# Preparation of chiral $\alpha$ -monofluoroalkylphosphonic acids and their evaluation as inhibitors of protein tyrosine phosphatase 1B

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Enantiomerically pure  $\alpha$ -monofluoroalkylphosphonic acids **4**–**9** were synthesized by diastereoselective electrophilic fluorination of  $\alpha$ -carbanions of asymmetric phosphonamidates bearing (–)-ephedrine as a chiral auxiliary. The diastereomeric excess of the fluorination reaction was highly dependent on the nature of the base and counterion with de's ranging from 2–72%. Diastereomerically pure  $\alpha$ -fluorophosphonamidates were obtained by column chromatography. The absolute stereochemistry of the fluorinated phosphonamidates was established by X-ray crystallography. Removal of the ephedrine auxiliary using MeOH–TFA followed by treatment with TMSBr afforded  $\alpha$ -monofluoroalkylphosphonic acids **4**–**9** in modest to good yields. <sup>19</sup>F-NMR analysis of the chiral phosphonic acids **4**–**9** in the presence of the chiral base quinidine indicated that the phosphonic acids were obtained in greater than 97% ee. Inhibition studies with **4**–**9** and protein tyrosine phosphatase 1B (PTP1B) revealed that the *R*-enantiomers were approximately 10-fold more potent inhibitors than the corresponding *S*-enantiomers, but 10-fold less potent than their  $\alpha$ , $\alpha$ -difluoro analogues. Possible reasons for these differences are discussed.

# Introduction

One of the most effective tactics for obtaining inhibitors of enzymes that bind or hydrolyze phosphate groups is to replace the phosphate group of the substrate with a non-hydrolyzable phosphate mimetic. The  $\alpha$ -fluoroalkylphosphonic acid moiety is considered to be a good phosphate mimetic<sup>1</sup> and there are numerous reports in the literature describing inhibitors of various enzymes that bind or hydrolyze phosphate esters that bear this moiety.<sup>2a-c</sup> Our interest in the synthesis of  $\alpha$ -fluoroalkylphosphonates stems from our involvement in the design and synthesis of inhibitors of a class of enzymes known as protein tyrosine phosphatases (PTPs).3-5 PTPs are enzymes that catalyze the removal of phosphate groups from phosphotyrosine residues in peptides and proteins.<sup>6</sup> They are key regulators in a wide variety of crucial kinase-dependent signal transduction pathways. One PTP that has attracted considerable attention from both academia and the pharmaceutical industry is PTP1B.6 Recently, it has been shown that PTP1B plays a major role in modulating both insulin sensitivity and fuel metabolism.<sup>7</sup> Consequently, inhibitors of this enzyme may be useful as therapeutics for the treatment of type II diabetes and obesity.7 Among the most potent inhibitors of PTP1B are those containing the  $\alpha, \alpha$ -diffuoromethylenephosphonic acid (DFMP) moiety.<sup>3,5,8-11</sup> Certain peptides bearing diffuoromethylenephosphonylphenylalanine (F<sub>2</sub>Pmp, 1) are nanomolar inhibitors of PTP1B and can bind up to  $2 \times 10^3$  times better than the analogous peptide bearing methylenephosphonylphenylalanine.<sup>8,9</sup> The high affinity of the DFMP group for PTP1B is such that even comparatively simple non-peptidyl compounds bearing this moiety, such as 2 and 3, are relatively good inhibitors of this enzyme while their non-fluorinated analogues are very poor inhibitors.<sup>3,11</sup> Why are α-fluoroalkylphosphonates dramatically better inhibitors than their nonfluorinated counterparts? Two possible explanations have been



put forward.<sup>9</sup> One is that the PTPs require the dianionic form of the phosphonates for binding. At pH 6-7, the nonfluorinated phosphonates exist only partially as the dianions while the fluorinated derivatives are almost completely ionized<sup>9</sup> and therefore bind more tightly. However, it has been shown that both peptidyl and non-peptidyl compounds bearing the DFMP group inhibit PTP1B in a pH-independent manner in the pH range spanning the  $pK_{a2}$  of the phosphonate moiety.<sup>3,9</sup> This indicates that the dianionic and monoanionic forms of these inhibitors bind equally well and that the enhanced inhibition of the DFMP-bearing inhibitors compared to their non-fluoro analogues is probably not due to  $pK_a$  differences. The other explanation is that the fluorines increase the affinity by H-bonding with specific residues in the active site. This explanation is supported by data obtained from the crystal structure of 2 complexed with PTP1B which was recently reported by Burke and co-workers.<sup>10</sup> On the basis of this X-ray structure and molecular dynamics calculations, Burke has suggested that an unusually strong fluorine hydrogen bond exists between the pro-R fluorine of 2 and the amido group of Phe-182.<sup>10</sup> Burke has proposed, based on molecular dynamics calculations, that the pro-R fluorine of 2 contributes an average of -4.6 kcal  $mol^{-1}$  more interaction energy than the *pro-S* fluorine when binding to the enzyme.<sup>10</sup> A similar interaction between PTP1B

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and the *pro-R* fluorine of an  $F_2$ Pmp-bearing peptide was noted in a recent molecular dynamics study by Tracey and Glover.<sup>12</sup> These results suggest that enantiomerically pure (*R*)- $\alpha$ -monofluoroalkylphosphonic acids may be as effective inhibitors of PTP1B as their difluoro analogues. To test this possibility and to gain further insight into the role of the fluorines in PTP1B inhibition, we report here the synthesis of enantiomerically pure  $\alpha$ -monofluorophosphonic acids **4–9** and their evaluation as inhibitors of human PTP1B.

# **Results and discussion**

To our knowledge, only two reports describing the synthesis of enantiomerically pure  $\alpha$ -monofluoroalkylphosphonic acids have appeared in the literature.<sup>13,14</sup> In both instances, the  $\alpha$ -monofluoroalkylphosphonic acids were obtained *via* stereo-selective hydrogenation of vinyl phosphonates ((EtO)<sub>2</sub>POCF= CRR').<sup>13,14</sup> However, this procedure would not be applicable to benzylic  $\alpha$ -monofluoroalkylphosphonates such as **4–9**. Indeed,



a general procedure for the synthesis of enantiomerically pure  $\alpha$ -monofluoroalkylphosphonic acids has never been reported. Shibuya and co-workers have attempted to prepare enantiomerically enriched benzylic  $\alpha$ -monofluoroalkylphosphonates by DAST fluorination of optically active benzylic  $\alpha$ -hydroxyphosphonate derivatives. However these reactions proceeded with very low ee (3–5%).<sup>15</sup>

The general approach we have examined for the preparation of enantiomerically enriched benzylic  $\alpha$ -monofluoroalkylphosphonic acids is outlined in Scheme 1. In this approach, the



fluorine is introduced in a diastereoselective manner by electrophilic fluorination of a-carbanions of asymmetric phosphonamides or phosphonamidates using a chiral amino alcohol or diamine as an auxiliary. Removal of the chiral auxiliary would yield the  $\alpha$ -monofluoroalkylphosphonic acids. This approach has been employed by a number of other groups for the preparation of enantiomerically enriched α-alkylphosphonic acids using alkyl halides as electrophiles.<sup>16-19</sup> Differding and Lang have shown that non-racemic  $\alpha$ -monofluorocarbonyl compounds can be obtained in modest ee's (10-70%) by fluorination of prochiral metal enolates using optically pure N-fluorosultams as enantioselective electrophilic fluorinating agents.<sup>20,21</sup> Later, Davis and co-workers<sup>22-26</sup> prepared a wide variety of chiral a-monofluorocarbonyl compounds in good to excellent de's by fluorination of chiral enolates bearing Evan's oxazolidinone<sup>27</sup> as a chiral auxiliary and using N-fluorobenzenesulfonimide (NFSI) as electrophilic fluorinating agent. In addition, Differding and co-workers have shown that racemic

Table 1Effect of base and counter-ion on the electrophilic fluorin-<br/>ation of phosphonamide 12 with NFSI

Base	Yield <sup><i>a</i></sup> of <b>13</b> (%)	${ m De}^{b,c}(\%)$
n-BuLi	68 <sup>d</sup>	68 <sup>d</sup>
LiHMDS	81 <sup>d</sup>	70 <sup>d</sup> , 16 <sup>e</sup>
NaHMDS	69 <sup>d</sup>	18 <sup>d</sup>
KHMDS	71 <sup>d</sup>	37 <sup>d</sup>

<sup>*a*</sup> Isolated yields. <sup>*b*</sup> De's were determined by obtaining the <sup>19</sup>F-NMR of the crude residue after aqueous workup of the reaction before chromatography. <sup>*c*</sup> Absolute stereochemistry not determined. <sup>*d*</sup> Performed using 0.95 equiv. base and 1.1 equiv. NFSI as described in the Experimental section. <sup>*e*</sup> Reverse addition: 1.1 equiv. of base was added to **12** (1 equiv.) and NFSI (1.1 equiv.) over a period of 1 h at -78 °C. After stirring an additional 2 h at -78 °C the reaction was warmed to rt and quenched as described in the Experimental section.

 $\alpha$ -monofluoroalkylphosphonates can be prepared in modest yield by electrophilic fluorination of  $\alpha$ -carbanions of achiral alkyl phosphonate esters with NFSI.<sup>28</sup> More recently, we have shown that racemic benzylic  $\alpha$ -monofluoroalkylphosphonic acids can be readily prepared in good yield *via* electrophilic fluorination using NFSI.<sup>29</sup> Consequently, we reasoned that the approach outlined in Scheme 1 may be a viable method for the preparation of chiral benzylic  $\alpha$ -monofluoroalkylphosphonic acids.

We examined *trans-(R,R)-1,2-bis(N-methylamino)cyclo*hexane (**10**) and (–)-ephedrine as chiral auxiliaries since these auxiliaries have been shown to be effective for the asymmetric synthesis of  $\alpha$ -alkylphosphonic acids and were readily obtainable.<sup>17,18</sup> The naphthyl derivatives were used as model systems. Chiral phosphonamide **12** was prepared by reacting the phosphonic acid **11** with oxalyl chloride–cat. DMF followed by reaction of the crude phosphoryl chloride with **10** in the presence of two equivalents of triethylamine (Scheme 2). Our previous



studies<sup>29</sup> and those of Differding<sup>28</sup> on the electrophilic fluorination of phosphonates with NFSI indicated that the yields of fluorinated products were dependent on the nature of the base and counter-ion. Consequently, electrophilic fluorination of **12** with NFSI was examined with different bases and counter-ions. The de of the reaction was determined by examining the crude reaction mixture by <sup>19</sup>F-NMR. Fluorination of **12** to give the fluorinated phosphonamides **13** was achieved by treating **12** with 0.95 equiv. of base at -78 °C for 2 h followed by the addition of 1.1 equiv. NFSI (Scheme 2). The yields and de's of these fluorination reactions are given in Table 1. The yield of the fluorination reaction was not highly dependent on the nature of the base or counter-ion with good yields being

**Table 2** Effect of base and counter-ion on the electrophilic fluorin-ation of *trans* isomer 19 with NFSI

Base	Yield <sup><i>a</i></sup> of <b>28</b> and <b>31</b> (%)	De <sup><i>b</i></sup> (%)	
LiHMDS NaHMDS KHMDS LDA n-BuLi t-BuLi	46° 75,° 68, <sup>d</sup> 62° 66° 38° 31°	2 (R) 54, c 50, d 72 c (R) 40 (R) 3 (S) 18 (S) 16 (S)	-

<sup>*a*</sup> Isolated yields. <sup>*b*</sup> De's were determined by obtaining the <sup>19</sup>F-NMR of the crude residue after aqueous workup of the reaction before chromatography. <sup>*c*</sup> Performed using 0.95 equiv. base and 1.1 equiv. NFSI as described in the Experimental section. <sup>*d*</sup> Same procedure as for <sup>*b*</sup> except 1.1 equiv. of base was used. <sup>*e*</sup> Reverse addition: 1.1 equiv. of base was added to **19** (1 equiv.) and NFSI (1.1 equiv.) over a period of 1 h at -78 °C. After stirring an additional 2 h at -78 °C the reaction was warmed to rt and quenched as described in the Experimental section.

obtained in all cases. However, the de of the reaction was highly dependent on the nature of the cation but not the base itself. Bases with lithium counter-ions (n-BuLi and LiHMDS) gave moderately good de's (68-70%) while NaHMDS and KHMDS gave low de's. <sup>19</sup>F-NMR analysis of the products obtained using KHMDS as base revealed preferential formation of the stereoisomer opposite from that obtained when using the lithium and sodium bases. Reverse addition of NFSI and LiHMDS (1.1 equiv. of LiHMDS added to a solution of the phosphonamide and 1.1 equiv. NFSI at -78 °C over a period of 1 h) resulted in a large decrease in the de (16%) and preferential formation of the stereoisomer opposite from that obtained when adding the base first. The de's obtained with the lithium bases are comparable to those obtained by Hanessian and coworkers (68–80%) on the asymmetric  $\alpha$ -alkylation of benzyl phosphonamides bearing 10 as auxiliary using alkyl halides as electrophiles and n-BuLi as base.<sup>18</sup> Unfortunately, separation of the diastereomeric products 13 proved to be exceedingly difficult. Even after several recrystallizations, diastereomerically pure 13 was not obtained. Attempts to separate the two diastereomers by silica gel column chromatography were also unsuccessful.

