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Stereoselective synthesis of 3-deoxy-piperidine iminosugars from L-lysine

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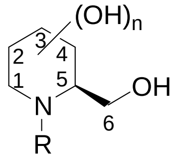
Abstract— A new method using electrochemical oxidation and/or OsO_4 oxidation has been exploited for the stereoselective synthesis of 2,3,6-trihydroxylated 5*S*-piperidine derivatives. The electrochemical method was successively used for the conversion of *N*-protected piperidines to *N*-protected 1-methoxypiperidines and for the conversion of 2,3-didehydro-1-methoxypiperidine derivatives to 2,3-*trans*-1,2,3-triacetoxypiperidine derivatives. These triacetates were easily transformed into 2*S*,3*S*,6-triacetoxy-5*S*-methyl-piperidine and 2*R*,3*R*,6-triacetoxy-5*S*-methylpiperidine. In addition, 2,3-*cis*-dihydroxylation of 2,3-didehydro-1-methoxypiperidine derivatives with OsO_4 afforded 2*R*,3*S*,6-tri-acetoxy-5*S*-methylpiperidine and 2*S*,3*R*,6-triacetoxy-5*S*-methylpiperidine.

1. Introduction

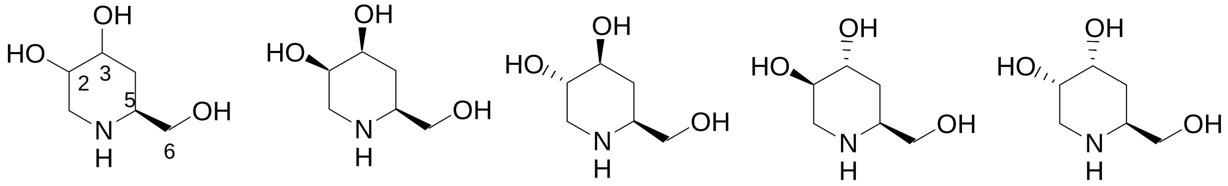
Polyhydroxylated 5*S*-methylpiperidines **1**, a class of piperidine iminosugars, have attracted great interest due to their biological properties.[1,2] Some of them are potential inhibitors of glycosidases and glycoprotein-processing enzymes. Now they are widely investigated as candidates for drugs to treat a variety of carbohydrate-mediated diseases such as diabetes, viral infections including HIV, and cancer metastasis. The inhibitory activities depend on the configuration and the number of hydroxyl groups. Among **1**, 2,3,6-trihydroxy-5*S*-methyl-piperidines **2** are noteworthy since recently it has been reported that 2*R*,3*S*,6-tri-hydroxy-5*S*-methylpiperidine (**2a**), one of the possible stereoisomers **2a-d** (Fig. 2), has high inhibitory activities toward glycosidases. However, there has not been any convenient synthetic method for **2a-d**.[3,4] We have exploited a facile method for the stereoselective synthesis of **2a-d**, and preliminarily reported the synthesis of **2b,c** using electrochemical 2,3-*trans*-diacetoxylation.[5] This paper describes the synthesis for **2b,c** as well as those for **2a,d** using 2,3-*cis*-dihydroxylation with OsO_4.



1

R=H or alkyl

Figure 1.



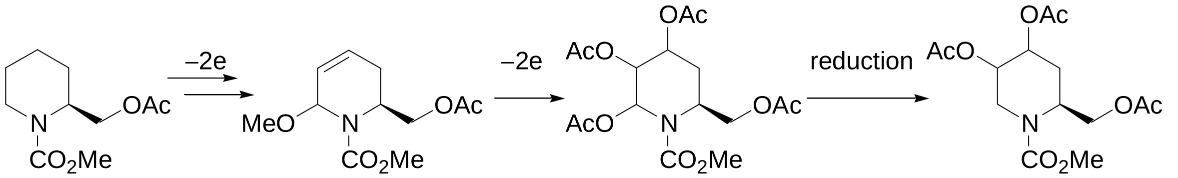
2	2a	2b	2c	2d
	2*R*,3*S*	2*S*,3*S*	2*R*,3*R*	2*S*,3*R*

Figure 2. Stereoisomers **2a-d** of 2,3,6-trihydroxy-5S-methylpiperidines **2**.

2. Result and discussion

2.1 Electrochemical 2,3-*trans*-diacetoxylation

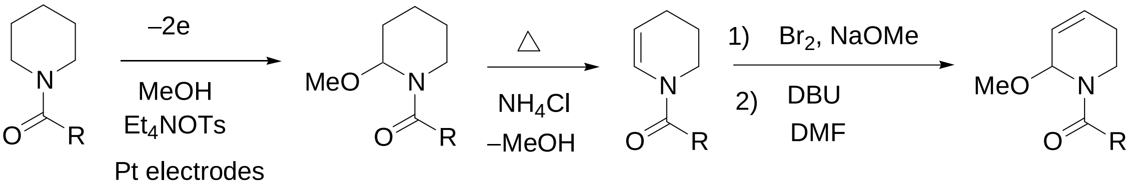
Our strategy to this end is based on preparation of triacetate **6**, a precursor of **2,** from 5*S*-acetoxymethylpiperidine derivative **3** by electrochemical oxidation; electrochemical 1-methoxylation of **3** and electrochemical triacetoxylation of 5*S*-acetoxymethyl-2,3-di-dehydro-1-methoxypiperidine derivative **4** (Eq. 1).



3 **4** **5** **6**

(1)

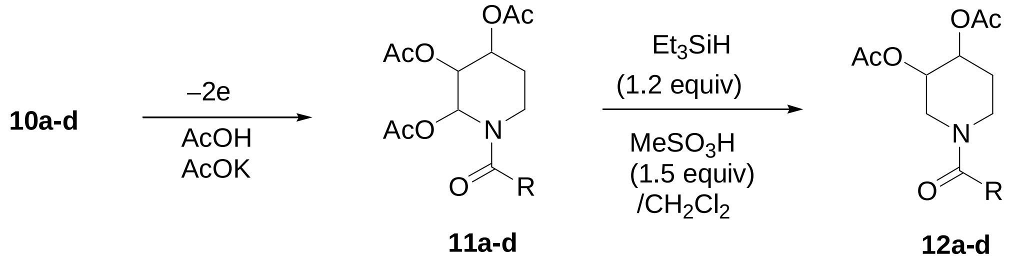
The first key electrochemical reaction in the scheme has already been used in the transformation of *N*-methoxycarbonylpiperidine **7a** to 2,3-didehydro-1-methoxypiperidine **10a**. The transformation consisted of electrochemical oxidation of **7a** to afford 1-methoxypiperidine **8a**,[6] elimination of MeOH from **8a** to 1,2-didehydropiperidine **9a**,[7] which then underwent bromine oxidation[8] followed by base-induced dehydrobromination to form 2,3-didehydro-1-methoxypiperidine **10a** (Eq. 2).[9] The other 2,3-didehydro-1-methoxypiperidines **10b-d** were similarly prepared from **7b-d**.



(2)

7a-d	**8a-d**	**9a-d**	**10a-d**
a: R=OMe	86%	90%	58%
b: R=OCH_2Ph	91%	92%	70%
c: R=H	97%	83%	68%
d: R=Ph	90%	84%	60%

With **10a-d** in hand, we examined the second key electrochemical triacetoxylation of **10a-d**, which was carried out in acetic acid containing potassium acetate (Eq. 3).[10] As expected, the oxidation gave triacetoxylated products **11a-d**, though their stereochemistry was not determined at this stage. Then we achieved the reductive elimination of 1-acetoxyl group of **11a-d** by Et_3SiH to afford 2,3-diacetoxypiperidines **12a-d**. The yields of **11a-d** and **12a-d** are shown together with the *trans*/*cis* ratio in Table 1.



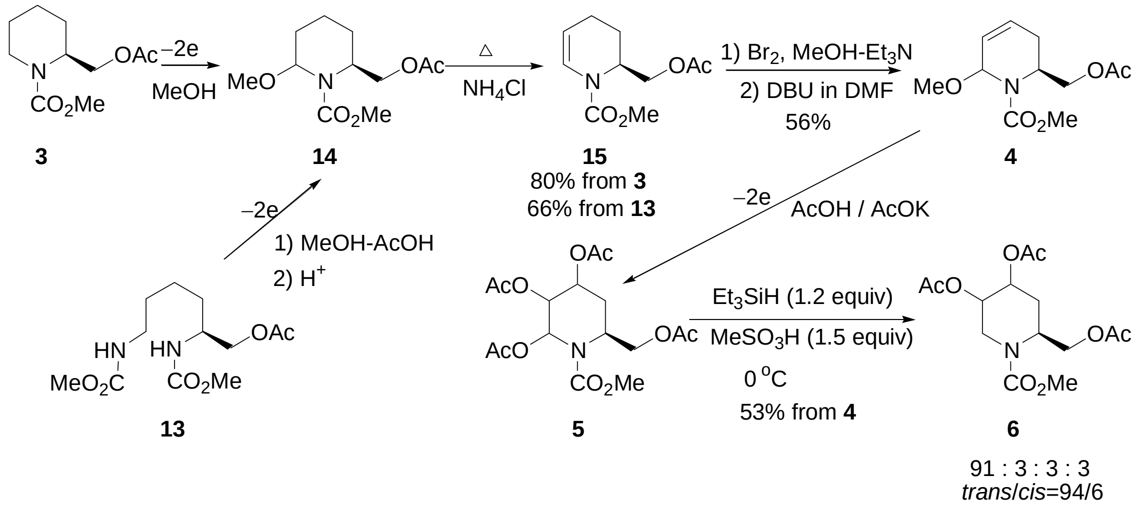
(3)

Table 1.

