A Short, Stereoselective Route to 16α-(Substituted-alkyl)estradiol Derivatives

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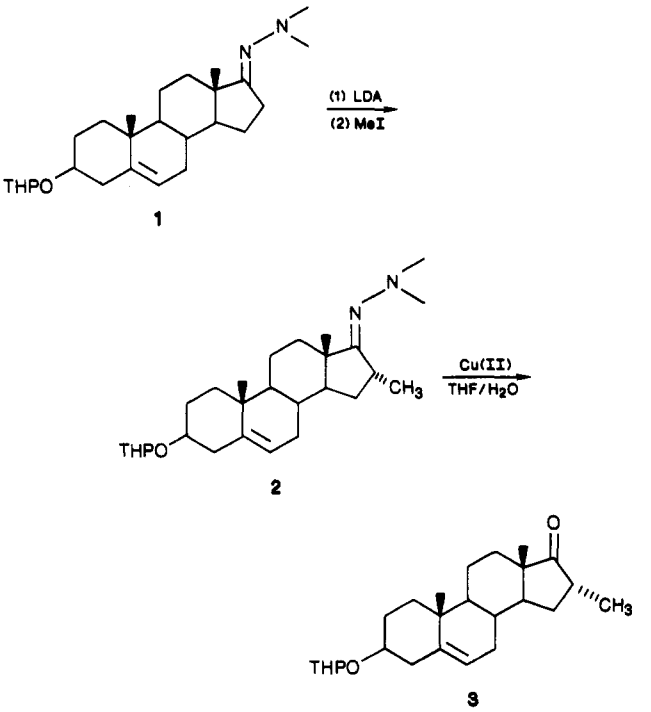
A variety of 16α-substituted 17β-estradiol derivatives can be prepared by a convenient two-step procedure: The lithium enolate of estrone 3-*O*-benzyl or 3-*O*-*tert*-butyldimethylsilyl ether undergoes clean, stereospecific alkylation with a variety of allylic, benzylic, or propargylic bromides (some bearing additional functionality) to furnish the 16α-substituted estrone ethers. Even with relatively bulky 16α-substituents, reduction of the C-17 ketone with lithium aluminum hydride proceeds with very high stereoselectivity to give the 16α-substituted 17β-estradiol 3-*O*-ethers. This sequence provides ready access to a wide variety of 16α-functionalized estradiol derivatives.

In connection with our studies on the estrogen receptor,[1a-e] we require fluorescent and photolabile probes capable of high affinity, selective binding to receptor. Since 16α-substituted estradiol (estra-1,3,5(10)-triene-3,17β-diol) derivatives are known to bind well to the estrogen receptor,[2] we decided to prepare such derivatives wherein the fluorescent or photolabile group would be attached to the steroid by a spacer chain of variable length and chemical nature.

Direct alkylation of 17-keto steroid enolates has been reported to give epimeric mixtures of monoalkylated products, in addition to bisalkylated material.[3] In 1978, Neef[4] et al. published a procedure which overcomes these problems. Using methods developed by Corey and Enders,[5a,b] these authors were able to metalate the *N*,*N*-dimethylhydrazone 1, to methylate it stereoselectively, and to convert the product to the ketone 3, without epimerization at C-16 (Scheme I).

While this route is efficient and stereoselective, for our purposes it has some undesirable characteristics: The hydrazone formation and hydrolysis steps, though efficient, might, ideally, be avoided; in addition, as we wished to introduce side chains already bearing relatively sensitive functionality, we feared that the strongly nucleophilic metalated hydrazone (or the hydrazine derivative released upon hydrolysis) might participate in unwanted side reactions. Consequently, we opted to reinvestigate the direct ketone enolate alkylation.

Scheme I



Results and Discussion

All of our enolate alkylations were performed on estrone (3-hydroxyestra-1,3,5(10)-trien-17-one) protected as a benzyl (**4a**) or *tert*-butyldimethylsilyl (**4b**) ether (see Experimental Section). Our initial attempts utilizing the lithium or sodium enolate of estrone and α-halo-ω-phthalimido or ω-cyanoalkanes gave elimination of hydrogen halide from the alkylating agent and virtually quantitative recovery of starting ketone. Alkylation of the lithium enolate with allyl bromide, on the other hand, proceeds smoothly at low temperature (≤−20 °C) and, if a deficiency of base (lithium diisopropyl amide, LDA) is employed, provides a single epimeric product, with none of the bisallylated material. Several other activated electrophiles were then examined under these conditions (Scheme II), and the results are compiled in Table I.

The yields shown in Table I were not rigorously optimized, and in many cases, using a larger excess of electrophile or simply prolonging the reaction time would probably give improved yields. Nevertheless, the reactions are generally very clean, TLC analysis indicating only starting material and desired product to be present in most cases. The isolated yields corroborate this observation. With entries e and f, however, it is necessary to use a rather large excess (at least 2 equiv) of the dibromide in order to suppress the formation of unidentified side products.[6a,b] Entries g and h were the most troublesome, giving low conversions to

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(2) (a) Heiman, D. F.; Senderoff, S. G.; Katzenellenbogen, J. A.; Neeley, R. L. *J. Med. Chem.* **1980**, *23*, 994. (b) Kiesewetter, D. O.; Katzenellenbogen, J. A.; Kilbourn, M. R.; Welch, M. J. *J. Org. Chem.* **1984**, *49*, 4900.

(3) González, F. B.; Neef, G.; Eder, U.; Wiechert, R.; Schillinger, E.; Nishino, Y. *Steroids* **1982**, *40*(2), 171.

(4) Neef, G.; Eder, U.; Wiechert, R. *J. Org. Chem.* **1978**, *43*, 4679.

