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, (2R,5S)-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. NaBH₄, EtOH, room temperature, 4 h, 60%; c. p-MeOC₆H₄CHO (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) mCPBA (1.2 eq.), CH₂Cl₂, -15°C - 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. 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). In consideration of these results, reactions of 6 with other Michael acceptors were carried out and configurations of the products were examined.

Scheme 2

\[
\begin{align*}
6 \quad & \xrightarrow{a} \quad 9 \quad \text{8% less polar} \quad + \quad 10 \quad \text{50% more polar} \\
& \xrightarrow{b} \quad 11 \quad \text{12%}
\end{align*}
\]

Reagents: a. CH=C=CHCOOMe (2 eq.), NaH (1 eq.), DMSO-THF (1:14), -15 ~ -10°C, 1 h; b. H₂ (1 atm), 5% Pd-C, EtOH, 30 min; c. AcOH-THF-H₂O (5:5:1), 100°C, 1 h; d. AcOH-THF-H₂O (2:8:1), 80°C, 30 min; e. AcOH-THF-H₂O (1:8:2), room temperature, 1.5 h; f. 1) HMDS (excess), 130°C, 3.5 h; 2) p-MeOC₆H₄CHO (2 eq.), TMSOTf (cat.), CH₂Cl₂-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. 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, ¹H-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 C2-Protons for N, O-Acetals

<table>
<thead>
<tr>
<th>R : α (R / Ar: cis)</th>
<th>C2 -H (ppm)</th>
<th>R : β (R / Ar: trans)</th>
<th>C2 -H (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (R=R'=H)</td>
<td>6.28</td>
<td>13 (R=CH2CH2COOMe, R'=H)</td>
<td>5.69</td>
</tr>
<tr>
<td>12 (R=CH2CH2COOMe, R'=H)</td>
<td>6.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (R=R'=H)</td>
<td>6.14</td>
<td>8 (R=X, R'=H)*</td>
<td>5.81</td>
</tr>
<tr>
<td>7 (R=X, R'=H)*</td>
<td>6.14</td>
<td>10 (R=CH2CH2COOMe, R'=H)</td>
<td>5.80</td>
</tr>
<tr>
<td>9 (R=CH2CH2COOMe, R'=H)</td>
<td>6.10</td>
<td>11 (R=R'=CH2CH2COOMe)</td>
<td>5.79</td>
</tr>
</tbody>
</table>

* X=

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. The configurations were confirmed by their $^1$H-nmr spectra (Table 1). For 5α-substituent products, signals of C2-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 C2-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

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.
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 ($\left[\alpha\right]_D^{29.6} +226.9^\circ$ (c=1.064, CHCl3)) of 4 obtained from 3 with that ($\left[\alpha\right]_D^{28.6} +235.6^\circ$ (c=1.077, CHCl3)) of 4 obtained by the hydrogenation of 6 over 5% Pd–C indicated no epimerization before or after these processes.
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: $\left[\alpha\right]_D^{26.0} +166.8^\circ$ (c=0.748, CHCl3); 18: $\left[\alpha\right]_D^{26.0} -162.2^\circ$ (c=0.609, CHCl3).

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