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I. INTRODUCTION

Positron Emission Tomography and Radiopharmaceuticals

Positron emission tomography (PET) is an imaging system that uses coincidence detection to detail positions of emitted positrons from a decaying radioactive source.[1] A decaying radionuclide releases a positron that collides into an electron after it has traveled 1-6 mm through matter. The collision produces two 511 KeV photons that scatter 180° apart from each other; only photons of this energy can be detected by a PET detector. PET has come into favor over other imaging modalities, such as computerized axial tomography (CAT) and magnetic resonance imaging (MRI), due to its ability to attain dynamic physiological data at radiotracer levels better than CAT or MRI.[2] Of the positron emitting radionuclides, fluorine-18 can be generated from natural compounds and has an adequate half-life ($t_{1/2}$ = 110 min) to chemically prepare without a large loss of radioactivity to decay.

Our research group has used fluorine-18 labeled steroids and spiperones to study biological receptor sites. These compounds have a natural specificity for certain biological sites, although not always specifically just one. These radiopharmaceuticals are being developed for possible use as non-surgical techniques to diagnose, study, and monitor ailments, such as estrogen receptor positive breast tumors and Alzhiemer's disease, that involve disturbances in receptor activity or the over proliferation of the receptor sites.

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All radiopharmaceutical candidates must have the potential to be prepared within one to two half-lives of fluorine-18 and are tested for their ability to meet the radiopharmaceutical requirements for practical clinical use. These criteria are listed briefly below: (1) the labeled molecules must be able to bind reversibly at the receptor site and have a high affinity and selectivity for the receptor, (2) the compound itself must be easily obtainable in high specific activity, and (3) the molecule must be metabolized into labeled molecules, which clear very rapidly with respect to the half-life of the radioisotope from the target tissues.[3]

An example of a steroid that has bound well and with specificity to its target receptor is 16α-[18F]fluoroestradiol-17β. This compound has the advantage of a fairly easy synthesis by radioactive fluorine displacement of the corresponding trifluoromethane sulfonate (triflate) precursor within a half-life of fluorine-18 and having high radiochemical purity and adequate specific activity.[4] The human clinical trials of this compound gave good PET images of estrogen receptor positive breast tumors and show a future potential of PET radiopharmaceuticals in medicine.[5]

Metabolic Defluorination

Selectivity is of major importance in the development of a good radiopharmaceutical and the success of 16α-[18F]fluoroestradiol-17β is largely based on its selectivity and metabolic stability (see Figure 4).

Metabolic defluorination or lability is a major hindrance to the development of selective radiopharmaceuticals that can give clear PET images. Free fluorine-18 ion has a high affinity for calcium and in the body quickly deposits into the main calcium site, the bone, where it does the least damage radioactively, but where it may interfere with the PET image by obscuring the target tissue.[6] The nature of the carbon fluorine bond and the mechanisms of defluorination in vivo must be understood to control for metabolic defluorination of radiopharmaceuticals.

Fluorine is somewhat isosteric to hydrogen, but is very different electronically than hydrogen. The overall differences that arise chemically between fluorine and hydrogen are due to (1) the great electronegativity of fluorine, (2) the presence of unpaired electrons on fluorine, which can invoke resonance effects, (3) the easier displacement of fluorine as F^-, and (4) the almost 20 kcal/mole stronger bond formed between carbon and fluoride (99.5 kcal/mole for C-H bond and 116 kcal/mole for C-F bond).[7] Fluorine has a strong resonance ability to stabilize positive charge formation; this stabilization is evident in the experimentally found Hammett coefficient for the solvolysis of cumyl chlorides which is $\sigma^+ = -0.07$ for fluorine. The electronegativity of fluorine also enhances the electrophilicity of the carbon to which it is attached.[8] The combination of these attributes causes fluorinated compounds to actually be more metabolically labile than unsubstituted compounds. This phenomena

has been documented by Li, Purdy, Klicka, and Li.[9] They tested the amounts of 2- and 4-hydroxylated products of tritiated estradiols that were recovered from liver microsomes of castrated hamsters. The fluorinated estradiols were broken down as much as 20 times faster (when fluorine was placed in the 2 position) than was the unsubstituted 17β-estradiol.[9]

Figure 1 P_{450} Metabolism of Cabrbon-Fluorine Bonds

$$\text{F-}\overset{|}{\underset{|}{\text{C}}}\text{-H} \xrightarrow[\text{O}_2]{\text{P}_{450}} \boxed{\text{F-}\overset{|}{\underset{|}{\text{C}}}\text{(O)H}} \dashrightarrow -\overset{\text{O}}{\overset{||}{\text{C}}}- + \text{ HF}$$

gem-halohydrin

The metabolism of fluorinated substances to fluoride ion mostly proceeds through a cytochrome P_{450} enzyme catalyzed oxidation reaction in the liver. This enzyme inserts oxygen between the carbon and hydrogen opposite the fluorine (see Figure 1).[10] Whether the mechanism is a true insertion reaction or proceeds through a radical intermediate is still unknown; however, some partial positive charge may develop on the carbon during the reaction. The geminal halohydrin intermediate formed is extremely unstable and quickly forms the corresponding carbonyl and expels a fluoride ion. Defluorination is also known to be stimulated by the addition of glutathione[11] and several mono and digeminal haloalkanes are known to dehalogenate in vivo by a mechanism catalyzed by the glutathione

S-transferase substitution reaction to yield glutathione (GSH) derivatives (see Figure 2).[10] GSH S-transferases conjugate electrophilic centers that may be potentially harmful to the cells and once conjugated allow the electrophile to be secreted into bile.[12]

Figure 2 Glutathione S-Transferase Metabolism

$$GSH + CH_2X_2 \xrightarrow{\quad -X^- \quad} GSCH_2X \xrightarrow[X^-]{\quad +H_2O \quad} GSCH_2OH$$
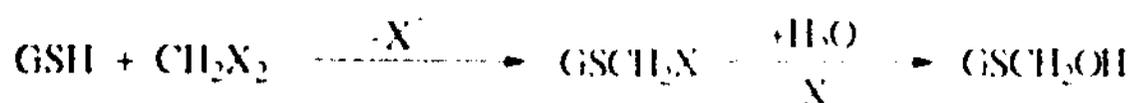
The β-Heteroatom Hypothesis

From previous tests, it can be seen that some fluorine-18 labeled radiopharmaceuticals are more metabolically stable than others. Comparison of the steroid and spiperone systems in Figures 3 and 4 show that some very similar compounds can have extremely different rates of defluorination. The fluorine on the long alkyl chain defluorinates readily as does a fluorine placed in a γ-position or even further away from a heteroatom (Figure 3). However, when these labile compounds are matched with similar molecules in Figure 4 the amount of defluorination dramatically decreases.[13] The one thing all of the metabolically stable compounds have in common is a heteroatom in the β-position with respect to fluorine-18. From these observations, it has been reasoned that the β-heteroatom substituent has a metabolically deactivating effect inductively on the α-carbon containing the fluorine. Therefore, all of the compounds like system
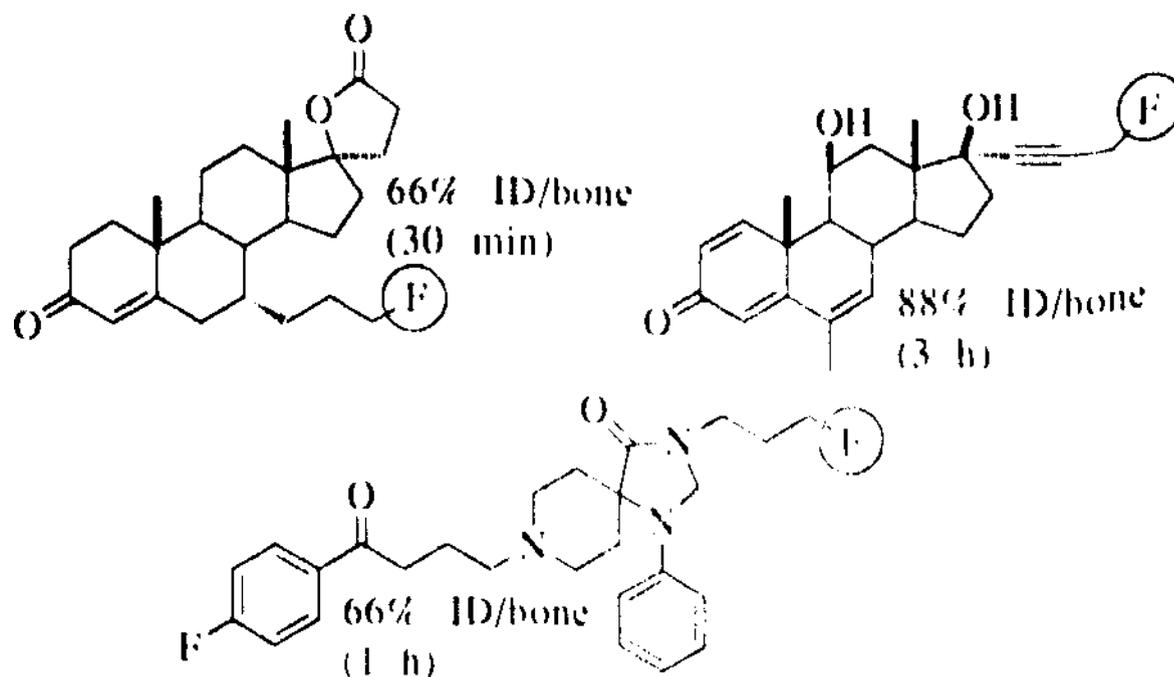
(I) below should be much less labile than compounds like system (II).[14] This phenomenon is very similar to the increased electrophilicity of β-carbons in organosilicon systems where the electropositive silicon stablizes inductively a positive charge on the β-carbon.

