

# Development of a Catalytic Cuprate 1,6-Conjugate Dienone Addition Process for the Manufacture of Fulvestrant EAS, a Key Intermediate in the Synthesis of Fulvestrant

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## Abstract:

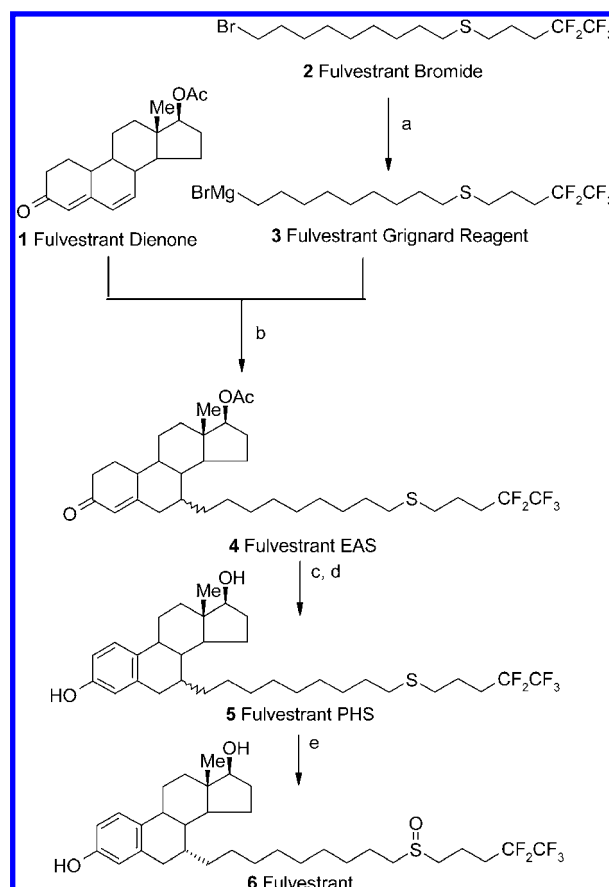
The paper describes the development of a process to a key steroidal intermediate in fulvestrant, the active pharmaceutical ingredient of the anticancer agent Faslodex. Synthesis of the intermediate, known within AstraZeneca as fulvestrant EAS, involves the copper-catalysed 1,6-conjugate addition of a Grignard reagent to a steroidal dienone. The reaction temperature and the order and rate of addition of the reagents have a dramatic effect on the overall yield of the desired compound. A novel aspect of the development was the monitoring of transient colour changes associated with the catalytic cycle as an important aid to process optimisation.

## Introduction

7 $\alpha$ -[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl]estra-1,3,5,(10)-triene-3,17 $\beta$ -diol, (fulvestrant, **6**) is the active pharmaceutical ingredient of faslodex, a steroidal anti-estrogen targeted towards advanced breast cancer. The research synthetic route of the active ingredient is well documented,<sup>1,2</sup> as is the manufacturing route (Scheme 1).<sup>3</sup> The key step is the carbon–carbon bond formation at C-7 on the steroid nucleus to give fulvestrant EAS, (**4**, Scheme 1, steps a and b). Fulvestrant **6** is then obtained after subsequent and sequential aromatization of the steroid A-ring, hydrolytic removal of the 17-acetate and oxidation of the side-chain sulfide (Scheme 1, steps c–e), followed by recrystallization to remove the unwanted 7 $\beta$ -isomer.

The 1,4-Michael addition of a Grignard reagent to a conjugated enone in the presence of a copper(I) salt is well-established methodology,<sup>4</sup> as is that of copper-mediated, 1,6-addition to a conjugated dienone.<sup>5</sup> Thus, in our synthetic route to fulvestrant we chose to use this methodology to introduce the alkyl group at the 7-position of the steroidal backbone, *via* the copper-mediated, conjugate addition of fulvestrant Grignard reagent, **3** to fulvestrant dienone, **1** (Scheme 1, steps a and b).

