Synthesis of β-Amino Esters by the Conjugate Addition of Nitrogen Nucleophiles to α,β-Unsaturated Esters Having Chiral *p*-Tolylsulfinyl Groups

Haruo Matsuyama,* Nobuhiro Itoh, Masato Yoshida, Nobumasa Kamigata, Sigeru Sasaki, and Masahiko Iyoda
Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Hachioji, Tokyo 192-03

(Received December 25, 1996)

The conjugate addition of nitrogen nucleophiles to *t*-butyl (*E*)-2-(*p*-tolylsulfinyl)cinnamates (**1**) afforded the corresponding chiral β-amino esters, which are important building blocks for synthesis of biologically active polyamine alkaloids. The diastereoselectivity of the reactions was 49 to 89%, and (*S*)-β-amino esters were obtained from (*R*)-**1** while (*R*)-β-amino esters were synthesized from (*S*)-**1**, respectively.

β-Amino acids are important compounds in pharmacology and synthetic organic chemistry and, recently, a few reports on asymmetric synthesis were published.[1] The group of macrocyclic lactams containing the biogenetic bases, spermine and spermidine, represents a new class of polyamine alkaloids which have the framework of β-amino acids and are of particular interest because of the broad biological properties such as antibiotic and antihypertensive activity.[2,3] Recently, the synthesis of 13-membered lactam alkaloid, (*S*)-(+)-dihydroperiphylline, starting from (*S*)-(-)-β-phenyl-β-alanine was reported.[4,5] Asymmetric induction in the conjugate addition of nucleophiles to chiral vinyl sulfoxides has proven to be a useful methodology for the synthesis of chiral compounds,[6] and the asymmetric synthesis of chiral β-amino sulfoxides by conjugate addition of amines to chiral vinyl sulfoxides[7] and the synthesis of β-amino esters by addition of enolate ions to chiral sulfinimines[8] were investigated.

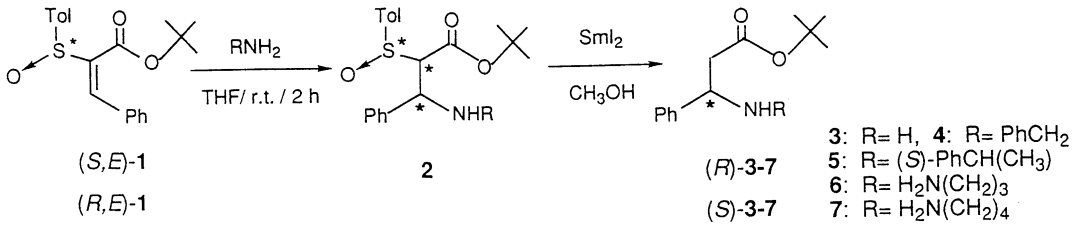
More recently, we reported the conjugate addition reaction of 6- and 5-membered cyclic hydrazines such as piperidazine and pyrazolidine to *t*-butyl 2-(*p*-tolylsulfinyl)cinnamates (**1**) and synthesized the chiral 9- and 8-membered lactams with high optical purity (up to 95% e.e.).[9,10] The asymmetric synthesis of 13-membered lactam alkaloid, celacinnine, and 8-membered lactam alkaloid, homaline, was accomplished by this method.[9,10] In the course of developing this method, we investigated the conjugate addition of acyclic nitrogen nucleophiles such as ammonia, benzylamine, 1,3-diaminopropane, and 1,4-diaminobutane to *t*-butyl 2-(*p*-tolylsulfinyl)cinnamates (**1**) and found that this reaction system is efficient for the synthesis of chiral amino esters (Scheme 1).

