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Optimization of Copper(I)-Catalyzed 1,6-Conjugate Addition of a Methyl Group to 17β-Acetoxy-4,6-estradien-3-one

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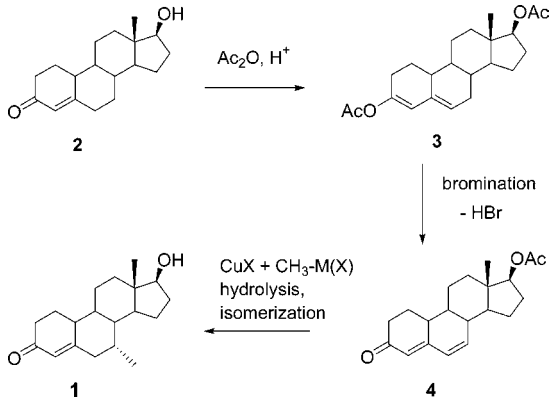
Abstract:

7α-Methyl-19-nortestosterone (1) was synthesized from 19-nortestosterone (2) via 17β-acetoxy-4,6-estradien-3-one (4). The critical parameters for the synthesis of compound (1) have been identified. An optimization procedure consisting of an iterative, two-stage reaction response surface analysis was carried out. As a result, the synthesis of the target compound (1) from the intermediate (4) was achieved under the newly determined conditions, in a repeatable manner. This afforded compound (1) in an yield of over 60%, essentially free from the 7β-Me isomer (6), under experimental conditions amenable for scale enhancement.

Introduction

Steroids attract considerable interest both as targets of commercial syntheses and as convenient substrates for the development of new synthetic methodologies.[1] A prominent position is occupied by 19-norsteroidal hormones[2] with their characteristic conformationally rigid molecular structure. Recently, hormone replacement therapeutic approaches not only are focused on the treatment of postmenopausal symptoms in women but also are increasingly used in the treatment of various disorders associated with aging in men. 7α-Methylnortestosterone (**1**) (7α-methyl-19-nortestosterone, 17β-hydroxy-7α-methyl-4-estren-3-one) is an interesting androgen, more potent than testosterone.[3−5] Importantly, in a number of clinical studies 7α-methylnortestosterone and its 17-esters have shown advantageous hormone replacement therapeutic properties, compared with testosterone and its esters. It has also been determined that 7α-methylnortestosterone is a potent inhibitor of spermatogenesis in mammals.[4−6] However, the synthesis of 7α-methylnortestosterone from commercially available steroids continues to be a complex task. Two synthetic routes stand out as viable options: (a) the synthesis from β-estradiol via 17β-hydroxy-3-methoxy-7α-methyl-1,3,5(10)-estratriene,[7,8] which can be achieved in seven or eight synthetic steps, and (b) the synthesis from 19-nortestosterone (**2**), which requires only three or four separate technological stages,[6,9−11] shown in Scheme 1.

Scheme 1



The reported methylating reagents required in route (b) for the conjugate addition reaction are either lithium dimethylcuprate[6,9] or methylmagnesium halides in the presence of copper salts.[10,11] The two-step synthesis of compound **4** from **2** (Scheme 1) is a modification of previously published procedures.[6] In our hands, compound **4** was obtained from **2** via 3,17β-diacetoxy-3,5-estradiene (**3**) in an isolated yield of 66%. Hence, route (b) was selected as a method of choice to obtain compound **1**. The selected synthetic pathway allowed us to operate outside the scope of the claims put forth in a recent patent application,[11b] where a 17β-trialkylsilyloxy group is documented to show a beneficial effect on the course of $Cu(OAc)_2$ catalyzed reactions of steroidal 19-nor-4,6-dien-3-ones with MeMgCl, carried out at −30 °C.

