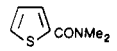
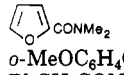
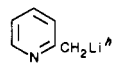
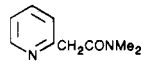
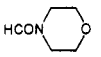
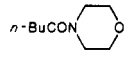
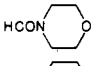
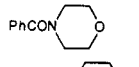
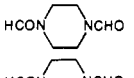
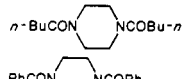
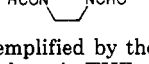
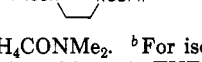
Table II. Magnesium 2-Ethoxyethoxide Promoted Carboxamidation of Various Organometallic Reagents[a]

entry	organometallic reagent	formamide	solvent	product	yield,[b] %	ref[j]
1	*n*-BuLi	$HCONMe_2$	MCH/CH	*n*-$BuCONMe_2$	65	11
2	Ph_2Mg[c]	$HCONMe_2$	toluene	$PhCONMe_2$	80	12
3	*s*-Bu_2Mg	$HCONMe_2$	MCH	*s*-$BuCONMe_2$	65	13
4		$HCONMe_2$	CH/THF		61	14
5		$HCONMe_2$	CH/THF		29	15
6	*o*-$MeOC_6H_4Li$[f]	$HCONMe_2$	CH/THF	*o*-$MeOC_6H_4CONMe_2$	71	16
7	$PhCH_2Li$[g]	$HCONMe_2$	CH/THF	$PhCH_2CONMe_2$	0	
8		$HCONMe_2$	CH/THF		0	
9	$PhCH(Me)CH_2Li$[i]	$HCONMe_2$	THF	$PhCH(Me)CH_2CONMe_2$	34	this work
10	*n*-BuLi	HCON(Ph)Et	MCH/CH	*n*-BuCON(Ph)Et	39	this work
11	*n*-BuLi		MCH/CH		53	17
12	Ph_2Mg		toluene		68	18
13	*n*-BuLi		MCH/CH		71	19
14	Ph_2Mg		toluene		17	20

[a] The experimental procedure is exemplified by the synthesis of *o*-$MeOC_6H_4CONMe_2$. [b] For isolation, spectroscopically pure product. [c] Reference 10. [d] By metalation of thiophene in THF with *n*-BuLi. [e] By metalation of furan in THF with *n*-BuLi. [f] By metalation of anisole in THF with *n*-BuLi. [g] By metalation of toluene in THF with *n*-BuLi. [h] By metalation of 2-picoline in THF with *n*-BuLi. [i] By reaction of $PhCH(Me)CH_2SPh$ with $Li^+C_{10}H_8^{\bullet-}$ in THF (ref 9). [j] The physical constants of the carboxamides as well as their NMR spectra agreed with those reported in the literature.

temperature, benzaldehyde (20 mmol) was added, and stirring was continued for 1 h at bath temperature and for 2 h at room temperature. The reaction mixture was hydrolyzed with cold, dilute H_2SO_4, extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was vacuum distilled and the $PhCH_2OH$/*n*-$BuCONMe_2$ codistillate (90 °C/4 mm) was collected. The yield of amide was calculated from the integrated ^1H NMR spectrum.

Preparation of *N,N*-Dimethyl-*o*-methoxybenzamide. This is given as a typical preparation of the amides in Table II. (*o*-Methoxyphenyl)lithium, prepared by addition of butyllithium (20 mmol as 1.7 M cyclohexane solution) to anisole (20 mmol) in 4 mL of THF at 5 °C, and after being stirred at room temperature overnight, was treated at 5 °C with 10 mmol of **4**. After being stirred at room temperature for 1 h, the reaction mixture was cooled in ice, and 20 mmol dimethylformamide was added. After the mixture was stirred at the bath temperature for 1 h and at room temperature for 2 h, 5.5 g of benzophenone were added, and stirring was continued overnight. The reaction mixture was hydrolyzed with cold, dilute H_2SO_4, extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was chromatographed on silica gel. Benzophenone and benzhydrol were eluted with toluene and the product with 1:1 CH_2Cl_2/AcOEt. Evaporation of the solvents gave 2.6 g (71%) of the title compound, mp 69–70 °C (lit.[16] mp 71 °C).

