# Synthesis and Conformational Preferences of Novel Steroidal 16-Spiro-1,3,2-Dioxaphosphorinanes

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**Abstract:** The diastereomeric pairs **a** and **b** of novel 16-spiro-dioxaphosphorinanes **3–11** were synthesised *via* the phosphorylation of 16,16-bis(hydroxymethyl)estrone 3-methyl ether (**1**) and its 17β-hydroxy analogue (**2**) and their stereostructures were investigated by different NMR methods.

**Keywords:** Steroids, spiro compounds, phosphorylations, dioxaphosphorinanes, stereostructure.

## INTRODUCTION

Mono- and bicyclic 1,3,2-dioxaphosphorinanes, including natural and synthetic cyclic nucleotides, have attracted much attention during the past few decades from both pharmacological and stereochemical aspects [1]. The main driving force behind the stereostructural studies was the desire to investigate the unique conformational behaviour of differently substituted six-membered P-containing hetero rings [2]. It has been demonstrated that, especially in conformationally biased bulky molecules, one of the two alternative chair forms or intermediate twist [3a] half-chair [3b] or boat [3c] conformations of the P heterocycle can predominate in solution. Furthermore, the conformational distribution of 2-oxo-1,3,2-dioxaphosphorinanes may be highly sensitive to the solvent, *i.e.* a more polar solvent may stabilize non-chair conformations [3d].

The construction of a dioxaphosphorinane ring on a relatively rigid sterane skeleton furnishes an excellent possibility *via* which to restrict the conformational flexibility of the hetero ring, though only a few examples of such systems have been described so far [4]. In this regard, we recently reported the synthesis and conformational analysis of diastereomeric dioxaphosphorinano[16,17–*d*]-estrone derivatives, where the geometry of the P-containing ring was strongly influenced by the condensed sterane framework, and an unusual distorted-boat conformation predominated in most cases, regardless of the P configuration and substituent preferences [4b].

## RESULTS AND DISCUSSION

As an extension of our earlier work, we now describe the synthesis of some new 16-spiro-dioxaphosphorinanes *via* the phosphorylation of estrone precursors with four P(V)-reagents. The transformations were performed on 16,16-bis(hydroxymethyl)estrone 3-methyl ether **1** [5] and the corresponding 17β-hydroxy derivative **2**, which is readily available from **1** by reduction (Scheme **1**). The reaction of **1** with $PhOP(O)Cl_2$ in refluxing $CH_2Cl_2$ in the presence of an amine base gave the diastereomeric pairs **a** and **b** of dioxaphosphorinane **3** in high yield, in a ratio of 2:3 (Table **1**). In order to study the electronic and steric effects of different P substituents on the conformation of the hetero ring, we carried out the analogous reactions with $PhP(O)Cl_2$, $POCl_3$ and bis(2-chloroethyl)phosphoramidic dichloride [6] to afford **4**-**6**, as 1:2 mixtures of the related isomers **a** and **b** for **4** and **6**, and as a 3:1 mixture for **5a** and **5b**. The overall yields of the desired products decreased in the sequence **3** > **4** > **5** > **6**. The diastereomers **a** and **b** of **3**-**6** were separated by column chromatography.

In view of the low yield of **6** from **1** with the bis(2-chloroethyl) reagent, the phosphorylations of **2** to furnish **7**-**9** were performed only with the other three P(V) reagents. The conversion of **2** proved poorer than that of **1** because of the more polar character and hence the lower solubility of **2** in the reaction solvent. Moreover, the presence of the 17-hydroxy group in **2** permitted the formation of minor side-products. Besides the major isomers **7a** and **7b**, cyclic phosphates **12a** and **12b** were obtained from **2** on reaction with $PhOP(O)Cl_2$, both pairs in ratios of close to 1:1, whereas the ring closure of **2** with $PhP(O)Cl_2$ led to only a single by-product **13b**, the major product comprising a 2:3 mixture of **8a** and **8b**. Ring closure of **2** with $POCl_3$ under similar conditions resulted in only a single diastereomer **9a**. The isomers **a** and **b** of **7** and **8** were also synthesised from the separated diastereomers of **3** and **4** with $KBH_4$, respectively. Six-membered P heterocycles are known to be relatively stable under both acidic and alkaline hydrolytic conditions [7] and undergo reduction without decomposition. In order to achieve lower polarity and facilitate the NMR characterisation, the 17β-acetates **10** and **11** of **7** and **8** were also prepared.

