Synthesis of acyclic and cyclic phosphonates based on substituted 2-hydroxybenzylic alcohols

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A convenient synthesis of benzylic phosphonates and 2,3-dihydrobenzo[*d*][1,2]oxaphosphole 2-oxides substituted at the aromatic ring, as well as their precursors, 2-hydroxybenzylic alcohols, from the derivatives of salicylic aldehyde, salicylic acid, and 2-hydroxyacetophenone bearing an additional hydroxy or methoxy group at the *para* position of the aromatic ring was developed. For the first time, the possibility of selective demethylation of the methoxy group positioned *ortho* to the methylene phosphonate fragment with retention of the methoxy group at the *para* position was shown.

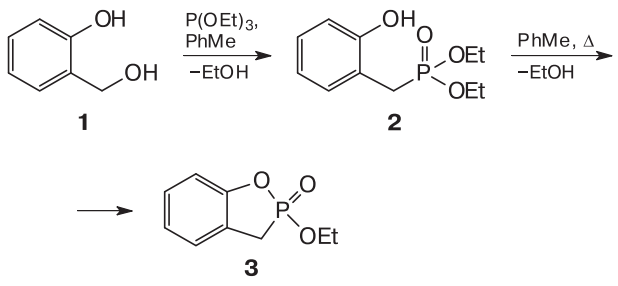
Key words: 2-hydroxybenzyl alcohol, triethyl phosphite, benzyl phosphonates, 2,3-dihydrobenzo[*d*][1,2]oxaphosphole 2-oxides.

Organophosphorus compounds attract great attention due to their wide application in industry,[1] biology and medicine,[2—6] and organic synthesis.[7,8] Among them acyclic and cyclic phosphonates[9] should be noted for their biological activity, in particular, their stability to hydrolytic enzymes. Due to this, phosphonates can be employed as the P—C-analogs of transition states at enzyme active sites during peptide synthesis and peptide bond hydrolysis[10,11] or secondary metabolites in microorganisms[5]. In the literature, special attention is paid to the development of the synthetic methods towards phosphonates of different structure.[12]

In the present work, we report a synthetic approach to functionally substituted phosphonates based on 2-hydroxybenzylic alcohols. The most common method to synthesize one of the closest analogs of the target compounds is the Arbuzov-type reaction between triethyl phosphite and 2-hydroxybenzylic alcohol (**1**) to give diethyl 2-hydroxybenzylphosphonate (**2**). This method can also be used to obtain cyclic 2-ethoxy-3*H*-benzo[*d*][1,2]-oxaphosphole 2-oxide (**3**)[13—15] (Scheme 1).

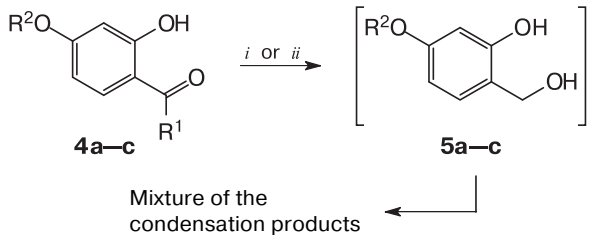
Nonetheless, this approach has not been used for the synthesis of salicylic alcohol derivatives with additional hydroxy or methoxy group at position 4 of the aromatic ring, probably, due to poor availability of these compounds. Hence, oxymethylation of resorcinol in the presence of boric acid[16] and reduction of aldehyde **4a**[17] or acid **4b**[18,19] led only to the mixtures of oligo/polymerization products

Scheme 1



of the target 2,4-dihydroxybenzylic (β-resorcylic) alcohol **5a** (Scheme 2). It is known that alkylation of the phenolic

Scheme 2



$R^1 = R^2 = H$ (**a**); $R^1 = OH$, $R^2 = H$ (**b**); $R^1 = H$, $R^2 = Me$ (**c**)

Reagents and conditions: *i.* (for **4a,c**) $NaBH_4$, EtOH; *ii.* (for **4b**) $LiAlH_4$, THF, 0 °C.

