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A New Route to 19-Substituted Steroids from 19-Nor Steroids: Sigmatropic [3,3] and [2,3] Rearrangements Revisited

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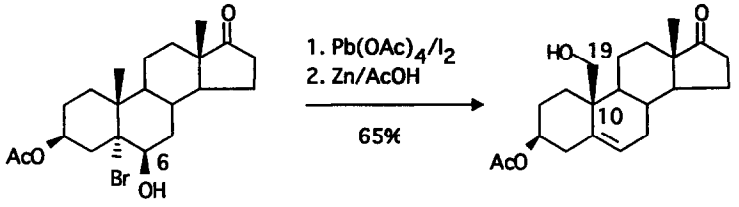
Abstract : *Sigmatropic [3,3] and [2,3] rearrangements of 11-substituted estradienedione derivatives gave rise to new 19-substituted androstenedione analogs .*

Introduction

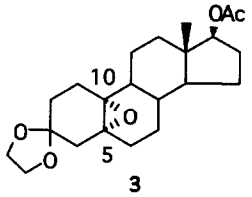
Up to now, two major routes have been used for the introduction of substituents on the 10- and/or 19-positions of the steroid nucleus. The first one, the well-known proximity functionalization of angular methyl groups[1] related to the 'Hofman-Löffler-Freytag' reaction,[2] allowed for the synthesis of the 19-hydroxyandrosterone derivative **2** from an hydroxyl group in the 6-position in 1963 (Scheme 1).[3] From there, elaboration at the hydroxyl function permitted the synthesis of various 19-substituted androstenedione analogs.[4] Nevertheless, the overall yields of these sequences are generally low, partly due to the difficulty of working at the hindered 19-neopentylic site.



1 2

Scheme 1

The second method involves the opening of 5,10-epoxides like **3**. A few heteroatoms like sulfur or nitrogen have been introduced directly in the 10-position using this method.[5a-c] These epoxides have also been opened with Grignard reagents but the yields were generally low and the reaction was complicated by the eliminative opening of the epoxide.[5d-g] Epoxides like **4**, bearing a double bond between the 9- and 11-positions, have been used extensively at Roussel[6a-g] and by others[6h-i] for the introduction of substituents in the 10-position. This route has provided a good entry into various alkyl, benzyl and allyl substituted androstenedione analogs. Nevertheless, the method did not prove applicable to the synthesis of aryl and vinyl groups or alkyl groups bearing heteroatom functionalities such as enolates.



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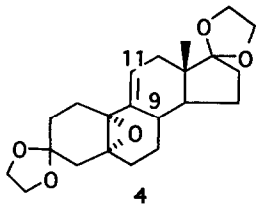

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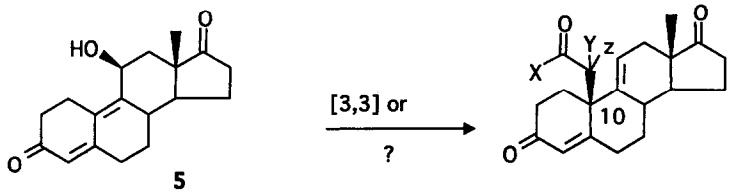
We speculated that the allylic alcohol function of **5**, an intermediate in the Roussel synthesis of Moxestrol[7] could allow sigmatropic [3,3] or [2,2] rearrangements to afford various 19-substituted androstenedione analogs (scheme 2).[8]

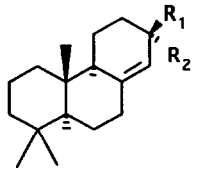


5

Scheme 2

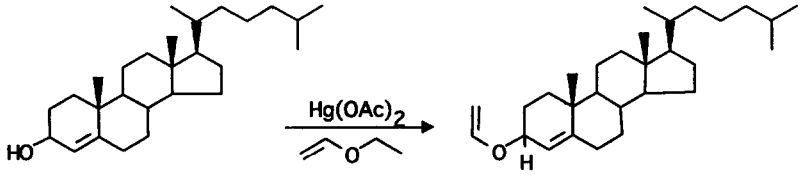
[3,3]-rearrangements : Claisen rearrangements

The net result of a Claisen type rearrangement in that position would be the introduction of an enolate equivalent on the 10-position of the steroid nucleus (scheme 2). The advantages would be numerous: (a) this route would be convergent and versatile, (b) the introduction of the 10-substituent would be 100% stereoselective and finally (c) there might be no need for the protection/deprotection steps included in all the other ways of access mentioned earlier. Yet potential problems might be overseen. Elimination reactions are common competitive reactions to the Claisen rearrangement and can become particularly acute when at least one olefin is contained in a ring [9]. Ireland and co-workers have synthesized the two isomeric allylic alcohols **6** and **7** and shown that the axial one **7** only gave dienic products in the conditions of vinyl ether formation.[10] This 11β alcohol **5** is already very prone to elimination or aromatization.[11]



