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ORIGINAL ARTICLE

Facile synthesis of hybrid sulfonophosphinodipeptides composing of taurines and 1-aminoalkylphosphinic acids

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Abstract Both sulfonopeptides and phosphonopeptides are important analogs of naturally occurring peptides and have been widely used as enzyme inhibitors and haptens for producing catalytic antibodies due to their tetrahedrally structural features. A series of hybrid sulfonophosphinodipeptides composing of taurines and 1-aminoalkylphosphinic acids were first and conveniently synthesized in satisfactory to good yields via a Mannich-type reaction of *N*-benzyloxycarbonylaminoalkanesulfonamides, aldehydes, and aryldichlorophosphines, and subsequent hydrolysis. The current method provides an efficient and direct synthesis of hybrid sulfonophosphinodipeptides.

Keywords Aminoalkanesulfonamide · Mannich reaction · Peptide · Phosphinopeptide · Synthesis

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Introduction

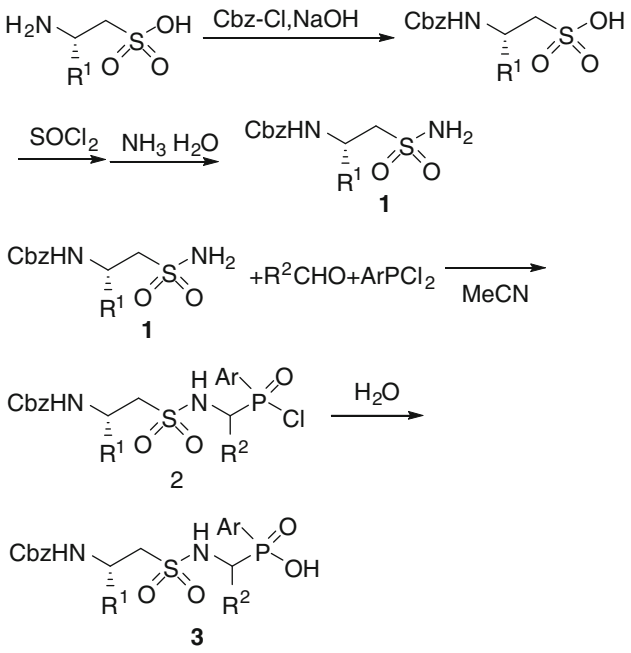
Phosphonopeptides and phosphinopeptides are important phosphorus analogs of naturally occurring peptides. Sulfonopeptides are significant sulfur analogs of naturally occurring peptides. All of them have been widely used as enzyme inhibitors and as haptens for catalytic antibody research because they can be considered as stable mimetics of tetrahedral transition states in ester and amide hydrolysis and formation (Kafarski and Lejczak 2000b; Yiotakis et al. 2004; Cunningham et al. 2008; Xu 2003; Carson et al. 1997). Several phosphonopeptides have also shown potent antibacterial activity (Kafarski and Lejczak 2000b; Atherton et al. 1986).

Phosphonopeptides, including phosphonamidate and phosphinamidate linkages, have been synthesized generally via the reaction of phosphonochloridates with amino acid esters or peptide esters (Kafarski and Lejczak 2000a), via the direct condensation of phosphonate monoesters with amino acid esters or peptide esters in the presence of coupling reagents (Galeotti et al. 1996; Campbell and Bermak 1994a, b; Karanewsky and Badia 1986), and via our Mannich-type condensation of benzyl carbamate, aldehydes, alkyl dichlorophosphite, and subsequent aminolysis with amino esters (Fu et al. 2006), or of *N*-Cbz protected amino amides/peptide amides, aldehydes, aryldichlorophosphines, and subsequent aminolysis with amino acid esters/peptide esters (Li et al. 2007; He et al. 2009).

Sulfonopeptides have been generally prepared from the reaction of *N*-protected aminoalkanesulfonyl chlorides with amino acid esters or peptide esters (Xu 2003; Lowik and Liskamp 2000; Gennari et al. 1994) or from the condensation of *N*-protected aminoalkanesulfinyl chlorides and amino esters or peptide esters, followed by subsequent oxidation (Xu 2003; Moree et al. 1993, 1995). Recently,

some sulfino amino acid derivatives, considered as mimetics of sulfonopeptides, have been synthesized (Kukhar et al. 2009; Sorochinsky and Soloshonok 2010).

