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A facial chemoenzymatic method for the preparation of chiral 1,2-dihydroxy-3,3,3,-trifluoropropanephosphonates☆

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Abstract

A convenient and effective method for the preparation of chiral trifluoromethylated 1,2-dihydroxypropanephosphonates based on a chemoenzymatic approach was described. Ethyl trifluoromethylacetate was reacted with anion of methylphosphonate to give 2-oxo-3,3,3-trifluoropropanephosphonate and its hydrates, 2,2-dihydroxy-3,3,3-trifluoropropanephosphonates, which are reduced with sodium boronhydride affording 2-hydroxy-3,3,3-trifluoropropanephosphonates. The product thus obtained was then transferred to corresponding 1,2-vinyl-3,3,3-trifluoropropanephosphonate and followed by 1,2-dihydroxylation via potassium permanganate treatment. Enzymatic kinetic resolution of the resultant racemate by CALB or IM provided optically active 1,2-dihydroxy-3,3,3-trifluoropropanephosphonate with satisfactory chemical and enantiomeric yield.

Keywords: Chemoenzymatic method; Trifluoromethylated hydroxyphosphonate; Hydroxyphosphonate; Kinetic resolution

1. Introduction

As phosphorus analogue of hydroxycarboxylates, hydroxyphosphonates are compounds with potential biological significance and practical application in organic synthesis [1]. Introduction of fluorine atom, trifluoromethyl moiety in particularly, is usually, as a rule, leading to enhancement of the bioactivity of the parent molecule [2]. It is, therefore, not surprised that synthetic study of fluorine-containing hydroxylphosphonates has been reported [3]. By careful examination of the published methods, we found that there is a huge room to be improved. Firstly, the reagents used including perfluoroalkyl aldehyde and osmium tetraoxide are not convenient to handle besides their toxicity. It is more important to point out that the method can provide, however, only racemic mixture. It is well-known that bioactivity of organic molecules in closely related to the chirality, of the compound [4–6]. Here, we show a chemoenzymatic approach leading to chiral 1,2-dihydroxy-3,3,3-trifluoropropanephosphonates.

2. Results and discussion

Our method is based on the following sequence of reactions. Trifluoromethyl acetate was reacted with carbanion of methylphosphonate in the usual manner to afford 2-oxo-3,3,3-trifluoropropanephosphonate (**1**) and its hydrate (**2**). The mixture consisting **1** and **2** was then treated with sodium boronhydrate to provide 2-hydroxy-3,3,3-trifluoropropanephosphonate (**3**) in almost quantitative yield. Upon elimation of a molecule of water in **3** with mesyl chloride in the presence of trimethylamine to provide an ethenyl derivative **4**. Dihydroxylation of the ester was taken place during the treatment of aqueous potassium permanganate solution. The two secondary alcohol groups in **5** are located in *cis*-position that is easily observed by ^{1}H NMR.

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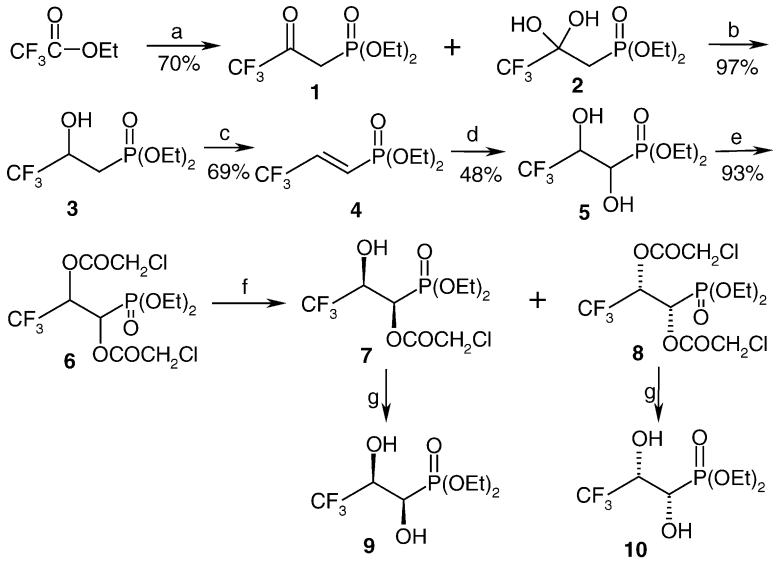

a, Mep(O)(OET)$_2$ / n-Buli; b, NaBH$_4$; c, Me$_3$N, MsCl; d, KMnO$_4$ / H$_2$O;
e, ClCH$_2$COOH, DCC, DMAP; f, CALB or IM,30 °C, n-BuOH, 40 h; g, NH$_4$OH;

