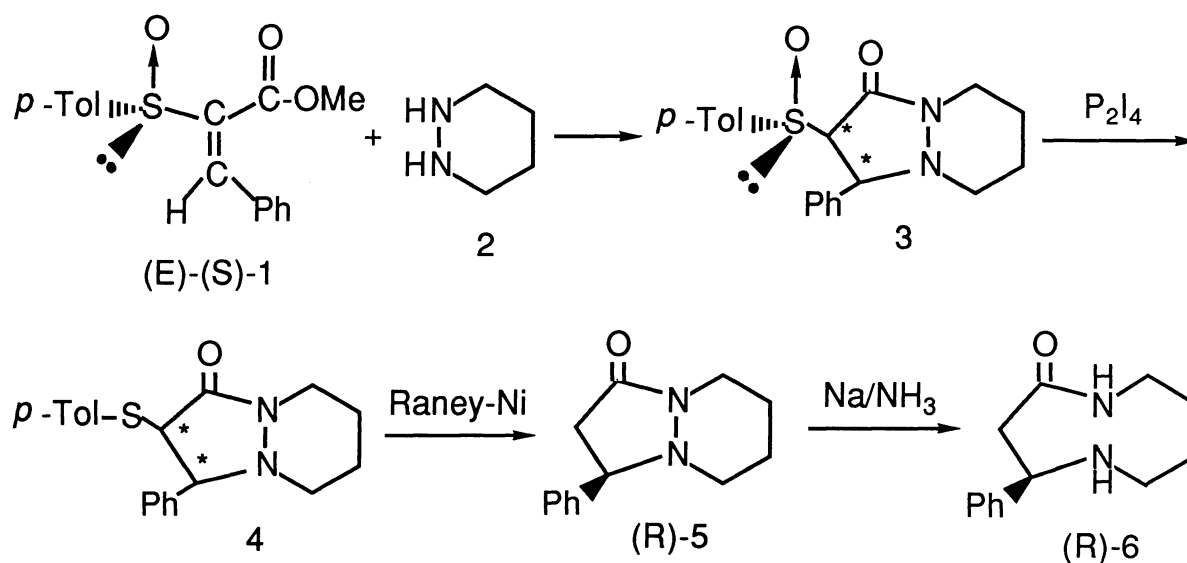


Diastereoselective Conjugate Addition of Cyclic Hydrazine to Optically Active Vinyl Sulfoxide. A Novel Synthesis of Optically Active Azalactams

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Optically active (*R*)-(+)-1,5-diaza-4-phenylbicyclo[4.3.0]nonan-2-one (**5**) was prepared in high optical purity by diastereoselective conjugate addition of piperidine to optically active (*E*)-(*S*)-1-(methoxycarbonyl)-2-phenylvinyl *p*-tolyl sulfoxide, followed by successive reduction of *p*-tolylsulfinyl group. Nine-membered azalactam was obtained by reductive cleavage of N-N bond of **5**.

Recently, much attention has been focused on the stereoselective synthesis of interesting natural compounds utilizing optically active sulfoxides.¹⁾ We have been interested in the conjugate addition of cyclic hydrazine to optically active vinyl sulfoxide for synthesis of optically active nine-membered azalactam, which is a key intermediate in the total synthesis of natural celacinnine.²⁾ We report here a new sequence for the synthesis of optically active azalactams (Scheme 1).



Scheme 1.

Piperidazine (2) (1 mmol) was allowed to react with (*E*)-(*S*)-1-(methoxycarbonyl)-2-phenylvinyl *p*-tolyl sulfoxide (1) ³⁾ (o.p. 93%) (0.5 mmol) in THF (10 cm³) at room temperature for 1.5 h to afford the bicyclic adduct, 1,5-diaza-3-(*S*)-*p*-tolylsulfinyl-4-phenylbicyclo[4.3.0]nonan-2-one (3). The reduction of 3 with diphosphorous tetraiodide⁴⁾ gave *cis*-4 (49%)⁵⁾ as the major product and *trans*-4 (2%) as the minor product. Similarly, (*S*)- and (*R*)-1 were allowed to react with 2 under several conditions, and the results are summarized in Table 1. When the reaction was performed in methanol, *trans*-4 (25%) and *cis*-4 (39%) were obtained (Entry 3). After removal of *p*-tolylthio group of 4 by reduction (25%) with Raney-Ni in ethanol, the absolute configuration and optical purity (o.p. %) of 5 were determined in comparison with the authentic compounds.⁶⁾ The bicyclic compound (+)-5 obtained from (*S*)-1 and 2 has (*R*)-configuration with 82% o.p. (stereoselectivity 88%) (Entry 1), on the other hand, the enantiomer having opposite absolute stereochemistry, (*S*)-(-)-5 with 50% o.p. (stereoselectivity 52%), was formed starting with (*R*)-1 and 2 (Entry 4). The reaction of (*S*)-1 and 2 was carried out in the presence of ZnCl₂, however, the optical purity (86%) of (*R*)-5 obtained was similar to that of the reaction in the absence of ZnCl₂ (Entry 5).

