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A Facile Asymmetric Synthesis of 1-Amino-2,2,2-Trifluoroethanephosphonic Acid*

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ABSTRACT: *Starting from the fundamental building block, trifluoromethylated N-(−)-α-methylbenzylacetimidoyl chloride, an asymmetric synthesis of 1-amino-2,2,2-trifluoroethanephosphonic acid was conveniently achieved by a base-catalyzed [1,3]-proton shift reaction of the intermediate dialkyl 1-imino-2,2,2-trifluoroethanephosphonate.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:536–540, 2000

INTRODUCTION

α-Amino phosphonic acids, the phosphorus analogues of natural occurring α-amino carboxylic acids, have received increasing interest in medicinal [1] and synthetic organic chemistry [2]. They serve as the fundamental building blocks in phosphonopeptides, which have been evaluated as inhibitors of the aspartic proteases pepsin and penicillopepsin [3]. On the other hand, the introduction of a trifluoromethyl group may remarkably enhance the biological activities of the parent molecules [4,5]. As an extension of our studies on the synthesis of trifluoromethylated α-amino phosphonic acids of biomedicinal importance [6], it is therefore interesting to investigate the asymmetric synthesis of the title compound.

Many α-amino phosphonic acids of enantiomerically pure form have been developed in recent years [7]. However, these methods require a particular catalyst [8] or a special structure of the substrate [9]. So the lure of a direct and effective asymmetric synthesis of trifluoromethylated α-amino phosphonic acids has been attracting our attention for many years.

A [1,3]-proton shift reaction, a reducing agent free biomimetic reductive amination [10], has emerged as a convenient, practical, and general method for the synthesis of various fluorine-containing amino compounds with a wide range of potential biomedicinal activities [11]. Herein, we wish to report a facile asymmetric synthesis of a trifluoromethylated α-amino phosphonic acid of moderate optical purity via an enantioselective biomimetic transamination of the corresponding dialkyl 1-imino-2,2,2-trifluoroethanephosphonates.

RESULTS AND DISCUSSION

Our synthetic approach leading to 1-amino-2,2,2-trifluoroethanephosphonic acid is based on the sequence of reactions as shown in Scheme 1.

The key building block trifluoromethylated *N*-(−)-α-methylbenzylacetimidoyl chloride **(−)-1** was conveniently prepared by a one-pot procedure [12]. The important intermediates, chiral dialkyl 1-*N*-(−)-α-methylbenzyl-2,2,2-trifluoroethanephosphonates **(−)-2** were obtained via the Arbuzov rearrangement with good yields. First, we tried to isomerize **(−)-2** under the conditions that triethylamine was used as a base and acetonitrile as solvent. Though the isomerization readily occurred, it gave a virtually racemic

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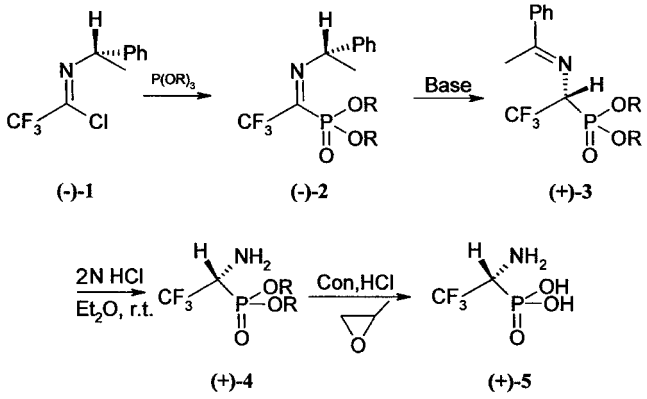

