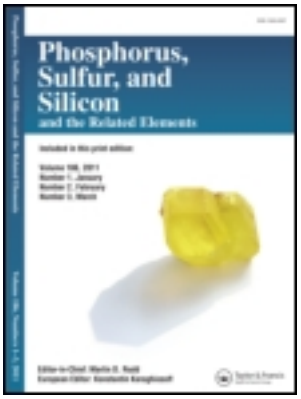

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Characterization of Novel Chiral (1R,2R)-1,2-Bis[5-(Aminomethylphospinic Acid)-1,3,4-Thiadiazol-2-YL]Ethane-1,2-Diols

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SYNTHESIS AND CHARACTERIZATION OF NOVEL CHIRAL (1*R*,2*R*)-1,2-BIS[5-(AMINOMETHYLPHOSPINIC ACID)-1,3,4-THIADIAZOL-2-YL]ETHANE-1,2-DIOLS

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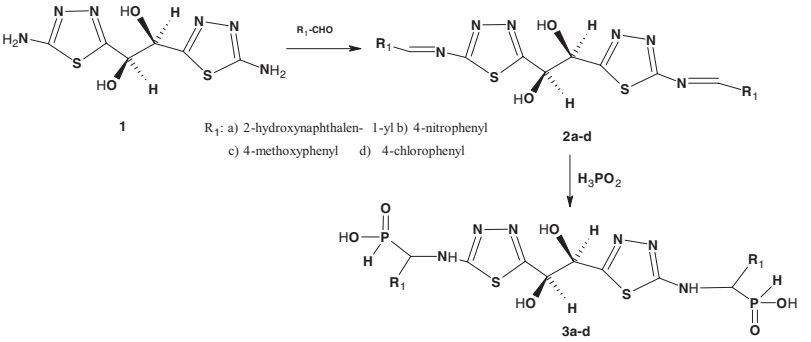
GRAPHICAL ABSTRACT



Abstract *(1R,2R)-1,2-bis[5-(arylideneamino)-1,3,4-thiadiazol-2-yl]ethane-1,2-diol (**2a–d**) were synthesized by using appropriate aldehydes and (1R,2R)-1,2-bis(5-amino-1,3,4-thiadiazol-2-yl)ethane-1,2-diol (**1**) as a starting compound. Then, the phosphinic acid component (**3a–d**) were obtained from (**2a–d**) and hypophosporus acid. In addition, the structures of the novel chiral compounds (**2a–d**) and (**3a–d**) were confirmed by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR spectra.*

^{1}H NMR and ^{13}C NMR spectra for 1, 2a, and 3a (Figures S1–S6) are available online in the Supplemental Materials.

Keywords 1,3,4-Thiadiazole; aminophosphinic acid; tartaric acid; ethane-1,2-diol

INTRODUCTION

Phosphinic acids are of growing importance in understanding and modulating biological processes.[1] In recent years, the synthesis of α-substituted phosphoryl derivatives (phosphonic and phosphinic acids) has attracted significant attention, due to their biological activities with broad application as enzyme inhibitors, antimetabolites, and antibiotics.[2]

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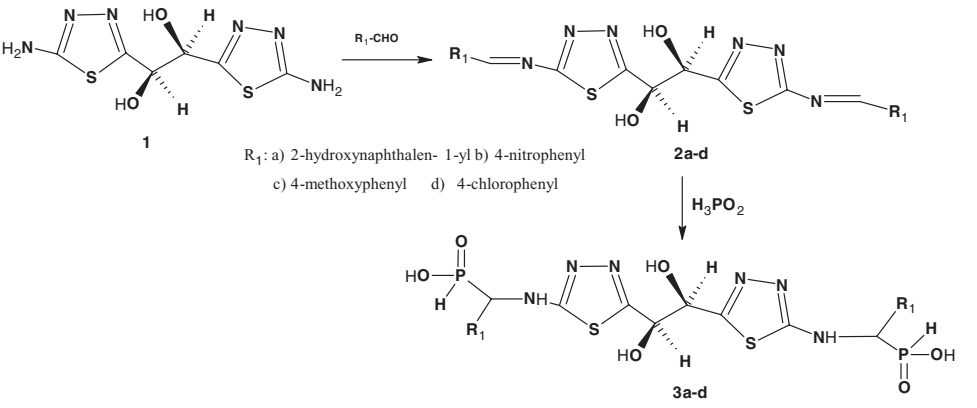
Among functionalized phosphinic acids, α-aminoalkylphosphinic derivatives have potential biological properties, such as antibacterial,[2] herbicidal,[3] and fungicidal activities.[4] 1-aminoalkylphosphinic acids, the phosphinic acid analogs of 1-amino carboxylic acids, are an important class of compounds that exhibit a variety of interesting and useful properties.[5]

