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An alternative synthesis of the breast cancer drug fulvestrant (Faslodex®): catalyst control over C–C bond formation†

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Fulvestrant (Faslodex®) was synthesized in four steps (35% overall yield) from 6-dehydronandrolone acetate. Catalyst controlled, room temperature, diastereoselective 1,6-addition of the zirconocene derived from commercially available 9-bromonon-1-ene was used in the key C–C bond forming step.

Breast cancer is the most frequently diagnosed cancer and is common in women from all regions of the world.[1] Faslodex® (active ingredient, fulvestrant, **1**, Fig. 1) is a breast cancer drug with a unique mechanism of action; it is a selective estrogen receptor (ER) downregulator with antiestrogenic and antiproliferative, but not estrogen agonist, activity.[2] Approved by the FDA in 2002[3] and more recently in Europe (2010)[4] and Japan (2011),[5] Faslodex® had 2014 sales of US$720 million.[6] The drug is prescribed to postmenopausal women with advanced, tamoxifen resistant, or metastatic ER-positive breast cancer. It may also be used as a first-line treatment[2,7] with results comparable to tamoxifen and anastrozole.[8] **1** has no significant adverse effects and the efficacy and ease of fulvestrant administration (three times 1st month, then once per month) is attractive[9] and offers options for combination treatments.[10,11]

Around 1990, ICI (now part of AstraZeneca) pharmaceuticals' research on 7α-alkylated estradiol analogues with pure antiestrogenic activity[12] led to **1**,[13] which is used as a mixture of sulfoxide isomers.[12,14]

The commercial-scale manufacturing route to **1** (Scheme 1), represents a tour-de-force in process development, and has produced tonne quantities of material.[15] The synthesis relies on selective addition of a Grignard reagent, which raised significant practical challenges. While these were ultimately overcome in the AZ manufacturing route, we became intrigued by the possibility of simplifying the synthesis of **1** by avoiding the use of highly reactive premade organometallic species. The route to **1** could (at least potentially) be improved by: (A) shortening the length of the synthesis of (or finding an alternative to) **2**; (B) improving the stereoselectivity, and conditions used, in the key C–C bond forming step; and (C) eliminating impurities observed in the final product, which are generated by use of impure **2** and by side-reactions resulting from the use of the Grignard reagent derived from **2**.

"Fulvestrant bromide" **2** is precursor to Grignard reagent **3**, which undergoes substrate controlled diastereoselective 1,6-conjugate addition to the steroidal dienone **4**.[15] The industrial scale routes, initially mediated by stoichiometric copper, and later refined into a catalytic process, require high purity **2**. Bromide **2** is produced in several steps followed by vacuum distillation using a wiped film evaporator (Scheme 1). Generation of Grignard reagent **3** requires temperature-sensitive (maintaining ~45 °C) portion-wise addition, and the optimized conjugate 1,6-addition to form **5** involves slow addition of **4** in THF over 3.5 h at −34 °C. Using this procedure, **5** is produced in 90–95% yield with an $\alpha:\beta$ ratio of 2.5 : 1 (yield of **5**α ~64–68%), with the isomers being separated at the end of the synthesis.

As detailed elsewhere,[16,17] such Cu-catalyzed reactions are extremely sensitive to solvent, temperature, concentration, method of addition and the presence of additives. Additionally, compatibility of the Grignard reagent with other functional groups limits the

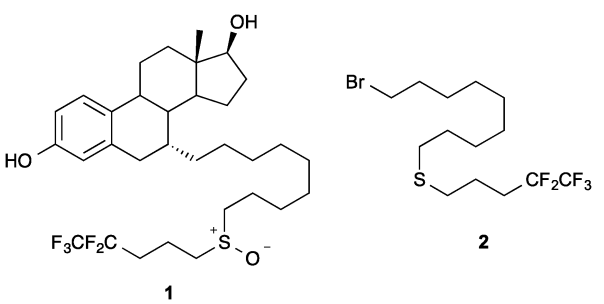

Fig. 1 Structures of fulvestrant (**1**) and fulvestrant bromide (**2**).

