NEW SILANE REDUCTION OF AROMATIC KETONES MEDIATED BY TITANIUM TETRACHLORIDE : A SYNTHESIS OF γ- AND δ-ARYL SUBSTITUTED AMINO ACIDS†

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Abstract - Several *N*-protected 4-aryl-2-aminobutanoic acids (γ-aryl substituted amino acids ; **7a-f**) and *N*-protected 5-aryl-2-aminopentanoic acids (δ-aryl substituted amino acids ; **8a,b** and **d**) were prepared in good yields by reduction of the corresponding aromatic or heteroaromatic ketones (**3** and **4**) with triethylsilane (Et_3SiH) or dimethylphenylsilane ($PhMe_2SiH$) in the presence of titanium tetrachloride ($TiCl_4$), respectively. The reduction proceeded without racemization and was successfully applied to the synthesis of optically active γ- and δ-aryl substituted amino acids (**14a** and **15a**).

INTRODUCTION

Although 4-aryl-2-aminobutanoic acids (γ-aryl substituted amino acids) have been widely used as pharmaceutical synthons, a few convenient methods are known for preparation of those compounds.[1] It is thought that among the plausible approaches to the synthesis of 4-aryl-2-aminobutanoic acids, reduction of 4-aryl-4-oxo-2-aminobutanoic acids is one of the convenient methods for the synthesis of amino acids. Reduction of aromatic ketones with Et_3SiH is one of the effective methods for converting ketones into methylene analogs.[2] Application to reduction of aromatic ketones (**3** and **4**) bearing amino acid moiety, however, has been restricted, owing to the accompanying undesirable side reactions or a poor yield.

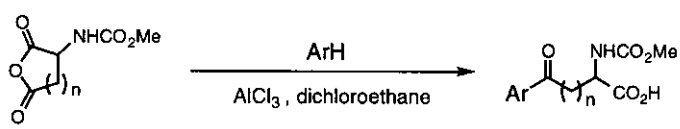
Nordlander and his co-workers reported the reduction of aromatic ketones bearing amino acid moiety with Et_3SiH in the presence of CF_3CO_2H or $BF_3 \cdot OEt_2$ for preparation of 4-phenyl-2-aminobutanoic acid derivatives.[1a] Their method gave satisfactory results only in the case of the substrates which carry methoxy groups on their aromatic ring. These results were thought to be due to the stabilization of an intermediate benzylic cation by electron-donating groups, e.g. methoxy groups. Indeed, in the case of the substrates without electron-donating groups on the aromatic ring, reductions resulted in the formation of 4-aryl-butyrolactones or in the poor yields of the desired products.

We recently reported a convenient method for preparation of several γ-aryl substituted amino acids (**7a-f**) by reduction of **3** and their trimethylsilyl esters using Et_3SiH and $TiCl_4$.[3,4a] In this paper, we wish to describe full details of our results and also describe that this reduction method can be applied to the synthesis of δ-aryl substituted amino acids (**8a,b** and **d**) successfully.

RESULTS AND DISCUSSION

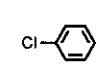
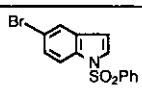
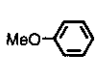
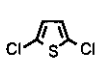
All the aromatic ketones (**3** and **4**) were prepared by the Friedel-Crafts acylation of aromatics with *N*-(methoxycarbonyl)aspartic anhydride (**1**) or *N*-(methoxycarbonyl)glutamic anhydride (**2**) respectively (Table 1).

Table 1. Preparation of Aromatic Ketones (**3** and **4**) by Friedel-Crafts Acylation.



1 : n=1
2 : n=2

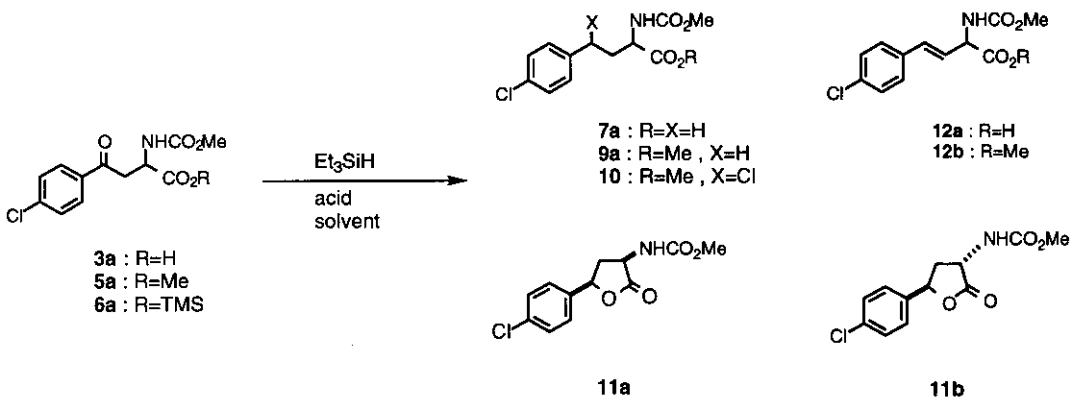
3a-f : n=1
4a,b,d : n=2

entry	ArH	n	product (yield %)	entry	ArH	n	product (yield %)
1		1	**3a** (85) (para)	6		1	**3f** (48) (3 position)
2		1	**3b** (73)	7		2	**4a** (66) (para)
3		1	**3c** (71) (para/ortho =3:1)[a]	8		2	**4b** (66)
4		1	**3d** (71) (5 position)	9		2	**4d** (54) (5 position)
5		1	**3e** (71) (3 position)				

a) *para*-isomer was isolated by recrystallization of crude product in 22% yield.

First, to determine the optimum reaction conditions, the Et_3SiH reduction of **3a** was examined under various conditions. The results are summerized in Table 2.

Table 2. Reduction of Aromatic Ketones (**3a** , **5a** and **6a**) with Et_3SiH.



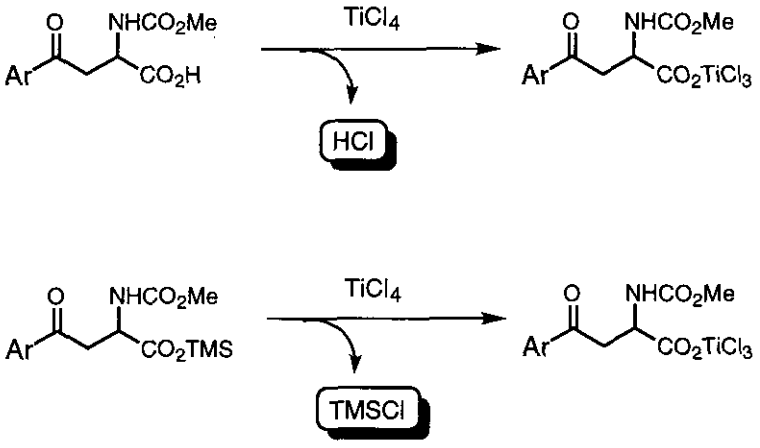
					yield (%)								
entry	substrate	acid	solvent	temp.	**3a**	**5a**	**7a**	**9a**	**10**	**11a**	**11b**	**12a**	**12b**
1	**3a**	TFA	none	reflux	-	-	-	-	-	54	7	-	-
2	**5a**	TFA	none	reflux	-	-	-	25	-	49	10	-	-
3	**3a**	$BF_3{\cdot}OEt_2$	none	70°C	-	-	-	-	-	65	6	-	-
4	**5a**	$BF_3{\cdot}OEt_2$	none	70°C	-	22	-	12[a]	-	-	-	-	28[a]
5	**3a**	$TiCl_4$	CH_2Cl_2	rt	-	-	67	-	-	-	-	-	-
6	**5a**	$TiCl_4$	CH_2Cl_2	rt	-	-	-	25	38	-	-	-	-
7	**6a**	$TiCl_4$	CH_2Cl_2	rt	-	-	88	-	-	-	-	-	-
8	**6a**	$AlCl_3$	CH_2Cl_2	rt	-	-	45[a]	-	-	-	-	23[a]	-
9	**6a**	$SnCl_4$	CH_2Cl_2	rt	100	-	-	-	-	-	-	-	-

a) The yield was determined by ^{1}H-NMR spectra.