Table 1. Conjugate addition of nitrogen nucleophiles to *t*-butyl 2-(*p*-tolylsulfinyl)cinnamates (**1**)[a] and subsequent reductive elimination

Entry	Config of **1**	Nitrogen Nucleophiles	Product	Yield/%[b]	e.e./% (*R*/*S*)
1	*S*	NH_3	**3**	68	81[c] (*R*)
2	*R*	NH_3	**3**	68	74[c] (*S*)
3	*S*	$C_6H_5CH_2NH_2$	**4**	41	49[d] (*R*)
4	*R*	$C_6H_5CH_2NH_2$	**4**	45	52[d] (*S*)
5	*S*	(*S*)-$C_6H_5CH(CH_3)NH_2$	**5**	37	17[e] (*R*,*S*)
6	*R*	(*S*)-$C_6H_5CH(CH_3)NH_2$	**5**	83	62[e] (*S*,*S*)
7	*S*	$H_2N(CH_2)_3NH_2$	**6**	89	67[f] (*R*)
8	*R*	$H_2N(CH_2)_3NH_2$	**6**	79	62[f] (*S*)
9	*S*	$H_2N(CH_2)_4NH_2$	**7**	67	58[f] (*R*)
10	*R*	$H_2N(CH_2)_4NH_2$	**7**	64	89[f] (*S*)

[a] The optical purity of *t*-butyl 2-(*p*-tolylsulfinyl)cinnamates (**1**) was determined by HPLC analysis using a chiral column (Daicel CHIRALPAK AS; hexane/ethanol = 95/ 5). (*S*)-**1**: $[\alpha]_D$ +241° (c 0.9, $CHCl_3$), 99% e.e.; (*R*)-**1**: $[\alpha]_D$ -243° (c 1.0, $CHCl_3$), 99% e.e. [b] Isolated yield. [c] The optical purity was determined by HPLC analysis, after converting **3** to *N*-acetyl derivative, using a chiral column (Daicel CHIRALPAK AD; hexane/ 2-propanol= 9/ 1). [d] The enantiomeric excess was determined by ^1H NMR using a shift reagent [Eu(hfc)3]. [e] The diastereomeric excess was determined by ^1H NMR. [f] The optical purity was determined by comparison with the $[\alpha]_D$ value of authentic compound: see References 14 and 15.

The conjugate addition of ammonia to *t*-butyl 2-(*p*-tolylsulfinyl)cinnamate, (*S*, *E*)-**1** (99% e.e.),[10] proceeded smoothly in THF at room temperature under nitrogen to give the ammonia adduct **2**, which was converted to (*R*)-(+)-*t*-butyl 3-amino-3-phenylpropanoate (**3**) [$[\alpha]_D$ +18° (c 1.3, $CHCl_3$); 81% e.e.][12] in 68% yield by the reductive elimination of the *p*-tolylsulfinyl group of **2** with samarium(II) iodide (6 equiv)[11] and methanol at 0 °C (Table 1, entry 1). Similarly, the conjugate addition of ammonia to (*R*, *E*)-**1** (99% e.e.),[10] followed by successive reduction of the *p*-tolylsulfinyl group of **2** with SmI_2 *in situ* proceeded smoothly to give (*S*)-(-)-**3** [$[\alpha]_D$ -13.3° (c 1.2, $CHCl_3$); 74% e.e.] in 68% yield (entry 2). The reaction of



Scheme 1. Conjugate addition of nitrogen nucleophiles to *t*-butyl (*E*)-2-[(*S*)- and (*R*)-*p*-tolylsulfinyl]cinnamates (**1**) and subsequent reductive elimination.

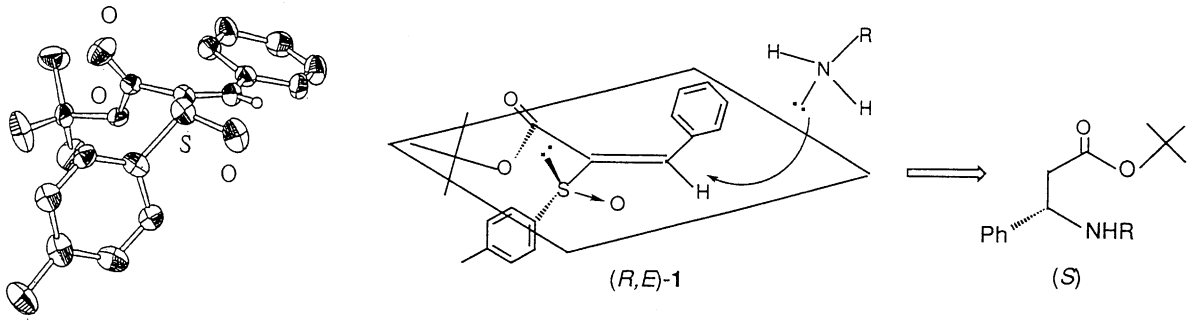


Figure 1. Molecular structure of *t*-butyl 2-(*p*-tolylsulfinyl)cinnamate, (*R*,*E*)-**1**, and proposed mechanism in the conjugate addition of nitrogen nucleophiles to (*R*,*E*)-**1** and subsequent reductive elimination.