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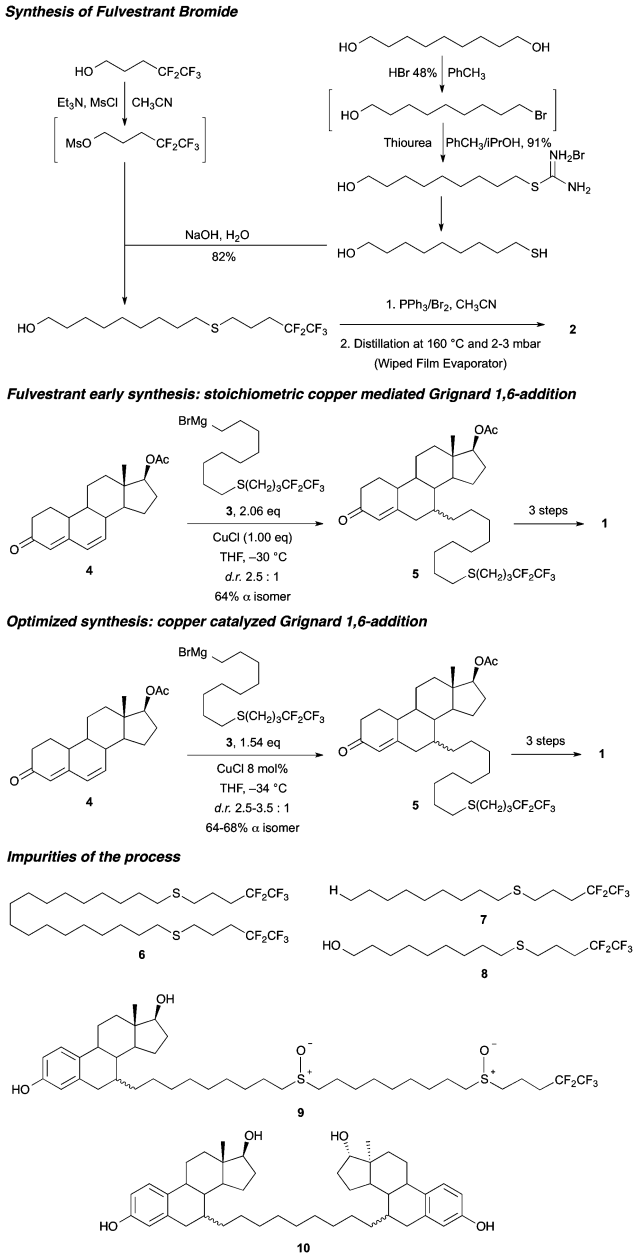


Scheme 1 AstraZeneca's synthesis of fulvestrant bromide, diastereoselective additions to form **5**, and then fulvestrant, and the main impurities of these processes.

options available in reaction/sequence design. In this case, a delicate purification of **2** is required to obtain high purity material, which is essential to both generating **3** effectively, and minimizing the formation of several impurities (**6** to **10**).[16]

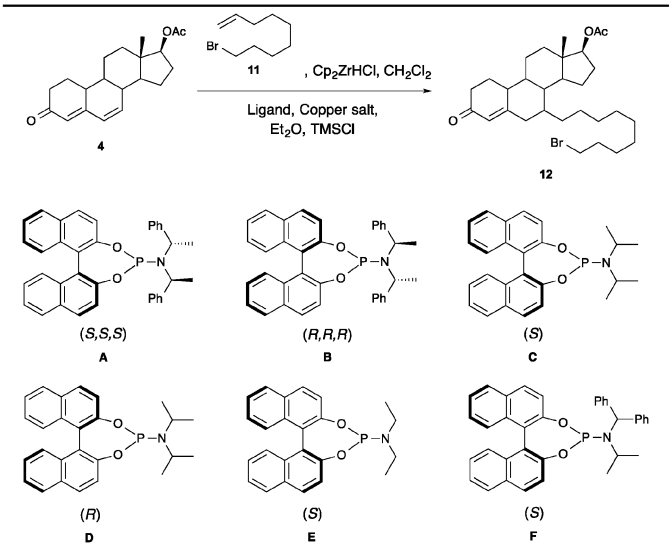
As part of research programme aimed at using alkenes as premade alkyl-metal equivalents in catalytic asymmetric additions[18] we have reported that 1,4 and 1,6-additions to steroid derivatives can occur at room temperature.[19] Here we use this approach in a streamlined four-step synthesis of **1** from two commercially available starting materials.

