

## A NEW APPROACH TO CHIRAL 5,5-DISUBSTITUTED 2-PYRROLIDINONES FROM (*S*)-PYROGLUTAMIC ACID

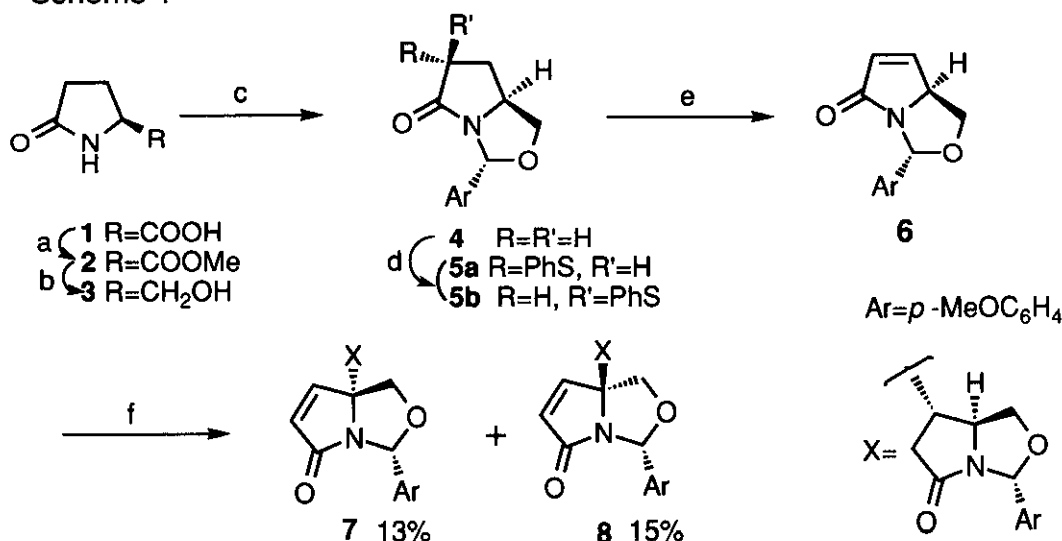
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**Abstract** - Two enantiomers of 5,5-disubstituted 2-pyrrolidinones with the certain configurations were synthesized, starting from (*S*)-pyroglutamic acid, via the bicyclic lactam, (2*R*, 5*S*)-2-aryl-1-aza-3-oxabicyclo[3.3.0]oct-5-en-7-one (**6**).

The asymmetric synthesis of  $\alpha$ ,  $\alpha$ -disubstituted cyclic amines is of interest for their use as versatile materials for alkaloid and  $\alpha$ -alkylated  $\alpha$ -amino acid syntheses.<sup>1</sup> Seebach reported the enantioselective synthesis of  $\alpha$ -substituted L-prolines using 2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one.<sup>2</sup> An analogous procedure using 2-(*p*-methoxyphenyl)-1-aza-3-oxabicyclo[3.3.0]oct-5-en-7-one (**6**) derived from (*S*)-pyroglutamic acid (**1**) was carried out in the present study. Data are presented in the following on asymmetric synthesis of 5,5-disubstituted 2-pyrrolidinones which are of use for obtaining stereoisomers.<sup>3</sup>

