Chemistry of Natural Compounds, Vol. 40, No. 4, 2004

PHOSPHORUS DERIVATIVES OF NATURAL LACTONES. SYNTHESIS OF NEW GROSSHEMIN DIALKYLPHOSPHONATES

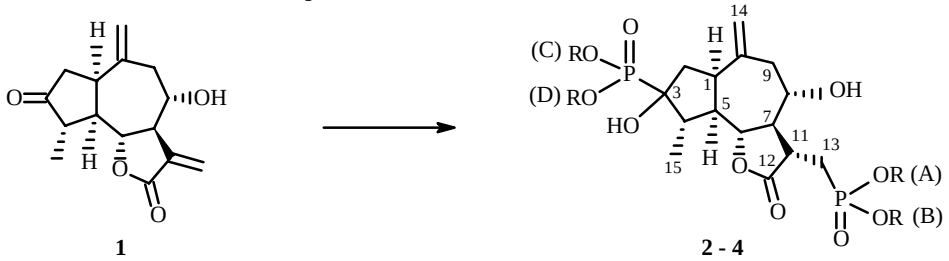
R. I. Dzhalmakhanbetova,[1] S. A. Ivasenko,[1] A. T. Kulyyasov,[1] B. B. Khasenov,[1] N. B. Kurmankulov,[2] and S. M. Adekenov[1]

UDC 547.314

New phosphorus-containing derivatives of grosshemin were synthesized in 68-70% yield by reacting this guaianolide with dialkylphosphites. Their structures were established by IR, PMR, ^{13}C NMR, and ^{31}P NMR spectroscopies and two-dimensional ^{1}H—^{1}H NMR spectroscopy (COSY). The reaction of grosshemin with dialkylphosphites was found to be highly stereoselective.

Key words: grosshemin, phosphorylation, PMR, ^{13}C NMR, ^{31}P NMR, ^{1}H—^{1}H NMR (COSY).

In continuation of studies on chemical modification of sesquiterpene lactones to introduce phosphorus-containing functional groups [1-3], we prepared new derivatives **2-4** from the guaianolide grosshemin, which is isolated from the aerial part of *Chartolepis intermedia* Boiss [4] and possesses high cytotoxic activity [5]. The conditions were analogous to those for synthesizing phosphonate derivatives of monoterpenes [6-9].



1 **2 - 4**

2: R = CH_2CH_3, **2a:** α-3OH, **2b:** β-3OH
3: R = $CH_2CH_2CH_3$
4: R = $CH_2CH_2CH_2CH_3$

IR spectra of **2-4** exhibit absorption bands at 1768, 1770, and 1779 cm^{-1} that are characteristic of γ-lactone C=O vibrations; at 1294, 1225, and 1221, P=O; and at 962, 990, and 985, P–O–C.

NMR spectra (Tables 1 and 2) of **2-4** were interpreted using data from two-dimensional (2D) ^{1}H—^{1}H and ^{13}C—^{1}H (COSY) NMR spectra.

The PMR spectra (Table 1) of **2-4** show signals for protons of the guaiane skeleton and multiplets for H-11 (J_{PH-11} = 28.0 Hz), H-13a and H-13b (J_{PH-13a} = 20.0, J_{PH-13b} = 18.0 Hz). The multiplets are complicated by additional splitting from the P atom of the dialkylphosphonate. The SSCC J_{PH} agree well with the literature [7]. The alkoxyls are diasterotopic and create an additional chiral center at C-11. The methylene protons have different chemical shifts. Splitting of the signals for these protons by the P atom further complicates the spectrum.

1) Institute of Phytochemistry, Ministry of Education and Science of the Republic of Kazakhstan, Republic of Kazakhstan, 470032, Karaganda, ul. Gazalieva 4, fax (3212) 43 37 73, e-mail: arglabin@phyto.kz; 2) A. Bekturov Institute of Chemical Sciences, Ministry of Education and Science of the Republic of Kazakhstan, Republic of Kazakhstan, 480100, Almaty, ul. Ualikhanova, 106, fax (3272)-91-24-80, e-mail: Ics@nas.kz. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 311-315, July-August, 2004. Original article submitted January 27, 2004.

