

FIGURE 1

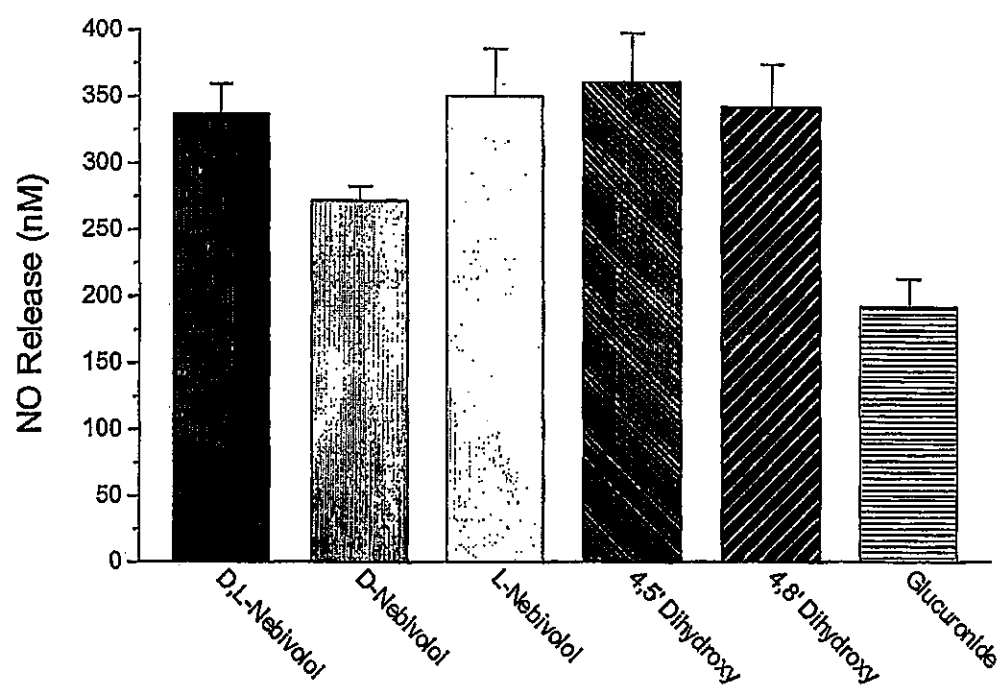


FIGURE 2

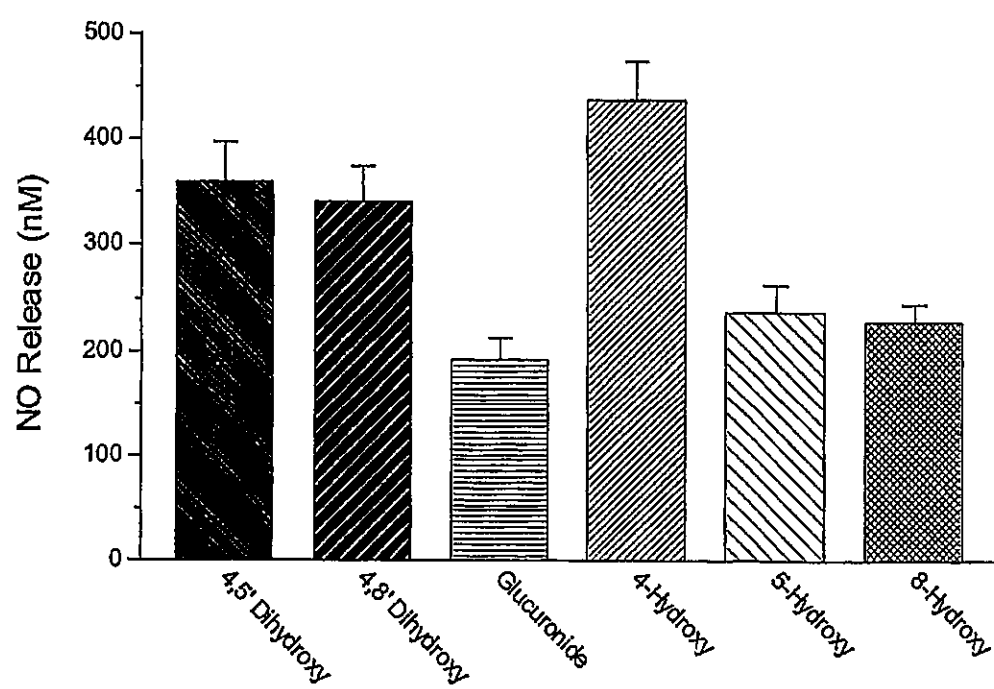


FIGURE 3

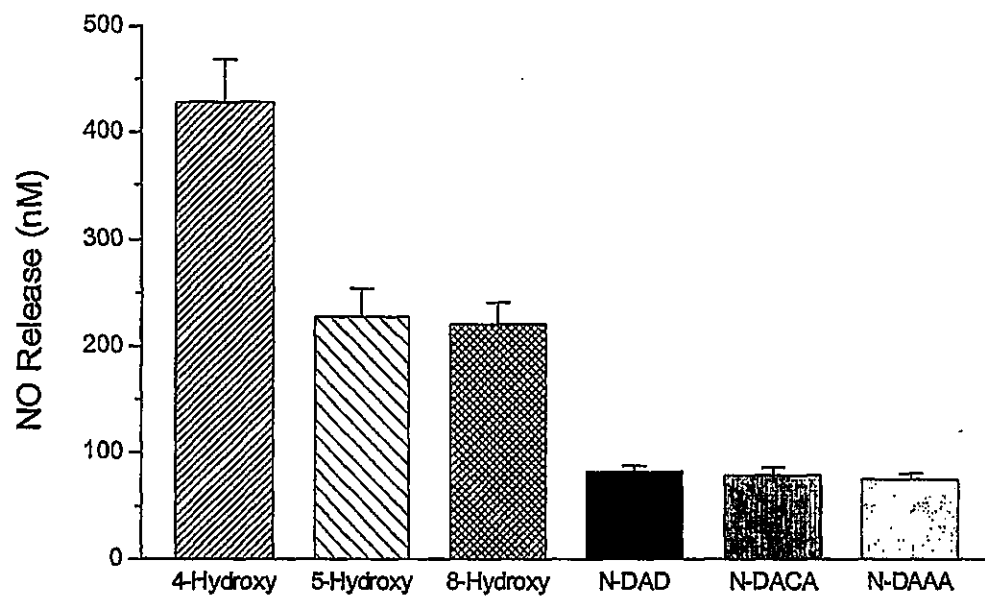


FIGURE 4

