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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 OsO₄ oxidation has been exploited for the stereoselective synthesis of 2,3,6-trihydroxylated 5S-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-triacetoxy-piperidine derivatives. These triacetates were easily transformed into 2S,3S,6-triacetoxy-5S-methylpiperidine and 2R,3R,6-triacetoxy-5S-methylpiperidine. In addition, 2,3-cis-dihydroxylation of 2,3-didehydro-1-methoxypiperidine derivatives with OsO₄ afforded 2R,3S,6-triacetoxy-5S-methylpiperidine and 2S,3R,6-triacetoxy-5S-methylpiperidine.

1. Introduction

Polyhydroxylated 5S-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-5S-methylpiperidines 2 are noteworthy since recently it has been reported that 2R,3S,6-trihydroxy-5S-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 OsO₄.

![Figure 1](image-url)
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 5S-acetoxyethylpiperidine derivative 3 by electrochemical oxidation; electrochemical 1-methoxylation of 3 and electrochemical triacetoxylation of 5S-acetoxyethyl-2,3-dehydro-1-methoxypiperidine derivative 4 (Eq. 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 \( 7b-d \).
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). 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 Et3SiH 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.

![Chemical structure]

Table 1.

Electrochemical oxidation of 10a-d followed by reduction of 11a-d with Et3SiH

<table>
<thead>
<tr>
<th>Entry</th>
<th>10a-d</th>
<th>Yield (%)</th>
<th>trans/cis (12a-d)</th>
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<tbody>
<tr>
<td></td>
<td>R</td>
<td>11a-d</td>
<td>12a-d</td>
</tr>
<tr>
<td>1</td>
<td>OMe</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>OCH2Ph</td>
<td>54</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>78</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>80</td>
<td>45</td>
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The stereochemistry (trans/cis) of 12a-d was a little bit dependent on R (70/30~54/46). We then, tried the preparation of 4 from easily available L-lysine derivative 13 instead of expensive L-pipeolic acid derivative 3 through 14 and 15 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 Et3SiH gave 2,3,6-triacetoxy-5S-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 $(2S,3S,5S)$ by its X-ray analysis (Fig. 3).\textsuperscript{14}

On the other hand, electrochemical oxidation of bicyclic carbamate 19, which was prepared from L-pipeolic acid derivative 16 or from L-lysine derivative 22 through 17\textsuperscript{13} and 18,\textsuperscript{15} followed by reduction of the oxidation product 20 (70% yield) with Et$_3$SiH gave a single stereoisomer 21 (Scheme 2), of which absolute stereochemistry was also determined by its X-ray analysis (Fig. 4).\textsuperscript{14}
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\textsuperscript{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\textsuperscript{10}. Similarly, electrochemical triacetoxylation of 4 and 19 may proceed via 3-acetoxyperidine 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'.\textsuperscript{15b}
The oxidation potentials of some 1,2-didehydro- and 2,3-didehydro-piperidine derivatives shown in Table 2 support this proposed mechanism.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Oxidation Potential (V)\textsuperscript{a}</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>9(\text{a})</td>
<td>1.44</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>1.72</td>
</tr>
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\textsuperscript{a}Values vs. 

A predominant formation of $5_{2S,3S,5S}$ and $20_{2R,3R,5S}$ 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. Therefore, the observed high diasteroselectivity in electrochemical oxidation of $24_{3S,5S}$ 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 $5_{2S,3S,5S}$ 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 $25_{3R,5S}$, acetate ion attack to cation radical H is easier from the equatorial direction than the axial direction to produce $20_{2R,3R,5S}$ 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 OsO₄

To prepare 2,3-cis-dihydroxylated compounds 2a and 2d, oxidation of 4 or 19 with OsO₄ seems to be convenient (Scheme 5).

