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The Synthesis of 17α-Methyl-11β-arylestradiol: Large-Scale Application of the Cerium (III)-Mediated Alkylation of a Ketone

John Patrick Larkin,[†] Christian Wehrey,[†] Philippe Boffelli,[‡] Henri Lagraulet,[‡] Guy Lemaitre,[‡] Alban Nedelec,[‡] and Denis Prat*[,‡]

Aventis Pharma, 102 Route de Noisy, 93235 Romainville Cedex, France

Abstract:

17α-Methyl-11β-arylestradiol (17α-methyl-11β-(4-(2-(1-piperidinyl)ethoxy)phenyl)estra-1,3,5(10)-triene-3,17β-diol) is a new molecule developed by Aventis Pharma for the treatment of osteoporosis. It was produced on the pilot plant scale from the norsteroid intermediate ethylene deltenone (3,3-ethylenedioxyestra-5(10)-9(11)-diene-17-one). Stereoselective epoxidation of the 5(10)-olefin was performed by hydrogen peroxide and hexachloroacetone, the most selective of the systems tested. The 11β-aryl appendage was introduced as a cuprate generated catalytically from the related Grignard reagent. The A-ring was aromatized by a mixture of acetyl bromide and acetic anhydride. This reaction was optimized by a Design Of Experiments carried out on an automated workstation. The advantages and limits of this approach are discussed. The last step consisted of the stereospecific alkylation of the 17-ketone by methylmagnesium bromide and dehydrated cerium trichloride. The drug substance was crystallized as a hydrate (overall yield = 23%).

Introduction

The treatment of osteoporosis is a key challenge of this century. The decrease in bone mineral density after menopose induces a risk of fractures (mainly hip and femur) in the increasingly senior female population.

The main preventive treatment consists of the regular intake of estradiol, which slows down the bone loss, but not without side effects. The ideal drug would have the beneficial effects of estradiol on bone without the side effects on the other tissues.

17α-Methyl-11β-arylestradiol **6** is a new molecule developed by Hoechst Marion Roussel, now Aventis Pharma, for the treatment of osteoporosis. Its steroid structure is an advantage in terms of tolerance and specificity of action.[1]

For the supply of the preclinical and phase I studies, several batches of drug substance were prepared in the pilot plant from the known norsteroid intermediate **1** (Scheme 1) by a short sequence involving: (1) stereoselective epoxidation by hydrogen peroxide catalyzed by hexachloroacetone, (2) protection of the 17-keto group as a silyl enol ether, (3) stereospecific arylation at the 11-position by a cuprate generated catalytically from the corresponding Grignard reagent, (4) aromatization of the A-ring by a mixture of acetyl bromide and acetic anhydride, (5) stereospecific alkylation at the 17α-position by methylmagnesium chloride and cerium trichloride at room temperature.

Although the synthesis itself was not changed during this development work, the scaling-up of the aromatization reaction and of the alkylation at the 17-position required significant optimization work.

Results

1. Epoxidation. Ethylene deltenone **1** was chosen as the starting material of the synthesis. It is a well-known industrial intermediate for norsteroids, particularly Trimegestone.[2] The introduction of the aromatic moiety at the 11β-position requires an almost diastereomerically pure 5(10)-α-epoxide **2**. As the previously described epoxidation of **1** using hydrogen peroxide and hexachloroacetone[3] or hexafluoroacetone[4] is poorly stereoselective (α/β ≈ 2/1) as a result of the lack of steric differentiation between both sides of the substrate, we investigated alternative, recently described systems[5−11] (Table 1).

With all systems, the α-isomer was the major isomer formed, but with different chemo- and regioselectivities observed. We tested first the catalysis by other electron-deficient ketones developed by Schering A.G.,[5] but we could not reproduce the excellent diastereoselectivities described (up to 9/1 with trifluoroacetophenone) (entry 3). Moreover,

[†] Chemical Development, Aventis Pharma.

[‡] Process Development, Aventis Pharma.

(1) Bouali, Y.; Nique, F.; Teutsch, G.; Van De Velde, P.; FR 2,757,519 (Roussel Uclaf).

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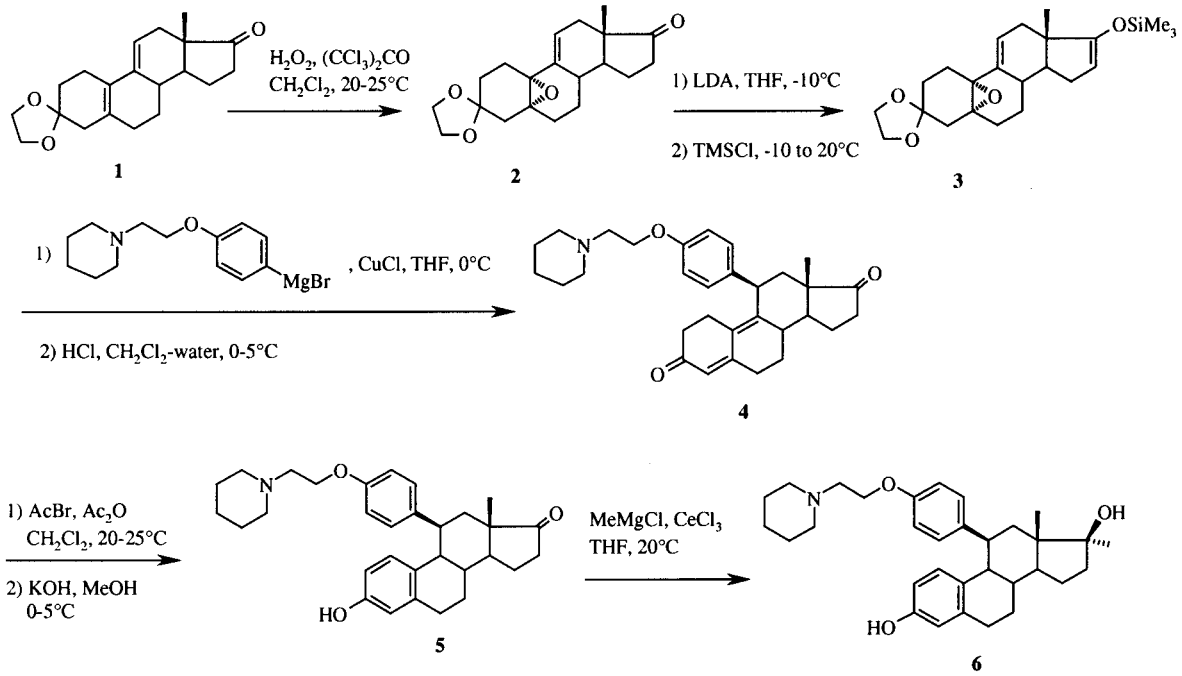
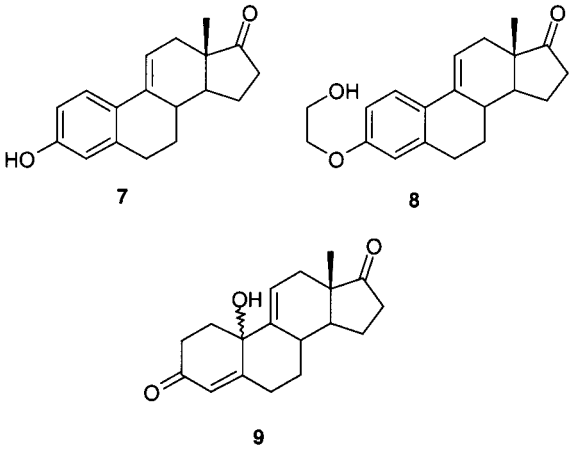
Scheme 1. **Industrial synthesis of 17α-Methyl-11*β*-arylestradiol**