The reduction of **3a** with Et_3SiH in boiling CF_3CO_2H or in $BF_3{\cdot}OEt_2$ at 70℃ involved cyclization giving a mixture of *cis*- and *trans*-butyrolactones (**11a** and **11b**) without desired product (**7a**), which is the similar results reported by Nordlander (entries 1 and 3).[1a] On the other hand, the reduction of methyl ester (**5a**) with Et_3SiH in CF_3CO_2H gave desired product (**9a**), however, the yield was only a 25% and the major product was also a mixture of *cis*- and *trans*-butyrolactones (**11a** and **11b**) (entry 2). In the case of $BF_3{\cdot}OEt_2$, reduction gave olefinic product (**12b**) in 28% yield and the yield of **9a** was a 12% (entry 4).

Then we examined the reduction of **3a** using Et_3SiH along with $TiCl_4$ which is known to be more oxophilic Lewis acid than CF_3CO_2H or $BF_3{\cdot}OEt_2$. When the reduction was carried out using small excess amounts (1.5 equivalent) of Et_3SiH and $TiCl_4$ in dichloromethane, respectively, desired product (**7a**) was obtained even if the substituent on its aromatic moiety was an electron-withdrawing group, halogen. The

isolated yield of product (**7a**) was, however, 67% (entry 5). Hydrogen chloride, generated *in situ* by the formation of titanium salt[5] from **3a** and $TiCl_4$, is likely to lower the yield of **7a** (Scheme 1).



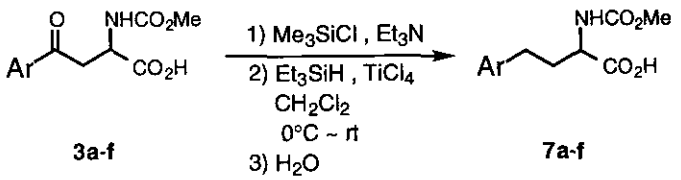
Scheme 1

In order to prevent the generation of hydrogen chloride, we converted the free acid (**3a**) into its methyl (**5a**) and trimethylsilyl ester (**6a**). The reduction of methyl ester (**5a**) gave the desired product (**9a**) in only 25% yield, which was accompanied with chlorinated product (**10**) in 38% yield (entry 6). On the other hand, the reduction of trimethylsilyl ester (**6a**), converted *in situ* from **3a**, gave the desired *N*-protected 4-aryl-2-aminobutanoic acid (**7a**) in an excellent yield (88%, entry 7). Chloroform or 1,2-dichloroethane as solvent also gave good results as similar as dichloromethane.

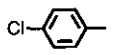
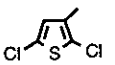
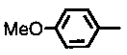
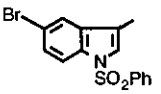
When the reduction was carried out using $AlCl_3$, reduction also proceeded smoothly, however, the isolated products were a mixture of **7a** and olefinic product (**12a**) (entry 8). No reaction occurred when the reduction was carried out using $SnCl_4$ as a Lewis acid (entry 9).

Several examples of the synthesis of γ-aryl substituted amino acids by the Et_3SiH- $TiCl_4$ reduction are demonstrated in Table 3. Besides phenyl and 4-methoxyphenyl ketone (**3b** and **3c**), halogen substituted aromatic and heteroaromatic ketones (**3a**, **3d**, **3e** and **3f**) were readily reduced, *via* trimethylsilyl ester, into the corresponding 2-(methoxycarbonylamino)butanoic acids (**7a-f**) without removal of halogen substituent in high yields (83-95%).[6]

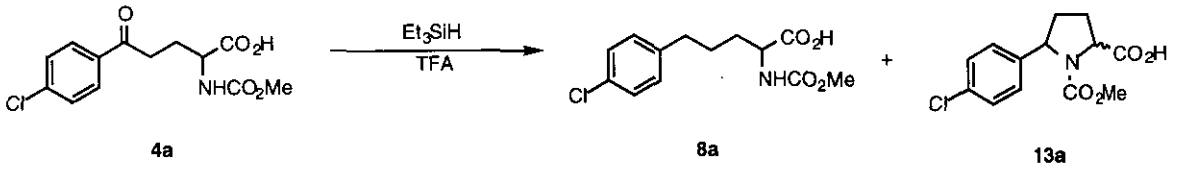
Table 3. Reduction of Aromatic Ketones (**3**) with Et_3SiH - $TiCl_4$.



3a-f **7a-f**

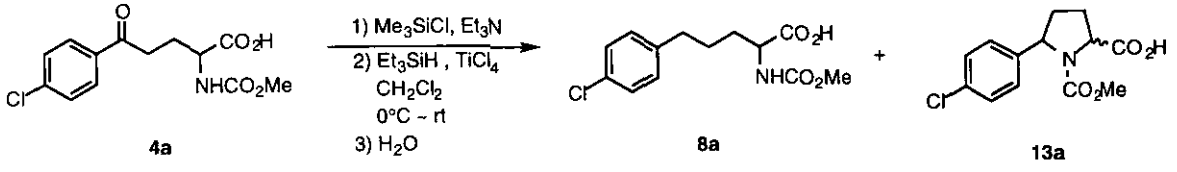
entry	Ar	product (yield %)	entry	Ar	product (yield %)
1		**7a** (88)	4		**7d** (95)
2		**7b** (95)	5		**7e** (85)
3		**7c** (83)	6		**7f** (82)

For application of this reduction to the synthesis of 5-aryl-2-aminopentanoic acids (δ-aryl substituted amino acids), we next examined the reduction of **4a** with Et_3SiH.



4a **8a** **13a**

87 % **8a** / **13a** = 4 / 96 (*cis* / *trans* = 1 / 1)



4a **8a** **13a**

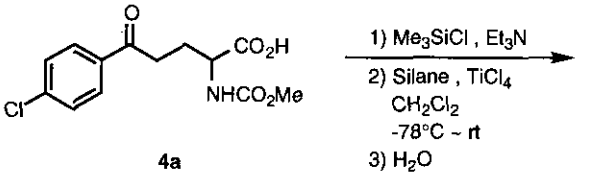
97% **8a** / **13a** = 75 / 25 (*cis* / *trans* = 1 / 1)

Scheme 2

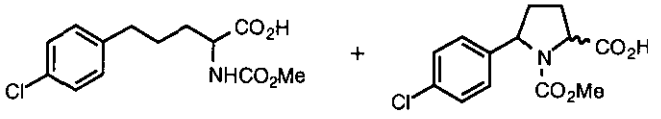
The reduction of **4a** with Et_3SiH-CF_3CO_2H caused unexpected cyclization giving *N*-methoxycarbonyl-5-(4-chlorophenyl)prolines (**13a**) as a main product. On the other hand, the reduction of **4a** with Et_3SiH-$TiCl_4$ under the conditions described above gave desired product (**8a**) mainly, however, the selectivity of the reaction was still insufficient as a practical method for the synthesis of δ-aryl substituted amino acids (Scheme 2).

After screening hydrosilanes under several conditions (Table 4), the combined use of phenyl hydrosilanes with $TiCl_4$ was found to show a good selectivity for reduction of carbonyl group increasing a fraction of **8a** (entries 4-7). The reduction using excess amounts of $PhMe_2SiH$ gave a mixture of **8a** and **13a** (98:2) in 95% yield (entry 7). Recrystallization of the mixture from i-Pr_2O gave pure **8a** as colorless crystals in 80% yield.

Table 4. Reduction of Aromatic Ketones (**4a**) with Silane - $TiCl_4$.



4a



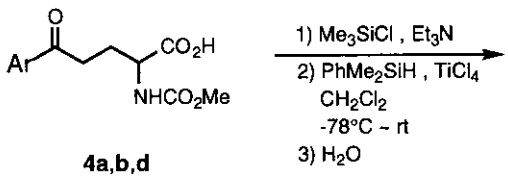
8a **13a**

entry	silane	equiv.	yield (%)	**8a** / **13a**[a)]
1	Et_3SiH	1.5	quant.	88 / 12
2	Et_3SiH	5.0	quant.	85 / 15
3	Ph_3SiH	1.5	98%	75 / 25
4	Ph_3SiH	5.0	quant.	93 / 7
5	Ph_2MeSiH	5.0	95%	95 / 5
6	$PhMe_2SiH$	1.5	85%	94 / 6
7	$PhMe_2SiH$	5.0	95%	98 / 2

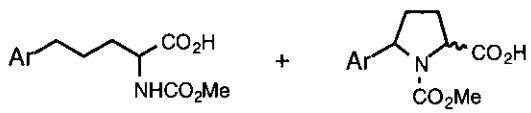
a) product ratio was determined by HPLC analysis.

Several examples of the $PhMe_2SiH$-$TiCl_4$ reduction affording δ-aryl substituted amino acids are demonstrated in Table 5.