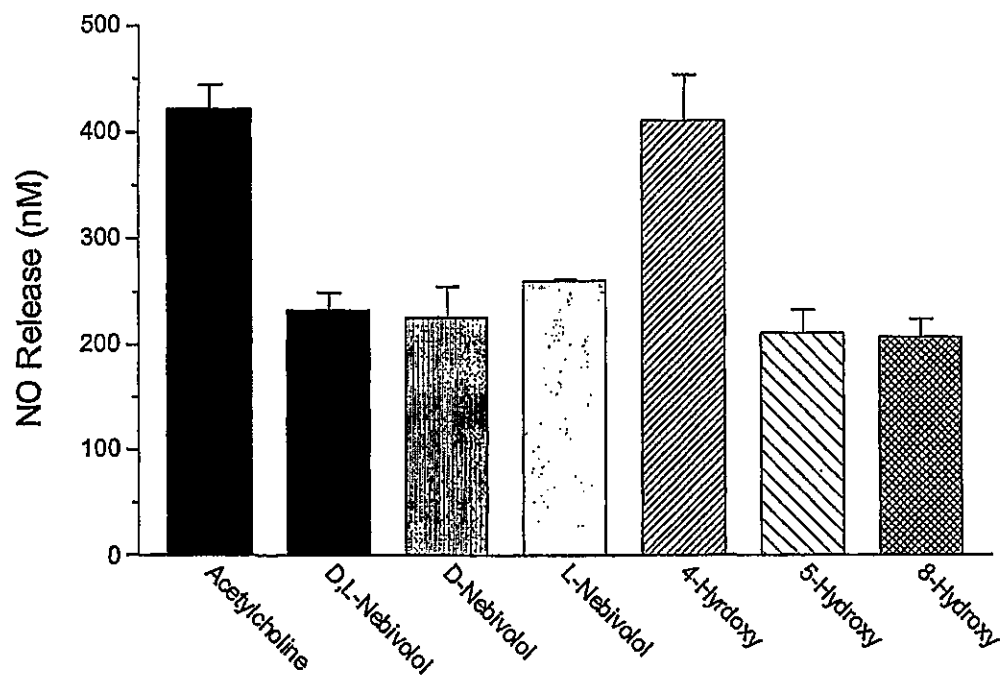


FIGURE 5

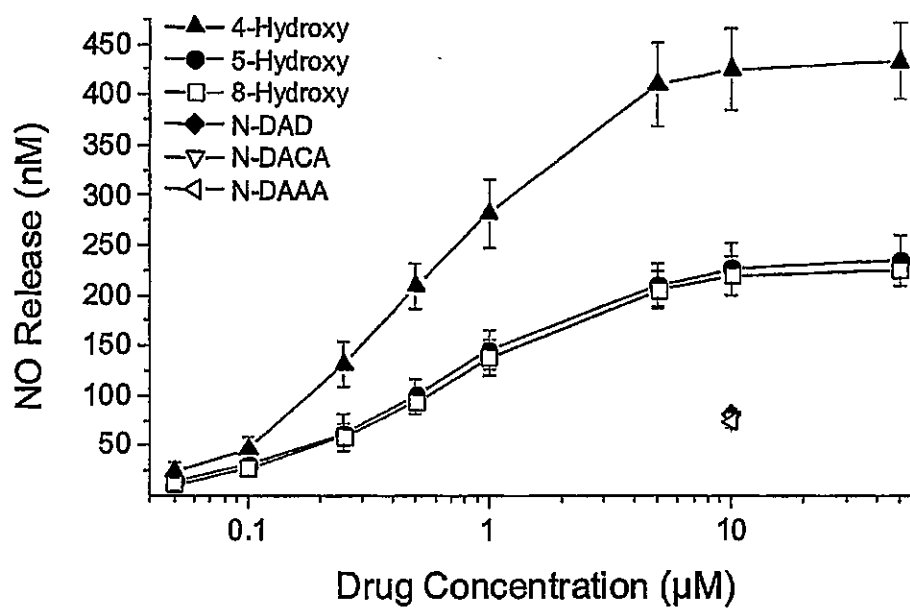


FIGURE 6

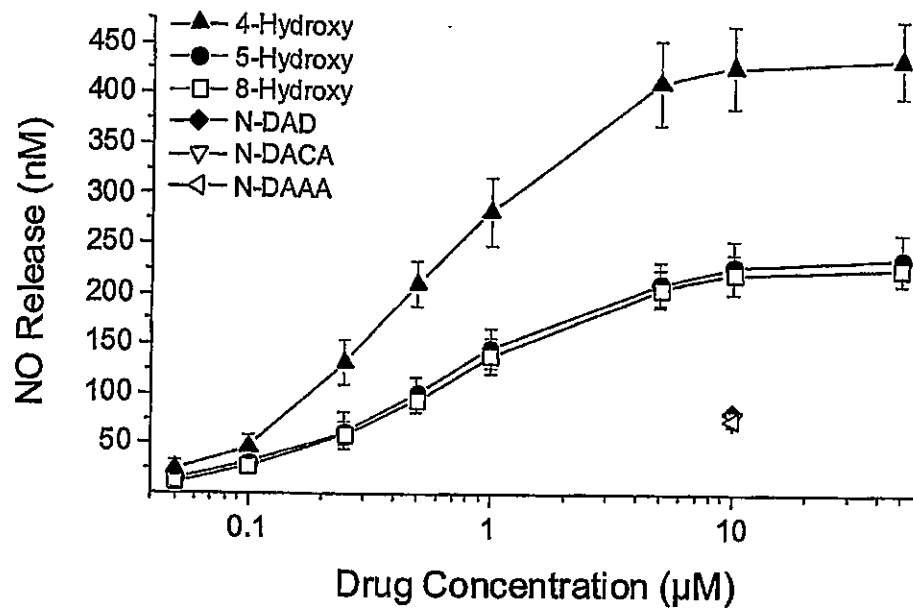
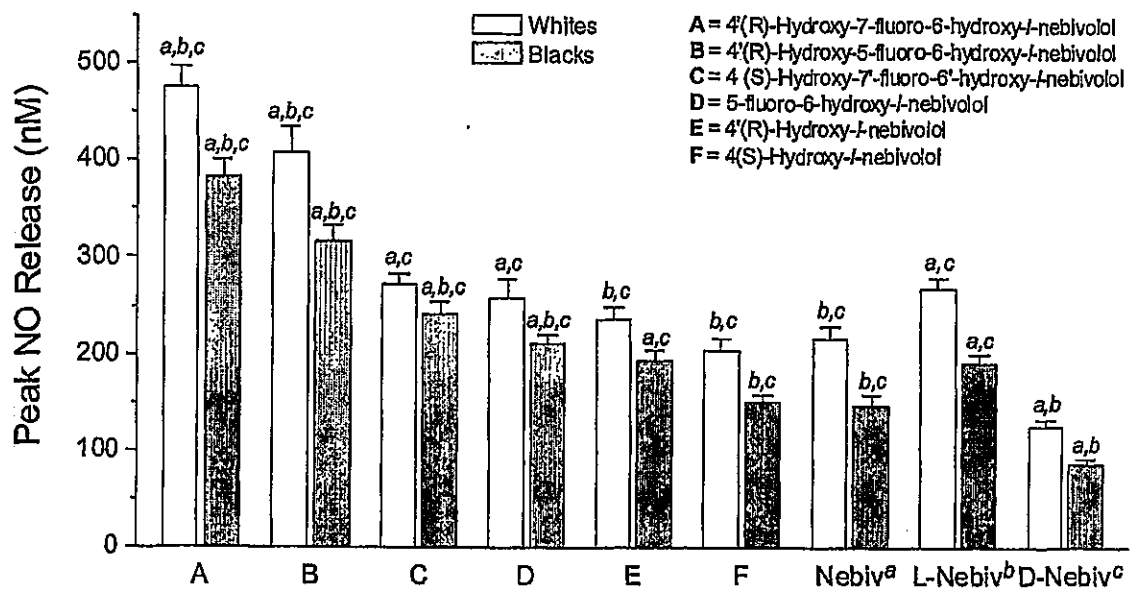