0009-3130/04/4004-0381

TABLE 1. PMR Data for Grosshemin Dialkylphosphonates **2-4** (500.13 MHz, $CDCl_3$, δ, ppm, J/Hz)

H atom	Compound		
	2	**3**	**4**
H-1	3.20 ddd (10.0, 10.0, 8.0)	3.22 ddd (11.0, 9.0)	3.18 m
H-2a	2.00-2.15 m (overlaps H-2b, H-5, H-9b)	2.00-2.15 m (overlaps H-2b, H-5, H-9b)	1.95-2.10 m (overlaps H-2b, H-5, H-9b)
H-2b	2.00-2.15 m (overlaps H-2a, H-5, H-9b)	2.00-2.15 m (overlaps H-2a, H-5, H-9b)	1.95-2.10 m (overlaps H-2a, H-5, H-9b)
H-4*	**2.36 ddq ($^3J_{PH4}$ = 7.0, $^3J_{4/5}$ = 7.0, $^3J_{4/15}$ = 7.0)**	**2.39 ddq ($^3J_{PH4}$ = 7.0, $^3J_{4/5}$ = 7.0, $^3J_{4/15}$ = 7.0)**	**2.32 ddq ($^3J_{PH4}$ = 7.0, $^3J_{4/5}$ = 7.0, $^3J_{4/15}$ = 7.0)**
H-5	2.00-2.15 m (overlaps H-2a, H-2b, H-9b)	2.00-2.15 m (overlaps H-2a, H-2b, H-9b)	1.95-2.10 m (overlaps H-2a, H-2b, H-9b)
H-6	3.86 dd ($^3J_{6/5}$ = 10.0, $^3J_{6/7}$ = 10.0)	3.87 dd ($^3J_{6/5}$ = 10.0, $^3J_{6/7}$ = 10.0)	3.83 dd ($^3J_{6/5}$ = 10.0, $^3J_{6/7}$ = 10.0)
H-7	2.24 ddd ($^3J_{7/11}$ = 12.0, $^3J_{7/6}$ = 10.0, $^3J_{7/8}$ = 10.0	2.25 ddd ($^3J_{7/11}$ = 12.0, $^3J_{7/6}$ = 10.0, $^3J_{7/8}$ = 10.0)	2.22 m (overlaps H-13b)
H-8	3.56 ddd ($^3J_{8/7}$ = 10.0, $^3J_{8/9b}$ = 10.0, $^3J_{9/9a}$ = 4.0)	3.58 ddd ($^3J_{8/7}$ = 10.0, $^3J_{8/9b}$ = 10.0, $^3J_{9/9a}$ = 4.0)	3.52 ddd ($^3J_{8/7}$ = 10.0, $^3J_{8/9b}$ = 10.0, $^3J_{9/9a}$ = 4.0)
H-9a	2.73 dd ($^2J_{9a/9b}$ = 12.0, $^3J_{9a/8}$ = 4.0)	2.76 dd ($^2J_{9a/9b}$ = 12.0, $^3J_{9a/8}$ = 4.0)	2.70 dd ($^2J_{9a/9b}$ = 12.0, $^3J_{9a/8}$ = 4.0)
H-9b	2.00-2.15 m (overlaps H-2a, H-2b, H-5)	2.00-2.15 m (overlaps H-2a, H-2b, H-5)	1.95-2.10 m (overlaps H-2a, H-2b, H-5)
H-11	**2.66 dddd ($^3J_{PH-11}$=28.0, $^3J_{11/7}$=12.0, $^3J_{11/13a}$ = 5.0, $^3J_{11/13b}$ = 5.0)**	**2.67 dddd ($^3J_{PH-11}$=28.0, $^3J_{11/7}$=12.0, $^3J_{11/13a}$ = 5.0, $^3J_{11/13b}$ = 5.0)**	**2.62 m**
H-13a	**2.49 ddd ($^2J_{PH-13}$ = 20.0, $^2J_{13a/13b}$ = 16.0, $^3J_{13a/11}$ = 5.0)**	**2.49 ddd ($^2J_{PH-13}$ = 20.0, $^2J_{13a/13b}$ = 16.0, $^3J_{13a/11}$ = 5.0)**	**2.46 m**
H-13b	**2.19 ddd ($^2J_{PH-13}$ = 18.0, $^2J_{13b/13a}$ = 16.0, $^3J_{13b/11}$ = 5.0)**	**2.20 ddd ($^2J_{PH-13}$ = 18.0, $^2J_{13b/13a}$ = 16.0, $^3J_{13b/11}$ = 5.0)**	**2.19 m (overlaps H-7)**
H-14a	4.95 br.s	4.97 br.s	4.91 br.s
H-14b	4.87 br.s	4.89 br.s	4.83 br.s
H-15	1.18 d (3H, $^3J_{15/4}$ = 7.0)	1.21 d (3H, $^3J_{15/4}$ = 7.0)	1.15 d (3H, $^3J_{15/4}$ = 7.0)
-OC$\underline{H}_2$-A(B)**	**4.06 m (4H)**	**3.98 m (4H)**	-
-OC$\underline{H}_2$-C(D)	**4.12 m (4H)**	**4.03 m (4H)**	**3.95-4.04 m (8H)**
-OCH$_2$C$\underline{H}_3$ A(B)	**1.29 m (6H)**	-	-
-OCH$_2$C$\underline{H}_3$ C(D)	**1.26 m (6H)**	-	-
-OCH$_2$C$\underline{H}_2$-A(B)	-	**1.65 m (4H)**	
-OCH$_2$CH$_2$-C(D)	-	**1.70 m (4H)**	**1.52-1.59 m (8H)**
-O(CH$_2$)$_2$C$\underline{H}_3$ A(B)C(D)	-	0.92 t (12H, 7.0)	-
-O(CH$_2$)$_2$C$\underline{H}_2$-A(B)C(D)	-	-	1.27-1.33 m (8H)
-O(CH$_2$)$_3$C$\underline{H}_3$ A(B)C(D)	-	-	0.84 t (12H, 7.0)

