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Synthesis and Antitubercular Activity of First Glucuronosyl Phosphates and Amidophosphates Containing Polymethylene Chains

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Abstract—Novel phosphorylated glycolipids based on glucuronic acid have been synthesized and shown to inhibit *M. Tuberculosis* H37Rv *in vitro* at a minimum inhibitory concentration of 12.5 μg/mL.

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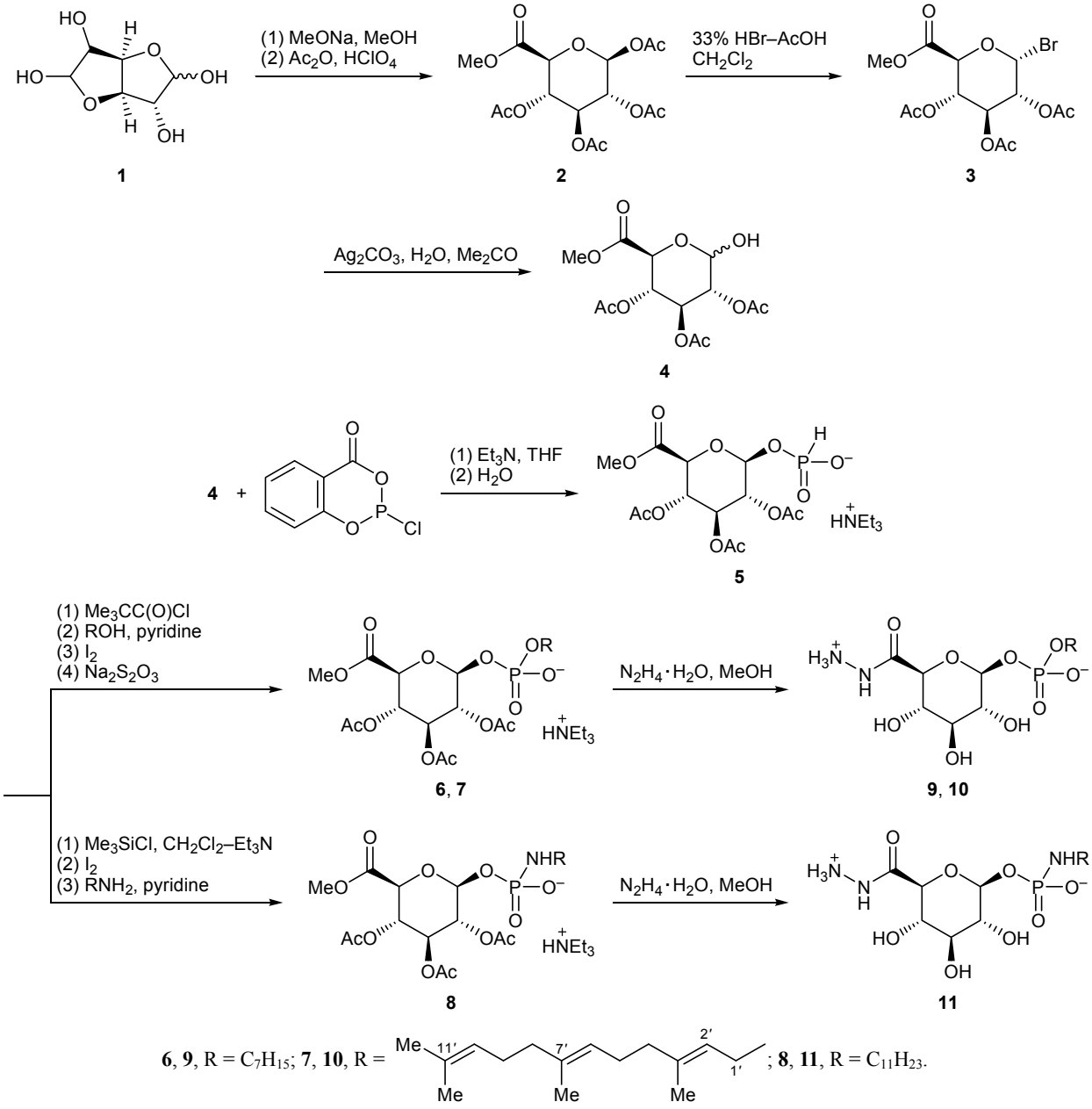
Increased interest of researchers in glucuronic acid conjugates, primarily in glucuronides, is determined by the fact that they are the most important products of second phase metabolism of xenobiotics, drugs, and hormones in humans [1, 2]. Glucuronides are just those compounds which are involved in transport from one part of organism to another and excretion therefrom. Glucuronidation not only ensures transformation of xenobiotics into readily soluble forms that are biologically friendly and conducive to excretion but also gives rise to new biologically active compounds [2–7]. Furthermore, in recent time glucuronides have been used as prodrugs for targeted delivery of, e.g., antibiotics or anticancer agents to damaged tissues where they are hydrolyzed by the action of β-D-glucuronidase to release the corresponding therapeutic agent [8–11]. Although glucuronidation of biomolecules in living matter is effected by uridine diphosphate glucuronic acid (UDP-glucuronosyltransferase) [2], phosphates derived from glucuronic acid itself have received little attention. On the other hand, numerous publications deal with phosphorylated glycolipids based on glucose [12, 13], glucosamine [13–15], galactose [13, 16, 17], mannose [18, 19], and arabinofuranose [20, 21], which have been synthesized with the goal of revealing efficient cell wall synthesis inhibitors active against pathogenic bacteria and mycobacteria, primarily against *Mycobacterium tuberculosis*.