FIGURE 7



^a $p < 0.001$ versus cognate Nebiv treatment; ^b $p < 0.05$ versus cognate L-Nebiv treatment;

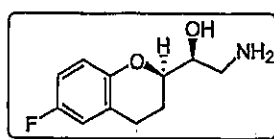
^c $p < 0.001$ versus cognate D-Nebiv treatment (p values from ANOVA Student-Newman-Keuls Multiple Comparisons Test)

FIGURE 8

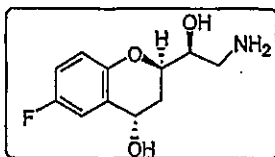
TARGET CHIRAL METABOLITES – (R,S,S,S) SERIES – 10 COMPOUNDS

Sample ID	Structure	Sample ID	Structure
4-(S)-OH- (R,S,S,S)- NEB (1)		4'-(R)-OH- (R,S,S,S)- NEB (6)	
5'-F-6'-OH- (R,S,S,S)- NEB (2)		5-F-6-OH- (R,S,S,S)- NEB (7)	
7'-F-6'-OH- (R,S,S,S)- NEB (3)		7-F-6-OH- (R,S,S,S)- NEB (8)	
4-(S)-OH- 5'-F-6'-OH- (R,S,S,S)- NEB (4)		4'-(R)-OH- 5-F-6-OH- (R,S,S,S)- NEB (9)	
4-(S)-OH- 7'-F-6'-OH- (R,S,S,S)- NEB (5)		4'-(R)-OH- 7-F-6-OH- (R,S,S,S)- NEB (10)	

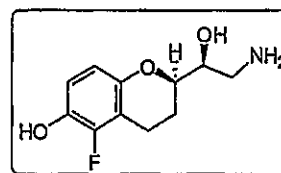
Eight segments as shown below are prepared for the synthesis of target molecules 1-10.



