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A Practical and Effective Asymmetric Synthesis of 2-Amino-3,3,3-Trifluoropropanephosphonic Acid

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ABSTRACT: *A practical and effective synthesis of 2-amino-3,3,3-trifluoropropanephosphonic acid of high stereochemical purity was successfully achieved by a base-induced [1,3]-proton shift reaction of the intermediate 2-imino-3,3,3-trifluoropropanephosphonate.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:541–545, 2000

INTRODUCTION

Since the discovery of 2-aminoethanephosphonic acid in various organisms [1], aminophosphonic acids, in place of naturally occurring amino carboxylic acids, have attracted considerable interest in serving as fundamental building blocks in various phosphonopeptides [2] and peptide-based enzyme inhibitors [3]. Recently, several general methods for the preparation of 2-aminoalkanephosphonic acids have been reviewed [4]. As we found [5], the introduction of a trifluoromethyl group often gives rise to unique chemical and biological activities of parent molecules. Although some methods for the preparation of fluoroinated 2-aminoalkane phosphonic acids acids have been reported [6], to the best of our knowledge, 2-amino-3,3,3-trifluoropropanephosphonic acid has not yet been prepared in optically active form.

A [1,3] proton shift reaction, essentially a reducing agent-free biomimetic reductive amination, has been applied in syntheses of various fluorine-containing amino compounds having a wide range of potential biomedicinal activities in recent years [7–9].

As an extension of our research on the asymmetric syntheses of 1-amino-2,2,2-trifluoroethane phosphonic acid [10], herein we wish to report a practical and effective synthesis of 2-amino-3,3,3-trifluoropropanephosphonic acid of high optical activity by a based-induced [1,3] proton shift reaction.

RESULTS AND DISCUSSION

Our synthetic route leading to 2-amino-3,3,3-trifluoropropanephosphonic acid is based on the sequence of reactions shown in Scheme 1.

The starting key building block trifluoromethylated *N*-(−)-α-methylbenzyl-acetimidoyl chloride **(−)-1** was easily synthesized by a one-pot procedure [11]. Upon reactions of this key building block with carbanions from methanephosphonates there resulted the important intermediates dialkyl 1-*N*-(−)-α-methylbenzylimino-3,3,3-trifluoropropane-phosphonates **(+)-2** and their isomeric enamines **(+)-2'** which were stablized by intramolecular hydrogen bonding. The mixture of intermediates **(+)-2** and **(+)-2'** were difficult to separate by column chro-

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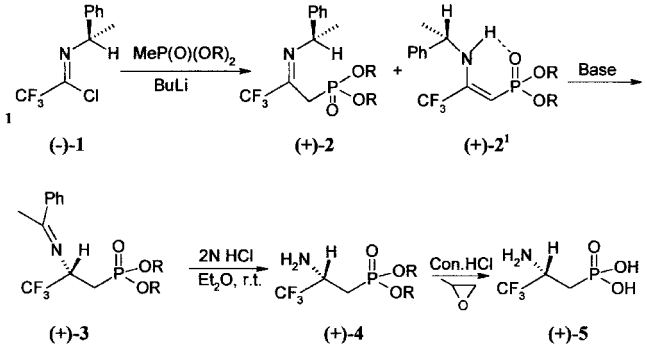

R=Me, Et, n-Pr, i-Pr, n-Bu

SCHEME 1

matography, but the ratio of isomeric products can be determined by ^{1}H or ^{19}F NMR spectroscopy, depending on the structures of the dialkyl ester groups, as shown in Table 1. Attempts to prepare the corresponding **(+)-2f** and **(+)-2f**[1] were unsuccessful probably due to the steric effect of the isobutyl group.

At first we treated **(+)-2** and **(+)-2**[1] in a solution of triethylamine by refluxing for several hours, but they were left intact. Then the addition of a strong base, 1,8-diazabicyclo[5,4,0]unclec-7-ene (DBU), caused the reaction to occur under mild conditions and with good stereochemical outcomes. As found by us, the amount of base used had an influence on the reaction rate and the yield of products, but showed no remarkable effect on the ee value. As a substrate-controlling, inductive asymmetric synthesis, the structure of the substrates is more important than the reaction conditions. When R was a methyl group, the mixture of **(+)-2a** and **(+)-2a**[1] was decomposed in this system because the dimethyl phosphonate was not very stable. Under the same conditions, the isomerization of imine **(+)-2c** and enamine **(+)-3c** with an *n*-propyl ester group gave the best result (72% yield, 83% ee value), (Table 2).