As demonstrated by us, both *Candida antarctica* Lipase B (CALB) and immobilized *Mucor miehei* (IM) showed satisfying activity and enantioselectivity in alcololysis of the chloroactyl derivatives of the hydroxyl function using butanol as nucleophile in anhydrous benzene of trifluoromethylated 1-hydroxy- or 2-hydroxyalkanephosphonates [7–10]. We would like to point out that this methodology was also applied successfully for the synthesis of trifluoromethylated 1,2-dihydroxyalkanephophonates with high enantiomeric excess. Quinine was adopted as a chiral solvating agent for direct simple ^{31}P NMR enantiomeric excess determination of chiral 1,2-dihydroxy-3,3,3-trifluoropropanephosphonates. Quinine efficiently discriminates between the enantiomers of different classes of compounds because of the simultaneous presence of different and suitable functional groups in the molecule. By intergrative approach we can estimate the ee value of the reaction [11]. **9** and **10** are enzymatic hydrolysis products of **7** and **8**, respectively. The ee value was calculated as $(77.25 - 9.41)/(77.25 + 9.41) = 78.3\%$ for **9**, while $(67.49 - 9.58)/(67.47 + 9.58) = 75.1\%$ for **10**. Based on Lejczak's empirical rule [12], the absolute configuration of compounds was tentatively assigned. The results are well reasonalized by Kazlauskas rule taking phosphoryl as L group [13].

3. Experimental

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP–5959A mass spectrometer. ^{1}H NMR (300 MHz), ^{31}P NMR (120 MHz) and ^{19}F NMR (282 MHz) spectra were taken on a Mercury Specterometer in $CDCl_3$ and chemical shift were reported in ppm downfield relative to TMS (internal standard) and 80% H_3PO_4 (external standard) in phosphorus spectra, trifluoroacetic acid, respectively. The racemic 3,3,3-trifluro-1,2-dihydroxypropanephosphonate was converted to its acyl derivative via reaction with $ClCH_2COOH$, DCC and DMAP in a standard procedure.[5,6] CALB (Novozym 345), *M. miehei* lipase (LIPOZYME IM) were gifts from NOVO Norvodise Co. Solvents used for enzymatic reactions were purified by standard methods and stored over 4 Å sieves prior to use. General procedure for ^{31}P NMR determination of ee value was carried out as follows: to 20 mg trimethylated dihydroxy phosphonates was added 1.5 equiv. quinine and 0.5 mL $CDCl_3$.

3.1. Diethyl 3,3,3-trifluoro-2-hydroxy-propane phosphonate (*3*)

Trifluoroacetic acid (114 g) was esterified by refluxing with absolute ethanol (46 g) in the presence of conc. H_2SO_4 (3 mL) for 3 h. The mixture thus obtained and was washed with $NaHCO_3$ solution, then fractional distilled. Ethyl trifluoroacetate was collected at 60–62 °C. Yield 120 g or 84.3% of theoretical.

Diethyl methylphosphonate was prepared by refluxing triethylphosphite (50 mL, 0.3 mol) and methyl iodide (47.4 g, 0.3 mol) for 3 h, followed by fractional distillation. Collected the fraction at 34–36 °C/55 Pa. Yield 42 g or 93% of theoretical.

For the reaction of trifluoroacetate with methylphosphonate, a mixture of THF (60 mL) and diethyl methylphosphonate (15 g, 98 mmol) was cooled to −70 °C and then added *n*-BuLi (1.6 mol) in *n*-hexane (67 mL) and then followed by graduately addition of ethyl trifluoroacetate (14.5 g, 105 mmol). So that the reaction temperature was kept under −65 °C. The mixture was stirred for an additional 3 h and the reaction was quenched by addition of 1N HCl (30 mL). The ether extract was washed with aqueous $NaHCO_3$ solution, dried over Na_2SO_4. Upon

evaporation of solvent, crystalline pale yellow product was obtained. When the mother liquid was treated with petroleum ether, additional crystalline product was obtained. 18.5 g or 70% yield. As demonstrated by spectroscopic data, the product is a mixture of **1** and **2** in 1:7 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.34–1.39 (6H, m, $P(OCH_2CH_3)_2$), 2.29–2.36 (2H, d, $C(OH)_2CH_2P$), 3.35–3.42 (2H, d, $COCH_2P$), 4.15–4.25 (4H, m, $P(OCH_2CH_3)_2$), 5.8 (2H, b, $C(OH)_2CH_2P$). ^{19}F NMR (282 MHz, $CDCl_3$) δ: 4.6 (**1**) and 10.2 (**2**).

