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High Specific Activity Steroids II: Microscale Synthesis of Norgestrel-[9,11-^{3}H]‡

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SUMMARY

The synthesis of the high specific activity (39 Ci/mmole) tritium labelled steroid norgestrel is described. A practical synthesis of the required substrate for tritium incorporation, 18-methyl -$\Delta^{9(11)}$- estradiol-3-methyl ether (**6**), was developed *from norgestrel itself*. Following reduction with carrier-free tritium gas, microscale conditions were employed for the conversion of the resulting labelled intermediate (**7**) back to norgestrel-[9,11-^{3}H], including a selective *in situ* protection of the A-ring ketone of 19-norandrost-4-ene-3,17-dione (**11**).

Key words: tritiated 19-norsteroids, high specific activity, norgestrel-[9,11-^{3}H]

INTRODUCTION

Norgestrel (**1**), a member of the class of 19-norsteroids such as ethynylestradiol and norethindrone, is an orally active progestational agent (1). Current work with these compounds is concerned primarily with development of enhanced formulations. In order to evaluate the relative bioavailabilities of new formulations, highly sensitive radioimmunoassay (RIA) methodology is usually employed, and as such, high specific activity material is required.

Although the synthesis of norgestrel has been reported by various groups (2), only one article describes the synthesis of high specific activity tritiated material (3). In that paper, norgestrel-[14,15-^{3}H] was prepared at 52 Ci/mmol. This synthesis, however, was carried out on the millimole scale using up to 60 Curies of material in a single operation. Motivated by safety, storage and disposal concerns we felt that working with this amount of activity was unacceptable. In order to avoid these potential problems and still deliver carrier-free material suitable for RIA studies would therefore require that the synthesis be carried out at the microscale level. A recent paper from this lab addressed that challenge, wherein ethynylestradiol-[9,11-^{3}H] and norethindrone-[9,11-^{3}H] were each prepared at 54 Ci/mmole *via* microscale syntheses (4). Furthermore, the methods developed to prepare these steroids appeared to be of a general nature.

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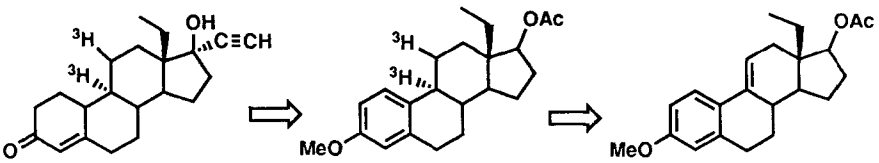
As an extension and demonstration of the general utility of that methodology, we describe herein the microscale synthesis of high specific activity norgestrel.

DISCUSSION

Our approach to the synthesis of tritiated norgestrel and, in general, other 19-norsteroids of this type is depicted in **Scheme I**. We prefer to incorporate the tritium atoms by reduction of the $\Delta^{9(11)}$-estrogen (6) to afford the labelled estrogen (7). We have found that reductions of this type are essentially quantitative and afford high specific activity material (4). The subsequent conversion of (7) to norgestrel (1-^{3}H) would then follow an analogous route to our synthesis of tritiated norethindrone. The key steps in this sequence are the microscale Birch reduction (4, 5) of the labelled estrogen and the selective introduction of acetylene at C17.

