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# Stereochemical Studies. XXI.[1] Studies on α-Alkyl-α-amino Acids. XV.[2] Application of Thermal Isocyanide-Cyanide Rearrangement to *R-S* Conversion of α-Methylphenylalanine

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*R–S* Conversion of *R*(+)-α-methylphenylalanine (*R*(+)-V), one of the typical α-alkyl-α-amino acids, was accomplished with 75.6% retention of its optical integrity, since the *R*(+)-isocyanide (*R*(+)-X) easily derived from *R*(+)-V afforded the *S*(+)-cyanide (*S*(+)-XI) with 75.6% retention of configuration when a diphenyl ether solution of *R*(+)-X was heated at 280°.

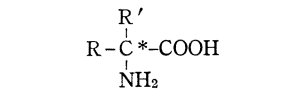
Preliminary experiments using racemic compounds were also reported in experimental part.

When preparation of optically active amino acid (I) is attempted using commercially available, optically inactive, and simple starting material, resolution of the synthetic intermediate or the compound easily derived from racemic final product, by means of chemical or biochemical methods, is always inevitable for obtaining optically active product.[4]

In the case of synthesis of optically active α-hydrogen-α-amino acid (Ia) (normal naturally occurring α-amino acid), undesired enantiomer (usually *R*-isomer) produced by chemical or biochemical resolution can be easily racemized by chemical treatment, and be recycled to resolution step.[4,5] However, application of the above-mentioned resolution and racemization procedures to the preparation of optically active α-alkyl-α-amino acid (Ib) is completely impossible since racemization of the undesired enantiomer yielded by resolution can not be easily achieved because of the absence of α-hydrogen.[6]

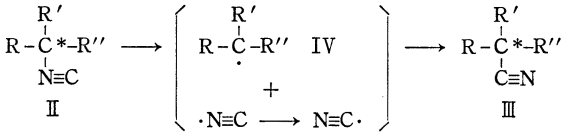
Recently, the authors carried out extensive investigations on the thermal isocyanide-cyanide rearrangement[7–9] using optically active isocyanide (II) carrying a quarternary asymmetric carbon. These studies clearly disclosed that this thermal reaction afforded the desired cyanide (III) with high retention of configuration when the isocyanide (II) having

1) Part XX: K. Hiroi and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 54 (1973).
2) Part XIV: K. Achiwa, S. Terashima, H. Mizuno, N. Takamura, T. Kitagawa, K. Ishikawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **18**, 61 (1970).
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John-Wiley & Sons, Inc., New York, London, 1961, pp. 715—760.
5) S. Akabori, *et al.*, "Chemistry of Protein," Vol. I, Ed., Kyoritsu Publishing Co., Ltd., Tokyo, Japan, 1969, p. 66.
6) Some synthetic devises which convert the undesired enantiomer to optically inactive starting material or to easily racemizable amino nitrile derivative have been introduced to save this kind of trouble encountered in the synthesis of biologically active (−)-α-methyl-3,4-dihydroxyphenylalanine. See, H.L. Slates, D. Taub, C.H. Kuo, and N.L. Wendler, *J. Org. Chem.*, **29**, 1424 (1964), and F.A. Firestone, D.F. Reinhold, W.A. Gaines, J.M. Chemerda, and M. Sletzinger, *J. Org. Chem.*, **33**, 1213 (1968).
7) *a*) S. Yamada, K. Takashima, T. Sato, and S. Terashima, *Chem. Comm.*, **1969**, 811; *b*) S. Yamada, M. Shibasaki, and S. Terashima, *ibid.*, **1971**, 1008.
8) S. Terashima, K. Takashima, T. Sato, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), in, press.
9) M. Shibasaki, T. Sato, N. Ohashi, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), in press.



