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BIFUNCTIONALIZED ALLENES. PART XVIII. SYNTHESIS OF 2,5-DIHYDRO-1,2-OXAPHOSPHOLES AND 2-PHOSPHORYL-2,5-DIHYDROFURANS BY ELECTROPHILIC CYCLIZATION AND COINAGE METAL-CATALYZED CYCLOISOMERIZATION OF PHOSPHORYLATED 3-(□-HYDROXY) ALLENES

Valerij Ch. Christov*, Hasan H. Hasanov and Ivaylo K. Ivanov

Department of Organic Chemistry & Technology, Faculty of Natural Sciences, Konstantin Preslavsky University of Shumen, 115, Universitetska str.,
BG-9712 Shumen, Bulgaria

ABSTRACT: *A convenient and efficient regioselective synthesis of phosphorylated 3-(□-hydroxy)allenes by an atom economical [2,3]-sigmatropic rearrangement of the mediated propargyl phosphite or phosphinite which can be readily prepared via reaction of protected 1,2,4-triphenyl-1-(tetrahydro-2H-pyran-2-yloxy)-but-3-yn-2-ol with dimethyl chlorophosphite or chlorodiphenyl phosphine respectively is described. This paper discusses a reaction of phosphorylated 3-(□-hydroxy)allenes with protected or unprotected hydroxy group involving 5-endo-trig cyclization. Reaction of dimethyl (4-hydroxy-1,3,4-triphenyl-buta-1,2-dienyl)phosphonate with electrophiles that produces 2-oxo-2,5-dihydro-1,2-oxaphospholes due to the participation of the phosphonate neighboring group in the cyclization is described. On the other hand, but-(3E)-en-1-yl phosphine oxides were prepared by chemo-, regio-, and stereoselective electrophilic addition to the C^2-C^3-double bond in the allene moiety and subsequent concurrent attack of the external (chloride anion) nucleophile. Phosphorylated 3-(□-hydroxy)allenes were smoothly converted into the corresponding 2-phosphoryl-2,5-dihydrofurans by using 5 mol % of coinage metal salt as catalyst in 5-endo-trig cycloisomerization reaction.*

KEYWORDS: Phosphorylated 3-(□-hydroxy) Allenes, Electrophilic Cyclization, 2,5-Dihydro-1,2-Oxaphospholes, Coinage Metal-Catalyzed Cycloisomerization, 2,5-Dihydrofurans.

INTRODUCTION

Functionalized allenes have attracted a growing attention because of their versatility as key building blocks for organic synthesis. The synthetic potential of functionalized allenes has been explored extensively in recent years, and this has led to the development of novel methods for the construction of a variety of functionalized heterocyclic and carbocyclic systems [1].

A plethora of methods exists for the construction of hydroxyallenes, including prototropic rearrangement of propargylic alcohols [2], metal-catalyzed nucleophilic addition of propargylic derivatives to aldehydes [3], Cu(I)-catalyzed reaction of propargylic chlorides with Grignard reagents [4], metal-catalyzed reaction of propargylic oxiranes with organometallic compounds [5] and ketones [6], and by other methods [7].

There are methods [8] for the synthesis of phosphorus-containing allenes (phosphonates [9], and phosphine oxides [10]) including reactions of □-alkynols with chloride-containing

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derivatives of phosphorus acids followed by [2,3]-sigmatropic rearrangement. Several diethylphosphono-substituted □-allenic alcohols were prepared by Brel [11] directly from alcohols by Horner-Mark rearrangement of unstable propargylic phosphites.

Transition metal-catalyzed cyclization of functionalized allenes bearing a nucleophilic center has attracted considearble attention in recent years [12]. Particularly, the cyclization reactions of allenols catalyzed by Ag(I) [13], Hg(II) [14], Pd(0) [15], Pd(II) [16], or Ru(III) [17] have become quite useful methodologies for the synthesis of five-, or six-membered oxygen-containing heterocycles. Krause's group has reported a highly efficient and stereoselective synthesis of 2,5-dihydrofurans by Au(I)- and Au(III)-catalyzed [18] cycloisomerization of α-hydroxyallenes [19]. Moreover, the method is not restricted to the cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans [18a, 19b], rather, it was recently extended by Krause's group to the corresponding endo-cyclization of β-hydroxyallenes [20] to the corresponding six-membered *O*-heterocycles. The method of choice, however, is the use of transition metal catalysts since this combines high reactivities and excellent yields with a tolerance to many functional groups.

Acyclic analogs of nucleotides containing an allenic skeleton were prepared by Brel and coworkers [21] directly from alcohols by Horner-Mark [2,3]-sigmatropic rearrangement of unstable propargylic phosphites. Intramolecular cyclization of the alkoxides tethered to the allenyl moiety in the presence of $AgNO_3$ yielded 3,6-dihydro-2*H*-pyran-4-yl- and 4,5-dihydro-3-furanyl-phosphonates [11c, 21].

On the other hand, the literature data on the reactions of phosphorylated allenes with electrophilic reagents reveal that the reactions proceed with cyclization of the allenic system bearing the phosphoryl group (O=P-C=C=C) to give heterocyclic compounds in most cases and the outcome depends on the structure of the starting allenic compound as well as the type of electrophile used [22].

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 □-hydroxyalkyl group in the third position to the allenic system of double bonds. The above mentioned groups attract increasing attention as useful functionalities in organic synthesis. Of particular interest are the applications of these groups as temporary transformers of chemical reactivity of the allenic system in the synthesis of eventually heterocyclic compounds. In a continuation to our previous reports on the synthesis [23] and cyclization reactions of phosphorylated α-hydroxy- and □-hydroxy-allenes [24], we have found a convenient and efficient method for regioselective synthesis of phosphorylated 3-(□-hydroxy)allenes by an atom economical [2,3]-sigmatropic rearrangement of the mediated 1,3-diphenyl-1-[phenyl-(tetrahydro-2*H*-pyran-2-yloxy)-methyl]-prop-2-ynyl phosphite or phosphinite, which to be used as starting materials in the electrophilic cyclization and coinage metal-catalyzed cycloisomerization reactions to 2,5-dihydro-1,2-oxaphospholes and 2-phosphoryl-2,5-dihydrofurans respectively.

