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Synthesis of Di(adamantylalkyl) Tosyloxymethylphosphonates and Di(adamantyloxyalkyl) Tosyloxymethylphosphonates

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Abstract—A simple method for the synthesis of esters of tosyloxymethylphosphonic acid based on the adamantane series of alcohols and diethyl tosyloxymethyl phosphonate was developed. The di(adamantylalkyl) and di(adamantyloxyalkyl) tosyloxymethylphosphonates are of interest as key compounds in the synthesis of antiviral drugs of the nucleoside phosphonate class.

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The phosphonic acids and esters containing adamantane are of great interest in terms of both their use in the synthesis of new drugs and their proper biological activity. Thus, dimethyl, diethyl, and diisopropyl tosyloxymethylphosphonates are the key compounds in the synthesis of the antiviral drugs of a new generation belonging to the class of nucleoside phosphonates, such as cidofovir and tenofovir [1, 2]. However, owing to the high polarity of phosphoryl group the medicines based on the phosphonic acids derivatives show low bioavailability. Solution of this problem lies in the development of the prodrugs based on modified phosphonates, that is, on the compounds decomposed under the action of enzymes affording the components that possess antiviral activity. For example, lipophilic analogs (prodrugs) of cidofovir are several orders of magnitude more active than the cidofovir itself, due to the greater bioavailability of the prodrugs [3]. The modification is aimed at two targets: first, enhancing bioavailability by increasing lipophilicity of the molecule and facilitating transport of the prodrug into the cell, and second, increasing the ability of the prodrug to release the active ingredient (phosphonic acid) gradually, maintaining its intracellular concentration sufficient for therapeutic effect. This leads to the reduction of a single dose of the drug and prolongation of its action [4]. In addition, the modifier can possess its own antiviral activity acting on different biological targets (double-acting drugs) [5, 6]. Similar properties should have the phosphonates modified by the adamantyl-containing lipophilic substituents that can be split off by hydrolysis. It is known that a number of adamantane derivatives have antiviral activity as the blockers of ion channels. Among these compounds, a number of substances is already in use as antiviral drugs (e.g., amantadine, rimantadine, and tromantadine) [5–9].

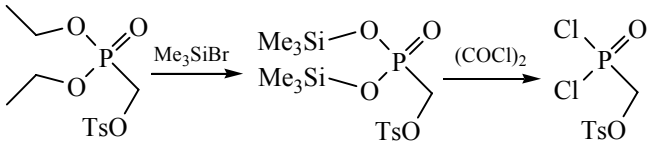
Previously, we reported on the synthesis of some sodium salts of the partial esters of tosyloxymethylphosphonic acid [10].

In order to create effective modifiers of nucleoside phosphonates we synthesized the adamantyl-containing esters of tosyloxymethylphosphonic acid with different length of aliphatic chain and with different amounts of “hinge” oxygen atoms, to be able to vary the lipophilicity of the obtained derivatives and the chain flexibility in a wide range.

The procedure of the synthesis based on the method proposed by Holstetler and coworkers for the preparation of monoalkoxyalkyl esters [11], which consists in sequential processing of diethyl tosyloxymethylphosphonate with bromotrimethylsilane, oxalyl chloride and alkoxyalkanol. We extended this method to the synthesis of complete esters of tosyloxymethylphosphonic acid. Use of the latter in the synthesis of the nucleoside phosphonates in some cases is preferable.

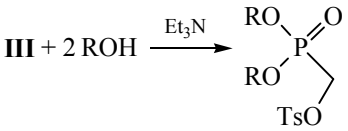
Adamantylalkyl and adamantyloxyalkyl tosyloxymethylphosphonates were obtained from the diethyl tosyloxymethylphosphonate **I** by the treatment with bromotrimethylsilane in methylene chloride followed

by involving the resulting bistrimethylsilyl ester **II** in the reaction with oxalyl chloride in the presence of catalytic amounts of *N*,*N*-dimethylformamide, and using the formed dichlorphosphonate in the reaction with alkoxyalkanols **I–III.**



