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Trifunctionalized allenes. Part V. Competitive electrophilic cyclization and cycloisomerization of 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates

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Dedicated to Professor Dr. Toru Minami of the Kyushu Institute of Technology, Tobata, Kitakyushu, Japan on the occasion of his 80th anniversary

The interest is focused on the reactions of 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates with protected or unprotected hydroxy groups involving 5-*endo-trig* cyclizations. Reactions with electrophiles result in mixtures of the 2,5-dihydro-1,2-oxaphosphole-5-carboxylates and the 5-phosphoryl-furan-2(5*H*)-ones by competitive electrophilic cyclization due to the neighboring phosphonate (phosphine oxide) and the carboxylate groups participation. 4-Phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates were smoothly transformed into the corresponding 4-phosphoryl-2,5-dihydrofuran-2-carboxylates by using 5 mol % of a silver salt as a catalyst in the 5-*endo-trig* cycloisomerization reaction.

Keywords: 4-Phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates, electrophilic cyclization, 2,5-dihydro-1,2-oxaphospholes, furan-2(5*H*)-ones, silver-catalyzed cycloisomerization, 2,5-dihydrofurans.

INTRODUCTION

Allenes have broad applications in modern synthetic chemistry due to their nature adaptable as building blocks [1-5]. They have provoked interest in scientists for years due to their unique cumulene structure and atypical biological activities. Allenes are considered to be key subunits in a variety of natural products and pharmaceutical molecules [2,5,6]. Phosphorylated allenes, allenyl phosphonates and phosphine oxides, are a very important class of allene-containing, extremely versatile reagents in organic chemistry, especially for the preparation of structurally diverse organophosphorus compounds and phosphorus heterocycles [7-12].

The study on the reactions of phosphorylated allenes (phosphonates, phosphinates, and phosphine oxides) with electrophilic reagents proves that reactions proceed with cyclization of the allenic system bearing phosphoryl group (O=P-C=C=C) to give heterocyclic compounds in most cases depending on the structure of the starting allenic compound, as well as on the type of the electrophile [13-21]. It means that the reaction of electrophilic reagents with dialkyl allenyl phosphonates [13-21] or allenyl phosphine oxides [22-24] leads to 2,5-dihydro-1,2-oxaphospholes or/and 2,1- or/and 2,3-adducts or a mixture of them, depending on the degree of substitution at the C^1 and C^3 atoms of the allenic system, the nature of these substituents, and the type of the reagents.

Furan-2(5*H*)-ones (*γ*-lactones) are important intermediates in organic synthesis [25-27] and much attention has been paid to the development of efficient and diverse synthetic methods for construction of this five-membered ring system. *α*-Allenecarboxylic acids and their esters, disubstituted on the *γ*-carbon atom, underwent electrophilic attack on the central atom and ring closure to furan-2(5*H*)-ones when treated with electrophile [28-40]. Among these, cyclization involving allenecarboxylic acids and their derivatives, the so-called lactonization reaction, is one of the most efficient pathways [28-40].

It is the transition metal-catalyzed cyclization of functionalized allenes bearing a nucleophilic center that has attracted considerable attention in recent years [41]. Particularly, the cyclization reactions of allenols catalyzed by Ag(I) [42-45], Hg(II) [46,47], Pd(0) [48-50], Pd(II) [51,52], or Ru(III) [53-60] 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 cycloisomerization of *α*-hydroxyallenes [63-65]. 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.

Intramolecular cyclization of the diethylphosphono-substituted α-allenic alcohols in the presence of $AgNO_3$ [61] and $CuCl_2$ [62] yielded

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3,6-dihydro-*2H*-pyran-4-yl- and 4,5-dihydro-3-furanyl phosphonates.

Our long-standing research program focuses on the synthesis [66] and the development of efficient cyclization reactions of trifunctionalized allenes. More specifically, our attention is drawn to 4-phosphorylated 5-hydroxyhexa-2,3-dienoates as 1,1,3-trifunctionalized allenes that comprise a phosphoryl, an ethoxycarbonyl and a hydroxymethyl group. The applications of these groups as temporary transformers of chemical reactivity of the allenic system in the synthesis of heterocyclic compounds are of particular interest. These molecules are considered to be a combination of an allenephosphonate or allenyl phosphine oxide, an allenecarboxylate and a hydroxyallene and they are supposed to have different reactivity profiles in cyclization reactions. In a continuation to our communications [67-72] on the synthesis and cyclization reactions of the bifunctionalized allenes, in this paper we present recent results of our studies dedicated towards the electrophilic cyclization and cycloisomerization reactions of a library of 4-phosphorylated 5-hydroxyhexa-2,3-dienoates, which strongly improve the scope of this method for synthesis of heterocyclic compounds.

