Bulgarian Chemical Communications, Volume 49, Special Edition B (pp. 33 – 41) 2017

Trifunctionalized allenes. Part I. A convenient and efficient regioselective synthesis of 4-phosphorylated 5-hydroxyalka-2,3-dienoates

I. E. Ismailov, I. K. Ivanov, V. Ch. Christov*

Department of Chemistry, Faculty of Natural Sciences, Konstantin Preslavsky University of Shumen, 115 Universitetska St., 9712 Shumen, Bulgaria

Received February 08, 2017; Revised March 16, 2017

Dedicated to Acad. Bogdan Kurtev on the occasion of his 100th birth anniversary

A convenient and efficient regioselective synthesis of 4-phosphorylated 5-hydroxyalka-2,3-dienoates by an atom economical [2,3]-sigmatropic rearrangement of the mediated ethyl 2-(dimethoxyphosphino)oxy- or 2-(diphenylphosphino)oxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoates which can be readily prepared *via* reaction of the protected alkyl 2-hydroxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoates with dimethyl chlorophosphite or chlorodiphenyl phosphine respectively in the presence of a base is described.

Key words: synthesis; protection of hydroxy group; [2,3]-sigmatropic rearrangement; 4-phosphorylated 5-hydroxyalka-2,3-dienoates

INTRODUCTION

The synthesis and the application of functionalized allenes have been thoroughly explored during the last three decades by the scientists in the preparative organic chemistry field. It is their versatility that attracts scientists` interest. That very specific charactecteristic makes them key building blocks in organic synthesis and lead to implementation of innovative methods for construction of number of functionalized heterocyclic and carbocyclic systems [1–7].

There are many methods explained by different researchers regarding the construction of alka-2,3-dienoates using Wittig [8–10], Wittig-Horner [11] or the Horner-Wadsworth-Emons [12] olefination of ketenes, iron-catalyzed olefination of ketenes with diazoacetate [13] and other methods [14].

Moreover, there are many methods for the construction of hydroxyallenes, including prototropic rearrangement of propargylic alcohols [15, 16], metal-catalyzed nucleophilic addition of propargylic derivatives to aldehydes [10–16], Cu(I)-catalyzed reaction of propargylic chlorides with Grignard reagents [17, 18], metal-catalyzed reaction of propargylic oxiranes with organometallic compounds [19–23] and ketones [24, 25], reduction of alcohols, ethers, oxiranes *etc.* with aluminium reagents [26–28], Pd(0)-catalyzed reaction of cyclic carbonates with acetylenic compunds [29, 30], S_N2' [31, 32] and A_N [33, 34] reactions of metalled alkoxy-allenes with oxiranes and ketones [35], and by other methods [36].

On the other hand, there are methods [37–40] for the synthesis of phosphorus-containing allenes (phosphonates [41–44], phosphinates [45, 46], and phosphine oxides [47–52]) including reactions of α-alkynols with chloride-containing derivatives of phosphorus acids followed by [2,3]-sigmatropic rearrangement. Several diethylphosphono-substituted α-allenic alcohols were prepared by Brel [53, 54] directly from alcohols by Horner-Mark rearrangement of unstable propargylic phosphites.

Our research on the chemistry of the trifunctionalized allenes enhanced us to find a convenient method to introduce the phosphonate or phosphine oxide in the fourth-position as well as the α-hydroxy group in the fifth position to the ester group of the allenecarboxylates. The above mentioned groups provoke organic researchers` interest because of their useful functionalities in organic synthesis. It is particularly interesting to explore the applications of these groups as temporary transformers of chemical reactivity of the allenic system in the synthesis of eventually heterocyclic compounds.

Based on our previous research background related to the synthesis of phosphorylated 1-(α-hydroxyalkyl)allenes [61, 63, 64], 1-(β-hydroxy-alkyl)allenes [62, 65], 4-hydroxy-1,3,4-triphenyl-buta-1,2-dienes [71] and 3-((β-hydroxyalkyl) allenes [72] as well as 4-phosphoryl-substituted

* To whom all correspondence should be sent:
E-mail: *vchristo@shu.bg*

allenecarboxylates [66] we managed to find a convenient and an efficient regioselective method for synthesis of 4-phosphorylated 5-hydroxyalka-2,3-dienoates by an atom economical [2,3]-sigmatropic rearrangement of the mediated ethyl 2-(dimethoxyphosphino)oxy- or 2-(diphenyl-phosphino)oxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoates formed in the reaction of the protected alkyl 2-hydroxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoates with dimethylchloro phosphite or chlorodiphenyl phosphine in the presence of a base.