Schiff bases **(+)-3** were conveniently hydrolyzed under mild conditions to give 2-amino-3,3,3-trifluoropropanephosphonates **(+)-4**, which were transformed to the corresponding title compounds **(+)-5** by further hydrolysis in concentrate hydrochloric acid (Table 3).

In conclusion, we first describe a practical and effective asymmetric synthesis of 2-amino-3,3,3-trifluoropropanephosphonic acid of high stereomerical purity by a [1,3] proton shift reaction, and it is the first report of an asymmetric synthesis of the title compound. We also found that such a reaction in this system is much more successful than that for the 1-amino-2,2,2-trifluoroethanephosphonic acid counterpart, because the acidity of the β-H is not so sensitive to bases as that of an α-H. The title compound can serve as a building block for other novel analogues in mechanistic enzymology and as a structural unit in phosphonopeptide synthesis.

TABLE 1 Preparation of Compounds **(+)-2** and **(+)-2**[1]

Compounds	*R*	*Yield* (%)	*Ratio of imine/enamine*[a]
(+)-2a (+)-2a[1]	Me	59	0/100
(+)-2b (+)-2b[1]	Et	59	82/100
(+)-2c (+)-2c[1]	*n*-Pr	42	69/100
(+)-2d (+)-2d[1]	*i*-Pr	42	6/8[b]
(+)-2e (+)-2e[1]	**n**-Bu	47	80/100
(+)-2f (+)-2f[1]	*i*-Bu	0	—

[a]Ratio determined by ^{1}H NMR.
[b]Ratio determined by ^{19}F NMR.

TABLE 2 Isomerization of **(+)-2** and **(+)-2**[1] to **(+)-3**

Compounds	*R*	*Base*	*Temp* (°C)	*Time* (h)	*Yield* (%)	*ee*[a] (%)
(+)-3b	Et	Et_3N	reflux	15	0	–
(+)-3b	Et	DBU (1equiv.)	74	4	50	60
(+)-3b	Et	DBU (2equiv.)	74	3	75	70
(+)-3b	Et	DBU (2equiv.)	r.t.	84	65	64
(+)-3b	Et	DBU (2equiv.)	40	24	82	73
(+)-3c	nPr	DBU (2equiv.)	40	30	72	83
(+)-3d	iPr	DBU (2equiv.)	40	24	83	80
(+)-3e	nBu	DBU (2equiv.)	40	24	73	72

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

TABLE 3 Preparation of Compounds **(+)-4** and **(+)-5**

Compounds	*R*	*Yield* (%)	*m.p.* (°C)	$[\alpha]_D^{22}$
(+)-4b	Et	90	70–71	+18.8
(+)-4c	*n*-Pr	80	67–68	+16.3
(+)-4d	*i*-Pr	85	39–40	+26.9
(+)-4e	*n*-Bu	88	60–62	+17.1
(+)-5	H	90	262–264	+21.0

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were taken on a Shimadzu IR400 spectra meter. The ^{1}H NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC-300 (300 MHz) spectrometer using 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 spec-

trometry (EI-MS) measurements were obtained on a HP5989A mass spectrometer. HRMS were recorded on a Finnigan MAT 8430 spectrometer. The elemental analyses were performed at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. All solvents were dried by standard procedures.

Diethyl 2-N-(−)-α-methylbenzylimino-3,3,3-trifluoropropanephosphonate **(+)-2b** *and its isomeric enamine* **(+)2b'**

