

Fulvestrant: From the Laboratory to Commercial-Scale Manufacture

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Abstract:

The development of a commercial manufacturing process for fulvestrant (the active ingredient in ‘Faslodex’) is described. Key steps in the synthesis are stereoselective 1,6-addition of an organocuprate to a steroidal dienone followed by copper-mediated aromatisation of the A-ring. The strategy for dealing with noncrystalline intermediates is outlined. The production of drug substance of acceptable quality is critically dependent on limiting the formation of key impurities. The origin of these impurities is discussed, and measures to prevent or control their formation are described.

Introduction

Fulvestrant **6** is the active ingredient in ‘Faslodex’, a novel oestrogen-receptor downregulator that has proved to be a safe and effective treatment for advanced breast cancer.¹ The drug is formulated as an oily solution and is administered as a long-acting intramuscular injection. Key steps in the synthesis are stereoselective 1,6-addition of an organocuprate to a steroidal dienone followed by copper-mediated aromatisation of the A-ring. Fulvestrant is produced as a mixture of sulfoxide isomers, both having essentially the same pharmacological and toxicological properties.

Several potential synthetic routes were considered that involve assembly of the molecule in a different order. 19-Nortestosterone, **1**, 1,9-nonanediol, **7**, and pentafluoropentanol, **10**, were commercially available (although expensive) and envisaged to be likely starting materials in any synthetic route. The most likely production route to **10** started from pentafluoroethyl iodide which is difficult to handle due to its volatility (bp 13 °C) and the environmental issues associated with iodine-containing compounds. Since the supply of **10** for initial manufacturing campaigns was uncertain, it seemed prudent to focus on a route which used this key raw material most economically and as late as possible in the synthesis. The synthetic route used to make the first gram quantities of fulvestrant involved preparation of silyl-protected 1-bromo-9-hydroxynonane and its conjugate addition to a steroidal dienone (Scheme 1).

Main areas of concern with the route were (a) the feasibility of making pentafluoropentanol **10** on the large scale, (b) the use of chromatography to purify several noncrystalline inter-

mediates, and (c) introduction of the C7 substituent by a low-temperature addition to a dienone which afforded a 1.9:1 ratio of isomers with the required 7 α -isomer predominating. Crystallisation of the final product provided the only opportunity for nonchromatographic purification and fortunately removed the unwanted 7 β -isomer.

Eventually, a supply of pentafluoropentanol **10** was established, and its contribution to the cost of manufacture diminished so this ceased to be a dominant factor in the choice of synthetic route. The steroidal starting material became by far the most expensive ingredient in the synthesis so it was appropriate to focus on ways of utilizing this material most efficiently. It seemed likely that this could be achieved by preassembly of the sulfide-bearing side chain, thus reducing the number of stages from the steroidal dienone to fulvestrant. This article describes the investigation and development of a second synthetic route in which the sulfide-bearing side chain is assembled before addition to the steroid (Scheme 2). The alternative approach of using the sulfoxide-bearing side chain in the organocopper-mediated coupling was discounted because of incompatibility of the alkyl sulfoxide with the reaction conditions. The second route involves fewer noncrystalline steroid intermediates than the first route, was found to give a rather more favorable ratio of 7 α - and 7 β -isomers in the organocuprate addition step (2.5:1 versus 1.9:1), and made significantly more efficient use of the expensive steroidal starting material. It became the route of choice for large-scale manufacture.²

Results and Discussion

Second Synthetic Route. A consideration in developing the second synthetic route was the choice of thiol to introduce the sulfide bond by displacement of a leaving group (e.g., mesylate ester) from the appropriate alkyl derivative. Since pentafluoropentaneethiol is relatively volatile (bp 112 °C) and very smelly, the alternative disconnection involving mercaptononanol **12** was preferred because this compound was expected to be much less volatile. This approach was developed into a scaleable manufacturing route to the required side-chain bromide **14** (Scheme 3).³ A key feature of this route is in situ formation of **12** from isothiuronium salt **17** and its reaction with pentafluoropentyl mesylate **11** (also a nonisolated intermediate). Bromination of the crystalline alcohol is performed with triphenylphosphine and bromine in acetonitrile because simpler methods (e.g., hydrogen bromide) give unacceptable levels of side reactions. Bromide

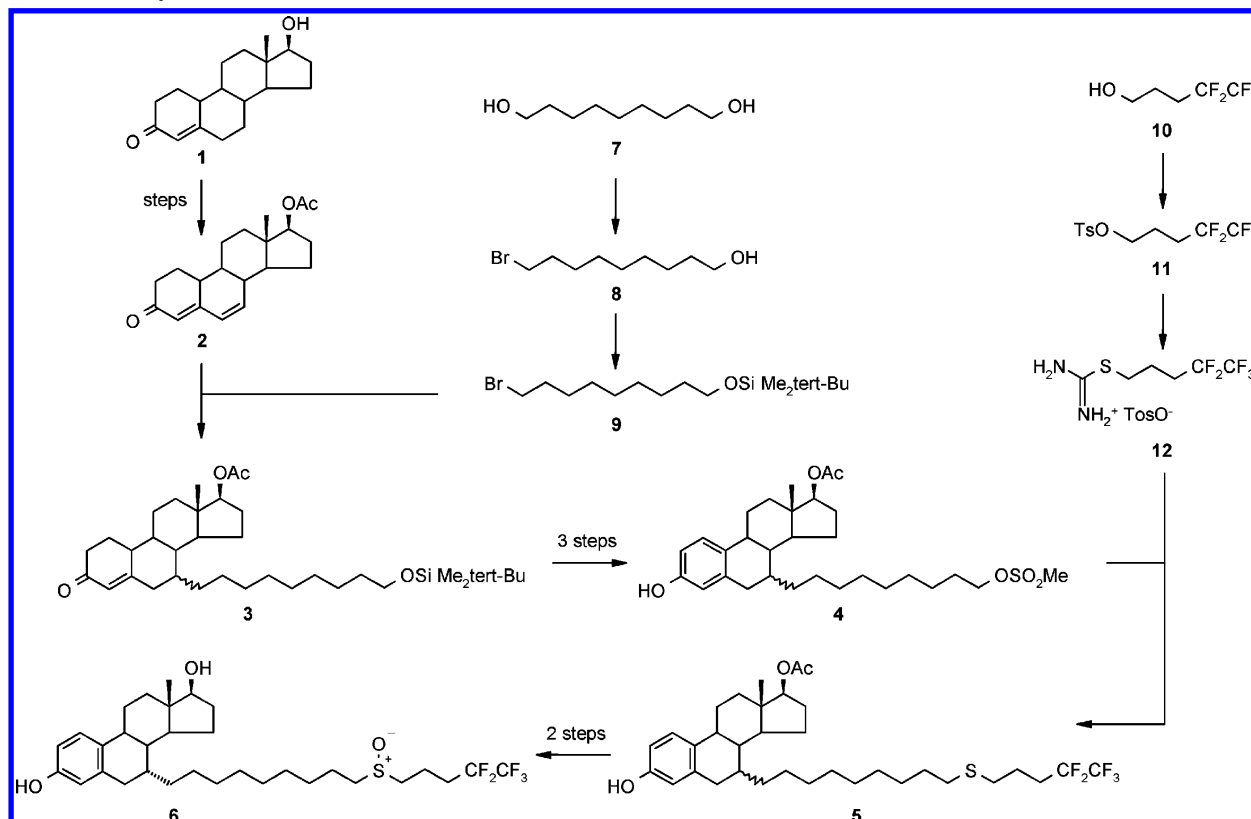
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(1) (a) Bowler, J.; Lilley, T. J.; Pittam, D. J.; Wakeling, A. E. *Steroids* **1989**, *54*, 71. (b) Morris, C.; Wakeling, A. E. *Endocr.-Relat. Cancer* **2002**, *9* (4), 267. (c) Bundred, N.; Howell, A. *Exp. Rev. Anticancer Ther.* **2002**, *2* (2), 151.

