A One-Pot Procedure for the Synthesis of α-Amino Phosphonates from Alkynes

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A new and highly flexible procedure for the synthesis of α,α-disubstituted α-amino phosphonates is described with disubstituted alkynes, primary amines and diethyl or dimethyl phosphite as starting materials. The reaction sequence, which is performed as a one-pot operation, starts with a Cp_2TiMe_2-catalyzed hydroamination of the alkyne. A subsequent nucleophilic addition of diethyl or dimethyl phosphite to the resulting imine, performed in the presence of catalytic amounts of Me_2AlCl, gives the desired α-amino phosphonate. The application of intermolecular and intramolecular hydroamination reactions leads to the formation of both, cyclic and acyclic α-amino phosphonates.

Introduction

Due to their potential biological activity and their use as building blocks for phosphorus-containing peptide mimetics, derivatives of phosphonic and phosphinic acid analogues of α-amino acids (Figure 1) are of considerable current interest. Several α-aminophosphonic and -phosphinic acid derivatives show activity as enzyme inhibitors, antibiotics, herbicides, fungicides or plant growth regulators.[1] For example, the phosphonic acid analogues of phenylalanine and histidine inhibit the corresponding ammonia-lyases in plants, yeasts and bacteria.[2] Other α-aminophosphonic acid derivatives are specific suicide inhibitors of phosphatases which are important in signal transduction processes.[3] In particular, phosphorus-containing peptide mimetics, in which the tetrahedral phosphorus moiety acts as a transition-state analogue of the peptide cleavage, selectively inhibit peptidases and proteinases (e. g. HIV-protease,[4] pepsin,[5] penicillopepsin[6] and serine protease[7]) as well as ligases involved in the peptidoglycan biosynthesis of bacteria cell walls.[8]

Because of the above-mentioned biological effects many procedures for the synthesis of α-aminophosphonic and α-aminophosphinic acid derivatives have been developed.[9] Among these methods nucleophilic and electrophilic transformations of 1-aminomethylphosphonic acid derivatives[9b−9d] and nucleophilic additions of dialkyl phosphites to imines[9e−9j] are the most general and powerful procedures. While both methods are useful for the synthesis of analogues of naturally occurring α-substituted α-amino acids, the synthesis of α,α-disubstituted derivatives

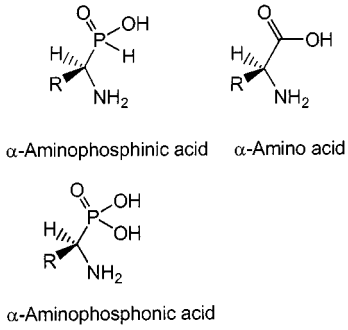

Figure 1. Comparison between α-aminophosphinic, α-aminophosphonic and α-amino acids

can only be achieved in special cases. Furthermore, both methods have drawbacks regarding the diversity of the synthesized products and their use in automated synthesis (e.g. reactions are run at −78 °C or use unstable starting materials). Due to these drawbacks we focused on the development of a highly flexible procedure for the synthesis of α,α-disubstituted α-aminophosphonic acid derivatives that is easy to perform and can be adapted for an automated synthesis. For diversity reasons, it was our goal to employ starting materials that are inexpensive and readily available in various forms. Furthermore, it was desirable to use starting materials that have never been used before for the synthesis of the target compounds. Due to these points, the fact that a wide variety of alkynes is easily accessible by cross-coupling[10] and metathesis[11] techniques, and that the use of alkynes for the synthesis of nitrogen-containing products has become well-established with the development of modern hydroamination protocols,[12] we decided to use disubstituted alkynes as suitable starting materials for the synthesis of α,α-disubstituted α-aminophosphonic acid derivatives.

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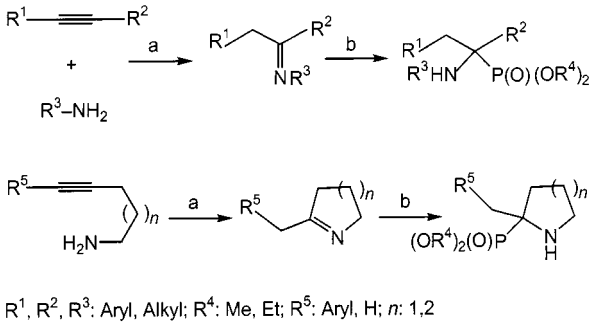
Results and Discussion

In this publication we describe a new and highly flexible procedure for the synthesis of cyclic and acyclic α,α-disubstituted α-amino phosphonates. Using the new procedure, the desired products can be obtained in good to excellent yields. Disubstituted alkynes, which are easily accessible in a wide variety, primary amines and diethyl or dimethyl phosphite are employed as starting materials. The reaction sequence, which is performed as a one-pot operation, starts with a Cp_2TiMe_2[13]-catalyzed hydroamination of the alkyne.[12j−12n] A subsequent nucleophilic addition of diethyl or dimethyl phosphite to the resulting imine, performed in the presence of catalytic amounts of Me_2AlCl, gives access to the desired α-amino phosphonate. The described one-pot procedure can be used for the synthesis of acyclic (intermolecular hydroamination[12j−12n]) and cyclic (intramolecular hydroamination[14]) products. The general synthetic strategy is shown in Scheme 1.

