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Stereochemistry of chiral pentacoordinate spirophosphoranes correlated with solid-state circular dichroism and ^{1}H NMR spectroscopy

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ABSTRACT

Two sets of diastereomers of pentacoordinate spirophosphoranes separately derived from L-valine (or D-valine) and L-leucine (or D-leucine) were synthesized, isolated, and structurally characterized both in the solid state (X-ray crystallography and solid-state CD spectroscopy) and in the solution (^{1}H NMR). The *Λ* and *Δ* absolute configurations of a pair of enantiomers **3a** and **4a** with distorted trigonal bipyramids (TBPs) geometry are directly determined by X-ray diffraction analysis, respectively. The chiral-at-phosphorus features of the related diastereomers were correlated with their solid-state CD and ^{1}H NMR spectra.

1. Introduction

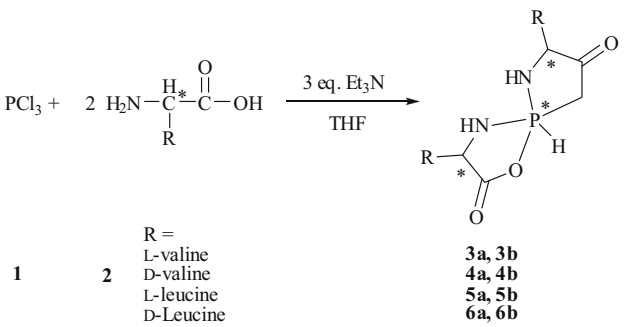
Pentacoordinate phosphorus compounds as intermediates or transition-state species, are indispensable in numerous biological processes such as hydrolyses of RNA[1] or phosphoryl transfer reactions,[2] which are formed by nucleophilic attack upon tetracoordinate phosphorus atoms. It is assumed that the steric and electronic effects of the intermediates or transition-state species greatly influence the outcome of the process.[3] To deduce a basic understanding of these processes, many model pentacoordinate phosphorus compounds have been studied.[4–8] However, previous studies have focused on the characteristic aspects of pseudorotation,[9] apicophilicity,[10] and anti-apicophilicity (*O-cis*)[11] of phosphoranes. Until now, investigations of the stereochemistry of pentacoordinate phosphoranes were rare.[12,13]

To investigate the stereochemistry of pentacoordinate phosphorus compounds with chiral chelate ligands, the diastereomers could be differentiated by high-performance liquid chromatography (HPLC), solution or solid-state circular dichroism (CD), nuclear magnetic resonance (NMR), and X-ray crystallography. Among them, HPLC is one of the most effective methods of separation means. X-ray single-crystal structure measurement is essential for the determination of the absolute configuration of chiral compounds. Solid-state CD spectroscopy is a necessary tool for chiral solid-state chemistry study and provides some subtle structural information to be directly correlated with that of X-ray single-crystal structure.[14]

Herein, two sets of diastereomers of chiral pentacoordinate spirophosphoranes derived from L-valine (or D-valine) and L-leucine (or D-leucine) were synthesized and separated, respectively. Their stereochemistry was examined by the modern analytical techniques mentioned above.

2. Result and discussion

The pentacoordinate spirophosphoranes were synthesized[7d] by the method described in Scheme 1. From the ^{31}P NMR, it was found



Scheme 1. Synthesis of pentacoordinated spirophosphoranes **3a–6b** derived from L- and D-amino acid, respectively.

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that a pair of isomeric products were formed (Table 1), which could be separated by silica gel column chromatography or recrystallization. Compounds **3b**, **4b**, **5b**, and **6b** are more readily soluble in dichloromethane and chloroform than **3a**, **4a**, **5a**, and **6a**, respectively.

The above diastereoisomers **a** and **b** were separated by reverse-phase HPLC chromatography with a TC-C_{18} column. The results of HPLC analysis are shown in Figure 1 using **3a**, **3b** and **4a**, **4b** as representative compounds. Compounds **3a** and **4a** have essentially the same retention time (9.78 and 9.77 min), while both **3b** and **4b** are retained longer (13.65 and 13.58 min). The retention times of **3a**–**6b** are shown in Table 2 where **5a**/**6a** and **5b**/**6b** have the same retention times, respectively. Hence, it is proposed that **3a**/**4a**, **3b**/**4b**, **5a**/**6a**, and **5b**/**6b**, respectively, could be a pair of enantiomers. HPLC analysis of both fractions revealed that every isomer could be obtained with an enantiopurity of 99%.

Table 1
^{31}P NMR and solubility data of the reactions giving **3a**–**6b**

Amino acid (**2**)	Product	δ_P[a] (ppm)	Ratio[b] (%)	Solubility[c]
L-Valine	**3a**	−64.80	38	□
	3b	−61.68	62	■
D-Valine	**4a**	−64.79	35	□
	4b	−61.70	65	■
L-Leucine	**5a**	−64.50	46	□
	5b	−63.83	54	■
D-Leucine	**6a**	−64.54	49	□
	6b	−63.83	51	■

[a] ^{31}P NMR data were obtained in the dimethylsulfoxide (DMSO) solution. After the reaction is completed, the tetrahydrofuran solvent was removed by rotary evaporation and the residue (diastereoisomers **a** and **b**) was completely dissolved in DMSO.

[b] The ratio of products was calculated from the integral area of ^{31}P NMR signals.

[c] The solubility in CH_2Cl_2 or $CHCl_3$: '□' shows that the solubility is poor, and '■' shows that the solubility is better.

Table 2
HPLC analysis of pentacoordinate spirophosphoranes **3a**–**6b** on reverse-phase TC-C_{18} column

Compound	Retention time (min)	
3a, **3b**	9.78	13.58
3a	9.78	
3b		13.65
4a, **4b**	9.78	13.59
4a	9.77	
4b		13.58
5a, **5b**[a]	14.14	20.52
5a[a]	14.17	
5b[a]		20.52
6a, **6b**[a]	14.12	20.55
6a[a]	14.16	
6b[a]		20.52

[a] Agilent, TC-C_{18} column, 5 μm, 4.6 × 250 mm. Mobile phase: eluent CH_3OH/H_2O (v/v) = 3:2, 0.8 mL/min; rt (≈25 °C); injection volume 20.0 μL; detection absorption at 214 nm.

