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Synthesis and Conformational Study of *P*-Heterocyclic Androst-5-ene Derivatives

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ABSTRACT: *The reactions of (20R)-3β-acetoxy-21-hydroxymethylpregn-5-en-20-ol (***2***) and (20R)-3β-acetoxypregn-5-ene-20,21-diol (***11***) with phenylphosphonic dichloride* **3** *and aryl dichlorophosphates* **4–6** *afforded novel types of P-heterocyclic androst-5-ene derivatives* **7–10** *and* **12** *as epimeric pairs. The diastereomers were separated by column chromatography and were characterized by NMR spectroscopy. Estimation of the stereostructures of the corresponding epimers by B3LYP/631G(d) DFT* ab initio *calculations suggested that the six-membered hetero ring in compounds* **7b** *and* **8a–10a** *adopts predominantly a chair conformation, with the P-substituents in their preferred orientation. The cyclic phosphonate moiety in* **7a** *or* **8b–10b**, *however, seems to exist as an equilibrium mixture of* chair–*distorted*-boat *or* chair–chair *forms. The theoretical calculations indicate that the conformational equilibrium is shifted toward the distorted*-boat *conformer for* **7a**, *with a pseudoequatorial P-phenyl substituent, whereas for* **8b–10b** *the* chair *conformer with an equatorial P-phenoxy group predominates.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:7–14, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20372

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INTRODUCTION

During the past few decades, the synthesis of cyclic phosphonates and phosphates has attracted considerable attention [1–3]. Especially dioxaphosphorinanes are of great interest, since cyclic nucleotides, e.g., adenosine 3′5′-cyclic monophosphate and related compounds involved in the regulation of many biological processes, contain such a framework [4,5]. Analogous cyclic phosphates have been synthesized, and their conformations analyzed in an effort to understand enzyme-regulated natural processes [6,7].

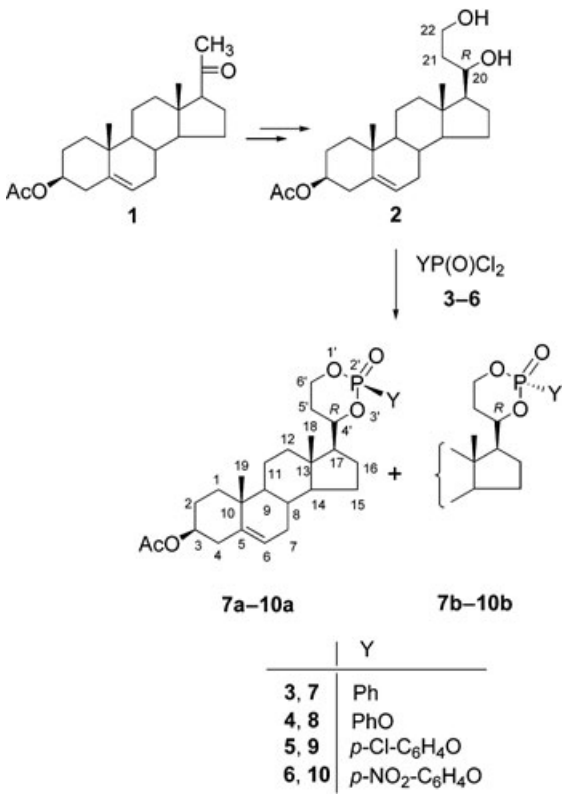
Although intensive research into new steroid derivatives has focused on the development of novel, potentially effective heterocyclic compounds, few *P*-ring systems have been synthesized so far [8,9]. In this regard, we recently reported the efficient syntheses of some new D-ring-fused dioxa- and oxazaphosphorinanes [10] via the phosphorylation of 17β-hydroxy-16β-hydroxymethyl estrone 3-methyl ether [11] and the corresponding 16β-aminomethyl derivative [12]. The dihydroxy compound with phenylphosphonic dichloride was demonstrated to have higher reactivity than the amino alcohol.

Our present goal was to extend the ring-closure reactions to the pregnane skeleton in order to obtain androst-5-ene derivatives with five- or six-membered P-hetero rings at position 17β. A number of compounds containing a heterocyclic moiety at position 17β in this series exhibit noteworthy pharmacological effects [13–16]. Analogous molecules containing a *P*-ring, however, have not

been studied. The present work describes the synthesis of cyclic phosph(on)ates from 20-hydroxy-21-hydroxymethyl- (**2**) and 20,21-dihydroxypregn-5-ene (**11**) precursors with different P(V) reagents. The influence of *P*-derivatization on the epimeric ratio and yields of the products was also studied.

RESULTS AND DISCUSSION

For the preparation of six-membered *P*-heterocycles, (20*R*)-3β-acetoxy-21-hydroxymethylpregn-5-en-20-ol (**2**), which is readily available from 3β-acetoxypregn-5-en-20-one (**1**) via a multistep pathway [17], was used as starting material (Scheme 1). Diol **2** was first phosphorylated with phenylphosphonic dichloride (**3**) and an excess of triethylamine under reflux in dichloromethane to afford the cyclic phosphonate **7** in excellent yield (95%). The analogous transformations of **2** with phenyl dichlorophosphate (**4**), 4-chlorophenyl dichlorophosphate (**5**), and 4-nitrophenyl dichlorophosphate (**6**) furnished the phenoxy **8**, *p*-chlorophenoxy **9**, and *p*-nitrophenoxy **10** dioxaphosphorinane derivatives, respectively, in moderate to good yields (34–83%). In all cases, two diastereomers (**a** and **b**) differing in their *P*-configuration were formed. Although compound **7**