***N,N*-Dimethyl-3-phenylbutyramide.** The product was isolated by column chromatography (see previous experiment) as an oil: yield 1.3 g, 34%; ^1H NMR (ppm, $CDCl_3$) 1.33 (d, 3 H), 2.54 (m, 2 H), 2.83 (d, 6 H), 3.31 (m, 1 H), 7.25 (s, 5 H); ^{13}C NMR (ppm, $CDCl_3$) 21.57 (CCH_3), 35.11 (NCH_3), 36.42 (CH_2), 36.97 (NCH_3), 41.51 (CH), 126.61, 126.79, 128.32, 146.44 (aromatic), 171.58 (CO).

***N*-Ethyl-*N*-phenylvaleramide**: Yield 1.6 g, 39%; Bp 120 °C/(2 mmHg); ^1H NMR (ppm, $CDCl_3$) 0.7–0.9 (m, 10 H), 1.95 (m, 2 H), 3.63 (q, 2 H), 7.3 (center of m, 5 H); ^{13}C NMR (ppm, $CDCl_3$) 13.05 (CH), 13.68 (CH_3), 22.27 ($CH_3CH_2CH_2$), 27.59 ($CH_2CH_2CH_2$), 34.03 (CH_2CO), 43.89 (NCH_2), 127.67, 128.37, 129.54, 142.64 (aromatic), 172.41 (CO).

Registry No. **4**, 116005-37-9; **5**, 22065-26-5; $HCONMe_2$, 68-12-2; *n*-$BuCONMe_2$, 6225-06-5; *o*-$MeOC_6H_4CONMe_2$, 7291-34-1; *o*-$MeOC_6H_4Li$, 31600-86-9; $PhCH(Me)CH_2CONMe_2$, 77515-93-6; *n*-BuCON(Ph)Et, 116005-38-0; *n*-BuLi, 109-72-8; $LiOCEtMe_2$, 53535-81-2; *n*-BuMgI, 1889-20-9; *n*-BuMgCl, 693-04-9; *n*-$Bu_2Mg(Et_2O)_2$, 110303-53-2; *n*-Bu_2Mg, 1191-47-5; Ph_2Mg, 555-54-4; $PhCONMe_2$, 611-74-5; *s*-Bu_2Mg, 17589-14-9; *s*-$BuCoNMe_2$, 5592-02-9; $PhCH_2Li$, 766-04-1; $PhCH(Me)CH_2Li$, 64740-49-4; HCON(Ph)Et, 5461-49-4; 2-thienyllithium, 2786-07-4; *N,N*-dimethyl-2-thiophenecarboxamide, 30717-57-8; 2-furyllithium, 2786-02-9; *N,N*-diemthyl-2-furylcarboxamide, 13156-75-7; (2-pyridinylmethyl)lithium, 116005-39-1; 4-morpholinecarboxaldehyde, 4394-85-8; 4-valerylmorpholine, 22342-18-3; 4-benzoylmorpholine, 1468-28-6; 2,3,5,6-tetrahydropyrazine-1,4-dicarboxaldehyde, 4164-39-0; 1,4-bis(1-oxopentyl)-2,3,5,6-tetrahydropyrazine, 18903-08-7; 1,4-dibenzoyl-2,3,5,6-tetrahydropyrazine, 6091-41-4.