Phosphinopeptides containing C-terminal α-aminoalkylphosphinic acids have been synthesized by coupling of *N*-protected amino acids or their active esters with alkyl α-aminoalkylphosphinates (Vassiliou et al. 2008; Ravaschino et al. 2006; Atherton et al. 1986), or with free α-aminoalkylphosphinic acids in organic media or in aqueous-organic media (Kafarski and Lejczak 1988; Solodenko et al. 1991; Lukas et al. 2002). All of these methods used phosphinic acid derivatives as starting materials, which were generally synthesized in multi-step procedure (Kukhar et al. 1994; Soloshonok et al. 1992; Xu and Yu 1999). Recently, we reported novel methods for the preparation of α-aminoalkylphosphonic acid derivatives via the phosphorus-Mannich-type reactions of carbamates, aldehydes, and chlorophosphites (Xu and Fu 2000, 2001; Xu and Wei 2001; Liu and Xu 2005; Xu and Gao 2005; Liu et al. 2006). We also prepared phosphinopeptides via the Mannich-type condensation of *N*-Cbz protected amino amides/peptide amides, aldehydes, aryldichlorophosphines, and subsequent aminolysis with amino acid esters/peptide esters (Li et al. 2007) and sulfonophosphinopeptides via the Mannich-type condensation of *N*-Cbz protected amino alkanesulfonamides, aldehydes, aryldichlorophosphines, and subsequent aminolysis with amino acid esters/peptide esters (He et al. 2009). The method has been applied to synthesize phosphinopeptides containing *C*-terminal α-aminoalkylphosphinic acids via the Mannich reaction and subsequent hydrolysis (Meng and Xu 2010). We herein present the facile synthesis of hybrid sulfonophosphinodipeptides composing of *β*-aminoalkanesulfonic acids and *C*-terminal α-aminoalkylphosphinic acids (Scheme 1).



Scheme 1 Facile synthesis of hybrid sulfonophosphinodipeptides

Materials and methods

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. The ^{1}HNMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a Varian Mercury Plus 300 (300 MHz) or Bruker 400 (400 MHz) spectrometer with TMS as an internal standard in the $CDCl_3$ solution. ^{31}P NMR spectra were obtained with use of broad-band ^{1}H decoupling; chemical shifts are reported as ppm referenced to 85% phosphoric acid with positive shift downfield. IR spectra were determined on a Nicolet AVATAR 330 FT-IR spectrometer. HRMS data were obtained with an Agilent LC/MSD TOF mass spectrometer. Optical rotations were measured on a PerkinElmer Model 341 polarimeter with a thermally jacketed 10 cm cell (concentration *c* expressed as g/100 mL). TLC separations were performed on silica gel G plates with petroleum ether (60–90°C)/ethyl acetate (1:1, *v/v*), and the plates were visualized with UV light.

Aryldichlorophosphines were prepared according to literature procedure (Buchner and Lockhart 1951) and their analytical data are identical to reported ones (Buchner and Lockhart 1951; Weinberg 1975). Aminoalkanesulfonic acids were prepared synthesized from vicinal amino alcohols according to our reported method (Zhang et al. 2008). 2-Benzyloxycarbonylaminoalkanesulfonic acids were prepared from benzyl chloroformate and 2-aminoalkanesulfonic acids according to our reported method (He et al. 2009). Acetonitrile was refluxed with calcium hydride and freshly distilled prior to use. All reactions were performed under a nitrogen atmosphere.

General procedure for the preparation of *N*-Cbz-aminoalkanesulfonamides

A solution of 2-Cbz-aminoalkanesulfonic acid (54 mmol) and DMF (0.5 mL) was added to thionyl chloride (50.3 g, 30 mL, 422 mmol). The resulting solution was refluxed under stirring for about 4 h. The cooled reaction mixture was passed through a Celite column with dry dichloromethane as an eluent. After removal of solvent, the residue was dissolved in dry dichloromethane and the solvent was removed twice to remove residual thionyl chloride. Pure 2-Cbz-aminoalkanesulfonyl chloride was obtained. It was dissolved in dichloromethane and the resulting solution was added dropwise into ammonia (50 mL) under stirring at −10°C. After addition, the resulting mixture was stirred for another 30 min at 5°C. Precipitates was collected after

filtration and crystallized from water or methanol to give colorless crystals (2-Cbz-aminoalkanesulfonamides).

2-Benzyloxycarbonylaminoethanesulfonamide (**1a**) Colorless needle crystals, m.p. 138.5–140°C. Lit. m.p. 138.5–140°C (He et al. 2009). Yield 42%. $R_f = 0.26$ (Silica gel plate, ethyl acetate:hexanes 1:1, *v/v*).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.12 (t, $J = 7.0$ Hz, 2H, CH_2), 3.40 (dt, $J = 6.8$, 7.0 Hz, 2H, CH_2), 5.02 (s, 2H, CH_2), 6.90 (s, 2H, NH_2), 7.30–7.39 (m, 6H, ArH, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 36.2, 54.4, 66.0, 128.2, 128.3, 128.8, 137.4, 156.5.

