Syntheses of (*R*)- and (*S*)-2- and 6-Fluoronorepinephrine and (*R*)- and (*S*)-2- and 6-Fluoroepinephrine: Effect of Stereochemistry on Fluorine-Induced Adrenergic Selectivities

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Several routes to the enantiomers of fluoronorepinephrines (**1**) and fluoroepinephrines (**2**) were explored. A catalytic enantioselective oxazaborolidine reduction and a chiral (salen)Ti^{IV} catalyzed asymmetric synthesis of silyl cyanohydrins proved efficacious in the key stereo-defining steps of two respective routes. Binding studies of the catecholamines with α_1-, α_2-, β_1-, and β_2-adrenergic receptors were examined. The assays confirmed that fluorine substitution had marked effects on the affinity of (*R*)-norepinephrine and (*R*)-epinephrine for adrenergic receptors, depending on the position of substitution. Thus, a fluoro substituent at the 2-position of (*R*)-norepinephrine and (*R*)-epinephrine reduced activity at both α_1- and α_2-receptors and enhanced activity at β_1- and β_2-receptors, while fluorination at the 6-position reduced activity at the β_1- and β_2-receptors. The effects of fluorine substitution on the *S*-isomers were less predictable.

Introduction

The use of fluorine substitution to modulate biological processes has been a strategy used effectively by medicinal chemists for nearly five decades. A major factor for the effectiveness of fluorine substitution in the design of analogues of biologically important molecules is the steric similarity of the C−F bond and the C−H or C−OH bond that facilitates the acceptance of a fluorinated analogue by a biological recognition site. On the other hand, the high electronegativity of fluorine often imparts altered physicochemical properties to the analogue that influence the consequences of biological recognition. These and other factors have been reviewed in several reports.[1]

Our own work in this area has included an examination of the effects of fluorine substitution on a series of catecholamines and amino acids. We felt at the beginning of this work that the electron-rich catechol system should be quite susceptible to electronic perturbations caused by a fluorine atom on the ring. A particularly rewarding aspect of this research was the discovery of the effects of fluorine substitution on the adrenergic receptor selectivities of adrenergic agonists.[2] For example, racemic 2-fluoronorepinephrine (**1b**, Chart 1) has markedly reduced activity at α-adrenergic receptors, but retains full β-adrenergic activity.[3] In contrast, racemic 6-fluoronorepinephrine (**1d**) has markedly reduced activity at β-adrenergic receptors, but retains full activity at α-adrenergic receptors. Fluorine substitution at the 5-position had relatively little effect on adrenergic activity. These initial results were extended to include fluorinated analogues of epinephrine (**2b**,**d**),[4] as well as the β-selective agonists isoproterenol (**3b**,**d**)[5] and *tert*-butylphenoxypropanolamine (**4b**,**d**),[6] and the α-selective phenylephrine (**5b**−**d**).[7] In all cases, fluorine in the 2-position diminished α-adrenergic activity of compounds possessing α-adrenergic activity and fluorine in the 6-position reduced β-adrenergic activity in compounds possessing β-adrenergic activity. In contrast, fluorine had relatively little effect on the weak adrenergic activity of dopamine (**6b**−**d**).[8,9] The fluorinated norepinephrines and epinephrines have proven to be very useful biological tools. For example, these selective agonists can be produced in vivo by biosynthetic enzymes, are metabolized by catecholamine-processing enzymes, and are efficiently translocated by transport mechanisms.[2] Although there are qualitative differences in behavior with enzymatic and transport processes, striking differences are only observed for adrenergic receptor selectivities.

We have carried out several studies in an attempt to determine the mechanism(s) of the fluorine-induced adrenergic selectivities, but we have not been able to reach concrete mechanistic conclusions. Since no adrenergic receptor selectivity was observed with fluorinated analogues of dopamine **6a**, the stereogenic benzylic hydroxyl group appeared to be an essential factor influencing the observed selectivities of norepinephrine and related agonists. We have considered models depicting hydrogen bonding or repulsion between fluorine and the benzylic hydroxyl group for the origin of the intramolecular interactions resulting in these effects.[2] Altered interactions of the catechol ring with the receptor protein have also been considered.[2a]

Classical pharmacological studies demonstrated that the *R*-isomer of **1** is the more active isomer and that the *S*-isomer has activity comparable to dopamine at adrenergic receptors. If selectivity requires fluorine on

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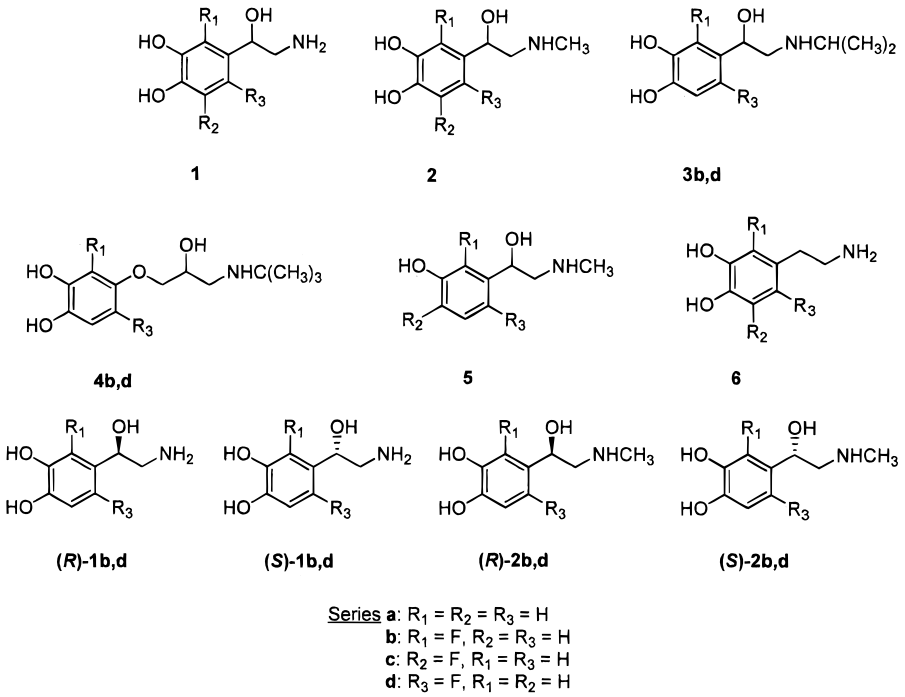
Chart 1



the catechol ring plus the benzylic hydroxyl group in the proper configuration, then the enantiopure *R*-fluoronorepinephrines may exhibit significantly greater selectivity patterns than the racemates. In other words, it seemed possible that the *S*-enantiomers could make major contributions to the binding of (±)-**1b** at the α-adrenergic receptors and (±)-**1d** at the *β*-adrenergic receptors. Therefore, clarification of the role of the stereogenic center could add to our understanding of the effects of fluorine on the selectivity and to assist us in solidifying a mechanistic understanding. To that end, we have prepared the enantiomers of 2- and 6-fluoronorepinephrine [(*R*)- and (*S*)-**1b**,**d**] and 2- and 6-fluoroepinephrine [(*R*)- and (*S*)-**2b**,**d**] and have determined their affinities at α_1-, α_2-, β_1-, β_2-adrenergic receptors.

Results and Discussion

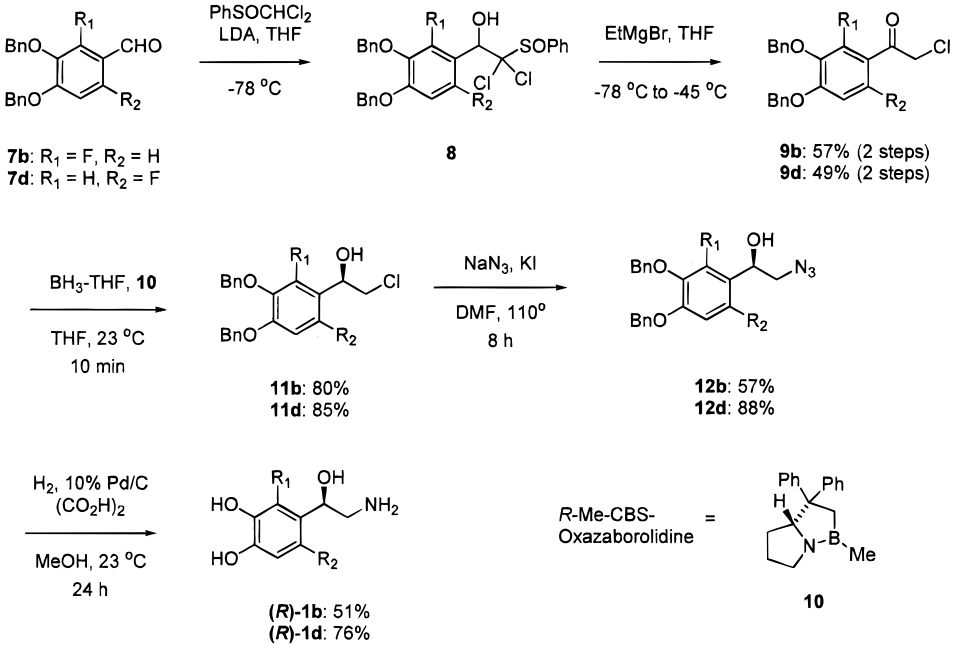
Synthesis of the Enantiomers of Fluorononrepinephrines. At the outset of this work, we recognized certain complications. First, the benzylic position of fluorinated catecholamines is very susceptible to solvolysis. Previous attempts to recrystallize the hydrochloride salt of **1d** from methanol/ether led to extensive methyl ether formation at the benzylic position.[10] Ding, Fowler, and co-workers reported that after separation of the enantiomers of **1d** by chiral HPLC, concentration of an acidic solution of the individual isomers led to extensive racemization.[11] Early attempts to resolve either **1b** or **1d** by recrystallization of diasteromeric salts were also unsuccessful. From this, it became clear that acid treatment as a final synthetic manipulation is not compatible with the high reactivity of the benzylic position. The catecholamines also are rapidly oxidized in basic medium. Another problem we encountered in our early work was the low electrophilicity of the carbonyl group of fluorinated 3,4-dibenzyloxybenzaldehydes (**7b**,**d**) and fluorinated veratraldehydes. For example, attempts to prepare cyanohydrins by addition of HCN under usual conditions failed. In contrast, the ZnI_2-catalyzed addition of trimethylsilyl cyanide was facile and provided ready access to racemic fluorononrepinephrines by side-chain elaboration.[3]

The lability of the benzylic OH group in fluorocatecholamino alcohols, and the low reactivity of precursor benzaldehydes placed certain limitations on synthetic approaches. However, recent advances have provided powerful new procedures for asymmetric syntheses, and we have applied two of these new procedures to the preparation of the *R*- and *S*-enantiomers of amines **1b**,**d** and **2b**,**d**.

