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Synthesis of Conformationally Restricted Progestational 13-Ethylsteroids

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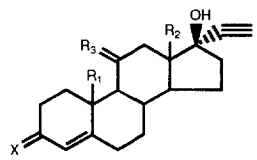
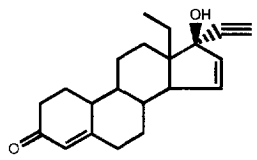
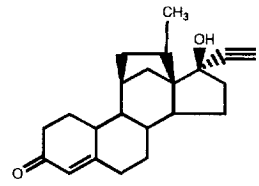
Abstract: As 3-Ketodesogestrel and Gestodene differ in the conformation of the 13-ethyl group, a series of progestagens was devised in which this conformation is fixed. Thus, both epimers of a steroid with a methyl-substituted 11,13-ethano bridge were prepared and their biological activities compared. From the receptor binding activity, it was concluded that the "Desogestrel conformation" is the more active one.

Introduction

The first synthetic steroid with progestational activity, identified in the thirties, was Ethisterone (**1a**)[1]. In the fifties, the discovery that the 19-nor analogue Norethisterone (**1b**) had an enhanced oral activity[2] led to the introduction of oral contraceptives. It was found that oral activity was further improved by extending the 13-methyl group to an ethyl substituent, as in Levonorgestrel (**1c**) and later in Desogestrel (**1d**) and Gestodene (**2**). Later, X-ray studies demonstrated[3] that the three latter compounds differ in the conformation of the 13-ethyl group. In both **1c** and **1e** (the active metabolite of **1d**) the ethyl group adopts an *anti* conformation, whereas in **2** the crystal consists of two conformations of approximately equal energy, one with the *anti* and one with the *gauche* conformation (figure 1). The occurrence of the *gauche* conformation, which is readily explained by the absence of an 18-methyl - 15βH interaction, made us ponder whether this conformation is relevant for the high biological activity of **2**. Therefore, we decided to prepare 13-ethylpregnanes in which the conformation of the 18-methyl group is fixed, and to assess the influence of this conformation on the biological activity[4]. To this end, 11,13-bridged compounds **3** seemed to us the best choice as model compounds.







1a $R_1 = R_2 = CH_3$, $R_3 = H_2$, X = O
1b $R_1 = H$, $R_2 = CH_3$, $R_3 = H_2$, X = O
1c $R_1 = H$, $R_2 = C_2H_5$, $R_3 = H_2$, X = O
1d $R_1 = H$, $R_2 = C_2H_5$, $R_4 = CH_2$, X = H_2
1e $R_1 = H$, $R_2 = C_2H_5$, $R_3 = CH_2$, X = O

2

3

Results

As a starting material, the keto-substituted bridged steroid **4a** prepared by us earlier[5] was used. We envisaged to introduce the required carbon atom by a Wittig reaction. Wittig methylenation of **4a** under standard conditions (NaH/DMSO) gave no reaction at all, but when the combination KO^{t}Bu/toluene[6] was employed, the

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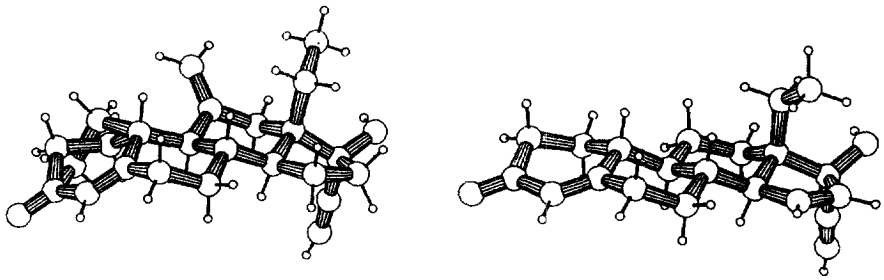
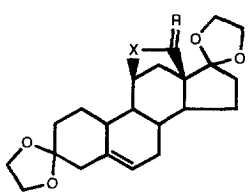
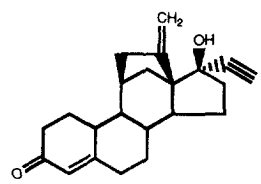


Figure 1. Left panel: X-ray structure of 3-Ketodesogestrel **1e** (two conformations of ring A) Right panel: *Gauche* conformation of Gestodene **2**. Reprinted with permission from ref. 9.



