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Chemoenzymatic formal synthesis of (*S*)-(–)-phosphonotrixin

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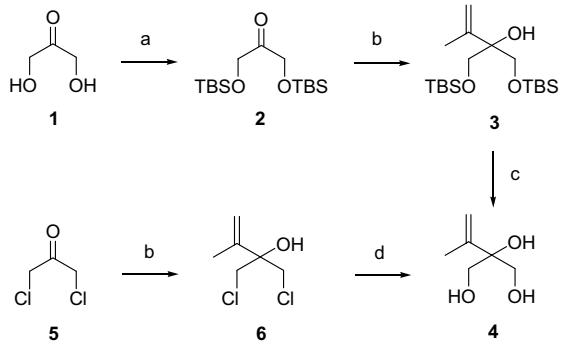
Abstract—Phosphonotrixin is a herbicidal antibiotic characterized by a unique structure bearing a C–P bond on an isoprene unit. The formal enantioselective synthesis of (*S*)-(−)-phosphonotrixin (ee = 93%) in nine steps and 12% overall yield from 1,3-dihydroxyacetone or in eight steps and 11% overall yield from 1,3-dichloroacetone is reported. The key reaction is the enzymatic desymmetrization of 2-isopropenylpropane-1,2,3-triol.

1. Introduction

Phosphonotrixin **14** was first isolated from the microorganism *Saccharotrix* sp. ST-888 by Takahashi et al.[1,2] in 1995. This secondary metabolite has attracted interest primarily due to its antibiotic and herbicidal properties[1,3] as well as its unique structure possessing a C–P bond on an isoprene unit. Two syntheses of racemic phosphonotrixin have been reported.[4,5] The assignment of the absolute configuration of natural (*S*)-(−)-phosphonotrixin is based on the synthesis of both enantiomers[6,7] and the use of the Sharpless' epoxidation prediction rule.[8] Herein we report an enantioselective formal synthesis of (*S*)-(−)-phosphonotrixin via the enzymatic desymmetrization of an achiral substrate.



Scheme 1. Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 94%, Ref. 9; (b) (i) isopropenylmagnesium bromide, THF, 0–20 °C, (ii) 3 M HCl, 84–87%; (c) TBAF, THF, 81%; (d) 6 M NaOH, 50 °C, 73%.

2. Results and discussion

Retrosynthetic analysis of the phosphonotrixin structure suggested that prochiral triol **4** might serve as a suitable substrate for an enzyme-catalyzed desymmetrization. The synthesis of triol **4** is described in Scheme 1. Readily available 1,3-dihydroxyacetone **1** was selected as the starting material. The bis-silyl ether **2** was prepared as described in the literature.[9] A Grignard reaction of isopropenylmagnesium bromide with the dihydroxyacetone derivative **2** in THF provided tertiary alcohol **3** in 87% yield. Desilylation of **3** with tetrabutylammonium fluoride (TBAF) afforded triol **4** in 81% yield. Compound **4** was also prepared in two steps from 1,3-dichloroacetone **5** without any group protection. Grignard reaction of isopropenylmagnesium bromide with **5** in THF gave tertiary alcohol **6** in 84% yield. Treatment of **6** with aqueous sodium hydroxide led to triol **4** in 73% yield. Next, we completed some screening experiments in order to find hydrolases with the ability to distinguish the enantiotopic groups of compound **4**. Of the enzymes and conditions studied, the esterification of **4** with vinyl acetate as the acylation reagent and solvent in the presence of porcine pancreatic lipase (PPL) gave the best result (Scheme 2) and provided chiral monoester (*S*)-**7** in high yield (88%) and high enantiomeric excess (93%) along with a small amount of the corresponding achiral

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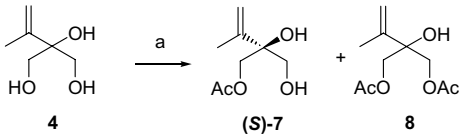


Scheme 2. Reagents and conditions: (a) PPL, vinyl acetate, 88%.

diester **8** (7%). Desymmetrizations of **4** with lipases from *Candida antarctica*, *Pseudomonas* sp., *Pseudomonas cepacia* and *Candida rugosa* resulted in lower enantiomeric excesses (ee <60%) or lower chemical yields (formation of achiral diester **8**). The enantiomeric composition of **7** was measured by ^{19}F NMR (376 MHz) analysis of the corresponding (+)-α-methoxy-α-trifluoromethyl-α-phenyl acetate (Mosher's ester). The absolute configuration of monoacetate (*S*)-**7** was determined by chemical correlation with **13**, an advanced intermediate in Nakamura's synthesis of phosphonotrixin **14**.

