Abstract

A series of novel (1-aminoalkyl)(trifluoromethyl)- and -(difluoromethyl)phosphinic acids – analogues of proteinogenic and nonproteinogenic α-amino acids were prepared. The synthetic methodology was based on nucleophilic addition of (trifluoromethyl)phosphonic acid or (difluoromethyl)phosphinic acid or its ethyl ester to substrates with C=N or activated C=C double bonds. Analogues of glycine, phenylglycine, alanine, valine, proline, aminomalonic and aspartic acids were thus prepared. Three-component one-pot reactions of (trifluoromethyl)phosphonic acid and dibenzylamine with aldehydes were also tested to prepare the title compounds.

Introduction

For a long time aminophosphonic and aminophosphinic acids as isosters of aminocarboxylic acids have attracted a particular interest for the preparation of analogues of numerous natural products. Among the literature concerning various aspects of the chemistry and biological activity of aminophosphonic and aminophosphinic acids, several monographs and reviews have appeared over the last decade [1-6]. The chemistry of fluorinated aminophosphonic and -phosphinic acids is a relatively new area of research. Incorporation of fluorine or fluorinated moieties can be used for the alteration of physiological properties of many biologically significant substances. The changes of their biological properties caused by this fluorination are
influenced by complex factors, however. The similarity of the diameters of fluorine and hydrogen atoms in organic compounds makes fluorine an obvious choice as a substituent for biologically active substances, frequently without disrupting the shape and geometry of the substituted molecules. Nevertheless fluorine influences the electronic properties of a compound drastically because of its strong electronegativity. This enables modulation of the lipophilicity profile, of electrostatic interactions with the target structure and inhibition of some metabolic pathways [7-9]. Data concerning the biological activity and synthetic approaches toward fluorinated aminophosphonates, bearing side chain C–F linkages are well documented in a review [10].

The isolation of phosphinothricin, a naturally occurring phosphorus analogue of glutamic acid and the discovery of its antibiotic, fungicidal and herbicidal properties [11] has led to an increased activity in the study of methylphosphinic acid analogues of the protein amino acids [12] and those of glycine [13], alanine [14], valine [15], proline [16], aspartic [17] and glutamic [11] acids and GABA [18] have been described. But almost nothing is known about phosphorus isosters of aminocarboxylic acids bearing a (trifluoromethyl)- or (difluoromethyl)phosphonoyl moiety instead of the carboxylate function. To the best of our knowledge there is only one report on the application of ethyl (difluoromethyl)phosphinate \( \text{CHF}_2\text{H}P(O)(\text{OEt}) \) in the synthesis of a (difluoromethyl)phosphinic acid analogue of GABA, as a potent agonist of the GABA\(_B\) receptor [18].

In light of the above and in connection with our interest in the chemistry of fluorinated compounds of phosphorus we report here the preparation of a series of novel \((1\text{-aminoalkyl})\)phosphinic acids bearing CF\(_3\) or CHF\(_2\) groups at phosphorus.

**Results and Discussion**

Research efforts have established H-phosphinates \( \text{R(H)P(O)(OR')} \) or appropriate P(III) acids \( \text{R(H)P(O)(OH)} \) as appropriate starting materials for the preparation of aminophosphinic acids. The most typical route involves the three-component reaction of an aldehyde, an amine and a P–H substrate in a one-pot Mannich type protocol [19–21]. An alternative to this approach involves the simple addition of alkyl H-phosphinates or H-phosphinic acids to Schiff bases [5,22]. In this paper we exploit both routes to prepare \((1\text{-aminoalkyl})(\text{trifluoromethyl})\)- and \((\text{difluoromethyl})\)phosphinic acids using P–H compounds bearing CF\(_3\) and CHF\(_2\) groups attached to phosphorus.