4a X = CH_2, R = O
4b X = R = CH_2
4c X = O, R = CH_2



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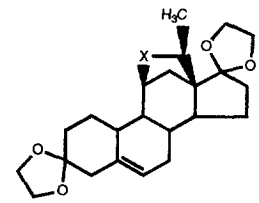
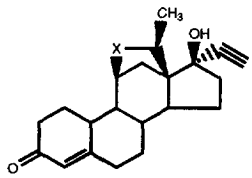
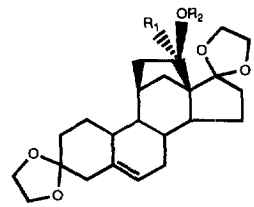


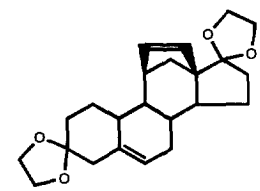
6a X = CH_2
6b X = O



7a X = CH_2
7b X = O



8a R_1 = CH_3, R_2 = H
8b R_1 = CH_3, R_2 = $OCOCOOCH_3$
8c R_1 = R_2 = H
8d R_1 = H, R_2 = Tos



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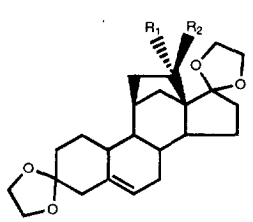
desired **4b** was obtained[7] in excellent yield. This compound was converted to pregnyne **5** using a standard procedure (selective deprotection[8] at C17, ethynylation (C_2H_2/KO^{t}Bu/ THF), deprotection at C3).

In order to prepare the 12aβ-methyl compound, we sought to hydrogenate the methylene group of **5**. This conversion proceeded readily with a palladium catalyst. The configuration at 12a was expected to be β because hydrogen addition is thought to occur from the least hindered face of the molecule; indirect spectroscopic evidence (*vide infra*) was also obtained. Conversion of **6a** to the analogous pregnyne **7a** was performed as described before. Although NOESY spectroscopy of the latter compound gave weak effects confirming the proposed configuration, we decided nevertheless to prepare the 12-oxa-analogue of **7a** as a model compound to corroborate configuration assignment. Starting material was enol ether[10] **4c**. For the hydrogenation of enol

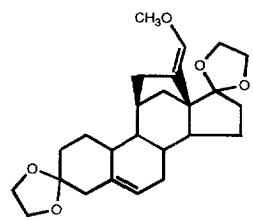
ethers, several methods have been reported[11]; in our case, it was found that **4c** could be readily hydrogenated over Adams' catalyst[12] to afford, in 87% yield, the corresponding methyl-substituted compound as a mixture of epimers, primarily consisting of the desired β-methyl product **6b**. Conversion of this product to its 17-ethynyl derivative took place through the usual sequence, affording the desired pregnenyne **7b**. The configuration of the methyl group was confirmed by NMR spectroscopy, where a NOE effect could be demonstrated between the CH_3CHO-proton, nicely visible at 4.33 ppm, and the proton in the 18β-position.

For the 12aα-methyl analogue of **7a** we again started from ketone **4a**. Addition of MeMgCl gave carbinol **8a** in 95% yield. NOESY spectroscopy of this compound showed a contact between the methyl group and the ketal signal, thus confirming the expected configuration. We now hoped to be able to remove the alcohol function with retention of configuration. Thus, we prepared oxalate **8b**; unfortunately, the hydride again is delivered from the least hindered side, and the 12aβ-methyl compound **6a** was obtained in 97% yield upon treatment[13] of **8b** with Bu_3SnH/AIBN. We then sought to employ the stereoselectivity of the additions to position 12a by introduction of a one-carbon moiety from the rear face of the molecule. Thus, alcohol **8c** (readily obtained by NaBH4 reduction of **4a**) was tosylated to **8d**, and this product was treated with a number of carbon nucleophiles, but methylcopper reagents[14] gave only starting material, as did treatment with CuCN/MeLi, while an attempt to effect a substitution with cyanide ion[15] gave the elimination product **12** in 65% yield.

