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Synthesis of trifluoromethyl γ-aminophosphonates by nucleophilic aziridine ring opening

T. Cytlak,* M. Saweliew, M. Kubicki and H. Koroniak

Phosphonated derivatives of trifluoromethyl aziridine were obtained with good yield from aziridine-2-carbaldehyde by two distinct methods, which resulted in different diastereoselectivity. Using thiols as nucleophiles ring opening reactions of trifluoromethylated derivatives of aziridines-2-phosphonates proceeded regio- and diastereoselectively, giving rise to γ-amino-γ-trifluoromethyl phosphonates.

Introduction

Aminophosphonates are an important class of compounds, because of their unique utilities as antibiotics, herbicides, antifungal agents, enzyme inhibitors, and pharmacological agents. They can also act as analogues of amino acids, and as such they constitute important motifs in medicinal chemistry. Among the various types of aminophosphonates, α-aminophosphonates and β-aminophosphonates and their biological importance have been widely described in literature. With regard to γ-aminophosphonates, only a few examples of biological activity have been found (e.g. receptors agonists and antagonists).

Aziridine derivatives are valuable functionalized building blocks for the asymmetric synthesis of aminophosphonates because of their ability to undergo highly regioand stereospecific ring opening reactions. Furthermore, the presence of CF₃ group, attached to aziridine ring, constitutes a promising route to obtain fluorinated amino acids analogues. The introduction of fluorine atoms in organic molecules often results in a deep modification of physical, chemical and biological properties of the parent compounds. Among them, fluorinated phosphonates structurally and functionally mimic the phosphate compounds. In contrast, they are resistant to phosphatase cleavage. The replacement of oxygen for CH₂ makes phosphonates hydrolytically stable. However the electronegativity of oxygen is distinctly different from CH₂, but the incorporation of one or two fluorine atoms onto methylene group changes the acidity of the compound due to electron withdrawing effect of the fluorine atom. Moreover, CF₃-phosphate analogues are structurally most closely resemble to the phosphate ester, due to similarity of the C-CF₂-P (117°) angle to the C-O-P system (119°). Recently, Berkowitz et al. reported the state of research on developing and application CF₂-phosphate analogs as tools for the study of protein phosphorylation, showing their potential importance in chemical biology by regulation of protein functions. From the other side, bulky lipophilic CF₃ group is numerous used to mimic side chain of miscellaneous amino acids involved in ligands interactions or in enzyme inhibitors, and also in modification of the agonist/antagonist nature of the ligands when the binding activity remains unchanged. Moreover, the hydrophobic nature of the CF₃ group prefer complementarity with the lipophilic pockets of the proteins. Furthermore, CF₃ group can replace the CO group of peptides and create a stable, nonbasic, amine that preserves excellent hydrogen bonding, as has been used in the design of various enzymes inhibitors.

According to huge synthetic utility of aziridine, this three-member ring is applied to synthesis of various aminophosphonates. One of the most useful approaches for synthesis of aminophosphonates is the addition of dialkyl phosphites to N-protected amino aldehydes known as Pudovik type reaction, which is a modification of Abramov reaction. However, to the best of our knowledge, there are only a few reports of synthesis of fluorinated aminophosphonates using aziridine-2-phosphonate route.

Considering reactivity of aziridine-2-carboxylates, a regio- and stereoselective synthesis of fluorinated anti-α-functionalised-β-amino acids through nucleophilic ring opening of racemic ethyl trans-N-benzyl-3-trifluoromethylaziridine-2-carboxylate in acidic conditions was described by Davoli. The ring opening reactions occurred with nucleophilic attack at the C2 carbon atom to give only one
regioisomer in a single anti diastereomeric form. Regiochemistry of this reaction is governed by CF₃ group. In contrast, non fluorinated 3-alkyl-aziridine-2-carboxylates underwent nucleophilic attack at C3 carbon atom. Stereochemistry is a consequence of the displacement mechanism involved the ring opening reactions of aziridine carboxylates. These assumptions were confirmed using opposite isomer, cis-N-benzyl-3-trifluoromethylaziridine-2-carboxylate which led to syn stereoisomer of β-functionalized-β-amino trifluoromethyl esters. These ring opening reactions of non activated CF₃-substituted aziridines are limited to only a few nucleophiles such as thiols, halides and carboxylates. Reactions with other nucleophiles, such as amines are more problematic and even with Lewis acids catalysts are mostly inert, except a method, described by D’hooge et al., involving activation of aziridine ring by N-alkylation, towards N-benzylmethylamines.

