STUDIES ON THE SYNTHESIS OF OPTICALLY ACTIVE AZALACTAMS

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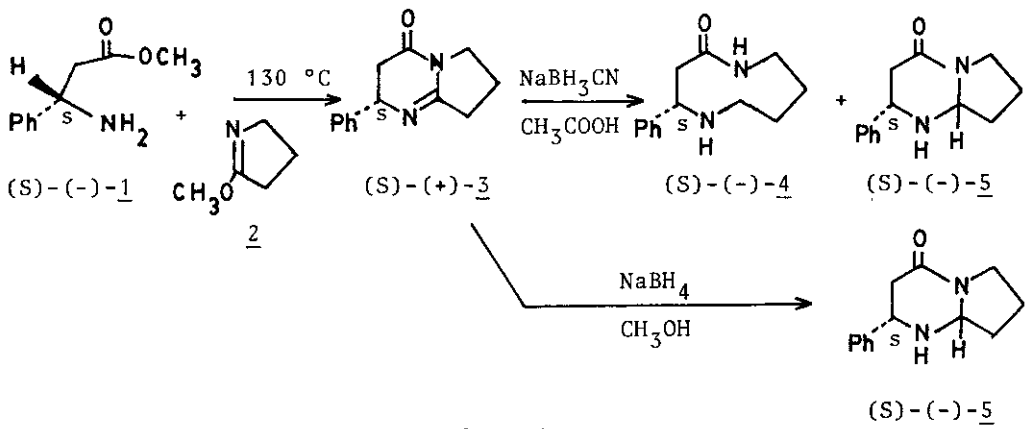
Abstract—The optically active nine-membered azalactam, (S)-(-)-1,5-diaza-4-phenylcyclononan-2-one has been prepared starting with optically active (S)-(-)-β-phenyl-β-alanine methyl ester and 2-methoxypyrroline. Other studies with chiral esters of trans-cinnamic acid and piperidazine are reported.

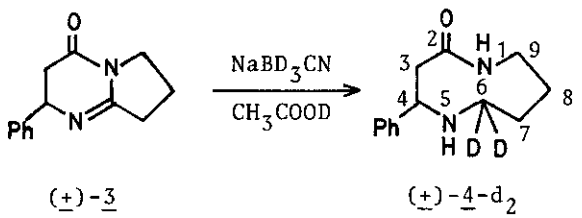
In recent years there has been considerable interest in developing synthetic routes to macrocyclic spermine- and spermidine-derived alkaloids.[1] We have previously described synthetic routes to azalactams such as (±)-celacinnine and (±)-dihydroperiphylline, involving condensation of a β-lactam with a cyclic imino ether and/or conjugate addition of a piperidazine to esters of α,β-unsaturated carboxylic acids and successive ring expansion.[2,3] 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)-(-)-celacinnine.[2,4]

Optically active (S)-(-)-β-phenyl-β-alanine methyl ester (1)[5] was heated with 2-methoxypyrroline (2) at 130 °C for 7 h to give the condensation product (S)-(+)-3 (76%) ($[\alpha]_D^{25}$ +61.1° (c 2.5 in $CHCl_3$))[6]. After reductive ring expansion of (S)-(+)-3 with 3 equiv. of $NaBH_3CN$ in acetic acid,[2] the nine-membered azalactam (S)-(-)-4 (31%) ($[\alpha]_D^{25}$ -134° (c 0.94 in $CHCl_3$))[7] was obtained along with (S)-(-)-5 (32%) ($[\alpha]_D^{25}$ -27° (c 1.4 in $CHCl_3$))[8]. (S)-(-)-5 ($[\alpha]_D^{25}$ -27° (c 1.5 in $CHCl_3$)) was also prepared by simple reduction of (S)-(+)-3 with $NaBH_4$ in methanol. (Scheme 1)



