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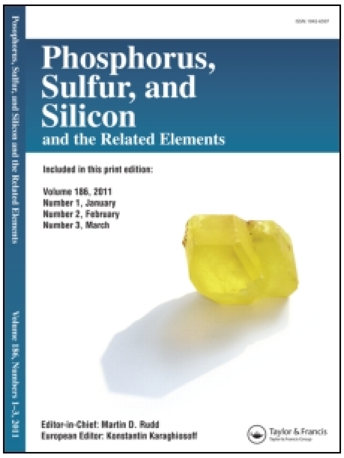

# Phosphorus, Sulfur, and Silicon and the Related Elements

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# Synthesis and Biological Activities of Phosphonothrixin

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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

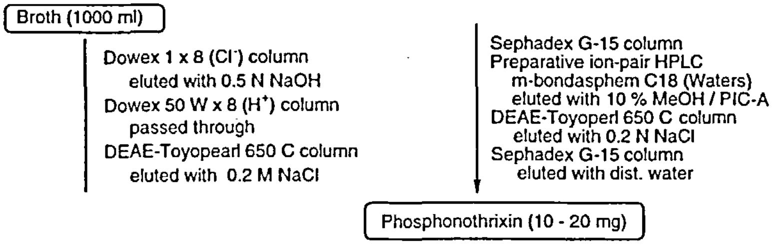
These has been much interest on the possible exploitation of novel natural products as safe and selective agrochemicals. Among them, bialaphos, phosphinothricin and phosalacine are known as herbicidal substances[1] from the fermentation broth of actinomycetes. The structure-activity relationships of 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.[2]

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 *Saccharothrix* 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]



Scheme 1 Isolation of phosphonothrixin

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 $H_3BO_3$–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 $^2J_{HP}$= 16.8 Hz and $^1J_{CP}$= 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).[4]

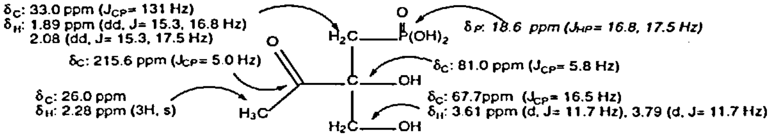


Figure 1 Structure of phosphonothrixin

## 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.[3]

| 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 |
| *Convolvulus arvensis* | 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

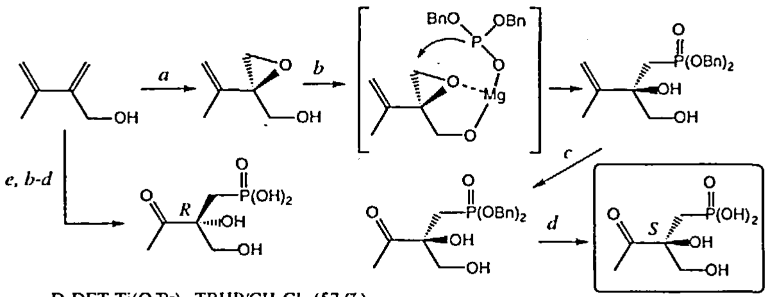
## TOTAL SYNTHESIS

The total synthesis of phosphonothrixin was accomplished in both a racemic[5] and an enantioselective manner.[6]

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, $H_2O$)) 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,[7] structural analogs of phosphonothrixin were also synthesized, however, compounds having activity higher than phosphonothrixin could not be obtained.



*a*. D-DET-Ti(O*i*Pr)$_4$-TBHP/CH$_2$Cl$_2$ (57 %).
*b*. ClMg-PO(OBn)$_2$ /Et$_2$O (40 %). *c*. O$_3$ /CH$_2$Cl$_2$ then Me$_2$S (79 %).
*d*. H$_2$-Pd(C)/MeOH-H$_2$O (quant.).
*e*. L-DET-Ti(O*i*Pr)$_4$-TBHP/CH$_2$Cl$_2$

Scheme 2 Synthesis of phosphonothrixin

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## *References*

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