**Results and discussion**

In the course of our studies we were able to synthesize trifluoromethyl aziridine derivatives of phosphonates which were subsequently used in ring opening reactions, leading to series of new derivatives of γ-amino-γ-trifluoromethyl phosphonates with high regio- and diastereoselectivity. Racemic cis-N-benzyl-trifluoromethylaziridine 1 was prepared in two steps from commercially available fluor via trifluoromethylated N-benzylamine, as described in the literature. Then, an ester group was reduced to provide the corresponding alcohol 2 in 84% yield.

Aldehyde 3 was used directly to introduce C-P bond by two distinct methods, using different bases and conditions, to yield 1-hydroxyphosphonates (Scheme 2). In the first one, aldehyde 3 was subjected to the TEA-catalyzed (10%) addition of diethyl phosphate to carbonyl group to furnish phosphonates 4a and 4b with 77% isolated yield (20:1 19F, 31P NMR ratio), which were very difficult to separate.

In the second route, aldehyde 3 was used in the reaction with lithium diethyl phosphate, generated in situ from diethyl phosphate/LTMP, in dry THF at -30°C, to afford phosphonates 4a and 4b (1:1 19F, 31P NMR ratio) with 84% isolated yield.

**Scheme 2** Addition of diethyl phosphate to carbonyl group of 3 by two methods, using different bases and conditions.

In order to determine geometry of phosphonates 4a and 4b, a reaction with (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(S)-(+)-MTPA-Cl] according to Mosher method was applied yielding two diastereomer 5a, 5c (1:1.2 1H, 31P NMR ratio) from rac-4a and 5b, 5d (1:1 1H, 31P NMR ratio) from rac-4b, respectively (Scheme 3).

According to the literature, for 1-hydroxyphosphonates exist two models for configuration assignment, using MTPA chloride. The first method is double derivatization, in which one enantiomer of 1-hydroxyphosphonate is converted separately with two enantiomers (S and R) of MTPA chloride. Then the absolute configuration is assigned on the basis of the δ₁H signs. The second method is performed with the mixture of enantiomers of 1-hydroxyphosphonate using only one enantiomer (S or R) of the MTPA chloride. Then the absolute configuration is assigned by comparison of the chemical shifts of the corresponding nuclei.

Using the second model, comparative 31P NMR analysis of crude mixtures of (2R)-esters 5a-d showed that chiral C1 carbon atom (in the phosphonate moiety) has configuration S for 5a and 5d, R for 5b and 5c (Table 1). It is due to the fact that diacylphosphono group is situated on the same side of the plane as the phenyl ring of the MTPA ester moiety and it is more shielded and moves upfield (δ₃ of 5b and 5c). When the diacylphosphono group is on the opposite side of the plane as the phenyl ring of the MTPA ester moiety, the chemical shift of the phosphorus signal is located downfield (δ₃ of 5a and 5d).

**Scheme 3** Reaction of azirinid-2-yl(hydroxy)phosphonates 4a and 4b with (S)-(+)-MTPA-Cl.
Table 1 Model for the assignment of the configuration of 1-hydroxyphosphonates 4a, 4b from the \(^{1}H, ^{31}P\) NMR spectra of their (R)-MTPA on the basis of the shielding and deshielding effects.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>(^{31}P) NMR(^a)</th>
<th>(^{1}H) NMR(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2R-(1S,2R,3S)-5a</td>
<td>16.36 (dd)</td>
<td>3.59 (s)</td>
</tr>
<tr>
<td>2</td>
<td>2R-(1R,2R,3S)-5b</td>
<td>14.73 (s)</td>
<td>3.55 (s)</td>
</tr>
<tr>
<td>3</td>
<td>2R-(1R,2S,3R)-5c</td>
<td>16.04 (dd)</td>
<td>3.55 (s)</td>
</tr>
<tr>
<td>4</td>
<td>2R-(1S,2S,3R)-5d</td>
<td>15.21 (s)</td>
<td>3.63 (s)</td>
</tr>
</tbody>
</table>

\(^a\) Chemical shifts of \(^{31}P\) NMR in ppm (CDCl\(_3\)).\(^a\) Chemical shifts of OMe group in \(^1H\) NMR in ppm (CDCl\(_3\)).