the removal of the catalyst was difficult. Epoxidation by MCPBA in dichloromethane,[6] which gave significant quantities of by-products, is shown here for comparison (entry 4). We also investigated the well-known catalysis by methyltrioxorhenium (MTO),[7] under different conditions, with 30% hydrogen peroxide[8−10] (entries 5−7) or the complex urea−hydrogen peroxide[11] (entry 8). However, the promising diastereoselectivities in these cases do not compensate for the low chemoselectivities.

The epoxides formed are very sensitive to protic media under either acidic or basic conditions and result in complex mixtures of products.[6a] For example, the products **7**−**9** were isolated from very acidic media (4 N HCl):



Therefore, one has to be very careful in the interpretation of the stereoselectivities given, as the α-epoxide is more sensitive in protic media than the *β*, and the apparent stereoselectivity refers only to the remaining epoxides. The apparent stereoselectivity may decrease as a result of degradation of the α-epoxide.

Thus, none of the alternative systems tested (some of them not described here for the sake of simplification) could compete with the hydrogen peroxide−hexafluoroacetone or −hexachloroacetone systems in dichloromethane, in terms of the amount of α-epoxide isolated, because of the particular mildness of these reagents, which avoids promoting significant degradation.

The isolation of the α-epoxide was facilitated by its high crystallinity. After reductive work-up, it was crystallized from acetonitrile, acetone, or ethyl acetate. On a 50 g scale, reaction with hexafluoroacetone and crystallization from ethyl acetate yielded 49% α-epoxide (isomer purity: 95%), whereas reaction with hexachloroacetone followed by the same crystallization gave 43% α-epoxide (isomer purity: 93%). Such purities were suitable for the subsequent reaction. More than 10 batches were made in the pilot plant with hexachloroacetone and gave comparable results.

2. Silylation. The introduction of the aryl group at the 11*β*-position was performed via a cuprate generated in situ from the corresponding Grignard reagent and copper (I) chloride[3c−e,4a,b,12] (Scheme 1).

It was possible to carry out the arylation reaction without protecting the keto group at C-17, but this required an additional equivalent of the expensive Grignard reagent to form the 16-17-enolate. Moreover, protection as a silyl enol ether[13] permitted halving the amount of copper (I) chloride catalyst needed, and the overall yield was increased.

The enolate from ketone **2** was obtained using a nonnucleophilic base to avoid epoxide opening. Lithium diisopropyl

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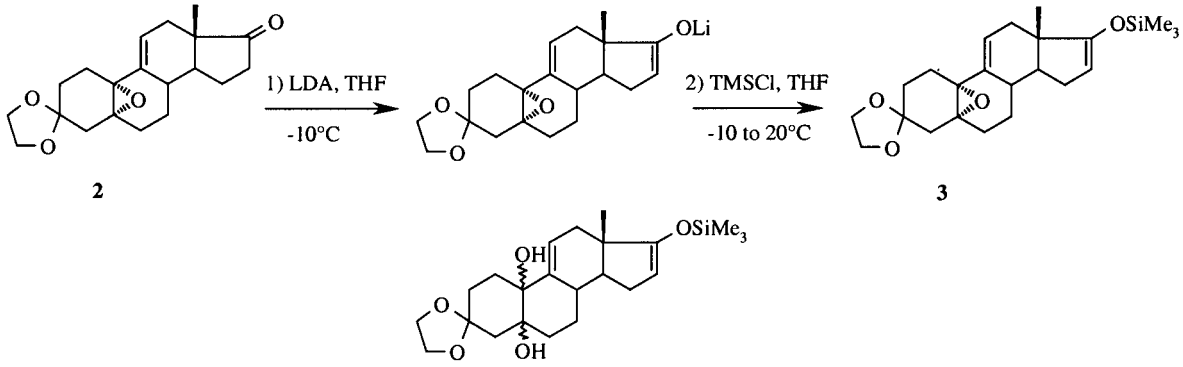
Table 1. **Epoxidation of ethylene deltenone 1**

entry	system	conditions	conversion (%)	α epoxide (%)	β epoxide (%)	diastereoselectivity
1	H_2O_2, hexachloroacetone (0.1 equiv)	18 h at 20 °C	100	64	36	1.8/1
2	H_2O_2, hexafluoroacetone (0.1 equiv)	18 h at 20 °C	98.5	67	32	2.1/1
3	H_2O_2, trifluoroacetophenone (0.2 equiv)	3 days at 0 to 20 °C	98	57	19	3/1
4	MCPBA (1.8 equiv), $NaHCO_3$ (1.8 equiv)	1 h at 0 °C	98	34	21	1.6/1
5	H_2O_2, MTO, pyridine	2 h at 20 °C	93	10	3	3.3/1
6	H_2O_2, MTO, pyrazole	4 h at 20 °C	59	8	2	4/1
7	H_2O_2, MTO, pyridine, 3-cyanopyridine	3 h at 20 °C	52	6	1.5	4/1
8	UHP, MTO	1 h at 20 °C	100	18	4.5	4/1

Scheme 2. **Silylation of 17-keto group**



amide (LDA)[14] and lithium hexamethyldisilazane (LHMDS)[15] both gave clean and quantitative conversion at 0 °C. The silylating agent was inexpensive chlorotrimethylsilane (TMSCl) (Scheme 2).