R=Et, n-Pr, i-Pr, n-Bu, i-Bu

SCHEME 1

3. A plausible rationale for this phenomenon is that polar solvents cause the reaction to proceed through a nonasymmetric reaction route. When we used a low-polar solvent, such as petroleum ether, the product was found to have optical purity, although its chemical yield was only 50% and the reaction rate was also low. Then we decided to use the base in a bifunctional manner, that is, to transfer the proton and as a solvent. By a change of the basicity, we were able to adjust both the isomerization rate and the enantiometric results (Table 1). We observed that the basicity of the base controlled the reaction. When a strong base, 1,8-dizabicyclo[5,4,0]undec-7-ene (DBU) was used, the isomerization proceeded immediately, but the elimination of HF then followed. This is apparently a major pathway to decomposition in this system. Even with a low temperature (−78°C), the isomerization also led to totally racemic product. This results from the location of the trifluoromethyl moiety and the phosphoryl group, which makes the α-proton very sensitive to strong bases. Use of another base, such as *N*-methylmorpholine, improved the optical purity (55% ee), but the chemical yield was poor. Finally, as shown in Table 1, when triethylamine was used as both a base and solvent, the conversion of **(−)-2** to **(+)-3** was easily achieved at room temperature, and the workup procedure was very simple. In this system, the Schiff bases **(+)-3**, were isolated in moderate to good yield with moderate enantiometric purity (42–67% ee). We also found that, under the same conditions, the isomerization of imine **(−)-2e**, bearing an isobutyl ester group, gave the isomerization product **(+)-3e** with a relatively good stereochemical result (67% ee).

Schiff bases **(+)-3** were conveniently hydrolyzed under mild conditions to give the corresponding target molecules, dialkyl 1-amino-2,2,2-trifluoroethanephosphonates **(+)-4**. Compound **(+)-4e** was then transformed to the corresponding phosphonic acid **(+)-5** by further hydrolysis in concentrated HCl. We also observed a positive Cotton effect ($\square$ = 256 nm) in the CD curve for compound **(+)-4e** (Table 2).

It is necessary to point out that, although Soloshonko failed to obtain a trifluoromethylated α-amino carboxylic acid by a [1,3] proton shift reaction [13], we have succeeded in obtaining a facile enantioselective synthesis of 1-amino-2,2,2-trifluoroethanephosphonic acid with moderate enantiomeric purity. This can serve as a building block for other analogous situations in mechanistic enzymology, as well as a structural unit in phosphonopeptide synthesis.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were taken on a Shimadzu IR400 spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ as a solution on a Bruker AC-300 (300 MHz) or an EM-360A (60 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. ^{19}F NMR spectra were obtained on a Varian EM 360A spectrometer using CF_3COOH as an external standard, positive for downfield shifts. Electron ionization-mass spectrometry (EI-MS) measurements were obtained on a HP5989A mass spectrometer. The CD spectra were recorded on a JASCO J-715 spectrometer. The elemental analyses were performed at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. All solvents used were dried by standard procedures.

Diethyl 1-N-(−)-α-methylbenzylimino-2,2,2-trifluoroethanephosphonate **(−)-2a**

To a 50 mL flask fitted with a $CaCl_2$ tube was added *N*-(−)-α-methylbenzylacetimidoyl chloride **(−)-1** (4.71 g, 20 mmol) and triethyl phosphite (3.84 g, 23.1 mmol). The mixture was stirred thoroughly at 80°C for 24 hours. The volatile components were removed under reduced pressure, and the resultant residue was subjected to flash chromatography on silica gel(EtOAc; petroleum ether = 1:3) giving a pale oil: 6.14 g, yield 91%. $[\alpha]_D^{22} = -58.2°$ (1.29, $CHCl_3$). IR(film) ν: 2990, 1740, 1270, 1200, 1150, 1010, 760, 700. ^{1}H NMR (60 MHz, CCl_4, ppm) δ: 7.40 (m, 5H, ArH); 5.85 (m, 1H, CH); 4.27 (q, 4H, J = 7.2 Hz, 2XOCH_2); 1.69 (d, 3H, J = 6.0 Hz, $CHCH_3$); 1.41 (t, 6H, J = 7.2 Hz, CH_2CH_3). ^{19}F NMR (56.4 MHz, TFA, CCl_4, ppm) δ: −8.9 (s, CF_3). MS (*m/e*, %): 337 (M^+,

TABLE 1 Isomerization of **(−)-2** to **(+)-3**

Compound	*R*	*Base*	*Solvent*	*Temp (°C)*	*Time (h)*	*Yield (%)*	*ee[a] (%)*
(+)-3a	Et	Et_3N	CH_3CN	r.t.	3	82	0
(+)-3a	Et	Et_3N	Petroleum ether	r.t.	120	50	61
(+)-3a	Et	DBU	—	−78	8.5	26	0
(+)-3a	Et	DBU	—	r.t.	—	0	—
(+)-3a	Et	N-methyl-morpholine	—	r.t.	42	65	55
(+)-3a	Et	Et_3N	Et_3N	r.t.	28	80	42
(+)-3b	*n*-Pr	Et_3N	Et_3N	r.t.	26	93	54
(+)-3c	*i*- Pr	Et_3N	Et_3N	r.t.	72	76	48
(+)-3d	*h*-Bu	Et_3N	Et_3N	r.t.	36	90	57
(+)-3e	*r*-Bu	Et_3N	Et_3N	r.t.	25	73	67

[a]ee values were determined by chiral HPLC analysis.