Initially, the reaction conditions making use of dimethylcuprate generated in situ from MeLi and CuI, in an Et_2O/

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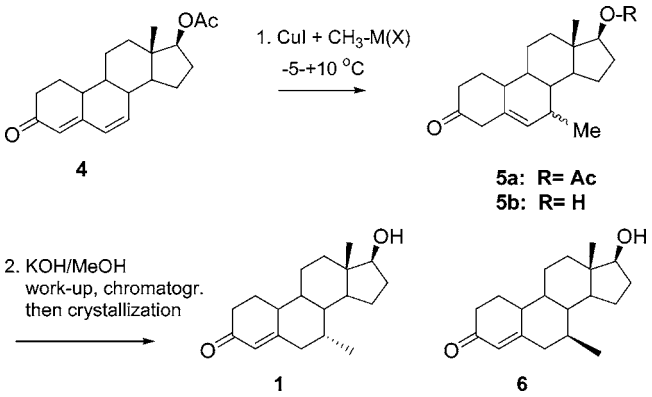
Scheme 2



THF mixture,[6,12] were selected. The molar ratio of dimethylcuprate to dienone (**4**) ranged from 2 to 4. The temperatures during the steroid-to-cuprate addition step were in the range of −40 °C to +10 °C. However, these initial attempts to synthesize 7α-methylnortestosterone (**1**) according to Scheme 2 were invariably associated with the formation of substantial amounts of the unwanted 7β-methyl isomer **6**, and the yield of the methylation reaction was low (30−58%). Moreover, the presence of diethyl ether not only caused our concerns related to safety, but it was also associated with the formation of a gummy precipitate of copper salts during workup, which led to clogging the filters. Such conditions are severe obstacles against further scale-up. Therefore, a more systematic study of the conjugate methylation stage (shown in Scheme 2) was undertaken.

Interestingly, the overall transformation depicted in Scheme 2 involves at least three distinct chemical reactions. A large excess of the dimethylcuprate is necessary to ensure satisfactory yields, but under these conditions a partial hydrolysis of the 17-acetoxy group was always observed. As a result, a mixture of **5a** and **5b** was initially isolated. However, a separation of **5a** and **5b** was not practical, and it was decided that the mixture could be used directly in the olefin isomerization step. Under the conditions of KOH in methanol, a deprotection of the 17-hydroxy group and isomerization to the olefin (**1**) were both easily effected.

Attempts towards increasing the yield and selectivity of this complex synthetic pathway were initiated. We chose to accommodate reaction conditions in a way predicted by theoretical analysis of the reaction response surface.

The choice of parameters, particularly solvents, used in this work was dictated by the intended scale-up of the optimized procedure. In this connection, only the solvents which are practical for a small plant scale were considered. From among such solvents, tetrahydrofuran, toluene, di-*n*-butyl ether, diethoxymethane (DEM) and their mixtures were preferable media. These solvents, routinely used in copper-mediated conjugate addition reactions are also discussed in the literature.[12]

After a careful consideration of the important aspects of a copper(I)-mediated conjugate addition,[12] the following process parameters were selected for a suitable variation and optimization: (a) the solvent system, (b) the concentration of the steroid solution, (c) the methylating agent, and (d) the molar ratio of the methylating reagent to the steroid. Earlier, we found that the temperature of the reaction mixture during the steroid addition step can be kept conveniently within the −5 to +10 °C range. Also, diethyl ether was eventually replaced with more convenient solvents such as diethoxymethane (DEM) and THF. The conjugate addition of reagents derived from methylmagnesium bromide[12] was also included in the scope of our investigation; however, the technical difficulties associated with troublesome workup procedures in this case prevented further application of this interesting synthetic variation.

Optimization

At the very beginning of our study it was not quite clear which ranges of the selected process variables should be taken into account. Therefore, the preliminary experiments were performed based on our laboratory experience. We considered two categorical (x_1, x_3) and two continuous (x_2, x_4) variables, each at three levels; see Table 1. Three reaction responses were monitored: the reaction yield (y_1), the 7α/7β isomer ratio (y_2), and the cumulative indicator $y_3 = (y_1{*}y_2)/100$. The latter response can reach large values in those regions where y_1 and y_2 attain simultaneously large values. This corresponds to the optimization of the vector-valued objective function (y_1, y_2) by means of the scalar-valued objective function $\log(y_3) = \log(y_1) + \log(y_2)$.

