A FACILE SYNTHESIS OF AZETIDIN-2-YLPHOSPHONIC ACID AND ITS 1-ALKYL DERIVATIVES

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Treatment of racemic diisopropyl [1,3-bis(mesyloxy)propyl]phosphonate with allyl-, benzyl-, 2-hydroxyethyl-, or propylamine gave the corresponding diisopropyl [(3-(alkylamino)-1-(mesyloxy)propyl]phosphonates. Heating of their toluene solution with aqueous potassium carbonate effected a cyclization to diisopropyl (1-alkylazetidin-2-yl)phosphonates. In the 1-benzyl- and [1-(2-hydroxyethyl)azetidin-2-yl]phosphonate, the isopropyl ester groups were removed by treatment with bromotrimethylsilane which gave 1-benzyl- and [1-(2-hydroxyethyl)azetidin-2-yl]phosphonic acid. Following hydrogenolysis of the benzyl group afforded azetidin-2-ylphosphonic acid.

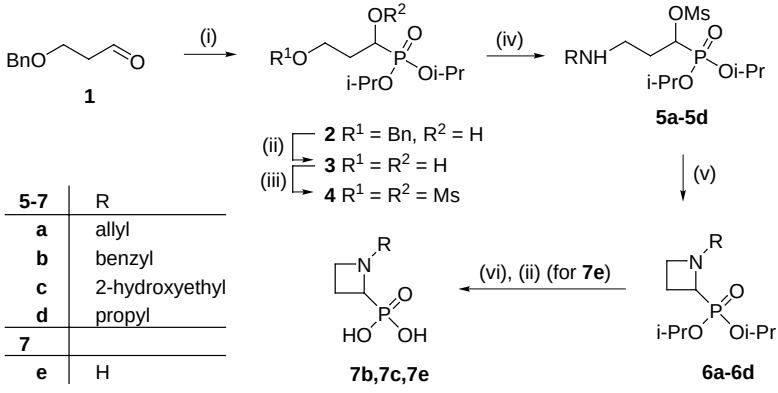
Keywords: Phosphonates; Phosphonopeptides; Azetidines; Aminophosphonates; Amino acids analogs; Cyclizations; Hydrolysis.

(α-Aminoalkyl)phosphonic acids have been frequently employed as attractive mimics of amino acids in biological systems; several of them are potent antibiotics, enzyme inhibitors (including HIV protease), ligands for excitatory amino acid receptors, pesticides, insecticides, and herbicides[1–5]. Numerous biologically active phosphonate analogues of proline have been described, among them, aziridin-2-yl-, pyrrolidin-2-yl-, and piperidin-2-ylphosphonic acid[6,7]. Paradoxically, there is not any phosphonate counterpart to L-azetidine-2-carboxylic acid[8], which is a potent proline antagonist in biological systems. We found only one related compound in the literature: dimethyl (1-tosylazetidin-2-yl)phosphonate[9] which was prepared (for a different purpose) by reaction of 2-(acetoxy)-1-tosylazetidine with trimethyl phosphite. This prompted us to attempt the synthesis of azetidin-2-ylphosphonic acid and its derivatives[10].

RESULTS AND DISCUSSION

For a construction of the azetidine ring bearing phosphonate function in position 2, we selected the current methodology which employs ring-closure of 1,3-dimesylates (1,3-ditosylates, 1,3-dihalides) with primary amines[11]. The required bifunctional synthon (having dialkylphosphonyl group in geminal position with respect to one of the mesylates) can be obtained by addition of a dialkyl phosphite to carbonyl group (Pudovik reaction[12]) of the suitably protected 3-hydroxyaldehyde, followed by deprotection and subsequent transformation of the formed 1,3-dihydroxy derivative to its dimesylate. Diisopropyl phosphite was selected for the Pudovik reaction, because the resulting isopropyl diesters are stable enough in a boiling aqueous potassium carbonate–toluene mixture used for the azetidine ring-closure and their bulkiness promoted the cyclization.

Treatment of 3-(benzyloxy)propanal[13] (**1**) with diisopropyl phosphite and triethylamine afforded diisopropyl [3-(benzyloxy)-1-hydroxypropyl]-phosphonate (**2**; Scheme 1). Benzyl group was then removed by hydrogenation and the formed diol **3** was converted to dimesylate **4**. The reaction of



(i) $HP(O)(Oi\text{-}Pr)_2$, Et_3N; (ii) H_2/Pd; (iii) MsCl, pyridine–CH_2Cl_2 (1 : 1); (iv) RNH_2,1,2-dimethoxyethane; (v) K_2CO_3, toluene–water (1 : 1), reflux; (vi) Me_3SiBr, CH_3CN

SCHEME 1

this intermediate with allyl-, benzyl-, 2-hydroxyethyl-, or propylamine at room temperature gave the corresponding diisopropyl [3-(alkylamino)-1-(mesyloxy)propyl]phosphonates (**5a**–**5d**) in high yields. Heating of their toluene solution with aqueous potassium carbonate resulted in a cyclization to the diisopropyl (1-alkylazetidin-2-yl)phosphonates (**6a**–**6d**).

This shows that the closure of 1,3-dimesylates to azetidine ring is not affected by the presence of diisopropylphosphonyl group in geminal position to one of the mesylates. 1-Benzyl **6b** and 1-(2-hydroxyethyl) derivative **6c** were subsequently converted to the free acids **7b** and **7c** by treatment with bromotrimethylsilane. No signs of a cleavage of the azetidine ring during deprotection were observed. Azetidin-2-ylphosphonic acid (**7e**) was finally obtained by hydrogenation of the compound **7b**.

