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Stereochemical Studies. XLIV.[1] Exploitation of the New Synthetic Scheme for Chiral Additives Usable in Asymmetric Syntheses. Novel Syntheses of optically Active γ-Amino Acids and Pyrrolidines from L-α-Amino Acids[2]

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Aiming to prepare optically active pyrrolidines (**2**) which are usable as chiral additives for asymmetric syntheses *via* enamines, and whose absolute configurations can correspond to that of D-proline (D-**3c**), an exploitation of the novel synthetic scheme for **2** from L-α-amino acids (L-**3**) *via* optically active γ-amino acids (**4**) was studied.

Reaction of (*S*) (−)-ditosylate ((*S*)(−)-**10a**) easily derivable from L-phenylalanine(L-**3a**), with diethyl potassiomalonate (3.0 eq.) in tetrahydrofuran, could directly give a mixture of (*R*)-pyrrolidine-2-one ((*R*)-**12a**) and (*R*)(−)-malonate ((*R*)(−)-**13a**) in 70—80% yield. Some mechanistic studies revealed that the malonate reaction proceeded through the regiospecific ring opening of (*S*) (+)-aziridine ((*S*) (+)-**11a**). Acidic hydrolysis of a crude mixture of (*R*)-**12a** and (*R*) (−)-**13a** afforded (*R*) (−)-**4a** without racemization in 49% yield based on (*S*) (−)-**10a**. The same synthetic route was applicable to L-valine (L-**3b**), giving (*R*) (+)-**4b**. However, (*S*)-**4c** could be obtained from L-proline(L-**3c**), by the treatment of (*S*) (−)-iodide ((*S*) (−)-**16c**) prepared from (*S*) (−)-ditosylate ((*S*) (−)-**10c**), with malonate anion, followed by acidic hydrolysis.

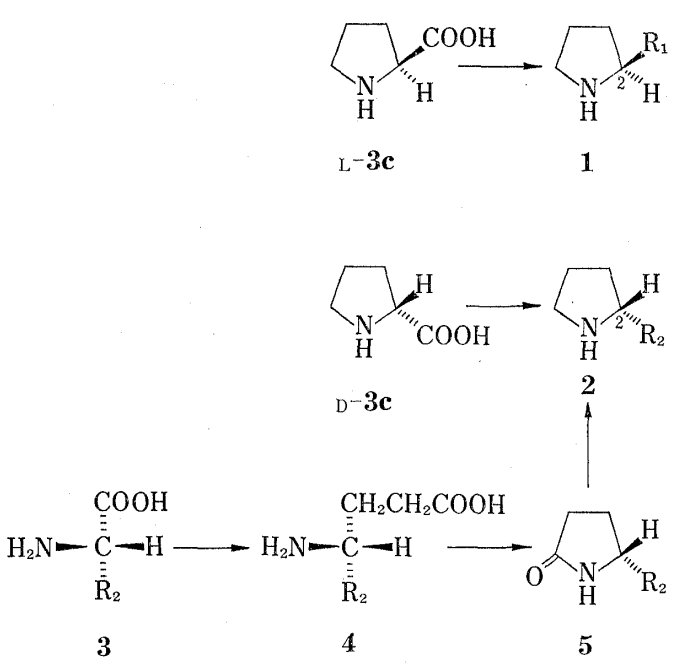
(*R*) (−)-**4a** and (*R*) (+)-**4b** thus obtained were readily converted into (*R*) (−)-**2a** and (*R*) (+)-**2b** by dehydration and reduction. When the asymmetric synthesis of 4-methyl-4-phenyl-2-cyclohexenone(**18**) was examined by using (*R*) (−)-**2a** and (*R*) (+)-**2b**, (*S*) (−)-**18**, being antipodal to that provided by using L-proline-derived pyrrolidines(**1**) as chiral additives, was successfully obtained.

Keywords——L-α-amino acids; derivatives of optically active β-aminoalcohol; malonate synthesis; regiospecific ring opening; optically active 2-alkyl-1-tosylaziridines; optically active pyrrolidine-3-carboxylates; optically active γ-amino acids; optically active pyrrolidines; asymmetric synthesis

Several kinds of optically active carbocyclic systems which are usable as starting materials for total syntheses of natural products[4] have been prepared by the asymmetric syntheses *via* enamines using optically active pyrrolidines (**1** or **2**) as chiral additives.[5]

Since **1** or **2** has been synthesized from L- or D-proline (L- or D-**3c**),[5a,c,d] they have intrinsic limitations concerning their structures and availabilities.[6] L- or D-**3c** can only afford **1** or **2**

1) Part XLIII: T. Sone, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **24**, 1293 (1976).
2) A part of this work was presented at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, April, 1975.
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) *a*) G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2125 (1973); *b*) K. Nagasawa, K. Hiroi, and S. Yamada, *Yakugaku Zasshi*, **95**, 46 (1975); *c*) M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 279 (1975); *d*) T. Sone, S. Terashima, and S. Yamada, *ibid.*, **24**, 1288 (1976).
5) *a*) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 246 (1972); *b*) K. Hiroi and S. Yamada, *ibid.*, **21**, 47, 54 (1973); *c*) G. Otani and S. Yamada, *ibid.*, **21**, 2112, 2119, 2125 (1973); *d*) T. Sone, K. Hiroi, and S. Yamada, *ibid.*, **21**, 2331 (1973); *e*) K. Nagasawa, H. Takahashi, K. Hiroi, and S. Yamada, *Yakugaku Zasshi*, **95**, 33 (1975); *f*) M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 272 (1975); *g*) K. Hiroi and S. Yamada, *ibid.*, **23**, 1103 (1975); *h*) T. Sone, S. Terashima, and S. Yamada, *ibid.*, **24**, 1273 (1976).
6) L- or D-Proline-derived optically active pyrrolidines (**1** or **2**) which have been used as chiral additives for asymmetric syntheses *via* enamines are as follows: L-proline esters (**1**: R_1=COOMe, COOEt, or COO-*t*-Bu)[5a]; L-proline tertiary amides (**1**: R_1=$CONMe_2$, $CONEt_2$, or $CONC_4H_8$)[5c]; 2-alkylpyrrolidines (**1**: R_1=Me, $CH(CH_3)_2$, CH_2NMe_2, CH_2NEt_2, or $CH_2NC_4H_8$)[5d] and (**2**: R_2=$CH_2NC_4H_8$)[4d]).



R_1 : see footnote 6
R_2 : $CH_2C_6H_5$, $CH(CH_3)_2$ *etc.*

Chart 1

whose substituents (R_1 or R_2) are easily derivable from the carboxyl group of L- or D-**3c** by chemical transformations.[6] While inexpensive commercially available L-**3c** can be used in a large scale as a starting material for preparation of **1**, it is almost impossible to utilize a large amount of expensive D-**3c** for synthesizing **2**. (*R*)(*S*)-Conversion of optically active carbocycles provided by the asymmetric syntheses using **1** as chiral additives, is considered as one tool to overcome difficulties mentioned later, and is successful in one instance,[7] but it is not applicable to every case.

Taking these problems in mind, the authors paid attention to possible preparation of **2** from inexpensive and readily available L-α-amino acids (**3**) by way of optically active γ-amino acids (**4**). According to this transformation, it might be easily accomplished to prepare **2** whose substituents (R_2) are the same as the side chains of **3** and whose absolute configurations can correspond to that of D-**3c**.

As synthesis of **2** from **4** *via* optically active pyrrolidin-2-one (**5**) was considered straightforward, an effective synthetic scheme which could afford **4** from **3** without racemization was sought.

This report concerns with exploitation of the new synthetic scheme for **4** from **3**, preparation of **2** from **4**, and use of **2** thus prepared, for asymmetric synthesis *via* enamine.

Result and Discussion

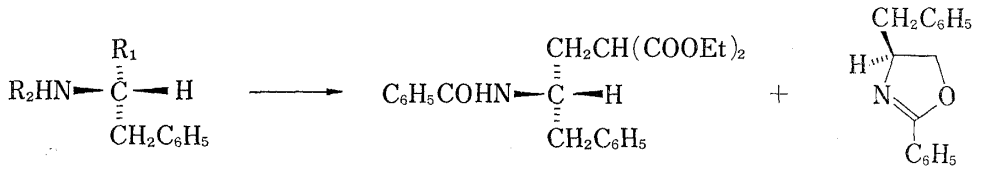
A. Exploitation of the Synthetic Scheme for optically Active γ-Amino Acids (4) from L-α-Amino Acids (3)

While many syntheses of γ-amino acids in racemic modifications, which utilize compounds other than α-amino acids as starting materials, have been delineated,[8] only two reports deal with syntheses of **4** from **3**.[9] In the latter cases, **4** can be prepared from L-alanine[9a] or L-leucine[9b] by applying the Doebner condensation to (*S*)(−)-2-phthalimidopropionaldehyde prepared from L-alanine, or repeating so-called Arndt-Eistert synthesis. Although the Arndt-Eistert reaction can proceed without racemization, it is impossible to prepare optically pure **4** by way of easily racemizable optically active 2-phthalimidoalkylaldehydes.

7) T. Sone, S. Terashima, and S. Yamada, *Synthesis*, **1974**, 725.
8) *a*) F. Knoop and H. Oesterlin, *Z. Physiol. Chem.*, **148**, 294 (1925) [*C.A.*, **20**, 56[6] (1926)]; *b*) W. Theilacker and G. Wendtland, *Ann.*, **570**, 33 (1950); *c*) Ya. L. Gol'dfard, B.P. Fabrichnyĭ, and I.F. Shalavina, *Zhur. Obshcheĭ. Khim.*, **29**, 3636 (1959) [*C.A.*, **54**, 19639*c* (1960)]; *d*) J. Cologne and J.M. Pouchol, *Bull. Soc. Chim. France*, **1962**, 598; *e*) M. Tomoeda, Y. Tani, and H. Okada, *Yakugaku Zasshi*, **86**, 1213 (1966); *f*) F. Galinovsky and A. Reichard, *Ber.*, **77**, 138 (1944); *g*) I. Murakoshi, *Yakugaku Zasshi*, **77**, 1062 (1957); *h*) B. Cavalleri, E. Bellasio, and E. Testa, *Gazz, Chim. Ital.*, **96**, 227 (1966); *i*) Y. Suhara, F. Sasaki, G. Koyama, K. Maeda, H. Umezawa, and M. Ohno, *J. Am. Chem. Soc*,. **94**, 6501 (1972).
9) *a*) K. Balenović and D. Cerar, *J. Chem. Soc.*, **1955**, 1631; *b*) A. Chimiak, *Rocz. Chem.*, **43**, 299 (1969) [*C.A.*, **71**, 3631*h* (1969)].

