Asymmetric Synthesis of α-Methylglutamic Acid and α-Methylornithine by a Chiral Isocyano Amide Reagent

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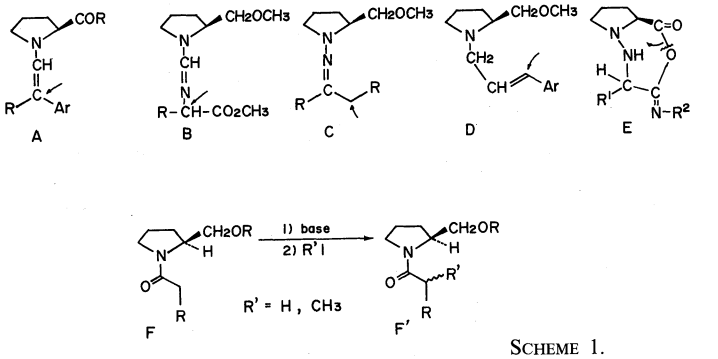
An efficient approach to the asymmetric syntheses of α-methylglutamic acid and α-methylornithine is described. Two chiral reagents, (2′*S*)-*N*-(2′-methoxymethylpyrrolidine)-2-isocyanopropionamide **4** and (2′*S*)-*N*-(2′-hydroxymethylpyrrolidine)-2-isocyanopropionamide **5**, were employed for the asymmetric induction. α-Methylglutamic acid **7** was synthesized by the asymmetric Michael-addition of methyl acrylate to **4** and **5** as the key step. The optical yield of **7** was 10～45% (R-form). α-Methylornithine **12** was also synthesized by the reaction of **4** with acrylonitrile as the key step. The optical yield of **12** was 31.7% (*R*-form).

α-Alkyl amino acids are of biochemical interest because of their properties as enzyme inhibitors. In the previous paper,[1,2] we have reported the asymmetric synthesis of α-methylornithine **12**, a potent competitive inhibitor of ornithine decarboxylase, involving the diastereoselective Michael-addition of acrylonitrile to (+)- and (−)-menthyl α-isocyanopropionate; however, the optical yields of (−)-**12** and (+)-**12** thus obtained were only 4.7 and 5.8% respectively.

Subsequently, although several synthetic methods for **12**[3～5] have been reported, investigations concerning the asymmetric synthesis of **12** and α-methylglutamic acid **7** have not been successful.

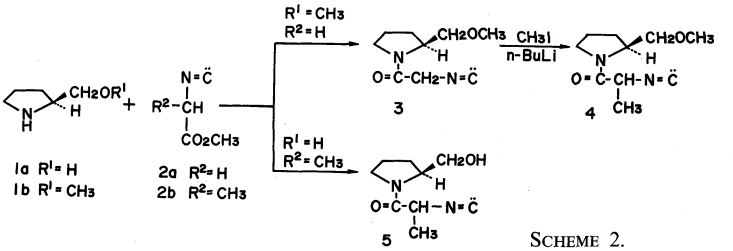
In recent years, successful syntheses of the chiral ketone, aldehyde, α-alkyl amino acid and dipeptide employing (*S*)-(−)-proline derivatives as a chiral auxiliary reagent have been reported as follows: (1) asymmetric induction of methyl vinyl ketone to the chiral enamine **A**,[6] (2) asymmetric alkylation (benzylation) of the chiral amidine ether **B**,[7] hydrazone **C**[8,9] and allylamide **D**,[10] (3) asymmetric synthesis of L,D-dipeptide *via* the chiral intermediate **E**.[11] Sonnet *et al.*[12] reported more recently that diastereoselective metalation and alkylation of the chiral amides **F** derived from (*S*)-(−)-prolinol and its methyl ether afforded α-alkyl amines **F′** in 12～82% *e.e.*



SCHEME 1.

The *S* configuration induced by (*S*)-(−)-prolinol was opposite to that induced by its methyl ether. According to the new technique for asymmetric induction, they[13] succeeded in obtaining both enantiomers of 10-methyl-1-dodecanol acetate, the sex pheromone complex of the smaller tea tortrix moth (*Adoxophyes* sp.), in 74% (*R*) or 80% (*S*) *e.e.*

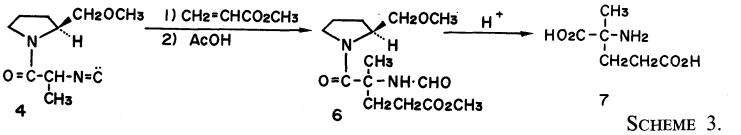
The present paper deals with the asymmetric synthesis of **7** and **12** by using (2′*S*)-*N*-(2′-methoxymethylpyrrolidine)-2-isocyanopropionamide **4** and (2′*S*)-*N*-(2′-hydroxymethylpyrrolidine)-2-isocyanopropionamide **5** as the chiral auxiliary reagents. The amide **4** was prepared by the reaction of (*S*)-(−)-prolinol methyl ether **1b** with methyl isocyanoacetate **2a**, and followed by C-methylation with methyl iodide.