(5) (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *1*, 3. (b) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, *41*, 3667.

(6) (a) We suspect that diisopropyl amine reacts with both of these dibromides, thus accounting for the large excess of electrophile required. Additional side products could arise via reaction of the desired product with diisopropyl amine or enolate. (b) The commercially available 1,4-dichloro-2-butyne did not react with the lithium enolate of **4b** at −20 °C and gave multiple products at higher temperatures.

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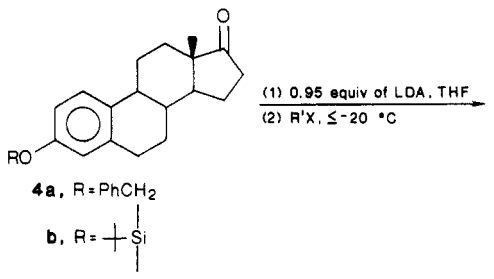
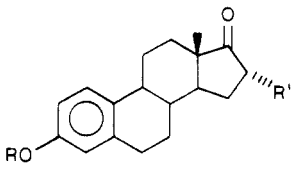
Table I. Alkylation of 4a or 4b with Various Activated Electrophiles (R'X)

entry[a]	ketone	R'X (molar equiv)	time, h	temp, °C	% yield recovered 4	% yield 5
a	**4a**	$BrCH_2CH{=}CH_2$ (1.1)	12	≤−20	29	70
b	**4a**	$BrCH_2Ph$ (1.5)	3.5	≤−20	22	75
c	**4b**	$BrCH_2C{\equiv}CSiMe_3$ (1.5)[b]	3	≤−20	26	71
d	**4b**	$BrCH_2CH{=}CHCH_2OPh$ (1.1)[c]	5	≤−20	34	60
e	**4b**	$BrCH_2CH{=}CHCH_2Br$ (3.0)	3	≤−35	12	81
f	**4b**	$BrCH_2C{\equiv}CCH_2Br$ (2.5)[d]	3	≤−35	16	66
g	**4a**	$BrCH_2CH{=}CHCN$ (1.1)[e]	0.5	−60	35	59
h	**4b**	$BrCH_2C{\equiv}CH$ (1.1)	5	≤−20	71	23

[a] Entry letter corresponds to the structure of the product ketone **5a–h** (cf. Scheme II). [b] See ref 15. [c] See ref 16. [d] See ref 17. [e] See ref 18.

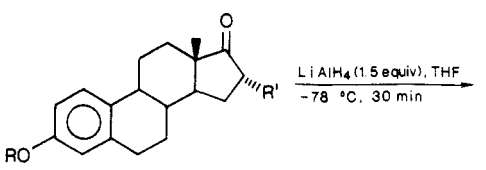
Scheme II



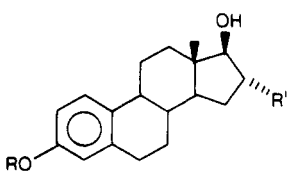


	R	R'
5a	$PhCH_2$	$CH_2CH{=}CH_2$
b	$PhCH_2$	CH_2Ph
c	*t*-Bu(Me$_2$)Si	$CH_2C{\equiv}CSiMe_3$
d	*t*-Bu(Me$_2$)Si	$CH_2CH{=}CHCH_2OPh$
e	*t*-Bu(Me$_2$)Si	$CH_2CH{=}CHCH_2Br$
f	*t*-Bu(Me$_2$)Si	$CH_2C{\equiv}CCH_2Br$
g	$PhCH_2$	$CH_2CH{=}CHCN$
h	*t*-Bu(Me$_2$)Si	$CH_2C{\equiv}CH$

Scheme III



5a–d



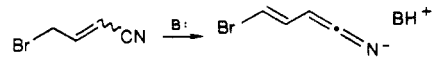
7a–d

Table II. $LiAlH_4$ Reduction of Ketones 5a–d to Alcohols 7a–d

entry[a]	R	R'	% yield of 7
a	$PhCH_2$	$CH_2CH{=}CH_2$	96
b	$PhCH_2$	CH_2Ph	98
c	*t*-Bu(Me$_2$)Si	$CH_2C{\equiv}CSiMe_3$	99
d	*t*-Bu(Me$_2$)Si	$CH_2CH{=}CHCH_2OPh$	100

[a] The entry letter corresponds to the structures of ketones **5a–d** and alcohols **7a–d** (cf. Schemes II and III).

product. This is mostly likely due to the high basicity of the enolate[7] and the relatively acidic electrophiles involved; a rapid proton transfer from electrophile to enolate ensues, quenching the reaction. The intense blue color which develops during the alkylation with γ-bromocrotononitrile (entry g), presumably arising from anion **6**, lends support to this hypothesis.[8] Lowering the reaction temperature to −100 °C does not alleviate the problem, and our best results with this electrophile are shown in Table I (entry g).



