Organic Process Research & Development **2004**, *8,* 219–228

Industrial Synthesis of 4-Chloro,11β-arylestradiol: How to Circumvent a Poor Diastereoselectivity

Denis Prat,* Françoise Benedetti, Gilles Franc Girard, Lahlou Nait Bouda, John Larkin, Christian Wehrey, and Jacques Lenay

Chemical/Process Development, Aventis Pharma, 102 Route de Noisy, 93235 Romainville Cedex, France

Abstract:

An industrial synthesis of 11β-arylestrone derivatives is described, based on the conjugate opening of a mixture of allylic 5(10)-α and -β epoxides by an aryl cuprate generated catalytically, followed by hydrolysis and subsequent aromatisation of the isomeric mixture of arylation products. An original method for selective 4-chlorination of estrone derivatives is also described.

Introduction

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

The main preventive treatment consisted of the regular intake of estradiol, which slows down the bone loss, but not without side effects. The ideal drug would have the benefit of estradiol on bone without the side effects on the other tissues. Such a drug is known as a "selective estrogen receptor modulator" (SERM).[1] The first SERM on the market, Eli Lilly's raloxifene (Evista) is not a steroid.[2]

In parallel, Hoechst Marion Roussel (now Aventis Pharma) has been developing a series of 11β-aryl,17β-estradiols, for the treatment of osteoporosis. Their steroid structure could be an advantage in terms of tolerance and specificity of action[3] (Figure 1). In 2002, we published in this journal the synthesis of one candidate, 11β-aryl,17α-methyl-estradiol **1**.[4] We report here the different synthetic approaches to another drug candidate, 4-chloro,11β-arylestradiol **2**.[3b]

First Preparative Synthesis

For the supply of the preclinical and phase 1 studies, the first batches of drug substance were prepared in the pilot plant from the known chiral norsteroid intermediate **3** (Scheme 1), in a similar synthesis used to prepare the 17-methyl derivative **1**.[4] Epoxidation by hydrogen peroxide catalyzed by hexachloroacetone[5] gave a 65/35 mixture of α-epoxide **4a** and β-epoxide **4b**. Crystallisation from acetonitrile afforded isomerically pure α-epoxide **4a** (33% yield).

The introduction of the aryl group at the 11β-position was carried out using a Cu(I)-mediated allylic opening of the α-epoxide by the corresponding Grignard reagent[5b,6] (Schemes 2 and 3). The keto group at C-17 was protected as a silyl enol ether[7] prior to this arylation. This protection allowed us to reduce by half the amount of copper(I) chloride catalyst and the expensive aryl side chain and also gave an increase in the overall yield.[4]

Ketone **4a** was silylated using lithium diisopropylamide[8] (LDA; 1.2 equiv) and the inexpensive chlorotrimethylsilane (TMSCl; 1.4 equiv), at 0 °C (Scheme 1). The silyl enol ether **5a** was not isolated but used as a solution in toluene.

The side-chain synthon **6** (4-(2-(diethylamino)ethoxy)-bromobenzene)[9] and the parent 4-(2-piperidino-ethoxy)-bromobenzene[2a,4] were previously prepared in homogeneous medium (DMF, K_2CO_3, or NaH) under harsh conditions, which resulted in modest yields. Therefore, we developed an improved procedure (Scheme 2), under phase transfer catalysis conditions,[4] under which 4-bromophenol and *N*-(2-chloroethyl)diethylamine hydrochloride (1 equiv), in the presence of 30% sodium hydroxide (2.2 equiv) and triethyl benzylammonium chloride (TEBAC, 5%), afforded the

* To whom correspondence should be addressed. E-mail: denis.prat@aventis.com. Telephone: (33) 15893 8262. Fax: (33) 15893 8274. Current address: Aventis Pharma, 13 Quai Jules Guesde, BP 14, 94403 Vitry/ Seine, France.

(1) (a) Grese, T. A.; Dodge, J. A. *Curr. Pharm. Design* **1998**, *4*, 71. (b) Jordan V. C. *J. Med. Chem.* **2003**, *46*, 883. (c) Jordan V. C. *J. Med. Chem.* **2003**, *46*, 1081.

(2) (a) Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057. (b) Vincenzi, J. T.; Zhang, T. Y.; Robey, R. L.; Alt, C. A. *Org. Process Res. Dev.* **1999**, *3*, 56. (c) Schmid, C. R.; Sluka, J. P.; Duke, K. M. *Tetrahedron Lett.* **1999**, *40*, 675. (d) Clemett, D.; Spencer, C. M. *Drugs* **2000**, *60*, 379.

(3) Bouali, Y.; Nique, F.; Teutsch, G.; Van De Velde, P. (Hoechst Marion Roussel.). FR 2,757,519, 1998.

(4) (a) Larkin, J. P.; Wehrey, C.; Boffelli, P.; Lagraulet, H.; Lemaitre, G.; Nedelec, A.; Prat, D. *Org. Process Res. Dev.* **2002**, *6*, 20. (b) Benedetti, F.; Mazurie, A.; Nique, F.; Prat, D.; Wehrey, C. (Aventis Pharma.). FR 2,-826,004, 2002.

(5) (a) Costerousse, G.; Teutsch, G. (Roussel Uclaf.). EP 5100, 1979. (b) Scholz, S.; Hofmeister, H.; Neef, G.; Ottow, E.; Scheidges, C.; Wiechert, R. *Liebiegs Ann. Chem.* **1989**, 151. (c) Neef, G.; Ast, G.; Michl, G.; Schwede, W.; Vierhufe, H. *Tetrahedron Lett.* **1994**, *35*, 8587. (d) Rao, P. N.; Taraporewala, I. B. *Steroids* **1992**, *57*, 154.

(6) (a) Teutsch, G.; Belanger, A. *Tetrahedron Lett.* **1979**, 2051. (b) Belanger, A.; Philibert, D.; Teutsch, G. *Steroids* **1981**, *37*, 361. (c) Napolitano, E.; Fiachi, R.; Hanson, R. N. *Gazz. Chim. Ital.* **1990**, *120*, 323. (d) Faraj, H.; Claire, M.; Rondot, A.; Aumelas, A.; Auzou, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3045. (e) Nique, F.; Van de Velde, P.; Brémaud, J.; Hardy, M.; Philibert, D.; Teutsch, G. *J. Steroid Biochem. Mol. Biol.* **1994**, *50*, 21. (f) Lobaccaro, C.; Pons, J. F.; Duchesne, M. J.; Auzou, G.; Pons, M.; Nique, F.; Teutsch, G.; Borgna, J. L. *J. Med. Chem.* **1997**, *40*, 2217.

(7) (a) Greene, T. W. and Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. (b) For a monograph, see: Van Look, G.; Simchen, G.; Heberle, J. *Silylating Agents*; Fluka Chemica, Fluka Chemie AG: Buchs, Switzerland, 1995.

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

(9) Pruitt, V. L.; Berlin, K. D.; Hirsch, K. S. *Org. Prep. Proced. Int.* **1990**, *22*, 235.

10.1021/op0341622 CCC: $27.50
Published on Web 01/31/2004

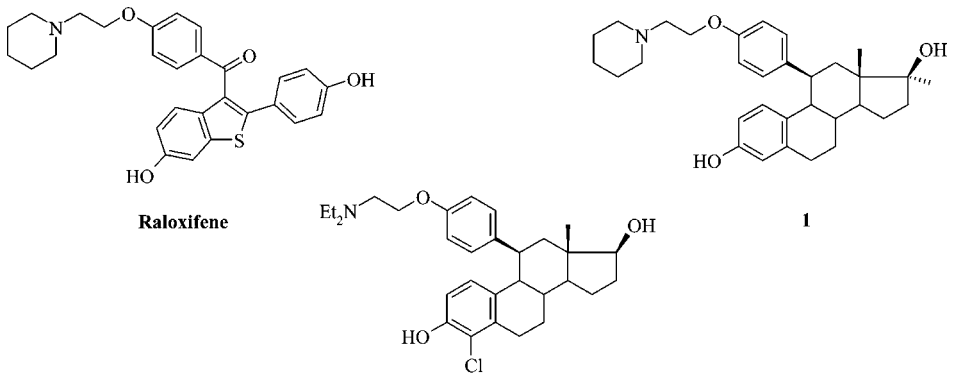
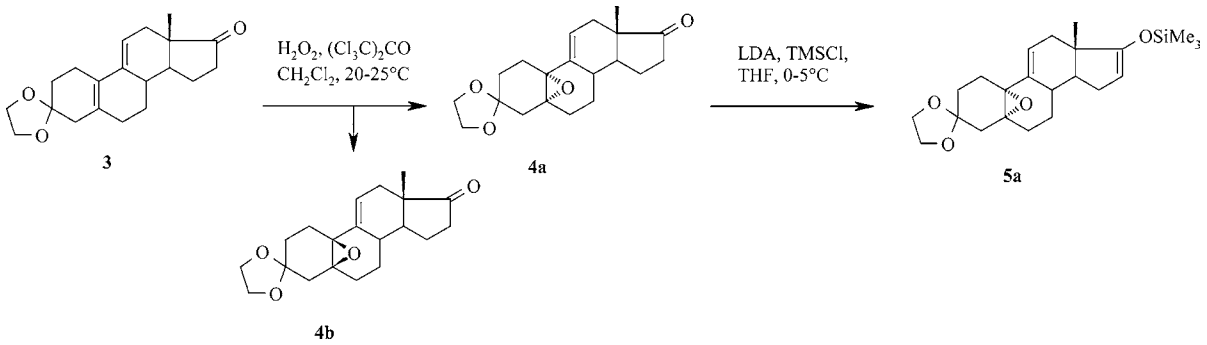
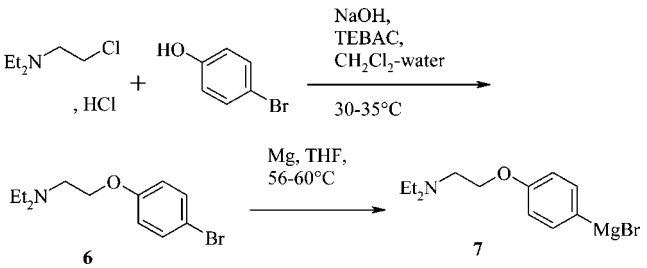


