

## Synthesis of diphenyl(X)phosphonium betaines (X = CH<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>, 2,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>) from hexafluoro-1,4-naphthoquinone

Leonid I. Goryunov,<sup>a\*</sup> Svetlana I. Zhivetyeva,<sup>a,b</sup> Georgy A. Nevinsky,<sup>c</sup>  
and Vitalij D. Shteingarts<sup>a</sup>

<sup>a</sup>*N.N. Vorozhtsov Institute of Organic Chemistry, Siberian Division of the Russian Academy of Sciences, 9 Ac. Lavrentjev Avenue, Novosibirsk, 630090, Russia*

<sup>b</sup>*Novosibirsk State University, 2 Pirogova Street, Novosibirsk, 630090, Russia*

<sup>c</sup>*Institute of Biological Chemistry and Fundamental Medicine, Siberian Division of Russian Academy of Sciences, 8 Lavrentiev Ave., 630090 Novosibirsk, Russia*

E-mail: [goryunov@nioch.nsc.ru](mailto:goryunov@nioch.nsc.ru)

Dedicated to Professor Usein M Dzhemilev on the occasion of his 65<sup>th</sup> birthday

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### Abstract

Betaines 5,6,7,8-tetrafluoro-3-(triphenyl- $\lambda^5$ -phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione, 5,6,7,8-tetrafluoro-3-(methyldiphenyl- $\lambda^5$ -phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione, and 3-[(2,5-difluorophenyl)diphenyl- $\lambda^5$ -phosphanylidene]-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalene-1,2,4-trione have been synthesized via fluorine substitution in the quinone ring of hexafluoro-1,4-naphthoquinone by tertiary phosphines RPh<sub>2</sub>P (R = Me, Ph, 2,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>) and methanol in 90, 30 and 62% yields, respectively. The first naphthalenetrione formed also upon interaction of pentafluoro-1,4-naphthoquinone with triphenylphosphine in methanol. The new 1,4-dibenzodioxine derivative – 6,11-difluoro-9-(triphenyl- $\lambda^5$ -phosphanylidene)-7,8,9,10-tetrahydro-5,12-dioxatetracene-7,8,10-trione – has been obtained in a 83% yield by fluorine substitution in the benzene moiety of a naphthoquinone skeleton of this betaine by the action of pyrocatechol at the presence of potassium carbonate in DMSO.

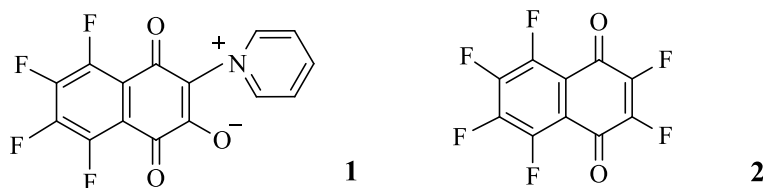
**Keywords:** Tertiary phosphines, polyfluorinated 1,4-naphthoquinones, phosphoniodefluorination, phosphonium betaines, 5,12-dioxatetracene.

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### Introduction

Amino derivatives of polyfluorinated 1,4-naphthoquinones are potential inhibitors of tumoral cells growth and antioxidants protecting cells against spontaneous mutagenesis.<sup>1</sup> Among them there is an ammonium betaine – 1,4-dioxo-3-(1-pyridinio)-1,4-dihydro-5,6,7,8-tetrafluoronaphthalene-2-olate **1**, obtained by fluorine substitution in the quinone ring of

hexafluoro-1,4-naphthoquinone **2** by action of pyridine and methanol.<sup>1</sup> The phosphonium analogues of ammonium betaine are also of interest for studying their biochemical properties. It was noted that the reaction of 2,3-dichloro-1,4-naphthoquinone with triphenylphosphine in methanol gave a phosphonium betaine – 3-(triphenylphosphoranylidene)-1,2,4(3*H*)-naphthalenetrione in a 68% yield.<sup>2,3</sup>