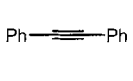
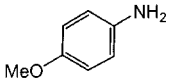
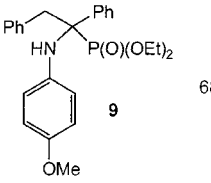
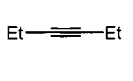
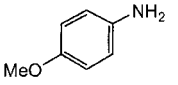
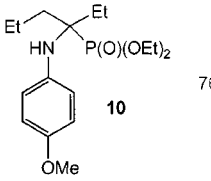
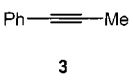
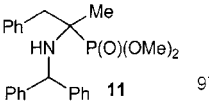
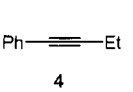
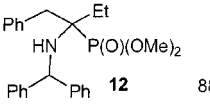


R^1, R^2, R^3: Aryl, Alkyl; R^4: Me, Et; R^5: Aryl, H; *n*: 1,2

Scheme 1. One-pot procedure for the synthesis of α-amino phosphonates from disubstituted alkynes, primary amines and dialkyl phosphites: a) 3.0−5.0 mol % Cp_2TiMe_2, 110 °C; b) $HPO(OR^4)_2$, 5.0 mol % Me_2AlCl, 25 °C

To demonstrate the efficiency of the developed one-pot process we first synthesized acyclic α-amino phosphonates from representative symmetrically substituted [diphenylacetylene (**1**), 3-hexyne (**2**)] and unsymmetrically substituted [1-phenylpropyne (**3**), 1-phenylbutyne (**4**)] alkynes. As amines we chose 4-methoxyaniline (**5**)[15] and benzhydrylamine (**6**)[12l,16] because both amines allow a final deprotection of the incorporated NH_2 groups. However, in principle any other amine which is suitable for the Cp_2TiMe_2-catalyzed intermolecular hydroamination of alkynes[12j−12n] can be used as well. The nucleophilic phosphite additions were performed using diethyl phosphite (**7**) or dimethyl phosphite (**8**). In general, the hydroamination reactions were performed in the presence of 3.0 mol % Cp_2TiMe_2 at 110 °C for 72 h (the reaction times have not been optimized). Reactions employing 4-methoxyaniline (**5**) were run in toluene whereas no solvent was added to reactions employing benzhydrylamine (**6**).[12l] Once the crude reaction mixtures obtained from the hydroamination step had been cooled to 0 °C the phosphite and 5.0 mol % Me_2AlCl were added directly to the reaction flask. After a reaction time of 2 h at room temperature the desired products **9**−**12** could be isolated in good to excellent yields (Table 1).

Table 1. One-pot procedure for the synthesis of acyclic α-amino phosphonates by intermolecular hydroamination and subsequent nucleophilic addition of phosphites

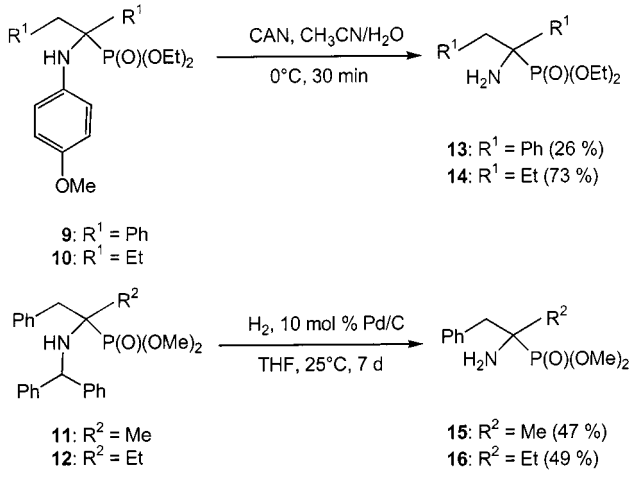
entry	alkyne	amine	product	yield[a]
1	 **1**	 **5**	 **9**	68 %
2	 **2**	 **5**	 **10**	76 %
3	 **3**	 **6**	 **11**	97 %[b]
4	 **4**	 **6**	 **12**	88 %[b]

[a] Reaction conditions: a) 1.4 mmol alkyne, 1.4 mmol amine, 3.0 mol % Cp_2TiMe_2, 0.5 mL toluene, 110 °C, 72 h (reaction times have not been optimized); b) 1.4 mmol $HP(O)(OEt)_2$ (**7**), 5.0 mol % Me_2AlCl, 25 °C, 2 h. Unless otherwise noted, yields represent isolated yields of pure compounds. [b] The hydroamination reaction was run without solvent (toluene). $HP(O)(OMe)_2$ (**8**) was used for the nucleophilic addition of phosphite.

Due to the fact that Cp_2TiMe_2-catalyzed hydroamination reactions of arylalkylamines are highly regioselective the unsymmetrically substituted alkynes **3** and **4** could be selectively converted into α-alkylated phosphonic ester analogues (**11**, **12**) of phenylalanine (Table 1, entries 3,4). While **11** and **12** are stable compounds, the obtained 4-methoxyaniline derivatives **9** and **10** tend to eliminate diethyl phosphite, for example during chromatography on SiO_2. The reason for this behavior is probably the electron-donating ability of the methoxy group located on the aromatic ring, which destabilizes the carbon phosphorus bonds in **9** and **10**.

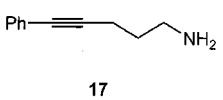
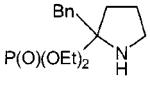
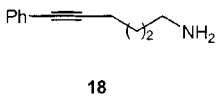
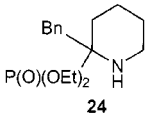
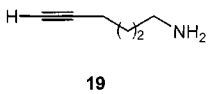
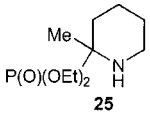
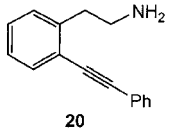
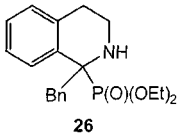
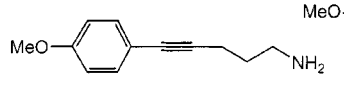
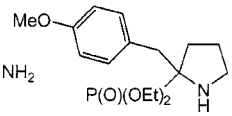
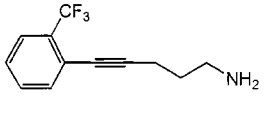
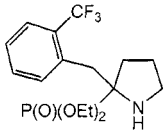
In addition to the described synthesis of **9**−**12**, we were able to remove the 4-methoxyphenyl protecting groups in **9** and **10** under standard oxidative reaction conditions [ceric ammonium nitrate (CAN)].[15] Furthermore, the benzhydryl groups in **11** and **12** could be removed reductively (H_2, Pd/C) (Scheme 2).[12l,16]

