ASYMMETRIC SYNTHESIS OF CELACINNINE UTILIZING OPTICALLY ACTIVE VINYL SULFOXIDES

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Abstract–First asymmetric synthesis of celacinnine (**10**) was achieved from the nine-membered azalactam, 3-phenyl-4-azaoctanelactam (**6**), which was synthesized by the addition of piperidazine (**4**) to optically active vinyl sulfoxides (**3**).

Polyamine conjugates are widespread in numerous plant families,[1] and many unique polyamine alkaloids are antibiotics and antihypertensive.[2] Our continuing interest in the development of synthetic pathways to the polyamine macrocycles has prompted us to investigate the synthesis of the optically active nine-membered azalactam, 3-phenyl-4-azaoctanelactam[3] (**6**), that is a key intermediate in the total synthesis of natural 13-membered polyamine alkaloids, celacinnine[4] and *N*(1)-acetyl-*N*(1)-deoxymayfoline.[5]

Celacinnine was isolated in 1974 from *Maytenus arbutifolia* and *Tripterugium wilfordii*. Although total synthesis of racemic celacinnine has been reported by three independent groups,[6] the absolute configuration of natural celacinnine has not yet been determined. The configuration at the benzylic position of (-)-celacinnine ($[\alpha]_D$ -19° (*c* 0.16, $CHCl_3$)) has only been estimated to be (*S*) according to the stereochemistry of the related alkaloid, (*S*,*S*)-homaline ($[\alpha]_D$ -34° (*c* 1, $CHCl_3$)).[7]

Recently, enantiomerically pure vinyl sulfoxides have proved to be useful reagents in stereoselective syntheses.[8] Our synthetic approach to **6** is outlined in Scheme 1, which involves the addition of six-memberd hydrazine (**4**) to optically active vinyl sulfoxides (**3**), followed by successive reduction of the *p*-tolylsulfinyl group with SmI_2[9] and reductive cleavage of the N-N bond of 9-phenyl-1,6-diazabicyclo[4.3.0]nonan-7-one (**5**). The optically pure vinyl sulfoxides (*S*)- and (*R*)-**3** were synthesized from (*S*)- and (*R*)-*t*-butyl *p*-tolylsulfinyl-acetate (**1**) *via* **2**.[10] Addition of the carbanion derived from *t*-butyl *p*-tolylsulfinylacetate (**1**) to

benzaldehyde,[10] followed by treatment with acetyl chloride and pyridine in ether gave optically active (*E*)-**3** [(*S*): o.p. 91%; (*R*): o.p. 93%] in 60% yield with a small amount of the (*Z*)-isomer. The optically pure vinyl sulfoxides (**3**) were easily obtained by recrystallization.

The reactions of (*S*)-**3** and (*R*)-**3** with piperidazine (**4**) in the presence or absence of potassium *t*-butoxide are summarized in Table 1. A catalytic amount of potassium *t*-butoxide is necessary for the reaction, and the conjugate addition-cyclization of **4** to (*S*)- and (*R*)-**3**, followed by successive reduction of the *p*-tolylsulfinyl group with SmI_2 *in situ* proceeded smoothly to give (*R*)-(+)- and (*S*)-(-)-**5** (95% e.e.) in 75 and 73% yields, respectively (Entries 2 and 4). When 1.0 equiv. of potassium *t*-butoxide was used, the optical purity of (*R*)-**5** was 95% e.e. and the chemical yield was decreased to 63% (Entry 3).

