# **Supporting Information**

# $\alpha, \alpha$ -Difluoro- $\beta$ -iminophosphonates, an alternative toward the synthesis of $\alpha, \alpha$ -difluoro- $\beta$ -aminophosphonate derivatives

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### I. General Considerations

<sup>1</sup>H NMR, <sup>13</sup>C NMR, <sup>31</sup>P NMR and <sup>19</sup>F NMR spectra were recorded on a BRUKER DRX (400 MHz); BRUKER (400 MHz) AVANCE III HD NMR, Varian GEMINI 300 (300 MHz) and Varian 400 (400 MHz) spectrometers, unless otherwise noted. The chemical shifts are expressed in parts per million (ppm). For NMR spectroscopy as an internal standards the tetramethylsilane (TMS) (<sup>1</sup>H NMR and <sup>13</sup>C NMR), and trichloromonofluoromethane (CFCl<sub>3</sub>) (<sup>19</sup>F NMR) were used. For (<sup>31</sup>P NMR) spectroscopy, 85% H<sub>3</sub>PO<sub>4</sub> as external standard was used. Coupling constants are expressed in Hertz (Hz). The following abbreviations were used to express the multiplicities: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), td (triplet of doublets), q (quartet), tg (triplet of quartets), m (multiplet), br d (broad doublet), br s (broad singlet), br t (broad triplet). Reactions monitored by <sup>19</sup>F, <sup>31</sup>P NMR during process were done with a DMSO-*d*<sub>6</sub> probe. <sup>31</sup>P NMR spectra and chosen of <sup>19</sup>F NMR were recorded with protons decoupled. <sup>13</sup>C NMR spectra were recorded as attached proton test experiment (APT). Gas Chromatography - Mass spectra (GC-MS) GC-MS spectra were performed on Varian GC-MS 4000 spectrometer (conditions: flow rate of 1 mL/min, injector temperature = 220 °C, column oven temperature 40 °C (3 min)  $\rightarrow$  15 °C/min  $\rightarrow$  280 °C (10 min), using chloroform as the solvent). Mass spectra (MS) High resolution spectra were performed by electrospray ionization (ESI): Laboratoire Mesures Physiques of University Montpellier II. Thin Layer Chromatography (TLC) was performed on commercially available Merck Kieselgel 60-F<sub>254</sub> with ethyl acetate/hexane; ethyl acetate/heptane as developing systems. Visualization was performed with UV light then permanganate solution followed by heating. Permanganate solution (KMnO<sub>4</sub>) was prepared in water (300 mL) with KMnO<sub>4</sub> (3 g), K<sub>2</sub>CO<sub>3</sub> (20 g) and 5% NaOH water solution (5 mL). Column chromatography was performed in a glass column with silica gel (Merck Kieselgel 60 (230-400 mesh) using ethyl acetate (EtOAc) and n-hexane. Flash Column Chromatography was performed on Interchim puriFlash<sup>®</sup>430 compatible with 15 µm silica column using ethyl acetate (EtOAc) and nheptane. *Purification of solvents and reagents* Solvents were purified by classical methodology: Toluene was distilled over calcium hydride (CaH<sub>2</sub>) than stocked over 4Å MS. Acetonitrile, dichloromethane, ethanol were distilled over calcium hydride (CaH<sub>2</sub>) prior to use. Tetrahydrofuran (THF) was distilled over sodium-benzophenone. Other reagents were supplied by Sigma-Aldrich and used without purification unless otherwise noted.

# II. Spectra of compounds

### (Z/E)-diethyl (2-(heptylamino)-2-phenylvinyl)phosphonate 12a

# (E/Z)-diethyl (2-(heptylimino)-2-phenylethyl)phosphonate 13a

*Note*: Ratio of enamines **12a** and imines **13a** after column chromatography equaled 92:8, respectively. Ratio of enamines (Z/E) **12a** equaled 85:15, respectively. Ratio of imines **13a** (E/Z) equaled 85:15, respectively.





#### GC-MS



#### HRMS

Single Mass Analysis Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 1643 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 0-100 H: 0-110 N: 0-30 O: 0-30 P: 0-1

SYNAPT G2-S Y-JP15011201	#UEB205 4 (0.175)	Cm (3:4	)			MS2921	f8-17				12 1: TO	2-Jan-2015 F MS ES+ 1.10e+008
100 321.33	24.17 326.	19 <sup>328.</sup>	19 332.6	2 340.	20 345.29	352.20	354.22 3	56.23 359.42	368.24 370.21	376.20	381.18	384.23
320.0	)	330	.0	340	.0	350.0		360.0	370.0	1.1.1.1	380.0	m/z
Minimum:					-1.5							
Maximum:			1.0	5.0	50.0							
Mass	Calc.	Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula			
354.2199	354.21	.98	0.1	0.3	4.5	1381.9	n/a	n/a	C19 H33 N O3	P		



# (Z/E)-diethyl (2-(octylamino)-2-phenylvinyl)phosphonate 12b

### (E/Z)-diethyl (2-(octylimino)-2-phenylethyl)phosphonate 13b

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 93:7, respectively. Ratio of enamines (Z/E) **12b** equaled 87:13, respectively. Ratio of imines **13b** (E/Z) equaled 80:20, respectively.



# <sup>1</sup>H NMR





#### GC-MS



# (Z/E)-diethyl (2-((4-methoxybenzyl)amino)-2-phenylvinyl)phosphonate

12c

# (*E*/Z)-diethyl (2-((4-methoxybenzyl)imino)-2-phenylethyl)phosphonate 13c

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 91:9, respectively. Ratio of enamines (Z/E) **12c** equaled 83:17, respectively. Ratio of imines **13c** (E/Z) equaled 81:19, respectively.



# <sup>1</sup>H NMR



Page 1

#### **Elemental Composition Report**

#### **Single Mass Analysis**

Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 750 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 P: 1-1 SYNAPT G2-S#UEB205 Y-JL15020622 29 (0.130) Cm (18:80) MS305 06-Feb-2015 1: TOF MS ES+ 8.73e+007 376.1676 389.1862 414.1232 100 183.0210 201.0315 229.0630 293.0754 444.0899 257.0943 279.0761 346.1571 m/z mmm 180 200 220 240 260 280 300 340 400 420 460 320 360 380 440

Minimum: -1.5 Maximum: 5.0 1.0 50.0

Mass Calc. Mass mDa PPM DBE i-FIT Norm Conf(%) Formula

376.1676 376.1678 -0.2 -0.5 8.5 3166.3 n/a n/a C20 H27 N O4 P



# (Z/E)-diethyl (2-((2-methylbenzyl)amino)-2-phenylvinyl)phosphonate 12d

# (E/Z)-diethyl (2-((2-methylbenzyl)imino)-2-phenylethyl)phosphonate 13d

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 91:9, respectively. Ratio of enamines (Z/E) **12d** equaled 84:16, respectively. Ratio of imines **13d** (E/Z) equaled 77:23, respectively.









Page 1

#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 660 formula(e) evaluated with 2 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 P: 1-1 SYNAPT G2-S#UEB205 Y-JL15020624 28 (0.127) Cm (20:89) MS286f.20-27

SYNAPT G2-S Y-JL15020624	#UEB205 28 (0.127) Cm	(20:89)		MS286f.20-27							
100	<del></del>	359.6573	360.1731	361.176	363.1817	364.1852	365.4025	368.2353	369.2386	71.2434	372.1711
Minimum: Maximum:	356.0	<b>358.0</b> 5.0	360.0 1.0	-1.5 50.0	. 36	6 <b>4.</b> 0	366.0	368.0	370.0	372	2.0
Mass	Calc. Mas	s mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula			
360.1731	360.1729 360.1734	0.2 -0.3	0.6	8.5 1.5	3511.9 3529.5	0.000 17.627	100.00	C20 H27 M C5 H23 N	1 03 P L3 04 P		



# (Z/E)-diethyl (2-(benzylamino)-2-phenylvinyl)phosphonate 12e

### (E/Z)-diethyl (2-(benzylimino)-2-phenylethyl)phosphonate 13e

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 91:9, respectively. Ratio of enamines (Z/E) **12e** equaled 84:16, respectively. Ratio of imines **13e** (E/Z) equaled 95:5, respectively.