EXPERIMENTAL Section

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

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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 F25460 (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 [26] for Synthesis of the Diphenyl-2-(tetrahydro-2H-pyran-2-yloxy)- Ethanone 2

A solution of the benzoin **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 6h at room temperature. Then the reaction was quenched with saturated $NaHCO_3$ end 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 (1:1) as an eluent. The pure product **2** had the following properties:

Diphenyl-2-(tetrahydro-2H-pyran-2-yloxy)-ethanone (**2**). This compound was obtained as colourless oil, yield: 92%. Eluent for TLC: ethyl acetate : hexane = 1:1, R_f 0.56; IR (neat, cm^{-1}): 1121 (C-O-C), 1449, 1495 (Ph), 1694 (C=O). ^{1}H-NMR (250.1 MHz): δ_H 1.32-1.43, 1.48-153, 3.55-3.77, 5.20-5.24 (overlapping multiplets, 9H, OTHP), 5.77 (m, 1H, CH), 7.18-8.09 (m, 10H, 2Ph). ^{13}C-NMR (62.9 MHz) δ_C 20.2 (CH_2), 24.7 (CH_2), 30.6 (CH_2), 64.4 (CH_2), 77.2 (CH), 98.5 (CH), 124.9-136.7 (2Ph), 195.4 (C). Anal. Calcd for $C_{19}H_{20}O_3$ requires: C 77.00, H 6.80. Found: C 76.94, H 6.85.

Procedure for Synthesis of the 1,2,4-Triphenyl-1-(tetrahydro-2H-pyran-2-yloxy)-but-3-yn-2-ol 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 2h. The solution of the prepared ethynyl magnesium bromide is added dropwise under stirring to the diphenyl-2-(tetrahydro-2*H*-pyran-2-yloxy)-ethanone **2** (100 mmol). The mixture is refluxed for 24 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 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 (1:3). The pure product **5** had the following properties:

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1,2,4-Triphenyl-1-(tetrahydro-2H-pyran-2-yloxy)-but-3-yn-2-ol (**3**). This compound was obtained as light orange oil, yield: 58%. Eluent for TLC: ethyl acetate : hexane = 1:3, R_f 0.53; IR (neat, cm^{-1}): 1119 (C-O-C), 1449, 1491 (Ph), 3401 (OH). $C_{27}H_{26}O_3$ (398.49). Calcd: C 81.38, H 6.58; found: C 81.45, H 6.62. ^{1}H-NMR (250.1 MHz): δ_H 1.15-1.24, 1.29-1.36, 3.50-3.61, 4.93-4.96 (overlapping multiplets, 9H, OTHP), 2.52 (s, 1H, OH), 4.41 (m, 1H, CH), 6.68-7.68 (m, 15H, 3Ph). ^{13}C-NMR (62.9 MHz) δ_C 19.7 (CH_2), 25.7 (CH_2), 31.4 (CH_2), 63.3 (CH_2), 84.67 (C), 85.9 (C), 90.3 (C), 90.9 (CH), 101.1 (CH), 124.0-139.97 (3Ph). Anal. Calcd for $C_{27}H_{26}O_3$ requires: C 81.38, H 6.58. Found: C 81.45, H 6.62.

Procedure for Synthesis of the Dimethyl [1,3,4-Triphenyl-4-(tetrahydro-2H-pyran-2-yloxy)-buta-1,2-dienyl]phosphonate 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 -70ºC was added dropwise with stirring a solution of the 1,2,4-triphenyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-but-3-yn-2-ol **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 6 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 (3:1) as an eluent to give the pure product **7** as an oil, which had the following properties:

Dimethyl [1,3,4-triphenyl-4-(tetrahydro-2H-pyran-2-yloxy)-buta-1,2-dienyl]phosphonate (**5**). This compound was obtained as orange oil, yield: 71%. Eluent for TLC: ethyl acetate : hexane = 3:1, R_f 0.42; IR (neat, cm^{-1}): 1117 (C-O-C), 1260 (P=O), 1447, 1495 (Ph), 1933 (C=C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.28-1.76, 3.43-3.71, 4.55-4.69 (overlapping multiplets, 9H, OTHP), 3.69 (d, *J* = 11.2 Hz, 3H, MeO), 5.94-5.97 (m, 1H, CH), 7.16-7.73 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 19.1 (CH_2), 25.6 (CH_2), 31.0 (CH_2), 53.2 (*J* = 5.8 Hz, CH_3), 62.7 (CH_2), 74.8 (*J* = 5.5 Hz, CH), 96.9 (CH), 100.9 (*J* = 187.7 Hz, C), 113.3 (*J* = 15.6 Hz, C), 127.1-139.6 (3Ph), 213.2 (*J* = 2.9 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 17.9. Anal. Calcd for $C_{29}H_{31}O_5P$ requires: C 71.01, H 6.37. Found: C 70.97, H 6.44.

Procedure for the Synthesis of the 2-(4-Diphenylphosphinoyl-1,2,4-triphenyl-buta-2,3-dienyloxy)-tetrahydro-2H-pyran 7

To a solution of the 1,2,4-triphenyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-but-3-yn-2-ol **3** (20 mmol) and triethylamine (2.23 g, 22 mmol) in dry diethyl ether (60 mL) at -70ºC, 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 9 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 (3:1) to give the pure product **9** as an oil, which had the following properties:

2-[4-(Diphenylphosphinoyl)-1,2,4-triphenyl-buta-2,3-dienyloxy]-tetrahydro-2H-pyran (**7**). This compound was obtained as yellow oil, yield: 74%. Eluent for TLC: ethyl acetate : hexane = 3:1, R_f 0.45; IR (neat, cm^{-1}): 1119 (C-O-C), 1157 (P=O), 1439, 1493 (Ph), 1937 (C=C=C).

