Syntheses of 2,5- and 2,6-Difluoronorepinephrine, 2,5-Difluoroepinephrine, and 2,6-Difluorophenylephrine: Effect of Disubstitution with Fluorine on Adrenergic Activity[1]

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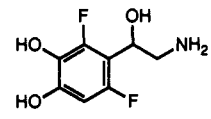
Received June 30, 1993•

Synthetic routes to difluorinated analogs of the adrenergic agonists, norepinephrine (NE), epinephrine (E), and phenylephrine (PE) have been developed. The syntheses were based on elaboration of the ethanolamine side chains from the appropriately polyfunctionalized benzaldehydes. The benzaldehydes were prepared from precursor difluorinated benzenes by sequential regioselective lithiations and reaction with electrophiles to introduce hydroxyl and carboxaldehyde functionalities. Binding and functional assay data demonstrate that the 2,6-difluorinated analogs are relatively inactive at both α- and β-adrenergic receptors. These results are consistent with earlier observations that 2-fluoro substitution of adrenergic agonists decreases α-adrenergic activity whereas 6-fluoro substitution decreases β-adrenergic activity.

We have described in several publications the striking effects of fluorine substitution on the agonist properties of a series of adrenergic agonists. In all phenolic phenethanolamines examined [the mixed α/β adrenergic agonists norepinephrine (NE)[2,3] and epinephrine (EPI);[4] the selective α-adrenergic agonist phenylephrine (PE);[5] and the selective β-adrenergic agonist, isoproterenol (ISO)[6]], a fluorine substituted at the 2-position of the aromatic ring greatly reduces affinity of the agonist for α-adrenergic receptors, while fluorine substituted at the 6-position markedly reduces affinities at β-adrenergic receptors. The resulting 2-fluoro derivatives thus are highly selective for β-adrenergic receptors, while the 6-fluoro derivatives are highly selective for α-adrenergic receptors. In certain systems, the 2-fluoro and 6-fluoro analogs were not only more selective, but were also more potent than the parent as β- and α-adrenergic agonists, respectively. Substitution of fluorine in the 5-position of NE and ISO had relatively little effect on adrenergic properties. Similar fluorine-induced adrenergic selectivities were found for the potent β-adrenergic agonist 3-(*N-tert*-butylamino)-1-(3,4-dihydroxyphenoxy)propanolamine.[7]

There has been considerable speculation as to the molecular mechanism(s) by which the presence of fluorine can cause such marked changes in receptor affinity.[1] For example, proposals were made that putative interactions of the benzylic hydroxyl group with an *ortho*-situated fluorine—hydrogen bonding or dipole–dipole repulsion—could introduce conformational biases that favored or inhibited binding to either α- or β-adrenergic receptors.[2,4,8,9] Alternative proposals not involving side-chain interactions invoked electronic perturbations caused by the presence of the highly electronegative fluorine substituent.[5,10] Examples of such perturbations are reduced electron density on the carbon to which fluorine is attached, altered frontier orbital characteristics, or the presence of the C–F dipole. These effects could lead to adrenergic selectivities by altering the interactions of the aromatic ring with critical sites on the adrenergic receptor. However, as yet, no clear definition of the molecular mechanism whereby fluorine substitution alters adrenergic selectivity has been obtained.

It is apparent that fluorine present on the 2- or 6-position of adrenergic agonists strongly influences agonist–receptor interactions. In view of this, we felt that substitution of a second fluorine on the aromatic ring might further alter the adrenergic activity of the 2- or 6-fluoro-substituted analog. For example, effects of intramolecular hydrogen bonding between fluorine and the benzylic OH group could be canceled in a 2,6-difluoro-substituted derivative, producing an active but nonselective analog. In contrast, negative effects of binding caused by dipole–dipole repulsion of the C–F bond and benzylic OH group, or intermolecular repulsive interactions of the C–F bond with the receptor, should be additive, producing an analogue with reduced activity at both α- and β-receptors. Perturbations of the electronic character of the aromatic ring caused by a single fluorine substituent also should be altered by the presence of a second fluorine. Herein we describe the syntheses of 2,6-difluoro-NE (1), 2,6-difluoro-PE (2), 2,5-difluoro-NE (3), and 2,5-difluoro-EPI (4) and discuss the mechanistic implications of the results.



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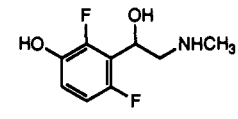

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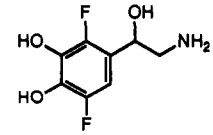

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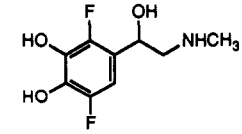

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Chemistry

The synthetic approach to the target phenethanolamines was based on side-chain elaboration of the appropriately substituted benzaldehyde precursors, as shown retrosynthetically in Scheme I.

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• Abstract published in *Advance ACS Abstracts*, October 15, 1993.

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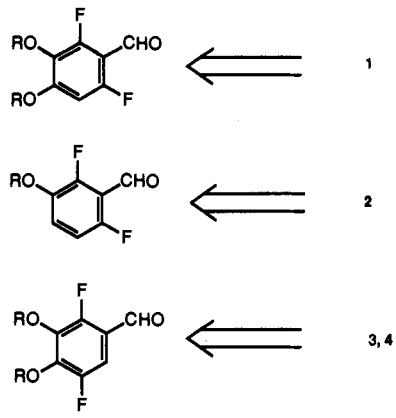
Scheme I

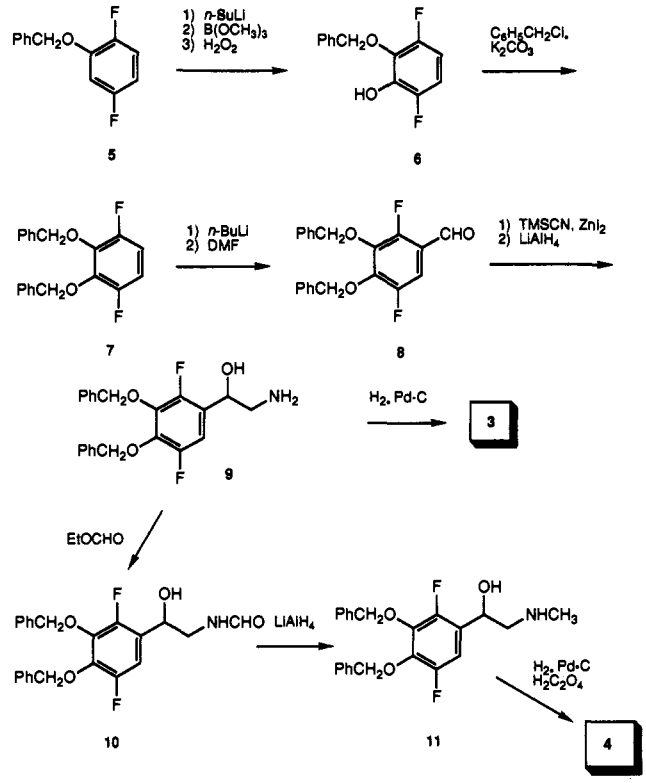


2,5-Difluorophenethanolamines. Benzylation of 2,5-difluorophenol[11] produced 1-(benzyloxy)-2,5-difluorobenzene (**5**). The double activation of the benzyloxy and fluorine substituents directed lithiation to the position ortho to each. Reaction of the lithiated intermediate with trimethylborate and oxidation of the derived boronic acid with hydrogen peroxide[12,13] gave 2-(benzyloxy)-3,6-difluorophenol (**6**), benzylation of which gave 1,2-bis(benzyloxy)-3,6-difluorobenzene (**7**). A second lithiation with *n*-butyllithium followed by DMF formylation provided the desired 3,4-bis(benzyloxy)-2,5-difluorobenzaldehyde (**8**).

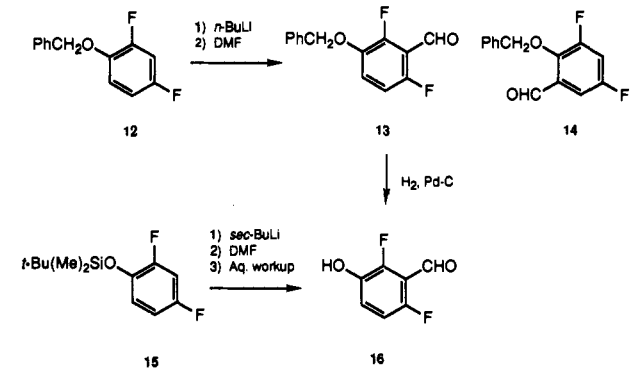
Elaboration of the ethanolamine side chain was carried out as previously described for the syntheses of monofluorinated analogs of NE and EPI.[2,3] (Trimethylsilyl)cyanohydrin formation followed by lithium aluminum hydride reduction gave [3,4-bis(benzyloxy)-2,5-difluorophenyl]ethanolamine (**9**). Formylation of **9** with ethyl formate gave **10**, lithium aluminum hydride reduction of which gave *N*-methyl[3,4-bis(benzyloxy)-2,5-difluorophenyl]ethanolamine (**11**). Palladium-catalyzed hydrogenolysis of **9** and **11** gave 2,5-difluoro-NE (**3**) and 2,5-difluoro-EPI (**4**), respectively (Scheme II).

