First synthesis of dialkyl phosphonate derivatives of sesquiterpene α-methylene-γ-lactone

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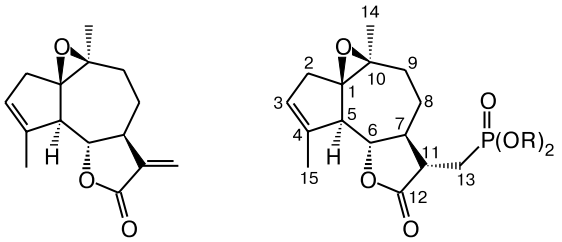
The stereoselective synthesis of two phosphorus-containing derivatives of the known guaianolide arglabin was carried out for the first time. The molecular structures of these products were established based on the spectroscopic data and the results of X-ray diffraction analysis of one of these compounds.

Key words: sesquiterpene lactones, arglabin, guaianolide, dialkyl phosphonates, phosphonates, two-dimensional NMR spectroscopy, X-ray diffraction analysis.

Among numerous classes of organophosphorus compounds,[1,2] organophosphorus derivatives of natural compounds exhibiting biological activities are of considerable interest.[3] In this connection, the synthesis of organophosphorus derivatives of terpenes attracts the attention of researchers.[4]

To our knowledge, data on the synthesis of phosphorus-containing derivatives of sesquiterpene lactones[5] are lacking in the literature. However, in our opinion, the preparation of such derivatives holds promise for chemical modifications of available natural compounds of this class.

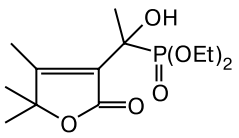
With the aim of synthesizing phosphorus-containing derivatives of guaianolide arglabin (**1**),[6,7] we studied the reactions of this lactone with sodium dimethyl and sodium diethyl phosphonates under the conditions analogous to those described for monoterpene α-enones.[4] Both reactions proceeded selectively at room temperature to give phosphonates **2** and **3**, respectively. It should be noted that the reaction with sodium diethyl phosphonate proceeded rather rapidly and afforded the reaction product in 85% yield after 1 h, whereas the reaction with sodium dimethyl phosphonate performed under the same conditions proceeded much more slowly and one-half of lactone **1** remained unconsumed.



1

2, **3**

R = Me (**2**), Et (**3**)



4

The three-dimensional structure of molecule **3** was established by X-ray diffraction analysis (Fig. 1). The bond lengths and bond angles in **3** are close to the average values[8] and are equal (to within 3σ) to the corresponding values in the molecule of lactone arborescin,[9] which is the closest analog of compound **3**. Of 204 structures of compounds containing the alkyl phosphonate group, which are available in the Cambridge Structural Database (CSD, 2001),[10] synthetic lactone **4** is most structurally similar to phosphonate **3**.[11] The P=O, P—O, and P—C bond lengths in the molecules of these 204 structures are in the ranges of 1.422—1.494, 1.493—1.608, and 1.744—1.889 Å, respectively. A comparison with the analogous bond lengths in molecule **3** (P=O, 1.449(4) Å; P—O, 1.545(5) and 1.577(5) Å; P—C 1.791(6) Å) shows that they fall within the above-mentioned corresponing ranges and are approximately equal to their average values. The seven-membered carbon ring in molecule **3** adopts a chair conformation whose approximate symmetry plane passes through the midpoint of the C(1)—C(10) bond and the C(7) atom.

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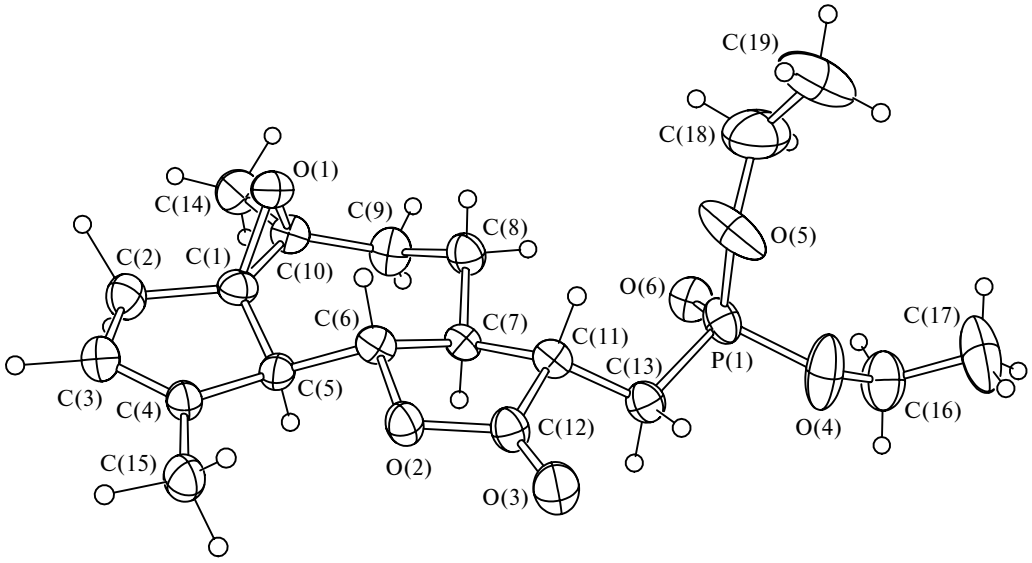

Fig. 1. Molecular structure of compound **3**.

