# 18-Functionalized steroids: synthesis of thioderivatives of progesterone

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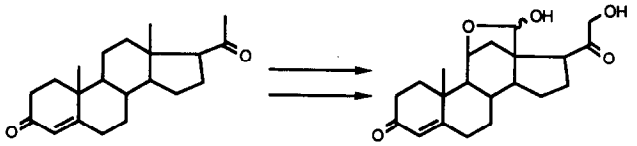
*The synthesis of new 18- or 18'-thioether derivatives of progesterone are reported, along with acid-catalyzed rearrangements occurring during the thioacetalization reactions.* (*Steroids* **55**:271–275, 1990)

**Keywords:** steroids; 18-functionalized steroids; progesterone 18-thioderivatives; aldosterone inhibition

## Introduction

In the course of our search for $k_{cat}$ inhibitors of aldosterone biosynthesis,[1,2] we have synthesized steroids modified at the 18-methyl group, and have shown that they efficiently inhibit the transformation of progesterone **1** to aldosterone **2** (Scheme 1).




1 2

**Scheme 1**

Within this program, we intended to prepare progesterone derivatives with sulfur-containing substituents at the 18-methyl group since 10β-thiiranylsteroids and 19-thiosteroids have proved to be efficient inhibitors of the P450-dependent aromatase which catalyzes the oxidative removal of C(19) and subsequent aromatization of ring A.[3,4]

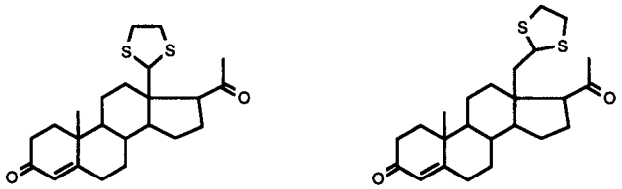
We report our results concerning the synthesis of C(18)-substituted progesterones **3** and **4** (Scheme 2).

## Experimental

Melting points (mp) were determined on a Kofler apparatus and were uncorrected. Recordings of $^{13}C$ and $^{1}H$ nuclear magnetic resonance (NMR) spectra were done either on a Jeol FX90Q or on a Bruker AC200 spectrometer in $CDCl_3$. Chemical shifts are reported as values (ppm) relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Analytical samples have been recrystallized in a methylene chloride/isopropyl ether mixture. Pregnenolone was provided by the Roussel-Uclaf Company.

### *(3β)-[(Tetrahydro-2H-pyran-2-yl)oxy]-(20R)-hydroxypregn-5-en-18-oic acid γ-lactone* **6a**

A solution of **5** (ref. 5) (80 mg), dihydropyran (0.13 ml), and pyridinium paratoluenesulfonate (24 mg) in methylene chloride (8 ml) was stirred at room temperature for 3 hours, then diluted with diethyl ether (50 ml), washed with brine, dried ($Na_2SO_4$), and concentrated under vacuum to afford a white solid, **6a**, which was recrystallized in a methylene chloride-isopropyl ether mixture to give 70 mg of pure **6a** (70%), mp 185 to 186° C. IR ($CHCl_3$): 1,750 $cm^{-1}$ (C=0). NMR: 1.08 (s, 3H, Me 19), 1.36 (d, J = 6 Hz, 3H, Me 21), 3.49 (m, 2H, $CH_2O$ THP ring), 3.87 (m, 1H, H3α), 4.34 (q, 1H, H-20), 4.71 (br. s, 1H, O—CH—O THP ring), 5.32 (m, 1H, H-6). $[\alpha]_D^{22} = -29$ (c = 0.2, $CHCl_3$). Anal. $C_{26}H_{38}O_4$: C, 75.13; H, 9.18 (calculated: C, 75.32; H, 9.24).