We examined a hydrometallation-copper-catalyzed 1,6-addition sequence using alkene **11**, bearing an alkyl bromide. This functional group is generally incompatible with Grignard reagents and is readily functionalized. Reactions were performed using previously optimized conditions[18a,19] with a combination of CH_2Cl_2 (for hydrometallation) and Et_2O (for conjugate addition), but we have shown that alkylzirconium additions are remarkably tolerant to changes in the solvent system,[18a] so other combinations can likely be used.

In situ hydrozirconation of commercially available 9-bromonon-1-ene **11** provides an alkylzirconium species which undergoes copper catalysed 1,6-addition to **4**. Using CuBr·Me_2S or Ph_3P as achiral ligands, allows addition (Table 1, entries 1 and 2) at room temperature but poor crude ratios (~1.3 : 1 and ~1.6 : 1) of isomers of **12**. However, pure desired 7α-isomer was easily isolated by flash chromatography with yields of 40 and 30% respectively.

We found we could increase the stereoselectivity in the 1,6-addition using phosphoramidite ligands in combination with *in situ* generated Cu(I)OTf (Table 1, entries 3–8). Of the ligands examined, **A** gave best d.r. and yield (4.6 : 1, 60% isolated yield). The use of TMSCl is essential to obtain good levels of conversion, without TMSCl, **12**α was obtained in 30% yield (not shown) together with 66% recovered starting material. We can also reverse the diastereoselectivity by using ligand **B** with the opposite absolute stereochemistry (*cf.* entries 3 with 4–6) but overall lower selectivity and yields were observed due to the inherent stereochemical control

Table 1 Diastereoselective hydrometallation-1,6-conjugate addition[a]



Entry	Ligand	Copper source	T (°C)	d.r.[b]	Yield[c] (%)
1	—	CuBr·Me_2S	r.t.	1.3 : 1	40α
2	PPh3	CuCl + AgOTf	r.t.	1.6 : 1	30α
3	A	CuCl + AgOTf	r.t.	4.6 : 1	60α
4	B	CuCl + AgOTf	r.t.	1 : 2.3	31β
5	C	CuCl + AgOTf	r.t.	2.3 : 1	19α
6	D	CuCl + AgOTf	r.t.	1 : 2.1	20β
7	E	CuCl + AgOTf	r.t.	1.6 : 1	28α
8	F	CuCl + AgOTf	r.t.	4.2 : 1	46α
9	A	CuCl + AgOTf	0	—	0
10	A	CuCl + AgOTf	40	2.9 : 1	46α

[a] Reaction conditions: ligand (10% mmol), copper (10% mmol), **11** (2.5 eq.), Cp_2ZrHCl (2.0 eq.), TMSCl (5.0 eq.). [b] Crude diastereomeric ratio (α : β) determined by ^1H NMR spectroscopy. [c] Isolated yield of pure isomer.

provided by dienone **4**. No improvements were observed when changing the reaction temperature (entries 9 and 10).

