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249. Akira Tahara and Ken-ichi Hirao*1 : Diterpenoids. IX.*2 Chemical Conversion to Diterpene Alkaloid from Abietic Acid.*3

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By confluence from *l*-abietic acid at the key intermediate (XXIV) for Nagata's total synthesis of *dl*-atisine (I), *dl*-veatchine (II) and *dl*-garryine (III), the first example of total synthesis of the natural diterpene alkaloid from the other natural diterpene, was accomplished.

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Recent achievement on the total synthesis of diterpene alkaloids, such as *dl*-atisine (I), *dl*-veatchine (II) and *dl*-garryine (III), independently submitted from three laboratories[1] have drawn much interest. However, in spite of many efforts to synthesize the diterpene alkaloids by chemical conversion from other natural diterpenoids, only one case of success was recently reported by Tsuchiya.[2] He accomplished to synthesize antipodal structure of the natural atisine by chemical correlation to the potential intermediate (V) for the Nagata's total synthesis[1a] from sciadin (IV), diterpene component of Kōya-maki (*Sciadopitys verticillata* Sieb. et Zucc.).

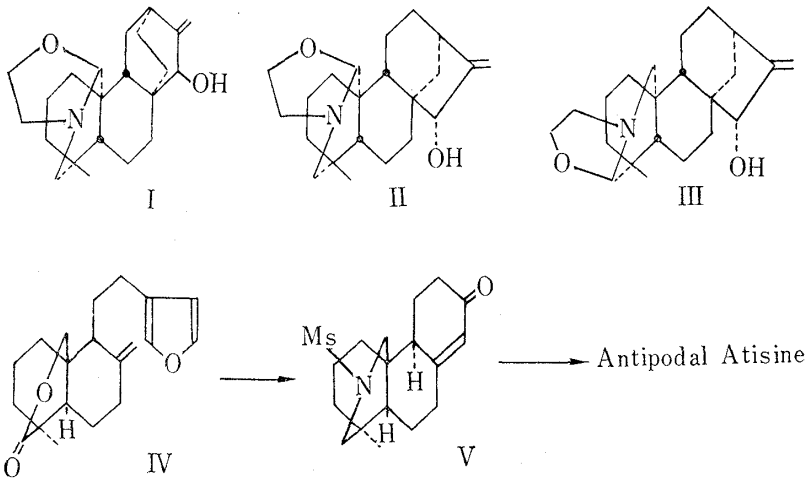

Fig. 1.

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*2 Previous communication : Tetrahedron Letters, **1966**, 1453; Part VIII : This Bulletin, **15**, 1785 (1967). This work was presented at the Local Meeting of the Pharmaceutical Society of Japan, Tokyo, July 24, 1965 and also at the 9th Symposium of Natural Organic Compounds, Osaka, October 14, 1965. cf. Symposium Abstract (in Japanese), p. 120.

*3 All m.p.s (except mixed m.p.) were measured on the Kofler block and were uncorrected. Gas-liquid chromatograms were measured under guidance of Dr. N. Ikekawa, this Institute, whom authors thank for his advice (abbreviation GC_{min} is used as retention time of the gas-liquid chromatography (GLC)).

1) *a*) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, Y. Hayase : J. Am. Chem. Soc., **85**, 2342 (1963); W. Nagata, M. Narisada, T. Wakabayashi, T. Sugasawa : *Ibid.*, **86**, 929 (1964). *b*) S. Masamune : *Ibid.*, **86**, 288, 289, 290, 291 (1964). *c*) Z. Valenta, K. Wiesner, C. M. Wong : Tetrahedron Letters, **1964**, 2437; R. W. Guthrie, A. Philipp, Z. Valenta, K. Wiesner : *Ibid.*, **1965**, 2945; R. W. Guthrie, W. A. Hendy, H. Immer, C. M. Wong, Z. Valenta, K. Wiesner : Coll. Czech., **31**, 602 (1966); R. W. Guthrie, Z. Valenta, K. Wiesner : Tetrahedron Letters, **1966**, 4645. cf. I. Iwai, A. Ogiso, B. Shimizu : Chem. Ind., **1962**, 1288; **1963**, 1084.

2) T. Tsuchiya : The 21st Meeting of Pharm. Soc. of Japan at Tokushima (Oct. 28, 1965). The abstract, p. 317.

