ELSEVIER

Journal of Fluorine Chemistry 77 (1996) 71–81

JOURNAL OF FLUORINE CHEMISTRY

A novel method for the preparation of fluoroaryl- and fluoroalkyl-substituted bis- and tris-phosphonic acids

R. Classen [1], G. Hägele *

Institute of Inorganic Chemistry and Structural Chemistry, Heinrich-Heine University of Düsseldorf, Universitätsstr. 1, D-40225 Düsseldorf, Germany

Received 12 August 1995; accepted 14 December 1995

Abstract

The formation of various aromatic fluorinated vinylphosphonates, geminal and vicinal bisphosphonates and trisphosphonates by the Wittig–Horner–Emmons reaction and Michael addition is presented. The regiospecific direction of Michael addition under basic catalysis is largely dependent on the substitution pattern of the vinylphosphonates. The pentafluorophenyl-substituted vinylphosphonate **8d** and diethyl phosphite react to yield the novel trisphosphonate **5**. This reaction sequence substitutes the *para*-fluorine atom of the C_6F_5 unit by nucleophilic substitution while a simultaneous nucleophilic addition of the phosphonate group to the vinylic double bond takes place. Explicit NMR studies are described.

Keywords: Aromatic fluorinated bis- and trisphosphonates; Wittig–Horner–Emmons reaction; Michael addition; Regioselectivity; NMR spectroscopy

1. Introduction

Geminal bisphosphonates have attracted considerable attention in chemistry, biochemistry and medicine. This important class of drugs is characterized by a P–C–P structure designed for diagnostic and therapeutic use in various diseases of bone and calcium metabolisms [1]. Technetium-99m-labelled bisphosphonates [2], important radiopharmaceuticals for practical bone scintigraphy, are used for the imaging of skeletal disorders. In addition, geminal bisphosphonates are physiological inhibitors of calcification and bone resorption. Vicinal bisphosphonates bearing the P–C–C–P unit have shown less biochemical activity, a fact which might be due to a lower capacity for the hydroxyapatite of mammalian tissue [3]. But other investigations have revealed that the vicinal bisphosphonates are useful corrosion inhibitors [4]. In further biochemical studies [5], halogenated geminal bisphosphonates have shown additionally the inhibition of virus-induced enzymes in infected cells by coordinating with metal ions at their active sites. Recent synthetic studies are aimed at target specific complexation of tailor-made ligands. Bearing these facts in mind, we wish to introduce strongly polarizing substituents, like fluorinated aliphatic and aromatic units, into the skeleton of phosphonic acid derivatives.

In previous work, we have reported the synthesis of various non-fluorinated aromatic and aliphatic bis- and tris-phosphonates [6]. Particular interest in our group has been paid towards the introduction of fluorinated substituents in phosphonic acid chemistry, which will give rise to an apparent enhancement of the acidity in $P(O)(OH)_2$ functions. This fact and the multiperspective concepts of biochemical activity with metal-chelating agents encouraged us to study the preparation of the novel aromatic fluorinated phosphonates **1–4** (Scheme 1).

Additionally, we synthesized the tetrafluorophenyl-substituted trisphosphonates **5** and **6** (Schemes 2 and 3) which were identified by ^1H, ^{19}F and $^{31}P\{^1H\}$ NMR investigations. The cyclohexylammonium salt **6** represents a stable storage form for the corresponding acid.

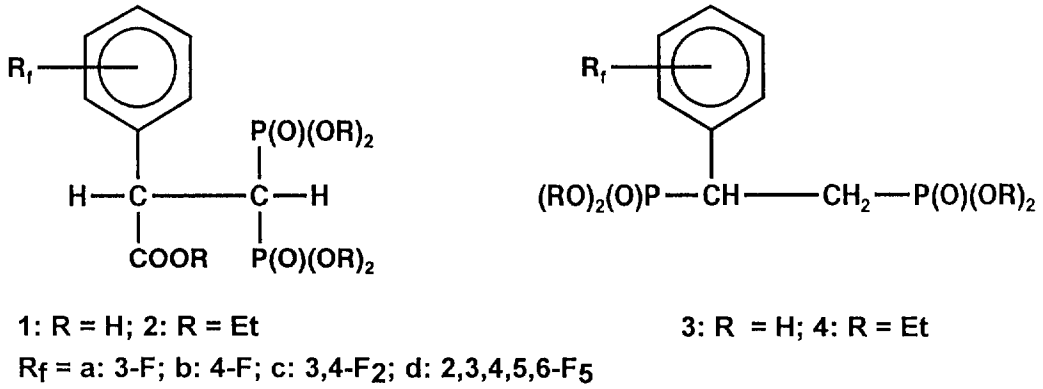
2. Results and discussion

The general Wittig–Horner–Emmons olefination [7] of fluorinated benzaldehydes or fluoroaryl-substituted α-keto esters with carbanions derived from methylenebisphosphonic acid tetraalkyl esters provides the vinylphosphonates **7** and **8**, precursors for the preparation of the bis- and tris-phosphonates **1–6**. The reactions of α-keto esters with tetraethyl methylenebisphosphonate carbanions lead to mixtures of *E*- and *Z*-isomers with *E*/*Z* ratios: **7a** (6:94), **7b** (7:93), **7c** (12:88), **7d** (83:17), as determined by ^{19}F NMR integration.

[1] Part of forthcoming dissertation of R. Classen.

* Corresponding author.

SSDI 0022-1139(95)03387-4

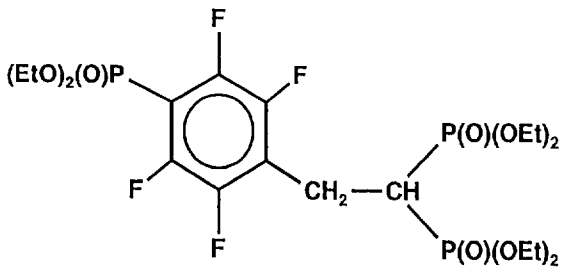


1: R = H; 2: R = Et

3: R = H; 4: R = Et

R_f = a: 3-F; b: 4-F; c: 3,4-F_2; d: 2,3,4,5,6-F_5

Scheme 1.



5

Scheme 2.

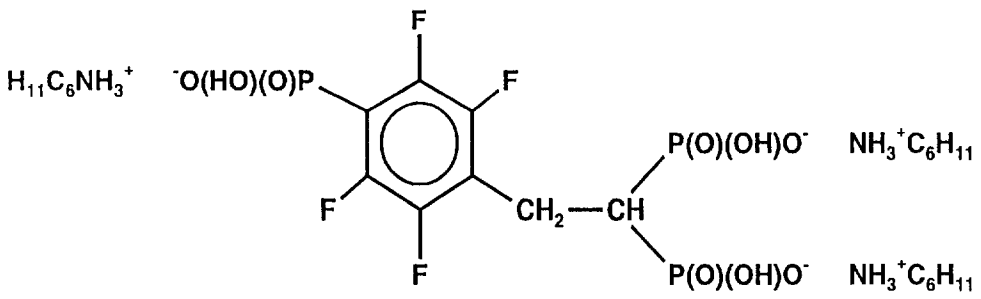
The Wittig–Horner–Emmon reaction with the benzaldehydes follow a highly stereospecific course [8]: in practice, only the *trans* isomers of vinylphosphonates **8** are isolated (Scheme 4).

A number of non-fluorinated phosphonocarboxylic acid esters have been prepared by base-catalyzed Michael addition of P–H acidic esters to activated double bonds [9]. In a similar step, the fluoroaryl-substituted vinylphosphonates **7** react with diethyl phosphite under basic catalysis to yield the geminal bisphosphonic acid esters **2**. Here a 1 M solution of sodium diethyl phosphite in THF was used as the catalyst. The nucleophilic attack of the diethyl phosphite anion is directed at α-C-vinylic atom of the corresponding β-alkoxycarbonyl phosphonic ester (Scheme 5).

The reaction of the vinylphosphonates **8a–c** with diethyl phosphite under identical conditions reveals a totally different regiospecific course. The phosphoryl group adds to the β-C-vinylic atom of the vinylphosphonates **8a–c** and consequently the vicinal bisphosphonic acid esters **4a–c** are obtained in good yield (Scheme 6).

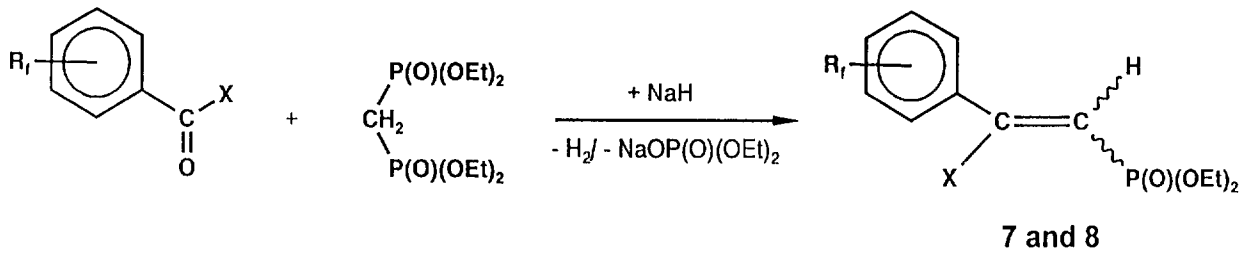
The pentafluorophenyl-substituted vinylphosphonate **8d**, diethyl phosphite and catalytic amounts of the diethyl phosphite sodium salt do not react under the standard conditions of a base-catalyzed Michael addition. But if an equimolar mixture of diethyl phosphite and sodium diethyl phosphite is used, the trisphosphonate **5** is obtained as the main product. The vicinal bisphosphonate **4d** is formed as a byproduct in low yield only. Two versions of the consequent addition–substitution reactions can be suggested to explain the formation of the final product: at the first stage, the nucleophilic addition of diethyl phosphite to the double bond takes place, and then the diethyl phosphite anion of the sodium salt substitutes the *para*-fluorine atom of the pentafluorophenyl unit (S_{NAr} mechanism); an inverse reaction sequence might also be possible as shown in Scheme 7.