Figure 1. **SERM drug substances.**

Scheme 1. **Initial steps**



Scheme 2. **Preparation of the side-chain synthon**



bromoaryl derivative **6** in 82% yield. Reaction of **6** with magnesium turnings in THF at 58 °C gave the Grignard reagent **7** in an almost quantitative yield. These steps were very reproducible on scale-up.

The 11β-aryl side chain was introduced by a Cu(I)-mediated addition of Grignard reagent **7** (1.5 equiv), with copper(I) chloride (0.1 equiv) (Scheme 3). The arylation was initially carried out at −5 °C, and then the temperature was raised to +20 °C. Aqueous workup and concentration afforded the 11β-aryl alcohol **8b** which was not isolated. This allylic opening of the epoxide (S_N2') is known to proceed in a regio- and stereospecific manner,[6] but the NMR spectrum of the crude arylation mixture was too complex (partial hydrolysis of silyl ether) to confirm the absence of other isomers. Acidic hydrolysis of the alcohol **8b** cleaved the ketal and silyl groups and eliminated the 5-hydroxyl group, thereby yielding the dienone **9b**. Such an acidic treatment also salified the (2-diethylamino)ethoxybenzene which was formed by hydrolysis of the excess Grignard reagent, and this hydrochloride salt was eliminated in the aqueous phase, whereas the hydrochloride salt of the dienone was extracted into dichloromethane. After neutralisation (pH = 8), the dienone **9b** was crystallised from diisopropyl ether, providing a 73−79% yield range in both the laboratory and the pilot plant. The deconjugated dienone **9c** was also formed (5−10%), but this oily product was easily eliminated in the mother liquors.[10]

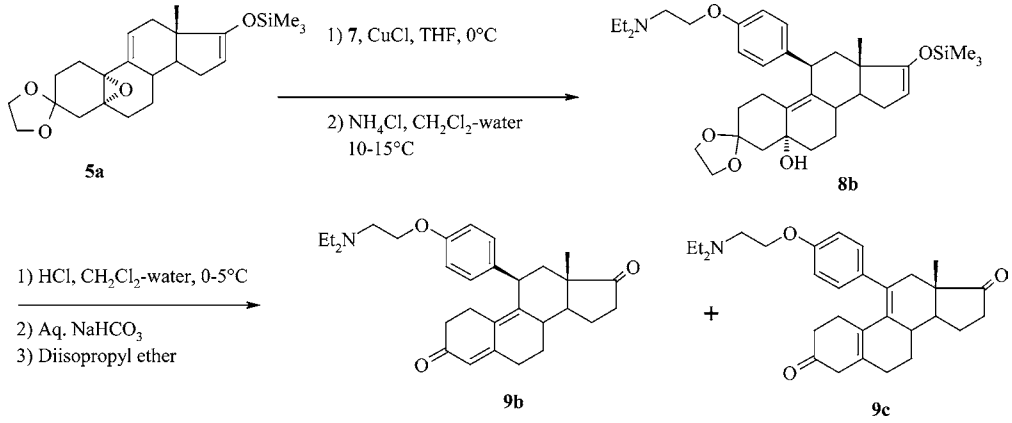
The dienone **9b** was chlorinated using sulfuryl chloride (1.5 equiv) and pyridine (29 equiv), in dichloromethane at −40 °C[11] (Scheme 4). 4-Chlorodienone hydrochloride **10** was crystallised from ethyl acetate (yield: 82%; purity: 73%). This reaction was incomplete and gave several secondary products, which will not be detailed here. Compound **10** was aromatised using a mixture of acetyl bromide (3.8 equiv) and acetic anhydride (3 equiv) in dichloromethane at room temperature,[6c,e,f,12] giving an estrone acetate which was immediately saponified. The aromatisation reaction afforded also ca. 10% of elimination product **12**. Fortunately, crystallisation of the 4-chloroarylestrone hydrochloride **11** from dichloromethane removed most of the numerous impurities generated in these chlorination and aromatisation steps. However, the yields (40% from **9b** in the lab, 44% in the pilot plant) and the purity (ca. 90%) were low.

(10) This type of dienone has already been described: see ref 6e.

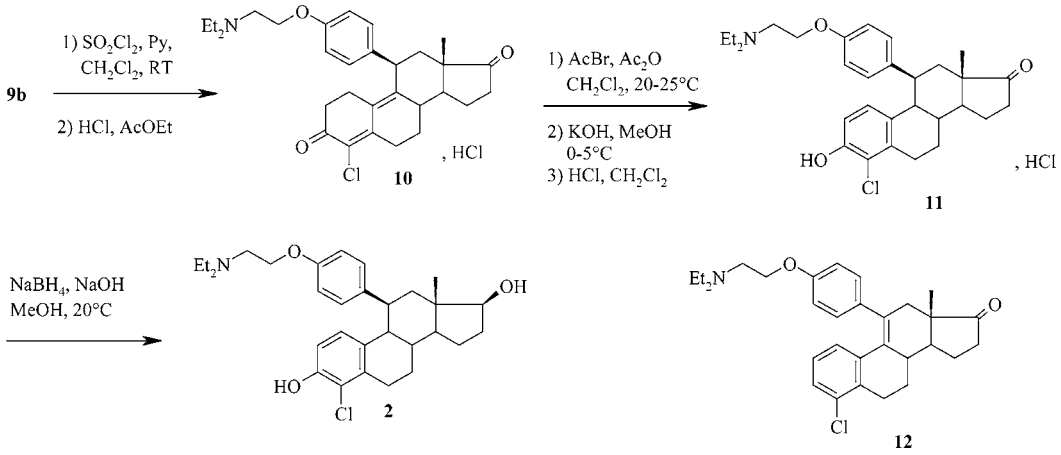
(11) (a) Nickisch, K.; Bittler, D.; Casals-Stenzel, J.; Laurent, H.; Nickolson, R.; Nishino, Y.; Petzoldt, K.; Wiechert, R. *J. Med. Chem.* **1985**, *28*, 546. (b) Bourban, C. Y. M.; Hanson, J. R.; Hitchcock, P. B. *J. Chem. Res. (S)* **1990**, 274. (c) Christiansen, R. G.; Bell, M. R.; D'Ambra, T. E.; Mallamo, J. P.; Herrmann, J. L.; Ackerman, J. H.; Opalka, C. J.; Kullnig, R. K.; Winneker, R. C.; Snyder, B. W.; Batzold, F. H.; Schane, H. P. *J. Med. Chem.* **1990**, *33*, 2094. (d) Hasrat, A.; Van Lier, J. E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2485.

(12) (a) Joly, R.; Joly, J. (Roussel Uclaf.). FR 81840, 1962. (b) Danishefsky, S.; Cain, P.; Nagel, A. *J. Am. Chem. Soc.* **1975**, *97*, 380; c) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1975**, *97*, 5282.

Scheme 3. **Arylation of the α-epoxide**



Scheme 4. **First pilot-scale synthesis: last steps**



The 4-chloroarylestrone hydrochloride **11** was neutralised with sodium hydroxide and reduced with sodium borohydride in methanol. This reduction is known to give very selectively the 17β-alcohol,[5d,6e,13] but to check the isomer purity, we prepared the 17α-alcohol, and this diastereomer could not be detected in the crude product (<0.3%) by HPLC. The drug substance **2** was crystallised from methanol, in two crops (yield: 85%). In the pilot plant, however, only the first crop was pure enough for clinical use. The yield was thus limited to 66−71%.

