Synthesis of Optically Active (2-Arylvinyl)glycine Derivatives by Palladium-Catalyzed Arylation of (*S*)-*N*-(Benzyloxycarbonyl)vinylglycine

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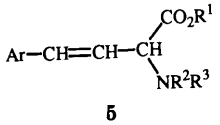
Phenyl, tolyl, anisyl, and 1-naphthyl iodides (7a—g, n) smoothly reacted with (*S*)-*N*-(benzyloxycarbonyl)-vinylglycine (6) in H_2O in the presence of $Pd(OAc)_2$, Bu_4NCl, and $NaHCO_3$ at 45 °C, producing [*S*-(*E*)]-(2-arylvinyl)glycine derivatives 8a—g, n of high enantiomeric purity. The yields of the reactions of 3- (7f), 2- (7e), and 4-iodoanisoles (7g) increased in this order. This relationship between the yield and the position of substitution has been found to hold for bromophenyl iodides (7i—k), although somewhat lower chemical and optical yields were realized in these cases. Phenyl iodide 7l carrying an electron-withdrawing 4-acetyl group gave an unsatisfactory result, and more electron-deficient 4-nitrophenyl iodide (7m) did not provide the desired product. All these results suggest that the reaction is advantageous with electron-sufficient substrates 7. However, this was not the case for 4-iodophenol (7h), as well as some heterocyclic iodides.

Key words (2-arylvinyl)glycine chiral synthesis; palladium-catalyzed coupling; vinylglycine arylation; stereoselectivity; chiral HPLC; enantiomeric excess

Wybutine (**4**), the minor base of yeast $tRNA^{Phe}$, was synthesized by us[1] in 1985 through the Wittig reaction[2] of **1** (Chart 1). The key intermediate **3** of this synthesis is the first example of nonenzymatically prepared optically active (2-arylvinyl)glycine derivatives,[3] which may be represented by the general structure **5**. Subsequently, chiral syntheses of compounds **5**, in which Ar stands for phenyl,[1b,4-7] 4-methoxyphenyl,[8] 3,4-(methylenedioxy)-phenyl[4] naphthalen-2-yl,[9] and 3-(ethoxycarbonyl)naphthalen-2-yl,[9] were reported by us and others. Compound **3** was alternatively synthesized by palladium-catalyzed coupling between the iodide **2** and (*S*)-*N*-(methoxycarbonyl)vinylglycine, and the nucleoside of **3** was synthesized for the first time in a similar manner[10] (Chart 1). This method of constructing optically active β,γ-unsaturated amino acid derivatives, which are difficult to synthesize owing to a marked tendency to racemization and isomerization,[4-11] has been successfully applied to the reaction of (*S*)-*N*-(benzyloxycarbonyl)vinylglycine (**6**) with 2-naphthyl and some endocyclic vinyl trifluoromethanesulfonates.[9] We investigated the reaction of 4-methoxyphenyl iodide (**7g**) with several *N*-protected and unprotected vinylglycines in $HCONMe_2$ in the presence of $Pd(OAc)_2$, Bu_4NCl, and base, and we reported that the *N*-benzyloxycarbonyl derivative **6** provided the highest yield of the coupling product; $NaHCO_3$ was the best among the bases tested; and replacement of the solvent with H_2O increased not only the chemical yield and (*E*)-selectivity, but also the optical yield.[8] This paper reports the scope and limitations of the palladium-catalyzed arylation of **6** conducted in H_2O in the presence of Bu_4NCl.

We first examined whether $NaHCO_3$ was also a good base for the reaction in H_2O. Thus, **7g** was treated with 1.1 mol eq of **6** (of 98% ee) in H_2O in the presence of 3 mol% of $Pd(OAc)_2$, 1 mol eq of Bu_4NCl, and an excess of base at 45 °C. The chemical and optical yields, as well as the geometrical predominance, of each reaction were determined according to the reported procedure.[8] As shown in Table 1, every reaction of **7g** in H_2O in the presence of the selected base gave a better result than that obtained in the corresponding reaction in $HCONMe_2$.[8] We considered from the viewpoint of chiral synthesis that $NaHCO_3$ was the best among the bases tested, notwithstanding it gave an inferior chemical yield to that obtained by employing K_2CO_3.

Having selected $NaHCO_3$, we checked the feasibility of this method for the reactions with various aryl iodides **7**. The chemical yield and stereoselectivity of each reaction were evaluated by isolating the product as the methyl ester **10**, because the carboxylic acid **8** was difficult to purify.



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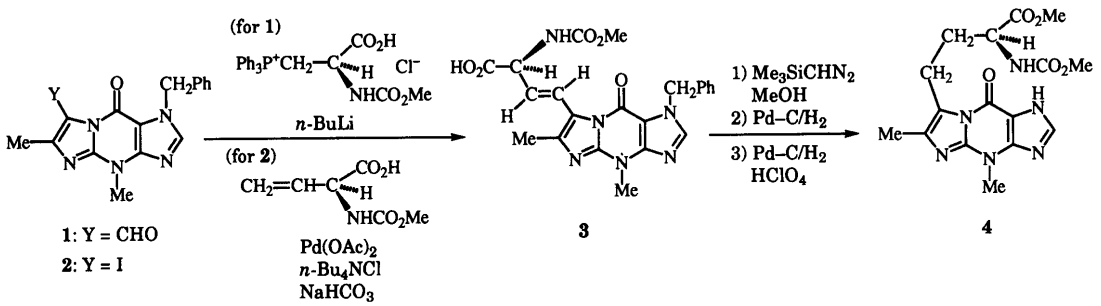

Chart 1

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The results, summarized in Table 2, show that 1-iodonaphthalene (**7n**) and unsubstituted iodobenzene (**7a**) provided the coupling products **10n, a** in 55% and 52% yields, respectively (entries 14, 1). Iodobenzenes **7b—d** carrying an electron-donating methyl group proved to be better substrates, regardless of the position of substitution, giving **10b—d** in 60—65% yields (entries 2—4). The yields (51—66%) of the reactions of 3-methoxyphenyl (**7f**), 2-methoxyphenyl (**7e**), and 4-methoxyphenyl iodides (**7g**) increased in this order (entries 5—7), suggesting a favorable electron-donating resonance effect and unfavorable electron-withdrawing inductive effect of the methoxy group on the yield. A similar relationship between the yield and the position of substitution has been found to hold for bromophenyl iodides (**7i—k**) (entries 9—11), and the somewhat lower yields (30—51%) might be a reflection of the unfavorable electronic effect of the substituent. Phenyl iodide **7l** bearing an electron-withdrawing 4-acetyl group afforded a mixture of coupling products (**10l** and its geometrical and positional isomers) in 39% yield (entry 12), and more electron-deficient 4-nitrophenyl iodide (**7m**) did not provide the olefinic product at all (entry 13). It may be concluded on the basis of these results that the reaction is favored by an electron-donating substituent on

Table 1. Base Effect on Palladium-Catalyzed Arylation of **6** with **7g**[a]

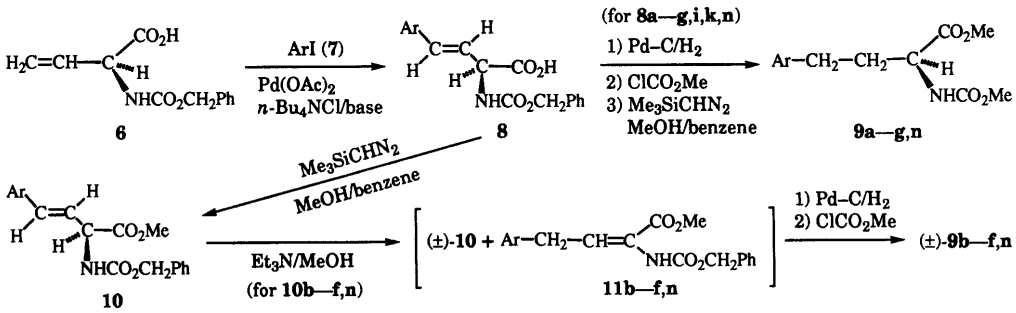
Entry	Base	Time (h)	**10g** and its (*Z*)-isomer		Optical yield (%)
			Yield (%)	*E*:*Z*[b]	
1	$NaHCO_3$	24	66	100:0	99
2	$KHCO_3$	24	61	100:0	99
3	K_2CO_3	24	74	100:0	92
4	Et_3N	6.5	61	84:16	95
5	Et_3N	2	—[c]	62:28	—[c]

a) A mixture of **7g** (0.5 mmol), **6** (0.55 mmol), $Pd(OAc)_2$ (0.015 mmol), Bu_4NCl (0.5 mmol), and the base (1.5 mmol) in H_2O (8 ml) was stirred at 45 °C. *b*) Determined by means of ^{1}H-NMR spectroscopy on the basis of the relative areas of the C(γ)-H signals. *c*) Not determined.

