A Simple Synthesis of Gestodene from 18-Methyl-4-estren-3,17-dione

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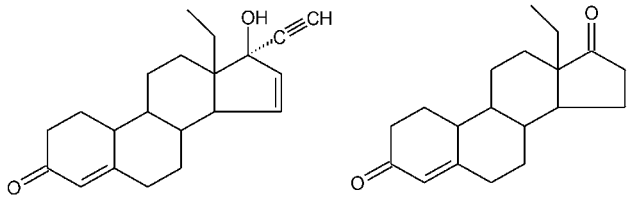
Abstract: A simple synthesis enables us to obtain the progestin, gestodene, in five steps and satisfactory yields from 18-methyl-4-estren-3,17-dione. This was accomplished through the selective protection of the C-3 carbonyl group as a cyclic ketal and the installation of a phenylsulfoxide group at the C-16 position.

Key words: drugs, steroids, sulfoxides, sulfinylation, progestagen

Gestodene (17α-ethynyl-17β-hydroxy-18-methyl-4,15-estradien-3-one) (**1**) is a potent synthetic progestin that is used, in combination with ethynylestradiol, as an oral contraceptive (Figure 1).[1]

Starting from the commercially available 18-methyl-4-estren-3,17-dione (**2**), the crucial step of the synthesis is the introduction of the double bond in the 15,16-position; usually this result is achieved by an elimination reaction carried out on a 15-hydroxy derivative, in turn prepared by means of a microbiological transformation.[2] In another two reported syntheses of gestodene starting from a 18-methyl estradiol derivative, the introduction of the 15,16 double bond is realized by treatment of the proper 17-enolsilylether with palladium(II) acetate.[3,4]



1 2

Figure 1

Considering the pharmacological relevance of gestodene, we planned to find an alternative method for an easy and convenient preparation. The known introduction of the 15-16 double bond by a bromination at the 16-position of a steroidal 17-ketal, by means of treatment with pyridinium tribromide followed by a dehydrobromination,[5] afforded negative results.[6]

Thinking that the best solution could be offered by a 16-functionalization performed in basic conditions, we selectively protected the 3-keto group of **2** as its cyclic ketal by treatment with 2,2-dimethyl-1,3-propandiol, triethylorthoformate and *p*-toluenesulfonic acid in dichloromethane. The 3-ketal,17-ketone **3** was obtained in 90% yield.[7] In principle, the D-ring enone could be obtained by means of a sulfoxide[8] as well as a selenoxide[9,10] elimination: at first, we studied the sulfenylation–dehydrosulfenylation procedure in order to use the less toxic reagents and in view of a possible scaling up of the method. The preliminary attempt of sulfenylation with phenyl disulfide and lithium diisopropylamide in THF and HMPA, followed by oxidation (*m*-chloroperbenzoic acid) of the obtained 16-phenylsulfide **4** to the sulfoxide **5** and thermolysis,[8] gave the Δ^{15}-derivative **6** in promising yield (30%); an improvement, in terms of reactions conditions and final yields, was achieved through a sulfinylation with the commercially available methyl benzenesulfinate as suggested by Wicha et al.[11] In fact, in this way it is possible to introduce a PhSO group directly at the α-position of a ketone in one step. We were able to prepare the phenylsulfoxide **5** as a diastereomeric mixture[12] with complete conversion of the starting 17-ketone **3**. We used the same reactant but replaced the reported sodium hydride as base and diethyl ether as solvent with potassium *t*-butylate and tetrahydrofuran, respectively.[13] The obtained phenylsulfoxide **5** was used directly to accomplish the gestodene **1** synthesis without any further purification.[14] Elimination in boiling xylene (in presence of triethylamine)[15] afforded the unsaturated ketone **6**,[16] which was transformed into the 17α-ethynyl derivative **7** by treatment with the lithium acetylide–ethylendiamine complex in tetrahydrofuran.[17]

Finally, acidic removal of the 3-protecting group afforded gestodene **1**[18] in 50% overall yield from **2**, comparable to the yields reported[2] for the microbiological approach (47% from **2**, see Scheme 1).

In conclusion, the introduction of the phenylsulfoxide as a functional group at the 16-position, preceded by the selective protection of 3-carbonylic function as a cyclic ketal, gave us a simple synthesis of gestodene **1** starting from 18-methyl-4-estren-3,17-dione (**2**) with satisfactory yields.

