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Synthesis of new asymmetrical frame phosphonates based on Sesamol

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Abstract: A method for synthesizing new asymmetrical frame phosphonates is proposed, based on the reaction of dichlorophosphonate with an equimolar mixture of two different phenols in toluene, in the presence of trifluoroacetic acid. The reaction of sesamol with resorcinol (or 2-methylresorcinol or pyrogallol) and 2-ethoxyvinyl dichlorophosphonate yielded an unexpected result—a crystalline product with good solubility in dimethyl sulfoxide, representing an inseparable mixture of asymmetrical and symmetrical frame phosphonates based on sesamol. Due to their similar chromatographic mobility, it was not possible to isolate the individual compounds. A similar outcome was observed when 2-ethoxyvinyl dichlorophosphonate reacted with a mixture of sesamol and 2,4-dimethylresorcinol: a mixture of symmetrical and asymmetrical frame phosphonates was formed, with the symmetrical product derived from 2,4-dimethylresorcinol. This synthetic outcome can be explained by the higher reactivity of 2,4-dimethylresorcinol compared to sesamol. Ultimately, in both reactions, the symmetrical frame phosphonate based on sesamol was formed and subsequently isolated in its pure form. The validity of the obtained results is supported by modern physicochemical analytical methods, including mass spectrometry (MALDI-TOF), IR spectroscopy, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, elemental analysis, and X-ray crystallography.

Keywords: *2-ethoxyvinyl dichlorophosphonate, Asymmetrical frame phosphonates, Equimolar mixture, Phenols, Resorcinol, Sesamol.*

1. Introduction

The chemistry of three-dimensional, spatially organized structures has been developing particularly actively in recent years, largely due to the creation of new efficient and selective heterogeneous and homogeneous catalysts. These catalysts contribute to the development of energy-saving technologies and the advancement of "green" chemistry [1-3]. Phosphorus-containing cage compounds with endocyclic phosphorus-carbon bonds exhibit unusual reactivity and physicochemical properties, making them promising both for fundamental research and practical applications [4-6]. A prominent example of such phosphorus-containing cage compounds is derivatives of 7-phospha-1,3,5-triazaadamantane, which are widely used as ligands in metal complexes involved in various homogeneous catalytic reactions. Moreover, their areneruthenium complexes (RAPTA-C, RAPTA-B) exhibit pronounced antitumor properties with low overall toxicity and are considered promising antimetastatic agents [7, 8].

Previously, we developed a simple new "one-pot" synthesis method for a class of phosphorus-containing cage compounds with two endocyclic phosphorus-oxygen bonds and one endocyclic phosphorus-carbon bond, previously unknown in the literature. This method is based on a novel cascade reaction of 2-ethoxyvinyl dichlorophosphonate with various phenols. It is worth noting that the proposed approach allows only the synthesis of symmetrical cage compounds [9, 10]. Asymmetrical cage phosphonates — a new class of phosphorus-organic compounds – were obtained by us relatively

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recently as a result of a new reaction of oxaphosphinines with various phenols followed by their cyclization [11, 12].

Expanding on these studies, the present article introduces a new method for the synthesis of asymmetrical cage phosphonates based on a naturally occurring phenol, namely sesamol (3,4-methylenedioxyphenol). Due to its pharmacological activity, sesamol is a component of various highly effective biologically active substances [13-15].

2. Material and Methods

NMR spectra were recorded using high-resolution pulsed NMR spectrometers: Bruker Avance-400 (^1H – 399.93 MHz; ^13C – 100.57 MHz; ^31P – 161.90 MHz), Bruker Avance-500 (^1H – 500.13 MHz; ^13C – 125.76 MHz; ^31P – 202.46 MHz), and Bruker Avance-600 (^1H – 600.13 MHz; ^13C – 150.92 MHz; ^31P – 242.94 MHz), in d6-DMSO (at 45 °C) or $CDCl_3$ (at 25 °C) solvents. Chemical shifts for protons and carbon atoms were referenced to the residual signals of the corresponding solvents (d6-DMSO or $CDCl_3$), with the δ scale calibrated against TMS used as the internal standard. Chemical shifts for phosphorus (^31P) were measured relative to an external standard — a solution of H_3PO_4. The following parameters were used for two-dimensional correlation NMR experiments: $^1H–^{13}C$ HSQC – optimized for ^1JCH = 165 Hz; $^1H–^{13}C$ HMBC – for ^1JCH = 165 Hz and ^3JCH = 8 Hz; $^1H–^{31}P$ HMBC – for J = 8 Hz.

IR spectra were recorded using a Bruker Vector-22 FT-IR spectrometer in the range of 400–4000 cm^{-1}. The samples were prepared as KBr pellets.

Mass spectra were obtained using matrix-assisted laser desorption/ionization (MALDI) on an UltraFlex III TOF/TOF mass spectrometer (Bruker Daltonics). Measurements were conducted in positive ion mode (detection of positively charged ions) in the m/z range of 100–5000, using a Nd:YAG laser (λ = 355 nm). Plastic and metal substrates were used as targets. 2,5-Dihydroxybenzoic acid (DHB) and para-nitroaniline (p-NA) served as matrices.

Elemental analysis (C, H, N content) was performed using a high-temperature dual-reactor analyzer Carlo-Erba EA 1108. Halogens were determined using the Schöninger method, and phosphorus was quantitatively determined via pyrolysis in an oxygen stream.

X-ray structural analysis of the compounds was performed using equipment from the Shared Research Center for Physical Methods of Investigating Substances and Materials at the N. S. Kurnakov Institute of General and Inorganic Chemistry of the Russian Academy of Sciences. Structure determination was carried out using the direct method with the SIR program [16] and the refined structural model was obtained using the SHELXL–97 program [17] in both isotropic and anisotropic approximations. Calculations were carried out using the WinGX [18] and APEX2[19] software packages. Hydrogen atom coordinates were calculated based on stereochemical considerations and refined using the "riding" model. Intermolecular interactions were analyzed using the PLATON program [20].