The sampling of x-variables space corresponded to a random walk rather than to a mathematically strict fractional factor design. The preliminary experiments presented in the Table 2 became a tradeoff among gradually increasing knowledge of the chemistry of the reaction, the workup economics, and the predictions based on theoretical analysis of reaction responses applied to the incoming data. After 10 experiments were completed, a first attempt to generalize results was performed. It is seen from Table 2 that high values of the cumulative indicator, $y_3 > 30$, correspond to those from experiment no. 8−10. This, in turn, suggests that one can use $x_1 = 1$ (corresponding to the 20% DEM + 80% THF mixed solvent) and low values of x_2 (low concentration of steroid after steroid addition, close to 0.1 M). Moreover, it appeared interesting to investigate a wider region of x_4 (ratio of methylating reagent to steroid). The present data were not sufficient, however, for definite selection of the x_3 levels (methylating reagent). Only vague inferences can be drawn based on the y_3 mean response corresponding to the nonempty cells of the (x_1, x_3)-contingency table. It appears that $x_1 = 1$ and $x_3 = 0$ would be the best choice. It is interesting to note that a similar conclusion ($x_1 = 1$, low x_2) can be drawn based on a crude theoretical model of the y_3-surface constructed using the multiple linear regression (MLR) method with the forward/backward and stepwise elimination of nonsignificant terms. The choice of the Me_2-CuLi methylating agent ($x_3 = 0$) was dictated mainly by our laboratory experience. The MeMgBr + CuI ($x_3 = 1$ or -1) agent has led to very substantial practical problems during the workup process, in each case studied. It was immediately

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Table 1. **Process variables and their levels used in the preliminary step of optimization**

variable	description	level [+1]	level [0]	level [-1]
x_1	solvent system	20% DEM[b] + 80% THF	60% Bu_2O + 20% DEM + 20% THF	60% Bu_2O + 20% DEM + 20% toluene
x_2	concentration of steroid[a] after steroid addition [M]	0.4	0.25	0.1
x_3	methylating reagent	MeMgBr + 1.0 equiv of CuI	Me_2CuLi ($x_3 = 0$)	MeMgBr + 0.2 equiv of CuI
x_4	ratio of methylating reagent to steroid	4.0:1	2.6:1	1.3:1

[a] Steroid: 17β-acetoxy-4,6-estradien-3-one (**4**). [b] DEM: diethoxymethane. Bu_2O: di-*n*-butyl ether.

Table 2. **Experimental data of the preliminary step of optimization[a]**

	variables				responses		
expmt no.	x_1	x_2	x_3	x_4	y_1	y_2	y_3
1	1	0.25	−1	4.0	35	50	17.5
2	−1	0.25	1	1.3	5	100	5.0
3	1	0.25	1	4.0	13	100	13.0
4	−1	0.40	1	1.3	35	50	17.5
5	1	0.40	1	4.0	22	20	4.4
6	0	0.10	0	2.6	58	9	5.2
7	1	0.25	−1	4.0	38	50	19.0
8	1	0.10	0	4.0	51	70	35.7
9	1	0.10	0	2.6	40	80	32.0
10	1	0.10	1	2.6	38	100	38.0

[a] See Table 1 for *x*-variables description; y_1 = yield of (**1**) [%]; y_2 = the ratio of 7α:7β isomers (**1/6**); $y_3 = 0.01*y_1*y_2$.

evident that this reagent was not appropriate for a large scale experiment because of the very difficult to handle precipitates formed. We attempted to change the workup in a few experiments (not included) by precipitating the solids with various solvents, but that added substantially to the workload and lowered the yields even further. The best yields obtained with the MeMgBr reagent were still lower than the yields obtained with MeLi ($x_3 = 0$).