Electrochemical oxidation of **10a-d** followed by reduction of **11a-d** with Et_3SiH

Entry	**10a-d**		Yield (%)	*trans*:*cis*
	R	**11a-d**	**12a-d**	**(12a-d)**
1	OMe	81	84	70:30
2	OCH_2Ph	54	82	58:42
3	H	78	65	66:34
4	Ph	80	45	54:46

The stereochemistry (*trans/cis*) of **12a-d** was a little bit dependent on R (70/30~54/46).[11] We then, tried the preparation of **4** from easily available L-lysine derivative **13**[12] instead of expensive L-pipecolic acid derivative **3** through **14** and **15**[13] to obtain **4** in a similar way to transformation of **7** to **10**. The result is shown in Scheme 1. Electrochemical oxidation of **4** under conditions similar to the oxidation of **10** to **11** afforded tetraacetoxylated piperidine **5**, of which reduction with Et_3SiH gave 2,3,6-triacetoxy-5*S*-methylpiperidine **6** as a mixture of stereoisomers. The ratio of the diastereoisomers was determined to be 91/3/3/3.



Scheme 1. Preparation of **6**$_{2S,3S,5S}$ starting from **3** or **13**.

Fortunately, the main product **6**$_{2S,3S,5S}$ crystallized, and the absolute stereochemistry was determined to be (2*S*,3*S*,5*S*) by its X-ray analysis (Fig. 3).[14]

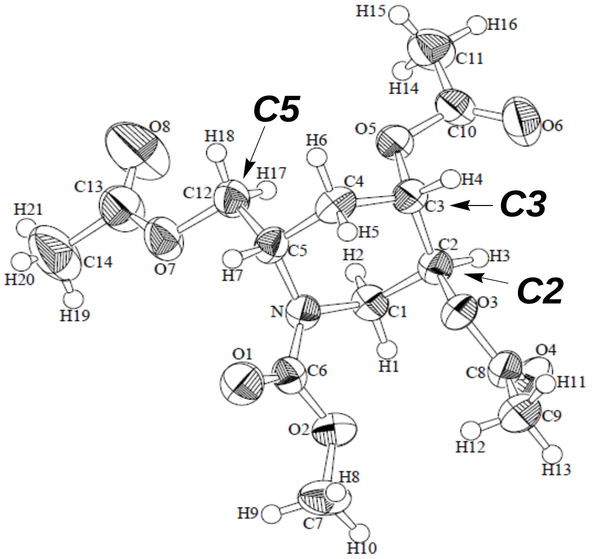
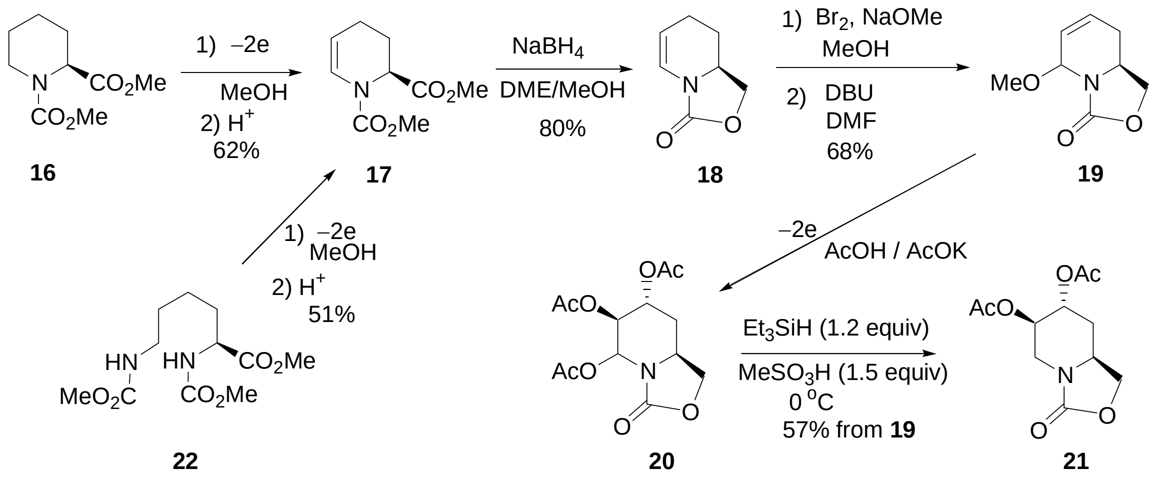


Figure 3. Ortep drawing of **6**$_{2S,3S,}$□$_{5S}$.

On the other hand, electrochemical oxidation of bicyclic carbamate **19**, which was prepared from L-pipecolic acid derivative **16** or from L-lysine derivative **22** through **17**[13] and **18**,[15] followed by reduction of the oxidation product **20** (70% yield) with Et_3SiH gave a single stereoisomer **21** (Scheme 2), of which absolute stereochemistry was also determined by its X-ray analysis (Fig. 4).[14]



Scheme 2. Preparation of **21**$_{2R,3R,5S}$ starting from **16** or **22**.

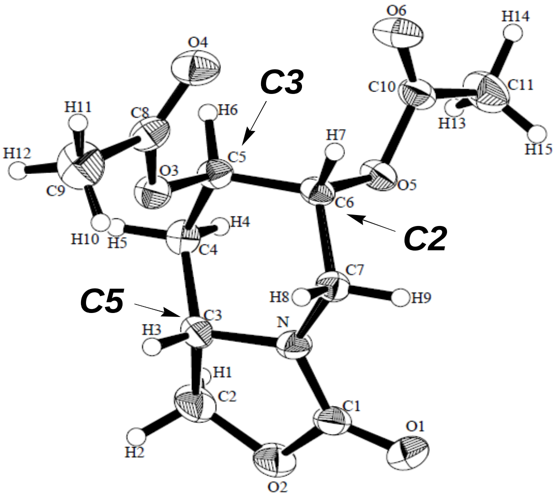
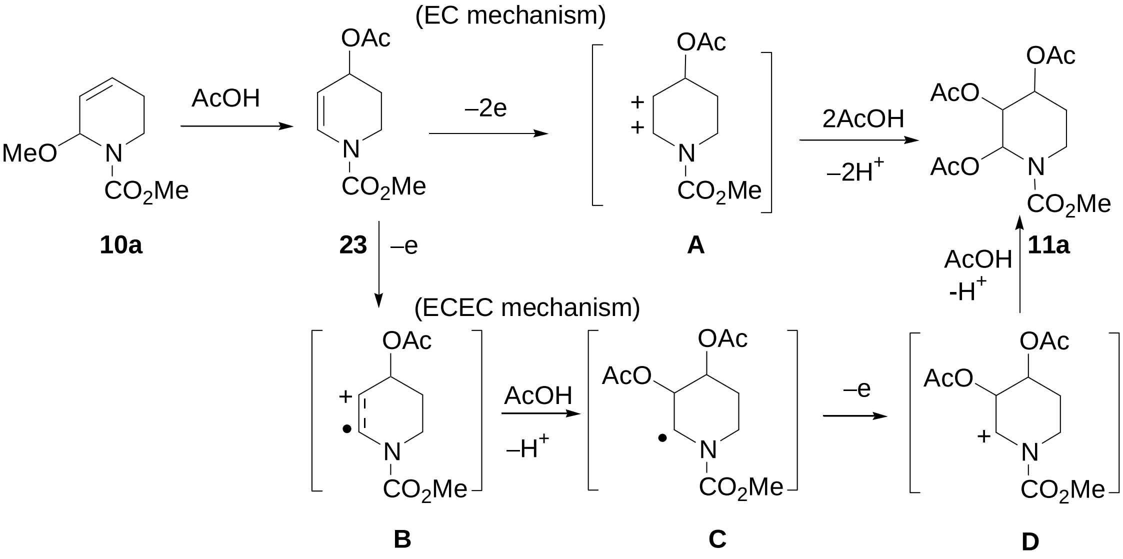


Figure 4. Ortep drawing of **21**$_{2R,3R,5S}$.

The reaction mechanism for electrochemical triacetoxylation is tentatively proposed as follows (Scheme 3). Since it was found that **10a** was immediately converted to 3-acetoxy-1,2-didehydropiperidine **23**[9i] under the reaction conditions, oxidation of **23** may be responsible for the formation of **11a** by EC mechanism through dication **A** or by ECEC mechanism through cation radical **B**, radical **C**, and cation **D**.[10] Similarly, electrochemical triacetoxylation of **4** and **19** may proceed *via* 3-acetoxypiperidine derivatives **24** and **25**, respectively (Fig. 5). Since *cis*-isomer **24** was thermodynamically more stable than its *trans*-isomer **24’**, **24** should be stereospecifically formed. On the other hand, treatment of **19** with acetic acid could generate a cationic species **E**, in which the endo side might be more crowded than the exo side, to afford exclusively a *trans*-isomer **25** without a *cis*-isomer **25’**.[15b]



Scheme 3. Plausible mechanism for electrochemical triacetoxylation of **10a**.

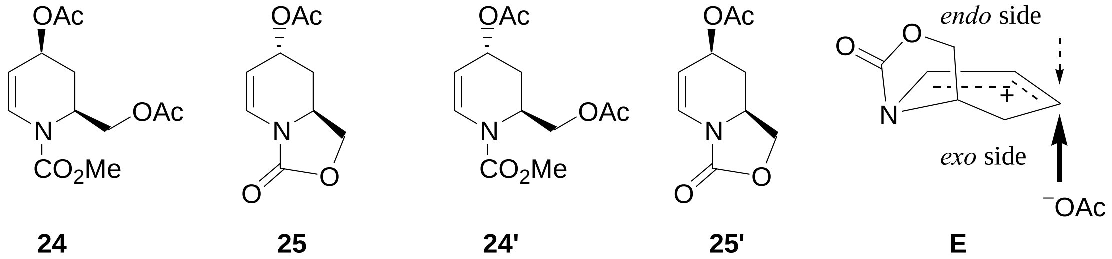
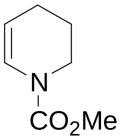
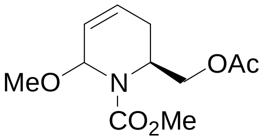


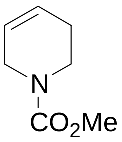
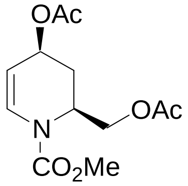
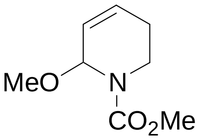
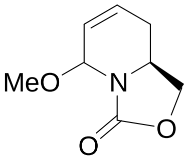
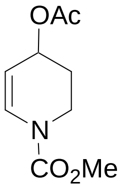
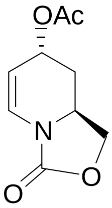
Figure 5. Plausible intermediary species for electrochemical oxidation of **4** and **19** in AcOH.