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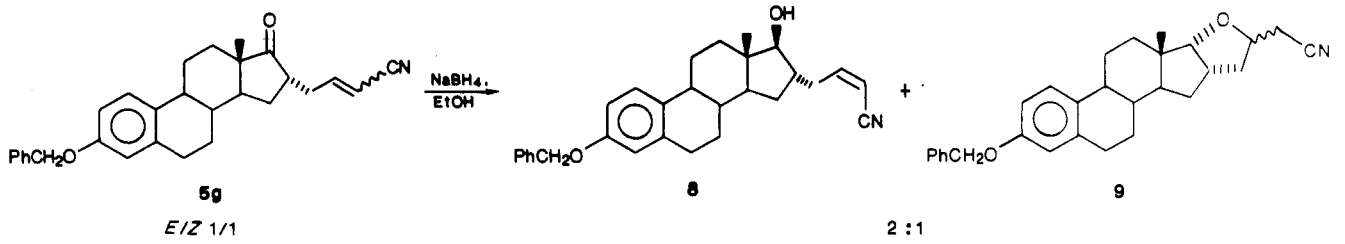
We next addressed the issue of ketone reduction. While the angular methyl group (C-18) provides excellent facial selectivity in the alkylation reaction at C-16 and in the reduction of 16-*un*substituted 17-keto steroids,[9] it is not obvious that with fairly bulky 16α-substituents, the methyl group will control the stereochemistry of reduction to a large degree. In fact, even the relatively unhindered 16α-halo-17-keto steroids[2,10] give substantial amounts of 17α-alcohol upon reduction with $LiAlH_4$ or $NaBH_4$, suggesting that reduction of ketones **5** would produce epimeric mixtures. However, reducing ketones **5a–d** with 1.5 equiv of $LiAlH_4$ in THF at −78 °C (Scheme III) gives highly satisfactory results (Table II). The yields reported are of crude products which were determined by ^1H NMR analysis to be single isomers, with the stereochemistry shown in Scheme III.[11] We believe that the poorer selectivity obtained with the 16α-halo 17-ketone reductions is a consequence of electronic repulsion between the electronegative halides and the aluminate (boronate) anion.

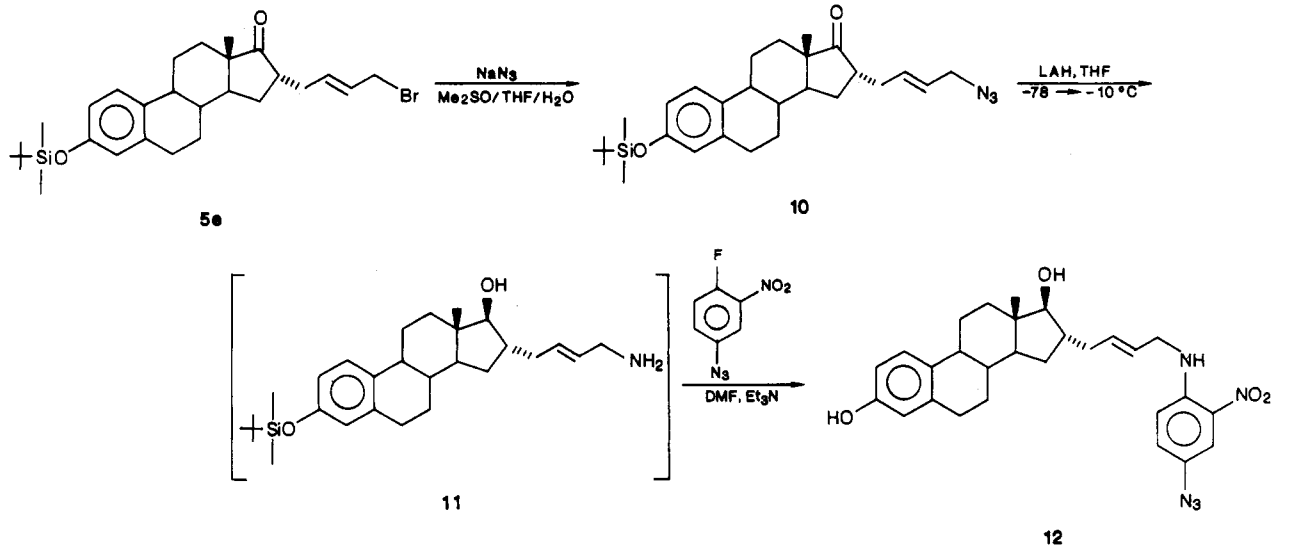
In contrast to our $LiAlH_4$ reductions, reduction of the more sensitive substrate, ketone **5g**, with the milder reductant $NaBH_4$ (Scheme IV), affords a substantial amount of the 17α-alcohol, which subsequently suffers a Michael addition to the unsaturated nitrile, giving the tetrahydrofuran **9**.[12] Interestingly, but at this point, inexplicably, the 17β-alcohol was isolated as a single olefin isomer

(7) Zook, H. D.; Kelly, W. L.; Posey, I. Y. *J. Org. Chem.* **1968**, *33*, 3477.
(8) Presumably, during the alkylation with propargyl bromide, the corresponding acetylide anion is formed.
(9) Wheeler, D. M. S.; Wheeler, M. M. In *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J. A., Eds.; Van Nostrand Reinhold: New York, 1972; Vol. 1, p 61.
(10) See, for example: (a) Mueller, G. P.; Johns, W. F. *J. Org. Chem.* **1961**, *26*, 2403. (b) Fajkos, J. *J. Chem. Soc.* **1959**, 3966.
(11) The ^1H NMR spectra of 16-substituted 17-hydroxy steroids have been extensively investigated. See, for example: (a) Schönecker, V. B.; Tresselt, D.; Ponsold, K. *Tetrahedron* **1975**, *31*, 2845. (b) Goto, G.; Yoshioka, K.; Hiraga, K.; Miki, T. *Chem. Pharm. Bull.* **1977**, *25*, 1295. In general, for 16α-alkyl 17β-alcohols, the 17α-proton appears as a doublet (J = 6–8 Hz) at ca. 3.2 ppm. All of our reduction products exhibit similar signals, and since the other three possible isomers give quite different characteristics, the assignments are considered unambiguous. Also, the products were pure within ^1H NMR detection limits (i.e. a single doublet at ~3.3 ppm, and a single C18 singlet).
(12) Goto et al (see ref 11b above) report that reduction of a 16α-ethyl-17-keto steroid with $NaBH_4$ in methanol gives the 17β-alcohol in 98% yield.