. 140 120 100 80 60 . 40 20 0 -10 -30 -50 f1 (ppm) -110 -140 -170 -200 -230 -70 -90





### GC-MS

ak#	Ret.T	ime	Start	Tm	End Tm	п	ı/z	Area	Area%	Heig	ht	Height %	A/H
	10	0.037	1(	0.017	10.06	3	TIC	129926	0.3	0 12	5955	2.79	1.
	12	2.680	12	2.523	13.02	ו	TIC	42836085	99.7	D 4383	3491	97.21	9.
Com	#1.5.#1											Pork 4 D S	com 4 b Gro
100,000)	H1-2001												Max Intensity : 4,4
2										Tim	ie 14.887 S	3can# 3,867 Inten. 9	60,927 Oven Tem
												1	
2.5	3.0 3	1.5 4.0	4.5	5.0 5.5	6.0 6.5	7.0 7.5	5 8.0 8.9	5 9.0 9.5	10.0 10.5 11	.0 11.5 12.0	0 12.5	13.0 13.5 14.0	14.5 15.0
							HR	MS					
							8 - 18 <b>- 1</b>						
Ele	menta	I Com	posit	ion Re	port								
Ele	menta	l Con	posit	ion Re	port								Page
Ele	menta alo Ma	l Com	iposit	ion Re	port								Page
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Ele Sin Tole	menta gle Ma erance =	ass An = 1.0 P	nalysi PM /	ion Re s DBE:	eport min = -1.5	, max =	50.0						Page
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Ele Sin Tole Eler Nun	menta gle Ma erance = nent pro	I Com ass An = 1.0 P edictio isotope	nalysi PM / n: Off e peaks	ion Re s DBE: s used	eport min = -1.5 for i-FIT =	, max = 3	50.0						Page
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Ele Sin Tole Eler Nun 589 Elem C: 5 SYN/ Y-JL1	menta gle Ma erance = nent prr nber of oisotopic formula( nents Us -100 I APT G2-5 15020621	I Com ass An = 1.0 P edictio isotope c Mass (e) eval sed: H: 0-10 S#UEB2 1 23 (0.1	PM / n: Off peaks Even F uated w 00 N: 05 08) Cm	ion Re DBE: bused Electron rith 1 re 0-30 (20:106)	min = -1.5 for i-FIT = lons sults within O: 0-30	, max = 3 limits (u P: 1-1	: 50.0 p to 20 be: N	st isotopic ma IS265	atches for ea	ch mass)		1:1	Page 06-Feb-20 FOF MS ES
Ele Sin Tole Eler Nun 589 Eler C: 5 SYN/ Y-JL1	menta gle Ma erance = nent pre- nber of oisotopic formula( nents Us -100 I APT G2-5 5020621	I Com ass Ai = 1.0 P edictio isotope c Mass (e) eval ed: H: 0-10 S#UEB2 1 23 (0.1	PM / n: Off e peaks Even F uated w 00 N: 05 08) Cm	ion Re s DBE: s used Electron rith 1 re 0-30 (20:106)	min = -1.5 for i-FIT = lons sults within O: 0-30	, max = 3 limits (u) P: 1-1 346.1	50.0 p to 20 be: N	st isotopic ma 15265	atches for ea	ch mass)		1:1	Page 06-Feb-20 FOF MS ES 4.43e+0
Ele Sin Tole Eler Num S89 Elem C: 5 SYN/ Y-JL1	menta gle Ma erance = nent pro- bisotopia formula formula nents Us -100 I APT G2-S 5020621	I Com ass Ar = 1.0 F edictio isotope c Mass c Mass	PM / nalysi PM / n: Off e peaks Even F uated w 00 N: 05 08) Cm	ion Re s DBE: s used Electron rith 1 re: 0-30 (20:106) 329.1	min = -1.5 for i-FIT = lons sults within O: 0-30	, max = 3 limits (u P: 1-1	50.0 p to 20 be: ^ <sup>573</sup> 350.13	st isotopic ma 15265 19 358.1572	atches for ea 368.1391	ch mass) 378.1471	3	1: T 95.1390.398.168	Page 06-Feb-20 FOF MS ES 4.43e+0 29 408.111
Eler Num S89 Eler C: 55 SYN/ Y-JL1 100	menta gle Ma erance = nent pre- ber of oisotopia formula( nents Us -100 I APT G2-5 15020621	I Com ass Ar = 1.0 F edictio isotope c Mass (e) eval sed: H: 0-1( S#UEB2 1 23 (0.1 318 ) 315	PM / n: Off peak Even f uated w 00 N: 05 08) Cm 1259 320	ion Re s DBE: s used Electron ith 1 re: 0-30 (20:106) <u>329.1</u> 325 33	min = -1.5 for i-FIT = lons sults within O: 0-30	, max = 3 limits (u P: 1-1 346.1	50.0 p to 20 be: 573 350.13 350 355	st isotopic ma 15265 19 358.1572 5 360 365	368.1391 370 375	ch mass) 378.1471 380 385	390	1: 1 <u>95. 1390 398. 166</u> 395 400 40	06-Feb-20 FOF MS ES 4.43e+0 99 408.11
Ele Sin Tole Eler Num 589 Elem C: 5 SYN/ Y-JL1 100 Tole SYN/ Y-JL1	menta gle Ma erance = nent pra- ber of oisotopia formula( nents Us -100   APT G2-5 15020621	I Com ass An = 1.0 P edictio isotope c Mass (e) eval ied: H: 0-1( S#UEB2 1 23 (0.1 316 ) 315	nalysii PM / n: Off peaks Even F uated w 00 N: 05 08) Cm .1259 320	ion Re DBE: bused Electron ith 1 re: 0-30 (20:106) <u>329.1</u> 325 33	min = -1.5 for i-FIT = lons sults within O: 0-30 <u>555,332,141</u> 0 335 3	, max = 3 limits (u P: 1-1 346.1	50.0 p to 20 be: 573 350.13 350 355	st isotopic ma 18265 19 358.1572 5 360 365	368.1391 370 375	ch mass) 378.1471 380 385	390	1: 1 95.1390.398.165 395 400 4(	06-Feb-20 TOF MS ES 4.43e+0 99 408.11 15 410
Ele Sin Tole Eler Nun Mon 589 Eler C: 5 SYN Y-JL1 100-7 3 Mini Maxi	menta gle Ma erance = nent pra- ber of oisotopia formula( nents Us -100   APT G2-5 15020621	I Com ass An = 1.0 P edictio isotope c Mass (e) eval ed: H: 0-1( S#UEB2 1 23 (0.1 316 ) 315	PM / n: Off peaks Even B uated w 00 N: 05 08) Cm 1259 320	ion Re DBE: b used Electron (20:106) <u>329.1</u> 325 33 5.0	min = -1.5 for i-FIT = lons sults within O: 0-30 555,332,141 0 335 3 1.0	, max = 3 limits (u P: 1-1 346.1 7 40 345 -1.2 50.(	50.0 p to 20 be: 573 350.13 350 355	st isotopic ma 18265 19 358.1572 5 360 365	368.1391 370 375	ch mass) 378.1471 380 385	390	1: 1 <u>95,1390,398,165</u> 395 400 40	06-Feb-20 TOF MS ES 4.43e+0 99 408.11 5 410
Ele Sin Tole Eler Nun Mon 589 Eler C: 5 SYNV Y-JL1 100- 3 Mini Maxi	menta gle Ma erance = nent pra- ber of oisotopia formula( nents Us -100   APT G2-5 15020621	I Com ass An = 1.0 P edictio isotope c Mass (e) eval ed: H: 0-1( S#UEB2 1 23 (0.1 316 ) 315	PM / n: Off peaks Even F uated w 00 N: 05 08) Cm .1259 320	ion Re DBE: DBE: s used Electron ith 1 re: 0-30 (20:106) <u>329.1</u> 325 33 5.0	min = -1.5 for i-FIT = lons sults within O: 0-30 555,332,141 0 335 3 1.0	, max = 3 limits (u P: 1-1 346.1 40 345 -1.2 50.0	50.0 p to 20 be: 573 350.13 350 355	st isotopic ma 15265 19 358.1572 5 360 365	368.1391 370 375	ch mass) 378.1471 380 385	390	1: 1 95.1390.398.165 395 400 40	06-Feb-20 TOF MS ES 4.43e+0 99 408.11 55 410
Ele Sin Tole Eler Nun Mon 589 Eler C: 5 SYNV Y-JL1 100 3 Mini Maxi Mass	menta gle Ma erance = nent pra- ber of oisotopia formula( nents Us -100   APT G2-5 15020621	I Com ass An = 1.0 P edictio isotope c Mass (e) eval ied: H: 0-1( S#UEB2 23 (0.1 318 ) 315 Calc	nalysii PM / n: Off peaks Even Buated w 00 N: 05 08) Cm .1259 320	ion Re DBE: DBE: s used Electron vith 1 re: 0-30 (20:106) <u>329.1</u> 325 33 5.0	min = -1.5 for i-FIT = lons sults within O: 0-30 555,332,141 0 335 3 1.0 PPM	, max = 3 limits (u P: 1-1 346.1 7 40 345 -1.2 50.0 DBE	50.0 p to 20 be: 573 350.13 350 355 5 1-FI	st isotopic ma 15265 19 358.1572 5 360 365 T Norm	368.1391 370 375 Conf (%)	ch mass) 378.1471 380 385 Formula	390	1: 1 95.1390.398.165 395 400 40	06-Feb-20 TOF MS ES 4.43e+0 99 408.111 5 410
Ele Sin Tole Eler Nun Mon. 589 Eler C: 5 SYN. Y-JL1 100-7 3 Minii Maxi Mass 346.	menta gle Ma erance = nent pra- ber of ioisotopia formula( nents Us -100   APT G2-5 15020621	I Com ass An = 1.0 P edictio isotope c Mass (e) eval ed: H: 0-1( S#UEB2 23 (0.1 315 ) 315 Calc 346.	nalysii PM / n: Off peaks Even Buated w 00 N: 05 08) Cm .1259 320	ion Re DBE: DBE: s used Electron vith 1 re: 0-30 (20:106) <u>329.1</u> 325 33 5.0 5.0 5.0 5.0	min = -1.5 for i-FIT = lons sults within O: 0-30 555,332,141 0 335 3 1.0 PPM 0.3	, max = 3 limits (u P: 1-1 346.1 7 40 345 -1.2 50.0 DBE 8.5	50.0 p to 20 bes 573 350 358 5 1-FI 3741	st isotopic ma 15265 19 358.1572 5 360 365 T Norm -2 n/a	368.1391 370 375 Conf (%)	ch mass) 378.1471 380 385 Formula	390	1: T 95.1390.398.166 395 400 40	06-Feb-20 TOF MS Es 4.43e+0 99 408.11 5 410

SYNAPT G2-S#UEB205 Y-JL15020621 23 (0.108) Cm (20:106)	MS265	06-Feb-2015 1: TOF MS ES+
100		4.4368
-		
-		
8	2	
347.1605		
257.0943		
122.9847 <sup>201.0317</sup> 348.1633 350.1319 479.3	2101 614.2442691.3066721.3167708.3708 959.3932 1066.4374 1143.5303	7 4701
0 100 200 300 400	500 600 700 800 900 1000 1100 1200	1300 1400 m/z

# (Z/E)-diethyl (2-((4-fluorobenzyl)amino)-2-phenylvinyl)phosphonate 12f

# (E/Z)-diethyl (2-((4-fluorobenzyl)imino)-2-phenylethyl)phosphonate 13f

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 90:10, respectively. Ratio of enamines (Z/E) **12f** equaled 86:14, respectively. Ratio of imines **13f** (E/Z) equaled 95:5, respectively.