Herein we report the synthesis of first glucuronosyl phosphates and amidophosphates containing polymethylene chains (phosphorylated glycolipids) (Scheme 1). As starting compound we used D-(+)-glucurono-3,6-lactone (**1**) which was converted to glucuronic acid methyl ester [22] by the action of sodium methoxide, and the subsequent acylation afforded methyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronate (**2**). In the ^{1}H NMR spectrum of **2**, the anomeric proton resonated at δ 5.77 ppm as a single doublet with a vicinal coupling constant ^3J of 7.7 Hz, indicating stereospecific opening of lactone **1** with formation of the β-anomer of **2**. The latter was converted to methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-β-D-glucopyranuronate (**3**) according to the procedure described in [23], and the hydrolysis of **3** in aqueous acetone in the presence of silver carbonate according to [24] gave methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate (**4**) which was isolated in quantitative yield as a mixture of α- and β-anomers (the ^{1}H NMR spectrum of **4** contained two sets of signals). The anomeric proton of the α-anomer of **4** resonated as a doublet at δ 5.48 ppm with a vicinal coupling constant of 2.9 Hz, whereas the corresponding signal of the β-anomer appeared as a doublet at δ 4.79 ppm (^3J 7.7 Hz). These findings were consistent with published data [23]. In the next stage, methyl ester **4** was subjected to phosphorylation at the anomeric hydroxy group according to a modified proce-

Scheme 1.



dure [25] with 2-chloro-2*H*,4*H*-1,3,2-benzodioxaphosphinin-4-one which was prepared in turn as described in [26]. Phosphonate **5** was thus isolated in 64% yield. Its ^{1}H NMR spectrum contained only one set of signals, and the anomeric proton resonated as a doublet of doublets at δ 5.75 ppm ($^3J_{1\text{-H},2\text{-H}}$ = 9.1, $^3J_{1\text{-H,P}}$ = 3.2 Hz). The PH proton signal was located at δ 6.84 ppm (d, $^1J_{PH}$ = 641.2 Hz). In the ^{31}P NMR spectrum of **5** we observed only one singlet at δ_P 0.9 ppm. These findings indicated formation of **5** as pure β-anomer.