## Scheme 1. Synthetic route to fulvestrant 6<sup>a</sup>



<sup>a</sup> Conditions: (a) Mg, THF, 45 °C; (b) CuCl, THF, –34 °C; (c) CuBr<sub>2</sub>, LiBr, Ac<sub>2</sub>O, CH<sub>3</sub>CN, 20 °C; (d) NaOH, H<sub>2</sub>O, CH<sub>3</sub>OH, 30 °C; (e) H<sub>2</sub>O<sub>2</sub>, EtOAc, 23 °C.

In early development, fulvestrant EAS, **4**, was prepared in a ‘stoichiometric’ process involving addition of dienone **1** to a dialkylcuprate reagent prepared from 1 mol equiv of copper(I) iodide (CuI) and 2.06 mol of Grignard, **3** at –30 °C. Subsequently, a much more efficient catalytic process was developed, which employed low levels of copper(I) chloride (0.08 mol equiv) and required significantly less Grignard **3** (1.54 mol equiv). The development of the stoichiometric process (during which the important by-products were identified) and

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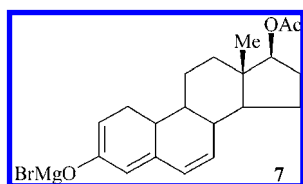
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(1) Bowler, J.; Tait, B. S.; Eur. Pat. Appl. EP 138504 1985.  
 (2) Bowler, J.; Lilley, T. J.; Pittam, J. D.; Wakeling, A. E. *Steroids* **1989**, *54* (1), 71–99.  
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 (4) (a) Normant, J. F. *Synthesis* **1972**, 63–80. (b) Erdick, E. *Tetrahedron* **1984**, *40*, 641–657. (c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038. (d) Taylor, R. J. K. *Synthesis* **1985**, 364–392. (e) Lipshutz, B. H. *Synthesis* **1987**, *32*, 5–341. (f) Ullenius, C.; Christenson, B. *Pure Appl. Chem.* **1988**, *60* (1), 57–64. (g) Lipshutz, B. H. *Synlett* **1990**, (3), 119–28.

that of the catalytic process for the formation of fulvestrant EAS, **4**, is described below.

## Results and Discussion

**Stoichiometric Process.** Addition of Grignard reagent **3** to dienone **1** at  $-30\text{ }^{\circ}\text{C}$  in tetrahydrofuran (THF) was found to occur exclusively with 1,6-selectivity in the presence of the Cu(I) salt with no indication of 1,2- or 1,4-addition products. In the absence of the Cu(I) salt at  $-30\text{ }^{\circ}\text{C}$ , mostly 1,2-addition products are formed together with fulvestrant dienone **1** regenerated on workup, resulting from enolised dienone **7**. Similar copper-mediated 1,6-selectivity has been observed by many other groups.<sup>5f</sup> With a view to the manufacturing process, cuprous chloride was chosen in favor of cuprous iodide as the Cu(I) source in order to avoid the unwanted ‘purple plume’ associated with incineration of iodide-containing aqueous waste liquors.

