

FIGURE 1

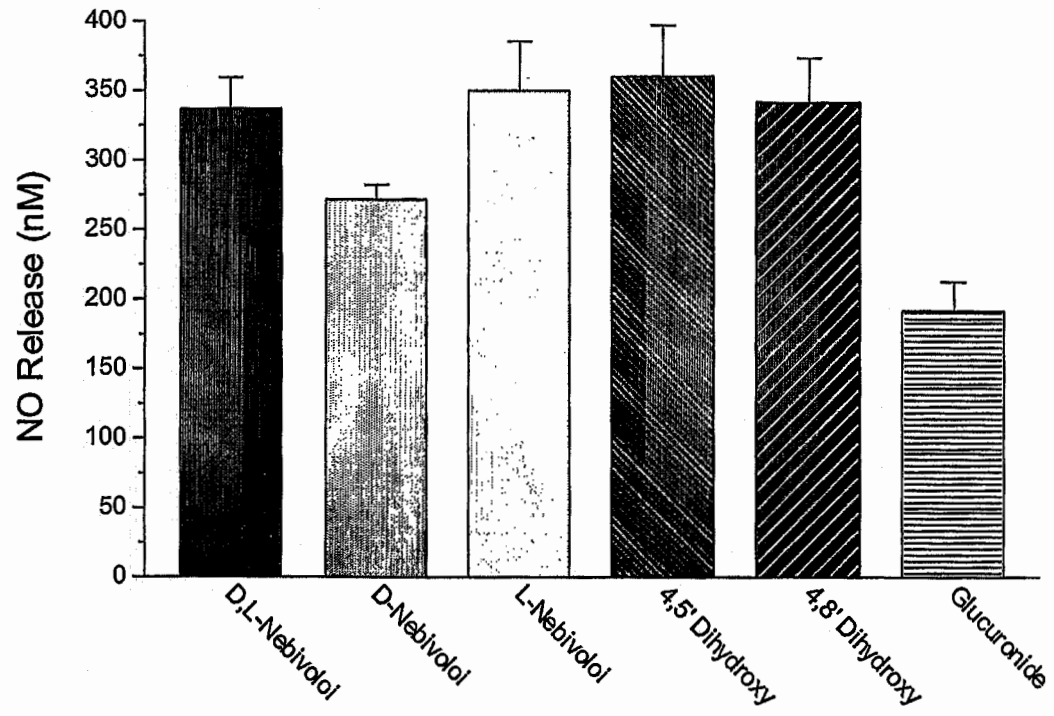


FIGURE 2

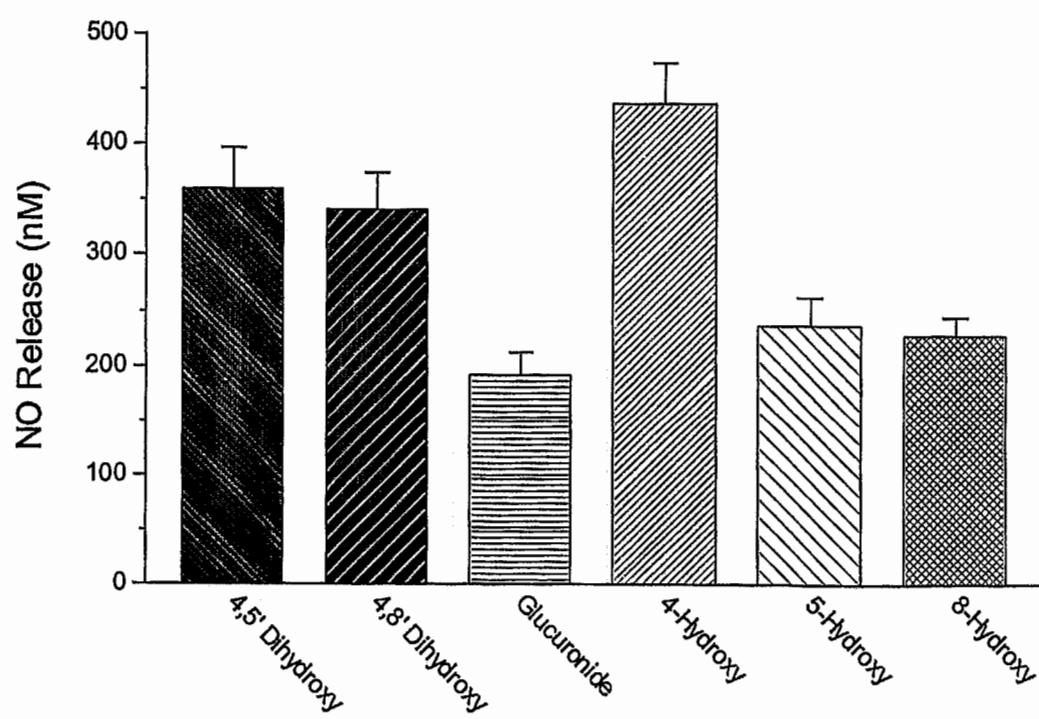


FIGURE 3

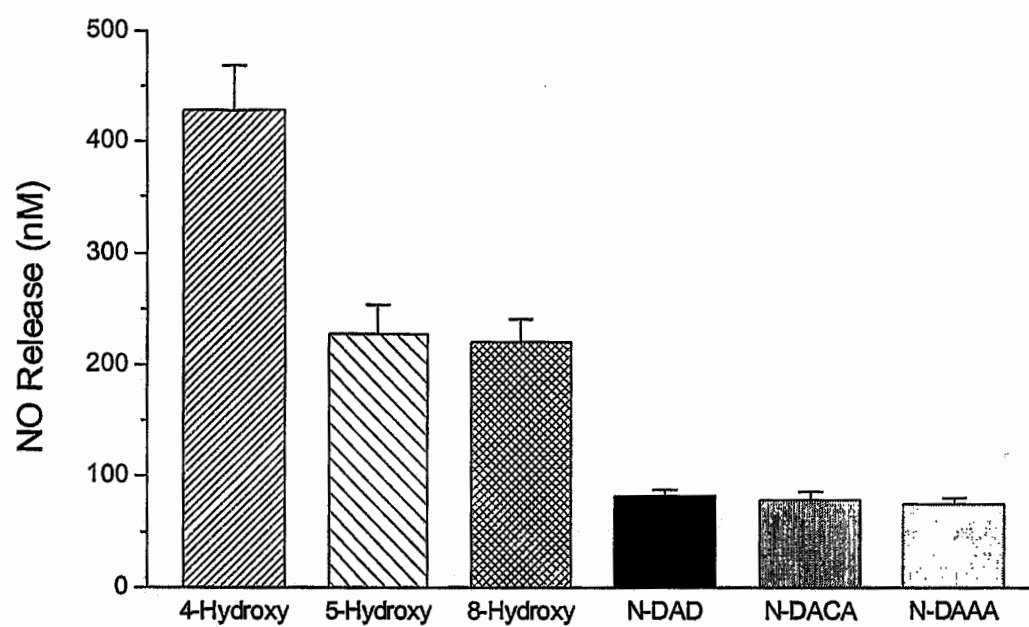


FIGURE 4

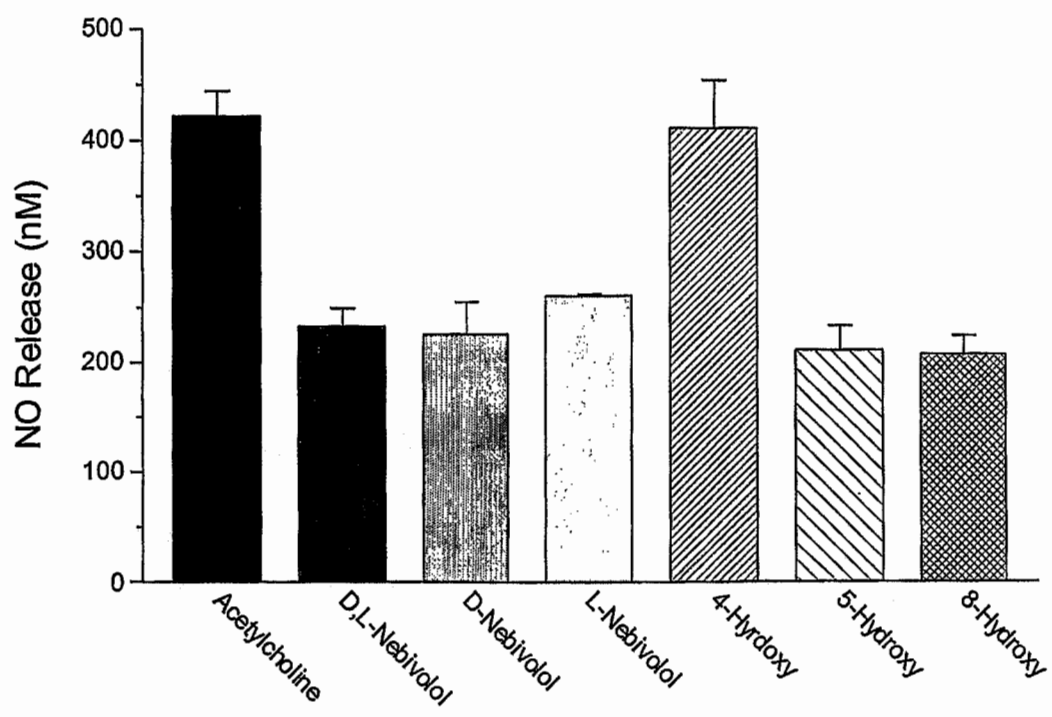


FIGURE 5