EXPERIMENTAL

General Information

All new synthesized compounds were purified by column chromatography and characterized based on NMR, IR, mass, and microanalytical data. NMR spectra were recorded on a Brucker Avance II+600 (^{1}H at 600.1 MHz, ^{13}C at 150.9 MHz, ^{31}P at 242.9 MHz) spectrometer for solutions in $CDCl_3$. All ^{1}H and ^{13}C NMR experiments were performed 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. Elemental analyses were carried out by the Microanalytical Service Laboratory using Vario EL*3* CHNS(O). HRMS were recorded on a Thermo Scientific Q Exactive hybrid quadrupole-orbitrap mass spectrometer. Column chromatography was performed on Kieselgel F_{254}60 (70-230 mesh ASTM, 0.063-0.200 nm, Merck). CH_2Cl_2 was distilled over CaH_2. 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).

Starting Materials

Diphenyl disulfide and sulfuryl chloride in dichloromethane were used to prepare benzenesulfenyl chloride which was distilled *in vacuo* (bp 80-81 °C/20 mm Hg) [80]. All other chemicals used in this study were commercially available and were used without additional purification unless otherwise noted. The starting 4-phosphorylated 5-hydroxyhexa-2,3-dienoates **1-4** were prepared according to earlier reported procedure [66].

General Procedure for the Reactions of the 4-Phosphorylated 5-Hydroxy-5-methylhexa-2,3-dienoates **1-4** *with Electrophilic Reagents*

To a solution of the 4-phosphorylated 5-hydroxyhexa-2,3-dienoates with protected (**1** or **2**) or unprotected (**3** or **4**) hydroxy group (3.0 mmol) in dry dichloromethane (10 mL) at -20 °C was added dropwise under stirring a solution of electrophilic reagent (sulfuryl chloride, 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 3 hours (**5** and **6**) and 5 hours (**7** and **8**) at room temperature. After evaporation of the solvent, the residue was purified by column chromatography on silica gel with ethyl acetate/hexane. The pure products **5-8** had the following properties:

Methyl 4-bromo-2-isopropoxy-3-(1-methyl-1-tetrahydro-2H-pyran-2-yloxyethyl)-2-oxo-5-phenyl-2,5-dihydro-1,2-oxaphosphole-5-carboxylate **(5a).** Yellow oil, yield: 41%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.43; IR (neat, cm^{-1}): 1024 (C-O-P), 1123 (C-O-C), 1269 (P=O), 1439, 1494 (Ph), 1578 (C=C), 1723 (C=O). ^{1}H NMR (600.1 MHz): δ 1.27 (t, *J*=6.8 Hz, 3H, MeCH_2O), 1.32 (d, *J*=6.1 Hz, 3H, Me_2CHO), 1.40-1.72 (m, 6H, OTHP), 1.60 (d, *J*=10.6 Hz, 3H, Me_2C), 3.69-3.82 (m, 2H, OTHP), 4.07-4.18 (m, 1H, Me_2CHO), 4.19 (q, *J*=6.8 Hz, 2H, MeCH_2O), 4.72-4.76 (m, 1H, OTHP), 7.45-7.64 (m, 5H, Ph). ^{13}C NMR (150.9 MHz): δ 13.9 (CH_3), 21.2 (CH_2), 23.9 (*J*=7.8, 2CH_3), 25.5 (CH_2), 31.8 (*J*=7.9, 2CH_3), 33.0 (CH_2), 62.5 (CH_2), 64.4 (CH_2), 66.6 (*J*=5.1, CH), 77.8 (*J*=6.0 Hz, C), 93.4 (*J*=9.8 Hz, C), 94.1 (*J*=5.0 Hz, CH), 127.1-136.4 (Ph), 134.5 (*J*=51.4 Hz, C), 136.6 (*J*=153.5 Hz, C), 169.9 (*J*=8.1 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 31.2. HRMS (ESI): *m/z* calcd for $C_{22}H_{31}BrO_7P$ $[M+H]^+$ 518.3551, found 518.3573. Anal. Calcd for $C_{22}H_{30}BrO_7P$: C 51.08, H 5.84. Found: C 51.14, H 5.88.

Diisopropyl [3-bromo-2-(1-methyl-1-tetrahydro-2H-pyran-2-yloxyethyl)-5-oxo-4-phenyl-2,5-

dihydrofuran-2-yl]-phosphonate **(6a).** Light yellow oil, yield: 28%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.65; IR (neat, cm^{-1}): 1117 (C-O-C), 1271 (P=O), 1441, 1489 (Ph), 1619 (C=C), 1747 (C=O). ^{1}H NMR (600.1 MHz): δ 1.26 (dd, *J*=6.1 Hz, *J*=6.2 Hz, 6H, $\underline{Me_2}CHO$), 1.39-1.63 (m, 6H, OTHP), 1.61, 1.74 (ss, 6H, $\underline{Me_2}C$), 4.62-4.79 (m, 1H, $Me_2C\underline{H}O$), 3.54-3.77 (m, 2H, OTHP), 4.91-4.97 (m, 1H, OTHP), 7.44-7.80 (m, 5H, Ph). ^{13}C NMR (150.9 MHz): δ 21.0 (CH_2), 24.1 (*J*=7.8, $2CH_3$), 25.4 (CH_2), 27.2 (*J*=8.0, CH_3), 28.1 (*J*=8.0, CH_3), 32.3 (CH_2), 64.2 (CH_2), 72.3 (*J*=5.0 Hz, CH), 84.3 (*J*=9.7 Hz, C), 93.3 (*J*=4.6 Hz, CH), 97.4 (*J*=137.7 Hz, C), 127.1-129.6 (Ph), 140.5 (*J*=50.4 Hz, C), 146.3 (*J*=7.9 Hz, C), 169.8 (*J*=7.8 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 15.7. Anal. Calcd for $C_{24}H_{34}BrO_7P$: C 52.85, H 6.28. Found: C 52.80, H 6.24.