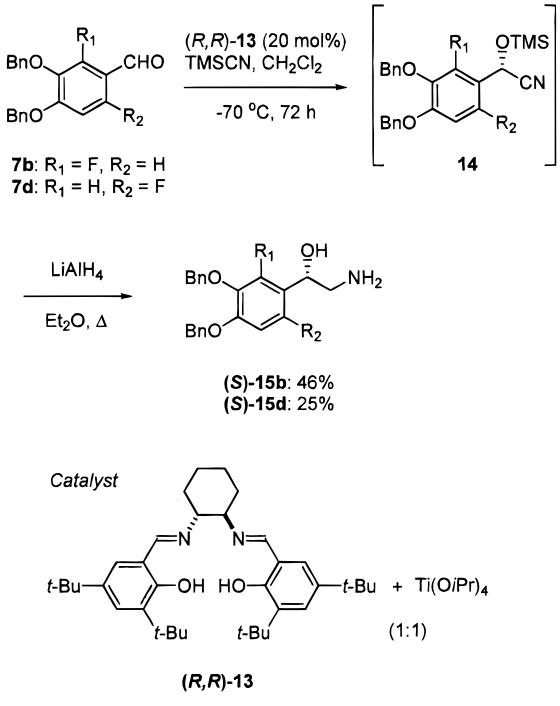
Asymmetric Carbonyl Reduction. The enzyme-like CBS catalysts (e.g., **10**) developed by Corey[12] have been applied to the enantioselective synthesis of arylethanolamines.[13] The remarkably high enantioselectivities obtained with these catalysts provided the basis for one approach to *R*-fluorononrepinephrines. Chloroketones **9b**,**d** were prepared from aldehydes **7b**,**d** in 57% and 49% yields, respectively, by the sequence depicted in Scheme 1. The reaction of ketones **9b**,**d** with BH_3·THF in the presence of CBS catalyst **10** gave *R*-chloro alcohols **11b** (80%) and **11d** (85%). A single recrystallization provided the chloro alcohols enriched to ≥ 95% e.e., as determined by chiral HPLC. After conversion to the azides (**12b**,**d**), catalytic hydrogenation in the presence of oxalic acid gave the oxalates of (*R*)-**1b** (76%) and (*R*)-**1d** (51%). In both cases, the enantiomeric excesses of the final product were identical to those of chloro alcohols **11**.

Asymmetric Cyanohydrin Formation. The key step in our original preparation of racemic fluorinated amines **1b** and **1d** was the ZnI_2-catalyzed addition of trimethylsilyl cyanide to fluorinated bis-benzyloxybenzladehydes **7b** and **7d**. A recent report amply demonstrated that chiral Lewis acid (salen)Ti^{IV} complexes (**13**) catalyze the addition of TMSCN to a variety of aldehydes in good yield and high enantioselectivity.[14]

Scheme 1



Scheme 2



This report prompted us to examine the application of the method to the less electrophilic fluorinated bisbenzyloxybenzaldehydes **7b** and **7d**. The fluorinated aldehydes **7b** and **7d** were allowed to react with TMSCN in the presence of titanium tetraisopropoxide and (*R*,*R*)-**13** at −50 °C. The resultant silyl cyanohydrins were separated from the salen ligand and subjected to reduction with $LiAlH_4$ to produce the corresponding phenethanolamines *S*-**15b** and *S*-**15d** in 22−46% yield (Scheme 2). The seemingly low yield for this transformation was the result of the instability of the silylcyanohydrins to silica gel chromatography. We discovered that a single recrystallization provided the products in >95% e.e. The benzyl protecting groups were removed by hydrogenolysis to give (*S*)-**1b** and (*S*)-**1d** in 68% and 87% yield, respectively. Both of the final products were obtained in >95% e.e. As predicted, the configuration of the product was opposite that of the material produced through CBS-catalyzed carbonyl reduction, as evidenced by the chiral HPLC retention times and the sign of the rotations.

Synthesis of the Enantiomers of Fluoroepinephrines. In the initial examination of enantioselective trimethylsilyl cyanohydrin formation, we chose the (*R*,*R*)-salen catalyst for the production of the antipodes of the amino alcohols **1b**,**d** that were synthesized by the asymmetric carbonyl reduction strategy. Subsequently, this shorter route was used to prepare both the *R*- and the *S*-isomers of the intermediate fluorinated bisbenzyloxyphenethanolamines (**15b**,**d**) for elaboration to both enantiomers of 2- and 6-fluoroepinephrines (**2b**,**d**). Following the procedure used to prepare racemic **2b**,**d**,[4] amines **15b** and **15d** were heated with ethyl formate to provide formamides **16b**,**d**. Reduction of the amides with lithium aluminum hydride gave the *N*-methyl intermediates **17b**,**d**. Hydrogenolysis in the presence of oxalic acid produced the salts of (*R*)-**2b**,**d** and (*S*)-**2b**,**d** (Scheme 3). The enantiomeric excess of each isomer was determined to be >95% ee.

Biological Activity. Affinities for α_1-, α_2-, β_1-, and β_2-adrenergic receptors of dopamines, norepinephrins, and epinephrines were determined by displacement of specific radioligands with rat brain membranes. For further details, see Experimental Section. The results are presented in Table 1.

α_1-Adrenergic Receptor. A 2-fluoro substituent markedly reduced the affinity of (*R*)-norepinephrine (8-fold) and (*R*)-epinephrine (16-fold) for α_1-adrenergic receptors, while having little effect on the affinity of dopamine, (*S*)-**1a**, and (*S*)-**2a** (Table 1). These results suggest that fluorine at the 2-position of the aromatic ring may prevent the benzylic hydroxyl group from proper interaction at the receptor site; i.e., for **1b** and **2b** the *R*-enantiomer now interacts poorly, and like the

Scheme 3

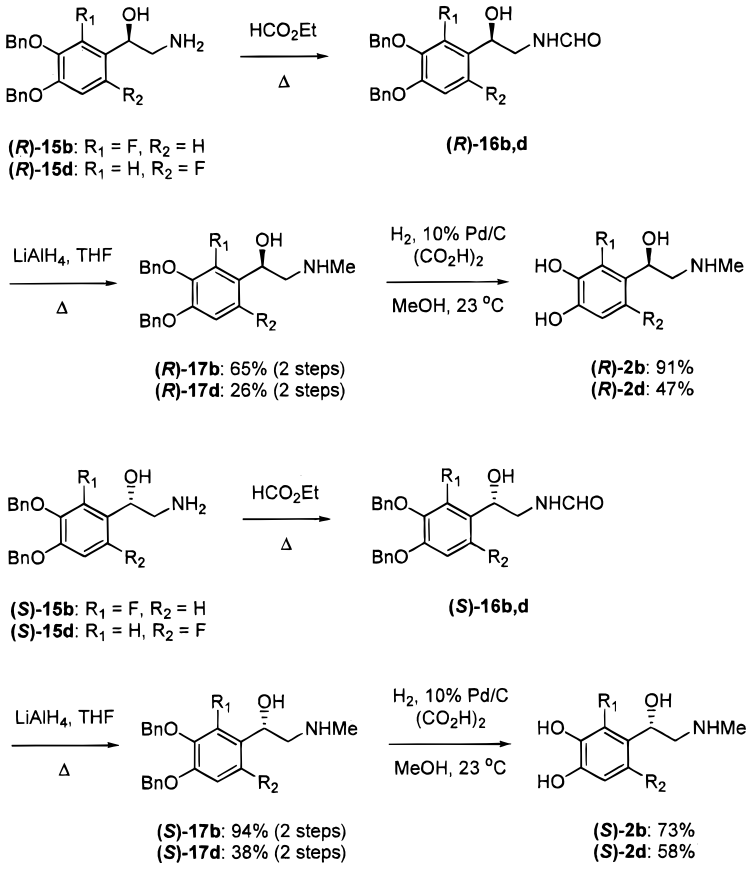


Table 1. Effect of Fluorine Substituents on the Affinity of Dopamines (**6**), Norepinephrines (**1**), and Epinephrines (**2**) at Adrenergic Receptors