Ia : R=alkyl, aryl, R′=H
Ib : R,R′=alkyl, aryl

Chart 1



R, R′, R″=alkyl, aryl, and not H

Chart 2

no functional group which stabilized a formed radical intermediate,[9,10] was employed under special reaction condition,[9,11] even though full informations about the reaction mechanism agreed with the intervention of radical intermediate (IV).[7,9]

Utilizing the experimental results accumulated on the isocyanide-cyanide rearrangement until now,[7-9] applicability of this novel thermal reaction to the possible *R-S* conversion of enantiomeric α-alkyl-α-amino acid, was studied taking *R*(+)-α-methylphenylalanine (*R*(+)—V), one of the most typical α-alkyl-α-amino acids, as an example, since the *R-S* conversion procedure established on Ia[12] was clearly not applicable to Ib because of the expected for-

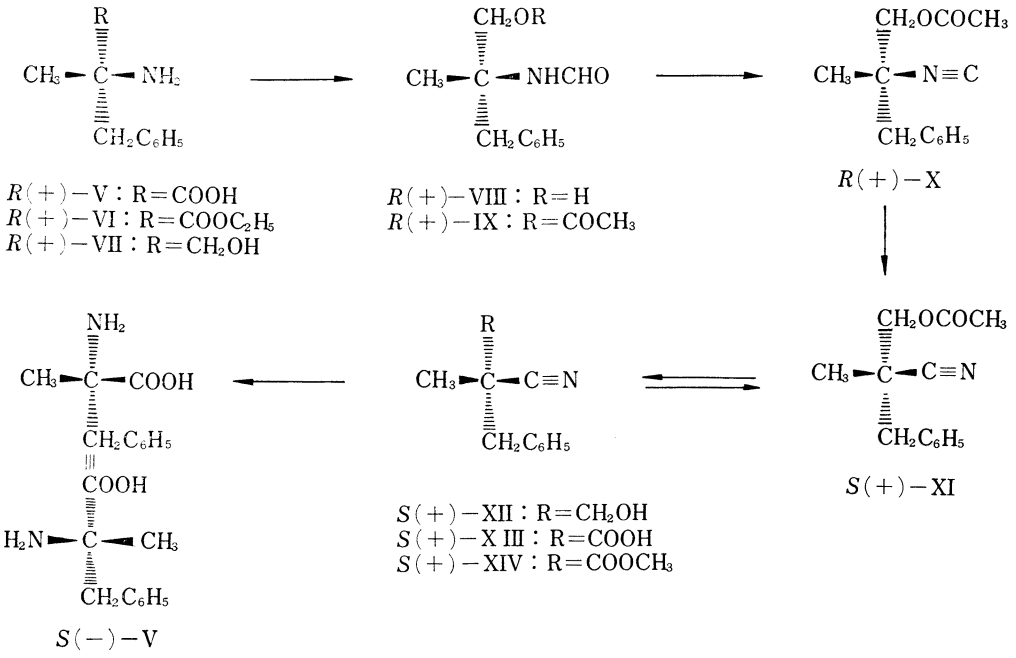
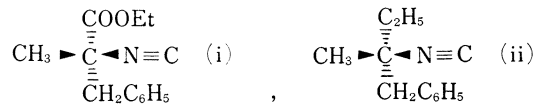


Chart 3

10) Although the isocyanide (i) afforded almost racemized cyanide when heated at 280° for 3.0 hr in diphenyl ether, the same treatment of the isocyanide (ii) as that employed on (i) gave the rearranged product with 90% retention of configuration. (See reference 9).



11) For instance, heating the isocyanide (ii) at 260° without solvent for 6.0 hr afforded the expected cyanide with 47% retention of configuration. However, improvement of the degree of configuration retention from 47% to 90% was achieved when a diphenyl ether solution of (ii) was heated at 280° for 3.0 hr (See reference 9).

12) E. Fischer, *Ann.*, **340**, 171 (1905); *Ber.*, **40**, 489 (1907).

mation of racemizable intermediate,[13] and other methods for *R-S* conversion of Ib have never been developed until now.

Chemical scheme employed for the *R-S* conversion of *R*(+)—V was shown in Chart 3. All preliminary experiments were carried out using recamic compounds, and were described in detail only in experimental part.