TABLE 2 Preparation of Compounds **(+)-4** and **(+)-5**

Compound	*R*	*m.p.(°C)*	*Yield(%)*	$[\alpha]_D^{22}$
(+)-4a	Et	—	91	+1.86
(+)-4b	*n*-Pr	—	96	+0.95
(+)-4c	*i*-Pr	—	76	+1.68
(+)-4d	*n*-Bu	—	85	+1.90
(+)-4e	*i*-Bu	—	85	+0.55
(+)-5	H	240–242	90	+1.93

2.04); 338 (M^+ + 1, 5.42), 105 (base). Anal. Calcd. for $C_{14}H_{19}F_3NO_3P$(337.3): C, 49.86; H, 5.68; N, 4.15. Found: C, 49.88; H, 5.68; N, 4.30.

Dipropyl 1-N-(−)-α-methylbenzylimino-2,2,2-trifluoroethanephosphonate **(−)-2b**

Compound **(−)-2b** was prepared similarly as for **(−)-2a**. A pale oil, yield 88%. $[\alpha]_D^{22} = -50.0°$ (0.71, $CHCl_3$). IR(cm^{-1}) *v*: 2980, 1370, 1200, 1140, 770, 700. ^1H NMR (60 MHz, CCl_4, ppm) *δ*: 7.51 (m, 5H, ArH); 5.99 (q, 1H, *J* = 6.0 Hz, CH); 4.26 (m, 4H, OCH_2); 2.00 (m, 4H, $\underline{CH_2}CH_3$); 1.76 (d, 3H, *J* = 6.0 Hz, $CH\underline{CH_3}$); 1.21 (m, 6H, $CH_2\underline{CH_3}$). ^{19}F NMR (56.4 MHz, TFA, CCl_4, ppm) *δ*: −9.1 (s, CF_3). MS (*m/e*, %): 365 (M^+, 0.52); 199 (base). Anal. Calcd. for $C_{16}H_{23}F_3NO_3P$(365.3): C, 52.61; H, 6.34; N, 3.84. Found: C, 52.91; H, 6.63; N, 4.09.

Diisopropyl 1-N-(−)-α-methylbenzylimino-2,2,2-trifluoroethanephosphonate **(−)-2c**

Compound **(−)-2c** was prepared similarly as for **(−)-2a**. A pale oil, yield 91%. $[\alpha]_D^{22} = -62.5°$ (1.03, $CHCl_3$). IR(cm^{-1}) *v*: 1690, 1380, 1140, 1000, 760, 700. ^1H NMR (60 MHz, CCl_4, ppm) *δ*: 7.40 (m, 5H, ArH); 5.95 (q, 1H, *J* = 6.0 Hz, N-CH); 4.85 (m, 2H, $\underline{CH}(CH_3)_2$); 1.65 (d, *J* = 6 Hz, N-$CH\underline{CH_3}$); 1.38 (m, 12H, CH_3). ^{19}F NMR (56.4 MHz, TFA, CCl_4, ppm) *δ*: −9.4 (s, CF_3). MS (*m/e*, %): 365 (M^+, 42.23); 199 (base). Anal. Calcd. for $C_{16}H_{23}F_3NO_3P$ (365.3): C, 52.60; H, 6.35; N, 3.83. Found: C, 52.35; H, 6.38; N, 3.98.