The $^{31}P\{^1H\}$, ^{19}F and ^1H NMR spectra of the reaction mixture and different fractions have shown evidence for the formation of the intermediate product A. Small amounts of compound A were isolated together with the vicinal bisphosphonate **4d** and other hitherto unidentified byproducts by



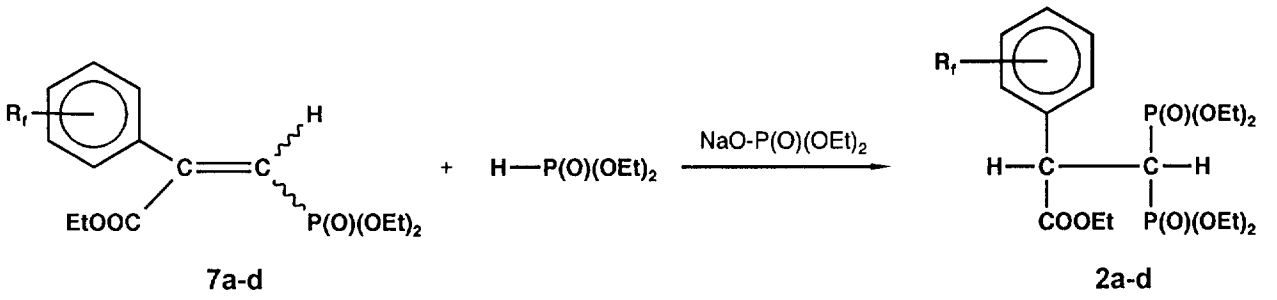
6

Scheme 3.

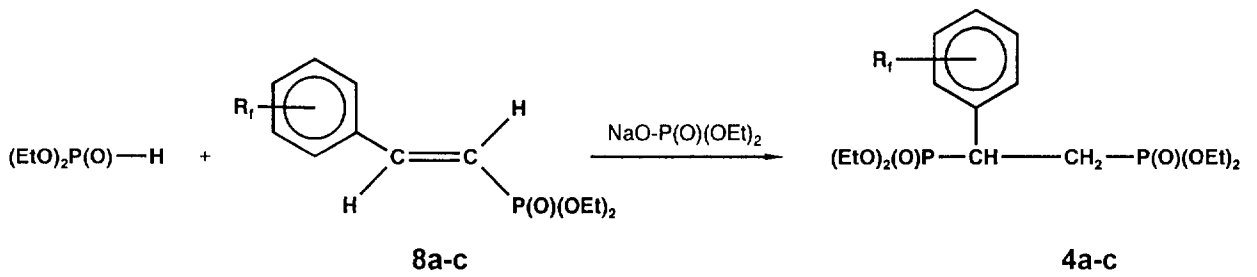


7: X = COOEt; R_f = a: 3-F; b: 4-F; c: 3,4-F_2; d: 2,3,4,5,6-F_5
8: X = H; R_f = a: 3-F; b: 4-F; c: 3,4-F_2; d: 2,3,4,5,6-F_5

Scheme 4.



Scheme 5.



Scheme 6.

vacuum distillation. Hitherto no NMR spectroscopic evidence for the formation of intermediate B was deduced.

The esters **2** and **4**, respectively, are cleaved by concentrated hydrochloric acid leading to the parent acids **1** and **3**. After drying in vacuo, the acids are isolated as colourless hygroscopic solids (Scheme 8).

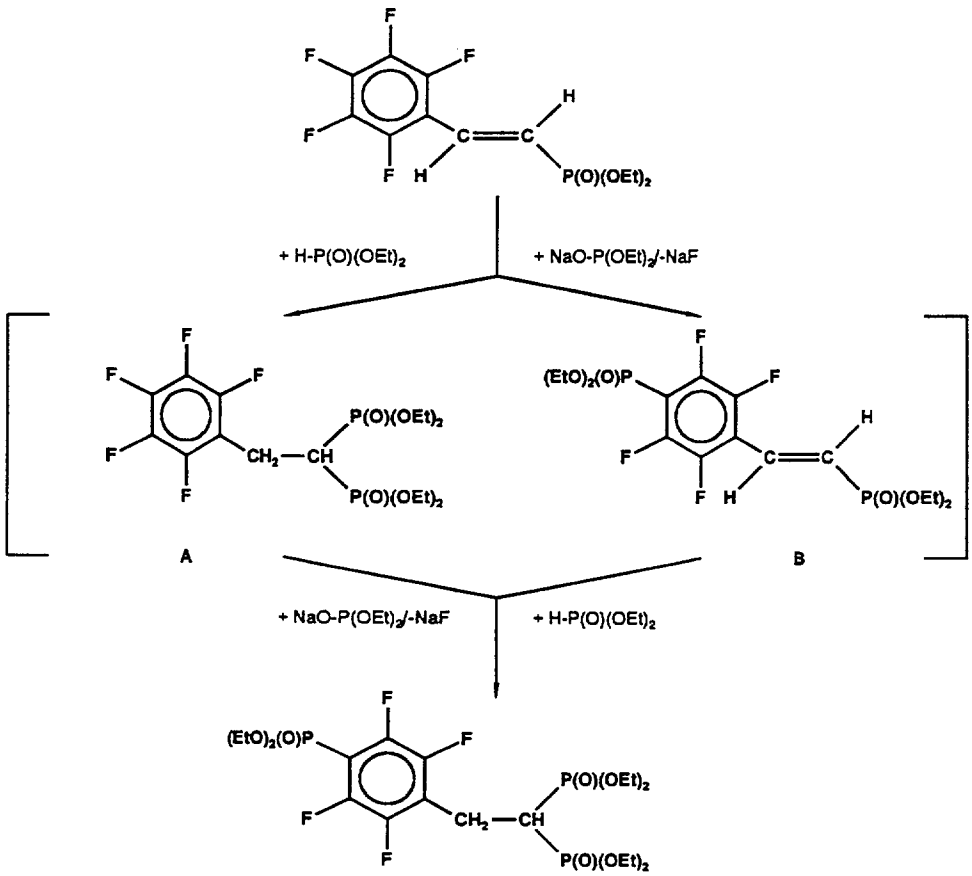
However, the hydrolysis of hexaethyl ester **5** with hydrochloric acid is accompanied by its partial decomposition and the acid obtained is contaminated by unidentified byproducts. In this case the ethyl ester groups have been cleaved with bromotrimethylsilane and distilled water. The free acid is precipitated with cyclohexylamine as the corresponding tris-cyclohexylammonium salt **6** (Scheme 9).

*2.1. The $^{19}F\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectroscopic investigation of compound **4c***

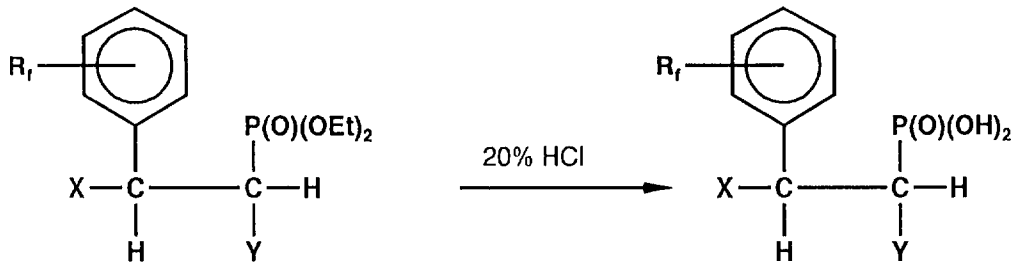
All the fluoroaryl-substituted vicinal bisphosphonates **3** and **4** are readily identified by $^{19}F\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectroscopy. Here we wish to introduce the NMR investigation and analysis of compound **4c** which is a typical representative for this class of vicinal bisphosphonates.

The $^{19}F\{^1H\}$ and the $^{31}P\{^1H\}$ NMR spectra of **4c** exhibit an ABXY spin system (see Scheme 10).

The fluorine atoms A and B from the aromatic ring system and the phosphorus nucleus Y show long-range couplings $^5J_{PF}$ and $^6J_{PF}$, respectively. Corresponding $^6J_{PF}$ and $^7J_{PF}$ couplings between the phosphorus X and the fluorine nuclei A and B were not resolved. The ABXY spectrum was iterated with WIN-DAISY [10] and the results are listed in Table 1. In the $^{19}F\{^1H\}$ NMR spectrum of **4c** (Fig. 1) the AB part of the ABXY spin system is easily recognized. At low field ($\nu_A = 4605.80$ Hz, $\delta_A = 24.46$ ppm), the A multiplet exhibits the $^2J_{FF}$ and $^5J_{PF}$ coupling constants. At high field ($\nu_B = 4255.76$ Hz, $\delta_B = 22.60$ ppm), the B multiplet shows the $^2J_{FF}$ and $^6J_{PF}$ couplings. As shown in Fig. 2, the phospho-



Scheme 7.



Scheme 8.

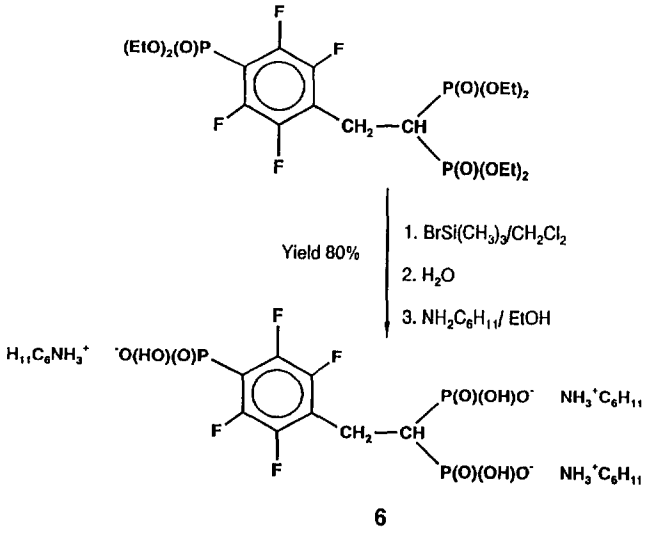
rus atoms X and Y represent the XY part of the ABXY spin system with resonance frequencies $\nu_X = 2299.55$ Hz ($\delta_X = 28.38$ ppm) and $\nu_Y = 2159.93$ Hz ($\delta_Y = 26.66$ ppm). The X and Y multiplets give access to $^3J_{PP}$ but only Y provides additionally the long-range phosphorus–fluorine couplings $^5J_{PF}$ and $^6J_{PF}$.