2,6-Difluorophenylephrine (2). Benzylation of commercially available 2,4-difluorophenol produced 1-(benzyloxy)-2,4-difluorobenzene (**12**). We anticipated that the acidity at the doubly activated proton between two fluorines would overcome chelation–abstraction ortho to the benzyloxy group. This would result in preferential lithiation of **12** between the fluorines. Lithiation of **12** followed by reaction with DMF produced a single aldehyde, tentatively identified as **13** (Scheme III). The aromatic proton NMR signals produced by the four-spin AMXY system of **13** are consistent with the assigned structure. The lower field aromatic proton displays a doublet of triplets from which coupling constants, $J_{H-H}ortho$ = 9.5, $J_{H-F}ortho$ = 9.5, and $J_{H-F}para$ = 1.8, were derived, while the upfield aromatic resonance is a more complex sextuplet. Unfortunately, the complexity of the spectrum, and the fact that the isomeric aldehyde **14** that would be produced by lithiation *ortho* to the benzyloxy group could produce a similar splitting pattern, particularly with respect to the downfield proton ($J_{H-F}ortho$, $J_{H-F}ortho$, and $J_{H-H}meta$), indicated more convincing evidence was warranted. We have shown that lithiation of *o*- or *p*-[(*tert*-butyldimethylsilyl)oxy]fluorobenzene occurs regiospecifically *ortho* to fluorine.[4] From this, we can predict with confidence that lithiation of 1,3-difluoro-4-[(dimethyl-*tert*-butylsilyl)oxy]-benzene (**15**) will occur at the 2-position doubly activated by two fluorines with no reaction occurring at the 4-position

Scheme II



Scheme III

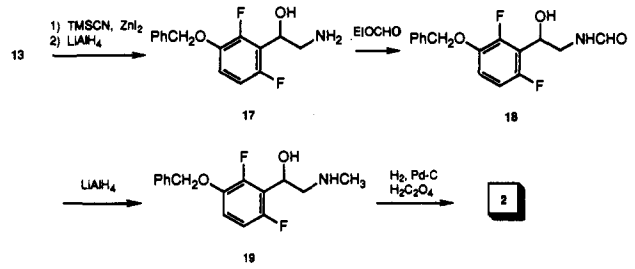


blocked by the *tert*-butyldimethylsilyloxy group. Lithiation of **15**, reaction with DMF, and desilylation during workup produced a single aldehyde, **16**. This was identical in all respects, including the NMR, with the product produced by debenzylation of **13** (Scheme III).

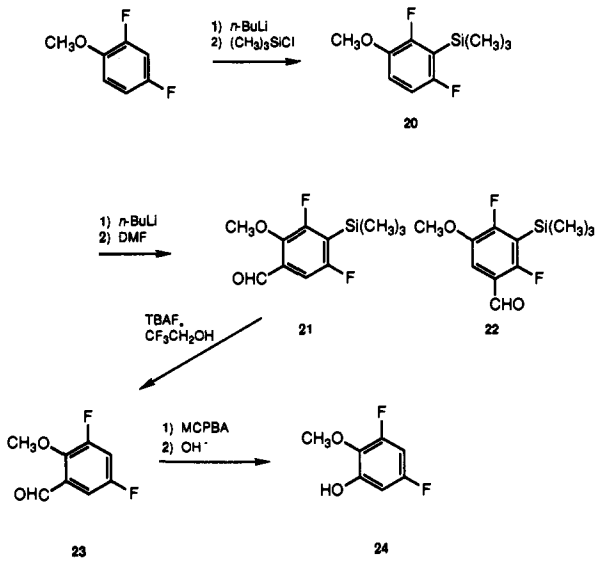
Elaboration of the *N*-methylethanolamine side chain was accomplished through intermediates **17** and **18**, as described for the 2,5-difluoroepinephrine series, to give the benzyl-protected 2,6-difluorophenylephrine **19**. Catalytic hydrogenation of **19** over 10% Pd–C in the presence of oxalic acid produced **2** as the neutral oxalate (Scheme IV).

2,6-Difluoronorepinephrine (1). The substitution pattern of the 3,4-dialkoxy-2,6-difluorobenzaldehyde precursor central to the syntheses of such 2,6-difluorophenethanolamines presents a more challenging synthetic problem than encountered in the 2,5-difluoro series. In fact, several routes that initially appeared attractive proved to be futile. Aromatic functionalization through organolithium intermediates again was an effective strategy. The most acidic 3-position of 2,4-difluoroanisole was protected by reaction of the 3-lithio intermediate with trimethylsilyl chloride to

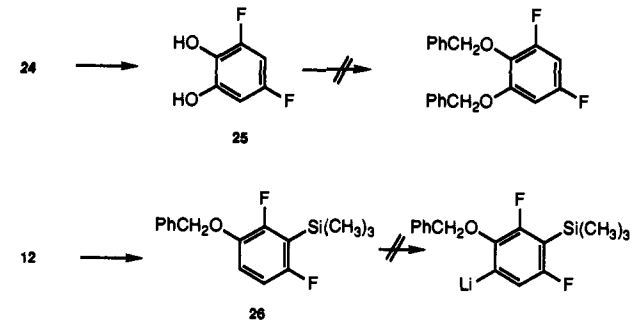
Scheme IV



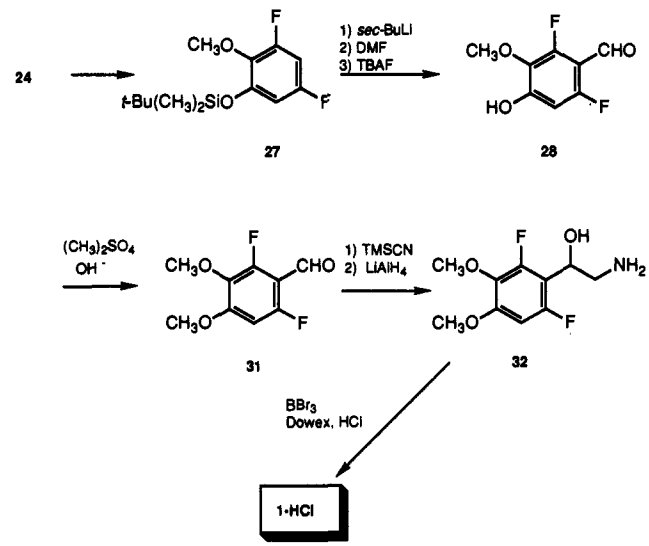
Scheme V



Scheme VI



Scheme VII



give **20**. Subsequent lithiation was expected to proceed predominantly in the position *ortho* to the methyl ether, based on literature precedents.[14,15] Attempts to introduce the phenolic hydroxyl group into **20** by a sequence of lithiation, reaction with trimethylborate, and oxidation of the borate intermediate were unsuccessful. However, under carefully controlled conditions, lithiation of **20** followed by reaction with DMF gave a 7:1 mixture of two aldehydes, assigned structures **21** and **22** based on NMR data (Scheme V). The NMR signal of the aromatic proton of the major isomer consisted of a quartet resulting from splitting with the *ortho* (J = 7.9 Hz) and *para* (J = 1.8 Hz) fluorines, establishing its structure as **21**.

Fluoride-mediated desilylation of **21** to give **23** presented unexpected difficulties. Under conditions described by Corey and Venkateswarlu[16] (tetrabutylammonium fluoride in THF containing a drop of water), only tars were formed. Shortening the reaction time and lowering the temperature to 0 °C gave no improvement. We assume that intermolecular condensation of the intermediate carbanion produced by desilylation with the product aldehyde may be the source of these problems, although benzyne formation may also contribute. To retard side reactions, desilylation was performed at −78 °C, and trifluoroethanol was used as a proton source. Under these conditions, **23** was formed in good yield. Bayer–Villager oxidation of **23** gave the required 2,4-difluoro-6-hydroxyanisole **24** (Scheme V).

Several attempts, under a variety of conditions, to dibenzylate 3,5-difluorocatechol **25**, derived from **24** by BBr_3 demethylation, were unsuccessful. In another approach to benzylated intermediates, we began the above sequence with 1-(benzyloxy)-2,4-difluoro-3-(trimethylsilyl)benzene (**26**), derived from **12**. While we had been able to lithiate the doubly activated positions of **5** and **12**, the acidity of the benzyl protons of **26** relative to the benzyloxy-activated 6-proton thwarted attempts to form the desired 6-lithio intermediate (Scheme VI). NMR analysis of the DMF-derived aldehyde indicated that lithiation had occured exclusively at the benzylic position.

