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Tetrahedron Letters 47 (2006) 1105–1108
Tetrahedron Letters

# Synthesis of some novel *D*-ring-fused dioxa- and oxazaphosphorinanes in the estrone series

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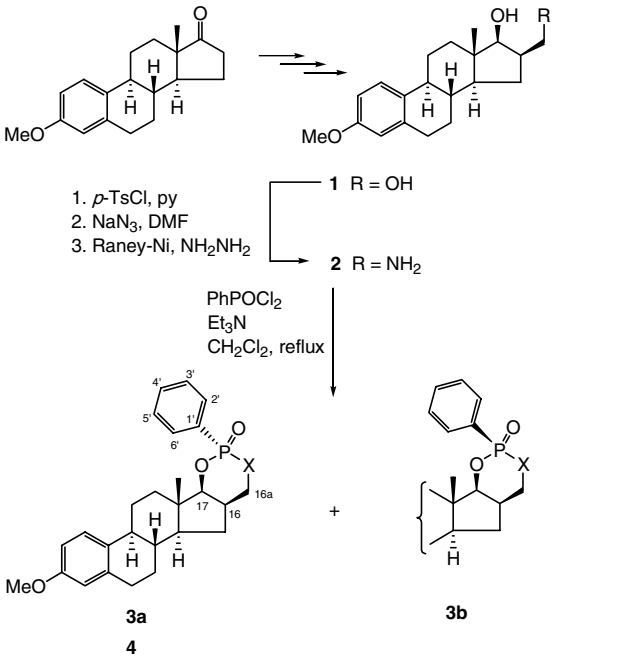
Received 4 October 2005; revised 30 November 2005; accepted 7 December 2005
Available online 27 December 2005

**Abstract**—New types of P-heterocyclic-fused steroids, such as dioxa- and oxazaphosphorinane derivatives, were synthetized from estrone-1,3-dihydroxy and 1,3-aminoalcohol precursors by cyclization with phenylphosphonic dichloride.


The reactions of diols and amino-alcohols with phosphonic dichlorides are well known and is a method for the formation of phosphorus-containing heterocycles.[1] Oxazaphosphorinanes especially are of great interest, since cyclophosphamide, one of the most potent drugs in the treatment of human cancers, contains this type of heterocyclic ring.[2] Besides evaluation of their biological activity,[3] a number of conformational studies have also been carried out to investigate the steric and electronic effects of various substituents in different positions of the parent oxazaphosphorinane ring.[3]

One of the major aims of steroid chemistry is to develop new heterocyclic derivatives to extend the already wide range of biological activity of these compounds. Formation of a hetero ring on the sterane skeleton is one of the possible methods of modifying the natural framework.[4] To the best of our knowledge, only a few phosphorus 17-spiro-compounds have so far been synthesized.[5]

This letter describes efficient syntheses of some new *D*-ring-fused dioxa- and oxazaphosphorinane ring systems via the reactions of estrone precursors with phenylphosphonic dichloride. For the transformations, 17β-hydroxy-16β-hydroxymethylestrone 3-methyl ether **1**[6] and the corresponding 16β-aminomethyl derivative **2**,[7] which is readily available from estrone 3-methyl ether via multistep pathway, were used as starting materials (Scheme 1). When the 1,3-diol **1** was reacted with




**3** X = O (93% from **1** as a 1:1 diastereomeric mixture of **3a** and **3b**)
**4** X = NH (15% from **2** as a single diastereomer)