Formylation of *R*(+)-amino-alcohol (*R*(+)-VII), $[\alpha]_D^{20}$+6.6° (ethanol) (100% optically pure)[14] prepared from *R*(+)-V by way of *R*(+)-ethyl ester (*R*(+)-VI),[15] with ethyl formate[16] afforded *R*(+)-N-formyl alcohol (*R*(+)-VIII), $[\alpha]_D^{20}$+110.0°(chloroform) in 71% yield. *R*(+)-alcohol (*R*(+)-VIII) obtained here was treated with acetic anhydride-pyridine, yielding *R*(+)-acetate (*R*(+)-IX), in quantitative yield, which was dehydrated with phosphorous oxychloride-pyridine to afford *R*(+)-isocyanide (*R*(+)-X), $[\alpha]_D^{18}$+10.2°(chloroform) in 61% yield.

Next, in order to precisely calculate the degree of configuration retention in the thermal rearrangement of *R*(+)-X, independent synthesis of the rearranged product, *S*(+)-(2-cyano-2-methyl-3-phenyl)propyl acetate (*S*(+)-XI) was attempted using *S*(+)-2-cyano-2-methyl-3-phenylpropionic acid (*S*(+)-XIII), $[\alpha]_D^{20}$+23.3°(chloroform), (85.0% optically pure).[17] That is, reduction of *S*(+)-XIII with sodium borohydride *via* its mixed anhydride[18] afforded *S*(+)-cyano-alcohol (*S*(+)-XII), $[\alpha]_D^{26}$+12.0°(chloroform), which was converted to *S*(+)-XI in quantitative yield by the treatment with acetic anhydride-pyridine. Produced *S*(+)-XI showed $[\alpha]_D^{18}$+9.8°(chloroform) and $[M]_{400}^{13}$+56.6°(chloroform).[19]

Thermal rearrangement of the previously obtained *R*(+)-X was accomplished by heating a diphenyl ether solution of *R*(+)-X at 280° (bath temperature) for 3.0 hr under nitrogen atmosphere. *S*(+)-XI yielded in quantitative yield by gas chromatographic analysis, showed $[\alpha]_D^{20}$+8.8°(chloroform) and $[M]_{400}^{15}$+50.3°(chloroform)[19] after chromatographic purification followed by fractional distillation.

Comparison of molecular rotations of *S*(+)-XI at 400 mμ, independently prepared from *R*(+)-X and *S*(+)-XIII,[20] which were respectively 100% and 85.0% optically pure, clearly disclosed that the thermal rearrangement of *R*(+)-X proceeded with 75.6% retention of configuration.

Subsequent alkaline hydrolysis of *S*(+)-XI (84% yield) followed by oxidation with potassium permanganate (92% yield) completed the objective *R-S* conversion of *R*(+)-V, since *S*(+)-XIII obtained here had already been converted to *S*(−)-α-methylphenylalanine (*S*(−)-V) with 100% retention of configuration by the well-known Hofmann rearrangement.[21]

Further confirmation of *S*(+)-XIII produced here was carried out by the conversion of crude *S*(+)-XIII to its methyl ester (*S*+)-XIV), $[\alpha]_D^{27}$+33.6°(chloroform) using diazomethane. Isolated oily *S*(+)-XIV was identified with the authentic sample by the usual manner.[22]

13) When Ib is submitted to the *R–S* conversion procedure reported in reference 12, that is, deaminative halogenation with nitrosyl bromide followed by substitution with ammonia, formation of easily racemizable carbonium ion intermediate at each step might be reasonably expected. See ,M. Kobayashi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, (Tokyo) **20**, 1898 (1972).

14) S. Terashima and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1953 (1968).

15) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1139 (1966).

16) Formation of a small amount of N,O-diformate was also observed by thin–layer chromatography (See experimental).

17) The optical purity of this compound was calculated to be 85.0% by assuming that *S*(+)-XIII showing $[\alpha]_D^{21}$ + 27.4° (chloroform) was 100% optically pure. (See reference 22).

18) K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 492 (1968).

19) Determined by the measurement of optical rotatory dispersion curve.