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**Scheme 2**

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*(3β)-[(Tetrahydro-2H-pyran-2-yl)oxy]-(20R)-hydroxypregn-5-en-18-al cyclic 18,20-hemiacetal* ***7a***

To a solution of **6a** (180 mg) in dry toluene (20 ml) at −75° C under argon was added a 1.5-M toluene solution of DIBAH (1.46 ml). The mixture was left for 1 hour at −75° C. A 2-M toluene solution of isopropanol (4 ml) was then added. After 45 minutes of stirring at −75° C, the mixture was allowed to warm to 0° C, and water (0.44 ml) was added. The solution was stirred again for 15 minutes at 0° C, then filtered, extracted with ether, washed (brine), dried ($Na_2SO_4$), and evaporated. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 45 : 10) to give 162 mg of **7a** (90%) as a mixture of 18(R) and 18(S) isomers, mp 199 to 200° C. NMR: 1.0 and 1.05 (s, 3H, Me-19), 1.3 and 1.35 (d, J = 6 and 7 Hz, 3H, Me-21), 3.52 (m, 2H, $CH_2O$ THP ring), 3.85 to 4.15 (m, 2H, H-3α + H-20), 4.72 (br. s, 1H, O—CH—O THP ring), 5.13 and 5.32 (s, 1H, H-18), 5.35 (m, 1H, H-6). IR ($CHCl_3$): 3, 600 $cm^{-1}$ (O—H).

*(3β)-Tertiobutyldimethylsilyloxy-(20R)-hydroxypregn-5-en-18-oic acid γ-lactone* ***6b***

A solution of **5** (ref. 5) (100 mg), tertiobutyldimethylsilyl chloride (50 mg), and 1,8-diazabicyclo[5.4.0] undec-7-en (DBU) (54 μl) in methylene chloride (2.5 ml) was stirred at room temperature overnight under argon, then worked up as usual (ethyl acetate extraction) to give, after flash chromatography (cyclohexane/ethyl acetate 5 : 1) 98 mg of **6b** (73%), mp 228 to 230° C. NMR: 0.05 (s, 6H, $SiMe_2$), 0.85 (s, 9H, tBuSi), 1.05 (s, 3H, Me 19), 1.35 (d, J = 7 Hz, 3H, Me 21), 3.45 (m, 1H, H-3α), 4.35 (q, 1H, H-20), 5.3 (m, 1H, H-6). IR ($CHCl_3$): 1,750 $cm^{-1}$ (C=0). Anal. $C_{27}H_{44}O_3Si$: C, 72.94; H, 12.87 (calculated: C, 72.92; H, 12.69). $[\alpha]_D^{22}$ = +268 (c = 0.116, $CHCl_3$).

*(3β)-Tertiobutyldimethylsilyloxy-(20R)-hydroxypregn-5-en-18-al cyclic 18,20-hemiacetal* ***7b***

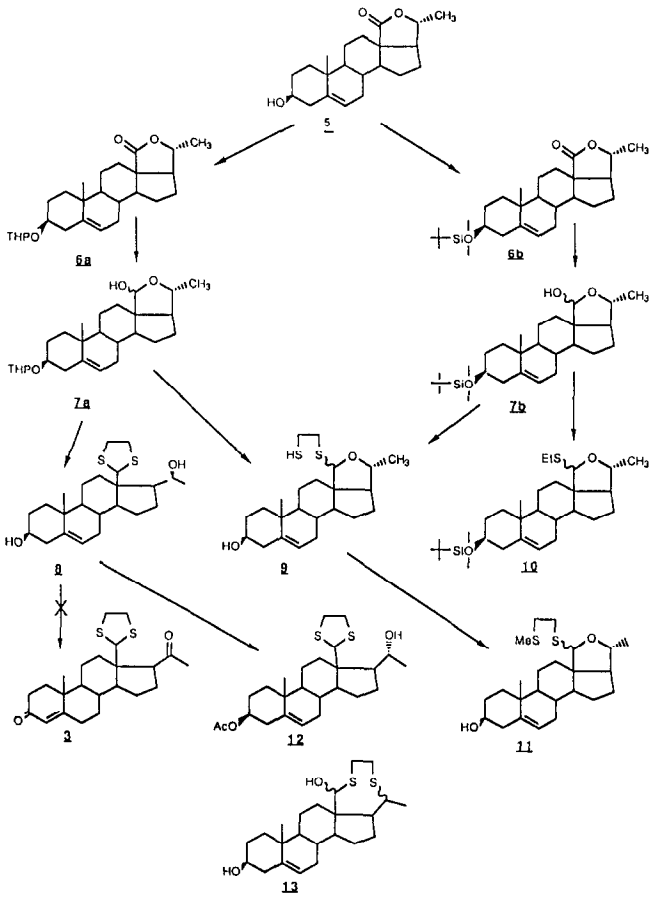
Compound **6b** (98 mg) was reduced by DIBAH as described above to yield 94 mg of **7b** (95%) which was used without purification. NMR: 0.04 (s, 6H, $SiMe_2$), 0.87 (s, 9H, tBuSi), 0.95 and 0.98 (s, 3H, Me 19), 1.24 and 1.31 (d, J = 6 and 7 Hz, 3H, Me 21), 3.49 (m, 1H, H-3α), 4.0 (m, 1H, H-20), 5.12 (s, 1H, H-18), 5.29 (m, 2H, H-6 + H-18).

