Synthesis of F-18 Fluoroestradiol (FES) T. J. Tewson

The routine synthesis of F-18 16α-fluoroestradiol (1), starting from the 3-methoxymethyl ether of 16α,17α-cyclic sulfate of estriol (2) will be discussed. There is an alternative synthesis in the literature using the 3, 16-ditriflate of 16β-hydroxy estrone (3)[1]. We have no experience with this substrate and its use will not be covered.

The substrate is commercially available (ABX) but we have always made our own[2]. The synthesis is straightforward provided that freshly distilled chloromethylmethyl ether is used to make 3-methoxymethyl ether and that the final product is purified at the end of synthesis. The product should have a M.Pt. of > 150ºC. Any residual imidazole, from the cyclic sulfate formation is hard to see and can seriously interfere with the fluorination. The fluorine-18 fluorination reaction is straightforward, using 10 micromoles (3 mg) and either tetrabutyl ammonium carbonate or potassium carbonate/Krypтоfix® under standard conditions. Fluoride incorporation yields are typically >90% and have exceeded 99%. Only one fluorination product is formed under these conditions. If much less than 10 micromoles of starting material is used there is a second radioactive product formed in very small amounts < 1%. The fluorination reaction can be monitored by HPLC using a C-18 column and a 50% ethanol/water eluant with UV detection at 284 nm. In our hands reverse phase chromatography of the intermediate sulfate salt (4), the product of the fluorination reaction, is much improved if the column has been pretreated with ammonium acetate solution.

Acid hydrolysis of the 3-methoxymethyl ether is straightforward but removal of the 17α-sulfate is more difficult. The hydrolysis is an acid catalyzed reaction but the rate of hydrolysis is not a function of acid strength. It is faster in non-aqueous media but it is not any cleaner. Only one major product is formed, the required FES (1) but an HPLC of the reaction mixture shows an elevated, lumpy baseline suggesting that many minor products are formed. We have hydrolysed the sulfate in 0.1 N HCl at 140ºC in a sealed vial for 30 minutes which gives total cleavage of both the sulfate and the methoxy methyl ether. Others have done the hydrolysis in 0.1 N HCl in acetonitrile and this apparently works well[3]. The final product is purified by prep HPLC on C-18 column using 1:1 EtOH/water as the eluant. Under our conditions the product comes of the column in about 5mls. This is then diluted with PBS so as to bring the final ethanol concentration of the final product to < 10%. However before the solution is diluted it must be kept away from plastic containers. The 50% ethanol solution will wash small amounts of the plasticizer nonyl phenol from the plastic. Nonyl phenol is mildly estrogenic and inclusion of it in the final product will lower the effective specific activity of the FES. The chemical specific activity of the product follows that of the F-18 fluoride, as would be predicted. The final yield, starting from 150 mCi’s of F-18 fluoride is typically 30 mCi’s with a synthesis time of ~ 2 hours.