Table 2. Palladium-Catalyzed Arylation of **6** with Various Aryl Iodides **7** in H_2O in the Presence of $Pd(OAc)_2$ (3 mol%), Bu_4NCl (1 eq), and $NaHCO_3$ (3 eq) at 45 °C

Entry	ArI	Ar	Reaction time (h)	Solvent[a]	Optical yield (%)	Yield of **10** (%)	Recovery (%)	
							6[b]	**7**
1	**7a**	C_6H_5	24	A	97	52	15	0
2	**7b**	2-MeC_6H_4	24	B and A	98	60	11	0
3	**7c**	3-MeC_6H_4	24	B	98	64	16	0
4	**7d**	4-MeC_6H_4	24	A	100	65	12	0
5	**7e**	2-$MeOC_6H_4$	75	B	97	56	7	3
6	**7f**	3-$MeOC_6H_4$	24	A	97	51	2	0
7	**7g**	4-$MeOC_6H_4$	24	A	99	66	8	Trace
8	**7h**	4-HOC_6H_4	96	C	—[c]	9	<7[d]	<5[d]
9	**7i**	2-BrC_6H_4	48	A	>87[e]	48[f]	2	4
10	**7j**	3-BrC_6H_4	24	B	—[c]	30[g]	21	Trace
11	**7k**	4-BrC_6H_4	47	B and A	>92[e]	51	16	0
12	**7l**	4-AcC_6H_4	51	B	—[c]	39[h]	1	15
13	**7m**	4-$O_2NC_6H_4$	24	—	—	0	61	64
14	**7n**	Naphthalen-1-yl	24	B and A	97	55	8	0
15	**7o**	Thiophen-2-yl	24	B	—[c]	11	33	0
16	**7p**	Imidazol-4-yl	48	—	—	0	91	88
17	**7q**	Uracil-5-yl	120	—	—	0	58	—[c]

a) Solvent employed for flash chromatography to obtain crude **8**. A: $CHCl_3$–MeOH–H_2O (20:7:1, v/v); B: $CHCl_3$–MeOH (3:1, v/v); C: $CHCl_3$–MeOH (2:1, v/v). *b*) Isolated as the methyl ester[11a] except for entry 17. *c*) Not determined. *d*) Could not be purified. *e*) Compound **8** was considered to contain the achiral α,β-unsaturated isomer to some extent. *f*) A 45:3 mixture of **10i** and **11i** [^{1}H-NMR δ: 3.68 [2H, d, *J*=7 Hz, C(γ)-H_2], 3.75 (3H, s, CO_2Me), 5.18 (2H, s, $PhCH_2$), 6.36 (1H, br, NH), 6.68 [1H, t, *J*=7 Hz, C(β)-H], 7.05—7.57 (m, aromatic protons)]. *g*) A 29:1 mixture of **10j** and **11j** [^{1}H-NMR δ: 3.53 [2H, d, *J*=7 Hz, C(γ)-H_2], 3.77 (3H, s, CO_2Me), 5.17 (2H, s, $PhCH_2$), 6.36 (1H, br, NH), 6.72 [1H, t, *J*=7 Hz, C(β)-H], 7.09—7.45 (m, aromatic protons)]. *h*) A 29:7:3 mixture of **10l**, **11l** [^{1}H-NMR δ: 3.62 [2H, d, *J*=7 Hz, C(γ)-H_2], 6.74 [1H, t, *J*=7 Hz, C(β)-H]], and the (*Z*)-isomer [^{1}H-NMR δ: 6.78 [d, *J*=11 Hz, C(γ)-H]] of **10l**.



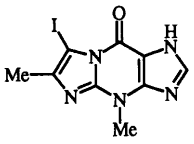
6 **8** **9a—g,n** **10** **11b—f,n** (±)-**10** + Ar–CH_2–CH=C(CO2Me)–NHCO2CH_2Ph (±)-**9b—f,n**

a: Ar = C_6H_5; **b**: Ar = 2-MeC_6H_4; **c**: Ar = 3-MeC_6H_4; **d**: Ar = 4-MeC_6H_4; **e**: Ar = 2-$MeOC_6H_4$; **f**: Ar = 3-$MeOC_6H_4$; **g**: Ar = 4-$MeOC_6H_4$; **h**: Ar = 4-HOC_6H_4; **i**: Ar = 2-BrC_6H_4; **j**: Ar = 3-BrC_6H_4; **k**: Ar = 4-BrC_6H_4; **l**: Ar = 4-AcC_6H_4; **n**: Ar = naphthalen-1-yl; **o**: Ar = thiophen-2-yl

Chart 2

the benzene ring. However, the situation is not simple: 4-iodophenol (**7h**) provided **10h** in only 9% yield (entry 8).

Next, the present method was tested for heterocyclic compounds. 2-Iodothiophene (**7o**) gave the coupling product **10o**, but in only 11% yield (entry 15), and neither 4-iodoimidazole (**7p**) nor 5-iodouracil (**7q**) afforded the coupling products at all (entries 16, 17). We finally attempted to prepare the key intermediates for the syntheses of the hypermodified bases and nucleosides of $tRNAs^{Phe}$ according to this procedure and found that none of the iodides **2**,[10] **12**, and **13**[10] afforded the desired products at all.[12] These discouraging results were in sharp contrast to the positive ones obtained in the reactions of the iodides (**2**, **13**) with (*S*)-*N*-(methoxycarbonyl)vinylglycine using $HCONMe_2$ as the solvent,[10] suggesting that $HCONMe_2$ is better than H_2O for the reactions with the heterocyclic substrates **7o—q**, **12**. However, neither these compounds nor the phenol **7h** gave a better result in the reaction in $HCONMe_2$. Compound **7m** also afforded no desired product, but gave 4,4'-dinitrobiphenyl[13] in 52% yield under these conditions.



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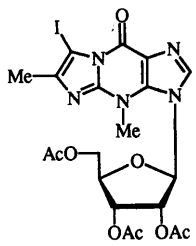

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The optical yields of the reactions with **7a—g, i, k, n**, which afforded the desired products in tolerable yields, were then evaluated. The optical purity of **10** or that of a derivative obtained through **10** might not necessarily reflect the optical yield, because **10** is prone to racemization.[4] Thus, crude carboxylic acids **8a—g, i, k, n** were converted into the configurationally stable saturated amino acid derivatives **9a—g, n** by hydrogenation, methoxycarbonylation, and methylation. Among (±)-**9a—g, n**, which are necessary to the chromatographic determination of the optical purities of **9a—g, n**, (±)-**9a**[4] and (±)-**9g**[8] have already been prepared. The requisite (±)-**9b—f, n** were obtained in the present study by treatment of **10b—f, n** with Et_3N in MeOH followed by catalytic hydrogenation of the resulting mixtures of (±)-**10** and the α,β-unsaturated isomer **11**, and methoxycarbonylation, as shown in Chart 2. Optical purities of **9a—g, n** were determined by HPLC on a chiral column under the conditions which had been established for complete resolution of (±)-**9a—g, n**. The results are summarized in Table 2.