General Method for Synthesizing Cage Phosphonates 4a–c and 5. A mixture of 0.73 g (5.3 mmol) sesamol, 0.58 g (5.3 mmol) resorcinol (or 0.66 g (5.3 mmol) 2-methylresorcinol, 0.67 g (5.3 mmol) pyrogallol, or 0.66 g (5.3 mmol) 2,4-dimethylresorcinol) and 0.6 g (5.3 mmol) trifluoroacetic acid in 30 mL of boiling toluene was treated dropwise with 1 g (5.3 mmol) of 2-ethoxyvinyl dichlorophosphonate in 5 mL of toluene. The reaction mixture was refluxed for 12 hours. The resulting precipitate was filtered, washed initially with distilled water, then with acetone, and dried under vacuum to constant weight, yielding a mixture of cage phosphonates. The filtrate was evaporated under vacuum, and the resulting solid was washed with diethyl ether, filtered, and dried under vacuum to constant weight. This gave 0.97–1.05 g (53–57%) of the symmetrical cage phosphonate 5 based on sesamol.

3-Hydroxy-13H-6,13-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-d]benzo[g][1,3,2]dioxaphosphocin 6-oxide (4a) and 13H-6,13-methano[1,3] dioxolo[4',5':4,5] benzo[1,2-d][1,3]dioxolo[4',5':4,5]benzo[1,2-g][1,3,2]dioxaphosphocin 6-oxide (5)

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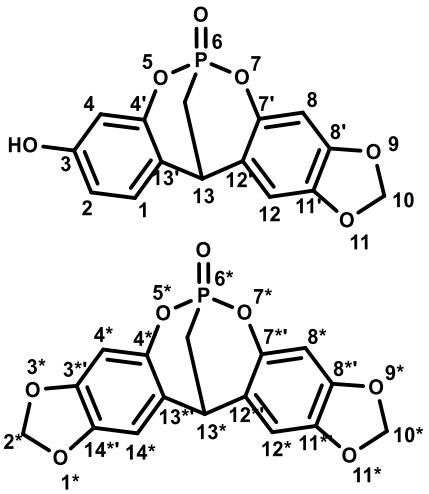


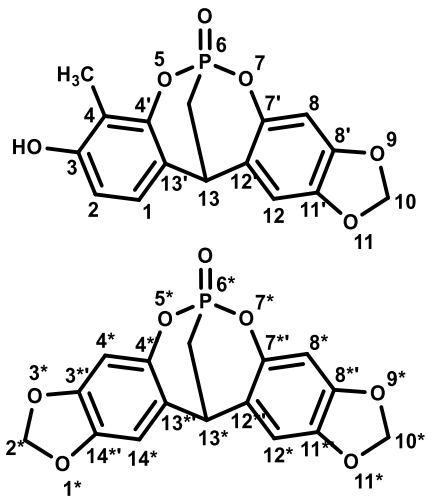
A fine white powder, m.p. >300 °C. ^{31}P NMR (242.94 MHz, d_6-DMSO, δ, ppm): 13.7 and 13.9. ^{1}H NMR (600.13 MHz, d_6-DMSO, δ, ppm, *J*/Hz): 2.63 (dd., 4H, $^{2}J_{PH}$=14.4, $^{3}J_{HH}$=3.7, CH_2P), 4.58 (dt, 2H, $^{3}J_{HH}$=3.8, $^{3}J_{PH}$=35.8, $PCH_2C\underline{H}$), 5.93 (c, 1H, H-10), 5.94 (s, 2H, H-2*), 6.00 (s, 1H, H-10), 6.01 (s, 2H, H-10*), 6.40 (d, 1H, $^{4}J_{HH}$=2.3, H-4), 6.48 (dd., 1H, $^{3}J_{HH}$=8.4, $^{4}J_{HH}$=2.3, H-2), 6.72 (s, 1H, H-8), 6.73 (s, 2H, H-4*,8*), 7.07 (s, 1H, H-12), 7.13 (s, 2H, H-12*,14*), 7.29 (d, 1H, $^{3}J_{HH}$=8.4, H-1), 9.69 (s, 1H, OH). IR spectrum (KBr pellet, ν/cm^{-1}): 1242 (P=O), 1624 (C=C_{Ar}), 3237 (OH). Mass spectrum (MALDI-TOF, *m/z*): 341 [M+Na]$^+$.

13*H*-6,13-Methano[1,3]dioxolo[4',5':4,5]benzo[1,2-d][1,3]dioxolo[4',5':4,5]benzo[1,2-g][1,3,2]dioxaphosphocin 6-oxide (*5*)

Yield: 0.97–1.05 g (53–57%), white powder, m.p. > 300 °C.

^{31}P NMR (242.94 MHz, d_6-DMSO, δ, ppm): 13.8. ^{1}H NMR (600.13 MHz, d_6- DMSO, δ, ppm, *J*/Hz): 2.64 (dd, 2H, $^{2}J_{PH}$=16.2, $^{3}J_{HH}$=3.8, CH_2P), 4.55 (dt, 1H, $^{3}J_{HH}$=3.8, $^{3}J_{PH}$=35.1, $PCH_2C\underline{H}$), 5.94 (s, 2H, H-2), 6.01 (s, 2H, H-10), 6.73 (s, 2H, H-4,8), 7.13 (s, 2H, H-12,14). ^{13}C NMR (150.92 MHz, d_6- DMSO, δ, ppm, *J*/Hz): 19.8 (d, $^{1}J_{PC}$=111.1, PCH_2), 39.7 (d, $^{2}J_{PC}$=20.8, $PCH_2\underline{C}H$), 100.8 (d, $^{3}J_{PC}$=8.3, C-4,8), 102.2 (s, C-2,10), 107.8 (s, C-12,14) 120.8 (d, $^{2}J_{PC}$=10.9, C-4',7'), 144.0 (s, C-3',8'), 145.3 (d, $^{3}J_{PC}$=7.6, C-12',13'), 147.5 (s, C-11',14'). IR Spectrum (KBr pellet, ν/cm^{-1}): 1292 (P=O), 1634 (C=C_{Ar}). Found (%): C 55.30, H 3,07, P 8,95. $C_{16}H_{11}O_7P$. Calculated (%):C 55.49, H 3.17, P 8.97. Mass Spectrum (MALDI-TOF, *m/z*): 346 [M]$^+$, 347 [M+H]$^+$, 369 [M+Na]$^+$, 385 [M+K]$^+$.

