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

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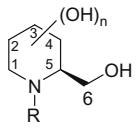
ABSTRACT

A new method using electrochemical oxidation and/or OsO_4 oxidation has been used 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*)-methylpiperidine and (2*R*,3*R*)-6-triacetoxy-(5*S*)-methylpiperidine. In addition, the 2,3-*cis*-dihydroxylation of 2,3-didehydro-1-methoxypiperidine derivatives with OsO_4 afforded (2*R*,3*S*)-6-triacetoxy-(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. They are widely investigated as candidates for drugs to treat a variety of carbohydrate-mediated diseases, such as diabetes, and viral infections including HIV, and cancer metastasis (see Fig. 1). Their inhibitory activities depend on the configuration and the number of hydroxyl groups. Amongst **1**, 2,3,6-trihydroxy-(5*S*)-methylpiperidines **2** are noteworthy since it has recently been reported that (2*R*,3*S*)-6-trihydroxy-(5*S*)-methylpiperidine **2a**, one of the possible stereoisomers **2a**–**d** (Fig. 2), has high inhibitory activities toward glycosidases. However, there have not been any convenient synthetic methods reported for **2a**–**d**.[3,4] We have exploited a facile method for the stereoselective synthesis of **2a**–**d**, and reported the synthesis of **2b** and **c** using electrochemical 2,3-*trans*-diacetoxylation.[5] Herein, we report the synthesis for **2b**,**c** as well as those for **2a**,**d** using 2,3-*cis*-dihydroxylation with OsO_4.



1

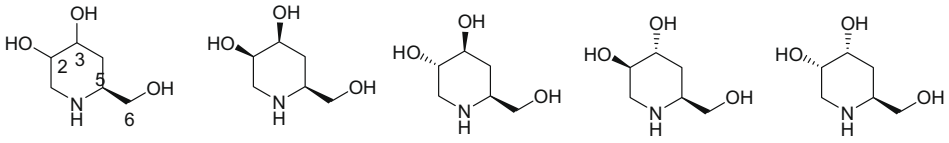
R = H or alkyl

Figure 1.

2. Results and discussion

2.1. Electrochemical 2,3-*trans*-diacetoxylation

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



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

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

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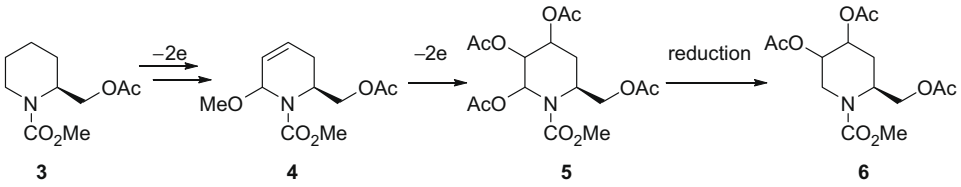
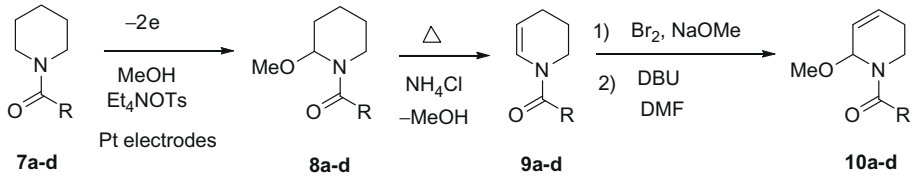


(1)

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 the electrochemical oxidation of **7a** to afford 1-methoxypiperidine **8a**,[6] the elimination of MeOH from **8a** to give 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**.

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

On the other hand, the electrochemical oxidation of bicyclic carbamate **19**, which was prepared from the L-pipecolic acid derivative **16** or from L-lysine derivative **22** via **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 the absolute stereochemistry was also determined by X-ray analysis (Fig. 4).[14]

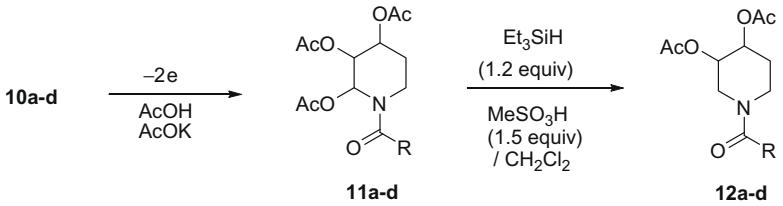


		8a-d	9a-d	10a-d
a:	R = OMe	86%	90%	58%
b:	R = OCH_2Ph	91%	92%	70%
c:	R = H	97%	83%	68%
d:	R = Ph	90%	84%	60%

(2)

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**, although their stereochemistry was not determined at this stage. Next, we achieved the reductive elimination of the 1-acetoxyl groups 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.