Regiospecific introduction of the formyl group into **24** requires protection of the phenol in such a manner that the activating influence of the two fluorine atoms for *ortho* lithiation can overwhelm the fluorine–oxygen activation. Formation of the dimethyl-*tert*-butylsilyl ether, **27**, followed by lithiation with *sec*-butyllithium, formylation with DMF, and fluoride-catalyzed desilylation gave an excellent yield of 2,6-difluoro-4-hydroxy-3-methoxybenzaldehyde (**28**) (Scheme VII).

At this stage, an attempt also was made to convert **28** into a dibenzyl analog **29**. Demethylation of **28** with BBr_3 gave 2,6-difluoroprocatechualdehyde **30**. However, consistent with our experience with 2-fluoroprocatechualdehyde,[2] benzylation presented serious problems. While we had been able eventually to prepare 3,4-bis(benzyloxy)-2-fluorobenzaldehyde in modest yield by benzylation of the derived dimethyl acetal,[5] all attempts to benzylate **30** or its dimethyl acetal were unsuccessful. Base-induced side reactions of an undetermined nature apparently intervene. In contrast, methylation of the remaining phenolic hydroxyl group in **28** gave **31** in excellent yield (Scheme VII).

The ready accessibility of **31** by the synthetic sequence we have developed provides a route to 2,6-difluoro analogs of catecholic amino acids, neurotransmitters, hormones, and their metabolites related to adrenergic and dopa-

Table I. Affinities of Norepinephrines for Adrenergic Receptors

amine	K_i (μM) α_1[a]	α_2[b]	β_1[c]	β_2[c]
(−)-NE	1.0 ± 0.2	0.038 ± 0.01	1.6 ± 0.2	4.2 ± 0.04
2-FNE	23 ± 4	2.1 ± 0.4	2.5 ± 0.1	1.5 ± 0.1
6-FNE	1.2 ± 0.8	0.08 ± 0.04	45 ± 2	29 ± 3
5-FNE	2.3 ± 0.1	0.15 ± 0.03	1.5 ± 0.1	5.5 ± 1.0
2,5-DiFNE	24 ± 0.1	3.5 ± 0.7	5.6 ± 1.6	
2,6-DiFNE		0.75	>50	

[a] K_i ± SEM (n = 3) versus [^{3}H]WB4101 in rat cerebral cortical membranes. [b] K_i ± SEM (n = 3) versus [^{3}H]clonidine in rat cerebral cortical membranes. [c] K_i ± SEM (n = 3) versus 1 nM [^{3}H]dihydroalprenolol in rat cerebral cortical (β_1) or cerebellar (β_2) membranes. The K_i's for 2,6-DiFNE are from single experiments in triplicate. Limited supplies precluded further study.

minergic activity. The utility of **31** is illustrated by the preparation of the synthetic target of this study, 2,6-difluoro-NE (1) (Scheme VII).

Lithium aluminum hydride reduction of the (trimethylsilyl)cyanohydrin derived from **31** produced 2,6-difluoro-3,4-dimethoxyphenethanolamine **32**. Demethylation of **32** to give 1 was achieved using BBr_3. Consistent with our previous experience involving the use of this reagent on ethanolamine-containing compounds,[2] separation of the product 1 from inorganic borate salts proved to be difficult. Following a procedure that we applied in our initial synthesis of 2-fluoro-NE,[2] this was accomplished by ion-exchange chromatography over Dowex-H^+. The final product was isolated as noncrystalline, hydroscopic solid hydrochloride. The identity and purity of 1·HCl was established by HPLC, NMR, and mass spectral data.

Biology

Affinities of 1–4 for α_1-, α_2-, β_1-, and β_2-adrenergic receptors were determined through binding assays using specific radioligands. Agonist activity at α_1-adrenergic receptors was assessed through stimulation of phosphoinositide break-down in synaptoneurosomes, while agonist activity at β-adrenergic receptors was determined through stimulation of cyclic AMP formation in a cultured cell line. For further details, see the Experimental Section.

Discussion

Influence of 2,6-Difluoro Substitution. Interpretation of the biological consequences of substitution of fluorine at both the 2- and 6-positions of NE requires that the resulting analog be compared not only with NE, but also with the α-selective 6-FNE and the β-selective 2-FNE. The same applies in the case of 2,6-difluoro substitution of phenylephrine (see below). In this type of comparison, addition of a 2-fluoro substituent to 6-FNE results in a marked decrease in affinity of 2,6-DiFNE for α_2-adrenergic receptors (Table I). Similarly, addition of a 6-fluoro substituent to 2-FNE results in a marked decrease in affinity of 2,6-DiFNE for β_1-adrenergic receptors (Table I). The same applies to the agonist activity of 2,6-DiFNE at α- and β-adrenergic receptors (Table IV). For both receptors, 2,6-DiFNE is a very weak agonist. Limited supplies of 2,6-DiFNE precluded further investigation.

In the case of phenylephrine, this type of comparison reveals that addition of a 2-fluoro substituent to 6-FPE markedly reduces α_1- and α_2-receptor affinity of 2,6-DiFPE, while addition of a 6-fluoro substituent reduces β_1-receptor affinity (Table II). Remarkably, a 2-fluoro substituent does not reduce the agonist potency of 6-FPE at α_1-adrenergic receptors (Table IV). Instead, a slight (2-fold) increase pertains for the resulting 2,6-DiFPE. This anomalous result does not agree with the low affinity of 2,6-diFPE at α_1-adrenergic receptors seen in binding assays (Table II).

Table II. Affinities of Phenylephrines for Adrenergic Receptors

amine	K_i (μM)[a] α_1	α_2	β_1
(−)-PE	6.1 ± 0.8	0.39 ± 0.10	13
2-FPE	17 ± 3	1.2 ± 0.02	4.0
6-FPE	2.1 ± 0.2	0.23 ± 0.05	180
2,6-DiFPE	17	0.94	81

[a] Values are from a prior publication,[5] except for 2,6-DiFPE. Values are means ± SEM (n = 3) or are from single experiments in triplicate. See legend Table I.

Table III. Affinities of Epinephrines for Adrenergic Receptors

amine	K_i (μM)[a] α_1	α_2	β_1	β_2
(−)-EPI	2.4 ± 0.5	0.038 ± 0.005	1.2 ± 0.2	0.72 ± 0.15
2-FEPI	16.5	0.066	1.8	
6-FEPI	0.7	0.009	63	
2,5-DiFEPI	39 ± 6	1.2 ± 0.2	2.3 ± 0.1	0.71 ± 0.12

[a] Values for 2-FEPI and 6-FEPI are from a prior publication.[4] Other values are means ±SEM (n = 3). See legend Table I.

In general, these results are consistent with our previous observations that a 2-fluoro substituent is detrimental to α-adrenergic activity, and a 6-fluoro substituent is detrimental to β-adrenergic activity. This suggests that 2-fluoro or 6-fluoro substitution exerts a negative influence on binding that is not altered by the presence the second fluoro substituent. The early proposal that hydrogen bonding between fluorine and the benzylic hydroxyl group stabilizes preferred conformations[8] would appear not to be consistent with our present findings. Conformational restrictions caused by electrostatic repulsion of the aromatic fluorine and the benzylic hydroxyl group have been previously proposed by Debernardis[9] and by us[5] as a possible mechanism by which fluorine-substitution blocks binding to adrenergic receptors. Such conformational restraints in the case of difluoro substitution would be expected to result in lower activity at both α- and β-adrenergic receptors, consistent with the present results. Likewise, repulsive intermolecular interactions between fluorine and the adrenergic receptor, as proposed by Kocjan et al.[10] would be consistent with the present results. Effects of a second fluorine on the already perturbed electronic properties of 2- or 6-fluoro-NE would be expected to be significant, although how this might influence binding is not obvious. We are currently carrying out calculations to try to determine the possible importance of such alterations.

Influence of 2,5-Difluoro Substitution. Substitution of fluorine in the 5-position has little effect on the adrenergic activity of 2-FNE, since 2,5-DiFNE has affinities (or potencies) comparable to 2-FNE at adrenergic receptors (Table I). Likewise, 2,5-DiFEPI is comparable to EPI at β_1- and β_2-adrenergic receptors, but, like 2-FEPI, has reduced affinity at α_1- and α_2-adrenergic receptors (Table III). However, 2,5-DiFEPI has much lower affinity (20-fold) than 2-FEPI for α_2-adrenergic receptors. These results in large part are consistent with our previous observation that substitution of fluorine in the 5-position of NE has little effect on adrenergic activity, although in certain systems studied previously, a slight increase in activity at β-adrenergic receptors was observed.