While the deprotected derivative **14** was formed smoothly in the presence of CAN, deprotection of the diphenyl-substituted compound **9** was only possible with low yield (26%) due to the initial formation of a stable intermediate under the oxidative reaction conditions. Further cleavage of this



Scheme 2. Oxidative and reductive deprotection of the NH_2 groups

Table 2. One-pot procedure for the synthesis of cyclic α-amino phosphonates by intramolecular hydroamination and subsequent nucleophilic addition of phosphite

entry	aminoalkyne	product	yield[a]
1	 **17**	 **23**	78 %
2	 **18**	 **24**	86 %
3	 **19**	 **25**	85 %
4	 **20**	 **26**	52 %[b]
5	 **21**	 **27**	66 %
6	 **22**	 **28**	58 %

[a] Reaction conditions: a) 1.0 mmol aminoalkyne, 5.0 mol % Cp_2TiMe_2, 1.0 mL toluene, 110 °C, 9 h; b) 1.0 mmol $HP(O)(OEt)_2$ (**7**), 5.0 mol % Me_2AlCl, 25 °C, 2 h. Unless otherwise noted, yields represent isolated yields of pure compounds. [b] Contaminated with the corresponding imine. A further purification could not be achieved.

intermediate, which was identified as the corresponding mono-imine of 1,4-quinone, is very slow. To obtain the reductively deprotected compounds **15** and **16** in acceptable yields long reaction times for the cleavage (1 atm. H_2, 10 mol % Pd/C) of **11** and **12** were necessary. Even after seven days the obtained yields were only about 50%. A possible explanation for this observation is that trace amounts of dimethyl phosphite which can be present in the starting materials or can be formed during the reaction poison the palladium catalyst.

Finally, we tried to use the developed one-pot procedure for the synthesis of cyclic α-amino phosphonates. For that purpose, we first cyclized the easily accessible aminoalkynes **17**−**22**[17] in the presence of 5.0 mol % Cp_2TiMe_2 at 110 °C.[14] A subsequent nucleophilic addition of diethyl phosphite (**7**) to the formed imines gave the desired cyclic α-amino phosphonates **23**−**28** in good yields (Table 2).

Among the products shown in Table 2, the derivatives **23**, **27** and **28** (Table 2, entries 1,5,6) are particularly interesting since they represent α-alkylated phosphonic ester analogues of the naturally occurring amino acid proline. However, the synthesis of piperidine derivatives (**24**, **25**, **26**) could also be achieved in good yields. In contrast to **24** and **25** the isoquinoline derivative **26** could only be obtained as a 5:1 mixture with the corresponding imine. Attempts to further purify **26** have so far failed.

Conclusion

In summary, the presented studies clearly indicate that the Cp_2TiMe_2-catalyzed hydroamination of alkynes combined with a nucleophilic addition of dialkyl phosphites to imines allows the synthesis of α,α-disubstituted α-amino phosphonates in good to excellent yields. Since acyclic and cyclic products can be synthesized from easily accessible starting materials, the developed procedure is characterized by a very high diversity. Therefore, an application for the generation of libraries of α-aminophosphonic acid derivatives is imaginable. Another important advantage of the described method is that only metal-catalyzed addition reactions are used for the synthesis of the target compounds, and no undesired side products are formed during the presented process. Furthermore, the simple experimental one-pot protocol should allow its use for automated synthesis. Using the presented method, an enantioselective approach towards α-aminophosphonic acid derivatives should be possible as well.

Experimental Section

General Remarks: All reactions were performed under an inert atmosphere of argon in flame dried Duran glassware (e.g. Schlenk tubes fitted with Teflon stopcocks). Toluene was distilled from molten sodium under argon. Dimethyltitanocene was synthesized according to ref.[13a] Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification. All products were characterized by ^1H NMR, ^{13}C

NMR, and IR spectroscopy, and mass spectrometry (MS). New compounds were further characterized by C, H N elemental analysis or high resolution mass spectrometry (HRMS). Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 MHz spectrometer. All ^1H NMR spectra are reported in δ units downfield from tetramethylsilane as internal standard. All ^{13}C NMR spectra are reported in δ units relative to the central line of the triplet for $CDCl_3$ at δ = 77.0. Infrared spectra were recorded on a Bruker Vector 22 spectrometer using an attenuated total reflection (ATR) method (neat). Mass spectra were recorded on a Finnigan MAT 312 or a VG Autospec (EI) with an ionization potential of 70 eV. Elemental analysis was carried out on an Elementar Vario EL machine. PE: light petroleum ether, b.p. 40−60 °C.

One-Pot Synthesis of Acyclic α-Amino Phosphonates from Alkynes. General Procedure A: The alkyne (1.40 mmol), the amine (1.40 mmol), toluene (0.5 mL) and a solution of Cp_2TiMe_2 (0.074 mL, 0.57 mol/L in toluene, 0.042 mmol, 3.0 mol %) were added to a Schlenk tube. The Schlenk tube was sealed with a Teflon stopcock and heated to 110 °C for 72 h. Then the mixture was cooled to 0 °C and $HP(O)(OEt)_2$ (**7**; 193 mg, 1.40 mmol) and a solution of Me_2AlCl (0.07 mL, 1.0 mol/L in hexane, 0.07 mmol, 5.0 mol %) were added. After 2 h of stirring at room temperature the mixture was diluted with water and 2.0 M KOH was added until pH 9 was reached. Then the mixture was extracted four times with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under vacuum and flash chromatography on silica gel afforded the pure α-amino phosphonate.