(*S*)-2-Benzyloxycarbonylaminopropanesulfonamide (**1b**) Colorless needle crystals, m.p. 150–151°C. Yield 43%. $R_f = 0.57$ (Silica gel plate, ethyl acetate:hexanes 1:1, *v/v*). $[\alpha]_D^{20} = +10.8$ (*c*, 1.0, MeOH).

IR ν (cm^{-1}): 1,668 (C=O), 1,342 and 1,142 (SO_2).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.24 (d, $J = 6.6$ Hz, 3H, CH_3), 3.04 (dd, $J = 7.5$, 13.9 Hz, 1H in CH_2SO_2), 3.25 (dd, $J = 5.3$, 13.9 Hz, 1H in CH_2SO_2), 4.01(ddq, $J = 5.3$, 7.5, 6.6 Hz, 1H, CHN), 5.03 (s, 2H, OCH_2), 6.90 (s, 2H, NH_2), 7.28–7.42 (m, 6H, ArH and NH).

^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.4, 43.2, 59.8, 65.3, 127.7, 127.8, 128.3, 137.0, 155.2.

HRMS (ESI) Calcd. for $C_{11}H_{17}N_2O_4S$ $[M + H]^+$ *m/z* 273.0904; Found 273.0902.

(*S*)-2-Benzyloxycarbonylamino-3-phenylpropanesulfonamide (**1c**) Colorless crystals, m.p. 168–170°C. Lit. m.p. 168–170°C (He et al. 2009). Yield 30%. $R_f = 0.57$ (Silica gel plate, ethyl acetate:hexanes 1:1, *v/v*). $[\alpha]_D^{20} = -14.4$ (*c*, 1.0, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.83–3.03 (m, 2H, CH_2), 3.15–3.38 (m, 2H, CH_2), 4.18 (s, 1H, CH), 4.99 (s, 2H, CH_2), 6.91 (s, 2H, NH_2), 7.23–7.40 (m, 11H, ArH, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 39.8, 49.3, 58.6, 65.6, 126.8, 127.9, 128.1, 128.7, 128.8, 129.7, 137.6, 138.6, 155.9.

(*S*)-2-Benzyloxycarbonylamino-3-methylbutanesulfonamide (**1d**) Colorless crystals, m.p. 113–114°C. Yield 60%. $R_f = 0.66$ (Silica gel plate, ethyl acetate:hexanes 1:1, *v/v*). $[\alpha]_D^{20} = +17.2$ (*c*, 1.0, MeOH).

IR ν (cm^{-1}): 1,696 (C=O), 1,327 and 1,143 (SO_2).

^{1}H NMR (300 MHz, DMSO-d_6)δ: 0.82 (d, $J = 6.4$ Hz, 6H, $2CH_3$), 1.81–1.90 (m, 1H, $CH(CH_3)_2$), 3.10 (d, $J = 6.0$ Hz, 2H, CH_2SO_2), 3.85–3.94 (m, 1H, CHN), 5.03 (s, 2H, OCH_2), 6.81 (s, 2H, NH_2), 7.30–7.36 (m, 6H, ArH and NH).

^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.3, 18.6, 31.6, 51.9, 56.0, 65.1, 127.5, 127.6, 128.3, 137.2, 155.8.

HRMS (ESI, *m/z*) Calcd. for $C_{13}H_{21}N_2O_4S$ $[M + H]^+$ *m/z* 301.1217; Found 301.1214.

(*S*)-2-Benzyloxycarbonylamino-4-methylpentanesulfonamide (**1e**) Colorless crystals, m.p. 128–129°C. Yield 50%. $R_f = 0.77$ (Silica gel plate, ethyl acetate:hexanes 1:1, *v/v*). $[\alpha]_D^{20} = -7.5$ (*c*, 1.0, MeOH).

IR ν (cm^{-1}): 1,683 (C=O), 1,326 and 1,152 (SO_2).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.86 (d, $J = 6.3$ Hz, 6H, $2CH_3$), 1.42–1.48 (m, 2H, $CHCH_2$), 1.56–1.65 (m, 1H, $CH(CH_3)_2$), 3.04 (dd, $J = 6.0$, 13.8 Hz, 1H in CH_2SO_2), 3.22 (dd, $J = 6.3$, 13.8 Hz, 1H in CH_2SO_2), 3.94–4.05 (m, 1H, CHN), 5.02 (s, 2H, CH_2Ph), 6.81 (s, 2H, NH_2), 7.29–7.36 (m, 6H, ArH and NH).