Table IV. Agonist Activity at α_1-Adrenergic and α_2-Adrenergic Receptors

amine	EC_{50} (μM)[a] α_1[b] (PI breakdown)	β[c] (cAMP accumulation)
(−)-NE	1.5 (100)	0.052 (100)
2-FNE	>180	0.063 (100)
6-FNE	4.2 (100)	>10
2,6-DiFNE	>100	>100
2,5-FNE	83 (80)	
(−)-EPI	0.4 (100)	0.23 (100)
2-FEPI	3.3 (100)	0.04 (100)
6-FEPI	0.8 (100)	>1.5
2,5-DiFEPI	2.6 (n = 2) (95)	
(−)-PE	6 (100)	
2-FPE	80 (100)	
6-FPE	8 (190)	
4-FPE	16 (100)	
2,6-DiFPE	4.3 (100)	

[a] Values are from prior publications except for the 2,6- and 2,5-difluoroamines. The efficacies are in parentheses and are relative to the parent amine set equal to 100. [b] Values are means for stimulation of [^{3}H]phosphoinositol formation in guinea pig synaptoneurosomes. [c] Values are means for stimulation of cyclic AMP accumulation in C6 glioma cells.

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Gas chromatographic analyses were performed on a Hewlett-Packard Model 5890A gas chromatograph using a 15-m fused silica DB-1 methylsilcone capillary column (0.25-μm film thickness). Reported gas chromatographic retention times were based upon the following temperature program: 55 °C (2 min), 20 °C/min (7.25 min), 200 °C (2 min). Chemical ionization mass spectra were obtained on a Finnigan/Extrel Model 1015 mass spectrometer with ammonia as reagent gas. Gas chromatography–electron impact mass spectra were obtained on a Hewlett-Packard Model 5710A gas chromatograph coupled to a V. G. Instruments Model 7070F mass spectrometer. ^{1}H-NMR spectra were recorded on a Varian XL300 or a Varian 220 spectrometer. All reactions run under anhydrous conditions were performed under an argon atmosphere. Anhydrous solvents (e.g. THF, DMF, and CH_2Cl_2) were purchased from Aldrich Chemical Co. in Sure/Seal bottles and used without further purification. Flash chromatography indicates low-pressure (<15 psi) column chromatography on 75–150-mesh, 60-Å silica gel from Analtech or Fluka.

1-(Benzyloxy)-2,5-difluorobenzene (5). A stirred mixture of 5.0 g (38 mmol) of 2,5-difluorophenol,[11] 6.9 mL (57 mmol) of α-bromotoluene, and 10.5 g (76 mmol) of powdered anhydrous K_2CO_3 in 100 mL of dry acetone was refluxed overnight. The mixture was cooled to room temperature, diluted with water, and stirred until the K_2CO_3 dissolved. The solution was extracted three times with ether, and the combined ether extracts were washed with water and brine and dried over Na_2SO_4. Concentration under vacuum gave an orange liquid. Flash chromatography (silica gel, 10% CH_2Cl_2–petroleum ether) afforded as the second fraction 7.02 g (84%) of **5** as a white crystalline solid, mp 45–47 °C. ^{1}H NMR ($CDCl_3$): δ 5.10 (s, 2H, ArCH_2), 6.50–6.54 (m, 1H, ArH), 6.74–6.68 (m, 1H, ArH), 7.05–6.95 (m, 1H, ArH), 7.43–7.32 (m, 5H, ArH). CI-MS (NH_3): 238 (M^+ + 18, base). Anal. ($C_{13}H_{10}F_2O$) C, H.

2-(Benzyloxy)-3,6-difluorophenol (6). To a stirred solution of 4.5 g (20 mmol) of **5** in 25 mL of anhydrous tetrahydrofuran, cooled to −78 °C, was added dropwise 9.0 mL (22.5 mmol) of 1.6 M n-butyllithium at a rate to maintain the temperature below −65 °C. The solution was stirred for 2 h at −75 °C, and then 2.34 g (22.5 mmol) of trimethyl borate in 30 mL of dry ether was added dropwise at a rate to maintain the temperature below −65 °C. After 15 min, the dry ice–acetone bath was removed, and stirring was continued for 1.25 h. A solution of 25 mL of 10% HCl then was slowly added, and stirring was continued for 30 min. The aqueous layer was separated and extracted twice with ether. The combined organic extracts were washed twice with water and once with brine and dried over Na_2SO_4. Concentration to dryness gave the boronic acid as a white crystalline solid. A solution of the crude boronic acid in 50 mL of warm toluene was treated dropwise with 16 mL of 30% H_2O_2 at such a rate as to maintain a slow reflux. The solution was refluxed for an additional 2 h and cooled to room temperature, and the aqueous and organic layers were separated. The aqueous layer was extracted twice with ether, and the organic layers were combined. The combined organic extracts were washed with water, twice with 10% $FeSO_4$, with water again, and then extracted with 10% NaOH. The NaOH extract was cooled in an ice bath, acidified with 20% HCl, and extracted with ether. The ether extract was washed with brine and dried over Na_2SO_4. Removal of solvent under vacuum gave a pale yellow liquid. Flash chromatography (silica gel, 10% ether–petroleum ether) afforded as the second fraction and first Pauli positive band 4.24 g (90%) of **6** as a white crystalline solid, mp 43–44 °C. ^{1}H NMR ($CDCl_3$): δ 5.11 (s, 2H, Ar-CH_2), 5.32 (s, 1H, ArOH), 6.56–6.48 (m, 1H, ArH), 6.72–6.64 (m, 1H, ArH), 7.32 (s, 5H, ArH). CI-MS (NH_3): 254 (M^+ + 18), 253 (M^+ − 1 + 18, base). Anal. ($C_{13}H_{10}F_2O_2$) C, H.

1,2-Bis(benzyloxy)-3,6-difluorobenzene (7). A stirred mixture of 4.0 g (17 mmol) of **6**, 3.22 g (25.4 mmol) of α-chlorotoluene, and 5.85 g (42.4 mmol) of powdered anhydrous K_2CO_3 in 40 mL of dry acetone was refluxed overnight under an argon atmosphere. The mixture was cooled to room temperature, and sufficient water was added to dissolve the K_2CO_3. The solution was extracted with ether, and the ether extract was washed with water and brine and dried over Na_2SO_4. After concentration under vacuum, flash chromatography (silica gel, 10% methylene chloride–petroleum ether) gave as the second fraction 4.88 g (88%) of **7** as a clear liquid. ^{1}H NMR ($CDCl_3$): δ 5.05 (s, 4H, ArCH_2), 6.73–6.68 (t, 2H, ArH, $J_{H-F}ortho$ = 7.4, $J_{H-F}meta$ = 7.4), 7.38–7.27 (m, 10H, ArH). CI-MS (NH_3): 344 (M^+ + 18). Anal. ($C_{20}H_{16}F_2O_2$) C, H.

3,4-Bis(benzyloxy)-2,5-difluorobenzaldehyde (8). To a stirred solution of 2.0 g (6.1 mmol) of **7** in 60 mL of anhydrous tetrahydrofuran, cooled −75 °C, was added dropwise 4.2 mL (6.8 mmol) of 1.6 M n-butyllithium in hexane at a rate to maintain the temperature below −65 °C. The solution was stirred at −75 °C for 1 h. Gas chromatographic analysis indicated the reaction to be complete at this time. Anhydrous dimethylformamide (0.52 mL, 6.75 mmol) was added, and stirring was continued for 15 min at −75 °C. The dry ice–acetone bath was removed, and the solution was stirred for an additional 1 h. Water was added, and the solution was extracted with ether. The ether extract was washed with water and brine and dried over Na_2SO_4. After concentration under vacuum, flash chromatography (silica gel, 10% ether–petroleum ether) gave as the sole fraction and DNP-positive band a white solid which was recrystallized from ether–petroleum ether to afford 1.82 g (84%) of **8** as a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 5.05 (s, 2H ArCH_2), 5.19 (s, 2H, ArCH_2), 7.32–7.05 (m, 11H, ArH), 10.13 (s, 1H, CHO). CI-MS (NH_3): 372 (M^+ + 18), 355 (M^+ + 1), 108 (M − 246, base). Anal. ($C_{21}H_{16}F_2O_3$) C, H.