I **II** **III**

The dichlorophosphonate **III** was used without isolation in the reaction with the corresponding alcohols of the adamantane series **IVa–IVl** in the presence of triethylamine as a base:



IVa–IVl **Va–Vl**

IV, V: R = $AdCH_2$ (**a**), $Ad(CH_2)_2$ (**b**), $AdCH(CH_3)CH_2$ (**c**), $Ad(CH_2)_3$ (**d**), $AdO(CH_2)_2$ (**e**), $AdO(CH_2)_4$ (**f**), $AdO(CH_2)_2O(CH_2)_2$ (**g**), 3-EtAdCH_2 (**h**), 3-EtAd$(CH_2)_2$ (**i**), 3-EtAd$O(CH_2)_2$ (**j**), 3-EtAd$O(CH_2)_4$ (**k**), 3-EtAd$O(CH_2)_2O(CH_2)_2$ (**l**).

EXPERIMENTAL

1-Adamantylmetanol **IVa** was obtained by the technique [12], 2-(1-adamantyl)ethanol **IVb** and 1-(1-adamantyl)ethanol **IVc** by the technique [13], 3-(1-adamantyl)propanol **IVg** by the technique [14] .

Compounds **IVh** and **IVi** were obtained by analogy with [12] through reduction of the appropriate adamantylcarboxylic acids esters with lithium aluminum hydride.

Synthesis of adamantyloxyalkanols **IVe–IVg** and **IVj–IVl** has been described in our earlier work [15].

Mass spectra of the synthesized compounds were obtained on a Finnigan Trace DCQ gas chromatograph–mass spectrometer using a BPX-5 30×0.32 capillary column of SGE Co at an energy of ionizing electrons 70 eV. The NMR spectra were recorded on a Brucker AM-300 instrument (300.13, 75.47, and 121.49 MHz for ^1H, ^{13}C, and ^{31}P resonance, respectively), solvent $CDCl_3$. Measurements were made without the use of a reference substance, referring frequency to the signal of the deuterated solvent.

Synthesis of esters of tosyloxymethylphosphonic acid (typical procedure). All operations were performed in an argon atmosphere. To 33.0 mmol of diethyl tosyloxymethylphosphonate in 215 ml of methylene chloride was added 186 mmol of trimethylbromosilane, and the reaction mixture was stirred at room temperature for 16 h. The solvent and the excess trimethylbromosilane were removed in a vacuum. The residue was dissolved in 200 ml of methylene chloride, cooled to 0°C, 0.25 ml of DMF was added to it and then 100 mmol of oxalyl chloride in 15 ml of methylene chloride was added dropwise with stirring, maintaining the temperature at 0–5°C. After adding all the oxalyl chloride, the reaction mixture was stirred at the same temperature for 6 h. The solvent was removed in a vacuum. The residue was dissolved in 60 ml of absolute diethyl ether and the solution was filtered. To the ether solution of dichlorphosphonate a solution of 69.3 mmol of triethylamine and 66.0 mmol of a compound **IVa–IVj** in 120 ml of ether was added dropwise with stirring at 0°C. The mixture was kept at 0°C for 12 h and then poured into 500 ml of cold water. The ether layer was separated, washed with saturated aqueous sodium hydrogen carbonate (2× 150 ml), and dried over sodium sulfate. The solvent was evaporated. The residue was chromatographed on silica gel with a diameter of grains 60–200 μm using as eluent petroleum ether (40–70°C)–ethyl acetate with gradual increase in polarity (0–20% of ethyl acetate). The product was recrystallized from 100 ml of a mixture of petroleum ether and ethyl acetate.