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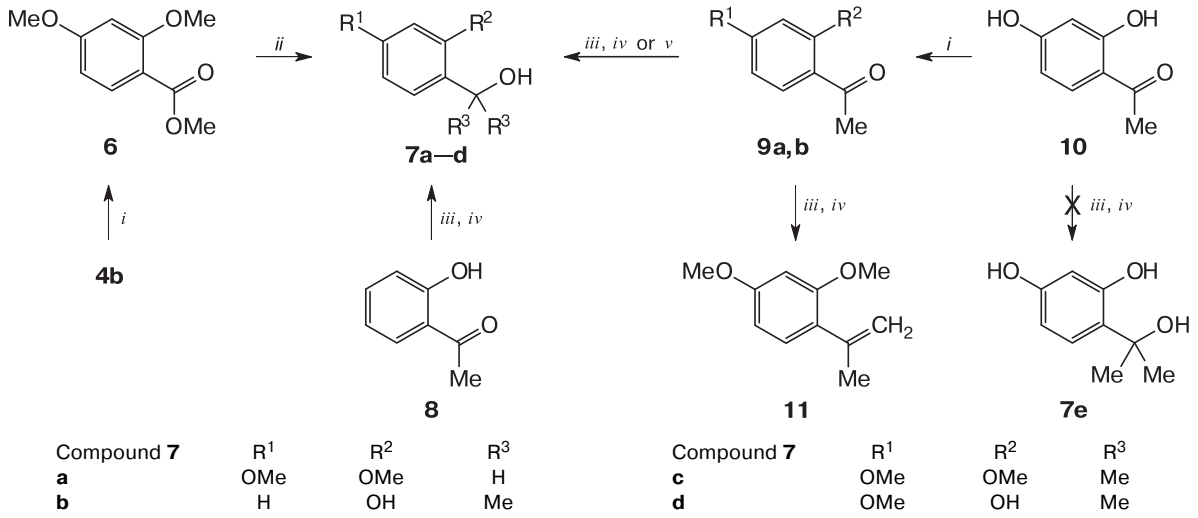
Scheme 3



9: $R^1 = R^2 = OMe$ (**a**), $R^1 = OMe$, $R^2 = H$ (**b**)

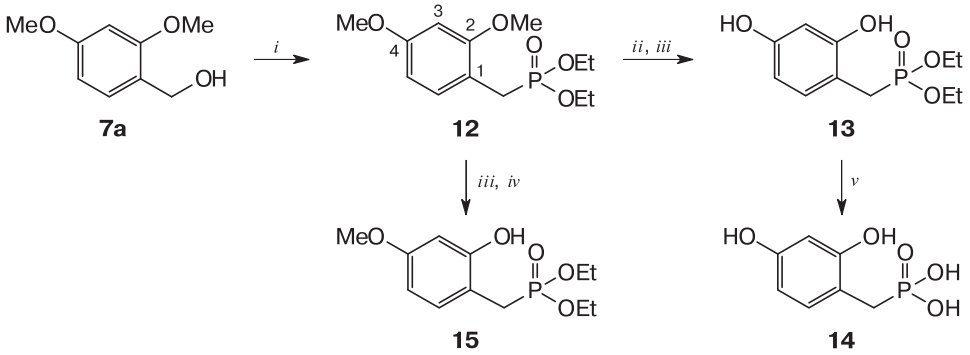
Reagents and conditions: *i*. Me_2SO_4, K_2CO_3, acetone; *ii*. $LiAlH_4$ (3 equiv.), Et_2O, 0 °C; *iii*. MeMgI, Et_2O; i*v*. H_2O, NH_4Cl; *v*. H_2O, $NaHCO_3$.

hydroxy groups weakens the tendency of the corresponding derivatives to self-condensation; however, reduction of monomethyl ether **4c**[20] also resulted in the self-condensation products (see Scheme 2).

Reduction of methyl benzoate **6**[21] allowed us to obtain the target alcohol **7a**[22] (Scheme 3). Alcohols **7b—d** were synthesized by the Grignard reaction of acetophenones **8**, **9a,b** and methylmagnesium iodide. Attempted synthesis of alcohol **7e** by the direct reaction of 2,4-dihydroxyacetophenone (**10**) with methylmagnesium iodide failed. In the reaction mixture magnesium salt of phenol **10** immediately precipitated, which did not react further, and the starting acetophenone **10** was recovered after hydrolysis. The reaction of ketone **9a**[23] with methylmagnesium iodide that was performed according to the reported procedure[24] after hydrolysis with aqueous NH_4Cl resulted mainly (>90%) in a dehydration product, styrene **11**, instead of the target alcohol **7c**. Only hydrolysis of the reaction mixture with aqueous $NaHCO_3$ afforded alcohol **7c**, which is highly tend to dehydration at temperatures above 30 °C and, therefore, is not suitable for phosphonate synthesis by this Arbuzov-type reaction. To solve this problem, acetophenone **9b**[25] was obtained. Its Grignard reaction afforded alcohol **7d** that is not prone to dehydration.

Then compounds **7a—d** were reacted with triethyl phosphite under the Arbuzov reaction conditions. In the absence of the phenolic hydroxy group *ortho* positioned to the oxymethyl fragment, alcohols **7** do not react with triethyl phosphite. The Arbuzov rearrangement catalyzed by tetrabutylammonium iodide (Bu_4NI)[26] afforded phosphonate **12** in 44% yield (Scheme 4). During the isolation of phosphonate **12** by flash-chromatography, three more

Scheme 4



Reagents and conditions: *i*. $(EtO)_3P$, Bu_4NI (3 mol.%); *ii*. BBr_3 (10 equiv.), CH_2Cl_2, −78 → 23 °C, 12 h; *iii*. MeOH, 23 °C; *iv*. BBr_3 (1.05 equiv.), CH_2Cl_2, −78 → 23 °C, 12 h; *v*. HCl, H_2O.

