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# PHOSPHATE DERIVATIVES OF NATURAL LACTONES. II. SYNTHESIS OF NOVEL DIALKYLPHOSPHONATES OF ARTEANNUIN B

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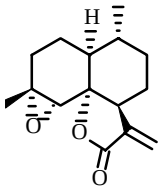
*Novel dialkylphosphonates of arteannuin B were synthesized in 45-47% yields by reaction of this cadinanolide with dialkylphosphites. Their structures were established using IR, PMR, $^{13}C$ and $^{31}P$ NMR spectroscopy, and two-dimensional $^{1}H$ — $^{1}H$ NMR (COSY) spectroscopy. The reaction of arteannuin B and dialkylphosphites is highly stereoselective.*

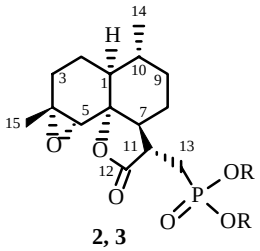
**Key words:** arteannuin B, phosphorylation, PMR, $^{13}C$ and $^{31}P$ NMR, $^{1}H$—$^{1}H$ NMR (COSY).

The sesquiterpene cadinane lactone arteannuin B (**1**) was first isolated from the aerial part of *Artemisia annua* L. (annual absinthe) and is a side component in the production of the antimalarial preparation based on artemisinin from this species. Chemical modification of this compound is promising because the literature contains data on the high antimicrobial activity of modified derivatives of arteannuin B [2].

Two dialkylphosphonate derivatives of arteannuin B (**2**, **3**) with potentially high biological activity were obtained from the synthesis of novel P-containing analogs of natural phosphates using a method analogous to that for synthesizing monoterpene derivatives [3, 4].



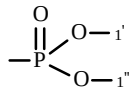
**1**



**2, 3**

-P(O)(OR)$_2$

**2:**



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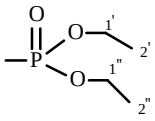

The IR spectra of **2** and **3** contain characteristic absorption bands at 1778 and 1777 cm$^{-1}$ corresponding to vibrations of the γ-lactone C=O; 1226 and 1220, P=O; 1065, 1056, 1028, 100, 960, and 959, P–O–C.

The NMR spectra (Tables 1 and 2) of **2** and **3** were interpreted using two-dimensional (2D) $^{1}H$—$^{1}H$ NMR (COSY) spectroscopy.

The PMR spectra (Table 1) of **2** and **3** exhibit signals for protons of the cadinane skeleton and multiplets for H-11 ($J_{P11_H}$ = 18.0 Hz) and H-13a and H-13b ($J_{P13_H}$ = 20.0, 18.0 Hz), the signals of which are complicated by additional splitting by the P of the dialkylphosphonate. The spin—spin coupling constants (SSCC) $J_{PH}$ agree well with those previously reported [3]. The signals of the methylene protons have different chemical shifts owing to the diastereotopic nature of the alkoxyls, which

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TABLE 1. PMR ($CDCl_3$, 500.13 Hz, δ, ppm, J/Hz) of Arteannuin B Dialkylphosphonates **2-3**

| H atom | **2** | **3** |
|---|---|---|
| 1 | 1.40 m (overl.with H-2b, H-10) | 1.35 m (overl.with H-2b, H-10) |
| 2a | 1.66 m (overl.with H-3b) | 1.63 m (overl.with H-3b) |
| 2b | 1.44 m (overl.with H-1, H-10) | 1.38 m (overl.with H-1, H-10) |
| 3a | 1.90 m | 1.85 m |
| 3b | 1.62 m (overl.with H-2a) | 1.53 m (overl.with H-2a) |
| 5 | 2.79 s | 2.73 s |
| 8a | 2.10 dddd (13.0; 3.0; 3.0; 3.0) | 2.08 dddd (13.0; 3.0; 3.0; 3.0) |
| 8b | 1.34 dddd (13.0; 13.0; 13.0; 3.0) | 1.30 dddd (13.0; 13.0; 13.0; 3.0) |
| 10 | 1.42 m (overl.with H-1, H-2b) | 1.36 m (overl.with H-1, H-2b) |
| **11** | **2.88 dddd (14.0; 9.0; 4.0, $^3J_{PH}$ = 18.0)** | **2.83 dddd (14.0; 9.0; 4.0, $^3J_{PH}$ = 18.0)** |
| **13a** | **2.39 ddd (16.0; 4.0, $^2J_{PH}$ = 20.0)** | **2.33 ddd (16.0; 4.0, $^2J_{PH}$ = 20.0)** |
| **13b** | **1.77 ddd (16.0; 9.0, $^2J_{PH}$ = 18.0)** | **1.71 ddd (16.0; 9.0, $^2J_{PH}$ = 18.0)** |
| 14 | 0.90 d (3H, 6.5) | 0.83 d (3H, 6.5) |
| 15 | 1.30 s (3H) | 1.24 s (3H) |
| **1′** | **3.69 d (3H, 11.0)** | **3.99 m (4H)** |
| **(1″)** | **3.71 d (3H, 11.0)** | |
| **2′** | - | **1.22 t (6H, 7.0)** |
| **(2″)** | | |