**P–H Substrates**

(Trifluoromethyl)phosphinic acid \( \text{CF}_3\text{P(O)(OH)} \) (1) was first prepared in 1954 [23], but since then little chemistry has been reported involving 1. Also monoesters of 1 such as \( \text{CF}_3\text{P(O)(OAlk)} \) [24,25] have not been widely applied. These compounds, contain a labile P–H bond and synthetic problems under their preparation. Emeléus and Haszeldine were the first [26] to prepare \( \text{CF}_3\text{P(III)} \) compounds via the interaction of red phosphorus and \( \text{CF}_3\text{I} \) in an autoclave. This gave mixtures of \( \text{CF}_3 \)-containing phosphanes and phosphate iodides but in poor yields. More recently, Ruppert described the reaction between \( \text{CF}_3\text{Br}, \text{P(NEt}_2)_3 \) and \( \text{PCl}_3 \), which gave \( \text{CF}_3\text{P(NEt}_2)_2 \) in a good yield [27]. We applied this procedure to prepare \( \text{CF}_3\text{PCl}_2 \) [27] by interaction of diamide \( \text{CF}_3\text{P(NEt}_2)_2 \) with gaseous HCl and then the chlorine was replaced by neutral hydrolysis to give (trifluoromethyl)phosphinic acid (1) [23] or by alcoholysis with ethanol or isopropanol to reach the appropriate esters 2–4 [24,25] (Scheme 1).

In our hands \( \text{CF}_3\text{PCl}_2 \) was hydrolyzed by two equivalents of water in hexane over the temperature range \(-10 \degree \text{C} \rightarrow 0 \degree \text{C}, \) to give water-free (trifluoromethyl)phosphinic acid (1). Acid 1 proved easy to handle as a distillable liquid when prepared in this way and is stable under storage for months in contrast to that prepared by Emeléus and Haszeldine [23]. Phosphinate 2 was prepared with anhydrous isopropanol. When stored under anhydrous conditions at room temperature, ester 2 was partially converted to acid 1 as determined by \(^{31}\text{P} \) NMR. Alcoholysis of \( \text{CF}_3\text{PCl}_2 \) with ethanol under the same conditions produced diethyl phosphinate 3 admixed with monoester 4 (~10%), as previously described [25]. \(^{31}\text{P} \) NMR of these products indicated that they were converted to esters 3 and 4 on storage in a ratio of ~ 3:2 with acid 1 as an impurity. The low stability of all three esters 2–4 can be attributed to the lability of the O–C ester bond, resulting from the electron-withdrawing effect of the CF\(_3\) group attached to phosphorus, therefore esters 2, 3 and 4 were used in the syntheses only when freshly prepared and distilled.
We next explored the CHF₂ group attached to phosphorus. Ethyl (difluoromethyl)phosphinate CHF₂P(O)(OH)(OEt) (5) was prepared as previously described [18]. The appropriate (difluoromethyl)phosphinic acid CHF₂P(OH)(OH) (6) was obtained from 5 by ester deprotection with NaHCO₃, as a viscous undistillable liquid, which was stable for weeks on storage.

Three-component reactions

At the outset of our work three-component reactions of formaldehyde, dibenzylamine and the esters 2 or 5 were explored as model transformations to evaluate the feasibility of the Kabachnik–Fields procedure [19,20] to the synthesis of fluorinated (1-aminoalkyl)phosphinate 7 (Scheme 2).

It turned out that this method is unsuitable for the synthesis of phosphinate 7. Formalin was added to an equimolar mixture of dibenzylamine and ester 2 at 80 °C under an oxygen-free atmosphere to give reaction mixtures with a low content of P–C products (³¹P NMR). A similar outcome was obtained when the reaction was run at room temperature or in dioxane with simultaneous water azeotropic distillation. Such an result might be explained by high reactivity of the starting ester, which readily reacted with formaldehyde, forming (α-hydroxymethyl)phosphinate 8. Its further irreversible rearrangement [28] to the corresponding phosphonate 9 was accompanied with hydrolysis of the ester function and formation of (trifluoromethyl)phosphonic acid (10) [29] as the main product. Analogue results were obtained, when CHF₂ containing ester 5 was introduced into the reaction with formaline and dibenzylamine to give CHF₂P(O)(OH)₂ (11) as the major product [30].

Such results prompted us to explore the Mannich-type procedure of Moedritzer and Irani [21] for the syntheses of the desired aminophosphinic acids starting from acid 1. This resulted in the preparation of the analogues of glycine 14a and phenylglycine 14b (Scheme 3).