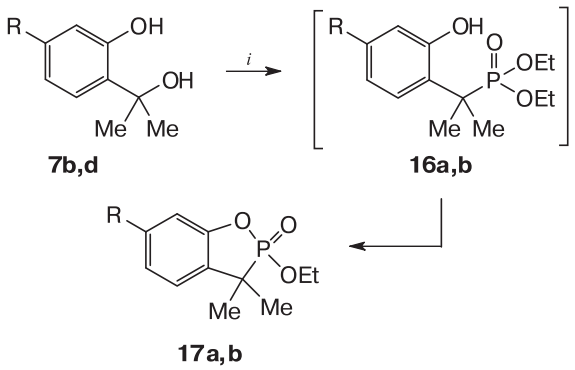
organic fractions that apparently contain different by-products of the alcohol **7a** condensation were obtained.

In order to obtain 2,4-dihydroxybenzylphosphonate **13**, compound **12** was demethylated with excess of BBr_3. Further acidic hydrolysis of compound **13** gave phosphonic acid **14**. Demethylation of phosphonate **12** with equimolar amount of BBr_3 carried out similarly to selective demethylation of methoxyphenyl substituent neighboring to the carbonyl group[27] resulted in diethyl (2-hydroxy-4-methoxybenzyl)phosphonate (**15**) (see Scheme 4). The structure of compound **15** was determined based on $^{13}C—\{^1H\}$ NMR data. Figure 1 shows the fragments of ^{13}C NMR spectra of compounds **12**, **13**, and **15** with the C(2) and C(4) atom resonances. The C(2) atom signals are easy to identify due to their position in stronger field and larger spin-spin coupling constant J ($^3J_{PC} \approx 5—7$ Hz), then that of the C(4) atom signal.

The C(2) and C(4) atoms of dimethoxy- (**12**) and dihydroxybenzylphosphonates (**13**) are notably less nonequivalent that these atoms of 2-hydroxy-4-methoxyphenyl derivative **15**.

Unlike compound **7a**, alcohols **7b,c** bearing *gem*-dimethyl fragment and *ortho* positioned to it hydroxy group react with triethyl phosphite to give initially phosphonates

Scheme 5



R = H (**7b, 16a, 17a**); R = OMe, (**7d, 16b, 17b**)

Reagents and conditions: *i*. $(EtO)_3P$, 144 °C, *o*-xylene.

16a,b that can be detected in the reaction mixture by ^{31}P NMR spectroscopy. Compounds **16a,b** under the reaction conditions immediately underwent cyclization to benzoxaphospholes **17a,b** (Scheme 5). Compounds **17b,c** have been previously synthesized in four steps from aceto-