Scheme 1

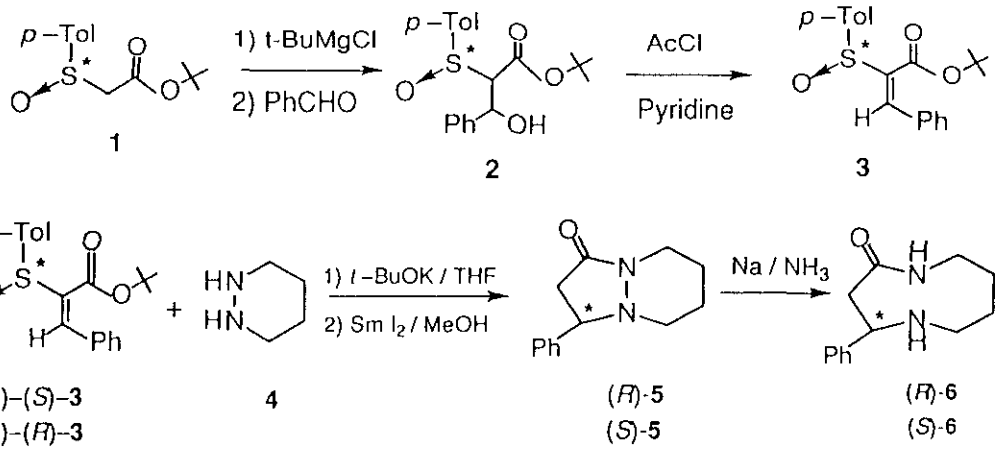


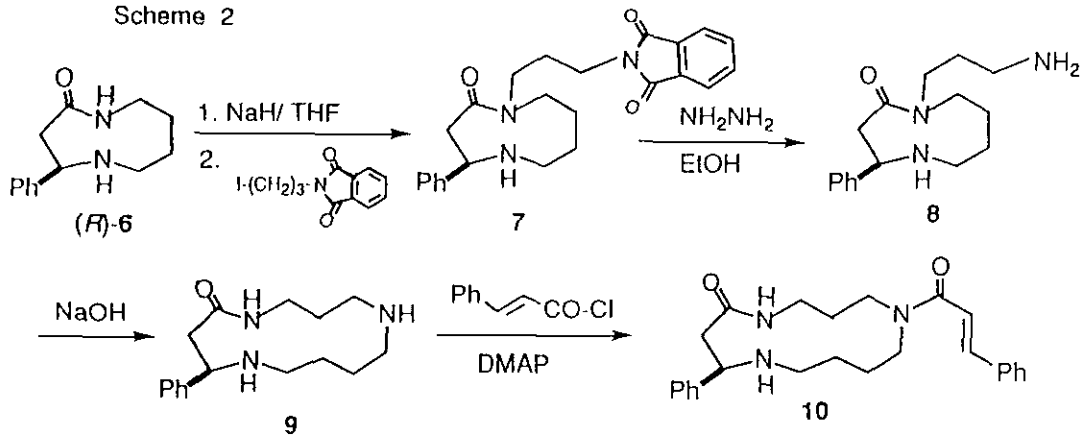
Table 1. Conjugate Addition-Cyclization of Piperidazine (**4**) to Vinyl Sulfoxides (**3**) [a]

Entry	Sulfoxide	Solvent	*t*-BuOK (equiv.)	Product	Yield/%[b]	$[\alpha]_D$/ deg [c]	e.e. /%[d]
1	(*S*)-**3**	THF	0	(*R*)-**5**	0 [e]	--	--
2	(*S*)-**3**	THF	0.1	(*R*)-**5**	75	+153	95
3	(*S*)-**3**	THF	1.0	(*R*)-**5**	63	+152	95
4	(*R*)-**3**	THF	0.1	(*S*)-**5**	73	-155	95

[a] The optical purity of vinyl sulfoxides (**3**) was determined by hplc analysis using a chiral column (Daicel CHIRALPAK AS; hexane/ethanol= 95/5). (*S*)-**3**: $[\alpha]_D$ +241° (*c* 0.9, $CHCl_3$), 100% e.e.; (*R*)-**3**: $[\alpha]_D$ -243° (*c* 1.0, $CHCl_3$), 100% e.e. [b] Isolated yield. [c] Measured in $CHCl_3$ (*c* 1.0) at 25 °C. [d] Determined by hplc using a chiral column (Daicel CHIRALPAK AD; hexane/2-propanol= 95/5). (*R*)-**5**: $[\alpha]_D$ +167° (*c* 1.3, $CHCl_3$), 100% e.e.; (*S*)-**5**: $[\alpha]_D$ -167° (*c* 1.9, $CHCl_3$), 100% e.e. [e] The conjugate addition of **4** to **3** took place to give the acyclic adduct in 72% yield.