3-Hydroxy-4-methyl-13H-6,13-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-d]benzo[g][1,3,2]dioxaphosphocin 6-oxide (4b) and 13H-6,13-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-d][1,3]dioxolo[4',5':4,5]benzo[1,2-g][1,3,2]dioxaphosphocin 6-oxide (*5*)



White powder, m.p. > 300 °C. ^{31}P NMR (161.90 MHz, d_6-DMSO, δ, м.д.): 13.6 and 13.8. ^{1}H NMR (399.93 MHz, d_6-DMSO, δ, ppm, *J*/Hz): 1.98 (s, 3H, CH_3), 2.60 (m, 4H, CH_2P), 4.56 (dt, 2H, $^{3}J_{HH}$=5.5, $^{3}J_{PH}$=38.2, $PCH_2C\underline{H}$), 5.92 (s, 1H, H-10), 5.94 (s, 2H, H-2*), 6.00 (s, 1H, H-10), 6.01 (s, 2H, H-10*), 6.51 (dd, 1H, $^{3}J_{HH}$=8.4, $^{4}J_{HH}$=5.9, H-2), 6.71 (s, 1H, H-8), 6.73 (s, 2H, H-4*,8*), 7.03 (s, 2H, H-12*,14*), 7.04 (s, 1H, H-12), 7.11 (d, 1H, $^{3}J_{HH}$=8.4, H-1), 9.53 (s, 1H, OH). IR Spectrum (KBr pellet, ν/cm^{-1}): 1267 (P=O), 1614 (C=C_{Ar}), 2926 (CH_3), 3229 (OH). Mass spectrum (MALDI-TOF, *m/z*): 355 [M+Na]$^+$, 371 [M+K]$^+$.

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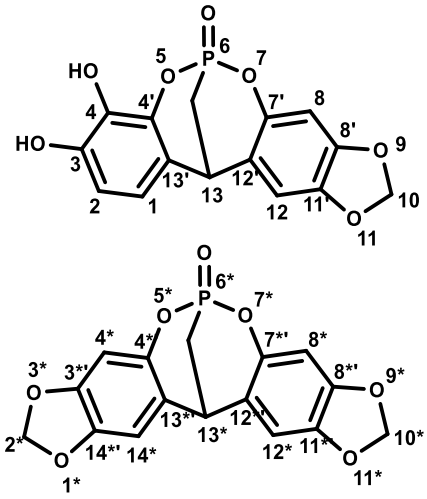
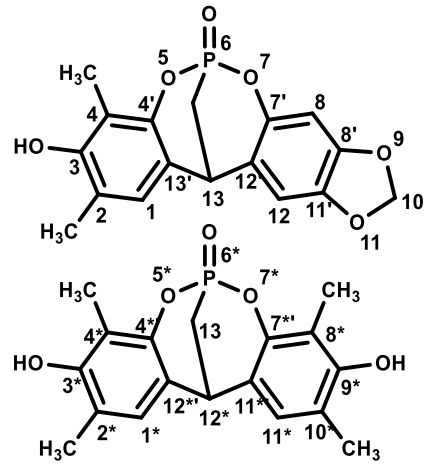
3,4-Dihydroxy-13H-6,13-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-d]benzo[g][1,3,2]dioxaphosphocin 6-oxide (4c) and 13H-6,13-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-d][1,3]dioxolo[4',5':4,5]benzo[1,2-g][1,3,2]dioxaphosphocin 6-oxide (5)



White powder, m.p. > 300 °C. ^{31}P NMR (161.90 MHz, d_6-DMSO, δ, ppm): 13.6 and 13.8. ^{1}H NMR (399.93 MHz, d_6-DMSO, δ, ppm, *J*/Hz): 2.63 (m, 4H, $^{3}J_{HH}$=3.8, $^{2}J_{PH}$=16.1, CH_2P), 4.55 (dt, 2H, $^{3}J_{HH}$=4.1, $^{3}J_{PH}$=35.1, $PCH_2C\underline{H}$), 5.92 (s, 1H, H-10), 5.94 (s, 2H, H-2*), 6.00 (s, 1H, H-10), 6.01 (s, 2H, H-10*), 6.46 (d, 1H, $^{3}J_{HH}$=8.3, H-2), 6.72 (s, 1H, H-8), 6.73 (s, 2H, H-4*,8*), 7.74 (d, 1H, $^{3}J_{HH}$=8.3, H-1), 7.04 (s, 1H, H-12), 7.13 (s, 2H, H-12*,14*), 8.86 (s, 1H, OH), 9.22 (s, 1H, OH). IR spectrum (KBr pellet, ν/cm^{-1}): 1246 (P=O), 1636 (C=C$_{Ar}$), 3424 (OH). Mass spectrum (MALDI-TOF, *m/z*): 357 [M+Na]$^+$, 369 [M*+Na]$^+$, 385 [M*+K]$^+$.

3-Hydroxy-2,4-dimethyl-13H-6,13-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-d]benzo[g][1,3,2]dioxaphosphocin 6-oxide (7) and 3,9-Dihydroxy-2,4,8,10-tetramethyl-12H-6,12-methanodibenzo[d,g][1,3,2]dioxaphosphocin 6-oxide (8).



White powder, m.p. > 300 °C. ^{31}P NMR (242.94 MHz, d_6-DMSO, δ, ppm): 13.8 and 14.1. ^{1}H NMR (399.93 MHz, d_6-DMSO, δ, ppm, *J*/Hz): 2.02-2.08 (s, 18H, CH_3), 2.60 (d, 4H, $^{2}J_{PH}$=17.0, CH_2P), 4.49 (m, 2H, $^{3}J_{HH}$=3.9, $^{3}J_{PH}$=31.6, $PCH_2C\underline{H}$), 5.92 (s, 1H, H-10), 6.00 (s, 1H, H-10), 6.72 (s, 1H, H-8), 6.97 (s, 1H, H-1), 7.05 (s, 2H, H-1*,11*), 7.06 (s, 1H, H-12), 8.50 (s, 1H, OH), 8.54 (s, 2H, OH). IR spectrum (KBr pellet, ν/cm^{-1}): 1276 (P=O), 1617 (C=C$_{Ar}$), 2923 (CH_3), 3574 (OH). Mass spectrum (MALDI-TOF, *m/z*): 347 [M+H]$^+$, 369 [M+Na]$^+$, 385 [M+K]$^+$, 715 [2M+Na]$^+$.