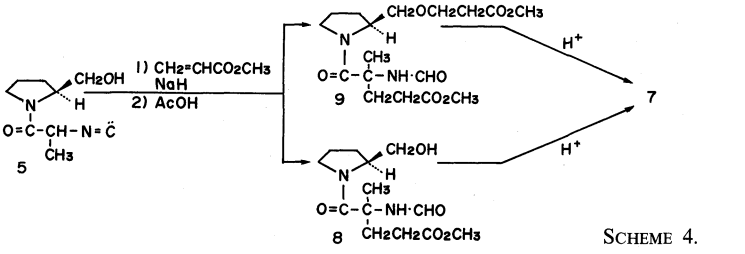
SCHEME 2.

The amide **5** was prepared from (*S*)-(−)-prolinol **1a** and methyl 2-isocyanopropionate **2b**. The Michael-addition of an equimolar amount of **4** to methyl acrylate in the presence of sodium hydride, and followed by treatment with acetic acid gave (*R*)-(−)-**7** ($[\alpha]_D$ −1.22°, 10% *e.e.*) in a 42% chemical yield. On the other hand, the amide **5** was treated with 1.6 equimolar amounts of methyl acrylate in the presence of 1 equimolar amount of sodium hydride, and followed by treatment with acetic acid to give a mixture consisting of 53% of C,O-dialkyl amide **9** and 23% of C-alkyl amide **8**.

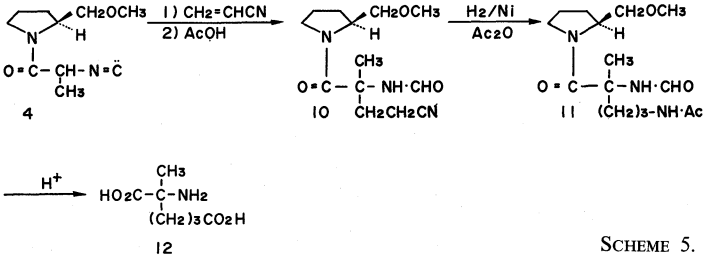
Acid hydrolysis of **9** and **8** with 2 N-HCl gave (*S*)-(+)-**7** ($[\alpha]_D$ +0.61°, 5% *e.e.*) and (*R*)-(−)-**7** ($[\alpha]_D$ −5.35°, 44% *e.e.*) respectively.



SCHEME 3.



SCHEME 4.



SCHEME 5.

In agreement with the investigation result described by Sonnet *et al.*,[12] the configuration of **7** induced by the (*S*)-(−)-prolinol alkyl ether was reversed from *R* to *S* as the size of the O-alkyl substituent becomes larger ($H \rightarrow CH_3 \rightarrow CH_2CH_2CO_2CH_3$).

Finally, **12** was synthesized in a manner similar to that already described. In this experiment, the amide **4** was employed as a chiral auxiliary reagent, because it gave a more favorable result for the Michael reaction than did **5**. The amide **4** was treated with a 1.2 equimolar amount of acrylonitrile, and followed by treatment with acetic acid in a similar manner to Scheme 3. The obtained **10** was hydrogenated over Raney Nickel catalyst in acetic anhydride to yield **11**. The acid hydrolysis of **11** with 6 N-HCl gave (*R*)-(−)-**12**·HCl ($[\alpha]_D$ −3.33°, 32% *e.e.*) in a 28% overall yield from **4**.

EXPERIMENTAL

Infrared spectra were taken with a JASCO IRA-2 spectrometer, and NMR spectra were recorded with JEOL JNM-MN60 spectrometer. Melting points were determined on Yanaco MP-S3 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-SL polarimeter.

(S)-N-(2-Methoxymethylpyrrolidine)-isocyanoacetamide **3**. To a solution of the methyl isocyanoacetate **2a** (3 g, 30.3 mmol) in MeOH (10 ml) was added a solution of the prolinole methyl ether **1b** (6.2 g, 53.9 mmol) in MeOH (5 ml), the mixture being stirred for 24 hr at ambient temperature. After removing the solvent, the residue was purified by silica gel column chromatography (eluting with an increasing amount of AcOEt in benzene) to afford **3** (4.69 g, 85% from **2a**), mp 52°C. $[\alpha]_D^{25}$ −79.56° (c=0.675, EtOH). IR ν_{max}^{KBr} cm^{-1}: 2150 (N=C:), 1660 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.68∼2.34 (4H, m), 3.14 (3H, s, O–CH_3). *Anal.* Found: C, 59.26; H, 7.76; N, 15.32. Calcd. for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.74; N, 15.37%.

