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

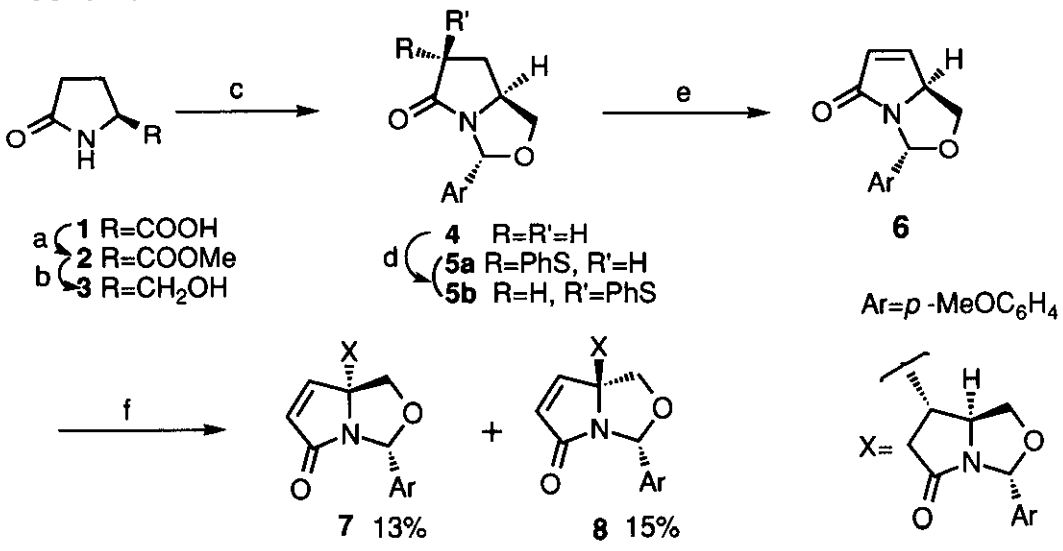
Tatsuo Nagasaka* and Tomoko Imai

Tokyo University of Pharmacy and Life Science, School of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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 α, α-disubstituted cyclic amines is of interest for their use as versatile materials for alkaloid and α–alkylated α-amino acid syntheses.[1] Seebach reported the enantioselective synthesis of α-substituted L-prolines using 2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one.[2] 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.[3]