2-Hydroxy-15H-8,15-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-d]naphtho[1,2-g][1,3,2]dioxaphosphocin 8-oxide (10).

To a boiling solution of 0.73 g (5.3 mmol) of sesamol, 0.85 g (5.3 mmol) of 2,7-naphthalenediol, and 0.6 g (5.3 mmol) of trifluoroacetic acid in 30 mL of toluene, a solution of 1.0 g (5.3 mmol) of 2-ethoxyvinyl dichlorophosphonate in 5 mL of toluene was added dropwise. The reaction mixture was refluxed for 10 hours. The resulting precipitate was filtered off, washed first with distilled water and then repeatedly with acetone, and dried under vacuum to constant weight, yielding the cage phosphonate 10.

The filtrate was evaporated under reduced pressure, and the resulting solid was washed with diethyl ether, filtered, and dried under vacuum to constant weight. As a result, 1.03 g (56%) of the symmetrical cage phosphonate 10 based on sesamol was obtained.

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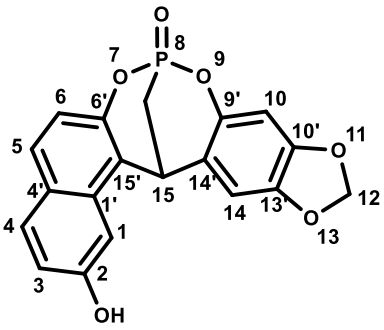


Yield: 0.68 g (35%), white powder, m.p. > 300 °C. ^{31}P NMR (242.94 MHz, d$_6$-DMSO, δ, ppm): 15.1. ^{1}H NMR (600.13 MHz, d$_6$-DMSO, δ, ppm, *J*/Hz): 2.76 (m, 2H, CH_2P), 5.31 (dt, 1H, $^{3}J_{HH}$=4.0, $^{3}J_{PH}$=34.5, $PCH_2C\underline{H}$), 5.88 (s, 1H, H-12), 6.02 (s, 1H, H-12), 6.77 (s, 1H, H-10), 7.00 (d, 1H, $^{3}J_{HH}$=8.8, H-6), 7.05 (dd, 1H, $^{3}J_{HH}$=8.8, $^{4}J_{HH}$=1.8, H-3), 7.17 (s, 1H, H-14), 7.71 (s, 1H, H-1), 7.72 (d, 1H, $^{3}J_{HH}$=8.8, H-5), 7.77 (d, 1H, $^{3}J_{HH}$=8.8, H-4), 10.02 (s, 1H, OH). ^{13}C NMR (150.92 MHz, d$_6$-DMSO, δ, ppm, *J*/Hz): 20.4 (d, $^{1}J_{CP}$=111.0, PCH_2); 35.8 (d, $^{2}J_{CP}$=10.0, $PCH_2\underline{C}H$); 101.0 (d, $^{3}J_{CP}$=8.4, C-10), 102.3 (s, C-12), 105.9 (s, C-1), 107.6 (s, C-14), 116.0 (d, $^{3}J_{CP}$=7.7, C-6), 117.9 (s, C-3), 119.4 (d, $^{3}J_{CP}$=10.1, C-15'), 119.8 (d, $^{2}J_{CP}$=10.5, C-14'), 125.4 (s, C-4'), 130.0 (s, C-5), 131.1 (s, C-4), 132.0 (s, C-1'), 143.7 (s, C-10'), 146.0 (d, $^{3}J_{CP}$=7.0, C-9'), 147.6 (s, C-13'), 149.5 (d, $^{2}J_{CP}$=7.9, C-6'), 157.4 (s, C-2). IR spectrum, (KBr pellet, ν/cm^{-1}): 1234 (P=O), 1623 (C=C$_{Ar}$), 3314 (OH). Found (%): C 61.92, H 3.48, P 8.34. $C_{19}H_{13}O_6P$. Calculated (%): C 61.97, H 3.56, P 8.41. Масс-спектр (MALDI-TOF, *m/z*): 369 [M+H]$^+$, 391 [M+Na]$^+$.

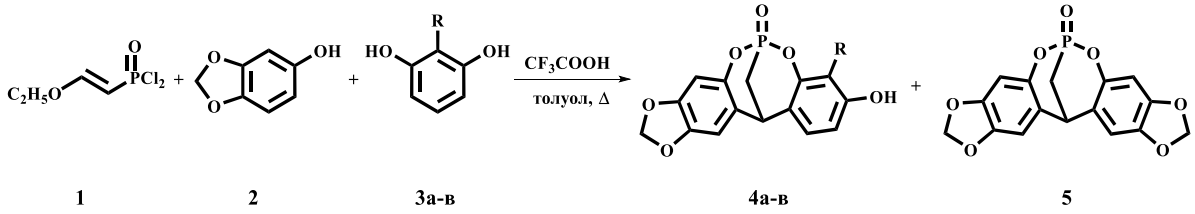
3. Results and Discussion

The synthesis was carried out according to our previously developed method for obtaining asymmetric cage phosphonates, which is based on the reaction of dichlorophosphonate 1 with an equimolar mixture of two different phenols in toluene in the presence of trifluoroacetic acid [11, 12].

In the first stage, we performed the reaction of a mixture of sesamol 2 with resorcinol 3a (or 2-methylresorcinol (3b) or pyrogallol (3c)) and 2-ethoxyvinyl dichlorophosphonate 1 (Scheme 1). As a result, an unexpected outcome was obtained: the product formed as crystals with good solubility in DMSO, representing an inseparable mixture of the asymmetric cage phosphonate 4a–c and the symmetric cage phosphonate based on sesamol 5. It turned out that these compounds possess very similar chromatographic mobility, and we were unable to isolate them as individual substances.