EXPERIMENTAL

General Information

All new synthesized compounds were purified by column chromatography and characterized on the basis of NMR, IR, and microanalytical data. NMR spectra were recorded on DRX Brucker Avance-250 (Bruker BioSpin, Karlsruhe, Germany) (^{1}H at 250.1 MHz, ^{13}C at 62.9 MHz, ^{31}P at 101.2 MHz) and Brucker Avance II+600 (Bruker BioSpin GmbH, Karlsruhe, Germany) (^{1}H at 600.1 MHz, ^{13}C at 150.9 MHz, ^{31}P at 242.9 MHz) spectrometers for solutions in $CDCl_3$. All ^{1}H and ^{13}C NMR experiments were measured referring to the signal of internal TMS and ^{31}P NMR experiments were measured referring to the signal of external 85% H_3PO_4. *J* values are given in hertz. IR spectra were recorded with an FT-IRAfinity-1 Shimadzu spectrophotometer (Shimadzu, Tokyo, Japan). Elemental analyses were carried out by the Microanalytical Service Laboratory of Faculty of Chemistry and Pharmacy, University of Sofia, Bulgaria, using Vario EL*3* CHNS(O) (Elementar Analysensysteme, Hanau, Germany). Column chromatography was performed on Kieselgel 60 F_{254} (70–230 mesh ASTM, 0.063-0.200 nm, Merck). Et_2O and THF were distilled from Na wire/benzophenone, CH_2Cl_2 was distilled over CaH_2, and other organic solvents used in this study were dried over appropriate drying agents by standard methods and distilled prior to use. All other chemicals used in this study were commercially available and were used without additional purification unless otherwise noted. Reactions were carried out in oven dried glassware under an argon atmosphere and exclusion of moisture. All compounds were checked for purity on TLC plates Kieselgel F_{254} 60 (Merck). Procedure for the synthesis of the (tetrahydro-2*H*-pyran-2-yloxy)-alkynols **2** (96-98% yield) by protection of the hydroxy-group by treatment of the alkynol **1** with DHP (3,4-dihydro-2*H*-pyran) in the presence of PPTS (pyridinium *p*-toluenesulfonate) as a catalyst is described in the literature [67–70].

Procedure for synthesis of alkyl 2-hydroxy-5-(tetrahydro-2H-pyran-2-yloxy)-alk-3-ynoates ***5***

Ethylmagnesium bromide [prepared from magnesium (1.2 g, 50.0 mmol) and ethyl bromide (5.5 g, 50.0 mmol) in dry THF (50 mL)] is added dropwise under stirring to (tetrahydro-2H-pyran-2-yloxy)-alkynol **2** (50.0 mmol) and then the mixture is refluxed for 2 h. The solution of the prepared alkynyl magnesium bromides is added dropwise under stirring to alkyl 2-oxoalkanoate (100.0 mmol). The mixture is refluxed for 2 h and after cooling is hydrolyzed with a saturated aqueous solution of ammonium chloride. The organic layer is separated, washed with water, and dried over anhydrous sodium sulfate. Solvent and the excess of the ester are removed by distillation. Purification of the residue is achieved by column chromatography (silica gel, Kieselgel Merck 60 F_{254}) with ethyl acetate-hexane. The pure products **5** had the following properties:

Ethyl 2-hydroxy-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-pent-3-ynoate (**5a**). Dark orange oil, yield: 89%. Eluent for TLC: ethyl acetate:hexane = 1:3, R_f 0.46; IR (neat, cm^{-1}): 1122 (C-O-C), 1442, 1495 (Ph), 1723 (C=O), 2253 (C≡C), 3418 (OH). ^{1}H-NMR (250.1 MHz): δ_H 1.44 (t, *J*=7.1 Hz, 3H, MeCH_2O)), 1.51-1.76, 3.43-3.57, 4.79-4.87 (overlapping multiplets, 9H, OTHP), 4.15-4.23 (m, 2H, OCH_2Me), 4.26-4.36 (m, 2H, CH_2), 4.43 (s, 1H, OH), 7.22-7.51 (m, 5H, Ph). ^{13}C-NMR (62.9 MHz) δ_C 13.8 (CH_3), 18.9 (CH_2), 25.4 (CH_2), 30.2 (CH_2), 54.6 (CH_2), 61.3 (CH_2), 63.2 (CH_2), 77.8 (C), 82.4 (C), 83.8 (C), 96.7 (CH), 126.2-136.4 (Ph), 171.8 (C). Anal. Calcd for $C_{18}H_{22}O_5$: C 67.91, H 6.97; found: C 67.96, H 7.01.

Ethyl 2-hydroxy-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-hex-3-ynoate (**5b**). Yellow oil, yield: 85%. Eluent for TLC: ethyl acetate:hexane = 1:6, R 0.53; IR (neat, cm^{-1}): 1123 (C-O-C), 1442, 1493 (Ph), 1725 (C=O), 2250 (C≡C), 3396 (OH). ^{1}H-NMR (250.1 MHz): δ_H 1.21 (t, *J*=7.1 Hz, 3H, MeCH_2O), 1.41-1.83, 3.49-3.77, 4.78-4.90 (overlapping multiplets, 9H, OTHP), 1.53 (t, *J*=6.9 Hz, 3H, MeCH), 4.21 (s, 1H, OH), 4.26-4.33 (m, 2H, OCH_2Me), 4.90-4.96 (m, 1H, CH), 7.22-7.48 (m, 5H, Ph). ^{13}C-NMR (62.9 MHz) δ_C 13.8 (CH_3), 15.3 (CH_2), 19.5 (CH_3), 22.4 (CH_2), 31.4 (CH_2), 60.5 (CH), 63.5 (CH_2), 65.9 (CH_2), 76.3 (C), 82.6

(C), 85.2 (C), 96.1 (CH), 124.6-137.6 (Ph), 172.1 (C). Anal. Calcd for $C_{19}H_{24}O_5$: C 68.66, H 7.28; found: C 68.70, H 7.23.