Scheme 1

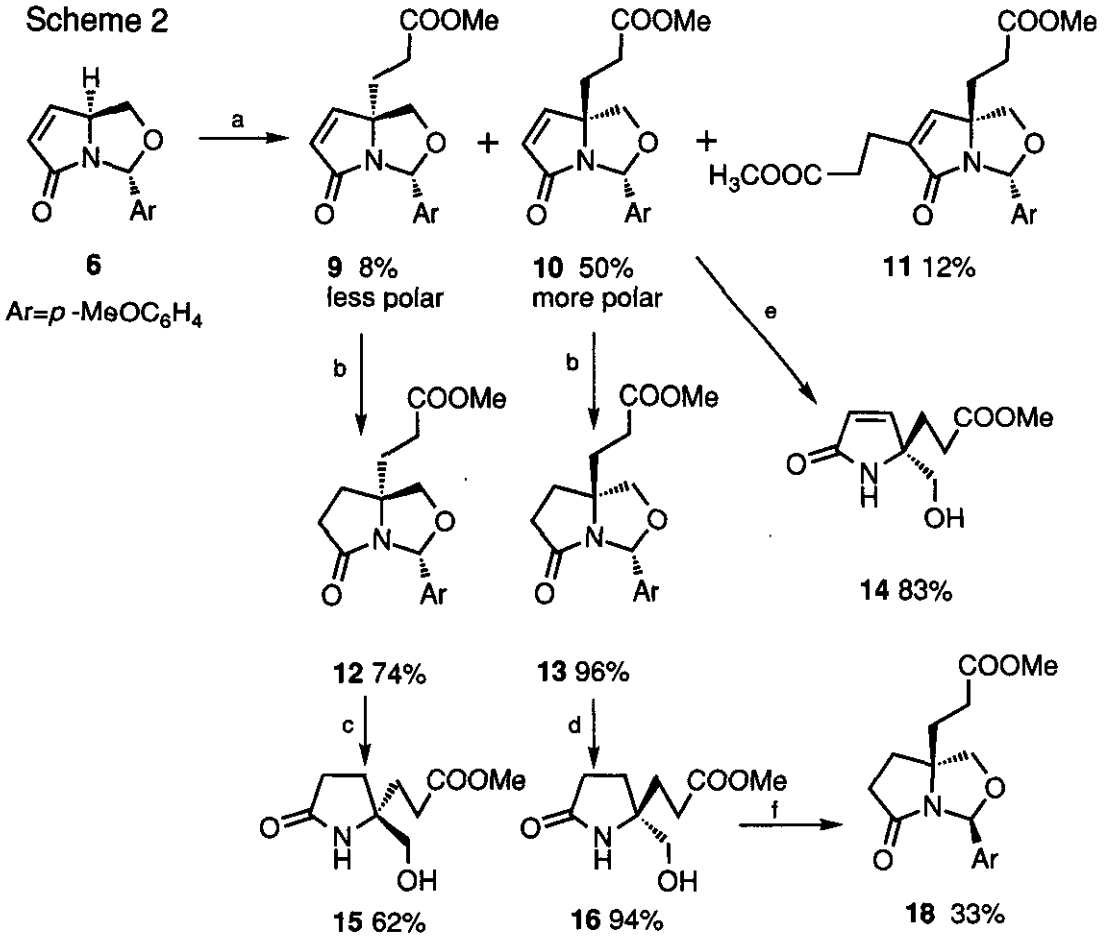


Reagents: **a**. MeOH, *p*-TsOH, reflux, 12 h, 90%; **b**. $NaBH_4$. EtOH, room temperature, 4 h, 60%; **c**. *p*-$MeOC_6H_4CHO$ (1.3 eq.), PPTS, toluene, reflux, 24 h, 72%; **d**. LDA (1.2 eq.), PhSSPh (1.2. eq.), THF, -78°C, 1 h, 73% (**5a**:**5b** 1:1); **e**. 1) *m*CPBA (1.2 eq.), CH_2Cl_2, -15° - 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)[4], obtained by reaction of (*S*)-5-hydroxymethyl-2-pyrrolidinone (**3**) with *p*-anisaldehyde, was converted to the α, β-unsaturated lactam (**6**)[5] which can be used to introduce

functional groups into the unsaturated double bond.[6] Treatment of **6** with sodium hydride (NaH, 0.15 eq.) in DMSO-THF (1 : 3) at -15 ~ -10°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).[7] In consideration of these results, reactions of **6** with other Michael acceptors were carried out and configurations of the products were examined.

Scheme 2



Reagebts : **a**. CH_2=CHCOOMe (2 eq.), NaH (1 eq.), DMSO-THF (1:14), -15 ~ -10°C, 1 h; **b**. H_2 (1 atm), 5% Pd-C, EtOH, 30 min; **c**. AcOH-THF-H_2O (5:5:1),100°C, 1 h; **d**. AcOH-THF-H_2O (2:8:1), 80°C, 30 min; **e**. AcOH-THF-H_2O (1:8:2), room temperature, 1.5 h; **f**. 1) *HMDS (excess), 130°C, 3.5 h; 2) p-MeOC*$_6$*H*$_6$*CHO* (2 eq.), TMSOTf (cat.), CH_2Cl_2-toluene, room temperature , 2 h then 60°C, 3 h.

Reaction of **6** with methyl acrylate (2 eq.) [NaH (1 eq.), DMSO-THF (1 : 14), -15 ~ -10°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 ~ 80°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**.[8] The solvation of more polar solvents (*t*-BuOH, DMSO) over the β–side of the bicyclic lactams would predominantly prevent the approach of methyl acrylate from the same side. Ir, ^{1}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**.[9] Hydrolysis of **10** under conditions similar to those for **12** and **13** gave 5,5-disubstituted 3-pyrrolin-2-one (**14**) in 83% yield.