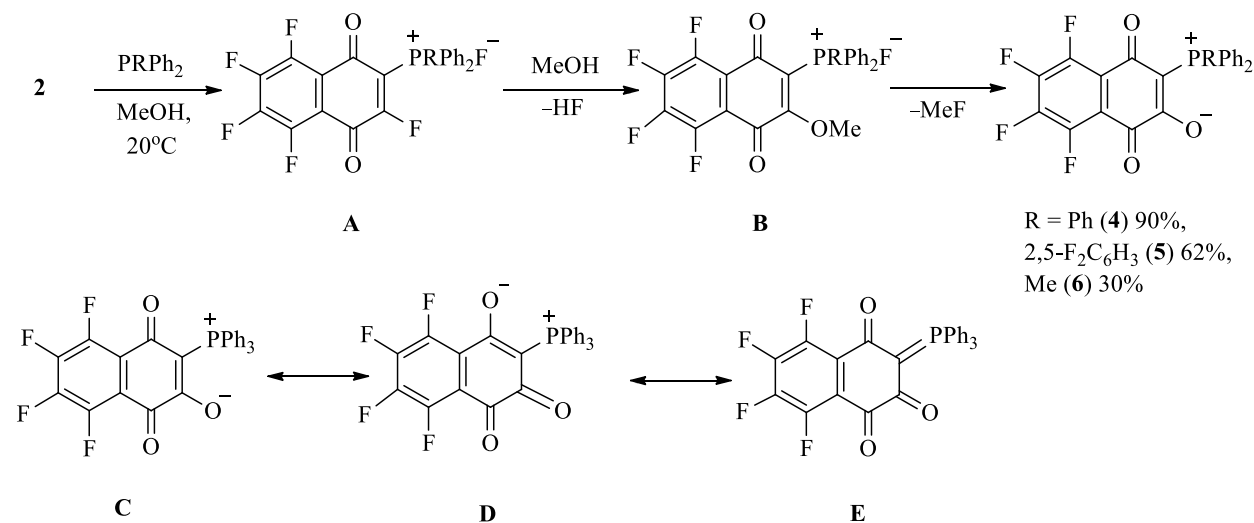


In this connection, in the present work we report the synthesis of 5,6,7,8-tetrafluoro-1,4-naphthoquinone phosphonium betaines via phosphoniodefluorination of quinone **2** and 2,5,6,7,8-pentafluoro-1,4-naphthoquinone **3** by the action of phosphines  $RPh_2P$  ( $R = Me, Ph, 2,4-F_2C_6H_3$ ) and methanol. The possibility to modify betaines of this type via fluorine nucleophilic substitution in the benzene ring of a naphthoquinone skeleton is exemplified by heterocyclization to construct a benzodioxin core.

## Results and Discussion

### Synthesis of phosphonium betaine derivatives of 5,6,7,8-tetrafluoro-1,4-naphthoquinone

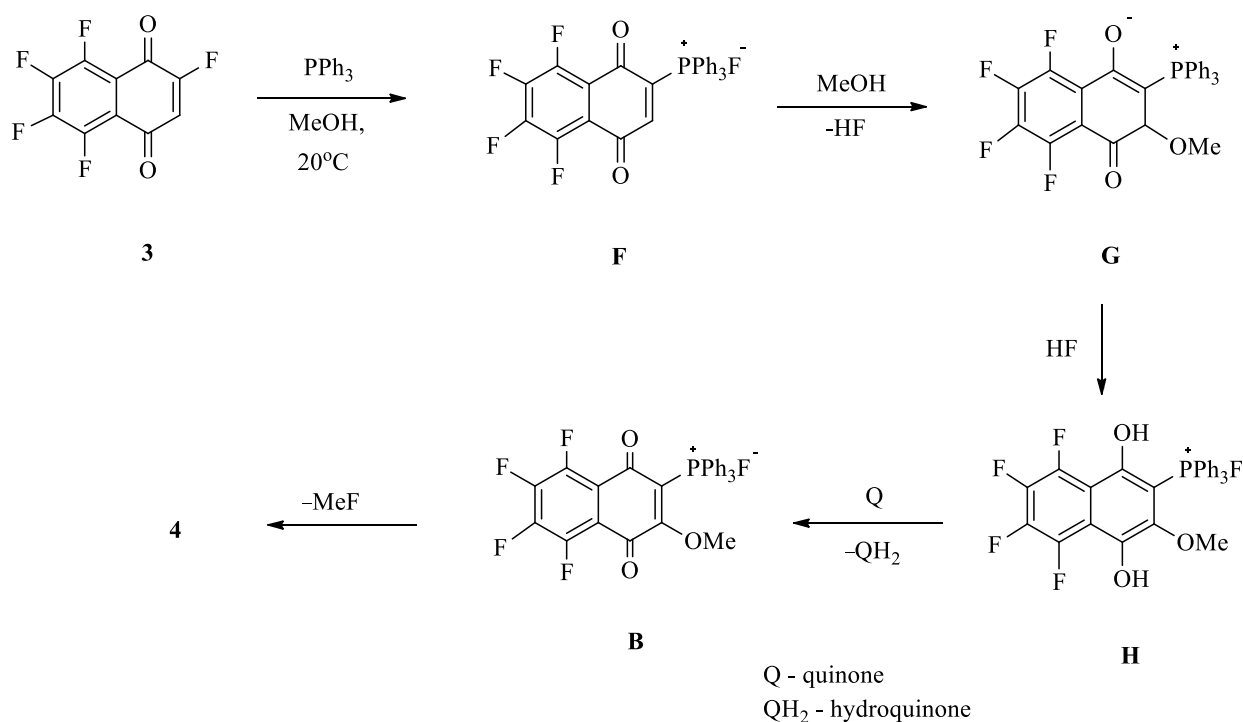
Interaction of quinone **2** with triphenylphosphine in methanol gave in a 90% yield a betaine – 5,6,7,8-tetrafluoro-3-(triphenyl- $\lambda^5$ -phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione **4** – whose electronic structure could be depicted in a first approximation by a resonance of structures **C**, **D**, and **E** (Scheme 1).



