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The Use of 3-Methoxymethyl-16β, 17β-Epiestriol-O-Cyclic Sulfone as the Precursor in the Synthesis of F-18 16α-Fluoroestradiol

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ABSTRACT. We have prepared 3-methoxymethyl-16β,17β-epiestriol-O-cyclic sulfone (1c) and used it as a substrate for the production of F-18 16α-fluoroestradiol, via nucleophilic fluorination with fluoride ion. The compound is straightforward to make from the commercially available epiestriol and is a stable crystalline compound that can be stored for at least a year at room temperature. Reaction with fluorine-18 fluoride provides excellent yields; typically >90% incorporation of the fluoride is achieved. Partial purification of the labeled product may be accomplished at this stage. Hydrolysis of the methoxymethyl protecting group and ring-opened sulfate occurs rapidly in ethanolic acid solution. In the presence of water the hydrolysis requires more vigorous conditions and additional time but still proceeds to completion. Labeled fluoroestradiol is isolated at the end of a 1–2 h synthesis, depending on the hydrolysis method of 30–45% chemical (decay corrected) yield with respect to fluoride, with a specific activity >1 Ci per micromole. *Copyright © 1996 Elsevier Science Inc.* NUCL MED BIOL 23;7:911–915, 1996.

KEY WORDS. 3-Methoxymethyl-16β,17β-epiestriol-O-cyclic sulfone, F-18 16α-fluoroestradiol, Cyclic sulfates

INTRODUCTION

Fluorine-18 16α-fluoroestradiol has proven to be a valuable radiopharmaceutical for the investigation of the estrogen receptor status of primary and metastatic breast cancer (1–3). The synthesis was based upon fluoride displacement of the 3,16-β-bistrifluoromethane sulfonate of 16-β-hydroxy-estrone (4, 5). When the reaction is performed with excess fluoride, the fluorine-19 situation, the reaction gives an initial pair of isomers at the 16 position, presumably by the fluoride acting as a base to epimerise the initial 16α fluorocompound, and then lithium aluminium hydride reduction creates a second pair of isomers at the 17 position, giving a total of four possible isomers. With fluorine-18 fluoride the epimerisation does not occur, but the epimeric 17 alcohols are produced by LAH reduction. A number of improvements in the original procedure have been published over the years, but the synthesis still requires the separation of the epimeric 17 alcohols (6–8). In the experience of the University of Washington this was not a robust synthesis.

We initially described a synthesis of 16α-fluoroestradiol utilizing the 16β,17β-cyclic sulfate from epiestriol and protecting the phenolic hydroxyl at the 3-position using an acetate **(1a)** (9). This worked well for the synthesis of the fluorine-19 compound but not when the reaction was attempted with no-carrier-added fluorine-18. Under labeling conditions, some hydrolysis of the 3-acetate occurred to give a free phenol, which then reacted with unopened cyclic sulfate to give oligomeric products (10). Subsequently, the same cyclic sulfate protected as the 3-vinyl ether **(1b)** was prepared. This fluorinated cleanly, and the vinyl ether was easily removed by acid hydrolysis, but both the preparation and the purification of the derivative were cumbersome (10). More recently we have prepared the 3-methoxymethyl ether of epiestriol followed by formation of the 16β,17β cyclic sulfate **(1c)** (11) (Fig. 1). This compound is stable and straightforward to prepare from commercially available starting materials. The synthesis is outlined in Scheme 1. Additionally, **1c** reacts with fluorine-18 fluoride in excellent yield, is deprotected by acid hydrolysis, and provides a convenient substrate for the routine preparation of fluorine-18 16α-fluoroestradiol as shown in Scheme 2. We have now implemented the routine synthesis of F-18 16α-fluoroestradiol using this cyclic sulfate as the precursor and prepare clinically useful quantities of the pure compound at high specific activity from short bombardments.