Methyl 3-(1-hydroxy-1-methyl-ethyl)-2-isopropoxy-2-oxo-5-phenyl-4-phenylsulfenyl-2,5-dihydro-1,2-oxaphosphole-5-carboxylate **(5b).** Orange oil, yield: 40%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.36; IR (neat, cm^{-1}): 1018 (C-O-P), 1267 (P=O), 1438, 1490 (Ph), 1580 (C=C), 1722 (C=O), 3411 (OH). ^{1}H NMR (600.1 MHz): δ 1.21 (d, *J*=6.1 Hz, 6H, $\underline{Me_2}CHO$), 1.31 (t, *J*=7.1 Hz, 3H, $\underline{Me}CH_2O$), 1.48 (d, *J*=10.5 Hz, 6H, $\underline{Me_2}CH$), 2.75 (s, 1H, OH), 4.18 (q, *J*=7.1 Hz, 2H, $MeC\underline{H_2}O$), 4.51-4.71 (m, 1H, $Me_2C\underline{H}O$), 7.09-7.61 (m, 10H, 2Ph). ^{13}C NMR (150.9 MHz): δ 13.8 (CH_3), 21.2 (*J*=7.8, $2CH_3$), 32.4 (*J*=8.0, $2CH_3$), 62.4 (CH_2), 71.5 (*J*=4.9 Hz, CH), 74.8 (*J*=9.8 Hz, C), 95.0 (*J*=9.9 Hz, C), 124.9-139.0 (2Ph), 141.5 (*J*=98.5 Hz, C), 155.8 (*J*=15.0 Hz, C), 167.7 (*J*=7.8 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 33.6. Anal. Calcd for $C_{23}H_{27}O_6PS$: C 59.73, H 5.88. Found: C 59.79, H 5.91.

Diisopropyl [2-(1-hydroxy-1-methylethyl)-5-oxo-4-phenyl-3-phenylsulfenyl-2,5-dihydrofuran-2-yl]-phosphonate **(6b).** Yellow oil, yield: 27%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.58; IR (neat, cm^{-1}): 1125 (C-O-C), 1272 (P=O), 1441, 1493 (Ph), 1620 (C=C), 1748 (C=O), 3424 (OH). ^{1}H NMR (600.1 MHz): δ 1.29 (dd, *J*=6.3 Hz, *J*=6.1 Hz, 6H, $\underline{Me_2}CHO$), 1.49, 1.63 (ss, 6H, $\underline{Me_2}C$), 4.14 (s, 1H, OH), 4.63-4.78 (m, 1H, $Me_2C\underline{H}O$), 7.11-7.94 (m, 10H, 2Ph). ^{13}C NMR (150.9 MHz): δ 24.1 (*J*=8.0, $2CH_3$), 27.4 (*J*=7.8, CH_3), 28.1 (*J*=7.8, CH_3), 72.4 (*J*=4.6 Hz, CH), 80.9 (*J*=10.1 Hz, C), 95.6 (*J*=140.2 Hz, C), 125.3-136.9 (2Ph), 131.7 (*J*=7.8 Hz, C), 163.2 (*J*=14.7 Hz, C), 168.8 (*J*=7.9 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 15.5. HRMS (ESI): *m/z* calcd for $C_{25}H_{32}O_6PS$ $[M+H]^+$ 491.5577, found 491.5590. Anal. Calcd for $C_{25}H_{31}O_6PS$: C 61.21, H 6.37. Found: C 61.28, H 6.32.