Having evaluated the optical purities of **8a—g, i, k, n**, we tried to isolate these compounds. For this purpose we carried out the reaction of **6** with 1.1 mol eq of **7**, because the carboxylic acid **8** is difficult to separate from **6**. Thus, compounds **8b, d, g** were obtained in 46—52% yields from **6** (of 99% ee) after chromatographic separation followed

Table 3. ^{1}H-NMR Data for [*S*-(*E*)]-4-Aryl-2-[(benzyloxycarbonyl)amino]-3-butenoic Acids (**8**)

Compd.	Chemical shift (δ) in $CDCl_3$						
	C(α)-H	C(β)-H	C(γ)-H	NH	$PhC\underline{H}_2$	Aromatic H	Me
8a	5.02 (1/5H, br)[a]	6.24 (dd[b])	6.71 (d[c])	5.51 (4/5H, br) 6.88 (1/5H, br)	5.15 (s)	7.22—7.43 (m)	
8b	4.92—5.23 (br)	6.10 (dd[b])	6.94 (d[c])	5.52 (br) 6.87 (br)	5.16 (s)	7.10—7.45 (m)	2.31 (s)
8c	4.99 (1/4H, br) 5.11 (3/4H, m)	6.21 (dd[b])	6.69 (d[c])	5.49 (3/4H, br d[d]) 6.80 (1/4H, br)	5.15 (s)	7.03—7.40 (m)	2.33 (s)
8d	4.95 (8/19H, m) 5.10 (11/19H, m)	6.16 (dd[b])	6.62 (8/19H, d[c]) 6.68 (11/19H, d[c])	5.50 (11/19H,[e] br d[d])	5.15 (s)	7.11 (2H, d[f]) 7.17—7.41 (m)	2.33 (s)
8e	5.16 (m)	6.29 (dd[b])	7.03 (d[c])	5.50 (10/13H,[e] br d[d])	5.16 (s)	6.86 (1H, d[f]) 6.91 (1H, dd[f]) 7.21—7.45 (m)	3.83 (s)
8f	5.00 (2/5H, br)[a]	6.23 (dd[b])	6.69 (br d[c])	5.53 (3/5H,[e] br d[d])	5.15 (s)	6.80—7.15 (3H, m) 7.20—7.45 (m)	3.81 (s)
8g	4.96 (7/23H, br) 5.09 (16/23H, m)	6.07 (dd[b])	6.66 (d[c])	5.48 (16/23H, br d[d]) 6.99 (7/23H, br)	5.15 (s)	6.84 (2H, m) 7.20—7.42 (m)	3.81 (s)
8i	5.02 (br)[a]	6.17 (m)	7.04 (d[c])	5.70 (br d[d]) 7.72 (br)	5.16 (s)	7.08—7.60 (m)	
8j	4.08 (br)[a]	6.24 (dd[b])	6.54 (1/3H, d[c]) 6.63 (2/3H, d[c])	5.53 (2/3H,[e] br)	5.15 (s)	7.12—7.60 (m)	
8k[g]	4.96 (7/17H, br)[a]	6.22 (dd[b])	6.64 (d[c])	5.54 (10/17H,[e] br)	5.16 (s)	7.10—7.55 (m)	
8l	5.1 (m)[h]	6.37 (dd[b])	6.73 (d[c])	5.70 (br d[d])	5.15 (s)	7.35 (m) 7.89 (2H, d[f])	2.59
8n	5.04—5.30 (m)	6.27 (dd[b])	—[i]	5.77 (4/5H, br d[d]) 6.85 (1/5H, br)	5.19 (s)	7.21—7.58 (m) 7.75—7.88 (2H, m) 7.90—8.06 (1H, m)	
8o	4.92 (br) 5.08 (br)	6.05 (dd[b])	6.83 (d[c])	5.56 (br d[f]) 6.72 (br)	5.14 (s)	6.89—7.05 (2H, m) 7.15—7.45 (6H, m)	

a) The major signal overlaps with the signal arising from $PhC\underline{H}_2$. *b*) J=5—7 and 16 Hz. *c*) J=15—16 Hz. *d*) J=5—7 Hz. *e*) The signal arising from the rest of NH probably overlaps with that of aromatic protons. *f*) J=8 Hz. *g*) Small signals at δ 3.73 (d) and 6.90 (t) (J=7 Hz each) are suggestive of contamination with a trace of the α,β-unsaturated isomer. *h*) The sample is not pure enough to identify the chemical shift accurately. *i*) Overlapping with a signal arising from aromatic protons at δ 7.21—7.58.

Table 4. ^{1}H-NMR Data for [*S*-(*E*)]-4-Aryl-2-[(benzyloxycarbonyl)amino]-3-butenoic Acid Methyl Esters (**10**)

Compd.	Chemical shift (δ) in $CDCl_3$						
	C(α)-H	C(β)-H	C(γ)-H	NH	$PhC\underline{H}_2$	Aromatic H	CO_2Me and other Me
10a	4.93 (br)[a] 5.08 (m)	6.18 (dd[b])	6.65 (d[c])	5.56 (1/5H, br) 5.70 (4/5H, br d[d])	5.12 (s)	7.20—7.40 (m)	3.74 (s)
10b	4.97—5.29 (m)	6.06 (dd[b])	6.89 (d[c])	5.55 (br)	5.15 (s)	7.10—7.50 (m)	3.79 (s) 2.31 (s)
10c	4.95 (br)[a] 5.07 (br dd[d])	6.16 (dd[b])	6.63 (d[c])	5.46 (br)[a] 5.62 (br d[d])	5.13 (s)	7.03—7.40 (m)	3.76 (s) 2.32 (s)
10d	4.96 (1/7H, br) 5.06 (6/7H, br dd[d])	6.12 (dd[b])	6.63 (d[c])	5.46 (1/7H, br) 5.60 (6/7H, br d[d])	5.13 (s)	7.10 (2H, d[e]) 7.24 (2H, d[e]) 7.34 (m)	3.76 (s) 2.32 (s)
10e	5.08 (m)	6.24 (dd[b])	6.98 (d[c])	5.34 (br)[a] 5.53 (br d[d])	5.14 (s)	6.86 (1H, d[f]) 6.91 (1H, dd[e]) 7.20—7.45 (m)	3.78 (br s) 3.83 (s)
10f	4.96 (br)[a] 5.08 (m)	6.18 (dd[b])	6.63 (d[c])	5.50 (br)[a] 5.63 (br d[e])	5.13 (s)	6.81 (1H, m) 6.88 (1H, s) 6.94 (1H, d[e]) 7.22 (1H, dd[e]) 7.27—7.46 (m)	3.77 (s) 3.79 (s)
10g	5.05 (m)	6.04 (dd[b])	6.61 (d[c])	5.38 (1/5H, br) 5.53 (4/5H, br d[d])	5.14 (s)	6.85 (2H, d[f]) 7.08—7.48 (m)	3.78 (s) 3.81 (s)
10h	5.03 (m)	5.99 (dd[b])	6.57 (d[c])	5.62 (br d[d])	5.14 (s)	6.76 (2H, d[f]) 7.18 (2H, d[f]) 7.36 (m)	3.78 (s)
10i	4.94—5.25 (m)	6.17 (dd[b])	7.02 (d[c])	5.42 (br)[a] 5.58 (br)	5.16 (s)	7.07—7.58 (m)	3.81 (s)
10j[g]	4.95 (br)[a] 5.08 (m)	6.20 (dd[b])	6.58 (d[c])	5.54 (br)[a] 5.64 (br d[d])	5.14 (s)	7.10—7.55 (m)	3.78 (s)
10k	4.97 (br)[a] 5.07 (m)	6.18 (dd[b])	6.59 (d[c])	5.53 (br)[a] 5.63 (br d[d])	5.13 (s)	7.10—7.50 (m)	3.78 (s)
10l	5.02—5.22 (m)	6.33 (dd[b])	6.70 (d[c])	5.52 (br)[a] 5.64 (br d[e])	5.15 (s)	7.37 (m) 7.43 (2H, d[e]) 7.91 (2H, d[e])	3.80 (s) 2.59 (s)
10n	5.00—5.29 (m)	6.21 (dd[b])	7.43 (d[c])	5.75 (br d[d])	5.16 (s)	7.23—7.55 (m) 7.71—7.86 (2H, m) 8.01 (1H, br d[d])	3.78 (s)
10o	4.93 (br)[a] 5.04 (m)	6.01 (dd[b])	6.79 (d[c])	5.42 (br)[a] 5.55 (br d[d])	5.14 (s)	6.92—7.02 (2H, m) 7.18 (1H, m) 7.36 (m)	3.78 (s)

a) A very small signal. *b*) J=6—7 and 16 Hz. *c*) J=16 Hz. *d*) J=6—7 Hz. *e*) J=8 Hz. *f*) J=9 Hz. *g*) Small signals at δ 3.53 (d) and 6.71 (t) (J=7 Hz each) are indicative of contamination with a trace of the α,β-unsaturated isomer **11j**.

by recrystallization. The optical purities of these compounds were determined to be 98—99% ee according to the procedure described above. We failed to purify **8a, c, e, f, i, k, n** by recrystallization. These compounds were isolated as their methyl esters **10a, c, e, f, i, k, n** in 19—68% yields. The optical purities of **10a, c, e, f, i, k, n** thus obtained, were estimated to be 80—98% ee after conversion into **9a, c, e, f, n** by catalytic hydrogenation followed by methoxycarbonylation.

