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Enantioselective Synthesis of Phosphonothrixin and Its Absolute Stereochemistry

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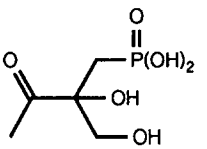
Abstract: The synthesis of both enantiomers of phosphonothrixin is described. On the basis of optical rotation and biological activity, the natural product was determined to have *S* configuration. Copyright © 1996 Elsevier Science Ltd

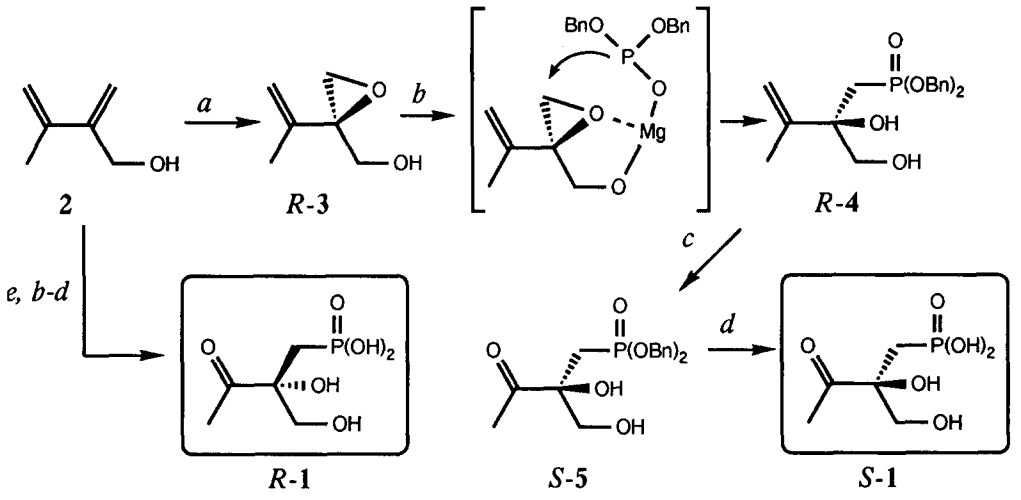
Phosphonothrixin (1), a novel C-P bond containing herbicidal antibiotic, has been isolated from the fermentation broth of *Saccharothrix* sp. ST-888 and its chemical structure was determined by means of spectroscopic analysis and a total synthesis of the racemate.[1-3] From a biological point of view, the biosynthetic pathway of C-P bond containing compounds is quite interesting, because distribution of this class of compounds in nature is very limited.[4] All of the known compounds were biosynthesized *via* phosphonopyrvate as the common intermediate. For the development of a new biosynthetic pathway suggested by the unusual structure of phosphonothrixin, its absolute stereochemistry first had to be clarified. However, natural phosphonothrixin was isolated as a colorless syrup, and no crystalline products were obtained by derivatization. In this report, the absolute structure of phosphonothrixin was unambiguously determined by means of synthetic methodology using Sharpless asymmetric epoxidation.[5]



phosphonothrixin (1)

The dienyl alcohol 2[6] was selected for the starting material. The catalytic Sharpless epoxidation[5] using D-DET gave a chiral epoxy alcohol *R*-3[7] 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 *R*-4.[7] This reaction proceeds assisted by the Lewis-acid nature of the magnesium cation, as shown in Scheme.[8] The ozonolysis of 4 gave the corresponding ketone *S*-5[7] in 79 % yield as colorless crystals from EtOAc-hexane (mp 84-86 °C). Finally, the benzyl ester was deprotected to afford the desired *S*-phosphonothrixin (*S*-1). The synthesis of the enantiomer (*R*-1)[7] was also achieved using L-DET at the step of Sharpless epoxidation (92 % ee).

