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A convenient synthesis of 8,8′-spiro-bi(chromano-1,2-oxaphosphinine) derivatives

Igor O. Nasibullin,[a] Andrey V. Nemtarev*[a,b] and Vladimir F. Mironov[a,b]

[a] *A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, 420088 Kazan, Russian Federation. E-mail: a.nemtarev@mail.ru*
[b] *Kazan (Volga Region) Federal University, 420008 Kazan, Russian Federation*

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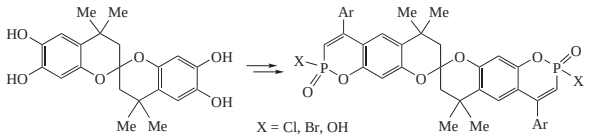
8,8′-Spirobi(chromano-1,2-oxaphosphinines) were obtained by the reaction between phosphorylated derivatives of spirodichromane and arylacetylenes with a high chemoselectivity.



Spirocyclic polyhydroxyarenes of chromane series are a special group of polyphenolic compounds that possess a broad spectrum of practically important properties. Spirocyclic compounds have nonlinear structures and comprise rigidly bound annular moieties, owing to which they can be used to obtain polymeric and supramolecular compounds with various structures.[1–5] Low-molecular spirochromane derivatives containing chromophoric groups form 3D holographic gratings and can be employed to create holographic data storage systems.[6]

Incorporation of four hydroxy groups, which form two catechol systems, into the spirochromane structure opens the way to phosphacoumarin (areno-1,2-oxaphosphinine) derivatives.[7] The structural similarity of this class of compounds to natural coumarins and the presence of a phosphorus atom predetermine the biological activity of phosphacoumarins and phosphaisocoumarins. For example, Li *et al.*[8] performed a rather comprehensive study of the inhibiting effect of phosphorus-containing compounds with isocoumarin structure on the activity of cholesterol esterase.

In this study, we suggest an easy and efficient access to 8,8′-spirobi(chromano[6,7-*e*]-1,2-oxaphosphinines) based on the reaction of phosphorylated derivatives of 6,6′,7,7′-tetrahydroxy-4,4,4′,4′-tetramethyl-2,2′-spirobichromane **1** with acetylenes. The starting spirochromane **1** was obtained by condensation of 1,2,4-triacetoxybenzene with acetone in the presence of acetic and hydrochloric acids.[9] The structure of the resulting tetraol was confirmed by spectral methods (^{1}H NMR spectroscopy, mass spectrometry).

It is known that polyhydroxyarenes are poorly soluble in most organic solvents. For this reason, tetraol **1** was converted to silyl ether **2** by the reaction with excess chlorotrimethylsilane in the presence of triethylamine (Scheme 1).† Compound **2** is a dark oily liquid well soluble in dichloromethane. Further, silyl ether **2** was treated with a phosphorus trihalide taken in excess.‡ The phosphorylation occurs under mild conditions to give phosphites **3a**,**b** in high yields. According to ^{31}P NMR data, the content of compounds **3a**,**b** in the reaction mixture was 90–95%. It should also be noted that compound **3a** manifests itself in the ^{31}P-{^{1}H}NMR spectrum as two closely-spaced singlets (δ_P 198.6 and 199.5) in 7.9 : 1 ratio. This suggests that stereoisomers exist, possibly with different orientations of the halogen atoms.

Halophosphites **3a**,**b** were converted to chloro- and bromophosphoranes **4a**,**b** by the reactions with phosphorus pentachloride and molecular bromine, respectively (see Scheme 1).§ Analysis of