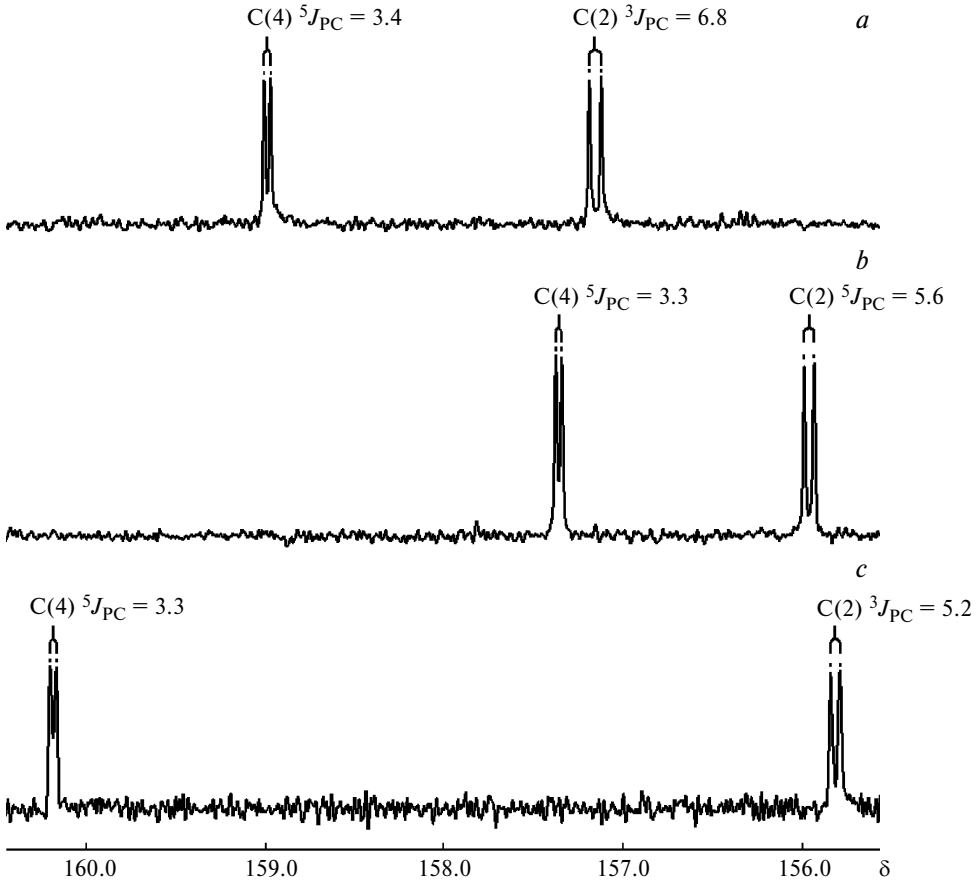


Fig. 1. Fragments of ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compounds **12** (*a*), **13** (*b*), and **15** (*c*). Spin-spin coupling constants (J_{PC}) are given in Hz.

phenone and 4-methoxyacetophenone *via* the Pd-catalyzed C—H activation.[28]

In summary, the presented work suggests a convenient synthesis of cyclic and acyclic phosphonates as well as the starting substituted 2-hydroxybenzylic alcohols. For the first time, selective *ortho*-demethylation of the methylenephosphonate moiety with retention of the *para*-methoxy group was reported.

Experimental

^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (working frequencies of 400 (^{1}H), 101 (^{13}C), and 162.0 MHz ^{31}(P)) in DMSO-d_6, D_2O or $CDCl_3$. Chemical shifts are reported on the δ scale relative to the residual solvent signal (^{1}H), the carbon atom of the solvent (^{13}C), and 85% H_3PO_4 as an external standard (^{31}P) and referred to Me_4Si. IR spectra were recorded on a Bruker Tensor-27 instrument in Nujol or in KBr pellets. ESI-MS spectra were recorded on a Bruker Daltonics Amazon X mass spectrometer operating in a positive ion mode in the range of *m/z* 200—1000. Capillary voltage was 4500 V. The data were processed using Data Analysis 4.0 software (Bruker Daltonics). Elemental analysis on carbon (C), hydrogen (H), nitrogen (N), and sulfur (S) was performed on an EuroEA3028-HT-OM CHNS-O analyzer (Eurovector SpA). Phosphorus content was determined by pyrolysis in the stream of oxygen. All the solvents were purified before use by the standard procedures, acetone was used as received. Compounds **4c**,[20] **6**,[21] **7a**,[22] **7b**,[29] and **9b**[25] were synthesized according to the previously reported procedures.

1-(2,4-Dimethoxyphenyl)ethan-1-one (9a) was synthesized similarly to compound **6**[21] from 2,4-dihydroxyacetophenone (5.0 g, 33 mmol), dimethyl sulfate (6.9 mL, 9.2 g, 73 mmol), and K_2CO_3 (13.8 g, 100 mmol). White crystals, yield 4.9 g (83%), b.p. 103 °C (0.1 Torr) (*cf.* Ref. 28: 121—122 °C (0.5 Torr)), m.p. 38—40 °C. IR, ν/cm^{-1}: 3000, 2977, 2943, 2841, 1662 (C=O), 1600, 1467, 1359, 1270, 1164, 1027, 836.

2-(2,4-Dimethoxyphenyl)propan-2-ol (7c). To a solution of methylmagnesium iodide in diethyl ether (prepared from Mg (0.36 g, 15 mmol) and iodomethane (0.94 mL, 2.13 g, 15 mmol) in diethyl ether (5 mL)), a solution of 2,4-dimethoxyacetophenone (1.8 g, 10 mmol) in diethyl ether (5 mL) was added dropwise maintaining the reaction temperature at ⩽20 °C. The resulting mixture was stirred at room temperature for 1 h and hydrolyzed with saturated aqueous $NaHCO_3$ at cooling with water bath (20 °C). The mixture was extracted with diethyl ether, the combined organic layers were dried over Na_2SO_4, and solvent was removed *in vacuo* at bath temperature of 20 °C to give 1.6 g (82%) of product **7c** as a colorless liquid. IR, ν/cm^{-1}: 3543, 3444, 3085, 2967, 2938, 2837, 1614, 1584, 1504, 1462, 1367, 1256, 1208, 1158, 1090, 1040. ^{1}H NMR ($CDCl_3$), δ: 1.58 (s, 6 H, CH_3); 3.80 (s, 3 H, OCH_3); 3.89 (s, 3 H, OCH_3); 6.45 (dd, 1 H, Ar, J = 8.6 Hz, J = 2.4 Hz); 6.51 (d, 1 H, Ar, J = 2.5 Hz); 7.21 (d, 1 H, Ar, J = 8.5 Hz).