The reaction mechanism for the 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, the electrochemical triacetoxylation of **4** and **19** may proceed via 3-acetoxypiperidine

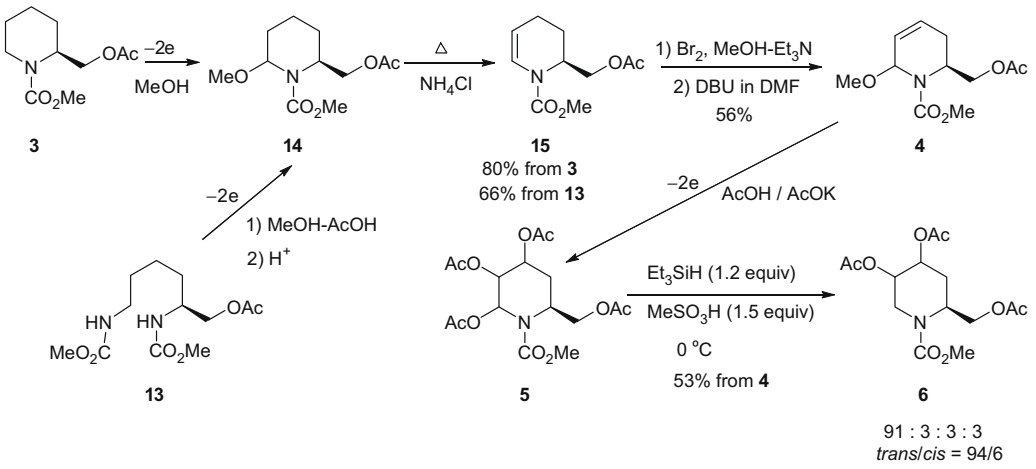


(3)

The stereochemistry (*trans*/*cis*) of **12a–d** was slightly dependent on R (70/30–54/46).[11] We attempted the preparation of **4** from the readily available L-lysine derivative **13**[12] instead of the expensive L-pipecolic acid derivative **3** through **14** and **15**[13] to obtain **4** in a similar way to the transformation of **7** to **10**. The result is shown in Scheme 1. The electrochemical oxidation of **4** under conditions similar to the oxidation of **10** to **11** afforded tetraacetoxylated piperidine **5**, which when reduced 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.

Table 1
Electrochemical oxidation of **10a–d** followed by reduction of **11a–d** with Et_3SiH

Entry	**10a–d** R	Yield (%)		*trans*:*cis* **12a–d**
		11a–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



Scheme 1. Preparation of (2*S*,3*S*,5*S*)-**6**starting from **3** or **13**.

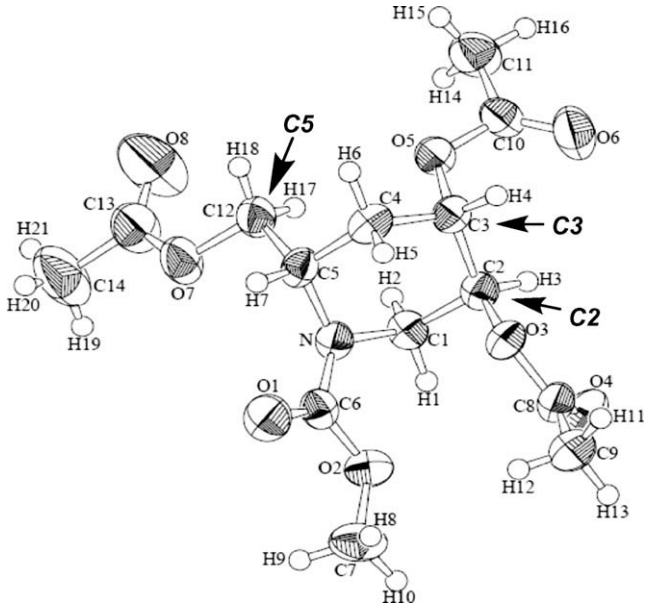


Figure 3. Ortep drawing of (2*S*,3*S*,5*S*)-**6**.

