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# An Efficient Synthesis of 11β-(4-Aminophenyl)spiro[estr-4-ene-17β,2′(5′*H*)-furan]-3,5′-dione

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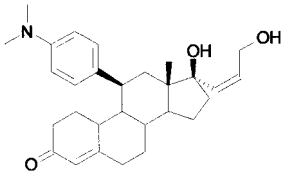
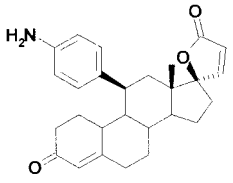
**Abstract**—An efficient synthesis has been developed affording 11β-(4-aminophenyl)spiro[estr-4-ene-17β,2′(5′*H*)-furan]-3,5′-dione (**2**), main metabolite of antiprogestin (*Z*)-11β-[4-(dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1-enyl)estr-4-en-3-one (**1**), in an overall yield of 21%. 

## Introduction

(*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1-enyl)estr-4-en-3-one (**1**) is a 19-nor steroid exhibiting progesterone antagonistic activity. The main metabolite of this compound in monkeys has been identified to be 11β-(4-aminophenyl)spiro[estr-4-ene-17β,2′(5′*H*)-furan]-3,5′-dione (**2**), an oxidative degradation product of **1**.




**1**




**2**

As a larger amount of this substance was required for toxicological studies and the known synthesis in our laboratories afforded **2** only in extremely low overall yields, we set out to develop a new synthesis of compound **2**.

Establishing an aromatic amino group in an 11β-phenyl steroid of the 19-nor-10-H-series proved difficult. Two routes to introduce a phenyl residue at the 11β-position of a steroid have been described, the copper salt catalyzed $S_N2'$-addition of aryl Grignard reagents to a $\Delta^{9(11)}$-5α,10α-epoxide,[1] and the aryl cross-coupling with steroidal 9(11)-enol triflates.[2] After introduction of the aryl moiety, the $S_N2'$ pathway includes a deprotection step, a Birch reduction of the dienone **5**, and an isomerization of the non-conjugated double bond in enones of type **6** under proton catalysis (Scheme 1).[3] Yields of the latter two steps normally are in the range of 50%. Therefore, the shorter cross-coupling sequence to 11β-arylestr-4-en-3-ones seemed more attractive for the synthesis of the metabolite.

11-Arylsteroids are easily obtained from Suzuki cross-coupling reactions of enol perfluoroalkylsulfonates like compound **8** with arylboronic acids (Scheme 2). Reduction of styrene **9** to the corresponding 9α,11α-dihydrosteroid **10** is achieved in stereospecific manner by reaction with lithium in liquid ammonia.

This Birch type reduction tolerates electron donating aryl substituents such as alkoxy and dialkylamino. However, in the presence of hydrogen bearing oxygen or nitrogen groups reduction does not takes place, because deprotonated hydroxy- or aminostyrenes are too electron rich to be attacked by solvated electrons. Cleavage of common acyl and silyl amino protecting groups by lithium in liquid ammonia is faster than reduction of the 9(11)-double bond. Protecting the amino group by alkyl substituents or as a pyrrole would permit clean reduction of the styrene system. In the presence of the respective oxygen functions at a later stage of the synthesis, cleaving such protecting groups is not expected to proceed in satisfactory yield.

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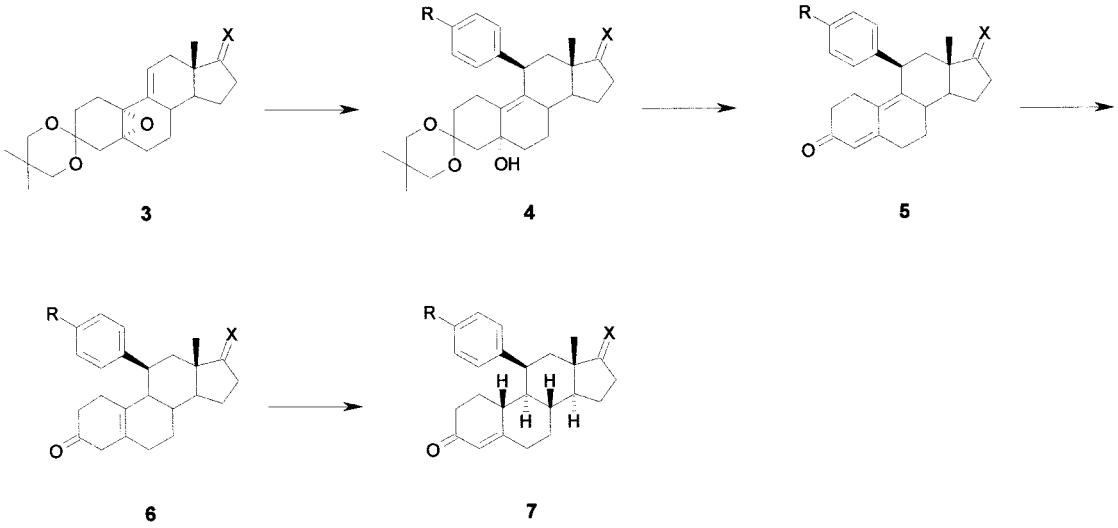



