Pergamon

Tetrahedron Vol. 51, No. 6, pp. 1675-1684, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01034-X

A Short Total Synthesis of Estrone Derivatives: A Novel 1,3-Rearrangement of an Allylic Nitro Group.

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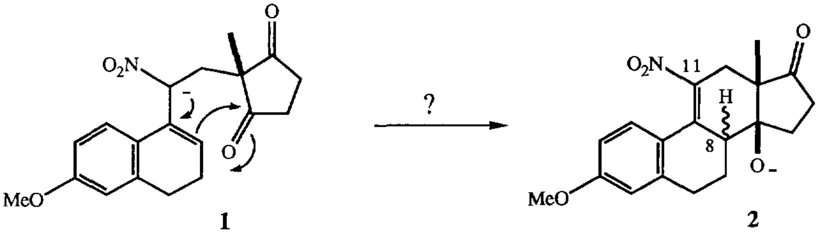
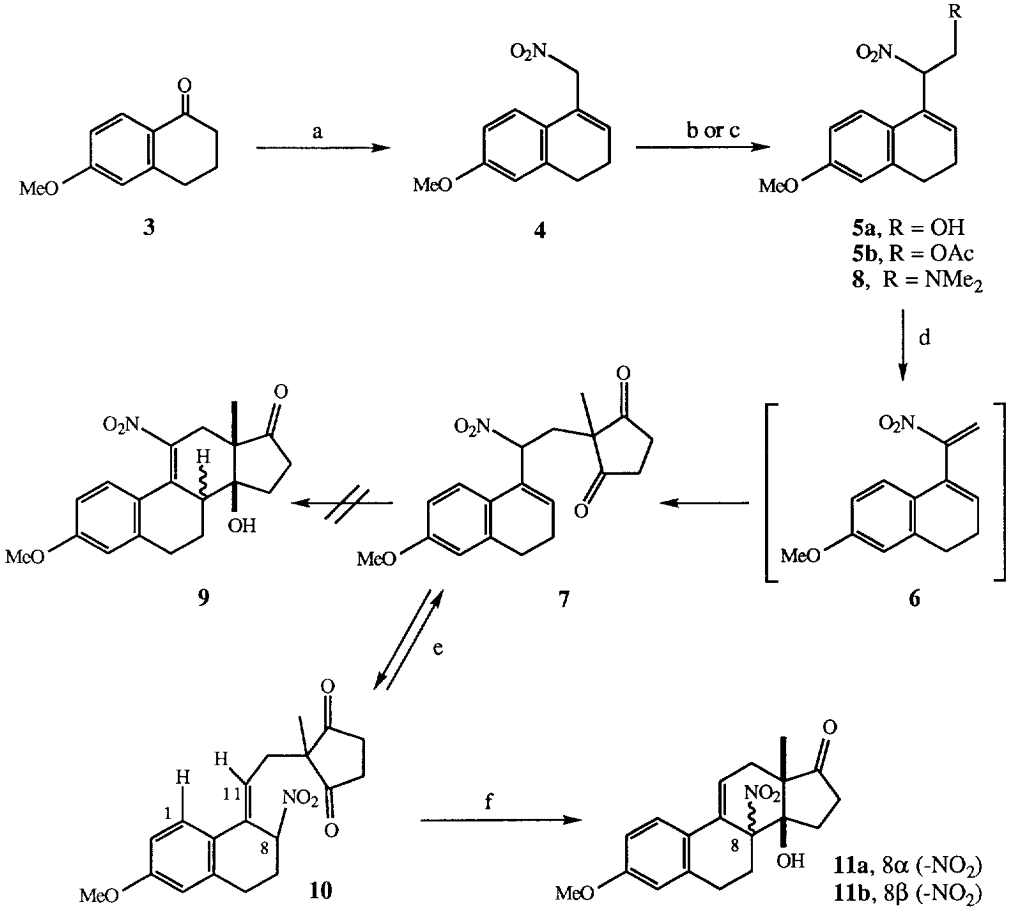
Abstract. Racemic 11β,14β-dihydroxyestrone has been preparared from 6-methoxytetralone in 5 steps involving a new acid catalysed 1,3-shift of an allylic nitro group.

The nitro group is arguably one of the most versatile and useful functional groups in organic synthesis. Not only does it lend itself easily to a large number of functional group interconversions but allows the creation of carbon carbon bonds under quite mild conditions, especially through the classical Michael and Henry reactions.[1] We have been interested in the chemistry of this group for some time and our studies in this area have led to several new reactions.[2] The special reactivity of allylic nitro compounds proved to be particularly useful in this respect. As an illustration of this work, we have applied our findings to an expedient synthesis of some estrone derivatives. In the course of this study, described recently in preliminary form,[3] we came across yet another facet of the chemistry of allylic nitro groups. This unexpected observation turned out in fact to be crucial for the success of our entreprise. We now wish to give a full account of our study.



Scheme 1

Our initial synthetic plan hinged upon the feasibility of a vinylogous intramolecular Henry reaction of nitronate **1** to give alkoxide **2**, as shown in scheme 1. This would introduce ring C with a nitro group in position 11 which could be then elaborated in a number of ways. Moreover, the control or modification of the stereochemistry at C-8 should be feasible through the extended nitronate form of the nitroolefin in **2**. The preparation of the desired precursor **7** corresponding to nitronate **1** is outlined in Scheme 1, and starts with the condensation of nitromethane with 6-methoxytetralone **3**. This ketone, like other aromatic ketones, is quite unreactive towards nitromethane in the presence of the usual catalysts for the Knovenagel reaction[4], but the desired condensation could be accomplished by using ethylenediamine or some of its congeners as catalyst. We had earlier developed this powerful procedure for the condensation of nitromethane with ketones in connection with the problem of constructing the corticosteroid side chain from 17-ketosteroids.[5] Thus heating tetralone **3** in nitromethane in the presence of a small amount of ethylenediamine gave nitro derivative **4** in 70% yield.