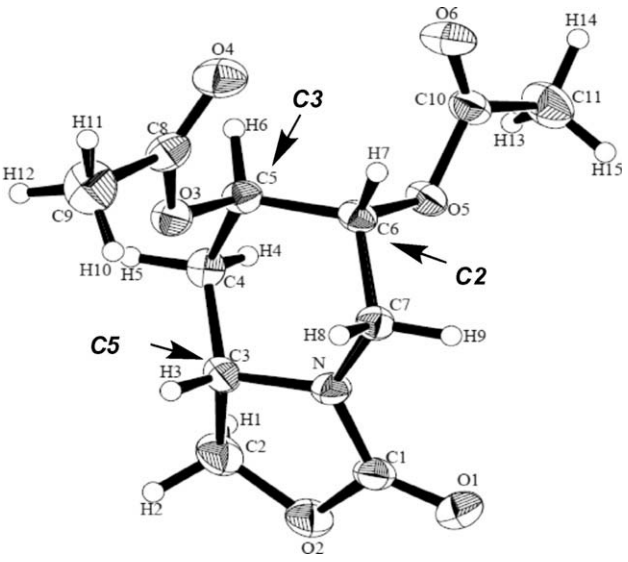
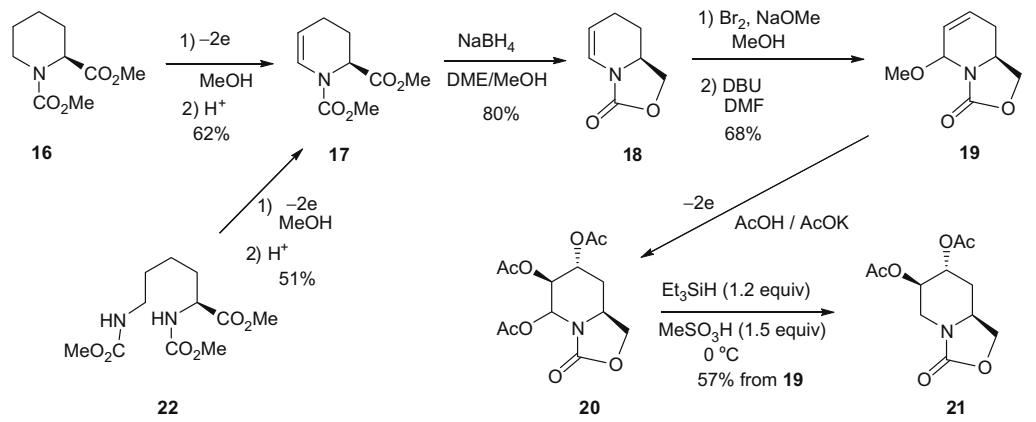


Figure 4. Ortep drawing of (2*R*,3*R*,5*S*)-**21**.

derivatives **24** and **25**, respectively (Fig. 5). Since the *cis*-isomer **24** was thermodynamically more stable than its *trans*-isomer **24′**, **24** should be formed stereospecifically. 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 exclusively afford a *trans*-isomer **25** without a *cis*-isomer **25′**.[15b]

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



Scheme 2. Preparation of (2*R*,3*R*,5*S*)-**21**starting from **16** or **22**.

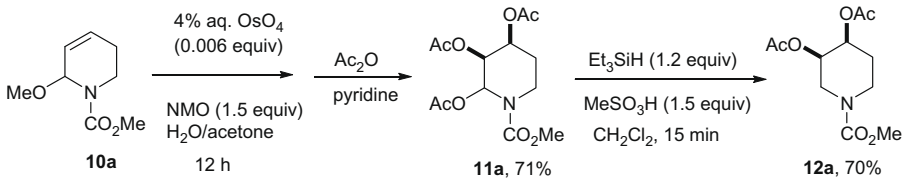
The predominant formation of (2*S*,3*S*,5*S*)-**5** and (2*R*,3*R*,5*S*)-**20** may be explained by an ECEC mechanism shown in Scheme 4. As for the 3-acetoxy-1,2-didehydropiperidine intermediate **24**, it is possible that the plausible intermediary species could be the electrochemically generated cation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

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

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

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

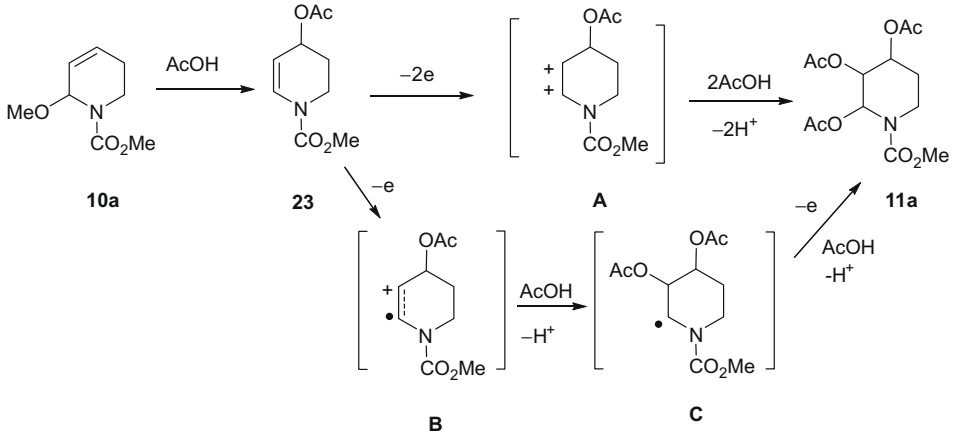
First, we investigated the OsO_4 oxidation of **10a**. Compound **10a** was oxidized with catalytic OsO_4 and 1.5 equiv of NMO followed by acetylation with acetic anhydride and pyridine to produce 2,3,4-triacetoxypiperidine **11a** in 71% yield. Compound **11a** was easily reduced with Et_3SiH to give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



(4)

Encouraged by this result, we attempted 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 the absolute stereochemistry of the two hydroxyl groups at the 2,3-position by X-ray analysis.