FT-IR monitoring of the reaction showed that the silylation of the lithium enolate was rapid and quantitative at 0 °C. The reaction was clean when fresh reagents (*n*-butyllithium, diisopropylamine, and TMSCl) were used, and the reaction was carried out under anhydrous conditions, as traces of water promoted impurities such as **10**. As silyl enol ether **3** has a low melting point and is not very stable, it was not isolated but was used as a solution in toluene in the subsequent reaction.

3. Arylation. The side chain synthon **11** was prepared from 4-bromophenol and 1-(2-chloroethyl)piperidine hydrochloride in basic medium (Scheme 3).

As the described procedures in homogeneous media[16] favored the formation of quaternary ammonium salt **13**, new conditions using phase-transfer catalysis were developed. In the presence of 2.2 equiv of 30% sodium hydroxide and 5% TEBAC (triethylbenzylammonium chloride), 4-bromo phenol was converted very selectively (>95%) into **11** within 18 h at 30−35 °C. Most often, alkaline extraction was sufficient to remove excess 4-bromophenol, which inhibits the formation of the cuprate. If necessary, arylbromide **11** was purified by crystallization of its hydrochloride salt from diisopropyl ether (yield: 90%). When an aged arylbromide **11** was used without purification in the arylation step, the aryl−aryl coupling product **14** was isolated. Nevertheless, the scaling-up of this arylation was successful even without purification of **11**, as on larger scales, freshly prepared reagents have always been used.

The arylation was performed from −5 to +20 °C with 1.5 equiv of Grignard reagent and 0.1 equiv of copper (I) chloride. Either of the addition sequences could be applied. Interestingly, there was little direct attack of the Grignard reagent on the epoxide function.

The intermediate alcohol **12** was not isolated. After aqueous work-up and concentration, it was submitted to acidic hydrolysis (aqueous 4 N HCl, dichloromethane, 0 °C), during which the hydroxyl group was eliminated and both protective groups were cleaved. The by-product (Ar−H) from the excess Grignard reagent was removed as the hydrochloride in the acidic aqueous phase, whereas the hydrochloride salt of enone **4** remained in the dichloromethane phase. After neutralization (aqueous sodium hydrogen carbonate), enone **4** was purified by crystallization from diisopropyl ether. The crystallization removed all the by-products, especially those derived from the β-epoxide. The yield was in the range 80−82% (from a 98% pure epoxide) in the laboratory or in the pilot plant (10−20 kg scale). It was not necessary to use a highly pure starting epoxide; it could contain up to 10% β-isomer without having significant impact on the quality of enone **4**. Of course, in this case, the yield was lower (∼70%).

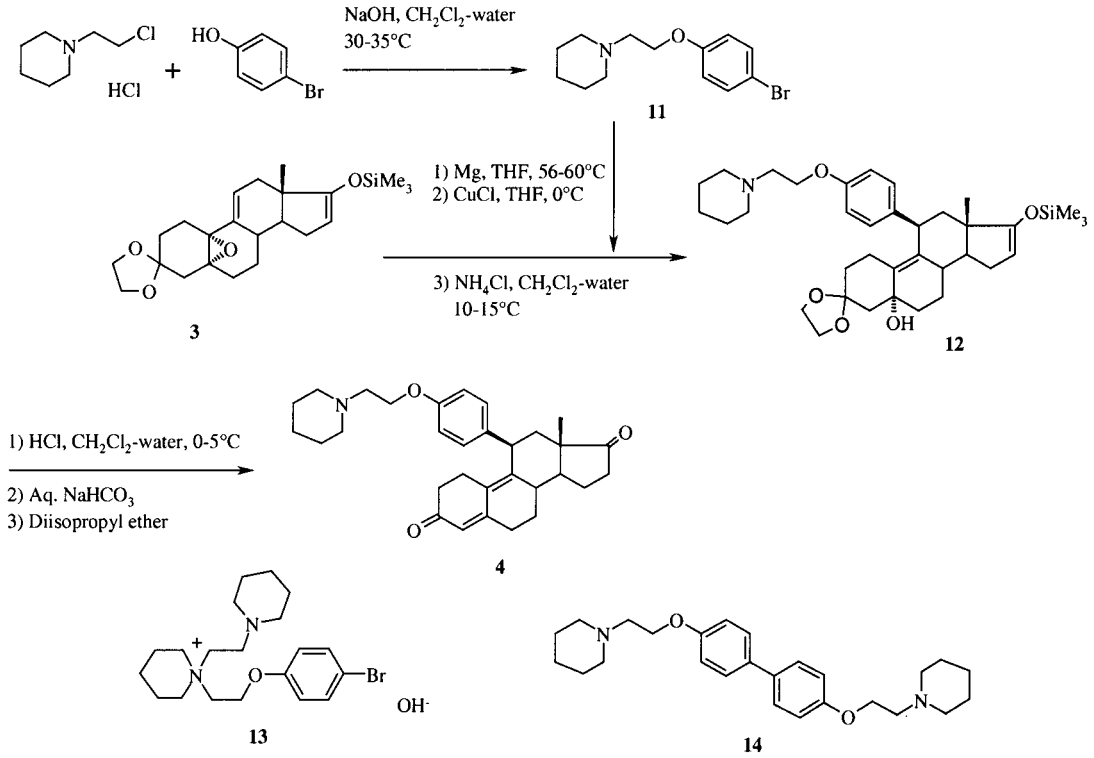
A safety study was carried out on this sequence of reactions: the highest exotherms were observed in the

(14) LDA was prepared in situ from *n*-butyllithium and diisopropylamine in THF at 0 °C.

