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ASYMMETRIC SYNTHESIS OF AZIRIDINYL PHOSPHONATES USING DARZENS-TYPE REACTION OF CHLOROMETHYL PHOSPHONATE TO CHIRAL SULFINIMINES

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Abstract : Darzens-type reaction of chloromethyl phosphonate with (*S*)-(+)-*N*-sulfinimines gave (*Ss, 2S, 3R*)-diethyl 3-aryl-2-*N*-(*p*-toluenesulfinyl)aziridinyl-phosphonate (**3**) in good yields.

Chiral aziridines have received an increasing amount of attention since they are key substrates in the synthesis of a number of useful chiral amines through regio- and stereoselective ring opening reaction with many types of nucleolephiles.[1] Aziridinyl phosphonates[2] are useful intermediates for the synthesis of α-aminoalkyl phosphonates which are of considerable utility as

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surrogates for α-amino acids[3] and have been utilized as enzyme inhibitors,[4] antibiotics and pharmaceuticals agents,[5] and heptens for catalytic antibodies.[6] Chiral aziridinyl phosphonate has been prepared by the stereoselective addition of carbanion of chiral chloromethyl phosphonamide to imines with high enantiomeric purity.[2b] In the continuation of our work on the development of synthetic methods to α-substituted phosphonates, we have reported preparation of aziridinyl phosphonates by the copper catalyzed aziridination of vinylphosphonates using [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane.[2c] A very recent publication[7] by Davis and McCoull prompts us to report our results in this area. Davis and McCoull investigated the asymmetric synthesis of aziridinyl phosphonates and azirinyl phosphonates from enantiopure sulfinimines.[8] We now report the synthesis of chiral aziridinyl phosphonates using Darzens-type addition of anion of chloromethyl phosphonate with (*S*)-(+)-*N*-sulfinimines. It was performed by the addition of chloromethyl phosphonate α-anion to (*S*)-(+)-*N*-sulfinimines. The lithiated chloromethyl phosphonate was treated with (*S*)-(+)-*N*-sulfinimines at –78 °C in the THF. The reaction mixture was allowed to warm at room temperature over 2 h and stirred for 3 h at room temperature.

Scheme 1.

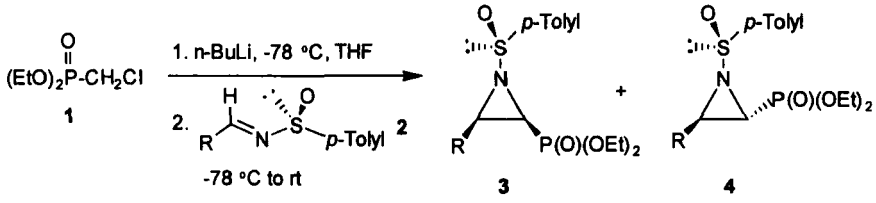


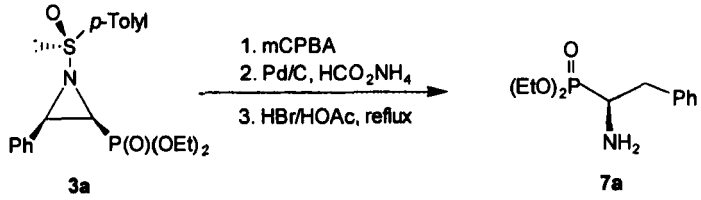
Table 1. Preparation of chiral aziridinyl phosphonates.

	R	3 : 4[a]	Yield(%)[b]	Absolute configuration of **3**
a	C_6H_5	6.1 : 1	91	(*Ss, 2S, 3R*)
b	*p*-Cl, C_6H_4	9.8 : 1	82	(*Ss, 2S, 3R*)
c	*p*-MeO, C_6H_4	11.1 : 1	88	(*Ss, 2S, 3R*)
d	*m*-NO_2, C_6H_4	12 : 1	87	(*Ss, 2S, 3R*)
e	2-Naphthyl	8.3 : 1	86	(*Ss, 2S, 3R*)

[a] Ratios were determined by ^{1}H NMR spectra.
[b] Isolated yields were based on sulfinimines.