Methyl 2-hydroxy-5-methyl-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-hex-3-ynoate (**5c**). Yellow oil, yield: 90%. Eluent for TLC: ethyl acetate:hexane = 1:6, R_f 0.52; IR (neat, cm^{-1}): 1125 (C-O-C), 1440, 1493 (Ph), 1727 (C=O), 2244 (C≡C), 3404 (OH). ^{1}H-NMR (250.1 MHz): δ_H 1.412-1.74, 3.54-3.69, 4.90-5.01 (overlapping multiplets, 9H, OTHP), 1.58 (s, 6H, Me_2), 3.75 (s, 3H, MeO), 4.18 (s, 1H, OH), 7.21-7.486 (m, 5H, Ph). ^{13}C-NMR (62.9 MHz) δ_C 20.4 (CH_2), 25.2 (CH_2), 29.9 (CH_3), 32.4 (CH_2), 53.0 (CH_3), 63.0 (CH_2), 70.1 (C), 774 (C), 80.1 (C), 87.2 (C), 97.0 (CH), 124.3-137.7 (Ph), 173.4 (C). Anal. Calcd for $C_{19}H_{24}O_5$: C 68.66, H 7.28; found: C 68.61, H 7.32.

*Procedure for synthesis of alkyl 4-(dimethoxyphosphoryl)-5-(tetrahydro-2H-pyran-2-yloxy)-alka-2,3-dienoates **7***

To a solution of phosphorus trichloride (2.75 g, 20 mmol) and triethylamine (2.23 g, 22 mmol) in dry diethyl ether (60 mL) at -70 ^{o}C was added dropwise with stirring a solution of the alkyl 2-hydroxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoate **5** (20 mmol) in the same solvent (20 mL). After 30 min stirring at the same condition a solution of pyridine (3,16 g, 44 mmol) and of methanol (1,28 g, 40 mmol) in dry diethyl ether (50 mL) were added. The reaction mixture was stirred for an hour at the same temperature and for 4 hours at room temperature. The mixture was then washed with water, 2N HCl, extracted with ether, washed with saturated NaCl, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographied on a column (silica gel, Kieselgel Merck 60 F_{254}) with a mixture of ethyl acetate and hexane as an eluent to give the pure product **7** as an oil, which had the following properties:

Ethyl 4-(dimethoxyphosphoryl)-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-penta-2,3-dienoate (**7a**). Orange oil, yield: 74%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.58; IR (neat, cm^{-1}): 1121 (C-O-C), 1262 (P=O), 1443, 1491 (Ph), 1723 (C=O), 1942 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.30 (t, *J*=6.9 Hz, 3H, Me), 1.21-1.63, 3.80-3.89, 4.42-4.53 (overlapping multiplets, 9H, OTHP), 3.79 (d, *J*=12.7 Hz, 6H, 2MeO), 4.21-4.61 (m, 4H, MeC<u>H</u>$_2$O, CH_2), 7.28-8.18 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.1 (CH_3), 18.9 (CH_2), 25.9 (CH_2), 29.8 (CH_2), 51.5 (*J*=13.1 Hz, CH_3), 60.7 (CH_2), 63.0 (CH_2), 66.3 (*J*=5.8 Hz, CH_2), 94.4 (*J*=181.5 Hz, C), 96.3 (*J*=4.4 Hz, CH), 106.5 (*J*=7.8 Hz, C), 128.5-133.9 (Ph), 169.1 (*J*=4.0 Hz, C), 218.5 (*J*=1.3 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 15.4. Anal. Calcd for $C_{20}H_{27}O_7P$: C 58.53, H 6.63; found: C 58.49, H 6.68.

Ethyl 4-(dimethoxyphosphoryl)-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-hexa-2,3-dienoate (**7b**). Yellow oil, yield: 72%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.43; IR (neat, cm^{-1}): 1120 (C-O-C), 1265 (P=O), 1439, 1490 (Ph), 1722 (C=O), 1937 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.29 (t, *J*=7.0 Hz, 3H, <u>Me</u>CH_2O), 1.30-1.66, 3.67-3.77, 4.50-4.62 (overlapping multiplets, 9H, OTHP), 1.44 (dd, *J*=3.5 Hz, *J*=6.5 Hz, 3H, <u>Me</u>-CH), 3.78 (d, *J*=12.5 Hz, 6H, 2MeO), 4.20-4.27 (m, 2H, MeC<u>H</u>$_2$O), 4.77-4.86 (Me-C<u>H</u>), 7.25-8.11 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.3 (CH_3), 19.3 (CH_2), 23.6 (*J*=1.7 Hz, CH_3), 25.6 (CH_2), 30.5 (CH_2), 51.4 (*J*=12.9 Hz, CH_3), 59.7 (CH_2), 62.6 (CH_2), 67.7 (*J*=5.9 Hz, CH), 94.2 (*J*=4.3 Hz, CH), 97.4 (*J*=183.0 Hz, C), 105.9 (*J*=7.7 Hz, C), 128.2-134.1 (Ph), 162.3 (*J*=4.0 Hz, C), 219.6 (*J*=1.3 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 15.2. Anal. Calcd for $C_{21}H_{29}O_7P$: C 59.43, H 6.89; found: C 59.37, H 6.92.