The negative optical rotation $\{[\alpha]_D^{22}$ -3.2° (*c* 1.00, $H_2O)\}$ of the synthetic *S*-phosphonothrixin was in good agreement with that of the natural product $\{[\alpha]_D^{22}$ -4.1°$\}$.[2] *S*-Phosphonothrixin also induced chlorosis of the coleptile of green foxtail (*Setaria viridis*) at 8 ppm by the germination test[1], but *R*-1 showed the same activity only at 125 ppm.[9] Thus, it can be concluded that natural phosphonothrixin has *S* configuration.



Scheme *Reagents and conditions*: *a*. D-DET (0.25 eq.) $Ti(O^iPr)_4$ (0.2 eq.) TBHP (2 eq.) in CH_2Cl_2, -20 °C, 1 day (57 %). *b*. ClMg-$PO(OBn)_2$ (3.0 eq.) in Et_2O, -50 - 0 °C, 2.5 hr. (40 %) *c*. O_3 in CH_2Cl_2, -78 °C, 3 min then Me_2S, r.t., 1 hr. (79 %) *d*. H_2-Pd(C) in MeOH-H_2O 1:1, r.t., overnight (quant.) *e*. L-DET (0.25 eq.) $Ti(O^iPr)_4$ (0.2 eq.) TBHP (2 eq.) in CH_2Cl_2, -20 °C, 1 day.

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7. *R*-**3**: $[\alpha]_D^{23}$ +55.6° (*c* 1.00, $CHCl_3$); IR (film) 3450, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.78 (3H, t, J= 1.2 Hz), 1.84 (1H, dd, J= 4.2, 8.8 Hz, OH), 2.75 (1H, d, J= 5.1 Hz), 3.03 (1H, d, J= 5.1 Hz), 3.78 (1H, dd, J= 8.8, 12.3 Hz), 3.94 (1H, dd, J= 4.2, 12.3 Hz), 5.04 (1H, quint, J= ~1.2 Hz), 5.10 (1H, m). *S*-**3**: $[\alpha]_D^{23}$ -58.4° (*c* 1.00, $CHCl_3$). *R*-**4**: $[\alpha]_D^{23}$ -7.2° (*c* 1.00, $CHCl_3$); IR (film) 3400, 1640, 1495, 1450 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.71 (3H, br. s), 2.21 (1H, dd, J= 15.6, 19.3 Hz), 2.35 (1H, dd, J= 15.6, 16.9 Hz), *ca.* 3.5 (2H, complex), 4.97 (1H, br. s), 4.98 (4H, d, J= 8.3 Hz), 5.23 (1H, br. s), 7.28-7.4 (10H, complex). *S*-**4**: $[\alpha]_D^{23}$ +6.9° (*c* 1.00, $CHCl_3$). *S*-**5**: mp 84-86 °C (EtOAC-hexane); $[\alpha]_D^{22}$ -9.7 (*c* 1.00, $CHCl_3$); IR (film) 3400, 1710, 1500, 1455 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.26 (3H, s), 2.26-2.32 (2H, complex), 3.62 (1H, d, J= 11.7 Hz), 3.67 (1H, dd, J= 11.7, 1.5 Hz), 4.90-5.02 (4H, complex), 7.30-7.37 (10H, complex). *R*-**5**: mp 84-86 °C (EtOAC-hexane); $[\alpha]_D^{23}$ +9.3° (*c* 1.00, $CHCl_3$). *S*-**1**: $[\alpha]_D^{23}$ -3.2° (*c* 1.00, H_2O). ^1H NMR (pD=8 D_2O buffer): δ 1.89 (1H, dd, J= 15.3, 16.8 Hz), 2.08 (1H, dd, J= 15.3, 17.5 Hz), 2.28 (3H, s), 3.61 (1H, d, J= 11.7 Hz), 3.79 (1H, d, J= 11.7 Hz). *R*-**1**: $[\alpha]_D^{23}$ +3.6° (*c* 1.00, H_2O).
8. Phosphonylation to the protected epoxy alcohols gave none of the desired products.
9. The biological activity of synthetic *R*-**1** might be ascribed to a contaminated enantiomer.

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