$R_1 = H$ $R_2 = OH$ **6**
$R_1 = OH$ $R_2 = H$ **7**

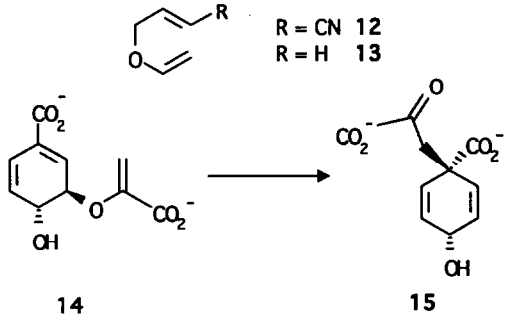
Furthermore, the alkenylation of this alcohol might be very challenging because of its axial orientation; for instance, Burgstahler[12] reported that the syntheses of the vinyl ethers **9** and **11** using the Watanabe conditions[13] only gave acceptable yield in the case of the equatorial starting alcohol **8** (scheme 3) . Moreover, the 1,3-diaxial interaction between the 11β-alcohol and the 13-methyl in **5** might complicate this alkenylation even more .



8 (β-OH) **9** (α-H) 65%
10 (α-OH) **11** (β-H) 5%

Scheme 3

Finally, the desired rearrangement would have to take place against the polarization of the dienone system. In fact, in a study of the electronic effects of substituents on the Claisen rearrangement, Carpenter and Burrows[14] have shown that the presence of a cyano group in the 6-position (like in **12**) slowed down the reaction by a factor 10 compared to the unsubstituted system **13**. To our knowledge such Claisen rearrangement where the allylic alcohol moiety is part of an enone or dienone system has not been yet described. There are however a few examples of such rearrangement where the allylic system is included in a conjugated ester, namely the famous chorismic acid **14** (and related analogues) rearrangement to the corresponding prephenic acid **15** (scheme 4).[15]

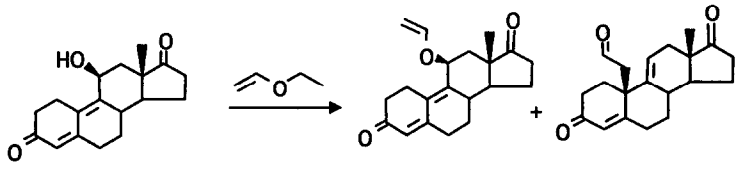


14 **15**

Scheme 4

Claisen rearrangements are not new in steroid chemistry (see e.g. ref 12) and there are in fact two precedents in the literature for their application to the functionalization of the 10-position of the

steroid nucleus.[16,17] A [3,3] Cope rearrangement between the 10- and 11-positions of the steroid nucleus has also been reported a few years ago.[18] Owing to the potential problems mentioned earlier, we first decided to study the formation of the vinyl ether using conditions similar to the ones described by Watanabe.[13] Thus when 11β-hydroxynordienedione **5** was treated with catalytic mercuric acetate (2.5mole%) in refluxing ethyl vinyl ether only 9% of the expected vinyl ether **16** was obtained along with 72% of starting material and to our surprise (and delight) 3% of expected rearranged product **17** (scheme 5). That this rearrangement took place at such a low temperature was quite unexpected. In fact, when the reaction was conducted at 80°C in a sealed vessel, the expected compound **17** became the major product. We found that the cleanest reactions were obtained with 25mole% of catalyst, giving rise to the expected aldehyde in one step, with a yield around 80%. This procedure is analogous to the one described by Dauben on octalin systems,[19] except their rearrangements required higher temperatures (200°C). Besides, they always observed the formation of dienic side-products resulting from elimination of the starting alcohol. Moreover, in a study of the influence of the temperature on the reaction they showed that at lower temperature (139°C) the rate dropped appreciably and that the ratio of product to side-product became close to 1. At 116°C, only traces of product were formed. In our case, not only did the reaction take place at a very low temperature, but it gave rise to essentially no elimination (or aromatization) products. One reason for such a smooth rearrangement might be the release of the 1,3-diaxial interaction between the 11β-substituent and the 13-methyl group. Furthermore, Dreiding models of the vinyl ether **16** show that a chair (or boat) transition state can form without changing the conformation and creating any steric constraint.