To an oven-dried 100 mL three-necked flask fitted with a stirring bar, thermometer, rubber septum, and charged with dried N_2 was added dry THF (20 mL) and diethyl methanephosphonate (1.52 g, 10 mmol). After cooling to −78°C, BuLi (2M in hexane, 5 ml, 10 mmol) was added dropwisely to the solution. After the solution had been stirred at −78°C for 45 minutes, a solution of N-(−)-α-methylbenzyl-acetimidoyl chloride **(−)-1** (2.35 g, 10 mmol) in THF (5 mL) was added dropwise. Stirring was continued at −78°C for 30 minutes, and then water (10 mL) was added to terminate the reaction. The aqueous solution was then extracted with ethyl ether (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 = 1:3) offered the mixture of **(+)-2b** and **(+)-2b'** 2.07 g as a pale yellow oil, yield 59%. $[\alpha]_D^{22}$ = +247° (1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.71(d, *J* = 11 Hz, NH, enamine); 7.34 (m, 5H, ArH); 5.02 (q, *J* = 6.6 Hz, N-CHCH$_3$); 4.64 (m, N-CHCH$_3$); 4.64 (m, N-CHCH$_3$, enamine); 4.47 (d, *J* = 8.1 Hz, C=CH, enamine); 4.08 (m, 4H, OCH_2); 3.09 (d, *J* = 23.6 Hz, CH_2-P); 1.54 (m, 3H, N-CHCH$_3$); 1.28 (m, 6H, CH_2CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) *δ*; −11.8 (s, CF_3); −6.3 (s, CF_3). MS (*m/e, %*): 351 (M^+, 22.61); 352 (M^+ + 1, 8.08); 105 (base). IR (cm^{-1}) *ν*: 2990, 1630, 1250, 1180, 1140, 1030, 760, 700. Anal. Calcd. for $C_{15}H_{21}F_3NO_3P$(351.3): C, 51.28; H, 6.02; N, 3.99. Found: C, 51.29; H, 6.12; N, 4.11.

Dimethyl 2-N-(−)-α-methylbenzylimino-3,3,3-trifluoropropanephosphonate **(+)-2a** *and its isomeric enamine* **(+)2a'**

Compounds **(+)-2b** and **(+)-2b'** were prepared similarly as for **(+)-2b** and **(+)-2b'**, yield 59%. $[\alpha]_D^{22}$ = +254° (1.30, $CHCl_3$) ^{1}H NMR (90 MHz, CCl_4, ppm) *δ*: 8.03 (d, 1H, *J* = 9.9 Hz, NH, enamine); 7.41 (m, 5H, ArH); 4.72 (m, 1H, CHCH$_3$); 4.47 (d, 1H, *J* = 8.1 Hz, C=CH, enamine); 3.80 (m, 6H, OCH_3); 1.66 (d, 3H, *J* = 6.3 Hz, N-CHCH$_3$). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) *δ*: −11.0 (s, CF_3), MS (*m/e, %*): 323 (M^+, 10.94); 324 (M^+ + 1, 2.33); 105 (base). IR (cm^{-1}) *ν*: 3000, 1630, 1450, 1180, 1030, 780, 700. Anal. Calcd. for $C_{13}H_{17}F_3NO_3P$(323.2): C, 48.31; H, 5.30; N, 4.33; Found: C, 48.18; H, 5.29; N, 4.34.

Dipropyl 2-N-(−)-α-methylbenzylimino-3,3,3-trifluoropropanephosphonate **(+)-2c** *and its isomeric enamine* **(+)2c'**

Compounds **(+)-2c** and **(+)-2c'** were prepared similarly as for **(+)-2b** and **(+)-2b'**, yield 42%. $[\alpha]_D^{22}$ = +142.4° (0.855, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.70 (d, *J* = 10.6 Hz, NH, enamine); 7.31 (m, 5H, ArH); 4.99 (q, *J* = 6.4 Hz, N-CHCH$_3$); 4.60 (m, N-CHCH$_3$, enamine); 4.47 (d, *J* = 7.9 Hz, C=CH, enamine); 3.94 (m, 4H, OCH_2); 3.09 (d, *J* = 23.5 Hz, CH_2-P); 1.70 (m, 4H, CH_2CH_3); 1.59 (m, 3H, CHCH$_3$); 0.95 (m, 6H, CH_2CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) *δ*: −11.3 (s, CF_3); −5.7 (s, CF_3). MS (*m/e*, *%*): 379 (M^+, 20.62); 380 (M^+ + 1, 14.61); 105 (base). IR (cm^{-1}) *ν*: 3000, 1630, 1260, 1200, 1150, 1000, 760, 700. Anal. Calcd. for $C_{17}H_{25}F_3NO_3P$(379.4): C, 53.82; H, 6.64; N, 3.69; Found: C, 53.54; H, 6.83; N, 3.77.