Structure of the azetidines **6a**–**6d**, **7b**, **7c**, and **7e** was unequivocally proved by NMR spectra. Formation of the azetidine ring from acyclic [3-(alkylamino)-1-(mesyloxy)propyl]phosphonates **5a**–**5d** has a significant influence on chemical shifts of individual hydrogen, carbon, as well as phosphorus atoms. Replacement of the electron-withdrawing mesyloxy group with amino function results in an upfield shift of α-H from 4.9–5.0 to 3.3–3.5 ppm and α-C from 74–75 to 60–61 ppm. β-Carbon (position 2 is precursors **5** corresponding to position 3 in azetidines **6**) shifts from 27–31 to 19 ppm, which is a value characteristic for 3-C of azetidines. The ring-closure is accompanied by a decrease in electron density at the (originally secondary) amino group. This causes a lowfield shift of γ-carbons from 44 to 53 ppm. The decreased distance between γ-carbon and phosphorus resulted in an increase in the coupling constant from 11–12 to 23–25 Hz. At 1′-C, a similar lowfield shift from 50–53 to 61–62 was observed. Appearance of spin coupling between 1′-C and phosphorus indicates a decrease in their distance on the azetidine ring-closure. In ^{31}P NMR spectra, the closure of azetidine ring is manifested by a lowfield shift from 16–17 to 22–23 ppm. Removal of isopropyl ester groups is manifested by an increase of all proton chemical shift values by 0.4–1.0 ppm and by a decrease of *J*(2-C,P) value by about 40 Hz.

The MS (EI) spectra of azetidines **6a**–**6d** are characterized by the presence of the most intensive peak M – 165 (100%), which is due to the loss of the fragment $P(O)(Oi\text{-}Pr)_2$. Surprisingly enough, the same peak dominates in MS (EI) spectra (contrary to FAB) of their precursors **5a** and **5d**. In the benzyl derivative **5b** and in the hydroxy derivative **5c**, its intensity is 19 and 30%, respectively. This suggests that the electron impact effected cyclization of the precursors **5a**–**5d** to azetidines **6a**–**6d** which are further fragmented (see above). MS (FAB) spectra of free acids **7b**, **7c**, and **7e** are characterized by very intensive peak M – 81 (60–100%) which represents a loss of $P(O)(OH)_2$ fragment. MS (FAB) spectrum of azetidin-2-ylphosphonic acid (**7e**) shows, in addition to the molecular peak 138 (100%, M + H), peaks with multiples of the molecular weight *m*/*z*: 275 (42%, 2 M + H), 412 (7%, 3 M + H), and 549 (4%, 4 M + H). In compound **7c**, besides of the mo-

lecular peak 182 (61%, M + H), a peak of a dimer 363 (24%, 2 M + H) is manifested in the spectrum. It shows a strong ability of these compounds to self-association by hydrogen-bonding.

In conclusion, the described method represents a convenient synthetic approach to azetidin-2-ylphosphonic acid and its 1-alkyl derivatives.

EXPERIMENTAL

General

Melting points were determined on a Kofler block and are uncorrected. Analytical TLC was performed on silica gel pre-coated aluminium plates with fluorescent indicator (Merck 5554, 60 F_{254}). Visualization was effected (i) by UV light (254 nm), (ii) by spraying with 4-(4-nitrobezyl)pyridine (1% solution in ethanol), a short heating to 300–400 °C followed by exposition to gaseous ammonia), or (iii) by spraying with ninhydrine (1% solution in ethanol) and a short heating to 300–400 °C. Column chromatography was carried out on silica gel (Sigma S-0507, 40–63 μm). Gas chromatography (GC) was carried out on an HP 5890 instrument (Hewlett–Packard) with flame ionization detector. For purity assays, an HP-Ultra 2 column with a temperature gradient of 8 °C/min (80–300 °C) was used; injection temperature 250 °C, detector temperature 300 °C. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer, using the EI (electron energy 70 eV), FAB (ionisation with Xe, accelerating voltage 8 kV, thioglycerol–glycerol 3 : 1 mixture or bis(2-hydroxyethyl) disulfide were used as matrixes). ^{1}H NMR spectra were recorded at 500 MHz on a Varian UNITY 500 instrument in DMSO-d_6 (referenced to the solvent signal δ 2.50 ppm) or in deuterium oxide with 3-(trimethylsilyl)propane-1-sulfonate as an internal standard. ^{13}C NMR APT spectra were recorded at 127.5 MHz on a Varian UNITY 500 instrument in DMSO-d_6 (referenced to the solvent signal δ 39.70) or in deuterium oxide with dioxane as an external reference (δ 66.86). ^{31}P NMR spectra were taken at 80.98 MHz on a Varian UNITY 200 instrument in DMSO-d_6 or in D_2O with the use of phosphoric acid as an external standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra were obtained on an FT IR Bruker IFS 88 spectrometer in chloroform at approximately 3% concentration.

