Studies on Anodic Selective Functionalization of Cyclic Amine Derivatives

Osamu Onomura

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PREFACE

The studies presented in this thesis have been carried out under the direction of Professor Tatsuya Shono at the Department of Synthetic Chemistry of Kyoto University during 1983-1988. The thesis is concerned with anodically selective functionalization of cyclic amine derivatives.

The author wishes to express his sincerest gratitude to Professor Tatsuya Shono for his constant guidance, valuable suggestions, and heartly encouragement throughout the course of the work. The author is also deeply grateful to Associate Professor Yoshihiro Matsumura for his continuous advice and helpful discussions during this work. He wishes to acknowledge the suggestions and criticisms of Drs. Shigenori Kashimura, Kenji Tsubata, Naoki-Kise, Kenji Inoue, and Kenshi Uchida. Furthermore, the author's grateful thanks are given to Messrs. Masaru Ogaki, Tsutomu Yoshida, Yasufu Yamada, and Masaaki Sato for their active collaborations. The author is indebted to the other members of the research group of Professor Tatsuya Shono.

The author wishes to thank Mrs. Yohko Ohmizu and Mr. Susumu Katoh for their affectionate encouragement throughout this work.

Finally, the author is grateful to his father, Yoshihiro Onomura and his wife Kayoko Onomura for their great and constant assistance and encouragement.

Osamu Onomura

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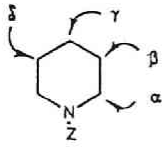
October, 1988.

CONTENTS

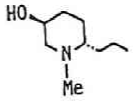
General Introduction

A lot of piperidine alkaloids have attracted much attention of synthetic organic chemists because of the biological activities.[1] Those alkaloids are characterized by the piperidine skeletons which have various substituents (for examples, see Scheme 1). Although many methods for the synthesis of piperidine derivatives have been exploited so far, they are not always convenient with respect to reaction steps, starting materials, reagents, and so on. Accordingly, exploiting highly effective methods for the preparation of such skeletons are worthwhile from a synthetic viewpoint.

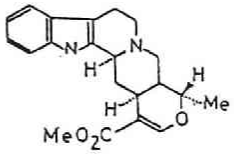
Scheme 1.



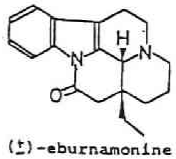
A



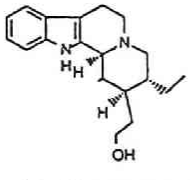
(+)-N-methyl-pseudoconhydrine



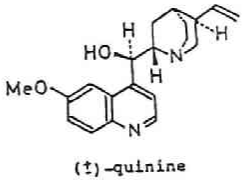
(±)-ajmalicine



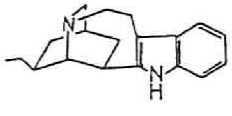
(±)-eburnamonine



(-)-dihydrocorynantheol

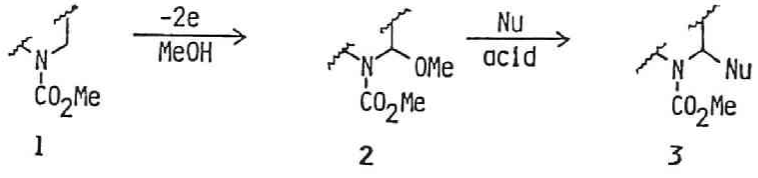


(±)-quinine



(-)-ibogamine

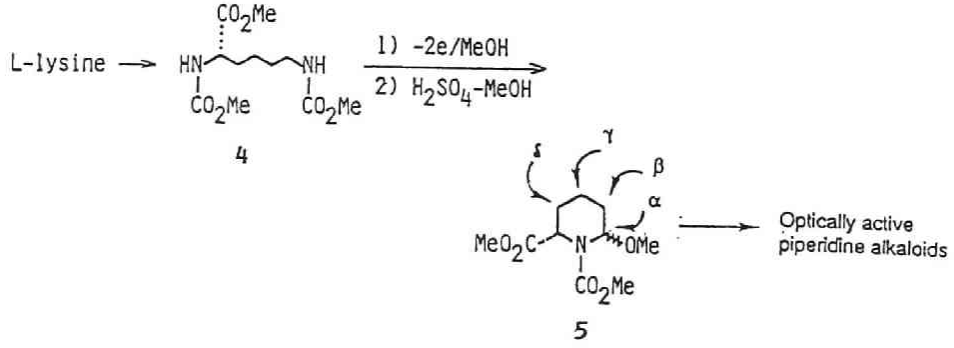
T. Shono et al. have already exploited a convenient method for introducing various nucleophiles (Nu) into the position α to the nitrogen atom of carbamates 1 using anodic oxidation followed by the reaction of oxidized products 2 with Nu as shown in eq 1.[3]



1 2 3 (1)

This method, however, has not been applicable to introduce substituents to the other positions than α.[4]

This thesis describes new methods for introducing various substituents into the β, γ, and/or δ-position of piperidine ring (A in Scheme 1) by using the anodic oxidation as key reactions. Furthermore, their application to the synthesis of some piperidine alkaloids as shown in Scheme 1 is described. This thesis also describes the transformations of L-pipecolinic acid derivative 5, which can be anodically prepared from L-lysine through 4, into optically active piperidine alkaloids utilyzing these methods (eq 2).[5] Some of exploited synthetic routes seem to be very interesting from a viewpoint of biosynthetic pathways.[6]



(2)

Chapter 1 is concerned with applications to asymmetric carbon-carbon bond forming reaction in the displacement of the methoxyl group of anodically prepared α-methoxylated cyclic amines with carbon nucleophiles.

Chapter 2-1 is concerned with anodic α, β-difunctionalization of cyclic amine derivatives and its application to synthesis of some useful intermediates for pyrrolidine and piperidine alkaloids.

Chapter 2-2 is concerned with the synthesis of (+)- and (-)-N-methylpseudoconhydrine from L-lysine using anodic oxidations.

Chapter 3 is concerned with introducing some active methylene or methyne groups to the β-position of cyclic amines and its application to synthesis of (±)-eburnamonine.

Chapter 4-1 is concerned with introducing a bis(methoxycarbonyl)methyl group to γ-position of piperidine ring, and its application to synthesis of (±)-meroquinene and (±)-epimeroquinene.

Chapter 4-2 is concerned with diastereoselective introducing 2-hydroxyethyl group to γ-position of anodically prepared pipecolinic acid derivative from L-lysine and an approach to synthesis of (-)-dihydrocorynantheol.

Chapter 5-1 is concerned with regioselective synthesis of 2- and 5-substituted 1,2-dihydropyridines.

Chapter 5-2 is concerned with optically pure 2-substituted 1,2-dihydropyridines and its application to preparation of optically active 2-aza-2,5,

6-tris(methoxycarbonyl)bicyclo[2.2.2]octane.

References and Notes

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3. For examples, see: a) Shono, T.; Matsumura, Y.; Tsubata, K. J. Am. Chem. Soc. 1981, 103, 1172. b) Idem. Tetrahedron Lett. 1981, 22, 2411. c) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. J. Org. Chem. 1984, 49, 300. d) Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. J. Org. Chem. 1985, 50, 3243.
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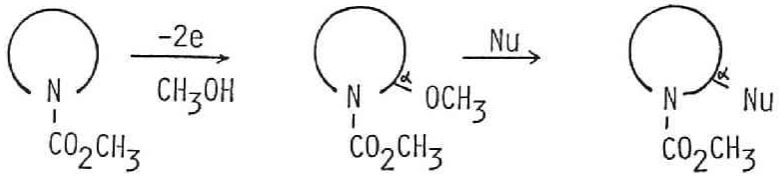
Chapter 1

Asymmetric Carbon-Carbon Bond Forming Reaction at the Position α to the Nitrogen Atom of Cyclic Amine Derivatives

Abstract: Two methodologies were applied for asymmetric carbon-carbon bond forming reaction in the displacement of the methoxyl group of anodically prepared α-methoxylated cyclic amines with carbon nucleophile. One of them was a method using substrates which possess a chirality at the α-position,and the other was a method in which a chiral auxiliary was located on the protecting group of nitrogen atom of substrates. Although the first method was not effective, the second method was found to be promising for the asymmetric carbon-carbon bond forming reaction.

Many groups have developed various methodologies for the introduction of nucleophiles (Nu) to the position α to the nitrogrn atom of cyclic amines and applied them to the synthesis of naturally occuring alkaloids which have physiologically important activities.[1] One of the methodologies involves anodic α-methoxylation of N-methoxycarbonylated cyclic amines 1 followed by Lewis acid catalyzed displacement of α-methoxyl group of the oxidation products 2 with Nu (eq.1).[2] Although this methodology is very convenient for the carbon-carbon bond formation at the α-position of 1 (Nu in eq.1; carbon nucleophile), an asymmetric carbon-carbon bond forming reaction has still remained to be explored. We report herein our approach for this purpose.

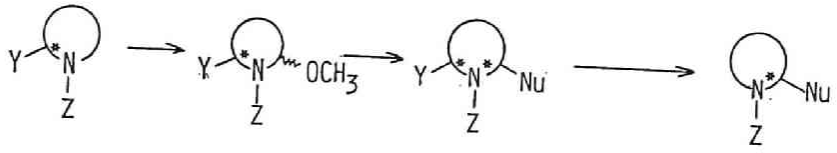


1 2 3 (1)

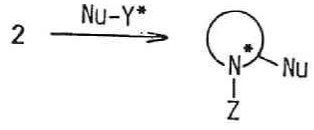
In order to achieve asymmetric carbon-carbon bond formation at the α-position, the following five methods (Scheme 1) may be effective depending on the location of chiral source; (1) A chiral source is located in the parent skeleton, though this method requires to remove the original chiral source on the course of reaction sequence. (2) A method utilizing nucleophiles which possess chiral auxiliaries. (3) A method in which Lewis acids are chiral. (4) Forth one is a special case of method (1) in which substrates 4 possessing a chirality at the α-position are used. This method, however, may be effective only in the case that the displacement of the leaving group (L of 4) with Nu proceeds with S_N2-like. (5) Last one is a method in which a chiral auxiliary is located on the protecting group of the nitrogen atom of substrates 6.

Among these, method (1) has already been proved by us to be effective for the purpose as exemplified by the synthesis of (+)-N-methylconiine, (+)-17, with high enantioselectivity (96%ee).[3] Recently, enantioselective synthesis of bicyclic alkaloids by method (2) has been reported.[5] Methods (3) and (4) have not been examined so far, and few reports concerning on method (5) have been appeared during the course of this study.[6] This paper describes our studies on methods (4) and (5).

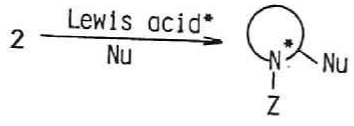
Method (1):



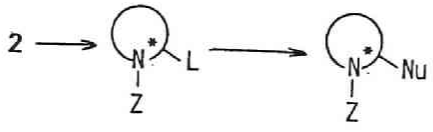
Method (2):



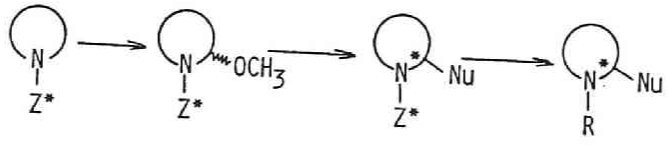
Method (3):



Method (4):



Method (5):

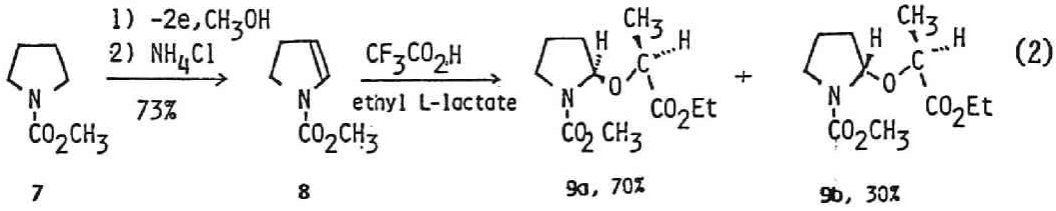


Scheme 1.

Results and Discussion

Synthesis of Compounds 4 possessing Chirality at the α-Carbon and Carbon-Carbon Bond Forming Reaction Using 4 (Method 4). Provided that nucleophilic attack of Nu on 4 proceeds with S_N2-like, it is expected that the displacement of a leaving group of chiral 4 with Nu may produce optically active products 5. Thus, we tried to prepare optically active 4 from ene-carbamate 8 and 11 which were easily obtainable from N-methoxycarbonylated cyclic amines 7 and 10, respectively.[8] Addition of ethyl L-lactate to 8 under acidic conditions gave optically active compounds 9a and 9b (eq.2).

Although each diastereoisomer was separable by column chromatography (the ratio of the diastereoisomers=70:30),[9] the identification of the structure of isolated stereoisomer was not accomplished. In contrast to 8, addition of ethyl L-lactate on 10 did not proceed since addition products 12 were unstable under acidic conditions to easily go back to the starting ene-carbamate 11 (eq.3).[10]



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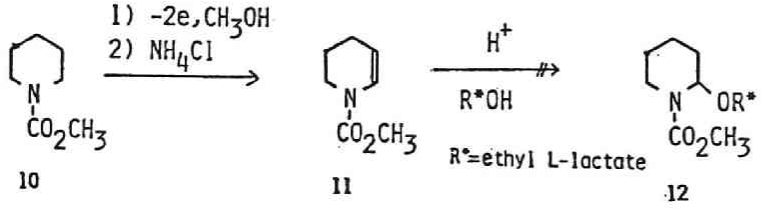
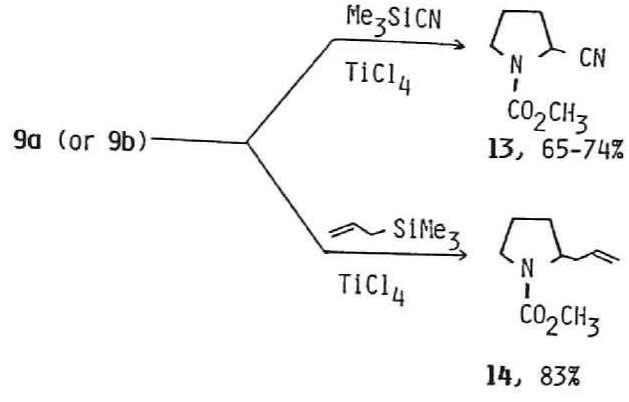


(3)

Although treatment of isolated 9a or 9b with Lewis acids in the presence of trimethylsilyl cyanide or allyltrimethylsilane gave cyanated or allylated products 13 or 14, these poroducts did not show any chirality (eq. . . 4).



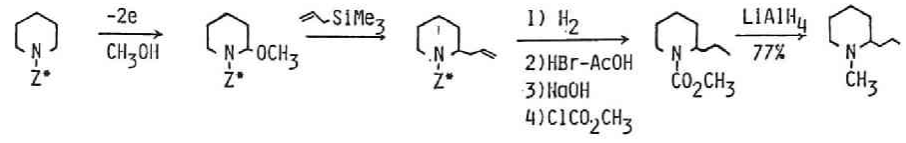
(4)

This result suggests a mechanism involving a carbon-carbon bond forming reaction which proceeds with S_N1-like,[3] and, thus, method (4) is not effective for asymmetric carbon-carbon bond forming reaction.

Carbon-Carbon Bond Forming Reaction of Compounds possessing Chiral Auxiliaryon the N-Protecting Group (Method 5). The effectiveness of method (5) on the asymmetric carbon-carbon bond formation at the α-position of 6 was examined with α-methoxylated piperidine derivatives possessing chiral auxiliary on the nitrogen atom. First, D-camphorsulfonylamide 13a and L-isomer 13b were prepared by usual methods, and they were oxidized to α-methoxylated compounds 14a and 14b by anodic oxidation. Treatment of 14 with allytrimethylsilane in the presence of $TiCl_4$ gave allylated product 15, which was hydrogenated, deprotected, and N-methoxycarbonylated, successively, to give 16 as shown in eq.5.

The obtained 17a by the reduction of 16a showed (+)-optical rotation, and the optical purity was found to be 15% ee by comparison with authentic sample.[11] Similarly, the product 17b obtained from 14b showed (-)-optical rotation with 15% ee. Although the optical yields were low, method (5) was found to be effective for asymmetric carbon-carbon bond forming reaction.

The lower optical yields seemed to be explainable in terms of long distance between the chiral center and reaction point. Thus, in the next place, we tried to prepare piperidine derivatives protected with L-lactic acid. Heating of piperidine with ethyl L-lactate gave N-protected piperidine derivative 18 in which the number of bonds between chiral center and reaction point was three but four in 14.

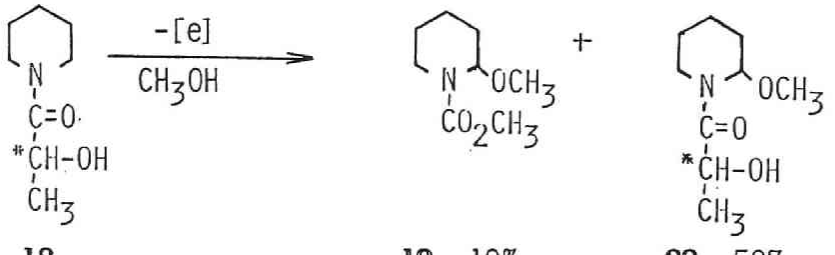


(5)

13a,b	14a, 90%	15a, 95%	16a, 38%	17a, 77%, (S) 15% ee
	b, 86%	b, 82%	b, 37%	b, 66%, (R) 15% ee

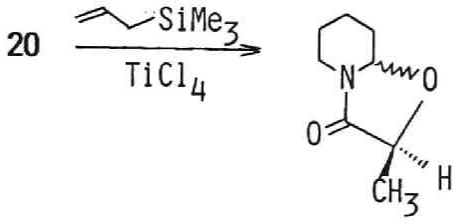
The anodic oxidation of 18 in methanol afforded a mixture of carbon-carbon bond cleaved product 19 and α-methoxylated product 20 in 10% and 58 % yields, respectively (eq.6),[13] and treatment of 20 with allyltrimethylsilane in the presence of $TiCl_4$ did not give α-allylated product but 21 (eq.7).

In order to avoid these undesirable reactions, 18 was mesylated with mesyl chloride to give 22.



18 19, 10% 20, 58%

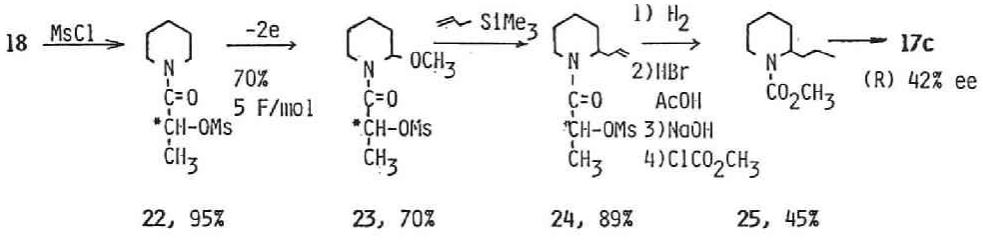
(6)



(7)

21, 70%

Anodic oxidation of 22 followed by allylation of anodically generated α-methoxylated product 23 afforded 24. Then, the deprotection and successive N-methoxycardonylation gave 25 (eq.8). Since optical rotation of obtained 17c was (-) with 42% ee, the absolute stereochimistry of main enantiomer of 17c was found to be R.[12]



(8)

This diastereoselectivity seems to be caused by the steric hindrance between the methyl group of N-protecting group and attacking Nu as shown in Fig.1.

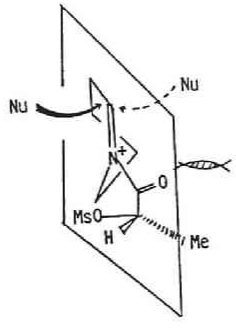


Fig. 1.

In conclusion, method (5) is effective for the synthesis of optically acitive piperidine derivatives but method (4) is not. It is supposed that by a suitable selection of N-protecting group may enable the optical purity higher.

Experimental Section

Materials. Compounds 8 and 11 were prepared according to the reported method.[8]

Hemiacetal 9a and 9b. Into a solution of enecarbamate 8 (2.655g, 20.9 mmol) and L-ethyl lactate (2.4mL, 20.9mmoL) in CH_2Cl_2 (5mL) was added CF_3CO_2H (40 μL) at room temperature. After the solution was stirred overnight, it was poured into aqueous Na_2CO_3 (15mL) and the organic portion was extracted with CH_2Cl_2 (3x30mL). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:10) to afford 9a and 9b in 70% and 30% yields, respectively.

9a (less polar isomer): $[\alpha]_D^{20}$ -54.0 ° ; IR (neat) 2990, 2962, 1748, 1715, 1451, 1382, 1197, 1142, 1100cm^{-1}; NMR (CCl_4) δ 1.24 (d, J=7Hz, 3H), 1.27 (t, J=7Hz, 3H),1.36-2.51(m, 4H), 3.03-3.61 (m, 2H), 3.64 (s, 3H), 3.70-4.40 (m, 1H), 4.15 (q, J=5Hz, 2H), 5.30 (br t, J=5Hz, 1H). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.96; H, 8.01, N, 5.62.

9b (polar isomer): $[\alpha]_D^{20}$ -89.0 ° (c 0.4, EtOH); IR (neat) 2990, 2962, 1748, 1715, 1451, 1382, 1197, 1142, 1100cm^{-1}; NMR (CCl_4) δ 1.15-2.40

(m, 7H), 1.30 (d, J=8Hz, 3H), 3.10-3.51 (m, 2H), 3.61 (s, 3H), 3.80-4.45 (m, 1H), 4.07 (q, J=7Hz, 2H), 5.33 (br s, 1H). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C,53.93; H, 8.06, N, 6.08.

Cyanation and Allylation of 9a or 9b was carried out under the similar conditions to those of 11 or 19 described bellow. Obtained 13 (74% yield)[14] and 14 (83% yield)[15] were racemic.

Sulfonamides 13a,b. Into a dispersion of piperidine (20mL, 231mmol) and K_2CO_3 (27g, 134mmol) in CH_2Cl_2 (100mL) was added D-comphorsulfonylchloride (16.8g, 67mmol). After it was stirred overnight, the solid was removed by filtration. After filtrated solution was washed with dil. HCl, the organic layer was dried over $MgSO_4$ and successively the solvent was removed in vacuo. The residue was recrystalyzed from ether to afford 13a (96%yield). By the similar procedure starting from L-comphorsulfonylchloride was yielded 13b (93%).

13a: mp.44-45℃ (from ether); $[\alpha]_D^{20}$ +30.3 ° (c 1.5, EtOH); IR (KBr) 2930, 1738, 1336, 1160, 1142, 1049, 936cm^{-1}; NMR ($CDCl_3$) δ 0.87 (s, 3H), 1.13 (s, 3H), 1.26-2.66 (m, 13H), 2.72 (d, J=16Hz, 1H), 3.17-3.37 (m, 2H), 3.33 (d, J=16Hz, 1H). Anal. Calcd for $C_{15}H_{25}NO_3S$: C, 60.17; H, 8.42; N, 4.68; S, 10.71. Found: C, 60.02; H, 8.61; N, 4.77; S, 10.65.

13b: mp 42-43℃ (from ether); $[\alpha]_D^{20}$ -31.2 ° (c 1.1, EtOH); Anal. Found: C, 60.43; H, 8.71; N, 4.69; S, 10.66.

Anodic Oxidation of 13a,b. α-Methoxylation of 13a,b was achieved under conditions similar to the anodic oxidation of 10. Usual working up gave 14a (90% yield, at 5F/mol) and 14b (86% yield, at 6F/mol).

14a: IR (neat) 2950, 1742, 1349, 1158, 1056, 937cm^{-1}; NMR ($CDCl_3$) δ 0.88 (br s, 1H), 1.14 (s, 3H), 1.28-3.92 (m,2H), 3.33 and 3.37 (2s, 1.27H and 1.73H), 5.03 (br s, 1H). Anal. Calcd for $C_{16}H_{27}NO_4S$: C, 58.33; H, 8.26; N, 4.25; S, 9.73.Found: C, 58.74; H, 8.00; N, 4.19; S, 9.66.

14b: IR (neat) 2950, 1742, 1349, 1158, 1056, 937cm^{-1}; NMR ($CDCl_3$) δ 0.88 (br s, 1H), 1.14 (s, 3H), 1.28-3.92 (m,2H), 3.33 and 3.37 (2s, 1.73H and 1.27H), 5.03 (br s, 1H). Anal. Calcd for $C_{16}H_{27}NO_4S$: C, 58.33; H, 8.26;;; N, 4.25; S, 9.73 Found: C, 58.32; H, 8.31; N, 4.20; S, 9.58.

Allylation of 14a,b was achieved under conditions similar to the allylation of 22 except for temperature (at -40℃).

15a: mp.92-93.5℃ (from ether); IR (KBr) 2945, 1743, 1644, 1336, 1166, 1147, 1052, 1003, 938cm^{-1}; NMR ($CDCl_3$) δ 0.89 (s, 3H), 1.15 (s, 3H), 1.37-1.43 (m, 1H), 1.52-1.71 (m, 7H), 1.90-1.95 (m, 1H), 2.00-2.09 (m, 2H), 2.34-2.59 (m, 4H), 2.80 (d, J=15Hz, 1H), 3.05 (br t, J=13Hz, 1H), 3.40 (d, J=15Hz, 1H), 3.72 (br d, J=14Hz, 1H), 4.08-4.10 (m, 1H), 5.07-5.14 (m, 2H), 5.74-5.84 (m, 1H); Anal. Calcd for $C_{18}H_{29}NO_3S$: C, 63.68; H, 8.61; N, 4.13; S, 9.44. Found: C, 63.65; H, 8.67; N, 3.94; S, 9.44.

15b: IR (KBr) 2945, 1743, 1644, 1336, 1166, 1147, 1052, 1003, 938cm^{-1};;; NMR ($CDCl_3$) δ 0.89 (s, 3H), 1.15 (s, 3H), 1.37-1.43 (m, 1H), 1.52-1.71 (m, 7H), 1.90-1.95 (m, 1H), 2.00-2.09 (m, 2H), 2.34-2.59 (m, 4H), 2.80 (d, J=15 Hz, 1H), 3.05 (br t, J=13Hz, 1H), 3.40 (d, J=15Hz, 1H), 3.72 (br d, J=14Hz, 1H), 4.08-4.10 (m, 1H), 5.07-5.14 (m, 2H), 5.74-5.84 (m, 1H). Anal. Calcd for $C_{18}H_{29}NO_3S$: C, 63.68; H, 8.61; N, 4.13; S, 9.44. Found: C, 63.80; H, 8.83; N, 3.94; S, 9.26.

Preparation of 16 from 19a,b was carried out according to general procedure described above.

Amide 18. A mixture of L-ethyl lactate (20mL, 176mmol) and piperidine (30mL,303mmoL) was refluxed for 6h. After excess of piperidine was removed, the residue was distilled to afford 18 (24.3g, 88% yield): bp 104-106 ℃ (8mm); IR (neat) 3425, 2950, 2870, 1648, 1455, 1115cm^{-1}; NMR (CCl_4) δ 1.30 (d, J=6Hz, 3H), 1.39-1.83 (m, 6H), 3.23-3.73 (m, 4H), 4.45 (q, J=6Hz, 1H), 4.64 (brs, 1H). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found : C, 61.37; H, 9.61; N, 8.70.

Anodic Oxidation of 18. Anodic oxidation of 18 was carried out by the procedure similar to the anodic oxidation of 19 to afford 19[16] and 20 in 10% and 58% yield, respectively at 5F/mol.

20: IR (neat) 3430, 2952, 1648, 1450, 1138, 1095, 1040, 1020, 962cm^{-1}; NMR (CCl_4) δ 1.27 (d, J=6Hz, 3H), 1.19-1.90 (m, 6H), 2.60-4.43 (m, 3H), 3.20 (s, 3H), 4.35 (br q, J=6Hz, 1H), 5.67 (br s, 1H); MS, m/e 187 (M^+), 172, 154, 142(base); exact mass calcd m/e 187.1208, found 187.1191.

Treatment of 20 with Allyltrimethylsilane: This reaction was carried out under conditions similar to the allylation of 11. Usual working up gave 21 in 70% yield: IR (neat) 2940, 2855, 1711, 1453, 1118, 1100, 984cm^{-1}; NMR (CCl_4) δ 1.28 and 1.31 (2d, J=6Hz, 3H), 1.33-2.25 (m, 6H), 2.39-2.98(m, 1H),3.74-4.33 (m, 2H), 4.70-5.03 (m, 1H); MS, m/e 155 (M^+), 154 (base), 127; exact mass calcd m/e 155.0946, found 155.0940.

Methanesulfonate 22. Into a solution of 18 (5g, 31.8mmol) and tri-

ethylamine (8mL, 50mmol) in CH_2Cl_2 (40mL) was added dropwise methanesulfonylchloride (4mL, 44mmol) at 0°C. After the reaction mixture was stirred for 30 min, it was poured into water (50mL). The organic portion was extracted with dichloromethane (3x30mL). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:1) to afford colorless solid 21 (5.85g, 88% yield): mp 57-58°C ; $[\alpha]_D^{20}$ -32.4 ° (c 1.0, EtOH); IR (KBr) 2945, 2855, 1652, 1355, 1190cm^{-1}; NMR ($CDCl_3$) δ 1.57 (d, J=8Hz, 3H), 1.53-1.80 (m, 6H), 3.13 (s, 3H), 3.20-3.90 (m, 4H), 5.46(q, J=8Hz, 1H). Anal. Calcd for $C_9H_{17}NO_4S$: C, 45.94; H,7.26; N,5.95; S, 13.63. Found: C, 46.02; H, 7.35; N, 5.86; S, 13.37.