In a forthcoming publication, we will report the details of the more complex spin analysis for the aromatic and aliphatic systems of the vicinal bisphosphonates **3** and **4** where the ^1H and ^{19}F NMR spectra exhibit a strong second-order character.

2.2. The ^{19}F and $^{31}P\{^1H\}$ NMR spectroscopic investigation of compound 5

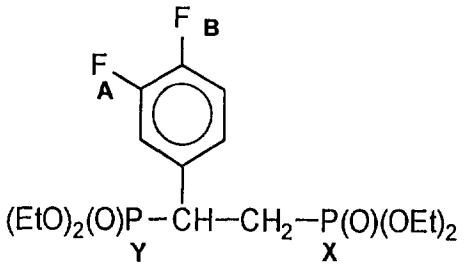
The ^{19}F and $^{31}P\{^1H\}$ NMR spectra of the aromatic substituent in the trisphosphonate **5** reveal an $[AB]_2X$-type spin system (see Scheme 11).

This $[AB]_2X$ five-spin system has been analyzed and iterated with WIN-DAISY. The ^{19}F and ^{31}P NMR chemical shifts, resonance frequencies and the coupling constants for the aromatic system in **5** are given in Table 2. The experimental and



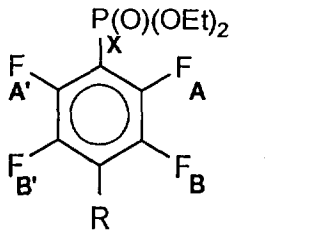
6

Scheme 9.



4c

Scheme 10.



5

Scheme 11.

simulated sub-spectra of the $[AB]_2X$-type spin system are presented in Figs. 3–5.

3. Experimental details

3.1. General

NMR spectra were recorded on a Bruker AM 200 SY spectrometer operating at 200 MHz for protons. $CDCl_3$, D_2O and 1 N D_2O/NaOH were used as internal locks. References:

Table 1
NMR data for compound **4c** (R_f = 3,4-F_2) [a]

NMR characteristics	Nucleus/ coupling constants	Magnitude	Error
Chemical shifts			
δ_A	$^{19}F\{^1H\}$	24.46	
δ_B	$^{19}F\{^1H\}$	22.60	
δ_X	$^{19}P\{^1H\}$	28.38	
δ_Y	$^{31}P\{^1H\}$	26.66	
Resonance frequencies			
ν_A	$^{19}F\{^1H\}$	4605.802	±0.002
ν_B	$^{19}F\{^1H\}$	4255.758	±0.001
ν_X	$^{31}P\{^1H\}$	2299.555	±0.001
ν_Y	$^{31}P\{^1H\}$	2159.937	±0.001
Coupling constants			
J_{AB}	$^3J_{FF}$	−21.257	±0.002
J_{AX}	$^6J_{PF}$	0.590	±0.004
J_{AY}	$^5J_{PF}$	1.914	±0.002
J_{BX}	$^7J_{PF}$	−1.237	±0.003
J_{BY}	$^6J_{PF}$	5.511	±0.002
J_{XY}	$^3J_{PP}$	80.358	±0.002

[a] Resonance frequencies ν_i in Hz, chemical shifts δ_i in ppm and coupling constants $^nJ_{ij}$ in Hz. $^{31}P\{^1H\}$ NMR: 81, 015 MHz, 5% in $CDCl_3$, 85% H_3PO_4 ext. $^{19}F\{^1H\}$ NMR: 188, 282 MHz, 2% in $CDCl_3$, C_6F_6 int. NMR data simulated and iterated with WIN-DAISY (final sum of squares = 29.356 409, number of spectral points = 10 408, degrees of freedom = 10 400, standard deviation of measurements = 0.053 129, *R*-factor = 0.325 377).

Table 2
NMR data for compound **5** [a]

NMR characteristics	Nucleus/ coupling constants	Magnitude	Error
Chemical shifts			
δ_A	^{19}F	28.648	
δ_B	^{19}F	21.272	
δ_X	$^{31}P\{^1H\}$	5.808	
Resonance frequencies			
ν_A	$^{19}F\{^1H\}$	5393.986	±0.003
ν_B	$^{19}F\{^1H\}$	4005.145	±0.004
ν_X	$^{31}P\{^1H\}$	470.559	±0.006
Coupling constants			
J_{AX}	$^3J_{PF}$	−3.587	±0.004
J_{BX}	$^4J_{PF}$	8.639	±0.010
J_{AB}	$^3J_{FF}$	−22.563	±0.005
$J_{AB'}$	$^5J_{FF}$	13.587	±0.005
$J_{AA'}$	$^4J_{FF}$	0.431	±0.014
$J_{BB'}$	$^4J_{FF}$	−5.565	±0.007

[a] Resonance frequencies ν_i in Hz, chemical shifts δ_i in ppm and coupling constants $^nJ_{ij}$ in Hz. $^{31}P\{^1H\}$ NMR: 81, 015 MHz, 5% in $CDCl_3$, 85% H_3PO_4 ext. ^{19}F NMR: 188, 282 MHz, 2% in $CDCl_3$, C_6F_6 int. NMR data simulated and iterated with WIN-DAISY (final sum of squares = 29.038 276, number of spectral points = 2392, degrees of freedom = 2382, standard deviation of measurements = 0.110 412, *R* factor = 0.543 173).

^{19}F NMR spectra in $CDCl_3$: internal C_6F_6, in D_2O: external C_6F_6. ^1H NMR spectra in $CDCl_3$: internal TMS, in D_2O: internal 3-trimethylsilylpropionic acid-d_4 sodium salt. $^{31}P\{^1H\}$ NMR spectra: external 85% H_3PO_4. The concentrations employed were 2% for ^1H and ^{19}F NMR spectra and

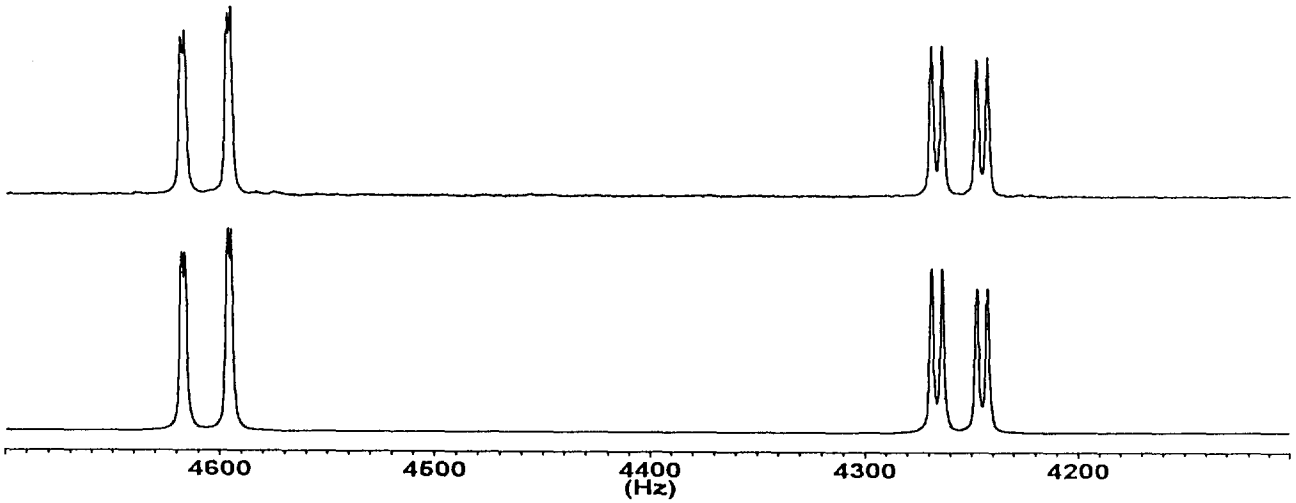


Fig. 1. (top) Experimental $^{19}F\{^1H\}$ NMR spectrum of **4c**. AB part of the ABXY system. (bottom) Simulation of WIN-DAISY results, 4150–4700 Hz.