A synthesis in the pilot plant without preparative chromatography was achieved, largely as a result of the crystallinity of most of the intermediates. However, because of the poorly stereoselective initial epoxidation and the numerous by-products generated in the chlorination−aromatisation sequence, the overall yield was unsatisfactory (7−8%). Therefore, efforts were directed to designing, optimizing, and scaling up new syntheses of this drug candidate.

Second Pilot-Scale Synthesis

Despite its drawbacks, the preparative synthesis described above was not abandoned, as the strategy was sound. Ethylene deltenone **3**, an industrial intermediate for norsteroids, particularly trimegestone,[14] was a suitable starting material for the synthesis. Epoxide **4a** was crystalline, in contrast to analogous epoxides bearing other functions at C-17. The introduction of the preformed aryl side chain made the route convergent, and the reduction was best performed at the last step.[15] Thus, in the pre-industrial phase, we carried out more detailed investigations of the epoxidation step and the chlorination−aromatisation sequence.

1. Epoxidation. The introduction of the aromatic moiety at the 11β-position required an almost diastereomerically pure 5,10α-epoxide **4a**.[6] Optimisation of the initial epoxidation permitted us to increase the yield from 33 to 49%,[4] first by using hexafluoroacetone[6c,d,16] as the catalyst, which is slightly more selective than hexachloroacetone[5] (α/β = 2.1 and 1.8, respectively), and second by crystallizing the α-epoxide **4a** from ethyl acetate instead of acetonitrile.

2. Aromatisation. In the first preparative synthesis, chlorination was performed first, and then the chlorodienone was aromatised. As mentioned above, both steps gave by-products, such as the elimination product **12** formed during the aromatisation step. On the other hand, aromatisation of non-chlorinated dienones such as **9b** is a classic reaction in

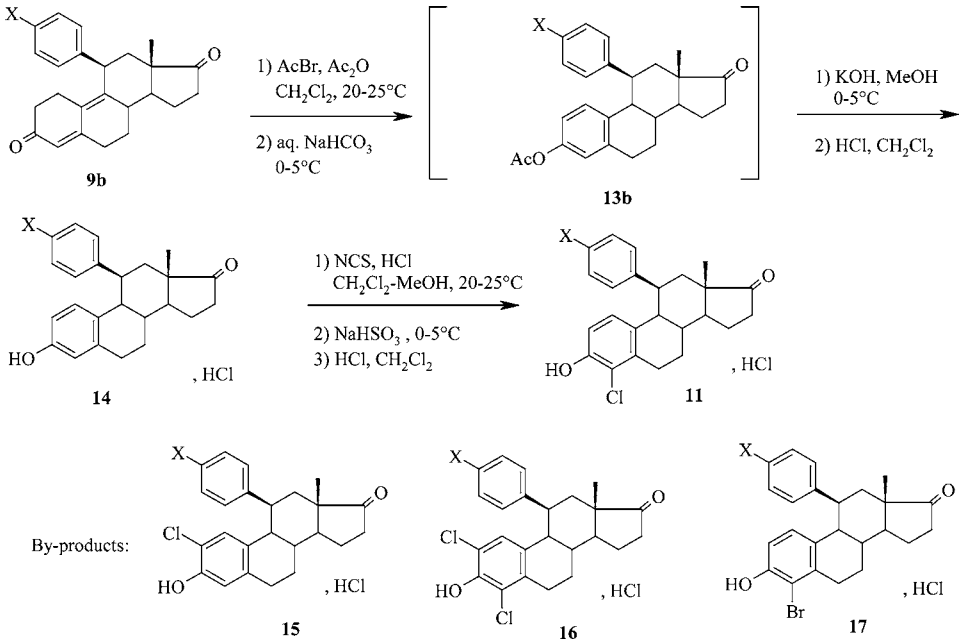
(13) (a) Shimada, K.; Xie, F.; Nambara, T. *Chem. Pharm. Bull.* **1986**, *34*, 179. (b) Bulman Page, P. C.; Hussain, F.; Maggs, J. L.; Morgan, P.; Park, B. K. *Tetrahedron* **1990**, *46*, 2059. (c) Tada, M.; Chiba, K.; Izumiya, K.; Tamura, M. *Bull. Chem. Soc. Jpn*. **1993**, *66*, 3532. (d) Aliau, S.; Delettre, G.; Mattras, H.; El Garrouj, D.; Nique, F.; Teutsch, G.; Borgna, J. L. *J. Med. Chem.* **2000**, *43*, 613. (e) Schneider, M. F.; Harre, M.; Pieper, C. *Tetrahedron Lett.* **2002**, *43*, 8751.

(14) Crocq, V.; Masson, C.; Winter J.; Richard, C.; Lemaitre, G.; Lenay, J.; Vivat, M.; Buendia, J.; Prat, D. *Org. Process Res. Dev.* **1997**, *1*, 2.

(15) The intermediates bearing a 17-hydroxyl group were less crystalline.

(16) Teutsch, G.; Belanger, A.; Philibert, D.; Tournemire, C. *Steroids* **1982**, *39*, 607.

Scheme 5. **Second pilot-scale synthesis (X = $Et_2NCH_2CH_2O$)**



norsteroid chemistry[6c,e,f,12] and proceeds cleanly, with little elimination. Thus, we decided to aromatise first and then to try to chlorinate the estrone ring as selectively as possible (Scheme 5).

Aromatisation of dienone **9b** was carried out using a mixture of acetyl bromide (2.5 equiv) and acetic anhydride (1 equiv) in dichloromethane at 20−25 °C. The estrone acetate **13b** formed was saponified (KOH, MeOH), affording 11β-arylestrone. The hydrochloride salt **14** was crystallised from methylethyl ketone in a good yield (ca. 85% from **9b**), in the lab and in the pilot plant.

3. Chlorination. Chlorination of estrogen derivatives has been studied, but not extensively.[17] Many reagents have been tested, such as sulfuryl chloride, chlorine, *N*-chlorosuccinimide (NCS), trichloroisocyanuric acid, *tert*-butylhypochlorite, and hexachloro-2,4-cyclohexanedienone. Most of these gave complex mixtures of 4-chloro and 2-chloro substitution products and also products from para-addition such as 10β-chloroestra 1,4-diene-3-one. The formation of the latter product could be prevented, using 11β-substituted estrogen derivatives. From these substrates, hexachloro-2,4-cyclohexanedienone afforded a relatively clean mixture of 4-chloro- and 2-chloroestrogens and the 4-Cl/ 2-Cl selectivity decreased with the size of the 11β-substituent,[17c] but no hypothesis has hitherto been proposed to account for this regioselectivity.

Many reagents and conditions have been described for the chlorination of phenols,[18] most often with the aim of influencing the regioselectivity. Although chlorodialkylamines and chlorotrialkylammonium chlorides have been used in acidic solutions,[19] the simple use of *N*-chlorosuccinimide, sometimes with an acid catalyst, has only very recently been reinvestigated.[20]

We rapidly abandoned sulfuryl chloride as chlorinating agent, which favored bis-chlorination of arylestrone hydrochloride **14**, even at low temperature (−40 °C). On the other hand, the use of NCS in the presence of strong acids gave promising results, notably a good 4-Cl/2-Cl selectivity (Scheme 5). Nevertheless, optimisation of this step required 45 experiments. For example, the reaction mixture was heterogeneous: both the starting arylestrone hydrochloride **14** and the 4-chloroarylestrone hydrochloride **11** crystallised from the mixture. As a result, some starting material cocrystallised with the product, and attempts to consume it totally resulted in bis-chlorination. Therefore, the reaction was better carried out in a mixture of methanol and dichloromethane, in which all the materials were soluble. Using 1.00 equiv of NCS at 10 °C and in the presence of hydrochloric acid (0.5 equiv),[21] the final reaction mixture contained (as HCl salts) ca. 1−2% of starting arylestrone **14**, 83−88% of the desired 4-chloroerylestrone **11**, 10−11% of the 2-chloro isomer **15** and 1−2% of the 2,4-dichloro derivative **16** (Scheme 5). After reductive workup (sodium

(17) (a) Schwenk, E.; Castle, C. G.; Erzsebet, J. *J. Org. Chem.* **1963**, *28*, 136. (b) Mukawa, F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 457. (c) Hasrat, A.; Van Lier, J. *Steroids* **1994**, *59*, 498. (d) Cummins, C. H. *Steroids* **1994**, *59*, 590.

