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Bifunctionalized allenes. Part XX. A convenient and efficient regioselective synthesis of phosphorylated 3-(α-hydroxyalkyl)allenes

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

A convenient and efficient regioselective synthesis of phosphorylated 3-(α-hydroxyalkyl)allenes by an atom-economical [2,3]-sigmatropic rearrangement of the mediated propargyl phosphites or phosphinites which can be readily prepared *via* reaction of (tetrahydro-2*H*-pyran-2-yloxy)-alkynols 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; phosphorylated 3-(α-hydroxyalkyl)allenes

INTRODUCTION

The synthesis and application of allene derivatives has had a great influence in preparative organic chemistry during the last three decades. The crucial structural characteristic of allenes is the presence of two π electron clouds separated by a single sp-hybridized carbon atom. Due to that very unique structural and electronic arrangement allenic compounds have an extraordinary reactivity profiles. Moreover, functionalized allenes have also attracted growing attention due to their versatility as key building blocks for organic synthesis. The synthetic potential of functionalized allenes has been thoroughly explored in recent years. The research in that area has led to the development of novel methods for the construction of a variety of functionalized heterocyclic and carbocyclic systems [1–6].

There are variety of methods for the construction of hydroxyallenes that include prototropic rearrangement of propargylic alcohols [7, 8], metal-catalyzed nucleophilic addition of propargylic derivatives to aldehydes [9–15], Cu(I)-catalyzed reaction of propargylic chlorides with Grignard reagents [16, 17], metal-catalyzed reaction of propargylic oxiranes with organometallic compounds [18–22] and ketones [23, 24], reduction of alcohols, ethers, oxiranes *etc.* with aluminium reagents [25–27], Pd(0)-catalyzed reaction of cyclic carbonates with acetylenic compounds [28, 29], S_N2' [30, 31] and A_N [32, 33] reactions of metalled alkoxy-allenes with oxiranes and ketones [34], and other routes [35].

In addition, there are methods [36–39] for the synthesis of phosphorus-containing allenes (phosphonates [40–43], phosphinates [44, 45], and phosphine oxides [46–51]) 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 [52, 53] directly from alcohols by Horner-Mark rearrangement of unstable propargylic phosphites.

As a part of our research program on the chemistry of the bifunctionalized allenes, we required a convenient method to introduce a phosphorus-containing group such as phosphonate or phosphine oxide group as well as a α-hydroxy group in the third position to the allenic system of double bonds. The above mentioned groups provoke organic researchers` interest because of their useful functionalities in organic synthesis. The emphasis is particularly on the applications of these groups as temporary transformers of chemical reactivity of the allenic system in the synthesis of eventually heterocyclic compounds.

Our scientific interest on the synthesis [54, 55] and electrophilic cyclization [56, 58] and cyclo-isomerisation reactions [57, 58] of phosphorylated 1-(α-hydroxyalkyl)allenes [54, 56, 57], 1-(β-hydroxyalkyl)allenes [55, 58], 4-hydroxy-1,3,4-triphenyl-buta-1,2-dienes [63] and 3-(β-hydroxy-alkyl)allenes [64] reported in our previous articles let to the discovery of a convenient and efficient

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regioselective synthesis of phosphorylated 3-(α-hydroxyalkyl)allenes by an atom economical [2,3]-sigmatropic rearrangement of the mediated (tetrahydro-2*H*-pyran-2-yloxy)-propargyl phosphite or phosphinite.

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 60 F_{254} (Merck).