The OsO_4 oxidation of **4** and successive reduction with Et_3SiH gave 2,3-dihydroxylated derivative **30** as a single diastereomer (Scheme 7). Compound **30** was then 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*) (see Fig. 6).[14]



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

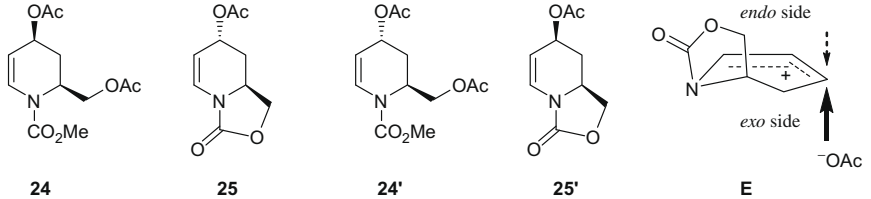
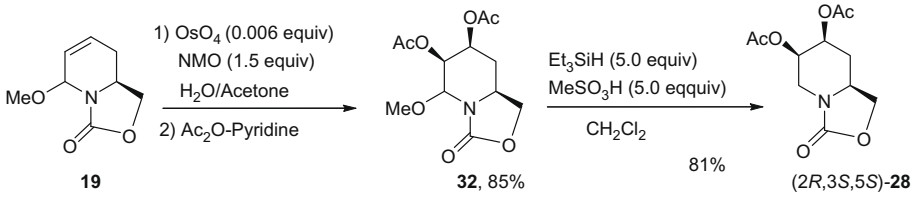


Figure 5. Plausible intermediary species for electrochemical oxidation of **4** and **19** in AcOH.

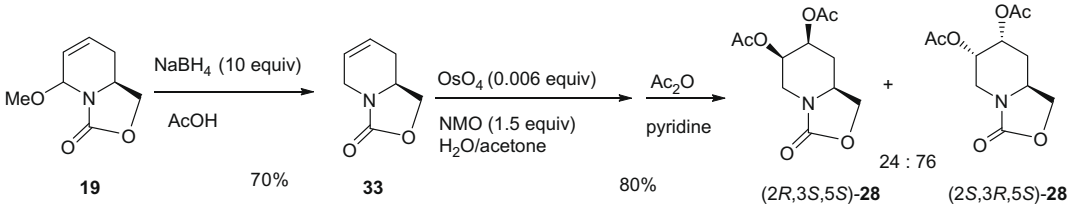
Next, the OsO_4 oxidation of bicyclic carbamate **19** and successive acetylation with Ac_2O–pyridine were examined to give 1-methoxy-2,3-diacetoxylated compound **32**. In this case, the 1-methoxy group remained unchanged under these reaction conditions. Finally, compound **32** was reduced by Et_3SiH 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)

The observed high diastereoselectivity by the OsO_4 oxidation in this case can be explained by the anomeric effect of the 1-methoxyl group. Since the methoxyl group is mainly located at the axial position, it is difficult for OsO_4 to get close to **19** from the lower 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 afforded dihydroxylated compound **J** as a precursor for (2*R*,3*S*,5*S*)-**28**.

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 (2*R*,3*S*,5*S*)-**28** and (2*S*,3*R*)-isomer (2*S*,3*R*,5*S*)-**28**, whose ratio was 24:76 (Eq. 6). This contrasting result for **33** and **19** supports our proposed stereochemical course as shown in Scheme 8. The result represents the importance of the steric effect of 1-methoxyl group on the observed high diastereoselectivity.



(6)

3. Conclusion

In conclusion, the stereoselective formal syntheses of 2,3,6-trihydroxylated (5*S*)-methylpiperidines **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. The reference electrode was $Ag/AgNO_3$ in saturated aqueous KCl; the working electrode was a glassy carbon, and the 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.

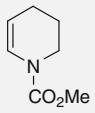
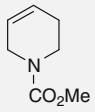
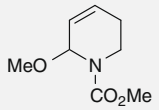
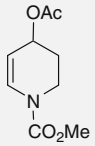
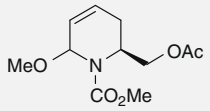
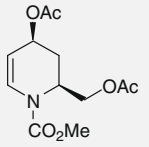
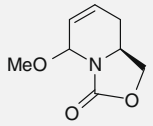
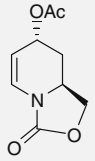
4.3.1. *N*-Benzyloxycarbonyl-2,3-didehydro-1-methoxypiperidine 10b

^{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.

4.3.2. 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

Table 2
Oxidation potential of didehydropiperidine derivatives

Entry	Compound		Oxidation potential[a] (V)
1		**9a**	1.44
2		**26**	1.96
3		**10a**	1.66
4		**23**	1.65
5		**4**	1.72
6		**24**	1.71
7		**19**	1.73
8		**25**	1.71

[a] V vs $Ag/AgNO_3$, 0.1 M Et_4NClO_4/MeCN, 100 mV/s.

(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.