	receptor affinity (K_i, μM, or percent inhibition)[a]			
amine	α_1	α_2	β_1	β_2
6a	14 ± 1	0.058 ± 0.010[b]	10 ± 1[b]	50 ± 6
6b	16 ± 2[b]	0.12 ± 0.02[b]	19 ± 5[b]	~70[c]
6d	6 ± 1[b]	0.040 ± 0.010[b]	41 ± 10[b]	~130[c]
(*R*)-**1a**	3.0 ± 0.7	0.020 ± 0.018	1.3 ± 0.2	5 ± 2
(*S*)-**1a**	18% (100 μM)	0.34 ± 0.02	26 ± 6	27 ± 1
(±)-**1a**	6.5 ± 0.9	0.030 ± 0.006	2.7 ± 0.9	11 ± 3
(*R*)-**1b**	~25[c]	0.55 ± 0.03	0.13 ± 0.03	0.067 ± 0.017
(*S*)-**1b**	12% (100 μM)	0.32 ± 0.02	52 ± 9	27 ± 2
(±)-**1b**[d]	~50[c]	0.60 ± 0.02	0.21 ± 0.03	0.14 ± 0.03
(*R*)-**1d**	3.7 ± 0.7	0.020 ± 0.004	24 ± 3	28 ± 3
(*S*)-**1d**	~12[c]	0.36 ± 0.03	~120[c]	~270[c]
(±)-**1d**	20% (100 μM)	0.028 ± 0.003	63 ± 8	58 ± 11
(*R*)-**2a**	1.6 ± 0.2	0.013 ± 0.002	1.1 ± 0.3	0.66 ± 0.02
(*S*)-**2a**	~20[c]	0.045 ± 0.003	13 ± 2	3.7 ± 0.5
(±)-**2a**	2.8 ± 0.3	0.015 ± 0.002	2.1 ± 0.6	1.1 ± 0.2
(*R*)-**2b**	~25[c]	0.067 ± 0.003	0.56 ± 0.03	0.11 ± 0.03
(*S*)-**2b**	~40[c]	0.053 ± 0.001	~150[c]	24 ± 7
(±)-**2b**	~25[c]	0.060 ± 0.001	1.8 ± 0.4	0.26 ± 0.05
(*R*)-**2d**	2.5 ± 0.1	0.013 ± 0.002	~100[c]	38 ± 7
(*S*)-**2d**	~70[c]	0.078 ± 0.001	~400[c]	~90[c]
(±)-**2d**	5.0 ± 0.7	0.014 ± 0.002	~140[c]	50 ± 3

[a] K_I values were derived by the Cheng−Prusoff equation from IC_{50} values ($n = 3$). [b] Values for dopamines from Nie et al.[9] [c] K_I values estimated from extrapolated inhibition curve. [d] The values reported previously[15] for (±)-**1b** were significantly higher than these values. The reason is not apparent.

S-enantiomer, has a low affinity for α_1-adrenergic receptors. Thus, the 2-fluoro substituent is poorly tolerated with respect to interaction of catechol amines with an *R*-configuration at the benzylic hydroxyl position with the α_1-adrenergic receptors.

A 6-fluoro substituent had no effect on the affinity of (*R*)-**1a** and (*R*)-**2a** at α_1-adrenergic receptors and had only slight effects on the affinity of dopamine, (*S*)-**1a**, and (*S*)-**2a**. Thus, a 6-fluoro substituent had little or no effect on the proper interaction of (*R*)-norepinephrine and (*R*)-epinephrine, while it either slightly reduced or slightly enhanced the interaction of dopamine and the *S*-enantiomers. Each of the norepinephrines had affinities similar to that of the corresponding epinephrines for the α_1-adrenergic receptors, which indicated that the methyl group of the epinephrines made little contribution to the binding.

The configuration of the benzylic hydroxyl group was profoundly influential on the affinity of catecholamines at the α_1-adrenergic receptors. For example, (*R*)-**1a** had a multiple-fold higher affinity than (*S*)-**1a**, and (*R*)-**2a** had a 12-fold higher affinity than (*S*)-**2a**. The α_1-adrenergic receptor also exhibited a high degree of enantioselection for the 2-fluoronorepinephrines, but not for the 2-fluoroepinephrines. Only a 2.5-fold selectivity was observed between the enantiomers of **1d**, while the 6-fluoroepinephrines exhibited a 30-fold selectivity; i.e., the 6-fluoro substituent reduced the α_1-adrenergic receptor enantioselectivity for norepinephrines, while it increased the receptor enantioselectivity for epinephrines.

α_2-Adrenergic Receptors. A 2-fluoro substituent reduced the affinity of (*R*)-norepinephrine by 25-fold for the α_2-adrenergic receptors, while it reduced the affinity of (*R*)-epinephrine by only 5-fold. A 2-fluoro substituent had little or no effect on the affinity of dopamine, (*S*)-**1a**, and (*S*)-**2a** for the α_2-adrenergic receptors. As was

the case for α_1-adrenergic receptors, a 2-fluoro substituent might have prevented the proper interaction of the benzylic hydroxyl group of (*R*)-**1** at the receptor site and to a lesser extent for (*R*)-**2**. Thus, the presence of the *N*-methyl to some extent overcame the negative effect of the 2-fluoro substituent on proper interaction of the *R*-enantiomers.

A 6-fluoro substituent had little or no effect on the affinity of dopamine, (*R*)- and (*S*)-norepinephrine, and (*R*)- and (*S*)-epinephrine for α_2-adrenergic receptors. Thus, a 6-fluoro had little or no effect on the proper interaction of (*R*)-**1a** or (*R*)-**2a**.

The configuration of the benzylic hydroxyl group was quite important for enantioselectivity of the α_2-adrenergic receptors for norepinephrines with (*R*)-norepinephrine having a 17-fold higher affinity than (*S*)-norepinephrine. This receptor enantioselectivity was retained in 6-fluoronorepinephrines, where the *R*-enantiomer had an 18-fold higher affinity than the *S*-enantiomer. The configuration of the benzylic hydroxyl group was less important for epinephrine, where the (*R*)-**2a** had only a 4-fold higher affinity than (*S*)-**2a**. Similarly, (*R*)-**2d** had only a 6-fold higher affinity than (*S*)-**2d**. The α_2-adrenergic receptor exhibited little or no enantiosectivity for the 2-fluoronorepinephrines and 2-fluoroepinephrines.

***β*$_1$-Adrenergic Receptor.** A 2-fluoro substituent slightly decreased the affinity of dopamine and (*S*)-norepinephrine for the β_1-adrenergic receptors, while it markedly decreased the affinity for (*S*)-epinephrine. In contrast, a 2-fluoro substituent increased the affinity of (*R*)-**1a** for β_1-adrenergic receptors by 10-fold and increased the affinity of (*R*)-**2a** by 2-fold. Thus, the presence of a 2-fluoro substituent enhanced the proper interaction of the benzylic hydroxyl group at the β_1-adrenergic receptor, particularly in the case of (*R*)-norepinephrine, and to a lesser extent for (*R*)-epinephrine.

A 6-fluoro substituent markedly reduced the affinity of (*R*)-**1a** (17-fold), (*R*)-**2a** (100-fold), and (*S*)-**2a** (34-fold), while slightly reducing the affinity of dopamine (4-fold) and (*S*)-**1a** (2-fold). Thus, the 6-fluoro substituent was poorly tolerated with respect to interaction of catecholamines with β_1-adrenergic receptors. The negative effect of the 6-fluoro substituent is greatest for (*R*)-**2a** and (*S*)-**2a**. Thus, although a negative effect of the 6-fluoro substituent on the proper interaction of the benzylic hydroxyl group appears likely to be the major factor for norepinephrines, the proper interaction of the *N*-methyl of the epinephrines with β_1-adrenergic receptors also seems to be reduced by the presence of a 6-fluoro substituent.

The β_1-adrenergic receptors exhibited a 20-fold preference for (*R*)-norepinephrine over (*S*)-norepinephrine and a 12-fold preference for (*R*)-epinephrine over the *S*-enantiomer. The receptor enantioselectivity for 2-fluoronorepinephrines was increased to over 300-fold, while that of 2-fluoroepinephrines was increased to nearly 300-fold. In contrast, the receptor enantioselectivity exhibited for **1d** and **2d** were only 5- and 4-fold, respectively; i.e., the configuration of the benzylic hydroxyl group became less important when a 6-fluoro substituent was present.

***β*$_2$-Adrenergic Receptors**. A 2-fluoro substituent increased the affinity of (*R*)-norepinephrine for the β_2-adrenergic receptors by a remarkable 60-fold and it increased the affinity of (*R*)-epinephrine by 6-fold. A 2-fluoro substituent had no effect on the affinity of dopamine or (*S*)-**1a**, whereas it reduced the affinity of (*S*)-**2a** for β_2-adrenergic receptors. Both (*R*)-**1b** and (*R*)-**2b** had the same affinity for β_2-adrenergic receptors. This is in marked contrast to the relative activity of (*R*)-norepinephrine and (*R*)-epinephrine at β_2-adrenergic receptors, where the affinity of (*R*)-**2a** is much greater than that of (*R*)-**1a**. Thus, the affinity of (*R*)-norepinephrine for the β_2-receptor was enhanced much more than it was for (*R*)-epinephrine by the presence of a 2-fluoro substituent. The *N*-methyl group of (*R*)-epinephrine appeared to be an important factor in determining the effect of a 2-fluoro substituent, with the 2-fluoro substituent apparently reducing the proper interaction of the *N*-methyl group.