First, we investigated the OsO₄ oxidation of 10a. Compound 10a was oxidized with catalytic OsO₄ and 1.5 equiv of NMO followed by acetylation with acetic anhydride and pyridine to produce 2,3,4-triacetoxy-piperidine 11a in 71% yield. Compound 11a was easily reduced with Et₃SiH to give cis-2,3-diacetoxy-piperidine 12a (Eq. 4).

Encouraged by this result, we continuously tried to apply the same conditions to 5S-acetoxy-methyl-piperidine derivatives 4 (Scheme 6). As expected, the OsO₄ oxidation and subsequent acetylation proceeded smoothly, but the reaction product was a mixture of 2,3-diacetoxy-5S-acetoxy-methyl-1-methoxy-N-methoxycarbonylpiperidine 29a and 1,2,3-triacetoxy-5S-acetoxy-methyl-N-methoxycarbonylpiperidine 29b. Without purification of the mixture, reduction with Et₃SiH was carried out to provide only one product, 2,3-diacetoxy-5S-acetoxy-methyl-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.](image)

The OsO₄ oxidation of 4 and successive reduction with Et₃SiH 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-ditosyloxyated derivative 31. The X-ray analysis of compound 31 determined its absolute stereoconfiguration, (2S,3R,5S).¹⁴

![Scheme 7. Preparation of 31_{2S,3R,5S}.](image)
Next, the OsO₄ oxidation of bicyclic carbamate 19 and successive acetylation with Ac₂O-pyridine was examined to give 1-methoxy-2,3-diacectoxylated compound 32. In this case, 1-methoxy group remained unchanged in this reaction condition. Finally, compound 32 was reduced by Et₃SiH to afford 2,3-diacectoxylated bicyclic carbamate 28 as a single diastereomer (Eq. 5). The absolute stereoconfiguration of 28 was determined by X-ray analysis to be 2R,3S,5S (Fig. 7).¹⁴
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 282$_{2R,3S,5S}$.

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 28$_{2R,3S,5S}$ and 2$S$,3$R$-isomer 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.
In summary, the stereoselective formal syntheses of 2,3,6-trihydroxylated 5S-methylpiperidines 2a-d from L-lysine and L-pipecolic acid has been accomplished by using tandem electrochemical oxidation or OsO₄ oxidation.

4. Experimental Section

4.1. General

Electrochemical reactions were carried out using DC Power Supply (GP 050–2) of Takasago Seisakusho, Inc. ¹H 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 Et₄NBF₄ was measured. Reference electrode was Ag/AgNO₃ 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 10d⁹d are known.
The characterization data for unknown compounds 10b and 10c are described below.

**N-Benzylxycarbonyl-2,3-didehydro-1-methoxypiperidine (10b):**$^1$H-NMR (CDCl$_3$) $\delta$ 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, 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$_3$) $\delta$ 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$_7$H$_{11}$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.

**5S-Acetoxymethyl-N-methoxycarbonylpiperidine (3):** $[\alpha]^{28}_D$ $-45.6$ (c 1.1, CHCl$_3$); $^1$H-NMR (CDCl$_3$) $\delta$ 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.

**5S-Acetoxymethyl-2,3-didehydro-1-methoxy-N-methoxycarbonylpiperidine (4):** $[\alpha]^{28}_D$ $+71.6$ (c 1.0, CHCl$_3$); $^1$H-NMR (CDCl$_3$) $\delta$ 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: 243.1107.

**5S-Acetoxymethyl-1,2-didehydro-N-methoxycarbonylpiperidine (15):** $[\alpha]^{27}_D$ $-72.2$ (c 1.2,
methanol); $^1$H-NMR (CDCl$_3$) $\delta$ 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. Caled 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.

2S,6-Bis(methoxycarbonylamino)hexyl acetate (13): $[\alpha]^{28}_D$ +17.1 (c 1.0, methanol); mp 97-98 $^\circ$C; $^1$H-NMR (CDCl$_3$) $\delta$ 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. Caled for C$_{12}$H$_{22}$N$_2$O$_6$: 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-pipeolic 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.

