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Bismuth(III) triflate-catalyzed rearrangement of 16α,17α-epoxy-20-oxosteroids. Synthesis and structural elucidation of new 16α-substituted 17α-alkyl-17β-methyl-Δ^{13}-18-norsteroids

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ABSTRACT

The use of bismuth(III) triflate for the rearrangement of 16α,17α-epoxy-20-oxosteroids is reported. The reactions occur under truly catalytic conditions to afford novel 17α-alkyl-17β-methyl-Δ^{13}-18-nor products bearing different *O*-containing substituents at C16. When the reaction is performed in the absence of acylation agent a mixture of isomeric 16α- and 16β-hydroxy derivatives is obtained, whereas when carried out in the presence of such reagents, the reaction selectively affords the corresponding 16α-acyl rearranged products. The chemoselective rearrangement of 5β,6β;16α,17α-diepoxy-20-oxopregnan-3β-yl acetate to afford a 'backbone' rearranged product bearing the 16α,17α-epoxide group is also reported. Some mechanistic considerations are provided. All rearranged products were the subject of comprehensive structural elucidation, by the use of X-ray crystallography and 2D NMR.

1. Introduction

Steroids are challenging substrates for the synthesis of a wide variety of important biologically active molecules.[1] In particular, steroid rearrangements have been the subject of intense research, which may be explained by the diversity of enthusiastic new skeletons obtained by single-step reactions.[2–4]

One of such family of rearrangements is the acid-catalyzed migration of the angular C18-methyl group to afford olefinic 18-norsteroids.[2,3] This transformation is a particular type of Wagner–Meerwein rearrangement,[5] which proceeds through the formation of a carbocation with 1,2-migration of the C18-methyl group to a neighbouring carbon, generally C17.[2,3]

C18-Methyl migration on steroid backbone was first reported by Cohen et al. by the use of $KHSO_4$ in the dehydration of a 17α-methylestradiol derivative.[6] A variety of C17-substituted steroids have been described to afford 17β-methyl-Δ^{13}-18-norsteroids by Wagner–Meerwein-type rearrangement.[2,3] Both 17β-hydroxy- and 17α-hydroxysteroids, with the alcohol functionality either secondary or tertiary, have been reported to undergo rearrangement to olefinic 18-Norsteroids under acid conditions.[7–12] A similar rearrangement has been described by Stöckl et al. during the study of perfluoracylation for gas chromatographic mass spectrometric determination of anabolic steroids bearing a tertiary C17-hydroxy group, corticosteroids and related compounds.[13–15] Schneider et al. reported that a steroid bearing the 16α,17α-fused oxetan group was converted into a 16α-hydroxymethyl-17β-methyl-Δ^{13}-18-nor derivative.[16] The formation of 17α,17β-dimethyl-Δ^{13}-18-norsteroids from 17β-sulfate derivatives of anabolic 17α-methylsteroids has also been described.[17] On the other hand, treatment of 17α-choro-20-oxo-5α-pregnan-3β-yl acetate with anhydrous NaOAc in glacial AcOH, afforded the corresponding 17β-methyl-Δ^{13}-18-norsteroid in good yield.[18] Quite recently, Iglesias-Arteaga et al. reported the use of the $BF_3 \cdot Et_2O/Ac_2O$ system in the synthesis of polyhydroxylated 17α,17β-dialkyl-Δ^{13}-18-norsteroids by regioselective cleavage of furostanols derived from diosgenin and sarsasapogenin.[19]

The Wagner–Meerwein-type rearrangement of 16α,17α-epoxysteroids has been reported to afford 17β-methyl-Δ^{13}-18-norsteroids bearing an *O*-containing function at C16, which constitutes an important synthetic advantage. The reaction has been initially

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performed with TsOH in Ac_2O, leading to 16α-acetoxy-17β-methyl-Δ^{13}-18-norsteroids in moderate to good yields.[20,21] The use of other Brønsted and Lewis acids, such as H_2SO_4,[22] BF_3[23] or $ZnCl_2$,[24] under stoichiometric conditions and in combination with Ac_2O, have also been described and similar results were obtained.

In the absence of acylation agent, the acid-catalyzed reaction of 16α,17α-epoxy-20-oxopregnane derivatives has been reported to afford a mixture of epimeric 16α-hydroxy- and 16β-hydroxy-17β-methyl-Δ^{13}-18-norsteroids.[25] Several acids, such as TsOH,[26] HF,[27,28] H_2SO_4[22] have been employed in this transformation. The formation of these epimers has been explained by an acid-catalyzed reverse-aldol equilibrium involving the 16-hydroxy-20-keto function of the rearranged steroid.[25] Thus, when the rearrangement is performed with substrates where the 20-keto group is absent, in both 16α,17α-epoxy-20β-hydroxypregnane and 16α,17α-epoxy-cholestane derivatives, using $HClO_4$/MeOH[29] and $HClO_4$/aqueous acetone,[30] respectively, no isomerization at C16 occurs and the corresponding 16α-hydroxy-17β-methyl-Δ^{13}-18-nor derivatives are obtained in good yields.

More recently, during an investigation related to the synthesis of the potent anti-tumour saponin OSW-1 aglycone, several 16α,17α-epoxysteroids were treated with 70% formic acid and the Wagner–Meerwein-type rearrangement took place to afford Δ^{13}-18-norsteroids, which, in some cases, underwent subsequent lactonization between the 17α-side chain and the 16α-formyl group.[31,32]

From the synthetic point of view, the rearrangement of the C18-methyl group to afford Δ^{13}-18-norsteroids allowed the introduction of a double bond at the C/D rings junction, along with migration of the angular methyl group to the 17β-position. This transformation has been used for aromatization of ring C of androstane[33–36] and pregnane compounds.[37] Δ^{13}-Steroids have been reported as useful intermediates for a number of active compounds.[8] Weak anti-androgenic activity by systemic administration has been found for some 17β-methyl-Δ^{13}-18-norsteroids.[38,39] However, a strong anti-androgenic effect has been observed with these compounds after topic administration, which led to their application as putative dermatics.[40]

The large amounts of toxic and corrosive reagents needed, associated with the rough reaction conditions and tedious work-up procedures, make the classical methods for the Wagner–Meerwein-type rearrangement of 16α,17α-epoxy-20-oxosteroids inconvenient, even at the laboratory scale. Therefore, new catalytic processes that use environmentally friendly, cheap, and easily available reactants, under catalytic conditions, combined with the reduction of the amounts of acylation agents employed to perform this ring D rearrangement, would be of considerable interest.

Bismuth(III) salts have emerged in the past few years as suitable reagents/catalysts for development of new chemical processes under more 'ecofriendly' conditions.[41–45] As part of our current interest on the development of new bismuth-based processes[46] applied to natural product chemistry,[47–51] we report herein the bismuth triflate-catalyzed Wagner–Meerwein-type rearrangement of 16α,17α-epoxy-20-oxosteroids. To the best of our knowledge, this is the first report on the use of truly catalytic conditions to promote the rearrangement of 16α,17α-epoxy-20-oxosteroids to the corresponding 17β-methyl-Δ^{13}-18-nor products bearing different *O*-containing substituents at C16. We also report the chemoselective rearrangement of 5β,6β;16α,17α-diepoxy-20-oxopregnan-3β-yl acetate to afford a 'backbone' rearranged product with its 16α,17α-epoxide group intact. Full and comprehensive structural elucidation of all rearranged products was made using X-ray crystallography and 2D NMR techniques.

2. Results and discussion

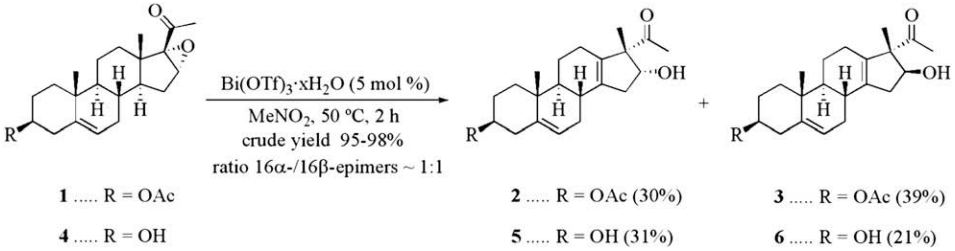
2.1. Bismuth(III) salt-catalyzed rearrangement of 16α,17α-epoxy-20-oxo-steroids

We have recently reported the use of bismuth(III) salts as catalysts for the Westphalen and 'backbone' rearrangements of 5β,6β-epoxysteroids. These reactions involve the migration of one or two of the angular C18 and C19 methyl groups with formation of a double bond on ring B or D of the steroid nucleus.[50] The success achieved with these reactions led us to explore the use of $Bi(OTf)_3 \cdot xH_2O$ as catalyst for the rearrangement of 16α,17α-epoxy-20-oxo-steroid **1**, using $MeNO_2$ as solvent. At rt, in the presence of 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, the reaction proceeded slowly, with low substrate conversion after 20 h. However, when the temperature was raised to 50 °C, under the same reaction conditions, full conversion of the starting epoxide **1** was observed and two products were formed, nearly in equal amounts, after 2 h (Scheme 1). Analysis of the ^1H NMR spectrum of the reaction crude showed a ratio of 52:48 between products **2** and **3**, as determined by integration of their 16-H signals. The 16α- and 16β-hydroxy-17β-methyl-Δ^{13}-18-norsteroids **2** and **3** were isolated by flash column chromatography in 30% and 39% yield, respectively, and identified as the result of a Wagner–Meerwein-type rearrangement, involving the migration of the angular C18-methyl group from C13 to C17 with formation of a double bond at C13=C14.