Another diagnostic signals are observed for methoxy group of the MTPA esters moiety, when L1 substituent, in the α position to the phosphonate part, contains bulky aryl group. The methoxy group is more shielded by the aryl ring when both are on the same side of the MTPA plane (5a and 5d). Beside, in the opposite enantiomer, the methoxy group is deshielded by the phosphorus substituent, which is on the same side of the plane (5b and 5c).\(^24,26\)

Moreover, when mixture of 4a,b (1:1 NMR ratio) was used in this reaction, diastereomer rac-4b was proved to be more reactive, yielding 5a,c,5b,d with 1:3.5 ratio (75% total yield; \(^1H, ^{31}P\) NMR), due to less steric hindrance around the hydroxyl group (further distance from CF\(_3\) group) than in case of 4a (Figure 1,2).

The structure and relative stereochemistry of compounds 4a and 4b were determined by X-ray diffraction analysis. Interestingly, 4a and 4b crystallize with different shape, 4a as a flat plate, 4b as a needle. Both compounds crystallize in the stereosymmetric space which means, that both enantiomers are present in the crystals. Analysis of crystal structures of racemic diastereomers showed that phosphonates 4a have syn/cis (syn/syn) conformation which is equal to (1S,2R,3S)-4a and (1R,2S,3R)-4a (Figure 1). Phosphonates 4b have anti/cis (anti/syn) conformation which is equal to (1R,2R,3S)-4b and (1S,2S,3R)-4b (Figure 2).

The reactivity of aziridine-2-phosphonates 4a and 4b was then investigated in nucleophilic ring opening reactions with representative number of thiol and catalyzed by the addition of trifluoromethanesulphonic acid.\(^27\) A large excess of thiol was necessary. The yield was dramatically increased when 3 equiv of thiol was used. The reaction provided a variety to number of sulfides 6a,b,12a,b (Table 2) with regio- and diastereoselectivity. Reaction of syn/cis isomer 4a led to anti/syn products 6a,12a, whereas anti/cis isomer 4b gave syn/syn products 6b,12b. It is noteworthy that the major product of ring opening is always anti/syn isomer due to steric hindrance of bulky phosphonate group. Using mixture of 4a,b (20:1 NMR ratio) led to obtain corresponding sulfides 6a,12a with slightly better yields than from the mixture of 4a,b (1:1 NMR ratio). Regio- and stereochemistry was confirmed by NMR analysis and X-ray crystal structure determination in case of racemic 6a (Figure 3) and 8a.

Compounds 6a, 8a crystallize in the centrosymmetric space groups, which means that both enantiomers are present in the crystals, with R(C1)-R(C2)-S(C3) (and SSR) combination of the chirality centers. Molecules 6a and 8a have very similar conformations (tables in supporting information list some relevant geometrical features).

In all the crystal structures the principal, directional interaction is the O–H—O11 hydrogen bond (table in supporting information); interestingly in 6a, 8a and 4a the hydrogen bonds forming the centrosymmetric dimers are built of different enantiomers, while in 4b the unichiral chains of
molecules along y directions are formed from a sole enantiomer (neighbouring chains are enantiomeric). In 6a and 8a additional N-H...O11 intermolecular hydrogen bonds add to the creation of crystal structures.

Table 2 Ring opening of aziridine-2-phosphonates 4a and 4b with thiols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substratea</th>
<th>RSHb</th>
<th>Time [h]</th>
<th>Temp. [°C]</th>
<th>Isolated product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a,b</td>
<td>4-FPhSH</td>
<td>3</td>
<td>90</td>
<td>6a</td>
<td>95</td>
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<td>4a,b</td>
<td>4-MePhSHc</td>
<td>3</td>
<td>90</td>
<td>6b</td>
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<tr>
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<td>4a,b</td>
<td>PhSH</td>
<td>3</td>
<td>90</td>
<td>8a</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>4a,b</td>
<td>BnSH</td>
<td>3</td>
<td>90</td>
<td>8b</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>4a,b</td>
<td>i-PnSH</td>
<td>3</td>
<td>90</td>
<td>8a</td>
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<td>4a,b</td>
<td>EtSH</td>
<td>48</td>
<td>25</td>
<td>12b</td>
<td>18</td>
</tr>
</tbody>
</table>

a Mixture of 4a:4b (1:1, d.r.). b 20 equiv of RSH were used. c Isolated yields of products 6a-12a were calculated according to substrate 4a and products 6b-12b according to substrate 4b. d 2 mL of CH2Cl2 was added to a reaction mixture, to dilute solid thiol.