To exploit a more effective synthetic scheme which can afford **4** from **3** without racemization, optically active β-aminoalcohols (**6**) are selected as suitable intermediates, because they are readily accessible from **3** without racemization[10,11] and the chiral centers of **6** are not prone to racemize by usual chemical elaborations. Conversion of the alcoholic functions of **6** into acetic acid groups is examined by malonate synthesis followed by hydrolysis and decarboxylation.

Attempt along the above-mentioned scheme was first carried out by using L-phenylalanine (L-**3a**) as shown in Chart 2.



L-**3a** : R_1=COOH, R_2=H
(*S*)(−)-**6a** : R_1=CH_2OH, R_2=H
(*S*)(−)-**7a** : R_1=CH_2Cl, R_2=COC_6H_5

(*R*)(−)-**8a**

(*S*)-**9**

Chart 2

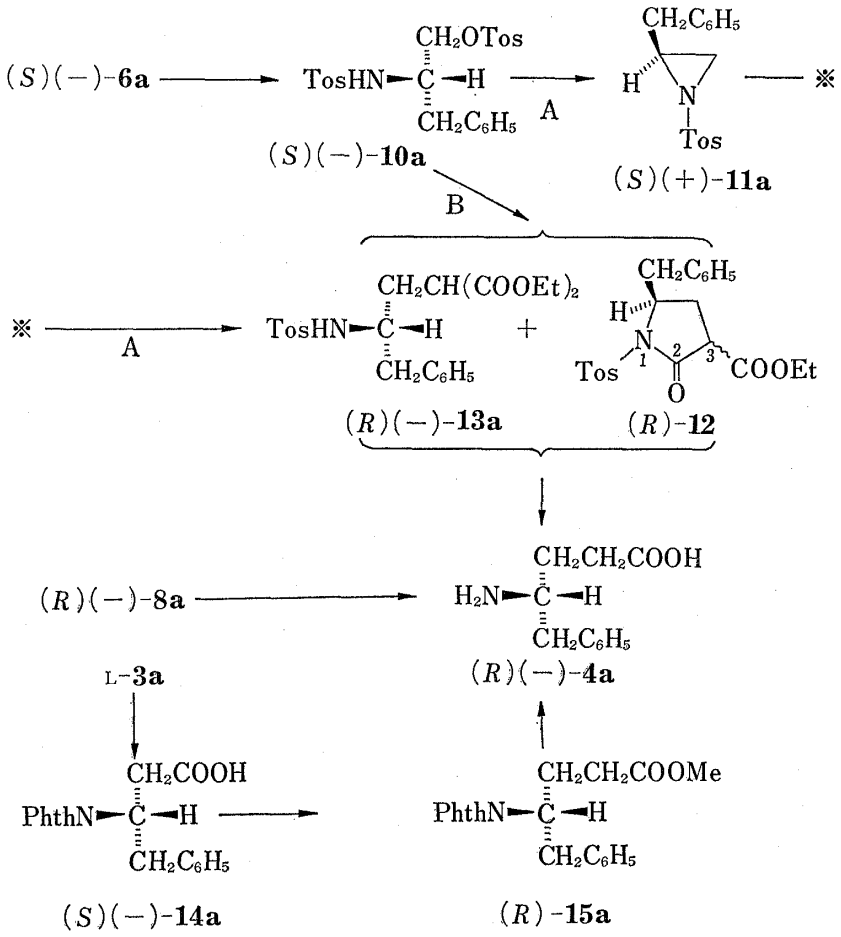
Among several kinds of possible substrates for malonate synthesis, (*S*)(−)-2-benzamido-3-phenylpropyl chloride ((*S*)(−)-**7a**), $[\alpha]_D^{20}$ −53.3° (ethanol), was chosen because of its ready accessibility,[12] and was prepared in 67% overall yield from (*S*)(−)-phenylalaninol ((*S*)(−)-**6a**), by successive dibenzoylation, hydrolysis, and chlorination.[12]

Treatment of (*S*)(−)-**7a** with diethyl potassiomalonate (3.0 eq.) prepared from diethyl malonate and potassium *t*-butoxide in anhyd. tetrahydrofuran (THF), afforded a mixture of two reaction products, from which (*R*)(−)-diethyl (2-benzamido-3-phenylpropyl)malonate ((*R*)(−)-**8a**), $[\alpha]_D^{18}$ −6.6° (benzene) was isolated in 38% yield. The other less polar reaction product was determined as (*S*)-4-benzyl-2-phenyl-Δ^2-oxazoline ((*S*)-**9**) by its spectral behavior.[13,14] The formation of (*S*)-**9** might be explained by the base-catalyzed ring closure of (*S*)(−)-**7a**.[13]

Aiming to improve the chemical yield of (*R*)(−)-**8a**, the same malonate synthesis was repeated by changing bases being necessary for the malonate anion formation, and solvent systems.[15] However, it turned out impossible to obtain (*R*)(−)-**8a** in more than 40% yield, and the oxazoline formation was always observed.[16]

10) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1965).
11) P. Karrer, P. Portmann, and M. Suter. *Helv. Chim. Acta*, **31**, 1617 (1948).
12) S. Yamada, K. Koga, and H. Matsuo, *Chem. Pharm. Bull.* (Tokyo), **11**, 1140 (1963).
13) *a*) E.E. van Tamelen, *J. Am. Chem. Soc.*, **74**, 2074 (1952); *b*) M.W. Horner, L. Hough, and A.C. Richardson, *J. Chem. Soc.*(*C*), **1971**, 99; *c*) M. Svoboda, M. Tichý, and J. Sicher, *Coll. Czech. Chem. Comm.*, **23**, 1958 (1958).
14) Since clear separation of (*S*)-**9** by column chromatography (silica gel, solvent ether: hexane 1: 2) was found to be unpromising because of the presence of a large quantity of diethyl malonate, the precise chemical yield of (*S*)-**9** could not be determined.
15) Following combinations of bases (3.0 eq.) and solvents were examined. The chemical yields of (*R*) (−)-**8a** were shown in parentheses: lithium hydride-THF (0%); sodium ethoxide-ethanol (0%); sodium hydride-THF (18%), -dimethylformamide (0%), -benzene (10%), and -dioxane (11%); potassium *t*-butoxide-*t*-butanol (0%), -dioxane (0%), -dimethylformamide (trace formation of (*R*) (−)-**8a** was observed), -benzene(trace formation of (*R*) (−)-**8a** was observed), and -dimethoxyethane (trace formation of (*R*) (−)-**8a** was observed); potassium hydride-THF (40%); cesium *t*-butoxide (prepared from metal cesium and *t*-butanol under nitrogen atmosphere)-THF (32—40%).
16) As substrates for the malonate synthesis which could not form oxazoline derivatives, (*S*)-(3-phenyl-2-phthalimido)propyl chloride and iodide were prepared. The malonate reactions using these substrates were found to be unpromising for affording the desired products and the ring opening of phthalimide group was always observed (C.C. Tseng, S. Terashima, and S. Yamada, unpublished results).

Hence, as a second method for converting **6** into **4**, an application of the nucleophilic ring opening of N-protected aziridines with malonate anion developed by Stamm, *et al.*,[17,18] was examined as visualized in Chart 3.



Tos : $SO_2C_6H_4CH_3$-*p*
Phth : $C_6H_4(CO)_2$

Chart 3

Ditosylation of (*S*)(−)-**6a** with tosyl chloride (4.0 eq.) in pyridine, gave (*S*)(−)-(3-phenyl-2-tosylamido)propyl tosylate ((*S*)(−)-**10a**), $[\alpha]_D^{20}$ −63.4° (benzene), in 94% yield. Treatment of (*S*)(−)-**10a** with anhyd. potassium carbonate (1.0 eq.) in acetone, afforded crystalline (*S*)(+)-2-benzyl-1-tosylaziridine ((*S*)(+)-**11a**), $[\alpha]_D^{20.5}$ +13.7° (benzene), in 86% yield.[19] Reflux of a THF solution containing (*S*)(+)-**11a** and diethyl potassiomalonate (2.0 eq.) for 10 min gave (*R*)-ethyl (5-benzyl-2-oxo-1-tosyl)pyrrolidine-3-carboxylate ((*R*)-**12a**) and (*R*)(−)-diethyl (3-phenyl-2-tosylamidopropyl)malonate ((*R*)(−)-**13a**), $[\alpha]_D^{19.5}$ −49.3° (benzene) as oily products in 17% and 54% yields, respectively.[20] Nuclear magnetic resonance (NMR) spectrum of (*R*)-**12a** exhibited the methyl group of ethyl ester as two sets of triplets at 1.17 and 1.26 ppm whose relative intensity was 1 : 2. This spectral feature could be explained by the presence of two diastereoisomers concerning the C_3-position. Due to this reason, the optical rotation of (*R*)-**12a** was not determined.

17) H. Stamm and L. Schneider, *Ber.*, **108**, 500 (1975), and its preceding papers.
18) O.C. Dermer and G.E. Ham, "Ethyleneimine and Other Aziridines," Academic Press, 1969, pp. 245—246.
19) See ref. 18, p. 48.
20) Formation of the reaction products similar to (*R*)-**12a** and (*R*) (−)-**13a** was reported for the malonate reactions of N-protected aziridines (see ref. 17 and 18).

