STUDIES ON THE SYNTHESIS OF OPTICALLY ACTIVE AZALACTAMS

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Abstract—The optically active nine-membered azalactam, (S)-(−)-1,5-diaza-4-phenylcyclonan-2-one has been prepared starting with optically active (S)-(−)-6-phenyl-6-α-alanine methyl ester and 2-methoxypyrroline. Other studies with chiral esters of trans-cinnamic acid and piperidazine are reported.

In recent years there has been considerable interest in developing synthetic routes to macrocyclic spermine- and spermidine-derived alkaloids. We have previously described synthetic routes to azalactams such as (+)-celacinine and (+)-dihydroperiphylline, involving condensation of a β-lactam with a cyclic imino ether and/or conjugate addition of a piperidazine to esters of α,β-unsaturated carboxylic acids and successive ring expansion. We now describe studies on the use of these methods in the synthesis of an optically active nine-membered azalactam which is a key intermediate in the total synthesis of (S)-(−)-celacinine.

Optically active (S)-(−)-6-phenyl-6-α-alanine methyl ester (1) was heated with 2-methoxypyrroline (2) at 130 °C for 7 h to give the condensation product (S)-(−)-3 (76%) ([α]$_D^{25}$ +61.1° (c 2.5 in CHCl$_3$)). After reductive ring expansion of (S)-(−)-3 with 3 equiv. of NaBH$_3$CN in acetic acid, the nine-membered azalactam (S)-(−)-4 (31%) ([α]$_D^{25}$ -134° (c 0.94 in CHCl$_3$)) was obtained along with (S)-(−)-5 (32%) ([α]$_D^{25}$ -27° (c 1.4 in CHCl$_3$)). (S)-(−)-5 ([α]$_D^{25}$ -27° (c 1.5 in CHCl$_3$)) was also prepared by simple reduction of (S)-(−)-3 with NaBH$_4$ in methanol. (Scheme 1)
In addition, from the deuterium labeled experiment (NaBD₃CN/CH₃COOD) outlined in Scheme 2, two deuterium atoms were observed at the 6-position of the nine-membered azalactam (+)-4-d₂. No deuterium was found at the C-4 benzylic position.⁹ These results show that one may retain chirality during the reductive cleavage and prepare chiral celacinnine without substantial racemization by this route.

Optically active nine-membered azalactam (4) could also be prepared by conjugate addition of the piperidazine 7 to chiral esters of trans-cinnamic acid (6) followed by a reductive ring expansion of 8 using Na/NH₃ (Scheme 3). Thus far, this method has shown only a small enrichment of one enantiomer by an asymmetric induction effect.

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*S-CC-~

Scheme 1.

Scheme 2.
Scheme 3.

Table 1. Conjugate Addition of Piperidazine 7 to Chiral Esters of trans-Cinnamic Acid 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ester 6</th>
<th>Reaction conditions</th>
<th>Condensation product 8</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Solvent  Temp. (°C)</td>
<td>Time (days)</td>
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<tr>
<td>1</td>
<td>6a</td>
<td>C6H6 80</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>6a</td>
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<tr>
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<td>6a</td>
<td>C6H6 25</td>
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<tr>
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<td>CH3OH 65</td>
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<tr>
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<td>25</td>
</tr>
<tr>
<td>6</td>
<td>6b</td>
<td>C6H6 80</td>
<td>2</td>
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</table>

a) Isolated yield.

b) The reaction was carried out in ether (20 ml) - HMPA (5 ml) using magnesium salts of 7 (20 mmol) and 6a (10 mmol) at room temperature.

In a typical procedure, a benzene solution (10 ml) of piperidazine 7 (30 mmol) and 1,2:5,6-diisopropylidene-D-glucosyl cinnamate 6a10 (15.9 mmol) was stirred for 2 days under benzene-reflux conditions to give the condensation product (-)-8 (8.8 mmol; 56%) ([α]25 D -18.4° (c 7 in CHCl3))11 after silica gel column
chromatography (ethyl acetate as an eluent) of the crude reaction mixture (Table 1, entry 1). The N-N bond of (-)-8 was readily cleaved (Na/NH₃)² to afford the nine-membered azalactam (-)-4 (70%) ([α]D²⁵ -16.8° (c 5.2 in CHCl₃))¹². In a similar manner, a benzene solution (6 ml) of 7 (16.3 mmol) and (-)-menthyl cinnamate 6b (10 mmol) was refluxed for 2 days to give (+)-8 (5.1 mmol; 51%) ([α]D²⁵ +15.4° (c 4.7 in CHCl₃))¹⁴ (Table 1, entry 6). The nine-membered azalactam (+)-4 (80%) ([α]D²⁵ +14.4° (c 2.1 in CHCl₃))¹⁵ was obtained by reduction (Na/NH₃) of (+)-8. The results, showing only a modest enantiomeric excess in the formation of 4, serve to permit the assignment of absolute configuration of (-)-4 as S and (+)-4 as R.