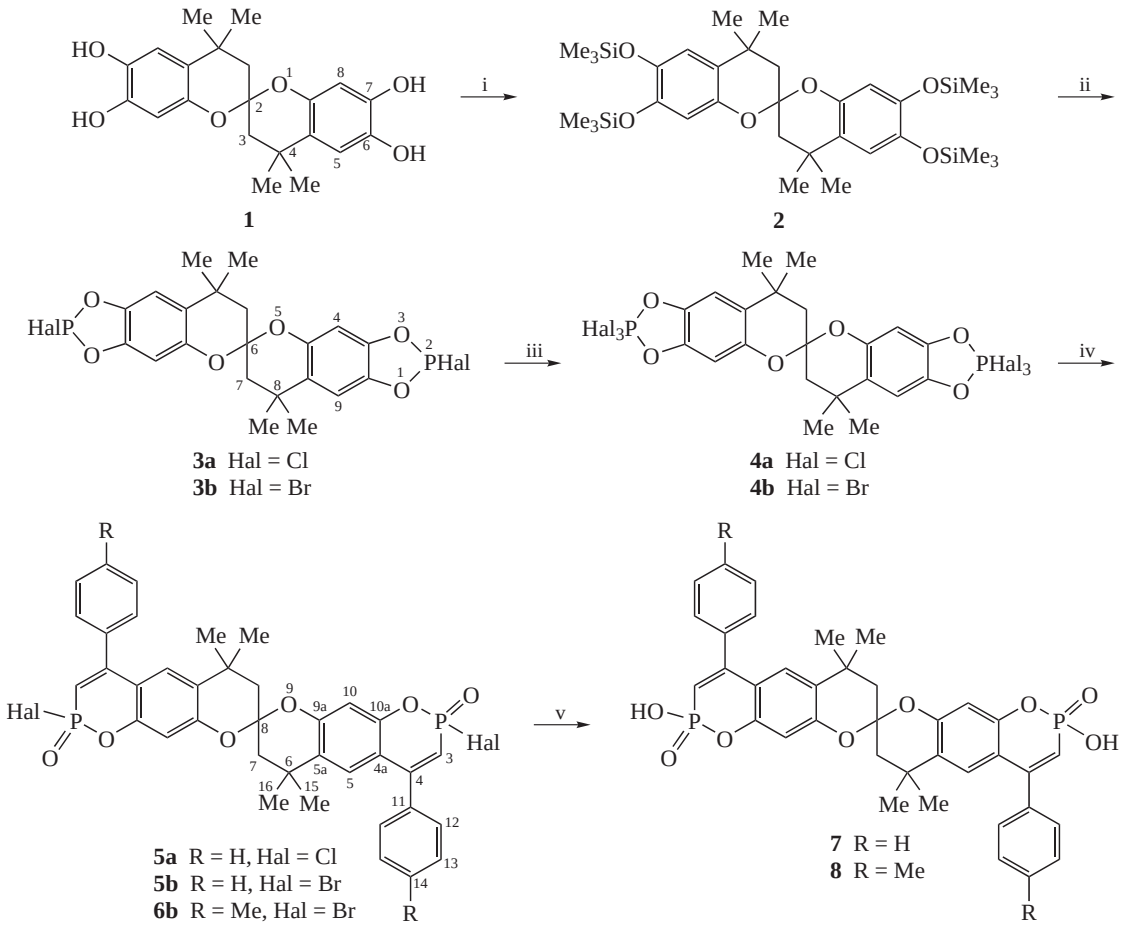
† *6,6′,7,7′-Tetrakis(trimethylsiloxy)-4,4,4′,4′-tetramethyl-2,2′-spirobichromane* **2**. A solution of chlorotrimethylsilane (2.9 ml, 23 mmol) in benzene (15 ml) was added dropwise to a solution of spiro chromane **1** (2.18 g, 5.8 mmol) and NEt_3 (3.2 ml, 23 mmol) in 100 ml of absolute benzene. The mixture was stirred at room temperature for 0.5 h. Further, the mixture was heated up to 90 °C and stirred for 1.5 h. On the next day, the mixture was filtered and the solvent was removed *in vacuo*. The residue was a dark oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.21 (s, 18H, $SiMe_3$), 0.25 (s, 18H, $SiMe_3$), 1.32 (s, 6H, Me), 1.53 (s, 6H, Me), 1.94 (d, 2H, CH_2, ^2J 13.9 Hz), 2.07 (d, 2H, CH_2, ^2J 13.9 Hz), 6.15 (s, 2H, H^8), 6.76 (s, 2H, H^5).