Compound 9 ($C_{25}H_{30}NO_4P$, M = 439.49 g/mol): General procedure A was used to convert diphenylacetylene (**1**) and 4-methoxyaniline (**5**) into the title compound. Purification by flash chromatography (PE/EtOAc, 2:1) afforded **9** (418 mg, 0.95 mmol, 68%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 5.6 Hz, 6 H), 3.03−3.12 (m, 1 H), 3.53−3.63 (m, 1 H), 3.68−3.79 (m, 2 H), 3.71 (s, 3 H), 3.83−3.92 (m, 2 H), 4.49 (d, *J* = 7.7 Hz, 1 H), 6.35 (d, *J* = 7.2 Hz, 2 H), 6.66 (d, *J* = 7.1 Hz, 2 H), 7.11−7.20 (m, 5 H), 7.29−7.35 (m, 1 H), 7.38 (t, *J* = 6.0 Hz, 2 H), 7.73 (br. d, *J* = 6.5 Hz, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 15.8 (d, *J* = 5.0 Hz, CH_3), 16.3 (d, *J* = 4.0 Hz, CH_3), 37.7 (CH_2), 55.5 (CH_3), 61.8 (d, *J* = 7.0 Hz, CH_2), 63.6 (d, *J* = 6.0 Hz, CH_2), 64.5 (d, *J* = 117 Hz, C), 114.3 (CH), 117.7 (CH), 126.5 (CH), 127.5 (CH), 127.5 (CH), 128.2 (d, *J* = 2.0 Hz, CH), 128.7 (d, *J* = 4.0 Hz, CH), 131.4 (CH), 136.3 (d, *J* = 2.0 Hz, C), 137.5 (d, *J* = 6.0 Hz, C), 138.6 (d, *J* = 12.0 Hz, C), 152.1 (C). IR: $\tilde{\nu}$ = 3404, 3059, 3031, 2980, 2930, 2906, 2832, 1735, 1509, 1444, 1391, 1296, 1235, 1180, 1097, 1020, 960, 821, 803, 774, 755, 731, 698, 642, 567 cm^{-1}. MS (110 °C): *m*/*z* (%) = 439 (4) [M^+], 348 (10), 302 (23), 210 (40), 123 (100), 108 (98), 80 (20). HRMS: calcd. 439.1912; found 439.1910.

Compound 10 ($C_{17}H_{30}NO_4P$, M = 343.40 g/mol): General procedure A was used to convert 3-hexyne (**2**) and 4-methoxyaniline (**5**) into the title compound. Purification by flash chromatography (PE/EtOAc, 1:1) afforded **10** (365 mg, 1.06 mmol, 76%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3 H), 1.01 (t, *J* = 7.5 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.42−1.54 (m, 2 H), 1.68−1.93 (m, 4 H), 3.56 (br. s, 1 H), 3.75 (s, 3 H), 3.92−4.10 (m, 4 H), 6.74 (d, *J* = 8.9 Hz, 2 H), 6.93 (d, *J* = 8.9 Hz, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 7.8 (d, *J* = 6.0 Hz, CH_3), 14.4 (CH_3), 16.2 (d, *J* = 6.0 Hz, CH_3), 16.3 (d, *J* = 6.0 Hz, CH_2), 26.7 (d, *J* = 3.0 Hz, CH_2), 35.8 (d, *J* = 3.0 Hz, CH_2), 55.3 (CH_3), 61.2 (d, *J* = 147 Hz, C), 61.6 (d, *J* = 2.0 Hz, CH_2), 113.7 (CH), 122.6 (CH), 138.5 (d, *J* = 4.0 Hz, C), 154.1 (C). IR: $\tilde{\nu}$ = 3337, 2962, 2873, 2833, 1722, 1613, 1509, 1464, 1442, 1390, 1292, 1232, 1164, 1097, 1022, 955, 826, 788, 760, 638, 555 cm^{-1}. MS (25 °C): *m*/*z* (%) = 343 (8) [M^+], 206 (100), 176 (25), 162 (20), 134 (5), 111 (6), 83 (5), 65 (4). HRMS: calcd. 343.1912; found 343.1922.

Compound 11 ($C_{24}H_{28}NO_3P$, M = 409.46 g/mol): General procedure A was used to convert 1-phenylpropyne (**3**) and benzhydrylamine (**6**) into the title compound. No solvent was used for the reaction and $HP(O)(OMe)_2$ (**8**) was used instead of $HP(O)(OEt)_2$ (**7**). Purification by flash chromatography (PE/EtOAc, 1:1) afforded **11** (556 mg, 1.36 mmol, 97%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 17.7 Hz, 3 H), 1.87 (br. s, 1 H), 2.94 (d, *J* = 9.6 Hz, 2 H), 3.72 (d, *J* = 3.3 Hz, 3 H), 3.74 (d, *J* = 3.3 Hz, 3 H), 5.41 (d, *J* = 3.0 Hz, 1 H), 7.03−7.40 (m, 15 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 19.0 (CH_3), 43.5 (d, *J* = 5.0 Hz, CH_2), 52.7 (d, *J* = 8.0 Hz, CH_3), 53.1 (d, *J* = 8.0 Hz, CH_3), 58.3 (d, *J* = 143 Hz, C), 61.5 (CH), 126.3 (CH), 126.5 (CH), 126.7 (CH), 127.0 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.4 (CH), 131.5 (CH), 135.9 (d, *J* = 11.0 Hz, C), 145.9 (C), 146.1 (d, *J* = 2.0 Hz, C). IR: $\tilde{\nu}$ = 3329, 3061, 3026, 2999, 2947, 2844, 1599, 1492, 1450, 1375, 1230, 1179, 1115, 1046, 1018, 910, 882, 820, 798, 784, 751, 697 cm^{-1}. MS (120 °C): *m*/*z* (%) = 410 (1) [M^+ + 1], 319 (47), 301 (17), 300 (52), 221 (12), 167 (100), 152 (35), 115 (7), 91 (12), 80 (26), 79 (26). HRMS: calcd. 409.1807; found 409.1815.