4.4. Preparation of optically active 2,3-didehydro-1-methoxy-*N*-methoxycarbonylpiperidine 4

Compound **4** was prepared from either 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.

4.4.1. (5*S*)-Acetoxymethyl-*N*-methoxycarbonylpiperidine 3

$[\alpha]_D^{28} = -45.6$ (c 1.1, $CHCl_3$); ^1H 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.

4.4.2. (5*S*)-Acetoxymethyl-2,3-didehydro-1-methoxy-*N*-methoxy carbonylpiperidine 4

$[\alpha]_D^{28} = +71.6$ (c 1.0, $CHCl_3$); ^1H 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.

4.4.3. (5*S*)-Acetoxymethyl-1,2-didehydro-*N*-methoxy carbonylpiperidine 15

$[\alpha]_D^{27} = -72.2$ (c 1.2, methanol); ^1H 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.

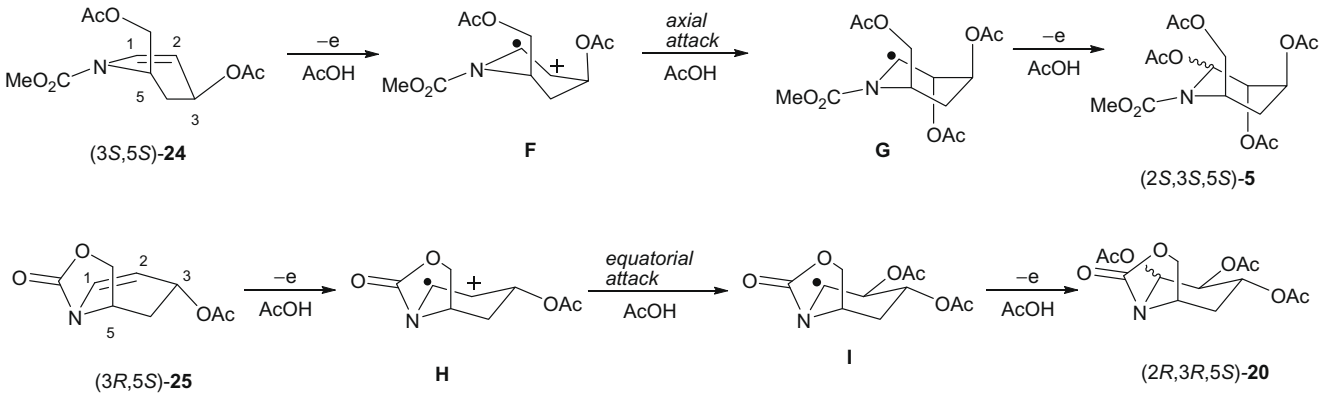
4.4.4. (2*S*)-6-Bis(methoxycarbonylamino)hexyl acetate 13

$[\alpha]_D^{28} = +17.1$ (c 1.0, methanol); mp 97–98 °C; ^1H 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.

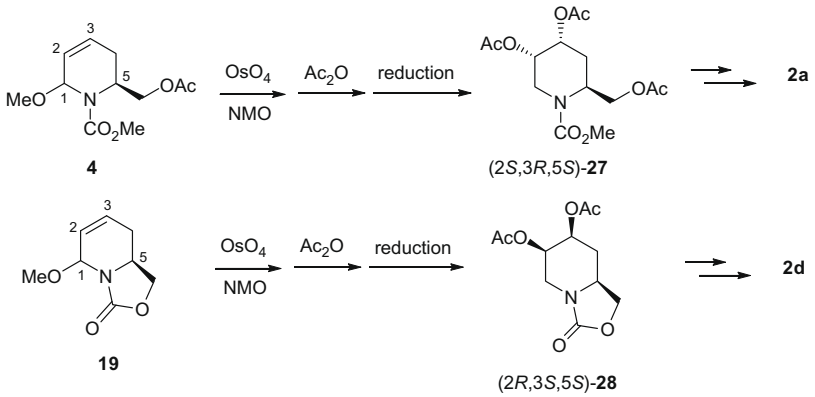
4.5. Preparation of optically active bicyclic compound 19

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

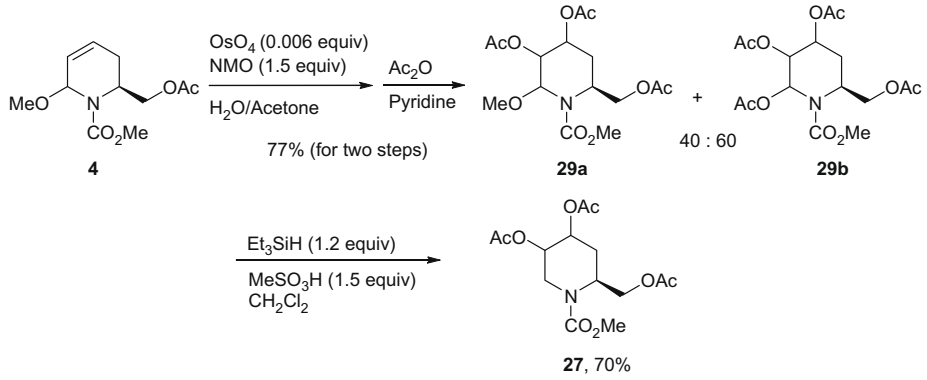
The characterization data for compounds **16**, **17**, **18**,[15] **19**,[15] and **22** are described below.