Reaction of the phosphonic acid dichloride derived from 11 with (-)-ephedrine yielded two diastereomeric phosphonamidates 16 and 19 which were readily separated by silica gel chromatography (Scheme 3). Diastereomer 16 was designated as the cis-isomer (phosphoryl and 3-methyl group cis) while diastereomer 19 was designated as the trans-isomer (phosphoryl and 3-methyl group trans).<sup>30</sup> The fluorination of 16 and 19 (Scheme 3) was first attempted by subjecting them to the same fluorination conditions as described above for 12. The results of these fluorination reactions are shown in Tables 2 and 3. For both isomers, the yield and the de of the reaction were highly dependent on the base and cation. NaHMDS gave the highest yields (54% for cis-isomer 16 and 75% for trans-isomer 19). Lithium bases gave very low de's (2-24%) for both 16 and 19. Modest de's were obtained with both 16 and 19 using NaHMDS (58% and 54%) and KHMDS (36% and 40%). Although the de's of the reactions were modest, the diastereomeric fluorinated phosphonamidates exhibited large differences in mobility on silica gel, ( $R_f$  differences ranged from 0.2–0.25) and could be readily separated by silica gel flash chromatography. We also found that, after chromatographic separation, the fluorinated cis-isomers 22 and 25 could be readily recrystallized and their absolute stereochemistry determined by X-ray crystallography. Attempts to obtain X-ray quality crystals of the *trans*-isomers 28 and 31 were unsuccessful. In an attempt to improve the de of the reactions, the reaction with NaHMDS was performed under a variety of different conditions. Fluorination with the trans-isomer 19 using 1.1 equiv. of NaHMDS resulted in a

Table 3Effect of base and counter-ion on the electrophilic fluorin-<br/>ation of cis isomer 16 with NFSI

E	Base	Yield <sup><i>a</i></sup> of <b>22</b> and <b>25</b> (%)	De <sup><i>b</i></sup> (%)
I N K I n t	LiHMDS NaHMDS KHMDS LDA I-BuLi -BuLi	29° 54,° 47 <sup>d</sup> 41° 44° 33° 24°	2 (S) 58, <sup>e</sup> 46 <sup>d</sup> (S) 36 (S) 8 (S) 24 (S) 20 (S)

<sup>*a*</sup> Isolated yields. <sup>*b*</sup> De's were determined by obtaining the <sup>19</sup>F-NMR of the crude residue after aqueous workup of the reaction before chromatography. <sup>*c*</sup> Performed using 0.95 equiv. base and 1.1 equiv. NFSI as described in the Experimental section. <sup>*d*</sup> Reverse addition: 1.1. equiv. of base was added to **16** (1 equiv.) and NFSI (1.1. equiv.) over a period of 1 h at -78 °C. After stirring an additional 2 h at -78 °C the reaction was warmed to rt and quenched as described in the Experimental section.

slight decrease in de and yield (Table 2). However, reverse addition of NFSI and NaHMDS (1.1 equiv. of NaHMDS added to a solution of the phosphonamidate and 1.1 equiv. NFSI at -78 °C over a period of 1 h) resulted in a increase in the de to 72% with **19** but a slight decrease in the yield (Table 2); this was not the case with the *cis*-isomer **16** which resulted in a decrease in de and yield (Table 3).

The *m*-(phenyl)benzyl phosphonamidates, 17 and 20, and benzyl phosphonamidates, 18 and 21, were also prepared (Scheme 3). These phosphonamidates were fluorinated using 0.95 equiv. NaHMDS and 1.1 equiv. NFSI to give the fluorinated cis-isomers 23, 24, 26 and 27 and the fluorinated transisomers 29, 30, 32 and 33 (Scheme 3). For each fluorination reaction, the fluorinated diastereomeric products could be readily separated from one another by silica gel flash chromatography. The fluorination reaction of the *m*-(phenyl)benzyl phosphonamidates (17 and 20) proceeded in overall good yields (68%, cis-isomer; 85%, trans-isomer) but with low de's (25%, cis-isomer; 26%, trans-isomer). The fluorination reaction of the benzyl phosphonamidates (18 and 21) also proceeded in overall modest yields (44%, cis-isomer; 47%, trans-isomer) and low de's (33% cis-isomer; 29% trans-isomer). cis-Isomers 23, 24, 26 and 27 were also found to be readily recrystallized and their structure and absolute stereochemistry were determined by X-ray crystallography.

The next step was to develop a racemization-free procedure for the removal of the ephedrine auxiliary from fluorinated isomers 22–33 to obtain the desired enantiomerically pure free acids 4-9. Since the absolute stereochemistry of all the fluorinated cis-isomers 22-27 was known, our initial studies were performed using these phosphonamidates. Sting and Steglich have reported that racemization-free hydrolysis of chiral ephedrine  $\alpha$ -alkylphosphonamidates can be accomplished by subjecting them to concentrated HCl at 110 °C for 20 h.17 However, applying these conditions to 22 and 25 resulted in a mixture of compounds and we were unable to purify 4 and 5 from the mixture. Nevertheless, we found that the auxiliary could be removed without racemization using a modified version of a procedure developed by Calvo (Scheme 3).<sup>31</sup> This involved treating **22–27** with 10% TFA-MeOH, followed by reaction with TMSBr (10 equiv.). The contaminating ammonium salts were removed using anhydrous ether followed by filtration. Hydrolysis of the TMS ester in methanol $-H_2O$  gave the free acids 4–9 in modest to good yields (39-70%). We found that the enantiomeric purity of 4-9 could be readily determined by preparing solutions of 4-9 and 1 equiv. of the chiral base quinidine in CDCl<sub>3</sub> followed by <sup>19</sup>F-NMR analysis of the salt solutions. For example, the <sup>19</sup>F-NMR spectra of the salts derived from phosphonic acids 4 and 5 consist of a single set of doublet of doublets with each set having a chemical shift significantly different from the other set (Fig. 1a and 1b). The quinidine salts of a racemic mixture of



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**4** and **5** appear as two distinct sets of doublet of doublets (Fig. 1c). These results indicate that removal of the ephedrine auxiliary proceeded without racemization and both **4** and **5** were obtained in high enantiomeric purity (>97% ee). Similar results were obtained with acids **6–9**. The ephedrine auxiliary was also removed from the fluorinated *trans*-isomers **28–33** to give acids **4–9** without racemization and in modest to good yields using the procedure described above (Scheme 3).

Since the absolute configuration of the phosphonic acids derived from *cis*-isomers 22–27 was known, it was then possible to determine the absolute configuration of the phosphonic acids derived from the *trans*-isomers 28–33 by analysis of their <sup>19</sup>F-NMR spectrum in the presence of one equiv. of quinidine. From the results of these studies, the absolute stereochemistry of the *trans*-fluorophosphonamidates 28–33 was also determined. The fluorination of the *trans*-isomers 19–21 using NaHMDS as base resulted in preferential formation of the *R*-enantiomers (28–30). The fluorination studies with the model *trans*-phosphonamidate 19 using a variety of different bases (Table 2) demonstrated that the stereochemical outcome of the fluorination reaction is dependent upon the nature of

the base and counter-ion. When HMDS bases were used, the reaction proceeded with preferential formation of the R-enantiomer 28; this preference was almost negligible when lithium was the counter-ion. When other lithium bases were used, the S-enantiomer 31 was formed preferentially although the de's were very low (3-18%, Table 2). In contrast to the fluorination reactions with the trans-isomers, the fluorination reactions with the cis-isomers 16-18 using NaHMDS proceeded with preferential formation of the S-enantiomers. Studies with the model *cis*-isomer 16 showed that this was the case regardless of the base and counter-ion, although with the lithium bases this preference was small to almost negligible (Table 3). The change or increase in stereoselectivity between lithium and sodium or potassium bases may be due to a number of factors such as differences in the degree of complexation of the cations with the phosphoryl and other heteroatoms of the phosphonamidate, differences in the degree of complexation of the cation with the solvent, differences in size of the cation, etc. Further studies are necessary to ascertain the origin of the effect of cation on diastereoselectivity.

Inhibition studies with phosphonic acids 2-9 and PTP1B



**Fig. 1** <sup>19</sup>F-NMR spectra of (a) quinidine salt of phosphonic acid **4**, (b) quinidine salt of phosphonic acid **5**, (c) quinidine salt of a racemic mixture of phosphonic acids **4** and **5**.

were performed at pH 6.5 in BIS-TRIS buffer-5% DMSO. The benzylphosphonic acids 8 and 9 were not inhibitors of the enzyme even at concentrations as high as 1.0 mM. The results of the inhibition studies with 4-7 and their difluoro analogues are given in Table 4. Compounds 4-7 were found to be competitive inhibitors of PTP1B. The *R*-enantiomers 4 and 6 are not as effective inhibitors as their difluoro analogues 2 and 3, being 9.5-fold less potent inhibitors than compounds 2 and 3. Thus, substitution of the pro-S fluorine with hydrogen in 2 or 3 results in a 9.5-fold decrease in affinity for the enzyme. These results indicate that the pro-S fluorine has some role in enhancing the affinity of the difluoro inhibitors and support the argument<sup>3,9</sup> that the fluorines do not enhance binding by reducing the  $pK_{a}$ of the phosphonic acid moiety. It is possible that this may be due to a direct contribution of the pro-S fluorine to binding involving specific interactions of the pro-S fluorine with residues in the active site. However, Burke's analysis of the PTP1B-2 complex did not uncover any significant role that the pro-S fluorine may have in binding besides the formation of van der

 Table 4
 Inhibition studies with phosphonic acids 2–7 and PTP1B

Phosphonic acid	$IC_{50}/\mu M^{a}$	$K_{\rm i}/\mu{ m M}^{a}$
2	71 ± 6	$34 \pm 4$
4	$675 \pm 40$	$345 \pm 24$
5	$7500 \pm 1000$	ND
3	$33 \pm 4$	$16 \pm 3$
6	$315 \pm 20$	$158 \pm 12$
7	$3500 \pm 500$	ND

Waals interactions with the phenyl ring of Phe-182.<sup>10</sup> Nevertheless, it is possible that this interaction is necessary in order for the difluoro inhibitors to be correctly positioned in the active site so that optimal interactions can be attained between the enzyme and other functionalities on the inhibitor. This may include the formation of an optimal fluorine H-bond between the *pro-R* fluorine and the N–H of Phe-182, hydrophobic interactions between the aryl rings of the inhibitors and the side chains of certain amino acids such as Tyr-46, Phe-182, Ala-217 and Ile-219, and electrostatic binding of the phosphate group to the positively charged phosphate binding site.<sup>10</sup> It is also possible that the strength of a FC–F···H–N hydrogen bond may be greater than a HC–F···H–N hydrogen bond. However, we are not aware of any experimental studies supporting such an argument.

S-Enantiomers 5 and 7 are approximately 105-fold poorer inhibitors than their diffuoro compounds 2 and 3. Thus, the substitution of the *pro-R* fluorine atoms in 2 and 3 with a hydrogen atom results in an approximately 105-fold decrease in affinity for PTP1B. On the basis of the X-ray structure of the PTP1B-2 complex and molecular dynamics calculations, Burke and co-workers have suggested that the H-bond between the pro-R fluorine of 2 and the backbone N-H of Phe-182 may contribute as much as -4.6 kcal mol<sup>-1</sup> to the binding process.<sup>10</sup> However, the 105-fold difference in affinity between 2 and 5 reported here corresponds to a difference of -2.75 kcal mol<sup>-1</sup> in binding energy which suggests that -4.6 kcal mol<sup>-1</sup> may be an overestimation of the strength of this H-bond. The subject of fluorine hydrogen bonds involving C–F is a subject of much controversy.<sup>32-34</sup> Nevertheless, there is little doubt now that such H-bonds can form in certain instances<sup>35</sup> although the optimal strength of such bonds is still unknown. To our knowledge, studies estimating the optimal strength of C-F···H-N hydrogen bonds have not been reported. However, ab initio calculations by O'Hagan and co-workers predict that the strength of an optimal C-F···H-O hydrogen bond in a  $HO-H \cdots F-CH_3$  complex to be 2.4 kcal mol<sup>-1.32</sup> This value is close to the value  $(-2.7 \text{ kcal mol}^{-1})$  that we have obtained for the difference in binding energy between 2 and 5.