In our laboratory, some attempts[3,4] have been executed for the preparation of physiologically acitive compounds, such as gibberellin and diterpene alkaloid, from *l*-abietic adid (Ⅶ), which has common structure of resin acid and is readily available from oleoresin of Japanese pine trees.

As shown in the preceding papers,[5] a synthesis of the compound (Ⅵ) having a characteristic nitrogen bridge of diterpene alkaloid skeleton (same absolute structure), was already succeeded from *l*-abietic acid (Ⅶ).

In extention of the above our chemical course, a chemical conversion to the diterpene alkaloid from *l*-abietic acid (Ⅶ) will be described herein. Namely, *l*-abietic acid (Ⅶ) could be related to the natural alkaloid by confluence at compound (XXⅡ) of the Nagata's synthentic route.[1a]

Firstly our effort was directed towards a preparation of a compound (XVⅢ) from the keto-lactone (Ⅷ)[5] synthesized from *l*-abietic acid (Ⅶ). The compound (XVⅢ) has the nitrogen bridge and 9-oxo group, therefore (XVⅢ) is suitable intermediate for selective substitution at 7-position to give the aimed (XXⅡ).

$NaBH_4$-reduction of the ketone (Ⅷ) is more available preparation of a hydroxy-lactone (Ⅸ) in comparison with the catalytic hydrogenation of (Ⅷ) reported previously.[5] Alkaline hydrolysis of the hydroxy-lactone (Ⅸ) afforded keto-diacid (X), m.p. 257~261° (decomp.) and oily part, which is a mixture of *cis*- (Ⅺ) and *trans*-A/B-ring fused isomer (Ⅻ) of 12-nor-methyl keto-acid.*4 Two carboxylic groups in the molecule of the keto-diacid (X) readily formed anhydride bridge by reflux in acetic anhydride. Then anhydride (XⅢ), m.p. 218~220°, was fused with urea at 190° to give the corresponding imide (XIV), 239~240°. The infrared spectra (KBr) of the compounds (XⅢ; 1800, 1760, 1680 cm^{-1} and XIV; 3330, 1710, 1680 cm^{-1}) satisfied their structure respectively. In $LiAlH_4$-treatment of the imide (XIV), 7-oxo group and imide bridge were together reduced to give hydroxy-amine (XV), which was used for next acethylation step without purification.

After usual acetylation, the resulted 9-acetoxy amino acetate (XVI), m.p. 190~191°, was hydrolized only its acetoxy group to give 9-hydroxy amino acetate (XVⅡ), m.p, 180~181°. Mild oxidation of 9-hydroxy group of (XVⅡ) with dichloro-dicyano-quinone at room temperature afforded the aimed useful intermediate, keto amino acetate (XVⅢ), m.p. 164~166°, whose infrared absorption (KBr) appeared at 1685, 1644, 1630 cm^{-1}. Additional evidence for the structure of (XVⅢ) was adduced from its otherwise synthesis by chromium trioxide-oxidation of amino acetate (Ⅵ) previously reported to have a definite structure.

Finally, for the synthesis of the intended 7-methoxy amino acetate (XXⅡ) from the 9-keto amino acetate (XVⅢ), the following usual treatments were successively performed without purification through each step. Nitration of (XVⅢ) afforded selectively 7-nitro-9-keto amino acetate (XIX), which was catalytically reduced on palladium-charcoal in acetic acid (H_2SO_4) to give 7-amino amino acetate (XX). The amine (XX) was treated with sodium nitrite, followed by methylation after hydrolysis of the diazonium salt to yield 7-methoxy amino acetate (XXⅡ) through 7-hydroxy amino acetate (XXI). The 7-methoxy amino acetate (XXⅡ) is optically active, $[\alpha]_D^{26.5} = -131.3$ (EtOH, c=0.21) and has the following physical constants; m.p. 146~147°, $\nu_{max}^{CCl_4}$ 1645, 1050 cm^{-1}, retention time of gas-liquid chromatography (1.5% SE-30 on Anakrom (Mesh 80~100), 4 mm.×1.85 m., 227°), 12.4 min.