Considering the reaction condition for the formation of (*S*)(+)-**11a** from (*S*)(−)-**10a**, it is quite reasonable to expect that when (*S*)(−)-**10a** is directly submitted to the same condition as that for the malonate reaction of (*S*)(+)-**11a**, a mixture of (*R*)-**12a** and (*R*)(−)-**13a** should be obtained by simultaneous aziridine formation and malonate synthesis.

This was found to be the case. A THF solution of (*S*)(−)-**10a** and diethyl potassiomalonate (3.0 eq.) was heated under reflux for 1 hr, giving (*R*)-**12a** and (*R*)(−)-**13a** in 55% and 19% yields, respectively. On the other hand, when the same reaction was attempted by using 1.5 eq. of diethyl potassiomalonate for 10 min, (*S*)(+)-**11a** was obtained in 37% yield in addition to (*R*)-**12a** and (*R*)(−)-**13a** (9% and 25% yields). These results clearly uncovers that the formation of (*R*)-**12a** and (*R*)(−)-**13a** exclusively proceeds *via* (*S*)(+)-**11a** (path A) even if a small of (*S*)(−)-**10a** might afford the reaction products by the direct displacement of tosylate with malonate anion (path B).[21]

When the malonate reaction of (*S*)(−)-**10a** was continued for 5 min, (*R*)-**12a** and (*R*)(−)-**13a** could be isolated in 26% and 46% yields. However, the reaction time was prolonged to 4 hr, the yields of (*R*)-**12a** and (*R*)(−)-**13a** changed to 79% and 1%, respectively. Change of the formation ratio of (*R*)-**12a** and (*R*)(−)-**13a** by the reflux period, clearly discloses that (*R*)-**12a** is produced from (*R*)(−)-**13a** during the reaction.

Heating a crude mixture containing (*R*)-**12a** and (*R*)(−)-**13a** in a ratio of 79:1, with 47% hydrobromic acid at reflux for 17 hr, gave (*R*)(−)-4-amino-5-phenylvaleric acid ((*R*)(−)-**4a**),

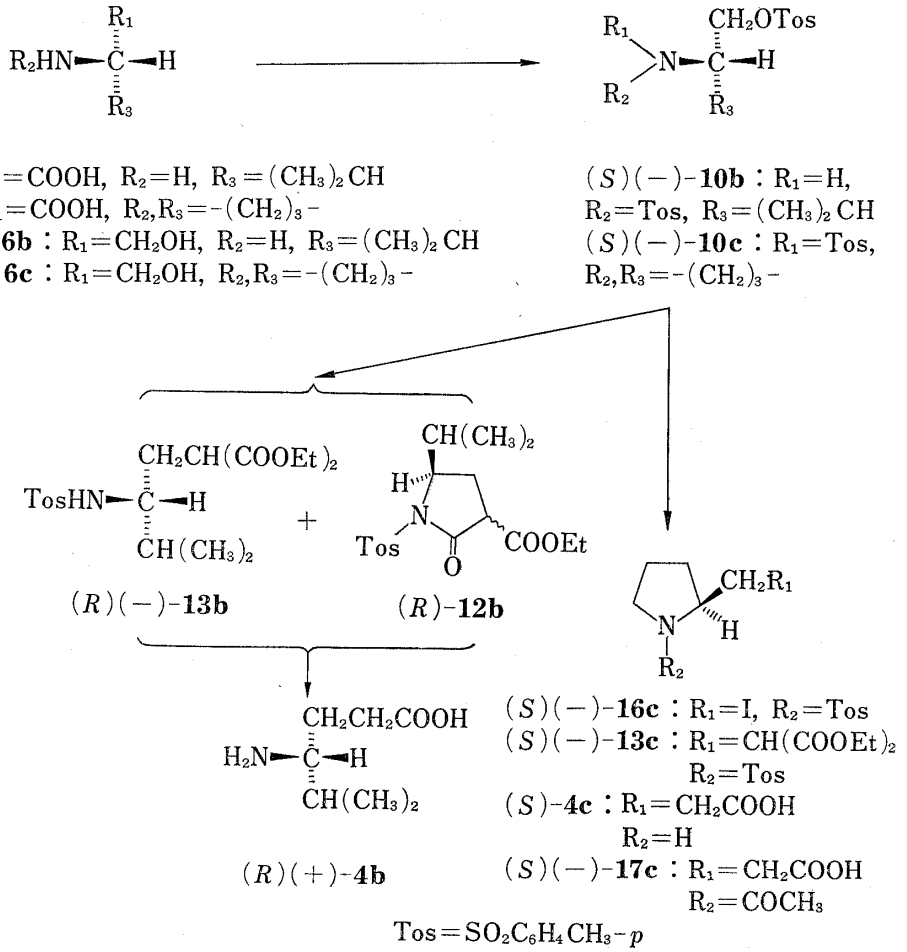


Chart 4

21) The reason why the path B was taken into consideration is that the malonate reaction with (*S*) (−)-**10c** which can not form the aziridine derivative, also gave the desired substituted product ((*S*) (−)-**13c**) in 15% yield after reflux for 8 hr (see later description).

$[\alpha]_D^{20}$ −33.8° (water), in 49% yield based on (*S*)(−)-**10a**. The same γ-amino acid, $[\alpha]_D^{20}$ −28.0° (water), was also obtained from (*R*)(−)-**8a** in 68% yield by the successive hydrolysis and decarboxylation.

Two modes of ring opening are theoretically possible when (*S*)(+)-**11a** is allowed to react with malonate anion. That the same (*R*)(−)-**4a** was obtained from (*R*)(−)-**8a** and a mixture of (*R*)-**12a** and (*R*)(−)-**13a**. clearly shows that nucleophilic attack of the malonate anion exclusively occurred at the unsubstituted carbon atom of the aziridine ring. However, in order to obtain further proof for the regiospecific ring opening,[22] an independent synthesis of (*R*)(−)-**4a** from L-**3a** was accomplished by repeating the Arndt-Eistert synthesis as shown in Chart 3. These studies which are described in detail in experimental part, definitely confirmed the observed regiospecificity.

Since the synthetic scheme for (*R*)(−)-**4a** from L-**3a** was completed, the same route was applied to L-valine (L-**3b**) and L-**3c**, respectively.

Ditosylation of (*S*)(+)-valinol ((*S*)(+)-**6b**)[23,24] and (*S*)(+)-prolinol ((*S*)(+)-**6c**),[11,25] which were prepared from L-**3b** and L-**3c** by the usual manner,[10,11] afforded two sorts of (*S*)(−)-tosylates ((*S*)(−)-**10b** and (*S*)(−)-**10c**),[26] $[\alpha]_D^{19.5}$ −68.2° (benzene) and $[\alpha]_D^{19}$ −125° (benzene), in 89% and 75% yields, respectively. The same treatment of (*S*)(−)-**10b** as that of (*S*)(−)-**10a** gave (*R*)-ethyl (5-isopropyl-2-oxo-1-tosyl)pyrrolidine-3-carboxylate ((*R*)-**12b**) as an oily diastereomeric mixture[27] and oily (*R*)(−)-diethyl (3-methyl-2-tosylamidobutyl)malonate ((*R*)(−)-**13b**), $[\alpha]_D^{20}$ −40.5° (benzene), in 43% and 25% yields after 1-hr's reaction. On the other hand, it was found that the malonate reaction proceeded very sluggishly when (*S*)(−)-**10c** was submitted to the same reaction condition as those for (*S*)(−)-**10a** and (*S*)(−)-**10b**, and that only 15% yield of desired (*S*)(−)-diethyl [2-(1-tosylpyrrolidino)methyl]malonate ((*S*)(−)-**13c**), $[\alpha]_D^{20}$ −75.5° (benzene), was obtained even after reflux for 8 hr in addition to the recovery of the starting material (64% recovery).[28] This might be construed by the lack of NH group in (*S*)(−)-**10c** which prevents the aziridine formation under the condition for malonate synthesis.[28] Therefore, (*S*)(−)-**10c** was converted into (*S*)(−)-2-iodomethyl-1-tosylpyrrolidine ((*S*)(−)-**16c**), $[\alpha]_D^{20}$ −148° (benzene), in 90% yield by treating with sodium iodide in dimethylformamide. Heating a dimethylformamide solution of (*S*)(−)-**16c** and diethyl potassiomalonate (3.0 eq.) at 110—120° for 4 hr, gave (*S*)(−)-**13c** in 45% yield as the sole reaction product.

Similar acidic treatment of the crude reaction product containing a mixture of (*R*)-**12b** and (*R*)(−)-**13b**, or (*S*)(−)-**13c**, to the preparation of (*R*)(−)-**4a**, afforded (*R*)(+)-4-amino-5-methylhexanoic acid ((*R*)(+)-**4b**), $[\alpha]_D^{20}$ +11.9° (6N HCl), or (*S*)-3-(2-pyrrolidino) propionic acid ((*S*)-**4c**), in 45% or 27% yield based on (*S*)(−)-**10b** or (*S*)(−)-**16c**. Since (*S*)-**4c** was a hygroscopic solid, it was confirmed as its N-acetyl derivative ((*S*)(−)-**17c**), $[\alpha]_D^{19.5}$ −7.6° (chloroform).

B. Preparation of optically Active Pyrrolidines (2) from optically Active γ-Amino Acids (4)

Conversion of **4** into **2** was examined by using (*R*)(−)-**4a** and (*R*)(+)-**4b** which were produced in Part A.

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22) Regiospecific attack of the malonate anion at the unsubstituted carbon atom might be explained by a combination of the steric and electronic effects of benzyl group. However, considering the results described in the following paper, it is evident that the electronic effect of benzyl group which increases electron density at the C_2-position of the aziridine ring, predominantly controls the observed regiospecificity (C.C. Tseng, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 166 (1977).

23) P. Karrer, P. Portmann, and M. Suter, *Helv. Chim. Acta*, **32**, 1156 (1949).