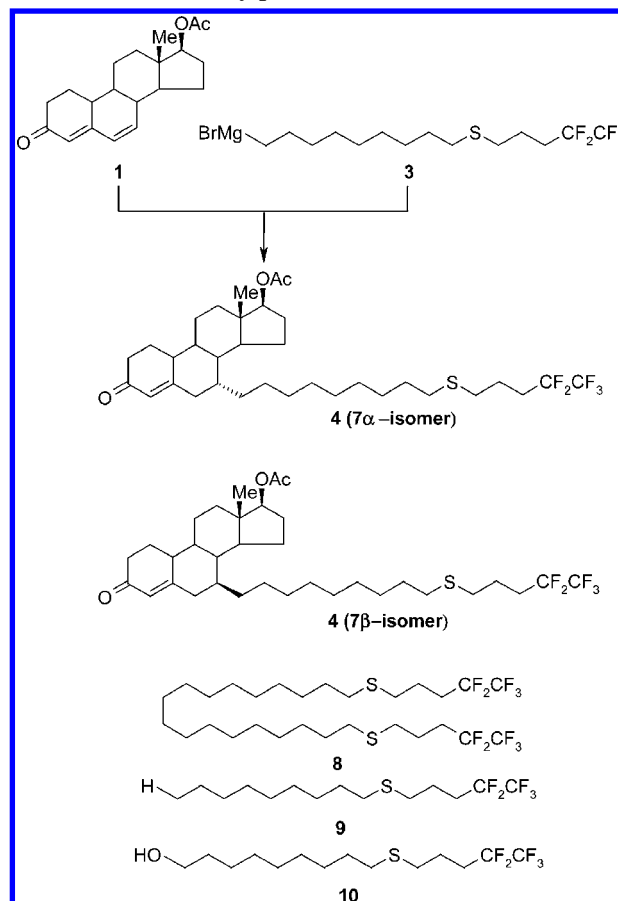


During early development, inconsistent formation of the Grignard **3** on scale-up was a serious issue. Successful and reproducible formation of **3** was found to be highly dependent upon the quality of the side-chain bromide. Fulvestrant bromide **2** was successfully purified using a wiped film evaporator since conventional vacuum distillation led to its degradation. It was also important to store the purified bromide **2** at low temperature in order to minimise degradation.

The overall yield of **4**, the fulvestrant ( $7\alpha+\beta$ )-EAS, by the ‘stoichiometric’ process was about 89%, with an  $\alpha:\beta$  isomer ratio of 2.5:1, i.e., about 64% (as  $7\alpha$ -isomer). In addition to the desired  $7\alpha$ -EAS isomer and its unwanted  $7\beta$ -EAS isomer, two major reaction by-products were observed (Scheme 2): the symmetrical ‘Wurtz’ dimer impurity **8**, and the alkane **9**, arising from homocoupling and hydrolysis of the alkyl group of the organocopper reagent, ( $\text{R}_2\text{CuMgBr}$ ). Minor quantities of alcohol **10** are also formed by aerial oxidation of the organocopper reagent.

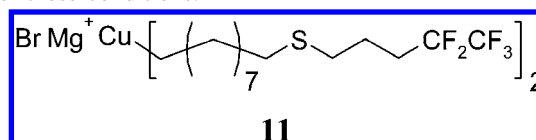
The highly crystalline **8**, which accounts for about 5% of the yield by weight, can be removed from the product oil by crystallization from methanol during workup. Much more troublesome, however, was impurity **9**. Impurity **9** is an oil at room temperature which in the ‘stoichiometric’ process is theoretically formed to the extent of 1 mol equiv on workup. Indeed, its removal necessitated the use of chromatography. Large-scale industrial use of chromatography was unattractive at the time (late 1980s to early 1990s), due to the large solvent usage and the lack of in-house facilities. Furthermore there are significant cost implications associated with the large excess of bromide **2** required in the stoichiometric process. Attempts based on the use of a dummy ligand,<sup>4e,f,5a</sup> to reduce the usage of **2** and hence the formation of high levels of **9** met with little success. The implications of these problems for potential large-

## Scheme 2. Reaction by-products



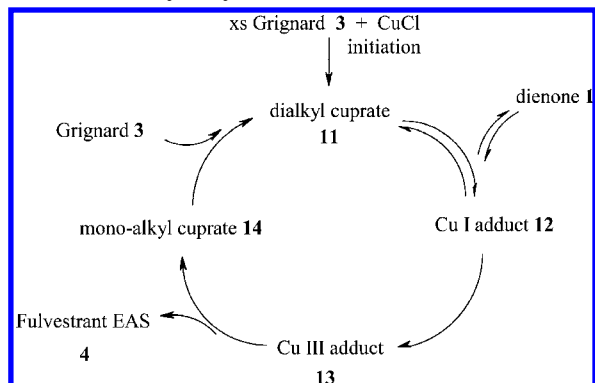
scale manufacture prompted the development of an alternative catalytic process.

