Transannular Rearrangement of Activated Lactams: Stereoselective Synthesis of Substituted Pyrrolidine-2,4-diones from Diketopiperazinones

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Current Literature Presentation
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09/15/07
Transannular Rearrangement of Activated Lactams (TRAL): A Serendipitous Finding


8 examples
yield: 60-84%
95-99% ee

11 examples
yield: 57-84%
67-99% de

Outline

• Biological Activities and Synthesis of 2,5-DKPs

• Biological Activities and Synthesis of Pyrrolidine-2,4-diones

• Title Paper

• Summary and Future Directions
2,5-Diketopiperazines (DKPs)

Characteristics:

1. The smallest cyclic peptide derived from the folding head-to-tail of a linear dipeptide
2. Structure is rigid and can be chiral molecule and can be functionalized

Biological Activities:

Inhibition of plasminogen activator inhibitor-1 (PAI-1), alteration of cardiovascular and blood-clotting functions, activity as antitumor, antiviral, antifungal, antibacterial agents etc.

antitumor activity (IC$_{50}$: 4.3-18nM); being tested in preclinical studies
antibiotic
Inhibition of glycogen phosphorylase

Reviews:
(b) “Recent advances in the synthesis of diketopiperazines” Dinsmore, C. J.; Beshore, D. C. Tetrahedron 2002, 58, 3297.
Synthesis of 2,5-Diketopiperazines

(a) Intramolecular formation of N1-C2

(i) Boc-AA-OH, DIC, DIEA; (ii) Boc-based solid-phase peptide synthesis; (iii) TFMSA, TFA; (iv) DIEA.

Synthesis of 2,5-Diketopiperazinines

(b) Intramolecular formation of N1-C6

Synthesis of 2,5-Diketopiperazines

(c) Tandem formation of N1-C2/C3-N4

(d) Tandem formation of N1-C2/N4-C5

Synthesis of 2,5-Diketopiperazines

(e) Tandem formation of C2-N1-C6

Pyrrolidine-2,4-diones (Tetramic Acids)

**Spectrum of biological activity:** antibiotic, antiviral, antiulcerative, cytotoxicity, mycotoxicity, tumor inhibition and fungicidal action

α-Cyclopiazonic acid
very toxic (LD$_{50}$: 2-6 mg kg$^{-1}$)
potent inhibitor of calcium uptake and Ca$^{2+}$ATP-ase activity

Discodermide
antifungal and antitumor agent

Dolastatin 15
potent cytostatic agent against P388 leukemia cells

Synthesis of Pyrrolidine-2,4-diones

Solid-phase synthesis of tetramic acids via Claisen-type condensation:

Enantioselective Lacey-Dieckmann Cyclizations:

Via urethane N-carboxyanhydrides (UNCAs or Leuchs’ anhydrides):

Reactions of Boc-DKPs under basic condition:

Example 1:

\[
\text{Ph} \quad \text{Boc} \quad \text{Ph} \\
\text{Boc} \quad \text{N} \quad \text{O} \quad \text{N} \\
\text{H} \quad \text{N} \quad \text{H} \quad \text{O}
\]

1N NaOH, 90% yield, no epimerization.

\[
\text{Ph} \quad \text{NHBoc} \quad \text{HOOC} \\
\text{NH2} \quad \text{NH} \quad \text{O}
\]

TMSI, 60% yield.

Example 2:

\[
\text{tBuOK, PhCHO} \\
\text{Ph} \quad \text{N} \quad \text{H} \\
\text{N} \quad \text{O} \quad \text{N} \\
\text{H} \quad \text{N} \quad \text{H} \quad \text{O}
\]

84% yield + 16% yield.

Stereoselective Ring Contraction of Unsymmetrical DKPs into 3-Aminotetramates

![Chemical Structure]

1. $\text{tBuOK, THF, RT}$
2. $H_3O^+$

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R</th>
<th>Product (ee)</th>
<th>Yield$^{[c]}$ [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>2a</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Me (S)</td>
<td>2b (&gt;99%)$^{[a]}$</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Me (R)</td>
<td>2c (&gt;99%)$^{[a]}$</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>iPr (S)</td>
<td>2d (&gt;99%)$^{[a]}$</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>iPr (R)</td>
<td>2e (&gt;99%)$^{[a]}$</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>sBu (S)</td>
<td>2f (&gt;95%)$^{[b]}$</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>Bn (S)</td>
<td>2g</td>
<td>16$^{[d]}$</td>
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</table>

[a] The diastereoisomeric excess was determined by chiral HPLC.  
[b] The $^{13}$C NMR spectrum gave only one set of peaks.  
[c] Yield of isolated product after purification by flash chromatography.  
[d] The product from thermodynamic enolate was obtained in 46% yield.
Stereoselective Ring Contraction of Symmetrical DKPs into Pyrrolidine-2,4-diones

