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SYNTHESIS OF PENTACYCLIC 1α,11-(2-OXETHANO) STEROIDS

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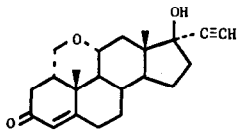
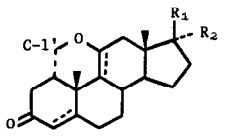
Summary: Treatment of a 1α,2α-methyleneandrostan analog (4) with hydrobromic acid/acetic acid gives an apparent intramolecular homoconjugate ring-opening, which serves as the key step in the synthesis of a new type of pentacyclic steroid analogs (2).

It has been proposed[2] that progestins bind to the uterine receptor protein via their β-faces and that the A-ring region is particularly important for promoting high affinity binding. All progesterone agonists that exhibit high relative binding affinity have a 4-ene-3-one system in common. The X-ray crystallographic data generated by Duax and Norton[3] indicated that the A-ring of natural hormones and of many synthetic analogs with the 4-ene-3-one system embrace conformations ranging from the 1α,2β half-chair to the 1α sofa. However, several steroids that display high binding relative to the progesterone receptor adopt the unusual A-ring 1β,2α inverted half-chair conformation, and it has been suggested that this is the preferred conformation for progesterone receptor binding, thus allowing a close contact between the receptor and the β-face of the rather flat area from C-2 through C-6 and the α-face of the conjugated system.[2] In an ongoing systematic investigation into the mode of action of binding of progesterone analogs to the uterine cytosol receptor, we are synthesizing conformationally rigid steroid analogs in order to more clearly understand the correlation between conformational shape and biological activity. We focused our attention on the steroid analog 1, in which the 1α,11α-(2-oxethano) bridge forces the A-ring to adopt a 1β,2α inverted, rigid half-chair conformation. This conformational freezing of the A-ring could lead to more specific biological activity. A similar approach to a study of conformational phenomena in corticosteroids, with the introduction of a 1,11α-ethano bridge in hydrocortisone and prednisolone in order to restrict the conformational mobility, has recently been reported.[4] This study prompts us to disclose the preliminary results from our synthesis of 1 and of some 1α,11-(2-oxethano) steriod analogs with the general structure 2.



1



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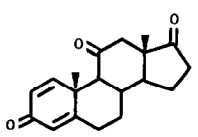

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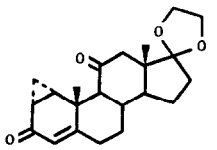

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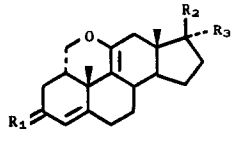
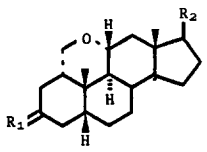
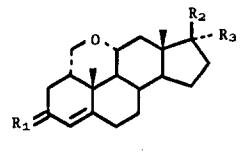


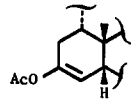
	R_1	R_2	R_3
5	O	‖O‖	
6	$-SCH_2CH_2S-$	‖O‖	
7	O	OH	C≡CH



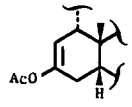
	R_1	R_2
8	$-SCH_2CH_2S-$	OH
9	O	OH
10	O	OAc
11	O	OCOPh



	R_1	R_2	R_3
13	O	OCOPh	H
14	$-SCH_2CH_2S-$	OCOPh	H
15	$-SCH_2CH_2S-$	OH	H
16	$-SCH_2CH_2S-$	‖O‖	
17	$-SCH_2CH_2S-$	OH	C≡CH