The structures of the 16-spiro-dioxaphosphorinanes **3**-**11** were investigated by solution-state multinuclear ($^1H$, $^{13}C$ and $^{31}P$) NMR techniques. The sequence of $^{31}P$ chemical shifts for diastereomers **a** and **b** of **3–11** is $\delta^{31}P(\mathbf{a}) < \delta^{31}P(\mathbf{b})$, which suggests that the Y substituent on P is axial in isomers **a** and equatorial in diastereomers **b** [8] (Table **2**). The orientation of Y may be axial in two chair conformations ($\mathbf{A}^{ax.}$ and $\mathbf{B}^{ax.}$), in which the P configurations are opposite (Table **3**). The

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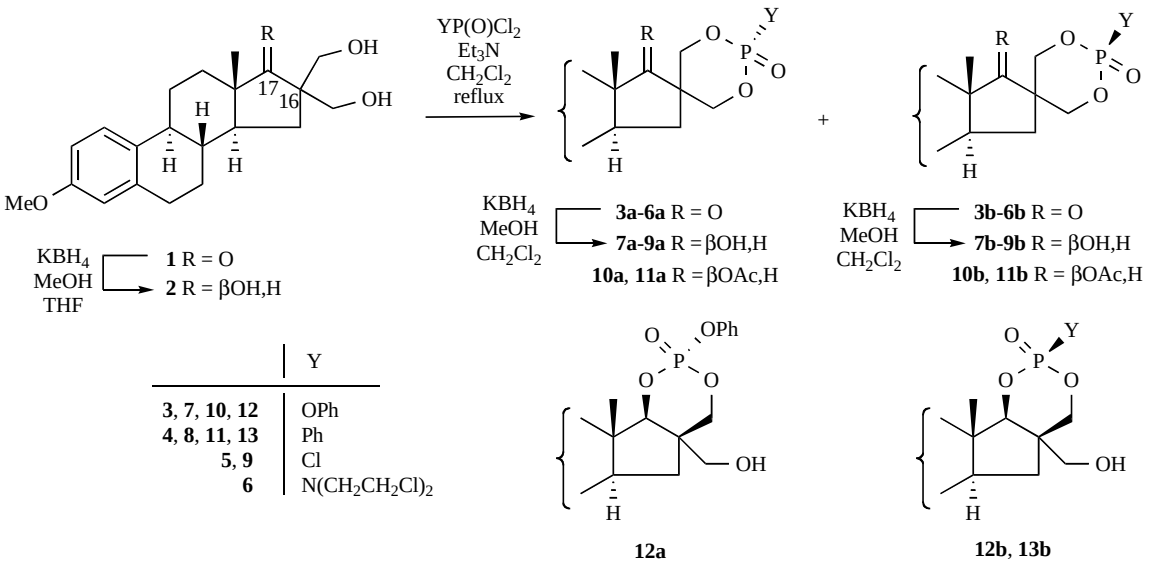



**Scheme 1.**

**Table 1. Dioxaphosphorinanes Afforded by the Phosphorylation of 1 and 2**

| Entry | Substrate | Reagent | Product(s) | Overall Yield[a] [%] | Diastereomeric Ratio[b] (a:b) |
|---|---|---|---|---|---|
| 1 | **1** | $PhOP(O)Cl_2$ | **3** | 91 | 2:3 |
| 2 | **1** | $PhP(O)Cl_2$ | **4** | 86 | 1:2 |
| 3 | **1** | $POCl_3$ | **5** | 40 | 3:1 |
| 4 | **1** | $Mu^cP(O)Cl_2$ | **6** | 13 | 1:2 |
| 5 | **2** | $PhOP(O)Cl_2$ | **7** | 69 | 1:1 |
| | | | **12** | 8 | 1:1 |
| 6 | **2** | $PhP(O)Cl_2$ | **8** | 55 | 2:3 |
| | | | **13b** | 2 | [d] |
| 7 | **2** | $POCl_3$ | **9a** | 12 | [d] |

[a]After purification by column chromatography.
[b]Determined from the $^1H$ NMR spectra of the crude products.
[c]Mu = $N(CH_2CH_2Cl)_2$.
[d]single diastereomer.