benzylamine (10 equiv) with **1** proceeded under similar conditions to afford *t*-butyl 3-benzylamino-3-phenylpropanoate (**4**), and the stereochemistry of **4** was determined by the specific rotation. Amino ester (*R*)-(+)-**4** [[α]$_D$ +13.2° (c 1.0, $CHCl_3$); 49% e.e.] was obtained in 41% yield by the reaction of benzylamine with (*S*)-**1**, and the reaction of benzylamine with (*R*)-**1** gave (*S*)-(-)-**4** [[α]$_D$ -14.8° (c 0.6, $CHCl_3$); 52% e.e.] in 45% yield (entries 3 and 4). The reaction of (*R*)-**1** with (*S*)-1-methylbenzylamine (5 equiv) proceeded in THF at room temperature to give two diastereoisomers of **5** in 83% yield with 62% d.e. The stereoselectivity of the conjugate addition of (*R*)-**1** with (*S*)-1-methylbenzylamine was about 10% better than that of the reaction of (*R*)-**1** with benzylamine. On the other hand, the stereoselectivity of the conjugate addition reaction of another pair, (*S*)-**1** and (*S*)-1-methylbenzylamine, decreased to 17% d.e. (entries 5 and 6).

Yamamoto *et al.* reported the synthesis of 13-membered spermidine alkaloid by the boron-templated cyclization of triamino esters.[5,13] If the conjugate addition of polyamine derivatives to *t*-butyl (*p*-tolylsulfinyl)cinnamates (**1**) can proceed stereo-selectively, the framework of the chiral polyamine alkaloids can be synthesized by successive cyclization. Accordingly, we investigated the conjugate addition of 1,3-diaminopropane and 1,4-diaminobutane, as the model compounds of polyamines such as spermine and spermidine, to **1**. The reaction of 1,3-diaminopropane (5 equiv) with (*S*)-**1** proceeded in THF in the presence of potassium *t*-butoxide (0.1 equiv) at room temperature and (*R*)-(+)-*t*-butyl 7-amino-3-phenyl-4-azaheptanoate (**6**) [[α]$_D$ +7.2° (c 1.0, $CHCl_3$); 67% e.e.] was obtained in 89% yield.[14] The reaction of 1,3-diaminopropane with (*R*)-**1** gave (*S*)-(-)-**6** [[α]$_D$ -6.7° (c 1.0, $CHCl_3$); 62% e.e.] in 79% yield (entries 7 and 8). The reaction of 1,4-diaminobutane (5 equiv) with (*R*)-**1** proceeded in THF in the presence of potassium *t*-butoxide (0.1 equiv) at room temperature to afford (*S*)-(-)-*t*-butyl 8-amino-3-phenyl-4-azaoctanoate (**7**) [[α]$_D$ -6.7° (c 1.0, $CHCl_3$); 89% e.e.] in 64% yield.[15] The reaction of 1,4-diaminobutane with (*S*)-**1** gave (*R*)-(+)-**7** [[α]$_D$ +4.4° (c 1.1, $CHCl_3$); 58% e.e.] in 67% yield (entries 9 and 10).