In addition, the structure of the phosphinic functional group mimics the transition state of peptide hydrolysis, and the symmetric nature of the phosphinic acid derivatives is expected to be of benefit in their binding to the homodimer of HIV-protease having C_2-axis symmetry.[5]

Proteolytic enzymes, responsible for cleavage of an amide bond in peptide substrates, are involved in variety of physiological and pathological processes, thus representing a group of the most attractive targets for drug design and development.[6,7] The discovery of highly potent and selective inhibitors of proteases, able to discriminate between different members of the same family of proteases, remains a continuous challenge. A phosphinic moiety ($-PO_2^-CH_2-$) is considered to mimic the high-energy tetrahedral transition state of peptide bond hydrolysis and due to this ability phosphinate pseudopeptides attract considerable interest providing a wide range of potent inactivators of proteolitic enzymes, particularly metalloproteases.[8–10]

The 1,3,4-thiadiazole ring is associated with diverse biological activities probably by virtue of incorporating a toxophoric $-N=C-S-$ linkage, the importance of which has been well stressed in many pesticides.[11–14] Various 2-amino/substituted-amino-1,3,4-thiadiazoles and their Schiff bases have recently received significant importance because of their diverse biological properties.[15] Enantiomerically pure 1,2-diols are valuable intermediates in the organic synthesis of biologically active compounds and natural products.[16] They are readily transformed into chiral epoxides,[17] aziridines, and amino alcohols.[18] Moreover, the 1,2-diol functionality is found in a number of synthetic and pharmaceutical intermediates.[19]

Compounds that have optical activity can change to another compound that has optical activity without breaking of covalent bonds, which is connected with asymmetric carbon atoms. In this change, the configuration stays unchanged. So, our synthesized compound configuration is the same as that of our starting compound (the reactions are shown in Scheme 1). However, this reaction mechanism shows that the stereochemistry of the products is unchanged, and the synthesized compound **2a–d** and **3a–d** are enantiomerically pure.



Scheme 1

In the present paper, we have investigated the preparation and characterization of various 1,3,4-thiadiazole containing Schiff bases (**2a–d**) and aminophosphinic acid (**3a–d**) derivatives of novel chiral compounds.

In light of the studies conducted on the synthetic chemistry of phosphinic acids during last 15 years, we have also partly contributed to this progress by developing a new chiral aminophosphinic acid synthesis.

RESULTS AND DISCUSSION

Chemistry

The reactions for the synthesis of **1–3**, are shown in Scheme 1. (1R,2R)-1,2-bis(5-amino-1,3,4-thiadiazol-2-yl)ethane-1,2-diol (**1**) was synthesized by treating thiosemicarbazide with the (2R,3R)-(+)-tartaric acid according to the published procedure.[20–23]

The amine (**1**), on treatment with aromatic aldehydes, furnished Schiff bases of thiadiazoles (**2a–d**), which, on reaction with hypophosphorus acid in the presence of acetonitrile yielded (1R,2R)-1,2-bis[5-(aminomethylphospinic acid)-1,3,4-thiadiazol-2-yl]ethane-1,2-diol (**3a–d**).

Natural chiral compounds (from the chiral pool) often offer an alternative to the synthesis of enantiomerically pure products. (2R,3R)-(+)-tartaric acid is one chiral carboxylic acid isolated from natural sources. In this study, we aimed to synthesized (1R,2R)-1,2-bis(5-amino-1,3,4-thiadiazol-2-yl)ethane-1,2-diol (**1**) by using (2R,3R)-(+)-tartaric acid as starting compound. In the light of above observations, we have selected **1** as the starting compound, which were synthesized according to the literature procedure published previously.[20–23]

The sulfuric acid was used as catalyst in the preparation of **2a–d**. In generally, the preparation of arylidene compounds containing heterocyclic structure is used sulfuric acid as catalyst.[22] This type of compounds is used due to low the steric effects of sulfuric acid as catalyst.

