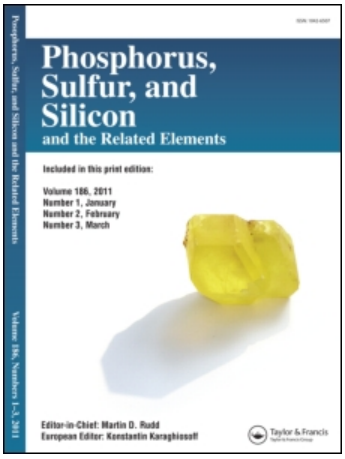

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SYNTHETIC APPROACH TO NEW α-AMINOPHOSPHONATES DERIVED FROM SIX-MEMBERED, SULFUR-CONTAINING HETEROCYCLIC IMINES

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SYNTHETIC APPROACH TO NEW α-AMINOPHOSPHONATES DERIVED FROM SIX-MEMBERED, SULFUR-CONTAINING HETEROCYCLIC IMINES

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Dialkyl phosphite adds to the C=N bond in *2H*-1,3-thiazines **4** to give α-aminophosphonic acid esters **6**. Starting from *2H*-1,4-benzothiazines **5**, the corresponding phosphonic acid esters **7** were obtained. For the first time C2-chiral *2H*-1,3-thiazines **4a** and **4b** were used to investigate the diastereoselectivity of the addition reaction of dialkyl phosphite to those imine compounds.

Keywords: α-Aminophosphonates; 1,3-thiazinan-4-yl-phosphonates; 3,4-dihydro-2*H*-1,4-benzothiazine-3-phosphonates

INTRODUCTION

The α-aminophosphonic acids and their derivatives, defined as phosphorus analogues of amino acids, are of interest because of their applications in pharmacological[1] and agriculture[2] areas.

In the course of our investigations on the synthesis of 4-thiazolidinyl phosphonates[3] of type **1** as intermediates of phosphonic acid analogues of penicillamine we became interested in the chemistry of the familiar six membered heterocyclic compounds.

We now wish to communicate[4] our results on the synthesis of the racemic 1,3-thiazinan-4-yl-phosphonates of type **2** and *2H*-1,4-benzothiazin-3-

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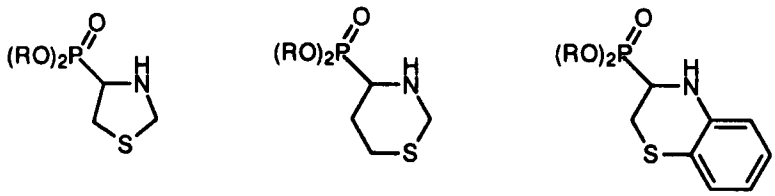


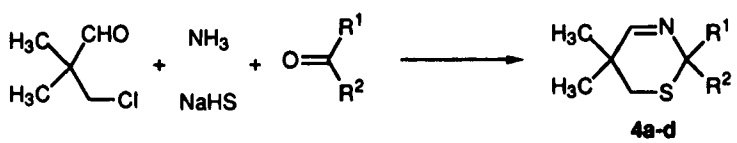
SCHEME 1 Familiar α-aminophosphoneates **1–3**.

phosphonates of type **3**. We synthesized the desired compounds **6** and **7** by the termal addition of dialkyl phosphites to the reactive C=N-double bond in heterocyclic imines, namely 2*H*-1,3-thiazines **4** and 2*H*-1,4-benzothiazines **5**. Furthermore we investigated the diastereoselectivity of the addition of dialkylphosphites to the imine components **4a** and **4b**.

RESULTS AND DISCUSSION

The new 2*H*-1,3-thiazines **4a–d** were prepared in a four component one pot reaction from 3-chloro-2,2-dimethylpropanol, a second carbonyl compound (aldehyde or ketone) in the presence of sodium hydrogen sulfide and aqueous ammonia as shown in scheme 2.

The 2*H*-1,4-benzothiazines **5** were prepared as recently described[5]. In practice, the synthesis of **6a–h** or **7a–c** is quite simple, requiring the reflux of a mixture of the cyclic imines **4** or **5** with dialkyl phosphite in ligroine for eighteen hours.