Methyl 4-(diisopropoxyphosphoryl)-5-methyl-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-hexa-2,3-dienoate (**7c**). Orange oil, yield: 75%. Eluent for TLC: ethyl acetate:hexane = 8:1, R_f 0.49; IR (neat, cm^{-1}): 1119 (C-O-C), 1269 (P=O), 1442, 1495 (Ph), 1724 (C=O), 1929 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.29 (dd, *J*=6.1 Hz, *J*=5.7 Hz, 6H, <u>Me</u>$_2$CHO), 1.32-1.64, 3.51-3.74, 4.77-4.83 (overlapping multiplets, 9H, OTHP), 1.58 (d, *J*=3.3 Hz, 6H, <u>Me</u>$_2$-C), 3.70 (s, 3H, MeO), 4.63-4.75 (m, 2H, 2Me$_2$C<u>H</u>O), 7.24-8.23 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 20.0 (CH_2), 23.9 (*J*=8.0 Hz, CH_3), 25.5 (CH_2), 30.2 (*J*=7.8 Hz, CH_3), 30.7 (CH_2), 52.9 (CH_3), 62.1 (CH_2), 67.1 (*J*=5.0 Hz, CH), 79.9 (*J*=9.8 Hz, C), 91.3 (*J*=4.6 Hz, CH), 104.7 (*J*=184.8 Hz, C), 105.4 (*J*=7.8 Hz, C), 128.2-135.0 (Ph), 165.3 (*J*=4.4 Hz, C), 219.1 (*J*=1.3 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 17.4. Anal. Calcd for $C_{25}H_{37}O_7P$: C 62.49, H 7.76; found: C 62.56, H 7.71.

*Procedure for the synthesis of alkyl 4-(diphenylphosphinoyl)-5-(tetrahydro-2H-pyran-2-yloxy)-alka-2,3-dienoates **9***

To a solution of the alkyl 2-hydroxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoate **5** (20 mmol) and triethylamine (2.23 g, 22 mmol) in dry diethyl ether (60 mL) at -70 ^{o}C, a solution of

freshly distilled diphenylchloro phosphine (4.41 g, 20 mmol) in the same solvent (20 mL) was added dropwise with stirring. The reaction mixture was stirred for an hour at the same temperature and for 6 h at room temperature and then washed with water, 2N HCl, extracted with diethyl ether, and the extract was washed with saturated NaCl, and dried over anhydrous sodium sulfate. The solvent was removed using a rotatory evaporator, and the residue was purified by column chromatography on a silica gel (Kieselgel Merck 60 F_{254}) with ethyl acetate-hexane to give the pure products **9** as an oil, which had the following properties:

Ethyl 4-(diphenylphosphinoyl)-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-penta-2,3-dienoate (**9a**). Yellow oil, yield: 82%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.56; IR (neat, cm^{-1}): 1121 (C-O-C), 1177 (P=O), 1439, 1486 (Ph), 1721 (C=O), 1937 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.32 (t, *J*=6.8 Hz, 3H, MeCH$_2$O), 1.30-1.59, 3.64-3.75, 4.49-4.59 (overlapping multiplets, 9H, OTHP), 1.44 (dd, *J*=3.5 Hz, *J*=6.5 Hz, 3H, Me-CH), 3.78 (d, *J*=12.5 Hz, 6H, 2MeO), 4.20-4.28 (m, 2H, MeCH$_2$O), 4.33-4.46 (CH_2), 7.26-8.14 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.2 (CH_3), 18.8 (CH_2), 25.4 (CH_2), 31.0 (CH_2), 59.4 (CH_2), 62.8 (CH_2), 69.3 (*J*=4.7 Hz, CH_2), 96.8 (*J*=5.8 Hz, CH), 106.1 (*J*=181.5 Hz, C), 111.4 (*J*=7.9 Hz, C), 127.4-136.4 (3Ph), 166.4 (*J*=4.7 Hz, C), 215.4 (*J*=1.6 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 28.5. Anal. Calcd for $C_{30}H_{31}O_5P$: C 71.70, H 6.22; found: C 71.77, H 6.19.

Ethyl 4-(diphenylphosphinoyl)-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-hexa-2,3-dienoate (**9b**). Yellow oil, yield: 79%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.58; IR (neat, cm^{-1}): 1117 (C-O-C), 1176 (P=O), 1439, 1485 (Ph), 1715 (C=O), 1940 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.35 (t, *J*=6.9 Hz, 3H, MeCH$_2$O), 1.37-1.66, 3.57-3.71, 4.53-4.64 (overlapping multiplets, 9H, OTHP), 1.42 (dd, *J*=3.4 Hz, *J*=6.6 Hz, 3H, Me-CH), 4.18-4.27 (m, 2H, MeCH$_2$O), 4.68-4.82 (m, 1H, Me-CH), 7.21-8.14 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.2 (CH_3), 19.5 (CH_2), 23.2 (*J*=1.6 Hz, CH_3), 25.4 (CH_2), 30.6 (CH_2), 59.4 (CH_2), 63.0 (CH_2), 69.5 (*J*=6.0 Hz, CH), 95.0 (*J*=4.4 Hz, CH), 106.5 (*J*=182.5 Hz, C), 109.6 (*J*=7.9 Hz, C), 128.4-135.7 (3Ph), 165.4 (*J*=4.6 Hz, C), 213.4 (*J*=1.4 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 28.7. Anal. Calcd for $C_{31}H_{33}O_5P$: C 72.08, H 6.44; found: C 72.04, H 6.49.

