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Sterically controlled cyclization of 3′,4′,5,7-tetramethyldihydroquercetin amidophosphites. New synthesis of phostones

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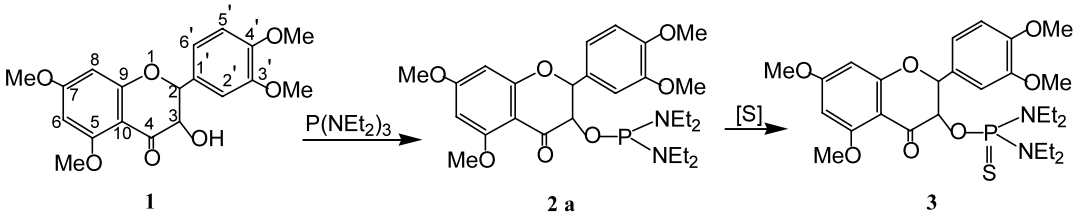
Abstract—A new sterically controlled reaction of α-hydroxyketones with phosphorus acid triamides resulting in new four-membered phostones is reported.

Chemical modifications of flavanoids with trivalent phosphorus reagents have not been studied previously. It was recently shown in our laboratory that dihydroquercetin, one of the most interesting natural compounds of this class, could undergo regioselective phosphorylation of some of its phenolic hydroxyls during reaction with phosphorus acid amides.[1] The aim of the present work was to study the modification of this flavanoid involving its α-hydroxyketone fragment under the action of phosphamide reagents. To isolate this fragment from the general dihydroquercetin system, we performed the complete methylation of its phenolic hydroxyl groups and thus obtained the corresponding dihydroquercetin 3′,4′,5,7-tetramethyl ether **1**.[2]

Product **1** was subjected to phosphorylation by reagents containing one or two amide groups. For identification purposes the phosphites obtained were converted into thionophosphates.[3,4]

Hexaethylphosphorus triamide was used as the phosphorylating reagent. The phosphorylation was monitored by ^{31}P NMR spectroscopy. After refluxing the reaction mixture in benzene for 30 min, almost complete formation of diamidophosphite **2** was observed, which was stabilised by transformation into the corresponding thionophosphate **3**, which was isolated as a pure isomer in 80% yield (Scheme 1).



1 **2 a** **3**

Scheme 1.

Keywords: phosphorylation; phosphorus acid amides; flavanoid; phostones; intramolecular rearrangement; X-ray crystal analysis.
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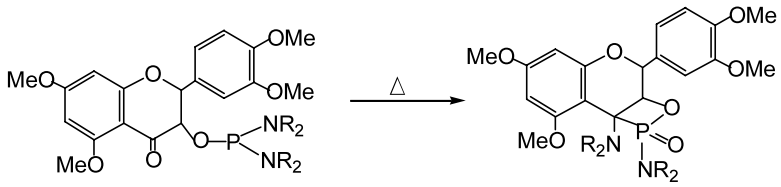


2a-c 4a-c

Scheme 2.

When primary amidophosphite **2a** was heated for a further 30 min, it underwent an intramolecular rearrangement into phostone **4a**, which was isolated as a pure isomer in 70% yield (Scheme 2).

The reaction is general; a similar result was obtained when hexamethylphosphorus triamide and phosphorus tripiperidide were used and the corresponding phostones **4b** and **4c** were obtained.

The structure of the phostones was supported by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy and by X-ray diffraction (for **4c**, see Fig. 1).

The rearrangement mechanism has not yet been determined. However, taking the published data[5,6] into account, we can suppose that it involves the formation of a complex of the phosphamide fragment with the amine chlorohydrate, a common impurity in phosphamides. The electrophilic phosphorus atom then attacks the carbonyl oxygen atom and an amino group is transferred from the phosphorus atom to a carbon atom of the pyran ring with the formation of the phostone ring.