*(3β,20R)-3,20-Dihydroxypregn-5-ene-18-thial cyclic 18-(1,2-ethanediyl mercaptal)* ***8*** *and (3β,20R)-18,20-epoxy-18-[(2-mercaptoethyl)thio]-pregn-5-ene-3-ol* ***9***

A solution of **7a** (200 mg) in distilled methylene chloride (10 ml), ethane dithiol (0.195 ml), and titanium chloride (0.158 ml of a 1-M solution in methylene chloride) was stirred at room temperature for 3 hours under argon. The mixture was then hydrolyzed (ice) and worked up as usual (methylene chloride extraction) to yield a colorless oil which was purified by flash chromatography (chloroform/ether 8 : 1) to give 134 mg of **9** (43%) and 50 mg of **8** (25%).

**Compound 8.** Melting point 210 to 211° C. $[\alpha]_D^{22}$ = −45 (c = 0.1, $CHCl_3$). $^1H$ NMR: 1.0 (s, 3H, Me 19), 1.15 (d, J = 6 Hz, 3H, Me 21), 3.0 to 3.45 (m, 4H, $SCH_2CH_2S$), 3.52 (m, 1H, H-3α), 4.4 (m, 1H, H-20), 4.95 (s, 1H, H-18), 5.35 (m, 1H, H-6). $^{13}C$ NMR: 19.3 (C-19), 22.1 (C-21), 35.1 and 39.5 (S—C—C—S), 56.5 (C-18), 68.0 (C-20), 71.5 (C-3), 121.0 (C-6), 140.9 (C-5). These attributions were deduced from a two-dimensional heteronuclear correlation experiment. Anal. ($C_{23}H_{36}O_2S_2$) found: C, 67.80; H, 9,15; S, 14.0; O, 8.0. Calculated: C, 67.62; H, 8.88; S, 15.6; O, 7.83. Mass spectrum (C.I./$NH_4^+$: m/z 315, 332, 391; (C.I./$NH_2^-$): m/z 407 $(M - H)^-$; 379, 347 $(M - C_2H_4S)^-$.

**Compound 9 (obtained as an oil).** NMR: 1.0 (s, 3H, Me 19), 1.3 (d, J = 6 Hz, 3H, Me 21), 2.6 to 3.0 (m, 4H, $SCH_2CH_2S$), 3.55 (m, 1H, H-3α), 4.05 (m, 1H, H-20), 5.25 (s, 1H, H-18), 5.35 (m, 1H, H-6). Mass spectrum (C.I./$NH_4^+$): m/z 315, 347 (fragmentation peaks). An attempt was made to stabilize **8** by alkylation with methyl chloride in liquid ammonia. The resulting product **11** (Scheme 3) showed the expected $^1H$ NMR



**Scheme 3**

$CH_3$—S absorption at 2.1 ppm and gave a satisfactory chemical negative ionization mass spectrum. (C.I./$NH_2^-$): m/z 421 $(M-H)^-$.