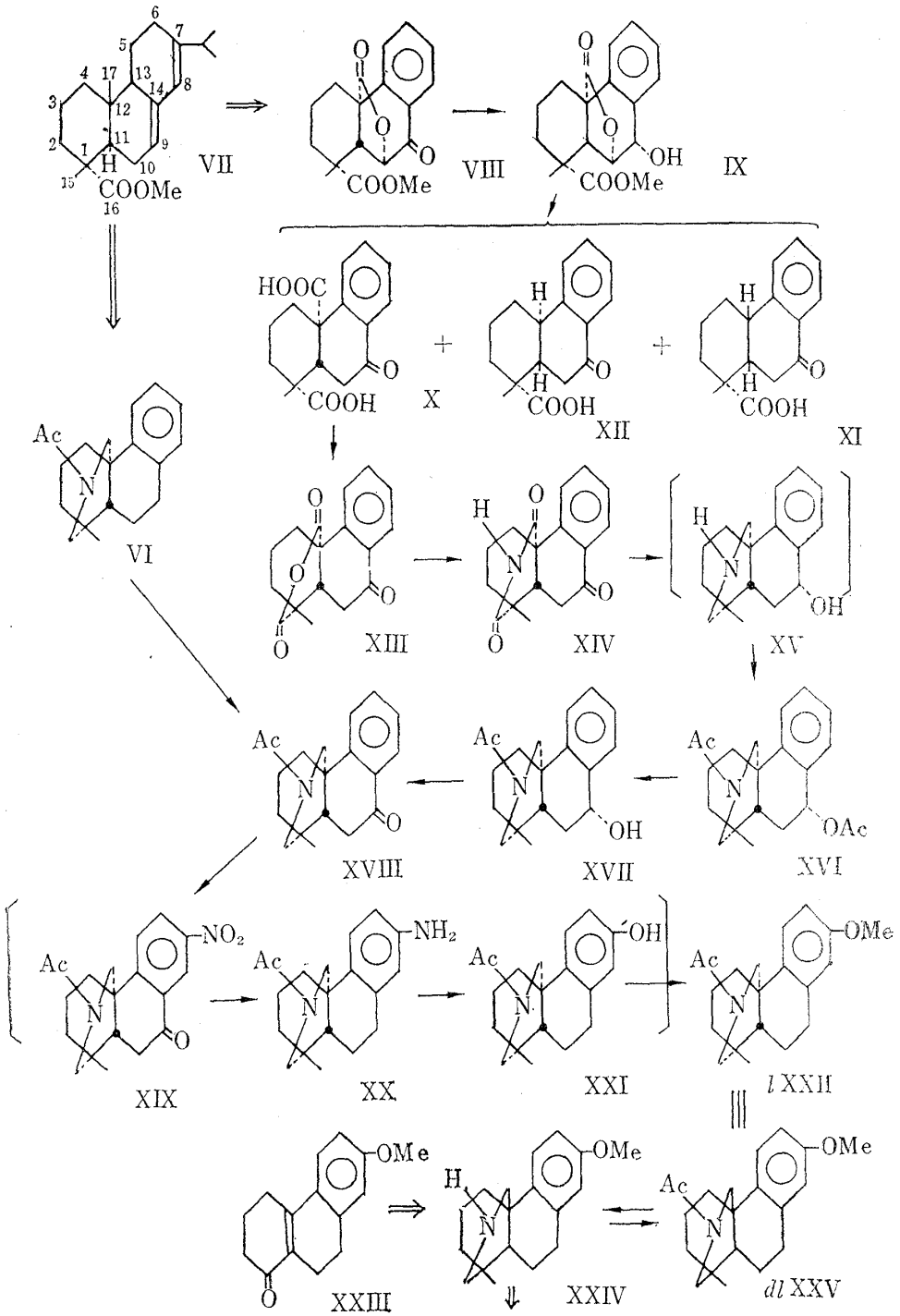
*4 Structure and conformation of the nor-12-methyl keto acid isomer (Ⅺ) and (Ⅻ) were published in the Chemical Communications, **1967**, 326.

3) A. Tahara: This Bulletin, **9**, 252 (1961); A. Tahara, O. Hoshino: *Ibid.*, **9**, 655 (1961); Sci. Papers Inst. Phys. Chem. Res., **56**, 84, 88 (1962); Tetrahedron Letters, **1966**, 3825, 5031.

4) A. Tahara, K. Hirao: This Bulletin, **12**, 984, 1458 (1964); A. Tahara, K. Hirao, Y. Hamazaki: Tetrahedron, **21**, 2133 (1965).

5) A. Tahara, K. Hirao, Y. Hamazaki: Chem. Ind., **1965**, 850; This Bulletin, **15**, 1785 (1967).

