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Asymmetric Synthesis of α-Methylornithine

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In mammalian tissues, the decarboxylation of ornithine to putrescine is catalyzed by ornithine decarboxylase (ODC). The biosynthesis and accumulation of polyamines, putrescine, spermidine and spermine were elevated shortly in neoplastic rapid-growth system. In order to elucidate the role of plyamines, a number of inhibitors of ODC have been synthesized and evaluated. Among the α-substituted analogs of (±)-ornithine, α-methyl-(±)-ornithine was found to be a potent, reversible and competitive inhibitor of ODC.[1] α-Methyl-(±)-ornithine was synthesized by various methods as follows; (1) hydrolysis of 5-methyl-5-(3-phthalimidopropyl)hydantoin[1] or 5-(3-aminopropyl)-5-methylhydantoin[2,3] prepared by the Bucherer-Lieb reaction. (2) catalytic hydrogenation and hydrolysis of 5-methyl-5-(3-nitropropyl)hydantoin[4] or 5-(cyanoethyl)-5-methylhydantoin.[5] (3) methylation and acid hydrolysis of metalated 3-imino-(4-nitrobenzyl)piperidine-2-one.[1]

Maehr *et al.*[6] prepared α-methyl-L-ornithine together with α-methyl-D-arginine by arginase-catalyzed hydrolysis of α-methyl-(±)-arginine. Abdel-Monem *et al.*[1] described that the inhibitory activity on ODC may reside mainly in one enantiomer of α-methylornithine; however, no experimental evidence is detected in their paper.

In this communication, we wish to report a novel synthetic method of optically active α-methylornithine as outlined in Scheme.

Optically active isocyano esters **1a** and **1b** were prepared from (+)- and (−)-menthyl esters of N-formyl-(±)-alanine, respectively, by usual way.[7] In the Michael type reaction of **1**, the carbanion of **1** approaches asymmetrically to acrylonitrile giving **2** containing a slight one diastereomer excess. In order to evaluate accurately asymmetric effect in this procedure, any purification and fractionation of intermediates were not undertaken in the all subsequent steps. The isocyano group of **2** was converted stepwise to amino group of **4** according to the method reported by Suzuki *et al.*[8] After the protection of amino group by acetylation, **5** was hydrogenated in acetic anhydride to give di-N-acetylamine derivative **6**, which gave optically active α-methylornithine **7** by acid hydrolysis.