The oxidation potentials of some 1,2-didehydro- and 2,3-didehydro-piperidine derivatives shown in Table 2 support this proposed mechanism.

Table 2.

Oxidation potential of didehydropiperidine derivatives

Entry	Compound		Oxidation Potential (V)^{a}	Entry	Compound		Oxidation Potential (V)^{a}
1		**9a**	1.44	5		**4**	1.72

2		**26**	1.96	6		**24**	1.71
3		**10a**	1.66	7		**19**	1.73
4		**23**	1.65	8		**25**	1.71

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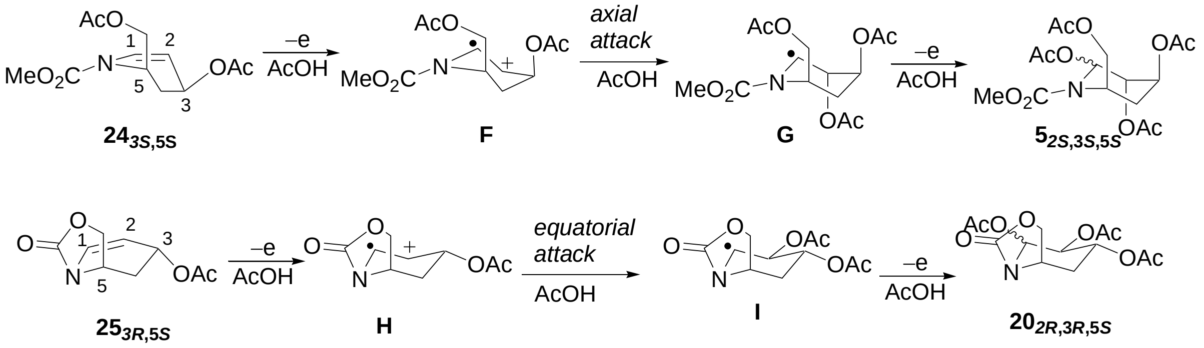
[a] V vs Ag/AgNO$_3$, 0.1 M Et$_4$NClO$_4$/MeCN, 100mV/s.

A predominant formation of $\mathbf{5}_{2S,3S,5S}$ and $\mathbf{20}_{2R,3R,5S}$ may be explained by an ECEC mechanism shown in Scheme 4. As for 3-acetoxy-1,2-didehydropiperidine intermediate **24**, it is possible that the plausible intermediary species could be electrochemically generated cation radical **F**.[10b,16] Therefore, the observed high diastereoselectivity in electrochemical oxidation of $\mathbf{24}_{3S,5S}$ can be explained as follows: acetate ion attack on the cationic intermediate **F** is easier from the axial direction than the equatorial direction to produce $\mathbf{5}_{2S,3S,5S}$ through the radical intermediate **G**. The stereoselectivity is explainable in terms of participating effect of 3-acetoxyl group or thermodynamic control of the product. On the other hand, in the case of electrochemical oxidation of $\mathbf{25}_{3R,5S}$, acetate ion attack to cation radical **H** is easier from the equatorial direction than the axial direction to produce $\mathbf{20}_{2R,3R,5S}$ through the radical intermediate **I**.

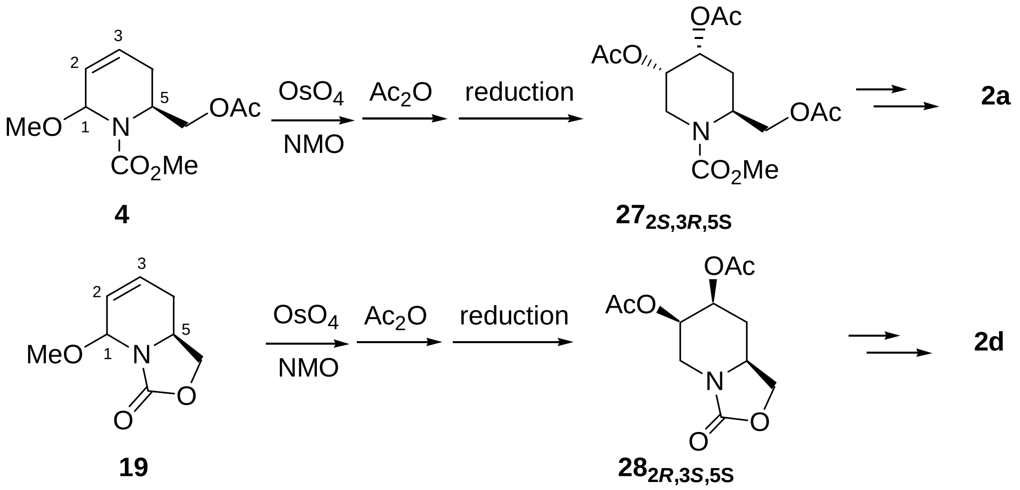
The less stereoselective triacetoxylation of **10a-d** may be due to a conformational flexibility of piperidine ring, which has no substituent at 5-position.



Scheme 4. Plausible mechanism for electrochemical 2,3-*trans*-acetoxylation of **24** and **25**.

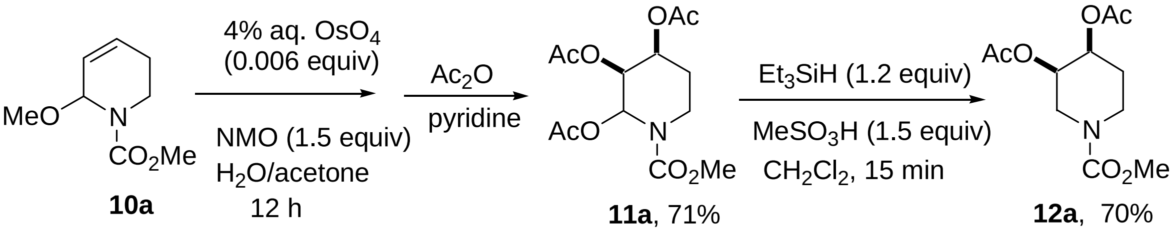
2.2 *cis*-Selective 2,3-dihydroxylation with OsO_4

To prepare 2,3-*cis*-dihydroxylated compounds **2a** and **2d**, oxidation of **4** or **19** with OsO_4 seems to be convenient (Scheme 5).[2e]



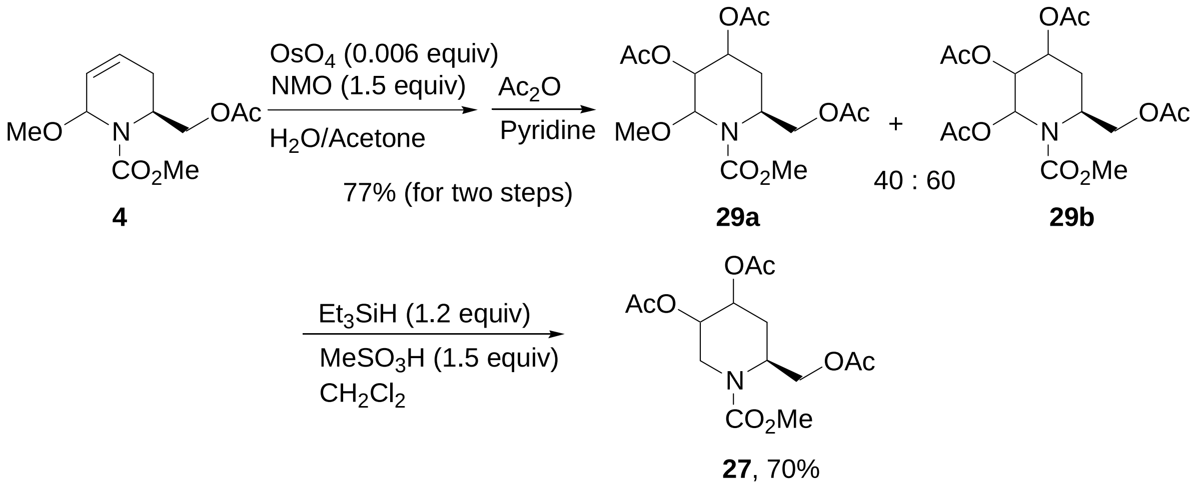
Scheme 5. Strategy for preparation of **2a** and **2d**.

First, we investigated the OsO_4 oxidation of **10a**. Compound **10a** was oxidized with catalytic OsO_4 and 1.5 equiv of NMO followed by acetylation with acetic anhydride and pyridine to produce 2,3,4-triacetoxypiperidine **11a** in 71% yield. Compound **11a** was easily reduced with Et_3SiH to give *cis*-2,3-diacetoxypiperidine **12a** (Eq. 4).