20) Values of molecular rotation at 400 mμ were preferably chosen instead of those of optical rotation at 589 mμ, because of the increased accuracy due to their larger absolute values.

21) K.K. Lee, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2540 (1969).

22) S. Terashima, K.K. Lee, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2533 (1969).

As mentioned above, *R*-*S* conversion of *R*(+)-α-methylphenylalanine was now successfully completed using the thermal isocyanide-cyanide rearrangement as a key step. Although the yield of each step and the degree of configuration retention in the thermal reaction should be further optimized, this conversion scheme will surely be recognized as one of the most effective methods for utilizing the undesired enantiomer after preparation of optically active α-alkyl-α-amino acid (Ib) has been accomplished by way of resolution step.

## Experimental[23]

**(+)- and *R*(+)-2-Amino-2-methyl-3-phenylpropanol** ((±)- and ***R*(+)-VII**)——These compounds prepared according to the reported procedure[14] showed bp 125—127° (5 mmHg) ((±)-VII) and mp 72—74°, $[\alpha]_D^{20}$ +6.6° (*c*=1.832, EtOH) (*R*(+)-VII). (Reported physical[14] constants are bp 134—135° (6 mmHg) ((±)-VII) and mp 72.5—75°, $[\alpha]_D^{25}$ +5.4° (*c*=0.956, EtOH) (*R*(+)-VII)).

**(±)-2-Formamido-2-methyl-3-phenylpropanol** ((±)-**VIII**)——A mixture of (±)-VII (7.47 g, 0.045 mole) and ethyl formate (225 ml) was stirred under reflux for 13 hr. Concentration of the whole reaction mixture *in vacuo* gave crude (±)-VIII as a pale brown oil, contaminated by a small amount of N,O-diformate on thin-layer chromatography (TLC) analysis (silica gel, solvent: ethyl acetate). Purification of crude (±)-VIII with column chromatography using silica gel afforded pure oily (±)-VIII (6.99 g, 80%) which solidified when kept at room temperature. This solid was twice recrystallized from benzene, to give an analytical sample as colorless pillars, mp 99.5—100.5°. *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 67.99; H, 7.81; N, 7.16. NMR (in $CDCl_3$): 1.17 (3H, singlet, $-\underset{\text{I}}{\text{C}}-CH_3$), 2.86, 3.00 (2H, singlet and quartet, $C_6H_5-CH_2$, *J*=15 cps),[24] 3.48, 3.63 (2H, 2 singlets, $CH_2O$),[24] 5.90 (1H, broad singlet, –NH), 7.24 (5H, singlet, $C_6H_5$), 7.85—8.15 (1H, multiplet, CHO). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1675 (amide).

***R*(+)-2-Formamido-2-methyl-3-phenylpropanol** (***R*(+)-VIII**)——Treatment of *R*(+)-VII ($[\alpha]_D^{20}$ +6.6° (EtOH), 100% optically pure) (9.6 g, 0.052 mole) similar to that of (±)-VII gave *R*(+)-VIII as a viscous oil after chromatographic purification. Trituration with ethyl acetate followed by filtration afforded almost pure *R*(+)-VIII as colorless needles (7.05 g, 71%), which was repeatedly recrystallized from ethyl acetate afforded an analytical sample as colorless prisms, mp 128—129.5°, $[\alpha]_D^{20}$ +110.0° (*c*=0.852, chloroform). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.20; H, 7.88; N, 7.26. IR and NMR spectra of *R*(+)-VIII obtained here were identical with those of authentic (±)-VIII in the same states.