5-Methoxycarbonyl-3-(1-methyl-1-tetrahydro-2H-pyran-2-yloxyethyl)-2,2,5-triphenyl-4-phenylselenenyl-2,5-dihydro-1,2-oxaphosphol-2-ium Chloride **(7a).** Orange oil, yield: 48%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.36; IR (neat, cm^{-1}): 1119 (C-O-C), 1437, 1493 (Ph), 1578 (C=C), 1721 (C=O). ^{1}H NMR (600.1 MHz): δ 1.29 (t, *J*=6.8 Hz, 3H, $\underline{Me}CH_2O$), 1.39-1.49 (m, 6H, OTHP), 1.63 (s, 6H, $\underline{Me_2}C$), 3.67-3.84 (m, 2H, OTHP), 4.11-4.20 (m, 2H, $MeC\underline{H_2}O$), 4.96-5.03 (m, 1H, OTHP), 6.83-8.31 (m, 20H, 4Ph). ^{13}C NMR (150.9 MHz): δ 14.0 (CH_3), 21.4 (CH_2), 25.7 (CH_2), 27.9 (*J*=7.7 Hz, $2CH_3$), 32.7 (CH_2), 62.4 (CH_2), 64.0 (CH_2), 86.7 (*J*=10.2 Hz, C), 95.8 (*J*=4.6 Hz, CH), 99.2 (*J*=9.9 Hz, C), 110.8-140.2 (4Ph), 138.1 (*J*=49.8 Hz, C), 170.3 (*J*=14.1 Hz, C), 177.1 (*J*=7.8 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 82.4. Anal. Calcd for $C_{37}H_{38}ClO_5PSe$: C 62.76, H 5.41. Found: C 62.82, H 5.45.

5-(Diphenylphosphinoyl)-5-(1-methyl-1-tetrahydro-2H-pyran-2-yloxyethyl)-3-phenyl-4-phenylselenenyl-5H-furan-2-one **(8a).** Yellow oil, yield: 26%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.63; IR (neat, cm^{-1}): 1125 (C-O-C), 1173 (P=O), 1437, 1488 (Ph), 1621 (C=C), 1747 (C=O). ^{1}H NMR (600.1 MHz): δ 1.34-1.64 (m, 6H, OTHP), 1.55, 1.72 (ss, 6H, $\underline{Me_2}C$), 3.54-3.77 (m, 2H, OTHP), 4.90-4.96 (m, 1H, OTHP), 7.41-7.95 (m, 20H, 4Ph). ^{13}C NMR (150.9 MHz): δ 21.2 (CH_2), 25.9 (CH_2), 25.8 (*J*=8.1 Hz, CH_3), 26.9 (*J*=8.1 Hz, CH_3), 64.1 (CH_2), 86.3 (*J*=10.2 Hz, C), 93.5 (*J*=4.6 Hz, CH), 99.7 (*J*=139.4 Hz, C), 126.6-132.0 (4Ph), 141.4 (*J*=50.1 Hz, C), 150.6 (*J*=7.9 Hz, C), 170.4 (*J*=7.8 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 15.2. HRMS (ESI): *m/z* calcd for $C_{36}H_{36}O_5PSe$ $[M+H]^+$ 658.6018, found 658.6079. Anal. Calcd for $C_{36}H_{35}O_5PSe$: C 65.75, H 5.36. Found: C 65.82, H 5.41.

4-Chloro-3-(1-hydroxy-1-methyl-ethyl)-5-methoxycarbonyl-2,2,5-triphenyl-2,5-dihydro-1,2-oxaphosphol-2-ium Chloride **(7b).** Yellow oil, yield: 47%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.39; IR (neat, cm^{-1}): 1439, 1492 (Ph), 1580 (C=C), 1726 (C=O), 3389 (OH). ^{1}H NMR (600.1 MHz): δ 1.23 (t, *J*=6.8 Hz, 3H, $\underline{Me}CH_2O$), 1.69 (s, 6H, Me_2C), 4.10-4.20 (m, 2H, $MeC\underline{H_2}O$), 5.64 (s, 1H, OH), 6.90-8.24 (m, 15H, 3Ph). ^{13}C NMR (150.9 MHz): δ 13.9 (CH_3), 34.7 (*J*=7.8 Hz, $2CH_3$), 62.3 (CH_2), 73.4 (*J*=9.8 Hz, C), 100.7 (*J*=10.2 Hz, C), 106.9-136.7 (3Ph), 137.1 (*J*=50.1 Hz, C), 158.2 (*J*=39.7 Hz, C), 167.9 (*J*=7.8 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 85.1. HRMS (ESI): *m/z* calcd for $C_{26}H_{26}Cl_2O_4P$ $[M+H]^+$ 504.3614, found 504.3637. Anal. Calcd for $C_{26}H_{25}Cl_2O_4P$: C 62.04, H 5.01. Found: C 61.97, H 4.95.

4-Chloro-5-(diphenylphosphinoyl)-5-(1-hydroxy-1-methyl-ethyl)-3-phenyl-5H-furan-2-one **(8b).** Yellow oil, yield: 27%. Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.64; IR (neat, cm^{-1}): 1119 (C-O-C), 1180 (P=O), 1435, 1488 (Ph), 1622 (C=C), 1745 (C=O), 3409 (OH). ^{1}H NMR (600.1 MHz): δ 1.55, 1.70 (ss, 6H, Me_2C), 5.59 (s, 1H, OH), 7.33-7.86 (m, 15H, 3Ph). ^{13}C NMR (150.9 MHz): δ 27.4 (*J*=7.8 Hz, CH_3), 28.3 (*J*=7.8 Hz, CH_3), 80.0 (*J*=10.2 Hz, C), 100.7 (*J*=139.4 Hz, C), 127.3-132.4 (3Ph), 144.3 (*J*=7.9 Hz, C), 155.1 (*J*=10.1 Hz, C), 168.0 (*J*=8.1 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 16.5. Anal. Calcd for $C_{25}H_{22}ClO_4P$: C 66.30, H 4.90. Found: C 66.26, H 4.96.