Reagents: a) Nitromethane, ethylenediamine (cat.), reflux; b) aq. CH_2O, Et_3N, THF-propan-2-ol; Ac_2O, DMAP (cat.), CH_2Cl_2 ; c) $(Me_2N)_2CH_2$, propan-2-ol; d) 2-methyl-1,3-cyclopentanedione, Et_3N, THF-propan-2-ol; e) AcOH, 55°C; f) DBU, MeOH.

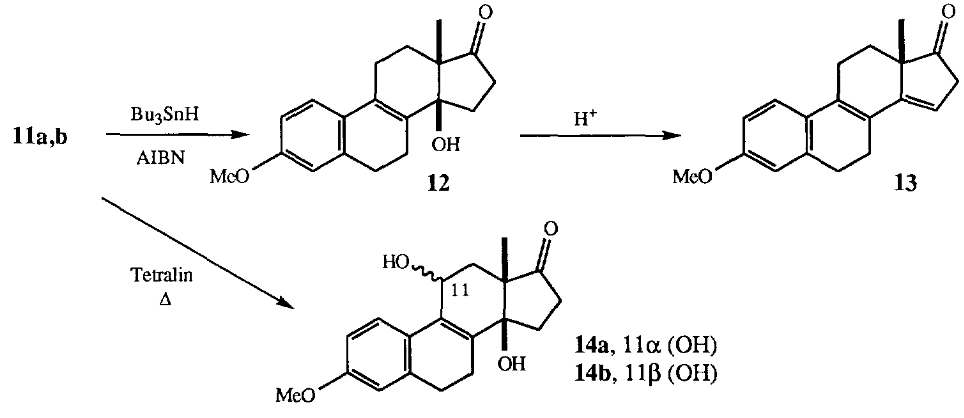
S

Scheme 2

Addition of the remaining carbons required for the synthesis of estrone could be achieved in two ways. Initially, we carried out a Henry reaction with aqueous formaldehyde using triethylamine as base followed by acetylation of the resulting nitroalcohol **5a** to give finally nitroacetate **5b** in 95% yield for the two steps. Reaction of the latter with 2-methyl-1,3-cyclopentanedione in the presence of triethylamine afforded the target substance **7** in good yield through Michael addition of the dione enolate to the intermediate nitrodiene **6** produced by base catalysed elimination of the acetate group. A simpler route to **7** consisted in stirring **4** with N,N,N',N'-tetramethyldiaminomethane to give the Mannich base **8** which, without purification, was heated with 2-methyl-1,3-cyclopentanedione in isopropanol to give **7** in 73% yield. Nitrodiene **6** is also an intermediate in this sequence.

With compound **7** in hand, we next examined the key intramolecular vinylogous Henry reaction to introduce ring C in compound **9**. Unfortunately, our attemps to accomplish this transformation under a variety of basic conditions failed utterly. In most cases, the main reaction was a retro Michael to give back nitrodiene **6**. In an ancillary study, we were even unable to perform a similar reaction on simpler allylic nitroketones even where a retro Michael was not so favoured. It is possible that the electronic density at the γ-terminus in nitronate **1** is insufficient to induce addition on the ketone group. These results are nevertheless not completely clear at the moment and further, more extensive, studies are necessary. The failure of the base induced cyclisation made us look into the feasibility of an acid catalysed equivalent. This again was not successful but we noticed that heating **7** in acetic or, as we later found, simply allowing a solution in unstabilised chloroform to stand at room temperature for some time, resulted in the clean formation of a new compound (77%; the remainder being starting material **7**) which had spectroscopic properties very similar to those of the staring material. This substance turned out unexpectedly to be isomer **10**, where the nitro group had undergone a formal 1,3-shift (see below for a mechanistic discussion).

The structure determination rested heavily on two-dimensional NMR experiments. In particular, a NOESY experiment showed a main correlation between the hydrogen on C-1 (7.42 ppm) and a hydrogen absorbing at low field (6.03 ppm) which can only be on C-11 in view of their proximity in space. Moreover, a heteronuclear shift correlation was established between the latter hydrogen (at 6.03 ppm) and a carbon resonating at 123.2 ppm (i.e. an olefinic carbon) but not with that resonating at 80.2 ppm ($C-NO_2$ type), which correlated with another hydrogen resonating at (5.76 ppm). Clearly, an olefinc bond involving C-11 was created, most probably as in structure **10**. This was confirmed by the following chemical transformations.