Diisopropyl 2-N-(−)-α-methylbenzylimino-3,3,3-trifluoropropanephosphonate **(+)-2d** *and its isomeric enamine* **(+)2d'**

Compounds **(+)-2d** and **(+)-2d'** were prepared similarly as for **(+)-2b** and **(+)-2b'**, yield 42%. $[\alpha]_D^{22}$ = + 211.1° (1.54, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) *δ*:e 7.73 (d, *J* = 11 Hz, NH, enamine); 7.36 (m, 5H, ArH); 5.03 (q, *J* = 6.9 Hz, N-CHCH$_3$); 4.73 (m, N-CHCH$_3$, enamine); 4.65 (m, 2H, OCH); 4.49 (d, *J* = 5.8 Hz, C = CH, enamine); 3.06 (d, *J* = 23.5 Hz, CH_2-P); 1.60 (m, 3H, CH-CH$_3$); 1.33 (m, 12H, OCHCH$_3$). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) *δ*: −12.0 (s, CF_3); −6.6 (s, CF_3). MS (*m/e, %*): 379 (M^+, 13.6); 380 (M^+ + 1, 3.13); 105 (base). IR (cm^{-1}) *ν*: 2980, 1630, 1250, 1180, 1140, 1000, 760, 700. Anal. Calcd. for $C_{17}H_{25}F_3NO_3P$(379.4): C, 53.82; H, 6.64; N, 3.69; Found: C, 54.02; H, 6.80; N, 3.80.

Dibutyl 2-N-(−)-α-methylbenzylimino-3,3,3-trifluoropropanephosphonate **(+)-2e** and its isomeric enamine **(+)2e'**

Compounds **(+)-2e** and **(+)-2e'** were prepared similarly as for **(+)-2b** and **(+)-2b'**, yield 47%. $[\alpha]_D^{22}$ = +139.3° (0.915, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.71 (d, 1H, *J* = 10.6 Hz, NH); 7.31 (m, 5H, ArH); 4.99 (q, *J* = 6.4 Hz, N-CHCH$_3$); 4.62 (m, N-CHCH$_3$, enamine); 4.45 (d, *J* = 8.0 Hz, C=CH); 3.98 (m, 4H, OCH_2); 3.09 (d, *J* = 23.5 Hz, CH_2-P); 1.56

(m, 8H, $\underline{CH_2CH_2}CH_3$); 1.49 (m, 3H, $CH\underline{CH_3}$); 0.94 (m, 6H, $CH_2\underline{CH_3}$). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −11.8 (s, CF_3); −6.2 (s, CF_3). MS (*m/e*, %): 407 (M^+, 44.76); 408 (M^+ + 1, 11.14); 41 (base). IR (cm^{-1}) *v*: 2960, 1620, 1250, 1180, 1140, 750, 700. HRMS: $C_{19}H_{29}F_3NO_3P$: Calcd: 407.1837; Found: 407:1845.

(+)-*Diethyl 2-methylbenzylideneamino-3,3,3-trifluoropropanephosphonate* **(+)-3b**

To a 25 mL flask charged with N_2 was added diethyl 2-*N*-(−)-α-methylbenzylimino-3,3,3-trifluoropropanephosphonate **(+)-2b** and its isomer **(+)-2b'** (0.351 g, 1 mmol) and DBU (0.304 g, 2 mmol). The mixture was stirred at 40°C for 24 hours. Completion of reaction was monitored by thin-layer chromatography. The resultant residue was subjected to flash chromatography on silica gel (EtOAc:Petroleum ether = 1:3) giving 0.288 g product as a pale oil, yield 82%. ee% = 73%. $[\alpha]_D^{22}$ = +100° (1.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.88–7.51 (m, 5H, ArH); 4.65 (m, 1H, N-CH); 4.09 (m, 4H, OCH_2); 2.44 (s, 3H, N=C–CH_3); 2.70–2.30 (m, 2H, P-CH_2); 1.26 (m, 6H, $CH_2\underline{CH_3}$). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −2.3 (d, J = 7.2 Hz, CF_3). IR (cm^{-1}) *v*: 2990, 1640, 1250, 1160, 1120, 1030, 760, 700.