**Scheme 1.** The $S_N2'$ aryl introduction pathway.

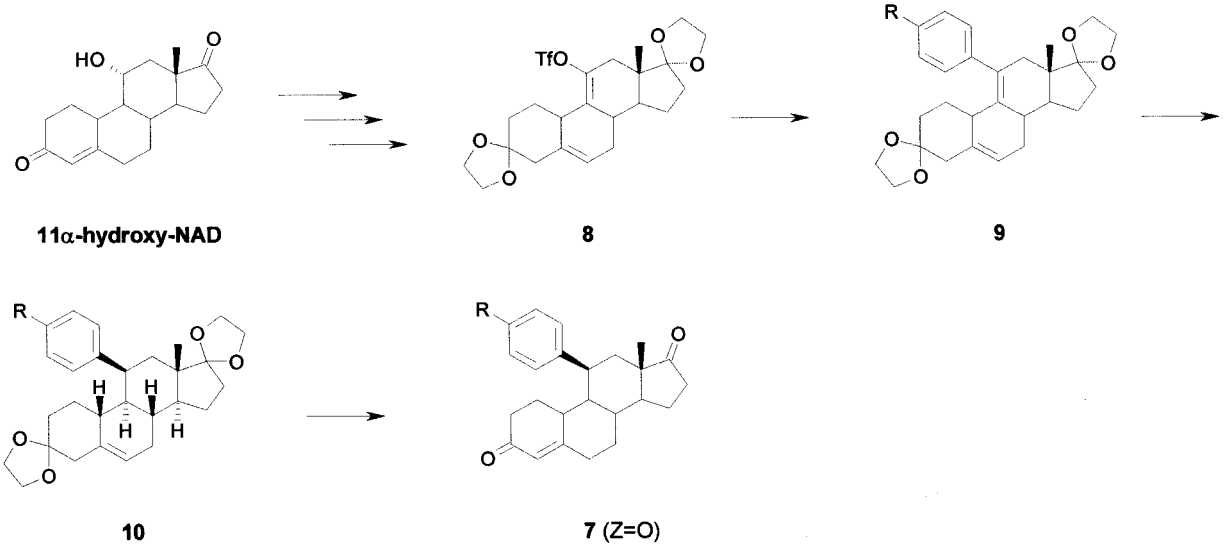
Therefore, introducing the nitrogen substituent after having established the 11β-aryl situation appeared to be the more promising synthetic strategy.

## Results and Discussion

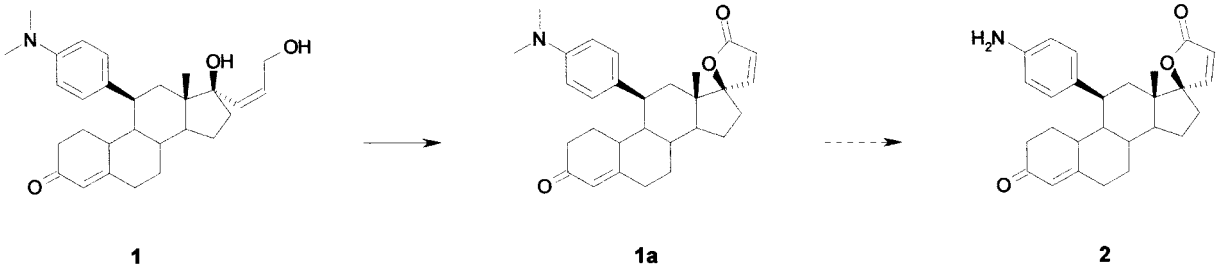
Before entering into a completely new synthesis, our first plan was to start with the available drug substance **1**. After oxidizing the alcohol in the side chain to the corresponding lactone **1a** and demethylating the dimethylamino group it was expected to obtain the desired compound **2** (Scheme 3).

