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Reaction of a 5α-bromo-6β,19-epoxysteroid with $BF_3{\cdot}Et_2O/Ac_2O$. An evidence of a cyclic bromonium cation

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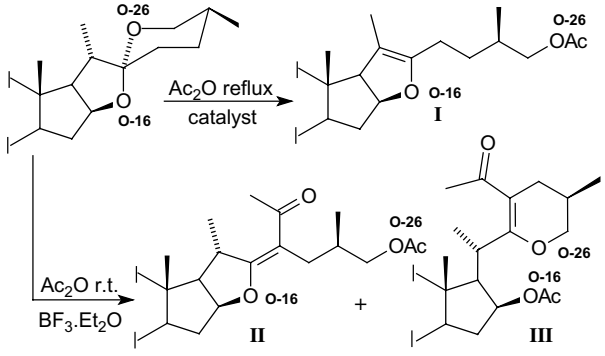
Abstract—Treatment of 3β-acetoxy-5-bromo-6β,19-epoxy-5α-androstan-17-one with Ac_2O and $BF_3{\cdot}OEt_2$, produced the cleavage of the epoxy moiety and migration of the bromine atom to afford 3β,19-diacetoxy-6α-bromo-5-hydroxy-5β-androst-17-one in high yield.

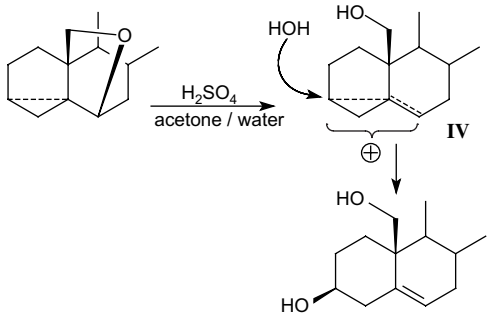
Acid catalyzed Ac_2O treatment of heterocycles is known to produce the cleavage of the ring to a variety of products depending on the nature of both the heterocycle and the catalyst used. A well known reaction is the Lewis acid catalyzed acetolysis of steroid sapogenins in which the tetrahydropyrane F ring is regioselectively cleaved to produce the furostene **I** (Scheme 1).[1] Recently Sandoval-Ramirez and co-workers[1f,1g] showed that $BF_3{\cdot}Et_2O$ promoted acetolysis of steroid sapogenins, in addition to the previously reported product **II**, also produces the 23-acetyl-22,26-epoxycholest-22-ene skeleton **III** due to cleavage of the tetrahydrofurane E ring (Scheme 1).



Scheme 1.

Some other reactions show that acid catalyzed cleavage of tetrahydrofurans are useful tools for the preparation of ω-functionalized butyl carboxylates in good yields.[2]

The presence of a tetrahydrofuran ring in an steroid opens the possibility to introduce functionality on the skeleton.[3] In particular, the acid hydrolysis of a cyclo-6β,19-epoxy-5α-steroid (Scheme 2) has been reported to produce a 3β,19-dihydroxy-Δ^5-steroid in a process in which the non-classic homoallylic carbocation **IV** is claimed as intermediate (Scheme 2).[3b]



Scheme 2.

After those facts we decided to study the reactivity of the 5α-bromo-6β,19-epoxy moiety through the $BF_3{\cdot}Et_2O/Ac_2O$

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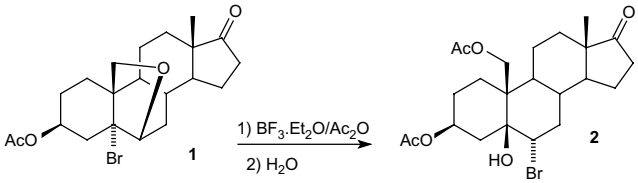
couple. Steroids bearing such moiety can be prepared by treatment of the corresponding 6β-hydroxysteroid with $Pb(OAc)_4$ and iodine,[4] or more conveniently by photolysis of a mixture of diacetoxy(iodobenzene), iodine, and the 6β-hydroxysteroid.[5] Such compounds have served as synthetic intermediates on the preparation of 19-functionalized- and 19-nor- steroids.[6]

Treatment of a suspension of 3β-acetoxy-5-bromo-6β,19-epoxy-5α-androstan-17-one (**1**) in Ac_2O with $BF_3{\cdot}Et_2O$ for 15 min produced, after addition of water, the 3β,19-diacetoxy-6α-bromo-5-hydroxy-5β-androst-17-one (**2**) in 73% (Scheme 3).



Scheme 3.

