Total Synthesis of (±)-Phosphonothrixin, a Novel Herbicidal Antibiotic Containing C-P Bond

KAZUHIKO NAKAMURA†, TAKASHI KIMURA, HISASHI KANNO and EISAKU TAKAHASHI*

Nishiki Research Laboratories, Kureha Chemical Industry Co., Ltd., Nishiki-machi Iwaki, Fukushima 974, Japan
†IDR Laboratory, Kureha Chemical Industry Co., Ltd., 3-25-1 Hyakunin-cho, Shinjuku, Tokyo 169, Japan

(Received for publication March 13, 1995)

Phosphonothrixin (**1**) is a novel herbicidal agent produced by *Saccharothrix* sp. ST-888, with a unique structure possessing a C-P bond and an isoprene unit. The total synthesis of this antibiotic was accomplished from methyl (bromomethyl)acrylate in six steps.

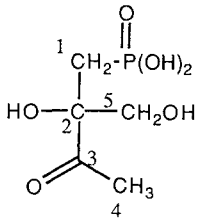
Phosphonothrixin (**1**) is a novel herbicidal antibiotic produced by *Saccharothrix* sp. ST-888. In the preceding papers,[1,2] we described the taxonomy, fermentation, isolation, biological activities and structural elucidation of phosphonothrixin. In addition to a novel structure containing a C-P bond,[3] **1** exhibited an unusually rapid proton-deuterium (H-D) exchange of the methyl ketone unit in D_2O solution, which could not be deduced from the proposed structure. These observations prompted us to verify the chemical structure by the total synthesis of **1**. Herein described is our investigation process.

Synthesis

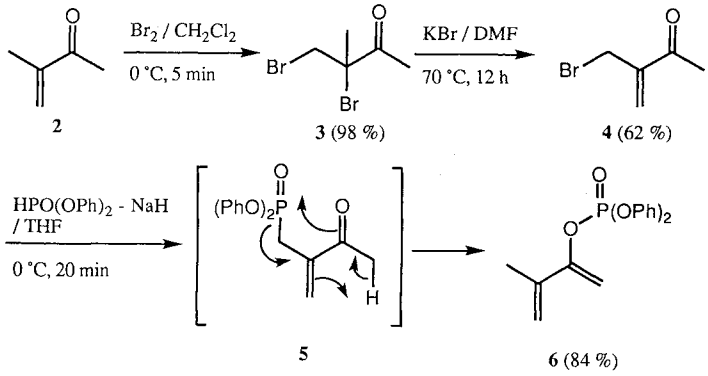
The first effort to synthesize **1** included introduction of a phosphorus atom to bromoallyl methyl ketone **4** as shown in Scheme 1. Two steps manipulation of commercially available isopropenyl methyl ketone (**2**) (1. Br_2, 98%; 2. KBr in DMF, 70°C, 62%) provided bromoallyl methyl ketone **4**. Treatment of **4** with $NaPO(OPh)_2$, according to Michaelis-Becker conditions[4], afforded an undesired butadiene derivative **6** as a sole product in 84% yield. The production of **6** might occur *via* a C→O rearrangement of the phosphorus atom after the C-P bond formation as shown in Scheme 1.

In the next strategy, introduction of a methyl ketone was planned to be undertaken in a later stage of the synthesis. As shown in Scheme 2, introduction of a phosphorus atom to the known methyl (bromomethyl)-acrylate[5] **7** was effected in 61% yield by sodium salt of dibenzyl phosphite under Michealis-Becker conditions. Exposure of **8** to a catalytic amount of osmium tetroxide and N-methylmorpholine-N-oxide (NMO) provided the desired diol **9** in 92% yield. The treatment of **9** with 2,2-dimethoxypropane gave the corresponding isopropylidene derivative **10** in 86% yield. When compound **10** was treated with methyl lithium to construct a