12a



12b

For our synthetic strategy, we knew that the one-carbon fragment (C-1') could be introduced stereospecifically by cyclopropanation with oxosulfonium methylide.[5-8] The tetrahydropyran ring in 1 was then projected to be formed by an intramolecular homoconjugate ring-opening of the 1α,2α-cyclopropane ring.[9] Androsta-1,4-dien-3,11,17-trione (3) was considered to be the readily available starting material that possesses all necessary key features for transformation into 1. The 1α,2α-methylene analog 4 was easily prepared from 3 in five steps by way of the intermediate 1,4,6-triene-3-one[8]: (i) ethylene glycol, p-TsOH, benzene, Δ; (ii) NBS, AIBN, CCl_4, Δ; (iii) LiBr, $CaCO_3$, DMF, Δ; (iv) $Me_3S(O)^+I^-$, NaH, DMSO, 25°C; (v) H_2, 5% Pd-$BaSO_4$, EtOH.[10] However, subsequent efforts to reduce the 11-ketone to the 11α-ol after protection (1,2-bis-trimethylsilyloxyethane, TMSOTf, CH_2Cl_2, 25°C)[11] of the 4-ene-3-one system were not successful. This led us to consider first opening the cyclopropane ring. Treatment of 1α,2α-methylene steroids with hydrobromic acid in acetic acid has previously been shown to afford 1α-bromomethyl steriods without phenol rearrangement.[8] Thus, when 4 was heated in a mixture of glacial acetic acid and 48% aqueous hydrobromic acid for 30 min, one product was formed and isolated.

Structure analysis revealed that the product was not the expected 1α-bromomethyl analog, but the pentacyclic derivative 5 [mp 152-153°C (EtOAc-hexane), 85%; ^1H NMR (300 MHz, $CDCl_3$) inter alia δ 0.957 (s, 3H, 18-CH_3), 1.471 (s, 3H, 19-CH_3), 3.636 (t, B of ABX, 1H, 1'-H, $J_{AB} = J_{BX} = 10.3$ Hz), 3.847 (dd, A of ABX, 1H, 1'-H, $J_{AB} = 10.3$ Hz, $J_{AX} = 3.1$ Hz. Decoupling experiment with irridation at 2.31 ppm gave a clean AB quartet, $J_{AB} = 10$ Hz), 5.728 (d, 1H, 4-H, $J = 0.9$ Hz); ^{13}C NMR inter alia δ 67.029 (C-1'), 112.782 (C-9), 121.472 (C-4), 148.127 (C-11), 166.809 (C-5), 197.369 (C-3), 219.501 (C-17)]. There is, however, reason to believe that the reaction proceeds via the bromomethyl analog (TLC monitoring). From inspection of Dreiding models and from the coupling constants, it appears that the A-ring and the dihydropyran ring adopt a 1β,2α inverted half-chair and a 1α sofa conformation, respectively ($\theta_{AX} \approx 60°$ and $\theta_{BX} \approx 180°$). For further elaboration, the 4-ene-3-one system was selectively protected (1,2-ethanedithiobistrimethylsilane, $ZnBr_2$, CH_2Cl_2, 25°C)[12] to give 6 (80%).[10] Reaction of 6 with lithium acetylide ethylenediamine complex (DMSO, 25°C), after aqueous workup, gave directly--and unexpectedly--the dithioketalized analog 7 (49%).[10] We next turned our attention to the reduction of the $\Delta^{9,11}$ double bond in 6. Reduction of $\Delta^{9,11}$ double bonds with triethylsilane under acid catalysis has been shown to give products with the natural 9α configuration.[13,14] Other encouraging results were the reported formation of ethers upon reduction of