Anodic Oxidation of 21. Into an undivided cell equipped with carbon rod anode and cathode (8mmϕ) was added a solution of 21 (2.35g, 10mmol) and Et_4NOTs (0.6g, 2mmol) in methanol (30mL), and 5F/mol of electricity was passed at a constant current of 0.5A (2.7h, terminal voltage; ca. 7V) through the solution which was cooled with ice-water. The solution was poured into water and the organic portion was extracted with C_2HCl_2 (4x 40mL). After the extract was dried over $MgSO_4$ and the solvent removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:2) to afford 22 in 70% yield: IR (neat) 2950, 1658, 1360, 1180cm^{-1}; NMR ($CDCl_3$) δ 1.10-2.22(m, 6H), 1.58 and 1.59 (2d, J=8Hz and 8Hz, 3H), 2.65-3.90 (m, 3H), 3.14 and 3.16 (2s,3H), 3.27 (s, 3H), 5.49 (q, J=8Hz, 1H), 5.70-5.93 (m, 1H); MS, m/e 234 (M^+-OMe), 233 (M^+-MeOH). Anal. Calcd for $C_{10}H_{19}NO_5S$: C, 45.27; H, 7.22; N, 5.28; S, 12.08. Found: C, 46.08; H, 7.14; N, 5.11; S, 11.52.

Allylation of 22. Into a solution of $TiCl_4$ (1mL, 4.4mmol) in dry CH_2Cl_2 (5mL) was added dropwise a solution of 22 (0.779mg, 2.94mmol) in dry CH_2Cl_2

(5mL) at -70°C under an atmosphere of nitrogen. After the solution was stirred at the temperature for 5min, a solution of allyltrimethylsilane (0.524g, 4.6mmol) in dry CH_2Cl_2 (5mL) was added dropwise. After the resulting reaction mixture was stirred for 1h at -70°C, water (15mL) was poured into the reaction mixture and stirred for 10min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x30mL). After the combined organic layers were dried over $MgSO_4$, the solvent removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:5) to afford 23 in 89% yield: IR (neat) 2945, 1652, 1360, 1180cm^{-1}; NMR ($CDCl_3$) δ 1.47 (d, J=7Hz, 3H), 1.38-1.81 (m, 6H), 2.17-2.55 (m, 2H), 2.71-5.91 (m, 7H), 3.01 and 3.07 (2s, 2.13H and 0.87H). Anal. Calcd for $C_{12}H_{21}NO_4S$: C, 52.34; H, 7.69; N, 5.09; S, 11.64. Found: C, 52.48; H, 7.73; N, 4.92; S,11.34.

Preparation of 17, General Procedure. After hydrogenation of 12 (1.052 g, 3.8mmol) in methanol containing catalytic amount of PtO_2 (1atm) overnight and followed by hydrolysis was carried out in 25% HBr-AcOH (10mL) at 80 °C for 20h, the resulting mixture was poured into 50% NaOH containing $ClCO_2Me$ (10mL, 12.9mmol). After it was stirred for 1h, the organic portion was extracted with CH_2Cl_2 (4x25mL). The extract was dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:5) and further distilled by kugel rohr (150 °C/1mm) to afford 13[13] (0.356g, 51% yield) in 42% ee.[8]

References and Notes

1. For examples, see; (a) Glasby, J. S. In "Encyclopedia of the Alkaloids," Plenum Press: New York and London, 1975; Vol.1 and 2: 1977; Vol. 3.

(b) Kocovsky, P.; Turecek, F.; Hazicek, J. In "Synthesis of Natural products: Problems of Stereoselectivity," CRC Press: Florida, 1986; Vol. 2. (c) Klyne, W.; Buckingham, J. In "Atlas of Stereochemistry," Fletcher and Son: London, 1974; p.137.

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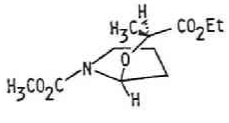
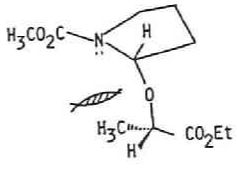
8. Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. J. Am. Chem. Soc. 1982, 104, 6697.
9. Less hindered isomer 9a was considered to be a main product.



9a



9b

10. Shono, T.; Matsumura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T. J. Org. Chem. 1987, 52, 536.
11. Enantiomeric excess (ee) of 16 was determined by 400MHz ^{1}HNMR. Namely,

a solution of 16 in $CDCl_3$ was measured in the presence of $Eu(hfc)_3$ (1equiv.) at 60 ℃. And absolute configuration of 16 was determined by optical rotations of 17 obtained from 16.[12]

12. Pure 17 {$[\alpha]_D$ +74.9° (95% ethanol, c 0.2-2.0)} is (S) configuration. Craig, J. C.; Lee, S.-Y. C.; Pereira, W.E.Jr.; Beyerman, H.C. Tetrahedron 1978, 34, 501.
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Chapter 2-1

β-Acetoxylation and β-Halogenation of N-Methoxycarbonyl Cyclic Amines

Abstract: Anodic oxidation of N-methoxycarbonyl-pyrrolidines and -piperidines in AcOH-AcOK, aqueous CH_3CN-NH_4Cl, CH_2Cl_2-Et_4NOTs, MeOH-NH_4Cl system gave α, β-disubstituted compounds. The α-substituents were easily removed by $NaBH_4$ under acidic conditions to give β-substituted compounds. This method was applied to the synthesis of racemic Conium alkaloids such as pseudoconhydrine and N-methylpseudoconhydrine.

Functionalization of a less reactive methylene group is one of the most interesting current topics, while generally effective methods have not always been found as yet. One of the methods hitherto exploited may be the remote oxidation, in which a methylene group at a remote position from an activating group can be oxidized with some efficient selectivity.[1]

In this chapter is described a convienient method for introducing an acetoxyl group or a halogen atom to the β-methylene group of N-methoxycarbonyl cyclic amines A .

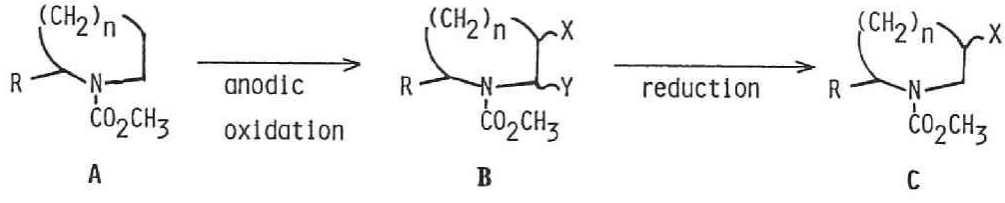
Shono et al., have already exploited the anodic oxidation for the α-methoxylation[2] or α-hydroxylation[3i] of a variety of carbamates. In continuing this study, we have found that the anodic oxidation of A under some selected conditions gave α, β-disubtituted products B in satisfactory yields instead of α-monosubstituted ones. Since the α-substituent of B is easily removable by reduction to give β-substituted compounds C, the over-

all transformation from A to final products C corresponds to a β-functionalization of A (Scheme 1).

This chapter describes these results together with brief discussion on the reaction mechanism of the α, β- disubstitution.

In addition, this paper also reports some utilization of B and C in organic synthesis as exemplified by the stereoselective synthesis of racemic Conium alkaloids such as pseudoconhydorine and N-methylpseudoconhydrine.[4]

Scheme 1



A B C

n=1,2 X=OAc or Cl

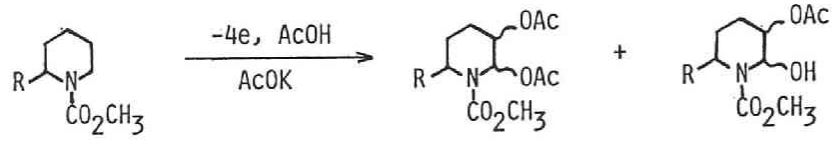
Y=OAc, OCH_3, or OH

Results and Discussion

Anodic α, β-Diacetoxylation of N-Methoxycarbonylpiperidines.

Although the anodic oxidation of N-methoxycarbonylpiperidines 1a-d in methanol using Et_4NOTs as a supporting electrolyte gives α-methoxylated products,[2] the anodic oxidation of 1a-d in acetic acid containing AcOK as a supporting electrolyte gave α, β-diacetoxylated products 2a-d (eq 1). Since the compounds 2 were somewhat unstable under the reaction conditions and at the step of workup, careful workup of the electrolyzed solution with

cold aqueous $NaHCO_3$ (method a) was necessary to get 2 as the main products, while the workup with water (method b) gave only α-hydroxy-β-acetoxy compounds 3. The yields of 2 and 3 are summarized in Table 1.



1a-d 2a,b 3a-d (1)

a, R=H d, $R=CH_2COCH_3$

b, $R=CH_3$

c, $R=n\text{-}C_3H_7$

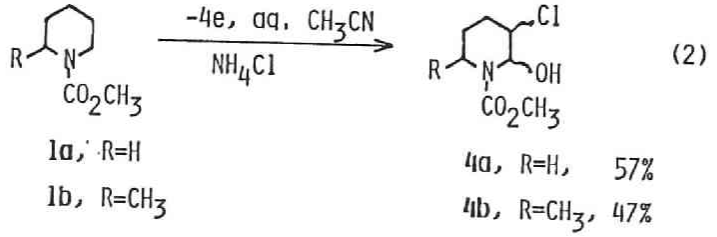
Table 1. Anodic Oxidation of N-Metyhoxycarbonylpiperidines 1a-d

Run	Compound	Method[a]	Isolated Yield(%)	
			2	3
1	1a	a		3a(88)
2	1a	b	2a(61)	3a(20)
3	1b	a		3b(92)
4	1b	b	2b(34)	3b(45)
5	1c	a		3c(93)
6	1d	a		3d(53)

[a] see text.

Anodic α-Hydroxy- β-chlorination of N-Methoxycarbonyl-piperidines and -pyrrolidines. Anodic oxidation of N-methoxycarbonyl-piperidines 1a,b and -pyrrolidines 5a,b in aqueous acetonitrile containing NH_4Cl gave α-hydroxy-β-chlorinated products 4a,b and 6a,b, respectively, in satisfactory yields

(eqs 2 and 3).[5]



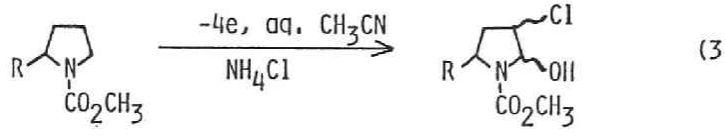
(2)

1a, R=H

1b, R=CH_3

4a, R=H, 57%

4b, R=CH_3, 47%



(3)

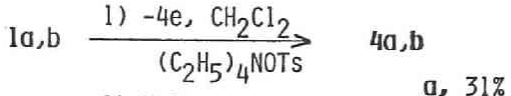
5a, R=H

5b, R=CO_2CH_3

6a, R=H, 47%

6b, R=CO_2CH_3, 68%

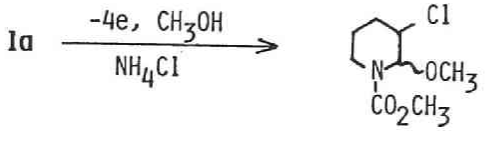
This type of β-chlorination was also achieved by anodic oxidation in dichloromethane containing Et_4NOTs (eq 4) or in methanol containing NH_4Cl (eq 5).



(4)

a, 31%

b, 61%



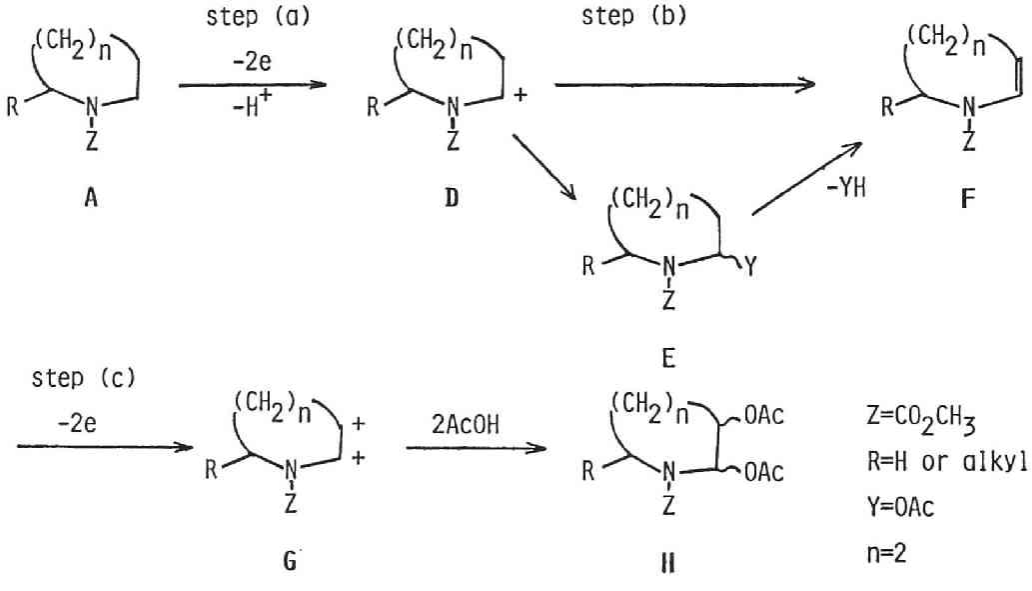
(5)

7, 90%

On the other hand, some devices were required to achieve β-bromination or -iodination of A, since the use of NH_4Br or NH_4I as a supporting electrolyte resulted in the recovery of A.

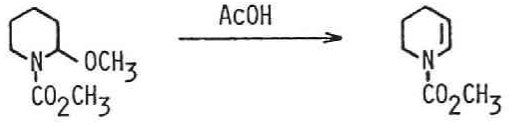
Reaction Mechanism of Anodic α, β-Diacetoxylation of N-Methoxycarbonylpiperidines. The acetoxylation of less reactive β-position of A may proceed through the following three steps (a-c), that is, (a) the formation of α-cation intermediate D by the anodic oxidation of A, (b) the conversion of D directly, or passing through α-acetoxylated compound E (Y=OAc) to α, β-unsaturated compound F, and (c) the subsequent anodic oxidation of F to diacetoxylated product H through the formation of dicationic intermediate G, as shown in Scheme 2.

Scheme 2



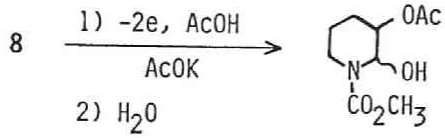
The α-acetoxylated intermediate E was, however, neither isolated,nor observed the existence throughout the anodic oxidation. Accordingly, the direct formation of F from D without the intervention of E is most likely.

Provided that the first intermediate E was generated, the acidic reaction conditions seemed to make E unstable. In fact, α-methoxy-N-methoxycarbonylpiperidine 8 was easily converted by treatment with acetic acid to α, β-unsaturated N-methoxycarbonylpiperidine 9a (eq 6).



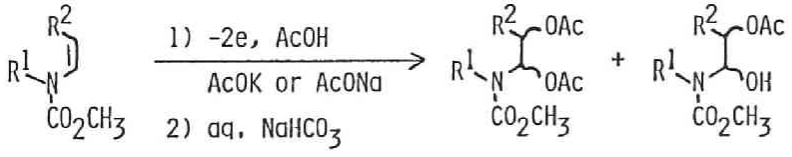
8 9a (6)

Also, 8 was converted to α, β-disubstituted compound 3a by the anodic oxidation in acetic acid (eq 7).



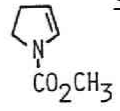
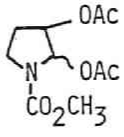
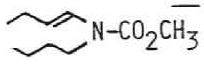
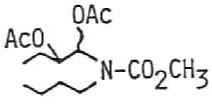
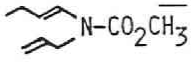
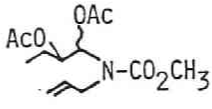
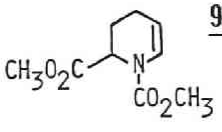
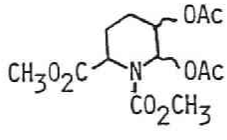
3a, 62% (7)

Although F was also not observed, its intermediary formation is reasonable since the anodic oxidation of independently prepared α, β-unsaturated compounds 9a-e [3e, f] in acetic acid also gave 2a, 10b-e and/or 3a (eq 8).[6] Yields of these products are shown in Table 2.[5]



9a-e 2a, 10b-e 3a (8)

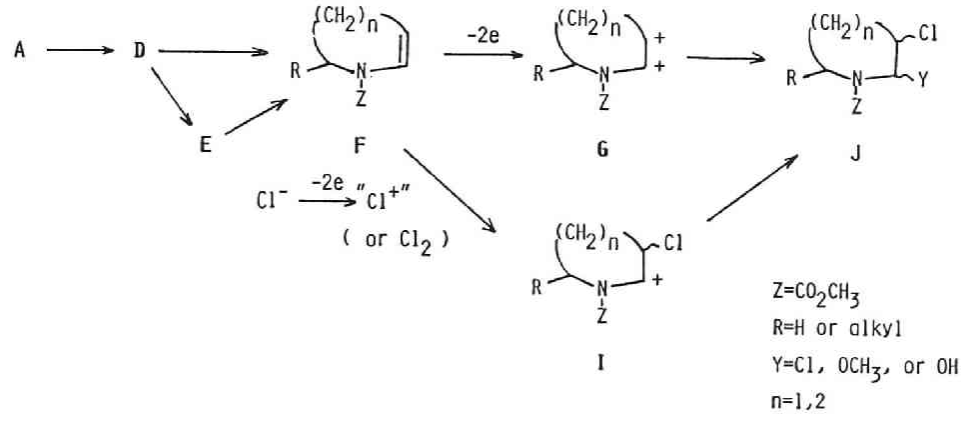
Table 2. Anodic Oxidation of α, β-Unsaturated Compounds 9a-e[a]

Run	Compound	Supporting Electrolyte	Isolated Yield(%)
1	9a	AcOK	2a(65) 3a(22)
2	 9b	AcONa	 10b(55)
3	 9c	AcONa	 10c(76)
4	 9d	AcONa	 10d(83)
5	 9e	AcOK	 10e(75)

[a] The workup was carried out by method b. See text.

Reaction Mechanism of Anodic β-Chlorination of N-Methoxycarbonyl-piperidines and -pyrrolidines. The anodic α-methoxyl-, or α-hydroxyl-β-chlorination may also proceed in a similar mechanism to the anodic α, β-diacetoxylation except step c (Scheme 3). Thus, the intermediate F may be generated in situ directly from D, or passing through E (Y=OMe,OH, or Cl).[7]

Scheme 3

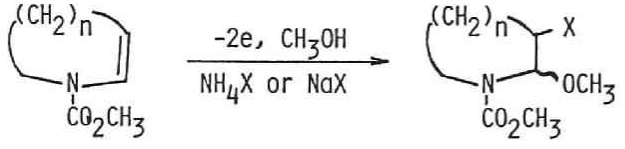


The intervention of F was strongly suggested by the facts that the anodic oxidation of independently prepared 9a in a reaction system of aqueous CH_3CN-NH_4Cl and CH_2Cl_2-Et_4NOTs gave the β-chlorinated product 4a in 79% and 34% yield, respectively, and that 7 was prepared by anodic oxidation of 9a in methanol containing NH_4Cl with 82% yield.

Although the β-chlorination of F seems to be explainable by the similar mechanism to the α, β-diacetoxylation in which the direct oxidation of F generates dication intermediate G, the attack of *Cl+*[9] or Cl_2 generated by anodic oxidation of Cl^-,[10] on F followed by the conversion of the intermediate cation I to J is more plausible[12] since β-chlorination of α, β-unsaturated compound F (9a) was achieved by treating F with tert-butylhypochlorite (eq 9),[5] and it has well been known that *Cl+* or Cl_2 generated anodically from Cl^- attaks on alkenes.[11b, 13]

$$9a \xrightarrow[CH_3OH]{t\text{-}C_4H_9OCl} \underset{70\%}{7} \qquad (9)$$

This mechanism suggests that the anodic oxidation of F in the presence of Br^- or I^- makes β-bromination and β-iodination of F possible, since Br^- and I^- are more easily oxidizable than Cl^-.[14] Thus, the anodic oxidation of 9a,b,f under the reaction conditions shown in eq 10 gave β-brominated and β-iodinated products 11, 12, and 13.[5]

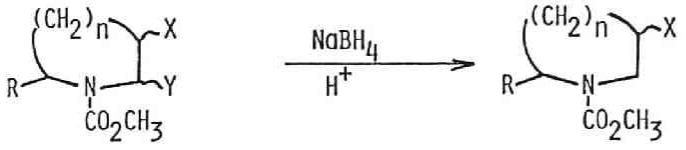


(10)

9b, n=1
9a, n=2
9f, n=3

11p, n=1, X=Br, 42% from 9b
11q, n=1, X=I, 38% from 9b
12p, n=2, X=Br, 81% from 9a
12q, n=2, X=I, 81% from 9a
13p, n=3, X=Br, 70% from 9f
13q, n=3, X=I, 66% from 9f

Reductive Elimination of α-Substituents of B and Synthesis of racemic Conium Alkaloids. α-Substituents (Y) of B (2a,b, 3c, 6b, 4a and 10b,e) were easily removable by reduction with $NaBH_4$ under acidic conditions (eq 11).[5]



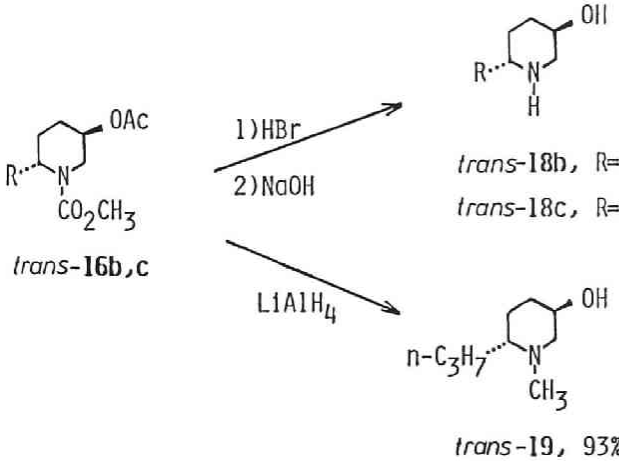
(11)

B C

10b, n=1, X=Y=OAc, R=H	14, n=1, X=OAc, R=H,	82% from 10b
6b, n=1, X=Cl, Y=OH, R=CO_2CH_3	15, n=1, X=Cl, R=CO_2CH_3,	46% from 6b
2a, n=2, X=Y=OAc, R=H	16a, n=2, X=OAc, R=H,	92% from 2a
2b, n=2, X=Y=OAc, R=CH_3	16b, n=2, X=OAc, R=CH_3,	84% from 2b
3c, n=2, X=OAc, Y=OH, R=n-C_3H_7	16c, n=2, X=OAc, R=n-C_3H_7,	78% from 3c
10e, n=2, X=Y=OAc, R=CO_2CH_3	16e, n=2, X=OAc, R=CO_2CH_3,	93% from 10e
4a, n=2, X=Cl, Y=OH, R=H	17, n=2, X=Cl, R=H,	80% from 4a

The stereoconfiguration of C was easily determined by GLC method except a proline derivative 15. The ratios of trans to cis were 8:2 in 16b and 9:1 in 16c.[15] The synthesis of racemic Conium alkaloids and the related compounds was easily achievable starting from 16. Hydrolysis of trans-16b with 47% HBr followed by treatment with aqueous NaOH gave trans-β-hydroxy-α-methylpiperidine, trans-18b.

Similar hydrolysis of trans-16c gave pseudoconhydrine, trans-18c. Also, reduction of trans-16c with $LiAlH_4$ gave N-methylpseudoconhydrine, trans-19 (eq 12). In conclusion, the synthesis of racemic Conium alkaloids, trans-18c and trans-19, was achieved almost diastereoselectively starting from A.



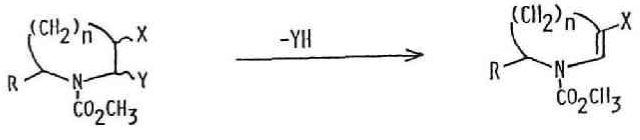
trans-18b, R=CH_3, 59% from *trans*-16b

trans-18c, R=n-C_3H_7, 58% from *trans*-16c

(12)

trans-19, 93% from *trans*-16c

Transformation of B to β-Acetoxylated or -Halogenated α, β-Unsaturated Compounds and β-Oxo Compounds. Heating α, β-disubstituted compounds B (2a,b, 3c, 4a, 6b, 10e, and 12p) easily gave β-substituted α ,β-unsaturated compounds (20-23) (eq 13).



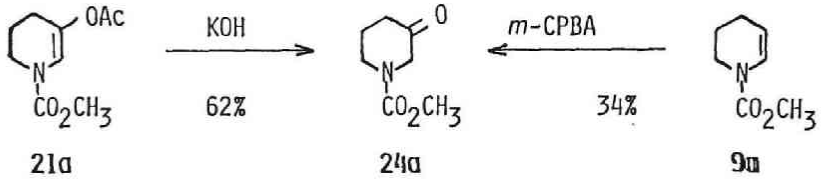
(13)

B

6b, n=1, X=Cl, Y=OH, R=H
2a, n=2, X=Y=OAc, R=H
2b, n=2, X=Y=OAc, R=CH_3
3c, n=2, X=OAc, Y=OH, R=n-C_3H_7
10e, n=2, X=Y=OAc, R=CO_2CH_3
12p, n=2, X=Br, Y=OCH_3, R=H
4a, n=2, X=Cl, Y=OH, R=H

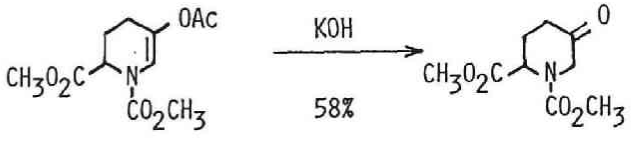
20, n=1, X=Cl, R=H, 94% from 6a
21a, n=2, X=OAc, R=H, 100% from 2a
21b, n=2, X=OAc, R=CH_3, 100% from 2b
21c, n=2, X=OAc, R=n-C_3H_7, 100% from 3c
21e, n=2, X=OAc, R=CO_2CH_3, 87% from 10e
22, n=2, X=Br, R=H, 96% from 12p
23, n=2, X=Cl, R=H, 76% from 4a

Furthermore, the β-substituted α, β-unsatureted compounds were good precursers for β-oxo compounds as exemplified by the synthesis of β-oxopiperidine derivatives 24a,e. The oxidation of 9a with m-CPBA was found to be an alternative route to 24a (eqs 14 and 15).



(14)

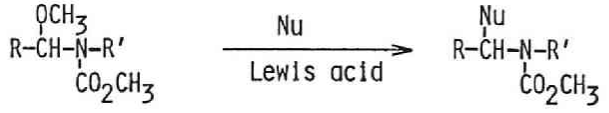
21a 24a 9a



(15)

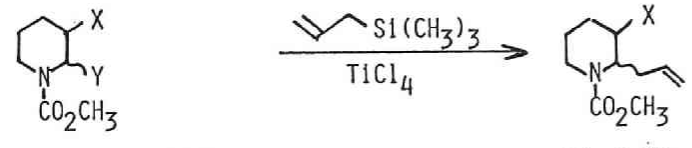
21e 24e

Substutution at the α-Position of B. Methods for the substitution of the α-methoxy group of α-methoxylated compounds K with a variety of nucleophiles (Nu) have already been exploited (eq 16).[3, 16]



K (16)

Application of these methods to B led to the facile preparation of a variety of α-substituted β-acetoxyl- or β-halogeno compounds. For example, allylation at the α-position of 3a and 12p according to the reported conditions[4] gave α-allylated compounds 25 and 26, respectively (eq 17).[5]



(17)

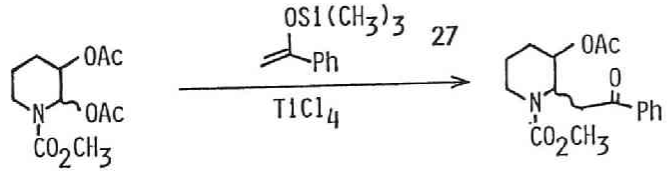
3a, X=OAc, Y=OH

12p, X=Br, Y=OCH_3

25, X=OAc, 68%

26, X=Br, 82%

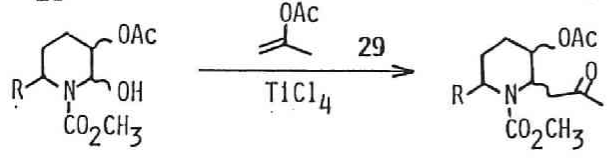
Also, the reaction of 2a or 3a,b with enol ether 27 or enol ester 29 afforded α-substituted products 29 or 30a,b (eqs 18 and 19).[5]



(18)

2a

28, 42%



(19)

3a,b

30a, R=H, 70%

30b, R=CH_3, 72%

Experimental Section

Anodic Oxidation. Anodic oxidation was carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Ltd. A glass beaker (50mL) equipped with Pt plate anode (20mm x 20mm) and carbon rod cathode (8mmφ) was used as an electrolysis cell.

Materials. The preparation of 1a,b,[2] 5a,[3f] 8,[2] 9a-d,[3f] and 9e,[17] has been reported. Compounds 1d and 9f were prepared according to the reported method.[3]

α-Acetonyl-N-methoxycarbonylpiperidine (1d) was prepared by the reaction of 8 with isoprppenyl acetate (29) in the presence of $TiCl_4$ in 69% yield: IR (neat) 2950, 2920, 1700, 1452, 1270, 1175, 762cm^{-1}; NMR (CCl_4) δ 1.46 (br s, 6H), 2.16 (s, 3H), 2.48 (d, J=7Hz, 2H), 2.85 (dt, J=3 and 14Hz, 1H), 3.67 (s, 3H), 3.96 (dd, J=14 and 3Hz, 1H), 4.52-4.83 (m, 1H). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.42; H, 8.75; N, 6.74.

N-Methoxycarbonylaza-2-cycloheptene (9f):86% yield from the corresponding α-methoxylated compound;[3h] bp 94-95℃ (25mm); IR (neat) 2940, 2860, 1712, 1655, 1448, 1220, 788cm^{-1}; NMR (CCl_4) δ 1.55-1.92 (m, 4H), 2.09-3.34 (m, 2H), 3.59-3.84 (m, 2H), 3.71 (s, 3H), 4.88 (dt, J=9 and 6Hz, 1H), 6.51 (br d, J=9Hz, 1H). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.64; H, 8.72; N, 8.81.