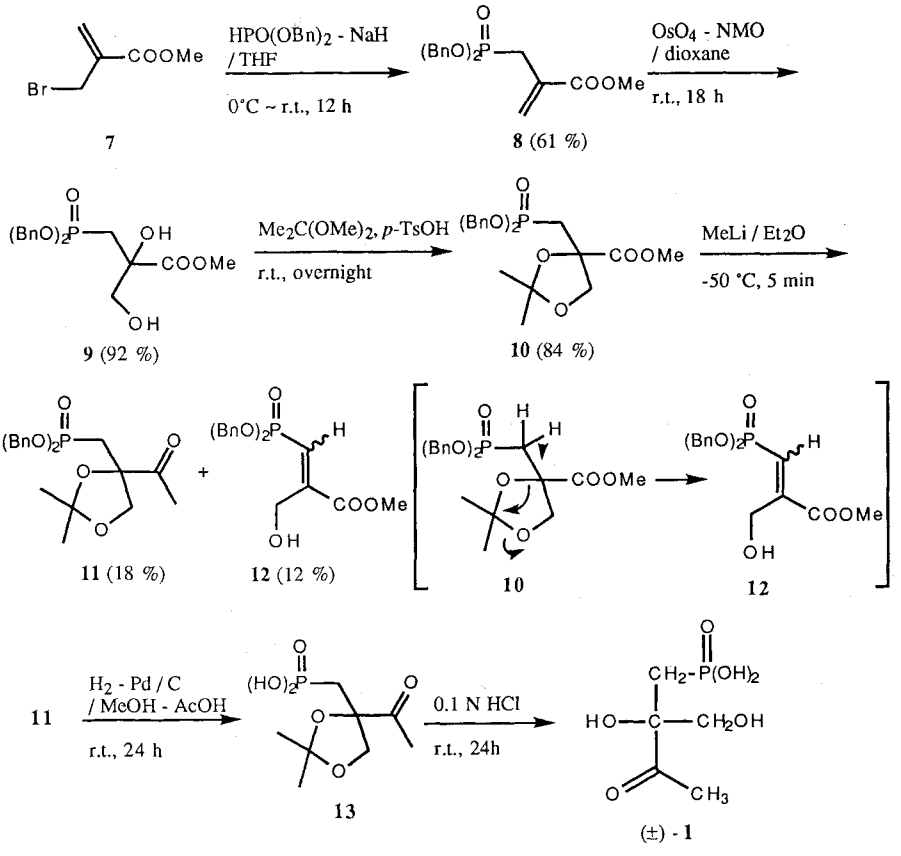
Fig. 1. Structure of phosphonothrixin (**1**).



Scheme 1.



Scheme 2.



methyl ketone moiety, two products (**11** and **12**) were obtained in 18 and 12% yield, respectively. The reaction mechanism to give the unexpected compound **12** was considered as shown in scheme 2.

Finally, phosphonothrixin **1** was synthesized from **11** in two steps. Compound **11** was subjected to catalytic hydrogenation to afford free acid **13** in quantitative yield. **13** was successively treated with 0.1 M HCl for 14 hours, then $NaHCO_3$ aq., followed by desalination using Sephadex G-15 to give the desired product (±)-**1** as mono sodium salt in 91% yield. This material was identical with natural phosphonothrixin in all the aspects of spectral data except for the optical rotation. The synthetic compound showed the same herbicidal activities as the natural one.[1)]

In conclusion, we successfully achieved the first total synthesis of phosphonothrixin (**1**) in six steps from known compound **7**. The synthesis unambiguously determined the structure of phosphonothrixin. Moreover, this synthetic route possess high generality to synthesize structural analogs. The synthesis and structure-activity relationships of phosphonothrixin analogs will be published elsewhere.

Experimental

General

Mass spectra were measured on a JEOL JMS-DX303 (EI-MS) spectrometer. IR spectra were recorded on a Perkin-Elmer model 1760 FT-IR spectrometer. NMR spectra were obtained on a JEOL JNM-GSX500 spectrometer with ^1H NMR spectra recorded at 500 MHz. Chemical shifts are given in ppm using TMS at 0 ppm for ^1H as the internal standard otherwise noted.

Ether and THF were distilled from $LiAlH_4$ under an argon atmosphere prior to use. Moisture sensitive reactions were carried out in predried glassware under an inert atmosphere of argon.

3,4-Dibromo-3-methyl-butan-2-one (3)

To a solution of isoprenyl methyl ketone (5.00 g, 59.5 mmol) in dichlolomethane (50 ml) was added bromine (3.04 ml, 1.0 eq) at 0°C. The color of bromine disappeared within 5 minutes, and the resultant solution was washed with H_2O three times, dried ($MgSO_4$), and concentrated to yield 14.22 g (98%) of **3**.