Scheme IV



Scheme V



(*Z*), though a ca. 1:1 mixture of geometric isomers was present initially. Apparently, the *E* isomer more effectively shields the α-face of the molecule and is consumed in the Michael reaction.

The excellent stereoselectivity of both the alkylation and the $LiAlH_4$ reduction reactions allows for the rapid and efficient synthesis of the desired fluorescent and photolabile probes. This is exemplified in the synthesis of the potential photoaffinity label for the estrogen receptor, compound **12** (Scheme V). Treatment of the bromo ketone **5e** with excess sodium azide in $Me_2SO/THF/H_2O$, affords the azido ketone **10** in quantitative yield, without epimerization at C-16. Lithium aluminum hydride reduction of the ketone proceeds as described earlier, but warming to −10 °C is required to reduce the azide. The amino alcohol **11** so obtained is treated directly with 4-fluoro-3-nitrophenyl azide[13] in DMF/Et_3N. Arylation of the amine is accompanied by cleavage of the silyl ether by the displaced fluoride ion, providing the target molecule **12** (82% from **10**), plus a small amount (15% from **10**) of the corresponding silyl ether.

In summary, we have developed a short, efficient, stereoselective synthesis of 16α-substituted estradiol derivatives which possesses substantial advantages over previously described methods. In addition, the availability of compounds such as **5e** and **5f** by this method, provides ready access to a wide variety of biologically interesting analogues. Our biochemical studies in this area will be reported elsewhere.

Experimental Section

General. Solvents and reagents were purchased from the following commercial sources: Aldrich, Alfa, Baker, Burdick and Jackson, Eastman Kodak, Fisher, Mallinckrodt, and Sigma. They were used as received or purified as follows: tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Diisopropyl amine, allyl bromide, and propargyl bromide were distilled for calcium hydride. Butyllithium solutions were periodically titrated[14] to determine concentrations. The following compounds were prepared by the literature procedures or modifications thereof: 4-fluoro-3-nitrophenyl azide,[13] 1-bromo-3-(trimethylsilyl)-2-propyne,[15] 4-bromo-1-phenoxy-2-butene,[16] 1,4-dibromo-2-butyne,[17] 4-bromo-2-butenenitrile (*E*/*Z* ≃ 1:1),[18] and 3-(benzyloxy)estra-1,3,5(10)-trien-17-one.[19] The compounds exhibited physical and spectral data consistent with those reported.

Analytical thin-layer chromatography (TLC) was performed with 0.25-mm silica gel coated plastic sheets with F-254 indicator (Merck). Visualization was accomplished by UV light, iodine vapor, or ceric sulfate. Preparative-layer chromatography was performed on 20 × 20 cm glass plates coated with Merck Silica Gel 60 PF-254 to a thickness of 2.5 mm. Flash chromatography[20] was performed with Woelm silica gel (32–64 μm).

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All IR spectra were recorded on a Perkin-Elmer Model 1320 spectrophotometer. All ^1H NMR spectra were obtained on a Varian XL-200 spectrometer. The resonances are reported relative to tetramethylsilane or $CHCl_3$ (7.26 ppm, for silylated compounds). Low-resolution electron impact mass spectra were obtained on a Finnigan MAT-CH-5 spectrometer. High-resolution electron impact spectra (HR-EIMS) were performed on a Finnigan MAT 731 instrument. Fast

(13) Fleet, G. W. J.; Porter, R. R.; Knowles, J. R. *Nature (London)* **1969**, *224*, 511.

(14) Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

(15) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267.

(16) Lüttringhaus, A.; Sääf, G.; Hauschild, K. *Chem. Ber.* **1938**, *71B* 1673.

(17) Johnson, A. W. *J. Chem. Soc.* **1946**, 1009.

(18) Couvreur, P.; Bruylants, A. *Bull. Chim. Soc. Belg.* **1952**, *61*, 253.

(19) Schulster, D.; Whitehead, J. K.; Kellie, A. E. *Biochem. J.* **1964**, *93*, 512.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

atom bombardment (FAB) mass spectra were obtained on a V. G. Instruments ZAB HF mass spectrometer. Elemental analyses were performed by the Microanalytical Services Laboratory of the University of Illinois School of Chemical Sciences.

Caution! All allylic, propargylic, and benzylic bromides mentioned herein are lachrymators and/or severe irritants and should be used with due care.

3-[(*tert*-Butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17-one (4b). Estrone[21] (1.350 g, 5.00 mmol) and imidazole (374 mg, 5.50 mmol) were dissolved in 10 mL of *N,N*-dimethylformamide (DMF) in a stoppered flask. *tert*-Butyldimethylsilyl chloride (829 mg, 5.50 mmol) was added, and the solution was stirred at room temperature. After 2 h, a 20-mL portion of ethyl acetate was added to dissolve the thick white precipitate which had formed. The reaction mixture was stirred for an additional 4 h, then poured into water, and extracted several times with ethyl acetate/dichloromethane. The organic phase was washed with water and brine and dried (Na_2SO_4). After filtration and solvent removal, the residue was crystallized from methanol/dichloromethane (two crops) to furnish white needles (1.669 g, 87.0%). Recrystallization from ethanol gave an analytical sample: mp 170–172 °C; IR (film) 1740 cm^{-1} (no OH band); ^1H NMR ($CDCl_3$) δ 0.19 (s, 6 H, $SiCH_3$), 0.91 (s, 3 H, C18-*H*), 0.98 (s, 9H, $C(CH_3)_3$), 1.20–2.91 (m, 15 H, B, C, and D ring *H*), 6.55–6.67 (m, 2 H, C2, C4-*H*), 7.11 (d, 1 H, J = 8 Hz, C1-H); MS (70 eV), m/z (relative intensity) 384 (M^+, 30), 327 (100), 163 (15). Anal. Calcd for $C_{24}H_{36}O_2Si$: C, 75.00; H, 9.38. Found: C, 74.84; H, 9.55.