Similarly, under the same reaction conditions, using 16α,17α-epoxy-20-oxo-steroid **4** as substrate, the 16α- and 16β-hydroxy-17β-methyl-Δ^{13}-18-norsteroids **5** and **6** were obtained in 31% and 21% yield, respectively, after separation by flash column chromatography (Scheme 1).

Complementary study was carried out to gain further insight on the Wagner–Meerwein-type rearrangement of 16α,17α-epoxy-20-oxo-steroids, catalyzed by $Bi(OTf)_3 \cdot xH_2O$.

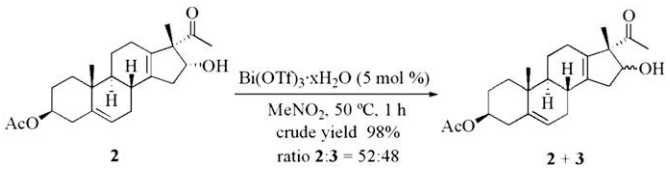
Thus, when the reaction of **1** was performed in 1,4-dioxane, a low dielectric constant solvent, in the presence of 10 mol % of $Bi(OTf)_3 \cdot xH_2O$, very low reactivity was detected after 24 h of reaction, at 50 °C, as observed by TLC. This result shows the importance of the reaction solvent for the reaction path, as has been previously noted by Mohan et al. on the bismuth triflate-catalyzed epoxyolefin cyclization reaction[52] and by ourselves, on the bismuth(III) salts-catalyzed Westphalen and 'backbone' rearrangements.[50] It is likely that a high dielectric constant solvent, such as



Scheme 1. $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement of 16α,17α-epoxy-20-oxo-steroids **1** and **4**.

$MeNO_2$, has a stronger contribution for the stabilization of intermediary cationic species, allowing a successful rearrangement.

Treatment of the 16α-hydroxy-17β-methyl-Δ^{13}-18-norsteroid **2** with 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, in $MeNO_2$, at 50 °C, afforded a mixture of both C16-epimers **2** and **3**, after 1 h of reaction, in a ratio of 52:48, as determined by integration of their 16-H signals in the ^1H NMR spectrum of the crude (Scheme 2). Thus, under the reaction conditions of the rearrangement of the 16α,17α-epoxy-20-oxo-steroid **1**, epimerization at C16 stereocenter occurred for compound **2**.

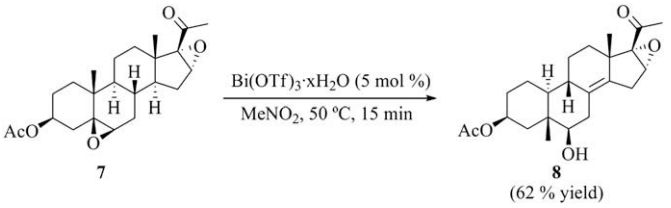


Scheme 2. $Bi(OTf)_3 \cdot xH_2O$-catalyzed epimerization at C16 of the 16α-hydroxy-17β-methyl-Δ^{13}-18-norsteroid **2**.

Taking into account our recent report related to the $Bi(OTf)_3 \cdot xH_2O$-catalyzed Wagner–Meerwein rearrangement of betulin to allobetulin wherein it has been demonstrated that participation of a Brønsted acid species formed in situ from bismuth(III) salt occurs,[51] we applied a similar set of experiments to determine whether the observed reactivity on the steroid ring D rearrangement is due to Lewis or Brønsted acid catalysis. Thus, the reaction of 16α,17α-epoxy-20-oxo-steroid **1** was therefore performed in the presence of both 2,6-di-*tert*-butylpyridine (DTBP)[53] and $BiPh_3$, two known proton scavengers, in two separate experiments [0.1 mmol of **1**, 5 mol % of $Bi(OTf)_3 \cdot xH_2O$ and 15 mol % of proton scavenger (DTBP or $BiPh_3$), in $MeNO_2$, at 50 °C]. In both cases, no reactivity was found after 2 h of reaction. Using 15 mol % of TfOH as catalyst, the rearrangement reaction of **1** was completed after 1 h of reaction, quantitatively affording compounds **2** and **3** [0.1 mmol of **1**, 15 mol % of TfOH, in $MeNO_2$ at 50 °C, ratio **2**/**3**=53:47, as determined by integration of their 16-H signals in the ^1H NMR spectrum of the reaction crude]. On the other hand, when the reaction was performed in the presence of 10 mol % of $La(OTf)_3$, a non-hydrolyzable Lewis acid catalyst,[54] no conversion of **1** was observed after 24 h. Thus, these results point to generation of a Brønsted acid in situ, as the true catalytic species involved in the $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement of the 16α,17α-epoxy-20-oxo-steroid **1**.

Based on these data, the obtention of the 16α-hydroxy-17β-methyl-Δ^{13}-18-norsteroids **2** and **5** can be rationalized as follows. An in situ generated Brønsted acid species from $Bi(OTf)_3 \cdot xH_2O$, catalyzes the ring opening of the 16α,17α-epoxide, creating a tertiary carbocation at C17, which induces stereoselective 1,2-migration of the C18-methyl group to the 17β-position. In fact, as pointed out by Kočovský et al., Wagner–Merwein nonconcerted rearrangements with development of carbocation centres result in 1,2-migration that occurs on the same plane (sp^2 alignment factor).[55] Due to the C18–CH_3 → C17–CH_3 shift, a carbocation centred at C13 is formed, and further 14α-H elimination originates the Δ^{13}-double bond (Scheme 3, A). Formation of the 16β-epimers **3** and **6** can be explained by the existence of an acid-catalyzed reverse-aldol equilibrium involving the 16-hydroxy-20-keto function of the rearranged steroid, under the reaction conditions employed, which is responsible for the epimerization at C16, as previously discussed by Herzog et al.[26,25] (Scheme 3, B).

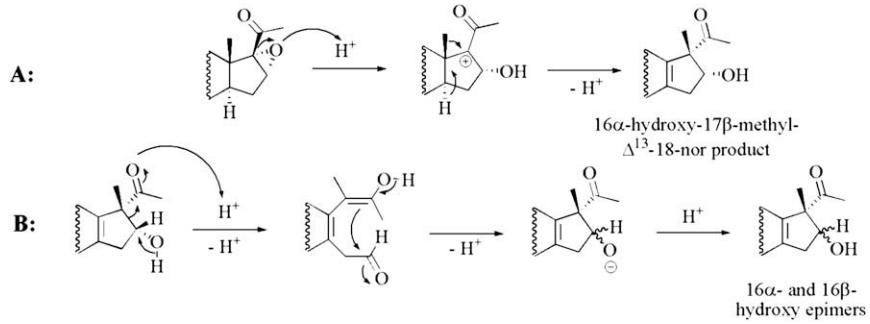
The $Bi(OTf)_3 \cdot xH_2O/MeNO_2$ system has also been used for the 'backbone' rearrangement of 5β,6β-epoxysteroids either 5β,14β-dimethyl-$\Delta^{13(17)}$-18,19-dinor- or 5β-methyl-$\Delta^{8(14)}$-18-norsteroids were obtained.[50] Thus, a chemoselectivity study was undertaken on the 5β,6β;16α,17α-diepoxysteroid **7** to determine whether the rearrangement would occur preferentially at the 5β,6β- or at the 16α,17α-epoxide group. In fact, with 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, in $MeNO_2$, at 50 °C, full conversion of the 5β,6β;16α,17α-diepoxide **7** was observed after 15 min of reaction, as observed by TLC control. The reaction crude was subjected to flash column chromatography, and the rearranged 5β-methyl-$\Delta^{8(14)}$-18-norsteroid **8**, bearing an intact 16α,17α-epoxide function, was isolated in 62% yield (Scheme 4).



Scheme 4. $Bi(OTf)_3 \cdot xH_2O$-catalyzed 'backbone' rearrangement of 5β,6β;16α,17α-diepoxysteroid **7**.