In conclusion,  $\alpha$ -monofluoroalkylphosphonic acids 4–9 were synthesized in high enantiomeric purity. This was accomplished *via* the electrophilic fluorination of  $\alpha$ -carbanions of asymmetric phosphonamidates bearing (-)-ephedrine as a chiral auxiliary, followed by chromatographic separation of the resulting diastereomers and removal of the auxiliary. The synthetic methodology outlined here should be applicable to the synthesis of chiral  $\alpha$ -monofluoroalkylphosphonic acid inhibitors of other enzymes that bind or hydrolyze phosphate esters. We are currently investigating other chiral auxiliaries in attempts to improve the de's of the fluorination reactions. Inhibition studies with phosphonic acids 4-7 and PTP1B indicated that the pro-S fluorine in diffuoro inhibitors 2 and 3 is essential for good inhibition. Moreover, our inhibition studies demonstrate that the *pro-R* fluorine in the diffuoro inhibitors contributes significantly more than the pro-S fluorine towards PTP1B affinity, however, the contribution of the pro-R fluorine to binding may have been overestimated by previous workers.10

### Experimental

#### General

Unless otherwise noted, all reagents for syntheses were obtained from commercial suppliers (Aldrich, Milwaukee, Wisconsin, USA or Lancaster Synthesis Inc. Windham, New Hampshire, USA) and were used without further purification. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium-benzophenone ketyl under argon. Dichloromethane and toluene were distilled from calcium hydride under argon. DMF was distilled under reduced pressure from calcium hydride and stored over 4 Å sieves under argon. Reactions involving moisture-sensitive reagents were executed under an inert atmosphere of dry argon or nitrogen. Flash chromatography was performed using silica gel 60 (Toronto Research Chemicals, 230-400 mesh ASTM). <sup>1</sup>H-, <sup>31</sup>P- and <sup>19</sup>F-NMR spectra were recorded on a Varian 200-Gemini NMR spectrometer. Unless stated otherwise, all <sup>13</sup>C spectra were recorded on a Varian-400 instrument. For <sup>1</sup>H-NMR spectra run in CDCl<sub>3</sub>, chemical shifts ( $\delta$ ) are reported in parts per million relative to the internal standard tetramethylsilane (TMS). For <sup>1</sup>H spectra run in CD<sub>3</sub>OD, chemical shifts ( $\delta$ ) are reported in parts per million relative to the residual CH<sub>3</sub> peak at  $\delta$  3.30 ppm. For <sup>13</sup>C spectra run in CDCl<sub>3</sub>, chemical shifts are reported in parts per million relative to the CDCl<sub>3</sub> residual carbons ( $\delta$  77.0 for the central peak). For <sup>13</sup>C spectra run in CD<sub>3</sub>OD, chemical shifts are reported in parts per million relative to the CD<sub>3</sub>OD carbon ( $\delta$  49.0 for the central peak). All <sup>31</sup>P-NMR spectra were proton decoupled and chemical shifts are reported in parts per million relative to 85% phosphoric acid (external). For <sup>19</sup>F-NMR, chemical shifts are reported in parts per million relative to trifluoroacetic acid (external). All NMR couplings are given in Hz. Electron impact (EI) were obtained on a Micromass 70-S-250 mass spectrometer. Electrospray mass spectra were obtained using a Micromass Platform mass spectrometer. IR spectra were recorded on an Avatar (Nicolet) 360 FTIR spectrophotometer. All melting points were taken on a Fisher-Johns melting point apparatus, and are uncorrected. Analytical HPLC was performed using a Waters LC 4000 System equipped with a Vydac 218TP54 analytical C-18 reversed phase column and a Waters 486 tunable absorbance detector set at 254 nM. Specific rotations were determined using a Perkin-Elmer 243B polarimeter.  $[a]_D$  values are given in  $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ . Buffer chemicals and bovine serum albumin (BSA) were obtained from Sigma Chemical Company. Enzyme assay solutions were prepared with deionized/distilled water. Fluorescein diphosphate (FDP) and human PTP1B were a gift from Merck-Frosst Canada Inc (Montreal, Canada).

# General procedure for the preparation of phosphonic acids 11, 14 and 15

Trimethylsilyl bromide (TMSBr, 5 equiv.) was added to a solution of one of naphthalen-2-ylmethylphosphonic acid methyl ester,<sup>36</sup> biphenyl-3-ylmethylphosphonic acid methyl ester<sup>29</sup> or benzylphosphonic acid diethyl ester (Aldrich, Milwaukee, Wisconsin, USA) in anhydrous  $CH_2Cl_2$  (approximately 5–10 cm<sup>3</sup> CH<sub>2</sub>Cl<sub>2</sub>/mmol of ester). For the methyl esters, the solution was stirred under an atmosphere of N<sub>2</sub> at room temperature for 12 h. For the ethyl ester, the solution was refluxed under an atmosphere of N<sub>2</sub> for 24 h. The mixture was then concentrated and placed under high vacuum for 2 h. The product was then re-dissolved in  $CH_2Cl_2$  and water (approximately 5–10 cm<sup>3</sup> H<sub>2</sub>O/mmol of phosphonate) was added. The mixture was stirred vigorously for 30 min during which time a white precipitate formed. The precipitate was then filtered, washed extensively with  $CH_2Cl_2$  and placed under high vacuum until dry.

**2-naphthylmethylphosphonic acid 11.** White solid (97% yield); mp 225–227 °C (from  $H_2O$ ) (lit.,<sup>37</sup> 229–230 °C);  $v_{max}(KBr)/cm^{-1}$ 

2925 (br), 2285 (br), 1597, 1506, 1407, 1281, 1166, 1003, 950, 826 and 744;  $\delta_{\rm H}(200$  MHz; CD<sub>3</sub>OD) 7.82–7.78 (4 H, br m), 7.46–7.44 (3 H, br m) and 3.29 (2 H, d,  $J_{\rm HP}$  20.5, CH<sub>2</sub>P);  $\delta_{\rm P}(80$  MHz; CD<sub>3</sub>OD) 26.3 (1P, s);  $\delta_{\rm C}(100$  MHz; CD<sub>3</sub>OD) 134.9 (d), 133.6 (d), 131.8 (d), 129.4 (d), 129.2 (d), 128.8 (d), 128.5 (d), 127.0, 126.6 and 36.0 (d,  $J_{\rm CP}$  134.8, CH<sub>2</sub>P); m/z (ES) 221 (100%).

**Biphenyl-3-ylmethylphosphonic acid 14.** White solid (79% yield); mp 172–174 °C (from H<sub>2</sub>O) (Found: C, 62.7; H, 5.2. C<sub>13</sub>H<sub>13</sub>O<sub>3</sub>P requires C, 62.9; H, 5.3%);  $v_{max}$ (KBr)/cm<sup>-1</sup> 2921 (br), 2312 (br), 1601, 1574, 1478, 1422, 1166, 1124, 1027, 939, 775 and 699;  $\delta_{\rm H}$ (200 MHz; CD<sub>3</sub>OD) 7.61–7.30 (9 H, m) and 3.18 (2 H, d,  $J_{\rm HP}$  22.0, CH<sub>2</sub>P);  $\delta_{\rm P}$ (80 MHz; CD<sub>3</sub>OD) 26.3 (1P, s);  $\delta_{\rm C}$ (100 MHz; CD<sub>3</sub>OD) 142.5 (d), 142.2, 134.8 (d), 129.9, 129.8, 129.6 (d), 128.3, 128.0, 127.8, 126.2 (d) and 35.8 (d,  $J_{\rm CP}$  134.7, CH<sub>2</sub>P); m/z (ES) 247 (100%).

**Benzylphosphonic acid 15.** White solid (99% yield); mp 171– 172 °C (from H<sub>2</sub>O) (lit.,<sup>38</sup> 169–171 °C);  $v_{max}$ (KBr)/cm<sup>-1</sup> 2865, 2359, 1496, 1457, 1262, 1217, 1075, 992, 943, 783 and 693;  $\delta_{\rm H}$ (200 MHz; CD<sub>3</sub>OD) 7.32–7.25 (5 H, m), 5.19 (2 H, s) and 3.11 (2 H, d,  $J_{\rm HP}$  22.0, CH<sub>2</sub>P);  $\delta_{\rm P}$ (80 MHz; CD<sub>3</sub>OD) 26.2 (1 P, s);  $\delta_{\rm C}$ (100 MHz; CD<sub>3</sub>OD) 134.4 (d), 131.0 (d), 129.4, 127.6 and 36.0 (d,  $J_{\rm CP}$  135.4, CH<sub>2</sub>P); m/z (ES) 171 (100%).

#### (3a*R*,7a*R*)-2-(2-Naphthylmethyl)-2,3,3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2 $\lambda^{5}$ -benzodiazaphosphol-2(1*H*)-one 12

To a suspension of phosphonic acid 11 (2.8 g, 12.7 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (25 cm<sup>3</sup>) and a catalytic quantity of DMF was added oxalyl chloride (4.83 g, 38.1 mmol) over a period of several minutes. The reaction was stirred for 4 h during which time the reaction mixture became a clear pale yellow solution. The solution was concentrated by rotary evaporation and placed under high vacuum overnight during which time the solution solidified yielding the crude phosphonic acid dichloride as a pale yellow solid. To a solution of the crude phosphonic acid dichloride in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (30 cm<sup>3</sup>) was added a solution of trans-(1R,2R)-N,N'-dimethyl-1,2-diaminocyclohexane  $10^{19}$  (1.80 g, 12.7 mmol) and Et<sub>3</sub>N (3.57 cm<sup>3</sup>, 25.6 mmol) in anhydrous  $CH_2Cl_2$  (30 cm<sup>3</sup>) dropwise over a period of 30 minutes under an atmosphere of nitrogen. After stirring for 12 h, the reaction mixture was filtered over a short pad of Celite and washed with EtOAc (100 cm<sup>3</sup>). The crude residue was purified by silica gel column chromatography using MeOH-EtOAc (2:98) as eluent to give pure 12 as a white solid (2.58 g, 62%). Mp 106–108 °C; v<sub>max</sub>(KBr)/cm<sup>-1</sup> 3058, 2933, 2814, 2657, 1980, 1782, 1629, 1599, 1503, 1467, 1337, 1315, 1057 and 942;  $\delta_{\rm H}(200$ MHz; CDCl<sub>3</sub>) 7.83-7.71 (4 H, m), 7.50-7.40 (3 H, m), 3.58-3.14 (2 H, m, CH<sub>2</sub>P), 2.72–2.66 (1 H, m, CHN), 2.60 (3 H, d, J 10.3, NCH<sub>3</sub>), 2.42 (3 H, d, J 11.7, NCH<sub>3</sub>), 2.06-1.65 (5 H, m) and 1.29–0.89 (4 H, m);  $\delta_{P}(80 \text{ MHz}; \text{CDCl}_{3})$  75.5 (1 P, s);  $\delta_{C}(100 \text{ mHz}; \text{CDCl}_{3})$ MHz; CDCl<sub>3</sub>) 133.4 (br s), 132.2 (br s), 130.7 (d), 128.5 (br m), 127.6 (br s), 127.4, 126.0, 125.4, 64.6 (d,  $J_{CP}$  5.5), 64.0 (d,  $J_{CP}$ 7.3), 35.1 (d,  $J_{CP}$  107.0, CH<sub>2</sub>P), 29.5, 28.5 (d,  $J_{CP}$  9.2), 28.1 (m) and 24.2 (d, J<sub>CP</sub> 7.3); m/z (EI) 328 (M<sup>+</sup>, 8%), 187 (35), 84 (100). Found: [M<sup>+</sup>], 328.1702. C<sub>19</sub>H<sub>25</sub>OPN<sub>2</sub> requires *m*/*z* 328.1705.