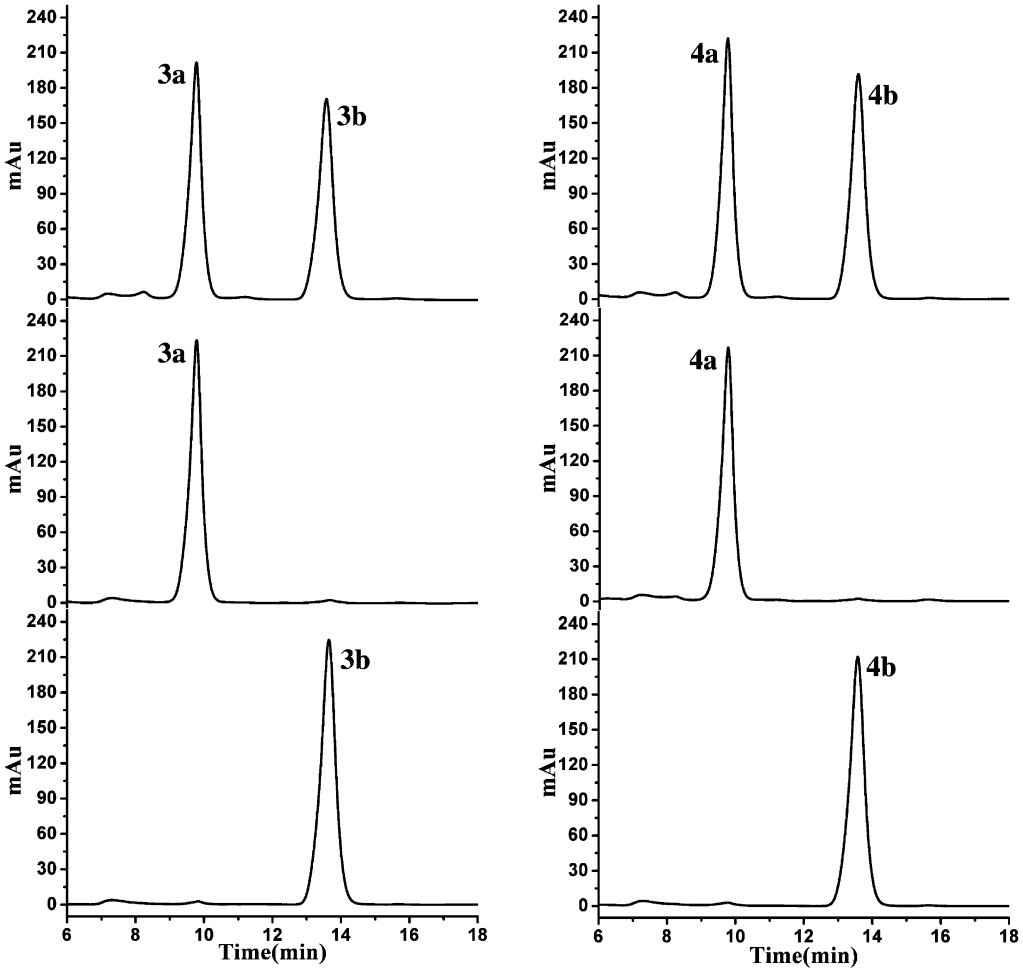

Figure 1. HPLC analysis of compounds **3a**, **3b** (left) and **4a**, **4b** (right) on reverse-phase TC-C_{18} column (Agilent, TC-C_{18} column, 5 μm, 4.6 × 250 mm), mobile phase: eluent CH_3OH/H_2O (v/v) = 11:9, 0.8 mL/min; rt (≈25 °C); injection volume 20.0 μL; detection absorption at 214 nm.

The absolute configurations of these pentacoordinate spirophosphoranes were proven when the single-crystal structures of a pair of enantiomers **3a**/**4a** were characterized by X-ray diffraction analysis. Crystals of **3a** and **4a** suitable for X-ray analysis were obtained from acetone solutions. ORTEP structures of **3a**/**4a** are shown in Figure 2.

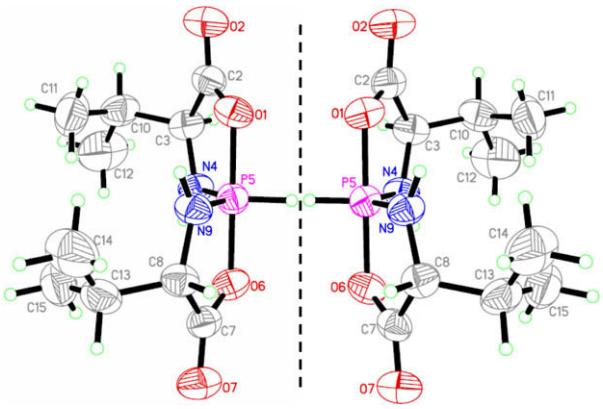

Figure 2. ORTEP drawing of compounds **3a** (left) and **4a** (right) with atom numbering scheme.