Table 1. Conjugate Addition of Piperidazine (2) to Vinyl Sulfoxides 1

Entry ^{a)}	Vinyl sulfoxide	Solvent	Product 4 from 1	Yield/% ^{b)}	[α] _D ^{c)}	Product 5 from 4	Yield/% ^{b)}	[α] _D ^{c)} (o.p.%) ^{d)}
1	(<i>S</i>)-1	THF	<i>cis</i> -4	49	+171	(<i>R</i>)-5	25	+120 (82)
			<i>trans</i> -4	2	-18	--e)		
2	(<i>R</i>)-1	THF	<i>cis</i> -4	55	-189	(<i>S</i>)-5	25	-71 (48)
			<i>trans</i> -4	3	+19	--e)		
3	(<i>S</i>)-1	MeOH	<i>cis</i> -4	39	+202	(<i>R</i>)-5	19	+120 (82)
			<i>trans</i> -4	25	-20	(<i>R</i>)-5	20	+120 (82)
4	(<i>R</i>)-1	MeOH	<i>cis</i> -4	4	-236	--e)		
			<i>trans</i> -4	28	+24	(<i>S</i>)-5	25	-74 (50)
5	(<i>S</i>)-1	THF ^{f)}	<i>cis</i> -4	56	+202	(<i>R</i>)-5	25	+127 (86)
			<i>trans</i> -4	4	-19	--e)		

a) The optical purity of vinyl sulfoxides 1 was determined by HPLC analysis using a chiral column (BakerbondTM Chiral Phase (DNBPG); solvent, hexane: *i*-PrOH= 95: 5; (*R*)-1-first eluted): (*S*)-1, 93%; (*R*)-1, 96%. b) Isolated yield. c) deg.; solvent: chloroform. d) The optical purity was determined in comparison with the authentic compound (*S*)-(-)-5: [α]_D -147° (o.p. 100%) (Ref. 6). e) The reduction of 4 did not be performed. f) ZnCl₂ (1 equiv.) was added.

On the basis of stereochemistry of (*R*)-**5** obtained from (*S*)-**1**, the mechanism of asymmetric induction may be explained as follows: the preferred non-chelate conformation of (*S*)-**1** will be expected to be that one in which the dipoles of the carbonyl and sulfinyl groups are oriented in opposite directions, as shown in Fig. 1.⁷⁾ The selectivity of diastereoface in conjugate addition of nitrogen nucleophile might be controlled by the hydrogen bonding interaction between sulfoxide (*S*)-**1** and piperidazine (**2**). Piperidazine attacks on β -carbon atom of (*S*)-**1** from *si*-face, followed by protonation of carbanion from the same face, and successive cyclization of hydrazine with ester to afford selectively *cis*-**3** in aprotic solvent, THF. In methanol, protonation of carbanion can take place from both faces to give *trans*-**3** and *cis*-**3**.

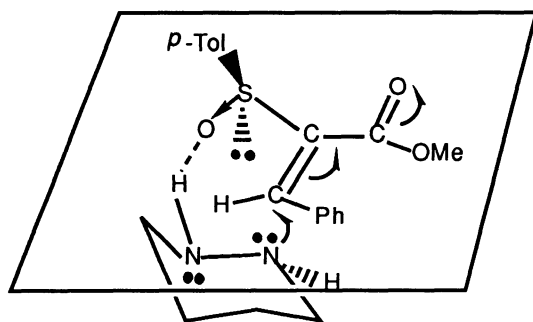


Fig. 1. Proposed mechanism in the conjugate addition of **2** to (*E*)-(*S*)-**1**.

The reductive cleavage of N-N bond of (*R*)-**5**, $[\alpha]_D^{+102^\circ}$ (c 1.7, CHCl_3) (o.p. 69%), with sodium in liquid ammonia gave nine-membered azalactam, (*R*)-1,5-diaza-4-phenylnonan-2-one (**6**), $[\alpha]_D^{+90^\circ}$ (c 0.5, CHCl_3) (o.p. 67%), in 77% yield.⁸⁾

This asymmetric synthesis of optically active azalactams utilizing optically active sulfoxide is a simple and useful process, and the application of this method for the synthesis of the natural polyamine alkaloids is in progress.⁹⁾

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celacinnine: H. H. Wasserman, R. P. Robinson, and H. Matsuyama, *Tetrahedron Lett.*, **1980**, 3493.