EXPERIMENTAL

Materials and Methods

Reagents and solvents were obtained from Aldrich Chemical Co. and used without further purification unless otherwise noted. The 16-epiestriol was obtained from Sigma Chemical. Melting points were recorded on an electrothermal melting point apparatus and are uncorrected. NMR spectroscopy was carried out on a Gemini-300 or a GE-Sun 7 Tesla instrument using tetramethylsilane as internal standard for protons and external capillary of trifluoroacetic acid as a reference for fluorine. The chemical shifts were reported in parts per million (ppm). Infrared spectra were obtained on a Beckman FT-100 spectrophotometer. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under argon prior to use. Aceto-

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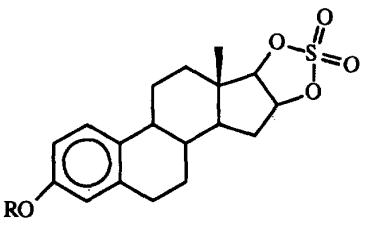


1a R= Ac

1b R= CH=CHCH$_3$

1c R= CH$_2$OCH$_3$

FIG. 1.

nitrile was freshly distilled from calcium hydride. Column chromatography was performed on 230 mesh silica gel. Analytical high-performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1050 system using either an Alltech Econosil C18 column (10 μm, 4.6 × 250 mm) eluted at 2 mL/min with a 10-min gradient from 0–100% acetonitrile in water, or an Alltech Econosil Silica column (10 μm, 4.6 × 250-mm) eluted at 2 mL/min with 0.35% methanol/chloroform or on a Waters system using a Phenomenex C-18 column (5 μm, 4.6 × 150 mm) eluted at 1 mL/min with 40% 0.1 M ammonium acetate solution/60% methanol. Thin-layer chromatography was performed on Merck F_{254} glass-backed silica plates. Combustion analysis was performed by Galbraith Laboratories (Knoxville, TN).

3-O-Methoxymethyl-16β-Epiestriol (2)

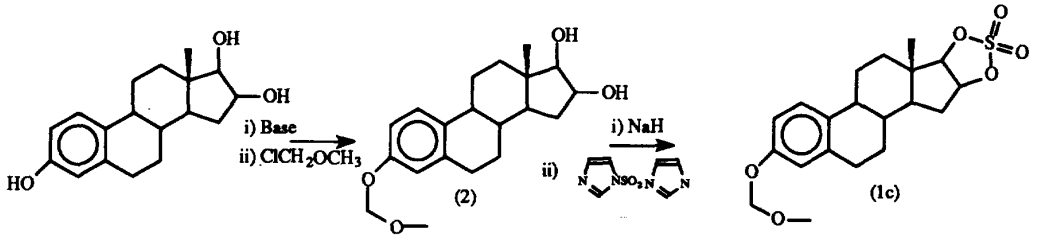
A mixture of 16-epiestriol (0.2 g, 0.7 mmol) and 0.7 mL of 1 N potassium hydroxide in acetonitrile was stirred at room temperature for 1 h. The solvent was then removed *in vacuo* and the reaction mixture was dried further by addition of anhydrous acetonitrile (2 × 10 mL) to obtain a white solid. The salt was then taken up in acetonitrile. To the mixture a solution of 60 mg (0.7 mmol) of freshly opened or distilled chloromethyl methyl ether in acetonitrile was added dropwise. The reaction mixture was left stirring at room temperature overnight. After the solvent had been removed *in vacuo* the crude solid was chromatographed on silica gel eluted with 30–40% EtOAc/petroleum ether to give **2** as a white solid (0.12 g, 53%): m.p. 139–140°C. ^{1}H-NMR ($CDCL_3$, 300 MHz) δ 7.20 (d, 1H, J = 9, H-1), 6.86 (dd, 1H, J = 9, 2.6, H-2), 6.78 (d, 1H, J = 2.6, H-3), 5.15 (s, 2H, OCH_2), 4.25–4.18 (m, 1H, H-16), 3.47 (s, 3H, CH_3O), 3.43 (d, 1H, H-17), 2.89–2.84 (br m, 2H), 2.58 (d, 1H, J = 8.6), 2.39 (d, 1H, J = 4), 2.36–2.17 (overlapping m, 3H), 2.02–1.96 (m, 1H), 1.92–1.86 (m, 1H), 1.54–1.46 (m, 2H), 1.41–1.27 (overlapping m, 3H), 1.09–1.02 (m, 1H), 0.84 (s, 3H, 18-CH_3). IR (KBr) 3363 (br, OH), 2918, 1502, 1252, 1149, 1077, 1018, 930, 787 cm^{-1}.