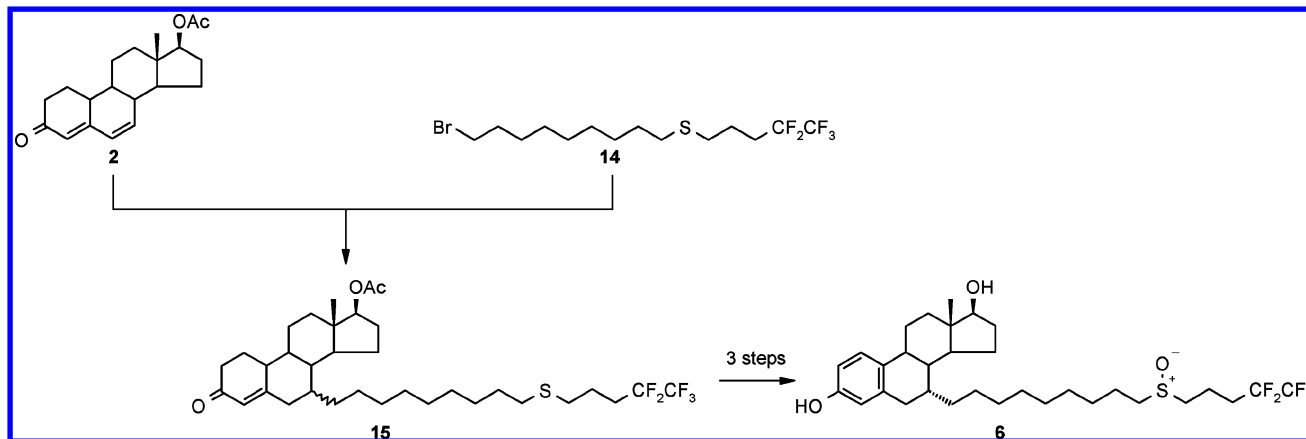
(2) Stevenson, R.; Kerr, F. W.; Lane, A. R.; Brazier, E. J.; Hogan, P. J.; Laffan, D. D. P. WO Patent 032922A1, 2002.

(3) Warren, K. E. H.; Kane, A. M. L. WO Patent 031399A1, 2003.

Scheme 1. First synthetic route



Scheme 2. Second synthetic route



14 is a liquid at ambient temperature, and its purification is achieved with a Wiped Film Evaporator.

Quality Considerations with Manufacture of Bromide

14. 1,9-Dibromononane **18**, dibromodisulfide **19**, and the extended side-chain bromide **20** are particularly troublesome impurities encountered in the manufacture of bromide **14** (Scheme 4).

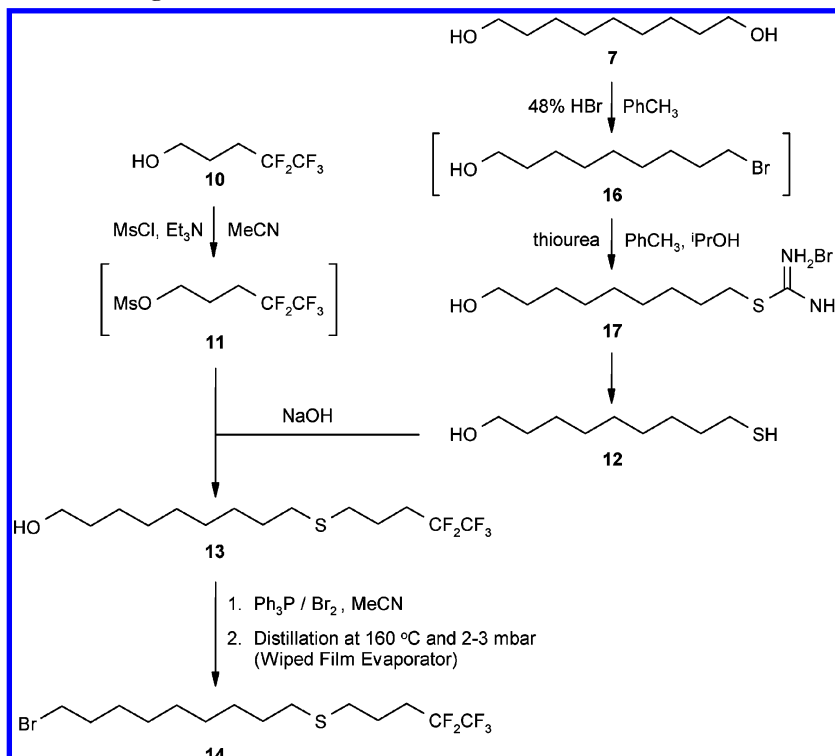
In early development, unpurified **14** behaved erratically in the Grignard-forming step, and some batches failed to initiate. GC analysis revealed several impurities in crude **14**, including **19** (typically at about 1% w/w), and collectively these impurities were found to inhibit formation of the Grignard reagent. This led to the requirement for purification of **14** by distillation. Distilled **14** contains <0.1% w/w **19** and has been found to undergo initiation reproducibly in the Grignard reaction. Dibromodisulfide **19** originates mainly from oxidation of **12** due

to the presence of traces of oxygen in the reaction vessel. It reacts with the Grignard reagent to produce impurity **20** which participates in the subsequent stages of the synthesis to give the corresponding impurity **25** in fulvestrant.