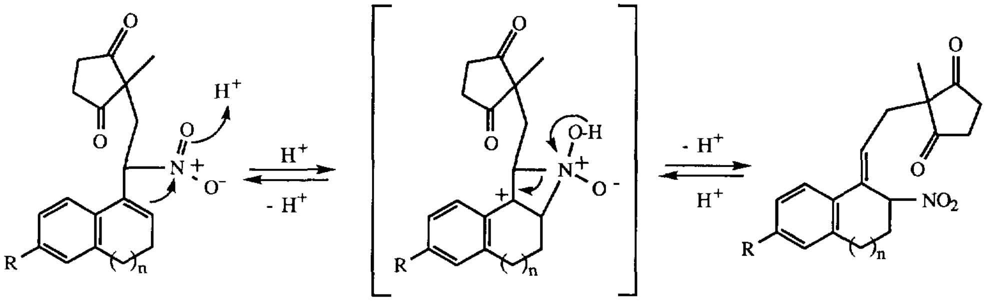


Scheme 3

Unlike its isomer **7**, allylic nitro derivative **10** underwent a smooth intramolecular Henry addition upon exposure to a catalytic quantity of DBU. When the reaction was performed in dichloromethane as solvent, a 1:1.2 mixture (by NMR) of **11a** and **11b** was produced. In methanol, however, a solid crystallized out which consisted of a 1:6 mixture of the same compounds (89%). The major isomer **11b** is therefore less soluble in methanol and, by precipitating, shifts the equilibrium between the two epimers. The reversibility of the Henry addition under these conditions was shown by quenching the reaction in methanol with acetic acid before crystallization set in. The ratio of **11a** : **11b** in this case is almost the same as that in dichloromethane (1:1.3). Further crystallization afforded the main isomer **11b** in pure form. The synthesis of a highly functionalised derivative of methyl estrone[6] has thus been accomplished in practically 4 steps and in high overall yield.

For correlation purposes, the 1: 6 mixture of **11a** : **11b** was denitrated with tributylstannane[7] to give the fragile, but known[8] steroid **12** in 59% yield, which on standing in unstabilised chlorofom gave a quantitative yield of diene **13** (Scheme 3). This latter compound had previously been converted into estrone itself.[9]

A more interesting transformation is the thermal sigmatropic rearrangement of the allylic nitro group which ultimately leads to an allylic alcohol, a reaction we recently discovered[2a]. Thus, heating **11a** and **11b** (separately) to 160°C in tetralin produced the corresponding allylic alcohols **14a** and **14b** in 67 and 63% yield respectively. The latter substance, which possesses the important 11β-hydroxy group, had been prepared earlier by a somewhat lengthier route.[10] This rearrangement of the allylic nitro group is remarkable in that the stereochemical information in each of the isomers is retained because of the suprafacial nature of the process, and that the specially fragile 14-hydroxy group is not affected by the high reaction temperature.



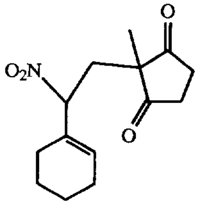
7, R = OMe ; n = 1
16, R = H ; n = 1
22, R = H ; n = 2

15a, R = OMe ; n = 1
15b, R = H ; n = 1
15c, R = H ; n = 2

9, R = OMe ; n = 1
17, R = H ; n = 1
23, R = H ; n = 2

Scheme 4

The conversion of **7** into **10** raises a number of interesting mechanistic questions which we examined briefly. 1,3-Migration of an allylic nitro group in simple systems had been reported previously by Burkhard and Brown[11a] and, later, by Hesse and Jaeger,[11b] who for example found that 3-nitro-2-methyl-1-butene could be reversibly transformed into its more stable isomer, 1-nitro-2-methyl-2-butene. Both groups presented clear evidence for a radical chain mechanism involving nitrogen dioxide. In our case, it was also easy to establish that the process was in fact an equilibrium: When a pure sample of compound **10** was exposed to warm acetic acid it reverted partially into its isomer **7**. The mechanism, in contrast, appears to be ionic in character. The reaction is induced by a weak acid (even silica turned out to be sufficiently acidic to catalyse this conversion) and inhibited by the presence of base such as triethylamine. A plausible pathway involving bridged cationic species **15a** is shown in scheme 4. Thus intermediate **15a** can collapse to give either of isomers **7** or **10**. The positive charge is stabilised through delocalisation into the aromatic ring with further stabilisation accruing from the presence of the methoxy group. This electron donating group is however not necessary for the reaction to occur. Derivative **16**, lacking this substituent, also underwent the 1,3-isomerisation under the same reaction conditions. The aromatic ring however is necessary since no such transposition was observed when the aromatic ring was absent, as for example in alicyclic compounds **18** and **20**. The latter substance, easily prepared from **19**, is an intermediate in an approach to the total synthesis of steroids that we are currently exploring.



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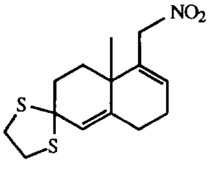

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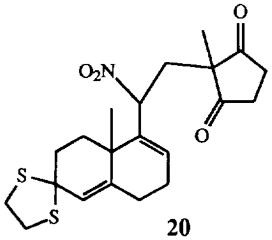

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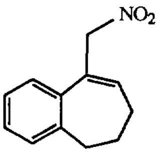

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Were it not for the results of the actual experiment, a superficial examination of structure **10** would seem to indicate that it is less stable than its endo-isomer **7**, since an endo double bond in cyclohexenes tends to be more stable than the corresponding exo isomer.[12] This can in fact be seen in compound **4** where the endo isomer is strongly dominant (a small amount, practically invisible by nmr, of the exo isomer is present which gives a yellowish tinge to samples of **4**). The driving force behind the shift in equilibrium towards the exo isomer is probably an unfavourable steric interaction between the side chain substituent and the aromatic hydrogen in position 1 (steroid numbering). This is presumably alleviated when the olefin shifts to the 9-11 position. Support for this hypothesis was obtained by examining the behaviour of the corresponding seven-membered ring analogue **22** made in the same way from compound **21**. We found that this derivative does not undergo the acid induced rearrangement, even though a similar bridged intermediate (i.e. **15c**) would enjoy the same stabilisation as for **16** (i.e. **15b**). When, in an additional confirming experiment, an equimolar mixture of **16** and **22** was heated gently in acetic acid, only the tetralone derivative **16** underwent the 1,3 isomerisation to give **17**. In the more flexible seven membered ring system, the substituents on carbon-11 can move away from the aromatic hydrogen thus avoid a peri interaction without need for shifting of the olefin which remains in the more stable endo position.

