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New steroid-fused *P*-heterocycles
Part II. Synthesis and conformational study of oxazaphosphorino[16,17-*e*]estrone derivatives

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ABSTRACT

16β-Aminomethyl-17β-hydroxyestrone 3-methyl ether **6** and its *N*-propyl (**17**), *N*-benzyl (**18**) and *N*-arylmethyl derivatives (**19–22**) were subjected to ring closure reactions with phenylphosphonic dichloride in order to synthetize *P*-epimeric oxazaphosphorinanes **23a**, **24–29** in which the hetero ring is condensed to ring D of the sterane skeleton. The stereostructures of the products were evaluated by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The geometry was optimized by utilizing the B3LYP DFT method. The NMR spectral data and the results of the *ab initio* calculations demonstrated that the stereostructure of the hetero ring was strongly affected by the rigid sterane framework condensed to it, and the phosphoramidate ring proved to adopt predominantly a distorted-boat conformation, regardless of the *P*-configuration.

1. Introduction

Six-membered *P*-heterocycles, especially oxazaphosphorinane derivatives, have been subjected to intense research during the past few decades in consequence of their pharmacological activity and their unique conformational behavior. These hetero rings are of great significance since they are an integral structural part of the clinically widely used anticancer drug cyclophosphamide and its analogs. Accordingly, a number of similar compounds have been studied in order to acquire more information on the mode of action of these agents and to reveal certain structure–activity relationships [1–6].

As pointed out by *Bentrude* and others, the stereostructures of monocyclic oxazaphosphorinanes differ significantly from those of cyclohexanes: the *P* ring relatively easily adopts conformations other than a chair, depending on the substitution pattern. The conformational preference of these heterocycles

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is mainly influenced by the steric and electronic properties of the *P* substituent, the size of the group on the ring *N* atom and the *P*-configuration [7–12]. Earlier studies concentrated mainly on derivatives in which the *P* atom was substituted with OR [2,11], Cl [13,14] or NR_2 groups [2,8], though some *P*-Ph hetero rings [14–16] were also examined. Compounds with hydrogen, Ph [2,8], Bn [17,18] and different alkyl substituents [19] on the *N* atom were studied. The results obtained for the mono- and bicyclic ring systems indicated that the *P*-Ph and the *P*-*bis*(2-chloroethyl)amino groups prefer to occupy an equatorial position, while the *P*-OPh group tends to locate axially [20]; consequently, the chair conformer is often forced to adopt twist forms so as to be able to fulfill this preference. The steric repulsion between the *P* and *N* substituents [2,21] and anomeric effects, however, may modify the predominant conformation considerably [22].

Interest has recently shifted towards fused cycloalkane and heterocycle-condensed derivatives, and new questions have been raised concerning the bioactivity and conformational behavior of these compounds [14,15,17,23]. Although the cyclohexane and six-membered heterocycle-condensed oxazaphosphorinanes have been thoroughly studied, there are only a few examples of cyclopentane-fused derivatives [24,25].

As reported preliminarily, D-ring-fused *P*-Ph dioxaphosphorinane and oxazaphosphorinane derivatives were readily obtained from 17β-hydroxy-16β-hydroxymethylestrone 3-methyl ether and 17β-hydroxy-16β-aminomethylestrone 3-methyl ether with phenylphosphonic dichloride as epimeric mixtures [26]. Further investigations with different *P*-substituted dioxaphosphorinanes led to the conclusion that the conformational preferences of the fused hetero ring were significantly influenced by the rigid sterane framework.[2] The NMR measurements and *ab initio* calculations supported by single-crystal X-ray analysis revealed that the phosphonate ring of the *P*-Ph-substituted epimer **1a** (P=O *trans* to 17-H) exists in a distorted-boat conformation, with the Ph group in a pseudoaxial position both in solution and in the solid state (Fig. 1). An upfield shift of the 17-H signal generated by the anisotropic shielding effect of the aromatic ring, was noted in this case. The preference of the Ph group for the equatorial position was not strong enough to effect a conformational conversion. At the same time, the hetero ring of the corresponding epimer **1b** (P=O *cis* to 17-H) seemed to adopt predominantly a similar distorted-boat conformation with the *P* substituent in a pseudoequatorial position. The shift in the conformational equilibrium toward the distorted-boat conformer in **1a** and **1b** was explained by the rigidity of the fused sterane skeleton. Analogous results were found for the *P*-OPh dioxaphosphorinane derivatives.

We now report the synthesis and conformational analysis of novel oxazaphosphorino[*e*:16β,17β]estrone derivatives **23a**, **24**–**29**, all containing a *P*-Ph group, prepared via newly

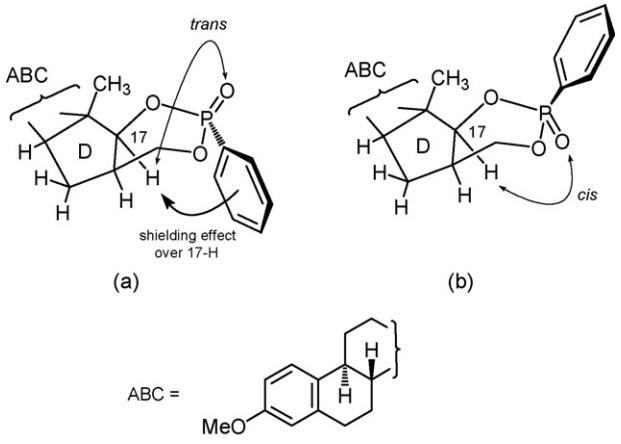


Fig. 1 – D-ring-fused dioxaphosphorinanes studied earlier (see footnote 2) [26].

described steroid intermediates **5**, **12**–**22**. Our aim was to investigate the epimeric ratios and the conformational preferences of the D-ring-fused *N*-unsubstituted (**23a**), *N*-Pr (**24**), *N*-Bn (**25**) and different *N*-arylmethyl (**26**–**29**) *P*-heterocycles as compared with the dioxaphosphorinane analog **1**. Steroid-condensed oxazaphosphorinane ring systems have not yet been studied, though they can also be important from a pharmacological aspect.

2. Experimental

2.1. General

The NMR spectra were recorded on a Bruker DRX 300, a Bruker DRX 400 or a Bruker DRX 500 spectrometer in $CDCl_3$, MeOD or DMSO-d_6 solution applying TMS (^{1}H and ^{13}C NMR) as an internal standard or 85% H_3PO_4 (^{31}P NMR) as an external standard. ^{13}C and ^{31}P NMR spectra were measured at 75 (or 100) MHz and 121 MHz, respectively. For determination of the ^{13}C NMR multiplicities, the APT pulse sequence was used. Chemical shifts (δ) are given in ppm, and coupling constants (J) in Hz. Mass spectra were obtained on Varian MAT 311A and VG-2ZAB instruments using electron ionization (EI), or fast atom bombardment (FAB), respectively. Melting points (Mps) were determined on a Kofler block and are uncorrected. The reactions were monitored by TLC on Kieselgel-G (Merck Si 254 F) layers (0.25 mm thick); flash chromatography: silica gel 60, 40–63 μm.

2.2. 3-Methoxy-16β-(N-benzylaminomethyl)estra-1,3,5(10)-trien-17-one (5)

Compound **3** [28,30] (600 mg, 2.00 mmol) was dissolved in benzylamine (10 mL), and 20% aqueous KOH (2 mL) was added. The mixture was stirred for 1 h at room temperature, and then poured into water (10 mL). The precipitate was filtered off, washed with water and dried to give **5** (687 mg, 85%) as a white solid. Mp 112-114 °C; R_f = 0.53 (MeOH/CH_2Cl_2 = 5/95); ^{1}H NMR (400 MHz, $CDCl_3$, δ [ppm]): 0.91 (s, 3H, 18-H_3), 2.84 (m, 1H, one of 16a-H_2), 2.92 (m, 2H, 6-H_2), 2.96 (m, 1H, the other

[2] Frank É, Körtvélyesi T, Czugler M, Mucsi Z, Keglevich Gy. New steroid-fused *P*-heterocycles. Part I. Synthesis and conformational study of dioxaphosphorino[16,17]estrone derivatives. Steroids 2007;72:437–45.

16a-H_2), 3.80 (s, 3H, 3-OMe), 3.83 (s, 2H, benzyl-H_2), 6.66 (d, 1H, J = 2.0 Hz, 4-H), 6.74 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz, 2-H), 6.97 (d, 1H, J = 8.4 Hz, 1-H), 7.27 (m, 1H, 4′-H), 7.34 (m, 4H, 2′-H, 3′-H, 5′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ [ppm]): 13.9 (C-18), 25.9 (CH_2), 26.7 (CH_2), 27.2 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 37.9 (CH), 44.1 (CH), 48.6 (C-13), 49.0 (CH), 49.5 (C-16), 51.0 and 54.0 (C-16a and benzyl-C), 55.2 (3-OMe), 111.5 (C-2), 113.9 (C-4), 126.2 (C-1), 126.9 (C-4′), 128.0 (2C) and 128.3 (2C): C-2′, C-3′, C-5′ and C-6′, 132.0 (C-10), 137.7 (C-5), 140.2 (C-1′), 157.6 (C-3), 221.9 (C-17); FAB-MS m/z (%): 404 (29) $[M+H]^+$, 120 (36), 91 (100), 77 (22); FAB-HRMS $(M+H)^+$ found: 404.2590 (4.3 ppm), requires: 404.2572.

2.3. *General procedure for the synthesis of benzylimino alcohols 12–16*

Compound **6** [29] (630 mg, 2.00 mmol) was suspended in absolute EtOH (30 mL) and benzaldehyde (**7**) or *para*-substituted benzaldehyde (**8–11**, 2 mmol) was added. The mixture was refluxed for 2 h under a nitrogen atmosphere, the solvent was then partially evaporated off, and the precipitate was filtered off and dried.