The (*Ss*)-*N*-sulfinylaziridinyl phosphonates (**3, 4**) were obtained with good yields. The ratios of (*Ss, 2S, 3R*)-(-)-**3** and (*Ss, 2R, 3R*)-(+)-**4** in the crude reaction mixture were 6.1:1 to 12:1 which are can be isolable with column chromatography. The ratios of (*Ss, 2S, 3R*)-(-)-**3** and (*Ss, 2R, 3R*)-(+)-**4** of crude products were determined with coupling constants and chemical shifts between C_2 and C_3 substituents.[2a,9] The absolute configuration of **3** was assigned by the optical rotation after conversion to authentic α-aminoalkyl phosphonate. Treatment of (*Ss, 2S, 3R*)-diethyl 3-phenyl-2-*N*-(*p*-toluenesulfinyl)aziridinyl-phosphonate (**3a**) with mCPBA in ethanol at room temperature for 8 h afforded (*2S, 3R*)-diethyl 3-phenyl-2-*N*-(*p*-toluenesulfonyl)aziridinyl-phosphonate (**5a**) in 87% yield. Reductive ring opening and detosylation of *N*-tosylaziridinyl phosphonate **5a** was accomplished successively to afford (*S*)-(1-amino-2-phenylethyl)phosphonic acid (**7a**) with 42% yield. The $[\alpha]_D$ of α-aminoalkyl phosphonic acid **7a** was +53.7(c=1.0, 1N NaOH).[10]

Scheme 2.



3a **7a**

Compared with Davis's result[7] which proceed with two steps via α-chloro-β-amino phosphonate, the present synthetic method for the aziridinyl phosphonates proceed with one-pot from chloromethyl phosphonate α-anion and chiral sulfinimines.

In summary, we have found that synthetic method for the preparation of chiral *cis*-aziridinyl phosphonates using Darzens-type reaction from chloromethyl phosphonate and chiral sulfinimines.

Experimental Section

General. ^{1}H NMR spectra were recorded on a Bruker AC 200F spectrometer using tetramethylsilane as an internal standard. Chemical shifts(δ) are measured in part per million and coupling constants, *J*, are reported in Hz. Multiplicity was simplified such as s=singlet, bs=broad singlet, d=doublet, t=triplet, dq=double quartet, and m=multiplet. Mass spectra were determined with a Hewlett-Packard 5985A or Jeol HX 100/110 through EI or FAB method. Optical rotations were measured using Jasco DIP-1000 polarimeter. All commercial chemicals were used as obtained without further purification, and all solvents were carefully dried and distilled by standard methods prior to use. Column chromatography was performed on Merck silica gel 60(230-400mesh). The (*S*)-(+)-*N*-sulfinimines[11] was prepared as reported previously.

Genaral procedure for Darzens-type reaction of chloromethyl phosphonate to (*S*)-*N*-sulfinimines. To stirred solution of diethyl chloromethyl phosphonate (45 mg, 0.24 mmol) in THF (1 mL) was added dropwise *n*-BuLi (2.15 M, 0.13 mL, 0.27 mmol) at 78 °C under nitrogen. Stirring was continued for 0.8 h. (*S*)-*N*-sulfinimine (0.12 mmol) in THF (1 mL) was added dropwise at the same temperature. The reaction mixture was allowed to warm to room temperature over 2 h, and stirred for 3 h at room temperature. The mixture was quenched with methanol (0.5 mL), diluted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel flash chromatography (ethyl acetate : *n*-hexane = 1 : 1) to give the corresponding aziridinyl phosphonate.

(*Ss, 2S, 3R*)-Diethyl 3-phenyl-2-*N*-(*p*-toluenesulfinyl)aziridinylphosphonate (**3a**) R_f : 0.14 (ethyl acetate : *n*-hexane = 1:1); $[\alpha]^{25}_D$: -30.3 (c= 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200MHz) δ 1.10~1.18(m, 6H), 2.39(s, 3H), 2.86(dd, 1H, $J_{H\text{-}P}$= 16.1, $J_{H\text{-}H}$=7.7Hz), 3.82 ~ 4.00(m, 5H), 7.04~7.38(m, 7H), 7.64~7.72(m, 2H); ^{13}C NMR($CDCl_3$, 50MHz) δ 16.24(d, *J*=6.0Hz), 21.47, 33.52 (d, *J* = 65.5Hz), 35.64(d, *J*=136.5Hz), 62.22(d, *J*=6.0Hz), 62.46(d, *J*=6.5Hz) 124.64, 125.19, 127.64, 127.74, 127.93, 128.54, 129.08, 129.44, 129.77; MS(70eV) *m/z* 393(M^+, 0.5%), 91, 106, 139, 228, 244, 275.

