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Tetrahedron Letters 45 (2004) 8177–8181
Tetrahedron Letters

Stereoselective synthesis of azasugars by electrochemical oxidation

Shigeru Furukubo, Noriaki Moriyama, Osamu Onomura and Yoshihiro Matsumura*

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

Received 17 August 2004; revised 2 September 2004; accepted 3 September 2004
Available online 21 September 2004

Abstract—A new method using electrochemical 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 1-methoxy-2,3-didehydropiperidine derivatives to 1,2,3-triacetoxypiperidine derivatives. The method provided a new synthetic route to 2*S*,3*S*,6-triacetoxy-5*S*-methylpiperidine and 2*R*,3*R*,6-triacetoxy-5*S*-methylpiperidine.

Polyhydroxylated 5*S*-methylpiperidines **1**, a class of azasugars, have attracted great interest due to their biological properties.[1] Some of them are potential inhibitors of glycosidases and glycoprotein-processing enzymes. Now they have being widely investigated as candidates of drugs to treat a variety of carbohydrate-mediated diseases such as diabetes, viral infection including HIV, and cancer metastasis. The inhibitory activities depend on the configuration and the number of hydroxyl groups (Fig. 1). Among **1**, 2,3,6-trihydroxy-5*S*-methylpiperidines **2** are worth of note since recently it has 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 towards glycosidases.[2] However, there has not been any synthetic method for **2b**–**d**.[2,3] This paper describes a new method for a stereoselective synthesis of precursors of **2b**,**c**.

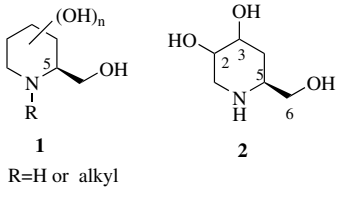
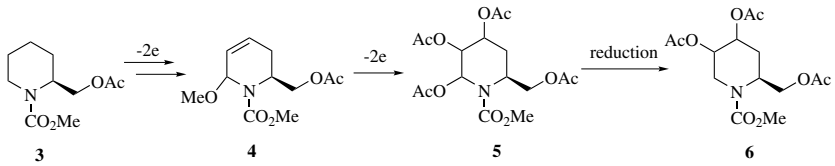


Figure 1.

Our strategy to this end is based on a 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 1-methoxy-2,3-didehydro-5*S*-acetoxymethylpiperidine derivative **4** (Eq. 1).

The first key electrochemical reaction in the strategy has already been used in the transformation of *N*-methoxycarbonylpiperidine **7a** to 1-methoxy-2,3-didehydropiperidine **10a**. The transformation consisted of electrochemical oxidation of **7a** in MeOH to afford 1-methoxypiperidine **8a**, elimination of MeOH from **8a** to 1,2-didehydropiperidine **9a**, bromine oxidation of **9a**



(1)

Keywords: Azasugar; Electrochemical oxidation; Stereoselective; Acetoxylation.
* Corresponding author. Tel.: +81 95 819 2429; fax: +81 95 819 2476; e-mail: matumura@net.nagasaki-u.ac.jp

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doi:10.1016/j.tetlet.2004.09.036

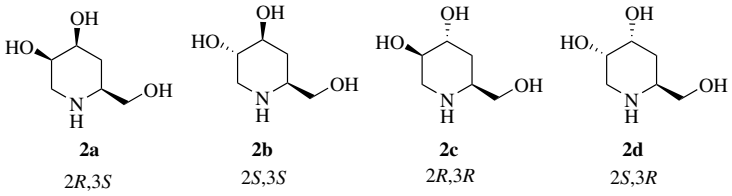
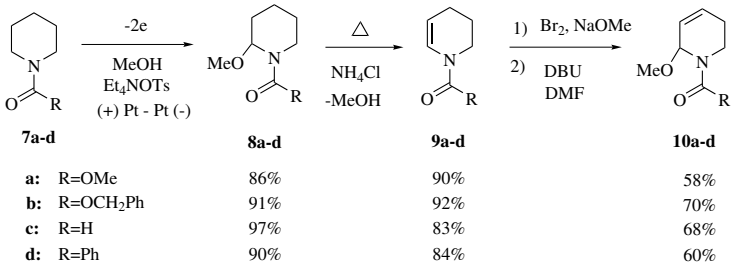


Figure 2. Stereoisomers **2a–d** of 2,3,6-trihydroxy-5*S*-methylpiperidines **2**.