2.3.1. *3-Methoxy-16β-(benzyliminomethyl) estra-1,3,5(10)-trien-17β-ol* (**12**)

In the general procedure, benzaldehyde (**7**, 0.20 mL) was used. Imine **12** (720 mg, 89%) was obtained, as a pure product. Mp 145-147 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ [ppm]): 0.73 (s, 3H, 18-H_3), 2.73 (m, 2H, 6-H_2), 3.31 (t, 1H, J = 11.0 Hz, one of 16a-H_2), 3.67 (s, 3H, 3-OMe), 3.73 (dd-like m, 1H, 17-H), 3.96 (dd, 1H, J = 11.0 Hz, J = 4.0 Hz, the other 16a-H_2), 4.71 (d, J = 4.8 Hz, OH), 6.57 (d, 1H, J = 2.5 Hz, 4-H), 6.65 (dd, 1H, J = 8.5 Hz, J = 2.5 Hz, 2-H), 7.14 (d, 1H, J = 8.5 Hz, 1-H), 7.43 (m, 3H, 3′-H, 4′-H and 5′-H), 7.72 (dd-like m, 2H, 2′-H and 6′-H), 8.32 (s, 1H, imine-H). EI-MS (70 eV) m/z (%): 403 (68) $[M^+]$, 375 (22), 202 (14), 174 (66), 146 (100), 106 (48), 91 (44); FAB-HRMS $(M+H)^+$ found: 404.2573 (4.1 ppm), requires: 404.2590.

2.3.2. *3-Methoxy-16β-((4′-methylbenzylimino) methyl)estra-1,3,5(10)-trien-17β-ol* (**13**)

In the general procedure, 4-methylbenzaldehyde (**8**, 302 mg) was used. Imine **13** (626 mg, 75%) was obtained. Mp 156–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ [ppm]): 0.74 (s, 3H, 18-H_3), 2.34 (s, 3H, 4′-H_3), 2.75 (m, 2H, 6-H_2), 3.29 (m, 1H, one of 16a-H_2), 3.68 (s, 3H, 3-OMe), 3.74 (dd, 1H, J = 10.0 Hz, J = 4.8 Hz, 17-H), 3.94 (dd, 1H, J = 11.4 Hz, J = 4.3 Hz, the other 16a-H_2), 4.68 (d, 1H, J = 4.8 Hz, OH), 6.57 (d, 1H, J = 2.0 Hz, 4-H), 6.65 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz, 2-H), 7.14 (d, 1H, J = 8.4 Hz, 1-H), 7.22 (d, 2H, J = 8.0 Hz, 3′-H and 5′-H), 7.59 (d, 2H, J = 8.0 Hz, 2′-H and 6′-H), 8.27 (s, 1H, imine-H); EI-MS (70 eV) m/z (%): 417 (100) $[M^+]$, 389 (38), 188 (33), 160 (68), 120 (21), 105 (34), 91 (9); FAB-HRMS $(M+H)^+$ found: 418.2722 (5.7 ppm), requires: 418.2746.

2.3.3. *3-Methoxy-16β-((4′-fluorobenzylimino) methyl)estra-1,3,5(10)-trien-17β-ol* (**14**)

In the general procedure, 4-fluorobenzaldehyde (**9**, 0.22 mL) was used. Imine **14** (590 mg, 70%) was obtained. Mp 161–163 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ [ppm]): 0.74 (s, 3H, 18-H_3), 2.74 (m, 2H, 6-H_2), 3.30 (m, 1H, one of 16a-H_2), 3.68 (s, 3H, 3-OMe), 3.74 (dd, 1H, J = 10.0 Hz, J = 4.8 Hz, 17-H), 3.95 (dd, 1H, J = 11.4 Hz, J = 4.0 Hz, the other 16a-H_2), 4.68 (d, 1H, J = 4.8 Hz, OH), 6.58 (d, 1H, J = 2.5Hz, 4-H), 6.66 (dd, 1H, J = 8.5 Hz, J = 2.5 Hz, 2-H), 7.16 (d, 1H, J = 8.5 Hz, 1-H), 7.26 (d, 2H, J = 8.6. Hz, 3′-H and 5′-H), 7.78 (dd, 2H, J = 8.6 Hz, J = 5.8 Hz, 2′-H and 6′-H), 8.34 (s, 1H, imine-H); EI-MS (70 eV) m/z (%): 421 (86) $[M^+]$, 393 (27), 192 (50), 164 (100), 137 (46), 124 (54), 109 (47); FAB-HRMS $(M+H)^+$ found: 422.2477 (4.3 ppm), requires: 422.2495.

2.3.4. *3-Methoxy-16β-((4′-chlorobenzylimino)methyl) estra-1,3,5(10)-trien-17β-ol* (**15**)

In the general procedure, 4-chlorobenzaldehyde (**10**, 281 mg) was used. Imine **15** (700 mg, 80%) was obtained. Mp 151–153 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ [ppm]): 0.74 (s, 3H, 18-H_3), 2.74 (m, 2H, 6-H_2), 3.32 (m, 1H, one of 16a-H_2), 3.68 (s, 3H, 3-OMe), 3.74 (dd, 1H, J = 10.0 Hz, J = 4.7 Hz, 17-H), 3.97 (dd, 1H, J = 11.4 Hz, J = 4.4 Hz, the other 16a-H_2), 4.68 (d, 1H, J = 4.8 Hz, OH), 6.58 (d, 1H, J = 2.5 Hz, 4-H), 6.66 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz, 2-H), 7.16 (d, 1H, J = 8.6 Hz, 1-H), 7.50 (d, 2H, J = 8.4 Hz, 3′-H and 5′-H), 7.75 (d, 2H, J = 8.4 Hz, 2′-H and 6′-H), 8.34 (s, 1H, imine-H); EI-MS (70 eV) m/z (%): 439 (34) $[M^+]$, 437 (100) $[M^+]$, 409 (26), 408 (18), 284 (16), 208 (18), 180 (31); FAB-HRMS $(M+H)^+$ found: 438.2186 (3.2 ppm), requires: 438.2200.

2.3.5. *3-Methoxy-16β-((4′-nitrobenzylimino)methyl) estra-1,3,5(10)-trien-17β-ol* (**16**)

In the general procedure, 4-nitrobenzaldehyde (**11**, 151 mg) was used. Imine **16** (695 mg, 77%) was obtained. Mp 154–155 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ [ppm]): 0.74 (s, 3H, 18-H_3), 2.73 (m, 2H, 6-H_2), 3.36 (m, 1H, one of 16a-H_2), 3.67 (s, 3H, 3-OMe), 3.74 (d, 1H, J = 9.9 Hz, 17-H), 4.03 (dd, 1H, J = 11.4 Hz, J = 3.7 Hz, the other 16a-H_2), 4.74 (d, 1H, J = 4.8 Hz, OH), 6.57 (d, 1H, J = 2.4 Hz, 4-H), 6.65 (dd, 1H, J = 8.6 Hz, J = 2.4 Hz, 2-H), 7.14 (d, 1H, J = 8.6 Hz, 1-H), 7.98 (d, 2H, J = 8.7 Hz, 2′-H and 6′-H), 8.28 (d, 2H, J = 10.0 Hz, 3′-H and 5′-H), 8.49 (s, 1H, imine-H); EI-MS (70 eV) m/z (%): 448 (100) $[M^+]$, 267 (24), 265 (55), 240 (36), 219 (42), 191 (63), 164 (64), 147 (40), 117 (24), 91 (12); FAB-HRMS $(M+H)^+$ found: 449.2418 (5.0 ppm), requires: 449.2440.

2.4. *3-Methoxy-16β-(propylaminomethyl) estra-1,3,5(10)-trien-17β-ol* (**17**)

Compound **3** [28,30] (600 mg, 2.00 mmol) was dissolved in *n*-propylamine (5 mL) and 20% aqueous KOH (2 mL) was added. The mixture was stirred for 30 min at room temperature, then diluted with MeOH/THF = 1:1 (10 mL), and $NaBH_4$ (150 mg, 4 mmol) was added portionwise. After stirring for 2 h, the mixture was neutralized with dilute HCl and partially evaporated. The precipitate was filtered off, washed with water, and dried. The white solid was recrystallized from aqueous MeOH to give **17** (536 mg, 75%) in pure form. Mp 257–259 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ [ppm]): 0.69 (s, 3H, 18-H_3), 0.91 (t, 3H, J = 7.5 Hz, 3′-H_3), 1.64 (m, 2H, 2′-H_2), 2.78 (m, 2H, 6-H_2), 2.84 (m, 2H, 1′-H_2), 3.10 (dd, 1H, J = 12.4 Hz, J = 7.8 Hz) and 3.26 (d, 1H, J = 7.8 Hz): 16a-H_2, 3.69 (s, 3H, 3-OMe), 3.72 (d, 1H, J = 9.9 Hz, 17-H), 6.59 (d, 1H, J = 2.5 Hz, 4-H), 6.67 (dd, 1H, J = 8.5 Hz, J = 2.5 Hz, 2-H), 7.05 (d, 1H, J = 8.5 Hz, 1-H); FAB-MS m/z (%): 358 (51) $[M+H]^+$, 307 (23), 154 (100), 136 (76), 107 (26), 79 (25); FAB-HRMS $(M+H)^+$ found: 358.2746 (5.0 ppm), requires: 358.2728.

2.5. *General procedure for the synthesis of benzylamino alcohols 18–22*

Imino alcohol (**12–16**) (1.40 mmol) was dissolved in MeOH/THF = 1:2 (30 mL), and $NaBH_4$ (150 mg, 4 mmol) was added portionwise. After stirring for 2 h, the mixture was neutralized with dilute HCl and partially evaporated. The precipitate of the crude product (**18–22**, respectively) was collected, washed with water, and dried.

2.5.1. *3-Methoxy-16β-(benzylaminomethyl) estra-1,3,5(10)-trien-17β-ol (18)*

Method A (from **12**): In the general procedure, imino alcohol **12** (605 mg) was reduced to give **18** (466 mg, 82%), as a pure product.