	Y
3, 7	Ph
4, 8	PhO
5, 9	*p*-Cl-C_6H_4O
6, 10	*p*-NO_2-C_6H_4O

SCHEME 1

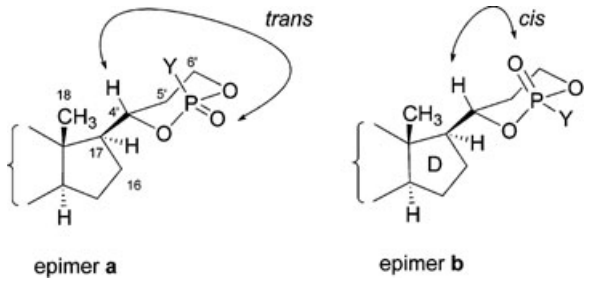


FIGURE 1 Possible stereostructures of diastereomers **a** and **b**, with the assumption of a chair conformation for the dioxaphosphorinane ring linked to the sterane skeleton at position 17β.

was obtained as an approximately 1:1 mixture of **7a** and **7b**, the epimeric ratio of **a** and **b** for the cyclic phosphate esters **8–10** was around 3:2.

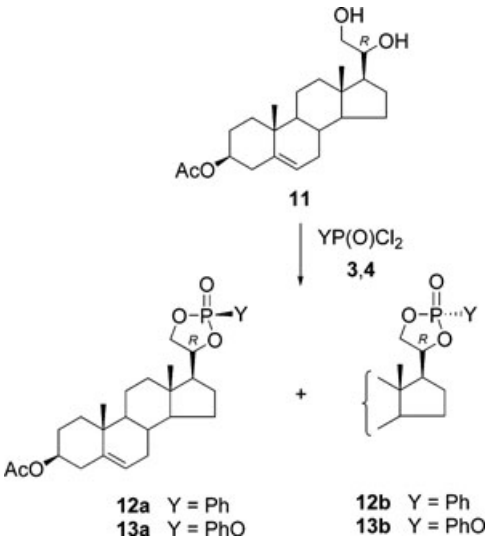
During the reactions of **2** with *p*-substituted aryl dichlorophosphates (**5** and **6**), side reactions were observed to occur, reducing the yields of the desired products (**9** and **10**). The polar byproducts were detected on the TLC plates of the reaction mixtures, but were not identified.

The series of diastereomer pairs **a** and **b** involves the stereogenic phosphorus (Fig. 1). One of the different NMR methods that can be used to determine the orientation of the P=O bonds is based on the ^{31}P NMR chemical shifts [18,19]. For other isomeric pairs of monocyclic and bicyclic 1,3,2-dioxaphosphorinanes [20,21], the ^{31}P NMR chemical shifts of the *trans* isomer (**a**: P=O *trans* to 4′-H) were situated upfield of those of the *cis* isomers (**b**: P=O cis to 4′-H). The ^{13}C NMR chemical shift of C-4′ also changes due to the shielding effect of the oxygen atom of the P=O group.

The epimeric mixtures of dioxaphosphorinanes (**7–10**) were separated by column chromatography and were distinguished on the basis of their NMR data. Of the related epimers, those with the more upfield ^{31}P NMR chemical shifts were classified in series **a**. The ^{13}C NMR chemical shifts of C-4′ for diastereomers **a** and **b** of **7–10** did not differ significantly, but met the requirements. The doublet of C-4′ is downfield for the **a** series as compared with the **b** series of compounds.

For the preparation of dioxaphospholane derivatives, (20*R*)-3β-acetoxypregn-5-ene-20,21-diol [22] (**11**) was reacted with phenylphosphonic dichloride (**3**) and phenyl dichlorophosphate (**4**) (Scheme 2). The cyclic phosphonate (**12**) was obtained in 48% yield as a 2:1 mixture of diastereomers **12a** and **12b**.

The low conversion of 1,2-diol **11** to **12** can be explained by the ring strain in the five-membered hetero ring formed. The greater tendency of **12** to



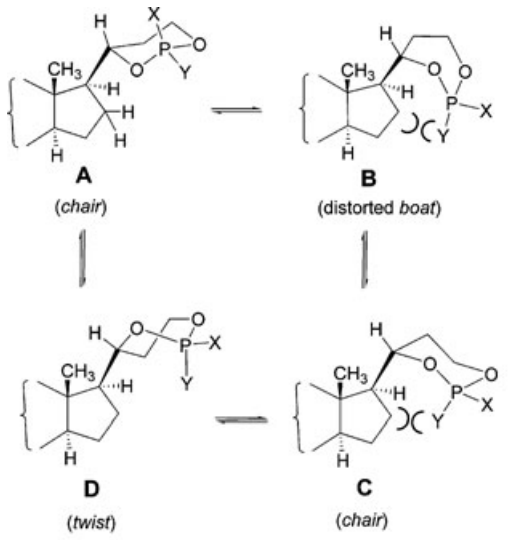
SCHEME 2

undergo hydrolysis during the workup and purification relative to its six-membered analogue (**7**) may also be responsible for the moderate yield. The epimers of cyclic ester **13** with a phenoxy group on the *P* atom were so unstable that they could be observed only on the TLC layers of the reaction mixture. Our experience is consistent with the literature data, suggesting the instability of five-membered cyclic phosphates under both acidic and alkaline hydrolytic conditions [23,24]. Diastereomers **12a** and **12b** were separated and identified through their NMR spectral parameters.