Within the group of three experiments in Table 2 with $x_3 = 0$, a single experiment that gave poor selectivity corresponded to the solvent other than the selected DEM−THF mixture. This was a major reason for the selection of this particular DEM−THF solvent system for further study. One can hypothesize that the strong metal ion coordinating ability of ethereal solvents[12] (DEM−THF) is a probable cause of the superiority of this mixture over other solvents tested. Indeed, we feel that a much more detailed study would be necessary to explain this effect more precisely. The particular composition of this mixture is, again, a result of practical considerations (the commercial availability of MeLi in DEM at ca. 3.0 M concentration, acceptable commercial price of solvents).

After a critical analysis of the results, both theoretical and experimental, obtained in the course of the preliminary step we decided to use $x_1 = 1$, expand slightly the size of the x_2 interval, set $x_3 = 0$ (the reference Me_2CuLi reagent), and expand the size of the x_4 interval; see Table 3. The exploratory step was organized according to the D-optimal plan. The results are given in the Table 4. It is seen that by using the present reaction conditions one can obtain a ratio

Table 3. **Process variables and their levels used in the exploratory step of optimization[a]**

variable	description	level [+1]	level [0]	level [−1]
x_2	concentration of steroid after steroid addition [M]	0.15	0.10	0.05
x_4	ratio of methylating reagent to steroid	7.0	6.0	5.0

[a] x_1 (Solvent system): 20% DEM + 80% THF ($x_1 = 1$). x_3 (Methylating reagent): Me_2CuLi ($x_3 = 0$).

Table 4. **Experimental data of the exploratory step of optimization[a]**

	variables				responses	
experim. no.	x_1	x_2	x_3	x_4	y_1	y_2
11	1	0.05	0	7.0	40	100
12	1	0.15	0	5.0	25	100
13	1	0.05	0	5.0	26	100
14	1	0.10	0	7.0	52	100
15	1	0.15	0	6.0	48	100
16	1	0.15	0	7.0	27	100
17	1	0.10	0	6.0	60	100

[a] See Table 1 for *x*-variables description; y_1 = yield of (**1**) [%]; y_2 = the ratio of 7α/7β isomers: (**1/6**)

of 7α/7β isomers (**1/6**) close to 100. To localize the (x_2, x_4)-area corresponding to the highest yield y_1, an additional fitting procedure was applied with the use of the MLR theory and the following expression:

$$\text{logit}(y_1) = d_0 + \sum d_i u_i + \sum_{i \le j} b_{ij} u_i u_j = z_1 \qquad (1)$$

where *i,j* indexes equal to 2 or 4. The *u*-variables are linearly transformed *x*-variables according to the procedure described in the Computational Section. Two sets of *d*-parameters were obtained. In the first set all linear and quadratic terms in eq 1 were included, and in the second set only those terms remained that were significant at the $\alpha = 0.15$ significance level after a combined forward/backward elimination procedure within the MLR theory. Both sets of *d*-parameters are given in the Computational Section. The first set of *d*-parameters leads to the local maximum of about 63% on the y_1 response surface at (x_2, x_4) = (0.09, 6.1) and the second set to the local maximum (also 63%) at (x_2, x_4) = (0.10, 6.0) (Figure 1. The standard deviation of y_1 theoretical surface is estimated to be about 5%. Hence, one

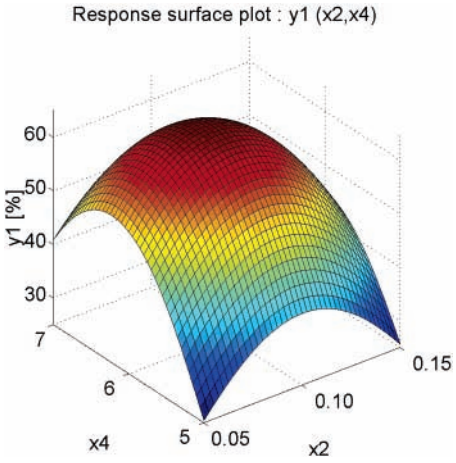

Figure 1. **Surface plot of the predicted reaction yield (y_1) in terms of the concentration of steroid after steroid addition (x_2) and the ratio of methylating agent to steroid (x_4). The calculations correspond to the second stage of the optimization procedure for the 20% DEM + 80% THF solvent system ($x_1 = 1$) and the Me_2CuLi methylating agent ($x_3 = 0$).**

can conclude that both theoretical surfaces lead to essentially similar predictions. The prediction of the maximum yield at (x_2, x_4) = (0.09, 6.1) obtained theoretically with the first set of *d*-parameters was verified experimentally.