Method B (from **5**): Compound **5** (687 mg, 1.70 mmol) was dissolved in MeOH/THF = 1:3 (40 mL) and $NaBH_4$ (100 mg, 2.67 mmol) was added portionwise. After stirring for 2 h, the mixture was neutralized with dilute HCl and partially evaporated. The precipitate was collected, washed with water, and dried to furnish **18** (565 mg, 82%). Mp 248–250 °C; ^{1}H NMR (400 MHz, MeOD, δ [ppm]): 0.77 (s, 3H, 18-H_3), 2.81 (m, 2H, 6-H_2), 3.01 (dd, 1H, J = 12.0 Hz, J = 5.2 Hz) and 3.25 (t, 1H, J = 12.0 Hz): 16a-H_2, 3.34 (bs, 1H, NH), 3.75 (s, 3H, 3-OMe), 3.89 (d, 1H, J = 9.7 Hz, 17-H), 4.19 (d, 1H, J = 13.2 Hz) and 4.29 (d, 1H, J = 13.2 Hz): benzyl-H_2, 6.61 (d, 1H, J = 2.3 Hz, 4-H), 6.68 (dd, 1H, J = 8.5 Hz, J = 2.3 Hz, 2-H), 7.16 (d, 1H, J = 8.5 Hz, 1-H), 7.19 (m, 3H, 2′-H, 4′-H and 6′-H), 7.34 (m, 2H, 3′-H and 5′-H); ^{13}C NMR (100 MHz, MeOD, δ [ppm]): 12.9 (C-18), 27.4 (CH_2), 28.6 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 37.3 (C-16), 38.4 (CH_2), 39.8 (CH), 45.1 (CH), 45.6 (C-13), 50.2 (CH), 50.9 (CH_2) and 52.2 (C-16a and benzyl-C), 55.6 (3-OMe), 82.1 (C-17), 112.6 (C-2), 114.7 (C-4), 127.2 (C-1), 130.3 (2C, C-2′ and C-6′), 130.6 (C-4′), 130.9 (2C, C-3′ and C-5′), 132.6 (C-10), 133.5 (C-1′), 138.8 (C-5), 159.0 (C-3); EI-MS (70 eV) m/z (%): 405 (9) [M^+], 314 (14), 121 (10), 120 (100), 106 (15), 91 (42); FAB-HRMS $(M+H)^+$ found: 406.2719 (6.7 ppm), requires: 406.2746.

2.5.2. *3-Methoxy-16β-((4′-methylbenzylamino) methyl)estra-1,3,5(10)-trien-17β-ol (19)*

In the general procedure, imino alcohol **13** (585 mg) was reduced to give **19** (575 mg, 98%), as a pure product. Mp 235–237 °C; ^{1}H NMR (400 MHz, MeOD, δ [ppm]): 0.79 (s, 3H, 18-H_3), 2.40 (s, 3H, 4′-H_3), 2.84 (m, 2H, 6-H_2), 3.01 (dd, 1H, J = 12.3 Hz, J = 5.2 Hz) and 3.25 (t, 1H, J = 12.3 Hz): 16a-H_2, 3.35 (bs, 1H, NH), 3.76 (s, 3H, 3-OMe), 3.91 (d, 1H, J = 9.7 Hz, 17-H), 4.17 (d, 1H, J = 13.2 Hz) and 4.26 (d, 1H, J = 13.2 Hz): benzyl-H_2, 6.62 (d, 1H, J = 2.6 Hz, 4-H), 6.68 (dd, 1H, J = 8.6 Hz, J = 2.6 Hz, 2-H), 7.18 (d, 1H, J = 8.6 Hz, 1-H), 7.30 (d, 2H, J = 8.0 Hz, 3′-H and 5′-H), 7.43 (d, 2H, J = 8.0 Hz, 2′-H and 6′-H); ^{13}C NMR (100 MHz, MeOD, δ [ppm]): 12.9 (C-18), 21.3 (4′-CH_3), 27.4 (CH_2), 28.6 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 37.3 (C-16), 38.4 (CH_2), 39.8 (CH), 45.2 (CH), 45.6 (C-13), 50.2 (CH), 50.7 (CH_2) and 51.9 (C-16a and benzyl-C), 55.6 (3-OMe), 82.0 (C-17), 112.6 (C-2), 114.7 (C-4), 127.2 (C-1), 129.5 (C-1′), 130.8 (2C) and 130.9 (2C): C-2′, C-3′, C-5′ and C-6′, 133.5 (C-10), 138.8 (C-5), 140.8 (C-4′), 159.0 (C-3); EI-MS (70 eV) m/z (%): 419 (14) [M^+], 314 (23), 134 (95), 105 (100); FAB-HRMS $(M+H)^+$ found: 420.2875 (6.6 ppm), requires: 420.2903.

2.5.3. *3-Methoxy-16β-((4′-fluorobenzylamino)methyl) estra-1,3,5(10)-trien-17β-ol (20)*

In the general procedure, imino alcohol **14** (590 mg) was reduced to furnish **20** (445 mg, 75%), as a pure product. Mp 254-258 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ [ppm]): 0.67 (s, 3H, 18-H_3), 2.61 (dd, 1H, J = 11.5, J = 7.1 Hz, one of 16a-H_2), 2.76 (m, 2H, 6-H_2), 2.91 (dd, 1H, J = 11.5 Hz, J = 8.3 Hz, the other 16a-H_2), 3.32 (bs, 1H, NH), 3.69 (s, 3H, 3-OMe), 3.88 (d, 1H, J = 14.0 Hz) and 3.92 (d, 1H, J = 14.0 Hz): benzyl-H_2, 6.60 (d, 1H, J = 2.5 Hz, 4-H), 6.67 (dd, 1H, J = 8.4 Hz, J = 2.5 Hz, 2-H), 7.15 (d, 1H, J = 8.4 Hz, 1-H), 7.20 (t, 2H, J = 8.8 Hz, 3′-H and 5′-H), 7.46 (t-like m, 2H, 2′-H and 6′-H); EI-MS (70 eV) m/z (%): 423 (12) [M^+], 314 (22), 138 (100), 109 (94); FAB-HRMS $(M+H)^+$ found: 424.2630 (5.1 ppm), requires: 424.2651.

2.5.4. *3-Methoxy-16β-((4′-chlorobenzylamino)methyl) estra-1,3,5(10)-trien-17β-ol (21)*

In the general procedure, imino alcohol **15** (613 mg) was reduced to give **21** (561 mg, 91%), as pure product. Mp 127–128 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ [ppm]): 0.69 (s, 3H, 18-H_3), 2.43 (dd-like m, 1H) and 2.69 (t-like m, 1H): 16a-H_2, 2.76 (m, 2H, 6-H_2), 3.66 (m, 3H): 17-H and benzyl-H_2, 3.68 (s, 3H, 3-OMe), 6.59 (d, 1H, J = 2.3 Hz, 4-H), 6.66 (dd, 1H, J = 8.4 Hz, J = 2.3 Hz, 2-H), 7.15 (d, 1H, J = 8.4 Hz, 1-H), 7.34 (m, 4H, 2′-H, 3′-H, 5′-H and 6′-H); EI-MS (70 eV) m/z (%): 441 (8) [M^+], 439 (20) [M^+], 314 (29), 156 (28), 154 (100), 125 (81); FAB-HRMS $(M+H)^+$ found: 440.2331 (5.8 ppm), requires: 440.2356.

2.5.5. *3-Methoxy-16β-((4′-nitrobenzylamino)methyl) estra-1,3,5(10)-trien-17β-ol (22)*

In the general procedure, imino alcohol **16** (628 mg) was reduced to give **22** (542 mg, 86%), as a pure product. Mp 242–245 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ [ppm]): 0.65 (s, 3H, 18-H_3), 2.77 (m, 3H, 6-H_2 and one of 16a-H_2), 3.14 (m, 1H, the other 16a-H_2), 3.69 (s, 3H, 3-OMe), 3.72 (d, 1H, J = 9.8 Hz, 17-H), 4.31 (m, 2H, benzyl-H_2), 6.59 (d, 1H, J = 2.3 Hz, 4-H), 6.67 (dd, 1H, J = 8.6 Hz, J = 2.3 Hz, 2-H), 7.16 (d, 1H, J = 8.6 Hz, 1-H), 7.88 (d, 2H, J = 8.6 Hz, 2′-H and 6′-H), 8.29 (d, 2H, J = 8.6 Hz, 3′-H and 5′-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ [ppm]): 12.6 (C-18), 26.3 (CH_2), 27.6 (CH_2), 29.8 (CH_2), 30.0 (CH_2), 37.8 (CH_2), 38.1 (CH), 38.7 (C-16), 43.8 (CH), 44.5 (C-13), 49.1 (CH), 52.4 and 53.0 (C-16a and benzyl-C), 55.2 (3-OMe), 82.4 (C-17), 111.4 (C-2), 113.8 (C-4), 123.7 (2C, C-3′ and C-5′), 126.3 (C-1), 128.7 (2C, C-2′ and C-6′), 132.6 (C-10), 137.8 (C-5), 146.8 and 147.2 (C-1′ and C-4′), 157.4 (C-3); EI-MS (70 eV) m/z (%): 450 (11) [M^+], 313 (11), 268 (10), 173 (9), 165 (100), 152 (18), 136 (31), 106 (13); FAB-HRMS $(M+H)^+$ found: 451.2567 (6.6 ppm), requires: 451.2597.

2.6. *(2′S*)-3-Methoxy-2′-oxo-2′-phenoxy[1′,3′,2′]oxaza-phosphorino[5′,6′-e:16β,17β]estra-1,3,5(10)-triene (23a)*

To a stirred suspension of compound **6** [29] (315 mg, 1.00 mmol) in CH_2Cl_2 (15 mL), Et_3N (0.5 mL, 5.00 mmol) and phenylphosphonic dichloride (0.15 mL, 1.00 mmol) were added at room temperature under a nitrogen atmosphere. The mixture was refluxed for 6 h and then left to stir overnight at room temperature. The solution was poured into water, and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4, and evaporated *in vacuo*. The crude

product was purified by column chromatography (silica gel, MeOH/EtOAc = 10:90 v/v), to give **23a** (66 mg, 15%), as a single epimer. Mp 248–250 °C; R_f = 0.74 (MeOH/EtOAc = 10:90); ^{1}H NMR (400 MHz, $CDCl_3$, δ [ppm]): 1.01 (s, 3H, 18-H_3), 2.56 (m, 1H, 16-H), 2.85 (m, 2H, 6-H_2), 3.32 (m, 1H) and 3.38 (m, 1H): 16a-H_2, 3.76 (s, 3H, 3-OMe), 3.85 (dd, 1H, J = 9.5 Hz, J = 1.1 Hz, 17-H), 6.61 (d, 1H, J = 2.6 Hz, 4-H), 6.69 (dd, 1H, J = 8.6 Hz, J = 2.6 Hz, 2-H), 7.16 (d, 1H, J = 8.6 Hz, 1-H), 7.46 (m, 2H, 3′-H and 5′-H), 7.53 (m, 1H, 4′-H), 7.89 (m, 2H, 2′-H and 6′-H); FAB-MS *m*/*z* (%): 438 (21) $[M+H]^+$, 307 (17), 154 (100), 136 (81), 107 (31), 91 (22), 77 (34); FAB-HRMS $(M+H)^+$ found: 438.2198 (5.7 ppm), requires: 438.2173.