**Development of a Catalytic Process.** Early literature reports described the successful use of catalytic copper(I) salts for coupling between simple alkyl Grignard reagents and steroidal dienone in an ‘all-in’ process at  $0\text{ }^{\circ}\text{C}$ , provided that oxygen was rigorously excluded during the quenching procedure. Yields obtained were in the region of 68–78% on exclusion of oxygen, compared with a variable 6–50%<sup>5b</sup> otherwise. An ‘all-in’ catalytic process, however, did not work well for our system. The active organocuprate **11** is less thermally stable than those previously used and has to be formed and used at temperatures below  $-20\text{ }^{\circ}\text{C}$  in order to avoid substantial degradation. At temperatures below  $-20\text{ }^{\circ}\text{C}$  the ‘all-in’ catalytic process gave mostly 1,2-addition products and unreacted **1**, an outcome similar to that observed in the absence of Cu(I) salts. The results pointed to the inability of the catalytic cycle to compete effectively with unwanted enolisation and 1,2-addition reactions under these conditions.

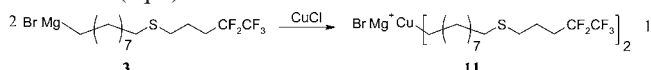


The widely accepted reaction mechanism for the catalytic process, based on NMR and other experimental evidence,<sup>6,7</sup> involves several steps. The first is the generation of **11** through

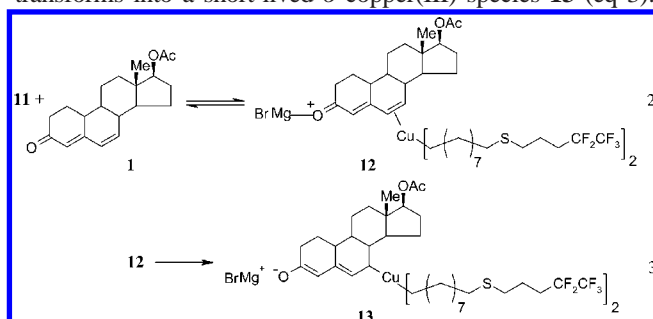
### Scheme 3. Catalytic cycle mechanism



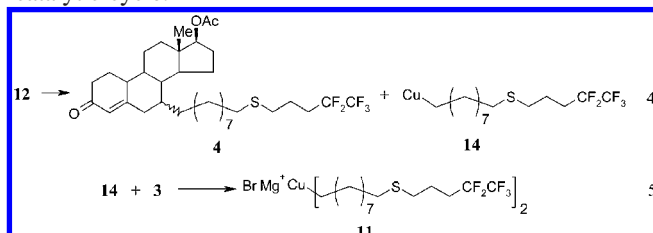
an initiation reaction between the excess Grignard reagent **3** and CuCl (eq 1).



This is followed by the reversible formation of a copper  $\pi$ -complex, **12**, between **11** and dienone **1** (eq 2), which then transforms into a short-lived  $\sigma$ -copper(III) species **13** (eq 3).



Reductive elimination to give the desired **4** and monoalkylcuprate **14**, which reacts with excess Grignard reagent **3** to reform the active dialkylcuprate **11** (eqs 4 and 5), completes the catalytic cycle.



The overall catalytic cycle is summarised in Scheme 3.

There are two obvious possibilities for the poor performance of the catalytic cycle in an 'all-in' process. The first is that at temperatures below  $-20^\circ\text{C}$ , enolisation of **1** by the excess Grignard **3** is inherently faster than the rate of formation of the  $\sigma$ -copper(III) species **13** and subsequent reductive elimination of the monoalkylcuprate **14**, thus disrupting the catalytic cycle.