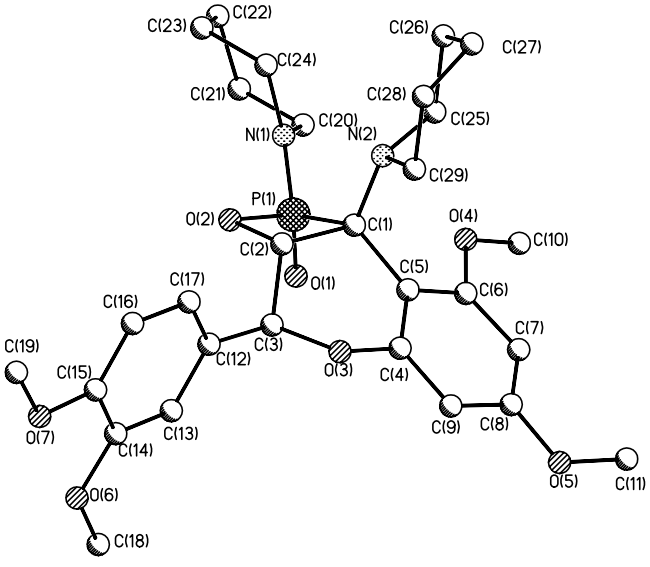


Figure 1. The structure of **4c**. Selected bond lengths (Å): P(1)–O(1) 1.465(2), P(1)–O(2) 1.612(2), P(1)–N(1) 1.613(2), P(1)–C(1) 1.835(3); bond angles (°): O(1)–P(1)–O(2) 115.9(1), O(1)–P(1)–N(1) 112.8(1), O(2)–P(1)–N(1) 106.6(1), O(1)–P(1)–C(1) 114.8(1), O(2)–P(1)–C(1) 82.3(1), N(1)–P(1)–C(1) 120.5(1).

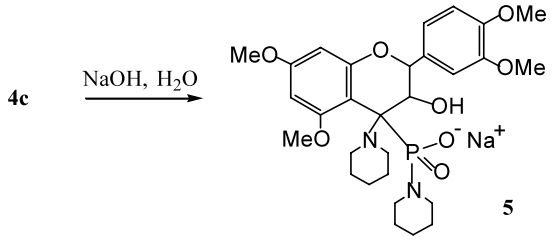
It should be noted that the interaction between linear α-hydroxyketones and phosphorus triamides has already been reported in the literature.[7] It was found that the reaction follows another pathway to form five-membered 1,3,2-dioxaphospholene systems. Differences in the directions of these formally related reactions are probably determined by the spatial features of the flavanoid structure.

The phosphones obtained seem to be very interesting compounds. They are highly electrophilic and react readily with nucleophiles (Scheme 3).

Thus we have shown that this new field of organic synthesis, which combines the chemistry of flavanoids and the chemistry of phosphorus acid amides, offers great promise.

Representative procedure for compounds 4a–c

A suspension of compound **1** (1 g, 0.028 mol) in benzene (20 ml) was treated with 0.0028 mol of phosphorus triamide under vigorous stirring. The reaction mixture was refluxed for 1 h. The solvent was evaporated in vacuo; the residue was applied to a column with silica gel and eluted with solvents: *A: benzene–dioxane 1:1*, *B: benzene–dioxane 3:1*, *C: benzene–dioxane 4:1*. The solvent was removed and the products were dried in vacuo.



Compound	Yield (%)	Mp (°C)	δ ^{31}P
3	65	109–111	81.72
4a	70	118–120	29.84
4b	70	160–162	30.40
4c	75	128–130	26.88
5	80	186–188	20.11

Scheme 3.

X-Ray structural analysis of compound 4c

X-Ray structural analysis of compound **4c**: at 100 K crystals of $C_{29}H_{39}N_2O_7P$ (**4c**) are triclinic, space group $P\bar{1}$, $a=12.245(7)$, $b=12.950(7)$, $c=13.142(7)$ Å, $\alpha=61.20(1)$, $\beta=70.13(1)$, $\gamma=66.20(1)°$, $V=1643(2)$ Å^3, $Z=2$, $M=636.70$, $D_{calcd}=1.287$ g cm^{-3}, $\mu(MoK\alpha)=1.35$ cm^{-1}, $F(000)=680$. Intensities of 8781 reflections were measured with a Smart 1000 CCD diffractometer at 100 K ($\lambda(MoK\alpha)=0.71072$ Å, ω-scans with 0.3° step in ω and 15 s per frame exposure, $2\theta<56°$), and 5759 independent reflections ($R_{int}=0.0348$) were used in further refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to $wR_2=0.1208$ and GOF = 0.906 for all independent reflections ($R_1=0.0543$ was calculated against F for 3504 observed reflections with $I>2\sigma(I)$). All calculations were performed using SHELXTL PLUS 5.0 on an IBM PC AT. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC-186169. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