Diisopropyl [3-(Benzyloxy)-1-hydroxypropyl]phosphonate (**2**)

Diisopropyl phosphite (15 ml, 90 mmol) and triethylamine (13 ml, 90 mmol) were added to 3-(benzyloxy)propanal[13] (**1**; 1.5 g, 90 mmol) and the reaction mixture was left to stand at room temperature overnight. Triethylamine was evaporated *in vacuo*, the residue was taken into ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and evaporated. Chromatography on a silica gel column with chloroform gave **2** (16.8 g, 62%) as a colourless oil. MS (FAB): 331 (83%, M + H), 289 (12%, M – i-Pr + 2 H), 247 (44%, M – 2 i-Pr + 3 H), 139 (37%), 91 (100%, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 7.25–7.38 m, 5 H (arom.); 5.44 t, J = 6.6 (OH); 4.45 s, 2 H (OCH_2Ph); 4.59 m, 2 H (P-OCH); 3.79 dtd, 1 H, J = 9.5, 6.6, 6.6, 3.9 (1-H); 3.52–3.60 m, 2 H (3-H); 1.91 m, 1 H (2a-H); 1.70 m, 1 H (2b-H); 1.245 d, 3 H, J = 6.3 (CH_3); 1.24 d, 3 H, J = 6.3 (CH_3); 1.23 d, 6 H, J = 6.3 (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 138.82 (arom.); 128.43, 2 C (arom.); 127.59, 2 C (arom.); 127.54 (arom.); 72.09

(CH_2-Ph); 70.03 d, *J* = 7.8 (CH-O-P); 69.81 d, *J* = 7.8 (CH-O-P); 65.93 d, *J* = 14.65 (3-C); 63.60 d, *J* = 168.0 (1-C); 31.91 d, *J* = 2.9 (2-C); 24.10 d, *J* = 3.9 (CH_3); 24.04 d, *J* = 3.9 (CH_3); 23.92 d, *J* = 3.9 (CH_3); 23.89 d, *J* = 3.9 (CH_3). For $C_{16}H_{27}O_5P$ (330.4) calculated: 58.18% C, 8.24% H, 9.38% P; found: 58.21% C, 8.01% H, 9.51% P.

Diisopropyl (1,3-Dihydroxypropyl)phosphonate (**3**)

To a solution of compound **2** (5 g, 15 mmol) in ethyl acetate (1 l), palladium (10 wt.%) on activated carbon was added under argon and the reaction mixture was hydrogenated under 20 kPa overpressure for 8 h. The catalyst was removed by filtration over Celite, the filtrate was evaporated and applied onto a silica gel column. Elution with chloroform gave compound **3** (3.4 g, 93%) as a colourless thick oil. MS (FAB): 241 (92%, M + H), 199 (23%, M – i-Pr + 2 H), 157 (100%, M - 2 i-Pr + 3 H). ^{1}H NMR (500 MHz, DMSO-d_6): 5.29 br t, 1 H, *J* = 6.8, 6.6 (1-OH); 4.58 dsept, 1 H, *J* = 7.6, 6.1 (POCH); 4.56 dsept, 1 H, *J* = 7.6, 6.1 (POCH); 4.46 t, 1 H, *J* = 5.4, 5.1 (3-OH); 3.77 dtd, 1 H, *J* = 10.3, 6.6, 6.6, 2.9 (1-H); 3.46–3.56 m, 2 H (3-H); 1.70–1.78 m, 1 H, *J* = 13.7, 8.8, 6.6, 6.6, 2.9 (2a-H); 1.55–1.63 m, 1 H, *J* = 13.7, 10.3, 9.8, 5.4, 4.6 (2b-H); 1.24 d, 3 H, *J* = 6.1 (CH_3); 1.23 d, 3 H, *J* = 6.1 (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 69.96 d, *J* = 6.8 (P-OCH); 69.73 d, *J* = 6.8 (P-OCH); 63.59 d, *J* = 167.0 (1-C); 57.05 d, *J* = 14.65 (3-C); 34.80 d, *J* = 2.0 (C-2); 24.15 d, *J* = 4.9 (CH_3); 24.09 d, *J* = 4.9 (CH_3); 23.95 d, *J* = 3.9 (CH_3); 23.93 d, *J* = 3.9 (CH_3). For $C_9H_{21}O_5P$ (240.2) calculated: 45.00% C, 8.81% H, 12.89% P; found: 44.89% C, 8.69% H, 13.05% P.

Diisopropyl [1,3-Bis(mesyloxy)propyl]phosphonate (**4**)

Compound **3** (3.5 g, 14.6 mmol) was co-evaporated with pyridine, dissolved in a dichloromethane–pyridine 1 : 1 mixture (100 ml), and cooled to 0 °C. Then mesyl chloride (2.5 ml, 32 mmol) was added and the mixture was kept at room temperature for 4 h. The mixture was cooled to 0 °C, excess water was added, reaction mixture was taken into ethyl acetate, washed with aqueous sodium hydrogencarbonate and brine, dried with anhydrous magnesium sulfate and evaporated. Chromatography on a silica gel column with chloroform gave the product **4** (4.8 g, 83%) as a colourless thick oil. MS (FAB): 397 (20%, M + H), 355 (12%, M – i-Pr + 2 H), 313 (100%, M – 2 i-Pr + 3 H), 217 (96%, M - 2 i-Pr – MsO + 2 H). ^{1}H NMR (500 MHz, DMSO-d_6): 4.93 td, 1 H, *J* = 9.3, 9.3, 4.2 (1-H); 4.71 m, 2 H (P-OCH); 4.37 dt, *J* = 10.7, 5.0, 5.0 (3a-H); 4.27 ddd, *J* = 10.7, 8.0, 5.6 (3b-H); 3.32 s, 3 H (Ms); 3.19 s, 3 H (Ms); 2.26 m, 1 H (2a-H); 2.15 m, 1 H (2b-H); 1.31 d, 3 H, *J* = 6.1 (CH_3); 1.30 d, 6 H (CH_3); 1.295 d, 3 H (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 72.40 d, *J* = 170.9 (1-C); 72.24 d, *J* = 6.8 (P-OCH); 72.21 d, *J* = 6.8 (P-OCH); 65.93 d, *J* = 12.7 (3-C); 38.71 (Ms); 36.91 (Ms); 30.28 (2-C); 23.97 d, *J* = 3.9 (CH_3); 23.88 d, *J* = 3.9 (CH_3); 23.74 d, *J* = 4.9 (CH_3); 23.65 d, *J* = 4.9 (CH_3). ^{31}P NMR (88.98 MHz, DMSO-d_6): 15.99 s. For $C_{11}H_{25}O_9PS_2$ (396.4) calculated: 33.33% C, 6.36% H, 7.81% P; found: 33.50% C, 6.48% H, 7.64% P.