On the basis of the stereochemistry of the (*S*)-β-amino ester obtained from (*R*,*E*)-**1**, the mechanism of the asymmetric conjugate addition of nitrogen nucleophiles to **1** can be explained as follows. The structure of (*R*,*E*)-**1** was determined by X-ray analysis as shown in Figure 1.[16] The oxygen of the sulfinyl group lies near the plane of the carbon-carbon double bond and the phenyl group. The *p*-tolyl group on sulfur is directed below the plane and the bulky *t*-butoxy group of the ester is also placed below the plane. Therefore, the front side of the plane shown in Figure 1 is less sterically crowded and the nitrogen nucleophiles can attack easily the β-carbon atom of the double bond of (*R*,*E*)-**1** from the front side of the plane (*re*-face). Thus, the reaction of (*R*,*E*)-**1** with amine afforded the (*S*)-β-amino ester, and the reaction of (*S*,*E*)-**1** with amine gave the (*R*)-β-amino ester.

References and Notes

1 D. C. Cole, *Tetrahedron*, **50**, 9517 (1994).
2 H. H. Wasserman and J. S. Wu, *Heterocycles*, **17**, 581 (1982).
3 S. Funayama, K. Yoshida, C. Konno, and H. Hikino, *Tetrahedron Lett.*, **21**, 1355 (1980) and references cited therein.
4 T. Kaseda, T. Kikuchi, and C. Kibayashi, *Tetrahedron Lett.*, **30**, 4539 (1989).
5 K. Ishihara, Y. Kuroki, and H. Yamamoto, *Synlett*, **1995**, 41.
6 M. C. Carreno, *Chem. Rev.*, **95**, 1717 (1995).
7 S. G. Pyne, P. Bloem, and R. Griffith, *Tetrahedron*, **45**, 7013 (1989) and references cited therein.
8 F. A. Davis, R. T. Reddy, and R. E. Reddy, *J. Org. Chem.*, **57**, 6387 (1992).
9 N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata, and M. Iyoda, *Heterocycles*, **41**, 415 (1995).
10 N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata, and M. Iyoda, *Bull. Chem. Soc. Jpn.*, **68**, 3121 (1995).
11 For SmI_2 reduction, see; Y. Arai, M. Matsui, and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1233.
12 Davies et al. reported the configuration of (*S*)-(-)-**3** [[α]$_D$ -21° ($CHCl_3$); 95% e.e.]; S. G. Davies, N. M. Garrido, O. Ichihara, and A. S. Walters, *J. Chem. Soc., Chem. Commun.*, **1993**, 1153.
13 H. Yamamoto and K. Maruoka, *J. Am. Chem. Soc.*, **103**, 6133 (1981).
14 The authentic (*R*)-(+)-**6** was prepared as follows. The conjugate addition of (*R*)-(+)-**3** [[α]$_D$ +18.0° (*c* 1.3, $CHCl_3$); 81% e.e.] to acrylonitrile gave (*R*)-(+)-*t*-butyl 6-cyano-3-phenyl-4-azahexanoate in 94% yield. The reduction (PtO_2/ H_2) of the cyano group gave amino ester (*R*)-(+)-**6** [[α]$_D$ +8.7° (*c* 1.1, $CHCl_3$); 81% e.e.] in 85% yield.
15 The authentic (*S*)-(-)-**7** was prepared as follows. The alkylation reaction of (*S*)-(-)-**3** (86% e.e.) with 4-bromobutyronitrile in ethanol solution in the presence of potassium carbonate gave (*S*)-(-)-*t*-butyl 7-cyano-3-phenyl-4-azaheptanoate [[α]$_D$ -30.9° (*c* 1.2, $CHCl_3$)]. The reduction (PtO_2/ H_2) of the cyano group afforded (*S*)-(-)-**7** [[α]$_D$ -6.5° (*c* 1.0, $CHCl_3$); 86% e.e.].
16 Crystal data of (*R*,*E*)-**1** [Rigaku AFC7R diffractometer, Mo-Kα radiation (λ= 0.71069 Å)]: $C_{20}H_{22}O_3S$, M= 342.45, monoclinic, space group $P2_1$, a= 10.511(7), b= 7.558(3), c= 11.938(3) Å, β= 92.19(4)°, V= 947.6(7) Å^3, Z= 2, D_{calcd}= 1.200 gcm^{-3}. The structure was solved by direct methods and refined by full-matrix least squares to R= 0.078, Rw= 0.083 using 2051 reflections with I >3.00σ(I).