*(3β)-Tertiobutyldimethylsilyloxy-18,20R-epoxy-18-(ethylthio)pregn-5-en* ***10***

A solution of **7b** (20 mg), ethanethiol (0.018 ml), and $TiCl_4$ (0.015 ml of a 1-M solution in $CH_2Cl_2$) in 1.5 ml of methylene chloride was stirred at room temperature for 5 hours, then hydrolyzed and extracted with methylene chloride as usual to give **10** (22 mg) obtained as an oil. NMR: 0.05 (s, 6H, $Me_2Si$), 0.85 (s, 9H, tBuSi), 1.25 (t, J = 7 Hz, 3H, $SCH_2CH_3$), 1.3 (d, J = 6 Hz, 3H, Me 21), 1.0 (s, 3H, Me 19), 2.6 (q, J = 7 Hz, 2H, $SCH_2CH_3$), 3.45 (m, 1H, H-3α), 4.0 (m, 1H, H-20). Mass spectrum (C.I./$NH_4^+$): m/z 429 $(M-SEt)^+$, 348, 315.

*(3β)-Tertiobutyldimethylsilyloxy-(17β)-2',6'-[1,2-ethanediyl(bisoxy)]-2',5',6',17-tetrahydro-2'-methyl-18-norandrostano[17,13-c]pyran* ***15*** *and (3β)-tertiobutyldimethylsilyloxy-20-oxopregn-5-ene-18'-carboxaldehyde cyclic 18'-(1,2-ethanediyl acetal)* ***16***

A solution of **14** (ref. 2) (800 mg) and ethanedithiol (0.0016 ml) in benzene (48 ml) containing $SiO_2/SOCl_2$ (320 mg) was stirred at room temperature for 2 hours, then filtered. The filtrate was washed with water, dried ($Na_2SO_4$), and concentrated to give, after flash chromatography (cyclohexane/ethyl acetate 5 : 1), 295 mg of **15** (37%) and 319 mg of **16** (40%).

**Compound 15.** Melting point 191 to 192° C. $[\alpha]_D^{22} = -43$ (c = 0.266, $CHCl_3$). $^1H$ NMR: 0.03 (s, 6H, $Me_2Si$), 0.85 (s, 9H, tBuSi), 1.0 (s, 3H, Me 19), 1.2 (s, 3H, Me 2'), 3.45 (m, 1H, H-3α), 3.72 (m, 4H, O—$CH_2$—$CH_2$—O), 5.0 (br. d, J = 3 Hz, 1H, H-6'), 5.3 (m, 1H, H-6). $^{13}C$ NMR: 4.55 ($Me_2Si$), 25.92 (tBu), 72.60 (C-3), 97.73 (C-6'), 102.08 (C-2'), 120.73 (C-6), 141.84 (C-5). Mass spectrum (C.I./$NH_4^+$): m/z 503 $(MH)^+$, m/z 445 (MH-tBu)$^+$, m/z 371 (MH-tBuSi$Me_2O$)$^+$, m/z 388 (M-tBuSi $Me_2O$ + $NH_4$)$^+$.

**Compound 16.** Melting point 156 to 157° C. $[\alpha]_D^{22} = +10$ (c = 0.2, $CHCl_3$). $^1H$ NMR: 0.04 (s, 6H, $Me_2Si$), 0.85 (s, 9H, tBuSi), 1.0 (s, 3H, Me 19), 2.15 (s, 3H, Me 21), 3.45 (m, 1H, H-3α), 3.73 (m, 4H, O—$CH_2$—$CH_2$—O), 4.75 (t, J = 6 Hz, 1H, H-18'), 5.3 (m, 1H, H-6). IR ($CHCl_3$): 1,690 $cm^{-1}$ (C=0). $^{13}C$ NMR: 4.55 ($Me_2Si$), 25.92 (tBu), 72.60 (C-3), 102.62 (C-18'), 120.73 (C-6), 140.84 (C-5), 209.29 (C-20). Anal. ($C_{30}H_{50}O_4Si$) found: C, 71.24; H, 10.14. Calculated: C, 71.66; H, 10.02.