I: X C—C—^{18}F   II: C-C-C-^{18}F   X = O, N
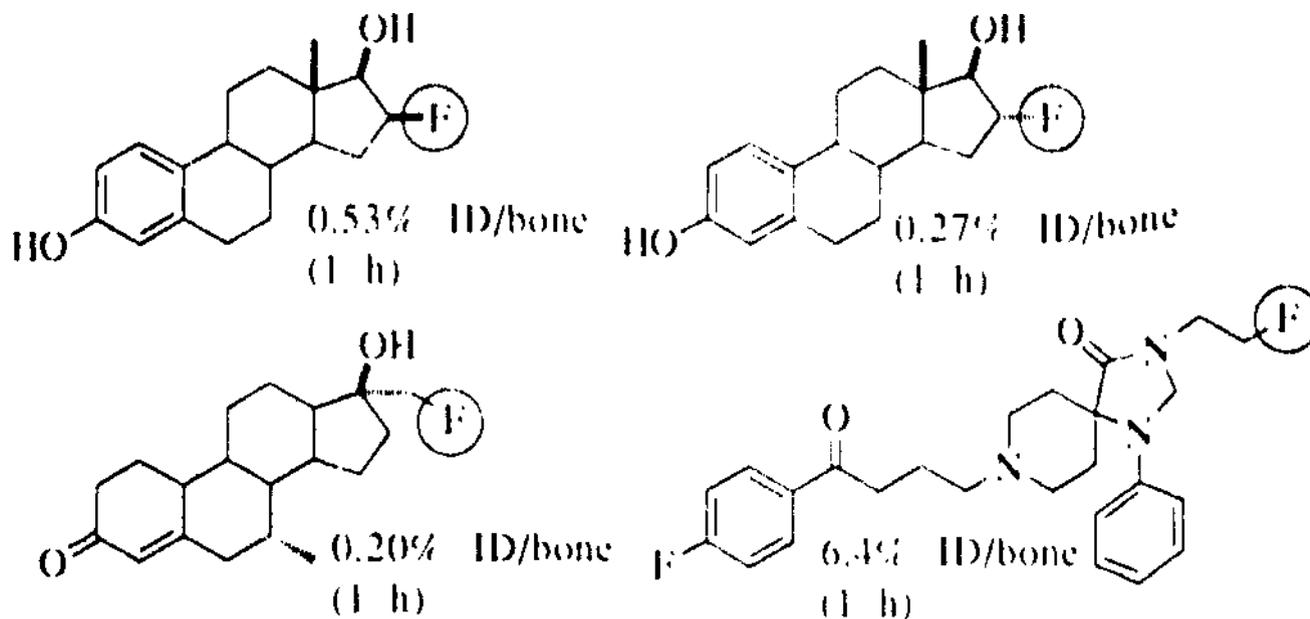 |β |α
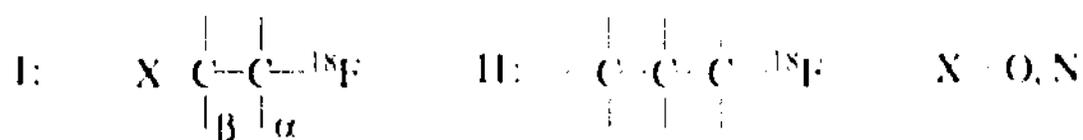
Andrew French performed a controlled study of this theory by preparing and comparing two closely related fluorine-18 labeled estrogens 1a and 1b. These compounds were injected into immature rats and after 3 hours the rats were sacrificed and tested for the amount of defluorination. As theorized, 1a showed a 28% ID (injected dose)/total bone, but 1b with the β-heteroatom showed only 1.3% ID/total bone.[15] Unfortunately, this study was slightly flawed by the fact that the alkyl chain on 1a is shorter than that of the alkoxy 1b. Steric hindrance could then be a significant factor in the different defluorination rates.

R = ^{18}F-CH$_2$-CH$_2$ (1a)
R = ^{18}F-CH$_2$-CH$_2$-O-   (1b)
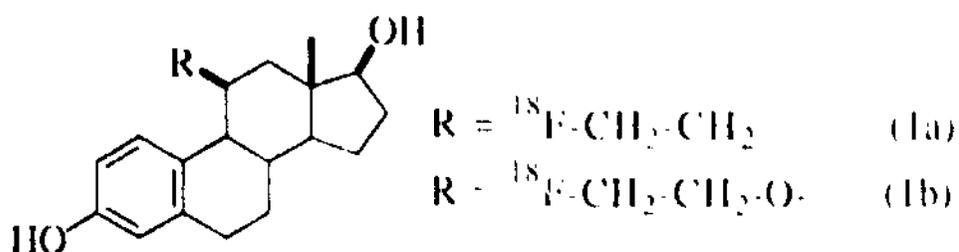
Figure 3 Metabolically Labile Fluoro Compounds

66% ID/bone
(30 min)

88% ID/bone
(3 h)

66% ID/bone
(1 h)

Figure 4 Metabolically Stable Fluoro Compounds

0.53% ID/bone
(1 h)

0.27% ID/bone
(1 h)

0.20% ID/bone
(1 h)

6.4% ID/bone
(1 h)

Specific Objectives

Since other structural and stereochemical features are present on the large steroid systems, which may contribute to steric inhibition

or other sources of electronic deterrents of defluorination, a series of smaller, easy to work with compounds have been proposed to test the importance of β-heteroatoms in the retardation of metabolic defluorination (Figure 5). The structure of these compounds were designed to try to minimize all other factors except the one which is being tested. In the top series, the degree of substitution on defluorination is being tested. In several systems, secondary fluorines have been shown to be more metabolically labile than primary, and tertiary fluoro compounds often show little or no defluorination.[16] Since alkyl groups are electron donating and can also stabilize positive charge formation and radicals, the increased lability of secondary fluorines is understandable. However, molecules with fluorine in the tertiary have no α-hydrogens to initiate the metabolic process of defluorination. The ether and digeminal fluoro series place the radiolabeled fluorine either in a γ or β position with respect to the electronegative heteroatoms to test the β heteroatom hypothesis of metabolic stabilization. According to the above hypothesis, the compounds with the β-heteroatoms should be more stable. These compounds will all be tested for defluorination by substituting fluorine-18 for the circled fluorines in Figure 5 and either injecting a small amount into Sprague Dawley rats for a specified length of time or by combining the compounds with liver microsomes and isolating the metabolized products.

Figure 5

Degree of Substitution
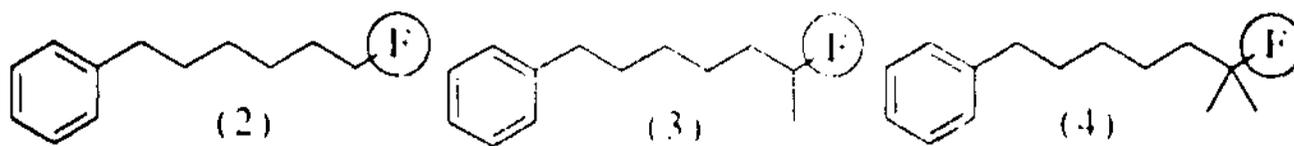
Ether Oxygen Substitution

### Geminal Fluorine Substitution

II. RESULTS AND DISCUSSION

Preparation of 3-Phenylpropyl 2-Fluoroethyl Ether

3-Phenylpropyl 2-fluoroethyl ether was synthesized from 3-phenylpropanol (9) (Scheme 1). The alkene 10 was made using KH and allyl bromide.[17] Cleavage of the alkene to the aldehyde (11) was accomplished in high yield through use of a catalytic amount of OsO_4 and $NaIO_4$ in a 50% aqueous tetrahydrofuran (THF) solution.[18]

Other cleavage methods were tried before we obtained good results with the catalytic OsO_4 reaction. First, ozonylsis was attempted and the reaction gave the aldehyde by mass spectroscopy but not in good yields or reliably. Potassium permanganate and 18-crown-6 ether was not reactive until the reaction was refluxed and then it resulted in a mixture of several products that all showed equivalent amounts of material by thin layer chromatography (TLC). The aldehyde produced through the catalytic OsO_4 reaction did not need any further purification after an aqueous workup and then drying over $MgSO_4$. This was fortunate, because the aldehyde would slowly decompose over a day even if it was stored at 0°C.