N-Methoxycarbonyl- α-propylpiperidine (1c) was prepared by the $TiCl_4$-catalyzed reaction of 8 with allyltrimethylsilane followed by hydrogenation

in 82% yield or by the reaction of 8 with propylmagnesium bromide in the presence of $BF_3.OEt_2$ in 45% yield:[18] IR (neat) 2935, 2865, 1685, 1445, 1370, 1260, 1180, 1148, 1090, 767cm^{-1}; NMR (CCl_4) δ 0.93 (t, J=6Hz, 3H), 1.10-1.92 (m, 10H), 2.78 (dt, J=12 and 3Hz), 3.60 (s, 3H), 3.81-4.40 (m, 2H). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.96; H, 10.64; N, 7.58.

Anodic Oxidation of 1a-d in AcOH Containing AcOK. A general procedure for α, β-diacetoxylation of 1a-d is exemplified by the anodic oxidation of 1a. Into an electrolysis cell as described above was added a solution of 1a (2.145g, 15mmol) and AcOK (3.0g, 30.6mmol) in acetic acid (30mL). After 12F/mol of electricity was passed at a constant current of 0.4A (12h, terminal voltage; ca.35 V) through the solution cooled with water, aqueous $NaHCO_3$ was added into the reaction mixture cooled ice-water (method b in Table 1, Run 2), and the organic portion was extracted with CH_2Cl_2 (30mLx4). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:1) to afford α, β-diacetoxy-N-methoxycarbonylpiperidine (2a) in 61% yield and β-acetoxy-α-hydroxy-N-methoxycarbonylpiperidine (3a) in 20% yield.

On the other hand, working up the reaction mixture by stirring with water at room temperature for 6h (method a in Table 1, Run 1) afforded only 3a in 88% yield (20F/mol). NMR spectra showed that 2a was a mixture of trans and cis isomer (2:1),[2] and 3a was a mixture of trans and cis isomers (1:1).

2a: IR (neat) 2953, 2880, 1740, 1708, 1442, 1368, 1238, 1222, 1160, 1044, 769cm^{-1}; NMR (CCl_4) δ 1.42-1.98 (m, 4H), 1.91 (s, 3H), 2.02 (s, 3H), 2.60-3.33 (m, 1H), 3.61-4.13 (m, 1H), 3.68 (s, 3H), 4.51-4.91 (m, 1H), 6.31

and 6.71 (2d, J=4 and 6Hz, 1/3 H and 2/3 H). Anal.Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40.Found: C, 51.10; H, 6.87; N, 5.40.

3a: IR (neat) 3440, 2953, 2865, 1738, 1698, 1450, 1367, 1242, 1155, 1052, 1002, 775cm^{-1}; NMR (CCl_4) δ 1.23-2.00 (m, 4H), 2.03 (s, 3H), 2.86-3.33(m, 1H), 3.66 (s, 3H), 3.60-3.93 (m, 1H), 4.43-5.30 (m, 2H), 5.47 and 5.70 (2d, J=3 and 4 Hz, 1/2 H and 1/2 H). Anal.Calcd for $C_9H_{15}NO_5$: C, 49.76 ; H, 6.96;N, 6.45. Found: C, 49.47; H, 6.97; N, 6.31.

Similarly, the anodic oxidation (20F/mol of electricity) of 1b followed by the workup (method b in Table 1, Run 4) gave 2b and 3b in 34 and 45% yields, respectively, while the workup (method a in Table 1, Run 3) gave only 3b in 92% yield. Similar anodic oxidation of 1c,d gave 3c,d. The stereochemistry of 2b and 3b-d could not be determined on the basis of their NMR spectra.

α, β-Diacetoxy-N-methoxycarbonyl- α'-methylpiperidine (2b): IR (neat) 2955, 1746, 1718, 1445, 1372, 1315, 1240, 1208, 785cm^{-1}; NMR (CCl_4) δ 1.03-2.27 (m, 4H), 1.18 (d, J=6Hz, 3H), 1.95, 2.03, and 2.07 (3s, 6H), 3.77 (s, 3H9, 4.06-4.51 (m, 1H), 4.70-4.91 (m, 1H), 6.46 and 6.76 (2d, J=1 and 3Hz, 1/4H and 3/4H). Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.98; H, 7.23; N, 5.17.

β-Acetoxy- α-hydroxy-N-methoxycarbonyl- α'-methylpiperidine (3b): IR (neat) 3450, 2965, 1740, 1702, 1688, 1456, 1375, 1242, 1034, 780 cm^{-1}; NMR (CCl_4) δ 1.15-2.27 (m, 4H), 1.27 (d, J=8Hz, 3H), 2.02 (s, 3H), 3.68 (s, 3H), 3.96-4.38 (m, 2H), 4.62-4.90 (m, 1H), 5.40 and 5.60 (2d, J=3 and 4 Hz, 1/6H and 5/6H); MS, m/e 214 (M^+-OH), 171 (base); exact mass calcd m/e

214.1080 (M^+-OH), found 214.1095 (M^+-OH).

β-Acetoxy- α-hydroxy-N-methoxycarbonyl- α'-propylpiperidine (3c): 93% yield at 21F/mol (method a in Table 1, Run 5); IR (neat) 3430, 2970, 2880, 1740, 1712, 1456, 1240, 1052, 778 cm^{-1}; NMR (CCl_4) δ 0.93 (t, J=7Hz, 3H), 0.99-2.30 (m, 8H), 2.03 (s, 3H), 3.53-4.24 (m, 1H), 3.68 (s, 3H), 4.41-4.90 (m, 1H), 5.43 and 5.67 (2d, J=3 and 4Hz, 1/4H and 3/4H), 6.13 (br s, 1H). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.34; H, 8.33; N, 5.41.

α'-Acetonyl- β-acetoxy- α-hydroxy-N-methoxycarbonylpiperidine (3d): 53% yield at 18F/mol (method a in Table 1, Run 6); IR (neat) 3400, 2950, 2865, 1740, 1680, 1452, 1378, 1246, 1030, 790 cm^{-1}; NMR (CCl_4) δ 1.20-2.24 (m, 4H), 2.01 (s, 3H), 2.11 (s, 3H), 2.77 (d, J=6Hz, 2H), 3.64 (br s, 1H), 3.66 (s, 3H), 4.28-4.87 (m, 2H), 5.42 and 5.66 (2d, J=3 and 4Hz, 1/6H and 5/6H). Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.64; H, 6.95; N, 4.85.

Anodic Oxidation of 1a,b and 5a,b in Aqueous MeCN Containing NH_4Cl. α-Hydroxy- β-chlorination of 1a,b and 5a,b in aqueous acetonitrile was carried out under the following conditions. Into an electrolysis cell as described above was added a solution of 1a (0.429g, 3mmol) and NH_4Cl (2.0g, 37.4mmol) in acetonitrile (30mL) and water (3mL). After 15F/mol of electricity was passed at a constant current of 0.5A (2.4h, terminal voltage; ca. 45V) through the solution, water (30mL) was added to the electrolyzed solution and the organic portion was extracted with CH_2Cl_2 (25mLx4). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:1) to afford

β-chloro-α-hydroxy-N-methoxycarbonylpiperidine (4a) in 57% yield. By the similar procedure were obtained 4b and 6a,b from 1b and 5a,b, respectively. Although these products consisted of stereoisomers, their ratios could not be determined.

4a: IR (neat) 3360, 2954, 2860, 1700, 1680, 1444, 1260, 1037, 768 cm^{-1}; NMR (CCl_4) δ 1.26-2.62 (m, 4H), 2.86-3.43 (m, 1H), 3.53-4.47 (m, 3H), 3.73 (s, 3H), 5.60-5.99 (br s, 1H), Anal. Calcd for $C_7H_{12}NO_3Cl$: C, 43.42, H, 6.25; N, 7.23; Cl, 18.31. Found: C, 43.52; H, 6.27; N, 7.17; Cl, 18.46.

β-Chloro-α-hydroxy-N-methoxycarbonyl- α'-methylpiperidine (4b): 47% yield at 15F/mol; IR (neat) 3400, 2950, 1708, 1442, 1090, 975, 788, 732 cm^{-1}; NMR (CCl_4) δ 1.15 (d, J=7Hz, 3H), 1.43-1.77 (m, 2H), 1.90-2.49 (m, 2H), 3.31 (br s, 1H), 3.79 (s, 3H), 4.05-4.56 (m, 2H), 5.90 (br s, 1H); MS, m/e 209, 207 (M^+), 194, 192 (base), 154; exact mass calcd m/e 207.0662, found 207.0648.

β-Chloro-α-hydroxy-N-methoxycarbonylpyrrolidine (6a): 47% yield at 20F/mol; mp 60-61 °C (from ether); IR (neat) 3500, 2968, 2905, 1692, 1458, 1387, 1208, 1126, 1030, 778 cm^{-1}; NMR ($CDCl_3$) δ 1.84-2.85 (m, 2H), 3.49 (br d, J=4Hz, 1H), 3.63 (br s, 1H), 3.72 (s, 3H), 4.17 (br d, J=4Hz, 1H), 5.21 (br s, 1H), 5.39 (br s, 1H). Anal. Calcd for $C_6H_{10}NO_3Cl$: C, 40.12; H, 5.61; N, 7.80; Cl, 19.74. Found: C, 40.07; H, 5.65; N, 8.00; Cl, 19.53.

β-Chloro-α',N-dimethoxycarbonyl-α-hydroxypyrrolidine (6b): 68% yield at 50F/mol; IR (neat) 3450, 2975, 1730, 1705, 1459, 1383, 1208, 1137, 1052, 1020, 780 cm^{-1}; NMR (CCl_4) δ 2.13-2.93 (m, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 4.12-5.40 (m, 3H), 5.67 (br s, 1H). Anal. Calcd for $C_8H_{12}NO_5Cl$:

C, 40.43; H, 5.09; N, 5.89; Cl, 14.92. Found: C, 40.41; H, 5.36; N, 5.66; Cl, 14.71.

Anodic Oxidation of 1a,b in CH_2Cl_2 Containing Et_4NOTs. Into an electrolysis cell as described above added a solution of 1a (0.429g, 3mmol) and Et_4NOTs (0.15g, 0.5mmol) in CH_2Cl_2 (10mL). After 5F/mol of electricity was passed at a constant current of 0.3A (1.4h, terminal voltage; ca. 30V) through the solution, the usual workup gave 4a in 31% yield. Similarly, 4b was obtained from 1b in 61% yield (11.2F/mol).

Anodic Oxidation of 1a in MeOH Containing NH_4Cl. Into an electrolysis cell as described above was added a solution of 1a (2.145g, 15mmol) and NH_4Cl (1.17g, 21.9mmol) in MeOH (40mL), and 15F/mol of electricity was passed at a constant current of 1A (6.4h, terminal voltage; ca. 12V) through the solution. After the solvent was removed in vacuo without heating, water (30 mL) was added to the residue, and the organic portion was extracted with CH_2Cl_2 (25mLx4). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt: hexane=1:5) to afford β-chloro-α-methoxy-N-methoxycarbonylpiperidine (7) in 90% yield. NMR spectrum showed that 7 was a mixture of stereoisomers (trans:cis=4:1).[20] The ratio was determined on the basis of the strength of peaks of the α-methoxy group.

7: IR (neat) 2970, 1710, 1452, 1279, 1182, 1085, 965, 949, 774, 706 cm^{-1}; NMR (CCl_4) δ 1.24-2.32 (m, 4H), 2.91 (br t, J=12 Hz, 1H), 3.29 and 3.35 (2s, 12/5H and 3/5H), 3.60-4.21 (m, 2H), 3.72 (s, 3H), 5.31 (br s, 1H); MS, m/e 209, 207 (M^+), 178, 176 (base); exact mass calcd m/e 207.0663, found 207.0687. Anal. Calcd for $C_8H_{14}NO_3Cl$: C, 46.27; H, 6.80; N, 6.75; Cl,

17.07. Found: C, 46.74; H, 7.04; N, 6.69; Cl; 16.67.

Transformation of 8 to 9a. A solution of 8 (1.039g, 6.0mmol) in AcOH (50mL) was stirred at room tmperature. After 12h, the solution was poured into aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, and subjected to column chromatography on silica gel (AcOEt:hexane= 1:5) to afford 9a in quantitative yield.

Transformation of 8 to 3a. Compound 3a was obtained from 8 in 62% yield at 7F/mol, by the procedure similar to the anodic diacetoxylation of 1a-d in AcOH containing AcOK (workup: method a).

Anodic Oxidation of 9a-e in AcOH. α, β-Diacetoxylation of 9a-e was achieved under conditions similar to the anodic oxidation of 1a-d in AcOH. After the workup (method b), products were isolated by column chromatography (silica gel). The yields of 2a and 3a were 65 and 22% yields (6F/mol), respectively. The ratios of trans to cis of 2a and 3a were identical with those of 2a and 3a obtained by the anodic oxidation of 1a. The stereochemistry of products 10b-e could not be determined.

α, β-Diacetoxy-N-methoxycarbonylpyrrolidine (10b): 55% yield at 3.8 F/mol; IR (neat) 2954, 1720, 1448, 1392, 1240, 1206, 1018, 952, 775 cm^{-1}; NMR (CCl_4) δ 1.83-2.23 (m, 2H), 2.01 (s, 3H), 2.06 (s, 3H), 3.23-3.60 (m, 2H), 3.67 (s, 3H), 4.86-5.10 (m, 1H), 6.21-6.77 (m, 1H); MS, m/e 202 (M^+-Ac), 186, 173, 160, 143 (base); exact mass calcd m/e 202.0715, found 202.0713.

N-(α, β-Diacetoxy)butyl-N-methoxycarbonylbutylamine (10c): 76% yield

at 4.2 F/mol; IR (neat) 2952, 2876, 1732, 1695, 1452, 1370, 1218, 1018, 775 cm^{-1}; NMR (CCl_4) δ 0.80-1.08 (m, 6H), 1.12-1.76 (m, 6H), 1.99 (s, 3H), 2.01 (s, 3H), 3.00-3.04 (m, 2H), 3.70 and 3.72 (2s, 3H), 4.97-5.26 (m, 1H), 6.39 (d, J=9Hz, 1H). Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.43; H, 8.31; N, 4.62. Found: C, 55.39; h, 8.53; N, 4.78.

N-(α, β-Diacetoxy)butyl-N-methoxycarbonylallylamine (10d): 83% yield at 5.9F/mol; IR (neat) 3080, 2972, 2880, 1732, 1705, 1450, 1370, 1312, 1220, 1020, 772 cm^{-1}; NMR (CCl_4) δ 0.85 and 0.90 (2t, J=8 and 9Hz, 3H), 1.24-1.80 (m, 2H), 1.95 (s, 3H), 1.98 (s, 3H), 3.67 (s, 3H), 3.71-3.88 (m, 2H), 4.90-5.30 (m, 3H), 5.51-6.03 (m, 1H), 6.34 (d, J=9Hz, 1H). Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.37; N, 4.88; Found: C, 54.20; H, 7.42; N, 4.85.

α, β-Diacetoxy- α',N-dimethoxycarbonylpiperidine (10e). 75% yield at 7F/mol; IR (neat) 2975, 1740, 1452, 1378, 1205, 1030, 1018 cm^{-1}; NMR (CCl_4) δ 1.64-2.35 (m, 4H), 2.03 (s, 3H), 2.10 m (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 4.91 (br s, 2H), 6.63-6.84 (m, 1H). Anal. Calcd for $C_{13}H_{19}NO_8$: C, 49.21; H, 6.04; N, 4.41. Found: C, 48.94; H, 6.15; N, 4.11.

α-Hydroxy- or α-Methoxy- β-chlorination of 9a. Compound 9a was transformed into 4a by the anodic oxidation similar to that of 1a in aqueous acetonitrile containing NH_4Cl (79%yield at 3.5 F/mol) or CH_2Cl_2 containing Et_4NOTs (34% yield at 6F/mol). Compound 7 was obtained from 9a by the similar anodic oxidation of 1a in MeOH containg NH_4Cl (82% yield at 6F/mol).

Transformation of 9a into 7 with tert-BuOCl in MeOH. Into a solution of 9a (2.822g, 20mmol) in methanol (30mL) at room temperature was added dropwise tert-butyl hypochlorite (2.98 mL, 25mmol) in a period of 2min.

After the solution was stirred for 10min, the usual workup afforded 7 (trans :cis=4:1) in 70% yield. NMR spectrum of 7 obtained by this method was identical with that of 7 obtained by anodic method of 1a.

Anodic Oxidation of 9a,b,f in MeOH Containing NH_4X or NaX. α-Methoxy-β-bromination and β-iodination of 9a,b,f in methanol were carried out by the procedures as exemplified by β-bromination of 9b. Into an electrolysis cell as described above was added a solution of 9b (0.636g, 5mmol) and NH_4Br (0.735g, 7.5mmol) in methanol (20mL), and 3.5F/mol of electricity was passed at a constant current of 0.3A (1h, terminal voltage; ca. 6V) through the solution. After the solvent was removed in vacuo without heating, aqueous $Na_2S_2O_3$ (20mL) was added to the residue, and the organic portion was extracted with CH_2Cl_2 (15mLx4). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt: hexane=1:5) to afford β-bromo- α-methoxy-N-methoxycarbonylpyrrolidine (11p) in 42% yield. Compounds 11q, 12p,q, and 13p,q were obtained according to the similar procedures. NMR spectra showed that 11p,q, 12q, and 13p,q were almost trans isomer, while 12p was a mixture of stereoisomers (trans:cis=5:1).[20]

11p: IR (neat) 2955, 1718, 1450, 1200, 1180, 1122, 1080, 778 cm^{-1}; NMR (CCl_4) δ 1.93-2.84 (m, 2H), 3.26-3.84 (m, 2H), 3.39 (s, 3H), 3.74 (s, 3H), 4.16 (br d, J=5Hz, 1H), 5.09-5.34 (m, 1H). Anal. Calcd for $C_7H_{12}NO_3Br$: C, 35.31; H, 5.08; N, 5.88; Br, 33.56. Found: C, 35.52; H, 5.07; N, 5.59; Br, 33.81.

β-Iodo-α-methoxy-N-methoxycarbonylpyrrolidine (11q): 38% yield at 5F/mol (supporting electrolyte: NH_4I); IR (neat) 2960, 1715, 1452, 1380,

1112, 1080, 958, 780 cm^{-1}; NMR (CCl_4) δ 2.03-2.81 (m, 2H), 3.20-3.80 (m, 2H), 3.34 (br s, 3H), 3.74 (s, 3H), 4.16 (br d, J=5Hz, 1H), 5.16-5.43 (m, 1H). Anal.Calcd for $C_7H_{12}NO_3I$: C, 29.49; H, 4.24; N, 4.91; I, 44.52. Found: C, 29.67; H, 4.30; N, 4.97; I, 44.52.

β-Bromo- α-methoxy-N-methoxycarbonylpiperidine (12p): 81% yield at 3.5F/mol (supporting electrolyte: NH_4Br); IR (neat) 2952, 1712, 1448, 1272, 1160, 1082, 968, 952, 778 cm^{-1}; NMR (CCl_4) δ 1.29-2.45 (m, 4H), 2.95 (br t, J=12Hz, 1H), 3.27 and 3.36 (2s, 5/2H and 1/2H), 3.63-4.63 (m, 2H), 3.74 (s, 3H), 5.44 (br s, 1H); MS, m/e 253, 251 (M^+), 222, 220 (base); exact mass calcd m/e 251.0157, found 251.0146.

β-Iodo-α-methoxy-N-methoxycarbonylpiperidine (12q): 81% yield at 4.0F/mol (supporting electrolyte: NH_4I); IR (neat) 2950, 1712, 1448, 1258, 1200, 1152, 1072, 940 cm^{-1}; NMR (CCl_4) δ 1.34-2.24 (m, 4H), 2.97 (br t, J= 12Hz, 1H), 3.26 (s, 3H), 3.75 (s, 3H), 3.79-4.14 (m, 1H), 4.41 (br s, 1H), 5.44 (br s, 1H); MS, m/e 268 (M^+-OMe), 172, 158 (base); exact mass calcd m/e 267.9837, found 267.9856.

β-Bromo- α-methoxy-N-methoxycarbonylazacycloheptane (13p): 70% yield at 5.0F/mol (supporting electrolyte: NaBr); IR (neat) 2948, 2855, 1703, 1438, 1335, 1118, 1095, 1085, 1010, 955, 776 cm^{-1}; NMR (CCl_4) δ 1.13-2.31 (m, 6H), 2.59-3.96 (m, 3H), 3.28 (s, 3H), 3.74 (s, 3H), 5.25-5.61 (m, 1H); MS, m/e 267, 265 (M^+), 236, 234, 208, 206, 186, 154, 144, 128 (base); exact mass calcd m/e 265.0314, found 265.0302.

β-Iodo-α-methoxy-N-methoxycarbonylazacycloheptane (13q): 66% yield at 4.5F/mol (supporting electrolyte: NaI); IR (neat) 2940, 2850, 1700,

1436, 1338, 1137, 1105, 1088, 1068, 1003, 943, 770 cm^{-1}; NMR (CCl_4) δ 1.23-2.51 (m, 6H), 2.69-3.09 (m, 1H), 3.18-4.13 (m, 2H), 3.32 (s, 3H), 3.79 (s, 3H), 5.36-5.73 (m, 1H); MS, m/e 313 (M^+), 282, 254, 196, 186 (base); exact mass calcd m/e 313.0176, found 313.0151.

Reduction of 2a,b, 3c, 4a, and 10b. A general procedure is exemplified by reduction of 10b. Into a solution of 10b (0.238g, 0.97mmol) in acetic acid (4mL) was added in portions 90% $NaBH_4$ (0.184g, 4.36mmol). After 1.5h, aqueous $NaHCO_3$ (20mL) was poured into the reaction mixture and the organic portion was extracted with CH_2Cl_2 (20mLx4). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the redisue was chromatographed on silica gel (AcOEt:hexane=1:2) to afford β-acetoxy-N-methoxycarbonylpyrrolidine (14) in 82% yield.

14: IR (neat) 2955, 2890, 1741, 1710, 1458, 1395, 1248, 1202, 775 cm^{-1}; NMR (CCl_4) δ 1.83-2.29 (m, 2H), 2.07 (s, 3H), 3.09-3.84 (m, 4H), 3.66 (s, 3H), 5.15-5.49 (m, 1H). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.00. Found: C, 51.05; H, 6.99; N, 7.20.

The reduction of 2a,b, 3c, and 4a under the similar conditions gave 16a,b,c, and 17, respectively. Compounds 16b,c consisted of mixtures of stereoisomers. The GLC (Silicon DC 550) and NMR spectra showed that the ratios of stereoisomers of 16b and 16c were 8:2 and 9:1, respectively. The main isomers (trans-isomers) of 16b,c could be separated by chromatography.

β-Acetoxy-N-methoxycarbonylpiperidine (16a): 92% yield from 2a; IR (neat) 2960, 2875, 1741, 1712, 1452, 1238, 1049, 776 cm^{-1}; NMR (CCl_4) δ

1.33-2.13 (m, 4H), 1.98 (s, 3H), 3.21-3.55 (m, 4H), 3.60 (s, 3H), 4.65-4.97 (m, 1H). Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.64; H, 7.63; N, 6.94.

β-Acetoxy-N-methoxycarbonyl- α'-methylpiperidine (trans:cis=8:2, 16b): 84% yield from 2b; IR (neat) 2960, 2865, 1740, 1452, 1372, 1235, 1165, 1027, 960, 942, 923, 873, 850, 825, 772 cm^{-1}; NMR (CCl_4) δ 1.17 (d, J=7Hz, 3H), 1.32-1.92 (m, 4H), 2.04 and 2.05 (2s, 12/5H and 3/5H), 2.78 (dd, J=15 and 11Hz, 1/5H), 3.05 (dd, J=15 and 2Hz, 4/5H), 3.69 and 3.71 (2s, 12/5 H and 3/5H), 4.10-4.92 (m, 3H). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.09; H, 8.18; N, 6.44.

trans-16b: NMR (400MHz, $CDCl_3$) δ 1.17 (d, J=7Hz, 3H), 1.32-1.92 (m, 4H), 2.04 (s, 3H), 3.05 (dd, J=15Hz and 2Hz, 1H), 3.69 (s, 3H), 4.15 (d, J= 15Hz, 1H), 4.50 (br s, 1H), 4.89 (br s, 1H).

β-Acetoxy-N-methoxycarbonyl- α'-propylpiperidine (trans:cis=9:1, 16c): 78% yield from 3c; IR (neat) 2950, 2860, 1736, 1695, 1444, 1368, 1230, 1158, 1020, 958, 840, 770 cm^{-1}; NMR (CCl_4) δ 0.93 (t, J=7Hz, 3H), 1.21-1.94 (m, 8H), 2.03 and 2.05 (2s, 27/10H and 3/10H), 2.69 (dd,J=13 and 11Hz, 1/10H), 2.97 (dd, J=15 and 2Hz, 9/10H), 3.68 and 3.69 (2s, 27/10H and 3/10H), 4.16-4.90 (m, 3H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.14; H, 8.87; N, 5.64.

trans-16c: NMR (400MHz, $CDCl_3$) δ 0.93 (t, J=7Hz, 3H), 1.26-1.81 (m, 8H), 2.03 (s, 3H), 2.97 (dd, J=15 and 2Hz, 1H), 3.68 (s, 3H), 4.18 (d, J=14 Hz, 1H), 4.32 (br s, 1H), 4.84 (br s, 1H).

β-Chloro-N-methoxycarbonylpiperidine (17): 80% yield from 4a; IR (neat) 2972, 2880, 1718, 1481, 1454, 1419, 1270, 1248, 1202, 1162, 1138,

972, 778, 770 cm^{-1}; NMR (CCl_4) δ 1.23-2.49 (m, 4H), 2.76-3.30 (m, 2H), 3.53-4.30 (m, 3H), 3.68 (s, 3H); MS, m/e 179, 177, 164, 162, 142, 102 (base); exact mass calcd m/e 177.0556, found 177.0543.

Reduction of 6a and 10e. The reduction of 6b and 10e required more acidic conditions. That is, into a solution of 10e (0.428g, 1.35mmol) and CF_3SO_3H (0.6mL, 6.75mmol) in acetic acid (10mL) was added in portions 90% $NaBH_4$ (1.134g, 27mmol). After stirred at room temperature for 2 days, the solution was worked up by usual method to give β-acetoxy- α',N-bis-(methoxycarbonyl)piperidine (16e) in 91% yield. GLC showed that 16e was a mixture of stereoisomers (9:1). On the other hand, the stereochemistry of β-chloro-α',N-bis(methoxycarbonyl)pyrrolidine (15) could not be determined on basis of GLC.

15: IR (neat) 2970, 1750, 1715, 1458, 1395, 1222, 1205, 1125, 1040, 718 cm^{-1};NMR (CCl_4) δ 1.91-3.10 (m, 2H), 3.47-4.70 (m, 4H), 3.76 (s, 3H), 3.80 (s, 3H). Anal. Calcd for $C_8H_{12}NO_4Cl$: C, 43.35; H, 5.46; N, 5.32; Cl, 16.00. Found: C, 43.10; H, 5.29; N, 6.45; Cl, 15.76.

16e: IR (neat) 2965, 1738, 1705, 1452, 1374, 1236, 1158, 1124, 1028 cm^{-1}; NMR (CCl_4) δ 1.38-2.21 (m, 4H), 2.04 (s, 3H), 3.11-3.41 (m, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.96-4.37 (m, 1H), 4.92 (br s, 2H). Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.18; H, 6.75; N, 5.30.

Synthesis of (±)-Pseudoconhydrine (trans-18c). A solution of trans-16c (0.243g, 1mmol) in 47% aqueous HBr was refluxed for 2h. Into the mixture was poured aqueous NaOH until the solution became to be pH 9 and the

organic portion was extracted with AcOEt (20mLx4). After the extract was dried over $MgSO_4$, the solvent was evaporated to give a redisue, which was distilled with kugel rohr to give trans-18c in 58% yield. The similar procedure yielded trans-18b from trans-16b in 59% yield. The spectroscopic data of trans-18b,c were identical with those of reported authentic samples.[15a, b]

Synthesis of (±)-N-Methylpseudoconhydrine (trans-19). Into a solution of trans-16c (0.243g, 1mmol) in ether (10mL) was added in portions LAH (0.076g, 2mmol) and the solution was refluxed for 3h. After the solution was quenched with water, the organic portions was extracted with AcOEt (15mLx4). The extract was dried over $MgSO_4$ and the solvent was removed by distillation to afford trans-19[4b] in 93% yield.

Transformation of 4a, 6b, 10e, and 12p to 20, 21e, 22, and 23. A mixture of 29a (0.332g, 1.85mmol) and NH_4Cl (0.01g, 0.19mmol) was heated (100 °C) under an atmosphere of nitrogen with reduced pressure (22mm) for 3h. After the reaction was completed, β-chloro-N-methoxycarbonyl-2-pyrroline (20) was isolated by kugel rohr distillation in 94% yield. β-Bromo- α, β-didehydro-N-methoxycarbonylpiperidine (22) was prepared in 96% yield by heating (225°C) 12p under reduced pressure (45mm). Also, β-acetoxy- α, β-didehydro- α',N-bis(methoxycarbonyl)piperidine (21e) was prepared in 87% yield by heating (165 °C) 10e under reduced pressure (16mm). On the other hand, 4a was transformed into β-chloro-α, β-didehydro-N-methoxycarbonylpiperidine (23) by heating (120 °C) without NH_4Cl in 76% yield.

20: bp 140°C (22mm); IR (neat) 2970, 2915, 1718, 1459, 1390, 1200, 1132 cm^{-1}; NMR (CCl_4) δ 1.97 (tt, J=6 and 6Hz, 2H), 2.46 (t, J=6Hz, 2H),

3.59 (t, J=6Hz, 2H), 3.75 (s, 3H), 7.12 (br s, 1H). Anal. Calcd for $C_7H_{10}NO_2Br$: C, 38.21; H, 4.58; N, 6.36; Br, 36.31. Found: C, 38.31; H, 4.56; N, 6.19; Br, 36.04.

23: bp 150-160 ℃ (2mm); IR (neat) 3100, 2951, 2872, 1713, 1657, 1442, 1190, 968, 914, 760, 690 cm^{-1}; NMR (CCl_4) δ 1.91 (t, J=6Hz, 2H), 2.33 (t, J=6Hz, 2H), 3.54 (t, J=6Hz, 2H), 3.73 (s, 3H), 6.93 (br s, 1H); MS, m/e 177, 175 (base, M^+), 140; exact mass calcd m/e 175.0400, found 175.0404.