The structure and composition of the cage phosphonate mixture 4a–c and 5 were determined based on ^31P NMR, ^1H NMR, IR spectroscopy, and elemental analysis.

Scheme 1



1 2 3а-в 4а-в 5

R = H (а); CH_3 (б); OH(в)

In the ^{31}P NMR spectra of the cage phosphonate mixture 4a–c and 5, two signals were observed with phosphorus chemical shifts in the region of 13–14 ppm. In the ^{1}H NMR spectrum, the signals of the methylene protons adjacent to the phosphorus atom (H-14 and H-14*) appear as a multiplet at δ 2.63 ppm ($^{3}J_{nn}$ = 3.8 Hz, $^{2}J_{pn}$ = 16.1 Hz), while the methine protons (H-13 and H-13*) appear as doublets of triplets at δ 4.55 ppm ($^{3}J_{nn}$ = 4.1 Hz, $^{2}J_{pn}$ = 35.1 Hz). The assignment of the remaining proton signals was made based on their multiplicity and integral intensity.

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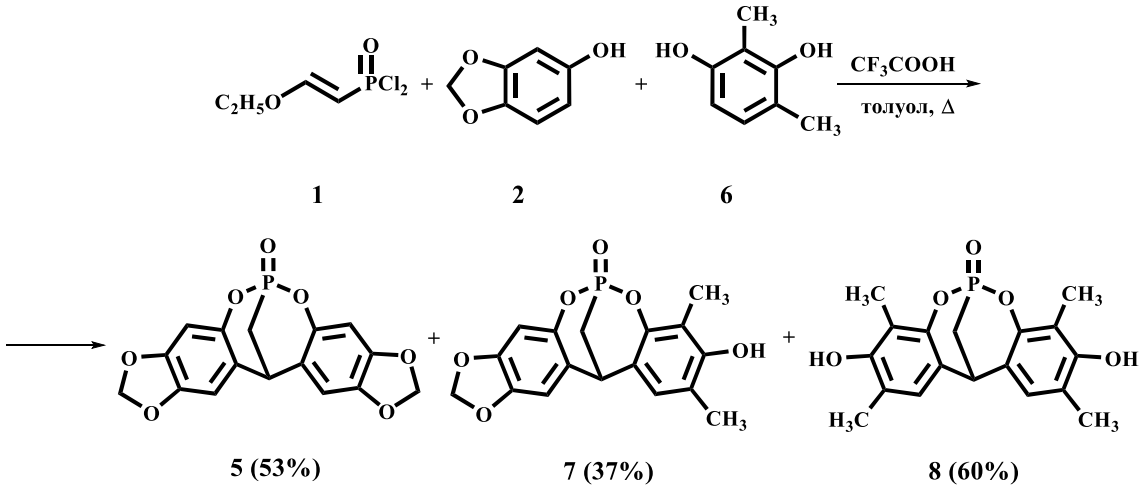
It is important to note that, in addition to the cage phosphonate mixture **4a–c** and ***5***, we were able to isolate the symmetric sesamol-based cage phosphonate ***5*** as an individual compound. It forms white crystals with good solubility in DMSO.

The structure and composition of the sesamol-derived cage phosphonate 5 were confirmed by ^{31}P-, ^{1}H-, ^{13}C- NMR spectroscopy, IR spectroscopy, elemental analysis, and MALDI mass spectrometry.

In the ^{31}P NMR phosphonate ***5*** displays a single signal at δ 13.8 ppm. In the ^{1}H NMR spectrum, the methylene protons adjacent to phosphorus appear as a doublet of doublets at δ 2.64 ppm ($^{3}J_{HH}$ 3.8 Hz, $^{2}J_{PH}$ 16.2 Hz), and the methine proton appears as a doublet of triplets at δ 4.52–4.59 ppm ($^{3}J_{HH}$ 3.8 Hz, $^{3}J_{PH}$ 35.1 Hz). The signals of the dioxymethylene group protons are observed as two singlets at δ 5.94 ppm and 6.01 ppm, while the sesamol fragment protons are seen as two singlets at δ 6.73 ppm and 7.13 ppm. In the ^{13}C-(^{1}H) NMR spectrum contains characteristic carbon signals: C-14 (δ_C 19.8 ppm, $^{1}J_{PC}$ 111.1 Hz), C-13 (δ_C 39.7 ppm, $^{2}J_{PC}$ 20.8 Hz), C-4,8 (δ_C 100.8 ppm, $^{3}J_{PC}$ 8.3 Hz), C-4',7' (δ_C 120.8 ppm, $^{3}J_{PC}$ 10.9 Hz), C-12',13' (δ_C 145.3 ppm, $^{3}J_{PC}$ 7.6 Hz), these carbons exhibit spin–spin coupling with the phosphorus nucleus and appear as doublets. The assignment of the aromatic carbon signals was based on their multiplicity and integral intensity. In the MALDI-TOF mass spectrum, molecular ion peaks were recorded at m/z 346 [M]+, 347 [M+H]+, 369 [M+Na]+, and 385 [M+K]+, corresponding to the sesamol-based cage phosphonate ***5***.

The reaction of 2-ethoxyvinyl dichlorophosphonate 1 with a mixture of sesamol 2 and 2,4-dimethylresorcinol 6 proceeds under analogous conditions (Scheme 2). In this case, the formation of a mixture of the symmetric cage phosphonate 8 and the asymmetric cage phosphonate 7 is also observed, with the only difference being that the symmetric cage phosphonate 8 is derived from 2,4-dimethylresorcinol. This synthetic outcome can be attributed to the higher reactivity of the 2,4-dimethylresorcinol molecule compared to sesamol. As in the previous reaction, we also observe the formation of the symmetric sesamol-based cage phosphonate ***5***, independently of the product mixture, which can subsequently be isolated as an individual compound.

Scheme 2



The structure and composition of the cage phosphonate mixture 7 and 8 were established based on data from ^31P and ^1H NMR spectroscopy, IR spectroscopy, and elemental analysis. The mixture of cage phosphonates 7 and 8 forms white crystals with good solubility in DMSO.