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^{1}H-NMR (600.1 MHz): δ_H 1.15-1.34, 1.40-1.78, 3.58-3.65, 4.40-4.70 (overlapping multiplets, 9H, OTHP), 5.49-5.52 (m, 1H, CH), 7.21-8.03 (m, 30H, 5Ph). ^{13}C-NMR (150.9 MHz) δ_C 20.9 (CH_2), 25.6 (CH_2), 30.8 (CH_2), 60.9 (CH_2), 67.0 (J = 1.8 Hz, CH), 95.8 (J = 122.5 Hz, C), 98.9 (CH), 115.6 (J = 14.5 Hz, C), 127.1-135.6 (5Ph), 210.7 (J = 2.5 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 34.6. Anal. Calcd for $C_{39}H_{35}O_3P$ requires: C 80.39, H 6.05. Found: C 80.47, H 5.99.

Procedure for the Synthesis of the Dimethyl (4-Hydroxy-1,3,4-triphenyl-buta-1,2-dienyl)phosphonate 8 and the 4-Diphenylphosphinoyl-1,2,4-triphenyl-buta-2,3-dien-1-ol 9

A solution of the dimethyl [1,3,4-triphenyl-4-(tetrahydro-2*H*-pyran-2-yloxy)-buta-1,2-dienyl]phosphonate **5** or the 2-(4-diphenylphosphinoyl-1,2,4-triphenyl-buta-2,3-dienyloxy)-tetrahydro-2*H*-pyran **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-1,3,4-triphenyl-buta-1,2-dienyl)phosphonate **(8)**. This compound was obtained as yellow oil, yield: 79%. Eluent for TLC: ethyl acetate : hexane = 3:1, R_f 0.61; IR (neat, cm^{-1}): 1258 (P=O), 1447, 1495 (Ph), 1933 (C=C=C), 3450 (OH). (406.41). Calcd: ^{1}H-NMR (600.1 MHz): δ_H 2.63 (s, 1H, OH), 3.68 (d, J = 11.3 Hz, 3H, MeO), 5.91-5.94 (m, 1H, CH), 7.09-7.73 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 53.2 (J = 5.7 Hz, CH_3), 74.5 (J = 5.4 Hz, CH), 100.8 (J = 184.5 Hz, C), 113.2 (J = 15.8 Hz, C), 126.0-140.3 (m, 3Ph), 208.1 (J = 3.0 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 17.9. Anal. Calcd for $C_{24}H_{23}O_4P$ requires: C 70.93, H 5.70. Found: C 70.99, H 5.65.

4-(Diphenylphosphinoyl)-1,2,4-triphenyl-buta-2,3-dien-1-ol **(9)**. This compound was obtained as light yellow oil, yield: 81%. Eluent for TLC: ethyl acetate : hexane = 3:1, R_f 0.60; IR (neat, cm^{-1}): 1161 (P=O), 1441, 1495 (Ph), 1921 (C=C=C), 3402 (OH). ^{1}H-NMR (600.1 MHz): δ_H 2.04 (s, 1H, OH), 4.52-4.56 (m, 1H, CH), 6.81-7.89 (m, 30H, 5Ph). ^{13}C-NMR (150.9 MHz) δ_C 79.4 (J = 5.9 Hz, CH), 98.7 (J = 132.6 Hz, C), 112.5 (J = 13.5 Hz, C), 126.7-138.9 (5Ph), 205.0 (J = 2.4 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 31.8. Calcd for $C_{34}H_{27}O_2P$ requires: C 81.91, H 5.46. Found: C 81.84, H 5.51.

General Procedure for the Reactions of the Phosphorylated 3-(α-Hydroxy)allenes 5, 7-9 with Electrophilic Reagents.

To a solution of the phosphorylated 3-(α-hydroxy)allene with protected (**5** or **7**) or unprotected (**8** or **9**) hydroxy group (3.0 mmol) in dry dichloromethane (10 mL) at -20 °C was added dropwise with stirring a solution of electrophilic reagent (bromine, benzenesulfenyl chloride or benzeneselenenyl chloride) (3.6 mmol) in the same solvent (10 mL). The reaction mixture was stirred at the same temperature for 2 hours and 3 hours at room temperature. After evaporation of the solvent, the residue was chromatographed on a silica gel column (ethyl acetate and hexane 1:1) as an eluent to give the pure products **10** or **11** as oils, which had the following properties:

2-[(4-Bromo-2-methoxy-2-oxo-3,5-diphenyl-2,5-dihydro-1,2-oxaphosphol-5-yl)(phenyl)methoxy]-tetrahydro-2H-pyran (**10a**). This compound was obtained as orange oil,

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yield: 81%. Eluent for TLC: ethyl acetate : hexane = 1:1, R_f 0.49; IR (neat, cm^{-1}): 1022 (C-O-P), 1121 (C-O-C), 1259 (P=O), 1436, 1495 (Ph), 1582 (C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.10-1.28, 1.46-1.90, 3.19-3.62, 4.70-4.73 (overlapping multiplets, 9H, OTHP), 3.73 (d, *J* = 11.2 Hz, 3H, MeO), 5.10-4.13 (m, 1H, CH), 7.24-8.02 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 14.9 (CH_2), 24.1 (CH_2), 31.6 (CH_2), 52.1 (*J* = 15.4 Hz, CH_3), 63.2 (CH_2), 83.5 (*J* = 7.9 Hz, CH), 96.3 (*J* = 10.0 Hz, C), 99.9 (CH), 126.0-136.6 (3Ph), 133.5 (*J* = 152.9 Hz, C), 138.3 (*J* = 48.7 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 31.8. Anal. Calcd for $C_{28}H_{28}BrO_5P$ requires: C 60.55, H 5.08. Found: C 60.62, H 5.04.