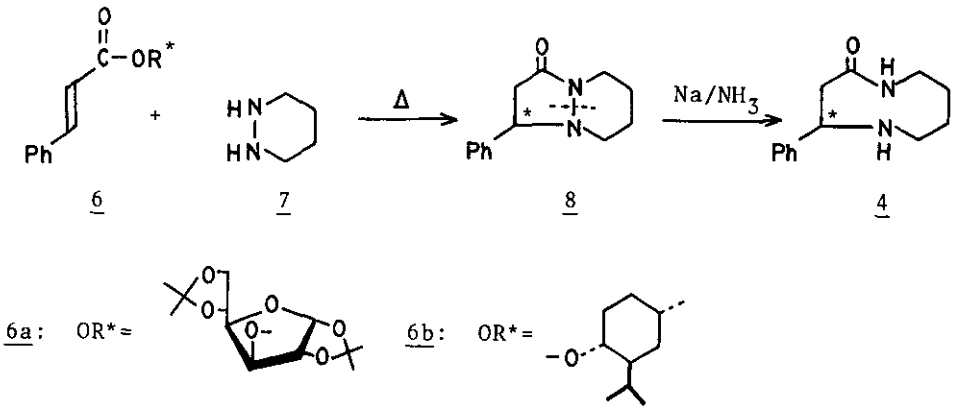
Scheme 1.

In addition, from the deuterium labeled experiment ($NaBD_3CN/CH_3COOD$) outlined in Scheme 2, two deuterium atoms were observed at the 6-position of the nine-membered azalactam (±)-4-d_2. 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.



Scheme 2.

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/NH_3 (Scheme 3). Thus far, this method has shown only a small enrichment of one enantiomer by an asymmetric induction effect.



6 7 8 4

6a: OR*= 6b: OR*=

Scheme 3.

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

Entry	Ester 6	Reaction conditions			Condensation product 8	
		Solvent	Temp. (°C)	Time (days)	Yield/%[a]	$[\alpha]_D^{25}$ ($CHCl_3$) (deg.)
1	6a	C_6H_6	80	2	56	-18.4
2	6a	C_6H_6	80	2	52	-16.0
3	6a	C_6H_6	25	6	31	-21.0
4	6a	CH_3OH	65	2	42	-0.3
5	6a	CH_3MgI[b]	25	1	80	0
6	6b	C_6H_6	80	2	51	+15.4

a) Isolated yield.

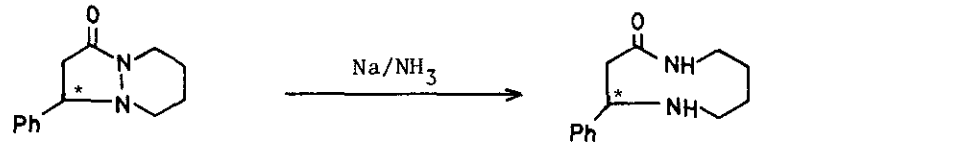
b) The reaction was carried out in ether (20 ml) - HMPA (5 ml) using magnesium salts of 7 (20 mmol) and 6a (10 mmol) at room temperature.

In a typical procedure, a benzene solution (10 ml) of piperidazine 7 (30 mmol) and 1,2:5,6-diisopropylidene-D-glucosyl cinnamate 6a[10] (15.9 mmol) was stirred for 2days under benzene-reflux conditions to give the condensation product (-)-8 (8.8 mmol; 56%) ($[\alpha]_D^{25}$ -18.4° (c 7 in $CHCl_3$))[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/NH_3)[2] to afford the nine-membered azalactam (-)-4 (70%) ($[\alpha]_D^{25}$ -16.8° (c 5.2 in $CHCl_3$))[12]. In a similar manner, a benzene solution (6 ml) of 7 (16.3 mmol) and (-)-menthyl cinnamate 6b[13] (10 mmol) was refluxed for 2 days to give (+)-8 (5.1 mmol; 51%) ($[\alpha]_D^{25}$ +15.4° (c 4.7 in $CHCl_3$))[14] (Table 1, entry 6). The nine-membered azalactam (+)-4 (80%) ($[\alpha]_D^{25}$ +14.4° (c 2.1 in $CHCl_3$))[15] was obtained by reduction (Na/NH_3) 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 ($[\alpha]_D^{25}$ -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.



(-)-8 $[\alpha]_D$ -18.4° (-)-4 $[\alpha]_D$ -16.8° (S) (12.5% ee)

(+)-8 $[\alpha]_D$ +15.4° (+)-4 $[\alpha]_D$ +14.4° (R) (10.7% ee)

Scheme 4.

