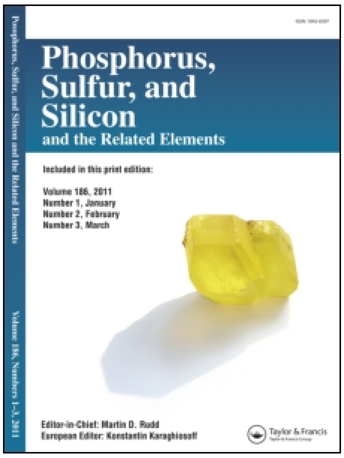

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Determination of absolute configuration of optically active 1-aminoalkanephosphonic acids by chemical correlations

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DETERMINATION OF ABSOLUTE CONFIGURATION OF OPTICALLY ACTIVE 1-AMINOALKANEPHOSPHONIC ACIDS BY CHEMICAL CORRELATIONS

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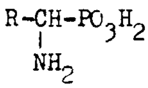
Abstract The absolute configurations of optically active phosphonic analogues of serine, β-chloroalanine, phenylalanine, tyrosine and 2-aziridinephosphonic acid have been established via chemical correlations with phosphonic analogues of alanine or aspartic acid of known configuration.

During the last ten years there has been some progress towards the synthesis and determination of absolute configuration of enantiomeric 1-aminoalkanephosphonic acids (1) related structurally to protein amino acids. Thus, taking advantage of X-ray crystallographic



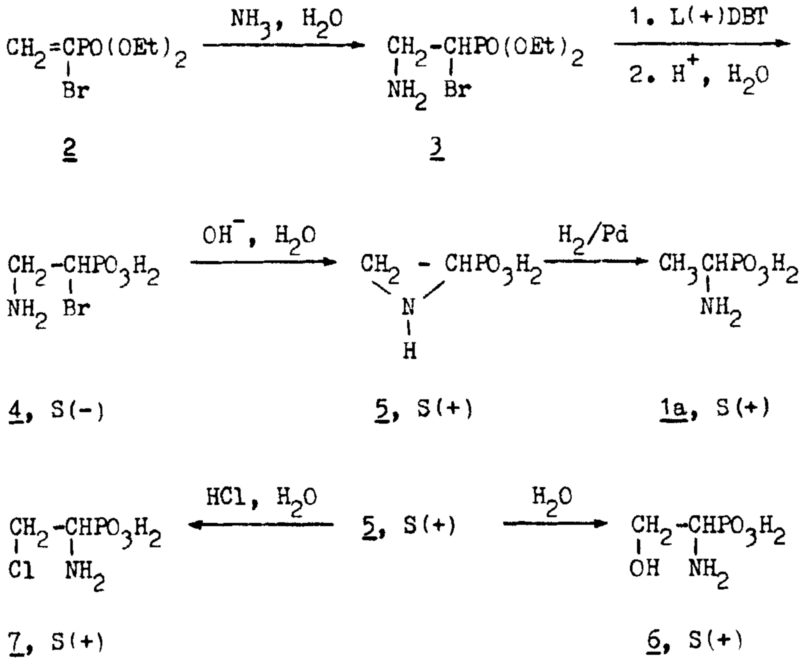
$$\underset{NH_2}{R-CH}-PO_3H_2$$

1

1a: $R=CH_3$; 1b: $R=(CH_3)_2CH$; 1c: $R=CH_2COOH$;
1d: $R=CH_2CONH_2$; 1e: $R=(CH_3)_2CHCH_2$;
1f: $R=CH_3SCH_2CH_2$; 1g: $R=C_6H_5CH_2$

methods there have been determined the configurations of R(-)AlaP (1a) and R(+)ValP (1b), the phosphonate analogues of alanine and valine[1,2], while the configurations of R(-)AspP (1c) and R(-)AsnP (1d) have been deduced from NMR analysis of suitable glycosidic precursors[3]. Most recently, the (-) enantiomers of LeuP (1e), MetP (1f) and PheP (1g) have been tentatively assigned the R configuration by comparing the chromatographic behaviour of their diastereomeric dipeptides with N-terminal L-phenylalanine[4].

Because the phosphonic analogues of some protein amino acids have rather interesting biological properties[5] it is desirable to extend the number of optically active 1 of unequivocally assigned configuration. To serve this purpose we have determined the configuration of (+)SerP (6) by chemical correlation with S(+)AlaP (1a) and of (-)PheP (1g) and (-)TyrP (11) by correlation with R(-)AspP (1c). The key compound for the correlation of SerP with AlaP was (+)-2-aziridinephosphonic acid (5) and the involved chemistry is shown in Figure 1.



DBT: dibenzoyl-L-(+)tartaric acid

4: $[\alpha]_{578}^{20} = -25^\circ$ (c 2.7, H_2O); 5: $[\alpha]_{578}^{20} = +31^\circ$ (c 2.5, H_2O)

1a: $[\alpha]_{578}^{20} = +16^\circ$ (c 2.0, H_2O); 6: $[\alpha]_{578}^{20} = +27^\circ$ (c 2.5, H_2O)

7: $[\alpha]_{578}^{20} = +34^\circ$ (c 1.6, H_2O)

FIGURE 1 Synthesis and ring opening reactions of S(+)-2-aziridinephosphonic acid.

