Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 765–768
Tetrahedron Letters

Recent developments in the synthesis of 11β-aryl-estrone derivatives

Denis Prat,* Françoise Benedetti, Lahlou Nait Bouda and Gilles Franc Girard

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

Received 6 October 2003; revised 3 November 2003; accepted 10 November 2003

Abstract—An industrial synthesis of 11β-aryl-estrone derivatives is described, based on the 1,4-addition of the aryl side-chain, as a cuprate, on to a mixture of allylic 5(10) alpha and beta epoxides, followed by hydrolysis and subsequent aromatization.
© 2003 Elsevier Ltd. All rights reserved.

1. Introduction

Substitution of estradiol derivatives with 11β-aryl groups is a way of modulating their affinity for estrogen receptors.[1] Recently, we described the synthesis of a 17α-methyl-11β-aryl estradiol derivative.[2]

These drug substances are generally prepared from 11β-aryl-estrone intermediates, the synthesis of which is based on the very efficient 1,4-addition[3] of the aryl side-chain, as a catalytically generated cuprate, on an allylic 5α,10α-epoxide such as **2a** or **3a** (Scheme 1). When a 17-keto group was present, this arylation was best performed on the silyl enol ether,[4] resulting in higher yield, and use of lower amounts of copper(I) chloride and Grignard reagent.[2]

Though this strategy was satisfactory for the preparation of batches of drug substances devoted to phase 1 and 2 clinical trial studies, the low diastereoselectivity of the initial epoxidation[5] of the 5,10-olefinic double bond of the dienone **1** was an issue to address in further scale-up studies. Using our best conditions (1.7 equiv of 50% hydrogen peroxide, 0.1 equiv of hexafluoroacetone, dichloromethane, 18 h, 20–25 °C), the α-epoxide **2a** was isolated in 49% yield after crystallization from ethyl acetate. Using hexachloroacetone as the catalyst, the yield was 43%.[2]

2. Observations during the pilot-scale synthesis

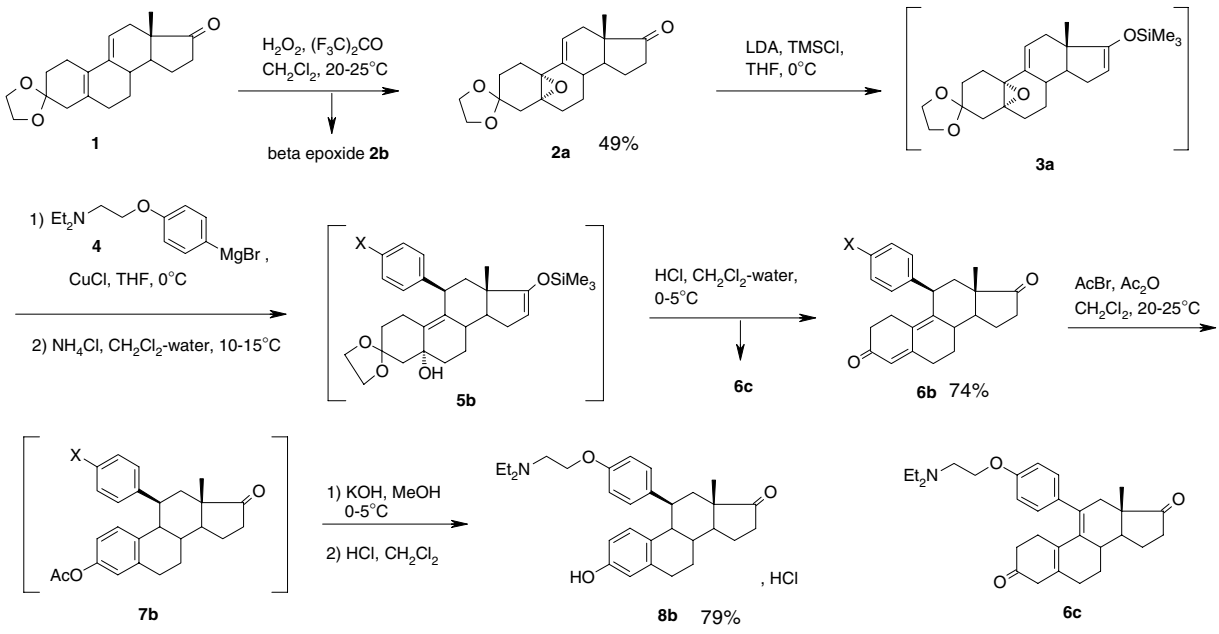
Apart from this initial moderate selectivity, the strategy of this synthesis is sound. Ethylene deltenone **1**, which is an industrial intermediate for norsteroids, particularly trimegestone,[6] is an appropriate starting material for the synthesis. Epoxide **2a** is crystalline, in contrast to parent epoxides bearing other functions at C-17. The introduction of the pre-formed aryl side-chain results in a convergent route.