In summary, we have uncovered an interesting, albeit not general, 1,3-rearrangement which, apart from revealing another facet of the chemistry of allylic nitro groups, has allowed us to accomplish a very short (5 steps) synthesis of highly functionalised estrone derivatives.

Acknowledgements: We wish to thank Roussel-Uclaf for generous financial support to one of us (B.B.) and Dr. Jean Buendia and his colleagues for stimulating discussions.

Experimental Section

All reactions were performed under inert atmosphere (nitrogen or argon). Melting points were determined using a Reichert hot stage apparatus. ^1H and ^{13}C n.m.r. spectra are for deuteriochloroform solutions with tetramethylsilane as internal standard (δ ppm). The terms "odd" (o) and "even" (e) used in conjunction with ^{13}C chemical shifts correspond to the type of carbon in the structure, i.e. $R\text{-}CH_3$, $R_3C\text{-}H$ and R_2CH_2, R_4C respectively. I.R. spectra are of Nujol mulls unless otherwise stated. Mass spectra (electron impact) were recorded on MS 50 or VG ZAB spectrometers. MATREX 60 (35-70 μm) silica gel was used for column chromatography. Solvents and reagents were purified according to standard laboratory techniques.

Typical Procedure for Preparation of Allylic Nitro Derivatives

6-Methoxy-1-nitromethyl-3,4-dihydronaphthalene (4). A solution of 6-methoxytetralone (6g) in a mixture of nitromethane (30 ml), toluene (100 ml) and N,N-dimethylethylenediamine (1 ml) was refluxed for 72 hrs in a round bottomed flask fitted with a Dean Stark apparatus. After evaporation of the solvents under reduced pressure, the crude residue was purified by silica gel column chromatography (eluent dichloromethane / petroleum ether: 1 / 3), affording the title compound **4** (5.2 g, 70%). m.p.: 58-9°C (dichloromethane-pentane); IR (cm^{-1}): 1550; n.m.r. ^1H: 7.11 (d, 1H, J = 7.9 Hz); 6.71 (m, 2H); 6.15 (t, 1H, J = 4.5 Hz); 5.26 (s, 2H); 3.77 (s, 3H); 2.78 (t, 2H, J= 8.2 Hz); 2.38 (m, 2H); n.m.r. ^{13}C: 159.2; 137.9; 133.2; 127.5; 125.0; 123.5; 114.5; 111.2; 78.2; 55.2; 27.9; 23.2. (Calc. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.23%. Found: C, 65.90; H, 5.99; N, 6.23%).

The following compounds were prepared by this procedure:

8a-Methyl-1-nitromethyl-4,7,8,8a-tetrahydro-6(3H)-ethylenedithioketal naphthalene (19). Obtained in quantitative yield from 2,3,4,7,8,8a-hexahydro 8a-methyl 6-ethylenedithioketal 1-naphthalenone (4.00g; prepared from Wieland-Miescher ketone according to ref. 13), nitromethane 70 ml, and N,N-dimethylethylenediamine (0.5 ml) after an 18 hours reflux time; eluent: dichloromethane. It was used without further purification in the next step. IR (cm^{-1}): 2924; 1553; 1432; 1374; 733; n.m.r. ^1H: 5.96 (s br, 1H); 5.56 (s, 1H); 4.93 (d, 1H, J = 13.0 Hz); 4.83 (d, 1H, J = 13.0 Hz); 3.4-3.2 (m, 4H); 2.4-1.5 (m, 8H); 1.19 (s, 3H); n.m.r. ^{13}C: 142.0 e; 134.7 e; 134.0 o; 125.2 o; 77.7 e; 64.7 e; 40.2 e ; 39.4 e; 37.7 e; 37.4 e; 33.5 e; 28.3 e; 27.4 e; 24.6 o; m/z.: 297 ($M^{+\cdot}$); 269; 250 (M - HNO_2); 190; 189

9-Nitromethyl-6,7-dihydro-5H-benzocycloheptene (20). Compound **20** (2.05g ; 30%) was obtained from 1-benzosuberone (5.5 g), nitromethane (30 ml), N,N-dimethylethylenediamine (1 ml), and toluene (100 ml) following a 50 hours reflux period; eluent dichloromethane / petroleum ether: 1 / 3). It was used without further purification in the next step IR (cm^{-1}): 1553; n.m.r. ^1H: 7.3-7.2 (4H, m); 6.46 (1H, br t, J = 7.2 Hz); 5.28 (2H, s); 2.69-2.62 (2H, m); 2.24-2.13 (2H, m); 2.06-1.93 (2H, m); n.m.r. ^{13}C: 141.88; 137.76; 136.90; 131.88; 129.45; 127.93; 126.38; 125.53; 80.72; 34.94; 32.17; 25.14.