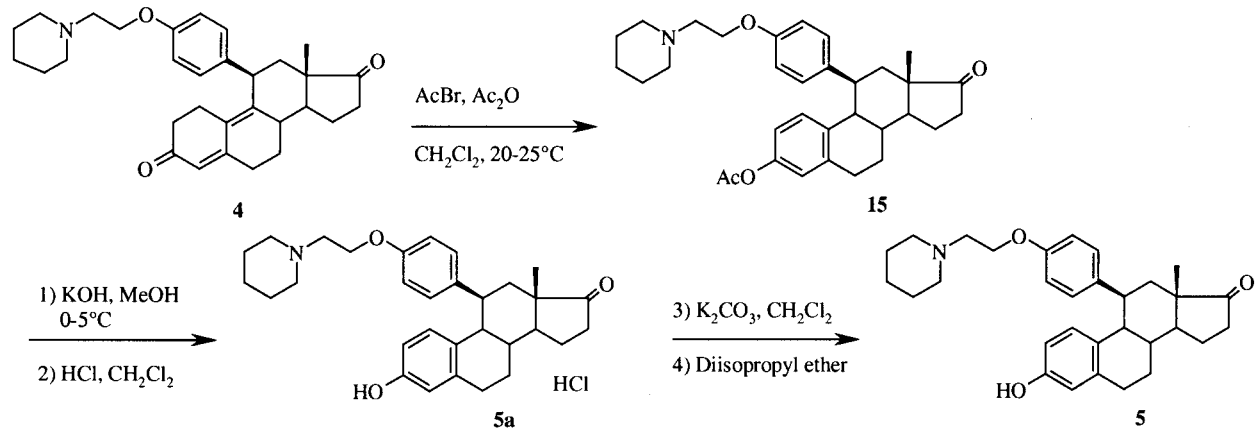
(15) A commercial solution in THF was used (Chemetall, 20% in weight or 1.1 M).

(16) (a) Lednicer, D.; Babcock, J. C.; Marlatt, P. E.; Lyster, S. C.; Duncan, G. W. *J. Med. Chem.* **1965**, *8*, 52. (b) Short, J. H.; Biermacher, U.; Dunnigan, D. A.; Lambert, G. F.; Martin, D. L.; Nordeen, C. W.; Wright, H. B. *J. Med. Chem.* **1965**, *8*, 223. (c) Robertson, D. W.; Katzenellenbogen, J. A. *J. Org. Chem*. **1982**, *47*, 2387.

Scheme 3. **Arylation at the 11β-position**



Scheme 4. **Ring aromatization**



formation of the Grignard reagent ($\Delta T_{adiab} = \sim 200$ °C) and the arylation ($\Delta T_{adiab} = \sim 70$ °C). These data (potential increase in temperature under adiabatic conditions) show that uncontrolled addition of arylbromide **11** onto the magnesium suspension in THF, or of the Grignard reagent, would cause boiling of the solvent, overpressure in the vessel, and eventually decomposition of the reaction mixture. Therefore, these addition steps were very carefully controlled in the pilot plant.

4. Aromatization. The aromatization of the A ring is a classic reaction in norsteroid chemistry.[4b,12d,e,17] On a laboratory scale it can be performed by palladium catalysis, but for an industrial application, the mixture of acetyl bromide and acetic anhydride was obviously preferred. An estrone acetate **15** was formed, which required saponification (Scheme 4).

Although this type of aromatization was applied at the industrial level in the former Roussel Uclaf, it was never optimized because it worked well and did not require expensive reagents. Nevertheless, we thought it would be worthwhile to have a closer look at this reaction, as the reagents used are hazardous and their quantities could probably be reduced. This optimization study was carried out in our new automation laboratory by coupling Design Of Experiments[18] (DOE) (STAVEX[19] and NEMROD[20] DOE software programs were used) and an automated workstation (Anachem SK 233).

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(18) See, for example: (a) Carlson, R. *Design and Optimization in Organic Synthesis*; Elsevier: Amsterdam, 1992. (b) Lewis, G. A.; Mathieu, D.; Phan-Tan-Luu, R. *Pharmaceutical Experimental Design*; Marcel Dekker: New York, 1999. (c) Goupy, J. *Plan d'Expériences pour Surfaces de Réponses*; Dunod: Paris, 1999.

Table 2. **Aromatization results**[a]

entry	Ac_2O (equiv)	AcBr (equiv)	T (°C)	yield (**5a**) (%)	purity (**5a**) by HPLC (%)	comments
1	3	3.8	23−27	77.3	98.1	former conditions
2	1.5	4	13−17	75.8	96.7	optimum of DOE
3	1	2.5	21−24	82.7	98.7	new conditions

[a] Conditions: 20 g enone; $t = 4-5$ h; yield of **5a** after crystallization (on dry substances).

Preliminary experiments demonstrated that the overall concentration and the order of additions of reagents were not significant factors. Hence, in the final protocol, enone **4**, dichloromethane (4 mL/g enone), and acetic anhydride were mixed first, and then acetyl bromide was added while the temperature was maintained constant (exothermic addition). The factors to be varied were the amounts of acetic anhydride ($(Ac_2O) \leq 3$ equiv) and of acetyl bromide ($1 \leq$ (AcBr) ≤ 4 equiv) and temperature ($0 \leq T \leq 30$ °C). Time was not considered as a factor, because it interacts generally with most of the factors. Thus, time was integrated in the response, which was the relative amount of estrone acetate **15** in the reaction mixture (determined by HPLC) at $t = 5$ h.[21] With only three factors to consider, an optimization design (quadratic model with interactions terms) could be selected. The experiments were run on the Anachem SK 233 workstation, in groups of four or five at the same temperature. The relative amounts of estrone acetate in the reaction mixtures after 5 h were analyzed by the softwares which generated quadratic models and plotted contour maps.