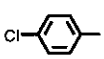
Table 5. Reduction of Aromatic Ketones (**4a,b** and **d**) with $PhMe_2SiH$ - $TiCl_4$



4a,b,d



8a,b,d **13a,b,d**

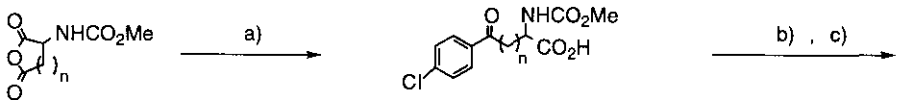
entry	Ar	product (yield %)	**8** / **13**[a]
1		**8a** (95)	98 / 2
2		**8b** (97)	94 / 6
3		**8d** (98)	> 99 / 1

a) product ratio was determined by HPLC analysis.

In this case also, besides phenyl ketone (**4b**), halogen substituted aromatic and heteroaromatic ketones (**4a** and **4d**) were readily reduced *via* trimethylsilyl ester into corresponding 2-(methoxycarbonylamino)-pentanoic acids (**8a,b** and **d**) without removal of halogen substituent in high yield (95-98%)[6] and in high selectivity (94:6->99:1).

Moreover, the present reduction were successfully applied to the synthesis of optically active γ- and δ-aryl substituted amino acids (**14a** and **15a**). The reduction of (2R)-4-(4-chlorophenyl)-2-methoxycarbonyl-amino-4-oxobutanoic acid ((R)-**3a**), which was prepared by the Friedel-Crafts acylation of chlorobenzene with (R)-*N*-(methoxycarbonyl)aspartic anhydride ((R)-**1**), with Et_3SiH-$TiCl_4$ proceeded smoothly without racemization to give (2R)-4-(4-chlorophenyl)-2-(methoxycarbonylamino)butanoic acid ((R)-**7a**) in 80% (>99% ee) yield.[7] Removal of *N*-protecting group with iodotrimethylsilane[9] affroded (2R)-4-(4-chlorophenyl)-2-aminobutanoic acid ((R)-**14a**) in 75% (>99% ee) yield.[8] In a similar manner, (2S)-isomer ((S)-**14a**) was obtained in 64% (>99% ee)[8] overall yield from (S)-**3a** (Scheme 3). The preparation of (2R)-5-(4-chlorophenyl)-2-(methoxycarbonylamino)pentanoic acid ((R)-**8a**) was achieved by the

reduction of (2R)-5-(4-chlorophenyl)-2-methoxycarbonylamino-5-oxopentanoic acid ((R)-**4a**), which was also prepared by the Friedel-Crafts acylation of chlorobenzene with (R)-*N*-(methoxycarbonyl)glutamic anhydride ((R)-**2**), with $PhMe_2SiH$-$TiCl_4$ without racemization in 89% (>99% ee) yield.[7] Treatment of (R)-**8a** with iodotrimethylsilane[9] gave (2R)-5-(4-chlorophenyl)-2-aminopentanoic acid ((R)-**15a**) in 62% (>99% ee) yield.[8] The (2S)-isomer ((S)-**15a**) was obtained in 60% (>99% ee)[8] overall yield from (S)-**4a** in a similar way (Scheme 3).



(R) - , (S) - **1** : n =1

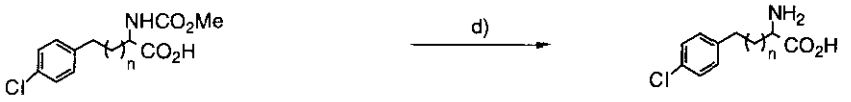
(R) - **3a** 91% $[\alpha]_D^{20}$ -96.4° (c 1.0 $CHCl_3$)

(S) - **3a** 98% $[\alpha]_D^{20}$ +96.8° (c 1.0 $CHCl_3$)

(R) - , (S) - **2** : n =2

(R) - **4a** 52% $[\alpha]_D^{20}$ -29.3° (c 1.0 $CHCl_3$)

(S) - **4a** 62% $[\alpha]_D^{20}$ +29.9° (c 1.0 $CHCl_3$)



(R) - **7a**	80%	$[\alpha]_D^{20}$	-48.9° (c 1.0 $CHCl_3$)	(R) - **14a**	75%	$[\alpha]_D^{20}$	-48.6° (c 0.5 1N HCl)
(S) - **7a**	88%	$[\alpha]_D^{20}$	+49.5° (c 1.0 $CHCl_3$)	(S) - **14a**	74%	$[\alpha]_D^{20}$	+48.8° (c 0.5 1N HCl)
(R) - **8a**	89%	$[\alpha]_D^{20}$	-31.1° (c 1.0 $CHCl_3$)	(R) - **15a**	62%	$[\alpha]_D^{20}$	-9.2° (c 0.5 1N NaOH)
(S) - **8a**	85%	$[\alpha]_D^{20}$	+31.5° (c 1.0 $CHCl_3$)	(S) - **15a**	71%	$[\alpha]_D^{20}$	+9.1° (c 0.5 1N NaOH)

a) Chlorobenzene, $AlCl_3$ / $ClCH_2CH_2Cl$; b) Me_3SiCl, Et_3N ; c) n =1 ; Et_3SiH, $TiCl_4$ / CH_2Cl_2, 0°C ~ rt, n = 2 ; $PhMe_2SiH$, $TiCl_4$ / CH_2Cl_2, -78°C ~ rt ; d) Me_3SiI / $CHCl_3$

Scheme 3

In conclusion, we have developed efficient methods for the preparation of γ- and δ-aryl substituted amino acids by new silane reduction of the corresponding aromatic ketones mediated by $TiCl_4$. The reduction proceeded easily without assistance of electron-donating substituents on the aromatic ring and was applicable to the synthesis of optically active γ- and δ-aryl substituted amino acids successfully.

EXPERIMENTAL

All melting points were taken in open capillary tubes on a melting point apparatus (Buchi 535) without correction. IR spectra were taken with an Analect RFX-65 spectrophotmeter. ^{1}H-NMR spectra were measured with a Gemmini (Varian, 300MHz), or a JNM GSX-400 (JEOL, 400MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. APCI-MS, ESI-MS, EI-MS, and FAB-MS were obtained with a SSQ7000C (Finnigan MAT Inc.), an INCOS 50 (Finnigan MAT Inc.) or a JMS-HX 100 (JEOL) spectrometer. Optical rotation were measured on a Horiba SEPA-200 digital polarimeter. HPLC analysis was done with a Hitachi 638-30 (ultraviolet detection). Elemental analyses were obtained by using a Perkin-Elmer 2400, a Yanagimoto MT-3 or a YEW ion chromato IC-7000.

The anhydride (**1**)[1b] and (**2**)[10] were prepared according to the literature. In general, reactions were carried out in dry solvents under argon atmosphere unless otherwise mentioned.

Preparation of Aromatic Ketones (3 and 4)

All the aromatic ketones (**3** and **4**) were prepared by Friedel-Crafts acylation of appropriate aromatics with anhydrides (**1** or **2**) in 1,2-dichloroethane. The general procedure is exemplified by the preparation of 4-(4-chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoic acid (**3a**) : $AlCl_3$ (2.79 g, 21 mmol) was added to a susupension of chlorobenzene (2.83 g, 25 mmol) and **1** (1.45 g, 8 mmol) in 1,2-dichloroethane (15 mL) at 0 ℃. The mixture was stirred for 4 h at rt and poured onto crashed ice. The aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. Removal of the solvent followed by recrystallization from AcOEt-hexane gave 2.03 g (85%) of **3a** as colorless needles, mp 141-142℃. IR (Nujol): 3400, 1710, 1680 cm^{-1}. EI-MS m/z : 287 and 285 (M^+, 1:3). ^{1}H-NMR (DMSO-d_6) δ: 3.45-3.80 (2H, m), 3.53 (3H, s), 4.47-4.59 (1H, m), 7.42 (1H, d, J =8.3 Hz), 7.61 (2H, d, J =8.7 Hz), 7.97 (2H, d, J =8.7 Hz), 12.72 (1H, s). *Anal.* Calcd for $C_{12}H_{12}NO_5Cl$: C, 50.45; H, 4.23; N, 4.90; Cl, 12.41. Found: C, 50.54; H, 4.20; N, 4.85; Cl, 12.47.

(R)-4-(4-Chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoic Acid ((R)-3a)

This compound was obtained from chlorobenzene and (R)-**1** in 91% (>99% ee) yield as a colorless oil. $[\alpha]_D^{20}$ -96.4° (c 1.00, $CHCl_3$). IR (Nujol): 3320, 1720, 1680 cm^{-1}. EI-MS *m/z* : 287 and 285 (M^+, 1:3). ^{1}H-NMR (DMSO-d_6) δ: 3.45-3.80 (2H, m), 3.53 (3H, s), 4.47-4.59 (1H, m), 7.42 (1H, d, J =8.3 Hz),

7.61 (2H, d, J=8.7 Hz), 7.97 (2H, d, J=8.7 Hz), 12.72 (1H, s).