2-(2-Hydroxypropan-2-yl)-5-methoxyphenol (7d) was synthesized as described earlier for alcohol **7b**[29] from Mg (0.36 g, 15 mmol), iodomethane (0.94 mL, 15 mmol), and 1-(2-hydroxy-4-methoxyphenyl)ethan-1-one (0.9 g, 5.4 mmol) in diethyl ether (10 mL). Yellowish oil, yield 0.96 g (97%). ^{1}H NMR ($CDCl_3$), δ: 1.67 (s, 6 H, CH_3); 3.79 (s, 3 H, OCH_3); 6.41 (dd, 1 H, Ar, J = 8.6 Hz, J = 2.6 Hz); 6.47 (d, 1 H, Ar, J = 2.6 Hz); 6.99 (d, 1 H, Ar, J = 8.6 Hz); 9.01 (s, 1 H, OH).

2,4-Dimethoxy-1-(prop-1-en-2-yl)benzene (11) was synthesized as described earlier for 2-(2,4-dimethoxyphenyl)propan-2-ol (**7c**).[24] Yellowish oil, yield 3.66 g (70%). The main characteristics coincide with those described previously.[30] IR, ν/cm^{-1}: 3556, 3079, 3000, 2967, 2836, 2572, 2505, 2363, 2067, 1946, 1893, 1789, 1609 (C=C), 1577, 1504, 1464, 1439, 1414, 1370, 1314, 1298, 1274, 1258, 1209, 1161, 1103, 1037, 975, 940, 894, 834, 803, 749, 734, 684, 635, 604, 589, 563, 504, 455. ^{1}H NMR ($CDCl_3$), δ: 2.10 (d, 3 H, CH_3, J = 1.0 Hz); 3.81 (s, 3 H, OCH_3); 3.82 (s, 3 H, OCH_3); 5.05 (dd, 1 H, CH of *E* isomer, J = 2.3 Hz, J = 1.0 Hz); 5.10 (dq, 1H, CH of *Z* isomer, J = 2.9 Hz, J = 1.5 Hz); 6.44 (d, 1 H, Ar, J = 2.4 Hz); 7.12 (d, 1 H, Ar, J = 8.0 Hz).

Diethyl (2,4-dimethoxybenzyl)phosphonate (12) was synthesized as described earlier.[26] A mixture of (2,4-dimethoxyphenyl) methanol (**7a**) (2.1 g, 12.5 mmol), $Bu_4N^+I^-$ (0.138 mg, 3 mol.%), and $(EtO)_3P$ (3.1 mL, 18.7 mmol) was heated at bath temperature of 135 °C for 24 h. The volatiles were removed *in vacuo*, phosphonate **12** was isolated by flash-chromatography (gradient elution with petroleum ether—ethyl acetate, 5 : 1→0 : 1, then CH_2Cl_2 to remove Bu_4NI, and EtOH to elute compound **12**). Yellowish viscous oil, yield 1.59 g (44%). Found (%): C, 54.20; H, 7.39; P, 10.68. $C_{13}H_{21}O_5P$. Calculated (%): C, 54.16; H, 7.34; P, 10.74. IR, ν/cm^{-1}: 3457, 2981, 2937, 2909, 2838, 1613, 1588, 1509, 1466, 1421, 1393, 1326, 1293, 1264 (P=O), 1210, 1187, 1156, 1099, 1032 (POC), 964, 835, 635, 584, 524, 501. ^{1}H NMR ($CDCl_3$), δ: 1.22 (t, 6 H, CH_3 J = 7.1 Hz); 3.15 (d, 2 H, CH_2, J = 21.1 Hz); 3.77 (s, 3 H, OCH_3); 3.79 (s, 3 H, OCH_3); 3.99 (m, 4 H, OCH_2); 6.43 (d, 1 H, Ar, J = 3.0 Hz); 6.45 (dd, 1 H, Ar, J = 2.5 Hz, J = 0.7 Hz); 7.20 (dd, 1 H, Ar, J = 9.2 Hz, J = 2.8 Hz). ^{13}C—{^{1}H} NMR ($CDCl_3$), δ_C: 15.4 (d, J = 6.2 Hz); 24.8 (d, J = 139.7 Hz); 54.4, 54.6, 60.8 (d, J = 6.7 Hz); 97.5 (d, J = 2.9 Hz); 103.7 (d, J = 3.2 Hz); 111.3 (d, J = 9.3 Hz); 130.5 (d, J = 5.5 Hz); 157.2 (d, J = 6.7 Hz); 159.0 (d, J = 3.5 Hz). ^{31}P—{^{1}H} NMR ($CDCl_3$), δ_P: 27.4 (s). MS (ESI), *m/z*: 289 $[M + H]^+$.