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Synthesis of 16α- and 16β-Fluoro-17β-estradiol by Fluorination of Estrone Enols

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Recently the stereospecific synthesis of 16α-fluoro-17β-estradiol (**1**) and 16β-fluoro-17β-estradiol (**2**) were reported by Katzenellenbogen et al. who used a method of displacement of triflate by fluoride to achieve stereospecificity.[1] The importance of **1** and **2** stems from their very high receptor binding affinities with estrogen receptor protein.[2] Thus, the high receptor binding affinities of **1** (RBA = 80) and **2** (RBA = 30) relative to estradiol (RBA

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0022-3263/88/1953-5153$01.50/0

Table I. Reaction of (Silyloxy)estrone 3 with Fluorinating Agents

fluorinating reagents (F)	condition	solvents	α/β ratio	% yield; mp, °C	^{19}F NMR, δ	amounts of F	3, mmol ((silyloxy)estrone)
$CsSO_4F$	25 °C, 17 h, N_2 atmosphere	CH_2Cl_2	9/1	15; 148–152	−191.9 (α), −184.7 (β)	0.423 mmol	0.140
XeF_2	25 °C, 30 min, N_2 atmosphere	CH_2Cl_2	all	44; 148–150	−191.6 (α), −164.4 (Ar)	0.178 mmol	0.056
F_2/N_2	−78 °C, 5 min	$CFCl_3$	7/1	12	−192 (α), −185 (β), −159.7 (Ar)	5–10% F_2	0.253
CF_3OF	0 °C, 5 min	CH_2Cl_2	all	10–15	−191.8 (α), −164.5 (Ar), −153.3 (Ar)	5–7% CF_3OF	0.0140

Table II. Reactions of Estrone Diacetate 4 with Fluorinating Agents

fluorinating reagents (F)	conditions	solvents	α/β ratio	% yield; mp, °C	^{19}F NMR	amounts of F	4, mmol (enol acetate)
$CsSO_4F$	25 °C, 17 h, N_2 atmosphere	CH_2Cl_2	20/1	22; 148–151	−191 (α), −184 (β)	0.152 mmol	0.355
XeF_2	25 °C, 17 h, N_2 atmosphere	CH_2Cl_2	9/1	99; 149–153	−191.9 (α), −184.3 (β)	0.320 mmol	0.210
F_2/N_2 (method I)	0 °C, 5 min	CH_2Cl_2	10/1	56	−133.8 (Ar), −184.9 (β), −188.2, −192.1 (α)	5–10% F_2	0.164
F_2/N_2 (method II)	−78 °C, 2–3 min	CH_2Cl_2	10/1	40	−133.8 (Ar), −164.8 (Ar), −184.9 (β), −187.9, −191.9 (α)	5–10% F_2	0.212
CF_3OF	0 °C, 15 min	CH_2Cl_2	12/1	65	−149.8, −171.6, −184.3 (β), −186.9, −191.9 (α)	5–10% CF_3OF	0.116

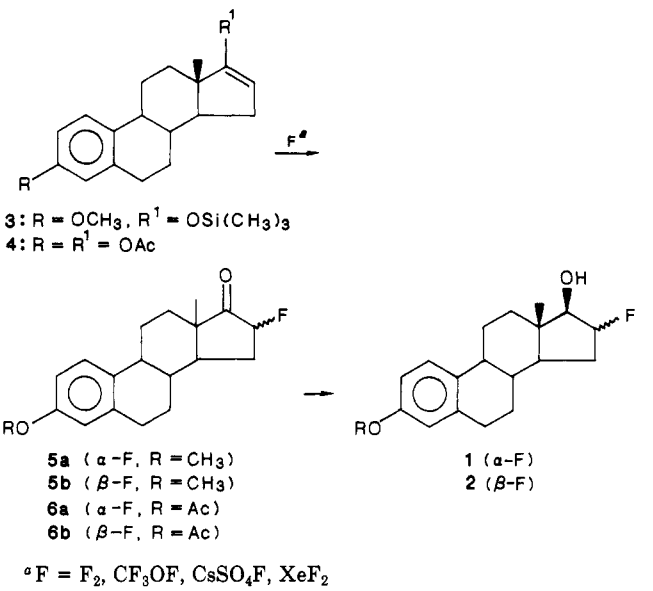
= 100) indicate that they may be useful in the treatment or detection of estrogen-responsive tumors.[3] Welch et al. have developed a robot-assisted method for the preparation of ^{18}F-labeled **1** and have conducted extensive studies into the biodistribution of **1** and its use in the detection of breast tumors.[4]