In the laboratory practice, we repeatedly obtained the reaction yield of about 60.5% that falls into the region of uncertainty of theoretical predictions (63 ± 5%). We estimate that the values of yield are within an experimental error of ca. 1−2%, based on the details provided in the Experimental Section.

The process of isolation of 7α-methylnortestosterone **1** from crude reaction mixtures required special attention. This is because the chromatographic separation of small amounts of compound **6** from compound **1** proved impossible under the conditions applicable to the intended larger scale experiment. However, it was necessary to prepurify the crude mixture before attempts to crystallize it are made. Various crystallization procedures were tested, and the best one is reported. In other solvent systems used for crystallization, the 7*β*-methyl isomer **6** cocrystallized with compound **1** to a greater extent (various EtOAc−hexane mixtures), or the crystallization was not occurring (MeOH, 2-propanol, heptane, acetone, or their mixtures). The best, in our hands, purification process selected for the synthesis of compound **1** is described in the Experimental Section. In this particular case, one of the ideas behind finding the best set of conditions for carrying out the reaction as cleanly as possible was to facilitate the isolation process: the greater the proportion of compound **6** to compound **1**, the more difficult the process would be. The entire transformation of compound **4** to **1**, including the 1,6-conjugate addition reaction, is not intrinsically straightforward not only because of the limited stereoselectivity dictated by the structure of the substrate but also because of the sensitivity of the product to decomposition in crude reaction mixtures. For example, on a few occasions we observed the formation of small amounts of nortestosterone **2**, which can be accounted for by an SET reduction process.[12] Increasing the temperature above the values reported in the manuscript was detrimental in conjugate addition reactions. Carrying out the addition[11b] below −20 °C is difficult for technical reasons. The practical aspect, then, dictated that in this case one should use the isolated yield because the crude yield was not a good parameter, and the composition of the crude reaction product as determined by HPLC was only of limited use.

Scanning a complex four dimensional reaction response surface with only 10 + 7 experimental points can lead at most to one of supposedly many local minima. There is no obvious way, however, how to determine whether there exist other local minima (presumably better) than the one localized here. The advantage of the present approach, which does not emerge explicitly from the mathematical procedure, is that it has been reliable and let us optimize the entire selected process to a level substantially exceeding the previous procedures.[6]

During the course of the synthetic work, we observed a lack of stability of compound **1** in crude reaction mixtures during workup, whenever the crude mixtures were exposed to air for longer than about an hour at room temperature. Admittedly, the entire process of synthesizing compound **1** from dienone **4** is a complex sequence of chemical events, only some of which are well understood,[12] yet we found that the optimization effort gave valuable, practical results. Also the application of a ca. 6-fold excess of the methylating reagent[6] is a necessary tradeoff between the efficiency of the process and the convenience (and the cost). One of the initial questions was how large the optimal excess should be, and one of the goals of the present study was to answer this question. We observed that one can carry out the transformation of **4** to **1** with a much smaller excess of the cuprate reagent, but the yields in this case are much lower and, quite surprisingly, such processes lead to a larger proportion of compound **6** to **1**. A smaller excess of the cuprate was always associated with a much longer reaction time, and the reaction could not be run to completion. Part of the difficulty may perhaps be explained by the quite hindered nature of the C(7) region in the dienone **4**; the C(15)-methylene protons are in close proximity to the positively partially charged terminus of the C(6)−C(3)═O conjugated bonds system.

