



## A NOVEL, STEREOCONTROLLED APPROACH TO RING B ALKYLATED ESTRATETRAENES

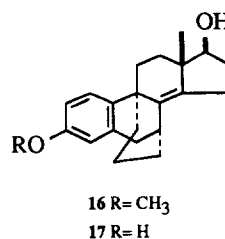
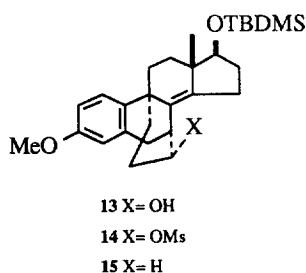
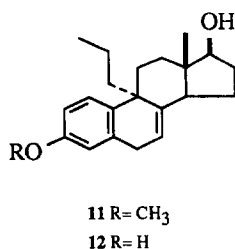
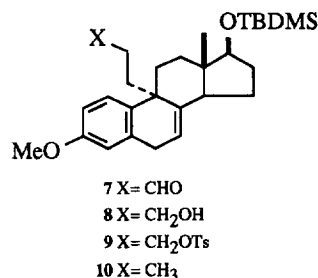
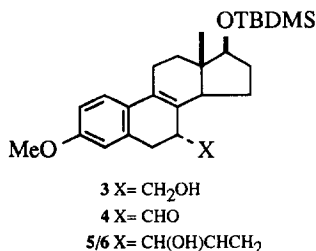
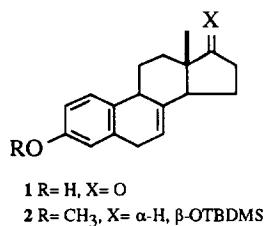
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**Summary.** A four-step reaction protocol, culminating in an oxy-Cope rearrangement, has been developed to transform **2** into **7**. 9 $\alpha$ -Alkylated derivatives of equilin, e.g., **12**, as well as C(7)-C(9) propano-bridged 19-norsteroids, like **17**, demonstrate synthetic potential for **7** in estrogen receptor ligand synthesis.

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Soon after their discovery some sixty years ago, equine estrogens have found widespread use in hormone replacement therapy.<sup>2</sup> Their impact on synthetic steroid chemistry, however, has been modest although the structurally unique equilin skeleton (**1**) is nicely set up for intriguing backbone modifications of potential pharmacological interest. Based on our earlier observation<sup>3</sup> that **2** readily enters into ene-type  $\alpha$ -hydroxy-alkylation at C(7), we have devised a novel approach to C(9)  $\alpha$ -alkylated equilin derivatives<sup>4</sup> and certain C(7)-C(9) propano-bridged 19-norsteroids. Both stratagems have now been exploited in estrogen receptor ligand syntheses, two representative examples of which are outlined below.

Attachment of a functionalized three-carbon chain to C(9) was envisioned to occur indirectly by way of an anion-accelerated [3,3]-sigmatropic reorganization<sup>5</sup> involving an appropriate C(7)  $\alpha$ -substituted intermediate. While the most straightforward access, ene reaction between **2** and acrolein, was prohibitively ineffective in our hands, a three-step alternative afforded ample quantities of the substrate(s) required for oxy-Cope rearrangement. Thus, oxidation of the known equilol-paraformaldehyde adduct **3**<sup>3</sup> (DMSO, Py-SO<sub>3</sub>, (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N, 22 °C; 77%), **3**→**4**, followed by vinylmagnesium bromide addition (THF, CH<sub>2</sub>CHMgBr, -78 °C; 66% combined yield), gave a separable mixture (silica gel; *t*-butyl methyl ether/hexane, 1:4; acetone/hexane, 1:9) of diastereoisomeric allylic alcohols **5** and **6**.



Both compounds furnished the same rearranged key intermediate **7** upon exposure to potassium hydride/18-crown-6 in tetrahydrofuran at 0 °C for two hours. Best results materialized (83% yield) when the reaction was quenched inversely into vigorously stirred ice/water via cannula. Otherwise, rearrangement efficacy was severely eroded as a consequence of aldehyde enolate/aldehyde selfcondensation.

