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A HIGHLY ASYMMETRIC PUMMERER-TYPE CYCLIZATION OF CHIRAL, NON-RACEMIC β-AMIDOSULFOXIDES INDUCED BY *O*-SILYLATED KETENE ACETALS

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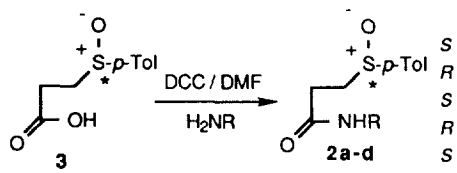
Abstract: The first highly asymmetric Pummerer-type cyclization of chiral, non-racemic β-amidosulfoxides leading to enantiomerically enriched β-lactams (80-85 % ee) is described. *S*-and *R*-sulfoxides (*S*-**2a-d** and *R*-**2a-c**) were treated with *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal (**1**) in the presence of a catalytic amount of $ZnCl_2$ in CH_2Cl_2 to predominantly give the corresponding 4*R*- and 4*S*-β-lactams (*R*-**4a-d** and *S*-**4a-c**) in more than 80 % ee. These results show that the stereoinduction is completely influenced by the absolute configuration of the sulfoxides.

The asymmetric Pummerer reaction of chiral, non-racemic sulfoxides,[1] which is one of the self-immolative-type asymmetric inductions, is of significant interest, because it would provide a means for the synthesis of enantiomerically pure α-substituted sulfides.[2] Especially the intramolecular version of the asymmetric Pummerer-type reaction is quite useful for the synthesis of optically active heterocyclic compounds.[3, 4] Only a few examples of these types of reactions have been reported, but the enantiomeric excess (ee) yields were low.[3, 4] We report here the first highly asymmetric Pummerer-type cyclization of chiral, non-racemic β-amidosulfoxides leading to enantiomerically enriched β-lactams (80-85 % ee).

Several years ago, we reported a novel silicon-induced Pummerer-type reaction of sulfoxides using *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal (**1**), which gave α-siloxy sulfides under mild conditions [5] and then applied it to the intramolecular cyclization of ω-amidosulfoxides to produce α-thio-*N*-heterocycles involving 4- to 7-membered α-thiolactams.[4, 6] Very recentry, we reported the first highly asymmetric Pummerer-type reaction of chiral, non-racemic acyclic sulfoxides which gave enantiomerically enriched α-siloxysulfides in high yields.[7] We have now applied this reaction to the asymmetric intramolecular cyclization of chiral, non-racemic β-amidosulfoxides (**2a-d**).

Starting materials **2a-d** were prepared in good yields from the known carboxylic acid (**3**) [8] by condensation with the corresponding amine in the presence of 1,3-dicyclohexylcarbodiimide (DCC) in dimethylformamide (DMF) (Scheme 1).



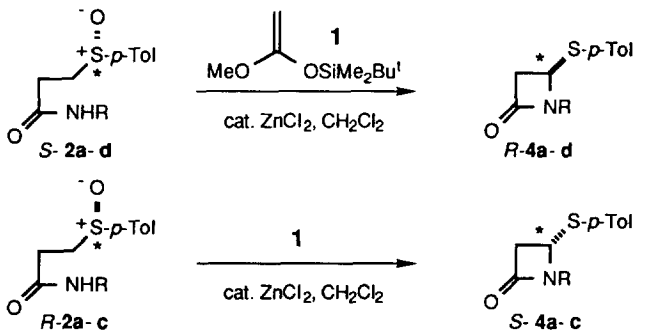
R-**3**: $[\alpha]_D^{15}$ +171° (c, 0.703, MeOH) (lit.[8] $[\alpha]_D$ +188°)
S-**3**: $[\alpha]_D^{15}$ -172° (c, 0.793, MeOH)