(2-Methoxy-2-oxo-3,5-diphenyl-4-phenylselenenyl-2,5-dihydro-1,2-oxaphosphol-5-yl)(phenyl)methanol (**10b**). This compound was obtained as light yellow oil, yield: 73%. Eluent for TLC: ethyl acetate : hexane = 1:1, R_f 0.52; IR (neat, cm^{-1}): 1018 (C-O-P), 1263 (P=O), 1444, 1493 (Ph), 1580 (C=C), 3422 (OH). ^{1}H-NMR (600.1 MHz): δ_H 3.32 (s, 1H, OH), 3.69 (d, *J* = 11.9 Hz, 3H, MeO), 5.29-5.33 (m, 1H, CH), 6.89-8.01 (m, 20H, 4Ph). ^{13}C-NMR (150.9 MHz) δ_C 52.0 (*J* = 14.8 Hz, CH_3), 75.8 (*J* = 7.2 Hz, CH), 101.4 (*J* = 9.6 Hz, C), 127.4-147.4 (4Ph), 134.8 (*J* = 98.5 Hz, C), 174.7 (*J* = 15.1 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 34.6. Anal. Calcd for $C_{29}H_{25}O_4PSe$ requires: C 63.63, H 4.60. Found: C 63.67, H 4.53.

2-*(2-Chloro-4-diphenylphosphinoyl-1,2,4-triphenyl-3-phenylselenenyl-but-(3E)-enyloxy)-tetrahydro-2H-pyran* (**11a**). This compound was obtained as dark orange oil, yield: 70%. Eluent for TLC: ethyl acetate : hexane = 1:1, R_f 0.54; IR (neat, cm^{-1}): 1120 (C-O-C), 1156 (P=O), 1440, 1493 (Ph), 1617 (C=C). ^{1}H-NMR (600.1 MHz): δ_H 1.16-1.22, 1.32-1.61, 3.61-3.66, 4.54-4.58 (overlapping multiplets, 9H, OTHP), 5.00-5.04 (m, 1H, CH), 6.94-8.10 (m, 30H, 6Ph). ^{13}C-NMR (150.9 MHz) δ_C 19.6 (CH_2), 25.4 (CH_2), 30.9 (CH_2), 65.4(CH_2), 94.8 (*J* = 5.0 Hz, CH), 96.6 (CH), 98.6 (*J* = 8.9 Hz, C), 126.1-138.9 (6Ph), 132.0 (*J* = 92.8 Hz, C), 152.5 (*J* = 15.2 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 36.3. Anal. Calcd for $C_{45}H_{40}ClO_3PSe$ requires: C 69.81, H 5.21. Found: C 69.77, H 5.15.

2-Chloro-4-(diphenylphosphinoyl)-1,2,4-triphenyl-3-phenylsulfenyl-but-(3E)-en-1-ol (**11b**). This compound was obtained as orange oil, yield: 64%. Eluent for TLC: ethyl acetate : hexane = 1:1, R_f 0.47; IR (neat, cm^{-1}): 1167 (P=O), 1441, 1493 (Ph), 1615 (C=C), 3410 (OH). ^{1}H-NMR (600.1 MHz): 0.97 (s, 1H, OH), 5.64 (m, 1H, CH), 7.07-8.21 (m, 30H, 6Ph). ^{13}C-NMR (150.9 MHz) δ_C 80.5 (*J* = 14.8 Hz, CH), 88.3 (*J* = 8.3 Hz, C), 126.7-135.8 (6Ph), 136.9 (*J* = 100.7 Hz, C), 160.5 (*J* = 14.6 Hz). ^{31}P-NMR (242.9 MHz): δ_P 38.5. Anal. Calcd for $C_{40}H_{32}ClO_2PS$ requires: C 74.70, H 5.01. Found: C 74.63, H 4.96.

General Procedure for Coinage Metal-catalyzed Cycloisomerization of the Dimethyl (4-Hydroxy-1,3,4-triphenyl-buta-1,2-dienyl)phosphonate 8 and the 4-Diphenylphosphinoyl-1,2,4-triphenyl-buta-2,3-dien-1-ol 9

Coinage metal salt catalyst (0.15 mmol) was added to a solution of the dimethyl (4-hydroxy-1,3,4-triphenyl-buta-1,2-dienyl)phosphonate **8** and the 4-diphenylphosphinoyl-1,2,4-triphenyl-buta-2,3-dien-1-ol **9** (3.0 mmol) in dry dichloromethane (10 mL). The mixture was stirred at room temperature and in the dark for the hours indicated in the **Table 1**. Saturated sodium chloride solution was added to precipitate the silver ions. The product was extracted by chloroform. The organic layer was dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a column (silica gel, Kieselgel Merck 60 F_{254}) with a mixture of ethyl acetate and hexane (1:1) as an eluent to give the pure products **12** as oils, which had the following properties:

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Dimethyl (2,4,5-triphenyl-2,5-dihydrofuran-2-yl)phosphonate (**12a**). This compound was obtained as orange oil, yield: 25-75%. Eluent for TLC: ethyl acetate : hexane = 1:1, R_f 0.53; IR (neat, cm^{-1}): 1121 (C-O-C), 1244 (P=O), 1447, 1495 (Ph), 1620 (C=C). ^{1}H-NMR (600.1 MHz): δ_H 3.69 (d, *J* =11.4 Hz, 6H, 2MeO), 5.30 (s, 1H, CH), 5.58 (d, *J* =4.1 Hz, 1H, HC=), 7.21-7.76 (m, 15H, 3Ph). ^{13}C-NMR (150.9 MHz) δ_C 53.1 (*J* = 10.4 Hz, CH_3), 78.2 (*J* = 5.1 Hz, CH), 87.5 (*J* = 126.8 Hz, C), 126.1 (*J* = 8.0 Hz, C), 126.9-144.3 (3Ph), 145.9 (*J* = 8.0 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 18.2. Anal. Calcd for $C_{24}H_{23}O_4P$ requires: C 70.93, H 5.70. Found: C 70.99, H 5.66.