Our initial goal was to transform the primary alcohol of compound **7** into a good leaving group and introduce the C–P bond by nucleophilic substitution. Tosylate **9** was easily prepared (Scheme 3) but the formation of **10** was unsuccessful with phosphorus nucleophiles under various conditions. To avoid this difficulty, we finally adopted the alternative reaction sequence illustrated in Scheme 3.

Formation of the tosylate in the presence of a stronger base, such as triethylamine, gave epoxide **11** in 71%. The acetate group of **11** was selectively removed by transesterification with ethanol in ether in the presence of *Candida antarctica* lipase. Epoxy-alcohol **12** is unstable to acidic media (e.g., silica gel, chloroform) and was immediately transformed into phosphonate **13**, whose data matched that reported by Nakamura et al.[6,7] thus completing a formal synthesis of natural (*S*)-(−)-phosphotrixin. This correlation confirmed the absolute configuration of **13** to be (*R*), which requires that the enzymatic desymmetrization of **4** leads to monoester **7** with an (*S*)-configuration at the newly created stereogenic centre.

3. Conclusion

In conclusion, enzymatic desymmetrization of achiral 2-isopropenylpropane-1,2,3-triol **4** has provided the corresponding (*S*)-monoacetate **7** in good yield (88%) with high enantiomeric excess (93%). This product is a key intermediate in the formal synthesis of (*S*)-(−)-phosphonotrixin.

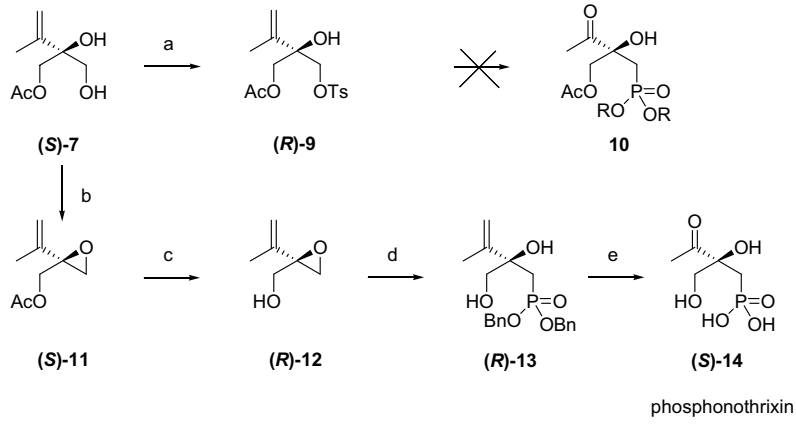
4. Experimental

4.1. General

NMR spectra were recorded on Bruker AC300 or Varian Inova AS400 spectrometers (300 and 400 MHz, respectively). Infrared spectra were recorded on a Bomem MB-100 spectrometer. Optical rotations were measured using a JASCO DIP-360 digital polarimeter (*c* as gram of compound per 100 mL). Flash column chromatography was carried out using 40–63 μm (230–400 mesh) silica gel. PPL (lipase, type II, crude, from porcine pancreas, 23% protein, 61 units/mg of protein using triacetin at pH 7.4) was purchased from Sigma Chem. Co. *Candida antarctica* lipase (Chirazyme L-2) was from Boehringer Mannheim.

4.2. 1,1-Bis-{[(*tert*-butyldimethylsilyl)oxy]methyl}-2-methylprop-2-en-1-ol 3

To a solution of isopropenylmagnesium bromide in anhydrous THF (25 mL) freshly prepared from magnesium powder (2.48 g, 102 mmol) and 2-bromopropene (3.02 mL, 34 mmol) cooled to 0 °C was added a solution of **2** (4.35 g, 13.7 mmol) in THF (15 mL). The mixture was stirred at room temperature for 1.5 h. The mixture was cooled to 0 °C and 3 M HCl (100 mL) then added. The aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (2 × 100 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by flash



Scheme 3. Reagents and conditions: (a) TsCl, pyridine, $CHCl_3$, 97%; (b) TsCl, Et_3N, DMAP, CH_2Cl_2, 71%; (c) *Candida antartica* lipase, EtOH, Et_2O, 90%; (d) Ref. 6; (e) two steps, Ref. 6.

