Synthesis of hydrophilic and lipophilic 4-arylcoumarin phosphates

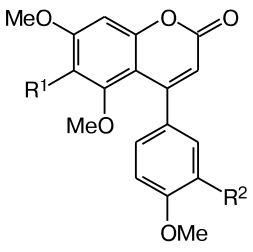
*A. N. Selikhov,[a] Y. B. Malysheva,[a] A. V. Nyuchev,[a] N. S. Sitnikov,[a] E. A. Sharonova,[a] A. S. Shavyrin,[b] S. Combes,[c] and A. Yu. Fedorov[a]**

[a]*N. I. Lobachevsky Nizhny Novgorod State University, 23 prosp. Gagarina, 603950 Nizhny Novgorod, Russian Federation. Fax: +7 (831) 462 3085. E-mail: afnn@rambler.ru*
[b]*G. A. Razyvaev Institute of Organometallic Chemistry, Russian Academy of Sciences, 49 ul. Tropinina, 603600 Nizhny Novgorod, Russian Federation. Fax: +7 (831) 462 7497. E-mail: andrew@imoc.sinn.ru*
[c]*Universites Aix-Marseille 1, 2 et 3, Faculte des Sciences Saint-Jerome, case 521, UMR 6264, 13397 Marseille Cedex 20, France. Fax: +33 (049) 128 8758. E-mail: Sebastien.Combes@univ-provence.fr*

Novel hydrophilic and lipophilic prodrugs, sodium 4-arylcoumarin dialkylphosphates and 4-arylcoumarin dioleyl phosphates, were synthesized by phosphorylation of 4-arylcoumarins with dialkylphosphites.

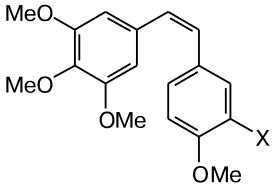
Key words: 4-arylcoumarins, water soluble prodrugs, lipophilic prodrugs, phosphorylation.

Natural[1] and synthetic[2] 4-arylcoumarins **1** possess high level of antitumor activity, *e.g.*, suppress mitotic spindle formation in the tumor cells thus inhibiting tubulin polymerization.[3] Two non-coplanar *syn* aryl moieties **A** and **B** linked by rigid C—C bond make structure of these derivatives similar to combretastatin A-4 (CA-4) **2a**, *cis*-stilbene separated from African plant *Combretum cafrum*, which exhibited significant antimitotic activity.[4] Low water solubility of 4-arylcoumarins **1** and CA-4 makes difficult their evaluation *in vivo*. Conversion of CA-4 and its analogs into water soluble prodrug forms[5] (**2b**) and amino acid derivatives[6] (**2c**) improve their pharmacokinetic profile, namely, make it possible to reach higher concentration of the therapeutic agent in blood, decrease the dose levels and, therefore, decrease its general toxicity.[7] Currently, fosbretabulin **2b** and ombrabulin **2c** are in phase III clinical trials.[8]



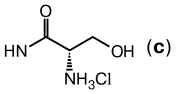
1

R^1, R^2 = H, OH, OMe



2

X = OH (**a**), $OP(O)(ONa)_2$ (**b**),



A serious drawback of CA-4 derivatives is that they are prone to *Z*,*E*-isomerization during storage and use, which significantly decrease antitumor activity.[4,9] This encourage us to synthesize a number of novel water soluble non-isomerizable neoflavonoid analogs of CA-4 phosphate derivatives, compounds **3** (Scheme 1).

The key step in the synthesis of 4-arylcoumarins **3** is Suzuki—Miyaura cross-coupling reaction[10] of coumarin triflates **4a—f** (see Ref. 11) with 3-hydroxy-4-methoxyphenylboronic acid bearing the methoxymethyl protecting group (see Scheme 1). Application of catalytic system $Pd(dppf)Cl_2$ (0.05 equiv.)—K_3PO_4 (3.0 equiv.)—Bu_4NBr (0.1 equiv.) (see Ref. 12) serves for the synthesis of target 4-arylcoumarins **5a—f** in high yields (58—95%) regardless of the number and position of the methoxy groups in the coumarin framework (see Scheme 1).

The methoxymethyl (MOM) protecting groups in compounds **5a—f** were cleaved by acid hydrolysis in acetone at 40 °C. Derivatives **6a—f** were obtained in 81—94% yields (see Scheme 1). Phosphorylation[13] of compounds **6a—f** by dibenzyl phosphite resulted in dibenzyl phosphates **7a—f** in good yields (59—81%). Debenzylation[14] of the latter by subsequent treatment with Me_3SiBr and MeONa afforded target products **3a—f** in 54—89% yields.

It is of note that water soluble prodrugs **3a—f** upon enzymatic dephosphorylation[15] in the cells can form 4-arylcoumarins **6a—f** exhibiting marked antitumor activity.[2a,b]

Along with hydrophilic coumarins **3a—f**, we synthesized lipophilic phosphate derivatives of 4-arylcoumarins, compounds **8a**,**d**,**f**, by the reaction of **6a**,**d**,**f** with dioleyl