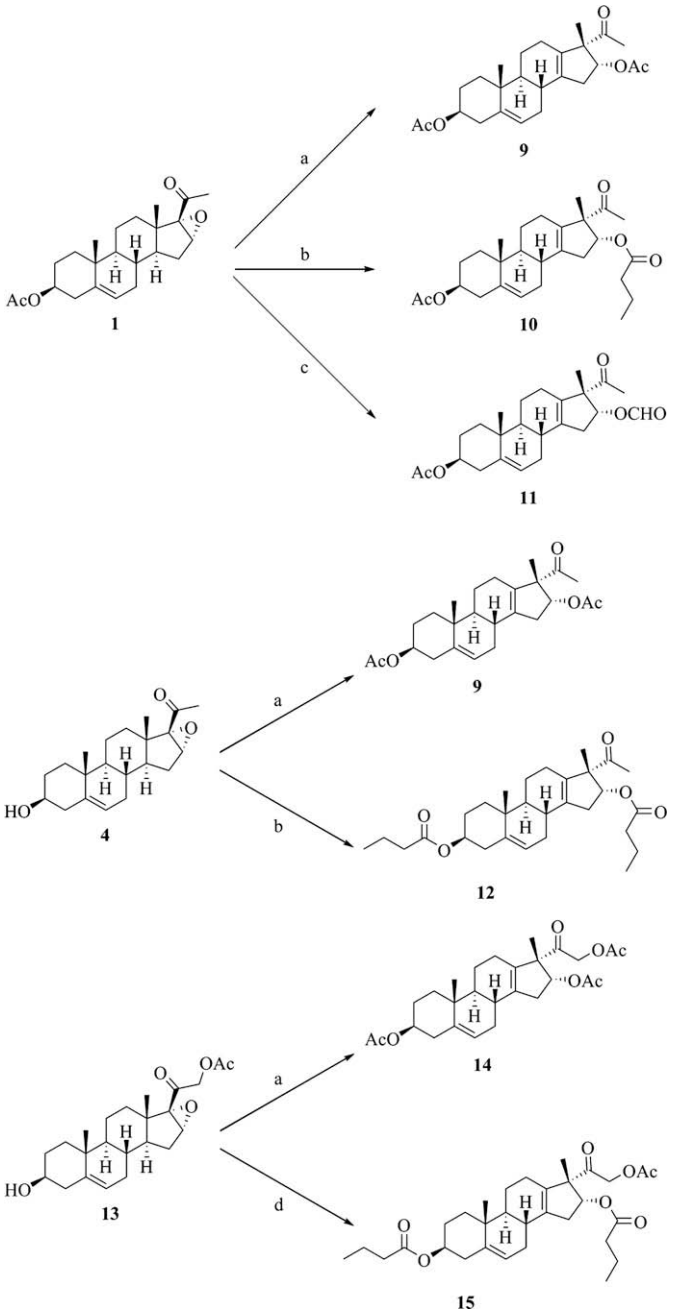
The results obtained so far evidenced the ability of $Bi(OTf)_3 \cdot xH_2O$ to catalyze the Wagner–Meerwein-type rearrangement of 16α,17α-epoxy-20-oxosteroids **1** and **4**. However, due to the presence of the 20-keto group, a reverse-aldol equilibrium establishes between the initially formed 16α-hydroxy-17β-methyl-Δ^{13}-18-norsteroids and their C16-epimers, which results in a decrease on the selectivity of the reaction. To overcome this situation, the reaction has been generally performed in Ac_2O as solvent.[23,24] Under these reaction conditions, it has been assumed that the rearrangement firstly affords the 16α-hydroxy rearranged products, which after fast acylation gives 16α-acetoxy-17β-methyl-Δ^{13}-18-norsteroids, in good to high yields. These compounds do not undergo further isomerization at C16, and therefore more selective transformations were achieved.[24]

Bismuth(III) salts have been reported as effective catalysts for acylation reactions.[56–58] Thus, we decided to perform the



Scheme 3. Proposed mechanism for the formation of 16α- and 16β-hydroxy-17β-methyl-Δ^{13}-18-norsteroids.

$Bi(OTf)_3 \cdot xH_2O$-catalyzed reaction of the 16α,17α-epoxide **1** in presence of acylation agents (Scheme 5, Table 1). Although several authors described the use of Ac_2O as solvent to perform this rearrangement,[23,24] we started our study using 1.5 equiv of Ac_2O in $MeNO_2$, at 50 °C, in the presence of 5 mol% of $Bi(OTf)_3 \cdot xH_2O$. However, as observed by TLC control, the C16-epimerization still occurred and both rearranged products **2** and **3** were detected, along with minor side products, after 24 h of reaction.



Scheme 5. $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement of 16α,17α-epoxy-20-oxosteroids **1**, **4** and **13** in the presence of an acylation agent. Reaction conditions: (a) Ac_2O (10 equiv), $Bi(OTf)_3 \cdot xH_2O$ (5 mol%), $MeNO_2$, rt; (b) $(CH_3CH_2CH_2CO)_2O$ (10 equiv), $Bi(OTf)_3 \cdot xH_2O$ (5 mol%), $MeNO_2$, rt; (c) $Bi(OTf)_3 \cdot xH_2O$ (5 mol%), HCO_2Et, reflux; (d) $(CH_3CH_2CH_2CO)_2O$ (10 equiv), $Bi(OTf)_3 \cdot xH_2O$ (10 mol%), $MeNO_2$, rt.

The reaction was then carried out with 50 equiv of Ac_2O, under the same reaction conditions, and the 3β,16α-diacetoxy-17β-methyl-Δ^{13}-18-norsteroid **9** was obtained in nearly quantitative amounts, after 1 h. The reaction was found to occur under mild conditions using 10 equiv of Ac_2O, in $MeNO_2$, at rt, and the rearranged product **9** was obtained from **1**, in 95% yield (Scheme 5, Table 1, entry 1).

Table 1
$Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement of 16α,17α-epoxy-20-oxosteroids **1**, **4** and **13** in the presence of an acylation agent[a]

Entry	Substrate (mmol)	Acylation agent	Time (h)	Product	Yield[b] (%)
1	**1** (0.50)	Ac_2O	1	**9**	95
2	**1** (0.60)	$(CH_3CH_2CH_2CO)_2O$	2.5	**10**	70
3	**1** (0.50)	HCO_2Et (10 mL)[c]	24	**11**	54
4	**4** (0.50)	Ac_2O	1	**9**	93
5	**4** (0.25)	$(CH_3CH_2CH_2CO)_2O$	1.5	**12**	71
6	**13** (0.25)	Ac_2O	2	**14**	90
7	**13** (0.25)	$(CH_3CH_2CH_2CO)_2O$[d]	2	**15**	77

[a] Reaction conditions: 5 mol% of $Bi(OTf)_3 \cdot xH_2O$, 10 equiv of acylation agent, $MeNO_2$ (3 mL/0.10 mmol of substrate), rt.
[b] Isolated yields.
[c] The reaction was performed in HCO_2Et (10 mL), at reflux temperature.
[d] The reaction was performed with 10 mol% of $Bi(OTf)_3 \cdot xH_2O$.

Using these optimized conditions, the 16α,17α-epoxy-20-oxosteroids **4** and **13** were converted into the 16α-acetoxy-17β-methyl-Δ^{13}-18-norsteroids **9** and **14**, in 93% and 90% yield, respectively, after a relatively short reaction time (Scheme 5, Table 1, entries 4 and 6).

To enlarge the scope of this new $Bi(OTf)_3 \cdot xH_2O$-catalyzed process for the rearrangement of 16α,17α-epoxy-20-oxosteroids, other acylation agents were screened, in order to obtain 17β-methyl-Δ^{13}-18-norsteroids bearing different acyl groups at positions C3, C16 and C21.

Thus, when butyric anhydride (10 equiv) was added to a solution of **1**, in $MeNO_2$, at rt, in the presence of 5 mol% of $Bi(OTf)_3 \cdot xH_2O$, the corresponding 3β-acetoxy-16α-butyryloxy-17β-methyl-Δ^{13}-18-nor derivative **10** was isolated in 70% yield, after 2.5 h (Scheme 5, Table 1, entry 2). The reaction performed with the 16α,17α-epoxide **4**, bearing a 3β-hydroxyl function, led to the preparation of the 3β,16α-dibutyryloxy rearranged product **12**, in 71% yield, after 1.5 h (Scheme 5, Table 1, entry 5). The 17β-methyl-Δ^{13}-18-norsteroid **15**, bearing an acetoxy group at C21 and two butyryloxy functions at C3 and C16, was obtained from 16α,17α-epoxy-20-oxosteroid **13** in 77% yield, after 2 h (Scheme 5, Table 1, entry 7). This reaction, was carried out with 10 mol% of $Bi(OTf)_3 \cdot xH_2O$, since 5 mol% of this catalyst was not enough to achieve full substrate conversion.