Figure 3 A perspective view of 6a with numbering scheme. Ellipsoids are drawn at the 50% probability level, hydrogen atoms are represented by spheres of arbitrary radii (ORTEP).

Conclusions

In summary, our results demonstrated synthesis of trifluoromethyl aziridine derivatives of phosphonates, as a mixture of diastereomers, by two distinct methods, different in diastereoselectivity. When equimolar amounts of strong and bulky base (LTMP) was used during addition reaction of diethyl phosphate to carbonyl group, reaction proceeded with lack of diastereoselectivity led to obtain two diastereomers in 1:1 ratio. Using catalytic amounts of TEA, at room temperature, reaction distinguished high diastereoselectivity, gave two diastereomers in 20:1 ratio. We suggest that, in the first method, the conditions of the reaction affect that kinetically controlled pathway reaction is favoured, when in the second method, the reaction carried out with thermodynamic control towards, almost purely, the major diastereomer. This study also explore the versatility of functionalized aziridines as building blocks for the phosphorylation of lateral groups by highly regio- and diastereoselectivity nucleophilic ring-opening under acidic conditions with aliphatic and aromatic thiols, that ultimately furnished γ-aminoglytrifluoromethyl phosphonates. Further deprotection of amino group could be considered in a design of important trifluoromethyl phosphonated building blocks employed in the synthesis of useful compounds such as peptide analogs.

Experimental

General Methods

1H NMR, 13C NMR, 19F NMR and 31P NMR spectra were performed on Varian GEMINI 300 (300 MHz), Varian 400 (400 MHz), Bruker ASCEND 400 (400 MHz), Bruker ASCEND 600 (600 MHz) and Bruker ULTRASHIELD 600 (600 MHz) spectrometers. Chemical shifts of 1H NMR were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard (δ = 0) in CDCl3. Chemical shifts of 13C NMR were expressed in parts per million downfield from CDCl3 as an internal standard (δ = 77.0). Chemical shifts of 19F NMR were expressed in parts per million upfield from CFCl3 as an internal standard (δ = 0) in CDCl3. Chemical shifts of 31P NMR were expressed in parts per million in CDCl3. Low-resolution resolution mass spectra were recorded by electron impact (MS-EI) techniques using AMD-402 spectrometer. High-resolution resolution mass spectra were recorded by electron spray (MS-ESI) techniques using micrOTOF-Q Bruker spectrometer. Reagent grade chemicals were used. Solvents were dried by refluxing with sodium metal-benzophenone (THF), with CaCl2 (CH2Cl2), NaH (Et2O) and distilled under argon.

Considering only a few examples of ring opening reactions of trifluoromethylated N-benzyl aziridines in the literature, we have tried to undergo ring opening reaction of aziridine-2-phosphonates with BnNH2 and piperidine under acid conditions, in the presence of Sc(O Tf)3, Yb(O Tf)3, Bi(O Tf)3, PBu3, Bi(C6F5)3, BiCl3, TiCl4 and under basic conditions as well, using TEA as catalyst. Unfortunately, no ring opening occurred.
Procedures for Swern oxidation of 2

DMSO (2.60 mmol, 0.23 mL) was added dropwise to a stirred solution of oxalyl chloride (4.33 mmol, 0.31 mL) in CH$_2$Cl$_2$ (20 mL) under argon at -78°C and the reaction mixture was stirred for 5 min. Then a solution of azidiryl alcohol 2 (2.16 mmol, 500 mg) in CH$_2$Cl$_2$ (2 mL) were added. After 30 min of stirring at -78°C, triethylamine (8.63 mmol, 1.2 mL) was added, and mixtures were allowed to warm to room temperature over 30 min. The reaction mixture was then diluted with H$_2$O (30 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic layers were washed with 1% HCl (15 mL), H$_2$O (15 mL), 5% NaHCO$_3$ (15 mL) and brine (15 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The resulting crude aziridine carbaldehyde 3 was used in next step without additional purification.