Scheme I



1-^{3}H 7 6

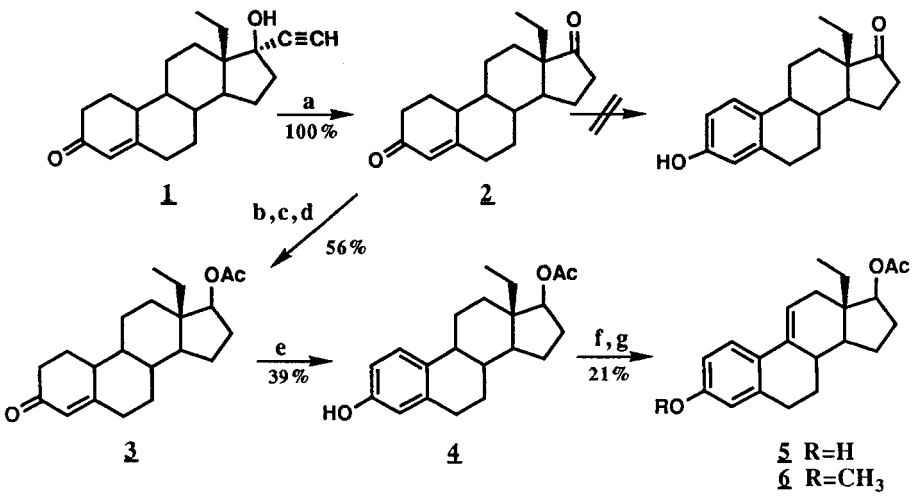
In contrast to our synthesis of tritiated norethindrone (4), the required substrate for labelling 18-methyl-19-norsteroids was not readily available. We therefore developed the general strategy for preparation of $\Delta^{9(11)}$-estrogens (such as 6) from 19-norsteroids depicted in **Scheme II**.

Treatment of (1) with Ag_2CO_3-celite in toluene gave the ketone (2) in quantitative yield (6). Attempts to aromatize the A ring of (2) under a variety of conditions were met with only limited success . Although at times we were able to obtain small amounts of desired product, the reactions were not clean and the isolation of the pure material was difficult. Since we felt the presence of the 17-ketone might be interfering in these reactions, (2) was converted to the 17-acetate (3) by a three step sequence: reduction to the diol ($LiAlH_4$), selective oxidation of the allylic hydroxyl to the enone with MnO_2, and then acylation with Ac_2O in 56% overall yield. As with (2), aromatization of (3) to give the phenol was not straightforward. The standard reagents (7) typically used to effect this transformation (eg., NCS, DDQ, $(PhSe)_2$ with m-IO_2PhCO_2H) gave complex reaction mixtures with little, if any, of the desired aromatic A-ring product. Ultimately we found that using a modified procedure (8) of Hartman *et.al.*, resulted in a modest yield of the phenol.

The enone (3) was treated with excess NBS in refluxing CCl_4 to give an unstable intermediate (9) which, when treated with DBU in refluxing toluene gave (4) in 39% isolated yield. It is interesting to note that the first step of this sequence stops at ca. 50% conversion (as judged by tlc), even when additional NBS was added. The final two transformations proceeded smoothly to

give the required substrate for labelling. Introduction of the $\Delta^{9(11)}$-olefin was accomplished by NCS oxidation (7a, 10) in the presence of K_2CO_3 to give (5) (32%, not optimized) and finally, the phenol was protected as the methyl ether (NaH, MeI) to give the tritiation substrate (6) in 66% isolated yield.

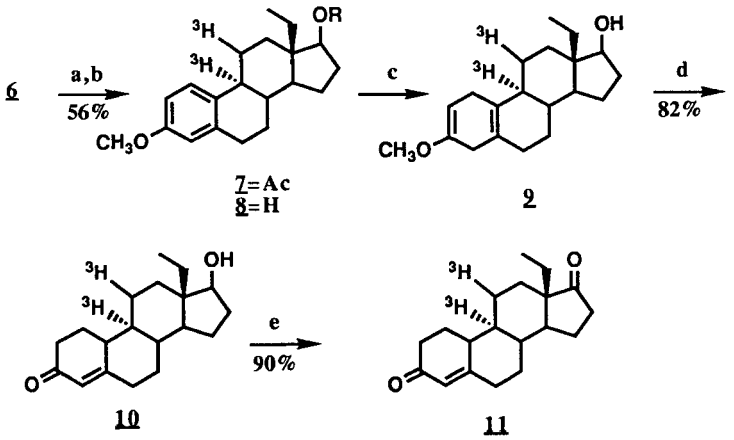
Scheme II



(a) Ag_2CO_3-celite, toluene, reflux, 3 hours; (b) LAH/THF, reflux; (c) MnO_2, $CHCl_3$, 16 hours; (d) Ac_2O, Et_3N, DMAP; (e) NBS/CCl_4, reflux, 20 min., then DBU/toluene, reflux, 30 min.; (f) NCS, MeCN, reflux, 30 min., then K_2CO_3, DMF, 150°C, 90 min.; (g) NaH, MeI, THF, 90 min.