**(±)-2-Formamido-2-methyl-3-phenylpropyl Acetate** ((±)-**IX**)——Acetic anhydride (2.68 g, 0.0263 mole) was gradually added with stirring in an ice-water bath to an anhydrous pyridine solution (16.5 ml) of (±)-VIII (3.38 g, 0.0175 mole). The whole reaction mixture was stirred at room temperature for 10 hr, and then was poured onto an ice-water. An oil separated was extracted with ethyl acetate, and combined organic layers were successively washed with 10% HCl and satd. NaCl, and finally dried over anhyd. $Na_2SO_4$. Filtration and evaporation *in vacuo* afforded almost pure (±)-IX as a slightly yellow viscous oil (4.21 g, quantitative yield). TLC (Silica gel, solvent: benzene–ethyl acetate 1: 1) of produced (±)-IX showed a single spot whose *Rf* value was 0.5. This sample was immediately used for the next step without further purification. NMR (in $CCl_4$): 1.27 (3H, singlet, –C–$CH_3$), 2.03, 2.08 (3H, 2 singlets, $COCH_3$),[24] 2.86, 3.08 (2H, singlet and quartet, $C_6H_5CH_2$, *J*=12 cps),[24] 6.22 (1H, broad singlet, –NH–), 7.14 (5H, singlet, benzene ring protons), 8.98—7.58 (1H, multiplet, CHO). IR $\nu_{max}^{Cap.}$ $cm^{-1}$: 3300 (NH), 1745 (ester), 1680, 1535 (amide).

***R*(+)-2-Formamido-2-methyl-3-phenylpropyl Acetate** (***R*(+)-IX**)——The same treatment of *R*(+)-VII (6.99 g, 0.036 mole) as that employed on (±)-VII gave almost pure *R*(+)-IX as a slightly yellow oil after evaporation of ethyl acetate extract. It weighed 7.96 g (quantitative yield), and showed $[\alpha]_D^{20}$ +27.2° (*c*=1.088, chloroform). This oil also showed a single spot on TLC (silica gel: solvent, benzene–ethyl acetate 1: 1), whose *Rf* value was the same as that of (±)-IX. IR spectrum of *R*(+)-IX in a chloroform solution was superimposable on that of (±)-IX measured in the same state, and NMR spectrum measured on *R*(+)-IX was also identical with that of (±)-IX in the same state.

23) All melting points and boiling points were uncorrected. Infrared (IR) spectra measurements were performed with Spectrometers, Model DS-402 and IR-S, Japan Spectroscopic Co. Ltd., nuclear magnetic resonance (NMR) spectra were measured using a Spectrometer Model 3H-60 (60 Mc), Japan Electron Optics Lab. and data are reported in parts per million downfield from internal tetramethylsilane. Optical rotations were determined using Yanaco OR-50 Automatic Polarimeter, and optical rotatory dispersion (ORD) curve measurements were carried out with a Spectrometer, Model ORD/UV-5, Japan Spectroscopic Co. Ltd. Gas chromatographic analyses were performed using a Yanagimoto Gas Chromatography, Model GCG-550T.

24) This appearance of NMR spectrum was considered to be due to the presence of conformational isomers.

**(±)-2-(1-Acetoxy-2-methyl-3-phenyl)propyl Isocyanide ((±)-X)**——Phosphorus oxychloride (1.23 g, 0.008 mole) was gradually added with stirring in an ice bath to a mixture of (±)-IX (3.72 g, 0.016 mole) and chloroform (3.82 g, 0.032 mole) in anhydrous pyridine (6.98 g, 0.088 mole). After stirred at room temperature for 24 hr, the whole was diluted with water and the lower chloroform layer was separated. Upper aqueous phase was further extracted with chloroform. Combined organic layers were washed with water and dried over anhyd. $Na_2SO_4$. Filtration and evaporation *in vacuo* afforded a brown oil, which was submitted to column chromatography using silica gel (150 g, solvent: petr. ether–ethyl acetate 8: 2). Fractions containing desired (±)-X were combined and evaporated *in vacuo*, giving an oily residue, which was distilled under reduced pressure, to give pure (±)-X as a colorless oil (1.98 g, 57%), bp 137—140° (0.09 mmHg). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.76; H, 6.91; N, 6.55. NMR (in $CCl_4$): 1.33 (3H, singlet, $-C-C\underline{H}_3$), 2.13 (3H, singlet, $COC\underline{H}_3$), 2.89 (2H, singlet, $C_6H_5C\underline{H}_2$), 3.99 (2H, singlet, $C\underline{H}_2O$), 7.23 (5H, singlet, $C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 2160 (NC), 1750 (ester).