Hence, no further improvement of reaction yield was expected, and we concluded that the optimal reaction conditions for the preparation of compound **1** were determined, within the given synthetic methodology. Very important is the ability of the present conditions to deliver a high proportion of 7α-Me/7*β*-Me isomers, which makes the purification procedures much simpler and reliable.

Conclusions

Essential parameters within the selected synthetic approach, which are responsible for an efficient synthesis of 7α-methylnortestosterone (**1**), have been identified. As a result of the present optimization procedure, a synthesis of the target compound from 17*β*-acetoxy-4,6-estradien-3-one (**4**) was carried out under newly determined conditions in a repeatable manner, which afforded the product **1** in an yield of over 60% and essentially free from the 7*β*-Me isomer

(**6**). This result was obtained with the use of an iterative, two-stage reaction response surface analysis facilitating a practical solution to the difficulties occurring in the course of chemical processes.

Experimental Section

General Procedures. The reagents and solvents used were of the specified grade. The progress of reactions and the purity of compounds were determined using TLC plates from Merck, art. no. 105549; spots were visualized with UV light and by heating the plates moistened with 8% sulfuric acid/water. Column flash chromatography was performed on silica gel 60 (Merck, art. no. 1.09385 or 1.09390), using the solvents indicated. Analytical high performance liquid chromatography (HPLC) was performed on a Phenomenex Synergy MAX RP 80A, 150 × 4.6 mm^2 column (4 micron ODS packing; 1.0 mL/min of 65% CH_3CN−35% H_2O; UV detection at 235 nm and 275 nm; retention time of compound **1**, 3.3 min; retention time of compound **6**, 3.6 min). HPLC results (not shown) paralleled the results presented in the tables. All optimization experiments were run on a convenient laboratory scale (ca. 1 g of the substrate **4**), substrate **4** was crystalline and of high purity, and product **1** was purified by crystallization and carefully dried. Masses of the substrate and of the pure, crystalline product were carefully determined on a certified analytical balance (Mettler Toledo AB104-S, readability 0.1 mg).

Infrared (IR) spectra were recorded on a Perkin-Elmer model 1725X FT-IR spectrometer in KBr tablets. Ultraviolet (UV) spectra were recorded on a Shimadzu model 160A UV−vis spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 200 MHz and a Bruker AM 500 MHz spectrometer. TMS was used as the internal standard. Mass spectra (MS) were recorded on an AMD Intectra GmbH model 604 spectrometer, in the EI mode at 70 eV. Optical rotations were determined on a Perkin-Elmer model 241 polarimeter. Melting points were measured on a Büchi model 535 capillary instrument and are uncorrected. Tap water was used in experiments, unless otherwise stated.

Synthesis of 3,17β-Diacetoxy-3,5-estradiene (3) from 19-Nortestosterone (2). 19-Nortestosterone (**2**) (33.0 g, 0.12 mol) was placed in a 1 L round-bottom flask and dried under vacuum (1 mmHg, 40 °C, 1 h). EtOAc (100 mL) was then added, and the mixture was vigorously stirred under nitrogen until a milky suspension formed. The flask was immersed in a water bath (18 °C), and Ac_2O (Fluka no. 45830; 300 mL) was added, immediately followed by 70% aqueous $HClO_4$ (0.35 mL). Vigorous stirring was maintained for 8 h. Afterwards, finely powdered $NaHCO_3$ (2.5 g) was added in one portion, and the mixture was stirred for another 2 h. The reaction mixture was then filtered. The filtrate was concentrated in vacuo (10 mmHg, t = 65 °C) to a viscous solid, which was dried in vacuo (0.5 mmHg, rt, 12 h). The crude product thus obtained was crystallized from hot acetone (Polish Chemical Reagents POCh, analytical grade; 150 mL). The crystallizing solution was set aside at +4 °C for 4 h. The product was filtered through a large diameter no. 3 sintered glass funnel. The precipitate was recrystallized from acetone (120 mL). This gave a precipitate which was filtered and dried (1 mmHg, rt, 6 h), affording the diene (**3**) as an off-white solid (36.43 g, 84.5%): mp; 165−169 °C; $[\alpha]_D$ = −155 ° (20 °C, c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.77 (1H, d, 2.2 Hz), 5.47 (1H, bt, 2.6 Hz), 4.62 (1H, dd, 9.2, 7.3 Hz), 2.45 (1H, m), 2.13 (3H, s, AcO), 2.05 (3H, s, AcO), 0.82 (3H, s, 18-Me); ^{13}C NMR ($CDCl_3$) δ 171.2, 169.2, 148.6, 134.5, 123.6, 117.5, 82.7, 50.2, 43.4, 42.5, 40.5, 36.5, 36.4, 30.8, 27.9, 27.4, 27.1, 26.2, 23.2, 21.1, 21.0, 11.9.

