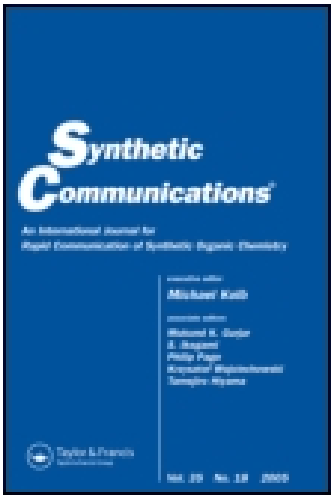

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Intramolecular Cyclization of 9,11-*Seco*-Estrane under Friedel–Crafts Reaction Conditions

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Abstract: An intramolecular cyclization of 17β-acetoxy-3-methoxy-9,11-*seco*-1,3,5(10)-estratriene-11-oic acid under different Friedel–Crafts reaction conditions is described.

Keywords: Friedel-Crafts reaction, *seco*-steroids, estrogens, Grignard reaction, intramolecular cyclization

Several structural modifications have been made in the steroidal framework that were achieved either by substitution at various positions of the steroidal nucleus or by changing its stereochemistry to get a desired drug.[1–3] Among various modifications, substitution of aryl residue at the 11β position of an estrane as well as a progestin, which led to the development of important compounds **1** and **2**, has been found to modulate their hormonal profile (Figure 1).[4,5] Further, *seco*-steroids, another class of compounds such as **3** and **4**, generally share structural features similar to those of their parent compounds for receptor affinity and are important because of their significant receptor affinity with the desired hormonal profile.[6–8]

Keeping these considerations in view, we targeted the synthesis of 11-aryl-substituted 3-methoxy-9,11-*seco*-estra-1,3,5(10)-trienes of type **5** as modified

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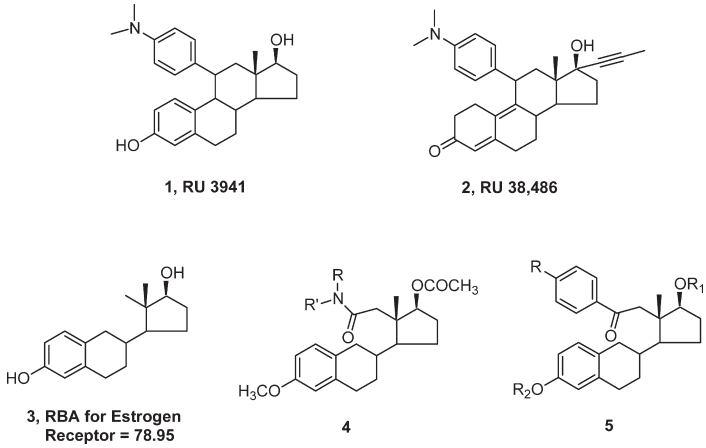
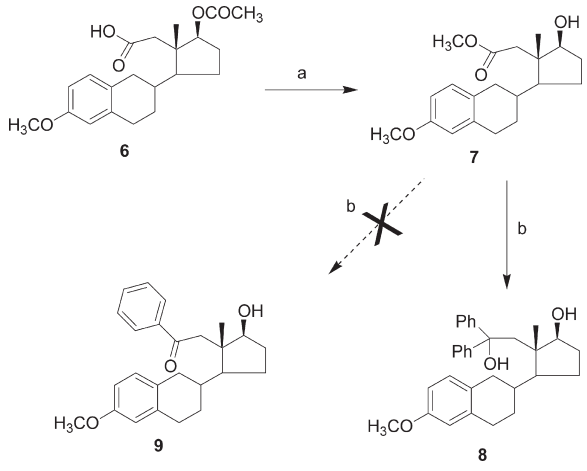


Figure 1. Biologically important steroidal material.

estrogens (Figure 1). During synthesis of targeted compound **5**, we noticed an intramolecular cyclization of 17β-acetoxy-3-methoxy-9,11-*seco*-estra-1,3,5(10)-triene-11-oic acid (**6**) under different Friedel–Crafts reaction conditions. This communication presents different approaches used to synthesize the desired compounds and an unexpected intramolecular cyclization of 17β-acetoxy-3-methoxy-9,11-*seco*-1,3,5(10)-estratriene-11-oic acid (**6**) under different Friedel–Crafts reaction conditions, yielding a cyclic ester in good yield.