(S)-4-(4-Chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoic Acid ((S)-3a)

This compound was obtained from chlorobenzene and (S)-**1** in 98% (>99% ee) yield as a colorless oil. $[\alpha]_D^{20}$ +96.8°(c 1.00, $CHCl_3$). IR (Nujol): 3320, 1720, 1680 cm^{-1}. EI-MS *m/z* : 287 and 285 (M^+, 1:3). ^{1}H-NMR (DMSO-d_6) δ: 3.45-3.80 (2H, m), 3.53 (3H, s), 4.47-4.59 (1H, m), 7.42 (1H, d, J=8.3 Hz), 7.61 (2H, d, J=8.7 Hz), 7.97 (2H, d, J=8.7 Hz), 12.72 (1H, s). Chiral HPLC analysis was carried out under the following conditions: column, chiralcel OD-R (4.6 x 250 mm); eluent, MeCN/ aq.$HClO_4$ (pH 2.0) (3:7), 0.5 mL/min; detector, 254 nm; retention time, (S)-**3a** (18 min), (R)-**3a** (21 min).

4-Phenyl-2-methoxycarbonylamino-4-oxobutanoic Acid (3b)

This compound was obtained from benzene and **1** in 73% yield as colorless needles, mp 135-137℃ (AcOEt-hexane). IR (Nujol): 3440, 3080, 1740, 1680 cm^{-1}. EI-MS *m/z* : 251 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.44 (2H, d, J=6.2 Hz), 3.54 (3H, s), 4.50-4.62 (1H, m), 7.43 (1H, d, J=8.4 Hz), 7.49-7.59 (2H, m), 7.61-7.70 (1H, m), 7.92-8.00 (2H, m), 12.72 (1H, s). *Anal.* Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.24; H, 5.19; N, 5.49.

4-(4-Methoxyphenyl)-2-methoxycarbonylamino-4-oxobutanoic Acid (3c)

This compound was obtained from anisole and **1** in 73% yield as a mixture of isomers (*ortho*/*para* =1:3). Recrystallization from MeCN-i-Pr_2O gave pure *para*-isomer (**3c**) (22%) as colorless crystals, mp 111-112℃ . IR (Nujol): 3440, 3010, 1755, 1735, 1680, 1660 cm^{-1}. EI-MS *m/z* : 281 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.51 (1H, dd, J=18.0, 4.4 Hz), 3.76 (1H, dd, J=18.0, 4.4 Hz), 3.69 (3H, s), 3.89 (3H, s), 4.75-4.81 (1H, m), 5.90 (1H, d, J=8.4 Hz), 6.95 (2H, d, J=7.8 Hz), 7.94 (2H, d, J=7.8 Hz). *Anal.* Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.34; H, 5.26; N, 4.91.

4-(5-Chlorothiophen-2-yl)-2-methoxycarbonylamino-4-oxobutanoic Acid (3d)

This compound was obtained from 2-chlorothiophene and **1** in 71% yield as pale yellow prisms, mp 128.5-129.5℃ (AcOEt-hexane). IR (Nujol): 3450, 1760, 1740, 1680, 1655 cm^{-1}. EI-MS *m/z* : 293 and 291(M^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 3.45 (1H, dd, J=17.6, 4.4 Hz), 3.62 (1H, dd, J=17.6, 3.9 Hz), 3.69 (3H, s),

4.75 (1H, ddd, J=8.3, 4.4, 3.9 Hz), 5.83 (1H, d, J=8.3 Hz), 6.97 (1H, d, J=4.1 Hz), 7.54 (1H, d, J=4.1 Hz), 9.60 (1H, br s). *Anal.* Calcd for $C_{10}H_{10}NO_5ClS$: C, 41.17; H, 3.46; N, 4.80; Cl, 12.15; S, 10.99. Found: C, 41.46; H, 3.50; N, 4.68; Cl, 11.85; S, 10.83.

4-(2,5-Dichlorothiophen-3-yl)-2-methoxycarbonylamino-4-oxobutanoic Acid (3e)

This compound was obtained from 2,5-dichlorothiophene and **1** in 71% yield as an amorphous solid. IR (Nujol): 3450, 1760, 1740, 1680, 1655 cm^{-1}. FAB-MS *m/z* : 330, 328 and 326 (MH^+, 1:6:9) . ^{1}H-NMR ($CDCl_3$) δ: 3.49 (1H, dd, J=18.7, 4.1 Hz), 3.68 (1H, dd, J=18.7, 3.9 Hz), 3.69 (3H, s), 4.70-4.81 (1H, m), 5.80 (1H, d, J=8.2 Hz), 7.20 (1H, s), 8.70 (1H, br s).

4-(5-Bromo-1-phenylsulfonylindol-3-yl)-2-methoxycarbonylamino-4-oxobutanoic Acid (3f)

This compound was obtained from 5-bromo-1-phenylsulfonylindole and **1** in 48% yield as colorless fine needles, mp 232-234℃ (decomp) (AcOEt-MeOH). IR (Nujol): 3330, 1735, 1680 cm^{-1}. EI-MS *m/z* : 511 and 509 (M^+, 1:1) . ^{1}H-NMR (DMSO-d_6) δ: 3.30-3.40 (1H, m), 3.42-3.59 (1H, m), 3.52 (3H, s), 4.01-4.56 (1H, m), 7.49 (1H, d, J=8.2 Hz), 7.60 (1H, dd, J=2.0, 9.0 Hz), 7.63-7.71 (2H, m), 7.74-7.83 (1H, m), 7.95 (1H, d, J=9.0 Hz), 8.14-8.22 (2H, m), 8.32 (1H, d, J=2.0 Hz), 8.93 (1H, s), 12.82 (1H, s). *Anal.* Calcd for $C_{20}H_{17}N_4O_7BrS$: C, 47.16; H, 3.36; N, 5.50; Br, 15.69; S, 6.29. Found: C, 46.94; H, 3.30; N, 5.39; Br, 15.79; S, 6.27.

5-(4-Chlorophenyl)-2-methoxycarbonylamino-5-oxopentanoic Acid (4a)

This compound was obtained from chlorobenzene and **2** in 78% yield as colorless needles, mp 179-181℃ (AcOEt). IR (Nujol): 3340, 1730, 1715, 1675 cm^{-1}. EI-MS *m/z* : 301 and 299 (M^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 2.07-2.19 (1H, m), 2.30-2.41 (1H, m), 2.94-3.15 (1H, m), 3.13 (1H, ddd, J=17.8, 8.8, 6.4 Hz), 3.65 (3H, s), 4.25-4.47 (1H, m), 5.50-5.70 (1H, m), 7.43 (2H, d, J=8.8 Hz), 7.89 (2H, d, J=8.8 Hz). *Anal.* Calcd for $C_{13}H_{14}NO_5Cl$: C, 52.10; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 52.07; H, 4.61; N, 4.54; Cl, 11.87.

(R)-5-(4-Chlorophenyl)-2-methoxycarbonylamino-5-oxopentanoic Acid ((R)-4a)

This compound was obtained from chlorobenzene and (R)-**2** in 52% (>99% ee) yield as colorless needles, mp 120-122℃. $[\alpha]_D^{20}$ -29.3° (c 1.00, $CHCl_3$). IR (Nujol): 3335, 1740, 1700, 1680 cm^{-1}. APCI-MS *m/z* : 302 and 300 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 2.07-2.19 (1H, m), 2.30-2.41 (1H, m), 2.94-3.15 (1H, m), 3.13 (1H, ddd, *J* =17.8, 8.8, 6.4 Hz), 3.65 (3H, s), 4.25-4.47 (1H, m), 5.50-5.70 (1H, m), 7.43 (2H, d, *J* =8.8 Hz), 7.89 (2H, d, *J* =8.8 Hz). *Anal.* Calcd for $C_{13}H_{14}NO_5Cl$: C, 52.10; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 51.82; H, 4.62; N, 4.52; Cl, 11.68.