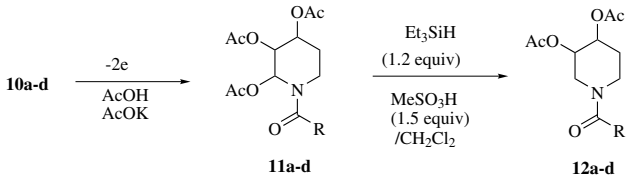
followed by base-induced dehydrobromination to 1-methoxy-2,3-didehydropiperidine **10a** (Eq. 2).[4] According to this method, the other 1-methoxy-2,3-didehydropiperidines **10b–d** were similarly prepared from **7b–d**.



(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).[5] 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**.[6] The yields of **11a–d** and **12a–d** are shown together with the *trans*/*cis* ratio in Table 1.

The stereochemistry (*trans*/*cis*) of **12a–d** was somewhat dependent on R (70/30 ~ 54/46).[7] Then, we tried the preparation of **4** from **3**[8] through **13** and **14**[9b] to obtain **4** in a similar way to a transformation of **7** to **10**. The result is shown in Eq. 4. The desired **4** was also obtained from ω-amino-2-amino alcohol derivative **15**, easily available from L-lysine.[9] Electrochemical oxidation of **4** afforded tetraacetoxylated piperidine **5**,[10] of which



(3)

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

Entry	**10a–d** R	Yields		*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	50%	45%	54:46

reduction with Et_3SiH gave 2,3,6-triacetoxy-5*S*-methylpiperidine **6** in 53% from **4** (Eq. 4). Although **6** was obtained as a mixture of stereoisomers (91/3/3/3),[11] the main isomer $\mathbf{6}_{2S,3S}$ (Fig. 3) fortunately crystallized.[12] The absolute stereochemistry was determined to be (2*S*,3*S*) by its X-ray analysis.[13]

In contrast to the electrochemical oxidation of **4**, that of bicyclic carbamate **19**, which was prepared from L-pipecolinic acid derivative **16**[9a] or from L-lysine derivative **22** through **17** and **18**,[14] followed by reduction of the oxidation product **20** (70% yield) with Et_3SiH gave a single stereoisomer **21** as a crystal (Eq. 5).[15] The absolute stereochemistry was also determined to be (2*R*,3*R*) by its X-ray analysis.[13]

The reaction mechanism for electrochemical triacetoxylation is tentatively proposed as follows (Eq. 6). Since it was found that **10a** was immediately converted to 3-acetoxy-1,2-didehydropiperidine **23** under the reaction conditions, oxidation of **23** may be responsible for the formation of **11a**. We already reported electrochemical 1,2-diacetoxylation of 1,2-didehydropiperidines.[5]

As for 3-acetoxy-1,2-didehydropiperidine intermediates involved in electrochemical triacetoxylation of **4** and

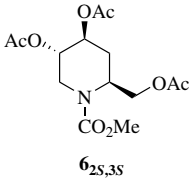
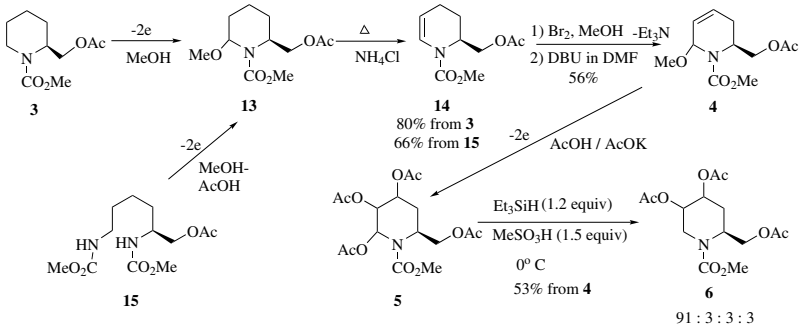
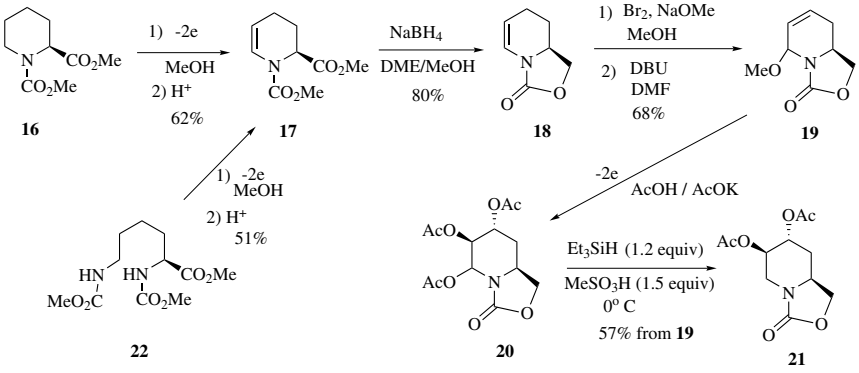


Figure 3.