*(3β)-Hydroxy-18-methyl-18',21-cyclopregna-5,18'(21)-dien-20-one* ***17***

A total of 50 mg of **14** in acetone (20 ml) was stirred at room temperature for 24 hours with a catalytic amount of paratoluenesulfonic acid. The solution was extracted with ethyl acetate and worked up as usual to give **17** which was purified by preparative thin-layer chromatography, yielding 14 mg (43%) of a white solid, mp 191 to 193° C. $^1H$ NMR: 1.0 (s, 3H, Me 19), 3.5 (m, 1H, H-3 α), 5.32 (m, 1H, H-6), 5.95 (dd, J = 11, 2.5 Hz, 1H, H-21), 6.82 (td, J = 6, 2.5 Hz, 1H, H-18'). $^{13}C$ NMR: 71.53 (C-3), 121.17 (C-6), 127.60 (C-21), 140.64 (C-5), 148.14 (C-18'), 201.98 (C-20). IR ($CHCl_3$): 1,660 $cm^{-1}$ (C=0); 1,630 $cm^{-1}$ (C=C), 2,930 $cm^{-1}$ (C-H). Mass spectrum (C.I./$NH_4^+$): m/z 327 $(MH)^+$. UV: $\lambda_{max}$ = 239 nm (ethanol).

*(3β)-Hydroxy-20-oxopregn-5-ene-18'-carboxaldehyde cyclic 18'-(1,2-ethanediyl mercaptal)* ***18***

A solution of **14** (100 mg), ethanedithiol (17 μl), and $BF_3 \cdot Et_2O$ (15 μl) in methylene chloride (50 ml) was stirred at −10° C for 3 hours. After the addition of a saturated solution of sodium carbonate (10 ml), the mixture was treated as usual. Flash chromatography of the residue (chloroform/ether 6 : 4) gave 51 mg of **18** (61%), mp 127 to 128° C. NMR: 1.0 (s, 3H, Me 19), 1.95 (d, J = 6 Hz, 2H, H-18), 2.25 (s, 3H, Me 21), 2.9 to 3.7 (m, 5H, S—$CH_2$—$CH_2$—S and H-3α), 4.1 (t, J = 6 Hz, 1H, H-18'), 5.3 (m, 1H, H-6). In addition, 9 mg (8%) of the 3β-tertiobutyldimethylsilyl derivative of **18** was also isolated.

*3,20-Dioxopregn-4-ene-18'-carboxaldehyde cyclic 18'-(1,2 ethanediyl mercaptal)* ***4***

A solution of **18** (44 mg) and *N*-methylpiperidone (0.33 ml) in dry toluene (4.3 ml) was refluxed in a Dean Stark apparatus. The first 0.5 ml of distillate was discarded. Aluminium isopropoxide (54 mg) was added and refluxing was continued for 3 hours. The mixture was acidified by hydrochloric acid (5 ml of a 10% solution in water), extracted with toluene, washed with brine, dried ($Na_2SO_4$), and evaporated. The residue was purified by thin-layer chromatography (chloroform/ether 6 : 4) yielding 26 mg of **4** (59%), mp 170 to 171°C. $[\alpha]_D^{22}$ = +234 (c = 0.23, $CHCl_3$). NMR: 1.17 (s, 3H, Me 19), 1.98 (d, J = 6 Hz, 2H, H-18), 2.23 (s, 3H, Me 21), 3.21 (m, 4H, S—$CH_2$—$CH_2$—S), 4.1 (t, J = 6 Hz, 1H, H-18'), 5.69 (br. s, 1H, H-4). Mass spectrum (C.I./$NH_4^+$): m/z 419 $(M + H)^+$, 436 $(M + NH_4)^+$.