#### General procedure for the fluorination of 12 to give diastereomeric (3aR,7aR)-2-[1-fluoro(2-naphthyl)methyl]-2,3,3a,4,5,6, 7,7a-octahydro-1,3-dimethyl-1,3,2 $\lambda^5$ -benzodiazaphosphol-2(1*H*)-one, 13

To a solution of phosphonamide **12** in anhydrous THF (approximately 5–10 cm<sup>3</sup> THF/mmol of phosphonamide) at -78 °C was added base (0.95 equiv.) over a period of 2 minutes. The resulting orange solution was stirred for 2 h at -78 °C. A solution of NFSI (1.1 equiv.) in anhydrous THF (approximately 2–4 cm<sup>3</sup> THF/mmol NFSI) was added over a period of 2 minutes, during which time the solution turned from orange to yellow–brown. After addition, the solution was stirred for 2 h at -78 °C, during which time a precipitate sometimes formed.

The reaction was quenched with 10% NH<sub>4</sub>Cl and the resulting solution (precipitate dissolves) was extracted with CHCl<sub>3</sub>. The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give a yellow residue. A reverse addition procedure was also examined in which 1.1 equiv. of LiHMDS was added to 12 (1 equiv.) and NFSI (1.1 equiv.) over a period of 1 h at -78 °C. After stirring an additional 2 h at -78 °C the reaction was warmed to rt and quenched as described above. Column chromatography of the crude residue gave 13 as a mixture of two diastereomers. For yields and de's see Table 1. v<sub>max</sub>(KBr)/cm<sup>-1</sup> 3058, 2936, 2863, 2817, 1663, 1601, 1506, 1446, 1368, 1260, 1211, 1170, 1059 and 922;  $\delta_{\rm H}$ (200 MHz; CD<sub>3</sub>OD) 7.96–7.86 (4 H, m), 7.64–7.47 (3 H, m), 6.18 (1 H, dd,  $J_{\rm HP}$  404 and  $J_{\rm HF}$  45.8, CHF), 5.89 (1 H, dd,  $J_{\rm HP}$  3.7 and  $J_{\rm HF}$  45.4, CHF), 2.82–2.42 (5 H, m), 2.12–1.71 (7 H, m) and 1.32–0.99 (4 H, m);  $\delta_{\rm P}(80$  MHz; CD<sub>3</sub>OD) 37.7 (d,  $J_{\rm PF}$  80.9) and 33.7 (d,  $J_{\rm PF}$  82.4);  $\delta_{\rm F}$ (188 MHz; CD<sub>3</sub>OD) -113.4 (1 F, dd,  $J_{\rm FH}$  45.8 and  $J_{\rm FP}$  82.4) and -120.9 (1 F, dd,  $J_{\rm FH}$  45.4 and  $J_{\rm FP}$  80.9);  $\delta_{\rm C}(100$  MHz; CD<sub>3</sub>OD) 134.9 (d), 134.4, 132.9 (br dd), 129.1 (br m), 128.0 (br m), 126.6 (br dd), 126.0 (br t), 124.9 (br m), 98.0–87.5 (m, CHF), 66.3 (d, J<sub>CP</sub> 6.4), 66.1 (d, J<sub>CP</sub> 4.6), 65.7 (br s), 65.5 (d, *J*<sub>CP</sub> 2.8), 64.9 (d, *J*<sub>CP</sub> 7.3), 30.8, 29.8–29.3 (m) and 25.3 (br m); m/z (EI) 346 (M<sup>+</sup>, 6%), 328 (10), 279 (6), 187 (100) and 153 (12). Found: [M<sup>+</sup>], 346.1612. C<sub>19</sub>H<sub>24</sub>OPN<sub>2</sub>F requires m/z 346.1610.

# General procedure for the preparation of phosphonamidates 16–21

A mixture of (1R,2S)-(-)-ephedrine (1 equiv.) and Et<sub>3</sub>N (2 equiv.) dissolved in anhydrous toluene (approximately 1.2 cm<sup>3</sup> toluene/mmol (-)-ephedrine) was added dropwise to a suspension of the crude phosphonic acid dichloride (1 equiv., prepared from phosphonic acids 11, 14 and 15 using the procedure described above during the preparation of 12) in anhydrous toluene (approximately 2 cm<sup>3</sup> toluene/mmol phosphonic acid dichloride) at -40 °C, under an atmosphere of nitrogen. After stirring for 1 h at -40 °C, the reaction mixture was stirred at room temperature overnight. The resulting yellow slurry (containing a white precipitate) was diluted with EtOAc (100 cm<sup>3</sup>), washed with brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. Separation and purification of the trans- and cisphosphonamidates 16-21 were achieved by silica gel column chromatography using MeOH-EtOAc (2:98) as eluent for 16, 17, 19 and 20 and MeOH-EtOAc (3:97) as eluent for 18 and **21**. The *cis*-isomers **16–18** exhibited larger  $R_{\rm f}$  values on silica TLC plates and eluted before the trans-isomers 19-21 during column chromatography.

#### (2R,4S,5R)-2-(2-Naphthylmethyl)-3,4-dimethyl-2-oxo-5-

phenyl-1,3,2 $\lambda^5$ -oxazaphospholidine (*cis*-isomer) 16. White solid (24%); mp 180–182 °C (from pentane– $CH_2Cl_2$ );  $[a]_D^{22}$  –73.2 (c 0.0284 in MeOH) (Found: C, 71.5; H, 6.4; N, 4.0. C<sub>21</sub>H<sub>22</sub>NO<sub>2</sub>P requires C, 71.8; H, 6.3; N, 4.0%); v<sub>max</sub>(KBr)/cm<sup>-1</sup> 3050, 2976, 2907, 1599, 1453, 1264, 1246, 1197, 986, 884, 862, 748 and 702; δ<sub>H</sub>(200 MHz; CDCl<sub>3</sub>) 7.82–7.74 (4 H, br m), 7.49–7.40 (3 H, br m), 7.30–7.19 (5 H, br m), 4.74 (1 H, br t, J 5.9, HCO), 3.60 (2 H, d, J<sub>HP</sub> 20.5, CH<sub>2</sub>P), 3.10–3.00 (1 H, m, HCN), 2.67 (3 H, d, J 8.8, NCH<sub>3</sub>) and 0.64 (3 H, d, J 5.9, CCH<sub>3</sub>); δ<sub>P</sub>(80 MHz; CDCl<sub>3</sub>) 38.4 (1 P, s);  $\delta_{\rm C}(100 \text{ MHz}; \text{CDCl}_3)$  135.9 (d), 133.1 (d), 131.8 (d), 129.7 (d), 127.9 (br m), 127.8, 127.5 (d), 127.4, 127.2, 126.0, 125.9, 125.6 (br d), 82.2 (PhCO), 58.1 (d,  $J_{CP}$  9.6, CH<sub>3</sub>CN), 34.4 (d, J<sub>CP</sub> 119.3, CH<sub>2</sub>P), 28.3 (d, J<sub>CP</sub> 5.8, NCH<sub>3</sub>) and 14.2 (CH<sub>3</sub>C); m/z (EI) 351 (M<sup>+</sup>, 70%), 294 (21), 210 (46), 141 (64), 104 (100), 84 (85). Found: [M]<sup>+</sup>, 351.1384. C<sub>21</sub>H<sub>22</sub>O<sub>2</sub>PN requires m/z 351.1388.

(2S,4S,5R)-2-(2-Naphthylmethyl)-3,4-dimethyl-2-oxo-5phenyl-1,3,2 $\lambda^5$ -oxazaphospholidine (*trans*-isomer) 19. White solid (54%); mp 132–134 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_D^{22}$  +1.1 (c 0.0239 in MeOH) (Found: C, 71.7; H, 6.3; N, 4.0.  $C_{21}H_{22}$ -NO<sub>2</sub>P requires C, 71.8; H, 6.3; N, 4.0%);  $\nu_{max}$ (KBr)/cm<sup>-1</sup> 3058, 2960, 2925, 1508, 1452, 1243, 1234, 1189, 980, 856, 827, 752 and 701;  $\delta_{H}$ (200 MHz; CDCl<sub>3</sub>) 7.82–7.78 (4 H, br m), 7.50–7.38 (3 H, br m), 7.22 (3 H, br s), 7.08 (2 H, br s), 5.70 (1 H, d, J 5.9, HCO), 3.59 (2 H, d,  $J_{HP}$  20.5, CH<sub>2</sub>P), 3.54–3.44 (1 H, m, HCN), 2.70 (3 H, d, J 8.8, NCH<sub>3</sub>) and 0.10 (3 H, d, J 7.3, CCH<sub>3</sub>);  $\delta_{P}$ (80 MHz; CDCl<sub>3</sub>) 36.8 (1 P, s);  $\delta_{C}$ (100 MHz; CDCl<sub>3</sub>) 135.4 (d), 133.0 (d), 131.9 (d), 129.7 (d), 128.3 (d), 127.9 (br m), 127.8, 127.6, 127.3 (br d), 127.1, 126.0, 125.4, 125.3, 79.8 (PhCO), 60.6 (d,  $J_{CP}$  8.1, CH<sub>3</sub>CN), 35.4 (d,  $J_{CP}$  122.3, CH<sub>2</sub>P), 29.8 (d,  $J_{CP}$  6.6, NCH<sub>3</sub>) and 13.3 (CH<sub>3</sub>C); *m*/*z* (EI) 351 (M<sup>+</sup>, 50%), 294 (17), 210 (41), 141 (62), 104 (100), 84 (20). Found: [M]<sup>+</sup>, 351.1378. C<sub>21</sub>H<sub>22</sub>O<sub>2</sub>PN requires *m*/*z* 351.1388.

(2*R*,4*S*,5*R*)-2-(*m*-Phenylbenzyl)-3,4-dimethyl-2-oxo-5-phenyl-1,3,2 $\lambda^5$ -oxazaphospholidine (*cis*-isomer) 17. Colourless oil (24%); [ $\alpha$ ]<sub>D</sub><sup>22</sup> -47.1 (*c* 0.0133 in MeOH);  $\nu_{max}$ (KBr)/cm<sup>-1</sup> 3029, 2972, 2905, 1599, 1479, 1454, 1297, 1060, 974, 886 and 701;  $\delta_{H}$ (200 MHz; CDCl<sub>3</sub>) 7.60–7.23 (9 H, m), 4.78 (1 H, t, *J* 5.9, HCO), 3.51 (2 H, d, *J*<sub>HP</sub> 20.5, CH<sub>2</sub>P), 3.22–3.09 (1 H, m, HCN), 2.70 (3 H, d, *J* 10.3, NCH<sub>3</sub>) and 0.70 (3 H, d, *J* 7.4, CCH<sub>3</sub>);  $\delta_{P}$ (80 MHz; CDCl<sub>3</sub>) 38.2 (1 P, s);  $\delta_{C}$ (100 MHz; CDCl<sub>3</sub>) 141.4 (d), 140.5, 136.1 (d), 133.0 (d), 129.0 (d), 128.8, 128.5 (d), 128.3 (d), 128.2, 128.1, 127.4, 127.0, 126.1, 125.6 (d), 82.5 (PhCO), 58.4 (d, *J*<sub>CP</sub> 9.5, CH<sub>3</sub>CN), 34.6 (d, *J*<sub>CP</sub> 119.3, CH<sub>2</sub>P), 28.5 (d, *J*<sub>CP</sub> 5.9, NCH<sub>3</sub>) and 14.4 (CH<sub>3</sub>C); *m*/*z* (EI) 377 (M<sup>+</sup>, 60%), 362 (19), 210 (28), 167 (17), 104 (100). Found: [M]<sup>+</sup>, 377.1545. C<sub>23</sub>H<sub>24</sub>O<sub>2</sub>PN requires *m*/*z* 377.1545.