We then decided to prepare the 12a-carboxaldehyde **10a,b** which we hoped to be able, whatever its initial configuration, to isomerise to the desired *exo*-isomer **10a**, which molecular energy calculations indicated to be the more stable one. A direct approach through treatment of ketone **4a** with $MeOCH_2P(Ph)_3Cl$ under a variety of conditions (NaH/DMSO, BuLi/ether, KO^{t}Bu/THF etc.) failed to produce the desired **11**. Hydroboration of the methylene group of **4b** to **10c** was considered, but the required selectivity was a problem in this case even when 9-BBN was employed. Eventually, conversion of **4a** to the epoxide gave the solution. Under the usual reaction conditions[16], the reaction did not proceed; however, when traces of crown ether were added to the reaction mixture, epoxide **12** was obtained in 70% yield. The stereochemistry of the epoxide could not be proven unambiguously, but is assumed to be 12aβ as indicated. This would be consistent with the observed preference for addition from the α face, and with similar selectivities reported previously[17]. In addition, the large downfield shift of one of the epoxide methylene protons, located at 3.37 ppm against a normal location around 2.6 ppm, could be explained by the close proximity of one of the C17-acetal oxygen atoms. Unfortunately, unequivocal interpretation of NOESY signals proved impossible.



10a R_1 = CHO, R_2 = H
10b R_1 = H, R_2 = CHO
10c R_1 = H, R_2 = CH_2OH
10d R_1 = CH_3, R_2 = H
10e R_1 = H, R_2 = CH_3



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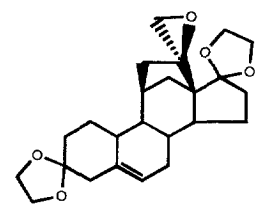

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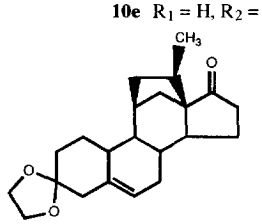

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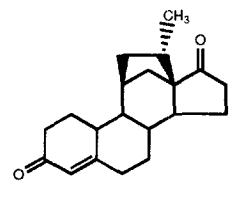

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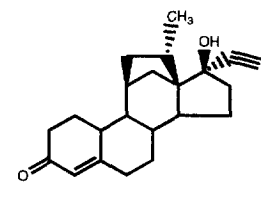

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Isomerisation of **12** to aldehyde **10b** was accomplished by treatment with BF_3 etherate[18]; a short reaction time was essential to maximise the yield, while basic work-up ensured that the ketal protecting groups remained intact. The product (quantitative yield) was shown to consist mainly of the 12aβ-isomer **10b**, as was apparent from a NOESY contact between the aldehyde proton and H8. To isomerise this compound to its epimer various bases were investigated; KO^{t}Bu gave no reaction; treatment with NaOMe overnight gave a 70% conversion, but the best results were obtained with strong methanolic KOH, which gave a practically quantitative yield of **10a** within 2 hours; the configuration was confirmed by NOESY spectroscopy, where an effect between the aldehyde proton and H18 was observed. The difference in outcome of the epimerisation step can be rationalised as a competition between thermodynamically and kinetically controlled processes. Force field calculations indicate the 12aα-isomer to be more stable by about 1 kcal/mol, which should make it the main product of the epimerisation. However, protonation of the intermediate enolate to either of the two aldehyde epimers more readily takes place from the least hindered (α) face, leading to the β epimer. Thus, thermodynamic and kinetic control tend to lead to products with opposite configuration at C12a; only when the proton donor is sufficiently small, as is the water molecule, approach from the more hindered face can take place, leading to the more stable product.