*Signals for protons coupling with ^{31}P are in bold.

**A and B (C and D) are diastereotopic groups (NMR parameters are given for underlined protons).

Atom C-11 in all phosphonate derivatives of grosshemin (**2-4**) has the *S*-configuration, i.e., the C-7 and C-11 protons are *trans*-oriented. This arrangement of these protons is consistent with the PMR spectra, in which a large SSCC is observed (12.0 Hz for **2-4**, Table 1) between H-7 and H-11. A SSCC of the same magnitude is observed in the spectrum of arglabin dialkylphosphonates, which have an analogous configuration for C-11 and for which three-dimensional structures were established by X-ray structure analyses [3].

TABLE 2. ^{13}C NMR Data for Grosshemin Dialkylphosphonates **2-4** (125.76 MHz, $CDCl_3$, δ, ppm, J/Hz)

C atom	Compound		
	2	**3**	**4**
C-1*	**43.50 dd ($^3J_{CP}$ = 14.5)**	**43.60 d ($^3J_{CP}$ = 12.9)**	**43.47 d ($^3J_{CP}$ = 11.3)**
C-2	**39.86 dt ($^2J_{CP}$ = 6.8)**	**39.87 dt ($^2J_{CP}$ = 3.3)**	**39.90 dt ($^2J_{CP}$ = 2.4)**
C-3	**78.78 d ($^1J_{CP}$ = 169.8)**	**78.80 d ($^1J_{CP}$ = 168.0)**	**78.70 d ($^1J_{CP}$ = 167.0)**
C-4	**44.70 dd ($^3J_{CP}$ = 9.6)**	**44.83 dd ($^3J_{CP}$ = 8.1)**	**51.09 dd ($^3J_{CP}$ = 7.7)**
C-5	**51.15 dd ($^3J_{CP}$ = 15.3)**	**51.17 dd ($^3J_{CP}$ = 14.3)**	**44.79 dd ($^3J_{CP}$ = 13.1)**
C-6	**80.89 d**	**80.96 d**	**80.87 d**
C-7	**58.25 dd ($^3J_{CP}$ = 4.3)**	**58.39 dd ($^3J_{CP}$ = 3.9)**	**58.01 dd ($^3J_{CP}$ = 3.6)**
C-8	74.65 d	74.69 d	74.75 d
C-9	46.01 t	46.09 t	46.02 t
C-10	143.49 s	143.55 s	143.51 s
C-11	**41.45 dd ($^2J_{CP}$ = 4.0)**	**41.48 dd ($^2J_{CP}$ = 2.9)**	**41.37 dd ($^2J_{CP}$ = 3.6)**
C-12	**175.97 d ($^3J_{CP}$ = 9.3)**	**175.90 d ($^3J_{CP}$ = 8.9)**	**175.83 d ($^3J_{CP}$ = 8.8)**
C-13	**24.26 dt ($^1J_{CP}$ = 141.9)**	**24.12 dt ($^1J_{CP}$ = 142.4)**	**24.20 dt ($^1J_{CP}$ = 142.4)**
C-14	114.14 t	114.14 t	114.31 t
C-15	**14.27 dq ($^3J_{CP}$ = 1.9)**	14.29 q ($^3J_{CP}$ = 0)	14.14 q ($^3J_{CP}$ = 0)
-O$\underline{C}$H$_2$-A(B)**	**62.83, 62.56 dt ($^2J_{CP}$ = 7.3)**	**68.33, 68.20, dt ($^2J_{CP}$ = 6.8)**	**66.18, 66.05 dt ($^2J_{CP}$ = 6.8)**
-O$\underline{C}$H$_2$-C(D)	**62.37, 62.48 dt ($^2J_{CP}$ = 6.7)**	**68.01, 67.83 dt ($^2J_{CP}$ = 6.5)**	**66.00, 65.87 dt ($^2J_{CP}$ = 6.8)**