Dibutyl 1-N-(−)-α-methylbenzylimino-2,2,2-trifluoroethanephosphonate **(−)-2d**

Compound **(−)-2d** was prepared similarly as for **(−)-2a**. A pale oil, yield 91%. $[\alpha]_D^{22} = -50.6°$ (1.09, $CHCl_3$). IR(cm^{-1}) *v*: 2950, 1270, 1190, 1140, 1110, 760, 700. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.34 (m, 5H, ArH); 5.68 (q, 1H, *J* = 6.3 Hz, CH); 4.12 (m, 4H, OCH_2); 1.65 (m, 4H, $OCH_2\underline{CH_2}$); 1.56 (d, 3H, *J* = 6.3 Hz, $CH\underline{CH_3}$); 1.34 (m, 4H, $\underline{CH_2}CH_3$); 0.94 (m, 6H, $CH_2\underline{CH_3}$). ^{19}F NMR (56.4 MHz, TFA, $CDCl_3$, ppm) *δ*: −9.3 (s, CF_3). MS (*m/e*, %): 393 (M^+, 4.63); 394 (M^+ + 1, 1.05); 199 (base). Anal. Calcd. for $C_{18}H_{27}F_3NO_3P$ (393.4): C, 54.96; H, 6.92; N, 3.56. Found: C, 54.91; H, 7.16; N, 3.57.

Diisobutyl 1-N-(−)-α-methylbenzylimino-2,2,2-trifluoroethanephosphonate **(−)-2e**

Compound **(−)-2e** was prepared similarly as for **(−)-2a**. A pale oil, yield 79%. $[\alpha]_D^{22} = -48.2°$ (0.71, $CHCl_3$). IR(cm^{-1}) *v*: 3010, 1290, 1210, 1010, 780, 700. ^1H NMR (60 MHz, $CDCl_3$, ppm) *δ*: 7.32 (m, 5H, ArH); 5.69 (q, 1H, *J* = 5.4 Hz, N-CH); 3.96 (m, 4H, $\underline{CH_2}CH$); 1.94 (m, 2H, $\underline{CH}(CH_3)_2$); 1.55 (d, 3H, *J* = 5.4 Hz, $NCH\underline{CH_3}$); 1.02 (m, 12H, CH_3); ^{19}F NMR (56.4 MHz, TFA, CCl_4, ppm) *δ*: −9.0 (s, CF_3). MS (*m/e*, %): 394 (M^+ + 1, 6.65); 199 (base). Anal. Calcd. for $C_{18}H_{27}F_3NO_3P$ (393.4): C, 54.96; H, 6.92; N, 3.56. Found: C, 55.09; H, 7.01; N, 3.66.

(+)-Diethyl 1-methylbenzyleneamino-2,2,2-trifluoroethanephosphonate **(+)-3a**

To a 25 mL flask charged with N_2 was added diethyl 1-*N*-(−)-α-methylbenzylimino-2,2,2-trifluoro-

ethanephosphonate **(−)-2a** (0.337 g, 1 mmol) and 4 mL triethylamine. The mixture was stirred at room temperature for 28 hours. Completion of reaction was monitored by thin layer chromatography. The triethylamine was removed from the mixture under reduced pressure, and the resultant residue was subjected to flash chromatography on silica gel (EtOAc:Petroleum ether = 1:3) giving a pale oil, 0.270 g, yield 80%. ee% = 42%. $[\alpha]_D^{22} = -50°$ (1.12, $CHCl_3$). IR(cm^{-1}) *v*: 2990, 1630, 1260, 1160, 1100, 760, 700. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.98–7.28 (m, 5H, ArH); 4.71 (dq, 1H, $J_{P\text{-}H}$ = 16.2 Hz, $J_{F\text{-}H}$ = 8 Hz, N-CH); 4.23 (m, 4H, OCH_2); 2.39 (s, 3H, CH_3); 1.38 (m, 6H, $CH_2\underline{CH_3}$). ^{19}F NMR (56.4 MHz, $CDCl_3$, TFA, ppm) *δ*: −10.5 (b, CF_3). MS (*m/e*, %): 337 (M^+ + 1, 19.99); 159 (base). Anal. Calcd. for $C_{14}H_{19}F_3NO_3P$ (337.3): C, 49.86; H, 5.68; N, 4.15. Found: C, 49.33; H, 5.75; N, 4.08.