S - **2a**:R=*S*-CH(Me)Ph, 60 %, $[\alpha]_D^{26}$ -217° (c, 0.158, $CHCl_3$)
R - **2a**:R=*S*-CH(Me)Ph, 66 %, $[\alpha]_D^{26}$ +110° (c, 0.542, $CHCl_3$)
S - **2b**:R=CH_2Ph, 95%, $[\alpha]_D^{26}$ -196° (c, 0.408, $CHCl_3$)
R - **2b**:R=CH_2Ph, 93 %, $[\alpha]_D^{26}$ +194° (c, 0.241, $CHCl_3$)
S - **2c**:R=$CHPh_2$ 92 %, $[\alpha]_D^{26}$ -168° (c, 2.17, $CHCl_3$)
R - **2c**:R=$CHPh_2$ 58%, $[\alpha]_D^{20}$ +171° (c, 1.13, $CHCl_3$)
S - **2d**:R=CH_2-*o*-BrPh, 87 %, $[\alpha]_D^{25}$ -149° (c, 0.612, $CHCl_3$)

Scheme 1

Under the standard silicon-induced Pummerer conditions [4, 6] (**1**, cat. ZnI_2, MeCN), treatment of optically pure *S*-sulfoxides (**2a**), which have the chiral amido group, gave *R*-β-lactam (**4a**) in 60 % de (72 % chemical yield) stereoselectively. The use of $ZnCl_2$ as a catalyst in CH_2Cl_2 was found to give the best results. Surprisingly high ee's were also obtained from **2b-d** having an achiral amido group under the same conditions. *S*-and *R*-Sulfoxides (*S*-**2** and *R*-**2**) were treated with **1** to predominantly give 4*R*- and 4*S*-β-lactams (*R*-**4** and *S*-**4**), respectively in more than 80 % ee's. These results show that the stereoinduction is influenced by the absolute configuration of the sulfoxides (Table 1). Optically pure *R*- and *S*-**4c** were readily obtained by simple recrystallization in about 60 % yield {*R*-**4c**; $[\alpha]_D^{17}$ - 47.03° (*c*=0.370, $CHCl_3$), *S*-**4c**; $[\alpha]_D^{20}$ + 49.4° (*c*=0.599, $CHCl_3$)}. The present Pummerer cyclization has the highest optical induction compared with the previously examined method.[3, 4]

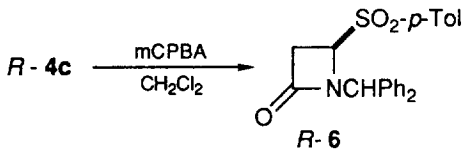
Table 1 Asymmetric Pummerer-type Cyclization of Chiral, Non-racemic Sulfoxides(**2**) with **1**



2a-d	R	Conditions	**4**	Product[a] % Ee [b] (% Yield)	$[\alpha]_D$ (*c*, $CHCl_3$)	CD (MeOH) λ ext (Δε)
S-**2a**	CH(Me)Ph [c]	0°C, 1d [d]	*R*-**4a**	60 [e] (72)	- 98.8 (1.96) [f]	253 (+2.9), 242 (0), 222 (-20.4)[f]
S-**2a**	CH(Me)Ph [c]	0°C, 3d	*R*-**4a**	82 [e] (96)	- 98.8 (1.96) [f]	253 (+2.9), 242 (0), 222 (-20.4)[f]
R-**2a**	CH(Me)Ph [c]	0°C, 3d	*S*-**4a**	85 [e] (89)	+116 (0.954) [f]	254 (-5.7), 240 (0), 221 (+24.5)[f]
S-**2b**	CH_2Ph	5°C, 6d	*R*-**4b**	80 (54)	-73.2 (1.01)	252 (+3.1), 239 (0), 220 (-16.6)
R-**2b**	CH_2Ph	5°C, 6d	*S*-**4b**	82 (54)	+75.2 (0.934)	252 (-2.6), 240 (0), 220 (+19.2)
S-**2c**	$CHPh_2$	15°C, 2d	*R*-**4c**	80 (84)	-37.0 (0.303)	253 (+5.1), 243 (0), 221 (-21.5)[g]
R-**2c**	$CHPh_2$	15°C, 2d	*S*-**4c**	83 (90)	+38.4 (0.522)	255 (-4.3), 243 (0), 221 (+21.4)[g]
S-**2d**	CH_2-*o*-BrPh	5°C, 7d	*R*-**4d**	83 (59)	-59.2 (1.49)	253 (+1.5), 240 (0), 221 (-14.4)

[a] Small amount of α-siloxy-β-amidosulfides were obtained as side-products in all reactions. [b] Ee value was determined by ^{1}H-NMR (C_6D_6) with Eu(hfc)$_3$. [c] *S*-Phenethylamine was used. [d] ZnI_2 is used as a catalyst in MeCN. [e] % De. [f] This value was obtained from the diastereomerically pure sample. [g] This value was obtained from the enantiomerically pure sample.