Although NEMROD stated that the quadratic model was valid, which could be checked by comparing the calculated values with the experimental amounts of estrone acetate in the mixtures, it is noteworthy that the optimum according to the DOE did not correspond to the best conditions in terms of isolated arylestrone hydrochloride **5a** (Table 2).

The main reason for this divergence is the limitation in the application of an automated workstation such as Anachem SK 233 to this particular problem. It is designed to handle and sample solutions in simple sequences. It could not be involved in a complex sequence involving the aromatization, saponification, and isolation by crystallization. Thus, we simplified the problem by the analysis by HPLC of the first reaction, a task for which the workstation is particularly well adapted. Under the optimal conditions of aromatization according to the HPLC analysis of the reaction mixture, a high excess of acetyl bromide was required (4 equiv). However, this excess had probably a negative impact on the subsequent work-up, saponification, and isolation procedures.

Nevertheless, this study (19 experiments in 4 groups) permitted the rapid establishment of the robust zone in the experimental domain, that is the conditions giving more than 90% of arylestrone in the reaction mixture: $15 \leq T \leq 30$ °C; $2 \leq$ (AcBr) ≤ 4 equiv; $(Ac_2O) \leq 3$ equiv. These values were confirmed by the experiments performed using 20 g of enone **4** and finally crystallization of arylestrone hydrochloride **5a**. The best conditions correspond roughly to the center of this robust zone (Table 2, entry 3).

To ensure the maximum purity before the final step, arylestrone was crystallized first as the hydrochloride salt **5a** from dichloromethane and then as the base **5** from diisopropyl ether.

The new conditions were applied successfully in the pilot plant on a 10−20 kg scale (overall yield in **5**: 74%). They resulted in a significant improvement in terms of cost, safety, hygiene, and environmental implications.

5. Methylation. Alkylation of enolisable ketones such as cyclopentanones has always been a challenge in synthesis because of the basicity of classical alkyllithium or Grignard reagents,[22] but the use of neutral organocerium reagents provides a solution to this problem in the laboratory.[23] These reagents are generally prepared from organolithium reagents and anhydrous cerium trichloride in THF, but the structure of the product is still unknown and probably cannot be simply described as "$RCeCl_2$". Residual water and the solvent (THF) also play an important role in the formation of these complexes.[24]

However, several problems are met in the scaling-up of this reaction: (1) Organolithium reagents are expensive and pyrophoric. (2) Low temperatures are recommended (−70 °C). (3) Rigorously anhydrous cerium trichloride is not available on a kg scale, and the driest grades still contain 5−10% water. (4) Dehydration of cerium trichloride requires high vacuum and careful heating to avoid its decomposition into hydrogen chloride and cerium oxychlorides.[25]

Nevertheless, we had no simple alternative for this tricky but attractive reaction, and we therefore decided to optimize it.

5.a. Dehydration of $CeCl_3$, $7H_2O$. As the stable and readily available form is the heptahydrate, we had to adapt the procedures described for the preparation of anhydrous cerium trichloride.[25] They consist of a sequential heating from 40 to 140 °C, at 0.01−0.05 Torr, but such a high vacuum could not be achieved in the pilot plant. Nevertheless, even in moderate vacuum (10−20 Torr), an almost anhydrous material was obtained (<2% water) and could be used for the alkylation. This simple procedure was applied in the pilot

(19) (a) Seewald, W.; Grize, Y. L. *Drug Inf. J.* **1997**; *31*, 597. (b) E-mail: stavex@aicos.com; site: www.aicos.com.

(20) NEMROD; Mathieu D.; Phan-Tan-Luu, R.; LPAI SARL, Marseille, F-13331, France; e-mail: LPRAI@nemrodw.com; site: www.nemrodw.com.

(21) This time was chosen for convenience. In the pilot plant, for noninstantaneous reactions, the most practical reaction times are in the range 2−5 h, or 16−18 h. In the design of experiments, we generally integrate this constraint which simplifies the studies by limiting the number of factors.

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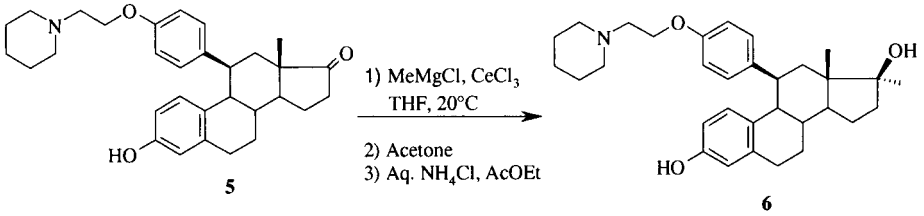
(25) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett*. **1996**, *37*, 6787.

Scheme 5. **Methylation at the 17α-position**



plant using 64 kg of cerium trichloride heptahydrate. The only issue was the deposit of product in the condenser.

5.b. Activation of $CeCl_3$. Anhydrous cerium trichloride does not form the desired complex by direct contact with the alkyllithium reagent. Formation of a complex with THF is the first essential step. Interestingly, the complex $CeCl_3$-(THF)(H_2O) has been characterized by X-ray diffraction.[24] It has even been recommended to mix cerium trichloride, THF, and the ketone at room temperature.[25] However, our results showed that simply refluxing anhydrous cerium trichloride in THF for 2 h was sufficient to give an activated form which then reacted rapidly with the organometallic reagent. The ketone was added afterwards.

5.c. Reaction Conditions. In the original procedure from medicinal chemistry, 5 equiv of cerium trichloride and 5 equiv of methyllithium in diethyl ether were used, at −70 °C. In the first preparation in the pilot plant, diethyl ether was avoided for safety reasons. The reaction was run in THF at −67 °C using 5.2 equiv of cerium trichloride and 6.3 equiv of methyllithium in diethoxymethane (8% solution). Yield (85−88%) and purity were the same from 25 g to 4−5 kg scale.