(+)-*Dipropyl 2-methylbenzylideneamino-3,3,3-trifluoropropanephosphonate* **(+)-3c**

Compound **(+)-3c** was prepared similarly as for **(+)-3b**, yield 72%. ee% = 83%. $[\alpha]_D^{22}$ = +92.4° (0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.95–7.41 (m, 5H, ArH); 4.62 (m, 1H, N-CH); 3.93 (m, 4H, OCH_2); 2.50–2.26 (m, 2H, P-CH_2); 2.38 (s, 3H, N=C–CH_3); 1.60 (m, 4H, $\underline{CH_2}CH_3$); 1.26 (m, 6H, $CH_2\underline{CH_3}$). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −2.5 (d, J = 7.2 Hz, CF_3). MS (*m/e*, %): 380 (M^+ + 1, 24.62); 214 (base). IR (cm^{-1}) *v*: 3000, 1650, 1260, 1130, 770, 700. Anal. Calcd. For $C_{17}H_{25}F_3NO_3P$(379.4): C, 53.82; H, 6.64; N, 3.69; Found: C, 53.83; H, 6.68; N, 3.79.

(+)-*Diisopropyl 2-methylbenzylideneamino-3,3,3-trifluoropropanephosphonate* **(+)-3d**

Compound **(+)-3d** was prepared similarly as for **(+)-3b**, yield 83%. ee% = 80%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.89–7.47 (m, 5H, ArH); 4.78 (m, 1H, N-CH); 4.61 (m, 2H, OCH); 2.60–2.30 (m, 2H, P-CH_2); 2.43 (s, 3H, N=C–CH_3); 1.26 (m, 12H, $CH\underline{CH_3}$), ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −3.0 (d, J = 7.2 Hz, CF_3). MS (*m/e*, %): 379 (M^+, 43.16); 43 (base). IR (cm^{-1}) *v*: 2980, 1640, 1260, 1160, 1120, 1000, 760, 700. Anal. Calcd. For $C_{17}H_{25}F_3NO_3P$ (379.4): C, 53.82; H, 6.64; N, 3.69; Found: C, 54.06; H, 6.66; N, 3.69.

(+)-*Dibutyl 2-methylbenzylideneamino-3,3,3-trifluoropropanphosphonate* **(+)3e**

Compound **(+)-3e** was prepared similarly as for **(+)-3b**, yield 73%. ee% = 72%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.96–7.47 (m, 5H, ArH); 4.63 (m, 1H, N-CH); 3.98 (m, 4H, OCH_2); 2.41 (s, 3H, N=C–CH_3); 2.40 (m, 1H, P-CH_2); 1.94 (m, 1H, P-CH_2); 1.40 (m, 8H, $\underline{CH_2CH_2}CH_3$); 0.85 (m, 6H, $CH\underline{CH_3}$). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −2.4 (d, J = 8.4 Hz, CF_3). MS (*m/e*, %): 408 (M^+ + 1, base); 409 (M^+ + 1, 21.59). Anal. Calcd. For $C_{19}H_{29}F_3NO_3P$(407.4): C, 56.01; H, 7.17; N, 3.44; Found: C, 56.13; H, 7.03; N, 3.54.

(+)-*Diethyl 2-amino-3,3,3-trifluoropropanephosphonate* **(+)-4b**

To a solution of (+)-diethyl 2-methylbenzylideneamino-3,3,3-trifluoropropanephosphonate **(+)-3b** (0.0794 g, 0.226 mmol) in 20 mL diethyl ether was added 2N HCl (2 mL). 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 between 8 and 9. 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) afforded 0.0506 g of pure **(+)-4b** as a colorless solid, yield 90%, m.p. 70–71°C. $[\alpha]_D^{22}$ = +18.8° (2.29, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.15 (m, 4H, OCH_2); 3.69 (m, 1H, CH); 2.17 (m, 1H, P-CH_2); 1.95 (m, 1H, P-CH_2); 1.36 (m, 6H, CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: + 0.17 (d, J = 7.2 Hz, CF_3). MS (*m/e*, %): 250 (M^+ +1, base). IR (cm^{-1}) *v*: 3386, 2989, 1253, 1116, 1033. Anal. Calcd. For $C_7H_{15}F_3NO_3P$ (249.2): C, 33.74; H, 6.07; N, 5.62; Found: C, 33.47; H, 5.97; N, 5.22.