(S)-5-(4-Chlorophenyl)-2-methoxycarbonylamino-5-oxopentanoic Acid ((S)-4a)

This compound was obtained from chlorobenzene and (S)-**2** in 62% (>99% ee) yield as colorless needles, mp 120-121℃. $[\alpha]_D^{20}$ +29.9° (c 1.00, $CHCl_3$). IR (Nujol): 3335, 1740, 1700, 1680 cm^{-1}. APCI-MS *m/z* : 302 and 300 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 2.07-2.19 (1H, m), 2.30-2.41 (1H, m), 2.94-3.15 (1H, m), 3.13 (1H, ddd, *J* =17.8, 8.8, 6.4 Hz), 3.65 (3H, s), 4.25-4.47 (1H, m), 5.50-5.70 (1H, m), 7.43 (2H, d, *J* =8.8 Hz), 7.89 (2H, d, *J* =8.8 Hz). *Anal.* Calcd for $C_{13}H_{14}NO_5Cl$: C, 52.10; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 52.01; H, 4.66; N, 4.55; Cl, 11.69. Chiral HPLC analysis was carried out under the following conditions: column, chiralcel OD-R (4.6 x 250 mm); eluent, MeCN/ aq.$HClO_4$ (pH 2.0) (3:7), 0.5 mL/min; detector, 250 nm; retention time, (S)-**4a** (19 min), (R)-**4a** (21 min).

5-Phenyl-2-methoxycarbonylamino-5-oxopentanoic Acid (4b)

This compound was obtained from benzene and **2** in 66% yield as colorless crystals, mp 159.5-160℃ (AcOEt-hexane). IR (Nujol): 3350, 1720, 1675 cm^{-1}. FAB-MS *m/z* : 266 (MH^+), 188. ^{1}H-NMR ($CDCl_3$) δ: 2.05-2.21 (1H, m), 2.27-2.39 (1H, m), 3.02-3.22 (2H, m), 3.65 (3H, s), 4.25-4.42 (1H, m), 6.05-6.20 (1H, m), 7.42-7.50 (2H, m), 7.53-7.61 (1H, m), 7.92-7.98 (2H, m). *Anal.* Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.72; H, 5.73; N, 5.13.

5-(5-Chlorothiophen-2-yl)-2-methoxycarbonylamino-5-oxopentanoic Acid (4d)

This compound was obtained from 2-chlorothiophene and **2** in 54% yield as colorless needles, mp 156-158℃ (AcOEt-hexane). IR (Nujol): 3350, 1720, 1650 cm^{-1}. FAB-MS *m/z* : 308 and 306 (MH^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 2.05-2.24 (1H, m), 2.24-2.42 (1H, m), 2.85-3.02 (1H, m), 3.03 (1H, ddd, *J* =17.1, 8.5, 6.6 Hz), 3.66 (3H, s), 4.29-4.44 (1H, m), 5.50-5.69 (1H, m), 6.95 (1H, d, *J* =4.1 Hz), 7.51 (1H, d,

J=4.1 Hz), 9.50 (1H, br s). *Anal.* Calcd for $C_{11}H_{12}NO_5ClS$: C, 43.21; H, 3.96; N, 4.58; Cl, 11.60; S, 10.49. Found: C, 43.25; H, 3.88; N, 4.52; Cl, 11.48; S, 10.58.

Reduction of 4-Aryl-2-methoxycarbonylamino-4-oxobutanoic Acid (3a-f) with Et_3SiH-$TiCl_4$

The general procedure is exemplified by the reduction of 4-(4-chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoic acid (**3a**) : A solution of Me_3SiCl (1.2 g, 11 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of **3a** (2.85 g, 10 mmol) and Et_3N (1.2 g, 11.1 mmol) in CH_2Cl_2 (30 mL) at 0 ℃. After being stirred at rt for 3 h, a solution of Et_3SiH (3.35 g, 30.1 mmol) in CH_2Cl_2 (15 mL) was added and the resulting mixture was cooled in an ice bath. To this mixture was added dropwise a 1.0 M solution of $TiCl_4$ (5.7 g, 30 mmol) in CH_2Cl_2 (30 mL) in the ice bath. After being stirred at rt for 20 h, the reaction mixture was poured into ice-water. The organic layer was extracted with 10% NaOH solution. The aqueous solution was acidified with 10% HCl solution, and then extracted with AcOEt. The organic layer was washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of the AcOEt and recrystallization of the residue from AcOEt-hexane gave 2.38 g (88%) of 4-(4-chlorophenyl)-2-(methoxycarbonylamino)butanoic acid (**7a**) as colorless needles, mp 114-115℃. IR (Nujol): 3340, 1755, 1700 cm^{-1}. DI-MS *m/z* : 273 and 271 (M^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 1.90-2.08 (1H, m), 2.10-2.32 (1H, m), 2.69 (2H, dd, J=8.1, 7.7 Hz), 3.71 (3H, s), 4.22 (1H, br s), 5.21 (1H, br s), 7.11 (2H, d, J =8.5 Hz), 7.25 (2H, d, J =8.5 Hz). *Anal.* Calcd for $C_{12}H_{14}NO_4Cl$: C, 53.05; H, 5.19; N, 5.16; Cl, 13.05. Found: C, 53.03; H, 5.09; N, 4.98; Cl, 13.00.

When $AlCl_3$ was used as a Lewis acid, the reduction gave a mixture of **7a** and **12a** (**7a**:**12a**≈45:23 ; The ratio was determined from ^{1}H-NMR spectra). **12a**:^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s), 4.95-5.07 (1H, m), 5.65-5.80 (1H, m), 6.25 (1H, dd, J=16.0, 5.9 Hz), 6.62 (1H, dd, J=16.0, 1.6 Hz), 7.17- 7.32 (4H, m).

(R)-4-(4-Chlorophenyl)-2-(methoxycarbonylamino)butanoic Acid ((R)-7a)

This compound was obtained from (R)-**3a** in 80% (>99% ee) yield as colorless needles, mp 120-121℃. $[\alpha]_D^{20}$ -48.9°(c 1.00, $CHCl_3$). IR (Nujol): 3420, 3400, 1750, 1720, 1680 cm^{-1}. EI-MS *m/z* : 273 and 271 (M^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 1.90-2.08 (1H, m), 2.10-2.32 (1H, m), 2.69 (2H, dd, J =8.1, 7.7 Hz), 3.71 (3H, s), 4.22 (1H, br s), 5.21 (1H, br s), 7.11 (2H, d, J =8.5 Hz), 7.25 (2H, d, J =8.5 Hz). *Anal.* Calcd for $C_{12}H_{14}NO_4Cl$: C, 53.05; H, 5.19; N, 5.16; Cl, 13.05. Found: C, 53.19; H, 5.14; N, 5.08; Cl,

12.83.

(S)-4-(4-Chlorophenyl)-2-(methoxycarbonylamino)butanoic Acid ((S)-7a)

This compound was obtained from (S)-**3a** in 88% (>99% ee) yield as colorless needles, mp 120-121℃. $[\alpha]_D^{20}$ +49.5° (c 1.00, $CHCl_3$). IR (Nujol): 3420, 3400, 1750, 1720, 1660 cm^{-1}. EI-MS *m/z* : 273 and 271 (M^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 1.90-2.08 (1H, m), 2.10-2.32 (1H, m), 2.69 (2H, dd, *J* =8.1, 7.7 Hz), 3.71 (3H, s), 4.22 (1H, br s), 5.21 (1H, br s), 7.11 (2H, d, *J* =8.5 Hz), 7.25 (2H, d, *J* =8.5 Hz). *Anal.* Calcd for $C_{12}H_{14}NO_4Cl$: C, 53.05; H, 5.19; N, 5.16; Cl, 13.05. Found: C, 53.11; H, 5.03; N, 5.05; Cl, 12.94. Chiral HPLC analysis was carried out under the following conditions: column, chiralcel OD-R (4.6 x 250 mm); eluent, MeCN/ aq.$HClO_4$ (pH 2.0) (3:7), 0.5 mL/min; detector, 220 nm; retention time, (S)-**7a** (27 min), (R)-**7a** (31 min).

4-Phenyl-2-(methoxycarbonylamino)butanoic Acid (7b)

This compound was obtained from **3b** in 95% yield as colorless crystals, mp 107-110℃ (AcOEt-hexane). IR (Nujol): 3340, 1720, 1695 cm^{-1}. EI-MS *m/z* : 237 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.93-2.10 (1H, m), 2.14-2.32 (1H, m), 2.71 (2H, dd, *J* =8.1, 7.8 Hz), 3.70 (3H, s), 4.24 (1H, br s), 5.22 (1H, br s), 7.15-7.22 (3H, m), 7.25-7.31 (2H, m). *Anal.* Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.71; H, 6.33; N, 5.82.