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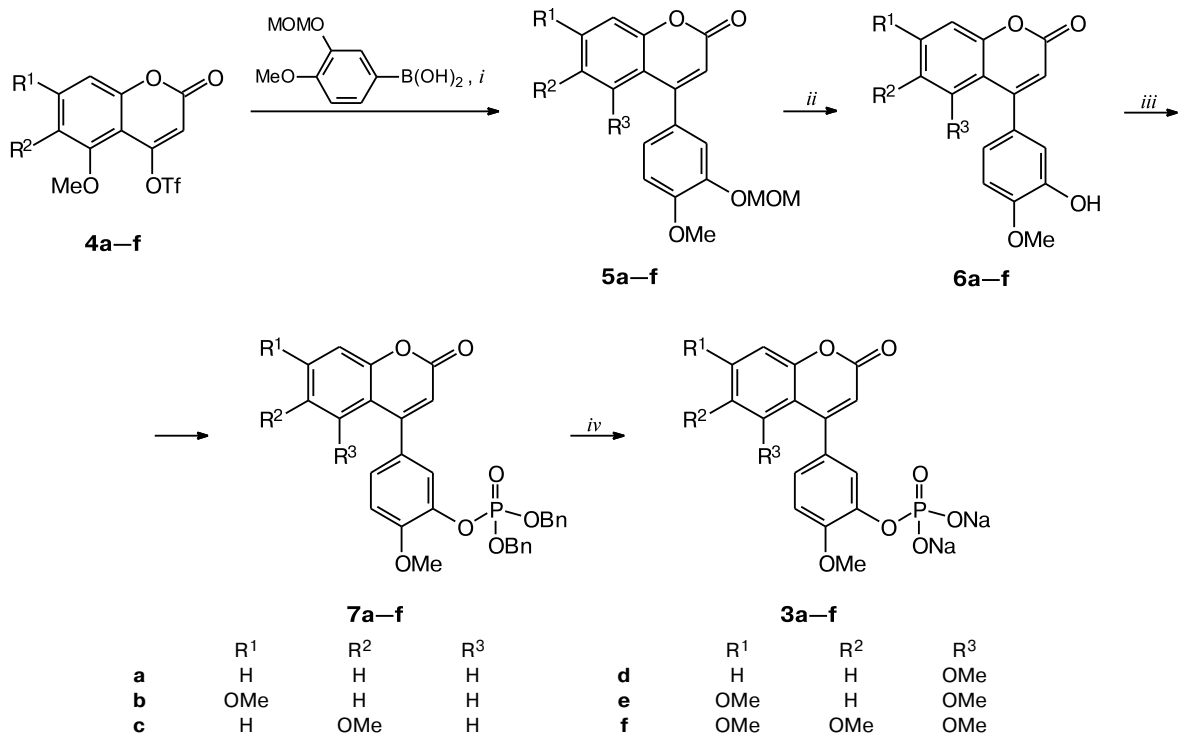
Схема 1

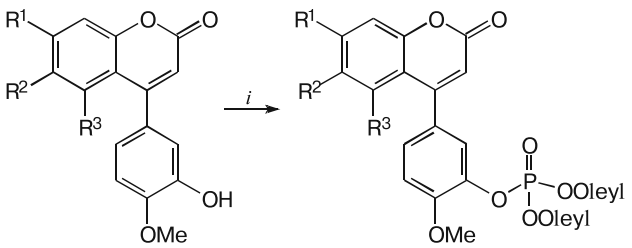


	R^1	R^2	R^3		R^1	R^2	R^3
a	H	H	H	**d**	H	H	OMe
b	OMe	H	H	**e**	OMe	H	OMe
c	H	OMe	H	**f**	OMe	OMe	OMe

Reagents and conditions: *i*. $Pd(dppf)Cl_2$ (0.05 equiv.), K_3PO_4 (3.0 equiv.), Bu_4NBr (0.1 equiv.), MeCN, 3 h, 80 °C; *ii*. HCl, acetone, 0.2—0.5 h, 40 °C; *iii*. $(BnO)_2P(O)H$ (1.7 equiv.), MeCN—CCl_4 (1 : 1), DIPEA (2.1 equiv.), DMAP (0.1 equiv.), 1 h, −10 °C; *iv*. 1) Me_3SiBr (6 equiv.), CH_2Cl_2, 1 ч, 20 °C; 2) MeONa (2 equiv.), MeOH, 0.5 h, 25 °C.

phosphite[16] (Scheme2). Lipophilic compounds **8a**,**d**,**f** were isolated in the yields of 61—69%.

Scheme 2



Oleyl is $Me(CH_2)_7CH{=}CH(CH_2)_8$

Reagents and conditions: *i*. $(OleylO)_2P(O)H$, CCl_4—MeCN—$CHCl_3$ (1 : 1 : 1), DIPEA (7 equiv.), DMAP (0.3 equiv.), 2 h, −10 °C.

Lipid prodrugs **8** can effectively be inserted into the lipid bilayer of targeted therapeutic liposome transport systems,[17] which could increase selectivity of therapeutic effect and reduce general toxicity[18] of 4-arylcoumarins **6**.

Currently, hydrophilic (**3a—f**) and hydrophobic (**8a**,**d**,**f**) prodrug forms of 4-arylcoumarins are in evaluation of *in vitro* cytotoxicity.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 in $CDCl_3$ at 400 and 101 MHz, respectively. The chemical shifts are given in the δ scale relative to Me_4Si. All commercially available reagents (Aldrich, Alfa Aesar) were used as purchased. The solvents were purified prior to use according to the standard procedures. Petroleum ether with b.p. 40—70 °C was used. 4-Arylcoumarin trifluoromethanesulfonates **4a—f** were synthesized by the known procedure.[19]

Compounds 5a—f (general procedure). A solution of coumarin 4-trifluoromethanesulfonate **4** (1 equiv.), arylboronic acid (1.3 equiv.), K_3PO_4 (3 equiv.), Bu_4NBr (0.1 equiv.), and $Pd(dppf)Cl_2$ (0.05 equiv.) in MeCN (1 mL per 0.086 mmol of compound **4**) was stirred at 80 °C for 3 h under argon. The solvent was removed *in vacuo*, purification of the residue by silica gel column chromatography yielded the target product.

4-(3′-Methoxymethoxymethyl-4′-methoxyphenyl)chromen-2-one (5a) was synthesized from coumarin 4-trifluoromethanesulfonate (121 mg, 0.41 mmol), 3-methoxymethoxymethyl-4-methoxyphenylboronic acid (112 mg, 0.53 mmol), $Pd(dppf)Cl_2$ (17 mg, 0.021 mmol), K_3PO_4 (261 mg, 1.23 mmol), and Bu_4NBr

(13 mg, 0.041 mmol). Elution with ethyl acetate—petroleum ether (3 : 2) afforded compound **5a** in a yield of 111 mg (86%), light yellow crystals, m.p. 142 °C. ^{1}H NMR ($CDCl_3$), δ: 3.52, 3.96 (both s, 3 H each, OCH_3); 5.26 (s, 2 H, CH_2); 6.36 (s, 1 H, H(3)); 7.02 (d, 1 H, H(5′), J = 8.4 Hz); 7.12 (dd, 1 H, H(6′), J = 8.4 Hz, J = 2.0 Hz); 7.23 (m, 2 H, H(2′), H(6)); 7.39 (d, 1 H, H(8), J = 7.6 Hz); 7.55 (m, 2 H, H(5), H(7)). ^{13}C NMR ($CDCl_3$), δ: 56.0, 56.3, 95.6, 111.8, 114.7, 116.9, 117.3, 119.0, 122.9, 124.0, 126.9, 127.7, 131.8, 146.5, 151.0, 154.2, 155.0, 160.8.