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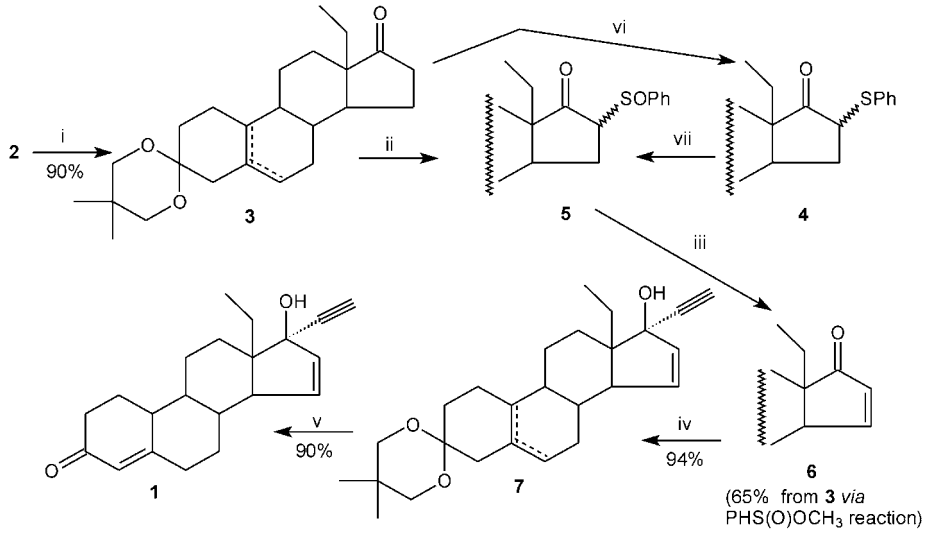

Scheme 1 *Reagents*: i. 2,2-Dimethyl-1,3-propandiol, $CH(OEt)_3$, TsOH, 10 °C; ii. $PhS(O)OCH_3$, *t*-BuOK, THF, r.t., 2 h; iii. Et_3N, xylene, reflux, 2.5 h; iv. Lithium acetylide–$H_2NCH_2CH_2NH_2$, THF, 0 °C, 2 h; v. 6 N HCl, acetone, r.t., 45 min; vi. $(PhS)_2$, LDA, THF, HMPA, from –78 °C to r.t., 2 h; vii. MCPBA, CH_2Cl_2, –78 °C, 30 min.

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(6) A mixture of Δ^{15}- and Δ^{14}-derivatives was obtained from the dehydrobromination and it is known that the conversion of the unconjugated ketone to the conjugated one, occurring in course of the acidic removal of 17-ketal, leads to an epimerization at C-14. See: Johnson, W. S.; Johns, W. F. *J. Am. Chem. Soc.* **1957**, *79*, 2005.

(7) **18-Methyl-3,3-(2′,2′-dimethyl-1′,3′-propylenedioxy)-5- and 5 (10)-estren-17-one (3).**
3-Carbonylic group of compound **2** (5 g, Keifeng, Shanghai) was selectively protected by reaction with 2,2-dimethyl-1,3-propanediol (3 equiv), triethyl-*ortho*-formate (1.7 equiv) and *p*-TsOH (0.5% w/w), in CH_2Cl_2, at 10 °C (3 h), and the title compound was obtained in 90% yield. Mp 90–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7 Hz, 0.9 H, 18-CH_3), 0.75 (t, *J* = 7 Hz, 2.1 H, 18-CH_3), 0.85 (s, 0.9 H, CH_3-C), 0.89 (s, 2.1 H, CH_3-C), 1.00 (s, 2.1 H, CH_3-C), 1.06 (s, 0.9 H, CH_3-C), 3.44–3.66 (m, 4 H, CH_2O), 5.50 (m, 0.7 H, CH=). IR (1% KBr): 3449.5, 2952.2, 2866.7, 1732.2. Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.45; H, 9.69; O, 12.95.

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(12) Due to the new stereocenters at the C-16 and SO group, four diastereoisomers were obtained, as shown by TLC (toluene–EtOAc 8:2) analysis.

(13) **3,3-(2′,2′-Dimethyl-1′,3′-propylenedioxy)-18-methyl-16ξ-phenylsulfoxide-5- and 5(10)-estren-17-one (5)**.
To a solution of **3** in anhyd THF, *t*-BuOK (4 equiv) was added. The mixture was kept, under N_2 atmosphere, under vigorous stirring at r.t., and after 10 min, methyl benzenesulfinate (Aldrich, 4 equiv) was added; upon disappearance of starting material (2 h), the crude product was recovered by extraction with EtOAc. The combined organic layers were washed with brine and H_2O, dried over Na_2SO_4 and the solvent was removed under reduced pressure. TLC (toluene–EtOAc 8:2) analysis showed a few spots with very similar R_f values (between 0.16 and 0.35). IR (1% KBr): 3449.9, 2954.9, 2868.9, 1735.9, 1129.6, 1106.5, 1093.8, 1048.7 cm^{-1}. MS: *m/z* = 497 [M + 1], 496 [M^+], 371, 370.