Methyl 4-(diphenylphosphinoyl)-5-methyl-2-phenyl-5-(tetrahydro-2H-pyran-2-yloxy)-hexa-2,3-dienoate (**9c**). Yellow oil, yield: 86%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.59; IR (neat, cm^{-1}): 1117 (C-O-C), 1171 (P=O), 1437, 1495 (Ph), 1724 (C=O), 1940 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.436-1.71, 3.52-3.75, 4.73-4.80 (overlapping multiplets, 9H, OTHP), 1.56 (d, *J*=3.2 Hz, 6H, Me$_2$-C), 3.70 (s, 3H, MeO), 7.20-8.18 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 19.7 (CH_2), 25.4 (CH_2), 29.9 (*J*=7.8 Hz, CH_3), 31.4 (CH_2), 53.2 (CH_3), 63.4 (CH_2),81.0 (*J*=9.7 Hz, C), 92.9 (*J*=4.6 Hz, CH), 108.1 (*J*=7.8 Hz, C), 114.5 (*J*=185.0 Hz, C), 128.4-136.4 (3Ph), 164.3 (*J*=4.6 Hz, C), 213.4 (*J*=0.9 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 272. Anal. Calcd for $C_{31}H_{33}O_5P$: C 72.08, H 6.44; found: C 72.13, H 6.48.

*Procedure for the synthesis of alkyl 4-(dimethoxyphosphoryl)-5-hydroxy-alka-2,3-dienoates **10** and alkyl 4-(diphenylphosphinoyl)-5-hydroxy-alka-2,3-dienoates **11***

A solution of the alkyl 4-(dimethoxyphosphoryl)-5-(tetrahydro-2*H*-pyran-2-yloxy)-alka-2,3-dienoates **7** or the alkyl 4-(diphenylphosphinoyl)-5-(tetrahydro-2*H*-pyran-2-yloxy)-alka-2,3-dienoate **9** (5 mmol) and PPTS (0.5 mmol) in ethanol (10 mL) was stirred at room temperature for 5 h. The mixture was then washed with water, extracted with methylene chloride and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographied on a column (silica gel, Kieselgel Merck 60 F_{254}) with a mixture of ethyl acetate and hexane as an eluent to give the pure products **10** or **11** as oils, which had the following properties:

Ethyl 4-(dimethoxyphosphoryl)-5-hydroxy-2-phenyl-penta-2,3-dienoate (**10a**). Yellow oil, yield: 92%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.42; IR (neat, cm^{-1}): 1265 (P=O), 1440, 1491 (Ph), 1717 (C=O), 1940 (C=C=C), 3428 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.34 (t, *J*=7.0 Hz, 3H, Me), 3.21 (s, 1H, OH), 3.79 (d, *J*=12.9 Hz, 6H, 2MeO), 4.19-4.27 (m, 2H, MeCH$_2$O), 4.57 (d, *J*=14.9 Hz, CH_2), 7.27-8.02 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.3 (CH_3), 51.4 (*J*=13.8 Hz, CH_3), 59.9 (CH_2), 61.0 (*J*=5.7 Hz, CH_2), 95.1 (*J*=183.0 Hz, C), 107.4 (*J*=7.6 Hz, C), 128.53-133.7 (Ph), 162.1 (*J*=4.3 Hz, C), 217.8 (*J*=1.4 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 16.3. Anal. Calcd for $C_{15}H_{19}O_6P$: C 55.22, H 5.87; found: C 55.16, H 5.82.

Ethyl 4-(dimethoxyphosphoryl)-5-hydroxy-2-phenyl-hexa-2,3-dienoate (**10b**). Orange oil, yield: 88%. Eluent for TLC: ethyl acetate:hexane = 1:1,

R_f 0.61; IR (neat, cm^{-1}): 1265 (P=O), 1437, 1489 (Ph), 1723 (C=O), 1939 (C=C=C), 3410 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.35 (t, *J*=7.1 Hz, 3H, MeCH$_2$O), 1.42 (dd, *J*=3.4 Hz, *J*=6.3 Hz, 3H, Me-CH), 3.37 (s, 1H, OH), 3.78 (d, *J*=13.0 Hz, 6H, 2MeO), 4.21-4.28 (m, 2H, MeCH$_2$O), 5.18-5.28 (m, 1H, Me-CH), 7.21-8.10 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.4 (CH_3), 24.0 (*J*=1.8 Hz, CH_3), 52.0 (*J*=13.0 Hz, CH_3), 60.2 (CH_2), 72.4 (*J*=6.1 Hz, CH), 98.0 (*J*=184.0 Hz, C), 106.4 (*J*=7.5 Hz, C), 127.9-135.0 (Ph), 162.7 (*J*=4.2 Hz, C), 217.4 (*J*=1.5 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 16.4. Anal. Calcd for $C_{16}H_{21}O_6P$: C 56.47, H 6.22; found: C 56.53, H 6.27.