Preparation of seco-steroids **(7), (16), (18),** ***and*** **(22).**

3-Methoxy-11-nitro-8,14-secoestra-1,3,5(10), 8-tetraene-14,17-dione (7). 6-Methoxy-1-nitromethyl-3,4-dihydronaphthalene **4** (4.06 g) was dissolved in 2-propanol by warming gently. To this solution, tetramethyldiaminomethane (4 ml) was added at 20°C. Three hours latter the solvent and excess N,N,N'N'-tetramethyl diaminomethane were evaporated under reduced pressure. The crude **8** thus obtained was then taken-up in a mixture of THF (50 ml) and 2-propanol (50 ml), and 2-methyl-1,3-cyclopentanedione (4.3 g) was added with vigourous stirring. After 24 hrs at 20°C, the solvent was evaporated and the residue purified by silica gel column chromatography (eluent ether/ petroleum ether: 3/2), to give the title compound 7 (4.65 g, 73%) as an oil. IR (cm^{-1}): 1720; 1540; n.m.r. ^1H: 7.03 (d, 1H, J = 9.3 Hz); 6.71 (m, 2H); 6.21 (t, 1H, J = 4.7 Hz); 5.61 (dd, 1H, J = 9.6 Hz, J' = 4.8 Hz); 3.77 (s, 3H, OMe); 2.93-2.63 (7H, m); 2.37-2.26 (3H, m); 1.19 (s, 3H); n.m.r. ^{13}C: 214.9 ; 213.8; 159.1; 138.2; 130.8; 128.9; 124.7; 123.0; 114.5; 111.1; 82.3 ; 55.2 (OMe); 54.5; 35.0; 34.6; 34.3; 27.8; 22.9; 22.6; m/z: 343 ($M^{\cdot+}$); 314; 297 (M - NO_2); 237; 185.

11-Nitro-8,14-secoestra-1,3,5(10),8-tetraene-14,17-dione (16). This compound was prepared in the same way (5 hrs at 20°C) from 1-nitromethyl-3,4-dihydro-naphthalene[5d] (1.00g) and N,N,N',N'-tetramethyl diaminomethane (1 ml) in 2-propanol (17 ml). After evaporation of the solvents, THF (12 ml), 2-propanol (12 ml) were added followed by 2-methyl-1,3-cyclopentane dione (1.05 g). the solution was kept for 5 hrs.at 20°C, and the solvents removed under reduced pressure The residue was recrystallized from methanol containing 1% triethylamine to yield light brown crystals (0.933 g, 56%). m.p.= 81°C; IR (cm^{-1}): 1723, 1551; n.m.r. ^{1}H: 7.26 -7.07 (4H); 6.38 (1H, dd, J = 4.7 Hz, J' = 4.7 Hz); 5.66 (1H, dd, J = 10 Hz, J' = 4.62 Hz); 2.98-2.64 (7H); 2.41-2.27 (3H); 1.22 (3H, s); n.m.r. ^{13}C (o):131.83; 131.68; 131.36; 128.23; 127.94; 126.90; 121.80 , (e): 214.96; 213.65; 136.32. (Calc. for $C_{18}H_{16}O_4N$: C, 68.90; H, 6.11; N, 4.49%. Found: C, 68.72; H, 6.35; N, 4.49%).

11-Nitro-des-A-8,14-secoestra-8-ene-14,17-dione (18). This compound was prepared in the same way (1 hr at 20°C) from 1-nitromethyl-1-cyclohexene[2c] (5,00g) ; 2-propanol (60 ml); N,N,N',N'-tetramethyl diaminomethane (6 ml). After evaporation of the solvents, THF (50 ml), 2-propanol (50 ml) were added followed by 2-methyl-1,3-cyclopentane dione (6.00 g). the solution was heated to reflux for 3 hrs and the solvents removed under reduced pressure The residue was purified by silica gel chromatography (eluent: dichloromethane), to give the title compound **18** (5.6 g, 60%). m.p.: 79-80°C (dichloromethane-pentane); IR (cm^{-1}): 1730; 1560; n.m.r. ^{1}H: 5.78 (s br, 1H); 4.90 (t, 1H, J= 7.6 Hz); 3.0-2.4 (m); 2.2-1.5 (m); 1.19 (s, 3H); n.m.r. ^{13}C: 214.7; 213.7; 132.1; 131.9; 88.3; 53.9; 34.2; 33.7; 25.1; 23.1; 22.3; 21.6; 21.1. (Calc. for $C_{14}H_{19}NO_4$: C, 63.78; H, 7.22; N, 5.28%. Found: C, 63.40; H, 7.05; N, 5.38%).

11-Nitro-B-homo-8,14-secoestra-1,3,5(10),8-tetraene-14,17-dione (22). This compound was prepared in the same way (15 hrs at 20°C) from 9-Nitromethyl-6,7-dihydro-5H-benzocycloheptene **20** (1g); 2-propanol (12 ml); N,N,N',N'-tetramethyl diaminomethane (1 ml). After evaporation of the solvents, THF (12.5 ml) and 2-propanol (12.5 ml) were added followed by 2-methyl-1,3-cyclopentane dione (1.14 g) and the mixture kept for 24 hrs.at 20°C.The solvents were removed under reduced pressure and the residue recrystallized from methanol. affording **22** as white crystals (0.964 g, 60%). m.p. = 139-140°C; IR (cm^{-1}): 1720, 1548; n.m.r. ^{1}H: 7.27-7.17 (4H, m); 6.46 (1H, dd, J = 7.4 Hz, J' = 7.4 Hz); 5.65 (1H, dd, J = 11.3 Hz, J' = 3.2 Hz); 2.96-1.67 (6H, m); 1.20 (3H, s); n.m.r. ^{13}C:.215.63; 213.34; 141.87; 137.19; 134.69; 133.42; 129.38; 128.08; 125.90; 85.59; 55.00; 35.11; 34.96; 34.75; 34.39; 31.93; 24.65; 22.75. (Calc. for $C_{19}H_{24}O_4N$: C, 69.71; H, 6.47; N, 4.28%. Found: C, 69.51; H, 6.46; N, 4.43%).