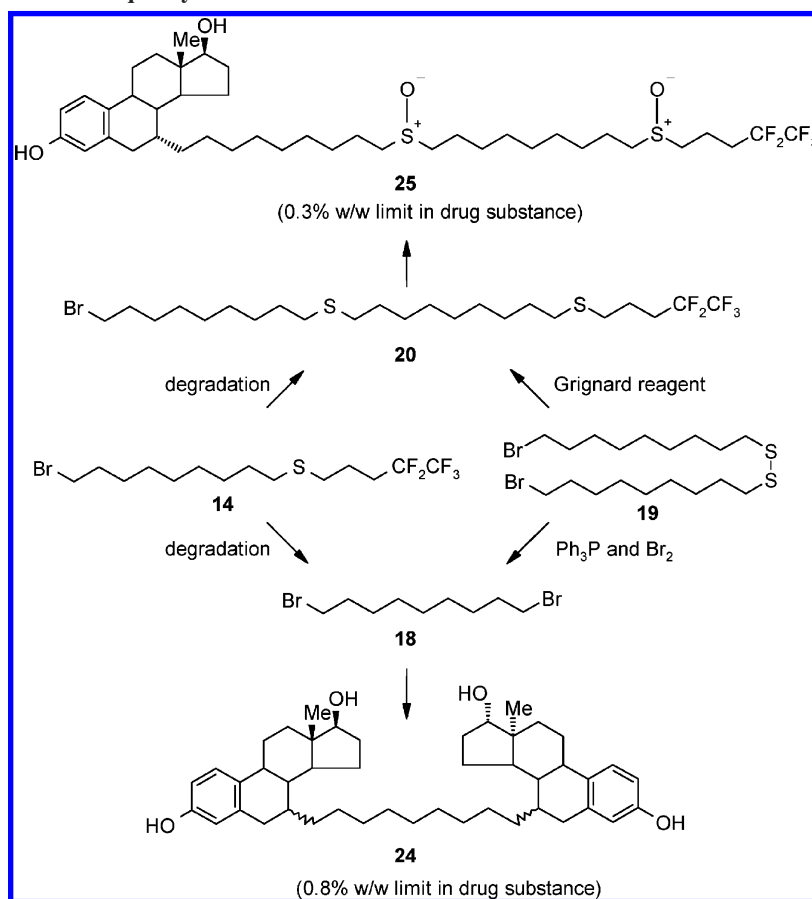
Dibromononane **18** is inevitably present due to overbromination of alcohol **16**. Another source of **18** is cleavage of disulfide **12** by triphenylphosphine during the bromination step, with subsequent bromination of the resulting mercaptononanol **12**. Dibromononane **18** itself forms a diorganocopper reagent, and this participates in 1,6-addition to two molecules of dienone **2**, generating the corresponding sterol dimer impurity **24** in the drug substance.

It is particularly important to control the levels of **18** and **20** in manufacture as the derived impurities in fulvestrant (**24** and **25**) are not significantly removed by the purification process. The limits for levels of impurities **24** and **25** (0.8% w/w and

Scheme 3. Large-scale manufacturing route for side-chain bromide



Scheme 4. Importance of bromide quality

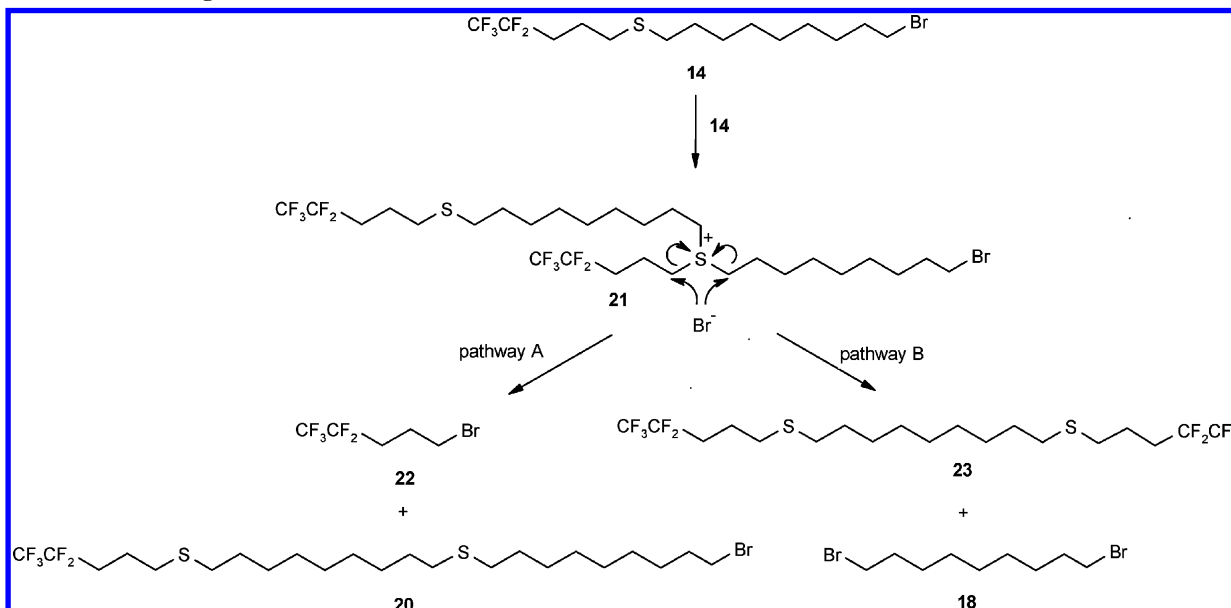


0.3% w/w, respectively) in drug substance are justified by appropriate toxicity studies.