The two compounds are arranged in a distorted TBP geometry. Two nitrogen atoms and a hydrogen atom form an equator plane and two oxygen atoms are in apical positions. The angles N(4)–P(5)–O(1), N(9)–P(5)–O(1), N(4)–P(5)–O(6), and N(9)–P(5)–O(6) around the phosphorus atom are close to 90°. However, the angles N(4)–P(5)–N(9) in **3a** and **4a** are not perfect with a deviation of 4.57° or 5.15° from the ideal angle of 120°, respectively. In the crystal lattice structures, the occurrence of N–H···O intermolecular hydrogen-bonding interactions led to the formation of a chain parallel to the *b*-axis and then the Van der Waals interactions provide stability for the crystal structures. The veracity of absolute stereochemistry of **3a** and **4a** can be evaluated by the Flack parameters which are −0.06(11) and 0.06(19), respectively. The crystal structure of **3a** was also obtained by Shu-Xia Cao.[7e] The crystal structure of **3a** or **4a** exhibits an *endo*-configuration which looks like a 'resting butterfly' with 'wings' of two isopropyl groups of valine. From the aforementioned results, we can deduce that the non-crystalline enantiomers **3b** and **4b** may have an *exo*-configuration which looks like a 'resting moth'. A similar crystal structure of the corresponding bis-alanine spirophosphorane has been obtained in our group.[7c]

In order to identify the absolute configuration of the phosphorus center, we adopted the nomenclature system for a coordination compound $[MX(AB)_2]$ (AB = hetero-bidentate ligand) which can be applied to a TBP or square-pyramidal (SP) geometry. In the TBP geometry, when a monodentate ligand X occupies one equatorial position, the chiral-at-metal configuration can be defined as Λ or Δ (Fig. 3).[15]

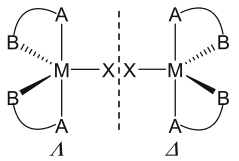

Figure 3. Possible chiral configurations of pentacoordinated complexes $[MX(AB)_2]$ in TBP geometry.

According to the above nomenclature, the X-ray diffraction analysis shows that the phosphorus center in **3a** should be assigned as Λ_P, and both α-carbons of the amino acids are in an (*S*)-configuration. Thus, the absolute configuration of compound **3a** is (Λ_P,*S*C,*S*C). Likewise, **4a** is (Δ_P,*R*C,*R*C). Since **3b**/**4b**, **5a**/**6a**, and **5b**/**6b** could not be obtained as suitable single crystals for structure determination, their absolute configurations cannot be assigned directly.

In order to correlate the absolute configurations of each pair of isomers of **3b**/**4b**, **5a**/**6a**, and **5b**/**6b**, their solid-state CD spectra were measured and are shown (Figs. 4 and 5). The solid-state CD spectra show that **3a**/**4a**, **5a**/**6a**, **3b**/**4b**, and **5b**/**6b** are indeed pairs of enantiomers. It is interesting to note that although **3a**/**3b** and **5a**/**5b** are synthesized from L-valine and L-leucine, respectively, they showed opposite Cotton effects. The same phenomenon was also found in **4a**/**4b** and **6a**/**6b**, which are derived from D-valine and D-leucine, respectively. It should be noted that the sign of the Cotton effects does not follow the chirality of the amino acid and the controlling factor for the asymmetry of these isomers **3a**–**6b** must be the chirality of the phosphorus center.

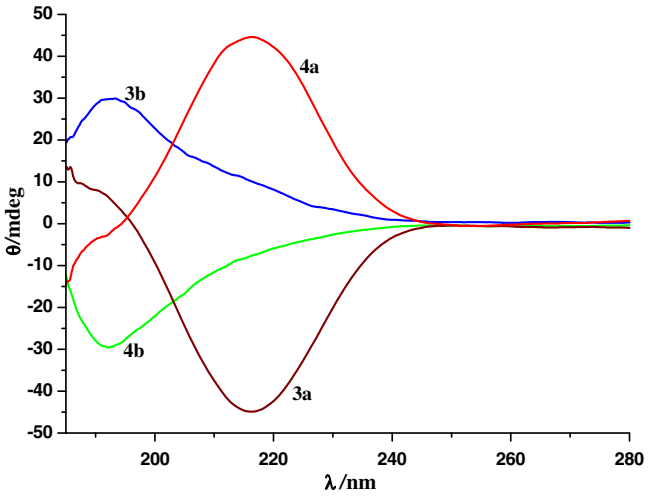

Figure 4. Solid-state CD spectra of compounds **3a**–**4b** (KCl disk).

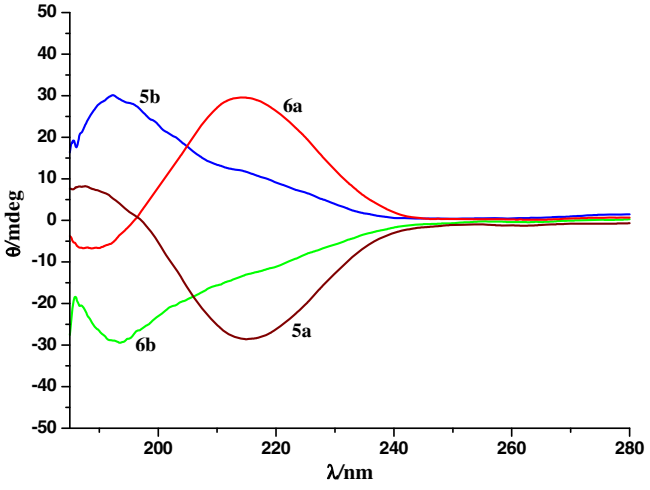

Figure 5. Solid-state CD spectra of compounds **5a**–**6b** (KCl disk).

For example, **3a**/**3b** is derived from L-valine, the absolute configurations of the two α-carbons are *S*, but they have opposite CD signs. Hence it is reasonable to conclude that they have opposite absolute configurations at the phosphorus atom. According to the absolute configuration of **3a** (Λ_P,*S*C,*S*C), we can thus assign the absolute configuration of **3b** as (Δ_P,*S*C,*S*C). Likewise, (Λ_P,*R*C,*R*C) is used to

describe the absolute configuration of compound **4b**. The side chain of valine and leucine is not chromogenic and the difference of them is only -CH_2 unit, so the Cotton effects of **5a**–**6b** are similar to those of **3a**–**4b** and the absolute configurations of **5a**–**6b** can also be correlated and are listed in Table 3.