Diisopropyl [3-(Alkylamino)-1-(mesyloxy)propyl]phosphonates (**5a**–**5d**).
General Procedure

Compound **4** (790 mg, 2 mmol) was dissolved in 1,2-dimethoxyethane (4 ml), a primary amine (5 mmol) was added, and the reaction mixture was kept at room temperature overnight. The solvent was evaporated and the residue was applied onto a silica gel column. Repeated chromatography with a gradient of 0–2 vol.% methanol in chloroform followed by

precipitation from a mixture of 0–25% ethyl acetate in petroleum ether afforded the title compounds **5a**–**5d** as thick colourless oils in 70–85% yield as free bases. Traces of the corresponding azetidines **6a**–**6d** (with higher R_F than compounds **5a**–**5d**) were detectable on TLC. Free bases **5b** and **5c** were further converted to hydrochlorides: they were dissolved in 1 M methanolic HCl (2 ml) and evaporated to dryness. Crystallization from petroleum ether–ethyl acetate (3 : 1) gave hydrochloride of compound **5b** as white crystals. Hydrochloride of **5c** was obtained by precipitation from petroleum ether–ethyl acetate (5 : 1) as a colourless thick oil. (Treatment of compound **5a** and **5d** with HCl did not afford crystalline hydrochlorides.)

Diisopropyl [3-(allylamino)-1-(mesyloxy)propyl]phosphonate (**5a**). Yield 88%, thick colourless oil. MS (FAB): 358 (100%, M + H), 274 (40%, M + H – CH_2=$CHCH_2NHCH_2CH_2$). MS (EI): 357 (7%, M), 273 (6%, M – CH_2=$CHCH_2NHCH_2CH_2$), 96 (100%, 1-allylazetidin-2-yl), 70 (27%, CH_2=$CHCH_2NHCH_2$), 41 (48%, allyl). HRMS (EI): for $C_{13}H_{28}NO_6PS$ calculated 357.1375, found 357.1355. ^{1}H NMR (500 MHz, DMSO-d_6): 5.82 ddt, 1 H, *J* = 17.3, 10.3, 5.9, 5.9 (2′-H); 5.15 dq, 1 H, *J* = 17.3, 1.7, 1.7, 1.5 (3′a-H, *trans*); 5.04 dq, 1 H, *J* = 10.3, 1.7, 1.5, 1.5 (3′b-H, *cis*); 4.93 td, 1 H, *J* = 8.8, 8.8, 3.9 (1-H); 4.68 m, 2 H (P-OCH); 3.14 dq, 2 H, *J* = 5.9, 1.5, 1.5, 1.5 (1′-H); 3.265 s, 3 H (Ms); 3.00 br, 1 H (NH); 2.67 ddd, 1 H, *J* = 12.0, 7.8, 4.9 (3a-H); 2.59 dt, 1 H, *J* = 12.0, 7.6, 7.6 (3b-H); 1.95 m, 1 H (2a-H); 1.84 m, 1 H (2b-H); 1.29 d, 3 H, *J* = 6.1 (CH_3); 1.285 d, 6 H, *J* = 6.1 CH_3); 1.28 d, 3 H, *J* = 6.1 (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 137.25 (2′-C); 115.68 (3′-C); 74.54 d, *J* = 169.9 (1-C); 71.69 d, *J* = 6.8 (P-OCH); 51.385 (1′-C); 43.96 d, *J* = 10.7 (3-C); 38.70 (Ms); 30.35 (2-C); 23.96 d, *J* = 3.9 (CH_3); 23.91 d, *J* = 3.9 (CH_3); 23.76 d, *J* = 4.9 (CH_3); 23.67 d, *J* = 4.9 (CH_3). ^{31}P NMR (88.98 MHz, DMSO-d_6): 16.99 s. For $C_{13}H_{28}NO_6PS$ (357.4) calculated: 43.69% C, 7.90% H, 3.92% N, 8.67% P; found: 44.01% C, 8.11% H, 3.75% N, 8.39% P.