Compound 12 ($C_{25}H_{30}NO_3P$, M = 423.49 g/mol): General procedure A was used to convert 1-phenylbutyne (**4**) and benzhydrylamine (**6**) into the title compound. No solvent was used for the reaction and $HP(O)(OMe)_2$ (**8**) was used instead of $HP(O)(OEt)_2$ (**7**). Purification by flash chromatography (PE/EtOAc, 1:1) afforded **12** (522 mg, 1.23 mmol, 88%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.5 Hz, 3 H), 1.25−1.43 (m, 1 H), 1.65−1.78 (m, 1 H), 1.98 (br. s, 1 H), 2.82 (dd, *J* = 16.2, 13.8 Hz, 1 H), 3.04 (dd, *J* = 13.5, 12.3 Hz, 1 H), 3.57 (d, *J* = 10.4 Hz, 3 H), 3.61 (d, *J* = 10.5 Hz, 3 H), 5.45 (d, *J* = 2.6 Hz, 1 H), 7.08−7.40 (m, 15 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 8.7 (d, *J* = 4.0 Hz, CH_3), 25.9 (d, *J* = 4.0 Hz, CH_2), 39.7 (d, *J* = 6.0 Hz, CH_2), 51.9 (d, *J* = 8.0 Hz, CH_3), 52.6 (d, *J* = 8.0 Hz, CH_3), 61.5 (CH), 63.0 (d, *J* = 136 Hz, C), 126.4 (CH), 126.5 (CH), 126.7 (CH), 127.1 (CH), 127.3 (CH), 127.7 (CH), 128.1 (CH), 128.4 (CH), 131.4 (CH), 136.3 (d, *J* = 8.0 Hz, C), 146.2 (C), 146.4 (C). IR: $\tilde{\nu}$ = 3467, 3060, 3027, 2950, 2848, 1736, 1600, 1494, 1453, 1373, 1235, 1182, 1024, 920, 815, 767, 744, 698 cm^{-1}. MS (80 °C): *m*/*z* (%) = 332 (8) [M^+ − Bn], 314 (17), 235 (3), 167 (100), 152 (8), 148 (8), 106 (6), 91 (21), 80 (9). HRMS: calcd. 423.1963; found 423.1963.

Deprotection of the NH_2 Groups. Oxidative Cleavage. General Procedure B: At 0 °C a solution of ceric ammonium nitrate (1.64 g, 3.00 mmol) in water (5.0 mL) was added dropwise to a solution of the 4-methoxyaniline derivative (1.00 mmol) in CH_3CN (5.0 mL). The mixture was stirred for 20 min at 0 °C and then for 30 min at 25 °C. Then 2 M KOH was added until pH 12 was reached. After four extractions with CH_2Cl_2 (100 mL), the combined organic layers were washed with an aqueous solution of $Na_2S_2O_3$ (10%) and brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel afforded the pure deprotected α-amino phosphonate.

Compound 13 ($C_{18}H_{24}NO_3P$, M = 333.37 g/mol): General procedure B was used to convert **9** into the title compound. The reaction was stirred for 20 h at 25 °C. Purification by flash chromatography (CH_2Cl_2/MeOH, 10:1) afforded **13** (87 mg, 0.26 mmol, 26%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.1 Hz, 3 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 1.84 (br. s, 2 H), 3.31 (dd,

J = 13.6, 8.3 Hz, 1 H), 3.55−3.67 (m, 2 H), 3.84−3.94 (m, 1 H), 4.13 (quin, *J* = 7.1 Hz, 2 H), 6.89 (br. d, *J* = 7.6 Hz, 2 H), 7.08−7.16 (m, 3 H), 7.23−7.29 (m, 1 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.66 (br. d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 16.3 (d, *J* = 5.0 Hz, CH_3), 16.4 (d, *J* = 6.0 Hz, CH_3), 44.3 (CH_2), 59.3 (d, *J* = 202 Hz, C), 62.4 (d, *J* = 8.0 Hz, CH_2), 63.5 (d, *J* = 7.0 Hz, CH_2), 126.6 (CH), 127.2 (CH), 127.3 (CH), 127.7 (CH), 128.0 (d, *J* = 3.0 Hz, CH), 130.8 (CH), 135.1 (d, *J* = 13.0 Hz, C), 139.0 (d, *J* = 2.0 Hz, C). IR: ṽ = 3377, 3060, 3029, 2979, 2928, 1601, 1495, 1446, 1390, 1233, 1161, 1097, 1050, 1020, 955, 846, 786, 765, 737, 699, 601, 571, 549 cm^{-1}. MS (50 °C): *m*/*z* (%) = 333 (1) [M$^+$], 263 (1), 242 (76), 196 (100), 178 (6), 149 (6), 121 (8), 111 (10), 105 (52), 104 (52), 91 (21), 83 (13), 81 (10), 77 (23). HRMS: calcd. 333.1494; found 333.1497.

Compound 14 ($C_{10}H_{24}NO_3P$, M = 237.28 g/mol): General procedure B was used to convert **10** into the title compound. Purification by flash chromatography (CH_2Cl_2/MeOH, 10:1) afforded **14** (173 mg, 0.73 mmol, 73%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H), 0.97 (t, *J* = 7.5 Hz, 3 H), 1.33 (t, *J* = 7.0 Hz, 6 H), 1.37−1.78 (m, 6 H), 4.14 (quin, *J* = 7.2 Hz, 4 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 7.4 (d, *J* = 6.0 Hz, CH_3), 14.4 (CH_3), 16.0 (d, *J* = 6.0 Hz, CH_2), 16.3 (d, *J* = 6.0 Hz, CH_3), 27.7 (d, *J* = 4.0 Hz, CH_2), 36.9 (d, *J* = 3.0 Hz, CH_2), 54.7 (d, *J* = 145 Hz, C), 61.7 (d, *J* = 8.0 Hz, CH_2). IR: ṽ = 3377, 2962, 2934, 2873, 1602, 1461, 1390, 1294, 1223, 1162, 1097, 1050, 1021, 951, 825, 785, 749, 680, 654, 559, 519 cm^{-1}. MS (25 °C): *m*/*z* (%) = 237 (1) [M$^+$], 208 (2), 194 (3), 123 (2), 111 (37), 100 (100), 98 (35), 83 (43), 70 (20), 65 (27). HRMS: calcd. 237.1494; found 237.1492.

