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

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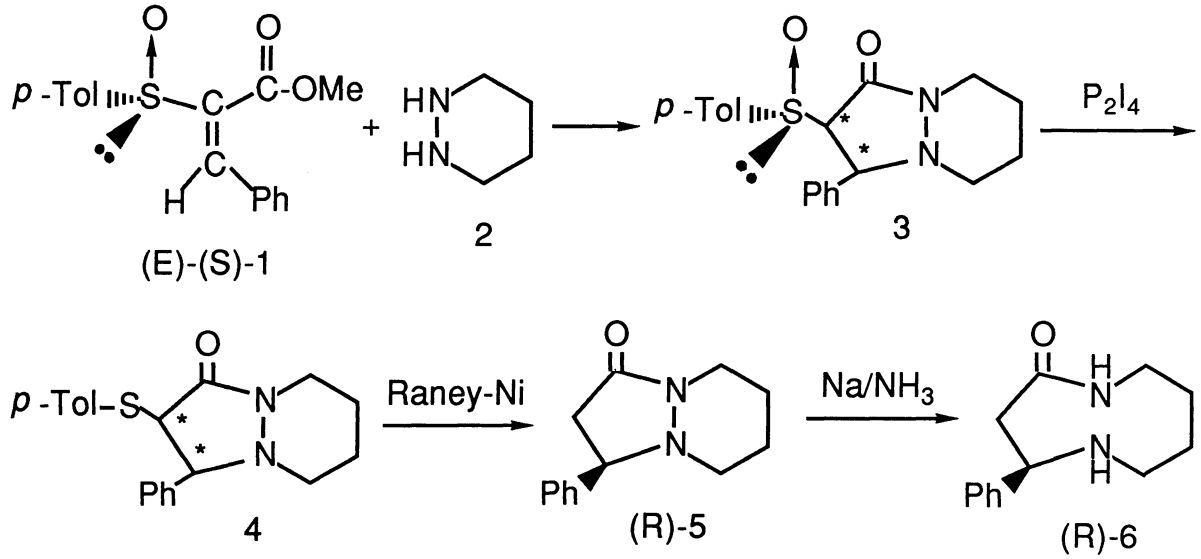
Optically active (*R*)-(+)-1,5-diaza-4-phenylbicyclo[4.3.0]nonan-2-one (**5**) was prepared in high optical purity by diastereoselective conjugate addition of piperidazine to optically active (*E*)-(*S*)-1-(methoxycarbonyl)-2-phenylviny *p*-tolyl sulfoxide, followed by successive reduction of *p*-tolylsulfinyl 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 cm^3) 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 tetraiodide[4] 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 $ZnCl_2$, however, the optical purity (86%) of (*R*)-**5** obtained was similar to that of the reaction in the absence of $ZnCl_2$ (Entry 5).

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

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

a) The optical purity of vinyl sulfoxides **1** was determined by HPLC analysis using a chiral column (Bakerbond™ 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**: $[\alpha]_D$ -147° (o.p. 100%) (Ref. 6). e) The reduction of **4** did not be performed. f) $ZnCl_2$ (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**.

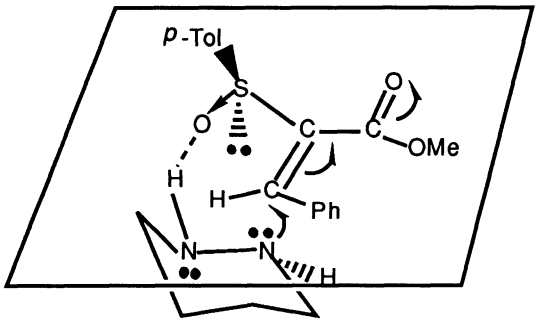


Fig. 1. Proposed mechanism in the conjugate addition of **2** to (*E*)-(*S*)-**1**.

The reductive cleavage of N-N bond of (*R*)-**5**, $[\alpha]_D$ +102° (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° (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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References

1) Asymmetric Diels-Alder reaction: Y. Arai, Y. Hayashi, M. Yamamoto, H. Takayama, and T. Koizumi, *J. Chem. Soc., Perkin Trans.* 1, **1988**, 3133; For a review: G. H. Posner, "Addition of Organometallic Reagents to Chiral Vinylic Sulfoxides," in "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1983), Vol. **2**, pp. 225-241.

2) For a review: H. H. Wasserman and J. S. Wu, *Heterocycles*, **17**, 581 (1982); 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.*, **42**, 3660 (1977); For total synthesis of (±)-

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

3) Sulfoxide (*E*)-(*S*)-**1**, $[\alpha]_D$ +219° (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° (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 C_6H_5-CH=); IR (KBr) 1720 (C=O), 1615 (C=C), 1055 cm^{-1} (S=O); HRMS: Calcd for $C_{19}H_{16}O_3S$: 300.0821. Found: 300.0886; (*E*)-(*R*)-**1**, $[\alpha]_D$ -224° (c 1.0, $CHCl_3$) (o.p. 96%), was also prepared from (*E*)-(*S*)-2-phenylvinyl *p*-tolyl sulfoxide, $[\alpha]_D$ -158° (c 1.0, $CHCl_3$) (o.p. 96%).

4) The bicyclic adduct **3** degradated 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° (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, C_6H_5-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° (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 C_6H_5-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°. (*R*)-(+)-**5**: IR ($CDCl_3$) 1675 cm^{-1} (C=O); HRMS: Calcd for $C_{13}H_{16}N_2O$: 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-CH_2CH_2-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, C_6H_5-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 $C_{13}H_{18}N_2O$: 218.1419. Found: *m/z* 218.1430 (M^+). Authentic nine-membered azalactam (*S*)-(-)-**6**, $[\alpha]_D$ -134° (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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