 g) of crude **10e** was purified by flash chromatography [column diameter, 50 mm; chloroform–methanol (10 : 1, v/v)] to afford pure **10e** (2.16 g) as a colorless foam, $[\alpha]_{365}^{27}$ −25.5° (c=0.505, $CHCl_3$); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 3.90 (1H, ddd, J=3.0, 12.9, 15.8 Hz, P^+CH), 4.82 and 4.85 (1H each, d, J=12.5 Hz, $PhC\underline{H}_2$ of the carbamate ester), 4.89 (1H, dddd, J=3.0, 8.9, 9.6, 12.9 Hz, $P^+CH_2C\underline{H}$), 5.11 (1H, ddd, J=9.6, 13.2, 15.8 Hz, P^+CH), 5.15 and 5.17 (1H each, d, J=12.4 Hz, $PhC\underline{H}_2$ of the carboxylate ester), 7.15—7.35 (10H, m, two $\underline{Ph}CH_2$'s), 7.39 (1H, d, J=8.9 Hz, NH), 7.55—7.89 (15H, m, Ph_3P^+).

(*R*)-[3-Benzyloxy-2-[(*tert*-butoxycarbonyl)amino]-3-oxopropyl]triphenylphosphonium Iodide (10f) A solution of **9f** (8.10 g, 20 mmol) and triphenylphosphine (5.77 g, 22 mmol) in dry toluene (60 ml) was kept at 50 °C for 6 d. The oily precipitate that resulted was collected by decantation, washed with toluene, and dried to give a slightly yellow foam (9.87 g). The mother liquor and the washings were combined, concentrated to *ca.* 30 ml, and kept at 50 °C for a further 5 d to give a second crop (3.62 g) of **10f**. The mother liquor was concentrated to *ca.* 15 ml and kept at 50 °C for another 5 d to afford a third crop (1.76 g) of **10f**. Flash chromatography [chloroform–methanol (25 : 1, v/v)] of crude **10f** afforded **10f** (7.27 g, 54%) as a colorless foam, $[\alpha]_D^{21}$ +12.9° (c=0.806, $CHCl_3$); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s, CMe_3), 3.94 (1H, m, P^+CH), 4.76—5.24 (2H, m, P^+CHCH), 5.13 and 5.16 (1H each, d, J=12.5 Hz, $PhC\underline{H}_2$), 6.73 (1H, d, J=9 Hz, NH), 7.2—7.4 (5H, m, $\underline{Ph}CH_2$), 7.6—7.9 (15H, m, Ph_3P^+).

(*R*)-[3-Benzyloxy-2-[(benzyloxycarbonyl)amino]-3-oxopropyl]triphenylphosphonium Chloride (11e) A solution of **10e** (196 mg, 0.279 mmol) in 50% (v/v) aqueous ethanol (10 ml) was passed through a column packed with Amberlyst A-26 (Cl^-) (2.2 ml) and the column was eluted with 50% (v/v) aqueous ethanol. The UV-absorbing (254 nm) eluates were combined and concentrated *in vacuo* to leave **11e** (165 mg, 97%) as a colorless glass, $[\alpha]_D^{19}$ +8.3° (c=3.16, $CHCl_3$); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 3.77 (1H, ddd, J=2.6, 13.2, 15.5 Hz, P^+CH), 4.75—4.90 (1H, m, $P^+CH_2C\underline{H}$), 4.80 and 4.84 (1H each, d, J=12.5 Hz, $PhC\underline{H}_2$ of the carbamate ester), 5.15 and 5.17 (1H each, d, J=12.5 Hz, $PhC\underline{H}_2$ of the carboxylate ester), 5.46 (1H, ddd, J=11, 11, 15 Hz, P^+CH), 7.14—7.38 (10H, m, two $\underline{Ph}CH_2$'s), 7.50—7.92 (15H, m, Ph_3P^+), 8.52 (1H, d, J=8.9 Hz, NH).

(*R*)-[3-Benzyloxy-2-[(*tert*-butoxycarbonyl)amino]-3-oxopropyl]triphenylphosphonium Chloride (11f) Compound **10f** (2.04 g, 3.06 mmol) was treated with ion exchange resin in the same way as described for the preparation of **11e** to afford **11f** (1.66 g, 94%) as a colorless foam, $[\alpha]_D^{22}$ +16.9° (c=0.600, $CHCl_3$); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.22 (9H, s, CMe_3), 3.84 (1H, ddd, J=3.0, 13.2, 15.8 Hz, P^+CH), 4.80 (1H, m, $P^+CH_2C\underline{H}$), 5.15 (2H, s, $PhC\underline{H}_2$), 5.38 (1H, ddd, J=9.9, 11.6, 15.8 Hz, P^+CH), 7.31 (5H, m, $\underline{Ph}CH_2$), 7.6—7.9 (16H, m, P^+Ph_3 and NH).

(*R*)-(2-Amino-2-carboxyethyl)triphenylphosphonium Chloride (12: X = Cl) A solution of **11e** (122 mg, 0.2 mmol) in methanol (20 ml) was hydrogenated over Pearlman's catalyst (0.12 g) at room temperature under atmospheric pressure for 1.5 h. The catalyst was filtered off and washed with methanol (20 ml). The filtrate and washings were combined, and concentrated *in vacuo*. The residue (72 mg) was purified by flash chromatography [column diameter, 10 mm; chloroform–methanol–water (20 : 7 : 1, v/v)] to afford **12** (X = Cl) (31 mg, 40%) as a colorless glass, 500 MHz ^{1}H-NMR ($CDCl_3$) δ: 3.58 (2H, m) and 3.98 (1H, m) (CH_2CH),

7.5—7.8 (15H, m, Ph_3P^+).