**Scheme 1.**

*Keywords*: Steroids; Estrone derivatives; Dioxaphosphorinanes; Oxazaphosphorinanes.
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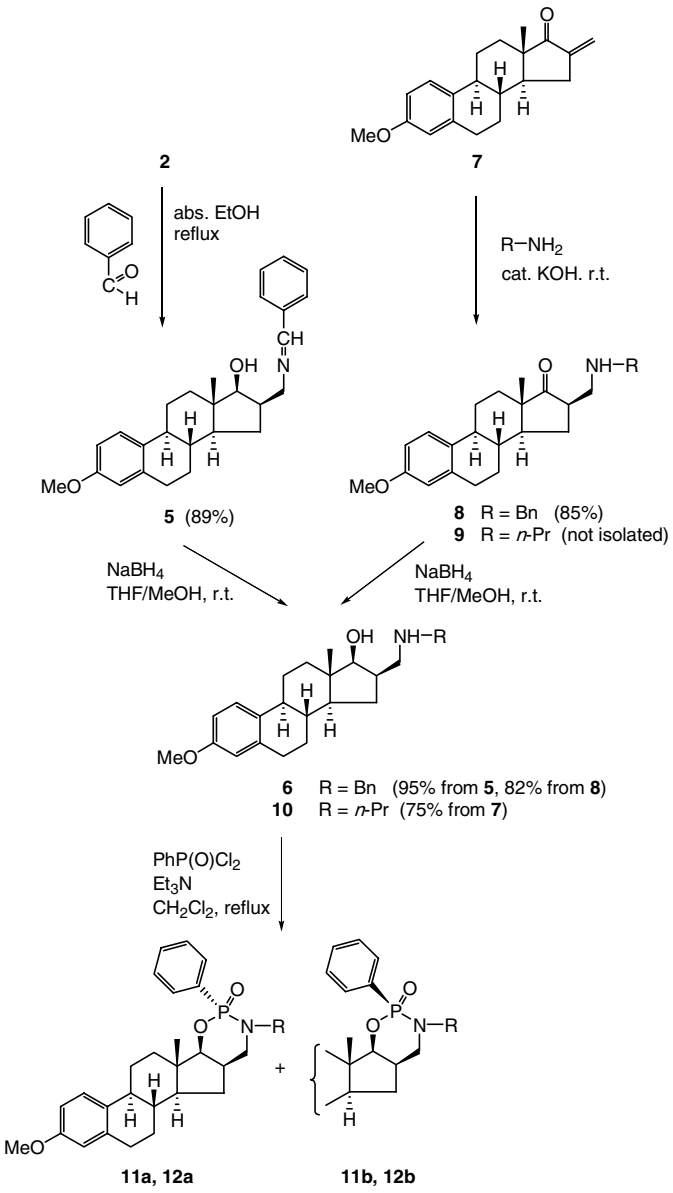
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.038

$PhP(O)Cl_2$ in the presence of $Et_3N$, the epimeric oxazaphosphorinanes **3a** and **3b** were formed in good yield in a nearly 1:1 ratio.[8] The diastereomeric pair was separated by column chromatography.

Ring closure of the corresponding amino-alcohol **2** with $PhP(O)Cl_2$ under similar conditions resulted in only a single diastereomer **4**. The low yield of oxazaphosphorinane **4** is not surprising, as a primary amino function is usually not very active in such reactions.[9]

Next, 17β-hydroxy-16β-aminomethylestrone 3-methyl ether **2** was reacted with benzaldehyde to furnish the corresponding imine **5**, which could be isolated as a crystalline product in spite of the fact that imines are usually unstable and difficult to isolate (Scheme 2).[10] After treatment of imine **5** with sodium borohydride in THF/MeOH solution, secondary amine **6** was obtained in good yield. Alternatively, this compound could also be synthesized from 16-methylene-estrone 3-methyl ether **7**[11] via the Michael-type addition of benzylamine and subsequent reduction of the C-17 keto function of intermediate **8**.

The benzyl-substituted aminoalcohol **6** was then converted to oxazaphosphorinane **11** in a much better yield than was found for the cyclization of intermediate **2** with a primary amine function. The heterocyclic product was formed as a mixture of the two possible diastereomers (**11a** and **11b**) in a ratio of 3:2.[12]




**Scheme 2.**

In order to study the substituent effect of the amine precursor of the oxazaphosphorinane, the analogous transformation was carried out with **7**, using *n*-propylamine, but the conversion of intermediate **10** to the corresponding oxazaphosphorinane **12** was sluggish. The epimeric ratio was found to be the same (**12a**:**12b** = 3:2).