Table 3
Absolute configurations of **3a**–**6b**, corresponding CD signs in the 185–240 nm range and ^{1}H NMR signals of the proton bound to phosphorus

Compound	CD signs	^{1}H NMR signals (–P*H*)	Configuration
3a	–	d	(Λ_P,S_C,S_C)
3b	+	dt	(Λ_P,S_C,S_C)
4a	+	d	(Λ_P,R_C,R_C)
4b	–	dt	(Λ_P,R_C,R_C)
5a	–	d	(Λ_P,S_C,S_C)
5b	+	dt	(Λ_P,S_C,S_C)
6a	+	d	(Λ_P,R_C,R_C)
6b	–	dt	(Λ_P,R_C,R_C)

The above compounds were also characterized by ^{1}H NMR solution spectroscopy. With respect to the signals arising from the P–H function of these pentacoordinate spirophosphoranes, the pairs of epimers **3a**/**3b**, **4a**/**4b**, **5a**/**5b**, and **6a**/**6b** show significantly different spectra while the spectra of enantiomers **3a**/**4a** and **5a**/**6a** are essentially identical as well as **3b**/**4b** and **5b**/**6b**. Whether the hydrogen bound to nitrogen is deuterated or not, the proton bound to phosphorus in **3a**/**4a** and **5a**/**6a** gives a doublet with splitting only by phosphorus. However, the P–H in **3b**/**4b** or **5b**/**6b** shows a double triplet from coupling to phosphorus and two magnetically equivalent protons. The ^{1}H NMR spectra of **3a**–**4b** are shown in Figure 6, and could support the conclusions from the CD spectra that each pair of **3a**/**4a**, **5a**/**6a**, **3b**/**4b**, and **5b**/**6b** is enantiomeric, respectively.

This special phenomenon of coupling was further confirmed by the ^{1}H–^{1}H COSY spectra of **3b**/**4b** and **5b**/**6b**. Whether the N–H proton was deuterated or not, the ^{1}H–^{1}H COSY spectra identified an interaction between the P–H proton and the α-hydrogen of the amino acid establishing an unusual four-bond distance coupling for these cases (the ^{1}H–^{1}H COSY spectra of **3b** in $CDCl_3$ and $CDCl_3$ + D_2O are shown in Figure 7). However, no such ^{1}H–^{1}H COSY effect was detected in the epimers **3a**/**4a** and **5a**/**6a**.

Apparently, the absolute configurations of **3a**–**6b** could also be correlated with the ^{1}H NMR signal. For the pentacoordinate spirophosphoranes derived from L-amino acids, when the proton bound to phosphorus gives a doublet signal, the absolute configuration of the phosphorus atom could be assigned as Λ_P, and when it shows a double triplet signal, the absolute configuration of phosphorus could be assigned as Δ_P. Likewise, for the pentacoordinate spirophosphoranes derived from D-amino acids, when the proton bound to phosphorus gives a doublet, the absolute configuration of phosphorus could be assigned as Δ_P, and when the proton bound to phosphorus shows a double triplet, the absolute configuration of phosphorus could be assigned as Λ_P. The absolute configurations of **3a**–**6b** were listed in Table 3.

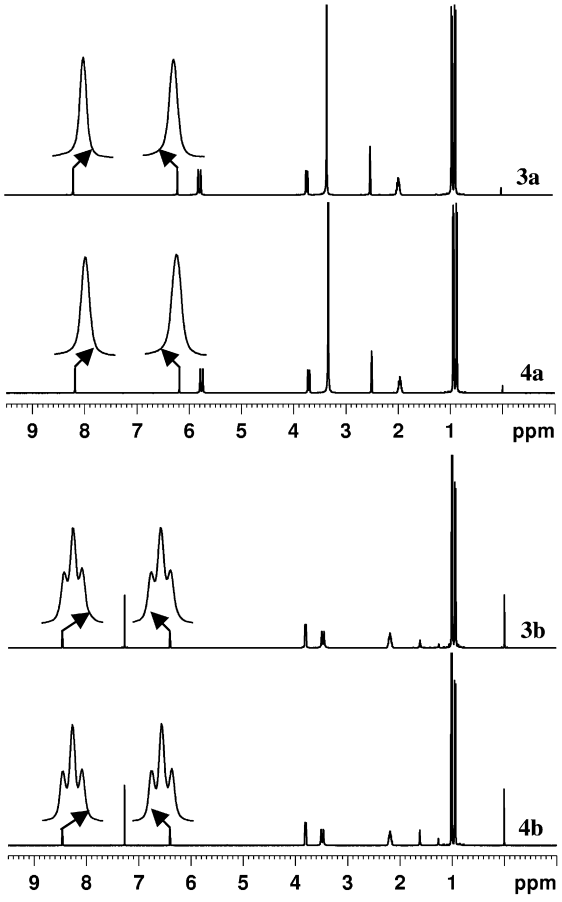

Figure 6. ^{1}H NMR spectra of compounds **3a**/**4a** (top) and **3b**/**4b** (bottom). (**3a**/**4a**: DMSO-d_6 as solvent, δ = 7.18 ppm, d, $^1J_{HP}$ = 798.5 Hz, solvent peaks at 2.50 ppm from DMSO and at 3.38 ppm from H_2O in DMSO-d_6; **3b**/**4b**: $CDCl_3$ as solvent, δ = 7.43 ppm, dt, $^1J_{HP}$ = 824.4 Hz, $^4J_{HH}$ = 2.4 Hz, solvent peaks at 7.26 ppm from $CHCl_3$ and at 1.61 ppm from H_2O in $CDCl_3$).