The absolute stereochemistry at the newly generated chiral center of the β-lactams was ascertained by its CD-spectrum, which had a strong positive or negative Cotton effect at 210-220 nm (Octant rule) in agreement with the value from monocyclic β-lactams reported by Reling and Jensen [9] and confirmed by the conversion of *R*-**4c** to the known (+)-PS-5 intermediate {(-)-**5**; $[\alpha]_D^{22}$ - 40.9° (*c*=1.02, $CHCl_3$), lit.[6f]; $[\alpha]_D^{25}$ -39.59° (*c*=2.92, $CHCl_3$)}.[10] Finally, the absolute stereochemistry was determined by X-ray crystallographic analysis [11] of oxidized derivertive (*R*-**6**) of *R*-**4c**. (Fig. 1)



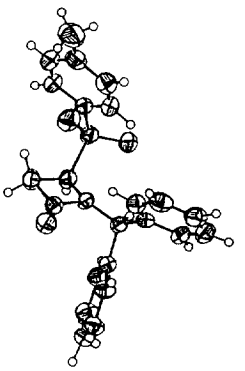


Fig 1. X-Ray Crystallographic Structure of *R*-**6**

The following mechanism is proposed to explain the results and the transition-state is representatively analyzed for the reaction of *S*-**2** with **1** (Fig. 2). Silylation of *S*-**2** with **1** affords an intermediate (A). Thus, A may yield a chiral pseudo isothiazolone derivative (B) [12] through axial attack of the amido anion generated by abstraction with ester anion and elimination of the siloxy ligand. Then, the hydrogen neighboring to the sulfur atom was removed by the siloxy anion and the amido ligand was rearranged from the α-face to give the β-lactam (*R*-**4**).

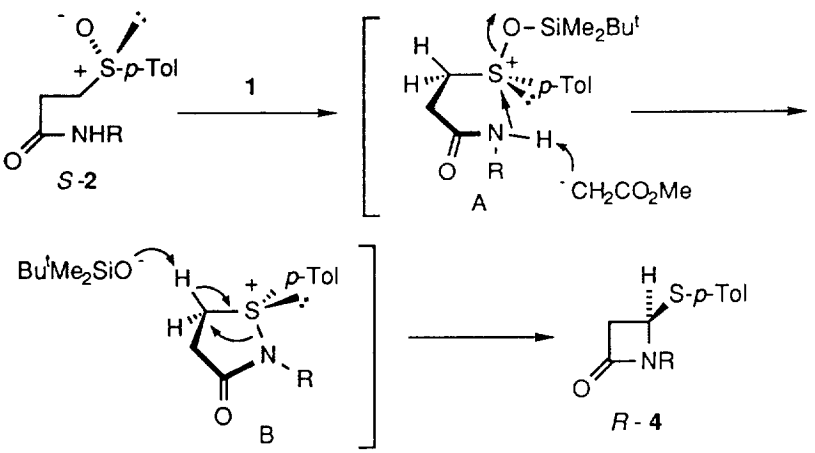
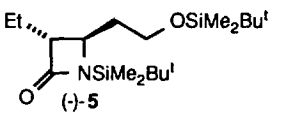