Diisopropyl [3-(benzylamino)-1-(mesyloxy)propyl]phosphonate hydrochloride (**5b**·HCl). Yield 83%, white crystals; m.p. 138–139 °C. MS (FAB): 408 (100%, M + H, free base), 324 (30%), 91 (76%, Bn). HRMS (FAB): for $C_{17}H_{31}NO_6PS$ (M + H) calculated 408.1610, found 408.1676. MS (EI): 407 (1.4%, M), 146 (18%, 1-benzylazetidin-2-yl), 136 (30%), 120 (16%, $BnNHCH_2$), 106 (54%, BnNH), 91 (100%, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 7.32 m, 4 H (arom.); 7.21 m, 1 H (arom.); 5.00 td, 1 H, *J* = 9.5, 9.5, 3.9 (1-H); 4.68 m, 2 H (P-OCH); 3.67 s, 2 H (1′-H); 3.27 s, 3 H (Ms); 2.70 ddd, 1 H, *J* = 12.0, 7.3, 4.9 (3a-H); 2.62 dt, 1 H, *J* = 12.0, 7.6, 7.6 (3b-H); 2.40 br, 2 H (NH_2^+); 2.00 m, 1 H (2a-H); 1.90 m, 1 H (2b-H); 1.29 d, 3 H, *J* = 6.1 (CH_3); 1.285 d, 6 H, *J* = 6.1 (CH_3); 1.28 d, 3 H, *J* = 6.1 (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 140.965 (arom.); 128.03, 2 C (arom.); 127.20, 2 C (arom.); 126.62 (arom.); 74.65 d, *J* = 168.95 (1-C); 71.67 d, *J* = 6.8 (P-OCH); 71.65 d, *J* = 6.8 (P-OCH); 52.97 (1′-C); 44.16 d, *J* = 11.7 (3-C); 38.72 (Ms); 30.59 (2-C); 23.95 d, *J* = 3.9 (CH_3); 23.89 d, *J* = 3.9 (CH_3); 23.75 d, *J* = 4.9 (CH_3); 23.66 d, *J* = 4.9 (CH_3). ^{31}P NMR (88.98 MHz, DMSO-d_6): 15.75 s. For $C_{17}H_{31}ClNO_6PS$ (443.9) calculated: 46.00% C, 7.04% H, 7.99% Cl, 3.16% N, 6.98% P; found: 46.01% C, 7.13 % H, 7.94% Cl, 3.25% N, 7.09% P.

Diisopropyl {3-[(2-hydroxyethyl)amino]-1-(mesyloxy)propyl}phosphonate hydrochloride (**5c**·HCl). Yield 80%, thick colourless oil. MS (FAB): 362 (76%, M + H, free base), 278 (23%), 57 (100%). HRMS (FAB): for $C_{12}H_{29}NO_7PS$ (M + H) calculated 362.1402, found 362.1345. MS (EI): 343 (6%, M – H_2O), 330 (28%, M – CH_2OH), 288 (21%), 260 (12%), 246 (100%, **6c** – H_2O – H), 150 (27%, $HP(O)(Oi\text{-}Pr)_2$ – Me), 100 (30%, 1-hydroxyazetidin-2-yl), 43 (55%, i-Pr). ^{1}H NMR (500 MHz, DMSO-d_6): 9.20 br, 2 H (NH_2^+); 5.30 t, 1 H, *J* = 5.1 (OH); 5.04 ddd, 1 H, *J* = 10. 3, 8.3, 4.6 (1-H); 4.69 m, 2 H (P-OCH); 3.66 br q, 2 H, *J* = 5.2 [+AcOD: t, 2 H, *J* = 5.2] (2′-H); 3.32 s, 3 H (Ms); 3.06 m, 2 H (3-H); 2.99 br t, 2 H, *J* = 5.2 (1′-H); 2.30 m, 1 H (2a-H);

2.20 m, 1 H (2b-H); 1.30 d, 6 H, *J* = 6.1 (CH_3); 1.295 d, 6 H, *J* = 6.1 (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 73.63 d, *J* = 170.9 (1-C); 72.65 d, *J* = 6.8 (P-OCH); 72.62 d, *J* = 6.8 (P-OCH); 56.75 (2′-C); 49.53 (1′-C); 43.71 d, *J* = 11.7 (3-C); 38.84 (Ms); 27.03 (2-C); 24.20 d, *J* = 2.9 (CH_3); 24.13 d, *J* = 2.9 (CH_3); 24.02 d, *J* = 4.9 (CH_3); 23.90 d, *J* = 4.9 (CH_3). ^{31}P NMR (88.98 MHz, DMSO-d_6): 15.77 s. For $C_{12}H_{29}ClNO_7PS$ (397.9) calculated: 36.23% C, 7.35% H, 8.91% Cl, 3.52% N, 7.79% P; found: 36.46% C, 7.19% H, 9.14% Cl, 3.25% N, 7.74% P.

Diisopropyl [1-(mesyloxy)-3-(propylamino)propyl]phosphonate (**5d**). Yield 82%, thick colourless oil. MS (FAB): 360 (100%, M + H), 276 (26%). HRMS (FAB): for $C_{13}H_{30}NO_6PS$ (M + H) calculated 360.1610, found 360.1656. MS (EI): 360 (10%, M + H), 330 (12%, M – Et), 246 (34%), 98 (100%, 1-propylazetidin-2-yl), 72 (31%, $PrNHCH_2$), 43 (37%, Pr). ^{1}H NMR (500 MHz, DMSO-d_6): 4.93 ddd, 1 H, *J* = 9.2, 8.6, 3.9 (1-H); 4.67 m, 2 H (P-OCH); 3.265 s, 3 H (Ms); 2.66 ddd, 1 H, *J* = 11.7, 7.3, 4.9 (3a-H); 2.58 dt, 1 H, *J* = 11.7, 7.6, 7.6 (3b-H); 2.46 dt, 1 H, *J* = 11.2, 7.1, 7.1 (1′a-H); 2.41 dt, 1 H, *J* = 11.2, 7.1, 7.1 (1′b-H); 2.10 br, 1 H (NH); 1.93 m, 1 H (2a-H); 1.82 m, 1 H (2b-H); 1.39 sext, 2 H, *J* = 7.3 (2′-H); 1.29 d, 3 H, *J* = 6.1 (CH_3); 1.285 d, 6 H, *J* = 6.1 (CH_3); 1.28 d, 3 H, *J* = 6.1 (CH_3); 0.86 t, 3 H, *J* = 7.3 (3′-C). ^{13}C NMR (127.5 MHz, DMSO-d_6): 73.83 d, *J* = 169.1 (1-C); 71.72 d, *J* = 6.8 (P-OCH); 71.70 d, *J* = 6.8 (P-OCH); 50.92 (1′-C); 44.53 d, *J* = 11.7 (3-C); 38.69 (Ms); 30.23 (2-C); 23.99 d, *J* = 3.9 (CH_3); 23.93 d, *J* = 3.9 (CH_3); 23.78 d, *J* = 4.9 (CH_3); 23.70 d, *J* = 4.9 (CH_3); 11.86 (3′-C). ^{31}P NMR (88.98 MHz, DMSO-d_6): 15.75 s. For $C_{13}H_{30}NO_6PS$ (359.4) calculated: 43.44% C, 8.41% H, 3.90% N, 8.62% P; found: 43.41% C, 8.22% H, 4.02% N, 8.49% P.