same is true for the equatorial Y in diastereomers **b**, where chair forms $\mathbf{A}^{eq.}$ and $\mathbf{B}^{eq.}$ may be considered. In order to determine the configuration, **10a** and **11b**, in which chair conformations were expected to predominate with regard to the substituent preferences, were subjected to NOESY measurements. The two-dimensional spectra of **10a** and **11b** revealed unambiguous cross-peaks between the 16b-protons and 17-H. The proximity of the equatorial 16a-$H^b$ to 18-$CH_3$ was also confirmed. The observed relationship is impossible in conformer $\mathbf{B}^{ax.}$ for **10a** and in $\mathbf{B}^{eq.}$ for **11b**, and the predominant population of chair conformation **A** is therefore suggested for both diastereomers **a** and **b**. A typical feature of 2-oxo-1,3,2-dioxaphosphorinanes, which are mainly in one conformation in solution, is the combination of large $^3J$(H,P) values for those protons equatorial and hence antiperiplanar to P, and small $^3J$(H,P) values for the axial protons synclinal to P. The relatively great differences in chemical shifts within the pairs 16a-$H^a$/16a-$H^b$ and 16b-$H^a$/16b-$H^b$ at 400 MHz allowed an accurate analysis of the vicinal coupling constants of **3–11** (Table **3**). Accordingly, the chair conformation $\mathbf{A}^{ax.}$ is assigned to the hetero ring in **3a**, **5a**, **7a**, **9a** and **10a**, which is evident from the small values (< 3.2 Hz) for $J$(16a-$H^a$,P) and $J$(16b-$H^a$,P) and the large values (> 22.2 Hz) for $J$(16a-$H^b$,P) and $J$(16b-$H^b$,P). The conformational equilibrium can be regarded as anancomeric in these cases, which is not surprising considering the strong axial preferences of the electronegative OPh and Cl substituents due to the anomeric effect [9]. However, substituent in **6a** proved to be insufficiently strong to drive the equilibrium towards conformation $\mathbf{T}^{ps.eq.}$ to a major extent, and the large contribution of conformer $\mathbf{A}^{ax.}$ therefore also seems certain. The large four-bond couplings $J_W \geq 2.8$ Hz, confirm the W arrangement of 16a-$H^b$ and 16b-$H^b$ in **3a**, **5a**–**7a**, **9a** and **10a**. In contrast with **6a**, extensive depopulation of the chair conformation occurred for **4a**, **8a** and **11a**, as indicated by the increased $J$(16a-$H^a$,P) values of about 17 Hz and the decreased $J$(16a-$H^b$,P) values of around 6 Hz. Conformation $\mathbf{A}^{ax.}$, which places the P-Ph in an unfavourable axial posi-

tion, is largely converted to the twist form with the Ph pseudo-equatorial. The results are somewhat surprising, as the preference of $NR_2$ for an equatorial position has been reported to be usually stronger than that of Ph [10]. Although 16a-$H^a$ and 16a-$H^b$ are essentially interchanged in conformers $\mathbf{A}^{ax.}$ and $\mathbf{T}^{ps.eq.}$, the coupling pattern of the 16b-protons remains almost unchanged relative to that in the chair conformation $\mathbf{A}^{ax.}$. The predominant twist conformer $\mathbf{T}^{ps.eq.}$ was also demonstrated by the NOESY spectrum of **11a**, which showed cross-peaks between both of the 16a-protons and the angular $CH_3$ on C-13. The conformational analysis of the **b** series of compounds was performed similarly to that in the **a** series. The small couplings of the equatorial 16a-$H^a$ and 16b-$H^a$ with the P and the large values of $J$(16a-$H^b$,P) and $J$(16b-$H^b$,P) led to the conclusion that the hetero ring in **4b** and **6b** is exclusively in conformation $\mathbf{A}^{eq.}$ with the Ph and bis(2-chloroethyl)amino substituent in their favoured equatorial orientation. The conformational equilibrium likewise seems to be strongly shifted towards the $\mathbf{A}^{eq.}$ conformer in **3b**, **8b** and **11b**. For **5b**, **7b** and **10b**, however, the contribution of the twist conformer $\mathbf{T}^{ps.ax.}$ is assumed to be larger since $J$(16a-$H^a$,P) > $J$(16a-$H^b$,P). This can be explained by OPh and Cl striving to take up an axial position. The minor population of $\mathbf{B}^{ax.}$ is also conceivable in these latter cases in view of the increased $J$(16b-$H^a$,P) and decreased $J$(16b-$H^b$,P) values. A further interesting conclusion emerges from a comparison of the conformational preferences of the differently substituted 16-spiro-dioxaphosphorinanes **3b**-**11b**. C-17 in the sterane skeleton is $sp^2$ hybridised in **3b**-**6b**, but in a $sp^3$ hybridisation state in **7b**-**11b**. This causes a slight change in the conformation of ring D and seems to affect the conformational equilibrium of the connected hetero ring. While the chair conformation $\mathbf{A}^{eq.}$ is assumed to predominate for **3b**, despite the unfavourable equatorial orientation of OPh, depopulation of this conformer towards $\mathbf{T}^{ps.ax.}$ and to a small extent $\mathbf{B}^{ax.}$ can occur in **7b** and **10b**. The same tendency may be observed by comparing **4b** with **8b** and **11b**. **4b** is highly biased toward the population of $\mathbf{A}^{eq.}$, while a certain presence of the twist form can be predicted from the coupling constants for **8b** and **11b**. These results suggest that the more rigid cyclopentanone-like ring D in **3b**–**6b** somewhat restricts the conformational mobility of the P-containing ring and thus overcompensates the substituent preferences to some degree.