Procedures for addition of diethyl phosphite to 3

**Method a**

A mixture of crude aldehyde 3 (2.16 mmol, 495 mg) and diethyl phosphite (2.59 mmol, 0.335 mL) containing triethylamine (0.23 mmol, 0.032 mL) was stirred at room temperature for 7 days. The crude product was isolated using column chromatography (chloroform/methanol 100:1, v/v) to give phosphonates 4a and 4b in unseparable mixture (20:1 $^{31}$P, $^{31}$P NMR ratio) (610 mg, 77%) as yellow oil, slowly crystallising.

**Method b**

Lithium 2,2,6,6-tetramethylpiperidine was prepared by adding of n-Buli (2.16 mmol, 138 mg, 2 M in cyclohexene) to a stirred solution of 2,2,6,6-tetramethylpiperidine (2.16 mmol, 304 mg) in dry THF (25 mL) under an atmosphere of argon at -78°C. The solution was stirred for additional 30 min. Then a solution of diethyl phosphite (2.16 mmol, 0.276 mL) in THF (2 mL) was added dropwise to the reaction mixture at -78°C. After 15 min the solution was allowed to warm to room temperature over 30 min and then cooled to -30°C. Crude aldehyde 3 (2.16 mmol, 495 mg) in THF (2 mL) were added dropwise into the solution. After the addition, the reaction mixtures were slowly allowed to warm to room temperature and stirred overnight, quenched by addition of saturated solution of NH$_4$Cl (10 mL). Crude products were extracted to AcOEt (3 x 10 mL), dried over MgSO$_4$, filtered, concentrated under reduced pressure and purified using column chromatography (chloroform/methanol 100:1, v/v) to give phosphonates 4a and 4b as a mixture (1:1 ratio).


**Diethyl 1-benzyl-3-(trifluoromethyl)aziridin-2-yl)(hydroxy)methylphosphonate (rac cis-4a):** Yellow oil, slowly crystallising (508 mg, 77% in two steps): $^1$H NMR (403 MHz, CDCl$_3$) $\delta$ = 7.43 – 7.22 (m, 5H, C$_6$H$_5$), 4.25 – 4.05 (m, 4H, CH$_2$CH$_2$O), 3.92 (t, 1H, J = 8.1 Hz, CH$_3$), 3.85 (d, 1H, J = 13.1 Hz, CH$_2$Ph), 3.56 (d, 1H, J = 13.2 Hz, CH$_2$Ph), 2.40 – 2.34 (m, 1H, CH$_2$CHF$_3$), 2.31 (pentet, 1H, J = 6.4 Hz, CH$_2$CHF$_3$), 1.33 and 1.31 (2 x t, 6H, J = 7.1 Hz, CH$_2$CH$_2$O) ppm. $^1$F (376 MHz, CDCl$_3$) $\delta$ = –76.47 (d, J = 6.3 Hz) ppm. $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 20.79 (s) ppm. HRMS (ESI) calc'd for C$_{12}$H$_{13}$F$_3$NO$_3$P ([M+Na]$^+$): 390.1053, found: 390.1065.

**Procedure for preparation of Mosher esters from 4a,b** Mosher esters of 4a,b were prepared according to Dale and Mosher method. Thus, mixture of aziridinyl phosphonates 4a,b (1:1 or 20:1 $^{19}$F, $^{31}$P NMR ratio) (0.14 mmol, 51 mg) was dissolved in the mixture of dry dichloromethane (5mL) and dry pyridine (0.72 mL) followed by addition of (S)-(+)MTMPA-Cl (0.32 mmol, 0.06 mL). The mixture was left for 3 days at room temperature with slowly shaking. Then the excess of 3-dimethylamino-1-propylamine (1 mmol, 0.1 mL) was added and after 10 minutes reaction mixture was diluted with ethyl ether (15 mL) and washed once with cold diluted HCl and then water. Organic layer was dried over anhydrous MgSO$_4$ and evaporated. The 1:1 NMR ratio mixture of 4a,b yielded 5a,c,b,d with 1:3.5 $^{19}$F, $^{31}$P NMR ratio, where the ratio of 5a:5c was 1:1.2 and 5b:5d was 1:1. The 20:1 NMR ratio mixture of 4a,b yielded 5a,c,b,d with 20:1 $^{19}$F, $^{31}$P NMR ratio, where the ratio of 5a:5c was 1:1.2 and 5b:5d was 1:1.