The structures of the products were determined by NMR spectroscopy, demonstrated here on representative compounds **3** and **11**. The $^{1}$H NMR spectra revealed an important difference between the related epimers (**3a** and **3b** or **11a** and **11b**). The doublet for 17-H in **3a** appears at 3.97 ppm (3.93 ppm for **11a**) with a coupling constant of 9.5 Hz (the same for **11a**), while the corresponding signals for **3b** and **11b** occur at higher chemical shifts (4.61 ppm with 9.0 Hz for **3b**, and 4.51 ppm with 11.5 Hz for **11b**). The significant upfield shift for 17-H in **3a** and **11a** can be explained by the magnetic anisotropic effect of the *P*-phenyl group. This fact confirms the α position of the aromatic ring in these diastereomers. In the $^{13}$C NMR spectra, the split signals of the carbon atoms in the proximity of the phosphorus proved to be of diagnostic value.

## Acknowledgments

This work was supported financially by the Hungarian Scientific Research Fund (OTKA T042673, T049366, and T042479).

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8. To a stirred solution of triethylamine (0.43 ml, 4 mmol) and **2** (316 mg, 1 mmol) in dichloromethane (15 ml), phenylphosphonic dichloride (0.15 ml, 1 mmol) was added dropwise at room temperature under a nitrogen atmosphere. The reaction mixture was refluxed for 2 h and then left to stir overnight at room temperature. The resulting mixture was poured into water, and extracted with dichloromethane (3 × 10 ml), and the combined organic phases were dried over $Na_2SO_4$, and evaporated in vacuo. Crude product **3** was separated by column chromatography on silica gel, using ethyl acetate/dichloromethane (20:80) as eluent. The fast-eluting isomer **3a** was crystallized from ethyl acetate/dichloromethane, while the slow-eluting isomer **3b** was crystallized from dichloromethane/hexane to give colorless crystals.
Compound **3a**: mp 194–197 °C. $^{31}$P NMR ($CDCl_3$): $\delta = 13.8$. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta = 1.03$ (s, 3H, 18-$H_3$), 1.16–1.30 (m, 3H), 1.35 (m, 1H), 1.53 (m, 2H), 1.87 (m, 1H), 1.94 (m, 1H), 2.06 (m, 1H), 2.18 (m, 1H), 2.28 (m, 1H), 2.76 (m, 1H, 16-H), 2.86 (m, 2H, 6-$H_2$), 3.77 (s, 3H, 3-OMe), 3.97 (d, 1H, $J = 9.5$ Hz, 17-H), 4.37 (m, 2H, 16a-$H_2$), 6.62 (d, 1H, $J = 2.5$ Hz, 4-H), 6.70 (dd, 1H, $J = 8.5$ Hz, $J = 2.5$ Hz, 2-H), 7.17 (d, 1H, $J = 8.5$ Hz, 1-H), 7.49 (m, 2H, 3′-H and 5′-H), 7.57 (m, 1H, 4′-H), 7.84 (m, 2H, 2′-H and 6′-H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 13.2$ (C-18), 26.2, 27.2, 27.6, 29.7, 37.4, 37.7 (d, $J = 5.1$ Hz, C-16), 38.1, 43.8, 45.1 (d, $J = 6.4$ Hz, C-13), 49.1, 55.3 (3-OMe), 68.7 (d, $J = 5.6$ Hz, C-16a), 86.8 (d, $J = 8.7$ Hz, C-17), 111.7 (C-2), 114.0 (C-4), 126.4 (C-1), 128.4 (d, $J = 190.2$ Hz, C-1′), 128.6 and 128.8 (C-3′ and C-5′), 131.7, 131.8, and 132.0 (C-2′, C-4′, and C-6′), 132.7 (d, $J = 3.1$ Hz, C-10), 137.7 (C-5), 157.7 (C-3). HRMS (FAB), $(M+H)^+$ found 439.2020, $C_{26}H_{32}O_4P$ requires 439.2038.