2.7. 3-Methoxy-2′-oxo-2′-phenoxy-3′-propyl[1′,3′,2′] oxazaphosphorino[5′,6′-e:16β,17β]estra-1,3,5(10)-triene (24)

To a stirred suspension of compound **17** (250 mg, 0.70 mmol) in CH_2Cl_2 (15 mL), Et_3N (0.5 mL, 5.00 mmol) and phenylphosphonic dichloride (0.10 mL, 0.70 mmol) were added at room temperature under a nitrogen atmosphere. The mixture was refluxed for 6 h and then left to stir overnight at room temperature. The solution was poured into water, and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4, and evaporated *in vacuo*. The crude product (**24a**:**24b** = ca. 3:2 by ^{1}H NMR) was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2 = 20:80 v/v) to give **24a** (80 mg, 17%) as the fast-eluting diastereomer. The less mobile epimer was identified as isomer **24b** (86 mg, 18%), with **24a** as a minor impurity (ca. 3:1 by ^{1}H NMR).

24a: R_f = 0.43 (EtOAc/CH_2Cl_2 = 20:80); NMR data (assigned from a 5:1 mixture of **24a** and **24b**): ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 18.9; ^{1}H NMR (500 MHz, $CDCl_3$, δ [ppm]): 0.83 (t, 3H, J = 7.4 Hz, propyl-H_3), 0.99 (s, 3H, 18-H_3), 2.66 (m, 1H, 16-H), 2.87 (m, 2H, 6-H_2), 3.12 (m, 1H) and 3.42 (m, 1H): 16a-H_2, 3.76 (s, 3H, 3-OMe), 3.83 (d, 1H, J = 9.6 Hz, 17-H), 6.61 (d, 1H, J = 2.6 Hz, 4-H), 6.69 (dd, 1H, J = 8.5 Hz, J = 2.6 Hz, 2-H), 7.15 (d, 1H, J = 8.5 Hz, 1-H), 7.48 (m, 2H, 3′-H and 5′-H), 7.54 (m, 1H, 4′-H), 7.85 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ [ppm]): 11.3 (propyl-CH_3), 13.3 (C-18), 22.2 (propyl-CH_2), 26.0 (CH_2), 27.5 (CH_2), 28.8 (CH_2), 29.7 (CH_2), 37.5 (CH_2), 38.0 (CH), 39.5 (C-16), 43.8 (CH), 44.8 (d, J = 7.1 Hz, C-13), 49.2 (CH), 49.5 (N-CH_2), 50.2 (C-16a), 55.2 (3-OMe), 86.8 (d, J = 9.2 Hz, C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 128.3 and 128.5 (C-3′ and C-5′), 130.7 (d, J = 192.8 Hz, C-1′), 131.6 (d, J = 2.8 Hz, C-10), 132.0 (C-4′), 132.4 and 132.5 (C-2′ and C-6′), 137.6 (C-5), 157.5 (C-3). FAB-MS *m*/*z* (%): 480 (50) $[M+H]^+$.

24b: R_f = 0.41 (EtOAc/CH_2Cl_2 = 20:80); NMR data (assigned from a 1:3 mixture of **24a** and **24b**): ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 18.4; ^{1}H NMR (500 MHz, $CDCl_3$, δ [ppm]): 0.76 (t, 3H, J = 7.4 Hz, propyl-H_3), 0.94 (s, 3H, 18-H_3), 2.81 (m, 1H, 16-H), 2.87 (m, 2H, 6-H_2), 3.02 (m, 1H) and 3.24 (m, 1H): 16a-H_2, 3.77 (s, 3H, 3-OMe), 4.47 (dd, 1H, J = 9.6 Hz, J = 1.4 Hz, 17-H), 6.63 (d, 1H, J = 2.6 Hz, 4-H), 6.70 (dd, 1H, J = 8.6 Hz, J = 2.6 Hz, 2-H), 7.19 (d, 1H, J = 8.6 Hz, 1-H), 7.43 (m, 2H, 3′-H and 5′-H), 7.54 (m, 1H, 4′-H), 7.82 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ [ppm]): 11.2 (propyl-CH_3), 13.6 (C-18), 22.6 (propyl-CH_2), 26.1 (CH_2), 27.6 (CH_2), 28.6 (CH_2), 29.7 (CH_2), 37.5 (CH_2), 38.0 (CH), 41.0 (C-16), 43.7 (CH), 45.3 (d, J = 8.3 Hz, C-13), 48.8 (CH), 49.3 (N-CH_2), 49.5 (C-16a), 55.2 (3-OMe), 84.0 (d, J = 6.8 Hz, C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 128.1 (CH), 130.0 (d, J = 181.2 Hz, C-1″), 131.3 (CH), 131.4 (CH), 131.6 (d, J = 2.8 Hz, C-10), 131.7 (CH), 131.9 (C-4″), 137.7 (C-5), 157.5 (C-3).

2.8. General procedure for the synthesis of N-arylmethyl oxazaphosphorinane derivatives (26-29)

To a stirred suspension of *p*-arylamino derivative (**19**–**22**) (1.00 mmol), Et_3N (0.3 mL, 3.00 mmol) and phenylphosphonic dichloride (0.15 mL, 1.00 mmol) were added at room temperature under a nitrogen atmosphere. The mixture was refluxed for 4 h and then left to stir overnight at room temperature. The solution was poured into water, and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4, and evaporated *in vacuo*. The crude product (**26**–**29**, respectively) was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2 = 20:80 v/v).

2.8.1. 3-Methoxy-3′-(4″-methylbenzyl)-2′-oxo-2′-phenoxy[1′,3′,2′]oxazaphosphorino[5′,6′-e:16β,17β] estra-1,3,5(10)-triene (26)

In the general procedure, amino alcohol **19** (420 mg) was used. After purification of the crude product (**26a**:**26b** = ca. 3:2 by ^{1}H NMR), compound **26a** (148 mg, 27%) as the fast-eluting diastereomer was obtained. The less mobile epimer was identified as isomer **26b** (150 mg, 28%), with **26a** as a minor impurity (ca. 3:1 by ^{1}H NMR).

26a: Mp 182–184 °C; R_f = 0.43 (EtOAc/CH_2Cl_2 = 20:80); ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 19.4; ^{1}H NMR (400 MHz, $CDCl_3$, δ [ppm]): 0.97 (s, 3H, 18-H_3), 2.33 (s, 3H, 4″-CH_3), 2.64 (m, 1H, 16-H), 2.81 (m, 2H, 6-H_2), 3.02 (m, 1H) and 3.19 (m, 1H): 16a-H_2, 3.75 (s, 3H, 3-OMe), 3.92 (d, 1H, J = 9.7 Hz, 17-H), 4.08 (m, 2H, benzyl-H_2), 6.61 (d, 1H, J = 2.5 Hz, 4-H), 6.68 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz, 2-H), 7.16 (d, 1H, J = 8.6 Hz, 1-H), 7.25 (d, 2H, J = 8.1 Hz, 3″-H and 5″-H), 7.25 (d, 2H, J = 8.1 Hz, 2″-H and 6″-H), 7.52 (m, 3H, 3′-H, 4′-H and 5′-H), 7.93 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ [ppm]): 13.2 (C-18), 21.1 (4″-CH_3), 26.0 (CH_2), 27.5 (CH_2), 28.9 (CH_2), 29.6 (CH_2), 37.4 (CH_2), 38.0 (CH), 39.0 (C-16), 43.7 (CH), 44.8 (d, J = 6.8 Hz, C-13), 49.0 (benzyl-CH_2), 49.1 (CH), 50.6 (d, J = 4.5 Hz, C-16a), 55.1 (3-OMe), 87.1 (d, J = 9.5 Hz, C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 128.2 (C-4′), 128.4 (2C, C-3″ and C-5″), 129.1 (2C, C-2″ and C-6″), 130.6 (d, J = 183.1 Hz, C-1′), 132.0 (2C, C-3′ and C-5′), 132.1 (C-4″), 132.3 (d, 2C, J = 9.9 Hz, C-2′ and C-6′), 134.3 (d, J = 4.9 Hz, C-1″), 137.1 (C-10), 137.6 (C-5), 158.0 (C-3); EI-MS (70 eV) *m*/*z* (%): 541 (100) $[M^+]$, 400 (60), 260 (48), 105 (32); FAB-HRMS $(M+H)^+$ found: 542.2824 (4.3 ppm), requires: 542.2801.

26b: R_f = 0.41 (EtOAc/CH_2Cl_2 = 20:80); NMR data (assigned from a 1:3 mixture of **26a** and **26b**): ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 18.5; ^{1}H NMR (400 MHz, $CDCl_3$, δ [ppm]): 0.94 (s, 3H, 18-H_3), 2.30 (s, 3H, 4″-CH_3), 2.65 (m, 1H, 16-H), 2.81 (m, 2H, 6-H_2), 2.96 (m, 1H) and 3.09 (m, 1H): 16a-H_2, 3.76 (s, 3H, 3-OMe), 4.00 (m, 1H) and 4.16 (m, 1H, benzyl-H_2), 4.51 (d, J = 9.6 Hz, 17-H), 6.61 (m, 1H, J = 2.5 Hz, 4-H), 6.70 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz, 2-H), 7.18 (d, 1H, J = 8.6 Hz, 1-H), 7.17 (m, 2H), 7.26 (m, 2H), 7.48 (m, 3H), 7.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ [ppm]): 13.5 (C-18), 21.1 (4″-CH_3), 26.1 (CH_2), 27.5 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 37.5 (CH_2), 38.0 (CH), 40.5 (d, J = 3.9 Hz, C-16), 43.6 (CH), 45.1 (d, J = 8.2 Hz, C-13), 48.8 (CH), 49.0 (benzyl-CH_2), 50.3 (d, J = 5.9 Hz, C-16a), 55.1 (3-OMe), 84.1 (d, J = 7.8 Hz, C-17), 111.5 (C-2), 113.8

(C-4), 126.3 (C-1), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.0 (CH), 131.4 (d, J = 254.7 Hz, C-1′), 131.3 (2C, C-2″ and C-6″), 131.7 (2C, C-3″ and C-5″), 132.1 (d, J = 180.1 Hz, C-1′), 132.2 (C-4″), 135.2 (d, J = 3.3 Hz, C-1″), 136.9 (C-10), 137.6 (C-5), 157.5 (C-3).