The aldehyde was reduced to the primary alcohol (12) by lithium aluminum hydride (LAH) in dry diethyl ether. The alcohol could easily be converted to its trifluoroethane sulfonate (tresylate) (13) in good yields by treatment of the alcohol with 2 equivalents of 2,2,2-trifluoroethane sulfonyl chloride (tresyl chloride) and

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Scheme 1 Synthesis of 3-Phenylpropyl 2-Fluoroethyl Ether
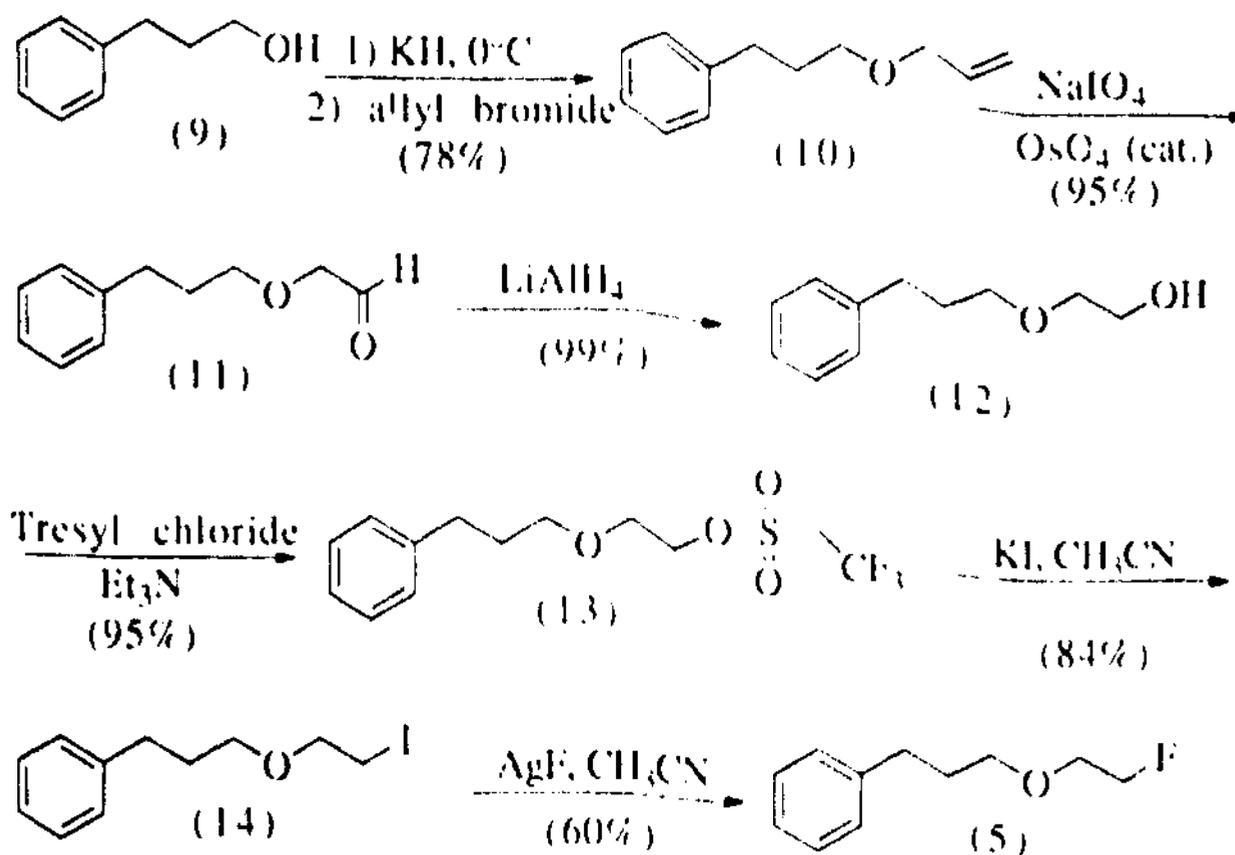
triethylamine (TEA) at 0°C. The tresylate is stable enough to purify by
flash column chromatography if the purification was performed
quickly after ending the reaction; however, purification was not
necessary and the yields of the subsequent iodo compound (14) are
not significantly changed when the tresylate is purified. The tresylate
will still decompose readily if left at room temperature for more than
an hour or if left at 0°C for more than a day.

From the tresylate the iodo compound was made by combining it
with KI in CH3CN. The reaction slowly turned yellow and eventually

the sulfonyl salt precipitated. The target fluoro compound can then be made by treatment of (14) with silver(I) fluoride in CH_3CN.[19] Yields of the fluoro compound were extremely low in the beginning because of the high volatility of this compound. Removing the solvent by steam distillation through a Vigreaux column increased the yields considerably from 21% to 67%.

Other methods of fluorination through displacement of sulfonate groups were also attempted. Both tetrabutylammonium fluoride (TBAF) and KF were unreactive toward the sulfonates even at high temperatures. The success of the iodo displacement can be explained in hard-soft acid-base (HSAB) terms in which large ions with delocalized charge (soft ions) have affinities for other soft ions and small ions, with dense charges (hard ions) have affinities for other hard ions. Silver is a soft ion and has an affinity for iodine (another soft ion). The coordination of silver to iodine enhances its leaving ability and facilitates the substitution reaction. The only problem with this procedure is the use of AgF as the fluorinating reagent. For radiochemical fluorination, both TBAF and KF are the preferred ways of introducing fluorine-18 into compounds. Luckily, silver ion was found only to be needed in the solution to facilitate the displacement of the iodine. Thus, a radiochemical synthesis using a silver salt ($AgCO_3$) as a source of Ag^+ and KF to fluorinate was devised. When all reagents are added in CH_3CN and heated to $60°C$, a 60% incorporation of fluorine was seen in 1.2h monitoring the reaction by gas

chromatography (GC).

Preparation of 3-Fluoropropyl 2-Phenylethyl Ether[20]

3-Fluoropropyl 2-phenylethyl ether was made from 2-phenylethanol (15) (Scheme 2). The first step was to convert the alcohol to the allyl ether 16. This reaction is similar to the reaction that forms the allyl ether 10 from 3-phenylpropanol (9), but does give the ether 16 in quantitative yield, which is somewhat better than when the reaction is performed with the propyl alcohol. The reason for the improved yield is not clear. The allyl ether 16 is converted to a terminal alcohol 17 using 9-borabicyclo[3.3.1]nonane (9-BBN) and hydrolysis of the borane with NaOH and H_2O_2[21]. 9-BBN was chosen for the hydroboration because of its extreme selectivity for attack at the least hindered (least substituted) carbon of the alkene. It gave good yields of the primary alcohol with minimal side products.

The fluoro compound 6 was prepared via its methanesulfonate ester (mesylate) (18). Fluorination was carried out using TBAF in tetrahydrofuran (THF). Unfortunately, it took several hours to displace the mesylate and future experiments must be performed to modify the reaction to yield the fluoro compound within an acceptable time limit (one in which fluorine 18 will not appreciably decay). Probably the reaction time can be shortened by using a better leaving group than the mesylate, such as a tresylate or a triflate group. Another solution could be to change the solvent and/or heat the

system.

Fluorination via the mesylate as was done in the γ-heteroatom system above, was not possible in the first system, the β-heteroatom system. The reluctance of the β-heteroatom system to develop partial charge in a S_N2 type reaction may be a consequence of the same hypothesized β-heteroatom effect that may slow down the metabolic defluorination of such compounds. Oxygen is an electronegative

Scheme 2 Synthesis of 3-Fluoropropyl 2-Phenylpropyl ether
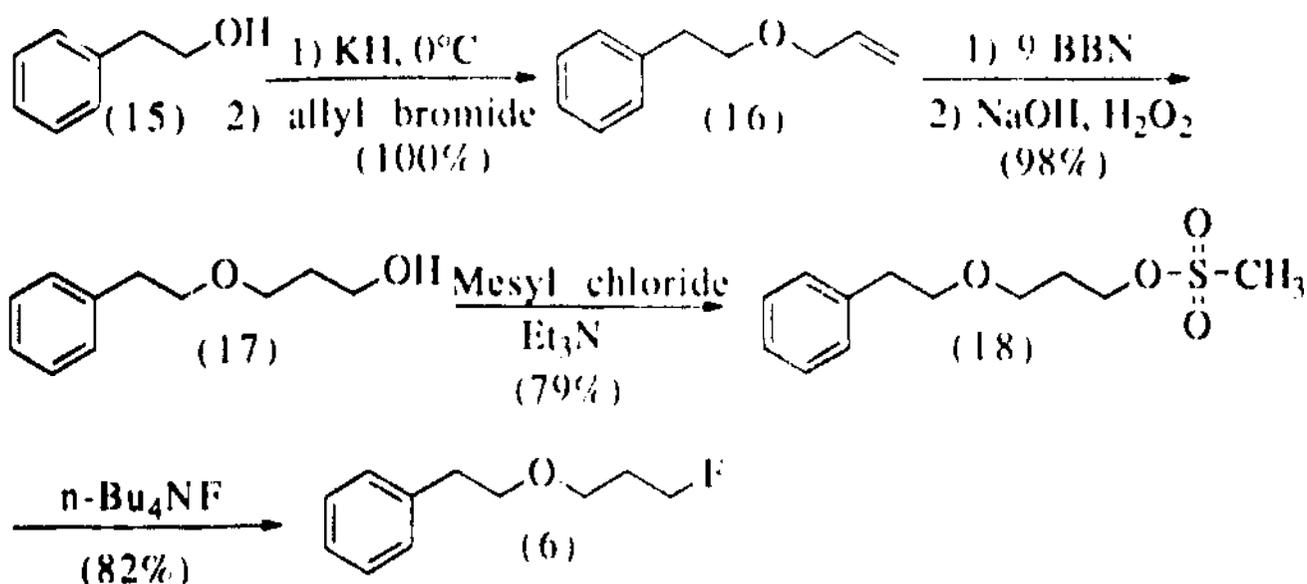
element; therefore, the dipole of the O-C bond places a partial negative charge on the oxygen and a partial positive charge on the α-carbon and to a lesser extent on the β-carbon (see Figure 6). Similarly, during a S_N2 substitution reaction, a partial positive charge forms at the carbon at which the substitution takes place. In a molecule with heteroatom in the β-position with respect to the carbon at which the