**Scheme 1.** General synthetic route to the title compounds **4–6**.

Analogously to the earlier described synthesis of ammonium betaine **1**,<sup>4</sup> one may believe that phosphonium salt **A** is originally formed, in which a triphenylphosphonium group activates effectively the neighboring position 3 for a nucleophilic attack, whereupon the rapid F<sup>3</sup> substitution occurs by methanol to give quinone **B**. Nucleophilic demethylation of this quinone by the action of a fluoride anion leads to **4**. Similarly, by the action of diphenyl(2,5-difluorophenyl)phosphine or biphenylmethylphosphine on quinone **2** synthesized are, respectively, 3-[(2,5-difluorophenyl)diphenyl-λ<sup>5</sup>-phosphanylidene]-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalene-1,2,4-trione **5** or 5,6,7,8-tetrafluoro-3-(methyldiphenyl-λ<sup>5</sup>-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione **6** (Scheme 1).

The interaction of naphthoquinone **3** with triphenylphosphine resulted in ~25% consumption of the starting material to give betaine **4** in 18% isolated yield (Scheme 2).



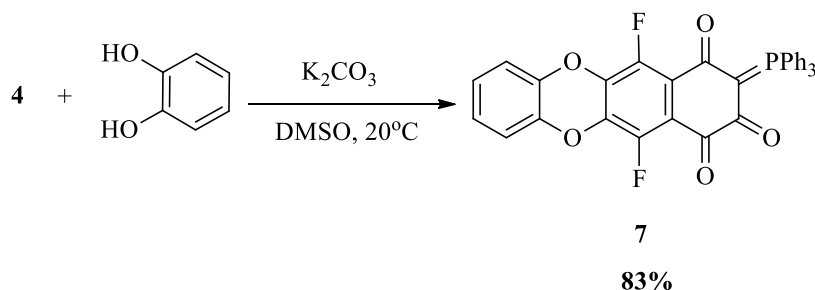
**Scheme 2.** Formation of betaine **4** from quinone **3**.

By analogy to Scheme 1 and literature data,<sup>5</sup> this transformation consists supposedly in formation of phosphonium salt **F** and the subsequent methanol addition to its position 3 to give betaine **G**. The latter adds HF to give hydroquinone **H**, which is oxidized, apparently, by quinones being present in the system to compound **B** that converts eventually to betaine **4**.

### Aryloxydefluorination of quinone **2** by action of pyrocatechol

Compounds **4–6** are promising building blocks for the synthesis of various derivatives as potentially biologically active compounds. Ample opportunities of their modification on a

benzene moiety are afforded by use of fluorine nucleophilic substitutions. In the present work this is exemplified by the equimolar interaction of **4** with pyrocatechol in the presence of potassium carbonate to yield a 1,4-dibenzodioxin derivative – 6,11-difluoro-9-(triphenyl- $\lambda^5$ -phosphanylidene)-7,8,9,10-tetrahydro-5,12-dioxatetracene-7,8,10-trione **7** (Scheme 3).