‡ *2,2′-Dichloro-8,8,8′,8′-tetramethyl-6,6′-spirobi(chromano[6,7-*d*]-1,3,2-dioxaphosphole)* **3a**. A solution of compound **2** (2.64 g, 4 mmol) in chloroform (15 ml) was added to a solution of phosphorus trichloride (2.0 ml, 23 mmol) in chloroform (10 ml). The mixture was stirred at room temperature for 1.5 h. The solvent and volatile compounds were removed *in vacuo* (12 Torr). Crystalline precipitate of compound **3a** was formed. Yield 1.8 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (s, 6H, Me), 1.61 (s, 6H, Me), 2.01 (br. d, 2H, two A-parts of two AB-spectra, $^2J_{AB}$ 14.0 Hz), 2.15 (br. d, 2H, two B-parts of two AB-spectra, $^2J_{AB}$ 14.1 Hz), 6.59 (br. s, 2H, HC^9), 7.22 (br. s, 2H, HC^4). ^{31}P-{^{1}H} NMR (162 MHz, $CDCl_3$) δ_P: 176.4 (s).

*2,2′-Dibromo-8,8,8′,8′-tetramethyl-6,6′-spirobi(chromano[6,7-*d*]-1,3,2-dioxaphosphole)* **3b**. A solution of compound **2** (3.83 g, 5.8 mmol) in chloroform (15 ml) was added to a solution of phosphorus tribromide (2.2 ml, 23 mmol) in chloroform (5 ml). The reaction mixture was stirred at room temperature for 1.5 h. Crystalline precipitate of compound **3b** was formed, mp 208 °C, yield **3g** (89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (br. s, 6H, Me), 1.63 (br. s, 6H, Me), 2.05 (br. d, 2H, two A-parts of two AB-spectra, $^2J_{AB}$ 14.1 Hz), 2.16 (br. d, 2H, two B-parts of two AB-spectra, $^2J_{AB}$ 14.1 Hz), 6.61 (br. s, 2H, H^8), 7.25 (br. s, 2H, H^5). ^{31}P NMR (162 MHz, CCl_4) δ_P: 198.6 (s), 199.5 (s).

§ *2,2,2,2′,2′,2′-Hexachloro-8,8,8′,8′-tetramethyl-6,6′-spirobi(chromano-[6,7-*d*]-1,3,2-dioxaphosphole)* **4a**. A solution of compound **3a** (1 g, 2 mmol) in dichloromethane (10 ml) was added to a suspension of phosphorus pentachloride (0.83 g, 4 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 2 h at room temperature until complete dissolution of phosphorus pentachloride. The solvent and volatile compounds were removed *in vacuo* (12 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 6H, Me), 1.57 (s, 6H, Me), 1.99 (d, 2H, two A-parts of two AB-spectra, $^2J_{AB}$ 14.0 Hz), 2.12 (d, 2H, two B-parts of two AB-spectra, $^2J_{AB}$ 14.0 Hz), 6.40 (br. s, 2H, H^9), 7.08 (br. s, 2H, H^4). ^{31}P-{^{1}H} NMR (162 MHz, $CDCl_3$) δ_P: –25.7 (s).

*2,2,2,2′,2′,2′-Hexabromo-8,8,8′,8′-tetramethyl-6,6′-spirobi(chromano-[6,7-*d*]-1,3,2-dioxaphosphole)* **4b**. Bromine (0.6 ml, 12 mmol) was added to a cooled (–20 °C) solution of compound **3b** (3.54 g, 6 mmol) in dichloromethane (15 ml). The orange precipitate was obtained. ^{31}P-{^{1}H} NMR (162 MHz, CH_2Cl_2) δ_P: –189.0 (br. s).



Scheme 1 *Reagents and conditions:* i, Me_3SiCl (4 equiv.), NEt_3 (4 equiv.); ii, PCl_3 or PBr_3; iii, PCl_5 or Br_2; iv, $PhC{\equiv}CH$ or 4-$MeC_6H_4C{\equiv}CH$; v, H_2O.

the ^{31}P NMR spectra of the reaction mixtures allowed us to determine the quantitative and qualitative composition of the products. In fact, the content of phosphorane **4b**, which manifested itself as a broadened signal near δ_p –189.0 in the ^{31}P NMR spectrum, was about 90%. Chlorophosphorane **4a** manifested itself in the ^{31}P spectrum as a singlet around δ_p –25.4; its content in the reaction mixture was 95%. Due to the hydrolytic and thermal (in the case of tribromophosphoranes) instability, compounds **4a**,**b** were not isolated pure and used in the further reactions with acetylenes as crude materials.