In the final stage, compound **5** was converted to target glucuronosyl phosphates **6** and **7** and amidophosphate **8**. By analogy with the procedure described in [27], phosphonate **5** activated by pivaloyl chloride was brought into reactions with heptan-1-ol and 3,7,11-trimethyldodeca-2,6,10-trien-1-ol (farnesol). The resulting alkyl phosphonates were oxidized *in situ* with iodine, and subsequent treatment of the reaction mixtures with sodium thiosulfate afforded phosphates **6** and **7**, which were isolated by column chromatography in 47 and 83% yield, respectively. In the ^{31}P NMR spectra of **6** and **7**, the phosphorus nucleus resonated as a singlet at δ_P –3.08 and –3.83 ppm, respectively, whereas no PH signal was observed in

their ^{1}H NMR spectra. Heptyl phosphate **6** displayed in the ^{1}H NMR spectrum the anomeric proton signal as a single doublet of doublets at δ 5.75 ppm with vicinal coupling constants $J_{1\text{-H,2-H}}$ = 7.8 and $J_{1\text{-H,P}}$ = 3.3 Hz. The corresponding signal of **7** was a doublet of doublets at δ 5.72 ppm with similar coupling constants ($J_{1\text{-H,2-H}}$ = 7.8, $J_{1\text{-H,P}}$ = 3.3 Hz). The above data indicated β-orientation of the glycoside bond in both glucuronosides.

Following the procedure reported in [25], phosphonate **5** was converted to amidophosphate **8**. In this case, unlike the synthesis of phosphates **6** and **7**, phosphonate **5** was activated by treatment with chloro(trimethyl)silane, and the phosphorus oxidation with iodine preceded the reaction with undecylamine as nucleophile. Amidophosphate **8** was isolated in 37% yield by chromatography. Its ^{31}P NMR spectrum contained only one singlet at δ_P 5.83 ppm, and only one set of signals from the carbohydrate moiety was observed in the ^{1}H NMR spectrum of **8**. The anomeric proton resonated at δ 5.72 ppm ($J_{1\text{-H,2-H}}$ = 7.9, $J_{1\text{-H,P}}$ = 3.2 Hz), indicating β-orientation of the glycoside bond. The NH signal of **8** appeared in the ^{1}H NMR spectrum as a broadened singlet at δ 2.12 ppm.

The acetate protection was removed from the carbohydrate moieties of **6–8** by treatment with hydrazine hydrate according to [6]. This procedure also ensured simultaneous transformation of the ester group into more reactive carbohydrazide [6]. The reactions were carried out in methanol at room temperature for 24 h, the precipitate was filtered off, and excess hydrazine hydrate and the solvent were removed under reduced pressure. Hydrazides **9** and **10** were isolated in 75 and 67% yield, respectively. Their formation was confirmed by the IR spectra which contained absorption bands due to the amide group at 1667, 1632, 1625, 1536, 1515, 1404, 1380, and 1376 cm^{-1}; in addition, their ^{1}H NMR spectra lacked signals from acetate protecting groups at δ 1.96–1.99 ppm and methoxy protons at δ 3.64–3.66 ppm, whereas proton signals of the carbohydrate ring shifted upfield. The anomeric proton of **9** and **10** resonated at δ 5.49 and 5.51 ppm, respectively, as a doublet of doublets with the vicinal coupling constants $^3J_{1\text{-H,2-H}}$ = 7.0, $^3J_{1\text{-H,P}}$ = 3.41 Hz (**9**) and $^3J_{1\text{-H,2-H}}$ = 7.0, $^3J_{1\text{-H,P}}$ = 3.47 Hz (**10**) corresponding to β-orientation of the glycoside bonds in their molecules. The ^{1}H NMR spectra of **9** and **10** lacked signals assignable to triethylammonium counterion, which were present in the spectra of initial phosphates **6** and **7**. These data allowed us to presume that hydrazides **9** and **10** were isolated as inner salts (betaines; Scheme 1). The reaction of amidophosphate **8** with hydrazine hydrate under the same conditions was accompanied by hydrolysis, and we failed to isolate hydrazide **11** in the pure state. Nevertheless, the formation of **11** followed from the presence of the molecular ion peak with *m/z* 440.4 $[M]^-$ (calculated for $C_{17}H_{35}N_3O_8P^-$: 440.2) in the ESI mass spectrum of the reaction mixture.