The five-membered rings have envelope conformations. In the lactone ring, the C(7) atom deviates from the plane through the remaining four atoms by −0.564(9) Å (the average deviation from the plane is 0.019 Å). In the cyclopentene fragment, the C(1) atom deviates from the plane though the remaining four atoms by −0.33(1) Å (the average deviation from the plane is 0.008 Å).

The asymmetric center at the C(11) atom in **3** has an *S* configuration, like in the molecule of another known product of the addition at the same bond, *viz.*, in 11,13-dihydro-13-dimethylaminoarglabin hydrochloride, whose structure has also been established by X-ray diffraction analysis.[12]

The mass spectra of compounds **2** and **3** each have an intense ion peak $[M - 18]^+$, whereas the molecular ion peak is observed only in the mass spectrum of product **3**.

The NMR spectra (Tables 1 and 2) of derivatives **2** and **3** were interpreted with the use of the data from 2D ^{1}H—^{1}H (COSY) and ^{13}C—^{1}H (COLOC) NMR spectroscopy. The spin-spin coupling constants $J_{P,H}$ agree well with the published data on analogous dialkyl phosphonates.[4] The ^{31}P NMR spectra of compounds **2** and **3** measured in the absence of proton spin-spin decoupling have symmetric multiplets at δ 30.79 and 28.03, respectively.

To summarize, the reactions of sodium dialkyl phosphonates with sesquiterpene lactones containing the conjugated exomethylene double bond in the lactone ring hold promise for the synthesis of organophosphorus derivatives of natural compounds of this class as exemplified by guaianolide arglabin.

Experimental

The melting points were determined on a Boetius instrument. The IR spectra were measured on a Vector 22 instrument in KBr pellets. The NMR spectra were recorded on a Bruker DRX-500 spectrometer (500.13, 125.76 and 202.46 MHz for ^{1}H, ^{13}C, and ^{31}P NMR, respectively, δ scale) in solutions in $CDCl_3$ with the use of the standard Bruker software for recording 2D COSY and COLOC (7 Hz) NMR spectra. The mass spectra (EI, 70 eV) were obtained on a Finnigan MAT 8200 instrument. The optical rotation was measured (at 580 nm) on a Polamat A polarimeter in solutions in $CHCl_3$. The TLC analysis was carried out on Silufol plates; spots were visualized by spraying with a 1% $KMnO_4$ aqueous solution.

The starting lactone **1** with m.p. 100—102 °C was isolated from the aerial part of the plant *Artemisia glabella* Kar et Kir.[6] The ^{1}H and ^{13}C NMR spectroscopic data, which were obtained for the first time with the use of the 2D ^{1}H—^{1}H and ^{13}C—^{1}H NMR spectra, are given in Tables 1 and 2, respectively.

Synthesis of phosphonates 2 and 3 (general procedure). Sodium (58 mg, 2.5 mmol) was dissolved in dialkyl phosphite (3.7 mL) and the solution was cooled to 0 °C. Then a solution of lactone **1** (500 mg, 2 mmol) in dialkyl phosphite (2.5 mL) was added with stirring. The reaction mixture was kept at ~20 °C for 1 h and then water (10 mL) was added. The reaction mixture was extracted with AcOEt (25 mL). The organic phase was washed successively with a 30% NaOH solution (3×10 mL) and a saturated aqueous solution of NaCl (15 mL). The resulting solution was dried over Na_2SO_4 and filtered. The solvent was distilled off *in vacuo*. The residue was chromatographed on a column with SiO_2 (15 g). Unconsumed lactone **1** (250 mg) and product **2** (250 mg, 69%) were successively isolated (a 1 : 1 mixture of hexane and AcOEt and ethanol, respectively, as the eluent) from the products of the reaction of lactone **1** with sodium dimethyl phosphonate. Analogously, unconsumed lactone **1** (50 mg) and compound **3** (643 mg, 85%) were isolated

Table 1. Data from ^{1}H NMR spectroscopy of lactones **1** and **2** ($CDCl_3$, Me_4Si, δ, *J*/Hz)