**General Procedure for ring opening of aziridinyl phosphonates (4a, 4b) with thiols** Aziridinyl phosphonates 4a, 4b (1:1 $^{19}$F, $^{31}$P NMR ratio) (0.14 mmol, 51 mg) were dissolved in an excess of thiol (2.8 mmol, 20 equiv) and then trifluoromethanesulfonic acid (0.16 mmol, 0.014 mL) was added. The solution was heated (Table 2) without any additional solvent (except reaction with 4-MePhSH which is solid at room temperature and addition of CH$_2$Cl$_2$ was needed). The reaction mixtures were then diluted with NaHCO$_3$ (10 mL), extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The crude products were isolated using column chromatography (chloroform/methanol 100:1, v/v).

**Diethyl 3-(benzylamino)-4,4,4-trifluoro-2-(2-fluorophenylthio)-1-hydroxybutylphosphonate (rac 6a):** Pale yellow crystals (32.9 mg, 95%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.62 (dd, 2H, J = 8.9, 5.2 Hz, SCCH), 7.40 – 7.25 (5H, C$_6$H$_5$), 6.98 (dd, 2H, J = 8.7, 8.7 Hz SCCCH), 4.43 – 4.08 (m, 6H, CH$_2$, CH$_2$CH$_2$OH, SCCH), 3.86 (d, 1H, J = 12.3 Hz, CH$_2$Ph), 3.82 (ddd, 1H, J = 8.4, 4.8, 1.8 Hz, CHS), 3.71 (br q, 1H, J = 6.8 Hz, CH$_2$Ph), 1.34 and 1.32 (2 x t, 6H, J = 7.0 Hz, CH$_2$CH$_2$O) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) C$_6$H$_5$ $\delta$ = 142.16 (2H, J = 248.1 Hz, CF), 138.17, 128.66, 128.44, 127.71 (4 x s, C$_6$H$_5$), 134.64 (d, J = 8.2 Hz, CHSCHF), 129.24 (d, J = 3.3 Hz, SCCHCHF), 128.21 (dq, J = 287.8, 3.6 Hz, CF$_3$), 116.05 (d, J = 21.9 Hz, CH$_2$), 71.67 (d, J = 170.2 Hz, CHPH), 63.54 and 62.44 (2 x d, J = 7.0 and 6.9 Hz, CH$_2$CH$_2$O), 61.46 (dq, J = 26.9, 12.2 Hz, CH$_2$CH$_2$O), 53.95 (s, CHS), 51.77 (s, CH$_2$Ph), 16.39 and 16.34 (2 x d, J = 5.5 and 5.6 Hz, CH$_2$CH$_2$O) ppm. $^1$F NMR (282 MHz, CDCl$_3$) F $\delta$ = –114.09 – 113.97 (m, J = 6.8 Hz) ppm. $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ = 20.49 (s) ppm. HRMS (ESI) calc'd for C$_{12}$H$_{13}$F$_4$NO$_4$P ([M+H]$^+$): 496.1329, found: 496.1281.