Di(1-adamantylmethyl) tosyloxymethylphosphonate (Va). Yield: 39.2%, mp 132°C. ^1H NMR spectrum, δ, ppm: 1.50 s (12H, CH_2, Ad), 1.65 q (12H, CH_2, Ad), 2.00 s (6H, CH, Ad), 2.45 s, (3H, CH_3, *p*-Tol), 3.60 m (4H, $AdCH_2O$), 4.20 d (2H, CH_2O, $^2J_{HP}$ 7.0 Hz), 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 21.71 s (CH_3, *p*-Tol), 27.98 s (CH, Ad), 33.93 d (C, Ad, $^3J_{CP}$ 6.0 Hz), 36.91 s (CH_2, Ad), 38.77 s (CH_2 , Ad), 60.99 d (CH_2O, 1 J_{CP} 169.8 Hz), 63.97 d ($AdCH_2$ O, $^2J_{CP}$ 32.5 Hz), 128.25 s (*m*-CH, *p*-Tol), 130.03 s (*o*-CH , *p*-Tol), 131.95 s (*i*-C, *p*-Tol), 145.47 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 16.05 ppm Mass spectrum, *m*/*z*: 563 $[M]^+$. Found, %: C 64.00; H 7.69. C 30 H 43 O 6 PS. Calculated, %: C 64.04, H 7.70.

Di[2-(1-adamantyl)ethyl] tosyloxymethylphosphonate (Vb). Yield: 35.0%, mp 67°C. ^1H NMR spectrum, δ, ppm: 1.45 t (4H, $AdCH_2CH_2O$), 1.49 s (12H, CH_2, Ad), 1.65 q (12H, CH_2, Ad), 1.95 s (6H , CH, Ad), 2.45 s (3H, CH_3, *p*-Tol), 4.12 m (4H, CH_2O), 4.19 d (2H, CH_2O, $^2J_{HP}$ 8.2 Hz), 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 21.77 s

(CH_3, *p*-Tol), 28.60 s (CH, Ad), 31.84 s (C, Ad), 37.01 s (CH_2, Ad), 42.54 s (CH_2, Ad), 44.28 d ($AdCH_2$·CH_2O, $^3J_{CP}$ 6.03 Hz), 61.20 d (CH_2O, 1 J_{CP} 167.5 Hz), 63.97 d ($AdCH_2CH_2O$, $^2J_{CP}$ 6.8 Hz), 128.32 s (*m*-CH, *p*-Tol), 130.08 s (*o*-CH, *p*-Tol), 131.97 s (*i*-C, *p*-Tol), 145.52 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 18.01 ppm. Mass spectrum, *m*/*z*: 591 $[M]^+$. Found, %: C 65.05; H 8.00. $C_{32}H_{47}O_6PS$. Calculated, %: C 65.06; H 8.02.

Di[1-(1-adamantyl)ethyl] tosyloxymethylphosphonate (Vc). Yield 35.0%, mp 165ºC. ^{1}H NMR spectrum, δ, ppm: 1.20 d (6H, CH_3, $^2J_{HH}$ 7.0 Hz), 1.40–5.2 m (30H, Ad), 2.45 s (CH_3, *p*-Tol), 4.12 m (4H, CH_2O, 2CHO), 7.35 d, 7.80 d (4H, *p*-Tol); ^{13}C NMR spectrum, δ_C, ppm: 15.46 d (CH_3, $^3J_{PC}$ 1.5 Hz), 21.73 s (CH_3, *p*-Tol), 28.16 s (CH_2, Ad), 36.68 s (C, Ad), 37.01 s (CH_2, Ad), 37.70 s (CH, Ad), 62.54 d (CH_2O, $^1J_{PC}$ 169.8 Hz), 83.12 d (CHO, $^2J_{PC}$ 7.54 Hz), 128.27 s (*m*-CH, *p*-Tol), 129.98 s (*o*-CH, *p*-Tol), 131.97 s (*i*-C, *p*-Tol), 145.38 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 14.16 ppm (first diastereomer), 14.63 ppm (second diastereomer). Mass spectrum, *m*/*z*: 591 $[M]^+$. Found, %: C 65.05; H 8.00. $C_{32}H_{47}O_6PS$. Calculated, %: C 65.06; H 8.02.