H atom	**1**	**2**
$H_a(2)$	2.12 (br.d, J = 18.0)	2.10 (m, coincides with H(9B))
$H_b(2)$	2.75 (br.d, J_{H_a,H_b} = 18.0)	2.71 (br.d., J_{H_a,H_b} = 18.0)
H(3)	5.54 (br.s)	5.52 (br.s)
H(5)	2.91 (br.d, $J_{H(5),H(6)}$ = 10.5)	2.80 (br.d, $J_{H(5),H(6)}$ = 10.0)
H(6)	3.97 (dd, $J_{H(6),H(7)}$ = 10.0; $J_{H(5),H(6)}$ = 10.5)	3.99 (t, $J_{H(5),H(6)} = J_{H(6),H(7)}$ = 10.0)
H(7)	2.22 (m)	1.62 (m)
$H_a(8)$	1.46 (dddd, J_{H_a,H_b} = 14.0; $J_{H_a(8),H_a(9)}$ = 12.7; $J_{H(7),H_a(8)}$ = 11.2, $J_{H_a(8),H_b(9)}$ = 2.5)	1.42 (dddd, J_{H_a,H_b} = 14.0; $J_{H_a(8),H_a(9)}$ = 13.5, $J_{H(7),H_a(8)}$ = 12.0, $J_{H_a(8),H_b(9)}$ = 2.5)
$H_b(8)$	1.82 (br.d, J_{H_a,H_b} = 14.0)	1.86 (br.d, J_{AB} = 14.0)
$H_a(9)$	2.10 (ddd, J_{H_a,H_b} = 15.5; $J_{H_a(8),H_a(9)}$ = 12.7; $J_{H_b(8),H_a(9)}$ = 2.7)	1.90 (m)
$H_b(9)$	2.17 (ddd, $J_{H_b(8),H_b(9)}$ = 4.8; $J_{H_a(8),H_b(9)}$ = 2.5)	2.10 (m)
H(11)	—	2.46 (dddd, $J_{P,H}$ = 24.0; $J_{H(11),H_a(13)}$ = 13.0; $J_{H(7),H(11)} = J_{H(11),H_b(13)}$ = 5.5)
$H_a(13)$	5.39 (d, $J_{H(7),H_a(13)}$ = 3.0)	1.93 (ddd, $J_{P,H}$ = 19.0; $J_{A,B}$ = 16.0)
$H_b(13)$	6.12 (d, $J_{H(7),H_b(13)}$ = 3.4)	2.26 (ddd, $J_{P,H}$ = 18.0)
$C(14)H_3$	1.31 (s)	1.30 (s)
$C(15)H_3$	1.94 (br.s)	1.90 (br.s)
$OC\underline{H}_3$*	—	3.72, 3.73 (both d, 3 H each, $J_{P,H}$ = 11.0)

* Diastereotopic groups.

(a 2 : 3 hexane—AcOEt mixture as the eluent) from the products of the reaction of lactone **1** with sodium diethyl phosphonate.

Table 2. Data from ^{13}C NMR spectroscopy of compounds **1** and **2** ($CDCl_3$, Me_4Si, δ, *J*/Hz)

C atom	**1**	**2**
1	72.32 s	62.33 s
2	39.53 t	22.49 t
3	124.76 t	124.82 d
4	140.33 s	140.45 s
5	52.61 d	52.28 d
6	82.72 d	82.66 d
7	50.61 d	41.11(dd, $^3J_{CP}$ = 4.4)*
8	21.24 t	33.42 t
9	33.24 t	39.45 t
10	62.53 s	72.12 s
11	138.88 s	52.85 (dd, $^2J_{C,P}$ = 4.8)
12	170.33 s	176.44 (d, $^3J_{C,P}$ = 9.6)
13	118.21 t	23.13 (dt, $^1J_{C,P}$ = 144.9)
14	22.64 q	22.61 q
15	18.14 q	18.22 q
$(\underline{C}H_3O)$-A	—	52.36 dq, $^2J_{C,P}$ = 6.5)
$(\underline{C}H_3O)$-B	—	52.50 (dq, $^2J_{C,P}$ = 6.5)

* The spin-spin coupling constants $J_{C,P}$ were determined from the ^{13}C NMR spectra measured with complete spin-spin decoupling of ^{13}C from ^{1}H.

Dimethyl (1*R*,5*R*,6*S*,7*S*,10*S*,11*S*)-1,10-epoxyguaia-3-ene-12,6-olid-13-ylphosphonate (2). Colorless crystals, m.p. 154—157 °C (from EtOH), $[\alpha]^{27}_{580}$ +53.4 (*c* 1.31; $CHCl_3$). R_f 0.07 (AcOEt : light petroleum = 2 : 3). IR (KBr), ν/cm^{-1}: 1772 (C=O), 1229 (P=O), 1191, 1122, 1117, 1093, 1065, 1033 (P—O—C), 997, 968 (P—O—C), 889, 817, 732, 710.