(*R*)-(2-Amino-2-carboxyethyl)triphenylphosphonium Chloride Hydrochloride (12·HCl: X=Cl) A mixture of **11e** (3.23 g, 5.29 mmol) and 6 N hydrochloric acid (40 ml) was heated under reflux for 2 h. The resulting solution was cooled, washed with chloroform (5 × 35 ml), and concentrated *in vacuo* to leave **12**·HCl (X=Cl) (1.84 g, 82%) as a colorless glass, ^{1}H-NMR ($CDCl_3$) δ: 4.28—4.66 (3H, m, $CHCH_2$), 7.71 (15H, m, Ph_3P^+).

(*R*)-2-Amino-3-(triphenylphosphonio)propanoate (13g) Compound **10e** was prepared from **9e** (5.44 g, 12.4 mmol) and hydrolyzed in a manner similar to that described for the hydrolysis of **11e**. A solution of the resulting **12**·HCl in 50% (v/v) aqueous ethanol (31 ml) was passed through a column packed with Amberlyst A-26 (HCO_3^-) (60 ml). The column was eluted with 50% (v/v) aqueous ethanol. The combined eluate was concentrated *in vacuo* to leave **13g**·3/2H_2O (2.77 g, 59% based on **9e**), mp 110—111 °C (dec.). Recrystallization of this product from a mixture of hexane and ethanol (4:1, v/v) gave an analytical sample of **13g**·3/2H_2O as colorless prisms, mp 128—130 °C (dec.); $[\alpha]_D^{18}$ −22° (*c*=0.220, MeOH); $[\alpha]_{365}^{18}$ −73.3° (*c*=0.220, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3380 and 3320 (NH_2), 1605 and 1581 (COO^- and NH_2); ^{1}H-NMR [$(CD_3)_2SO$] δ: 3.37—4.01 (3H, m, CH_2CH), 7.69 (15H, m, Ph_3P^+). *Anal.* Calcd for $C_{21}H_{20}NO_2P$·3/2H_2O: C, 67.01; H, 6.16; N, 3.72. Found: C, 67.14; H, 6.24; N, 3.77.

When **13g** was dried over phosphorus pentoxide at 70 °C or treated with molecular sieves in chloroform or dichloromethane, it decomposed to unidentified products.

(*R*)-2-[(Methoxycarbonyl)amino]-3-(triphenylphosphonio)propanoate (13h) A solution of **1**[2u] (6.12 g, 13.8 mmol) in 50% (v/v) aqueous ethanol (200 ml) was passed through a column packed with Amberlyst A-26 (HCO_3^-) (105 ml) and the column was eluted with 50% (v/v) aqueous ethanol until the eluate no longer absorbed UV light (254 nm). The combined eluates were concentrated *in vacuo* and the residue was dissolved in chloroform (100 ml). A small amount of insoluble substance was removed by filtration, and the filtrate was concentrated *in vacuo* to leave **13h** (5.60 g, 100%) as a colorless foam, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1707 (carbamate ester), 1630 (carboxylate ion); $[\alpha]_D^{27}$ +119° (*c*=0.508, $CHCl_3$); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s, Me), 3.74 (2H, m, CH_2), 4.32 (1H, m, CH), 6.54 (1H, d, *J*=3.6 Hz, NH), 7.56—7.88 (15H, m, Ph_3P^+).

(*R*)-2-[(Benzyloxycarbonyl)amino]-3-(triphenylphosphonio)propanoate (13i) i) Hydrogenolysis of **11e**: A solution of **11e** (183 mg, 0.3 mmol) in ethanol (15 ml) was hydrogenated over 10% palladium on carbon (186 mg) under atmospheric pressure at room temperature for 4 h. The catalyst was filtered off and washed with hot ethanol. The filtrate and washings were combined and then concentrated *in vacuo*. The residue was purified by flash chromatography [column diameter, 20 mm; chloroform–methanol (5:1, v/v)] to afford **13i** (103 mg, 71%) as a colorless glass, $[\alpha]_D^{23}$ +95° (*c*=0.46, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1707 (carbamate ester), 1632 (carboxylate ion); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 3.64—3.87 (2H, m, $C\underline{H}_2CH$), 4.35 (1H, m, CH), 4.85 and 4.93 (1H each, d, *J*=12.5 Hz, $PhC\underline{H}_2$), 6.61 (1H, d, *J*=4.3 Hz, NH), 7.2—7.4 (5H, m, $\underline{Ph}CH_2$), 7.5—7.8 (15H, m, Ph_3P^+).

In a separate run, flash chromatography with ethyl acetate–methanol (1:1, v/v) was performed to provide a product, which was suggested to be a mixture of **13i** and **13i**·HCl by the Beilstein and silver nitrate tests, and the ^{1}H-NMR spectrum. Treatment of this product with Amberlyst A-26 (HCO_3^-) afforded pure **13i**.

ii) Hydrolysis of **10e** Followed by Benzyloxycarbonylation: Compound **10e** (7.92 g, 11.3 mmol) was hydrolyzed in a manner similar to that described for the hydrolysis of **11e** to afford **12**·HCl (4.69 g). Sodium bicarbonate (392 mg, 4.67 mmol) and a portion of **12**·HCl (400 mg) were dissolved in a mixture of water (3 ml) and dioxane (3 ml). Benzyl chloroformate (199 mg, 1.17 mmol) was then added and the whole was stirred at 0 °C for 1.5 h. The reaction mixture was brought to pH 2 with 10% hydrochloric acid and then extracted with chloroform (3 × 10 ml). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography [column diameter, 30 mm; chloroform–methanol (6:1, v/v)] to afford **13i** (215 mg, 46%), which was identical (^{1}H-NMR) with a sample obtained by method (i); $[\alpha]_D^{28}$ +88° (*c*=0.45, $CHCl_3$). HPLC analysis of **22**, which was prepared from this sample through **18i** in a manner similar to that described below, showed that **13i** thus obtained was of *ca.* 82% ee.