2.8.2. 3-Methoxy-3′-(4″-fluorobenzyl)-2′-oxo-2′-phenoxy[1′,3′,2′]oxazaphosphorino[5′,6′-e:16β,17β] estra-1,3,5(10)-triene (27)

In the general procedure, amino alcohol **20** (424 mg) was used. After purification of the crude product (**27a**:**27b** = ca. 3:2 by ^{1}H NMR), compound **27a** (127 mg, 23%) as the fast-eluting diastereomer was obtained. The less mobile epimer was identified as isomer **27b** (168 mg, 31%), with **27a** as a minor impurity (ca. 3:1 by ^{1}H NMR). With 2 equiv. of $PhP(O)Cl_2$, **27a** (236 mg, 43%) and **27b** (222 mg, 41%), latter with **27a** as a minor impurity (ca. 4:1 by ^{1}H NMR), were obtained.

27a: Mp 187–190 °C; R_f = 0.46 (EtOAc/CH_2Cl_2 = 20:80); ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 19.3; ^{1}H NMR (400 MHz, $CDCl_3$, δ [ppm]): 0.97 (s, 3H, 18-H_3), 2.64 (m, 1H, 16-H), 2.84 (m, 2H, 6-H_2), 3.00 (m, 1H) and 3.19 (m, 1H): 16a-H_2, 3.75 (s, 3H, 3-OMe), 3.92 (d, 1H, J = 9.7 Hz, 17-H), 4.18 (m, 2H, benzyl-H_2), 6.60 (d, 1H, J = 2.6 Hz, 4-H), 6.69 (dd, 1H, J = 8.6 Hz, J = 2.6 Hz, 2-H), 7.00 (t, 2H, J = 8.6 Hz, 3″-H and 5″-H), 7.18 (d, J = 8.6 Hz, 1-H), 7.36 (m, 2H, 2″-H and 6″-H), 7.54 (m, 3H, 3′-H, 4′-H and 5′-H), 7.92 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ [ppm]): 13.3 (C-18), 26.0 (CH_2), 27.5 (CH_2), 28.9 (CH_2), 29.6 (CH_2), 37.4 (CH_2), 38.0 (CH), 38.9 (C-16), 43.7 (CH), 44.8 (d, J = 6.7 Hz, C-13), 49.1 (CH), 49.4 (benzyl-CH_2), 50.4 (d, J = 4.4 Hz, C-16a), 55.2 (3-OMe), 87.1 (d, J = 9.4 Hz, C-17), 111.5 (C-2), 113.8 (C-4), 115.3 (d, 2C, J = 21.2 Hz, C-3″ and C-5″), 126.3 (C-1), 128.5 (d, 2C, J = 15.9 Hz, C-2″ and C-6″), 130.0 (d, 2C, J = 8.0 Hz, C-3′ and C-5′), 130.4 (d, J = 148.4 Hz, C-1′), 132.1 (C-4′), 132.2 (C-1″), 132.3 (d, 2C, J = 10.0 Hz, C-2′ and C-6′), 134.0 (C-10), 137.7 (C-5), 157.5 (C-3), 163.5 (C-4″); FAB-MS m/z (%): 546 (38) $[M+H]^+$, 154 (100), 136 (67), 109 (45), 77 (30); FAB-HRMS $(M+H)^+$ found: 546.2573 (3.5 ppm), requires: 546.2554.

27b: R_f = 0.44 (EtOAc/CH_2Cl_2 = 20:80); NMR data (assigned from a 1:4 mixture of **27a** and **27b**): ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 18.4; ^{1}H NMR (400 MHz, $CDCl_3$, δ [ppm]): 0.95 (s, 3H, 18-H_3), 2.64 (m, 1H, 16-H), 2.84 (m, 2H, 6-H_2), 2.93 (m, 1H) and 3.16 (m, 1H): 16a-H_2, 3.76 (s, 3H, 3-OMe), 3.98 (m, 2H, benzyl-H_2), 4.50 (dd, 1H, J = 9.6 Hz, J = 1.4 Hz, 17-H), 6.61 (d, 1H, J = 2.6 Hz, 4-H), 6.70 (dd, 1H, J = 8.5 Hz, J = 2.6 Hz, 2-H), 6.94 (t, J = 8.6 Hz, 3″-H and 5″-H), 7.20 (d, J = 8.6 Hz, 1-H), 7.23 (m, 2H, 2″-H and 6″-H), 7.46 (m, 3H, 3′-H, 4′-H and 5′-H), 7.85 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ [ppm]): 13.6 (C-18), 26.1 (CH_2), 27.6 (CH_2), 28.6 (CH_2), 29.7 (CH_2), 37.5 (CH_2), 38.0 (CH), 40.6 (d, J = 4.0 Hz, C-16), 43.6 (CH), 45.1 (d, J = 7.8 Hz, C-13), 48.8 (CH), 49.3 (benzyl-CH_2), 50.0 (d, J = 5.8 Hz, C-16a), 55.2 (3-OMe), 84.2 (d, J = 7.8 Hz, C-17), 111.5 (C-2), 113.8 (C-4), 115.2 (d, 2C, J = 21.4 Hz, C-3″ and C-5″), 126.3 (C-1), 128.4 (d, 2C, J = 15.2 Hz, C-2″ and C-6″), 129.8 (d, 2C, J = 7.9 Hz, C-3′ and C-5′), 130.3 (d, J = 148.9 Hz, C-1′), 131.3 (d, 2C, J = 9.6 Hz, C-2′ and C-6′), 131.8 (C-4′), 132.2 (C-1″), 134.1 (C-10), 137.6 (C-5), 157.5 (C-3), 163.4 (C-4″).

2.8.3. 3-Methoxy-3′-(4″-chlorobenzyl)-2′-oxo-2′-phenoxy[1′,3′,2′]oxazaphosphorino[5′,6′-e:16β,17β] estra-1,3,5(10)-triene (28)

In the general procedure, amino alcohol **21** (440 mg) was used. After purification of the crude product (**28a**:**28b** = ca. 3:2 by ^{1}H NMR), compound **28a** (194 mg, 35%) as the fast-eluting diastereomer was obtained. The less mobile epimer was identified as isomer **28b** (121 mg, 21%).

28a: Mp 242–245 °C; R_f = 0.59 (EtOAc/CH_2Cl_2 = 20:80); ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 19.4; ^{1}H NMR (300 MHz, $CDCl_3$, δ [ppm]): 0.97 (s, 3H, 18-H_3), 2.64 (m, 1H, 16-H), 2.83 (m, 2H, 6-H_2), 2.96 (m, 1H) and 3.20 (m, 1H): 16a-H_2, 3.76 (s, 3H, 3-OMe), 3.92 (dd, 1H, J = 9.6 Hz, J = 0.9 Hz, 17-H), 4.02 (m, 1H) and 4.15 (m, 1H): benzyl-H_2, 6.60 (d, 1H, J = 2.7 Hz, 4-H), 6.69 (dd, 1H, J = 8.4 Hz, J = 2.7 Hz, 2-H), 7.16 (d, 1H, J = 8.4 Hz, 1-H), 7.28-7.36 (m, 4H, 2″-H, 3″-H, 5″-H and 6″-H), 7.54 (m, 3H, 4′-H, 3′-H és 5′-H), 7.90 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ [ppm]): 13.3 (C-18), 26.0 (CH_2), 27.5 (CH_2), 28.9 (CH_2), 29.6 (CH_2), 37.4 (CH_2), 38.0 (CH), 39.0 (d, J = 2.2 Hz, C-16), 43.7 (CH_2), 44.9 (d, J = 6.9 Hz, C-13), 49.3 (CH), 49.5 (d, J = 2.0 Hz, benzyl-CH_2), 50.5 (d, J = 5.1 Hz, C-16a), 55.2 (3-OMe), 87.2 (d, J = 9.5 Hz, C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 128.6 (d, 2C, J = 13.4 Hz, C-2′ and C-6′), 128.7 (2C, C-3″ and C-5″), 129.9 (2C, C-2″ and C-6″), 130.6 (d, J = 217.5 Hz, C-1′), 132.0 (C-4″), 132.2 (d, J = 2.9 Hz, C-4′), 132.3 (d, 2C, J = 10.1 Hz, C-3′ and C-5′), 133.3 (C-1″), 136.1 (d, J = 4.2 Hz, C-10), 137.6 (C-5), 157.5 (C-3); FAB-MS m/z (%): 562 (22) $[M+H]^+$, 154 (100), 136 (78), 107 (33), 69 (41); FAB-HRMS $(M+H)^+$ found: 562.2252 (4.6 ppm), requires: 562.2278.

28b: Mp 188–190 °C; R_f = 0.53 (EtOAc/CH_2Cl_2 = 20:80); ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 18.4; ^{1}H NMR (300 MHz, $CDCl_3$, δ [ppm]): 0.96 (s, 3H, 18-H_3), 2.65 (m, 1H, 16-H), 2.84 (m, 2H, 6-H_2), 2.94 (m, 1H) and 3.17 (m, 1H): 16a-H_2, 3.77 (s, 3H, 3-OMe), 3.97 (m, 1H) and 4.19 (m, 1H): benzyl-H_2, 4.51 (dd, 1H, J = 9.9 Hz, J = 1.5 Hz, 17-H), 6.62 (d, 1H, J = 2.7 Hz, 4-H), 6.70 (dd, 1H, J = 8.4 Hz, J = 2.7 Hz, 2-H), 7.19 (d, 1H, J = 8.4 Hz, 1-H), 7.22 (m, 3H), 7.31 (m, 1H), 7.54 (m, 3H), 7.87 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ [ppm]): 13.6 (C-18), 26.1 (CH_2), 27.6 (CH_2), 28.6 (CH_2), 29.7 (CH_2), 37.5 (CH_2), 38.0 (CH), 40.7 (d, J = 4.4 Hz, C-16), 43.7 (CH_2), 45.2 (d, J = 7.7 Hz, C-13), 48.7 (CH), 49.4 (d, J = 3.5 Hz, benzyl-CH_2), 50.2 (d, J = 6.2 Hz, C-16a), 55.2 (3-OMe), 84.2 (d, J = 8.1 Hz, C-17), 111.5 (C-2), 113.9 (C-4), 126.3 (C-1), 128.4 (d, 2C, J = 15.9 Hz, C-2′ and C-6′), 128.6 (2C, C-3″ and C-5″), 129.6 (2C, C-2″ and C-6″), 131.4 (d, 2C, J = 9.6 Hz, C-3′ and C-5′), 131.8 (d, J = 179.9 Hz, C-1′), 131.9 (d, J = 2.9 Hz, C-4′), 132.2 (C-4″), 133.2 (C-1″), 137.0 (d, J = 4.0 Hz, C-10), 137.6 (C-5), 157.6 (C-3); FAB-MS m/z (%): 562 (21) $[M+H]^+$, 307 (26), 154 (100), 136 (85), 107 (37), 91 (35); FAB-HRMS $(M+H)^+$ found: 562.2252 (4.6 ppm), requires: 562.2278.