Exhaustive studies have been carried out on substituted monocyclic dioxaphosphorinanes [7,25,26] and monocycle-condensed cyclic phosph(on)ate derivatives [6,18–20,27–29] to reveal a conformational flexibility of the hetero ring for *P*-substitution [8,14,15,21–23]. The specific conformational behavior of these rings has been handled in terms of a *chair*-alternative *boat* or a *chair–twist* equilibrium, and the coupling constants ^3J(H,H) and ^3J(H,P) have been used as indicators of possible dynamic processes [30]. The NMR data have usually been interpreted as supporting the existence of a chair conformation, though mixtures of conformations have been reported in which the *P*-substituent was in an unpreferred orientation, e.g. the phenoxy group was equatorial [26] or the phenyl group was axial [31]. The *P*-substituents endeavor to adopt their preferred orientation and convert the original chair conformation to some degree. For the above-mentioned ring systems, the fused ring or the presence of substituents in the monocyclic dioxaphosphorinane ring simplified the evaluation of the vicinal-coupling constants. For compounds **7–10**, the coupling pattern of 4′-H and 6′-H_2 could be theoretically informative as concerns prediction of the predominant conformations of the corresponding epimers **a** and **b**. The signals of these protons, however, gave complex multiplets with unsolvable splitting due to their coupling with the P and 5′-H_2. Determination of the coupling constants was further complicated by the occasionally overlapping signals. Without single-crystal X-ray analyses, it was not possible to confirm the complete stereostructures of the molecules. The conformational flexibility of the hetero ring is accompanied by possible rotation around the C-17–C-4′ axis.

In order to predict the conformational situation in products **7, 8**, and **12**, B3LYP/631G(d) DFT calculations [32] using Gaussian 03 [33] were carried out on epimers **a** and **b**. Although the estimated stereostructures could not be confirmed by NMR measurements for **7–10**, the high-level theoretical method applied has been well tested for the conformational evaluation of analogous steroidal model compounds and the earlier results were in good accordance with the conformations assumed from the vicinal coupling constants [34,35].

Inspection of the Dreiding models suggested two possible chair forms (A and C) of the six-membered phosphate ring in **7–10**, as depicted in Fig. 2. In the



7a	X: Ph	Y: =O
7b	X: =O	Y: Ph
8a	X: PhO	Y: =O
8b	X: =O	Y: PhO
9a	X: *p*-Cl-C_6H_4O	Y: = O
9b	X: =O	Y: *p*-Cl-C_6H_4O
10a	X: *p*-NO_2-C_6H_4O	Y: =O
10b	X: =O	Y: *p*-NO_2-C_6H_4O

FIGURE 2 Possible conformations of dioxaphosphorinanes **7–10**, substantiated on the basis of literature data for cyclic phosphates [7,19].

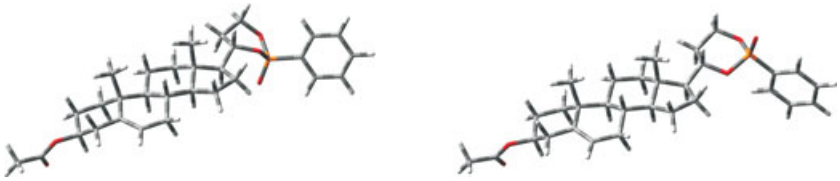


FIGURE 3 Perspective views of compounds **7a** (left) and **7b** (right), with bond lengths (Å), bond angles and torsion angles (°) obtained by B3LYP/6-31G(d) calculations. **7a**: O(1′)–P(2′) 1.633; P(2′)–O(3′) 1.626 C(3′)–C(4′) 1.468; C(4′)–C(5′) 1.539 C(5′)–C(6′) 1.528; C(6′)–C(1′) 1.443; P(2′)=O 1.485; C(2′)–C(1″) 1.800; O(1′)–P(2′)–O(3′) 101.17; P(2′)–O(3′)–C(4′) 119.45; C(6′)–O(1′)–P(2′) 118.19; O(1″)–P(2′)=O 114.92; O(1″)–P(2′)–O(1′) 104.93; C(6′)–O(1′)–P(2′)–O(3′) −24.37; O(1′)–P(2′)–O(3′)–C(4′) 58.87; C(6′)–O(1′)–P(2′)=O 102.51; C(6′)–O(1′)–P(2′)–C(1″) −131.00; O(3′)–C(4′)–C(17)–C(16) 52.05. **7b**: O(1′)–P(2′) 1.632; P(2′)–O(3′) 1.629; O(3′)–C(4′) 1.465; C(4′)–C(5′) 1.535; C(5′)–C(6′) 1.532; C(6′)–C(1′) 1.446; P(2′)=O 1.486; C(2′)–O(1″) 1.796; O(1′)–P(2′)–O(3′) 101.24; P(2′)–O(3′)–C(4′) 116.75; C(6′)–O(1′)–P(2′) 114.96; O(1″)–P(2′)=O 113.63; O(1″)–P(2′)–O(1′) 104.35; C(6′)–O(1′)–P(2′)–O(3′) 53.78; O(1′)–P(2′)–O(3′)–C(4′) −56.10; C(6′)–O(1′)–P(2′)=O −71.91; C(6′)–O(1′)–P(2′)–C(1″) 160.88; O(3′)–C(4′)–C(17)–C(16) 53.96.