Because of the extreme potential of **1** and **2** in the study of estrogen responsive tumors, we directed attention to their synthesis by short effective procedures, which can also possibly be used in the preparation of the ^{18}F-labeled derivatives. Our synthetic routes to **1** and **2** centered around the reaction of easily available enol derivatives of estrone with common fluoropositive fluorination agents and are shown in Scheme I. Thus, both the silyl enol ether **3** and the enol acetate **4** were used in our study.[5] The results of fluorination of **3** and **4** with several fluorination agents ($CsSO_4F$, XeF_2, F_2, and CF_3OF) are given in Tables I and II. The products from the fluorination of **3** (R = CH_3) are the 16α-fluoroestrone (**5a**) and 16β-fluoroestrone (**5b**), and from enol **4** (R = OAc) the 16α-fluoroestrone (**6a**) and 16β-fluoroestrone (**6b**). Although the focus of this study is the fluorination of enol derivatives, the reduction and deprotection of **5** and **6** constitute the complete synthesis of **1** and **2** and are both well-known processes.[1] We have converted pure **6** (R = OAc) to **1** by reduction with lithium aluminum hydride in 95% yield (85% β-OH).

Enol derivatives are known to undergo fluorination with a variety of reagents, and in some cases stereoselectivity is observed.[5] A very high degree of stereoselectivity is observed in the fluorination of **3** and **4** with 90% or greater preference for the formation of the α isomer, as determined from ^{19}F NMR resonances of the products **5a** and **6a** at −191 ppm for the α-fluoro isomer and, for **5b** and **6b** at −184 ppm for the β-fluoro isomer relative to $CFCl_3$.[1] Such high stereoselectivity is understandable in terms of steric retardation of the fluorination from the β side by the 18β-methyl group.

Fluorination with dilute fluorine gas or CF_3OF produced mixtures that contained products from fluorination of the steroid aromatic ring. Cesium fluoroxy sulfate gave high

Scheme I



[a] F = F_2, CF_3OF, $CsSO_4F$, XeF_2

stereoselectivity, and products yields were fair to moderate. Xenon difluoride gave the best results with high stereoselectivity, and in the case of **3**, gave complete stereospecificity for the α isomer.

Extension of this work to radiolabeled products appears likely through the use of ^{18}F-radiolabeled XeF_2, which is known,[6] or through ^{18}F-labeled $CsSO_4F$, which is possible by reaction of ^{18}F–F with $CsSO_4$.[7-9]

Experimental Section

The fluorination agents used in this research are strong oxidizing materials, and extreme care should be exercised in their use. Cesium fluoroxy sulfate was prepared by the method of Appleman et al.[8] Xenon difluoride and fluoroxytrifluoromethane

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(9) The use of fluorine-18 labeled **1** or **2** as imaging agents requires that they be prepared with high specific activity because the receptor sites at which they are localized have low capacity. Present technology for the preparation of electrophilic fluorination agents labeled with fluorine-18 poses limitations on their ability to achieve radiolabeling with high specific activities.

were purchased from PCR, Gainesville, FL. Fluorine was purchased from Air Products.

Preparation of 3-Methoxy-17-[(trimethylsilyl)oxy]estrone (3). Diisopropylamine (110 μL, 0.785 mmol) was dissolved in 3 mL of dry THF under N_2 atmosphere. The mixture was cooled to 0 °C, and 500 μL (1.00 mmol) of 2 M *n*-butyllithium was added dropwise by syringe. 3-Methyl estrone ether (73 mg, 0.26 mmol) in 5 mL of dry THF was added dropwise by syringe, followed by addition of an excess amount of trimethylsilyl chloride (165 μL, 1.30 mmol). The mixture was stirred at 0 °C for 1 h. The solvent was evaporated and dried under high vacuum. The residue was purified by dry-flash chromatography. Ethyl acetate–hexane (1/4) was used as a solvent for the purification. The product weight was 85 mg (0.24 mmol, 90% yield): δ 0.21 (TMS), 0.85 (s, CH_3), 2.04–2.89 (m, CH_2), 3.77 (s, CH_3), 4.53 (m, CH=C), 6.65–7.16 (m, Ar); TLC showed one spot (R_f 0.75). Anal. C, H.