21e: bp 165 ℃ (22mm); IR (neat) 3020, 2960, 1755, 1720, 1448, 1360, 1220, 1200, 772 cm^{-1}; NMR ($CDCl_3$) δ 1.90-2.60 (m, 4H), 2.15 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.76-5.07 (m, 1H), 7.06 (br d, J=10Hz, 1H). Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.46. Found: C, 51.33; H, 5.91; N, 5.49.

Synthesis of 21a-c from 2a,b or 3c. A solution of 2a,b or 3c (5mmol) in acetic acid (10mL) was refluxed in flask equipped with a reflux condenser. After 10min, acetic acid was distilled and the residue was chromatographed on silica gel (AcOEt:hexane=1:5) to afford 21a-c in quantitative yields.

β-Acetoxy- α, β-didehydro-N-methoxycarbonylpiperidine (21a): IR (neat) 3113, 2950, 2876, 1748, 1693, 1442, 1392, 1358, 1220, 1192, 1100, 1043, 980, 920, 760 cm^{-1}; NMR (CCl_4) δ 1.73-2.06 (m, 2H), 2.08 (s, 3H), 2.24 (t, J=6Hz, 2H), 3.47-3.63 (m, 2H), 3.71 (s, 3H), 6.65 (br s, 1H). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.45; H, 6.69; N, 6.83.

β-Acetoxy- α, β-didehydro-N-methoxycarbonyl- α'-methylpiperidine (21b): IR (neat) 2952, 1759, 1711, 1442, 1360, 1340, 1199, 1099, 1086, 765 cm^{-1}; NMR (CCl_4) δ 1.15 (d, J=7Hz, 3H), 1.33-2.67 (m, 4H), 2.18 (s, 3H), 3.71 (s, 3H), 4.09-4.51 (m, 1H), 6.58 (br s, 1H); MS, m/e 213 (M^+), 171 (base), 156; exact mass calcd m/e 213.1000, found 213.0978.

β-Acetoxy- α, β-didehydro-N-methoxycarbonyl- α'-propylpiperidine (21c): IR (neat) 2960, 2940, 2870, 1752, 1704, 1442, 1360, 1220, 1190, 1098, 788, 764 cm^{-1}; NMR (CCl_4) δ 0.95 (t, J=3Hz, 3H), 1.07-2.26 (m, 8H), 2.07 (s, 3H), 3.69 (s, 3H), 3.93-4.43 (m, 1H), 6.64 (br s, 1H); MS, m/e 241 (M^+), 199, 156 (base); exact mass calcd m/e 241.1313, found 241.1312.

Preparation of β-Oxo compounds (24a,e). Into a flask was added a solution of 21a (0.136g, 0.683mmol) and 85% KOH (0.057g, 0.935mmol) in water (5.6mL) and the resulting solution was stirred with cooling in ice-water. After 15min, the organic portion was extracted with CH_2Cl_2 (15mLx4) and the extract was dried over $MgSO_4$. Then, the solvent was removed in vacuo to give a residue which was chromatographed on silica gel (AcOEt:hexane=1:2) to afford N-methoxycarbonyl- β-oxopiperidine (24a) in 62% yield. By the similar procedure was obtained α',N-bis(methoxycarbonyl)- β-oxopiperidine (24e) from 21e in 58% yield.

The preparation of 24a was achieved by oxidation of 9a. That is, a solution of 9a (1.41g, 10mmol) and 80% m-CPBA (2.158g, 10mmol) in CH_2Cl_2 was stirred at room temperature. After 18h, p-TsOH $\cdot H_2O$ (0.41g, 2.15mmol) was added to the reaction mixture, which was then stirred at room temperature overnight. The reaction mixture was washed with 0.5% aqueous NaOH (50 mLx4) and the organic portion was separated. After the aqueous layer was

extracted with CH_2Cl_2 (30mLx4), the combined extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The product 24a was isolated in 37% yield by column chromatography: IR (neat) 2965, 2880, 1700, 1454, 1225, 1120, 964, 772 cm^{-1}; NMR (CCl_4) δ 2.03 (tt, J=6 and 7Hz, 2H), 2.40 (t, J= 7Hz, 2H), 3.59 (t, J=6Hz, 2H), 3.67 (s, 3H), 3.91 (s, 2H). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.72; H, 7.19; N, 8.69.

24e: IR (neat) 2960, 1738, 1715, 1700, 1450, 1224, 1202, 788 cm^{-1}; NMR (CCl_4) δ 2.11-2.64 (m, 4H), 3.85 (s, 3H), 3.89 (s, 3H), 4.01-5.11 (m, 3H). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.04; H, 6.13; N, 6.48.

α-Alkylation of α, β-Disubstituted Piperidines 2a, 3a,b, and 12p. α-Alkyl- β-acetoxy(or bromo)-N-methoxycarbonylpiperidines 25, 26, 28, and 30a,b were prepared according to the reported method.[3] A general procedure is exemplified by preparation of 25. Into a solution of $TiCl_4$ (0.95mL, 8.62 mmol) in dry CH_2Cl_2 (10mL) was added dropwise a solution of 3a (1.288g, 5.75mmol) in dry CH_2Cl_2 (5mL) at -20°C under an atmosphere of nitrogen. After the solution was stirred at the temperature for 5min, a solution of allyltrimethylsilane (0.95mL, 8.62mmol) in dry CH_2Cl_2 (5mL) was added dropwise in a period of 10min. The resulting reaction mixture was stirred for 2h at -20 °C and allowed to stand until it was warmed to room temperature. After stirred overnight, the reaction mixture was poured into a cold brine (100mL) and stirred for 10min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30mLx4). The combined organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:2) to afford β-acetoxy-α-allyl-N-methoxycarbonylpiperidine (25) in 68% yield.

α-Alkylations of 12p, 2a, and 3a,b with allyltrimethylsilane, enol ether 27, and enol ester 29 were carried out under the similar conditions. Among the products, 25, 26, 28, and 30a,b, the ratios of stereoisomers of 25, 26, and 30a were determined by GLC to be 8:2, 9:1, and 8:2, respectively.

25: IR (neat) 2955, 2855, 1740, 1702, 1645, 1453, 1372, 1242, 772 cm^{-1}; NMR (CCl_4) δ 1.27-1.87 (m, 4H), 1.99 (s, 3H), 2.34 (t, J=7Hz, 2H), 2.80 (dt, J=10 and 4Hz, 1H), 3.62 (s, 3H), 3.81-4.33 (br d, J=10Hz, 1H), 4.27 (t, J=9Hz, 1H), 4.60-4.83 (br s, 1H), 4.86-5.18 (m, 2H), 5.50-5.59 (m, 1H). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.84; N, 5.81. Found: C, 59.68; H, 8.08; N, 5.78.

α-Allyl- β-bromo-N-methoxycarbonylpiperidine (26): 82% yield from 12p with allyltrimethylsilane; IR (neat) 2960, 2863, 1698, 1645, 1455, 1270, 1195, 1125, 920, 768 cm^{-1}; NMR (CCl_4) δ 1.37-1.66 (m, 1H), 1.82-2.27 (m, 3H), 2.43 (br t, J=8Hz, 2H), 2.62-3.03 (m, 1H), 3.68 (s, 3H), 3.95-4.66 (m, 3H), 4.96-5.26 (m, 2H), 5.52-6.06 (m, 1H); MS, m/e 222, 220 ($M^+-CH_2CH{=}CH_2$), 141 (base); exact mass calcd m/e 219.9997, found 219.9996. Anal. Calcd for $C_{10}H_{16}NO_2Br$: C, 45.82; H, 6.15; N, 5.34; Br, 30.48. Found: C, 46.14; H, 6.30; N, 5.57; Br, 29.84.

β-Acetoxy-N-methoxycarbonyl- α-phenacylpiperidine (28): 42% yield from 2a with 27; IR (neat) 2953, 2925, 1737, 1692, 1681, 1595, 1580, 1448, 1375, 1256, 1200, 1142, 760 cm^{-1}; NMR ($CDCl_3$) δ 1.30-2.02 (m, 4H), 2.03 (s, 3H), 3.21 (d, J=12Hz, 2H), 2.73-3.38 (m, 1H), 3.59 (s, 3H), 3.90-4.42 (m, 1H), 4.71-5.08 (m, 2H), 7.34-7.66 (m, 3H), 7.86-8.13 (m, 2H). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.11; H, 6.84; N,

4.43.

α-Acetonyl-β-acetoxy-N-methoxycarbonylpiperidine (30a): 70% yield from 3a with 29; IR (neat) 2970, 2880, 1745, 1703, 1457, 1246, 1048, 788 cm^{-1}; NMR (CCl_4) δ 1.24-2.20 (m, 4H), 2.00 and 2.08 (2s, 3H), 2.13 and 2.16 (2s, 3H), 2.35-3.10 (m, 1H), 2.58 (d, J=9Hz, 2H), 3.64 (s, 3H), 3.60-4.21 (m, 1H), 4.56-4.98 (m, 2H). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.85; H, 7.31; N, 5.30.

α-Acetonyl-β-acetoxy-N-methoxycarbonyl- α'-methylpiperidine (30b): 72% yield from 3b with 29; IR (neat) 2952, 1735, 1698, 1445, 1362, 1242, 1090, 1024, 788 cm^{-1}; NMR (CCl_4) δ 1.10-2.15 (m, 4H), 1.17 (d, J=8Hz, 3H), 2.07 (s, 3H), 2.19 (s, 3H), 2.53 (d, J=9Hz, 2H), 3.69 (s, 3H), 4.03-5.01 (m, 3H). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80, N, 5.16. Found: C, 57.43; H, 7.80; N, 5.21.

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10. Under the conditions of CH_2Cl_2-Et_4NOTs system, Cl^- may be generated by the cathodic reduction of CH_2Cl_2.[11a]
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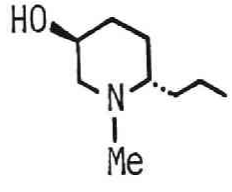
Chapter 2-2

Synthesis of (+)- and (-)-N-Methylpseudoconhydrine from L-Lysine Using Anodic Oxidation as the Key Reaction

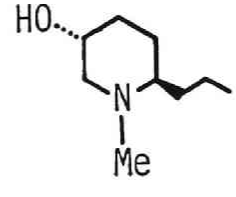
Abstract: (+)- and (-)-N-Methylpseudoconhydrine were synthesized with high optical purity from L-Lysine by utilyzing both anodic decarboxylation of pipecolinic acid derivatives and anodic diacetoxylation at 2- and 3- positions of piperidine skeleton as key reactions.

Synthesis of optically active piperidine alkaloids from L-lysine is particularly interesting since the piperidine skeleton found in some natural piperidine alkaloids has been known to be formed from L-lysine.[1]

As we have already reported, the anodic transformation of L-lysine to optically active pipecolinic acid is an excellent method of synthesis of piperidine skeleton from L-lysine.[2] Our previously reported enantioselective synthesis of (+)-N-methylconiine (5) from L-lysine was a typical example of applying this anodic transformation as the key reaction.[3,4] We report herein a first synthesis of optically active (+)- and (-)-N-methylpseudoconhydrine,(+)- and (-)-1, from L-lysine using anodic oxidation as the key reaction.



(+)-1



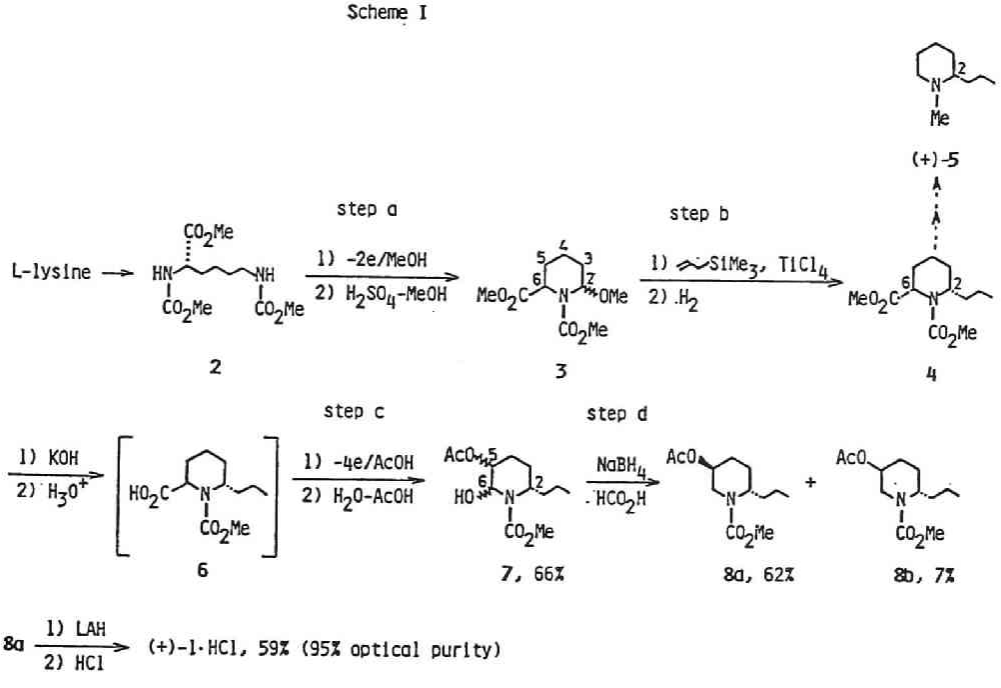
(-)-1

(+)-N-Methylpseudoconhydrine, (+)-1, is an alkaloid yielded from South African Conium species and possesses a structure of (2S,5S)-5-hydroxy-1-

methyl-2-propylpiperidine.[5] Although some methods have been exploited for the diastereoselective construction of 5-hydroxy-2-propylpiperidines,[6] no studies on the synthesis of optically active ones have been carried out so far except a synthesis of (+)-pseudoconhydrine from D-glucosamine.[7]

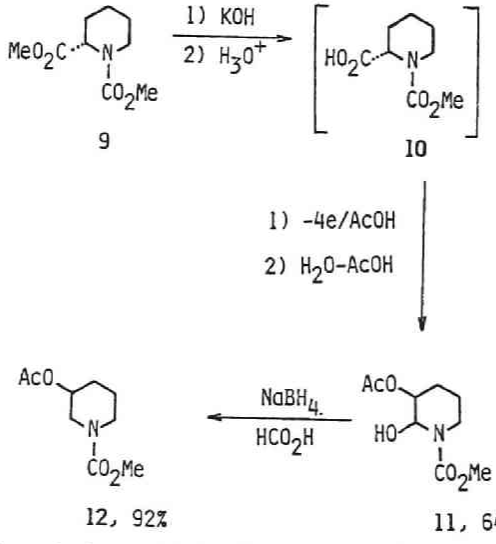
Synthesis of (+)-N-Methylpseudoconhydrine {(+)-1 }. Our methodology for synthesis of (+)-1 is shown in Scheme I in which (1) a chiral piperidine N,O-acetal 3 is prepared from L-lysine derivative 2 (step a), (2) a propyl group is diastereoselectively introduced to the 2-position of 3 under the influence of the methoxycarbonyl group on the chiral 6-position (step b), (3) an acetoxyl group is introduced to the 5-position of 4 under the influence of the propyl group on the chiral 2-position (step c), and (4) the 6-hydroxyl group of 7 is eliminated to afford 8 (step d). Of these steps, anodic oxidations are utilized in steps (a) and (c).

Scheme I



The synthesis of 4 from L-lysine has been described in our previous report,[3] in which the 2-methoxyl group of 3 was substituted by an allyl group and the product was hydrogenated and decarboxylated to give finally 5. Since the stereochemistry at the 2-position of the resulting 5 was (S) and its optical purity was more than 96%, 4 is expected to be an excellent precursor for the synthesis of (+)-1 provided that both elimination of a methoxycarbonyl group at the 6-position of 4 and stereoselective introduction of a hydroxyl group into the 5-position are achievable.

Using compound 9 as a model, we have examined the effectiveness of the anodic oxidation as the key method and found that it worked nicely. Namely, hydrolysis of 9 and subsequent anodic oxidation of 10 in acetic acid gave 11 which was easily reduced to 12 in 59% overall yield (eq 1).

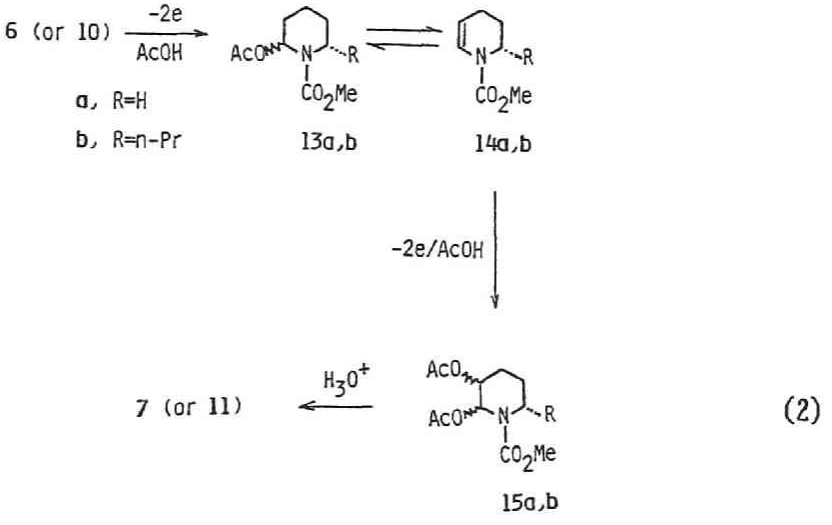


(1)

Compound 7, a key intermediate for the synthesis of (+)-1, was obtained from 4 in 71% yield by similar procedures. The hydroxyl group of 7 was easily removed by reducing 7 with $NaBH_4$ and a stereoisomeric mixture of 8a and 8b was obtained in 69% yield. Stereochemistry of 5-acetoxyl group of 7

was unknown, but the stereochemistry of 8 was found to mainly be trans (9:1). After each stereoisomer was separated by column chromatography, the reduction of main isomer 8a with LAH followed by treatment with HCl gave (+)-1·HCl in 95% optical purity.[5]

The anodic oxidation of 6 to 7 (or 10 to 11) probably proceeded through the intermediary formation of 13, 14, and 15 (eq. 2). Anodic decarboxylation of α-amino acid derivatives has been known[8] and anodic diacetoxylation of 1-(methoxycarbonyl)-1,2,3,4-tetrahydropyridines has already been reported by us.[9]



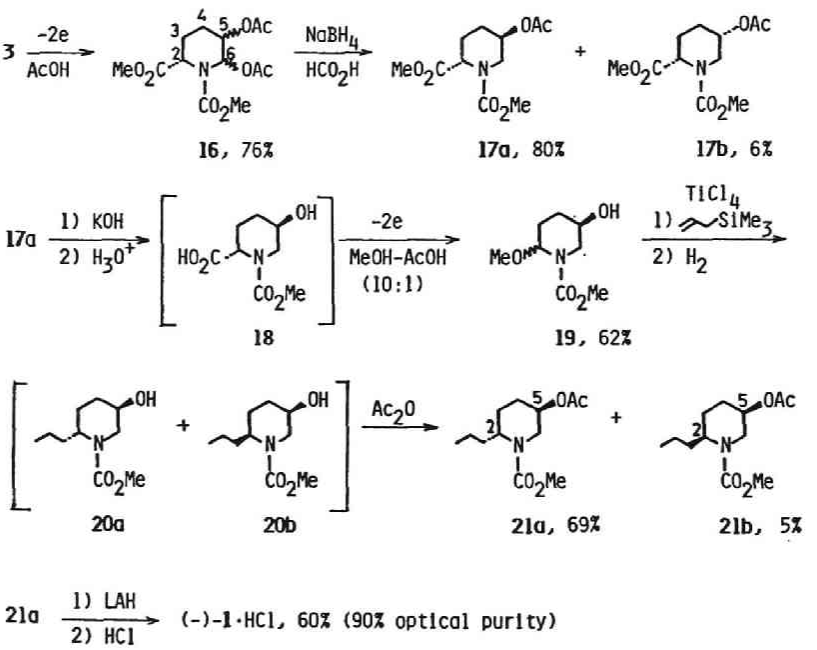
(2)

Synthesis of (-)-N-Methylpseudoconhydrine {(-)-1}. Unnatural type alkaloid (-)-1 has a structure of (2R,5R)-5-hydroxy-1-methyl-2-propylpiperidine. Hence, the key intermediate 4 was not utilizable for the synthesis of (-)-1 since the stereochemistry at the 2-position of 4 was (S).

Scheme II shows a route for the synthesis of (-)-1 from L-lysine. Anodic oxidation of 3 in acetic acid gave 16 in which the stereochemistry is unknown.[9,10] Then, treatment of 16 with $NaBH_4$ under acidic conditions gave trans-isomer 17a (80% yield) together with small amount of cis-isomer 17b (6% yield). The ratio of 17a and 17b (93:7) was measured by separation with

column chromatography. The stereochemistry at the 5-position of the main product 17a was (R), which was determined at the final stage. Alkaline hydrolysis of 17a followed by anodic decarboxylation in a mixed solvent of methanol and acetic acid gave 19 (62% yield),[11] which was then treated with allyltrimethylsilane in the presence of $TiCl_4$ and hydrogenated successively to give a mixture of 20a and 20b. It was then acetylated and each isomer was separated by column chromatography. The main product,(2R,5R)-isomer 21a (69% yield) was reduced with LAH to give (-)-1, which was identified as its HCl salt,(-)-1·HCl (90% optical purity).[5] The stereochemistry of the minor isomer 21b (5% yield) was (2S,5R).

Scheme II



In conclusion, the anodic methods, namely, both anodic decarboxylation of pipecolinic acid derivatives and anodic 2,3-diacetoxylation of 1-(methoxycarbonyl)piperidines have been shown to be highly effective in the

synthesis of optically active piperidine alkaloids from L-lysine.

Experimental Section

^{1}H NMR spectra were measured on a Varian Associates EM-360 or EM-390 spectrometer with chemical shifts given in parts per million (δ) downfield from tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 260-10 spectrometers. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Optical rotations were measured with Perkin-Elmer 241 polarimeter. Mass specra were recorded on a JEOL IMS-DS300 mass spectrometer. Melting points are uncorrected.

Anodic oxidation was carried out with a DC power supply (GP 050-2) of Takasago Seisakusho, Ltd. A glass beaker (50mL) equipped with a carbon-rod anode and cathode (8mm Φ) was used as an electrolysis cell.

Preparation of 5-Acetoxy-6-hydroxy-1-(methoxycarbonyl)-2-propylpiperidine(7). A solution of 4 [3] (1.868g, 7.69mmol) and 85% KOH (2.5g, 38.4mmol) in a mixed solvent of methanol (10mL) and water (10mL) was stirred at 0 ℃ and gradually warmed to room temperature. After stirring for 10h, the solvent was evaporated to remove methanol. The residual aqueous layer was acidified with conc.HCl and the organic portion was extracted with CH_2Cl_2 (3x20mL). The combined organic layer was dried over $MgSO_4$, and the solvent was removed to give crude carboxylic acid 6 (1.874g),[3] which was used without purification.

Into an electrolysis cell described above was added a solution of crude 6 (1.874g) and AcOK (3g, 26.3mmol) in acetic acid(50mL). After 13F/mol of electricity was passed at a constant current of 0.2A (2.9h, terminal voltage;ca.30V) through the solution cooled with water, water (100mL) was added

to the reaction mixture and stirred for 3h. The organic portion was extracted with CH_2Cl_2 (3x50mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 7 (1.412g, 5.45mmol) in 71% yield. Spectroscopic data of 7 were consistent with those of known racemic sample.[9]

Reduction of 7. Into a solution of 7 (0.698g, 2.7mmol) in formic acid (10ml) was added, in portions, 90% $NaBH_4$ (0.46g, 10.9mmol). After 1h, water (30 mL) was poured into the reaction mixture and the organic portion was extracted with CH_2Cl_2 (3x30mL). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford (2S,5S)-5-acetoxy-1-(methoxycarbonyl)-2-propylpiperidine (8a) and (2S,5R)-isomer (8b) in 62% (0.406g, 1.67mmol) and 7% (0.046g, 0.19mmol) yields, respectively.

8a (polar isomer): IR (neat) 2950, 2860, 1736, 1695, 1444, 1368, 1230, 1158,1020, 958, 840, 770cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, J=7Hz, 3H), 1.26-1.81 (m, 8H), 2.03 (s, 3H), 2.97 (dd, J=15 and 2Hz, 1H), 3.68 (s, 3H), 4.18 (d, J =14 Hz, 1H), 4.32 (br s, 1H), 4.84 (br s, 1H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.14; H, 8.87; N, 5.64.

8b (less polar isomer): IR (neat) 2952, 2865, 1736, 1698, 1442, 1362, 1235, 1160, 1092, 1039, 768cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, J=7Hz, 3H), 1.21-1.94 (m, 8H), 2.05 (s, 3H), 2.69 (dd, J=13 and 11Hz, 1H), 3.69 (s, 3H), 4.16 -4.35 (m,2H), 4.64 (m, 1H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.99; H, 8.41; N, 5.63.

3-Acetoxy-1-(methoxycarbonyl)piperidine (12) was prepared according to

a similar procedure described above through 10 and 11[9] from 9[2] in 59% overall yield: IR (neat) 2960, 2875, 1741, 1452, 1238, 1049, 776 cm^{-1}; NMR (CCl_4) δ 1.33-2.13 (m, 4H), 1.98 (s, 3H), 3.21-3.55 (m, 4H), 3.60 (s, 3H), 4.56-4.67 (m, 1H). Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.64;H, 7.63; N, 6.94.

(+)-N-Methylpseudoconhydrine hydrochloride {(+)-1·HCl}. To a stirred suspension of LAH (0.078g, 2.05mmol) in dry ether (10ml) was added dropwise a solution of 8a (0.29g, 1.19mmol) in dry ether (10mL). The mixture was refluxed for 2h and then cooled to room temperature. Usual working up followed by treatment with HCl gas, gave a crude solid (0.245g). After the solid was washed with AcOEt, (+)-1·HCl was crystallized from methanol-acetone (1:9) at -20°C in 95% optical purity[5] (0.137g, 0.7mmol, 59% yield) : mp 169-170°C; $[\alpha]_D^{25}$ + 23.8 (c 0.7, MeOH). The free base: liquid, MS, m/e 157 (M^+), 128, 115, 114 (base), 96. IR ($CHCl_3$) 3602, 2965, 2945, 2875, 2800, 1467, 1382, 1098, 1060, 1008, 968, 888cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, J= 7Hz, 3H), 1.00-2.33 (m, 11H), 2.24 (s, 3H), 2.95 (ddd, J=10, 4, and 2 Hz, 1H), 3.35-3.93 (m, 1H).

Anodic oxidation of 3[2] in acetic acid was carried out according to a similar procedure to the anodic oxidation of 6 described above. 2,3-Diacetoxy-1,2-bis(methoxycarbonyl)piperidine (16)[9] was obtained in 76% yield (8F/mol).

Reduction of 16. Into a solution of 16 (1.828g, 5.77mmol) in formic acid (20 mL) was added, in portions, 90% $NaBH_4$ (1.21g, 28.9mmol). After stirring at room temperature for 1h, the solution was worked up by a similar method described above to give trans-5-acetoxy-1,2-bis(methoxycarbonyl)pipe-

ridine (17a) and cis-isomer (17b) in 80% (1.200g, 4.63mmol) and 6% (0.096g, 0.37mmol) yields, respectively.

17a (polar isomer): IR (neat) 2965, 1740, 1710, 1452, 1374, 1236, 1158, 1124, 1024cm^{-1}; NMR (CCl_4) δ 1.38-2.21 (m, 4H), 2.04 (s, 3H), 3.11-3.41 (m, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.96-4.37 (m,1H), 4.92 (br s, 2H). Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.18; H, 6.75; N, 5.30.

17b (less polar isomer): IR (neat) 2965, 1740, 1710, 1450, 1370, 1242, 1232, 1162, 1048cm^{-1}; NMR (CCl_4) δ 1.40-2.30 (m, 4H), 1.98 (s, 3H), 2.57-3.00 (m, 1H), 3.71 (s,3H), 3.77 (s, 3H), 3.95-4.33 (m, 1H), 4.47-4.97 (m, 2H); MS, m/e 258 (M^+-H), 230, 200, 140 (base). Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.25; H, 6.66; N, 5.26.

Preparation of 5-Hydroxy-2-methoxy-1-(methoxycarbonyl)piperidine (19). Carboxylic acid 18 was obtained as a white solid by hydrolysis of 17a (1.988 g, 7.68mmol) carried out as described above (1.56g). Into an electrolysis cell as described above was added a solution of the crude 18 (1.56g) and AcOK (2g, 20mmol) in methanol (20mL) and acetic acid (2ml). After 5F/mol of electricity was passed at a constant current of 0.2A (5.1h, terminal voltage; ca. 10V) through the solution cooled with water, water (20mL) was poured into the resulting reaction mixture. The organic portion was extracted with CH_2Cl_2 (3x20mL) and the combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo to give a residue, which was chromatographed on silica gel (AcOEt:hexane=1:2) to afford 19 (0.900g, 4.76mmol) in 62% yield: IR (neat) 3450, 2948, 1695, 1260, 1155, 1070, 1001cm^{-1}; NMR (CCl_4) δ 1.30-2.06(m, 4H), 2.30-4.20 (m, 4H), 3.14(s, 3H), 3.62 (s, 3H),5.10 (br s, 1H); MS, m/e 172 (M^+-OH), 157 (M^+-MeOH), 140, 114 (base); exact mass calcd m/e 157.0739 (M^+-MeOH), found 157.0722 (M^+-MeOH). Anal. Calcd for $C_8H_{15}NO_4$:

C,50.78; H, 7.99, N, 7.40. Found: C, 51.05; H, 8.13; N, 7.10.