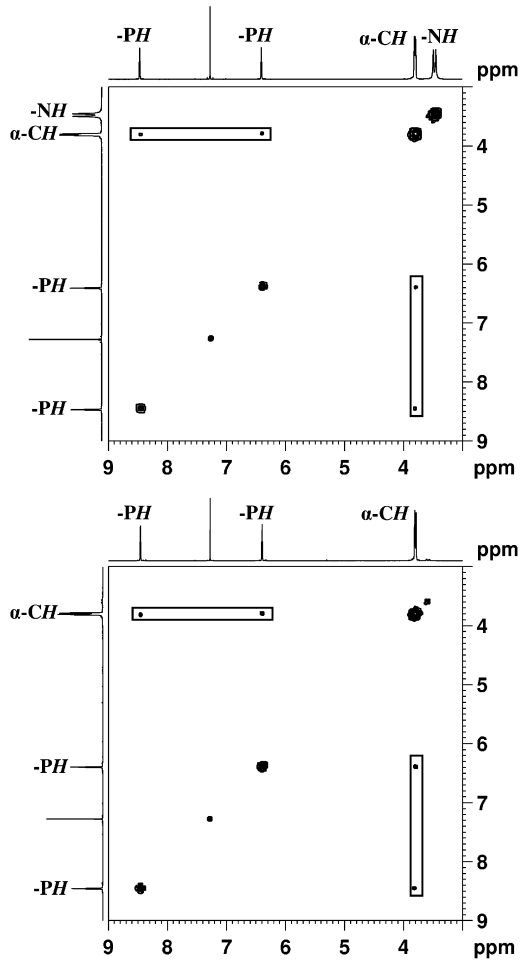

Figure 7. ^{1}H–^{1}H COSY spectra of compound **3b** (top: in $CDCl_3$; bottom: in $CDCl_3$ + D_2O).

Potential epimerization of these isomers was monitored by ^{1}H and ^{31}P NMR at 30 °C using DMSO-d_6 (**3a**–**4b**) or $CDCl_3$ (**5a**–**6b**) as solvent to investigate the stability of these pentacoordinate spirophosphoranes. No epimerization was observed over a period of one month. The high configurational stability of these isomers is a key precondition of the stereochemistry study and for further investigation of these compounds as simple models for pre-biological activity.

3. Conclusion

In conclusion, the stereochemistry of two sets of diastereomers of chiral pentacoordinate spirophosphoranes derived from L- and D-amino acids (valine or leucine) was studied. Four pairs of diastereomers could be easily separated by reverse-phase HPLC. The solid-state CD spectra showed that the CD signs of these isomers are very sensitive to the chirality of the phosphorus centers. Supported by ^{1}H–^{1}H COSY correlation, the pairs of epimers showed significantly different NMR spectra while those of enantiomers are essentially identical. The absolute configurations of a pair of enantiomers **3a** and **4a** were determined by X-ray diffraction analysis, the other pairs of enantiomers **3b**/**4b**, **5a**/**6a**, and **5b**/**6b** could be correlated with solid-state CD and ^{1}H NMR spectra and named by the nomenclature rule in coordination stereochemistry. The penetrating analysis of the CD spectra of these isomers and study on their biological activity are currently under investigation.

4. Experimental

4.1. General information

Melting points were determined (uncorrected) on a Yanaco MP-500 micro-melting point apparatus. Optical rotations were recorded using AUTOMATIC Polarimeter of RUDOLPH Research Analytical (AUTOPOL-IV). NMR experiments were performed at rt on a Bruker AV-400 or Bruker AVANCE DRX-500 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz using DMSO-d_6 or $CDCl_3$ as solvent, ^{13}C NMR spectra were determined at 100 MHz using DMSO-d_6 or $CDCl_3$ as solvent, ^{31}P NMR spectra were determined at 162 MHz using DMSO-d_6 or $CDCl_3$ as solvent, ^{15}N NMR spectra were determined at 40.5 MHz using DMSO-d_6 or $CDCl_3$ as solvent and ^{1}H–^{1}H COSY spectra were recorded at 400 or 500 MHz using DMSO-d_6 or $CDCl_3$ as solvent. ^{1}H NMR, ^{1}H–^{1}H COSY and ^{13}C NMR chemical shifts are relative to TMS or the peak of solvent, ^{31}P NMR chemical shifts are relative to 85% H_3PO_4 and ^{15}N NMR chemical shifts are relative to the saturated solution of $^{15}NH_4Cl$. Infrared (IR) spectra (film) were recorded on a Nicolet Avatar 360 FT-IR spectrometer in the range of 400–4000 cm^{-1}. ESI-MS data were determined with Bruker ESQYIRE∼3000 plus. Mass spectra were registered in the scan range 50–800 *m/z*, while high-resolution MS data were determined with Bruker Daltonics, Inc. APEX III 7.0 TESLA FTMS or Varian, Inc. IonSpec 4.7 Tesla FTMS. Solid-State CD spectra were recorded by using a JASCO J-810 spectropolarimeter at rt. The disks were prepared by mixing and grinding a crystal sample (0.3 mg) with KCl (100 mg). Thirty milligrams of the mixture were collected and weighed before pressing it for 0.5 min at 20 ton into a disk (13 mm dia). Reverse-phase HPLC experiments were carried out using an Agilent model 1100 series HPLC system (Agilent 1100 Technologies, Wilmington, DE). Methanol (HPLC quality) was obtained from Tedia (Fairfield, USA). Deionized water was obtained from a Milli-Q (Millipore, USA) system. The HPLC column was Agilent, TC-C_{18} column, 5 μm, 4.6 × 250 mm (Agilent, Co., USA). Mobile phases for HPLC were filtered through a 0.45 μm filter (Millipore, USA) and degassed before use. Sample solutions were filtered before analysis through 0.45 μm membrane filters (Millipore, USA). Samples were introduced into column using a model injection valve with a 20 μL sample loop at rt (≈25 °C). The mobile phase consisted of methanol (Solvent A) and deionized water (Solvent B).