^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.4, 23.1, 24.1, 42.7, 45.4, 59.2, 65.1, 127.5, 127.7, 128.2, 137.1, 155.5.

HRMS (ESI) Calcd. for $C_{14}H_{22}N_2O_4S$ $[M + H]^+$ *m/z* 315.1373; Found 315.1370.

General procedure for the synthesis of hybrid sulfonophosphinodipeptides

To a solution of Cbz-aminoalkanesulfonamide (1.9 mmol) and aldehyde (2.0 mmol) in dried acetonitrile (10 mL) was added arylphosphine dichloride (2.0 mmol) under the nitrogen atmosphere. The resulting solution was stirred at 45°C for 12 h. After cooling and addition of water (0.5 mL), the reaction mixture was stirred for another 2 h. After removal of solvent, the residue was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium bicarbonate. The aqueous solution was adjusted to pH 1. Colorless precipitates appeared. After filtration and washing with water, the solid was crystallized in ethyl acetate or in methanol to afford colorless powder crystals.

Phenyl[(*R,S*)-*N*-[*N*-benzyloxycarbonylaminoethanesulfonyl]-1-aminophenylmethyl]phosphinic acid (3**a**) Colorless crystals, m.p. 140–143°C, yield 81%. $R_f = 0.42$ (Silica gel plate, CH_2Cl_2:MeOH:HOAc 20:1:1, *v/v*).

IR ν (cm^{-1}): 1,713 (C=O), 1,313 and 1,185 (SO_2), 1,246 (P=O).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.72 (s, 2H, SO_2CH_2), 3.20–3.21 (m, 2H, NCH_2), 4.43 (dd, $J = 8.5$, 15.9 Hz, 1H, NCH), 5.01 (s, 2H, OCH_2), 7.13–7.74 (m, 17H, ArH and 2NH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 35.1, 52.2, 58.7 (d, $J_{P\text{-}C} = 97.6$ Hz), 65.2, 126.2, 127.1,127.2, 127.6, 128.1, 128.2, 130.1, 131.9, 132.0, 137.0, 138.3, 155.7.

^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 25.5.

HRMS (ESI) Calcd. for $C_{23}H_{26}N_2O_6PS$ $[M + H]^+$ *m/z* 489.1249; Found 489.1260.

4-Methylphenyl[(*R,S*)-*N*-[*N*-benzyloxycarbonylaminoethanesulfonyl]-1-amino-phenylmethyl]phosphinic acid (3**b**) Colorless crystals, m.p. 196–202°C, yield 80%; major rotamer:minor rotamer = 79:21.

$R_f = 0.5$ (Silica gel plate, CH_2Cl_2:MeOH:HOAc 20:1:1, *v*/*v*).

IR *v* (cm^{-1}): 1,714 (C=O), 1,337 and 1,176 (SO_2), 1,244 (P=O).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.31 (s, 3H, CH_3, minor), 2.33 (s, 3H, CH_3, major), 2.54–2.64 (m, 2H, SO_2CH_2), 3.08–3.14 (m, 2H, NCH_2), 4.68 (dd, $J = 9.8$, 17.2 Hz, 1H, PCH), 5.00 (s, 2H, OCH_2), 7.12–7.59 (m, 15H, ArH and NH), 8.21 (d, $J = 9.8$ Hz, 1H, SNH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.8 (minor), 21.0 (major), 34.9, 52.7, 57.4 (d, $J_{P\text{-}C} = 102.3$ Hz, minor), 57.5 (d, $J_{P\text{-}C} = 105.7$ Hz, major), 65.3, 127.3, 127.7, 127.74, 127.8, 128.3, 128.4, 128.5, 128.6, 129.2, 131.9, 131.96, 132.3, 132.4, 136.0, 136.9, 141.7, 155.7.

^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 29.9 (minor), 29.7 (major).

HRMS (ESI) Calcd. for $C_{24}H_{28}N_2O_6PS$ $[M + H]^+$ *m/z* 503.1406; Found 503.1410.

Phenyl[(*R,S*)-*N*-[*N*-benzyloxycarbonylaminoethanesulfonyl]-1-amino-(4-methylphenyl)methyl]phosphinic acid (3**c**) Colorless crystals, m.p. 199–203°C, yield 78%. $R_f = 0.39$ (Silica gel plate, CH_2Cl_2:MeOH:HOAc 20:1:1, *v*/*v*).