4a-d

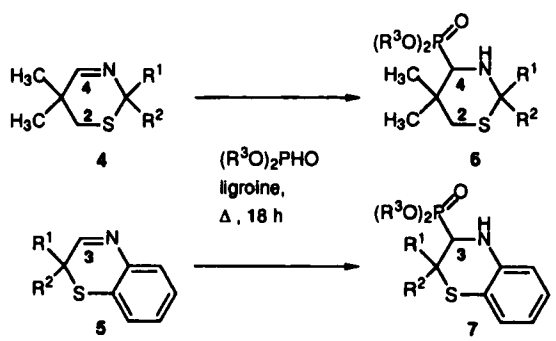
4	R^1	R^2	*Yield [%]*	*bp [°C]*
4a	H	$C(CH_3)_3$	34[a]	38–47 (0.002 mbar)
4b	H	$C(CH_3)_2CH_2CH_2Cl$	20	67 (0.005 mbar)
4c		$-(CH_2)_4-$	36	56 (0.002 mbar)
4d		$-(CH_2)_5-$	40	73-75 (0.002 mbar)

[a]The product **4a** contains small amounts of impurities still after distillation and was used without further purification.

SCHEME 2 One pot synthesis of 2*H*-1,3-thiazines **4a–d**.

We received the dialkylphosphite adducts **6, 7** in satisfying to good yields up to 62%. The results are summarized in scheme 3. The observed—and earlier discussed[4]—spectroscopical data are in correspondence with the structures **6** and **7**.

When the C2-chiral heterocyclic imines **4a** and **4b** were allowed to react with dimethyl- and diethyl phosphite, the formation of each of the two α-amino phosphonic acid diester diastereomers in ratios up to 88:12 was observed, depending on the kind of substituent R^3. Starting from 2*H*-1,3-thiazine **4a** the dialkylphosphite adducts **6a** (R^3 = methyl) and **6b** (R^3 = ethyl) were formed with diastereoselectivities of *dr* = 52:48 (R^3 = methyl) and *dr* = 60:40 (R^3 = ethyl), respectively. The substitution of the *t*-butyl group by the 2-chloro-1,1-dimethylethyl substituent in C2-position of 2*H*-1,3-thiazines led to increased *dr* values of the products **6c** (R^3 = methyl) and **6d** (R^3 = ethyl) with *dr* = 84:16 and *dr* = 88:12. Due to the bulkier 2-chloro-1,1-dimethylethyl substituent in



6,7	R^1	R^2	R^3	Yield [%]	*dr*[a]	mp [°C][b]
6a	H	$C(CH_3)_3$	CH_3	48	52:48	63-64
6b	H	$C(CH_3)_3$	C_2H_5	45	60:40	35-37
6c	H	$C(CH_3)_2CH_2Cl$	CH_3	17	88:12	28
6d	H	$C(CH_3)_2CH_2Cl$	C_2H_5	19	84:16	38-39
6e		$-(CH_2)_4-$	CH_3	12	—	61
6f		$-(CH_2)_4-$	C_2H_5	41	—	77-78
6g		$-(CH_2)_5-$	CH_3	47	—	78-79
6h		$-(CH_2)_5-$	C_2H_5	54	—	84
7a	CH_3	CH_3	CH_3	40	—	115-117
7b	CH_3	CH_3	C_2H_5	62	—	110-111
7c	C_2H_5	C_2H_5	C_2H_5	54	—	97

SCHEME 3 Dialkyl phosphite adducts **6** and **7**.

C2-position (as compared with the *t*-butyl group) diastereoselectivity *via* 1,3-induction is increased. Diastereomerically pure α-aminophosphonates could be obtained from the mixtures of diastereomers by simple recrystallization from CH_2Cl_2/n-Hexane. Diastereomerical purity of the isolated pure phosphonates **6a–d** ($dr \geq 95:5$) was determined by NMR spectroscopy.

In summary we described a versatile two step synthetic route to the new sulfur containing heterocyclic α-aminophosphonates of type **6** and **7**. Asymmetric additions of phosphites to the C=N-double bond of the chiral 2*H*-1,3-thiazines **4a** and **4b** were carried out forming the corresponding α-aminophosphonic acid derivatives **6a–d** with good diastereoselectivities up to dr = 88:12. Thereby, all the crystallized products **6a–d** could be obtained in diastereomeric pure form.

EXPERIMENTAL

Melting points were determined in an open capillary tube on a Dr. Linström instrument and are uncorrected. Elemental analyses were carried out on a Carlo Erba Stumentalione analyzer (MOD 1104). The ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded on a Bruker AM 300 spectrometer, in $CDCl_3$ as a solvent and TMS or H_3PO_4 (^{31}P-NMR) as an internal standard. The mass spectroscopy data were recorded on a Finnigan-MAT 212 spectrometer (Datasystem SS 300). The compounds 3-chloro-2,2-dimethylpropanal[6] and the 2*H*-1,4-benzothiazines **5a,b**[5] were prepared as described in the literature.