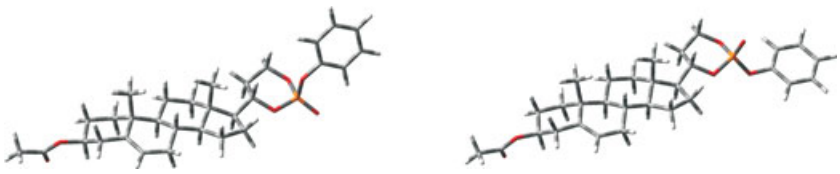


FIGURE 4 Perspective views of compounds **8a** (left) and **8b** (right), with bond lengths (Å), bond angles and torsion angles (°) obtained by B3LYP/6-31G(d) calculations. **8a**: O(1′)–P(2′) 1.612; P(2′)–O(3′) 1.600 C(3′)–C(4′) 1.470; C(4′)–C(5′) 1.531 C(5′)–C(6′) 1.528; C(6′)–C(1′) 1.447; P(2′)=O 1.470; C(2′)–C(1″) 1.634; O(1′)–P(2′)–O(3′) 105.07; P(2′)–O(3′)–C(4′) 120.43; C(6′)–O(1′)–P(2′) 117.72; O(1″)–P(2′)=O 113.63; O(1″)–P(2′)–O(1′) 104.35; C(6′)–O(1′)–P(2′)–O(3′) 42.23; O(1′)–P(2′)–O(3′)–C(4′) −43.63; C(6′)–O(1′)–P(2′)=O 169.33; C(6′)–O(1′)–P(2′)–C(1″) −62.07; O(3′)–C(4′)–C(17)–C(16) 54.95. **8b**: O(1′)–P(2′) 1.624; P(2′)–O(3′) 1.609; O(3′)–C(4′) 1.470; C(4′)–C(5′) 1.534; C(5′)–C(6′) 1.531; C(6′)–C(1′) 1.448; P(2′)=O 1.477; C(2′)–O(1″) 1.608; O(1′)–P(2′)–O(3′) 102.83; P(2′)–O(3′)–C(4′) 116.36; C(6′)–O(1′)–P(2′) 114.55; O(1″)–P(2′)=O 115.25; O(1″)–P(2′)–O(1′) 102.43; C(6′)–O(1′)–P(2′)–O(3′) 53.30; O(1′)–P(2′)–O(3′)–C(4′) −54.99; C(6′)–O(1′)–P(2′)=O −75.36; C(6′)–O(1′)–P(2′)–C(1″) 155.37; O(3′)–C(4′)–C(17)–C(16) 54.85.

chair conformation A for **7b**, the phenyl group can occupy its preferred equatorial orientation, whereas conformer A for **8a** places the phenoxy substituent in a favored axial position. As a consequence, the A form may be proposed for **7b** and **8a**, which is also suggested by the theoretical calculations (Figs. 3 and 4; Table 1). In **7a** and **8b**, however, with regard to the substituent preferences, conformer A was predicted to convert to other forms (B, C, or D). The results indicated that this conformational conversion occurred toward the distorted-boat conformer B and chair form C in **7a**, ensuring that the phenyl group adopts a pseudoequatorial or an equatorial position. The higher proportion of conformer B in the equilibrium B ⇌ C is attributed to the steric repulsions between the P=O group and the sterane skeleton in conformer C. Although the axial preference of the phenoxy group in **8b** would be satisfied in conformer C, this conformation was predicted to be less favorable energetically (Table 1). The equilibrium A ⇌ C in **8b** seems to be shifted toward conformer A with an equatorial *P*-phenoxy substituent, again presumably for steric reasons (Table 1).

The presence of *p*-chloro and *p*-nitro substituents on the benzene ring in **9** and **10** does not exert any additional influence on the conformation of the hetero ring, and similar chair forms are therefore assumed for the epimers **a** and **b** of **9** and **10**, respectively, as for **8**.

TABLE 1 Computed Relative Energies (kJ mol^{-1}) and Percentage Distribution (%) of Four Different Conformers for Compounds **7** and **8**[a]

			E (distrib.)			
	X	*Y*	*A*	*B*	*C*	*D*
7a	Ph	=O	–	0.00 (69.87)	2.11 (30.13)	–
7b	=O	Ph	0.00 (99.96)	–	–	19.22 (0.04)
8a	OPh	=O	0.00 (99.04)	14.12 (0.34)	13.12 (0.51)	17.10 (0.10)
8b	=O	OPh	0.00 (70.11)	6.71 (4.76)	2.58 (24.92)	14.45 (0.21)

[a]Computed absolute energies in hartree: **7a**–A: –; **7a**–B: −1885.44424444; **7a**–C: −1885.44434444; **7a**–D: –; **7b**–A: −1885.44769717; **7b**–B: –; **7b**–C: –; **7b**–D: −1810.19839940; **8a**–A: −1960.68453067; **8a**–B: −1960.67902233; **8a**–C: −1960.67934541; **8a**–D: −1960.67778186; **8b**–A: −1960.68138736; **8b**–B: −1960.67879952; **8b**–C: −1960.68036733; **8b**–D: −1960.67582108. **12a**: −1846.12996104; **12b**: −1846.12994374.