4-(4-Methoxyphenyl)-2-(methoxycarbonylamino)butanoic Acid (7c)

This compound was obtained from **3c** in 83% yield as a colorless oil. IR (Nujol): 3320, 1720, 1615 cm^{-1}. EI-MS *m/z* (rel intensity): 267 (M^+, 3.6), 235 (2.9), 133 (49), 121 (base peak), 115 (58). ^{1}H-NMR ($CDCl_3$) δ: 1.91-2.04 (1H, m), 2.13-2.25 (1H, m), 2.66 (2H, t, *J* =8.0 Hz), 3.70 (3H, s), 3.78 (3H, s), 4.37-4.43 (1H, m), 5.23 (1H, d, *J* =8.1 Hz), 6.82 (2H, d, *J* =8.6 Hz), 7.10 (2H, d, *J* =8.6 Hz).

4-(5-Chlorothiophen-2-yl)-2-(methoxycarbonylamino)butanoic Acid (7d)

This compound was obtained from **3d** in 95% yield as colorless crystals, mp 68-71℃ (i-Pr_2O-hexane). IR (Nujol): 3420, 1750, 1730, 1680 cm^{-1}. EI-MS *m/z* : 279 and 277 (M^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 1.90-2.15 (1H, m), 2.15-2.35 (1H, m), 2.84 (2H, t, *J* =7.8 Hz), 3.71(3H, s), 4.25-4.55 (1H, m), 5.24 (1H, d, *J*

=7.8 Hz), 6.20 (1H, d, J =3.9 Hz), 6.58 (1H, d, J =3.9 Hz), 8.45 (1H, br s). *Anal.* Calcd for $C_{10}H_{12}NO_4ClS$: C, 43.24; H, 4.36; N, 5.04; Cl, 12.77; S, 11.55. Found: C, 43.19; H, 4.29; N, 4.95; Cl, 12.61; S, 11.56.

4-(2,5-Dichlorothiophen-3-yl)-2-(methoxycarbonylamino)butanoic Acid (7e)

This compound was obtained from **3e** in 85% yield as colorless crystals, mp 90-91℃ (AcOEt-hexane). IR (Nujol): 3370, 1725, 1645 cm^{-1}. FAB-MS *m/z* : 316, 314 and 312 (MH^+, 1:6:9). ^{1}H-NMR ($CDCl_3$) δ: 1.89-2.02 (1H, m), 2.10-2.25 (1H, m), 2.60-2.66 (2H, m), 3.72 (3H, s), 4.35-4.45 (1H, m), 5.25 (1H, d, J =7.8 Hz), 6.67 (1H, s). *Anal.* Calcd for $C_{10}H_{11}NO_4Cl_2S$: C, 38.48; H, 3.55; N, 4.49; Cl, 22.71; S, 10.27. Found: C, 38.24; H, 3.67; N, 4.31; Cl, 22.90; S, 10.24.

4-(5-Bromo-1-phenylsulfonylindol-3-yl)-2-(methoxycarbonylamino)butanoic Acid (7f)

This compound was obtained from **3f** in 82% yield as colorless fine needles, mp 192-194℃ (AcOEt-hexane). IR (Nujol): 3320, 1735, 1685 cm^{-1}. EI-MS *m/z* : 495 and 493 (M^+, 1:1) . ^{1}H-NMR (DMSO-d_6) δ: 1.80-2.05 (2H, m), 2.60-2.80 (2H, m), 3.58 (3H, s), 3.80-3.98 (1H, m), 7.49 (1H, dd, J =8.7, 1.9 Hz), 7.55-7.75 (5H, m), 7.86 (1H, d, J =8.7 Hz), 7.87 (1H, d, J =1.9 Hz), 7.93-8.01 (1H, m), 7.95 (1H, s), 12.66 (1H, s). *Anal.* Calcd for $C_{20}H_{19}N_4O_6BrS$: C, 48.49; H, 3.87; N, 5.66; Br, 16.13; S, 6.47. Found: C, 48.26; H, 3.70; N, 5.47; Br, 15.88; S, 6.32.

Reduction of 4-(4-Chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoic Acid (3a) with Et_3SiH-CF_3CO_2H

Et_3SiH (1.6 g, 13.8 mmol) was added to a solution of **3a** (1.0 g, 3.5 mmol) in TFA (20 mL) at rt. The mixture was heated at reflux temperature for 2 h. The reaction mixture was concentrated in vacuo. The residue was extracted with AcOEt. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Removal of the AcOEt gave a mixture of **11a** and **11b**, which was separated by flash column chromatography on silica gel. Elution with hexane-AcOEt (3:1) gave 62 mg (7%) of *trans*-isomer (**11b**) as colorless needles, mp 139-140℃ (toluene-i-Pr_2O). IR (Nujol): 3320, 1785, 1700 cm^{-1}. GC-MS *m/z* : 271 and 269 (M^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 2.61-1.84 (2H, m), 3.71 (3H, s), 4.51-4.65 (1H, m), 5.30 (1H, br s), 5.70 (1H, dd, J =7.8, 2.9 Hz), 7.25 (2H, d, J =8.8 Hz), 7.38 (2H, d, J =8.8 Hz). *Anal.* Calcd for

$C_{12}H_{12}NO_4Cl$: C, 53.44; H, 4.49; N, 5.19; Cl, 13.15. Found: C, 53.49; H, 4.29; N, 5.04; Cl, 12.91. Further elution with hexane-AcOEt (3:1) gave 510 mg (54%) of *cis*-isomer (**11a**) as colorless needles, mp 120-121℃ (toluene-i-Pr_2O). IR (Nujol): 3340, 1760, 1710 cm^{-1}. GC-MS *m/z* : 271 and 269 (M^+, 1:3). ^{1}H-NMR ($CDCl_3$) δ: 2.19 (1H, q, *J* =12.0 Hz), 3.10 (1H, ddd, *J* =12.7, 8.3, 5.4 Hz), 3.73 (3H, s), 4.51-4.65 (1H, m), 5.38 (1H, dd, *J* =11.2, 5.4 Hz), 5.39 (1H, br s), 7.32 (2H, d, *J* =8.8 Hz), 7.37 (2H, d, *J* =8.8 Hz). *Anal.* Calcd for $C_{12}H_{12}NO_4Cl$: C, 53.44; H, 4.49; N, 5.19; Cl, 13.15. Found: C, 53.50; H, 4.29; N, 5.00; Cl, 12.95.

Reduction of Methyl 4-(4-Chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoate (5a) with Et_3SiH-CF_3CO_2H

$SOCl_2$ (1.2 g, 10.1 mmol) was added dropwise to a solution of **3a** (1.4 g, 4.8 mmol) in MeOH (15 mL) at 0 ℃. The mixture was stirred at 0 ℃ for 16 h. The reaction mixture was concentrated in vacuo. The residue was extracted with AcOEt. The AcOEt was washed with sat. $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from i-Pr_2O-hexane to afford 1.3 g (88%) of **5a** as colorless crystals, mp 80-81℃. IR (Nujol): 3380, 1735, 1720, 1680 cm^{-1}. APCI-MS *m/z* : 302 and 300 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 3.43-3.45 (2H, m), 3.54 (3H, s), 3.64 (3H, s), 4.55-4.68 (1H, m), 7.57-7.66 (1H, m), 7.62 (2H, d, *J* =8.6 Hz), 7.97 (2H, d, *J* =8.6 Hz). *Anal.* Calcd for $C_{13}H_{14}NO_5Cl$: C, 52.10; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 51.84; H, 4.55; N, 4.61; Cl, 11.73.

Et_3SiH (240 mg, 2.1 mmol) was added to a solution of **5a** (196 mg, 0.7 mmol) in TFA (5 mL) at rt. The mixture was heated at reflux temperature for 3 h. The reaction mixture was concentrated in vacuo. The residue was extracted with AcOEt. The organic layer was washed with sat. $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After removal of the solvent, the oily residue was subjected to silica gel preparative TLC (eluent; hexane-AcOEt=2:1) to afford 46 mg (25%) of **9a** as colorless crystals and 103 mg (59%) of a mixture of **11a** and **11b** (**11a**:**11b**≈5:1). **9a** : mp 65-68℃, IR (Nujol): 3485, 1755, 1690 cm^{-1}. APCI-MS *m/z* : 288 and 286 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.86-2.01 (1H, m), 2.06-2.23 (1H, m), 2.60-2.70 (2H, m), 3.70 (3H, s), 3.73 (3H, s), 4.34-4.46 (1H, m), 5.16-5.33 (1H, m), 7.11 (2H, d, *J* =8.4 Hz), 7.25 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64; N, 4.90; Cl, 12.41. Found: C, 54.91; H, 5.58; N, 4.79; Cl, 12.36.