(*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(triphenylphosphonio)propanoate (13j) i) From **11f**: A solution of **11f** (1.57 g, 2.73 mmol) in ethanol (35 ml) was hydrogenated over 10% palladium on carbon (1.57 g) at room temperature for 8 h. More catalyst (0.77 g) was added and the reduction was continued for a further 7 h. The catalyst was filtered off and washed with hot ethanol. The filtrate and the washings were combined and concentrated *in vacuo* to afford **13j**·HCl (1.01 g, 77%) as a light yellow foam, 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.25 (9H, s, CMe_3), 3.96 (1H, m, P^+CH), 4.44—4.85 (2H, m, P^+CHCH), 6.69 (1H, br d, *J*=7 Hz, NH), 7.6—7.9 (15H, m, Ph_3P^+). A portion (0.82 g) of this sample was dissolved in 50% (v/v) aqueous ethanol (20 ml) and the solution was passed through a column packed with Amberlyst A-26 (HCO_3^-) (13 ml). Elution with 50% (v/v) aqueous ethanol and concentration of the eluate *in vacuo* afforded **13j** (0.72 g, 73% overall yield) as a light yellow foam, $[\alpha]_D^{27}$ +112° (*c*=0.395, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1697 (carbamate ester), 1632 (carboxylate ion); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.34 (9H, s, CMe_3), 3.56—3.83 (2H, m, CH_2), 4.27 (1H, m, CH), 6.17 (1H, br, NH), 7.5—7.8 (15H, m, Ph_3P^+).

ii) From **12** (X=Cl): Compound **12** (X=Cl), which was prepared from **11e** (1.10 g, 1.82 mmol) by hydrogenolysis over Pearlman's catalyst, and sodium bicarbonate (0.55 g, 6.5 mmol) were dissolved in a mixture (10 ml) of water and dioxane (1:1, v/v). Di-*tert*-butyl dicarbonate (513 mg, 2.35 mmol) was added to the solution with cooling with ice, and the whole was stirred at room temperature for 5 h. The resulting mixture was concentrated *in vacuo* to a small volume, brought to pH 2 with 10% hydrochloric acid and then extracted with dichloromethane (10 × 10 ml). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*. Purification of the residue by flash chromatography [column diameter, 30 mm; chloroform–methanol (5:1, v/v)] gave **13j** (571 mg, 70%).

(*R*)-2-(1,3-Dioxo-2-azaindan-2-yl)-3-(triphenylphosphonio)propanoate (13k) Crude **10e** (7.92 g, 11.3 mmol) was hydrolyzed with 6 N hydrochloric acid in a manner similar to that described for the preparation of **12**·HCl (X=Cl) to afford **12**·HCl (4.69 g) as a yellowish foam. *N*-(Ethoxycarbonyl)phthalimide (188 mg, 0.86 mmol) was added to a mixture of **12**·HCl (400 mg) and triethylamine (0.22 ml) in anhydrous dimethyl sulfoxide (2 ml). The whole was stirred at room temperature for 4 h. The resulting mixture was neutralized with 10% aqueous phosphoric acid and partitioned between water (8 ml) and chloroform (12 ml). The aqueous layer was extracted with chloroform (2 × 12 ml). The organic phases were combined, dried over magnesium sulfate, and concentrated *in vacuo* to afford a yellow oil (524 mg). This was purified by flash chromatography [chloroform–methanol (5:1, v/v)] to afford a light yellow foam (339 mg). A portion (40 mg) of this material was dissolved in 50% (v/v) aqueous ethanol (1 ml). The solution was passed through a column of Amberlyst A-26 (HCO_3^-) (1 ml). The column was eluted with 50% (v/v) aqueous ethanol. The eluate was concentrated *in vacuo* to give **13k** (36 mg) as a colorless foam, which was contaminated with dimethyl sulfoxide; the overall yield was estimated to be 65% by NMR spectroscopy; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1711 (carbamate ester), 1643 (carboxylate ion); ^{1}H-NMR ($CDCl_3$) δ: 2.62 (0.8H, s, Me_2SO), 3.68—4.08 (1H, m) and 4.67—5.24 (2H, m) (CH_2CH), 7.32—7.84 (19H, m, aromatic protons).

(*S*)-*N*-(9-Phenylfluoren-9-yl)-*O*-(*p*-toluenesulfonyl)serine Methyl Ester (15) *p*-Toluenesulfonyl chloride (4.00 g, 21 mmol) was added to a solution of **14**[18] (5.03 g, 14 mmol) in dry pyridine (17 ml) at −10 °C and the mixture was stirred at −10—−5 °C for 7 h. The reaction mixture was then poured onto crushed ice (140 ml) with vigorous stirring. The resulting oily precipitate was extracted with benzene (3 × 60 ml). The organic layers were combined, washed successively with 5% aqueous citric acid (3 × 60 ml) and saturated aqueous sodium bicarbonate (2 × 60 ml), dried over magnesium sulfate, and concentrated *in vacuo* to leave a solid. This was washed with methanol (20 ml) and then dried to give **15** (6.44 g, 90%), mp 124—127 °C. Recrystallization of crude **15** from a mixture of hexane and ethyl acetate (1:1, v/v) afforded an analytical sample as colorless prisms, mp 130—131 °C; $[\alpha]_D^{24}$ −180° (*c*=0.401, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH), 1736 (CO); ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s, CMe), 2.80 (1H, dd, *J*=4.5, 5 Hz, CH), 3.34 (3H, s, OMe), 3.82 (1H, dd, *J*=5, 9.5 Hz) and 3.99 (1H, dd, *J*=4.5, 9.5 Hz) (CH_2), 7.10—7.40 (11H, m, aromatic protons of the 9-phenylfluorenyl group), 7.33 (2H, m, aromatic protons *meta* to the sulfonyl group), 7.59—7.67 (2H, m, aromatic protons of the 9-phenylfluorenyl group), 7.74 (2H, m, aromatic protons *ortho* to the sulfonyl group). *Anal.* Calcd for $C_{30}H_{27}NO_5S$: C, 70.16; H, 5.30; N, 2.73. Found: C, 70.23; H, 5.25; N, 2.75.