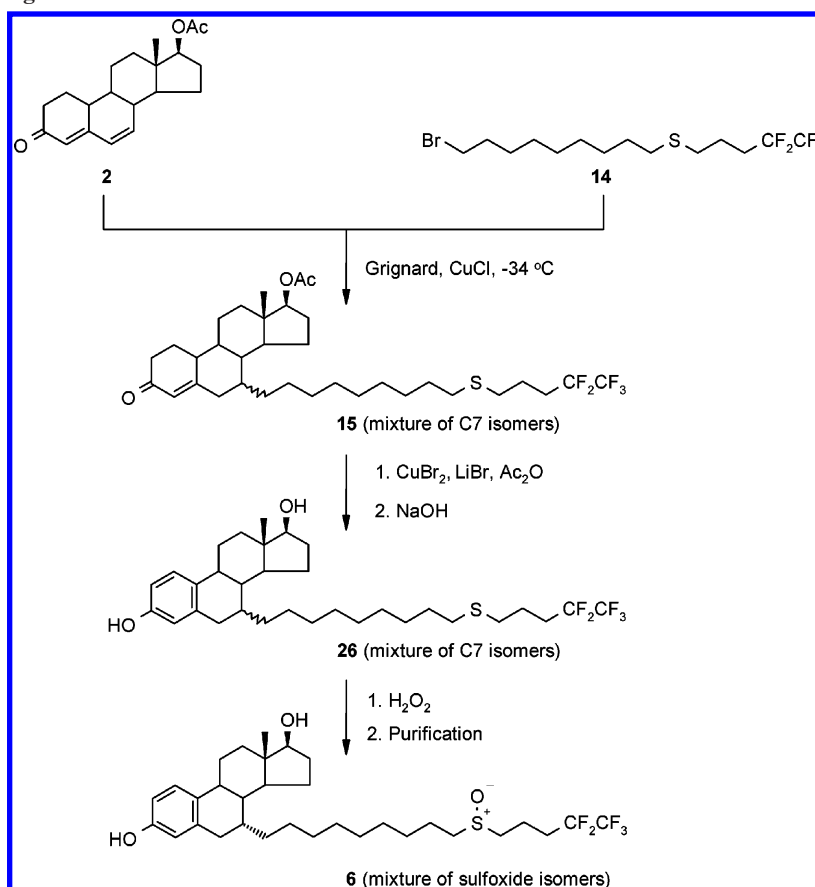
An additional source of **18** is degradation of **14** on storage. Thermally induced decomposition of **14** presumably arises via

intermolecular alkylation of the sulfur atom followed by bromide ion attack on the sulfonium intermediate **21** to give several degradation products (Scheme 5). Of these, the extended bromide **20** forms most rapidly (pathway A). A corresponding

Scheme 5. Thermal degradation of the side-chain bromide



Scheme 6. Route from registered raw materials



increase in the level of pentafluoropentyl bromide **22** is not observed, possibly because this component is volatile. Evaporation of **22** would drive the equilibrium to the right, thus explaining why decomposition appears to favor formation of **20**. The alternative mode of cleavage (pathway B) affords **18** and bis(pentafluoropentyl)thiononane **23**. It is beneficial to store the bromide **14** at 4 °C to extend its useful life.

Final Synthetic Route from Registered Raw Materials. During the course of development, suppliers of both the steroidal dienone **2** and bromide **14** were established, leading to a shorter in-house manufacturing sequence (Scheme 6).

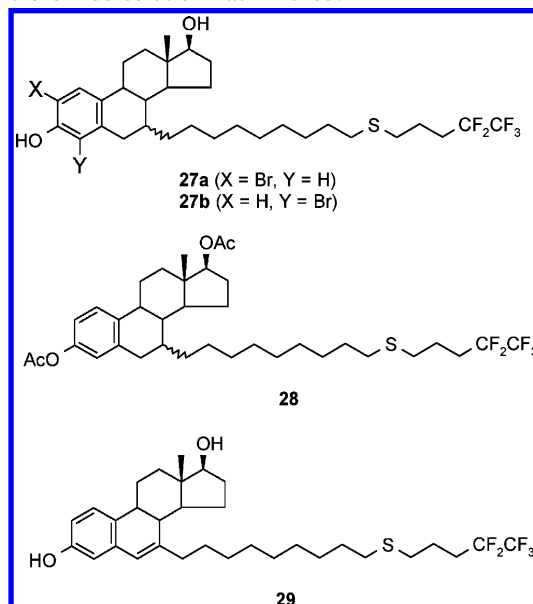
Impact of Noncrystalline Intermediates. The lack of crystalline intermediates between dienone **2** and the drug substance was a major concern because of the limited op-

portunity for removing impurities. Unfortunately, attempts to prepare crystalline derivatives of the hydroxyl group at C17 were unhelpful. With successive manufacturing campaigns and increasing scale during development, the level of impurities in the drug substance increased (eventually reaching a total of 2.8%) w/w, and this was a major cause of concern. Whilst some impurities could be removed (or their levels decreased) during recrystallisation of the drug substance, the levels of others were unchanged, and some actually increased. A detailed investigation into the origin of the troublesome impurities was necessary before technology transfer to the commercial manufacturing plant. In the case of impurities that cannot be removed by recrystallisation of the final compound, it was essential to introduce methods for controlling their formation (e.g., as described above for the side-chain bromide).

Introduction of the Side Chain. Development of a low-temperature, copper-catalysed process for 1,6-addition of the alkyl side chain to dienone **2** is described in detail elsewhere.² The Grignard reagent is prepared at 45 °C in about 88% yield and with a solution strength of about 0.4 M (as measured by titration); in routine plant manufacture, the first batch is initiated with a small amount of specially prepared reagent (made with iodine as initiator) whereas the second and subsequent batches are initiated with a heel of Grignard reagent retained from the previous batch. Since formation of the Grignard reagent is exothermic (65 kcal/mol, equivalent to a potential adiabatic temperature rise of 65 °C), safety considerations dictate that it should be added in four aliquots. The organocuprate is generated at –34 °C by addition of cuprous chloride (0.08 mol equiv). Controlling the temperature in the range –28 to –37 °C (set point –34 °C) during the addition of **2** affords optimum conversion; lower temperatures lead to 1,2-addition of the side chain due to incomplete formation of the organocuprate, and higher temperatures result in deacylation which is wasteful of the Grignard reagent. The reaction affords the required enone **15** as a 2.5:1 mixture of 7 α - and 7 β -isomers in about 90% yield. Since the product is an oil, it is not readily purified without resorting to chromatography. The required enone **15** and byproducts generated during formation of the Grignard reagent are extracted into isohexane for use in the next stage (isohexane was chosen as a suitable solvent for extraction of the product because it permits an easy swap to acetonitrile prior to performing the aromatisation step).

Aromatisation of the Steroid A-Ring. *Control of Bromo-Impurities.* A mixture of cupric bromide and lithium bromide in acetonitrile was found to be a highly effective system for the aromatisation of **15**. On first scale-up of the process in the pilot plant, 2- and 4-bromo-impurities **27a** and **27b** were generated at a level of about 1%. Unfortunately, the corresponding sulfoxide derivatives of **27a** and **27b** could not be removed during crystallisation of the drug substance. Indeed, their level actually increased. Reaction monitoring by HPLC indicated that the bromo-impurities began to form towards the end of the aromatisation and their level increased significantly when the reaction mixture was quenched. The problem was attributed to the susceptibility of the phenol ring towards electrophilic bromination. We reasoned that protection of the phenol as an acetate (compound **28**) would greatly reduce its

reactivity. To achieve this, 2.0 mol equiv of acetic anhydride was added to the solution of cupric bromide and lithium bromide in acetonitrile. This procedure prevented formation of the bromo-impurities but led to a slightly elevated level of the Δ 6,7-impurity **29**. To counteract this, in the optimised process half the acetic anhydride is added to the cupric bromide solution, and the remainder is added immediately after addition of the cupric bromide solution has finished.