(+)-Dipropyl 1-methylbenzyleneamino-2,2,2-trifluoroethanephosphonate **(+)-3b**

Compound **(+)-3b** was prepared similarly as for **(+)-3a**. A pale oil, yield 93%, ee% = 54%. $[\alpha]_D^{22} = +45.6°$ (1.13, $CHCl_3$). IR(cm^{-1}) *v*: 3010, 1650, 1280, 1180, 1130, 1010, 780, 700. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.93–7.45 (m, 5H, ArH); 4.71 (dq, 1H, $J_{P\text{-}H}$ = 16.2 Hz, $J_{F\text{-}H}$ = 8.1 Hz, N-CH); 4.07 (m, 4H, OCH_2CH); 2.38 (s, 3H, CH_3); 1.68 (m, 4H, $\underline{CH_2}CH_3$); 0.97 (m, 6H, $CH_2\underline{CH_3}$). ^{19}F NMR (56.4 MHz, CCl_4/TFA, ppm) *δ*: −9.7 (t, *J* = 8.1 Hz, CF_3). MS (*m/e*, %): 365 (M^+, 1.49); 366 (M^+ + 1, 4.92); 159 (base). Anal. Calcd. for $C_{16}H_{23}F_3NO_3P$ (365.3): C, 52.60; H, 6.35; N, 3.84. Found: C, 52.98; H, 6.50; N, 4.06.

(+)-Diisopropyl 1-methylbenzyleneamino-2,2,2-trifluoroethanephosphonate **(+)-3c**

Compound **(+)-3c** was prepared similarly as for **(+)-3a**. A pale oil, yield 76%, ee% = 48%. $[\alpha]_D^{22} = +47.2°$ (1.35, $CHCl_3$). IR(cm^{-1}) *v*: 2990, 1740, 1640, 1260, 1160, 1110, 1000, 760, 700. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.98–7.37 (m, 5H, ArH); 4.83 (m, 2H, $\underline{CH}CH_3$); 4.66 (dq, 1H, $J_{P\text{-}H}$ = 17.6 Hz, $J_{F\text{-}H}$ = 8.1 Hz, N-CH); 2.39 (s, 3H, CH_3); 1.34 (m, 12H, $CH(CH_3)_2$). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) *δ*: −10.5 (t, *J* = 8.1 Hz, CF_3). MS (*m/e*, %): 365 (M^+, base); 159 (64.89). Anal. Calcd. for $C_{16}H_{23}F_3NO_3P$ (365.3): C, 52.60; H, 6.35; N, 3.84. Found: C, 52.04; H, 6.46; N, 4.38.

(+)-Dibutyl 1-methylbenzyleneamino-2,2,2,-trifluoroethanephosphonate **(+)-3d**

Compound **(+)-3d** was prepared similarly as for **(+)-3a**. A pale oil, yield 90%, ee% = 57%. $[\alpha]_D^{22} = +47.0°$ (1.13, $CHCl_3$). IR(cm^{-1}) *v*: 2950, 1630, 1260, 1160, 1120, 1010, 760, 700. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.91–7.46 (m, 5H, ArH); 4.71 (dq, 1H, $J_{P\text{-}H}$ = 16.2 Hz, $J_{F\text{-}H}$ = 8.1 Hz, N-CH); 4.12 (m, 4H, OCH_2); 2.42 (s, 3H, CH_3); 1.66 (m, 4H, $\underline{CH_2}CH_2$); 1.39 (m, 4H, $\underline{CH_2}CH_3$); 0.96 (m, 6H, $CH_2\underline{CH_3}$). ^{19}F NMR (56.4 MHz, CCl_4/TFA, ppm) *δ*: −9.8 (t, *J* = 8.1 Hz, CF_3). MS (*m/e*, %): 393 (M^+, 3.38); 394 (M^+ + 1, 0.68); 159 (base). Anal. Calcd. for $C_{18}H_{27}F_3NO_3P$ (393.4): C, 54.96; H, 6.92; N, 3.56. Found: C, 55.11; H, 6.86; N, 3.78.