Protons coupling with $^{31}P$ are shown in bold.

TABLE 2. $^{13}C$ NMR (75.47 MHz, $CDCl_3$, δ, ppm, J/Hz) of **2-3**

| C atom | **1*** | **2** | **3** |
|---|---|---|---|
| 1 | 43.68 d | 44.28 d | 44.33 d |
| 2 | 16.25 t | 16.05 t | 16.09 t |
| 3 | 24.41 t | 24.34 t | 24.36 t |
| 4 | 58.39 s | 57.58 s | 57.57 s |
| 5 | 58.38 d | 57.44 d | 57.45 d |
| 6 | 77.15 s | 80.88 s | 80.88 s |
| **7** | 52.71 d | **38.10 dd ($^3J_{CP}$ = 3.40)** | **38.11 dd ($^3J_{CP}$ = 3.39)** |
| 8 | 21.73 t | 22.91 t | 22.90 t |
| 9 | 34.02 t | 34.45 t | 34.47 t |
| 10 | 30.63 d | 30.37 d | 30.38 d |
| **11** | 138.60 s | **53.75 dt ($^2J_{CP}$ = 2.85)** | **53.77 dt ($^2J_{CP}$ = 2.89** |
| **12** | 169.75 s | **176.03 d ($^3J_{CP}$ = 16.32)** | **176.00 d ($^3J_{CP}$ = 16.35)** |
| **13** | 117.11 t | **25.20 dt ($^1J_{CP}$ = 145.8)** | **25.20 dt ($^1J_{CP}$ = 145.8)** |
| 14 | 18.61 q | 18.43 q | 18.44 q |
| 15 | 22.72 q | 22.75 q | 22.76 q |
| **1′** | - | **51.18 dq ($^2J_{CP}$ = 6.4)** | **61.95 dt ($^2J_{CP}$ = 6.4)** |
| **(1″)** | - | **50.91 dq ($^2J_{CP}$ = 6.4)** | **61.65 dt ($^2J_{CP}$ = 6.5)** |
| **2′** | - | - | **16.34 dq ($^3J_{CP}$ = 4.5)** |
| **(2″)** | - | - | **16.29 dq ($^3J_{CP}$ = 4.5)** |

*Signals of C atoms of starting arteannuin B were assigned by comparison with the literature [5].
Signals of C atoms coupling with $^{31}P$ are shown in bold.

is caused by the introduction of an additional chiral center on C-11. The splitting of these protons by P leads to additional complication of their signals (protons on C-1′, C-1″, C-2′, C-2″, Tables 1 and 2). The $^{31}$P NMR spectra have signals at 30.08 and 29.12 ppm for the dialkylphosphonates as symmetric multiplets.

The $^{13}$C NMR spectra provide data that a C-13–P bond is present (i.e., an organophosphorus derivative of the cadinanolide arteannuin B was formed). For example, the signal for C-13 in the $^{13}$C NMR spectrum of **2** appears as a doublet with large SSCC 145.8 Hz, which agrees well with $J_{CP}$ SSCC [3]. Additional splitting of the signals of the other C atoms occurs in the $^{13}$C NMR spectrum owing to the effect of the dialkylphosphonate $^{31}$P atom. For example, the signal for the C atom of the γ-lactone C=O of **2** at 176.00 ppm is split into a doublet with SSCC 16.35 Hz (Table 2). The signals of C-7 and C-11 at 38.11 and 53.77 ppm are also additionally split because of coupling with $^{31}$P (SSCC 3.39 and 2.89 Hz). Signals of the methylene C atoms of the dialkylphosphonate are also split owing to coupling with $^{31}$P with SSCC 6.4 and 6.5 Hz for C-1′ and C-1″ and 4.5 Hz for C-2′ and C-2″ (Table 2).