5S,N-Bis(methoxycarbonyl)piperidine (16): $[\alpha]^{25}_D$ –60.9 (c 1.5, methanol); $^1$H-NMR (CDCl$_3$) $\delta$ 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. Caled for C$_9$H$_{15}$NO$_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.70; H, 7.74; N, 6.67.

1,2-Didehydro-5S,N-bis(methoxycarbonyl)piperidine (17): $[\alpha]^{27}_D$ –46.9 (c 1.0, CHCl$_3$); $^1$H-NMR (CDCl$_3$) $\delta$ 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. Caled for C$_9$H$_{13}$NO$_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.17; H, 6.73; N, 6.74.

(6S)-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 $^\circ$C; $^1$H-NMR (CDCl$_3$) $\delta$ 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. Caled for C$_7$H$_9$NO$_2$: C, 60.43; H, 6.51; N, 10.07. Found: C, 60.16; H, 6.56; N, 9.90.
(6S)-1-Aza-3,4-didehydro-2-methoxy-8-oxabicyclo[4.3.0]nonan-9-one (19): \([\alpha]_{D}^{28} -226.6 (c 1.0, \text{CHCl}_3)\); mp 34-36°C; \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 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\(_8\)H\(_{11}\)NO\(_3\) (M\(^+\)): 169.0739. Found: 169.0731.

Methyl 2S,6-Bis(methoxycarbonylamino)hexanoate (22): \([\alpha]_{D}^{28} +16.5 (c 1.0, \text{CHCl}_3)\); mp 50-51 °C (uncorrected); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.27-1.44 (m, 2H), 1.46-1.59 (m, 2H), 1.61-1.75 (m, 1H), 1.77-1.90 (m, 1H), 3.15-3.20 (m, 2H), 3.66 (s, 3H), 3.69 (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\(_2\)O\(_6\): 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\(_3\)) \(\delta\) 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\(_9\)H\(_{13}\)NO\(_4\) (M\(^+\)): 199.0845. Found: 199.0822.

3S-Acetoxy-5S-acetoxymethyl-1,2-didehydro-\(N\)-methoxycarbonylpiperidine (24): \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 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, 1364, 1235, 1007, 768 cm\(^{-1}\); HRMS (EI) \(m/z\) Calcd for C\(_{12}\)H\(_{17}\)NO\(_6\) (M\(^+\)): 271.1056. Found: 271.1066.

(4R,6S)-1-Aza-4-acetoxy-2,3-didehydro-8-oxabicyclo[4.3.0]nonan-9-one (25): mp 77-79 °C; \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.72 (td, \(J = 12.8\) and 3.8 Hz, 1H), 2.06 (s, 3H), 2.24 (d, \(J = 12.8\) Hz,
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, 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 NaHCO₃ (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 NaHCO₃ (20 mL). After the extract was dried over MgSO₄ 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-5S-acetoxy-methyl-N-methoxycarbonylpiperidine (5) in 85% yield.

5: ¹H-NMR (CDCl₃) 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 C₁₄H₁₉NO₈ (M⁺−AcOH): 329.1111. Found: 329.1111.

1,2,3-Triacetoxy-N-methoxycarbonylpiperidine (11a): ¹H-NMR (CDCl₃) 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 C₁₃H₁₉NO₈: C, 49.21; H, 6.04; N, 4.41. Found: C, 49.14; H, 6.22; N, 4.35.

1,2,3-Triacetoxy-N-benzzyloxy carbonylpiperidine (11b): ¹H-NMR (CDCl₃) 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 C₁₉H₂₃NO₈ (M⁺): 393.1424. Found: 393.1464.

1,2,3-Triacetoxy-N-formylpiperidine (11c): ¹H-NMR (CDCl₃) 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 C₁₂H₁₇NO₇ (M⁺): 287.0981. Found: 287.0981.