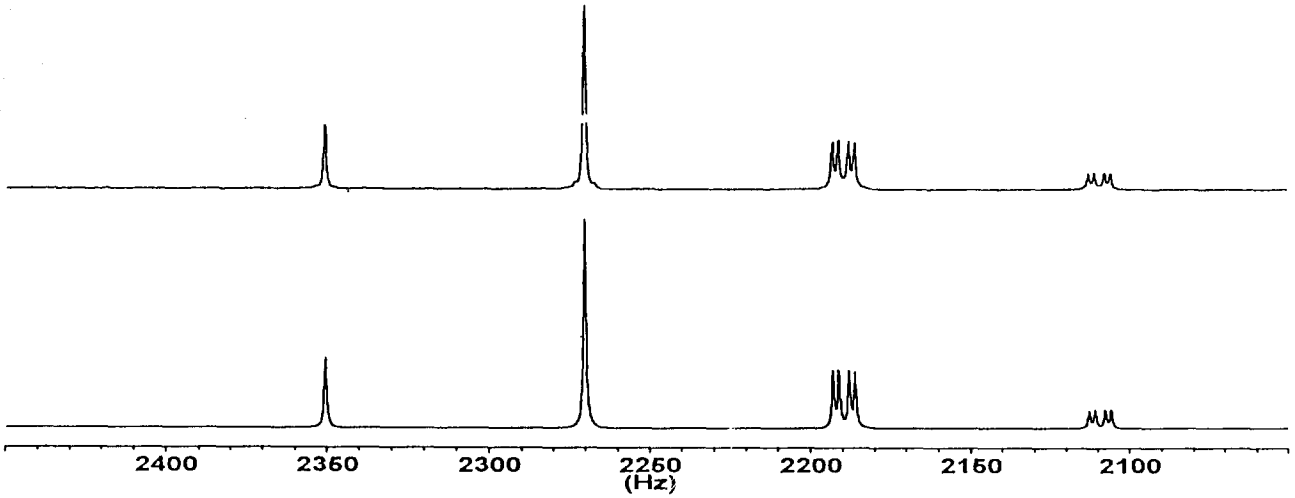


Fig. 2. (top) Experimental $^{31}P\{^1H\}$ NMR spectrum of **4c**. XY part of the ABXY system. (bottom) Simulation of WIN-DAISY results, 2050–2450 Hz.

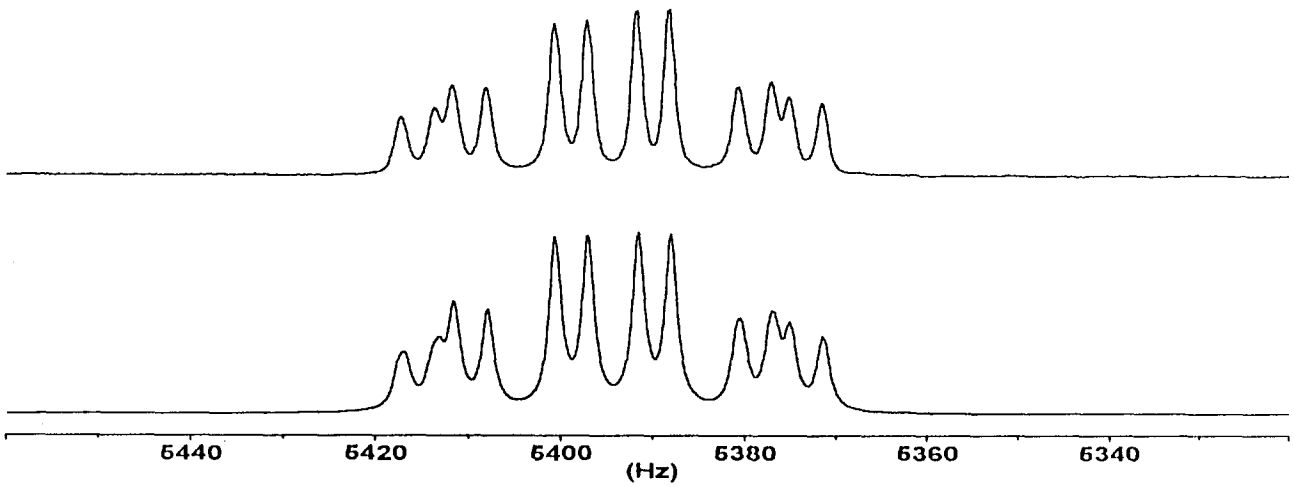


Fig. 3. (top) Experimental ^{19}F NMR spectrum of **5**. A part of the $[AB]_2X$ system. (bottom) Simulation of the WIN-DAISY results, 5320–5460 Hz.

10% for ^{31}P NMR spectra. All measurements were performed in non-degassed, unsealed, open samples (5-mm NMR tubes). Elemental analyses were determined on a C–H–N Analyzer 263 Perkin-Elmer (Institute of Pharmacy, Heinrich-Heine University, Düsseldorf). Melting points were determined using a Büchi 510 apparatus and were not cor-

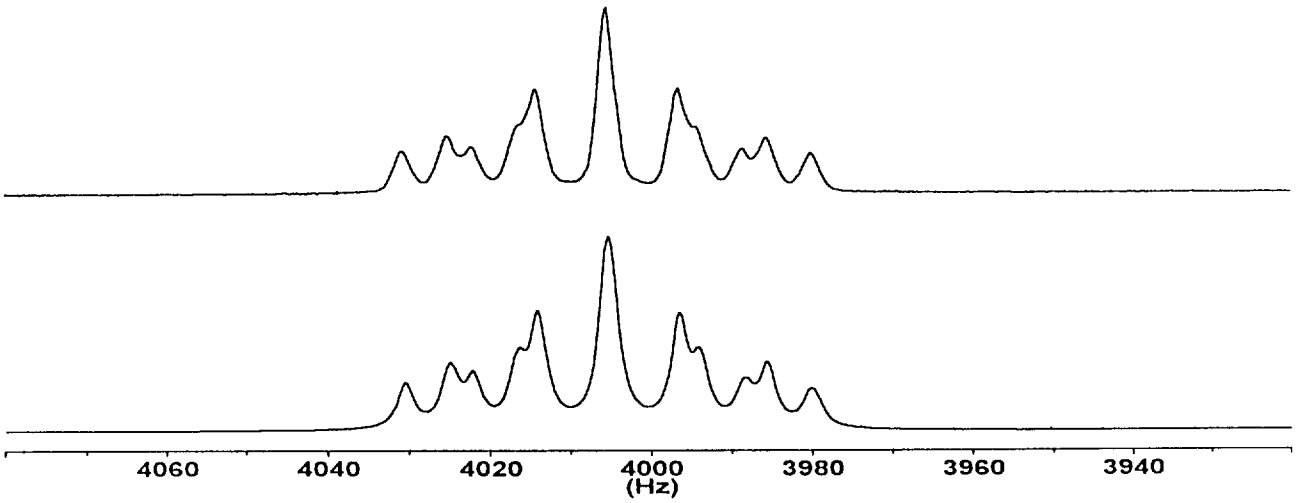


Fig. 4. (top) Experimental ^{19}F NMR spectrum of **5**. B part of the $[AB]_2X$ system. (bottom) Simulation of WIN-DAISY results, 4080–3920 Hz.

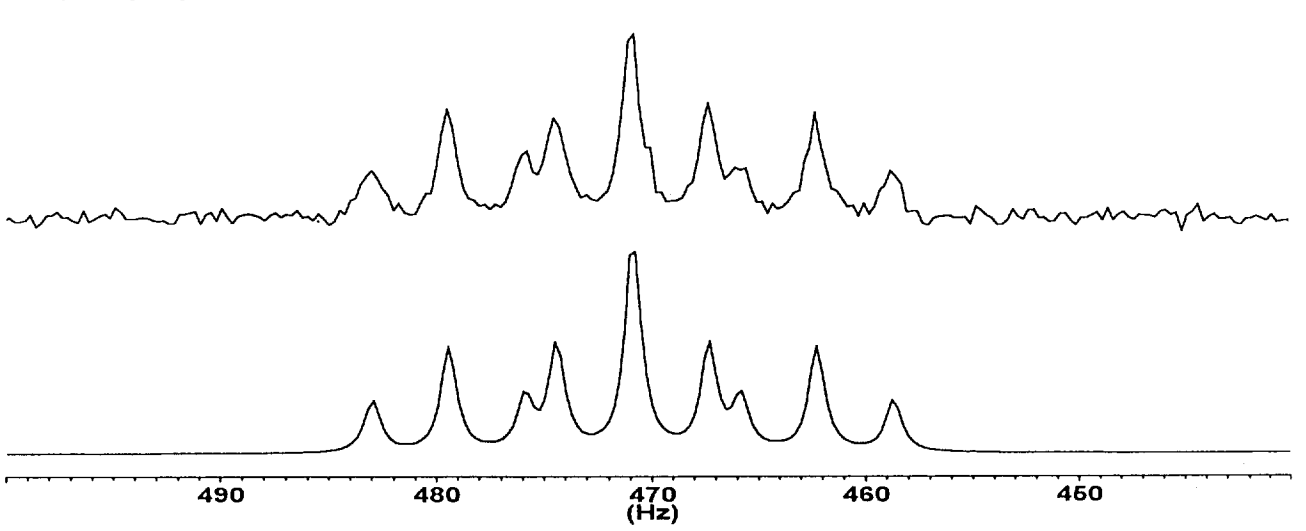


Fig. 5. (top) Experimental $^{31}P\{^1H\}$ NMR spectrum of **5**. X part of the $[AB]_2X$ system. (bottom) Simulation of WIN-DAISY results, 500–440 Hz.

rected. Syntheses were performed with commercial chemicals from Aldrich, Jansen, Merck and Riedel–de Haën. All liquid educts and solvents were purified by distillation. THF was dried with 97% sodium hydride under reflux. The solvent was stored under dry N_2 in a pressure bottle. All reactions were performed under nitrogen atmosphere.

3.2. *Vinylphosphonates 7 and 8*

In a 250 ml three-necked flask fitted with a magnetic stirrer, reflux condenser, dropping funnel and nitrogen bubbler, 14.41 g (0.05 mol) of methylenebisphosphonic acid tetraethyl ester were added dropwise to a stirred suspension of 1.24 g of sodium hydride (97% NaH) (0.05 mol) in 50 ml of THF. The reaction mixture was stirred until hydrogen formation had ceased (1 h). Then, a solution of the corresponding benzaldehyde or α-keto ester (0.05 mol) in THF (5 ml) was added in several portions under nitrogen to the THF solution of sodium methylenebisphosphonate. After the exothermic reaction was completed, the reaction mixture was refluxed for 1 h, then cooled to ambient temperature, diluted with 50 ml of water and the organic layer separated. The aqueous layer was extracted with diethyl ether and the organic layer concentrated under reduced pressure. The residue was combined with the etheral extract and dried over Na_2SO_4 and then concentrated to give a liquid which was purified by distillation in vacuo (oil pump).