We thought, it worthwhile to synthesize a new series of Schiff bases (**2a–d**) and aminophosphinic acids (**3a–d**) having a 1,3,4-thiadiazole moiety with the objective of obtaining new biologically active compounds.

Finally, we have also partly contributed to this progress by obtaining chiral Schiff bases and chiral aminophosphinic acid derivatives, which involve 1,3,4-thiadiazole groups.

In the IR spectrum of **2a–d**, **3a–d** the most characteristic absorptions are at 3405–3501 cm^{-1} (OH), 3269–3301 cm^{-1} (NH), 1625–1630 cm^{-1} (N=CH), 1601–1613 cm^{-1} (C=N), 1252–1259cm^{-1} (P=O), 989–1112 cm^{-1} (P−O), and 2314–2402 cm^{-1} (P−H). In the ^{1}H-NMR spectra, characteristic signals due to the −NH protons appeared at 5.44–5.49. The signals due to the (N=CH) protons appeared at 8.05–8.11 and those arising from the (PH) protons appeared at 5.09–5.12. The signals due to the (CH–P) protons appeared at 4.76–4.79. The signals due to the aromatic protons appeared as multiples at 6.95–8.37. ^{31}P-NMR spectrum of the product (**3a–d**) exhibited peaks 28.3–28.4 and compares well with the value reported previously 15.3–28.3.[24] The data for all compounds are given in the experimental section. Spectra for **1** (Figures S1 and S2), **2a** (Figures S3 and S4), and **3a** (Figures S5 and S6) can be found in the Supplemental Materials available online.

The yield of **2b** was high. The reason for this could be the lack of conjugation between *n*-electrons on nitrogen atoms with the aromatic ring in intermediate compounds of **2b**.

On the other hand, yields of **2a**, **2c**, and **2d** were more moderate, because of an effective conjugation they have with the aromatic ring in intermediate compounds of **2a**, **2c**, and **2d**.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and use uncorrected, but checked by differential scanning calorimeter (DSC). Specific rotations were recorded on a POLS-1 high-sensitivity polarimeter, with a fixed sodium lamp of wavelength 589 nm. The IR spectra were measured with Perkin–Elmer Spectrum One FTIR spectrophotometer. The ^{1}H, ^{13}C, and ^{31}P spectra were taken on Bruker AC-300 and Bruker AC-400 NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 161.9 MHz for ^{31}P NMR. Compounds were dissolved in $CDCl_3$, D_2O and chemical shifts were referenced to DSS, TMS, (^{1}H and ^{13}C NMR) and 85% H_3PO_4 (^{31}P NMR). Elemental analyses were performed on a LECO-CHNS-938. Starting chemicals were obtained from Merck or Aldrich.

Synthesis of (1R,2R)-1,2-Bis(5-Amino-1,3,4-Thiadiazol-2-yl)Ethane-1,2-Diol (1)

The synthesis of **1** was carried out according to a method given in the literature.[20]

White solid, yield 77%, m.p. 138–139 °C. IR (KBr, cm^{-1}) υ: 3413 (−OH), 3195 ($-NH_2$) 1621 (−C=N), 980 (−C=S=C) cm^{-1}. ^{1}H NMR (400 MHz, D_2O, δ, ppm): 4.16 (s, 2H, 2 × CH), 4.65 (s, 6H, HDO form 2 × NH_2 and 2 × OH). ^{13}C NMR (100 MHz, $CDCl_3$, TMS, δ, ppm): 178.6, 165.0, 74.0. Elemental analysis: $C_6H_8N_6O_2S_2$ Calculated: C, 27.69; H, 3.10; N, 32.29. Found: C, 27.63; H, 3.09; N, 32.18. $[\alpha]_D^{20}$ −173° (*c* 4, water).