Deprotection of the NH_2 Groups. Reductive Cleavage. General Procedure C: Pd/C (212 mg, 5% Pd, 10.6 mg Pd, 0.10 mmol Pd, 10.0 mol %) was stirred in THF (5.0 mL) at 25 °C under 1 atm. of H_2 for 30 min. Then a solution of the benzhydrylamine derivative (1.00 mmol) in THF (3.0 mL) was added. The resulting mixture was stirred under 1 atm. H_2 at 25 °C for seven days. Filtration, concentration and purification by flash chromatography on silica gel afforded the pure α-amino phosphonate.

Compound 15 ($C_{11}H_{18}NO_3P$, M = 243.24 g/mol): General procedure C was used to convert **11** into the title compound. Purification by flash chromatography (CH_2Cl_2/MeOH, 10:1) afforded **15** (114 mg, 0.47 mmol, 47%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 18.0 Hz, 3 H), 1.77 (br. s, 2 H), 2.92 (dd, *J* = 13.4, 9.1 Hz, 1 H), 2.99 (dd, *J* = 13.3, 9.3 Hz, 1 H), 3.80 (d, *J* = 5.6 Hz, 3 H), 3.82 (d, *J* = 5.5 Hz, 3 H), 7.20−7.34 (m, 5 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 22.2 (CH_3), 42.7 (d, *J* = 4.0 Hz, CH_2), 53.0 (d, *J* = 154 Hz, C), 53.4 (d, *J* = 5.0 Hz, CH_3), 53.6 (d, *J* = 4.0 Hz, CH_3), 126.8 (CH), 128.0 (CH), 131.0 (CH), 135.1 (d, *J* = 13.0 Hz, C). IR: ṽ = 3374, 3028, 2953, 2851, 1603, 1496, 1455, 1373, 1227, 1182, 1124, 1053, 1027, 822, 776, 750, 705, 686 cm^{-1}. MS (25 °C): *m*/*z* (%) = 243 (1) [M$^+$], 228 (1), 212 (1), 178 (1), 166 (2), 152 (100), 134 (80), 111 (18), 93 (26), 92 (28), 91 (30), 80 (20), 79 (41). HRMS: calcd. 243.1024; found 243.1020.

Compound 16 ($C_{12}H_{20}NO_3P$, M = 257.27 g/mol): General procedure C was used to convert **12** into the title compound. Purification by flash chromatography (CH_2Cl_2/MeOH, 10:1) afforded **16** (126 mg, 0.49 mmol, 49%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.6 Hz, 3 H), 1.54−1.69 (m, 2 H), 1.90 (br. s, 2 H), 2.91−3.04 (m, 2 H), 3.74 (d, *J* = 4.8 Hz, 3 H), 3.76 (d, *J* = 4.8 Hz, 3 H), 7.18−7.35 (m, 5 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 8.6 (d, *J* = 4.0 Hz, CH_3), 28.9 (d, *J* = 2.0 Hz, CH_2), 40.8 (d, *J* = 4.0 Hz, CH_2), 53.1 (d, *J* = 8.0 Hz, CH_3), 53.2 (d, *J* = 8.0 Hz, CH_3), 56.5 (d, *J* = 150 Hz, C), 126.8 (CH), 128.0 (CH), 131.0 (CH), 135.5 (d, *J* = 11.0 Hz, C). IR: ṽ = 3377, 3028, 2951, 2850, 1712, 1601, 1495, 1454, 1380, 1349, 1233, 1182, 1107, 1053, 1024, 818, 768, 741, 701, 669 cm^{-1}. MS (25 °C): *m*/*z* (%) = 257 (4) [M$^+$], 228 (15), 183 (9), 166 (80), 148 (98), 134 (10), 105 (15), 91 (100), 83 (37), 80 (32), 79 (37), 77 (11), 65 (22). HRMS: calcd. 257.1181; found 257.1177.

One-Pot Synthesis of Cyclic α-Amino Phosphonates from Aminoalkynes. General Procedure D: The aminoalkyne (1.0 mmol), a solution of Cp_2TiMe_2 (0.11 mL, 0.45 mol/L in toluene, 0.05 mmol, 5.0 mol %) and toluene (1.0 mL) were added to a Schlenk tube. The Schlenk tube was sealed with a Teflon stopcock and heated to 110 °C for 9 h. Then the mixture was cooled to 0 °C and $HP(O)(OEt)_2$ (**7**; 138 mg, 1.00 mmol) and a solution of Me_2AlCl (0.05 mL, 1.0 mol/L in hexane, 0.05 mmol, 5.0 mol %) were added. After 2 h of stirring at room temperature the mixture was diluted with EtOAc and filtered through SiO_2 (prior to its use the SiO_2 was washed with EtOAc/NEt_3, 100:1). Evaporation of the solvent under vacuum and flash chromatography on silica gel afforded the pure (unless otherwise noted) α-amino phosphonate.