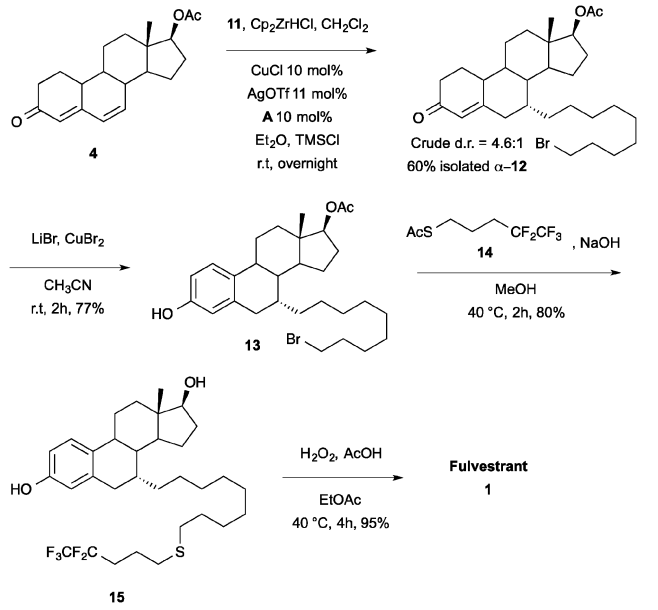
We have run the formation of **12** on a gram scale with no loss of yield or selectivity. With **12** in hand (Scheme 2), we used a mixture of $CuBr_2$ and LiBr to aromatize the enone to **13** (77%) without any observable over-bromination products;[15] aromatization is required at this stage to avoid conjugate addition of thiol to the enone unit in the next step.

In situ hydrolysis of (4,4,5,5,5)-pentafluoropentyl ethanthiolate **14**[20] at 40 °C liberates the thiol, displacing the bromide and giving **15** (80%); these conditions avoid isolation of malodorous (4,4,4,5,5)-pentafluoropentanthiol and remove the acetate protecting group on the **17**β alcohol moiety.

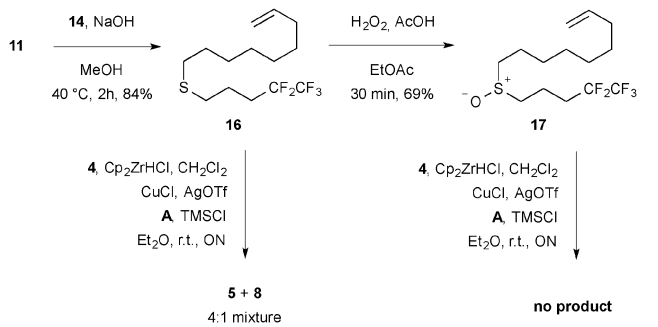
Oxidation to sulfoxides **1** (35% H_2O_2, AcOH, EtOAc, 40 °C) gave no observable overoxidation, and fulvestrant **1** as a ~1:1 mixture of isomers (observable by ^{13}C NMR) in 95% yield.

We also examined hydrometallation-addition of alkenes bearing a sulphide and sulfoxide (Scheme 3). In both cases unsatisfactory results were obtained. 1,6-Addition of **16** to give **5** provided 40% of the desired 7α-isomer, but it was obtained as an inseparable 4:1 mixture with alcohol **8**. Hydrometallation of **17** was not effective and 1,6-addition products were not obtained.

In conclusion, an alternative synthetic route to fulvestrant involving hydrozirconation of a commercially available alkene and copper-catalyzed 1,6-addition has been developed. As the reaction tolerates an alkylbromide the 1,6-addition product can be readily functionalized, avoiding use of **2** and streamlining the synthesis. The main cause of source of impurities in previous routes was the use of **2**. Diastereoselectivity of 4.6:1 in favour of the desired α-anomer is observed using 10 mol% of a chiral copper catalyst. The overall yield of the four-step sequence is 35%.



Scheme 2 Synthesis of fulvestrant.



Scheme 3 1,6-Addition of alkyl chains bearing a sulphur atom. Reaction conditions: **4** (1.0 eq.), **A** (20 mol%), CuCl (20 mol%), AgOTf (22 mol%), alkene (2.5 eq.), Cp_2ZrHCl (2.0 eq.), TMSCl (5 eq.).