Ethyl 4-(dimethoxyphosphoryl)-5-hydroxy-2-phenyl-hexa-2,3-dienoate (**10c**). Yellow oil, yield: 86%. Eluent for TLC: ethyl acetate:hexane = 3:1, R_f 0.55; IR (neat, cm^{-1}): 1268 (P=O), 1441, 1495 (Ph), 1723 (C=O), 1933 (C=C=C), 3418 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.30 (dd, *J*=6.0 Hz, *J*=5.5 Hz, 6H, Me$_2$CHO), 1.51 (d, *J*=3.4 Hz, 6H, Me$_2$C), 3.81 (s, 1H, OH), 4.64-4.78 (m, 2H, 2Me$_2$CHO), 7.20-8.13 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 23.5 (*J*=8.0 Hz, CH_3), 31.4 (*J*=7.9 Hz, CH_3), 53.4 (CH_3), 68.1 (*J*=4.5 Hz, CH), 73.7 (*J*=10.1 Hz, C), 104.3 (*J*=185.7 Hz, C), 106.5 (*J*=7.9 Hz, C), 127.8-133.9 (Ph), 164.0 (*J*=4.7 Hz, C), 215.8 (*J*=1.1 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 12.7. Anal. Calcd for $C_{20}H_{29}O_6P$: C 60.60, H 7.37; found: C 60.55, H 7.40.

Ethyl 4-(diphenylphosphinoyl)-5-hydroxy-2-phenyl-penta-2,3-dienoate (**11a**). Orange yellow oil, yield: 94%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.41; IR (neat, cm^{-1}): 1180 (P=O), 1439, 1485 (Ph), 1721 (C=O), 1934 (C=C=C), 3396 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.36 (t, *J*=6.9 Hz, 3H, MeCH$_2$O), 3.18 (s, 1H, OH), 4.19-4.27 (m, 2H, MeCH$_2$O), 4.64 (d, *J*=15.1 Hz, CH_2), 7.20-8.04 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.3 (CH_3), 60.1 (CH_2), 65.7 (*J*=4.8 Hz, CH_2), 105.7 (*J*=182.1 Hz, C), 110.7 (*J*=7.7 Hz, C), 128.9-136.0 (3Ph), 163.4 (*J*=4.7 Hz, C), 213.5 (*J*=1.5 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 31.3. Anal. Calcd for $C_{25}H_{23}O_4P$: C 71.76, H 5.54; found: C 71.80, H 5.57.

Ethyl 4-(diphenylphosphinoyl)-5-hydroxy-2-phenyl-hexa-2,3-dienoate (**11b**). Yellow oil, yield: 92%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.52; IR (neat, cm^{-1}): 1179 (P=O), 1439, 1485 (Ph), 1717 (C=O), 1944 (C=C=C), 3389 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.32 (t, *J*=7.0 Hz, 3H, MeCH$_2$O), 1.40 (dd, *J*=3.5 Hz, *J*=6.4 Hz, 3H, Me-CH), 3.41 (s, 1H, OH), 4.21-4.30 (m, 2H, MeCH$_2$O), 5.09-5.17 (m, 1H, Me-CH), 7.20-8.10 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.3 (CH_3), 22.9 (*J*=1.7 Hz, CH_3), 60.2 (CH_2), 75.7 (*J*=5.8 Hz, CH), 107.5 (*J*=183.2 Hz, C), 108.4 (*J*=8.0 Hz, C), 127.4-137.1 (3Ph), 163.7 (*J*=4.7 Hz, C), 214.5 (*J*=1.5 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 32.2. Anal. Calcd for $C_{26}H_{25}O_4P$: C 72.21, H 5.83; found: C 71.27, H 5.87.

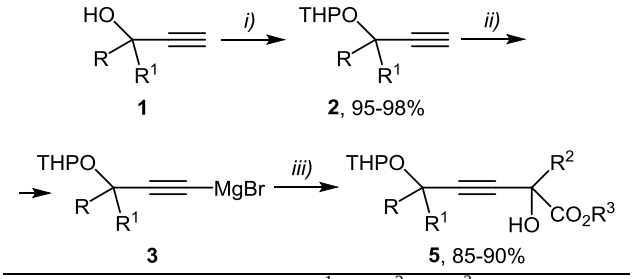
Methyl 4-(diphenylphosphinoyl)-5-hydroxy-5-methyl-2-phenyl-hexa-2,3-dienoate (**11c**). Yellow oil, yield: 93%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.60; IR (neat, cm^{-1}): 1170 (P=O), 1437, 1495 (Ph), 1722 (C=O), 1940 (C=C=C), 3396 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.46 (t, *J*=3.5 Hz, 6H, Me$_2$C), 3.71 (s, 3H, MeO), 3.94 (s, 1H, OH), 7.20-8.04 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 30.7 (*J*=7.9 Hz, CH_3), 53.7 (CH_3), 74.8 (*J*=10.1 Hz, C), 110.5 (*J*=8.0 Hz, C), 115.4 (*J*=183.2 Hz, C), 128.2-136.9 (3Ph), 165.0 (*J*=4.6 Hz, C), 211.5 (*J*=1.0 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 29.7. Anal. Calcd for $C_{26}H_{25}O_4P$: C 72.21, H 5.83; found: C 72.15, H 5.78.