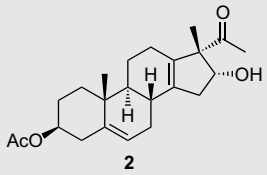
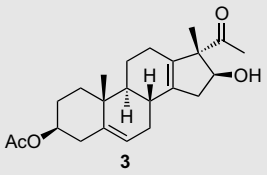
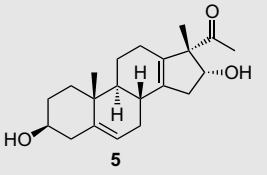
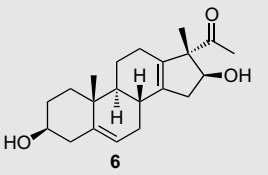
The use of ethyl formate as formylation agent is well established, and several bismuth(III) salts have been reported as effective catalysts for the formylation of primary and secondary alcohols.[59] The method described by Mohammadpoor-Baltork et al. uses ethyl formate both as solvent and acylation agent, at reflux temperature, in the presence of catalytic amounts of $BiCl_3$, $Bi(TFA)_3$ or $Bi(OTf)_3 \cdot xH_2O$.[59]

Thus, the reaction of 16α,17α-epoxy-20-oxosteroid **1** in refluxing ethyl formate, in the presence of 5 mol% of $Bi(OTf)_3 \cdot xH_2O$ led to full substrate conversion after 24 h. The major product, as observed on TLC plates, was isolated by flash column chromatography in 54% yield, and characterized as the 3β-acetoxy-16α-formyloxy-17β-methyl-Δ^{13}-18-nor derivative **11** (Scheme 5, Table 1, entry 3).

2.2. Structural elucidation of 16α-substituted 17α-alkyl-17β-methyl-Δ^{13}-18-norsteroids

The rearranged products **3**,[60] **5**[22] and **6**,[22] bearing a hydroxyl group at C16, have been previously obtained, but the available analytical data are not complete. Compound **9** has also been previously described.[24] However, as far as we known, the 16α-hydroxy-17β-methyl-Δ^{13}-18-norsteroid **2**, the 'backbone' rearranged 5β-methyl-$\Delta^{8(14)}$-18-norsteroid **8** and the 16α-acyl-17β-methyl-

Table 2
Selected ^{1}H and ^{13}C NMR data of compounds **2**, **3**, **5** and **6**[a,b]

	 **2**		 **3**		 **5**		 **6**	
Position	δH	δC	δH	δC	δH	δC	δH	δC
3	4.60, m	73.9	4.61, m	73.9	3.52, m	71.8	3.53, m	71.8
3β-OCOCH$_3$	—	170.5	—	170.5	—	—	—	—
3β-OCOCH$_3$	2.03, d, 0.5 Hz	21.4	2.04, s	21.4	—	—	—	—
5	—	140.3	—	140.3	—	141.4	—	141.4
6	5.43, m	122.3	5.44, m	122.2	5.39, m	121.3	5.40, m	121.3
13	—	135.8	—	136.0	—	135.8	—	136.0
14	—	140.0	—	138.2	—	140.0	—	138.3
16	4.12, t, 7.4 Hz	81.6	4.51, dd, 7.0 and 5.5 Hz	75.5	4.13, t, 7.3 Hz	81.5	4.50, dd, 7.0 and 5.5 Hz	75.5
17	—	64.9	—	66.5	—	65.0	—	66.5
17β-CH$_3$	1.25, d, 1.0 Hz	19.7	1.17, s	13.5	1.23, s	19.7	1.16, s	13.5
19	0.99, s	18.5	0.99, s	18.6	0.96, s	18.6	0.97, s	18.7
20	—	212.4	—	211.5	—	212.6	—	211.7
21	2.13, d, 0.66 Hz	28.3	2.11, s	26.5	2.12, s	28.3	2.10, s	26.5

[a] ^{1}H NMR: δ ppm, multiplicity, *J* Hz; ^{13}C NMR: δ ppm.
[b] NMR samples prepared in $CDCl_3$.

Δ^{13}-18-norsteroids **10**, **11**, **12**, **14** and **15** are new steroid compounds. The complete structural elucidation of these seven new steroid products, as well as the other previously known compounds obtained in this study, was made using 2D NMR and X-ray crystallography techniques.

The most significant ^{1}H and ^{13}C NMR data of the 16α-hydroxy-17β-methyl-Δ^{13}-18-norsteroids **2** and **5**, and their 16β-hydroxy-epimers **3** and **6** are presented on Table 2. These values were determined by combining 1D and 2D NMR techniques.

EIMS spectra of the rearranged Δ^{13}-18-norsteroids showed a molecular ion peak with the same value of their corresponding starting 16α,17α-epoxy-20-oxosteroid (372 *m*/*z* for **2** and **3** and 330 *m*/*z* for **5** and **6**), which is indicative of rearrangement involving formation of isomeric products. In addition to the presence of a band located at 3455–3464 cm^{-1} in the IR spectra of the 3β-acetoxy derivatives **2** and **3**, the absence of the 16β-H signal characteristic of 16α,17α-epoxy-20-oxosteroids, together with the signal at 4.12–4.13 ppm for **2** and **5** or at 4.50–4.51 ppm for **3** and **6**, in the ^{1}H NMR spectra, confirmed the ring opening of the epoxide function and its conversion into an hydroxyl group. Analysis of the ^{13}C NMR spectra showed the presence of two olefinic carbons other than C5 and C6. These signals were not found in the DEPT experiment, which suggests that a new double bond, located at a ring fusion, should be present on compounds **2**, **3**, **5** and **6**. HMBC experiment provided additional data that allowed confirmation of the 17β-methyl-Δ^{13}-18-nor structure (Fig. 1). The methyl protons at 1.16–1.25 ppm are correlated with the quaternary carbon at 64.9–66.5 ppm, attributed to C17, as well as with the carbonyl C20 at 211.5–212.6 ppm, the C16 at 81.5–81.6 ppm (compounds **2** and **5**) or at 75.5 ppm (compounds **3** and **6**) and the quaternary olefinic carbon at 135.8–136.0 ppm. Thus, the methyl group at 1.16–1.25 ppm is bound to C17, and was assigned as 17-CH$_3$.The quaternary olefinic carbons at 135.8–136.0 ppm and 138.2–140.0 ppm were attributed to C13 and C14, respectively. Both C13 and C14 showed also HMBC correlation with 16-H. The chemical shift values of these quaternary olefinic carbons are in agreement with those reported by De Brabandere et al. for related 17,17-dialkyl-Δ^{13}-18-norsteroids.[15] The configuration of the hydroxyl group at C16 was deduced from the NOESY experiment (Fig. 1). Both compounds **2** and **5**, showed a strong NOE interaction between their 16-H signal at 4.12–4.13 ppm and the 17β-CH$_3$ group at 1.23–1.25 ppm, while no cross-peak was found between the 16-H signal (4.50–4.51 ppm) and the 17β-CH$_3$ (1.16–1.17 ppm) in the NOESY spectra of the rearranged Δ^{13}-18-norsteroids **3** and **6**. Thus, the 16-H of compounds **2** and **5** has β-conformation while their C16-hydroxyl function is α-oriented. The C16-hydroxyl group present in compounds **3** and **6** has opposite conformation and is β-oriented.

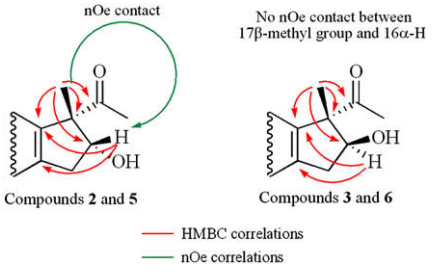


Figure 1. Key HMBC and NOE spectroscopy correlations for the 16α- and 16β-hydroxy-17β-methyl-Δ^{13}-18-norsteroids **2**, **5**, **3** and **6**.

The Bi(OTf)$_3$·*x*H$_2$O-catalyzed reaction of 5β,6β;16α,17α-diepoxysteroid **7** in MeNO$_2$ afforded the 5β-methyl-Δ$^{8(14)}$-18-norsteroid **8** as the major reaction product, as the result of a partial 'backbone' rearrangement. EI-mass spectrometry performed on a sample of compound **8** showed the same 346 *m*/*z* molecular ion of the 5β,6β;16α,17 α-diepoxysteroid **7**, which is indicative of an isomeric product. A band located at 3383 cm^{-1} in the IR spectrum confirmed the existence of a hydroxyl group. The ^{13}C NMR spectrum displayed two carbonyl carbons, which were attributed to the acetyl group (170.4 ppm) and to C20 (204.5 ppm), respectively. Another two high field signals were observed in the ^{13}C NMR spectrum at 131.8 ppm and 132.4 ppm. These signals were absent in the DEPT experiment, which is indicative of olefinic quaternary carbons. In the ^{1}H NMR spectrum, methyl proton signals were found at 1.04, 1.25, 2.02 and 2.04 ppm. The signal at 2.02 ppm, which is correlated with the carbon at 21.5 ppm in the HMQC experiment and the carbonyl carbon at 170.4 ppm in the HMBC spectrum, was attributed to the acetoxy methyl group, whereas the signal at 2.04 was attributed to the methyl at C21 (26.0 ppm). The three protons with high chemical shift values (5.05 ppm, 3.77 ppm and 3.13 ppm), which were found to be bound to the carbons located at 69.2 ppm (C3), 60.6 ppm (C16) and 79.1 ppm (C6), were assigned as 3-H, 16-H and 6-H, respectively. A number of key proton connectivities were determined by COSY spectroscopy for these signals. The 3-H (5.05 ppm) couples with protons located at 2.16,

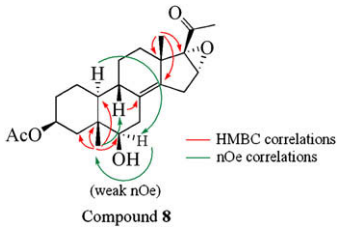
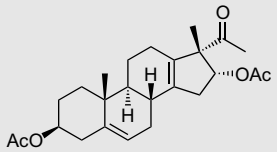


Figure 2. Key HMBC and NOE spectroscopy correlations for the 5β-methyl-$\Delta^{8(14)}$-18-norsteroid **8**.

