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ASYMMETRIC SYNTHESIS OF (+)-PHOSPHINOTHRICIN and (+)-2-AMINO-4-PHOSPHONOBUTYRIC ACID

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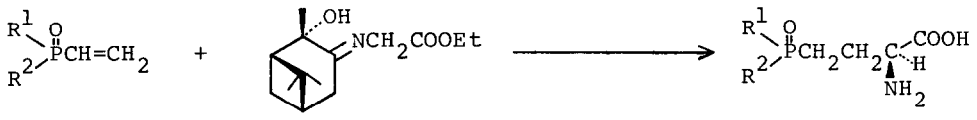
Summary: Asymmetric synthesis of (+)-phosphinothricin, (+)-2-amino-4-phosphonobutyric acid, and their enantiomers has been achieved by the Michael addition of chiral glycine Schiff bases to vinyl phosphorus compounds.

Phosphorus analogues of glutamic acid are interesting as biologically active substances. Thus, (+)-phosphinothricin ((S)-(+)-1) and its alanylalanine derivative (bialaphos) (2), produced by two strains of Streptomyces,[1] have strong herbicidal activity.[2] (+)-2-Amino-4-phosphonobutyric acid ((S)-(+)-3) competes with glutamate for receptors in nerve cells, and has been reported to have an antiviral activity.[3]

We have recently reported a practical synthesis of (+)-phosphinothricin by the Michael addition of glycine Schiff base to vinylphosphinate (4a).[4] As an extention of the preceding study, we now report an effective asymmetric synthesis of 1 and 3. According to this method, both of the S- and R-enantiomers can be prepared by the asymmetric Michael addition of chiral Schiff bases (5)[5] to vinyl phosphorus compounds 4a and 4b. Although a number of asymmetric reactions with chiral acceptors has been reported,[6] there have been a few examples using chiral Michael donors.[7]

Scheme 1



4a: R^1=Me, R^2=MeO (-)-5: (1S,2S,5S) (S)-(+)-1: R^1=Me, R^2=OH
4b: R^1=R^2=EtO (S)-(+)-3: R^1=R^2=OH

Table 1. Asymmetric Michael Addition using Chiral Glycine Schiff Bases (5)[a]

Entry	Michael acceptor	Michael donor	Additive	Amino acid Compd. no.	Total yield(%)	$[\alpha]_D^{25}$,deg.	Optical purity (%) (Confign.), [Calcd.][h]
1	4a	(-)-5		1	66	+13.4[b]	79[c] (S) [85]
2	4a	(+)-5		1	64	-12.4[b]	73[c] (R) [88]
3	4a	(-)-5	HMPA[d]	1	42	+7.6[b]	45[c] (S) [48]
4	4a	(-)-5	18-crown-6[d]	1	51	+6.8[b]	40[c] (S) [43]
5	4b	(-)-5		3	68	+14.6[e]	50[f] (S) [54]
6	4b	(+)-5		3	65	-13,0[e]	45[f] (R) [54]
7	CH_2=CHCOOMe	(-)-5		7	57	-17.7[e]	56[g] (R) [61]
8	CH_2=CHCOOMe	(+)-5		7	55	+14.9[e]	47[g] (S) [58]

a) All reactions were carried out at -78°C using two equivalents of t-BuOK. b) c 1.0 in H_2O. c) Based on $[\alpha]_D^{23}$ +17°(c 1.0, H_2O) in ref. 8. d) Five equivalents of the additive was used. e) c 1.0 in 6N-HCl. f) Based on $[\alpha]_D$ +29°(6N-HCl) in ref. 3. g) Based on $[\alpha]_D$ +31.4° of (+)-glutamic acid. h) Corrected for the optical purity of the ketol, see: ref. 9.