The synthesis of norgestrel-[9,11-^{3}H] from (6) is outlined in **Scheme III** . Reduction of 0.1 mmoles of (6) with 10 Ci carrier free tritium gas over 10% Pd/C afforded 1500 mCi of (7) . For convenience, the acetate was removed (K_2CO_3/MeOH) to give (8), in preparation for the

Scheme III



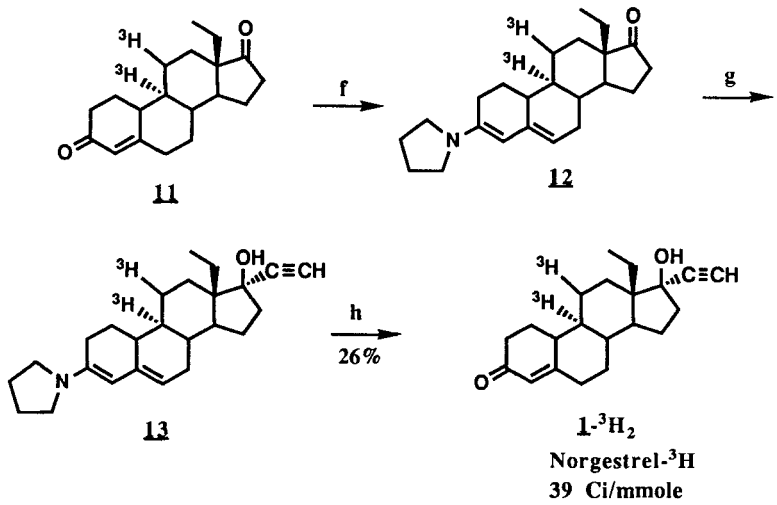
(a) $^3H_2$-10% Pd/C, EtOAc, 16 hours; (b) K_2CO_3/MeOH, reflux, 5 hours; (c) Na/NH_3, THF-ethanol, -78°C, 25 min.; (d) (aq) HCl, methanol, 70°C, 90 min.; (e) CrO_3-H_2SO_4-acetone-water, 0°C, 1 hour.

microscale Birch reduction. As described earlier (4,5), it is essential to control the reaction conditions and workup of this step. If not run under carefully controlled conditions yields decrease substantially and the resulting diene (9) will reoxidize rapidly back to (8) (11). To this end, a solution of (8) in THF/EtOH was added to doubly distilled NH_3 at -78°C, and treated with freshly cut and washed (toluene) Na. After tlc analysis indicated complete consumption of starting material the reaction was quenched with methanol and water. Acidic hydrolysis (HCl) of the Birch product (9) afforded an excellent yield (82%) of the enone (10) after chromatographic purification. Jones oxidation gave the ketone (11) in near quantitative yield.

Direct alkynylations at C17 on steroids such as (11) have been attempted, however the selectivity of these reactions has typically been low. For this reason a number of methods have been developed for protection of the A-ring enone (12). For example, selective protection can be accomplished by treatment with pyrrolidine to give the 3,5-dieneamine which crystallizes from solution and is easily isolated. On a large scale (i.e., > 0.1 mmoles), this procedure is convenient. However, difficulties arose when this and other methods were attempted during the microscale synthesis of tritiated norethindrone (4) rendering selective protection unfeasible. Resorting to alkylation of unprotected material in that case resulted in a low yield (7.5%) of the desired mono-alkynylated product.

The disadvantage with that approach is evident not only in the low yield, but also with the challenging experimental protocol and purification. Because of competitive alkynylation at C3 only a slight excess of acetylide could be employed. In order to get a reasonable conversion to the desired product, long reaction times (up to 4 days at ambient temperature) and recycling of the (recovered) starting material were necessary. Following aqueous workup, column chromatography and two preparative tlcs were required in order to obtain radiochemically pure material. We therefore believed a closer investigation into selective protection was warranted, and are gratified to report that a convenient protocol compatible with this scale was found (Scheme IV).