1. tBuOK, THF, RT
2. H₃O⁺

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product (de)</th>
<th>Yield[ε] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (S)</td>
<td>3h (67%)[a,b]</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>iPr (S)</td>
<td>3i[c]&gt;95%)[b,d]</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>MeO₂C(CH₂)₂ (S)</td>
<td>3j (95%)[d]</td>
<td>29[f]</td>
</tr>
</tbody>
</table>

[a] The diastereoisomeric excess was determined by HPLC of crude.
[b] The relative configuration was determined by nOe analysis (concerning 3h: this determination occurred after separation of the two diastereoisomers)
[c] 3i was not isolated because 3i was obtained during the activation of cyclo-[L-Val-L-Val] in conventional conditions (Boc₂O, DMAP, DMF, r.t.).
[d] The ¹³C NMR spectrum gave only one set of peaks.
[e] Yield of isolated product after purification by flash chromatography.
[f] The product from retro-Michael reaction was obtained in 42% yield.
Tandem Rearrangement-alkylation of Symmetrical DKPs

1. LHMDS (2eq) THF, -78°C
2. RX (2eq)

1a

Boc- \begin{array}{c} \text{N} \\ \text{N} \\ \text{O} \\ \text{O} \end{array} \text{N-Boc}

\begin{align*}
\text{H} \\
\text{R} \\
\text{R} \\
\text{Boc} \\
\text{N} \\
\text{O} \\
\text{O} \\
\text{N-Boc}
\end{align*}

4a (R = allyl, 62%, de>95%)
4b (R = Bn, 57%, de>95%)
Tandem Rearrangement-alkylation of Unsymmetrical DKPs

1. LHMDS, THF, -78°C or NaH, THF, 0°C
2. R²X

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R¹</th>
<th>R²X</th>
<th>Product</th>
<th>Base</th>
<th>Yield[^b] [%] (de)</th>
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<tbody>
<tr>
<td>1</td>
<td>1e</td>
<td>iPr (R)</td>
<td>MeI</td>
<td>5a[^a]</td>
<td>LiHMDS</td>
<td>60 (&gt;95%)[^c]</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>NaH</td>
<td>63 (&gt;95%)[^c]</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>tBuOK</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1e</td>
<td>iPr (R)</td>
<td>BnBr</td>
<td>5b[^a]</td>
<td>LiHMDS</td>
<td>72 (&gt;95%)[^c]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaH</td>
<td>62 (&gt;95%)[^c]</td>
</tr>
<tr>
<td>3</td>
<td>1e</td>
<td>iPr (R)</td>
<td>EtO₂CCH₂I</td>
<td>5c</td>
<td>LiHMDS</td>
<td>69 (&gt;95%)[^c]</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>NaH</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>iPr (R)</td>
<td>CH₂=CHCH₂Br</td>
<td>5d</td>
<td>LiHMDS</td>
<td>76 (&gt;99%)[^d]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaH</td>
<td>75 (&gt;99%)[^d]</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>iPr (R)</td>
<td>(CH₃)₂C=CHCH₂Br</td>
<td>5e</td>
<td>LiHMDS</td>
<td>84 (&gt;95%)[^c]</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>sBu (S)</td>
<td>CH₂=CHCH₂Br</td>
<td>5f</td>
<td>LiHMDS</td>
<td>68 (&gt;95%)[^c]</td>
</tr>
</tbody>
</table>

[^a] The relative configuration was determined by nOe analysis.
[^b] Yield of isolated product after purification by flash chromatography.
[^c] The ¹³C NMR spectrum gave only one set of peaks.
[^d] The diastereoisomeric excess was determined by comparison of HPLC crude analysis between 5d and 7.
Plausible Mechanism to Explain the Stereochemistry

Related reactions: Dieckmann and Gabriel-Colman reaction; Dakin-West reaction
Scope Expansion: TRAL-Claisen Rearrangement

Stereochemistry controlled via chair-like TS

What can you do with compound 7?

Statin: constituent of the naturally occurring peptide antibiotic Pepstatin, which functions as an unselective inhibitor of acid proteases such as renin, pepsin and cathepsin D.
Summary and Future Directions

- Pyrrolidine-2,4-diones was synthesized in a single step via ring contraction from DKPs;

- Reaction conditions are mild and the reaction is highly stereoselective;

- This methodology will be extended to make statine derivatives;

- Diversity can be introduced to these heterocyclic building blocks for library synthesis;

- Pyrrolidine-2,4-diones may have potential use as chiral auxillary;

- These new amino-acid derivatives can be used for the synthesis of pseudo-peptides or peptoids.
Comments from the Audience

(1) A similar acyclic version of this kind of rearrangement has been published from the Wipf group (*Org. Lett.* 2001, 3, 1261.) The mechanism of this rearrangement is not totally clear. (Radical may be involved?)

(2) The stereochemistry of compounds 5(a-f) was not shown in Table 3, although in the supporting information they have this information.