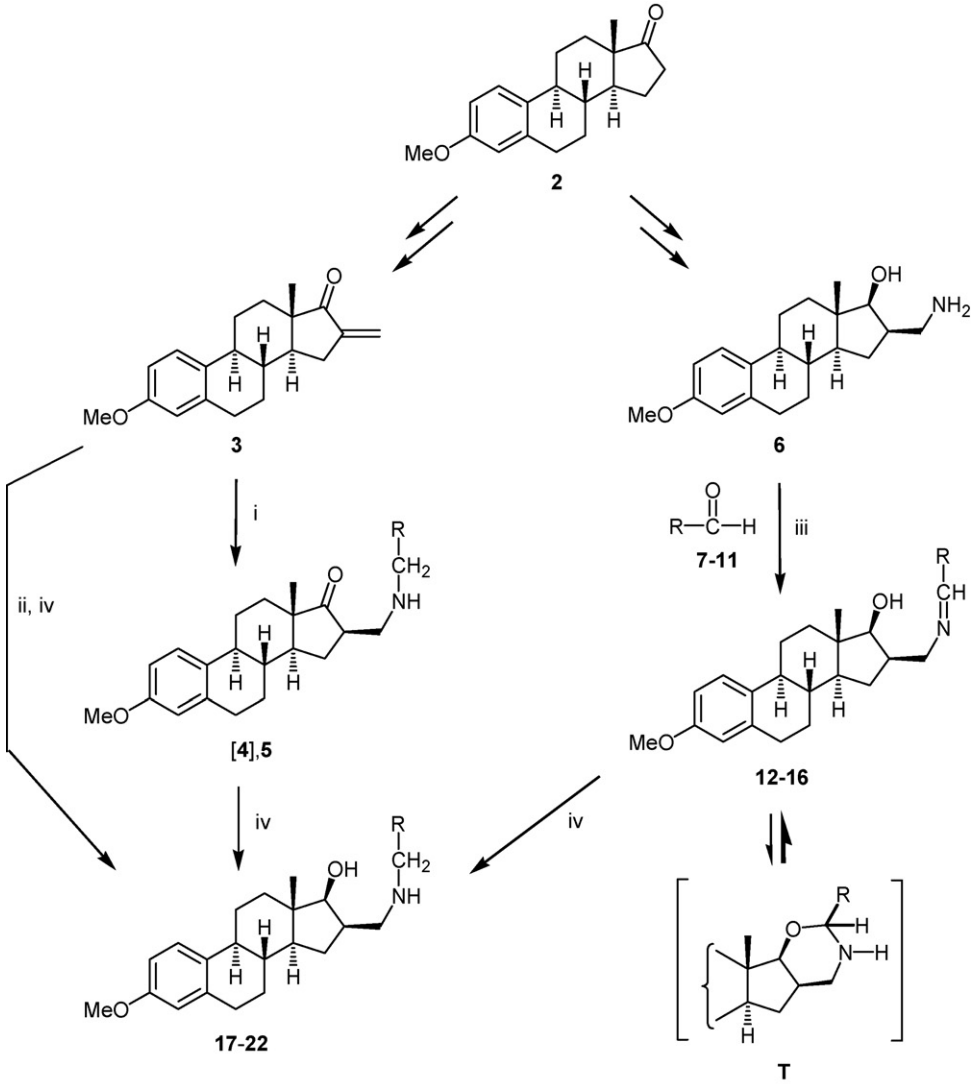
2.8.4. 3-Methoxy-3′-(4″-nitrobenzyl)-2′-oxo-2′-phenoxy[1′,3′,2′]oxazaphosphorino[5′,6′-e:16β,17β] estra-1,3,5(10)-triene (29)

In the general procedure, amino alcohol **22** (451 mg) was used. After purification of the crude product (**29a**:**29b** = ca. 3:2 by ^{1}H NMR), compound **29a** (162 mg, 28%) as the fast-eluting diastereomer was obtained. The less mobile epimer was identified as isomer **29b** (96 mg, 17%).

29a: Mp 266–269 °C; R_f = 0.43 (EtOAc/CH_2Cl_2 = 20:80); ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 19.3; ^{1}H NMR (400 MHz, $CDCl_3$, δ [ppm]): 0.98 (s, 3H, 18-H_3), 2.70 (m, 1H, 16-H), 2.83 (m, 2H, 6-H_2), 2.96 (m, 1H) and 3.26 (m, 1H): 16a-H_2, 3.76 (s, 3H, 3-OMe), 3.95 (d, 1H, J = 9.6 Hz, 17-H), 4.13 (m, 1H) and 4.32 (m, 1H): benzyl-H_2, 6.60 (d, 1H, J = 2.4 Hz, 4-H), 6.69 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz, 2-H), 7.16 (d, 1H, J = 8.8 Hz, 1-H), 7.52 (m, 2H), 7.58

(m, 3H), 7.90 (m, 2H), 8.18 (d, 2H, J = 8.8 Hz, 3″-H és 5″-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ [ppm]): 13.3 (C-18), 26.0 (CH_2), 27.5 (CH_2), 28.8 (CH_2), 29.6 (CH_2), 37.3 (CH_2), 37.9 (CH), 38.8 (d, J = 2.0 Hz, C-16), 43.7 (CH), 44.8 (d, J = 7.1 Hz, C-13), 49.1 (CH), 50.3 (d, J = 2.3 Hz, benzyl-CH_2), 50.9 (d, J = 5.3 Hz, C-16a), 55.1 (3-OMe), 87.3 (d, J = 9.6 Hz, C-17), 111.5 (C-2), 113.8 (C-4), 123.8 (2C, C-3″ and C-5″) 126.2 (C-1), 128.7 (d, 2C, J = 14.4 Hz, C-2′ and C-6′), 129.1 (2C, C-2″ and C-6″), 129.8 (d, J = 174.5 Hz, C-1′), 132.0 (C-1″), 132.2 (d, 2C, J = 10.2 Hz, C-3′ and C-5′), 132.4 (d, J = 2.9 Hz, C-4′), 137.5 (C-4″), 145.2 (d, J = 3.3 Hz, C-10), 147.5 (C-5), 157.5 (C-3); EI-MS (70 eV) m/z (%): 572 (100) [M$^+$], 436 (46), 304 (50), 268 (64), 173 (50), 165 (70), 136 (40); FAB-MS m/z (%): 573 (52) [M + H]$^+$, 305 (24), 154 (100), 138 (94), 107 (38), 77 (36). FAB-HRMS (M + H)$^+$ found: 573.2518 (4.1 ppm), requires: 573.2495.

29b: Mp 221–224 °C; R_f = 0.41 (EtOAc/CH_2Cl_2 = 20:80); ^{31}P NMR (121 MHz, $CDCl_3$, δ [ppm]): 18.5; ^{1}H NMR (400 MHz, $CDCl_3$, δ [ppm]): 0.99 (s, 3H, 18-H_3), 2.69 (m, 1H, 16-H), 2.84 (m, 2H, 6-H_2), 2.92 (m, 1H) and 3.27 (m, 1H): 16a-H_2, 3.78 (s, 3H, 3-OMe), 4.15 (m, 1H) and 4.30 (m, 1H): benzyl-H_2, 4.55 (dd, 1H, J = 9.6 Hz, J = 1.3 Hz 17-H), 6.63 (d, 1H, J = 2.5 Hz, 4-H), 6.72 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz, 2-H), 7.20 (d, 1H, J = 8.6 Hz, 1-H), 7.46 (d,



	R
4, **17**	Et
5, **7**, **12**, **18**	Ph
8, **13**, **19**	*p*-CH_3-C_6H_4
9, **14**, **20**	*p*-F-C_6H_4
10, **15**, **21**	*p*-Cl-C_6H_4
11, **16**, **22**	*p*-NO_2-C_6H_4

Scheme 1 – Reagents and conditions: (i) $BnNH_2$, KOH, rt, 1 h; (ii) $PrNH_2$, KOH, rt, 30 min; (iii) abs. EtOH, 78 °C, 2 h, N_2 atm; (iv) $NaBH_4$, THF/MeOH, rt, 2 h.

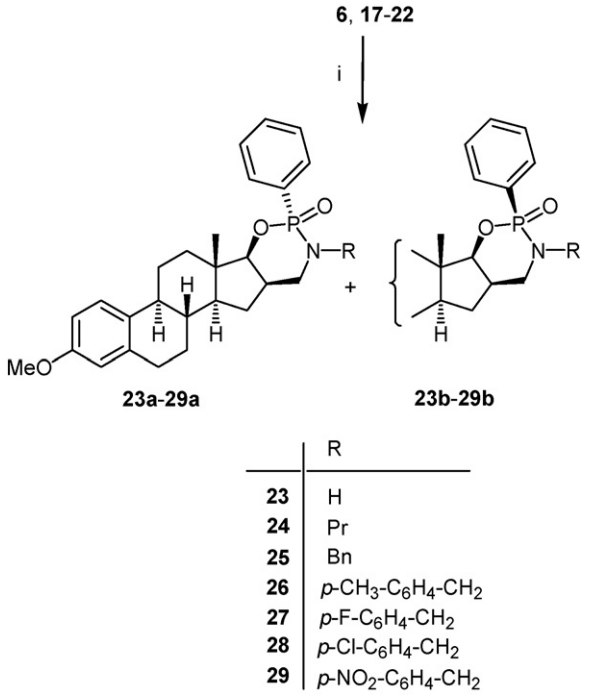
2H, J = 8.6 Hz, 2″-H and 6″-H), 7.50 (m, 2H), 7.56 (m, 1H), 7.87 (m, 2H), 8.13 (d, 2H, J = 8.6 Hz, 3″-H and 5″-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ [ppm]): 13.5 (C-18), 26.1 (CH_2), 27.5 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 37.4 (CH_2), 38.0 (CH), 40.6 (d, J = 3.8 Hz, C-16), 43.6 (CH), 45.1 (d, J = 7.3 Hz, C-13), 48.7 (CH), 50.0 (d, J = 1.7 Hz, benzyl-CH_2), 50,4 (d, J = 6.2 Hz, C-16a), 55.2 (3-OMe), 84.2 (d, J = 8.3 Hz, C-17), 111.5 (C-2), 113.8 (C-4), 123.7 (2C, C-3″ and C-5″), 126.3 (C-1), 128.5 (d, 2C, J = 14.8 Hz, C-2′ and C-6′), 128.8 (2C, C-2″ and C-6″), 130.1 (d, J = 175.0 Hz, C-1′), 132.2 (d, 2C, J = 9.5 Hz, C-3′ and C-5′), 132.1 (C-4′), 132.7 (C-1″), 137.6 (C-4″), 146.3 (d, J = 2.8 Hz, C-10), 147.3 (C-5), 157.5 (C-3); EI-MS (70 eV) m/z (%): 572 (94) [M^+], 268 (100); FAB-MS m/z (%): 573 (21) [$M+H]^+$, 215 (79), 201 (100), 69 (55); FAB-HRMS $(M+H)^+$ found: 573.2518 (3.9 ppm), requires: 573.2496.