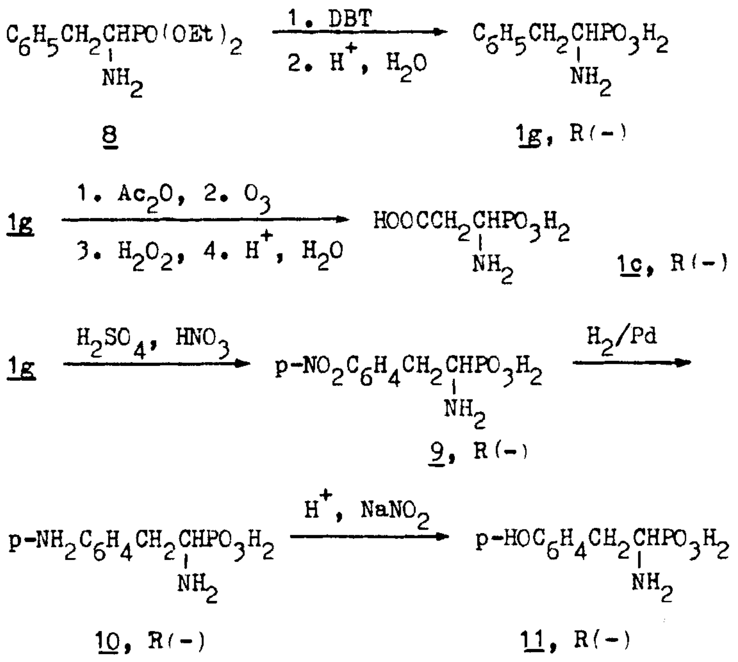
As described earlier[6], 5 undergoes nucleophilic ring opening reactions leading exclusively to 2-substituted derivatives of AlaP. We found that also a reductive ring fission is regiospecific and gives AlaP as the only reaction product. Therefore, the ring opening reactions do not affect the chiral atom and are suitable for establishing the relative configurations of substrate and products.

Optical activity was introduced by resolution of crude, racemic diethyl 1-bromo-2-aminoethanephosphonate 3 (an undistillable oil[6]) with DBT. Crystallization of the less soluble DBT salt of 3 to constant parameters and hydrolysis gave levorotatory 4 which was cyclized to dextrorotatory 5. Hydrogenation of 5 afforded 1a of specific rotation in accord with the literature value for S(+)AlaP[1]. It follows that the configuration of 2-aziridinephosphonic acid is S(+). Considering that the cyclization of 4 to 5 most probably follows an internal S_N2 mechanism it appears safe to assume the S(-) configuration for the acid 4 (priority rules!).

Hydrolysis of 5 gave the dextrorotatory analogue of serine 6. Thus, SerP has the S(+) configuration. Similarly, the S(+) configuration of the chloroalanine analogue 7 follows from the transformation of 5 to 7.

To determine the configuration of PheP we have converted (-)PheP to (-)AspP by ozonolytic destruction of the phenyl ring, as shown in Figure 2. We obtained (+) and (-)PheP from the racemic ester 8 (prepared as described earlier[7]), by resolution with DBT, followed by hydrolysis. Ozonolysis of acetylated 1g proceeded smoothly and, upon oxidative work-up and hydrolysis yielded (-)AspP (1c) which has been assigned the R configuration by Vasella et al[3]. This result establishes the R(-) configuration for PheP.

Finally, by conversion of (-)PheP to (-)TyrP (11), we have established the configuration of TyrP as R(-). The conversion was accomplished by nitration, reduction and diazotization. Specific rotations shown in Figure 2 indicate that the p-nitro (9) and p-amino (10) congeners of TyrP also have the R(-) configuration.



$$\underset{\mathbf{8}}{C_6H_5CH_2\underset{NH_2}{CH}PO(OEt)_2} \xrightarrow[2.\ H^+,\ H_2O]{1.\ DBT} \underset{\mathbf{1g},\ R(-)}{C_6H_5CH_2\underset{NH_2}{CH}PO_3H_2}$$

$$\mathbf{1g} \xrightarrow[3.\ H_2O_2,\ 4.\ H^+,\ H_2O]{1.\ Ac_2O,\ 2.\ O_3} HOOCCH_2\underset{NH_2}{CH}PO_3H_2 \quad \mathbf{1c},\ R(-)$$

$$\mathbf{1g} \xrightarrow{H_2SO_4,\ HNO_3} \underset{\mathbf{9},\ R(-)}{p\text{-}NO_2C_6H_4CH_2\underset{NH_2}{CH}PO_3H_2} \xrightarrow{H_2/Pd}$$

$$\underset{\mathbf{10},\ R(-)}{p\text{-}NH_2C_6H_4CH_2\underset{NH_2}{CH}PO_3H_2} \xrightarrow{H^+,\ NaNO_2} \underset{\mathbf{11},\ R(-)}{p\text{-}HOC_6H_4CH_2\underset{NH_2}{CH}PO_3H_2}$$

1g: $[\alpha]^{20}_{578}=-47^{\circ}$ (c 2.3, 1N NaOH); **1c**: $[\alpha]^{20}_{578}=-35^{\circ}$ (c 2.1, H_2O)

10: $[\alpha]^{20}_{578}=-52^{\circ}$ (c 1, 1N HCl); **11**: $[\alpha]^{20}_{578}=-53^{\circ}$ (c 1.5, 1N HCl)

FIGURE 2 Conversion of PheP to AspP and TyrP

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