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#### **Elemental Composition Report**

#### **Single Mass Analysis**

Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 1422 formula(e) evaluated with 2 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 F: 1-3 P: 1-1 SYNAPT G2-S#UEB205 MS298 06-Feb-2015 Y-JL15020619 52 (0.223) 1: TOF MS ES+ 3.37e+006 363.12 364.15 365.15 366.15 353.65 354.22 355.22 370.70 372.05 374.03 375.03 m/z 100 359.24 360.60 369.53 min 354.0 352.0 356.0 358.0 360.0 362.0 366.0 368.0 370.0 372.0 374.0 364.0 Minimum: -1.5 5.0 1.0 Maximum: 50.0 Calc. Mass mDa PPM DBE i-FIT Norm Conf(%) Formula Mass 364.1477 364.1478 -0.1 -0.3 364.1474 0.3 0.8 1124.2 0.000 100.00 C19 H24 N 03 F P 1136.1 11.921 0.00 C9 H22 N7 03 F3 P 8.5 1.5



# (*Z*/*E*)-(*S*)-diethyl (2-phenyl-2-((1-phenylethyl)amino)vinyl)phosphonate 12g

*(E/Z*)-(*S*)-diethyl (2-phenyl-2-((1-phenylethyl)imino)ethyl) phosphonate 13g

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 92:8, respectively. Ratio of enamines (Z/E) **12g** equaled 90:10, respectively. Ratio of imines **13g** (E/Z) equaled 70:30, respectively.





130 120 110 100 90 f1 (ppm) 210 200 . 140 . 60 . 30 -10 

<sup>1</sup>H NMR

COSY <sup>1</sup>H-<sup>1</sup>H



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#### **Elemental Composition Report**

#### **Single Mass Analysis**

Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 660 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 P: 1-1

SYNAPT G Y-JL150206	2-S#UEB205 625 48 (0.208)	)			264 f.10	D-16			06-Feb-2015 1: TOF MS ES+ 1 59e+006
100	182.0372	200.0477	228.0791	256.1104	293.0762	346.1577	360.1728	9 <sup>398.1291</sup> 435.2	241 453.2312
<b>V</b> minim	160 180	200	220 24	0 260	280 300	320 340	360 380	400 420 4	40 460
Minimum: Maximum:		5	5.0 1.1	-1.! 0 50.0	5 0				
Mass	Calc.	Mass n	nDa PPI	M DBE	i-FIT	Norm Con	f(%) Formula		
360.1728	3 360.17	- 29	0.1 -0	.3 8.5	915.0	n/a n/a	C20 H27	N 03 P	



# (Z)-diethyl (2-phenyl-2-(phenylamino)vinyl)phosphonate 12h

# (E/Z)-diethyl (2-phenyl-2-(phenylimino)ethyl)phosphonate 13h

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 67:33 respectively. Only (*Z*)-enamine was formed. Ratio of imines **13h** (*E*/*Z*) equaled 91:9, respectively.





23.58 23.37 21.43



140 120 100 80 60 40 20 0 -10 -50 f1 (ppm) -110 -140 -170 -200 -230 -30 -90 -70



7.23 7.23 7.23 7.24 7.25 



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#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 520 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 P: 1-1 SYNAPT G2-S#UEB205 MS316 06-Feb-2015 1: TOF MS ES+ 2.56e+008 Y-JL15020618 29 (0.131) Cm (19:101)

100-	dia kalimaka	an Carrier	n a na									332.1	4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	180.08 183.0	2 201.03	213.1	0 229.	06 240.0	6 25	7.09 2	76.08 286	.10 3	304.11	318.13		335.15
	180 190	200	210	220 23	0 240	250	260 270	280	290 30	0 310	320	330	340
Minimu Maximu	.m: .m:		5.0	1.0	-1.5 50.0								
Mass	Cal	c. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	) Formul	a			

332.1416 332.1416 0.0 0.0 8.5 3500.4 n/a C18 H23 N O3 P n/a



# (Z/E)-diethyl (2-((4-fluorophenyl)amino)-2-phenylvinyl)phosphonate 12i

# (Z/E)-diethyl (2-((4-fluorophenyl)imino)-2-phenylethyl)phosphonate 13i

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 63:37, respectively. Ratio of enamines (Z/E) **12i** equaled 99:1, respectively. Ratio of imines **13i** (E/Z) equaled 92:8, respectively.

















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#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 914 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 P: 1-1 F: 1-2

SYNAPT G2-S#UEB Y-JL15020620 47 (0.: 100-=122.98 201.03	205 205) 350.1	<sup>3</sup>	MS289		06-Feb-2015 1: TOF MS ES+ 8.82e+006
0 100 200	) 300	400 500 600	700 800 900	1013.58 11/4.46 1000 1100 1200	1397.70 m/z 1300 1400 1500
Minimum: Maximum:	5	-1.5 .0 1.0 50.0			

350.1321 C18 H22 N O3 P F 350.1320 -0.1 -0.3 8.5 1553.3 n/a n/a



## (Z)-diethyl (2-((2-fluorophenyl)amino)-2-phenylvinyl)phosphonate 12j

### (E/Z)-diethyl (2-((2-fluorophenyl)imino)-2-phenylethyl)phosphonate 13j

*Note*: Ratio of enamines **12** and imines **13** after column chromatography equaled 61:39, respectively. Only (*Z*)-enamine was formed. Ratio of imines **13**j (*E*/*Z*) equaled 80:20, respectively.














#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 527 formula(e) evaluated with 2 results within limits (up to 20 closest results for each mass) Elements Used: C: 1-150 H: 1-200 N: 0-50 O: 0-50 F: 1-1 P: 1-1 SYNAPT G2-S#UEB205 Y-JP15030909 3 (0.141) Cm (3:4) MS324 f20-24 000 40

100 31	1.08 320.0	07_322.10	329.13	331.13	343.14	4 350.13	359	.14 367.	08 374.13	376.11 384.09	386.09	396.12397.62
310	.0	320.0	330.	0	340.0	350.0	36	60.0	370.0	380.0	390.0	400.0
Minimum: Maximum:		1	.0	1.0	-1.5 50.0							
Mass	Calc.	Mass m	Da	PPM	DBE	i-FIT	Norm	Conf(%)	Formula			
350.1321	350.13 350.13	21 0 26 -	.0 0.5	0.0 -1.4	8.5 1.5	1388.8 1396.5	0.000 7.699	99.95 0.05	C18 H22 N C3 H18 N1	103 F P .304 F P		

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09-Mar-2015 1: TOF MS ES+ 1.74e+006



## Additional data for compounds 13 a-j

Table 1 <sup>1</sup> H I	NMR data for minor	(E/Z)-forms of	β-iminophos	phonates 13a-j
--------------------------	--------------------	----------------	-------------	----------------



R <sub>1</sub> : <b>a</b> = CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> , <b>b</b> = CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> , <b>c</b> = 4-OCH <sub>3</sub> Bn, <b>d</b> = 2-CH <sub>3</sub> Bn, <b>e</b> = Bn, <b>f</b> = 4-FBn, <b>g</b> = (S)-(CH <sub>3</sub> )CHPh, <b>h</b> = Ph	,
i= 4-FPh, j= 2-FPh	

	δ [ppm]	13a	13b	13c	13d	13e
H ( <i>E</i> )	(d) <sup>2</sup> ./ <sub>40</sub> [Hz]	3.38 23.4	3.41 23.4	3.40 23.4	3.53 23.4	3.53 23.4
H <sub>(Z)</sub>	(d) <sup>2</sup> J <sub>HP</sub> [Hz]	3.15 21.5	3.23 21.9	3.21 22.0	3.37 22.1	3.35 22.1
	δ [ppm]	13f	13g	13h	13i	13j
H ( <i>E</i> )	(d) <sup>2</sup> J <sub>HP</sub> [Hz]	3.50 23.4	3.34 3.33 23.3ª	3.32 23.3	3.30 23.3	3.33 23.4
			20.0			

<sup>a</sup> signal derived from non chemically equivalent protons (diastereotopic) observed as two pair of doublets with the same coupling constant

## (Z)-diethyl (1,1-difluoro-2-(heptylimino)-2-phenylethyl)phosphonate 14a







#### **Elemental Composition Report**

#### Single Mass Analysis

Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons

638 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass) Elements Used: C: 1-150 H: 1-200 N: 0-50 O: 0-50 F: 2-2 P: 1-1 SYNAPT G2-S#UEB205 MS331 UV Y-JP15030911 3 (0.141) Cm (3:4)