General Procedure for the Synthesis of (1R,2R)-1,2-Bis[5-(Arylideneamino)-1,3,4-Thiadiazol-2-yl]Ethane-1,2-Diol (2a–d)

A mixture of (1R,2R)-1,2-bis(5-amino-1,3,4-thiadiazol-2-yl)ethane-1,2-diol (**1**) (10 mmol) and aromatic aldehydes (20 mmol) were added to of ethanol- chloroform (7:3) (100 mL). Then a few drops of concentrated sulfuric acid were added as a catalyst and the solution was refluxed for 12 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give **2a–d**.

(1R,2R)-1,2-Bis(5-{[(2-Hydroxynaphthalen-1-yl)Methylidene]Amino}-1,3,4-Thiadiazol-2-yl)Ethane-1,2-Diol (2a)

Shining white solid, yield 51%, m.p. 156–157 °C. IR (KBr, cm^{-1}) υ: 3450 (−OH), 1628 (−HC=N), 1607 (−C=N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.68 (d, 2H, 2 × CH−OH, J = 10.14), 6.89–6.98 (br, 4H, OH), 7.22 (d, 2H, $J_{1,2}$ = 8.05, H-1, H-1′), 7.55–7.74 (m, 4H, H-4, H-4′; H-5, H-5′), 8.02 (d, 2H, $J_{2,1}$ = 10.53, H-2, H-2′), 8.07 (br, 2H, 2 × N=CH), 8.18 (dd, 2H, $J_{6,5}$ = 7.80, $J_{6,4}$ = 1.17, H-6, H-6′), 8.37 (dd, 2H, $J_{3,4}$ = 6.63, $J_{3,5}$ = 1.17, H-3, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$, TMS, δ, ppm): 175.6, 165.1, 153.4, 149.3, 130.9, 127.8, 127.4, 127.0, 120.4, 115.9, 113.5, 73.9. Elemental analysis: $C_{28}H_{20}N_6O_4S_2$ Calculated: C, 59.14; H, 3.55; N, 14.78. Found: C, 59.09; H, 3.49; N, 14.77. $[\alpha]_D^{20}$ −3.907° (*c* 1, ethanol).

(1R,2R)-1,2-Bis(5-{[(4-Nitrophenyl)Methylidene]Amino}-1,3,4-Thiadiazol-2-yl)Ethane-1,2Diol (2b)

Shining white solid, yield 80%, m.p. 196–197 °C. IR (KBr, cm^{-1}) υ: 3460 (−OH), 1630 (−HC=N), 1602 (−C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.67 (d, 2H, 2 × CH−OH), 6.88–6.96 (br, 2H, OH), 7.47–8.17 (m, 10H, Ar−H and 2 × N=CH). ^{13}C NMR (100 MHz, $CDCl_3$, TMS, δ, ppm): 175.4, 173.4, 169.4, 168.2, 153.6, 140.6, 131.6, 125.4, 125.5, 73.8. Elemental analysis: $C_{20}H_{14}N_8O_6S_2$ Calculated: C, 45.62; H, 2.68; N, 21.28. Found: C, 45.59; H, 2.65; N, 21.30. $[\alpha]_D^{20}$ −5.852° (*c* 1, ethanol).

(1R,2R)-1,2-Bis(5-{[(4-Methoxyphenyl)Methylidene]Amino}-1,3,4-Thiadiazol-2-yl)Ethane-1,2-Diol (2c)

White solid, yield 49%, m.p. 211–210 °C. IR (KBr, cm^{-1}) υ: 3475 (−OH), 1625 (−HC=N), 1611 (−C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.80 (s, 6H, 2 × OCH_3), 6.66 (d, 2H, 2 × CH−OH), 6.82–6.86 (br, 2H, 2 × OH), 6.91–7.37 (m, 8H, Ar−H), 8.05 (br, 2H, 2 × N=CH). ^{13}C NMR (100 MHz, $CDCl_3$, TMS, δ, ppm): 174.9, 173.4, 169.4, 168.1, 164.6, 132.4, 127.9, 113.1, 73.8, 56.4. Elemental analysis: $C_{22}H_{20}N_6O_4S_2$ Calculated: C, 53.20; H, 4.06; N, 16.92. Found: C, 53.17; H, 4.01; N, 17.00. $[\alpha]_D^{20}$ −5.462° (*c* 1, ethanol).