RESULTS AND DISCUSSION

A range of the 4-phosphorylated 5-hydroxy-allenecarboxylates **7**, **9**, **10**, and **11** was prepared by the following four-step procedure including: i) protection of hydroxy group in the alk-3-yn-2-ols; ii) subsequent reaction with Grignard reagent and alkyl 2-oxoalkanoates to give the alkyl 2,5-dihydroxy-alk-3-ynoates with protected hydroxy group at second position; iii) interaction with chloride of phosphorus acid in the presence of a base; and finally iv) [2,3]-sigmatropic rearrangement of the mediated protected ethyl 2-(dimethoxyphosphino)oxy- or 2-(diphenylphosphino)oxy-5-hydroxy-alk-3-ynoates on order to assess the approach applied for 1,1,3-trifunctionalized allenes.

The fisrt thing we examined was the protection of hydroxy group in the alk-3-yn-2-ols **1** with DHP in the presence of PPTS [67–70] (Scheme 1). The formed (tetrahydro-2*H*-pyran-2-yloxy)-alk-3-yn-2-ols **2** were isolated by column chromatography with excellent yield (96-98%). The reaction of the protected alkynols **2** with ethyl magnesium bromide and subsequent dropwise addition of the *in situ* generated alkynyl magnesium bromide **3** to the alkyl 2-oxoalkanoates **4** and reflux for 2 hours gives the alkyl 2-hydroxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoates **5**, which are stable and were isolated by column chromatography in 85-89% yields as is shown in Scheme 1.

Having already in hand the required alkyl 2,5-dihydroxy-alk-3-ynoates **5** with protected hydroxy group at second position, we were able to investigate the proposed reactions with the corresponding chloro-containing phosphorus reagents such as dimethyl chlorophosphite and chlorodiphenyl phosphine in the presence of a base and subsequent [2,3]-sigmatropic rearrangement of the mediated phosphites **6** or phosphonites **8**.



Entry	Product	R	R^1	R^2	R^3	Yield, %	
						2	**5**
1	**a**	H	H	Ph	Et	95	89
2	**b**	H	Me	Ph	Et	96	85
3	**c**	Me	Me	Me	Me	98	90

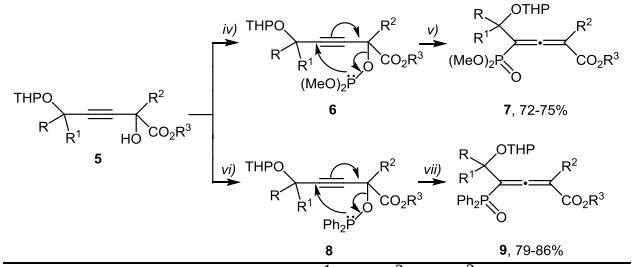
Reagents and Conditions: *i)* DHP (1.5 eq), PPTS (0.1 eq), CH_2Cl_2, rt, 2h, distillation; *ii)* EtMgBr (1 eq), THF, reflux, 2h; *iii)* dropwise addition of **3** to $R^2C(O)CO_2R^3$ (**4**) (2 eq), reflux, 2h, column chromatography.

Scheme 1. Synthesis of the alkyl 2-hydroxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoates **5**.

It became obvious that the alkyl 4-(dimethoxyphosphoryl)-5-(tetrahydro-2*H*-pyran-2-yloxy)-alka-2,3-dienoates **7** can be readily prepared *via* an atom economical 2,3-sigmatropic rearrangement of the alkyl 2-(dimethoxy-phosphino)oxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoates **6**, intermediate formed by reaction of the alkyl 2-hydroxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-alk-3-ynoates **5** with dimethyl chloro-phosphite, prepared *in situ* from phosphorus trichloride and 2 *equiv* of methanol in the presence of triethylamine, and 2 *equiv* of pyridine, according to Scheme 2.

Further, reaction of the (tetrahydro-2*H*-pyran-2-yloxy)-alkynols **5** with chlorodiphenyl phosphine in the presence of triethylamine at -70 ^oC gave the expected alkyl 4-(diphenylphosphinoyl)-5-(tetrahydro-2*H*-pyran-2-yloxy)-alka-2,3-dienoates **9** in very good yield (79-82%) as a result of [2,3]-sigmatropic rearrangement of the ethyl 2-(diphenylphosphino)oxy-5-(tetrahydro-2*H*-pyran-2-yloxy)-pent-3-ynoates **8** for 6 hours at room temperature, according to the reaction sequence outlined in Scheme 2.

It was the 4-phosphorylated 5-hydroxyalka-2,3-dienoates with protected hydroxy group **7** and **9** that were synthesized *via* an atom economical and regioselective [2,3]-sigmatropic rearrangement of the intermediate formed hydroxy- and carboxy-substituted propargyl phosphites **6** or phosphinites **8** in the reaction of protected hydroxy- and carboxy-substituted alkynols **5** with dimethylchloro phosphite or chlorodiphenyl phosphine in the presence of triethylamine.



Entry	Product	R	R^1	R^2	R^3	Yield, %	
						7	**9**
1	**a**	H	H	Ph	Et	74	82
2	**b**	H	Me	Ph	Et	72	79
3	**c**	Me	Me	Me	Me	75	86

Reagents and Conditions: *iv)* PCl_3 (1 eq), Et_3N (1.1 eq), Et_2O, -70 ^oC, 30 min stirring, pyridine (2.2 eq), MeOH (2 eq), Et_2O, -70 ^oC; *v)* [2,3-σ]-rearrangement, -70 ^oC, 1h, rt, 4h, column chromatography; *vi)* Ph_2PCl (1 eq), Et_3N (1.1 eq), Et_2O, -70 ^oC; *vii)* [2,3-σ]-rearrangement, -70 ^oC, 1h, rt, 6h, column chromatography.