Figure 6 Partial charge distribution during S$_N$2 reaction

I: δ (δ^+) O
  ~O~C~C~O-S-R ___Nu___ → δO δ^+C~H
      δ^+ O   C   H
                                        δ^+
                                                 OSO$_2$R
                                                 δ

                                        δNu

II: δ (δ^+) O
  ~O~C~C~C~O-S-R ___Nu___ → δO~C~C~C~H
       δ^+ O δ^+ δ^+ H

                                       δNu

R= CH$_3$, CF$_3$, CH$_2$CF$_3$ OSO$_2$R
Nu= nucleophile δ

substitution is occurring (I), the formation of the positive charge is unfavorable since the oxygen is inducing a positive charge on the carbon next to it; this is a destabilizing effect. In the case where the heteroatom is in the γ-position with respect to the site of substitution (II), there is no or little positive charge on the carbon next to the site of substitution; little or no destabilizing effects are observed and the S$_N$2 reaction occurs much more readily.

Preparation of 1,2,2-Trifluoro-6-phenylhexane.

4-Phenyl-1-butanol (19) is the starting material for the synthesis of 1,2,2-trifluoro-6-phenylhexane (7) (Scheme 3). The

alcohol is first oxidized in good yield to the aldehyde 20 by pyridinium chlorochromate (PCC).[22] Cooling the PCC in methylene chloride to -78°C before adding the alcohol raised the product yield by almost 20% when compared to the yields recovered when addition of the alcohol was performed at room temperature. The acid was more often seen in the crude product mixture when the reaction was run completely at room temperature; the cooling of the PCC to 78°C probably retards this over oxidation by slowing down the reaction process. Another modification that raised the yield of this reaction slightly was the addition of a small amount of silica to the crude reaction mixture before filtering the reaction. When diethyl ether is added to a PCC mixture, a large amount of black, tarry chromate salts fall out of solution. Separating the products from this substance is very difficult and is often reflected in the lower than expected yields that sometimes occur with PCC oxidations. However, the silica helps to break up this tar and keeps it and some of the product from sticking to the inside of the flask.

The aldehyde was converted to the geminal difluoro compound 21 through a Reformatsky-type reaction with activated zinc and ethyl bromodifluoroacetate.[23] Several ways to convert the secondary alcohol to the alkane 24 were attempted. Simple triflation of the alcohol and then hydride displacement with LAH was originally tried; this would also reduce the ester to the primary alcohol, a favorable transformation. However, the reaction gave extremely poor yields

when it did work, and it was difficult to recover any unreacted primary alcohol or triflate.   Dehydration and subsequent hydrogenation was also tried.   Unfortunately, the secondary alcohol positioned near the two highly electronegative geminal difluorines made it very unreactive toward dehydration because this would involve positive charge formation on the β carbon.   Finally, the iodo compound (23) was made via the triflate (22).   Obtaining moderate to high yields of the iodo compound also proved to be difficult.   Using acetonitrile the solvent, caused the reaction to be completed within a few hours, but the high volatility of (23) made the separation of the product from the solvent a problem.   On the other hand, acetone and NaI proved to be easier to evaporate without the significant loss of product, but the reaction took almost a day at reflux to perform.   The yields improved from 30% to 60%.   The iodine could be converted in high yields to the saturated compound by the use of tributyl tin hydride.[24]

Further synthesis has not been completed on this trifluoro compound.   The ethyl ester can easily be reduced to the primary alcohol (25) using LAH.   The formation of the primary fluoride via the sulfonate will hopefully not present any major problems.   However, the displacement problem seen in the sulfonate displacement to form the β-fluoro ether (5) could present itself for the same reasons as discussed above in the fluorination of the geminal difluoro compound.

## Scheme 3 Synthesis of 1,2,2-Trifluoro-6-phenylhexane
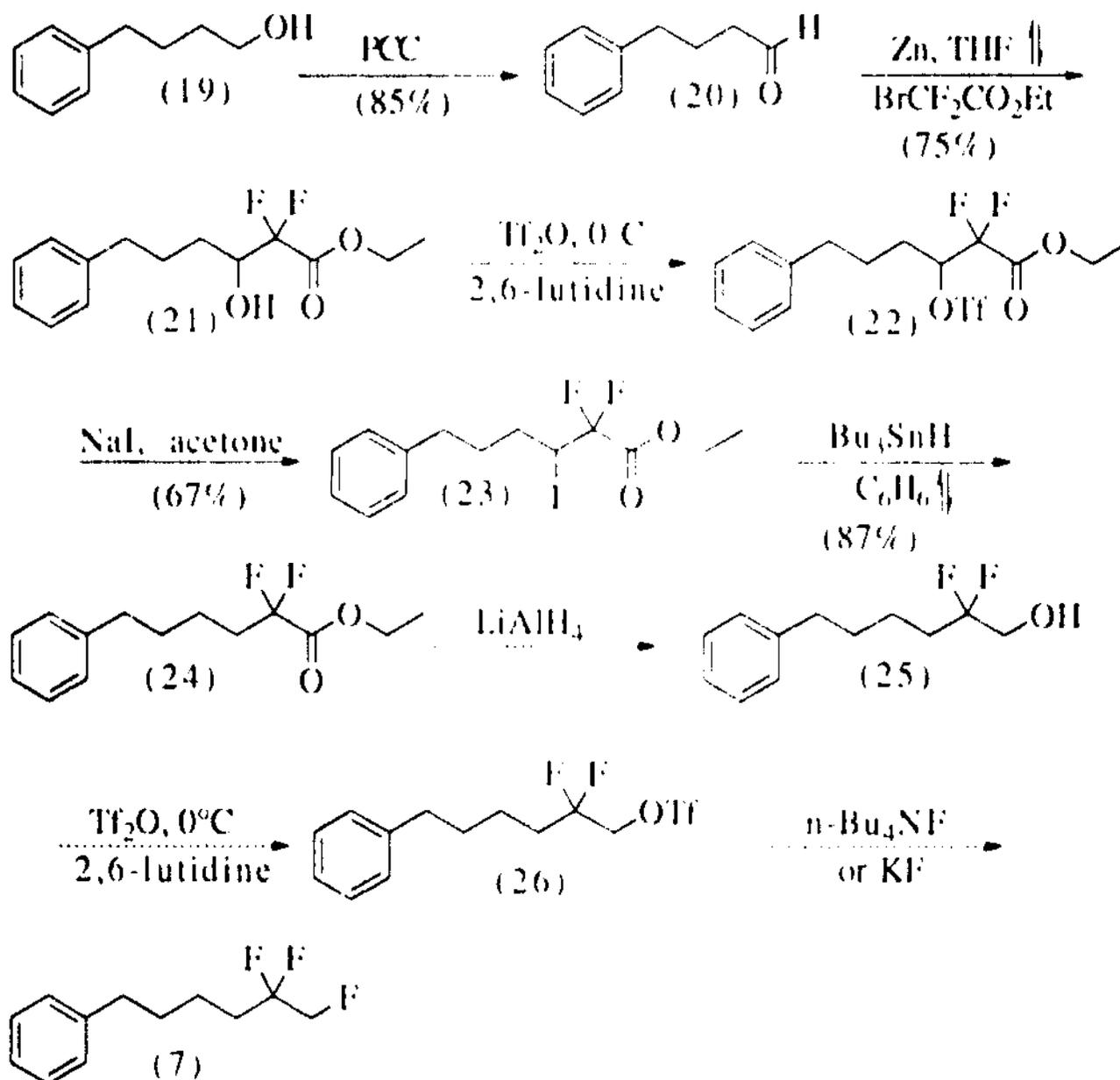
Preparation of 1-Fluoro-6-phenylhexane.[25]

6-Phenyl-1-hexanol (27) was used as the starting material in the facile synthesis of 1-fluoro-6-phenylhexane (2) (Scheme 4). The mesylate 28 was prepared with mesyl chloride and triethylamine.

The mesylate quickly decomposed, but required no further purification to be used in the subsequent step. Treatment of the mesylate with TBAF at room temperature yielded the fluoro compound 2 in high yield.