General procedure [59-62] *for synthesis of (tetrahydro-2H-pyran-2-yloxy)-alkanone **2***

A solution of the α-hydroxy-alkanones **1** (120 mmol) and DHP (3,4-dihydro-2*H*-pyran) (15.14 g, 180 mmol) in dry methylene chloride (100 mL) containing PPTS (pyridinium *p*-toluenesulfonate) (3 g, 12 mmol) is stirred for 10 h at room temperature. Then the reaction was quenched with saturated $NaHCO_3$ and extracted with methylene chloride. The organic layer was 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. The pure products **2** had the following properties:

1-(Tetrahydro-2H-pyran-2-yloxy)-propan-2-one (**2a**). Pale yellow oil, yield: 95%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.59; IR (neat, cm^{-1}): 1120 (C-O-C), 1721 (C=O). ^{1}H-NMR (250.1 MHz): δ_H 1.45-1.83, 3.55-3.71, 4.37-4.46 (overlapping multiplets, 9H, OTHP), 2.07 (s, 3H, Me), 4.11-4.27 (m, 2H,CH_2). ^{13}C-NMR (62.9 MHz) δ_C 19.5 (CH_2), 25.3 (CH_2), 26.7 (CH_3), 30.1 (CH_2), 62.1 (CH_2), 74.4 (CH_2), 99.0 (CH), 205.7 (C). Anal. Calcd. for $C_8H_{14}O_3$: C 60.74, H 8.92; found: C 60.68, H 8.87.

3-(Tetrahydro-2H-pyran-2-yloxy)-butan-2-one (**2b**). Pale yellow oil, yield: 96%. Eluent for TLC: ethyl acetate:hexane = 1:2, R_f 0.53; IR (neat, cm^{-1}): 1125 (C-O-C), 1721 (C=O).). ^{1}H-NMR (250.1 MHz): δ_H 1.20 (d, *J*=6.3 Hz, 3H, Me-CH), 1.49-1.71, 3.60-3.73, 4.59-4.67 (overlapping multiplets, 9H, OTHP), 2.19 (s, 3H, Me), 4.03-4.11 (m, 2H, CH). ^{13}C-NMR (62.9 MHz) δ_C 16.5 (CH_3), 19.5 (CH_2), 25.0 (CH_3), 25.7 (CH_2), 30.7 (CH_2), 63.1 (CH_2), 77.0 (CH), 95.4 (CH), 211.5 (C). Anal. Calcd. for $C_9H_{16}O_3$: C 62.77, H 9.36; found: C 62.72, H 9.40.

Phenyl-[1-(tetrahydro-2H-pyran-2-yloxy)-cyclohexyl]-methanone (**2c**). Colourless oil, yield: 93%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.44; IR (neat, cm^{-1}): 1123 (C-O-C), 1442, 1489 (Ph), 1680 (C=O). ^{1}H-NMR (250.1 MHz): δ_H 1.35-2.11, 3.49-3.79, 5.15-5.24 (overlapping multiplets, 19H, OTHP, cyclohexyl), 7.34-8.02 (m, 5H, Ph). ^{13}C-NMR (62.9 MHz) δ_C 20.2 (CH_2), 24.0 (2xCH_2), 25.2 (CH_2), 26.0 (CH_2), 31.6 (CH_2), 35.2 (2xCH_2), 62.4 (CH_2), 82.7 (C), 97.2 (CH), 128.1-133.0 (Ph), 201.4 (C). Anal. Calcd. for $C_{18}H_{24}O_3$: C 74.97, H 8.39; found: C 75.02, H 8.43.

Synthesis and spectral data of *diphenyl-2-(tetrahydro-2H-pyran-2-yloxy)-ethanone* **2d** were described in our previous paper [63].

*General procedure for synthesis of (tetrahydro-2H-pyran-2-yloxy)-alkynols **3***

Ethylmagnesium bromide [prepared from magnesium (1.22 g, 50 mmol) and ethyl bromide (5.50 g, 50 mmol) in dry THF (50 mL)] is added dropwise under stirring to the phenylacetylene (50

mmol) and then the mixture is refluxed for 2 h. The solution of the prepared ethynyl magnesium bromide is added dropwise under stirring to the (tetrahydro-*2H*-pyran-2-yloxy)-alkanones **2** (100 mmol). The mixture is refluxed for 16 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 ketone 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 **3** had the following properties:

2-Methyl-4-phenyl-1-(tetrahydro-2H-pyran-2-yloxy)-but-3-yn-2-ol (**3a**). Yellow oil, yield: 75%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.52; IR (neat, cm^{-1}): 1123 (C-O-C), 1443, 1489 (Ph), 3420 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.58 (s, 3H, Me), 1.63-1.92, 3.99-4.09, 4.67-4.78 (overlapping multiplets, 9H, OTHP), 3.31 (s, 1H, OH), 3.60-3.90 (m, 2H, CH_2), 7.26-7.43 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 19.4 (CH_2), 25.3 (CH_2), 26.2 (CH_3), 30.6 (CH_2), 62.8 (CH_2), 67.6 (C), 76.2 (CH_2), 83.7 (C), 99.9 (C), 105.5 (CH), 122.6-131.4 (Ph). Anal. Calcd. for $C_{16}H_{20}O_3$: C 73.82, H 7.74; found: C 73.76, H 7.78.

3-Methyl-1-phenyl-4-(tetrahydro-2H-pyran-2-yloxy)-pent-1-yn-3-ol (**3b**). Yellow oil, yield: 79%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.51; IR (neat, cm^{-1}): 1123 (C-O-C), 1441, 1491 (Ph), 3412 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.10-1.23, 3.53-3.68, 4.73-4.80 (overlapping multiplets, 9H, OTHP), 1.36 (d, *J*=5.4 Hz, 3H, Me-CH), 1.44 (s, 3H, Me), 2.89 (s, 1H, OH), 3.89-3.97 (m, 2H, CH_2), 7.18-7.32 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 15.4 (CH_3), 19.0 (CH_2), 23.3 (CH_3), 25.7 (CH_2), 31.6 (CH_2), 62.6 (CH_2), 71.9 (C), 80.8 (C), 90.0 (C), 91.1 (CH), 96.5 (CH), 120.6-133.0 (Ph). Anal. Calcd. for $C_{17}H_{22}O_3$: C 74.42, H 8.08; found: C 74.46, H 8.05.

1,3-Diphenyl-1-[1-(tetrahydro-2H-pyran-2-yloxy)-cyclohexyl]-prop-2-yn-1-ol (**3c**). Pale yellow oil, yield: 65%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.63; IR (neat, cm^{-1}): 1125 (C-O-C), 1443, 1489 (Ph), 3395 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.35-1.65, 3.49-3.79, 5.01-5.07 (overlapping multiplets, 9H, OTHP), 1.71-2.10 (overlapping multiplets, 10H, cyclohexyl), 2.91 (s, 1H, OH), 7.12-7.59 (m, 10H, 2Ph). ^{13}C-NMR (150.9 MHz) δ_C 20.8 (CH_2), 23.9 (2xCH_2), 25.0 (CH_2), 25.8 (CH_2), 31.4 (CH_2), 33.1 (2xCH_2), 63.6 (CH_2), 82.1 (C), 84.2 (C), 87.1 (C), 87.8 (C), 99.2 (CH), 123.0-142.4 (2Ph). Anal. Calcd. for $C_{26}H_{30}O_3$: C 79.97, H 7.74; found: C 80.01, H 7.69.

Synthesis and spectral data of *1,2,4-triphenyl-1-(tetrahydro-2H-pyran-2-yloxy)-but-3-yn-2-ol* **3d** were described in our previous paper [63].

*General procedure for synthesis of dimethyl (tetrahydro-2H-pyran-2-yloxy)-alka-1,2-dienephosphonates **5***

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 °C was added dropwise with stirring a solution of the (tetrahydro-2*H*-pyran-2-yloxy)-alkynol **3** (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 12 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 **5** as an oil, which had the following properties:

Dimethyl 3-methyl-1-phenyl-4-(tetrahydro-2H-pyran-2-yloxy)-buta-1,2-dienephosphonate (**5a**). Yellow oil, yield: 72%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.40; IR (neat, cm^{-1}): 1121 (C-O-C), 1263 (P=O), 1445, 1495 (Ph), 1950 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.46-1.84, 3.64-3.75, 4.39-4.44 (overlapping multiplets, 9H, OTHP), 2.02 (d, *J*=7.7 Hz, 3H, Me), 3.77 (d, *J*=12.1 Hz, 6H, 2MeO), 4.19-4.33 (m, 2H, CH_2), 7.22-7.80 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 15.5 (*J*=5.7 Hz, CH_3), 19.3 (CH_2), 24.9 (CH_2), 29.7 (CH_2), 52.6 (*J*=14.4 Hz, 2xCH_3), 61.7 (CH_2), 68.0 (*J*=5.0 Hz, CH_2), 95.5 (*J*=182.6 Hz, C), 97.4 (CH), 104.5 (*J*=8.3 Hz, C), 117.6-129.7 (Ph), 208.8 (*J*=1.8 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 18.6. Anal. Calcd. for $C_{18}H_{25}O_5P$: C 61.36, H 7.15; found: C 61.43, H 7.20.

Dimethyl 3-methyl-1-phenyl-4-(tetrahydro-2H-pyran-2-yloxy)-penta-1,2-dienephosphonate (**5b**). Yellow oil, yield: 77%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.44; IR (neat, cm^{-1}): 1119 (C-O-C), 1260 (P=O), 1445, 1495 (Ph), 1946 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.46 (d, *J*=5.7 Hz, 3H, Me-CH), 1.47-1.58, 3.55-3.71, 4.51-4.62

(overlapping multiplets, 9H, OTHP), 1.85 (d, *J*=6.9 Hz, 3H, Me), 3.76 (d, *J*=12.4 Hz, 6H, 2MeO), 3.89-3.97 (m, 1H, CH), 7.18-7.91 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 12.4 (*J*=4.5 Hz, CH_3), 19.7 (CH_2), 20.3 (CH_3), 25.7 (CH_2), 30.8 (CH_2), 53.4 (*J*=13.0 Hz, 2xCH_3), 63.4 (CH_2), 74.6 (*J*=4.6 Hz, CH), 94.0 (*J*=185.0 Hz, C), 95.8 (CH), 106.7 (*J*=7.7 Hz, C), 118.7-129.4 (Ph), 209.7 (*J*=2.0 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 18.9. Anal. Calcd. for $C_{19}H_{27}O_5P$: C 62.28, H 7.43; found: C 62.34, H 7.47.

Dimethyl 1,3-diphenyl-3-[1-(tetrahydro-2H-pyran-2-yloxy)-cyclohexyl]-propa-1,2-diene-phosphonate (**5c**). Yellow oil, yield: 73%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.42; IR (neat, cm^{-1}): 1125 (C-O-C), 1258 (P=O), 1447, 1493 (Ph), 1925 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.30-2.03, 3.51-3.59, 4.38-4.77 (overlapping multiplets, 19H, OTHP, cyclohexyl), 3.78 (d, *J*=12.0 Hz, 6H, 2MeO), 7.18-7.98 (m, 10H, 2Ph). ^{13}C-NMR (150.9 MHz) δ_C 18.5 (CH_2), 22.5 (2xCH_2), 24.4 (CH_2), 25.0 (CH_2), 30.6 (CH_2), 42.5 (2xCH_2), 51.7 (*J*=14.8 Hz, 2xCH_3), 62.9 (CH_2), 78.7 (*J*=4.9 Hz, C), 95.2 (*J*=182.8 Hz, C), 97.5 (CH), 113.7 (*J*=7.8 Hz, C), 118.0-138.8 (2Ph), 211.5 (*J*=1.7 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 18.5. Anal. Calcd. for $C_{28}H_{35}O_5P$: C 69.69, H 7.31; found: C 69.63, H 7.28.

Synthesis and spectral data of *dimethyl 1,3,4-triphenyl-4-(tetrahydro-2H-pyran-2-yloxy)-buta-1,2-dienephosphonate* **5d** were described in our previous paper [63].