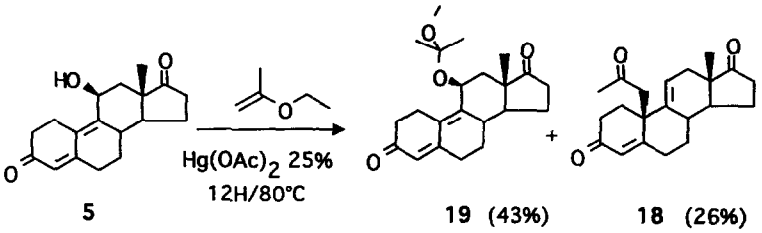


5 **16** **17**

$Hg(OAc)_2$ 2.5% 12h/reflux — 9% — 3% + 72% SM 77%

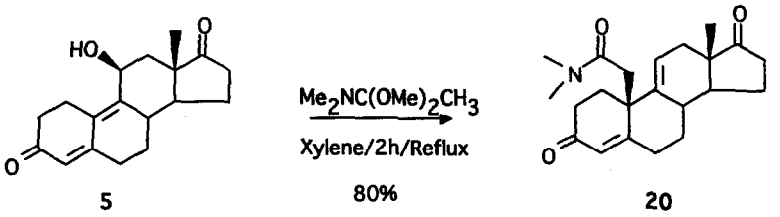
Scheme 5

These conditions applied with methyl propenyl ether however gave expected ketone **18** in only 26% yield along with 43% of the ketal **19** (scheme 6). In an attempt to carry out this type of transformation in two steps on octalin and hydrindenyl ring systems, Dauben[19] observed very low yields (<30%) on both sequences, vinyl ether formation and thermolysis. The acidic catalysis described by Saucy[20] did not give any of the expected ketones in these cases. We did not try to apply these conditions to our own allylic alcohol.



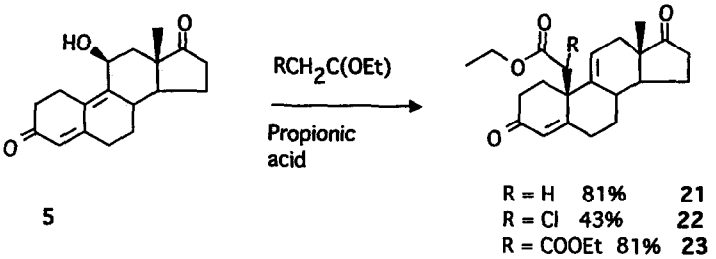
Scheme 6

When the dienone **5** was submitted to dimethylacetamide dimethylacetal[21] the expected 19-NN-dimethylaminocarboxamide androstenedione **20** was obtained with a good yield (scheme 7).

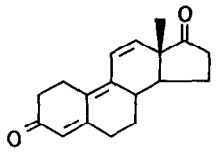


Scheme 7

Similarly, reaction with triethylorthoacetate[22] gave a good yield of the 19-ethoxycarbonylandrostenedione **21** (scheme 8).The reaction could also be extended to substituted orthoesters to provide original 19-disubstituted compounds:[23] Upon reaction with triethyl orthochloroacetate, 43% of the 19-chloro analog **22** was obtained, while reaction with tetraethyl orthomalonate afforded malonate **23** with 81% yield (scheme 8). Both compounds **22** and **23** were obtained as 1:1 mixtures of diastereoisomers in the 19-position. These conditions gave rise to a few more side reactions than the previous ones: **21** was accompanied by 2% of trienone **24** and 3% of aromatic material **25**. The latter was also obtained this time with a 43% yield during the synthesis of **22**. These side-reactions probably arise from the elevated temperatures required for the alcohol exchange reaction, not necessarily for the rearrangement.[9].



Scheme 8



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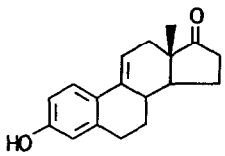
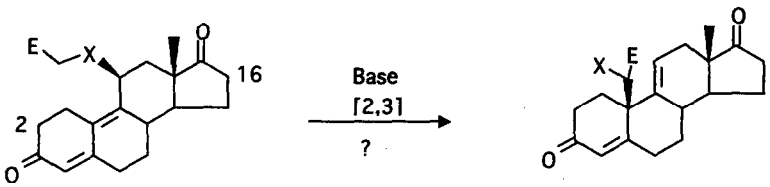


25

These new applications of Claisen rearrangements to the steroidal skeleton clearly open the way to a whole new array of androstenedione analogs bearing various chains in the 19-position.

[2,3]-rearrangements : Wittig rearrangements

With these results in hands we speculated that since the geometry seemed to be optimal for these rearrangements one might be able to carry out [2,3] sigmatropic rearrangements[24] of an ylid anion generated at the suitable site.This type of rearrangement would in principle lead to a one-carbon functionalization , the net result being the introduction of an alpha-heterosubstituted anion in the 10-position of the steroid nucleus (scheme 9).