(*R*)-[3-Methoxy-2-[(9-phenylfluoren-9-yl)amino]-3-oxopropyl]triphenylphosphonium *p*-Toluenesulfonate (16) A solution of **15** (206 mg, 0.401 mmol) and triphenylphosphine (210 mg, 0.80 mmol) in dry toluene (10 ml) was kept at 80 °C for 10 d. The resulting oily precipitate was collected by decantation, washed five times with toluene, and purified by flash chromatography [column diameter, 20 mm; chloroform–methanol (7:1, v/v)]. As the tosylate anion of **16** was lost to some extent during this treatment, a solution of the product in a little 50% (v/v) aqueous

ethanol was passed through a column packed with Amberlyst A-26 (TsO^-) (2.5 ml). The column was eluted with 50% (v/v) aqueous ethanol. The eluate was concentrated *in vacuo* to afford **16** (145 mg, 47%) as a slightly brown foam, $[\alpha]_D^{28}$ −68.2° (c=0.249, MeOH); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s, CMe), 2.96 (3H, s, OMe), 3.11 (1H, m, CH), 3.89 (1H, ddd, J=7.8, 12.1, 15.9 Hz) and 4.09 (1H, ddd, J=5.6, 13.8, 15.9 Hz) (CH_2), 6.9—7.8 (33H, m, aromatic protons and NH).

The Wittig Reaction between 13h and Benzaldehyde i) The Effect of the Amount of *n*-Butyllithium on the Yield: A dry solution of **13h** (1.39 g, 3.42 mmol) in HMPA (23 ml) was prepared in the same way as will be described below for the reaction with piperonal. THF (35 ml) was added to a half volume of the solution. The Wittig reaction with benzaldehyde (0.18 ml, 1.7 mmol) was conducted according to the reported procedure[2u] using 2 molar eq of *n*-butyllithium. The reaction mixture was treated in a similar manner (HMPA was removed by evaporation under reduced pressure at 80—90 °C) to afford crude **24**, ^{1}H-NMR ($CDCl_3$) δ: 3.75 (3H, s, Me), 5.09 (1H, m, =CHC<u>H</u>), 5.55 (1H, d, J=6 Hz, NH), 6.25 (1H, dd, J=6, 16 Hz, =C<u>H</u>CH), 6.73 (1H, dd, J=1, 16 Hz, C<u>H</u>=CHCH), 7.45 (5H, m, Ph), which contained small amounts of HMPA and (*R*)-2-[(methoxycarbonyl)amino]-3-(diphenylphosphinyl)propanoic acid.[2u] The yield was estimated to be 43% by ^{1}H-NMR spectroscopy. Compound **24** thus obtained was converted into **29** according to the reported procedure.[2u] The product was then transformed into **30**, $[\alpha]_{365}^{24}$ −4.6° (c=3.46, MeOH), in a manner similar to that described below under item (i) for the preparation of **30**. The reaction of this compound with the Mosher reagent was conducted in the same way as will be described for the preparation of [*R*-(*R**,*S**)]-**31**. The HPLC analysis of **31** thus obtained indicated that it was contaminated with [*R*-(*R**,*R**)-**31**] by 4%.

The second half of the solution of **13h** in HMPA was used in a separate run under the same conditions except for employing an equimolar amount of the base, to afford crude **24** (27% estimated on the basis of ^{1}H-NMR spectroscopy).

ii) Evaluation of the Optical Purity: The reaction of **13h** (611 mg, 1.50 mmol) and benzaldehyde (0.139 ml, 1.36 mmol) was conducted in the same way as described above using 2 molar eq of *n*-butyllithium. The reaction mixture was treated in a manner similar to that described below for the preparation of **18h** to afford a semisolid (187 mg). This product was a mixture of **24** and HMPA in a molar ratio of 3 : 1 according to its ^{1}H-NMR spectrum. A portion (182 mg) of this sample was transformed into **29** according to the reported procedure.[2u] Crude **29** was purified by flash chromatography [column diameter, 20 mm; hexane–ethyl acetate (2 : 1, v/v)] to afford pure **29** (112 mg, 34% based on benzaldehyde) as a colorless oil. This sample was of *ca.* 98% ee as determined by HPLC analysis using a Sumichiral OA-4600 column. Transformation of this sample into **31** was performed in the same way as will be described below for the preparation of authentic [*R*-(*R**,*S**)]-**31**. The HPLC analysis of **31** thus obtained showed that it was contaminated with its diastereomer to the extent of *ca.* 1%.

(±)-α-[(Methoxycarbonyl)amino]benzenebutanoic Acid [(±)-25] This compound was prepared from (±)-**26** (271 mg, 1.51 mmol) in 99% yield according to the reported procedure for the preparation of **25**.[2u] Recrystallization from benzene gave an analytical sample of (±)-**25** as colorless needles, mp 110—112.5 °C. The ^{1}H-NMR spectrum ($CDCl_3$) was identical with that of **25**.[2u] *Anal.* Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.78; H, 6.47; N, 5.90.

(±)-α-[(Methoxycarbonyl)amino]benzenebutanoic Acid Methyl Ester [(±)-29] This compound[31] was obtained from (±)-**25** (48 mg, 0.202 mmol) according to the reported procedure for the synthesis of **29**,[2u] as a colorless oil in 98% yield. The ^{1}H-NMR and IR spectra of this compound were identical with those of **29**.[2u]