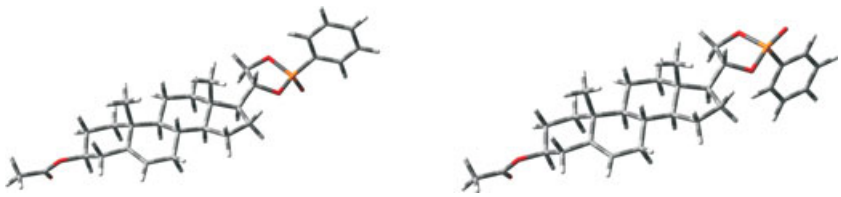


FIGURE 5 Perspective views of compounds **12a** (left) and **12b** (right), with bond lengths (Å), bond angles and torsion angles (°) obtained by B3LYP/6-31G(d) calculations. **12a**: O(1′)–P(2′) 1.641; P(2′)–O(3′) 1.640; O(3′)–C(4′) 1.454; C(4′)–C(5′) 1.537; C(5′)–C(1′) 1.441; P(2′)=O 1.480; C(2′)–O(1″) 1.804; O(1′)–P(2′)–O(3′) 95.58; P(2′)–O(3′)–C(4′) 109.95; C(5′)–O(1′)–P(2′) 119.00; O(1″)–P(2′)=O 119.00; O(1″)–P(2′)–O(1′) 104.07; C(5′)–O(1′)–P(2′)–O(3′) −18.44; O(1′)–P(2′)–O(3′)–C(4′) −4.18; C(5′)–O(1′)–P(2′)=O 103.32; C(5′)–O(1′)–P(2′)–C(1″) −129.21; O(3′)–C(4′)–C(17)–C(16) 52.05. **12b**: O(1′)–P(2′) 1.643; P(2′)–O(3′) 1.638; O(3′)–C(4′) 1.457; C(4′)–C(5′) 1.538; C(5′)–C(1′) 1.436; P(2′)=O 1.480; C(2′)–O(1″) 1.804; O(1′)–P(2′)–O(3′) 95.54; P(2′)–O(3′)–C(4′) 110.64; C(5′)–O(1′)–P(2′) 111.72; O(1″)–P(2′)=O 114.32; O(1″)–P(2′)–O(1′) 108.38; C(5′)–O(1′)–P(2′)– O(3′) −2.41; O(1′)–P(2′)–O(3′)–C(4′) −19.97; C(5′)–O(1′)–P(2′)=O −127.83; C(5′)–O(1′)–P(2′)–C(1″) 104.68; O(3′)–C(4′)–C(17)–C(16) 52.05.

TABLE 2 Computed Relative Energies (kJ mol^{-1}) for the Most Stable Conformers of Products **7, 8**, and **12** at B3LYP/631G(d)

	7	**8**	**12**
$\Delta E_{b\rightarrow a}$	9.06	−8.23	−0.05

In compound **12**, which contains a five-membered hetero ring, the two epimers (**12a** and **12b**) have very similar energy contents (Fig. 5; Table 2). The difference observed in the epimeric ratio may be ascribed not only to the thermodynamic but also to the kinetic control of the process. This assumption is supported by the relative energy content of the corresponding epimers of **7**, showing that **7b** with 9.06 kJ mol^{-1} is more favorable than **7a**, although they were produced as a 1:1 mixture.

CONCLUSIONS

In summary, novel androst-5-ene derivatives substituted at position 17β with dioxaphosphorinane or dioxaphospholane rings were synthesized and characterized by NMR methods. Because of the lack of sufficient information about the vicinal coupling constants, a theoretical analysis of the stereostructures of the products predicted that the *P*-substituent of the six-membered hetero ring can influence the conformational equilibrium significantly. Preference of the Ph group for an equatorial position was predicted in both configurational isomers. The axial-seeking nature of the OPh substituent, however, did not seem strong enough to affect the conversion of A → C to a large degree. These synthesized compounds are of interest in view of their potential pharmacological activities.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker DRX 300 or a Bruker DRX 400 spectrometer in $CDCl_3$ solution, TMS (^1H and ^{13}C NMR) being applied as an internal and 85% H_3PO_4 (^{31}P NMR) as an external standard. ^{13}C and ^{31}P NMR spectra were measured at 75 (or 100) and 121 (or 161) MHz, respectively. Chemical shifts (δ) are given in ppm, and coupling constants (J) in Hz. Mass spectra were recorded on a Varian MAT 311A spectrometer. IR spectra were obtained on a Tensor 37 IR spectrometer (Bruker). Melting points (mp) were measured on a Kofler hot-stage apparatus and are uncorrected. Flash chromatography: Merck silica gel 60, 40–63 μm. Solvent systems (ss): ethyl acetate/dichloromethane (50/50, v/v) (A); ethyl acetate/dichloromethane (20/80, v/v) (B); ethyl acetate/dichloromethane (10/90, v/v) (C).

General Procedure for the Preparation of Cyclic Phosphonate **7** *and Cyclic Phosphates* **8–10**

(20*R*)-3β-Acetoxy-21-hydroxymethylpregn-5-ene-20-ol **2** (391 mg, 1.00 mmol) was dissolved in dichloromethane (30 mL), and triethylamine (0.5 mL, 4.70 mmol) and phenylphosphonic dichloride **3** or aryl dichlorophosphate **4–6** (1.20 mmol) were added at room temperature under a nitrogen atmosphere. The mixture was refluxed for 2 h, then cooled, poured into water (30 mL), and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo.

*(4′R)-3β-Acetoxy-17β-(2′-oxo-2′-phenyl[1′,3′,2′]dioxaphosphorinan-4′-yl)androst-5-ene (***7***).* In accordance with the general procedure, phenylphosphonic dichloride **3** (0.17 mL) was used. The crude

product (**7**) was purified by column chromatography (silica gel, ss A) to give 240 mg (47%) of **7a** and 246 mg (48%) of **7b**.