For the further batches, we turned to Grignard reagents.[25,26] They have several advantages compared to organolithium reagents. They are more stable, less expensive, and do not react with THF. Moreover, for the reaction of the cerium complex with the ketone they do not require low temperatures. Methylmagnesium chloride was preferred, as its commercial solutions in THF are more concentrated (3 M) than those of methylmagnesium bromide (1 M). After some optimization work, 4 equiv of methylmagnesium chloride gave a rapid, quantitative, and stereospecific alkylation at C-17 at 20 °C, in the presence of 3 equiv of dehydrated and activated cerium (III) chloride.[27] This procedure was applied successfully in the pilot plant, without modification (up to 12 kg scale) (Scheme 5).

5.d. Work-Up and Purification. The alkylation process is the last step of the synthesis. Therefore, efficient removal of cerium traces and purification were required, especially because impurities promote discolouration of the active molecule on storage.

Excess Grignard reagent was consumed by addition of acetone to the reaction mixture, then quenching and washing with aqueous ammonium chloride removed all metal traces. Methylarylestradiol was crystallized, first as the hydrochloride salt from ethyl acetate (yield: 87.3% (7 kg scale); color index: 2; cerium < 20 ppm). Then, the hydrochloride salt was neutralized using aqueous potassium carbonate at 97 °C, and methylarylestradiol was crystallized from water, as a hydrate which was the stable form (overall yield: 86.1%, purity (HPLC): 99.8%). The active ingredient thus obtained was submitted to jet milling and delivered for the preclinical and clinical studies.

(26) Bunnelle, W. H.; Narayanan, B. A. *Org. Synth.* **1990**, *69*, 89.
(27) Silylation of the phenol function would permit the use one equivalent less of Grignard reagent. However it was simpler not to protect the phenol.

Conclusions

Four years ago, we described in this journal the first application of bakers' yeast-mediated reduction of a norsteroid ketone at the industrial level.[2] The present study shows that this old family of molecules is still in the race for new active ingredients, because of the low toxicity, low dosage, and high specificity they often demonstrate. It also shows that despite all that is known about these molecules they are still challenging in terms of chemistry. Methylarylestradiol gave us the opportunity to scale up an alkylation with cerium trichloride and a Grignard reagent at room temperature. Thus, this useful reaction for readily enolisable ketones is not limited to laboratory applications.

Experimental Section

General. NMR spectra were recorded on a Bruker 300 MHz, in $CDCl_3$; IR spectra, on a Nicolet FTIR SSXB spectrometer, in chloroform; MS spectra, on Micromass Autospec or Micromass Platformspectrometers. Water content was determined by Karl Fischer titration in methanol on a Mettler titrator.

3,3 Ethylenedioxy-5,10-α-epoxy-estr-9(11)-ene-17-one (2). Ethylene deltenone **1** (46 kg; MW: 314.4; 146.3 mol), hexachloroacetone (Janssen, 98%; 4.0 kg; MW: 264.7; 0.1 equiv), pyridine (230 mL), 50% hydrogen peroxide (∼18 M; 13.8 L; 1.7 equiv) and dichloromethane (230 L) were stirred vigorously for 18 h at 20−25 °C (TLC monitoring: *n*-heptane-ethyl acetate 6/4 (v/v)). After reductive work-up (aqueous sodium metabisulfite), washing (water) and extractions (dichloromethane), the organic phase was concentrated to a total volume of 184 L. Then, dichloromethane was replaced by ethyl acetate by continuous distillation at constant volume, until temperature of the liquid reached 77 °C. The mixture was cooled to 30 °C. The epoxide **2** crystallized spontaneously. The suspension was cooled to 0 °C and stirred for 1 h, then **2** was filtered and dried under vacuum for 18 h at 40 °C (21.1 kg white solid; yield: 43.7%; purity: 95%): $C_{20}H_{26}O_4$; MW: 330.4; IR ($CHCl_3$, cm^{-1}): ν 1733, 1636; NMR ^1H ($CDCl_3$, ppm): δ 0.88 (s, 3H), 3.94 (m, 4H), 6.05 (m, 1H); mp = 154 °C.

Crystallization of the mother liquors from diisopropyl ether gave a ∼2/1 mixture of β- and α-isomers (21.4 g white solid; yield: 41%). Pure β-isomer: NMR ^1H ($CDCl_3$,

ppm): δ 0.87 (s, 3H), 3.94 (m, 4H), 5.86 (m, 1H); mp = 143 °C.

1-(2-(4-Bromophenoxy)ethyl)piperidine (11). To a stirred solution of 4-bromophenol (ACROS Organics; MW: 173.0; 15.5 kg; 89.6 mol), 1-(2-chloroethyl) piperidine hydrochloride (ACROS Organics; MW: 184.1; 17.9 kg; 1.08 equiv), and TEBAC (Merck; 1.55 kg) in dichloromethane (93 L) at 20 °C was added a 30% aqueous solution of sodium hydroxide (MW: 40.0; 26.3 kg; 2.2 equiv). The mixture was stirred vigorously at 30−35 °C for 18 h (TLC monitoring: dichloromethane/ ethyl acetate/ TEA 45/45/10 (v/v)). Sodium chloride crystallized out. The mixture was then diluted with water, the lower organic phase was decanted, washed with water, dried over sodium sulfate and concentrated in vacuo to dryness (25 kg yellow oil; yield: 98.2%; GC purity: 98%): $C_{13}H_{18}BrNO$; MW: 284.2; IR ($CHCl_3$, cm^{-1}): ν 1591, 1579, 1489; NMR ^1H ($CDCl_3$, ppm): δ 1.44 (m, 2H), 1.59 (m, 4H), 2.48 (m, 4H), 2.75 (t, J = 6 Hz, 2H), 4.06 (t, J = 6 Hz, 2H), 6.78 and 7.35 (AA′BB′, 4H); MS (ES^+; m/z): 284 (M^+), 111, 85.