(*S*)-[1-(Hydroxymethyl)-3-phenyl-2-propenyl]carbamic Acid Methyl Ester (27) Sodium borohydride (8 mg, 0.2 mmol) and lithium chloride (9 mg, 0.2 mmol) were added to a solution of **28** (25 mg, 0.1 mmol) in a mixture of dry ethanol (0.8 ml) and dry THF (0.6 ml).[32] The mixture was stirred at room temperature under argon for 5 h. The resulting mixture was neutralized with 10% aqueous phosphoric acid and concentrated to a small volume. Water (1 ml) was added and then the mixture was extracted with diethyl ether (6 × 2 ml). The combined ethereal extracts were dried over magnesium sulfate and concentrated *in vacuo* to leave **28** (16 mg, 73%) as a colorless solid, mp 80—87 °C, $[\alpha]_D^{19}$ −2° (c=0.16, MeOH); 60 MHz ^{1}H-NMR ($CDCl_3$) δ: 2.20 (1H, br, OH), 3.65 (3H, s, Me), 3.73 (2H, s, CH_2), 4.35 (1H, m, NHC<u>H</u>), 5.17 (1H, br d, J=8 Hz, NH), 6.06 (1H, dd, J=6, 16 Hz, =C<u>H</u>CH), 6.48 (1H, d, J=16 Hz, PhC<u>H</u>=CH), 7.25 (5H, m, Ph). HPLC analysis of **31** derived from this sample of **27** indicated that almost complete racemization had occurred.

(*S*)-[1-(Hydroxymethyl)-3-phenylpropyl]carbamic Acid Methyl Ester (30) i) From **29**: Compound **29**[2u] (53 mg, 0.21 mmol) was treated with sodium borohydride in the presence of lithium chloride in a manner similar to that described for the preparation of **27**. The resulting mixture was concentrated *in vacuo* after neutralization with 10% aqueous phosphoric acid, and the residue was partitioned between water (2 ml) and diethyl ether (4 ml). The aqueous layer was extracted with diethyl ether (6 × 4 ml). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo* to leave a colorless oil (43 mg). This was purified by layer chromatography on silica gel [hexane–ethyl acetate (1 : 1, v/v)] to afford **30** (28 mg, 60%) as a colorless oil, $[\alpha]_D^{23}$ −4.7° (c=1.85, MeOH); $[\alpha]_{365}^{23}$ −5.0° (c=1.85, MeOH); ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.94 (2H, m, $PhCH_2C\underline{H}_2$), 2.11 (1H, br, OH), 2.70 (2H, m, $PhC\underline{H}_2$), 3.42—3.79 (3H, m, $CHCH_2O$), 3.69 (3H, s, Me), 4.81 (1H, d, J=5 Hz, NH), 7.22 (5H, m, Ph).

ii) From **27**: A solution of **27** (15 mg, 0.068 mmol) in methanol (4 ml) was hydrogenated over 10% palladium on carbon (17 mg) at room temperature for 1 h. The catalyst was filtered off and washed with methanol (10 ml). The combined filtrate and washings were concentrated *in vacuo* to leave a colorless oil (15 mg, 100%), $[\alpha]_D^{30}$ −0.1° (c=1.0, MeOH). The ^{1}H-NMR and IR spectra of this sample were in accordance with those of the sample of **30** described under item (i).

(±)-1-[(Hydroxymethyl)-3-phenylpropyl]carbamic Acid Methyl Ester [(±)-30] Compound (±)-**29** (20 mg, 0.08 mmol) was treated in a manner similar to that described for the reduction of **29** to afford (±)-**30** (16 mg, 89%) as a partly crystallized oil. The ^{1}H-NMR spectrum of (±)-**30** thus obtained was identical with that of **30**.

The Esters of (±)-30 with (*S*)-(−)-α-Methoxy-α-(trifluoromethyl)-phenylacetic Acid [[*S*-(*R,*R**)]- and [*S*-(*R**,*S**)]-31]** Compound (±)-**30** (16 mg, 0.072 mmol) was treated with (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[21] in a manner similar to that described below for the preparation of [*R*-(*R**,*S**)]-**31** to afford a mixture of the diastereomers **31** (13 mg, 42%) as a colorless glass, ^{1}H-NMR ($CDCl_3$) δ: 1.76 (2H, m, $CHC\underline{H}_2CH_2$), 2.65 (2H, m, $PhC\underline{H}_2$), 3.52 (3H, m, CF_3COMe), 3.66 (3H, s, CO_2Me), 3.96 (1H, br, CH), 4.35 (2H, m, CH_2O), 4.61 (1H, br d, NH), 6.84—7.56 (10H, m, two Ph's).

The Ester of 30 with (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid [[*R*-(*R,*S**)]-31]** A mixture of **30** (27 mg, 0.12 mmol), which was obtained from **29**, (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[21] (45 mg, 0.18 mmol) prepared from the (*R*)-(+)-acid (>99% ee),[33] and dry pyridine (0.12 ml) was stirred at room temperature for 1 h. Water (1 ml) was added to the mixture, and the whole was stirred for a further 1 h. The resulting mixture was extracted with ether (8 × 2.5 ml). The organic phases were combined, washed successively with 5% hydrochloric acid (3 ml) and saturated aqueous sodium bicarbonate (2 × 2 ml), dried over magnesium sulfate, and concentrated *in vacuo* to leave a colorless oil. This was purified by layer chromatography on silica gel [hexane–ethyl acetate (2 : 1, v/v)] to afford [*R*-(*R**,*S**)]-**31** (44 mg, 83%) as a colorless oil, $[\alpha]_D^{22}$ +25° (c=0.49, MeOH); ^{1}H-NMR ($CDCl_3$) δ: 1.78 (2H, m, $CHC\underline{H}_2CH_2$), 2.65 (2H, m, $PhC\underline{H}_2$), 3.52 (3H, q, J=1 Hz, CF_3COMe), 3.66 (3H, s, CO_2Me), 3.96 (1H, br, CH), 4.30 (1H, dd, J=4, 11 Hz) and 4.41 (1H, dd, J=4.5, 11 Hz) (CH_2O), 4.60 (1H, d, J=8 Hz, NH), 6.85—7.56 (10H, m, two Ph's).

The Wittig Reaction between 13h—j and Piperonal The procedure employed for the conversion of **13h** into **18h** will be described below in detail as a typical example. The other reactions were performed similarly, and the products were characterized as described below.