7a: mp 198–200°C; $R_f = 0.55$ (ss A); ^{31}P NMR (121 MHz, $CDCl_3$): δ 11.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (s, 3H, 18-H_3), 1.04 (s, 3H, 19-H_3), 2.03 (s, 3H, 3-OAc-H_3), 4.20 (m, 2H, 6′-H_2), 4.48 (m, 4′-H), 4.61 (m, 1H, 3-H), 5.37 (m, 1H, 6-H), 7.52 (m, 2H, 3″-H and 5″-H), 7.58 (m, 1H, 4″-H), 7.70 (m, 2H, 2″-H and 6″-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.5 (C-18), 19.3 (C-19), 20.9, 21.4 (3-OAc-CH_3), 24.3, 24.6 (C-16), 27.7, 31.4 (d, $J = 7.6$ Hz, C-5′), 31.7 (C-8), 31.9, 36.6 (C-10), 37.0 (C-1), 38.1 (C-4), 39.2, 42.5 (C-13), 49.9 (C-9), 55.5 (d, $J = 6.5$ Hz, C-17), 55.9 (C-14), 67.1 (d, $J = 6.2$ Hz, C-6′), 73.9 (C-3), 81.6 (d, $J = 7.6$ Hz, C-4′), 122.2 (C-6), 128.0 (d, $J = 179.9$ Hz, C-1″), 128.9 (d, 2C, $J = 14.8$ Hz, C-2″ and C-6‴), 131.0 (d, 2C, $J = 10.0$ Hz, C-3″ and C-5″), 132.3 (d, $J = 3.0$ Hz, C-4″), 139.9 (C-5), 170.5 (3-OAc-C); DCI-MS (70 eV): *m/z* (%): 530 (100) $[M + NH_4]^+$, 513 (8) $[M + H]^+$, 324 (10); IR (KBr disk) 2907, 1733, 1438, 1375, 1250 (P=O) cm^{-1}; anal. calcd for $C_{30}H_{41}O_5P$ (512.63): C, 70.29; H, 8.06; found C, 70.07; H 7.92.

7b: $R_f = 0.45$ (ss A); NMR data (assigned from the 1:5 mixture of **7a** and **7b**): ^{31}P NMR (121 MHz, $CDCl_3$): δ 16.4; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (C-18), 19.3 (C-19), 20.7, 21.4 (3-OAc-CH_3), 24.5 (2C), 27.7, 31.7 (C-8), 31.9, 32.2 (d, $J = 5.3$ Hz, C-5′), 36.6 (C-10), 37.0 (C-1), 38.1 (C-4), 39.1, 42.7 (C-13), 50.1 (C-9), 55.5 (d, $J = 7.4$ Hz, C-17), 56.1 (C-14), 65.2 (d, $J = 5.7$ Hz, C-6′), 73.9 (C-3), 78.8 (d, $J = 6.4$ Hz, C-4′), 122.2 (C-6), 127.7 (d, $J = 194.8$ Hz, C-1″), 128.4 (d, 2C, $J = 15.4$ Hz, C-2″ and C-6″), 131.9 (d, 2C, $J = 10.1$ Hz, C-3″ and C-5″), 132.8 (d, $J = 3.0$ Hz, C-4″), 139.9 (C-5), 170.5 (3-OAc-C).

*(4′R)-3β-Acetoxy-17β-(2′-oxo-2′-phenoxy [1′,3′,2′]dioxaphosphorinan-4′-yl)androst-5-ene (**8**)*. In accordance with the general procedure, phenyl dichlorophosphate **4** (0.18 mL) was used. The crude product (**8**) was purified by column chromatography (silica gel, ss C) to afford 243 mg (50%) of **8a** and 161 mg (33%) of **8b**.

8a: mp 247–249°C; $R_f = 0.82$ (ss C); ^{31}P NMR (121 MHz, $CDCl_3$): δ −13.8; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.60 (s, 3H, 18-H_3), 1.00 (s, 3H, 19-H_3), 2.03 (s, 3H, 3-OAc-H_3), 4.39–4.54 (m, 3H, 4′-H and 6′-H_2), 4.60 (m, 1H, 3-H), 5.36 (m, 1H, 6-H), 7.17 (m, 1H), 7.28 (m, 2H), 7.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8 (C-18), 19.3 (C-19), 20.6, 21.4 (3-OAc-CH_3), 24.4, 24.7 (d, $J = 1.8$ Hz, C-16), 27.7, 31.2 (d, $J = 5.9$ Hz, C-5′), 31.7 (C-8), 31.9, 36.6 (C-10), 37.0 (C-1), 38.1 (C-4), 39.0, 42.5 (C-13), 49.9 (C-9), 54.9 (d, $J = 8.3$ Hz, C-17), 55.8 (C-14), 68.5 (d, $J = 7.0$ Hz, C-6′), 73.9 (C-3), 83.4 (d, $J = 7.8$ Hz, C-4′), 119.4 (d, 2C, $J = 5.3$ Hz, C-2″ and C-6″), 122.2 (C-6), 124.9 (C-4″), 129.9 (2C, C-3″ and C-5″), 139.9 (C-5), 150.5 (d, $J = 6.5$ Hz, C-1″), 170.7 (3-OAc-C); DCI-MS *m/z* (%): 546 (100) $[M + NH_4]^+$; IR (KBr disk) 2950, 1734, 1490, 1297, 1245 (P=O) cm^{-1}; anal. calcd for $C_{30}H_{41}O_6P$ (528.26): C, 68.12; H, 7.83; found C, 68.16; H, 7.82.

8b: $R_f = 0.61$ (ss C); NMR data (assigned from the 2:5 mixture of **8a** and **8b**): ^{31}P NMR (121 MHz, $CDCl_3$): δ −11.8; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2 (C-18), 19.3 (C-19), 20.7, 21.4 (3-OAc-CH_3), 24.5, 24.7 (C-16), 27.7, 30.5 (d, $J = 8.2$ Hz, C-5′), 31.7 (C-8), 31.9, 36.6 (C-10), 37.0 (C-1), 38.1 (C-4), 39.0, 42.7 (C-13), 50.0 (C-9), 54.7 (d, $J = 5.9$ Hz, C-17), 55.9 (C-14), 67.4 (d, $J = 5.9$ Hz, C-6′), 73.9 (C-3), 82.6 (d, $J = 7.0$ Hz, C-4′), 120.3 (d, 2C, $J = 4.7$ Hz, C-2″ and C-6″), 122.2 (C-6), 125.2 (C-4″), 129.7 (2C, C-3″ and C-5″), 139.9 (C-5), 150.6 (d, $J = 7.6$ Hz, C-1″), 170.5 (3-OAc-C).