ketones with triethylsilane/H^+ in the presence of an alcohol[15] and the reduction of hemiacetals to ethers under similar conditions.[16] In both cases the reduction presumably proceeds via an oxonium intermediate. Thus, treatment of 6 with 10 equiv. of triethylsilane and 50 equiv. of trifluoroacetic acid (CH_2Cl_2, 50°C, 20 hr) afforded, after hydrolysis of the 17-trifluoroacetate (KOH, MeOH, THF, 25°C) and isolation by column chromatography (silica gel, EtOAc-hexane 1:1), the steroid analog 8 (73%).[10] Lower concentrations of TFA gave only reduction of the Δ^4 double bond and the 17-ketone. Assignment of the configurations at C-5, -9, -11, and -17 follows, in addition to spectral data, on the known, thermodynamically controlled trans-addition of triethylsilane/H^+ to double bonds.[14] Also, with respect to compound 8 the 5β, 9α, and 11β configuration allows the A, B, C and the tetrahydropyran rings to assume strain-free chair conformations. Moreover, reduction of 4-ene-3-one steroids under similar conditions gives 3α-hydroxy 5β products.[14] Dethioketalization of 8 (H_5IO_6, H_2O, CH_2Cl_2, MeOH, 25°C)[17] to give 9 (83%)[10] followed by acetylation (Ac_2O, DMAP, Et_3N, CH_2Cl_2, 25°C) afforded the acetate 10 (80%).[10] Benzoylation of 8 (92%)[10] and subsequent deprotection gave, under similar conditions, the benzoate 11 (76%).[10] Treatment of 11 with isopropenyl acetate and p-TsOH gave a mixture of the two isomeric enol acetates 12a [^{1}H NMR (60 MHz, $CDCl_3$) inter alia δ 5.12 (br s, 1H, 4-H), 2.13 (s, 3H, $OCOCH_3$)] and 12b [^{1}H NMR (60 MHz, $CDCl_3$) inter alia δ 5.28 (br s, 1H, 2-H), 2.13 (s, 3H, $OCOCH_3$)] in a ratio of approximately 70:30. The two isomers were separated by preparative TLC. Equilibration of the minor isomer improved the yield of isolated 12a (57%). The predominance of 12a is presumably ascribable to the absence of the diaxial interaction between the 4α and the 7α hydrogens. Bromination of 12a and dehydrobromination were accomplished in one step (NBS, CCl_4, Δ) to give the 4-ene-3-one analog 13 (74%).[10] Protection (ethanedithiol, p-TsOH, AcOH, 25°C, 95%) followed by hydrolysis of the benzoate ester (KOH, MeOH, THF, 25°C, 100%) and oxidation of the alcohol (PCC, NaOAc, CH_2Cl_2, 25°C, 68%)[18] afforded compound 16.[10] Treatment of 16 with ethynylmagnesium bromide (DMSO, 25°C, 78%)[10] and subsequent deprotection (H_5IO_6, H_2O, MeOH, CH_2Cl_2, 25°C, 96%) gave the main target compound 1.[10]

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10. Satisfactory spectral data (IR, NMR, MS) have been obtained for all compounds reported in this communication. Elemental composition as determined by combustion analysis or high-resolution mass spectroscopy has been obtained for compounds 1, 5, 7, 10, and 13. Following are ^{1}H NMR (300 MHz, $CDCl_3$) data for some representative compounds: 10 δ 0.829 (s, 3H, 18-CH_3), 1.288 (s, 3H, 19-CH_3), 2.040 (s, 3H, OCOCH_3), 2.743 (t, 1H, 4-H, J = 13.8 Hz), 2.982 (t, 1H, 2-H, J = 13.7 Hz), 3.440 (dd, B of ABX, 1H, 1'-H, J_{AB} = 12.0 Hz, J_{BX} = 1.0 Hz), 3.621 (dt, 1H, 11-H, J = 10.5 Hz, and 4.7 Hz), 4.059 (dd, A of ABX, 1H, 1'-H, J_{AB} = 12.0 Hz, J_{AX} = 2.7 Hz), 4.636 (dd, X of ABX, 1H, 17-H, J_{AX} + J_{BX} = 16.8 Hz); 13 δ 1.002 (s, 3H, 18-CH_3), 1.397 (s, 3H, 19-CH_3), 2.640 (ddt, 1H, 6-H, J = 13.0 Hz, 5.2 Hz and 1.1 Hz), 2.838 (t, 1H, 2-H, J = 15.7 Hz), 3.568 (dt, 1H, 11-H, J = 10.6 Hz and 4.6 Hz), 3.651 (d, B of ABX, 1H, 1'-H, J_{AB} = 12.4 Hz, J_{BX} = 0 Hz), 4.065 (dd, A of ABX, 1H, 1'-H, J_{AB} = 12.4 Hz, J_{AX} = 3.3 Hz), 4.846 (dd, X of ABX, 1H, 17-H, J_{AX} + J_{BX} = 16.6 Hz), 5.829 (s, 1H, 4-H), 7.41-8.04 (m, 5H, ArH); 1 δ 0.895 (s, 3H, 18-CH_3), 1.388 (s, 3H, 19-CH_3), 2.580 (s, 1H, CCH), 2.624 (ddt, 1H, 6-H, J = 13.0 Hz, 5.3 Hz and 1.1 Hz), 2.864 (t, 1H, 2-H, J = 15.6 Hz), 3.564 (dt, 1H, 11-H, J = 10.6 Hz and 4.9 Hz), 3.660 (d, B of ABX, 1'-H, J_{AB} = 12.3 Hz, J_{BX} = 0 Hz), 4.109 (dd, A of ABX, 1H, 1'-H, J_{AB} = 12.3 Hz, J_{AX} = 3.3 Hz), 5.818 (s, 1H, 4-H).
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