The second is that at catalytic levels of copper, the bulk of Grignard **3** and dienone **1** are necessarily outside the catalytic cycle for the majority of the reaction and are free to react together in a competing 'copper-free' reaction to give enolate plus 1,2-addition. In the latter case the most likely solution would be the controlled addition of **1** or **3** (or both) to the reaction mixture at a rate that would prevent buildup of the reagents and thus minimise competing enolisation and 1,2-addition reactions. Earlier workers have reported the successful use of controlled addition of enone or Grignard or both to achieve moderate-to-high yielding catalytic processes.<sup>5c-f,7b,8-11</sup>

Of the three possible controlled addition modes, we rejected a simultaneous, doubly controlled addition of equi-molar reagents to the catalyst reaction mixture because of anticipated difficulties on scale-up to our manufacturing plant. Furthermore, it was found that at low Cu (I) levels, addition of dienone (**1**) to a mixture of Grignard **3** and the copper salt gave substantially better yields than the alternative addition of **3** to the dienone **1** and copper salt. In the best case, a 90% yield of **4**, in the former mode was achieved, compared with 66% in the latter, although the  $\alpha:\beta$  ratio was less favorable at 3.5:1 compared with 4.6:1. We therefore concentrated development work on the controlled addition of dienone **1** to a mixture of Grignard **3** and the copper salt.

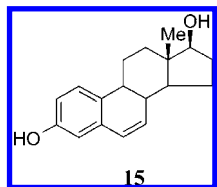
**Process Optimisation.** Distinctive and helpful colour changes occur during our mode of addition. Thus, addition of a portion of a THF solution of **1** to the stirred yellow-green mixture of **3** and a catalytic quantity of CuCl in THF at below  $-20^\circ\text{C}$  leads to the immediate formation of a bright orange-red colour. This orange-red colouration reverts back to yellow-green in a few seconds, depending on the rate of the dienone addition and the reaction temperature. If the addition rate is too fast, the orange-red colour persists, and on workup the reaction gives lower yields of **4**, together with 1,2-addition products and recovered **1**. The formation of transient colour, which persists in the excess of reagent, has been noted by other workers.<sup>12</sup> At temperatures below  $-40^\circ\text{C}$  the solution also remains orange-red, and the yield is lowered. With decreasing temperature, at  $-60$  to  $-78^\circ\text{C}$ , mostly **1** is recovered from the reaction mixtures.

These colour changes may be reasonably explained with respect to the accepted reaction mechanism and importantly we

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- (10) Van Klaveren, M.; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D. M.; Van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6135–6138.
- (11) Seebach, D.; Jaeschke, G.; Pichota, A.; Audergon, L. *Helv. Chim. Acta* **1997**, *80*, 2515–2519.
- (12) (a) Davis, B. R.; Johnson, S. J. *J. Chem. Soc., Perkin Trans. I* **1979**, 2840–2844. (b) Hauptmann, H.; Metzger, J.; Schnitzbauer, A.; Cuilleron, C. Y.; Mappus, E.; Lippa, P. B. *Steroids* **2003**, *68*, 629–639.

were able to use them to optimise the reaction conditions. We believe the orange-red colour to be associated with the formation of the copper  $\pi$ -complex **12**, such complexes being known to be yellow to deep orange-red in colour.<sup>6a,d,e</sup> Correspondingly, we relate the disappearance of the colour to product formation, as have others.<sup>6c</sup> Thus, if the rate of addition of dienone is too fast, the catalytic cycle becomes saturated with respect to dienone, indicated by persistence of the colour, and the excess dienone reacts with Grignard **3**, leading to a poor reaction outcome. If the addition rate is too slow or the temperature too high, then the solution goes black due to decomposition of the organocuprate **11**, and conjugate addition thus ceases. The system can be reactivated with fresh CuCl, but higher levels of impurities, removal of an increased amount of the 17-acetate protecting group, and recovery of **1** after workup is observed. At the extreme of low temperatures employed for the reaction ( $\sim -40$  °C), the orange-red colour again persists, in this case because of slow turnover of the cycle and unreacted **1** remains even after long reaction times. We note that it is important in our case to consume all of **1**, as failure to do so results in the formation at the subsequent aromatisation stage of **15**, a  $\Delta^6$  estradiol impurity which is difficult to remove from the final product **6**.