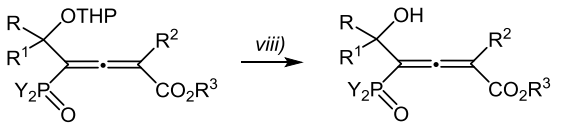
Scheme 2. Synthesis of the alkyl 4-(dimethoxy-phosphoryl)-5-(tetrahydro-2*H*-pyran-2-yloxy)-alka-2,3-dienoates **7** and the alkyl 4-(diphenylphosphinoyl)-5-(tetrahydro-2*H*-pyran-2-yloxy)-alka-2,3-dienoates **9**.

Compounds **7** and **9** were stable enough to be handled at ambient temperature. The hydroxy group was deprotected by stirring the ethanol solution of the protected alkyl 4-(dimethoxyphosphoryl)- or 4-(diphenyl-phosphinoyl)-5-(tetrahydro-2*H*-pyran-2-yloxy)-alka-2,3-dienoates **7** or **9** in the presence of 0.1 *equiv* PPTS at room temperature for 6 hours to give the alkyl 4-(dimethoxyphosphoryl)-5-hydroxy-alka-2,3-dienoates **10** and the alkyl 4-(diphenyl-phosphinoyl)-5-hydroxy-alka-2,3-dienoates **11**, according to Scheme 3.

It should be stated that all allenic products **7**, **9**, **10**, and **11** that were isolated as stable yellow or orange oils by column chromatography and identified by ^1H, ^{13}C, and ^{31}P NMR and IR spectra as well as by elemental analysis.

A series of new 4-phosphorylated 5-hydroxyalka-2,3-dienoates with protected **7** and **9** and unprotected hydroxy group **10** and **11** were

synthesized by a convenient, efficient, atom economical and regioselective method.



7, **9**

10, Y=MeO, 88-92%
11, Y=Ph, 92-94%

Entry	Product	R	R^1	R^2	R^3	Yield, %	
						10	**11**
1	**a**	H	H	Ph	Et	92	94
2	**b**	H	Me	Ph	Et	88	92
3	**c**	Me	Me	Me	Me	86	93

Reagents and Conditions: *viii)* PPTS (0.1 eq), EtOH, rt, 6h, stirring, column chromatography.

Scheme 3. Synthesis of the alkyl 4-(dimethoxyphosphoryl)-5-hydroxy-alka-2,3-dienoates **10** and the alkyl 4-(diphenylphosphinoyl)-5-hydroxy-alka-2,3-dienoates **11**.

CONCLUSION

In conclusion, a convenient and efficient method for regioselective synthesis of a new family of 1,1,3-trifunctionalized allenes has been explored. 4-Phosphorylated 5-hydroxyalka-2,3-dienoates prepared were derived from [2,3]-sigmatropic rearrangement of the intermediate hydroxy- and carboxy-substituted propargyl phosphites or phosphinites formed in the reaction of protected hydroxy- and carboxy-substituted alkynols with dimethylchloro phosphite or chlorodiphenyl phosphine in the presence of a base.

Further investigations on this potentially important synthetic methodology are currently in progress. At the same time, the synthetic application of the prepared 4-phosphorylated 5-hydroxyalka-2,3-dienoates with protected or unprotected hydroxy group for synthesis of different heterocyclic compounds is now under investigation in our laboratory as a part of our general synthetic strategy for investigation of the scope and limitations of the electrophilic cyclization and cycloisomerization reactions of trifunctionalized allenes. Results of these investigations will be reported in due course. Moreover, results of an initial investigation of the biological activity of the compounds prepared were encouraging, and the antibacterial and antifungal activities of selected compounds as well as potential precursors of effective anticancer drugs are now under investigation in our university.

Acknowledgements: *Support from the Research Fund of the Konstantin Preslavsky University of Shumen (Projects Nos. RD-08-109 / 2016 and RD-08-98 / 2017) is acknowledged.*

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ТРИФУНКЦИОНАЛИЗИРАНИ АЛЕНИ. ЧАСТ I. УДОБЕН И ЕФИКАСЕН РЕГИОСЕЛЕКТИВЕН СИНТЕЗ НА 4-ФОСФОРИЛИРАНИ 5-ХИДРОКСИАЛКА-2,3-ДИЕНОАТИ

И. Е. Исмаилов, И. К. Иванов, В. Х. Христов*

Катедра по химия, Факултет по природни науки, Шуменски университет „Епископ Константин Преславски“, ул. „Университетска“ 115, 9712 Шумен, България

Постъпила на 08 февруари 2017 г.; Коригирана на 16 март 2017 г.

(Резюме)

Описан е удобен и ефикасен региоселективен синтез на 4-фосфорилирани 5-хидроксиалка-2,3-диеноати чрез атом-икономична [2,3]-сигматропна прегрупировка на междинно образуваните 2-(диметоксифосфино)окси- или 2-(дифенилфосфино)окси-5-(тетрахидро-2*H*-пиран-2-илокси)-алк-3-иноати, които лесно се получават чрез реакция на защитените 2-хидрокси-5-(тетрахидро-2*H*-пиран-2-илокси)-алк-3-иноати с диметил хлорофосфит или хлородифенил фосфин съответно в присъствие на база.