(2R,5R)- and (2S,5R)-Acetoxy-2-propyl-1-(methoxycarbonyl)piperidine (21a) and (21b). To a stirred solution of $TiCl_4$ (0.42mL, 3.83mmol) in CH_2Cl_2 (7mL) was added dropwise a solution of 19 (0.723g, 3.83mmol) and allyltrimethylsilane (0.91 mL, 5.75mmol) in CH_2Cl_2 (17mL) at -70°C under an atmosphere of nitrogen. The mixture was gradually warmed to room temperature. Water (25mL) was added to the solution and the organic portion was extracted with CH_2Cl_2 (3x30mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed. A mixture of the residue and a catalytic amount of PtO_2 in acetic acid (10mL) was stirred overnight at room temperature under an atmosphere of hydrogen (1atm). After the catalyst and solvent were removed, the residue was dissolved in a mixed solvent of acetic anhydride (1.08mL, 11.5mmol) and pyridine (0.93mL, 11.5mmol). After the solution was stirred for 2h, dil.HCl (20mL) was added into the reaction mixture. The organic portion was extracted with CH_2Cl_2 (3x30mL) and the combined organic layer was dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford (2R,5R)-isomer 21a and (2S,5R)-isomer 21b in 69% (0.635g, 2.64mmol) and 5% (0.050g, 0.21mmol) yields, respectively. Their spectroscopic data were consistent with those of 8a,b.

(-)-N-Methylpseudoconhydrine hydrochloride {(-)-1·HCl}. Treatment of 21a with LAH in a similar way to the synthesis of (+)-1 from 8a gave (-)-1 in more than 70%. IR, NMR, and MS spectrum of (-)-1 were consistent with those of (+)-1. The optical purity of synthesized (-)-1 was determined as its HCl salt (60% yield from 21a, 90% optical purity):[5] mp 157-158°C ; $[\alpha]_D^{25}$ -22.6 ° (c 1.0, MeOH).

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10. In contrast with 6-acetoxyl group of 15, 6-acetoxyl group of 16 was not hydrolyzed at the step of working up.
11. The yield of 19 was 32% in a case using only methanol as a solvent. Improvement of yields by adding acetic acid into reaction systems has also been observed in anodic α-methoxylation of aliphatic ethers.[12]
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Chapter 3

A New Method for Introducing Some Active Methylene or Methine Groups to the 3-Position of Pyrrolidine or Piperidine Skeleton, and Its Application to Preparation of Key Intermediate for the (±)-Eburnamonine Synthesis

Abstract: A new mehtod for introducing a bis(methoxycarbonyl)methyl or 2-oxopropyl group to the 3-position of pyrrolidine or piperidine skeleton has been exploited, and this method could be used in the synthesis of a key intermediate for the (±)-eburnamonine synthesis.

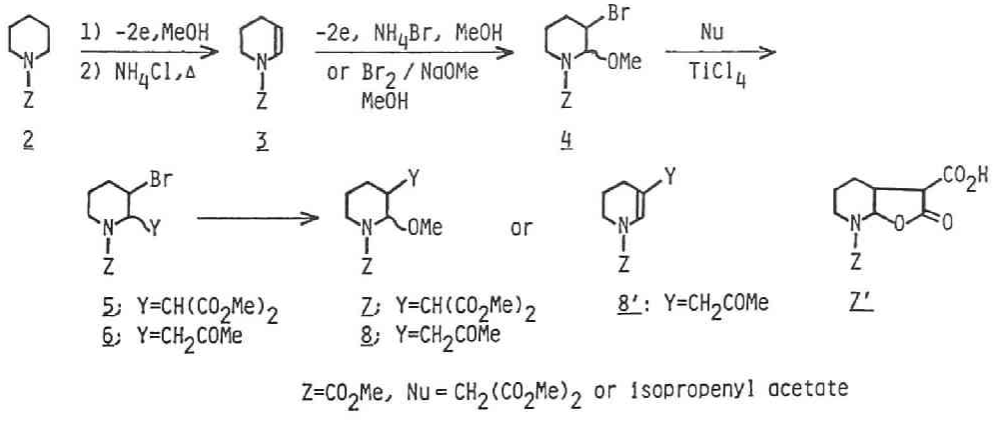
Introducing a variety of substituents to certain positions of pyrrolidine or piperidine skeleton is worthwhile in organic synthesis since substituted pyrrolidine or piperidine skeleton is found in many types of alkaloid.[1]

In continuing our studies carried out from this standpoint,[2] we found a new method for the introduction of some active methylene or methine groups (Y) such as a bis(methoxycarbonyl)methyl or 2-oxopropyl group to the 3-position of pyrrolidine or piperidine skeleton and succeeded in its application to synthesis of 26, a key intermediate in the synthesis of (±)-eburnamonine 1,[3] an indole alkaloid isolated from Hunteria eburnea Pichon.[4]

Our method for introducing Y group to the 3-position of piperidine skeleton is shown in scheme 1 which consists of the following four steps: (1) the synthesis of 1,2,3,4-tetrahydro-1-methoxycarbonylpyridine 3 from 1-

methoxycarbonylpiperidine 2, (2) the bromomethoxylation of 3 yielding 3-bromo-2-methoxy-1- methoxycarbonylpiperidine 4, (3) the introduction of Y group to the 2-position of 4 affording 2-Y-3-bromo-1-methoxycarbonylpiperidine 5 or 6, and (4) the base treatment of 5 or 6 giving piperidine derivatives 7 or 8 bearing a substituent Y at the 3-position.

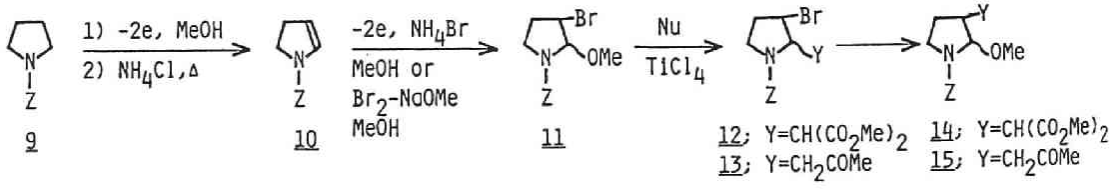
The experimental procedures of these steps were very simple as described below. The preparation of 4 from 2 has already been reported (3[2b, c], 83% yield from 2 : 4 [2d], 81%.yield from 3).[5] Subsequent introduction of Y group to the 2-position of 4 was achievable according to our reported method.[2a] That is a solution of 4 in CH_2Cl_2 and a solution of a mixture of dimethyl malonate (1.5 equiv.) and Et_3N (1.5 equiv.) in CH_2Cl_2 were succesively added into a solution of $TiCl_4$ (1.0 equiv.) in CH_2Cl_2 at -78 °C, and then the resulting solution was warmed to room temperature. The usual workup gave 5 in 75 % yield. Compound 6 was obtained in 78% yield by the reaction of 4 with isopropenyl acetate (1.5 equiv.) in the presence of $TiCl_4$ (1.0 equiv.).



Scheme 1

The final step was the rearrangement of the substituent Y from the 2-position to the 3-position. The rearrangement of 5 yielding 7 was found to be easily achieved by treating 5 with NaOMe (1.2 equiv.) in methanol. Similar treatment of 5 with aqueous methanol containing KOH gave an amino lactone 7'. On the other hand, the transformation of 6 to 8 required the treatment of 6 with NaOMe (1.2 equiv.) in methanol followed by acidifying the resulting solution with conc.HCl,and the compound 8' was obtained instead of 8.

Our method is also applicable to the introduction of Y group to the 3-position of pyrrolidine skeleton (Scheme 2). That is, compounds 14 and 15 were preparable from 9 from intermediates 10-13 which were formed by similar procedures to the preparation of 3-6 (10, 91% yield [2c]: 11, 42% yield [2d, 5]: 12, 81% yield : 13, 82% yield).



Z=CO_2Me, Nu = $CH_2(CO_2Me)_2$ or isopropenyl acetate

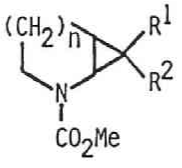
Scheme 2

The yields of 7, 7', 8', 14, and 15, and the reaction conditions for the rearrangement are summarized in Table 1.

Table 1. Rearrangement of 5, 6, 12, and 13 to 7, 7', 8', 14 and 15.

Substrate	Reaction conditions	Product	Isolated yield/%
5	NaOMe/MeOH, rt, 22h	7	59
5	NaOH/MeOH-H_2O(2:1), rt,5h	7'	68
6	NaOMe/MeOH,rt, 15h, then conc HCl, rt, 18h	8'	72
12	NaOMe/MeOH, rt, 22h	14	82
13	NaOMe/MeOH,rt, 12h, then conc HCl, rt, 15h	15	48

The rearrangement of Y group from 2-position to 3-position in compounds 5, 6, 12, and 13 may proceed through the formation of cyclopropane intermediates 16-19. In fact, the formation of 18 or 19 was observed in the reaction of 6 or 13 with bases, whereas 16 or 17 was not detected in the reaction of 5 or 12 with bases.

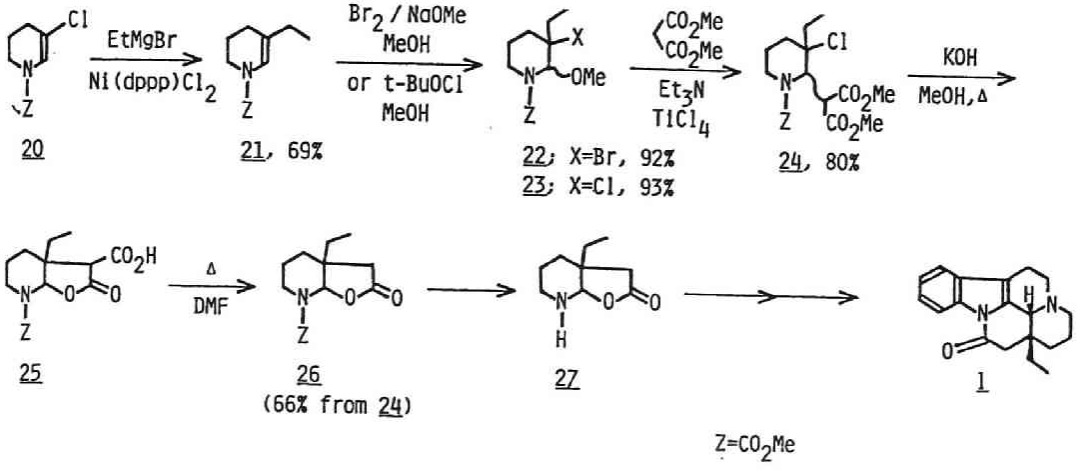


16; n=1, R^1=R^2=CO_2Me 17; n=2, R^1=R^2=CO_2Me

18; n=1, R^1=COMe, R^2=H 19; n=2, R^1=COMe, R^2=H

Among the products, the structure of 7' is interesting since it is similar to an amino lactone 27 which is a key intermediate in the synthesis of 1. Wenkert et al. have reported the synthesis of 27 using a cyclopropane intermediate prepared by copper catalyzed reaction of ethyl diazoacetate with 21.[6] Ban et al. have synthesized 26 by utilizing anodic oxidation of 3-ethyl-3-carboxymethyl-1-methoxycarbonylpiperidine, and converted 26 to 1 through 27 .[7] More recently, Hanaoka et al. have also succeeded in the synthesis of 27 starting from 1,6-dihydro-3(2H)-pyridinone.[3]

Thus, our effort has been directed toward the application of our method to the synthesis of 27 (Scheme 3). The starting compound 21 was prepared in 69% yield by Ni-catalyzed reaction of 3-chloro-1-methoxycarbonyl-1,4,5,6-tetrahydropyridine 20[2d] with ethylmagnesium bromide.[8,9] The bromomethoxylation of 21 giving 22 was easily carried out by treating 21 with bromine in methanol containing NaOMe (1.1 equiv.) (92% yield). However, in contrast with the transformation of 4 to 5, introducing a bis(methoxycarbonyl)methyl group tothe 2-position of 22 was unsuccessful possibly because of the steric constraint of substituents at the 3-position of 22. On the other hand, fortunately, chloromethoxylated compound 23, prepared by the reaction of 21 with t-butyl hypochrolite (1.2 equiv.) in methanol (93% yield), reacted with dimethyl malonate affording 24 (80% yield). Compound 24 was transformed to 25 on treatment with KOH (20 equiv.) in methanol for 20h at 65°C, and 25 was decarboxylated by heating 25 in DMF for 11h to give 26 (66% yield from 24). The hydrolysis of 26 giving 27 and the easy transformation of 27 to 1 have already been reported.[3,6,7]



Scheme 3

Experimental Section

Starting materials 4,[2c] 11,[2c] and 20[2d] were prepared according to our prviously reported method.

Reaction of 4, 11, 22, and 23 with Nucleophiles. A general procedure is exemplified by the reaction of 4 with dimethyl malonate. Into a solution of $TiCl_4$ (0.66mL, 6mmol) in dry CH_2Cl_2 (8mL) was dropwise a solution 4 (1.34 g, 5.33mmol) in dry CH_2Cl_2 (8mL) at -70 °C under an atmosphere of nitrogen. After the solution was stirred at the temperature for 5min, a solution of dimethyl malonate (0.91mL, 8mmol) and triethylamine (1.12mL, 8mmol) in dry CH_2Cl_2 (8mL) was added dropwise in a period of 10min. The resulting mixture was stirred for 14h and allowed to stand until it was warmed to room temperature. The reaction mixture was poured into water (20mL) and stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted

with CH_2Cl_2 (3x20mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:5) to afford 5 (1.41g, 75% yield).

The reaction of 4 and 11 with isopropenyl acetate as nucleophile did not use triethylamine.

5: IR (neat) 2970, 1760, 1740, 1710, 1450, 1415, 1300, 1270, 1155cm^{-1}; NMR (CCl_4) δ 1.30-1.70 (m, 1H), 1.72-2.15 (m, 3H), 2.50-3.20 (m,1H), 3.55-4.30 (m, 2H), 3.59 (s, 3H), 3.61 (s, 3H), 3.77(s, 3H), 4.25-4.50 (m, 1H), 4.80-5.15 (m, 1H). Anal. Calcd for $C_{12}H_{18}BrNO_6$: C, 40.93; H, 5.15; Br, 22.69; N, 3.98. Found: C, 40.92; H, 5.14; Br, 22.84; N, 3.82.

6: IR (neat) 2950, 2860, 1700, 1450, 1410, 1270, 1120, 1050, 760cm^{-1}; NMR (CCl_4) δ 1.25-1.73 (m, 1H), 1.80-2.15 (m,3H), 2.12 (s, 3H), 2.65 (d, J=7 Hz, 2H), 2.50-3.20 (m, 1H), 3.58 (s, 3H), 3.87-4.30 (m,2H), 4.56-4.90 (m, 1H). Anal. Calcd for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; Br, 28.73; N, 5.04. Found: C, 43.34; H, 5.83; Br, 28.70; N, 5.23.

12: IR (neat) 2955, 1740, 1710, 1450, 1395, 1200, 1160cm^{-1}; NMR (CCl_4) δ 1.90-2.55 (m, 2H), 3.10-4.08 (m, 3H), 3.60 (s, 3H), 3.62 (s, 3H), 3.65 (s, 3H), 4.37-4.70 (m,2H). Anal.Calcd for $C_{11}H_{16}BrNO_6$: C, 39.07; H, 4.77; Br, 23.63; N, 4.14. Found: C, 39.08; H, 4.72; Br, 23.68; N, 4.32.

13: IR (neat) 2950, 1700, 1450, 1380, 1120cm^{-1}; NMR (CCl_4) δ 2.13 (s, 3H), 2.03- 2.50 (m, 2H), 2.53 (d, J=9Hz, 1H), 2.83 (d, J=4Hz, 1H), 3.30-3.75 (m, 2H), 3.62 (s, 3H), 4.12- 4.43 (m, 2H). Anal.Calcd for $C_9H_{14}BrNO_3$: C, 40.93; H, 5.34; Br, 30.25; N, 5.30. Found: C, 41.10; H, 5.38; Br, 30.10; N, 5.35.

24: IR (neat) 2960, 1760, 1740, 1705, 1450, 1280, 1140cm^{-1}; NMR (CCl_4) δ 0.80-2.30 (m, 9H), 2.40-3.10 (m, 1H), 3.40-4.25 (m, 2H), 3.60 (s, 3H), 3.63 (s, 3H), 3.70 (s, 3H), 4.95-5.35 (m, 1H); MS, m/e 337, 335.1163 (calcd for $C_{14}H_{22}ClNO_6$: 335.1136), 300, 299, 276, 232, 206, 204, 168 (base).

3-Ethyl-1-(methoxycarbonyl)-1,4,5,6-tetrahydropyridine (21). Into a solution of EtMgBr (59.3mmol) in dry ether (10mL) was added Ni(dppp)Cl_2 (0.16g, 0.30mmol) at 5℃ under an atmosphere of nitrogen. After the solution was stirred at the temperature for 10min, a solution of 20 (5.21g, 29.7 mmol) in dry ether (15mL) was added dropwise in a period of 10 min. After stirred for 6h, the reaction mixture was poured into dil. HCl and stirred for 15min. The organic layer was washed with sodium bicarbonate and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel(AcOEt:hexane=1:10) to afford 21 (3.46g, 69% yield).

Preparation of 22 and 23. Into a solution of 21 (0.24g, 1.43mmol) in MeOH (10mL) was added Na (0.04g, 1.57mmol). After the solution was stirred at the temperature for 10min, a solution of bromine (0.08mL, 1.57mmol) was added dropwise in a period of 10 min. After stirred for 30min, the reaction mixture was poured into aqueous $Na_2S_2O_3$ and stirred for 15min. The organic layer was extracted with CH_2Cl_2 (3x15mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel (AcOEt:hexane=1:10) to afford 22 (0.37g, 92% yield).

Similary the reaction of 21 with tert.-BuOCl gave 23.

22: IR (neat) 2970, 1710, 1455, 1418, 1290, 1205, 1168, 1083, 975cm^{-1}; NMR (CCl_4) δ 1.10 (t, J=6.5Hz, 3H), 1.30-1.68 (m, 1H), 1.69-2.52 (m, 5H), 2.54-3.12 (m, 1H), 3.25 (s, 3H), 3.55-4.31 (m, 1H), 3.71 (s, 3H), 5.13 and

5.33 (2s, 1H). Anal.Calcd for $C_{10}H_{18}BrNO_3$: C, 42.87; H, 6.48; Br, 28.52; N, 5.00. Found: C, 42.61; H, 6.36; Br, 28.48;N, 5.13.

23: NMR (CCl_4) δ 1.00 (t, J=7Hz, 3H), 1.30-2.30 (m, 6H), 2.40-3.10 (m, 1H), 3.20 (s, 3H), 3.50-4.20 (m, 1H), 3.60 (s, 3H), 4.95 and 5.13 (2s, 1H). Anal.Calcd for $C_{10}H_{18}ClNO_3$: C, 50.96; H, 7.70; Cl, 15.04; N,5.94. Found: C, 50.91; H, 7.81; Cl, 15.07; N, 5.79.

Rearrangement of 5, 6, 12, 13, and 24. A general procedure is exemplified by preparation of 7. Into a solution of 5 (0.63g, 1.79mmol) in MeOH (8mL) was added Na (0.05g, 2.15mmol). After stirred for 22h, the reaction mixture was poured into water and the organic layer was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:3) to afford 7 (0.32g, 59%).

7: IR (neat) 2950, 1760, 1735, 1705, 1440, 1265, 1155, 1080cm^{-1}; NMR (CCl_4) δ 1.20-1.80 (m, 4H), 1.90-2.45 (m, 1H), 2.50-3.00 (m, 1H), 3.12 and 3.20 (2s, 3H), 3.40-4.20 (m, 2H), 3.60 (s, 3H), 3.63 (s, 3H), 3.69 (s, 3H), 5.00 (br s, 0.4H), 5.23 (d, J=3Hz, 0.6H). Anal.Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.23; H, 6.84; N, 4.69

After treatment of 6 with NaOMe, the reaction mixture was acidified with conc. HCl and stirred for 18h. The resulting reaction mixture was poured into aqueous $NaHCO_3$, and the similar procedure described above gave 8' in 72% yield.

8': IR (neat) 2960, 1710, 1680, 1450, 1400, 1320, 1265cm^{-1}; NMR(CCl_4)

δ 1.45-2.10 (m, 4H), 2.02 (s, 3H), 2.93 (br s, 2H), 3.30-3.70 (m, 2H), 3.60 (s, 3H), 6.60 (br s, 1H). Anal.Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.92; H, 7.82; N, 6.88.

Compound 12 was transformed into a mixture of two stereoisomers 14a and 14b in 56% and 26% yields, respectively.

14a: IR (neat) 3060, 1755, 1740, 1710, 1450, 1400, 1380, 1280cm^{-1}; NMR (CCl_4) δ 1.60-2.15 (m, 2H), 2.20-2.80 (m, 1H), 3.23 and 3.30 (2s, 3H), 3.30-3.75 (m, 3H), 3.60 (s, 3H), 3.63 (s, 3H), 3.80 (s,3H), 5.05 (d, J=4Hz, 1H). Anal.Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.95; H, 6.56; N, 4.73.

14b: IR (neat) 2970, 1760, 1740, 1720, 1460, 1390, 1090cm^{-1}; NMR (CCl_4) δ 1.50-2.90 (m, 3H), 3.15-3.80 (m, 3H), 3.28 (s, 3H), 3.63 (s, 3H), 3.68 (s, 3H), 3.70 (s,3H), 4.82 (s, 1H). Anal.Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.68; H, 6.57; N, 5.10.

15: IR (neat) 2960, 1715, 1450, 1380, 1120, 1080cm^{-1}; NMR (CCl_4) δ 1.50-2.20 (m, 3H), 2.16 (s, 3H), 2.30-2.75 (m, 2H), 3.10-3.60 (m, 2H), 3.63 (s, 3H), 5.00 (d, J=4Hz, 1H). Anal.Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.91; H, 8.12; N, 6.44.

7': IR (neat) 3700-2600, 1790, 1730, 1460, 1360, 1180cm^{-1}; NMR (CCl_4) δ 1.07-2.30 (m, 4H), 2.50-3.16 (m, 2H), 3.35 (br s, 1H), 3.60-4.20 (m, 1H), 3.73 (s,3H), 6.45 (d, J=4.5Hz, 1H), 8.46 (br s, 1H). Anal. Calcd for $C_{10}H_{13}NO_6$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.57; H,5.32; N, 5.73.

After the solution of 24 (0.36g, 1.07mmol) and 85% KOH (1.32g, 20mmol) in MeOH (10mL) was refluxed for 20h, the reaction mixture was acidified with dil. HCl. The organic portion was extracted with CH_2Cl_2 and dried over $MgSO_4$. After the solvent was removed in vacuo, into the residue was added DMF (5mL). After the solution was heated at 90 ℃ for 11h, the solvent was removed. The residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 26 (0.16g, 66%).

26: mp 66-67 ℃ (lit[7] 66-67.5℃); IR ($CDCl_3$) 1770, 1710cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, J=7Hz, 3H), 1.30-1.90 (m, 6H), 2.40 (d, J=4Hz, 2H), 2.70 -3.20 (m, 1H), 3.35 (br s, 1H), 3.60-4.20 (m, 1H), 3.72 (s,3H), 5.95 (br s, 1H).

References and notes

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5. The transformation of 3 to 4 or of 10 to 11 was also achieved by adding bromine (1.2 equiv.) to a solution of 3 or 10 in methanol containing NaOMe (1.2 equiv.) (4, 80% yield: 11, 71% yield).
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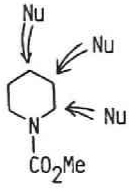
Chapter 4-1

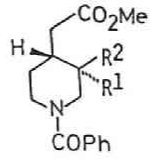
A New Method for Introducing A Bis(methoxycarbonyl)methyl Group to 4-Position of Piperidine Skeleton, and Its Application to Synthesis of (±)-Meroquinene and (±)-Epimeroquinene Derivatives

Abstract: A new method for introducing a bis(methoxycarbonyl)methyl group to 4-position of piperidine skeleton was exploited, and this method was applied to the synthesis of (±)-meroquinene and (±)-epimeroquinene derivatives starting from 1-(methoxycarbonyl)piperidine.

We have already exploited convenient methods for introducing various nucleophiles (Nu) to the unactivated 2- and/or 3-positions of 1-(methoxycarbonyl)piperidine (1) using anodic oxidation as a key reaction and synthesized some piperidine alkaloids.[1, 2]



1



2; R^1=-CH=CH_2, R^2=H

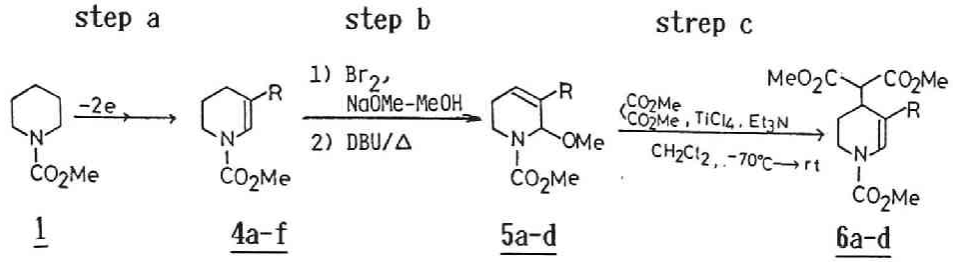
3; R^1=H, R^2=-CH=CH_2

This chapter describes a new method for introducing a bis(methoxycarbonyl)methyl group to the 4-position of 1[3] and its application to synthesis of (±)-meroquinene derivative 2[4] and (±)-epimeroquinene derivative 3,[5] synthetic key intermediates of (±)-quinine and (±)-ajmalicine, respectively.

Our method consists of three steps (a)-(c) which are shown in Scheme 1. Namely, 1 is transformed to 3-substituted enecarbamates 4 utilizing anodic

oxidation (step a), 4 is transformed into 3-substituted 2-methoxy-1,2,5,6-tetrahydropyridines 5 (step b), and a bis(methoxycarbonyl)methyl group is introduced to the 4-position of 5 to afford 6 (step c).

Scheme 1



a; R=H, b; R=Me, c; R=Et, d; R=Br, e; R=CHO, f; R=COMe

The detail of each step is as follows (Scheme 2): step a; Anodic oxidation of 1 in methanol followed by removal of methanol from the oxidized product 7 gave 4a.[6] The Vilsmeyer reaction or the Friedel-Crafts reaction to 4a afforded 4e,f,[6] and then the reduction of 4e,f (5 mmol) with $NaBH_4$ (12.5 mmol) in acetic acid (10 mL) and a treatment of the products with CF_3SO_3H (0.5 mL), successively, gave 4b,c.[7] 3-Bromo enecarbamate 4d was obtained by adding bromine (11 mmol) into a methanolic solution of 4a (10 mmol) and NaOMe (11 mmol) at room temperature followed by heating the product 8 in the presence of NH_4Cl[8] : step b; Addition of bromine (11 mmol) into a methanolic solution of 4a-d (10mmol) and NaOMe (11 mmol) at room temperature followed by treatment (90 ℃, 1.5 h) with DBU (15 mmol) afforded 5[9] : step c; a solution of dimethyl malonate (15mmol) and triethylamine (10 mmol) in CH_2Cl_2 (15mL) was added dropwise into a solution of 5 (10mmol) and $TiCl_4$ (10 mmol) in CH_2Cl_2 (15 mL) at -70℃ under an atmosphere of nitrogen and the resulting reaction mixture was gradually warmed to room temperature.

After the solution was stirred for 15 h, the usual working up gave 6. Yields of 4-6 are shown in Table 1.

Scheme 2[a]

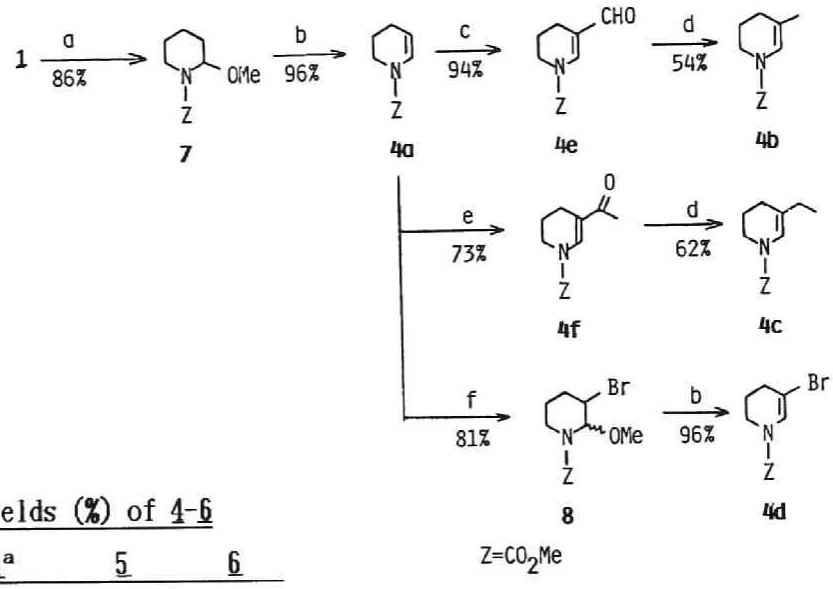


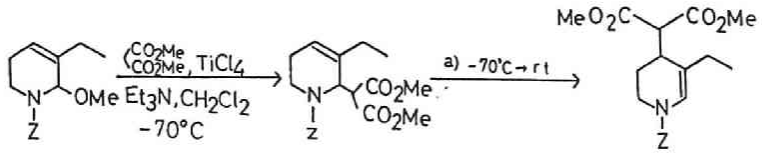
Table 1. Yields (%) of 4-6

	R	4[a]	5	6
a	H	83	58	6
d	Me	48	54	52
c	Et	33	73	91
d	Br	65	47	0

[a] Overall yield of 4 from 1.

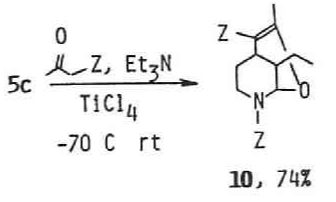
[a] (a) -2e/MeOH; (b) NH_4Cl/Δ; (c) i, DMF, $POCl_3$; ii, AcONa, H_2O; (d) i, $NaBH_4$, AcOH; ii, CF_3SO_3H; (e) AcCl, $SnCl_4$; (f) Br_2, NaOMe-MeOH

The reaction mechanism for alkylation of 5 at the 4-position with dimethyl malonate was scrutinized in the reaction of 5c with dimethyl malonate (eq 1). Namely, when the reaction was carried out at -70 °C, 9c was obtained in high yield. Furthermore, when the reaction mixture was warmed without isolation of 9c to room temperature, 6c was formed with disappearance of 9c. These results suggest that 9c is a kinetically controlled product and 6c is a thermodynamically controlled product.[10]

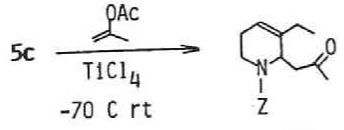


5c 9c, 89% 6c, 91% from 5c (1)

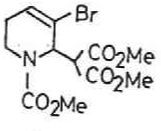
The formation of 6 seems to depend on the stability of Nu^- and/or the electronegativity of a substituent at 3-position of piperidine skeleton. Namely, while using methyl acetoacetate as Nu afforded bicyclic compound 10 (eq 2), isopropenyl acetate as Nu gave 2-substituted compound 11 (eq 3). Also, the reaction of dimethyl malonate with 5f possessing a bromo substituent at the 3-position gave 2-substituted product 9d (79%).