2*H*-1,3-thiazines 4; General Procedure (GP1)

25.6 g (213 mmol) of freshly prepared 3-chloro-2,2-dimethylpropanal was added to a solution of 14.3 g (256 mmol) sodium hydrogen sulfide, 42.6 ml of aqueous ammonia and 639 mmol of the oxo component in 100 ml of CH_2Cl_2 at 5–10°C. After stirring at ambient temperature for 18 h, 100 ml of CH_2Cl_2 were added, the two phases were separated and the aqueous layer was extracted twice with 50 ml of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, evaporated in vacuo and the residue was distilled in vacuo.

(RS)-5,5-Dimethyl-2-(1,1-dimethylethyl)-2H-1,3-thiazine **4a**

The preparation based on **GP1** from 296 mmol (35.7g) 3-chloro-2,2-dimethylpropanal, 888 mmol (76.5g) 1,1-dimethylpropanal, 888 mmol (59.2mL) concentrated, aqueous ammonia and 355 mmol (19.9g) sodium hydrogen sul-

fide. The product contains small amounts of impurities after distillation and was used without further purification.

Yield: 18.68 g (34%). Bp.: 38–47°C, 0.002 mbar. n_D^{23} = 1.4479. IR (film): ν = 1660 cm^{-1} (C=N).

(RS)-5,5-Dimethyl-2-(2-chloro-1,1-dimethylethyl)-2H-1,3-thiazine **4b**

The preparation based on **GP1** from 213 mmol (25.6g) 3-chloro-2,2-dimethylpropanal, 639 mmol (42.6mL) concentrated, aqueous ammonia and 256 mmol (14.34g) sodium hydrogen sulfide.

Yield: 4.70 g (20%). bp.: 67°C, 0.005 mbar. n_D^{23} = 1.5102. IR (film): ν = 1660 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$): δ = 1.04, 1.17 (2s, 6 H, C5-$(CH_3)_2$); 1.10 (s, 6 H, C2-C($\underline{CH_3}$)$_2$$CH_2Cl$); 2.49, 2.77 (2d, J = 13.6 Hz, 2 H, 2 × H6); 3.50, 3.79 (2d, J = 10.6 Hz, 2 H, C2-C$(CH_3)_2$$\underline{CH_2}$Cl); 4.69 (m, 1 H, H2) 7.46 (m, 1 H, H4). ^{13}C-NMR ($CDCl_3$): δ = 21.49, 22.63, 25.02, 26.56 (C5-($\underline{C}H_3)_2$, C2-C($\underline{C}H_3)_2CH_2Cl$); 32.00 (C2-$\underline{C}$$(CH_3)_2CH_2Cl$); 36.22 (C6); 40.67 (C5); 53.74 (C2-C$(CH_3)_2$$\underline{C}H_2Cl$); 66.56 (C2); 168.80 (C4). MS (CI, *i*-butane): m/z (%) = 220 (100), [MH^+]. $C_{10}H_{18}ClNS$ (219.1): Calc. C 54.77; H 8.28; N 6.39. Found: C 54.89; H 8.33; N 6.21.

3,3-Dimethyl-1-thia-5-azaspiro[5.4]dec-4-ene **4c**

The preparation based on **GP1** from 213 mmol (25.6g) 3-chloro-2,2-dimethylpropanal, 639 mmol (53.7g) cyclopentanone, 256 mmol (14.3g) sodium hydrogen sulfide and 42.6 mL concentrated ammonia.

Yield: 13.9 g (36%). bp.: 56°C, 0.002 mbar. n_D^{23} = 1.5143. IR (film): ν = 1645 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$): δ = 1.11 (s, 6 H, C3-$(CH_3)_2$); 1.72–1.97 (m, 8 H, $(CH_2)_4$); 2.58 (s, 2 H, 2 × H2); 7.26 (s, 1 H, H4). ^{13}C-NMR ($CDCl_3$): δ = 24.32, 31.54 ($(CH_2)_4$); 25.66 (C3-($\underline{C}H_3)_2$); 36.13 (C2); 42.09 (C3); 70.44 (C6); 165.93 (C4). MS (CI, *i*-butane): m/z (%) = 184 (100), [MH^+]. $C_{10}H_{17}NS$ (183.1): Calc. C 65.54; H 9.36; N 7.65. Found: C 65.69; H 9.17; N 7.60.

3,3-Dimethyl-1-thia-5-azaspiro[5.5]undec-4-ene **4d**

The preparation based on **GP1** from 213 mmol (25.6g) 3-chloro-2,2-dimethylpropanal, 639 mmol (62.7g) cyclohexanone, 256 mmol (14.3g) sodium hydrogen sulfide and 42.6 mL concentrated ammonia.