Di[3-(1-adamantyl)propyl] tosyloxymethylphosphonate (Vd). Yield 35.4%. ^{1}H NMR spectrum, δ, ppm: 1.05 m (4H, $AdCH_2CH_2CH_2O$), 1.45 t (4H, $AdCH_2$·CH_2CH_2O), 1.49–1.65 m (24H, CH_2, Ad), 1.95 s (6H, CH, Ad), 2.45 s (3H, CH_3, *p*-Tol), 4.00 m (4H, CH_2O), 4.20 d (2H, CH_2O, $^2J_{HP}$ 8.2 Hz) , 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 21.77 s (CH_3, *p*-Tol), 28.60 s (CH_2, Ad), 31.84 s (C, Ad), 37.01 s (CH_2, Ad), 42.54 s (CH, Ad), 44.28 d ($AdCH_2CH_2CH_2O$, $^3J_{PC}$ 6.0 Hz), 61.20 d (CH_2O, $^1J_{PC}$ 167.5 Hz), 63.97 d ($AdCH_2CH_2$ CH_2O, $^2J_{PC}$ 6.8 Hz), 128.32 s (*m*-CH, *p*-Tol), 130.08 s (*o*-CH, *p*-Tol), 131.97 s (*i*-C, *p*-Tol), 145.52 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 15.95 ppm. Mass spectrum, *m*/*z*: 619 $[M]^+$. Found, %: C 65.97; H 8.32. $C_{34}H_{51}O_6PS$. Calculated, %: C 65.99; H 8.31.

Di[2-(1-Adamantyloxy)ethyl] tosyloxymethylphosphonate (Ve). Yield 38.7%, mp 53–55ºC. ^{1}H NMR spectrum, δ, ppm: 1.52 q (12 H, Ad), 1.70 s (12H, Ad), 2.12 s (6H, Ad), 2.45 s (3H, CH_3, *p*-Tol), 3.58 m (4H, $AdOCH_2CH_2O$), 4.15 m (4H, $AdOCH_2CH_2O$), 4.30 d (2H, CH_2O, $^2J_{HP}$ 8.20 Hz), 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 21.66 s (CH_3, *p*-Tol), 30.47 s (CH_2, Ad), 36.36 s (CH_2, Ad), 41.39 s (CH, Ad), 59.11 d ($AdOCH_2CH_2O$, $^3J_{PC}$ 5.0 Hz), 61.74 d (CH_2O, $^1J_{PC}$ 169.8 Hz), 67.02 d ($AdOCH_2$·CH_2O, $^2J_{PC}$ 7.5 Hz), 72.62 s (CO, Ad), 128.26 s (*m*-CH, *p*-Tol), 129.92 s (*o*-CH, *p*-Tol), 132.01 s (*i*-C, *p*-Tol), 145.24 s (*p*-C, *p*-ol); ^{31}P NMR spectrum, δ_P 18.16 ppm. Mass spectrum, *m*/*z*: 623 $[M]^+$. Found, %: C 61.70; H 7.62. $C_{32}H_{47}O_8PS$. Calculated, %: C 61.72; H 7.61.

Di[4-(1-Adamantyloxy)butyl] tosyloxymethylphosphonate (Vf). Yield: 38.7%. ^{1}H NMR spectrum, δ, ppm: 1.55–2.18 m (30H, Ad, 8H, $4CH_2$), 2.45 s (3H, CH_3, *p*-Tol), 3.38 t [4H, $AdOCH_2(CH_2)_3O$, $^2J_{HH}$ 7.00 Hz], 4.10 m [4H, $AdO(CH_2)_3CH_2O$], 4.18 d (2H, CH_2O, $^2J_{HP}$ 8.20 Hz), 7.38 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 21.78 s (CH_3, *p*-Tol), 26.53 s ($AdOCH_2CH_2CH_2CH_2O$), 27.59 d ($AdOCH_2CH_2$·CH_2CH_2O, $^3J_{PC}$ 6.0 Hz), 30.57 s (CH_2, Ad), 36.58 s (CH_2, Ad), 41.67 s (CH, Ad), 58.92 s [$AdOCH_2(CH_2)_3O$], 61.26 d (CH_2O, $^1J_{CP}$ = 169.1 Hz), 67.36 d [$AdO(CH_2)_3$·CH_2O, $^2J_{PC}$ = 6.8 Hz], 71.94 s (CO, Ad), 128.32 s (*m*-CH, *p*-Tol), 130.10 s (*o*-CH, *p*-Tol), 131.84 s (*i*-C, *p*-Tol), 145.54 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 16.10 ppm. Mass spectrum, *m*/*z*: 679 $[M]^+$. Found, %: C 63.70; H 8.18. $C_{36}H_{55}O_8PS$. Calculated, %: C 63.69; H 8.17.