***R*(+)-2-(1-Acetoxy-2-methyl-3-phenyl)propyl Isocyanide (*R*(+)-X)**——The same treatment of *R*(+)-IX (7.30 g, 0.031 mole) as that of (±)IX gave *R*(+)-X as a colorless oil (4.17 g, 61%), bp 123—130° (0.13 mmHg), which gradually solidified on standing, mp 30°, $[\alpha]_D^{18}$ +10.2° (*c*=1.272, chloroform). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.90; H, 7.05; N, 6.58. IR and NMR spectra of *R*(+)-X thus obtained were identical with those of (±)-X in the same states.

**Thermal Rearrangement of (±)-X**——A mixture of (±)-X (0.50 g, 0.0023 mole) and diphenyl ether (5 ml) was heated at 280° (bath temperature) under nitrogen atmosphere. After 3 hr heating, gas chromatographic analysis of the reaction mixture (column: 15% SE-30 on Diasolid L, 2.25 m, 150°: internal standard, acenaphthene: retention time, 5.8 min; (±)-XI: retention time, 9.8 min) clearly showed completion of the rearrangement in quantitative yield. Isolation of the rearranged product was achieved using silica gel column chromatography (25 g). Diphenyl ether was first washed out with petr. ether, and then all reaction products were thoroughly eluted from the column using a mixture of petr. ether and ethyl acetate (8: 2). Combined fractions containing all reaction products were evaporated *in vacuo* to give crude (±)-XI as a pale yellow oil (0.46 g, 92%). IR $\nu_{max}^{Cap.}$ $cm^{-1}$: 2250 (CN), 1750 (ester). This spectrum was identical with that of the authentic (±)-XI measured in the same state.

**Thermal Rearrangement of *R*(+)-X**——Heating a diphenyl ether solution (20 ml) of *R*(+)-X (2.0 g, 0.0092 mole) under the same reaction condition as that established on (±)-X afforded the desired *S*(+)-XI in quantitative yield by gas chromatographic analysis. In order to isolate the formed *S*(+)-XI, the whole reaction mixture was submitted to column chromatography (silica gel, 100 g). Diphenyl ether was first eluted from the column using petr. ether as an eluent, and then the rearranged cyanide (*S*(+)-XI) was eluted with petr. ether–ethyl acetate (8: 2). Concentration of the combined eluates containing *S*(+)-XI *in vacuo*, followed by fractional distillation under reduced pressure, gave pure *S*(+)-XI as a colorless oil (1.63 g, 82%), bp 152—158° (0.45 mmHg). This oil solidified when kept at room temperature and showed mp 44.5—48°, $[\alpha]_D^{20}$ +8.8° (*c*=1.266, chloroform). ORD $[M]^{15}$ (*c*=1.266, chloroform) (mμ): +19.5° (589); +28.6° (500); +50.3° (400). IR spectrum of this sample in chloroform was identical with that of the authentic *S*(+)-XI in the same state. Comparison of the molecular rotation $[M]^{400}$ obtained on the rearranged *S*(+)-XI using optical rotatory dispersion measurement with that of the authentic *S*(+)-XI clearly disclosed that this rearrangement proceeded with 75.6% retention of configuration.

**(±)-2-(1-Acetoxy-2-methyl-3-phenyl)propyl Cyanide ((±)-XI)**——Acetic anhydride (0.42 g, 0.0031 mole) was gradually added with stirring in an ice bath to an anhydrous pyridine solution (0.4 ml) of (±)-XII (0.47 g, 0.0027 mole). The whole was stirred at room temperature for 11 hr, and then poured onto an ice-water (5 ml). Separated oil was extracted with ethyl acetate, and combined organic layer were successively washed with 10% HCl, water, 10% $Na_2CO_3$ and water. After drying over anhyd. $Na_2SO_4$, filtration and evaporation *in vacuo* afforded a pale yellow oil (480 mg, 81%), which was submitted to fractional distillation under reduced pressure, giving pure (±)-XI as a colorless oil (0.40 g, 68%), bp 135—140° (0.45 mmHg). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.72; H, 7.18; N, 6.43. NMR (in $CCl_4$): 1.28 (3H, singlet, $-C-C\underline{H}_3$), 2.13 (3H, singlet, $COC\underline{H}_3$), 2.85 (2H, quartet, $C_6H_5C\underline{H}_2$, $J$=13.5 cps), 4.02 (2H, singlet, $-C\underline{H}_2-O$), 7.25 (5H, singlet, $C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 2250 (CN), 1750 (ester).