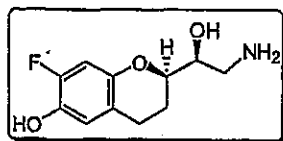
Amine 1



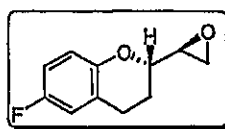
Amine 2



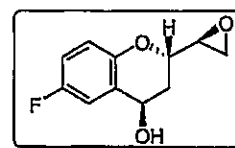
Amine 3



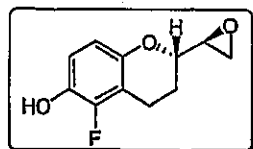
Amine 4



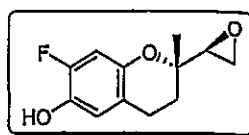
Epoxide 1



Epoxide 2



Epoxide 3



Epoxide 4

FIGURE 9

The Synthesis of Amine 1

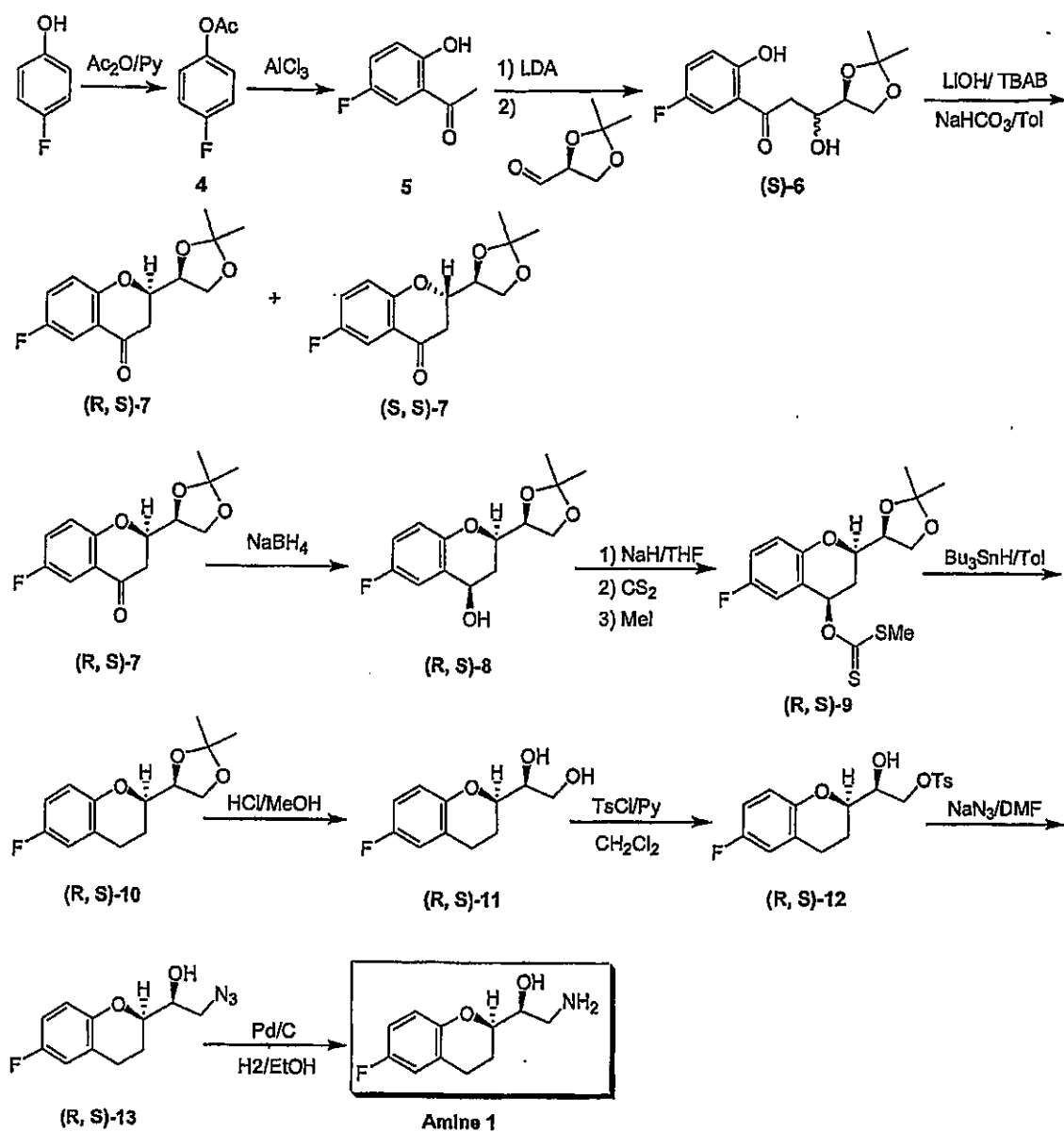


FIGURE 10

The Synthesis of Epoxide 1

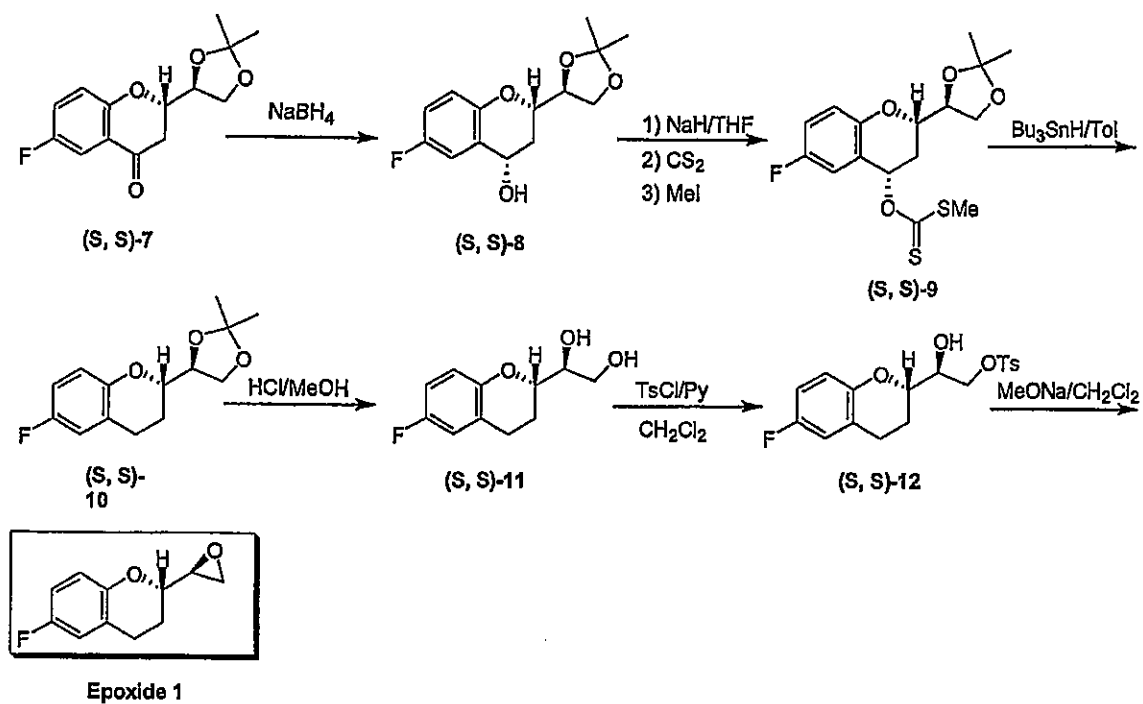


FIGURE 11