(2'S)-N-(2'-Methoxymethylpyrrolidine)-2-isocyanopropionamide **4**. To a stirred solution of the compound **3** (1.82 g, 10 mmol) in dry THF (20 ml) was added a solution of *n*-BuLi (10 mmol, 15% in hexane) at −78°C. After the mixture had been stirred for 30 min at −78°C, a solution of methyl iodide (1.42 g, 10 mmol) in dry THF (5 ml) was added, and the reaction mixture was stirred for 2 hr at −78°C and then kept for 3 hr at 0°C. After removing the solvent, the residue was dissolved in CH_2Cl_2 (50 ml), washed with water (10 ml) and dried over Na_2SO_4. Evaporation of the solvent gave the crude product **4**, which was purified by silica gel column chromatography (eluting with an increasing amount of AcOEt in benzene) to give 1.7 g of pure **4** as an oil (85% yield). IR ν_{max}^{KBr} cm^{-1}: 2140 (N=C:), 1650 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.33∼1.52 (3H, d, J=8 Hz, CH_3), 3.12 (3H, s, O–CH_3). *Anal.* Found: C, 61.09; H, 8.16; N, 14.20. Calcd. for $C_{10}H_{16}O_2N_2$: C, 61.20; H, 8.22; N, 14.28%.

(2'S)-N-(2'-Hydroxymethylpyrrolidine)-2-isocyanopropionamide **5**. To a solution of the methyl 2-isocyanopropionate **2b** (1 g, 8.8 mmol) in MeOH (5 ml) was added a solution of the prolinole **1a** (2 g, 19.8 mmol) in MeOH (3 ml), the mixture being stirred for 2 hr at ambient temperature.

After removing the solvent, the residue was purified by silica gel column chromatography (eluting with an increasing amount of AcOEt in benzene) to afford **5** as an oil (1.5 g, 93%). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 2130 (N=C:), 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.24∼1.68 (3H, d, J=7 Hz, CH_3), 4.0∼4.34 (1H, br.s, OH). *Anal.* Found: C, 59.35; H, 7.76; N, 15.32. Calcd. for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.74; N, 15.37%.

α-Methylglutamic acid **7**.

Method A: A solution of **4** (1.96 g, 10 mmol) in dry THF (10 ml) was added to a stirred suspension of NaH (240 mg, 10 mmol) in dry THF (50 ml), and the mixture was stirred for 10 min at −78°C. To the reaction mixture was added a solution of methyl acrylate (1.03 g, 12 mmol) in dry THF (10 ml), the mixture being stirred for 3 hr at −78°C and then kept for 3 hr at between −30 and −35°C. The reaction mixture was then acidified with acetic acid (5 ml) and the solvent evaporated *in vacuo* (40∼50°C) to afford the adduct **6**. This product was purified by silica gel column chromatography (eluting with an increasing amount of AcOEt in benzene) to give 2.1 g of pure **6** as a colorless oil (70% from **3**). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH–CHO), 1760 (C=O). ^{1}H-NMR δ: 1.75 (3H, s, CH_3), 3.22 (3H, s, O–CH_3), 3.56 (3H, s, O–CH_3). *Anal.* Found: C, 55.91; H, 8.11; N, 9.28. Calcd. for $C_{14}H_{24}O_5N_2$: C, 55.98; H, 8.05; N, 9.32%.

A solution of **6** (1.06 g, 3.51 mmol) in 3 N-HCl (30 ml) was heated for 10∼12 hr at 80∼90°C. After removing the generated amine by CH_2Cl_2 extraction, the aqueous phase was adjusted to pH 7 with $NaHCO_3$ and applied to a Dowx 50×8 column (H^+ form). The column was washed with water, and then the α-methylglutamic acid **7** was eluted with 5% NH_4OH.

The eluted fraction was concentrated *in vacuo* and the residual oil was adjusted to pH 3 with 0.5 N-HCl to obtain **7**. Recrystallization from EtOH gave **7** in its pure state (237 mg, 42% yield), mp 170°C, $[\alpha]_D^{20}$ −1.22° (c=1.31, 6 N-HCl). This product was identical with the authentic compound by TLC, IR and NMR analyses.

Method B: A solution of **5** (911.1 mg, 5 mmol) in dry THF (10 ml) was added to a stirred suspension of NaH (120 mg, 5 mmol) in dry THF (30 ml), and the mixture was stirred for 10 min at −78°C. To the reaction mixture was added a solution of methyl acrylate (686.7 mg, 8 mmol) in dry THF (10 ml), the mixture being stirred for 3 hr at −78°C and then kept for 3 hr at between −30 and −35°C. The reaction mixture was acidified with acetic acid (5 ml) and the solvent was evaporated *in vacuo* at 40 ~ 50°C. The residue was dissolved in CH_2Cl_2 (70 ml), washed with water (10 ml) and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a mixture of the C-alkyl amide **8** and C,O-diakyl amide **9** (1 : 2), which were separated into the pure oily products **8** (337 mg, 27% yield) and **9** (880 mg, 53% yield) by silica gel column chromatography (eluting with an increasing amount of AcOEt in benzene).