Diethyl (2,4-dihydroxybenzyl)phosphonate (13). To a mixture of compound **12** (0.36 g, 1.25 mmol) in dichloromethane (6 mL) cooled to −78 °C, 1 *M* solution of BBr_3 (12.5 mL, 10 equiv.) in dichloromethane was added dropwise. The reaction mixture was stirred at −78 °C for 10 min and the cooling was removed. After temperature reached ambient, the mixture was stirred for 12 h. The mixture was treated with methanol (3×5 mL) and the volatiles were removed *in vacuo* using a rotary evaporator. Water (5 mL) was added to the residue and the organic phase was extracted with dichloromethane. Removal of the solvent *in vacuo* afforded pure phosphonate **13** as brownish oil, yield 0.16 g (49%). Found (%): C, 50.82; H, 6.57; P, 11.78. $C_{11}H_{17}O_5P$. Calculated (%): C, 50.77; H, 6.59; P, 11.90. ^{1}H NMR ($CDCl_3$), δ: 1.19 (t, 6 H, CH_3, J = 7.1 Hz); 3.10 (d, 2 H, CH_2, J = 20.3 Hz); 4.02—3.96 (m, 4 H, OCH_2); 6.35 (dd, 1 H, Ar, J = 8.3 Hz, J = 2.4 Hz); 6.51 (d, 1 H, Ar, J = 2.4 Hz); 6.88 (dd, 1 H, Ar, J = 8.3 Hz, J = 2.5 Hz); 7.83 (s, 2 H, OH). ^{13}C—{^{1}H} NMR ($CDCl_3$), δ_C: 16.3 (d, J = 6.0 Hz); 27.8 (d, J = 139.3 Hz); 63.0 (d, J = 7.0 Hz); 105.1 (d, J = 3.2 Hz); 108.4 (d, J = 2.6 Hz); 109.0 (d, J = 9.2 Hz); 131.8 (d, J = 6.9 Hz); 156.0 (d, J = 5.6 Hz); 157.4 (d, J = 3.3 Hz). ^{31}P—{^{1}H} NMR ($CDCl_3$), δ_P: 30.2 (s).

(2,4-Dihydroxybenzyl)phosphonic acid (14) was synthesized as described above for phosphonate **13** with some changes. The

reaction mixture was treated with methanol and the volatiles were removed *in vacuo*. The residue was treated with 10 *M* HCl (1 mL) in water (5 mL) and stirred at 23 °C for 14 h. Water was removed *in vacuo*, to give compound **14** as brown viscous oil, yield 0.43 g (77%). Found (%): C, 41.10; H, 4.31; P, 15.09. $C_7H_9O_5P$. Calculated (%): C, 41.19; H, 4.44; P, 15.17. IR, ν/cm^{-1}: 3274, 1619, 1520, 1460, 1400, 1310, 1211 (P=O), 1166, 1138, 1090, 933, 975, 937, 842, 811, 764, 742, 702, 669, 627, 543, 485, 459. ^{1}H NMR (D_2O), δ: 3.12 (d, 1 H, CH_2, J = 20.5 Hz); 6.49—6.39 (m, 2 H, Ar); 7.12—7.07 (m, 1 H, Ar). ^{13}C—{^{1}H} NMR (D_2O), δ_C: 27.4 (d, J = 134.1 Hz); 103.0 (d, J = 2.4 Hz); 107.6 (br.s); 111.1 (d, J = 9.7 Hz); 132.1 (d, J = 5.7 Hz); 154.8 (d, J = 3.4); 155.41 (s). ^{31}P—{^{1}H} NMR (D_2O), δ_P: 26.8 (s). MS (ESI), *m/z*: 205 $[M + H]^+$.

Diethyl (2-hydroxy-4-methoxybenzyl)phosphonate (15) was synthesized using the published procedure[25] with minor changes. Amount of BBr_3 was reduced to 1.05 equiv. Compound **15** was obtained as reddish highly viscous oil, yield 0.57 g (42%), m.p. 80—83 °C. Found (%): C, 52.68; H, 7.03; P, 11.18. $C_{12}H_{19}O_5P$. Calculated (%): C, 52.55; H, 6.98; P, 11.29 IR, ν/cm^{-1}: 3216 (OH), 2960, 2926, 2873, 2854, 2740, 2366, 2306, 1619, 1599, 1521, 1509, 1465, 1445, 1396, 1369, 1320, 1290, 1230 (P=O), 1203, 1164, 1096, 1035, 984, 961, 841, 810, 734, 701, 634, 577, 513, 489, 467, 413. ^{1}H NMR ($CDCl_3$), δ: 1.21 (t, 6 H, CH_3, J = 7.1 Hz); 3.08 (d, 2 H, CH_2P, J = 20.6 Hz); 3.71 (s, 3 H, OCH_3); 4.04—3.87 (m, 4 H, OCH_2); 6.43 (dd, H(5), 1 H, J = 8.4 Hz, J = 2.5 Hz); 6.51 (d, H(3), 1 H, J = 2.5 Hz); 6.97 (dd, H(6), 1 H, J = 8.3 Hz, J = 2.2 Hz); 8.47 (s, 1 H, OH). ^{13}C—{^{1}H} NMR ($CDCl_3$), δ_C: 16.2 (d, CH_3, J = 6.1 Hz), 28.3 (d, CH_2P, J = 139.9 Hz); 55.24 (s, OCH_3); 62.6 (d, OCH_2, J = 6.7 Hz); 103.4 (s, C(4)); 107.0 (s, C(6)); 110.4 (d, C(2), J = 9.4 Hz); 132.0 (d, C(7), J = 6.6 Hz); 155.7 (d, C(3), J = 4.6 Hz); 160.1 (s, C(5)). ^{31}P—{^{1}H} NMR ($CDCl_3$), δ_P: 30.8 (s). MS (ESI), *m/z*: 245 $[M - C_2H_5]^+$.