3,4-Bis(benzyloxy)-2,5-difluorophenethanolamine (9). To a stirred solution of 2.2 g (6.1 mmol) of **8** in 10 mL of $CHCl_3$ were added under an argon atmosphere 10 mg of ZnI_2 and 1.56 mL (12.3 mmol) of trimethylsilyl cyanide. The solution was stirred overnight at room temperature at which time TLC (silica gel, ethyl acetate) indicated the reaction to be complete. The excess trimethylsilyl cyanide and $CHCl_3$ were removed by heating to 50 °C under vacuum. The residue was dissolved in 15 mL of anhydrous ether and added dropwise to a chilled stirred suspension of 257 mg (6.75 mmol) of lithium aluminum hydride in 25 mL of anhydrous ether under an argon atmosphere. The mixture was refluxed for 3 h and cooled to 0 °C in an ice bath, and the excess hydride was decomposed by the method of Fieser.[17] The suspension of salts was stirred for 15 min, filtered, and washed three times with hot ethyl acetate. Concentration of the extracts under vacuum gave a white solid which was recrystallized from ethyl acetate–petroleum ether to afford 1.2 g (51%) of **9** as a white solid, mp 125–6 °C. ^{1}H NMR ($CDCl_3$): δ 2.66–2.60 (m, 1H, CHN), 2.99–2.94 (m, 1H, CHN), 4.80–4.77 (m, 1H, CHOH), 5.02 (s, 2H, ArCH_2), 5.04 (s, 2H, ArCH_2), 6.97–6.91 (m, 1H, ArH),

7.37–7.22 (m, 10H, Ar*H*). CI-MS (NH_3): 386 ($M^+ + 1$), 368 ($M^+ + 1 - 18$, base). Anal. ($C_{22}H_{25}F_2NO_3$) C, H, N.

2,5-Difluoronorepinephrine Oxalate (3·Oxalate). A mixture of 100 mg (0.259 mmol) of **9**, 18 mg (0.142 mmol) of oxalic acid dihydrate, and 50 mg of 10% Pd/C in 30 mL of methanol was hydrogenated at 40 psi for 6 h. After removal of the catalyst by filtration under an argon stream, the solvent was removed under vacuum and the residue was crystallized from methanol–ether to give 47.9 mg (74%) of 2,5-difluoronorepinephrine oxalate (3·oxalate) as a white solid. ^1H NMR ($CDCl_3$): δ 3.33–3.18 (m, 2H, CH_2N), 5.19–5.15 (m, 1H, C*H*OH), 6.84–6.78 (q, 1H, Ar*H*, $J_{H\text{-}F}ortho = 11.1$, $J_{H\text{-}F}meta = 6.3$). CI-MS (NH_3): 206 ($M^+ + 1$), 188 ($M + 1 - 18$, base). Anal. ($C_9H_{10}F_2NO_5$) C, H, N.

***N*-Formyl-3,4-bis(benzyloxy)-2,5-difluorophenethanolamine (10).** A suspension of 400 mg (1.04 mmol) of **9** in 10 mL of ethyl formate was refluxed for 4 h to give a homogeneous solution. TLC (silica gel, ethyl acetate) indicated that the reaction was complete. Ethyl formate was removed under vacuum leaving a pale orange liquid. Flash chromatography (silica gel, ethyl acetate) afforded a clear liquid which crystallized from ethyl acetate–petroleum ether to give 364 mg (85%) of **10** as a white crystalline solid, mp 83–84 °C. ^1H NMR ($CDCl_3$): δ 3.49–3.37 (m, 1H, C*H*N), 3.74–3.67 (m, 1H, C*H*N), 5.07 (s, 1H, C*H*OH), 5.10 (s, 2H, ArCH_2), 5.12 (s, 2H, ArCH_2), 5.80 (s, 1H, N*H*), 7.04–6.98 (q, 1H, Ar*H*, $J_{H\text{-}F}ortho = 10.9$, $J_{H\text{-}F}meta = 6.4$), 7.41–7.34 (m, 10H, Ar*H*), 8.16 (s, 1H, NC*H*O). CI-MS (NH_3): 431 ($M^+ + 18$), 413 (M^+), 396 ($M^+ + 1 - 18$, base). Anal. ($C_{23}H_{21}F_2NO_4$) C, H, N.

***N*-Methyl-3,4-bis(benzyloxy)-2,5-difluorophenethanolamine (11).** A solution of 320 mg (0.775 mmol) of **10** in 10 mL of anhydrous tetrahydrofuran was added dropwise to a cold, stirred suspension of 147 mg (3.87 mmol) of lithium aluminum hydride in 40 mL of tetrahydrofuran. The mixture was refluxed for 4 h and cooled in an ice bath, and the excess hydride was decomposed by the method of Fieser.[21] The suspension of salts was filtered and washed three times with ethyl acetate. The filtrate was dried over Na_2SO_4 and concentrated under vacuum to give a white solid residue which was crystallized from ethyl acetate–petroleum ether to give 159 mg (51%) of **11** as a white crystalline compound, mp 79–80 °C. ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, NCH_3), 2.64–2.57 (m, 1H, C*H*N), 2.89–2.84 (m, 1H, C*H*N), 4.96–4.92 (m, 1H, C*H*OH), 5.09 (s, 2H, ArCH_2), 5.10 (s, 2H, ArCH_2), 7.06–7.00 (q, 1H, Ar*H*, $J_{H\text{-}F}ortho = 11.3$, $J_{H\text{-}F}meta = 6.4$), 7.44–7.33 (m, 10H, Ar*H*). CI-MS (NH_3): 400 ($M^+ + 1$, base), 382 ($M^+ + 1 - 18$). Anal. ($C_{23}H_{23}F_2NO_3$) C, H, N.

2,5-Difluoroepinephrine Oxalate (4·Oxalate). A mixture of 100 mg (0.250 mmol) of **11**, 17.5 mg (0.138 mmol) of oxalic acid dihydrate, and 50 mg of 10% Pd/C in 30 mL of methanol was hydrogenated at 40 psi for 7 h. Filtration of the catalyst under an argon stream, removal of the solvent under vacuum, and crystallization of the residue from methanol–ether gave 25.5 mg (39%) of 2,5-difluoroepinephrine oxalate as a white solid. ^1H NMR (D_2O): δ 2.79 (s, 3H, NCH_3), 3.32 (s, 1H, C*H*N), 3.34 (s, 1H, C*H*N), 5.26–5.23 (m, 1H C*H*OH), 6.87–6.81 (q, 1H, Ar*H*, $J_{H\text{-}F}ortho = 11.2$, $J_{H\text{-}F}meta = 6.4$). CI-MS (NH_3): 220 ($M^+ + 1$, base), 202 ($M^+ + 1 - 18$). Anal. ($C_{10}H_{12}F_2NO_5$) C, H, N.

1-(Benzyloxy)-2,4-difluorobenzene (12). A stirred mixture of 10.0 g (76.8 mmol) of 2,4-difluorophenol, 14.6 g (115.3 mmol) of α-chlorotoluene, and 26.5 g (192.2 mmol) of anhydrous K_2CO_3 in 100 mL of acetone was refluxed under a nitrogen atmosphere overnight. The progress of the reaction was monitored by TLC (silica gel, 10% ether–petroleum ether). Upon completion of the reaction, water was added and the mixture stirred until all the K_2CO_3 dissolved. The acetone was removed under vacuum, and the aqueous phase was extracted three times with ether. The combined ether extracts were washed with water and brine and dried over Na_2SO_4. Purification by flash chromatography (silica gel, 10% CH_2Cl_2–petroleum ether) afforded as the second fraction 15.1 g (90%) of **12** as a white crystalline solid, mp 49–50 °C. ^1H NMR ($CDCl_3$): δ 5.07 (s, 2H, ArCH_2), 7.00–6.63 (m, 3H, Ar*H*), 7.45–7.25 (m, 5H, Ar*H*). CI-MS (NH_3): 238 ($M^+ + 18$, base). Anal. ($C_{13}H_{10}F_2O$) C, H, N.

3-(Benzyloxy)-2,6-difluorobenzaldehyde (13). A solution of 15.5 g (0.704 mmol) of **12** in 100 mL of anhydrous tetrahydrofuran was cooled in a dry ice–acetone bath to −75 °C under an argon atmosphere. To this stirred solution was added dropwise 48.4 mL (0.774 mmol) of 1.6 M *n*-butyllithium in hexane while the temperature was maintained below −65 °C. After the reaction had stirred for an additional 30 min at −75 °C, 6.0 mL (77 mmol) of dimethylformamide in 10 mL of anhydrous tetrahydrofuran was added dropwise. The solution was stirred for an additional 15 min at −75 °C, the dry ice–acetone bath was removed, and stirring was continued for 30 min. Completion of the reaction was monitored by TLC (silica gel GF, 10% ether–petroleum ether) and was observed to be complete at this time. Water was added, and the solution was extracted three times with ether. The combined ether extracts were washed with water and brine and dried over Na_2SO_4. Purification by flash chromatography (silica gel, 10% ether–petroleum ether) afforded as the second fraction 12.3 g (71%) of **13** as a white crystalline solid. A sample was recrystallized from ether–petroleum ether for analytical analysis, mp 73–4 °C. ^1H NMR ($CDCl_3$): δ 5.15 (s, 2H, ArCH_2), 6.90–6.83 (dt, 1H, 5-Ar*H*, $J_{H\text{-}H} = 9.5$, $J_{H\text{-}F}ortho = 9.5$, $J_{H\text{-}F}para = 1.8$), 7.22–7.14 (m, 1H, 4-Ar*H*), 7.43–7.34 (m, 5H, Ar*H*), 10.36 (s, 1H, C*H*O). CI-MS (NH_3): 266 ($M^+ + 18$, base), 249 ($M^+ + 1$), 248 (M^+). Anal. ($C_{14}H_{10}F_2O_2$) C, H.