Procedure for Silver-catalyzed Cycloisomerization of the 4-Phosphorylated 5-Hydroxy-5-methylhexa-2,3-dienoates **3** *and* **4**.

Method A: Silver perchlorate (0.15 mmol) was added to a solution of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoate **3** or **4** (3.0 mmol) in dry dichloromethane (10 mL). The mixture was stirred at room temperature in the dark for 7 hours (in case of **3**) and 9 hours (in case of **4**). 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 with a mixture of ethyl acetate and hexane as an eluent to give the pure products **9** as oils.

Method B: The 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoate **3** or **4** (3.0 mmol) is dissolved in 40:60 water/acetone (10 mL) containing calcium carbonate (1 mmol) and silver nitrate (0.3 mmol). The mixture was stirred at room temperature in the dark for 12 hours (in case of **3**) and 15 hours (in case of **4**). The product was taken up in diethyl ether and the ether solution was washed with saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on a column with a mixture of ethyl acetate and hexane as an eluent to give the pure products **9** as oils, which had the following properties:

Methyl 4-(diisopropylphosphoryl)-5,5-dimethyl-2-phenyl-2,5-dihydrofuran-2-carboxylate **(9a).** Yellow oil, yield: 83% (*Method A*), 61% (*Method B*). Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.50; IR (neat, cm^{-1}): 1122 (C-O-C), 1267 (P=O), 1438, 1489 (Ph), 1624 (C=C), 1721 (C=O). ^{1}H NMR (600.1 MHz): δ 1.54, 1.63 (ss, 6H, Me_2C), 3.66 (d, *J*=10.7 Hz, 6H, 2MeO), 3.81 (s, 3H, MeO), 7.16 (d, *J*=10.5 Hz, 1H, =CH), 7.20-7.84 (m, 5H, Ph). ^{13}C NMR (150.9 MHz): δ 28.4 (*J*=7.9 Hz, CH_3), 28.8 (*J*=7.9 Hz, CH_3), 52.4 (*J*=14.6 Hz, $2CH_3$), 53.2 (CH_3), 89.7 (*J*=9.8 Hz, C), 90.5 (*J*=7.7 Hz, C), 126.4-139.6 (Ph), 138.5 (*J*=21.7 Hz, C), 142.5 (*J*=7.8 Hz, CH), 169.4 (*J*=4.0 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 16.6. HRMS (ESI): *m/z* calcd for $C_{20}H_{30}O_6P$ $[M+H]^+$ 397.4224, found 397.4303. Anal. Calcd for $C_{20}H_{29}O_6P$: C 60.60, H 7.37. Found: C 60.54, H 7.40.

Methyl 4-(diphenylphosphinoyl)-5,5-dimethyl-2-phenyl-2,5-dihydrofuran-2-carboxylate **(9b).** Colourless oil, yield: 84% (*Method A*), 64% (*Method B*). Eluent for TLC: ethyl acetate:hexane = 1:4, R_f 0.46; IR (neat, cm^{-1}): 1122 (C-O-C), 1173 (P=O), 1442, 1493 (Ph), 1623 (C=C), 1726 (C=O). ^{1}H NMR (600.1 MHz): δ 1.50, 1.58 (ss, 6H, Me_2C), 3.78 (s, 3H, MeO), 7.20-7.84 (m, 15H, 3Ph), 7.35 (d, *J*=10.5 Hz, 1H, =CH). ^{13}C NMR (150.9 MHz): δ 27.3 (*J*=7.8 Hz, CH_3), 27.9 (*J*=7.8 Hz, CH_3), 52.8 (CH_3), 91.3 (*J*=9.7 Hz, C), 92.0 (*J*=7.6 Hz, C), 126.3-140.5 (3Ph), 143.5 (*J*=20.9 Hz, C), 144.4 (*J*=8.1 Hz, CH), 169.0 (*J*=4.2 Hz, C). ^{31}P NMR (242.9 MHz): δ_P 82.5. Anal. Calcd for $C_{26}H_{25}O_4P$: C 72.21, H 5.83. Found: C 72.26, H 5.90.