Y-JP15030911 3 (0.141) Cm (3:4)																		3	I: TOF I	MS ES+
100	100 293.08 0 290 300		315.06 326.19 334.14		.14	354.	354.22 362.17 372		2.21	.21 390.20		408.21_41		12.18 424.16442.42		450.31		468.30 474		
0 1	290	300	310	320	330	340	350	360	370	380	390	400	410	420	430	440	450	460	470	11112
Minim Maxim	um: um:			1.	0	1.0	-1. 50.	5 0												
Mass		Calc	. Mas	s mD	a	PPM	DBE	2	i-FIT	Nor	cm	Conf(%	5) F	ormula	1					
390.2	008	390.	2010	-0	. 2	-0.5	4 . 5	5	1722.1	n/a	a .	n/a	С	19 НЗ1	N 03	F2 P	,			

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## (Z)-diethyl (1,1-difluoro-2-(octylimino)-2-phenylethyl) phosphonate 14b











**Elemental Composition Report** 

#### Page 1

#### **Single Mass Analysis**

Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 1994 formula(e) evaluated with 2 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 F: 1-3 P: 1-1 SYNAPT G2-S#UEB205 Y-JL15020616 28 (0.127) Cm (18:89) MS302f.23-27 06-Feb-2015 1: TOF MS ES+ 2.69e+008 401.13 402.20 404.22 405.22 100 386.23 394.15 396.34 397.42 398.17 387.23 390.20 400.13 406.22408.22.408.65 392.16 386.0 388.0 390.0 392.0 394.0 396.0 398.0 400.0 402.0 404.0 406.0 408.0

Minimum: Maximum:		5.0	1.0	-1.5 50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula			
404.2163	404.2166 404.2160	-0.3 0.3	-0.7 0.7	4.5 1.5	3444.9 3463.7	0.000 18.817	100.00 0.00	C20 H33 N C8 H28 N1	03 F2 3 03 F	P P	



(1,1-difluoro-2-((4-methoxybenzyl)imino)-2-phenylethyl)

phosphonate 14c

(*Z*)-diethyl



<sup>31</sup>P NMR







#### HRMS

#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 753 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass) Elements Used: C: 1-150 H: 1-200 N: 0-50 O: 0-50 F: 2-2 P: 1-1 SYNAPT G2-S#UEB205 Y-JP15031604 3 (0.141) Cm (3:4) MS337 WU

Y-JP15031604	3 (0.141) Cm	(3:4)						1: TOF MS ES+ 5.39e+006						
100 390.15 394.18		408	8.16 412	2.15 414.15	42	8.12,430.18	444.14 450.10 452.10			466.21	474.07	481.64	484.19	492.19
385 390	395 400	40	5 410	415 42	0 425	430 435	440 445	450 45	5 460	465 4	70 475	480 4	485 490	11/2
Minimum: Maximum:			1.0	2.0	-1.5 50.0									
Mass	Calc. Ma	SS	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formu	la				
412.1483	412.1489		-0.6	-1.5	8.5	1821.1	n/a	n/a	C20 H	25 N 04	F2 P			

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16-Mar-2015

SYNAPT G2-S#UEB205	MS337 WU	16-Mar-2015
Y-JP15031604 3 (0.141) Cm (3:4)	412.15	1: TOF MS ES+ 5.39e6
-		
-		
-		
~		
0		
-		
	413.15	
394.18	414.15 428.12 430.18	
390.15 395.18 408.16	415.16 426.16 434.13 444.14 450.10451.25 460.13 466.21 474.07 481.64	84.19 492.19 m/z
385 390 395 400 405	410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 4	85 490

# (*Z)*-diethyl

(1,1-difluoro-2-((2-methylbenzyl)imino)-2-phenylethyl)

phosphonate 14d













#### **Elemental Composition Report**

#### Single Mass Analysis Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 664 formula(e) evaluated with 2 results within limits (up to 20 closest results for each mass) Elements Used: C: 1-150 H: 1-200 N: 0-50 O: 0-50 F: 2-2 P: 1-1 SYNAPT G2-S#UEB205 MS339 WU Y-JP15031605 4 (0.175) Cm (3:4)

SYNAPT G2- Y-JP1503160	S#UE 5 4 (0	EB205 ().175) C	Cm (3:4)				MS	339 WU		16-Mar-2015 1: TOF MS ES+ 3 48e+007					
100 315	.06	332.14	339.19	357.20	360.17	378.16	396.15	412.12	418.14 4	34.11 445.26 462	2.22	482.23	496.20 m	/z	
310	320	330	340	350	360	370 380	390 40	0 410	420 430	0 440 450 460	470	480 4	190 500	-	
Minimum: Maximum:				1.0	2.0	-1.5 50.0									
Mass	Ca	alc. N	lass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula					
396.1540	39	96.15	40 45	0.0 -0.5	0.0 -1.3	8.5 1.5	1992.0 2015.5	0.000 23.474	100.00 0.00	C20 H25 N O3 F C5 H21 N13 O4	'2 P F2 P				

Y-JP15031605 4 (0.175) Cm (3:4) 100 396.15 3.4867
<u>%</u>
397.16
360.17
237.01
105.07 203.08 410.19.482.23 777.30 203.0
0

#### Page 1

## (Z)-diethyl (2-(benzylimino)-1,1-difluoro-2-phenylethyl)phosphonate 14e









## HRMS

Elemental	Compositio	n Repo	rt				Page 1
Single Mas Tolerance = Element pre Number of is	ss Analysis 1.0 PPM / I diction: Off sotope peaks	DBE: min used for i	= -1.5, max = 5 -FIT = 3	50.0			
Monoisotopic 1662 formula Elements Use C: 5-100 H SYNAPT G2-S Y-JL15020615	Mass, Even Ek (e) evaluated w ed: 1: 0-100 N: C #UEB205 29 (0.131) Cm (1	ectron lons ith 1 result )-30 O: 9:85)	s ts within limits (up 0-30 F: 1-3	o to 20 best isotopic P: 1-1 MS313f.103-108	matches for each r	nass)	06-Feb-2015 1: TOF MS ES+ 1.60e+008
100 373.1	0 374.34	376.09	378.13.378.44	380.12 381.13	382.14 383.14 384.1	4 385.15 386.11	387.12 388.13388.39,
• <b>•</b> •••••	374.0	376.0	378.0	380.0	382.0 384.0	386.0	388.0
Minimum: Maximum:		5.0	-1.5 1.0 50.0				
Mass	Calc. Mass	mDa	PPM DBE	i-FIT Norr	n Conf(%) For	mula	
382.1384	382,1384	0.0	0.0 8.5	3297.8 n/a	n/a C19	H23 N 03 F2	P



# (*Z*)-diethyl

## (1,1-difluoro-2-((4-fluorobenzyl)imino)-2-phenylethyl)

phosphonate 14f



<sup>31</sup>P NMR







**Elemental Composition Report** Page 1 **Single Mass Analysis** Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3 Monoisotopic Mass, Even Electron lons 1936 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 F: 1-3 P: 1-1 SYNAPT G2-S#UEB205 Y-JL15020614 34 (0.150) Cm (19:108) MS308 f.20-28 06-Feb-2015 1: TOF MS ES+ 3.18e+008 400.13 401.13 403.14 406.23 407.24 411.11 412.09 414.11 m/z 380.12 382.14 383.14 386.11 388.13 390.07 392.22 393.22 396.24 398.17 100 405.0 380.0 385.0 390.0 395.0 400.0 410.0 Minimum: -1.5 Maximum: 5.0 1.0 50.0 Mass Calc. Mass mDa PPM DBE i-FIT Norm Conf(%) Formula 400.1291 400.1289 0.2 3525.0 n/a C19 H22 N O3 F3 P 0.5 8.5 n/a SYNAPT G2-S#UEB205 Y-JL15020614 34 (0.150) Cm (19:108) 06-Feb-2015 1: TOF MS ES+ 3.18e8 MS308 f.20-28 400.13 100



## (1,1-difluoro-2-phenyl-2-((1-phenylethyl)imino)ethyl)

# (*S,Z)*-diethyl phosphonate 14g









Page 1

1.32e+008

#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 1869 formula(e) evaluated with 2 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 F: 1-3 P: 1-1 SYNAPT G2-S#UEB205 MS Y-JL15020617 29 (0.131) Cm (17:107) MS279f.22-34 06-Feb-2015 1: TOF MS ES+ 396.15 100 292.09 308.06

10%-1	80.06	21.	218.02	236.03	1	264.06		292.09	3	08.06	333.1	1 35	57.20	382.14		1.	418.1	4	4	54.20	4/1	1.08	486.0	5
• • • • •	180	200	220	240	2	260	280	300		320	3	340	360	38	0	400	420	)	440	460	) 4	180		12
Minim	um:							-1.5																ç,
Maxim	um:			5.	0	1.0		50.0																
Mass	. <sup>н</sup>	Calc	. Mas	s mD	a	PPM		DBE		i-Fl	T	Norr	n .	Conf	(응)	For	nula					i yezi	۱. 	
396.15	537	396.	1540	-0	.3	-0.	8	8.5		3253	.3	0.00	00	100.0	00	C20	H25	N O	3 F2	P				
		396.	1534	. 0.	3	0.8		5:5		3267	. 9	14.	48	0.00		C8	120 N	13 (	) 3 F	P				