4-(3′-Methoxymethoxymethyl-4′-methoxyphenyl)-7-methoxychromen-2-one (5b) was synthesized from 7-methoxycoumarin 4-trifluoromethanesulfonate (**4b**) (133 mg, 0.41 mmol), 3-methoxymethoxymethyl-4-methoxyphenylboronic acid (112 mg, 0.53 mmol), Pd(dppf)Cl_2 (17 mg, 0.021 mmol), K_3PO_4 (261 mg, 1.23 mmol), and Bu_4NBr (13 mg, 0.041 mmol). Elution with ethyl acetate—petroleum ether (3 : 2) afforded compound **5b** in a yield of 121 mg (86%), light yellow crystals, m.p. 135 °C. ^{1}H NMR ($CDCl_3$), δ: 3.53, 3.89, 3.96 (all s, 3 H each, OCH_3); 5.26 (s, 2 H, OCH_2O); 6.21 (s, 1 H, H(3)); 6.81 (dd, 1 H, H(6), J = 8.9 Hz, J = 2.4 Hz); 6.89 (d, 1 H, H(8), J = 2.4 Hz); 7.02 (d, 1 H, H(5′), J = 8.3 Hz); 7.11 (dd, 1 H, H(6′), J = 8.3 Hz, J = 1.5 Hz); 7.27 (d, 1 H, H(2′), J = 1.5 Hz); 7.48 (d, 1 H, H(5), J = 8.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.94, 56.20, 56.50, 95.78, 101.25, 111.67, 111.93, 112.44, 112.75, 117.05, 123.03, 128.12, 128.30, 135.37, 143.21, 151.16, 156.24, 161.60, 162.88.

4-(3′-Methoxymethoxymethyl-4′-methoxyphenyl)-6-methoxychromen-2-one (5c) was synthesized from 6-methoxycoumarin 4-trifluoromethanesulfonate (**4c**) (133 mg, 0.41 mmol), 3-methoxymethoxymethyl-4-methoxyphenylboronic acid (112 mg, 0.53 mmol), Pd(dppf)Cl_2 (17 mg, 0.021 mmlo), K_3PO_4 (261 mg, 1.23 mmlo), and Bu_4NBr (13 mg, 0.041 mmol). Elution with ethyl acetate—petroleum ether (3 : 2) afforded compound **5c** in a yield of 81 mg (58%), light yellow crystals, m.p. 155 °C. ^{1}H NMR ($CDCl_3$), δ: 3.52, 3.76, 3.97 (all s, 3 H each, OCH_3); 5.27 (s, 2 H, OCH_2O); 6.37 (s, 1 H, H(3)); 7.04 (d, 1 H, H(5′), J = 11.0 Hz); 7.05 (s, 1 H, H(5)); 7.09—7.16 (m, 2 H, H(7), H(8)); 7.30 (d, 1 H, H(2′), J = 1.8 Hz); 7.33 (d, 1 H, H(6′), J = 9.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.8, 56.0, 56.3, 95.6, 101.1, 111.8, 113.6, 116.9, 117.1, 122.9, 128.1, 128.4, 135.4, 139.6, 143.0, 144.2, 150.9, 156.1, 162.7.

4-(3′-Methoxymethoxymethyl-4′-methoxyphenyl)-5-methoxychromen-2-one (5d) was synthesized from 5-methoxycoumarin 4-trifluoromethanesulfonate (**4d**) (133 mg, 0.41 mmol), 3-methoxymethoxymethyl-4-methoxyphenylboronic acid (112 mg, 0.53 mmol), Pd(dppf)Cl_2 (17 mg, 0.021 mmol), K_3PO_4 (261 mg, 1.23 mmol), Bu_4NBr (13 mg, 0.041 mmol). Elution with ethyl acetate—petroleum ether (3 : 2) afforded compound **5d** in a yield of 111 mg (79%), light yellow crystals, m.p. 150 °C. ^{1}H NMR ($CDCl_3$), δ: 3.51, 3.54, 3.94 (all s, 3 H each, OCH_3); 5.22 (s, 2 H, OCH_2O); 6.18 (s, 1 H, H(3)); 6.69 (d, 1 H, H(6), J = 8.3 Hz); 6.91 (d, 1 H, H(5′), J = 8.3 Hz); 6.96 (dd, 1 H, H(6′), J = 8.3 Hz, J = 1.3 Hz); 7.02 (d, 1 H, H(8), J = 8.3 Hz); 7.10 (d, 1 H, H(2′), J = 1.3 Hz); 7.46 (t, 1 H, H(7), J = 8.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.72, 56.09, 56.37, 95.78, 106.78, 109.42, 110.16, 110.77, 116.16, 116.55, 121.53, 132.38, 132.55, 145.58, 150.02, 154.96, 155.65, 157.46, 160.70.

4-(3′-Methoxymethoxymethyl-4′-methoxyphenyl)-5,7-dimethoxychromen-2-one (5e) was synthesized from 5,7-dimethoxycoumarin 4-trifluoromethanesulfonate (**4e**) (209 mg, 0.59 mmol), 3-methoxymethoxymethyl-4-methoxyphenylboronic acid (163 mg, 0.77 mmol), Pd(dppf)Cl_2 (24 mg, 0.03 mmol), K_3PO_4 (375 mg, 1.77 mmol), and Bu_4NBr (19 mg, 0.059 mmol). Elution with ethyl acetate—petroleum ether (3 : 2) afforded compound **5e** in a yield of 209 mg (95%), light yellow crystals, m.p. 135 °C. ^{1}H NMR ($CDCl_3$), δ: 3.51 (s, 6 H, OCH_3); 3.87, 3.93 (both s, 3 H each, OMe); 5.21 (s, 2 H, CH_2); 6.01 (s, 1 H, H(3)); 6.25 (d, 1 H, H(6), J = 2.2 Hz); 6.52 (d, 1 H, H(8), J = 2.2 Hz); 6.92 (m, 2 H, H(5′), H(6′)); 7.09 (d, 1 H, H(2′), J = 1.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.5, 55.7, 55.9, 56.2, 93.6, 95.6, 95.8, 103.5, 110.6, 112.7, 116.6, 121.4, 132.5, 145.4, 150.0, 155.1, 157.2, 158.2, 160.9, 163.3.