*General procedure for synthesis of diphenyl (tetrahydro-2H-pyran-2-yloxy)-alka-1,2-dien-1-yl phosphine oxides **7***

To a solution of the (tetrahydro-2*H*-pyran-2-yloxy)-alkynol **3** (20 mmol) and triethylamine (2.23 g, 22 mmol) in dry diethyl ether (60 mL) at -70 °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 8 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 product **7** as oil, which had the following properties:

Diphenyl 3-methyl-1-phenyl-4-(tetrahydro-2H-pyran-2-yloxy)-buta-1,2-dien-1-yl phosphine oxide (**7a**). Yellow oil, yield: 79%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.42; IR (neat, cm^{-1}): 1119 (C-O-C), 1178 (P=O), 1437, 1493 (Ph), 1948 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.49-1.83, 3.63-3.77, 4.44-4.59 (overlapping multiplets, 9H, OTHP), 2.08 (d, *J*=7.6 Hz, 3H, Me), 4.18-4.40 (m, 2H, CH_2), 7.20-8.02 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.5 (CH_3), 19.3 (CH_2), 25.3 (CH_2), 30.5 (CH_2), 60.8 (CH_2), 66.5 (*J*=4.9 Hz, CH_2), 98.4 (*J*=185.9 Hz, C), 101.5 (CH), 107.5 (*J*=7.8 Hz, C), 128.4-135.2 (3Ph), 209.7 (*J*=2.3 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 31.3. Anal. Calcd. for $C_{28}H_{29}O_3P$: C 75.66, H 6.58; found: C 75.70, H 6.63.

Synthesis and spectral data of *2-[4-(diphenylphosphinoyl)-1,2,4-triphenyl-buta-2,3-dienyloxy]-tetrahydro-2H-pyran* **7d** were described in our previous paper [63].

*General procedure for synthesis of dimethyl 3-(α-hydroxyalkyl)-alka-1,2-dienephosphonates **8** and diphenyl 3-(α-hydroxyalkyl)-alka-1,2-dienyl phosphine oxides **9***

A solution of the dimethyl (tetrahydro-2*H*-pyran-2-yloxy)-alka-1,2-dienephosphonates **5** or the diphenyl (tetrahydro-2*H*-pyran-2-yloxy)-alka-1,2-dien-1-yl phosphine oxides **7** (5 mmol) and PPTS (0.5 mmol) in ethanol (10 mL) was stirred at room temperature for 6 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 (3:1) as an eluent to give the pure products **8** or **9** as oils, which had the following properties:

Dimethyl 4-hydroxy-3-methyl-1-phenylbuta-1,2-dienephosphonate (**8a**). Pale yellow oil, yield: 80%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.58; IR (neat, cm^{-1}): 1258 (P=O), 1447, 1491 (Ph), 1948 (C=C=C), 3376 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.98 (d, *J*=7.5 Hz, 3H, Me), 2.73 (s, 1H, OH), 3.77 (d, *J*=11.8 Hz, 6H, 2MeO), 5.18-5.26 (m, 2H, CH_2), 7.21-7.79 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 15.4 (*J*=5.0 Hz, CH_3), 51.7 (*J*=14.9 Hz, 2xCH_3), 62.5 (*J*=4.5 Hz, CH_2), 94.9 (*J*=182.5 Hz, C), 104.7 (*J*=7.8 Hz, C), 117.1-129.4 (Ph), 209.4 (*J*=1.8 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 18.5. Anal. Calcd. for $C_{13}H_{17}O_4P$: C 58.21, H 6.39; found: C 58.14, H 6.44.

Dimethyl 4-hydroxy-3-methyl-1-phenylpenta-1,2-dienephosphonate (**8b**). Yellow oil, yield: 83%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.61; IR (neat, cm^{-1}): 1262 (P=O), 1443, 1495 (Ph), 1944 (C=C=C), 3420 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.47 (d, *J*=5.5 Hz, 3H, Me-CH), 1.94 (d, *J*=7.0 Hz, 3H, Me), 2.47 (s, 1H, OH), 3.78 (d, *J*=12.1 Hz, 6H, 2MeO), 4.30-4.39 (m, 1H, CH), 7.18-7.90 (m, 5H, Ph). ^{13}C-NMR (150.9 MHz) δ_C 13.1 (*J*=4.4 Hz, CH_3), 19.0 (CH_3), 51.7 (*J*=14.0 Hz, 2xCH_3), 73.2 (*J*=4.7 Hz, CH), 95.1 (*J*=184.7 Hz, C), 107.4 (*J*=8.0 Hz, C), 120.7-129.1 (Ph), 209.3 (*J*=1.6 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 18.6. Anal. Calcd. for $C_{14}H_{19}O_4P$: C 59.57, H 6.78; found: C 59.61, H 6.83.