3: colorless oil

^1H NMR ($CDCl_3$): δ 1.98 (3H, br s), 2.44 (3H, s), 3.81 (1H, d, J=10.1 Hz) and 4.12 (1H, d, J=10.1 Hz). IR (film): 1719, 1449, 1380, 1359, 1150, 1050 and 606 cm^{-1}.

3-Bromomethyl-3-buten-2-one (**4**)

To a solution of compound **3** (8.71 g, 35.7 mmol) in DMF (70 ml) was added powdered KBr (7.0 g, 1.6 eq.) at 70°C. After standing for 12 hours, the reaction mixture was partitioned between pentane and H_2O, and the organic layer was washed with sat. $NaHCO_3$ aq. and brine. Evaporation of the solvent provided 3.41 g (62%) of **4**.

4: dark brown liquid

^1H NMR ($CDCl_3$): δ 1.94 (3H, s), 4.22 (2H, s), 5.92 (1H, q, J=*ca.* 1 Hz), and 6.04 (1H, s). IR (film): 1721, 1693, 1677 and 1064 cm^{-1}. EI-MS (relative intensity): 163.90 (9.5, M^+), 161.80 (7.2), 123.00 (26), 121.10 (13) and 94.95 (3.9).

Diphenyl 2-(3-Methyl-1,3-butadienyl)phosphate (**6**)

To a suspension of sodium hydride (112 mg, 1.8 eq., 60% dispersion in mineral oil, washed with dry hexane prior to use) in THF (20 ml) was added diphenylphosphite (0.45 ml, 1.5 eq.) at 0°C. After 10 minutes, a clear solution was obtained, and compound **4** (300 mg, 1.84 mmol) was added to provide immediate turbidity. After being stirred for 20 minutes at the same temperature, the mixture was poured into dil HCl, and extracted with EtOAc; the organic layer was washed with sat $NaHCO_3$ and brine, dried and concentrated. The residue was subjected to flash chromatography on silica gel (hexane - EtOAc = 10 : 1) to give 409 mg (84%) of **6**.

6: colorless oil

^1H NMR ($CDCl_3$): δ 1.89 (3H, s), 4.95 (1H, q, J=*ca.* 1 Hz), 5.04 (1H, s), 5.19 (1H, s), 5.32 (1H, s), 7.20~7.26 and 7.33~7.38 (total 10H, complex).

α-(Dibenzyloxooxophosphoriomethyl)acrylic Acid Methyl Ester (**8**)

To a suspension of sodium hydride (268 mg, 1.2 eq., 60% dispersion in mineral oil, washed with dry hexane prior to use) in dry THF (50 ml), was added dibenzyl phosphite (1.76 g, 1.2 eq.) at 0°C. After being stirred for 5 minutes, methyl (bromomethyl)acrylate (**7**, 1.00 g, 5.58 mmol) was added; the mixture was stirred at same temperature for 2 hours and then at room temperature for 12 hours. The resulting mixture was poured into dil HCl and EtOAc; the organic layer was washed with sat $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by silica gel column chromatography (hexane - EtOAc 1 : 2) gave 1.22 g (61%) of **8**.

8: colorless oil

^1H NMR ($CDCl_3$): δ 2.99 (2H, d, J_{HP}=22.9 Hz), 3.66 (3H, s), 4.98 and 5.04 (4H, dABq, J_{HP}=7.8 Hz and J_{AB}=11.9 Hz), 5.78 (1H, d, J=5.5 Hz), 6.30 (1H, d, J=6.4 Hz) and 7.30~7.36 (10H, complex). IR (film): 1723, 1632, 1456, 1440, 1321, 1251, 1215, 1176 and 997 cm^{-1}. EI-MS (relative intensity): 360 (0.4, M^+), 327 (4.6), 268 (12), 163 (100) and 91 (81).