-OCH$_2\underline{C}$H$_3$ A(B)	**16.32 dq ($^3J_{CP}$ = 5.4)**	-	-
-OCH$_2\underline{C}$H$_3$ C(D)	**16.01 dq ($^3J_{CP}$ = 6.0)**	-	-
-OCH$_2\underline{C}$H$_2$-A(B)	-	**23.81 dt ($^3J_{CP}$ = 2.6)**	**32.34 dt ($^3J_{CP}$ = 3.8)**
-OCH$_2\underline{C}$H$_2$-C(D)	-	**23.62 dt ($^3J_{CP}$ = 2.8)**	**32.18 dt ($^3J_{CP}$ = 3.5)**
-O(CH$_2$)$_2\underline{C}$H$_3$ A(B)	-	9.87 q	-
-O(CH$_2$)$_2\underline{C}$H$_3$ C(D)	-	9.87 q	-
-O(CH$_2$)$_2\underline{C}$H$_2$-A(B)	-	-	18.42 t
-O(CH$_2$)$_2\underline{C}$H$_2$-C(D)	-	-	18.38 t
-O(CH$_2$)$_3\underline{C}$H$_3$ A(B)	-	-	13.27 q
-O(CH$_2$)$_3\underline{C}$H$_3$ C(D)	-	-	13.25 q

*Signals for C atoms coupling with ^{31}P are in bold.

**A and B (C and D) are diastereotopic groups (NMR parameters are given for underlined C atoms).

The presence of a direct C-13–P bond is consistent with the ^{13}C NMR spectra. For example, the signal for C-13 in the ^{13}C NMR spectrum of **2** appears as a doublet with a large SSCC of 141.9 Hz. This agrees well with the SSCC J_{CP} in the literature [2]. Signals of other C atoms are also split as a result of the influence of the ^{31}P of the dialkylphosphonate. For example, the signal for the C atom of the γ-lactone C=O of **2** at 175.97 ppm is split into a doublet with SSCC 9.3 Hz (Table 2). Signals for C atoms of the dialkylphosphonate methylenes are also split as a result of coupling with the ^{31}P. For example, SSCC of 7.3 (6.7) Hz for –O$\underline{C}$H$_2$– (A, B, C, D) and 5.4 (6.0) Hz for –OCH$_2\underline{C}$H$_3$ are observed.

Furthermore, spectral data of **2-4** differ from those of previously prepared phosphorus-containing derivatives of other sesquiterpene lactones arglabin, arteannuin B, and isoalantolactone [1-3]. For example, the ^{31}P NMR spectrum of **3** contains signals for two dialkylphosphonates at 31.67 and 26.63 ppm as symmetric multiplets. Secondly, the PMR spectrum of the diethylphosphonate derivative of grosshemin has signals for methylenes (at 4.06 and 4.12 ppm) and methyls (at 1.29 and 1.26 ppm) of the –OCH$_2$CH$_3$ fragment of the diethylphosphonate as two multiplets of total integrated intensity corresponding to 8 protons for CH_2 and 12 protons for CH_3. This indicates that there are two of these groups in **2**.

