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New Synthetic Method of Optically Active α-Methylproline and α-Methylpipecolinic Acid using Electrochemical Oxidation as a Key Reaction

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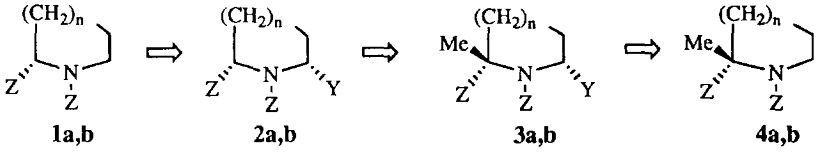
Abstract: A new method for the stereoselective α-methylation of *N*-protected L-proline and L-pipecolinic acid esters is presented. The method consisted of electrochemical α'-methoxylation of the α-amino acid derivatives, the replacement of the α'-methoxy group with a phenylthio group, α-methylation, and reductive removal of the α'-phenylthio group, successively. The intermediates in this method could be used for the preparation of optically active acyclic α-methylated α-amino acids. Copyright © 1996 Elsevier Science Ltd

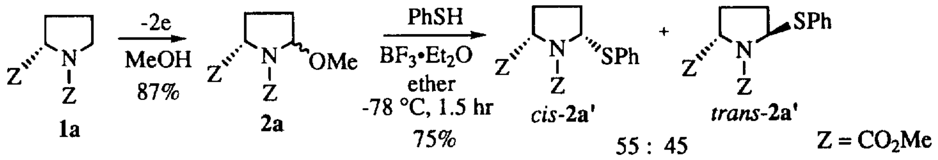
In view of the biological importance of optically active α-alkyl-α-amino acids,[1] organic chemists have targeted the synthesis of these compounds. Although some synthetic methods have been reported,[2] the development of new methods which are characterized by the use of easily available starting compounds, convenient procedures and/or wide applicability is still very important. We describe herein a new synthetic method of optically active α-methylproline and α-methylpipecolinic acid starting from L-proline and L-pipecolinic acid or L-lysine. Scheme 1 shows our strategy which consists of the following steps: (1) a substituent Y is introduced into the α'-position of *N*-protected L-proline ester **1a** and L-pipecolinic acid ester **1b** to give α'-substituted α-amino acid esters **2a,b**, (2) a methyl group is stereoselectively introduced to the α-position of **2a,b** under the influence of α'-substituent Y to give α'-substituted α-methyl-α-amino acid esters **3a,b**, and (3) α'-substituent Y of **3a,b** is reductively removed to afford α-methylproline and α-methylpipecolinic acid esters **4a,b**.



a : n=1 **b** : n=2
$Z = CO_2Me$

Scheme 1

We first intended to introduce a methyl group into the α-position of *N*-methoxycarbonyl-L-proline methyl ester (**1a**) using its α'-methoxylated ester **2a** since **1a** has been known to be easily converted to **2a** by electrochemical oxidation in methanol.[3] However, **2a** was a mixture of stereoisomers (55/45) of which separation by column chromatography proved very difficult. Thus, the α'-methoxy group of **2a** was replaced with a phenylthio group by the treatment of **2a** with thiophenol in the presence of Lewis acid to give α'-phenylthioproline ester **2a'** which was also a mixture of stereoisomers *cis*- and *trans*-**2a'** in a ratio of 55 to 45 (75% yield) (eq 1). Fortunately, each of these stereoisomers could be easily separated by column chromatography. The stereochemistry of *cis*- and *trans*-**2a'** was determined at the stage of α-methyl-L- and D-prolines (**5a** and **5a'**) as described below.

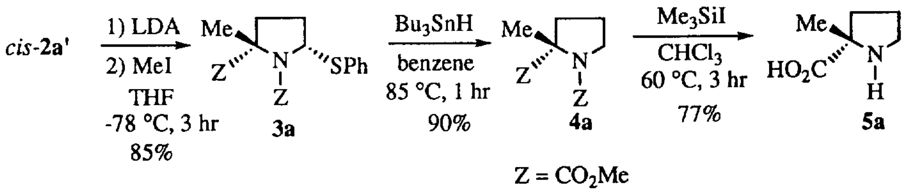


(1)

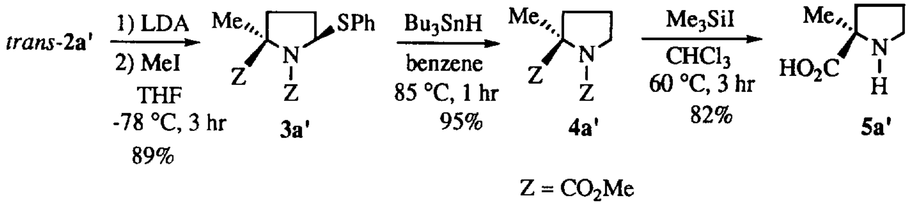
Isolated *cis*- and *trans*-**2a'** were deprotonated by LDA followed by treatment with iodomethane to give the corresponding α-methylated derivatives **3a** and **3a'**, respectively (eqs 2 and 3).[4] The stereochemical relationship between the α-methyl and α'-phenylthio groups in **3a** and **3a'** was suggested to be *trans* by NOE,[5] indicating that the enolate intermediates generated from *cis*-**2a'** and *trans*-**2a'** were predominantly attacked by iodomethane from the direction opposite to the α'-phenylthio group.