Fig. 2

References and Notes

1. Asymmetric Pummerer rearrangement; a) McCormick, J. E.; McElhinney, R. S. *Chem. Commun.* **1969**, 171; b) Glue, S.; Kay, I. T.; Kipps, M. R. *Chem. Commun.* **1970**, 1158; c) Numata, T.; Oae, S. *Tetrahedron Lett.* **1977**, 1337; d) Numata, T.; Itoh, O.; Oae, S. *Chem. Lett.* **1977**, 909; e) Mikolajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B.; Midura, W. *J. Org. Chem.* **1978**, *43*, 2518; f) Numata, T.; Itoh, O.; Oae, S. *Tetrahedron Lett.* **1979**, 1869; g) Masuda, T.; Numata, T.; Furukawa, N.; Oae, S. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1302; h) Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 257; i) Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 266. Asymmetric additive Pummerer reaction (enantioselective 3,3-sigmatropic rearrangement); Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643.
2. Reviews, see: a) Oae, S.; Numata, T. " The Pummerer and Pummerer Type of Reactions," in "*Isotopes in Organic Chemistry*," ed. by Buncel, E.; Lee, C. C. Elsevier, New York, **1980**, Vol. 5. Chapter 2; b) Lucchi, O. D.; Miotti, U.; Modena, G. *Organic Reactions* **1990**, *40*, 157.
3. a) Stridsberg, B.; Allenmark, S. *Acta Chem. Scand.* **1974**, *B28*, 591; Stridsberg, B.; Allenmark, S. *Acta Chem. Scand.* **1976**, *B30*, 219; b) Wolfe, S.; Kazmaier, P. M.; Auksi, H. *Can. J. Chem.* **1979**, *57*, 2404; c) Kaneko, T.; Okamoto, Y.; Hatada, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1511.
4. Kita, Y.; Tamura, O.; Miki, T.; Tono, H.; Shibata, N.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 729.
5. a) Kita, Y.; Yasuda, H.; Tamura, O.; Itoh, F.; Tamura, Y. *Tetrahedron Lett.* **1984**, *25*, 4681; b) Kita, Y; Yasuda, H.; Tamura, O.; Itoh, F.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4235; c) Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Miki, T.; Tamura, Y. *Chem. Pharm. Bull.* **1987**, *35*, 562.
6. a) Kita, Y.; Tamura, O.; Miki, T.; Tamura, Y. *Tetrahedron Lett.* **1987**, *28*, 6479; b) Kita, Y.; Tamura, O.; Shibata, N.; Miki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1862; c) Kita, Y.; Tamura, O.; Shibata, N.; Miki, T. *Chem. Pharm. Bull.* **1990**, *38*, 1473; d) Kita, Y.; Shibata, N.; Miki, T.; Takemura, Y.; Tamura, O. *J. Chem. Soc., Chem. Commun.* **1990**, 727; e) Kita, Y.; Shibata, N.; Tamura, O.; Miki, T. *Chem. Pharm. Bull.* **1991**, *39*, 2225; f) Kita, Y.; Shibata, N.; Miki, T.; Takemura, Y.; Tamura, O. *Chem. Pharm. Bull.* **1992**, *40*, 12.
7. a) Kita, Y.; Shibata, N.; Yoshida, N. *Tetrahedron Lett.* **1993**, *34*, 4063; b) Kita, Y.; Shibata, N.; Yoshida, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* **1994**, *35*, 2569; c) Kita, Y.; Shibata, N.; Kawano, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* **1994**, *35*, 3575.
8. Albinati, A.; Bravo, P.; Ganazzoli, F.; Resnati, G.; Viani, F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1405.
9. Rehling, H.; Jensen, H. *Tetrahedron Lett.* **1972**, 2793.
10. The full details of this method for the formal total synthesis of (+)-PS-5 will be reported elsewhere.



(-)-**5**

11. The crystal data for *R*-**6** are as follow: orthorhombic; $P2_12_12_1$ with a=8.914(3), b=37.70(1), c=5.928(2) Å, V=1992(1) $Å^3$, Z=4, and μ(Cu Kα)=15.29 cm^{-1} by Mac Science MXC 18 instrument. Final R value was 0.038 for 1956 reflections. The supplementary materials have been deposited at the Cambridge Crystallographic Data Centre.
12. The formation of the acylaminosulfonium ion (isothiazolone B) as an intermediate has been widely accepted under Pummerer-type conditions; a) Uchida, Y.; Kozuka, S. *J. Chem. Soc., Chem. Commun.* **1981**, 510; b) Kaneko, T. *J. Am. Chem. Soc.* **1985**, *107*, 5490; c) Uchida, Y.; Oae, S. *Cazzetta Chimica Italiana* **1987**, *117*, 640; d) Yamamoto, K.; Yamazaki, S.; Murata, I. *J. Org. Chem.* **1987**, *52*, 5239; e) Wright, S. W.; Abelman, M. M.; Bostrom, L. L.; Corbett, R. C. *Tetrahedron Lett.* **1992**, *33*, 153.

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