MS, *m*/*z* (I_{rel} (%)): 338 $[M - H_2O]^+$ (49), 323 (7), 295 (12), 269 (20), 267 (33), 228 (21), 216 (11), 215 (59), 210 (16), 185 (33), 184 (100), 183 (13), 182 (25), 177 (13), 176 (7), 175 (39), 174 (14), 173 (12), 169 (17), 165 (22), 164 (33), 163 (14), 159 (32), 157 (80), 147 (21), 145 (22), 144 (9), 143 (11), 142 (7), 138 (12), 133 (15), 132 (11), 124 (78), 110 (47), 109 (16), 107 (16), 105 (33). Found, *m*/*z*: 338.12910 $[M - H_2O]^+$. $C_{17}H_{23}O_5P$. Calculated: M = 338.12830.

The ^{1}H and ^{13}C NMR spectroscopic data are given in Tables 1 and 2, respectively. ^{31}P NMR, δ: 30.79 (m).

Diethyl (1*R*,5*R*,6*S*,7*S*,10*S*,11*S*)-1,10-epoxyguaia-3-ene-12,6-olid-13-ylphosphonate (3). Colorless crystals, m.p. 156—158 °C (from AcOEt : hexane = 2 : 3), $[\alpha]^{25}_{580}$ +77.9 (*c* 2.31; $CHCl_3$). R_f 0.08 (AcOEt : hexane = 1 : 4). IR (KBr), ν/cm^{-1}: 1768 (C=O), 1229 (P=O), 1189, 1172, 1120, 1094, 1062, 1031 (P—O—C), 997, 961 (P—O—C), 814, 733, 712. MS, *m*/*z* (I_{rel} (%)): 384 $[M]^+$ (5), 366 $[M - H_2O]^+$ (100), 351 (6), 338 (10), 325 (8), 324 (9), 323 (14), 322 (10), 320 (6), 297 (21), 296 (7), 295 (21), 269 (10), 267 (10), 239 (7), 233 (9), 223 (14), 216 (9), 215 (8), 211 (10), 210 (24), 191 (12), 187 (14), 185 (24), 184 (72), 175 (26), 174 (11), 173 (8), 169 (11), 166 (19), 165 (14), 159 (22), 158 (11), 157 (51), 152 (33), 147 (13), 145 (11), 144 (6), 143 (9), 138 (21), 136 (9), 135 (7), 133 (12), 131 (17),

129 (7), 125 (33), 108 (11), 105 (13). Found, *m/z*: 366.15940 $[M - H_2O]^+$. Calculated for $C_{19}H_{27}O_5P$: 366.15960.

^{1}H NMR ($CDCl_3$, Me_4Si), δ: 4.05 (m, 4 H, $(OC\underline{H}_2CH_3)_2$), 1.28 (t, 6 H, $(OCH_2C\underline{H}_3)_2$, ^3J = 7.0 Hz). All other signals are identical with the signals observed in the spectrum of compound **2** (see Table 1). ^{13}C NMR ($CDCl_3$, $SiMe_4$), δ: 61.60 and 61.74 (both dt, $O\underline{C}H_2CH_3$, $^2J_{C,P}$ = 6.4 Hz); 16.35 (dq, $OCH_2\underline{C}H_3$, $^3J_{C,P}$ = 6.3 Hz). All other signals are identical with the signals observed in the spectrum of compound **2** (see Table 2). ^{31}P NMR, δ: 28.03 (m).

X-ray diffraction study was carried out on a Syntex $P2_1$ diffractometer (Cu-Kα radiation, graphite monochromator, 2θ/θ scan technique in the range of 2θ < 140°). The X-ray data were collected from a single crystal of compound **3** of dimensions 1.00×0.15×0.04 mm^3. The crystals are orthorhombic: a = 5.981(1), b = 11.264(2), c = 29.713(5) Å, V = 2001.8(7) Å^3, space group $P2_12_12_1$, Z = 4, $C_{19}H_{29}O_6P$, d_{calc} = 1.275 g cm^{-3}, μ = 1.485 mm^{-1}. The intensities of 2216 independent reflections were measured. The absorption correction was applied taking into account the crystal habitus (transmission was 0.62—0.95). The structure was solved by direct methods using the SHELXS-97 program package. The positions of the hydrogen atoms were calculated geometrically. The structure was refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms and isotropic thermal parameters for H atoms using the SHELXL-97 program package. The positions of the H atoms of the ethyl groups were not refined and were calculated from the coordinates of the corresponding carbon atoms in each cycle of the refinement. The final refinement based on all F^2 converged to wR_2 = 0.0970, S = 1.067, 312 parameters were refined (R = 0.0570 for 1459 $F > 4\sigma$). The coordinates and equivalent isotropic thermal parameters of the nonhydrogen atoms of molecule **3** were deposited with the Cambridge Structural Database.

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