## (Z)-diethyl (1,1-difluoro-2-phenyl-2-(phenylimino)ethyl)phosphonate 14h







HRMS

Elemental Composition Report	Page 1
Single Mass Analysis Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3	
Monoisotopic Mass, Even Electron lons 1724 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 F: 1-3 P: 1-1 SYNAPT G2-S#UEB205 MS303 f.11-15 Y-JL15020612 28 (0.127) Cm (19:64)	06-Feb-2015 1: TOF MS ES+ 1.01e+008
100 237.01 265.04 293.08 330.05 358.08 398.17 420.13 459.18 477.16 513.17	550.22 568.21
220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520	540 560
Minimum: -1.5 Maximum: 5.0 1.0 50.0	
Mass Calc. Mass mDa PPM DBE i-FIT Norm Conf(%) Formula	
386.1136 386.1133 0.3 0.8 8.5 3065.7 n/a n/a C18 H20 N O3 F3 P	



(1,1-difluoro-2-((4-fluorophenyl)imino)-2-phenylethyl)

phosphonate 14i

(Z)-diethyl





- 20.03 - 5.31 - 5.31 - 5.31 - 4.69 - 4.69 - 4.22 - 3.63 - 3.63 - 1.41 - 1.41








Elementa	I Comp	ositio	n Repor	t										Page 1
Single Ma Tolerance = Element pro Number of	ass Ana = 1.0 PP ediction: isotope	alysis PM / E Off peaks u	)BE: min Ised for i-	= -1.5, ma FIT = 3	ax = 50.0	) )								
Monoisotopi 1724 formula Elements Us C: 5-100 SYNAPT G2- Y-JL15020612	c Mass, I a(e) eval sed: H: 0-100 S#UEB20 2 28 (0.12	Even Ele uated wit 0 N: 0- 5 7) Cm (19	ctron lons th 1 results -30 O: 0 9:64)	s within lim )-30 F:	its (up to 1-3 P:	20 bes 1-1 MS303	t isotopic r f.11-15	natches	for each	ı mass	)		06 1: TOF 1	Feb-2015 MS ES+ 1.01e+008
100	237.01	265.04	293.08	330.05	358.08	386.	11 398.17	420.13	459.18	477.	<sup>16</sup> 513.	.17	550.22	568.21
220	240	260 2	80 300	320 3	40 360	380	400 42	20 440	460	480	500	520 54	0 560	
Minimum: Maximum:			5.0	1.0	-1.5 50.0									
Mass	Calc.	Mass	mDa	PPM	DBE	i-FIT	Norm	Conf	(%) Fo	rmula				
386.1136	386.1	133	0.3	0.8	8.5	3065.	7 n/a	n/a	C1	8 H20	N 03	F3 P		



# (*Z*)-diethyl

## (1,1-difluoro-2-((2-fluorophenyl)imino)-2-phenylethyl)

phosphonate 14i



## <sup>19</sup>F NMR {H}



## <sup>13</sup>C NMR



### HRMS

#### **Elemental Composition Report**

#### Single Mass Analysis

Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 494 formula(e) evaluated with 2 results within limits (up to 20 closest results for each mass) Elements Used: C: 1-150 H: 1-200 N: 0-50 O: 0-50 F: 3-3 P: 1-1 SYNAPT G2-S#UEB205 MS325 f8-15 Y-JP15030908 3 (0.141) Cm (2:4)

Y-JP1503090	08 3 (0.141)	, Cm (2:4	4)			Moc	201010		1: TOF MS ES- 2.65e+00				
100 333.0	7 341.31	354	.22	368.123	74.05 384.1	5386.11	394.14 4	02.08404.08	418.05 424.	07426.06	437.19_440.	04 450.09 <sup>453.1</sup>	17 /z
	340	350	360	370	380	390	9 40	0 41	0 420	430	440	450	
Minimum: Maximum:			1.0	1.0	-1.5 50.0								
Mass	Calc.	Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula				
386.1137	386.1 386.1	133 138	0.4 -0.1	1.0 -0.3	8.5 1.5	980.5 993.3	0.000	100.00 0.00	C18 H20 N ( C3 H16 N13	03 F3 P 04 F3 P	,		

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09-Mar-2015



### III. By-products of electrophilic fluorination - diagnostic data



By-products:



### Diagnostic signals for 2,2-difluoro-1-phenylethanone 19

<sup>1</sup>H NMR (CDCI<sub>3</sub>):  $\delta_{H_{\sim}}$  6.3 (t, <sup>2</sup>J<sub>HF</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ -122.6 (d, <sup>2</sup>J<sub>FH</sub> = 53.5 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>):  $\delta_{F_{\sim}}$ Hz, 2F)

### **Diagnostic signals for 20**

<sup>1</sup>H NMR (CDCI<sub>3</sub>): δ= 6.2 (t, <sup>2</sup>J<sub>HF</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ -118.1 (d, <sup>2</sup>J<sub>FH</sub> = 55.4 Hz, 1H), <sup>19</sup>F NMR (CDCI<sub>3</sub>): δ=  $_{\sim}$ Hz, 2F)

### **Diagnostic signals for 21**

<sup>19</sup>**F NMR (CDCI<sub>3</sub>):** δ= -81.1 (d,  ${}^{2}J_{FP}$  966 Hz, 1F), <sup>31</sup>**P NMR (CDCI<sub>3</sub>):** δ= -9.2 (d,  ${}^{2}J_{PF}$  966 Hz, 1P), **GC-MS**: m/z = 156.1 [M<sup>+</sup>]; retention time: 6 min

### **Diagnostic signals for 22**

 $^{19}\text{F}$  NMR (CDCl\_3):  $\delta_{F\,\sim}$  -71.6 (s)

### diethyl (1,1-difluoro-2-(heptylamino)-2-phenylethyl)phosphonate 15a



### <sup>1</sup>H NMR







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#### Elemental Composition Report

#### **Single Mass Analysis**

Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 2649 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 F: 0-3 P: 1-1 SYNAPT G2-S#UEB205 MS314 f.4-6 06-Feb-2015 Y-JL15020606 42 (0.180) 1: TOF MS ES+ 4.62e+006 392.22 393.22 395.22 398.17 399.17 402.54.403.17 406.23 408.19 410.18 411.18 m/z 100 379.21 382.41384.15 386.13 388.39 390.20 Ling T 1 380.0 382.5 395.0 397.5 385.0 387.5 390.0 400.0 402.5 405.0 407.5 410.0 392.5 Minimum: -1.5 Maximum: 5.0 1.0 50.0

Mass Calc. Mass mDa PPM DBE i-FIT Norm Conf(%) Formula

392.2166 392.2166 0.0 0.0 3.5 1206.3 n/a n/a C19 H33 N O3 F2 P





## diethyl (1,1-difluoro-2-(octylamino)-2-phenylethyl)phosphonate 15b





<sup>1</sup>H NMR



Page 1

#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 2956 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) 
 Elements Used:
 C: 5-100
 H: 0-100
 N: 0-30
 O: 0-30
 F: 0-3
 P: 1-1

 SYNAPT G2-S#UEB205
 MS

 Y-JL15020607 28 (0.127) Cm (20:80)
 MS
 06-Feb-2015 1: TOF MS ES+ 2.73e+008 MS310f.7-12 106 22

100 387.23	388.12	390.20	392.22	393.22	396.42	398.17	399.17	402.27	404.22	400.23	407.24 409	3.24 410.24	1
386.0	388.0	390.0	392.0	394.0	396.0	398.0	400.0	402.0	404.0	406.0	408.0	410.0	H 11/2
Minimum:					-1.5							1.44	

Maximum: 5.0 1.0 50.0

i-FIT Norm Calc. Mass mDa PPM DBE Conf(%) Formula Mass

406.2325 406.2323 0.2 0.5 3.5 3499.1 n/a n/a C20 H35 N O3 F2 P



(1,1-difluoro-2-((4-methoxybenzyl)amino)-2-phenylethyl)

phosphonate 15c

diethyl











110 100 f1 (ppm) 130 120 

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06-Feb-2015

#### **Elemental Composition Report**

#### **Single Mass Analysis**

Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 2159 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 F: 1-3 P: 1-1 SYNAPT G2-S#UEB205 MS315 Y-JL15020610 25 (0.115) Cm (20:96)

Y-JL15020610 2	5 (0.115) Cm (20.96)					: TOF MS ES+ 1.42e+008
100 374.15	382.14 384.15 388.13 392.22	398.17 402.14 406.23	412.15 414.16 416.17 4	19.35 428.18 43	0.13 432.13 436	.15 441.17
	380.0 390.0	400.0	410.0 420.	0 43	30.0	440.0
Minimum: Maximum:	5.0 1.0	-1.5 50.0				
Mass	Calc. Mass mDa PPM	DBE i-FIT	Norm Conf(%)	Formula		

414.1645 414.1646 -0.1 -0.2 7.5 3192.6 n/a n/a C20 H27 N 04 F2 P



## (1,1-difluoro-2-((2-methylbenzyl)amino)-2-phenylethyl)

phosphonate 15d

diethyl









<sup>1</sup>H NMR

77.33 33.57 33.52 34.57 37.73 37.73 37.73 37.73 37.73 37.73 37.73 37.73 37.73 37.73 37.73 37.73 37.73 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75 37.75





#### **Elemental Composition Report**

#### Page 1

Single	Mass	Analys	sis	
Toloran		DDM	/ DE	E mi

Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

 Monoisotopic Mass, Even Electron Ions

 1897 formula(e) evaluated with 2 results within limits (up to 20 best isotopic matches for each mass)