In the ^{31}P NMR spectrum of the cage phosphonate mixture 7 and 8, two signals corresponding to phosphorus atoms are observed at δ 13.8 and 14.1 ppm. In the ^1H NMR spectrum, signals from methyl

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group protons appear as singlets in the high-field region at δ 2.02–2.08 ppm. The methylene protons (H-14 and H-13*) adjacent to the phosphorus atom appear as a doublet at δ 2.60 ppm ($^{2}J_{PH}$=17.0 Гц); the signals of the methine protons (H-13 and H-12*) appear as a multiplet at δ 4.49 ppm. ($^{3}J_{HH}$ 3.9 Гц, $^{3}J_{PH}$ 31.6 Гц). The aromatic proton signals appear in the ^1H NMR spectrum as singlets in the region of δ 5.92–7.06 ppm. The structure of cage phosphonates 7 and 8 was further confirmed by X-ray crystallographic analysis. The crystals obtained from the synthesis represent a cocrystal of compounds 7 and 8 in a 1:1 ratio (Figure 1). Compound **8**, despite its chemically symmetric structure, is not entirely symmetric geometrically. The bond lengths between the phosphorus atom and the oxygen atoms O1 and O2 are 1.574(5) Å and 1.595(6) Å, respectively, while the bond length to O3 is 1.461(6) Å. Compound **7**, which is chemically nonequivalent to compound 8, exhibits very similar geometry. The phosphorus–oxygen bond lengths are 1.596(5) Å and 1.587(6) Å, respectively, and the length of the P=O double bond is 1.468(6) Å.

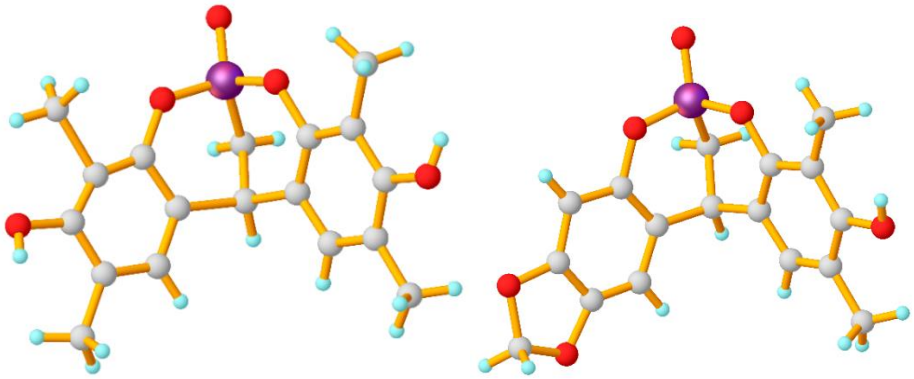

Figure 1.
Molecular structure of compounds **7** and **8** in the cocrystal.

The angles between the planes of the bicyclic fragments are 81.52° in the symmetric compound **8** and 74.20° in the asymmetric compound **7**. The molecular packing in the cocrystal of compounds **8** and **7** is shown in Figure 2.

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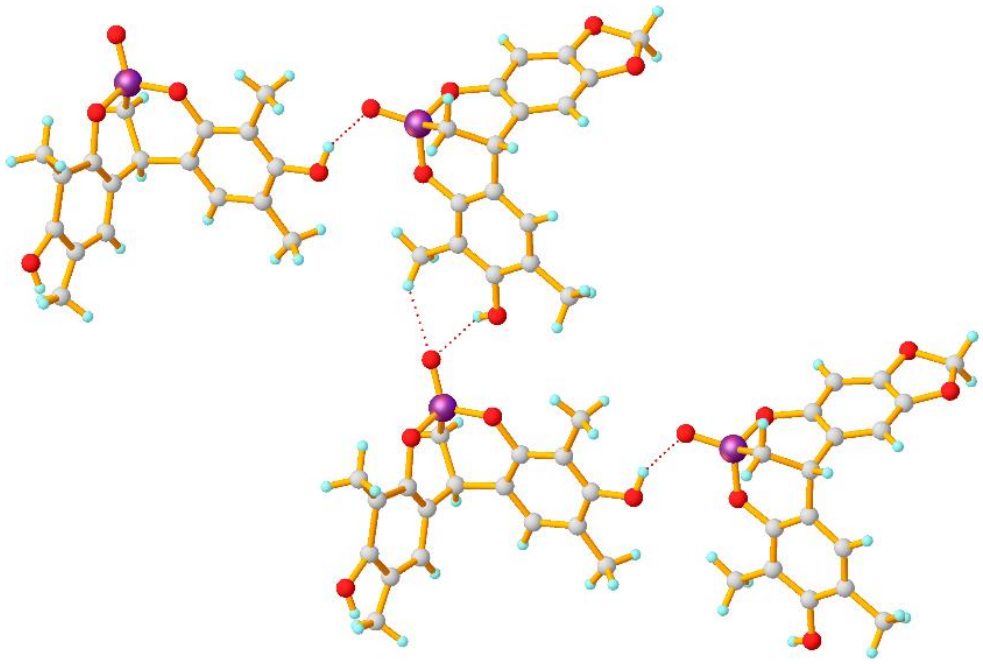


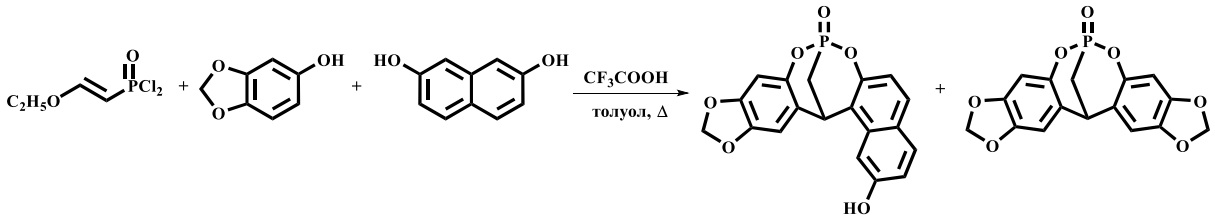
Figure 2.
Molecular packing in the **7/8** cocrystal.

The molecules of compounds **7** and **8** are connected in the crystal by classical hydrogen bonds between the hydroxyl group of one molecule and the phosphoryl oxygen atom of another, resulting in infinite zigzag chains, which are further linked into a three-dimensional network through weaker C–H…π and π…π interactions.