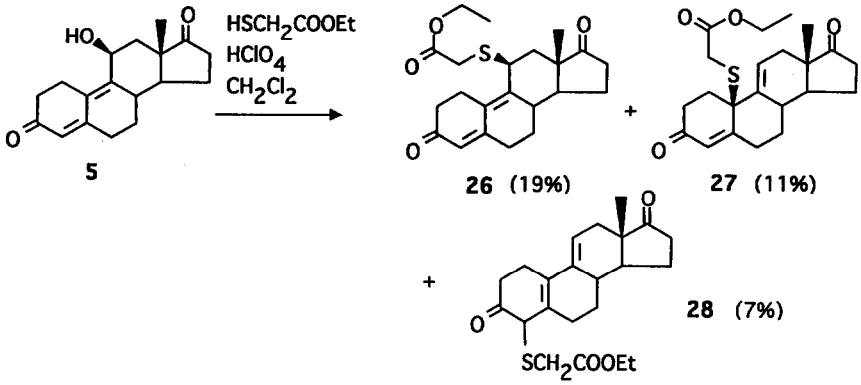


E = electron withdrawing group

Scheme 9

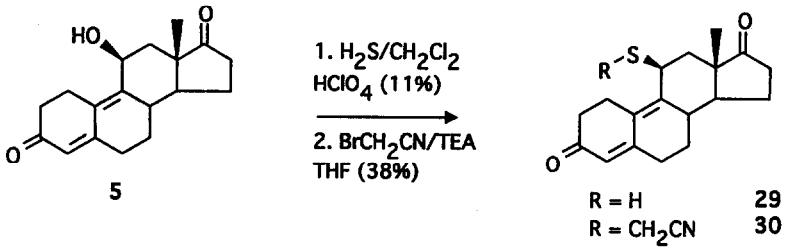
We chose to start the study with compounds where X is a sulfur atom. [2,3] sigmatropic rearrangements have been know to proceed well from α-thiocarbonyl compounds.[25] Furthermore, in the case of sulfur we should be able to avoid competition with the two other acidic positions (2 and 16) as well as competition between [2,3] and [3,3] rearrangements for the generated carbanion.[9]

The synthesis of 11β-((ethoxy)acetyl)thio)-estra-4,9(10)-diene-3,17-dione **26** proceded from 11β-hydroxynordienedione **5** by treatment with ethyl 2-mercaptoacetate in the presence of perchloric acid as described by Pierdet[26] in the case of methylmercaptan (scheme 10). In this case also the reaction was complicated by the formation of the two possible regioisomers **27** and **28**.



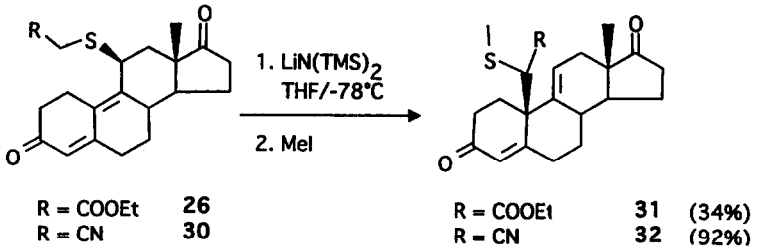
Scheme 10

An alternative route was developed for the synthesis of the analogous nitrile **30** since the starting mercaptoacetonitrile was not commercially available. 11β-mercaptoandrostenedione **29** was synthesized from 11β-hydroxyandrostenedione by reaction with hydrogen sulfide[26] and then reacted with bromoacetonitrile (scheme 11).



Scheme 11

To our pleasure, compounds **26** and **30** gave rise to the expected rearrangement when submitted to lithium hexamethyldisilylamide at low temperature and quenched with methyl iodide (scheme 12). The new compounds **31** and **32** were obtained as mixtures of diastereoisomers at the 19-position. In the case of **26**, 4% of compound **28** probably arising from a double rearrangement was also obtained. The rearrangement to **31** was not optimized. We have not yet explored all the possibilities of this interesting reaction but no doubt it is obviously of great potential towards the synthesis of new analogs of androstenedione.



Scheme 12

Conclusion

Sigmatropic rearrangements are amazing tools for organic chemists. This new method of functionalization of the 10- and 19-positions of the steroid nucleus allowed us to obtain new functionalized analogs of androstenedione, some of them would have required multi-steps procedures for their synthesis. Moreover, these sigmatropic [3,3] and [2,3] rearrangements where the allylic system is part of an enone or dienone are new. Both of these rearrangements, specially the anionic [2,3] rearrangement, go against the polarization of the enone system, which makes them conceptually even more interesting.

Experimental section

Tetrahydrofuran was distilled from sodium and benzophenone. $Hg(OAc)_2$, ethyl vinyl ether, NN-dimethylacetamide dimethyl acetal, triethyl orthoacetate, propionic acid, ethyl 2-mercaptoacetate and bromoacetonitrile were purchased from Aldrich and used without further purification. Triethyl orthochloroacetate and tetraethyl orthomalonate were synthesized respectively from chloroacetonitrile and ethyl cyanoacetate as described in the literature.[27] ^1H NMR spectra were recorded with Bruker AC300, AM250 and WH90 using $CDCl_3$ solution. Chemical shifts are reported in part per million (ppm) with tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are given in Hertz. The abbreviations s,d,t,q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. Mass spectra were recorded with a MATT 311 (ionization potential, 3kV; electron accelerating potential, 70 eV; ion source temperature, 200°C). High resolution mass spectra were recorded on a V6-ZABHFQ (70eV, resolution 7000, mass domain 50-500). Infrared spectra were recorded on a Nicolet 20SX or 5SX using chloroform solutions. Thin layer chromatography was performed with DC Plastiekfolien Kieselgel 60 F254 (E.Merck). UV, iodine, or sulfuric acid were used to visualize the developped plates. Flash chromatography[28] was performed with silicagel (Merck, 230-400 mesh grade).