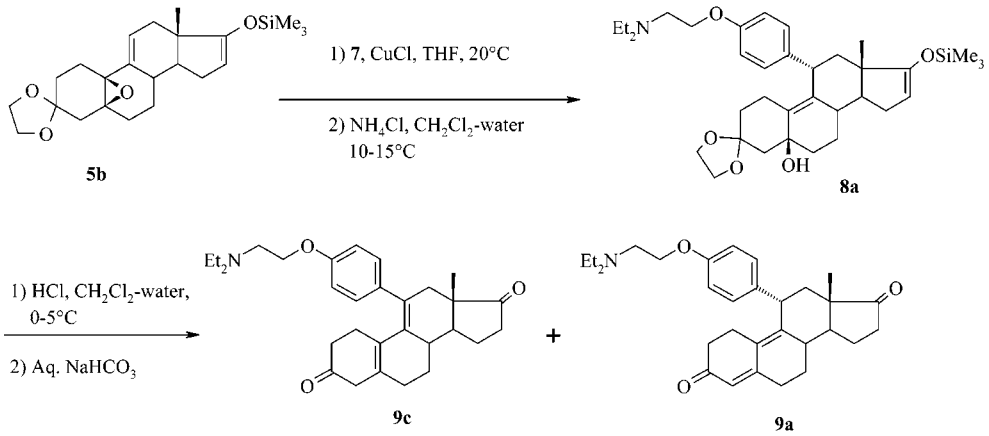
(18) (a) Guy, A.; Lemaire, M.; Guetté, J. P. *Tetrahedron* **1982**, *38*, 2339. (b) Watson, W. D. *J. Org. Chem.*, **1985**, *50*, 2145. (c) Schmitz, E.; Pagenkopf, I. *J. Prakt. Chem.* **1985**, *327*, 998. (d) Onyiriuka, S. O.; Suckling, C. J. *J. Org. Chem.* **1986**, *51*, 1900. (e) Smith, K.; Butters, M.; Nay B. *Tetrahedron Lett.* **1988**, *29*, 1319. (f) Kamigata, N.; Satoh, T.; Yoshida, M.; Matsuyama, H.; Kameyama, M. *Bull. Chem. Soc. Jpn* **1988**, *61*, 2226. (g) Chung, K. H.; Kim, H. J.; Kim, H. R.; Ryu, E. K. *Synth. Commun.* **1990**, *20*, 2991. (h) Gnaim, J. M.; Sheldon, R. A. *Tetrahedron Lett.* **1995**, *36*, 3893. (i) Deshmukh, A. P.; Padiya, K. J.; Jadhav, V. K.; Salunkhe, M. M. *J. Chem. Res. (S)* **1998**, 828. (j) Mukhopadhyay, S.; Chandnani, K. H.; Chandalia, S. B. *Org. Process Res. Dev.* **1999**, *3*, 196. (k) Mamaghani, M.; Zoligol, M. A.; Shojaei, M. *Synth. Commun.* **2002**, *32*, 735.

(19) (a) Lindsay Smith, J. R.; McKeer, L. C. *Tetrahedron Lett.* **1983**, *24*, 3117. (b) Lindsay Smith, J. R.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 385.

(20) (a) Rama Rao, A. V.; Chakraborty, T. K.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1994**, *35*, 5043. (b) Madsen, P. *J. Med. Chem.* **2002**, *45*, 5755. (c) Speicher, A.; Koltz, J.; Sambanje, R. P. *Synthesis* **2002**, 2503. (d) Das, S. K.; Reddy, K. A.; Abbineni, C.; Iqbal, J.; Suresh, J.; Premkumar, M.; Chakrabarti, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 399.

(21) The hydrochloride salt of the trisubstituted amine on the side chain was not acidic enough to catalyze the reaction.

Scheme 6. **Arylation of the β-epoxide**



thiosulfate), the 4-chloroarylestrone hydrochloride **11** was crystallised from dichloromethane in 75−77% yield in the pilot plant (purity: 98%). The higher solubility of the 2-isomer facilitated purification. In the initial experiments, traces of the 4-bromo analogue **17** were also detected in compound **11** and this impurity could not be totally removed, even by crystallisation. The bromine came from the previous steps: acetyl bromide was used in the aromatisation reaction, and some of it survived the intermediate hydrolysis, and was cleaved during the saponification of the arylestrone acetate. The bromide ions thus generated were present in the crystallised arylestrone **14**, as the hydrobromide salt. In the presence of NCS, this hydrobromic acid may have formed BrCl, an effective brominating agent.[22,23] Extensive aqueous washing of the organic phases, after aromatisation and saponification, avoided the formation of the 4-bromo impurity.

As a conclusion, inversion of the chlorination−aromatisation steps resulted in an increase in the overall yield (**9b** to **11**) from 44 to 65% in the pilot plant and an improvement in the purity of the product **11** from 90 to 98%.

4. Crystallisation of the Drug Substance. The first two pilot-plant batches were crystallised from methanol. The first one, in 66% yield; the second, in 71% yield, as a result of the higher purity of the product. For the subsequent batches (dedicated to phase 2 studies), we selected 2-propanol as a crystallisation solvent. The drug substance was obtained in one crop, in 83% (lab) to 89% (pilot) yield. As the selected form was a monohydrate (ca. 3.5% water), the 2-propanol solvate was suspended into water at 80 °C and then filtered at 20 °C, dried, and micronised under an atmosphere of nitrogen saturated with steam.

Industrial Synthesis

Despite the improvements described above, which increased the overall yield from 7−8 to ca. 20%, the synthesis still suffered from a modest yield in the epoxidation step (49%). In an ideal route, both α and β epoxides **4a** and **4b** would be used.

It had been observed that silyl enol ether **5b** derived from the epoxyketone **4b** reacted slower than in α series, requiring more copper chloride (0.2 equiv), higher temperatures (20 °C), and more Grignard reagent (2 equiv) (Scheme 6). An 11α-aryl,5β-alcohol **8a** was obtained, the hydrolysis of which gave mainly the deconjugated dienone **9c**, with minor amounts (ca. 10%, NMR estimation) of the 11α-aryl dienone **9a**. The exact mass balance could not be established, compound **9c** being neither stable (especially on silica gel) nor crystalline: after chromatography, only 6% of **9c** and 3% of **9a** were isolated. These results were at first glance of little synthetic interest.

The aromatisation reaction also gave unexpected results. During its optimisation, we observed that starting 11β-dienone **9b** disappeared within 1 h in the reaction mixture (AcBr, Ac_2O, CH_2Cl_2), giving an intermediate which rearranged within 4 h into the 11β-estrone acetate **13b** (Scheme 7). According to LC−MS it had the same molecular mass as the estrone acetate, and we proposed the structure **13d** for this intermediate. Later, we succeeded in isolating it, and to our surprise, it was the isomeric trienol acetate **13c**. Compound **13d** probably formed as a very unstable intermediate.[24]

The structure of the trienol acetate **13c** was established unambiguously by NMR spectroscopy. The axial Me_{18} group displayed a singlet at 1.02 ppm, in contrast to the 11β-aryl derivatives, in which the shielding effect of the axial aromatic ring gave a chemical shift of 0.3 to 0.5 ppm. Moreover, no benzylic proton (H_{11}) was detected, and only one olefinic proton, at 5.52 ppm (H_4).[25]

In compound **13c**, the 11-aryl group was no longer β, but it transformed into the β-aryl product **13b** in a highly

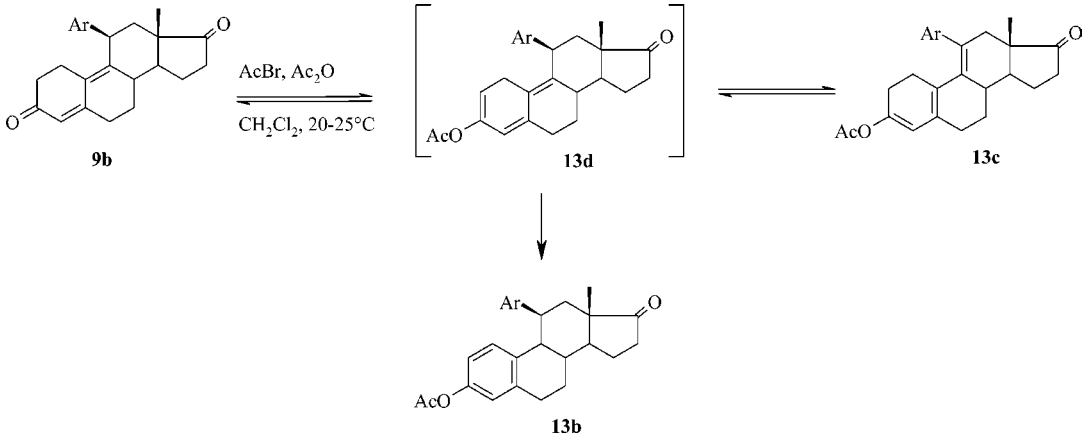
(22) (a) Fieser, M.; Fieser, L. *Reagents for Organic Synthesis*; Wiley Interscience and John Wiley & Sons: New York, 1967; Vol. 1, p 72; Vol. 2, p 38; Vol. 6, p 102. (b) Focht, G. D.; Klobucar, W. D. (Albermarle Corp.). U.S. Patent 6,271,417, 2001. (c) Muatten, H. A. *Synthesis* **2002**, 169.

(23) As bromination of arylestrone hydrochloride **14** using *N*-bromosuccinimide (NBS, 1.5 equiv) and HCl (0.5 equiv) resulted in a very slow reaction, NBS is probably not the actual brominating agent in the presence of NCS.