According to published data, cell wall synthesis inhibitors active against *Micobacterium tuberculosis* were sought for among synthetic glycophospholipids based on mannose [18, 19] and arabinofuranose [20, 21]. Therefore, phosphates **6** and **7** and amidophosphate **8** were tested for antitubercular activity. Glycophospholipids **6–8** inhibited the growth of *Micobacterium tuberculosis* H37Rv *in vitro* for 10 days at a minimum inhibitory concentration (MIC) of 12.5 μg/mL. The observed activity can be regarded as moderate since the antitubercular drug isoniazid is active at 0.1 μg/mL under analogous conditions. However, the following is important. First, arabinofuranosides functionalized with a long-chain alkyl phosphate group, including those containing a farnesyl group as in phosphate **7**, did not inhibit *M. Tuberculosis* at MIC values of up to 100 μg/mL [21]. Second, the antitubercular activity of glucuronosides **6–8** was similar to the activity of pyrazinamide (MIC 12.5 μg/mL) [28]. The fact that phosphates **6** and **7** possessing no nitrogen atoms showed antitubercular activity at a level comparable to the nitrogen-containing compound suggests a different mechanism (target) of their action. Obviously, this problem requires a separate study.

EXPERIMENTAL

The IR spectra (400–4000 cm^{-1}) were recorded on a Bruker Vector 22 spectrometer (Germany) with Fourier transform from samples prepared as thin films. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured on Bruker Avance-400 and Avance-600 spectrometers (Germany). The mass spectra were obtained on a Bruker Daltonik AmazonX mass spectrometer (Bremen, Germany); negative electrospray ionization, a.m.u. range 100–1500; capillary voltage 4500 V; drying gas nitrogen, temperature 200°C, flow rate 8 L/min; samples were dissolved in chloroform or methanol to a concentration of 10^{-5} M. The data were processed using DataAnalysis 4.0 (Bruker Daltonik). The optical rotations were measured on a Perkin Elmer 341 polarimeter (USA). The progress of reactions and the purity of the isolated compounds were monitored

by TLC on Sorbfil PTSKh-AF-A plates (Krasnodar, Russia); spots were detected by treatment with 5% H_2SO_4 or a solution of $H_3PO_4 \cdot 12\,MoO_3 \cdot H_2O$, followed by heating. The products were isolated by column chromatography on silica gel (0.06–0.20 mm; Acros Organics).

Compound **2** was synthesized according to the procedure reported in [22]; mp 177°C (from MeOH), $[\alpha]_D^{20}$ = 8.1° (*c* = 1.1, $CHCl_3$); published data: mp 176°C [22]; mp 177–178°C (from EtOH), $[\alpha]_D^{25}$ = 7.4 (*c* = 2.0, $CHCl_3$) [29]. Compound **3** was prepared according to [23]; mp 105–106°C (from EtOAc); published data [29]: mp 106–107°C (from EtOH). Compound **4** was synthesized as described in [24]; mp 83°C; published data [24]: mp 81°C.