Reduction of Methyl 4-(4-Chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoate (5a) with Et_3SiH- $TiCl_4$

A 1.0 M solution of $TiCl_4$ (0.48 g, 1.8 mmol) in CH_2Cl_2 (1.8 mL) was added to a solution of **5a** (175 mg, 0.5 mmol) and Et_3SiH (212 mg, 1.8 mmol) in CH_2Cl_2 (3 mL) in an ice bath. After 20 h, the reaction mixture was poured into ice-water. The organic layer was extracted with AcOEt. The organic layer was washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of the AcOEt to give 110 mg of a mixture of **9a** and **10** (**9a**:**10**≈25:38) as an oil (The ratio was determined from NMR spectra). **10** : FAB-MS *m/z* : 324, 322 and 320 (MH^+, 9:6:1). ^{1}H-NMR ($CDCl_3$) δ: 2.24-2.40 (1H, m), 2.57-2.72 (1H, m), 3.71 (3H, s), 3.73 (3H, s), 4.54-4.56 (1H, m), 4.97 (1H, dd, *J* =9.7, 4.9 Hz), 5.05-5.40 (1H, m), 7.33 (4H, s).

Reduction of 5-Aryl-2-methoxycarbonylamino-5-oxopentanoic Acid (4a,b and d) with $PhMe_2SiH$-$TiCl_4$

The general procedure is exemplified by the reduction of 4-(4-chlorophenyl)-2-methoxycarbonylamino-5-oxopentanoic acid (**4a**) : A solution of Me_3SiCl (610 mg, 5.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of **4a** (1.55 g, 5.2 mmol) and Et_3N (570 mg, 5.6 mmol) in CH_2Cl_2 (15 mL) at 0 ℃. After being stirred at rt for 3 h, a solution of $PhMe_2SiH$ (7.06 g, 52 mmol) in CH_2Cl_2 (10 mL) was added and the resulting mixture was cooled to -78 ℃. To this mixture was added dropwise a 1.0 M solution of $TiCl_4$ (4.1 g, 16 mmol) in CH_2Cl_2 (16 mL) at the same temperature, and then the whole was allowed to warm up to rt during 20 h. The reaction mixture was poured into ice-water, and organic layer was extracted with 10% NaOH solution. The alkaline solution was acidified with 10% HCl solution, and then extracted with AcOEt. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Evaporation of the AcOEt gave 1.41 g (95%) of a mixture of **8a** and **13a** (**8a**:**13a**=98:2) which was recrystallized from i-Pr_2O to afforded 1.19 g (80%) of **8a** as colorless crystals, mp 112-113℃. IR (Nujol): 3345, 1710, 1665 cm^{-1}. APCI-MS *m/z* : 288 and 286 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.59-1.77 (3H, m), 1.77-2.01 (1H, m), 2.50-2.70 (2H, m), 3.69 (3H, s), 4.30-4.50 (1H, m), 5.10-5.20 (1H, m), 7.08 (2H, d, *J* =8.4 Hz), 7.24 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64; N, 4.90; Cl, 12.41. Found: C, 54.93; H, 5.67; N, 4.82; Cl, 12.37. Product ratio was determined by HPLC analysis under the following conditions: column, L-column ODS (4.6 x 150 mm); eluent, MeCN/ 20 mM NaH_2PO_4 (pH 3.0) (2:3), 1.0 mL/min; detector, 220

nm; retention time, **8a** (10 min), **13a** (7 min).

(R)-4-(4-Chlorophenyl)-2-(methoxycarbonylamino)pentanoic Acid ((R)-8a)

This compound was obtained from (R)-**4a** in 89% (>99% ee) yield as colorless needles, mp 80-81℃. $[\alpha]_D^{20}$ -31.1°(c 1.00, $CHCl_3$). IR (Nujol): 3370, 3355, 1710, 1665 cm^{-1}. ESI-MS *m/z* : 286 and 284 (M^+-H). ^{1}H-NMR ($CDCl_3$) δ: 1.59-1.77 (3H, m), 1.77-2.01 (1H, m), 2.50-2.70 (2H, m), 3.69 (3H, s), 4.30-4.50 (1H, m), 5.10-5.20 (1H, m), 7.08 (2H, d, *J* =8.4 Hz), 7.24 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64; N, 4.90; Cl, 12.41. Found: C, 54.67; H, 5.64; N, 4.83; Cl, 12.44.

(S)-4-(4-Chlorophenyl)-2-(methoxycarbonylamino)pentanoic Acid ((S)-8a)

This compound was obtained from (S)-**4a** in 85% (>99% ee) yield as colorless needles, mp 80-81℃. $[\alpha]_D^{20}$ +31.5°(c 1.00, $CHCl_3$). IR (Nujol): 3370, 3355, 1710, 1665 cm^{-1}. ESI-MS *m/z* : 286 and 284 (M^+-H). ^{1}H-NMR ($CDCl_3$) δ: 1.59-1.77 (3H, m), 1.77-2.01 (1H, m), 2.50-2.70 (2H, m), 3.69 (3H, s), 4.30-4.50 (1H, m), 5.10-5.20 (1H, m), 7.08 (2H, d, *J* =8.4 Hz), 7.24 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64; N, 4.90; Cl, 12.41. Found: C, 54.67; H, 5.64; N, 4.83; Cl, 12.44. Chiral HPLC analysis was carried out under the following conditions: column, chiralcel OD-R (4.6 x 150 mm); eluent, MeCN/ aq.$HClO_4$ (pH 2.0) (3:7), 0.5 mL/min; detector, 220 nm; retention time, (R)-**8a** (24 min), (S)-**8a** (35 min).

5-Phenyl-2-(methoxycarbonylamino)pentanoic Acid (8b)

Reduction of **4b** gave a mixture of **8b** and **13b** in 97% yield (**8b**:**13b**=94:6). Recrystallization of the mixture from i-Pr_2O gave **8b** (78%) as colorless crystals, mp 99-100℃. IR (Nujol): 3350, 1710, 1665 cm^{-1}. ESI-MS *m/z* : 250 (M^+-H). ^{1}H-NMR ($CDCl_3$) δ: 1.60-1.80 (3H, m), 1.81-2.02 (1H, m), 2.53-2.74 (2H, m), 3.69 (3H, s), 4.30-4.50 (1H, m), 5.09-5.42 (1H, m), 7.13-7.22 (3H, m), 7.24-7.31 (2H, m). *Anal.* Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.24; H, 6.81; N, 5.37. Product ratio was determined by HPLC analysis under the following conditions: column, L-column ODS (4.6 x 150 mm); eluent, MeCN/ 20 mM NaH_2PO_4 (pH 3.0) (2:3), 1.0 mL/min; detector, 205 nm; retention time, **8b** (10 min), **13b** (6 min).

5-(5-Chlorothiophen-2-yl)-2-(methoxycarbonylamino)pentanoic Acid (8d)

This compound was obtained from **4d** in 98% yield as colorless crystals, mp 120-121℃ (i-Pr_2O). IR (Nujol): 3365, 1745, 1715, 1665 cm^{-1}. ESI-MS *m/z* : 292 and 290 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.63-1.83 (3H, m), 1.84-2.10 (1H, m), 2.70-2.82 (2H, m), 3.70 (3H, s), 4.20-4.50 (1H, m), 5.10-5.15 (1H, m), 6.55 (1H, d, *J* =3.7 Hz), 6.70 (1H, d, *J* =3.7 Hz). *Anal.* Calcd for $C_{11}H_{14}NO_4ClS$: C, 45.40; H, 4.89; N, 4.74; Cl, 12.09; S, 11.27. Found: C, 45.29; H, 4.84; N, 4.80; Cl, 12.15; S, 10.99.