In the absence of potassium *t*-butoxide in THF, only the conjugate addition of **4** to vinyl sulfoxide ((*S*)-**3**) took place, and no cyclization product (*R*)-**5** was obtained (Entry 1). In methanol solution the conjugate addition-cyclization of **4** to (*S*)-**3** took place in the absence of potassium *t*-butoxide, however the yield and stereoselectivity of (*R*)-**5** were very low (19% yield; 49% e.e.). Enantiomerically pure (*R*)-**5** and (*S*)-**5** were obtained by one-recrystallization of the products. The reductive cleavage of N-N bond of enantiomerically pure (*R*)-**5** with sodium (3 equiv.) in liquid ammonia gave nine-membered azalactam ((*R*)-**6**),[3] $[\alpha]_D$ +142° (*c* 1.2, $CHCl_3$), 97% e.e., in 87% yield. Similarly, (*S*)-**6**,[3] $[\alpha]_D$ -149° (*c* 1.2, $CHCl_3$), 99% e.e., was obtained from enantiomerically pure (*S*)-**5**, in 61% yield. Starting from the optically active nine-membered lactam (**6**), the synthesis of chiral celacinnine was achieved according to the ring-expansion procedure[6b] as shown in Scheme 2.

Scheme 2



Conversion of (*R*)-(+)-**6** to (*R*)-(+)-**10** was accomplished in four steps. Treatment of (*R*)-(+)-**6**, $[\alpha]_D$ +142° (*c* 1.2, $CHCl_3$), 97% e.e., with sodium hydride (5 equiv.) in THF at 50 °C followed by addition of *N*-(3-iodopropyl)phthalimide (3 equiv.) gave the tertiary amide **7** (49%, $[\alpha]_D$ +58.3° (*c* 0.95, $CHCl_3$)). Removal of the phthalimide function with ethanolic hydrazine (10 equiv.) generated *N*-(3-aminopropyl)lactam (**8**) which upon warming with dilute sodium hydroxide (1M NaOH, 50 °C, 12 h) underwent transannular ring expansion to **9** ($[\alpha]_D$ +8.5° (*c* 0.58, $CHCl_3$)) in 52% overall yield from **7**. Synthetic (*R*)-(+)-celacinnine (**10**) (57%, $[\alpha]_D$ +13.6° (*c* 0.13, $CHCl_3$)) was obtained by regioselective acylation with cinnamoyl chloride according to the method of Yamamoto.[6c] Although the value of optical rotation of (*R*)-(+)-**10** is smaller than that of natural celacinnine, one may consider that during the conversion of (*R*)-**6** to (*R*)-**10** the configuration around chiral center is retained. Synthetic (*R*)-**10** was in good agreement with natural (*S*)-(-)-celacinnine in all spectroscopic data.[4,11] Similarly, (*S*)-**9** (($[\alpha]_D$ -10.5° (*c* 0.58, $CHCl_3$)) was prepared from (*S*)-(-)-**6** (99% e.e.) in 50% overall yield and the optical rotation of (*S*)-celacinnine (**10**) ($[\alpha]_D$ -5.5° (*c* 0.10, $CHCl_3$)) was levorotatory

though the chemical yield of (*S*)-**10** was low. In summary, highly stereocontrolled synthesis of optically active azalactams has been developed and the absolute configuration of (-)-celacinnine was determined to be *S*-form.

Typical Procedure for the Reaction of (S)-3 with Piperidazine (4).
To a mixture of (*S*)-**3** (100% e.e.) (0.3 mmol) and *t*-BuOK (0.03 mmol) in THF (5 ml) was added **4** (1.5 mmol) under nitrogen atmosphere, and the mixture was stirred at room temperature for 6 h. A SmI_2 solution in THF (1.5 mmol; 0.1 M, 15 ml) and methanol (0.1 ml) were added.[9] After 30 min cold saturated sodium carbonate solution (10 ml) was added to the mixture. After the separation of organic phase, the aqueous layer was extracted with dichloromethane (3 x 20 ml). The combined organic phase was washed with brine, dried, and evaporated. The product was purified by column chromatography on silica gel with 19/1 chloroform/methanol as eluent. The results are listed in Table 1.