***S*(+)-2-(1-Acetoxy-2-methyl-3-phenyl)propyl Cyanide (*S*(+)-XI)**——The same treatment of *S*(+)-XII (0.43 g, 0.0025 mole) as that of (±)-XII afforded crude *S*(+)-XI as a pale yellow oil (0.51 g, 86%). Fractional distillation of the obtained *S*(+)-XI gave pure *S*(+)-XI as a colorless oil (0.40 g, 68%), bp *ca.* 135° (0.6 mmHg). This oil gradually solidified when kept at room temperature, and showed mp 46—48.5°, $[\alpha]_D^{18}$ +9.8° (*c*=0.980, chloroform). ORD: $[M]^{24}$ (*c*=0.980, chloroform) (mμ): +21.3° (589), +31.9° (500), +56.6° (400). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.01; H, 7.06; N, 6.62. IR and NMR spectra of *S*(+)-XI were identical with those of (±)-XI measured in the same states.

**(±)-2-Cyano-2-methyl-3-phenylpropanol ((±)-XII)**——a) (±)-XII fron (±)-XI: A mixture of (±)-XI (0.34 g, 0.016 mole) and potassium hydroxide (0.12 g, 0.0021 mole) in ethanol (6 ml) was stirred at room temperature overnight. After evaporation of the ethanol *in vacuo*, the whole reaction mixture was diluted with water, and then extracted with ether. Combined ethereal layers were washed with satd. NaCl, and dried over anhyd. $Na_2SO_4$. Filtration and evaporation *in vacuo* gave crude (+)-XII as a pale yellow oil

(0.23 g, 82%). This oil was almost pure by TLC analysis (silica gel; solvent; benzene–ethyl acetate 1: 1; $Rf$=0.6), and used for the next step without further purification. IR spectrum of (±)-XII measured in capillary, was identical with that of the authentic sample (see b) in the same state.

b) (±)-XII from (±)-XIII: Ethyl chloroformate (3.27 g, 0.030 mole) was added to a mixture of (±)-XIII[22] (5.65 g, 0.030 mole) and triethylamine (3.03 g, 0.030 mole) in tetrahydrofuran (45 ml) with stirring at −5° (ice-salt bath). The whole was stirred at the same temperature for 30 min, and then a white precipitate appeared, was collected by filtration and washed with tetrahydrofuran. Combind tetrahydrofuran filtrates were gradually added at 10—15° to a suspension of sodium borohydride (2.84 g, 0.075 mole) in water (34 ml). The aqueous mixture was stirred at room temperature for 6 hr, and subsequently acidified in an ice bath with 10% HCl, to decompose an excess amount of sodium borohydride. The upper organic layer was separated, and the lower aqueous layer was further extracted with ether. Combined organic layers were successively washed with 10% $Na_2CO_3$, and satd. NaCl, and finally dried over anhyd. $Na_2SO_4$. Filtration and evaporation *in vacuo* afforded a pale yellow oil (4.53 g), which was submitted to fractional distillation under reduced pressure, giving pure (±)-XII as a colorless oil (3.20 g, 61%), bp 157—160° (0.75 mmHg). *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.51; H, 7.69; N, 7.98. NMR (in $CCl_4$): 1.19 (3H, singlet, –C–C$\underline{H}_3$), 2.83 (2H, quartet, $C_6H_5C\underline{H}_2$–, $J$=13.5 cps), 3.51 (2H, singlet, C$\underline{H}_2$OH), 3.74 (1H, singlet, O$\underline{H}$), 7.20 (5H, singlet, $C_6\underline{H}_5$). IR $\nu_{max}^{cap.}$ $cm^{-1}$: 3480 (OH), 2260 (CN), 1060 (–C–O$\underline{H}$).