It is known that this reaction with monoterpene ketones produces derivatives that are formed by attack of a dialkylphosphoryl anion on the ketone [6, 7]. We proposed an analogous addition for grosshemin also. A second dialkylphosphite adds to the ketone at C-3. Unfortunately, the magnitudes of the SSCC that correspond to coupling of ^{31}P with protons of the five-membered carbocycle could not be determined from the PMR spectra owing to overlap of the signals for H-2a,

H-2b, and H-5 with other signals. However, the ^{13}C NMR data clearly show signals for C-1, C-2, C-3, C-4, and C-5 that are additionally split by the second dialkylphosphonate (Table 2). This is most evident for the C-3 signal, which in starting grosshemin is observed as a singlet near 210 ppm. This is characteristic of an isolated carbonyl. It shifts in **2-4** to 78-79 ppm and appears as a doublet with a large SSCC (167-169 Hz). This agrees with the literature [7].

The stereochemistry of C-3 was established using PMR and ^{13}C NMR spectra and calculations.

The configuration of C-3 in the PMR of **2-4** can be determined by examining the signal of neighboring proton H-4. The signal for this proton appears as a symmetric sextet with integrated intensities of the components in the ratio 1:5:10:10:5:1. This arises for identical values of $^3J_{P\text{-}H(4)}$, $^3J_{H(5)\text{-}H(4)}$, and $^3J_{H(15)\text{-}H(4)}$ of 7.0 Hz, i.e., in this instance a doublet of doublets of quartets is observed (Table 1). The small value for the SSCC $^3J_{P\text{-}H(4)}$ of 7.0 Hz indicates that H-4 and the dialkylphosphonate in the bisphosphonates **2-4** have a synclinal arrangement or are *cis*-oriented.

Thus, the value of the SSCC $^3J_{P\text{-}H(4)}$ obtained from the PMR data enables the configuration of C-3 to be unambiguously defined as structure **2a**, i.e., with an α-oriented hydroxyl.

Data from the ^{13}C NMR spectra lead to the same conclusion. The vincinal SSCC for C–C–C–P obey the Karplus equation [10, 11]. Therefore, the SSCC as a function of the corresponding torsion angles for isomers **2a** and **2b** can be examined. For example, SSCC obtained from the ^{13}C NMR spectra for **2** are rather large ($^3J_{C(5)\text{-}C(4)\text{-}C(3)\text{-}P}$ = 15.3 Hz). This indicates an anticlinal arrangement for the C(4)–C(5) and C(3)–P bonds. In fact, according to calculations, the corresponding torsion angle for **2a** is 151.6°; for **2b**, 93.3° (according to the Karplus equation, the SSCC would be 0-2 Hz in this instance, in conflict with the experimental data).

The SSCC $^3J_{C(15)\text{-}C(4)\text{-}C(3)\text{-}P}$ = 1.9 Hz obtained experimentally is rather small. This indicates an orthogonal arrangement for the C(4)–C(15) and C(3)–P bonds. In fact, according to calculations, the torsion angle for **2a** is 84.1°; for **2b**, 36.3° (according to the Karplus equation, the SSCC would be 5-6 Hz in this instance, which is also in conflict with the experimental data). The value of this constant for the other derivatives (**3** and **4**) is zero (Table 2).

Thus, the experimental data obtained from PMR and ^{13}C NMR spectra and the results of quantum-chemical calculations indicate that isomer **2a** is produced by the reaction of grosshemin with dialkylphosphorous acids.

Ab initio quantum-chemical calculations of the total energy E_{tot} of isomers **2a** and **2b** were performed using a limited Hartree—Fock method (RHF), basis set 6-311G, Stevens—Basch—Krauss (SBK) potentials, and Moller—Plesset electronic correlations (MP 2/6-311G) in order to determine the stereochemistry. During the investigation it has been found that the total energy of **2a** is less than that of **2b** by 12.56 kJ/mol.