IR *v* (cm^{-1}): 1,714 (C=O), 1,337 and 1,176 (SO_2), 1,176 (P=O).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 2.57–2.68 (m, 2H, SO_2CH_2), 3.12–3.13 (m, 2H, NCH_2), 4.68 (dd, $J = 10.2$, 16.9 Hz, 1H, PCH), 4.99 (s, 2H, OCH_2), 7.08–7.72 (m, 15H, ArH and NH), 8.13 (d, $J = 10.0$ Hz, 1H, SNH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.6, 34.9, 52.7, 57.1 (d, $J_{P\text{-}C} = 106.5$ Hz), 65.3, 127.7, 127.74, 127.8, 128.0, 128.3, 128.33, 128.37, 128.4, 131.2, 131.7, 131.8, 131.9, 132.5, 132.8, 136.5, 136.9, 155.7.

^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 29.6.

HRMS (ESI) Calcd. for $C_{24}H_{28}N_2O_6PS$ $[M + H]^+$ *m/z* 503.1406; Found 503.1410.

Phenyl[(*R,S*)-*N*-[*N*-benzyloxycarbonylaminoethanesulfonyl]-1-amino-2-methylpropyl]phosphinic acid (3**d**) Colorless crystals, m.p. 165–170°C, yield 80%. $R_f = 0.42$ (Silica gel plate, CH_2Cl_2:MeOH:HOAc 20:1:1, *v*/*v*).

IR *v* (cm^{-1}): 1,716 (C=O), 1,145 (P=O), 1,309 and 1,178 (SO_2).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.92 (d, $J = 6.6$ Hz, 3H, CH_3), 0.94 (d, $J = 6.6$ Hz, 3H, CH_3), 1.97–2.09 (m, 1H, $CH(CH_3)_2$), 2.63–2.75 (m, 2H, SO_2CH_2), 3.17–3.30 (m, 2H, NCH_2), 3.55 (ddd, $J = 3.2$, 10.4, 13.2 Hz, 1H, PCH), 5.00 (s, 2H, OCH_2), 7.25–7.78 (m, 12H, ArH and 2NH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 17.9 (d, $J_{P\text{-}C} = 2.8$ Hz), 20.9 (d, $J_{P\text{-}C} = 10.9$ Hz), 28.0 (d, $J_{P\text{-}C} = 4.8$ Hz), 35.2, 52.9, 57.9 (d, $J_{P\text{-}C} = 108.8$ Hz), 65.3, 127.6, 127.7, 128.0, 128.1, 128.2, 131.6, 131.61, 131.63, 131.7, 132.3, 133.5, 136.9, 155.7.

^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 32.7.

HRMS (ESI) Calcd. for $C_{20}H_{28}N_2O_6PS$ $[M + H]^+$ *m/z* 455.1406; Found 455.1403.

Phenyl[(*R,S*)-*N*-[(*S*)-*N*-benzyloxycarbonyl-2-aminopropanesulfonyl]-1-aminophenylmethyl]phosphinic acid (3**e**) Colorless crystals, m.p. 192–197°C; (*S,S*):(*S,R*) = 54:46. $R_f = 0.38$ (Silica gel plate, CH_2Cl_2:MeOH:HOAc 20:1:1, *v*/*v*). $[\alpha]_D^{20} = +5.8$ (*c*, 1.0, MeOH).

IR *v* (cm^{-1}): 1,718 (C=O), 1,312 and 1,249 (SO_2), 1,193 (P=O).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.91 [d, $J = 6.4$ Hz, 3H, CH_3, (*S,S*)] and 0.98 [d, $J = 6.4$ Hz, 3H, CH_3, (*S,R*)], 2.33–2.38 (m, 1H in CH_2SO_2), 2.67–2.78 (m, 1H in CH_2SO_2), 3.72–3.82 (m, 1H, NCH), 4.67–4.74 (m, 1H, CHP), 4.99 (s, 2H, OCH_2), 7.15–7.53 (m, 15H, 15ArH), 7,67–7.71 [m, 2H, 2NH, (*S,S*)], 8.11 [s, br, 1H, NH, (*S,R*)], 8.19 [d, $J = 10.8$ Hz, 1H, NH, (*S,R*)].

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.2, 42.46 (*S,R*), 42.52 (*S,S*), 57.4 [d, $J_{p\text{-}c} = 105.1$ Hz, (*S,R*)], 57.5 [d, $J_{p\text{-}c} = 105.1$ Hz, (*S,S*)], 58.5 (*S,R*), 58.53 (*S,S*), 65.1, 127.2, 127.26, 127.52, 127.55, 127.6, 127.72, 127.74, 127.8, 127.9, 128.2, 128.37, 128.4, 128.47, 128.5, 131.1, 131.2, 131.6, 131.78, 131.8, 131.9, 132.4, 132.5, 136.0, 136.9, 154.8, 154.9.

^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 29.3 (*S,R*), 29.5 (*S,S*) (85% H_3PO_4 as an external standard).