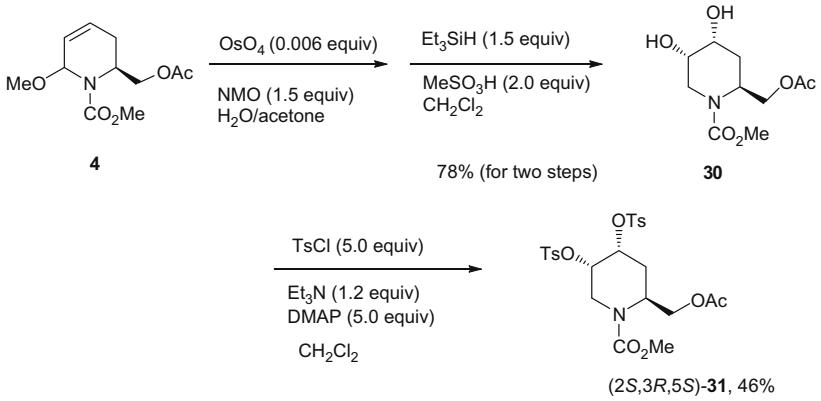
Scheme 4. Plausible mechanism for electrochemical 2,3-*trans*-acetoxylation of **24** and **25**.



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



Scheme 6. Preparation of **27**.



Scheme 7. Preparation of (2*S*,3*R*,5*S*)-**31**.

4.5.1. (5*S*)-*N*-Bis(methoxycarbonyl)piperidine 16

$[\alpha]_D^{25} = -60.9$ (*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.

4.5.2. 1,2-Didehydro-(5*S*)-*N*-bis(methoxycarbonyl)piperidine 17

$[\alpha]_D^{27} = -46.9$ (*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.

4.5.3. (6*S*)-1-Aza-2,3-didehydro-8-oxabicyclo[4.3.0]nonan-9-one 18

$[\alpha]_D^{28} = +164.9$ (*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.

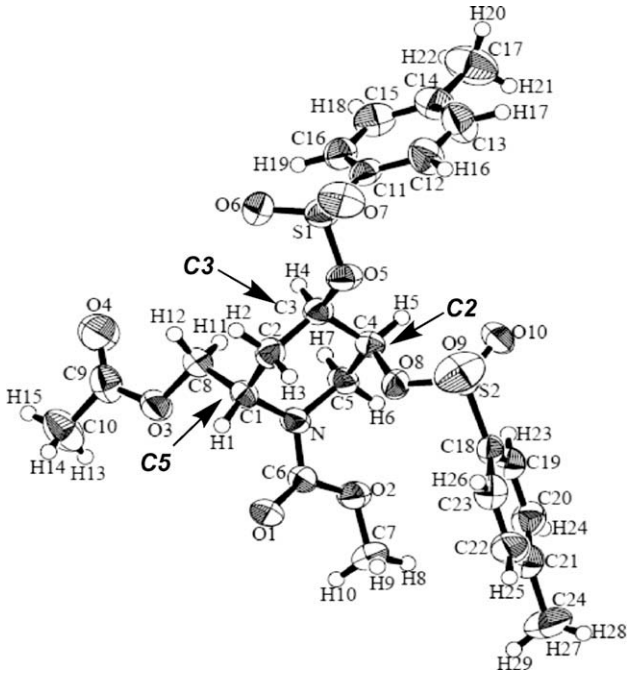


Figure 6. Ortep drawing of (2*S*,3*R*,5*S*)-**31**.

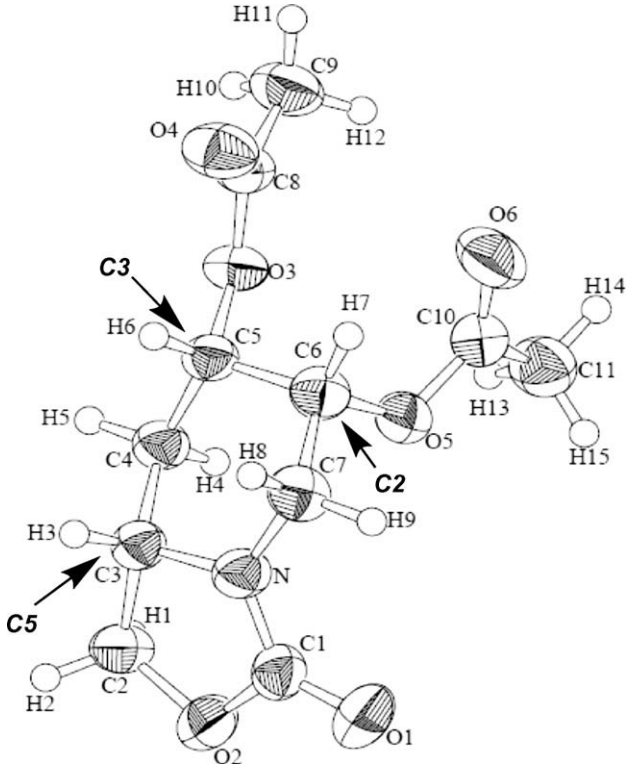


Figure 7. Ortep drawing of (2*R*,3*S*,5*S*)-**28**.