The configuration of C-11 in **2** and **3** was established as *S* based on the SSCC $^{3}J_{7,11}$ = 14.0 Hz for H-7 and H-11. This indicates they have the *trans*-orientation.

Thus, two novel dialkylphosphonate derivatives, the structures of which are unambiguously established using PMR and $^{13}$C and $^{31}$P NMR, were obtained based on the cadinane sesquiterpene lactone arteannuin B, which was isolated from the aerial part of annual absinthe. The reaction of arteannuin B with dialkylphosphites is highly stereoselective.

## EXPERIMENTAL

Melting points were determined using a Boetius apparatus. IR spectra were recorded on a Vector 22 instrument.

NMR spectra were recorded on Bruker DRX-500 and AM-200 spectrometers at working frequencies 500.13 MHz for $^{1}$H and 75.47 MHz for $^{13}$C. Standard Bruker programs were used to record 2D $^{1}$H—$^{1}$H and $^{13}$C—$^{1}$H (7 Hz) COSY spectra. Signals were assigned using $^{13}$C NMR spectra recorded using J-modulation (zero proton decoupling, opposite phases for signals of atoms with even and uneven numbers of protons with tuning at constant J = 135 Hz). $^{31}$P NMR spectra were recorded under the same conditions on a Bruker AC-200 instrument ($^{31}$P 81.02 MHz, external standard 80% $H_3PO_4$, $\delta_P$ = 0.0 ppm).

Column flash chromatography was carried out over silica gel (Chemapol 40/100) using petroleum ether—ethylacetate with an increasing (from 0 to 60%) content of the latter. TLC used Silufol plates with development by spraying with vanillin in $H_2SO_4$ (1%) and aqueous $KMnO_4$ (1%).

Starting arteannuin B with mp 152-153°C was isolated from *Artemisia annua* L. (annual absinthe) for the chemical modifications.

**Preparation of Arteannuin B Dialkylphosphonates.** Dialkylphosphite (3 mL) was stirred and treated with metallic sodium (48 mg, 2.1 mmole). After the metal had dissolved, **1** (200 mg, 0.81 mmole) was added. After 15 min water (10 mL) was added. The mixture was extracted with ethylacetate. The organic layer was washed with NaOH (30%, 4×6 mL) and saturated NaCl solution (10 mL), dried over calcined $Na_2SO_4$, and filtered. The solvent was removed in a rotary evaporator. The solid was chromatographed over a silica-gel column (petroleum ether—ethylacetate, 1:1).

**(1*S*,4*R*,5*R*,6*R*,7*S*,10*R*,11*S*)-4,5-Epoxycadin-12,6-olide-13-ylphosphonic Acid Dimethyl Ester (2).** Oil. Yield 45%.

IR spectrum (KBr, ν, cm$^{-1}$): 2958, 2926, 2874, 2855 (CH), 1778 (C=O γ-pyrone), 1737, 1463, 1422, 1380, 1262, 1226 (P=O), 1226, 1186, 1166, 1131, 1065 (P–O–C), 1000 (P–O–C), 960, 934, 916, 859, 799, 775, 669, 612, 595, 539, 515.

$^{31}$P NMR spectrum ($CDCl_3$, δ, ppm): 28.88.

**(1*S*,4*R*,5*R*,6*R*,7*S*,10*R*,11*S*)-4,5-Epoxycadin-12,6-olide-13-ylphosphonic Acid Diethyl Ester (3).** Oil. Yield 47%.

IR spectrum (KBr, ν, cm$^{-1}$): 2953, 2925, 2874, 2855, 1777 (C=O γ-lactone), 1734, 1629, 1454, 1424, 1392, 1381, 1362, 1262, 1220 (P=O), 1220, 1165, 1132, 1098, 1056 (P–O–C), 1028 (P–O–C), 999, 959 (P–O–C), 929, 890, 854, 813, 725, 709, 688, 668, 609, 593, 538, 515.

$^{31}$P NMR spectrum ($CDCl_3$, δ, ppm): 28.88.

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