(+)-Diisobutyl 1-methylbenzyleneamino-2,2,2-trifluoroethanephosphonate **(+)-3e**

Compound **(+)-3e** was prepared similarly as for **(+)-3a**. A pale oil, yield 73%, ee% = 67%. $[\alpha]_D^{22} = +50.0°$ (0.70, $CHCl_3$). IR (cm^{-1}) *v*: 3000, 1650, 1270, 1180, 1130, 1010, 770, 700. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.90–7.42 (m, 5H, ArH); 4.72 (dq, 1H, $J_{P\text{-}H}$ = 17.5 Hz, $J_{F\text{-}H}$ = 8.0 Hz, N-CH); 3.89 (m, 4H, OCH_2); 2.38 (s, 3H, CH_3); 1.96 (m, 2H, $\underline{CH}(CH_3)_2$); 0.89 (m, 12H, CH_2CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) *δ*: −9.8 (t, *J* = 8.0 Hz, CF_3). MS (*m/e*, %): 394 (M^+ + 1, 68.76); 159 (base). Anal. Calcd. for $C_{18}H_{27}F_3NO_3P$ (393.4): C, 54.96; H, 6.92; N, 3.56. Found: C, 55.11; H, 7.01; N, 3.77.

(+)-Diethyl 1-amino-2,2,2-trifluoroethanephosphonate **(+)-4a**

To a solution of (+)-diethyl 1-methylbenzyleneamino-2,2,2-trifluoroethanephosphonate **(+)-3a** (0.168 g, 5 mmol) in 20 mL diethyl ether was added 5 mL 2N HCl. The reaction mixture was then stirred for 5 hours at room temperature. After completion of the reaction, Na_2CO_3 was added to adjust the pH to 8.0–9.0. The aqueous solution was then extracted with ethyl acetate (20 mL × 3), and the organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure. Isolation of the product by column chromatography on silica gel (EtOAc:petroleum ether = 2:1) offered a pale oil, 0.107 g, yield 91%. $[\alpha]_D^{22} = -1.86°$ (4.0, $CHCl_3$). IR(cm^{-1}) *v*: 3406, 3326, 2990, 1261, 1026. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 4.23 (m, 4H, OCH_2); 3.60 (dq, 1H, $J_{P\text{-}H}$ = 18 Hz, $J_{F\text{-}H}$ = 9 Hz, $\underline{CH}CF_3$); 1.39 (t, 6H, *J* = 10 Hz, CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) *δ*: −5.9 (b, CF_3). MS (*m/e*, %): 235 (M^+, 0.21); 236 (M^+ + 1, 1.42); 82 (base). Anal. Calcd. for $C_6H_{13}F_3NO_3P$ (235.1): C, 30.65; H, 5.57; N, 5.96. Found: C, 30.66; H, 5.43; N, 6.12.

(+)-Dipropyl 1-amino-2,2,2-trifluoroethanephosphonate **(+)-4b**

This compound was obtained analogously by the method used for **(+)-4a**. A pale oil, yield 96%. $[\alpha]_D^{22}$

= +0.95° (2.81, $CHCl_3$). IR(cm^{-1}) *v*: 2406, 3326, 2975, 1623, 1263, 1008. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.10 (m, 4H, OCH_2); 3.56 (dq, 1H, $J_{P\text{-}H}$ = 18.5 Hz, $J_{F\text{-}H}$ = 8.5 Hz, $\underline{CH}CF_3$); 1.70 (m, 4H, $\underline{CH_2}CH_3$); 0.95 (t, 6H, J = 7.4 Hz, CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −6.3 (t, J = 8.5 Hz, CF_3). MS (*m/e*, *%*): 264 (M^+ + 1, 8.27); 42 (base). Anal. Calcd. for $C_8H_{17}F_3NO_3P$ (263.2): C, 36.51; H, 6.51; N, 5.32. Found: C, 36.89; H, 6.74; N, 5.80.

(+)-Diisopropyl 1-amino-2,2,2-trifluoroethanephosphonate (+)-4c

This compound was obtained analogously by the method used for **(+)-4a**. A pale oil, yield 76%. $[\alpha]_D^{22}$ = +1.68° (2.72, $CHCl_3$). IR(cm^{-1}) *v*: 3409, 3327, 2986, 1623, 1253, 997. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.83 (m, 2H, OCH); 3.51 (dq, 1H, $J_{P\text{-}H}$ = 19.6 Hz, $J_{F\text{-}H}$ = 8.4 Hz, $\underline{CH}CF_3$); 1.37 (m, 12H, CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −6.7 (t, J = 8.4 Hz, CF_3). ^{31}P NMR (400 MHz, D_2O + CD_3COCD_3, ppm) δ: 16.601 (d, J = 19.2 Hz). MS (*m/e*, *%*): 264 (M^+ + 1, 2.95); 43 (base). Anal. Calcd. for $C_8H_{17}F_3NO_3P$ (263.2): C, 36.51; H, 6.51; N, 5.32. Found: C, 36.62; H, 6.67; N, 5.42.