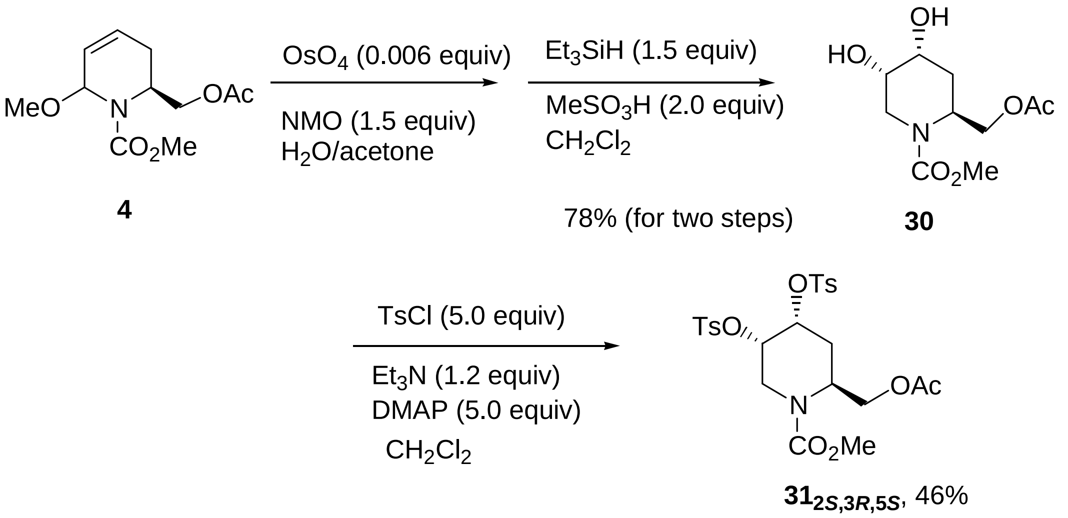
(4)

Encouraged by this result, we continuously tried to apply the same conditions to 5*S*-acetoxymethylpiperidine derivatives **4** (Scheme 6). As expected, the OsO_4 oxidation and subsequent acetylation proceeded smoothly, but the reaction product was a mixture of 2,3-diacetoxy-5*S*-acetoxymethyl-1-methoxy-*N*-methoxycarbonylpiperidine **29a** and 1,2,3-triacetoxy-5*S*-acetoxymethyl-*N*-methoxycarbonylpiperidine **29b**. Without purification of the mixture, reduction with Et_3SiH was carried out to provide only one product, 2,3-diacetoxy-5*S*-acetoxymethyl-*N*-methoxycarbonylpiperidine **27**. Since **27** did not crystallize, we tried to prepare its tosylated derivatives to determine absolute stereochemistry of the two hydroxyl groups at the 2,3-position by X-ray analysis.



Scheme 6. Preparation of **27**.

The OsO_4 oxidation of **4** and successive reduction with Et_3SiH gave 2,3-dihydroxylated derivative **30** as a single diastereomer (Scheme 7). Then, compound **30** was treated with tosyl chloride to afford crystal 2,3-ditosyloxylated derivative **31**. The X-ray analysis of compound **31** determined its absolute stereoconfiguration, (2*S*,3*R*,5*S*).[14]



Scheme 7. Preparation of $\mathbf{31}_{2S,3R,5S}$.

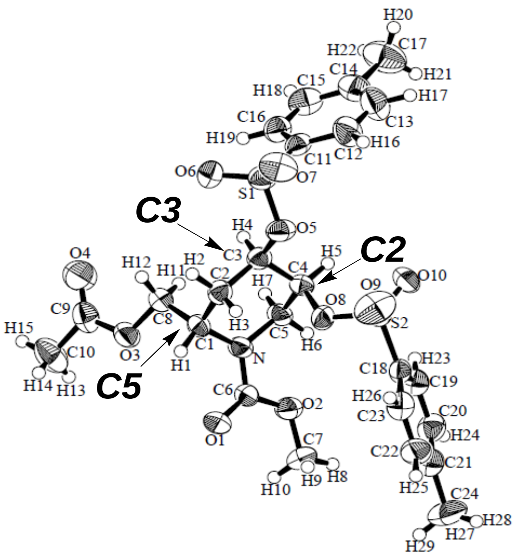
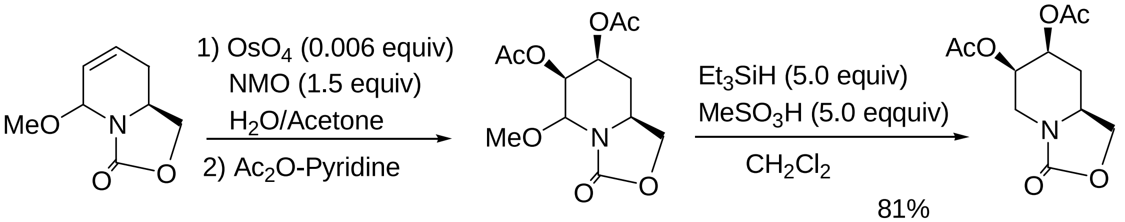


Figure 6. Ortep drawing of $\mathbf{31}_{2S,3R,5S}$.

Next, the OsO_4 oxidation of bicyclic carbamate **19** and successive acetylation with Ac_2O-pyridine was examined to give 1-methoxy-2,3-diacetoxylated compound **32**. In this case, 1-methoxy group remained unchanged in this reaction condition. Finally, compound **32** was reduced by Et_3SiH to afford 2,3-diacetoxylated bicyclic carbamate **28** as a single diastereomer (Eq. 5). The absolute stereoconfiguration of **28** was determined by X-ray analysis to be 2*R*,3*S*,5*S* (Fig. 7).[14]



(5)

19

32, 85%

$\mathbf{28}_{\mathbf{2R,3S,5S}}$

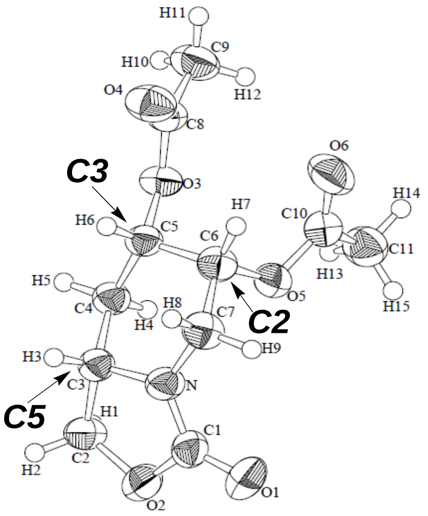
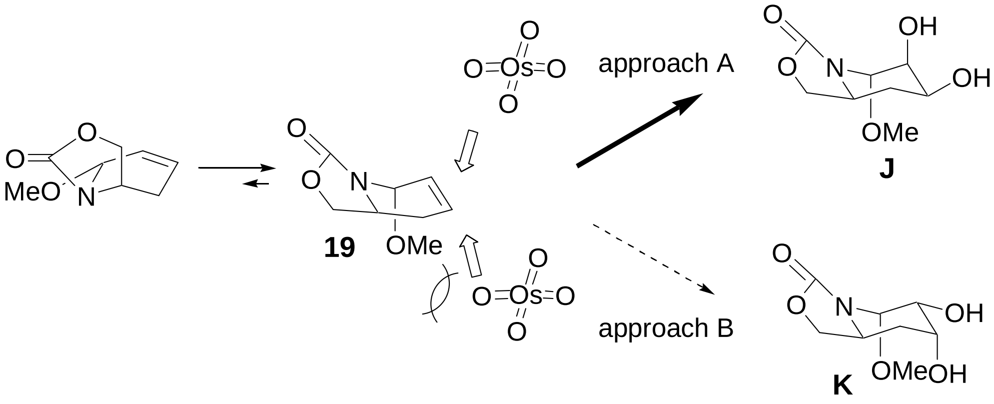


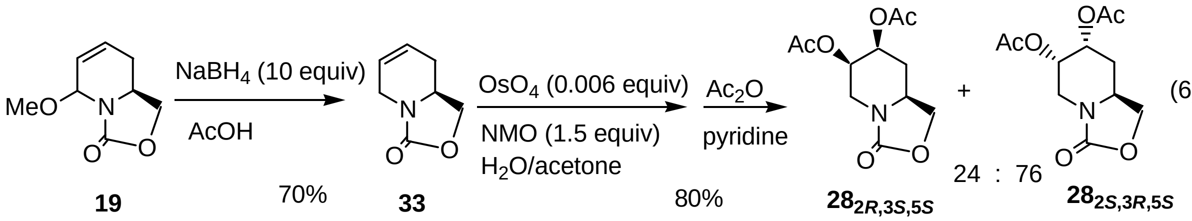
Figure 7. Ortep drawing of $\mathbf{28}_{2R,3S,5S}$.

The observed high diastereoselectivity by the OsO_4 oxidation in this case can be explained by anomeric effect of 1-methoxyl group. That is, since the methoxyl group is mainly located at the axial position, it is difficult for OsO_4 to get close to **19** from down side (approach B), while OsO_4 can easily get close to **19** from the upper side (approach A) (Scheme 8). Accordingly, the OsO_4 oxidation of **19** and successive reduction exclusively afford dihydroxylated compound **J** as a precursor for $\mathbf{28}_{2R,3S,5S}$.



Scheme 8. Effect of methoxyl group at the 1-position of **19.**

Next, bicyclic carbamate **33**, which has no 1-methoxyl group, was examined. OsO_4 oxidation of **33** followed by acetylation afforded a mixture of 2*R*,3*S*-isomer $\mathbf{28}_{2R,3S,5S}$ and 2*S*,3*R*-isomer $\mathbf{28}_{2S,3R,5S}$, whose ratio was 24:76 (Eq. 6). This contrasting result for **33** and **19** supports our proposed stereochemical course shown in Scheme 8. The result can represent the importance of the steric effect of 1-methoxyl group on the observed high diastereoselectivity.



(6)

In summary, the stereoselective formal syntheses of 2,3,6-trihydroxylated 5*S*-methyl-piperidines **2a-d** from L-lysine and L-pipecolic acid has been accomplished by using tandem electrochemical oxidation or OsO_4 oxidation.

4. Experimental Section

4.1. General

Electrochemical reactions were carried out using DC Power Supply (GP 050–2) of Takasago Seisakusho, Inc. ^{1}H NMR spectra were measured on a Varian Gemini 300 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Mass spectra were obtained on a JEOL JMS-DX 303 instrument. HPLC analyses were achieved by using a LC-10AT *VP* and a SPD-10A *VP* of Shimadzu Seisakusho, Inc. Specific rotations were measured with JASCO DIP-1000. Melting points are uncorrected. Elemental analyses were carried out at the Center for Instrumental Analysis, Nagasaki University.