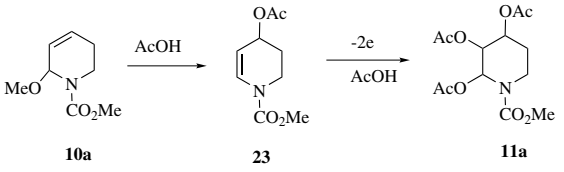


(4)



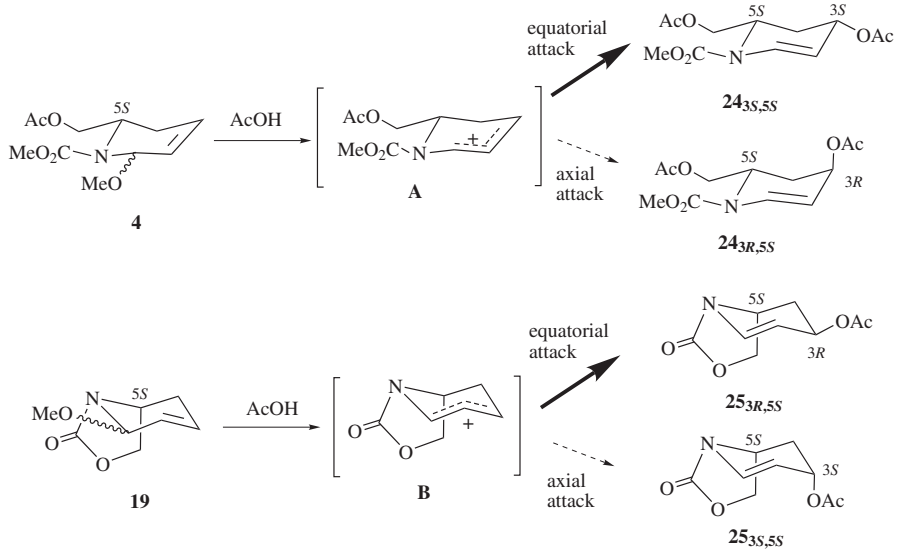
(5)

19, the stereochemistry must be taken into an account. The plausible intermediates may be **24**$_{3S,5S}$ and **25**$_{3R,5S}$ but not **24**$_{3R,5S}$ and **25**$_{3S,5S}$, respectively, because of easier attack of acetic acid on the C-3 of allylic cations **A** and **B** from the equatorial direction than from the axial direction (Scheme 1).[16]

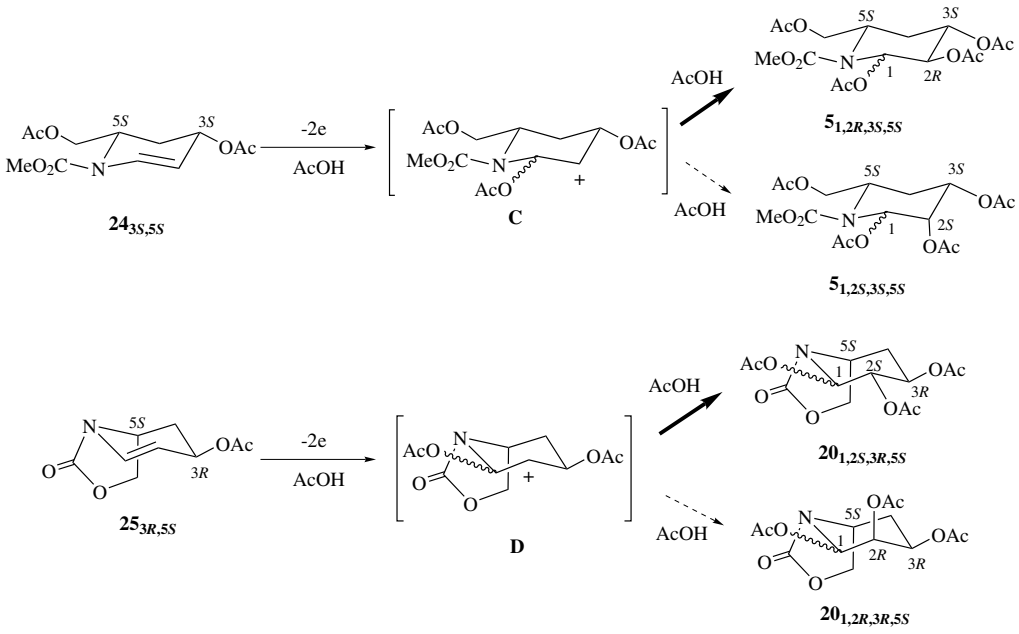


(6)

The observed high stereoselectivity in electrochemical oxidation of **24**$_{3S,5S}$ and **25**$_{3R,5S}$ may be also explainable in terms of equatorial attack of acetic acid on the C-2 of plausible cationic intermediates[17] **C** and **D** to produce **5**$_{1,2R,3S,5S}$ and **20**$_{1,2S,3R,5S}$, respectively (Scheme 2).[16] The less stereoselective triacetoxylation of **10a–d** may be due to a conformational flexibility of the piperidine ring, which has no substituent at the 5-position.