Scheme IV



(f) Pyrrolidine/methanol, reflux, 25 min.; (g) Li-acetylide-EDA, THF, 25°C, 16 hours; (h) (aq) NaOAc/HOAc/MeOH, reflux, 4 hours.

Treatment of 100 mCi (0.7 mg, 0.0025 mmoles) (**11**) with 50 uL (200 eq.) pyrrolidine (12) in refluxing methanol gave (**12**) (13). The reaction mixture was concentrated *in vacuo* (to remove all volatiles), redissolved in THF and exposed to an excess of lithium acetylide-ethylenediamine complex for 16 hours. The crude reaction mixture containing (**13**) was then hydrolysed with an aqueous solution of NaOAc/HOAc/MeOH. When conversion to the desired product (**1**-^{3}H) reached a maximum radiochemical yield of ca. 40% after 4 hours at reflux, the reaction was stopped. Although the remaining activity was primarily baseline material, there was no detectable formation of the either the bis-alkynylated material or the starting enedione (**11**). Following extractive workup and purification by radial chromatography (14) 26 mCi (26% yield) of greater than 99% pure norgestrel-^{3}H was isolated. The specific activity was determined to be 39 Ci/mmole by UV and radioassay.

This synthesis of norgestrel-^{3}H further demonstrates that high specific activity 19-norsteroids are accessible using microscale technology. In this case, an 8 step synthesis of the title compound in 16% radiochemical yield from the labelled estrogen (**7**) was realized. Furthermore, a method has been developed which allows one to prepare the required substrate for tritium incorporation in the 18-methyl steroid series from the unlabelled target compound itself. These protocols, when used in tandem, provide a direct route to carrier-free, tritiated 19-norsteroids in good overall yield.

EXPERIMENTAL

All reagents were purchased from Aldrich Chemical Company (except where noted) and were used without purification. Carrier free tritium gas was purchased from DuPont NEN Research Products. Solvents were purchased from Beckman and were HPLC grade. Radiochromatography was performed on a Bioscan 200 scanner. Radioassays were obtained on a Packard 4000 liquid scintillation counter. UV spectra were obtained on an Hitachi UV-265 spectrophotometer. NMR spectra were obtained on a Bruker 300 MHz instrument in $CDCl_3$ with selected chemical shifts (15) given in ppm relative to TMS. Mass spectra were obtained on a Finnigan-Mat 8230 spectrometer.

18-Methyl-4-estren-3,17-dione (2). Norgestrel (0.5 g, 1.6 mmol) was added to a slurry of silver carbonate (2.5 g, 9 mmol) and celite (2.5 g) in toluene (30 mL). The mixture was heated at reflux for 3 hours, cooled to room temperature and filtered. The solids were washed with toluene (3 X 15mL) and the combined organics concentrated to give a quantitative yield of (**2**) as a pale yellow solid which was used without further purification. R_f (hexane-EtOAc, 2:1) 0.23; ^{1}H NMR δ 5.85(1H, s, H_4), 0.80(3H, t, CH_3); ms 286(M^+), 258, 242, 200; HRMS (calcd. for $C_{19}H_{26}O_2$) 286.1933; found 286.1936.

18-Methyl-4-estren-17ß-ol-3-one acetate (3). To a solution of 4-estren-3,17-dione (**2**) (100 mg, 0.35 mmol) in THF (10 mL) was added 1.75 mL $LiAlH_4$/THF (1M, 1.75 mmol). The mixture was heated at reflux for 30 minutes, cooled to room temperature and the excess $LiAlH_4$ destroyed by addition of ethyl acetate (5 mL) and saturated Na_2SO_4. An additional 1 gram of solid Na_2SO_4 was added and the solids filtered and washed with THF (3 X10 mL). The combined organic phase was