In summary, we have synthesised novel steroidal 16-spiro-1'3',2'-dioxaphosphorinanes. Stereostructural study of the hetero rings revealed that a conformational bias in favour of one or other conformer can be induced by the joint sterane framework.

## EXPERIMENTAL

### General

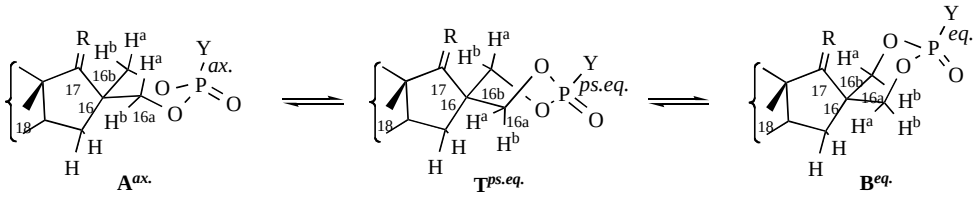
TLC: silica gel 60 $F_{254}$ plates (0.25 mm; Merck). Column chromatography: silica gel 60 (0.040-0.063 mm; Merck). Melting points: Kofler block; uncorrected; EI-MS: Varian MAT 311A spectrometer with ionisation energy 70eV. $^1$H NMR (400 or 500 MHz), $^{13}$C NMR (100 or 125 MHz) and $^{31}$P NMR (121 MHz) spectra: Bruker DRX 400 or Bruker DRX 500 in $CDCl_3$ at 300 K; TMS as internal standard ($^1$H, $^{13}$C) and $H_3PO_4$ as external standard ($^{31}$P); chemical shifts in ppm.

**Table 2. Selected $^{31}$P and $^1$H Chemical Shifts of 3-11 in $CDCl_3$**

| | δ (ppm) | | | | |
|---|---|---|---|---|---|
| **Compd** | **$^{31}$P** | **16a-$H^a$** | **16a-$H^b$** | **16b-$H^a$** | **16b-$H^b$** |
| **3a** | -13.9 | 4.73 | 4.22 | 4.56 | 4.11 |
| **3b** | -11.3 | 4.76 | 4.20 | 4.62 | 4.09 |
| **4a** | 14.4 | 4.28 | 4.37 | 4.24 | 4.16 |
| **4b** | 18.0 | 4.98 | 4.12 | 4.80 | 3.99 |
| **5a** | -7.5a | 4.70 | 4.27 | 4.52 | 4.16 |
| **5b** | -2.7a | 4.44 | 4.52 | 4.33 | 4.46 |
| **6a** | 6.3 | 4.75 | 4.12 | 4.59 | 4.02 |
| **6b** | 6.5 | 4.82 | 4.08 | 4.65 | 3.97 |
| **7a** | -12.2 | 4.69 | 4.29 | 4.48 | 3.95 |
| **7b** | -10.9 | 4.79 | 4.27 | 4.21 | 4.42 |
| **8a** | 15.1 | 4.30 | 4.36 | 4.17 | 4.10 |
| **8b** | 18.4 | 5.10 | 4.25 | 4.89 | 3.91 |
| **9a** | [b] | 4.68 | 4.35 | 4.47 | 3.98 |
| **10a** | -12.8 | 4.31 | 4.26 | 4.66 | 4.01 |
| **10b** | -12.2 | 4.59 | 4.25 | 4.27 | 4.39 |
| **11a** | 14.9 | 4.32 | 4.08 | 4.30 | 4.20 |
| **11b** | 17.9 | 4.70 | 4.19 | 4.69 | 3.93 |

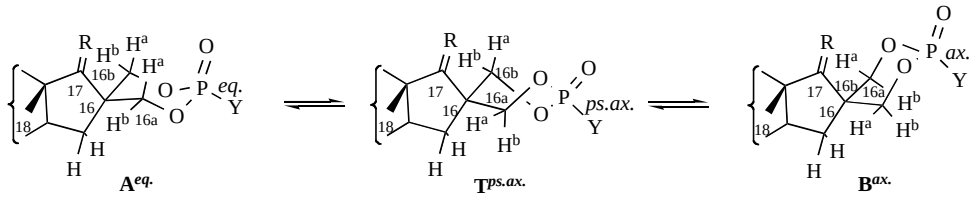
[a]measured in DMSO-$d_6$.
[b]not measured.