The phenylthio group of **3a** and **3a'** was easily removed by the reaction with tributyltin hydride to give **4a** and **4a'**, and the deprotection of **4a** and **4a'** was achieved by the reaction with iodotrimethylsilane to give α-methyl-L-proline **5a** and α-methyl-D-proline **5a'** (eqs 2 and 3).[6] The enantiomeric excesses of **5a** and **5a'** were 88-89% and 85%, respectively.

On the basis of the absolute stereochemistry of the obtained **5a** and **5a'**, the structures of **4a** and **4a'**, of **3a** and **3a'**, and of *cis*- and *trans*-**2a'** were identified as the assigned structures.

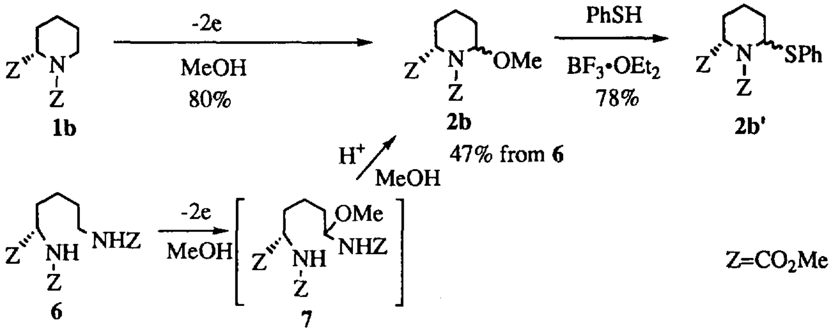


(2)



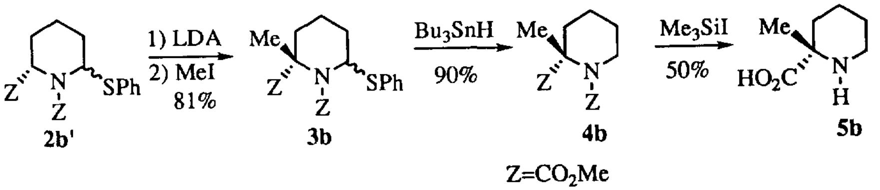
(3)

Next, our method was applied to the preparation of optically active α-methylpipecolinic acid. Electrochemical oxidation of L-pipecolinic acid derivative **1b** in methanol gave α'-methoxypipecolinic acid ester **2b**, which was also inexpensively obtainable from L-lysine derivative **6** through **7** by electrochemical oxidation (eq 4).[8] The replacement of the α'-methoxy group of **2b** with a phenylthio group was carried out by the procedure used from **2a** to **2a'** to afford α'-phenylthiopipecolinic acid ester **2b'** in 78% yield.



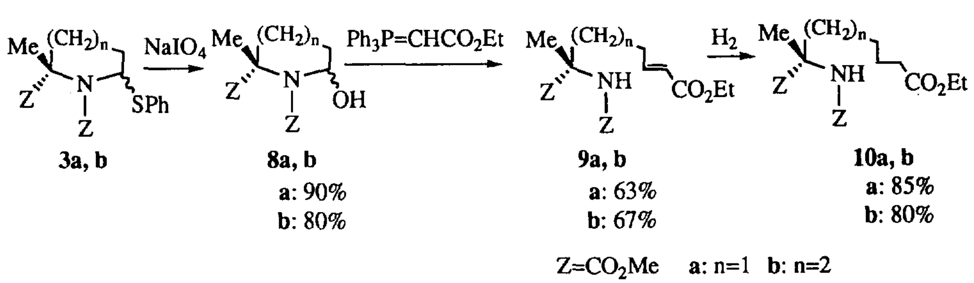
(4)

In contrast with **2a'**, the compound **2b'** gave only one spot on TLC under several conditions.[9] Accordingly, it was subjected to the following α-methylation without further purification. α-Methylation of **2b'** affording **3b** was carried out under the reaction conditions similar to that of **2a'**. The reductive removal of the α'-phenylthio group of **3b** followed by the hydrolysis of **4b** gave the desired **5b** in 84%ee (eq 5).[10] This result suggests that the α'-position of **2b'** might have exclusively an *S*-configuration.