4.5.4. (6*S*)-1-Aza-3,4-didehydro-2-methoxy-8-oxabicyclo[4.3.0] nonan-9-one 19

$[\alpha]_D^{28} = -226.6$ (*c* 1.0, $CHCl_3$); mp 34–36 °C; ^1H 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.

4.5.5. Methyl (2*S*)-6-Bis(methoxycarbonylamino)hexanoate 22

$[\alpha]_D^{28} = +16.5$ (*c* 1.0, $CHCl_3$); mp 50–51 °C (uncorrected); ^1H 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.

4.6. 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 derivatives **23**, **24,** and **25** by stirring in acetic acid for a few minutes with quantitative yield.

4.6.1. 3-Acetoxy-1,2-didehydro-*N*-methoxycarbonylpiperidine 23

^1H 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.

4.6.2. (3*S*)-Acetoxy-(5*S*)-acetoxymethyl-1,2-didehydro-*N*-methoxycarbonylpiperidine 24

^1H 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.

4.6.3. (4*R*,6*S*)-1-Aza-4-acetoxy-2,3-didehydro-8-oxabicyclo[4.3.0] nonan-9-one 25

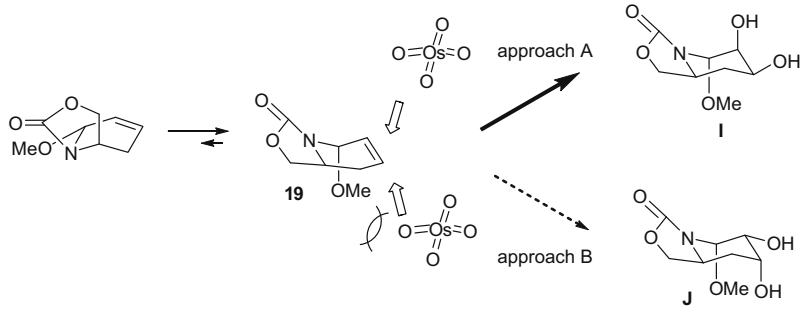
Mp 77–79 °C; ^1H NMR ($CDCl_3$) δ 1.72 (td, *J* = 12.8 and 3.8 Hz, 1H), 2.06 (s, 3H), 2.24 (d, *J* = 12.8 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 4.07–4.21 (m, 1H), 4.67 (t, *J* = 8.1 Hz, 1H), 5.25–5.33 (m, 2H), 6.87 (d, *J* = 6.6 Hz, 1H); IR (KBr) 2905, 1784, 1644, 1426, 1269, 1055, 992, 756 cm^{-1}; HRMS *m*/*z* Calcd for $C_9H_{11}NO_4$ (M^+): 197.0689. Found: 197.0668.

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

A typical procedure is illustrated by the anodic oxidation of **4**. Into a glass beaker (15 mL) equipped with two Pt plate electrodes (10 mm × 20 mm) was added a solution of **4** (0.243 g, 1 mmol) 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 × 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*)-acetoxymethyl-*N*-methoxycarbonylpiperidine **5** in 85% yield. ^1H 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.

4.7.1. 1,2,3-Triacetoxy-*N*-methoxycarbonylpiperidine 11a

^1H 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



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

(2 m, 2H), 6.56–6.78 and 6.93–7.08 (2 m, 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.

4.7.2. 1,2,3-Triacetoxy-*N*-benzyloxycarbonylpiperidine 11b

^1H 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.

4.7.3. 1,2,3-Triacetoxy-*N*-formylpiperidine 11c

^1H 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.

4.7.4. 1,2,3-Triacetoxy-*N*-benzoylpiperidine 11d

^1H 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 (2 m, 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.

4.7.5. (3*R*,4*R*,6*S*)-2,3,4-Triacetoxy-1-aza-8-oxabicyclo[4.3.0] nonan-9-one 20

^1H 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.

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

A typical procedure is illustrated 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 × 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. Recrystallization of **6** from AcOEt and *n*-hexane afforded (2*S*,3*S*,5*S*)-**6**: $[\alpha]_D^{26} = +40.0$ (c 0.5, $CHCl_3$); mp 102–104 °C; ^1H 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 cm × 15 cm), *n*-hexane/ethanol = 10:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 11.4 min.