[*S*-(*E*)]-4-(1,3-Benzodioxol-5-yl)-2-[(methoxycarbonyl)amino]-3-butenoic Acid (18h) A solution of **13h** (629 mg, 1.5 mmol), which had been dried by coevaporation with a mixture of chloroform and benzene (1 : 1, v/v) three times followed by drying over phosphorus pentoxide at 2 mmHg and 50 °C for 10 h, in dry HMPA (15 ml) was dried over molecular sieves 4A (6 g) under nitrogen at 30 °C for 2 d. The solution was then transferred to a reaction vessel with a syringe through a funnel with a fritted disk under argon. THF (45 ml) was added to the solution, and then a 1.11 M solution of *n*-butyllithium in hexane (2.7 ml, 3 mmol) was added at −70 °C over a period of 5 min. The mixture was stirred at that temperature for 20 min, a solution of piperonal (203 mg, 1.35 mmol) in THF (4 ml) was added at −70 °C, and the whole was stirred at the same temperature for 1 h, then allowed to warm to 0 °C. The resulting mixture was neutralized with 10% hydrochloric acid and concentrated *in vacuo* without heating (**18h** underwent racemization to the extent of *ca.* 10% when it was heated for removal of HMPA) to remove THF. Then the solution was diluted with water (100 ml), brought to pH 2 with 10% hydrochloric acid, and extracted with ethyl acetate (4 × 30 ml). The organic layers were combined

and extracted with saturated aqueous sodium bicarbonate (3 × 30 ml). The combined aqueous layers were brought to pH 2 with 10% hydrochloric acid, and then extracted with diethyl ether (4 × 30 ml). The ethereal extracts were combined, dried over magnesium sulfate, and concentrated *in vacuo* without heating to leave a yellow viscous oil (199 mg). Its ^{1}H-NMR spectrum indicated that it was **18h** contaminated with small amounts of (*R*)-2-[(methoxycarbonyl)amino]-3-(diphenylphosphinyl)propanoic acid,[2u] HMPA, and ethyl acetate. The yield of **18h** was estimated to be 38% on the basis of the ^{1}H-NMR spectrum of the mixture. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s, Me), 4.99 (1H, m, C<u>H</u>CO_2H), 5.65 (1H, d, J=7 Hz, NH), 5.94 (2H, s, CH_2), 6.08 (1H, dd, J=6, 16 Hz, =C<u>H</u>CH), 6.59 (1H, dd, J=1, 16 Hz, C<u>H</u>=CHCH), 6.75—6.89 (3H, m, aromatic protons).

[*S*-(*E*)]-4-(1,3-Benzodioxol-5-yl)-2-[(benzyloxycarbonyl)amino]-3-butenoic Acid (18i) The reaction was carried out on the same scale as that for the preparation of **18h** using HMPA (25 ml) and THF (83 ml). After THF was removed by evaporation, the residue was diluted with water (200 ml) and extracted with ethyl acetate (4 × 40 ml). The organic layers were combined and extracted with saturated aqueous sodium bicarbonate (15 × 40 ml). The aqueous layers were combined, brought to pH 2 with 10% hydrochloric acid and then extracted with diethyl ether. The ethereal extracts were dried over magnesium sulfate and concentrated *in vacuo* to leave a mixture of **18i** and HMPA. This was purified by layer chromatography on silica gel [chloroform–methanol (5 : 1, v/v)] and then partitioned between diethyl ether and dilute hydrochloric acid (pH 2). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford **18i** (186 mg, 39%) as a slightly yellow oil, 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 4.93 (1H, br, C<u>H</u>CO_2H), 5.14 (2H, s, PhC<u>H</u>$_2$), 5.56 (1H, d, J=6.9 Hz, NH), 5.94 (2H, s, OCH_2O), 6.03 (1H, dd, J=6, 15.5 Hz, =C<u>H</u>CH), 6.60 (1H, d, J=15.5 Hz, C<u>H</u>=CHCH), 6.71—6.90 [3H, m, aromatic protons of the 3,4-(methylenedioxy)phenyl group], 7.25—7.35 (5H, m, <u>Ph</u>CH_2).

A small amount of **18i** was hydrogenated over 10% palladium on carbon in a manner similar to that described for the preparation of **22** from **18h** to give crude **21**. This was suspended in water and washed with dichloromethane. The aqueous solution was treated with methyl chloroformate in the presence of sodium bicarbonate. The resulting mixture was brought to pH 1 with 10% hydrochloric acid and the solution was extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to leave **19h** as a colorless oil. This was treated with trimethylsilyldiazomethane[30] in the usual manner. The resulting crude product was purified by layer chromatography on silica gel [hexane–ethyl acetate (2 : 1, v/v)] to afford **22** as a colorless oil. This sample was of *ca.* 99% ee as determined by HPLC analysis on a Sumichiral OA-4600 column.

[*S*-(*E*)]-4-(1,3-Benzodioxol-5-yl)-2-[(*tert*-butoxycarbonyl)amino]-3-butenoic Acid (18j) This compound was obtained from piperonal (209 mg, 1.39 mmol) and **13j** (694 mg, 1.54 mmol) as a mixture (215 mg) with HMPA and (*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-(diphenylphosphinyl)propanoic acid [270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.35 (9H, s, CMe_3), 2.88 and 3.20 (1H each, m, CH_2), 4.53 (1H, m, CH), 5.82 (1H, br, NH), 7.43—7.93 (10H, m, Ph_2)]. The molar ratio (1 : 0.31 : 0.45) of these compounds in the mixture was determined by ^{1}H-NMR spectroscopy for estimation of the yield (28%) of **18j**, 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s, CMe_3), 4.99 (1H, br, C<u>H</u>CO_2H), 5.30 (1H, br, NH), 5.95 (2H, s, OCH_2O), 6.07 (1H, dd, J=6, 16 Hz, =C<u>H</u>CH), 6.60 (1H, br d, J=16 Hz, C<u>H</u>=CHCH), 6.75 [1H, d, J=7.9 Hz, C(6)-H], 6.81 [1H, dd, J=7.9, 1.7 Hz, C(5)-H], 6.90 [1H, d, J=1.7 Hz, C(3)-H].