The Synthesis of Amine 2, part 1

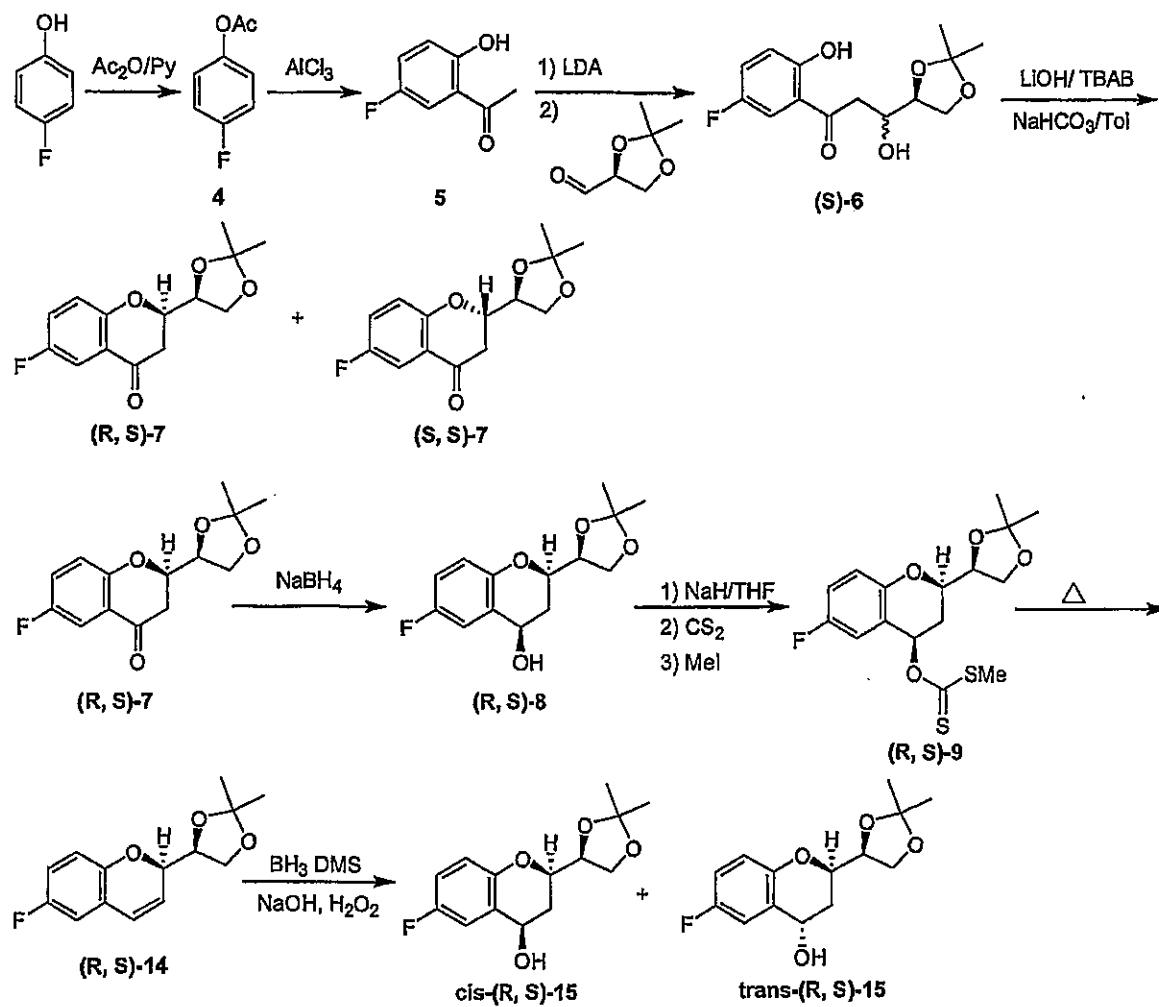


FIGURE 12

The Synthesis of Amine 2, part 2

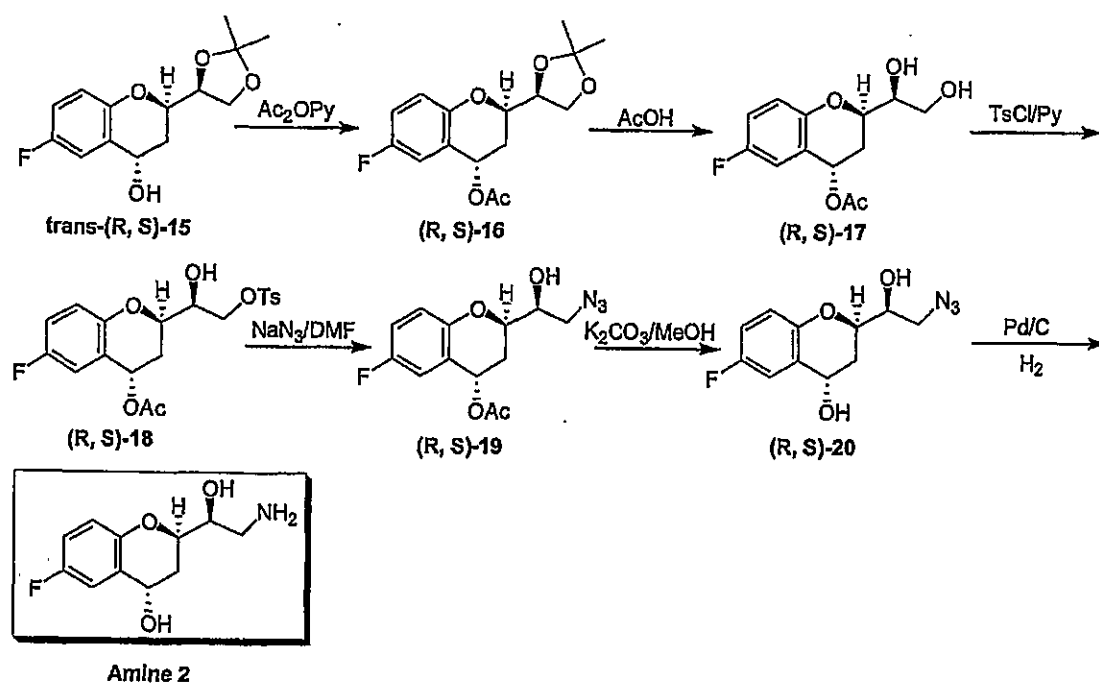
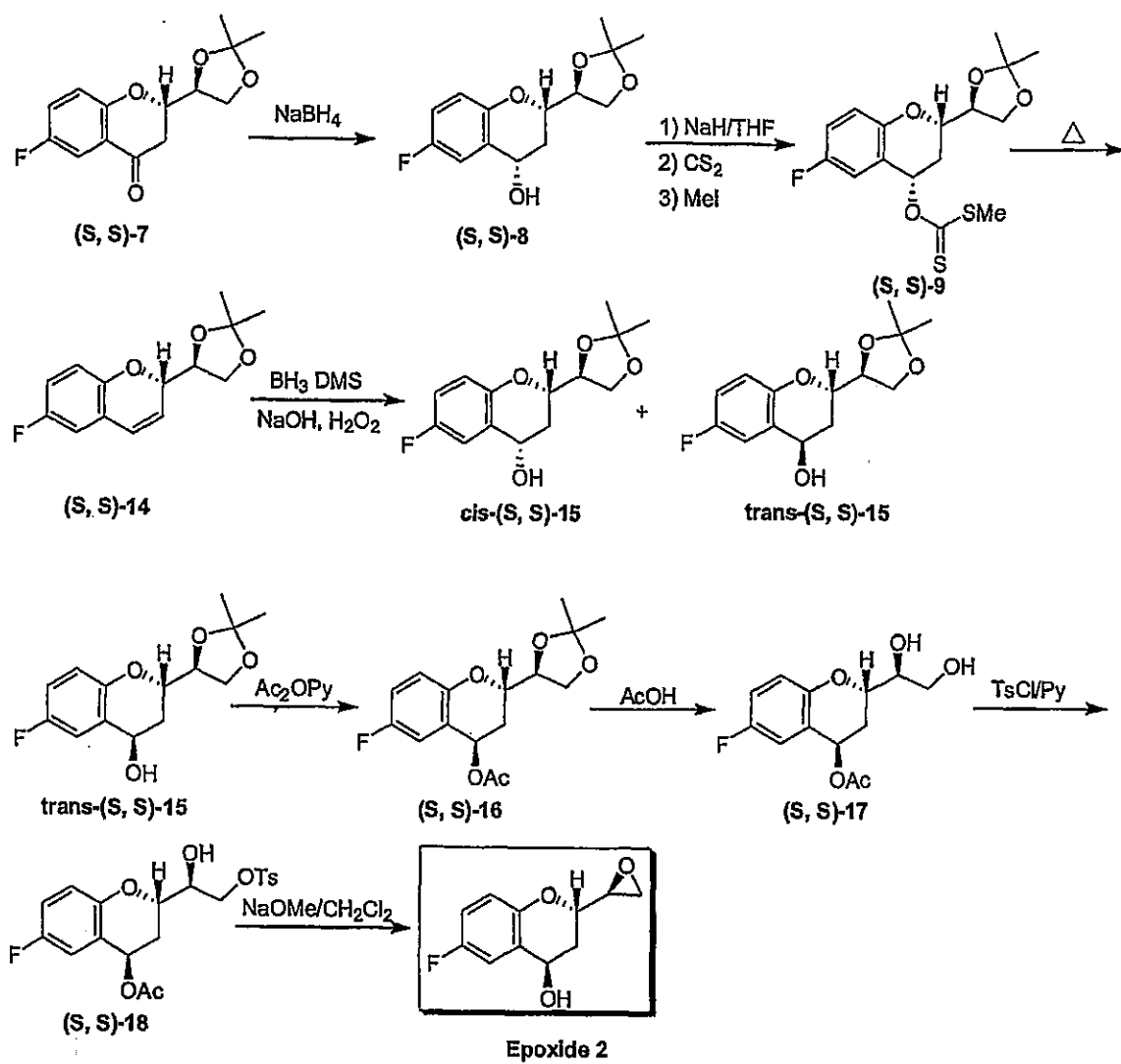


FIGURE 13

The Synthesis of Epoxide 2



CN(C)C=O $\xrightarrow[\text{CH}_2\text{Cl}_2, -20^\circ\text{C}]{\text{AcCl, Pyr.}}$ CN(C)C=O

c1ccc(O)c(F)c1 $\xrightarrow{\text{Me}_2\text{SO}_4}$ c1ccc(OC)c(F)c1 (22)

(22) $\xrightarrow[2) \text{ 21}]{1) \text{ BuLi}}$ CC(=O)c1ccc(OC)c(F)c1 (23)