On the other hand, W. Nagata, *et al.* had accomplished the total synthesis of *dl*-atisine (I), *dl*-veatchine (II) and *dl*-garryine (III) using *dl*-7-methoxy amine (XXIV) as the key intermediate,[1a] therefore, their amine (XXIV)*5 was acetylated to give the corresponding *dl*-amino acetate (XXV), m.p. 167~169°, whose infrared spectrum (CCl_4)



Nagata's Synthesis of
Diterpene Alkaloid I, II, III

Fig. 2.

*5 Authors thank Dr. W. Nagata, Shionogi and Co., Ltd., Osaka, for donation of the valuable sample (XXIV).

and gas-liquid chromatogram were found to be superimposable with those of our respective *l*-compound (XXII).

Since the *dl*-7-methoxy amino acetate (XXV) was reverted to the original *dl*-7-methoxy amine (XXIV) by alkaline hydrolysis with potassium hydroxide and hydrazine, it constitutes the first example of total synthesis of the diterpene alkaloids by chemical conversion from the other naturally occurring diterpenes.

Experimental

9-Hydroxy Lactone (IX)——9-Oxo lactone (VIII) (150 mg.), m.p. 194~195°, obtained from *l*-abietic acid (VII),[5] was treated with $NaBH_4$ (120 mg.) in dioxane (1.5 ml.)-MeOH (15 ml.) for 3 hr. at 30° and then acetone (3 ml.) was added to consume excess $NaBH_4$. After the solvent was evaporated and then H_2O was added, the aquous solution was extracted with ether. The ether extract was wased with H_2O and then was dried over Na_2SO_4. Removal of ether gave prisms, m.p. 150~159° (135 mg.), which were recrystallized from MeOH to give colorless prisms (XV), m.p. 160~163°. The material was proved to be identical with the sample obtained by catalytic hydrogenation of (VIII).[5]

Decarboxylation of 9-Hydroxy Lactone (IX). 9-Oxo Diacid (X) and 12-nor-Methyl 9-Oxo Acid (XI) and (XII)——9-Hydroxy lactone (IX) (300 mg.) was hydrolyzed by reflux in a solution of KOH (400 mg.)-diethylene glycol (15 ml.)-H_2O (0.5 ml.) for 30 min. at 195~200° (bath temp.). The reaction solution was diluted with H_2O (35 ml.), acidified with 10% HCl aq. under ice-cooling and then was extracted with ether. After the ether extract was washed with 10% KOH aq., the alkaline layer was acidified under ice-cooling and was extracted again with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and then the solvent was evaporated. The resulted oily crystals (254 mg.) were treated with a small amount of ether to separate an ether soluble oil (131 mg.) and an ether insoluble crystals (123 mg.). The latter crystals were recrystallized from MeOH to give colorless fine needles (X), m.p. 257~261° (decomp.). *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.18; H, 6.30. IR ν_{max}^{KBr} cm^{-1}: 3100 (broad, COOH), 1725 (COOH), 1690 (CO), 1650 (COOH), 1600 (arom.).

The former oil will be reported elsewhere to determine as a mixture of *cis*- (XI), m.p. 75~77°, and *trans*-A/B-ring fused isomer (XII), m.p. 77~79°, of 12-nor-methyl 9-oxo acid.*4

9-Oxo Anhydride (XIII)——A solution of 9-oxo diacid (X) (74 mg.) in Ac_2O (2 ml.) was refluxed for 2.5 hr. and then the sovent was evaporated in vacuum. An ether solution of the obtained residue was washed with 3% KOH aq. under ice-cooling, then with water and was dried over Na_2SO_4. Removal of ether gave crystals (67 mg.), which were sublimated at 160~185°/3 mm. and then were recrystallized from MeOH to give colorless fine plates (XIII), m.p. 218~220°. *Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.48; H, 5.23. IR ν_{max}^{KBr} cm^{-1}: 1800, 1760 (anhydride), 1688 (CO), 1600 (arom.).

9-Oxo Imide (XIV)——A homogeneous mixture of 9-oxo anhydride (XIII) (20 mg.) and urea (100 mg.) was fused at 140~150° for 3 min. and then at 190° for 15 min. The reaction mixture was treated with H_2O and was extracted with $CHCl_3$. The chloroform extract was washed with H_2O and dried over $CaCl_2$. Removal of the solvent gave oily crystals (14 mg.), which were recrystallized from EtOH to colorless needles (XIV), m.p. 239~240°. *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.50; H, 5.93; N, 5.02. IR ν_{max}^{KBr} cm^{-1}: 3330 (NH), 1710 (imide), 1680 (CO), 1603 (arom.).