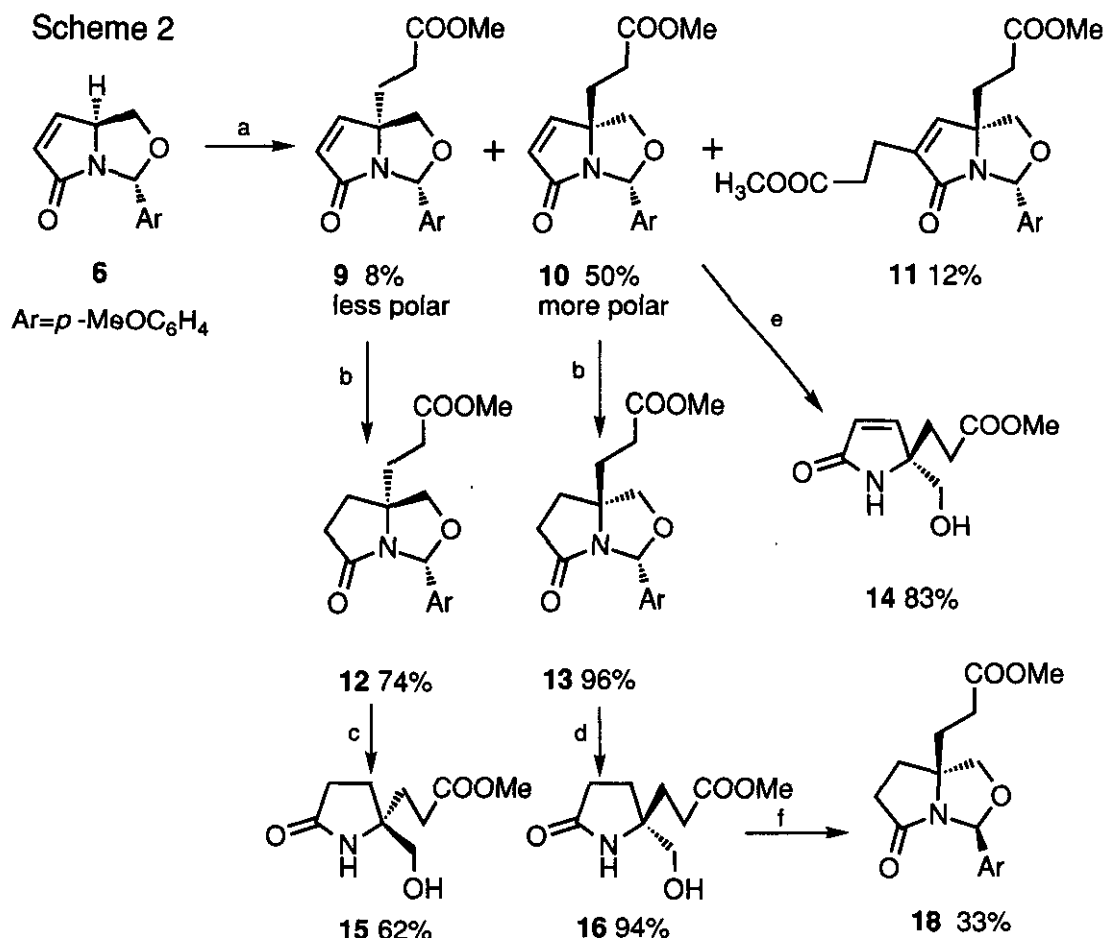
### Scheme 1



**Reagents:** a. MeOH, *p*-TsOH, reflux, 12 h, 90%; b. NaBH<sub>4</sub>, EtOH, room temperature, 4 h, 60%; c. *p*-MeOC<sub>6</sub>H<sub>4</sub>CHO (1.3 eq.), PPTS, toluene, reflux, 24 h, 72%; d. LDA (1.2 eq.), PhSSPh (1.2 eq.), THF, -78°C, 1 h, 73% (**5a**:**5b** 1:1); e. 1) *m*CPBA (1.2 eq.), CH<sub>2</sub>Cl<sub>2</sub>, -15° - room temperature; 2) toluene, py (2 eq.), reflux, 45 min, 86%; f. NaH (0.15 eq.), THF, room temperature, 30 min.

*N*, *O*-Acetal (**4**, Thottathil's acetal)<sup>4</sup>, obtained by reaction of (*S*)-5-hydroxymethyl-2-pyrrolidinone (**3**) with *p*-anisaldehyde, was converted to the  $\alpha$ ,  $\beta$ -unsaturated lactam (**6**)<sup>5</sup> which can be used to introduce

functional groups into the unsaturated double bond.<sup>6</sup> Treatment of **6** with sodium hydride (NaH, 0.15 eq.) in DMSO-THF (1 : 3) at  $-15 \sim -10^\circ\text{C}$  gave dimer (**7**) in 54% yield. Reaction in THF at room temperature gave two dimers (**7**) and (**8**) in 13 and 15% yields, respectively (Scheme 1).<sup>7</sup> In consideration of these results, reactions of **6** with other Michael acceptors were carried out and configurations of the products were examined.