11β-Ethenyloxy-4,9-diene-3,17-dione **16**

0.5g (1.75mmoles) of 11β-hydroxyestr-4,10-diene-3,17-dione **5**, 13.4mg (2.4mol%) of $Hg(OAc)_2$ and 5.2 ml of ethylvinylether were refluxed for 48 hours. After evaporation of the ethylvinylether, the crude product was flash chromatographed over silicagel with AcOEt:Cyclohexane 1:1 to afford a first fraction of 11β-vinyloxyestr-4,10-diene-3,17-dione **16** as a colorless oil (47.6mg, 9%) (Rf = 0.4). The next fraction (Rf = 0.28) was the aldehyde **17** (13.1mg, 2.4%). Finally, the last fraction was starting material (360mg, 72%). NMR of **16** (300MHz) 1.15 (18-Me), 4.2-4.35 (CH_2=), 6.25 (=CH), 5.10 (H11), 5.82 (H4); IR 3115, 1737, 1662, 1635, 1614, 1590 and 1406 cm^{-1}.

3,17-Dioxo androsta-4, 9(11)-diene-19-carboxaldehyde **17**

4.5g (15.7mmoles) of 11β-hydroxyestr-4,10-diene-3,17-dione **5**, 1.251g (25mol%) of $Hg(OAc)_2$ and 18 ml of ethylvinylether were introduced in a 100ml autoclave equipped with a magnetic stirrer. The mixture was heated for 12 hours at 80°C. It was then cooled to room temperature and partitioned between dichloromethane and aqueous saturated ammonium chloride (about 100 ml of each). The aqueous phase was extracted with dichloromethane (about 3 X 30ml). The organic extracts were combined, dried over MgSO4 and concentrated to afford 6.06g of crude product. Trituration with diethylether gave 3.79g of pure aldehyde as a white powder. An analytical sample was obtained upon two recrystallizations from ethanol followed by drying at 150°C under vacuum. Yield: 77%; Rf = 0.28, AcOEt:Hexane 1:1; MP = 214°C; NMR (250MHz) 0.85 (s, 18-Me), 5.7 (H11), 5.87 (H4), 9.66 (t, CHO); IR (CHCl3) 2740, 1736, 1721, 1671, 1632, 1615 and 1406 cm^{-1}; Elemental analysis: calc: 76.89%C, 7.74%H; found: 76.7%C, 8.0%H.

10-(2-Oxopropyl) estra-4,9(11)-diene-3,17-dione **18** and 11β-(2-methoxy isopropoxy) estra-4,9-diene-3,17-dione **19**

3g (10.49mmoles) of 11β-hydroxyestr-4,10-diene-3,17-dione **5**, 0.834g (25mol%) of $Hg(OAc)_2$ and 12 ml of 2-methoxypropene were introduced in a 100ml autoclave equipped with a magnetic stirrer. The mixture was heated for 12 hours at 80°C. It was then cooled to room temperature and partitioned between dichloromethane and aqueous saturated ammonium chloride (about 100 ml of each). The aqueous phase was extracted with dichloromethane (about 3 X 30ml). The organic extracts were combined, dried over $MgSO_4$ and concentrated. The crude mixture was flash chromatographed with AcOEt:hexane 1:1. The first fraction corresponded to **19** (Rf = 0.35) obtained as a white powder. One recrystallization from ether gave white crystals very sensitive to moisture (1.5g, 43%). The second fraction corresponded to **18** obtained as an oil (Rf = 0.21, 0.89g, 26%). An analytical sample of cubic colorless crystals was obtained upon recrystallization from ether/ethanol. **19**: MP = 165°C; NMR (250MHz) 1.22 (s, 18-Me), 1.29 and 1.41 (2s, $(Me)_2$), 3.07 (s, OMe), 4.98 (t,H11), 5.78 (H4); IR (CHCl3) 1736, 1660, 1617 and 1589 cm^{-1}; **18**: MP = 142-144°C; NMR (250MHz) 0.91 (s, 18-Me), 2.16 (s, COMe), 2.16 and 2.88 (2d, $COCH_2$, J = 15Hz), 5.66 (m,H11), 5.83 (bs, H4), IR (CHCl3) 3455, 1734, 1669, 1642 cm^{-1}; Elemental analysis: calc: 74.97%C, 8.39%H; found: 75%C, 8.4%H.