Silylation was carried out using LDA as the base (1.2 equiv) and TMSCl (1.4 equiv) as the silylating agent, at 0 °C in THF. To the toluene solution of **3a** was added 0.1 equiv of copper chloride and 1.3 equiv of the Grignard reagent **4**,[7] at 0 °C. Aqueous work-up of the arylation mixture (aq NH_4Cl, dichloromethane) gave the 11β-aryl,5α-alcohol **5b**, the acidic hydrolysis of which afforded a mixture of 11β-aryl-dienone **6b** with minor amounts (5–10%) of the deconjugated dienone **6c**,[8] which was oily and easily removed by crystallizing **6b** from diisopropyl ether (yield: ca. 74%, lab and pilot scale).[9]

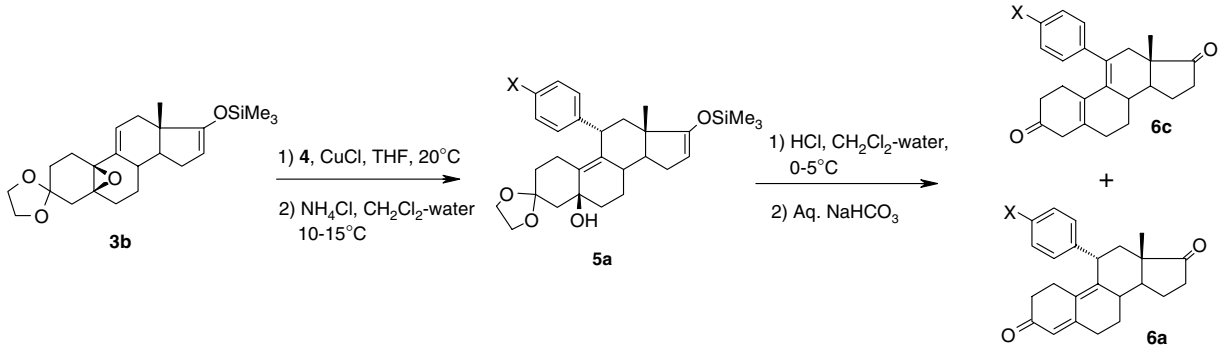
The β-epoxide **3b** reacted more slowly than the α-isomer, thus requiring more copper(I) chloride (0.2 equiv), higher temperatures (20 °C), and more Grignard reagent (2 equiv). An 11α-aryl,5β-alcohol **5a** was obtained, the hydrolysis of which gave a ca. 9/1 mixture (estimated by NMR) of the deconjugated dienone **6c** and the expected 11α-aryl-dienone **6a** (Scheme 2). The dienone **6c** is unstable and mainly decomposed during chromatography (isolated yield: 6%).[10] The 11α-aryl-dienone **6a** was isolated in 3% yield after chromatography.[11] These results were at first glance of little synthetic interest.

Keywords: Estrone derivatives; Industrial synthesis; Aromatization; 11-β-Aryl estrogen.
* Corresponding author. Tel.: +33-15893-8262; fax: +33-15893-8274; e-mail: denis.prat@aventis.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.028



Scheme 1. Preparative synthesis of 11β-aryl-estrones (X = $Et_2NCH_2CH_2O$).