Synthesis of 17β-Acetoxy-4,6-estradien-3-one (4) from 3,17β-Diacetoxy-3,5-estradiene (3). Compound **3** (155.5 g, 0.434 mol) was placed under nitrogen in a three-necked, 2 L flask, equipped with a thermometer, a dropping funnel, and a reflux condenser. Dimethylformamide (Fluka no. 40228; 1 L) was added, followed by H_2O (30 mL). The mixture was stirred, and the flask was immersed in an ice−water cooling bath. When the temperature dropped to 0 °C, NBS (Aldrich no. B8,125-5; 82 g, 0.46 mol) was added in 10 identical portions, with vigorous stirring, over 35 min. Care was taken to avoid overheating the reaction mixture above +7 °C. After stirring for another 45 min, LiBr (Fluka no. 62463; 75 g) was added, followed by Li_2CO_3 (Riedel-de-Hahn no. 13010; 152 g). The mixture was stirred under nitrogen, the cooling bath was replaced with a heating mantle, and the reaction mixture was allowed to reach 110 °C over 40 min. This temperature was maintained for another 45 min, then the mixture was cooled to 20 °C and poured into water (6 L) containing AcOH (500 mL). The mixture was stirred for 15 min. The product precipitated in the form of a gummy solid, which was filtered and dissolved in dichloromethane (270 mL), and the remainder of water was removed in a separatory funnel. The organic phase was flash-chromatographed on a silica gel column (10.5 cm o.d.; 230−400 mesh, 1 kg, 25% EtOAc/hexane). Eluting the column with 30% EtOAc−10% CH_2Cl_2−60% hexane afforded a yellow solid (121 g), which crystallized from hot diisopropyl ether (250 mL) to give dienone (**4**) (95.9 g; 70.3%). On standing, the mother liquors afforded a second crop of 17β-acetoxy-4,6-estradien-3-one crystals (10.7 g), bringing the yield of compound **4** to 78.2%: mp; 104−106 °C; $[\alpha]_D$ = −39° (20 °C, c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.18 (2H, bs), 5.78 (1H, bt, 1.0 Hz), 4.65 (1H, dd, 9.1, 7.5 Hz), 2.55 (1H, m), 2.06 (3H, s, AcO), 0.88 (3H, s, 18-Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200.0, 171.1, 158.8, 141.4, 128.8, 124.4, 82.1, 47.7, 45.9, 43.4, 41.1, 40.8, 37.7, 36.4, 27.3, 26.9, 25.0, 22.9, 21.1, 11.8.

Synthesis of 17β-Hydroxy-7α-methyl-4-estren-3-one (7α-Methylnortestosterone) (1) under Optimized Conditions. Copper(I) iodide (Fluka; 3.63 g, 19.06 mmol) was placed in a dry, 200 mL round-bottom flask. Anhydrous THF (21 mL) was added, and the mixture was cooled, under N_2, to 0 °C. With vigorous stirring, a 3.1 M solution of MeLi in diethoxymethane (Chemetall; 12.3 mL, 38.2 mol) was slowly added. **CAUTION**: *the rate of MeLi addition should be such that the temperature of the reaction mixture does not exceed +10 °C.* The resulting mixture was stirred and cooled at 0 °C, after which a solution of 17β-acetoxy-4,6-estradien-3-one (**4**) (0.976 g, 3.10 mmol) in anhydrous THF (5 mL) was