(2*S*,4*S*,5*R*)-2-(*m*-Phenylbenzyl)-3,4-dimethyl-2-oxo-5-phenyl-1,3,2λ<sup>5</sup>-oxazaphospholidine (*trans*-isomer) 20. White solid (56%); mp 120–122 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_{22}^{25}$  –58.7 (*c* 0.0267 in MeOH) (Found: C, 73.4; H, 6.4; N, 3.7. C<sub>23</sub>H<sub>24</sub>NO<sub>2</sub>P requires C, 73.2; H, 6.4; N, 3.7%);  $v_{max}$ (KBr)/cm<sup>-1</sup> 3021, 2971, 2909, 1597, 1479, 1452, 1252, 1213, 1064, 972, 887 and 703;  $\delta_{\rm H}$ (200 MHz; CDCl<sub>3</sub>) 7.59–7.11 (9 H, m), 5.69 (1 H, d, *J* 5.9, HCO), 3.51 (2 H, d, *J*<sub>CP</sub> 19.0, CH<sub>2</sub>P), 3.55–3.45 (1 H, m, HCN), 2.74 (3 H, d, *J* 8.8, NCH<sub>3</sub>) and 0.08 (3 H, d, *J* 7.3, CCH<sub>3</sub>);  $\delta_{\rm P}$ (80 MHz; CDCl<sub>3</sub>) 37.0 (1 P, s);  $\delta_{\rm C}$ (100 MHz; CDCl<sub>3</sub>) 141.2 (d), 140.3, 135.4 (d), 132.8 (d), 128.7 (m), 128.6, 127.9, 127.7, 127.2, 126.7, 125.4, 79.8 (PhCO), 60.9 (d, *J*<sub>CP</sub> 7.4, CH<sub>3</sub>CN), 35.0 (d, *J*<sub>CP</sub> 122.3, CH<sub>2</sub>P), 29.7 (d, *J*<sub>CP</sub> 6.6, NCH<sub>3</sub>) and 13.2 (*C*H<sub>3</sub>C); *m*/*z* (EI) 377 (M<sup>+</sup>, 100%), 362 (30), 210 (29), 167 (25), 104 (85). Found: [M]<sup>+</sup>, 377.1549. C<sub>23</sub>H<sub>24</sub>O<sub>2</sub>PN requires *m*/*z* 377.1545.

(2*R*,4*S*,5*R*)-2-Benzyl-3,4-dimethyl-2-oxo-5-phenyl-1,3,2λ<sup>5</sup>oxazaphospholidine (*cis*-isomer) 18. White solid (20%); mp 133– 134 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>); [ $\alpha$ ]<sub>D</sub><sup>22</sup> –40.2 (*c* 0.0438 in MeOH) (Found: C, 67.4; H, 6.7; N, 4.6. C<sub>17</sub>H<sub>20</sub>NO<sub>2</sub>P requires C, 67.8; H, 6.7; N, 4.65%); *v*<sub>max</sub>(KBr)/cm<sup>-1</sup> 3029, 2943, 2874, 1954, 1881, 1602, 1494, 1452, 1240, 1059, 982, 897 and 699;  $\delta_{\rm H}$ (200 MHz; CDCl<sub>3</sub>) 7.36–7.23 (10 H, m), 4.67 (1 H, t, *J* 5.9, HCO), 3.44 (2 H, d, *J*<sub>HP</sub> 19.0, CH<sub>2</sub>P), 3.17–3.03 (1 H, m, HCN), 2.68 (3 H, d, *J* 10.3, NCH<sub>3</sub>) and 0.68 (3 H, d, *J* 5.9, CCH<sub>3</sub>);  $\delta_{\rm P}$ (80 MHz; CDCl<sub>3</sub>) 38.4 (1 P, s);  $\delta_{\rm C}$ (100 MHz; CDCl<sub>3</sub>) 136.5 (br s), 132.8 (d), 129.7 (d), 128.6, 128.3, 128.1, 126.9 (br s), 126.3, 82.5 (PhCO), 58.6 (d, *J*<sub>CP</sub> 9.1, CH<sub>3</sub>CN), 34.8 (d, *J*<sub>CP</sub> 119.8, CH<sub>2</sub>P), 28.5 (d, *J*<sub>CP</sub> 5.5, NCH<sub>3</sub>) and 14.4 (CH<sub>3</sub>C); *m/z* (EI) 301 (M<sup>+</sup>, 26%), 147 (24), 104 (100), 91 (39), 84 (47). Found: [M]<sup>+</sup>, 301.1233. C<sub>17</sub>H<sub>20</sub>O<sub>2</sub>PN requires *m/z* 301.1232.

(2*S*,4*S*,5*R*)-2-Benzyl-3,4-dimethyl-2-oxo-5-phenyl-1,3,2 $\lambda^5$ oxazaphospholidine (*trans*-isomer) 21. White solid (41%); mp 169–171 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_D^{22}$  –6.2 (*c* 0.0488 in MeOH) (Found: C, 67.9; H, 6.8; N, 4.7. C<sub>17</sub>H<sub>20</sub>NO<sub>2</sub>P requires C, 67.8; H, 6.7; N, 4.65);  $\nu_{max}$ (KBr)/cm<sup>-1</sup> 3031, 2925, 2818, 1966, 1901, 1818, 1601, 1494, 1455, 1239, 1064, 980 and 701;  $\delta_{\rm H}$ (200 MHz; CDCl<sub>3</sub>) 7.30–7.09 (10 H, m), 5.69 (1 H, d, J 5.8, HCO), 3.58–3.42 (1 H, m, HCN), 3.42 (2 H, d, J<sub>HP</sub> 22.0, CH<sub>2</sub>P),

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2.69 (3 H, d, *J* 8.7, NCH<sub>3</sub>) and 0.15 (3 H, d, *J* 7.3, CCH<sub>3</sub>);  $\delta_{\rm P}(80 \text{ MHz}; \text{CDCl}_3)$  37.0 (1 P, s);  $\delta_{\rm C}(100 \text{ MHz}; \text{CDCl}_3)$  136.1 (d), 132.7 (d), 130.1 (d), 128.6 (d), 128.3, 128.0, 126.9 (d), 125.8, 80.2 (PhCO), 61.3 (d, *J*<sub>CP</sub> 7.4, CH<sub>3</sub>CN), 35.8 (d, *J*<sub>CP</sub> 123.6, CH<sub>2</sub>P), 30.2 (d, *J*<sub>CP</sub> 5.4, NCH<sub>3</sub>) and 13.7 (CH<sub>3</sub>C); *m/z* (EI) 301 (M<sup>+</sup>, 19%), 147 (46), 104 (79), 97 (100), 91 (46), 84 (93). Found: [M]<sup>+</sup>, 301.1239. C<sub>17</sub>H<sub>20</sub>O<sub>2</sub>PN requires *m/z* 301.1232.

#### General procedure for the preparation of fluorophosphonamidates 22–33

The same procedure as that described for the fluorination of 12 was used except phosphonamidates 16-21 were used as substrates. For the fluorination of phosphonamidates 17, 18, 20 and 21, NaHMDS was used as base. The fluorination of 16 and 19 was examined in detail using a variety of bases, counter-ions and conditions. For the conditions and results of these studies see Tables 2 and 3. Separation and purification of the fluorinated cis-isomers 22-27 was achieved by silica gel column chromatography using EtOAc-hexane (1:1) as eluent. In the case of the cis-isomers 22-27, the S-enantiomers (stereochemistry at the  $\alpha$ -carbon) exhibited larger  $R_{\rm f}$  values on silica TLC plates and eluted before the *R*-enantiomers during column chromatography. Separation and purification of the fluorinated trans-isomers 28-33 was achieved by silica gel column chromatography using EtOAc-hexane (7:3) as eluent. In the case of the trans-isomers 28-33, the R-enantiomers (stereochemistry at the  $\alpha$ -carbon) exhibited larger  $R_f$  values on silica TLC plates and eluted before the S-enantiomers during column chromatography.

(2R,4S,5R)-2-[(1S)-Fluoro(2-naphthyl)methyl]-3,4-dimethyl-2-oxo-5-phenyl-1,3,2 $\lambda^5$ -oxazaphospholidine 22. White solid (see Table 3 for yields); mp 169–171 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_{D}^{22}$ -102.5 (c 0.0268 in MeOH) (Found: C, 67.7; H, 5.8; N, 3.8. C<sub>21</sub>H<sub>21</sub>FNO<sub>2</sub>P requires C, 68.3; H, 5.7; N, 3.8%); v<sub>max</sub>(KBr)/ cm<sup>-1</sup> 3059, 2980, 2933, 1505, 1454, 1260, 1191, 1060, 971, 913, 890, 827, 757 and 701;  $\delta_{\rm H}$ (200 MHz; CDCl<sub>3</sub>) 8.04 (1 H, s), 7.93– 7.84 (3 H, br m), 7.71 (1 H, d, J 8.8), 7.52 (2 H, s), 7.37 (5 H, s), 6.21 (1 H, dd,  $J_{\rm HP}$  8.8 and  $J_{\rm HF}$  45.7, CHF), 5.72 (1 H, d, J 5.9, HCO), 3.77-3.69 (1 H, m, HCN), 2.23 (3 H, d, J 8.8, NCH<sub>3</sub>) and 0.78 (3 H, d, J 5.9, CCH<sub>3</sub>);  $\delta_{P}(80 \text{ MHz}; \text{CDCl}_{3})$  28.9 (1 P, d,  $J_{\rm PF}$  76.3);  $\delta_{\rm F}$ (188 MHz; CDCl<sub>3</sub>) –125.1 (1 F, dd,  $J_{\rm FH}$  45.7 and  $J_{\rm FP}$  76.3);  $\delta_{\rm C}$ (100 MHz; CDCl<sub>3</sub>) 135.8 (d), 133.1, 132.8 (d), 130.9 (d), 128.3, 128.2, 128.2, 128.0, 127.7, 126.4, 125.8, 124.4 (dd), 123.0 (dd), 89.8 (dd,  $J_{CP}$  149.4 and  $J_{CF}$  188.9, CHF), 82.5 (PhCO), 58.6 (d,  $J_{CP}$  9.5, CH<sub>3</sub>CN), 29.5 (d,  $J_{CP}$  4.3, NCH<sub>3</sub>) and 14.0 (CH<sub>3</sub>C); m/z (EI) 369 (M<sup>+</sup>, 66%), 210 (42), 159 (100), 104 (48). Found: [M]<sup>+</sup>, 369.1298. C<sub>21</sub>H<sub>21</sub>O<sub>2</sub>PNF requires *m*/*z* 369.1294.

(2R,4S,5R)-2-[(1R)-Fluoro(2-naphthyl)methyl]-3,4-dimethyl-**2-oxo-5-phenyl-1,3,2\lambda^5-oxazaphospholidine 25.** White solid (see Table 3 for yields); mp 135–137 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_{D}^{22}$ +40.8 (c 0.0135 in MeOH) (Found: C, 68.5; H, 5.7; N, 3.9. C<sub>21</sub>H<sub>21</sub>FNO<sub>2</sub>P requires C, 68.3; H, 5.7; N, 3.8%); v<sub>max</sub>(KBr)/ cm<sup>-1</sup> 3060, 2968, 2876, 1506, 1456, 1297, 1214, 1190, 1011, 976, 869, 748 and 701;  $\delta_{\rm H}(200 \text{ MHz}; \text{CDCl}_3)$  7.99 (1 H, s), 7.89–7.81 (3 H, br m), 7.64 (1 H, d, J 7.3), 7.57-7.44 (2 H, br m), 7.32 (5 H, s), 6.15 (1 H, dd,  $J_{\rm HP}$  4.4 and  $J_{\rm HF}$  45.7, CHF), 5.45 (1 H, br t, J 6.6, HCO), 3.77-3.73 (1 H, m, HCN), 2.82 (3 H, d, J 10.2, NCH<sub>3</sub>) and 0.79 (3 H, d, J 5.8, CCH<sub>3</sub>);  $\delta_{\rm P}(80 \text{ MHz}; \text{CDCl}_3)$  29.5  $(1 \text{ P}, d, J_{\text{PF}} 85.5); \delta_{\text{F}}(188 \text{ MHz}; \text{CDCl}_3) - 119.8 (1 \text{ F}, dd, J_{\text{FH}} 45.7)$ and  $J_{\rm FP}$  85.5);  $\delta_{\rm C}(100$  MHz; CDCl<sub>3</sub>) 135.8 (d), 133.4, 132.9 (d), 130.8 (dd), 128.4 (br d), 128.3, 128.3, 128.2, 127.7, 126.6, 126.4, 126.4, 126.1 (t), 123.8 (dd), 89.8 (dd,  $J_{CP}$  147.9 and  $J_{CF}$  186.0, CHF), 82.9 (PhCO), 58.5 (d,  $J_{CP}$  10.2, CH<sub>3</sub>CN), 28.5 (d,  $J_{CP}$ 6.6, NCH<sub>3</sub>) and 14.9 (d,  $J_{CP}$  3.6, CH<sub>3</sub>C); m/z (EI) 369 (M<sup>+</sup>, 31%), 210 (27), 159 (100), 104 (60). Found: [M]<sup>+</sup>, 369.1291. C<sub>21</sub>H<sub>21</sub>O<sub>2</sub>PNF requires *m*/*z* 369.1294.