**Reagents** : a. CH<sub>2</sub>=CHCOOMe (2 eq.), NaH (1 eq.), DMSO-THF (1:14),  $-15 \sim -10^\circ\text{C}$ , 1 h; b. H<sub>2</sub> (1 atm), 5% Pd-C, EtOH, 30 min; c. AcOH-THF-H<sub>2</sub>O (5:5:1),  $100^\circ\text{C}$ , 1 h; d. AcOH-THF-H<sub>2</sub>O (2:8:1),  $80^\circ\text{C}$ , 30 min; e. AcOH-THF-H<sub>2</sub>O (1:8:2), room temperature, 1.5 h; f. 1) HMDS (excess),  $130^\circ\text{C}$ , 3.5 h; 2) *p*-MeOC<sub>6</sub>H<sub>4</sub>CHO (2 eq.), TMSOTf (cat.), CH<sub>2</sub>Cl<sub>2</sub>-toluene, room temperature, 2 h then  $60^\circ\text{C}$ , 3 h.

Reaction of **6** with methyl acrylate (2 eq.) [NaH (1 eq.), DMSO-THF (1 : 14),  $-15 \sim -10^\circ\text{C}$ , 1 h] gave **9** (8%), **10** (50%) and **11** (12%) (Scheme 2). The product ratio depended on the bases, solvents, and/or temperature. At room temperature  $\sim 80^\circ\text{C}$  and/or the protic solvent (*t*-BuOH), the ratio of **9** increased, while NaH (1.2 eq.) in THF at room temperature for 10 h gave **10** (31%) and **11** (11%) without **9**.<sup>8</sup> The solvation of more polar solvents (*t*-BuOH, DMSO) over the  $\beta$ -side of the bicyclic lactams would predominantly prevent the approach of methyl acrylate from the same side. Ir, <sup>1</sup>H-nmr, and mass spectra of **9** and **10** indicated these products to be the diastereomers of each other. The catalytic hydrogenation

of **9** and **10** gave **12** and **13** in good yields, respectively, which were hydrolyzed to chiral 5,5-disubstituted 2-pyrrolidinones (**15**) (62%) and (**16**) (94%), respectively. The direct cyclization of **16** with *p*-anisaldehyde to **18** was unsuccessful. However, the reaction of *O*-trimethylsilyl ether of **16** with aldehyde proceeded smoothly to give **18**, but in a rather low yield (33%), thus indicating a thermodynamically stable isomer to be an enantiomer of **12**.<sup>9</sup> Hydrolysis of **10** under conditions similar to those for **12** and **13** gave 5,5-disubstituted 3-pyrrolin-2-one (**14**) in 83% yield.

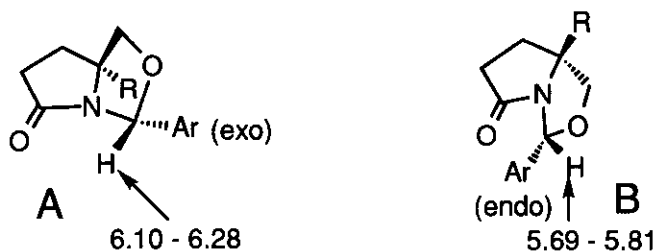
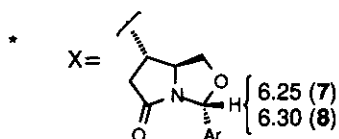


Figure 1

Configurations of the compounds obtained in this study were determined on the basis of chemical behavior and spectral data. *R<sub>f</sub>* of the more stable diastereomers (**7**, **9**, and **12**) on chromatography always exceeded those of the less stable diastereomers (**8**, **10**, and **13**), respectively. The latter were observed to decompose gradually in organic solvents at room temperature to eliminate *p*-anisaldehyde.