The result of these indicative colour changes is that the reaction in the laboratory can effectively be run as a 'titration', with each successive aliquot of **1** being added following the 'end-point' from the previous aliquot. In this way the reaction temperature, the addition rate and the cuprous chloride charge were optimised at  $-30$  to  $-35$  °C, 3 to 5 h and 0.08 mol equiv, respectively, giving rise to a combined isolated yield of about 90%, with an  $\alpha$ : $\beta$  ratio of 2.5–3.5:1.

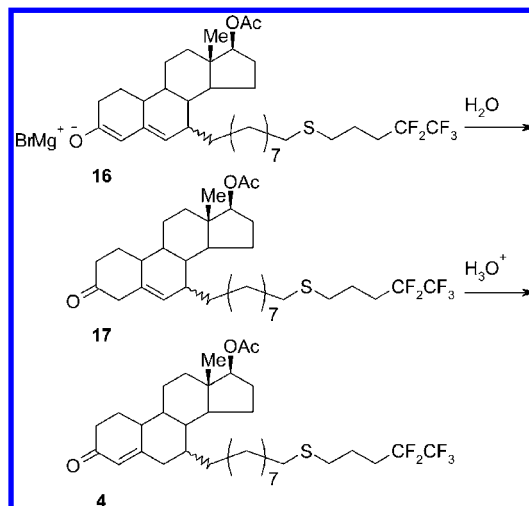
Although UV<sup>13</sup> and NMR<sup>6b,d,e,7b,13,14</sup> spectroscopy have been used to follow the reaction, to the best of our knowledge, this is the first time that titration by colour (or indeed visible spectra) has been used to follow and optimise a conjugate cuprate addition reaction. Earlier workers<sup>6b,d,e,7b,13,14</sup> have shown spectroscopically the disappearance of a transient intermediate species associated with the copper  $\pi$ -complex; conjugate addition can be slow below  $-40$  °C with acid quenching of the copper  $\pi$ -complex at  $-78$  °C giving only starting enone.<sup>6d</sup>

Finally, the mixture of **3** and cuprous chloride in THF was found to be stable under a nitrogen atmosphere for at least 12 h at  $-34$  °C. This may be related to the dialkyl sulfide structure of **3**.<sup>15</sup>

**HPLC Analysis.** Analysis of the reaction mixture by HPLC during the addition of **1** was used to back-up the 'titration' method. Drown-out conditions for the reaction samples were

(13) Kraus, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141–148.  
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 (15) (a) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425–434. (b) Olmstead, M. M.; Power, P. P. *J. Am. Chem. Soc.* **1990**, *112*, 8008–8014. (c) Powell, L.; Mahmood, A.; Robinson, G. E. Submitted to *Org. Process Res. Dev.* 2010.

#### Scheme 4. Product isomerisation



found to be critical to the success of the analyses and indeed for the workup of the final reaction mixture. Anaerobic sampling and drown-out into nitrogen-degassed glacial acetic acid, followed by further dilution with the eluent, gave reproducible results and resulted in the direct formation of the desired conjugated  $\Delta^4$ -3-ketone **4**. Quenching with glacial acetic acid has been employed by others<sup>5c,8e</sup> and was also adopted in our reaction workup procedure to prevent impurity formation. In contrast, quenching in nitrogen-degassed water or aqueous ammonium chloride solution gave **17**, the unconjugated  $\Delta^5$ -3-ketone product through kinetic protonation of the intermediate enolate **16**, and required isomerisation to **4** with acid<sup>17</sup> (Scheme 4).