3-O-Methoxymethyl-16β, 17β-O-Epiestriol Cyclic Sulfone (1c)

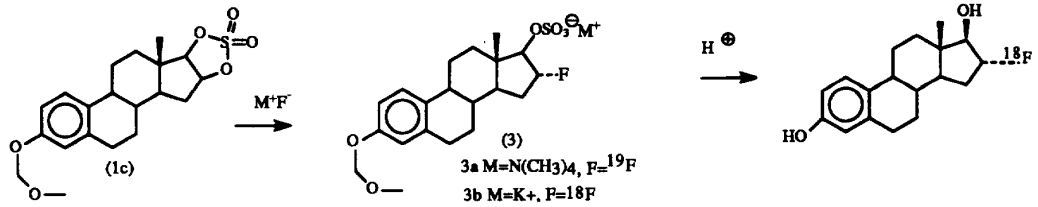
Compound **1c** was prepared according to a procedure previously reported (10). Briefly, a mixture of **2** (0.3 g, 0.9 mmol) and sodium hydride (0.085 g, 3.5 mmol) in anhydrous THF (10 mL) was stirred for 15 min. To this mixture a solution of sulfonyldiimidazole (12) (0.175 g, 0.9 mmol) in THF was slowly added, and the reaction mixture was allowed to stir for 1 h. The solution was then filtered through Celite and washed with EtOAc. The solvent was evaporated and the residue was recrystallized from a mixture of EtOAc/petroleum ether or from heptane to give **1c** as a crystalline solid (0.17 g, 50%): m.p. 152–153°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, 1H, J = 8.7, H-1), 6.85 (dd, 1H, J = 8.7, 2.6, H-2), 6.79 (d, 1H, J = 2.6, H-3), 5.17 (m overlapping s, 1H, H-16), 5.15 (s, 2H, OCH_2), 4.60 (d, 1H, J = 7.5, H-17), 3.47 (s, 3H, CH_3O), 2.90–2.86 (br m, 2H), 2.49–2.25 (overlapping m, 3H), 2.14–2.10 (m, 1H), 1.89–1.77 (overlapping m, 2H), 1.69–1.59 (m, 1H), 1.57–1.40 (overlapping m, 3H), 1.35–1.28 (m, 1H), 1.01 (s, 3H, 18-CH_3). IR (KBr) 2900, 1495, 1390, 1200, 1150, 990, 865, 840 cm^{-1}. Analytical calculations for $C_{20}H_{26}O_6S$: C, 60.89%; H, 6.64%; S, 8.13%. Found: C, 60.68%; H, 6.87%; S, 8.26%.