RESULTS AND DISCUSSION

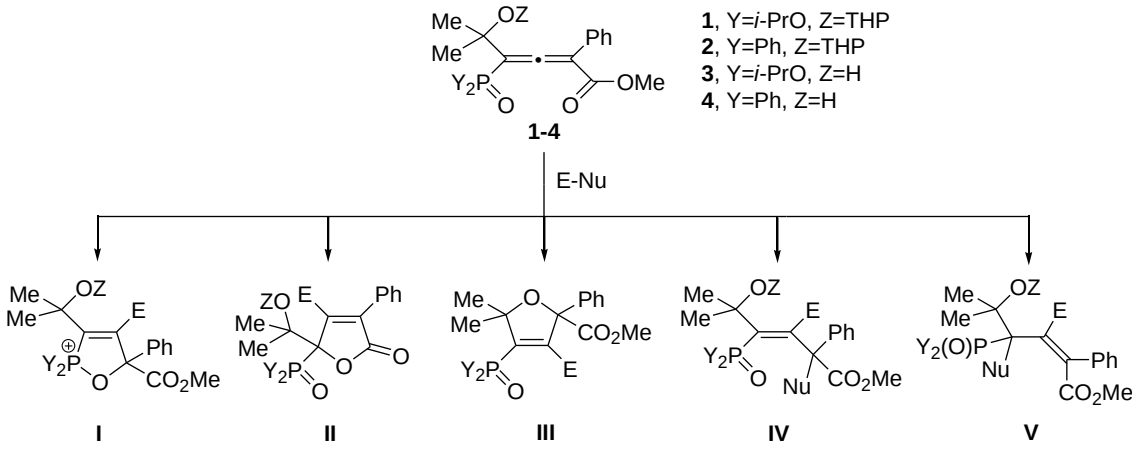
Synthesis of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates 1-4

We applied a convenient, efficient, atom-economical and regioselective four-step method to achieve a range of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **1-4** [66]. The allenylphosphonates **1** and **3** and allenyl phosphine oxides **2** and **4** isolated in preparative amounts allowed us to study its chemical behavior in the reactions with electrophilic reagents and the silver-catalyzed cycloisomerization reactions. The present paper is a recent part of our long-term objective to investigate both the scope and the limitations of the electrophilic cyclization and cycloisomerization reactions of the trifunctionalized allenes, namely the phosphorylated hydroxyallenecarboxylates.

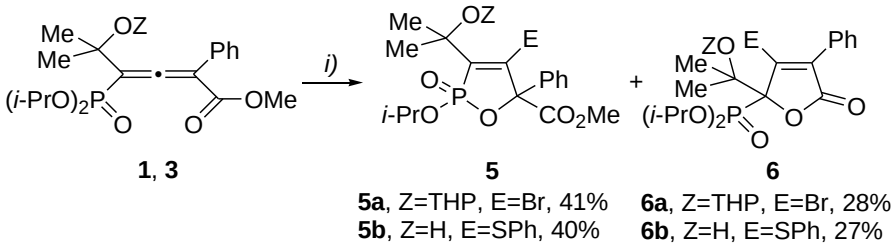
Competitive Electrophilic Cyclization of the 4-phosphorylated 5-hydroxy-5 methylhexa-2,3-dienoates 2 and 4

It is necessary to draw attention to the fact that conceptually three distinct modes of cyclization of the 4-phosphorylated 5-hydroxyhexa-2,3-dienoates **1-4** are possible. They depend on the electrophilic atom that forms a new bond with the central carbon of the allenic system, which seems likely [13-24,73-78]. It is evident that these pathways are closely connected with the intramolecular

neighboring group participation of the phosphoryl, ethoxycarbonyl and/or the hydroxymethyl groups as internal nucleophile(s) in the final step of the cyclization. Besides the 5-*endo-trig* cyclizations [79] to the 2,5-dihydro-1,2-oxaphosphole-5-caboxylates **I**, the 5-phosphoryl-furan-2(5*H*)-ones **II** or the 4-phosphoryl-2,5-dihydrofuran-2-carboxylates **III**, the electrophilic addition might afford the 2,3-adducts **IV** and/or the 2,1-adducts **V** (Scheme 1). We started the present study with the reaction of the 4-(dimethoxyphosphoryl)-5-hydroxy-5-methylhexa-2,3-dienoates with protected (**1**) or unprotected (**3**) hydroxy group with bromine or benzenesulfenyl chloride (Scheme 2). We conducted the reactions under the optimized reaction conditions determined in the similar reactions of the bifunctionalized allenes [67,68,70] – 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 under this set of standard reaction conditions in the favored 5-*endo-trig* mode affords mixtures of the 2-oxo-2,5-dihydro-1,2-oxaphosphole-5-carboxylates **5** and 5-oxo-2,5-dihydrofuran-2-ylphosphonates **6** at the ratio 1.48:1 and 1.46:1 by competitive electrophilic cyclization of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **1** and **3** with the neighboring group participation of phosphonate and carboxylate groups in the cyclization in very good overall yields (69 and 67%). To outline the general terms of this methodology, the reaction of the 4-(diphenylphophinoyl)-5-hydroxy-5-metylhexa-2,3-dienoates with protected and unprotected hydroxyl group **2** and **4** with benzenselenenyl chloride or sulfuryl chloride was investigated.

