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A convenient method for synthesis of optically active 2,3-methanopipecolic acid

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Abstract

2,3-Didehydro-1,2-bis(methoxycarbonyl)-6-methoxypiperidine (**4**), prepared from L-lysine by using electrochemical oxidation, was cyclopropanated with high diastereoselectivity (96.6% de), and the cyclopropanated product was transformed to optically active 2,3-methanopipecolic acid (**1**). In this transformation, the 6-methoxy group of **4** was found to be an effective chiral auxiliary.

Keywords: amino acids and derivatives; electrochemical reactions; cyclopropanation; asymmetric synthesis.

Optically active 2,3-methanoamino acids have become very important as enzyme inhibitors and mechanistic probes because of their interesting properties due to the restricted conformation.[1] One such compound of recent interest is optically active 2,3-methanopipecolic acid (**1**) since L-pipecolic acid is found as a constituent in pharmaceutically important compounds such as the immunosuppressive agents FK-506[2] and rapamycin.[3] However, there has been reported only one method for the synthesis of **1**,[4] while a variety of synthetic methods have been developed for optically active or inactive acyclic and five-membered 2,3-methanoamino acids.[5] We describe herein a new convenient method for the synthesis of optically active **1** starting from L-lysine.

Scheme 1 shows our strategy which consists of the following five steps: (1) transformation of N^{α},N^{ω}-bisprotected L-lysine ester **2** to 6-methoxypipecolate **3**; (2) didehydrogenation of **3** at the 2,3-position; (3) diastereoselective cyclopropanation of 2,3-didehydrogenated pipecolate **4** affording 2,3-methano-6-methoxypipecolate **5**; (4) reductive removal of 6-methoxy group of **5** for the conversion to 2,3-methanopipecolate **6**, and (5) deprotection of **6** to afford optically active **1**. A satisfactory result by means of this scheme would depend on both the chirality of **4** at the 6-position and the diastereoselectivity in the cyclopropanation of **4**.

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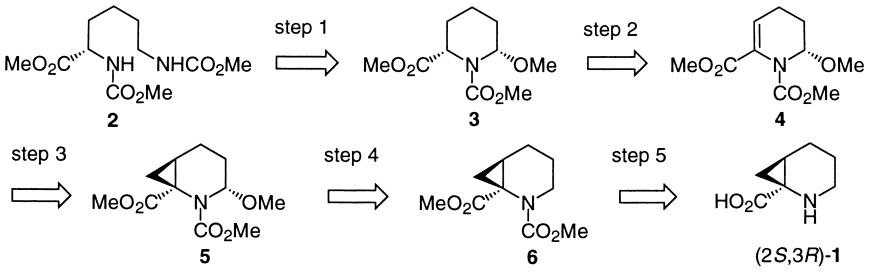
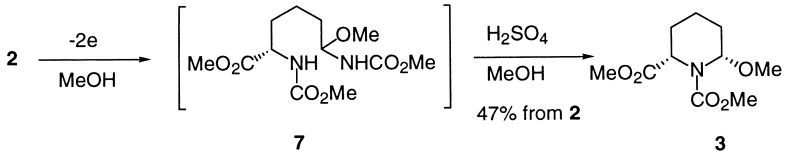


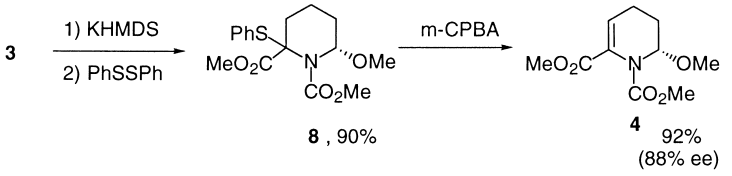
Scheme 1.

The transformation of **2** to **3** in step 1 was easily achieved according to our reported method; namely, an electrochemical oxidation of **2** in methanol followed by an acid-catalyzed cyclization without the isolation of the oxidation product **7** (Eq. (1)).[6] The presence of diastereomers of **3** was not clarified at this stage since **3** showed one spot in the chromatography and ambiguous NMR spectra possibly due to the existence of rotamers.[7] On the other hand, the fact that no optical loss of the chirality at the 2-position occurred in step 1 was ascertained by converting **3** to optically pure methyl 1-methoxycarbonylpipecolate.[8,9]



(1)

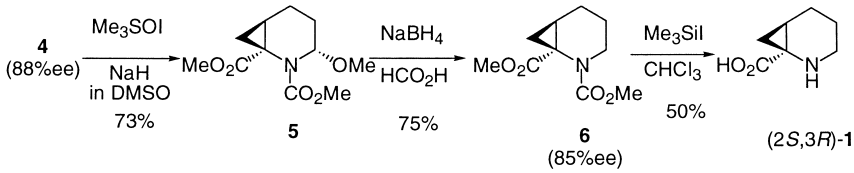
Then, in step 2, **3** was phenylthiolated at the 2-position by the treatment with potassium bis(trimethylsilyl)amide (KHMDS) and diphenyldisulfide, successively, and the resulting product, 2-phenylthiolated **8**, was oxidized with *m*-CPBA to give 2,3-didehydropipecolate **4** in good yield (Eq. (2)). The optical purity of **4** was determined to be 88% ee by CSP (chiral stationary phase)-HPLC analysis.[10] On the basis of this result, the ratio of diastereomers of **3** was found to be 94:6.