Unfortunately, the reaction conditions employed for the subsequent Wolff-Kishner reaction to remove the aldehyde function again shifted the equilibrium, and a 2:1 α/β mixture of methyl isomers **10d** and **10e** was obtained. The isomers could not be separated in this stage; however, a kind of "kinetic resolution" was made possible by the fact that upon selective hydrolysis of the 17-ketal function by treatment with silica gel/oxalic acid[8] the β-isomer reacts very much faster; the resulting ketone **13** could easily be separated from the remaining **10d**. In fact, the eventual hydrolysis of **10d** required rather forcing conditions (2N H_2SO_4 at 50 °C for 5 hours), but **14** was obtained in good yield. Conversion to the corresponding enol ether presented no problems, but as expected the ethynylation proceeded with difficulty. Both potassium acetylide and lithium acetylide/$H_2NCH_2CH_2NH_2$-complex gave no reaction at all, but a Grignard addition (EtBr/Mg/acetylene gas) gave a fair yield of the adduct, which was hydrolysed to **15**. An X-ray analysis confirmed the configuration at C-12a.

Biological results

To assess the activity of the compounds prepared in this series, they were screened in the normal test battery for progestagenic compounds. Both the relative binding affinity for the progesterone receptor[19] and the *in vivo* activity (McPhail test[20]) were established. The results are summarised in table 1. From the large difference between **8** and **18** it can be concluded that the "Desogestrel conformation" for the ethyl group is the more active. Thus, the effect of the Δ^{15} double bond in Gestodene is not to enable the ethyl group to adopt a more favourable conformation, but that it makes an autonomous contribution to that compound's activity.

Table 1 Summary of biological data.

compound	RBA[a]	McPhail[b]
1b	21	~ 500
1c	81	40
1e	192	15
2	180	8
5	24	1000
7a	19	125
12	1	> 4000
15	186	~ 32

[a] Relative binding affinity to the progesterone receptor (MCF-7, cytosol); ORG 2058 = 100%; [b] ED_2 McPhail (oral); dose in μg/kg

Acknowledgement We would like to thank Dr. W Schoonen and Mr. G. Deckers and their staff of the Department of Endocrinology for the determination of the biological activities. The X-ray analysis of compound **15** was performed by prof. J. Kroon, of the University of Utrecht, the Netherlands