(5)

The advantage of our method is its applicability to the preparation of optically active acyclic α-methyl-α-amino acids utilizing α'-phenylthiolated intermediates **3a,b**. We found this time that **3a,b** were easily converted to the corresponding α'-hydroxy derivatives **8a,b** by treatment with sodium periodate in acetonitrile containing 10% water. The reaction of **8a,b** with ethoxycarbonylmethylenetriphenylphosphorane gave



(6)

unsaturated acyclic α-methyl-α-amino acid esters **9a,b** and the hydrogenation of **9a,b** afforded acyclic α-methyl-α-amino acid esters **10a,b** (eq 6).[12]

In summary, we have disclosed a new method which is applicable to the preparation of the optically active α-methyl-L- and D-prolines (**5a** and **5a'**), α-methyl-L-pipecolinic acid **5b**, and acyclic α-amino acid esters **9a,b** and **10a,b** from L-proline and L-pipecolinic acid or L-lysine. Further studies on more stereoselective α-methylation and other α-alkylations are under way.

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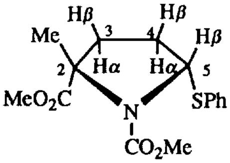
3. Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985,** *63,* 206-213.
4. *cis*-**2a'**: oil. $[\alpha]_D^{25}$-116.9°(*c* 0.65 MeOH). *trans*-**2a'**: oil. $[\alpha]_D^{25}$-78.8°(*c* 1.36 MeOH). **3a**: oil. $[\alpha]_D^{25}$ -70.6°(*c* 0.65 MeOH). **3a'**: oil. $[\alpha]_D^{25}$ +69.3°(*c* 0.76 MeOH).
5. ^{1}H NMR of **3a**; (500 MHz, $CDCl_3$) δ 1.51 (s, 1.3H), 1.53 (s, 1.7H), 1.92-1.99 (m, 1H, H_β at C_3), 2.10-2.15 (m, 1H, H_α at C_4), 2.24-2.38 (m, 1H, H_β at C_4), 2.53-2.65 (m, 1H, H_α at C_3), 3.59 (s, 1.7H), 3.72 (s, 1.3H), 3.77 (s, 1.3H), 3.80 (s, 1.7H), 5.34 (d, J = 6.0 Hz, 1H, H_β at C_5), 7.27-7.34 (m, 3H), 7.48-7.60 (m, 2H). This spectrum suggested that **3a** was a mixture of rotamers (1.3:1.7). **3a'** gave the same ^{1}H NMR spectrum. The NOEs between the following groups of **3a** were observed; Me at $C_2 \rightarrow H_\beta$ at C_3 and H_β at C_4; H_α at $C_3 \rightarrow H_\beta$ at C_3 and H_α at C_4; H_β at $C_3 \rightarrow$ Me at C_2, H_α at C_3, and H_β at C_4; H_α at $C_4 \rightarrow H_\alpha$ at C_3, H_β at C_4, and H_β at C_5; H_β at $C_4 \rightarrow$ Me at C_2, H_β at C_3, H_α at C_4, and H_β at C_5; H_β at $C_5 \rightarrow H_\alpha$ at C_4 and H_β at C_4.



3a

6. **5a**: mp 250-253℃. $[\alpha]_D^{22}$-63.5° (*c* 0.98 MeOH).[lit.[7] $[\alpha]_D^{RT}$-71.1°to -72.1° (*c* 1.0 MeOH)]. **5a'**: mp 250-253℃.$[\alpha]_D^{24}$+62.2° (*c* 0.65 MeOH). [lit.[7]$[\alpha]_D^{RT}$+73.1° (*c* 1.7 MeOH)]
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8. Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986,** *51,* 2590-2592.
9. It also could not be determined by NMR spectra if **2b'** was a mixture of stereoisomers or not .
10. **5b**: $[\alpha]_D^{22}$-4.0°(*c* 0.6 H_2O). [lit.[11] $[\alpha]_D^{23}$-4.0°(*c* 0.97 H_2O)]. The ^{1}H NMR spectrum of the amide prepared from **5b** and Mosher's acid chloride showed that the obtained **5b** had 84%ee.
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12. **9a**:oil. $[\alpha]_D^{24}$ -8.6° (*c* 0.55 MeOH). **10a**: oil. $[\alpha]_D^{22}$ -8.5° (*c* 0.78 MeOH). **9b**:oil. $[\alpha]_D^{24}$ -6.8° (*c* 0.96, MeOH). **10b**: oil. $[\alpha]_D^{25}$-4.9° (*c* 1.05 MeOH).

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