

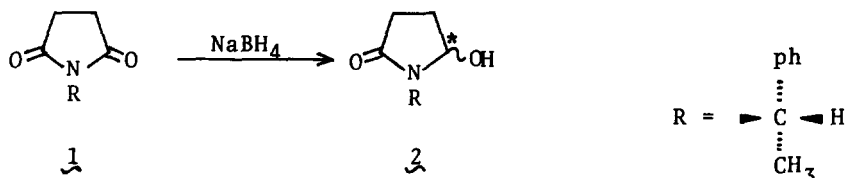
BIOMIMETIC ASYMMETRIC SYNTHESIS OF PYRROLIDINE DERIVATIVES<sup>1</sup>

Toshio Wakabayashi\*, and Masahiko Saito  
 Teijin Institute for Biomedical Research  
 4-3-2 Asahigaoka, Hino, Tokyo 191, Japan

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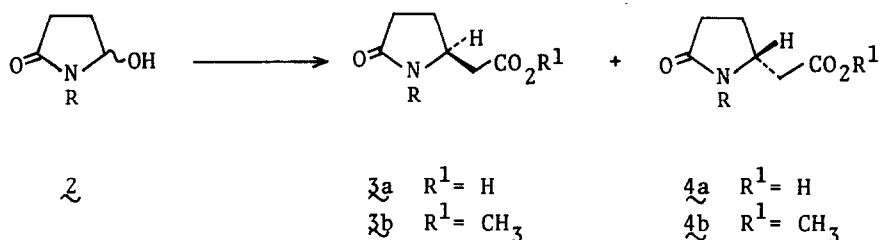
Previous investigations of the synthesis of (S)-(-)-ecgoninic acid demonstrated a major potential of the novel asymmetric intramolecular Michael addition of the chiral amide anion onto the double bond of the unsaturated ester.<sup>2</sup> We now report another aspect of above cyclization starting from 5-hydroxylactams (**2**).

Reaction of succinic anhydride with (S)-(-)- $\alpha$ -phenylethylamine at 180°C for 6 hr afforded the optically active imide **1** [mp 67-68.5°C,  $[\alpha]_D^{26}$ -69.8° (C=1.0, EtOH)]. The imide **1** was reduced with NaBH<sub>4</sub> to give a diastereomeric mixture of 5-hydroxy lactams (**2**) in 53% yield.

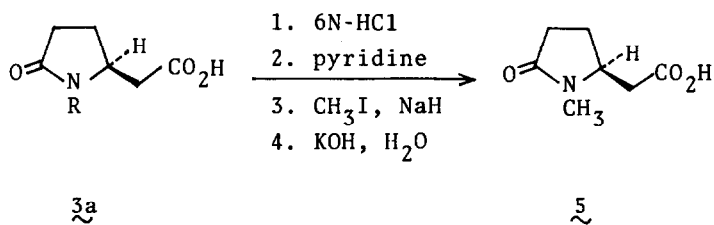


Interestingly, it was found that the above diastereomers were easily separable from each other by silica gel column chromatography. The ratio of the diastereomers was ca. 3.5:1, although their configurations are not yet elucidated.

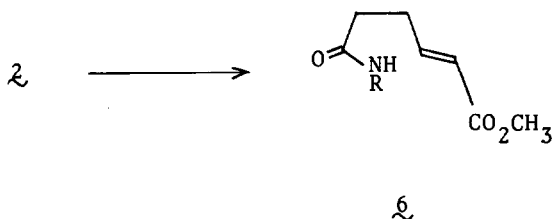
Conversion of **2** to a diastereomeric mixture of esters (**3b** and **4b**) was accomplished by applying the recently developed elegant Wittig-type condensation<sup>3</sup> of  $\omega$ -carbinol lactams with triethylphosphonoacetate. Treatment of **2** with methyl diethylphosphonoacetate and sodium hydride in dimethoxyethane at -35 ~ -30°C for 2 hr gave a mixture of methyl esters **3b** and its diastereomer at C-5, **4b** in 58% yield. The nmr assay of the methyl signals (in CDCl<sub>3</sub>,  $\delta$  3.53 and 3.61 ppm) of the ester groups in these diastereomers revealed 47% optical purity for **3b**.