**Scheme 3.** Synthesis of 5,12-dioxatetracene **7**.

Its structure is confirmed by the presence in the  $^{19}\text{F}$  NMR spectrum of two doublets with  $^{para}J_{\text{FF}} = 13.6$  Hz belonging to  $\text{F}^6$  and  $\text{F}^{11}$ . Two isomers of **7** were also observed in the product mixture in amounts of 4 to 10% emerging obviously via substitution of  $\text{F}^5$  and  $\text{F}^6$  or  $\text{F}^7$  and  $\text{F}^8$  in **4**. They manifest themselves by the presence of doublets with  $^{ortho}J_{\text{FF}} = 19\text{--}20$  Hz in a  $^{19}\text{F}$  NMR spectrum.

All new compounds were characterized by  $^1\text{H}$ ,  $^{19}\text{F}$ , and  $^{31}\text{P}$  NMR spectra and MS data (see the experimental section). The  $^{19}\text{F}$  NMR characteristics of quinones **4–6** nicely agree with similar data for pyridinium betaine: 4 signals in these spectra are multiplets located at  $\delta$  22–24 for  $\text{F}^5$  and  $\text{F}^8$  and 11–17 ppm for  $\text{F}^6$  and  $\text{F}^7$ , their spin coupling structures being typical for *ortho* disubstituted tetrafluorobenzenes ( $^{ortho}J_{\text{FF}} \approx 19$ ,  $^{meta}J_{\text{FF}} = 8\text{--}10$ ,  $^{para}J_{\text{FF}} = 13.6\text{--}13.8$  Hz).

## Experimental Section

**General.**  $^1\text{H}$  NMR,  $^{19}\text{F}$ , and  $^{31}\text{P}$  spectra were recorded on a Bruker AV-300 spectrometer [300.13, 282.36, and 121.50 MHz, respectively] with residual protons in deuterated solvents, external  $\text{C}_6\text{F}_6$  and internal  $\text{H}_3\text{PO}_4$  as standards. HRMS data were obtained with a “DFS” spectrometer. The melting points were determined on an FP 900 Thermosystem microscope melting point apparatus (Mettler-Toledo International Inc., Zürich, Switzerland). Solvents and reagents were reagent quality.

Compounds **2**,<sup>6</sup> **3**<sup>7</sup> and diphenyl(2,5-difluorophenyl)phosphine<sup>8</sup> were prepared according to the literature procedures. Methanol and methylene chloride were distilled. DMSO was dried by molecular sieves 3Å. Triphenylphosphine was crystallized from diethyl ether.

**5,6,7,8-Tetrafluoro-3-(triphenyl- $\lambda^5$ -phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione (4).** **Method A.** A mixture of quinone **2** (0.048 g, 0.180 mmol), triphenylphosphine (0.049 g, 0.187 mmol) and methanol (0.75 mL) was stirred under argon for 48 h at 20 °C. A precipitate was centrifuged off, washed with methanol (2×0.5 mL), dried in vacuum (0.5 torr) to obtain compound **4** (0.048 g, 53%). After evaporation of the solvent, the dry residue was crystallized from ethanol to yield an additional amount (0.034 g) of the product, an overall yield of **4** being 0.082 g (90%), bright yellow crystals thermally decomposing without melting.  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ),  $\delta$  7.8 (m, 6H, CH), 7.7 (m, 3H, CH), 7.6 (m, 6H, CH).  $^{19}\text{F}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ),  $\delta$  22.4 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 10$  Hz,  $para J_{\text{FF}} = 13.8$  Hz,  $\text{F}^5$  or  $8$ ), 21.8 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 8$  Hz,  $para J_{\text{FF}} = 13.8$  Hz,  $\text{F}^5$  or  $8$ ), 15.9 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 10$  Hz,  $\text{F}^6$  or  $7$ ), 11.0 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 8$  Hz,  $\text{F}^6$  or  $7$ ).  $^{31}\text{P}\{^1\text{H}\}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ),  $\delta$  15.3 (s). MS,  $m/z$  ( $I_{\text{rel.}}$ , %): 506 [ $\text{M}$ ] $^+$  (14), 477 [ $\text{M}-\text{H}-\text{CO}$ ] $^+$  (48), 262 [ $\text{M}-\text{C}_{10}\text{F}_4\text{O}_3$ ] $^+$  (100). HRMS for  $\text{C}_{28}\text{F}_4\text{H}_{15}\text{O}_3\text{P}$  [ $\text{M}$ ] $^+$ : calcd. 506.0690, found 506.0685.