The absolute configuration and enantiomeric excess (%) ee of 4 formed by asymmetric conjugate addition were determined in comparison with authentic nine-membered azalactam (S)-(-)-4 ([α]D²⁵ -134°) (Scheme 4). According to the above results, the enantiomeric excess of 4 is 11 to 13% ee.

Application of these procedures to a total synthesis of optically active (S)-(-)-celacinnine is in progress.

Scheme 4.

(-)-8 [α]D -18.4°
(+)-8 [α]D +15.4°

(-)-4 [α]D -16.8° (S) (12.5% ee)
(+)-4 [α]D +14.4° (R) (10.7% ee)
REFERENCES


5. (S)-(-)-5 could be obtained as its L-(+)-tartrate salt according to the procedure of Pietsch. [α]D -13.7° (neat) (lit. [α]D -12.9° (neat); H. Pietsch, Tetrahedron Lett., 1972, 2789).

6. (S)-(+) -3: mp 109 - 110 °C (cyclohexane); Mass (m/e) 214 (M⁺); ir (KBr) 1700, 1670 cm⁻¹; ¹H-nmr (60 MHz, CDC13) δ 1.70 - 2.30 (2 H, m, N-C-CH₂-C), 2.40 - 3.00 (4 H, m, CO-CH₂, CH₂-N-CO), 3.73 (2 H, t, J= 7 Hz, N=C-CH), 4.50 - 5.00 (1 H, m, Ph-CH), 7.27 (5 H, s, phenyl); (S)-(+) -1,5-diaza-4-phenylbicyclo[4.3.1]non-5-en-2-one; Borman has reported a synthesis of racemic-5 (D. Borman, Chem. Ber., 1970, 103, 1797).

7. (S)-(--) -4: Mass (m/e) 218 (M⁺); ir (CDCl₃) 3340, 1670, 1550 cm⁻¹; ¹H-nmr (60 MHz, CDCl₃) δ 1.33 - 2.00 (5 H, m, N-C-CH₂CH₂-C-N, NH), 2.37 (1 H, s, CO-CH), 2.50 (1 H, d, J= 5 Hz, CO-CH), 2.63 - 3.10 (3 H, m, CH₂-N, CH-N-CO), 3.40 - 4.00 (2 H, m containing dd at 3.58 (J= 4, 10 Hz, Ph-CH), CH-N-CO), 6.80 - 7.10 (1 H, broad s, NH-CO), 7.27 (5 H, s, phenyl); (S)-(--) -1,5-diaza-4-phenylcycloheptan-2-one.

8. (S)-(--) -5: Mass (m/e) 216 (M⁺); ir (CDCl₃) 1630 cm⁻¹; ¹H-nmr (60 MHz, CDCl₃) δ 1.50 - 2.80 (5 H, m containing d at 2.78 (J= 6 Hz), N-C-CH₂CH₂-C-N, NH, CO-CH₂), 3.40 - 3.80 (1 H, m, CO-N-CH), 4.00 - 4.30 (1 H, m, Ph-CH), 4.40 -
4.70 (1 H, m, CO-N-CH), 7.27 (5 H, s, phenyl); (S)-(-)-1,5-diaza-4-phenylbicyclo[4.3.0]nonan-2-one.

9. 4-d2: Mass (m/e) 220 (M+); 1H-nmr (60 MHz, CDCl3) δ 1.40 - 2.20 (5 H, m, N-C-CH2CH2-C-N, NH), 2.37 (1 H, s, CO-CH), 2.38 (1 H, d, J= 6 Hz, CO-CH), 2.67 - 3.10 (1 H, m, CH-N-CO), 3.40 - 4.00 (2 H, m containing dd at 3.62 (J= 4, 10 Hz, Ph-CH), CH-N-CO), 6.80 - 7.10 (1 H, broad s, NH-CO), 7.27 (5 H, s, phenyl).

10. 6a: [α]D25 75.6° (c 3.57 in C6H6) (lit. [α]D8 70° (c 3.28 in C6H6); M. Kawana and S. Emoto, Bull. Chem. Soc. Jpn., 1966, 39, 910).

11. (-)-8: Mass (m/e) 216 (M+); ir (CDCl3) 1675 cm^-1; 1H-nmr (60 MHz, CDCl3) δ 1.20 - 1.90 (4 H, m, N-C-CH2CH2-C-N), 2.07 - 3.20 (5 H, m, CH2-N-N-CO, CH-N-CO, CO-CH2), 3.83 (1 H, dd, J= 8, 11 Hz, N-CH-Ph), 4.00 - 4.30 (1 H, broad d, CH-N-CO), 7.27 (5 H, s, phenyl); 1,5-diaza-4-phenylbicyclo[3.4.0]nonan-2-one.

12. (-)-4: Mass (m/e) 218 (M+); ir (CDCl3) 3340, 1670, 1550 cm^-1.


14. (+)-8: Mass (m/e) 216 (M+); ir (CDCl3) 1675 cm^-1.

15. (+)-4: Mass (m/e) 218 (M+); ir (CDCl3) 3340, 1670, 1550 cm^-1.

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