2-Ethoxy-3,3-dimethyl-3*H*-benzo[*d*][1,2]oxaphosphole 2-oxide 3 (17a). A mixture of compound **7b** (4.17 g, 27 mmol, 1 equiv.), triethyl phosphite (4.78 mL, 4.63 g, 27 mmol) and *o*-xylene (50 mL) was refluxed for 48 h. The solvent was distilled off at normal pressure and the residue was distilled under vacuum to give product **17a** as slightly yellow oil. Yield 4.72 g (76%), b.p. 85—90 °C (0.1 Torr). Physicochemical properties of product **17a** coincide with those described previously.[26] IR, ν/cm^{-1}: 3064, 1609, 1588, 1475, 1455, 1268, 1242 (P=O), 1200, 1035, 859. ^{1}H NMR ($CDCl_3$), δ: 1.35 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1 Hz); 1.49 (d, 3 H, C(3)H_3, J = 2.5 Hz); 1.53 (d, 3 H, C(3′)H_3, J = 2.3 Hz); 4.35—4.25 (m, 2 H, OCH_2); 6.99 (br.d, 1 H, H(7), J = 8.0 Hz); 7.07 (br.t, 1 H, H(5), J = 7.5 Hz); 7.16 (td, 1 H, H(4), J = 7.6 Hz, J = 1.4 Hz); 7.21 (td, 1 H, H(6), J = 7.8 Hz, J = 1.6 Hz). ^{31}P—{^{1}H} NMR ($CDCl_3$), δ_P: 51.0 (s). MS (ESI), *m/z*: 227 $[M + H]^+$.

2-Ethoxy-6-methoxy-3,3-dimethyl-3*H*-benzo[*d*][1,2]oxaphosphole 2-oxide (17b). A mixture of alcohol **7d** (0.93 g, 5.1 mol), triethyl phosphite (0.88 mL, 0.85 g, 5.1 mmol), and *o*-xylene (30 mL) was refluxed for 48 h. The solvent was distilled off at normal pressure and the residue was dried *in vacuo* (0.05 Torr) at 120 °C. Yield 0.91 g (70%), yellowish oil. Physicochemical properties of product **17b** coincide with those described previously.[26] ^{1}H NMR ($CDCl_3$), δ: 1.39 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1 Hz); 1.49 (d, 3 H, C(3)H_3, J = 2.4 Hz); 1.54 (d, 3 H, C(3′)H_3, J = 2.2 Hz); 3.81 (s, 3 H, OCH_3 J = 1.8); 4.39—4.27 (m, 2 H, OCH_2); 6.61 (dd, 1 H, H(7), J = 2.5, J = 0.8 Hz); 6.66 (ddd, 1 H, H(5), J = 8.4 Hz, J = 2.5 Hz, J = 0.9 Hz); 7.08 (dd, 1 H, H(4), J = 8.4 Hz, J = 1.5 Hz). ^{31}P—{^{1}H} NMR ($CDCl_3$), δ_P: 51.3 (s).