Oxidation of compound **1** in toluene with silver carbonate/Celite® at reflux for 1 h[4] gave the desired lactone **1a** in 98% yield without further purification. The demethylation of an aromatic dimethylamino group to a monomethylamino group is a well-known procedure in literature. Oxidative demethylation using oxidizing agents like palladium salts[5,6] or peroxides[7,8] and the reaction with chloroformates[9] are described. All attempts applying these methods to compound **1a** only resulted in the formation of the corresponding monomethylamino derivative. In no case a double demethylation took place. Reacting compound **1** under various oxidizing conditions (silver carbonate/Celite®, Ru-salts/*t*-BuOOH, $Mn(OAc)_3$/AcOH, $FeCl_3/H_2O_2$) ended in the formation of lactone **1a**, but the desired compound **2** was not observed.

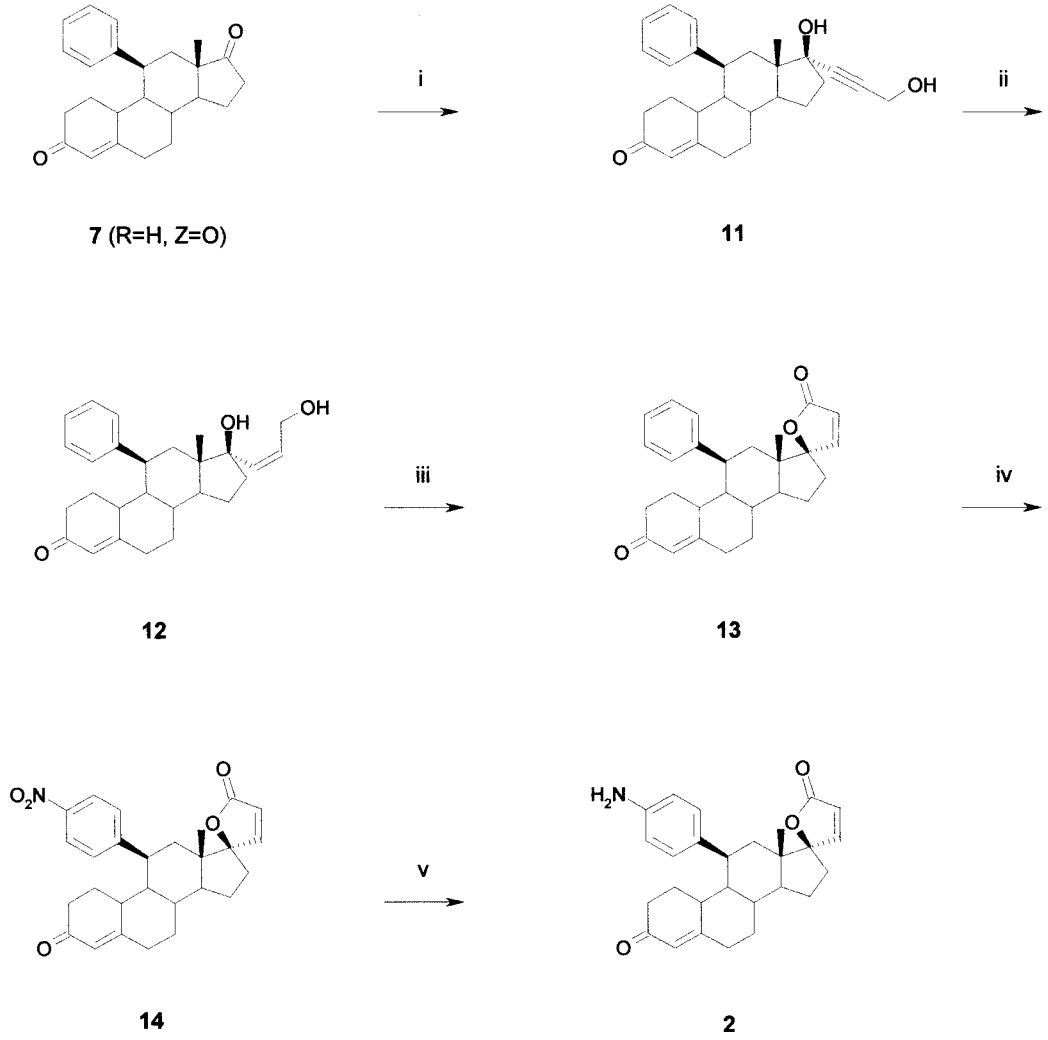
These results prompted us to establish a new synthetic route to aminolactone **2**. Our approach was based on 11β-phenyl-estr-4-ene-3,17-dione **7** (R=H, X=O). This compound was obtained from 11α-hydroxy-NAD in six chemical steps according to the protocol of Ottow et al.[2] (Scheme 2). Reaction of compound **7** (R=H, X=O) with the potassium salt of propargyl alcohol in tetrahydrofuran resulted in the formation of compound **11** in a very clean reaction, and after chromatography the propargyl compound was obtained in 99% yield (Scheme 4). Catalytic hydrogenation of acetylene




**Scheme 2.** The Suzuki cross-coupling aryl introduction pathway.




**Scheme 3.**




**Scheme 4.** (i) Propargyl alcohol, KO$^t$Bu, THF, 99%; (ii) $H_2$, Pd/$CaCO_3$, pyridine, THF, 98%; (iii) $Ag_2CO_3$/Celite®, toluene, 69%; (iv) nitronium tetrafluoroborate, sulpholane, $CH_2Cl_2$, 72%; (v) Fe, acetic acid, ethyl acetate, 43%.