Yield: 16.7 g (40%). bp.: 73–75°C, 0.005 mbar. mp.: 43–44°C. IR (film): ν = 1645 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$): δ = 1.10, 1.14 (2s, 6 H, C3-$(CH_3)_2$); 1.12–1.41 (m, 1 H, $(CH_2)_5$); 1.59–1.81 (m, 9 H, $(CH_2)_5$); 2.53 (s, 2 H, 2 × H2); 7.37 (s, 1 H, H4). ^{13}C-NMR ($CDCl_3$): δ = 22.33, 25.48, 32.19 ($(CH_2)_5$); 25.88

(C2-$(CH_3)_2$); 33.22 (C2); 38.90 (C3); 64.97 (C6); 165.20 (C4). MS (CI, *i*-butane): m/z (%) = 198 (100), $[M\text{-}H^+]$. $C_{11}H_{19}NS$ (197.1): Calc. C 66.96; H 9.71; N 7.10. Found: C 67.11; H 9.79; N 7.10.

Phosphonates of the 2*H*-1,3-thiazines 4 and 2*H*-1,4-benzothiazines 5; General procedure (GP2)

A mixture of 5 mmol of the cyclic imine **4** or **5** and 5 mmol of the corresponding dialkyl phosphite was refluxed for 18h in 30 ml of ligroine (petroleum ether 90/110). After cooling to ambient temperature and storage for 18h–10d at −28°C the solid was filtered, washed with ligroine and ether and dried to give white to pale brown crystals (**6**, **7**).

In the case of **6a–d** the diastereomeric ratios of the products were determined by ^{31}P-NMR spectroscopy (results: see scheme 3).

(2R,4S*)- or (2R*,4R*)-2-(1,1-Dimethylethyl)-5,5-dimethyl-1,3-thiazinan-4-yl-dimethyl phosphonate* **6a**

Yield: 0.71 g (48%). mp.: 63–64°C. IR (KBr): ν = 3280 cm^{-1} (N-H); 1230 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 1.04 (s, 9 H, C2-C$(CH_3)_3$); 1.16, 1.25 (2s, 6 H, C5-$(CH_3)_2$); 1.48 (m, 1 H, NH); 2.44 (dd, J = 9.9 Hz, J = 13.2 Hz, 1 H, 1 × H6); 2.92 (d, J = 13.7 Hz, 1 H, 1 × H6); 3.03–3.07 (m, 1 H, H4); 3.72 (m, 1 H, H2); 3.76 (d, J = 10.7 Hz, 3 H, $POCH_3$); 3.82 (d, J = 10.3 Hz, 3 H, $POCH_3$). ^{13}C-NMR ($CDCl_3$): δ = 19.98, 28.29 (C5-$(CH_3)_2$); 26.80 (C2-C($\underline{C}H_3)_3$); 27.78 (d, J = 3.9 Hz, (C2-$\underline{C}(CH_3)_3$); 35.52 (C6); 44.14 (d, J = 17.4 Hz, C5); 52.26 (d, J = 7.5 Hz, $POCH_3$); 53.90 (d, J = 6.9 Hz, $POCH_3$); 64.70 (d, J = 156.3 Hz, C4); 74.90 (d, J = 18.5 Hz, C2). ^{31}P-NMR ($CDCl_3$): δ = 23.59. MS (CI, *i*-butane): m/z (%) = 296 (100), $[MH^+]$. $C_{12}H_{26}NO_3PS$ (295.1): Calc. C 48.79; H 8.88; N 4.74. Found: C 48.70; H 9.02; N 4.70.

(2R,4S*)- or (2R*,4R*)-2-(1,1-Dimethylethyl)-5,5-dimethyl-1,3-thiazinan-4-yl-diethyl phosphonate* **6b**

Yield: 0.72 g (45%). mp.: 35–37°C. IR (KBr): ν = 3270 cm^{-1} (N-H); 1240 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 1.03 (s, 9 H, C2-C$(CH_3)_3$); 1.17, 1.24 (2s, 6 H, C5-C$(CH_3)_2$); 1.29–1.34 (m, 6 H, P$(OCH_2C\underline{H}_3)_2$); 1.47 (m, 1 H, NH); 2.42 (dd, J = 9.9 Hz, J = 13.6 Hz, 1 H, 1 × H6); 2.90 (d, J = 13.9 Hz, 1 H, 1 × H6); 2.93–2.98 (m, 1 H, H4); 3.73 (d, J = 12.6 Hz, 1 H, H2); 4.08–4.20 (m, 4 H, P$(OC\underline{H}_2CH_3)_2$). ^{13}C-NMR ($CDCl_3$): δ = 16.31 (d, J = 5.9 Hz, $POCH_2\underline{C}H_3$); 16.48 (d, J = 5.7 Hz, $POCH_2\underline{C}H_3$); 19.93, 28.30 (C5-$(\underline{C}H_3)_2$); 26.73 (C2-