A 6-fluoro substituent greatly reduced the affinity of (*R*)-epinephrine (60-fold) and (*S*)-epinephrine (24-fold) for β_2-adrenergic receptors. The 6-fluoro substituent caused smaller reductions in the affinities of dopamine (2.6-fold), (*R*)-**1a** (6-fold), and (*S*)-**1a** (10-fold). Thus, in norepinephrine and epinephrine the negative effect of the 6-fluoro substituent at β_2-adrenergic receptors appeared relatively unrelated to the configuration of the benzylic hydroxyl group. A 6-fluoro substituent had a much greater negative effect on the affinity of epinephrines than for norepinephrines, suggesting that the proper interaction of the *N*-methyl of the **2a** is reduced by a 6-fluoro substituent.

The β_2-adrenergic receptors exhibited a 5-fold enantioselectivity between (*R*)-norepinephrine and (*S*)-norepinephrine, and a 6-fold preference for (*R*)-epinephrine over the *S*-enantiomer. The receptor enantioselectivity for the 2-fluoronorepinephrines was increased to 400-fold, while for 2-fluoroepinephrines it was increased to 200-fold. The receptor preference for the enantiomers of 6-fluoronorepinephrines was 10-fold, while that for the 6-fluoroepinephrines was only 3-fold. Dopamine had a 10-fold lower affinity than (*R*)-**1a** at β_2-receptors. Thus, the presence and configuration of the benzylic hydroxyl group was important for the binding of norepinephrines and epinephrines at β_2-adrenergic receptors, but the presence of an *N*-methyl group in **2b** and **2d** decreased the enantioselectivity compared to that of the corresponding norepinephrines.

(*R*)-2-Fluoronorepinephrine and (*R*)-2-Fluoroepinephrine: "Selective" Agonists for *β*-Adrenergic Receptors. A 2-fluoro substituent markedly reduced the affinity of (*R*)-norepinephrine and (*R*)-epinephrine for α_1- and α_2-adrenergic receptors and enhanced the affinity for β_1- and β_2-adrenergic receptors. The effect was most dramatic for (*R*)-**1a** (Table 1). Thus, (*R*)-**1b** became a more selective β-adrenergic agonist than (*R*)-**1a**, exhibiting a 4-fold and 8-fold higher affinity for β_1- and β_2-adrenergic receptors, respectively, than for the α_1-adrenergic receptors. However, because of the very high affinity of both (*R*)-**1a** and (*R*)-**2a** for α_2-adrenergic receptors, (*R*)-2-fluoroepinephrine had an 8-fold higher affinity for α_2-receptors than for β_1-receptors and a 2-fold higher affinity for α_2-receptors than for β_2-receptors.

(*R*)-6-Fluoronorepinephrine and (*R*)-6-Fluoronepinephrine: Selective Agonists for α-Adrenergic Receptors. A 6-fluoro substituent markedly reduced the affinity of (*R*)-norepinephrine and (*R*)-epinephrine for β_1- and β_2-adrenergic receptors (Table 1). Thus, these 6-fluoro analogues became more selective for α-adrenergic receptors than the parent (*R*)-**1** and (*R*)-**2**. (*R*)-6-Fluoronorepinephrine (**1d**) had a 7-fold higher affinity for α_1-receptors than for β_1- and β_2-adrenergic receptors, while having a 1200-fold higher affinity for α_2 receptors than for β_1- and β_2-adrenergic receptors. (*R*)-6-Fluoroepinephrine (**2d**) had a 40-fold higher affinity for α_1-receptors than for β_1-adrenergic receptors and a 15-fold higher affinity for α_1-receptors than for β_2-adrenergic receptors. At α_2-adrenergic receptors (*R*)-**1d** had an 8000- and 3000-fold higher affinity than for β_1- and β_2-receptors, respectively.

Summary

Several routes to the enantiomers of fluoronorepinephrines (**1**) and fluoroepinephrines (**2**) were explored. A catalytic enantioselective oxazaborolidine reduction was used to control the formation of the stereogenic center in the preparation of norepinephrines (*R*)-**1b** and (*R*)-**1d**. The chiral (salen)Ti^{IV} catalyzed asymmetric synthesis of silyl cyanohydrins was used in the key stereo-defining steps of the enantiomeric series (*S*)-**1b** and (*S*)-**1d**. The versatility of the asymmetric trimethylsilyl hydrocyanation was demonstrated by the preparation of (*R*)-fluoronorepinephrines **1b** and **1d**. Both enantiomers of fluoroepinephrines **2b** and **2d** were prepared from a common intermediate from the synthesis of the fluoronorepinephrines, namely amino alcohols **15b** and **15d**. Both asymmetric routes produced the products in excellent (≥95%) enantiomeric excess.

These isomers were examined for the effects of stereochemistry and the position of fluorine substitution on the binding affinity at a series of α- and *β*-adrenergic receptors. Our expectation that the modest activity of 2-fluoro racemates at α-receptors would be due mainly or entirely to contributions of the *S*-enantiomer and that the modest activity of 6-fluoro racemates at *β*-receptors[3] would be due mainly or entirely to contributions of the *S*-enantiomer was not realized. Instead, the (*R*)-2-fluoro enantiomers retained low but significant activity at α-receptors, while (*R*)-6-fluoro enantiomer retained low but significant activity at *β*-receptors. The affinities of norepinephrines and epinephrines for adrenergic receptors were markedly affected by 2- and 6-fluoro substituents in a manner that was predictable for the *R*-enantiomers. Thus, a 2-fluoro substituent inhibited proper interaction of the *R*-enantiomers at α_1-adrenergic receptors, while a 6-fluoro substituent had little effect. A 2-fluoro substituent enhanced the proper interaction of the *R*-enantiomers at *β*-adrenergic receptors, particularly for (*R*)-norepinephrine, while a 6-fluoro substituent inhibited the proper interaction. The presence of a *N*-methyl substituent, as in (*R*)-epinephrine, altered the magnitude of the effects of fluoro substituents. Fluorine substituents generally had no effect on the binding affinity of the *S*-enantiomers. In a few cases, however, fluorine markedly reduced the binding affinity and in one case enhanced it. Thus, the presence of a benzylic hydroxyl group even in the less active *S*-enantiomers can influence the effects caused by fluoro substituents.

Experimental Section

General. All reactions were performed under an atmosphere of N_2 in flame or oven (90 °C) dried glassware unless otherwise stated. Anhydrous solvents used for reactions were purchased from Aldrich and used as received. Chromatography refers to the flash chromatographic method of Still[17] and was performed on 230−400 mesh E. Merck silica gel purchased from Bodman. Preparative thin-layer chromatography was performed on 2000 μm silica gel plates from Analtec. ^{1}H (300 MHz) and ^{19}F NMR (282.3 MHz) spectra were obtained on a Varian Gemini 300 spectrometer. Coupling constants *J* are given in hertz (Hz). Chemical shifts are given in ppm (δ) relative to the following internal standards: TMS and HOD for ^{1}H NMR and $CFCl_3$ for ^{19}F NMR unless otherwise noted. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer Polarimeter 241. Electron impact (EI) and chemical ionization (CI) mass spectra were recorded on a Finnigan MAT 312. Chiral HPLC was performed on a HPLC system from GBC using an analytical CHIRALPAK AD column with UV monitoring (λ = 273 nm) unless otherwise noted.

Biological Assay. Affinities for α_1-adrenergic receptors were determined through inhibition of binding of [^{3}H]prazosin to rat cerebral cortical membranes.[9] Affinities for α_2-adrenergic receptors were determined through inhibition of binding at [^{3}H]clonidine to rat cerebral cortical membranes.[9] Affinities for β_1-adrenergic and β_2-adrenergic receptors were determined through inhibition of binding of [^{3}H]dihydroalprenolol to rat cerebral cortical and cerebellar membranes, respectively.[9]

1-Chloro-2-(3,4-dibenzyloxy-6-fluorophenyl)ethan-2-one (9d). A solution of dichloromethyl phenylsulfoxide (587 mg, 2.75 mmol, 1.0 eqiv) in THF (5 mL) was added dropwise to a −78 °C solution of LDA (1.5 M in THF/cyclohexane, 2.2 mL, 3.3 mmol, 1.2 eq.) in THF (10 mL). After 15 min, aldehyde **7d** (1.0 g, 3.0 mmol, 1.1 eq.) was added to the reaction flask, and the reaction mixture was allowed to stir at −78 °C for 1 h before it was quenched with 2.5 N HCl. The mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated to afford crude **8d** as a light yellow, amorphous solid which was used for the next reaction directly.

To a −78 °C solution of crude **8d** in THF (25 mL) under an atmosphere of argon was added ethylmagnesium bromide (3.0 M in Et_2O, 5.0 mL, 15 mmol, 5 eq.). The reaction mixture was allowed to stir for 1 h at −78 °C, then for 1 h at −45 °C, and was then quenched by the addition of 2.5 N HCl. The volatile solvents were removed under reduced pressure, and the resultant aqueous suspension was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography (petroleum ether/ethyl acetate, 95/5) to afford 560 mg (49%) of chloroketone **9d** as colorless needles. Data for **9d**: mp 121−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (d, *J* = 3.9, 2H, $COCH_2$), 5.17 and 5.21 (two s, 4H, two $ArCH_2$), 6.67 (d, *J* = 11.7, 1H, 3- or 6-Ar*H*), 7.31−7.46 (m, 10H, two Ar*H*), 7.54 (d, *J* = 6.9, 1H, 3- or 6-Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −35.47 (d, *J* = 8.2); MS (CI, CH_4) *m*/*z* 402 ($M^+ + NH_4^+$). Anal. ($C_{22}H_{18}ClFO_3$) C, H, F, Cl.