11-Nitro-3-ethylenedithioketal 8,14-secoandrosta-4,8-diene-14,17-dione (21). a) To a solution of 8a-Methyl 1-nitromethyl 4,7,8,8a-tetrahydro 6(3H)-ethylenedithioketal naphthalene **19** (3.9 g) in a mixture of THF/2-propanol (60 ml, 5:1), were successively added a 40% aqueous solution of formaldehyde (6 ml) and triethylamine (0.5 ml). After 3hrs at 20°C, the solvent was concentrated by evaporation under reduced pressure. The reaction mixture was then poured into an aqueous solution of citric acid and extracted with ether. The usual work-up gave a residue which was taken-up in dichloromethane (30 ml). Acetic anhydride (10 ml) and 4,4'-dimethylaminopyridine (100 mg) were added to this solution. After 3hrs at room temperature, excess acetic anhydride was destroyed by addition of methanol. The reaction mixture was poured into water and extracted with dichloromethane. The crude residue was purified by silica gel chromatography (eluent ether/petroleum ether/dichloromethane: 1/3/1) affording 8a-methyl 1-(2'-acetoxy 1'-nitroethyl) 4,7,8,8a-tetrahydro 6(3H)-ethylenedithioketal naphthalene as a 1/1 mixture of diastereoisomers which was used as such in the next step; (3.88 g, 80%); IR (cm^{-1}): 1746; 1560; 1431; 1367; 1224; 1122; 1046; n.m.r. ^{1}H: 6.15 (m, 1H); 5.58 (s, 1H); 5.20 (dd, 1H, J = 10.9 Hz, J' = 3 Hz); 4.57 (dd, 1H, J = 12.5 Hz, J' = 3 Hz); 4.30 (m, 1H); 3.45-3.2 (m, 4H); 2.5-1.5 (m); 2.07 (s, 3H); 1.34 and 1.20 (s, 3H, 50%); n.m.r. ^{13}C: 170.3 e; 141.7 e; 141.3 e; 136.4 e; 129.3 o; 128.5 o; 126.1 o; 125.9 o; 83.4 o; 83.0 o; 65.3 e; 64.7 e; 64.6 e; 40.4 e; 39.5 e; 38.1 e; 38.0 e; 37.7 e; 33.8 e; 33.6 e; 28.6 e; 28.4 e; 27.4 e; 27.3 e; 24.4 o; 24.3 o; 20.6 o.

b) A solution of the above nitroacetate (3.38 g) in THF (30 ml) was added to a solution of 2-methyl-1,3-cyclopentanedione (2.9 g) and triethylamine (2.4 ml) in 2-propanol (20 ml). The reaction mixture was heated under refluxed for 150 mn. The solvents were then removed by evaporation under reduced pressure, and the crude residue purified by silica gel chromatography (eluent ether/petroleum ether/dichloromethane: 1/2/1) yielding the title compound **21** (2.4 g, 62%) as slightly yellowish crystals. m.p.: 182-198 °C (dec.; petroleum ether/dichloromethane); IR (cm^{-1}): 2925; 1722; 1549; 1421; 1265; 741; n.m.r. ^{1}H: 6.13 (m, 1H);

5.55 (s br, 1H); 5.12 (t br, 1H, J = 12.2 Hz); 3.5-3.2 (m, 4H); 3.0-2.7 (m, 4H); 2.5-1.2 (m); 1.20 and 1.17 (s, 6H); n.m.r. ^{13}C: 215.4 e; 215.2 e; 213.4 e; 213.0 e; 142.5 e; 141.8 e; 139.4 e; 139.2 e; 130.2 o; 129.2 o; 125.8 o; 125.6 o; 80.9 o; 65.0 e; 64.8 e; 54.7 e; 40.4 e; 39.6 e; 38.6 e; 38.1 e; 37.9 e; 34.8 e; 34.5 e; 33.7 e; 33.2 e; 28.7 e; 27.5 e; 24.3 o; 22.4 o; 21.8 o; m/z: 421 ($M^{+\cdot}$); 378; 307; 201.