Compound 23 ($C_{15}H_{24}NO_3P$, M = 297.33 g/mol): General procedure D was used to convert **17** into the title compound. Purification by flash chromatography (PE/EtOAc/NEt_3, 500:100:1) afforded **23** (232 mg, 0.78 mmol, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.62−1.73 (m, 1 H), 1.80−1.94 (m, 2 H), 2.10−2.23 (m, 1 H), 2.68−2.75 (m, 1 H), 2.82−2.89 (m, 1 H), 2.95 (dd, *J* = 13.6, 10.2 Hz, 1 H), 3.04 (dd, *J* = 13.7, 9.4 Hz, 1 H), 4.08−4.20 (m, 4 H), 7.23−7.32 (m, 5 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 16.4 (CH_3), 25.7 (CH_2), 31.3 (CH_2), 41.1 (d, *J* = 8.0 Hz, CH_2), 47.1 (d, *J* = 7.0 Hz, CH_2), 62.1 (d, *J* = 8.0 Hz, CH_2), 62.4 (d, *J* = 8.0 Hz, CH_2), 63.2 (d, *J* = 166 Hz, C), 64.0 (C), 126.6 (CH), 128.0 (CH), 130.8 (CH), 136.3 (C). IR: ṽ = 3462, 2980, 2908, 2423, 1495, 1479, 1444, 1392, 1251, 1163, 1098, 1028, 958, 784, 748, 704, 600, 547 cm^{-1}. MS (25 °C): *m*/*z* (%) = 297 (1) [M$^+$], 240 (1), 206 (59), 178 (8), 160 (100), 150 (15), 111 (15), 91 (31), 83 (16), 65 (12). $C_{15}H_{24}NO_3P$ (297.3): calcd. C 60.06, H 8.14, N 4.71; found C 60.86, H 7.68, N 4.67.

Compound 24 ($C_{16}H_{26}NO_3P$, M = 311.36 g/mol): General procedure D was used to convert **18** into the title compound. Purification by flash chromatography (PE/EtOAc/NEt_3, 100:100:1) afforded **24** (268 mg, 0.86 mmol, 86%) as a colorless oil. The product was contaminated with trace amounts of $HP(O)(OEt)_2$ (**7**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H), 1.43−1.57 (m, 2 H), 1.60−1.70 (m, 2 H), 1.75−2.05 (m, 3 H), 2.93−3.06 (m, 3 H), 3.18 (dd, *J* = 24.6, 13.9 Hz, 1 H), 3.82−4.00 (m, 2 H), 4.02−4.12 (m, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 16.1 (d, *J* = 6.0 Hz, CH_3), 16.4 (d, *J* = 6.0 Hz, CH_3), 19.8 (d, *J* = 8.0 Hz, CH_2), 25.4 (CH_2), 29.5 (CH_2), 38.9 (d, *J* = 4.0 Hz, CH_2), 41.0 (d, *J* = 9.0 Hz, CH_2), 57.1 (d, *J* = 154 Hz, C), 61.4 (d, *J* = 8.0 Hz, CH_2), 62.1 (d, *J* = 8.0 Hz, CH_2), 126.2 (CH), 127.7 (CH), 130.9 (CH), 137.0 (C). IR: ṽ = 3466, 2980, 2930, 2422, 1495, 1443, 1391, 1367, 1231, 1163, 1098, 1023, 955, 762, 701, 658, 608, 575 cm^{-1}. MS (25 °C): *m*/*z* (%) = 311 (1) [M$^+$], 220 (42), 192 (4), 174 (100), 172 (64), 148 (8), 117 (16), 111 (20), 91 (28), 83 (17), 65 (13). HRMS: calcd. 311.1650; found 311.1648.

Compound 25 ($C_{10}H_{22}NO_3P$, M = 235.26 g/mol): General procedure D was used to convert **19** into the title compound. Purification by flash chromatography (PE/EtOAc/NEt_3, 400:100:1) afforded **25** (200 mg, 0.85 mmol, 85%) as a colorless oil. ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 1.31−1.38 (m, 9 H), 1.55−1.65 (m, 5 H), 1.68−1.78 (m, 1 H), 1.83−1.94 (m, 1 H), 2.80−2.88 (m, 1 H), 2.92−3.00 (m, 1 H), 4.11−4.21 (m, 4 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 16.5 (CH_3), 19.5 (d, *J* = 9.0 Hz, CH_2), 20.4 (CH_3), 25.8 (CH_2), 30.9 (CH_2), 40.7 (d, *J* = 10.0 Hz, CH_2), 52.8 (d, *J* = 316 Hz, C), 62.0 (d, *J* = 8.0 Hz, CH_2). IR: ṽ = 3462, 3308, 2977, 2932, 2867, 1442, 1391, 1366, 1232, 1190, 1163, 1123, 1096, 1022, 951, 787, 748, 637, 577 cm^{-1}. MS (25 °C): *m/z* (%) = 235 (3) [M^+], 220 (1), 137 (1), 123 (2), 111 (40), 98 (100), 83 (43), 65 (30). $C_{10}H_{22}NO_3P$ (235.3): calcd. C 51.06, H 9.43, N 5.95; found C 51.42, H 9.17, N 5.71.