3-Phosphono-2-(3-fluorophenyl) acrylic acid triethyl ester (**7a**): Yield 44%; b.p. 133–135 °C/0.001 Torr. ^1H NMR ($CDCl_3$; TMS int.) δ_H, $^nJ_{ij}$: *E*-isomer: 1.15 (t, $^3J_{HH}=7.1$ Hz, 6H, CH_3); 1.29 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 3.82–3.97 (m, 4H, CH_2); 4.26 (q, $^3J_{HH}=7.1$ Hz, 2H, CH_2); 7.00 (d, $^2J_{PH}=-15.0$ Hz, 1H, =C*H*–); 7.10–7.39 (m, $4H_{arom.}$, 3-F-C_6H_4–) ppm. *Z*-isomer: 1.35 (t, $^3J_{HH}=7.1$ Hz, 6H, CH_3); 1.38 (t, $^3J_{HH}=7.2$ Hz, 3H, CH_3); 4.07–4.24 (m, 4H, CH_2); 4.40 (q, $^3J_{HH}=7.2$ Hz, 2H, CH_2); 6.14 (d, $^2J_{PH}=-12.1$ Hz, 1H, =C*H*–); 7.10–7.39 (m, $4H_{arom.}$, 3-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: *E*-isomer: 13.59 (s) ppm. *Z*-isomer: 14.09 (s) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: *E*-isomer: 48.26–48.38 (m, $1F_{meta}$) ppm. *Z*-isomer: 50.01–50.13 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_{15}H_{20}O_5PF$: C, 54.54; H, 6.12%. Found: C, 54.36; H, 6.05%.

3-Phosphono-2-(4-fluorophenyl)acrylic acid triethyl ester (**7b**): Yield 76%; b.p. 147–148 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$; TMS int.) δ_H: *E*-isomer: 1.17 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH_3); 1.31 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3); 3.84–3.96 (m, 4H, CH_2); 4.28 (q, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2); 6.99 (d, $^2J_{PH}$ = −15.2 Hz, 1H, =C*H*–); 7.04–7.16 (m, 2H$_{meta}$, 4-F-C_6H_4–); 7.38–7.54 (m, 2H$_{ortho}$, 4-F-C_6H_4–) ppm. *Z*-isomer: 1.37 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH_3); 1.40 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3); 4.10–4.25 (m, 4H, CH_2); 4.42 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2); 6.09 (d, $^2J_{PH}$ = −12.1 Hz, 1H, =C*H*–); 7.04–7.16 (m, 2H$_{meta}$, 4-F-C_6H_4–); 7.44–7.54 (m, 2H$_{ortho}$, 4-F-C_6H_4–) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: *E*-isomer: 14.01 (s) ppm. *Z*-isomer: 14.55 (s) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: *E*-isomer: 49.52–49.67 (m, 1F$_{para}$) ppm. *Z*-isomer: 51.89–52.03 (m, 1F$_{para}$) ppm. Analysis: Calc. for $C_{15}H_{20}O_5PF$: C, 54.54; H, 6.12%. Found: C, 54.30; H, 6.20%.

3-Phosphono-2-(3,4-difluorophenyl)acrylic acid triethyl ester (**7c**): Yield 78%; b.p. 141–146 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$; TMS int.) δ_H: *E*-isomer: 1.20 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3); 1.31 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3); 3.84–4.01 (m, 4H, CH_2); 4.28 (q, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2); 7.02 (d, $^2J_{PH}$ = −14.9 Hz, 1H, =C*H*–); 7.13–7.38 (m, 3H$_{arom.}$, 3,4-F-C_6H_3–) ppm; *Z*-isomer: 1.38 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH_3); 1.39 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3); 4.10–4.25 (m, 4H, CH_2); 4.41 (q, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2); 6.10 (d, $^2J_{PH}$ = −11.8 Hz, 1H, =C*H*–); 7.13–7.38 (m, 3H$_{arom.}$, 3,4-F_2-C_6H_3–) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: *E*-isomer: 13.39 (s) ppm. *Z*-isomer: 13.84 (s) ppm. ^{19}F{^{1}H} NMR ($CDCl_3$; C_6F_6 int.) δ_F: *E*-isomer: 25.88, 27.49 (AB system, J_{AB} = $^3J_{FF}$ = 21.1 Hz) ppm. *Z*-isomer: 23.75, 24.90 (AB system, J_{AB} = $^3J_{FF}$ = 21.4 Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: *E*-isomer: 23.66–23.87 (m, 1F$_{para}$); 24.81–24.96 (m, 1F$_{meta}$) ppm. *Z*-isomer: 25.00–25.99 (m, 1F$_{para}$); 27.41–27.64 (m, 1F$_{meta}$) ppm. Analysis: Calc. for $C_{15}H_{19}O_5PF_2$: C, 51.72; H, 5.51%. Found: C, 51.54; H, 5.71%.

3-Phosphono-2-(2,3,4,5,6-pentafluorophenyl)acrylic acid triethyl ester (**7d**): Yield 55%; b.p. 104–106 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$; TMS int.) δ_H: *E*-isomer: 1.32 (t, $^3J_{HH}$ = 7.1 Hz, 9H, CH_3); 4.02–4.42 (m, 6H, CH_2); 7.35 (d, $^2J_{PH}$ = −12.4 Hz, 1H, =C*H*–) ppm. *Z*-isomer: 1.40 (t, $^3J_{HH}$ = 7.1 Hz, 9H, CH_3); 4.02–4.42 (m, 6H, CH_2); 6.40 (d, $^2J_{PH}$ = −11.0 Hz, 1H, =C*H*–) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: *E*-isomer: 10.58 (s) ppm. *Z*-isomer: 10.84 (s) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: *E*-isomer: −0.85 to −0.55 (m, 2F$_{meta}$); 8.67–8.91 (m, 1F$_{para}$); 22.50–22.69 (m, 2F$_{ortho}$) ppm. *Z*-isomer: 0.75–1.05 (m, 1F$_{meta}$); 10.35–10.60 (m, 1F$_{para}$); 22.30–22.48 (m, 2F$_{ortho}$) ppm. Analysis: Calc. for $C_{15}H_{16}O_5PF_5$: C, 44.78; H, 4.02%. Found: C, 44.67; H, 4.01%.

1-(3-Fluorophenyl)ethylene-2-phosphonic acid diethyl ester (**8a**): Yield 67%; b.p. 106–107 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$; TMS int.) δ_H: 1.36 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3); 4.15 (5 lines, 4H, CH_2), 6.28, 7.46 (AB part of ABX system, J_{AB} = $^3J_{HH}$ = 17.3 Hz, J_{AX} = $^2J_{PH}$ = −22.2 Hz, J_{BX} = $^3J_{PH}$ = 17.2 Hz, 2H, –C*H*=C*H*–P); 7.02–7.42 (m, 4H$_{arom.}$, 3-F-C_6H_4–) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 19.17 (d, $^6J_{PF}$ = 0.9 Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 49.29–49.41 (m, 1F$_{meta}$) ppm. Analysis: Calc. for $C_{12}H_{16}O_3PF$: C, 55.81; H, 6.26%. Found: C, 55.96; H, 6.29%.

1-(4-Fluorophenyl)ethylene-2-phosphonic acid diethyl ester (**8b**): Yield 67%; b.p. 110–113 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$; TMS int.) δ_H: 1.36 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3); 4.14 (5 lines, 4H, CH_2), 6.19, 7.47 (AB part of ABX system, J_{AB} = $^3J_{HH}$ = 17.2 Hz, J_{AX} = $^2J_{PH}$ = −22.4 Hz, J_{BX} = $^3J_{PH}$ = 17.3 Hz, 2H, –C*H*=C*H*–P); 7.04–7.14 (m, 2H$_{meta}$, 4-F-C_6H_4–); 7.46–7.53 (m, 2H$_{ortho}$, 4-F-C_6H_4–) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 19.85 (d, $^7J_{PF}$ = 1.3 Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 51.98–52.13 (m, 1F$_{para}$) ppm. Analysis: Calc. for $C_{12}H_{16}O_3PF$: C, 55.81; H, 6.26%. Found: C, 55.61; H, 6.42%.

1-(3,4-Difluorophenyl)ethylene-2-phosphonic acid diethyl ester (**8c**): Yield 75%; b.p. 117–118 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$; TMS int.) δ_H: 1.37 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3); 4.15 (5 lines, 4H, CH_2), 6.20, 7.42 (AB part of ABX system, J_{AB} = $^3J_{HH}$ = 17.2 Hz, J_{AX} = $^2J_{PH}$ = −22.3 Hz, J_{BX} = $^3J_{PH}$ = 17.0 Hz, 2H, –C*H*=C*H*–P); 7.12–7.35 (m, 3H$_{arom.}$, 3,4-$F_2C_6H_3$–) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 18.96 (X part of ABX system, J_{AX} = $^7J_{PF}$ = 1.3 Hz, J_{BX} = $^6J_{PF}$ = 0.9 Hz) ppm. ^{19}F{^{1}H} NMR ($CDCl_3$; C_6F_6 int.) δ_F: 25.24, 27.46 (AB part of ABX system, J_{AB} = $^3J_{FF}$ = 20.8 Hz, J_{AX} = $^7J_{PF}$ = 1.3 Hz, J_{BX} = $^6J_{PF}$ = 0.9 Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 25.07–25.27 (m, 1F$_{para}$); 27.28–27.51 (m, 1F$_{meta}$) ppm. Analysis: Calc. for $C_{12}H_{15}O_3PF_2$: C, 52.17; H, 5.48%. Found: C, 51.67; H, 5.51%.