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7. All products gave spectroscopic data and elemental analyses in agreement with the proposed structures. Key data are as follows: **(11α,13α)-12a-methylene-11,18-cyclo-C-homoestr-5-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) 4b**, mp 156.8-157.9 °C. ^{1}H NMR: 5.45 (m, 1H, H6), 5.03 and 4.82 (m and m, 1 H each, $=CH_2$), 4.0-3.85 (m, 8H, OCH_2CH_2O); **(11α,13α,17α)-17-hydroxy-12a-methylene-11,18-cyclo-C-homo-19-norpregn-4-en-20-yn-3-one 5**, mp 181.7-182.7 °C. $[\alpha]_D^{20}$ -26.4° (c = 1.02, $CHCl_3$). ^{1}H NMR: 5.88 (m, 1H, H4), 5.21 and 4.92 (t and t, 1H each, $=CH_2$). ^{13}C NMR: 199.7 (s), 166.6 (s), 148.8 (s), 125.3 (d), 108.1 (t), 88.4 (s), 76.4 (s), 71.7 (s), 62.1 (s), 51.9 (d), 51.2 (d), 42.2 (t), 41.8 (d), 41.4 (t), 39.6 (d), 36.5 (t), 35.9 (t), 35.5 (t), 33.3 (d), 30.5 (t), 26.6 (t), 24.2 (t). Calculated for $C_{22}H_{26}O_2$: C, 81.95%; H, 8.13%; O, 9.92%. Found: C, 81.5%; H, 8.2%; **(11α,12aβ,13α)-12a-methyl-11,18-cyclo-C-homoestr-5-ene-3,17-dione cyclic bis- (1,2-ethanediyl acetal) 6a**, mp 135.9-137.5 °C. ^{1}H NMR: 5.48 (m, 1H, H6), 4.0-3.85 (m, 8H, OCH_2CH_2O), 1.12 (d, 3H, CH_3); **(20S)-13,11β-(ethylideneoxy)gon-5-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) 6b**, mp 155-157 °C. ^{1}H NMR: 5.5 (m, 1H, H6), 4.35 (dd, 1H, H11), 4.2 (q, 1H, $OCHCH_3$), 4.0-3.9 (m, 8H, OCH_2CH_2O), 1.39 (d, 3H, CH_3); **(11α,12aβ,13α,17α)-17-hydroxy-12a-methyl-11,18-cyclo-C-homo-19-norpregn-4-en-20-yn-3-one 7a**, mp 148.6-150.1 °C. $[\alpha]_D^{20}$ -55.8° (c = 1.015, $CHCl_3$). IR: 3362 (OH), 3268 (C≡CH), 1653 (C=O), 1624, 1455, 1375, 1259, 1107, 1052, 877, 766, 712, 660. ^{1}H NMR (C_6D_6): 5.93 (m, 1H, H4), 2.55-2.40 (m, 2H, H12a and H16α), 2.30 (dtd, 1H, H2 α), 2.20 (s, 1H, H21), 2.15-2.05 (ddd, H16β), 2.05-2.0 (ddd, H6), 2.0-1.9 (m, 4H, H6, H2β and H18), 1.14 (d, J = 9, CH_3), 0.9 (ddd, 1H, H12), 0.8-0.6 (m, 2H, H7α and H9α). ^{13}C NMR: 200.0 (s), 167.3 (s), 125.2 (d), 88.9 (s), 76.6 (s), 71.5 (d), 57.2 (s), 53.6 (d), 51.1 (d), 44.5 (t), 41.1 (t), 40.6 (d), 38.9 (d), 36.5 (t), 35.6 (t), 34.8 (d), 34.2 (d), 33.8 (t), 30.9 (t), 26.5 (t), 24.2 (t), 15.6 (q). Calculated for $C_{22}H_{28}O_2$: C, 81.44%; H, 8.70%; O, 9.86%. Found: C, 81.0%; H, 8.9%; **(17α,22S)-13,11β-(ethylidene- oxy)-17-hydroxy-18,19-norpregn-4-en-20-yn-3-one 7b,** mp 215-217 °C, $[\alpha]_D^{20}$ +25.9° (c = 1.015, $CHCl_3$). IR: 3297 (OH), 3251 (C≡CH), 1732, 1650 (C=O), 1612, 1368, 1272, 1211, 1093, 974, 700, 660. ^{1}H NMR (C_6D_6 + $CDCl_3$): 5.88 (m, 1H, H4), 4.33 (q, 1H, H22), 4.11 (d, 1H, H11), 2.35 (dd, 1H, H12β), 1.4 (d, 3H, CH_3). ^{13}C NMR: 200.0 (s), 166.8 (s) 125.6 (d), 87.7 (s), 77.9 (d), 75.1 (s), 73.8 (d), 72.3 (s), 56.4 (s), 54.3 (d), 49.6 (d), 42.9 (t), 41.1 (t), 40.6 (d), 38.6 (d), 36.5 (t), 35.5 (t), 30.3 (t), 26.6 (t), 24.2 (t), 15.5 (q). UV: λ_{MAX} (EtOH) 239.5 nm, ε = 15025. Calculated for $C_{21}H_{26}O_2$: C, 77.27%; H, 8.03%; O, 14.70%. Found: C, 77.05%; H, 8.2%; **(11α,12aβ,13α)-12a-hydroxy-12a-methyl-11,18-cyclo-C-homo-estr-12-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) 8a**, mp 203.5-205.2 °C. IR: 3544 (OH), 1244, 1170, 1130, 1101, 1032, 956, 835, 789, 695. ^{1}H NMR: 5.47 (m, 1H, H6), 4.30 (br m, 1H, OH), 4.3-3.85 (m, 8H, OCH_2CH_2O), 1.47 (s, H, CH_3). ^{13}C NMR: 136.4 (s), 122.4 (d), 118.5 (s), 109.3 (s), 80.9 (s), 65.7 (t), 64.3 (t), 64.1 (t), 62.9 (t), 58.7 (s), 51.9 (d), 49.6 (d), 45.6 (t), 44.2 (t), 39.0 (t), 38.3 (d), 36.4 (d), 34.3 (t), 33.9 (t), 33.5 (d), 31.0 (q), 30.5 (t), 29.1 (t), 23.1 (t); **(11α,12aβ,13α)-12a-methoxy-oxoacetyloxy-12a-methyl-11,18-cyclo-C-homoestr-5-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) 8b,** ^{1}H NMR: 5.46 (m, 1H, H6), 4.0-3.85 (m, 8H, OCH_2CH_2O), 3.86 (s, 3H, ester CH_3), 1.75 (s, 3H, CH_3); **(11α,12aβ,13α)-12a-hydroxy-11,18-**