1-Chloro-2-(3,4-dibenzyloxy-2-fluorophenyl)ethan-2-one (9b). The same procedure used for the preparation of ketone **9d** provided ketone **9b** in 57% yield from aldehyde **7b**. Data for **9b**: mp 86−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (d, *J* = 3.0, 2H, $COCH_2$), 5.11 and 5.20 (two s, 4H, two $ArCH_2$), 6.86 (d, *J* = 7.8, 1H, 5- or 6-Ar*H*), 7.31−7.41 (m, 10H, Ar*H*), 7.69 (t, *J* = 8.7, 1H, 5- or 6-Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −48.43 (d, *J* = 8.2); MS (CI, CH_4) *m*/*z* 402 ($M^+ + NH_4^+$). Anal. ($C_{22}H_{18}ClFO_3$) C, H, F, Cl.

(1*R*)-2-Chloro-1-(3,4-dibenzyloxy-6-fluorophenyl)ethanol (11d). A solution of (*R*)-2-Me-CBS (**10**) (1 M in toluene, 26 μL, 0.026 mmol, 0.1 eq.) and BH_3·THF (1 M in THF, 26 μL, 0.026 mmol, 0.1 eq.) in THF (1 mL) was allowed to stir for 10 min at ambient temperature. BH_3·THF (1 M in THF, 130 μL, 0.13 mmol, 0.5 eq.) and a solution of ketone **9d** (66 mg, 0.26 mmol) in THF (1 mL) were added simultaneously, and the reaction mixture was allowed to stir for an additional 10 min. The reaction mixture was cooled to 0 °C and quenched by the addition of MeOH (0.15 mL). After 5 min, the reaction mixture was diluted with 1 N HCl in ethyl ether (5 mL), thereby producing a white precipitate in 30 min. The solvent was removed, and the residue was subjected to preparative thin-layer chromatography to afford 57 mg (85%) of alcohol **11d** as colorless needles. A single recrystallization from EtOAc/hexane provided **11d** in 95% enantiomeric excess. Data for (*R*)-**11d**: mp 83−85 °C; $[\alpha]^{20}_D$ −12.2° ($CHCl_3$, c = 1.02); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (d, J = 3.9, 1H, −O*H*), 3.54 (dd, J = 8.7, 10.5, 1H, 2-H_a), 3.74 (dd, J = 3, 10.8, 1H, 2-H_b), 5.09 (m, 1H, 1-*H*), 5.12 (s, 4H, two ArCH_2), 6.66 (d, J = 11.7, 1H, 3- or 6-Ar*H*), 7.09 (d, J = 6.9, 1H, 3- or 6-Ar*H*), 7.44−7.31 (m, 10H, 2Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −49.26 (d, J = 16.4); MS (CI, CH_4) m/z 404 ($M^+ + NH_4^+$); t_R (−)-**11d**, 46.2 min (97.5%); t_R (+)-**11d**, 50.5 min (2.5%) (hexane/2-propanol, 90/10, 0.5 mL/min). Anal. ($C_{22}H_{20}ClFO_3$) C, H, F, Cl.

(1*R*)-2-Chloro-1-(3,4-dibenzyloxy-2-fluorophenyl)ethanol (11b). The same procedure used for the preparation of alcohol **11d** provided alcohol **11b** in 80% yield from ketone **9b**. Data for **11b**: mp 61−62 °C; $[\alpha]^{20}_D$ −20.7° ($CHCl_3$, c = 7.2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (d, J = 3, 1H, O*H*), 3.60 (dd, J = 8.8, 10.5, 1H, 2-H_a), 3.76 (dd, J = 2.7, 10.5, 1H, 2-H_b), 5.10 and 5.12 (two apparent s, 5H, ArCH_2 and 1-*H*), 6.78 (d, J = 9, 1H, 5- or 6-Ar*H*), 7.14 (t, J = 7.8, 1H, 5- or 6-Ar*H*), 7.30−7.41 (m, 10H, Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.09 (d, J = 8.5); MS (CI, CH_4) m/z 404 ($M^+ + NH_4^+$); t_R (−)-**11b**, 15.3 min (99.5%); t_R (+)-**11b**, 19.0 min (0.5%) (hexane/2-propanol, 90/10, 0.5 mL/min). Anal. ($C_{22}H_{20}ClFO_3$) C, H, F.

(1*R*)-2-Azido-1-(3,4-dibenzyloxy-2-fluorophenyl)ethanol (12d). A mixture of chloro alcohol **11d** (196 mg, 0.51 mmol), 120 mg of NaN_3 (120 mg, 1.9 mmol, 3.7 eq.), and KI (50 mg, 0.3 mmol, 0.6 eq.) in DMF (5 mL) was heated at 110 °C for 8 h under an atmosphere of argon. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate (100 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography (petroleum ether/ethyl acetate, 4/1) to afford 175 mg (88%) of azide **12d** as a light yellow oil. Data for **12d**: $[\alpha]^{20}_D$ −30.7° ($CHCl_3$, c = 1.1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (dd, J = 7.8, 12.6, 1H, 2-H_a), 3.42 (dd, J = 3.9, 12.6, 1H, 2-H_b), 5.07 (m, 1H, 1-*H*), 5.11 (s, 4H, ArCH_2), 6.65 (d, J = 10.8, 1H, 3- or 6-Ar*H*), 7.07 (d, J = 7.8, 1H, 3- or 6-Ar*H*), 7.31−7.44 (m, 10H, 2Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −49.45 (dd, J = 8.2, 12.4); MS (CI, CH_4) m/z 411($M^+ + NH_4^+$). Anal. ($C_{22}H_{20}FN_3O_3$) C, H, F, N.

(1*R*)-2-Azido-1-(3,4-dibenzyloxy-2-fluorophenyl)ethanol (12b). The same procedure used for the preparation of azide **12d** provided azide **12b** in 57% yield from chloro alcohol **11b**. Data for **12b**: mp 65−66 °C; $[\alpha]^{20}_D$ −49.9° ($CHCl_3$, c = 3.5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (d, J = 3.9, 1H, O*H*), 3.39−3.50 (m, 2H, 2-H_a and 2-H_b), 5.10−5.13 (m, 5H, two ArCH_2 and 1-*H*), 6.78 (d, J = 9, 1H, 5- or 6-Ar-*H*), 7.13 (dd, J = 7.8, 8.1, 1H, 5- or 6-Ar*H*), 7.31−7.43 (m, 10H, Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.26 (d, J = 8.5 Hz); MS (CI, CH_4) m/z 411 ($M^+ + NH_4^+$). Anal. ($C_{22}H_{20}FN_3O_3$) C, H, F, N.

General Procedure for the Preparation of Nonracemic Amino Alcohols 15 by Enantioselective Trimethylsilyl Cyanohydrin Preparation/Cyanohydrin Reduction. Ti(O-*i*-Pr)$_4$ (25 μL, 0.013 mmol) was added to a solution of salen (*R*,*R*)-**13** (85 mg, 0.155 mmol) in CH_2Cl_2 (3 mL), and the solution was allowed to stir for 1.5 h at room temperature. The reaction mixture was cooled to −50 °C, and a solution of the aldehyde (1 mmol) and TMSCN (400 mg, 3.6 mmol) in CH_2Cl_2 (3 mL) was added. After 5 days at −50 °C, the catalyst was removed by filtration through a column of silica gel (cyclohexane/ether, 1/1). The cyanohydrin was separated from the remaining salen by chromatography (cyclohexane/ether, 4/1 to 1/1).

The trimethylsilyl cyanohydrin was dissolved in ether (10 mL) and added to a cold (0 °C) suspension of $LiAlH_4$ (90 mg, 2.5 mmol) in ether (10 mL). After the reaction was allowed to stir at room temperature for 3 h, 90 μL of H_2O, 90 μL of NaOH (15%), 270 μL of H_2O, and a small amount of $MgSO_4$ were added. The suspension was filtered, and the filter cake was washed three times with hot ethyl acetate. The solvent was evaporated, and the product was purified by chromatography (CH_2Cl_2/MeOH, 9/1−7/3) and recrystallization (ethyl acetate/hexanes) to provide the (1*S*) isomer of amino alcohol **15**. Substitution of salen (*S*,*S*)-**13** in this procedure provides the (1*R*) isomers.

(1*S*)-2-Amino-1-(3,4-dibenzyloxyphenyl)ethanol [(*S*)-15a]. Using the enantioselective cyanohydrin procedure with salen (*R*,*R*)-**13**, amino alcohol **15a** was obtained as colorless needles in 25% yield from 3,4-dibenzyloxybenzaldehyde. Data for (+)-**15a**: mp 89−92 °C; $[\alpha]_D^{20}$ +16.38° (CH_2Cl_2, c = 1.007); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (br s, 1H, O*H*), 3.00−2.65 (m, 2H, 2-H_2), 4.57 (m, 1H, *1-H*), 5.12 and 5.16 (two s, 4H, two ArCH_2), 7.00−6.75 (m, 3H, 2,5,6 ArH), 7.52−7.18 (m, 10H, two Ph-H); MS (EI, 70 eV) m/z 349 (M^+); t_R (−)-**15a**, 29.2 min (4%); t_R (+)-**15a**, 27.0 min (96%) [Phenominex 3022, hexane/(120/20/1) dichloroethane/MeOH/TFA, 75/25, 1.0 mL/min].