Hydrolysis of the above mixture of the esters  $\text{3b}$  and  $\text{4b}$  to a mixture of the acids  $\text{3a}$  and  $\text{4a}$  and subsequent recrystallization from ethanol afforded optically pure  $\text{3a}$ <sup>4</sup> [mp 205-206°C,  $[\alpha]_D^{23} -161.7^\circ$  (C=1.0, EtOH)]. The stereochemistry at C-5 position in  $\text{3a}$  was unambiguously established as S by the efficient conversion of  $\text{3a}$  to enantiomerically pure (S)-(-)-ecgoninic acid ( $\text{5}$ ),<sup>5</sup> the degradation product of natural (-)-ecgonine, as already described.<sup>2</sup>



A remarkable change in the product of the Wittig-type condensation of  $\text{2}$  was observed when the solvent was changed. When  $\text{2}$  was treated with methyl diethylphosphonoacetate and sodium hydride in chlorobenzene-THF (2.5:1) at  $-30^\circ\text{C}$ , the product isolated in 54% yield was found not to be the



mixture of cyclized esters (**3b** and **4b**), but the optically active trans-olefinic ester **6** [ $[\alpha]_D^{23} -69.2^\circ$  (C=0.8, EtOH), nmr (in  $\text{CDCl}_3$ ,  $\delta$ ); 5.83 (1H, d,  $J=16.0$  Hz,  $-\text{CH}_2-\text{CH}=\text{CH}-\text{CO}_2\text{CH}_3$ ), 6.93 (1H, dt,  $J=16.0, 7.0$  Hz,  $-\text{CH}=\text{CH}-\text{CO}_2\text{CH}_3$ )].

Cyclization of **6** with catalytic amount of potassium t-butoxide (0.1-0.2 eq moles) in various solvents gave the mixture of esters **3b** and **4b** with a different ratio of **3b** to **4b**. The solvent effect obtained is summarized in Table I.

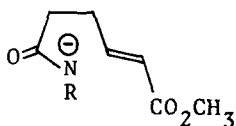
Table I. Solvent Effect in Asymmetric Cyclization of trans-Olefinic Ester **6** with  $\text{KO}^t\text{Bu}$  (0.1-0.2 equiv.)

Entry	Solvent ( $D^a$ at $25^\circ$ )	Temp ( $^\circ\text{C}$ )	Time (min)	Yield (%)	Optical purity <sup>b</sup> for <b>3b</b> (%)
1	chlorobenzene (5.62)	-40	30	96	40
2	dimethoxyethane (7.20)	-40	30	94	48
3	tetrahydrofuran (7.58)	-68	120	93	56
4	dimethylformamide (36.71)	-45	30	87	11

a. Dielectric constant

b. Determined by NMR assay

The nature of the solvent influences the diastereoselectivity. In tetrahydrofuran or dimethoxyethane, reaction is rather selective. In a more polar solvent such as dimethylformamide, in which solvent dissociation of an ion-pair is expected to be large, the diastereoselectivity is less. Thus, solvent dissociation of the chiral amide anion **8** and potassium ion might play an important role in determination of the product ratio.



**8**

In view of the fact that the fairly high optical yield for  $3b$  in the 1, 6-asymmetric cyclization ( $6 \rightarrow 3b + 4b$ ) was observed, the steric repulsion between the amide carbonyl and phenyl groups in  $6$  appears to suppress the free rotation of  $\alpha$ -methylbenzyl grouping. The rather high reaction rate in this cyclization ( $6 \rightarrow 3b + 4b$ ) considering low reaction temperature can be understood by the entropy effect in the five membered ring transition state. This intramolecular cyclization, thus, provides a useful model for enzymatic processes.

In conclusion, the above condensation of chiral five membered  $\omega$ -carbinollactams with Horner-type reagents<sup>6</sup> constitutes a useful asymmetrically induced intramolecular Michael reaction which is applicable to asymmetric synthesis of piperidine derivatives.<sup>7</sup>

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#### References and Notes

1. A part of this work was presented at the 20th Symposium on the Chemistry of the Natural Products, Sendai, Oct. 10th, 1976.
2. T. Wakabayashi, Y. Kato, and K. Watanabe, Chemistry Letters, 1283 (1976).
3. J. J. J. de Boer and W. N. Speckamp, Tetrahedron Lett., 4039 (1975).
4. a. The compound  $3a$  was quite useful for the resolution of dl-amines (e. g., dl- $\alpha$ -methylbenzylamine, dl-2-aminobutanol, etc.).  
b. Optically active  $\alpha$ -methylbenzyl alcohols were successfully obtained by column chromatographic separation of the diastereomeric esters from  $3a$  and dl- $\alpha$ -methylbenzyl alcohol and subsequent hydrolysis. These results will be published elsewhere.
5. a. R. Willstätter and A. Bode, Chem. Ber., 34, 519 (1901).  
b. E. Hardegger and H. Ott, Helv. Chim. Acta, 38, 312 (1955).
6. Cf. J. Boutagy and R. Thomas, Chem. Rev., 74, 87 (1974).
7. T. Wakabayashi, K. Watanabe, Y. Kato, and M. Saito, Chemistry Letters, in submission.