4.2. Experimental procedures

Following a general procedure,[7d] phosphorus trichloride (60 mmol) was added to a stirred solution of amino acid (120 mmol) in 200 mL anhydrous tetrahydrofuran under a nitrogen atmosphere at rt within 0.5 h. After stirring at rt for 0.5 h, triethylamine (3 equiv, 180 mmol) was added dropwise to the solution (1 mL/min) at −10 °C to induce reaction. The solution was stirred for 2 h. The solvent was removed under reduced pressure and the residue was washed rapidly with water. Yield of crude product was ∼75%. Crude product was purified and separated by silica gel (300–400 mesh) column chromatography or recrystallization.

4.3. Characterization data for 3a–6b

4.3.1. (3*S*,5*Δ*,8*S*)-3,8-Di(propan-2-yl)-1,6-dioxa-4,9-diaza-5λ^5-phosphaspiro[4.4]-nonane-2,7-dione 3a

Recrystallized in chloroform; separating efficiency: 15.2%; white solid; mp >180 °C (decomposition); $[\alpha]_D^{20} = -60.3$ (*c* 1.0, DMSO); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ 7.18 (d, *J* = 798.5 Hz, 1H, PH), 5.76 (d, *J* = 20.3 Hz, 2H, 2 × NH), 3.71 (ddd, *J* = 13.0, 3.0, 1.4 Hz, 2H, 2 × α-CH), 2.02–1.91 (m, 2H, 2 × β-CH), 0.94 (d, *J* = 7.0 Hz, 6H, 2 × CH_3), 0.87 (d, *J* = 6.8 Hz, 6H, 2 × CH_3) ppm; ^{13}C {H} NMR (100.6 MHz, DMSO-d_6): δ 171.1 (d, *J* = 7.4 Hz), 59.5 (d, *J* = 4.6 Hz), 30.9 (d, *J* = 1.8 Hz), 18.5, 17.1 ppm; ^{31}P {H} NMR (162.0 MHz, DMSO-d_6): δ −64.95 ppm; ^{15}N {H} NMR (40.5 MHz, DMSO-d_6): δ 57.86 (d, *J* = 35.0 Hz) ppm; IR (film): 3307, 2963, 2934, 2875, 2428, 1740, 1466, 1431, 1288, 1165, 1067, 994, 898, 819 cm^{-1}; MS (ESI) *m/z* (%): 263.0 (100) $[M+H]^+$, 285.0 (45) $[M+Na]^+$, 547.1 (8) $[2\,M+Na]^+$; HRMS (MALDI) calcd for $C_{10}H_{20}N_2O_4P^+$: 263.1161, found: 263.1156.

4.3.2. (3*S*,5*Δ*,8*S*)-3,8-Di(propan-2-yl)-1,6-dioxa-4,9-diaza-5λ^5-phosphaspiro[4.4]-nonane-2,7-dione 3b

R_f = 0.34 (TLC (silica gel), CH_2Cl_2 as eluent); separating efficiency: 20.8%; white solid; mp > 181 °C (decomposition); $[\alpha]_D^{20} = +22.6$ (*c* 1.0, DMSO); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.43 (dt, *J* = 824.4, 2.4 Hz, 1H, PH), 3.82–3.78 (m, 2H, 2 × α-CH), 3.47 (d, *J* = 17.1 Hz, 2H, 2 × NH), 2.23–2.14 (m, 2H, 2 × β-CH), 1.00 (d, *J* = 7.0 Hz, 6H, 2 × CH_3), 0.94 (d, *J* = 6.7 Hz, 6H, 2 × CH_3) ppm; ^{13}C {H} NMR (100.6 MHz, $CDCl_3$): δ 171.0 (d, *J* = 5.8 Hz), 59.5 (d, *J* = 3.6 Hz), 31.3 (d, *J* = 5.1 Hz), 18.8, 16.2 ppm; ^{31}P {H} NMR (162.0 MHz, $CDCl_3$): δ −63.74 ppm; ^{15}N {H} NMR (40.5 MHz, $CDCl_3$): δ 55.66 (d, *J* = 32.7 Hz) ppm; IR (film): 3299, 2964, 2934, 2875, 2428, 1735, 1466, 1428, 1287, 1162, 1068, 994, 897, 820 cm^{-1}; MS (ESI) *m/z* (%): 263.0 (84) $[M+H]^+$, 285.0 (100) $[M+Na]^+$, 547.1 (14) $[2\,M+Na]^+$; HRMS (MALDI) calcd for $C_{10}H_{20}N_2O_4P^+$: 263.1161, found: 263.1159.

4.3.3. (3*R*,5*Δ*,8*R*)-3,8-Di(propan-2-yl)-1,6-dioxa-4,9-diaza-5λ^5-phosphaspiro[4.4]-nonane-2,7-dione 4a

Recrystallized in chloroform; separating efficiency: 18.7%; white solid; mp > 180 °C (decomposition); $[\alpha]_D^{20} = +60.1$ (*c* 1.0, DMSO); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ 7.18 (d, *J* = 798.6 Hz, 1H, PH), 5.76 (d, *J* = 20.3 Hz, 2H, 2 × NH), 3.70 (ddd, *J* = 13.0, 3.0, 1.5 Hz, 2H, 2 × α-CH), 2.02–1.90 (m, 2H, 2 × β-CH), 0.94 (d, *J* = 7.0 Hz, 6H, 2 × CH_3), 0.87 (d, *J* = 6.8 Hz, 6H, 2 × CH_3) ppm; ^{13}C {H} NMR (100.6 MHz, DMSO-d_6): δ 171.1 (d, *J* = 7.6 Hz), 59.4 (d, *J* = 4.7 Hz), 30.9 (d, *J* = 2.1 Hz), 18.5, 17.1 ppm; ^{31}P {H} NMR (162.0 MHz, DMSO-d_6): δ −64.91 ppm; ^{15}N {H} NMR (40.5 MHz,

DMSO-d_6): δ 57.87 (d, J = 34.9 Hz) ppm; IR (film): 3299, 2964, 2934, 2875, 2428, 1736, 1467, 1430, 1286, 1162, 1069, 993, 897, 819 cm^{-1}; MS (ESI) m/z (%): 263.0 (78) [M+H]$^+$, 285.0 (100) [M+Na]$^+$, 547.1 (28) [2 M+Na]$^+$; HRMS (MALDI) calcd for $C_{10}H_{20}N_2O_4P^+$: 263.1161, found: 263.1159.