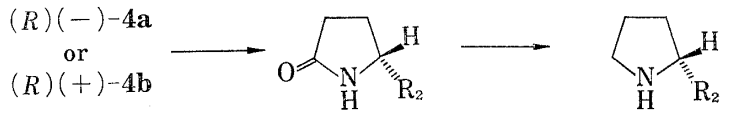
24) H. Rubinstein, B. Feibush, and E. Gil-Av, *J. Chem. Soc. Perkin II*, **1973**, 2094.

25) M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **24**, 315 (1976).

26) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

27) The ratio of two diastereoisomers was determined as 3:1 by its NMR spectrum.

28) Similar unreactivity for malonate anion was observed for (*R*) (+)-1-tosyl-2-tosyloxymethylpiperidine prepared from (*R*) (−)-2-hydroxymethylpiperidine (K. Aketa, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 621 (1976)).



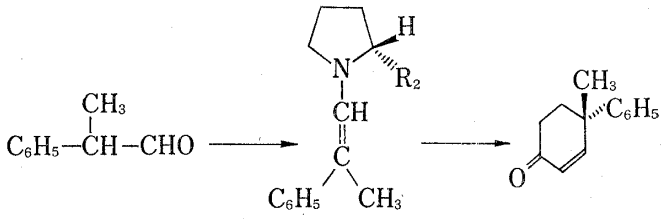
(*R*)(+)-**5a** : $R_2=CH_2C_6H_5$ (*R*)(−)-**2a** : $R_2=CH_2C_6H_5$
(*R*)(+)-**5b** : $R_2=CH(CH_3)_2$ (*R*)(+)-**2b** : $R_2=CH(CH_3)_2$

Chart 5

Reflux of a dioxane solution dissolving (*R*)(−)-**4a** or (*R*)(+)-**4b**, followed by removal of the solvent *in vacuo*,[8e] afforded (*R*)(+)-5-benzylpyrrolidin-2-one ((*R*)(+)-**5a**), $[\alpha]_D^{20}$ +39.6° (ethanol), or (*R*)(+)-5-isopropylpyrrolidine-2-one ((*R*)(+)-**5b**), $[\alpha]_D^{19.5}$ +6.0° (ethanol), in almost quantitative yields. Reduction of (*R*)(+)-**5a** and (*R*)(+)-**5b** with lithium aluminum hydride (LAH) by the usual manner gave (*R*)(−)-2-benzylpyrrolidine ((*R*)(−)-**2a**), $[\alpha]_D^{20}$ −43.3° (2N HCl), and (*R*)(+)-2-isopropylpyrrolidine ((*R*)(+)-**2b**), $[\alpha]_D^{20}$ +13.9° (ethanol), in 70% and 40% yields, respectively. The latter compound was definitely confirmed by comparing its spectral properties with those of (*S*)(−)-**2b**, $[\alpha]_D^{20}$ −14.4° (ethanol), independently prepared from L-**3c**.[5d]

C. Use of optically Active Pyrrolidines (2) for Asymmetric Synthesis *via* Enamine

Since two kinds of optically active pyrrolidines ((*R*)(−)-**2a** and (*R*)(+)-**2b**), whose absolute configurations just correspond to that of D-**3c**, have become available, their uses as chiral additives are examined for the asymmetric synthesis of optically active 4-methyl-4-phenyl-2-cyclohexenone (**18**).[5c,d] It has been reported that when **1** are used as chiral sources for the asymmetric synthesis, (*R*)(+)-**18** can be obtained with at most 54% optical purity.[5c,a]



dl-**20** (*R*)-**19a,b** (*S*)(−)-**18**

$R_2=CH_2C_6H_5$ or $CH(CH_3)_2$

Chart 6

Similarly to the reported procedure,[5d] Michael addition of the enamines ((*R*)-**19a**, **b**) prepared from *dl*-2-phenylpropanal (*dl*-**20**) and (*R*)(−)-**2a** or (*R*)(+)-**2b**, to methyl vinyl ketone, followed by the acid-catalyzed ring closure, gave (*S*)(−)-**18**, $[\alpha]_D^{19}$ −40.3° (ethanol) or $[\alpha]_D^{20}$ −37.6° (ethanol), in 43% or 14% yield.[29] Optical integrities of these (*S*)(−)-**18** were calculated as 31% or 29%, respectively.[30]

As exemplified above, it is evident that **2**, being obtainable from L-**3** according to the exploited synthetic scheme, can be used as chiral additives similarly to L-proline-derived **1**. Since preparations of both antipodes of optically active carbocycles are now possible by employing **1** or **2** as chiral sources, an usefulness of the asymmetric reactions *via* enamines[5] for natural products syntheses[4] has been clearly improved.

Experimental[31]

(*S*) (−)-Phenylalaninol ((*S*) (−)-**6a**)——Prepared from L-**3a** according to the established procedure.[10]

29) When the asymmetric synthesis was examined by using (*S*) (−)-**2b** as a chiral source, (*R*) (+)-**18**, $[\alpha]_D^{20}$ +34.3° (ethanol), 26% optically pure, was obtained in 27% yield (see ref. **5d**).
30) (*S*) (−)-**18** showing $[\alpha]_D^{20}$ −130° (ethanol) was assumed to be optically pure (see ref. 5*c*).
31) All melting and boiling points are uncorrected. IR spectra measurements were performed with a spectrometer, JASCO-IRA-1 Grating Infrared Spectrometer. NMR spectra were measured with spectrometers, JNM-PS 100 and Hitachi R-24 High Resolution NMR Spectrometers. All signals are expressed by the ppm downfield from internal standards (tetramethylsilane for $CDCl_3$ and sodium trimethylsilylpropanesulfonate for D_2O). Following abbreviations are used: singlet (*s*); doublet (d); triplet (t); quartet (q); multiplet (m); broad (br.). Optical rotations were recorded with YANACO OR-50 Automatic Polarimeter. Mass spectra measurements were carried out with JEOL JMS-01 SG-2 Mass Spectrometer.

This sample showed mp 92—94° and $[\alpha]_D^{20}$ −24.2° (c=1.53, EtOH) (lit.,[10] mp 91—93° and $[\alpha]_D^{25}$ −25.6° (c=1.037, EtOH)).

(*S*) (+)-Valinol ((*S*) (+)-6b)——This was prepared from L-**3b** according to the reported method.[23,24] An oily sample obtained, showed bp 85—89° (10 mmHg) and $[\alpha]_D^{20}$ +17.4° (c=2.46, EtOH) (lit.,[23] bp 88° (11 mmHg) and $[\alpha]_D^{20}$ +15.6° (EtOH); lit.,[24] bp 96° (22 mmHg) and $[\alpha]_D$ +16.42° (c=10, EtOH)).

(*S*) (+)-Prolinol ((*S*) (+-6c)——An oily sample which was prepared from L-**3c** according to the reported method,[11,25] showed bp 75—79° (5 mmHg) and $[\alpha]_D^{19.5}$ +1.5° (c=6.99, EtOH) (lit.,[25] bp 87—89.5° (12 mmHg) and $[\alpha]_D^{20}$ +2.8° (c=2.046, EtOH)).

(*S*) (−)-2-Benzamido-3-phenylpropyl Chloride ((*S*) (−)-7a)——Successive treatments of (*S*) (−)-**6a** with benzoyl chloride (2.0 eq.) in pyridine, sodium hydroxide (1.0 eq.) in ethanol, and thionyl chloride (3.8 eq.), according to the reported procedure for (*R*) (+)-**6a**,[12] gave (*S*) (−)-**7a** in 67% overall yield from (*S*) (−)-**6a**. The chloride which was recrystallized as needles from ethyl acetate-hexane, exhibited mp 132—134° and $[\alpha]_D^{20}$ −53.3° (c=0.94, EtOH) (lit.,[12] mp 132—134° and $[\alpha]_D^{24}$ +55.6° (c=0.716, EtOH) for (*R*) (+)-**7a**). IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH); 1640, 1530 (CONH). NMR (in $CDCl_3$): 3.00 (2H, d, J=6 Hz, $C_6H_5C\underline{H}_2$), 3.63 (2H, m, $C\underline{H}_2$-Cl), 4.55 (1H, m, C<u>H</u>–N), 6.47 (1H, br d, J=8 Hz, N<u>H</u>), 6.85—7.95 (10H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{16}ONCl$: C, 70.23; H, 5.85; N, 5.12. Found: C, 70.15; H, 5.90; N, 5.13.

(*R*) (−)-Diethyl (2-Benzamido-3-phenylpropyl)malonate((*R*) (−)-8a) and (*S*)-4-Benzyl-2-phenyl-Δ^2-oxazoline((*S*)-9)——A mixture of diethyl malonate (0.48 g, 3.0 mmole) and potassium *t*-butoxide (0.34 g, 3.0 mmole) in anhyd. THF (10 ml) was heated under reflux with stirring, giving a suspension containing diethyl potassiomalonate. To the suspension thus obtained, was added (*S*) (−)-**6a** (0.27 g, 1.0 mmole), and the mixture was stirred under reflux for 3 hr. After cooling, the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (50 ml). The ethyl acetate solution was successively washed with a mixture of satd. NaCl and 10% HCl (3: 1) (×1), and satd. NaCl (×2), then dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* afforded an oily residue, which on TLC analysis (silica gel, solvent ether: hexane 1: 2), showed three spot (*Rf* 0.1, 0.4, and 0.5 (diethyl malonate)). Purification of the residue by column chromatography (silica gel, solvent ether: hexane 1: 2) gave pure (*R*) (−)-**8a** (*Rf* 0.1) as a colorless solid (0.15 g, 38%). Several recrystallizations from ether–hexane (2: 1) afforded an analytical sample as colorless needles, mp 112°, $[\alpha]_D^{18}$ −6.6 (c=1.38, benzene). IR ν_{max}^{Nujol} cm^{-1}: 1760, 1730 (COOEt); 1640, 1540 (amide). NMR (in $CDCl_3$): 1.07, 1.17 (6H, two t, J=each 7 Hz, 2×$CH_2C\underline{H}_3$), 2.00—2.50 (2H, m, CH–C<u>H</u>$_2$–CH), 2.92 (2H, d, J=6 Hz, C_6H_5-$C\underline{H}_2$), 3.43 (1H, t, J=7 Hz, C<u>H</u>(COOEt)$_2$), 3.65—4.75 (5H, m, 2×C<u>H</u>$_2$+C<u>H</u>N), 6.15 (1H, br d, J=8 Hz, N<u>H</u>), 6.95—7.85 (10 H, m, aromatic protons). *Anal.* Calcd. for $C_{23}H_{27}O_5N$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.45; H, 6.89; N, 3.43.