HRMS (ESI) Calcd. for $C_{24}H_{28}N_2O_6PS$ $[M + H]^+$ *m/z* 503.1400; Found 503.1409.

Phenyl[(*R,S*)-*N*-[(*S*)-*N*-benzyloxycarbonyl-2-amino-3-phenylpropanesulfonyl]-1-aminophenylmethyl]phosphinic acid (3**f**) Colorless crystals, m.p. 201–203°C, yield 72%; (*S,S*):(*S,R*) = 57:43. $R_f = 0.45$ (Silica gel plate, CH_2Cl_2:MeOH:HOAc 20:1:1, *v*/*v*). $[\alpha]_D^{20} = +14.0$ (*c*, 0.1, MeOH).

IR *v* (cm^{-1}): 1,714 (C=O), 1,337 and 1,176 (SO_2), 1,176 (P=O).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.50–2.64 (m, 2H, $PhCH_2$), 2.71–2.98 (m, 2H, SO_2CH_2), 3.98–4.02 (m, 1H, NCH), 4.29–4.33 (m, 1H, PCH), 4.97 (dd, $J = 12.0$, 13.1 Hz), 7.07–7.61 (m, 22H, ArH and 2NH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 35.7, 42.0, 44.0, 57.8 (d, $J_{P\text{-}C} = 106.8$ Hz), 65.8, 126.8, 127.8, 128.2, 128.7, 128.8, 130.7, 132.5, 137.6, 138.9, 156.3.

^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 20.8.

HRMS (ESI) Calcd. for $C_{30}H_{31}N_2O_6PS$ $[M + H]^+$ 579.1719; Found 579.1712.

Phenyl[*N*-(*R,S*)-[(*S*)-*N*-benzyloxycarbonyl-2-amino-3-methylbutanesulfonyl]-1-aminophenylmethyl]phosphinic acid (3 **g**) Colorless crystals, m.p. 172–176°C, yield 71%; (*S,S*):(*S,R*) = 59:41. $R_f = 0.6$ (Silica gel plate, CH_2Cl_2:MeOH:HOAc 20:1:1, *v*/*v*). $[\alpha]_D^{20} = +18.0$ (*c*, 0.1, MeOH).

IR ν (cm^{-1}): 1,698 (C=O), 1,330 and 1,144 (SO_2), 1,218 (P=O).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.57 (d, J = 16.5 Hz, 6H, $2CH_3$), 1.48 (br, 1H, $CH(CH_3)_2$), 2.37–2.74 (m, 2H, SO_2CH_2), 3.66 (s, 1H, NH*CH*), 4.75 (s, br, 1H, CHP), 5.00 (s, 2H, OCH_2), 7.21–8.19 (m, 17H, ArH and 2NH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 17.0 (*S*,*S*), 17.1 (*S*,*R*),18.3 (*S*,*S*), 18.4 (*S*,*R*), 31.7 (*S*,*S*), 31.71 (*S*,*R*), 50.9 (*S*,*S*), 51.1 (*S*,*R*), 54.8 (*S*,*R*), 55.0 (*S*,*S*), 57.4 [d, $J_{P\text{-}C}$ = 105.9 Hz, (*S*,*R*)], 57.5 [d, $J_{p\text{-}c}$ = 105.5, (*S*,*S*)], 64.9 (*S*,*S*), 65.0 (*S*,*R*), 127.4, 127.6, 127.8, 128.0, 128.2, 128.6, 131.7, 131.8, 131.9, 136.1, 137.2, 155.6, 155.8.

^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 29.5 (*S*,*S*), 29.7 (*S*,*R*) (85% H_3PO_4 as an external standard).

HRMS (ESI) Calcd. for $C_{26}H_{32}N_2O_6PS$ $[M + H]^+$ *m/z* 531.1713; Found 531.1714.

Phenyl[*N*-(*R*,*S*)-[(*S*)-*N*-benzyloxycarbonyl-2-amino-4-methylpentanesulfonyl]-1-aminophenylmethyl]phosphinic acid (3 **h**) Colorless crystals, m.p. 119–125°C, yield 80%, (*S*,*S*):(*S*,*R*) = 66:34. R_f = 0.55 (Silica gel plate, CH_2Cl_2:MeOH:HOAc 20:1:1, *v*/*v*). $[\alpha]_D^{20}$ = +1.0 (*c*, 0.1, MeOH).