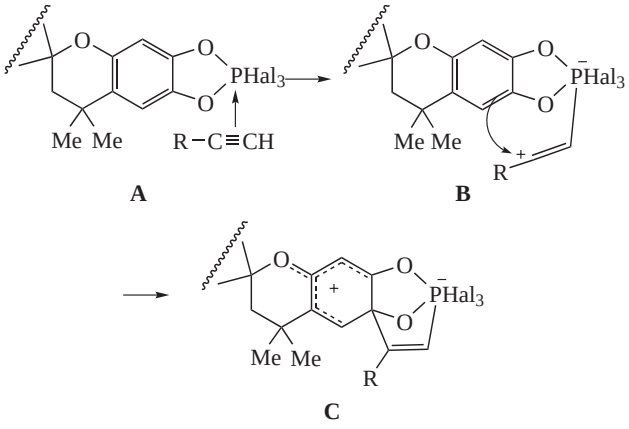
On addition of arylacetylenes to phosphorane **4b**,¶ dissolution of the latter to give a homogeneous light-brown solution was observed, which indicates that the reaction occurs rather quickly. In the ^{31}P spectrum of the reaction mixture, compound **5b** exhibited three doublets (δ_p 9.7, 9.8, and 10.4) in 1 : 1 : 2 ratio with similar coupling constants ($^2J_{PCH}$ 25.8–26.9 Hz). This set of signals indicates the formation of a mixture of phosphinine **5b** stereoisomers due to the chirality of the two phosphorus atoms and the pseudochirality of the C^8 atom.

The reaction of chloro derivative **4a** with terminal acetylenes occurs by a similar pathway to afford oxaphosphinine **5a (**see Scheme 1**)**. As shown previously,[10] the reactions of trichlorophospholes with acetylenes often involve the migration of a chlorine atom to the aromatic ring of oxaphosphorines with replacement of hydrogen or one of the substituents (bromine, *tert*-butyl). In this case, the chromane system is not attacked by a halogen atom. This fact is probably due to the donor effect of the oxygen

¶ *2,2'-Dichloro-6,6,6',6'-tetramethyl-4,4'-diphenyl-8,8'-spirobi(chromano-[6,7-e]-1,2-oxaphosphinine)-2,2'-dioxide* **5a**. Phenylacetylene (0.88 ml, 8 mmol) was added to a mixture containing compound **4a** (1.3 g, 2 mmol). After the reaction was complete (30 min), the volatiles were removed *in vacuo* (12 Torr) to afford the pale brown glassy substance being the mixture of diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22, 1.25 (both s, 6H, Me), 1.52, 1.55 (both s, 6H, Me), 2.02 (br. d, 2H, two A-parts of two AB-spectra, $^2J_{AB}$ 14.3 Hz), 2.16 (br. d, 2H, two B-parts of two AB-spectra, $^2J_{AB}$ 14.3 Hz), 6.18, 6.23 (both d, 2H, H^3, $^2J_{PCH}$ 24.3 Hz), 6.65, 6.68 (both s, 2H, H^{10}), 7.25 (br. s, 2H, H^5), 7.38–7.46 (br. m, 4H, Ph), 7.48–7.59 (br. m, 6H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 30.67, 30.71 (both s, C^6), 32.23, 32.40 (both s, Me), 45.72 (s, C^7), 99.07 (s, C^8), 108.22, 108.28 (both d, C^{10}, $^3J_{POCC}$ 8.7 and 8.4 Hz), 111.51, 111.93 (both d, C^3, $^1J_{PC}$ 156.5 and 156.6 Hz), 115.89, 116.11 (both d, C^{4a}, $^3J_{PCCC}$ 18.2 and 18.1 Hz), 126.42, 126.62 (both s, C^5), 127.36, 127.42 (both s, C^{5a}), 128.53, 128.58 (both s, C^{13}), 128.78, 128.83 (both s, C^{12}), 129.86, 130.01 (both s, C^{14}), 137.63, 137.70 (both d, C^{11}, $^3J_{PCCC}$ 21.0 and 21.3 Hz), 150.27, 150.31 (both d, C^{10a}, $^2J_{POC}$ 9.2 and 9.4 Hz), 153.15, 153.19 (both s, C^{9a}), 156.80, 157.03 (both d, C^4, $^2J_{PCC}$ 2.2 and 2.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ_P: 20.0 (d, $^2J_{PCH}$ 24.5 Hz), 20.3 (d, $^2J_{PCH}$ 24.5 Hz).