2-(Diphenylphosphinoyl)-2,4,5-triphenyl-2,5-dihydrofuran (**12b**). This compound was obtained as yellow oil, yield: 20-83%. Eluent for TLC: ethyl acetate : hexane = 1:1, R_f 0.57; IR (neat, cm^{-1}): 1118 (C-O-C), 1177 (P=O), 1440, 1493 (Ph), 1622 (C=C). ^{1}H-NMR (600.1 MHz): δ_H 5.87 (s, 1H, CH), 6.52 (d, *J* =5.3 Hz, 1H, HC=), 7.27-7.89 (m, 25H, 5Ph). ^{13}C-NMR (150.9 MHz) δ_C 87.4 (*J* = 125.8 Hz, C), 90.9 (*J* = 7.7 Hz, CH), 128.0 (*J* = 7.9 Hz, C), 127.4-142.6 (5Ph), 147.2 (*J* = 8.1 Hz, C). ^{31}P-NMR (242.9 MHz): δ_P 21.6. Anal. Calcd for $C_{34}H_{27}O_2P$ requires: C 81.91, H 5.46. Found: C 81.85, H 5.53.

RESULTS AND DISCUSSION

Synthesis of Phosphorylated 3-(α-Hydroxy)allenes

Our strategy for the synthesis of the phosphorylated 3-(α-hydroxy)allenes, using our experience on the preparation of the phosphorylated α-hydroxy- [23] and β-hydroxy-allenes [24c], relies on the well-precedented [2,3]-sigmatropic shift of propargylic phosphites to allenephosphonates [9] and propargylic phosphinites to allenyl phosphine oxides [10]. In order to assess this approach towards the target 1,3-bifunctionalized allenes, a range of the phosphorylated 3-(α-hydroxy)allenes **5**, **7-9**, was prepared by the following four-step procedure [25] including i) protection of the hydroxy group in the benzoin **1**; ii) subsequent reaction with Grignard reagent and phenylacetylene to give the 1,2,4-triphenyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-but-3-yn-2-ol **3** with protected hydroxy group at position 1; iii) interaction with chloride of phosphorus acid in the presence of a base; and finally iv) [2,3]-sigmatropic rearrangement of the mediated protected propargyl phosphite or phosphinite.

As a starting point for our investigation, we first examined the protection of hydroxy group in the benzoin **1** with DHP in the presence of PPTS [26] (**Scheme 1**). Thus, the protected benzoin **2** was isolated by column chromatography with excellent yield (92%). Reaction of the protected benzoin **2** with *in situ* the generated ethynylmagnesium bromide from ethyl magnesium bromide and phenylacetylene to give the 1,2,4-triphenyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-but-3-yn-2-ol **3**, which is stable and was isolated by column chromatography in 58% yield. With the required 1,2,4-triphenyl-but-3-yn-1,2-diol with protected hydroxy group at 1 position **3** in hand, we were then 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 1,3-diphenyl-1-[phenyl-(tetrahydro-2*H*-pyran-2-yloxy)-methyl]-prop-2-ynyl phosphite **4** or phosphinite **6**. In the first instance, the dimethyl [1,3,4-triphenyl-4-(tetrahydro-2*H*-pyran-2-yloxy)-buta-1,2-dienyl]phosphonate **5** can be readily prepared *via* an atom economical 2,3-sigmatropic rearrangement of the protected propargyl phosphite **4**, intermediate formed by reaction of the 1,2,4-triphenyl-1-(tetrahydro-2*H*-pyran-2-

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yloxy)-but-3-yn-2-ol **3** with dimethyl chlorophosphite, prepared *in situ* from phosphorus trichloride in the presence of triethylamine and 2 *equiv* of methanol and 2 *equiv* of pyridine, according to **Scheme 1**.

Next, the reaction of the 1,2,4-triphenyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-but-3-yn-2-ol **3** with chlorodiphenyl phosphine in the presence of triethylamine at -70ºC gave the expected 2-[4-(diphenylphosphinoyl)-1,2,4-triphenyl-buta-2,3-dienyloxy]-tetrahydro-2*H*-pyran **7** in very good yield (74%) as a result of [2,3]-sigmatropic rearrangement of the protected propargyl phosphinite **6** for 9 hours at room temperature, according to the reaction sequence outlined in **Scheme 1**.

A new family of phosphorylated 3-(□-hydroxy)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 phosphite **4** or phosphinite **6** in the reaction of the protected 1,2,4-triphenyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-but-3-yn-2-ol **3** with dimethylchloro phosphite or chlorodiphenyl phosphine in the presence of triethylamine. 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-(□-hydroxy)-allenephosphonate **5** and 3-(□-hydroxy)-allenyl phosphine oxide **7** in the presence of 0.1 *equiv* PPTS at room temperature for 6 hours, according to **Scheme 2**.

After a conventional work-up, all allenic products **5**, **7-9** were isolated as stable yellow or orange oils by column chromatography and identified by ^{1}H, ^{13}C, and ^{31}P NMR and IR spectra as well as by elemental analysis.

Phosphorylated 3-(□-hydroxy)allenes **5, 7-9** isolated in preparative amounts allowed us to study its chemical behavior in the reactions with electrophilic reagents and the coinage metal-catalyzed cycloisomerization. The present paper is a part of our long-term objective to investigate both the advantages and the limitations of the electrophilic cyclization and cycloisomerization reactions of the phosphorylated 3-(□-hydroxy)allenes **5**, **7**–**9**.