*(4′R)-3β-Acetoxy-17β-(2′-(4″-chlorophenoxy)-2′-oxo[1′,3′,2′]dioxaphosphorinan-4′-yl)androst-5-ene (**9**)*. In accordance with the general procedure, 4-chlorophenyl dichlorophosphate **5** (0.19 mL) was used. The crude product (**9**) was purified by column chromatography (silica gel, ss C) to furnish 174 mg (31%) of **9a** and 118 mg (21%) of **9b**.

9a: mp 231–234°C; $R_f = 0.76$ (ss C); ^{31}P NMR (161 MHz, $CDCl_3$): δ −14.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63 (s, 3H, 18-H_3), 1.02 (s, 3H, 19-H_3), 2.03 (s, 3H, 3-OAc-H_3), 4.42–4.53 (m, 3H, 4′-H and 6′-H_2), 4.60 (m, 1H, 3-H), 5.36 (m, 1H, 6-H), 7.23 (m, 2H, 2″-H and 6″-H), 7.32 (m, 2H, 3″-H and 5″-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0 (C-18), 19.3 (C-19), 20.6, 21.4 (3-OAc-CH_3), 24.4, 24.7 (C-16), 27.7, 31.1 (d, $J = 5.4$ Hz, C-5′), 31.6 (C-8), 31.8, 36.6 (C-10), 36.9 (C-1), 38.1 (C-4), 39.0, 42.5 (C-13), 49.8 (C-9), 54.8 (d, $J = 8.1$ Hz, C-17), 55.7 (C-14), 68.7 (d, $J = 6.6$ Hz, C-6′), 73.8 (C-3), 83.7 (d, $J = 7.7$ Hz, C-4′), 120.8 (d, 2C, $J = 5.1$ Hz, C-2″ and C-6″), 122.1 (C-6), 129.7 (2C, C-3″ and C-5″), 130.1 (C-4″), 139.8 (C-5), 149.0 (d, $J = 5.7$ Hz, C-1″), 170.5 (3-OAc-C); DCI-MS *m/z* (%): 580 (100) $[M + NH_4]^+$; IR (KBr disk) 2945, 1728, 1488, 1301, 1247 (P=O) cm^{-1}; anal. calcd for $C_{30}H_{40}ClO_6P$ (563.08): C, 63.53; H, 7.11; found C, 63.99; H, 7.16.

9b: $R_f = 0.59$ (ss C); NMR data (assigned from the 2:1 mixture of **9a** and **9b**): ^{31}P NMR (161 MHz, $CDCl_3$): δ −11.4; ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2 (C-18), 19.3 (C-19), 20.7, 21.4 (3-OAc-CH_3), 24.5, 24.7 (C-16), 27.7, 30.6 (d, $J = 7.9$ Hz, C-5′), 31.6 (C-8), 31.8, 36.6 (C-10), 36.9 (C-1), 38.1 (C-4), 38.9, 42.7 (C-13), 49.9 (C-9), 54.7 (d, $J = 5.7$ Hz, C-17), 55.9 (C-14), 67.6 (d, $J = 5.4$ Hz, C-6′), 73.9 (C-3), 82.9 (d, $J = 6.9$ Hz, C-4′), 121.7 (d, 2C, $J = 4.1$ Hz, C-2″ and C-6″), 122.1 (C-6), 129.6 and 129.8 (C-3″ and C-5″),

130.5 (C-4″), 139.9 (C-5), 149.0 (d, $J = 5.7$ Hz, C-1″), 170.5 (3-OAc-C).

*(4′R)-3β-Acetoxy-17β-(2′-(4″-nitrophenoxy)-2′-oxo[1′,3′,2′]dioxaphosphorinan-4′-yl)androst-5-ene (**10**).* In accordance with the general procedure, 4-nitrophenyl dichlorophosphate **6** (307 mg) was used. The crude product (**10**) was purified by column chromatography (silica gel, ss C) to give 116 mg (20%) of **10a** and 78 mg (14%) of **10b**.

10a: mp 229–231°C; $R_f = 0.61$ (ss C); ^{31}P NMR (161 MHz, $CDCl_3$): δ −15.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63 (s, 3H, 18-H_3), 1.01 (s, 3H, 19-H_3), 2.03 (s, 3H, 3-OAc-H_3), 4.42–4.54 (m, 3H, 4′-H and 6′-H_2), 4.60 (m, 1H, 3-H), 5.36 (m, 1H, 6-H), 7.45 (m, 2H, 2″-H and 6″-H), 8.26 (m, 2H, 3″-H and 5″-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0 (C-18), 19.3 (C-19), 20.6, 21.4 (3-OAc-CH_3), 24.4, 24.7 (C-16), 27.6, 31.1 (d, $J = 5.7$ Hz, C-5′), 31.6 (C-8), 31.8, 36.5 (C-10), 36.9 (C-1), 38.0 (C-4), 39.0, 42.5 (C-13), 49.8 (C-9), 54.7 (d, $J = 8.0$ Hz, C-17), 55.7 (C-14), 68.9 (d, $J = 6.8$ Hz, C-6′), 73.8 (C-3), 84.2 (d, $J = 8.0$ Hz, C-4′), 120.1 (d, 2C, $J = 5.6$ Hz, C-2″ and C-6″), 122.0 (C-6), 125.7 (2C, C-3″ and C-5″), 139.8 (C-5), 144.5 (C-4″), 155.3 (d, $J = 5.5$ Hz, C-1″), 170.5 (3-OAc-C); DCI-MS *m/z* (%): 591 (100) $[M + NH_4]^+$, 324 (24), 174 (16); IR (KBr disk) 2947, 1728, 1525, 1350, 1300, 1246 (P=O) cm^{-1}; anal. calcd for $C_{30}H_{40}NO_8P$ (573.25): C, 62.57; H, 6.98 N, 2.42; found C, 62.82; H, 7.03; N, 2.44.