Scheme 4 Synthesis of 1-Fluoro-6-phenylhexane
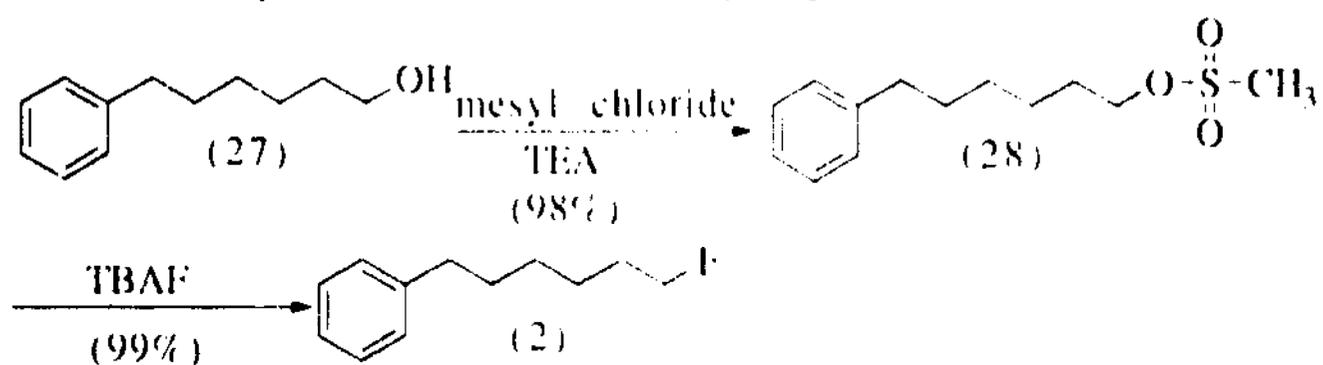
IV. CONCLUSION

Future Objectives

The main concern at the moment is to prepare the rest of the molecules proposed for the project, especially the 1,2,2-trifluoro-6-phenylhexane compound that is very near completion. The other geminal difluoro compound, 1,3,3-trifluoro-6-phenylhexane, has been attempted earlier (Scheme 5).

The aldehyde 20 was converted into the secondary alcohol 29 by a reaction with an allyl Grignard reagent. This alcohol was oxidized, although in low yields, to the ketone 30.[22] Carbonyls form geminal

Scheme 5 Attempted Synthesis of 1,3,3-Trifluoro-6-phenylhexane
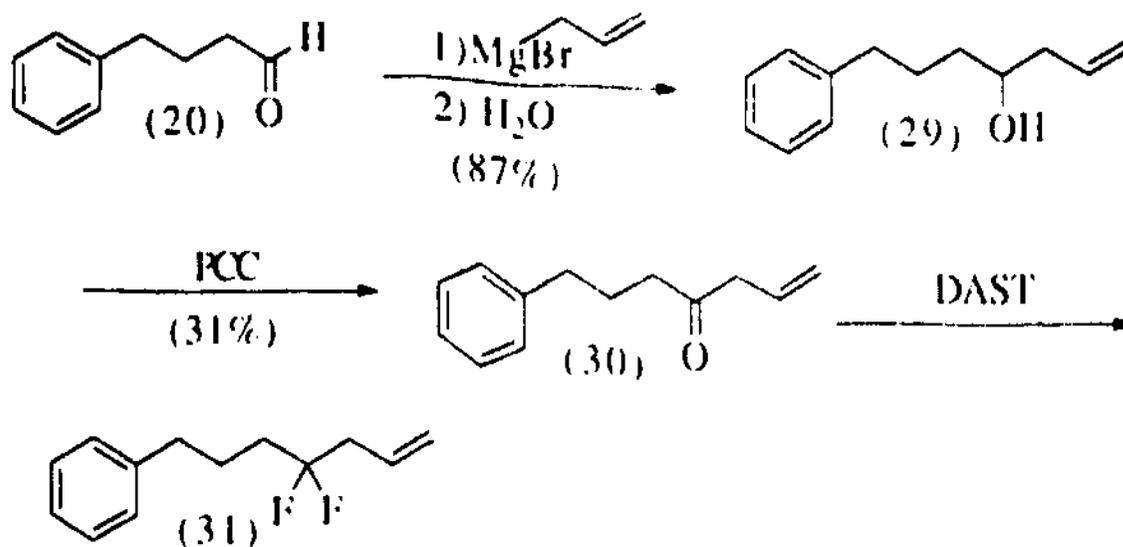
difluorides when reacted with two equivalents of diethylaminosulfur trifluoride (DAST).[26] However, reaction of 30 with DAST was not clean; several spots of similar amounts were detected by TLC. The most probable reason for the failure of this reaction and the low yield in the oxidation to the ketone 30 is that the carbon-carbon double bond positioned near the preferred site of reaction is also subject to electrophilic attack and will react with the reagents used in the reactions and react with itself intermolecularly. Many possible side reactions could and did occur and prevented this synthetic scheme from being plausible. Another plan has to be worked out to prepare this compound.

The remaining molecules that also need to be synthesized are in the series that tests the degree of alkyl substitution around the fluorine on the amount of metabolic defluorination. Most likely both of the remaining compounds will be made by halofluorination of the corresponding alkenes and then a further synthetic step will be needed to obtain the desired products.[27]

Once these compounds are synthesized, modifications must be made for radiochemical synthesis. Then the actual biological tests for metabolic defluorination, measured by the amount of radioactivity that appears in the bone in an animal distribution study, must be performed. These tests will be performed at the Mallinckrodt Institute, Washington University, in collaboration with Dr. Michael Welch and his research group.

Summary

The problem of metabolic defluorination can be a fatal flaw in a radiopharmaceutical to be used in PET imaging. Various compounds for use in PET studies have been designed and tested by Dr. John Katzenellenbogen's research group. Through their data it has been observed that compounds in which the fluorine 18 label is placed in the β-postition with respect to some eletronegative heteroatom defluorinate much less than similar compounds in which there is no heteroatom in the β-position.

To test the effects of the positioning of heteroatoms within molecules with respect to fluorine-18 and the degree of alkyl substitution of fluorine on a compound's ability to be metabolically defluorinated, a series of model compounds have been proposed (Figure 5). These compounds were designed to minimize all other interactions except one, the one which is of interest. So far, only the ether series of compounds have been completed. Work has been done and is under way on the completion of the other series of molecules.

IV. EXPERIMENTAL

Solvents and reagents were purchased from the following commercial sources: Aldrich, Eastman, Fisher, and Sigma. THF and diethyl ether were distilled from sodium/benzophenone and other solvents were distilled from CaH.

The silica gel used in flash column chromatography was 32-63 μm (Merck). Proton magnetic resonance (^{1}H NMR) spectra were all run on a Varian XL 200 MHz spectrometer with chemical shifts reported as parts per million downfield from an internal tetramethylsilane standard (δ scale) and all samples were solutions in $CDCl_3$. Low resolution electron impact (LREI) mass spectra and high resolution electron impact exact mass determinations were obtained on Finnigan MAT CH-5 and MAT 731 instruments, respectively. Fast atom bombardment (FAB) mass spectra were taken on a ZAB-SE instrument. All significant peaks in the mass spectra are reported with their respective peak percentage in parenthesis for LREI. Elemental analyses were preformed by the Microanalytical Service Laboratory of the University of Illinois.

All products were clear oils unless otherwise stated.

3-Phenylpropyl allyl ether (10). Potassium hydride (4.75 g, 40.37 mmol) was stirred in 100 mL of dry diethyl ether and the mixture was cooled to 0 °C. 3-Phenyl-1-propanol (9) (36.7 mmol) was

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slowly added to the KH mixture and the solution was allowed to warm to room temperature. Allyl bromide (73.4 mmol) was dripped into the reaction mixture; the evolution of gas was observed. The reaction stirred for 10h and excess KH was quenched by the slow addition of water. The solution was extracted with diethyl ether (3 x 20 mL) and the organic layers were collected, successively washed with sodium bicarbonate and brine, dried over anhydrous $MgSO_4$, and concentrated by reduced pressure rotary evaporation. Isolation of the product was accomplished by flash chromatography using a 20/1 mixture of pentane/diethyl ether as the eluent. This yielded 5.02 g (78%) of the product 10. ^1H NMR δ 1.92 (quint, J= 7 Hz, 2H, PhCH$_2$CH$_2$), 2.72 (t, J= 8 Hz, 2H, PhCH$_2$CH$_2$), 3.46 (t, J= 6 Hz, 2H, CH$_2$CH$_2$O), 3.98 (dd, J= 5 Hz, J= 2 Hz, 2H, OCH$_2$CHCH2), 5.20 (d, J= 17 Hz, 1H, CH$_2$CHCH$_2$-cis), 5.27(d, J= 24 Hz, 1H, CH$_2$CHCH$_2$-trans), 5.93 (ddt, J$_{trans}$= 17 Hz, J$_{cis}$= 9 Hz, J= 5 Hz,1H, OCH$_2$CHCH$_2$), 7.15-7.33 (m, 5H, Ph); mass spectrum (LREI, 70 eV offscale) m/z 176 (M$^+$), 119 (70), 118 (100), 117 (100), 105 (100), 103 (36), 92 (100), 91 (100), 79 (46), 78 (37), 77 (66), 65 (83), 51 (48), 41 (100), 39 (100); HRMS calcd. for $C_{12}H_{16}O$: 176.1201; found: 176.1200; Anal. calcd. for $C_{12}H_{16}O$: C,81.77; H, 9.15; found: C, 81.59; H, 9.00.