Di{2-[2-(1-adamantyloxy)ethyloxy]ethyl} tosyloxymethylphosphonate (Vg). Yield 36.4%. ^{1}H NMR spectrum, δ, ppm: 1.45–2.20 m (30H, Ad), 2.45 s (3H, CH_3, *p*-Tol), 3.55 m (8H, $4CH_2O$), 3.70 m (4H, $2CH_2O$), 4.20 m (4H, $2CH_2O$), 4.28 d (2H, CH_2O, $^2J_{HP}$ 8.2 Hz), 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 21.77 s (CH_3, *p*-Tol), 30.62 s (CH_2, Ad), 35.94 s (CH_2, Ad), 36.15 s (CH_2, Ad), 40.98 s (CH_2, Ad), 41.05 s (CH_2, Ad), 45.90 s (CH, Ad), 59.52 d (OCH_2CH_2O), 61.63 d (CH_2O, $^1J_{PC}$ 171.3 Hz), 66.30 d (OCH_2CH_2OP, $^2J_{PC}$ 6.79 Hz), 70.14 d (OCH_2CH_2OP, $^3J_{PC}$ 5.3 Hz), 71.28 s (OCH_2CH_2O), 72.71 s (CO, Ad), 128.33 s (*m*-CH, *p*-Tol), 130.04 s (*o*-CH, *p*-Tol), 132.03 s (*i*-C, *p*-Tol), 145.40 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 17.25 ppm. Mass spectrum, *m*/*z*: 711 $[M]^+$. Found, %: C 60.82; H 7.82. $C_{36}H_{55}O_{10}PS$. Calculated, %: C 60.83; H 7.80.

Di(3-ethyl-1-adamantylmethyl) tosyloxymethylphosphonate (Vh). Yield 39.2%. ^{1}H NMR spectrum, δ, ppm: 0.76 t (6H, CH_3CH_2Ad, $^2J_{HH}$ 7.0 Hz), 1.08 q (4H, CH_3CH_2Ad, $^2J_{HH}$ 7.00 Hz), 1.50 s (12H, CH_2, Ad), 1.65 q (12H, CH_2, Ad), 2.08 s (4H, CH, Ad), 2.45 s (3H, CH_3, *p*-Tol), 3.60 m (4H, $AdCH_2O$), 4.20 d (2H, CH_2O, $^2J_{HP}$ 7.00 Hz) 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 7.18 s (CH_3CH_2Ad), 21.7 s (CH_3, *p*-Tol), 27.98 s (CH_2, Ad), 33.93 d (C, Ad, $^3J_{PC}$ = 6.0 Hz), 35.85 s (CH_3CH_2Ad), 36.91 s (CH_2, Ad), 38.77 s (CH, Ad), 60.99 d (CH_2O, $^1J_{PC}$ 169.80 Hz), 63.97 d ($AdCH_2O$, $^2J_{PC}$ 32.50 Hz),

128.25 s (*m*-CH, *p*-Tol), 130.03 s (*o*-CH, *p*-Tol), 131.95 s (*i*-C, *p*-Tol), 145.47 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 16.05 ppm. Mass spectrum, *m*/*z*: 619 $[M]^+$. Found, %: C 65.98; H 8.30. $C_{34}H_{51}O_6PS$. Calculated, %: C 65.99; H 8.31.