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References

1. E. Rott, H. Steinmetz, J. W. Metzger, *Sci. Total Environ.*, 2018, **615**, 1176; DOI: 10.1016/j.scitotenv.2017.09.223.
2. U. Pradere, E. C. Garnier-Amblard, S. J. Coats, F. Amblard, R. F. Schinazi, *Chem. Rev.*, 2014, **114**, 9154; DOI: 10.1021/cr5002035.
3. R. M. N. Kalla, H. R. Lee, J. Cao, J.-W. Yoo, I. Kim, *New J. Chem.*, 2015, **39**, 3916; DOI: 10.1039/C5NJ00312A.
4. Z. Rádai, T. Windt, V. Nagy, A. Füredi, N. Z. Kiss, I. Ranđelović, J. Tóvári, G. Keglevich, G. Szakács, S. Tóth, *New J. Chem.*, 2019, **43**, 14028; DOI: 10.1039/C9NJ02144B.
5. G. P. Horsman, D. L. Zechel, *Chem. Rev.*, 2017, **117**, 5704; DOI: 10.1021/acs.chemrev.6b00536.
6. V. A. Erdmann, *Chemical Biology of Nucleic Acids: Fundamentals and Clinical Applications*, Springer-Verlag, Berlin—Heidelberg, 2014, 599 pp.
7. M. Mikołajczyk, *Pure Appl. Chem.*, 2019, **91**, 811; DOI: 10.1515/pac-2018-1117.
8. J. A. Bisceglia, L. R. Orelli, *Curr. Org. Chem.*, 2015, **19**, 744; DOI: 10.2174/1385272819666150311231006.
9. J.-N. Volle, R. Guillon, F. Bancel, Y.-A. Bekro, J.-L. Pirat, D. Virieux, *Adv. Heterocycl. Chem.*, 2016, **118**, 129—193; DOI: 10.1016/bs.aihch.2015.10.004.
10. N. Venkatesan, B. Kim, *Curr. Med. Chem.*, 2002, **9**, 2243—2270; DOI: 10.2174/0929867023368692.
11. K. Gluza, P. Kafarski, in *Drug Discovery*, Ed. H. A. El-Shemy, InTech, 2013, p. 325—372; DOI: 10.5772/52504.
12. C. S. Demmer, N. Krogsgaard-Larsen, L. Bunch, *Chem. Rev.*, 2011, **111**, 7981—8006; DOI: 10.1021/cr2002646.
13. B. E. Ivanov, A. A. Ageeva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1967, **16**, 228; DOI: 10.1007/BF00907150.
14. B. E. Ivanov, A. B. Ageeva, A. G. Abul′khanov, T. A. Zyablikova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1969, **18**, 1770; DOI: 10.1007/BF00905803.
15. D. W. Chasar, *J. Org. Chem.*, 1983, **48**, 4768.
16. M. L. Belyanin, V. D. Filimonov, E. A. Krasnov, *Russ. J. Appl. Chem.*, 2001, **74**, 103; DOI 10.1023/A:1012708319679.
17. H. Li, Y. Xiong, G. Zhang, *Adv. Synth. Catal.*, 2018, **360**, 4246; DOI: 10.1002/adsc.201800796.
18. M. Bergner, D. C. Duquette, L. Chio, B. M. Stoltz, *Org. Lett.*, 2015, **17**, 3008; DOI: 10.1021/acs.orglett.5b01292.
19. J. V. B. Kanth, M. Periasamy, *J. Org. Chem.*, 1991, **56**, 5964; DOI: 10.1021/jo00020a052.
20. J. X. Zhang, Z. Y. Li, Y. C. Wang, W. B. Ma, M. Hou, S. H. Cao, K. H. Tang, H. B. Dong, *J. Asian Nat. Prod. Res.*, 2017, **19**, 903; DOI: 10.1080/10286020.2016.1275583.
21. S. Spatz, M. Korai, *J. Org. Chem.*, 1959, **24**, 1381; DOI: 10.1021/jo01091a633.

22. O. Falana, M. E. Al-Farhan, P. M. Keehn, R. Stevenson, *Tetrahedron Lett.*, 1994, **35**, 65; DOI: 10.1016/0040-4039(94)88163-4.
23. R. N. Mirrington, G. I. Feutrill, *Org. Synth.*, 1973, **53**, 90; DOI: 10.15227/orgsyn.053.0090.
24. R. W. Hartmann, W. Schwarz, A. Heindl, H. Schoenenberger, *J. Med. Chem.*, 1985, **28**, 1295; DOI: 10.1021/jm00147a031.
25. C. Proença, H. M. T. Albuquerque, D. Ribeiro, M. Freitas, C. M. M. Santos, A. M. S. Silva, *Eur. J. Med. Chem.*, 2016, **115**, 381; DOI 10.1016/j.ejmech.2016.03.043.
26. X. Ma, Q. Xu, H. Li, C. Su, L. Yu, X. Zhang, H. Cao, L. B. Han, *Green Chem.*, 2018, **20**, 3408—3413; DOI: 10.1039/c8gc00931g.
27. T. Basak, K. Grudzień, M. Barbasiewicz, *Eur. J. Inorg. Chem.*, 2016, 3513; DOI: 10.1002/ejic.201600435.
28. D. Eom, Y. Jeong, Y. R. Kim, E. Lee, W. Choi, P. H. Lee, *Org. Lett.*, 2013, **15**, 5210; DOI: 10.1021/ol402736v.
29. S. Biswas, A. Ghosh, R. V. Venkateswaran, *Synth. Commun.*, 1991, **21**, 1865; DOI: 10.1080/00397919108021777.
30. V. C. Purohit, S. P. Allwein, R. P. Bakale, *Org. Lett.*, 2013, **15**, 1650; DOI: 10.1021/ol400432x.

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