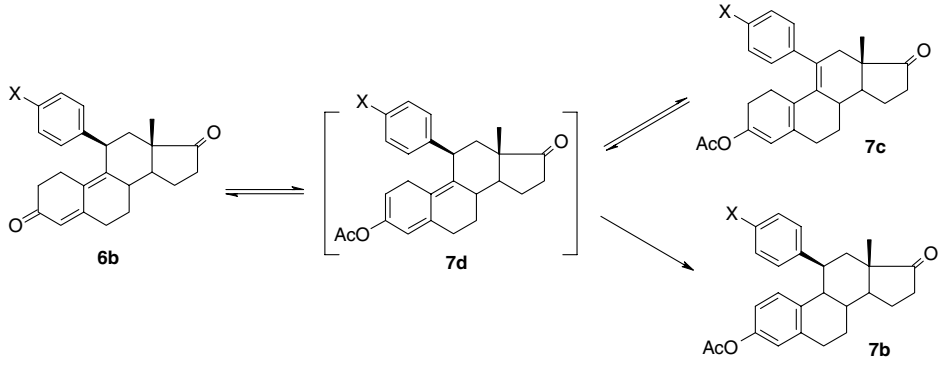
Scheme 2. Arylation at the 11α-position (X = $Et_2NCH_2CH_2O$).

Aromatization of **6b** was carried out using a mixture of acetyl bromide (2.5 equiv) and acetic anhydride (1 equiv), in dichloromethane at 20–25 °C.[12] An estrone acetate **7b** was formed, which required saponification (1.5 equiv of KOH, MeOH, 0–5 °C). Aryl-estrone hydrochloride **8b** was crystallized from methyl ethyl ketone in good yield (ca. 79% from **6b**), in the lab and in the pilot plant.[13]

The study of the aromatization reaction also gave unexpected results. During its optimization,[2] we observed that the starting 11β-dienone **6b** rapidly disappeared from the reaction mixture, giving an intermediate, which slowly rearranged into 11β-aryl-estrone acetate **7b**. According to LC–MS it had the same molecular mass as the aryl-estrone acetate, and we proposed the structure **7d** for this intermediate (Scheme 3). Later we succeeded in isolating it, and to our surprise, it was not **7d** but the isomeric trienol acetate **7c**. Compound **7d** probably formed as a transient intermediate. It was interesting to note that the 11-aryl group was no longer β in **7c**, but it recovered the β configuration after isomerization, thus giving **7b** as the predominant product: only ca. 0.5% of the 11α-aryl isomer was detected by HPLC in the crude mixture after aromatization and saponification.

3. Design of the industrial synthesis

These observations paved the way to the synthetic exploitation of the hitherto 'undesired' β-epoxide **2b**. The deconjugated dienone **6c** was the main product of arylation of **3b**, and we expected **7c** to be the kinetic product in the aromatization of **6c**, and that **7c** would then transform into the β-aryl product **7b** in the same way. It would be tempting to submit the crude mixture of epoxides ($\alpha/\beta \sim 65/35$) to the sequence arylation, aromatization, and saponification, as the final product should be **8b**. Moreover, this should permit the use of the small amount of dienone **6c**, which was formed from **3a** (Scheme 1), and which was previously lost during the purification of **6b**. Of course, to transform a preliminary experiment into an industrial process took some time.



Scheme 3. Proposed mechanism of A-ring aromatization (conditions: AcBr, Ac_2O, CH_2Cl_2, rt).

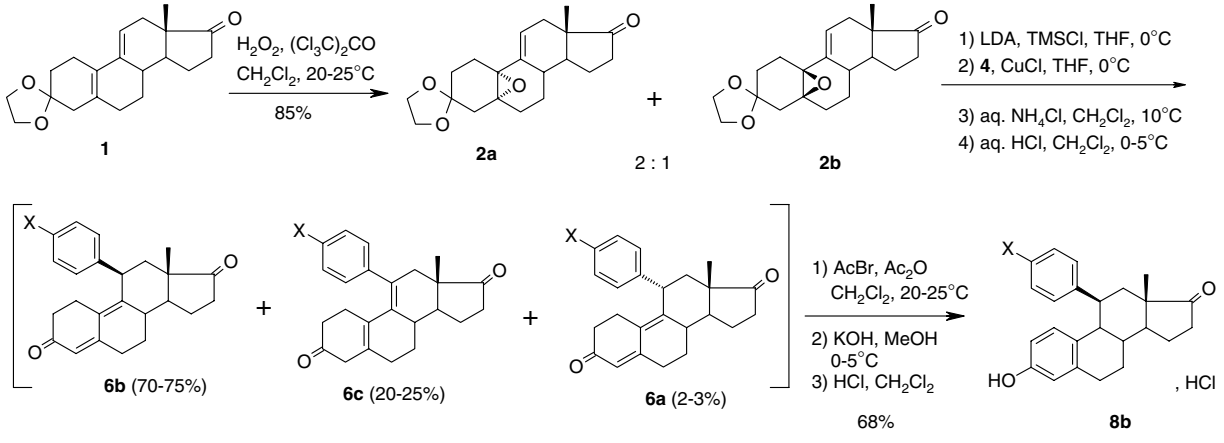
The crude mixture of isomers ($\alpha/\beta \sim 2/1$) was crystallized from diisopropyl ether, leaving minor impurities in the mother liquors. The yield was higher using hexachloroacetone (85%) than hexafluoroacetone (80%). Although the latter catalyst was slightly more stereoselective, it gave more side products.