(23) $\xrightarrow{\text{HI}}$ CC(=O)c1ccc(O)c(F)c1 (24)

(24) $\xrightarrow[2) \text{ 25}]{1) \text{ LDA}}$ CC(=O)C(O)C1OC(C)(C)OC1 (25)

(25) $\xrightarrow[\text{NaHCO}_3/\text{Tol}]{\text{LiOH/TBAB}}$ CC(=O)C1OC(C)(C)OC1 (R,S)-26 + CC(=O)C1OC(C)(C)OC1 (S,S)-26

(R,S)-26 $\xrightarrow{\text{NaBH}_4}$ CC(=O)C1OC(C)(C)OC1 (R,S)-27

(R,S)-27 $\xrightarrow[3) \text{ MeI}]{1) \text{ NaH/THF}, 2) \text{ CS}_2}$ CC(=O)C1OC(C)(C)OC1 (R,S)-28

(R,S)-28 $\xrightarrow{\text{Bu}_3\text{SnH/Tol}}$ CC(=O)C1OC(C)(C)OC1 (R,S)-29

(R,S)-29 $\xrightarrow[3) \text{ H}_2\text{O}_2]{1) \text{ s-BuLi}, 2) (\text{MeO})_3\text{B}}$ CC(=O)C1OC(C)(C)OC1 (R,S)-30

(R,S)-30 $\xrightarrow{\text{BnBr/Py}}$ CC(=O)C1OC(C)(C)OC1 (R,S)-31

(R,S)-31 $\xrightarrow{\text{HCl/MeOH}}$ CC(=O)C1OC(C)(C)OC1 (R,S)-32

(R,S)-32 $\xrightarrow{\text{TsCl/Py}}$ CC(=O)C1OC(C)(C)OC1 (R,S)-33

(R,S)-33 $\xrightarrow{\text{NaN}_3/\text{DMF}}$ CC(=O)C1OC(C)(C)OC1 (R,S)-34

(R,S)-34 $\xrightarrow{\text{Pd/H}_2}$ CC(=O)C1OC(C)(C)OC1 (R,S)-35

(R,S)-35 $\xrightarrow{\text{H}_2\text{N}} \text{Product}$

The final product is a 6-fluoro-2,3-dihydro-2H-chromene derivative with a 2-amino-2-hydroxyethyl side chain.