cyclo-C-homoestr-12-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) 8c, ^{1}H NMR: 5.48 (m, 1H, H6), 4.6-4.5 (m, 1H, H12a), 4.0-3.85 (m, 8H, OCH_2CH_2O); **(11α,12aβ,13α)-12a-[(4-methylphenyl) sulfonyloxy]-11,18-cyclo-C-homoestr-5-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) 8d**, ^{1}H NMR: 7.81 and 7.33 (AB system, 4 H, $C_6H_4SO_2$), 5.45 (m, 1H, H6), 4.0-3.9 (m, 4H, OCH_2CH_2O at C3), 3.9-3.75 (m, 4H, OCH_2CH_2O at C17), 2.5 (s, 3H, CH_3). ^{13}C NMR: 144.4 (s), 136.7 (s), 134.0 (s), 129.5 (d, 2x), 128.0 (d, 2x), 122.1 (d), 116.7 (s), 109.2 (s), 84.1 (d), 65.5 (t), 64.5 (t), 64.3 (t), 64.1 (t), 57.5 (s), 50.8 (d), 49.5 (d), 44.4 (t), 38.3 (d), 37.5 (t), 36.4 (d), 35.7 (d), 34.7 (t), 34.5 (t), 33.5 (t), 30.5 (t), 29.3 (t), 23.7 (t), 21.7 (q); **(11α,13α)-11,18-cyclo-C-homoestra-5,12-diene-3,17-dione cyclic bis(1,2-ethanediyl acetal) 9**, ^{1}H NMR: 5.97 (dd, J = 6 and 3, 1H, H12), 5.82 (d, J = 6, H12a), 5.5 (m, 1H, H6), 4.0-3.9 (m, 8H, OCH_2CH_2O), 2.78 (m, 1H). ^{13}C NMR: 137.1 (s), 133.4 (d), 132.2(d), 122.9 (d), 117.3 (s), 109.2 (s), 61.0 (s), 45.8 (d), 44.7 (t), 44.3 (t), 44.1 (d), 41.4 (d), 40.6 (d), 39.4 (d), 35.8 (t), 34.4 (t), 30.5 (t), 29.4 (t), 25.6 (t); **(11′α,12a′α,13′α)-dispiro[[1,3]dioxolane-2,3′-(11′,18′-cyclo-C-homoestr-5′-ene-17′,2′′[1,3]dioxolane]-12a′-carboxaldehyde 10a**, ^{1}H NMR: 9.60 (d, J = 5, 1H, CHO), 5.4 (m, 1H, H6), 4.0-3.8 (m, 8H, OCH_2CH_2O); **(11′α,12′aβ,13′α)-dispiro[[1,3]dioxolane-2,3′-(11′,18′-cyclo-C-homoestr-5′-ene)-17′,2′′-[1,3]dioxolane]-12a′-carboxaldehyde 10b**, ^{1}H NMR: 9.92 (d, J = 3, CHO), 5.43 (m, 1H, H6), 4.0-3.9 (m, 8H, OCH_2CH_2O), 3.12 (ddd, J = 1, 6 and 3, H12a), 3.10-3.05 (m, 1H, H4), 2.95 (m, 1H, H4); **(11α,13α,17α)-12a-methyl-11,18-cyclo-C-homoestr-5-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) 10d/10e** ^{1}H NMR: 1.12 (CH_3 at C12aβ), 1.01 (CH_3 at C12aα); **(11α,12aα,13α)-spiro[11,18-cyclo-C-homoestr-5-ene-12a,2′-oxirane]-3,17-dione cyclic bis(1,2-ethanediyl acetal) 12**, ^{1}H NMR 5.43 (m, 1H, H6), 4.0-3.5 (m, 8H, OCH_2CH_2O), 3.37 (d, J = 6, 1H, CHO), 2.61 (d, J = 6, 1H, CHO). ^{13}C NMR: 136.6(s), 122.2 (d), 117.1 (s), 109.2 (s), 76.4 (s), 65.9 (t), 64.5 (t), 64.3 (t), 63.4 (t), 54.6 (s), 54.2 (t), 51.9 (d), 48.7 (d), 44.4 (t), 39.1 (t), 38.8 (d), 37.2 (d), 36.5 (t), 34.6 (t), 34.2 (t), 30.4 (t), 29.5 (t), 23.9 (t); **(11α,12aβ,13α,17α)-12a-methyl-11,18-cyclo-C-homoestr-5-ene-3,17-dione cyclic 3-(1,2-ethanediyl acetal) 13,** mp 171-172 °C. ^{1}H NMR: 5.5 (m, 1H, H6), 4.0-3.9 (m, 4H, OCH_2CH_2O), 1.3 (dd, J = 14 and 2.5, H12α), 1.10 (d, 3H, CH_3). ^{13}C NMR: 224, 137.3 (s), 121.7 (d), 109.2 (s), 64.5 (t), 64.3 (t), 58.5 (s), 52.8 (d), 50.3 (d), 44.5 (t), 43.9 (d), 40.7 (t), 39.0 (t), 38.1 (d), 36.1 (d), 34.5 (t), 33.8 (t), 30.3 (t), 29.4 (t), 24.9 (t), 15.4 (q); **(11α,12aα,13α,17α)-12a-methyl-11,18-cyclo-C-homoestr-4-ene-3,17-dione 14**, ^{1}H NMR: 5.87 (m, 1H, H4), 0.83 (d, J = 7, 3H, CH_3); **(11α,12aα,13α,17α)-17-hydroxy-12a-methyl-11,18-cyclo-C-homo-19-norpregn-4-en-20-yn-3-one 15**, mp 276.5-277.8 °C, $[\alpha]_D^{20}$ -16.7° (c = 0.635, $CHCl_3$). IR: 3340 (OH), 3262 (C≡CH), 1651 (C=O), 1618, 1267, 1102, 876. ^{1}H NMR: 5.85 (m, 1H, H4), 2.49 (s, 1H, H21), 1.13 (d, J = 13, CH_3). ^{13}C NMR: 200.0 (s), 167.3 (s), 125.1 (s), 89.0 (s), 77.8 (s), 71.5 (d), 56.3 (s) 52.3 (d), 50.5 (d), 41.3 (d), 39.3 (d), 38.0 (t), 37.3 (t), 37.0 (t), 36.5 (t), 35.7 (t), 34.2 (d), 30.5 (t), 26.5 (t), 22.4 (t), 22.0 (q). Calculated for $C_{22}H_{28}O_2$: C, 81.44%; H, 8.70%; O, 9.86%. Found: C, 81.5%; H, 8.5%.

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