Arylation was carried out using 1.8 equiv of Grignard reagent **4** and 0.15 equiv of copper(I) chloride, at 20 °C. Work-up (aqueous ammonium chloride) and acidic hydrolysis gave a mixture of aryl-dienones **6b**, **6c**, and **6a** (Scheme 4; the ratio of enones was estimated by NMR spectroscopy). As mentioned above, **6c** is not stable; therefore, this mixture was rapidly submitted to aromatization (2.5 equiv of acetyl bromide, 1 equiv of acetic anhydride, dichloromethane, rt), giving after 4–5 h 11β-aryl-estrone acetate **7b** as the main product. Again, it was not isolated,[14] but saponified to give the 11β-aryl-estrone, which was crystallized as the hydrochloride **8b**. The yield from the mixture of epoxides was ca. 68%. Only ca. 1% of the 11α-aryl isomer was detected in the crude reaction mixture after saponification, and 0.15% in the crystallized aryl-estrone hydrochloride. The purity of **8b** thus obtained (95%) was only slightly lower than the purity (98%) of the previous batches starting from 95% pure α-epoxide. To keep the same profile of impurities in this key intermediate was very important, as the batches of Drug Substances derived from it were used in clinical trials.

These results were confirmed, using different mixtures of epoxides containing from 50% to 75% of the β-isomer: the overall yield (**2a/b** to **8b**) was always in the range 55–65%.

Thus, as expected, the deconjugated aryl-dienone **6c** was mainly transformed into 11β-aryl-estrone acetate **7b**. On the other hand, the fate of the small amount of 11α-dienone **6a** is less clear. As the amount of **8a** in the crude reaction mixture (1%) was lower than the initial proportion of **6a** in the mixture of dienones (2–3%), we suggest that aromatization of the α-isomer also involved the trienol acetate **7c** as the kinetic product.

In conclusion, observation, and careful analysis of secondary reactions permitted a breakthrough in a classical sequence of reactions. Though we were unable to achieve good stereoselectivity in the initial epoxidation, we found a way to transform both epoxides at the same time, thus doubling the overall yield. The complete synthesis of the drug substance will be published elsewhere.[15] Again, despite all the knowledge accumulated on norsteroids, they still reveal surprises to the chemist.



Scheme 4. Industrial synthesis of 11β-aryl-estrones.

Acknowledgements

We would like to thank particularly François Nique, Christian Moratille, and John Larkin, for fruitful discussions. Among the many colleagues involved in this development work at the Romainville Research Center, Marie Fenneteau (trainee), Joëlle Bousquet and Pascal Caboche are recognized for their contribution.