3′,4′,5,7-Tetramethyldihydroquercetin 4-*N*,*N*-dimethylcyclophosphonate 4b. Yellow powder. ^{1}H NMR (200 MHz): δ 2.20 (s, 6H, C–N(CH_3)$_2$, 2CH_3); 2.74 (d, $^3J_{PH}=9.01$ Hz, 6H, P–N(CH_3)$_2$, 2CH_3); 3.34 (s, 3H, OMe); 3.35 (s, 3H, OMe); 3.36 (s, 3H, OMe); 3.40 (s, 3H, OMe); 4.63 (dd, $^3J_{PH}=17.50$ Hz, $^3J_{HH}=9.35$ Hz, 1H, H3); 5.08 (d, $^3J_{HH}=9.35$ Hz, 1H, H2); 6.31 (d, $^4J_{HH}=2.20$ Hz, 1H, H6); 6.37 (d, $^4J_{HH}=2.2$ Hz, 1H, H8); 6.65 (d, $^3J_{HH}=8.80$ Hz, 1H, H5′); 7.08 (s, 1H, H2′); 7.18 (d, $^3J_{HH}=8.80$ Hz, 1H, H6′). ^{13}C NMR (50 MHz): δ 36.51 (d, $^3J_{CP}=4.71$ Hz, 2C, C–N(CH_3)$_2$, 2CH_3); 41.65 (d, $^2J_{CP}=9.81$ Hz, 2C, P–N(CH_3)$_2$, 2CH_3); 54.96 (s, 1C, OMe); 55.55 (s, 1C, OMe); 55.61 (s, 1C, OMe); 55.93 (s, 1C, OMe); 77.71 (d, $^1J_{CP}=112.41$ Hz, 1C, C4); 80.23 (d, $^2J_{CP}=20.91$ Hz, 1C, C3); 84.86 (d, $^3J_{CP}=3.51$ Hz, 1C, C2); 95.58 (s, 1C, C8); 95.81 (s, 1C, C6); 103.14 (d, $^2J_{CP}=2.72$ Hz, 1C, C10); 110.79 (s, 1C, C5′); 112.36 (s, 1C, C2′); 118.97 (s, 1C, C6′); 131.24 (s, 1C, C1′); 150.21 (s, 1C, C3′); 150.31 (s, 1C, C4′); 160.43 (d, $^3J_{CP}=4.71$ Hz, 1C, C9); 160.81 (d, $^3J_{CP}=11.52$ Hz, 1C, C5); 161.32 (s, 1C, C7). Anal. calcd for $C_{23}H_{31}N_2O_7P$: C, 57.74; H, 6.48; N, 5.86; P, 6.49. Found: C, 57.32; H, 6.57; N 5.97; P 6.59.

3′,4′,5,7-Tetramethyldihydroquercetin 4-*N*,*N*-diethylcyclophosphonate 4a. Yellow powder. ^{1}H NMR (200 MHz): δ 0.97 (t, $^2J_{HH}=7.03$ Hz, 6H, C–N(CH_2-CH_3)$_2$, 2CH_3); 1.10 (t, $^2J_{HH}=7.14$ Hz, 6H, P–N(CH_2-CH_3)$_2$, 2CH_3); 2.86 (m, 4H, C–N(CH_2-CH_3)$_2$, 2CH_2); 2.99 (m, 2H, P–N(CH_2-CH_3)$_2$, CH_2); 3.33 (s, 3H, OMe); 3.35 (s, 3H, OMe); 3.38 (s, 3H, OMe); 3.41 (s, 3H, OMe); 3.80 (m, 2H, P–N(CH_2-CH_3)$_2$, CH_2); 4.82 (dd, $^3J_{PH}=17.61$ Hz, $^3J_{HH}=9.90$ Hz, 1H, H3); 5.15 (d, $^3J_{HH}=9.90$ Hz, 1H, H2); 6.29 (d, $^4J_{HH}=2.20$ Hz, 1H, H6); 6.38 (d, $^4J_{HH}=2.20$ Hz, 1H, H8); 6.61 (d, $^3J_{HH}=8.25$ Hz, 1H, H5′); 7.10 (s, 1H, H2′); 7.15 (d, $^3J_{HH}=8.80$ Hz, 1H, H6′). ^{13}C NMR (50 MHz): δ 15.43 (s, 2C, C–N(CH_2-CH_3)$_2$, 2CH_3); 15.52 (s, 2C, P–N(CH_2-CH_3)$_2$, 2CH_3); 41.19 (d, $^3J_{CP}=3.87$ Hz, 2C, C–N(CH_2-CH_3)$_2$, 2CH_2); 46.24 (d, $^2J_{CP}=10.23$ Hz, 2C, P–N(CH_2-CH_3)$_2$, 2CH_2); 55.04 (s, 1C, OMe); 55.49 (s, 1C, OMe); 55.62 (s, 1C, OMe); 55.77 (s, 1C, OMe); 78.93 (d, $^1J_{CP}=113.12$ Hz, 1C, C4), 80.23 (d, $^2J_{CP}=20.91$ Hz, 1C, C3); 84.85 (d, $^3J_{CP}=3.07$ Hz, 1C, C2); 95.65 (s, 1C, C8); 95.75 (s, 1C, C6); 106.62 (d, $^2J_{CP}=2.81$ Hz, 1C, C10); 110.78 (s, 1C, C5′); 112.29 (s, 1C, C2′); 119.17 (s, 1C, C6′); 131.27 (s, 1C, C1′); 150.22 (s, 1C, C3′); 150.28 (s, 1C, C4′); 160.26 (d, $^3J_{CP}=5.02$ Hz, 1C, C9); 160.39 (d, $^3J_{CP}=10.92$ Hz, 1C, C5); 161.31 (s, 1C, C7). Anal. calcd for $C_{27}H_{39}N_2O_7P$: C, 60.67; H, 7.30; N, 5.24; P, 5.81. Found: C, 60.30; H, 7.42; N, 5.15; P, 5.71.