**Nature of the Copper Catalyst.** Several copper compounds have been used to catalyse the addition of Grignard reagents to dienones.<sup>9c</sup> The following copper(I) catalysts were purchased or prepared and investigated as alternatives to CuCl in the catalytic process: tetrakis[iodo(tri-*n*-butylphosphine)copper(I)], phenylthiocopper, cuprous bromide·dimethyl sulphide complex, cuprous acetate, cuprous cyanide, and lithium 2-thienylcuprate. With the exception of cuprous iodide and acetate, in the other cases the  $\alpha$ / $\beta$ -isomer ratios were poorer than with CuCl, and there was evidence of decomposition. Finally, dilithium tetrachlorocuprate gave an  $\alpha$ / $\beta$ -isomer ratio of 3.3:1 but in a disappointing 50% yield of **4**.

We note also that trimethylsilyl chloride<sup>6a,8e,16</sup> and tetramethylenediamine (TMEDA)<sup>17</sup> have been used by other workers to activate the conjugate addition, but in our case they offered no advantages and resulted in lower yields.

**Reaction Workup.** The reaction mixture was quenched into acetic acid under anaerobic conditions and the mixture diluted with water. THF was removed by distillation and the required product **4**, extracted into isohexane. The product **4** is an oil and is not readily purified at this stage, but the isohexane solution, which also contains by-product from the preparation of **3**, can be used satisfactorily in the next stage.

**Fulvestrant Grignard (3) Manufacture.** Conversion of **2** to **3** is exothermic and calculations indicated that the heat output

(16) Sakata, H.; Kuwajima, I. *Tetrahedron Lett.* **1987**, *28*, 5719–5722.  
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 (18) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27–30.

(270 kJ mol<sup>-1</sup>) would lead to an unacceptable adiabatic temperature rise of 65 °C. A strategy for safe operation of the process was developed which involved adding **2** in four portions to a suspension of magnesium and initiator in THF at 45 °C. After each addition, reaction was confirmed by observing a temperature rise of 5–10 °C before addition of the next portion of **2**. Strength determination was by anaerobic titration with a dry alcohol, such as *sec*-butanol, in a dry nonaqueous solvent, such as xylene, using 1,10-phenanthroline as indicator.<sup>19</sup> The yield was typically in the range 85–90%, with the main by-product being **8**, together with small amounts of **9** and **10** (Scheme 2) formed from moisture and oxygen ingress, respectively. In the laboratory, the Grignard initiation was accomplished with iodine. On a plant-scale manufacturing campaign, a small quantity of **3** prepared separately in our Large Scale Laboratory, using iodine as initiator, was used to initiate the first batch of **3**. The bulk of the resulting solution of **3** was transferred to a second reactor vessel for the conjugate addition, with a small residue (or heel) being left behind to initiate the subsequent batch. This process of using a small heel from the previous batch as an initiator for subsequent formation of **3** has proven extremely reliable in development and commercial manufacture, allowing several batches to be prepared without the need for analytical monitoring before use in the next stage.

The heel solution of **3** could be stored for long periods under an inert nitrogen atmosphere without detriment to its performance as an initiator.

**Process Stoichiometry.** The optimum molar stoichiometry, based on the best yields of **4** from **1** of 85–90%, was the following:

1.54 **3** : 1.0 **1** : 0.08 CuCl.

This may be compared to the “stoichiometric” cuprate process, which employed the following:

2.06 **3** : 1.0 **1** : 1.0 CuCl.

## Summary and Conclusions

By utilising the colour changes accompanying the catalytic cycle in laboratory reactions, we have been able to develop a robust and reproducible catalytic cuprate process to produce **4** in excellent yields. The catalytic procedure employs 25% less **2** and 92% less cuprous chloride than the original stoichiometric organocuprate process, affording both economic and environmental savings. This process has scaled up well and has been employed in our commercial manufacturing unit, producing tonne quantities of **4**.