Typical Procedure for Acid-catalysed Rearrangement of Allylic Nitro Derivatives

3-Methoxy-8-nitro-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (10). A solution of the nitro derivative **7** (1.94 g) in acetic acid (5 ml) was heated at 55°C for 8 hrs. The solvent was then evaporated under reduced pressure and the residue thus obtained purified by silica gel column chromatography (eluent dichlomethane/petroleum ether 1/1) to yield the title compound **10** (1.49 g, 77%). m.p.: 118-120°C (methanol); IR (cm^{-1}): 1725; 1545; n.m.r. ^{1}H d: 7.42 (d, 1H, J = 8.7 Hz, 1); 6.74 (dd, 1H, J = 8.7 Hz, J' = 2.6 Hz, 2); 6.59 (d, 1H, J = 2.6 Hz, 4); 6.03 (dd, 1H, J = 9.6 Hz, J' = 7 Hz, 11); 5.76 (t, 1H, J = 4 Hz, 8); 3.78 (s, 3H, OMe); 2.88-2.56 (9H, m); 2.2-1.95 (1H, m); 1.21 (s, 3H, 18); n.m.r. ^{13}C: 216.1; 215.7; 159.4 (3); 136.4; 131.3; 125.7 (1); 124.9; 123.2 (11); 113.4 (2); 112.9 (4); 80.2 (8); 56.9 (13); 55.2 (OMe); 35.2; 32.9; 27.2; 24.9; 20.5 (18). (Calc. for $C_{19}H_{21}NO_5$:. C, 66.46; H, 6.16; O, 23.30%. Found C, 66.16; H, 5.97; O, 23.68%).

8-Nitro-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (17). The same procedure as above was applied to nitro derivative **16** (80 mg, acetic acid 2ml, 55°C for 8 hrs) and gave the title compound **17** (41 mg, 51 %). m.p. = 128-9°C (methanol); IR (cm^{-1}): 1718, 1543; n.m.r. ^{1}H: 7.46 (1H, m); 7.26-7.06 (3H); 6,17 (1H, dd, J = 9.8, J = 6.92); 5,80 (1H, dd, J = 4.09, J = 4.09); 2.94-2,.51 (9H, 2.22-2.09); n.m.r. ^{13}C: (o) 215.84; 215.47; 135.10; 131.96; 56.93; 20.67; (e) 132.41; 128.90; 128021; 126.84; 125.66; 124.40; 80.38; 35.22 (2C); 32.97; 27.41; 24.81. (Calc. for $C_{18}H_{19}O_4N$: C, 68.90; H, 6.11; N, 4.49%. Found: C, 68.34; H, 6.02; N, 4.48%)..

14β-Hydroxy-3-methoxy-8α-nitroestra-1,3,5(10),9(11)-tetraene-17-one (11a). DBU (10 mg) was added to a solution of allylic nitro derivative **10** (482 mg) in dichloromethane (25 ml). After completion of the reaction (15 mn. at 20°C as judged by T.L.C.), acetic acid (100 mg) was added. Evaporation of the solvents afforded a residue which was chromatographed on silica gel (eluent ether/petroleum ether 3/1). Tetracyclic compounds **11a** (200 mg, 42 %) and **11b** (105 mg, 22%) were thus isolated. The major product **11a** has the following characteristics: m.p.: 161-4°C (methanol); IR (cm^{-1}): 3360; 1740; 1535; n.m.r. ^{1}H (pyridine-d_5): 7.59 (d, 1H, J = 8.8 Hz, 1); 6.94 (dd, 1H, J = 8.8 Hz, J' = 2.5 Hz, 2); 6.68 (d, 1H, J = 2.5 Hz, 4); 6.14 (dd, 1H, J = 6.6 Hz, J' = 2.0 Hz, 11); 3.66 (s, 3H, OMe); 3.6-3.5 (m, 1H); 3.1-2.9 (m, 2H); 2.7-2.3 (m, 5H); 2.2-2.0 (m, 2H); 1.42 (s, 3H, 18); n.m.r. ^{13}C (pyridine-d_5): 216.5 (17); 159.8 (3); 133.5; 128.6; 126.9 (1); 122.1; 114.0 (2); 113.2 (4); 97.1 (8); 79.1 (14); 56.3 (13); 55.2 (OMe); 32.8; 31.9; 31.0; 30.2; 26.4; 14.5 (18). (Calc. for $C_{19}H_{21}NO_5$: C, 66.46, H, 6.16; N, 4.08%. Found: C, 66.54; H, 6.23; N, 4.15%).

14β-Hydroxy-3-methoxy-8β-nitroestra-1,3,5(10),9(11)-tetraene-17-one (11b). DBU (10 mg) was added to a solution of the nitro derivative **10** (640 mg) in methanol (20 ml). After 30 min. a precipate began to appear. The reaction mixture was then cooled to -20°C and maintained at this temperature for 3 hrs. The precipitate, which contained **11a** and **11b**, was then collected (570 mg, 89 %, ratio 1/6). Recrystallization from methanol/dichloromethane gave pure **11b**. m.p.: 137-9°C; IR (cm^{-1}): 3460; 1740; 1540; n.m.r. ^{1}H (pyridine-d_5): 7.69 (d, 1H, J = 8.8 Hz, H1); 6.94 (dd, 1H, J = 8.8 Hz, J' = 2.7 Hz, H2); 6.67 (d, 1H, J = 2.7 Hz, H4); 6.44 (dd, 1H, J = 4.9 Hz, J' = 3.2 Hz, H11); 3.66 (s, 3H, OMe); 3.4-3.2 (m, 1H, H15); 3.0-2.8 (m, 2H, H16); 2.7-2.5 (m, 2H, H6); 2.5-2.2 (m, 2H, H12, and 1H, H7); 2.2-2.0 (m, 2H, H15 and H7); 1.59 (s, 3H, Me18); n.m.r. ^{13}C (pyridine-d_5): 217.3 (C17); 159.8 (C3); 135.0; 130.8; 127.0 (C1); 126.0; 122.6 (C11); 114.1 (C2); 113.5 (C4); 93.2 (C8); 80.0 (C14); 55.2 (OMe); 51.9 (C13); 33.7 (C12); 32.4 (C6); 31.5 (C7); 28.4 (C15); 26.0 (C16); 14.6 (C18); m/z: 343 ($M^{\cdot+}$); 312; 296 (M - HNO_2); 278; 250; 240; 184. (Calc. for $C_{19}H_{21}NO_5$: C 66.46, H 6.16, O 23.30%. Found: C 66.05, H 6.25, O 23.78%).