Although clean separation of (*S*)-**9**(*Rf* 0.4) from diethyl malonate (*Rf* 0.5) by the column chromatography cited above was found to be difficult because of a large quantity of the latter compound, a small amount of (*S*)-**9** could be obtained as a faint yellow oil in an almost pure state. IR ν_{max}^{film} cm^{-1}: 1655 (C=N); 1610, 1590 (aromatic ring). NMR (in $CDCl_3$): 2.75 (1H, doubled d, J=15, 9 Hz, one of $C_6H_5C\underline{H}_2$), 3.20 (1H, doubled d, J=15, 6 Hz, one of $C_6H_5C\underline{H}_2$), 3.90—4.90 (3H, m, C<u>H</u>C<u>H</u>$_2$O), 7.00—8.10 (10H, m, aromatic protons).

Other experiments described in footnote 15, were carried out in a similar manner to that described above.

(*S*) (−)-(3-Phenyl-2-tosylamido)propyl Tosylate ((*S*) (−)-10a)——A mixture of (*S*) (−)-**6a** (30.2 g, 0.20 mole) and tosyl chloride (156 g, 0.80 mole) in pyridine (200 ml) was stirred at room temperature for 24 hr, then was poured onto an ice-water (500 ml). The whole mixture was extracted with ethyl acetate (×3), and the combined ethyl acetate solutions were successively washed with 10% HCl (×3), satd. $CuSO_4$ (×2), H_2O (×1), satd. $NaHCO_3$ (×2), and satd. NaCl (×4). After drying over anhyd. $MgSO_4$, filtration and evaporation *in vacuo* gave crude (*S*) (−)-**10a** as a dark brown oil (80 g, 94%), which solidified on standing at room temperature. Two recrystallizations of a part of this solid from benzene–hexane gave pure sample as colorless crystals, mp 98—99.5°, $[\alpha]_D^{20}$ −63.4° (c=1.05, benzene). IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH); 1320, 1175, 1145 (SO_2). NMR (in $CDCl_3$): 2.36, 2.43 (6H, two s, 2×$C_6H_4C\underline{H}_3$), 2.70 (2H, m, $C_6H_5C\underline{H}_2$), 3.20—4.20 (3H, m, NC<u>H</u>C<u>H</u>$_2$O), 5.10 (1H, br d, J=6 Hz, N<u>H</u>), 6.60—7.90 (13H, m, aromatic protons). *Anal.* Calcd. for $C_{23}H_{25}O_5NS_2$: C, 60.11; H, 5.48; N, 3.05. Found: C, 60.55; H, 5.50; N,3.32.

(*S*) (−)-(3-Methyl-2-tosylamido)butyl Tosylate ((*S*) (−)-10b)——The same treatment of (*S*) (+)-**6b** (1.91 g 18 mmole) as that of (*S*) (−)-**6a** gave crude (*S*) (−)-**10b** as a reddish brown solid after evaporation of the ethyl acetate extracts, mp 81—91°. One recrystallization from benzene–hexane afforded almost pure (*S*) (−)-**10b** as a yellow solid (6.74 g, 89%), mp 103—106°. Further repeated recrystallizations from the same solvent system gave pure (*S*) (−)-**10b** as colorless prisms, mp 111—113°, $[\alpha]_D^{19.5}$ −68.2° (c=1.03, benzene). IR ν_{max}^{Nujol} cm^{-1}: 3260 (NH), 1320, 1155 (SO_2). NMR (in $CDCl_3$): 0.75 (6H, d, J=6 Hz, $(C\underline{H}_3)_2CH$), 1.85 (1H, m, $(CH_3)_2$-C<u>H</u>), 2.40 (6H, s, 2×$C_6H_4C\underline{H}_3$), 3.15 (1H, m, C<u>H</u>N), 3.88 (2H, m, $C\underline{H}_2O$), 5.10 (1H, d, J=8 Hz, N<u>H</u>), 7.05—7.95 (8H, m, aromatic protons). *Anal.* Calcd. for $C_{19}H_{25}O_5NS_2$: C, 55.45; H, 6.12; N, 3.40. Found: C, 55.18; H, 6.12; N, 3.65.

(*S*) (−)-2-Tosyloxymethyl-1-tosylpyrrolidine ((*S*) (−)-10c)——Treatment of (*S*) (+)-**6c** (870 mg, 8.6 mmole) in a similar manner to the case for (*S*) (−)-**6a**, afforded crude (*S*) (−)-**10c** as a colorless oil (2.63 g, 75%) after evaporation of the ethyl acetate extracts. The oily product solidified on leaving at room temperature. Several recrystallizations from benzene–hexane gave pure (*S*) (−)-**10c** as colorless crystals, mp 104—107°, $[\alpha]_D^{19}$ −125° (c=1.05, benzene) (lit.,[26] mp 104—105°).

(*S*) (+)-**2-Benzyl-1-tosylaziridine** ((*S*) (+)-**11a**)——Anhyd. potassium carbonate (0.42 g, 3.0 mmole) was added to a solution of (*S*) (−)-**10a** (1.38 g, 3.0 mmole) in acetone (6 ml), and the whole suspension was stirred at room temperature overnight. After dilution with methylene chloride (18 ml) and filtration, the clear filtrate was evaporated *in vacuo*, giving crude (*S*) (+)-**11a** as a brown solid (0.71 g, 86%). Several recrystallizations from benzene–hexane afforded an analytical sample as colorless prisms, mp 92—94°, $[\alpha]_D^{20.5}$ +13.7° (c=1.32, benzene). IR ν_{max}^{Nujol} cm^{-1}: 1320, 1160 (SO_2). NMR (in $CDCl_3$): 2.11 (1H, d, J=4 Hz, one of CH_2N), 2.39 (3H, s, $C_6H_4CH_3$), 2.52—3.18 (4H, m, $C_6H_5CH_2CHCH$–H), 6.78—7.88 (9H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{17}O_2NS$: C, 66.87; H, 5.96; N, 4.87. Found: C, 67.12; H, 6.02; N, 4.85.

(*S*) (−)-**2-Iodomethyl-1-tosylpyrrolidine** ((*S*) (−)-**16c**)——Sodium iodide (27.5 g, 0.183 mole) was gradually added to a solution of (*S*) (−)-**10c** (25.0 g, 0.061 mole) in anhyd. dimethylformamide (150 ml), and the whole mixture was stirred at 50—60° (bath temperature) for 30 hr. After diluted with ethyl acetate (250 ml), the mixture was successively washed with H_2O (×2), 10% HCl (×1), aqueous $Na_2S_2O_3$ (×1), satd. $NaHCO_3$ (×1), and satd. NaCl (×1), and finally dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave crude (*S*) (−)-**16c** as a pale yellow solid (20.1 g, 90%). Repeated recrystallizations from benzene–hexane afforded pure (*S*) (−)-**16c** as colorless prisms, mp 104—106°, $[\alpha]_D^{20}$ −148° (c=2.00, benzene). IR ν_{max}^{Nujol} cm^{-1}: 1345, 1155 (SO_2). NMR (in $CDCl_3$): 1.14—2.00 (4H, m, $NCH_2CH_2CH_2$), 2.40 (3H, s, $C_6H_4CH_3$), 2.94—3.86 (5H, m, CH_2NCHCH_2I), 7.26 (2H, d, J=9 Hz, aromatic protons *ortho* to CH_3), 7.66 (2H, d, J=9 Hz, aromatic protons *ortho* to SO_2). Mass Spectrum *m/e*: 237, 224, and 155.[32] *Anal.* Calcd. for $C_{12}H_{16}O_2NSI$: C, 39.46; H, 4.42; H, N, 3.84. Found: C, 39.84; H, 4.37; N, 3.58.

(*R*)-**Ethyl (5-Benzyl-2-oxo-1-tosyl)pyrrolidine-3-carboxylate** ((*R*)-**12a**) **and** (*R*) (−)-**Diethyl (3-Phenyl-2-tosylamidopropyl)malonate** ((*R*) (−)-**13a**)——a) (*R*)-**12a** and (*R*) (−)-**13a** from (*S*) (+)-**11a**: A mixture of diethyl malonate (320 mg, 2.0 mmole) and potassium *t*-butoxide (224 mg, 2.0 mmole) in anhyd. THF (10 ml) was heated under reflux with stirring to give a suspension containing diethyl potassiomalonate, To this suspenasion was added (*S*) (+)-**11a** (287 mg, 1.0 mmole), and the whole was stirred under reflux for 10 min. After cooling evaporation of THF *in vacuo* gave a residue, to which was added a two layer solution of benzene (20 ml), satd. NaCl (17 ml), and 10% HCl (3 ml). The upper benzene layer was separated, washed with satd. NaCl (×2), then dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* afforded a pale yellow oil (546 mg). A part of the oil (234 mg) was purified by preparative TLC (silica gel, solvent ether: hexane 1: 1), giving (*R*)-**12a** as an oily diastereomeric mixture (30 mg, 17%) and (*R*) (−)-**13a** as an oil (103 mg, 54%). These oily products showed the following physical data. (*R*)-**12a**: IR ν_{max}^{film} cm^{-1}: 1750;, 1735 (COOEt and CONH); 1365, 1170 (SO_2). NMR (in $CDCl_3$): 1.17, 1.26 (3H, two t, the intensity of two triplets was 1: 2, J=each 7 Hz, CH_2CH_3), 1.50—3.70 (5H, m, $C_6H_5CH_2CHCH_2$), 2.42 (3H, s, $C_6H_4CH_3$), 4.13, 4.25 (2H, two q, J=each 7 Hz, CH_2CH_3), 4.65 (1H, m, CHCO), 7.10—7.50 (7H, m, C_6H_5+aromatic protons *ortho* to CH_3), 8.06 (2H, d, J=9 Hz, aromatic protons *ortho* to SO_2). Optical rotation of this sample was not measured because this was a mixture of two diastereoisomers due to the α-position of the ester group. (*R*)(−)-**13a**: IR ν_{max}^{film} cm^{-1}: 3290 (NH); 1755, 1740 (COOEt); 1335, 1160 (SO_2). NMR (in $CDCl_3$): 1.25 (6H, t, J=7 Hz, 2×CH_2CH_3), 1.53—2.24 (2H, m, CH_2CH–$(COOEt)_2$), 2.43 (3H, s, $C_6H_4CH_3$), 2.24—2.81 (2H, m, $C_6H_5CH_2$), 3.22—3.89 (2H, m, CHN+CH-$(COOEt)_2$), 4.15 (4H, q, J=7 Hz, 2×CH_2CH_3), 4.70 (1H, d, J=10 Hz, NH), 6.78—7.60 (7H, m, C_6H_5+aromatic protons *ortho* to CH_3), 7.76 (2H, d, J=9 Hz, aromatic protons *ortho* to SO_2). $[\alpha]_D^{19.5}$ −49.3° (c=2.82, benzene). Mass Spectrum: *m/e*: 274, 155, and 91.[32]