2,6-Difluoro-3-hydroxybenzaldehyde (16) (from 2,4-Difluorophenol). A mixture of 1.3 g (10 mmol) of 2,4-difluorophenol, 2.25 g (15 mmol) of *tert*-butyldimethylsilyl chloride, and 2.04 g (30 mmol) of imidazole in 25 mL of anhydrous DMF was stirred overnight. The mixture was diluted with water and extracted with petroleum ether. The extract was washed with 10% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to give 2.23 g (91%) of **15** as a colorless liquid. ^1H NMR ($CDCl_3$): δ 0.15 [s, 6H, $Si(CH_3)_2$], 0.97 [s, 9H, $SiC(CH_3)_3$], 6.69–6.83 (m, 2H, Ar*H*). CI-MS (NH_3): 245 ($M^+ + 1$). To a stirred solution of 1.95 g (8 mmol) of **16** in 36 mL of anhydrous THF, cooled to −78 °C under an argon atmosphere, was added dropwise 11.5 mL (15 mmol) of 1.3 M *sec*-butyllithium in hexane. The solution was maintained below −65 °C during the addition. A solution of 1.04 mL (15 mmol) of anhydrous DMF in 2.0 mL of THF was then added. The cooling bath was removed, and the solution was stirred for 2.5 h at room temperature. Water was added, and the solution was stirred an additional hour. Ether was added, and the layers were separated. The organic layer was extracted with water and the combined water layers were cooled in an ice bath, acidified with 10% HCl, and extracted with ether. The ether extract was washed with water and brine and dried over Na_2SO_4. There was obtained 215 mg (17%) of **16** as a white solid, mp 125–130 °C. ^1H NMR ($CDCl_3$): δ 6.86–6.93 (dt, 1H, 5-Ar*H*, $J_{HF}ortho = 9.6$, $J_{HF}para = 1.9$), 7.18–7.26 (m, 1H, 4-Ar*H*), 10.31 (s, 1H, C*H*O). CI-MS (NH_3): 292 ($M^+ + 18$), 275 ($M^+ + 1$).

2,6-Difluoro-3-hydroxybenzaldehyde (16) (from 13). A solution of 124 mg of **13** in 80 mL of anhydrous methanol was stirred overnight with 0.2 g of Dowex HCR-% (which had been washed several times to remove water). The solution was filtered, 0.5 mL of triethylamine was added to the filtrate, and the mixture was hydrogenated over 120 mg of 15% Pd–C at 40 psi overnight. Removal of the catalyst and evaporation of the solvent gave 0.14 g of white solid. This solid was treated with 50 mL of 10% HCl, stirred overnight, and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and evaporated. There was obtained 44 mg of **16**, identical in all respects to that obtained above.

3-(Benzyloxy)-2,6-difluorophenethanolamine (17). To a stirred solution of 2.0 g (8.1 mmol) of **13** in 5 mL of $CHCl_3$ under a nitrogen atmosphere was added 2.2 mL (16.2 mmol) of trimethylsilyl cyanide and 10 mg of ZnI_2. The solution was refluxed for 4 h, at which time TLC (silica gel GF, 20% ethyl acetate–petroleum ether) indicated the reaction to be complete. The solvent and unreacted trimethylsilyl cyanide were removed by heating to 50 °C under a vacuum for 1 h. The red oil was dissolved in 5 mL of anhydrous ether and slowly added to a chilled suspension of 607 mg (16.2 mmol) of lithium aluminum hydride in 20 mL of anhydrous ether under a nitrogen atmosphere. The solution was refluxed for 4 h and then allowed to stir overnight at room temperature. The excess lithium aluminum hydride was decomposed according to the method of Fieser.[17] The suspension of salts was stirred for 15 min, filtered, and washed three times with hot ethyl acetate. After drying over Na_2SO_4, removal of solvent under vacuum and trituration of the residue

with ether afforded an amorphous white-orange solid. Recrystallization from ethyl acetate–petroleum ether gave 1.44 g (64%) of **17** as a white solid. ^{1}H NMR ($CDCl_3$): δ 3.04–2.90 (m, 1H, C*H*N), 3.22–3.10 (m, 1H, C*H*N), 5.04–4.94 (m, 1H, C*H*OH), 5.10 (s, 2H, ArCH_2), 6.80–6.69 (m, 1H, Ar*H*), 6.93–6.80 (m, 1H, Ar*H*), 7.50–7.28 (m, 5H, Ar*H*). CI-MS (NH_3): 280 (M^+ + 1, base), 262 (M^+ + 1 − 18). Anal. ($C_{15}H_{16}F_2NO_2$) C, H, N.

***N*-Formyl-3-(benzyloxy)-2,6-difluorophenethanolamine (18).** A solution of 9.06 g (32.4 mmol) of **17** in 20 mL of ethyl formate was refluxed for 4 h at which time TLC (silica gel GF, ethyl acetate) indicated that the reaction had gone to completion. The ethyl formate was removed under vacuum leaving an orange liquid. Flash chromatography (silica gel, ethyl acetate) gave as the first fraction a clear oil which was crystallized from ethyl acetate–petroleum ether to afford 7.74 g (78%) of **18** as a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 3.77–3.72 (m, 2H, CH_2N), 5.09 (s, 2H, ARCH_2), 5.19–5.15 (m, H, C*H*OH), 6.82–6.75 (m, 1H, 5-Ar*H*, J_{H-H} = 9.4, J_{H-F}*ortho* = 9.4, J_{H-F}*para* = 2.0), 6.95–6.87 (m, 1H, 4-Ar*H*, J_{H-H}*ortho* = 9.3, J_{H-F}*meta* = 9.1, J_{H-F}*meta* = 5.2), 7.43–7.33 (m, 5H, Ar*H*), 8.25 (s, H, NC*H*O). CI-MS (NH_3): 325 (M^+ + 18), 324 (M^+ + 17), 308 (M^+ + 1), 307 (M^+), 290 (M^+ + 1 − 18), 289 (M^+ − 17, base).

***N*-Methyl-3-(benzyloxy)-2,6-difluorophenethanolamine Oxalate (19·Oxalate).** A solution of 1.22 g (3.98 mmol) of **18** in 10 mL of anhydrous tetrahydrofuran was added dropwise to a cold, stirred suspension of 604 mg (15.9 mmol) of lithium aluminum hydride in 50 mL of tetrahydrofuran. The mixture was refluxed for 4 h, at which time TLC (silica gel GF, ethyl acetate, ninhydrin) indicated that the reaction had gone to completion. The excess hydride was decomposed by the method of Fieser.[17] The suspension of salts was filtered, and the organic salts were washed with hot ethyl acetate. The combined organic solution was dried over Na_2SO_4 and concentrated under vacuum. Crystallization of the residue from ethanol–ether with the addition of oxalic acid gave 1.15 g (76%) of **19**·oxalate as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H, NCH_3), 3.01–2.84 (m, 1H, C*H*N), 3.16–3.05 (m, 1H, C*H*N), 5.10–4.98 (m, 1H, C*H*OH), 6.93–6.87 (m, 1H, Ar*H*), 5.14 (s, 2H, ArCH_2), 7.03–6.96 (m, 1H, Ar*H*), 7.45–7.36 (m, 5H, Ar*H*). CI-MS (NH_3): 294 (M^+ + 1, base), 276 (M^+ + 1 − 18).

2,6-Difluorophenylephrine Oxalate (2·Oxalate). A mixture of 1.0 g (2.6 mmol) of **19**·oxalate and 100 mg of 10% Pd/C in 50 mL of 95% ethanol was hydrogenated at 40 psi for 8 h. Filtration of the catalyst under an argon stream, concentration of the filtrate, and crystallization of the residue from methanol–ether gave 365 mg (47.9%) of **2**·oxalate as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, NCH_3), 3.54–3.46 (m, 1H, C*H*N), 3.79–3.68 (m, 1H, C*H*N), 5.24–5.21 (m, 1H, C*H*OH), 6.74–6.62 (m, 1H, Ar*H*), 6.83–6.76 (m, 1H, Ar*H*). CI-MS (NH_3): 204 (M^+ + 1, base), 186 (M^+ + 1 − 18). Anal. ($C_{10}H_{12}F_2NO_4$) C, H, N.