In conclusion, the present investigation revealed that palladium-catalyzed arylation of **6** in H_2O was not necessarily applicable to a wide range of aryl iodides **7**. Nevertheless, this reaction proved useful to multiply the members of the small family of optically active **5** in an exclusively (*E*)-selective manner.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or Büchi model 530 capillary melting point apparatus and values are corrected. Optical rotations were measured with a Horiba SEPA-300 polarimeter using a 1-dm sample tube. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Hitachi model 320 UV spectrophotometer, a Shimadzu FTIR-8100 IR spectrophotometer, a JEOL JNM-EX-270 or a JNM-GSX-500 NMR spectrometer (measured in $CDCl_3$ at 25 °C with Me_4Si as an internal standard). The HPLC system employed consisted of a Tosoh CCPD pump, an injection valve unit, a UV-8020 detector (operated at 254 nm), and a Chromatocorder 21 integrator, or a Waters 6000A pump, a U6K injector, and a model 440 absorbance detector (operated at 254 nm) equipped with a Takeda Riken TR-2217 automatic integrator. Elemental analyses and MS measurements were performed by Dr. M. Takani and her associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[14] Preparative TLC was performed on Merck Silica gel 60 F_{254} plates (0.5 mm thickness). The following abbreviations are used: br=broad, d=doublet, dd=doublet-of-doublets, ddd=doublet-of-doublets-of-doublets, m=multiplet, s=singlet, sh=shoulder, t=triplet.

Palladium-Catalyzed Coupling of 6 with Aryl Iodide 7 (Tables 1 and 2) The procedure for arylation with 2-methoxyphenyl iodide (**7e**) (Table 2, entry 5) will be described below in detail as a typical example of the experiments summarized in Tables 1 and 2.

Reaction with 7e Compound **6**[9,11a] (of 98% ee) (129 mg, 0.55 mmol) was added to a mixture of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), **7e** (117 mg, 0.5 mmol), $NaHCO_3$ (126 mg, 1.5 mmol), Bu_4NCl (139 mg, 0.5 mmol), and H_2O (8 ml), and the whole was stirred at 45 °C for 75 h. The resulting mixture was brought to pH 3 by addition of 10% aqueous H_3PO_4 and extracted with AcOEt (5×10 ml). The organic layers were combined, washed with 10% aqueous H_3PO_4 (3×20 ml), dried ($MgSO_4$), and

concentrated *in vacuo* to leave a brown foam (200 mg). This was subjected to flash chromatography [$CHCl_3$–MeOH (3 : 1, v/v)]. Crude **7e** obtained from earlier fractions was purified by preparative TLC (AcOEt) to give **7e** (3 mg, 3%) as a colorless oil. The fractions containing [*S*-(*E*)]-2-[(benzyloxycarbonyl)amino]-4-(2-methoxyphenyl)-3-butenoic acid (**8e**) were collected and concentrated. The residue was mixed with 10% aqueous H_3PO_4 (5 ml), and the mixture was extracted with $CHCl_3$ (4 × 10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated to afford crude **8e** (156 mg) as a brown foam, ^{1}H-NMR (Table 3). A portion (82 mg) of crude **8e** was treated with 2 M Me_3SiCHN_2–hexane (0.2 ml) in MeOH–benzene (1 : 4, v/v) (2 ml), and the resulting yellow solution was concentrated *in vacuo*. The oily residue was subjected to flash chromatography [hexane–AcOEt (3 : 1, v/v)] followed by repeated preparative TLC [hexane–AcOEt (2 : 1, v/v) and benzene–AcOEt (15 : 1, v/v)], providing (*S*)-2-[(benzyloxycarbonyl)-amino]-3-butenoic acid methyl ester (5 mg, 7%), which was identical (by comparison of the ^{1}H-NMR spectrum and TLC mobility) with an authentic specimen,[11a] and [*S*-(*E*)]-2-[(benzyloxycarbonyl)amino]-4-(2-methoxyphenyl)-3-butenoic acid methyl ester (**10e**) (52 mg, 56%), mp 77.5—79.5 °C. Recrystallization of this sample from hexane afforded an analytical sample of **10e** as colorless plates, mp 89.5—90 °C; $[\alpha]_D^{31}$ +78.7° (c = 0.500, MeOH); MS m/z: 355 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3357 (NH), 1742 (ester CO), 1698 (carbamate CO); ^{1}H-NMR (Table 4). *Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.61; H, 5.99; N, 3.96.

The rest (74 mg) of the crude **8e** was hydrogenated over 10% Pd–C (75 mg) in MeOH (5 ml) at room temperature for 4 h. The catalyst was filtered off and washed with hot MeOH (80 ml). The filtrate and washings were combined and concentrated *in vacuo*. The solid residue (40 mg) was treated with $ClCO_2Me$ (50 mg) in a mixture of dioxane (2.5 ml) and H_2O (2.5 ml) in the presence of $NaHCO_3$ (250 mg) at room temperature for 5 h. The resulting mixture was brought to pH 1 with 10% aqueous HCl and extracted with $CHCl_3$ (5 × 5 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give a slightly yellow foam (62 mg), which was subjected to flash chromatography [$CHCl_3$–MeOH (4 : 1, v/v)] to give a colorless oil (8 mg). This was dissolved in benzene–MeOH (4 : 1, v/v) (1 ml), and 2 M Me_3SiCHN_2–hexane (0.05 ml) was added. The yellow solution was concentrated *in vacuo* to leave a colorless foam (8 mg), which was purified by repeated preparative TLC [hexane–AcOEt (2 : 1, v/v) and then benzene–AcOEt (15 : 1, v/v)] to give (*S*)-α-[(methoxycarbonyl)amino]-2-methoxybenzenebutanoic acid methyl ester (**9e**) (3 mg) as a colorless foam. This sample showed identical ^{1}H-NMR spectrum and TLC mobility with those of (±)-**9e** (*vide infra*) and was of 95% ee on the basis of HPLC.

In a separate run, crude **8e** (143 mg) was obtained as a colorless foam from the reaction of **6**[9,11a] (of 99% ee) (118 mg, 0.5 mmol) and **7e** (129 mg, 0.55 mmol) after flash chromatography [$CHCl_3$–MeOH–H_2O (20 : 7 : 1, v/v)]. As this sample could not be crystallized, it was converted into **10e** in a manner similar to that described above, and the product was recrystallized from hexane, giving **10e** (99 mg, 56%), mp 87.5—88 °C; $[\alpha]_D^{23}$ +75.7° (c = 0.502, MeOH). A portion (13 mg) of this sample was hydrogenated over 10% Pd–C (15 mg) in a mixture of 0.1 N aqueous HCl (1 ml) and MeOH (10 ml), and the product was treated with $ClCO_2Me$ in a manner similar to that described above to give **9e** (8 mg) as a colorless oil after preparative TLC [hexane–AcOEt (3 : 1, v/v)]. This sample was of 97% ee as judged from HPLC.