Triethylammonium (2*S*,3*R*,4*S*,5*S*,6*S*)-3,4,5-tris-(acetyloxy)-6-(methoxycarbonyl)oxan-2-yl phosphonate (5). Compound **4**, 1 g (3.0 mmol), was dissolved in 8 mL of anhydrous THF, 3 mL of anhydrous triethylamine and 0.67 g (3.3 mmol) of 2-chloro-2*H*,4*H*-1,3,2-benzodioxaphosphinin-4-one were added, the mixture was stirred for 24 h at room temperature, 3 mL of water was added, and the mixture was left to stand for 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using methylene chloride–methanol–triethylamine (50:1:0.5 to 50:2:0.5) as eluent. Yield 0.95 g (64%), light yellow oily material, $[\alpha]_D^{20}$ = 33.5° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.30 t (9H, $CH_2C\mathbf{H}_3$, *J* = 7.4 Hz), 1.93 s (3H, CH_3CO), 1.94 s (3H, CH_3CO), 1.96 s (3H, CH_3CO), 3.02 q (6H, $C\mathbf{H}_2CH_3$, *J* = 7.5 Hz), 3.63 s (3H, CH_3O), 4.55 d (1H, 5-H, *J* = 10.2 Hz), 4.89–4.94 m (1H, 2-H), 5.09 t (1H, 4-H, *J* = 9.6 Hz), 5.52 t (1H, 3-H, *J* = 9.7 Hz), 5.77 d.d (1H, 1-H, *J* = 9.1, 3.4 Hz), 6.87 d (1H, PH, *J* = 640.4 Hz). ^{13}C NMR spectrum (100.6 MHz, $CDCl_3$), δ_C, ppm: 8.41 s (3C, $CH_2\mathbf{C}H_3$), 20.27 s ($\mathbf{C}H_3CO$), 20.43 s (2C, $\mathbf{C}H_3CO$), 45.64 s (3C, $\mathbf{C}H_2CH_3$), 52.48 s (CH_3O), 68.89 s (C^3), 69.08 s (C^5), 69.42 s (C^4), 70.07 d (C^2, J_{CP} = 5.5 Hz), 90.79 d (C^1, J_{CP} = 4.8 Hz), 167.92 s ($\mathbf{C}OOCH_3$), 169.37 s ($CH_3\mathbf{C}O$), 169.66 s (2C, $CH_3\mathbf{C}O$). ^{31}P NMR spectrum (400 MHz, $CDCl_3$): δ_P 0.9 ppm, s. Mass spectrum: *m*/*z* 397.1 (I_{rel} 100%) $[M]^-$. $C_{13}H_{18}O_{12}P^-$. Calculated: *M* 397.1.

Phosphates 6 and 7 (*general procedure*). A solution of 0.5 g (1.0 mmol) of phosphonate **5** and 2.0 mmol of heptan-1-ol or farnesol in 15 mL of anhydrous pyridine was cooled to –15°C, and a solution of 408 μL (3.3 mmol) of pivaloyl chloride in 3 mL of pyridine was added. The mixture was stirred for 1.5 h, 1 mL of water was added, the mixture was allowed to warm up to room temperature, and 254 mg (1.0 mmol) of iodine was added. The mixture was stirred for 1 h, and a 1 M solution of $Na_2S_2O_3$ was added until the mixture became colorless. The solvent was removed under reduced pressure, and the product was isolated by silica gel column chromatography (CH_2Cl_2–MeOH–Et_3N, 95:5:1).

Triethylammonium heptyl (2*S*,3*R*,4*S*,5*S*,6*S*)-3,4,5-tris(acetyloxy)-6-(methoxycarbonyl)oxan-2-yl phosphate (6). Yield 0.29 g (47%), yellow oily material, $[\alpha]_D^{20}$ = 50.0° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 0.82 t (3H, $C^7\mathbf{H}_3$, *J* = 6.8 Hz), 1.18–1.28 m (8H, CH_2), 1.31 t (9H, $NCH_2C\mathbf{H}_3$, *J* = 7.3 Hz), 1.49–1.61 m (2H, $OCH_2C\mathbf{H}_2$), 1.96 s (3H, CH_3CO), 1.97 s (3H, CH_3CO), 1.99 s (3H, CH_3CO), 3.08 q (6H, NCH_2, *J* = 7.3 Hz), 3.66 s (3H, CH_3O), 3.82 q (2H, OCH_2, *J* = 6.7 Hz), 4.57 d (1H, 5-H, *J* = 10.2 Hz), 4.84–4.91 m (1H, 2-H), 5.11 t (1H, 4-H, *J* = 9.8 Hz), 5.53 t (1H, 3-H, *J* = 9.8 Hz), 5.74 d.d (1H, 1-H, *J* = 7.8, 3.3 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 8.56 s (3C, $NCH_2\mathbf{C}H_3$), 13.92 s (C^7H_3), 20.37 s ($\mathbf{C}H_3CO$), 20.53 s ($\mathbf{C}H_3CO$), 20.56 s ($\mathbf{C}H_3CO$); 22.44 s, 25.58 s, 28.90 s, 31.67 s (2C, CH_2); 30.58 d ($OCH_2\mathbf{C}H_2$, J_{CP} = 7.7 Hz), 45.91 s (3C, $N\mathbf{C}H_2CH_3$), 52.54 s (CH_3O), 66.07 d (OCH_2, J_{CP} = 6.2 Hz), 68.79 s (C^3), 69.08 s (C^5), 69.55 s (C^4), 70.32 d (C^2, J_{CP} = 7.3 Hz), 91.69 d (C^1, J_{CP} = 5.1 Hz), 168.07 s ($\mathbf{C}OOCH_3$); 169.47 s, 169.71 s, 169.88 s ($CH_3\mathbf{C}O$). ^{31}P NMR spectrum (400 MHz, $CDCl_3$): δ_P –3.1 ppm, s. Mass spectrum, *m*/*z* (I_{rel}, %): 511.3 (100) $[M]^-$. $C_{20}H_{32}O_{13}P^-$. Calculated: *M* 511.2.