NN-Dimethyl -3,17-dioxo- androsta-4, 9(11)-diene-19-carboxamide **20**

500mg (1.75mmoles) of 11β-hydroxyestr-4,9-diene-3,17-dione **5**, 350 mg (1.5 eq) of dimethylacetamide dimethylacetal and 30 ml of xylene were introduced into a 25 ml flask equipped with a dean-stark, a reflux condenser, a magnetic stirrer and refluxed under inert atmosphere for 2 hours. The crude mixture was then concentrated to dryness at the rotary evaporator. The crude product was crystallized ifrom diisopropyl ether to afford to afford 495 mg of amide as a white powder (80%) (Rf = 0.3, AcOEt:MeOH 5:1). One recrystallization from AcOEt afforded an analytical sample as a white powder. MP = 158°C. NMR (300MHz) 0.89 (s, 18-Me), 2.72 (m, 19-

CH_2), 2.90 and 3.06 (2s, $CONMe_2$), 5.71 (H11), 5.87 (H4); IR 1735, 1665 and 1643 cm^{-1}; Elemental analysis: calc: 74.3%C, 8.2%H, 3.9%N; found: 74.1%C, 8.1%H, 3.7%N.

Ethyl 3,17-dioxo- androsta-4, 9(11)-diene-19-carboxylate **21**

500mg (1.75mmoles) of 11β-hydroxyestr-4,10-diene-3,17-dione **5**, 5ml of triethylorthoacetate and 6.4 mg (0.05 eq) of propionic acid were introduced into a 25 ml flask equipped with a Dean Stark, a reflux condenser, a magnetic stirrer and heated in an oil bath (temp = 137°C) under inert atmosphere for 4 hours. The reaction mixture was concentrated to dryness at the rotary evaporator equipped with a membrane vacuum pump. The crude mixture was flash chromatographed on silicagel with AcOEt:Cyclohexane 1:1. A first fraction (9.4mg, 2%) consisted in the trienone **24** (Rf = 0.51; IR 1741, 1652 and 1577 cm^{-1}; NMR (90MHz) 1.03(s,18-Me) 5.87(s,H4), 6.53 (m,H11 and H13). HRMS calcd for C_{18} H_{20} O_2 (M+) 268.1463, found 268.1475. The next fraction (8.4 mg,2%) was the aromatic compound **25** (Rf = 0.41; NMR 300 MHz) 0.94 (s,18Me), 4.84 (s, OH), 6.13 (m, H11), 6.57 (d, H4), J = 2.5 Hz), 6.65 (dd, H2, J = 2.5 and 8.5 Hz), 7.49 (d, H1, J = 8.5 Hz). IR 3595, 1734, 1625, 1609, 1576 and 1497 cm^{-1}. The last fraction (Rf = 0.33) was the expected product (503 mg, 81%) obtained as a white foam. NMR (250MHz) 0.94 (18-Me), 1.23 (t, $COOCH_2$ CH_3), 3.94 to 4.29 (m, $COOCH_2$), 5.61 (m, H11), 5.84 (bs, H4); IR 1732, 1662 and 1612 cm^{-1} HRMS calcd for C_{22} H_{28} O_4 (M+) 356.1987, found 356.1970.

Ethyl 3,17-dioxo -androsta-4, 9(11)-diene-19-chloro-19-carboxylate **22**

300mg (1.05mmoles) of 11β-hydroxyestr-4,9-diene-3,17-dione **5**, 3ml of triethylorthochloroacetate and 10µl (0.05 eq) of propionic acid were introduced into a 25 ml flask equipped with a Dean Stark, a reflux condenser, a magnetic stirrer and heated in an oil bath (temp = 137°C) under inert atmosphere for 2 hours. The reaction mixture was concentrated to about 1ml at the rotary evaporator equipped with a membrane vacuum pump. At that point a white precipitate formed. It was filtered and dried under vacuum to afford 117 mg of aromatic compound **25** as a white powder (43%) (Rf = 0.43, AcOEt:Cyclohexane 3:7). The filtrate was evaporated to dryness and flash chromatographed on silicagel with AcOEt:Cyclohexane 3:7. The major fraction was the expected compound obtained as a white foam (177 mg, 43%) (Rf = 0.2). NMR (300MHz) Mixture 5:1 of diastereomers 0.93 and 0.94 (18-Me), 1.24 and 1.28 (t, $COOCH_2CH_3$), 4.3 to 4.5 (m, $COOCH_2$), 4.89 and 4.99 (2s, CHCl), 5.78 (H11), 5.92 and 6.01 (H4); IR 1739, 1672, 1636 and 1616 cm^{-1}. HRMS calcd for C_{22} H_{27} O_4 Cl (M+) 390.1597, found 390.1579.