concentrated and the residue redissolved in 10 mL $CHCl_3$. To this solution was added MnO_2 (1 g, 11.5 mmol) and the mixture was stirred at room temperature for 16 h. Column chromatography (a gradient of 10-20% ethyl acetate in toluene) of the crude gave 60 mg of pure 4-estren-17ß-ol-3-one (60%). R_f (toluene-EtOAc, 3:1) 0.3; ^1H NMR δ 5.83(1H, s, H_4), 3.75(1H, t, $H_{17\alpha}$), 1.02(3H, t, CH_3); ms 288(M^+), 245, 229, 110. A mixture of 4-estren-17ß-ol-3-one (250 mg, 0.86 mmol), acetic anhydride (2.2 mL, 23 mmol), triethylamine (3.2 mL, 23 mmol) and dimethylaminopyridine (ca. 5 mg) was stirred at room temperature for 16 hours. Column chromatography of the crude (hexane-EtOAc, 3:1) gave 236 mg of pure 4-estren-17ß-ol-3-one acetate (**3**) (82.5%) yield. R_f (toluene-EtOAc, 7:3) 0.6; ^1H NMR δ 5.83(1H, s, H_4), 4.65(1H, m, H_{17}), 2.04(3H, s, OAc), 0.90(3H, t, CH_3); ms 330(M^+), 288, 270, 241, 229.

18-Methyl-1,3,5(10)-estratrien-3,17ß-diol-17-acetate (4). A mixture of 4-estren-17ß-ol-3-one acetate (**3**) (580 mg, 1.76 mmol), N-bromosuccinimide (563 mg, 3.16 mmol) in carbon tetrachloride (20mL) was heated at reflux for 20 minutes. After cooling to room temperature the mixture was filtered, concentrated, dissolved in toluene (5 mL) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.1 mL, 0.6 mmol). This mixture was heated at reflux for 30 minutes. After extractive work up and chromatographic purification (silica gel, hexane-ethyl acetate 3:1), the title compound (**4**) was isolated in 39% yield (based on recovered starting material). R_f(toluene-EtOAc, 4:1) 0.6; ^1H NMR δ 7.13-7.11(1H, d, H_1), 6.62(1H, dd, H_2), 6.56(1H, s, H_4), 4.75(1H, m, H_{17}), 2.05(3H, s, OAc), 0.92(3H, t, CH_3); ms 328(M^+), 268, 239, 227, 160, 146; HRMS (calcd. for $C_{21}H_{28}O_3$) 328.2038; found 328.2041.

18-Methyl-1,3,5(10),9(11)-estratetraen-3,17ß-diol-17-acetate (5). A mixture of the 17ß-estradiol-17-acetate (**4**) (156 mg, 0.48 mmol) and N-chlorosuccinimide (95 mg, 0.71 mmol) in acetonitrile (30 mL) was heated at reflux for 30 minutes, cooled to room temperature, filtered and concentrated. The crude intermediate was dissolved in DMF (30 mL), treated with potassium carbonate (397 mg, 2.88 mmol) and heated 150°C for 90 minutes. The reaction mixture was partitioned between water-brine-ethyl acetate (1:1:1) and the aqueous layer extracted with additional ethyl acetate. The combined organic phase was washed with brine and dried (Na_2SO_4). Chromatotron purification (2mm rotor, hexane-EtOAc-Et_3N, 80:15:5) gave 50 mg (32%) of analytically pure estratetraen-3,17ß-diol-17-acetate (**5**). R_f (Hexane-EtOAc-Et_3N, 80:15:5) 0.3; ^1H NMR δ 7.47 (1H, d, H_1), 6.53(1H, dd, H_2), 6.04(1H, m, H_{11}), 4.83(1H, t, H_{17}), 2.05 (3H, s, OAc), 0.90(3H, t, CH_3); ms 326(M^+), 266, 237, 160; HPLC: Vydac 201TP54, C-18, 5µm, 4.6mm X 250 mm, 55% acetonitrile in water, 1 mL/min, 225nm.