Amine 3

FIGURE 15

The Synthesis of Epoxide 3

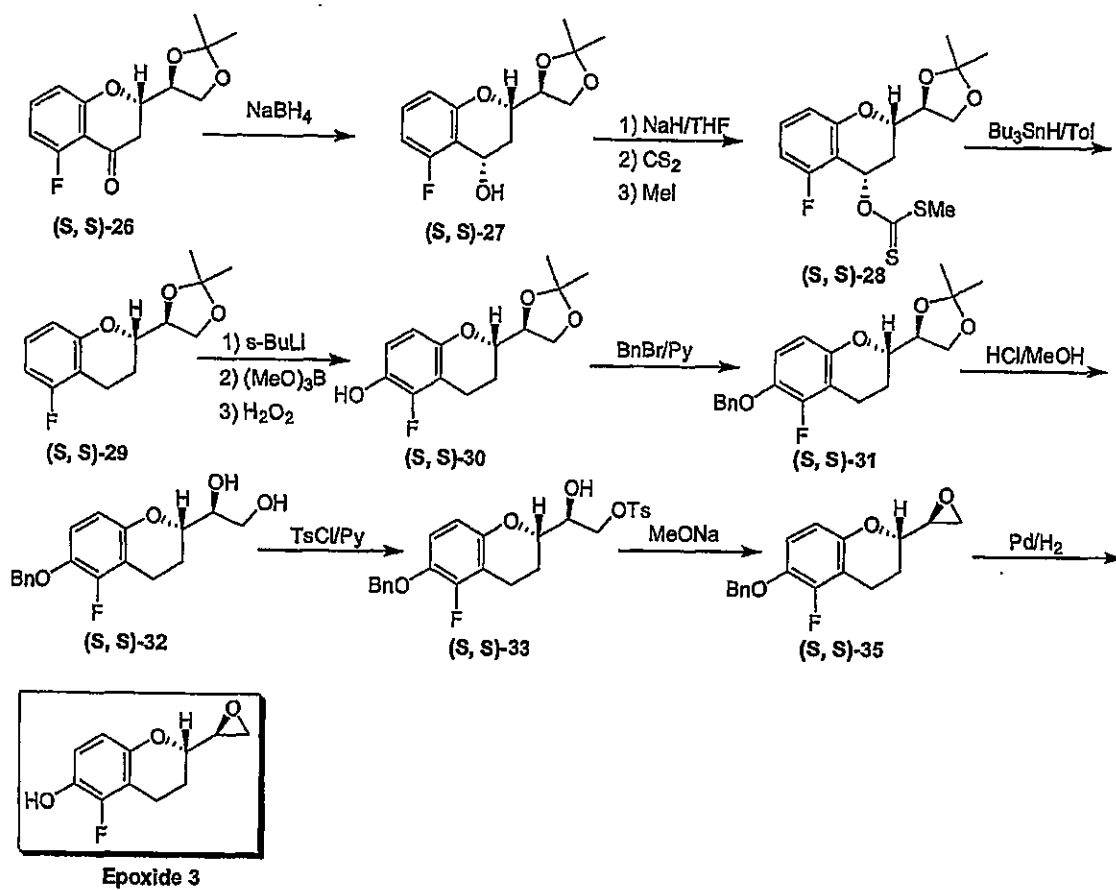


FIGURE 16

The synthesis of Amine 4

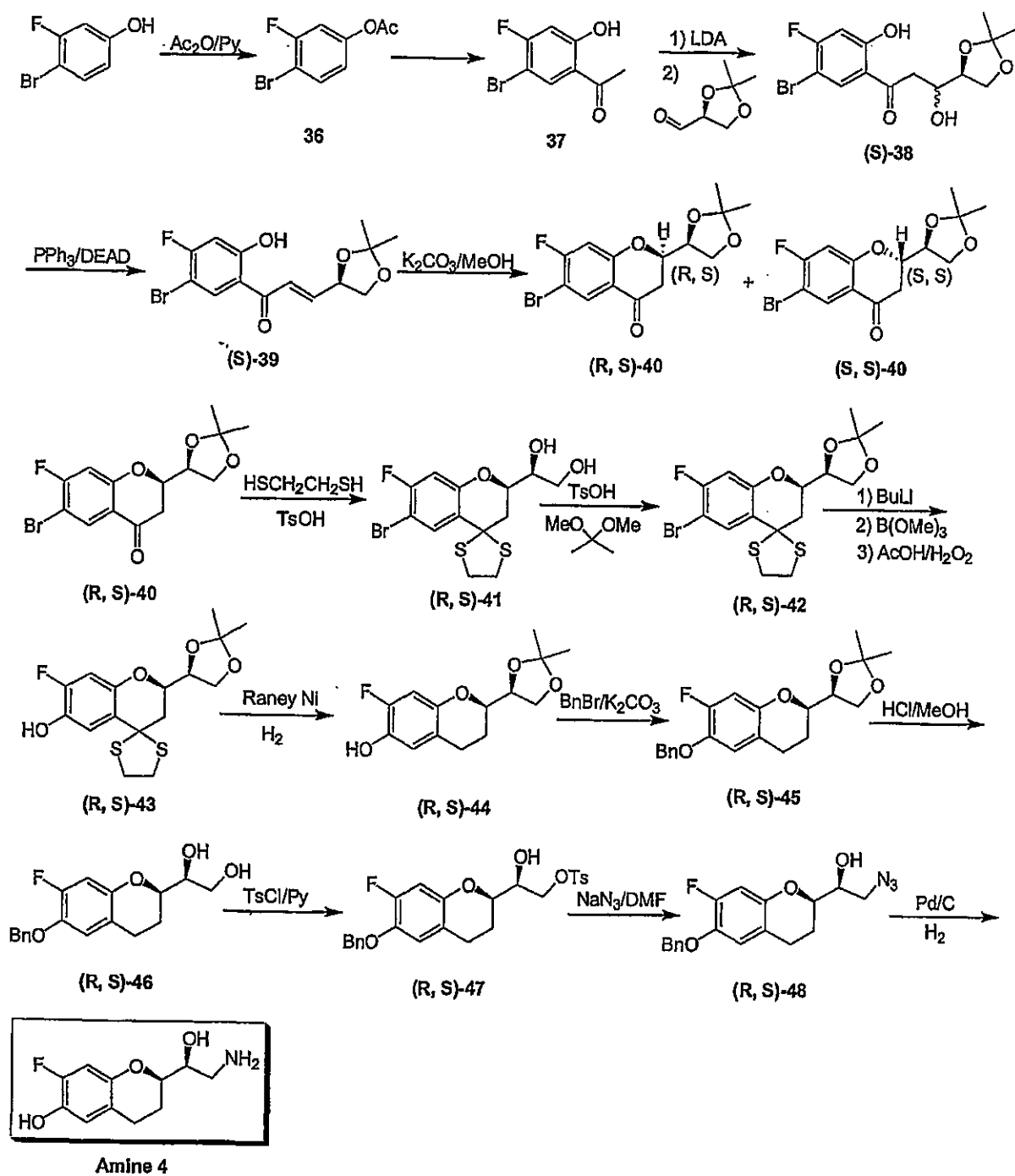


FIGURE 17

The synthesis of Epoxide 4

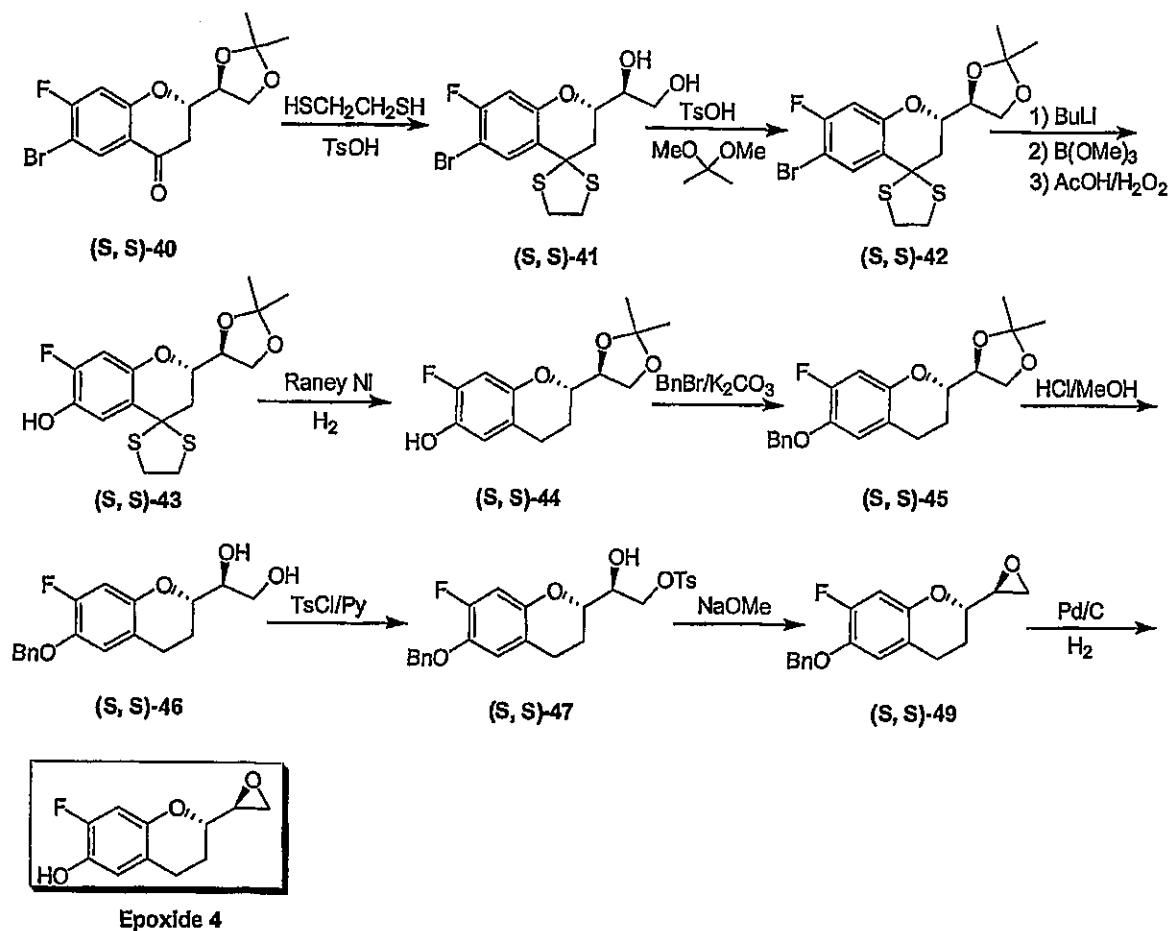
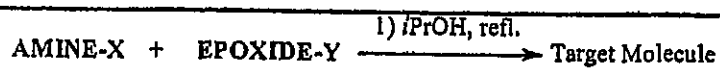


FIGURE 18a

Coupling of AMINE-X and EPOXIDE-Y: the synthesis of final nebiivolol metabolites, part 1