(1*S*)-2-Amino-1-(3,4-dibenzyloxy-6-fluorophenyl)ethanol [(*S*)-15d]. Using the enantioselective cyanohydrin procedure with salen (*R*,*R*)-**13**, amino alcohol **15d** (172 mg, 47%) was obtained from aldehyde **1d** (336 mg, 1 mmol). Data for (+)-**15d**: mp 95−99 °C; $[\alpha]^{20}_D$ +11.36° (CH_2Cl_2, c = 1.04); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (br s, 3H, O*H*, NH_2), 2.78 and 2.97 (two br m, 2H, 2-H_2), 4.85 (m, 1H, 1-*H*), 5.17 and 5.20 (two s, 4H, ArCH_2), 6.64 (d, J = 11.4, 3-Ar*H*), 7.08 (d, J = 7.2, 6-Ar*H*), 7.21−7.44 (m, 10H, 2 Ar*H*); ^{19}F NMR (282 MHz) δ −126.22 (dd, J = 11.4, 7.2); MS (EI, 70 eV) m/z 367 (M^+); t_R (−)-**15d**, 33.7 min (4%); t_R (+)-**15d**, 31.1 min (96%) [Phenominex 3022, hexane/(120/20/1) dichloroethane/MeOH/TFA, 75/25, 1.0 mL/min].

(1*S*)-2-Amino-1-(3,4-dibenzyloxy-2-fluorophenyl)ethanol [(*S*)-15b]. Using the enantioselective cyanohydrin procedure with salen (*R*,*R*)-**13**, amino alcohol **15b** (170 mg, 46%) was obtained from aldehyde **7b** (336 mg, 1 mmol). Data for (+)-**15b**: mp 131 °C; $[\alpha]^{20}_D$ +30.19° (CH_2Cl_2, c = 1.02); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (br s, 3H, O*H*, NH_2), 2.78 and 3.00 (two br m, 2H, 2-H_2), 4.86 (m, 1H, 1-*H*), 5.08 (s, 4H, two ArCH_2), 6.75 (dd, 1H, J = 8.1, 17, 5-Ar*H*), 7.09 (dd, 1H, J = 8.1, 7.9, 6-Ar*H*), 7.43−7.23 (m, 10H, two Ph*H*); ^{19}F NMR (282 MHz) δ −135.65 (d, J = 7.9); MS (EI, 70 eV) m/z 367 (M^+); t_R (−)-**15b**, 37.8 min (0.5%); t_R (+)-**15b**, 40.8 min (99.5%) [Phenominex 3022, hexane/(120/20/1) dichloroethane/MeOH/TFA, 75/25, 1.0 mL/min].

(1*R*)-2-Amino-1-(3,4-dibenzyloxy-6-fluorophenyl)ethanol [(*R*)-15d]. Using the enantioselective cyanohydrin procedure with salen (*S*,*S*)-**13**, amino alcohol **15d** was obtained in 22% yield from aldehyde **7d**. Data for (−)-**15d**: mp 77−80 °C; $[\alpha]^{20}_D$ −9.1° (CH_2Cl_2, c = 0.5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (broad s, NH_2), 2.73 (dd, J = 7.8, 12.6, 1H, 2-H_a), 2.97 (dd, J = 3.9, 12.6, 1H, 2-H_b), 4.85 (dd, J = 3.9, 7.8, 1H, 1-*H*), 5.10 (s, 4H, 2-PhCH_2), 6.63 (d, J = 12.0, 1H, 3-Ar*H*), 7.09 (d, J = 6.9, 1H, 6-Ar*H*), 7.29−7.44 (m, 10H, Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −50.00 (dd, J = 6.2, 10.4); MS (CI, CH_4) m/z 368 ($M^+ + 1$); t_R (−)-**15d**, 33.7 min (4%); t_R (+)-**15d**, 31.1 min (96%) [Phenominex 3022, hexane/(120/20/1) dichloroethane/MeOH/TFA, 75/25, 1.0 mL/min]. HRMS (CI): Calcd for $C_{22}H_{22}FNO_3$, 367.1584; Found, 367.1575.

(1*R*)-2-Amino-1-(3,4-dibenzyloxy-2-fluorophenyl)ethanol [(*R*)-15b]. Using the enantioselective cyanohydrin procedure with salen (*S*,*S*)-**13**, amino alcohol **15b** was obtained as colorless needles in 33% yield from aldehyde **7b**. Data for (−)-**15b**: mp 123−125 °C; $[\alpha]^{20}_D$ −26° (CH_2Cl_2, c = 0.25); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (br s, 2H, NH_2), 2.76 (dd, J = 12.6, 7.8, 1H, 2-H_a), 3.01 (dd, J = 12.6, 3.0, 1H, 2-H_b), 4.86 (dd, J = 6.9, 3.9, 1H, 1-*H*), 5.10 and 5.11 (two s, 4H, two ArCH_2), 6.76

(dd, J = 8.7, 1.8, 1H, 5-Ar*H*), 7.11 (dd, J = 8.7, 7.8, 1H, 6-Ar*H*), 7.30−7.44 (m, 10H, Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.82 (d, J = 8.2); MS (CI, CH_4) m/z 368 ($M^+ + 1$); t_R (−)-**15b**, 37.8 min (99.5%); t_R (+)-**15b**, 40.8 min (0.5%) [Phenominex 3022, hexane/(120/20/1) dichloroethane/MeOH/TFA, 75/25, 1.0 mL/min]. HRMS (CI): Calcd for $C_{22}H_{22}FNO_3$, 367.1584; Found, 367.1586.

(1*R*)-1-(3,4-Dibenzyloxy-6-fluorophenyl)-2-(*N*-methylamino)ethanol [(*R*)-17d]. A solution of (*R*)-**15d** (662 mg, 1.8 mmol) in ethyl formate (20 mL) was heated to reflux under an atmosphere of argon. After 8.5 h, the volatiles were removed in vacuo to afford the formamide **16d** (676 mg, 93%) as a colorless solid. To a cold (0 °C) suspension of $LiAlH_4$ (376 mg) in THF (5 mL) under argon was added dropwise a solution of **16d** (676 mg, 1.7 mmol) in THF (20 mL). The mixture was heated at reflux for 3 h and then cooled to 0 °C and quenched by the addition of H_2O (0.36 mL), 15% NaOH (0.36 mL), and H_2O (1.1 mL). Anhydrous $MgSO_4$ (16 g) was added, and the solution was stirred vigorously for 15 min. The solid was filtered and washed with hot EtOAc (5 × 15 mL). The filtrate was concentrated, and the residue was diluted with CH_2Cl_2 and filtered through a short column of silica gel (CH_2Cl_2/MeOH, 7/3) to afford **17d** (409 mg) as a white solid. Recrystallization from hexanes−EtOAc resulted in a low recovery of mass with low optical purity (e.e. = 14%). However, evaporation of the mother liquor gave 185 mg (26% from **15d**) of (*R*)-**17d** with 92% e.e. Data for (−)-**17d**: mp 95−97 °C; $[\alpha]^{20}_D$ −2.8° (CH_2Cl_2, c = 0.4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, C*H*$_3$), 2.63 (dd, J = 8.7, 11.7, 1H, 2-H_a), 2.81 (dd, J = 3.0, 11.7, 1H, 2-H_b), 4.95 (dd, J = 2.7, 7.8, 1H, 1-*H*), 5.11 and 5.12 (two s, 4H, two ArC*H*$_2$), 6.64 (d, J = 11.7, 1H, 3-Ar*H*), 7.12 (d, J = 7.8 Hz, 1H, 6-Ar*H*), 7.26−7.45 (m, 10H, Ar-*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −50.30 (dd, J = 7.3, 11.3); MS (CI, CH_4) m/z 382 ($M^+ + 1$); t_R (−)-**17d**, 21.5 min (97%); t_R (+)-**17d**, 30.0 min (3%) (hexane/2-propanol, 80/20, 0.5 mL/min). HRMS(CI): Calcd for $C_{23}H_{24}FNO_3$, 381.1740; Found, 381.1732.

(1*R*)-1-(3,4-Dibenzyloxy-2-fluorophenyl)-2-(*N*-methylamino)ethanol [(*R*)-17b]. The same procedure used for the preparation of *N*-methylamine (*R*)-**17d** provided *N*-methylamine (*R*)-**17b** in 65% yield from amine (*R*)-**15b**. Data for (−)-**17b**: mp 100−101 °C; $[\alpha]^{20}_D$ −30.5° (CH_2Cl_2, c = 0.2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H, C*H*$_3$), 2.68 (dd, J = 9.0, 12.0, 1H, 2-H_a), 2.83 (dd, J = 3.9, 12.9, 1H, 2-H_b), 4.97 (dd, J = 3.9, 8.7, 1H, 1-*H*), 5.09 and 5.10 (two s, 4H, two ArC*H*$_2$), 6.75 (dd, J = 8.7, 1.8, 1H, 5-Ar*H*), 7.13 (dd, J = 7.8, 8.7, 1H, 6-Ar*H*), 7.28−7.44 (m, 10H, Ar-*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.93 (d, J = 8.5); MS (CI, CH_4) m/z 382 ($M^+ + 1$); t_R (−)-**17b**, 20.6 min (100%); t_R (+)-**17b**, 23.0 min (0%) (hexane/2-propanol, 80/20, 0.5 mL/min). HRMS (CI) Calcd for $C_{23}H_{24}FNO_3$, 381.1740; Found, 381.1749.