chromatography (100% hexane to hexane/ethyl acetate, 95:5) to yield **3** (4.94 g, 87%) as a colourless oil. IR (neat) 3559, 2955–2858, 1471, 1256, 1096, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 12H), 0.86 (s, 18H), 1.77 (dd, $J = 1.5$ and 0.9 Hz, 3H), 3.53 (d, $J = 9.5$ Hz, 2H), 3.65 (d, $J = 9.5$ Hz, 2H), 4.89 (m, 1H), 4.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4, 18.4, 19.8, 26.0, 65.5, 76.4, 111.8, 146.3; HRMS (CI, NH_3) calcd for $C_{18}H_{41}O_3Si_2$ $(M+H)^+$: 361.2594. Found: 361.2588.

4.3. 2-Isopropenylpropane-1,2,3-triol 4

To a solution of **3** (4.521 g, 12.5 mmol) in THF (30 mL) was added a solution of tetrabutylammonium fluoride in THF (1 M, 38 mL, 38 mmol). The mixture was stirred overnight at room temperature. The solvent was evaporated and the crude product purified by flash chromatography (AcOEt/hexane, 9:1 to pure AcOEt) to afford **4** (1.342 g, 81%) as a white solid. Mp 56 °C; IR (KBr) 3600–3100, 1645, 1449, 1084, 1048, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.74 (dd, $J_1 \sim J_2 \sim 1$ Hz), 2.87 (br s, 1H), 3.62 (d, $J = 11.4$ Hz, 2H), 3.70 (d, $J = 11.4$ Hz, 2H), 5.01 (m, 1H), 5.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 66.3, 77.9, 113.3, 145.0; HRMS (CI, NH_3) calcd for $C_6H_{16}O_3N$ $(M+NH_4)^+$: 150.1130. Found: 150.1125.

4.4. 1-Chloro-2-(chloromethyl)-3-methylbut-3-en-2-ol 6

To a solution of isopropenylmagnesium bromide in THF (0.5 M, commercially available, 150 mL, 75 mmol) cooled to 0 °C under a dry atmosphere was added dropwise a solution of 1,3-dichloroacetone **5** (3.147 g, 24.8 mmol) in THF (15 mL). The mixture was stirred at room temperature for 45 min. The mixture was cooled to 0 °C and 3 M HCl (125 mL) then added. The aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (2 × 100 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (100% hexane to hexane/ethyl acetate, 90:10) to give **6** (3.513 g, 84%) as an oil. IR (neat) 3548, 3483, 3095, 2966–2863, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.80 (s, 3H), 2.52 (br s, 1H), 3.75 (d, $J = 11.6$ Hz, 2H), 3.68 (d, $J = 11.6$ Hz, 2H), 5.12 (s, 1H), 5.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 49.2, 76.4, 115.6, 143.7; HRMS (EI, 70 eV) calcd for $C_6H_{10}O_1Cl_2$ $(M)^+$: 168.0109. Found: 168.0114.

4.5. 2-Isopropenylpropane-1,2,3-triol 4 from 6

A solution of **6** (943 mg, 5.58 mmol) in 6 M NaOH (50 mL) was stirred at 50 °C for 66 h. The solution was cooled to 0 °C and neutralized with concentrated HCl. The solution was filtered and evaporated. Residual water was eliminated by azeotropic evaporation with benzene (4 × 50 mL). The residue was dissolved in ethyl acetate (150 mL) and the organic phase dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (100% AcOEt to 95% AcOEt/5% MeOH) to give **4** (538 mg, 73%) as a white solid (analytical data as above).

4.6. Enzymatic desymmetrization of 4

To a solution of **4** (500 mg, 3.8 mmol) in vinyl acetate (50 mL) were added molecular sieves (4 Å, 200 mg) and porcine pancreatic lipase (PPL, 800 mg) and the mixture stirred at rt. The progress of the reaction was monitored by TLC. As the reaction proceeded, the amount of diacetate in the reaction mixture increased before the complete disappearance of the starting material. The reaction was stopped when the trace of diacetate became as visible as the trace of the starting diol (5 h). The mixture was then filtered and concentrated. The crude product was purified by flash chromatography (AcOEt/hexane, 3:2 to pure AcOEt) to give monoacetate **7** (583 mg, 88%) and diacetate **8** (57.5 mg, 7%) as colourless oils.