**Table 3. Selected Coupling Constants *J*(H,P) and *J*(H,H) for the Hetero Rings of 3-11**



$\mathbf{A}^{ax.}$ $\mathbf{T}^{ps.eq.}$ $\mathbf{B}^{eq.}$

| | | | *J* (Hz) | | | | | | | Predicted Conformational Preferences |
|---|---|---|---|---|---|---|---|---|---|---|
| **Compd** | **R** | **Y** | **16a-H$^a$,P** | **16a-H$^b$,P** | **16b-H$^a$,P** | **16b-H$^b$,P** | **16a-H$^a$,16a-H$^b$** | **16b-H$^a$,16b-H$^b$** | **$J_w$$^b$** | |
| **3a** | O | OPh | 0.8 | 23.2 | 0 | 23.5 | -11.2 | -11.2 | 3.0 | $\mathbf{A}^{ax.}$ |
| **4a** | O | Ph | 17.6 | 5.9 | 5.7 | 17.7 | -11.2 | -11.3 | 2.2 | $(\mathbf{A}^{ax.}) \rightleftharpoons \mathbf{T}^{ps.eq.}$ |
| **5a** | O | Cl | 2.8 | 28.3 | 0 | 28.2 | -11.3 | -11.5 | 3.2 | $\mathbf{A}^{ax.}$ |
| **6a** | O | Mu$^a$ | 4.3 | 20.0 | 2.1 | 20.8 | -11.3 | -11.2 | 3.1 | $\mathbf{A}^{ax.} \rightleftharpoons (\mathbf{T}^{ps.eq.})$ |
| **7a** | βOH,H | OPh | 2.0 | 23.2 | 0 | 22.8 | -11.6 | -11.0 | 2.8 | $\mathbf{A}^{ax.}$ |
| **8a** | βOH,H | Ph | 17.0 | 7.2 | 6.1 | 16.6 | -11.6 | -11.0 | 1.8 | $(\mathbf{A}^{ax.}) \rightleftharpoons \mathbf{T}^{ps.eq.}$ |
| **9a** | βOH,H | Cl | 3.2 | 28.4 | 0 | 28.2 | -11.8 | -11.1 | 3.1 | $\mathbf{A}^{ax.}$ |
| **10a** | βOAc,H | OPh | 2.8 | 22.2 | 0 | 23.5 | -11.2 | -11.2 | 2.8 | $\mathbf{A}^{ax.}$ |
| **11a** | βOAc,H | Ph | 17.0 | 7.3 | 5.0 | 17.1 | -11.4 | -11.2 | 2.0 | $(\mathbf{A}^{ax.}) \rightleftharpoons \mathbf{T}^{ps.eq.}$ |