A small portion of **18j** was hydrogenated over 10% palladium on carbon in methanol at room temperature for 1 h. The crude product was purified by layer chromatography on silica gel [chloroform–methanol (5 : 1, v/v)] and then partitioned between dilute hydrochloric acid (pH 2) and dichloromethane. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford a mixture of **19j** and HMPA as a yellowish oil, 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, CMe_3), 1.95 and 2.13 (1H each, m, CH_2C<u>H</u>$_2$CH), 2.64 (d, J=9.2 Hz, HMPA overlapped with a signal due to C<u>H</u>$_2$C<u>H</u>$_2$CH), 4.33 (1H, m, CH_2C<u>H</u>), 5.14 (1H, d, J=6.9 Hz, NH), 5.91 (2H, s, OCH_2O), 6.63 [1H, dd, J=1.6, 7.9 Hz, C(5)-H], 6.67 [1H, d, J=1.6 Hz, C(3)-H], 6.71 [1H, d, J=7.9 Hz, C(6)-H]. This was treated with a mixture of equal volumes of 6 N hydrochloric acid and dioxane at room temperature for 1 h. The resulting solution was washed with dichloromethane. The aqueous layer was treated with methyl chloroformate in the usual manner. The resulting solution was brought to pH 2 with 10% hydrochloric acid and extracted with dichloromethane. The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo* to leave a yellowish oil. Compound **19h** thus obtained was treated with trimethylsilyldiazomethane[30] in the usual manner. Purification of the crude product by layer chromatography as described above afforded **22** as a colorless glass. This sample was of *ca.* 99% ee as determined by HPLC analysis on a Sumichiral OA-4600 column.

[*S*-(*E*)]- and [*S*-(*Z*)]-4-(1,3-Benzodioxol-5-yl)-2-[(9-phenylfluoren-9-yl)amino]-3-butenoic Acid Methyl Esters (17) A solution of **16** (192 mg, 0.247 mmol), which had been dried by azeotropic distillation with a mixture of chloroform and benzene (1 : 1, v/v) three times, in THF (10 ml) was dried over molecular sieves 4A (1 g) under nitrogen at 30 °C for 2 d. The solution was transferred to a reaction vessel as described for the preparation of **18h**. A 1.11 M solution of butyllithium in hexane (0.22 ml, 0.24 mmol) was added to the solution under argon at −78 °C over a period of 5 min and the mixture was stirred for a further 20 min. A solution of piperonal (33 mg, 0.22 mmol) in THF (2 ml) was added to the mixture and the whole was stirred at −78 °C for 1 h and then allowed to warm to 0 °C. The resulting mixture was brought to pH 4 with 10% aqueous phosphoric acid and concentrated *in vacuo*. The residue was partitioned between chloroform (5 ml) and saturated aqueous sodium bicarbonate (5 ml). The aqueous layer was extracted with chloroform (2 × 5 ml). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo* to give a brown oil (202 mg). This was purified by flash chromatography [column diameter, 20 mm; hexane–ethyl acetate (4 : 1, v/v)] to afford a mixture (17 mg) of piperonal and the expected olefins as a colorless oil. Layer chromatography of this product on silica gel [benzene–methanol (50 : 1, v/v)] afforded a mixture of equal amounts (according to the NMR spectrum) of the geometrical isomers **17** (13 mg, 12%) as a colorless oil. Repeated layer chromatography of **17** on silica gel [hexane–1,2-dichloroethane (1 : 1, v/v)] provided incomplete separation of **17**, but was sufficient to allow assignment of the NMR spectrum. The (*E*)-isomer, ^{1}H-NMR ($CDCl_3$) δ: 3.40 (3H, s, Me), 3.44 (1H, d, J=6.5 Hz, C<u>H</u>CO_2Me), 5.77 (1H, dd, J=6.5, 15.5 Hz, =C<u>H</u>CH), 5.92 (2H, s, CH_2), 6.27 (1H, d, J=15.5 Hz, C<u>H</u>=CHCH), 7.0—7.8 (m, aromatic protons). The (*Z*)-isomer, ^{1}H-NMR ($CDCl_3$) δ: 3.45 (3H, s, Me), 3.92 (1H, d, J=10.5 Hz, C<u>H</u>CO_2Me), 5.31 (1H, dd, J=10.5, 11 Hz, =C<u>H</u>CH), 5.92 and 5.95 (1H each, d, J=1.5 Hz, CH_2), 6.15 (1H, d, J=11 Hz, C<u>H</u>=CHCH), 6.9—7.5 (m, aromatic protons).