For the preparation of **3**, a mixture of **1** and **2** (0.744 g, 2.8 mmol) was added to 10 mL aqueous ethanol (1:1). After the cooling down by ice, added graduately $NaBH_4$ (0.12 g, 3.2 mmol) and the mixture was stirring overnight. The reaction mixture was filtered and then diluted with brine (30 mL), extracted with ether (50 mL × 2). The combined ether was evaporated. Flash column chromatography on silica gel using petroleum ether:ethyl acetate (2:1) as eluent afforded 0.68 g **3** as colorless oily liquid, yield 97.5%. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.26–1.38 (6H, m, $P(OCH_2CH_3)_2$), 2.06–2.19 (2H, m, $CH(OH)CH_2P$), 4.09–4.21 (4H, m, $P(OCH_2CH_3)_2$), 4.36–4.42 (1H, m, $CH(OH)CH_2P$). ^{19}F NMR (282 MHz, $CDCl_3$) δ: 4.0 (s). ^{31}P NMR (120 MHz, $CDCl_3$) δ: 30.1 (s). Anal Calcd. for $C_7H_{14}O_4F_3P$: C, 33.01; H, 5.60. Found C, 33.46; H, 5.63.

3.2. Diethyl 3,3,3-trifluoropropenylphosphonates (*4*)

To an ice chilled mixture of **3** (7.5 g, 0.03 mol) and triethylamine (8.1 g, 0.03 mol) in dichloromethane (20 mL) was added dropwisely mesyl chloride (4.6 g, 0.04 mol). After the reaction mixture was warmed up to room temperature stirring overnight. Flash column chromatography on silica gel using petroleum ether:ethyl acetate (3:1) as eluent gave **4** as colorless liquid 4.8 g or 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.26–1.38 (6H, m, $P(OCH_2CH_3)_2$), 4.11–4.21 (4H, m, $P(OCH_2CH_3)_2$), 6.42–6.71 (2H, m, CH=CHP). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −9.7 (s). ^{31}P NMR (120 MHz, $CDCl_3$) δ: 12.5 (s).

3.3. Diethyl 1,2-dihydroxy-3,3,3-trifluoropropanephosphonate (*5*)

To an ice-cold suspension of **4** (1.57 g, 6.78 mmol) in water (20 mL) was added dropwisely under stirring an aqueous (30 mL) solution of $KMnO_4$ (1.12 g, 7.1 mmol). After that the mixture was stirred additionally hours at room temperature. The reaction mixture was extracted with ethyl acetate (4 × 50 mL), washed with brine and dried over Na_2SO_4. Flash column chromatography on silica gel using petroleum ether:ethyl acetate (1:1) as eluent gave product **5** as colorless solid, mp 39 °C. Yield 0.79 g or 48% of theoretical. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.34–1.39 (6H, t, $P(OCH_2CH_3)_2$), 4.19–4.29 (6H, m, $CF_3CHOHCHOH + CH(OH)CH_2P$), 4.89 (1H, b, CHOHP), 5.56 (1H, b, CH_3CHOH). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −0.5 (d, J = 12 Hz, 3F). ^{31}P NMR (120 MHz, $CDCl_3$) δ: 20.6 (s). Anal Calcd. for $C_7H_{14}O_5F_3P$: C, 31.59; H, 5.30. Found C, 31.51; H, 5.52.

3.4. Diethyl 1,2-di(β-chloroacetyloxy)-3,3,3-trifluoropropanephosphonate (*6*)

A mixture of **5** (5 mmol), chloroacetic acid (0.95 g, 10 mmol) DCC (2.45 g, 12 mmol) in 10 mL CH_2Cl_2 was cooled down to 0 °C then DMAP (50 mg) was introduced and stirring was continued for 2 h. The reaction mixture was stirring overnight at room temperature. Remove the precipate formed by filtration and washed with CH_2Cl_2 (5 mL). The organic solution was dried over Na_2SO_4 and evaporated under reduced pressure to give a crude product, which was subject to flash chromatography on silica gel using petroleum ether:ethyl acetate (3:1) as eluent. **6** was obtained as colorless liquid 1.93 g, yield 90%. FT-IR (KBr, cm^{-1}) 2960, 1755, 1413, 1193, 1146, 960, 794, 544 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.32–1.39 (6H, q, $P(OCH_2CH_3)_2$), 4.10–4.31 (8H, m, $2 \times CHOCOCH_2Cl + P(OCH_2CH_3)_2$), 5.77–5.92 (2H, m, CF_3CHCH). EIMS *m/z* (rel, intensity): 419 ($M^+ + 1$)(2.58), 265 (27.40), 155 (100, base), 109 (65.15). Anal Calcd. for $C_{15}H_{15}N_3O_2P$: C, 31.52; H, 3.58. Found C, 31.61; H, 4.14.