4.8.1. 2,3-Diacetoxy-*N*-methoxycarbonylpiperidine 12a

^1H 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. Diastereomeric ratio of **12a** was determined by HPLC method; YMC-Pack SIL (0.46 cmø × 15 cm), *n*-hexane/ethanol = 10:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 8.2 min for *trans*-isomer, 9.1 min for *cis*-isomer.

4.8.2. 2,3-Diacetoxy-*N*-benzyloxycarbonylpiperidine 12b

^1H 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 × 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.

4.8.3. 2,3-Diacetoxy-*N*-formylpiperidine 12c

^1H 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 × 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.

4.8.4. 2,3-Diacetoxy-*N*-benzoylpiperidine 12d

^1H 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 × 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.

4.8.5. (3*R*,4*R*,6*S*)-3,4-Diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one 21

$[\alpha]_D^{26} = -75.2$ (*c* 0.6, $CHCl_3$); mp 127–129 °C (from AcOEt and n-hexane), (uncorrected); ^1H 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 × 15 cm), *n*-hexane/ethanol = 5:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 18.9 min.

4.9. Preparation of 2,3-didehydropiperidine derivative 33

Into a round-bottomed flask (25 mL) equipped with a magnetic stirrer and containing **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 × 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.

4.9.1. 6*S*-1-Aza-3,4-didehydro-8-oxabicyclo[4.3.0]nonan-9-one 33

$[\alpha]_D^{30} = -166.9$ (*c* 1.0, $CHCl_3$); ^1H 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 (2 m, 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.

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

A typical procedure is illustrated 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 (4 wt % solution in water, two 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 was 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 × 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. Compound **11a**: ^1H 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 mentioned 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). ^1H 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}.

4.10.1. (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**): ^1H 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 (2*S*,3*R*,5*S*)-**28** and (3*R*,4*S*,6*S*)-isomer (2*R*,3*S*,5*S*)-**28** [(2*S*,3*R*,5*S*)-**28**: (2*R*,3*S*,5*S*)-**28** = 76:24] in 80% yield.

4.10.2. (3*S*,4*R*,6*S*)-3,4-Diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (2*S*,3*R*,5*S*)-28

$[\alpha]_D^{28} = -53.3$ (*c* 1.5, $CHCl_3$), [containing 4% of (3*R*,4*S*,6*S*)-isomer (2*S*,3*R*,5*S*)-**28**]; ^1H 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.

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

A typical procedure is illustrated 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), after which methanesulfonic acid (0. 192 g, 2.0 mmol) was added at 0 °C. After stirring for 10 min, the reaction mixture was added into a mixture of AcOEt (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic portion was extracted with AcOEt (20 mL × 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 cis-**12a***: ^1H 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.

4.11.1. (2*S*,3*R*)-Diacetoxy-(5*S*)-acetoxymethyl-*N*-methoxycarbonylpiperidine (2*S*,3*R*,5*S*)-27 (70% yield from a mixture of 29a and 29b)

$[\alpha]_D^{30} = +37.0$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.75 and 1.78 (2d, *J*=4.4 Hz, 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 × 15 cm), *n*-hexane/ethanol = 10:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 12.2 min.

4.11.2. (3*R*,4*S*,6*S*)-3,4-Diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (2*R*,3*S*,5*S*)-28 (81% yield from 32)

$[\alpha]_D^{29} = -48.0$ (*c* 0.5, $CHCl_3$); mp 122–123 °C (from AcOEt and *n*-hexane), (uncorrected); ^1H 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 × 15 cm), *n*-hexane/ethanol = 5:1, wavelength: 210 nm, flow rate: 0.5 mL/min, retention time: 21.6 min.

4.12. Synthesis of (5*S*)-acetoxymethyl-(2*S*,3*R*)-dihydroxy-*N*-methoxycarbonylpiperidine (2*S*,3*R*,5*S*)-30 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 (4 wt % solution in water, two 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 and to the residue was added water (1 mL). The organic portion was extracted with AcOEt (15 mL × 8). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a crude mixture of (5*S*)-acetoxymethyl-1,2,3-trihydroxy-*N*-methoxycarbonylpiperidine and (5*S*)-acetoxymethyl-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, the reaction mixture was added to a mixture of AcOEt (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic portion was extracted with AcOEt (20 mL × 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*-methoxycarbonylpiperidine (**30**$_{2S,3R,5S}$) in 78% yield from **4**. (2*S*,3*R*,5*S*)-**30**: $[\alpha]_D^{30} = -6.0$ (*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 (2*S*,3*R*,5*S*)-**30** (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 three 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 × 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 (2*S*,3*R*,5*S*)-**31** in 46% yield. $[\alpha]_D^{30} = +32.4$ (*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 (2*S*,3*S*,5*S*)-**6**, (2*R*,3*R*,5*S*)-**21**, (2*S*,3*R*,5*S*)-**31**, and (2*R*,3*S*,5*S*)-**28**: 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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