2-(3-Phenylpropoxy)ethanal (11). The phenylpropyl allyl ether (10) (100 mg, 0.568 mmol) and 325 mg of sodium periodate (1.53 mmol) was added to 15 mL of a 50% aqueous mixture of THF in a round bottom flask with stirring. A 0.1% solution of osmium tetroxide (1 mL) in THF was added to the reaction mixture via syringe. The

reaction was allowed to stir for 10h. Brine was then added to the reaction and the mixture was extracted with diethyl ether (3 x 20 mL). The organics were combined and washed with a saturated solution of sodium thiosulfate until no color was seen in the water layer. The organics were again washed with brine, dried over anhydrous $MgSO_4$, and concentrated by reduced pressure rotary evaporation. Isolation of the product was usually not necessary and the aldehyde 11 was often used in the next step without further purification because it quickly decomposed. However, purification is possible by quickly performing flash column chromatography using 1/4 ethyl acetate (EtOAc)/hexane (Hex) as the eluent and this provided a 95% yield. ^1H NMR δ 1.99 (quint, J = 7 Hz, 2H, PhCH$_2$CH$_2$), 2.76 (t, J = 8 Hz, 2H, PhCH$_2$CH$_2$), 3.54 (t, J = 6 Hz, 2H, CH$_2$CH$_2$O), 4.11 (d, J = 7 Hz, 2H, OCH$_2$CHO), 7.17-7.28 (m, 5H, Ph), 9.73 (s, 1H, CHO); mass spectrum (LREI, 70 eV offscale) m/z 178 (M$^+$), 118 (31), 91 (100); HRMS calcd. for $C_{10}H_{14}O_2$: 178.0994; found: 178.0992.

2-(3-Phenylpropoxy) ethanol (12). A 1M solution of LAH (24 mL) in diethyl ether was diluted with 10 mL more dry diethyl ether and cooled to 0°C. The aldehyde (11) (2.12 g, 11.91 mmol) was slowly added to the LAH solution. The reaction was warmed to room temperature and stirred for 6h. Unreacted LAH was quenched by the slow addition of water and the lithium salts were filtered off. The filtrate was extracted with diethyl ether (3 x 20 mL) and the organic layers were collected, dried over $MgSO_4$, concentrated by reduced

pressure rotary evaporation, and isolated by flash chromatography using 1/2 mixture of EtOAc/Hex as the eluent. This gave a 99% yield of 12. ^{1}H NMR δ 1.94 (m, 2H, PhCH$_2$CH$_2$), 2.72 (t, J= 7 Hz, 2H, PhCH$_2$CH$_2$), 3.40 (m, 2H, CH$_2$CH$_2$OH), 3.50 (t, J= 7 Hz, 2H, CH$_2$CH$_2$O), 3.52 (t, J= 4 Hz, 2H, OCH$_2$CH$_2$OH), 7.16-7.34 (m, 5H, Ph); ^{13}C NMR δ 31.2 (1C, PhCH$_2$CH$_2$), 32.3 (1C, PhCH$_2$CH$_2$), 61.8 (1C, CH$_2$CH$_2$OH), 70.4 (1C, CH$_2$CH$_2$O), 71.8 (1C, OCH$_2$), 125.8 (1C, p-PhCH$_2$), 128.3 (2C, o-PhCH$_2$), 128.4 (2C, m-PhCH$_2$), 141.8 (1C, PhCH$_2$); mass spectrum (LREI, 70 eV offscale) m/z 180 (M$^+$), 119 (100), 118 (100), 177 (100), 105 (47), 91 (100), 92 (100), 78 (46), 77 (69), 65 (100), 51 (57), 45 (100), 41 (100); HRMS calcd. for C$_{11}$H$_{16}$O$_2$: 180.1151; found: 180.1150; Anal. calcd. for C$_{11}$H$_{16}$O$_2$: C, 73.30; H, 8.95; found: C, 73.26; H, 9.02.

(3-Phenylpropoxy) ethyl 2,2,2 trifluoroethanesulfonate (13). In 30 mL of dry CH$_2$Cl$_2$, 230 mg of the alcohol (12) (1.28 mmol) and 358 µL triethylamine (2.55 mmol) were added and the solution was cooled to 0°C. Trifluoroethane sulfonyl chloride (282 µL, 2.55 mmol) was slowly added via a syringe. Some white vapors evolved upon this addition. The reaction was allowed to stir at 0 C for 1h; then, it was filtered through a silica plug, and concentrated using reduced pressure rotary evaporation. Isolation of the product 13 was accomplished with flash chromatography using 1/5 mixture of diethyl ether/pentane as the eluent. This afforded the product 13 in a 95% yield. ^{1}H NMR δ 1.90 (quintet, J= 7 Hz, 2H, PhCH$_2$CH$_2$), 2.68 (t, J= 8 Hz, 2H, PhCH$_2$CH$_2$), 3.49 (t, J= 7 Hz, 2H, CH$_2$CH$_2$O), 3.69 (m, 2H, OCH$_2$CH$_2$).

4.04 (quartet, J_{HF}= 9 Hz, 2H, OSO$_2$C$\underline{H}_2$CF$_3$), 4.45 (m, 2H, C$\underline{H}_2$CH$_2$OSO$_2$), 7.15-7.32 (m, 5H, Ph); mass spectrum (LREI, 70 eV offscale) m/z 326 (M$^+$), 191 (40), 147 (100), 119 (100), 118 (100), 117 (100), 115 (55), 105 (100), 104 (71), 103 (76), 92 (100), 91 (100), 83 (100), 79 (59), 78 (76), 77(100), 65 (100), 51 (70), 45 (100), 40 (95).

3-Phenylpropyl 2-iodoethyl ether (14). The tresylate 13 (0.417 mmol) was combined with 238.4 mg of potassium iodide (1.25 mmol) in 2 mL of dry acetonitrile. The reaction was allowed to stir at room temperature for 12h. At this time, the reaction mixture was filtered through a small plug of silica to remove any salts. The filtrate was concentrated by reduced pressure rotary evaporation. Product isolation was carried out by using flash column chromatography with 10/1 pentane/diethyl ether as the eluent. This yielded 102 mg of the iodo compound 14 (84%). ^{1}H NMR δ 1.83-1.97 (m, 2H, PhCH$_2$C$\underline{H}_2$), 2.71 (t, J= 8 Hz, 2H, PhC$\underline{H}_2$CH$_2$), 3.25 (t, J= 7 Hz, 2H, C$\underline{H}_2$CH$_2$I), 3.48 (t, J= 6 Hz, 2H, CH$_2$C$\underline{H}_2$O), 3.68 (t, J= 7 Hz, 2H, OC$\underline{H}_2$CH$_2$), 7.18-7.32 (m, 5H, Ph); mass spectrum (LREI, 70 eV) m/z 290 (M$^+$), 118 (100), 117 (30), 91 (48); HRMS calcd. for C$_{11}$H$_{15}$OI: 290.0168; found: 290.0161; Anal. calcd. for C$_{11}$H$_{15}$OI: C, 45.54; H, 5.21; I, 43.74; found: C, 45.79; H, 5.28; I, 43.42.

3-Phenylpropyl 2-fluoroethyl ether (5). Silver(I) fluoride (52 mg) was suspended in 0.5 mL of dry acetonitrile. A solution of the iodo compound 14 in 0.3 mL of acetonitrile was dripped into the reaction mixture. The mixture was then heated to 50°C with stirring

for 2h. At this time the reaction was cooled and filtered through a short silica plug and concentrated by steam distillation using a vigreaux column. The product 5 was isolated in 60% yield through flash column chromatography using 1/10 diethyl ether/pentane as the eluent. ^{1}H NMR δ 1.92 (m, 2H, PhCH$_2$C$\underline{H}_2$), 2.70 (t, J = 8 Hz, 2H, Ph$\underline{CH}_2$CH$_2$), 3.50 (t, J = 7 Hz, 2H, CH$_2$$\underline{CH}_2$O), 3.66 (dt, J = 4 Hz, J$_{HF}$ = 30 Hz, 2H, O$\underline{CH}_2$CH$_2$), 4.56 (dt, J = 4 Hz, J$_{HF}$ = 48 Hz, 2H, CH$_2$$\underline{CH}_2$F), 7.14-7.31 (m, 5H, Ph); mass spectrum (LREI, 70 eV offscale) m/z 183 (M+1), 182 (M$^+$), 119 (100), 118 (100), 117 (100), 105 (100), 104 (52), 103 (100), 92 (100), 91 (100), 89 (42), 78 (100), 77 (100), 65 (100), 63 (65), 51 (100), 50 (43), 47 (100), 45 (52), 41 (97), 39 (100); HRMS calcd. for C$_{11}$H$_{15}$OF: 182.1107; found: 182.1106.