Preparation of 8 Compounds **8** were prepared from **6**[9,11a] (of 99% ee) and 1.1 mol eq of **7** in a manner similar to that described above for the preparation of crude **8e**. The resulting crude products were purified by flash chromatography (the eluents are shown in Table 2) followed by recrystallization.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(2-methylphenyl)-3-butenoic Acid (8b) Crude **8b** (113 mg) (mp 80—95 °C), which was obtained from **6** (118 mg, 0.5 mmol), was purified by precipitation from AcOEt–hexane (1 : 10, v/v) to afford **8b** (85 mg, 52%), mp 97.5—98 °C; $[\alpha]_D^{22}$ +84.3° (c = 0.502, MeOH). A small portion of this sample was converted into (*S*)-α-[(methoxycarbonyl)amino]-2-methylbenzenebutanoic acid methyl ester (**9b**) in a manner similar to that described above for the preparation of **9e**, and the product was purified by repeated preparative TLC [hexane–AcOEt (3 : 1, v/v) and then benzene–AcOEt (15 : 1, v/v)] to provide **9b** as a colorless oil, which showed an identical ^{1}H-NMR spectrum with that of (±)-**9b** (*vide infra*). This sample was of 99% ee on the basis of HPLC analysis. The rest of **8b** was further purified by precipitation from hexane–AcOEt (10 : 1, v/v) to afford an analytical sample of **8b** as colorless needles, mp 101—101.5 °C; $[\alpha]_D^{25}$ +81° (c = 0.108, MeOH); MS m/z: 325 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3293 (NH), 1696 (CO_2H and carbamate CO); ^{1}H-NMR (Table 3). *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.04; H, 5.94; N, 4.26.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(4-methylphenyl)-3-butenoic Acid (8d) Crude **8d** (130 mg), which was obtained from **6** (118 mg, 0.5 mmol), was recrystallized from benzene to give **8d** (75 mg, 46%), mp 148.5—149 °C; $[\alpha]_D^{16}$ +99.8° (c = 0.502, MeOH). A portion of this sample was converted into (*S*)-α-[(methoxycarbonyl)amino]-4-methylbenzenebutanoic acid methyl ester (**9d**), and the crude product was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)], giving **9d** as a colorless oil. This sample was of 98% ee on the basis of HPLC analysis. Further recrystallization of the rest of **8d** from benzene afforded an analytical sample as colorless needles, mp 148.5—149 °C; $[\alpha]_D^{19}$ +94.7° (c = 0.502, MeOH); MS m/z: 325 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3306 (NH), 1727 (CO_2H), 1688 (carbamate CO); ^{1}H-NMR (Table 3). *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.27; H, 5.88; N, 4.26.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(4-methoxyphenyl)-3-butenoic Acid (8g) Crude **8g** (185 mg), which was obtained from **6** (118 mg, 0.5 mmol), was recrystallized from benzene to give **8g** (80 mg, 49%), mp 139.5—140.5 °C; $[\alpha]_D^{15}$ +104° (c = 0.502, MeOH). The optical purity of this sample was determined to be 99% ee according to the reported procedure.[8] Further recrystallization of this sample from benzene afforded an analytical sample of **8g** as colorless needles, mp 141.5—142.5 °C; $[\alpha]_D^{19}$ +113° (c = 0.502, MeOH); MS m/z: 341 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3306 (NH), 1725 (CO_2H), 1684 (carbamate CO); ^{1}H-NMR (Table 3). *Anal.* Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.92; H, 5.64; N, 4.03.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-phenyl-3-butenoic Acid Methyl Ester (10a) The crude product (478 mg), which was obtained from the reaction of **6**[9,11a] (of 99% ee) (518 mg, 2.2 mmol) with **7a** (494 mg, 2.42 mmol), was recrystallized from hexane–AcOEt (1 : 1, v/v) to give [*S*-(*E*)]-2-[(benzyloxycarbonyl)amino]-4-phenyl-3-butenoic acid (**8a**) (71 mg), mp 164.5—165.5 °C. The mother liquor was concentrated *in vacuo*, and the residue was recrystallized from benzene to afford a second crop of **8a** (48 mg, the total yield was 17%), mp 165.5—166 °C. Further recrystallization from hexane–AcOEt (2 : 1, v/v) provided an analytical sample of (±)-**8a** (*vide infra*) as colorless needles, mp 167—167.5 °C. *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.29; H, 5.40; N, 4.37. The ^{1}H-NMR spectrum of this sample was identical with that of **8a** (Table 3). A portion of this sample was converted into **9a**[1b] in a manner similar to that described for the preparation of **9e**. The product was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v) and then benzene–AcOEt (15 : 1, v/v)]. HPLC analysis[4] of this sample showed that it was most likely (±)-**9a**.

In a separate run, crude **8a** (117 mg) was obtained from the reaction of **6** (of 99% ee) (118 mg, 0.5 mmol) and **7a** (112 mg, 0.55 mmol). It was dissolved in MeOH–benzene (1 : 4, v/v) (2 ml), and 2 M Me_3SiCHN_2–hexane (0.5 ml) was added. The resulting solution was concentrated *in vacuo* to leave a colorless oil (120 mg). A portion (57 mg) of this material was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)] to afford **10a** (46 mg, 60%) as a colorless oil, $[\alpha]_D^{23}$ +66.7° (c = 0.458, MeOH); MS m/z: 325 (M^+); ^{1}H-NMR (Table 4). This sample was converted into **9a**[1b] by catalytic hydrogenation followed by methoxycarbonylation in a manner similar to that described above for the preparation of **9e** from **10e**, and the product was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)]. This sample of **9a** was of 82% ee on the basis of HPLC analysis.[4]

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(2-methylphenyl)-3-butenoic Acid Methyl Ester (10b) (Table 2, entry 2) Crude **10b** was purified by flash chromatography [benzene–AcOEt (15 : 1, v/v)] to afford **10b**, mp 76.5—78 °C. Recrystallization of **10b** from hexane provided an analytical sample as colorless needles, mp 78.5—79.5 °C; $[\alpha]_D^{22}$ +71.3° (c = 0.502, MeOH); MS m/z: 339 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3297 (NH), 1740 (ester CO), 1690 (carbamate CO); ^{1}H-NMR (Table 4). *Anal.* Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.68; H, 6.26; N, 4.08.

This sample of **10b** was converted into **9b** in a manner similar to that described above for the transformation of **10e** into **9e**. The product was purified by preparative TLC [benzene–AcOEt (15 : 1, v/v)] to afford **9b** as a colorless oil. This sample was identical (by comparison of the ^{1}H-NMR spectrum and TLC mobility) with **9b**, which was prepared from **8b** as described above, and was of more than 99% ee on the basis of HPLC analysis.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(3-methylphenyl)-3-butenoic

Acid Methyl Ester (10c) Crude **8c** (516 mg) (mp 70—80 °C) obtained from the reaction of **6**[9,11a] (of 99% ee) (518 mg, 2.2 mmol) and **7c** (528 mg, 2.42 mmol), was recrystallized from hexane–AcOEt (2 : 1, v/v) to afford [*S*-(*E*)]-2-[(benzyloxycarbonyl)amino]-4-(3-methylphenyl)-3-butenoic acid (**8c**) (55 mg, 8%), mp 159—160.5 °C; $[\alpha]_D^{17}$ +8.7° (*c* = 0.502, MeOH). A portion of this sample was converted into (*S*)-α-[(methoxycarbonyl)-amino]-3-methylbenzenebutanoic acid methyl ester (**9c**), and the product was purified by repeated preparative TLC [hexane–AcOEt (2 : 1, v/v) and then benzene–AcOEt (15 : 1, v/v)] to give a colorless oil. This sample of **9c** was of 10% ee on the basis of HPLC analysis. Two more recrystallizations of the above sample of **8c** from hexane–AcOEt (2 : 1, v/v) afforded an analytical sample, most likely of (±)-**8c**, as colorless needles, mp 162.5—163 °C; MS *m/z*: 325 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3281 (NH), 1732 (CO_2H), 1682 (carbamate CO). *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.21; H, 5.99; N, 4.25. The ^{1}H-NMR spectrum of this sample was identical with that of crude **8c** (Table 3).

In a separate run, crude **8c** (97 mg) was obtained from the reaction of **6** (of 99% ee) (118 mg, 0.5 mmol) and **7c** (120 mg, 0.55 mmol). It was dissolved in MeOH–benzene (1 : 4, v/v) (2 ml), and 2 M Me_3SiCHN_2–hexane (0.52 ml) was added. The resulting solution was concentrated *in vacuo* to leave a colorless oil (93 mg). A portion (47 mg) of this material was purified by preparative TLC [benzene–AcOEt (15 : 1, v/v)] to afford **10c** (40 mg, 46%) as a colorless oil, $[\alpha]_D^{25}$ +64.2° (*c* = 0.373, MeOH); MS *m/z*: 339 (M^+); ^{1}H-NMR (Table 4). This sample was converted into **9c** by catalytic hydrogenation followed by methoxycarbonylation, and the product was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)]. This sample of **9c** showed an identical ^{1}H-NMR spectrum with that of (±)-**9c** (*vide infra*) and was of 80% ee on the basis of HPLC analysis.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(4-methylphenyl)-3-butenoic Acid Methyl Ester (10d) (Table 2, entry 4) This compound **10d** was obtained as a colorless oil after flash chromatography [benzene–AcOEt (15 : 1, v/v)], ^{1}H-NMR (Table 4).