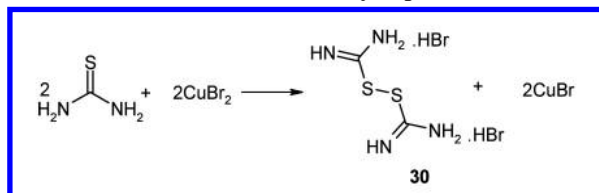


Removal of Copper. The optimised process uses 2.37 equiv of cupric bromide (the precise charge being determined by the preference for using whole bags in commercial manufacture). Various methods for removal of used copper reagent at the end of the process were investigated. Removal of cuprous bromide by filtration and multiple washes with aqueous ammonium chloride or potassium chloride were relatively inefficient. Advantage was taken of the highly insoluble complex with thiourea. When aromatisation is complete, copper is precipitated by the addition of an aqueous solution of thiourea and the required diacetate **28** extracted into toluene. Because the reaction mixture is very acidic at this point, it is necessary to adjust the pH with dipotassium phosphate to avoid the risk of corrosion to filtration equipment.

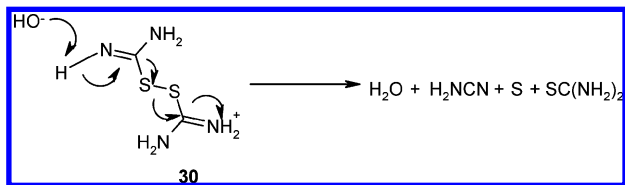
Ester Hydrolysis. The toluene extract of **28** is subjected to a solvent swap by distillation, and the acetate groups are removed with aqueous sodium hydroxide in methanol. At this point there is an opportunity to remove hydrocarbons and related impurities (carried forward from the Grignard reaction) by extraction with isohexane. The required intermediate **26** (also an oil) is obtained by acidification and extraction into ethyl acetate, the preferred solvent for the next stage.

Discovery of a New Impurity. HPLC analysis (225 nm) of the first batch of **26** in the Technology Transfer Campaign revealed a new impurity at a level of 1.3% by area with RRT 0.96. An attempt to identify the impurity by LC–MS failed as no molecular ion was observed. Laboratory use trials showed the level of impurity and its HPLC retention time were unchanged on processing a sample of the intermediate **26** to pure fulvestrant. A sample of the impurity was isolated by chromatography, and its mass spectrum (EI) was characteristic

Scheme 7. Oxidation of thiourea by cupric bromide



Scheme 8. Mechanism for formation of sulfur from 30



of elemental sulfur. An HPLC method developed specifically to measure sulfur levels showed that the contaminant has a response factor approximately 4 times greater than that of **26** at the detection wavelength (264 nm).

Suspicion was immediately directed at thiourea as the source of the problem. At the end of the aromatisation step there is unreacted cupric bromide (an excess of at least 0.37 mol equiv is used in the process), and this is likely to oxidise thiourea rapidly to formamidine disulfide **30** (Scheme 7).

A literature search revealed that **30** decomposes in aqueous solution to give thiourea, cyanamide, and sulfur (Scheme 8). The measured half-life for this decomposition decreases extremely rapidly with increasing pH. Based on data in the literature, the half-life of formamidine disulfide at pH 2.43 is 126 min, but at pH 4.12 it is only 4 min.⁴

To check the relevance of this information to the manufacturing process for **26**, solutions ranging in pH from 1 to 6 were prepared by adding dipotassium hydrogen phosphate to a 2% w/w aqueous solution of **30** (from the commercially available hydrochloride salt). Within 5 min the pH dropped in all the samples, indicating deprotonation and potential decomposition of **30**, consistent with the above mechanism. Above pH 4.5 a heavy yellow precipitate of sulfur was also observed. On standing overnight, sulfur was observed in all except the pH 1 sample.

Control of Sulfur in the Process. Reasons for batch-to-batch variation and previous nondetection of sulfur were sought, and clues were found in the hydrolysis step. There was a correlation between extended ester hydrolysis times (which could be attributed to an insufficiency of sodium hydroxide) and elevated sulfur levels. This suggested that nondetection of sulfur in previous manufacture might have been due to its decomposition during the base-catalysed hydrolysis step.

S₈ is known to undergo ring-opening by nucleophiles such as cyanide and triphenylphosphine in a stepwise manner.⁵ The sulfur ring is also cleaved by hydroxide to give ultimately thiosulfate.⁶

Polysulfide ions (e.g., S₅²⁻) are thought to be intermediates in the above process. On the basis of this information, it is

possible to propose an explanation for the observed variability in sulfur levels in **26**. The charge of sodium hydroxide was on a knife edge and did not allow for variable levels of acetic anhydride remaining after the brine washes. With some plant batches the apparent deficiency of sodium hydroxide led to slow or incomplete hydrolysis of diacetate **28** and, crucially, incomplete decomposition of sulfur to thiosulfate. Any polysulfide remaining after the hydrolysis would regenerate elemental sulfur upon neutralisation of the reaction mixture (to pH 5–6) with acetic acid.

For subsequent batches, the charge of sodium hydroxide was increased from 2.40 to 2.79 equiv, resulting in faster hydrolysis of **28**. This solved the problem, and there was no sulfur in the isolated **26**.

Physical Methods of Removing Sulfur. Methods of removing sulfur from contaminated batches of **26** were sought. Treatment of the ethyl acetate solution with 5% w/w activated carbon (20 °C for 4 h) reduced the level of sulfur by about two-thirds although several cycles were required to produce material of acceptable quality. The method was scaled up to mobilise valuable material for development studies.

Oxidation to Fulvestrant and its Purification. In early development manufacture, sulfoxidation was performed with sodium periodate in aqueous methanol. The process suffered from variable conversion, and there was concern regarding the need to filter off and dispose of sodium iodate. Hydrogen peroxide (17.5% w/w) and acetic acid in ethyl acetate were found to be much more reliable, affording the product in high yield with less than 1% conversion to sulfone. Several recrystallisations from ethyl acetate are required to reduce the content of 7β-isomer to an acceptable level (<0.1%) and remove other impurities. From the Validation Campaign pure fulvestrant was obtained in 28% overall yield from dienone **2**. The sequence of crystallisation process gives an approximately 55:45 ratio of sulfoxide diastereoisomers.