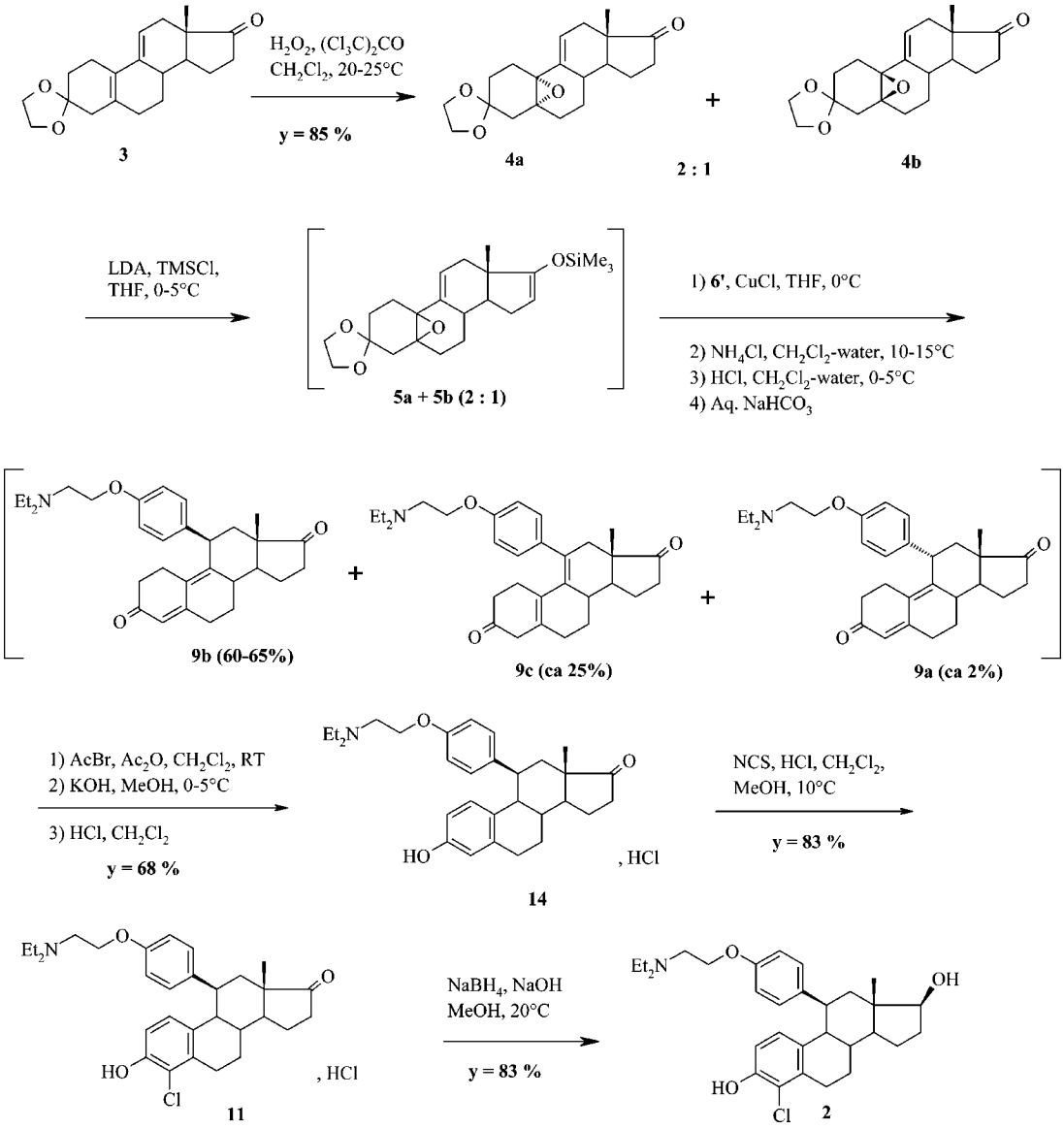
(24) At first glance, it may look obvious that **13c** would be more stable than **13d**, in which the axial aryl group interacts with the axial Me_{18}. On the other hand, conjugation with the aryl group in **13c** imposes important strain between the aryl group and H_1.

(25) F. Nique, and J. L. Borgna et al. isolated a deconjugated dienone such as **9c** after alkaline treatment of an aromatisation mixture (ref 13d). This dienone was probably the saponification product of a trienol acetate similar to **13c**.

Scheme 7. **Proposed mechanism of A-ring aromatisation**



Scheme 8. **Industrial synthesis of 4-chloro,11β-estradiol 2**



stereoselective way. Thus, starting from pure α-epoxide **4a**, only ca. 0.5% of the 11α-aryl isomer was detected in the crude mixture after aromatisation and saponification.

These observations opened the way to the synthetic use of the hitherto "undesired" β-epoxide **4b**: the deconjugated dienone **9c** was the main product of silylation−arylation of the epoxide **4b**, and we expected the trienol acetate **13c** to be the first intermediate in the aromatisation of dienone **9c** and that compound **13c** would eventually transform into the 11β-aryl product **13b** in the same way.

It would therefore be tempting to submit the crude mixture of epoxides (α/β = 65/35) to the sequence silylation, arylation, aromatisation, and saponification, as the final product should be the arylestrone hydrochloride **14** (Scheme 8). Moreover, this would put to good use the small amount of the deconjugated dienone **9c** which was formed from epoxide **5a** (Scheme 3) and which was previously lost during the purification of dienone **9b**.

Ethylene deltenone **3** was epoxidised using hydrogen peroxide and hexachloroacetone, and a single crystallisation from diisopropyl ether afforded the epoxide mixture ($\alpha/\beta \approx$ 2/1), leaving minor impurities in the mother liquors. Silylation gave a ca. 2/1 mixture of silyl enol ethers **5a** and **5b**, which was not separated. The arylation was carried out using 2 equiv of Grignard reagent **7** and 0.15 equiv of copper(I) chloride, at 20 °C. Workup (aqueous ammonium chloride) and acidic hydrolysis resulted in a mixture of aryl dienones **9b**, **9c**, and **9a** (Scheme 8; the ratio of enones was estimated by NMR spectroscopy). The mixture was rapidly aromatised, affording, after 4−5 h at room temperature, 11β-arylestrone acetate **13b** as the main product. Again, it was not isolated but saponified to give the 11β-arylestrone, which was crystallised as the hydrochloride **14**. The yield from the mixture of epoxides was ca. 68%, on the laboratory and pilot-plant scale. Thus, from ethylene deltenone **3**, this "recycling process" permitted us to increase the overall yield in arylestrone hydrochloride **14** from 28 to 58%.[26] The purity was only slightly lower (95%) than the purity (98%) of the previous batches prepared from 95% pure α-epoxide. Ca. 1% of 11α-aryl isomer was detected in the crude reaction mixture after aromatisation and saponification, and only 0.15% in the crystallised product **14**. Chlorination and reduction gave the drug substance **2** with the same purity as previously obtained and in the same yield (ca. 69%). Maintaining the same profile of impurities in the drug substance was very important, since the batches were used in clinical trials. For the same reasons, the last steps (chlorination and reduction) were not modified. As is usual in the development of a drug candidate, these last steps were optimised first, and then the core of the synthesis was optimised.

Conclusions

The first preparative synthesis of 4-chloro, 11β-aryl estradiol **2** suffered mostly from a poorly stereoselective epoxidation and an inappropriate chlorination−aromatisation sequence, thus resulting in a low overall yield (7−8%). However, it allowed the delivery of the drug batches in time for the pre-clinical studies and the phase 1 clinical trials.

Optimisation of the epoxidation and implementation of an original chlorination of an estrone derivative resulted in a ca. 20% overall yield, which facilitated the delivery of the drug substance for the phase 2 clinical studies. This synthesis would have been acceptable for further scale-up, especially because of the very low dosage of the drug substance.

Nevertheless, we found a way to transform both epoxides at the same time, thus providing another 2-fold increase in the overall yield of the synthesis (ca. 40%). Silylation and arylation of the by-product of epoxidation, the β-epoxide **4b**, afforded an unstable deconjugated aryl dienone **9c**. Its structure suggested that it could converge to the same unstable intermediate **13c** in the aromatisation reaction, as that obtained from the α-epoxide **4a**. This intermediate eventually gave the final product **2** with the desired configuration. Hence, these seemingly undesired and unstable products were the cornerstone of a new industrial synthesis.

Again, norsteroids still reveal surprises to the chemist, despite all the knowledge accumulated on this old family of products.

Experimental Section

General. Except for the isolation of intermediates, all the steps described here were launched in the pilot plant on a multikilogram scale. However, for the sake of confidentiality, only the experimental procedures from the laboratory will be given here. Nevertheless, they were reproducible on scale-up.

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

For all the TLC monitoring, Merck Si 60 F254 plates were used.