(14) The ^{1}H NMR spectrum of **5** was very complex due to the presence of four diastereoisomers of a mixture of Δ^5 and $\Delta^{5\,(10)}$ isomers. Except for the signals due to the 5,6-double bond (two multiplets at δ = 5.38 and 5.44 ppm in a ratio 4:6, respectively), it was not possible to assign any other signals. For analytical purposes, the 18-methyl-16ξ-phenylsulfoxide-4-estren-3,17-dione was prepared by removal (6 N HCl in acetone) of the 3-cyclic ketal from **5**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.63, 0.69, 0.74, 0.75 (4 t, *J* = 8Hz, in a ratio 0.14:0.11:0.35:0.40, 18-CH_3), 3.20 (dd, *J* = 8.4 and 10 Hz, 0.34 H, CHSO), 3.41 and 3.43 (two overlapped dd, 0.53 H, CHSO), 3.48 (dd, *J* = 8.4 and 10 Hz, 0.13 H, CHSO), 5.72, 5.73, 5.75 (three m, in a ratio 0.18:0.32:0.50, CH=), 7.27–7.42 (m, 5 H, Ar).

(15) We observed a cleaner reaction by employing Et_3N instead of the *N*,*N*-dimethylaniline reported in the original paper (ref.[11]).

(16) **3,3-(2′,2′-Dimethyl-1′,3′-propylenedioxy)-18-methyl-5-and 5(10),15-estradien-17-one (6).**
A solution of **5** in xylene (20 mL/g substrate) and Et_3N (1 mL/g substrate) was kept at 140 °C under N_2 atmosphere and the reaction progress was monitored by TLC (toluene–EtOAc 8:2) until the starting material disappeared (2.5 h). After cooling to r.t. the crude product was recovered after addition of toluene, washing of the organic phase with brine and H_2O and usual work-up. Purification by silica gel column chromatography (1:25, elution with hexane–EtOAc 9:1) afforded pure **6**, in 65% yield from **3**. Mp 115–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 8 Hz, 1.2 H, 18-CH_3), 0.77 (t, *J* = 8 Hz, 1.8 H, 18-CH_3), 0.86 (s, 1.8 H, CH_3-C), 0.90 (s, 1.2 H, CH_3-C), 1.01 (s, 1.2 H, CH_3-C), 1.08 (s, 1.8 H, CH_3-C), 3.40–3.70 (m, 4 H, CH_2O), 5.50 (m, 0.4 H, CH=), 5.99 (dd, *J* = 2.8 and 5.6 Hz 1 H, CH=), 7.47 (d, *J* = 5.6 Hz, 0.6 H, CH=), 7.54 (d, *J* = 5.6 Hz, 0.4 H, CH=). IR (1% KBr): 3454.0, 2951.3, 2863.7, 1706.0 cm^{-1}. MS: *m/z* = 371 [M + 1], 370 [M^+], 341.

(17) **3,3-(2′,2′-Dimethyl-1′,3′-propylenedioxy)-17α-ethynyl-17β-hydroxy-18-methyl-5-and 5(10),15-estradiene (7).**
To a solution of **6** in anhyd THF (25 mL/g of substrate) the commercially available (Fluka) lithium acetylide–ethylene-diamine complex (4 equiv) was added, at 0 °C and under N_2 atmosphere. The mixture was kept at 0 °C (2 h) under stirring. The reaction progress was monitored by TLC (toluene–EtOAc 8:2) until the starting material disappeared. To this mixture, 6 N HCl was added to pH 6 and the mixture was brought to r.t. Extraction with EtOAc and usual work-up afforded 17α-ethynyl derivative **7** (94%). Differential Scanning Calorimetry (DSC, 5 °C/min): two endothermic peaks at 174 °C and 192 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 8 Hz, 1.35 H, 18-CH_3), 0.85 (s, 1.35 H, CH_3-C), 0.86 (t, *J* = 8 Hz, 1.65 H, 18-CH_3), 0.90 (s, 1.65 H, CH_3-C), 1.00 (s, 1.65 H, CH_3-C), 1.06 (s, 1.35 H, CH_3-C), 2.60 (s, 0.45 H, H-21), 2.61 (s, 0.55 H, H-21), 3.40–3.70 (m, 4 H, CH_2O), 5.46 (m, 0.55 H, CH=), 5.67 (dd, *J* = 3.5 and 5.6 Hz, 1 H, CH=), 5.90 (dd, *J* = 2.0 and 6.0 Hz, 0.55 H, CH=), 5.99 (dd, *J* = 2.0 and 6.0 Hz, 0.45 H, CH=).

(18) **Gestodene (17α-ethynyl-18-methyl-4,15-estradien-3-one) (1).**
A solution of **7** in acetone was treated with 6 N HCl (1.2 equiv) for 45 min at r.t. Neutralization with a sat. $NaHCO_3$ solution, extraction with EtOAc and usual work-up afforded crude product that gave pure **1** (90%) by crystallization (hexane–acetone). DSC (5 °C/min): endothermic peak at 199.75 °C (onset a 198.90 °C). $[\alpha]_D^{20}$ –187.8 (*c* 1, CH_2Cl_2). The other chemical-physical data are in agreement with the reported ones. See: Von Cleve, G.; Frost, E.; Hoyer, G.-A.; Rosenberg, D.; Seeger, A. *Arzneim.-Forsch.* **1986**, *36 (I)*, 784.