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1. For reviews: (a) H. H. Wasserman and J. S. Wu, Heterocycles, 1982, 17, 581; H. Matsuyama, J. Synth. Org. Chem. Jpn., 1981, 39, 1151.
2. H. H. Wasserman, R. P. Robinson, and H. Matsuyama, Tetrahedron Lett., 1980, 3493.
3. H. H. Wasserman and H. Matsuyama, J. Am. Chem. Soc., 1981, 103, 461.
4. The absolute configuration of natural celacinnine ($[\alpha]_D$ -19° (c 0.16 in $CHCl_3$)) has not yet been determined. According to the stereochemistry of the related alkaloid, (S)-(-)-homaline ($[\alpha]_D$ -31° (c 0.40 in $CHCl_3$)), the configuration at the benzylic position of (-)-celacinnine would be (S): for (-)-celacinnine: S. M. Kupchan, H. P. J. Hintz, R. M. Smith, A. Karim, M. W. Cass, W. A. Court, and M. Yatagai, J. Org. Chem., 1977, 42, 3660. For total synthesis of (S)-(-)-homaline: (a) H. H. Wasserman, G. D. Berger, and K. R. Cho, Tetrahedron Lett., 1982, 465; (b) L. Crombie, R. C. F. Jones, A. R. Mat-Zin, and S. Osborne, J. Chem. Soc., Chem. Commun., 1983, 960.
5. (S)-(-)-1 could be obtained as its L-(+)-tartrate salt according to the procedure of Pietsch. $[\alpha]_D^{24}$ -13.7° (neat) (lit. $[\alpha]_D^{24}$ -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}; ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.70 - 2.30 (2 H, m, N-C-CH_2-C), 2.40 - 3.00 (4 H, m, CO-CH_2, CH_2-N-CO), 3.73 (2 H, t, J= 7 Hz, N=C-CH_2), 4.50 - 5.00 (1 H, m, Ph-CH), 7.27 (5 H, s, phenyl); (S)-(+)-1,5-diaza-4-phenylbicyclo[4.3]-non-5-en-2-one; Borman has reported a synthesis of racemic-3 (D. Borman, Chem. Ber., 1970, 103, 1797).
7. (S)-(-)-4: Mass (m/e) 218 (M^+); ir ($CDCl_3$) 3340, 1670, 1550 cm^{-1}; ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.33 - 2.00 (5 H, m, N-C-CH_2CH_2-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, CH_2-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-phenylcyclononan-2-one.
8. (S)-(-)-5: Mass (m/e) 216 (M^+); ir ($CDCl_3$) 1630 cm^{-1}; ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.50 - 2.80 (5 H, m containing d at 2.78 (J= 6 Hz), N-C-CH_2CH_2-C-N, NH, CO-CH_2), 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-phenyl-bicyclo[4.3]nonan-2-one.

9. 4-d_2: Mass (m/e) 220 (M^+); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.40 - 2.20 (5 H, m, N-C-CH_2CH_2-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: $[\alpha]_D^{25}$ -75.6° (c 3.57 in C_6H_6) (lit. $[\alpha]_D^{18}$ -70° (c 3.28 in C_6H_6); M. Kawana and S. Emoto, Bull. Chem. Soc. Jpn., 1966, 39, 910).
11. (-)-8: Mass (m/e) 216 (M^+); ir ($CDCl_3$) 1675 cm^{-1}; ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.20 - 1.90 (4 H, m, N-C-CH_2CH_2-C-N), 2.07 - 3.20 (5 H, m, CH_2-N-N-CO, CH-N-CO, CO-CH_2), 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]-nonan-2-one.
12. (-)-4: Mass (m/e) 218 (M^+); ir ($CDCl_3$) 3340, 1670, 1550 cm^{-1}.
13. 6b: $[\alpha]_D^{25}$ -60.2° (c 8.82 in $CHCl_3$) (lit. $[\alpha]_D$ -59.7° ; H. Nozaki, H. Ito, D. Tsunemoto, and K. Kondo, Tetrahedron, 1966, 22, 441).
14. (+)-8: Mass (m/e) 216 (M^+); ir ($CDCl_3$) 1675 cm^{-1}.
15. (+)-4: Mass (m/e) 218 (M^+); ir ($CDCl_3$) 3340, 1670, 1550 cm^{-1}.

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