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(3-methoxyphenyl)-3-butenoic Acid Methyl Ester (10f) Crude **8f**, which was obtained from the reaction of **6**[9,11a] (of 99% ee) (118 mg, 0.5 mmol) and **7f** (129 mg, 0.55 mmol) followed by flash chromatography [$CHCl_3$–MeOH–H_2O (20 : 7 : 1, v/v)], was methylated, and the product was purified by flash chromatography [benzene–AcOEt (15 : 1, v/v)], giving **10f** (122 mg, 69%) as a colorless oil, $[\alpha]_D^{21}$ +67.6° (*c* = 0.502, MeOH); MS *m/z*: 355 (M^+); ^{1}H-NMR (Table 4). A portion of this sample was converted into (*S*)-α-[(methoxycarbonyl)amino]-3-methoxybenzenebutanoic acid methyl ester (**9f**) [purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)]]. This sample showed an identical ^{1}H-NMR spectrum with that of (±)-**9f** (*vide infra*) and was of 91% ee on the basis of HPLC analysis.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(4-methoxylphenyl)-3-butenoic Acid Methyl Ester (10g) (Table 1, entry 1 and Table 2, entry 7) This compound was obtained as a colorless oil after flash chromatography [hexane–AcOEt (3 : 1, v/v)], ^{1}H-NMR (Table 4).

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(4-hydroxylphenyl)-3-butenoic Acid Methyl Ester (10h) (Table 2, entry 8) Obtained as a colorless oil after flash chromatography [hexane–AcOEt (3 : 2, v/v)], ^{1}H-NMR (Table 4).

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(2-bromophenyl)-3-butenoic Acid Methyl Ester (10i) Crude **10i**, which was obtained from **6**[9,11a] (of 99% ee) (118 mg, 0.5 mmol) and **7i** (156 mg, 0.55 mmol), was purified by flash chromatography [benzene–AcOEt (15 : 1, v/v)] to afford **10i** (86 mg) as a partly crystallized oil. Recrystallization of this sample from hexane provided **10i** (38 mg, 19%), mp 78.5—79 °C; $[\alpha]_D^{23}$ +52.6° (*c* = 0.502, MeOH). A portion of this sample was converted into **9a** by catalytic hydrogenation followed by methoxycarbonylation. This sample was identical (by comparison of the ^{1}H-NMR spectrum and TLC mobility) with authentic **9a**[1b] and of 98% ee on the basis of HPLC analysis. Further recrystallization of **10i** from hexane provided an analytical sample as colorless needles, mp 78.5—79.5 °C; $[\alpha]_D^{20}$ +52.1° (*c* = 0.502, MeOH); MS *m/z*: 403, 405 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3349 (NH), 1742 (ester CO), 1696 (carbamate CO); ^{1}H-NMR (Table 4). *Anal.* Calcd for $C_{19}H_{18}BrNO_4$: C, 56.45; H, 4.49; N, 3.46. Found: C, 56.71; H, 4.46; N, 3.20.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(3-bromophenyl)-3-butenoic Acid Methyl Ester (10j) (Table 2, entry 10) This compound was obtained as a colorless oil after flash chromatography [benzene–AcOEt (15 : 1, v/v)], MS *m/z*: 403, 405 (M^+); ^{1}H-NMR (Table 4). The ^{1}H-NMR spectrum indicated that this sample was contaminated with a trace of the α,β-unsaturated isomer **11j**.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(4-bromophenyl)-3-butenoic Acid Methyl Ester (10k) Crude **8k** (109 mg) obtained as a colorless oil from the reaction of **6**[9,11a] (of 99% ee) (118 mg, 0.5 mmol) and **7k** (156 mg, 0.55 mmol) was methylated with Me_3SiCHN_2 in the usual manner, and the product was subjected to preparative TLC [benzene–AcOEt (15 : 1, v/v)] to give **10k** (84 mg, 41%) as a colorless oil, $[\alpha]_D^{23}$ +52.6° (*c* = 0.797, MeOH); MS *m/z*: 403, 405 (M^+); ^{1}H-NMR (Table 4). A portion of this sample was converted into **9a** by catalytic hydrogenation followed by methoxycarbonylation. This sample of **9a** was of 80% ee on the basis of HPLC analysis.

[*S*-(*E*)]-4-(4-Acetylphenyl)-2-[(benzyloxycarbonyl)amino]-3-butenoic Acid Methyl Ester (10l) (Table 2, entry 12) A 29 : 7 : 3 mixture of **10l**, 4-(4-acetylphenyl)-2-[(benzyloxycarbonyl)amino]-2-butenoic acid methyl ester (**11l**), and the (*Z*)-isomer of **10l** was obtained after flash chromatography [hexane–AcOEt (5 : 3, v/v)] followed by preparative TLC [hexane–AcOEt (2 : 1, v/v)], ^{1}H-NMR (Table 4).

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(naphthalen-1-yl)-3-butenoic Acid Methyl Ester (10n) Crude **8n** (127 mg) was obtained as a foam from the reaction of **6**[9,11a] (of 99% ee) (118 mg, 0.5 mmol) and **7n** (140 mg, 0.55 mmol). It was crystallized from hexane–AcOEt (2 : 1, v/v) to give [*S*-(*E*)]-2-[(benzyloxycarbonyl)amino]-4-(1-naphthyl)-3-butenoic acid (**8n**) (26 mg, 14%), mp 170—171 °C. A portion of this sample was converted into (*S*)-α-[(methoxycarbonyl)amino]-1-naphthalenebutanoic acid methyl ester (**9n**) by hydrogenation, methoxycarbonylation, and methylation. The product was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)] to give a colorless oil. This showed an identical ^{1}H-NMR spectrum with that of (±)-**9n** (*vide infra*) and was of 7% ee on the basis of HPLC analysis. Three more recrystallizations of the above sample of **8n** from hexane–AcOEt (2 : 1, v/v) afforded an analytical sample, most likely of (±)-**8n**, as colorless needles, mp 174—175 °C; MS *m/z*: 361 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3287 (NH), 1734 (CO_2H), 1678 (carbamate CO). *Anal.* Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.06; H, 5.34; N, 3.77.

In a separate run, crude **8n** (145 mg) obtained from the reaction of **6** (of 99% ee) (118 mg, 0.5 mmol) and **7n** (140 mg, 0.55 mmol) was methylated with Me_3SiCHN_2 in the usual manner to give **10n** (153 mg) as a colorless oil. A portion (72 mg) of this material was subjected to preparative TLC [hexane–AcOEt (2 : 1, v/v)] to give **10n** (51 mg, 57%) as a colorless oil, $[\alpha]_D^{23}$ +47.9° (*c* = 0.490, MeOH); MS *m/z*: 375 (M^+); ^{1}H-NMR (Table 4). A portion of this sample was converted into **9n** by catalytic hydrogenation followed by methoxycarbonylation, and the crude product was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)] to give a colorless oil. This sample of **9n** was of 86% ee on the basis of HPLC analysis.

[*S*-(*E*)]-2-[(Benzyloxycarbonyl)amino]-4-(thiophen-2-yl)-3-butenoic Acid Methyl Ester (10o) (Table 2, entry 15) This compound was obtained as a colorless oil after flash chromatography [benzene–AcOEt (15 : 1, v/v)] followed by repeated preparative TLC [benzene–AcOEt (15 : 1, v/v)], MS *m/z*: 331 (M^+); ^{1}H-NMR (Table 4).