IR ν (cm^{-1}): 1,700 (C=O), 1,327 and 1,145 (SO_2), 1,225 (P=O).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.74 (s, 6H, $2CH_3$), 0.96–1.24 (m, 2H in CH_2CH), 1.35–1.41 (m, 1H in $CH(CH_3)_2$), 2.30–2.35 (m, 1H in CH_2SO_2), 2.61–2.76 (m, 1H in CH_2SO_2), 3.78 (m, 1H, N*CH*), 4.69 (dd, J = 9.6, 16.8 Hz, 1H, CHP), 5.05 (s, 2H, OCH_2), 7.12–7.51 (m, 15H, ArH), 7.68 (t. J = 8.8 Hz, 2H, 2NH), 7.93 (d, J = 10.8 Hz, 1H, NH, epimer), 8.11 (d, J = 10.0 Hz, 1H, NH, epimer).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 21.2 (*S*,*S*), 21.3 (*S*,*R*), 22.8 (*S*,*R*), 22.9(*S*,*S*), 23.8 (*S*,*S*), 23.9 (*S*,*R*), 42.6 (*S*,*S*), 42.8 (*S*,*R*), 44.7 (*S*,*R*), 44.8 (*S*,*S*), 57.5 [d, $J_{P\text{-}C}$ = 102.7 Hz, (*S*,*S*)], 57.6 [d, $J_{P\text{-}C}$ = 104.3 Hz, (*S*,*R*)], 57.51(*S*,*R*), 58.12 (*S*,*S*), 64.9, 127.1, 127.13, 127.3, 127.4, 127.5, 127.6, 127.7, 128.1, 128.4, 128.5, 131.4, 131.8, 131.9, 136.2, 137.1, 155.1 (*S*,*R*), 155.3 (*S*,*S*).

^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 28.8 (85% H_3PO_4 as an external standard).

HRMS (ESI) Calcd. for $C_{27}H_{34}N_2O_6PS$ $[M + H]^+$ *m/z* 545.1870; Found 545.1868.

Results and discussion

First, *N*-benzoxylcarbonyl protected taurine was prepared from taurine and benzyl chloroformate under basic conditions and it was further converted into 2-(*N*-benzoxycarbonylamino)ethanesulfonyl chloride with thionyl chloride. After aminolysis with ammonia, 2-(*N*-benzoxycarbonylamino)ethanesulfonamide (**1**a) was obtained according to the reported method (He et al. 2009). It was used as an amine component in the Mannich-type reaction with benzaldehyde, phenyldichlorophosphine in anhydrous acetonitrile, and subsequent hydrolysis with water to afford a hybrid sulfonophosphinodipeptide **3a** in a good yield (Table 1, entry 1). Benzyl carbamate and toluenesulfonamide was also used as an amine component in the Mannich-type reaction to prepare *N*-tolyl-aminobenzylphosphinic acid previously (Zhang et al. 1993; Chen and Dai 1995). In the current method, an aminoalkanesulfonic acid and an aminoalkylphosphinic acid were linked together to generate the hybrid sulfonophosphinodipeptide in a one-pot pseudo-four component condensation reaction. The current route provides a new and efficient pathway to synthesize sulfonophosphinopeptides via the Mannich-type reaction. To our best knowledge, this is the first synthesis of the hybrid sulfonophosphinodipeptides. The synthetic method is a convergent and atom-economic strategy for synthesis of hybrid sulfonophosphinopeptides.

Following the procedure, a series of hybrid sulfonophosphinodipeptides were prepared by the use of different aldehydes, 2-*N*-Cbz-aminoalkanesulfonamides, and

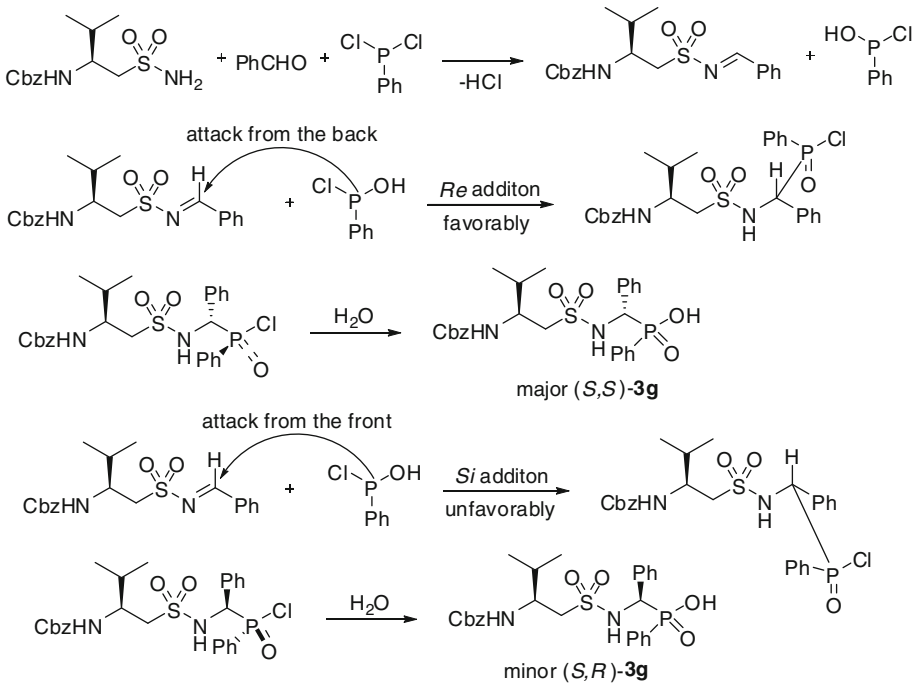
Table 1 Facile synthesis of hybrid sulfonophosphinodipeptides