Notes and references

1 *Global Cancer Facts & Figures*, American Cancer Society, Atlanta, 3rd edn, 2015.
2 S. M. Scott, M. Brown and S. E. Come, *Expert Opin. Drug Saf.*, 2011, **10**, 819–826.
3 P. F. Bross, *Oncologist*, 2002, **7**, 477–480.
4 AstraZeneca, http://www.astrazeneca.co.uk/home/search-results/Article/faslodextm-fulvestrant-500mg-approved-in-europe-for-the-treatm, accessed July 2015.
5 AstraZeneca, http://www.astrazeneca.com/Media/Press-releases/Article/20110926-astrazeneca-announces-first-approval-of-faslodex, accessed July 2015.
6 DrugAnalyst, http://consensus.druganalyst.com/AstraZeneca/Faslodex/, accessed July 2015.
7 J. D. Croxtall and K. McKeage, *Drugs*, 2011, **71**, 363–380.
8 AstraZeneca, http://www.astrazeneca-us.com/media/press-releases/Article/20141212-faslodex, accessed July 2015.
9 S. E. Jones, *Breast Cancer Res. Treat.*, 2002, **75**(suppl 1), S19–S21; discussion S33–S35.
10 C. Morris and A. Wakeling, *Endocr. Relat. Cancer*, 2002, **9**, 267–276.
11 N. Bundred and A. Howell, *Expert Rev. Anticancer Ther.*, 2002, **2**, 151–160.
12 J. Bowler, T. J. Lilley, J. D. Pittam and A. E. Wakeling, *Steroids*, 1989, **54**, 71–99.
13 A. E. Wakeling, M. Dukes and J. Bowler, *Am. Assoc. Cancer Res.*, 1991, 3867–3873.
14 J. Bowler and B. Tait, *Eur. Pat. Appl.*, EP 138504, 1985.
15 E. J. Brazier, P. J. Hogan, C. W. Leung, A. O. Kearney-McMullan, A. K. Norton, L. Powell, G. E. Robinson and E. G. Williams, *Org. Process Res. Dev.*, 2010, **14**, 544–552.
16 P. J. Hogan, L. Powell and G. E. Robinson, *Org. Process Res. Dev. Dev.*, 2010, **14**, 1188–1193.
17 G. P. Howell, *Org. Process Res. Dev.*, 2012, **16**, 1258–1272.
18 (*a*) R. M. Maksymowicz, P. M. C. Roth and S. P. Fletcher, *Nature Chem.*, 2012, **4**, 649–654; (*b*) M. Sidera, P. M. C. Roth, R. M. Maksymowicz and S. P. Fletcher, *Angew. Chem. Int. Ed.*, 2013, **52**, 7995–7999; (*c*) R. M. Maksymowicz, M. Sidera, P. M. C. Roth and S. P. Fletcher, *Synthesis*, 2013, 2662–2668; (*d*) P. M. C. Roth, M. Sidera, R. M. Maksymowicz and S. P. Fletcher, *Nature Protocols*, 2014, **9**, 104–111; (*e*) E. E. MacIver, R. M. Maksymowicz, N. Wilkinson, P. M. C. Roth and S. P. Flethcer, *Org. Lett.*, 2014, **16**, 3288–3291; (*f*) L. Mola, M. Sidera and S. P. Fletcher, *Aust. J. Chem.*, 2015, **68**, 401–403; (*g*) H. You, E. Rideau, M. Sidera and S. P. Fletcher, *Nature*, 2015, **517**, 351–355; (*h*) R. M. Maksymowicz, A. J. Bissette and S. P. Fletcher, *Chem. Eur. J.*, 2015, **21**, 5668–5678; (*i*) P. M. C. Roth and S. P. Fletcher, *Org. Lett.*, 2015, **17**, 912–915; (*j*) M. Sidera and S. P. Fletcher, *Chem. Comm.*, 2015, **51**, 5044–5047; (*k*) E. Rideau, F. Masing and S. P. Fletcher, *Synthesis*, 2015, **47**, 2217–2222.
19 R. M. Maksymowicz, P. M. C. Roth, A. L. Thompson and S. P. Fletcher, *Chem. Commun.*, 2013, **49**, 4211–4213.
20 Y. Kanbe, M.-H. Kim, M. Nishimoto, Y. Ohtake, N. Kato, T. Tsunenari, K. Taniguchi, I. Ohizumi, S. Kaiho, K. Morikawa, J.-C. Jo, H.-S. Lim and H.-Y. Kim, *Bioorg. Med. Chem.*, 2006, **14**, 4803–4819.