*(3β)-Acetoxy-(20R)-18,20-epoxy-18-methylene pregn-5-ene* ***20***

A solution of **19** (ref. 6) (20 mg), boron trifluoride etherate (25 μl), and ethane dithiol (5 μl) in methylene chloride (0.5 ml) was stirred for 5 hours at room temperature under argon. Hydrolysis and subsequent conventional work-up yielded 15 mg of **20** (95%) as a white solid, mp 137 to 146° C. $[\alpha]_D^{22} = -35$ (c = 0.115, $CHCl_3$). $^1H$ NMR: 1.05 (s, 3H, Me 19), 1.25 (d, J = 7 Hz, 3H, Me 21), 2.0 (s, 3H, $CH_3CO$), 3.8 and 4.3 (br. s, 2H, $CH_2$=C), 4.5 (m, 2H, H-3α + H-20), 5.4 (m, 1H, H-6). $^{13}C$ NMR: 122 (C-6), 140 (C-5), 139 and 166 (C-18 + C-18'), 170 (C=O). Mass spectrum (C.I./$NH_4^+$): m/z 371 $(MH)^+$. Treatment of **20** with potas-

sium carbonate in methanol afforded the already described[6] alcohol **22**, mp 138 to 140°C.

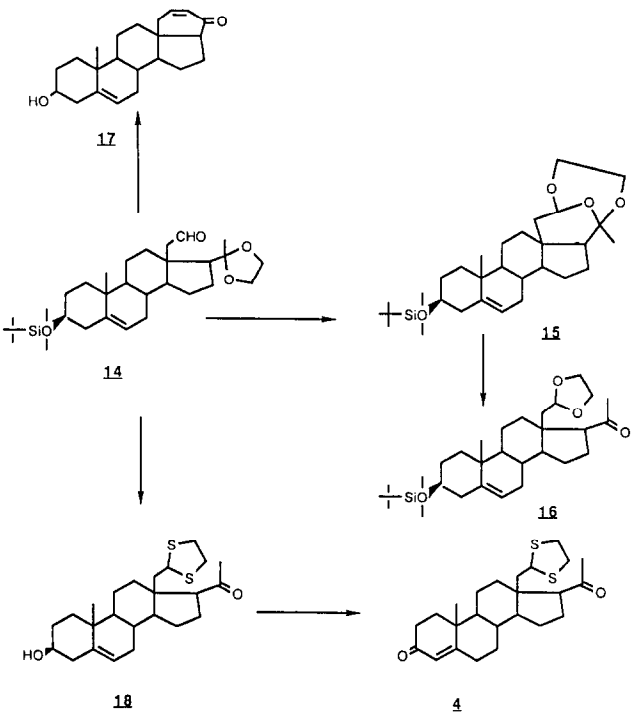
## Results and discussion

The synthetic strategy leading to 18-ethylene dithioprogesterone **3** is outlined in Scheme 3 and involves the hemiacetals **7a** and **7b** as key intermediates. According to literature precedents,[7,8] it was expected that these compounds, on treatment with 1,2-ethanedithiol, would easily yield the thioacetal **8** in the presence of Lewis acid catalysts such as $TiCl_4$ or $BF_3$-$Et_2O$. Subsequent oxidation of thioacetal **8** was anticipated to yield 20-ketone **3.**

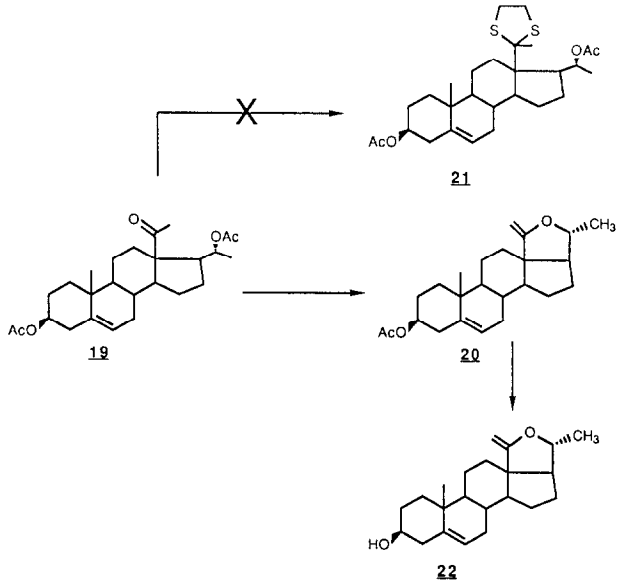
The hemiacetals **7a** and **7b** were prepared in two steps from the readily available lactone **5** (ref. 5) using established methods. However, when the derivative **7a** was treated with 1,2-ethanedithiol in the presence of $TiCl_4$ at 25° C, a mixture (1 : 1.7) of compounds **8** and **9** was obtained.