**Diethyl 3-(benzylamino)-4,4,4-trifluoro-2-(2-fluorophenylthio)-1-hydroxybutylphosphonate (rac 6b):** Pale yellow crystals (13.2 mg, 38%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.50 (dd, 2H, J = 8.9, 5.2 Hz, SCCH), 7.40 – 7.25 (5H, C$_6$H$_5$), 7.03 (dd, 2H, J = 8.8, 8.5 Hz SCCCH), 4.69 (br q, 1H, J = 7.2 Hz, CH$_2$Ph), 4.30 – 4.05 (m, 6H, CH$_2$, CH$_2$CH$_2$OH, CH$_2$Ph), 3.98 (d, 1H, J = 12.3 Hz, CH$_2$Ph), 3.64 (dd, 1H, J = 5.0, 2.9 Hz, CHS), 1.34 and 1.32 (2 x t, 6H, J = 7.1 Hz, CH$_2$CH$_2$O) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) C$_6$H$_5$ $\delta$ = 162.99 (d, J = 249.4 Hz, CF), 137.85, 128.78, 128.52, 127.88 (4 x s, C$_6$H$_5$), 135.99 (d, J = 8.4 Hz, CH$_2$CH$_2$O), 127.70 (d, J = 3.3 Hz, SCCCHCHF), 125.03 (q, J = 287.6 Hz, CF$_3$),
Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(phenylthio)butylyphosphonate (rac 7a): Pale yellow oil, slowly crystallising (28.9 mg, 84%). 1H NMR (300 MHz, CDCl3) δ = 7.49 (d, 2H, J = 8.1 Hz, SCCH), 7.42 – 7.27 (m, 5H, C6H5), 7.10 (d, 2H, J = 7.9 Hz, SCCHCH), 4.32 – 4.07 (m, 6H, CHP, CH2OCH2, CHPH3), 3.91 – 3.83 (m, 2H, CH3PH, CH3H), 3.76 (dq, 1H, J = 7.2, 1.7 Hz, CHF2), 2.32 (s, 1H, PhCH3), 1.35 and 1.32 (2 x t, 6H, J = 7.1 Hz, CH3(CH2)O) ppm. 13C NMR (75 MHz, CDCl3) δ = 138.46, 128.58, 128.40, 127.57 (4 x s, C6H5), 137.72, 132.31, 130.47, 129.74 (4 x s, CH2), 125.40 (dq, J = 287.8, 3.3 Hz, CHF), 70.92 (d, J = 169.4 Hz, CHP), 63.42 and 62.47 (2 x d, J = 7.0 and 6.8 Hz, CH3(CH2)O), 61.14 (dq, J = 26.9, 10.7 Hz, CH3H), 53.87 (s, CHS), 51.82 (s, PhCH3), 21.02 (s, PhCH3), 16.37 and 16.33 (2 x d, J = 5.6 and 5.8 Hz, CH3(CH2)O) ppm. 19F NMR (282 MHz, CDCl3) δ = -69.27 (s) ppm. 31P NMR (121 MHz, CDCl3) δ = 20.79 (s) ppm. HRMS (ESI) calcd for C23H20F4NO5PS ([M+H]+): 492.1580, found: 492.1554.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(phenylthio)butylyphosphonate (rac 7b): Pale yellow oil, slowly crystallising (8.5 mg, 32%). 1H NMR (300 MHz, CDCl3) δ = 7.42 – 7.25 (m, 7H, C6H5, SCCH), 7.12 (d, 2H, J = 8.5 Hz SCCHCH), 4.68 (br q, 1H, J = 7.2 Hz, CHF2F), 4.29 – 4.03 (m, 6H, CHP, CH2OCH2, CHPH3), 3.97 (dq, 1H, J = 12.3 Hz, CH3PH), 3.68 (dd, 1H, J = 4.8, 2.5 Hz, CH2), 2.34 (s, 3H, PhCH3), 1.36 and 1.28 (t, 6H, J = 7.0 and 7.1 Hz, CH3(CH2)O) ppm. 13C NMR (151 MHz, CDCl3) δ = 138.58, 128.77, 128.41, 127.75 (4 x s, C6H5), 138.35, 133.60, 130.05, 129.82 (4 x s, CH2), 125.23 (q, J = 287.7 Hz, CHF2), 71.74 (d, J = 158.0 Hz, CHP), 63.59 and 62.34 (2 x d, J = 6.9 and 7.5 Hz, CH3(CH2)O), 60.32 (dq, J = 27.4, 1.3 Hz, CH3H), 52.23 (s, CH3PH), 48.88 (dd, J = 7.3, 1.3 Hz, CHS), 21.14 (s, PhCH3), 16.50 and 16.39 (2 x d, J = 5.4 Hz, CH3(CH2)O) ppm. 19F NMR (282 MHz, CDCl3) δ = -68.74 (s) ppm. 31P NMR (121 MHz, CDCl3) δ = 21.24 (s) ppm. HRMS (ESI) calcd for C23H20F4NO5PS ([M+H]+): 492.1580, found: 492.1571.