Scheme 1. Synthesis of the phosphorylated 3-(□-hydroxy)allenes with protected hydroxyl group **5** and **7** by 2,3-sigmatropic rearrangement of the propargyl phosphite **4** and phosphinite **6**.

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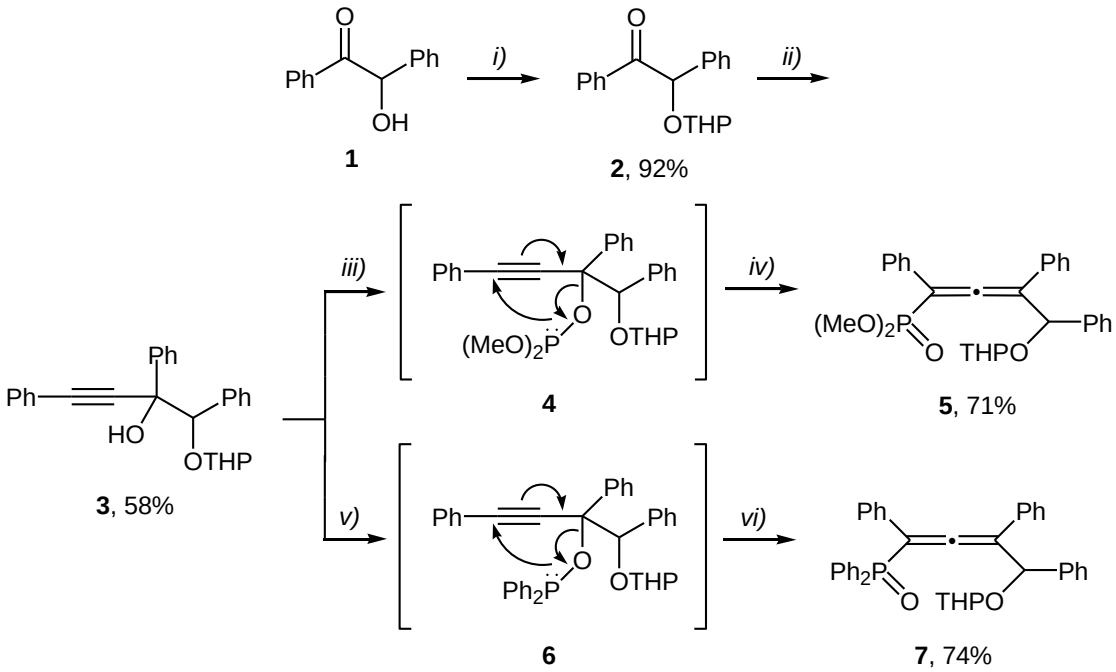
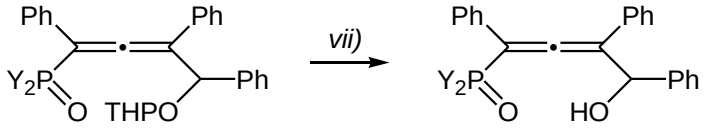


Reagents and Conditions: *i)* Benzoin (1 eq), DHP (1.5 eq), PPTS (0.1 eq), CH_2Cl_2, rt, 6h, column chromatography; *ii)* dropwise addition of EtMgBr (1 eq) to phenylacetylene (1 eq), THF, reflux, 2h, dropwise addition of prepared ethynylmagnesium bromide to **2** (2 eq), THF, reflux, 24h, column chromatography; *iii)* 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; *iv)* [2,3-□]-rearrangement, -70 ^oC, 1h, rt, 6h, column chromatography *v)* Ph_2PCl (1 eq), Et_3N (1.1 eq), Et_2O, -70 ^oC; *vi)* [2,3-□]-rearrangement, -70 ^oC, 1h, rt, 9h, column chromatography.

Scheme 2. Synthesis of the phosphorylated 3-(□-hydroxy)allenes **8** and **9**.



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

Electrophilic Cyclization of Phosphorylated 3-(□-hydroxy)allenes

It is necessary to draw attention to the fact that conceptually two distinct modes of cyclization of the phosphorylated 3-(□-hydroxy)allenes are possible. They depend on the electrophilic atom that forms a new bond with the central carbon of the allenic system, which seems likely [11c, 22]. It is evident that these pathways are closely connected with the intramolecular neighboring group participation of the phosphoryl and/or the hydroxymethyl groups as internal nucleophile(s) in the final step of the cyclization. Besides the 5-*endo-trig* cyclization [27] to