4-(3′-Methoxymethoxymethyl-4′-methoxyphenyl)-5,6,7-trimethoxychromen-2-one (5f) was synthesized from 5,6,7-trimethoxycoumarin 4-trifluoromethanesulfonate (**4f**) (100 mg, 0.26 mmol), 3-methoxymethoxymethyl-4-methoxyphenylboronic acid (72 mg, 0.34 mmol), Pd(dppf)Cl_2 (11 mg, 0.013 mmol), K_3PO_4 (165 mg, 0.78 mmol), and Bu_4NBr (8 mg, 0.026 mmol). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **5e** in a yield of 86 mg (82%), light yellow crystals, m.p. 141 °C. ^{1}H NMR ($CDCl_3$), δ: 3.32, 3.49, 3.79, 3.93, 3.93 (all s, 3 H each, OCH_3); 5.23 (s, 2 H, OCH_2O); 6.07 (s, 1 H, H(3)); 6.71 (s, 1 H, H(8)); 6.92 (d, 1 H, H(5′), J = 8.3 Hz); 6.98 (dd, 1 H, H(6′), J = 8.3 Hz, J = 2.0 Hz); 7.16 (d, 1 H, H(2′), J = 2.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 56.08, 56.30, 56.40, 61.21, 61.26, 95.78, 96.40, 107.41, 110.77, 114.20, 116.48, 121.64, 131.67, 139.63, 145.56, 149.88, 151.28, 151.88, 155.00, 156.90, 160.89.

Compounds 6a—f (general procedure). To a solution of coumarin **5** in acetone (3 mL of acetone per 0.45 mmol of **5**), conc. HCl (10 drops per 0.15 mmol of **5**) was added dropwise over a period of 30 min at 40 °C. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate, the organic layer was washed with saturated aqueous $NaHCO_3$ (three times). The organic layer was separated and dried with anh. Na_2SO_4. The product was purified by silica gel column chromatography. The NMR spectra of compounds **6a—f** are in agreement with that published earlier.[20]

4-(3′-Hydroxy-4′-methoxy)chromen-2-one (6a) was synthesized from compound **5a** (94 mg, 0.3 mmol), acetone (2 mL), and conc. HCl (20 drops). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **6a** in a yield of 76 mg (94%), light yellow crystals, m.p. 193 °C.

4-(3′-Hydroxy-4′-methoxy)-7-methoxychromen-2-one (6b) was synthesized from compound **5b** (103 mg, 0.3 mmol), acetone (2 mL), and conc. HCl (20 drops). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **6b** in a yield of 72 mg (81%), light yellow crystals, m.p. 173 °C.

4-(3′-Hydroxy-4′-methoxy)-6-methoxychromen-2-one (6c) was synthesized from compound **5c** (68 mg, 0.2 mmol), acetone (1.5 mL), and conc. HCl (15 drops). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **6c** in a yield of 49 mg (83%), light yellow crystals, m.p. 167 °C.

4-(3′-Hydroxy-4′-methoxy)-5-methoxychromen-2-one (6d) was synthesized from compound **5d** (103 mg, 0.3 mmol), acetone (2 mL), and conc. HCl (20 drops). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **6d** in a yield of 73 mg (82%), light yellow crystals, m.p. 180 °C.

4-(3′-Hydroxy-4′-methoxy)-5,7-dimethoxychromen-2-one (6e) was synthesized from compound **5e** (112 mg, 0.3 mmol), acetone (2 mL), and conc. HCl (20 drops). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **6e** in a yield of 87 mg (88%), light yellow crystals, m.p. 148 °C.

4-(3′-Hydroxy-4′-methoxy)-5,6,7-trimethoxychromen-2-one (6f) was synthesized from compound **5f** (80 mg, 0.2 mmol), acetone (1.5 mL), and conc. HCl (15 drops). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **6f** in a yield of 65 mg (91%), light yellow crystals, m.p. 157 °C.

Compounds 7a—f (general procedure). To a solution of compound **6** (1 equiv.), DIPEA (2.1 equiv.), and DMAP (0.1 equiv.) in CH_3CN, equal volume of CCl_4 was added at −10 °C under argon. Then dibenzyl phosphite (1.7 equiv.) was slowly added by drops and the reaction mixture was stirred for 1 h. After completion of the reaction, the mixture was washed with 2 *M* KH_2PO_4, extracted with ethyl acetate, organic layer was washed with brine, and dried with anh. Na_2SO_4. The solvent was removed *in vacuo*. The product was purified by silica gel column chromatography.

Dibenzyl[2-methoxy-5-(2-oxochromen-4-yl)phenyl]phosphate (7a) was synthesized from compound **6a** (76 mg, 0.283 mmol), dibenzyl phosphite (126 mg, 0.482 mmol), DIPEA (77 mg, 0.594 mmol), and DMAP (3.4 mg, 0.028 mmol). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **7a** in a yield of 88 mg (59%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 3.88 (s, 3 H, OCH_3); 5.19 (dd, 4 H, OCH_2, J = 8.3 Hz, J = 3.0 Hz); 6.26 (s, 1 H, H(3)); 7.04 (d, 1 H, H(5′), J = 8.2 Hz); 7.25—7.15 (m, 3 H, H(7), H(8), H(2′)); 7.27—7.37 (m, 10 H, Ph); 7.40 (dd, 1 H, H(6′), J = 8.2 Hz, J = 1.0 Hz); 7.48 (dd, 1 H, H(5), J = 8.0 Hz, J = 1.4 Hz); 7.54 (dt, 1 H, H(7), J = 8.0 Hz, J = 1.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 56.19, 70.15, 70.20, 112.95, 115.07, 117.43, 118.86, 122.02 (d, J = 3.0 Hz); 124.36, 126.31, 126.99, 127.63, 128.07, 128.69, 128.76, 132.03, 135.53, 135.56 (d, J = 7.0 Hz); 139.85 (d, J = 7.2 Hz); 152.05 (d, J = 5.1 Hz); 154.26 (d, J = 2.3 Hz); 160.78. ^{31}P NMR ($CDCl_3$), δ: −5.93.