(2R,4S,5R)-2-[(1S)-α-Fluoro(m-phenyl)benzyl]-3,4-dimethyl-**2-oxo-5-phenyl-1,3,2\lambda^5-oxazaphospholidine** 23. White solid (43%); mp 126–128 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_{D}^{22}$  –85.3 (c 0.0252 in MeOH) (Found: C, 69.4; H, 5.8; N, 3.5. C<sub>23</sub>H<sub>23</sub>FNO<sub>2</sub>P requires C, 69.9; H, 5.9; N, 3.55%); v<sub>max</sub>(KBr)/cm<sup>-1</sup> 3030, 2965, 2919, 2840, 1957, 1887, 1596, 1453, 1263, 1216, 1185, 1040, 992, 856 and 703;  $\delta_{\rm H}(200 \text{ MHz}; \text{CDCl}_3)$  7.83 (1 H, s), 7.66–7.30 (8 H, m), 6.12 (1 H, dd,  $J_{\rm HP}$  8.8 and  $J_{\rm HF}$  45.8, CHF), 5.69 (1 H, d, J 5.9, HCO), 3.80-3.66 (1 H, m, HCN), 2.31 (3 H, d, J 10.2, NCH<sub>3</sub>) and 0.81 (3 H, d, J 5.9, CCH<sub>3</sub>);  $\delta_{\rm P}(80~{\rm MHz};{\rm CDCl}_3)$  28.9  $(1 \text{ P, d}, J_{\text{PF}} 76.3); \delta_{\text{F}}(188 \text{ MHz}; \text{CDCl}_3) - 125.8 (1 \text{ F, dd}, J_{\text{FH}} 45.8)$ and  $J_{\rm FP}$  76.3);  $\delta_{\rm C}(100$  MHz; CDCl<sub>3</sub>) 141.4, 140.4, 135.8 (d), 134.1 (d), 128.9, 128.8, 128.4, 128.2, 127.6, 127.2, 127.1, 125.8, 124.3 (dd), 124.0 (dd), 89.7 (dd, J<sub>CP</sub> 149.8 and J<sub>CF</sub> 189.3, CHF), 82.5 (PhCO), 58.7 (d, J<sub>CP</sub> 9.6, CH<sub>3</sub>CN), 29.5 (d, J<sub>CP</sub> 4.4, NCH<sub>3</sub>) and 14.1 (*C*H<sub>3</sub>C); *m/z* (EI) 395 (M<sup>+</sup>, 45%), 210 (71), 185 (60), 146 (42), 104 (100). Found: [M]<sup>+</sup>, 395.1464. C<sub>23</sub>H<sub>23</sub>O<sub>2</sub>PNF requires *m*/*z* 395.1460.

(2R,4S,5R)-2-[(1R)-a-Fluoro(m-phenyl)benzyl]-3,4-dimethyl-**2-oxo-5-phenyl-1,3,2**λ<sup>5</sup>-oxazaphospholidine 26. White solid (25%); mp 147–149 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_D^{22}$  +28.5 (c 0.0215 in MeOH) (Found: C, 69.6; H, 5.9; N, 3.5. C<sub>23</sub>H<sub>23</sub>FNO<sub>2</sub>P requires C, 69.9; H, 5.9; N, 3.55%); v<sub>max</sub>(KBr)/cm<sup>-1</sup> 3036, 2970, 2866, 1950, 1886, 1597, 1476, 1258, 1212, 1044, 960, 862 and 700; δ<sub>H</sub>(200 MHz; CDCl<sub>3</sub>) 7.75 (1 H, s), 7.66–7.34 (8 H, m), 6.06 (1 H, dd, J<sub>HP</sub> 4.4 and J<sub>HF</sub> 45.0, CHF), 5.44 (1 H, t, J 6.6, HCO), 3.83-3.72 (1 H, m, HCN), 2.82 (3 H, d, J 10.3, NCH<sub>3</sub>) and 0.81 (3 H, d, J 7.3, CCH<sub>3</sub>); δ<sub>P</sub>(80 MHz; CDCl<sub>3</sub>) 29.6 (1 P, d, J<sub>PF</sub> 86.2);  $\delta_{\rm F}(188 \text{ MHz}; \text{CDCl}_3) - 120.6 (1 \text{ F}, \text{ dd}, J_{\rm FH} 45.0 \text{ and } J_{\rm FP} 86.2);$  $\delta_{\rm C}(100 \text{ MHz}; \text{CDCl}_3)$  141.5 (br d), 140.5, 135.8 (d), 133.9 (dd), 129.0, 128.7, 128.4, 128.3, 127.7, 127.5, 127.2, 126.4, 125.4 (dd), 89.6 (dd, J<sub>CP</sub> 150.8 and J<sub>CF</sub> 186.0, CHF), 83.0 (PhCO), 58.5 (d, J<sub>CP</sub> 10.2, CH<sub>3</sub>CN), 28.4 (d, J<sub>CP</sub> 6.6, NCH<sub>3</sub>) and 14.9 (CH<sub>3</sub>C); *m*/*z* (EI) 395 (M<sup>+</sup>, 45%), 210 (73), 185 (63), 146 (42), 104 (100). Found: [M]<sup>+</sup>, 395.1460. C<sub>23</sub>H<sub>23</sub>O<sub>2</sub>PNF requires *m*/*z* 395.1450.

(2R,4S,5R)-2-[(1S)-a-Fluorobenzyl]-3,4-dimethyl-2-oxo-5phenyl-1,3,2 $\lambda$ <sup>5</sup>-oxazaphospholidine 24. White solid (29%); mp 129-131 °C (from pentane-CH<sub>2</sub>Cl<sub>2</sub>); [a]<sub>D</sub><sup>22</sup> -93.9 (c 0.0411 in MeOH) (Found: C, 63.4; H, 6.0; N, 4.4.  $C_{17}H_{19}FNO_2P$  requires C, 63.9; H, 6.0; N, 4.4%);  $\nu_{max}(KBr)/cm^{-1}$  3086, 2974, 2867, 1495, 1452, 1324, 1265, 1218, 1187, 987, 956 and 700;  $\delta_{\rm H}(200$ MHz; CDCl<sub>3</sub>) 7.53–7.26 (10 H, m), 5.98 (1 H, dd, J<sub>HP</sub> 4.4 and J<sub>HF</sub> 45.4, CHF), 5.38 (1 H, t, J 6.6, HCO), 3.79–3.67 (1 H, m, HCN), 2.81 (3 H, d, J 9.5, NCH<sub>3</sub>) and 0.80 (3H, d, J 5.8, CCH<sub>3</sub>);  $\delta_{P}(80 \text{ MHz}; \text{CDCl}_{3})$  29.5 (1 P, d,  $J_{PF}$  86.2);  $\delta_{F}(188 \text{ MHz};$ CDCl<sub>3</sub>) -120.4 (1 F, dd,  $J_{FH}$  45.4 and  $J_{FP}$  86.2);  $\delta_{C}$ (100 MHz; CDCl<sub>3</sub>) 136.1 (d), 133.8 (d), 128.9 (br d), 128.5 (br s), 128.4, 126.8 (d), 126.6 (d), 126.5, 90.0 (dd,  $J_{CP}$  148.2 and  $J_{CF}$  185.8, CHF), 82.9 (PhCO), 58.5 (d, *J*<sub>CP</sub> 9.2, CH<sub>3</sub>*C*N), 28.5 (d, *J*<sub>CP</sub> 5.5, NCH<sub>3</sub>) and 14.9 (d,  $J_{CP}$  2.7,  $CH_3C$ ); m/z (EI) 319 (M<sup>+</sup>, 18%), 210 (58), 192 (29), 104 (100), 84 (98). Found: [M]<sup>+</sup>, 319.1145. C<sub>17</sub>H<sub>19</sub>O<sub>2</sub>PNF requires *m*/*z* 319.1137.

(2R,4S,5R)-2-[(1R)-α-Fluorobenzyl]-3,4-dimethyl-2-oxo-5-

**phenyl-1,3,2λ<sup>5</sup>-oxazaphospholidine 27.** White solid (15%); mp 114–116 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_{D}^{22}$  +26.3 (*c* 0.0404 in MeOH) (Found: C, 63.6; H, 6.05; N, 4.4. C<sub>17</sub>H<sub>19</sub>FNO<sub>2</sub>P requires C, 63.9; H, 6.0; N, 4.4%);  $v_{max}$ (KBr)/cm<sup>-1</sup> 3442, 3059, 2983, 1644, 1494, 1453, 1336, 1263, 1218, 1195, 1058, 958 and 701;  $\delta_{H}$ (200 MHz; CDCl<sub>3</sub>) 7.57–7.27 (10 H, m), 6.01 (1 H, dd,  $J_{HP}$  8.0 and  $J_{HF}$  45.8, CHF), 5.61 (1 H, br t, *J* 2.9, HCO), 3.74–3.60 (1 H, m, HCN), 2.25 (3 H, d, *J* 10.2, NCH<sub>3</sub>) and 0.76 (3 H, d, *J* 5.9, CCH<sub>3</sub>);  $\delta_{P}$ (80 MHz; CDCl<sub>3</sub>) 28.9 (1 P, d,  $J_{PF}$  79.4);  $\delta_{C}$ (100 MHz; CDCl<sub>3</sub>) 136.2 (br d), 133.9 (d), 128.5 (br s), 126.1 (br s), 125.6 (br s), 90.1 (dd,  $J_{CP}$  149.2 and  $J_{CF}$  188.5, CHF), 82.6 (PhCO), 58.9 (d,  $J_{CP}$  9.2, CH<sub>3</sub>CN), 29.4 (d,  $J_{CP}$  4.6, NCH<sub>3</sub>) and 14.2 (d,  $J_{CP}$  2.7, CH<sub>3</sub>C); *m/z* (EI) 319 (M<sup>+</sup>, 19%), 210 (59),

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192 (27), 104 (100). Found:  $[M]^+$ , 319.1126.  $C_{17}H_{19}O_2PNF$  requires *m*/*z* 319.1137.

(2S,4S,5R)-2-[(1R)-Fluoro(2-naphthyl)methyl]-3,4-dimethyl-2-oxo-5-phenyl-1,3,2 $\lambda^5$ -oxazaphospholidine 28. White solid (see Table 2 for yields); mp 125–127 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_{D}^{22}$ +238.6 (c 0.0331 in MeOH) (Found: C, 68.4; H, 6.1; N, 3.7. C21H21FNO2P requires C, 68.3; H, 5.7; N, 3.8%); vmax(KBr)/ cm<sup>-1</sup> 3059, 2986, 2966, 1507, 1455, 1259, 1178, 1065, 1024, 965, 862, 829, 756 and 704;  $\delta_{\rm H}$ (200 MHz; CDCl<sub>3</sub>) 7.99 (1 H, s), 7.93– 7.84 (3 H, br m), 7.66 (1 H, d, J 7.3), 7.55–7.47 (2 H, br m), 7.39 (5 H, s), 6.22 (1 H, dd, J<sub>HP</sub> 8.1 and J<sub>HF</sub> 45.8, CHF), 5.84 (1 H, d, J 5.8, HCO), 3.74-3.61 (1 H, m, HCN), 2.33 (3 H, d, J 8.8, NCH<sub>3</sub>) and 0.90 (3 H, d, J 7.3, CCH<sub>3</sub>); δ<sub>P</sub>(80 MHz; CDCl<sub>3</sub>) 28.0  $(1 \text{ P}, d, J_{\text{PF}} 80.9); \delta_{\text{F}}(188 \text{ MHz}; \text{CDCl}_3) - 119.7 (1 \text{ F}, dd, J_{\text{FH}} 45.8)$ and  $J_{\rm FP}$  80.9);  $\delta_{\rm C}(100$  MHz; CDCl<sub>3</sub>) 135.4 (d), 133.1, 132.8 (d), 130.8 (d), 128.2, 128.2, 128.1, 128.0, 127.6, 126.4, 126.3, 125.7, 124.8 (dd), 123.1 (dd), 88.0 (dd, J<sub>CP</sub> 152.0 and J<sub>CF</sub> 192.3, CHF), 80.5 (PhCO), 61.1 (d, J<sub>CP</sub> 9.5, CH<sub>3</sub>CN), 30.8 (d, J<sub>CP</sub> 5.1, NCH<sub>3</sub>) and 14.8 (d, J<sub>CP</sub> 3.7, CH<sub>3</sub>C); m/z (EI) 369 (M<sup>+</sup>, 61%), 210 (40), 159 (100), 104 (43). Found: [M]<sup>+</sup>, 369.1301. C<sub>21</sub>H<sub>21</sub>O<sub>2</sub>PNF requires m/z 369.1294.