Diisopropyl (1-Alkylazetidin-2-yl)phosphonates (**6a**–**6d**). General Procedure

To a solution of compound **4** (3.2 g, 8 mmol) in toluene (50 ml), a primary amine (9 mmol), water (16 ml), and potassium carbonate (3.3 g, 24 mmol) were added and the reaction mixture was refluxed for 8 h. The reaction mixture was taken into ethyl acetate, washed with brine, dried with anhydrous magnesium sulfate, and evaporated. Repeated chromatography on a silica gel column using toluene–ethyl acetate or chloroform–methanol solvent systems followed by precipitation from petroleum ether–ethyl acetate (0–5 vol.%) gave azetidines **6a**–**6d** (free bases) as thick colourless oils. Treatment with HCl did not afford crystalline hydrochlorides.

Diisopropyl (1-allylazetidin-2-yl)phosphonate **6a**. Yield 62%, thick colourless oil. MS (EI): 261 (11%, M), 96 [100%, M – P(O)(Oi-Pr)$_2$], 41 (44%, allyl). HRMS (EI): for $C_{12}H_{24}NO_3P$ calculated 261.1494, found 261.1484. GC retention time: 22.94 min. ^{1}H NMR (500 MHz, DMSO-d_6): 5.71 dddd, 1 H, *J* = 17.3, 10.0, 7.1, 4.6 (2′-H); 5.13 br dq, 1 H, *J* = 17.3, 2.0, 1.7, 1.7 (3′a-H, *trans*); 5.06 br d, 1 H, *J* = 10.0, 2.0, 1.0 (3′b-H, *cis*); 4.62 d sept, 1 H, *J* = 7.6, 6.1 (P-OCH); 4.59 d sept, 1 H, *J* = 7.6, 6.1 (P-OCH); 3.43 td, 1 H, *J* = 8.0, 8.0, 6.8 (2-H); 3.30 ddt, 1 H, *J* = 13.7, 4.6, 1.7, 1.7 (1′a-H); 3.30 m, 1 H (4a-H, covered); 2.90 td, 1 H, *J* = 8.5, 8.5, 7.3 (4b-H); 2.84 brdd, 1 H, *J* = 13.7, 7.1, ≈1, ≈1 (1′b-H); 2.19 d quint, 1 H, *J* = 10.7, 9.0, 9.0, 9.0, 9.0 (3a-H); 2.06 m, 1 H (3b-H); 1.28 d, 3 H, *J* = 6.1 (CH_3); 1.25 d, 3 H, *J* = 6.1 (CH_3); 1.24 d, 3 H, *J* = 6.1 (CH_3); 1.22 d, 3 H, *J* = 6.1 (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 134.60 (2′-C); 116.97 (3′-C); 69.82 d, *J* = 6.9 (P-OCH); 69.52 d, *J* = 6.9 (P-OCH); 60.77 d, *J* = 2.9 (1′-C); 60.02 d, *J* = 171.9 (2-C); 53.15 d, *J* = 23.4 (4-C); 24.17 d, *J* = 2.9 (CH_3); 24.01 d, 2 C, *J* = 3.9 (CH_3); 23.92 d, *J* = 4.9 (CH_3); 18.77 d, *J* = 5.9 (3-C). ^{31}P NMR (88.98 MHz, DMSO-d_6): 22.58 s.

Diisopropyl (1-benzylazetidin-2-yl)phosphonate **6b**. Yield 58%, thick colourless oil. MS (EI): 311 (7%, M), 146 [100%, M – P(O)(Oi-Pr)$_2$], 91 (85%, Bn). HRMS (EI): for $C_{16}H_{26}NO_3P$ cal-

culated 311.1650, found 311.1664. ^{1}H NMR (500 MHz, DMSO-d_6): 7.31 m, 2 H (arom.); 7.23, 3 H (arom.); 4.69 d sept, 1 H, *J* = 7.6, 6.1 (P-OCH); 4.63 d sept, 1 H, *J* = 7.6, 6.1 (P-OCH); 3.90 d, 1 H, *J* = 13.2 (1′a-H); 3.54 td, 1 H, *J* = 8.5, 8.5, 6.4 (2-H); 3.35 d, 1 H, *J* = 13.2 (1′b-H); 3.15 m, 1 H (4a-H); 2.91 td, 1 H, *J* = 8.6, 8.6, 7.1 (4b-H); 2.20 sept, 1 H, *J* = 9.0 (3a-H); 2.06 m, 1 H (3b-H); 1.32 d, 3 H, *J* = 6.1 (CH_3); 1.28 d, 3 H, *J* = 6.1 (CH_3); 1.26 d, 3 H, *J* = 6.1 (CH_3); 1.24 d, 3 H, *J* = 6.1 (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 137.99 (arom.); 128.43, 2 C (arom.); 128.34, 2 C (arom.); 127.08 (arom.); 70.32 d, *J* = 5.8 (P-OCH); 69.83 d, *J* = 6.8 (P-OCH); 61.91 d, *J* = 3.9 (1′-C); 60.11 d, *J* = 171.9 (2-C); 53.16, *J* = 25.4 (4-C); 24.21 d, *J* = 3.9 (CH_3); 24.08 d, *J* = 4.9 (CH_3); 24.01 d, *J* = 3.9 (CH_3); 23.93 d, *J* = 4.9 (CH_3); 18.85 d, *J* = 5.8 (3-C). ^{31}P NMR (88.98 MHz, DMSO-d_6): 22.33 s. For $C_{16}H_{26}NO_3P$ (311.4) calculated: 61.72% C, 8.42% H, 4.50% N, 9.95% P; found: 61.59% C, 8.31% H, 4.28% N, 10.16% P.