 Elements Used:

 C: 5-100
 H: 0-100
 N: 0-30
 C: 0-30
 F: 1-3
 P: 1-1

 SYNAPT G2-S#UEB205
 MS293 f.9-15
 06-Feb-2015

 Y-JL15020611 24 (0.111) Cm (18:94)
 1: TOF MS ES+

 3381 14
 389 13
 395 12 core
 398.17 399.17 401 18 403 15
 407 24 409 32
 417 14

100-381.	14 384.15 385.16 38 385.0	38.13 <sup>389.13</sup> 390.0	392.22 39	395.0	15	400.0	403.15 40 405.0	6.23407.24	409.32 <sub>41</sub> 410.0	2.19414.144 415.0	<u>16.14</u> 417.14 m/z
Minimum: Maximum:		5.0	1.0	-1.5 50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula			
398.1693	398.1697 398.1690	-0.4 0.3	-1.0 0.8	7.5 4.5	3546.2 3564.9	0.000 18.688	100.00 0.00	C20 H27 C8 H22	N 03 F N13 03	2 P F P	



2-M8A

## diethyl (2-(benzylamino)-1,1-difluoro-2-phenylethyl)phosphonate 15e













-110.5 -111.5 f1 (ppm)

-10

-20

en de se la contra de la contra d

-40

-50

-60

-70

-80

-30

-121.0 -121.5 -122.0 -122.5 f1 (ppm)

1.00 1.00 -130 -120

ويوجز المتأولية الأل فالرويدين وبالألا أيطا بالتلفية فيتأقر أياد فيواطعهم

-160

-170

-180

-190

-140

-150

-100 f1 (ppm) -90 -110

### <sup>1</sup>H NMR





#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off

Number of isotope peaks used for i-FIT = 3

 Monoisotopic Mass, Even Electron Ions

 600 formula(e) evaluated with 2 results within limits (up to 20 closest results for each mass)

 Elements Used:

 C: 1-150
 H: 1-200

 SYNAPT G2-S#UEB205

 YJP15030906 10 (0.437) Cm (10:11)

 100

 950.07

 950.07

 950.07

 950.07

 950.07

 950.07

100 329	01 331.18 3	339.10 341.3	0 353.27 356	12365.113	67.13 <sup>370.1</sup>	4 00	386.16	400.12	402.12	410.1341	8.11.42	0.11	430.92 m/z
320 325	5 330 335	340 345	350 355	360 36	5 370 3	375 380	385 390	395 400	405 41	0 415	420	425	430
Minimum: Maximum:		1.0	1.0	-1.5 50.0									
Mass	Calc. Ma	iss mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula					
384.1541	384.1540	0.1 -0.4	0.3 -1.0	7.5	1651.5 1675.0	0.000	100.00	C19 H25 C4 H21 N	N 03 F: 113 04 1	2 P F2 P			



Page 1

## diethyl

## (1,1-difluoro-2-((4-fluorobenzyl)amino)-2-phenylethyl)

phosphonate 15f









<sup>1</sup>H NMR

## 



## <sup>13</sup>C NMR



### HRMS

Elemental	Composi	tion Repo	rt (j. d. j. j.					Pa	ge 1
Single Ma Tolerance = Element pre Number of i	ss Analys 1.0 PPM ediction: Off sotope peal	<b>is</b> / DBE: min <s for="" i<="" th="" used=""><th>= -1.5, max = -FIT = 3</th><th>50.0</th><th></th><th></th><th></th><th></th><th></th></s>	= -1.5, max = -FIT = 3	50.0					
Monoisotopic 1969 formula Elements Us C: 5-100 I SYNAPT G2-S Y-JL15020608	C Mass, Even (e) evaluated ed: H: 0-100 N S#UEB205 52 (0.223)	Electron Ion d with 2 resul I: 0-30 O:	s ts within limits (u 0-30 F: 1-3	p to 20 best is P: 1-1 MS297\	sotopic matches fo	r each mass)		06-Feb- 1: TOF MS 1.45e	2015 ES+ +006
100 38	384.15	390.15	392.22,393.22	4 398.17	403.15 406.2	<sup>3</sup> 408.24 412.09	416.12	418.11 420.11 4	22.37
380.0	385.0	390.0	395.0	400.0	405.0	410.0	415.0	420.0	m/z
Minimum: Maximum:		5.0	-1.5 1.0 50.0						
Mass	Calc. Ma	ss mDa	PPM DBE	i-FIT	Norm Conf (	) Formula			
402.1445	402.1446	-0.1	-0.2 7.5	735.4	0.004 99.58	C19 H24	N 03 F3	P	



(*R*/*S*)-diethyl (1,1-difluoro-2-phenyl-2-(((*S*)-1-phenylethyl)amino) ethyl) phosphonate 15g



<sup>19</sup>F NMR {H}



## <sup>13</sup>C NMR



#### HRMS

#### **Elemental Composition Report**

Page 1

Single Mass Analysis Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 2789 formula(e) evaluated with 3 results within limits (up to 20 best isotopic matches for each mass) Elements Used: C: 5-100 H: 0-100 N: 0-30 O: 0-30 F: 0-3 P: 1-1 SYNAPT G2-S#UEB205 Y-JL15020605 36 (0.157) Cm (19:117) MS282 06-Feb-2015 1: TOF MS ES+ 3.30e+008

100 359.2120 370.1380 380.1787 384.1537 398.1693 401.1776	414.1398420.1512 <sup>429.2401</sup> 436.1251 441.1749
360.0 370.0 380.0 390.0 400.0 4	10.0 420.0 430.0 440.0
Minimum: -1.5 Maximum: 5.0 1.0 50.0	
Mass Calc. Mass mDa PPM DBE i-FIT Norm Co	onf(%) Formula
398.1693         398.1697         -0.4         -1.0         7.5         3599.4         0.000         1           398.1692         0.1         0.3         2.5         3619.6         20.189         0           398.1690         0.3         0.8         4.5         3626.2         26.811         0	00.00 C20 H27 N O3 F2 P .00 C14 H29 N3 O8 P .00 C8 H22 N13 O3 F P





<sup>19</sup>F{<sup>1</sup>H} NMR of 15g in acetonitrile (CD<sub>3</sub>CN)

Major



<sup>19</sup>F{<sup>1</sup>H} NMR of 15g in chloroform (CDCl<sub>3</sub>)

diethyl (1,1-difluoro-2-phenyl-2-(phenylamino)ethyl)phosphonate 15h




<sup>19</sup>F NMR



<sup>1</sup>H NMR



#### HRMS

Page 1

#### **Elemental Composition Report**

### Single Mass Analysis

Tolerance = 1.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

 Monoisotopic Mass, Even Electron Ions

 2220 formula(e) evaluated with 2 results within limits (up to 20 best isotopic matches for each mass)

 Elements Used:

 C: 5-100
 H: 0-100
 N: 0-30
 O: 0-30
 F: 0-3
 P: 1-1

 SYNAPT G2-S#UEB205
 MS321 WV
 06-Feb-2015

 Y-JL15020604 31 (0.138)
 1: TOF MS ES+

 100
 182.0970221.0179
 502.2070
 686.2036
 761.2518
 839.1979
 952.3841
 1070.4446
 1172.4602

0	TITITITITITI	TITTTTTT	002.2070	TITETT	101.2010			1.	/11/2.40	02		
100	200 300	400	500 6	00 7	700 80	00 900	0 1000	1100	1200	1300	1400	1500
Minimum: Maximum:		5.0	1.0 5	1.5 0.0								
Mass	Calc. Mass	mDa	PPM D	BE	i-FIT	Norm	Conf(%)	Formula				i sa ba Agente
370.1382	370,1384 370,1379	-0.2 0.3	-0.5 7 0.8 2	.5 .5	1180.8 1194.8	0.000 14.014	100.00	C18 H23 C12 H25	N 03 E N3 08	72 P P		



## (1,1-difluoro-2-((4-fluorophenyl)amino)-2-phenylethyl)

diethyl phosphonate 15i









## <sup>19</sup>F NMR



## <sup>13</sup>C NMR



HRMS

Ele

montal Compositio

m.