1,2,3-Triacetoxy-N-benzoylpiperidine (11d): ^1^H-NMR (CDCl₃) 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 C₁₈H₂₁NO₇: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.23; H, 6.23; N, 3.65.

(3R,4R,6S)-2,3,4-Triacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (20): ^1^H-NMR (CDCl₃) 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 C₁₁H₁₃NO₆ (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 Et₃SiH (0.140 g, 1.2 mmol) in CH₂Cl₂ (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 NaHCO₃ (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 NaHCO₃ (20 mL). After the extract was dried over MgSO₄ and the solvent was removed in vacuo, the residue was chromatographed on silica gel (AcOEt: n-hexane = 1:2) to afford 2,3-diacetoxy-5S-acetoxymethyl-N-methoxycarbonylpiperidine (6) in 62% yield as a mixture of stereoisomers. Recrystallization of 6 from AcOEt and n-hexane afforded 2S,3S,5S-isomer.

6_{2S,3S,5S}: [α]_{D}^{26} +40.0 (c 0.5, CHCl₃); mp 102-104°C; ^1^H-NMR (CDCl₃) 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: 210 nm, flow rate: 0.5 mL/min, retention time: 11.4 min.

2,3-Diacetoxy-$N$-methoxycarbonylpiperidine (12a): $^1$H-NMR (CDCl$_3$ $\delta$ 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: 0.5 mL/min, retention time: 8.2 min for trans-isomer, 9.1 min for cis-isomer.

2,3-Diacetoxy-$N$-benzyloxy carbonylpiperidine (12b): $^1$H-NMR (CDCl$_3$ $\delta$ 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$_3$ $\delta$ 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$_3$ $\delta$ 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.

\[(3R,4R,6S)-3,4-Diacetoxyl-1-aza-8-oxabicyclo[4.3.0]nonan-9-one\] \((21)\): \([\alpha]_{26}^{20} -75.2\ (c 0.6, \text{CHCl}_3)\); mp 127-129°C (from AcOEt and n-hexane), (uncorrected); \(^1\text{H}-\text{NMR} (\text{CDCl}_3) \delta 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, 1272, 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 cm\(\times\) 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-didehydro-3,4-didehydro-8-oxabicyclo[4.3.0]nonan-9-one 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 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.

\[6S-1-Aza-3,4-didehydro-8-oxabicyclo[4.3.0]nonan-9-one\] \((33)\): \([\alpha]_{30}^{20} -166.9\ (c 1.0, \text{CHCl}_3)\); \(^1\text{H}-\text{NMR} (\text{CDCl}_3) \delta 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, 1078, 961, 764 cm\(^{-1}\); HRMS (EI) \(m/z\) Calcd for C\(_7\)H\(_9\)NO\(_2\) (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\(_2\)O (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 Na₂S₂O₃ (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 MgSO₄, 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 (CDCl₃) $\delta$ 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 C₁₃H₁₉NO₈ (M⁺): 317.1111. Found: 317.1116.

By similar procedures as above, 4 was converted into a mixture of 2,3-diacetoxy-5S-acetoxy-methyl-1-methoxy-N-methoxycarbonylpiperidine (29a) and 1,2,3-triacetoxy-5S-acetoxy-methyl-N-methoxycarbonylpiperidine (29b) was obtained in 77% yield (29a:29b = 0.4:0.6). 

\(^1\)H-NMR (CDCl₃) $\delta$ 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\(^{-1}\).

(3S,4S,6S)-3,4-Diacetoxy-2-methoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (32) (85% yield from 19): \(^1\)H-NMR (CDCl₃) $\delta$ 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 C₁₂H₁₇NO₇ (M⁺): 287.1005. Found: 287.1014.