Triethylammonium 3,7,11-trimethyldodeca-2,6,10-trien-1-yl (2*S*,3*R*,4*S*,5*S*,6*S*)-3,4,5-tris(acetyloxy)-6-(methoxycarbonyl)oxan-2-yl phosphate (7). Yield 0.6 g (83%), yellow oily material, $[\alpha]_D^{20}$ = 19.2° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.37 t (9H, $NCH_2C\mathbf{H}_3$, *J* = 7.4 Hz), 1.52 s and 1.60 s (12H, 3′-CH_3, 7′-CH_3, 11′-CH_3), 1.85–2.04 m (17H, CH_2, CH_3CO), 3.14 q (6H, $NC\mathbf{H}_2CH_3$, *J* = 7.4 Hz), 3.64 s (3H, CH_3O), 4.33 t (2H, OCH_2, *J* = 6.5 Hz), 4.50 d (1H, 5-H, *J* = 10.1 Hz), 4.79–4.84 m (1H, 2-H), 4.97–5.05 m (2H, 6′-H, 10′-H), 5.08 t (1H, 4-H, *J* = 9.9 Hz), 5.25–5.29 m (1H, 3-H), 5.49 t (2H, OCH_2, *J* = 9.8 Hz), 5.72 d.d (1H, 1-H, *J* = 7.8, 3.2 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 8.66 s (3C, $NCH_2\mathbf{C}H_3$); 15.78 s, 16.18 s, 17.48 s (3′-CH_3, 7′-CH_3, 11′-CH_3); 20.32 s, 20.47 s, 20.51 s ($\mathbf{C}H_3CO$); 23.17 s, 25.48 s, 25.52 s, 25.97 s, 26.25 s, 26.36 s, 26.53 s, 27.01 s, 31.76 s, 39.37 s, 39.50 s, 39.64 s (CH_2); 46.28 s (3C,

N**C**H_2CH_3), 52.62 s (CH_3O), 62.65 s (OCH_2), 68.74 s (C^3), 68.83 s (C^5), 69.34 s (C^4), 70.27 s (C^2), 91.66 d (C^1, J_{CP} = 5.1 Hz); 123.50 s, 124.06 s, 124.26 s, 131.12 s, 131.34 s, 135.21 s, 135.32 s, 140.00 s, 140.17 s (CH=C); 167.86 s (**C**$OOCH_3$); 169.33 s, 169.64 s, 169.78 s (CH_3**C**O). ^{31}P NMR spectrum (400 MHz, $CDCl_3$): δ_P –3.8 ppm, s. Mass spectrum (MALDI): *m*/*z* 616.70 (I_{rel} 100%) $[M]^-$. $C_{28}H_{42}O_{13}P^-$. Calculated: *M* 617.24.