The aromatisation reactions, and the subsequent steps, were monitored by HPLC with the following system: Hypersil DBS 3 μm CN; 150 mm × 4.6 mm; eluent: water + 0.1% TFA: 65, acetonitrile: 30, methanol: 5; flow rate: 1 mL/min; detection: UV 210 nm.

3,3-Ethylenedioxy-5(10)-epoxy-estr-9(11)-ene-17-one (2/1 Mixture of Isomers 4a[4] and 4b[4]). Ethylene deltenone **3** (50 g; MW: 314.4; 0.159 mol), hexachloroacetone (Janssen, 98%; MW: 264.7; 4.35 g; 0.1 equiv), pyridine (0.25 mL), 50% hydrogen peroxide (ca. 18 M; 15 mL; 1.7 equiv) and dichloromethane (250 mL) were stirred vigorously for 18 h at 20−25 °C (TLC monitoring: *n*-heptane 6, ethyl acetate 4). After reductive workup (aqueous sodium thiosulfate), washing (water), and extraction (dichloromethane), the organic phase was concentrated to a total volume of 150 mL. Then, dichloromethane was exchanged for diisopropyl ether by continuous distillation at constant volume, until the temperature of the liquid reached 68 °C. The mixture was cooled to 20 °C. The mixture of epoxides crystallised spontaneously. The suspension was cooled to 0 °C and stirred for 1 h, then **4a,b** was filtered and dried under vacuum for 18 h at 40 °C (44.6 g white solid; yield: 84.9%; purity (LC): 97%): $C_{20}H_{26}O_4$; MW: 330.4; ^{1}H NMR ($CDCl_3$, ppm): δ 0.87 (s, 3H, **4b**), 0.88 (s, 3H, **4a**), 3.94 (m, 4H), 5.86 (m, 1H, **4b**), 6.05 (m, 1H, **4a**).

3,3-Ethylenedioxy-5(10)-epoxy-17-(trimethylsilyloxy)-estra-9(11),16-diene (2/1 Mixture of Isomers 5a[4] and 5b). This procedure was used to silylate any mixture of epoxides. *n*-Butyllithium (Chemetall, 17% solution in cyclohexane; 68 g; 1.2 equiv) was added over 30 min to a stirred solution of diisopropylamine (MW: 101.2; d: 0.714;

(26) Using hexachloroacetone as the epoxidation catalyst, the yield in crystallised **4a** was 43%.

30 mL; 1.4 equiv) in anhydrous THF (100 mL), at −10 °C. This solution was added over 30 min at 0 °C to a solution of epoxides **4a,b** (50 g; 151 mmol) in THF (150 mL), and the mixture was stirred for 15 min at 0 °C. Trimethylchlorosilane (MW: 108.6; d: 0.856; 27 mL; 1.4 equiv) was added over 15 min at 0 °C, and the mixture was stirred for 1 h at 0 °C (TLC monitoring: toluene 1, ethyl acetate 1). Methanol (MW: 32.0; d: 0.792; 5 mL; 0.8 equiv) was added at 0 °C, and the mixture was stirred for 30 min at ca. 10 °C and then poured into a biphasic mixture of aqueous sodium dihydrogen phosphate (MW: 156.0; 26 g; 1.1 equiv) and toluene. After decantation, the organic phase was dried over sodium sulfate and stored as a solution in toluene (ca. 100 mL). Concentration under vacuum afforded a waxy solid in quantitative yield. $C_{23}H_{34}O_4Si$; MW: 402.6; ^{1}H NMR ($CDCl_3$, 250 MHz, 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, **5a**), 4.52 (m, 1H, **5b**), 5.86 (m, 1H, **5b**), 6.03 (m, 1H, **5a**).

4-(2-(Diethylamino)ethoxy)bromobenzene (6).[9] To a stirred solution of 4-bromophenol (Fluka; MW: 173.0; 150 g; 0.867 mol), (2-chloroethyl)diethylamine hydrochloride (ACROS Organics; MW: 172.1; 150 g; 1.00 equiv), and TEBAC (Merck; 15 g) in dichloromethane (750 mL) at 25−30 °C was added a 30% aqueous solution of sodium hydroxide (MW: 40.0; 271 g; 2.3 equiv). The mixture was stirred vigorously at 30−35 °C for 18 h (TLC monitoring: dichloromethane 45, ethyl acetate 45, TEA 10). Sodium chloride crystallised 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 (192.6 g yellow oil; yield: 81.6%; purity (GC): 99%): $C_{12}H_{18}BrNO$; MW: 272.2; IR ($CHCl_3$, cm^{-1}): ν 1592, 1579, 1490; ^{1}H NMR ($CDCl_3$, ppm): δ 1.06 (t, J = 7 Hz, 6H), 2.62 (q, J = 7 Hz, 4H), 2.85 (t, J = 6.5 Hz, 2H), 4.00 (t, J = 6.5 Hz, 2H), 6.78 and 7.35 (AA′BB′, 4H); MS (EI; m/z): 271 (M^+), 256, 185, 171, 86.

Grignard Reagent (7). A mixture of magnesium turnings (MW: 24.3; 7.5 g; 1.13 equiv) and 25 mL of a solution of 4-(2-(diethylamino)ethoxy)bromobenzene (MW: 272.2; 74 g; 0.272 mol) in THF (250 mL) was stirred at 60 °C until the reaction started (exotherm; gray colour). The rest of the solution was added cautiously over ca. 60 min at 58 °C, and the mixture was stirred for an additional hour at 58 °C and then allowed to cool to room temperature. Assay (potentiometry): ca. 1.0 M.

11-(4-(2-(Diethylamino)ethoxy)phenyl)estra-5(10),9(11)-diene-3,17-dione (9c) and 11α-(4-(2-(Diethylamino)ethoxy)phenyl)estra-4,9-diene-3,17-dione (9a). Copper(I) chloride (99%; MW = 99.0; 600 mg; 0.2 equiv) was added at 20 °C to a solution of silyl enol ether **5b** (β isomer; 12.2 g; 30.3 mmol) in THF (30 mL). A solution of 1 M Grignard reagent **7** in THF (61 mL; 2 equiv) was then added at ca −3 °C. The mixture was stirred for 1 h at 20 °C (TLC monitoring: toluene 1, ethyl acetate 1) and then poured into a biphasic mixture of 25% aqueous solution of ammonium chloride and dichloromethane. The organic phase was washed with water and then concentrated under vacuum to dryness. Dichloromethane (80 mL) and aqueous hydrochloric acid (4.75 equiv; 42 mL) were added at 0−5 °C (exothermic). The biphasic mixture was stirred vigorously during 2 h at 0−5 °C and then diluted with water (50 mL). The organic phase was decanted, washed with water, and then neutralised (pH = 8) with aqueous 10% sodium bicarbonate solution (50 mL), washed with water, dried over sodium sulfate, and concentrated to dryness. The residue (11 g, 79%) was purified by chromatography on silica gel (eluent: *n*-heptane 50, ethyl acetate 45, triethylamine 5). Concentration of the purest fractions afforded:

800 mg of 9c (5.7%; oil): $C_{30}H_{39}NO_3$; MW: 461.6; IR ($CHCl_3$, cm^{-1}): ν 1733, 1712, 1607, 1568, 1508; ^{1}H NMR ($CDCl_3$, ppm): δ 1.03 (s, 3H); 1.12 (t, J = 7 Hz, 6H); 2.72 (q, J = 7 Hz, 4H); 2.94 (t, J = 6 Hz, 2H); 4.09 (t, J = 6 Hz, 2H); 6.82 and 7.07 (AA′BB′, 4H); MS (EI, m/z): 461 (M^+), 100.

444 mg of 9a (3.2%; oil): $C_{30}H_{39}NO_3$; MW: 461.6: ^{1}H NMR ($CDCl_3$, ppm): δ 1.02 (s, 3H); 1.12 (t, J = 7 Hz, 6H); 2.69 (q, J = 7 Hz, 4H); 2.91 (t, J = 7 Hz, 2H); 4.05 (m, 3H); 5.72 (s, 1H); 6.79 and 6.95 (AA′BB′, 4H); MS (ESP, m/z): 426 (MH^+).