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9. For a SmI_2 reduction, see; Y. Arai, M. Matsui, and T. Koizumi, *J. Chem. Soc., Perkin Trans.* 1, **1990**, 1233.
10. (*R*)-(+)-*t*-Butyl *p*-tolylsulfinylacetate (**1**) was prepared in 97% yield according to the modified method of the literature, see; C. Mioskowski and G. Solladie, *Tetrahedron*, **1980**, 36, 227.

t-Butyl β-Hydroxy-β-phenyl-α-(p-tolylsulfinyl)propionate (2).

To a solution of (*R*)-*t*-butyl *p*-tolylsulfinylacetate (**1**) (3.7 g, 14.5 mmol) in THF (100 ml) at -78 °C was added a THF solution (22 ml) of *t*-butylmagnesium chloride (22.0 mmol, 1.5 equiv.) over a period of 20 min. The mixture was then stirred for 1 h at -78 °C and benzaldehyde (4.6 ml, 45 mmol, 3 equiv.) in THF (30 ml) was added. After stirring for 1 h at -78 °C, the mixture was decomposed by addition of saturated aqueous ammonium chloride solution (50 ml) and extracted with ether (2 x 100 ml). The combined extracts were dried with sodium sulfate and concentrated. The product was purified by column chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent; yield: 3.65 g (70%) of (*Rs,R,R*)-*t*-butyl β-hydroxyl-β-phenyl-α-(*p*-tolylsulfinyl)propionate and 0.71 g (17%) of (*Rs,R,S*)-*t*-butyl β-hydroxyl-β-phenyl-α-(*p*-tolylsulfinyl)propionate; (*Rs,R,R*)-**2**: mp 105-106 °C; ir ($CHCl_3$) 3440 (OH), 1715 (C=O), 1145 (SO) cm^{-1}; $[\alpha]_D^{25}$ +195° (c 1.0, $CHCl_3$) (o.p. 96%); $[\alpha]_D^{25}$ +201° (*c* 1.4, $CHCl_3$) (o.p. 100% after recrystallization).

(S)-t-Butyl α-(p-Tolylsulfinyl)cinnamate ((S)-3).
To the (*Rs,R,R*)-ester (**2**) (18.0 g, 50 mmol) in ether (50 ml) was added pyridine (50 ml) and acetyl chloride (4.7 ml, 55 mmol, 1.1 equiv.) at room temperature and the mixture was stirred for 12 h. The solution was washed with water (200 ml), 10% HCl (200 ml), 10% $NaHCO_3$ (200 ml) and dried with sodium sulfate, and concentrated. The product was purified by column chromatography on silica gel with 2/1 hexane/ethyl acetate as eluent; yield: 10.4 g (60%). (*E*)-(*S*)-**3**: mp 111.5 °C; ir (KBr) 1695 (C=O), 1150 (C-O), 1065 (SO) cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz) δ= 1.22 (9 H, s, *t*-butyl), 2.38 (3 H, s, CH_3 of tolyl), 7.28 and 7.62 (4 H, ABq, J= 8.0 Hz, -C_6H_4-), 7.26-7.66 (5 H, m, C_6H_5-), 7.61 (1 H, s , C=CH-); mass (70 eV) *m/z* 342 (M^+), 294, 238, 140, 91, 77, 57 (100%); $[\alpha]_D^{25}$ +218° (*c* 1.1, $CHCl_3$); $[\alpha]_D^{25}$ +241° (*c* 0.9, $CHCl_3$) (100% e.e. after recrystallization from ether-hexane).
11. We are grateful to Professor K. Maruoka of Nagoya University for providing spectroscopic data of spermidine alkaloids and 13-membered azalactam (±)-**9**.

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