10, 74% (2)

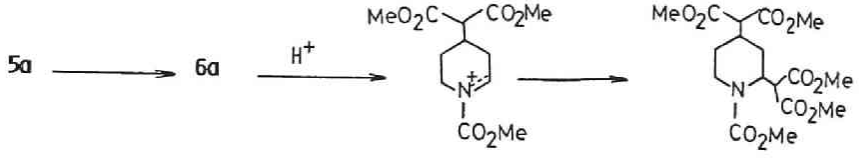


11, 61% (3)



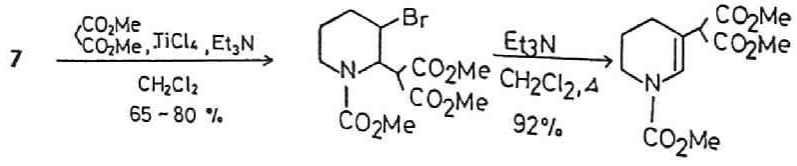
9d

In the case of 5a in which a substituent at the 3-position is a hydrogen, the initially formed 4-substituted product 6a was easily protonated at the uncrowded 3-position and thus 2,4-disubstituted compound 12 (54%) was obtained as main product (eq 4).



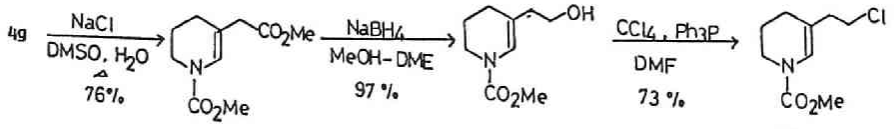
12 (4)

Next, our effort has been directed toward a synthesis of 2 and 3 using our method. A preparation of starting material 5j[11] was carried out by the method described bellow. Compound 4g was prepared according to our previously reporeted method in which a bis(methoxycarbonyl)methyl group could be introduced into 3-position of piperidine skeleton (eq 5).[2]

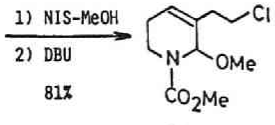


13 4g (5)

Demethoxycarbonylation of 4g and reduction of the product 4h gave 4i, which was transformed into 3-(2-chloroethyl)enecarbamate 4j. Then, iodomethoxylation[12] of 4j and dehydroiodination, successively, gave 5j (eq 6).



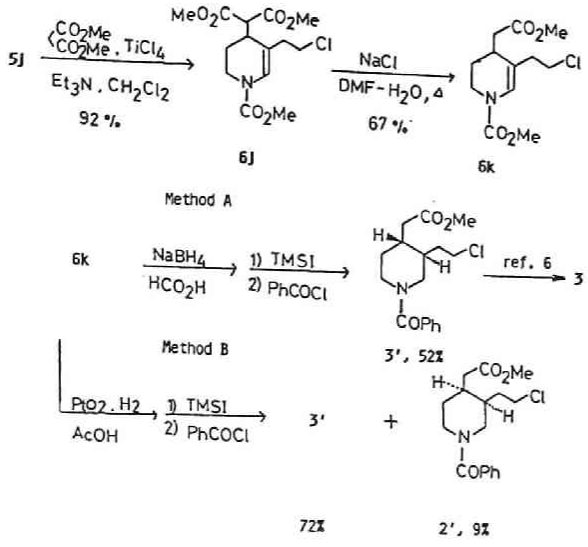
4h 4i 4j (6)



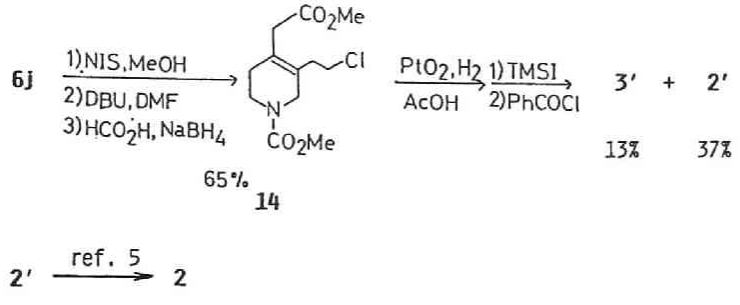
5j

The reaction of 5j with dimethyl malonate gave 6j in excellent yield. Decarboxylation of 6j gave 6k. By the reduction of 6k with $NaBH_4$ and successive 1-benzoylation(Method A) was obtained only trans-isomer 3'. Similarly the reduction of 6i with hydrogen (Method B) was yielded mainly trans-isomer (Scheme 3).

Scheme 3



To obtain selectively, 2' was thought to be needed the migration of unsaturated bond. In fact, compound 14 was hydrogenated to yield mainly 2' (eq 7). The easy transformation of 2' and 3' into 2 and 3, respectively, have already been reported.[4, 5, 13]



Experimental Section

Materials 4a,e,f,[6] 4d,[8] 5a,[9] and 13[2] were prepared by our previously

reported methods.

Preparation of 3-Alkylated Enecarbamates 4b and 4c. A general procedure is exemplified by preparation of 4c. Into a solution of 4f (0.82g, 4.5mmol) in acetic acid (20mL) was added in portions 90% $NaBH_4$ (2.54g, 67 mmol). After stirred at room temperature for 3h, into the solution was poured water (30mL). The organic layer was extracted with CH_2Cl_2 (3x30mL) and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane= 1:10) to afford 4c (0.37g, 52%).[8]

Similarly 4b [7] was prepared from 4e in 62% yield.

Bromomethoxylation[10] and dehydrobromination[10] was carried out according to known methods.

5b: IR (neat) 2940, 1705, 1440, 1200, 1180, 1080, 1060 cm^{-1}; NMR (CCl_4) δ 1.30-2.20 (m, 5H), 2.55-3.35 (m, 1H), 3.17 (s, 3H), 3.53 (s, 3H), 4.90 (br s, 1H), 5.30 (br s, 1H); MS, m/e 185.1067 (M^+, calcd for $C_9H_{15}NO_3$: 185.1052), 170, 155, 154 (base).

5c: IR (neat) 2940, 1710, 1450, 1342, 1208, 1075, 970, 772cm^{-1}; NMR (CCl_4) δ 1.01 (t, J=6.5Hz, 3H), 1.50-2.59 (m, 4H), 2.67-3.40 (m, 1H), 3.22 (s, 3H), 3.48-4.20 (m, 1H) 3.60 (s, 3H), 5.06 (br s, 1H), 5.27-5.57 (m, 1H). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.33; H, 8.73; N, 6.98.

5d: NMR (CCl_4) δ 1.80-2.40 (m, 2H), 3.35 (s, 3H), 3.68 (s, 3H), 5.72 (br s, 1H), 6.07-6.27 (m, 1H). Anal. Calcd for $C_8H_{12}BrNO_3$: C, 38.42; H,

4.84; Br, 31.95; N, 5.60. Found: C, 38.45; H, 4.88; Br, 32.19; N, 5.62.

$TiCl_4$-Catalyzed C-C Bond Formation. A General Procedure. Into a solution of $TiCl_4$ (1.4mL, 12.6mmol) in dry CH_2Cl_2 (10mL) was added dropwise a solution of 5c (2.5g, 12.5mmol) in dry CH_2Cl_2 (15mL) at -70°C under an atmosphere of nitrogen. After stirred for 10min at the temperature, into the solution was added dropwise a solution of dimethyl malonate (2.1mL, 18.8 mmol) and triethylamine (1.4mL, 12.5mmol) in dry CH_2Cl_2 (10mL). The resulting reaction mixture was stirred for 15h until it was warmed to room temperature. The solution was poured into water (25mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x20mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 6c (3.4g, 91%). Similarly 6a,b, 9d, 10, 11, and 12 were obtained. On the other hand, in order to obtain 9c from 6c was carried out this reaction at -70°C for 1h.

6c: IR (neat) 2960, 1750, 1710, 1665, 1445, 1320, 1295cm^{-1}; NMR (CCl_4) δ 1.00 (t, J=7Hz, 3H), 1.70-2.20 (m, 4H), 2.75-3.05 (m, 1H), 3.15-3.65 (m, 3H), 3.69 (m, 9H), 6.57 (br s, 1H). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 55.93; H, 7.30; N, 4.43.

6a: IR (neat) 2975, 1760, 1740, 1720, 1660, 1450, 1200cm^{-1}; NMR (CCl_4) δ 1.35-2.35 (m,2H), 2.50-4.05 (m, 4H), 3.68 (s, 9H), 4.45-4.82 (m, 1H), 6.55-6.90 (m, 1H); MS, m/e 271.1054 (M^+, calcd for $C_{12}H_{17}NO_6$: 271.1056), 212, 140 (base).

6b: IR (neat) 2960, 1760, 1740, 1710, 1670, 1450 cm^{-1}; NMR (CCl_4) δ

1.75 (br s, 3H), 1.80-2.05 (m, 2H), 2.65-3.05 (m, 1H), 3.35-3.70 (m, 3H), 3.70 (s, 9H), 6.60 (br s, 1H). Anal Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.68; H, 6.71; N, 4.78.

9c: IR (neat) 2969, 1760, 1670, 1445, 1300, 1200, 1160cm^{-1}; NMR (CCl_4) δ 1.03 (t, J=7Hz, 3H), 1.60-2.30 (m,4H), 2.70-4.23 (m, 4H), 3.63 (s, 3H), 3.65 (s, 3H), 3.67 (s, 3H), 5.05 (br d, J=6H, 1H), 5.43 (br s, 1H). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 55.99; H, 7.04; N, 4.73.

9d: IR (neat) 2965, 1745, 1715, 1658, 1450, 1292cm^{-1}; NMR (CCl_4) 2.00 -2.48 (m, 2H), 2.85-3.60 (m,1H), 3.60-4.30 (m, 4H), 3.67 (s, 9H), 5.05-5.30 (m, 1H), 6.07-6.45 (m, 1H). Anal. Calcd for $C_{12}H_{16}BrNO_6$: C, 41.16; H, 4.61; Br, 22.82; N, 4.00. Found: C,40.91; H, 4.62; Br, 23.10; N, 4.12.

10: IR (neat) 2960, 1760, 1740, 1670, 1445, 1300, 1200, 1160cm^{-1}; NMR (CCl_4) δ 0.80-2.05 (m, 3H), 2.26 (s, 3H), 2.60-3.06 (m, 1H), 3.60-4.10 (m, 1H), 3.63 (s, 3H), 3.69 (s, 3H), 5.75-6.10 (m, 1H). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.24; H, 7.52; N, 4.87.

11: IR (neat) 2980, 1720, 1708, 1675, 1455 cm^{-1}; NMR (CCl_4) δ 1.06 (br s, 3H), 1.64-3.20 (m, 5H), 2.12 (s, 3H), 3.60 (s, 3H), 3.70-4.22 (m, 1H), 4.50-4.85 (m, 1H), 5.40 (br s, 1H); MS, m/e 225.1369 (M^+, calcd for $C_{12}H_{19}NO_3$: 225.1365), 168 (base), 166.

12: IR (neat) 2970, 1760, 1740, 1705, 1455, 1280, 1200, 1030cm^{-1}; NMR (CCl_4) δ 0.90-2.50 (m, 4H), 2.70-4.40 (m, 5H), 3.53, 3.63, and 3.69 (3s,

15H), 4.60-5.05 (m, 1H). Anal. Calcd for $C_{17}H_{25}NO_{10}$: C, 50.62; H, 6.25; N, 3.47. Found: C, 50.39; H, 6.19; N, 3.50.

Preparation of 4g. After the solution of 13 (4.28g, 12.2mmol) and triethylamine in CH_2Cl_2 (14mL) was refluxed for 22h, the reaction mixture was poured into water. The organic portion was extracted with CH_2Cl_2 and the solvent was dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:5) to afford 4g (3.04g, 92%): IR (neat) 2970, 1760, 1740, 1720, 1670, 1450, 1270, 1200cm^{-1}; NMR (CCl_4) δ 1.50-2.30 (m, 4H), 3.40-4.00 (m, 3H), 3.69 (s, 9H), 6.68 (br s, 1H). Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16. Found: C, 52.84; H, 6.35; N, 5.09.

Demethoxycarbonylation of 4g. The solution of 4g (6.01g, 22.2mmol), NaCl (1.66g, 28.4mmol), and water (1.6mL, 89mmol) in DMSO (32mL) was heated at 170°C for 7h. After the solution was cooled down to room temperature, it was poured into water. The organic portion was extracted with CH_2Cl_2 and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 4h (3.61g, 76%): IR (neat) 2960, 1740, 1720, 1710, 1670, 1445, 1400, 1260, 1200cm^{-1}; NMR (CCl_4) δ 1.60-2.23 (m, 4H), 2.90 (br s, 2H), 3.40-3.60 (m, 2H), 3.60 (s, 3H), 3.67 (s, 3H), 6.65 (br s, 1H). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.25; H, 7.26; 6.53.

3-(2-Hydroxyethyl)-1-methoxycarbonyl-1,4,5,6-tetrahydropyridine (4i). Into a solution of 4h (3.6g, 16.9mmol) in DME (1mL) and MeOH (2.5mL) was added in portions 90% $NaBH_4$ (1.28g, 23.9mmol). After the reaction mixture was stirred at room temperature for 18h, it was poured into water (10mL).

The organic portion was extracted with CH_2Cl_2 (3x20mL) and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:2) to afford 4i (2.84g, 91%): IR (neat) 3450, 2950, 2900, 1710, 1700, 1680, 1460, 1400cm^{-1}; NMR (CCl_4) δ 1.55-2.30 (m, 6H), 3.35-3.70 (m, 5H), 3.67 (s, 3H), 6.57 (br s, 1H). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.08; H, 8.46; N, 7.36.

3-(2-Chloroethyl)-1-methoxycarbonyl-1,4,5,6-tetrahydropyridine (4j). A solution of 4i (0.7g, 3.8mmol), CCl_4 (0.42mL, 4.38mmol), and triphenylphosphine (1.14g, 4.38mmol) in DMF (10mL) was stirred at room temperature for 14h. After it was poured into water (15mL), the organic portion was extracted with ether (3x25mL). The solvent was dried over $MgSO_4$ and removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:3) to afford 4j(0.56g, 73%): IR (neat) 2960, 2880, 1720, 1710, 1670, 1445, 1400, 1320, 1260, 1195cm^{-1}; NMR (CCl_4) δ 1.60-2.20 (m, 4H), 2.30 (t, J=7Hz, 2H), 3.35-3.70(m, 4H), 3.67 (s, 3H), 6.65 (br s, 1H). Anal. Calcd for $C_9H_{14}ClNO_2$: C, 53.08; H, 6.93; Cl, 17.41; N, 6.88. Found: C, 52.86; H, 7.13; Cl, 17.14; N, 6.83.

3-(2-Chloroethyl)-2-methoxy-1-methoxycarbonyl-1,2,5,6-tetrahydropyridine (5j). Into a solution of 4j (0.19g, 0.93mmol) in methanol (8mL) was added NIS (0.31g, 1.4mmol). After stirred for 0.5h, it was poured into aqueous Na_2SO_3 (15mL). After the organic portion was extracted with CH_2Cl_2 (3x15mL), the solution was dried over $MgSO_4$. The solvent was removed in vacuo. The solution OF DBU (0.15mL, 1.03mmol) and the residue in DMF (18mL) was stirred at room temperature for 13h. The resulting reaction mixture was poured into water (30mL) and the organic portion was extracted with ether (3x30mL). It was dried over $MgSO_4$ and the solvent was removed in

vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 5j (0.18g, 81%): IR (neat) 3010, 2950, 1715, 1680, 1475, 1450, 1210, 1085, 1065cm^{-1}; NMR (CCl_4) δ 1.90-2.30 (m, 2H), 2.45 (t, J=7Hz, 2H), 2.70-3.15 (m, 1H), 3.27 (s, 3H), 3.20-3.70 (m, 2H), 3.65 (s, 3H), 3.70-4.10 (m, 1H), 5.17 (br s,1H), 5.65 (br s, 1H). Anal. Calcd for $C_{10}H_{16}ClNO_3$: C, 51.40 ; H, 6.90; Cl, 15.17; N, 5.99. Found: C, 51.33; H, 7.17; Cl, 14.88; N, 6.03.

4-Bis(methoxycarbonyl)-3-(2-chloroethyl)-methoxycarbonyl-1,4,5,6-tetrahydropyridine (6j) was prepared by the reaction of 5j with dimethyl malonate according to the general procedure described above: IR (neat) 2950, 1750, 1735, 1710, 1660, 1445, 1300, 1195cm^{-1}; NMR (CCl_4) δ 1.65-2.05 (m, 2H), 2.10-2.60 (m, 2H), 2.75-3.13 (m, 1H), 3.30-3.85 (m, 5H), 3.72 (s, 9H), 6.78 (br s, 1H); MS, m/e 333.0976 (M^+, calcd for $C_{14}H_{20}ClNO_6$: 333.0979), 284, 204, 202 (base).

4-(Methoxycarbonyl)methyl-3-(2-chloroethyl)-1-methoxycarbonyl-1,4,5,6-tetrahydropyridine (6k). A solution of 6j (0.302g, 0.906mmol), NaCl (0.082 g, 1.4mmol), and water (0.079mL, 4.37mmol) in DMF (3mL) was refluxed for 2.8 h. After the reaction mixture was poured into water (10mL), the organic portion was extracted with ether (3x15mL). It was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 6k (0.167g, 67%): IR (neat) 2960, 1740, 1715, 1670, 1450, 1400, 1200, 770cm^{-1}; NMR (CCl_4) δ 1.55-1.95 (m, 2H), 2.10-2.75 (m, 4H), 3.00-3.90 (m, 5H), 3.56 (s, 3H), 3.60 (s, 3H), 6.60 (br s, 1H). Anal. Calcd for $C_{12}H_{18}ClNO_4$: C, 52.28; H, 6.58; Cl, 12.86; N, 5.08. Found: C, 52.45; H,6.63; Cl, 12.63; N, 5.09.

trans-1-Benzoyl-3-(2-chloroethyl)-4-(methoxycarbonyl)piperidine (3').

Method A. Into a solution of 6k (0.099g, 0.36mmol) in formic acid (4mL) was added in portions 90% $NaBH_4$ (0.27g, 7.19mmol). After stirred for 0.5h, the reaction mixture was poured into aqueous $NaHCO_3$ (15mL). The organic portion was extracted with CH_2Cl_2 (3x15mL) and dried over $MgSO_4$. After the solvent removed in vacuo, into a solution of the residue in $CHCl_3$ (3mL) was added iodotrimethylsilane (0.077mL, 0.54mmol). After the reaction mixture was heated at 50°C for 1h, it was cooled down to room temperature. Into it was added MeOH (2mL) and stirred 0.5h. Into it was added aqueous K_2CO_3 (10mL) and benzoyl chloride (0.04mL, 0.36mmol) and stirred for 6h. Into the resulting reaction mixture was poured water (10mL) and the organic portion was extracted with CH_2Cl_2 (3x10mL). The extract was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:3) to afford 3'(0.058g, 52%).[5]

Metod B. A solution of 6k (0.26g, 0.94mmol) in acetic acid (5mL) containing cat.amt. of PtO_2 was stirred under hydrogen atmosphere (10kg/cm^2) at room temperature. After stirred for 20h, the treatment similar to Method A afforded 2' (0.027g, 9%)[4] and 3' (0.22g, 72%).

3-(2-Chloroethyl)-1-(methoxycarbonyl)-4-(methoxycarbonyl)methyl-1,2,5,6-tetrahydropyridine (14). Into a solution of 6j (0.465g, 1.69mmol) in methanol (5 mL) was added NIS (0.417g, 1.85mmol). After stirred for 1h, it was poured into aqueous Na_2SO_3 (10mL). After the organic portion was extracted with CH_2Cl_2 (3x15mL), the solution was dried over $MgSO_4$. The solvent was removed in vacuo. The solution OF DBU (0.15mL, 1.03mmol) and the residue in DMF (18mL) was stirred at room temperature for 13h. The resulting reaction mixture was poured into water (30mL) and the organic

portion was extracted with ether (3x30mL). It was dried over $MgSO_4$ and the solvent was removed in vacuo. Into a solution of the residue in formic acid (8mL) was added a portion 90% $NaBH_4$ (0.32g, 8.4mmol). After stirred for 0.5h, the reaction mixture was poured into aqueous $NaHCO_3$ (15mL). The organic portion was extracted with CH_2Cl_2 (3x15mL) and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 14 (0.303g, 65%): IR (neat) 2960, 1740, 1705, 1450, 1250cm^{-1}; NMR (CCl_4) δ 1.95-2.35 (m, 2H), 2.52 (br t, J= 8Hz, 2H), 3.05 (br s, 2H), 3.30-3.70 (m, 4H), 3.65 (s, 6H), 3.70-3.97 (m, 2H). Anal. Calcd for $C_{12}H_{18}ClNO_4$: C, 52.28; H, 6.58; Cl, 12.86; N, 5.08. Found: C, 52.20; H, 6.69; Cl, 12.67; N, 5.00.

cis-1-Benzoyl-3-(2-chloroethyl)-4-(methoxycarbonyl)piperidine (2'). The procedure similar to Method B gave 2' (37%) and 3' (13%).

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b) Idem. Org. Synth. 1984, 63, 206, and references cited therein.

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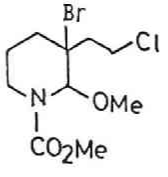
8. Shono, T.; Matsumura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T. J. Org. Chem. 1987, 52, 536.
9. Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. Tetrahedron Lett. 1987, 28, 4073.
10. The Lewis acid induced reaction of 1-ethoxycarbonyl-4-hydroxy-1,2,3,4-tetrahydropyridine with heteroatom nucleophiles gave 4-substituted compounds, while it with carbon nucleophiles gave 2-substituted ones, see: Kozikowski, A. P.; Park, P. J. Org. Chem. 1984, 49, 1674.
11. Uskokovic et al. synthesized 2 and 3 via cis-1-benzoyl-3-(2-chloroethyl)-4-(methoxycarbonyl)methylpiperidine 2' and trans-isomer 3',[4,5] we selected 2' and 3' as synthetic targets.
12. Since the dehydrobromination of 15 gave 6j in low yield, the iodomethoxylation of 4j was carried out.



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Chapter 4-2

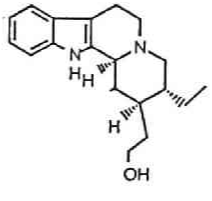
An Approach to Synthesis of (-)-Dihydrocorynantheol from L-Lysine Using Anodic Oxidation.

Abstract: A key intermediate for the (-)-Dihydrocorynantheol synthesis was prepared with high optical purity by utilyzing stereoselective introducing carbon chain into the 2-, 4-, and 5-position of anodically prepared pipecolinic acid derivative from L-lysine.

Synthesis of optically active piperidine alkaloids from L-lysine is particularly interesting since the piperidine skeleton found in some natural piperidine alkaloids has been known to be formed from L-lysine.[1]

In this viewpoint we have synthesized optically active piperidine alkaloids from L-lysine using anodic oxidation as key reactions.[2]

This paper describes a synthesis of (-)-dihydrocorynantheol (1), which was first isolated from Aspidosperma marcgravianum.[3,4] Our synthetic route is shown in Scheme 1, which containes two our previously reported methods. Namely, one is the anodic transformation of L-lysine to optically active pipecolinic acid.[5] The other is an introducing carbon chain into the 3- and /or 4-position of piperidine skeleton.[6]



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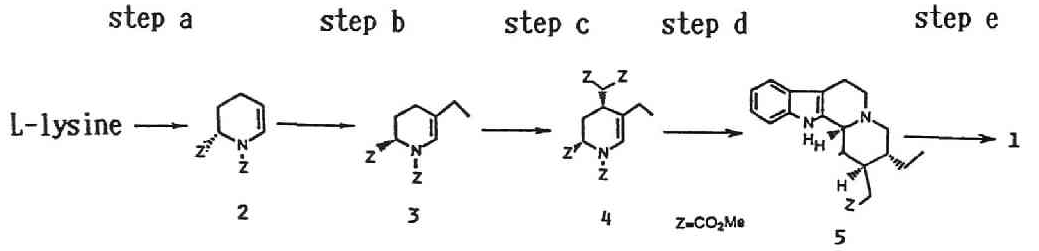
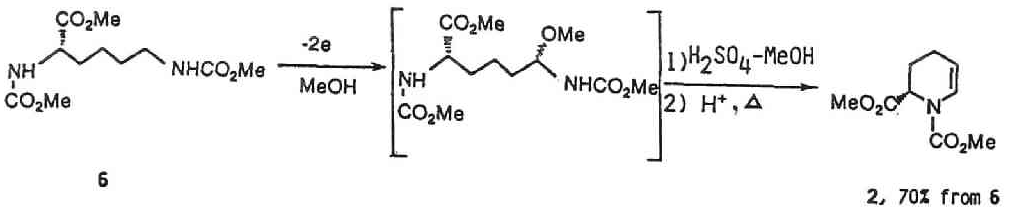
Scheme 1



This route consists of four steps: step a; Pipecolinic acid derivatives 2 was prepared by anodic oxidation of L-lysine derivatives and treatment of the product with acid: step b; Introduction of ethyl group of into the 5-position of 2: step c; Introduction of bis(methoxycarbonyl)-methyl group into the 4-position of 3: step d; Condensation of 4 with tryptphyl bromide: step e; Transformation of 5 into 1.

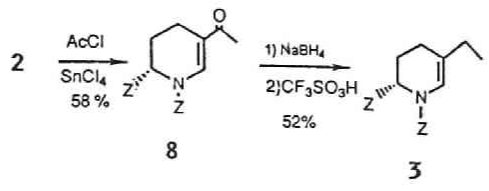
The details of each step is described bellow.

step a. The content of this step was reported by us (eq 1).[4]



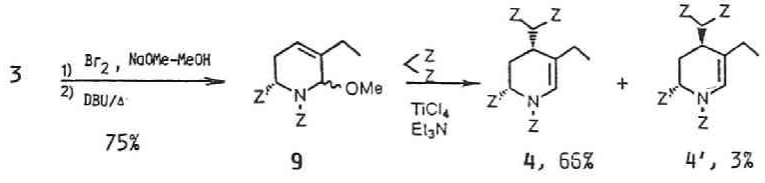
(1)

step b. Friedel-Crafts reaction of 2 with acetyl chloride gave 5-acetylated product 7 in 58% yield,[7] which was transformed into 5-ethyl compound 3 by the reduction of 2 with $NaBH_4$ in acetic acid and the treatment of the product with CF_3SO_3H in 52% yield (eq 2).



(2)

step c. Bromomethoxylation of 3 and followed by base treatment of the product afforded 9 (75% yield from 3).[8] Then, by $TiCl_4$-catalyzed condensation of 9 with dimethyl malonate was obtained cis-4-substituted compound 4 (66% yield) together with small amountof trans-isomer 4' (3% yield) (eq 3).[6] The ratio of 4 and 4' (96:4) was measured by separation with column chromatography.

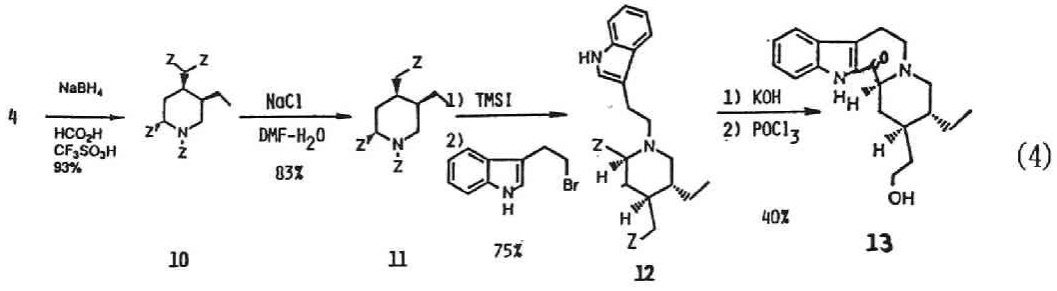


(3)

step d. Reduction of 4 with $NaBH_4$ in acidic solvent gave (2S,4S,5R)-1,2,4,5-tetrasubstituted piperidine derivative 10 in 93% yield, which was transformed into 11 by the demethoxycarbonylation in 83% yield. Transformation of 1-methoxycarbonyl group of 11 into tryptphyl group gave 12 in 75% yield. By hydrolysis of 12 and follwed by the treatment with $POCl_3$,however, was obtained 13 in 40% yield (eq 4) instead of 5.[9]

On the other hand, the hydrogenation of 4 afforded (2S,4R,5R)-isomer 13 (eq 5). This compound may be a important precurcer for syntheses of hetero-

reserpine alkaloids.



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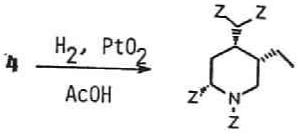

(5)

step e. The reduction of 5 with LAH may afford (-)-1 (eq 6).

(6)

In conclusion, anodically prepared pipecolinic acid derivative from L-lysine was trnasformed into a key intermediate for the (-)-dihydrocorynantheol synthesis with high optical purity. This method will be effective in the synthesis of various optically active piperidine alkaloids.

