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# Phosphorus, Sulfur, and Silicon and the Related Elements

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# Synthesis and Biological Activities of Phosphonothrixin

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## Synthesis and Biological Activities of Phosphonothrixin

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A novel herbicidal compound phosphonothrixin possessing a C-P bond, was isolated from the fermentation broth of *Saccharothrix* sp. ST-888. The biological activity against various weeds and total synthesis of phosphonothrixin are described herein.

Keywords: phosphonothrixin; herbicidal antibiotic; total synthesis

#### INTRODUCTION

These has been much interest on the possible exploitation of novel natural products as safe and selective agrochemicals. Among them, bialaphos, phosphinothricin and phosalacine are known as herbicidal substances<sup>1</sup> from the fermentation broth of actinomycetes. The structure-activity relationships of these compounds are attractive for agrochemist as they contain a C-P bond in their structure. The C-P bond containing compounds are also interesting because of their biosynthetic pathways.<sup>2</sup>

In the course of our screening for new herbicidal antibiotics, we found that a soil sample produced a novel active compound, phosphonothrixin. Phosphonothrixin also possesses a C-P bond in the structure.

#### **ISOLATION AND STRUCTURE DETERMINATION**

The herbicidal compound producing strain ST-888, isolated from a soil sample collected at Iwaki, Japan, was selected from about 1,600 microorganisms. The strain was identified as *Succharothrix* sp., and was successfully cultured in vegetable juice medium.

The active compound was purified by repeating ion-exchange chromatography and gel filtration as shown in Scheme  $1.^{3}$ 



The active compound, phosphonothrixin was obtained as a colorless syrup, and its molecular weight was determined as 198 ( $C_5H_{11}PO_4$ ) by FAB-MS spectroscopy. The positive reaction to Hanes-Isherwood reagent indicated that this compound was a derivative of phosphonic acid.

The NMR spectra were measured in a pH 8  $H_2O$  buffer (0.1 M  $H_2BO_3$ -KCl-NaOH solution, containing *ca* 10%  $D_2O$ ). The chemical shifts of these spectra were sensitive to variations in pH, so all spectra were recorded using pH 8 buffer as solvent.

From the NMR spectrum, methylene signals at  $\delta_{H}$  1.89, 2.08 and  $\delta_{C}$  33.0 ppm with the coupling constants  ${}^{2}J_{HP}$ = 16.8 Hz and  ${}^{1}J_{CP}$ = 131 Hz indicate direct C-P bonding. The structure of an active compound was thus determined to be a phosphonic acid derivative with an isoprene skeleton (figure 1).<sup>4</sup>



Figure 1	Structure	of phos	phonothrixin

#### **BIOLOGICAL ACTIVITIES**

The coleoptile of green foxtail (*Sativa viridis*) when treated with phosphonothrixin at a concentration of 0.3 mg/ml turned into white, while the growth of the coleoptile was not affected. Herbicidal activity of foliar application on the 2- to 4-leaf stage of plant is shown in Table 1. Phosphonothrixin induced chlorosis at the rate of 50 g/a against all the tested plants including broad leaf weeds, so plant-selectivity was not observed. In addition, the herbicidal activity was observed only by foliar application, but not by soil application. Phosphonothrixin is more effective early-post than late-post emergency.<sup>3</sup>

Plant	12.5 g/a	50 g/a
Sativa viridis	4.5	4.9
Echinochloa frumentaceum	2.5	3.5
Avena fatua	3.0	3.5
Digitaria adscendes	3.5	4.0
Amaranthus retroflexus	4.5	4.5
Bidens pilosa	3.75	4.0
Sinapis arvensis	4.0	4.5
Stellaria media	4.0	4.0
Cassia obtusifolia	3.5	4.0
Solanum nigrum	4.0	4.5
Abutilon threophrasti	4.0	4.5
<u>Convolvulus arvensis</u>	3.0	4.5

Herbicidal activities were evaluated through visual observation of the degree of foliar killing as 0 (no kills) ~ 5 (> 90 % killed).

Table 1 Herbicidal activity of phosphonothrixin by foliar application

#### TOTAL SYNTHESIS

The total synthesis of phosphonothrixin was accomplished in both a racemic<sup>5</sup> and an enantioselective manner.<sup>6</sup>

For a stereoselective synthesis of the above, the known dienyl alcohol was selected as the starting material (Scheme 2). The catalytic Sharpless epoxidation using D-DET gave a chiral epoxy alcohol in 57 % yield (92 % ee determined by derivatization to MTPA ester). The C-P bond formation using chloro magnesium salt of dibenzyl phosphite (generated from dibenzyl phosphite and isopropyl magnesium chloride) was accomplished in 40 % yield to give the desired phosphonate. This reaction is assisted by the Lewis-acid nature of the magnesium cation, as shown in Scheme 2. The ozonolysis and hydrogenolysis of the phosphonate afford the desired S-phosphonothrixin. The synthesis of the enantiomer was also achieved using L-DET at the step of Sharpless epoxidation (92 % ee).

The negative optical rotation ( $\{\alpha\}_D$  -3.2° (c 1.00, H<sub>2</sub>O)) of the synthetic *S*-phosphonothrixin was in good agreement with that of the natural product ( $\{\alpha\}_D$  -4.1°). *S*-Phosphonothrixin also induced chlorosis of the coleoptile of green foxtail (*S. viridis*) at 8 ppm by the germination test, but its enantiomer showed the same activity only at 125 ppm. Thus, it can be concluded that natural phosphonothrixin exists in the *S* configuration.

Based on synthesis of the racemate,<sup>7</sup> structural analogs of phosphonothrixin were also synthesized, however, compounds having activity higher than phosphonothrixin could not be obtained.



a. D-DET-Ti(OiPr)<sub>4</sub>-TBHP/CH<sub>2</sub>Cl<sub>2</sub> (57 %). b. ClMg-PO(OBn)<sub>2</sub> /El<sub>2</sub>O (40 %). c. O<sub>3</sub> /CH<sub>2</sub>Cl<sub>2</sub> then Me<sub>2</sub>S (79 %). (natural phosphonothrixin) d. H<sub>2</sub>-Pd(C)/McOH-H<sub>2</sub>O (quant.). e. L-DET-Ti(OiPr)<sub>4</sub>-TBHP/CH<sub>2</sub>Cl<sub>2</sub>



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