Entry	Dipeptide	R^1	R^2	Ar	Yield (%)	Dr (*S*,*S*):(*S*,*R*)
1	**3a**	H	Ph	Ph	81	–
2	**3b**	H	Ph	*p*-MePh	80	–
3	**3c**	H	*p*-MePh	Ph	78	–
4	**3d**	H	^{i}Pr	Ph	80	–
5	**3e**	Me	Ph	Ph	75	54:46[a] (59:41[b])
6	**3f**	Bn	Ph	Ph	72	57:43[c]
7	**3g**	^{i}Pr	Ph	Ph	71	59:41[a]
8	**3h**	^{i}Bu	Ph	Ph	80	66:34[c]

[a] Diastereomeric ratio value on the basis of integration in ^{31}P NMR analysis

[b] Diastereomeric ratio value on the basis of integration in ^{1}H NMR analysis

[c] Diastereomeric ratio value on the basis of integration in ^{13}C NMR analysis



Scheme 2 Formation mechanism and stereostructures of diastereomeric hybrid sulfonophosphinodipeptide **3g**

aryldichlorophosphines. The results are summarized in Table 1. The results indicated that different aldehydes, 2-*N*-Cbz-aminoalkanesulfonamides, and aryldichlorophosphines do not affect the yields obviously. All reactants used work very well for the reaction (Table 1, entries 1–8). The structures of all sulfonophosphinopeptides **3** were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and MS spectrometries.

On stereochemistry of the product sulfonophosphinodipeptides, for *N*-Cbz-taurine amide, racemic sulfonophosphinodipeptides **3a–d** were obtained. However, interestingly, two stereostructural isomers of product **3b** were determined in all NMR spectra, revealing that two different rotamers rather than epimers exist in its solution because there is only one chiral carbon atom in the racemic product. For optically active (*S*)-*N*-Cbz-2-aminoalkanesulfonamides **1b–e**, low degree of asymmetric induction was observed in each of cases because the chiral center is too far away from the reactive center in the addition step of the arylchlorophosphonous acid to the *N*-alkanesulfonyl imine in the reaction (Scheme 2). The diastereomeric ratio of products was determined on the basis of integration in NMR analysis. The (*S,S*)-epimer of the products was assumed as major diastereomer in the products on the basis of the reaction mechanism (Scheme 2). The reaction of (*S*)-2-Benzyloxycarbonylamino-3-methylbutanesulfonamide (**1d**), benzaldehyde, and phenyldichlorophosphine was selected as an example to illustrate the reaction mechanism and diastereoselectivity. The sulfonamide, benzaldehyde, and phenyldichlorophosphine react to produce an *N*-sulfonylimine and phenylchlorophosphonous acid similar to previous reports (Li et al. 2007; He et al. 2009). The phenylchlorophosphonous acid then attacks the imine favorably from its *Re* side due to the existence of steric isopropyl group, and subsequent proton transfer affords the key intermediate as the *N*-sulfonylaminoalkylphosphinic chloride, which undergoes hydrolysis to generate the product hybrid sulfonophosphinodipeptide (*S,S*)-**3g** with *S,S* configuration as major product. Similarly, the phenylchlorophosphonous acid attacks the imine disfavorably from its *Si* side to afford the sulfonophosphinodipeptide (*S,R*)-**3g** with *S,R* configuration as minor product (Scheme 2).

Conclusion

In conclusion, a series of novel hybrid sulfonophosphinodipeptides composing of 2-aminoalkanesulfonic acids and 1-aminoalkylphosphinic acids were synthesized in good yields in a facile and one-pot Mannich-type reaction of *N*-Cbz-2-aminoalkanesulfonamides, aldehydes, and aryldichlorophosphines, and subsequent hydrolysis. The current method is the first, convergent, and atom-economic synthesis of hybrid sulfonophosphinodipeptides.

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