- 3) Sulfoxide (*E*)-(*S*)-1, $[\alpha]_D +219^\circ$ (c 1.0, CHCl_3) (o.p. 93%), was prepared by one-pot α -lithiation of (*E*)-(*R*)-2-phenylvinyl *p*-tolyl sulfoxide, $[\alpha]_D +153^\circ$ (c 1.0, CHCl_3) (o.p. 93%), followed by carboxylation and esterification in 64% yield: S. House, P. R. Jenkins, J. Fawcett, and D. R. Russel, *J. Chem. Soc., Chem. Commun.*, **1987**, 1844; G. H. Posner, J. P. Mallamo, and K. Miura, *J. Am. Chem. Soc.* **103**, 2886 (1981). (*E*)-(*S*)-1: mp 67-69 °C (hexane-ether); MS m/z 300 (M^+), 284, 252 (100%), 213, 193; ^1H NMR (60MHz, CDCl_3) δ 2.36 (3H, s, *p*- CH_3), 3.54 (3H, s, OCH_3), 7.00-7.70 (10H, m, C_6H_4 - and $\text{C}_6\text{H}_5\text{-CH=}$); IR (KBr) 1720 (C=O), 1615 (C=C), 1055 cm^{-1} (S=O); HRMS: Calcd for $\text{C}_{19}\text{H}_{16}\text{O}_3\text{S}$: 300.0821. Found: 300.0886; (*E*)-(*R*)-1, $[\alpha]_D -224^\circ$ (c 1.0, CHCl_3) (o.p. 96%), was also prepared from (*E*)-(*S*)-2-phenylvinyl *p*-tolyl sulfoxide, $[\alpha]_D -158^\circ$ (c 1.0, CHCl_3) (o.p. 96%).
- 4) The bicyclic adduct **3** degraded slowly to afford the unsaturated bicyclic compound and *p*-toluenesulfenic acid (GC-MS, m/z 140 (M^+)) by *syn*-elimination at room temperature: For P_2I_4 reduction of sulfoxides: J. N. Denis and A. Krief, *Tetrahedron Lett.*, **1979**, 3995.
- 5) *Cis*-1,5-diaza-3-*p*-tolylthio-4-phenylbicyclo[4.3.0]nonan-2-one (**4**): $[\alpha]_D +171^\circ$ (c 0.40, CHCl_3); (R_f = 0.27 on silica gel TLC; hexane: AcOEt = 2: 1); ^1H NMR (60MHz, CDCl_3) δ 3.98 (1H, d, J = 7.8 Hz, S-CH), 4.19 (1H, d, J = 7.8 Hz, $\text{C}_6\text{H}_5\text{-CH}$); IR (neat) 1675 cm^{-1} (C=O); MS m/z 338 (M^+), 215, 173, 131, 124, 103, 91, 77. *Trans*-4: $[\alpha]_D -20^\circ$ (c 1.0, CHCl_3); (R_f = 0.19; hexane: EtOAc = 2: 1); ^1H NMR (60 MHz, CDCl_3) δ 3.58 (2H, s, S-CH and $\text{C}_6\text{H}_5\text{-CH}$); MS m/z 338 (M^+).
- 6) The absolute configuration of (+)-**5** was reported as being the (*R*)-form, and (-)-**5** as the (*S*)-form: H. Matsuyama, M. Kobayashi, and H. H. Wasserman, *Heterocycles*, **26**, 85 (1987); The calculated value of optically pure (*S*)-(-)-**5** is $[\alpha]_D -147^\circ$. (*R*)-(+)-**5**: IR (CDCl_3) 1675 cm^{-1} (C=O); HRMS: Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$: 216.1263. Found: m/z 216.1283 (M^+).
- 7) B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).
- 8) (*R*)-(+)-**6**: ^1H NMR (200 MHz, CDCl_3) δ 1.33-2.00 (5H, m, N-C- $\text{CH}_2\text{CH}_2\text{-C-N}$, NH), 2.54 (1H, dd, J = 3.2, 12.5 Hz, CO-CH), 2.80-3.10 (3H, m, CH_2N , CH-N-CO), 3.34 (1H, t, J = 12.5 Hz, CO-CH), 3.74-3.94 (1H, m, CH-N-CO), 4.22 (1H, dd, J = 3.2, 12.5 Hz, $\text{C}_6\text{H}_5\text{-CH}$), 7.22-7.50 (5H, m, C_6H_5), 7.59 (1H, broad s, NH-CO); IR (CDCl_3) 3340, 1670, 1550 cm^{-1} ; HRMS: Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$: 218.1419. Found: m/z 218.1430 (M^+). Authentic nine-membered azalactam (*S*)-(-)-**6**, $[\alpha]_D -134^\circ$ (c 0.94, CHCl_3), was prepared using optically active (*S*)-(-)- β -phenyl- β -alanine methyl ester (o.p. 100%) and 2-methoxypyrroline (Ref. 6).
- 9) The β -phenyl- β -alanyl residue has generally been found in various natural products; For total synthesis of (*S*)-(+)-dihydroperiphylline: T. Kaseda, T. Kikuchi, and C. Kibayashi, *Tetrahedron Lett.*, **1989**, 4539, and references cited therein.

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