4.3.4. (3*R*,5*Λ*,8*R*)-3,8-Di(propan-2-yl)-1,6-dioxa-4,9-diaza-5λ^5-phosphaspiro[4.4]-nonane-2,7-dione 4b

R_f = 0.34 (TLC (silica gel), CH_2Cl_2 as eluent); separating efficiency: 24.3%; white solid; mp > 181 °C (decomposition); $[\alpha]_D^{20} = -22.6$ (c 1.0, DMSO); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.43 (dt, J = 824.4, 2.4 Hz, 1H, PH), 3.82–3.78 (m, 2H, 2 × α-CH), 3.48 (d, J = 17.1 Hz, 2H, 2 × NH), 2.22–2.14 (m, 2H, 2 × β-CH), 1.00 (d, J = 7.0 Hz, 6H, 2 × CH_3), 0.94 (d, J = 6.7 Hz, 6H, 2 × CH_3) ppm; ^{13}C {H} NMR (100.6 MHz, $CDCl_3$): δ 171.0 (d, J = 5.9 Hz), 59.5 (d, J = 3.7 Hz), 31.3 (d, J = 5.2 Hz), 18.8, 16.2 ppm; ^{31}P {H} NMR (162.0 MHz, $CDCl_3$): δ −63.76 ppm; ^{15}N {H} NMR (40.5 MHz, $CDCl_3$): δ 55.56 (d, J = 32.7 Hz) ppm; IR (film): 3290, 2964, 2926, 2875, 2424, 1736, 1467, 1435, 1286, 1162, 1069, 993, 897, 819 cm^{-1}; MS (ESI) m/z (%): 263.0 (100) [M+H]$^+$, 285.0 (59) [M+Na]$^+$, 547.1 (7) [2 M+Na]$^+$; HRMS (MALDI) calcd for $C_{10}H_{20}N_2O_4P^+$: 263.1161, found: 263.1157.

4.3.5. (3*S*,5*Λ*,8*S*)-3,8-Bis(2-methylpropyl)-1,6-dioxa-4,9-diaza-5λ^5-phosphaspiro[4.4]-nonane-2,7-dione 5a

R_f = 0.40 (TLC (silica gel); CH_2Cl_2/CH_3OH (v/v) = 200:1 as eluent); separating efficiency: 29.5%; white solid; mp > 183 °C (decomposition); $[\alpha]_D^{20} = -55.7$ (c 1.0, acetone); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.37 (d, J = 823.4 Hz, 1H, PH), 3.90 (dddd, J = 14.5, 9.0, 4.0, 1.1 Hz, 2H, 2 × α-CH), 3.55 (d, J = 18.1 Hz, 2H, 2 × NH), 1.82–1.71 (m, 4H, 2 × β-CH_2), 1.57–1.48 (m, 2H, 2 × γ-CH), 0.98 (d, J = 6.3 Hz, 6H, 2 × CH_3), 0.95 (d, J = 6.2 Hz, 6H, 2 × CH_3) ppm; ^{13}C {H} NMR (100.6 MHz, $CDCl_3$): δ 171.4 (d, J = 6.3 Hz), 52.6 (d, J = 5.4 Hz), 43.4 (d, J = 1.7 Hz), 24.8, 23.0, 21.5 ppm; ^{31}P {H} NMR (162.0 MHz, $CDCl_3$): δ −67.07 ppm; ^{15}N {H} NMR (40.5 MHz, DMSO-d_6): δ 62.55 (d, J = 32.4 Hz) ppm; IR (film): 3304, 2956, 2929, 2870, 2452, 1732, 1467, 1296, 1159, 999, 918, 854, 778 cm^{-1}; MS (ESI) m/z (%): 291.2 (54) [M+H]$^+$, 313.2 (100) [M+Na]$^+$, 329.1 (22) [M+K]$^+$, 603.3 (34) [2M+Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{24}N_2O_4P^+$: 291.1474, found: 291.1470.

4.3.6. (3*S*,5*Λ*,8*S*)-3,8-Bis(2-methylpropyl)-1,6-dioxa-4,9-diaza-5λ^5-phosphaspiro[4.4]-nonane-2,7-dione 5b

R_f = 0.54 (TLC (silica gel); CH_2Cl_2/CH_3OH (v/v) = 200:1 as eluent); separating efficiency: 28.4%; white solid; mp > 185 °C (decomposition); $[\alpha]_D^{20} = +31.7$ (c 1.0, acetone); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.44 (dt, J = 826.6, 2.4 Hz, 1H, PH), 3.90–3.86 (m, 2H, 2 × α-CH), 3.64 (d, J = 17.2 Hz, 2H, 2 × NH), 1.80–1.68 (m, 4H, 2 × β-CH_2), 1.57–1.48 (m, 2H, 2 × γ-CH), 0.98 (d, J = 6.3 Hz, 6H, 2 × CH_3), 0.94 (d, J = 6.2 Hz, 6H, 2 × CH_3) ppm; ^{13}C {H} NMR (100.6 MHz, $CDCl_3$): δ 172.0 (d, J = 5.7 Hz), 52.2 (d, J = 5.0 Hz), 42.9 (d, J = 5.3 Hz), 24.8, 23.0, 21.2 ppm; ^{31}P {H} NMR (162.0 MHz, $CDCl_3$): δ −66.34 ppm; ^{15}N {H} NMR (40.5 MHz, DMSO-d_6): δ 62.63 (d, J = 28.4 Hz) ppm; IR (film): 3320, 2957, 2934, 2870, 2459, 1737, 1469, 1297, 1167, 999, 921, 863, 846, 779 cm^{-1}; MS (ESI) m/z (%): 291.1 (100) [M+H]$^+$, 313.1 (78) [M+Na]$^+$, 603.2 (15) [2 M+Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{24}N_2O_4P^+$: 291.1474, found: 291.1470.