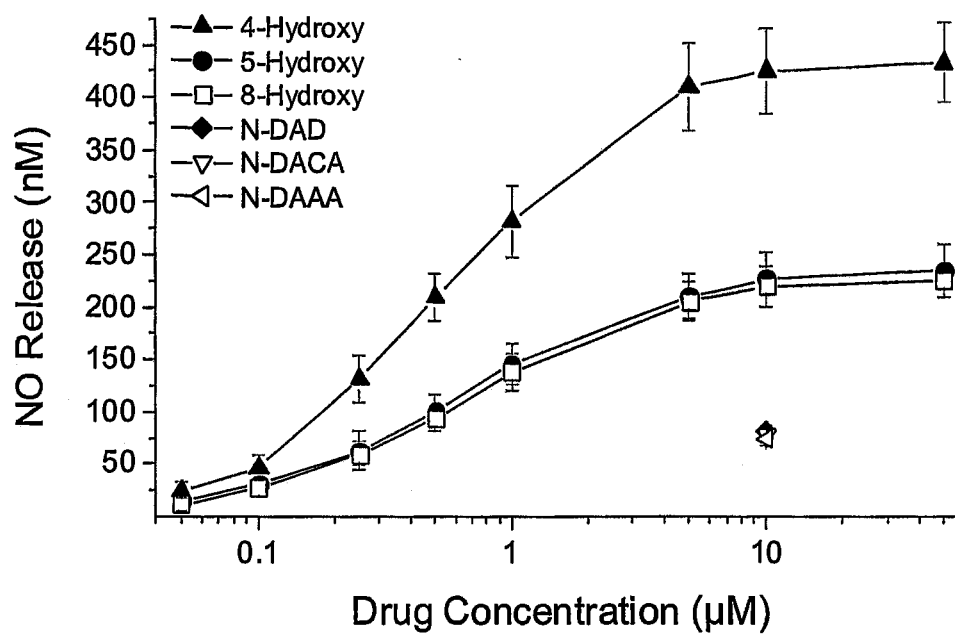


FIGURE 6

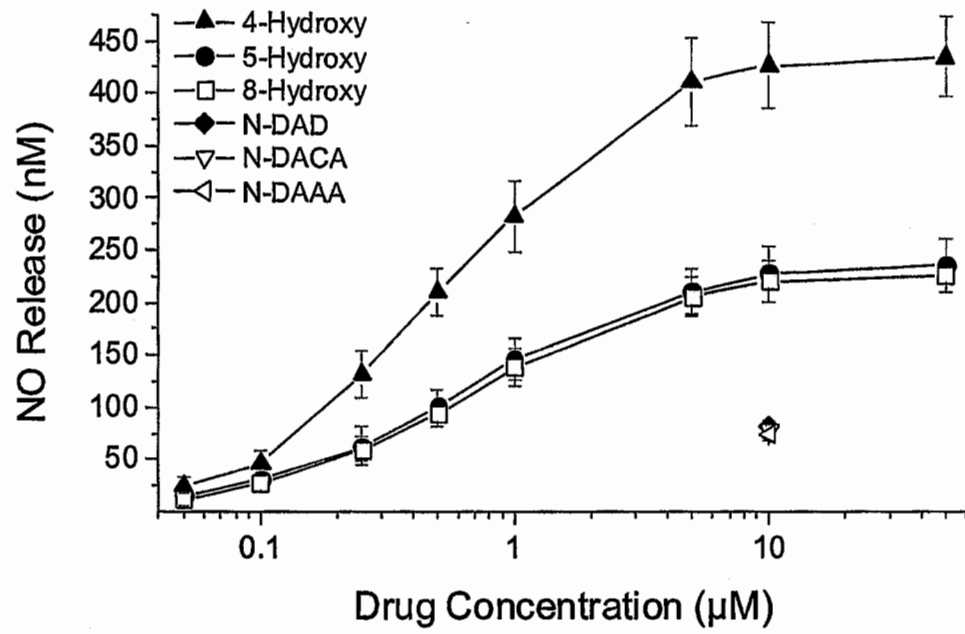
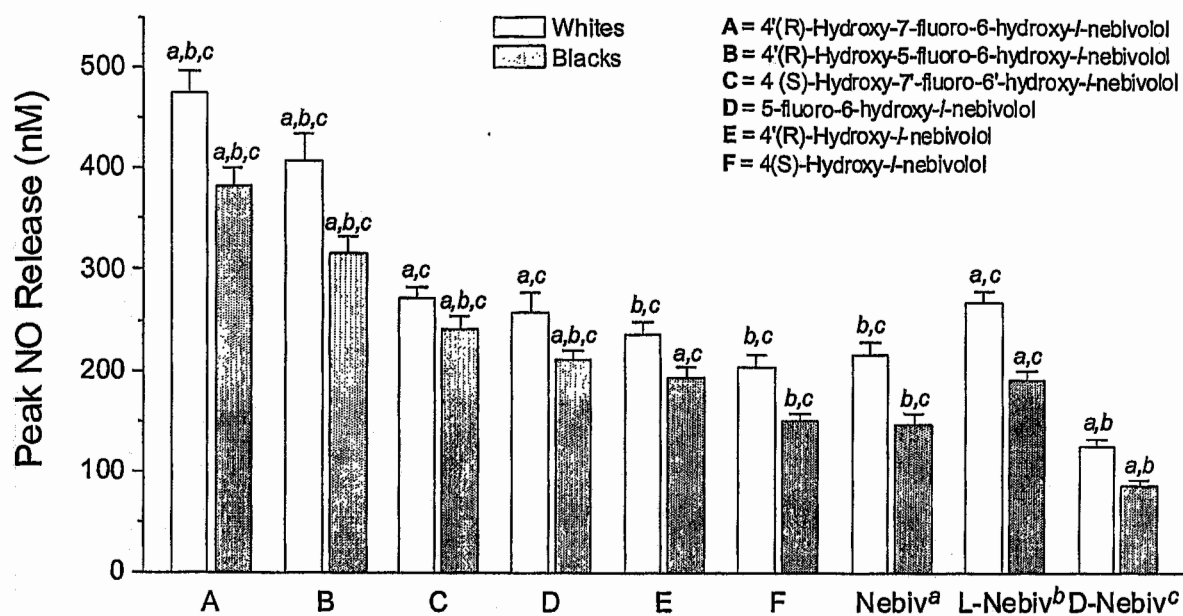


FIGURE 7



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

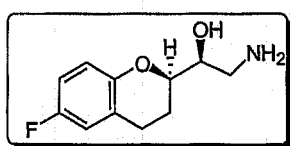
^c $p < 0.001$ versus cognate D-Nebiv treatment (p values from ANOVA Student-Newman-Keuls Multiple Comparisons Test)

FIGURE 8

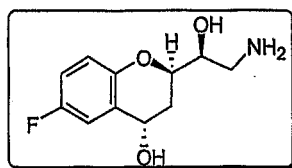
TARGET CHIRAL METABOLITES – (R,S,S,S) SERIES – 10 COMPOUNDS

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)	

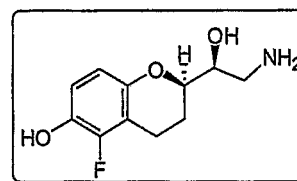
Eight segments as shown below are prepared for the synthesis of target molecules 1-10.