Alkylation of Ketone Enolates. A representative procedure is given here for the preparation of **16α-allyl-3-(benzyloxy)estra-1,3,5(10)-trien-17-one (5a).** Dry THF (9 mL) and diisopropyl amine (0.18 mL, 1.30 mmol) were combined in a dry, three-necked flask under nitrogen. The solution was cooled to 0 °C, and *n*-butyllithium (0.72 mL of a 1.55 M hexane solution, 1.12 mmol) was added dropwise. After the solution was stirred for 0.5 h at 0 °C, ketone **4a**[19] (424 mg, 1.18 mmol) was added in one portion, and stirring was continued at 0 °C for 1 h. The solution was cooled to −45 °C (CCl_4/*i*-PrOH, CO_2), and allyl bromide (157 mg, 1.30 mmol, in 1 mL of THF) was added dropwise. The reaction mixture was stirred at or below −20 °C for 12 h, then poured into water, and extracted with several portions of ethyl acetate. The organic phase was washed with brine and dried (Na_2SO_4). After filtration and solvent removal, the residue was chromatographed (8:1 hexane/ethyl acetate) to give the starting ketone (122 mg, 28.8%) and the title compound (330 mg, 70.0%) as a white solid: mp 95–99 °C; IR (film) 1740, 1010, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 3 H, CH_3), 1.25–2.94 (m, 16 H, B, C, and D ring *H*, $CH_2CH{=}CH_2$), 5.02 (s, 2 H, OCH_2Ph), 5.09 (m, 2 H, $CH{=}CH_2$), 5.78 (m, 1 H, $CH{=}CH_2$), 6.73 (d, 1 H, J = 2.5 Hz, C4-*H*), 6.78 (dd, 1 H, J = 8.5, 2.5 Hz, C2-*H*), 7.19 (d, 1 H, J = 8.5 Hz, C1-*H*), 7.25–7.61 (m, 5 H, Ar *H*); MS (70 eV), m/z (relative intensity) 400 (M^+, 11), 121 (3), 91 (100). Anal. Calcd for $C_{28}H_{32}O_2$ (HR-EIMS): 400.2402. Found: 400.2393.

All of the following alkylated products were prepared by the general procedure described above. The particular reaction conditions and product yields for each case are listed in Table I.

16α-Benzyl-3-(benzyloxy)estra-1,3,5(10)-trien-17-one (5b): IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 3 H, CH_3), 1.15–2.42 (m, 11 H, B, C, and D ring *H*), 2.56 (dd, 1 H, J = 14, 10 Hz, $CHCH_2Ph$), 2.82 (m, 3 H, C6-*H*, C16β-*H*), 3.13 (dd, 1 H, J = 14, 4 Hz, $CHCH_2Ph$), 5.01 (s, 2 H, OCH_2Ph), 6.70 (d, 1 H, J = 3 Hz, C4-*H*), 6.77 (dd, 1 H, J = 9, 3 Hz, C2-*H*), 7.10–7.48 (m, 11 H, C1-*H*, Ar *H*); MS (70 eV), m/z (relative intensity) 450 (M^+, 11), 135 (3), 91 (100). Anal. Calcd for $C_{32}H_{34}O_2$ (HR-EIMS): 450.2559. Found: 450.2553.

16α-[3-(Trimethylsilyl)-2-propynyl]-3-[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17-one (5c): mp 69–72 °C; IR (film) 2180, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 9 H, $Si(CH_3)_3$), 0.20 (s, 6 H, $Si(CH_3)_2$), 0.97 (s, 3 H, C18-*H*), 0.98 (s, 9 H, $C(CH_3)_3$), 1.21–2.92 (m, 16 H, B, C, and D ring *H*), 6.55–6.67 (m, 2 H, C2, C4-*H*), 7.13 (d, 1 H, J = 9 Hz, C1-*H*); MS (70 eV), m/z (relative intensity) 494 (M^+, 100), 479 (5), 437 (90), 323 (12), 231 (10), 229 (12), 211 (30), 205 (12), 163 (14), 147 (14). Anal. Calcd for $C_{30}H_{46}O_2Si_2$ (HR-EIMS): 494.3036. Found: 494.3031.

16α-(4-Phenoxy-2-butenyl)-3-[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17-one (5d): IR (film) 1740, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (s, 6 H, $SiCH_3$), 0.95 (s, 3 H, C18-*H*), 0.98 (s, 9 H, $C(CH_3)_3$), 1.25–2.90 (m, 16 H, B, C, and D ring *H*, $CH_2CH{=}CH$), 4.50 (d, 2 H, J = 4 Hz, CH_2OPh), 5.79 (m, 2 H, $CH{=}CH$), 6.56–6.67 (m, 2 H, C2, C4-*H*), 6.87–6.99 (m, 3 H, Ar *H*), 7.12 (d, 1 H, J = 9 Hz, C1-*H*), 7.23–7.34 (m, 2 H, Ar *H*); MS (10 eV), m/z (relative intensity) 530 (M^+, 20), 437 (100), 419 (5), 409 (7), 384 (14), 367 (6), 327 (34), 273 (9), 271 (6), 247 (5). Anal. Calcd for $C_{34}H_{46}O_3Si$ (HR-EIMS): 530.3216. Found: 530.3204.