(±)-α-[(Methoxycarbonyl)amino]-2-methylbenzenebutanoic Acid Methyl Ester [(±)-9b] A solution of **10b** (39 mg) in Et_3N–MeOH (1 : 10, v/v) (3 ml) was kept at room temperature for 2 h (until it lost optical rotation) and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (10 ml), and the solution was washed with 10% aqueous H_3PO_4 (3 × 5 ml), dried ($MgSO_4$), and concentrated *in vacuo* to leave a colorless oil (37 mg), which was shown to be a 7 : 5 mixture of (±)-**10b** and a single geometrical isomer of 2-[(benzyloxycarbonyl)amino]-4-(2-methylphenyl)-2-butenoic acid methyl ester (**11b**) by analysis of the ^{1}H-NMR spectrum [^{1}H-NMR δ: 2.24 (5/7 × 3H, s, CMe of **11b**), 2.30 [3H, s, CMe of (±)-**10b**], 3.51 [5/7 × 2H, d, *J* = 7 Hz, C(γ)-H_2 of **11b**], 3.73 (5/7 × 3H, s, CO_2Me of **11b**), 3.77 [3H, s, CO_2Me of (±)-**10b**], 5.14 [2H, s, overlapping with a 1H multiplet arising from C(α)-H of (±)-**10b**, $PhC\underline{H}_2$ of (±)-**10b**], 5.17 (5/7 × 2H, s, $PhC\underline{H}_2$ of **11b**), 5.62 [1H, br d, *J* = 8 Hz, NH of (±)-**10b**], 6.06 [1H, dd, *J* = 7, 16 Hz, C(β)-H of (±)-**10b**], 6.40 (5/7H, br, NH of **11b**), 6.69 [5/7H, t, *J* = 7 Hz, C(β)-H of **11b**], 6.89 [1H, d, *J* = 16 Hz, C(γ)-H of (±)-**10b**], 7.08—7.44 (m, aromatic protons)]. This mixture was subjected to hydrogenation followed by methoxycarbonylation, giving (±)-**9b** (28 mg), which was purified by preparative TLC [benzene–AcOEt (15 : 1, v/v)] to afford (±)-**9b** as a colorless oil, ^{1}H-NMR δ: 1.93, 2.11 [1H each, m, C(β)-H_2], 2.28 (3H, s, CMe), 2.64 [2H, m, C(γ)-H_2], 3.71, 3.74 (3H each, s, two CO_2Me's), 4.45 [a total of 1H with a small broad signal at 4.32, m, C(α)-H], 5.30 (a total of 1H with a small broad signal at 5.15, br d, *J* = 7 Hz, NH), 7.05—7.20 (4H, m, aromatic protons).

(±)-α-[(Methoxycarbonyl)amino]-3-methylbenzenebutanoic Acid Methyl Ester [(±)-9c] Compound **10c** (54 mg) was treated with Et_3N

in a manner similar to that described above for the reaction of **10b** to give a mixture (45 mg) of (±)-**10c** and 2-[(benzyloxycarbonyl)amino]-4-(3-methylphenyl)-2-butenoic acid methyl ester (**11c**) [^{1}H-NMR δ: 2.31 (3H, s, CMe of **11c**), 2.33 [5/6 × 3H, s, CMe of (±)-**10c**], 3.51 [2H, d, J=7 Hz, C(γ)-H$_2$ of **11c**], 3.73 (3H, s, CO_2Me of **11c**), 3.77 [5/6 × 3H, s, CO_2Me of (±)-**10c**], 5.07 [a total of 5/6H with a small broad signal at 4.95, br dd, J=7 Hz each, C(α)-H of (±)-**10c**], 5.13 [5/6 × 2H, s, PhC$\underline{H}_2$ of (±)-**10c**], 5.17 (2H, s, PhC$\underline{H}_2$ of **11c**), 5.62 [a total of 5/6H with a small broad signal at 5.46, br d, J=8 Hz, NH of (±)-**10c**], 6.17 [5/6H, dd, J=6, 16 Hz, C(β)-H of (±)-**10c**], 6.40 (1H, br, NH of **11c**), 6.63 [5/6H, d, J=16 Hz, C(γ)-H of (±)-**10c**], 6.77 [1H, t, J=7 Hz, C(β)-H of **11c**], 7.08—7.44 (m, aromatic protons)]. This mixture was subjected to hydrogenation followed by methoxycarbonylation, giving (±)-**9c** (34 mg), which was purified by preparative TLC [benzene–AcOEt (15 : 1, v/v)] to afford (±)-**9c** (18 mg) as a colorless foam, ^{1}H-NMR δ: 1.97, 2.17 [1H each, m, C(β)-H$_2$], 2.32 (3H, s, CMe), 2.63 [2H, m, C(γ)-H$_2$], 3.70, 3.72 (3H each, s, two CO_2Me's), 4.28 (1/7H, br), 4.41 (6/7H, m) [C(α)-H], 5.10 (1/7H, br), 5.26 (6/7H, br d, J=7 Hz) (NH), 6.98 [3H, m, C(2)-, C(4)-, C(6)-H], 7.17 [1H, dd, J=7 Hz each, C(5)-H].

(±)-α-[(Methoxycarbonyl)amino]-4-methylbenzenebutanoic Acid Methyl Ester [(±)-9d] Compound **10d** (47 mg) was treated with Et_3N in a manner similar to that described above for the reaction of **10b** to give a mixture (27 mg) of (±)-**10d** and 2-[(benzyloxycarbonyl)amino]-4-(4-methylphenyl)-2-butenoic acid methyl ester (**11d**) [^{1}H-NMR δ: 2.31 (3/7 × 3H, s, CMe of **11d**), 2.32 [3H, s, CMe of (±)-**10d**], 3.51 [3/7 × 2H, d, J=7 Hz, C(γ)-H$_2$ of **11d**], 3.72 (3/7 × 3H, s, CO_2Me of **11d**), 3.76 [3H, s, CO_2Me of (±)-**10d**], 5.06 [a total of 1H with a small broad signal at 4.96, m, C(α)-H of (±)-**10d**], 5.13 [2H, s, PhC$\underline{H}_2$ of (±)-**10d**], 5.16 (3/7 × 2H, s, PhC$\underline{H}_2$ of **11d**), 5.60 [a total of 1H with a small broad signal at 5.46, br d, J=7 Hz, NH of (±)-**10d**], 6.12 [1H, dd, J=6, 16 Hz, C(β)-H of (±)-**10d**], 6.39 (3/7H, br, NH of **11d**), 6.63 [1H, d, J=16 Hz, C(γ)-H of (±)-**10d**], 6.76 [3/7H, t, J=7 Hz, C(β)-H of **11d**], 7.02—7.48 (m, aromatic protons)]. This mixture was subjected to hydrogenation followed by methoxycarbonylation. The product was purified by preparative TLC [benzene–AcOEt (15 : 1, v/v)] to afford (±)-**9d** as a colorless solid, mp 77—78 °C; IR ν_{max}^{Nujol} cm^{-1}: 3333 (NH), 1755 (ester CO), 1694 (carbamate CO); ^{1}H-NMR δ: 1.94, 2.15 [1H each, m, C(β)-H$_2$], 2.31 (3H, s, CMe), 2.63 [2H, dd, J=8 Hz each, C(γ)-H$_2$], 3.70, 3.72 (3H each, s, two CO_2Me's), 4.40 [a total of 1H with a small broad signal at 4.26, m, C(α)-H], 5.24 (a total of 1H with a small broad signal at 5.08, br d, J=7 Hz, NH), 7.02—7.16 (4H, m, aromatic protons).