Dibenzyl[2-methoxy-5-(7-methoxy-2-oxochromen-4-yl)-phenyl]phosphate (7b) was synthesized from compound **6b** (72 mg, 0.242 mmol), dibenzyl phosphite (108 mg, 0.411 mmol), DIPEA (66 mg, 0.508 mmol), and DMAP (3 mg, 0.028 mmol). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **7b** in a yield of 110 mg (81%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 3.87, 3.88 (both s, 3 H each, OCH_3); 5.19 (dd, 2 H, OCH_2, J = 8.3 Hz, J = 2.1 Hz); 6.10 (s, 1 H, H(3)); 6.75 (dd, 1 H, H(6), J = 8.9 Hz, J = 2.1 Hz); 6.88 (d, 1 H, H(8), J = 2.1 Hz); 7.03 (d, 1 H, H(5′), J = 8.4 Hz); 7.19 (s, 1 H, H(2′)); 7.22 (d, 1 H, H(6′), J = 8.4 Hz); 7.35—7.28 (m, 10 H, Ph); 7.37 (d, 1 H, H(5), J = 8.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.95, 56.21, 70.16, 70.22, 101.30, 111.79, 112.45, 112.94, 122.00 (d, J = 3.1 Hz); 126.25, 128.00, 128.10, 128.72, 128.79, 135.61 (d, J = 7.0 Hz); 139.84 (d, J = 7.1 Hz); 151.98 (d, J = 4.9 Hz); 154.42, 156.13, 161.29, 162.92. ^{31}P NMR ($CDCl_3$), δ: −5.93.

Dibenzyl[2-methoxy-5-(6-methoxy-2-oxochromen-4-yl)-phenyl]phosphate (7c) was synthesized from compound **6c** (49 mg, 0.164 mmol), dibenzyl phosphite (73 mg, 0.279 mmol), DIPEA (44 mg, 0.344 mmol), and DMAP (2 mg, 0.028 mmol). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **7c** in a yield of 57 mg (62%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 3.73, 3.88 (both s, 3 H each, OMe); 5.19 (dd, 4 H, OCH_2, J = 8.3 Hz); 6.27 (s, 1 H, H(3)); 6.95 (d, 1 H, H(5), J = 2.8 Hz); 7.05 (d, 1 H, H(5′), J = 8.4 Hz); 7.13 (dd, 1 H, H(7), J = 9.0 Hz, J = 2.8 Hz); 7.21 (s, 1 H, H(2′)); 7.25 (d, 1 H, H(8), J = 9.0 Hz); 7.28—7.36 (m, 11 H, H(6′), Ph). ^{13}C NMR ($CDCl_3$), δ: 55.94, 56.18, 70.17, 70.23, 109.37, 113.07, 115.44, 118.40, 119.23, 119.72, 121.98 (d, J = 3.0 Hz); 126.20, 127.73, 127.74, 128.09, 128.71, 128.80, 135.58 (d, J = 6.9 Hz); 139.88 (d, J = 7.1 Hz); 148.69, 152.06 (d, J = 5.2 Hz); 153.96, 156.10, 161.01. ^{31}P NMR ($CDCl_3$), δ: −5.92.

Dibenzyl[2-methoxy-5-(5-methoxy-2-oxochromen-4-yl)-phenyl]phosphate (7d) was synthesized from compound **6d** (73 mg, 0.245 mmol), dibenzyl phosphite (109 mg, 0.417 mmol), DIPEA (66 mg, 0.515 mmol), and DMAP (3 mg, 0.025 mmol). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **7d** in a yield of 97 mg (71%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 3.47, 3.86 (both s, 3 H each, OCH_3); 5.18 (d, 4 H, J = 8.0 Hz); 6.09 (s, 1 H, H(3)); 6.64 (d, 1 H, H(6), J = 8.3 Hz); 6.93 (d, 1 H, H(8), J = 8.3 Hz); 6.98—7.04 (m, 2 H, H(5′), H(2′)); 7.07 (d, 1 H, H(6′), J = 8.2 Hz); 7.41—7.22 (m, 10 H, Ph); 7.46 (t, 1 H, H(7), J = 8.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.80, 56.10, 70.01 (d, J = 5.8 Hz); 106.73, 109.10, 109.97, 111.63, 116.17, 121.38 (d, J = 3.1 Hz), 124.60, 128.02, 128.67, 128.70, 132.32 (d, J = 1.7 Hz); 132.48, 135.71 (d, J = 7.2 Hz); 138.84 (d, J = 7.3 Hz); 150.84 (d, J = 5.0 Hz); 154.04, 155.55, 157.39, 160.49. ^{31}P NMR ($CDCl_3$), δ: −6.02.

Dibenzyl[2-methoxy-5-(5,7-dimethoxy-2-oxochromen-4-yl)phenyl]phosphate (7e) was synthesized from compound **6e** (87 mg, 0.265 mmol), dibenzyl phosphite (118 mg, 0.451 mmol), DIPEA (72 mg, 0.557 mmol), and DMAP (3.3 mg, 0.027 mmol). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **7e** in a yield of 105 mg (67%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 3.43, 3.86, 3.87 (both s, 3 H each, OMe); 5.18 (d, 4 H, OCH_2, J = 8.0 Hz); 5.93 (s, 1 H, H(3)); 6.19 (d, 1 H, H(6), J = 1.8 Hz); 6.51 (d, 1 H, H(8), J = 1.8 Hz); 6.92 (d, 1 H, H(5′), J = 8.4 Hz); 7.02 (s, 1 H, H(2′)); 7.06 (d, 1 H, H(6′), J = 8.4 Hz); 7.22—7.40 (m, 10 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 55.69, 55.89, 56.09, 69.97, 70.03, 93.64, 95.82, 103.40, 111.59, 112.87, 121.44 (d, J = 3.1 Hz); 124.63, 128.02, 128.67, 128.69, 132.41, 132.42, 135.72 (d, J = 7.3 Hz); 138.78 (d, J = 7.3 Hz); 150.78 (d, J = 4.9 Hz); 154.34, 157.31, 158.31, 160.89, 163.51. ^{31}P NMR ($CDCl_3$), δ: −6.03.