Mixture of 11β-(4-(2-(Diethylamino)ethoxy)phenyl)-estra-4,9-diene-3,17-dione (9b), and of Diene-diones 9c and 9a. Copper(I) chloride (MW = 99.0; 2.25 g; 0.15 equiv) was added at 20 °C to a ca. 1 M solution of Grignard reagent **7** in THF (300 mL; 2.0 equiv). A solution of silyl enol ethers (**5b**/**5a** ≈ 2/1) (60.8 g; 151 mmol) in toluene (100 mL) and THF (100 mL) was added during ca. 30 min at 20 °C (exothermic). The mixture was then stirred for 1 h at 20 °C (TLC monitoring: toluene−ethyl acetate 1/1) and then poured into a biphasic mixture of aqueous ammonium chloride (15 equiv; 600 mL) and dichloromethane at 10−15 °C. The organic phase was separated, washed with water, concentrated under vacuum to ca. 100 mL and diluted with dichloromethane (250 mL). Aqueous hydrochloric acid (6 equiv; 200 mL) was added at 0−5 °C (exothermic). The biphasic mixture was stirred vigorously for 2 h at 0−5 °C and then diluted with water (250 mL). The organic phase was decanted and washed with water. The organic phase was carefully neutralised (pH = 8) with aqueous 10% sodium bicarbonate (250 mL) (evolution of carbon dioxide), washed with water, and dried over sodium sulfate. Concentration to dryness afforded a semi-crystalline material (67.5 g; 97% yield). Compound **9b** could be isolated by crystallisation from diisopropyl ether: $C_{30}H_{39}NO_3$; MW: 461.6; mp (DSC): 188 °C; IR ($CHCl_3$, cm^{-1}): ν 1735, 1658, 1609, 1581, 1509; ^{1}H NMR ($CDCl_3$, ppm): δ 0.56 (s, 3H), 1.06 (t, J = 7 Hz, 6H), 2.63 (q, J = 7 Hz, 4H), 2.85 (t, J = 6 Hz, 2H), 4.01 (t, J = 6 Hz, 2H), 4.38 (ld, J = 7 Hz, 1H), 5.80 (s, 1H), 6.82 and 7.07 (AA′BB′, 4H); MS (EI, m/z): 461 (M^+).

11β-(4-(2-(Diethylamino)ethoxy)phenyl)estra-1,3,5(10)-trien-3-ol-17-one Hydrochloride (14). To the solution of enones **9b,c,a** described above (67.5 g; 146 mmol) in dichloromethane (200 mL) were slowly added at 20−25 °C acetic anhydride (MW: 102.1; d: 1.09; 14 mL; 1.0 equiv) and then acetyl bromide (MW: 123.0; d: 1.66; 27 mL; 2.5 equiv) (exothermic addition). The brown solution was stirred

for 5 h at 20−25 °C (HPLC monitoring) and then carefully poured into an aqueous suspension of sodium bicarbonate (500 mL; 10 equiv) (evolution of carbon dioxide). The mixture was stirred vigorously during 18 h at ca. 20 °C, and then the organic phase was separated and washed with 1 N aqueous sodium hydroxide (250 mL), and then water. The organic phase containing mainly arylestrone acetate **13b** was concentrated to 150 mL. Then, dichloromethane was exchanged for methanol by azeotropic distillation at constant volume (150 mL) at ca. 40 °C (the pressure was progressively reduced). The mixture was cooled to 0−5 °C, and a solution of potassium hydroxide (12.3 g; MW: 56.0; 1.5 equiv) in methanol (100 mL) was added (exothermic). The mixture was stirred for 1.5 h at 0−5 °C (HPLC monitoring) and then poured into water (250 mL) and dichloromethane (250 mL). The organic phase was decanted and washed with water until no trace of bromide ions was detected ($AgNO_3$ test). The organic phase was acidified to pH < 2 by addition of aqueous hydrochloric acid (2.0 equiv; 275 mL). The organic phase was decanted, dried over sodium sulfate, and adjusted to 300 mL. Dichloromethane was exchanged for methyl ethyl ketone (MEK) by distillation at constant volume (300 mL), until the inner temperature reached 78 °C. The resulting suspension of arylestrone hydrochloride **14** was cooled and stirred for 1 h at 20−25 °C. The off-white crystals were washed with MEK (2 × 50 mL) and dried under vacuum at ca. 70 °C for 18 h: 51.0 g (based on dry product); yield: 70% (68% from **4a/b**); purity (LC): 95%; solvation: 1.4%; $C_{30}H_{40}ClNO_3$; MW: 498.1; mp(DSC): 189 °C; IR ($CHCl_3$, cm^{-1}): ν 3601, 2456, 1733, 1610, 1584, 1511; ^1H NMR ($CDCl_3$, ppm): δ 0.42 (s, 3H), 1.31 (t, J = 7 Hz, 6H), 3.16 (q, J = 7 Hz, 4H), 3.31 (t, J = 6.5 Hz, 2H), 3.96 (t, J = 6 Hz, 1H), 4.17 (t, J = 6.5 Hz, 2H), 6.51 (m, 1H), 6.68 (m, 1H), 6.73 (m, 1H), 6.51 and 6.95 (AA′BB′, 4H), 11.36 (1 exch. H); MS (EI; m/z): 461 (M^+), 446, 362, 86, 38, and 36 (HCl).

4-Chloro,11β-(4-(2-(diethylamino)ethoxy)phenyl)estra-4,9-diene-3,17-dione Hydrochloride (10). To a solution of dienone **9b** (20 g; 43.3 mmol) in dichloromethane (100 mL) at 20 °C was added pyridine (100 mL; MW: 79.1; d: 0.98; 28.6 equiv). The solution was cooled to −40 °C and then sulfuryl chloride (8.85 g; MW: 135.0; 1.5 equiv) was slowly added. The mixture was stirred for 2 h at −40 °C (TLC monitoring: heptane 45, ethyl acetate 45, TEA 10) and then poured into aqueous hydrochloric acid (27 equiv, 500 mL). The biphasic mixture (pH: 1) was stirred for 15 min and then the organic phase was collected, washed with water, dried (sodium sulfate), and concentrated to 80 mL. The solvent was exchanged for ethyl acetate, under vacuum at ca. 40 °C. The yellow solid was filtered at 20 °C, washed with ethyl acetate, and dried in vacuo at room temperature, affording 18.9 g of compound **10** (based on dry product). Yield: 82%; purity (LC): 73%; solvation: 3.2%; $C_{30}H_{39}Cl_2NO_3$; MW: 532.5; mp: 179 °C; ^1H NMR ($CDCl_3$, ppm): δ 0.57 (s, 3H), 1.46 (t, J = 7 Hz, 6H), 1.40−1.70 (m, 4H), 3.25 (m, 4H), 3.44 (m, 2H), 4.39 (d, J = 7 Hz, 1H), 4.52 (m, 2H), 6.83 and 7.09 (AA′BB′, 4H), 12.62 (1 exch. H); base (purified by chromatography): $C_{30}H_{38}ClNO_3$; MW: 496.0: IR ($CHCl_3$, cm^{-1}): ν 1736, 1677, 1609, 1580, 1549, 1509; ^1H NMR ($CDCl_3$, ppm): δ 0.57 (s, 3H), 1.06 (t, J = 7 Hz, 6H), 2.62 (q, J = 7 Hz, 4H), 2.85 (t, J = 6.5 Hz, 2H), 3.25 (dt, J = 16.5 and 3 Hz, 1H), 4.00 (t, J = 6.5 Hz, 2H), 4.38 (d, J = 7 Hz, 1H), 6.82 and 7.05 (AA′BB′, 4H); MS (EI; m/z): 496 (MH^+), 495, 86.

4-Chloro-11β-(4-(2-(diethylamino)ethoxy)phenyl)estra-1,3,5(10)-trien-3-ol-17-one Hydrochloride (11). To a solution of chlorodienone **10** (40 g; 75.1 mmol) in dichloromethane (160 mL) at room temperature was added acetic anhydride (21 mL; 3.0 equiv) and then acetyl bromide (21 mL; 3.8 equiv) (exothermic addition). The brown solution was stirred for 6 h at 20−25 °C (HPLC monitoring) and then carefully poured into an aqueous suspension of sodium bicarbonate (84 g; 13.4 equiv) in water (400 mL) (evolution of carbon dioxide). The mixture was stirred vigorously during 2 h at ca. 20 °C; the organic phase was then collected and acidified (pH: 1) with aqueous hydrochloric acid (3.3 equiv; 240 mL). The organic phase was dried (sodium sulfate), filtered, and concentrated to 120 mL. Dichloromethane was exchanged for methanol by azeotropic distillation at constant volume (120 mL) at ca. 40 °C (the pressure was progressively reduced). The mixture was cooled to 0−5 °C, and a solution of potassium hydroxide (10.5 g; MW: 56.0; 2.5 equiv) in methanol (80 mL) was added (exothermic). The mixture was stirred for 1.5 h at 0−5 °C (HPLC monitoring) and then poured into aqueous hydrochloric acid (3.0 equiv; 240 mL) and dichloromethane (200 mL). The organic phase was decanted, dried over sodium sulfate, and concentrated to 120 mL. Residual methanol was exchanged for dichloromethane by azeotropic distillation under normal pressure. The suspension was cooled and stirred for 1 h at 15−20 °C. The light-pink crystals of **11** were washed with dichloromethane and dried under vacuum at ca. 20 °C for 18 h: 19 g (based on dry product); yield: 47.5% (40% from **9b**); purity (LC): 90%; solvation: 4.1%; $C_{30}H_{39}Cl_2NO_3$; MW: 532.6; IR ($CHCl_3$, cm^{-1}): ν 1727, 1610, 1582, 1568, 1511, 1493; ^1H NMR ($CDCl_3$, ppm): δ 0.45 (s, 3H), 1.41 (t, J = 7 Hz, 6H), 3.21 (q, J = 7 Hz, 4H), 3.37 (t, J = 6.5 Hz, 2H), 3.99 (t, J = 6 Hz, 1H), 4.38 (t, J = 6.5 Hz, 2H), 5.87 (1 exch. H), 6.68 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.60 and 6.94 (AA′BB′, 4H), 12.30 (1 exch. H); MS (ES^+; m/z): 498, 496 (MH^+).