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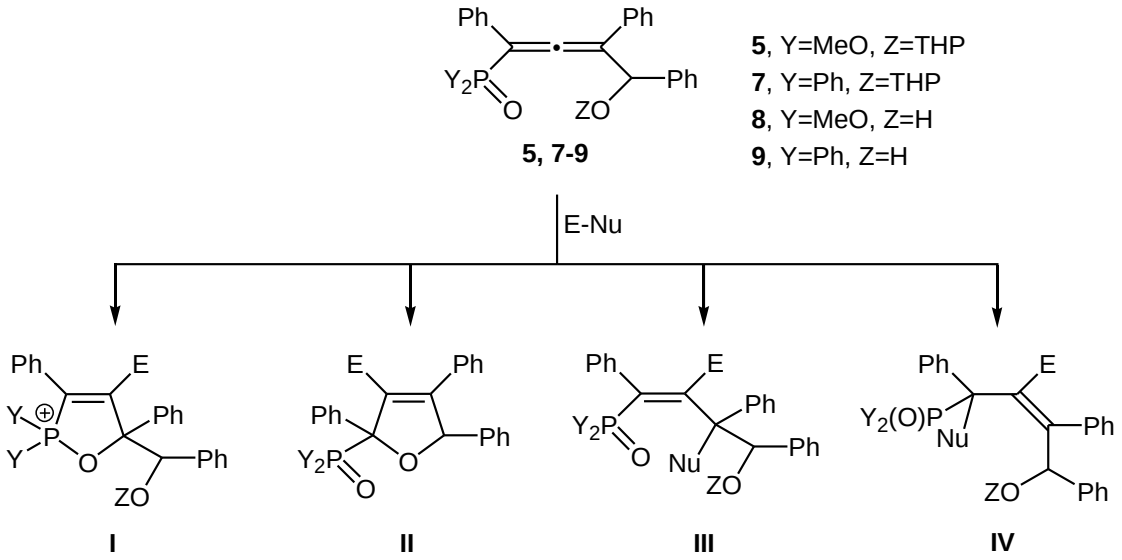
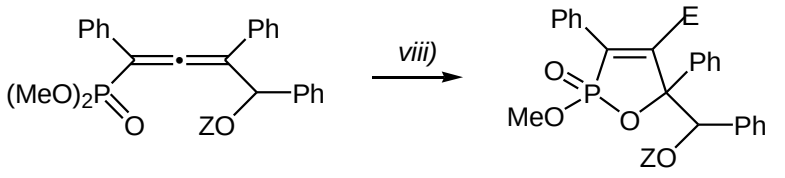
the 2,5-dihydro-1,2-oxaphospholes **I** or to the 2-phosphoryl-2,5-dihydrofurans **II**, the electrophilic addition might afford the 2,3-adducts **III** and/or the 2,1-adducts **IV** (**Scheme 3**).

Scheme 3. Probable products of the electrophilic reaction of the phosphorylated 3-(□-hydroxy)allenes **5**, **7**–**9**.



We started the present study with the reaction of the dimethyl 1,3,4-triphenyl-4-hydroxy-buta-1,2-dienephosphonate with protected (**5**) or unprotected (**8**) hydroxy group with bromine or benzeneselenenyl chloride (**Scheme 4**). We conducted the reactions under the optimized reaction conditions determined in the similar reactions of the phosphorylated □-hydroxy- and □-hydroxy-allenes earlier [24] – solvent CH_2Cl_2 at −20 °C using 1.0 *equiv* of the allenephosphonate and 1.2 *equiv* of the electrophilic reagent. We have to say that the reaction in the favour of 5-*endo-trig* mode afforded the 2-methoxy-2-oxo-2,5-dihydro-1,2-oxaphospholes **10a,b** to have very good yields (81 and 73 %) and it does not depend on the nature of the substituent on the hydroxy group, as a result of the neighboring group participation of phosphonate group in the cyclization.

Scheme 4. Synthesis of the 2-oxo-2,5-dihydro-1,2-oxaphospholes **10** by electrophilic cyclization of the phosphorylated 3-(□-hydroxy)allenes **5** and **8**.



Reagents and Conditions: *ix)* Br_2 or PhSeCl (1.2 eq), CH_2Cl_2, -20 °C, 2 h, rt, 3h, stirring, column chromatography.

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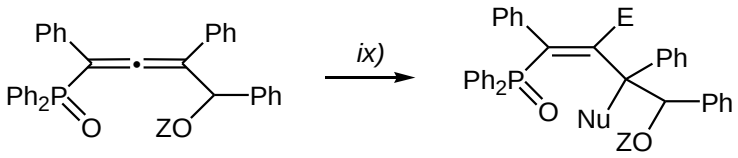
In order to outline the general terms of this methodology, the reaction of the 1,3,4-triphenyl-4-hydroxy-buta-1,2-dienyl phosphine oxides with protected and unprotected hydroxyl group **7** and **9** with benzeneselenenyl or benzensulfenyl chloride was thorougly investigated. Surprisingly, once we applied the current standard conditions to the 1,3-bifunctionalized allenes comprising a phosphine oxide and a 3-(□-hydroxymethyl) groups such as **7** and **9** (**Scheme 5**), the interaction afforded the 1-hydroxy-but-(3*E*)-en-4-yl diphenyl phosphine oxides **11a,b** in 70% and 64% yields. These reaction pathways may be interpreted as a result of the highly regio- and stereoselective association of the external nucleophile, indicating a highly chemoselectively addition reaction of the electrophilic reagent to the C^2-C^3-double bond of the allenic system with formation of the (1*E*)-2,3-adducts **11a**,**b**.

The stereoselectivity could be explained by the favorable *trans* arrangement of the electrophile and the phosphine oxide group and *anti*-attack of the external nucleophile. This is supposed to arise from attack on the allenic C^2-C^3 double bond *anti* to the phosphoryl group which assists in the cyclization by neighboring group participation as an internal nucleophile.

Scheme 5. Synthesis of the 1-hydroxy-but-(3*E*)-en-4-yl phosphine oxides **11** by reaction of the phosphorylated 3-(□-hydroxy)allenes **7** and **9** with electrophilic reagents.



7, 9

11a, Z=THP, E=SePh, 70%
11b, Z=H, E=SPh, 64%

Reagents and Conditions: *x)* PhSeCl or PhSCl (1.2 eq), CH_2Cl_2, -20 °C, 2h, rt, 3h, stirring, column chromatography.

Coinage Metal-catalyzed Cycloisomerization of Phosphorylated 3-(□-hydroxy)allenes

In addition to the above mentioned preparation of 2,5-dihydro-1,2-oxaphospholes by electrophilic cyclization of the 3-(□-hydroxymethyl)-allenephosphonates **5** and **8** and allenyl phosphine oxides **7** and **9** due to the participation of the phosphonate or phosphine oxide neighboring group in the 5-*endo-trig* cyclization, the next step in our study was to explore the possibilities of the cycloisomerization reaction of the above mentioned compounds **8** and **9** in the presence of coinage metal salts as catalysts. We conducted the reaction under the optimized reaction conditions determined in the similar reactions of the phosphorylated □-hydroxy- [24b] and□ □-hydroxy-allenes earlier [24c] – solvent methylene chloride, 5 mol % catalyst and room temperature. The reaction occurred via an 5-*endo-trig* cyclization to give the 2-phosphoryl-2,5-dihydrofurans **12a,b** (**Scheme 6**).