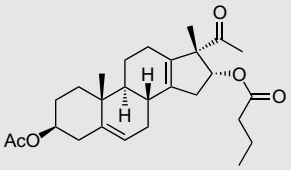
1.90, 1.47 and 1.23 ppm. The geminal pair at 2.16 and 1.23 ppm is attached to a carbon located at 40.9 ppm (C4), which showed cross-peaks with 6-H and the methyl protons at 1.04 ppm, in the HMBC spectrum. The other geminal pair, 1.90 ppm and 1.47 ppm, is bound to the carbon atom at 30.6 ppm (C2). The 16-H showed two cross-peaks in the COSY experiment, with the signals at 2.81 ppm and 2.39 ppm, which are bound to C15 (30.1 ppm). Strong correlations were observed between the 6-H signal at 3.13 ppm and both protons at 2.26 and 2.02 ppm, which are connected to a carbon atom with chemical shift value of 35.6 ppm (C7). The location of the olefinic quaternary carbons and both methyl groups attached to the steroid nucleus was deduced from correlations found in the HMBC experiment (Fig. 2). The methyl group at 1.25 ppm, which showed a cross-peak with the carbon at 21.0 ppm in the HMQC spectrum, is located on its usual position bound to C13 (43.1 ppm). It correlates with the quaternary C17 (70.9 ppm), C13, and an olefinic carbon at 132.4 ppm. As the double bond is tetra-substituted, this olefinic carbon was assigned as C14 and the other olefinic carbon as C8 (131.8 ppm). The methyl protons at 1.04 ppm showed correlation with the carbon at 12.3 ppm in HMQC experiment. This methyl group is bound to C5. The sequence of C4 to C10 was elucidated from the correlations observed with the 5-CH_3 protons at 1.04 ppm and 6-H (3.13 ppm) in the HMBC experiment. A cross peak between 6-H and the methyl carbon at 12.3 ppm was found as well as between the methyl protons at 1.04 ppm and C6. Correlations were also found between C4 (40.9 ppm), a quaternary carbon at 39.3 ppm and a methine carbon at 45.9 ppm, with both the methyl protons at 1.04 ppm and 6-H. These findings allowed the assignment of the quaternary carbon as C5 (39.3 ppm). This carbon is bound to C4, C6, the methyl carbon at 12.3 ppm (5-CH_3), and to the methine carbon at 45.9 ppm, which was assigned as C10. This carbon showed a cross-peak with the signal at 1.01 ppm (10-H) in the HMQC. The COSY experiment showed that 10-H is coupled with the protons at 1.89 ppm, 1.63 ppm and 1.38 ppm. The germinal pair at 1.63 ppm and 1.38 ppm is connected to the carbon at 19.7 ppm (C1). The proton at 1.89 ppm, showed a cross-peak with the olefinic C8 on the HMBC, and was then assigned as 9-H. The orientation of both 9-H and 10-H was deduced from the NOESY experiment (Fig. 2). A strong NOE interaction was found between 5-CH_3 (1.04 ppm) and the signal at 1.89 ppm (9-H). On the other hand, 6-H (3.13 ppm), which has no cross-peak with the signal at 1.89 (9-H) in the NOESY spectrum, showed correlation with 10-H (1.01 ppm) and also a weak NOE interaction with the methyl protons at 1.04 ppm,. Thus, alike 5-CH_3, 9-H is β-oriented and 10-H has α-configuration, which results on a trans-fused (5β,10α) structure for rings A and B.

The most significant ^{1}H and ^{13}C NMR data for the 16α-acyl-17α-alkyl-17β-methyl-Δ^{13}-18-norsteroids **9**, **10**-**12**, **14** and **15** are depicted on Tables 3 and 4. The great similarity observed between the ^{13}C NMR chemical shifts values of C13, C14, C16 and C17, the carbon atoms involved in the rearrangement reaction, with those of their parent 16α-hydroxy derivatives **2** and **5**, is quite evident. The location of the new double bond at C13═C14 and the position of the 17β-methyl group have been deduced from the NMR data in a similar fashion to what has been done for rearranged compounds **2**, **3**, **5** and **6**. The main features previously described have also been found in the spectra of 16α-acyl-17α-alkyl-17β-methyl-Δ^{13}-18-norsteroids **9**, **10**, **12**, **14** and **15**. The ^{1}H NMR chemical shift values of 17β-CH_3 (1.18–1.27 ppm) and 19-CH_3 (0.98–1.01 ppm) are similar to the values found in the rearranged compounds **2**, **3**, **5** and **6**. Due to the presence of an acyl group at C16, 16β-H resonates at higher field (5.16–5.29 ppm). The presence of the 21-acetoxyl group present in compounds **14** and **15** is confirmed by the presence of methyl

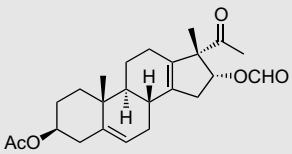
Table 3
Selected ^{1}H and ^{13}C NMR data of compounds **9**–**11**[a,b]



9



10

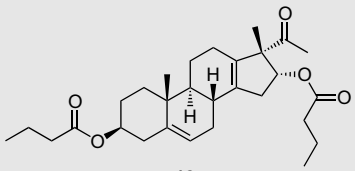


11

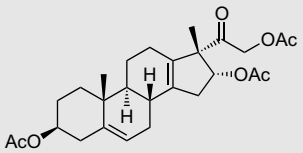
Position	δH	δC	δH	δC	δH	δC
3	4.60, m	73.8	4.59, m	73.8	4.62, m	73.8
3β-OCOCH$_3$	—	170.4	—	170.4	—	170.5
3β-OCOC*H*$_3$	2.02, s	21.3	2.01, s	21.3	2.04, s	21.4
5	—	140.5	—	140.5	—	140.6
6	5.43, m	122.0	5.42, m	122.0	5.45, m	122.0
13	—	136.9	—	136.9	—	137.1
14	—	139.1	—	139.1	—	139.1
16	5.16, dd, 8.3 and 6.2 Hz	81.7	5.16, dd, 8.2 and 6.2 Hz	81.5	5.29, t, 7.2 Hz	81.5
16α-*O*-acyl	COCH$_3$: 1.99, s	*C*OCH$_3$: 170.4; COC*H*$_3$: 21.0	16α-OCOCH$_2$CH$_2$CH$_3$. CH$_3$: 0.89, t, 7.4 Hz; CH$_2$: 1.58, m, 7.4 Hz; *C*H$_2$CO: 2.21, t, 7.4 Hz	16α-OCO: 173.1	16α-OCHO: 8.02, s	16α-OCHO: 160.4
17	—	65.1	—	65.0	—	65.0
17β-CH$_3$	1.19, s	19.9	1.18, s	19.8	1.23, s	19.9
19	0.99, s	18.5	0.98, s	18.5	1.01, s	18.6
20	—	208.8	—	208.8	—	208.6
21	2.11, s	27.5	2.10, s	27.5	2.14, s	27.6

[a] ^{1}H NMR: δ ppm, multiplicity, *J* Hz; ^{13}C NMR: δ ppm.
[b] NMR samples prepared in CDCl$_3$.