Reaction of 3-O-methoxymethyl-16β, 17βepiestriol-O-cyclicsulfone (1c) with tetramethylammonium fluoride

Tetramethyl ammonium fluoride tetrahydrate (157 mg, 1 mmol) was dissolved in acetonitrile (3 × 20 mL) and dried by azeotropic distilation of the acetonitrile. The dried salt was then dissolved in 30 mL of anhydrous acetonitrile and 3-O-methoxymethyl-16β,17βepiestriol-O-cyclicsulfone (**1c**) (395 mg, 1 mmol) was added. The solution was refluxed under dry nitrogen for 5 min, the acetonitrile evaporated, and the residue crystallized from ethyl acetate to give 450 mg of tetramethylammonium 3-O-methoxymethyl-16α-fluoro-estradiol-17β-sulfate (**3a**). ^{1}H NMR δ 7.15 (d 1H J = 8.4 Hz) H-4, δ 6.806 (q 1H J = 2.7, 8.4 Hz) H-2, δ 6.75 (d 1H (J = 2.7 Hz)) H-1, δ 5.16 (double multiplet 1H J = 52.8 Hz) H-16β, δ 5.123 (s 2H) -OCH_2O δ 4.44 (dd, 1H J = 27.6, 6.00 Hz) H17α, δ 3.456 (s 3H) -OCH_3, δ 3.338 (s 12 H) $(CH_3)_4N^+$, δ 0.804 (s 3H) 18-methyl group. ^{19}F NMR δ -164.42 multiplet.



SCHEME 1.



SCHEME 2.

Hydrolysis of Tetramethylammonium 3-O-methoxymethyl-16α-Fluoro-Estradiol-17β-Sulfate (3a)

Tetramethylammonium 3-O-methoxymethyl-16α-fluoro-estradiol-17β-sulfate **3a** (250 mg 0.5 mmol) was dissolved in methanol (20 mL) and the solution added to 1 g of strong cation exchange resin in the hydrogen form (Rexyn 101 research grade) that had been washed with methanol several times. The solution was refluxed for 30 min, cooled, the ion exchange resin filtered off, and the methanol evaporated to give an oil. Chromatography on silica with 4% methanol/methylene chloride and crystallization from methanol gave 16α-fluoroestradiol (230 mg 80%) identical to the reported compound (4).

Preparation of F-18 16α-Fluoroestradiol

Fluorine-18 fluoride was prepared by the $^{18}O(p,n)^{18}F$ reaction using O-18 enriched water as the target material (13). The fluoride was isolated from the enriched water by trapping on 20 mg of an anion exchange resin in the hydroxide or carbonate form and then eluting with 400 μL of 0.1 M potassium carbonate solution onto 15 mg of [2,2,2] Kryptofix. This solution was dried by azeotropic distillation with acetonitrile (3 × 2 mL) and then **1c** in acetonitrile was added.

METHOD A. The reaction was carried out by heating 3 mg of **1c** in 2 mL acetonitrile in an oil bath at 100°C for 10 min under a slow stream of argon. The acetonitrile was evaporated and the residue was then dissolved in 1 mL of 40% ethanol/water. This solution was put on a semi-prep HPLC (Phenomenex C18 7 μM 10 × 250 mm) column running at 5 mL/min. Very little activity was left in the reaction vessel, but up to 10% could be left in the HPLC syringe. The unreacted fluoride was eluted at 2 min, and the fluoroestradiol sulfate salt **(3b)** was eluted at 5.5 min. The fluoride incorporation, as measured by counting the two fractions, varied between 80–98%, averaging 92%. Analysis of the sulfate salt fraction on analytical HPLC showed only one radioactive peak corresponding to the sulfate salt **(3b)**, and after the void volume disturbance there was only one UV-absorbing peak, at 284 nm, corresponding to the authentic sulfate salt. The size of the peak was such that it was visible but difficult to quantify and typically corresponded to a specific activity of >3 Ci per μmol. The ethanol/water solution was then evaporated and the residue dissolved in 1 mL of 0.1 N HCl and heated to 140°C in a closed vessel for 40 min. This hydrolyzes both the 3-methoxymethyl ether and the 17-sulfate.