3′,4′,5,7-Tetramethyldihydroquercetin 4-piperidylcyclophosphonate 4c. Yellow powder. ^{1}H NMR (200 MHz): δ 1.57 (m, 6H, C–N(CH_2)$_5$, 2βCH_2 and γCH_2); 1.64 (m, 6H, P–N(CH_2)$_5$, 2βCH_2 and γCH_2); 2.71 (t, $^3J_{HH}=6.05$ Hz, 4H, C–N(CH_2)$_5$, 2αCH_2); 3.36 (t, $^3J_{PH}=10.01$ Hz, $^3J_{HH}=6.04$ Hz, 4H, P–N(CH_2)$_5$, 2αCH_2); 3.39 (s, 3H, OMe); 3.41 (s, 3H, OMe); 3.43 (s, 3H, OMe); 3.44 (s, 3H, OMe); 4.65 (dd, $^3J_{PH}=16.50$ Hz, $^3J_{HH}=9.34$ Hz, 1H, H3); 5.08 (d, $^3J_{HH}=9.34$ Hz, 1H, H2); 6.37 (d, $^4J_{HH}=2.2$ Hz, 1H, H6); 6.42 (d, $^4J_{HH}=2.2$ Hz, 1H, H8); 6.69 (d, $^3J_{HH}=8.25$ Hz, 1H, H5′); 7.10 (s, 1H, H2′); 7.20 (d, $^3J_{HH}=8.25$ Hz, 1H, H6′). ^{13}C NMR (50 MHz): δ 24.87 (s, 1C, C–N(CH_2)$_5$, γCH_2); 25.06 (s, 1C, P–N(CH_2)$_5$, γCH_2); 27.16 (s, 2C, C–N(CH_2)$_5$, 2βCH_2); 27.32 (s, 2C, P–N(CH_2)$_5$, 2βCH_2); 46.11 (d, $^3J_{CP}=3.87$ Hz, 2C, C–N(CH_2)$_5$, 2αCH_2); 51.37 (d, $^2J_{CP}=10.21$ Hz, 2C, P–N(CH_2)$_5$, 2αCH_2); 54.98 (s, 1C, OMe); 55.54 (s, 1C, OMe); 55.61 (s, 1C, OMe); 56.17 (s, 1C, OMe); 77.09 (d, $^1J_{CP}=107.91$ Hz, 1C, C4); 80.22 (d, $^2J_{CP}=20.94$ Hz, 1C, C3); 84.91 (d, $^3J_{HH}=4.12$ Hz, 1C,C2); 95.71 (s, 1C,C8); 95.94 (s, 1C, C6); 104.25 (d, $^2J_{CP}=2.53$ Hz, 1C, C10); 110.85 (s, 1C, C5′); 112.39 (s, 1C, C2′); 118.82 (s, 1C, C6′); 131.38 (s, 1C, C1′); 150.25 (s, 1C, C3′); 150.35 (s, 1C, C4′); 160.49 (d, $^3J_{CP}=4.57$ Hz, 1C, C9); 160.68 (d, $^3J_{CP}=11.72$ Hz, 1C, C5); 161.3 (s, 1C, C7). Anal. calcd for $C_{29}H_{39}N_2PO_7$: C, 62.36; H, 6.99; N, 5.02; P, 5.55. Found: C, 62.18; H, 7.18; N, 4.78; P, 5.23.

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