(2S,4S,5R)-2-[(1S)-Fluoro(2-naphthyl)methyl]-3,4-dimethyl-2-oxo-5-phenyl-1,3, $2\lambda^5$ -oxazaphospholidine 31. White solid (see Table 2 for yields). mp 181–183 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>); [a]<sup>22</sup><sub>D</sub> -215.3 (c 0.0273 in MeOH) (Found: C, 68.3; H, 6.1; N, 3.8. C<sub>21</sub>H<sub>21</sub>FNO<sub>2</sub>P requires C, 68.3; H, 5.7; N, 3.8%); v<sub>max</sub>(KBr)/ cm<sup>-1</sup> 3061, 2985, 2969, 1507, 1454, 1251, 1185, 1062, 973, 955, 876, 857, 752 and 702;  $\delta_{\rm H}$ (200 MHz; CDCl<sub>3</sub>) 8.06 (1 H, s), 7.95– 7.84 (3 H, br m), 7.73 (1 H, d, J 7.4), 7.54-7.48 (2 H, br m), 7.42–7.27 (5 H, m), 6.04 (1 H, dd, J<sub>HP</sub> 4.4 and J<sub>HF</sub> 45.8, CHF), 5.82 (1 H, d, J 5.8, HCO), 3.82-3.75 (1 H, m, HCN), 2.89 (3 H, d, J 8.8, NCH<sub>3</sub>) and 0.79 (3 H, d, J 7.3, CCH<sub>3</sub>); δ<sub>P</sub>(80 MHz; CDCl<sub>3</sub>) 28.5 (1 P, d,  $J_{PF}$  87.0);  $\delta_{F}$ (188 MHz; CDCl<sub>3</sub>) -114.9 (1 F, dd,  $J_{\text{FH}}$  45.8 and  $J_{\text{FP}}$  87.0);  $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$  135.4 (d), 133.4, 132.9 (d), 130.9 (dd), 128.4 (br d), 128.3, 128.1, 128.1, 127.7, 126.5, 126.4, 126.3 (m), 125.6, 123.9 (dd), 87.9 (dd, J<sub>CP</sub> 151.6 and J<sub>CF</sub> 189.7, CHF), 80.8 (PhCO), 61.1 (d, J<sub>CP</sub> 8.8, CH<sub>3</sub>CN), 29.5 (d, J<sub>CP</sub> 6.6, NCH<sub>3</sub>) and 14.1 (d, J<sub>CP</sub> 2.9, CH<sub>3</sub>C); m/z (EI) 369 (M<sup>+</sup>, 66%), 210 (38), 159 (100), 104 (42). Found: [M]<sup>+</sup>, 369.1297. C<sub>21</sub>H<sub>21</sub>O<sub>2</sub>PNF requires *m*/*z* 369.1294.

(2S,4S,5R)-2-[(1R)-α-Fluoro(m-phenyl)benzyl]-3,4-dimethyl-2-oxo-5-phenyl-1,3,2 $\lambda^5$ -oxazaphospholidine 29. White hygroscopic solid (53%);  $[a]_{D}^{22}$  +27.1 (c 0.0240 in MeOH) (Found: C, 69.4; H, 6.05; N, 3.5.  $C_{23}H_{23}FNO_2P$  requires C, 69.9; H, 5.9; N, 3.55%);  $v_{max}(KBr)/cm^{-1}$  3031, 2970, 2933, 2829, 1954, 1888, 1732, 1599, 1478, 1258, 1184, 1064, 971, 860 and 701;  $\delta_{\rm H}(200$ MHz; CDCl<sub>3</sub>) 7.85 (1 H, s), 7.71–7.34 (8 H, m), 6.19 (1 H, dd,  $J_{\rm HP}$  8.1 and  $J_{\rm HF}$  45.8, CHF), 5.93 (1 H, d, J 5.9, HCO), 3.80– 3.74 (1 H, m, HCN), 2.50 (3 H, d, J 8.8, NCH<sub>3</sub>) and 0.95 (3 H, d, J 5.9, CCH<sub>3</sub>); δ<sub>P</sub>(80 MHz; CDCl<sub>3</sub>) 27.9 (1 P, d, J<sub>PF</sub> 82.4);  $\delta_{\rm F}(188~{\rm MHz};~{\rm CDCl_3})$  –120.3 (1 F, dd,  $J_{\rm FH}$  45.8 and  $J_{\rm FP}$  82.4);  $\delta_{\rm C}(100 \text{ MHz}; \text{CDCl}_3)$  141.3 (br d), 140.3, 135.5 (d), 134.1 (d), 128.9, 128.7, 128.3, 128.2, 127.5, 127.3, 127.0, 125.8, 124.6 (dd), 124.3 (dd), 87.9 (dd,  $J_{CP}$  151.9 and  $J_{CF}$  195.2, CHF), 80.6 (PhCO), 61.2 (d,  $J_{CP}$  9.5, CH<sub>3</sub>CN), 30.9 (d,  $J_{CP}$  5.9, NCH<sub>3</sub>) and 14.9 (CH<sub>3</sub>C); m/z (EI) 395 (M<sup>+</sup>, 49%), 210 (69), 185 (63), 146 (37), 104 (100). Found: [M]<sup>+</sup>, 395.1464. C<sub>23</sub>H<sub>23</sub>O<sub>2</sub>PNF requires m/z 395.1454.

(2*S*,4*S*,5*R*)-2-[(1*S*)-α-Fluoro(*m*-phenyl)benzyl]-3,4-dimethyl-2-oxo-5-phenyl-1,3,2 $\lambda$ <sup>5</sup>-oxazaphospholidine 32. White solid (32%); mp 131–133 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>); [*a*]<sub>D</sub><sup>22</sup> – 234.6 (*c* 0.0251 in MeOH) (Found: C, 70.1; H, 5.9; N, 3.7. C<sub>23</sub>H<sub>23</sub>FNO<sub>2</sub>P requires C, 69.9; H, 5.9; N, 3.55%);  $\nu_{max}$ (KBr)/cm<sup>-1</sup> 3032, 2970, 2937, 2824, 1947, 1878, 1737, 1597, 1478, 1255, 1114, 1064, 954, 859 and 699;  $\delta_{\rm H}$ (200 MHz; CDCl<sub>3</sub>) 7.92 (1 H, s), 7.72–7.34 (8 H, m), 6.15 (1 H, dd,  $J_{\rm HF}$  45.6 and  $J_{\rm HP}$  4.4, CHF), 5.90 (1 H, d, J 5.8, HCO), 3.90–3.83 (1 H, m, HCN), 2.98 (3 H, d, J 8.7, NCH<sub>3</sub>) and 0.84 (3 H, d, J 7.3, CCH<sub>3</sub>);  $\delta_{\rm P}(80$  MHz; CDCl<sub>3</sub>) 28.3 (1 P, d,  $J_{\rm PF}$  88.5);  $\delta_{\rm F}(188$  MHz; CDCl<sub>3</sub>) –115.6 (1 F, dd,  $J_{\rm FH}$  45.8 and  $J_{\rm FP}$  88.5);  $\delta_{\rm C}(100$  MHz; CDCl<sub>3</sub>) 141.4 (d), 140.3, 135.3 (d), 134.1 (dd), 128.9, 128.6, 128.2, 128.1, 127.5, 127.4, 127.0, 125.5, 125.4, 87.7 (dd,  $J_{\rm CP}$  150.5 and  $J_{\rm CF}$  187.8, CHF), 80.6 (PhCO), 61.0 (d,  $J_{\rm CP}$  8.8, CH<sub>3</sub>CN), 29.4 (d,  $J_{\rm CP}$  6.6, NCH<sub>3</sub>) and 13.9 (CH<sub>3</sub>C); *m*/*z* (EI) 395 (M<sup>+</sup>, 52%), 210 (73), 185 (65), 146 (40), 104 (100). Found: [M]<sup>+</sup>, 395.1445. C<sub>23</sub>H<sub>23</sub>O<sub>2</sub>PNF requires *m*/*z* 395.1450.

(2S,4S,5R)-2-[(1R)-α-Fluorobenzyl]-3,4-dimethyl-2-oxo-5-

**phenyl-1,3,2** $\lambda^5$ **-oxazaphospholidine 30.** Colorless oil (30%);  $[a]_{12}^{22}$  +26.3 (*c* 0.0476 in MeOH)  $v_{max}$ (KBr)/cm<sup>-1</sup> 3440, 3063, 2914, 1633, 1495, 1453, 1333, 1257, 1214, 1181, 972 and 699;  $\delta_{\rm H}$ (200 MHz; CDCl<sub>3</sub>) 7.56–7.26 (10 H, m), 6.04 (1 H, dd,  $J_{\rm HP}$  8.0 and  $J_{\rm HF}$  45.8, CHF), 5.83 (1 H, d, *J* 5.9, HCO), 3.74–3.61 (1 H, m, HCN), 2.38 (3 H, d, *J* 8.6, NCH<sub>3</sub>) and 0.86 (3H, d, *J* 6.6, CCH<sub>3</sub>);  $\delta_{\rm P}$ (80 MHz; CDCl<sub>3</sub>) 27.9 (1 P, d,  $J_{\rm PF}$  79.3);  $\delta_{\rm F}$ (188 MHz; CDCl<sub>3</sub>) –120.3 (1 F, dd,  $J_{\rm FH}$  45.8 and  $J_{\rm FP}$  79.3);  $\delta_{\rm C}$ (100 MHz; CDCl<sub>3</sub>) 135.8 (d), 133.8 (d), 128.4 (br s), 125.9 (br s), 88.3 (dd,  $J_{\rm CP}$  151.9 and  $J_{\rm CF}$  190.4, CHF), 80.7 (PhCO), 61.4 (d,  $J_{\rm CP}$  9.2, CH<sub>3</sub>*C*N), 30.9 (d,  $J_{\rm CP}$  5.5, NCH<sub>3</sub>) and 14.9 (d,  $J_{\rm CP}$  3.7, *C*H<sub>3</sub>C); *m*/z (EI) 319 (M<sup>+</sup>, 31%), 210 (69), 192 (33), 104 (100). Found: [M]<sup>+</sup>, 319.1137. C<sub>17</sub>H<sub>19</sub>O<sub>2</sub>PNF requires *m*/z 319.1137.

(2S,4S,5R)-2-[(1S)-α-Fluorobenzyl]-3,4-dimethyl-2-oxo-5phenyl-1,3,2 $\lambda^5$ -oxazaphospholidine 33. White solid (17%); mp 165–167 °C (from pentane–CH<sub>2</sub>Cl<sub>2</sub>);  $[a]_{D}^{22}$  –108.3 (c 0.0263 in MeOH) (Found: C, 63.5; H, 6.0; N, 4.4.  $C_{17}H_{19}FNO_2P$  requires C, 63.9; H, 6.0; N, 4.4%);  $v_{max}(KBr)/cm^{-1}$  3383, 3059, 2971, 1603, 1494, 1455, 1334, 1259, 1184, 1067, 977 and 699;  $\delta_{\rm H}(200$ MHz; CDCl<sub>3</sub>) 7.62–7.11 (10 H, m), 5.87 (1 H, dd, J<sub>HP</sub> 4.4 and J<sub>HF</sub> 45.5, CHF), 5.81 (1 H, d, J 5.8, HCO), 3.83–3.70 (1 H, m, HCN), 2.86 (3 H, d, J 8.8, NCH<sub>3</sub>) and 0.76 (3 H, d, J 7.3, CCH<sub>3</sub>);  $\delta_{P}(80 \text{ MHz}; \text{CDCl}_{3}) 28.3 (1 \text{ P}, \text{d}, J_{PF} 87.0); \delta_{F}(188 \text{ MHz};$ CDCl<sub>3</sub>) -115.2 (1 F, dd,  $J_{FH}$  45.5 and  $J_{FP}$  87.0);  $\delta_{C}$ (100 MHz; CDCl<sub>3</sub>) 135.7 (d), 133.7 (d), 129.9, 128.6, 128.4, 128.3, 126.9 (br t), 125.8, 88.2 (dd, J<sub>CP</sub> 151.9 and J<sub>CF</sub> 189.4, CHF), 80.9 (PhCO), 61.5 (d,  $J_{CP}$  8.3, CH<sub>3</sub>CN), 29.7 (d,  $J_{CP}$  6.4, NCH<sub>3</sub>) and 14.3 (d, J<sub>CP</sub> 2.7, CH<sub>3</sub>C); m/z (EI) 319 (M<sup>+</sup>, 13%), 210 (43), 147 (100), 104 (72), 84 (38). Found:  $[M]^+$ , 319.1147.  $C_{17}H_{19}O_2PNF$ requires *m*/*z* 319.1137.