b) (*R*)-**12a** and (*R*) (−)-**13a** from (*S*)(−)-**10a**: To a suspension of diethyl potassiomalonate in anhyd. THF (20 ml) similarly prepared from diethyl malonate (960 mg, 6.0 mmole) and potassium *t*-butoxide (673 mg, 6.0 mmole), was added (*S*) (−)-**10a** (855 mg, 2.0 mmole), and the mixture was refluxed with stirring for 1 hr. After cooled, the reaction mixture was worked up in a similar fashion to the case of a), giving an oily residue (1.16 g) after evaporation of the benzene extracts. Purification by column chromatography (silica gel, solvent ether hexane 1: 1) afforded oily (*R*)-**12a** (440 mg, 55%) and (*R*) (−)-**13a** (170 mg, 19%). Spectral (IR and NMR) properties of these oily products were identified with those of the samples obtained in a).

When the reaction mixture was worked up after reflux for 5 min, the extractive isolation, followed by purification in the same manner as that described above, gave oily (*R*)-**12a** and (*R*) (−)-**13a** in 26% and 46% yields. On the other hand, when reflux of the reaction mixture was continued for 4.0 hr, the same work-up procedure as that cited above, afforded (*R*)-**12a** and (*R*)(−)-**13a** in 79% and 1% yields. These reaction products were respectively identified with the sample obtained in a) by spectral (IR and NMR) and chromatograpic (TLC) comparisons.

c) (*S*) (+)-**11a**, (*R*)-**12a**, and (*R*) (−)-**13a** from (*S*) (−)-**10a**: To a suspension of diethyl potassiomalonate in anhyd. THF prepared from diethyl malonate (240 mg, 1.5 mmole) and potassium *t*-butoxide (168 mg, 1.5 mmole), was added (*S*) (−)-**10a** (427 mg, 1.0 mmole), and the whole was refluxed with stirring for 10 min. After cooling, the extractive isolation followed by evaporation *in vacuo* in a similar manner to that described in a), afforded a brown oil (475 mg). TLC analysis of this oil showed three UV-active spots whose *Rf* values were 0.3 ((*R*) (−)-**13a**), 0.35 ((*R*)-**12a**), and 0.5 ((*S*) (+)-**11a**) (silica gel solvent ether: hexane 1: 1). Separation of a part of the residual oil (164 mg) by preparative TLC (silica gel, solvent ether: hexane 1: 1) gave (*S*) (+)-

32) The molecular ion was not observed.

11a (37 mg, 37%), (*R*)-**12a** (13 mg, 9%), and (*R*) (−)-**13a** (38 mg, 25%). These products were respectively identified with the samples prepared above, by comparing their spectral(IR) and chromatographic(TLC) behavior.

(*R*)-Ethyl (5-Isopropyl-2-oxo-1-tosyl)pyrrolidine-3-carboxylate ((*R*)-12b) and (*R*) (−)-Diethyl (3-Methyl-2-tosylamidobutyl)malonate ((*R*) (−)1-3b)——Treatment of (*S*) (−)-**10b** (412 mg, 1.0 mmole) with diethyl potassiomalonate (3.0 eq.) in a similar manner to the case for (*S*) (−)-**10a**, gave a brown oily residue (0.62 g) after evaporation of the ethyl acetate extracts. In this case, reflux of the reaction mixture was continued for 1 hr. A part of this oil (0.30 g) was purified by preparative TLC (silica gel, solvent ether: hexane 1: 1), giving (*R*)-**12b** as an oily diastereomeric mixture (73 mg, 43%) and (*R*) (−)-**13b** as an oil (49 mg, 25%). These products showed the following physical properties. (*R*)-**12b**: IR ν_{max}^{film} cm^{-1}: 1750, 1735 (COOEt and CONH); 1370, 1170 (SO_2). NMR (in $CDCl_3$): 0.69, 0.96 (6H, two d, J=each 8 Hz, $(C\underline{H}_3)_2CH$), 1.18, 1.23 (3H, two t, the intensity of two triplets was 1: 3, J=each 7 Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, $C_6H_4C\underline{H}_3$), 1.60—3.08 (3H, m, $(CH_3)_2C\underline{H}+C\underline{H}_2$), 3.47 (1H, t, J=10 Hz, $C\underline{H}CO$), 3.90—4.60 (1H, m, $C\underline{H}N$), 4.14, 4.18 (2H, two q, J=each 7 Hz, $C\underline{H}_2CH_3$), 7.32 (2H, d, J=9 Hz, aromatic protons *ortho* to CH_3), 7.92 (2H, d, J=9 Hz, aromatic protons *ortho* to SO_2). Optical rotation of this sample was not determined because the NMR spectrum clearly disclosed that this was a mixture of two diastereoisomers. (*R*)(−)-**13b**: IR ν_{max}^{film} cm^{-1}: 3300 (NH); 1740 (COOEt); 1330, 1160 (SO_2). NMR (in $CDCl_3$): 0.71, 0.76 (6H, two d, J=7 Hz, $(C\underline{H}_3)_2CH$), 1.26 (6H, t, J=7 Hz, 2× $CH_2C\underline{H}_3$), 1.43—2.15 (3H, m, $(CH_3)_2C\underline{H}+C\underline{H}_2CH(COOEt)_2$), 2.40 (3H, s, $C_6H_4C\underline{H}_3$), 2.95—3.65 (2H, m, $C\underline{H}N+C\underline{H}(COOEt)_2$), 4.14 (4H, q, J=7 Hz, 2×$C\underline{H}_2CH_3$), 4.91 (1H, d, J=10 Hz, $N\underline{H}$), 7.36 (2H, d, J= 9 Hz, aromatic protons *ortho* to CH_3), 7.74 (2H, d, J=9 Hz, aromatic protons *ortho* to SO_2). $[\alpha]_D^{20}$ −41.5° (c=0.936, benzene). Mass Spectrum *m/e*: 244, and 155.[32]

(*S*) (−)-2-(2,2-Bisethoxycarbonylethyl)-1-tosylpyrrolidine ((*S*) (−)-13c)——a) (*S*) (−)-**13c** from (*S*) (−)-**10c**: To a suspension of diethyl potassiomalonate in anhyd. THF (10 ml) prepared from diethyl malonate (480 mg, 3.0 mmole) and potassium *t*-butoxide (340 mg, 3.0 mmole), was added (*S*) (−)-**10c** (410 mg, 1.0 mmole) with stirring, and the whole was heated under reflux for 8 hr. Usual extractive isolation followed by evaporation *in vacuo*, gave a colorless oil (670 mg). Separation by column chromatography (silica gel, solvent ether: hexane 1: 1) gave pure (*S*) (−)-**13c** as a colorless oil (60 mg, 15%) and (*S*)(−)-**10c** as a colorless solid (264 mg, 64% recovery). (*S*) (−)-**13c** thus obtained, showed the following physical properties. $[\alpha]_D^{20}$ −75.5° (c=0.602, benzene). IR ν_{max}^{film} cm^{-1}: 1775, 1740 (COOEt); 1350, 1160 (SO_2). NMR (in $CDCl_3$); 1.27 (6H, t, J=7 Hz, 2×$CH_2C\underline{H}_3$), 1.05—1.66 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.08 (2H, m, $C\underline{H}_2(COOEt)_2$), 2.42 (3H, s, $C_6H_4C\underline{H}_3$), 3.25 (2H, m, $C\underline{H}_2N$), 3.75 (2H, m, $C\underline{H}N+C\underline{H}(COOEt)_2$), 4.18, 4.23 (4H, two q, J=each 7 Hz, 2×$C\underline{H}_2CH_3$), 7.22 (2H, d, J=9 Hz, aromatic protons *ortho* to CH_3), 7.62 (2H, d, J=9 Hz, aromatic protons *ortho* to SO_2). Mass Spectrum *m/e* 242, 224, 173, and 155.[32]

Recovered (*S*) (−)-**10c** was confirmed by spectral (IR) comparison with the starting material.

b) (*S*) (−)-**13c** from (*S*) (−)-**16c**: A dimethylformamide solution (4 ml) containing (*S*) (−)-**16c** (110 mg, 0.30 mmole) and diethyl potassiomalonate (3.0 eq.) was stirred at 110—120° (bath temperature) for 4 hr. After cooling, the mixture was poured onto benzene (20 ml), and the benzene solution was successively washed with dil. HCl (×1), and satd. NaCl (×2), and finally dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave an oily residue (160 mg), which was purified by column chromatography (silica gel, solvent ether: hexane 1: 1), giving almost pure (*S*) (−)-**13b** as a pale yellow oil (54 mg, 45%). This was identified with the sample obtained in a) by comparing their spectral (IR) and chromatographic (TLC) properties.