16α-(4-Bromo-2-butenyl)-3-[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17-one (5e): mp 72–75 °C; IR (film) 1740, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (s, 6 H, $SiCH_3$), 0.96 (s, 3 H, C18-*H*), 0.98 (s, 9 H, $C(CH_3)_3$), 1.13–2.98 (m, 16 H, B, C, and D ring *H*, $CH_2CH{=}CH$), 3.95 (m, 2 H, CH_2Br), 5.75 (m, 2 H, $CH{=}CH$), 6.55–6.68 (m, 2 H, C2, C4-*H*), 7.11 (d, 1 H, J = 8.5 Hz, C1-*H*); MS (10 eV), m/z (relative intensity) 518 (M^+, 34), 516 (M^+, 35), 503 (2), 501 (3), 461 (14), 459 (15), 437 (100), 425 (24), 381 (18), 351 (19), 327 (16), 295 (13), 271 (16), 269 (11), 191 (6), 151 (20), 109 (9), 107 (11). Anal. Calcd for $C_{28}H_{41}BrO_2Si$ (HR-EIMS): 516.2059. Found: 516.2045.

16α-(4-Bromo-2-butynyl)-3-[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17-one (5f): IR (film) 2240, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (s, 6 H, $SiCH_3$), 0.97 (s, 3 H, C18-*H*), 0.99 (s, 9 H, $C(CH_3)_3$), 1.20–2.93 (m, 16 H, B, C, and D ring *H*, $CH_2C{\equiv}C$), 3.89 (t, 2 H, J = 2 Hz, CH_2Br), 6.57–6.68 (m, 2 H, C2, C4-*H*), 7.12 (d, 1 H, J = 8 Hz, C1-*H*); MS (10 eV), m/z (relative intensity) 516 (M^+, 99), 514 (M^+, 100), 459 (17), 457 (13), 436 (7), 435 (4), 389 (19), 387 (17), 384 (12), 379 (7), 327 (14), 297 (7), 295 (14), 293 (6), 271 (5), 269 (5), 149 (18), 109 (10), 107 (11). Anal. Calcd for $C_{28}H_{39}BrO_2Si$ (HR-EIMS): 514.1903. Found: 514.1900.

16α-(3-Cyano-2-propenyl)-3-(benzyloxy)estra-1,3,5(10)-trien-17-one (5g): IR (film) 2230, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.966 (*Z*), 0.969 (*E*) (s, 3 H, CH_3), 1.25–2.95 (m, 16 H, B, C, and D ring *H*, $CH_2CH{=}CH$), 5.033 (*Z*), 5.036 (*E*) (s, 2 H, OCH_2Ph), 5.417 (*Z*) (d, 1 H, J = 11 Hz, $CHCN$), 5.397 (*E*) (d, 1 H, J = 16 Hz, $CHCN$), 6.47–6.61 (*Z*) (m, 1 H, $CH{=}CHCN$), 6.69–6.83 (*Z*) (m, 2 H, C2, C4-*H*), 6.62–6.84 (*E*) (m, 3 H, $CH{=}CHCN$, C2, C4-*H*), 7.19 (d, 1 H, J = 8.5 Hz, C1-*H*), 7.25–7.48 (m, 5 H, Ar *H*); (70 eV), m/z (relative intensity) 425 (M^+, 10), 91 (100). Anal. Calcd for $C_{29}H_{31}NO_2$ (HR-EIMS): 425.2355. Found: 425.2363.

16α-(2-Propynyl)-3-[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17-one (5h): IR (film) 3300, 2120, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (s, 6 H, $SiCH_3$), 0.98 (s, 12 H, C18-*H*, $C(CH_3)_3$), 1.20–2.92 (m, 17 H, B, C, and D ring *H*, $CH_2C{\equiv}CH$), 6.56–6.67 (m, 2 H, C2, C4-*H*), 7.12 (d, 1 H, J = 9 Hz, C1-*H*); MS (10 eV), m/z (relative intensity) 422 (M^+, 81), 365 (100). Anal. Calcd for $C_{27}H_{38}O_2Si$ (HR-EIMS): 422.2641. Found: 422.2641.

Ketone Reduction. A representative example is given here for the preparation of **16α-allyl-3-(benzyloxy)estra-1,3,5(10)-trien-17β-ol (7a).** Ketone **5a** (151 mg, 0.38 mmol) was dissolved in 5 mL of dry THF in a flask with a nitrogen inlet. The solution was cooled to −78 °C and treated with solid $LiAlH_4$ (22 mg, 0.57 mmol). The mixture was stirred vigorously at −78 °C for 0.5 h and then cautiously quenched with water. When hydrogen evolution had subsided, the mixture was poured into water and extracted several times with dichloromethane. The organic phase was washed with brine and dried (Na_2SO_4). After filtration, the organic phase was concentrated and percolated through silica gel (eluting with CH_2Cl_2), affording a white solid, mp 83–85 °C, after solvent removal: IR (film) 3300, 1030, 910 cm^{-1} (no carbonyl band); ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H, CH_3), 1.02–2.45 (m, 15 H, B, C, and D ring *H*, $CH_2CH{=}CH_2$, O*H*), 2.82 (m, 2 H, C6-*H*), 3.31 (d, 1 H, J = 7.7 Hz, C17α-*H*), 5.01 (s, 2 H, CH_2Ph), 5.03–5.19 (m, 2 H, $CH{=}CH_2$), 5.87 (ddt, 1 H, J = 15, 10, 7 Hz, $CH{=}CH_2$), 6.71 (d, 1 H, J = 2.5 Hz, C4-*H*), 6.78 (dd, 1 H, J = 8.5, 2.5 Hz, C2-*H*), 7.19 (d, 1 H, J = 8.5 Hz, C1-*H*), 7.27–7.58 (m, 5 H, Ar *H*); MS (70 eV), m/z (relative intensity) 402 (M^+, 18), 167 (3), 149 (15), 117 (5), 97 (5), 91 (100). Anal. Calcd for $C_{28}H_{34}O_2$ (HR-EIMS): 402.2559. Found: 402.2551.