## Recent Developments

Subsequent work on small-scale reactions has shown that high yields of **4** (93%,  $7\alpha:7\beta = 12.1$ ), may be achieved by slow addition of **3** to the dienone **1** and copper salt (CuCl) at –20 °C, provided that higher levels of CuCl, (typically 0.5 equiv) are used. Full details are given elsewhere.<sup>20</sup>

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## Experimental Section

**Preparation of Grignard (**3**) Initiator.** The terms relative volume and relative weight refer to (**2**).

Fulvestrant bromide **2** (0.2 mol equiv) is added to magnesium raspings (1.15 mol equiv) and THF (2.0 relative volumes). Iodine (0.001 relative weight) is added to initiate the reaction. The mixture is diluted with more THF (2.75 relative volumes), and the temperature is raised to about 45 °C. Further **2** (0.8 mol equiv) is added in several portions. The mixture is cooled, excess magnesium is allowed to settle out, and the solution of **3** is decanted prior to use in the next stage.

**Preparation of Fulvestrant EAS **4**.** The term relative volume refers to the weight of **1**.

To a solution of Grignard initiator **3** (about 0.05 mol equiv), maintained under an inert nitrogen atmosphere, is added magnesium raspings (2.19 mol equiv) and THF (8.4 relative volumes), and the mixture is heated to about 45 °C. Fulvestrant bromide **2** (0.247 mol equiv) is added to initiate the reaction; then the mixture is diluted with THF (2.2 relative volumes), and more **2** (1.54 mol equiv) is added in several portions, maintaining the temperature at about 45 °C. The mixture is cooled, and excess magnesium is allowed to settle out. To initiate subsequent batches of **3**, 17% of the solution is retained, and the remaining 83% of the solution of **3** is decanted for use in the next stage.

The solution of **3** (1.35 mol equiv) in THF is diluted with more THF (2.1 relative volumes) and cooled to –34 °C, and then cuprous chloride (0.078 mol equiv) is added. A solution of (**1**) (1.00 mol equiv) in THF (4.7 relative volumes) is added over about 3.5 h at –34 °C. The reaction is quenched with a solution of glacial acetic acid (4.47 mol equiv) in THF (1.3 relative volumes), and the mixture is warmed to 20 °C and then diluted with water (7.0 relative volumes). THF is removed by distillation, and after the addition of more water (3.0 relative volumes), the product is extracted into isohexane (5.0 relative volumes). The organic phase is separated and washed with 25% w/v aqueous potassium chloride solution (4.9 relative volumes). The solution of **4** in isohexane thereby obtained is suitable for use directly in the next stage. Alternatively, the product may be recovered as a viscous oil by removal of the isohexane solvent under reduced pressure. The yield of **4** is in the range 90–95% with an  $\alpha:\beta$  isomer ratio of 2.5:1, corresponding to a yield of (**4** $\alpha$ ) of around 64–68%. If desired, the  $\alpha$  and  $\beta$  isomers may be separated by column chromatography using Merck 9385 silica gel and gradient elution with 10 to 25% v/v ethyl acetate in isohexane. Plates may be visualized by UV at 254 nm or via 1% w/v aqueous potassium permanganate solution.

**Spectral information for Fulvestrant EAS (**4**, Scheme 2),** [(10*R*,13*S*,17*S*)-13-methyl-3-oxo-7-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)nonyl]-2,6,7,8,9,10,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl] acetate):

**$\alpha$ -EAS isomer:**

<sup>1</sup>H NMR (600 MHz, 300 K, CDCl<sub>3</sub>)  $\delta$  0.87 (3H, s), 0.90–2.60 (46H, complex m), 4.63 (1H, t), 5.84 (1H, s).

**$\beta$ -EAS isomer:**

<sup>1</sup>H NMR (600 MHz, 300 K, CDCl<sub>3</sub>)  $\delta$  0.87 (3H, s), 0.90–2.60 (46H, complex m), 4.58 (1H, t), 5.81 (1H, s).

MS: accurate mass MS data for both  $\alpha$  and  $\beta$  isomers was consistent with a molecular formula of  $C_{34}H_{52}F_5O_3S$  as the elemental formula for the  $(M + H)^+$  ion with a measurement error of 1.1 mDa (2.3 ppm).

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