Table 1. Chemical Shifts of C<sub>2</sub>-Protons for *N,O*-Acetals

	R : α (R / Ar: <i>cis</i> )	C <sub>2</sub> -H (ppm)	R : β (R / Ar: <i>trans</i> )	C <sub>2</sub> -H (ppm)
 (Ar: <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> )	<b>4</b> (R=R'=H)	6.28	-----	
	<b>12</b> (R=CH <sub>2</sub> CH <sub>2</sub> COOMe, R'=H)	6.25	<b>13</b> (R=CH <sub>2</sub> CH <sub>2</sub> COOMe, R'=H)	5.69
 (Ar: <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> )	<b>6</b> (R=R'=H)	6.14	-----	
	<b>7</b> (R=X, R'=H)*	6.14	<b>8</b> (R=X, R'=H)*	5.81
	<b>9</b> (R=CH <sub>2</sub> CH <sub>2</sub> COOMe, R'=H)	6.10	<b>10</b> (R=CH <sub>2</sub> CH <sub>2</sub> COOMe, R'=H)	5.80
	-----		<b>11</b> (R=R'=CH <sub>2</sub> CH <sub>2</sub> COOMe)	5.79



Examination of molecular models indicated that, in the unstable diastereomers, the *p*-methoxyphenyl group at the 2-position was *trans*-related to the substituent at the angular 5-position and at the endo

position facing the bicyclic lactam (B in Figure 1). Product ratio data supported these configurations. For instance, yield of **9** (more stable diastereomer) increased at higher temperature.<sup>8</sup> The configurations were confirmed by their <sup>1</sup>H-nmr spectra (Table 1). For 5 $\alpha$ -substituent products, signals of C<sub>2</sub>-protons appeared from 6.10-6.28 ppm, while for 5 $\beta$ -products, 5.69-5.81 ppm. These observation can be explained based on molecular models which indicate chemical shifts of C<sub>2</sub>-protons in 5 $\alpha$ -diastereomers (A) to be shielded downfield by anisotropy effects of amido carbonyls (Figure 1).

The reactions presented in this paper, starting from (*S*)-pyroglutamic acid, are shown to provide routes for two chiral 5,5-disubstituted 2-pyrrolidinones and should thus prove useful for the synthesis of many chiral pyrrolidine derivatives and related alkaloids.

## REFERENCES AND NOTES

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2. D. Seebach, M. Boes, R. Naef, and W. B. Schweizer, *J. Am. Chem. Soc.*, 1983, **105**, 5390.
3. During the preparation of this paper, the total synthesis of (+)-lactacystin from (*R*)-pyroglutamate, with key reactions similar to ours, was reported: H. Uno, J. E. Baldwin, and A. T. Russell, *J. Am. Chem. Soc.* 1994, **116**, 2139.
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5. **6** was prepared by a modified and more convenient method with the phenylsulfonation of **4** followed by thermolysis; cf, references 3, 4, and 6. Comparison of the specific rotation ( $[\alpha]_D^{29.6} +226.9^\circ$  ( $c=1.064$ , CHCl<sub>3</sub>)) of **4** obtained from **3** with that ( $[\alpha]_D^{28.6} +235.6^\circ$  ( $c=1.077$ , CHCl<sub>3</sub>)) of **4** obtained by the hydrogenation of **6** over 5% Pd-C indicated no epimerization before or after these processes.
6. Y. Hamada, A. Kawai, Y. Kohno, O. Hara, and T. Shioiri, *J. Am. Chem. Soc.*, 1989, **111**, 1524; S. Hanessian and V. Ratovelomanana, *Synlett*, 1990, 501; J. E. Baldwin, M. G. Moloney, and S. B. Shim, *Tetrahedron Lett.*, 1991, **32**, 1379.
7. Satisfactory spectral data and elemental analysis results for the new compounds in this paper were obtained.
8. The data will appear in a full paper.
9. **12**:  $[\alpha]_D^{26.6} +166.8^\circ$  ( $c=0.748$ , CHCl<sub>3</sub>); **18**:  $[\alpha]_D^{26.0} -162.2^\circ$  ( $c=0.609$ , CHCl<sub>3</sub>).

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