Compound **2** presented mp 166–168 °C (EtOAc) and ^1H NMR (300 MHz, $CDCl_3$): 5.26 (m, 1H, H-3); 4.64 (dd, $J = 4.8$, 13.1 Hz, 1H, H-6); 4.41 (d, $J = 12.0$ Hz, 1H, H-19a); 4.35 (d, $J = 12.0$ Hz, 1H, H-19b); 2.10 (s, 3H, CH_3 acetyl); 2.09 (s, 3H, CH_3 acetyl); 0.85 (s, 3H, H-18). ^{13}C NMR (75.5 MHz): C-1 23.8; C-2 21.2; C-3 69.3; C-4 31.9; C-5 74.8; C-6 60.8; C-7 38.8; C-8 36.7; C-9 42.9; C-10 45.9; C-11 20.9; C-12 31.5; C-13 47.8; C-14 51.6; C-15 21.6; C-16 35.6; C-17 219.4; C-18 13.7; C-19 65.2; CH_3 acetyl 21.4, 21.3; C=O acetyl 170.4, 169.3. MS (70 eV): 485, 487 M^+, 467, 469 $M^+ - H_2O$, 407, 409 $M^+ - H_2O - CH_3COOH$, 347, 349. See Figure 1 for crystal structure.[7]

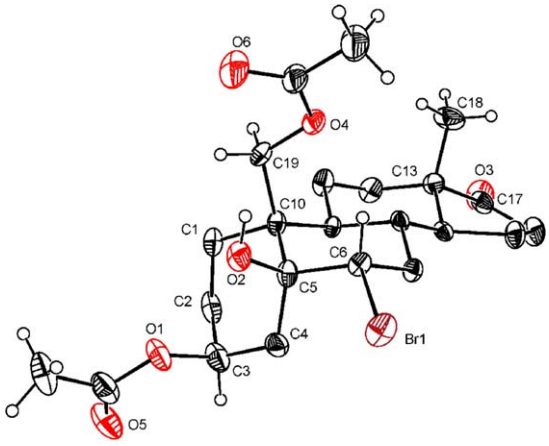


Figure 1. Crystal structure of **2**.

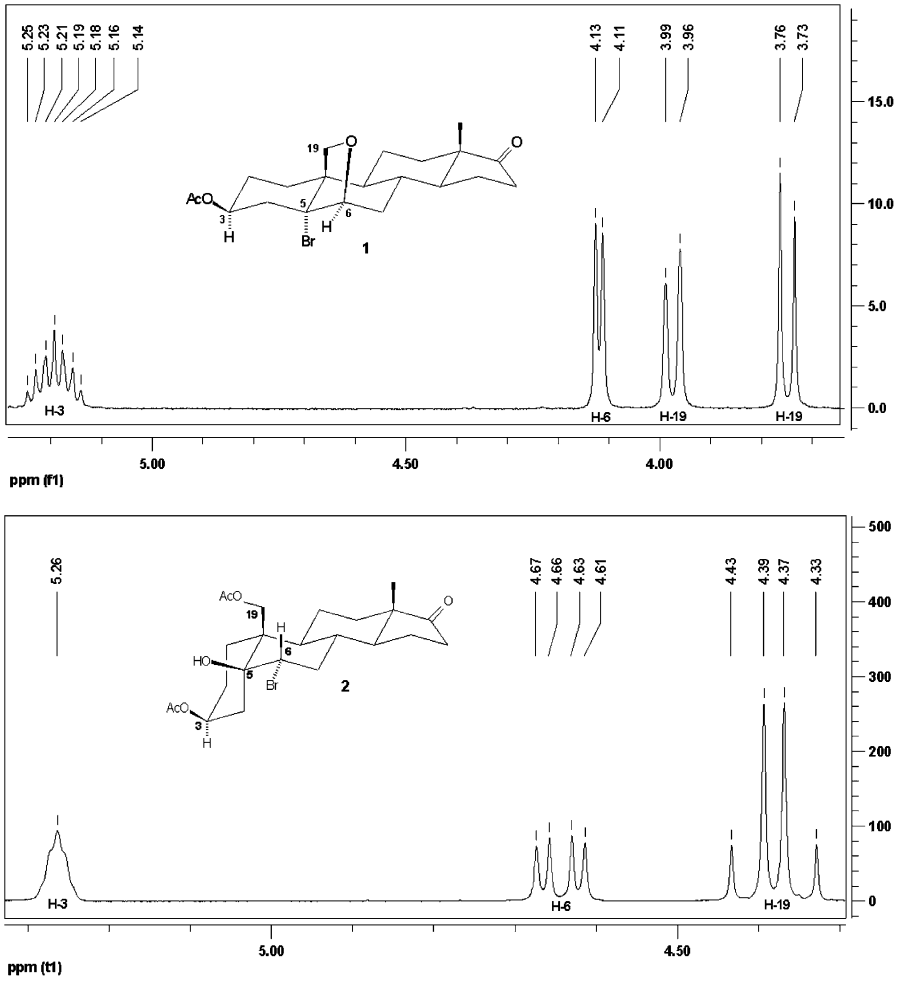
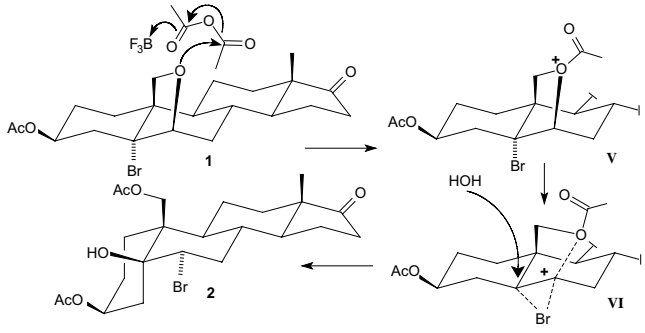


Figure 2. Fragments of ^1H NMR spectra of starting material **1** and rearranged product **2**.