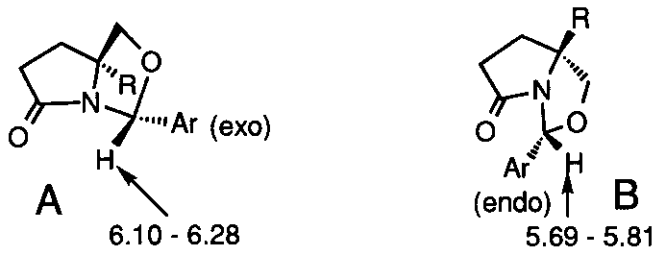
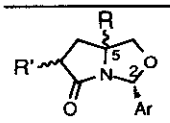
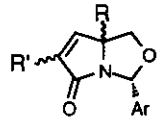
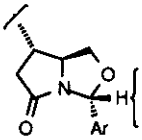


Figure 1

Configurations of the compounds obtained in this study were determined on the basis of chemical behavior and spectral data. *Rf* 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_2-Protons for *N*,*O*-Acetals

	R : α (R / Ar: *cis*)	C_2 -H (ppm)	R : β (R / Ar: *trans*)	C_2 -H (ppm)
 (Ar:*p*-$MeOC_6H_4$)	**4** (R=R'=H)	6.28	----------	
	12 (R=CH_2CH_2COOMe , R'=H)	6.25	**13** (R=CH_2CH_2COOMe, R'=H)	5.69
 (Ar:*p*-$MeOC_6H_4$)	**6** (R=R'=H)	6.14	----------	
	7 (R=X, R'=H)*	6.14	**8** (R=X , R'=H)*	5.81
	9 (R=CH_2CH_2COOMe,R'=H)	6.10	**10** (R=CH_2CH_2COOMe , R'=H)	5.80
	----------		**11** (R=R'=CH_2CH_2COOMe)	5.79

* X=  6.25 (**7**) / 6.30 (**8**)

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 diasteromer) increased at higher temperature.[8] The configurations were confirmed by their ^{1}H-nmr spectra (Table 1). For 5α-substituent products, signals of C_2-protons appeared from 6.10-6.28 ppm, while for 5β-products, 5.69-5.81 ppm. These observation can be explained based on molecular models which indicate chemical shifts of C_2-protons in 5α-diasteromers (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

1. M. E. Kuehne, W. G. Bornmann, W. H. Parsons, T. D. Spitzer, J. F. Blount, and J. Zubieta, *J. Org. Chem.*, 1988, **53,** 3439; G. I. Georg and X. Guan, *Tetrahedron Lett.*, 1992, **33,** 17.
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.
4. J. K. Thottathil, C. Przybyla, M. Malley, and J. Z. Gougoutas, *Tetrahedron Lett.*, 1986, **27,** 1533; J. K. Thottathil, J. L. Moniot, R. H. Mueller, M. K. Y. Wong, and T. P. Kissick, *J. Org. Chem.*, 1986, **51,** 3140. In our study, *N,O*-acetal of *p*-anisaldehyde instead of benzaldehyde was used since it could be easily removed under mild acidic conditions: T. Nagasaka and T. Imai, *Chem. Pharm. Bull.*, 1995, **43**, 1081.
5. **6** was prepared by a modified and more convenient method with the phenylsulfination of **4** followed by thermolysis; cf, references 3, 4, and 6. Comparison of the specific rotation ($[\alpha]_D^{29.6}$ +226.9° (c=1.064, $CHCl_3$)) of **4** obtained from **3** with that ($[\alpha]_D^{28.6}$ +235.6° (c=1.077, $CHCl_3$)) 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° (c=0.748, $CHCl_3$); **18**: $[\alpha]_D^{26.0}$ -162.2° (c=0.609, $CHCl_3$).

Received, 12th May, 1995