Diisopropyl [1-(2-hydroxyethyl)azetidin-2-yl]phosphonate **6c**. Yield 66%, thick colourless oil. MS (EI): 266 (0.5%, M + H), 265 (0.2%, M), 234 (73%, M – CH_2OH), 150 [21%, HP(O)(Oi-Pr)$_2$ – Me], 100 [100%, M – P(O)(Oi-Pr)$_2$]. HRMS (EI): for $C_{11}H_{25}NO_4P$ calculated 266.1521, found 266.1540; for $C_{11}H_{24}NO_4P$ calculated 265.1443, found 265.1409. GC retention time: 25.35 min. IR ($CHCl_3$): 3 362 m (OH, assoc.), 3 005 s,sh, 2 983 s, 2 936 m, 2 873 m, 2 850 m, 1 387 m, 1 376 m, 1 170 m,sh, 1 142 m, 1 016 s,sh, 999 vs, 981 s,sh. ^{1}H NMR (500 MHz, DMSO-d_6): 4.64 d sept, 1 H, *J* = 7.6, 6.1 (P-OCH); 4.57 d sept, 1 H, *J* = 7.6, 6.1 (P-OCH); 4.45 br, 1 H (OH); 3.42 td, 1 H, *J* = 8.5, 8.3, 7.1 (4a-H); 3.39–3.29 m, 3 H (2-H and 2′-H); 3.00 td, 1 H, *J* = 8.8, 8.8, 7.1 (4b-H); 2.66 dt, 1 H, *J* = 11.9, 6.1, 6.1 (1′a-H); 2.38 dt, *J* = 11.9, 6.1, 6.1 (1′b-H); 2.18 br sept, 1 H, *J* = 9.0 (3a-H); 2.07 dqd, 1 H, *J* = 10.5, 8.1, 8.1, 8.1, 2.7 (3b-H); 1.30 d, 3 H, *J* = 6.1 (CH_3); 1.26 d, 3 H, *J* = 6.1 (CH_3); 1.23 d, 3 H, *J* = 6.1 (CH_3); 1.22 d, 3 H, *J* = 6.1 (CH_3). ^{13}C NMR (127.5 MHz, DMSO-d_6): 70.40 d, *J* = 5.9 (P-OCH); 69.79 d, *J* = 7.8 (P-OCH); 61.17 d, *J* = 3.9 (1′-C); 60.90 d, *J* = 171.9 (2-C); 59.50 (2′-C); 54.48 d, *J* = 24.4 (4-C); 24.18 d, *J* = 2.9 (CH_3); 24.01 d, *J* = 4.9 (CH_3); 23.90 d, *J* = 4.9 (CH_3); 23.97 d, *J* = 3.9 (CH_3); 19.19 d, *J* = 5.9 (3-C). ^{31}P NMR (88.98 MHz, DMSO-d_6): 22.91 s.

Diisopropyl (1-propylazetidin-2-yl)phosphonate **6d**. Yield 48%, thick colourless oil. MS (FAB): 264 (80%, M + H), 98 [100%, M – P(O)(Oi-Pr)$_2$]. HRMS (FAB): for $C_{12}H_{26}NO_3P$ (M + H) calculated 264.1729, found 264.1673. MS (EI): 263 (3.9%, M), 98 [100%, M – P(O)(Oi-Pr)$_2$]. GC retention time 23.09 min. ^{1}H NMR (500 MHz, DMSO-d_6): 4.62 d sept, 1 H, *J* = 7.6, 6.2 (P-OCH); 4.57 d sept, 1 H, *J* = 7.6, 6.2 (P-OCH); 3.32 m, 2 H (2-H and 4a-H); 2.85 td, 1 H, *J* = 8.6, 8.6, 7.1 (4b-H); 2.56 dt, 1 H, *J* = 11.2, 7.8, 7.8 (1′a-H); 2.21 dt, 1 H, *J* = 11.2, 5.5, 5.5 (1′b-H); 2.15 m, 1 H (3a-H); 2.04 m, 1 H (3b-H); 1.29 d, 3 H, *J* = 6.2 (CH_3); 1.25 d, 3 H, *J* = 6.2 (CH_3); 1.25 m, 2 H (2′-H); 1.235 d, 3 H, *J* = 6.2 (CH_3); 1.22 d, 3 H, *J* = 6.2 (CH_3); 0.81 t, 3 H, *J* = 7.3 (3′-H). ^{13}C NMR (127.5 MHz, DMSO-d_6): 70.15 d, *J* = 5.9 (P-OCH); 69.63 d, *J* = 6.8 (P-OCH); 60.87 d, *J* = 172.9 (2-C); 60.65 br, *J* ≈ 3.0 (1′-C); 53.40 d, *J* = 24.4 (4-C); 24.18 d, *J* = 3.9 (CH_3); 24.01 d, *J* = 4.9 (CH_3); 23.97 d, *J* = 3.9 (CH_3); 23.86 d, *J* = 4.9 (CH_3); 20.14 (2′-C); 18.70 d, *J* = 5.9 (3-C); 11.79 (3′-C). ^{31}P NMR (88.98 MHz, DMSO-d_6): 22.56 s.