Thus, three new P-containing derivatives of the guaiane-type sesquiterpene lactone grosshemin were prepared. Their structures were established using PMR, ^{13}C NMR, and ^{31}P NMR spectroscopies, 2D ^1H—^1H NMR spectroscopy (COSY), and calculations. The reaction was found to be highly stereoselective for phosphorylation of this compound.

EXPERIMENTAL

Melting points were determined on a Boetius instrument. IR spectra were recorded on a Vector 22 instrument; NMR spectra, on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^1H; 125.76 MHz for ^{13}C; 81.02 MHz for ^{31}P, internal standard 80% H_3PO_4, δ_P 0.0 ppm), using standard Bruker programs to record 2D ^1H—^1H and ^{13}C—^1H (7 Hz) spectra. Signals were assigned using ^{13}C NMR spectra recorded in the J-modulation regime (zero proton decoupling, opposite phase for signals of atoms with an even and odd number of bonded protons with tuning at J = 135 Hz).

Column flash-chromatography was performed over silica gel (Chemapol 40/100) using mixtures of petroleum ether and ethylacetate with increasing (from 0 to 100%) content of the latter as eluent. TLC used Silufol plates with development by spraying vanillin in H_2SO_4 (1%) and aqueous $KMnO_4$ (1%).

Starting grosshemin (**1**, mp 200-202°C, $[\alpha]_D^{20}$ +159.9°, *c* 1.14, $CHCl_3$) for chemical modifications was isolated from the aerial part of *Chartolepis intermedia* Boiss [4].

Dialkylphosphites were synthesized as before [12]. We present the physicochemical constants for **2-4**:

Dialkylphosphites	Boiling point, °C/mm	Refr. index, n_D^{20}	Density
Diethylphosphite (**2**)	72-73/9	1.4060	1.072
Dipropylphosphite (**3**)	203/9	1.4170	1.018
Dibutylphosphite (**4**)	118-119/11	1.4230	0.995

Quantum-chemical calculations were performed using the PC GAMESS program [13] on an Intel computer cluster in the Laboratory of Chemical Cybernetics of the Chemistry Department of M. V. Lomonosov Moscow State University (Moscow, Russia). Geometric parameters were optimized using SBK potentials.

Preparation of Dialkylphosphonates (2-4) (General Method). Metallic sodium (22.8 mg) was dissolved in dialkylphosphite (2.5 mL). The solution was cooled to 0°C, stirred, and treated with grosshemin (**1**, 200 mg, 0.76 mmol) dissolved in dialkylphosphite (2 mL). The reaction mixture was held at room temperature for 40 min, treated with water, and extracted with ethylacetate. The organic layer was washed with NaOH (30%) and saturated NaCl solution, dried over Na_2SO_4, and filtered. The solvent was vacuum distilled. The solid was chromatographed over a SiO_2 (6 g) column with elution by mixtures of petroleum ether and ethylacetate with increasing content of the latter (0 to 100%).

(1*R*,3*R*,4*S*,5*R*,6*R*,7*R*,8*S*,11*S*)-3-Diethylphosphoryl-3,8-dihydroxyguai-10(14)-en-12,6-olid-13-ylphosphonic Acid Diethylester (2). Oily product. Yield 270 mg (68%).

IR spectrum (KBr, ν, cm^{-1}): 3365 (OH), 2985, 2920, 1768 (γ-lactone C=O), 1637, 1445, 1392, 1294 (P=O), 1162, 1130, 1100, 962 (P–O–C), 751, 668, 586, 537.

Table 1 lists the PMR spectrum; Table 2, ^{13}C NMR spectrum.

(1*R*,3*R*,4*S*,5*R*,6*R*,7*R*,8*S*,11*S*)-3-Dipropylphosphoryl-3,8-dihydroxyguai-10(14)-en-12,6-olid-13-ylphosphonic Acid Dipropylester (3). Oily product. Yield 320 mg (71%).

IR spectrum (KBr, ν, cm^{-1}): 3363 (OH), 2924, 1770 (γ-lactone C=O), 1638, 1460, 1391, 1347, 1225 (P=O), 1129, 990 (P–O–C), 906, 854, 753, 668, 589, 533.

Table 1 lists the PMR spectrum.