18-Methyl-1,3,5(10),9(11)-estratetraen-3,17ß-diol-17-acetate-3-methyl ether (6). To a solution of the estratetraen-3,17-diol-17-acetate (**5**) (50 mg, 0.15 mmol) in THF (5 mL) was added sodium hydride (7.2 mg, 0.3 mmol). After stirring under N_2 for 90 minutes, methyl iodide (0.2 ml, 3.2 mmol) was added dropwise and the mixture stirred for 90 minutes. The reaction was quenched with water, dilute HCl and concentrated. The aqueous residue was made basic with sodium

bicarbonate and the product extracted into ethyl acetate. The organic phase was washed once with water, brine and dried (Na_2SO_4). Column chromatography (silica gel, hexane-ethyl acetate, 7:1) gave 33 mg (66%) of the title compound (**6**). R_f (hexane-EtOAc, 7:1) 0.5; ^1H NMR δ 7.50 (1H, d, H_1), 6.72-6.68(1H, m, H_2), 6.59(1H, d, H_4), 6.06(1H, m, H_{11}), 4.83(1H, t, H_{17}), 3.70 (3H, s, OMe), 2.05(3H, s, OAc), 0.90(3H, t, CH_3); ms 340(M^+), 280, 251, 172; HRMS (calcd. for $C_{22}H_{30}O_3$) 342.2195; found 342.2199.

18-Methyl-1,3,5(10)-estratrien-[9,11-^{3}H]-3,17ß-diol-17-acetate-3-methyl ether (7). A 10 mL septum side arm flask containing a stirring bar and 10% Pd/C (15 mg) was connected to a high vacuum line and evacuated overnight. A solution of the estratetraene-3-methyl ether (**6**) (22 mg, 0.065 mmoles) in ethyl acetate (3 mL) was injected over the catalyst. The mixture was freeze-degassed and 10 Ci (58 Ci/mmol) of tritium gas was transferred into the cold (liq. N_2) reaction vessel by means of a Toepler pump. The mixture was allowed to warm to room temperature and stir for 16 h. After the removal of the labile radioactivity, the crude reaction mixture was passed through a filter disc (Gelman, Acro LC 25 PVDF, 0.45µm with methanol (5 x 10 mL) and concentrated. The residue was further concentrated from methanol (2 x 10 mL) to ensure complete removal of any remaining labile radioactivity. Radioassay and HPLC analysis revealed a total of 2900 mCi of (**7**) at 55% radiochemical purity. Purification by HPLC (Vydac C-18) gave 1550 mCi of ca. 90% radiochemically pure estratrien-[9,11-^{3}H]-3,17ß-diol-17-acetate-3-methyl ether (**7**) which was used without further purification. R_f (hexane-EtOAc, 6:1) 0.6; HPLC: Vydac 218TP54, C-18, 10µm, 4.6 mm x 250 mm, 70% acetonitrile in water, 1 mL/min, 282 nm.

18-Methyl-1,3,5(10)-estratrien-[9,11-^{3}H]-3,17ß-diol-3-methyl ether (8). Estratrien-17-acetate-3-methyl ether (**7**) (1550 mCi, 0.0397 mmol) was dissolved in methanol (30 mL), treated with potassium carbonate (100 mg, 0.72 mmol) and heated at the reflux temperature for 5 hours. The mixture was concentrated and the crude product partitioned between ethyl acetate and water. The organic phase was washed with brine and dried (Na_2SO_4) to give 1400 mCi of pure estratrien-[9,11-^{3}H]-3,17-diol-3-methyl ether (**8**) (90%). Radio-tlc: R_f (hexane-EtOAc, 6:1) 0.15.

18-Methyl-4-estren-[9,11-^{3}H]-17ß-ol-3-one (10). Approximately 10 mL of freshly distilled liquid ammonia was distilled under N_2 into a 3 neck, 25 mL round bottom flask at -78°C. A solution of (**8**) (1400 mCi, 0.0359 mmol) in THF (5 mL) and ethanol (4 drops) was added to the ammonia at -78°C. A small (ca. 3 mm^2) piece of sodium metal (cut and washed under toluene) was added as previously described (4) resulting in a deep blue solution which cleared after 10 minutes. The reaction was quenched with methanol at -50°C, followed by slow addition of water over a period of 10 minutes. The mixture was allowed to warm to room temperature and the ammonia evaporated with a gentle stream of nitrogen. The remaining solution was concentrated, dissolved in methanol and treated with a dilute HCl . The mixture was taken to 70°C for 90 minutes, cooled to room temperature, partitioned between ethyl acetate and water, made basic with sodium bicarbonate and extracted with ethyl acetate. The combined organic phase was washed once with water, brine and

dried ($MgSO_4$). Column chromatography (silica gel, hexane-ethyl acetate, 4:1) gave 1147 mCi of ca. 95% pure 4-estren-[9,11-^{3}H]-17ß-ol-3-one (**10**) (82%). Radio-tlc: R_f (hexane-EtOAc, 2:1) 0.27.