The **7/8** cocrystals are monoclinic, with space group Cc. Unit cell parameters: a=9.3130(3)Å, b=13.3105(5)Å, c=25.1206(9) Å, β=90.857(2)°, V=3113.62(19)Å^3.

Expanding the synthetic scope of this reaction, we carried out the reaction of 2-ethoxyvinyl dichlorophosphonate **1** with sesamol **2** and 2,7-naphthalenediol **9** in boiling toluene in the presence of trifluoroacetic acid (Scheme 3). As a result, a new representative of the class of asymmetric cage phosphonates based on sesamol, compound **10**, was obtained and successfully isolated as an individual substance. As in the previously described reactions, the formation of the symmetric sesamol-based cage phosphonate **5** was also observed.

Scheme 3



1 **2** **9** **10 (37%)** **5 (60%)**

The structure and composition of the new asymmetric cage phosphonate 10 were confirmed by ^{1}H, ^{31}P и ^{13}C NMR spectroscopy, IR spectroscopy, MALDI mass spectrometry, and elemental analysis.

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In the ^{31}P NMR spectrum of cage phosphonate 10, shown in Figure 3, a single signal is observed with a phosphorus chemical shift at approximately δ 15 ppm. In the ^{1}H NMR spectrum of compound **10** (figure 3), the methylene protons in the α-position to the phosphorus atom (H-16) appear as a multiplet at δ 2.76 ppm, while the methine proton (H-15) appears as a doublet of triplets at δ 5.31 ppm ($^{3}J_{HH}$ 4.0 Hz, $^{3}J_{PH}$ 34.5 Hz). The naphthalene ring protons are represented in the ^{1}H NMR spectrum as follows a doublet of doublets at δ 7.05 ppm (H-3, $^{3}J_{HH}$=8.8 Hz, $^{4}J_{HH}$=1.8 Hz), doublets at δ 7.00 ppm (H-6, $^{3}J_{HH}$ 8.8 Hz), δ 7.72 ppm (H-5, $^{3}J_{HH}$ 8.8 Hz), and δ 7.77 ppm (H-4,$^{3}J_{HH}$ 8.8 Hz), as well as a singlet at δ 7.71 ppm (H-1). The protons of the dioxobenzene fragment (H-10, H-12, H-14) are observed as singlets. In the ^{13}C NMR spectrum of the asymmetric cage phosphonate 10 (shown in Figure 4), carbon atoms C-16 (δ_C 20.4 ppm, $^{1}J_{PC}$ 111.0 Hz) and C-15 (δ_C 35.8 ppm, $^{2}J_{PC}$ 10.0 Hz), show spin–spin coupling with the phosphorus atom and appear as doublets. In thearomatic region of the ^{13}C NMR spectrum the following carbon atoms also appear as doublets due to phosphorus coupling: C-10 (δ_C 101.0 ppm, $^{3}J_{PC}$ 8.4 Hz), C-6 (δ_C 116.0 ppm, $^{3}J_{PC}$ 7.7 Hz), C-15' (δ_C 119.4 ppm, $^{3}J_{PC}$ 10.1 Hz), C-14' (δ_C 119.8 ppm, $^{2}J_{PC}$ 10.5 Hz), C-9' (δ_C 146.0 ppm, $^{3}J_{PC}$ 7.0 Hz) and C-6' (δ_C 149.5 ppm, $^{2}J_{PC}$ 7.9 Hz) appears as doublets. The assignment of the remaining aromatic carbon signals was made based on their multiplicity and integral intensity. In the MALDI-TOF mass spectrum, molecular ion peaks were recorded at m/z 369 [M+H]+ and 391 [M+Na]+, consistent with the molecular composition of asymmetric cage phosphonate 10.