(S)-2-Hydroxy-2-(hydroxymethyl)-3-methylbut-3-enyl acetate **7**: $[\alpha]_D^{25} = +17.3$ (*c* 1.1, $CHCl_3$); IR (neat) 3600–3100, 2957–2890, 1727, 1646, 1450, 1378, 1242, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.76 (dd, $J = 1.5$ and 0.8 Hz, 3H), 2,06 (s, 3H), 2.47 (br s, 1H), 3.58 (d, $J = 11.4$ Hz, 1H), 3.61 (d, $J = 11.4$ Hz, 1H), 4.18 (d, $J = 11.7$ Hz, 1H), 4.24 (d, $J = 11.7$ Hz, 1H), 5.02 (m, 1H), 5.1 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 21.0, 65.4, 67.0, 77.0, 113.7, 144.4, 171.7; HRMS (CI, NH_3) calcd for $C_8H_{15}O_4$ $(M+H)^+$; 175.0970. Found: 175.0968.

2-[(Acetyloxy)methyl]-2-hydroxy-3-methylbut-3-enyl acetate **8**: IR (neat) 3477, 3094, 2960, 1742, 1645, 1450, 1376, 1229, 1164, 1134, 1047, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.77 (dd, $J = 1.4$ and 0.8 Hz, 3H), 2.06 (s, 6H), 4.16 (d, $J = 11.2$ Hz, 2H), 4.19 (d, $J = 11.2$ Hz, 2H), 5.03 (m, 1H), 5.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 21.0, 66.9, 75.7, 114.3, 143.9, 171.2; HRMS (CI, NH_3) calcd for $C_{10}H_{17}O_5$ $(M+H)^+$: 217.1076. Found: 217.1080.

4.7. (*R*)-2-Hydroxy-3-methyl-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)but-3-enyl acetate 9

To a solution of **7** (350 mg, 2 mmol) in anhydrous chloroform (4 mL) were added anhydrous pyridine (6 mL) and *p*-toluenesulfonyl chloride (1.00 g. 5.2 mmol). The solution was stirred overnight at room temperature. Water was added (2 mL) and the reaction mixture extracted with CH_2Cl_2 (100 mL). The organic phase was washed with 1 M HCl (3 × 40 mL), saturated aqueous $NaHCO_3$ (2 × 40 mL) and brine (2 × 40 mL). The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 2:1) to give **9** (640 mg, 97%) as an oil: $[\alpha]_D^{25} = -2.3$ (*c* 0.81, $CHCl_3$); IR (neat) 3491, 2958–2923, 1743, 1646, 1598, 1451, 1362, 1234, 1177, 1097, 1048, 985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.03 (s, 3H), 2.45 (s, 3H), 2.60 (br s, 1H), 4,03–4.21 (m, 4H), 5.03 (m, 1H), 5.09 (m, 1H),

7.35 (d, $J = 7.0$ Hz, 2H), 7.78 (d, $J = 7$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 20.9, 21.9, 66.5, 71.8, 115.0, 128.2, 130.2, 132.6, 142.9, 145.4, 171.1; HRMS (CI, NH_3) calcd for $C_{15}H_{21}O_6S$ $(M+H)^+$: 329.1059. Found: 329.1052.

4.8. (*S*)-(2-Isopropenyloxiran-2-yl)methyl acetate 11

To a solution of monoacetate **7** (100 mg, 0.57 mmol) in anhydrous CH_2Cl_2 (10 mL) were added 4-(*N*,*N*-dimethylamino)pyridine (13 mg, 0.11 mmol), triethylamine (1.5 mL, 10 mmol) and *p*-toluenesulfonyl chloride (130 mg, 0.68 mmol). The solution was stirred at room temperature for 72 h. The volatiles were evaporated, water (10 mL) added and the mixture extracted with ether (3×30 mL). The organic layer was washed with 1 M HCl (3×20 mL), saturated $NaHCO_3$ (2×20 mL), brine (2×20 mL), dried over $MgSO_4$ and activated charcoal and evaporated to give **11** (64 mg, 71%) as a yellow oil. $[\alpha]_D^{25} = +35.8$ (*c* 0.94, $CHCl_3$); IR (neat) 2977, 1743, 1652, 1450, 1368, 1333, 1231, 1145, 1088, 1051, 977 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (dd, $J_1 \sim J_2 \sim 1$ Hz, 3H), 2.05 (s, 3H), 2.73 (d, $J = 5.3$ Hz, 1H), 2.86 (d, $J = 5.3$ Hz, 1H), 4.04 (d, $J = 12.3$ Hz, 1H), 4.48 (d, $J = 12.3$ Hz, 1H), 5.01 (m, 1H), 5.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.9, 20.7, 51.6, 58.9, 64.9, 114.2, 140.6, 170.6; HRMS (CI, NH_3) calcd for $C_8H_{13}O_3$ $(M+H)^+$: 157.0864. Found: 157.0868.