9-Acetoxy Amino Acetate (XVI)——A mixture of 9-oxo imide (XIV) (98 mg.) and $LiAlH_4$ (240 mg.) in ether (4 ml.)-dioxane (20 ml.) was refluxed for 36 hr. After H_2O was added and then the solvent was evaporated, the resulted mixture was extracted with ether and the ether extract was washed with 10% HCl aq. The acidic extract was alkalized with 10% KOH aq., then extracted with ether and the extract was washed with H_2O and was dried over Na_2SO_4. Removal of the solvent gave oily crystals (XV) (69 mg.), which were used without purification in the next step.

The crude 9-hydroxy amine (XV) (69 mg.) was acetylated by reflux in Ac_2O (8 ml.) and pyridine (2 drops) for 1.5 hr. Removal of the solvent in vacuum gave oily crystals (72 mg.), which were treated with a small amount of ether to give insoluble crystals (XVI) (43 mg.). The crystals were recrystallized from ether to colorless sands (XVI), m.p. 190~191°. *Anal.* Calcd. for $C_{21}H_{27}O_3N$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.83; H, 7.78; N, 3.75. IR ν_{max}^{KBr} cm^{-1}: 1730, 1720 (OAc), 1640, 1620 (NAc).

9-Hydroxy Amino Acetate (XVII)——A solution of diacetate (XVI) (30 mg.) in 10% KOH aq. (5 drops)-MeOH (7 ml.) was refluxed for 30 min. and then the solvent was evaporated in vacuum. The residue was diluted with H_2O and was extracted with ether. The ether extract was washed with H_2O and dried over Na_2SO_4. Removal of ether gave crystals (XVII) (28 mg.), which were recrystallized from ether to colorless prisms (XVII), m.p. 180~181°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400 (OH), 1650 (NAc).

9-Oxo Amino Acetate (XVIII). i) Dichloro Dicyano Quinone (DDQ)-Oxidation of 9-Hydroxy Amino Acetate (XVII)——A reaction mixture of hydroxy amino acetate (XVII) (7 mg.) and DDQ (42 mg.) in dioxane (3 ml.) was left standing at room temperature for 3 days. Precipitate was filtrated off and was washed with $CHCl_3$. The combined filtrate was evaporated in vacuum below 40°. An ether solution of the residue was

washed with 3% $NaHCO_3$ aq., then with H_2O and was dried over Na_2SO_4. Removal of ether gave oil (5 mg.), which was chromatographed on neut. Al_2O_3 to give crystals (4 mg.) in petr. ether–ether (5:1) fraction. The fraction was recrystallized from ether to give colorless fine needles (XVII), m.p. 164~166°. *Anal.* Calcd. for $C_{19}H_{23}O_2N$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.22; H, 7.59; N, 4.71. IR ν_{max}^{KBr} cm^{-1}: 1685 (CO), 1644, 1630 (NAc), 1598 (arom.). GC_{min} 8.15 (1% SE-30 on Shimalite (60~80 mesh), 3 mm.×4 m., 231°).

ii) CrO_3-Oxidation of Amino Acetate (VI)——To a solution of amino acetate (VI)[5] (24 mg.) in AcOH (2 ml.), CrO_3 (30 mg.) in AcOH aq. was slowly added. After the reaction mixture was warmed at 52~55° for 45 min., MeOH was added to decompose excess CrO_3 and the solvent was evaporated in vacuum. The obtained residue was diluted with H_2O, then was extracted with ether and the ether extract was dried over Na_2SO_4. Removal of ether gave oil (14 mg.), which was chromatographed on neut. Al_2O_3 to separate crystals (7 mg.) in petr. ether–ether (5:1) fraction. The crystals were recrystallized from ether to give colorless fine needles (XVIII), m.p. 162~164°, whose physical constants (m.p., m.m.p., IR and GLC) were completely identical with those of the sample obtained from 9-hydroxy amino acetate (XVII).