Downfield shift and changes on the coupling pattern of the two H-19 signals indicate the cleavage of the 6β,19-epoxy moiety. Additionally the new dd multiplicity of H-6 evidences its axial orientation and the α-orientation of the bromine atom now attached to C-6. The new shape of H-3 signal indicates its equatorial orientation, which arises from the inverted chair conformation of ring A after rearrangement to a 5β-androstane. See Figure 2 for comparison of the spectra of starting material (**1**) and rearranged product (**2**).

After the observed rearrangement it can be assumed that $BF_3{\cdot}Et_2O$ activates the acetic anhydride, which adds to the oxygen attached to both C-6 and C-19 to produce **V**. Cleavage of the C-6–O bond is assisted by the formation of the cyclic bromonium cation **VI**, which is stable enough to remain in solution until water is added; then nucleophilic attack of the solvent to C-5 from the β-side leads to the observed product (Scheme 4).



Scheme 4. Reaction mechanism.

The absence of products of nucleophilic attack to C-5 from the α-side or from both α- and β-sides of C-6, suggests an intermediate like **VI** in which the α-sides of positions C-5 and C-6 are hindered by the cyclic bromonium and the β-side of position 6 is blocked by the breaking C-6–O bond.

In summary we have found that reaction of the 5α-bromo-6β,19-epoxy moiety with acetic anhydride and $BF_3{\cdot}Et_2O$ produces the regioselective cleavage of the C-6–O bond in a process assisted by the formation of a cyclic bromonium cation, which is stable enough to remain unchanged until addition of water.

This high yield rearrangement opens a one reaction path to the rare and useful 6α-bromo-5β,19-dihydroxy moiety (*see the diequatorial bromohydrin in* **4**), which has been previously prepared from **3** in three steps (Scheme 5) and used for the introduction of the 5β,19-dihydroxy group characteristic of cardiotonic steroid strophanthidin (**5**).[8] Synthetic applications and investigations on the reaction mechanism are on development.

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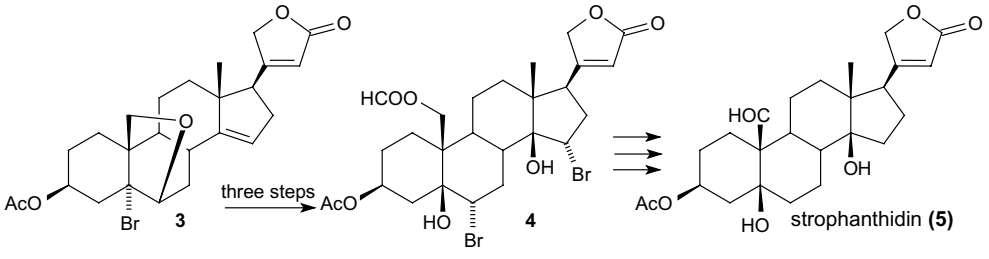

Scheme 5.

Denot, E.; Halpern, O. *J. Am. Chem. Soc.* **1962**, *84*, 3204–3205; (c) Rabinowitz, M. H.; Djerassi, C. *J. Am. Chem. Soc.* **1992**, *114*, 304–317.

7. *Crystal data for* **2**: $C_{23}H_{33}BrO_6$, $M = 485.40$ g/mol^{-1}, colorless lamina, $0.60 \times 0.23 \times 0.10$ mm^3, monoclinic, space group $P2(1)$, cell parameters $a = 9.7550(15)$, $b = 9.8440(14)$, $c = 12.4390(16)$ Å, $\beta = 101.416(16)°$, $Z = 2$, $D_c = 1.377$ g cm^{-3}. 3203 Reflections collected on a Siemens P4 four-cycle diffractometer at room temperature, with the Mo K$_\alpha$ radiation ($\lambda = 0.71073$ Å) in the range $2\theta = 3–52°$, of which 2715 are unique ($R_{int} = 0.0450$). Goodness-of-fit on $F^2 = 1.084$, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0449$, $wR_2 = 0.1118$, R indices (all data) $R_1 = 0.0659$, $wR_2 = 0.1194$, largest difference peak and hole 0.273 and -0.328 e Å^{-3}. Complete data have been deposited with the Cambridge Crystallographic Data Centre, CCDC, reference 263324.
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