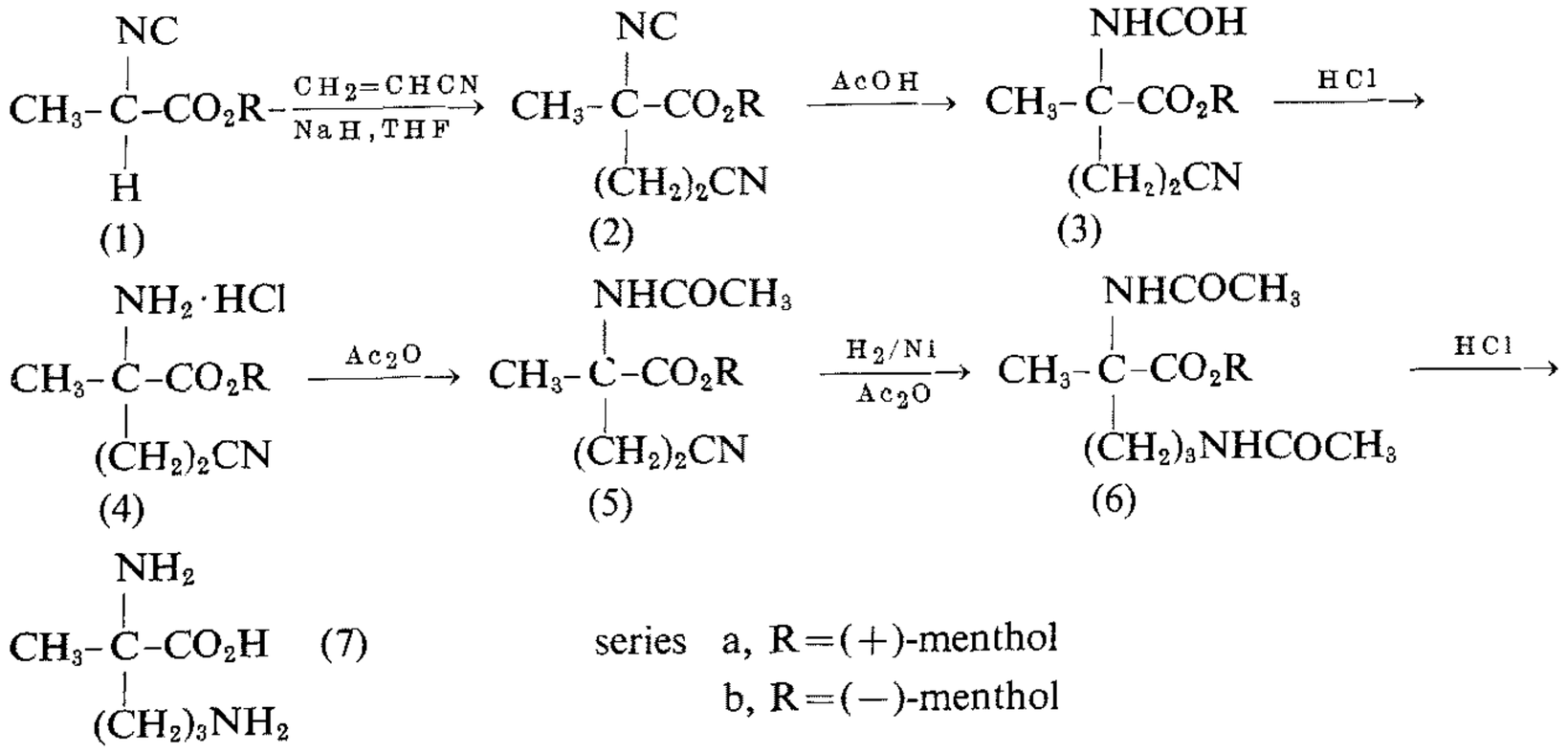
Asymmetric synthesis of **7** from (+)-menthyl ester **1a** gave (−)-**7** (4.7% e.e*) and from (−)-menthyl ester **1b** gave (+)-**7** (5.8% e.e*).

EXPERIMENTAL

*(+)- and (−)-Menthyl 4-cyano-2-isocyano-2-methylbutanoate (**2a** and **2b**)*

To a suspension of sodium hydride (50% in oil, 2.9 g, 60 mmol) and (+)- or (−)-menthyl 2-isocyanopropionate (**1a** or **1b**) (11.9 g, 50 mmol) in 20 ml of dry tetrahydrofuran was added acrylonitrile (3.2 g, 60 mmol) in 15 ml of dry tetrahydrofuran over a period of 20 min with stirring at −25°C. After stirring was continued for 2 hr at the same temperature, the mixture was neutralized with acetic acid, and then the solvent was evaporated under reduced pressure. The residual oil was dissolved in 60 ml of ethyl acetate and the solution was washed with water, dried and concentrated *in vacuo*. The resulting product was fractionated over

* The enantiomer excess (e.e) was estimated on the basis of the known rotation of enantiomerically pure **7**·HCl ($[\alpha]_D$ +10.5°, c=0.76, 5 N HCl).[6]



silica gel column. **2a** (**2b**) was eluted with benzene as yellow oil and was found to be homogeneous on TLC. Yields 9.5 g (66%). **2a**: IR ν_{max}^{NaCl} cm^{-1}: 2950 (CH_2), 2250 (–C≡N), 2140 (–N=C=O), 1730 (C=O). NMR $\delta_{TMS}^{CDCl_3}$: 1.68 (3H, s, CH_3), 2.45 (4H, m, $-CH_2CH_2-$). **2b**: IR ν_{max}^{NaCl} cm^{-1}: 2930, 2250, 2140, 1740. NMR $\delta_{TMS}^{CDCl_3}$: 1.65, 2.48.