Phenylethyl allyl ether (16). KH (3.10 g, 27.0 mmol) in a 30% suspension in mineral oil was added to 250 mL round bottom flask and the mineral oil was careful washed off using dry hexane. Dry THF was added to the KH and the mixture was cooled to 0°C. 2-Phenyl-1-ethanol (15) (2.93 mL, 24.6 mmol) was slowly added to the cooled reaction mixture. Some bubbles did appear upon addition. The mixture was allowed to warm to room temperature. Allyl bromide (4.25 mL, 49.1 mmol) was slowly dripped into the room temperature solution. This addition caused some bubbling and warming of the reaction mixture and after 1h a white precipitate fell out solution. The reaction stirred at room temperature for 10h. Water was slowly added to quench any unreacted KH and the entire solution was

extracted with diethyl ether (3 x 30 mL). The organics were then collected, washed with 30 mL each of saturated bicarbonate solution and brine, dried over $MgSO_4$, and purified by flash column chromatography using 15/1 EtOAc/Hex as the eluent. This gave a quantitative yield of 16. ^{1}H NMR δ 2.91 (t, J= 7 Hz, 2H, PhC$\underline{H}_2$CH$_2$), 3.65 (t, J= 7 Hz, 2H, PhCH$_2$C$\underline{H}_2$O), 3.99 (dt, J= 6 Hz, J$_{HH}$= 2, 2H, OC$\underline{H}_2$CH), 5.24 (d, J= 14 Hz, 1H, OCH$_2$CHC$\underline{H}_2$ cis), 5.30 (d, J= 20, 1H, OCH$_2$CHC$\underline{H}_2$-trans), 5.90 (ddt, J$_{trans}$= 26 Hz, J$_{cis}$= 16 Hz, J= 5 Hz, 1H, CH$_2$C$\underline{H}$CH$_2$), 7.17-7.34 (m, 5H, Ph); mass spectrum (LREI, 70 eV) m/z 162 (M$^+$), 105 (65), 91 (100), 41 (65); HRMS calcd. for $C_{11}H_{14}O$: 162.1045; found: 162.1045; Anal. calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70; found: C, 81.37; H, 8.80.

3-(2-Phenylethoxy) propanol (17). The alkene 16 above (2.00 g, 12.32 mmol) was dissolved in dry THF. Slowly a 0.5M solution of 9-BBN (49.28 mL, 24.64 mmol) in THF was added over a 30 min. period to the alkene via an addition funnel. When the addition was complete, the reaction was allowed to stir at room temperature for 3.5h. After this time, a 3M aqueous solution of NaOH (8.21 mL) was dripped into the reaction and a small evolution of bubbles appeared during addition. Once all the bubbles disappeared, a 30% aqueous solution of H_2O_2 (8.21 mL) was slowly added. This addition generated a large amount of heat and foam in the reaction mixture. The reaction then stirred for 10h. The salts were filtered off and the solution concentrated by reduced pressure rotary evaporation. Water was added to the filtrate and it was extracted with ethyl acetate (3 x 35

mL). The organics were collected, washed with a portion of brine, dried over MgSO$_4$, and purified by flash chromatography using 1/2 EtOAc/Hex as the eluent, giving a 98% yield of 17. ^{1}H NMR δ 1.80 (quintet, J= 6 Hz, OCH$_2$CH$_2$), 2.87 (t, J= 6 Hz, 2H, PhCH$_2$), 3.61 (t, J= 7 Hz, 2H, CH$_2$CH$_2$O), 3.71 (t, J= 6 Hz, OCH$_2$CH$_2$), 4.11 (quartet, J= 7 Hz, 2H, CH$_2$CH$_2$OH), 7.16-7.34 (m, 5H, Ph); mass spectra (LRFAB) m/z 181 (M+1), 155, 135, 119, 105; HRMS calcd. for C$_{11}$H$_{16}$O$_2$: 180.1229; found: 180.1225.

3-Methanesulfonoxypropyl-2-phenylethyl ether (18). The alcohol 17 from above (500 mg, 2.77 mmol) and triethylamine (1.93 mL, 13.87 mmol) were dissolved in dry THF. Mesyl chloride was slowly dripped into the solution. A yellowish precipitate fell out upon addition. The reaction stirred at room temperature for 15 min. After this time, the precipitate and the yellow color of the reaction mixture was removed by filtering it through a short silica plug. The filtrate was concentrated by reduced pressure rotary evaporation and purified by flash column chromatography using 1/2 EtOAc/Hex as the eluent. The yield of the product 18 was 79%. ^{1}H NMR δ 1.97 (quintet, J= 6 Hz, 2H, OCH$_2$CH$_2$), 2.83-2.90 (m, 5H, PhCH$_2$ and OSO$_2$CH$_3$), 3.52 (t, J= 6 Hz, 2H, PhCH$_2$CH$_2$O), 3.64 (t, J= 7 Hz, 2H, OCH$_2$), 4.26 (t, J= 6 Hz, CH$_2$CH$_2$OSO$_2$CH$_3$), 7.18-7.29 (m, 5H, Ph); mass spectrum (LREI, 70 eV offscale) m/z 258 (M$^+$), 137 (100), 109 (100), 105 (100), 104 (100), 103 (49), 97 (57), 91 (100), 79 (100), 77 (86), 65 (76), 61 (58), 59 (100), 57 (56), 45 (100), 43 (100), 42 (100); HRMS calcd. for

$C_{12}H_{18}O_4S$: 258.0926; found: 258.0942; Anal. calcd. for $C_{12}H_{18}O_4S$: C, 55.79; H, 7.02; S, 12.41; found: C, 55.76; H, 7.04; S, 12.26.

3-Fluoropropyl 2-phenylethyl ether (6). The above mesylate 18 (100 mg, 0.387 mmol) was dissolved in dry THF. Then a 1M solution of TBAF in THF (0.774 mL, 0.774 mmol) was added to the reaction via a syringe. The reaction was allowed to stir at room temperature for 20h. The reaction mixture was filtered through a silica plug and concentrated by steam distillation through a Vigreaux column. Further purification of the product was preformed by flash column chromatography using 20/1 pentane/diethyl ether as the eluent. This provided a 82% yield of 6. ^1H NMR δ 1.93 (d quintet, J_{HF}= 26 Hz, J= 6 Hz,2H, CH$_2$CH$_2$CH$_2$F), 2.88 (t, J= 7 Hz, 2H, PhCH$_2$), 3.55 (t, J= 6 Hz, 2H, OCH$_2$CH$_2$), 3.64 (t, J= 7 Hz, 2H, PhCH$_2$CH$_2$O), 4.51 (dt, J_{HF}= 47 Hz, J= 6 Hz, 2H, CH$_2$CH$_2$F), 7.19-7.33 (m, 5H, Ph); mass spectrum (LREI, 70 eV) m/z 183 (M+1), 182 (M$^+$), 91 (100), 61 (55), 43 (29), 42 (38); HRMS calcd. for $C_{11}H_{15}OF$: 182.1107; found: 182.1115; Anal. calcd. for $C_{11}H_{15}OF$: C, 72.50; H, 8.30; F, 10.43; found: C, 72.46; H, 8.41; F, 10.36.

4-Phenylbutanal (20). PCC (2.16 g, 10.00 mmol) was dissolved in 200 mL of dry methylene chloride and cooled to -78°C. 4-Phenyl-1-butanol (19) (1.00 g, 6.66 mmol) was diluted with 10 mL of methylene chloride and slowly dripped into the PCC solution. The reaction mixture was then allowed to warm to room temperature and stirred for 2h. A small amount of silica was then added to the reaction followed by the addition of diethyl ether (50 mL). The slurry was

then filtered through a small silica plug. The product was concentrated under reduced pressure rotary evaporation and the product isolated by flash column chromatography using 1/9 EtOAc/Hex as the eluent. This afford 843.1 mg of the product 20 for a 85% yield. ^{1}H NMR δ 1.96 (quintet, J= 7 Hz, 2H, PhCH$_2$CH$_2$), 2.45 (t, J= 7 Hz, 2H, CH$_2$CH$_2$O), 2.66 (t, J= 7 Hz, 2H, PhCH$_2$CH$_2$), 7.16-7.33 (m, 5H, Ph), 9.76 (t, J= 2 Hz, 1H, CHO); mass spectrum (LREI, 70 eV) m/z 148 (M$^+$), 104 (100), 91 (48); HRMS calcd. for C$_{10}$H$_{12}$O: 148.0888; found: 148.0888; Anal. calcd. for C$_{10}$H$_{12}$O: C, 80.70; H, 8.13; found: C, 81.04; H, 8.16.