(1*S*)-1-(3,4-Dibenzyloxy-6-fluorophenyl)-2-(*N*-methylamino)ethanol [(*S*)-17d]. The same procedure used for the preparation of *N*-methylamine (*R*)-**17d** provided *N*-methylamine (*S*)-**17d** in 38% yield from amine (*S*)-**15d**. Data for (+)-**17d**: mp 97−99 °C; $[\alpha]^{20}_D$ +3.5° (CH_2Cl_2, c = 0.3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, Me), 2.63 (dd, J = 8.7, 11.7, 1H, 2-H_a), 2.82 (dd, J = 3, 11.7, 1H, 2-H_b), 4.95 (dd, J = 3.9, 9.0, 1H, 1-*H*), 5.11 and 5.12 (two s, 4H, two ArC*H*$_2$), 6.64 (d, J = 11.7, 1H, 3-Ar-*H*), 7.12 (d, J = 6.9, 1H, 6-Ar*H*), 7.30−7.45 (m, 10H, Ar-*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −50.31 (dd, J = 7.3, 11.3); MS (CI, CH_4) m/z ($M^+ + 1$); t_R (−)-**17d**, 21.5 min (1.5%); t_R (+)-**17d**, 28.5 min (98.5%) (hexane/2-propanol, 80/20, 0.5 mL/min). HRMS (CI): Calcd for $C_{23}H_{24}FNO_3$, 381.1740; Found, 381.1742.

(1*S*)-1-(3,4-Dibenzyloxy-2-fluorophenyl)-2-(*N*-methylamino)ethanol [(*S*)-17b]. The same procedure used for the preparation of *N*-methylamine (*R*)-**17d** provided *N*-methylamine (*S*)-**17b** in 94% yield from amine (*S*)-**15b**. Data for (+)-**17b**: mp 99−100 °C; $[\alpha]^{20}_D$ +29.0° (CH_2Cl_2, c = 0.36); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H, C*H*$_3$), 2.69 (dd, J = 8.7, 11.7, 1H, 2-H_a), 2.85 (dd, J = 3.0, 12.6, 1H, 2-H_b), 4.97 (dd, J = 3.0, 8.7, 1H, 1-*H*), 5.09 and 5.10 (two s, 4H, two ArC*H*$_2$), 6.75 (pseudo d, J = 8.7, 1H, 5-Ar*H*), 7.13 (dd, J = 7.8, 8.7, 1H, 6-Ar*H*), 7.30−7.43 (m, 10H, Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.95 (d, J = 8.5); t_R (−)-**17b**, 20.6 min (0%); t_R (+)-**17b**, 23.0 min (100%) (hexane/2-propanol, 80/20, 0.5 mL/min); MS (CI, CH_4) m/z 382 ($M^+ + 1$). HRMS (CI) Calcd for $C_{23}H_{24}FNO_3$, 381.1740; Found, 381.1740.

(1*R*)-2-Amino-1-(3,4-dihydroxy-6-fluorophenyl)ethanol Oxalate Salt: (*R*)-6-Fluoronorepinephrine Oxalate Salt [(*R*)-1d]. A mixture of azide (*R*)-**12d** (414 mg, 1.05 mmol), oxalic acid (45 mg, 0.5 mmol, 0.5 eq.), and 10% Pd−C in methanol (5 mL) was allowed to stir under an atmosphere of H_2 (45 psi) for 24 h. The reaction mixture was filtered under a blanket of N_2, and the solution was concentrated in vacuo. The solid residue was recrystallized from methanol to afford 185 mg (76%) of oxalate (*R*)-**1d** as an off-white solid. Data for (−)-**1d**: mp 165−166 °C (decomp.); $[\alpha]^{20}_D$ −27.5° (MeOH, c = 0.3);[18] ^{1}H NMR (300 MHz, D_2O) δ 3.40−3.22 (m, 2H, 2-H_a and 2-H_b), 5.15 (dd, J = 5.1, 7.8, 1H, 1-*H*), 6.74 (d, J = 11.7, 1H, 2- or 5-Ar*H*), 6.97 (d, J = 6.9, 1H, 2- or 5-Ar*H*); ^{19}F NMR (282 MHz, D_2O, CF_3CO_2H as external standard) δ −51.79 (dd, J = 5 0.9, 12.4); MS (CI, CH_4) m/z 188 ($M^+ + 1$), 205 ($M^+ + NH_4^+$); t_R (−)-**1d**, 18.4 min (99.5%); t_R (+)-**1d**, 23.0 min (0.5%) (CROWNPAK CR (+), 0.02 M $HClO_4$, 0.7 mL/min).

(1*R*)-2-Amino-1-(3,4-dihydroxy-2-fluorophenyl)ethanol Oxalate Salt: (*R*)-2-Fluoronorepinephrine Oxalate Salt [(*R*)-1b]. The same procedure used for the preparation of oxalate (*R*)-**1d** provided oxalate (*R*)-**1b** in 51% yield from azide (*R*)-**12b**. Data for (−)-**1b**: mp 70−73 °C; $[\alpha]^{20}_D$ −35.9° (MeOH, c = 1.9);[18] ^{1}H NMR (300 MHz, D_2O) δ 3.33−3.28 (m, 2H, 1-H_a and 1-H_b), 5.17 (m, 1H, 2-*H*), 6.70−6.91 (m, 2H, 5- and 6-Ar*H*); ^{19}F NMR (282 MHz, D_2O, CF_3CO_2H as external standard) −65.43 (m) ppm; MS (CI, CH_4) m/z 188 ($M^+ + 1$), 205 ($M^+ + NH_4^+$); t_R (−)-**1b**, 10.1 min (99.5%); t_R (+)-**1b**, 12.8 min (0.5%) (CROWNPAK CR (+), 0.02 M $HClO_4$, 0.7 mL/min).

(1*S*)-2-Amino-1-(3,4-dihydroxy-6-fluorophenyl)ethanol Oxalate Salt: (*S*)-6-Fluoronorepinephrine Oxalate Salt [(*S*)-1d]. The same procedure used for the preparation of oxalate (*R*)-**1d** provided oxalate (*S*)-**1d** in 87% yield from amine (*S*)-**15d**. Data for (+)-**1d**: $[\alpha]^{20}_D$ +36.3° (MeOH, c = 0.21);[18] ^{1}H NMR (300 MHz, D_2O) δ 3.23−3.35 (m, 2H, 2-H_a and 2-H_b), 5.15 (dd, J = 5.1, 7.8, 1H, 1-*H*), 6.75 (d, J = 11.7, 1H, 2- or 5-Ar*H*), 6.97 (d, J = 6.7, 1H, 2- or 5-Ar*H*); ^{19}F NMR (282 MHz, D_2O, CF_3CO_2H as external standard) δ −51.67 to −51.73 (m); MS (CI, CH_4) m/z 188 ($M^+ + 1$), 205 ($M + NH_4^+$); t_R (−)-**1d**, 18.4 min (1.5%); t_R (+)-**1d**, 23 min (98.5%) (CROWNPAK CR (+), 0.02 M $HClO_4$, 0.7 mL/min).

(1*S*)-2-Amino-1-(3,4-dihydroxy-2-fluorophenyl)ethanol Oxalate Salt: (*S*)-2-Fluoronorepinephrine Oxalate Salt [(*S*)-1b]. The same procedure used for the preparation of oxalate (*R*)-**1d** provided oxalate (*S*)-**1b** in 68% yield from amine (*S*)-**15b**. Data for (+)-**1b**: $[\alpha]^{20}_D$ +41.8° (MeOH, c = 0.76);[18] ^{1}H NMR (300 MHz, D_2O) δ 3.34−3.24 (m, 2H, 2-H_a and 2-H_b), 5.16 (dd, J = 4.8, 7.8, 1H, 1-*H*), 6.76−6.92 (m, 2H, 5- and 6-Ar*H*); ^{19}F NMR (282 MHz, D_2O, CF_3CO_2H as external standard) −65.38 (m); MS (CI, CH_4) m/z 188 ($M^+ + 1$), 205 ($M + NH_4^+$); t_R (−)-**1b**, 10.1 min (2.5%); t_R (+)-**1b**, 12.8 min (97.5%) (CROWNPAK CR (+), 0.02 M $HClO_4$, 0.7 mL/min).

(1*R*)-1-(3,4-Dihydroxy-6-fluorophenyl)-2-(*N*-methylamino)ethanol Oxalate Salt: (*R*)-6-Fluoroepinephrine Oxalate Salt [(*R*)-2d]. The same procedure used for the preparation of oxalate (*R*)-**1d** provided oxalate (*R*)-**2d** in 47% yield from *N*-methylamine (*R*)-**17d**. Data for (−)-**2d**: $[\alpha]^{20}_D$ −46.7° (MeOH, c = 0.12);[18] ^{1}H NMR (300 MHz, D_2O) δ 2.79 (s, 3H, C*H*$_3$), 3.29−3.39 (m, 2H, 2-H_a and 2-H_b), 5.19 (dd, J = 4.8, 7.8, 1H, 1-*H*), 6.75 (d, J = 10.8, 1H, 5-Ar*H*), 6.96 (d, J = 7.8, 1H, 2-Ar*H*); ^{19}F NMR (282 MHz, D_2O, CF_3CO_2H as external standard) δ −51.63 (dd, J = 7.6, 10.7); t_R (−)-**2d**, 18.1 min (100%); t_R (+)-**2d**, 27.9 min (0%) (hexane/EtOH/TFA/diethylamine, 93/7/0.13/0.08, 1 mL/min); MS (CI, CH_4) m/z 202 ($M^+ + 1$). HRMS (CI): Calcd for $C_9H_{12}FNO_3$, 201.0801; Found, 201.0800.