(*R*) (−)-4-Amino-5-phenylvaleric Acid ((*R*) (−)-4a)——a) (*R*) (−)-**4a** from (*R*)-**12a** and (*R*) (−)-**13a**. Reflux of a mixture of (*S*) (−)-**10a** (12.8 g, 30 mmole) and diethyl potassiomalonate (3.0 eq.) in anhyd. THF for 4.0 hr, followed by the work-up similar to that described above, gave a dark brown oil containing (*R*)-**12a** and (*R*) (−)-**13a** in a ratio of 79: 1, after evaporation of the benzene extracts.

A part of this oil (17.2 g) was directly diluted with 47% HBr (30 ml), and the acidic solution was heated at reflux. Reflux started at *ca.* 60°, and a low boiling material was removed until the temperature of the mixture reached at *ca.* 100°. After further amount of 47% HBr (20 ml) was added to the hot solution, the whole was refluxed for 17 hr. The cooled colored solution was diluted with H_2O (200 ml) and washed with ether (×2). The aqueous layer was treated with charcoal, and evaporated *in vacuo* after filtration. The residue was diluted with H_2O (20 ml) and was poured onto a column of ion exchanger (Amberlite IR-120, H^+ form). The column was first washed with H_2O until the eluate became neutral, then eluted with dil. aqueous NH_4OH. Fractions being positive to ninhydrin test, were combined, and evaporated *in vacuo*, giving crude (*R*) (−)-**4a** as a pale yellow solid (2.24 g, 49% overall from (*S*) (−) **10a**). Repeated recrystallizations from ethanol–ether–H_2O, gave pure (*R*) (−)-**4a** as colorless crystals, mp 189.5—191.5°, $[\alpha]_D^{20}$ −33.8° (c=1.01, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 1650, 1642, 1583, 1555 (NH_4^+ and COO^-). NMR (in D_2O): 1.87 (2H, m, $CH_2C\underline{H}_2COO^-$), 2.43 (2H,m, $C\underline{H}_2COO^-$), 2.98 (2H, m, $C_6H_5C\underline{H}_2$), 3.58 (1H, m, $C\underline{H}N$), 7.42 (5H, s, aromatic protons). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.32; H, 7.80; N, 7.17.

b) (*R*) (−)-**4a** from (*R*) (−)-**8a**: A mixture of (*R*) (−)-**8a** (885 mg, 2.0 mmole) and 47% HBr (8 ml) was heated at reflux for 4 hr, then treated in a similar fashion to the case for a), affording crude (*R*) (−)-**4a** as a colorless solid (264 mg, 68%) after evaporation of the aqueous NH_4OH eluate. One recrystallization from ethanol–ether–H_2O, gave almost pure (*R*) (−)-**4a** as colorless crystals, mp 180—185°, $[\alpha]_D^{20}$ −28.0° (c=1.02, H_2O). Spectral (IR and NMR) behavior of this sample were supperimposable on those of pure (*R*) (−)-**4a** prepared in a).

Independent Synthesis of (*R*) (−)-4-Amino-5-phenylvaleric Acid ((*R*) (−)-4a) from L-Phenylalanine (L-3a) by Arndt-Eistert Reaction——a) (*S*) (−)-4-Phenyl-3-phthalimidobutyric Acid ((*S*) (−)-**14a**): An ethereal solution (120 ml) of (*S*)-3-phenyl-2-phthalimidopropionyl chloride (mp 85.5—87.5°) (lit.,[33] mp 83—84°) (12.0 g, 38 mmole) prepared from L-3a according to Sheehan's method.[33] was added to a solution of excess diazomethane (prepared from nitrosomethylurea (115 mmole) by the usual manner) in ether (150 ml) in an ice bath. The whole solution was stirred in an ice bath for 1.5 hr, then left in a cold room overnight. A precipitate was collected by filtration. It weighed 13.1 g (quantitative yield). IR ν_{max}^{Nujol} cm^{-1}: 2100 (CHN_2); 1785, 1755, 1720 (phthaloyl group); 1660 ($COCHN_2$). This diazoketone was immediately used for the next step.

To an aqueous mixture (150 ml) of silver oxide (7.0 g, 59 mmole) and sodium thiosulfate (7.4 g, 30 mmole) preheated at 70°, was gradually added a solution of the diazoketone (8.0 g, 25.5 mmole) in dioxane (110 ml) with stirring. The whole was stirred at *ca.* 78° for 5 hr. After 1 and 2.5 hr's reaction, further amounts of silver oxide (each 3.5 g, total 7.0 g, 59 mmole) were added to the reaction mixture. After cooling, the mixture was twice filtered to remove silver oxide, and the silver oxide collected was washed with satd. $NaHCO_3$. The combined filtrates were acidified with concd. HCl (pH≒1—2), then concentrated *in vacuo*, giving a clear solution containing crystals. After keeping at 0° overnight, the whole crystals were collected by filtration. It weighed 1.74 g (22%), and showed mp 102—103°. Recrystallization from H_2O gave pure (*S*) (−)-**14a** as colorless needles, mp 128—130°, $[\alpha]_D^{20.5}$ −143° (*c*=0.254, chloroform). IR ν_{max}^{Nujol} cm^{-1}: 1780, 1750, 1730 (phthaloyl); 1700 (COOH). NMR (in $CDCl_3$): 2.54—3.74 (4H, m, $C\underline{H}_2CHC\underline{H}_2COOH$), 4.93 (1H, m, $C\underline{H}N$), 6.50 (*ca.* 3H, br s, $COO\underline{H}+\underline{H}_2O$), 7.17 (5H, s, $C_6\underline{H}_5$), 7.68 (4H, s, $C_6\underline{H}_4(CO)_2$). *Anal.* Calcd. for $C_{18}H_{15}O_4N\cdot 2/3H_2O$: C, 67.27; H, 5.12; N, 4.35. Found: C, 67.15; H, 4.75; N, 4.44. When dried at 50—60° *in vacuo* to remove the crystal water, this sample changed to hygroscopic crystals.

b) (*R*) (−)-**4a** from (*S*) (−)-**14a**: To a benzene solution (20 ml) of (*S*) (−)-**14a** (1.86 g, 6.0 mmole) was added thionyl chloride (2.14 g, 18.0 mmole) at room temperature. After reflux for 2 hr, the reaction mixture was concentrated under ordinary pressure to remove the solvent and excess thionyl chloride, affording the crude acid chloride as a dark brown oil (2.1 g). IR ν_{max}^{film} cm^{-1}: 1850, 1790 (COCl); 1780, 1720 (phthaloyl). This was directly submitted to the next diazoketone formation.

An ethereal solution (10 ml) of the crude acid chloride (2.1 g) was added to a solution of excess diazomethane (prepared from nitrosomethylurea (*ca.* 24 mmole) by the usual manner) in ether (30 ml) under ice cooling. After stirring for 5 hr in an ice bath, filtration and evaporation *in vacuo*, gave the crude diazoketone as a brown oil (1.75 g). IR ν_{max}^{film} cm^{-1}: 2100 (CHN_2); 1780, 1720 (phthaloyl); 1640 ($COCHN_2$). This oil was immediately used for the next step.

Silver oxide (1.61 g, 7.0 mmole) was gradually added to a solution of the diazoketone (1.75 g, 5.0 mmole) in methanol (10 ml). After stirring at room temperature overnight the whole was filtered, and the silver oxide collected, was washed with methanol. The combined methanolic solution was evaporated *in vacuo*, giving a brown oi (1.56 g) which was purified by column chromatography (silica gel, solvent ether: chloroform: hexane 2: 1: 1), to afford pure (*R*)-**15a** as a pale yellow oil (1.02 g, 51% overall from (*S*) (−)-**14a**). IR ν_{max}^{film} cm^{-1}: 1780, 1720 (phthaloyl), 1745 (COOMe). NMR (in $CDCl_3$): 2.32 (4H, m, $C\underline{H}_2C\underline{H}_2COOMe$), 3.26 (2H, m, $C_6H_5C\underline{H}_2$), 3.58 (3H, s, $OC\underline{H}_3$), 4.60 (1H, br m, $C\underline{H}N$), 7.21 (5H, s, $C_6\underline{H}_5$), 7.76 (4H, s, $C_6\underline{H}_4(CO)_2$).

A solution of (*R*)-**15a** (1.52 g, 4.5 mmole) in a mixture of 47% HBr (5 ml) and acetic acid (5 ml) was heated at reflux for 3 hr, then was diluted with H_2O (30 ml). After washing with ether (×3), the aqueous solution was treated in a similar manner to the preparation of (*R*) (−)-**4a** from a mixture of (*R*)-**12a** and (*R*) (−)-**13a**, affording crude (*R*) (−)-**4a** as a colorless powder (0.28 g, 27%) after evaporation of the aqoeous NH_4OH eluate from a column of ion exchanger. Recrystallization from ethanol–ether–H_2O afforded pure (*R*) (−)-**4a** as colorless crystals, mp 189—191°, $[\alpha]_D^{20}$ −34.1° (*c*=0.77, H_2O). Spectral (IR and NMR) behavior of this sample were identical with those of (*R*) (−)-**4a** prepared from (*S*) (−)-**10a** *via* (*R*)-**12a** and (*R*) (−)-**13a**. This sample also showed no depression on mixed melting point measurement with the sample prepared from (*S*) (−)-**10a**, mp 190—191°.