2,4-Difluoroanisole.[18] A mixture of 50.0 g (0.384 mol) of 2,4-difluorophenol, 72.7 mL (0.768 mol) of dimethyl sulfate, and 106 g (0.768 mol) of powdered anhydrous K_2CO_3 in 1 L of dry acetone was stirred with a mechanical stirrer and refluxed for 2 d under a N_2 atmosphere, at which time TLC (10% ether–petroleum ether) indicated the reaction to be complete. After cooling to room temperature, the mixture was diluted with water, stirred until the K_2CO_3 dissolved, and extracted three times with ether. The combined ether extracts were washed with water and stirred over 15% NH_4OH for 1 h. Separation of the layers, followed by washing the ether layer three times with water and drying over Na_2SO_4, gave after removal of solvent under vacuum a pale yellow liquid. Vacuum distillation afforded 53.1 g (95%) of 2,4-difluoroanisole as a clear liquid. ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H, OCH_3), 6.94–6.76 (m, 3H, Ar*H*). CI-MS (NH_3): 145 (M^+ + 1), 144 (M^+, base). Anal. ($C_7H_6F_2O$) C, H.

2,4-Difluoro-3-(trimethylsilyl)anisole (20). *n*-Butyllithium (2.5 M, 30.5 mL, 76 mmol) in hexane was added dropwise to a stirred solution of 10.0 g (69 mmol) of 2,4-difluoroanisole in 200 mL of anhydrous tetrahydrofuran cooled to −78 °C in a dry ice–acetone bath. The temperature was maintained below −65 °C during the addition, and the solution was stirred for an additional 30 min at −78 °C. Trimethylsilyl chloride (9.7 mL, 76 mmol) in 10 mL of cold, anhydrous tetrahydrofuran was then added dropwise over 5 min. After 15 min at −78 °C the dry ice–acetone bath was removed and the solution stirred for 1 h. At this time, gas chromatographic analysis and TLC (silica gel GF, 10% ether–petroleum ether) indicated the reaction to be complete. Water was added, and the solution was extracted with ether. The ether extract was washed with water and brine and dried over Na_2SO_4. Purification by flash chromatography (silica gel, 5% ether–petroleum ether) afforded as the first fraction 14.1 g (94%) of **20** as a clear liquid. ^{1}H NMR ($CDCl_3$): δ 0.36 (d, 9H, Si(CH_3)$_3$, J_{H-F} = 1.57), 3.84 (s, 3H, OCH_3), 6.75–6.69 (m, H, 5-Ar*H*, J_{H-F}*ortho* = 8.5, J_{H-H}*ortho* = 8.4, J_{H-F}*para* = 1.5), 6.93–6.85 (m, 1H, 6-Ar*H*, J_{H-H}*ortho* = 9.3, J_{H-F}*meta* = 9.2, J_{H-F}*meta* = 5.3). CI-MS (NH_3): 217 (M^+ + 1), 216 (M^+, base). Anal. ($C_{10}H_{14}F_2OSi$) C, H.

3,5-Difluoro-2-methoxy-4-(trimethylsilyl)benzaldehyde (21). *n*-Butyllithium (1.6M, 31.8 mL, 0.051 mol) in hexane was added dropwise to a stirred solution of 10.0 g (0.046 mol) of **20** in 100 mL of anhydrous tetrahydrofuran cooled to −78 °C in a dry ice–acetone bath under an argon atmosphere. During the addition, the temperature was maintained below −65 °C, and then the stirring was continued for 3 h at −78 °C. Anhydrous dimethylformamide (3.9 mL, 0.051 mol) in 4 mL of cold anhydrous tetrahydrofuran was added dropwise over 5 min. After 15 min at −78 °C, the dry ice–acetone bath was removed, and stirring was continued for 1 h. At this time, gas chromatographic analysis indicated the disappearance of starting material and the appearance of two products in a ratio of 71 to 12. Water was added, and the solution was extracted with ether. The ether extract was washed with water and brine and dried over Na_2SO_4. Purification by flash chromatography (silica gel, 10% ether–petroleum ether) gave as the second fraction and first DNP positive band 4.65 g (46%) of **21** as a clear yellow liquid. ^{1}H NMR ($CDCl_3$): δ 0.40 (d, 9H, Si(CH_3)$_3$, J_{H-F} = 1.5 Hz), 4.02 (d, 3H, OCH_3, J_{H-F} = 1.7 Hz), 7.21 (d of d, 1H, Ar*H*, J_{H-F}*ortho* = 7.9, J_{H-F}*para* = 1.6), 10.35–10.34 (d, 1H, C*H*O, J_{H-F} = 3.5 Hz). CI-MS (NH_3): 262 (M^+ + 18), 245 (M^+ + 1, base). Anal. ($C_{11}H_{14}F_2O_2Si$) C, H.

3,5-Difluoro-2-methoxybenzaldehyde (23). To a stirred solution of 5.0 g (22 mmol) of **21** and 1.64 mL (23 mmol) of 2,2,2-trifluoroethanol in 200 mL of anhydrous tetrahydrofuran, cooled to −78 °C in a dry ice–acetone bath under an argon atmosphere, was added dropwise 22.5 mL (0.022 mol) of 1 M tetrabutylammonium fluoride. The solution was stirred for 15 min at −78 °C, the cooling bath was removed, and the solution was stirred for an additional 15 min. Gas chromatographic analysis indicated 65% product formation. Chilled water was added, and the solution was extracted with ether. The ether extract was washed with water and brine and dried over Na_2SO_4. Purification by flash chromatography (silica gel, 10% ether–petroleum ether) gave as the first fraction and DNP-positive band 2.11 g (43%) of **23** as a white crystalline solid. An analytically pure sample was prepared by sublimation. ^{1}H NMR ($CDCl_3$): δ 4.07 (d, 3H, OCH_3, J_{H-F} = 2.3), 7.15–7.08 (m, 1H Ar*H*), 7.34–7.29 (m, 1H, Ar*H*), 10.36 (d, 1H, C*H*O, J_{H-F} = 3.2 Hz). CI-MS (NH_3): 173 (M^+ + 1), 172 (M^+, base). Anal. ($C_8H_6F_2O_2$) C, H.

3,5-Difluoro-2-methoxyphenol (24). A mixture of 4.66 g (27 mmol) of **23** and 6.98 g (55 mmol) of *m*-chloroperbenzoic acid in 100 mL of anhydrous CH_2Cl_2 was refluxed under an argon atmosphere for 4 d. The methylene chloride was removed under vacuum, and the white solid was dissolved in ethyl acetate. This solution was washed two times with 20% $NaHCO_3$ and with brine and dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was dissolved in 25 mL of methanol, cooled in an ice bath, and treated with 15 mL of 10% KOH. After the mixture had stirred for 1 h under an argon atmosphere, the solution was cooled in an ice bath, acidified with 10% HCl, and extracted with ether. The combined ether extracts were washed with $NaHCO_3$ and with brine and then dried over Na_2SO_4. Purification by flash chromatography (silica gel) gave as the first fraction and Pauli positive band 2.78 g (64%) of **24** as a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 3H, OCH_3), 5.90 (s, 1H, O*H*), 6.52–6.36 (m, 2H, Ar*H*). CI-MS (NH_3): 161 (M^+ + 1), 160 (M^+). Anal. ($C_7H_6F_2O_2$) C, H.

1-[(*tert*-Butyldimethylsilyl)oxy]-3,5-difluoro-2-methoxybenzene (27). A mixture of 1.09 g (6.84 mmol) of **24**, 2.16 g (8.21 mmol) of *tert*-butyldimethylsilyl chloride, and 1.16 g (17.1 mmol) of imidazole in 4 mL of anhydrous dimethylformamide was stirred overnight. Gas chromatographic analysis and TLC (silica gel GF, 20% ether–petroleum ether) showed the reaction

to be complete at this time. The mixture was diluted with water and extrcted with petroleum ether. The petroleum ether extract was washed with 10% $NaHCO_3$ and water and dried over Na_2SO_4. Purification by flash chromatography (silica gel, 10% CH_2Cl_2–petroleum ether) gave as the first fraction 1.80 g (96%) of **27** as a clear liquid. ^1H NMR ($CDCl_3$): δ 0.20 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 9H, $SiC(CH_3)_3$), 3.95 (s, 3H, OCH_3), 5.91 (s, 1H, OH), 6.62–6.36 (m, 2H, ArH). CI-MS (NH_3): 292 ($M^+ + 18$), 275 ($M^+ + 1$), 217 ($M^+ - 57$, base).