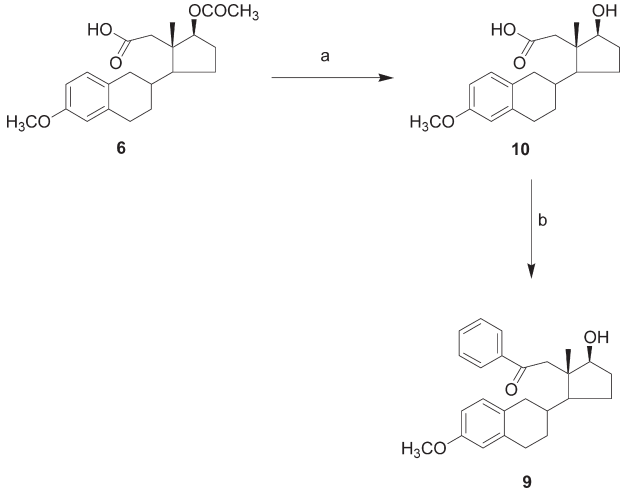
Initially the synthesis of **5** was attempted though the Grignard reaction on methyl-17β-hydroxy-3-methoxy-9,11-*seco*-estra-1,3,5(10)-triene-11-carboxylate (**7**) (obtained from 17β-acetoxy-3-methoxy-9,11-*seco*-1,3,5(10)-estratriene-11-oic acid **6**) using phenyl magnesium bromide, which led to the formation of 11,17β-dihydroxy-11,11-diphenyl-3-methoxy-9,11-*seco*-estra-1,3,5(10)-triene (**8**) in 88% yield instead of the desired compound 11-oxo-11-phenyl-9,11-*seco*-estra-1,3,5(10)-trien-17β-diol 3-methyl ether (**9**) (**5**, **R**, $\mathbf{R_1 = H}$, $\mathbf{R_2 = CH_3}$) (Scheme 1). Therefore, synthesis of **5** was made though controlled addition of acid **10** (obtained by deacetylation of **6**), dissolved in dry tetrahydrofuran (THF), to the solution of phenyl lithium in dry THF under inert reaction conditions, which gave compound **9** in 20% yield (Scheme 2). With this approach, we were able to synthesize the desired compound **9** (**5**, **R**, $\mathbf{R_1 = H}$, $\mathbf{R_2 = CH_3}$); however, complexity of the reaction with other substituted phenyl lithium and low yield prevented us for further experimentation in this direction.

In an alternate approach, Friedel–Crafts reaction on *seco*-estrane acid **6** with phenol under various conditions (Scheme 3) was attempted. Friedel–Crafts reaction of **6** with phenol in the presence of polyphosphoric acid (PPA), boron trifluoride–etherate complex (BF_3–OEt_2), or anhydrous $AlCl_3$ at a temperature ranging from 80 to 120 °C led to the formation of cyclic

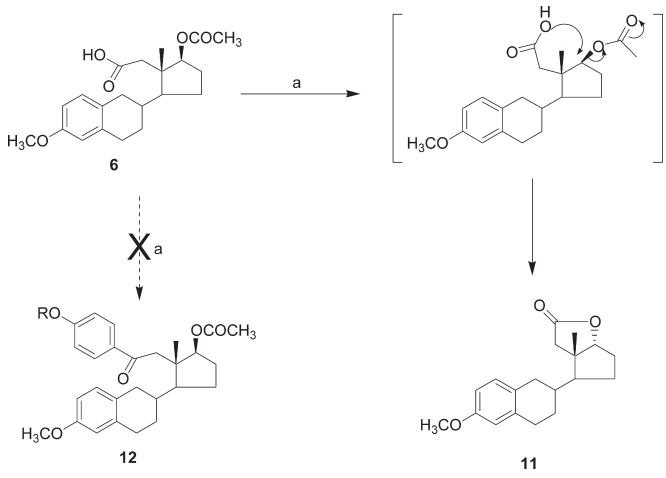


Scheme 1. (a) HCl, CH_3OH; (b) PhMgBr, dry ether, room temperature.

ester **11** in good yield along with other unidentified side products instead of the desired compound **12** (**R** = **H**). We had earlier observed the formation of compound **11** from **6** and its other derivatives at elevated temperature (e.g., 237 °C) with copper and quinoline.[9] We presumed that in this case too, temperature might have played a critical role in the formation of the cyclized product **11**. We therefore tried the Friedel–Crafts reaction with $SnCl_4$ in benzene, $SnCl_4$ (neat), and anhydrous $AlCl_3$ in benzene at temperatures ranging from 0 °C to room temperature (rt). Interestingly, even under such mild conditions, formation of compound **11** in good yield was observed.