$\mathbf{A}^{eq.}$ $\mathbf{T}^{ps.ax.}$ $\mathbf{B}^{ax.}$

| | | | *J* (Hz) | | | | | | | Predicted Conformational Preferences |
|---|---|---|---|---|---|---|---|---|---|---|
| **Compd** | **R** | **Y** | **16a-H$^a$,P** | **16a-H$^b$,P** | **16b-H$^a$,P** | **16b-H$^b$,P** | **16a-H$^a$,16a-H$^b$** | **16b-H$^a$,16b-H$^b$** | **$J_w$$^b$** | |
| **3b** | O | OPh | 4.7 | 19.4 | 4.7 | 19.4 | -11.3 | -11.3 | 2.3 | $\mathbf{A}^{eq.} \rightleftharpoons (\mathbf{T}^{ps.ax.})$ |
| **4b** | O | Ph | 2.4 | 20.4 | 0 | 20.8 | -11.2 | -11.2 | 2.6 | $\mathbf{A}^{eq.}$ |
| **5b** | O | Cl | 13.2 | 11.3 | 9.3 | 15.6 | -11.6 | -11.3 | 0 | $\mathbf{A}^{eq.} \rightleftharpoons \mathbf{T}^{ps.ax.} \rightleftharpoons \mathbf{B}^{ax.}$ |
| **6b** | O | Mu$^a$ | 0.8 | 22.6 | 0 | 22.6 | -11.3 | -11.2 | 3.1 | $\mathbf{A}^{eq.}$ |
| **7b** | βOH,H | OPh | 13.0 | 10.6 | 9.5 | 14.3 | -11.2 | -11.2 | 1.0 | $\mathbf{A}^{eq.} \rightleftharpoons \mathbf{T}^{ps.ax.} \rightleftharpoons \mathbf{B}^{ax.}$ |
| **8b** | βOH,H | Ph | 3.8 | 18.8 | 3.9 | 18.2 | -11.4 | -11.0 | 2.2 | $\mathbf{A}^{eq.} \rightleftharpoons \mathbf{T}^{ps.ax.}$ |
| **10b** | βOAc,H | OPh | 14.8 | 8.8 | 8.8 | 15.4 | -11.2 | -11.2 | 1.3 | $\mathbf{A}^{eq.} \rightleftharpoons \mathbf{T}^{ps.ax.} \rightleftharpoons \mathbf{B}^{ax.}$ |
| **11b** | βOAc,H | Ph | 3.3 | 18.7 | 4.4 | 19.2 | -11.3 | -11.1 | 2.3 | $\mathbf{A}^{eq.} \rightleftharpoons (\mathbf{T}^{ps.ax.})$ |

[a]Mu = $N(CH_2CH_2Cl)_2$.
[b]couplings of the equatorial protons on C-16a and C-16b.

## A Typical Procedure is as Follows

**4a** and **4b**: To a stirred solution of $Et_3N$ (0.43 ml, 4 mmol) and **1** (344 mg, 1 mmol) in dichloromethane (15 ml), $PhP(O)Cl_2$ (0.17 ml, 1.2 mmol) was added drop-wise at room temperature under a nitrogen atmosphere. The reaction mixture was refluxed for 3 h then 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*. The crude product **4** was separated by column chromatography on silica gel, using ethyl acetate/ dichloromethane (20:80) as eluent. Compound **4a**: Mp. 247-250 °C; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 14.1 (C-18), 25.6 ($CH_2$), 26.6 ($CH_2$), 29.5 ($CH_2$), 30.9 ($CH_2$), 31.8 ($CH_2$), 37.8 (CH), 44.0 (CH), 47.5 (CH), 49.7 (C-13), 52.0 (d, *J* = 7.2 Hz, C-16), 55.2 (3-OMe), 71. 5 (d, *J* = 6.7 Hz, C-16b), 74.2 (d, *J* = 6.7 Hz, C-16a), 111.8 (C-2), 113.9 (C-4), 125.8 (d, *J* = 182.9 Hz, C-1'), 126.2 (C-1), 129.1 (d, 2C, *J* = 15.3 Hz, C-2' and C-6'), 131.3 (C-10), 131.4 (d, 2C, *J* = 10.5 Hz, C-3' and C-5'), 133.0 (d, *J* = 3.0 Hz, C-4'), 137.6 (C-5), 157.8 (C-3), 216.2 (C-17). MS(EI): m/z = 466 (100) [M+], 389 (12), 341 (11). Compound **4b**: Mp. 117-120 °C; $^{13}$C NMR (100

MHz, $CDCl_3$): δ = 13.9 (C-18), 25.6 ($CH_2$), 26.7 ($CH_2$), 29.5 ($CH_2$), 30.6 ($CH_2$), 31.6 ($CH_2$), 37.8 (CH), 44.0 (CH), 47.4 (CH), 49.4 (C-13), 52.7 (d, *J* = 5.3 Hz, C-16), 55.2 (3-OMe), 69.1 (d, *J* = 6.2 Hz, C-16b), 72.7 (d, *J* = 6.2 Hz, C-16a), 111.7 (C-2), 113.9 (C-4), 125.7 (d, *J* = 196.9 Hz, C-1'), 126.2 (C-1), 128.5 (d, 2C, *J* = 15.7 Hz, C-2' and C-6'), 131.4 (C-10), 132.2 (d, 2C, *J* = 10.4 Hz, C-3' and C-5'), 133.0 (d, *J* = 3.0 Hz, C-4'), 137.4 (C-5), 157.7 (C-3), 215.7 (C-17). MS(EI): m/z = 466 (100) [M+], 341 (20), 172 (24).

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