3. Results and discussion

3.1. Synthetic studies

For the phosphorylation reactions, first the amino alcohols **6** and **17–22** were synthetized (Scheme 1). 17β-Hydroxy-16β-aminomethylestrone 3-methyl ether **6** was obtained from estrone 3-methyl ether **2** in several steps according to the procedures described in the literature [27–29]. For comparison of the cyclization propensities, **6** containing a primary amino function, and *N*-substituted secondary amines such as *N*-Pr (**17**), *N*-Bn (**18**) and different *N*-arylmethyl **19–22** derivatives were also prepared. Compound **17** was synthetized from 16-methylidene-estrone 3-methyl ether **3** [28,30] via the 1,4-addition of *n*-propylamine and the *in situ* reduction of the C-17 keto group in intermediate **4**. Although Michael adducts of this type are sensitive and exhibit a great tendency to undergo the retro-type reaction in solution,[3] the benzylamino derivative **5** could be isolated during the reaction of **3** with benzylamine. The subsequent reduction with $NaBH_4$ led to the benzylamino alcohol **18** in high yield. The addition of both amines to the double bond of **3**, and the following reductions of **4** and **5**, occurred in a stereoselective manner, leading to 16β, 17β-substituted derivatives **17** and **18**.

Compound **18** and its *para*-substituted benzylamino analogs **19–22** could also be obtained in an alternative way from **6** with different benzaldehydes (**7–11**) to furnish first the corresponding imino alcohols **12–16**, respectively. These intermediates were characterized only via their ^{1}H NMR spectral data due to their poor solubility in the usually applied NMR solvents. Benzimino alcohols containing an alcoholic hydroxyl group and an imino function in the 1,3 position have been reported to display tendency to ring-chain tautomerism in solution, depending on the substitution pattern of the aromatic moiety [31,32]. Therefore, they often exist as an equilibrium mixture of the open-chain imine and the related 1,3-oxazine forms. The ^{1}H NMR spectra of the Schiff bases **12–16** indicated that only the imine form was present in solution, despite the different substituents in the *para* position of the Ph group. The imine proton could be identified at around



Scheme 2 – Reagents and conditions: (i) $PhP(O)Cl_2$, Et_3N, CH_2Cl_2, rt, N_2 atm → 40 °C, 6 h → rt, 24 h.

8.3 ppm in all cases. No signal indicative of the presence of the tautomeric 1,3-oxazine (**T**) could be observed. Reduction of **12–16** with $NaBH_4$ resulted in secondary amines **18–22** in good yields.

Amino alcohols **6** and **17–22** were cyclized with phenylphosphonic dichloride in the presence of Et_3N. In most cases, two epimers (**a** and **b**), differing in their *P* configuration, were formed and were separated by column chromatography. The ring-closure reaction of **6** proceeded with complete diastereoselectivity to give **23a**; no traces of the corresponding *P* epimer (**23b**) could be detected even in the crude product (Scheme 2). However, the yield was, quite low (15%), which is not surprising at all for a primary amine such as **6** [17,33], whereas better yields (35–82%) were achieved in the phosphorylation reactions of secondary amines **17–22** with an equivalent amount of phenylphosphonic dichloride. In the particular case of the cyclization of **20**, a 2-fold excess of the *P* reagent was applied in order to improve the conversion. Thus, 84% of **27** could be obtained, which was commensurable with the yield of the unsubstituted *N*-benzyl derivative **25**. The epimeric ratios were determined for the ^{1}H NMR spectra of the reaction mixtures, which revealed a ratio of **a** and **b** of *ca.*3:2 for **24–29**.

The structures of the oxazaphosphorinanes (**23–29**) were confirmed by multinuclear (^{1}H, ^{13}C and ^{31}P) NMR methods, and the stereostructures were evaluated by means of B3LYP/3-21G* *ab initio* calculations. The structure of **1a** was previously determined by single-crystal X-ray analysis (see footnote 2). The ^{1}H and ^{13}C chemical shifts were assigned with the aid of 2D homonuclear (COSY) and heteronuclear (HMQC and HMBC) correlation measurements.

[3] Unpublished results in this laboratory.

Table 1 – Selected ^{1}H and ^{13}C chemical shifts in $CDCl_3$

Compound	δ [ppm]				
	16-H	16-H_β	16-H_α	17-H	C-17
23a[a]	2.56	3.38	3.32	3.85	-
24a	2.66	3.42	3.12	3.83	86.8
24b	2.81	3.24	3.02	4.47	84.0
25a[b]	2.64	3.21	3.01	3.93	87.4
25b[b]	2.67	3.15	2.94	4.51	84.3
26a	2.64	3.19	3.02	3.92	87.1
26b	2.65	3.09	2.96	4.51	84.1
27a	2.64	3.19	3.00	3.92	87.1
27b	2.64	3.16	2.93	4.50	84.2
28a	2.64	3.20	2.96	3.92	87.2
28b	2.65	3.17	2.94	4.51	84.2
29a	2.70	3.26	2.96	3.95	87.3
29b	2.69	3.27	2.92	4.55	84.2

[a] Characterized only by ^{1}H NMR.
[b] Values from [26].

The ^{1}H chemical shifts and coupling constants were analyzed by an iterative method with the PERCH NMR software [34,35].

3.2. *Stereostructures (configuration and conformation)*

The phosphorylation reactions resulted in a series of diastereomeric pairs **a** and **b** due to the stereogenic *P* atom. The *P*-configuration, and thus the orientation of the P=O bond, can be determined by different NMR methods. The following indicators were used earlier for the identification of the isomers: (i) ^{31}P NMR chemical shifts [36]; (ii) ^{1}H chemical shifts due to the 1,3-diaxial interactions; (iii) changes in ^{13}C chemical shifts arising from the shielding effect of oxygen; (iv) NOE effects between the *P* substituent and other ring protons; and (v) ^{1}J(P,N) coupling constants [37].

In previous studies on isomeric pairs of oxazaphosphorinanes, the ^{31}P NMR chemical shifts of the *trans* isomer **a**: (P=O is *trans* to 17-H) were mostly upfield of those for their *cis* counterpart **b**: (P=O is *cis* to 17-H). Inspection of the ^{31}P chemical shifts for the epimers of **24**–**29**, however, was in itself not enough for the configurational assignment, since there was only a slight difference between the values for the related isomeric phosphoramidates. Anomalous ^{31}P chemical shifts for isomeric phosphorinane structures have been reported [12,38], but have been left unexplained or interpreted in terms of a chair to chair [39] or a chair to twist-boat equilibration [12]. Hence, other corroborative NMR parameters, such as characteristic ^{1}H and ^{13}C chemical shifts were used for identification. The sequence of the 17-H chemical shifts was found to be very similar to that for **1a** and **1b**: δ(17-H) for **24a–29a** < δ(17-H) for **24b–29b** (Table 1), which can be attributed to the P=O effect. Moreover, the difference between the values was about 0.6 ppm, and therefore the same anisotropic effect of the *P*-Ph group *cis* to 17-H was presumed for diastereomers **a**, as was the situation previously for the corresponding *O*-containing analog **1a**. Since only one diastereomer of **23** was isolated, the assignment was confirmed by comparison of its characteristic ^{1}H chemical shifts with those of the other isomeric pairs, which revealed good accordance with the values for the **a** series of compounds. With respect to the ^{13}C NMR chemical shifts, C-17 resonates at somewhat higher field in the **b** series (around 84 ppm) as compared with that for the **a** series of compounds (around 87 ppm), because of the deshielding effect of the axial P=O bond.

Exhaustive studies have been carried out on oxazaphosphorinane derivatives fused with cyclohexane- or six-membered hetero rings to reveal a conformational flexibility of the *P*,*N*-ring for 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 ^{3}J(H,H) and ^{3}J(H,P) have been used as indicators of possible dynamic processes [40]. To the best of