Triethylammonium (2*S*,3*R*,4*S*,5*S*,6*S*)-3,4,5-tris-(acetyloxy)-6-(methoxycarbonyl)oxan-2-yl *N*-undecylphosphoramidate (8). A solution of 0.5 g (1.0 mmol) of phosphonate **5** in 10 mL of anhydrous methylene chloride was cooled to 0°C, and 1 mL of anhydrous triethylamine and 0.38 mL (3.0 mmol) of chloro(trimethyl)silane were added. The mixture was stirred for 30 min, 0.25 g (1.0 mmol) of crystalline iodine was added, the mixture was stirred for 20 min, 0.24 mL (3.0 mmol) of anhydrous pyridine was added, the mixture was stirred for 5 min, and 0.22 g (1.3 mmol) of undecylamine was added. The mixture was allowed to warm up to room temperature and stirred for 24 h, the solvent was removed under reduced pressure, the residue was dissolved in methylene chloride (50 mL), and the solution was washed with water (50 mL) and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography using methylene chloride–methanol (10 : 1 to 5 : 1 with addition of 1 vol % of triethylamine) as eluent. Yield 0.25 g (37%), yellow oily material, $[\alpha]_D^{20}$ = 42.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm: 0.83 t (3H, $C^{11'}H_3$, *J* = 6.8 Hz), 1.16–1.24 m (16H, CH_2), 1.29 t (9H, NCH_2C**H**$_3$, *J* = 7.4 Hz), 1.36–1.44 m (2H, $NHCH_2C$**H**$_2$), 1.96 s (3H, CH_3CO), 1.97 s (3H, CH_3CO), 1.99 s (3H, CH_3CO), 2.12 br.s (1H, NH), 2.80 q (2H, NHC**H**$_2$, *J* = 7.6 Hz), 3.04 q (6H, N**C**H_2CH_3, *J* = 7.4 Hz), 3.66 s (3H, CH_3O), 4.61 d (1H, 5-H, *J* = 10.5 Hz), 4.86–4.91 m (1H, 2-H), 5.12 t (1H, 4-H, *J* = 9.8 Hz), 5.55 t (1H, 3-H, *J* = 9.7 Hz), 5.72 d.d (1H, 1-H, *J* = 7.9, 3.2 Hz). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ_C, ppm: 8.42 s (3C, NCH_2**C**H_3), 13.96 s ($C^{11'}$); 20.39 s, 20.57 s, 20.60 s (**C**H_3CO); 22.54 s, 26.86 s, 29.21 s, 29.37 s, 29.51 s, 29.52 s, 29.57 s, 31.78 s (CH_2); 32.09 d ($NHCH_2$**C**H_2, J_{CP} = 7.2 Hz), 41.96 s ($NHCH_2$), 45.47 s (3C, N**C**H_2CH_3), 52.49 s (CH_3O), 68.67 s (C^3), 69.44 s (C^5), 69.74 s (C^4), 70.51 d (C^2, J_{CP} = 7.2 Hz), 91.27 d (C^1, J_{CP} = 5.3 Hz), 168.37 s (**C**$OOCH_3$); 169.52 s, 169.85 s, 169.90 s (CH_3**C**O). ^{31}P NMR spectrum (400 MHz, $CDCl_3$): δ_P 5.8 ppm, s. Mass spectrum: *m*/*z* 566.4 (I_{rel} 100%) $[M]^-$. $C_{24}H_{41}NO_{12}P^-$. Calculated: *M* 566.2.

Hydrazides 9 and 10 (*general procedure*). Phosphate **6** or **7**, 0.2 mmol, was dissolved in 7 mL of methanol, 6.0 mmol of hydrazine hydrate was added, and the mixture was stirred for 24 h at room temperature. The precipitate was filtered off, and the solvent and excess hydrazine hydrate were removed under reduced pressure.