#### General procedure for synthesis of chiral phosphonic acids 4-9

A solution of the oxazaphospholone (22-33) in 10% TFA-MeOH (approximately 1 cm3 10% TFA-MeOH/0.1 mmol of 22–33) was stirred at 25 °C overnight. The solution was then concentrated in vacuo, re-dissolved in benzene and reconcentrated a total of 3 times prior to being placed under high vacuum for 2 h. The resulting product was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (approximately 3–5 cm<sup>3</sup>/1 mmol of 22–33) and stirred at 25 °C for 24 h in the presence of TMSBr (10 equiv.). The solution was concentrated in vacuo and placed under high vacuum for several hours. Anhydrous ether was then added followed by filtration and concentration of the filtrate (if a precipitate formed during the rotary evaporation, more anhydrous ether was added and the suspension re-filtered). The filtrate was dissolved in MeOH, containing 1 drop of water, and stirred for 15 min. The solution was then concentrated in vacuo and the resulting product was washed extensively with benzene and CH<sub>2</sub>Cl<sub>2</sub> to yield pure product. In addition to spectroscopic analysis of phosphonic acids 4-9 (see below), their purity was also examined by analytical reversed phase HPLC (solvent A: acetonitrile; solvent B: water with 0.1% TFA modifier) using the following gradient: 0 min: 25% A; 5 min: 25% A; 10 min: 100% A; 15 min: 100% A; 20 min: 75% A; 30 minutes: 25% A. All of the phosphonic acids were indicated to be pure by the criterion of analytical HPLC. The ee's of the phosphonic acids were

	22	23	24
Chemical formula	C <sub>21</sub> H <sub>21</sub> FNO <sub>2</sub> P	C <sub>23</sub> H <sub>23</sub> FNO <sub>2</sub> P	C <sub>17</sub> H <sub>19</sub> FNO <sub>2</sub> P
Formula weight	369.36	395.39	319.30
Crystal system	orthorhombic	orthorhombic	orthorhombic
Space group	P2(1)2(1)2(1)	P2(1)2(1)2	P2(1)2(1)2(1)
Absorption coefficient	$0.172 \text{ mm}^{-1}$	$0.167 \text{ mm}^{-1}$	$0.191 \text{ mm}^{-1}$
Unit cell dimensions			
a/Å	5.7212(4)	11.8451(5)	5.7208(2)
b/Å	11.5757(16)	27.3815(19)	11.2412(8)
c/Å	28.177(4)	6.0985(8)	24.5839(15)
a/°	90	90	90
βI°	90	90	90
y/°	90	90	90
Unit cell volume/Å <sup>3</sup>	1866.1(4)	1978.0(3)	1580.96(16)
Temperature/K	100.0(1)	100.0(1)	100.0(1)
Z	4	4	4
Reflections collected	6987	9348	7844
Independent reflections	1586 [R(int) = 0.143]	3440 [R(int) = 0.090]	3556 [R(int) = 0.070]
<i>R</i> indices (all data)			
<i>R</i> 1	0.0887	0.1102	0.0717
wR2	0.1171	0.1080	0.1000
Final R indices			
<i>R</i> 1	0.0521	0.0552	0.0452
wR2	0.1049	0.0949	0.0924
Goodness-of-fit on $F^2$	1.004	0.952	0.949

determined to be >97% using the  $^{19}$ F-NMR method described below.

(*R*)-Fluoro(2-naphthyl)methylphosphonic acid 4. Obtained as a white solid in 57% yield from 25 and 62% yield from 28; mp 180–181 °C (decomp.); HPLC retention time = 3.65 min;  $[a]_{22}^{12}$  +45.7 (*c* 0.0433 in MeOH);  $v_{max}$ (KBr)/cm<sup>-1</sup>2790 (br), 2265 (br), 1602, 1509, 1369, 1236, 1209, 1047, 940, 817 and 742;  $\delta_{\rm H}$ (200 MHz; CD<sub>3</sub>OD) 7.97 (1 H, s), 7.89–7.85 (3 H, br m), 7.63 (1 H, d, *J* 8.8), 7.50–7.46 (2 H, br m) and 5.88 (1 H, dd, *J*<sub>HP</sub> 8.8 and *J*<sub>HF</sub> 45.8, CHF);  $\delta_{\rm P}$ (80 MHz; CD<sub>3</sub>OD) 15.4 (1 P, d, *J*<sub>PF</sub> 83.9);  $\delta_{\rm F}$ (188 MHz; CD<sub>3</sub>OD) –120.2 (1 F, dd, *J*<sub>FH</sub> 45.8 and *J*<sub>FP</sub> 83.9);  $\delta_{\rm C}$ (100 MHz; CD<sub>3</sub>OD) 134.9, 134.4 (d), 133.1 (dd), 129.1, 129.0 (br d), 128.7, 127.6, 127.6 (m), 127.4, 125.5 (br dd) and 91.7 (dd, *J*<sub>CP</sub> 166.2 and *J*<sub>CF</sub> 180.1, CHF); *m/z* (ES) 239 (100%).

(S)-Fluoro(2-naphthyl)methylphosphonic acid 5. Obtained as a white solid 58% yield from 22 and 65% yield from 31. HPLC chromatogram, mp, and all spectral data were identical to those reported for 4. Optical rotation was approximately the same as that obtained for 4 but of opposite sign.

(*R*)-*a*-Fluoro(*m*-phenyl)benzylphosphonic acid 6. Obtained as a white solid in 64% yield from 26 and 70% yield from 29; HPLC retention time = 3.35 min;  $[a]_{D}^{22}$  +31.1 (*c* 0.0211 in MeOH); mp 175 °C (decomp.);  $\nu_{max}(\text{KBr})/\text{cm}^{-1}$  3035 (br), 2333 (br), 1598, 1478, 1253, 1183, 1025, 952, 753 and 699;  $\delta_{\text{H}}(200 \text{ MHz}; \text{CD}_{3}\text{OD})$  7.76 (1 H, s), 7.63–7.30 (8 H, br m) and 5.78 (1 H, dd,  $J_{\text{HP}}$  8.8 and  $J_{\text{HF}}$  44.0, CHF);  $\delta_{\text{P}}(80 \text{ MHz};$ CD<sub>3</sub>OD) 15.1 (1 P, d,  $J_{\text{PF}}$  85.4);  $\delta_{\text{F}}(188 \text{ MHz}; \text{CD}_{3}\text{OD})$  -120.6 (1 F, dd,  $J_{\text{FH}}$  44.0 and  $J_{\text{FP}}$  85.4);  $\delta_{\text{C}}(100 \text{ MHz}; \text{CD}_{3}\text{OD})$  142.5, (d), 141.9, 136.4 (d), 129.9, 129.9, 128.6, 128.4, 128.0, 127.0 (t), 126.7 (t) and 91.5 (dd,  $J_{\text{CP}}$  165.5 and  $J_{\text{CF}}$  180.1, CHF); *m*/*z* (ES) 265 (100%).

(S)- $\alpha$ -Fluoro(*m*-phenyl)benzylphosphonic acid 7. Obtained as a white solid in 69% yield from 23 and 67% yield from 32. HPLC chromatogram, mp and all spectral data were identical to those reported for 6. Optical rotation was approximately the same as that obtained for 6 but of opposite sign.

(*R*)-Fluoro(phenyl)methylphosphonic acid 8. Obtained as a white solid in 39% yield from 27 and 47% yield from 30; HPLC retention time = 3.57 min;  $[a]_{D}^{22}$  +36.9 (*c* 0.0489 in MeOH); mp 114–115 °C;  $v_{max}$ (KBr)/cm<sup>-1</sup> 3421, 2355, 1634, 1494, 1454, 1196,

1020, 946, 783, 732, 697, 631 and 542;  $\delta_{\rm H}(200 \text{ MHz; CD}_3\text{OD})$ 7.51–7.37 (5 H, m) and 5.68 (1 H, dd,  $J_{\rm HP}$  8.1 and  $J_{\rm HF}$  44.7, CHF);  $\delta_{\rm P}(80 \text{ MHz; CD}_3\text{OD})$  15.2 (1 P, d,  $J_{\rm PF}$  85.5);  $\delta_{\rm F}(188 \text{ MHz; CD}_3\text{OD})$  –120.5 (1 F, dd,  $J_{\rm FH}$  44.7 and  $J_{\rm FP}$  85.5);  $\delta_{\rm C}(100 \text{ MHz; CD}_3\text{OD})$  135.8 (d), 129.9, 129.3, 128.2 (br t) and 91.7 (dd,  $J_{\rm CP}$  166.6 and  $J_{\rm CF}$  179.4, CHF); m/z (ES) 189 (100%).

(S)-Fluoro(phenyl)methylphosphonic acid 9. Obtained as a white solid in 46% yield from 24 and 41% yield from 33. HPLC chromatogram, mp and all spectral data were identical to those reported for 8. Optical rotation was approximately the same as that obtained for 8 but of opposite sign.

### Determination of enantiomeric excess of phosphonic acids 4-9

A mixture of the phosphonic acid (4–9, 10–15 mg) and quinidine (1 equiv.) was dissolved in  $\text{CDCl}_3$  (approximately 1 cm<sup>3</sup>), shaken until a homogeneous solution was obtained, and the <sup>19</sup>F-NMR was recorded. For each of the phosphonic acids 4–9, only a single set of doublet of doublets was evident in the spectra indicating that 4–9 were obtained in >97% ee.

# Kinetic studies with PTP1B

Rates of PTP1B-catalyzed dephosphorylation in the presence or absence of inhibitors were determined using FDP as substrate in assay buffer containing 100 mM BIS-TRIS, 4 mM EDTA, 5 mM DTT (dithiothreitol) and 0.2 mg mL<sup>-1</sup> BSA, pH 6.5 at 25 °C as previously described<sup>3</sup> except 5% DMSO was present in the reaction mixture. IC<sub>50</sub> determinations were determined at nine or ten different inhibitor concentrations with FDP at  $K_m$  concentration (20 µM).  $K_i$ 's for **2**, **3**, **4**, and **6** were determined by measuring the initial rate ( $\nu$ ) using various FDP concentrations (20, 25, 35, 50 and 100 µM FDP) at various fixed concentrations of inhibitor, [(0, 20, 40, 60, 80 and 100 µM) **2**, (0, 20, 40, 50, 60 and 80 µM) **3**, (0, 300, 500, 750, 1000 and 1500 µM) **4**, (0, 100, 200, 300, 500 and 750) **6**] as previously described.<sup>3</sup> All assays were performed in duplicate.

#### X-Ray structural characterization †

A summary of selected crystallographic data is given in Tables 5 and 6. Data were collected on a Nonius KappaCCD diffract-

<sup>†</sup> CCDC reference number 207/399. See http://www.rsc.org/suppdata/ p1/a9/a908086d for crystallographic files in .cif format.

	25	26	27
Chemical formula	C <sub>11</sub> H <sub>11</sub> FNO <sub>2</sub> P	C,,H,,FNO,P	C17H10FNO3P
Formula weight	369.36	395.39	319.30
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	P2(1)	P2(1)2(1)2	P2(1)
Absorption coefficient	$0.171 \text{ mm}^{-1}$	$0.162 \text{ mm}^{-1}$	$0.189 \text{ mm}^{-1}$
Unit cell dimensions			
a/Å	6.6666(4)	12.272(2)(5)	9.9593(7)
b/Å	12.1266(5)	24.9928(3)	9.9593(7)
c/Å	11.6697	6.6447(7)	9.9593(7)
a/°	90	90	90
βl°	96.743(3)	90	92.346(3)
y/°	90	90	90
Unit cell volume/Å <sup>3</sup>	936.89(8)	2038.1(2)	798.51(9)
Temperature/K	200.0(1)	100.0(1)	100.0(1)
Z	2	4	2
Reflections collected	6432	12421	10240
Independent reflections	3690 [R(int) = 0.032]	4608 [R(int) = 0.051]	3541 [R(int) = 0.055]
R indices (all data)			
<i>R</i> 1	0.0393	0.0473	0.0416
wR2	0.0800	0.0796	0.0937
Final R indices			
<i>R</i> 1	0.0328	0.0354	0.0366
w <i>R</i> 2	0.0771	0.0766	0.0915
Goodness-of-fit on $F^2$	1.050	1.052	1.034

ometer using graphite monochromated Mo-K $\alpha$  radiation  $(\lambda = 0.71073 \text{ Å})$ . A combination of 1° phi and omega (with kappa offsets) scans was used to collect sufficient data. The data frames were integrated and scaled using the Denzo-SMN package.39 The structures were solved and refined using the SHELXTL/PC V5.1<sup>40</sup> package. Refinement was by full-matrix least-squares on  $F^2$  using all data (negative intensities included).

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