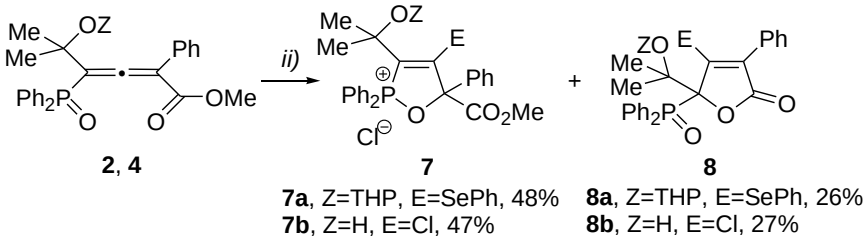


Scheme 1. Probable products of the reaction of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **1**-**4** with electrophilic reagents



Reagents and Conditions: *i)* Br_2 or PhSCl (1.2 eq), CH_2Cl_2, -20 °C, 3 h, rt, 5h, stirring, column chromatography.

Scheme 2. Synthesis of the 2-oxo-2,5-dihydro-1,2-oxaphosphole-5-carboxylates **5** and the 5-oxo-2,5-dihydrofuran-2-ylphosphonates **6** by electrophilic cyclization of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **2** and **4**.

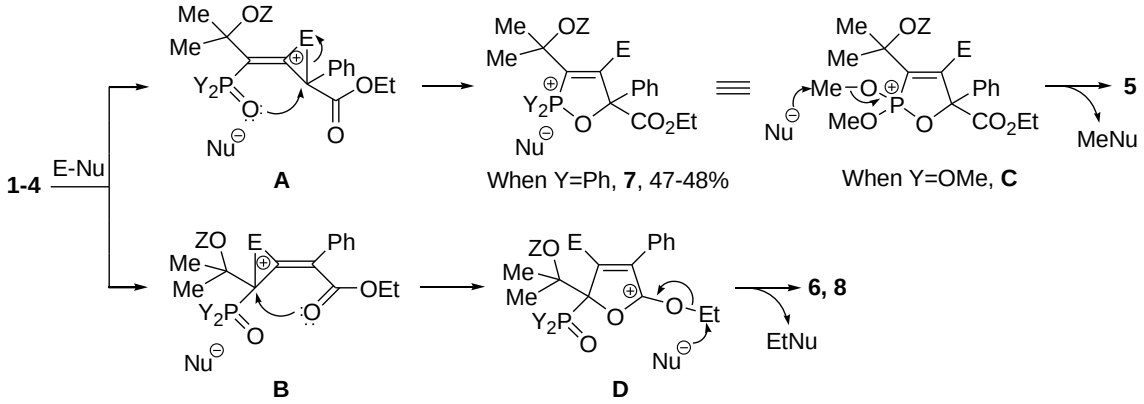


Reagents and Conditions: *ii)* PhSeCl or SO_2Cl_2 (1.2 eq), CH_2Cl_2, -20 °C, 3h, rt, 5h, stirring, column chromatography.

Scheme 3. Synthesis of the 5-carbonylated 2,5-dihydro-1,2-oxaphosphol-2-ium chlorides **7** and the 5-phosphorylated furan-2(5*H*)-ones **8** by electrophilic cyclization of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **2** and **4**.

Surprisingly, once we applied the current standard conditions to the 1,1,3-trifunctionalized allenes comprising a phosphine oxide, an ethoxycarbonyl and a hydroxymethyl group such as **2** and **4** (Scheme 3), the interaction afforded mixtures of the 5-ethoxycarbonyl-2,5-dihydro-1,2-oxaphosphol-2-ium chlorides **7** and 5-(diphenylphosphinoyl)-furan-2(5*H*)-ones **8** in overall yields (74% and 74%) at the ratio 1.74:1 and 1.85:1. These reaction pathways may be interpreted as a result of the neighboring phosphine oxide and ethoxycarbonyl groups participation as the internal nucleophiles in the favored 5-*endo-trig* mode cyclization.

The simplest - although by no means unique - mechanistic rationale for this reaction based on available literature data [13-24,73-78] and on our recent results [67,68,70] is depicted in Scheme 4. The starting point is the attack of the electrophile (Cl^+, Br^+, S^+ or Se^+) on the most nucleophilic atom of the allenic system of π-bonds (central C^3-atom) with formation of the cyclic onium (chloronium, bromonium, thiiranium or seleniranium) ions **A** and **B** after attack on both C^2-C^3- and C^3-C^4-double bonds. Then the ions **A** and **B** are easily transformed into the more stable five-membered cyclic ions **C** (the isolated compounds **7** in the case of the phosphine oxides **2** and **4** (Y=Ph)) and **D** *via* the attachment of the oxygen atom of the phosphonate and carboxylate functionality. Further, the intermediates **C** undergo nucleophilic attack on the MeO group and elimination of methyl halide (MeNu) affording the final cyclic products **5** (when Y is OMe). Analogously, the ions **D** transform in the furan-2(5*H)*-ones **6** and **8** after nucleophilic attack on the EtO group and elimination of ethyl halide (EtNu). Formation of the cyclic products **5-8** can be considered in terms of the assumption of concurrent attacks of the external nucleophiles (phosphoryl and carboxyl groups) on the cyclic three-membered onium ion **A** and **B**. When Y=Ph (starting compounds are phosphine oxides **2** and **4**), the reaction stops in the stage of formation of the cyclic phosphonium salts **7**, since in this case the stabilization by elimination of methyl halide (second stage of an Arbuzov-type rearrangement) and formation of products with tetracoordinated phosphorus is impossible [17,19,21-24].