2,6-Difluoro-4-hydroxy-3-methoxybenzaldehyde (28). To a stirred solution of 500 mg (1.83 mmol) of **27** in 18 mL of anhydrous tetrahydrofuran, cooled to −78 °C in a dry ice–acetone bath under an argon atmosphere, was added dropwise 1.54 mL (2.01 mmol) of 1.3 M *sec*-butyllithium. The solution was maintained below −65 °C during the addition and was stirred for 30 min more at −78 °C. Then 0.155 mL (2.00 mmol) of dimethylformamide in 1 mL of cold tetrahydrofuran was added. The dry ice–acetone bath was removed and the solution stirred for 1 h at room temperature. Gas chromatographic analysis and TLC (silica gel GF, 10% ether–petroleum ether) indicated the reaction to be complete at this time. Water was added, and the solution was stirred an additional 1 h. Ether was added, and the layers were separated. The organic layer was extracted with water. The combined water extracts were cooled in an ice bath, acidified with 10% HCl, and extracted with ether. The ether extract was washed with water and brine and dried over Na_2SO_4. Purification by flash chromatography (silica gel, 10% ether–petroleum ether) gave as the sole fraction 425 mg (98%) of yellow-white crystals. An analytical sample was prepared by sublimation at 70 °C under a water aspirator vacuum to afford 320 mg (74%) of **28** as a white crystalline solid, mp 135–7 °C. ^1H NMR ($CDCl_3$): δ 3.96 (d, 3H, OCH_3, $J_{H\text{-}F}$ = 1.7); 6.51 (dd, 1H, ArH, $J_{HF}ortho$ = 11.3, $J_{H\text{-}F}para$ = 1.9), 10.12 (s, 1H, CHO). CI-MS (NH_3): 206 ($M^+ + 18$), 189 ($M^+ + 1$, base). Anal. ($C_8H_6F_2O_3$) C, H.

2,6-Difluoro-3,4-dihydroxybenzaldehyde (30). To a stirred solution of 313 mg (1.66 mmol) of **28** in 10 mL of anhydrous methylene chloride under nitrogen at −78 °C was added 472 μL (4.99 mmol) of boron tribromide in 5 mL of methylene chloride. The reaction mixture was allowed to warm to room temperature and stirred overnight under nitrogen. After the reaction was cooled in an ice bath, water was added slowly, and the resulting solution was extracted four times with ether. The ether layer was washed with water and with brine and then extracted with aqueous NaOH. The basic aqueous extract was acidified with dilute HCl and then extracted with ether. The ether extract was dried over Na_2SO_4, the solvent was removed, and the residue was sublimed to give 193 mg (73%) of **30** as white crystals. Anal. ($C_7H_4F_2O_3$) C, H, F.

2,6-Difluoroveratraldehyde (31). A mixture of 532 mg (2.38 mmol) of **28**, 0.295 mL (3.11 mmol) of dimethyl sulfate, and 782 mg (5.66 mmol) of potassium carbonate in 60 mL of dry acetone was stirred at room temperature overnight. Gas chromatographic analysis and TLC (silica gel GF, 50% ethyl acetate–petroleum ether) indicated the reaction to be complete at this time. Water was added and the mixture stirred until the K_2CO_3 dissolved. The acetone was removed under vacuum and the aqueous solution exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, twice with 10% NH_4OH, two times with water, and with brine and dried over Na_2SO_4. Purification by flash chromatography (silica gel, 40% ethyl acetate–petroleum ether) gave as the sole fraction 541 mg (95%) of **31** as a pale purple crystalline solid. An analytical sample was prepared by sublimation at 75 °C under water aspirator vacuum to afford a white crystalline solid, mp 79–80 °C. ^1H NMR ($CDCl_3$): δ 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.53 (dd, 1H, ArH, $J_{H\text{-}F}ortho$ = 12.2, $J_{H\text{-}F}para$ = 1.8), 10.21 (s, 1H, CHO). CI-MS (NH_3): 220 ($M^+ + 18$, base), 203 ($M^+ + 1$). Anal. ($C_9H_6F_2O_3$) C, H.

2,6-Difluoro-3,4-dimethoxyphenethanolamine (32). To a stirred solution of 375 mg (1.98 mmol) of **39** in 5 mL of chloroform were added 10 mg of ZnI_2 and 0.792 mL (5.94 mmol) of trimethylsilyl cyanide under an argon atmosphere. The solution was stirred at room temperature overnight. Gas chromatographic analysis and TLC (silica gel GF, 30% ether–petroleum ether) indicated the reaction to be complete at this time. The excess trimethylsilyl cyanide and chloroform were removed by heating to 50 °C under vacuum. The residue was dissolved in 2 mL of ether and added dropwise to a chilled, stirred suspension of 225 mg (5.94 mmol) of lithium aluminum hydride in 18 mL of anhydrous ether under an argon atmosphere. The mixture was refluxed for 2 h and then allowed to stir overnight at room temperature. Thin-layer chromatography (silica gel GF, ethyl acetate) showed no migration and a ninhydrin positive spot at the origin indicating that the reaction was complete. The excess hydride was decomposed by the method of Fieser.[17] The suspension of salts was filtered and washed three times with hot ethyl acetate. After drying over Na_2SO_4, concentration under vacuum and crystallization from hot ether afforded 336 mg (73%) of **32** as a white amorphous solid, mp 115–7 °C. ^1H NMR ($CDCl_3$): δ 3.01–2.97 (m, 1H, CHN), 3.47–3.18 (m, 1H, CHN), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.00–4.96 (m, 1H, CHOH), 6.46 (d, 1H, ArH, $J_{H\text{-}F}ortho$ = 12.1). CI-MS (NH_3): 234 ($M^+ + 1$), 216 ($M^+ + 1 - 18$, base). Anal. ($C_{10}H_{13}F_2NO_3$) C, H, N.

2,6-Difluoronorepinephrine Hydrochloride (1·HCl). To a stirred solution of 50.0 mg (0.215 mmol) of **32** in 4 mL of CH_2Cl_2, cooled to −78 °C in a dry ice–acetone bath under an argon atmosphere, was added 0.811 mL (0.858 mmol) of a BBr_3 solution prepared by a 1:10 dilution of BBr_3 with cold CH_2Cl_2 under an argon atmosphere. After 10 min, the cooling bath was removed. After the solution stirred overnight at room temperature, it was cooled to 0 °C in an ice bath, and 4 mL of water was slowly added. The methylene chloride was removed under vacuum, and the water layer was concentrated to a minimum volume. The residue was applied to a Dowex 50X4-100 strongly acidic cationic exchange resin (10-mL bed volume, prewashed with water), which was eluted with water until the eluant was neutral to pH paper and then stepwise with 20 mL of 0.5 N HCl, 40 mL of 1 N HCl, and 50 mL of 3 N HCl. The 3 N HCl fractions were lyophilized on a speed vac concentrator overnight without heating to give 19.6 mg (38%) of **1**·HCl as a red crystalline solid. ^1H NMR ($CDCl_3$): δ 3.37–3.31 (m, 1H, CHN), 3.88–3.53 (m, 1H, CHN), 5.27–5.22 (m, 1H, CHOH), 6.60 (dd, 1H, ArH, $J_{H\text{-}F}ortho$ = 11.7, $J_{H\text{-}F}para$ = 2.1). CI-MS (NH_3): 206 ($M^+ + 1$), 188 $M^+ + 1 - 18$, base). Exact mass: calcd for $C_8H_7O_2NF_2$ 187.0444851, found 187.0456.

Biological Activity. The affinities of **1**–**4** for α_1-adrenergic receptors were determined through inhibition of binding of [^{3}H]-prazosin or [^{3}H]WB4101 to rat or guinea pig cerebral cortical membranes according to the procedure of Glossman and Hornung[19] and U'Prichard et al.,[20] respectively. Affinities for α_2-adrenergic receptors were determined through inhibition of binding of [^{3}H]clonidine to guinea pig cerebral cortical membranes according to the procedure of U'Prichard et al.[20] The affinities of **1**–**4** for β-adrenergic receptors were determined through inhibition of binding of [^{3}H]dihydroalprenolol to rat cerebral cortex membranes, where the predominant subclass of β-receptors is β_1, and to rat cerebellar membranes where the predominant subclass of β-receptors is β_2, as described by Williams et al.[21] α_1-Adrenergic agonist activity was measured by the stimulation of [^{3}H]phosphoinositol formation in guinea pig synaptoneurosomes according to the procedure of Gusovsky et al.[22] β-Adrenergic agonist activity was determined through stimulation of cyclic AMP production in rat C6 glioma cells.[3] The binding affinities (K_i) and agonist potencies (EC_{50}) are summarized in Tables I–IV.

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