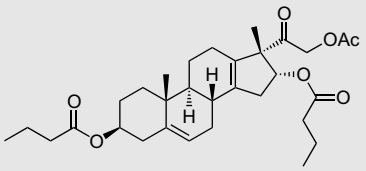
Table 4
Selected ^{1}H and ^{13}C NMR data of compounds **12**, **14** and **15**[a,b]



12



14



15

Position	δ H	δ C	δ H	δ C	δ H	δ C
3	4.62, m	73.5	4.61, m	73.8	4.63, m	73.5
5	—	140.6	—	140.6	—	140.7
6	5.43, m	122.0	5.44, m	121.9	5.44, m	121.9
13	—	136.9	—	136.3	—	136.3
14	—	139.1	—	140.1	—	140.2
16	5.17, dd, 8.3 and 6.3 Hz	81.5	5.20, dd, 8.2 and 6.6 Hz	81.5	5.22, dd, 7.8 and 7.1 Hz	81.3
17	—	65.0	—	63.2	—	63.3
17β-CH_3	1.19, s	19.6	1.27, s	19.7	1.27, s	19.7
19	0.99, s	18.6	1.00, s	18.5	1.00, s	18.6
20	—	208.9	—	203.0	—	203.0
21	2.11, s	27.5	4.79, d, 16.6 Hz and 4.90, d, 16.6 Hz	66.8	4.77, d, 16.5 Hz and 4.93, d, 16.5 Hz	66.7
21-$OCOCH_3$	—	—	—	170.1	—	170.2
21-$OCOCH_3$	—	—	2.15, s	20.5	2.15, s	20.5
3β-*O*-acyl and 16α-*O*-acyl groups	3β- and 16α-$OCOCH_2CH_2CH_3$. CH_3: 0.93, t, 7.4 Hz and 0.90, t, 7.4 Hz; CH_2: 1.55–1.66, 4H, m; CH_2CO: 2.25, t, 7.4 2.22, t, 7.4 Hz	3β- OCO: 173.1; 16α-OCO: 173.1	3β-$OCOCH_3$: 2.04, s; 16α-$OCOCH_3$: 2.03, s	3β-$OCOCH_3$: 21.3; 3β-$OCOCH_3$: 170.5; 16α-$OCOCH_3$: 21.0; 16α-$OCOCH_3$: 170.5	3β- and 16α-$OCOCH_2CH_2CH_3$. CH_3: 0.97, t, 7.4 Hz and 0.92, t, 7.4 Hz; CH_2: 1.58–1.68, 4H, m; CH_2CO: 2.27, t, 7.4 Hz and 2.25, t, 7.4 Hz	3β- OCO: 173.1; 16α-OCO: 173.1

[a] ^{1}H NMR: δ ppm, multiplicity, *J* Hz; ^{13}C NMR: δ ppm.
[b] NMR samples prepared in $CDCl_3$.

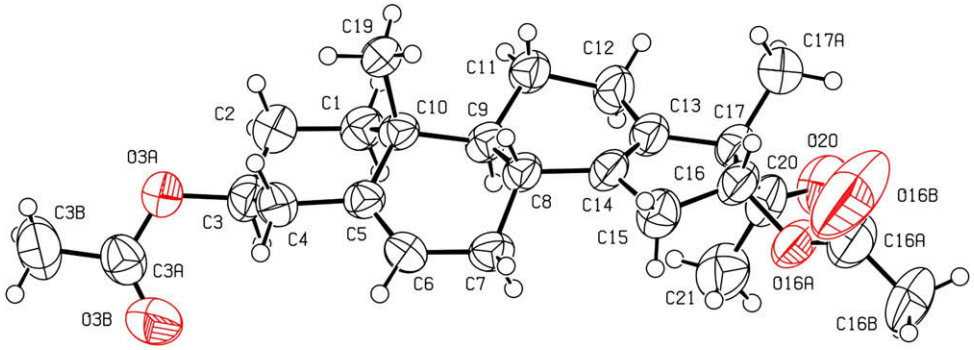


Figure 3. ORTEP diagram of **9** (50% probability level, H atoms of arbitrary sizes).

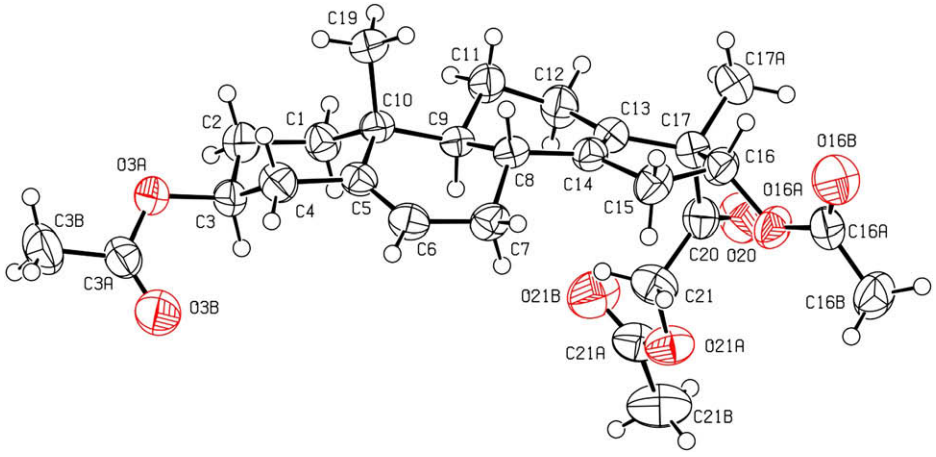


Figure 4. ORTEP diagram of **14** (50% probability level, H atoms of arbitrary sizes).

protons at 2.15 ppm and an additional carbonyl at 170.1–170.2 ppm, in the ^{1}H and ^{13}C NMR spectra, respectively. The butyryloxy group present in compounds **10**, **12** and **15** is clearly confirmed by the existence of the typical triplets (*J*=7.4 Hz) at 0.89–0.97 ppm and 2.21–2.27 ppm, respectively attributed to CH_3 and CH_2CO protons, and a multiplet at 1.55–1.68 ppm of the CH_3CH_2 moiety. When two butyryloxy groups are present, as in compounds **12** and **15**, the ^{1}H NMR signals mentioned above are almost overlapped. Integration

of these signals was consistent with the presence of two butyryloxy functions.

Unequivocal evidence of the molecular structure of both 16α-acetoxy-17β-methyl-Δ^{13}-18-norsteroids **9** and **14** was obtained by the use of single-crystal X-ray crystallography. The molecular structures of compounds **9** and **14** are shown in Figures 3 and 4, as an ORTEP diagram with the corresponding atom numbering scheme. In both molecules, the five-membered D-ring has a C15-envelope conformation as shown by the Cremer and Pople parameters[61] [**9**: q_2=0.180(7) Å, φ_2=108(2)° **14**: 0.174(3) Å, φ_2=112.9(9)°] and asymmetry parameters[62] [**9**: $\Delta C_s(16)=\Delta C_s(13,14)=0.2(6)°$;; **14**: $\Delta C_s(16)=\Delta C_s(13,14)=1.9(3)°$;]. The typical 18-$CH_3$ group is absent on their structure and a C13═C14 double bond is present at rings C and D fusion, with a bond length of 1.318(7) Å and 1.327(3) Å, for compounds **9** and **14**, respectively. In both molecules, ring A adopts a chair conformation while ring C shows a half-chair conformation. The C5═C6 double bond is clearly defined in both structures [1.311(7) Å and 1.328(3) Å for **9** and **14**, respectively]. The acetoxy group at C3 is equatorial to ring A with β-orientation. The X-ray study performed in these two molecules shows that the 16-acetoxy group possesses α-configuration. The migrating methyl group that shifted from C13 to C17 is β-oriented, while the side chain is axial to ring D with α-configuration.

3. Conclusions

In summary, we have developed a new catalytic process for the Wagner–Meerwein-type rearrangement of 16α,17α-epoxy-20-oxosteroids, using the 'ecofriendly' $Bi(OTf)_3 \cdot xH_2O$ as catalyst. The reactions can be performed in the absence of an acylation agent, leading to nearly equal amounts of both C16-epimeric 16α- and 16β-hydroxy-17β-methyl-Δ^{13}-18-norsteroids. When the reactions are carried out in the presence of an acylation agent, 16α-acyl-17β-methyl-Δ^{13}-18-norsteroids are selectively obtained in moderate to very high yields. Using our new process, starting with different 16α,17α-epoxy-20-oxosteroids, 17β-methyl-Δ^{13}-18-norsteroids with different acyl groups at positions C3, C16 and C21 can be easily obtained in an one-pot procedure, using selected acylation agents. When 5β,6β;16α,17α-diepoxy-20-oxopregnan-3β-yl acetate was used as substrate, a 'backbone' rearranged 5β-methyl-$\Delta^{8(14)}$-18-norsteroid product, with the 16α,17α-epoxide group intact was selectively synthesized in good yield. Some mechanistic aspects of this $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement have been discussed. In this work, seven new steroid compounds have been prepared, and their structural elucidation was adequately made using X-ray crystallography and 2D NMR techniques.