Di[2-(3-ethyl-1-adamantyl)ethyl] tosyloxymethylphosphonate (Vi). Yield 32.6%. ^{1}H NMR spectrum, δ, ppm: 0.76 t (6H, CH_3CH_2Ad, $^2J_{HH}$ 7.0 Hz), 1.08 q (4H, CH_3CH_2Ad, $^2J_{HH}$ 7.00 Hz), 1.35 t (4H, $AdCH_2CH_2O$, $^2J_{HH}$ 7.0 Hz), 1.50 s (12H, CH_2, Ad), 1.65 q (12H, CH_2, Ad), 2.08 s (4H, CH, Ad), 2.45 s (3H, CH_3, *p*-Tol), 4.12 m (4H, $AdCH_2CH_2O$), 4.30 d (2H, CH_2O, $^2J_{HP}$ 8.2 Hz), 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 7.18 s (CH_3 CH_2 Ad), 21.71 s (CH_3, *p*-Tol), 27.98 s (CH_2, Ad), 33.93 d (C, Ad, $^3J_{CP}$ 6.00 Hz), 35.85 s (CH_3 CH_2 Ad), 36.91 s (CH_2, Ad), 38.77 s (CH, Ad), 60.99 d (CH_2O, $^1J_{PC}$ 169.8 Hz), 63.97 d ($AdCH_2O$, $^2J_{PC}$ = 32.5 Hz), 128.25 s (*m*-CH, *p*-Tol), 130.03 s (*o*-CH, *p*-Tol), 131.95 s (*i*-C, *p*-Tol), 145.47 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 16.08 ppm. Mass spectrum, *m*/*z*: 647 $[M]^+$. Found, %: C 66.80; H 8.59. $C_{36}H_{55}O_6PS$. Calculated, %: C 66.84; H 8.57.

Di[2-(3-ethyl-1-adamantyloxy)ethyl] tosyloxymethylphosphonate (Vj). Yield 36.4%. ^{1}H NMR spectrum, δ, ppm: 0.76 t (6H, CH_3CH_2Ad, $^2J_{HH}$ 7.0 Hz), 1.15 q (4H, CH_3CH_2Ad, $^2J_{HH}$ 7.0 Hz), 1.22–2.18 m (28H, Ad), 2.45 s (3H, CH_3, *p*-Tol), 3.58 m (4H, $AdOCH_2CH_2O$), 4.15 m (4H, $AdOCH_2CH_2O$), 4.30 d (2H, CH_2O, $^2J_{HP}$ 8.2 Hz), 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 7.18 s (CH_3CH_2 Ad), 21.73 s (CH_3, *p*-Tol), 30.57 s (CH_2, Ad), 35.85 s (CH_3 CH_2 Ad), 35.89 s (CH_2, Ad), 36.05 s (CH_2, Ad), 40.99 s (CH_2, Ad), 41.05 s (C–Et, Ad), 45.78 s (CH, Ad), 59.30 d ($AdOCH_2CH_2O$, $^3J_{PC}$ 5.3 Hz), 61.77 d (CH_2O, $^1J_{PC}$ = 170.6 Hz), 67.08 d ($AdOCH_2CH_2O$, $^2J_{PC}$ 6.8 Hz), 73.69 s (CO, Ad), 128.30 s (*m*-CH, *p*-Tol), 129.99 s (*o*-CH, *p*-Tol), 132.06 s (*i*-C, *p*-Tol), 145.31 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 17.18 ppm. Mass spectrum, *m*/*z*: 679 $[M]^+$. Found, %: C 63.68; H 8.19. $C_{36}H_{55}O_8PS$. Calculated, %: C 63.69; H 8.17.