**Method B.** A mixture of quinone **3** (0.0925 g, 0.373 mmol), triphenylphosphine (0.0978 g, 0.373 mmol) and methanol (1.5 mL) was stirred for 2 weeks under argon at 20 °C and analyzed by  $^{19}\text{F}$  NMR and  $^{31}\text{P}$  NMR (Scheme 2). Methanol was distilled off up to a residual volume of 0.5 mL, a precipitate was centrifuged off and purified by TLC (Sorbfil, diethyl ether) to yield compound **4** (0.033 g, 18%).

**3-[(2,5-Difluorophenyl)diphenyl- $\lambda^5$ -phosphanylidene]-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalene-1,2,4-trione (5).** A mixture of quinone **2** (0.076 g, 0.285 mmol), diphenyl(2,5-difluorophenyl)phosphine (0.085 g, 0.285 mmol) and methanol (1.3 mL) was stirred for 48 h under argon at 20 °C. A precipitate was centrifuged off, washed with methanol (2×0.2 mL) and dried in vacuum (0.5 torr) to give the title compound **5** (0.096 g, 62%) as bright yellow crystals thermally decomposing without melting.  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ,  $\text{CH}_2\text{Cl}_2$ ),  $\delta$  7.92–7.81 (m, 4H,  $\text{C}_6\text{H}_5$ ), 7.80–7.71 (m, 2H,  $\text{C}_6\text{H}_5$ ), 7.69–7.58 (m, 4H,  $\text{C}_6\text{H}_5$ ), 7.51 (m, 1H,  $\text{C}_6\text{F}_2\text{H}_3$ ), 7.29 (m, 1H,  $\text{C}_6\text{F}_2\text{H}_3$ ), 7.05 (m, 1H,  $\text{C}_6\text{F}_2\text{H}_3$ ).  $^{19}\text{F}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ,  $\text{CH}_2\text{Cl}_2$ ),  $\delta$  61.8 (m, 1F,  $\text{C}_6\text{F}_2\text{H}_3$ ), 46.7 (m, 1F,  $\text{C}_6\text{F}_2\text{H}_3$ ), 23.6 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 10$  Hz,  $para J_{\text{FF}} = 13.8$  Hz,  $\text{F}^5$  or  $8$ ), 22.7 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 9$  Hz,  $para J_{\text{FF}} = 13.8$  Hz,  $\text{F}^5$  or  $8$ ), 17.1 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 10$  Hz,  $\text{F}^6$  or  $7$ ), 12.5 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 9$  Hz,  $\text{F}^6$  or  $7$ ).  $^{31}\text{P}\{^1\text{H}\}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ,  $\text{CH}_2\text{Cl}_2$ ),  $\delta$  9.4 (dd,  $^3J_{\text{PF}} \sim ^4J_{\text{PF}} = 3$  Hz). MS,  $m/z$  ( $I_{\text{rel.}}$ , %): 542 [ $\text{M}$ ] $^+$  (7), 513 [ $\text{M}-\text{H}-\text{CO}$ ] $^+$  (28), 298 [ $\text{M}-\text{C}_{10}\text{F}_4\text{O}_3$ ] $^+$  (100). HRMS for  $\text{C}_{28}\text{F}_6\text{H}_{13}\text{O}_3\text{P}$  [ $\text{M}$ ] $^+$ : calcd. 542.0501, found 542.0490.