References and notes

1. (a) Teutsch, G.; Belanger, A.; Philibert, D. *Steroids* **1981**, *37*, 361; (b) Nique, F.; Van de Velde, P.; Brémaud, J.; Hardy, M.; Philibert, D.; Teutsch, G. *J. Steroid Biochem. Mol. Biol.* **1994**, *50*, 21; (c) Van de Velde, P.; Nique, F.; Bouchoux, F.; Brémaud, J.; Hameau, M. C.; Lucas, D.; Moratille, C.; Viet, S.; Philibert, D.; Teutsch, G. *J. Steroid Biochem. Mol. Biol.* **1994**, *48*, 187; (d) Jin, L.; Borras, M.; Lacroix, M.; Legros, N.; Leclercq, G. *Steroids* **1995**, *60*, 512; (e) Aliau, S.; Delettre, G.; Mattras, H.; El Garrouj, D.; Nique, F.; Teutsch, G.; Borgna, J. L. *J. Med. Chem.* **2000**, *43*, 613.
2. Larkin, J. P.; Wehrey, C.; Boffelli, P.; Lagraulet, H.; Lemaitre, G.; Nedelec, A.; Prat, D. *Org. Process. Res. Dev.* **2002**, *6*, 20.
3. (a) Teutsch, G.; Belanger, A. *Tetrahedron Lett.* **1979**, *20*, 2051; (b) Rao, P. N.; Taraporewala, I. B. *Steroids* **1992**, *57*, 154; (c) Scholz, S.; Hofmeister, H.; Neef, G.; Ottow, E.; Scheidges, C.; Wiechert, R. *Lieb. Ann. Chem.* **1989**, 151; (d) Napolitano, E.; Fiachi, R.; Hanson, R. N. *Gazz. Chim. Ital.* **1990**, *120*, 323; (e) 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.
4. (a) Greene, T. W.; 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; (c) Lipshutz, B. H.; Wood, M. R.; Lindsley, C. W. *Tetrahedron Lett.* **1995**, *36*, 4385.
5. Costerousse, G.; Teutsch, G. EP 5100, 1979 (Roussel Uclaf).
6. 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.
7. The Grignard reagent was prepared in two steps from 4-bromo-phenol, 2-chloroethyl diethylamine hydrochloride, and magnesium turnings, as described in Ref. 2 with the parent piperidine derivative.
8. This type of dienone has been described by F. Nique, Ref. 1b.
9. Analytical data for **6b**: 11β-(4-(2-(diethylamino)ethoxy)-phenyl)-estra-4,9-diene-3,17-dione: $C_{30}H_{39}NO_3$, MW: 461.6, mp = 188 °C; IR ($CHCl_3$, cm^{-1}): 1735, 1658, 1609, 1581, 1509; ^1H NMR (250 MHz, $CDCl_3$, ppm): 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 (d, $J = 7$ Hz, 1H), 5.80 (s, 1H), 6.82 and 7.07 (AA′BB′, 4H); MS (EI, m/z): 461 (M^+).
10. Analytical data for **6c**: 11-(4-(2-(diethylamino)ethoxy)-phenyl)-estra-5(10),9(11)-diene-3,17-dione: $C_{30}H_{39}NO_3$, MW: 461.6; IR ($CHCl_3$, cm^{-1}): 1733, 1712, 1607, 1568, 1508; ^1H NMR (250 MHz, $CDCl_3$, ppm): 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.
11. Analytical data for **6a**: 11α-(4-(2-(diethylamino)ethoxy)-phenyl)-estra-4,9-diene-3,17-dione: $C_{30}H_{39}NO_3$, MW: 461.6; ^1H NMR (250 MHz, $CDCl_3$, ppm): 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): 462 (MH^+).
12. (a) Danishefsky, S.; Cain, P.; Nagel, A. *J. Am. Chem. Soc.* **1975**, *97*, 380; (b) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1975**, *97*, 5282; (c) Joly, R.; Joly, J. FR 81840, 1962 (Roussel Uclaf); *Chem. Abstr.* **1964**, *60*, 14566.
13. Analytical data for **8b**: 11β-(4-(2-(diethylamino)ethoxy)-phenyl)-estra-1,3,5(10)-trien-3-ol-17-one hydrochloride: $C_{30}H_{40}ClNO_3$, MW: 498.1, mp = 189 °C; IR ($CHCl_3$, cm^{-1}): 3601, 2456, 1733, 1610, 1584, 1511; ^1H NMR (250 MHz, $CDCl_3$, ppm): 0.42 (s, 3H), 1.31 (m, 6H), 3.16 (m, 4H), 3.31 (m, 2H), 3.96 (t, $J = 6$ Hz, 1H), 4.17 (m, 2H), 6.51 (m, 1H), 6.68 (m, 1H), 6.73 (m, 1H), 6.51 and 6.95 (AA′BB′, 4H), 11.36 (s, 1H); MS (EI, m/z): 461 (M^+), 446, 362, 86, 38, and 36 (HCl).
14. Variable amounts of **8b** (as base) were formed during the aqueous work-up after aromatization. Isolation of **7b** would thus have resulted in some loss of this intermediate.
15. Prat, D.; Benedetti, F.; Franc Girard, G.; Nait Bouda, L.; Larkin, J.; Wehrey, C.; Lenay, J. *Org. Process. Res. Dev.*, submitted.