Ketones 5b–d were reduced according to the general procedure described above (see Table II for yields).

16α-Benzyl-3-(benzyloxy)estra-1,3,5(10)-trien-17β-ol (7b): mp 121.5–123.5 °C; IR (film) 3580, 3440 cm^{-1} (no carbonyl band); ^1H NMR ($CDCl_3$) δ 0.82 (s, 3 H, CH_3), 1.10–2.97 (m, 17 H, B, C,

(21) Estrone was a generous gift from Dr. John Baran of Searle Laboratories.

and D ring *H*, $CHCH_2Ph$, O*H*), 3.44 (d, 1 H, J = 7.6 Hz, C17α-*H*), 5.04 (s, 2 H, OCH_2Ph), 6.72 (d, 1 H, J = 2.5 Hz, C4-*H*), 6.79 (dd, 1 H, J = 8, 2.5 Hz, C2-*H*), 7.10–7.48 (m, 11 H, C1-*H*, Ar *H*); MS (70 eV), m/z (relative intensity) 452 (M^+, 22), 91 (100). Anal. Calcd for $C_{32}H_{36}O_2$: C, 84.96; H, 7.96. Found: C, 84.67; H, 7.97.

16α-[3-(Trimethylsilyl)-2-propynyl]-3-[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17β-ol (7c): mp 125–132 °C; IR (film) 3340, 2170 cm^{-1} (no carbonyl band); ^1H NMR ($CDCl_3$) δ 0.16 (s, 9 H, $Si(CH_3)_3$), 0.19 (s, 6 H, $Si(CH_3)_2$), 0.84 (s, 3 H, C18-*H*), 0.98 (s, 9 H, $C(CH_3)_3$), 1.23–2.90 (m, 17 H, B, C, and D ring *H*, $CH_2C{\equiv}C$, O*H*), 3.53 (d, 1 H, J = 7.3 Hz, C17α-*H*), 6.54–6.68 (m, 2 H, C2, C4-*H*), 7.13 (d, 1 H, J = 8 Hz, C1-*H*); MS (70 eV), m/z (relative intensity) 496 (M^+, 63), 481 (3), 439 (98), 273 (5), 271 (5), 231 (17), 229 (10), 217 (10), 215 (10), 205 (14), 191 (11), 163 (22), 147 (11). Anal. Calcd for $C_{30}H_{48}O_2Si_2$ (HR-EIMS): 496.3139. Found: 496.3138.

16α-(4-Phenoxy-2-butenyl)-3-[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17β-ol (7d): IR (film) 3400, 960 cm^{-1} (no carbonyl band); ^1H NMR ($CDCl_3$) δ 0.20 (s, 6 H, $SiCH_3$), 0.82 (s, 3 H, C18-*H*), 0.99 (s, 9 H, $C(CH_3)_3$), 1.15–2.49 (m, 15 H, B, C, and D ring *H*, $CH_2CH{=}CH$, O*H*), 2.80 (m, 2 H, C6-*H*), 3.32 (d, 1 H, J = 7.6 Hz, C17α-*H*), 4.51 (d, 2 H, J = 5 Hz, CH_2OPh), 5.70–6.02 (m, 2 H, $CH{=}CH$), 6.57 (d, 1 H, J = 2.5 Hz, C4-*H*), 6.62 (dd, 1 H, J = 8, 2.5 Hz, C2-*H*), 6.90–7.43 (m, 6 H, Cl-*H*, Ar *H*); MS (10 eV), m/z (relative intensity) 532 (M^+, 52), 517 (1), 475 (3), 438 (100), 386 (16), 381 (59), 357 (9), 329 (23), 327 (8), 273 (8), 271 (3), 233 (7). Anal. Calcd for $C_{34}H_{48}O_3Si$ (HR-EIMS): 532.3373. Found: 532.3370.

16α-(3-Cyano-2-propenyl)-3-(benzyloxy)estra-1,3,5(10)-trien-17β-ol (8). Ketone **5g** (224 mg, 0.53 mmol) was dissolved in 30 mL of ethanol in a flask with a nitrogen inlet and cooled to 0 °C. Solid $NaBH_4$ (80 mg, 2.11 mmol) was added and the mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h. The reaction mixture was poured into brine and extracted several times with ethyl acetate. The organic phase was dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (2:1 hexane/ethyl acetate) of the residue afforded two major products. The more polar title compound (**8**), an oil (104 mg, 46.2%), gave the following spectral data: IR (film) 3480, 2230 cm^{-1} (no carbonyl band); ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H, CH_3), 1.04–3.00 (m, 17 H, B, C, and D ring *H*, $CH_2CH{=}CH$, O*H*), 3.34 (d, 1 H, J = 7.6 Hz, C17α-*H*), 5.02 (s, 2 H, OCH_2Ph), 5.36 (d, 1 H, J = 11 Hz, $CH{=}CHCN$), 6.58 (dt, 1 H, J = 11, 7.5 Hz, $CH{=}CHCN$), 6.68–6.85 (m, 2 H, C2, C4-*H*), 7.19 (d, 1 H, J = 9 Hz, C1-*H*), 7.27–7.59 (m, 5 H, Ar *H*); MS (70 eV), m/z (relative intensity) 427 (M^+, 6), 91 (100). Anal. Calcd for $C_{29}H_{33}NO_2$ (HR-EIMS): 427.2511. Found: 427.2505.