Reduction of 5-(4-Chlorophenyl)-2-methoxycarbonylamino-5-oxopentanoic Acid (4a) with Et_3SiH-CF_3CO_2H

Et_3SiH (176 mg, 1.5 mmol) was added to a solution of **4a** (151 mg, 0.5 mmol) in TFA (3 mL) at rt. The mixture was heated at reflux temperature for 14 h. The reaction mixture was concentrated in vacuo. The residue was extracted with 10% NaOH solution. The aqueous solution was washed with AcOEt and acidified with 10% HCl solution, and then extracted with AcOEt. The AcOEt was washed with brine and dried over Na_2SO_4. Evaporation of the AcOEt gave a mixture of **8a** and **13a** (*cis-trans* mixture) in 87% yield (**8a**:**13a**=4:96). Treatment of the mixture with $SOCl_2$ (71 mg, 0.6 mmol) in MeOH (3 mL) gave methyl esters, which were subjected to silica gel preparative TLC (eluent; hexane-AcOEt=2:1) to afford **8a** methyl ester (3 mg, 2%) and *trans*-**13a** methyl ester (62 mg, 43%), and *cis*-**13a** methyl ester (53 mg, 37%). *trans*-**13a** methyl ester (less polar isomer) : mp 85-88℃. IR (Nujol): 1750, 1700, 1655 cm^{-1}. MS *m/z* : 317 and 315 (M^++NH_4). ^{1}H-NMR ($CDCl_3$) δ: 1.72-1.83 (1H, m), 1.91-2.06 (1H, m), 2.13-2.66 (2H, m), 3.55-3.80 (6H, m, rotamer was observed), 4.60 (1H, dd, *J* =17.2, 9.2 Hz), 5.14 (1H, dd, *J* =15.0, 8.4 Hz), 7.29 (2H, d, *J* =8.4 Hz), 7.70 and 7.13 (2H, d, *J* =8.4 Hz, rotamer was observed). *Anal.* Calcd for $C_{14}H_{16}NO_4Cl$: C, 56.47; H, 5.42; N, 4.70; Cl, 11.91. Found: C, 56.25; H, 5.45; N, 4.55; Cl, 11.77. *cis*-**13a** methyl ester (more polar isomer) : mp 94-97℃. IR (Nujol): 1745, 1710 cm^{-1}. ESI-MS *m/z* : 317 and 315 (M^++NH_4). ^{1}H-NMR ($CDCl_3$) δ: 1.83-2.15 (2H, m), 2.15-2.42 (2H, m), 3.50-3.70 (3H, m, rotamer was observed), 3.81 (3H, s), 4.41-4.55 (1H, m), 4.83-4.95 (1H, m), 7.30 (2H, d, *J* =8.4 Hz), 7.50 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{14}H_{16}NO_4Cl$: C, 56.47; H, 5.42; N, 4.70; Cl, 11.91. Found: C, 56.43; H, 5.36; N, 4.54; Cl, 11.75. The configuration of less polar and more polar isomer were determined to be 2,5-*trans* and 2,5-*cis*, respectively, by NOE experiments. Irradiation of C-2 and C-5 proton of less polar isomer led to 4.7% and 11.1% of the enhancement of aromatic protons, respectively. On the other hand, irradiation

of the C-5 proton of more polar isomer brought about the enhancement (13.9%) of aromatic protons, whereas no NOE was observed between C-2 proton and aromatic protons.

Preparation of Amino Acids (14 and 15) ------ Deprotection of 2-Methoxycarbonyl Group with Iodotrimethylsilane

The general procedure is exemplified by the preparation of (R)-4-(4-chlorophenyl)-2-aminobutanoic acid ((R)-**14a**) : Iodotrimethylsilane (1.05 g, 5.1 mmol) was added to a solution of (R)-**7a** (603 mg, 2.2 mmol) in chloroform (12 mL) at 0 ℃. The mixture was stirred at rt for 5 h. The reaction was quenched with MeOH (2 mL) at 0 ℃ and the whole was stirred at the same temperature for 10 min. The solvent was removed in vacuo and the residue was diluted with 10% HCl solution. The aqueous layer was washed with Et_2O, then made pH 8.7 with 28% NH_4OH. Resulting colorless solid was collected by filtration and then recrystallized from 80% aqueous MeOH to give 354 mg (75%, >99% ee) of (R)-**14a** as colorless plates, mp 261-263℃ (decomp). (Optical purity was confirmed by reconversion of (R)-**14a** into (R)-**7a**.) $[\alpha]_D^{20}$ -48.6° (c 0.50, 1N HCl). IR (Nujol): 1600, 1580 cm^{-1}. EI-MS *m/z* : 215 and 213 (M^+, 1:3). ^{1}H-NMR (DMSO-d_6+TFA) δ: 2.00-2.13 (2H, m), 2.51-2.68 (1H, m), 2.70-2.81 (1H, m), 3.90 (1H, m), 7.26 (2H, d, *J* =8.4 Hz), 7.37 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.66; N,6.56; Cl, 16.59. Found: C, 56.23; H, 5.63; N, 6.48; Cl, 16.52.

(S)-4-(4-Chlorophenyl)-2-aminobutanoic Acid ((S)-14a)

This compound was obtained from (S)-**7a** in 74% (>99% ee) yield as colorless plates, mp 261-264℃ (decomp). (Optical purity was confirmed by reconversion of (S)-**14a** into (S)-**7a**.) $[\alpha]_D^{20}$ +48.8°(c 0.50, 1N HCl). IR (Nujol): 1600, 1580 cm^{-1}. EI-MS *m/z* : 215 and 213 (M^+, 1:3). ^{1}H-NMR (DMSO-d_6+TFA) δ: 2.00-2.13 (2H, m), 2.51-2.68 (1H, m), 2.70-2.81 (1H, m), 3.90 (1H, m), 7.26 (2H, d, *J* =8.4 Hz), 7.37 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.66; N,6.56; Cl, 16.59. Found: C, 56.01; H, 5.59; N, 6.45; Cl, 16.54.

(R)-5-(4-Chlorophenyl)-2-aminopentanoic Acid ((R)-15a)

This compound was obtained from (R)-**8a** in 62% (>99% ee) yield as colorless plates, mp 232-233℃. (Optical purity was confirmed by reconversion of (R)-**15a** into (R)-**8a**.) $[\alpha]_D^{20}$ -9.2°(c 0.50, 1N NaOH). IR

(Nujol): 1610 cm^{-1}. ESI-MS *m/z* : 228 and 226 (M^+-H). ^{1}H-NMR (DMSO-d_6+TFA) δ: 1.50-1.85 (4H, m), 2.54-2.65 (2H, m), 3.86-3.99 (1H, m), 7.23 (2H, d, *J* =8.4 Hz), 7.35 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.03; H, 6.20; N,6.15; Cl, 15.57. Found: C, 57.73; H, 6.10; N, 6.07; Cl, 15.65.

(S)-5-(4-Chlorophenyl)-2-aminopentanoic Acid ((S)-15a)

This compound was obtained from (S)-**8a** in 71% (>99% ee) yield, as colorless plates mp 230-232℃. (Optical purity was confirmed by reconversion of (S)-**15a** into (S)-**8a**.) $[\alpha]_D^{20}$ +9.1°(c 0.50, 1N NaOH). IR (Nujol): 1610 cm^{-1}. ESI-MS *m/z* : 228 and 226 (M^+-H). ^{1}H-NMR (DMSO-d_6+TFA) δ: 1.50-1.85 (4H, m), 2.54-2.65 (2H, m), 3.86-3.99 (1H, m), 7.23 (2H, d, *J* =8.4 Hz), 7.35 (2H, d, *J* =8.4 Hz). *Anal.* Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.03; H, 6.20; N,6.15; Cl, 15.57. Found: C, 57.84; H, 6.21; N, 6.06; Cl, 15.68.

Reconversion of (R)-14a into (R)-7a with Methyl Chloroformate

Methyl chloroformate (46 mg, 0.49 mmol) was added dropwise to a solution of (R)-**14a** (70 mg, 0.33 mmol) in 1N NaOH solution (1.5 mL) at 0 ℃. After being stirred at 0 ℃ for 3 h, the mixture was acidified with 10% HCl solution and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of AcOEt gave 88 mg (quant.) of (R)-**7a** as colorless crystals, mp 120-121℃, shown by chiral HPLC analysis to be >99% ee. In a similar manner, (S)-**14a**, (R)-**15a** and (S)-**15a** were reconverted into the original *N*-methoxycarbonyl analogs ((S)-**7a**, (R)-**8a** and (S)-**8a**)(99-100% yield) and their optical purities (>99% ee) were confirmed by HPLC analysis.

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† This paper is dedicated to Prof. Bernhard Witkop on the occasion of his 80th birthday.

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6. D. G. Melillo *et al.*[1b] reported the hydrogenation of (R)-4-(3-chloro-4-methoxyphenyl)-2-(methoycarbonylamino)-4-oxobutanoic acid on a palladium catalyst involved removal of halogen substituent giving (R)-4-(4-methoxyphenyl)-2-methoxycarbonylamino-4-butanoic acid in 94% yield.
7. Optical purity of the products was determined by HPLC analysis. See experimental section.
8. Optical purity of the products was confirmed by reconverting them into the original *N*-methoxy-carbamate. See experimental section.
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