(+)-Dibutyl 1-amino-2,2,2-trifluoroethanephosphonate (+)-4d

This compound was obtained analogously by the method used for **(+)-4a**. A pale oil, yield 85%. $[\alpha]_D^{22}$ = +1.902° (2.03, $CHCl_3$). IR(cm^{-1}) *v*: 3406, 3325, 2966, 1623, 1261, 1025. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.67 (m, 4H, OCH_2); 3.58 (dq, 1H, $J_{P\text{-}H}$ = 19.9 Hz, $J_{F\text{-}H}$ = 8.6 Hz, $\underline{CH}CF_3$); 1.69 (m, 4H, $OCH_2\underline{CH_2}$); 1.43 (m, 4H, $\underline{CH_2}CH_3$); 0.95 (m, 8.6 Hz, CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −6.4 (t, J = 8.6 Hz, CF_3). ^{19}P NMR ($CDCl_3$, ppm) δ: 16.941 (q, J = 18.8 Hz). MS (*m/e*, *%*): 292 (M^+ + 1, 1.15); 83 (base). Anal. Calcd. for $C_{10}H_{21}F_3NO_3P$ (291.2): C, 41.24; H, 7.27; N, 4.81. Found: C, 41.33; H, 7.33; N, 4.59.

(+)-Diisobutyl 1-amino-2,2,2-trifluoroethanephosphonate (+)-4e

This compound was obtained analogously by the method used for **(+)-4a**. A pale oil, yield 85%. $[\alpha]_D^{22}$ = +0.55° (2.23, $CHCl_3$). CD: 256 nm, +3.30. IR(cm^{-1}) *v*: 3406, 3326, 2976, 1623, 1473, 1260, 1016. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 3.93 (m, 4H, OCH_2); 3.60 (dq, 1H, $J_{P\text{-}H}$ = 19.8 Hz, $J_{F\text{-}H}$ = 8.5 Hz, $\underline{CH}CF_3$); 1.97 (m, 2H, $OCH_2\underline{CH}$); 0.95 (d, 12H, J = 6.6 Hz, CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −6.3 (t, J = 8.5 Hz, CF_3). MS(*m/e*, *%*): 292 (M^+ +1); 57 (base). Anal. Calcd. for $C_{10}H_{21}F_3NO_3P$ (291.2): C, 41.24; H, 7.27; N, 4.81. Found: C, 41.32; H, 7.38; N, 4.63.

(+)-1-amino-2,2,2-trifluoroethanephosphonic acid (+)-5

To a 25 mL round-bottom flask containing 10 mL concd hydrochloric acid was added (+)-diisobutyl 1-amino-2,2,2-trifluoroethylphosphonate **(+)-4e** (0.123 g, 0.423 mmol), and the mixture was refluxed for 24 hours. The solution was treated with propylene oxide until the pH was between 5 and 6, then refluxed for another 15 minutes. The precipitate was recrystallized from ethanol-water to afford compound **(+)-5**, 0.068 g, yield 90%; m.p. 240–242°C. $[\alpha]_D^{22}$ = +1.93° (0.83, $CHCl_3$). IR(cm^{-1}) *v*: 2897, 1642, 1539, 1388, 1230, 1174, 1090. ^1H NMR (300 MHz, D_2O, ppm) δ: 4.08 (dq, 1H, $J_{P\text{-}H}$ = 17.4 Hz, $J_{F\text{-}H}$ = 8.7 Hz, $\underline{CH}CF_3$). ^{19}F NMR (56.4 MHz, D_2O/TFA, ppm) δ: −10.0 (dd, $J_{P\text{-}F$ = 7.2 Hz, $J_{H\text{-}F}$ = 8.7 Hz, CF_3). MS (*m/e*, *%*): 179 (M^+, 3.86); 180 (M^+ + 1, 5.23); 98 (base). Anal. Calcd. for $C_2H_5F_3NO_3P$(179.0): C, 13.42; H, 2.81; N, 7.82. Found: C, 13.27; H, 2.69; N, 7.78.

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