The three-component reaction with formaldehyde gave the best results and N-protected aminophosphinic acid 13a was isolated in a moderate yield, alongside phosphonic acid 10. The analo-
gous reaction with benzaldehyde provided acid 13b in 28% yield and the main product of this reaction was an adduct of acid 1 with benzaldehyde which was isolated from the reaction mixture as ammonium salt 15 in 60% yield. Reaction with acetaldehyde was less successful and generated aminophosphinic acid 13c in low yield (<10%). Attempts to improve conversions products 13a–c by increasing the reaction temperature or varying the amino component (MeC(O)NH₂, BnOC(O)NH₂ or NH₄OAc instead of Bn₂NH) and molar equivalent of HCl were unsuccessful. It should be noted, that in contrast to the non-fluorinated counterparts the adducts 13a,b did not form hydrochlorides under this procedure consistent with the strongly acidic nature of the CF₃ phosphinic acid group. Catalytic hydrogenation of intermediates 13a,b with Pd/C removed the benzyl groups and produced the corresponding acids 14a,b in high yields.

The hydrophosphinylation of azomethines

The addition of the P–H functionality to C=N double bonds is a very general procedure for the formation of P–C–N systems. Based on our experience of these three-component reactions (Scheme 2 and Scheme 3) we investigated the scope and limitations of the addition of (trifluoromethyl)phosphinic acid (1) to a series of N-benzylimines 16a–e in order to obtain fluorinated phosphorus analogues of glycine 14a, phenylglycine 14b, alanine 14c, valine 14d and proline 14e (Table 1).

Table 1: The interaction of (trifluoromethyl)phosphinic acid (1) with Shiff bases.

| Entry | Shiff base | R   | 17 (yield, %)ᵇ | 14 (yield, %)ᵇ |
|-------|------------|-----|----------------|----------------|
| 1c    |            | H   | 17a (83)       | 14a (95)       |
| 2     |            | Ph  | 17b (79)       | 14b (96)       |
| 3d    |            | Me  | 17c (59)       | 14c (96)       |
| 4     |            | iPr | 17d (92)       | 14d (98)       |
| 5c    |            |     | 14e (66)       |                |

ᵃReagents and conditions: i) an equimolar mixture of acid 1 and Shiff base, DME, rt, ³¹P NMR control; ii) H₂, ethanol, catalysis 10% Pd/C, rt, normal pressure. ᵇIsolated yields. cSymmetrical cyclic triazinanes (masked imines) were used to generate unstable imines. dThe best yield was obtained with 2 mol equivalents of imine.
The transformations were mildly exothermic and were monitored by $^{31}$P NMR. Acid 1 undergoes the typical P–C bond forming reactions with Shiff bases to give adducts 17 in satisfactory yields and these were successfully transformed into the appropriate free acids 14.

The same series of Shiff bases was used to explore the reactivity of ethyl (difluoromethyl)phosphinate (5) in reactions with C=N double bonds and the desired (α-aminoalkyl)phosphinic acids 20a–e were accordingly prepared (Table 2).

### Table 2: The interaction of ethyl (difluoromethyl)phosphinate (5) with Shiff bases.\(^a\)

| Entry | Shiff base | R  | 18 (yield, %)\(^b\) | 19 (yield, %)\(^b\) | 20 (yield, %)\(^b\) |
|-------|------------|----|---------------------|---------------------|---------------------|
| 1\(^c\) | H          | 18a (78)\(^d\) | 19a (68) | 20a (91) |
| 2     | Ph         | 18b (58)\(^a\) | 19b (86)\(^f\) | 20b (96) |
| 3\(^g\) | Me         | 18c (56)\(^a\) | 19c (80)\(^f\) | 20c (95) |
| 4     | iPr        | 18d (36)\(^a\) | 19d (82)\(^f\) | 20d (95) |
| 5\(^c\) |            | –             | –            | 20e (79) |