All reagents and solvents were used as supplied without further purification.

4.2. Measurement of oxidation potentials

BAS CV-50W was used as a voltametric analyzer. A solution of substrate (0.1 mmol) in MeCN (10 mL) containing 0.1 M Et_4NBF_4 was measured. Reference electrode was $Ag/AgNO_3$ in saturated aqueous KCl, a working electrode was a glassy carbon, and a counter electrode was a platinum wire. Scan rate was 100 mV/s.

4.3. **Preparation of 2,3-didehydro-1-methoxy-*N*-acylpiperidines 10a-d**

Transformations of 1-acylpiperidines **7a-d** to 2,3-didehydro-1-methoxy-*N*-acylpiperidines **10a-d** were carried out according to our reported method.[9] Compounds **8a**,[6a] **8b**,[6c] **8c**,[6b] **8d**,[9c] **9a**,[7b] **9b**,[7d] **9c**,[7a] **9d**,[7c] **10a**,[9b] and **10d**[9d] are known.

The characterization data for unknown compounds **10b** and **10c** are described below.

***N*-Benzyloxycarbonyl-2,3-didehydro-1-methoxypiperidine (10b):** ^{1}H-NMR ($CDCl_3$) δ 1.92-2.05 (m, 1H), 2.10-2.30 (m, 1H), 3.05-3.25 (m, 1H), 3.29 and 3.39 (2s, 3H), 4.02-4.25 (m, 1H), 5.12-5.26 (m, 2H), 5.40-5.55 (m, 1H), 5.70-5.84 (m, 1H), 5.95-6.06 (m, 1H), 7.36 (s, 5H); IR (neat) 3038, 2936, 1713, 1655, 1428, 1200, 1082, 982, 698 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{14}H_{17}NO_3$ (M^+): 247.1208. Found: 247.1181.

2,3-Didehydro-*N*-formyl-1-methoxypiperidine (10c): ^{1}H-NMR ($CDCl_3$) δ 2.02-2.35 (m, 2H), 2.98 (td, *J* = 13.1 and 6.0 Hz, 2/3H), 3.30 and 3.39 (2s, 2H and 1H), 3.45-3.52 (m, 2/3H), 4.35 (dd, *J* = 13.5 and 6.4 Hz, 2/3H), 4.75 and 5.63 (2d, *J* = 3.0 and 3.0 Hz, 2/3H and 1/3H), 5.78-5.88 (m, 1H), 5.92-6.10 (m, 1H), 8.26 and 8.29 (2s, 1/3H and 2/3H); IR (neat) 3567, 2938, 1692, 1655, 1433, 1084, 957, 669 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_7H_{11}NO_2$ (M^+): 141.0790. Found: 141.0770.

Preparation of optically active 2,3-didehydro-1-methoxy-*N*-methoxycarbonylpiperidine (4)

Compound **4** was prepared from L-lysine derivative **13** or L-pipecolic acid derivative **3** by our reported method.[12b] Compound **14** was transformed into compound **15** without purification. The characterization data for compounds **3**, **4**, **13**, and **15** are described below.

5*S*-Acetoxymethyl-*N*-methoxycarbonylpiperidine (3): $[\alpha]^{28}_D$ –45.6 (*c* 1.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.34-1.55 (m, 2H), 1.58-1.74 (m, 4H), 2.04 (s, 3H), 2.88 (t, *J* = 12.9 Hz, 1H), 3.69 (s, 3H), 4.00-4.10 (m, 1H), 4.15 (dd, *J* = 11.4 and 6.6 Hz, 1H), 4.24 (dd, *J* = 11.4 and 8.7 Hz, 1H), 4.51 (br s, 1H); IR (neat) 2944, 1748, 1655, 1449, 1262, 1049, 841, 770 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{10}H_{17}NO_4$ (M^+): 215.1157. Found: 215.1146.

5*S*-Acetoxymethyl-2,3-didehydro-1-methoxy-*N*-methoxycarbonylpiperidine (4): $[\alpha]^{28}_D$ +71.6 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.08-2.17 (m, 1H), 2.28-2.46 (m, 1H), 3.37 and 3.42 (2br s, 3H), 3.77 (s, 3H), 4.09-4.26 (m, 2H), 4.57-4.85 (m, 1H), 5.34-5.61 (m, 1H), 5.72-5.94 (m, 2H); IR (neat) 2957, 1744, 1709, 1445, 1368, 1231, 1123, 1082, 980, 770 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{11}H_{17}NO_5$ (M^+): 243.1107. Found: 243.1090.

5*S*-Acetoxymethyl-1,2-didehydro-*N*-methoxycarbonylpiperidine (15): $[\alpha]^{27}_D$ –72.2 (*c* 1.2, methanol); ^{1}H-NMR ($CDCl_3$) δ 1.69-2.07 (m, 4H), 2.06 (s, 3H), 3.77 (s, 3H), 4.01 (dd, *J* = 10.8 and 7.2 Hz, 1H), 4.06-4.22 (m, 1H), 4.45-4.70 (m, 1H), 4.82-5.02 (m, 1H), 6.71 and 6.85 (2d, *J* = 8.7 and 9.0 Hz, 1H); IR (neat) 2965, 1742, 1712, 1660, 1448, 1362, 1240 cm^{-1}; 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.

2*S*,6-Bis(methoxycarbonylamino)hexyl acetate (13): $[\alpha]^{28}_{D}$ +17.1 (*c* 1.0, methanol); mp 97-98 °C; ^{1}H-NMR ($CDCl_3$) δ 1.35-1.60 (m, 6H), 2.07 (s, 3H), 3.10-3.26 (m, 2H), 3.66 (s, 3H), 3.67 (s, 3H), 3.82-3.93 (m, 1H), 4.04-4.12 (m, 2H), 4.64-4.84 (m, 2H); IR (KBr) 3335, 2980, 1755, 1700, 1555, 1230, 1068 cm^{-1}; 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.

Preparation of optically active bicyclic compound 19

Compound **19** was prepared from L-lysine derivative **22**[12a] or L-pipecolic acid derivative **16** by procedures similar to preparation of **4**.

The characterization data for compounds **16**, **17**, **18**,[15] **19**,[15] and **22** are described below.

5*S*,*N*-Bis(methoxycarbonyl)piperidine (16): $[\alpha]^{25}_{D}$ –60.9 (*c* 1.5, methanol); ^{1}H-NMR ($CDCl_3$) δ 1.16-1.52 (m, 2H), 1.58-1.75 (m, 3H), 2.16-2.30 (m, 1H), 2.88-3.11 (m, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 3.92-4.19 (m, 1H), 4.75-4.99 (m, 1H); IR (neat) 2950, 1750, 1710, 1450, 1265, 1210, 1170, 1095 cm^{-1}; Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.70; H, 7.74; N, 6.67.

1,2-Didehydro-5*S*,*N*-bis(methoxycarbonyl)piperidine (17): $[\alpha]^{27}_{D}$ –46.9 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.83-2.05 (m, 3H), 2.30-2.42 (m, 1H), 3.74 (s, 3H), 3.75 and 3.80 (2s, 2H and 1H), 4.81-4.91 (m, 1H), 4.93-5.02 (m, 1H), 6.81 and 6.94 (2d, *J* = 9.0 and 8.7 Hz, 2/3H and 1/3H); IR (neat) 2950, 1755, 1720, 1445, 1360 cm^{-1}; Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.17; H, 6.73; N, 6.74.

(6*S*)-1-Aza-2,3-didehydro-8-oxabicyclo[4.3.0]nonan-9-one (18): $[\alpha]^{28}_{D}$ +164.9 (*c* 1.0, $CHCl_3$); mp 45-46 °C; ^{1}H-NMR ($CDCl_3$) δ 1.50-1.80 (m, 1H), 2.05-2.32 (m, 3H), 3.95-4.15 (m, 2H), 4.50-4.70 (m, 1H), 5.03-5.15 (m, 1H), 6.60 (d, *J* = 10.0 Hz, 1H); IR (KBr) 1752, 1720, 1445, 1360 cm^{-1}; 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.

(6*S*)-1-Aza-3,4-didehydro-2-methoxy-8-oxabicyclo[4.3.0]nonan-9-one (19): $[\alpha]^{28}_{D}$ –226.6 (*c* 1.0, $CHCl_3$); mp 34-36°C; ^{1}H-NMR ($CDCl_3$) δ 2.09-2.35 (m, 2H), 3.45 (s, 3H), 3.92-4.04 (m, 1H), 4.09 (dd, *J* = 8.7 and 3.6 Hz, 1H), 4.56 (t, *J* = 8.4 Hz, 1H), 5.14 (d, *J* = 1.2 Hz, 1H), 5.81-5.91 (m, 1H), 5.94-6.02 (m, 1H); IR (KBr) 2982, 1767, 1414, 982, 763 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_8H_{11}NO_3$ (M^+): 169.0739. Found: 169.0731.

Methyl 2*S*,6-Bis(methoxycarbonylamino)hexanoate (22): $[\alpha]^{28}_{D}$ +16.5 (*c* 1.0, $CHCl_3$); mp 50-51 °C (uncorrected); ^{1}H-NMR ($CDCl_3$) δ 1.27-1.44 (m, 2H), 1.46-1.59 (m, 2H), 1.62-1.76 (m, 1H), 1.78-1.90 (m, 1H), 3.15-3.20 (m, 2H), 3.66 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 4.31-4.39 (m, 1H), 4.77 (br s, 1H), 5.31 (br s, 1H); IR (KBr) 3290, 2950, 1730, 1695, 1550, 1275 cm^{-1}; Anal. Calcd for $C_{11}H_{20}N_2O_6$: C, 47.82; H, 7.30; N, 10.14. Found: C, 48.05; H, 7.40; N, 10.27.