Dimethyl 3-(1-hydroxycyclohexyl)-1,3-diphenyl-propa-1,2-dienephosphonate (**8c**). Yellow oil, yield: 85%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.63; IR (neat, cm^{-1}): 1256 (P=O), 1445, 1493 (Ph), 1933 (C=C=C), 3364 (OH). ^{1}H-NMR (600.1 MHz): δ_H 1.27-1.99 (overlapping multiplet, 10H, cyclohexyl), 2.31 (s, 1H, OH), 3.74 (d, *J*=12.1 Hz, 6H, 2MeO), 7.24-7.71 (m, 10H, 2Ph). ^{13}C-NMR (150.9 MHz) δ_C 21.5 (2xCH_2), 24,7 (CH_2), 39.8 (2xCH_2), 51.7 (*J*=14.8 Hz, 2xCH_3), 74.1 (*J*=5.0 Hz, C), 97.1 (*J*=180.5 Hz, C), 113.8 (*J*=7.9 Hz, C), 119.1-140.0 (2Ph), 210.0 (*J*=1.5 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 18.6. Anal. Calcd. for $C_{23}H_{27}O_4P$: C 69.33, H 6.83; found: C 69.37, H 6.86.

Synthesis and spectral data of *dimethyl 4-hydroxy-1,3,4-triphenyl-buta-1,2-dienephosphonate* **8d** were described in our previous paper [63].

4-(Diphenylphosphinoyl)-2-methyl-4-phenyl-buta-2,3-dien-1-ol (**9a**). Yellow oil, yield: 84%. Eluent for TLC: ethyl acetate:hexane = 1:1, R_f 0.62; IR (neat, cm^{-1}): 1180 (P=O), 1439, 1493 (Ph), 1948 (C=C=C), 3381 (OH). ^{1}H-NMR (600.1 MHz): δ_H 2.07 (d, *J*=7.5 Hz, 3H, Me), 2.71 (s, 1H, OH), 4.71-4.94 (m, 2H, CH_2), 7.32-7.89 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.7 (*J*=5.0 Hz, CH_3), 62.7 (*J*=4.6 Hz, CH_2), 97.4 (*J*=184.3 Hz, C), 110.5 (*J*=8.0 Hz, C), 124.0-139.7 (m, 3Ph), 211.0 (*J*=2.0 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 32.8. Anal. Calcd. for $C_{23}H_{21}O_2P$: C 76.65, H 5.87; found: C 76.69, H 6.92.

Synthesis and spectral data of *4-(diphenyl-phosphinoyl)-1,2,4-triphenyl-buta-2,3-dien-1-ol* **9d** were described in our previous paper [63].

RESULTS AND DISCUSSION

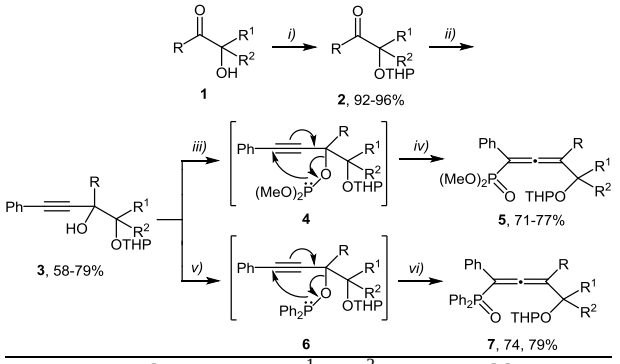
We based our strategy for the synthesis of the phosphorylated 3-(α-hydroxyalkyl)allenes on our experience in preparation of the phosphorylated 1-(α- [54] and β- [55] hydroxyalkyl)allenes, and relied on the well-precedented [2,3]-sigmatropic shift of propargylic phosphites to allene-phosphonates [40–43] and propargylic phosphinites to allenyl phosphine oxides [46–51]. We were aware of the fact that a precedent exists for such an approach to the synthesis of the diethylphosphono-substituted α-allenic alcohols [52, 53], but as far as we know, a general useful method for regioselective synthesis of phosphorylated (phosphonates and phosphine oxides) 3-(α-hydroxyalkyl)allenes with protected or unprotected hygroxy group with protected or unprotected hygroxy group has not been reported yet.