4. Experimental

4.1. General

16-Dehydropregnenolone acetate (16-DPA, 20-oxopregna-5,16-dien-3β-yl acetate) and 16α,17α-epoxy-21-acetoxypregnenolone **13** (16α,17α-epoxy-3β-hydroxy-20-oxopregn-5-en-21-yl acetate), ethyl formate and all reagents used for the synthesis of epoxysteroids, were purchased from Sigma–Aldrich Co. 16α,17α-Epoxy-20-oxosteroid **4** was prepared from 16-DPA using H_2O_2 30 mol%/NaOH 4 N, in methanol.[63] Subsequent acylation with 1.5 equiv of Ac_2O in the presence of 2.5 mol% of 4-(dimethylamino)-pyridine (DMAP) gave the 16α,17α-epoxide **1**.[63] The 5β,6β;16α,17α-diepoxysteroid **7**[64] was obtained by selective β-epoxidation of the Δ^5-double bond of **1** using the $KMnO_4/Fe_2(SO_4)_3 \cdot nH_2O$ mixture.[65] Solvents were obtained from VWR Portugal and were purified according to standard procedures.[66] Bismuth triflate, $Bi(OTf)_3 \cdot xH_2O$ (with $1<x<4$), was prepared according to the literature.[67] Kieselgel 60 F_{254}/Kieselgel 60G was used for TLC plates. Silica gel 60 (230–400 mesh ASTM) was used for flash column chromatography. Melting points were determined on a Buchi Melting point B-540 apparatus and are uncorrected. IR spectroscopy was performed on a Jasco FT/IR 420 spectrophotometer. ^1H, ^{13}C NMR, 2D Homonuclear Correlation (COSY), Nuclear Overhauser Enhancement Spectroscopy (NOESY), 2D Heteronuclear Multiple Quantum Correlation (HMQC), and 2D Heteronuclear Multiple Bond Correlation (HMBC) were recorded on a Varian 600 MHz spectrometer or on a Bruker Avance III 400 MHz. The NMR samples were prepared in $CDCl_3$ solution with Me_4Si as internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are presented in hertz. Mass spectral analysis was performed by direct injection on a Thermo Finnigan PolarisQ GC/MS Benchtop Ion Trap equipped with a direct insertion probe. Single-crystal X-ray diffractometry analysis was made on a Bruker-Nonius Kappa Apex II CCD diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å). The structures were solved by direct methods and conventional Fourier synthesis (SHELXS-97). The refinement of the structures was made by full matrix least-squares on F^2 (SHELXL-97). All non-H-atoms were refined anisotropically. The H atoms positions were initially placed at idealized calculated positions and refined with isotropic thermal factors while allowed to ride on the attached parent atoms using SHELXL-97 defaults. Supplementary crystallography data have been deposited at the Cambridge Crystallographic Data Center (CCDC deposition numbers 723676 and 723675, respectively, for compounds **9** and **14**). Copies can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk.

4.2. $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement of 16α,17α-epoxy-20-oxopregn-5-en-3β-yl acetate 1

To a solution of 16α,17α-epoxy-20-oxopregn-5-en-3β-yl acetate **1** (372.5 mg, 1.0 mmol) in $MeNO_2$ (30 mL), $Bi(OTf)_3 \cdot xH_2O$ (36.4 mg, 0.05 mmol) was added. The colour of the reaction mixture gradually became dark brown. After 2 h under magnetic stirring at 50 °C, full conversion of the starting compound was observed and two products were formed, as verified by TLC control [petroleum ether 40–60 °C/ethyl acetate 1:1 (v/v)]. The reaction was stopped by addition of 10% aq Na_2CO_3 (150 mL) and the organic solvent was removed under reduced pressure. The resulting mixture was then extracted with ethyl acetate (3×100 mL). The combined organic phase was washed with 10% aq $NaHCO_3$ (50 mL), water (50 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give a yellowish oil. Analysis of the ^1H NMR spectrum of the reaction crude showed a ratio of 52:48 for the 17β-methyl-Δ^{13}-18-norsteroid derivatives **2** and **3**, as determined by integration of their 16-H signals [δ=4.12 ppm (1H, t, 7.4 Hz, 16β-H of **2**) and δ=4.51 ppm (1H, dd, 7.0 and 5.5 Hz, 16α-H of **3**)]. By flash column chromatography [petroleum ether 40–60 °C/ethyl acetate 7:3 (v/v)], products **2** (112 mg, 0.30 mmol) and **3** (145 mg, 0.39 mmol) were isolated in 30% and 39% yield, respectively.

16α-Hydroxy-17β-methyl-20-oxo-18-nor-17α-pregna-5,13-dien-3β-yl acetate **2**. Mp (*n*-hexane/acetone): 140–143 °C; TLC [petroleum ether 40–60 °C/ethyl acetate 1:1 (v/v)]: R_f=0.55; IR 3455, 2929, 1738, 1700, 1242, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 2; ^{13}C NMR ($CDCl_3$, 150.8 MHz) see Table 2; EIMS *m*/*z* (%): 372 (42) M^+, 354 (15), 311 (23), 251 (100), 157 (74), 131 (85), 105 (59), 91 (72).

16β-Hydroxy-17β-methyl-20-oxo-18-nor-17α-pregna-5,13-dien-3β-yl acetate **3**. Mp (*n*-hexane/acetone): 108–110 °C; lit.[60] 111–113 °C; TLC [petroleum ether 40–60 °C/ethyl acetate 1:1 (v/v)]: R_f=0.42; IR 3464, 2932, 1733, 1700, 1243, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 2; ^{13}C NMR ($CDCl_3$, 150.8 MHz) see Table 2; EIMS *m*/*z* (%): 372 (4) M^+, 328 (4), 251 (12), 185 (15), 147 (38), 129 (100), 111 (64), 55 (96).

4.3. $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement of 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one 4

Under the above described reaction conditions, 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one **4** (330.5 mg, 1.0 mmol) was converted into the two 17β-methyl-Δ^{13}-18-norsteroids derivatives **5** and **6**, along with trace amounts of minor by-products, as observed by TLC control [petroleum ether 40–60 °C/ethyl acetate 1:1 (v/v)], after 2 h. Analysis of the ^{1}H NMR spectrum of the reaction crude showed a ratio of 66:34 for compounds **5** and **6**, as determined by integration of their 16-H signals [δ=4.13 ppm (1H, t, 7.3 Hz, 16β-H of **5**) and δ=4.50 ppm (1H, dd, 7.0 and 5.5 Hz, 16α-H of **6**)]. By flash column chromatography [petroleum ether 40–60 °C/ethyl acetate 7:3 (v/v)], products **5** (103 mg, 0.31 mmol) and **6** (70 mg, 0.21 mmol) were isolated in 31% and 21% yield, respectively.

3β,16α-Dihydroxy-17β-methyl-18-nor-17α-pregna-5,13-dien-20-one **5**. Mp (*n*-hexane/acetone): 187–190 °C; lit.[22] 191–193 °C; TLC [petroleum ether 40–60 °C/ethyl acetate 1:1 (v/v)]: R_f=0.30; IR 3378, 2929, 1696, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) see Table 2; ^{13}C NMR ($CDCl_3$, 150.8 MHz) see Table 2; EIMS *m*/*z* (%): 330 (16) M^+, 312 (12), 287 (45), 269 (90), 251 (100), 209 (33), 195 (34), 157 (59).

3β,16β-Dihydroxy-17β-methyl-18-nor-17α-pregna-5,13-dien-30-one **6**. Mp (*n*-hexane/acetone): 164–165 °C; lit.[22] 171–173 °C; TLC [petroleum ether 40–60 °C/ethyl acetate 1:1 (v/v)]: R_f=0.22; IR 3398, 2930, 1699, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) see Table 2; ^{13}C NMR ($CDCl_3$, 150.8 MHz) see Table 2; EIMS *m*/*z* (%): 330 (14) M^+, 313 (14), 287 (84), 269 (97), 251 (67), 173 (64), 157 (100), 131 (66).

4.4. 16α,17α-Epoxy-6β-hydroxy-5β-methyl-20-oxo-19-norpregn-8(14)-en-3β-yl acetate 8

To a solution of 5β,6β;16α,17α-diepoxy-20-oxopregnan-3β-yl acetate **7** (97.1 mg, 0.25 mmol) in $MeNO_2$ (7.5 mL), $Bi(OTf)_3 \cdot xH_2O$ (9.1 mg, 0.013 mmol) was added. The colour of the reaction mixture gradually became dark brown. After 15 min under magnetic stirring at 50 °C, full conversion of the starting compound was observed and a major product was clearly detected, as verified by TLC control [petroleum ether 40–60 °C/ethyl acetate 1:1 (v/v)]. The reaction was stopped by addition of 10% aq Na_2CO_3 (30 mL) and the organic solvent was removed under reduced pressure. Additional 30 mL of 10% aq Na_2CO_3 were added and the resulting mixture was then extracted with ethyl acetate (4×30 mL). The combined organic phase was washed with 10% aq $NaHCO_3$ (25 mL), water (25 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give a yellow solid. Purification by flash column chromatography [petroleum ether 40–60 °C/ethyl acetate 6:4 (v/v)] afforded product **8** as a white solid (60 mg, 0.15 mmol, 62%). Mp (*n*-hexane/acetone): 108–111 °C; TLC [petroleum ether 40–60 °C/ethyl acetate 1:1 (v/v)]: R_f=0.32 (weak UV absorption at 254 nm); IR 3383, 2940, 1732, 1705, 1593, 1252, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.04 (s, 3H, 5β-CH_3), 1.25 (s, 3H, 18-CH_3), 2.02 (s, 3H, 3β-$OCOCH_3$), 2.04 (s, 3H, 21-CH_3), 3.13 (dd, 11.7 and 4.8 Hz, 1H, 6α-H), 3.77 (br s, 1H, 16β-H), 5.05 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ 12.3 (5β-CH_3), 18.9, 19.7 (C1), 21.0 (C18), 21.5 (3β-$OCOCH_3$), 24.5 (C12), 26.0 (C21), 30.1 (C15), 30.6 (C2), 35.1, 35.6 (C7), 39.3 (C5), 40.9 (C4), 43.1 (C13), 45.9 (C10), 60.6 (C16), 69.2 (C3), 70.9 (C17), 79.1 (C6), 131.8 (C8), 132.4 (C14), 170.4 (3β-$OCOCH_3$), 204.5 (C20); EIMS *m*/*z* (%): 388 (16) M^+, 370 (83), 328 (57), 310 (100), 298 (72), 266 (99), 199 (63), 145 (65).