(*S*)-α-[(Methoxycarbonyl)amino]-1,3-benzodioxole-5-butanoic Acid Methyl Ester (22) Crude **18h** (188 mg) was dissolved in methanol (15 ml) and hydrogenated over 10% palladium on carbon (0.19 g) at room temperature under atmospheric pressure for 1 h. The catalyst was removed by filtration and washed with methanol (30 ml). The filtrate and the washings were combined and concentrated *in vacuo* to afford crude **19h** (174 mg) as a yellow viscous oil, 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.97 and 2.16 (1H each, m, CH_2C<u>H</u>$_2$CH), 2.63 (2H, t, J=7.8 Hz, C<u>H</u>$_2$CH$_2$CH), 3.71 (3H, s, Me), 4.40 (1H, m, CH_2C<u>H</u>), 5.26 (1H, d, J=7.9 Hz, NH), 5.91 (2H, s, OCH_2O), 6.63 [1H, dd, J=1.6, 7.9 Hz, C(5)-H], 6.67 [1H, d, J=1.6 Hz, C(3)-H], 6.72 [1H, d, J=7.9 Hz, C(6)-H]. This was dissolved in a mixture of methanol (1.2 ml) and benzene (4.2 ml), and *ca.* 10% solution of trimethylsilyldiazomethane[30] in hexane (0.9 ml) was added. The resulting yellow solution was concentrated *in vacuo* to leave a yellow oil (174 mg). This was purified by flash chromatography [hexane–ethyl acetate (4 : 1, v/v)] to afford crude **22** (118 mg, 30% overall yield based on piperonal), mp 79.5—81 °C. This sample was optically pure according to HPLC analysis on a Sumichiral OA-4600 column. Recrystallization from hexane–ethyl acetate (6 : 1, v/v) afforded an analytical sample of **22** as colorless prisms, mp 81—82 °C; $[\alpha]_D^{23}$ −11° (c=0.599, MeOH); $[\alpha]_{365}^{24}$ −17.5° (c=0.599, MeOH); MS m/z: 295 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 1731 (carboxylate ester), 1685 (carbamate ester); 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 1.91 and 2.12 (1H each, m, CH_2C<u>H</u>$_2$CH), 2.59 (2H, m, C<u>H</u>$_2$CH$_2$CH), 3.70 and 3.73 (3H each, s, two Me's), 4.38 (1H, m, CH_2C<u>H</u>), 5.19 (1H, d, J=5 Hz, NH), 5.92 (2H, s, OCH_2O), 6.62 [1H, dd, J=1.7, 7.9 Hz, C(5)-H], 6.66 [1H, d, J=1.7 Hz, C(3)-H], 6.72 [1H, d, J=7.9 Hz, C(6)-H]. *Anal.* Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 56.93; H, 5.96; N, 4.77.

(±)-α-[(Methoxycarbonyl)amino]-1,3-benzodioxole-5-butanoic Acid Methyl Ester [(±)-22] Crude **18h** (300 mg) was obtained from piperonal (465 mg, 3.1 mmol) in a manner similar to that described above. A portion (250 mg) of this product was treated with trimethylsilyldiazomethane[30] in the usual manner to afford crude [*S*-(*E*)]-4-(1,3-benzodioxol-5-yl)-2-[(methoxycarbonyl)amino]-3-butenoic acid methyl ester (**20**) (239 mg) as a yellow viscous oil, 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 3.71 and 3.79 (3H each, s, two OMe's), 5.02 (1H, m, C<u>H</u>CO_2Me), 5.43 (1H, br, NH), 5.95 (2H, s, CH_2), 6.00 (1H, dd, J=6.6, 15.8 Hz, =C<u>H</u>CH), 6.58 (1H, dd, J=1.3, 15.8 Hz, C<u>H</u>=CHCH), 6.75 [1H, d, J=8.1 Hz, C(6)-H], 6.81 [1H, dd, J=1.7, 8.1 Hz, C(5)-H], 6.90 [1H, d, J=1.7 Hz, C(3)-H]. On addition

of triethylamine (5 drops), a solution of the whole amount of **20** in methanol (10 ml) almost lost optical rotation in 1 h at room temperature. The resulting mixture was concentrated *in vacuo*. A solution of the residue in dichloromethane (10 ml) was washed successively with 5% aqueous citric acid (2 × 5 ml) and saturated aqueous sodium bicarbonate (5 ml), dried over magnesium sulfate, and concentrated *in vacuo* to leave a yellow oil (206 mg). The NMR spectrum of this sample indicated that it was (±)-**20** contaminated with a single geometrical isomer of 4-(1,3-benzodioxol-5-yl)-2-[(methoxycarbonyl)amino]-2-butenoic acid methyl ester (**32**), 270 MHz ^{1}H-NMR ($CDCl_3$) δ: 3.47 (2H, d, J=7.2 Hz, $C\underline{H}_2CH$), 3.75 and 3.77 (3H each, s, two OMe's), 5.93 (2H, s, OCH_2O), 6.26 (1H, br s, NH), 6.64 [1H, dd, J=1.3, 7.9 Hz, C(5)-H], 6.69 [1H, d, J=1.3 Hz, C(3)-H], 6.73 (1H, t, J=7.2 Hz, $CH_2C\underline{H}$), 6.74 [1H, d, J=7.9 Hz, C(6)-H]; the ratio of (±)-**20** to **32** was 8.5 : 1. Flash chromatography [hexane–ethyl acetate (2 : 1, v/v)] of this product afforded (±)-**20** (121 mg, 16% overall yield), mp 98—103 °C, still contaminated with a small amount of **32**. As **32** could not be removed by recrystallization from methanol, crude (±)-**20** (50 mg, 0.17 mmol) was hydrogenated over 10% palladium on carbon (50 mg) in methanol (10 ml) at room temperature under atmospheric pressure for 1 h. The catalyst was removed by filtration and washed with methanol (15 ml). The filtrate and the washings were combined, and concentrated *in vacuo* to leave (±)-**22** (47 mg, 15% overall yield) as a colorless viscous oil, whose ^{1}H-NMR spectrum was identical with that of **22**. When the solution of **20** and triethylamine in methanol was refluxed for 3 h, a 1 : 1 mixture of (±)-**20** and **32** was obtained.

Determination of Optical Purity by HPLC HPLC analyses were performed on pre-packed columns of 4 mm inner diameter and 250 mm length at the flow rate of 0.5 ml per min at room temperature. The peak areas of the components were determined by using a UV absorbance detector operated at 254 nm and a Takeda Riken TR-2217 automatic integrator.

Partial separation of **31** was attained on a Merck LiChrosorb Si-60 column (5 μm) using hexane–ethyl acetate (90 : 10, v/v) as an eluent [retention time: (*R**,*R**)-**31**, 71 min; (*R**,*S**)-**31**, 74 min].

Compounds (±)-**22** and (±)-**29** were cleanly resolved on a Sumichiral OA-4600 column (5 μm) [hexane–ethanol (98 : 2, v/v)] [retention time: the enantiomer of **22**, 22 min; **22**, 25 min; the enantiomer of **29**, 14.5 min; **29**, 15.4 min].

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References and Notes

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