Experimental Section

Compound 2 was prepared according to our previously reported method.[4]

Acetylation of 2. Into a solution of AcCl (12.2mL, 172mmol) in dry CH_2Cl_2 (30mL) was added dropwise a solution of $SnCl_4$ (8.1mL, 69mmol) in dry CH_2Cl_2 (30mL) at -70°C under an atmosphere of nitrogen. After stirring for 10min, into the reaction mixture was added dropwise a solution of 2 (6.84g, 34.4mmol) in dry CH_2Cl_2 (30mL). After the solution was gradually warmed to room temperature and stirred overnight. The mixture was poured into cold water (50mL) and the organic layer was separated. The solution was washed with aq. Na_2CO_3 (50mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel (AcOEt:hexane=1:2) to afford 8 in 58% yield: IR (neat) 2975, 1740, 1660, 1640, 1448, 1255, 1200 cm^{-1}; NMR (CCl_4) δ 1.57-2.77 (m, 4H), 2.24 (s, 3H), 3.74 (s, 3H), 3.86 (s, 3H), 4.77 (br s, 1H), 7.90 (br s, 1H); MS, m/e 241 (M^+), 226, 182 (base); exact mass calcd m/e 241.0950, found 241.0930.

Preparation of 3. Into a solution of 8 (0.64g, 2.66mmol) in HCO_2H (20 mL) was added, in portions, 90% $NaBH_4$ (0.892g, 21.2mmol). After stirring for 1h, into the solution was added water (20mL). The product was extracted with CH_2Cl_2 (3x30mL) and dried over $MgSO_4$. After the solvent was removed in vacuo, into the residue was added CF_3SO_3H (0.1mL). After stirring for 1h, into the solution was poured water (20mL). The product was extracted with CH_2Cl_2 (3x 30mL) and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:5) to afford 3 (0.311g, 52%): IR (neat) 2980, 1760, 1720, 1685, 1455, 800, 745 cm^{-1}; NMR (CCl_4) δ 1.01 (t, J=7.5Hz, 3H), 1.70-2.50 (m, 6H),3.63 (s, 3H),

3.68 (s, 3H), 4.50-4.80 (m, 1H), 6.50 (br d, J=7Hz, 1H). Anal.Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.14. Found: C, 58.08; H, 7.73; N, 6.22.

Preparation of 9. Into a solution of 3 (1.213g, 5.34mmol) and Na (0.15g, 6.41mmol) in MeOH (15mL) was added dropwise bromine (0.33mL, 6.41 mmol). After stirring for 10min, into the solution was poured aq. $Na_2S_2O_3$ (20mL). The product was extracted with CH_2Cl_2 (3x20mL) and dried over $MgSO_4$. After the solvent was removed in vacuo, a solution of the residue and DBU (1.6mL, 10.7mmol) in DMF (5mL) was heated (95 °C) for 2h. The solvent was removed in vacuo and the residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 9 (1.029g, 75%): IR (neat) 2952, 1748, 1710, 1444, 1310, 1208, 1070cm^{-1}; NMR (CCl_4) δ 1.01 (t, J=7Hz, 3H), 1.50-2.70 (m, 4H), 3.30 (br s, 3H), 3.67, 3.70, and 3.74 (3s, 6H), 4.60-5.70 (m, 3H); MS, m/e 257.1278 (calcd for $C_{12}H_{19}NO_5$: 257.1263), 226, 198, 166 (base).

$TiCl_4$-Catalyzed Condensation. Into a solution of $TiCl_4$ (1.13mL, 10.3 mmol) in dry CH_2Cl_2 (10mL) was added dropwise a solution of 9 (1.758g, 6.84 mmol) in dry CH_2Cl_2 (10mL) at -70 °C under an atmosphere of nitrogen. After stirring for 10min, into the solution was added dropwise a solution of dimethyl malonate (1.17mL, 10.2mmol) and Et_3N (1.43mL, 10.3mmol) in dry CH_2Cl_2(10mL). After the solution was gradually warmed to room temperature and stirred overnight. Into the mixture was poured water (20mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2x20mL). The combined organic layer was dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane=1:4) to afford 4 (1.608g) and 4' (0.075g) in 66% and 3% yields, respectively.

4 (less polar isomer): IR (neat) 2970, 1760, 1740, 1725, 1452, 1215cm^{-1} ; NMR (CCl_4) δ 0.98 (br t, J=7Hz, 3H), 1.70-3.30 (m, 6H), 3.62 (s, 12H), 4.20-4.80 (m, 1H), 6.60 (br d, J=7.5Hz, 1H). Anal. Calcd for $C_{16}H_{23}NO_8$: C, 53.78; H, 6.49; N, 3.92. Found: C, 53.98; H, 6.45; N, 3.70.

4' (polar isomer): IR (neat) 2975, 1740, 1720, 1450, 1200cm^{-1}; NMR (CCl_4) δ 1.07 (br t, J=7Hz, 3H), 1.70-3.30 (m, 4H), 1.80 (br s, 2H), 3.57, 3.63, and 3.70 (3s, 12H), 4.50-4.75 (m, 1H), 6.65 (br d, J=7Hz, 1H).

Reduction of 4. Into a solution of 4 (0.707g, 1.98mmol) in HCO_2H (10 mL) and CF_3SO_3H (0.5mL) was added, in portions, 90% $NaBH_4$ (0.25g, 5.94mmol). After stirring for 2h, into the solution was poured water (15mL). The product was extracted with CH_2Cl_2 (3x20mL). The solution was dried over $MgSO_4$ and the solution was removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:2) to afford 10 (0.663g, 83% yield): IR (neat) 2960, 2930, 1740, 1705, 1450, 1245, 1200, 1015cm^{-1}; NMR (CCl_4) δ 0.93 (t, J=4.5Hz, 3H), 1.00-2.25 (m, 6H), 2.90-5.00 (m, 4H), 3.70 (s, 12H). Anal. Calcd for $C_{16}H_{25}NO_8$: C, 53.47; H, 7.01; N, 3.90. Found: C, 53.69; H, 6.99; N, 3.67.

Catalytic Hydrogenation of 4. A mixture of 4 and a catalytic amount of PtO_2 in acetic acid was stirred overnight at room temperature under an atmosphere of hydrogen (1atm). After the catalyst and the solvent was removed to afford 14: IR (neat) 2980, 1744, 1715, 1452, 1202cm^{-1}; NMR (CCl_4) δ 0.73-2.05 (m, 9H), 2.80-4.00 (m, 3H), 3.60 (s, 6H), 3.64 (s, 3H), 3.68 (s, 3H), 4.68 (br d, J=10H, 1H).

Demethoxycarbonylation of 10. A solution of 2 (0.798g, 2.22mmol), NaCl (0.2g, 3.33mmol), and water (0.2mL) in DMF (10mL) was heated (150 ℃). After 7h, into the solution was poured water (20mL). The product was extracted with CH_2Cl_2 (3x30mL). The solution was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane=1:2) to afford 11 (0.558g, 83% yield): IR (neat) 2970, 1742, 1710, 1450cm^{-1}; NMR (CCl_4) δ 0.94 (br t, J=5Hz, 3H), 1.10-3.40 (m, 9H), 3.61 and 3.67 (2s, 9H), 3.70-4.93 (m, 2H). Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 56.01; H, 7.75; N, 4.60.

Preparation of 12. A solution of 11 (0.558g, 1.85mmol) and TMSI (0.5mL, 3.51mmol) in $CHCl_3$ (10mL) was heated (50℃). After 4.5h, into the solution was poured MeOH (5mL) at room temperature. After stirred for 30min, water (10mL) was poured into the reaction mixture. The organic portion was separated and the aqueous layer was extracted with CH_2Cl_2 (2x10mL). The combined organic layer was dried over $MgSO_4$ and the solution was removed in vacuo. A solution of the residue, tryptophile bromide (0.6g, 2.68mmol), and $NaHCO_3$ (0.78g, 9.29mmol) in CH_3CN (10mL) was stirred for 18h. After water (20mL) was poured into the reaction mixture, the product was extracted with AcOEt (3x30mL). The solution was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on alumina ($CHCl_3$:MeOH= 10:1) to afford 12 (0.535g, 75% yield): IR (neat) 3400, 2950, 1740, 1620, 1460, 1438, 1200, 1165, 740cm^{-1}; NMR ($CDCl_3$) δ 0.70-3.40 (m, 18H), 3.60 (s, 3H), 3.66 (s, 3H), 6.83-7.59 (m, 4H), 8.10 (br s, 1H); MS, m/e 386 (M^+), 327, 314, 257, 257 (base); exact mass calcd m/e 386.2205, found 386.2175.

Preparation of 13. A solution of 12 (0.252g, 0.65mmol) and KOH (0.21g, 3.25mmol) in MeOH (10mL) and water (10mL) was heated at 60℃. After 7h,

dil. HCl was poured into the solution in order to be acidic. The solvent was removed in vacuo and into the residue was added $POCl_3$ (5mL). The reaction mixture was heated at 70℃ for 1h. This solution was added to a mixture of AcOEt (50mL) and saturated $NaHCO_3$ (100mL) and stirred for 1h. The sepatatedorganic layer was evaporated and into the residue was poured MeOH (10mL). In the solution was blew dry HCl. After stirring overnight, the solvent was evaporated. Into the residue was added water (10mL) and the aqueous layer was washed with CH_2Cl_2 (10mL). The aqueous layer was basified with K_2CO_3 and extracted with CH_2Cl_2 (3x10mL). The extracts was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on alumina (AcOEt:hexane=1:5) to afford yellow crystal 5 (0.085g, 0.26mmol) in 40% yield: mp 175-176℃ (CH_2Cl_2-hexane); IR (KBr) 3340, 1740, 1618, 1060, 742cm^{-1}; 0.70-3.70 (m, 17H), 3.60 and 3.63 (2s, 3H), 6.80-7.67 (m, 4H), 8.93-9.33 (m, 1H); MS, m/e 355, 354 (M^+ ,base), 325, 229, 184.

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Chapter 5-1

A New Method for Regioselective Synthesis of 2-Substituted-1-(methoxycarbonyl)-1,2-dihydropyridines and 5-Substituted Ones

Abstract: 2-Substituted 1,2-dihydropyridines were regioselectively prepared starting from 2-substituted piperidines through three intermediates, that is, (a) 1,2,3,4-tetrahydropyridines, (b) 5-bromo-6-methoxypiperidines, and (c) 1,2,3,6-tetrahydro-6-methoxypyridines. By the similar procedure was obtained 5-substituted 1,2-dihydropyridines.

Since 1-acyl-1,2-dihydropyridines have been known to be useful synthetic intermediates as exemplified by their Diels-Alder type reaction to form nitrogen-heterocycles,[1] a variety of methods have been reported for synthesis of these dienes.[2]

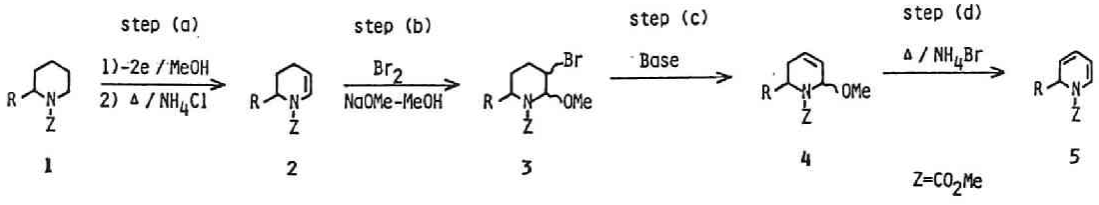
Although the reported syntheses known to be useful ones have been carried out by reduction of pyridinium salts[3] or by addition of organometallic reagents to pyridinium salts,[4] these methods form both 1,2- and 1,4-dihydropyridines. Thus, convenient methods for the synthesis of 1,2-dihydropyridines, especially those possessing substituents at certain positions of pyridine nucleus, are quite few so far.[5]

In this chapter is described a new facile method for the regioselective synthesis of 2-substituted-1-(methoxycarbonyl)-1,2-dihydropyridines 5 and 5-substituted ones 11 from piperidines 1.

Scheme I shows our method which comprises four steps (a)-(d), that is, (a) preparation of 1,2,3,4-tetrahydropyridines 2 from 1 , (b) bromomethoxylation of 2 giving 5-bromo-6-methoxy compounds 3,(c) dehydrobromination of 3 giving 1,2,3,6-tetrahydro-6-methoxypyridines 4, and

(d) elimination of methanol from 4 affording 5.

Scheme I



The preparation of 2a-d was achieved according to our previously reported method which consisted of anodic oxidation of 1a-d in methanol and elimination of methanol from the oxidized products.[6]
The subsequent transformation of 2a-d to 5a-d was carried out as follows: The addition of bromine (1.1eq.) to a solution of 2a-d in methanol containing sodium methoxide (1.1eq.) at room temperature gave 3a-d,[7] which was then dehydrobrominated by treatment with bases[8] (DBU in DMF, 90°C or electrochemically generated 2-pyrrolidone anion[9] in DMF at room temperature) to afford 4a-d. The desired 5a-d were obtained by heating (90-100°C) 4 in the presence of a catalytic amount of NH_4Br(0.01eq.) under reduced pressure (70 ~ 100 mmHg) for 60 ~120 min.[6] The yields of 2a-d-5a-d are summarized in Table 1.

The compounds 4 and 5 were found to give the Diels-Alder type adducts upon reaction with dienophiles. For example, the reaction of 4c with dimethyl fumarate gave the [4+2]cycloadduct 6 in 54% yield (eq 1).

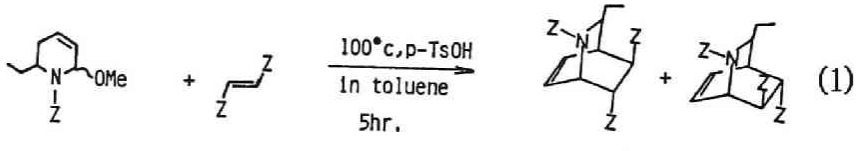


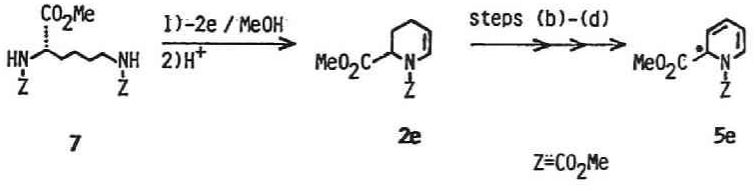
Table 1. Isolated Yields(%) of Compounds 2a-d-5a-d.

	R	2	3	4		5
a	H	83	80	72[a]	(77)[b]	65
b	Me	64	80	50[a]		65
c	Et	74	84	74[a]		89
d	CH_2COMe	60	56	78[a]		85

[a] DBU was used as a base.

[b] Electrochemically generated 2-pyrrodine anion was used as a base.

Our method was applied to the synthesis of the optically active diene 5e, which might be an useful intermediate for the construction of optically active nitrogen heterocycles. The optically active key intermediate 1,2,3,4-tetrahydropyridine 2e was preparable by our reported method starting from L-lysine derivative 7 (eq 2).[10] The optical purity of 5e [11] {$[\alpha]_D^{25}$ -516.7° (c 1.2, MeOH)}, obtained according to the procedures shown above (3e, 72%; 4e, 80%; 5e, 80%), was found to be at least 77% ee after it was converted to 1e(R=CO_2Me) by hydrogenation and the optical purity of 1e {$[\alpha]_D^{25}$ -46.9° (c 1.5, MeOH)} was compared with that of an authentic sample {$[\alpha]_D^{25}$ -60.9° (c 1.5, MeOH)}.



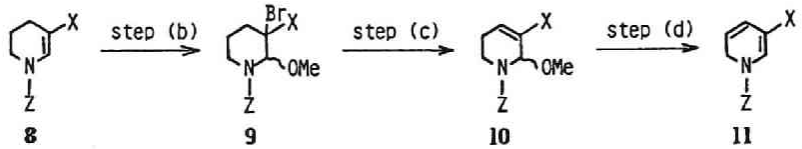
7 2e 5e

Z=CO_2Me

(2)

Although the optical purity is not satisfactory at present, 5e is the first example of optically active 1,2-dihydropyridine. In the next Chapter is described the synthesis of optically pure 1,2-dihydropyridines, and their utilization in organic synthesis.

Furthermore, since 1,2-dihydropyridines bearing sustituents at the 5-position are frequently required in natural product synthesis,[2b, 5a] by utilizing this method were prepared 5-substituted 1,2-dihydropyridines 11 from 5-substituted 1,2,3,4-tetrahydropyridines 8 which were obtained electrochemically (eq 3).



8 9 10 11 (3)

f, X=Ac
g, X=Cl
h, X=Et

In summary, advantages of our method are as follows: (i) The products, 1,2-dihydropyridines 5 are completely uncontaminated with 1,4-isomers, (ii) the each step is simple, (iii) the starting compounds 1 possessing a variety of substituents R is easily preparable by our reported method,[8, 11] and (iv) optically acitve 1,2-dihydropyridines could be prepared as shown above.

Experimental Section

Compounds 2a,[6] 2b,[6] 2e,[10] 8f,[6] 8g,[7] 8h[12] were prepared according to our previously reported method.[6] Similarly 1c, 2c, and 2d were synthesized.

1c: bp 80 °C/6mmHg; IR (neat) 2940, 2870, 1700, 1452, 1260 cm^{-1}; NMR (CCl_4) δ 0.84 (t, J=9Hz, 3H), 1.17-1.91 (m, 8H), 2.53-2.98 (m, 1H), 3.57

(s, 3H), 3.75-4.25 (m, 2H). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18. Found: C, 62.85; H, 10.20; N, 8.26.

2c: IR (neat) 2970, 1714, 1658, 1445, 1415, 1361, 1120, 772 cm^{-1}; NMR (CCl_4) δ 0.90 (t, J=6.5 Hz, 3H),1.20-2.21 (m, 6H), 3.62 (s, 3H), 3.80-4.31 (m, 1H), 4.35-4.90 (m, 1H), 6.36-6.75 (m, 1H). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found:C, 63.71; H, 9.00; N, 8.11.

2d: IR (neat) 2975, 1718, 1660, 1450, 1367 cm^{-1}; NMR (CCl_4) δ1.60-2.27 (m, 4H), 2.10 (s, 3H), 2.51 (d, J=7Hz, 2H), 3:65 (s, 3H), 4.33-4.90 (m, 2H), 6.40-6.85 (m,1H); MS, m/e 197.1059 (M^+, calcd for $C_{10}H_{15}NO_3$: 197.1052), 140, 139, 138 (base).

Bromomethoxylation of 2 or 8. General procedure. Into a solution of 2 or 8 (20mmol) and Na (22mol) in methonl (25mL) was added bromine (22mol) at 5 ℃. After stirred for 10min, aq. Na_2SO_3 (30mL) was poured into the reaction mixtue. The organic portion was extracted with CH_2Cl_2 (3x30mL). The extract was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on silica gel (AcOEt-hexane) to afford 3 or 8. The spectroscopic data of 3a was consistent with the authentic sample.[7]

3b: IR (neat) 2965, 1715, 1448, 1358, 1305, 1069 cm^{-1}; NMR (CCl_4) δ 1.23 and 1.26 (2d, J=7 and 7Hz, 3H), 1.54-2.55 (m, 4H), 3.23 and 3.33 (2s, 3H), 3.62 and 3.65 (2s, 3H), 4.10-4.50 (m, 2H), 5.33 (br s, 1H). Anal. Calcd for $C_9H_{16}BrNO_3$: C, 40.63; H, 6.06; Br, 30.02; N, 5.26. Found: C, 40.60; H, 6.15; Br, 30.27; N, 5.20.

3c: IR (neat) 2970, 1718, 1448, 1360, 1305, 1075, 946, 779 cm^{-1}; NMR (CCl_4) δ 0.89 (t, J=6.5Hz, 3H), 1.21-2.67 (m, 6H), 3.25 and 3.33 (2s, 3H), 3.62 (s, 3H), 3.70-4.30 (m, 2H), 5.28 (br s, 1H). Anal. Calcd for $C_{10}H_{18}BrNO_3$: C, 42.87; H, 6.48; Br, 28.52; N, 5.00. Found: C, 42.92; H, 6.59; Br, 28.74; N, 4.99.

3d: IR (neat) 2965, 1722, 1715, 1450, 1363, 1300, 1078 cm^{-1}; NMR (CCl_4) δ 1.00-2.84 (m, 6H), 2.05 (s, 3H), 3.19 (s, 3H), 3.58 (s, 3H), 4.01-4.19 (m, 1H), 4.27 (m, 1H), 5.17 (br s, 1H). Anal. Calcd for $C_{11}H_{18}BrNO_4$: C, 42.87; H, 5.89; Br, 25.93; N, 4.55. Found: C, 43.16; H, 5.98; Br, 26.00; N, 4.45.

3e: IR (neat) 2965, 1742, 1715, 1444, 1083 cm^{-1}; NMR (CCl_4) δ 1.55-2.60 (m, 4H), 3.27 (s, 3H), 3.65 (s, 3H), 3.73 (s, 3H), 4.06-4.30 (m, 1H), 4.52-4.95 (m, 1H), 5.29 (br d, J=9Hz, 1H). Anal. Calcd for $C_{10}H_{16}BrNO_5$: C, 38.73; H, 5.20; Br,25.76; N, 4.52. Found: C, 38.79; H, 5.17; Br, 25.55; N, 4.55.

9f: IR (neat) 2960, 1718, 1450, 1235, 1180cm^{-1}; NMR (CCl_4) δ 1.47-2.16 (m, 4H), 2.33 (s, 3H), 2.57-3.10 (m, 1H), 3.25 (s, 3H), 3.70-4.23 (m, 1H), 3.73 (s, 3H), 5.47-5.77 (m, 1H). Anal. Calcd for $C_{10}H_{16}BrNO_4$: C, 40.83; H, 5.48; Br,27.16; N, 4.76. Found: C, 40.55; H, 5.42; Br, 27.28; N, 4.88.

9g: IR (neat) 2965, 1715, 1452, 1405, 1280, 1085, 777cm^{-1}; NMR (CCl_4) δ 1.36-3.17 (m, 5H), 3.40 (s, 3H), 3.64-4.26 (m, 1H), 3.74 (s, 3H), 5.21-5.61 (m, 1H). Anal. Calcd for $C_8H_{13}BrClNO_3$: C, 33.53; H, 4.57; Br,27.88; Cl, 12.37; N, 4.89. Found: C, 33.52; H, 4.62; Br, 27.64; Cl, 12.27; N,

4.94.

9h: IR (neat) 2970, 1720, 1455, 1290, 1083cm^{-1}; NMR (CCl_4) δ 1.10 (t, J=6.5Hz, 3H), 1.30-1.68 (m, 1H), 1.69-2.52 (m, 5H), 2.54-3.12 (m, 1H), 3.25 (s, 3H), 3.55-4.31 (m, 1H), 3.71 (s, 3H), 5.13 and 5.33 (2s, 1H). Anal. Calcd for $C_{10}H_{18}BrNO_3$: C, 42.87; H, 6.48; Br,28.52; N, 5.00. Found: C, 42.61; H, 6.36; Br, 28.48; N, 5.13.

Dehydrobromination of 3 or 9. General procedure. A solution of 3 or 9 (10 mmol) and DBU (15mmol) in DMF (10mmol) was heated (95 ℃) for 2h. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt-hexane) to afford 4 or 9. In the case of 8f was afforded 10f by the this procedure.

4a: IR (neat) 3000, 1710, 1658, 1472, 1448 cm^{-1}; NMR (CCl_4) δ1.87-2.27 (m, 2H), 2.86-3.35 (m, 1H), 3.29 (s, 3H), 3.70 (s, 3H), 3.78-4.17 (m, 1 H), 5.34 (br s, 2H), 5.57-6.08 (m, 1H). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.34; H, 7.90; N, 8.21.

4b: IR (neat) 2980, 2945, 1710, 1665, 1450, 1350, 1340, 1120, 1078 cm^{-1}; NMR (CCl_4) δ 1.26 (d, J=10Hz, 3H), 1.72-2.57 (m, 2H), 3.31 (s, 3H), 3.70 (s, 3H), 4.34-4.73 (m, 1H), 5.33 (br s, 1H), 5.79 (br s, 2H); MS, m/e 153, 138 (base), 94.

4c: IR (neat) 2970, 2945, 1710, 1670, 1450, 1354, 1325, 1125, 1078 cm^{-1}; NMR (CCl_4) δ 0.87 (t, J=10Hz, 3H), 1.30-2.50 (m, 4H), 3.30 (s, 3H), 3.63 (s, 3H), 3.90-4.41 (m, 1H), 5.23 (br s, 1H), 5.63 (br s, 2H). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28;H, 8.60; N, 7.03. Found: C, 59.45; H, 8.57;

N, 6.91.

4d: IR (neat) 2978, 1730, 1718, 1672, 1456, 1358, 1330, 1080, 960, 781 cm^{-1}; NMR (CCl_4) δ 1.94-2.45 (m, 2H), 2.07 (s, 3H), 2.76 (t, J=3.5Hz, 2H), 3.28 (s, 3H), 3.68 (s, 3H), 4.57-5.01 (m, 1H), 5.26 (br s, 1H), 5.66 (br s, 2H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 59.32; H, 7.79; N, 6.07.

4e: IR (neat) 2965, 1745, 1715, 1670, 1450, 1325 cm^{-1}; NMR (CCl_4) δ 2.15-2.58 (m, 2H), 3.17 and 3.21 (2s, 3H), 3.53 and 3.56 (2s, 3H), 3.63 (s, 3H), 4.63-5.00 (m, 1H), 5.05-5.40 (m, 1H), 5.45-5.97 (m, 2H). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.55; H, 6.82; N, 5.82.

10g: IR (neat) 2950, 1710, 1658, 1442, 1318, 1295, 1095, 1082, 975 cm^{-1}; NMR (CCl_4) δ 1.90-2.50 (m, 2H), 2.85-3.40 (m, 1H), 3.38 (s, 3H), 3.65-4.20 (m, 1H), 3.73 (s, 3H) 5.25 (br s, 1H), 5.93 (dd, J=6 and 3Hz, 1H); MS, m/e 207, 205.0491 (M^+, calcd for $C_8H_{12}ClNO_3$: 205.0505), 190, 176, 174 (base).

10h: IR (neat) 2940, 1710, 1668, 1450, 1342, 1208, 1075, 970, 772 cm^{-1}; NMR (CCl_4) δ 1.01 (t, J=6.5Hz, 3H), 1.59-2.50 (m, 4H), 2.67-3.40 (m, 1H), 3.22 (s, 3H), 3.48-4.20 (m, 1H), 3.60 (s, 3H), 5.06 (br s, 1H), 5.27-5.57 (m, 1H). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.33; H, 8.73; N, 6.98.

Preparation of 5 or 11. General procedure. A mixture of 4 or 10 (5mmol) and NH_4Cl (10mg) was heated (100℃) under reduced pressure (80mmHg). After 2h, the product was isolated by distillation directly from the reaction

flask.

1,2-Dihydropyridines 5a,[4b] b,[2f] c,[5d] and 11h[1a] were known compounds. New dienes 5d,e and 11f,g were charactized by spectroscopic data.

5d: IR (neat) 2975, 1726, 1718, 1655, 1650, 1587. 1450, 1353, 1270, 1122, 776, 732 cm^{-1}; NMR (CCl_4) δ 2.17 (s. 3H), 2.51-3.04 (m, 2H), 3.81 (s, 3H), 4.96- 5.43 (m, 2H), 5.54-6.04 (m, 2H), 6.51-6.92 (m, 1H); MS, m/e 195.0883 (M^+, calcd for $C_{10}H_{13}NO_3$: 195.0895), 138 (base), 94.

5e: IR (neat) 2965, 1755, 1730, 1652, 1446, 1032 cm^{-1}; NMR (CCl_4) δ 3.76 (s, 3H), 3.80 (s, 3H), 4.73-5.99 (m, 4H),6.53-6.87 (m, 1H). IR (neat) 1755, 1730, 1652, 1590 cm^{-1}; MS, m/e 197.0668 (M^+, calcd for $C_9H_{11}NO_4$: 197.0687), 138 (base), 94.

11f: IR (KBr) 2952, 1730, 1715, 1645, 1600, 1445, 935, 775, 738 cm^{-1}; NMR (CCl_4) δ 2.27 (s, 3H), 3.85 (s, 3H), 4.40 (dd, J=6 and 3Hz, 2H), 5.33-5.70 (m, 1H), 6.27-6.57 (m, 1H), 7.73 (br s, 1H); MS, m/e 181.0747 (base, M^+, calcd for $C_9H_{11}NO_3$: 181.0755), 180, 166, 136.

11g: IR (neat) 2950, 1710, 1648, 1590, 1440, 1290, 1115, 762 cm^{-1}; NMR (CCl_4) δ 3.80 (s, 3H), 4.33 (dd, J=5 and 2Hz, 2H), 5.40-6.00 (m, 2H), 6.70-7.00 (m, 1H); MS, m/e 175, 174, 173.0264 (base, M^+, calcd for $C_7H_8ClNO_2$: 173.0244).

Diels-Alder reaction. A solution of 4c (0.199mg, 1mmol), dimethyl malonate (0.173mg, 1.2mmol), p-TsOH (10mg), and dihydroquinone (5mg) in toluene (2mL) was heated (at 100℃). After 5h, the reaction mixture was

chromatographed on silica gel (AcOEt:hexane=3:1) to afford [4+2]cycloadduct 6 in 54% yield: mp 85-87℃ (from AcOEt-hexane); IR (CCl_4) 2960, 1740, 1708, 1620, 1447, 1390, 1200 cm^{-1}; 0.87 (t, J=6.5Hz, 3H), 1.00-2.00 (m, 2H), 2.63 -3.70 (m, 4H), 3.60, 3.67, and 3.73 (3s, 9H), 4.67-5.07 (m, 1H), 6.10-6.67 (m, 2H); MS, m/e 311.1366 (M^+, calcd for $C_{15}H_{21}NO_6$: 311.1368), 282, 280, 167, 139, 138 (base).