Preparation of racemic 3-acetoxy-1,2-didehydro-*N*-methoxycarbonylpiperidine 23, and optically active 3-acetoxy-1,2-didehydro-*N*-acylpiperidines 24 and 25

Compounds **10a**, **4**, and **19** were easily transformed into 3-acetoxylated derivative **23**, **24** and **25** by stirring in acetic acid for a few minutes with quantitative yield.

3-Acetoxy-1,2-didehydro-*N*-methoxycarbonylpiperidine (23) : ^{1}H-NMR ($CDCl_3$) δ 1.83-2.03 (m, 2H), 2.05 (s, 3H), 3.30-3.45 (m, 1H), 3.79 (s, 3H), 3.87-4.10 (m, 1H), 4.97-5.15 (m, 1H), 5.17-5.25 (m, 1H), 6.97 and 7.11 (2br d, *J* = 9.2 Hz, 1H); IR (neat) 2957, 1717, 1648, 1447, 1364, 1235, 1007, 768 cm^{-1}; HRMS (M^+) *m/z* Calcd for $C_9H_{13}NO_4$ (M^+): 199.0845. Found: 199.0822.

3*S*-Acetoxy-5*S*-acetoxymethyl-1,2-didehydro-*N*-methoxycarbonylpiperidine (24): ^{1}H-NMR ($CDCl_3$) δ 1.93-2.23 (m, 1H), 2.02 (s, 3H), 2.05 (s, 3H), 2.18-2.30 (m, 1H), 3.80 (s, 3H), 4.15-4.31 (m, 2H), 4.53-4.78 (m, 1H), 5.02-5.24 (m, 2H), 6.95 and 7.09 (2d, *J* = 7.0 and 6.4 Hz, 1H); IR (neat) 2959, 1752, 1648, 1447, 1334, 1073, 768 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{12}H_{17}NO_6$ (M^+): 271.1056. Found: 271.1066.

(4*R*,6*S*)-1-Aza-4-acetoxy-2,3-didehydro-8-oxabicyclo[4.3.0]nonan-9-one (25): mp 77-79 °C; ^{1}H-NMR ($CDCl_3$) δ 1.72 (td, *J* = 12.8 and 3.8 Hz, 1H), 2.06 (s, 3H), 2.24 (d, *J* = 12.8 Hz, 1H), 4.01 (t, J = 9.0 Hz, 1H), 4.07-4.21 (m, 1H), 4.67 (t, J = 8.1 Hz, 1H), 5.25-5.33 (m, 2H), 6.87 (d, J = 6.6 Hz, 1H); IR (KBr) 2905, 1784, 1644, 1426, 1269, 1055, 992, 756 cm^{-1}; HRMS *m/z* Calcd for $C_9H_{11}NO_4$ (M^+): 197.0689. Found: 197.0668.

Electrochemical acetoxylation of 2,3-didehydro- and 1,2-didehydropiperidine derivatives 10a-d, 4, 19 and 23

A typical procedure is exemplified by the anodic oxidation of **4**. Into a glass beaker (15 mL) equipped with two Pt plate electrodes (10 mm x 20 mm) was added a solution of **4** (0.243g, 1mmol) and AcOK (1.00 g, 10 mmol) in acetic acid (10 mL). After 15 *F*/mol of electricity was passed at a constant current of 0.1A (4 h, terminal voltage: ca 15 V) through the solution cooled with water, saturated aqueous $NaHCO_3$ (20 mL) was added into the reaction mixture. The organic portion was extracted with AcOEt (20 mL x 3) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL). After the extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*, the residue was chromatographed on silica gel (AcOEt:*n*-hexane = 1:3) to afford 1,2,3-triacetoxy-5*S*-acetoxy-methyl-*N*-methoxycarbonylpiperidine (**5**) in 85% yield.

5: ^{1}H-NMR ($CDCl_3$) δ 1.91-2.24 (m, 14H), 3.69-3.82 (m, 3H), 4.03-4.39 (m, 2H), 4.45-4.60 (m, 1H), 4.88-5.07 (m, 1H), 5.15-5.38 (m, 1H), 6.64-6.90 (m, 1H); IR (neat) 2952, 1755, 1597, 1447, 1372, 1240, 1044, 776 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{14}H_{19}NO_8$ (M^+−AcOH): 329.1111. Found: 329.1111.

1,2,3-Triacetoxy-*N*-methoxycarbonylpiperidine (11a): ^{1}H-NMR ($CDCl_3$) δ 1.77-2.25 (m, 11H), 3.08-3.17 (m, 1H), 3.74 and 3.76 (2s, 3H), 3.95-4.14 (m, 1H), 4.82-5.02 and 5.14-5.28 (2m, 2H), 6.56-6.78 and 6.93-7.08 (2m, 1H); IR (neat) 2980, 1786, 1420, 1375, 1256, 1051, 764 cm^{-1}; Anal. Calcd for $C_{13}H_{19}NO_8$: C, 49.21; H, 6.04; N, 4.41. Found: C, 49.14; H, 6.22; N, 4.35.

1,2,3-Triacetoxy-*N*-benzyloxycarbonylpiperidine (11b): ^{1}H-NMR ($CDCl_3$) δ 1.75-2.24 (m, 11H), 3.09-3.27 (m, 1H), 3.97-4.26 (m, 1H), 4.95-5.31 (m, 4H), 6.80 and 7.10 (2d, J = 1.0 and 4.0 Hz, 1H), 7.35 (s, 5H); IR (neat) 2953, 1748, 1717, 1370, 1215, 1053, 698 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{19}H_{23}NO_8$ (M^+): 393.1424. Found: 393.1464.

1,2,3-Triacetoxy-*N*-formylpiperidine (11c): ^{1}H-NMR ($CDCl_3$) δ 1.80-2.29 (m, 11H), 2.81-3.17 (m, 1H), 4.15-4.46 (m, 1H), 4.91-5.08 (m, 1H), 5.22-5.37 (m, 1H), 5.95, 6.04, 6.35 and 6.43 (4d, *J* = 0.8, 1.0, 3.0 and 4.0 Hz, 1H), 8.25 and 8.28 (2s, 1H); IR (neat) 3567, 2942, 1759, 1698, 1433, 1374, 1256, 1053, 704 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{12}H_{17}NO_7$ (M^+): 287.1005. Found: 287.0981.

1,2,3-Triacetoxy-*N*-benzoylpiperidine (11d): ^{1}H-NMR ($CDCl_3$) δ 1.84-2.38 (m, 11H), 3.10-3.49 (m, 1H), 4.18-4.59 (m, 1H), 4.92-5.13 (m, 1H), 5.21-5.41 (m, 1H), 6.15-6.44 and 6.61-6.88 (2m, 1H), 7.24-7.51 (m, 5H); IR (neat) 3063, 2940, 1755, 1659, 1374, 1252, 1057, 702 cm^{-1}; Anal. Calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.23; H, 6.23; N, 3.65.

(3*R*,4*R*,6*S*)-2,3,4-Triacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (20): ^{1}H-NMR ($CDCl_3$) δ 1.94 (td, *J* = 12.0 and 1.8 Hz, 1H), 2.05-2.18 (m, 10H), 4.02 (dd, *J* = 8.6 and 6.6 Hz, 1H), 4.20-4.30 (m, 1H), 4.52-4.58 (m, 1H), 5.06-5.10 (m, 2H), 6.31 and 6.59 (2d, *J* = 1.0 and 1.8 Hz, 3/4H and 1/4H); IR (neat) 2940, 1782, 1420, 1374, 1285, 1048, 764 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{11}H_{13}NO_6$ (M^+−AcOH): 255.0743. Found: 255.0726.

Reduction of 1,2,3-triacetoxy-*N*-acylpiperidine derivatives 5, 11a-d, and 20

A typical procedure is exemplified by the reduction of **5**. Into a solution of **5** (0.389 g, 1 mmol) and Et_3SiH (0.140 g, 1.2 mmol) in CH_2Cl_2 (3 mL) was added methanesulfonic acid (0.144 g, 1.5 mmol) at 0 °C. After stirring for 10 min, into a mixture of AcOEt (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) was poured the reaction mixture. The organic portion was extracted with AcOEt (20 mL x 3) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL). After the extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*, the residue was chromatographed on silica gel (AcOEt:*n*-hexane = 1:2) to afford 2,3-diacetoxy-5*S*-acetoxymethyl-*N*-methoxycarbonylpiperidine (**6**) in 62% yield as a mixture of stereoisomers. Recrystalization of **6** from AcOEt and *n*-hexane afforded 2*S*,3*S*,5*S*-isomer.

$6_{2S,3S,5S}$: $[\alpha]^{26}_D$ +40.0 (*c* 0.5, $CHCl_3$); mp 102-104°C; ^{1}H-NMR ($CDCl_3$) δ 1.77-1.87 (m, 1H), 2.04 (s, 3H), 2.06 (s, 3H), 2.10 (s, 3H), 2.10-2.23 (m, 1H), 3.34 (d, *J* = 15.0 Hz, 1H), 3.71 (s, 3H), 4.13 (dd, *J* = 11.3 and 5.9 Hz, 1H), 4.23 (d, *J* = 15.0 Hz, 1H), 4.40 (t, *J* = 9.7 Hz, 1H), 4.54-4.70 (m, 1H), 4.76-4.87 (m, 1H), 4.91-4.99 (m, 1H); IR (KBr) 2959, 1750, 1701, 1441, 1374, 1223,1069, 772 cm^{-1}; Anal. Calcd for $C_{14}H_{21}NO_8$: C, 50.75; H, 6.39; N, 4.23. Found: C, 50.88; H, 6.68; N, 4.26. Major isomer of **6** was detected by HPLC method; YMC-Pack SIL (0.46 cmø x 15 cm), *n*-hexane/ethanol = 10:1, wavelength: 210nm, flow rate: 0.5 mL/min, retention time:11.4 min.