Elemental compositio	пкероп				Page 1
Single Mass Analysis Tolerance = 1.0 PPM / Element prediction: Off Number of isotope peaks u	DBE: min = -1.5, m used for i-FIT = 3	nax = 50.0			
Monoisotopic Mass, Even Ele 1757 formula(e) evaluated wi Elements Used: C: 5-100 H: 0-100 N: 0 SYNAPT G2-S#UEB205 Y-JL15020609 21 (0.100)	ectron lons th 1 results within li -30 O: 0-30 F:	mits (up to 20 best it 1-3 P: 1-1 MS304 f.	otopic matches for 5-17	each mass)	06-Feb-2015 1: TOF MS ES+ 2 59e+006
100 325.12 332.07 <sub>339.13</sub>	348.12 357.12	360.10368.16 370.14	374.11 384.12 38	38.13 390.14	402.15_404.10 410.11 416.09
330.0 340.0	350.0	360.0 370.0	380.0	390.0 40	0.0 410.0
Minimum: Maximum:	5.0 1.0	-1.5 50.0			
Mass Calc. Mass	mDa PPM	DBE i-FIT	Norm Conf(%)	Formula	
388,1289 388,1289	0.0 0.0	7.5 897.4	n/a n/a	C18 H22 N O	3 F3 P



## (1,1-difluoro-2-((2-fluorophenyl)amino)-2-phenylethyl)

diethyl phosphonate 15j





-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 f1 (ppm) -20 -30 -40 -50



## <sup>13</sup>C NMR



#### HRMS

#### **Elemental Composition Report**

Single Mass Analysis Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 499 formula(e) evaluated with 2 results within limits (up to 20 closest results for each mass) Elements Used: C: 1-150 H: 1-200 N: 0-50 O: 0-50 F: 3-3 P: 1-1 SYNAPT G2-S#UEB205 Y-JP15030910 3 (0.141) Cm (3:4) MS326 f7-12

SYNAPT G2-Si Y-JP15030910	#UEB205 3 (0.141) Cm (3:4	4)			MS3	326 f7-12					09-Mar-2015 1: TOF MS ES+ 4.04e+006
100 <u>360.10</u> 36 360.0	<sup>52.11</sup> 368.12 3 370.0	74.11	381.30 384 380.0	388.13 <sub>390</sub> 4.15 390.0	.13 40	00.68 404 400.0	. <u>10 410.1</u> 410.0	<u>1 415.21</u> )	422.09426.0 420.0	8 <sup>428.08</sup> 430.0	437.19 440.0
Minimum: Maximum:		1.0	1.0	-1.5 50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula			
388.1291	388.1289 388.1294	0.2 -0.3	0.5 -0.8	7.5 0.5	1865.0 1882.0	0.000 17.018	100.00 0.00	C18 H22 C3 H18 1	N 03 F3 P N13 04 F3 P		



## **IV.Additional information**

*Note:* Due to the fact that some cases of **14** were contaminated by **17** the crude reaction mixture contained traces of diethyl (1,1-difluoro-2-hydroxy-2-phenylethyl)phosphonate **18 (scheme 1)**. Diagnostic signals for **18**:  $\delta_{F}$ : -125.46 (ddd,  ${}^{2}J_{FF} = 304.9 \text{ Hz}$ ,  ${}^{2}J_{FP} = 105.5 \text{ Hz}$ ,  ${}^{3}J_{FH} = 20.3 \text{ Hz}$ , 1F), -115.18 (ddd,  ${}^{2}J_{FF} = 304.9 \text{ Hz}$ ,  ${}^{2}J_{FP} = 100.1 \text{ Hz}$ ,  ${}^{3}J_{FH} = 6.3 \text{ Hz}$ , 1F);  $\delta_{P}$ : 6.82 (dd,  ${}^{2}J_{PF} = 105.5 \text{ Hz}$ ,  ${}^{2}J_{PF} = 100.1 \text{ Hz}$ , 1P);  $R_{f} = 0.1$ . The separation of  $\alpha, \alpha$ -difluoromethylene- $\beta$ -aminophosphonates **15** from **18** has been relatively easy to handle due to 0.35 difference in  $R_{f}$  (hexane:ethyl acetate 7:3).

### difluoro-2-hydroxy-2-phenylethyl)phosphonate 18



Scheme 1 Reduction of  $\beta$ -ketophosphonate 17 with the use of NaBH<sub>3</sub>CN reagent

## V. Tables

Table 1 <sup>31</sup>P, <sup>13</sup>C, <sup>1</sup>H NMR  $\delta$  for major (*Z/E*)-form of  $\beta$ -enaminophosphonates 12a-j.

				R <sup>1</sup> NH	O , P(OEt)₂	H.		D II P(OEt) <sub>2</sub>			
				(Z) <b>-12</b>			(E) <b>-12</b>				
	δ [ppm]	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j
Р	(s) <i>J</i> [Hz]	25.87	25.89	25.09	25.26	24.96	24.87	24.98	23.58	23.64	22.87
C <sub>a(Z)</sub>	(δ)	75.2	75.1	77.8	77.4	77.8	78.5	79.1	84.4	84.0	84.0
	<sup>1</sup> J <sub>CP</sub> [Hz]	189.8	189.7	188.5	189.1	188.5	188.5	188.1	187.3	187.5	187.5
C <sub>a(E)</sub>	(δ)	75.4	75.5	76.7	76.8	77.1	77.5	78.7	-	-	-
	<sup>1</sup> <i>J</i> <sub>CP</sub> [Hz]	218.3	218.4	217.4	217.6	217.4	217.3	217.7			
$C_{\beta(Z)}$	(δ)	167.0	167.0	166.6	166.7	166.7	166.5	166.4	160.7	159.3	161.0
	<sup>2</sup> J <sub>CP</sub> [Hz]	7.0	7.1	6.8	6.8	6.8	6.7	6.8	5.5	5.0	5.8
$C_{\beta(E)}$	(δ)	160.7	160.7	160.3	_	_	137.4	138.1	137.3	136.0	137.1
	<sup>2</sup> J <sub>CP</sub> [Hz]	17.7	17.6	17.5			20.0	20.1	19.4	19.1	19.6
C <sub>ipso(Z)</sub>	(δ)	138.1	138.0	137.6	137.7	137.6	160.2	-	-	-	-
	<sup>3</sup> Ј <sub>СР</sub> [Hz]	20.1	20.1	20.0	19.9	20.1	17.5				
H <sub>(Z)</sub>	(δ)	3.67	3.75	3.80	3.91	3.83	3.93	3.81	4.30	4.41	4.28
	<sup>2</sup> J <sub>HP</sub> [Hz]	13.3	13.3	13.1	13.0	13.0	13.0	13.1	12.3	12.1	12.2
$H_{(E)}$	(δ)	4.10	4.18	4.16	4.33	4.30	4.26	_	_	4.66	
	<sup>2</sup> J <sub>HP</sub> [Hz]	9.4	9.4	9.1	9.2	9.0	9.4	-	-	8.9	-

 $R^{1}: \boldsymbol{a} = CH_{3}(CH_{2})_{6}, \boldsymbol{b} = CH_{3}(CH_{2})_{7}, \boldsymbol{c} = 4-MeOC_{6}H_{4}CH_{2}, \boldsymbol{d} = 2-MeC_{6}H_{4}CH_{2}, \boldsymbol{e} = Bn, \boldsymbol{f} = 4-FC_{6}H_{4}CH_{2}, \boldsymbol{g} = (S)-Ph(CH_{3})CH, \boldsymbol{h} = Ph, \boldsymbol{i} = 4-FC_{6}H_{4}, \boldsymbol{j} = 2-FC_{6}H_{4}$ 

## Table 2 <sup>31</sup>P NMR of compounds 12-(*Z*:*E*) and 13-(*E*:*Z*)

Entry	Compound	$R^1$	<b>12</b> enamine (Z:E) / <b>13</b> imine (E:Z) <sup>a</sup>	<sup>31</sup> P NMR for <i>major</i> 12 ( <i>Z</i> )-enamine / 13 ( <i>E</i> )-imine	<sup>31</sup> P NMR for <i>minor</i> <b>12</b> ( <i>E</i> )- enamine / <b>13</b> ( <i>Z</i> )-imine
1	12-13a	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub>	92(85:15) / 8(85:15)	25.87 / 22.40	24.74 / 24.24
2	12-13b	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	93(87:13) / 7(80:20)	25.89 / 22.41	24.82 / 24.26
3	12-13c	4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	91(83:17) / 9(81:19)	25.09 / 22.16	24.30 / 24.07
4	12-13d	$2-\text{MeC}_6\text{H}_4\text{CH}_2$	91(84:16) / 9(77:23)	25.26/22.27	24.25 / 24.14
5	12-13e	Bn	91(84:16) / 9(95:5)	25.10 / 22.14	24.05 / 23.72
6	12-13f	4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	90(86:14) / 10(95:5)	24.87 / 22.00	23.88 / 24.27
7	12-13g	(S)-Ph(CH <sub>3</sub> )CH	92(90:10) / 8(70:30)	24.98 / 22.14	23.88 / 23.97
8	12-13h	Ph	67 / 33(91:9)	23.58 / 21.43	- / 23.37
9	12-13i	4-FC <sub>6</sub> H <sub>4</sub>	63(99:1) / 37(92:8)	23.64 / 21.32	24.87 / 23.23
10	12-13j	2-FC <sub>6</sub> H <sub>4</sub>	61 / 39(80:20)	23.03 / 20.92	- / 23.74

<sup>a</sup> Ratio has been assigned on the basis of  $\square$  <sup>31</sup>P NMR in CDCl<sub>3</sub> after column chromatography.