added. Care was taken not to exceed +10 °C during the addition procedure. Subsequently, the mixture was cooled to 0 °C and stirred for 30 min, and then saturated NH_4Cl/H_2O solution (60 mL) was very slowly introduced, followed by the addition of a 25% aqueous solution of ammonia (15 mL). The cooling bath was removed, toluene (30 mL) was added, and the mixture was stirred for 30 min. The phases were separated, the organic phase was diluted with methanol (40 mL), and 4 N KOH/H_2O (20 mL) was added. This mixture was stirred and heated under nitrogen at 40 °C for 2 h. More toluene (50 mL) and a 12% NaCl solution (100 mL) were added, and the mixture was vigorously agitated for 5 min. The phases were carefully separated, and the organic phase was washed with dilute brine (50 mL), then dried over anhydrous Na_2SO_4, filtered, concentrated, and dried in vacuo. This gave the crude product as a solid (0.90 g), which was purified over a flash column packed with silica gel (Merck Darmstadt, 230−400 mesh, 20 g, a gradient of 30−60% EtOAc in hexanes). The fractions containing compound **1** were concentrated and dried in vacuo. This afforded a solid, which was crystallized from a 1:2 mixture of THF and diisopropyl ether (2 mL). This gave pure 17β-hydroxy-7α-methyl-4-estren-3-one (**1**) (0.542 g, 60.5% yield) as a white solid: mp 141−142 °C; $[\alpha]_D = +59.6°$ (26 °C, $c = 1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.83 (1H, bs), 3.68 (1H, bt, 7.4 Hz), 0.81 (3H, s, 18-Me), 0.76 (3H, d, 7.0 Hz, 7α-Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 199.8, 165.4, 126.4, 81.6, 46.5, 43.5, 43.1, 43.0, 42.6, 42.3, 36.6, 36.3, 30.6, 30.2, 26.7, 26.6, 22.5, 12.8, 11.1.

The mother liquors were concentrated and dried in vacuo. This afforded a white solid (0.22 g), which besides enone (**1**) contained ca. 3% of the isomer (**6**), based on the integration of the 4-H in a ^{1}H NMR spectrum. After an additional chromatographic separation of this material on silica gel, a sample (8 mg) containing both isomers **1** and **6** in a ca. 1:1 ratio was obtained. The 7β-Me compound (**6**) was identified in the ^{1}H NMR spectrum of the mixture: ($CDCl_3$, 200 MHz) δ 5.78 (1H, bs), 3.61 (1H, bt, 7.5 Hz), 1.04 (3H, d, 6.4 Hz, 7β-Me), 0.80 (3H, s, 18-Me).

Computational Section

The process variables, x_2, x_4, and the reaction response, y_1, were transformed in the course of mathematical modeling. We generated the u_2 and u_4 variables that were coded by means of a linear transformation of x_2 and x_4 variables. Such a transformation known as an orthogonal scaling,[13,15] $u = (x - M)/R$, where M = midrange and R = Range/2, allowed a projection of each of $\langle x_{min}; x_{max}\rangle$ interval into the $\langle -1;1\rangle$ interval. The y-response was transformed with the use of nonlinear logit transform to obtain the z-response of the form $z = \log_{10}(y/(100 - y))$. Then, the z-response was approximated with a quadratic function, as in eq 1. For the exploratory step the reaction yield y_1 was approximated with the use of an expression of eq 1 with two sets of d-parameters. Set 1 (all linear and quadratic terms): $d_0 = 0.229$, $d_2 = -0.057$, $d_4 = 0.094$, $d_{24} = -0.058$, $d_{22} = -0.260$, $d_{44} = -0.341$. Set 2 (terms significant at $a = 0.15$ significance level): $d_0 = 0.240$, $d_{22} = -0.270$, $d_{44} = -0.339$.

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