(±)-α-[(Methoxycarbonyl)amino]-2-methoxybenzenebutanoic Acid Methyl Ester [(±)-9e] Compound **10e** (30 mg) was treated with Et_3N in a manner similar to that described above for the reaction of **10b** to give a mixture (27 mg) of (±)-**10e** and 2-[(benzyloxycarbonyl)amino]-4-(2-methoxyphenyl)-2-butenoic acid methyl ester (**11e**) [^{1}H-NMR δ: 3.51 [2H, d, J=8 Hz, C(γ)-H$_2$ of **11e**], 3.71 (3H, s, CO_2Me of **11e**), 3.77 [7/11 × 3H, s, CO_2Me of (±)-**10e**], 3.82 [18/11 × 3H, s, C$_6$H$_4$OM$\underline{e}$'s of (±)-**10e** and **11e**], 5.07 [7/11H, m, C(α)-H of (±)-**10e**], 5.14 [7/11 × 2H, s, PhC$\underline{H}_2$ of (±)-**10e**], 5.18 (2H, s, PhC$\underline{H}_2$ of **11e**), 5.56 [a total of 7/11H with a small broad signal at 5.35, br d, J=8 Hz, NH of (±)-**10e**], 6.24 [7/11H, dd, J=6, 16 Hz, C(β)-H of (±)-**10e**], 6.61 [1H, t, J=7 Hz, overlapping with a 1H broad signal arising from NH of **11e**, C(β)-H of **11e**], 6.81—6.95 (aromatic protons), 6.98 [7/11H, d, J=16 Hz, C(γ)-H of (±)-**10e**], 7.08—7.46 (m, aromatic protons). This mixture was subjected to hydrogenation followed by methoxycarbonylation, giving (±)-**9e**, which was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)] to afford (±)-**9e** (15 mg) as a colorless solid, mp 69—71 °C; IR ν_{max}^{Nujol} cm^{-1}: 3341 (NH), 1748 (ester CO), 1694 (carbamate CO); ^{1}H-NMR δ: 1.97, 2.11 [1H each, m, C(β)-H$_2$], 2.67 [2H, m, C(γ)-H$_2$], 3.68, 3.70 (3H each, s, two CO_2Me's), 3.82 (3H, s, C$_6$H$_4$OM$\underline{e}$), 4.39 [a total of 1H with a small broad signal at 4.25, m, C(α)-H], 5.32 (a total of 1H with a small broad signal at 5.11, br d, J=7 Hz, NH), 6.84 [1H, d, J=8 Hz, C(3)-H], 6.88 [1H, dd, J=8, 7 Hz, C(5)-H], 7.11 [1H, dd, J=7, 1.5 Hz, C(6)-H], 7.19 [1H, ddd, J=8, 8, 1.5 Hz, C(4)-H].

(±)-α-[(Methoxycarbonyl)amino]-3-methoxybenzenebutanoic Acid Methyl Ester [(±)-9f] Compound **10f** (43 mg) was treated with Et_3N in a manner similar to that described above for the reaction of **10b** to give a mixture of (±)-**10f** and 2-[(benzyloxycarbonyl)amino]-4-(3-methoxyphenyl)-2-butenoic acid methyl ester (**11f**) [^{1}H-NMR δ: 3.53 [2H, d, J=7 Hz, C(γ)-H$_2$ of **11f**], 3.74, 3.77, 3.79 (OMe's), 5.08 [7/10H, m, C(α)-H of (±)-**10f**], 5.14 [7/10 × 2H, s, PhC$\underline{H}_2$ of (±)-**10f**], 5.17 (2H, s, PhC$\underline{H}_2$ of **11f**), 5.63 [a total of 7/10H with a small broad signal at 5.50, br d, J=8 Hz, NH of (±)-**10f**], 6.18 [7/10H, dd, J=6, 16 Hz, C(β)-H of (±)-**10f**], 6.41 (1H, br, NH of **11f**), 6.63 [7/10H, d, J=16 Hz, C(γ)-H of (±)-**10f**], 6.70—6.99 [m, C(β)-H of **11f** and aromatic protons], 7.16—7.26, 7.36 (m each, aromatic protons)]. This mixture was subjected to hydrogenation followed by methoxycarbonylation, and the product was purified by preparative TLC [hexane–AcOEt (2 : 1, v/v)] to afford (±)-**9f** (10 mg) as a colorless foam, ^{1}H-NMR δ: 1.98, 2.16 [1H each, m, C(β)-H$_2$], 2.65 [2H, m, C(γ)-H$_2$], 3.70, 3.73, 3.79 (3H each, s, three OMe's), 4.41 [a total of 1H with a small broad signal at 4.29, m, C(α)-H], 5.24 (a total of 1H with a small broad signal at 5.08, br d, J=8 Hz, NH), 6.67—6.81 [3H, m, C(2)-, C(4)-, and C(6)-H], 7.20 [1H, dd, J=7.5 Hz each, C(5)-H].

(±)-α-[(Methoxycarbonyl)amino]-1-naphthalenebutanoic Acid Methyl Ester [(±)-9n] Compound **10n** (56 mg) was treated with Et_3N in a manner similar to that described above for the reaction of **10b** to give a mixture of (±)-**10n** and 2-[(benzyloxycarbonyl)amino]-4-(naphthalen-1-yl)-2-butenoic acid methyl ester (**11n**) [^{1}H-NMR δ: 3.68 (3H, s, CO_2Me of **11n**), 3.79 [1/4 × 3H, s, CO_2Me of (±)-**10n**], 3.97 [2H, d, J=7 Hz, C(γ)-H$_2$ of **11n**], 5.11 [1/4H, m, C(α)-H of (±)-**10n**], 5.16 [1/4 × 2H, s, PhC$\underline{H}_2$ of (±)-**10n**], 5.20 (2H, s, PhC$\underline{H}_2$ of **11n**), 5.74 [1/4H, br d, J=8 Hz, NH of (±)-**10n**], 6.21 [1/4H, dd, J=6, 16 Hz, C(β)-H of (±)-**10n**], 6.56 (1H, br, NH of **11n**), 6.81 [1H, t, J=7 Hz, C(β)-H of **11n**], 7.44 [d, J=16 Hz, C(γ)-H of (±)-**10n**], 7.26—7.57, 7.67—7.95 (m each, aromatic protons)]. This mixture was subjected to hydrogenation followed by methoxycarbonylation, and the product was purified by preparative TLC [benzene–AcOEt (15 : 1, v/v)] to afford (±)-**9n** as a colorless foam, ^{1}H-NMR δ: 2.12, 2.31 [1H each, m, C(β)-H$_2$], 3.13 [2H, dd, J=8 Hz each, C(γ)-H$_2$], 3.72 (6H, s, two CO_2Me's), 4.52 [a total of 1H with a small broad signal at 4.38, m, C(α)-H], 5.38 (a total of 1H with a small broad signal at 5.30, br d, J=7 Hz, NH), 7.28—7.58 [4H, m, C(2)-, C(3)-, C(6)-, C(7)-H], 7.72, [1H, d, J=8 Hz, C(4)-H], 7.85 [1H, m, C(5)-H], 7.95 [1H, m, C(8)-H].

7-Iodo-4,6-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (12) A solution of I_2 (223 mg, 0.879 mmol) in CH_2Cl_2 (5 ml) was added to a stirred mixture of 4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]-purine[15] (150 mg, 0.738 mmol), $NaHCO_3$ (678 mg, 8.07 mmol), H_2O (12 ml), and CH_2Cl_2 (12 ml) over a period of 15 min at room temperature. The resulting mixture was stirred for a further 15 min and filtered. The filter cake was washed successively with $CHCl_3$ (10 ml) and H_2O (5 ml), and dried to give **12** (214 mg, 86%), mp 210—211 °C (dec.). Recrystallization of this sample from MeOH afforded an analytical sample of **12** as colorless needles, mp 210—211 °C (dec.); MS m/z: 329 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 239 nm (ε 36000), 259 (sh) (6200), 313 (5600); IR ν_{max}^{Nujol} cm^{-1}: 1700 (CO). *Anal.* Calcd for $C_9H_8IN_5O \cdot 1/2H_2O$: C, 31.97; H, 2.68; N, 20.71. Found: C, 31.75; H, 2.62; N, 20.46.

Determination of Optical Purity of 9 by HPLC HPLC analyses were performed on pre-packed columns of 4 mm inner diameter and 250 mm length at room temperature. Clean resolution of (±)-**9d—f, n** (on a Sumichiral OA-4600 column) and **9b, c** (on a Sumichiral OA-3200 column) was attained according to the procedure reported for (±)-**9a**.[4]

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13) The product was identical (by comparison of the IR spectrum and TLC mobility) with a commercial sample (purchased from Tokyo Chemical Industry Co., Ltd.). The formation of this compound has been reported in the palladium-catalyzed reaction between **7m** and 1-[4-(methoxycarbonyl)phenyl]-1,3-butadiene: Mitsudo T., Fischetti W., Heck R. F., *J. Org. Chem.*, **49**, 1640—1646 (1984).
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