Diethyl 19-dioxo- androsta-4, 9(11)-diene-19-2-propane dioate **23**

300mg (1.05mmoles) of 11β-hydroxyestr-4,9-diene-3,17-dione **5**, 2ml of tetraethylorthomalonate and 10µl (0.05 eq) of propionic acid were introduced into a 25 ml flask equipped with a Dean Stark, a reflux condenser, a magnetic stirrer and heated in an oil bath (temp = 137°C) under inert atmosphere for 23 hours. A few drops of triethylamine were added to the reaction mixture which

was then concentrated to dryness at the rotary evaporator equipped with a membrane vacuum pump. The crude mixture was flash chromatographed on silicagel with AcOEt:Cyclohexane 3:7 The major fraction was the expected compound obtained as a colorless oil (360 mg, 81%) (Rf = 0.54, AcOEt:Cyclohexane 1:1). NMR (300 MHz) 0.87 (18-Me), 1.22 (m, $COOCH_2$ CH_3), 4.15 (m, $COOCH_2$), 4.26 (s, CHCOOEt), 5.74 (H11), 5.91 (s, H4); IR 1734, 1669, 1636 and 1620 cm^{-1}.

Ethyl [(3,17-dioxoandrostane-4,9-dien-11-yl) thio]-acetate **26**, ethyl [(3,17-dioxoandrostane-4,9(11)-dien-10-yl)thio]-acetate **27** and ethyl [(3,17-dioxoandrostane-55(10), 9(11)-dien-4-yl)-thio]-acetate **28**.

10 g (35 mmoles) of 11β-hydroxyestr-4,9-diene-3,17-dione **5** were placed in a 500 ml round bottom flask equipped with a magnetic stirrer and dissolved in 50 ml of dichloromethane. 15.3 g (140 mmoles, 4 eq) of ethyl mercaptoacetate were added all at once. The mixture was maintained on a very efficient stirring, then 0.4 ml of 50% perchloric acid were added. After 2 minutes of stirring at room temperature the mixture was treated with about 20 ml of a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted with dichloromethane (3 X 50 ml). The organic extracts were washed with water (2 X 40 ml), then dried over $MgSO_4$ and concentrated to dryness. The crude mixture was flash chromatographed on silicagel with AcOEt:Cyclohexane 2:8. The first fraction was 4-substituted compound **28** (1g, 7.3%) (Rf = 0.69, AcOEt:Cyclohexane 1:1). The next fraction consisted in the expected compound **26** obtained as a yellow foam (2.6g 19.2%) (Rf = 0.5, AcOEt:Cyclohexane 1:1). The last fraction was 10-substituted compound **27** (1.44 g, 10.7%) (Rf = 0.41 , AcOEt:Cyclohexane 1:1). **26**: NMR (300MHz) 1.28 (18-Me and OCH_2CH_3), 3.1 to 3.4 ($COCH_2S$), 4.1 to 4.25 (OCH_2), 4.59 (d, H11), 5.78 (H4); IR 1736, 1659, 1605 and 866 cm^{-1}; **27**: NMR (300MHz) 0.87(s, 18-Me), 1.28 (t, OCH_2CH_3), 2.97 and 3.14 (d, $COCH_2S$, J = 14.5Hz), 4.17 (q, OCH_2), 5.69 (H11), 5.92 (H4); IR 1673, 1627, 1612 and 1406 cm^{-1}; M+ = 388. **28**: NMR (300MHz) Mixture of stereoisomers in 4-position 0.88 and 0.91 (s, 18-Me), 1.30 (t, OCH_2CH_3), 3.23 and 3.45 (2d, $COCH_2S$), 3.59 and 3.65 (s, COCHS), 4.21 (q, OCH_2), 5.73 and 5.75 (H11); IR 1733 (b) cm^{-1}; M+ = 388.

11β--Mercapto estra-4,9-diene-3,17-dione **29**

Hydrogen sulfide was bubbled in dichloromethane (500ml) for 15 minutes. 20 g (70 mmoles) of 11β-hydroxyestr-4,10-diene-3,17-dione **5** was added all at once to this solution cooled to 0°c. The mixture was maintained on a very efficient stirring, then 0.8 ml of 50% perchloric acid were added. After 15 minutes of stirring at this temperature the mixture was treated with about 100 ml of a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted with dichloromethane . The organic extracts were washed with water then dried over $MgSO_4$ and concentrated to dryness. The TLC showed a complex mixture of products including trienone **24** and aromatic **25**. The crude mixture was flash chromatographed on silicagel with AcOEt:Cyclohexane 3:7. The more polar fraction corresponded to the expected compound and was obtained as a

yellow oil (Rf = 0.29, AcOEt:Cyclohexane 1:1) . NMR (300MHz) 1.31 (s, 18-Me), 4.70 (t, H11), 5.78 (s, H4); IR 1659, 1602 and 864 cm^{-1}; M+ 302.