3-Dibenzyloxooxophosphorio-2-hydroxy-2-hydroxymethylpropionic Acid Methyl Ester (**9**)

To a solution of compound **8** (2.51 g, 6.97 mmol) and N-methyl morpholine N-oxide (2.51 g, 1.3 eq.) was added osmium tetroxide (*ca.* 400 mg); and the mixture was stirred at ambient temperature for 19 hours. The aqueous suspension of sodium bisulfate and talc was added to the stirring mixture. The insoluble matter was filtered off through a Celite pad, and the filtrate was poured into EtOAc and H_2O. The aqueous layer was extracted with EtOAc twice, and the combined organic extract were washed with brine, dried ($MgSO_4$). Concentration of the residue gave 2.49 g (92%) of **9**.

9: light green oil

^1H NMR ($CDCl_3$): δ 2.31 (1H, dd, J_{HH}=15.6 and J_{HP}=28.4 Hz), 2.35 (1H, dd, J_{HH}=15.6 and J_{HP}=29.8 Hz), 2.38 (1H, br t, J=*ca.* 5.7 Hz, OH), 3.65 (1H, dd, J=11.5, 5.7 Hz) 3.65 (3H, s), 3.71 (1H, dd, J=11.5, 5.7 Hz), 4.25 (1H, br s) 4.95~5.05 (4H, complex) and 7.32~7.37 (10H, complex). IR (film): 3369, 1746, 1230, 1180 and 997 cm^{-1}. EI-MS (relative intensity): 394 (0.38, M^+), 362 (3.9), 334 (3.6), 302 (6.3), 285 (3.9), 197 (55) and 91 (100).

3-Dibenzyloxooxophosphorio-2-hydroxy-2-[4-(2',2'-dimethyl-1',3'-dioxolane)]propionic Acid Methyl Ester (**10**)

To a solution of compound **9** (2.50 g, 6.37 mmol) in 2,2-dimethoxy propane (50 ml) was added *p*-toluenesulfonic acid (100 mg). After being stirred at room temperature overnight, the reaction mixture was poured into EtOAc and sat $NaHCO_3$ aq., the organic layer was washed with brine, dried, and concentrated. The residue was subjected to flash chromatography on silica gel ($CHCl_3$ - MeOH = 10 : 1) to give 2.32 g (84%) of **10**.

10: pale yellow oil

^1H NMR ($CDCl_3$): δ 1.40 (3H, s), 1.43 (3H, s), 2.48 (2H, d, J_{HP}=18.8 Hz), 3.63 (3H, s), 4.02 (1H, d, J=9.2 Hz), 4.36 (1H, dd, J_{HH}=9.2 and J_{HP}=1.8 Hz), 4.93~5.05 (4H, complex) and 7.31~7.36 (10H, complex). IR (film): 1746, 1499, 1456, 1437, 1374, 1158 and 996 cm^{-1}. EI-MS (relative intensity): 434 (2.5, M^+), 418 (6.4), 374 (7.4), 342 (3.1), 237 (48), 181 (10), 151 (8.0) and 91 (100).

2-[4-(2',2'-Dimethyl-1',3'-dioxolane)]-3-oxobutylphosphonic Acid Dibenzyl Ester (**11**)

To a solution of compound **10** (109 mg, 0.252 mmol) in dry ether (10 ml) was added 1.4 M solution of methyl lithium in ether (0.38 ml, 2.1 eq.) at −50°C. The reaction mixture was stirred at the same temperature for 5 minutes. The reaction was quenched with 0.1 M hydrochloric acid (0.5 ml), poured into EtOAc and dil HCl. The organic layer was washed with sat $NaHCO_3$ aq., brine, dried, and concentrated. The residue was subjected

to flash chromatography on silica gel (EtOAc - hexane = 1 : 1) to afford 18.3 mg (18%) of **11** and 12.0 mg (12%) of **12**.

11: colorless oil

^{1}H NMR ($CDCl_3$): δ 1.40 (3H, s), 1.44 (3H, s), 2.78 (3H, s), 2.30 (1H, dd, J_{HH} = 15.1 Hz and J_{HP} = 17.9 Hz), 2.65 (1H, dd, J_{HH} = 15.1 Hz and J_{HP} = 18.8 Hz), 3.87 (1H, d, J = 9.2 Hz), 4.08 (1H, dd, J_{HH} = 9.2 Hz and J_{HP} = 3.6 Hz), 4.90 and 4.98 (2H, dABq, J_{HH} = 11.9 Hz and J_{HP} = 7.8 or 8.7 Hz), 5.00 (2H, d, J_{HP} = 8.3 Hz) and 7.30 ~ 7.33 (10H, complex). IR (film): 1719, 1456, 1383, 1259, 1217, 1026, 997, 736 and 698 cm^{-1}. EI-MS (int.): 418 (0.16, M^+), 402 (1.2), 374 (21), 356, (2.1), 326 (3.8), 284 (6.7), 181 (8.0), 163 (4.5), 137 (9.8) and 91 (100).