$C(\underline{C}H_3)_3$); 27.78 (d, J = 3.7 Hz, C2-$\underline{C}(CH_3)_3$); 35.48 (C6); 44.17 (d, J = 17.2 Hz, C5); 61.69 (d, J = 7.4 Hz, $PO\underline{C}H_2CH_3$); 62.90 (d, J = 6.8 Hz, $PO\underline{C}H_2CH_3$); 64.72 (d, J = 155.9 Hz, C4); 74.81 (d, J = 18.5 Hz, C2). ^{31}P-NMR ($CDCl_3$): δ = 21.10. MS (CI, *i*-butane): m/z (%) = 324 (100), [MH^+]. $C_{14}H_{30}NO_3PS$ (323.2): Calc. C 51.99; H 9.36; N 4.33. Found: C 51.82; H 9.41; N 4.24.

(2R,4S*)- or (2R*,4R*)-2-(2-Chloro-1,1-dimethylethyl)-5,5-dimethyl-1,3-thiazinan-4-yl-dimethyl phosphonate* **6c**

Yield: 0.27 g (17%). mp.: 28°C. IR (KBr): ν = 3260 cm^{-1} (N-H); 1235 cm^{-1} (P=O). ^{1}H-NMR ($CDCl_3$): δ = 1.10, 1.11 (2s, 6 H, C5-$(CH_3)_2$); 1.16, 1.24 (2s, 6 H, C2-$C(\underline{C}H_3)_2CH_2Cl$); 1.49 (m, 1 H, NH); 2.45 (dd, J = 9.8 Hz, J = 13.7 Hz, 1 H, 1 × H6); 2.96 (d, J = 13.8 Hz, 1 H, 1 × H6); 3.09 (m, 1 H, H4); 3.41, 3.69 (2d, J = 10.6 Hz, 2 H, C2-$C(CH_3)_2C\underline{H}_2Cl$); 3.76 (d, J = 10.7 Hz, 3 H, $POCH_3$); 3.82 (d, J = 10.4 Hz, 3 H, $POCH_3$); 4.05 (m, 1 H, H2). ^{13}C-NMR ($CDCl_3$): δ = 20.03, 21.54, 22.82, 28.18 (C5-$(\underline{C}H_3)_2$, C2-$C(\underline{C}H_3)_2CH_2Cl$); 27.98 (C2-$\underline{C}(CH_3)_2CH_2Cl$); 40.03 (C6); 44.12 (d, J = 17.2 Hz, C5); 52.23 (d, J = 7.4 Hz, $POCH_3$); 53.36 (C2-$C(CH_3)_2\underline{C}H_2Cl$); 53.74 (d, J = 6.8 Hz, $POCH_3$); 64.40 (d, J = 156.2 Hz, C4); 70.20 (d, J = 19.0 Hz, C2). ^{31}P-NMR ($CDCl_3$): δ = 23.29. MS (CI, *i*-butane): m/z (%) = 330 (100), [$M\text{-}H^+$]. $C_{12}H_{25}ClNO_3PS$ (329.1): Calc. C 43.76; H 7.66; N 4.25. Found: C 43.57; H 7.81; N 4.15.

(2R,4S*)- or (2R*,4R*)-2-(2-Chloro-1,1-dimethylethyl)-5,5-dimethyl-1,3-thiazinan-4-yl-diethyl phosphonate* **6d**