Dibenzyl[2-methoxy-5-(5,6,7-trimethoxy-2-oxochromen-4-yl)phenyl]phosphate (7f) was synthesized from compound **6f** (65 mg, 0.182 mmol), dibenzyl phosphite (82 mg, 0.309 mmol), DIPEA (49 mg, 0.382 mmol), and DMAP (2.2 mg, 0.018 mmol). Elution with ethyl acetate—petroleum ether (1 : 1) afforded compound **7f** in a yield of 74 mg (66%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 3.26, 3.76, 3.86, 3.94 (all s, 3 H each, OMe); 5.17 (d, 4 H, OCH_2, J = 8.1 Hz); 5.98 (s, 1 H, H(3)); 6.71 (s, 1 H, H(8)); 6.94 (d, 1 H, H(5′), J = 8.7 Hz); 7.10 (dd, 1 H, H(6′), J = 8.7 Hz, J = 0.7 Hz); 7.11 (d, 1 H, H(2′), J = 0.7 Hz); 7.27—7.35 (m, 10 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 56.13, 56.42, 61.22, 70.01, 70.07, 96.37, 107.21, 111.72, 114.38, 121.18 (d, J = 3.0 Hz); 125.07 (d, J = 1.2 Hz); 128.06, 128.68, 128.71, 131.49 (d, J = 1.5 Hz); 135.72 (d, J = 7.1 Hz); 138.81 (d, J = 7.2 Hz); 139.58 (d, J = 5.1 Hz); 150.78, 151.16, 151.81, 154.04, 157.02, 160.67. ^{31}P NMR ($CDCl_3$), δ: −5.97.

Compounds 3a—f (general procedure). To a solution of coumarin dibenzyl phosphite **7** (1 equiv.) in CH_2Cl_2 (1 mL per 0.07 mmol of **7**), trimethylsilyl bromide (6 equiv.) was added over a period of 40 min. Then 25% MeONa in MeOH (2 equiv.) was added and the reaction mixture was stirred for 30 min. Removal of the solvent *in vacuo* and precipitation of the resulted crystals with acetone from a solution in water resulted in pure product.

Disodium [2-methoxy-5-(2-oxochromen-4-yl)phenyl]phosphate (3a) was synthesized from compound **7a** (56 mg, 0.106 mmol), trimethylsilyl bromide (97 mg, 0.636 mmol), and 25% MeONa

in MeOH (48 μL) in a yield of 23 mg (54%), colorless crystals, m.p. 156 °C. ^{1}H NMR (MeOD), δ: 3.93 (s, 3 H, OMe); 6.45 (s, 1 H, H(3)); 7.13 (s, 2 H, H(5′), H(8)); 7.32 (t, 1 H, H(6), J = 7.7 Hz); 7.39 (d, 1 H, H(6′), J = 8.2 Hz); 7.60 (t, 1 H, H(7), J = 7.7 Hz); 7.70—7.89 (m, 2 H, H(2′), H(5)). ^{13}C NMR (MeOD), δ: 56.59 (d, J = 6.9 Hz); 113.29, 115.00 (d, J = 3.5 Hz); 117.97, 120.25, 121.96 (d, J = 2.5 Hz); 123.90, 125.68, 128.58, 128.80, 133.13, 145.16 (d, J = 6.2 Hz); 153.37 (d, J = 5.9 Hz); 155.41, 157.73, 163.06. ^{31}P NMR (MeOD), δ: −0.82.

Disodium [2-methoxy-5-(7-methoxy-2-oxochromen-4-yl)-phenyl]phosphate (3b) was synthesized from compound **7b** (76 mg, 0.136 mmol), trimethylsilyl bromide (125 mg, 0.816 mmol), and 25% MeONa in MeOH (62 μL) in a yield of 51 mg (88%), colorless crystals, m.p. 195 °C (decomp.). ^{1}H NMR (MeOD), δ: 3.86, 3.90 (both s, 3 H each, OMe); 6.29 (s, 1 H, H(3)); 6.89—6.91 (m, 2 H, H(6), H(8)); 7.03 (d, 1 H, H(5′), J = 8.3 Hz); 7.07 (d, 1 H, H(6′), J = 8.3 Hz); 7.68 (d, 1 H, H(5), J = 8.6 Hz); 7.87 (s, 1 H, H(2′)). ^{13}C NMR (MeOD), δ: 56.41 (d, J = 6.6 Hz); 56.59 (d, J = 6.6 Hz); 101.99, 111.58 (d, J = 4.4 Hz); 112.76, 113.52, 113.81, 121.30, 122.81, 129.13, 126.30, 130.04 (d, J = = 2.2 Hz); 145.96 (d, J = 5.3 Hz); 152.78 (d, J = 6.7 Hz); 157.22, 158.37, 163.76, 164.49. ^{31}P NMR (MeOD), δ: 1.77.

Disodium [2-methoxy-5-(6-methoxy-2-oxochromen-4-yl)-phenyl]phosphate (3c) was synthesized from compound **7c** (55 mg, 0.098 mmol), trimethylsilyl bromide (90 mg, 0.588 mmol), and 25% MeONa in MeOH (45 μL) in a yield of 33 mg (80%), colorless crystals, m.p. 195 °C (decomp.). ^{1}H NMR (MeOD), δ: 3.74, 3.91 (both s, 3 H each, OMe); 6.47 (s, 1 H, H(3)); 7.04—7.09 (m, 2 H, H(5′), H(8)); 7.17 (s, 2 H, H(7), H(5)); 7.30 (d, 1 H, H(6′), J = 9.6 Hz); 7.89 (s, 1 H, H(2′)). ^{13}C NMR (MeOD), δ: 56.35 (d, J = 3.3 Hz); 56.59 (d, J = 3.3 Hz); 110.96, 112.77, 115.44 (d, J = 1.5 Hz); 119.00, 120.69, 120.82, 121.32, 122.72, 128.79, 146.20 (d, J = 5.4 Hz); 149.70, 152.89 (d, J = 6.8 Hz); 157.64, 157.82, 163.41. ^{31}P NMR (MeOD), δ: 1.75.