Reaction of 3 with $CsSO_4F$. Compound **3** (50 mg, 0.140 mmol) was dissolved in 3 mL of dry methylene chloride. The mixture was stirred at room temperature followed by addition of 105 mg (0.423 mmol) of $CsSO_4F$. The reaction mixture was stirred under N_2 for 17 h. At this time, 5 mL of dry CH_2Cl_2 was added, and the mixture was washed with 2 × 10-mL portions of water. The methylene chloride layer was separated, dried over anhydrous $MgSO_4$, and removed in vacuo. The residue was subjected to dry-flash chromatography to give 5–7 mg (0.019 mmol, 10–15% yield) of **5a** and **5b**.

The identities of **5a** and **5b** were confirmed by comparison of their ^1H and ^{19}F NMR data with known data reported by Katzenellenbogen et al.[1]

Reaction of 3 with XeF_2. In a 25-mL flask under N_2 atmosphere was placed 20 mg (0.056 mmol) of **3** in 3 mL of dry CH_2Cl_2 followed by addition of 30 mg (0.178 mmol) of XeF_2. The mixture was stirred at 25 °C for 30 min. After this time, dry CH_2Cl_2 (2 mL) was added, and the methylene chloride solution was washed with 2 × 5-mL portions of water. The organic layer was separated, dried over anhydrous $MgSO_4$, and removed in vacuo. The residue was subjected to flash chromatography to give 7.0 mg (0.022 mmol, 44% yield) of **5a**.

Reaction of 3 with F_2/N_2. To a well-stirred mixture of 90 mg (0.253 mmol) of **3** in 20 mL of freon at −78 °C was bubbled a mixture of 5–10% F_2/N_2. TLC analysis did not show any traces of the starting material after 5 min. Fluorine gas flow was shut off, and nitrogen gas was run into the solution for 1–2 more minutes. The solvent was removed on a rotary evaporator, and the residue was purified by flash chromatography to give 9–10 mg (0.031 mmol, 12% yield), mp 118–120 °C. The ^{19}F NMR spectrum shows that the aromatic ring has been fluorinated as well.

Reaction of 3 with CF_3OF. In a dry flask was dissolved 50 mg (0.140 mmol) of **3** in 8 mL of dry CH_2Cl_2. Fluoroxytrifluoromethane was bubbled into the mixture at 0 °C for approximately 5 min. To the reaction mixture was added 5 mL of dry CH_2Cl_2 followed by extraction with 2 × 10-mL portions of water. The organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography. The yield based on the NMR spectroscopy was determined to be 10–15%.

Preparation of 4. Into a 50-mL round-bottomed flask was dissolved 270 mg (1.00 mmol) of estrone in 15 mL of isopropenyl acetate, followed by addition of 1.0 mL of concentrated H_2SO_4. The mixture was refluxed for 2 h under nitrogen atmosphere. Approximately 5 mL of the solvent was collected and discarded. An additional 5 mL of isopropenyl acetate and 1.0 mL of H_2SO_4 were added, and the mixture was refluxed for 45 more minutes. Once again, 5 mL of the solvent was distilled off and discarded. Anhydrous ether (10 mL) was added, and ether solution was washed twice with water and then with 10 mL of ice-cold sodium bicarbonate solution and another time with water. Ether layer was separated, dried over anhydrous $MgSO_4$, and evaporated on a rotary evaporator. The residue was purified chromatographically on a silica gel column with 40% ethyl acetate–hexane as the solvent to give 150 mg (0.424 mmol, 42%, mp 149–150 °C [lit.[10] mp 145–149 °C]) of the product: ^1H NMR ($CDCl_3$) δ 0.98 (s, CH_3), 2.30 (s, CH_3), 2.40 (s, CH_3), 2.50–3.00 (m, CH_2), 5.54 (d, CH=COAC), 6.8–7.3 (m, Ar). TLC showed only one spot (R_f 0.52).