Di[4-(3-ethyl-1-adamantyloxy)butyl] tosyloxymethylphosphonate (Vk). Yield 38.7%. ^{1}H NMR spectrum, δ, ppm: 0.76 t (6H, CH_3CH_2Ad, $^2J_{HH}$ 7.0 Hz), 1.15 q (4H, CH_3CH_2Ad, $^2J_{HH}$ 7.0 Hz), 1.22–2.18 m (28H, Ad, 8H, $4CH_2$), 2.45 s (3H, CH_3, *p*-Tol), 3.40 m [4H, $AdOCH_2(CH_2)_3O$], 4.10 m [4H, $AdO(CH_2)_3CH_2O$], 4.18 d (2H, CH_2O, $^2J_{HP}$ 8.2 Hz), 7.35 d, 7.8 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 7.19 s (CH_3CH_2Ad), 21.77 s (CH_3, *p*-Tol), 26.54 s ($AdOCH_2CH_2CH_2CH_2O$), 27.58 d ($AdOCH_2CH_2CH_2CH_2O$, $^3J_{PC}$ 5.28 Hz), 30.60 s (CH_2, Ad), 35.79 s (CH_3CH_2 Ad), 35.95 s (CH_2, Ad), 36.19 s (CH_2, Ad), 41.01 s (CH_2, Ad), 41.16 s (CH_2, Ad), 46.02 s (CH, Ad), 59.05 s [AdO $CH_2(CH_2)_3O$], 61.24 d (CH_2O, $^1J_{PC}$ 169.1 Hz), 67.34 d [$AdO(CH_2)_3CH_2O$, $^2J_{PC}$ 6.8 Hz], 72.91 s (CO, Ad), 128.30 s (*m*-CH, *p*-Tol), 130.08 s (*o*-CH, *p*-Tol), 131.82 s (*i*-C, *p*-Tol), 145.52 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 16.11 ppm. Mass spectrum, *m*/*z*: 735 $[M]^+$. Found, %: C 65.38; H 8.66. $C_{40}H_{63}O_8PS$. Calculated, %: C 65.37; H 8.64.

Di{2-[2-(3-ethyl-1-adamantyloxy)ethyloxy]ethyl} tosyloxymethyl-phosphonate (Vl). Yield 39.2%. ^{1}H NMR spectrum, δ, ppm: 0.76 t (6H, CH_3CH_2 d, $^2J_{HH}$ 7.0 Hz), 1.15 q (4H, CH_3CH_2Ad, $^2J_{HH}$ 7.0 Hz), 1.30–2.20 m (28H, Ad), 2.45 s (3H, CH_3, *p*-Tol), 3.55 m (8H, $4CH_2O$), 3.65 m (4H, $2CH_2O$), 4.20 m (4H, $2CH_2O$), 4.28 d (2H, CH_2O, $^2J_{HP}$ 8.2 Hz), 7.35 d, 7.80 d (4H, *p*-Tol, AB-system); ^{13}C NMR spectrum, δ_C, ppm: 7.20 s (CH_3 CH_2 Ad), 21.77 s (CH_3, *p*-Tol), 30.62 s (CH_2, Ad), 35.85 s (CH_3CH_2Ad), 35.94 s (CH_2, Ad), 36.15 s (CH_2, Ad), 40.98 s (CH_2, Ad), 41.05 s (CH_2, Ad), 45.90 s (CH, Ad), 59.52 d (OCH_2CH_2O), 61.63 d (CH_2O, $^1J_{PC}$ 171.3 Hz), 66.30 d (OCH_2CH_2OP, $^2J_{PC}$ 6.8 Hz), 70.14 d (OCH_2CH_2OP, $^3J_{PC}$ = 5.3 Hz), 71.28 s (OCH_2CH_2O), 72.71 s (CO, Ad), 128.33 s (*m*-CH, *p*-Tol), 130.04 s (*o*-CH, *p*-Tol), 132.03 s (*i*-C, *p*-Tol), 145.40 s (*p*-C, *p*-Tol); ^{31}P NMR spectrum, δ_P 17.30 ppm. Mass spectrum, *m*/*z*: 767 $[M]^+$. Found, %: C 62.63; H 8.30. $C_{40}H_{63}O_{10}PS$. Calculated, %: C 62.64; H 8.28.

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