# Table 3 <sup>1</sup>H NMR data for minor (*E*/Z)–forms of $\beta$ –iminophosphonates 13a-j



 $\mathsf{R}_1: \mathbf{a} = \mathsf{CH}_3(\mathsf{CH}_2)_6, \mathbf{b} = \mathsf{CH}_3(\mathsf{CH}_2)_7, \mathbf{c} = 4 - \mathsf{OMeC}_6\mathsf{H}_4\mathsf{CH}_2, \mathbf{d} = 2 - \mathsf{Me} \ \mathsf{C}_6\mathsf{H}_4\mathsf{CH}_2, \mathbf{e} = \mathsf{Bn}, \mathbf{f} = 4 - \mathsf{F} \ \mathsf{C}_6\mathsf{H}_4\mathsf{CH}_2, \mathbf{g} = (S) - \mathsf{Ph}(\mathsf{CH}_3)\mathsf{CH}, \mathbf{h} = \mathsf{Ph}, \mathbf{i} = 4 - \mathsf{F} \ \mathsf{C}_6\mathsf{H}_4, \mathbf{j} = 2 - \mathsf{F} \ \mathsf{C}_6\mathsf{H}_4$ 

	δ [ppm]	2.6a	2.6b	2.6c	2.6d	2.6e
H (E)	(d)	3.38	3.41	3.40	3.53	3.53
	<sup>2</sup> J <sub>HP</sub> [Hz]	23.4	23.4	23.4	23.4	23.4
H (Z)	(d)	3.15	3.23	3.21	3.37	3.35
	<sup>2</sup> J <sub>HP</sub> [Hz]	21.5	21.9	22.0	22.1	22.1
	δ [ppm]	2.6f	2.6g	2.6h	2.6i	2.6j
	(d)	3 50	3.34	3 32	3 30	3 33
H (E)	$^{2}J_{\text{up}}[\text{Hz}]$	23.4	3.33	23.3	23.3	23.4
	OHP [=]	2011	23.3 <sup>a</sup>	2010	2010	2011
Н.,_	(d)	3.32	3.20	3.39	3.37	3.26
11 (Z)	<sup>2</sup> J <sub>HP</sub> [Hz]	22.1	22.1	22.5	22.5	22.9

<sup>a</sup> signal derived from non chemically equivalent protons (diastereotopic) observed as two pair of doublets with the same coupling constance

## Table 4 <sup>31</sup>P, <sup>13</sup>C, <sup>1</sup>H NMR data for $\alpha, \alpha$ -difluoromethylene- $\beta$ iminophosphonates 14

	$ \begin{array}{c}                                     $													
	14a δ [ppm]	14b	14c	14d	14d	14 14e	14f	14g <sup>ibj</sup>	14h	14i	14j			
Р	(t)	5.82	5.85	5.75	5.63	5.60	5.64	5.73	5.29	5.31	4.83			
F <sup>[a]</sup>	(d)	-107.31	-107.31	-107.7	-107.2	-107.17	-107.40	-107.9	-107.10	-107.24	-107.44			
Cα	<sup>2</sup> J <sub>FP</sub> [Hz] (td)	101.7 116.4	101.7 116.4	100.7 116.5	100.5 114.8	100.6 116.5	100.6 116.4	101.6 116.3	100.4 114.9	100.5 116.5	100.2 116.2			
	<sup>1</sup> J <sub>CF</sub> [Hz] <sup>1</sup> J <sub>CP</sub> [Hz]	265.2 212.6	265.4 212.5	265.4 212.4	265.7 213.2	265.7 212.8	265.8 212.8	265.5 212.4	267.0 212.2	267.1 212.2	267.2 211.3			
Cβ	(td)	162.8	162.8	163.7	162.2	164.1	164.3	161.7	160.7	162.8	165.7 <sup>[c]</sup>			
	<sup>2</sup> J <sub>CF</sub> [Hz] <sup>2</sup> J <sub>CP</sub> [Hz]	26.0 14.4	26.0 14.5	26.6 14.7	26.8 14.4	24.8 12.6	26.6 14.5	26.4 14.2	26.2 14.3	26.1 13.4	26.1 20.9			
											13.5			

 $R_1: \mathbf{a} = CH_3(CH_2)_6, \ \mathbf{b} = CH_3(CH_2)_7, \ \mathbf{c} = 4 - MeOC_6H_4CH_2, \ \mathbf{d} = 2 - MeC_6H_4CH_2, \ \mathbf{e} = Bn, \ \mathbf{f} = 4 - FC_6H_4CH_2, \ \mathbf{g} = (S) - Ph(CH_3)CH, \ \mathbf{h} = Ph, \ \mathbf{i} = 4 - FC_6H_4, \ \mathbf{j} = 2 - FC_6H_4.$ 

[a] <sup>19</sup>F{1H} NMR. [b] Spectrum made in CD<sub>3</sub>CN. [c] Signal appeared as (ddd).

## Table5Spectroscopicdataof $\alpha, \alpha$ -difluoromethylene- $\beta$ -aminophosphonates15

				(OEt) <sub>2</sub>		
			15	D		
δ [p]	pm]	15a	15b	15c	15d	15e
P	(dd)	7.41	7.31	7.04	7.05	7.10
	$^{2}J_{PF}$ [Hz]	102.5	104.5	105.7	106.6	103.8
		101.1	102.7	102.0	102.4	
Fa	(dd)	-109.35	-111.16	-110.99	-110.98	-111.06
	<sup>2</sup> J <sub>FP</sub> [Hz]	300.0	300.9	303.2	303.4	303.3
		100.8	102.5	101.9	102.4	100.9
Fb	(dd)	-123.57	-121.56	-121.38	-121.33	-121.48
	<sup>2</sup> J <sub>FP</sub> [Hz]	300.1	300.4	302.7	303.4	302.6
		102.9 Hz	101.6	105.8	106.7	105.7
H <sub>β</sub>	(m)	4.26-3.96 <sup>°</sup>	4.26-3.98 <sup>°</sup>	4.24-3.92 <sup>c</sup>	4.23-3.92 <sup>c</sup>	4.34-4.12 <sup>c</sup>
$C_{\alpha}$	(ddd)	119.4	118.4	119.4	119.3	119.3
	] <i>J</i> <sub>CF</sub> [Hz]	269.3	268.9	268.5	268.6	268.3
	J <sub>CF</sub> [Hz]	263.0	265.9	265.5	265.8	265.5
	' <i>J</i> <sub>CP</sub> [Hz]	210.0	210.2	210.3	211.1	210.7
$C_{\beta}$	(ddd)	64.3-63.6	63.6	63.5	64.1	63.7
	<sup>2</sup> J <sub>CF</sub> [Hz]		24.3	23.6	23.6	23.6
	<sup>2</sup> J <sub>CP</sub> [Hz]		19.4	19.5	19.4	19.5
			15.4	15.4	15.3	15.4
δ[pp	pm]	15f	15g <sup>ab</sup>	15h	15i	15j
Р	(dd)	6.83	7.05	6.57	6.65	6.44
	<sup>2</sup> J <sub>PF</sub> [Hz]	105.3	103.5	105.1	104.6	103.5
_		102.4	102.0	102.2	101.7	101.1
Fa	_ (dd)	-111.21	-109.60	-110.30	-110.48	-111.19
	<sup>2</sup> J <sub>FP</sub> [Hz]	303.8	300.5	304.1	304.1	305.1
_	<i>(</i> <b>, , )</b>	101.8	101.8	102.0	101.6	103.4
Fb	(dd)	-121.27	-121.71	-120.27	-120.33	-120.94
	<sup>-</sup> J <sub>FP</sub> [HZ]	304.4	300.5	304.1	304.0	305.1
	(-1-1-1)	104.1	103.7	105.2	104.3	101.3
Ηβ		4.21-3.93	4.26-3.98	4.92	4.83	4.98
	<sup>3</sup> J <sub>HF</sub> [HZ]			20.5	20.7	20.5
				8.4	8.2	8.0
0	J <sub>HP</sub> [⊓∠] (ddd)	110.0	110.0	D.9	0.0	D.2
$\mathbf{U}_{\alpha}$	(000)	119.3	119.9	110.0	110.4	122.3-113.8
		200.1	209.0	200.2	200.4	
		Z00 M	200.0	200.0	200.0	
	J <sub>CF</sub> [HZ] <sup>1</sup> / [Hz]	210.7	210.3	200.8	200.2	
C.	J <sub>CF</sub> [HZ] <sup>1</sup> J <sub>CP</sub> [HZ] (ddd)	210.7	210.3	209.8	209.2	60.1
Cβ	$J_{CF} [HZ]$ $^{1}J_{CP} [HZ]$ $(ddd)$ $^{2}I_{CF} [HZ]$	210.7 63.6 23.5	210.3 62.0 23.7	209.8 60.6 24.9	209.2 61.5 24.7	60.1 25.4
C <sub>β</sub>	J <sub>CF</sub> [Hz] <sup>1</sup> J <sub>CP</sub> [Hz] (ddd) <sup>2</sup> J <sub>CF</sub> [Hz] <sup>2</sup> I <sub>CF</sub> [Hz]	210.7 63.6 23.5	210.3 62.0 23.7	209.8 60.6 24.9 21.1	209.2 61.5 24.7 21.1	60.1 25.4 21.0
Cβ	$J_{CF} [HZ]$ $^{1}J_{CP} [HZ]$ $^{2}J_{CF} [HZ]$ $^{2}J_{CF} [HZ]$ $^{2}J_{CF} [HZ]$	210.7 63.6 23.5 19.6 15.5	210.3 62.0 23.7 19.3 15.2	209.8 60.6 24.9 21.1 14 7	209.2 61.5 24.7 21.1 14.8	60.1 25.4 21.0 14.9

 $R': \mathbf{a} = CH_3(CH_2)_6, \mathbf{b} = CH_3(CH_2)_7, \mathbf{c} = 4-MeOC_6H_4CH_2, \mathbf{d} = 2-MeC_6H_4CH_2, \mathbf{e} = Bn, \mathbf{f} = 4-FC_6H_4CH_2, \mathbf{g} = (S)-Ph(CH_3)CH, \mathbf{h} = Ph, \mathbf{i} = 4-FC_6H_4, \mathbf{j} = 2-FC_6H_4$ 

<sup>a</sup> diastereomeric ratio of isolated product **15 g** (dr = 91:1) based on NMR.<sup>b</sup>Signals of major compound.<sup>c</sup> signal observed as multiplet