**11** with Pd/$CaCO_3$ in tetrahydrofuran/pyridine resulted in a 98% yield of *Z*-olefin **12** after chromatography. Compound **12** was oxidized to unsaturated lactone **13** by silver carbonate on Celite® in 69% yield. The nitration of compound **13** by nitronium tetrafluoroborate in sulpholane and methylene chloride proceeded smoothly without formation of regioisomers. After chromatography, the desired compound was obtained in 72% yield. Finally, the reduction of nitro compound **14** with iron powder in acetic acid gave target compound **2**. After purification of the raw material we obtained the metabolite in 43% yield.

## Experimental

Flash column chromatography was performed on Merck silica gel (grade 60, 230–400 mesh); TLC was performed on Merck HPTLC plates 60 $F_{254}$. The melting points are uncorrected. IR spectra were measured on a Bruker FT-IFS 25 spectrometer. Mass spectra were recorded on a Micromass AutoSpec EQ mass spectrometer. $^1$H NMR spectra (300 MHz) were recorded using TMS or the solvent as internal standard on a Bruker AC 300 spectrometer.

**17β-Hydroxy-17α-(3-hydroxyprop-1-inyl)-11β-phenylestr-4-en-3-one (11).** To a suspension of potassium *tert*-butoxide (34.4 g, 306 mmol) in dry THF (270 ml) at 0°C, 11β-phenylestr-4-ene-3,17-dione **7** (15.25 g, 44 mmol) in dry THF (200 ml) was slowly added and stirring was continued for 30 min. Propargyl alcohol (10.3 ml, 17.5 mmol) was added and stirring was continued for 2 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed twice with water and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure affording a crude product, which was purified by column chromatography (ethyl acetate–hexane 7:3) to give **11** (17.64 g, 99.7%): mp 126–130°C; HRMS (EI, *m/z*) found: 404,2347 ($M^{+\cdot}$); calcd for $C_{27}H_{32}O_3$: 404,2351; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.63 (3H, s, 18-$CH_3$), 2.80–2.92 (1H, m, 10-CH), 3.40–3.44 (1H, m, 11-CH), 4.35 (2H, s, 22-$CH_2$), 5.86 (1H, s, 4-CH), 7.15–7.20 (1H, m, ar-CH), 7.26–7.28 (2H, m, ar-CH), 7.40–7.43 (2H, m, ar-CH).

**(*Z*)-17β-Hydroxy-17α-(3-hydroxyprop-1-enyl)-11β-phenylestr-4-en-3-one (12).** To a solution of **11** (17.6 g, 44 mmol) in dry THF (94 ml) and pyridine (18 ml), palladium on calcium carbonate (5%, 1.76 g) was added, and the reaction mixture was stirred at room temperature under hydrogen atmosphere. After 30 min, the mixture was filtered through Celite® and washed with THF. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate–hexane 8:2) to give **12** (17.45 g, 98%): mp 198–200°C; HRMS (EI, *m/z*) found: 406,2495 ($M^{+\cdot}$); calcd for $C_{27}H_{34}O_3$: 406,2508; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.70 (3H, s, 18-$CH_3$), 2.80–2.92 (1H, m, 10-CH), 3.35–3.39 (1H, m, 11-CH), 4.24–4.26 (2H, m, 22-$CH_2$), 5.61–5.68 (1H, m, 21-CH), 5.72–5.76 (1H, m, 20-CH), 5.85 (1H, s, 4-CH), 7.15–7.20 (1H, m, ar-CH), 7.25–7.30 (2H, m, ar-CH), 7.40–7.43 (2H, m, ar-CH).