Scheme 2. 2% NaOH, CH_3OH, Rt; (b) PhLi, dry THF, 0 °C.



Scheme 3. (a) Phenol or anisole with PPA, heat; or BF_3-OEt_2, heat, or $SnCl_4$, 0 °C–Rt.

When the Friedel–Crafts reaction was performed with anisole (a protected phenol) instead of phenol, under similar reaction conditions, it also yielded **11** in good yield. To find out any role of phenolic compound in cyclization of **6**, we stirred **6** with $SnCl_4$ in dry benzene, $SnCl_4$ (neat), and anhydrous $AlCl_3$ in dry benzene at a temperature ranging from 0 °C to rt, which gave **11** in almost similar quantities. Thus, we concluded that the Friedel–Crafts reaction conditions are sufficient for intramolecular cyclization of **6** to yield **11** in good yield. We noticed during our experiments that the observed cyclization is reproducible. The newly synthesized compounds were characterized by ^{1}H NMR, IR, mass spectroscopy, and microanalysis.

EXPERIMENTAL

Anhydrous reactions were performed under an inert atmosphere; the setup was assembled and cooled under dry nitrogen. Unless otherwise noted, starting material, reactant, and solvents were obtained commercially and used as such or purified and dried by standard means. The reported melting points were determined in open capillaries and are uncorrected. The ^{1}H NMR was recorded on a Brucker Avans DRX 200 (200-MHz, FT NMR) spectrometer using TMS as internal standard. The chemical shifts are expressed in δ (ppm) values, and coupling constants are in hertz. Multiplicities are described by the following abbreviations: s for singlet, d for doublet, t for triplet, and bs for broad singlet. Mass spectra were recorded on a Jeol JMS-D-300 spectrometer. The IR spectra were recorded in KBr on a Perkin-Elmer model 881. Elemental analyses were carried out on a Carlo-Erba EA 1108 instrument, and results were within $\pm 0.4\%$ of theoretical values. The purity of the products was

checked on precoated silica-gel 60 F254 thin-layer chromatography (TLC) plates, and the spots were visualized by inspection under short (254-nm) wavelength UV light or by the colors developed with iodine vapors. The column chromatography was performed on silica gel 60 (Merck).

Synthesis of Methyl-17β-hydroxy-3-methoxy-9,11-*seco*-estra-1,3,5(10)-triene-11-carboxylate (7)

A mixture of **6** (1.0 g, 2.78 mmol), methanol (25 ml), and conc. HCl (0.5 ml) was refluxed for 4 h. On completion, solvent was removed under vacuum. The residue was treated with water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated. The solid thus obtained was crystallized from benzene–hexane.

Yield: 98%, mp 87–89 °C. EIMS: M^+ m/e 332; IR (cm^{-1}): 3500, 1725, 1600, 1580, 1500; ^1H NMR (δ): 0.93 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.10 (m, 1H, CH), 6.32–6.88 (m, 3H, ArH). Anal. calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.70.

Synthesis of 11,17β-Dihydroxy-11,11-diphenyl-3-methoxy-9,11-*seco*-estra-1,3,5(10)-triene (8)

A solution of **7** (1.0 g, 3.01 mmol) in anhydrous benzene (20 ml) was added dropwise to a magnetically stirred solution of C_6H_5MgBr (20.0 mmol) in anhydrous ether (20 ml) during 1 h at 5 °C. The reaction mixture was stirred at room temperature for another 6 h. The mixture was cooled in ice, and saturated ammonium chloride solution was added slowly until the aqueous layer became clean. The organic layer was separated, and the precipitated Mg salts were washed well with ether. The combined organic extracts were then steam-distilled to remove biphenyl. Extraction with ether followed by washing with water, drying over anhydrous sodium sulfate, and evaporating the solvent gave a gum, which was chromatographed over silica gel to give **8**, which was crystallized from benzene–hexane.

Yield: 88%, mp 78–80 °C. EIMS: M^+ ($-H_2O$) m/e 438; IR (cm^{-1}): 3300, 1600, 1580, 1500; ^1H NMR (δ): 0.46 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.08 (m, 2H, CH), 6.55–7.02 (m, 3H, ArH), 7.08–7.64 (m, 10H, ArH). Anal. calcd. for $C_{31}H_{36}O_3$; C, 81.54; H, 7.93. Found: C, 81.10; H, 8.14.