(*R*) (+)-4-Amino-5-methylhexanoic Acid ((*R*) (+)-4b)——Complete the same treatment of (*S*) (−)-**10b** (16.5 g, 40 mmole) as that for the preparation of (*R*) (−)-**4a** from (*S*) (−)-**10a** afforded crude (*R*) (+)-**4b** as a pale brown solid (2.60 g, 45% overall from (*S*) (−)-**10b**) after evaporation of the aqueous NH_4OH eluate from a column of an ion exchanger. Repeated recrystallizations from ethanol–ether–H_2O gave pure (*R*) (+)-**4b** as colorless needles, mp>200° (gradually sublimes), $[\alpha]_D^{20}$ +11.9° (*c*=1.07, 6N HCl). IR ν_{max}^{Nujol} cm^{-1}: 1640, 1570 1550 (NH_3^+ and COO^-). NMR (in D_2O): 0.92 (6H, d, *J*=7 Hz, $(C\underline{H}_3)_2CH$), 1.53—2.53 (5H, m, $(CH_3)_2C\underline{H}+C\underline{H}_2C\underline{H}_2COO^-$), 3.04 (1H, m, $C\underline{H}N$). *Anal.* Calcd. for $C_7H_{15}O_2N$: C, 57.90; H, 10,41; N, 9.65. Found: C, 57.69; H, 10.38; N, 9.75.

(*S*)-3-(2-Pyrrolidino) propionic Acid ((*S*)-4c)——Crude (*S*) (−)-**13c** (11.2 g) which was obtained from (*S*) (−)-**16c** (9.1 g, 25 mmole) after evaporation of the benzene extract was directly submitted to hydrolysis without further purification.

Similar treatment of the crude oil (11.2 g) to the case for (*R*) (−)-**4a**, afforded crude (*S*)-**4c** as a very hygroscopic solid (0.95 g, 27% overall from (*S*) (−)-**16c**) after evaporation of the aqueous NH_4OH eluate from a

33) J.C. Sheehan, D.W. Chapman, and R.W. Roth, *J. Am. Chem. Soc.*, **74**, 3822 (1952).

column of an ion exchanger. This was converted into its N-acetyl derivative ((*S*) (−)-**17c**) by the usual manner, mp 105.5—107.5° (recrystallized from ethyl acetate-hexane), $[\alpha]_D^{19.5}$ −7.6° (*c*=0.53, chloroform). IR ν_{max}^{Nujol} cm^{-1}: 1730 (COOH); 1600 (CONH). NMR (in $CDCl_3$): 1.40—2.20 (6H, m, $C\underline{H}_2CH_2COOH+NCH_2C\underline{H}_2C\underline{H}_2$), 2.05 (3H, s, $COC\underline{H}_3$), 2.28 (2H, t, *J*=7 Hz, $C\underline{H}_2COOH$), 4.20 (1H, m, $NC\underline{H}CH_2$). 9.38 (1H, br s, $COO\underline{H}$). *Anal.* Calcd. for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.34; H, 8.12; N, 7.26.

(*R*) (+)-5-Benzylpyrrolidine-2-one ((*R*) (+)-5a)——A solution of (*R*) (−)-**4a** (1.9 g, 10 mmole) in dioxane (20 ml) was heated under reflux for 22 hr's. After 7 hr's reaction, further amount of dioxane (10 ml) wasa dded to the mixture. After cooling, a pale yellow solution was treated with charcoal and filtered. The filtrate was evaporated *in vacuo* afforded crude (*R*) (+)-**5a** (1.96 g, quantitative yield). TLC analysis (silica gel, solvent ether: chloroform 1: 1) of this oil showed an almost single spot whose *Rf* value (*Rf* 0.15) was the same as that of the pure sample prepared below.

Purification of crude (*R*) (+)-**5a** was carried out by column chromatography (silica gel, solvent ether: chloroform 1: 1), affording pure (*R*) (+)-**5a** which gradually solidified on standing. Recrystallization from ether–petr. ether gave an analytical sample as colorless prisms, mp 58—61°, $[\alpha]_D^{20}$ +39.6° (*c*=1.19, EtOH) IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH); 1700 (CONH). NMR (in $CDCl_3$): 1.60—2.44 (4H, m, $C\underline{H}_2C\underline{H}_2CONH$), 2.77 (2H, d, *J*=7 Hz, $C_6H_5C\underline{H}_2$), 3.84 (1H, m, $C\underline{H}N$), 6.39 (1H, br, s, $N\underline{H}$), 7.00—7.40 (5H, m, aromatic protons). *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.10; H, 7.54; N, 8.03.

(*R*) (+)-5-Isopropylpyrrolidine-2-one ((*R*) (+)-5b)——Treatment of (*R*) (+)-**4b** (1.02 g, 7.0 mmole) in a similar manner to that of (*R*) (−)-**4a** gave crude (*R*) (+)-**5b** as a pale yellow solid (0.87 g, 98%) after evaporation of the dioxane solution. Recrystallization from ether–petr. ether gave pure (*R*) (+)-**5b** as colorless crystals, mp 64—66°, $[\alpha]_D^{19.5}$ +6.0° (*c*=1.41, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3180 (NH); 1700 (CONH). NMR (in $CDCl_3$): 0.85, 0.90 (6H, two d, *J*=each 7 Hz, $(C\underline{H}_3)_2CH$), 1.25—2.55 (5H, m, $(CH_3)_2C\underline{H}CHC\underline{H}_2C\underline{H}_2CO$), 3.36 (1H, m, $C\underline{H}N$), 7.25 (1H, br s, $N\underline{H}$). *Anal.* Calcd. for $C_7H_{13}ON$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.46; H, 10.33; N, 11.18.

(*R*) (−)-2-Benzylpyrrolidine ((*R*) (−)-2a)——A heterogeneous solution of (*R*) (+)-**5a** (0.72 g, 4.1 mmole) and LAH (0.21 g, 5.5 mmole) in anhyd. THF (10 ml) was stirred under reflux for 18.5 hr. To the residue which was obtained by removal of THF *in vacuo*, was added anhyd. ether. After 15% aqueous NaOH (1 ml) was added to the ethereal solution, the whole was stirred at room temperature for 20 min, then dried over anhyd. K_2CO_3. Filtration and evaporation *in vacuo* afforded crude (*R*) (−)-**2a** as a pale yellow oil (0.46 g, 70%). IR spectrum of this oil was identical with that of pure sample measured in the same state. Fractional distillation of this oil gave pure (*R*) (−)-**2a** as a colorless oil (0.30 g, 46%), bp 95—98° (4 mmHg), $[\alpha]_D^{20}$ −43.3° (*c*=3.20, 2N HCl). IR ν_{max}^{film} cm^{-1}: 3280 (NH). NMR (in $CDCl_3$): 1.20—2.00 (4H, m, $C\underline{H}_2C\underline{H}_2CH_2N$), 2.36 (1H, s, $N\underline{H}$), 2.68 (2H, d, *J*=7 Hz, $C_6H_5C\underline{H}_2$), 2.56—3.36 (3H, m, $C\underline{H}NC\underline{H}_2$), 7.14 (5H, s, aromatic protons). This oil gave crystalline picrate, mp 140.5—142.5° (recrystallized from ethanol). *Anal.* Calcd. for $C_{17}H_{18}O_7N_4$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.33; H, 4.62; N, 14.12.

(*R*) (+)-2-Isopropylpyrrolidine ((*R*) (+)-2b)——Reduction of (*R*) (+)-**5b** (3.17 g, 25 mmole) with LAH (1.42 g, 37 mmole) in anhyd. THF (45 ml) in a similar fashion to the case for (*R*) (+)-**5a**, gave an ethereal solution of (*R*) (+)-**2b** after filtration of the ethereal extract. Anhyd. ethanol containing 11% HCl (25 ml) was added to the above-mentioned ethereal solution, and was evaporated *in vacuo* to give a residue. Addition of benzene to the residue, followed by evaporation *in vacuo*, gave crude (*R*) (+)-**2b** hydrochloride as a pale pink solid (2.84 g). Recrystallization from ethyl acetate–chloroform–petr. ether gave the pure hydrochloride as colorless crystals (1.75 g, 47%), mp 140—142° (lit.,[5d] mp 146°). According to the reported procedure,[5d] the hydrochloride (1.6 g) was converted into its free base ((*R*) (+)-**2b**) (1.2 g, 39%), bp *ca.* 130° (760 mmHg) (bath temperature, 138—153°), $[\alpha]_D^{20}$ +13.9° (*c*=0.46, EtOH) (lit.,[5d] bp 130—137° (760 mmHg) and $[\alpha]_D^{20}$ −14.4° (*c*=0.45, EtOH) for (*S*) (−)-**3b**). Spectral (IR and NMR) properties of this oil were superimposable on those of (*S*) (−)-**2b**[5d] previously prepared from L-**3c**.

Asymmetric Synthesis of (*S*) (−)-4-Methyl-4-phenyl-2-cyclohexenone ((*S*) (−)-18)——The experimental procedure described here is complete the same as that previously reported.[5d]

Condensation of *dl*-**20** (329 mg, 2.5 mmole) and (*R*) (−)-**2a** (395 mg, 2.5 mmole) in benzene (15 ml) in the presence of Molecular Sieves 4A, gave the crude enamine ((*R*)-**19a**) (717 mg, quantitative yield). IR ν_{max}^{film} cm^{-1}: 1640 (double bond). The reaction of (*R*)-**19a** with methyl vinyl ketone (343 mg, 4.9 mmole) in methanol (7 ml) at room temperature for 20 hr, followed by the addition of 33% acetic acid (0.5 ml) and reflux for 2 hr, afforded (*S*) (−)-**18** as an oil (196 mg, 43%), $[\alpha]_D^{19}$ −40.3° (*c*=1.25, ethanol), 31% optically pure,[30] after extractive isolation and purification by preparative TLC (silica gel, solvent ether: hexane 1: 4). Spectral (IR and NMR) properties of this oil were completely identical with those of an authentic sample.[5d]

When the asymmetric synthesis was attempted by using (*R*) (+)-**2b** as a chiral additive, (*S*) (−)-**18** showing $[\alpha]_D^{20}$ − 37.6° (*c*=1.53, ethanol), 29% optically pure,[20] was obtained as a colorless oil in 14% yield.

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