3.5. Enzymatic resolution of *6* using CALB

To 210 mg (0.5 mmol) of **6**, was added a benzene (2 mL) solution of CALB (100 mg) followed by 0.4 mL *n*-BuOH. The mixture was stirred constantly at 30 °C for 40 h. The residue CALB was removed by filtration and washed with acetone (5 mL). The combined organic solution was evaporated and the residue subject to flash chromatography on silica gel using petroleum ether:EtOAc (2:1) as eluent. Chiral diethyl 1-chloroacetyloxy-2-hydroxy-3,3,3-trifluoropropane phosphonate **7** was obtained as colorless liquid, 65 mg (38% yield), $[\alpha]_D^{20} = -11.6$ (c = 2.5, $CHCl_3$).

Chiral diethyl 1,2-bis(chloroacetyloxy)-3,3,3-trifluoropropane phosphonate (**8**) was resulted as colorless liquid, 82 mg (39% yield), $[\alpha]_D^{20} = -19.1$ (c = 0.5, $CHCl_3$).

3.6. Enzymatic resolution of *6* using IM

Analogously, **6** was enzymatic resolution by IM in the same manner. **7** was obtained as colorless liquid, 60 mg (35% yield), $[\alpha]_D^{20} = -11.9$ (c = 1.5, $CHCl_3$).

Chiral diethyl 1,2-bis(chloroacetyloxy)-3,3,3-trifluoropropane phosphonate (**8**) was collected as colorless liquid, 78 mg (37% yield), $[\alpha]_D^{20} = -22.1$ (c = 1.3, $CHCl_3$).

3.7. Diethyl (R,R)-1,2-dihydroxy-3,3,3-trifluoropropane phosphonate (*9*)

7 (50 mg, 0.2 mmol) was dissolvent in methanol (10 mL) followed by addition of aqueous ammonia solution (0.5 mL). The mixture was stirred at room temperature. The hydrolysis was completed in 3 h as monitored by TLC. The reaction mixture was evaporated under diminished pressure to remove solvent. The resultant residue was extracted with EtOAc (2 × 20 mL) and then the extract was washed with brine and dried over Na_2SO_4. The mixture was then subjected to flash

chromatography on silica gel using petroleum ether:EtOAc (2:1) as eluent. **9** was obtained 340 mg or 88% yield, ee 78.3%, $[\alpha]_D^{20} = -7.3$ (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.34 (6H, t, J = 7 Hz), 4.00–4.42 (6H, m), 4.61–4.63 (2H, br, s). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −0.6 (d, J = 12 Hz, 3F). ^{31}P NMR (120 MHz, $CDCl_3$) δ: 21.0. Anal Calcd. for $C_7H_{14}O_5F_3P$: C, 31.58; H, 5.27. Found C, 31.72; H, 5.02.

*3.8. Diethyl (S,S)-1,2-dihydroxy-3,3,3-trifluoropropane phosphonate (**10**)*

8 (50 mg, 0.2 mmol) was dissolved in methanol (10 mL) followed by addition of aqueous ammonia solution (0.5 mL). The mixture was stirred at room temperature. The hydrolysis was completed in 3 h as monitored by TLC. The reaction mixture was then evaporated under diminished pressure to remove solvent. The resultant residue was extracted with EtOAc (2 × 20 mL) and then the extract was washed with brine and dried over Na_2SO_4. The mixture was then subjected to flash chromatography on silica gel using petroleum ether:EtOAc (2:1) as eluent. **10** was obtained 46 mg or 90% yield, ee 75.1% $[\alpha]_D^{20} = +7.01$ (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.32–1.35 (6H, m), 4.20–4.32 (6H, m), 4.62–4.64 (2H, br, s). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −0.6 (d, J = 12 Hz, 3F). ^{31}P NMR (120 MHz, $CDCl_3$) δ: 21.5. Anal Calcd. for $C_7H_{14}O_5F_3P$: C, 31.58; H, 5.27. Found C, 32.00; H, 5.22.

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