\(^a\)Reagents and conditions: i) an equimolar mixture of ester 5 and Shiff base, DME, rt, $^{31}$P NMR control, under argon atmosphere; ii) H$_2$, ethanol, catalysis 10% Pd/C, rt, normal pressure. \(^b\)Isolated yields. \(^c\)Symmetrical cyclic triazinanes (masked imines) were used to generate unstable imines. \(^d\)Yield was defined with $^{31}$P NMR. \(^e\)Diastereomeric ratio: 18b (~7:2), 18c (~3:2), 18d (~3:2). \(^f\)Yields were defined as the sum of yields of compounds 19b–d, isolated from the reaction mixture and obtained after hydrolysis of intermediates 18b–d. \(^g\)The maximum yield was obtained with 2 mol equivalents of imine.
−137 ppm for CHF$_2$ ones. Some distinctive characteristics of the reactivity of ester 5 were observed. This ester readily reacted with azomethines, but in contrast to its nonfluorinated counterparts this ester generated mixtures of the adducts 18 and 19. The interaction of ester 5 with imine 16a gave adduct 18a (Table 2, entry 1) in high conversion yield but after purification over silica gel only the appropriate acid 19a was isolated. In the case of the reaction of ester 5 with imine 16e no adduct was formed. Ethyl phosphinates 18b–d were obtained as a mixture of two diastereoisomers, which were not separated but they are clearly observed by $^1$H NMR as separate signals for the CHF$_2$ group. The adducts 18b–d were hydrolyzed to acids 19b–d in quantitative yields and did not form hydrochlorides similar to the CHF$_3$ aminophosphonic acids 13a–b and 17a–d. Hydrogenolysis of the 17a–d and 19a–d efficiently gave free acids 14 and 20, but required column ion-exchange chromatography to produce analytically pure products.

We then explored the addition of acid 1 to imine 21 [31], which is N-Boc protected, typically used for amino acid protection (Scheme 4). This produced acid 14b in one step, but in only 32% yield. The N-tert-butoxycarbonyl group was removed during the reaction due to the high acidity of the CHF$_3$ phosphinic acid group.

The variability of Schiff bases ensures access to a range of structurally diverse phosphonic acid analogues of amino acids in the relatively simple way. Thus, we investigated the hydrophosphinylation of some Schiff bases bearing a carboxylate functionality to obtain aminocarboxylic acids, containing pendant CF$_3$ or CHF$_2$ phosphonic acid linkages. Thus, phosphonic acids 1 and 6 reacted with the N-Boc-protected Schiff base of ethyl glyoxalate 22 [32] under mild conditions to produce the N-deprotected phosphinylglycines 23 and 24 in satisfactory yields (Scheme 5).

Attempts to convert ester 23 to the free acid failed. Removal of the ester group from 23 by acidolysis with HCl or HI was accompanied by cleavage of the P–C bond to give only (trifluoromethyl)phosphonic acid (10) after an ion-exchange chromatography. Attempts to remove the ester group in anhydrous base with 1 equivalent of sodium silanolate (Me$_3$SiONa) at room temperature efficiently produced the highly stable sodium salt of acid 23. With an excess of Me$_3$SiONa and heating to 50 °C, fluoroform liberation from 23 was observed to give fluorine-free products.

In contrast the CHF$_2$-containing ester 24 was stable toward acidic hydrolysis under mild conditions, but in the presence of an excess of sodium silanolate, free phosphinylglycine 25 was obtained, but in a poor yield (Scheme 6).

The reactions of substrates 1 and 6 with imine 26, which is available from valine [33], readily gave adducts 27 and 28, which were decarboxylated under acidolysis to afford the phosphinic acid analogues of valine 14d and 20d (Scheme 7).

The hydrophosphinylation of substrates with activated C=C double bonds

The high reactivity of (trifluoromethyl)phosphonic acid (1) with C=N double bonds prompted us to explore its reactivity towards activated C=C double bonds. By analogy with the synthesis of the phosphonic acid analogue of aspartic acid, developed by Chambers and Isbell [34], the P–H substrate 1 was reacted with N-Boc-protected aminoacrylate 29 [35], and this gave the precursor of the aspartic acid analogue 30 (Scheme 8).
Surprisingly, under the mild conditions of our experiment only the addition of acid 1 to the C=N double bond of the acrylic ester 29, occurred to produce the tertiary phosphinyl derivative of alanine 31 in a satisfactory yield. Ester 31 was then hydrolyzed to give the free acid 32 in a moderate yield.

For the synthesis of the aspartic acid analogue 34, a reaction between a mixture of the freshly prepared esters 3 and 4 and N-acetyl-protected aminoacrylic acid 33 was carried out [34] (Scheme 9).