Synthesis of 3,17β-Dihydroxy-9,11-*seco*-estra-1,3,5(10)-triene-11-oic Acid 3-Methyl Ether (10)

The acid **6** (0.50 g, 1.4 mmol) was stirred with 2% methanolic sodium hydroxide at room temperature for 30 min. After completion of the reaction,

the reaction mixture was acidified with 5% HCl. On acidification, a solid precipitated that was filtered, washed with water, and dried under suction. The solid was obtained in 80% yield and used as such in the subsequent step.

Synthesis of 11-Oxo-11-phenyl-9,11-*seco*-estra-1,3,5(10)-trien-17β-diol 3-Methyl Ether (9)

17β-Hydroxy-3-methoxy-9,11-*seco*-1,3,5(10)-estratrien-11-oic acid (**10**) (0.50 g, 1.6 mmol) in dry THF (5 ml) was added to the stirred solution of the phenyl lithium (16.0 mmol) in dry ether (10 ml) at 0 °C under an inert atmosphere. Stirring was continued for another 1 h, and the reaction mixture was poured dropwise into ice water (50 ml), made acidic with dil. HCl, extracted with ether, and worked up in the usual manner. An oily residue was obtained, which on chromatography over silica gel gave compound **9** in 20% yield.

Yield: 20%, mp 108–110 °C. FABMS: 378; IR (cm^{-1}): 3400, 1675, 1608, 1440, 1370, 1038, 746, 687; ^{1}H NMR (δ): 1.01 (s, 3H, CH_3), 1.45 (m, 2H, CH_2), 1.54 (bs, 4H, CH_2), 1.77 (m, 1H, CH), 2.05 (m, 1H, CH), 2.65–2.73 (m, 4H, CH_2), 2.87 (bs, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.12 (m, 1H, CH), 4.42 (bs, 1H, OH), 6.67–6.75 (m, 2H, ArH), 7.01 (d, $J = 8.00$ Hz, 1H, ArH), 7.49–7.54 (m, 3H, ArH), 7.99 (d, $J = 8.00$ Hz, 1H, ArH). Anal. calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.62; H, 7.72.

Synthesis of 17β-Hydroxy-3-methoxy-9,11-*seco*-estra-1,3,5(10)-trien-11-oic Acid 11,17-Lactone (11)

Method A

In a round-bottomed flask, a mixture of acid **6** (0.50 g, 1.4 mmol), phenol (0.14 g, 1.4 mmol), and boron–diethyl ether complex (BF_3–OEt_2, 1.5 ml) was heated under reflux for 6–8 h. The reaction mixture was then poured onto ice-cold water and extracted with ethyl acetate. The organic layer was then dried over anhydrous sodium sulfate and concentrated. The crude material on chromatography yielded pure compound **11** in 60% yield.

Yield: 60%, mp 82–84 °C (lit. 84–86 °C[9]). FABMS: 300; IR (cm^{-1}): 2925, 1774, 1610, 1502, 1462; ^{1}H NMR (δ): 1.14 (s, 3H, CH_3), 1.68–2.45 (m, 6H, CH_2), 2.50 (s, 2H, CH_2), 2.71–2.82 (m, 4H, CH_2), 3.77 (s, 3H, OCH_3), 4.45 (m, 1H, CH), 6.61–6.70 (m, 2H, ArH), 6.96 (d, $J = 8.00$ Hz, 1H, ArH).

Method B

A mixture of acid **6** (0.50 g, 1.4 mmol), phenol (0.14 g, 1.5 mmol), and polyphosphoric acid (10 g) was taken in a round-bottomed flask. The reaction

mixture was heated for 10–12 h on a water bath at 90–100 °C. The reaction mixture was then poured onto ice, extracted with ethyl acetate, and washed with sodium bicarbonate, and water until neutral. The organic layer was dried over sodium sulfate and concentrated. The oily residue on chromatography yielded pure compound **11** in 50% yield.

Method C

A mixture of acid **6** (0.50 g, 1.4 mmol) and phenol (1.40 g, 1.5 mmol) in dry benzene (10 ml) was strried with $SnCl_4$ (6 ml) at a temperature ranging from 0 °C to rt for 10 h. The reaction mixture was then poured onto ice and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate and water untill neutral and concentrated after drying over sodium sulfate. The oily residue was then crystallized from ethyl acetate–hexane, which gave **11** in 60% yield.

CONCLUSIONS

In conclusion, this communication describes an intramolecular cyclization of 17β-acetoxy-3-methoxy-9,11-*seco*-1,3,5(10)-estratriene-11-oic acid under different Friedel–Crafts reaction conditions, yielding a cyclic ester in good yield.

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