Scheme 1. Plausible mechanism for stereoselective formation of **24**$_{3S,5S}$ and **25**$_{3R,5S}$.



Scheme 2. Plausible mechanism for stereoselective formation of $\mathbf{5}_{1,2R,3S,5S}$ and $\mathbf{20}_{1,2S,3R,5S}$.

In summary, a stereoselective formal synthesis of two stereoisomers **2b**,**c** of 2,3,6-trihydroxyl-5*S*-methylpiperidines **2** from L-lysine and L-pipecolinic acid has been accomplished by using electrochemical oxidation. Exploitation of the synthetic method for the other stereoisomer **2d** is now under investigation.

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 412: Exploitation of Multi-Element Cyclic Molecules) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by a Grant-in-Aid for Scientific Research (C) (No. 15550094) from Japan Society for the Promotion of Sciences.

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7. The ratio of $\mathbf{12}_{cis}$ and $\mathbf{12}_{trans}$ was determined on the basis of the NMR spectrum of $\mathbf{12b}_{trans}$; Williams, S. J.; Hoos, R.Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 2223–2235.
8. Compound **3** was prepared by hydrogenation of **14**. **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).
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10. Electrochemical oxidation of **4**; into a glass beaker (15 mL) equipped with two Pt plate electrodes (10 mm × 20 mm) without a diaphragm 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 0.1 A (4 h) through the solution, a saturated aqueous $NaHCO_3$ solution (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 a saturated aqueous $NaHCO_3$ solution (20 mL). After the extract was dried over $MgSO_4$ and the solvent was removed in vacuo, the residue was subjected on chromatography (silica gel) (AcOEt:*n*-hexane = 1:3) to afford 1,2,3-triacetoxy-5*S*-acet-

oxymethyl-*N*-methoxycarbonyl piperidine (**5**) in 85% yield.

11. Determined 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 of major isomer: 11.4 min.
12. **$6_{2S,3S}$**; mp 102–104 °C (from AcOEt–*n*-hexane), $[\alpha]_D^{26}$ +40.0 (*c* 0.5 $CHCl_3$).
13. Crystallographic data for **$6_{2S,3S}$**: $C_{14}H_{21}NO_8$, FW = 331.32, orthorhombic, $P2_12_12_1$(#19) space group, *a* = 6.7419(7), *b* = 10.5386(3), *c* = 23.9189(7) Å, *V* = 1699.4(2) Å^3, *Z* = 4, D_{calc} = 1.295 g cm^{-3}, μ(Mo,Ka) = 1.07 cm^{-1}, F_{000} = 704, *T* = 296 K, Crystal size (mm) = 0.55 × 0.40 × 0.30. Crystallographic data for **21**: $C_{11}H_{15}NO_6$, FW = 257.24, orthorhombic, $P2_12_12_1$(#19) space group, *a* = 6.6474(7), *b* = 8.7625(2), *c* = 20.4793(6) Å, *V* = 1192.9(1) Å^3, *Z* = 4, D_{calc} = 1.432 g cm^{-3}, μ(Mo,Ka) = 1.17 cm^{-1}, F_{000} = 544, *T* = 297 K, crystal size (mm) = 0.55 × 0.25 × 0.20. Compounds **$6_{2S,3S}$** and **21** were mounted on a glass fiber. All measurements were made on a Quantum CCD area detector coupled with a Rigaku AFC7 diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å) at 296–297 K. Data were collected in 0.50° oscillations with 30.0 s exposures. A sweep of data was done using ϕ oscillations from 0.0° to 190.0° at χ = 0° and a second sweep was performed using *w* oscillations between −19.0° and 23.0° at χ = 90.0°. The crystal-to-detector distance was 40.7 mm, and the detector swing angle was −5.0°. The data were corrected for Lorentz and polarization effects. The structures were solved by direct methods (SIR92) and refined by full matrix least squares methods. All calculations were performed using TEXSAN.
CCDC 246337 & 246338 contains 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 e-mailing 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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15. **21**: mp 127–129 °C (from AcOEt–*n*-hexane), $[\alpha]_D^{26}$ −75.2 (*c* 0.6 $CHCl_3$).
16. The stereoselectivity can be also explainable in terms of a participating effect of 3-acetoxyl group or thermodynamic control of the products.
17. A mechanism involving an initial attack of acetic acid on C-2 of a cation (C-2) radical (C-1) intermediate cannot be denied.