It was thought that diester 3 might esterify amidocrylic acid 33 [17,34] to produce ethyl 2-acetamidoacrylate and this compound in turn might add to monoester 4 to give the protected phosphinic acid analogue of aspartic acid 34. Unfortunately, the only addition of 4 to the C=N double bond occurred similar to the previous transformation illustrated in Scheme 8. Insoluble in the reaction mixture phosphinic acid 37 was filtered off and characterized. $^{31}$P NMR analysis of filtrate showed the presence of adduct 35 and the decarboxylation product 36 in an approximate 1:10 ratio along with starting esters 3 and 4 and (trifluoromethyl)phosphonic acid (10) (<5%). Products 35 and 36 were separated by chromatography and characterized. Ester 36 was obtained as a mixture of two diastereoisomers, which are clearly seen by $^1$H- and $^{19}$F NMR. This ester was then readily converted by acidolysis into the phosphinic acid analogue 37, of N-acetylalanine, which was isolated in the 56% from acid 33, and then transformed into free amino acid 14c.

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We have been able to prepare the isomeric aspartic acid analogue 41 with phosphorous α- to the amino group by the analogy with the published method [17,36]. The synthesis of phosphinic acid 41 was accomplished by addition of acid 1 to the activated C=C double bond of malonate 38 followed by hydrolysis and decarboxylation to generate adduct 39 in two steps (Scheme 10).

![Scheme 10: Interaction of a mixture of the acid 1 with diethyl acetamidomethylenemalonate (38). Reagents and conditions: i) an equimolar mixture of reagents, acetonitrile, rt, 31P NMR control, under argon atmosphere, 44%. ii) 5 N HCl, reflux, 12 h, 82%. iii) 5 N HCl, in an ampoule, 130 °C, 5 h, 43%.](image)

**Conclusion**

In conclusion, we have presented a variety of approaches to novel fluorinated (1-aminoalkyl)phosphonic acids starting from the appropriate fluorinated P–H compounds with CF₃ or CHF₂ groups attached to phosphorus. Three-component one pot Mannich-type reactions of CF₃(H)P(O)(OH) with dibenzylamine and aldehydes were investigated. Also nucleophilic addition of CF₃(H)P(O)(OH) or CHF₂(H)P(O)(OEt) to Shiff bases, aminoacrylates and acetaminomethylenemalonate have been used to prepare the title compounds.

**Experimental**

All reactions with P–H compounds were performed under an argon atmosphere. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM) and Aldrich ion-exchange resin Dowex WX-50. The NMR spectra were recorded on Varian VXR-300 or Bruker Avance DRX-500 spectrometers for 1H (TMS); on a Bruker Avance DRX-500 spectrometer for 13C {H} (TMS); on Varian Gemini-200 or Varian VXR-300 spectrometers for 19F (CFCI₃) and for 31P (H₃PO₄).

**Synthesis of starting materials**

(Trifluoromethyl)phosphonic acid (1). To an emulsion of water (3.2 g, 180 mmol) in anhydrous hexane (20 mL), cooled to −78 °C CF₃PCl₂ [27] (16.5 g, 96.5 mmol) was added under stirring and the temperature was slowly raised to −10 °C, when hydrolysis started. The reaction mixture was allowed to come to 0 °C at such a rate to avoid a vigorous reaction (~3 h) and then to room temperature and stirring was continued overnight. Hexane was evaporated under reduced pressure and the residue was distilled to give 1 as a colorless liquid (10.84 g, 84%), bp 35 °C (0.05 mm Hg); 1H NMR (300 MHz, DMSO-d₆) δ 7.05 (d, 1JHH = 638.9 Hz, 1H, 2JHH = 4.2 Hz, PH); 13.6 (1H, s, OH); 31P NMR (121 MHz) δ 6.1 (dq, 1JHP = 639 Hz, 2JPF = 82 Hz); 19F NMR (188 MHz) δF ~76.8 (dd, 2JFP = 82 MHz, 3JFP = 4 Hz). **Caution:** Safety precautions are necessary, because CF₃PCl₂ reacts violently with air. Care must be taken not to warm the reaction system rapidly, because rapid volatilization of gaseous HCl will be accompanied by carrying off CF₃PCl₂, which can inflame.