1-(2,3,4,5,6-Pentafluorophenyl)ethylene-2-phosphonic acid diethyl ester (**8d**): Yield 60%; b.p. 129–131 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$; TMS int.) δ_H: 1.38 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3); 4.17 (5 lines, 4H, CH_2); 6.65, 7.44 (AB part of ABX system, J_{AB} = $^3J_{HH}$ = 17.8 Hz, J_{AX} = $^2J_{PH}$ = −24.2 Hz, J_{BX} = $^3J_{PH}$ = 17.5 Hz, 2H, –C*H*=C*H*–P) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 16.95–16.98 (m) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 0.07–0.37 (m, 2F$_{meta}$); 10.45–10.70 (m, 1F$_{para}$); 21.01–21.23 (m; 2F$_{ortho}$) ppm. Analysis: Calc. for $C_{12}H_{12}O_3PF_5$: C, 43.64; H, 3.67%. Found: C, 43.78; H, 3.62%.

3.3. Penta- and tetra-ethyl esters 2 and 4

In a 100 ml three-necked flask fitted with a magnetic stirrer, reflux condenser and dropping funnel were placed 1.38 g (0.01 mol) of diethyl phosphite and (0.01 mol) of vinylphosphonate **7** or **8** in 5 ml of dry THF. This solution was stirred under nitrogen at room temperature and then several drops of a 1 M sodium diethyl phosphite THF solution were added. While the temperature rose to 50 °C, the colour of the mixture changed to deep yellow. After stirring for 2 h at reflux and then neutralizing the solution with several drops of half concentrated acetic acid, the THF phase was evaporated and 5 ml of water was poured into the residue. The water phase

was extracted with 20 ml of CH_2Cl_2 and the combined organic phases dried over Na_2SO_4. After removal of the solvent, the crude product was distilled in vacuo and compounds **2** and **4** were obtained as highly viscous oils.

3,3-Bisphosphono-2-(3-fluorophenyl)propionic acid pentaethyl ester (**2a**): Yield 72%; b.p. 164–165 °C/0.001 Torr. $^1H\{^{31}P\}$ NMR ($CDCl_3$; TMS int.) δ_H: 1.15 (t, $^3J_{HH}=7.1$ Hz, 6H, CH_3); 1.23 (t, $^3J_{HH}=7.2$ Hz, 3H, CH_3); 1.37 (t, $^3J_{HH}=7.0$ Hz, 3H, CH_3); 1.38 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 3.54, 4.16 (AB system, $J_{AB}=^3J_{HH}=10.6$ Hz, –*CH*–*CH*–); 3.67–4.32 (m, 10H, CH_2); 6.94–7.35 (m, $4H_{arom.}$, 3-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 20.57, 22.07 (XY system, $J_{XY}=^2J_{PP}=3.4$ Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 48.14–48.27 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_{19}H_{31}O_8P_2F$: C, 48.71; H, 6.68%. Found: C, 47.95; H, 6.74%.

3,3-Bisphosphono-2-(4-fluorophenyl)propionic acid pentaethyl ester (**2b**): Yield 74%; b.p. 164–169 °C/0.001 Torr. $^1H\{^{31}P\}$ NMR ($CDCl_3$; TMS int.) δ_H: 1.16 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.21 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.22 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.38 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.39 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 3.54, 4.49 (AB system, $J_{AB}=^3J_{HH}=10.6$ Hz, –*CH*–*CH*–); 3.66–4.49 (m, 10H, CH_2); 6.97–7.05 (m, $2H_{meta}$, 4-F-C_6H_4–); 7.39–7.47 (m, $2H_{ortho}$, 4-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 20.77, 22.19 (XY system, $J_{XY}=^2J_{PP}=3.3$ Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 47.21–47.36 (m, $1F_{para}$) ppm. Analysis: Calc. for $C_{19}H_{31}O_8P_2F$: C, 48.71; H, 6.68%. Found: C, 48.58; H, 6.70%.

3,3-Bisphosphono-2-(3,4-difluorophenyl)propionic acid pentaethyl ester (**2c**): Yield 75%; b.p. 162–168 °C/0.001 Torr. $^1H\{^{31}P\}$ NMR ($CDCl_3$; TMS int.) δ_H: 1.16 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.19 (t, $^3J_{HH}=7.0$ Hz, 3H, CH_3); 1.21 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.34 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.35 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 3.48, 4.22 (AB system, $J_{AB}=^3J_{HH}=10.1$ Hz, –*CH*–*CH*–); 3.74–4.27 (m, 10H, CH_2); 7.01–7.34 (m, $3H_{arom.}$, 3,4-F_2-C_6H_3–) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 20.52, 21.80 (XY system, $J_{XY}=^2J_{PP}=3.7$ Hz) ppm. $^{19}F\{^1H\}$ NMR ($CDCl_3$; C_6F_6 int.) δ_F: 22.89, 23.67 (AB system, $J_{AB}=^3J_{FF}=21.2$ Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 22.77–22.98 (m, $1F_{para}$); 23.00–23.79 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_{19}H_{30}O_8P_2F_2$: C, 46.91; H, 6.23%. Found: C, 46.78; H, 6.32%.

3,3-Bisphosphono-2-(2,3,4,5,6-pentafluorophenyl)-propionic acid pentaethyl ester (**2d**): Yield 63%; b.p. 144–148 °C/0.001 Torr. $^1H\{^{31}P\}$ NMR ($CDCl_3$/TMS int.) δ_H: 1.24 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.26 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.27 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.40 (t, $^3J_{HH}=7.0$ Hz, 3H, CH_3); 1.41 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 3.77, 4.58 (AB system, $J_{AB}=^3J_{HH}=10.5$ Hz, –*CH*–*CH*–); 3.98–4.31 (m, 10H, CH_2) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 19.74, 21.51 (XY system, $J_{XY}=^2J_{PP}=6.8$ Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: −1.09 to −0.81 (m, $2F_{meta}$); 7.68–7.93 (m, $1F_{para}$); 24.05 (bs, $2F_{ortho}$) ppm. Analysis: Calc. for $C_{19}H_{27}O_8P_2F_5$: C, 42.23; H, 5.05%. Found: C, 42.10; H, 4.99%.

1-(3-Fluorophenyl)ethane-1,2-bisphosphonic acid tetraethyl ester (**4a**): Yield 70%; b.p. 139–142 °C/0.001 Torr. $^1H\{^{31}P\}$ NMR ($CDCl_3$; TMS int.) δ_H: 1.06 (t, $^3J_{HH}=7.0$ Hz, 3H, CH_3); 1.11 (t, $^3J_{HH}=6.9$ Hz, 3H, CH_3); 1.15 (t, $^3J_{HH}=6.9$ Hz, 3H, CH_3); 1.35 (t, $^3J_{HH}=7.0$ Hz, 3H, CH_3); 2.41, 2.48, 3.45 (ABX system, $J_{AB}=^2J_{HH}=-13.7$ Hz, $J_{AX}=^3J_{HH}=4.3$ Hz, $J_{BX}=^3J_{HH}=11.4$ Hz, –*CH*–*CH*$_2$–); 3.61–4.15 (m, 8H, CH_2); 6.92–7.35 (m, $4H_{arom.}$, 3-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 26.88, 28.55 (XY part of AXY system, $J_{XY}=^3J_{PP}=80.4$ Hz, $J_{AX}=^6J_{PF}=-0.2$ Hz, $J_{AY}=^5J_{PF}=2.0$ Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 48.76–48.90 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_{16}H_{27}O_6P_2F$: C, 48.48; H, 6.88%. Found: C, 48.34; H, 6.78%.

1-(4-Fluorophenyl)ethane-1,2-bisphosphonic acid tetraethyl ester (**4b**): Yield 68%; b.p. 150–154 °C/0.001 Torr. $^1H\{^{31}P\}$ NMR ($CDCl_3$; TMS int.) δ_H: 1.06 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.11 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.17 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.32 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 2.42, 2.48, 3.46 (ABX system, $J_{AB}=^2J_{HH}=-15.6$ Hz, $J_{AX}=^3J_{HH}=1.9$ Hz, $J_{BX}=^3J_{HH}=11.4$ Hz, –*CH*–*CH*$_2$–); 3.60–4.15 (m, 8H, CH_2); 6.99–7.08 (m, $2H_{meta}$, 4-F-C_6H_4–); 7.35–7.42 (m, $2H_{ortho}$, 4-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 27.28, 28.55 (XY part of BXY system, $J_{XY}=^3J_{PP}=80.4$ Hz, $J_{BX}=^7J_{PF}=-0.5$ Hz, $J_{BY}=^6J_{PF}=5.2$ Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 46.94–47.11 (m, $1F_{para}$) ppm. Analysis: Calc. for $C_{16}H_{27}O_6P_2F$: C, 48.48; H, 6.88%. Found: C, 48.30; H, 7.11%.

1-(3,4-Difluorophenyl)ethane-1,2-bisphosphonic acid tetraethyl ester (**4c**): Yield 79%; b.p. 147–148 °C/0.001 Torr. $^1H\{^{31}P\}$ NMR ($CDCl_3$; TMS int.) δ_H: 1.09 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 1.15 (t, $^3J_{HH}=7.0$ Hz, 3H, CH_3); 1.18 (t, $^3J_{HH}=7.0$ Hz, 3H, CH_3); 1.32 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3); 2.35, 2.46, 3.42 (ABX system, $J_{AB}=^2J_{HH}=-15.6$ Hz, $J_{AX}=^3J_{HH}=2.2$ Hz, $J_{BX}=^3J_{HH}=12.6$ Hz, –*CH*–*CH*$_2$–); 3.68–4.15 (m, 8H, CH_2); 7.09–7.29 (m, $3H_{arom.}$, 3,4-F_2-C_6H_3–) ppm. $^{31}P\{^1H\}$ and $^{19}F\{^1H\}$ NMR: NMR values are given in Table 1. ^{19}F NMR ($CDCl_3$; C_6F_6 int.) δ_F: 22.48–22.73 (m, $1F_{para}$); 24.31–24.62 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_{16}H_{26}O_6P_2F_2$: C, 46.37; H, 6.34%. Found: C, 46.11; H, 6.51%.