11α,14β-Dihydroxy-3-methoxyestra-1,3,5(10),8(9)-tetraene-17-one (14a). A solution of nitro derivative **11a** (180 mg) in tetraline (4 ml) was heated at 160°C for 20 min. The crude reaction mixture was chromatographed over silica gel (eluent ether), yielding the title compound **14a** (110 mg, 67%). m.p.: 175-200°C (acetone, dec.); IR (cm^{-1}): 3400; 1710; n.m.r. ^{1}H (DMSO-d$_6$): 7.32 (d, 1H, J = 9.4 Hz, H-1); 6.71 (m, 2H, H-2 and H-4); 4.83 (s, 1H); 4.62 (d, 1H, J = 5.6 Hz); 4.55 (m, 1H, H-11); 3.73 (s, 3H); 2.8-1.6 (m); 0.91 (s, 3H); n.m.r. ^{13}C (pyridine-d$_5$): 220.5 (C-17); 159.1 (C-3); 138.8; 137.3; 132.1; 128.5; 127.0 (C-1); 113.5 (C-2); 111.9 (C-4); 79.2 (C-14); 63.4 (C-11); 55.3 (OMe); 52.5 (C-13); 39.8; 36.1; 33.0; 29.6; 24.1; 18.6 (C-16). (Calc. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05%. Found C, 72.38; H, 7.09%).

11β,14β-Dihydroxy-3-methoxyestra-1,3,5(10),8(9)-tetraene-17-one (14b). A solution of nitro derivative **11b** (155 mg) in tetraline (3 ml) was heated at 160°C for 15 min. The crude reaction mixture was chromatographed over silica gel (eluent ether), yielding the title compound **14b** (90 mg, 63%). m.p.: 195-210°C (acetone; dec.; lit.[10] :185-196°C); IR (cm^{-1}): 3250; 1730; n.m.r. ^{1}H (DMSO-d$_6$): 7.31 (d, 1H, J = 8.7 Hz, H1); 6.69 (m, 2H, H-2 and H-4); 5.07 (s, 1H, OH); 4.81 (d, 1H, J= 5.6 Hz, OH); 4.38 (m, 1H, H-11); 3.73 (s, 3H); 2.7-1.6 (m); 1.02 (s, 3H); n.m.r. ^{13}C (pyridine-d$_5$): 220.2 (C17); 159.0 (C-3); 139.0; 136.9; 134.0; 128.0; 127.6 (C-1); 113.4 (C2); 111.7 (C4); 79.0 (C14); 62.7 (C-11); 55.2 (OMe); 52.2 (C-13); 37.7; 35.1; 31.3; 29.3; 23.9; 19.2 (C-18); m/z: 314 ($M^{\cdot+}$); 296 ($M-H_2O$). (Calc. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05%. Found C, 72.32; H, 7.01%).

14β-Hydroxy-3-methoxyestra-1,3,5(10),8(9)-tetraene-17-one (12). Tributyltin hydride (0.3 ml) and AIBN (5 mg) were added to a suspension of compounds **11a** and **11b** (55 mg, 6:1) in toluene (5 ml). The reaction mixture was then heated under reflux for 2 hrs. The solvent was removed by evaporation under reduced pressure and the crude residue purified by silica gel chromatography (eluent ether/petroleum ether 2/3), yielding the title compound **12** [8] (28 mg, 59%); n.m.r. ^{1}H: 7.12 (d, 1H, J = 9.0 Hz, H1); 6.72 (m, 2H, H2 and H4); 3.80 (s, 3H, OMe); 2.75 (t, 2H, J = 8.1 Hz); 2.5-1.4 (m, 11H); 1.10 (s, 3H); n.m.r. ^{13}C: 220.7 (C17); 158.8 (C3); 137.8; 132.7; 130.4; 128.6; 124.2 (C1); 113.4 (C2); 111.2 (C4); 79.6 (C14); 55.4 (OMe); 52.3 (C13); 35.0; 31.1; 29.3; 27.3; 22.9; 22.5; 17.3 (18).

3-Methoxyestra-1,3,5(10),8(9),14(15)-pentaene-17-one (13). Compound **12** underwent dehydration simply by dissolution in unstabilised deuterated chloroform. After 72 hrs at 20°C, **13** was obtained quantitatively. m.p.: 111-3°C (petroleum ether; lit.[8] m.p.: 111-2°C); IR (cm^{-1}): 1735; n.m.r. ^{1}H: 7.25 (d, 1H, J = 9.1 Hz, H1); 6.75 (m, 2H, H2 and H4); 5.87 (s br, 1H, H15); 3.81 (s, 3H, OMe); 3.4-1.5 (m); 1.14 (s, 3H, Me18); n.m.r. ^{13}C: 220.2 (C17); 158.7 (C3); 147.0; 138.3; 129.9; 128.7; 125.4; 124.2; 114.8 (C15); 113.7 (C2); 111.2 (C4); 55.4 (OMe); 49.1; 42.0; 28.5; 27.4; 23.0; 22.8; 20.7 (C18).

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(*Received in Belgium* 7 *September* 1994)