Yield: 0.33 g (19%). mp.: 38–39°C. IR (KBr): ν = 3280 cm^{-1} (N-H); 1240 cm^{-1} (P=O). ^{1}H-NMR ($CDCl_3$): δ = 1.10 (s, 6 H, C5-$(CH_3)_2$); 1.18, 1.24 (2s, 6 H, C2-$C(\underline{C}H_3)_2CH_2Cl$); 1.30–1.60 (m, 7 H, $P(OCH_2\underline{C}H_3)_2$, NH); 2.45 (dd, J = 9.6 Hz, J = 13.7 Hz, 1 H, 1 × H6); 2.92 (d, J = 13.6 Hz, 1 H, 1 × H6); 3.00 (m, 1 H, H4); 3.40, 3.69 (2d, J = 10.6 Hz, 2 H, C2-$C(CH_3)_2C\underline{H}_2Cl$); 4.03 (s, 1 H, H2); 4.04–4.21 (m, 4 H, $P(O\underline{C}H_2CH_3)_2$). ^{13}C-NMR ($CDCl_3$): δ = 16.30 (d, J = 6.5 Hz, $POCH_2\underline{C}H_3$); 16.47 (d, J = 5.7 Hz, $POCH_2\underline{C}H_3$); 19.99, 21.47, 22.78, 28.25 (C5-$(\underline{C}H_3)_2$, C2-$C(\underline{C}H_3)_2CH_2Cl$); 27.97 (d, J = 3.6 Hz, C2-$\underline{C}(CH_3)_2CH_2Cl$); 40.01 (C6); 44.21 (d, J = 17.0 Hz, C5); 53.31 (C2-$C(CH_3)_2\underline{C}H_2Cl$); 61.69 (d, J = 7.2 Hz, $PO\underline{C}H_2CH_3$); 62.80 (d, J = 6.9 Hz, $PO\underline{C}H_2CH_3$); 64.50 (d, J = 155.9 Hz, C4); 70.12 (d, J = 18.8 Hz, C2). ^{31}P-NMR ($CDCl_3$): δ = 21.01. MS (CI, *i*-butane): m/z (%) = 358 (100), [MH^+]. $C_{14}H_{29}ClNO_3PS$ (357.1): Calc. C 47.04; H 8.18; N 3.92. Found: C 46.81; H 8.21; N 3.69.

(4RS)-3,3-Dimethyl-1-thia-5-azaspiro[5.4]decan-4-yl-dimethyl phosphonate **6e**

Yield: 0.17 g (12%). mp.: 61°C. IR (KBr): ν = 3295 cm^{-1} (N-H); 1240 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 1.11, 1.19 (2s, 6 H, C3-$(CH_3)_2$); 1.68–2.03 (m, 9 H, $(CH_2)_4$, NH); 2.22 (dd, J = 9.1 Hz, J = 13.9 Hz, 1 H, 1 × H2); 2.89 (d, J = 13.9 Hz, 1 H, 1 × H2); 3.14 (d, J = 23.6 Hz, 1 H, H4); 3.68 (d, J = 10.7 Hz, 3 H, $POCH_3$); 3.73 (d, J = 10.3 Hz, 3 H, $POCH_3$). ^{13}C-NMR ($CDCl_3$): δ = 19.80, 28.17 (C3-$(\underline{C}H_3)_2$); 23.37, 24.10, 27.44, 37.64 ($(CH_2)_4$); 41.88 (d, J = 17.2 Hz, C3); 42.41 (C2), 52.25 (d, J = 7.5 Hz, $POCH_3$); 53.94 (d, J = 6.7 Hz, $POCH_3$); 59.64 (d, J = 156.8 Hz, C4); 70.17 (d, J = 17.6 Hz, C6). MS (CI, *i*-butane): m/z (%) = 294 (100), [MH^+]. $C_{12}H_{24}NO_3PS$ (293.1): Calc. C 49.13; H 8.25; N 4.78. Found: C 49.10; H 8.31; N 4.62.

(4RS)-3,3-Dimethyl-1-thia-5-azaspiro[5.4]decan-4-yl-diethyl phosphonate **6f**

Yield: 0.66 g (41%). mp.: 77–78°C. IR (KBr): ν = 3300 cm^{-1} (N-H); 1230 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 1.19, 1.27 (2s, 6 H, C3-$(CH_3)_2$); 1.28–1.35 (m, 6 H, $P(OCH_2\underline{CH_3})_2$); 1.72–1.95 (m, 9 H, $(CH_2)_4$, NH); 2.28 (dd, J = 8.9 Hz, J = 13.9 Hz, 1 H, 1 × H2); 2.96 (d, J = 13.9 Hz, 1 H, 1 × H2); 3.17 (d, J = 23.5 Hz, 1 H, H4); 4.08–4.12 (m, 4 H, $P(O\underline{CH_2}CH_3)_2$). ^{13}C-NMR ($CDCl_3$): δ = 16.39 (d, J = 6.9 Hz, $POCH_2\underline{C}H_3$); 16.47 (d, J = 6.6 Hz, $POCH_2\underline{C}H_3$); 19.90, 28.41 (C3-$(\underline{C}H_3)_2$); 23.54, 24.25, 27.58, 37.78 ($(CH_2)_4$); 42.12 (d, J = 17.1 Hz, C3); 42.58 (C2), 59.86 (d, J = 156.8 Hz, C4); 61.74 (d, J = 7.2 Hz, $PO\underline{C}H_2CH_3$), 63.13 (d, J = 6.8 Hz, $PO\underline{C}H_2CH_3$); 70.35 (d, J = 17.7 Hz, C6). MS (CI, *i*-butane): m/z (%) = 322 (100), [MH^+]. $C_{14}H_{28}NO_3PS$ (321.2): Calc. C 52.31; H 8.79; N 4.36. Found: C 52.51; H 8.77; N 4.21.