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(phenylthio)butylyphosphonate (rac 8a): Pale yellow crystals (24.7 mg, 74%). 1H NMR (403 MHz, CDCl3) δ = 7.62 – 7.20 (2 x m, 10H, C6H5), 4.31 – 4.07 (m, 6H, CHP, CH2OCH2, CHPH3), 3.94 (ddd, 1H, J = 9.1, 5.4, 1.8 Hz, CHS), 3.88 (dd, 1H, J = 12.8 Hz, CHPH3), 3.76 (dq, 1H, J = 7.0, 1.7 Hz, CHF2F), 1.33 and 1.30 (2 x t, 6H, J = 7.1 Hz, CH3(CH2)O) ppm. 13C NMR (101 MHz, CDCl3) δ = 138.23, 128.67, 128.49, 127.61 (4 x s, C6H5), 134.08, 132.05, 129.00, 127.70 (4 x s, SC6H5), 125.28 (q, J = 287.8 Hz, CF3), 71.23 (d, J = 169.6 Hz, CHP), 63.52 and 62.53 (2 x d, J = 6.8 Hz, CH3CH2O), 61.33 (d, J = 27.8, 11.6 Hz, CHF2F), 53.32 (s, CHS), 51.83 (s, CH3PH), 16.41 and 16.37 (2 x d, J = 5.6 and 5.5 Hz, CH3(CH2)O) ppm. 19F NMR (282 MHz, CDCl3) δ = -69.34 (d, J = 7.0 Hz) ppm. 31P NMR (121 MHz, CDCl3) δ = 20.60 (s) ppm. HRMS (ESI) calcd for C21H18F4NO5PS ([M+H]+): 478.1423, found: 478.1378.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(phenylthio)butylyphosphonate (rac 8b): Pale yellow crystals (9.7 mg, 29%). 1H NMR (300 MHz, CDCl3) δ = 7.51 – 7.25 (2 x m, 10H, C6H5), 4.70 (br q, 1H, J = 6.9 Hz, CHF3), 4.30 – 4.02 (m, 6H, CHP, CH2OCH2, CHPH3), 3.98 (d, 1H, J = 12.4 Hz, CHPH3), 3.76 (br dd, 1H, J = 4.7, 3.0 Hz, CHS), 1.34 and 1.33 (2 x t, 6H, J = 7.1 Hz, CH3(CH2)O) ppm. 13C NMR (151 MHz, CDCl3) δ = 138.22, 128.77, 128.44, 127.79 (4 x s, C6H5), 133.10, 132.86, 129.26, 128.05 (4 x s, SC6H5), 125.19 (q, J = 287.7 Hz, CF3), 71.89 (d, J = 158.3 Hz, CHP), 63.63 and 62.35 (2 x d, J = 6.9 and 7.5 Hz, CH3(CH2)O), 60.23 (q, J = 27.0 Hz, CHF2F), 52.24 (s, CH3PH), 48.65 (d, J = 7.5 Hz, CH3), 16.49 and 16.38 (2 x d, J = 5.4 and 5.5 Hz, CH3(CH2)O) ppm. 19F NMR (282 MHz, CDCl3) δ = -68.81 (d, J = 7.0 Hz) ppm. 31P NMR (121 MHz, CDCl3) δ = 21.06 (s) ppm. HRMS (ESI) calcd for C21H18F4NO5PS ([M+H]+): 478.1423, found: 478.1449.
Diethyl 3-(benzylamino)-2-(ethylthio)-4,4,4-trifluoro-1-hydroxybutyrophosphonate (rac 11b): Pale yellow oil (4.5 mg, 14%): \( ^1H\) NMR (403 MHz, CDCl\(_3\)) \( \delta = 7.30 – 7.27 (m, 5H, C6H5),\)
\( 4.20 – 4.05 (m, 5H, CH3CH2O, CH2PPh), 3.87 – 3.78 (m, 2H, CH2CH2PPh), 3.59 (dd, 1H, J = 10.1, 2.4 Hz, CH3P), 3.53 (dd, 1H, J = 14.4, 10.1 Hz, CH3), 1.35 – 1.28 (m, 15H, (CH2)3C, CH3CHOH) ppm. \( ^13C\) NMR (101 MHz, CDCl\(_3\)) \( \delta = 139.33, 128.40, 128.37, 127.26 (4 x, C6H5), 126.32 (q, J = 287.5 Hz, CF3), 64.99 (d, J = 166.1 Hz, CHF), 62.88 and 62.70 (2 x, d, J = 7.1 and 6.6 Hz, CH3CH2O), 58.97 (q, J = 26.3 Hz, CHF3), 52.04 (s, CH2Ph), 46.79 (s, CHS), 44.92 (s, C(CH3)), 31.48 (s, C(CH3)), 16.38 and 16.36 (2 x, d, J = 5.9 and 5.7 Hz, CH3CH2O) ppm. \( ^19F\) NMR (282 MHz, CDCl\(_3\)) \( \delta = -99.99 (d, J = 7.2 Hz) ppm. \( ^31P\) NMR (121 MHz, CDCl\(_3\)) \( \delta = 22.92 (s) ppm.\) HRMS (ESI) calcd for C24H23F6NO3PS ([M+H]+\(^\)?): 458.1736, found: 458.1691.

Notes and references