Disodium [2-methoxy-5-(5-methoxy-2-oxochromen-4-yl)-phenyl]phosphate (3d) was synthesized from compound **7d** (50 mg, 0.089 mmol), trimethylsilyl bromide (82 mg, 0.534 mmol), and 25% MeONa in MeOH (41 μL) in a yield of 32 mg (86%), colorless crystals, m.p. 201 °C (decomp.). ^{1}H NMR (MeOD), δ: 3.46, 3.81 (both s, 3 H each, OMe), 6.39 (d, 1 H, H(6′), J = 8.7 Hz); 6.44 (d, 1 H, H(6), J = 8.3 Hz); 6.58 (d, 1 H, H(8), J = 8.3 Hz); 6.67—6.77 (m, 2 H, H(3), H(5′)); 7.11 (t, 1 H, H(7), J = 8.3 Hz); 7.87 (s, 1 H, H(2′)). ^{13}C NMR (MeOD), δ: 56.04 (d, J = 5.8 Hz); 56.45 (d, J = 9.3 Hz); 104.28 (d, J = 2.0 Hz); 111.69, 113.00, 118.60 (d, J = 3.7 Hz); 120.52, 121.51 (d, J = 1.7 Hz); 127.61, 129.70, 136.85, 139.78, 144.94 (d, J = 6.0 Hz); 150.87 (d, J = 6.4 Hz); 158.00, 159.97, 177.11. ^{31}P NMR (MeOD), δ: 2.06.

Disodium [2-methoxy-5-(5,7-dimethoxy-2-oxochromen-4-yl)phenyl]phosphate (3e) was synthesized from compound **7e** (48 mg, 0.081 mmol), trimethylsilyl bromide (74 mg, 0.486 mmol), and 25% MeONa in MeOH (37 μL) in a yield of 29 mg (79%), colorless crystals, m.p. 257 °C (decomp.). ^{1}H NMR (MeOD), δ: 3.44, 3.75, 3.81 (all s, 3 H each, OMe); 5.98 (s, 1 H, H(6)); 6.13 (s, 1 H, H(8)); 6.47 (d, 1 H, H(5′), J = 8.4 Hz); 6.66 (s, 1 H, H(3)); 6.72 (d, 1 H, H(6′), J = 8.4 Hz); 7.84 (s, 1 H, H(2′)). ^{13}C NMR (MeOD), δ: 55.53 (d, J = 7.8 Hz); 56.01 (d, J = 5.1 Hz); 56.50 (d, J = 8.3 Hz); 91.30, 98.03—97.84 (m); 111.79, 113.20, 118.64, 121.70, 127.31, 137.33, 140.29, 144.90 (d, J = 6.0 Hz); 150.81 (d, J = 6.5 Hz); 160.52, 162.22, 177.32. ^{31}P NMR (MeOD), δ: 2.19.

Disodium [2-methoxy-5-(5,6,7-trimethoxy-2-oxochromen-4-yl)phenyl]phosphate (3f) was synthesized from compound **7f** (70 mg, 0.113 mmol), trimethylsilyl bromide (104 mg, 0.678 mmol), and 25% MeONa in MeOH (52 μL) in a yield of 48 mg (89%), colorless crystals, m.p. 187 °C (decomp.). ^{1}H MNR (MeOD), δ: 3.40, 3.66 (both s, 3 H each, OMe); 3.82 (s, 6 H, OMe); 6.37 (s, 1 H, H(3)); 6.50 (dd, 1 H, H(6′); J = 8.5 Hz, J = 1.8 Hz); 6.66 (s, 1 H, H(8)); 6.77 (d, 1 H, H(5′), J = 8.5 Hz); 7.80 (d, 1 H, H(2′), J = 1.8 Hz). ^{13}C NMR (MeOD), δ: 56.20, 56.27, 61.19, 61.25, 100.13 (d, J = 5.0 Hz); 111.85, 117.91, 118.34, 119.13, 121.89, 127.76, 137.64, 140.12, 145.09 (d, J = 5.0 Hz); 151.07 (d, J = 6.5 Hz); 153.21, 154.71, 161.46, 177.05. ^{31}P NMR (MeOD), δ: 2.20.

Dioleyl phosphite. To a stirred solution of oleyl alcohol (2.001 g, 7.5 mmol) and pyridine (0.395 g, 5 mmol, distilled prior to use) in CH_2Cl_2, PCl_3 (0.343 g, 2.5 mmol) was added dropwise at 0—5 °C. The reaction mixture was stirred for 1.5 h with slow warming up to ambient temperature. After completion of the reaction, the mixture was washed with 2 *M* KH_2PO_4 and extracted with ethyl acetate, the organic layer was washed with brine, and dried with anh. Na_2SO_4. The solvent was removed *in vacuo*. Purification of the residue by column chromatography (silica gel, elution with diethyl ether—petroleum ether, 1 : 1) afforded dioleyl phosphite in a yield of 1.02 g (70%), transparent oil. ^{1}H NMR ($CDCl_3$), δ: 0.84 (t, 6 H, Me, J = 6.6 Hz); 1.13—1.44 (m, 44 H, CH_2); 1.52—1.75 (m, 4 H, $OCH_2C\underline{H}_2$); 1.82—2.04 (m, 8 H, $C\underline{H}_2CH{=}CHC\underline{H}_2$); 4.01 (dd, 4 H, OCH_2, J = 7.3 Hz, J = 14.2 Hz); 5.16—5.41 (m, 4 H, CH=CH); 6.74 (d, 1 H, H—P, $J_{P,H}$ = 692.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 14.1, 22.6, 25.5, 27.1, 27.2, 29.0, 29.1, 29.3, 29.4, 29.5, 29.7, 29.7, 30.3, 30.4, 31.9, 65.7, 129.7, 129.9. ^{31}P NMR ($CDCl_3$), δ: 7.65.

Compounds 8a,d,f (general procedure). A mixture of coumarin **5** (1 equiv.), DIPEA (7 equiv.), DMAP (0.3 equiv.), and CCl_4 was dissolved in MeCN—$CHCl_3$ (1 : 1) at −10 °C under argon. Then dioleyl phosphite (5 equiv.) was added dropwise and the reaction mixture was stirred for 2 h. After completion of the reaction, the mixture was washed with 2 *M* KH_2PO_4, extracted with ethyl acetate, the organic layer was washed with water, brine, dried with anh. Na_2SO_4, and the solvent was removed *in vacuo*. The product was purified by column chromatography (silica gel, elution with petroleum ether—ethyl acetate, 2 : 1).