[(3,17-Dioxoandrostane-4,9-dien-11-yl)thio] acetonitrile **30**

1g (3mmoles) of crude steroid **29** was dissolved in 20 ml of THF and placed in a flask equipped with a magnetic stirrer and under inert atmosphere. The temperature was brought to 0°C with an ice bath and 0.45 ml of triethylamine (3mmoles) were added. After 5 minutes stirring, 0.3 ml (4 mmoles) of bromoacetonitrile were added. After 1 hour of stirring at room temperature, the reaction was hydrolyzed by addition of a saturated solution of ammonium chloride. The mixture was extracted with ethylacetate, dried over $MgSO_4$ and concentrated to dryness. The crude mixture was flash chromatographed on silicagel with AcOEt:Hexane 3:7. The expected compound was obtained as a white foam (430 mg, 38%) (Rf = 0.39, AcOEt:Cyclohexane 1:1). NMR (300MHz) 1.25 (s, 18-Me), 3.28 (SCH_2), 4.64 (d, H11), 5.82 (s, H4), 1.35-3.03. IR 1739, 1661 and 1607 cm^{-1}. HRMS calcd for C_{20} H_{23} O_2 NS (M+) 341.1449, found 341.1452.

Ethyl 19-methylthio-3,17-dioxoandrostane-4,9(11)-diene-19-carboxylate **31**

350mg (1.05mmoles) of ethyl [(3,17-dioxoandrostane-4,9-dien-11-yl) thio]-acetate **26** were placed in a flame-dried flask equipped with a magnetic stirrer and under an atmosphere of argon and dissolved in 5 ml of dry THF. The temperature was lowered to -78°C with an acetone-dry ice bath and 0.51 ml (0.51mmole, 0.5 eq) of $LiN(TMS)_2$ (1M solution in THF) was added and the mixture stirred for 45 minutes at -78°C. Then 0.28 ml (4.5 mmoles, 5 eq) of methyl iodide were added and the cold bath removed so that the mixture slowly came back to room temperature. After 2 hours the reaction mixture was treated with an aqueous saturated ammonium chloride solution and the aqueous phase was extracted with dichloromethane (3 X 15 ml). The organic extracts were dried ($MgSO_4$) and concentrated to dryness. The crude mixture was flash chromatographed on silicagel with AcOEt:hexane 3:7 along with the crude of another run on 500mg of starting material to afford 3 fractions. The first one consisted of compound **28** (Rf = 0.69) (40 mg, 4.7%). The second fraction corresponded to the expected compound as a 2:1 mixture of diastereoisomers (NMR) (Rf = 0.47) (160 mg, 18.2%, 34% based on recovery). One recrystallization from diisopropylether afforded an analytical sample as a white solid. The last fraction consisted of starting material (400 mg, 47%). **31**: MP =118°C; NMR (300MHz) Mixture 3:2 of diastereomers 0.90 and 0.97 (18-Me), 1.24 and 1.26 (t, $COOCH_2CH_3$), 2.12 and 2.15 (CH_3S), 3.97 and 4.01 (s, SCHCO), 4.0 to 4.35 (m, $COOCH_2$), 5.70 and 5.75 (H11), 5.87 and 5.98 (d, H4); IR 1670 and 1619 cm^{-1}; Elemental analysis: calc: 68.7%C, 7.5%H, 7.97%S; found: 68.4%C, 7.7%H, 8.1%S.

19-Methylthio-3,17-dioxoandrostane-4,9(11)-diene-19-carbonitrile **32**

500 mg (1.5 mmoles) of [(3,17-dioxoandrostane-4,9-dien-11-yl)thio] acetonitrile **30** were placed in a flame-dried vessel equipped with a magnetic stirrer and under an atmosphere of argon and

dissolved in 15 ml of dry THF. The temperature was lowered to -78°C with an acetone-dry ice bath and 1.5 ml (1.5mmole, 1 eq) of LiN(TMS)$_2$ (1M solution in THF) was added and the mixture stirred for 45 minutes at -78°C. Then 0.45 ml (7 mmoles, 5 eq) of methyl iodide were added and the cold bath removed so that the mixture slowly came back to room temperature. After 1 hour the reaction mixture was treated with an aqueous saturated ammonium chloride solution and the aqueous phase was extracted with dichloromethane (3 X 20 ml). The organic extracts were dried ($MgSO_4$) and concentrated to dryness. The crude mixture was flash chromatographed on silicagel with AcOEt:hexane 2:8 to afford 490 mg (92%) of the expected compound as a white solid (Rf = 0.26, AcOEt:Cyclohexane 1:1) . MP = 222°C; NMR (300MHz) Mixture 1:1 of diastereomers 0.94 and 0.95 (18-Me), 2.35 and 2.36 (CH_3S), 4.12 and 4.29 (s, SCHCN), 5.80 and 5.94 (H11), 5.98 and 6.03(H4); IR 2236, 1737, 1676, 1637 and 1622 cm^{-1}; Elemental analysis: calc: 70.95%C, 7.0%H, 9.0%S, 3.9%N; found: 71.0%C, 7.1%H, 8.8%S, 3.9%N.

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