Compound **8**. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1730 (C=O), 1660 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s, CH_3), 3.68 (3H, s, O–CH_3), 8.1 ~ 8.15 (1H, br.s, CHO). *Anal.* Found: C, 54.43; H, 7.76; N, 9.66. Calcd. for $C_{13}H_{22}O_5N_2$: C, 54.53; H, 7.75; N, 9.78%.

Compound **9**. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O), 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, s, CH_3), 3.6 (6H, s, O–CH_3 × 2), 8.0 ~ 8.15 (1H, m, CHO). *Anal.* Found: C, 54.76; H, 7.55; N, 7.61. Calcd. for $C_{17}H_{28}O_7H_2$: C, 54.84; H, 7.58; N, 7.52%.

According to the same procedure as that used for **6**, the amides **8** and **9** afforded **7**.

Compound **7** from **8**. Yield 66%, mp 169 ~ 170°C, $[\alpha]_D^{22}$ −5.35° (c = 0.71, 6 N-HCl).

Compound **7** from **9**. Yield 50%, mp 169 ~ 172°C. $[\alpha]_D^{22}$ +0.61° (c = 0.99, 6 N-HCl).

These compounds **7** were identical with the sample obtained in *Method A* in all respects except for the optical rotation.

α-*Methylornthine* **12**.

Michael-addition adduct **10**. A solution of **4** (1.9 g, 9.7 mmol) in dry THF (10 ml) was added to a stirred suspension of NaH (240 mg, 10 mmol) in dry THF (30 ml) at −78°C.

After the mixture had been stirred for 10 min at −78°C, a solution of acrylonitrile (673 mg, 12 mmol) in dry THF (10 ml) was added, the resulting mixture being stirred for 3 hr at −78°C and then kept for 3 hr at between −35 and −30°C. The reaction mixture was acidified with acetic acid (5 ml) and the solvent was evaporated *in vacuo* (40 ~ 50°C) to afford crude **10**. This product was purified by silica gel column chromatography (eluting with an increasing amount of AcOEt in benzene) to give 2.03 g of pure **10** as an oil (76% from **3**). IR ν_{max}^{KBr} cm^{-1}: 3250 (NH–CHO), 2250 (CN), 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, d, J = 7 Hz, CH_3), 2.30 (3H, s, CH_3), 7.61 (1H, s, NH), 8.16 (1H, s, CHO). *Anal.* Found: C, 58.33; H, 7.96; N, 15.66. Calcd. for $C_{13}H_{21}O_3N_3$: C, 58.41; H, 7.92; N, 15.72%.

N-Acetyl compound **11**. A suspension of **10** (2.67 g, 10 mmol) in acetic anhydride (20 ml) was catalytically hydrogenated with Raney nickel (R-100, approx. 2 g) under 30 ~ 50 kg/cm^2 pressure at 50°C until four equivalents of hydrogen had been absorbed. After removing the solvent and catalyst, the residue was dissolved in CH_2Cl_2 (100 ml), washed with water (10 ml) and dried over Na_2SO_4. Evaporation of the solvent gave crude **11**, which was purified by silica gel column chromatography (eluting with an increasing amount of AcOEt in benzene) to afford 1.9 g of pure **11** as an oil (71% yield). IR ν_{max}^{KBr} cm^{-1}: 3270 (NH–CHO), 1660 (C=O), 1620 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.30 (3H, s, O–CH_3), 7.3 (1H, br.s, NH), 8.1 (1H, s, CHO). *Anal.* Found: C, 57.40; H, 8.65; N, 13.35. Calcd. for $C_{15}H_{27}O_4N_3$: C, 57.48; H, 8.68; N, 13.41%.

α-*Methylornithine* **12**. A mixture of **11** (1.5 g, 4.79 mmol) and 6 N-HCl (50 ml) was heated for 2 hr at 90 ~ 100°C and then extracted with CH_2Cl_2 to remove the generated amine. The aqueous phase was adjusted to pH 7 with $NaHCO_3$ and applied to a column containing 15 g of cation (H^+) exchange resin (Dowex 50 × 8).

The column was initially washed with water and then **12** was eluted with 5% NH_4OH. The eluted fraction was concentrated under reduced pressure and the residue was adjusted to pH 5 with 0.5 N-HCl to yield **12**-HCl (453 mg, 51.9%). $[\alpha]_D^{26}$ −3.33° (c = 1.05, 5 N-HCl).

This product was identical with the sample reported previously in all respects.[14]

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