(Difluoromethyl)phosphonic acid (6). A mixture of 5 [18] (8 g, 56 mmol) and NaHCO₃ (7 g, 83 mmol) in ether (50 mL) was stirred overnight at room temperature to produce a bulky precipitate of CHF₂PO(O)(H)O⁻Na⁺ [31P NMR (121 MHz, H₂O): δP 11.9 (ddt, 1JPF = 570 Hz, 2JFP = 87 Hz, 2JFP = 25 Hz). This precipitate was filtered, thoroughly washed with ether, solved in water (25 mL) and passed down an ion-exchange column. Water from the resulting solution was evaporated under reduced pressure and the residue was kept in vacuo (0.05 mmHg) for 24 h at room temperature to give 6 as a viscous colorless undistillable liquid (7.19 g, 78%); Anal. calcd for CH₃F₂O₂P: C, 10.35; H, 2.61; P, 26.71; found: C, 10.48; H, 2.70; P, 26.59; 1H NMR (300 MHz, DMSO-d₆) δH 6.15 (tdd, 2JHH = 48.6 Hz, 2JHP = 24.5 Hz, 3JHH = 1.5 Hz, 1H, CHF₂), 6.9 (dm, 1JHP = 566.5 Hz, 1H, PH), 12.7 (s, 1H, OH); 31P NMR (121 MHz) δP 12.1 (ddt, 1JPF = 566 Hz, 2JFP = 86 Hz, 2JFP = 25 Hz); 19F NMR (188 MHz) δF 9.6 (dd, 2JFP = 86 Hz, 2JFP = 49 Hz).

**Three-component reactions**

The general procedure for the condensation of the acid 1 with dibenzylamine and aldehydes (I). An equimolar mixture of I (2.68 g, 20 mmol) and dibenzylamine (3.94 g, 20 mmol) in 1 N HCl (20 mL) was heated at 80 °C under stirring. In the course of ~1 h aldehydes 12a,b were added with a syringe and the reaction mixture was kept at this temperature for additional 1 h. The resulting mixture was left overnight at room temperature to produce the precipitate, which was filtered, washed with acetone–water (10:1) and dried to afford 13a or 13b. The filtrate was evaporated to the dryness, the residue was triturated with acetone–water (10:1) to give an additional quantity of 13a,b.

[[Dibenzylamino]methyl][trifluoromethyl]phosphonic acid (13a). Following the general procedure (I) using 3.2 mL of 37% aqueous formaldehyde solution (20 mmol) 13a was obtained as a white solid (3.57 g, 52%), mp 229 °C; Anal. calcd for
C_{16}H_{19}F_{2}NO_{3}P: C, 55.98; H, 4.99; N, 4.08; found: C, 55.69; H, 5.28; N, 4.15; 1H NMR (300 MHz, DMSO-\text{d}_{6}) \delta_{H} 2.94 (d, J_{HF} = 9.3 Hz, 2H, CH_{2}P), 4.45 (s, 4H, CH_{2}Ph), 7.47–7.59 (m, 10H, H_{arom}); 31P NMR (121 MHz) \delta_{P} 3.8 (qt, J_{PF} = 81 Hz, J_{PH} = 9 Hz); 19F NMR (188 MHz) \delta_{F} -73.8 (d, J_{PF} = 81 Hz).

The general procedure for N-deprotection of compounds with N-Bn function under the catalytic hydrogenation conditions (II). To a solution of compounds, containing N-Bn fragment (5 mmol) in ethanol (10 mL) 10% Pd/C (0.05 g) was added, and the mixture was hydrogenated at room temperature and normal pressure. After ~3 h the precipitation commenced, and water (5 mL) was added to dissolve this precipitate. The hydrogenation was then continued with a fresh portion of the catalyst (0.05 g) for a further 3 h. Last procedure was repeated whenever necessary and the reaction was left overnight. To the resulting mixture water was added until a white solid was fully dissolved, and the catalyst was then filtered off. The filtrate was evaporated to dryness, the residue was dissolved in acetone and filtered to give the corresponding adducts precipitated and this was filtered off. The resulting mixture was washed with acetone and dried to give compounds with the free NH_{2} function.

(Aminomethyl)(trifluoromethyl)phosphinic acid (14a).