3.4. Bisphosphonic acids 1 and 3

In a 50 ml flask fitted with a reflux condenser and magnetic stirrer (0.004 mol), bisphosphonic acid esters **2 or 4** were dissolved in 20 ml of hydrochloric acid. The reaction mixture was heated to reflux for 8 h. Afterwards, the hydrolysis solution was concentrated under reduced pressure and the residue was diluted repeatedly with doubly distilled water and evaporated again until compounds **1** and **3** were hydrochloric acid-free. Acids **1** and **3** are colourless, highly hygroscopic solids which were dried in vacuo.

3,3-Bisphosphono-2-(3-fluorophenyl)propionic acid (**1a**): Yield 89%; m.p. 192 °C. ^{1}H NMR (D_2O/NaOH, degree of titration $\tau=4$; 3-trimethylsilylpropionic acid-d_4 sodium salt int.) δ_H: 2.84, 4.01 (AB part of ABMX system, $J_{AB}=^3J_{HH}=9.3$ Hz, $J_{AM}=^3J_{PH}=8.2$ Hz, $J_{AX}=^3J_{PH}=12.8$ Hz, $J_{BM}=J_{BX}=^2J_{PH}=-21.3$ Hz, –C*H*–C*H*P_2); 6.88–7.31 (m, $4H_{arom.}$, 3-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR (in D_2O/NaOH, $\tau=4$; 85% H_3PO_4 ext.) δ_P: 17.89, 19.33 (MX system, $J_{MX}=^2J_{PP}=2.9$ Hz) ppm. ^{19}F NMR (D_2O/NaOH, $\tau=4$; C_6F_6 ext.) δ_F: 52.27–52.44 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_9H_{11}O_8P_2F\cdot H_2O$: C, 31.23; H, 3.79%. Found: C, 31.31; H, 3.43%.

3,3-Bisphosphono-2-(4-fluorophenyl)propionic acid (**1b**): Yield 91%; m.p. 139 °C. ^{1}H NMR (D_2O/NaOH, $\tau=4$; 3-trimethylsilylpropionic acid-d_4 sodium salt int.) δ_H: 2.82, 3.92 (AB part of ABMX system, $J_{AB}=^3J_{HH}=9.9$ Hz, $J_{AM}=^3J_{PH}=7.4$ Hz, $J_{AX}=^3J_{PH}=11.2$ Hz, $J_{BM}=J_{BX}=^2J_{PH}=-21.2$ Hz, –C*H*–C*H*P_2); 6.90–6.99 (m, $2H_{meta}$, 4-F-C_6H_4–); 7.42–7.49 (m, $2H_{ortho}$, 4-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR (D_2O/NaOH, $\tau=4$; 85% H_3PO_4 ext.) δ_P: 18.73, 19.65 (MX system, $J_{MX}=^2J_{PP}=2.8$ Hz) ppm. ^{19}F NMR (D_2O/NaOH, $\tau=4$; C_6F_6 ext.) δ_F: 49.06–49.21 (m, $1F_{para}$) ppm. Analysis: Calc. for $C_9H_{11}O_8P_2F\cdot 2H_2O$: C, 29.68; H, 4.16%. Found: C, 29.73; H, 4.12%.

3,3-Bisphosphono-2-(3,4-difluorophenyl)propionic acid (**1c**): Yield 98%; m.p. 128 °C. ^{1}H NMR (D_2O/NaOH, $\tau=4$; 3-trimethylsilylpropionic acid-d_4 sodium salt int.) δ_H: 2.82, 3.94 (AB part of ABMX system, $J_{AB}=^3J_{HH}=9.9$ Hz, $J_{AM}=^3J_{PH}=7.6$ Hz, $J_{AX}=^3J_{PH}=11.4$ Hz, $J_{BM}=J_{BX}=^2J_{PH}=-21.1$ Hz, –C*H*–C*H*P_2); 7.02–7.38 (m, $3H_{arom.}$, 3,4-F_2-C_6H_3–) ppm. $^{31}P\{^1H\}$ NMR (D_2O/NaOH, $\tau=4$; 85% H_3PO_4 ext.) δ_P: 17.84, 19.19 (MX system, $J_{MX}=^2J_{PP}=3.2$ Hz) ppm. $^{19}F\{^1H\}$ NMR (D_2O/NaOH, $\tau=4$; C_6F_6 ext.) δ_F: 24.94, 27.08 (AB system, $J_{AB}=^3J_{FF}=21.8$ Hz) ppm. ^{19}F NMR (D_2O/NaOH, $\tau=4$; C_6F_6 ext.) δ_F: 24.83–25.06 (m, $1F_{para}$); 26.97–27.19 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_9H_{10}O_8P_2F_2\cdot 3H_2O$: C, 27.01; H, 4.04%. Found: C, 27.11; H, 3.97%.

3,3-Bisphosphono-2-(2,3,4,5,6-pentafluorophenyl)-propionic acid (**1d**): Yield 86%; very highly viscous oil. ^{1}H NMR (D_2O/NaOH, $\tau=4$; 3-trimethylsilylpropionic acid-d_4 sodium salt int.) δ_H: 3.01, 4.60 (AB part of ABMX system, $J_{AB}=^3J_{HH}=11.1$ Hz, $J_{AM}=^3J_{PH}=3.5$ Hz, $J_{AX}=^3J_{PH}=11.4$ Hz, $J_{BM}=J_{BX}=^2J_{PH}=-20.3$ Hz, –C*H*–C*H*P_2) ppm. $^{31}P\{^1H\}$ NMR (D_2O/NaOH, $\tau=4$; 85% H_3PO_4 ext.) δ_P: 17.71, 19.27 (MX system) ppm. ^{19}F NMR (D_2O/NaOH, $\tau=4$; C_6F_6 ext.) δ_F: 1.59–1.83 (m, $2F_{meta}$); 6.98–7.20 (3 lines, $1F_{para}$); 28.59 (bs, $2F_{ortho}$) ppm. Analysis: Calc. for $C_9H_7O_8P_2F_5\cdot 2H_2O$: C, 24.79; H, 2.55%. Found: C, 24.70; H, 2.59%.

1-(3-Fluorophenyl)ethane-1,2-bisphosphonic acid (**3a**): Yield 91%; m.p. 193 °C. $^1H\{^{31}P\}$ NMR (D_2O/NaOH, $\tau=3$; 3-trimethylsilylpropionic acid-d_4 sodium salt int.) δ_H: 2.03, 2.37, 3.23 (ABX system, $J_{AB}=^2J_{HH}=-15.4$ Hz, $J_{AX}=^3J_{HH}=6.5$ Hz, $J_{BX}=^3J_{HH}=11.4$ Hz, –C*H*–CH_2–); 6.96–7.39 (m, $4H_{arom.}$, 3-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR (D_2O/NaOH, $\tau=3$; 85% H_3PO_4 ext.) δ_P: 22.00, 22.29 (XY part of AXY system, $J_{XY}=^3J_{PP}=58.7$ Hz, $J_{AX}=^6J_{PF}=-0.9$ Hz, $J_{AY}=^5J_{PF}=2.0$ Hz) ppm. ^{19}F NMR (D_2O/NaOH, $\tau=3$; C_6F_6 ext.) δ_F: 52.55–52.69 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_8H_{11}O_6P_2F$: C, 33.82; H, 3.91%. Found: C, 33.32; H, 4.01%.

1-(4-Fluorophenyl)ethane-1,2-bisphosphonic acid (**3b**): Yield 88%; m.p. 199 °C. $^1H\{^{31}P\}$ NMR (D_2O/NaOH, $\tau=3$; 3-trimethylsilylpropionic acid-d_4 sodium salt int.) δ_H: 1.98, 2.35, 3.19 (ABX system, $J_{AB}=^2J_{HH}=-15.1$ Hz, $J_{AX}=^3J_{HH}=7.1$ Hz, $J_{BX}=^3J_{HH}=6.9$ Hz, –C*H*–CH_2–); 7.01–7.10 (m, $2H_{meta}$, 4-F-C_6H_4–); 7.30–7.37 (m, $2H_{ortho}$, 4-F-C_6H_4–) ppm. $^{31}P\{^1H\}$ NMR (D_2O/NaOH, $\tau=3$; 85% H_3PO_4 ext.) δ_P: 22.55, 23.22 (XY part of BXY system, $J_{XY}=^3J_{PP}=33.5$ Hz, $J_{BX}=^7J_{PF}=-0.3$ Hz, $J_{BY}=^6J_{PF}=4.1$ Hz) ppm. ^{19}F NMR (D_2O/NaOH, $\tau=3$; C_6F_6 ext.) δ_F: 49.20–49.38 (m, $1F_{para}$) ppm. Analysis: Calc. for $C_8H_{11}O_6P_2F\cdot 2H_2O$: C, 30.01; H, 4.73%. Found: C, 29.90; H, 4.76%.

1-(3,4-Difluorophenyl)ethane-1,2-bisphosphonic acid (**3c**): Yield 89%; m.p. 89 °C. $^1H\{^{31}P\}$ NMR (D_2O/NaOH, $\tau=3$; 3-trimethylsilylpropionic acid-d_4 sodium salt int.) δ_H: 2.03, 2.37, 3.21 (ABX system, $J_{AB}=^2J_{HH}=-15.2$ Hz, $J_{AX}=^3J_{HH}=6.5$ Hz, $J_{BX}=^3J_{HH}=7.6$ Hz, –C*H*–CH_2–); 7.11–7.33 (m, $3H_{arom.}$, 3,4-F_2-C_6H_3–) ppm. $^{31}P\{^1H\}$ NMR (D_2O/NaOH, $\tau=3$; 85% H_3PO_4 ext.) δ_P: 21.78, 23.04 (XY part of ABXY system, $J_{XY}=^3J_{PP}=37.7$ Hz, $J_{AX}=^6J_{PF}=-0.1$ Hz, $J_{BX}=^7J_{PF}=-0.2$ Hz, $J_{AY}=^5J_{PF}=1.7$ Hz, $J_{BY}=^6J_{PF}=4.8$ Hz) ppm. $^{19}F\{^1H\}$ NMR (D_2O/NaOH, $\tau=3$; C_6F_6 ext.) δ_F: 24.37, 27.32 (AB part of ABXY system, $J_{AB}=^3J_{FF}=21.8$ Hz) ppm. ^{19}F NMR (D_2O/NaOH, $\tau=3$; C_6F_6 ext.) δ_F: 24.24–24.50 (m, $1F_{para}$); 27.40–27.63 (m, $1F_{meta}$) ppm. Analysis: Calc. for $C_8H_{10}O_6P_2F_2\cdot 2H_2O$: C, 28.41; H, 4.18%. Found: C, 28.43; H, 4.19%.