3,3-Ethylenedioxy- 5,10-α-epoxy-17-(trimethylsilyloxy)-estra-9(11),16-diene (3). *n*-Butyllithium (Chemetall, 1.6 M solution in hexanes; 18.5 L; 1.06 equiv) was added over 20−30 min to a stirred solution of diisopropylamine (Fluka; MW: 101.2; d: 0.714; 4.63 L; 1.16 equiv) in anhydrous THF (28 L), at −10 °C. A solution of epoxide **2** (9.26 kg; 28.0 mol) in THF (56 L) was added over 30−40 min at −10 °C, and the mixture was stirred for 15 min at −10 °C. Trimethylchlorosilane (Aldrich, 99%; MW: 108.6; d: 0.856; 4.63 L; 1.3 equiv) was added over 20−30 min at −10 °C, and the mixture was stirred for 1 h at 20 °C (TLC monitoring: toluene/ ethyl acetate 1/1 (v/v)), then concentrated in vacuo to a final volume of 18.5 L. The solvents were then replaced by toluene at constant volume at 30 °C maximum. The salts were filtered off and washed with toluene. The filtrate was concentrated to ∼18.5 L, and this solution of silyl enol ether was used for the next step. Concentration of an aliquot to dryness gave **3** as a white solid: $C_{23}H_{34}O_4Si$; MW: 402.6; IR ($CHCl_3$, cm^{-1}): ν 1621, 1254, 849; NMR ^1H ($CDCl_3$, ppm): δ 0.19 (s, 9H), 0.80 (s, 3H), 3.85−4.00 (m, 4H), 4.47 (dd, J = 1.5 and 1 Hz, 1H), 6.03 (m, 1H); MS (m/z): 402 (M^+), 387 (M^+-CH_3), 99; mp∼ 30−40 °C.

11β-(4-(2-(1-Piperidinyl)ethoxy)phenyl)estra-4,9-diene-3,17-dione (4). To a stirred suspension of magnesium (turnings; MW = 24.3; 1.29 kg; 1.89 equiv) in THF (4.1 L) at 20−22 °C was added 0.8 L of a solution of arylbromide **11** (13.73 kg; MW = 284.2; 1.72 equiv) in THF (41 L). The mixture was stirred at 56−60 °C until the Grignard reagent formed (exotherm; gray color). The rest of the solution was then added carefully during ∼90 min at 56−60 °C, and the gray, fine suspension was stirred for 60 min at the same temperature, then was allowed to cool. (vol: 52 L; assay (potentiometry): 0.90 M). Copper chloride (99%; MW = 99.0; 0.28 kg; 0.10 equiv) was added at 20 °C and the suspension was cooled to 0 °C. The solution of silyl enol ether **3** (28.0 mol) in toluene described above was diluted with THF (18.5 L) and added over 1 h at 0 °C to the mixture of Grignard and cuprate reagents. The mixture was stirred for 1 h at 0 °C (TLC monitoring: toluene/ ethyl acetate 1/1), then poured into a biphasic mixture of ammonium chloride (56 kg) in water (185 L) and dichloromethane (93 L) at 10−15 °C. The organic phase was washed with water and concentrated in vacuo to ∼18.5 L. Dichloromethane (46 L) and water (28 L) were added. The mixture was cooled to 0−5 °C, and 36% hydrochloric acid (13.9 L; 5.8 equiv) was added over 30 min. The biphasic system was stirred vigorously for 2 h at 0−5 °C. The organic phase was decanted and washed with water: the amino by-products from the Grignard reagent were removed in the acidic aqueous phase, whereas the hydrochloride salt of enone **4** remained in dichloromethane. The organic phase was neutralized by aqueous sodium hydrogencarbonate (10% solution), washed with water and concentrated to a final volume of ∼46 L. Dichloromethane was replaced by diisopropyl ether at 40−45 °C in vacuo at constant volume. Enone **4** crystallized. It was filtered at 20−22 °C and dried in vacuo at 35−40 °C. (11.05 kg white solid; HPLC purity: 97%; yield: 83.2% (82% as dry product; from epoxide **2**): $C_{31}H_{39}NO_3$; MW: 473.7; IR ($CHCl_3$, cm^{-1}): ν 1735, 1658, 1609, 1581, 1509; NMR ^1H ($CDCl_3$, ppm): δ 0.56 (s, 3H), 2.50 (m, 4H), 2.75 (t, J = 7 Hz, 2H), 4.06 (t, J = 7 Hz, 2H), 4.37 (bd, J = 7 Hz, 1H), 5.79 (bs, 1H), 6.82 and 7.07 (AA′BB′, 4H).

3-Hydroxy-11β-(4-(2-(1-piperidinyl)ethoxy)phenyl)-estra-1,3,5(10)-trien-1-one (5). To a solution of enone **4** (10 kg; 21.1 mol) in dichloromethane (40 L) were added acetic anhydride (MW = 102.1; d = 1.09; 2.0 L; 1.0 equiv) and acetyl bromide (MW = 123.0; d = 1.66; 3.9 L; 2.5 equiv), at 20−25 °C (exothermic addition). The brown solution was stirred for 5 h at 20−25 °C (HPLC monitoring: Hypersil BDS 3 μ CN; l = 15 cm; d = 4.6 mm; eluent: water (+0.1% TFA)/methanol/ acetonitrile: 65/30/5; 1 mL/min; detection: UV 210 nm), then poured carefully into a solution of sodium hydrogencarbonate (MW = 84.0; 17.7 kg; 10 equiv) in water (180 L) (evolution of carbon dioxide). After the mixture had been stirred vigorously overnight at 20−25 °C, the organic phase was washed with water and concentrated to a final volume of 30 L. Dichloromethane was replaced by methanol at constant volume by distillation in vacuo at ∼40 °C. Saponification of estrone acetate **15** was performed by adding a solution of potassium hydroxide (MW = 56.0; 1.77 kg; 1.5 equiv) in methanol (20 L) at 0−5 °C. The mixture was stirred for 1.5 h at 0−5 °C (HPLC monitoring: same conditions as above), then poured into water (50 L) and dichloromethane (50 L). The organic phase was washed with water. Water (50 L) and 36% hydrochloric acid (3.6 L; 2 equiv) were added. After stirring, the organic phase was collected and dried over sodium sulfate, filtered and concentrated to a final volume of 50 L. Residual methanol was replaced by dichloromethane at constant volume (bp of azeotrope dichloromethane-methanol 92.7/7.3 (m/m): 37.8 °C[28]). Arylestrone hydrochloride crystallized spontaneously and was filtered at 0 °C, but not dried. Dichloromethane (80

(28) Horsley, L. H. *Azeotropic Data III*; Advances in Chemistry Series 116; American Chemical Society: Washington, DC, 1973.