The other major product (50 mg, 22.2%), a white solid, mp 145–150 °C, is tentatively assigned structure **9** on the basis of the following ^1H NMR and mass spectral data: ^1H NMR ($CDCl_3$) δ 0.84 (s, 3 H, CH_3), 1.10–2.91 (m, 15 H, B, C, D, and E ring *H*), 2.67 (d, 2 H, J = 5 Hz, CH_2CN), 4.05 (d, 1 H, J = 10 Hz, C17β-*H*), 4.19 (quintet, 1 H, J = 5 Hz, $CHCH_2CN$), 5.03 (s, 2 H, OCH_2Ph), 6.65–6.82 (m, 2 H, C2, C4-*H*), 7.19 (d, 1 H, J = 8.5 Hz, C1-*H*), 7.27–7.54 (m, 5 H, Ar *H*); MS (70 eV), m/z (relative intensity) 427 (M^+, 14), 91 (100).

16α-(4-Azido-2-butenyl)-3-[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17-one (10). Bromo ketone **5e** (76 mg, 0.15 mmol) was combined with NaN_3 (94 mg, 1.45 mmol), dimethyl sulfoxide (Me_2SO, 10 mL), THF (4 mL), and water (2 mL) in a stoppered flask. The homogeneous mixture was stirred at room temperature for 20 h, then poured into 10 volumes of water, and extracted several times with dichloromethane. The organic phase was washed with water and brine and dried (Na_2SO_4). After filtration and concentration of the product solution, the residue was filtered through silica gel (eluting with CH_2Cl_2) to provide 70 mg (99.5%) of a pale yellow oil, which solidified on standing: mp 76–80 °C; IR (film) 2100, 1740, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.18 (s, 6 H, $SiCH_3$), 0.96 (s, 3 H, C18-*H*), 0.98 (s, 9 H, $C(CH_3)_3$), 1.20–2.91 (m, 16 H, B, C, and D ring *H*, $CH_2CH{=}CH$), 3.74 (m, 2 H, CH_2N_3), 5.49–5.85 (m, 2 H, $CH{=}CH$), 6.56–6.67 (m, 2 H, C2, C4-*H*), 7.11 (d, 1 H, J = 8.5 Hz, C1-*H*); MS (10 eV), m/z (relative intensity) 479 (M^+, 69), 464 (4), 451 (54), 436 (13), 433 (12), 422 (23), 394 (52), 382 (24), 376 (26), 351 (9), 340 (18), 327 (23), 325 (19), 312 (36), 274 (22), 272 (17), 271 (16), 258 (26), 232 (20), 217 (16), 151 (18), 107 (17), 95 (100). Anal. Calcd for $C_{28}H_{41}N_3O_2Si$ (HR-EIMS): 479.2968. Found: 479.2963.

16α-[4-((4-Azido-2-nitrophenyl)amino)-2-butenyl]-3-hydroxyestra-1,3,5(10)-trien-17β-ol (12). Azido ketone **10** (183 mg, 0.38 mmol) was treated with $LiAlH_4$ (44 mg, 1.15 mmol) in 10 mL of THF according to the general procedure described above for compound **7a**. After being stirred for 0.5 h at −78 °C, the reaction mixture was warmed to −10 °C, stirred for an additional 3 h, and quenched with water. The mixture was then poured into brine and extracted with several portions of dichloromethane. The organic phase was dried (Na_2SO_4), filtered, and concentrated. There remained a pale yellow oil (182 mg). A portion of this crude material (36 mg) was dissolved in 5 mL of DMF and 0.05 mL of triethylamine in a flask with a nitrogen inlet. Solid 4-fluoro-3-nitrophenyl azide[13] (17 mg) was added in one portion, and the resulting red solution was stirred at room temperature for 3.5 h. The reaction mixture was then poured into water and extracted several times with dichloromethane. The organic phase was washed with water and brine, and dried (Na_2SO_4). The product solution was filtered and concentrated, and the residue was subjected to preparative-layer chromatography (1:1 hexane/acetone). The title compound (**12**) (31 mg, 81.6% from azido ketone **10**) was obtained as an orange solid, mp 141–145 °C. In addition, 7 mg (15.0% from azido ketone **10**) of the corresponding silylated material was isolated. Only data for the former compound is presented here: IR (film) 3390, 2130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (s, 3 H, CH_3), 1.08–2.52 (m, 15 H, B, C, and D ring *H*, $CH_2CH{=}CH$, O*H*), 2.75 (m, 2 H, C6-*H*), 3.27 (d, 1 H, J = 7.6 Hz, C17α-*H*), 4.07 (m, 2 H, CH_2N), 5.55–5.94 (m, 2 H, $CH{=}CH$), 6.52 (d, 1 H, J = 2.5 Hz, C4-*H*), 6.59 (dd, 1 H, J = 8, 2.5 Hz, C2-*H*), 7.08 (d, 1 H, J = 8 Hz, C1-*H*), 7.13 (d, 1 H, J = 9 Hz, Ar *H* ortho to NH), 7.27 (dd, 1 H, J = 9, 3 Hz, Ar *H* ortho to azide), 7.78 (d, 1 H, J = 3 Hz, Ar *H* ortho to nitro), 7.91 (br s, 1 H, O*H*), 8.22 (m, 1 H, N*H*); MS (FAB), 504 (M + H)$^+$. Anal. Calcd for $C_{28}H_{33}N_5O_4{}^+H$ (HR-FABMS): 504.2611. Found: 504.2593.

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