3-Acetoxy-11β-(4-(2-(diethylamino)ethoxy)phenyl)estra-1,3,5(10)-trien-17-one Hydrochloride (13b, HCl) and 3-Acetoxy-11-(4-(2-(diethylamino)ethoxy)phenyl)estra-3,5(10),9(11)-trien-17-one Hydrochloride (13c, HCl). To a solution of dienone **9b** (10 g; 21.7 mmol) in dichloromethane (40 mL) were slowly added at 20−25 °C acetic anhydride (6.1 mL; 3.0 equiv) and then acetyl bromide (6.1 mL; 3.8 equiv) (exothermic addition). The brown solution was stirred for *only 1 h* at 20−25 °C (HPLC monitoring) and then carefully poured into an aqueous suspension of sodium bicarbonate (13 equiv; 100 mL) (evolution of carbon dioxide). The mixture was stirred vigorously during 30 min at ca. 20 °C; the organic phase was then decanted, washed with water, and dried over sodium sulfate. Concentration under vacuum afforded an oily residue which was purified

by chromatography on silicagel (eluent: cyclohexane 75, ethyl acetate 20, triethylamine 5). The purest fractions were concentrated to dryness, diluted into dichloromethane, acidified to pH < 2 using 1 N hydrochloric acid, dried, and concentrated under vacuum.

The less polar fractions gave **13c, HCl** (1.3 g yellow solid; yield: 11%): $C_{32}H_{42}ClNO_4$; MW: 540.1; IR ($CHCl_3$, cm^{-1}): ν 1736, 1664, 1606, 1570, 1507; ^1H NMR ($CDCl_3$, ppm): δ 1.02 (s, 3H), 1.47 (t, $J = 7$ Hz, 6H), 2.10 (s, 3H), 3.27 (m, 4H), 3.47 (m, 2H), 4.51 (m, 2H), 5.52 (d, $J = 1.5$ Hz, 1H), 6.79 and 7.12 (AA′BB′, 4H), 12.4 (1 exch. H); MS (EI; *m*/*z*): 503 (M^+) 461, 100, 86, 38, and 36 (HCl).

The more polar fractions gave **13b, HCl** (6.09 g white solid; 52%): $C_{32}H_{42}ClNO_4$; MW: 540.1; IR ($CHCl_3$, cm^{-1}): ν 1734, 1610, 1582, 1512, 1494; ^1H NMR ($CDCl_3$, ppm): δ 0.45 (s, 3H), 1.43 (t, $J = 7$ Hz, 6H), 2.25 (s, 3H), 3.22 (m, 4H), 3.39 (m, 2H), 4.40 (m, 2H), 4.04 (d, $J = 4.5$ Hz, 1H), 6.63 and 6.99 (AA′BB′, 4H), 6.65 (dd, $J = 8.5$ and 1.5 Hz, 1H), 6.86 (d, $J = 1,5$ Hz, 1H), 6.94 (d, $J = 8,5$ Hz, 1H), 12.3 (1 exch. H); MS (EI; *m*/*z*): 503 (M^+), 86, 38, and 36 (HCl).

4-Chloroarylestrone Hydrochloride (11), by Chlorination of 14. To a solution of arylestrone **14** (50 g; 100 mmol) in dichloromethane (250 mL) and methanol (250 mL) was added at ca. 10 °C 36% hydrochloric acid (4 mL; 0.5 equiv) and then portions of *N*-chlorosuccinimide (13.4 g; MW: 133.5; 1.0 equiv) (exothermic). The solution was stirred for 1−3 h at 8−12 °C (HPLC monitoring). As arylestrone **14** was more difficult to eliminate by crystallisation than the dichloroarylestrone **16**, NCS (0.03 equiv) was added portionwise until compound **14** was totally (>99%) consumed. The solution was poured into a mixture of water (500 mL), sodium thiosulfate (25 g), sodium hydroxide (1.5 equiv), and dichloromethane (250 mL). The mixture was stirred for 15 mn at 20−25 °C. The organic phase was decanted and acidified to pH < 2 with aqueous hydrochloric acid (1.5 equiv; 140 mL). After decantation, the aqueous phase was extracted with a 2/1 mixture of dichloromethane and methanol. The organic phases were combined, dried over sodium sulfate, and concentrated to 250 mL. Methanol was exchanged for dichloromethane by azeotropic distillation at normal pressure (ca. 900 mL of DCM were necessary; final *T*: 39.8 °C). Chloroarylestrone hydrochloride **11** crystallised and was filtered at 20 °C and dried at ca. 40 °C under vacuum for 18 h: 44.1 g (based on dry product) white solid; yield: 82.5%; purity (HPLC): 98%; solvation: 3%; mp (DSC): 175 °C; $C_{30}H_{39}Cl_2NO_3$; MW: 532.6; IR, ^1H NMR, MS: see above.

4-Chloro-11β-(4-(2-(diethylamino)ethoxy)phenyl)estra-1,3,5(10)-trien-3,17-diol (2). To a solution of **11** (25 g; 47 mmol) in methanol (250 mL) was added at ca. 10 °C 30% aqueous sodium hydroxide (4.6 mL; 1.05 equiv). The mixture was stirred until complete dissolution was obtained and then cooled to ca. 0 °C. Sodium borohydride (1.4 g; MW: 37.8; 37 mmol) was added portionwise (slightly exothermic; evolution of hydrogen) during 15 min, keeping the temperature below 5 °C. The mixture was stirred for 1 h at 0−5 °C (HPLC monitoring). Excess hydride was consumed by addition of acetone (20 mL; 5.8 equiv). The suspension was stirred for 1 h at 5−10 °C and then poured into water (250 mL) and dichloromethane (250 mL). The organic phase was washed with 2/1 mixture of water and methanol, the washings were re-extracted with a 1/1 mixture of dichloromethane and methanol. The organic phase was dried over sodium sulfate and concentrated to 100 mL. The solvents were exchanged for 2-propanol by distillation at constant volume (normal pressure). At ca. 56 °C, seeding crystals of **2** (0.1 g) were added. Distillation was continued (final *T*: 82 °C); the crystallisation developed. The suspension was cooled to 0−5 °C during 1 h and stirred for 1 h at 0−5 °C. The white crystals (2-propanol solvate of **2**) were filtered, washed with 2-propanol (25 mL) and then suspended into water (500 mL). The suspension was stirred for 1 h at 80 °C, the white crystals (hydrate of **2**) were filtered at 80 °C, washed with warm water, and dried under moderate vacuum for 18 h at 40 °C. 19.4 g (based on dry product); yield: 83%; purity (HPLC): 99.2%; solvation: 3.7% water (monohydrate). $C_{30}H_{40}ClNO_3$; MW: 498.1; mp (DSC): 107 °C (dehydration then melting); $[\alpha]_D = -95°$ ($c = 1\%$ m/v in ethanol; based on dry product); IR ($CHCl_3$, cm^{-1}): ν 3608, 3536, 1610, 1580, 1512; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 0.32 (s, 3H), 1.03 (t, $J = 7$ Hz, 6H), 1.21 (dd, $J = 13$ and 2 Hz, 1H), 1.35 (m, 2H), 1.40 (m, 1H), 1.73 (m, 1H), 1.78 (dd, $J = 13$ and 5.5 Hz, 1H), 2.10 (m, 3H), 2.50 (dd, $J = 13$ and 2 Hz, 1H), 2.61 (q, $J = 7$ Hz, 4H), 2.77 (m, 1H), 2.81 (t, $J = 6.5$ Hz, 2H), 2.82 (m, 1H), 3.11 (dd, $J = 17.5$ and 4.5 Hz, 1H), 3.66 (dd, $J = 8.5$ and 7 Hz, 1H), 3.91 (t, $J = 5.5$ Hz, 1H), 3.94 (t, $J = 6.5$ Hz, 2H), 6.60 (d, $J = 8.5$ Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 1H), 6.60 and 6.89 (AA′BB′, 4H); MS (EI, *m*/*z*): 497, 482, 86.

Acknowledgment

This development work (lab and pilot) was carried out in the Romainville Research Center. Many collegues involved in this work are thanked for their significant contributions. Among them, we would particularly like to thank François Nique and Christian Moratille (Medicinal Chemistry) for fruitful discussions.

Received for review November 14, 200.

OP0341622