The structure of the thiol derivative **9** was assigned on the basis of its $^1H$ and $^{13}C$ NMR characteristics and its positive Ellman test,[9] and was confirmed by the reaction with methyl chloride, yielding the thioether **11.**

The $^1H$ NMR spectrum of thioacetal **8** showed a singlet at 4.95 ppm, rather downfield-shifted compared with other thioacetals, like **18** (Scheme 4). This led us to consider compound **13** as a possible alternative structure. It was, however, ruled out on the basis of additional selective decoupling experiments: after treatment of derivative **8** with $Ac_2O$-pyridine, the monoacetate **12** was isolated in 50% yield. The unreactive second hydroxyl group is unequivocally attached to C(20) since in $C_6D_6$, containing 4 Å molecular sieve, the hydroxyl proton couples with the C(20) proton which definitively rules out the alternative structure **13.**




**Scheme 4**




**Scheme 5**

Reaction of the lactol **7b** under the same conditions furnished the oxathioacetal **9** as the only product. This is another example of a known,[2] but still unexplained, long-range effect of the protecting group at C(3) on the reactions at the position 18. The pronounced tendency of the silyl derivative **7b** to form oxathioacetals instead of thioacetals is also exemplified by its reaction with ethanethiol leading exclusively to the thiolactol derivative **10.** It should be noted that the preferential formation of compound **9** in the presence of $TiCl_4$ is in contrast to the observation of Paquette and colleagues,[8] who reported that the conversion of oxathioacetals to thioacetals is readily accomplished under these conditions, due to the nucleophilicity of the sulfur and the tendency of titanium to bind to oxygen rather than sulfur.

The oxidation of alcohol **8** under different conditions (Swern, Oppenauer) failed to give the desired ketone **3.** In a similar way, oxidation of alcohol **12** to the corresponding ketone proceeded in very low yield. The low reactivity of the C(20) hydroxyl group in alcohols **8** and **12** may be attributed to steric factors.

We then focused our efforts on the preparation of the thioacetal **4** starting from the well-known aldehyde **14** (ref. 2) (Scheme 4). Thioacetalization according to Kamitori et al.[10] was unsuccessful due to the intramolecular transfer of the protecting group from C(20) to C(18'), which leads to acetal **16** via the derivative **15.** Since aldehydes are reported to be selectively protected in the presence of ketones using that method,

preparation of the ketoaldehyde corresponding to **14** was tried under mild conditions. However, the intramolecular aldol condensation favored the conversion to the conjugated ketone **17.**

The efficiency of the neighboring group participation between positions 18 and 20 is also revealed by the experiments represented in Scheme 5. During our attempts to prepare the thioketal **21** from ketone **19** (ref. 6) under Lewis acid catalysis, the cyclic enol ether **20** was the only product obtained. Its saponification leads to the corresponding alcohol **22,** already described by Baddeley et al.[6]

Finally, thioacetalization of aldehyde **14** was achieved with a catalytic amount of $BF_3$-$Et_2O$ at −10°C, yielding selectively the thioacetal **18** (Scheme 4). The 3-alcohol **18** was subjected to Oppenauer oxidation to give the desired progesterone analog **4.**

The biologic activity of the thioacetal **4** as an inhibitor of aldosterone biosynthesis has been studied. Compared with progesterone analogs bearing vinyl, ethynyl, and halogen substituents at C(18), this compound shows a much weaker activity.[11]

Work is in progress to synthesize more potent sulfur-containing derivatives.

## Acknowledgments

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