Having established a reliable access to **7**, we next focused on estrogen receptor ligands derived thereof. In a first series of experiments, formation of a 9 $\alpha$ -propyl analogue was addressed. The desired side-chain oxidation state was adjusted by formyl group reduction (CH<sub>3</sub>OH, NaBH<sub>4</sub>, 0 °C; 93%), **7**→**8**, tosylation (CHCl<sub>3</sub>, pyridine, *p*-TsCl, 0 °C, 24 h; 84%), **8**→**9**, and tosylate displacement (THF, LiB(C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>H, 22 °C, 1 h; 88%), **9**→**10**. Removal of the *t*-butyldimethylsilyl protecting group (THF, HCl, H<sub>2</sub>O, 22 °C, 16 h; 91%) and cleavage of the phenolic methyl ether (toluene, DIBAH, reflux, 2 h; 95%) completed the synthesis of **12**. Further investigations into the synthetic potential of **7** revealed an attractive option to bridge positions C(7) and C(9) by a three-carbon unit.<sup>6</sup> Treatment of **7** with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane (22 °C, 1 h) triggered off a remarkably facile, stereocontrolled intramolecular ene-type reaction. The pentacyclic steroid **13** was obtained in 84% yield. Attempts to rid the bridge of the sterically hindered secondary hydroxyl group via mesylation (CHCl<sub>3</sub>, pyridine, CH<sub>3</sub>SO<sub>2</sub>Cl, 22 °C, 48 h), **13**→**14**, and substitution/reduction (diglyme, H<sub>2</sub>O, NaI, Zn, 100 °C, 2 h),<sup>7</sup> **14**→**15**, had to cope with an elimination by-product in an additional hydrogenation step (C<sub>2</sub>H<sub>5</sub>OH, CH<sub>3</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, Pd/C, H<sub>2</sub>, 22 °C, 4 h; 80% overall). The deprotection scheme utilized above delivered **17** in 91% overall yield for these last two operations.<sup>8</sup>

Estrogen receptor affinity for both **12** and **17** turned out to be low.

### References and Notes

1. Postdoctoral Associate (a) 1993-1994, (b) 1995-1996.
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3. Künzer, H.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 743.
4. For alternative routes to certain 9 $\alpha$ -alkylated steroids, consult: (a) Coombs, R. V.; Koletar, J.; Danna, R.; Mah, H.; Galantay, E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2095. (b) Guy, A.; Doussot, J.; Guetté, J.-P.; Garreau, R.; Lemaire, M. *Synlett* **1992**, 821.
5. (a) For a review on anion-assisted sigmatropic processes, see: Wilson, S. R. In *Organic Reactions*, Vol. 43; Paquette, L. A. et al., Eds.; Wiley & Sons, Inc.: New York, 1993; Chapter 2. (b) For recent work on sigmatropic reactions in the steroid field, see: Lesuisse, D.; Canu, F.; Tric, B. *Tetrahedron* **1994**, *50*, 8491.
6. Propano-bridging has been achieved across other centers of the steroid skeleton. See, e.g., (a) Pitt, C. G.; Rector, D. H.; Cook, C. E.; Wani, M. C. *J. Med. Chem.* **1979**, *22*, 966. (b) Bull, J. R.; Mountford, P. G. *Synlett* **1994**, 711.
7. (a) Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1976**, *17*, 3325. (b) Kocovsky, P.; Cerny, V. *Collection Czechoslov. Chem. Commun.* **1979**, *44*, 246.
8. Physical data for selected steroids are as follows. **4**: mp 111-113 °C (pentane);  $[\alpha]_D^{22} +268.8^\circ$  (c 0.51, CH<sub>2</sub>Cl<sub>2</sub>). **8**: amorphous;  $[\alpha]_D^{22} +40.0^\circ$  (c 0.51, CHCl<sub>3</sub>). **9**: mp 163-164 °C (acetone/hexane);  $[\alpha]_D^{22} +32.0^\circ$  (c 0.52, CHCl<sub>3</sub>). **12**: mp 202-204 °C (acetone/hexane); <sup>13</sup>C NMR (75 MHz, C<sub>5</sub>D<sub>3</sub>N)  $\delta$  156.0, 139.2, 135.4, 134.6, 127.3, 117.0, 114.7, 114.1, 81.2, 45.5, 45.0, 43.3, 42.0, 37.1, 34.8, 30.6, 30.3, 21.8, 17.5, 14.3, 11.3;  $[\alpha]_D^{22} +64.9^\circ$  (c 0.51, CH<sub>3</sub>OH). **16**: amorphous;  $[\alpha]_D^{22} +65.0^\circ$  (c 0.51, CHCl<sub>3</sub>). **17**: mp 212-213 °C (acetone/hexane); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  155.5, 140.1, 138.2, 135.9, 134.3, 126.9, 114.3, 114.2, 83.0, 44.4, 44.4, 40.1, 38.0, 35.9, 34.2, 33.8, 33.4, 30.0, 23.5, 21.2, 17.4;  $[\alpha]_D^{22} +71.0^\circ$  (c 0.47, CH<sub>3</sub>OH).

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