Compound **3b**: mp 219–222 °C. $^{31}$P NMR ($CDCl_3$): $\delta = 16.0$. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta = 1.01$ (s, 3H, 18-$H_3$), 1.16 (m, 1H), 1.34 (m, 1H), 1.40–1.58 (m, 4H), 1.90 (m, 1H), 1.96 (m, 1H), 2.10 (m, 1H), 2.26 (m, 1H), 2.35 (m, 1H), 2.89 (m, 2H, 6-$H_2$), 3.06 (m, 1H, 16-H), 3.79 (s, 3H, 3-OMe), 4.06 (m, 1H) and 4.29 (m, 1H): [16a-$H_2$], 4.61 (d, 1H, $J = 9.0$ Hz, 17-H), 6.65 (d, 1H, $J = 2.5$ Hz, 4-H), 6.73 (dd, 1H, $J = 8.5$ Hz, $J = 2.5$ Hz, 2-H), 7.21 (d, 1H, $J = 8.5$ Hz, 1-H), 7.49 (m, 2H, 3′-H and 5′-H), 7.59 (m, 1H, 4′-H), 7.87 (m, 2H, 2′-H and 6′-H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 13.5$ (C-18), 26.2, 27.4, 27.7, 29.8, 37.5, 38.2, 38.7 (d, $J = 6.6$ Hz, C-16), 43.8, 45.2 (d, $J = 7.4$ Hz, C-13), 48.8, 55.4 (3-OMe), 69.3 (d, $J = 5.5$ Hz, C-16a), 84.5 (d, $J = 7.4$ Hz, C-17), 111.8 (C-2), 114.0 (C-4), 126.5 (C-1), 128.5 (d, $J = 183.5$ Hz, C-1′), 128.6 and 128.8 (C-3′ and C-5′), 131.5, 131.6, and 132.2 (C-2′, C-4′, and C-6′), 132.8 (d, $J = 3.1$ Hz, C-10), 137.8 (C-5), 157.8 (C-3). HRMS (FAB), $(M+H)^+$ found 439.2021, $C_{26}H_{32}O_4P$ requires 439.2038.
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12. A solution of **2** (315 mg, 1 mmol) and benzaldehyde (0.10 ml, 1 mmol) in abs ethanol (15 ml) was refluxed for 2 h under a nitrogen atmosphere and then left to stir overnight at room temperature. The mixture was cooled and the crystals that separated out were filtered off to give 359 mg (89%) of pure **5**. Imine **5** was then 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 amine **6** was collected, washed with water, and dried (343 mg, 95% from **5**).
To a stirred solution of triethylamine (0.43 ml, 4 mmol) and **6** (343 mg, 0.85 mmol) in dichloromethane (15 ml), phenylphosphonic dichloride (0.13 ml, 0.85 mmol) was added dropwise at room temperature under a nitrogen atmosphere. The reaction mixture was refluxed for 6 h and then left to stir overnight at room temperature. The mixture was poured into water, and extracted with dichloromethane ($3 \times 10$ ml), and the combined organic phases were dried over $Na_2SO_4$, and evaporated in vacuo. The crude product was subjected to column chromatography on silica gel, using ethyl acetate/dichloromethane (20:80) as eluent to give the fast-eluting **11a** in pure form. Compound **11a** was crystallized from ethyl acetate/dichloromethane to afford colorless crystals. Compound **11b** could not be isolated in pure form, but the slow-eluting epimeric mixture of **11a** and **11b**, in a ratio of 1:3, permitted the assignment of **11b** from the spectra.