3.5. Trisphosphonic acid hexaethyl ester 5

A 50 ml round-bottomed flask was equipped with a reflux condenser, dropping funnel, Teflon-coated spin bar and nitrogen bubbler. Under a nitrogen atmosphere, 0.02 mol of 2-pentafluorophenylvinyl phosphonic acid diethyl ester (**8d**) and 0.02 mol of diethyl phosphite were dissolved in 10 ml of dry THF. The mixture was stirred at room temperature and 0.02 mol of the 1 M sodium diethyl phosphite THF was added dropwise. After addition of the base, the reaction mixture was refluxed for 8 h and the reaction solution neutralized with 50% aq. acetic acid. The solid formed was filtrated. Afterwards the solvent and byproducts were removed in vacuo. A pale yellow brown, very highly viscous oil was isolated which could not be distilled under oil pump vacuum without decomposition.

1-(4-Phosphono-2,3,5,6-tetrafluorophenyl)ethane-2,2-bisphosphonic acid hexaethyl ester (**5**): Yield 46%; highly viscous oil. $^1H\{^{31}P\}$ NMR ($CDCl_3$/TMS int.) δ_H: 1.25 (t, $^3J_{HH}=7.1$ Hz, 6H, CH_3); 1.30 (t, $^3J_{HH}=7.1$ Hz, 6H, CH_3); 1.36 (t, $^3J_{HH}=7.1$ Hz, 6H, CH_3); 2.78 (t, $^3J_{HH}=7.4$ Hz, 1H,

–CH_2–C*H*–); 3.35 (d, 2H, –CH_2–CH–); 4.08–4.31 (m, 12H, CH_2) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 5.81 (X part of aromatic $[AB]_2X$ system, coupling constants are given in Table 2.); 21.54 (s) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 int.): NMR data listed in Table 2. Analysis: Calc. for $C_{20}H_{33}O_9P_3F_4$: C, 40.96; H, 5.68%. Found: C, 40.29; H, 5.62%.

(a) NMR spectroscopic evidence for the intermediate product A (a non-isolated byproduct)

$^1H\{^{31}P\}$ NMR ($CDCl_3$; TMS int.) δ_H: 1.28 (t, $^3J_{HH}=7.1$ Hz, 6H, CH_3); 1.32 (t, $^3J_{HH}=7.1$ Hz, 6H, CH_3); 2.70 (t, $^3J_{HH}=7.5$ Hz, 1H, –CH_2–C*H*–); 3.30 (d, 2H, –CH_2–CH–); 4.10–4.23 (m, 8H, CH_2) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 21.68 (s) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 ext.) δ_F: −1.47 to −1.17 (m, $2F_{meta}$); 5.03–5.26 (3 lines, $1F_{para}$); 19.85–19.97 (m, $2F_{ortho}$) ppm.

*(b) NMR spectroscopic data of 1-(2,3,4,5,6-pentafluorophenyl)ethane-1,2-bisphosphonic acid tetraethyl ester (**4d**) (a non-isolated byproduct)*

$^{31}P\{^1H\}$ NMR ($CDCl_3$; 85% H_3PO_4 ext.) δ_P: 27.25, 23.48 (XY part of $[AB]_2MXY$ system, $J_{XY}=^3J_{PP}=76.7$ Hz, $J_{AX}=^5J_{PF}=1.1$ Hz, $J_{AY}=^4J_{PF}=6.0$ Hz, $J_{BY}=^5J_{PF}=2.2$ Hz, $J_{MY}=^6J_{PF}=6.0$ Hz) ppm. ^{19}F NMR ($CDCl_3$; C_6F_6 ext.) δ_F: −0.89 to −0.27 (m, $2F_{meta}$); 6.73–6.97 (m, $1F_{para}$); 24.65 (bs, $2F_{ortho}$) ppm.

3.6. Trisphosphonic acid triscyclohexylammonium salt 6

The hexaethyl phosphonate ester **5** (2 mmol) and bromotrimethylsilane (20 mmol) in dry CH_2Cl_2 were stirred magnetically under dry nitrogen in a 50 ml two-necked flask fitted with reflux condenser and nitrogen bubbler. This reaction mixture was heated to reflux for 3 h and stirred afterwards at ambient temperature overnight. The solvent was removed by distillation and the brownish residue treated with 5 ml of water. The water was evaporate in vacuo and the crude acid dissolved in 5 ml of ethanol. The cyclohexylamine (8 mmol) was poured dropwise into the solution and the precipitated cyclohexylammonium salt **6** was filtrated. The white yellow solid was dried under an oil pump vacuum.

1-(4-Phosphono-2,3,5,6-tetrafluorophenyl)ethane-2,2-bisphosphonic acid triscyclohexylammonium salt (**6**): Yield 80%; m.p. > 269 °C (dec.). $^1H\{^{31}P\}$ NMR (D_2O; 3-trimethylsilylpropionic acid-d_4 sodium salt int.) δ_H: 1.14–1.97, 3.14–3.26 (m, 42H, NH_3^+–C_6H_{11}); 2.41 (t, $^3J_{HH}=7.4$ Hz, 1H, –CH_2–C*H*–); 3.65 (d, 2H, –CH_2–CH–) ppm. $^{31}P\{^1H\}$ NMR (D_2O; 85% H_3PO_4 ext.) δ_P: 0.55 (X part of aromatic $[AB]_2X$ system); 18.66 (s) ppm. ^{19}F NMR (D_2O; C_6F_6 ext.) δ_F: 20.87, 27.39 ($[AB]_2$ part of $[AB]_2X$ system, $J_{AX}=^3J_{PF}=-1.7$ Hz, $J_{BX}=^4J_{PF}=6.9$ Hz, $J_{AB}=^3J_{FF}=-23.9$ Hz, $J_{AB'}=^5J_{FF}=13.2$ Hz, $J_{AA'}=^4J_{FF}=2.4$ Hz, $J_{BB'}=^4J_{FF}=-0.2$ Hz) ppm. Analysis: Calc. for $C_{26}H_{48}N_3O_9P_3F_4$: C, 43.63; H, 6.78; N, 5.87%. Found: C, 43.55; H, 7.27; N, 6.05%.

Acknowledgements

Thanks are due to the Fonds der Chemischen Industrie e.V. for material support. This study was performed within the 'Arbeitsgemeinschaft Fluorchemie Nordrhein-Westfalen'. Financial support from the Ministerium für Wissenschaft und Forschung Nordrhein-Westfalen is acknowledged. Our special thanks are directed to Dr. Kleiner, Hoechst AG, Frankfurt am Main for methylene bisphosphonic acid tetraethyl ester and to Dr. Schmand, Riedel-de Haën, Seelze for the generous supply of fluorinated benzaldehydes and bromobenzenes.

References

[1] (a) H. Fleisch, *Bone, 8* (1987) S23; (b) H. Fleisch, *Drugs, 42* (1991) 919; (c) F.H. Ebetino, S.M. Kaas and R.J. Crawford, *Phosphorus, Sulfur, Silicon, Relat. Elem., 76* (1993) 151; (d) H. Blum, *J. Prakt. Chem., 336* (1994) 492.

[2] (a) M.J. Clarke and L. Podbielski, *Coord. Chem. Rev., 78* (1987) 253; (b) A. Steinsträßer, A. Schwarz, C. Alexander, R. Berberich and M. Zimmer, *Nucl. Med., 31* (1992) 164.

[3] M.D. Francis and R.L. Center, *J. Chem. Educ., 55* (1978) 760.

[4] L. Horner and D. Schödel, *Werkst. Korros., 25* (1974) 711.

[5] (a) D.W. Hutchinson and P.A. Cloud, *Nucleic Acids Res., 11* (1983) 5621; (b) D.W. Hutchinson, M. Naylor and G. Semple, *Chem. Scr., 26* (1986) 91.

[6] (a) U. Fischer and G. Hägele, *Z. Naturforsch., 40b* (1985) 1152; (b) U. Fischer, *Ph.D. Thesis,* Heinrich-Heine-Universität, 1986; (c) H. Blum, S. Goudetsidis, G. Hägele, M. Murray, J. Seega and E. Wilke, *Phosphorus, Sulfur, Silicon, Relat. Elem., 48* (1990) 131; (d) Ch. Papadopoulos, *Ph.D. Thesis,* Heinrich-Heine-Universität, 1990; (e) G. Hägele, M. Ackermann, M. Batz, R. Fuhler, Ch. Papadopoulos, U. Prior, J. Ollig, E. Wilke and M. Murray, *Phosphorus, Sulfur, Silicon, Relat. Elem., 77* (1993) 320.

[7] T. Minami and J. Motoyoshiya, *Chem. Rev., 92* (1992) 333.

[8] D. Gloyna, H. Köppel and H.-G. Henning, *J. Prakt. Chem., 316* (1974) 832.

[9] K.-H. Worms, H. Blum and H.U. Hempel, *Z. Anorg. Allg. Chem., 457* (1979) 219.

[10] (a) V.N. Zinin, A.V. Il'yasov, U. Weber, G. Hägele and H. Thiele, *J. Fluorine Chem., 70* (1995) 289; (b) G. Hägele, *J. Fluorine Chem., 71* (1995) 223.