(+)-*Dipropyl 2-amino-3,3,3-trifluoropropanephosphonate* **(+)-4c**

Compound **(+)-4c** was prepared similarly as for **(+)-4b**, yield 80%. m.p. 67–68°C. $[\alpha]_D^{22}$ = +16.3° (0.753, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 5.33 (b, 2H, NH_2); 4.05 (m, 4H, OCH_2); 3.97 (m, 1H, CH); 2.22 (m, 2H, P-CH_2); 1.70 (m, 4H, $\underline{CH_2}CH_3$); 0.97 (m, 6H, CH_3). ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −0.06 (d, J = 7.2 Hz, CF_3). MS (*m/e*, %): 278 (M^+ + 1, 10.52); 124 (base). IR (cm^{-1}): *v*: 3383, 3320,

2976, 1255, 1116. Anal. Calcd. For $C_9H_{19}F_3NO_3P$ (277.2): C, 38.99; H, 6.91; N, 5.05; Found: C, 38.92; H, 6.83; N, 5.04.

(+)-*Diisopropyl 2-amino-3,3,3-trifluoropropanephosphonate* **(+)-4d**

Compound **(+)-4d** was prepared similarly as for **(+)-4b**, yield 85%. m.p. 39–40°C. $[\alpha]_D^{22} = +26.9°$ (0.93, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.79 (m, 2H, OCH); 4.44 (b, 2H, NH_2); 3.82 (m, 1H, CH); 2.15 (m, 2H, P-CH_2); 1.35 (m, 12H, CH_3) ^{19}F NMR (56.4 MHz, $CDCl_3$/TFA, ppm) δ: −4.3 (b, CF_3). MS (*m/e*, %): 278 (M^+ + 1, 5.60); 124 (base). IR (cm^{-1}) *v*: 3377, 3321, 2988, 1254, 1116. Anal. Calcd. For $C_9H_{19}F_3NO_3P$(277.2): C, 38.99; H, 6.91; N, 5.05; Found: C, 38.74; H, 6.86; N, 4.88.

(+)-*Dibutyl 2-amino-3,3,3-trifluoropropanephosphonate* **(+)-4e**

Compound **(+)-4e** was prepared similarly as for **(+)-4b**, yield 88%, m.p. 60–62°C. $[\alpha]_D^{22} = +17.1°$ (1.13, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.98 (b, 2H, NH_2); 4.10 (m, 4H, OCH_2); 4.02 (m, 1H, CH); 2.23 (m, 2H, P-CH_2); 1.65 (m, 4H, $OCH_2\underline{CH_2}$); 1.41 (m, 4H, $\underline{CH_2}CH_3$); 0.94 (m, 6H, CH_3). ^{19}F NMR (282 MHz, $CDCl_3$/TFA, ppm) δ: −0.09 (d, J = 5.4 Hz, CF_3). MS (*m/e*, %): 305 (M^+, 3.55); 306 (M^+ + 1, 26.59); 307 (M^+ + 2, 3.92); 124 (base). IR (cm^{-1}) *v*: 3385, 3321, 2964, 1253, 1115. Anal. Calcd. For $C_{11}H_{23}F_3NO_3P$(305.3): C, 43.28; H, 7.59; N, 4.59; Found: C, 43.29; H, 7.75; N, 4.50.

(+)-*2-amino-3,3,3-trifluoropropanephosphonic acid* **(+)-5**

To a 25 mL round-bottom flask containing concd hydrochloric acid (10 mL) was added (+)-dipropyl 2-amino-3,3,3-trifluoropropanephosphonate **(+)-4c** (0.059 g, 0.213 mmol), and the mixture was refluxed for 14 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 0.037 g of pure **(+)-5** as a white solid, yield 90%, m.p. 262–264°C. $[\alpha]_D^{22} = +21.0°$ (0.453, $CHCl_3$). ^1H NMR (300 MHz, D_2O, ppm) δ: 4.21 (m, 1H, N-CH); 2.20 (m, 1H, P-CH_2); 1.98 (m, 1H, P-CH_2). ^{19}F NMR (282 MHz, D_2O/TFA, ppm) δ: 3.59 (d, J = 5.56 Hz, CF_3). MS (*m/e*, %): 193 (M^+, 2.87); 194 (M^+ + 1, 5.65); 106 (base). IR (cm^{-1}) *v*: 2800, 1630, 1554, 1174. Anal. Calcd. For $C_3H_7F_3N\ O_3P$ (193.1): C, 18.66; H, 3.65; N, 7.26; Found: C, 18.46; H, 3.82; N, 7.43.

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