Certain cross-peaks in the 2D ^1H—^1H PMR spectrum (COSY): H-8/H-9b, H-8/H-9a, H-7/H-11, H-6/H-7, H-7/H-11, H-7/H-8, H-11/H-13b, H-11/H-13a, H-13a/H-13b, H-9a/H-9b, H-4/H-15, H-1A(B,C,D)/H-2A(B,C,D) H-2A(B,C,D)/H-3A(B,C,D).

Certain cross-peaks in the 2D ^1H—^{13}C NMR spectrum (COSY): H-4/C-4, H-5/C-5, H-8/C-8, H-6/C-6, H-7/C-7, H-11/C-11, H-13a(H-13b)/C-13, H-9a(H-9b)/C-9, H-1A(B,C,D)/C-1A(B,C,D), H-2A(B,C,D)/C-2A(B,C,D), H-3A(B,C,D)/C-3A(B,C,D).

Table 2 lists the ^{13}C NMR spectrum. ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 31.67, 26.63 ppm.

(1*R*,3*R*,4*S*,5*R*,6*R*,7*R*,8*S*,11*S*)-3-Dibutylphosphoryl-3,8-dihydroxyguai-10(14)-en-12,6-olid-13-ylphosphonic Acid Dibutylester (4). Oily product. Yield 350 mg (71%).

IR spectrum (KBr, ν, cm^{-1}): 3335 (OH), 2961, 1779 (γ-lactone C=O), 1640, 1463, 1384, 1221 (P=O), 985 (P–O–C), 910, 834, 589.

Table 1 lists the PMR spectrum; Table 2, ^{13}C NMR spectrum.

ACKNOWLEDGMENT

The work was supported financially by the Ministry of Education and Science of the Republic of Kazakhstan (Basic Research Program F.0286 "Search for new biologically active plant substances and development of practically valuable preparations based on them," theme 01.01.01. "New sesquiterpene lactones of plants, their chemical modification and biological activity," State Registration No. 0103RK00176).

REFERENCES

1. R. I. Dzhalmakhanbetova, B. B. Rakhimova, N. A. Talzhanov, G. K. Rustembekova, A. T. Kulyyasov, and S. M. Adekenov, *Khim. Prir. Soedin.*, 437 (2002).
2. R. I. Dzhalmakhanbetova, E. M. Suleimenov, B. B. Rakhimova, N. A. Talzhanov, A. T. Kulyyasov, and S. M. Adekenov, *Khim. Prir. Soedin.*, 440 (2002).
3. R. I. Dzhalmakhanbetova, B. B. Rakhimova, V. A. Raldugin, I. Yu. Bagryanskaya, Yu. V. Gatilov, M. M. Shakirov, A. T. Kulyyasov, S. M. Adekenov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, No. 3, 715 (2003).
4. S. M. Adekenov, Doctoral Disseration in Chemical Sciences, IBOC RAS, Moscow (1992).
5. P. Barbetti, G. Fardella, I. Ghiappini, V. Scarcia, and C. A. Furlani, "New cytotoxic guaianolides and derivatives from *Grossheimia macrocephala*," *Farmacol. Ed. Sci.*, **40**, No. 10, 755 (1985).
6. V. D. Kolesnik and A. V. Tkachev, International Conference on Natural Products and Physiologically Active Substances, Novosibirsk (1998), 97.
7. V. D. Kolesnik, M. M. Shakirov, and A. V. Tkachev, *Mendeleev Commun.*, 141 (1997).
8. V. D. Kolesnik and A. V. Tkachev, *Izv. Akad. Nauk, Ser. Khim.*, No. 4, 620 (2002).
9. V. D. Kolesnik, T. V. Rybalova, Yu. V. Gatilov, and A. V. Tkachev, *Mendeleev Commun.*, **11**, 98 (2001).
10. W. G. Bentrude and W. N. Setzer, in: *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*, J. G. Verkade and L. D. Quin, eds., VCH Publishers, Deerfield Beach (1987), 365.
11. D. G. Gorenstein, "Non-biological aspects of phosphorus-31 NMR spectroscopy," in: *Progress in Nuclear Magnetic Resonance Spectroscopy*, (1983), Vol. 16, part 1.
12. L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York (1967).
13. M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. J. Jensen, and S. Koseki, *J. Comput. Chem.*, **11**, 1347 (1993).