**5,6,7,8-Tetrafluoro-3-(methyl-diphenyl- $\lambda^5$ -phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione (6).** A mixture of quinone **2** (0.100 g, 0.376 mmol), diphenylmethylphosphine (0.075 g, 0.376 mmol) and methanol (1.5 mL) was stirred for 48 h under argon at 20 °C to give the mixture containing compounds **6** and **2** (64 and 18%, accordingly). The solvent was distilled off, a residue was crystallized from ethanol (1 mL) and purified by TLC (Sorbfil, chloroform) to yield the title compound **6** (0.05 g, 30%), bright yellow crystals, mp 179 °C.  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ),  $\delta$  7.92–7.81 (m, 4H,  $\text{C}_6\text{H}_5$ ), 7.76–7.68 (m, 2H,  $\text{C}_6\text{H}_5$ ), 7.66–7.58 (m, 4H,  $\text{C}_6\text{H}_5$ ), 2.6 (d,  $^2J_{\text{PH}} = 14.2$  Hz, 3H,  $\text{CH}_3$ ).  $^{19}\text{F}$  NMR ( $(\text{CD}_3)_2\text{CO}$ ),  $\delta$  22.5 (ddd,  $ortho J_{\text{FF}} \approx 19$  Hz,  $meta J_{\text{FF}} \approx 10$

Hz,  $^{para}J_{FF} = 13.8$  Hz,  $F^{5 \text{ or } 8}$ ), 21.8 (ddd,  $^{ortho}J_{FF} \approx 19$  Hz,  $^{meta}J_{FF} \approx 8$  Hz,  $^{para}J_{FF} = 13.8$  Hz,  $F^{5 \text{ or } 8}$ ), 15.9 (ddd,  $^{ortho}J_{FF} \approx 19$  Hz,  $^{meta}J_{FF} \approx 10$  Hz,  $F^{6 \text{ or } 7}$ ), 11.1 (ddd,  $^{ortho}J_{FF} \approx 19$  Hz,  $^{meta}J_{FF} \approx 8$  Hz,  $F^{6 \text{ or } 7}$ ).  $^{31}P\{^1H\}$  NMR (( $CD_3$ ) $_2CO$ ),  $\delta$  13.6 (s). MS,  $m/z$  ( $I_{rel.}$ , %): 444 [ $M$ ] $^+$  (6), 200 [ $M-C_{10}F_4O_3$ ] $^+$  (62). HRMS for  $C_{23}F_4H_{13}O_3P$  [ $M$ ] $^+$ : calcd. 444.0533, found 444.0535.

#### **6,11-Difluoro-9-(triphenyl- $\lambda^5$ -phosphanylidene)-7,8,9,10-tetrahydro-5,12-dioxatetracene-**

**7,8,10-trione (7).** A mixture of betaine **4** (0.051 g, 0.101 mmol), pyrocatechol (0.011 g, 0.101 mmol), potassium carbonate (0.028 g, 0.203 mmol) and DMSO (1.5 mL) was stirred for 6 h at 20 °C and analyzed by  $^{19}F$  and  $^{31}P$  NMR (Scheme 3). Water (3 mL) was added, a precipitate was centrifuged off, washed with water (1 mL), dried on air and the titled compound **7** (0.048 g, 83%) was isolated by TLC (Sorbfil, chloroform–methylene chloride, 1:1) as bright yellow crystals decomposing at heating without melting.  $^1H$  NMR ( $CDCl_3$ ),  $\delta$  7.73–7.64 (m, 6H,  $C_6H_5$ ), 7.64–7.56 (m, 3H,  $C_6H_5$ ), 7.55–7.46 (m, 6H,  $C_6H_5$ ), 7.02–6.97 (m, 4H,  $C_6H_4$ ).  $^{19}F$  NMR ( $CDCl_3$ ),  $\delta$  24.0 (d,  $^{para}J_{FF} = 13.6$  Hz,  $F^{6 \text{ or } 11}$ ), 21.6 (d,  $^{para}J_{FF} = 13.6$  Hz,  $F^{6 \text{ or } 11}$ ).  $^{31}P\{^1H\}$  NMR ( $CDCl_3$ ),  $\delta$  14.8 (s). MS,  $m/z$  ( $I_{rel.}$ , %): 577 [ $M+H$ ] $^+$  (2), 547 [ $M-H-CO$ ] $^+$  (25), 262 [ $M-C_{16}H_5F_2O_5$ ] $^+$  (52). HRMS for  $C_{34}F_2H_{19}O_5P$  [ $M+H$ ] $^+$ : calcd. 577.1011, found [ $M+H$ ] $^+$  577.1310.

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