Reaction of 4 with $CsSO_4F$. To a solution of 54 mg (0.154 mmol) of **4** in 3 mL of dry CH_2Cl_2, was added 88 mg (0.355 mmol) of $CsSO_3F$. The mixture was stirred, under nitrogen atmosphere, for 17 h at room temperature. After this time, 15 mL of dry CH_2Cl_2 was added, and the mixture was washed with 2 × 10-mL portions of water. The organic layer was separated, dried over anhydrous $MgSO_4$, and removed on a rotary evaporator. The residue was purified on a silica gel column with 40% ethyl acetate–hexane as the solvent. The product weight was 11 mg (0.033 mmol, 22% yield, mp 148–151 °C).

Reaction of 4 with XeF_2. To a mixture of 74 mg (0.210 mmol) of **4** in 3 mL of dry CH_2Cl_2 was added 54 mg (.320 mmol) of xenon difluoride. The mixture was stirred under dry atmosphere of N_2 for 17 h. TLC showed no traces of the starting material after this period of time. Dry methylene chloride (10 mL) was added, and the mixture was washed with 2 × 10-mL portions of water. The organic layer was separated and dried over anhydrous $MgSO_4$. The weight of the product was 69 mg (0.21 mmol, 99% yield, mp 149–153 °C).

Reaction of 4 with F_2/N_2 (Method I). In a 50-mL pear-shaped flask was dissolved 58 mg (0.164 mmol) of **4** in 3 mL of dry CH_2Cl_2, and the mixture was cooled in an ice bath to 0 °C. F_2/N_2 (5–10% F_2) gas was bubbled through the CH_2Cl_2 mixture for 5 min. Dry CH_2Cl_2 (5 mL) was added, and the mixture was washed with 2 × 5-mL portions of water. The organic layer was separated, dried over anhydrous $MgSO_4$, and was removed in vacuo. The residue was purified chromatographically to give 33 mg (0.094 mmol, 56% yield, mp 118–121 °C).

Reaction of 4 with F_2/N_2 (Method II). To a mixture of 75 mg (0.212 mmol) of **4** in 5 mL of dry CH_2Cl_2 at −78 °C was bubbled a mixture of F_2/N_2 (5–10% F_2). TLC showed no traces of the starting substrate after 2–3 min. Dry CH_2Cl_2 (10 mL) was added, and the mixture was washed twice with water. The methylene chloride layer was separated and dried over anhydrous $MgSO_4$. After evaporating the solvent on a rotary evaporator, the residue was subjected to flash chromatography to give 30 mg (40% yield, 0.086 mmol) of the product (mp 118–121 °C).

Reaction of 4 with CF_3OF. Compound **4** (41 mg, 0.116 mmol) was dissolved in 3 mL of dry CH_2Cl_2. The mixture was chilled to 0 °C and stirred for 5 min. CF_3OF was bubbled into the reaction mixture for approximately 15 min. The TLC did not show any evidence of the starting material remaining in the reaction vessel. Dry CH_2Cl_2 (5 mL) was added, and the mixture was washed with water. The organic layer was separated, dried over anhydrous $MgSO_4$, and then removed in vacuo. The residue was subjected to flash chromatography, but all attempts to purify the product failed. The crude weight of the product was 25 mg (65% yield, 0.075 mmol).

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Search for Nucleophilicity Effect on the Face Selectivity of Addition to a Sterically Unbiased Ketone[1]

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In an earlier paper, we reported[2] the easily detectable face selectivity in the addition of nucleophiles to 5-sub-

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