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A [4+1] CYCLOPENTANNULATION ROUTE TO RING A AROMATIC, C(1)-C(11) METHANO-BRIDGED STEROIDS

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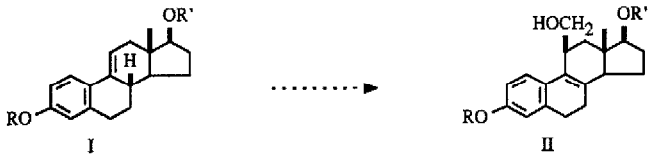
Summary. In a novel, one-pot [4+1] cyclopentannulation procedure, the steroidal olefin **2** and CH_2O are converted into the corresponding C(1)-C(11) methano-bridged derivative **3** by two sequential Lewis acid-promoted electrophilic substitutions. Birch reduction of the olefin **3**, followed by removal of the protecting groups, affords 1,11α-methano-9β-estra-1,3,5(10)-triene-3,17β-diol (**6**).

The pharmacological characterization of recently discovered biologically active classes of steroid hormone analogues, featuring a broad variety of substituents on the steroid β-face at C(11),[1] depends critically on efficient, stereoselective reactions for the production of bulk quantities of these compounds and additional derivatives. In this context, we were led to consider one-carbon homologation of readily available derivatives of estra-1,3,5(10),9(11)-tetraene-3,17β-diol[2] by a concerted, but contrasteric ene-type reaction with paraformaldehyde, involving the allylic hydrogen atom H(8β), as a potentially attractive route to an important key intermediate, I → II.



I II

This communication reports on the dimethylaluminum chloride-mediated Prins reaction[3] between paraformaldehyde and the steroidal olefin **2**, a transformation which did not result in the desired homoallylic alcohol, but in a novel access to C(1)-C(11) methano-bridged 19-norsteroids by an interesting one-pot [4+1] cyclopentannulation.

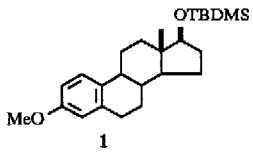
Since derivatives of estradiol are known to give hydroxymethylation in ring A at positions C(2) and C(4) in the presence of acid,[4] conditions had to be defined under which aromatic substitution could be suppressed. We were pleased to observe, in a model study, that the methyl ether **1** was completely resistant to chemical change in the presence of excess paraformaldehyde and dimethylaluminum chloride at temperatures ranging from -78 °C to +22 °C.

On the other hand, when the olefin **2**, obtained by methylation (acetone, Me_2SO_4, K_2CO_3, 70-80 °C, 8 h; 84%), reduction (MeOH, $NaBH_4$, 0-22 °C; 82%), and silylation (DMF, TBDMSCl, imidazole, 16 h, 22 °C; 93%)[5] of 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one,[2] was added to a stirred mixture of paraformaldehyde and dimethylaluminum chloride in anhydrous methylene chloride at -78 °C under an atmosphere of argon and then warmed to -10/-5 °C, evolution of methane from the reaction mixture was a first indicator for a transformation taking place. After an additional stirring period of 3 h at 0 °C, aqueous work-up and chromatography on silica gel (cyclohexane-toluene, 7:3) afforded the annulated steroid **3**[6] as a viscous oil, which crystallized on standing. A modest 29% overall yield for this transformation stems in part from the

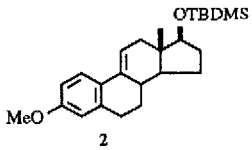
sensitivity of this reactive olefin; decomposition on TLC plates (silica gel) of the purified product became obvious following multiple development.

As to the formation of this compound, we assume that the formaldehyde-Lewis acid complex adds to $\Delta^{9(11)}$ on the α-side at C(11) thus generating a zwitterion, in which the negative charge resides at aluminum and the positive charge at the benzylic position C(9). After stabilization of this intermediate by loss of the proton from C(11), the resulting allylic aluminum alcoholate forms an allylic cation-like species, which cyclizes in a second electrophilic substitution at C(1) to give the pentacyclic steroid **3**.

To arrive at more stable derivatives, suitable for biological testing, the olefin **3** was converted into the 9β,11β-diastereoisomer **4** by Birch reduction (NH_3, THF, Li, -50 °C, 2 h; 83%).[6] The parent steroid **6** in this series was finally obtained after removal of the silyl protecting group (THF, aqueous HCl, 22 °C, 16 h; 94%) and cleavage of the methyl ether (toluene, DIBAH, 120 °C, 4 h; 79%),[7] **4** → **5** → **6**.[8]



1



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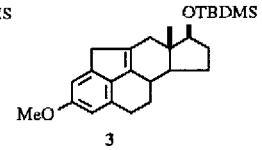

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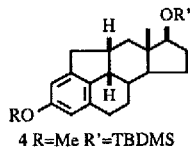

4 R=Me R'=TBDMS
5 R=Me R'=H
6 R=H R'=H

The assignment of stereochemistry at C(9) and C(11) in reduction products **4-6** is based on a chemical shift argument and the splitting pattern of the H(12α) resonance (**5**: δ 0.47 ppm (t, J= 12.2 Hz, 1H); 300 MHz, CD_2Cl_2). The *cis* B-C ring fusion forces H(12α) in the shielding cone of the aromatic ring giving rise, at least in part, to the unusual upfield shift for this resonance.

References and Notes

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6. A methyl derivative in this series has been prepared by a different, stepwise procedure. Consult: Pitt, C. G.; Rector, D. H.; White, D. H.; Wani, M. C.; McPhail, A. T.; Miller, R. W. *J. Chem. Soc. Perkin Trans. I* **1976**, 2374.
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8. Physical data for steroids **3**, **5**, and **6** are as follows. **3**: mp 98-100 °C (methanol), $[\alpha]_D^{22}$ +46.6 ° (c 0.50, dioxane); **5**: mp 90-92 °C (ether-pentane), $[\alpha]_D^{22}$ -34.6 ° (c 0.50, $CHCl_3$); **6**: mp 213-214 °C (acetone-hexane), $[\alpha]_D^{22}$ -36.4 ° (c 0.51, dioxane).

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