Ethyl 2,2-difluoro-7-phenyl-3-heptanoate (21) Activated zinc (154.3 mg, 2.36 mmol) was refluxed in 5 mL of dry THF. A 2 mL solution of the above aldehyde (250 mg, 1.69 mmol) and ethyl bromo-1,1-difluoroacetate (238.5 μL, 1.86 mmol) was added to the refluxing zinc mixture in a slow enough fashion as to not disturb the refluxing. After 35 min., the reaction mixture was cooled to room temperature. EtOAc and water were added to the mixture and the excess zinc was filtered off. The filtrate was then extracted with EtOAc and the organic layers collected, washed with brine, and dried over MgSO$_4$. Purification of the product was carried out by flash column chromatography using 1/4 EtOAc/Hex as the eluent. The afforded 21 in a 70% yield. ^{1}H NMR δ 1.34 (t, J= 7 Hz, 3H, CO$_2$CH$_2$CH$_3$), 1.56-2.02 (m, 4H, PhCH$_2$CH$_2$CH$_2$), 2.66 (t, J= 7 Hz, 2H, PhCH$_2$), 4.11 (m, 1H, CH$_2$CHOH), 4.33 (quartet, J= 7 Hz, CO$_2$CH$_2$CH$_3$), 7.19-7.32 (m, 5H,

Ph); mass spectrum (LREI, 70 eV offscale) m/z 273 (M+1), 272 (M+),
164 (100), 131 (100), 117 (47), 105 (100), 104 (100), 92 (88), 91
(100), 79 (40), 78 (46), 77 (51), 65 (78), 48 (55); HRMS calcd. for
$C_{14}H_{18}O_3F_2$: 272.1225; found: 272.1224; Anal. calcd. for $C_{14}H_{18}O_3F_2$:
C, 61.76; H, 6.66; F, 13.95; found: C, 61.70; H, 6.85; F, 13.69.

Ethyl 2,2-difluoro-3-iodo-7-phenylheptanoate (23). The
secondary alcohol 22 from above (250 mg, 0.918 mmol) and 2,6-
lutidine (268 µL, 2.30 mmol) were dissolved in dry methylene
chloride and cooled to 0°C. Triflic anhydride (268 µL, 2.30 mmol) was
slowly dripped into the reaction mixture. A color change was
observed in which the solution went from clear to pink to purple to
orange. After stirring for 30 min., the reaction was filtered through a
silica plug and concentrated by reduced pressure rotary evaporation.
The liquid remaining was quickly dissolved in a acetone solution of
NaI (675 mg, 4.50 mmol). The reaction mixture was then refluxed for
20h. The solution was cooled and diethyl ether was added causing a
white precipitate to fall out of solution. Water was added and the
mixture was extracted with diethyl ether (5 x 15 mL). The organics
were collected, dried over MgSO₄, concentrated by steam distillation,
and purified by flash column chromatography using 1/20
ether/pentane as the eluent. This afforded a 67% yield of the product
23. ^{1}H NMR δ 1.32 (t, J= 7Hz, 3H, CO₂CH₂C<u>H₃</u>), 1.78-2.49 (m, 5H,
PhCH₂C<u>H₂</u>C<u>H₂</u>C<u>H</u>I), 2.66 (m, 2H, Ph<u>CH₂</u>), 4.32 (quartet, 2H, CO₂<u>CH₂</u>CH₃),
7.15-7.34 (m, 5H, Ph); mass spectrum (LREI, 70 eV offscale) m/z 383

(M+1), 382 (M⁺), 255 (100), 181 (56), 161 (44), 119 (59), 117 (100), 105 (100), 101 (97), 103 (41), 92 (100), 91 (100), 79 (52), 77 (91), 65 (100), 51 (49), 40 (47); HRMS calcd. for $C_{14}H_{15}O_2F_5I$: 382.0241; found: 382.0241.

Ethyl 2,2-difluoro-7-phenylheptanoate (24). The iodo compound 23 (50 mg, 0.131 mmol) from above was combined with tributyl tin hydride (42 µL, 0.157 mmol) in freshly distilled benzene in a 3-neck round-bottom flask equipped with a reflux condenser. The solution was then refluxed for 21h. The solution was concentrated by steam distillation. Purification was accomplished by flash column chromatography using 1/20 diethyl ether/pentane as the eluent. This gave a 87% yield of the product 24. ^1H NMR δ 0.91-0.84 (m, 2H, PhCH₂CH₂), 1.26 (dt, J_{HF}= 21 Hz, J = 7 Hz, 3H, CO₂CH₂CH₃), 1.50-1.72 (m, 2H, PhCH₂CH₂CH₂), 1.96-2.12 (m, 2H, CH₂CH₂CF₂), 2.62 (t, J = 7 Hz, 2H, PhCH₂), 3.92 (dquartet, J_{HF}= 172 Hz, J = 7 Hz, 2H, CO₂CH₂CH₃), 7.14-7.32 (m, 5H, Ph); mass spectra (LREI, 70 eV) m/z 256 (M⁺), 92 (19), 91 (100); HRMS calcd. for $C_{14}H_{18}O_2F_2$: 256.1275; found: 256.1266.

6-Phenyl-hexyl methansulfonate (28). 6-Phenyl-1-hexanol (27) (500 mg, 2.80 mmol) was combined with triethylamine (1.95 mL, 14.00 mmol) in dry THF. Mesyl chloride (0.433 mL, 5.60 mmol) was then dripped into the solution. The reaction stirred at room temperature for 30 min. It was then filtered through a small silica plug and concentrated by reduced pressure rotary evaporation. Purification of 28 was accomplished by flash column chromatography

using 1/3 EtOAc/Hex as the eluent; however, purification was not necessary for use in the following reaction. ^{1}H NMR δ 0.87 (quintet, J= 4 Hz, 2H, PhCH$_2$CH$_2$CH$_2$), 1.39 (quintet, J = 4 Hz, 2H, CH$_2$CH$_2$CH$_2$OSO$_2$CH$_3$), 1.56-1.77 (m, 4H, PhCH$_2$CH$_2$ and CH$_2$CH$_2$OSO$_2$CH$_3$), 2.60 (t, J = 7 Hz, 2H, PhCH$_2$), 2.98 (s, 3H, OSO$_2$CH$_3$), 7.11-7.31 (m, 5H, Ph).

6-Phenyl-1-fluorohexane (2) The mesylate 28 (100 mg, 0.39 mmol) and a 1M solution of TBAF in THF (0.78 ml) were combined in THF at room temperature. The reaction was allowed to stir for 3h. It was then filtered through a silica plug and concentrated by steam distillation through a Vigreaux column. Purification was performed by flash column chromatography using pentane as the eluent. The product 2 yield was 99%. ^{1}H NMR 0.93 (quintet, J = 4 Hz, 2H, PhCH$_2$CH$_2$), 1.23-1.78 (m, 6H, CH$_2$CH$_2$CH$_2$CH$_2$F), 2.61 (t, J = 8 Hz, 2H, PhCH$_2$), 4.43 (dt, J$_{HF}$ = 47 Hz, J = 6 Hz, 2H, CH$_2$CH$_2$F), 7.13-7.32 (m, 5H, Ph); mass spectrum (LREI, 70 eV) 181 (M+1), 180 (M$^+$), 92 (56), 91 (100);

7-Phenyl-4-hydroxy-1-heptene (29) Allyl Grignard (1.0M solution in diethyl ether, 3.37 mmol) was diluted with more diethyl ether and cooled to 0°C. 4-Phenylbutanal (20) (100 mg, 0.675 mmol) was dissolved in diethyl ether and dripped into the Grignard solution. The reaction was allowed to warm to room temperature. Any unreacted Grignard reagent was quenched with a ammonium chloride aqueous solution. The organics were then separated, dried over MgSO$_4$, concentrated by reduced pressure rotary evaporation, and

purified by flash column chromatography using 1/10 EtOAc/Hex as the eluent. This provided a 87% yield of the product 29. ^{1}H NMR δ 0.85 (quintet, J= 6 Hz, 2H, PhCH$_2$CH$_2$), 1.48-2.33 (m, 4H, CH$_2$CHOHCH$_2$), 2.63 (t, J= 7 Hz, 2H, PhCH$_2$), 3.60-3.69 (m, 1H, CHOH), 5.09 (d, J= 3 Hz, 1H, CHCH$_2$-trans), 5.15 (s, 1H, CHCH$_2$ cis), 5.70-5.88 (m, 1H, CH$_2$CHCH$_2$), 7.12-7.31 (m, 5H, Ph); mass spectrum (LREI, 70 eV) m/z 190 (M+), 131 (100), 105 (22), 104 (60), 91 (59), 43 (27), 41 (30); HRMS calcd. for C$_{13}$H$_{18}$O: 190.1358; found: 190.1358.

7-Phenyl-1-hepten-4-one (30) PCC (118 mg, 0.552 mmol) was dissolved in dry methylene chloride and cooled to -78 C. The alcohol **29** was diluted in methylene chloride and slowly added in the PCC mixture. The reaction was then warmed to room temperature and allowed to stir for 1h. It was filtered through a silica plug, concentrated with reduced pressure rotary evaporation, purified by flash column chromatography using 10/1 Hex/EtOAc as the eluent. This gave a 31% yield of the ketone 30. ^{1}H NMR δ 1.91 (quintet, J= 7 Hz, 2H, PhCH$_2$CH$_2$), 2.45 (t, J= 7 Hz, 2H, CH$_2$COCH$_2$CH), 2.62 (t, J= 7 Hz, 2H, PhCH$_2$), 3.14 (d, J= 7 Hz, COCH$_2$CHCH$_2$), 5.07 (d, J= 2 Hz, 1H, CHCH$_2$-trans), 5.14-5.17 (m, 1H, CHCH$_2$-cis), 5.91 (ddt, J$_{trans}$= 17 Hz, J$_{cis}$= 10 Hz, J= 3 Hz, COCH$_2$CHCH$_2$), 7.15-7.33 (m, 5H, Ph).

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