(*Ss, 2S, 3R*)-Diethyl 3-(4-chlorophenyl)-2-*N*-(*p*-toluenesulfinyl)aziridinylphosphonate (**3b**). R_f : 0.18 (ethyl acetate : *n*-hexane = 1:1); $[\alpha]^{25}_D$: -41.8 (c= 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200MHz) δ 1.09~1.25(m, 6H), 2.38(s, 3H), 2.84(dd, 1H, $J_{H\text{-}P}$=15.5, $J_{H\text{-}H}$=7.4Hz), 3.84~4.03(m, 5H) 6.92~7.38(m, 6H), 7.63~7.72(m, 2H); ^{13}C NMR($CDCl_3$, 50MHz) δ 16.25(d, *J*=6.0Hz), 21.48, 33.20(d, *J*=23.1Hz), 35.33(d, *J*=178.9Hz), 62.39(d, *J*=7.5Hz), 62.53(d, *J*=7.0Hz), 124.52, 127.93, 129.33, 129.81, 130.52, 132.23, 140.27, 142.71.

(*Ss, 2S, 3R*)-Diethyl 3-(*p*-methoxyphenyl)-2-*N*-(*p*-toluenesulfinyl)aziridinylphosphonate (**3c**). R_f : 0.23 (ethyl acetate : *n*-hexane = 1:1); $[\alpha]^{25}_D$: -43.4 (c=1.7, $CHCl_3$); ^1H NMR($CDCl_3$, 200MHz) δ 1.13~1.21(m, 6H), 2.38(s, 3H), 2.81(dd, 1H, $J_{H\text{-}P}$=16.0, $J_{H\text{-}H}$=7.6Hz), 3.73(s, 3H), 3.82 ~ 4.00(m, 5H), 6.69(d, 2H, *J*=2.5Hz), 6.99(d, 2H, *J*=2.0Hz), 7.29(d, 2H, *J*=2.5Hz), 7.72(d, 2H, *J*=2.0Hz); ^{13}C NMR($CDCl_3$, 50MHz) δ 16.27(d, *J*=4.0Hz), 21.45, 33.24(d, *J*=44.0Hz), 35.36(d, *J* = 158.1Hz), 52.09, 62.30(d, *J*=7.7Hz), 113.11, 124.58, 124.94,

129.02, 129.70, 133.91, 140.53, 140.96; MS(70eV) *m/z* 423(M^+, 5.8%), 97, 113, 129, 221, 295, 313, 367.

(*Ss, 2S, 3R*)-Diethyl 3-(*m*-nitrophenyl)-2-*N*-(*p*-toluenesulfinyl)aziridinylphosphonate (**3d**). R_f : 0.23 (ethyl acetate : *n*-hexane = 1:1); $[\alpha]^{25}_D$: -30.3 (c= 2.1, $CHCl_3$); ^1H NMR($CDCl_3$, 200MHz) δ 1.13~1.29(m, 6H), 2.41(s, 3H), 2.91(dd, 1H, J_{H-P}=15.5, J_{H-H}=7.4Hz), 3.82~4.17(m, 5H) 7.23~8.09(m, 8H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.32(d, *J*=6.1Hz), 21.50, 32.40(d, *J*=45.5Hz), 34.97(d, *J*=206.7Hz), 62.75(d, *J*=9.5Hz), 122.69, 123.17, 124.31, 125.00, 128.70, 129.75, 129.99, 134.19; MS(70eV) *m/z* 438(M^+, 4.8%), 91, 125, 139, 152, 197, 243, 271, 301, 327.

(*Ss, 2S, 3R*)- Diethyl 3-(2-naphthyl)-2-*N*-(*p*-toluenesulfinyl)aziridinylphosphonate (**3e**). R_f : 0.15 (ethyl acetate : *n*-hexane = 1:1); $[\alpha]^{25}_D$: -141.2 (c= 2.1, $CHCl_3$); ^1H NMR($CDCl_3$, 200MHz) δ 1.02~1.10(m, 6H), 2.37(s, 3H), 2.94(dd, 1H, J_{H-P}=16.1, J_{H-H}=7.7Hz), 3.66~4.27(m, 5H), 7.20~7.79(m, 11H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 15.26, 21.54, 31.63(d, *J*=47.2Hz), 36.78(d, *J*=162.7Hz), 65.84(d, *J*=7.2Hz), 124.68, 125.66, 126.06, 127.36, 129.80, 133.12, 135.07, 137.56; MS(70eV) *m/z* 443(M^+, 1.8%), 91, 139, 155, 167, 230, 248, 276, 304.