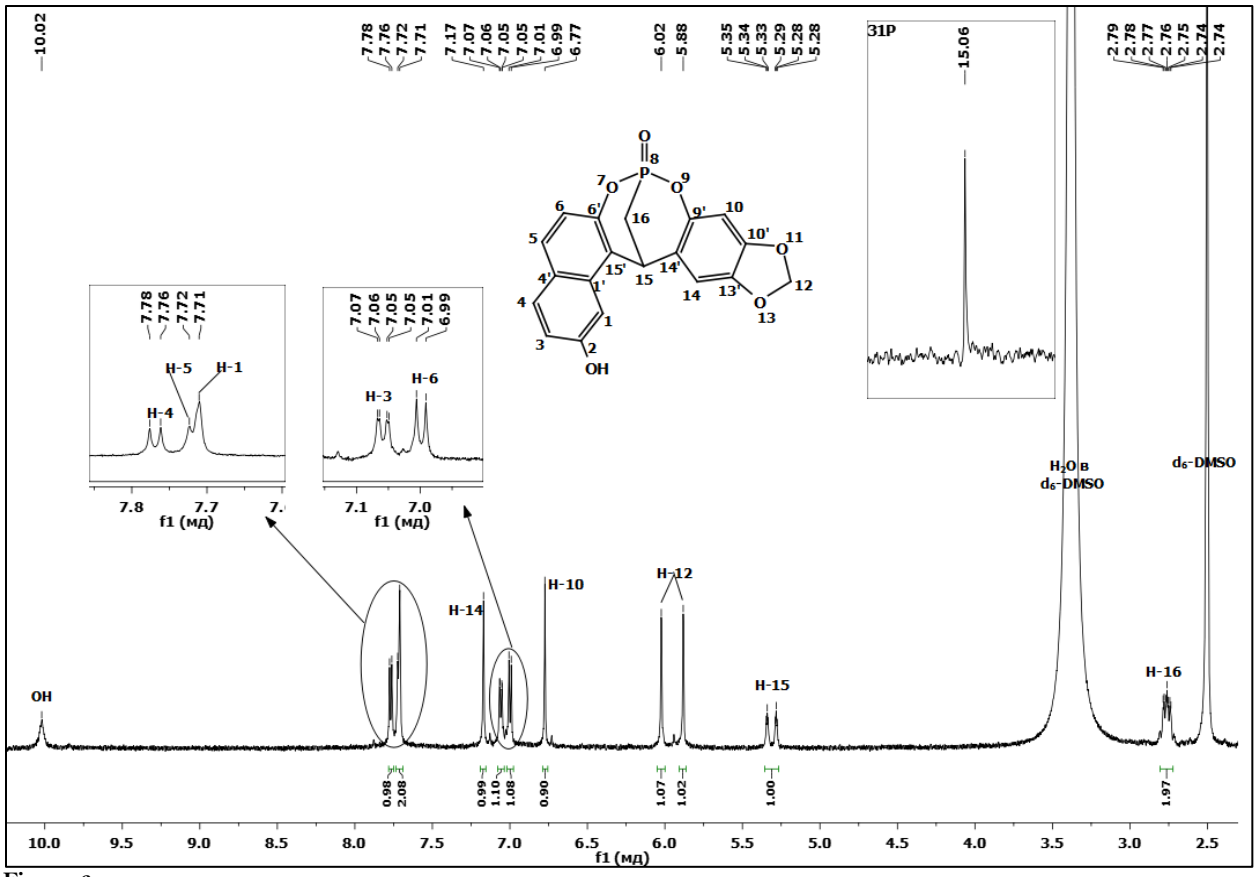

Figure 3.
–^{1}H NMR spectrum (600.13 MHz, d6-DMSO) of the compound 10.

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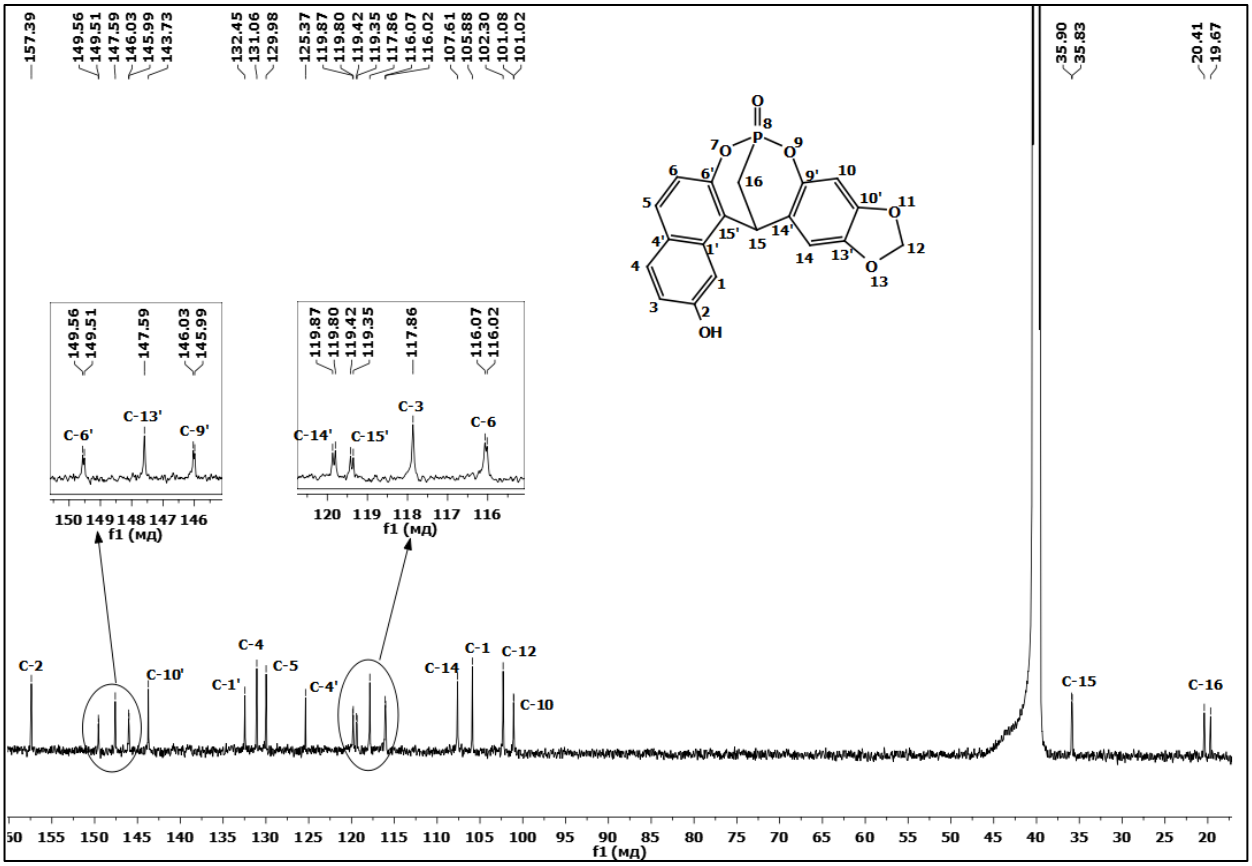

Figure 4.
–^{13}C-(^{1}H) NMR spectrum (150.92 MHz, d6-DMSO) of the compound 10.

Thus, as a result of the conducted study, we have developed a method for the synthesis of asymmetric cage phosphonates based on sesamol. The first representative of this class was obtained, and a molecular mixture of symmetric and asymmetric cage phosphonates was characterized using X-ray crystallographic analysis (XRD).

4. Conclusions

Thus, as a result of the reaction of a mixture of sesamol with resorcinol (or 2-methylresorcinol or pyrogallol) with 2-ethoxyvinyl dichlorophosphonate, an unexpected outcome was obtained—a crystalline product with good solubility in dimethyl sulfoxide, representing an inseparable mixture of asymmetric cage phosphonate and symmetric cage phosphonate based on sesamol.

In the reaction of 2-ethoxyvinyl dichlorophosphonate with a mixture of sesamol and 2,4-dimethylresorcinol, the formation of a mixture of symmetric and asymmetric cage phosphonates was also observed, with the only difference being that the symmetric phosphonate was derived from 2,4-dimethylresorcinol.

Ultimately, the formation of the symmetric sesamol-based cage phosphonate was observed in all cases, occurring independently of the product mixture and allowing for its isolation as an individual compound.

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Transparency:
The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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