**11β-Phenylspiro[estr-4-ene-17β,2′(5′*H*)-furan]-3,5′-dione (13).** To a solution of **12** (17.45 g, 43 mmol) in dry toluene (425 ml), silver carbonate on Celite® (122.15 g, 21.4 mmol) was added. After refluxing the for 3 h, the reaction mixture was cooled to room temperature. The mixture was filtered through Celite® and washed with ethyl acetate. The organic layer was washed twice with water and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate–hexane 7:3) to give **13** (11.88 g, 69%): mp>220°C; HRMS (EI, *m/z*) found: 402,2190 ($M^{+\cdot}$); calcd for $C_{27}H_{30}O_3$: 402,2195; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.81 (3H, s, 18-$CH_3$), 2.85–2.97 (1H, m, 10-CH), 3.32–3.35 (1H, m, 11-CH), 5.87 (1H, s, 4-CH), 5.96 (1H, d, *J*=5 Hz, 21-CH), 7.16–7.19 (1H, m, ar-CH), 7.25–7.30 (2H, m, ar-CH), 7.31–7.35 (2H, m, ar-CH), 7.45 (1H, d, *J*=5 Hz, 20-CH).

**11β-(4-Nitrophenyl)spiro[estr-4-ene-17β,2′(5′*H*)-furan]-3,5′-dione (14).** To a solution of **13** (8.4 g, 20.9 mmol) in dichloromethane (180 ml) at 5°C, a solution of nitronium tetrafluoroborate in sulpholane (0.5 M, 85 ml, 42.5 mmol) was slowly added and stirring was continued for 30 min at 5°C. Solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography (ethyl acetate–hexane 8:2) to give **14** (6.7 g, 72%): mp>220°C; HRMS (EI, *m/z*) found: 447,2062 ($M^{+\cdot}$); calcd for $C_{27}H_{29}NO_5$: 404,2351; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.78 (3H, s, 18-$CH_3$), 2.73–2.85 (1H, m, 10-CH), 3.40–3.47 (1H, m, 11-CH), 5.90 (1H, s, 4-CH), 5.99 (1H, d, *J*=5 Hz, 21-CH), 7.44 (1H, d, *J*=5 Hz, 20-CH), 7.57 (2H,d, *J*=8.5 Hz, ar-CH), 8.17 (2H, d, *J*=8.5 Hz, ar-CH).

**11β-(4-Aminophenyl)spiro[estr-4-ene-17β,2′(5′*H*)-furan]-3,5′-dione (2).** To a suspension of iron powder (6.5 g, 116 mmol) in acetic acid (5%, 500 ml) at 60°C, a solution of **14** (10.28 g, 23 mmol) in ethyl acetate (260 ml) and acetic acid (260 ml) was slowly added and stirring was continued for 60 min at 80°C. The reaction mixture was cooled to room temperature, filtered through Celite® and washed with ethyl acetate. Solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and water, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) to give **2** (4.1 g, 43%): mp>230°C (decomp.); IR (KBr, $cm^{-1}$): 1760 (C=O), 1668 (C=O); HRMS (EI, *m/z*) found: 417,2302 ($M^{+\cdot}$); calcd for $C_{27}H_{31}NO_3$: 417,2304; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.86 (3H, s, 18-$CH_3$), 2.77–2.90 (1H, m, 10-CH), 3.18–3.26 (1H, m, 11-CH), 3.68 (2H, br s, $NH_2$), 5.86 (1H, s, 4-CH), 5.95 (1H, d, *J*=5 Hz, 21-CH), 6.61 (2H, d, *J*=8.5 Hz, ar-CH), 7.11 (2H,d, *J*=8.5 Hz, ar-CH), 7.48 (1H, d, *J*=5 Hz, 20-CH).

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## References

1. Bélanger, A.; Philibert, D.; Teutsch, G. *Steroids* **1981**, *37*, 361.
2. Ottow, E.; Cleve, A.; Neef, G.; Schwede, W. *J. Prakt. Chem.* **1997**, *339*, 365.
3. Cleve, A.; Scheidges, C.; Neef, G.; Ottow, E.; Elger, W.; Beier, S. Eur. Pat. EP 404,283 (27.12.1990); [*Chem. Abstr.* **1991**, *114*, P 164625f].
4. McKillop, A.; Young, D. W. *Synthesis* **1979**, 402.
5. Sakakibara, T.; Hamakawa, T. *Chem. Lett.* **1982**, 1823.
6. Sakakibara, T.; Karasumaru, S.; Kawano, I. *J. Am. Chem. Soc.* **1985**, *107*, 6417.
7. Albini, A.; Fasani, E.; Pietra, S. *J. Chem. Soc., Perkin Trans. 2* **1986**, 681.
8. Maruyama, K.; Kusukawa, T.; Higuchi, Y.; Nishinaga, A. *Chem. Lett.* **1991**, 1093.
9. Bachelet, J.; Caubere, P. *J. Org. Chem.* **1982**, *47*, 234.