The main target in our research, and namely 1,3-bifunctionalized allenes, was achieved as a range of the phosphorylated 3-(α-hydroxyalkyl)allenes **5**, **7**, **8**, and **9**, was prepared by applying the following four-step procedure: (i) protection of hydroxy group in the α-hydroxy-alkanones **1**; (ii) subsequent reaction of Grignard reagent and the protected ketones **2** to give the (tetrahydro-2*H*-pyran-2-yloxy)-alkynols **3** with protected hydroxy group at 4 position; (iii) interaction with dimethyl chlorophosphite or chlorodiphenyl phosphine in the presence of a base; and finally (iv) [2,3]-sigmatropic rearrangement of the mediated hydroxy-protected propargyl phosphites or phosphinites.

The first step in our investigation was to examine the hydroxy group protection in the α-hydroxy-alkanones **1** with 3,4-dihydro-2*H*-pyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS) [59–62] (Scheme 1). Thus, the formed (tetrahydro-2*H*-pyran-2-yloxy)-alkanones **2** were isolated by column chromatography with excellent yield (92-96%). Reaction of the protected alkanones **2** with the *in situ* generated phenylethynylmagnesium bromide from ethyl magnesium bromide and phenylacetylene to give the (tetrahydro-2*H*-pyran-2-yloxy)-alkynols **3** which are stable and were isolated by column chromatography in 58-79% yield.

Once we had the required alk-1-yn-3,4-diols **3** with protected hydroxy group at 4 position, we were then able to investigate the proposed reactions with the corresponding chloro-containing phosphorus reagents such as dimethyl chloro-phosphite and chlorodiphenyl phosphine in the presence of a base and subsequent [2,3]-sigmatropic rearrangement of the mediated propargyl phosphites **4** or phosphinites **6**.

Let us start with the dimethyl (tetrahydro-2*H*-pyran-2-yloxy)-alka-1,2-dienephosphonates **5** that can be easily prepared *via* an atom economical 2,3-sigmatropic rearrangement of the protected propargyl phosphites **4**, intermediate formed by reaction of the alkynols **3** with dimethyl chlorophosphite, *in situ* prepared from phosphorus trichloride in the presence of triethylamine and 2 *equiv* of methanol and 2 *equiv* of pyridine, according to Scheme 1.



Entry	Product	R	R^1	R^2	Yield, %			
					2	**3**	**5**	**7**
1	**a**	Me	H	H	95	75	72	79
2	**b**	Me	Me	H	96	79	77	-
3	**c**	Ph	$-(CH_2)_5-$		93	65	73	-
4	**d** [63]	Ph	Ph	H	92	58	71	74

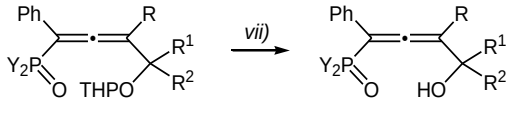
Reagents and Conditions: *i)* (α-hydroxyalkyl)ketone (1 eq), DHP (1.5 eq), PPTS (0.1 eq), CH_2Cl_2, rt, 10h, column chromatography; *ii)* dropwise addition of EtMgBr (1 eq) to phenylacetylene (1 eq), THF, reflux, 2h, dropwise addition of prepared ethynylmagnesium bromide to **2** (2 eq), THF, reflux, 16h, column chromatography; *iii)* PCl_3 (1 eq), Et_3N (1.1 eq), Et_2O, -70 °C, 30 min stirring, pyridine (2.2 eq), MeOH (2 eq), Et_2O, -70 °C; *iv)* [2,3-σ]-rearrangement, -70 °C, 1h, rt, 12h, column chromatography *v)* Ph_2PCl (1 eq), Et_3N (1.1 eq), Et_2O, -70 °C; *vi)* [2,3-σ]-rearrangement, -70 °C, 1h, rt, 8h, column chromatography.