The asymmetric Michael addition was undertaken as shown in Scheme 1. The general procedure is as follows. To a stirred solution of potassium t-butoxide (t-BuOK) (2.0 eq) in tetrahydrofuran (THF) was added a solution of the chiral Schiff base 5 (1.0 eq) in THF at -78°C, followed by addition of a solution of vinyl compound (1.0 eq) in THF at -78°C under argon. After stirred for 1 hr at -78°C, 1N hydrochloric acid was added to the resulting yellow solution and the solvent was removed. To the residue was added 6N hydrochloric acid and the solution was refluxed for 24 hr. After concentration of the resulting solution, the residue was dissolved in ethanol-water (1:1) and a large excess amount of propylene oxide was added. The solution was stirred at 25°C for 1 hr. The resulting solution was concentrated and purified by ion-exchange resin (Dowex 50X2) to give the amino acid. The results are summarized in Table 1.

Treatment of vinylphosphinate (4a) and vinylphosphonate (4b) with the chiral Schiff base (-)-5, obtained by the condensation of glycine ethyl ester and (1S, 2S, 5S)-2-hydroxypinan-3-one,[9] afforded the desired (+)-phosphinothricin ((S)-(+)-1) and (+)-2-amino-4-phosphonobutyric acid ((S)-(+)-3), respectively, in high optical purities (entries 1 and 5). On the other hand, the reactions of 4a and 4b with the other chiral Schiff base (+)-5, similarly prepared from (1R, 2R, 5R)-2-hydroxypinan-3-one,[9] gave their enantiomers, (-)-phosphinothricin ((R)-(-)-1) and (-)-2-amino-4-phosphonobutyric acid ((R)-(-)-3), respectively, in high optical purities (entries 2 and 6). Since both enantiomers of α-pinene, from which the chiral ketols are prepared, are readily available from natural sources, the present method has advantage in providing both (S)-(+)- and (R)-(-)-isomers of 1 and 3 in high optical purities.

In order to clarify the high chiral induction observed for the vinyl phosphorus compounds, the following studies were carried out. Addition of (-)-5 to 4a in the presence of hexamethylphosphoric triamide (HMPA) or dicyclohexyl-18-crown-6 (18-crown-6), which has strong ability to solvate cations,[10] gave lower optical purity of the product (S)-(+)-1 (entries 3 and 4). These results may be explained by the existence of the chelate intermediate as shown in Fig. 1, which is similar to those proposed by Meyers et al.[11] and Koga et al.[12] It is assumed that the coordination of the electron pairs on the nitrogen atom and the oxygen atom of phosphoryl group to the potassium of potassium alkoxide plays a central role in this highly orientated addition. Interestingly, treatment of (-)-5 and (+)-5 with methyl acrylate (6) gave (-)-glutamic acid ((R)-(-)-7) and the (+)-isomer ((S)-(+)-7), respectively, in good optical yields (entries 7 and 8). That is, the stereochemical course of the addition of 5 to methyl acrylate was the same as that of alkylation[5] of 5 and opposite to that of the addition to vinyl phosphorus compounds. Further studies on the detailed mechanism are now in progress.

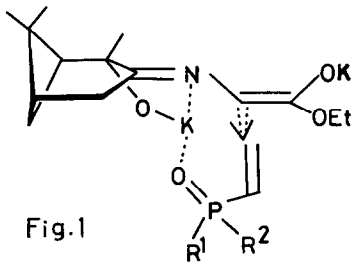


Fig.1

The herbicidal activity of (S)-(+)-1 was remarkably stronger than those of (±)-1 and (R)-(-)-1 in foliage treatment.

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9) According to the method of Carlson and Pierce [J. Org. Chem., 36, 2319 (1971)], (S)-2-hydroxypinan-3-one, $[\alpha]_D^{25}$ -37.0°(c 2.60, $CHCl_3$) [lit.[5] $[\alpha]_D^{25}$ -38.9°(c 2.64, $CHCl_3$)], was prepared from (+)-α-pinene, $[\alpha]_D^{22}$ +47.1° (neat) and the (R)-isomer, $[\alpha]_D^{25}$ +33.0°(c 2.60, $CHCl_3$), was obtained from (-)-α-pinene, $[\alpha]_D^{22}$ -42.0°(neat). The optical purities of the (S)- and (R)-ketols were estimated to be at least 92.5% and 82.5%, respectively.[5]

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