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Chapter 5-2

Synthesis of Optically Pure 2-Substituted-1-(methoxycarbonyl)-1,2-dihydropyridines. Preparation of Optically Active 2-Aza-2,5,6-tris(methoxycarbonyl)bicyclo[2.2.2]octane

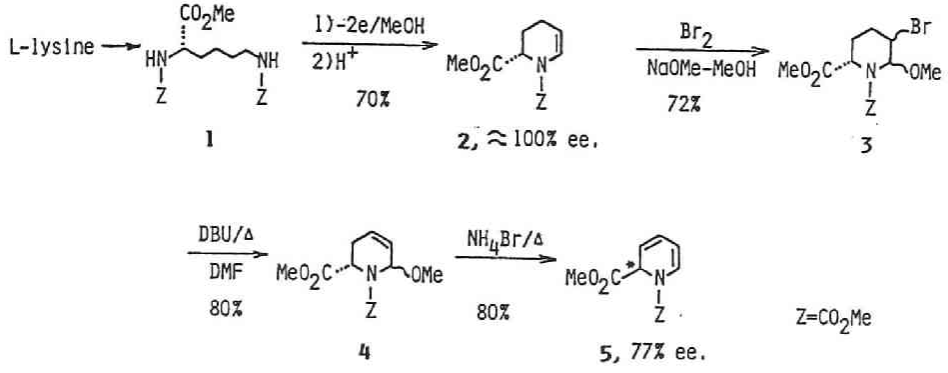
Abstract: Optically pure 2-substitued 1,2-dihydropyridines were prepared from L-lysine using anodic oxidation as a key reaction, which were transformed into optically active 2-aza-2,5,6-tris(methoxycarbonyl)bicyclo[2.2.2]octane by Diels-Alder reaction.

Since 1-acyl-1,2-dihydropyridines have been known to be useful synthetic intermediates as exemplified by their Diels-Alder type reaction to form nitrogen-heterocycles,[1] a variety of methods have been reported for synthesis of these dienes.[2]

In preceding chapter (5-1) was described a new method for regioselective preparation of 2-substituted 1,2-dihydropyridines starting from 2-substituted piperidines through three intermediates.[3] In this chapter that convenient method was applied to the synthesis of optically pure 1,2-dihydropyridine from L-lysine, which was transformed into optically active 2-aza-2,5,6-tris(methoxycarbonyl)bicyclo[2.2.2]octane by Diels-Alder reaction.

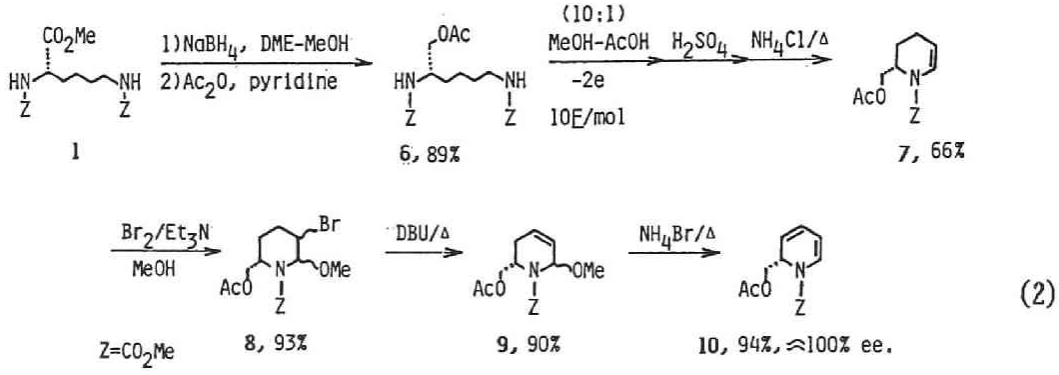
Optically Pure 2-Sustituted-1-(methoxycarbonyl)-1,2-dihydropyridines. In chapter 5-1 our method was applied to the synthesis of the optically active diene 5, which might be an useful intermediate for the construction of optically active nitrogen heterocycles. The optically active key inter-

mediate 1,2,3,4-tetrahydropyridine 2 was preparable by our reported method starting from L-lysine (eq 1).[3] To our regret, the optical purity of 5 was found to be 77% ee.



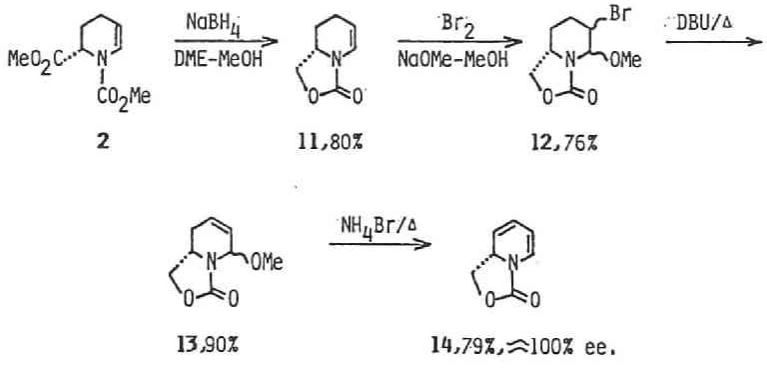
(1)

Consequently, our effort was directed to the synthesis of optically pure 1,2-dihydropyridines and their utilizations in organic synthesis. Since the racemization of 5 seemed to be caused by the electron-withdrawing effect of 2-methoxycarbonyl group of 5, 2-acetoxymethyl-1,2-dihydropyridine 10 was prepared. Namely, the subsequent transformation of 1 to 10 was carried out as follows (eq 2): The reduction of 1 with $NaBH_4$ in dimethoxyetane-methanol and followed by thetreatment with acetic anhydride gave 6. The preparation of 7 was achieved according to our previously reported method[4] of the oxidized products and the elimination of methanol from the cyclized product. The addition of bromine to a solution of 7 in methanol containing triethylamine at room temperature gave 8, which was then dehydrobrominated by treatment with DBU in DMF at 90 ℃ to afford 9. The desired 10 was obtained by heating (130 ℃) 9 in the presence of a catalytic amount of NH_4Br under reduced presure (25 mmHg) for 1h. According to expectation compound 10 was found to be optically pure and as described bellow was a key intermediate for a preparation of optically active 2-aza-2,5,6-tris (methoxycarbonyl)bicyclo[2.2.2]octane.



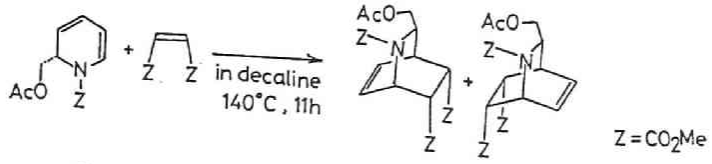
(2)

On the other hand, bicyclic 1,2-dihydropyridine 14 (100 % ee) was prepared according to the method described above from 11 which was obtained by the reduction of 2 (eq 3). Compound 14, however, was less reactive with dienophile.

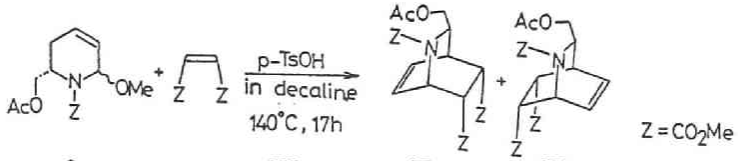


(3)

Optically Active 2-Aza-2,5,6-tris(methoxycarbonyl)bicyclo[2.2.2]octane. The compound 10 was found to give the Diels-Alder type adducts upon reaction with dimethyl maleate (eq 4).[1] Similarly an intermediate 9 was reactive with dimethyl maleate in the presence of p-TsOH (eq 5). In these reactions as minor products were obtained [4+2]cycloadducts of 10 with dimethyl fumarate (9% from 10, 2% from 9).[5]



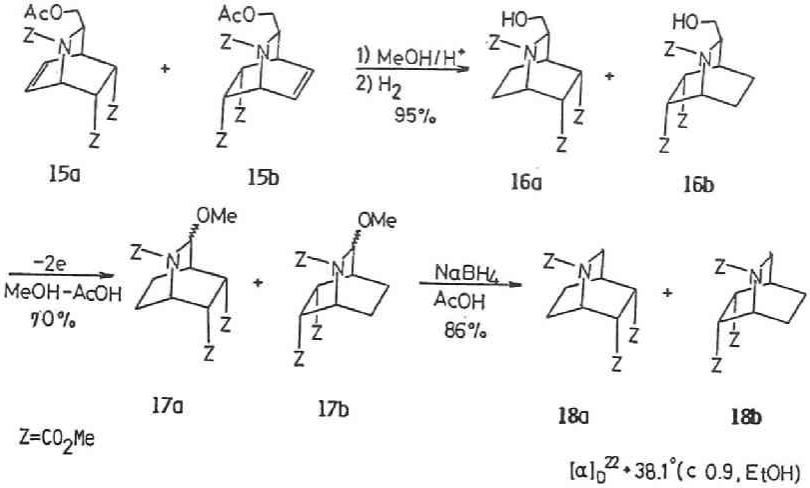
10 56% 15a 15b (4)



9 65% 15a 15b (5)

Each of these Diels-Alder reactions seemed to be carried out diastereoselectively in the ratio of 9 to 1, which was determined by HPLC. In fact, the mixture of 15a and 15b was transformed into optically active 2-azabicyclo[2.2.2]octane 18a,b. That is, as shown in Scheme 1, hydrolysis of 15a,b and followed by hydrogenation afforded 16a,b, which were transformed into 17a,b by the anodically carbon-carbon bond cleavage[6] and then the reduction of 17a,b with $NaBH_4$ gave 18a,b.[7]

Scheme 1



Since the diastereoselectivity seemed to be caused by the steric effect of 2-acetoxymethyl group of 10, a main isomer was thought to be 15a (figure 1).

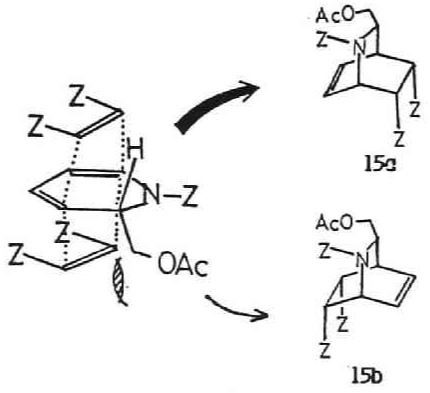
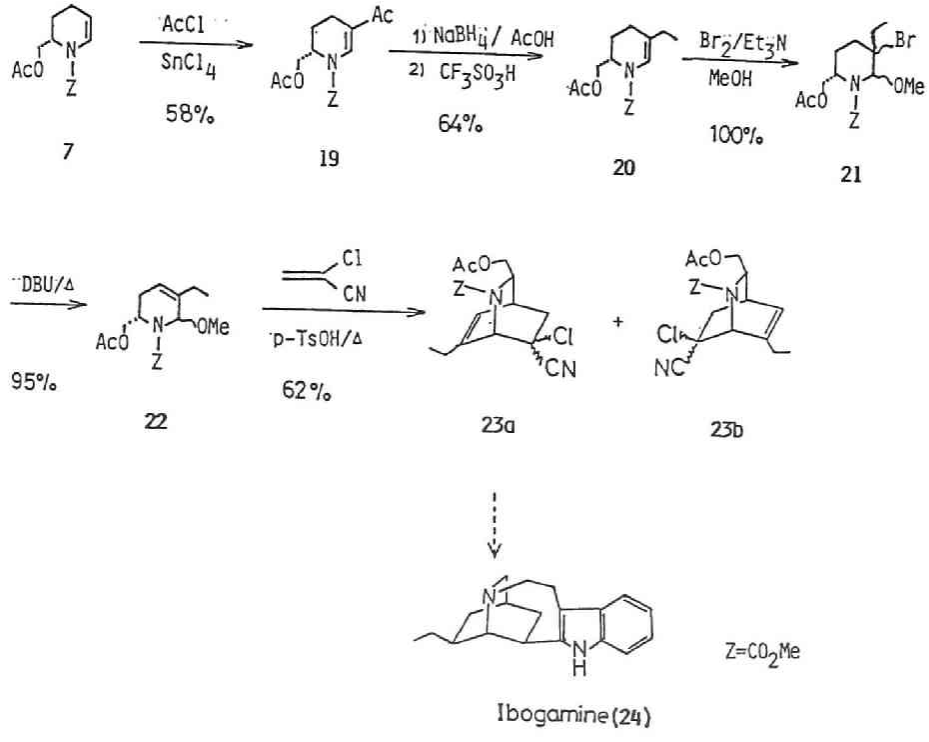


figure 1.

An Approach to Synthesis of (-)-Ibogamine. (-)-Ibogamine (24) is isolated from Tabernanthe iboga Baill, which is of interest because of an inherent pharmacological activity.[8] Our synthetic route is shown in Scheme 2. As a precurcer for synthesis of 24 we selected 23, which was thought to be obtained Diels-Alder reaction of 22 and α-chloroacrylonitrile. In first, in order to introduce ethyl group into the β-position of 7, Friedel-Craft acetylation of 7 and a reduction of the product 19 was carried out. By the method described above 20 was transformed into a mixture of 23a and 23b. The transformation of 23 into 24 may be carried out according to the known methods.[8,9]

Scheme 2



Experimental Section

Carbamate 1 was known compound.[4] Products 9, 10, and 13 were not submitted for sufficient analytical data due to their instability.

Reduction of 1 and 2 with $NaBH_4$. In a solution of 1 (26.8g, 97mmol) in a mixture of DME (40mL) and MeOH (8mL) was added a portion of $NaBH_4$ (3.06g, 81mmol). After it was stirred overnight, the reaction mixture was poured into H_2O (50mL). The organic portion was extracted with CH_2Cl_2 (3x40 mL) and dried over $MgSO_4$. The solvent removed in vacuo and into the residue

was poured Ac_2O (18.9mL, 200mmol) and successively pyridine (20mL, 250 mmol). After stirred for 2.5h, into the reaction mixture was water (30ml). The organic layer was extracted with CH_2Cl_2 (3x40mL) and dried over $MgSO_4$. The solvent removed in vacuo and the residue was washed with a mixture of ether and hexane: mp.97-98℃ (from methanol); IR (KBr) 3355, 2980, 1755, 1700, 1555, 1230, 1068 cm^{-1}; NMR ($CDCl_3$) δ 1.21-1.83 (m, 6H), 2.10 (s, 3H), 3.06-3.37 (m, 2H), 3.60-4.20 (m, 1H), 3.71 (s, 6H), 4.12 (d, J=4Hz, 2H), 4.53-5.03 (m, 2H). Anal. Calcd for $C_{12}H_{22}N_2O_6$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.38; H, 7.79; N, 9.90.

Compound 11 was by the similar procedure from 2 except for an amount of $NaBH_4$ (6.7equiv): mp 45-46℃; IR (CCl_4) 1752, 1650, 1420, 1280, 1180, 1058cm^{-1}; NMR ($CDCl_3$) 1.50-2.43 (m, 4H),3.60-5.25 (m, 4H), 6.60 (br d, J=8 Hz, 1H). Anal. Calcd for $C_7H_9NO_2$: C, 60.43; H, 6.51; N, 10.07. Found: C, 60.16; H, 6.56; N, 9.90.

Anodic Oxidation of 6. Into a beker with carbon rod anode and cathode (8mmφ) was added a mixture of 6 (4.24g, 14.62mmol) and Bu_4NBF_4 (1.5g) in MeOH (60mL) and AcOH (6mL). After 10F/mol of electricity was passed at a constant current of 1A (3.9h, terminal voltage; ca.16V) at -10℃, H_2SO_4 (3 mL) was added the reaction mixture and stirred for 1h at the temperature. Into the resulting reaction mixture was poured CH_2Cl_2 (100mL) and the solution was washed with water (50mL) and successively aq. Na_2CO_3 (50mL). The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was distillation by kugel rohr to afford 7 (2.66g, 66%): bp 160 ℃ (2mm); IR (neat) 2965, 1742, 1712, 1660, 1448, 1362, 1240cm^{-1}; NMR (CCl_4) δ 1.70-2.25 (m, 4H), 1.98 (m, 3H), 3.73 (s, 3H), 3.98 (t, J=7Hz, 2H), 4.28-4.93 (m, 2H), 6.53-6.90 (m, 1H). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.07; H, 7.17; N, 6.40.

Bromomethoxylation of 7 and 11. Into a solution of 7 (10.9g, 50.7mmol) and Et_3N (8.5mL, 60.8mmol) in MeOH (60mL) was added slowly Br_2 (3.1mL, 60.8 mmol) at 5℃. After stirred for 30min, aq. $Na_2S_2O_3$ was poured into the solution. The organic portion was extracted with CH_2Cl_2 (3x50mL) and the dried over $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel to afford 8 (15.37g, 93% yield): IR (neat) 2970, 1748, 1718, 1448, 1305, 1240, 1082, 1068cm^{-1}; NMR (CCl_4) δ 1.40-2.50 (m, 4H), 1.97 (s, 3H), 3.29 and 3.37 (2s, 3H), 3.67 (s, 3H), 3.70-4.50 (m, 4H), 5.10-5.50 (m, 1H). Anal. Calcd for $C_{11}H_{18}BrNO_5$: C, 40.76; H, 5.60; Br, 24.65; N, 4.32. Found: C, 40.81; H, 5.81; Br; 24.37; N, 4.23.

By the similar procedure except for base (Et_3N) was obtained 12 from 11: IR (neat) 2940, 1760, 1410, 1260, 1062, 970, 762cm^{-1}; NMR (CCl_4) δ 1.55-2.40 (m, 4H), 3.32 and 3.40 (2s, 3H), 3.55-4.60 (m, 4H), 4.93 (d, J=2 Hz, 1H). Anal.Calcd for $C_8H_{12}BrNO_3$: C, 38.43; H, 4.84; Br, 31.95; N, 5.60. Found: C, 38.49; H, 4.80; Br; 32.12; N, 5.54.

Dehydrobromination of 8 and 12. A solution of 8 (15.37g, 47.15mmol) and DBU (13.7mL, 100mmol) in DMF (50mL) was heated at 100 ℃. After 2h, the solvent was removed in reduced pressure. The residue was chromatographed on silica gel (AcOEt:hexane=4:1) to afford 9 (10.4g, 90% yield):

NMR (CCl_4) δ 1.80-2.30 (m, 2H), 2.02 (s, 3H), 3.40 and 3.47 (2s, 3H), 3.76 (s, 3H), 3.80-4.83 (m, 3H), 5.43 (br s, 1H), 5.82 (br s, 2H); MS, m/e 243.1090 (calcd for $C_{11}H_{17}NO_5$: 243.1107), 212, 184, 170 (base), 152, 138.

By the similar procedure was obtained 13 from 12: IR (neat) 2935, 1758, 1412, 1215, 1080, 780, 760cm^{-1}; NMR (CCl_4) δ 1.98-2.33 (m, 2H), 3.34 (s,

3H), 3.55-4.67 (m, 3H), 4.93 (br s, 1H), 5.80 (br s, 2H). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 55.37; H, 6.57; N, 8.08.

Preparation of 1,2-Dihydropyridines 10 and 14. A mixture of 9 (0.325g, 1.327mmol) and NH_4Br (0.01g) was heated at 150℃ in reduced pressure (100 mm Hg). After 5min, by the distillation (150℃, 2mmHg) was afforded 10 (0.265 g, 94%): IR (neat) 2955, 1745, 1720, 1640, 1580, 1442, 1355, 1328, 1258, 1230, 1120, 1046cm^{-1}; NMR (CCl_4) δ 1.97 (s, 3H), 3.79 (s, 3H), 3.82-4.10 (m, 2H), 4.85-5.60 (m, 3H), 5.85-6.12 (m, 1H), 6.59-6.92 (m, 1H); MS, m/e 151, 139, 138 (base), 94.

14: IR (neat) 3025, 2402, 1765, 1520, 1425, 1216cm^{-1}; NMR (CCl_4) δ 4.10-4.90 (m, 3H), 5.20-5.60 (m, 2H), 5.83-6.20 (m, 1H), 6.63 (d, J=8Hz, 1H); MS, m/e 137.0463 (base, calcd for $C_7H_7NO_2$: 137.0476), 93, 77.

Diels-Alder reaction. A solution of 10 (0.231g, 1.095mmol), dimethyl maleate (0.68mL, 5.47mmol), and dihydroquinone (5mg) in decaline (3mL) was heated at 140 ℃ for 11h. The solvent was removed in vacuo and the residue was chromatographed on silica gel (AcOEt-hexane=1:2) to afford a mixture of 15a and 15b (215mg, 55%) and cycloadducts with dimethyl fumarate (37mg, 10%).

15: IR (neat) 2975, 1755, 1712, 1455, 1390, 1205, 1180, 1046cm^{-1}; NMR (CCl_4) δ 2.03 (s, 3H), 2.73-4.20 (m, 6H), 3.59 (s, 6H), 3.73 (s, 3H), 4.83 (br s, 1H), 6.30-6.50 (m, 2H); MS, m/e 295, 282, 151, 138, 121, 119, 117 (base). Anal. Calcd for $C_{16}H_{21}NO_8$: C, 54.08; H, 5.96; N, 3.94. Found: C, 54.05; H, 6.02; N, 3.92.

The ratio of 15a and 15b was determined by HPLC. HPLC was performed on a Simazu LC-6A with a Shim-pack CLC-ODS coulmn (6mmφ x 150mm). An

elution of 10mM phosphoric acid buffer (pH 2.6) /acetonitrile=4/1 was applied at 1.5mL/min. The peaks were detected by RID-6A (0.16x10 Riufs) at 40°C in 8.4min and 10.4min (1:9).

Cycloadducts with Dimethyl Fumarate: IR (neat) 2955, 1740, 1702, 1442, 1337, 1220, 1038cm^{-1}; NMR (CCl_4) δ 2.02 and 2.05 (2s, 3H), 2.65-4.15 (m, 6H), 3.66, 3.69, 3.74, and 3.74 (4s, 9H), 4.70-5.17 (m, 1H), 6.17-6.70 (m, 2H); MS, m/e 295, 282, 151, 138 (base). Anal. Calcd for $C_{16}H_{21}NO_8$: C, 54.08; H, 5.96; N, 3.94. Found: C, 53.83; H, 5.97; N, 3.84.

By adding p-TsOH (catalytic amount) from 9 with dimethyl maleate was prepared 15 under the similar conditions.

Preparation of 16a and 16b. Into a solution of 15a,b (1.22g, 3.44mmol) in MeOH (20mL) was added HCl gas. After stirred overnight, the solvent was removed in vacuo. A solution of the residue and 5% Pd-C (cat amt.) was stirred for 12h under an atmosphere of hydrogen (10atm). The reaction mixture was filterded and the filtrate was condensed in vacuo to afford 16a,b (1.02g, 95% yield): IR (neat) 3470, 2970, 1740, 1705, 1458, 1395, 1220 cm^{-1}; NMR (CCl_4) δ 1.40-1.93 (m, 4H), 2.37-2.97 (m, 3H), 3.15-4.37 (m, 5H), 3.59 (s, 3H), 3.63 (s, 3H), 3.71 (s, 3H); MS, m/e 297, 285, 284 (base). Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.03; H, 6.69; N, 4.27.

Anodic Carbon-Carbon Bond Cleavage of 16a,b. Into an electrolysis cell described above was added a solution of 16a,b (0.329g, 1.044mmol) and n-Bu_4NBF_4 (0.150g) in MeOH (10mL) and AcOH (2mL). After 9F/mol electlicity was passed at a constant current (0.2A, terminal voltage; ca. 12V). Into the reaction mixture was poured water (15mL). The organic portion was

extracted with CH_2Cl_2 (3x15mL) and was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel (AcOEt-hexane=1:3) to afford 17a,b (0.229g, 70%): IR (neat) 2960, 1750, 1718, 1452, 1202cm^{-1}; NMR (CCl_4) δ 1.20-1.90 (m, 4H), 2.30-2.65 (m, 2H), 2.90-3.50 (m, 1H), 3.40 (m,1H), 3.62 (s, 3H), 3.69 (s, 3H), 3.75 (s, 3H), 4.00-4.40 (m, 1H), 4.78 (br s, 1H); MS, m/e 300.0173 (M^+-Me, calcd for $C_{13}H_{18}NO_7$: 300.1082), 285, 284 (base), 138.

Preparation of Optically Active 2-Aza-2,5,6-tris(methoxycarbonyl)-bicyclo[2.2.2]octane. Into a solution of 17a,b (0.13g, 0.42mmol) in AcOH (5mL) was added a portion of $NaBH_4$ (.174g, 4.2mmol). After stirred for 3h, into the solution was poured water (10mL). The organic portion was extracted with CH_2Cl_2 (3x15mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel (AcOEt-hexane=1:3) to afford 18a,b (0.102g, 86%): $[\alpha]_D^{22}$ +38.1 (c 0.9, EtOH); IR (neat) 2955, 1748, 1700, 1455, 1400, 1198, 1120, 1060cm^{-1}; NMR (CCl_4) δ 1.44-2.07 (m, 4H), 2.30 (br s, 1H), 2.80-3.50 (m, 2H), 3.33 (br s, 2H), 3.63 (s, 9H), 4.15-4.40 (m, 1H); MS, m/e 285.1195 (M^+, calcd for $C_{13}H_{19}NO_6$: 285.1121), 254, 140, 139 (base).

Friedel-Crafts reaction. Into a solution of AcCl (6.6mL, 95.8mmol) in CH_2Cl_2 (15mL) was added dropwise a solution of $SnCl_4$ (4.4mL, 38.3mmol) in CH_2Cl_2 (10mL) at -50°C under an atmosphere of nitrogen. After stirred for 10min, a solution of 7 (4.08g, 19.15mmol) in CH_2Cl_2 (10mL) was added dropwise. After the reaction mixture was stirred for 10h at room temperature, it was poured into ice-water. The organic portion was separated and the aqeous layer was extracted with CH_2Cl_2 (3x30mL). A combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo . The

residue was chromatographed on silica gel (AcOEt-hexane=2:1) to afford 19 (2.725g, 56%): mp. 65-67 °C; NMR (CCl_4) δ 1.40-2.77 (m, 4H), 2.00 (s, 3H), 2.34 (s, 3H), 3.82 (s, 3H), 3.98 (t, J=3Hz, 2H), 4.30-4.73 (m, 1H), 7.92 (s, 1H). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.23; H, 6.76;N, 5.53.

Preparation of 20. Into a solution of 19 (1.500g, 5.88mmol) in AcOH (15mL) was added a portion of 90% $NaBH_4$ (1.236g, 29.4mmol). After stirred for 3h, water (15mL) was poured into the solution. The organic portion was extracted with CH_2Cl_2 (3x20mL) and the solution was dried over $MgSO_4$. Into the residue was poured a mixture of HCO_2H (3mL) and CF_3SO_3H (0.3mL). After stirred for 2h, into the resulting reaction mixture was poured CH_2Cl_2 (10mL). The organic layer was washed with water (10mL) and successively aqueous Na_2CO_3. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo and the residue was chromatographed on silica gel (AcOEt: hexane=1:5) to afford 20 (0.910g 64%): IR (neat) 2970, 1750, 1712, 1680, 1448, 1238, 1045cm^{-1}; NMR (CCl_4) δ 1.03 (t, J=7.5Hz, 3H), 1.45-2.23 (m, 6H), 1.94 (s, 3H), 3.67 (s, 3H), 3.88 (t, J=7Hz, 2H), 4.13-4.57 (m, 1H), 6.58 (br s, 1H). Anal.Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.48; H, 8.03; N, 5.67.

Preparations of 21, 22, and 23 were carried out according to the method described above.

21: IR (neat) 2955, 1748, 1715, 1448, 1312, 1235, 1072cm^{-1}; NMR (CCl_4) δ 1.08 (br t, J=7Hz, 3H), 1.20-2.30 (m, 6H), 1.97 (s, 3H), 3.28 and 3.30 (2s, 3H), 3.53-4.70 (m, 3H), 3.69 (s, 3H), 5.13-5.43 (m, 1H). Anal. Calcd for $C_{13}H_{22}BrNO_5$: C, 44.33; H, 6.30; Br, 22.69; N, 3.98. Found: C, 44.27, H, 6.23, Br, 22.55, N, 3.91.

22: IR (neat) 2970, 1750, 1712, 1450, 1240, 1075cm^{-1}; NMR (CCl_4) δ 1.05 (t, J=5Hz, 3H), 1.53-2.63 (m, 4H), 2.00 (s, 3H), 3.40 (s, 3H), 3.73 (s, 3H), 4.00-4.27 (m, 2H), 4.37-4.77 (m, 1H), 5.20-5.57 (m, 1H). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.28; H, 7.90; N, 5.17.

23: IR (neat) 2975, 1745, 1718, 1450, 1385, 1240, 1040cm^{-1}; NMR (CCl_4) δ 1.11 (t, J=6Hz, 3H), 1.90-2.80 (m, 4H), 2.09 (s, 3H), 3.06 (br s, 1H), 3.70-4.40 (m, 3H), 3.83 (s, 3H), 4.98 (dd, J=20 and 2Hz, 0.3H), 5.06 (dd, J=20 and 2Hz, 0.7H), 5.97-6.20 (m, 1H). Anal. Calcd for $C_{15}H_{19}ClN_2O_4$: C, 55.13; H, 5.86; Cl, 10.85; N, 8.57. Found: C, 54.86; H, 5.74; Cl, 10.78; N, 8.18.

Optical purities of 10 and 14 were determined by comparing optical rotatory of the hydrogenated product 10' and 14' with their authentic samples.

10': $[\alpha]_D^{25}$ -37.0 (c 1.38, EtOH); IR (neat) 2950, 2870, 1748,1700, 1450, 1260, 1228, 1050cm^{-1}; NMR (CCl_4) δ 1.58 (br s, 6H), 1.95 (s, 3H), 2.60-3.10 (m, 1H), 3.63 (s, 3H), 3.73-4.60 (m, 4H). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.85; H, 7.94; N, 6.45.

14': $[\alpha]_D^{25}$ +18.8 (c 1.38, EtOH); IR (neat) 2950, 2870, 1750, 1430, 1248, 1078, 1045cm^{-1}; NMR (CCl_4) δ 1.10-2.10 (m, 6H), 2.50-3.07 (m, 1H), 3.30-4.45 (m, 4H). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.28; H, 7.96; N, 9.66.

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List of Publications

Chapter 1 Shono, T.; Matsumura, Y.; Onomura, O.
To be published.

Chapter 2-1 Shono, T.; Matsumura, Y.; Onomura, O.; Kanazawa, T.; Habuka, M. Chem. Lett. 1984, 1101.
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Chapter 4-1 Shono, T.; Matsumura, Y.; Ogaki, M.; Onomura, O.
To be published.

Chapter 4-2 Shono, T.; Matsumura, Y.; Sato, M.; Onomura, O.
To be published.

Chapter 5-1 Partly reported in Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. Tetrahedron Lett. 1987, 28, 4073.

Chapter 5-2 Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M.
To be published.

Pubulication Not Included in The Thesis

Anodic α-Methoxylation of Aliphatic Ethers.
Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. Synthesis 1987, 1099.