Next, the acid solution was injected directly onto a semi-prep HPLC Zorbax-stabilized phenyl column (10 μM 10 × 250 mm) and eluted with 50% ethanol/water at 5 mL/min. The product was eluted at 7 min in 4–5 mL of solvent, diluted into 25 mL of isotonic phosphate-buffered saline—to reduce the ethanol concentration to below 10%—and then passed through a 0.2-μM sterilizing filter into a storage vial. Typically, 20 to 30 mCi (30–40%) of activity were obtained ready for use. Analytical HPLC of the solution was performed prior to dilution and showed only one detectable radioactive peak and, after the void volume disturbance, only one UV absorbing peak, at 284 nM, both of which had retention times corresponding to authentic 16α-fluoroestradiol. The measured UV adsorption gave a specific activity >1 Ci/μmol.

METHOD B. The reaction was carried out using 2 mg of **1c** in 0.5 mL acetonitrile at 110°C for 15 min. After cooling the reaction mixture, diethyl ether (6 mL) was added, and the solution was passed through a silica cartridge. More than 99% of the radioactivity remained on the silica, which then was eluted with 4 mL of 100% EtOH (USP, no further purification). The silica retained 10–30% of the total activity. To the EtOH eluent 10 μL of concentrated sulfuric acid was added (0.25%, 0.045 M) and the mixture was heated to 110°C for 5 min. The hydrolysis yield was 92–97% (HPLC and TLC 5% MeOH/CH_2Cl_2 R_f 0.6). After evaporation of the EtOH, the residue was dissolved in the HPLC solvent (0.35% EtOH in $CHCl_3$), which left behind 97% of the acid, and injected onto an Alltech Econosil (5 × 250 mm) column. The retention times were: fluoroestradiol 11.5 min; epiestriol (fully hydrolyzed starting material) > 2 h. The product fraction (4–5 mL) was collected and evaporated at 80°C using a helium gas stream. The residue was dissolved in 0.3 mL EtOH in the warm reaction vessel, 6 mL USP saline solution was added, and the resulting solution filtered through a 0.22-μm sterilizing filter. The effective specific activity of the final product, measured at 70 min EOB, was >1 Ci/mmol. The calculation includes all mass peaks observed in the product chromatogram as being equivalent to fluoroestradiol (~0.3 nmol). The true effective specific activity is higher, because a fraction, difficult to quantify but at least 50%, of that observed mass was clearly due to chromatogram noise at the high sensitivity setting. The observed mass that was directly associated with the radiolabeled product peak was below the detection limit of about 50 pmol.

RESULTS

The cyclic sulfate **1c** is stable, and samples have been kept at room temperature for more than a year with no sign of deterioration, either visually or to the melting point of the compound.

The fluorination reaction goes in high yield with this substrate, typically greater than 90% and as high as 98%. There is no sign, either with fluorine-19 or fluorine-18, of attack by fluoride at the other position of the cyclic sulfate, the 17 position, to give the 17-fluoro, 16-sulfate salt or from the other face of the molecule to give β-substituted products. The reaction mixture has been examined both by chromatography and fluorine-19 NMR, and no other isomer has been detected. Also, the intermediate sulfate salt is very

easily separated from unreacted cyclic sulfate by HPLC and is also well resolved from other reaction products that are present before hydrolysis, such as the compound from reaction with hydroxide. We would expect traces of the compound from reaction with chloride ion but could not find any sign of it in the reaction mixture.

The sulfate salt **(3a)** is a stable compound soluble in chloroform and insoluble in water, and is easily characterised. Although it is a salt, it is well retained on reverse-phase columns, typically requiring mobile phases of ≥50% organic solvent for elution. With the fluorine-18 reaction a satisfactory purification of the salt **3b** was not obtained with small normal or reverse-phase separation cartridges despite the relatively good separations seen on HPLC. However, passage of the crude reaction mixture in ethanol (100%, USP) over a silica cartridge removed carbonate, Kryptofix, unreacted fluoride, and some mass impurities to give a solution that could be used directly for the hydrolysis step.