Compound **11a**: mp 120–122 °C. $^{31}P$ NMR ($CDCl_3$): $\delta = 19.5$. $^{1}H$ NMR (500 MHz, $CDCl_3$): $\delta = 0.98$ (s, 3H, 18-$H_3$), 1.09–1.35 (m, 4H), 1.48 (m, 2H), 1.84 (m, 1H), 2.00 (m, 1H), 2.11 (m, 2H), 2.24 (m, 1H), 2.64 (m, 1H, 16-H), 2.83 (m, 2H, 6-$H_2$), 3.01 (m, 1H) and 3.21 (td, 1H, $J = 12.0$ Hz, $J = 3.0$ Hz): [16a-$H_2$], 3.76 (s, 3H, 3-OMe), 3.93 (d, 1H, $J = 9.5$ Hz, 17-H), 4.12 (m, 2H, benzyl-$H_2$), 6.60 (d, 1H, $J = 2.5$ Hz, 4-H), 6.69 (dd, 1H, $J = 8.5$ Hz, $J = 2.5$ Hz, 2-H), 7.15 (d, 1H, $J = 8.5$ Hz, 1-H), 7.24–7.40 (m, 5H, 2″-H, 3″-H, 4″-H, 5″-H, and 6″-H), 7.50 (m, 2H, 3′-H and 5′-H), 7.60 (m, 1H, 4′-H), 7.93 (m, 2H, 2′-H and 6′-H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 13.5$ (C-18), 26.3, 27.7, 29.1, 29.8, 37.6, 38.2, 39.2 (d, $J = 2.0$ Hz, C-16), 43.9, 45.0 (d, $J = 6.9$ Hz, C-13), 49.3, 49.4 (d, $J = 7.7$ Hz, Ph–$CH_2$), 51.1 (d, $J = 5.0$ Hz, C-16a), 55.4 (3-OMe), 87.4 (d, $J = 9.4$ Hz, C-17), 111.7 (C-2), 114.0 (C-4), 126.5 (C-1), 127.7, 128.6 (2C), 128.7, 128.8 (3C), 128.9, 130.6 (d, $J = 173.7$ Hz, C-1′), 132.3, 132.5, 132.7, 137.6 (d, $J = 5.0$ Hz, C-10), 137.8 (C-5), 157.7 (C-3). HRMS (FAB), $(M+H)^+$ found 528.2643, $C_{33}H_{39}NO_3P$ requires 528.2668.
Compound **11b**: $^{31}P$ NMR ($CDCl_3$): $\delta = 18.6$. $^{1}H$ NMR (500 MHz, $CDCl_3$): $\delta = 0.95$ (s, 3H, 18-$H_3$), 1.03–2.32 (m, 11H), 2.67 (m, 1H, 16-H), 2.83 (m, 2H, 6-$H_2$), 2.94 (m, 1H) and 3.15 (t, 1H, $J = 16.0$ Hz): [16a-$H_2$], 3.76 (s, 3H, 3-OMe), 4.05 (m, 1H) and 4.21 (m, 1H): [benzyl-$H_2$], 4.51 (d, 1H, $J = 11.5$ Hz, 17-H), 6.61 (d, 1H, $J = 3.0$ Hz, 4-H), 6.69 (dd, 1H, $J = 11.0$ Hz, $J = 3.0$ Hz, 2-H), 7.18 (d, 1H, $J = 11.0$ Hz, 1-H), 7.23–7.39 (m, 5H, 2″-H, 3″-H, 4″-H, 5″-H, and 6″-H), 7.45 (m, 2H, 3′-H and 5′-H), 7.51 (m, 1H, 4′-H), 7.86 (m, 2H, 2′-H and 6′-H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ (C-18), 26.3, 27.8, 28.8, 29.9, 37.7, 38.2, 40.7 (d, $J = 4.5$ Hz, C-16), 43.9, 45.3 (d, $J = 8.0$ Hz, C-13), 49.0, 49.3 (d, $J = 8.5$ Hz, Ph–$CH_2$), 50.8 (d, $J = 6.0$ Hz, C-16a), 55.4 (3-OMe), 84.3 (d, $J = 8.2$ Hz, C-17), 111.7 (C-2), 114.0 (C-4), 126.5 (C-1), 127.5, 128.4 (2C), 128.5, 128.6 (3C), 128.7, 131.5, 131.6, 132.2, (d, $J = 181.0$ Hz, C-1′), 132.4, 137.9 (C-5), 138.6 (d, $J = 4.3$ Hz, C-10), 157.8 (C-3).