(+)- and (−)-Menthyl 4-cyano-2-amino-2-methylbutanoate hydrochloride (***4a and 4b***)

A mixture of **2** (6 g, 21 mmol), 15 ml of glacial acetic acid and 1 ml of water was heated at 40~50°C with stirring. After the reaction was completed, the solvent was evaporated *in vacuo* to yield oily product **3**. This product was hydrolysed in a solution of 30 ml of methanol and 7 ml of 3 N–hydrochloric acid at 40~50°C for 6 hr. The solvent and excess hydrochloric acid were evaporated under reduced pressure. The resulting residue was dissolved in methanol and then concentrated to dryness *in vacuo*; this treatment was repeated more than 5 times to remove hydrochloric acid completely. The precipitate thus obtained was washed with ether and *n*-hexane to offer **4** in high pure state. IR ν_{max}^{KBr} cm^{-1}: **4a** 3450 (NH_2), 2950 (CH_2), 2360 (–C≡N), 1740 (C=O); **4b** 3450, 2950, 2360, 1750.

(+)- and (−)-Menthyl 4-cyano-2-N-acetylamino-2-methylbutanoate (***5a and 5b***)

To a solution of **4** (8.4 g, 27 mmol) in 40 ml of water containing 15 ml of tetrahydrofuran was added acetic anhydride (3.6 g, 35 mmol) slowly at −5°C with vigorous stirring. The pH value of the solution was kept at 8~9 by addition of aqueous sodium hydrogen carbonate solution during the whole reaction. After all acetic anhydride has been added, the solution was concentrated *in vacuo* and the residue was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to afford **5**, 8.3 g, (97%) as colorless solid. **5a**: IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 2930 (CH_2), 2350 (–C≡N), 1720 (C=O), 1660 (C=O). NMR $\delta_{TMS}^{CDCl_3}$: 1.62 (3H, s, CH_3), 2.04 (3H, s, $COCH_3$), 6.50 (1H, broad s, NH). **5b**: IR ν_{max}^{KBr} cm^{-1}: 3350, 2930, 2350, 1730, 1630. NMR $\delta_{TMS}^{CDCl_3}$: 1.57, 2.00, 6.45.

(+)- and (−)-Menthyl 2,4-di-N-acetylamino-2-methylpentanoate (***6a and 6b***)

A solution of **5** (9.7 g, 30 mmol) and sodium acetate (4 g, 40 mmol) in 100 ml of acetic anhydride was hydrogenated over Raney nickel (R–100, *ca*, 1 g) for 3 hr at 40°C under 10 kg/cm^2 initial pressure. After removal of catalyst by filtration, the filtrate was evaporated to dryness *in vacuo*; the resulting product was washed successively with *n*-hexane and ether to yield **6** as colorless solid. **6a**; IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1720 (C=O), 1650 (C=O). NMR $\delta_{TMS}^{CDCl_3}$: 1.58 (3H, s, CH_3), 1.98 (3H×2, s, $COCH_3$), 3.18 (2H, q, J=7 Hz, $-CH_2-$N), 5.80 (1H, broad s, NH), 6.60 (1H, s, NH). **6b**: IR ν_{max}^{KBr} cm^{-1}: 3300, 1730, 1650. NMR $\delta_{TMS}^{CDCl_3}$: 1.56, 1.98, 3.20, 5.90, 6.55. *Anal.* Found: C, 65.29; H, 9.98; N, 7.72; O, 17.57. Calcd. for $C_{20}H_{36}N_2O_4$: C, 65.18; H, 9.85; N, 7.60; O, 17.37%.

α-Methylornithine (**7**)

A solution of **6** (7 g, 19 mmol) in 50 ml of 5 N–hydrochloric acid was heated at 80~90°C for 24 hr. After removal of menthol by ether extraction, the aqueous phase was adjusted to pH 2 with sodium hydrogen carbonate and applied to a Dowex 50×8 column (H^+ form). The column was washed with water and then the amino acid was eluted with 5% aqueous ammonia. The eluted fraction was concentrated *in vacuo* and the residual oil was adjusted to pH 5 with ethanolic hydrochloric acid to yield **7**·HCl (3.2 g, 90%) in pure state. **7**·HCl: IR ν_{max}^{KBr} cm^{-1}: 3450 (COOH), 3200~3100 (NH_2), 2990 (CH_2). NMR $\delta_{TMS}^{D_2O}$: 1.96 (3H, s, CH_2), 1.85~2.50 (4H, m, $-CH_2CH_2-$), 3.50 (2H, t, J=7 Hz, $-CH_2-$N). $[\alpha]_D^{18}$ +0.61° (c=2.13, 5 N–HCl) (from **1a**), $[\alpha]_D^{18}$ −0.49° (c=1.86, 5 N–HCl) (from **1b**).

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