Scheme 1. Synthesis of the 3-(α-hydroxyalkyl)-allenephosphonates **5** and 3-(α-hydroxyalkyl)-allenyl phosphine oxides **7** with protected hydroxy-group.

Next, the reaction of the (tetrahydro-2*H*-pyran-2-yloxy)-alkynols **3** with chlorodiphenyl phosphine in the presence of triethylamine at -70 °C gave the expected diphenyl (tetrahydro-2*H*-pyran-2-yloxy)-alka-1,2-dien-1-yl phosphine oxides **7** in very good yield (74 and 79%) as a result of [2,3]-sigmatropic rearrangement of the protected propargyl phosphinites **6**, according to the reaction sequence outlined in Scheme 1.

A new family of the phosphorylated 3-(α-hydroxyalkyl)allenes with protected hydroxy group **5** and **7** were synthesized *via* an atom economical and regioselective [2,3]-sigmatropic rearrangement of the intermediate formed propargyl phosphites **4** or phosphinites **6** in the reaction of the alk-1-yn-3,4-diols with protected hydroxy group at 4 position **5** with dimethylchloro phosphite or chlorodiphenyl phosphine in the presence of triethylamine.

Allenic compounds **5** and **7** were stable enough to be handled at ambient temperature. The hydroxy group was deprotected by stirring the ethanol solution of the protected 3-(α-hydroxyalkyl-allenephosphonates **5** and 3-(α-hydroxyalkyl-allenyl phosphine oxide **7** in the presence of 0.1 *equiv* PPTS at room temperature for 6 hours, according to Scheme 2.



Entry	Product	Y	R	R^1	R^2	Yield, %
1	**8a**	MeO	Me	H	H	80
2	**8b**	MeO	Me	Me	H	83
3	**8c**	MeO	Ph	$-(CH_2)_5-$		85
4	**8d** [63]	MeO	Ph	Ph	H	79
5	**9a**	Ph	Me	H	H	84
6	**9d** [63]	Ph	Ph	Ph	H	81

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

Scheme 2. Synthesis of the 3-(α-hydroxyalkyl)-allenephosphonates **8** and 3-(α-hydroxyalkyl)-allenyl phosphine oxides **9**

After a conventional work-up, all allenic products **5**, **7**, **8**, and **9** 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 phosphorylated 3-(α-hydroxyalkyl)allenes with protected (**5** and **7**) and unprotected hydroxy group (**8** and **9**) were synthesized by a convenient, efficient, atom economical and regioselective method.

CONCLUSION

In conclusion, a convenient and efficient regioselective synthesis of a new family of 1,3-bifunctionalized allenes has been explored. Phosphorylated 3-(α-hydroxyalkyl)allenes prepared were derived from [2,3]-sigmatropic rearrangement of the intermediate propargyl phosphites or phosphinites formed in the reaction of protected 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 phosphorylated 3-(α-hydroxyalkyl)allenes 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 bifunctionalized 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.

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БИФУНКЦИОНАЛИЗИРАНИ АЛЕНИ. ЧАСТ XX. УДОБЕН И ЕФЕКТИВЕН РЕГИОСЕЛЕКТИВЕН СИНТЕЗ НА ФОСФОРИЛИРАНИ 3-(α-ХИДРОКСИАЛКИЛ)АЛЕНИ

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(Резюме)

Описан е удобен и ефикасен региоселективен синтез на фосфорилирани 3-(α-хидроксиалкил)алени чрез атом-икономична [2,3]-сигматропна прегрупировка на междинно образуваните пропаргилови фосфити или фосфонити, които лесно се получават чрез реакция на (тетрахидро-2*H*-пиран-2-илокси)-алкиноли с диметил хлорофосфит или хлородифенил фосфин съответно в присъствие на база.