2,2'-Dibromo-6,6,6',6'-tetramethyl-4,4'-diphenyl-8,8'-spirobi(chromano-[6,7-e]-1,2-oxaphosphinine)-2,2'-dioxide **5b**. Phenylacetylene (2.5 ml, 23.2 mmol) was added to a cooled mixture containing compound **4b** (5.4 g, 6 mmol). The reaction mixture was heated up to room temperature, the formed precipitate fully dissolved. After the reaction was complete (30 min), the solvent and volatiles were removed *in vacuo* (12 Torr) to give diastereosomers of compound **5b** as a pale brown glassy substance. ^{31}P NMR (162 MHz, CH_2Cl_2) δ_P: 9.7 ($^2J_{PCH}$ 25.8 Hz), 9.8 ($^2J_{PCH}$ 26.9 Hz), 10.4 ($^2J_{PCH}$ 26.9 Hz).

2,2'-Dibromo-6,6,6',6'-tetramethyl-4,4'-bis(4-methylphenyl)-8,8'-spirobi(chromano[6,7-e]-1,2-oxaphosphinine)-2,2'-dioxide **6b**. 4-Methylphenylacetylene (1.85 g, 16 mmol) was added to a cooled mixture containing compound **4b** (3.6 g, 4 mmol). The reaction mixture was heated up to room temperature, the formed precipitate fully dissolved. After reaction was complete (30 min), the volatiles were removed *in vacuo* (12 Torr) to leave the pale brown glassy substance being the mixture of diastereoisomers **6b**. ^{31}P NMR (202.5 MHz, CH_2Cl_2) δ_P: 10.3 (d, $^2J_{PCH}$ 25.4 Hz), 10.4 (d, $^2J_{PCH}$ 26.8 Hz), 11.1 (d, $^2J_{PCH}$ 26.8 Hz).



Scheme 2

††*2,2′-Dihydroxy-6,6,6′,6′-tetramethyl-4,4′-diphenyl-8,8′-spirobi(chromano[6,7-e]-1,2-oxaphosphinine)-2,2′-dioxide* **7**. Hydrolysis of the reaction mixture containing **5a** or **5b** in dioxane affords the colorless crystals of compound **7**. Yield 2.5 g (63%), mp 340 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (s, 6H, Me), 1.42 (s, 6H, Me), 2.04 (d, 2H, two A-parts of two AB-spectra, $^2J_{AB}$ 14.5 Hz), 2.17 (d, 2H, two B-parts of two AB-spectra, $^2J_{AB}$ 14.4 Hz), 6.11 (d, 2H, H^3, ^2J 18.1 Hz), 6.58 (s, 2H, H^{10}), 7.11 (s, 2H, H^5), 7.38–7.41 (m, 4H, Ph), 7.52–7.54 (m, 6H, Ph). ^{13}C-{^{1}H} NMR (100.6 MHz, DMSO-d_6) δ_C: 30.36 (s, C^6), 32.46 (s, Me), 45.01 (s, C^7), 99.35 (s, C^8), 107.70 (d, C^{10}, $^3J_{POCC}$ 6.8 Hz), 113.60 (d, C^3, $^1J_{PC}$ 170.1 Hz), 117.04 (d, C^{4a}, $^3J_{PCCC}$ 16.4 Hz), 127.09 (s, C^5), 127.35 (s, C^{5a}), 128.77 (s, C^{13}), 129.15 (s, C^{12}), 129.50 (s, C^{14}), 139.05 (d, C^{11}, $^3J_{PCCC}$ 18.7 Hz), 150.81 (d, C^{10a}, $^2J_{POC}$ 6.8 Hz), 152.06 (C^{9a}), 152.35 (d, C^4, $^2J_{PCC}$ 1.9 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ_P: 5.8 (d, $^2J_{PCH}$ 18.0 Hz). MS (MALDI-TOF), *m/z:* 668.9 (calc. for $C_{37}H_{34}O_8P_2$, *m/z:* 668.6).