The type of catalyst and its influence on the yields and the reaction time of the cycloisomerization of the 3-(□-hydroxymethyl)-allenephosphonate **8** and allenyl phosphine oxide **9** was also of great interest to us. We performed a series of experiments with the sole intention of determining the best catalysts bearing in mind two criteria – highest yield and shortest reaction time (**Scheme 6**). We applied the following coinage metal salts as catalysts: $AgNO_3$, $AgClO_4$, AuCl, $AuCl_3$, $Pd(PPh_3)_4$, $PtCl_2$, $CuCl_2$, $NiCl_2$, $SnCl_2$, $AlCl_3$, $PdCl_2$, $ZnCl_2$, CuCl, CuBr, and CuI. The data reveal that both Au and Ag are excellent catalysts. Pd(I), Pt, and Cu(II) are very good catalysts for our experiments. It becomes obvious that Ni, Sn, Al, and

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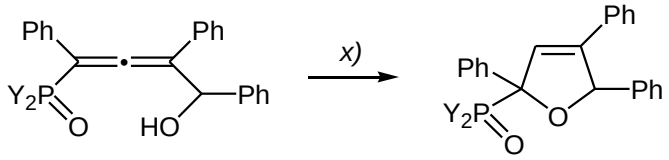
Pd(II) are relatively good catalysts. It is the Zn and Cu(I) catalysts that are bad. **Table 1** presents the characteristics of all the above-mentioned catalysts in the cycloisomerization reaction of the allenic compounds **8** and **9**.

Scheme 6. Synthesis of the 2-phosphoryl-2,5-dihydrofurans **12** by coinage metal-catalyzed cycloisomerization of the phosphorylated 3-(□-hydroxy)allenes **8** and **9**



8, 9 **12a**, Y=OMe, 25-75% (Table 1)
12b, Y=Ph, 20-83% (Table 1)

Reagents and Conditions: *xi)* Coinage metal catalyst (5 mol %, **Table 1**), CH_2Cl_2, rt, stirring (**Table 1**), column chromatography.

The results are explicit enough – a catalytic 5-*endo-trig* cycloisomerization occurs and the hydroxy group participates as an internal nucleophile to give the 2-phosphoryl-2,5-dihydrofurans **12a,b** in good yields.

CONCLUSIONS

In conclusion, a couple of new phosphorylated □-hydroxyallenes were synthesized by a convenient, efficient, atom economical and regioselective method.

Table 1. Synthesis of the 2-phosphoryl-2,5-dihydrofurans 12a,b by coinage metal-catalyzed cycloisomerization of the phosphorylated 3-(□-hydroxy)allenes 8 and 9

Entry	Catalyst	Reaction time[a] **8** (h)	**12a**, Yield (%)	Reaction time[a] **9** (h)	**12b**, Yield (%)
1	$AgNO_3$	6	68[b]	7	76[c]
2	$AgClO_4$	5	69[c]	6	75[c]
3	AuCl	3	75[c]	3	83[c]
4	$AuCl_3$	3	72[b]	4	79[c]
5	$Pd(PPh_3)_4$	7	62[c]	8	67[b]
6	$PtCl_2$	8	63[b]	9	67[c]
7	$CuCl_2$	8	59[c]	10	64[b]
8	$NiCl_2$	10	55[c]	10	50[b]
9	$SnCl_2$	11	51[b]	12	48[c]
10	$AlCl_3$	10	50[b]	12	52[c]
11	$PdCl_2$	11	50[b]	10	41[c]
12	$ZnCl_2$	12	42[c]	11	36[b]
13	CuCl	19	34[c]	17	27[b]
14	CuBr	22	28[b]	20	25[c]
15	CuI	26	25[b]	25	20[c]

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[a] On the average; [b] Yields determined by ^{1}H- and ^{31}P-NMR analysis; [c] Isolated yield by chromatographic purification on silica gel.

Reaction of the phosphorylated □-hydroxyallenes with protected or unprotected hydroxy groups with different electrophilic reagents occurs via 5-*endo-trig* cyclization. Treatment of the 1-(2-hydroxypropyl)-allenephosphonates with electrophiles gives the 2-methoxy-2-oxo-2,5-dihydro-1,2-oxaphospholes as a result of the neighboring group participation of the phosphonate group in the cyclization, while the hept-1*E*-en-1-yl phosphine oxides were prepared as mixtures with the 2,5-dihydro-1,2-oxaphosphol-2-ium halides in a ratio of about 1:2 by chemo-, regio-, and stereo-selective electrophilic addition to the C^2-C^3-double bond in the allene moiety and subsequent concurrent attack of the external (chloride anion) and internal (phosphine oxide group) nucleophiles.

We have developed a coinage metal-catalyzed cycloisomerization reaction of the phosphorylated □-hydroxyallenes, which provides an efficient route to the 4-phosphoryl-3,6-dihydro-2*H*-pyrans which are produced as a result of the participation of the neighboring hydroxy group as an internal nucleophile in the cyclization process.

Due to the easy availability of starting materials, the convenient operation and mild conditions, the readily availability of the reagents and catalysts, the good yields and the usefulness of the 2,5-dihydro-1,2-oxaphospholes and the 4-phosphoryl-3,6-dihydro-2*H*-pyrans, the cyclization reactions may show potential and will be useful in organic synthesis as well in their application in target-oriented synthesis. Further investigation on the chemistry of other phosphorylated allenols for the synthesis of different heterocyclic systems is being intensively carried out in our laboratory. 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 are now under investigation in our University.

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