Strategy in Commercial Manufacture. Although the two noncrystalline intermediates are isolated and stored as solutions, it is assumed for charging purposes at the next stage that the yield of both intermediates is 100%. The rationale is that impurities present will also consume reagents. A further simplification involves using whole batches of one intermediate in the next stage. For containment reasons, none of the intermediate solids in the sequence of crystallisations at the final stage is discharged from the filter; in each case the solid is removed from the filter by dissolution in ethyl acetate and transferred to the crystallisation vessel. In effect, the synthetic route can be regarded as one continuous process involving about 500 unit operations with 11 distillations and 14 phase separations. During the Validation Campaign, yields of pure fulvestrant were consistent, and all impurities were controlled within their specification limits. Remarkably, all this was achieved with just one In Process Control (a test for the water content of an ethyl acetate solution prior to the first crystallization).

Conclusion

An alternative synthetic route to fulvestrant **6** has been developed and successfully implemented in commercial-scale manufacture. Key to success has been understanding the origin

(4) Rio, L. G.; Munkley, C. G.; Stedman, G. J. *Chem. Soc., Perkin Trans II* **1996**, 2, 159.

(5) (a) Bartlett, P. D.; Meguerian, G. J. *Am. Chem. Soc.* **1956**, 78, 3710.

(b) Bartlett, P. D.; Davis, R. E. *J. Am. Chem. Soc.* **1958**, 80, 2513.

(6) Licht, S.; Davis, J. J. *Phys. Chem. B* **1997**, 101, 2540.

of certain impurities and then devising methods for their control or removal. The alkyl bromide **14** used to introduce the side chain is a potential source of analogous impurities in fulvestrant, in particular **24** and **25**. Since the impurities in **14** also prevent reliable initiation of the Grignard reaction, it is important to purify the material by distillation. Copper-catalysed 1,6-addition of the alkyl side chain at low temperature affords a 2.5:1 mixture of α - and β -isomers in good yield; the success of the reaction depends on precise control of the temperature.

Cupric bromide is a highly effective reagent for aromatising the A-ring. The newly formed phenol is prone to bromination, giving related impurities **27a** and **27b** in fulvestrant that are not readily removed. Formation of these bromo-impurities is prevented by including acetic anhydride in the reaction mixture. Upon completion of the aromatisation, copper is removed by precipitation of its complex with thiourea. During the technology transfer phase, elemental sulfur (a previously unseen impurity) was detected in the aromatisation product at a significant level. Sulfur, which is evidently produced by oxidation of thiourea followed by hydrolytic cleavage of the resulting disulfide, is readily transformed into water-soluble byproducts by increasing the charge of aqueous alkali during the ester hydrolysis step.

Intermediates in the manufacture of fulvestrant are oils, and they are processed further without any purification. The final oxidation step affords fulvestrant (a crystalline compound) plus significant amounts of accumulated organic-soluble impurities from previous stages. Multiple crystallisations are required to achieve the desired purity.

Experimental Section

General. Starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. IR spectra were recorded using a Thermo Electron Avatar FT-IR instrument. Melting points were obtained with a Mettler Toledo DSC822e instrument. NMR spectra were obtained using a Bruker DPX 400 instrument; ^1H spectra were measured with reference to an internal standard of tetramethylsilane at 0 ppm, and ^{13}C spectra were measured with reference to the DMSO signal at 39.5 ppm. HPLC analyses were performed with an Agilent 1100 instrument using the following conditions: analysis of **15**, Spherisorb ODS2 column (4.6 mm \times 250 mm, 5 μm) at 20 $^\circ\text{C}$ and 220 nm with a flow rate of 2.0 mL/min and a mobile phase consisting of CH_3CN and water (49:1 v/v); analysis of **26**, Spherisorb ODS2 column (4.6 mm \times 250 mm, 5 μm) at 20 $^\circ\text{C}$ and 220 nm with a flow rate of 2.0 mL/min and a mobile phase consisting of CH_3CN and water (9:1 v/v); analysis of sulfoxide isomers of **6**, Spherisorb CN (4.6 mm \times 250 mm, 5 μm) at 20 $^\circ\text{C}$ and 280 nm with a flow rate of 2.0 mL/min and a mobile phase consisting of dichloromethane, isohexane, and ethanol (33:66:1 v/v). Strengths (% w/w) of isolated products (or their solutions) were measured by HPLC analysis (or GC analysis in the case of bromide **14**) using a purified reference standard.

3-Oxo-7 α -[9-(4,4,5,5,5-pentafluoropentylsulfanyl)nonyl]estra-4-en-17 β -yl Acetate (15**).** The reactor and associated equipment were rigorously dried, and the process steps were carried out under a nitrogen atmosphere. To initiate the first batch in full-scale manufacture, a 0.4 M solution of Grignard reagent (about 37 L) was prepared separately using iodine as initiator. The

first batch of Grignard reagent in full-scale manufacture was prepared on a larger scale and with an excess of magnesium so that a heel (186 L) could be left in the reactor to initiate the next batch. The following procedure describes the procedure for the second and subsequent batches in a manufacturing campaign.

Magnesium raspings (9.76 kg, 401 mol) and THF (738 L) were added to the heel (186 L of approximately 0.4 M solution plus excess magnesium) from the previous batch, and the mixture was heated to 45 $^\circ\text{C}$. Bromide **14** (160.4 kg, 401 mol) was added in four portions; a temperature rise of 4–10 $^\circ\text{C}$ after each addition indicated formation of the Grignard reagent. The addition was followed by a line wash of THF (34 L). The mixture was cooled to 10 $^\circ\text{C}$, and excess magnesium was allowed to settle out. The solution of Grignard reagent in THF (minus the heel) was transferred to a cryogenic vessel via a dip-leg, diluted with tetrahydrofuran (170 L) and cooled to –34 $^\circ\text{C}$. Cuprous chloride (2.0 kg, 20 mol) was added, followed by a solution of 17 β -acetoxyestra-4,6-dien-3-one (**2**) (82 kg, 261 mol) in THF (350 L). The transfer of this solution took 3.5 h, and the temperature was maintained at –34 $^\circ\text{C}$ throughout. The addition was followed by a line wash of THF (35 L). The reaction was quenched by adding a solution of acetic acid (70 kg, 1165 mol) in THF (79 L); the addition took 3 min and resulted in a temperature rise of 15–20 $^\circ\text{C}$. The mixture was warmed to 20 $^\circ\text{C}$, transferred to a standard reactor with a line wash of THF (39 L), and then diluted with water (570 L). Topanol (2 kg) was added to inhibit peroxide formation, and THF was removed by distillation under atmospheric pressure. The residual solution was cooled to <30 $^\circ\text{C}$, diluted with more water (250 L), and extracted with isohexane (410 L). The mixture was passed through Harborlite filter aid followed by a wash of isohexane (125 L), and the phases were separated. The organic phase was washed with a solution of potassium chloride (100 kg) in water (400 L). The resulting solution of **15** in isohexane was used directly in the next stage. The yield of **15** (an approximately 2.5:1 mixture of 7 α - and 7 β -isomers) was estimated by HPLC analysis to be 90–95% (RRT of 7 α -isomer 1.00 and 7 β -isomer 1.24). The strength of the solution (both isomers) was approximately 27% w/w. For charging purposes at the next stage, the yield was assumed to be 165.6 kg (100%). Two batches of **15** were combined for use in the next stage.