4.5. General procedure for the synthesis of 16α-acyl-17α-alkyl-17β-methyl-Δ^{13}-18-norsteroids

To a solution of 16α,17α-epoxy-20-oxopregn-5-en-3β-yl acetate **1** (186.2 mg, 0.50 mmol) in $MeNO_2$ (15 mL), Ac_2O (0.47 mL, 5.0 mmol) and $Bi(OTf)_3 \cdot xH_2O$ (18.2 mg, 0.025 mmol) were successively added. The colour of the reaction mixture gradually became dark purple. After 1 h under magnetic stirring at rt, full conversion of the starting compound was observed, as verified by TLC control [toluene/diethyl ether 7:3 (v/v)]. The reaction was stopped by addition of 10% aq Na_2CO_3 (80 mL) and the organic solvent was removed under reduced pressure. The resulting mixture was then extracted with diethyl ether (3×60 mL). The combined organic phase was washed with 10% aq $NaHCO_3$ (30 mL), water (30 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give 17β-methyl-20-oxo-18-nor-17α-pregna-5,13-diene-3β,16α-diyl diacetate **9** (197 mg, 0.47 mmol, 95%), as a pale yellow solid. Recrystallization from MeCN at rt afforded colourless single crystals suitable for X-ray crystallography. Compound **9** crystallizes in hexagonal cell, $P6_5$ space group, and its structure was refined down to a $R1$=0.0562 for 1325 reflections with $I>2\sigma(I)$, 277 parameters and $wR(F^2)$ was 0.1603 (all data, 2267 reflections). Mp: 207–210 °C; lit.[24] 201–201 °C; TLC [toluene/diethyl ether 7:3 (v/v)]: R_f=0.69; IR 2937, 1735, 1707, 1238, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ see Table 3; ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ see Table 3; EIMS *m*/*z* (%): 414 (7) M^+, 371 (4), 355 (5), 311 (14), 251 (100), 195 (14), 157 (35), 131 (33).

4.5.1. 17β-Methyl-20-oxo-18-nor-17α-pregna-5,13-diene-3β,16α-diyl 3-acetate 16-butyrate ***10***

Obtained from 16α,17α-epoxy-20-oxopregn-5-en-3β-yl acetate **1** (223 mg, 0.60 mmol), under the above described reaction conditions, in the presence of $(CH_3CH_2CH_2CO)_2O$ (0.98 mL, 6.0 mmol), after 2.5 h. The product was purified by flash column chromatography on SiO_2 using ethyl petroleum ether 40–60 °C/ethyl acetate 4:1 (v/v) and isolated as a white solid in 70% yield (186 mg). Mp (MeOH): 136–138 °C; TLC [toluene/diethyl ether 7:3 (v/v)]: R_f=0.70; IR 2966, 1735, 1708, 1241, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ see Table 3; ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ see Table 3; EIMS *m*/*z* (%): 442 (100) M^+, 397 (10), 381 (52), 353 (25), 309 (31), 293 (27), 250 (21), 130 (48).

4.5.2. 17β-Methyl-20-oxo-18-nor-17α-pregna-5,13-diene-3β,16α-diyl dibutyrate ***12***

Obtained from 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one **4** (82.6 mg, 0.25 mmol), under the above described reaction conditions, in the presence of $(CH_3CH_2CH_2CO)_2O$ (0.41 mL, 2.5 mmol), after 1.5 h. The product was purified by flash column chromatography on SiO_2 using petroleum ether 40–60 °C/ethyl acetate 4:1 (v/v) and isolated as a white solid in 71% yield (83.5 mg). Mp (*n*-hexane/acetone): 65–66 °C; TLC [petroleum ether 40–60 °C/ethyl acetate 4:1 (v/v)]: R_f=0.78; IR 2965, 1736, 1709, 1180, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ see Table 4; ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ see Table 4; EIMS *m*/*z* (%): 470 (90) M^+, 441 (10), 381 (100), 337 (29), 293 (42), 250 (31), 130 (42), 104 (46).

4.5.3. 17β-Methyl-20-oxo-18-nor-17α-pregna-5,13-diene-3β,16α,21-triyl triacetate ***14***

Obtained from 16α,17α-epoxy-21-acetoxypregnenolone **13** (97.1 mg, 0.25 mmol), under the above described reaction conditions, in the presence of Ac_2O (0.23 mL, 2.5 mmol), after 2 h, in 90% yield (106 mg). Recrystallization from *n*-hexane/acetone, at rt, afforded colourless single crystals suitable for X-ray crystallography. Compound **14** crystallizes in orthorhombic cell, $C2\ 2\ 2_1$ space group, and its structure was refined down to a $R1$=0.0428 for 2882 reflections with $I>2\sigma(I)$, 312 parameters and $wR(F^2)$ was 0.1135 (all data, 3433 reflections). Mp 172–173 °C; TLC [toluene/diethyl ether 7:3 (v/v)]: R_f=0.38; IR 2938, 1750, 1731, 1236, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ see Table 4; ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ see Table 4; EIMS *m*/*z* (%): 472 (9) M^+, 413 (11), 351 (7), 311 (12), 251 (100), 195 (26), 157 (50), 131 (54).

4.5.4. 17β-Methyl-20-oxo-18-nor-17α-pregna-5,13-diene-3β,16α,21-triyl 21-acetate 3,16-dibutyrate **15**

Obtained from 16α,17α-epoxy-21-acetoxypregnenolone **13** (97.1 mg, 0.25 mmol), under the above described reaction conditions, in the presence of 10 mol% of $Bi(OTf)_3 \cdot xH_2O$ and $(CH_3CH_2CH_2CO)_2O$ (0.41 mL, 2.5 mmol), after 2 h. The product was purified by flash column chromatography on SiO_2 using petroleum ether 40–60 °C/ethyl acetate 9:1 (v/v) and isolated as a white solid in 77% yield (102 mg). Mp (MeCN): 115–117 °C; TLC [petroleum ether 40–60 °C/ethyl acetate 4:1 (v/v)]: R_f=0.52; IR 2959, 1732, 1232, 1180, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ see Table 4; ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ see Table 4; EIMS m/z (%): 528 (28) M^+, 455 (6), 439 (72), 351 (33), 249 (249), 103 (73), 89 (83), 80 (100).

4.6. 17β-Methyl-20-oxo-18-nor-17α-pregna-5,13-diene-3β,16α-diyl 3-acetate 16-formate 11

To a solution of 16α,17α-epoxy-20-oxopregn-5-en-3β-yl acetate **1** (186.2 mg, 0.50 mmol) in HCO_2Et (10 mL), $Bi(OTf)_3 \cdot xH_2O$ (18.2 mg, 0.025 mmol) was added. The colour of the reaction mixture gradually became dark purple. After 24 h under magnetic stirring at reflux temperature, full conversion of the starting compound was observed, as verified by TLC control [toluene/diethyl ether 7:3 (v/v)]. The solvent was removed under reduced pressure, and the resulting mixture was dissolved in diethyl ether (180 mL). The organic phase was washed with 10% aq $NaHCO_3$ (30 mL), water (30 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give a yellow solid. Purification by flash column chromatography [petroleum ether 40–60 °C/ethyl acetate 4:1 (v/v)] afforded product **11** as a white solid (108 mg, 0.27 mmol, 54%). Mp (*n*-hexane/acetone): 158–159 °C; TLC [petroleum ether 40–60 °C/ethyl acetate 4:1 (v/v)]: R_f=0.26; IR 2937, 1731, 1709, 1241, 1169, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 3; ^{13}C NMR ($CDCl_3$, 150.8 MHz) see Table 3; EIMS m/z (%): 400 (41) M^+, 354 (66), 338 (100), 310 (56), 294 (95), 250 (71), 156 (78), 130 (73).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.043.

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