(*2S, 3R*) –Diethyl 3-phenyl-2-*N*-(*p*-toluenesulfonyl)aziridinylphosphonate (5a). To a stirred solution of **3a** (20 mg, 0.05 mmol) in ethanol (2 mL) was added mCPBA (16 mg, 0.08 mmol) at room temperature under nitrogen. Stirring was continued for 8 h at room temperature. Reaction mixture was concentrated in vacuo, diluted with ethyl acetate, washed with water, dried($MgSO_4$), concentrated in vacuo. The residue was purified by the flash chromatography (ethyl acetate : *n*-hexane = 1 : 2) to give the **5a** (17 mg, 87%). R_f : 0.4 (ethyl acetate : *n*-hexane = 2:1); $[\alpha]^{25}_D$: -68.0 (c= 0.5, $CHCl_3$); ^1H NMR($CDCl_3$, 200MHz) δ 0.95~1.44(m, 6H), 2.45(s, 3H), 3.14(dd, 1H, J_{H-P}=14.7, J_{H-H}= 7.5Hz), 3.44~3.56(m, 1H), 3.72~4.20(m, 4H), 7.23~7.45(m, 7H), 7.85~7.92(m, 2H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.01(d, *J*=5.5Hz), 21.66, 38.82(d, *J* = 198.5Hz), 44.03(d, *J*=4.0Hz), 62.45(d, *J*=3.0Hz), 62.51(d, *J*=3.0Hz) 127.02, 127.22, 128.08, 128.23, 128.35, 129.17, 129.34, 129.51; HRMS: calcd for $C_{19}H_{24}NO_5PS$ 409.1113, found 409.1120.

(*S*)-Diethyl 2-phenyl-1-*N*-(*p*-toluenesulfonyl)aminoethylphosphonate (6a). A mixture of **5a** (12 mg, 0.03 mmol), ammonium formate (10 mg, 0.15 mmol), and palladium on charcoal(10%, 12 mg) in methanol (2 mL) was stirred at room temperature for 24 h. The reaction mixture was then filtered through a short plug of Celite and washed with ethyl ether and methanol. The filterate was evaporated under reduced pressure. The resulting residue was extracted with ethyl acetate, dried($MgSO_4$), concentrated in vacuo. Purification by flash chromatography provided **6a** (11.8 mg, 93%) as a white solid. R_f : 0.21 (ethyl acetate : *n*-hexane = 1:1); mp 104-105 °C; $[\alpha]^{25}_D$: -39.0 (c= 1.0, $CHCl_3$); ^1H NMR($CDCl_3$, 200MHz) δ 1.17~1.38(m, 6H), 2.39(s, 3H), 2.80~3.19(m, 2H), 3.90~4.20(m, 5H), 5.02~5.07(m, 1H), 7.06~7.30(m, 7H), 7.51~7.61(m, 2H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.28(d, *J*=6.5Hz), 21.39, 36.62, 51.82(d, *J*=156.5Hz), 61.34(d, *J*=6.5Hz), 62.38(d, *J*=7.0Hz), 126.57, 126.74, 126.97, 127.18, 128.24, 128.88, 129.42, 129.62, 136.29, 136.47, 138.29, 142.89; HRMS: calcd for $C_{19}H_{26}NO_5PS$ 411.1269, found 411.1258.

(*S*)-(1-Amino-2-phenylethyl)phosphonic acid (7a). A mixture of **6a** (45 mg, 0.11 mmol), phenol (1.0 g) in 33% HBr/HOAc (3 mL) was refluxed with stirring for 12 h. The mixture was then cooled, concentrated in vacuo, and azotropically dried with benzene. The residue was dissolved in refluxing ethanol and treated propylene oxide. Filteration furnished **7a** (19.3 mg, 45%) as a white solid. R_f : 0.12 (methanol); mp 258-260 °C (lit.[10] mp 265 °C); $[\alpha]^{25}_D$: +53.7(c=1.0, 1N NaOH); ^1H NMR ($NaOD/D_2O$, 200MHz) δ 2.75~3.00(m, 1H), 3.20~3.49(m, 2H), 7.35~7.55(m, 5H).

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