7 α -[9-(4,4,5,5,5-Pentafluoropentylsulfanyl)nonyl]estra-1,3,5(10)-triene-3,17 β -diol (26**).** A solution of **15** (assumed content 331 kg, 521 mol as a mixture of 7 α - and 7 β -isomers) was heated to remove most of the isohexane by distillation under atmospheric pressure. The residue (approximately 500 L) was diluted with acetonitrile (1420 L) and distillation was continued until the batch temperature reached 85 $^\circ\text{C}$ (residual volume approximately 600 L). The residual solution cooled to 20 $^\circ\text{C}$ and its volume was adjusted to 1000 L with acetonitrile. A solution of cupric bromide (275 kg, 1231 mol), lithium bromide (75 kg, 864 mol) and acetic anhydride (61 kg, 597 mol) in acetonitrile (1056 L) was prepared and added over 3 h to the solution of **15** in acetonitrile, maintaining the temperature at about 20 $^\circ\text{C}$. A further portion of acetic anhydride (45 kg, 441 mol) was added followed by a line wash of acetonitrile (235 L) and the mixture was held at 20 $^\circ\text{C}$ for a further 4 h. The

solution was then added over 1 h to a stirred mixture of toluene (1000 L) and a solution of thiourea (150 kg, 1970 mol) in water (1650 L) cooled to 10 °C. The addition was followed by a line wash of acetonitrile (330 L) and toluene (70 L). The mixture was cooled to 0 °C, and the pH was adjusted to about 3 by the addition of dipotassium hydrogen phosphate (200 kg, 1148 mol). After stirring for 1 h at 0 °C, the precipitated copper/thiourea complex was removed by filtration, and the filter cake was washed with toluene (1315 L). The phases in the filtrate were separated, and the toluene phase containing diacetate **28** was washed with water (100 L) at 2 °C and then with 10% w/v sodium chloride solution (3 × 1000 L) at 60 °C. The toluene solution was concentrated by distillation under reduced pressure (200 mbar) to about 760 L. Methanol (990 L) was added to the residual solution, and distillation was continued at atmospheric pressure until 660 L of distillate had been collected. The solution was cooled to 25 °C and diluted with more methanol (600 L). 47% w/w Sodium hydroxide solution (124 kg, 1457 mol) was added, followed by a line wash of methanol (55 kg), and the mixture was stirred at 30 °C for 5 h. When hydrolysis was complete, the aqueous methanolic solution was extracted with isohexane (3 × 890 L) to remove nonpolar impurities carried through from the Grignard reaction. The aqueous methanolic solution was diluted with more methanol (100 L) and neutralised with glacial acetic acid (74 kg, 1232 mol) followed by a line wash of EtOAc (65 kg). Methanol was removed by distillation at atmospheric pressure, leaving a residue of about 500 L that was partitioned between water (437 L) and EtOAc (1190 kg) at 23 °C. The organic phase was concentrated by distillation at atmospheric pressure to about 600 L, providing Fulvestrant PHS as an approximately 50% w/w solution in EtOAc which is suitable for use directly in the next stage. The yield of **26** (a mixture of 7 α - and 7 β -isomers) was estimated by HPLC analysis to be 80–85% (RRT of 7 α -isomer 1.00 and 7 β -isomer 1.05). For charging purposes at the next stage, the yield was assumed to be 308 kg (100%).

7 α -[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl]estra-1,3,5-(10)-triene-3,17 β -diol (Fulvestrant) (6). An approximately 50% w/w solution of **26** (assumed content 308 kg, 521 mol as a mixture of 7 α - and 7 β -isomers) in EtOAc was diluted with more EtOAc (695 kg) and glacial acetic acid (188 kg, 3131 mol). Aqueous hydrogen peroxide (17.5% w/v, 203 kg, 1045 mol) was added, followed by a line wash of water (60 kg), and the mixture was stirred at 23 °C for 8 h. A further portion of EtOAc (555 kg) was added, and excess hydrogen peroxide was destroyed with a solution of sodium sulfite (100 kg) in water (1080 L). The mixture was neutralised with a solution of 47% w/w aqueous sodium hydroxide (279.6 kg) in water (525 kg), keeping the temperature below 30 °C. The mixture was passed through Harborlite filter aid followed by a wash of EtOAc (140 kg), and the phases were separated. The organic phase was washed with water (615 L); to assist phase separation the mixture was again passed through Harborlite filter aid followed by a wash of EtOAc (140 kg). The organic phase was dried by heating to reflux, collecting water in a binary separator, and then was passed through Harborlite filter aid (to remove insoluble inorganic material) followed by a wash of EtOAc (665 kg). The EtOAc solution was concentrated by distillation at

atmospheric pressure to about 920 L, then cooled to 10 °C over 10 h with seeding to promote crystallisation. The solid was collected in a pressure filter and washed with cold EtOAc (208 kg). The crude product was removed from the pressure filter by dissolution in hot EtOAc, and the resulting solution was subjected to another crystallisation cycle. In total, four crystallisations were carried out to achieve the required purity (<0.1% 7 β -isomer). With each successive crystallisation, the EtOAc solution was concentrated to a predetermined volume that decreased in proportion to the estimated weight of product present (based on laboratory experiments and HPLC analysis). After the final crystallisation the product was dried in a stream of nitrogen at 60 °C. The yield of pure fulvestrant at 100% w/w strength was 88.4 kg (mean of five batches) which represents 28% overall yield from dienone **2**. Ratio of sulfoxide A to sulfoxide B = 46:54 by HPLC analysis (the retention times of sulfoxide A and sulfoxide B are approximately 20.0 and 23.5 min); mp 104–112 °C by DSC analysis (sulfoxide A and sulfoxide B have mp 102 and 117 °C).