(1*R*)-1-(3,4-Dihydroxy-2-fluorophenyl)-2-(*N*-methylamino)ethanol Oxalate Salt: (*R*)-2-Fluoroepinephrine Oxalate Salt [(*R*)-2b]. The same procedure used for the preparation of oxalate (*R*)-**1d** provided oxalate (*R*)-**2b** in 91% yield from *N*-methylamine (*R*)-**17b**. Data for (−)-**2b**: $[\alpha]^{20}_D$ −40°

(MeOH, $c = 0.14$);[18] ^{1}H NMR (300 MHz, D_2O) δ 2.79 (s, 3H, CH_3), 3.29−3.42 (m, 2H, 2-H_a and 2-H_b), 5.21 (dd, $J = 3.9, 7.8$, 1H, 1-*H*), 6.95−6.76 (m, 2H, 5-Ar*H* and 6-Ar*H*); ^{19}F NMR (282 MHz, D_2O, CF_3CO_2H as external standard) δ -65.34 (d, $J = 7.6$); t_R (−)-**2b**, 20.9 min (100%); t_R (+)-**2b**, 18.6 min (0%) (hexane/EtOH/TFA/diethylamine, 93/7/0.13/0.08, 1 mL/min); MS (CI, CH_4) *m*/*z* 202 ($M^+ + 1$). HRMS (CI): Calcd for $C_9H_{12}FNO_3$, 201.0801; Found, 201.0797.

(1*S*)-1-(3,4-Dihydroxy-6-fluorophenyl)-2-(*N*-methylamino)ethanol Oxalate Salt: (*S*)-6-Fluoroepinephrine Oxalate Salt [(*S*)-2d]. The same procedure used for the preparation of oxalate (*R*)-**1d** provided oxalate (*S*)-**2d** in 58% yield from *N*-methylamine (*S*)-**17d**. Data for (+)-**2d**: $[\alpha]^{20}_D$ +35° (MeOH, $c = 0.13$);[18] ^{1}H NMR (300 MHz, D_2O) δ 2.79 (s, 3H, C*H*$_3$), 3.28−3.39 (m, 2H, 2-H_a and 2-H_b), 5.19 (dd, $J = 4.8, 7.8$, 1H, 1-*H*), 6.74 (d, $J = 10.8$, 1H, 5-Ar*H*), 6.96 (d, $J = 6.9$, 1H, 2-Ar*H*); ^{19}F NMR (282 MHz, D_2O, CF_3CO_2H as external standard) δ −51.60 (dd, $J = 5.9, 10.4$); t_R (−)-**2d**, 18.1 min (0%); t_R (+)-**2d**, 27.9 min (100%) (hexane/EtOH/TFA/diethylamine, 93/7/0.13/0.08, 1 mL/min); MS (CI, CH_4) *m*/*z* 202 ($M^+ + 1$). HRMS (CI): Calcd for $C_9H_{12}FNO_3$, 201.0801; Found, 201.0795.

(1*S*)-1-(3,4-Dihydroxy-2-fluorophenyl)-2-(*N*-methylamino)ethanol Oxalate Salt: (1*S*)-2-Fluoroepinephrine Oxalate Salt [(*S*)-2b]. The same procedure used for the preparation of oxalate (*R*)-**1d** provided oxalate (*S*)-**2b** in 73% yield from *N*-methylamine (*S*)-**17b**. Data for (+)-**2b**: $[\alpha]^{20}_D$ +43° (MeOH, $c = 0.17$);[18] ^{1}H NMR (300 MHz, D_2O) δ 2.79 (s, 3H, C*H*$_3$), 3.27−3.42 (m, 2H, 2-H_a and 2-H_b), 5.22 (dd, $J = 3.9, 7.8$, 1H, 2-H), 6.76−6.95 (m, 2H, 5-Ar*H* and 6-Ar*H*); ^{19}F NMR (282 MHz, D_2O, CF_3CO_2H as external standard) δ −65.32 (d, $J = 7.6$); t_R (−)-**2b**, 20.9 min (0%); t_R (+)-**2b**, 18.6 min (100%) (hexane/EtOH/TFA/diethylamine, 93/7/0.13/0.08, 1 mL/min); MS (CI, CH_4) *m*/*z* 202 ($M^+ + 1$). HRMS (CI): Calcd for $C_9H_{12}FNO_3$, 201.0801; Found, 201.0793.

Supporting Information Available: Combustion analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Kirk, K. L.; Filler, R. Biological Properties. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, D.C., 1996; pp 1−24. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (c) Kirk, K. L. *Biochemistry of Halogenated Organic Compounds, Biochemistry of the Elements*, Vols. 9A, 9B; Frieden, E., Series Ed.; Plenum: New York, 1991.

(2) (a) Kirk, K. L. Fluorine Substituted Neuroactive Amines. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, D.C., 1991; pp 136−155. (b) Kirk, K. L. Chemistry and Pharmacology of Ring-Fluorinated Catecholamines. *J. Fluorine Chem.* **1995**, *72*, 261−266.

(3) Kirk, K. L.; Cantacuzene, D.; Nimitkitpaisan, Y.; McCulloh, D.; Padgett, W. L.; Daly, J. W.; Creveling, C. R. Synthesis and Biological Properties of 2, 5, and 6-Fluoronorepinephrines. *J. Med. Chem.* **1979**, *22*, 1493−1497.

(4) Adejare, A.; Gusovsky, F.; Creveling, C. R.; Daly, J. W.; Kirk, K. L.: Synthesis and Adrenergic Activities of Ring-Fluorinated Epinephrines, *J. Med. Chem.* **1988**, *31*, 1972−1977.

(5) Kirk, K. L.; Cantancuzene, D.; Collins, B.; Chen, G. T.; Nimit, Y.; Creveling, C. R. Syntheses and Adrenergic Agonist Properties of Ring-Fluorinated Isoproterenols. *J. Med. Chem.* **1982**, *25*, 680−684.

(6) Adejare, A.; Nie, J.-y.; Hebel, D.; Brackett, L. E.; Choi, O.; Gusovsky, F.; Padgett, W. L.; Daly, J. W.; Creveling, C. R.; Kirk, K. L. Effect of Fluorine Substitution on the Adrenergic Properties of 3-(*tert*-Butylamino)-1-(3,4-dihydroxyphenoxy)-2-propanol. *J. Med. Chem.* **1991**, *34*, 1063−1068.

(7) Kirk, K. L.; Olubajo, O.; Buchhold, K.; Lewandowski, G. A.; Gusovsky, F.; McCulloh, D.; Daly, J. W.; Creveling, C. R. Synthesis and Adrenergic Activity of Ring-Fluorinated Phenylephrines. *J. Med. Chem.* **1986**, *29*, 1982−1988.

(8) Nimit, Y.; Cantacuzene, D.; Kirk, K. L.; Creveling, C. R.; Daly, J. W. The Binding of Fluorocatecholamines to Adrenergic and Dopaminergic Receptors in Rat Brain Membranes. *Life Sci.* **1980**, *27*, 1577−1585.

(9) Nie, J.-Y.; Shi, D.; Daly, J. W.; Kirk, K. L. Synthesis of Fluorodopamines: Effect of Aryl Fluoro Substituents on Affinities for Adrenergic and Dopaminergic Receptors. *Med. Chem. Res.* **1996**, *6*, 318−331.

(10) Cantacuzene, D.; Kirk, K. L. Unpublished results.

(11) Ding, Y. S.; Fowler, J. S.; Gatley, S. J.; Dewey, S. L.; Wolf, A. P. Synthesis of High Specific Activity (+) and (−)-6-[^{18}F]Fluoronorepinephrine via the Nucleophilic Aromatic Substitution Reaction. *J. Med. Chem.* **1991**, *34*, 767−771.

(12) Corey, E. J.; Bakshi, R. K.; Shibata, S. Highly Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.

(13) Corey, E. J.; Link, J. O. A Catalytic Enantioselective Synthesis of Denopamine, a Useful Drug for Congestive Heart Failure. *J. Org. Chem.* **1991**, *56*, 442−444.

(14) Belekon', Y.; Flego, M.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Chiral (Salen)Ti^{IV} Complexes. *J. Chem. Soc., Perkin Trans. I* **1997**, 1293−1295.

(15) Chen, B.-H.; Daly, J. W.; Kirk, K. L. Investigation of the Relationship Between Phenol Ionization and Affinity of Norepinephrine for Adrenergic Receptors using Ring-fluorinated Analogues. *Med. Chem. Res.* **1993**, *3*, 589−599.

(16) Lands, A. M.; Arnold, A.; McAuliff, J. P.; Ludnena, F. P.; Brown, T. G.; Differentiation of Receptor Systems Activated by Sympathomimetic Amines. *Nature* **1967**, *215*, 597−598.

(17) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(18) In our previous work, racemic 2- and 6-fluoronorepinephrines and epinephrines were isolated consistently as the hemi-oxalates. In this study, we used NMR, HRMS, and chiral HPLC to confirm identity and purity, including enantio-purity, of the target compounds, initially assuming that the hemi-oxalates again would be obtained. However, comparison of apparent specific rotations of *R*- and *S*- **1b, 1d**, and **2d** made it clear that *R*-**1b**, *R*-**1d**, and *S*-**2d** were present as the acid oxalates.

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