(1-Alkylazetidin-2-yl)phosphonic acids **7**. General Procedure

Diisopropyl ester **6** (2 mmol) was dissolved in acetonitrile (10 ml), bromotrimethylsilane (2.6 ml, 20 mmol) was added, and the reaction mixture was kept at room temperature overnight. The solvent was evaporated, the residue was dissolved in water (10 ml), alkalified with ammonia, and applied on a Dowex 1X2 (100–200 mesh, 50 ml) column in acetate cycle. Elution was performed with a gradient 0–0.3 M acetic acid. Fractions were analyzed by TLC in 1-propanol–ammonia–water 30 : 10 : 3; detection by spraying with ninhydrine

and heating. Appropriate fractions were collected, evaporated, and co-evaporated with an ethanol–toluene (1 : 1) mixture. Crystallization of the residue from ether–methanol 3 : 1 gave products **7** as white crystals.

(1-Benzylazetidin-2-yl)phosphonic acid (**7b**). Yield 70%, white crystals; m.p. 152–155 °C. MS (FAB): 228 (55%, M + H), 146 [65%, M – $P(O)(OH)_2$], 132 (31%), 91 (100%, Bn). HRMS (FAB): for $C_{10}H_{15}NO_3P$ (M + H) calculated 228.0790, found 228.0762. ^{1}H NMR (500 MHz, DMSO-d_6): 9.00 br, 2 H (P-OH); 7.59 m, 2 H (arom.); 7.36 m, 3 H (arom.); 4.34 d, 1 H, *J* = 13.1 (1′a-H); 4.20 d, 1 H, *J* = 13.1 (1′b-H); 4.14 br q, 1 H, *J* = 8.5, 8.5, 7.8 (2-H); 3.75 br q, 1 H, *J* = 8.9, 8.9, 8.9 (4a-H); 3.66 m, 1 H (4b-H); 2.43 m, 2 H (3-H). ^{13}C NMR (127.5 MHz, DMSO-d_6): 130.985 (arom.); 130.96 (arom.); 129.05 (arom.); 128.70, 2 C (arom.); 64.05 d, *J* = 137.7 (2-C); 57.72 br s (1′-C); 50.01 d, *J* = 8.7 (4-C); 19.23 br, *J* ≈ 3 (3-C). ^{31}P NMR (88.98 MHz, DMSO-d_6): 7.34 s.

[1-(2-Hydroxyethyl)azetidin-2-yl]phosphonic acid (**7c**). Yield 63%, very hygroscopic white crystals. MS (FAB): 363 (24%, 2 M + H), 182 (61%, M + H), 100 [100%, M – $P(O)(OH)_2$], 57 (18%, azetidin), 56 (22%, azetidin – H). HRMS (FAB): for $C_5H_{13}NO_4P$ (M + H) calculated 182.0582, found 182.0600. ^{1}H NMR (500 MHz, DMSO-d_6): 8.50 br, 3 H (P-OH and 2′-OH); 4.27 td, 1 H, *J* = 8.8, 8.8, 7.6 (2-H); 4.00 m, 1 H (4a-H); 3.92 q, 1 H, *J* = 9.4, 9.4, 9.4 (4b-H); 3.67 t, 2 H, *J* = 4.6, 4.6 (2′-H); 3.21 m, 2 H (1′-H); 2.43 m, 2 H (3-H). ^{13}C NMR (127.5 MHz, DMSO-d_6): 64.33 d, *J* = 139.2 (2-C); 58.01 br (1′-C); 56.54 (2′-C); 52.69 d, *J* = 8.3 (4-C); 19.25 d, *J* = 3.0 (3-C). ^{31}P NMR (88.98 MHz, DMSO-d_6): 7.66 s.

Azetidin-2-ylphosphonic Acid (**7e**)

A solution of compound **7b** (1 mmol, 230 mg) in methanol (20 ml) was acidified with 1 M HCl in methanol (1 ml) and palladium on activated carbon (10 wt.%, 50 mg) was added under argon. The reaction mixture was hydrogenated under slight overpressure overnight. The catalyst was filtered off over cellite and the filtrate was evaporated. The residue was purified as described above in general procedure. Yield 110 mg (80%), white crystals; m.p. 261–263 °C. MS (FAB): 549 (4%, 4 M + H), 412 (7%, 3 M + H), 275 (42%, 2 M + H), 138 (100%, M + H), 57 (33%, azetidin), 56 [60%, M – $P(O)(OH)_2$]. HRMS (FAB): for $C_3H_9NO_3P$ (M + H) calculated 138.0320, found 138.0354. ^{1}H NMR (500 MHz, D_2O): 4.51 dt, 1 H, *J* = 9.6, 8.0, 8.0 (2-H); 4.14 dt, 1 H, *J* = 12.2, 7.8, 7.8 (4a-H); 4.04 m, 1 H (4b-H); 2.53–2.71 m, 2 H (3-C). ^{13}C NMR (127.5 MHz, D_2O): 55.72 d, *J* = 141.6 (2-C); 47.00 d, *J* = 6.3 (4-C); 22.30 d, *J* = 3.9 (3-C). ^{31}P NMR (88.98 MHz, D_2O): 10.75 s.

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