***S*(+)-2-Cyano-2-methyl-3-phenylpropanol (*S*(+)-XII)**——a) *S*(+)-XII from *S*(+)-XI: The same treatment of *S*(+)-XI (1.0 g, 0.0046 mole) obtained by the thermal reaction of *R*(+)-X, as that of (±)-XI gave crude *S*(+)-XII as a colorless oil (0.68 g, 84%), $[\alpha]_D^{19}$ +11.6° ($c$=1.052, chloroform). This oil was almost pure on TLC analysis (silica gel; solvent; benzene–ethyl acetate 1: 1), and its $Rf$ value was identical with that of the authentic (±)-XII. IR spectrum of *S*(+)-XII thus obtained was also superimposable on that of the authentic (±)-XII in the same state. This oil was directly used for the next step without further purification.

b) *S*(+)-XII from *S*(+)-XIII: Treatment of *S*(+)-XIII ($[\alpha]_D^{20}$ +23.3° ($c$=0.814, chloroform), 85.0% optically pure)[17] (0.82 g, 0.0043 mole) similar to the case of (+)-XIII gave pure *S*(+)-XII as an almost colorless oil (0.51 g, 68% ), $[\alpha]_D^{20}$ +12.0° ($c$=1.378, chloroform). IR and NMR spectra were superimposable on those of the aythentic (±)-XII in the same states.

**(±)-2-Cyano-2-methyl-3-phenylpropionic Acid ((±)-XIII) from (±)-XII**——Potassium permanganate (3.0 g, 0.019 mole) in water (29 ml) was gradually added with vigorous stirring to a mixture of (±)-XII (1.50 g, 0.0086 mole) and sodium hydroxide (0.29 g, 0.0072 mole) in water (2.3 ml). After stirring overnight, an excess amount of potassium permanganate was decomposed by the addition of ethanol. Formed manganese dioxide was filtered off, and washed with water. Evaporation of the combined filtrates, followed by evaporation *in vacuo*, gave a residue, which was dissolved in water. The aqueous solution thus obtained was made alkaline with 10% NaOH, and washed with ether. Residual lower aqueous phase was acidified with 10% HCl, and then acidic product was extracted with ether. Combined acidic ethereal layers were washed with satd. NaCl, and dried over anhyd. $Na_2SO_4$. Filtration and evaporation *in vacuo* afforded crude (±)-XIII as a pale yellow oil (1.34 g, 82%), containing a trace amount of acetic acid. IR spectrum of this acid in a chloroform solution was identical with that of the authentic (±)-XIII[22] in the same state. This oil gradually solidified when kept standing at room temperature, mp 67—87° (lit.[22] mp 94—95°).

***S*(+)-2-Cyano-2-methyl-3-phenylpropionic Acid (*S*(+)-XIII) and Its Methyl Ester (*S*(+)-XIV) from *S*(+)-XII**——Oxidation of *S*(+)-XII (0.62 g, 0.0035 mole) prepared from *S*(+)-XI in a manner similar to the case of (±)-XII afforded crude *S*(+)-XIII as a yellow oil (0.61 g, 92%), which gradually solidified on standing at room temperature. Since purification of this solid by the usual recrystallization procedure seemed to be difficult because of its optical purity (about 75.6% optically pure), the whole was converted to its methyl ester (*S*(+)-XIV) by the treatment with diazomethane in ether according to the reported procedure.[22] NMR spectrum of the obtained *S*(+)-XIV in $CDCl_3$ was identical with that reported.[22] IR spectrum of *S*(+)-XIV was also superimposable on that of the authentic sample[22] in the same state. This ester showed $[\alpha]_D^{27}$ +33.6° ($c$=0.810, chloroform).

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