Scheme 4. A rationale for the reaction of the 4-phosphorylated 5-hydroxyhexa-2,3-dienoates **1**-**4** with electrophilic reagents.

Obviously, this mechanistic rationale could be explained by the assumption of favorable *trans* arrangement of the electrophile and the internal nucleophile (phosphoryl or carboxyl groups) and *anti*-attack of the internal nucleophiles Nu on the onium ions **A** and **B**. This is supposed to arise from attacks on the allenic C^2-C^3- and C^3-C^4-double bonds *anti* to the phosphoryl and carboxyl groups, respectively.

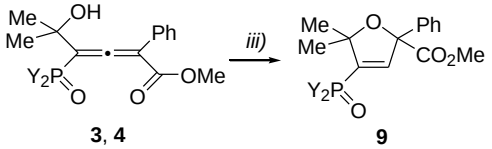
The above mentioned explanation should account for the results on the study of the reactions of other trifunctionalized allenes with electrophilic reagents. Further work in this area shall focus on exploiting and extending the synthetic utility of the trifunctionalized allenes for the preparation of different heterocyclic systems by application of the electrophilic cyclization methodology.

Silver-catalyzed cycloisomerization of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates 3 and 4

In addition to the above mentioned preparation of 2,5-dihydro-1,2-oxaphosphole-5-caboxylates **5** and **7** and the 5-phosphoryl-furan-2(5*H*)-ones **6** and **8** by electrophilic cyclization of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **1-4** due to the phosphonate (phosphine oxide) or carboxylate neighboring group

participation in the 5-*endo-trig* mode cyclization, the next step in our study was to explore the possibilities of the cycloisomerization reaction of the above 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **3** and **4** in the presence of silver salts as catalysts. We conducted the reaction under the optimized reaction conditions determined earlier in the similar reactions of the phosphorylated (α-hydroxy)- [69,71] and (β-hydroxy)-allenes [71,72] – solvent methylene chloride, 5 mol % catalyst and room temperature. The reaction occurred *via* a 5-*endo-trig* cyclization to give the 4-phosphoryl-2,5-dihydrofuran-2-carboxylates **9** (Scheme 4).

The results are explicit enough – a catalytic 5-*endo-trig* cycloisomerization occurs and the hydroxy group participates as an internal nucleophile to give the 4-phosphoryl-2,5-dihydrofuran-2-carboxylates **9** in good yields in the silver-catalyzed cycloisomerization reaction of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **3** and **4**.



3, **4** **9**

9a, Y=*i*-PrO, 83% (Method A); 61% (Method B)
9b, Z=Ph, 84% (Method A); 64% (Method B)

Reagents and Conditions: *iii) Method A:* $AgClO_4$ (5 mol %), CH_2Cl_2, rt, stirring in the dark 7 h (for **9a**) and 9 h (for **9b**), work-up (NaCl, $CHCl_3$, Na_2SO_4), column chromatography; *Method B:* 40:60 water/acetone with $CaCO_3$ (1 mol %), $AgNO_3$ (10 mol %), rt, stirring in the dark 12 h (for **9a**) and 15 (for **9b**), work-up (Et_2O, NaCl, $MgSO_4$), column chromatography.

Scheme 4. Synthesis of 4-phosphorylated 2,5-dihydrofuran-2-carboxylates **9** by silver-catalyzed cycloisomerization of the 4-phosphorylated 5-hydroxy-5-methylhexa-2,3-dienoates **3** and **4.**

CONCLUSIONS

In conclusion, we have developed the competitive electrophilic cyclization and silver-catalyzed cycloisomerization reactions of 4-phosphorylated 5-hydroxypenta-2,3-dienoates, which provided an efficient route to 2,5-dihydro-1,2-oxaphospholes, 5-phosphorylated furan-2(5*H*)-ones and 4-phosphorylated 2,5-dihydrofurans which are produced as a result of the participation of the neighboring phosphonate (phosphine oxide), carboxylate or hydroxy groups as internal nucleophiles in the 5-*endo-trig* cyclization processes. Due to the convenient operation and mild conditions, the ready availability of the reagents and catalysts, the good yields and the usefulness of the heterocyclic compounds prepared, the cyclization reactions may show potential and will be useful in their application in target-oriented synthesis. The successful synthesis of these compounds opens a new access to novel heterocyclic molecules with interesting properties, as well as a broad range of biological activities.

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