L) and a solution of potassium carbonate (MW = 138.2; 2.73 kg; 0.94 equiv) in water (40 L) were added to the solid at 20−22 °C. The mixture was stirred until dissolution was achieved, and then the organic phase was collected, washed with water, and concentrated to a final volume of 50 L. Acetone (100 L) and then silicagel (Merck Si 60; 10 kg) were added at 20−22 °C. The suspension was stirred for 1 h at 20−22 °C, and the silica was filtered off and washed with a 2/1 mixture of acetone and dichloromethane. The filtrate was concentrated to 50 L, and the solvents were replaced by diisopropyl ether at constant volume (final T = 64 °C). Arylestrone **5** crystallized during the distillation and was filtered at 20−22 °C and then dried in vacuo at 40−50 °C (7.37 kg white solid; yield: 73.7% (73.9% as dry product); HPLC purity: 99.9%): $C_{31}H_{39}NO_3$; MW: 473.7; IR ($CHCl_3$, cm^{-1}): ν 3598, 1732, 1610, 1580, 1512; NMR ^1H ($CDCl_3$, ppm): δ 0.49 (s, 3H), 3.90−4.05 (m, 3H), 6.38 (dd, J = 8.5 and 2.5 Hz, 1H), 6.44 (bs, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.44 and 6.95 (AA′BB′, 4H); MS (FAB^+; m/z): 474 (MH^+), 112, 98.

Dehydration of Cerium Trichloride Heptahydrate. Cerium trichloride heptahydrate (Johnson Matthey; MW = 372.5; 11.9 kg; 31.95 mol) was sequentially heated from 20 to 140 °C at 10−20 Torr within 4 h under stirring, then at 140 °C for 11 h; significant amounts of material were lost in the condenser. The solid was allowed to cool in an argon atmosphere. (6.33 kg white material; yield: 79.5% (as dry product); assay (Karl Fischer, methanol): 1.1% water)): $CeCl_3$; MW: 246.5.

17α-Methyl-11β-(4-(2-(1-piperidinyl)ethoxy)phenyl)-estra-1,3,5(10)-triene-3,17β-diol (6). A suspension of 10.92 kg of cerium trichloride (dehydrated as described above; water: 1.6%; MW = 246.5; 3.0 equiv) in THF (140 L) was stirred at reflux (67 °C) for 2 h and then cooled to 20−22 °C. Methylmagnesium chloride (Chemetall; 3 M solution in THF; 19.7 L; 4.0 equiv) was added over 15−20 min at 20−22 °C. The gray suspension was stirred for 1 h at 20−22 °C. A solution of Arylestrone **5** (7.00 kg; 14.78 mol) in THF (28 L) was added over 15−20 min at 20−22 °C, and the mixture was stirred for 1 h at 20−22 °C (TLC monitoring: dichloromethane/ethyl acetate/TEA: 50/45/5). Acetone (MW = 58.1; d = 0.79; 4.5 L; 4.1 equiv) was added over 15−20 min at 20−22 °C. The mixture was stirred for 15 min at 20−22 °C and then poured into a stirred mixture of aqueous saturated ammonium chloride (70 L), water (70 L), and ethyl acetate (140 L). The organic phase was washed with aqueous ammonium chloride (200 g/L), dried over sodium sulfate, and concentrated in vacuo. The white solid was dissolved in methanol (42 L) at 45−50 °C, and the solution was acidified to pH 5.5 by addition of aqueous 36% hydrochloric acid, at 33−37 °C. Methylarylestradiol hydrochloride crystallized on cooling. The suspension was stirred for 30 min at 20−22 °C, and then ethyl acetate (140 L) was added; the hydrochloride salt was filtered at 0−2 °C and dried in vacuo at 40 °C (7.50 kg white solid; yield: 96.4% (87.3% as dry product); HPLC purity: 99.9%): $C_{32}H_{44}ClNO_3$; MW: 526.2. Methylarylestradiol hydrochloride was dissolved in methanol (37.5 L) at 50−52 °C, and then water (75 L) was added at the same temperature. The pH was adjusted to 5.6−6.0 by addition of a 3.3% aqueous solution of potassium carbonate (0.40 L) to avoid degradation in acidic media. The solution was concentrated to a final volume of 75 L, and then methanol was replaced by water at constant volume (final T = 97 °C). Under these conditions, anhydrous hydrochloride crystallized on cooling at 80 °C and was stirred for 30 min at 80−82 °C. It was very important to isolate the anhydrous form by this approach; otherwise, undesirable forms of methylarylestradiol were obtained after neutralization. The hydrochloride was neutralized at 80−82 °C by adding a 3.3% aqueous solution of potassium carbonate (52 L) over 30 min. The suspension was stirred for 4h at 80−82 °C to complete the transformation of anhydrous hydrochloride into methylarylestradiol hydrate. The white solid was filtered at 20−22 °C, washed with water, and dried in vacuo at 35−40 °C. (6.43 kg white solid; overall yield: 88.8% (86.1% as dry product); HPLC purity: 99.8%): $C_{32}H_{43}NO_3$; MW: 489.7; differential scanning calorimetry: broad endotherm at 120 °C (dehydration + melting); IR ($CHCl_3$, cm^{-1}): ν 3602, 1610, 1580, 1512; NMR ^1H ($CDCl_3$, ppm): δ 0.51 (s, 3H), 1.29 (s, 3H), 3.98 (m, 3H), 6.41 (m, 2H), 6.78 (d, J = 8 Hz, 1H), 6.41 and 6.94 (AA′BB′, 4H); MS (FAB^+; m/z): 490 (MH^+), 112, 98.

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