(1R,2R)-1,2-Bis(5-{[(4-Chlorophenyl)Methylidene]Amino}-1,3,4-Thiadiazol-2-yl)Ethane-1,2-Diol (2d)

Shine white, solid yield 60%, m.p. 224–225 °C. IR (KBr, cm^{-1}) υ: 3501 (−OH), 1627 (−HC=N), 1602 (−C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.66 (d, 2H, 2 × CH−OH), 6.83–6.85 (br, 2H, 2 × OH), 7.02–7.29 (m, 8H, Ar−H), 8.11 (br, 2H, 2 × N=CH) ^{13}C NMR (100 MHz, $CDCl_3$, TMS, δ, ppm): 174.8, 173.4, 169.3, 168.0, 164.6, 132.4, 127.8, 112.1, 73.6. Elemental analysis $C_{20}H_{14}Cl_2N_6O_2S_2$ Calculated: C, 47.53; H, 2.79; N,16.63. Found: C, 46.99; H, 2.80; N,16.59. $[\alpha]_D^{20}$ −5.662° (*c* 1, ethanol).

General Procedure for the Synthesis of (1R,2R)-1,2-Bis[5-(Aminomethylphospinic Acid)-1,3,4-Thiadiazol-2-yl]Ethane-1,2-Diol (3a–d)

Schiff base **2a–d** (5 mmol) was dissolved in acetonitrile (10 mL) and H_3PO_2 (10 mmol), and the mixture was refluxed for 5 h, then stirred at room temperature for 24 h. The formed precipitate was collected by filtration, which was then dissolved in 0.1 M NaOH. The solution was filtrated and acidified to precipitate the product, which was collected by filtration.

[({5-[(1R,2R)-1,2-Dihydroxy-2-(5-{[(2-Hydroxynaphthalen-1-yl)(Hydroxyphosphonoyl) Methyl]Amino}-1,3,4-Thiadiazol-2-yl)Ethyl].-1,3,4-Thiadiazol-2-yl}Amino)(2-Hydroxynaphthalen-1-yl)Methyl]phosphinic acid (3a)

White solid, yield 57%, m.p. 337–338 °C. IR (KBr, cm^{-1}) υ: 3495 (−OH), 3299 (−NH), 2389 (−P−H), 1607 (−C=N), 1254 (−P=O), 1081 (−P−O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.76 (d, 2H, 2 × CHP), 5.10 (d, 2H, 2 × PH), 5.45 (br, 2H, 2

× NH), 6.67 (d, 2H, 2 × CHOH), 6.88–6.98 (br, 4H, OH), 7.21 (d, 2H, $J_{1,2} = 8.05$, H-1, H-1′), 7.56–7.74 (m, 4H, H-4, H-4′; H-5, H-5′), 8.02 (d, 2H, $J_{2,1} = 10.53$, H-2, H-2′), 8.18 (dd, 2H, $J_{6,5} = 7.80$, $J_{6,4} = 1.17$, H-6, H-6′), 8.36 (dd, 2H, $J_{3,4} = 6.63$, $J_{3,5} = 1.17$, H-3, H-3′), 8.81 (br, 2H, 2 × POH). ^{13}C NMR ($CDCl_3$, TMS, δ, ppm): 175.6, 167.0, 165.0, 159.8, 153.4, 136.1, 130.9, 127.8, 127.4, 127.0, 120.3, 101.9, 73.9. ^{31} P NMR (161,9 MHz, CDCl3, δ, ppm): 28.4; Elemental analysis $C_{28}H_{26}N_6O_8P_2S_2$ Calculated: C, 48.00; H, 3.74; N, 12.00. Found: C, 47.98; H, 3.75; N, 12.07. $[\alpha]_D^{20}$ −4.907° (*c* 1, ethanol).