(2)

The reactions with respect to steps 3–5 are shown in Eq. (3). The treatment of **4** with dimethylsulfoxonium methylide in DMSO gave 2,3-methano-6-methoxypipecolate **5** in good yield (step 3). The subsequent reductive elimination of the 6-methoxy group of **5** was nicely done by adding $NaBH_4$ in portions to a solution of **5** in formic acid at ambient temperature to afford 2,3-methanopipecolate **6** (step 4). The optical purity of **6** could be determined to be 85% ee by CSP-GC.[11]

Thus, the cyclopropanation of **4** was found to proceed with 96.6% de since **4** with 88% ee was used. Finally, **6** was hydrolyzed into (2*S*,3*R*)-**1** by treatment with trimethylsilyl iodide in $CHCl_3$ (step 5). The absolute stereoconfiguration of (2*S*,3*R*)-**1** was determined as the assigned structure by comparison of the optical rotation with the reported data.[12]



(3)

As described above, the cyclopropanation of **4** proceeded with excellent diastereoselectivity (96.6% de). The high diastereoselectivity might be explained in terms of the steric or electrostatic repulsion between sulfoxonium ylide and the 6-methoxy group of **4** (Fig. 1).[13] That is, sulfoxonium yilde may approach **4** from the side opposite to the 6-methoxy group which occupies the quasi-axial orientation of the chair form of **4** owing to the allylic 1,3-strain in **4**.

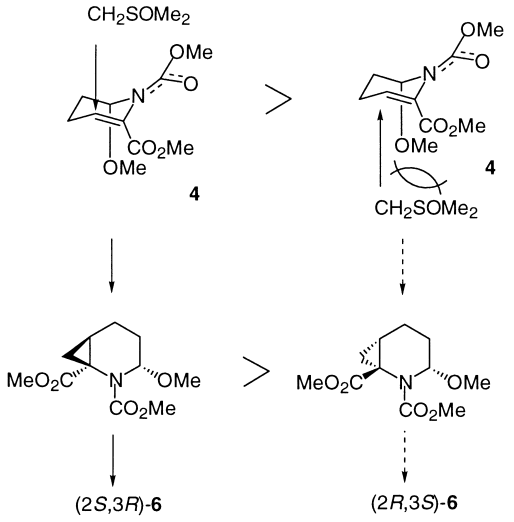


Figure 1. Mechanism for diastereoselective cyclopropanation of **4**

In summary, we have presented a new route to the facile synthesis of optically active 2,3-methanopipecolic acid **1** starting from easily available L-lysine, and also demonstrated that the 6-methoxy group of the key intermediate **4** is an effective chiral auxiliary for the synthesis of optically active **1**.

Acknowledgements

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7. ^{1}H NMR spectrum of **3**: (200 MHz, $CDCl_3$) δ 1.40–1.70 (m, 3H), 1.80–2.00 (m, 2H), 2.25–2.40 (m, 1H), 3.23–3.38 (m, 3H), 3.70–3.80 (m, 6H), 4.67–4.75 and 4.88–4.95 (2m, 1H), 5.26 and 5.44 (2br s, 1H).
8. The conversion of **3** to optically pure methyl 1-methoxycarbonylpipecolate (> 99.9% ee) was achieved by treating with $NaBH_4$ in acetic acid (80% yield). Daicel Chiralcel OD (4.6 mmϕ, 25 cm) [*n*-hexane:ethanol = 15:1 (v/v), 1.0 mL/min, detection at 210 nm, 5.5 min for (*S*)-isomer, 10 min for (*R*)-isomer].
9. The absolute configuration at the 6-position of **3** could not be determined but the main isomer was estimated to possess a *cis*-structure as described in the literature; Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633–635.
10. Daicel Chiralcel OD (4.6 mmϕ, 25 cm) [*n*-hexane:ethanol = 9:1 (v/v), 1.0 mL/min, detection at 210 nm, 5.5 min for (*S*)-**4**, 7 min for (*R*)-**4**]. (*S*)-**4** (88% ee): $[\alpha]_D^{20}$ +29.3 (*c* 0.9, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70–1.90 (m, 1H), 1.94–2.44 (m, 3H), 3.42 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 5.50 (t, J = 2.5 Hz, 1H), 6.15 (t, J = 3.8 Hz, 1H). Anal. calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.78; H, 6.59; N, 5.92.
11. Astec Criraldex G-TA (0.25 mmϕ, 30 m) [130°C, 38 min for (2*S*,3*R*)-**6**, 39 min for (2*R*,3*S*)-**6**]. (2*S*,3*R*)-**6** (85% ee): $[\alpha]_D^{25}$ –25.6 (*c* 0.9, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80–0.91 (m, 1H), 1.32–1.42 (m, 1H), 1.57–2.04 (m, 5H), 2.65–2.90 (m, 1H), 3.69 (s, 3H), 3.71 and 3.73 (2s, 3H), 3.70–3.94 (m, 1H). Anal. calcd for $C_{10}H_{15}NO_5$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.12; H, 6.99; N, 6.42.
12. $[\alpha]_D^{21}$ –45.6 (*c* 0.3, MeOH) [lit.[4] $[\alpha]_D^{27}$ –57.5 (*c* 1, MeOH)].
13. Methylation of 2,3-didehydro-1,2-bis(methoxycarbonyl)-6-(TBS-ethyl)piperidine, an analogue of **4**, proceeded with excellent diastereoselectivity, see: Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, *59*, 943–945.