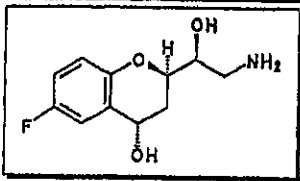
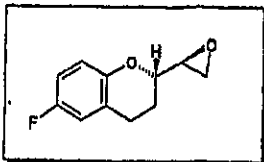
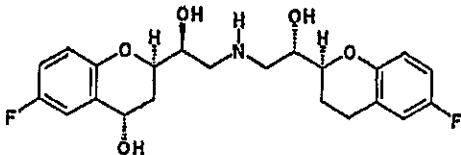
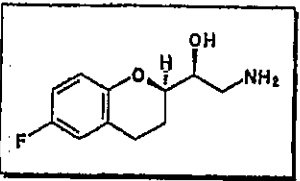
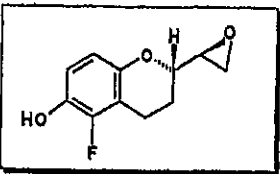
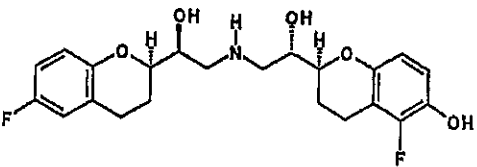
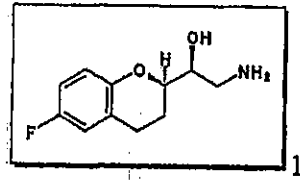
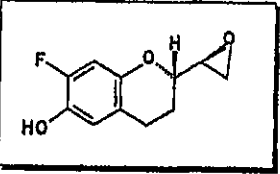
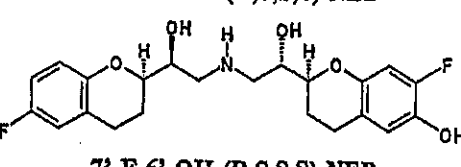
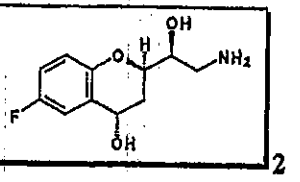
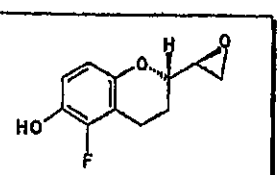
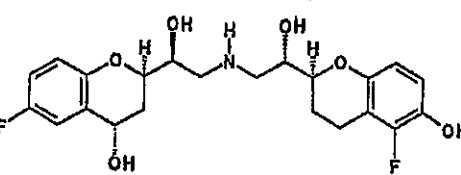
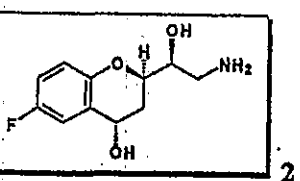
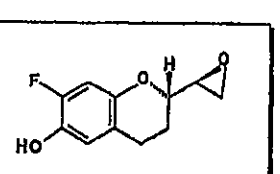
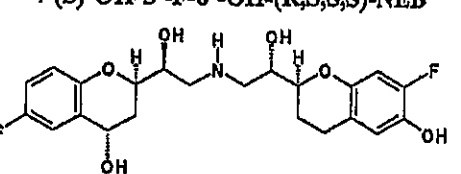
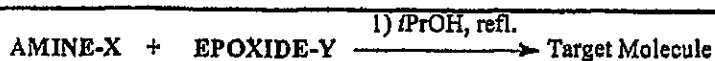
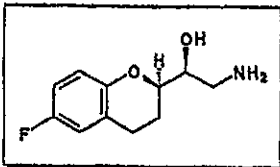
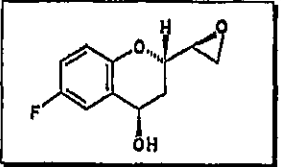
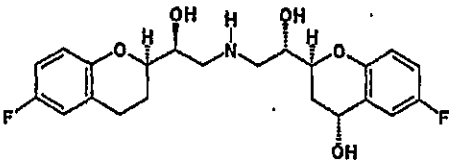
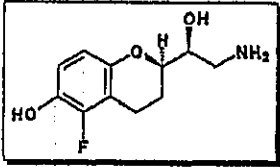
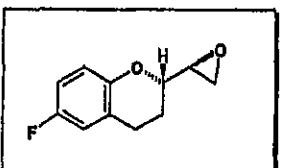
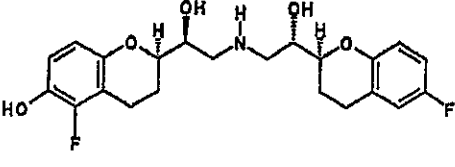
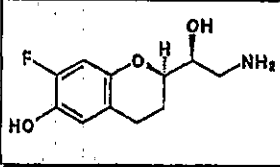
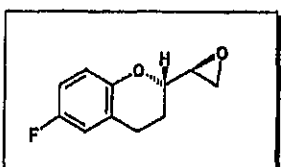
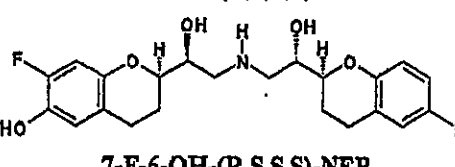
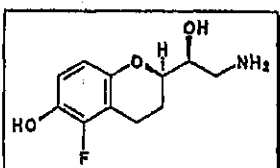
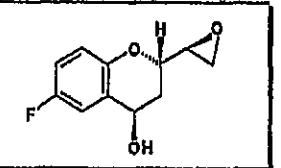
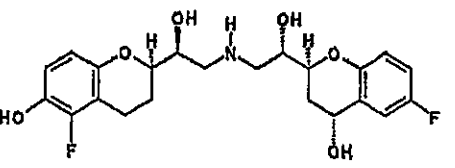
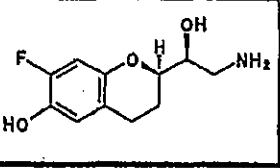
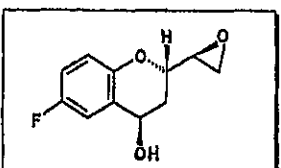
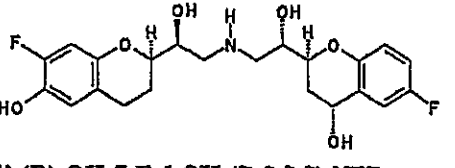
Entry	Amine	Epoxide	Target molecules
1			 4-(S)-OH-(R,S,S,S)-NEB
2			 5'-F-6'-OH-(R,S,S,S)-NEB
3			 7'-F-6'-OH-(R,S,S,S)-NEB
4			 4-(S)-OH-5'-F-6'-OH-(R,S,S,S)-NEB
5			 4-(S)-OH-7'-F-6'-OH-(R,S,S,S)-NEB

FIGURE 18b

Coupling of AMINE-X and EPOXIDE-Y: the synthesis of final neбиволol metabolites, part 2



Entry	Amine	Epoxide	Target molecules
6	 1	 2	 4'-(R)-OH-(R,S,S,S)-NEB
7	 3	 1	 5-F-6-OH-(R,S,S,S)-NEB
8	 4	 1	 7-F-6-OH-(R,S,S,S)-NEB
9	 3	 2	 4'-(R)-OH-5-F-6-OH-(R,S,S,S)-NEB
10	 4	 2	 4'-(R)-OH-7-F-6-OH-(R,S,S,S)-NEB