The methoxymethyl ether hydrolyzed rapidly under all acid conditions. Hydrolysis of the 17β sulfate, however, was more difficult than anticipated. Although on the macroscopic scale the hydrolysis was quick and clean in methanol with a strong cation exchange resin, the reaction is sensitive to water. Addition of 5% water stopped the hydrolysis of the sulfate completely. Investigation of this reaction in aqueous and alcoholic solution showed that the rate of hydrolysis was largely independent of acid concentration, in the range of 0.1–5 N HCl and 0.025–20% H_2SO_4, but that the by-product concentration increased with acid concentration. This suggests that it is not the protonation of the anion to give the sulfuric acid but the solvolysis of the protonated bisulfate to the alcohol and sulfuric acid which is the rate-determining step.

Alternative hydrolysis, by a S_N1 solyvolysis of the carbon-oxygen bond followed by reaction of the carbocation with water is unlikely as this would be expected to give a mixture of products at C-17. Inspection of the crude hydrolysis reaction mixture, by both proton and fluorine NRM, showed no sign of any product attributable to the 17α-hydroxy compound. Hydrolysis attempts in nonaqueous solution following reverse-phase column purification of the intermediate salt failed because of the difficulty of drying the compound in the hot cell environment using solvents that would be compatible with later reactions. In this case the optimum hydrolysis conditions were 0.1 N HCl at 140°C for 40 min, to give >90% hydrolysis and only traces of impurities. If the reverse-phase HPLC purification of the intermediate sulfate salt was not used, instead substituting a silica cartridge filtration in ethanol to remove strongly ionic impurities, 95% hydrolysis could be accomplished in 5 min at 110°C after addition of 10 μL sulfuric acid (0.045 M), leaving a product that still contained substantial quantities of unlabeled impurities and so needed further HPLC purification.

Regardless of the method of purification and hydrolysis of the sulfate salt **(3b)**, final purification was performed by HPLC. Following HPLC purification and aqueous HCl hydrolysis, the product was purified using a stabilized phenyl HPLC column that is resistant to 0.1 N HCl and removes it, along with the radiochemical impurities produced during hydrolysis and a little unhydrolysed sulfate salt to give a high specific activity and high purity product. This column was run using the same pump and injector as the first one, with a switching valve to select either of the two columns. The output from both columns was run over the same radiation detector but through separate loops. Thus, the additional equipment required for the second chromatography step was a switching valve and the column.

When silica cartridge filtration of **3b** was used instead of HPLC purification, to permit rapid hydrolysis in ethanol, the purity of the crude hydrolysed product was of course low. In this case reverse-phase HPLC was not sufficient to separate the labeled product quantitatively from the product of hydroxyl substitution. Final purification was achieved by HPLC on silica, giving a high specific activity product.

The sulfate salt and 16α-fluoroestradiol are "sticky" in that radioactivity is found in vessels and in syringes after aqueous solutions are transferred from them. Subsequent washing with ethanol and examination of the washings with analytical HPLC showed that these residues are identical to the bulk products. They are not impurities that are selectively absorbed by the materials but simply represent "nonspecific" binding of the labeled products to the walls. During the synthesis, these losses combine such that typically about 50% of the product is lost. The specific activity of the final product is high and agrees with the initial specific activity of the fluoride, as determined by ion chromatography and by determinations made using other labeled materials, and so there is no unusual extraneous fluoride introduced during the synthesis. The final product does not contain any other UV-absorbing material other than the 16α-fluoroestradiol, and so the effective specific activity is not lowered by extraneous unlabelled estrogens.

To date we have performed approximately 50 runs using both versions of this procedure either for certification of the method or for patient use, and we have had consistent yields and purities of the product without any failures.

CONCLUSION

High specific activity fluorine-18 16α-fluoroestradiol is obtained with high purity and specific activity from a convenient and robust synthesis using the rapid reaction of fluorine-18 labeled fluoride with 3-methoxymethyl-16β,17β-epiestriol cyclic sulfate.

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