Pergamon

Tetrahedron Letters, Vol. 37, No. 34, pp. 6103-6104, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01342-1

A NOVEL, STEREOCONTROLLED APPROACH TO RING B ALKYLATED ESTRATETRAENES

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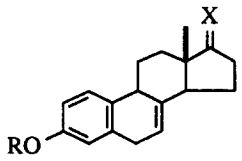
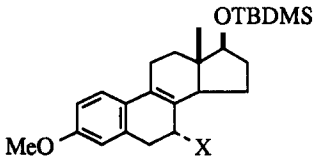
Summary. A four-step reaction protocol, culminating in an oxy-Cope rearrangement, has been developed to transform **2** into **7**. 9α-Alkylated derivatives of equilin, e.g., **12**, as well as C(7)-C(9) propano-bridged 19-norsteroids, like **17**, demonstrate synthetic potential for **7** in estrogen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

Soon after their discovery some sixty years ago, equine estrogens have found widespread use in hormone replacement therapy.[2] 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[3] that **2** readily enters into ene-type α-hydroxyalkylation at C(7), we have devised a novel approach to C(9) α-alkylated equilin derivatives[4] 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.

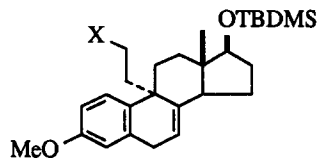
Attachment of a functionalized three-carbon chain to C(9) was envisioned to occur indirectly by way of an anion-accelerated [3,3]-sigmatropic reorganization[5] involving an appropriate C(7) α-substituted intermediate. While the most straightforward access, ene reaction between **2** and acrolein, was 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**[3] (DMSO, Py-SO_3, $(C_2H_5)_3N$, 22 °C; 77%), **3**→**4**, followed by vinylmagnesium bromide addition (THF, $CH_2CHMgBr$, -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**.



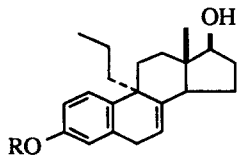
1 R= H, X= O
2 R= CH_3, X= α-H, β-OTBDMS



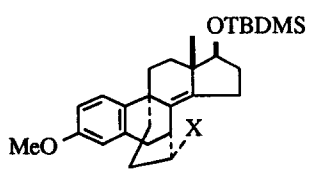
3 X= CH_2OH
4 X= CHO
5/6 X= $CH(OH)CHCH_2$



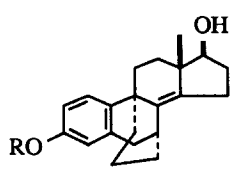
7 X= CHO
8 X= CH_2OH
9 X= CH_2OTs
10 X= CH_3



11 R= CH_3
12 R= H



13 X= OH
14 X= OMs
15 X= H



16 R= CH_3
17 R= H

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 9α-propyl analogue was addressed. The desired side-chain oxidation state was adjusted by formyl group reduction (CH_3OH, $NaBH_4$, 0 °C; 93%), **7**→**8**, tosylation ($CHCl_3$, pyridine, *p*-TsCl, 0 °C, 24 h; 84%), **8**→**9**, and tosylate displacement (THF, $LiB(C_2H_5)_3H$, 22 °C, 1 h; 88%), **9**→**10**. Removal of the *t*-butyldimethylsilyl protecting group (THF, HCl, H_2O, 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.[6] 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 ($CHCl_3$, pyridine, CH_3SO_2Cl, 22 °C, 48 h), **13**→**14**, and substitution/reduction (diglyme, H_2O, NaI, Zn, 100 °C, 2 h),[7] **14**→**15**, had to cope with an elimination by-product in an additional hydrogenation step (C_2H_5OH, $CH_3CO_2C_2H_5$, Pd/C, H_2, 22 °C, 4 h; 80% overall). The deprotection scheme utilized above delivered **17** in 91% overall yield for these last two operations.[8]

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.
2. Bhavnani, B. R. *Endocrine Rev.* **1988**, *9*, 396.
3. Künzer, H.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 743.
4. For alternative routes to certain 9α-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° (c 0.51, CH_2Cl_2). **8**: amorphous; $[\alpha]_D^{22}$ +40.0° (c 0.51, $CHCl_3$). **9**: mp 163-164 °C (acetone/hexane); $[\alpha]_D^{22}$ +32.0° (c 0.52, $CHCl_3$). **12**: mp 202-204 °C (acetone/hexane); ^{13}C NMR (75 MHz, C_5D_5N) δ 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° (c 0.51, CH_3OH). **16**: amorphous; $[\alpha]_D^{22}$ +65.0° (c 0.51, $CHCl_3$). **17**: mp 212-213 °C (acetone/hexane); ^{13}C NMR (75 MHz, CD_3OD) δ 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° (c 0.47, CH_3OH).

(*Received in Germany* 13 *June* 1996; *accepted* 2 *July* 1996)