7-Methoxy Amino Acetate (XXII) from 9-Oxo Amino Acetate (XVIII) *via* (XIX), (XX) and (XXI)——To a solution of 9-oxo amino acetate (XVIII) in conc. H_2SO_4 (0.2 ml.), a mixed solution of HNO_3 (0.1 ml.)–conc. H_2SO_4 (0.4 ml.) was slowly added under ice-cooling and was stirred for 15 min. The solution was diluted with ice-water and then extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulted oil (XIX) (39 mg.) showed one spot by TLC (silica gel, benzene–acetone (4:1)). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (CO), 1640 (NAc), 1530, 1350 (NO_2).

A solution of the nitro-compound (XIX) (39 mg.) in AcOH (12 ml.) containing conc. H_2SO_4 (1 drop) was shaken in H_2-atmosphere with 10% Pd-C (60 mg.) under warming by IR-lamp. After H_2-absorption was ceased, catalyst was filtrated off. The filtrate was neutralized with K_2CO_3 powder, then was evaporated in vacuum and the residue was extracted with ether. The ether extract was washed with 1% HCl aq. The acidic layer was neutralized with 10% K_2CO_3 aq. and was extracted with ether. The ether extract was dried over Na_2SO_4 and was evaporated to give oily amine (XX) (25 mg.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3550, 3400 (NH_2), 1640 (NAc).

To a solution of the oily amine (XX) (17 mg.) in 20% H_2SO_4 aq. (3 ml.), $NaNO_2$ (30 mg.) in H_2O was added under ice-cooling and stirring. After the reaction mixture was stirred for 10 min. under ice-cooling and successively, urea (30 mg.) was added, it was continued to stir for 15 min. under ice-cooling and then for 30 min. at 80~83°. The reaction solution was diluted with H_2O (20 ml.) and was extracted with AcOEt. The AcOEt extract was extracted with 10% KOH aq., then the alkaline layer was acidified and extracted again with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4 and was evaporated. A solution of the obtained solid (XXI) (10 mg.) in MeOH was treated overnight with ether solution of CH_2N_2. Removal of solvent gave oil (11 mg.), which was chromatographed on Al_2O_3 (2.0 g.) to separate crystals (6 mg.) in *n*-hexane–ether (5:1) elution. Recrystallization of the crystals from EtOH–H_2O afforded coloress fine needles (XXII). m.p. 146~147°. *Anal.* Calcd. for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.49; H, 8.71; N, 4.47. $[\alpha]_D^{28.5}$ −131.3 (EtOH, c=0.21). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1645 (NAc), 1050 (OMe). GC_{min} 12.4 (1.5% SE-30 on Anakrom (mesh 80~100), 4 mm.×1.85 m., 227°). The amino acetate (XXII) was identified by comparison of its physical constants (IR (CCl_4), GLC) with *dl*-compound (XXV) (m.p. 167~169°) obtained by acetylation of Nagata's amine (XXIV)*5 as described later.

Acetylation of *dl*-7-Methoxy Amine (XXIV)——*dl*-7-Methoxy amine (XXIV) was totally synthesized by W. Nagata's group.[1a] After a solution of *dl*-amine (XXIV)*5 (30 mg.) in Ac_2O (0.4 ml.) and pyridine (1 drop) was refluxed for 1 hr., solvent was removed in vacuum. The obtained crystals were recrystallized twice from EtOH–H_2O to give colorless needles (XXV), m.p. 167~169°. *Anal.* Calcd. for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.87; H, 8.55; N, 4.49. IR ν_{max}^{KBr} cm^{-1}: 1628 (CO). Physical constants (IR (CCl_4), GLC) of *dl*-amino acetate (XXV) were completely identical with those of our *l*-amino acetate (XXII).

Hydrolysis of *dl*-7-Methoxy Amino Acetate (XXV)——After a solution of *dl*-amino acetate (XXV) (18 mg.), KOH (350 mg.) and hydrazine hydrate (4 drops) in diethylene glycol (2 ml.) was refluxed for 5 hr., the reaction mixture was diluted with H_2O and was extracted with ether. The ether extract was washed with 10% HCl aq., the acidic layer was neutralized and was extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulted *dl*-7-methoxy amine (XXIV) was treated with picric acid in EtOH to give picrate, which was recrystallized from EtOH–ether to orange yellow sands, m.p. 188~190°. *Anal.* Calcd. for $C_{24}H_{28}O_8N_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.99; H, 5.61; N, 11.19. The picrate was identical (m.p. and m.m.p.) with the picrate of the original *dl*-7-methoxy amine (XXIV).

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