4.9. (*R*)-(2-Isopropenyloxiran-2-yl)methanol 12

To a solution of **11** (200 mg, 1.75 mmol) in diethyl ether (15 mL) were added *Candida antarctica* lipase (500 mg, total weight enzyme on carrier, 500 U/mg dry carrier) and dry ethanol (0.5 mL), and the reaction mixture stirred at room temperature. The reaction was monitored by thin layer chromatography and stopped when all the starting materials were consumed (72 h). The reaction mixture was filtered and evaporated to give **12** (180 mg, 90%) as a colourless oil. Product **12** was unstable on silica gel or in acidic media (e.g., $CDCl_3$) and was used in the next step immediately after work-up. $[\alpha]_D^{25} = +62.4$ (*c* 1.37, C_6H_6); lit.[6] $[\alpha]_D^{23} = +55.6$ (*c* 1.00, $CHCl_3$); IR (neat) 3432, 2970, 2925, 2865, 1634, 1604, 1453, 1363, 1247, 1172, 1092, 976, 906 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 1.54 (dd, $J_1 \sim J_2 \sim 1$ Hz, 3H), 2.33 (d, $J = 5.7$ Hz, 1H), 2.66 (d, $J = 5.7$ Hz, 1H), 3.52 (d, $J = 2.4$ Hz, 1H), 3.68 (d, $J = 2.4$ Hz, 1H), 4.84 (m, 1H), 5.07 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 17.5, 49.0, 59.7, 60.9, 111.8, 140.7.

4.10. Dibenzyl (*R*)-2-hydroxy-2-(hydroxymethyl)-3-methylbut-3-enylphosphonate 13

To a solution of dibenzyl phosphite (0.46 mL, 2.09 mmol) in anhydrous THF (15 mL) cooled to −78 °C was added dropwise a solution of isopropylmagnesium chloride in THF (2 M, 0.46 mL, 2.09 mmol). After stirring for 1 h, a solution of epoxy-alcohol **12** (78.8 mg, 0.69 mmol) in anhydrous THF (2 mL) was added and the solution stirred for 2 h at −78 °C. The reaction mixture was allowed to warm to 0 °C at which time water (10 mL) was added dropwise. The mixture was extracted with ethyl acetate (3×20 mL). The organic layer was washed with 1 M HCl (3×20 mL), saturated $NaHCO_3$ (2×20 mL), brine, dried over $MgSO_4$ and concentrated. Flash chromatography (hexane/ethyl acetate, 4:1 to pure ethyl acetate) afforded **13** (102 mg, 40%) as a colourless oil. $[\alpha]_D = -7.1$ (*c* 1.00, $CHCl_3$); lit.[6] $[\alpha]_D^{23} = -7.2$ (*c* 1.00, $CHCl_3$). Analytical data were consistent with published results.[6,7]

References and notes

1. Takahashi, E.; Kimura, T.; Nakamura, K.; Arahira, M.; Iida, M. *J. Antibiot.* **1995**, *48*, 1124–1129.
2. Kimura, T.; Nakamura, K.; Takahashi, E. *J. Antibiot.* **1995**, *48*, 1130–1133.
3. Lange, B. M.; Ketchum, R. E. B.; Croteau, R. B. *Plant Physiol.* **2001**, *127*, 305–314.
4. Fields, S. C. *Tetrahedron Lett.* **1998**, *39*, 6621–6624.
5. Nakamura, K.; Kimura, T.; Kanno, H.; Takahashi, E. *J. Antibiot.* **1995**, *48*, 1134–1137.
6. Nakamura, K.; Yamamura, S. *Tetrahedron Lett.* **1997**, *38*, 437–438.
7. Nakamura, K.; Kimura, T.; Takahashi, E. *Phosphorus, Sulfur and Silicon and the Related Elements* **1999**, *144–146*, 613–616.
8. Johnson, R. A.; Sharpless, K. B. Asymmetric Methods of Epoxidation. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon: New York, 1991; Vol. 7, p 389.
9. Sodeaka, M.; Yamada, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4906–4911.