Dioleyl[2-methoxy-5-(2-oxochromen-4-yl)phenyl]phosphate (8a) was synthesized from compound **5a** (89 mg, 0.332 mmol), dioleyl phosphite (968 mg, 1.66 mmol), DIPEA (300 mg, 2.324 mmol), DMAP (12 mg, 0.01 mmol), CCl_4 (0.75 mL), MeCN 0.75 mL), and $CHCl_3$ (0.75 mL) in a yield of 189 mg (67%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 0.87 (t, 6 H, Me(Oleyl), J = 6.8 Hz); 1.17—1.45 (m, 44 H, CH_2(Oleyl)); 1.64—1.76 (m, 4 H, $OCH_2C\underline{H}_2$); 1.92—2.07 (m, 8 H, $C\underline{H}_2CH{=}CHC\underline{H}_2$); 3.95 (s, 3 H, OMe); 4.12—4.24 (m, 4 H, OMe); 5.27—5.42 (m, 4 H, CH=CH); 6.36 (s, 1 H, H(3)); 7.08 (d, 1 H, H(5′), J = 8.5 Hz); 7.21—7.30 (m, 2 H, H(6), H(8)); 7.39—7.42 (m, 2 H, H(7), H(6′)); 7.51—7.61 (m, 2 H, H(2′), H(5)). ^{13}C NMR ($CDCl_3$), δ: 14.25, 22.81, 25.56, 27.34 (d, J = 3.5 Hz); 29.00—30.03 (m); 30.34, 30.41, 32.04, 32.73 (d, J = 2.9 Hz); 56.26, 68.87 (d, J = = 6.3 Hz); 113.00, 115.14, 117.52, 118.95, 121.98 (d, J = 2.8 Hz); 127.73 (d, J = 1.6 Hz); 124.37, 126.17, 127.04, 129.87, 130.13, 132.07, 140.22, 152.16, 154.38 (d, J = 4.0 Hz); 160.83. ^{31}P NMR ($CDCl_3$), δ: −5.7.

Dioleyl[2-methoxy-5-(5-methoxy-2-oxochromen-4-yl)-phenyl]phosphate (8d) was synthesized from compound **5d**

(44 mg, 0.148 mmol), dioleyl phosphite (431 mg, 0.74 mmol), DIPEA (134 mg, 1.036 mmol), DMAP (5.4 mg, 0.044 mmol), CCl_4 (0.3 mL), MeCN (0.3 mL), and $CHCl_3$ (0.3 mL) in a yield of 79 mg (61%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 0.87 (t, 6 H, Me(Oleyl), J = 6.8 Hz); 1.18—1.43 (m, 44 H, CH_2(Oleyl)); 1.68 (dt, 4 H, $OCH_2C\underline{H}_2$, J = 13.7 Hz, J = 6.8 Hz); 1.91—2.07 (m, 8 H, $C\underline{H}_2CH{=}CHC\underline{H}_2$); 3.56, 3.92 (both s, 3 H each, OMe); 4.09—4.22 (m, 4 H, OCH_2); 5.27—5.41 (m, 4 H, CH=CH); 6.16 (s, 1 H, H(3)); 6.68 (d, 1 H, H(6), J = 8.3 Hz); 6.95 (d, 1 H, H(8), J = 8.3 Hz); 7.00 (d, 1 H, H(5′), J = 8.4 Hz); 7.09 (dd, 1H, H(6′), J = 8.4 Hz, J = 1.7 Hz); 7.22 (s, 1 H, H(2′)); 7.45 (t, 1 H, H(7), J = 8.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 14.26, 22.82, 25.59, 27.34 (d, J = 3.1 Hz); 29.28—29.90 (m); 30.34, 30.41, 32.04, 55.89, 56.12, 68.71 (d, J = 6.5 Hz); 106.70, 110.04, 111.59, 116.25, 121.33 (d, J = 2.8 Hz); 124.49, 129.87, 130.13, 132.51, 139.07 (d, J = 7.0 Hz); 150.89 (d, J = 5.2 Hz); 154.19, 155.59, 157.45, 160.54. ^{31}P NMR ($CDCl_3$), δ: −5.77.

Dioleyl[2-methoxy-5-(5,6,7-trimethoxy-2-oxochromen-4-yl)phenyl]phosphate (8f) was synthesized from compound **5f** (53 mg, 0.148 mmol), dioleyl phosphite (431 mg, 0.74 mmol), DIPEA (134 mg, 1.036 mmol), DMAP (5.4 mg, 0.044 mmol), CCl_4 (0.3 mL), MeCN (0.3 mL), and $CHCl_3$ (0.3 mL) in a yield of 96 mg (69%), yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 0.87 (t, 6 H, Me(Oleyl), J = 6.8 Hz); 1.14—1.45 (m, 44 H, CH_2(Oleyl)); 1.68 (dt, 4 H, $OCH_2C\underline{H}_2$, J = 14.1 Hz, J = 6.9 Hz); 1.93—2.04 (m, 8 H, $C\underline{H}_2CH{=}CHC\underline{H}_2$); 3.33, 3.79, 3.91, 3.93 (all s, 3 H each, OMe); 4.11—4.21 (m, 4 H, OCH_2); 5.27—5.40 (m, 4 H, CH=CH); 6.04 (s, 1 H, H(3)); 6.70 (s, 1 H, H(8)); 6.96 (d, 1 H, H(5′), J = 8.4 Hz); 7.11 (dd, 1 H, H(6′), J = 8.4 Hz, J = 2.0 Hz); 7.28 (s, 1 H, H(2′)). ^{13}C NMR ($CDCl_3$), δ: 14.24, 22.81, 25.57, 27.33 (d, J = 2.4 Hz); 29.01—30.08 (m); 30.33, 30.40, 32.03, 56.15, 56.38, 61.23 (d, J = 5.7 Hz); 68.75 (d, J = 6.2 Hz); 96.40, 107.25, 111.70, 114.41, 121.11 (d, J = 2.9 Hz); 124.93, 129.87, 130.11, 131.54, 151.21, 151.83, 154.18, 157.02, 160.68. ^{31}P NMR ($CDCl_3$), δ: −5.80.

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