18-Methyl-4-estren-[9,11-^{3}H]-3,17-dione (11). To 300 mCi (0.0077 mmol) (**10**) in acetone (20 mL) was added 5 µL (ca. 0.013 mmol) of freshly prepared Jones reagent (16) at 0°C. After stirring for 1 hour, the reaction was quenched by addition of water (20 mL), and partitioned between ethyl acetate and water. The organic phase was washed with sodium bicarbonate, brine and dried (Na_2SO_4) to give 300 mCi of ca. 90% pure 4-estren-[9,11-^{3}H]-3,17-dione (**11**). Radio-tlc: R_f (toluene-EtOAc, 2:1) 0.5.

Norgestrel-^{3}H (1). Pyrrolidine (50 µL, 0.6 mmol) was added to a solution of 4-estren-[9,11-^{3}H]-3,17-dione (**11**) (100 mCi, 2.56 umol) in methanol (5 mL) and heated at 85°C for 25 minutes. The reaction solvent was evaporated and the residue dissolved in anhydrous THF and concentrated. This process was repeated (2 x 10 mL) to remove any residual pyrrolidine. The remaining residue was dissolved in THF (5 mL) and treated with lithium acetylide-ethylenediamine complex (15 mg, 0.16 mmol) at room temperature. After stirring overnight (ca. 16 hours), the reaction was quenched by a solution of water (2 mL), ether (2 mL), and glacial acetic acid (1 mL). The THF and ether were evaporated under a gentle stream of nitrogen, then replaced with methanol (10 mL) and aqueous sodium acetate (2 mL, 0.5 M). The mixture was heated at reflux for 4 hours, cooled to room temperature and concentrated. The resulting aqueous phase was partitioned between ethyl acetate and 10% HCl, and the organic phase as washed once with sodium bicarbonate, brine and dried (Na_2SO_4). Chromatotron chromatography (1 mm rotor, hexane-EtOAc, 4:1) gave 34 mCi of ca. 90% pure title compound (**1-^{3}H**). Additional purification on the Chromatotron (1mm rotor, hexane-EtOAc, 6:1) afforded 26.3 mCi of 99% pure product, having a specific activity of 39 Ci/mmol as determined by UV and radioassay. Radio-tlc: R_f (hexane-EtOAc, 2:1) 0.4 ; Reverse phase C-18, R_f (acetone-water, 7:3) 0.4; HPLC: Vydac 201HS104, C-18, 5µm, 4.6mm x 250mm, 60% acetonitrile in water, 1 mL/min, 240 nm, R_t (15.7 min.), UV: λ_{max} 240nm (ethanol), ε 16,200.

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9. At this time the position where bromination occurs has not been conclusively established. The intermediate formed during bromination was never fully characterized since it slowly converts to the phenol on standing.
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11. As described in ref. 4, the Birch diene is very susceptible to reoxidation on this scale. Attempts to oxidize the alcohol (C17) of the Birch diene resulted in some rearomatization. Therefore it is important to hydrolize the diene to the enone as soon as possible.
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13. The dienamine (**12**) was not characterized on this scale, however large scale (cold) runs gave the solid dienamine which always revealed some decomposition when analysed by HPLC or tlc. Therefore the hot reaction was run until tlc analysis revealed complete consumption of starting material.
14. Radial chromatography was performed on the Chromatotron model #7924, Harrison Research, Palo Alto, California.
15. All new compounds gave satisfactory ^1H NMR, ^{13}C NMR and mass data. Only selectected ^1H NMR data is presented for the sake of clarity.
16. The Jones reagent was prepared by dissolving 267 mg (2.67 mmol) of CrO_3 in 0.23 mL H_2SO_4 and 0.7 mL water.