2,2′-Dihydroxy-6,6,6′,6′-tetramethyl-4,4′-bis(4-methylphenyl)-8,8′-spirobi(chromano[6,7-e]-1,2-oxaphosphinine)-2,2′-dioxide **8**. Hydrolysis of the reaction mixture containing **6b** in dioxane affords the colorless crystals of compound **8**. Yield 1.6 g (58%), mp 343 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15 (s, 6H, Me), 1.42 (s, 6H, Me), 2.03 (d, 2H, two A-parts of two AB-spectra, $^2J_{AB}$ 14.4 Hz), 2.16 (d, 2H, two B-parts of two AB-spectra, $^2J_{AB}$ 14.4 Hz), 2.39 (C^{14}Me, 6H), 6.04 (d, 2H, H^3, $^2J_{PH}$ 18.1 Hz), 6.54 (s, 2H, H^{10}), 7.14 (s, 2H, H^5), 7.28 (m, 4H, H^{13}, AA′-part of AA′ BB′-spectrum, $^3J_{HH}$ 7.6 Hz), 7.33 (m, 4H, H^{13}, BB′-part of AA′ BB′-spectrum, ^3J 7.6 Hz). ^{13}C-{^{1}H} NMR (150.9 MHz, DMSO-d_6) δ_C: 21.32 (C^{14}Me), 30.39 (s, C^6), 31.14 (s, C^{15}), 32.49 (s, C^{16}), 45.06 (C^7), 99.36 (C^8), 107.70 (d, C^{10}, $^3J_{POCC}$ 6.9 Hz), 113.20 (d, C^3, $^1J_{PC}$ 170.4 Hz), 117.10 (d, C^{4a}, $^3J_{PCCC}$ 16.2 Hz), 127.08 (s, C^5), 127.43 (s, C^{5a}), 128.73 (s, C^{13}), 129.74 (s, C^{12}), 136.18 (d, C^{11}, $^3J_{PCCC}$ 18.8 Hz), 139.11 (s, C^{14}), 150.86 (d, C^{10a}, $^2J_{POC}$ 6.8 Hz), 152.03 (s, C^{9a}), 152.34 (d, C^4, $^2J_{PCC}$ 1.9 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ_P: 6.1 (d, $^2J_{PCH}$ 17.8 Hz). MS (MALDI-TOF), *m/z*: 696.9 (calc. for $C_{38}H_{36}O_8P_2$, *m/z:* 696.6).

atom of the chromane system that participates in positive charge delocalization at the stage of formation of the σ-complex (structure **C**) after the formation of a π-complex (**A**) and σ-complex (**B**) in the reaction of phosphorane **4** with acetylene (Scheme 2).

Oxaphosphinines **5a**,**b** and **6b** were hydrolyzed in a dioxane/acetone medium to give individual phosphinines **7** and **8**†† as colourless crystalline compounds (see Scheme 1).

Based on the detailed analysis of the spectral data, one can conclude that the reaction of halophosphoranes **4a**,**b** with terminal arylacetylenes proceeds with a high regioselectivity. Namely, the *ipso*-substitution of an oxygen atom in the dioxaphospholane ring occurs at the *para*-position to the oxygen atom of the spirochromane system, in agreement with the assumed reaction mechanism that we discussed previously.[11]

In conclusion, we suggested an efficient chemoselective approach to 8,8′-spirobi(chromano[6,7-*e*]-1,2-oxaphosphinines) that are structural analogues of natural chromanocoumarins, based on the reaction of phosphorylated derivatives of 6,6′,7,7′-tetrahydroxy-4,4,4′,4′-tetramethyl-2,2′-spirobichromane with arylacetylenes.

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