¹H NMR (400 MHz, 300 K, CDCl₃) δ 0.78 (3H, s), 0.95–1.82 (23H, m), 1.91 (1H, ddd, J = 12.2, 2.9, 2.7 Hz), 2.03–2.40 (8H, m), 2.56–2.90 (6H, m), 3.75 (1H, m), 6.56 (1H, d, J = 2.37 Hz), 6.60–6.66 (1H, m), 6.61 (1H, s), 6.76 (1H, s), 7.12 (1H, d, J = 8.62 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 11.1, 14.7, 22.6, 22.7, 25.1, 27.3, 27.4, 28.6, 28.8, 29.0, 29.3, 29.4, 29.6 (t, J_{CF} = 21.9 Hz), 30.6, 33.3, 34.7, 37.0, 38.3, 42.1, 43.4, 46.5, 50.9, 52.5, 82.0, 113.1, 115.4 (tq, J_{CF} = 253 Hz, 38 Hz), 116.2, 118.9 (qt, J_{CF} = 285 Hz, 36 Hz), 127.0, 131.2, 136.9, 154.1.

2-(9-Hydroxynonyl)-2-thiopseudourea Hydrobromide (17).

A mixture of 1,9-nonanediol (140 kg, 874 mol), toluene (1646 L), and 48% w/w hydrobromic acid was heated under reflux (about 93 °C) for 7 h. After cooling to 75 °C, the layers were separated, and the upper organic phase was washed with water (125 L) at 70–75 °C. The organic solution of 9-bromononyl alcohol was concentrated by distillation to 820 L and cooled to ambient temperature. A solution of thiourea (63.5 kg, 834 mol) in isopropanol (387 kg) was added, and the mixture was heated under reflux (about 86 °C) for 20 h. The reaction mixture was cooled to 0 °C over 5 h and stirred at 0 to –4 °C for 4 h. The solid was collected by filtration, washed with octane bp ca. 120 °C (210 kg) and dried in a stream of cold nitrogen. The yield of **17** at 100% w/w strength was 238.5 kg (91%).

9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl alcohol (13).

All process operations described below were performed under a nitrogen atmosphere, and water was degassed with nitrogen before use.

Triethylamine (86.1 kg, 852 mol) was added to a stirred solution of 4,4,5,5,5-pentafluoropentanol (119 kg, 669 mol) in acetonitrile (284.5 kg) at 20 °C. To the resulting mixture was added a solution of methanesulfonyl chloride (87.0 kg, 760 mol) in acetonitrile (214 kg), maintaining the temperature at 20 °C. Analysis showed mesylation to be complete after about 2 h. **17** (190.8 kg at 95.0% w/w assay, 606 mol) was dissolved in degassed water (545 L) at 40 °C and the solution was added over 15 min to the mesylate ester solution prepared above, followed by a line wash of water (90.5 L). Sodium hydroxide solution (47% w/w, 310.3 kg, 3646 mol) was added over about

3 h at 40 °C, and the reaction mixture was heated under reflux (72 °C) for 80 h. After cooling to 40 °C, the layers were separated. The upper organic phase was diluted with octane bp ca. 120 °C (680 kg), washed at 40–45 °C with water (181 L), then with a solution of 36% w/w hydrochloric acid (77 kg, 759 mol) in water (362.5 L), and finally with water (2 × 181 L). The organic solution was concentrated by distillation under reduced pressure to 1075 L, cooled, and stirred at 10 °C for 1.5 h. The solid was collected by filtration, washed with octane bp ca. 120 °C (270 kg) precooled to 10 °C, and dried in a stream of cold nitrogen. The product required no further purification. The yield of **13** (mp 40–42 °C) was 167.6 kg (82%).

¹H NMR (400 MHz, 300 K, CDCl₃) δ 1.30 (10H, m), 1.58 m (4H, m), 1.65 (1H, s), 1.90 (2H, m), 2.17 (2H, m), 2.50 (2H, t), 2.59 (2H, t), 3.60 (2H, t); ¹³C NMR (68 MHz, 300 K, CDCl₃) δ 20.2 (t, *J* = 3.4 Hz), 25.6, 28.7, 29.0, 29.4, 29.4 (t, *J* = 23.5 Hz), 29.2, 29.3, 31.1, 31.76, 32.60, 62.85, 116.2 (tq, *J* = 253 Hz, 37.2 Hz), 118.9 (qt, *J* = 285.6 Hz, 36.2 Hz).

9-(4,4,5,5-Pentafluoropentylsulfanyl)nonyl Bromide (14). Bromine (96.0 kg, 601 mol) was added over 2 h to a slurry of triphenylphosphine (158.4 kg, 603 mol) in dry acetonitrile (290 L) at 20 °C. The mixture is stirred for 1 h to complete the formation of dibromotriphenylphosphorane. Alcohol **13** (165.3 kg at 98% assay, 482 mol) was dissolved in acetonitrile (290 kg) at 40 °C, and the solution was added to the brominating agent over 1 h at 23 °C followed by a wash of acetonitrile (30 kg). The mixture was stirred at 23 °C for 2 h to complete the reaction. Triethylamine (78.0 kg, 771 mol) was added to the mixture over 1.5 h, followed by a wash of acetonitrile (30 kg). The mixture was diluted with water (162 L) and concentrated by distillation under reduced pressure (200 mbar) at <60 °C to 750 L. The residual solution was extracted with isohexane (425 kg). The isohexane solution was washed with aqueous aceto-

nitrile (1:1 v/v, 2 × 324 L) and then with acetonitrile (162 L) to remove the bulk of the triphenylphosphine oxide (all the washes were carried out at 30 °C). The isohexane solution was concentrated by distillation under reduced pressure (490 mbar initially, reducing to 50 mbar) at <60 °C, leaving the crude product as an oil (95.0% w/w by GC). The yield of crude **14** at 100% w/w strength 168.6 kg (87%). The product was purified by distillation in a Wiped Film Evaporator (WFE) with a jacket temperature of about 160 °C and a pressure of 2–3 mbar.

¹H NMR (400 MHz, 300 K, CDCl₃) δ 1.31 (8H, m), 1.43 (2H, m), 1.58 (2H, m), 1.89 (4H, m), 2.17 (2H, m), 2.51 (2H, t), 2.59 (2H, t), 3.41 (2H, t); ¹³C NMR (68 MHz, 300 K, CDCl₃) δ 20.2 (t, *J* = 3.4 Hz), 28.0, 28.5, 28.6, 28.9, 29.4, 29.4 (t, *J* = 24.5 Hz), 29.1, 31.1, 31.7, 32.6, 33.8, 115.7 (tq, *J* = 251.5 Hz, 37.6 Hz), 119.1 (qt, *J* = 285.4 Hz, 36.3 Hz).

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Supporting Information Available

NMR spectra of fulvestrant. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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