Compound 26 ($C_{20}H_{26}NO_3P$, M = 359.40 g/mol): General procedure D was used to convert **20** into the title compound. Purification by flash chromatography (PE/EtOAc/NEt_3, 500:100:1) afforded 219 mg of a colorless oil. According to the ^1H NMR spectrum **26** was contaminated with 15% of the corresponding imine. Therefore, only 186 mg (0.52 mmol, 52%) of **26** were obtained. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.1 Hz, 3 H), 1.16 (t, *J* = 7.1 Hz, 3 H), 2.15−2.50 (br. s, 1 H), 2.47−2.57 (m, 1 H), 2.68−2.88 (m, 2 H), 3.12−3.20 (m, 1 H), 3.34−3.60 (m, 3 H), 3.82−4.08 (m, 3 H), 7.03 (d, *J* = 7.5 Hz, 1 H), 7.05−7.11 (m, 2 H), 7.12−7.32 (m, 5 H), 7.90 (d, *J* = 7.4 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 16.2 (CH_3), 16.2 (CH_3), 30.3 (CH_2), 38.9 (CH_2), 43.8 (CH_2), 60.6 (d, *J* = 153 Hz, C), 61.8 (d, *J* = 8.0 Hz, CH_2), 63.4 (d, *J* = 7.0 Hz, CH_2), 125.8 (d, *J* = 3.0 Hz, CH), 126.6 (CH), 126.8 (d, *J* = 3.0 Hz, CH), 127.8 (CH), 128.3 (*J* = 4.0 Hz, CH), 129.3 (d, *J* = 2.0 Hz, CH), 130.8 (CH), 133.9 (d, *J* = 2.0 Hz, C), 136.1 (d, *J* = 10.0 Hz, C), 136.8 (d, *J* = 7.0 Hz, C). IR: ṽ = 3359, 3060, 3027, 2979, 2928, 1674, 1622, 1601, 1572, 1494, 1453, 1390, 1365, 1235, 1162, 1049, 1022, 956, 786, 753, 738, 719, 700, 667, 595, 554 cm^{-1}. MS (25 °C): *m/z* (%) = 268 (3) [M^+ − Bn], 220 (100), 204 (5), 178 (3), 155 (3), 111 (17), 83 (15), 65 (10).

Compound 27 ($C_{16}H_{26}NO_4P$, M = 327.35 g/mol): General procedure D was used to convert **21** into the title compound. Purification by flash chromatography (EtOAc/NEt_3, 100:1) afforded **27** (216 mg, 0.66 mmol, 66%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15−1.26 (m, 1 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 1.40−2.05 (br. s, 1 H), 1.65−1.75 (m, 1 H), 1.78−1.88 (m, 1 H), 2.07−2.21 (m, 1 H), 2.67−2.77 (m, 1 H), 2.80−2.94 (m, 2 H), 3.00 (dd, *J* = 13.8, 9.4 Hz, 1 H), 3.79 (s, 3 H), 4.08−4.22 (m, 4 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 7.16 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 16.4 (d, *J* = 2.0 Hz, CH_3), 16.4 (d, *J* = 2.0 Hz, CH_3), 25.8 (d, *J* = 4.0 Hz, CH_2), 31.2 (d, *J* = 2.0 Hz, CH_2), 40.1 (d, *J* = 8.0 Hz, CH_2), 41.1 (d, *J* = 7.0 Hz, CH_2), 55.1 (CH_3), 62.0 (d, *J* = 8.0 Hz, CH_2), 62.3 (d, *J* = 7.0 Hz, CH_2), 63.2 (d, *J* = 165 Hz, C), 113.5 (CH), 128.2 (d, *J* = 12.0 Hz, C), 131.7 (CH), 158.4 (C). IR: ṽ = 3377, 2929, 2869, 2838, 1673, 1609, 1582, 1510, 1461, 1442, 1391, 1300, 1244, 1177, 1097, 1022, 957, 834, 788, 756, 673, 663, 637, 578, 527 cm^{-1}. MS (80 °C): *m/z* (%) = 327 (1) [M^+], 271 (4), 225 (7), 206 (100), 190 (77), 178 (59), 150 (72), 121 (73), 103 (5), 91 (13), 83 (19), 65 (17). HRMS: calcd. 327.1599; found 327.1597.

Compound 28 ($C_{16}H_{23}NO_3PF_3$, M = 365.33 g/mol): General procedure D was used to convert **22** into the title compound. Purification by flash chromatography (EtOAc/NEt_3, 100:1) afforded **28** (212 mg, 0.58 mmol, 58%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15−1.28 (m, 1 H), 1.34 (t, *J* = 7.0 Hz, 3 H), 1.35 (t, *J* = 7.0 Hz, 3 H), 1.50−1.62 (m, 1 H), 1.65−1.80 (m, 1 H), 1.95 (br. s, 1 H), 2.04−2.20 (m, 1 H), 2.74−2.82 (m, 1 H), 2.94−3.02 (m, 1 H), 3.14 (dd, *J* = 14.6, 6.3 Hz, 1 H), 3.32 (dd, *J* = 14.6, 8.3 Hz, 1 H), 4.23−4.11 (m, 4 H), 7.27−7.39 (m, 1 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 7.63 (d, *J* = 7.7 Hz, 1 H), 7.80 (d, *J* = 7.8 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 16.3 (d, *J* = 5.0 Hz, CH_3), 16.4 (d, *J* = 5.0 Hz, CH_3), 25.5 (*J* = 3.0 Hz, CH_2), 30.3 (CH_2), 36.5 (d, *J* = 9.0 Hz, CH_2), 46.5 (d, *J* = 3.0 Hz, CH_2), 62.1 (d, *J* = 8.0 Hz, CH_2), 62.4 (d, *J* = 8.0 Hz, CH_2), 63.1 (d, *J* = 155 Hz, C), 124.4 (q, *J* = 274 Hz, CF_3), 125.9 (q, *J* = 6.0 Hz, CH), 126.7 (CH), 129.9 (q, *J* = 29.0 Hz, C), 131.0 (CH), 133.5 (CH), 135.8 (d, *J* = 13.0 Hz, C). IR: ṽ = 3335, 2972, 2908, 2860, 2834, 1610, 1583, 1512, 1469, 1441, 1428, 1392, 1367, 1303, 1227, 1178, 1115, 1099, 1024, 947, 841, 825, 807, 763, 738, 682, 584, 567, 530, 513 cm^{-1}. MS (25 °C): *m/z* (%) = 365 (6) [M^+], 292 (32), 278 (10), 252 (13), 240 (15), 228 (88), 199 (31), 183 (20), 158 (100), 130 (16), 111 (88), 93 (31), 91 (13), 83 (87), 77 (8), 65 (67). $C_{16}H_{23}NO_3PF_3$ (365.3): calcd. C 52.60, H 6.35, N 3.83; found C 53.08, H 6.04, N 3.92.

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