2,3-Diacetoxy-*N*-methoxycarbonylpiperidine (12a): ^{1}H-NMR ($CDCl_3$) δ 1.86-2.19 (m, 8H), 3.20-3.50 (m, 2H), 3.70 (s, 3H), 3.77-3.98 (m, 1H), 4.71-4.87 (m, 1H), 4.88-4.98 (m, 1H), 4.99-5.13 (m, 1H); IR (neat) 2959, 1755, 1471, 1374, 1057, 770 cm^{-1}; HRMS *m/z* Calcd for $C_{11}H_{17}NO_6$ (M^+): 259.1055. Found: 259.1042. Diastereomer ratio of **12a** was determined by HPLC method; YMC-Pack SIL (0.46 cmø x 15 cm), *n*-hexane/ethanol = 10:1, wavelength: 210 nm, flow rate: 0.5mL/min, retention time: 8.2 min for *trans*-isomer, 9.1 min for *cis*-isomer.

2,3-Diacetoxy-*N*-benzyloxycarbonylpiperidine (12b): ^{1}H-NMR ($CDCl_3$) δ 1.90-2.12 (m, 8H), 3.30-4.05 (m , 4H), 4.18-5.12 (m, 4H), 7.35 (s, 5H); IR (neat) 3033, 2942, 1752, 1433, 1254, 1055, 766, 700 cm^{-1}; HRMS *m/z* Calcd for $C_{17}H_{21}NO_6$ (M^+): 335.1369. Found: 335.1349. Diastereomer ratio of **12b** was determined by HPLC method; YMC-Pack SIL (0.46 cmø x 15 cm), *n*-hexane/ethanol = 15:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 9.3 min for *trans*-isomer, 10.4 min for *cis*-isomer.

2,3-Diacetoxy-*N*-formylpiperidine (12c): ^{1}H-NMR ($CDCl_3$) δ 1.80-2.08 (m, 8H), 3.15-3.75 and 3.95-4.35 (2m, 4H), 4.75-4.88 and 4.95-5.45 (2m, 2H), 7.95, 7.97, 8.08, and 8.10 (4s, 1H); IR (neat) 3650, 2940, 1759, 1690, 1439, 1372, 1260, 1046 cm^{-1}; HRMS *m/z* Calcd for $C_{10}H_{15}NO_5$ (M^+): 229.0950. Found: 229.0975. Diastereomer ratio of **12c** was determined by HPLC method; YMC-Pack SIL (0.46 cmø x 15 cm), *n*-hexane/ethanol = 10:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 9.0 min for *trans*-isomer, 9.7 min for *cis*-isomer.

2,3-Diacetoxy-*N*-benzoylpiperidine (12d): ^{1}H-NMR ($CDCl_3$) δ 1.70-2.20 (m, 8H), 3.20-4.40 (m, 4H), 4.68-5.22 (m, 2H), 7.41 (s, 5H); IR (neat) 2940, 1744, 1640, 1431, 1372, 1248, 706 cm^{-1}; HRMS *m/z* Calcd for $C_{16}H_{19}NO_5$ (M^+): 305.1263. Found: 305.1273. Diastereomer ratio of **12d** was determined by HPLC method; YMC-Pack SIL (0.46 cmø x 15 cm), *n*-hexane/ethanol = 10:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 25.9

min for *trans*-isomer, 29.5 min for *cis*-isomer.

(3*R*,4*R*,6*S*)-3,4-Diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (21): $[\alpha]^{26}_{D}$ –75.2 (*c* 0.6, $CHCl_3$); mp 127-129˚C (from AcOEt and n-hexane), (uncorrected); ^{1}H-NMR ($CDCl_3$) δ 1.90-2.05 (m, 2H), 2.09 (s, 3H), 2.13 (s, 3H), 3.33 (dd, *J* = 15.0 and 2.1 Hz, 1H), 3.92-4.05 (m, 3H), 4.38-4.48 (m, 1H), 4.80-4.85 (m, 1H), 5.08-5.12 (m, 1H); IR (neat) 2932, 1744, 1422, 1372, 1221, 1061, 914, 768 cm^{-1}; Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.45. Found: C, 51.49; H, 6.08; N, 5.44. Major isomer of **21** was detected by HPLC method; YMC-Pack SIL (0.46 cmø x 15 cm), *n*-hexane/ethanol = 5:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 18.9 min.

Preparation of 2,3-didehydropiperidine derivative 33.

Into a round-bottomed flask (25 mL) equipped with a magnetic stirrer and containg **19** (0.423 g, 2.5 mmol) in acetic acid (10 mL) was added $NaBH_4$ (0.946 g, 10 mmol). The reaction vessel was cooled with water. After stirring for 10 min, water (10 mL) was added slowly to the reaction solution at 0 °C. The mixture was extracted with AcOEt (20 mL x 3). The combined extracts were washed with saturated aqueous $NaHCO_3$ (20 mL). After the extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo, the residue was chromatographed on silica gel (AcOEt:*n*-hexane = 1:2) to afford **33** in 70% yield.

6*S*-1-Aza-3,4-didehydro-8-oxabicyclo[4.3.0]nonan-9-one (33): $[\alpha]^{30}_{D}$ –166.9 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.11-2.37 (m, 2H), 3.64-3.75 (m, 1H), 3.76-3.89 (m, 1H), 4.03 (dd, *J* = 8.7 Hz and 5.7 Hz, 1H), 4.08-4.14 and 4.16-4.21 (2m, 1H), 4.52 (t, *J* = 8.3 Hz, 1H), 5.70-5.89 (m, 2H); IR (neat) 2977, 1777, 1457, 1242, 1208, 1078, 961, 764 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_7H_9NO_2$ (M^+): 139.0633, Found: 139.0609.

Osmium oxidation of 2,3-didehydropiperidine derivatives 4, 19, 10a, and 33 and the successive acetoxylations.

A typical procedure is exemplified by the osmium oxidation of **10a**. Into a round-bottomed flask (25 mL) equipped with a magnetic stirrer was added a solution of **5** (0.171 g, 1 mmol) and NMO (50% in water, 0.351 g, 1.5 mmol) in acetone (0.5 mL) and H_2O (2.5 mL). To a stirred solution at room temperature was added osmium tetraoxide (4wt % solution in water, 2 drops, 0.01 mmol). After the mixture was stirred overnight at room temperature, 10% aqueous $Na_2S_2O_3$ (5 mL) was added into the reaction mixture. The resulting mixture was concentrated under reduced pressure. Pyridine (2 mL) and acetic anhydride (2 mL) were then added to the residue and the mixture stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. To the residue was added water (10 mL) and the organic portion was extracted with AcOEt (20 mL x 3). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt:*n*-hexane = 1:5) to afford 1,2,3-triacetoxy-*N*-methoxycarbonylpiperidine (**11a**) in 71% yield.

11a: ^{1}H-NMR ($CDCl_3$) δ 1.78-1.88 (m, 1H), 1.92-2.05 (m, 1H), 2.01, 2.10 and 2.11 (3s, 9H), 3.09-3.23 (m, 1H), 3.76 (s, 3H), 4.06-4.29 (m, 1H), 5.18-5.28 (m, 2H), 6.71 (br s, 1H); IR (neat) 2959, 1748, 1449, 1372, 1223, 1057, 772 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{13}H_{19}NO_8$ (M^+): 317.1111. Found: 317.1116.

By similar procedures as above, **4** was converted into a mixture of 2,3-diacetoxy-5*S*-acetoxymethyl-1-methoxy-*N*-methoxycarbonylpiperidine (**29a**) and 1,2,3-triacetoxy-5*S*-acetoxymethyl-*N*-methoxycarbonylpiperidine (**29b**) was obtained in 77% yield (**29a**:**29b** = 0.4:0.6) . ^{1}H-NMR ($CDCl_3$) δ 1.85-1.95 (m, 2H), 2.02, 2.03, 2.06, 2.07, 2.096, 2.100, 2.12 (7s, 10.8H), 3.34 and 3.37 (2s, 1.2H), 3.75 and 3.77 (2s, 3H), 4.07-4.20 (m, 1H), 4.22-4.41 (m, 1H), 4.54-4.79 (m, 1H), 5.18-5.52 (m, 2H), 5.72-5.84 (m, 0.4H), 6.70-6.90 (m, 0.6H); IR (neat) 2959, 1744, 1445, 1370, 1225, 1090, 774 cm^{-1}.

(3*R*,4*S*,6*S*)-3,4-Diacetoxy-2-methoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (32) (85% yield from **19**): ^{1}H-NMR ($CDCl_3$) δ 1.84-2.02 (m, 2H), 2.04 (s, 3H), 2.11 (s, 3H), 3.38 (s, 3H), 3.98-4.10 (m, 2H), 4.48-4.56 (m, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 5.19-5.29 (m, 2H); IR (neat) 2940, 1771, 1414, 1374, 1238, 1102, 970, 764 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{12}H_{17}NO_7$ (M^+): 287.1005. Found: 287.1014.

Using similar oxidation procedure, **33** was successively oxidized and acetoxylated to afford a mixture of (3*S*,4*R*,6*S*)-3,4-diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (**28**$_{2S,3R,5S}$) and (3*R*,4*S*,6*S*)-isomer (**28**$_{2R,3S,5S}$) (**28**$_{2S,3R,5S}$:**28**$_{2R,3S,5S}$ = 76:24) in 80% yield. **(3*S*,4*R*,6*S*)-3,4-Diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (28$_{2S,3R,5S}$):** $[\alpha]^{28}_{D}$ –53.3 (*c* 1.5, $CHCl_3$), (containing 4% of (3*R*,4*S*,6*S*)-isomer **28**$_{2S,3R,5S}$); ^{1}H-NMR ($CDCl_3$) δ 1.70-1.83 (m, 1H), 2.03 (s, 3H), 2.07-2.13 (m, 1H), 2.14 (s, 3H), 3.22 (t, *J* = 12.0 Hz, 1H), 3.89-4.09 (m, 3H), 4.46 (t, *J* = 9.3 Hz, 1H), 4.80-4.90 (m, 1H), 5.50 (br s, 1H); IR (neat) 2940, 1781, 1485, 1375, 1266, 1177, 1071, 974, 762 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{11}H_{15}NO_6$ (M^+): 257.0899. Found: 257.0892.