10b: $R_f = 0.39$ (ss C); NMR data (assigned from the 2:3 mixture of **10a** and **10b**): ^{31}P NMR (161 MHz, $CDCl_3$): δ −12.6; ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1 (C-18), 19.2 (C-19), 20.7, 21.4 (3-OAc-CH_3), 24.4, 24.7 (C-16), 27.6, 30.4 (d, $J = 9.1$ Hz, C-5′), 31.6 (C-8), 31.8, 36.5 (C-10), 36.9 (C-1), 38.0 (C-4), 39.1, 42.7 (C-13), 49.8 (C-9), 54.7 (d, $J = 4.2$ Hz, C-17), 55.8 (C-14), 67.9 (d, $J = 5.7$ Hz, C-6′), 73.8 (C-3), 83.5 (d, $J = 7.1$ Hz, C-4′), 120.8 (d, 2C, $J = 5.0$ Hz, C-2″ and C-6″), 122.0 (C-6), 125.5 (2C, C-3″ and C-5″), 139.8 (C-5), 144.7 (C-4″), 155.3 (d, $J = 6.1$ Hz, C-1″), 170.5 (3-OAc-C).

*(4′R)-3β-Acetoxy-17β-(2′oxo-2′-phenyl)[1′,3′,2′]dioxaphospholan-4′-yl)androst-5-ene (**12**).* (20*R*)-3β-Acetoxypregn-5-ene-20,21-diol **11** (450 mg, 1.00 mmol) was dissolved in dichloromethane (30 mL), and triethylamine (0.5 mL, 4.70 mmol) and phenylphosphonic dichloride **3** (0.20 mL 1.40 mmol) were added at room temperature under a nitrogen atmosphere. The mixture was refluxed for 6 h, then cooled, poured into water (10 mL), and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product (**12**) was purified by column chromatography (silica gel, ss B) to provide 191 mg (32%) of **12a** and 95 mg (16%) of **12b**.

12a: mp 281–284°C (decomp.); $R_f = 0.61$ (ss B); ^{31}P NMR (121 MHz, $CDCl_3$): δ 35.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 3H, 18-H_3), 1.01 (s, 3H, 19-H_3), 2.02 (s, 3H, 3-OAc-H_3), 4.19 (m, 1H, 4′-H), 4.38 (m, 1H, one of 5′-H_2), 4.58 (m, 2H, 3-H and other 5′-H_2), 5.37 (m, 1H, 6-H), 7.49 (m, 2H, 3″-H and 5″-H), 7.59 (m, 1H, 4″-H), 7.81 (m, 2H, 2″-H and 6″-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.5 (C-18), 19.3 (C-19), 20.6, 21.4 (3-OAc-CH_3), 23.3, 24.8 (C-16), 27.7, 31.7 (C-8), 31.9, 36.6 (C-10), 36.9 (C-1), 38.1 (C-4), 38.6, 43.0 (C-13), 50.0 (C-9), 53.2 (d, $J = 5.1$ Hz, C-17), 55.6 (C-14), 70.5 (C-5′), 73.9 (C-3), 81.4 (C-4′), 122.2 (C-6), 127.5 (d, $J = 186.9$ Hz, C-1″), 128.7 (d, 2C, $J = 15.8$ Hz, C-2″ and C-6″), 131.9 (d, 2C, $J = 10.7$ Hz, C-3″ and C-5″), 133.0 (d, $J = 3.0$ Hz, C-4″), 139.8 (C-5), 170.5 (3-OAc-C); DCI-MS *m/z* (%): 516 (100) $[M + NH_4]^+$, 376 (12), 239 (14), 106 (24). IR (KBr disk) 2941, 1731, 1271, 1249, 1130 cm^{-1}; anal. calcd for $C_{29}H_{39}O_5P$ (498.60): C, 68.42; H, 7.87; found C, 69.86; H, 7.88.

12b: $R_f = 0.57$ (ss B); NMR data (assigned from the 2:3 mixture of **12a** and **12b**): ^{31}P NMR (121 MHz, $CDCl_3$): δ 36.2; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4 (C-18), 19.3 (C-19), 20.6, 21.4 (3-OAc-CH_3), 22.7, 23.3, 24.7 (C-16), 27.7, 31.6 (C-8), 31.9, 36.6 (C-10), 36.9 (C-1), 38.1 (C-4), 38.6, 43.2 (C-13), 50.1 (C-9), 53.8 (d, $J = 7.5$ Hz, C-17), 55.7 (C-14), 71.7 (C-5′), 73.8 (C-3), 79.7 (C-4′), 122.1 (C-6), 127.5 (d, $J = 150.0$ Hz, C-1″), 128.5 and 128.7 (C-3″ and C-5″), 131.8 and 132.0 (C-2″ and C-6″), 132.1 (C-4″), 139.9 (C-5), 170.5 (3-OAc-C).

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