(4RS)-3,3-Dimethyl-1-thia-5-azaspiro[5.5]undecan-4-yl-dimethyl phosphonate **6g**

Yield: 0.72 g (47%). mp.: 78–79°C. IR (KBr): ν = 3290 cm^{-1} (N-H); 1240 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 1.12, 1.18 (2s, 6 H, C3-$(CH_3)_2$); 1.33–1.91 (m, 11 H, $(CH_2)_5$, NH); 2.18 (dd, J = 7.8 Hz, J = 14.0 Hz, 1 H, 1 × H2); 2.80 (d, J = 14.0 Hz, 1 H, 1 × H2); 3.20 (d, J = 23.9 Hz, 1 H, H4); 3.71 (d, J = 10.7 Hz, 3 H, $POCH_3$); 3.79 (d, J = 10.4 Hz, 3 H, $POCH_3$). ^{13}C-NMR ($CDCl_3$): δ = 20.57, 27.77 (C3-$(\underline{C}H_3)_2$); 21.95 (d, J = 13.0 Hz, $(CH_2)_5$); 25.78 ($(CH_2)_5$); 28.65 (d, J = 4.3 Hz, $(CH_2)_5$); 34.20 ($(CH_2)_5$); 39.70 (d, J = 16.3 Hz, C3); 40.36 (C2), 52.14 (d, J = 7.3 Hz, $POCH_3$); 54.11 (d, J = 6.9 Hz, $POCH_3$); 56.64 (d, J = 157.8 Hz, C4); 63.62 (d, J = 17.7 Hz, C6). MS (CI, *i*-butane): m/z (%) = 308 (100), [MH^+]. $C_{13}H_{26}NO_3PS$ (307.1): Calc. C 50.79; H 8.53; N 4.56. Found: C 50.60; H 8.66; N 4.70.

(4RS)-3,3-Dimethyl-1-thia-5-azaspiro[5.5]undecan-4-yl-diethyl phosphonate **6h**

Yield: 0.91 g (54%). mp.: 84°C. IR (KBr): ν = 3280 cm^{-1} (N-H); 1230 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 1.14, 1.19 (2s, 6 H, C3-$(CH_3)_2$); 1.25–1.33 (m, 6 H, $P(OCH_2C\underline{H}_3)_2$); 1.40–1.90 (m, 11 H, $(CH_2)_5$, NH); 2.17 (dd, J = 7.6 Hz, J = 14.0 Hz, 1 H, 1 × H2); 2.79 (d, J = 14.0 Hz, 1 H, 1 × H2); 3.15 (d, J = 23.8 Hz, 1 H, H4); 4.04–4.17 (m, 4 H, $P(OC\underline{H}_2CH_3)_2$). ^{13}C-NMR ($CDCl_3$): δ = 16.33 (d, J = 6.2 Hz, $POCH_2\underline{C}H_3$); 16.50 (d, J = 5.6 Hz, $POCH_2\underline{C}H_3$); 20.58, 27.89 (C3-$(\underline{C}H_3)_2$); 21.89 (d, J = 12.3 Hz, $(CH_2)_5$); 25.81 ($(CH_2)_5$); 28.75 (d, J = 4.3 Hz, $(CH_2)_5$); 34.21 ($(CH_2)_5$); 39.82 (d, J = 16.1 Hz, C3); 40.40 (C2); 56.72 (d, J = 157.9 Hz, C4); 61.51 (d, J = 7.3 Hz, $PO\underline{C}H_2CH_3$); 63.14 (d, J = 7.0 Hz, $PO\underline{C}H_2CH_3$); 63.68 (d, J = 17.8 Hz, C6). MS (CI, *i*-butane): m/z (%) = 336 (100), [M-H^+]. $C_{15}H_{30}NO_3PS$ (335.2): Calc. C 53.70; H 9.02; N 4.18. Found: C 53.66; H 9.20; N 4.10.