Reduction of α-alkoxyl group of 11a, 29a, 29b and 32.

A typical procedure is exemplified by the reduction of **11a**. To 1 mmol of **11a** was added Et_3SiH (0.174 g, 1.5 mmol) in CH_2Cl_2 (3 mL), methanesulfonic acid (0. 192 g, 2.0 mmol) was then added at 0 °C. After stirring for 10 min, into a mixture of AcOEt (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) was poured the reaction mixture. The organic portion was extracted with AcOEt (20 mL x 3) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL). After the extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo, the residue was chromatographed on silica gel (AcOEt:*n*-hexane = 1:5) to afford 2,3-diacetoxy-*N*-methoxycarbonylpiperidine (**12a**) in 70% yield. ***cis*-2,3-Diacetoxy-*N*-methoxycarbonylpiperidine (12a*cis*):** ^{1}H-NMR ($CDCl_3$) δ 1.72-1.83 (m, 1H), 1.87-2.02 (m, 1H), 2.07 and 2.08 (2s, 6H), 3.20-3.48 (m, 2H), 3.70 (s, 3H), 3.87 and 3.91 (2d, *J* = 6.0 and 6.0 Hz, 2H), 4.98-5.13 (m, 2H); IR (neat) 2959, 1755, 1474, 1372, 1278, 1057, 770 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{11}H_{17}NO_6$ (M^+): 259.1056. Found: 259.1049.

2*S*,3*R*-Diacetoxy-5*S*-acetoxymethyl-*N*-methoxycarbonylpiperidine (27$_{2S,3R,5S}$) (70% yield from a mixture of 29a and 29b): $[\alpha]^{30}_D$ +37.0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.75 and 1.78 (2d, *J*=4.4Hz, 1H), 2.02 and 2.07 and 2.08 (3s, 9H), 2.09-2.11 (m, 1H), 3.19 (d, *J* = 15.0 Hz, 1H), 3.72 (s, 3H), 4.10 and 4.15 (2d, *J* = 5.7 Hz, 1H), 4.23-4.38 (m, 2H), 4.69-4.82 (br s, 1H), 5.03-5.13 (m, 1H), 5.19 (br s, 1H); IR (neat) 2959, 1755, 1709, 1451, 1374, 1256, 1055, 770 cm^{-1}; HRMS *m/z* Calcd for $C_{14}H_{21}NO_8$ (M^+): 331.1267. Found: 331.1258. Major isomer of **27** was detected by HPLC method; YMC-Pack SIL (0.46 cmø x 15 cm), *n*-hexane/ethanol = 10:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 12.2 min.

(3*R*,4*S*,6*S*)-3,4-Diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (28$_{2R,3S,5S}$) (81% yield from 32): $[\alpha]^{29}_D$ –48.0 (*c* 0.5, $CHCl_3$); mp 122-123°C (from AcOEt and *n*-hexane), (uncorrected); ^{1}H-NMR ($CDCl_3$) δ 1.89-1.99 (m, 2H), 2.05 (s, 3H), 2.11 (s, 3H), 3.13 (dd, *J* = 12.8 and 1.8 Hz, 1H), 3.84-3.95 (m, 1H), 4.04 (dd, *J* = 8.4 and 3.3 Hz, 1H), 4.10 (d, *J* = 12.5 Hz, 1H), 4.44 (t, *J* = 7.8 Hz, 1H), 4.92-5.03 (m, 1H), 5.19 (br s, 1H); IR (KBr) 2936, 1763, 1431, 1374, 1258, 1073, 986, 764 cm^{-1}; Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.45. Found: C, 51.43; H, 5.93; N, 5.40. Major isomer of **11** was detected by HPLC method; YMC-Pack SIL (0.46 cmø x 15 cm), *n*-hexane/ethanol = 5:1, wavelength: 210nm, flow rate: 0.5 mL/min, retention time: 21.6 min.

Synthesis of 5*S*-acetoxymethyl-2*S*,3*R*-dihydroxy-*N*-methoxycarbonylpiperidine (30$_{2S,3R,5S}$) and successive tosylation.

Into a round-bottomed flask (25 mL) equipped with a magnetic stirrer and containing a solution of **4** (0.243 g, 1 mmol) in acetone (0.5 mL) and H_2O (2.5 mL) was added NMO (50% in water, 0.351 g, 1.5 mmol). To a stirred solution at room temperature was added osmium tetraoxide (4wt % solution in water, 2drops, 0.01 mmol). After the mixture was stirred overnight at room temperature, 10% aqueous $Na_2S_2O_3$ (5 mL) was added into the reaction mixture. The resulting mixture was concentrated under reduced pressure and to the residue was added water (1 mL). The organic portion was extracted with AcOEt (15 mL x 8). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a crude mixture of mixture of 5*S*-acetoxymethyl-1,2,3-trihydroxy-*N*-methoxycarbonylpiperidine and 5*S*-acetoxy-methyl-2,3-dihydroxy-1-methoxy-*N*-methoxycarbonylpiperidine (0.5:0.5) **:** ^{1}H-NMR ($CDCl_3$) δ 1.70-1.85 (m, 1H), 1.89-2.04 (m, 1H), 2.06 (s, 3H), 3.33 (s, 1.5H), 3.74 and 3.76 (2s, 3H), 3.91-4.08 (m, 1H), 4.10-4.20 (m, 1H), 4.21-4.42 (m, 2H), 4.47-4.75 (m, 1H), 5.35-5.44 and 5.51-5.62 and 5.79-5.84 (3m, 1H); IR (neat) 3413, 2959, 1742, 1449, 1356, 1240, 1086, 774 cm^{-1}.

To the mixture was added Et_3SiH (0.174 g, 1.5 mmol) in CH_2Cl_2 (3 mL) and added methanesulfonic acid (0.192 g, 2.0 mmol) at 0 °C. After stirring for 10 min, into a mixture of AcOEt (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) was poured the reaction mixture. The organic portion was extracted with AcOEt (20 mL x 3) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL). After the extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo, the residue was chromatographed on silica gel (AcOEt:*n*-hexane = 3:1) to afford 5*S*-acetoxymethyl-2*S*,3*R*-dihydroxy-*N*-methoxy-carbonylpiperidine (**30**$_{2S,3R,5S}$) in 78% yield from **4**. **(30$_{2S,3R,5S}$):** $[\alpha]^{30}_{D}$ −6.0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.73 and 1.77 (2d, *J* = 4.2 Hz, 1H), 1.91-2.02 (m, 1H), 2.05 (s, 3H), 2.24 (d, *J* = 6.5 Hz, 1H), 2.31-2.48 (br s, 1H), 3.10 (d, *J* = 15.0 Hz, 1H), 3.72 (s, 3H), 3.80-3.96 (m, 2H), 4.06-4.38 (m, 3H), 4.57-4.73 (br s, 1H); IR (neat) 3447, 2959, 1744, 1698, 1456, 1370, 1258, 1140, 1080, 770 cm^{-1}; HRMS *m/z* Calcd for $C_{10}H_{17}NO_6$ (M^+): 247.1056. Found: 247.1058.

To **30**$_{\boldsymbol{2S,3R,5S}}$ (0.1 g, 0.4 mmol) was added *p*-toluenesulfonyl chloride (0.381 g, 2 mmol), Et_3N (0.049 g, 0.48 mmol), and DMAP (0.244 g, 2 mmol) in CH_2Cl_2 (2 mL). After the mixture was stirred for 3 days at room temperature, into a mixture of AcOEt (20 mL) and saturated aqueous $NaHCO_3$ (10 mL) was poured the reaction mixture. The organic portion was extracted with AcOEt (20 mL x 3). After the extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo, the residue was chromatographed on silica gel (AcOEt:*n*-hexane = 1:6) to afford 5*S*-acetoxymethyl-2*S*,3*R*-bis(*p*-toluenesulfonyloxy)-*N*-methoxycarbonylpiperidine (**31**$_{\boldsymbol{2S,3R,5S}}$) in 46% yield.

31$_{\boldsymbol{2S,3R,5S}}$**:** $[\alpha]^{30}_{D}$ +32.4 (*c* 1.0, $CHCl_3$); mp 136-139°C (from AcOEt and *n*-hexane); ^{1}H-NMR ($CDCl_3$) δ 1.64 and 1.71 (2d, *J* = 3.6 Hz, 1H), 2.01 (s, 3H), 2.10-2.26 (m, 1H), 2.46 (s, 6H), 3.09 (d, *J* = 15.3 Hz, 1H), 3.69 (s, 3H), 3.97-4.16 (m, 2H), 4.45 (d, *J* = 15.3 Hz, 1H), 4.55-4.72 (m, 3H), 7.30-7.39 (m, 4H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H); IR (KBr) 2957, 1748, 1701, 1449, 1364, 1246, 1140, 1124, 918, 770 cm^{-1}; Anal. Calcd for $C_{24}H_{29}NO_{10}S_2$: C, 51.88; H, 5.26; N, 2.52. Found: C, 51.92; H, 5.39; N, 2.52.

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13. Methoxylated compound **14** purified with silica gel column chromatography was transformed into a certain amount of unsaturated compound **15** as a by-product. Accordingly the yield of **15** by two steps without purification of **14** was better than that with purification of **14**. The yield of **17** was improved without purification of the corresponding methoxylated compound.
14. Crystallographic data for **6**$_{2S,3S,5S}$, **21**$_{2R,3R,5S}$, **31**$_{2S,3R,5S}$, and **28**$_{2R,3S,5S}$: CCDC 246337, 246338, 746282, and 746283, contain the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)-1223-336033.
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