(2*S*,3*R*,4*S*,5*S*,6*S*)-6-(Diazan-2-ium-1-carbonyl)-3,4,5-trihydroxyoxan-2-yl heptyl phosphate (9). Yield 0.13 g (75%), light yellow oily material. IR spectrum, ν, cm^{-1}: 3292 br (NH_2, OH), 1667, 1625, 1536, 1376 (HNC=O), 1219, 1073 (P=O). ^{1}H NMR spectrum (600 MHz, CD_3OD), δ, ppm: 0.89 t (3H, $C^{7'}H_3$, *J* = 6.8 Hz), 1.24–1.41 m (8H, CH_2), 1.56–1.65 m (2H, OCH_2C**H**$_2$), 3.45–3.50 m (1H, 2-H), 3.54 t (1H, 3-H, *J* = 9.8 Hz), 3.71 t (1H, 4-H, *J* = 9.3 Hz), 3.89 q (2H, OCH_2, *J* = 6.5 Hz), 4.20 d (1H, 5-H, *J* = 9.9 Hz), 5.49 d.d (1H, 1-H, *J* = 7.0, 3.41 Hz), 7.88 s (1H, NH). ^{31}P NMR spectrum (400 MHz, CD_3OD): δ_P –1.2 ppm, s. Mass spectrum: *m*/*z* 385.2 (I_{rel} 100%) $[M]^-$. $C_{13}H_{26}N_2O_9P^-$. Calculated: *M* 385.1.

(2*S*,3*R*,4*S*,5*S*,6*S*)-6-(Diazan-2-ium-1-carbonyl)-3,4,5-trihydroxyoxan-2-yl 3,7,11-trimethyldodeca-2,6,10-trien-1-yl phosphate (10). Yield 0.11 g (67%), light yellow oily material. IR spectrum, ν, cm^{-1}: 3443 br (NH_2, OH), 1632, 1515, 1404, 1380 [C(O)NH], 1219, 1096 (P=O). ^{1}H NMR spectrum (400 MHz, CD_3OD), δ, ppm: 1.57–1.61 m (6H, CH_3), 1.64–1.68 m (6H, CH_3), 1.92–2.12 m (8H, CH_2), 3.48–3.53 m (1H, 2-H), 3.56 t (1H, 3-H, *J* = 9.5 Hz), 3.72 t (1H, 4-H, *J* = 9.35 Hz), 4.21 d (1H, 5-H, *J* = 9.9 Hz), 4.46 t (2H, OCH_2, *J* = 6.5 Hz), 5.05–5.14 m (2H, 6′-H, 10′-H), 5.36–5.41 m (1H, 2′-H), 5.51 d.d (1H, 1-H, *J* = 7.0, 3.47 Hz); 8.10–8.16 m, 8.58–8.63 m, 8.93–8.97 m (3H, NH). ^{31}P NMR spectrum (400 MHz, CD_3OD): δ_P –1.0 ppm, s. Mass spectrum, *m*/*z* 491.3 (I_{rel} 100%): $[M]^-$. $C_{21}H_{36}N_2O_9P^-$. Calculated: *M* 491.2.

The antiturbercular activity of compounds **6**–**8** was assayed by the vertical diffusion method on a *Novaya* solid nutrition medium inoculated with *Mycobacterium tuberculosis* H37Rv. Nutrition medium was placed into test-tubes in 5-mL portions, inoculated with 0.1 mL of a suspension of different mycobacteria strains diluted to a turbidity value of 10 GKI units, and incubated for 24 h at a constant temperature to grow *Mycobacterium tuberculosis* (MBT). After 24 h, the test tubes were placed vertically, and 0.3 mL of a solution of **6**–**8** in aqueous ethanol with a concentration of 12.5, 6.2, 3.1, 1.5, 0.7, 0.35, and 0.1 μg/mL was added to each test tube. The test tubes were then placed in a thermostat

and were incubated under sterile conditions at 37°C for 10 days. The growth of MBT was evaluated according to the standard procedure. An MBT growth inhibition zone of larger than 10 mm indicated tuberculostatic activity. The size of the inhibition zone (mm) is proportional to the tuberculostatic activity. An inhibition zone of 100 mm and larger was considered as complete inhibition of MBT growth. Isoniazid was used as control drug.

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