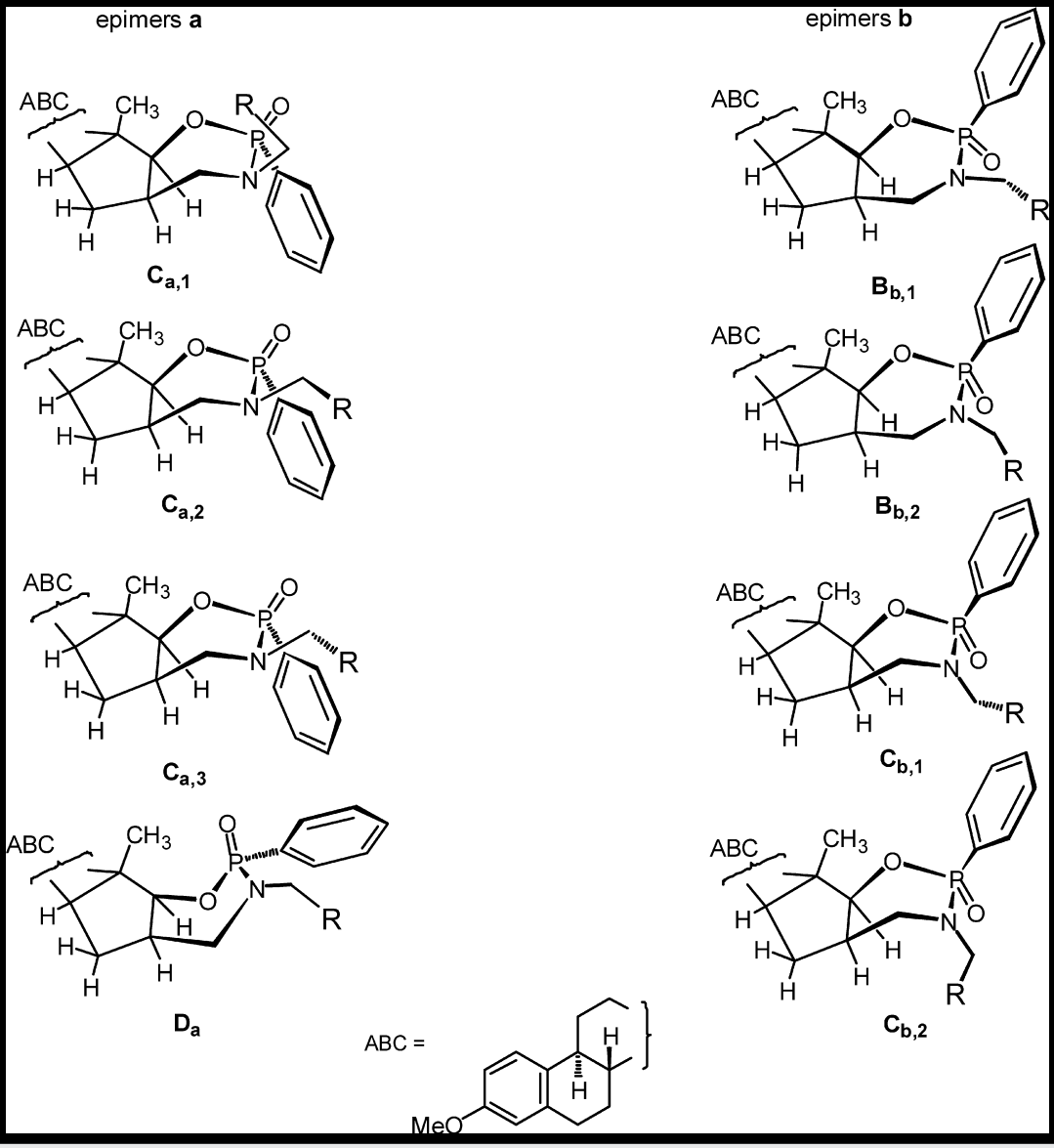
Table 2 – Selected coupling constants *J*(H,H) and *J*(H,P)

Compound	*J* [Hz]					
	16a-H_β, 16a-H_α	16a-H_β, P	16a-H_β, 16-H	16a-H_β, P	16a-H_β, 16-H	17-H, P
1a[a]	−10.8	4.6	10.8	25.1	6.5	<1.0
1b[a]	−10.7	1.4	12.0	21.5	6.2	<1.0
23a	−12.0	3.9	11.8	24.1	6.0	1.1
24a	−12.0	2.6	12.0	20.7	6.0	<1.0
24b	−12.7	<1.0	12.7	20.5	6.0	1.4
25a	−12.1	2.8	12.0	20.7	6.1	1.4
25b	−12.7	<1.0	12.7	19.2	6.0	<1.0
26a	−12.0	2.3	12.6	20.4	6.0	0.9
26b	−12.6	<1.0	12.6	19.5	6.0	1.5
27a	−12.2	2.6	12.2	20.6	6.0	<1.0
27b	−12.8	<1.0	12.8	19.2	6.0	1.4
28a	−12.0	2.4	12.0	20.4	6.3	0.9
28b	−12.9	<1.0	12.9	24.9	5.9	1.5
29a	−12.0	2.0	12.0	19.9	6.0	<1.0
29b	−12.6	<1.0	12.6	19.0	5.8	1.3

[a] See footnote 2.

our knowledge, however, the stereostructures of *P*-substituted heterocycles *cis*-fused to a five-membered ring have been investigated only for 1,3,2-dioxaphosphorinanes [41,42]. Conformational restriction is expected in these cases with regard to the fused strained five-membered ring. Although the greater length of the P–N bond in oxazaphosphorinanes, as compared with the P–O in dioxaphosphorinanes, and the presence of a substituent other than hydrogen on the ring N atom, should result in appreciable differences in the conformational properties [8], the stereostructures described for cyclopentane-condensed dioxa derivatives [41] and also suggested by the inspection of Dreiding models were taken as starting points. Consequently, two possible chair (A and B) and two alternative boat forms (C and D) of the *P*-hetero ring can be assumed. These conformers are depicted in Fig. 2.

Table 3 – Computed relative energies (kcal/mol) for the existing conformers of products 23–29 at the BLYP/6-31G(d) level of theory.



	Epimers a				Epimers b			
	$C_{a,1}$	$C_{a,2}$	$C_{a,3}$	D_a	$B_{b,1}$	$B_{b,2}$	$C_{b,1}$	$C_{b,2}$
23	–	1.76	–	4.92	6.50	–	0.00	–
24	0.59	1.56	2.14	3.54	6.57	6.42	0.00	0.16
25	1.26	2.18	3.85	6.89	7.83	6.85	0.00	0.92
26	1.28	2.22	3.81	6.91	7.81	6.90	0.00	0.91
27	1.22	2.45	3.74	7.18	7.77	7.13	0.00	1.03
28	1.13	2.51	3.74	7.24	7.71	7.02	0.00	1.02
29	1.05	2.64	3.63	7.40	7.60	7.06	0.00	0.82

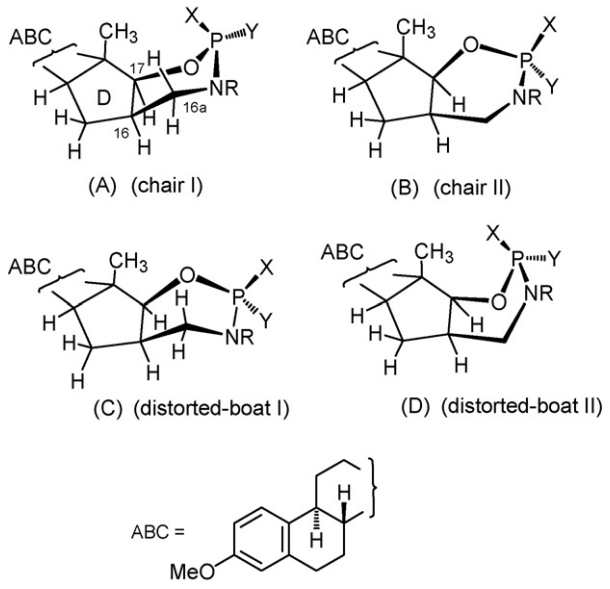


Fig. 2 – Possible conformations of the phosphoramidate ring of 23–29.

A typical feature of 2-oxo-1,3,2-oxazaphosphorinanes, which exist predominantly in one conformation in solution, is the combination of large ^3J(H,P) values for the protons equatorial and hence antiperiplanar to the *P* and small ^3J(H,P) values for the axial protons synclinal to the *P*. In conformations A and D, the *P* atom and 17-H are in an antiperiplanar orientation, and thus *J*(17-H,P) would be >20 Hz. In contrast, the dihedral angle P–O_{17}–C_{17}–H_{17} in conformations B and C is about 90°, leading to a small *J*(17-H,P) value, which indeed holds true for **23–29** (*J*(17-H,P) ≤ 1.5 Hz) (Table 2). Moreover, the observed extra upfield shift of 17-H for epimers **a** can not be explained in the case of conformer A or D. The ^3J(H,P) data on the 16a protons, however, suggest that all compounds (**23–29**) seem to adopt predominantly the distorted-boat conformer **C** almost exclusively, regardless of the relative configuration on the *P* atom. This is consistent with the combination of a small ^3J(16a-H_β, P) with a large ^3J(16a-H_α, P) for **23–29**. The dihedral angle P–O_{16a}–C_{16a}–$H_{16-H\beta}$ in conformer B is about 180°, so that ^3J(16a–H_β, P) >20 Hz would be predicted. There is obvious similarity between the corresponding coupling constants of **1a** and **23a** in Table 2. The small differences may arise from the stereostructural modification effect caused by the change of the *O* atom in **1a** to the *N* atom in **23a**. The coupling constants ^3J(H,H) and ^3J(H,P) for the epimers **a** and **b** of the *N*-substituted oxazaphosphorinanes **24–29** suggested the same conformational dominance as noted for **1a** and **1b**. In order to support these considerations, B3LYP/6–31 + G(d)) DFT calculations [43] using Gaussian03 [44] were carried out on diastereomers **a** and **b** of **23–29**.

The DFT-calculated energies listed in Table 3 show that the six-membered hetero ring of **23–29** adopts predominantly the distorted-boat conformer C, regardless of the *P*-configuration, as expected from the observed values of the coupling constants. Conformers $C_{a,1}$ and $C_{b,1}$, containing the *N* substituent and the *P*-Ph group in opposite spatial directions, are most stable due to steric and stereoelectronic effects. Moreover, the $C_{b,1}$ forms, bearing the *P*-Ph group in a pseudoequatorial position (**23b–29b**), are energetically more favorable. The observed difference in the epimeric ratios of **24–29** (**a**:**b** = 3:2) may be attributed both to the thermodynamic and the kinetic control of the process. This assumption is supported by the fact that isomers **b** are theoretically more stable, whereas **23a** was isolated diastereoselectively, and compounds **24a–29a** were obtained as major isomers. Additionally, conformers B (B_a, $B_{b,1}$ and $B_{b,2}$) are not preferred in consequence of the steric interactions caused by the unfavorable eclipsed position of the hetero ring hydrogen atoms. Theoretical calculations precluded the existence of conformer A which was converted to other conformations due to steric repulsion between the *P*-group and the angular methyl group at position 13 of the sterane skeleton.

In summary, epimers of D-ring-fused oxazaphosphorinanes (**23–29**) were prepared via newly described intermediates (**5**, **12–22**) in the estrone series, and their preferred conformations were calculated. In accord with the NMR measurements, the results indicated that the stereostructure of the hetero ring is mainly determined by the rigidity of the sterane skeleton. The *P*-rings of compounds **23–29** adopt predominantly a distorted-boat conformation, independently of the *P*-configuration and the substituent preferences, very similarly as for the corresponding dioxaphosphorinane analogs.

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