Using similar oxidation procedure, 33 was successively oxidized and acetoxylated to afford a mixture of (3S,4R,6S)-3,4-diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (28_{2S,3R,5S}) and (3R,4S,6S)-isomer (28_{2R,3S,5S}) (28_{2S,3R,5S}:28_{2R,3S,5S} = 76:24) in 80% yield. 

(3S,4R,6S)-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, CHCl₃), (containing 4% of (3R,4S,6S)-isomer 28_{2S,3R,5S}); \(^1\)H-NMR (CDCl₃) $\delta$ 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,
Reduction of α-alkoxy group of 11a, 29a, 29b and 32.

A typical procedure is exemplified by the reduction of 11a. To 1 mmol of 11a was added Et3SiH (0.174 g, 1.5 mmol) in CH2Cl2 (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 NaHCO3 (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 NaHCO3 (20 mL). After the extracts were dried over anhydrous MgSO4, 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 (12acis): 1H-NMR (CDCl3) 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, 1057, 770 cm⁻¹; HRMS (EI) m/z Calcd for C11H17NO6 (M⁺): 259.1056. Found: 259.1049.

2S,3R-Diacetoxy-5S-acetoxymethyl-N-methoxycarbonylpiperidine (272S,3R,5S) (70% yield from a mixture of 29a and 29b): [α]30D +37.0 (c 1.0, CHCl3); 1H-NMR (CDCl3) δ 1.75 and 1.78 (2d, J=4.4Hz, 1H), 2.02 and 2.07 and 2.08 (2s, 6H), 2.02-2.11 (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 C14H21NO8 (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.

(3R,4S,6S)-3,4-Diacetoxy-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (283R,4S,6S) (81% yield from 32): [α]29D −48.0 (c 0.5, CHCl3); mp 122-123°C (from AcOEt and n-hexane), (uncorrected); 1H-NMR (CDCl3) 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 cm\(\times\) 15 cm), \(n\)-hexane/ethanol = 5:1, wavelength: 210nm, flow rate: 0.5 mL/min, retention time: 21.6 min.

**Synthesis of 5S-acetoxymethyl-2S,3R-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\(_2\)O (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, 2 drops, 0.01 mmol). After the mixture was stirred overnight at room temperature, 10% aqueous Na\(_2\)S\(_2\)O\(_3\) (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 \(\times\) 8). The combined extracts were dried over anhydrous MgSO\(_4\), filtered, and concentrated in vacuo to afford a crude mixture of mixture of 5S-acetoxymethyl-1,2,3-trihydroxy-N-methoxycarbonylpiperidine and 5S-acetoxy-methyl-2,3-dihydroxy-1-methoxy-N-methoxycarbonylpiperidine (0.5:0.5): \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 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\(_3\)SiH (0.174 g, 1.5 mmol) in CH\(_2\)Cl\(_2\) (3 mL) and added methanesulfonic acid (0.192 g, 2.0 mmol) at 0 \(^\circ\)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 \(\times\) 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 5S-acetoxymethyl-2S,3R-dihydroxy-N-methoxycarbonylpiperidine (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\(_3\)) \(\delta\) 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$_{2S,3R,5S}$ (0.1 g, 0.4 mmol) was added $p$-toluenesulfonyl chloride (0.381 g, 2 mmol), Et$_3$N (0.049 g, 0.48 mmol), and DMAP (0.244 g, 2 mmol) in CH$_2$Cl$_2$ (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 5S-acetoxymethyl-2S,3R-bis($p$-toluenesulfonyloxy)-N-methoxycarbonylpiperidine (31$_{2S,3R,5S}$) in 46% yield.

31$_{2S,3R,5S}$: $[\alpha]_{D}^{30}$ +32.4 (c 1.0, CHCl$_3$); mp 136-139$^\circ$C (from AcOEt and n-hexane); $^1$H-NMR (CDCl$_3$) $\delta$ 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.

References and Notes


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 62S,3S,5S, 212R,3R,5S, 312S,3R,5S, and 282R,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.