4.3.7. (3*R*,5*Λ*,8*R*)-3,8-Bis(2-methylpropyl)-1,6-dioxa-4,9-diaza-5λ^5-phosphaspiro[4.4]-nonane-2,7-dione 6a

R_f = 0.40 (TLC (silica gel); CH_2Cl_2/CH_3OH (v/v) = 200:1 as eluent); separating efficiency: 27.1%; white solid; mp > 185 °C (decomposition); $[\alpha]_D^{20} = +55.4$ (c 1.0, in acetone); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.37 (d, J = 823.5 Hz, 1H, PH), 3.90 (dddd, J = 14.5, 9.1, 4.0, 1.1 Hz, 2H, 2 × α-CH), 3.54 (d, J = 18.1 Hz, 2H, 2 × NH), 1.81–1.71 (m, 4H, 2 × β-CH_2), 1.56–1.48 (m, 2H, 2 × γ-CH), 0.98 (d, J = 6.2 Hz, 6H, 2 × CH_3), 0.95 (d, J = 6.2 Hz, 6H, 2 × CH_3) ppm; ^{13}C {H} NMR (100.6 MHz, $CDCl_3$): δ 171.4 (d, J = 6.3 Hz), 52.6 (d, J = 5.4 Hz), 43.4 (d, J = 1.8 Hz), 24.8, 23.0, 21.5 ppm; ^{31}P {H} NMR (162.0 MHz, $CDCl_3$): δ −67.13 ppm; ^{15}N {H} NMR (40.5 MHz, DMSO-d_6): δ 62.37 (d, J = 32.3 Hz) ppm; IR (film): 3302, 2956, 2929, 2870, 2451, 1731, 1468, 1294, 1160, 999, 918, 853, 778 cm^{-1}; MS (ESI) m/z (%): 291.1 (76) [M+H]$^+$, 313.1 (100) [M+Na]$^+$, 603.2 (33) [2 M+Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{24}N_2O_4P^+$: 291.1474, found: 291.1465.

4.3.8. (3*R*,5*Λ*,8*R*)-3,8-Bis(2-methylpropyl)-1,6-dioxa-4,9-diaza-5λ^5-phosphaspiro[4.4]-nonane-2,7-dione 6b

R_f = 0.54 (TLC (silica gel); CH_2Cl_2/CH_3OH (v/v) = 200:1 as eluent); separating efficiency: 24.7%; white solid; mp > 185 °C (decomposition); $[\alpha]_D^{20} = -31.9$ (c 1.0, acetone); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.44 (dt, J = 826.8, 2.4 Hz, 1H, PH), 3.90–3.86 (m, 2H, 2 × α-CH), 3.70 (d, J = 17.2 Hz, 2H, 2 × NH), 1.81–1.66 (m, 4H, 2 × β-CH_2), 1.58–1.49 (m, 2H, 2 × γ-CH), 0.98 (d, J = 6.3 Hz, 6H, 2 × CH_3), 0.94 (d, J = 6.2 Hz, 6H, 2 × CH_3) ppm; ^{13}C {H} NMR (100.6 MHz, $CDCl_3$): δ 172.2 (d, J = 5.6 Hz), 52.2 (d, J = 4.9 Hz), 42.8 (d, J = 5.5 Hz), 24.7, 23.0, 21.2 ppm; ^{31}P {H} NMR (162.0 MHz, $CDCl_3$): δ −66.44 ppm; ^{15}N {H} NMR (40.5 MHz, DMSO-d_6): δ 62.64 (d, J = 28.6 Hz) ppm; IR(film): 3324, 2958, 2934, 2869, 2455, 1736, 1468, 1301, 1167, 998, 922, 862, 844, 777 cm^{-1}; MS (ESI) m/z (%): 291.2 (100) [M+H]$^+$, 313.2 (74) [M+Na]$^+$, 603.3 (18) [2M+Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{24}N_2O_4P^+$: 291.1474, found: 291.1467.

4.4. X-ray structure analysis

Crystals of **3a** and **4a** suitable for X-ray diffraction measurements were grown from acetone solution. Light white needle (**3a**, **4a**) crystals were mounted on glass fibers. Intensity data were collected on a Bruker APEX area-detector diffractometer, using graphite-monochromator Mo K_α radiation (λ = 0.71073 Å) at 293(2) K. Structures were solved by direct methods with the program SHELXS-97.[16]

4.4.1. Crystal data for 3a

Monoclinic, $P2_1$, a = 10.307(2) Å, b = 5.9991(12) Å, c = 11.119(2) Å, V = 668.8(2) Å^3, Z = 2, D_{calcd} = 1.302 mg cm^{-3}, T = 293(2) K, R_1 = 0.0439, wR_2 = 0.1117 [$I > 2\sigma(I)$], R_1 = 0.0444, wR_2 = 0.1125 for all data, Absolute structure parameter is −0.06(11).

4.4.2. Crystal data for 4a

Monoclinic, $P2_1$, a = 10.248(3) Å, b = 5.9670(18) Å, c = 11.058(4) Å, V = 657.8(4) Å^3, Z = 2, D_{calcd} = 1.324 mg cm^{-3}, T = 293(2) K, R_1 = 0.0505, wR_2 = 0.1474 [$I > 2\sigma(I)$], R_1 = 0.0517, wR_2 = 0.1499 for all data, Absolute structure parameter is 0.06(19).

Crystallographic data for the structures of **3a** and **4a** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 726764 (**3a**) and 726765 (**4a**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ ccdc.cam.ac.uk].

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