[({5-[(1R,2R)-1,2-Dihydroxy-2-(5-{[(Hydroxyphosphonoyl)(4-Nitrophenyl)Methyl]Amino}-1,3,4-Thiadiazol-2-yl)Ethyl]-1,3,4-Thiadiazol-2-yl}Amino)(4-Nitrophenyl)Methyl]Phosphinic Acid (3b)

White solid, yield 82%, m.p. 321–322°C. IR (KBr, cm^{-1}) υ: 3465 (−OH), 3301 (−NH), 2402 (−P−H), 1613 (−C=N), 1258 (−P=O), 1112 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.78 (d, 2H, 2 × CHP), 5.12 (d, 2H, 2 × PH), 5.49 (br, 2H, 2 × NH), 6.65 (d, 2H, 2 × CHOH), 6.89–6.96 (br, 2H, 2 × OH), 7.46–8.11 (m, 8H, Ar−H), 8.79 (br, 2H, 2 × POH) ^{13}C NMR ($CDCl_3$, TMS, δ, ppm): 174.0, 167.1, 165.8, 164.0, 150.1, 140.2, 131.2, 124.5, 72.9. ^{31} P NMR ($CDCl_3$, TMS, δ, ppm): 28.4; Elemental analysis $C_{20}H_{20}N_8O_{10}P_2S_2$ Calculated: C, 36.48; H, 3.06; N, 17.02. Found: C, 36.44; H, 3.01; N, 16.98. $[\alpha]_D^{20}$ −6.523° (*c* 1, ethanol).

[({5-[(1R,2R)-1,2-Dihydroxy-2-(5-{[(Hydroxyphosphonoyl)(4-Methoxyphenyl)Methyl]Amino}-1,3,4-Thiadiazol-2-yl)Ethyl]-1,3,4-Thiadiazol-2-yl}Amino)(4-Methoxyphenyl)Methyl]Phosphinic Acid (3c)

White solid, yield 51%, m.p. 331–332°C. IR (KBr, cm^{-1}) υ: 3501 (−OH), 3272 (−NH), 2314 (−P−H), 1602 (−C=N), 1252 (−P=O), 989 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3,79 (s, 6H, 2 × OCH_3), 4.77 (d, 2H, 2 × CHP), 5.09 (d, 2H, 2 × PH), 5.44 (br, 2H, 2 × NH), 6.67 (d, 2H, 2 × CHOH), 6.88–6.95 (br, 2H, 2 × OH), 7.01–7.16 (m, 8H, Ar−H), 8.83 (br, 2H, 2 × POH) ^{13}C NMR ($CDCl_3$, TMS, δ, ppm): 174.9, 165.9, 163.5, 160.8, 130.4, 129.0, 116.0, 72.9, 56.5. ^{31} P NMR ($CDCl_3$, TMS, δ, ppm): 28.3; Elemental analysis $C_{22}H_{26}N_6O_8P_2S_2$ Calculated: C, 42.04; H, 4.17; N, 13.37. Found: C, 41.96; H, 4.21; N, 13.07. $[\alpha]_D^{20}$ −6.702° (*c* 1, ethanol).

[({5-[(1R,2R)-1,2-Dihydroxy-2-(5-{[(Hydroxyphosphonoyl)(4-Chloroyphenyl)Methyl]Amino}-1,3,4-Thiadiazol-2-yl)Ethyl]-1,3,4-Thiadiazol-2-yl}Amino)(4-Chlorophenyl)Methyl]Phosphinic Acid (3d)

White solid, yield 59%, m.p. 356–357 °C. IR (KBr, cm^{-1}) υ: 3405 (−OH), 3269 (−NH), 2369 (−P−H), 1601 (−C=N), 1259 (−P=O), 1077 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.79 (d, 2H, 2 × CHP), 5.11 (d, 2H, 2 × PH), 5.47 (br, 2H, 2 × NH), 6.68 (d, 2H, 2 × CHOH), 6.88–6.98 (br, 2H, 2 × OH), 7.08–7.27 (m, 8H, Ar−H), 8.81 (br, 2H, 2 × POH). ^{13}C NMR ($CDCl_3$, TMS, δ, ppm): 173.9, 165.8, 164.0, 139.0, 139.4, 136.0, 134.0, 129.7, 72.5. ^{31} P NMR ($CDCl_3$, TMS, δ, ppm): 28.4; Elemental analysis

$C_{20}H_{20}Cl_2N_6O_6P_2S_2$ Calculated: C, 37.69; H, 3.16; N, 13.18. Found: C, 37.58; H, 3.15; N, 13.20. $[\alpha]_D^{20}$ −6.572° (*c* 1, ethanol).

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