Ethyl (benzylamino)(phenyl)methyl)(difluoromethyl)phosphinate (18b, Table 2, entry 2). Following the general procedure (I) a crude solid, obtained from 5 (0.49 g, 3.4 mmol) and 16b (0.68 g, 3.4 mmol) was extracted with boiling hexane (3 × 30 mL), this extract was evaporated to the dryness to afford 18b as a yellowish solid (0.67 g, 58%); mp 85–93 °C, as a mixture of two diastereoisomers in an approximately 1:3.5 ratio due to 1H NMR (300 MHz, CDCl$_3$) \delta_{H} 0.97 (t, J_{HH} = 7.6 Hz, 0.7H, CH$_3$ minor isomer), 1.25 (t, J$_{HH}$ = 7.6 Hz, 2.3H, CH$_3$ major isomer), 2.17 (br s, 1H, NH); 1H NMR (300 MHz, DMSO-\text{d}_{6}) \delta_{H} 3.46 (d, J_{AB} = 12.6 Hz, 0.22H, CH$_2$Ph, minor isomer), 3.51 (d, J$_{AB}$ = 12.6 Hz, 0.77H, CH$_2$Ph, major isomer), 3.78 (d, J$_{AB}$ = 12.6 Hz, 1H, CH$_2$Ph), 3.9 (dm, J$_{HP}$ = 16.9 Hz, 0.22H, PCH, minor isomer), 4.08 (d, J$_{HP}$ = 17.1 Hz, 0.8H, PCH, major isomer), 4.1–4.25 (m, 2H, OCH$_2$), 5.88 (td, J$_{HP}$ = 49.2 Hz, J$_{HH}$ = 27.8 Hz, 0.8H, CHF$_2$, major isomer), 6.25 (td, J$_{HP}$ = 49.3 Hz, J$_{HH}$ = 27.6 Hz, 0.2H, CHF$_2$, minor isomer), 7.15–7.40 (m, 10H, H$_{arom}$); 31P NMR (81 MHz) \delta$_{P}$ 30.8 (m); 19F NMR (188 MHz) \delta$_{F}$ -132 to -140.5 (complex multiplet). To the viscous residue after extraction of 18b water (20 mL) was added, resulting solution was decolorized with activated charcoal, filtrated and allowed to stand at 5 °C until crystallization completed, producing ([benzylamino-(phenyl)methyl](difluoromethyl)phosphinic acid (19b) as a white solid (0.32 g, 30%); mp 247 °C; Anal. calcld for C$_{15}$H$_{10}$F$_{2}$NO$_{3}$P: C, 57.88; H, 5.18; N, 4.50; found: C, 57.91; H, 5.04; N, 4.48; 1H NMR (300 MHz, DMSO-\text{d $_{6}$}) \delta_{H} 3.95 (d, J$_{AB}$ = 12.9 Hz, 1H, CH$_2$Ph), 4.04 (d, J$_{HP}$ = 10.2 Hz, 1H, PCHF), 4.10 (d, J$_{AB}$ = 12.9 Hz, 1H, CH$_2$Ph), 5.63 (td, J$_{HP}$ = 49.2 Hz, J$_{HH}$ = 21.9 Hz, 1H, CHF$_2$), 7.30–7.42 (m, 10H, H$_{arom}$); 31P NMR (81 MHz) \delta$_{P}$ 13.4 (m, J$_{HP}$ = 68 Hz). An additional quantity of 19b was obtained by hydrolysis of 18b (0.67 g, 2 mmol) with 1N HCl (15 mL) at room temperature until the starting ester has dissolved. The resulting solution was evaporated to dryness at reduced pressure and the residue was recrystallized from water to give 19b (0.6 g, 97%). The overall yield of 19b is 0.92 g (87%).

See Supporting Information for details of the syntheses, characteristics and NMR spectra of all new compounds.

Supporting Information

Experimental procedures and full characterization data for all new compounds including elemental analysis and NMR spectra of the most typical compounds.

Supporting Information File 1
Experimental procedures, elemental analysis and NMR spectra for all new compounds.

Supporting Information File 2
NMR spectra of the most typical compounds.
Supporting Information File 3
NMR spectra of the most typical compounds (continuation).
[http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-10-66-S3.pdf]

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