(3RS)-2,2-Dimethyl-3,4-dihydro-2H-1,4-benzothiazine-3-dimethylphosphonate **7a**

Yield: 0.58 g (40%). mp.: 115–117°C. IR (KBr): ν = 3220 cm^{-1} (N-H); 1035 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 1.54, 1.60 (2s, 6 H, C2-$(CH_3)_2$); 3.75–3.79 (m, 6 H, $P(OCH_3)_2$); 3.89 (d, 1 H, J = 12.1 Hz, H3); 5.35 (br s, 1 H, NH); 6.60–6.95 (m, 4 H, aromat. H). ^{13}C-NMR ($CDCl_3$): δ = 25.59, 28.31 (C2-$(\underline{C}H_3)_2$); 40.78 (C2); 53.00 ($P(OCH_3)_2$); 60.14 (d, J = 148 Hz, C3); 115.44–138.83 (aromat. C). MS (CI, *i*-butane): m/z (%) = 288 (46), [M-H^+], 178 (100) [M-H^+—H(O)$P(OCH_3)_2$]. $C_{12}H_{18}NO_3PS$ (287.3): Calc. C 50.17; H 6.31; N 4.88. Found: C 49.94; H 6.05; N 4.49.

(3RS)-2,2-Dimethyl-3,4-dihydro2H-1,4-benzothiazine-3-diethylphosphonate **7b**

Yield: 0.98 g (62%). mp.: 110–111°C. IR (KBr): ν = 3300 cm^{-1} (N-H); 1010 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 1.30–1.37 (m, 6 H, $P(OCH_2C\underline{H}_3)_2$); 1.56, 1.61 (2s, 6 H, C2-$(CH_3)_2$); 3.89 (d, 1 H, J = 12.7 Hz, H3); 4.10–4.21 (m, 4 H, $P(OC\underline{H}_2CH_3)_2$); 6.58–6.95 (m, 4 H, aromat. H). ^{13}C-NMR ($CDCl_3$): δ = 16.20 ($P(OCH_2\underline{C}H_3)_2$); 25.40, 27.79 (C2-$(\underline{C}H_3)_2$); 41.00 (C2); 60.66 (d, J = 147 Hz, C3); 62.45 (d, J = 7 Hz, $P(O\underline{C}H_2CH_3)_2$); 115.21–139.14 (aromat. C). MS (CI, *i*-butane): m/z (%) = 316 (24) [MH^+], 178 (100) [MH^+—H(O)$P(OC_2H_5)_2$]. $C_{14}H_{22}NO_3PS$ (315.3): Calc. C 53.32; H 7.03; N 4.44. Found: C 53.12; H 7.20; N 4.41.

(3RS)-2,2-Diethyl-3,4-dihydro-2H-1,4-benzothiazine-3-diethylphosphonate **7c**

Yield: 0.92 g (54%). mp.: 97°C. IR (KBr): ν = 3300 cm^{-1} (N-H); 1020 cm^{-1} (P═O). ^{1}H-NMR ($CDCl_3$): δ = 0.94 (d, J = 7.4 Hz, 3 H, C2-$CH_2C\underline{H}_3$); 1.00 (d,

J = 7.6 Hz, 3 H, C2-$CH_2\underline{C}H_3$); 1.19 (d, J = 7.1 Hz, 3 H, $POCH_2\underline{C}H_3$); 1.28 (d, J = 7.1 Hz, 3 H, $POCH_2\underline{C}H_3$); 1.69–2.16 (m, 4 H, C2-$(\underline{C}H_2CH_3)_2$); 3.84 (d, J = 12.2 Hz, 1 H, H3); 4.01–4.13 (m, 4 H, $P(O\underline{C}H_2CH_3)_2$)); 6.54–7.02 (m, 4 H, aromat. H). ^{13}C-NMR ($CDCl_3$): δ = 7.94, 8.17 (C2-$(CH_2\underline{C}H_3)_2$); 16.24 (d, J = 6.0 Hz, $POCH_2\underline{C}H_3$); 16.39 (d, J = 6.0 Hz, $POCH_2\underline{C}H_3$); 26.76 (C2-$\underline{C}H_2CH_3$); 28.89 (d, J = 7.8 Hz, C2-$\underline{C}H_2CH_3$); 48.38 (C2); 56.32 (d, J = 151.8 Hz, C3); 61.85 (d, J = 6.5 Hz, $PO\underline{C}H_2CH_3$); 62.66 (d, J = 6.7 Hz, $POC\underline{H}_2CH_3$); 115.20–139.15 (aromat. C). MS (CI, *i*-butane): m/z (%) = 344 (40) [MH^+], 206 (100) [MH^+ - $H(O)P(OC_2H_5)_2$]. $C_{16}H_{26}NO_3PS$ (343.4): Calc. C 55.96; H 7.63; N 4.08. Found: C 55.64; H 7.40; N 3.90.

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