12: colorless oil

^{1}H NMR ($CDCl_3$): δ 2.62 (1H, br t, J = 6.4 Hz, OH), 3.71 (3H, s), 4.37 (2H, br d, J = 6.4 Hz), 5.01 and 5.02 (4H, dABq, J_{HH} = 14.9 Hz and J_{HP} = 11.9 or 13.3 Hz), 6.20 (1H, td, J = 1.9, 15.1 Hz) and 7.30 ~ 7.34 (10H, complex). IR(film): 3368, 1735, 1636, 1497, 1455, 1436, 1306, 1215, 1045, 1010, 999, 737 and 698 cm^{-1}.

2-[4-(2',2'-Dimethyl-1',3'-dioxolane)]-3-oxobutylphosphonic Acid (**13**)

A vigorously stirred mixture of compound **11** (82 mg, 0.197 mmol) and 10% palladium on carbon (catalytic amount *ca.* 2 mg) in H_2O (8 ml) and AcOH (8 drops) was degassed under vacuum and saturated with hydrogen. The mixture was stirred at room temperature for 24 hours under slightly positive pressure of H_2. The mixture was filtered through a Celite pad, and the filtrate was concentrated to afford 49.3 mg of **13** in a quantitative yield.

13: colorless oil

^{1}H NMR (D_2O; HDO = 4.70 ppm): δ 1.38 (6H, s), *ca.* 2.27 (1H, dd, J_{HH} = 16.6 Hz and J_{HP} = 17.6 Hz), 2.28 (3H, s), 2.35 (1H, dd, J_{HH} = 16.6 Hz and J_{HP} = 18.3 Hz), 3.93 (1H, d, J = 9.0 Hz), 4.33 (1H, dd, J_{HH} = 9.0 Hz and J_{HP} = 0.8 Hz).

(±)-Phosphonothrixin (**1**)

The solution of compound **13** (35.4 mg, 0.149 mmol) in 0.1 M hydrochloric acid (1.0 ml) was stirred for 24 hours. The saturated solution of $NaHCO_3$ (3.0 ml) was added to the mixture. The mixture was concentrated, the residue was subjected to desalination on Sephadex G-15 to give 29.4 mg (90%) of (±)-**1** as monosodium salt. The product was spectroscopically identical with the natural material.

Acknowledgments

We are grateful to Mr. TAKUJI HOSOI, Dr. YUKIHIKO OSUMI and Dr. YUTAKA KONAI for encouraging support. We also thank Mr. TAKAFUMI SHIDA, Dr. HIROSHI CHUMAN and Mr. YOSHIKAZU KUBOTA for valuable advices and discussions.

References

1) TAKAHASHI, E.; T. KIMURA, K. NAKAMURA, M. ARAHIRA & M. IIDA: Phosphonothrixin, a novel herbicidal antibiotic produced by *Saccharothirix* sp. ST-888. I. Taxonomy, fermentation, isolation and biological properties. J. Antibiotics 48: 1124 ~ 1129, 1995
2) KIMURA, T.; K. NAKAMURA & E. TAKAHASHI: Phosphonothrixin, a novel herbicidal antibiotic produced by *Saccharothirix* sp. ST-888. II. Structure determination. J. Antibiotics 48: 1130 ~ 1133, 1995
3) For reviews of C-P compounds, see HORI, T.; M. HORIGUCHI & A. HAYASHI (*Eds.*): Biochemistry of Natural C-P Compounds. Japanese Association of Research on the Biochemistry of C-P Compounds, Maruzen, Kyoto, 1984
4) KOSOLAPOFF, G. M.: The synthesis of phosphonic and phosphinic acids. Org. React. 6: 273 ~ 338, 1951
5) MARSCHALL, H.; F. VOGEL & P. WEYERSTAHL: Synthese von α-methylene-δ-lactone. Chem. Ber. 107: 2852 ~ 2859, 1974