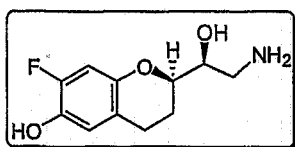
Amine 1



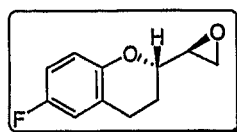
Amine 2



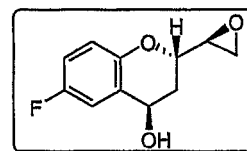
Amine 3



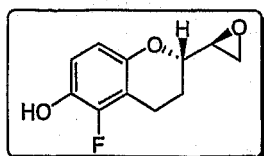
Amine 4



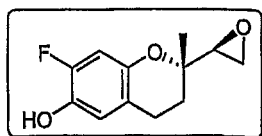
Epoxide 1



Epoxide 2



Epoxide 3



Epoxide 4

FIGURE 9

The Synthesis of Amine 1

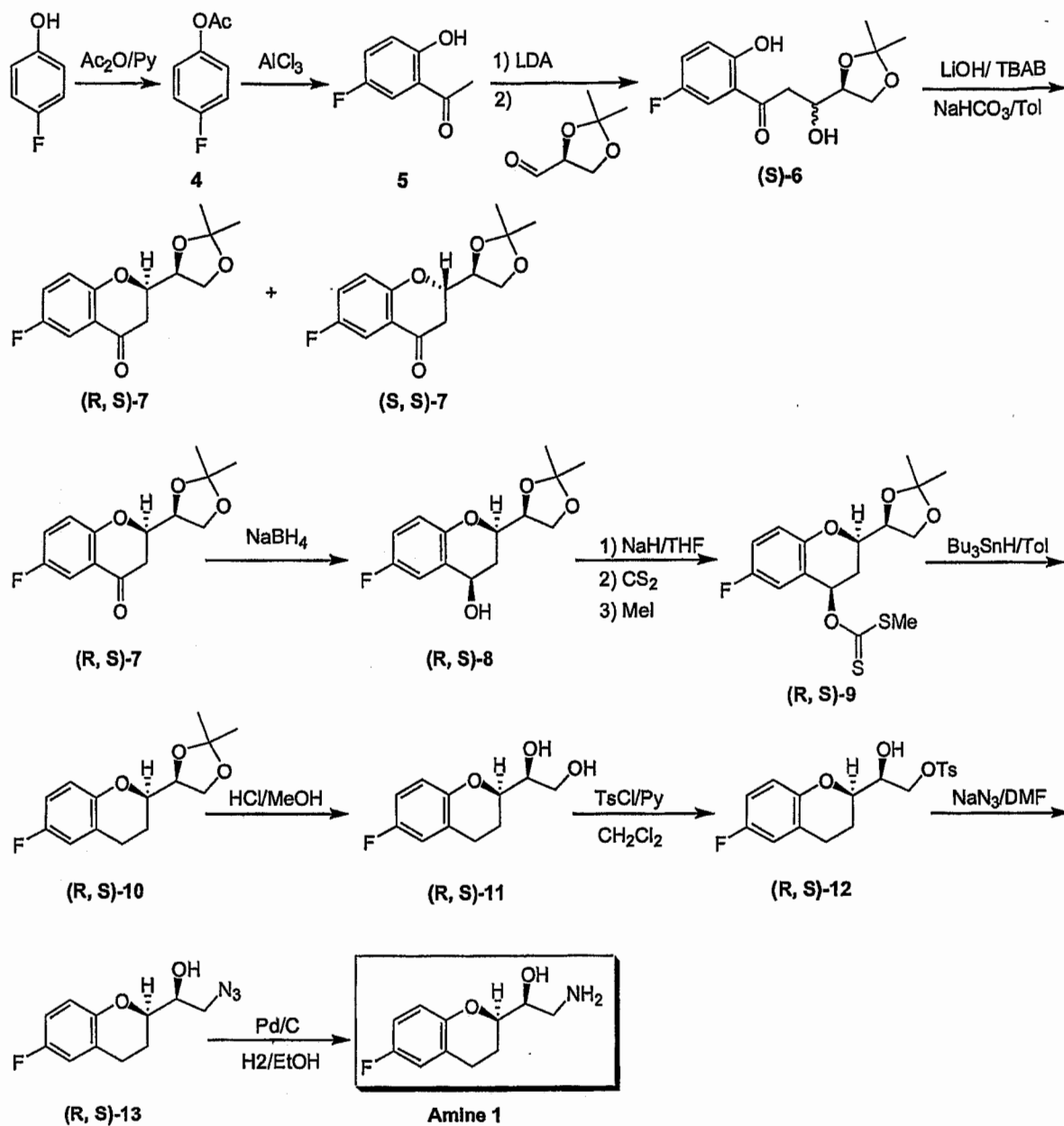


FIGURE 10

The Synthesis of Epoxide 1

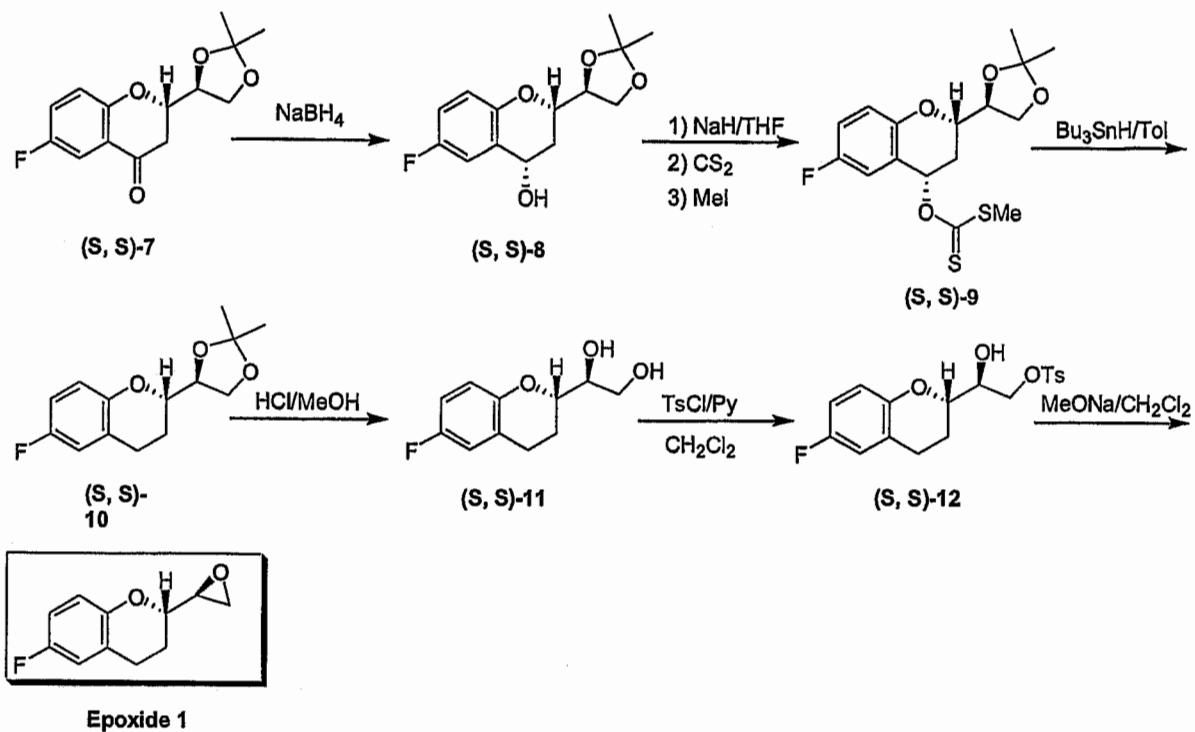


FIGURE 11

The Synthesis of Amine 2, part 1

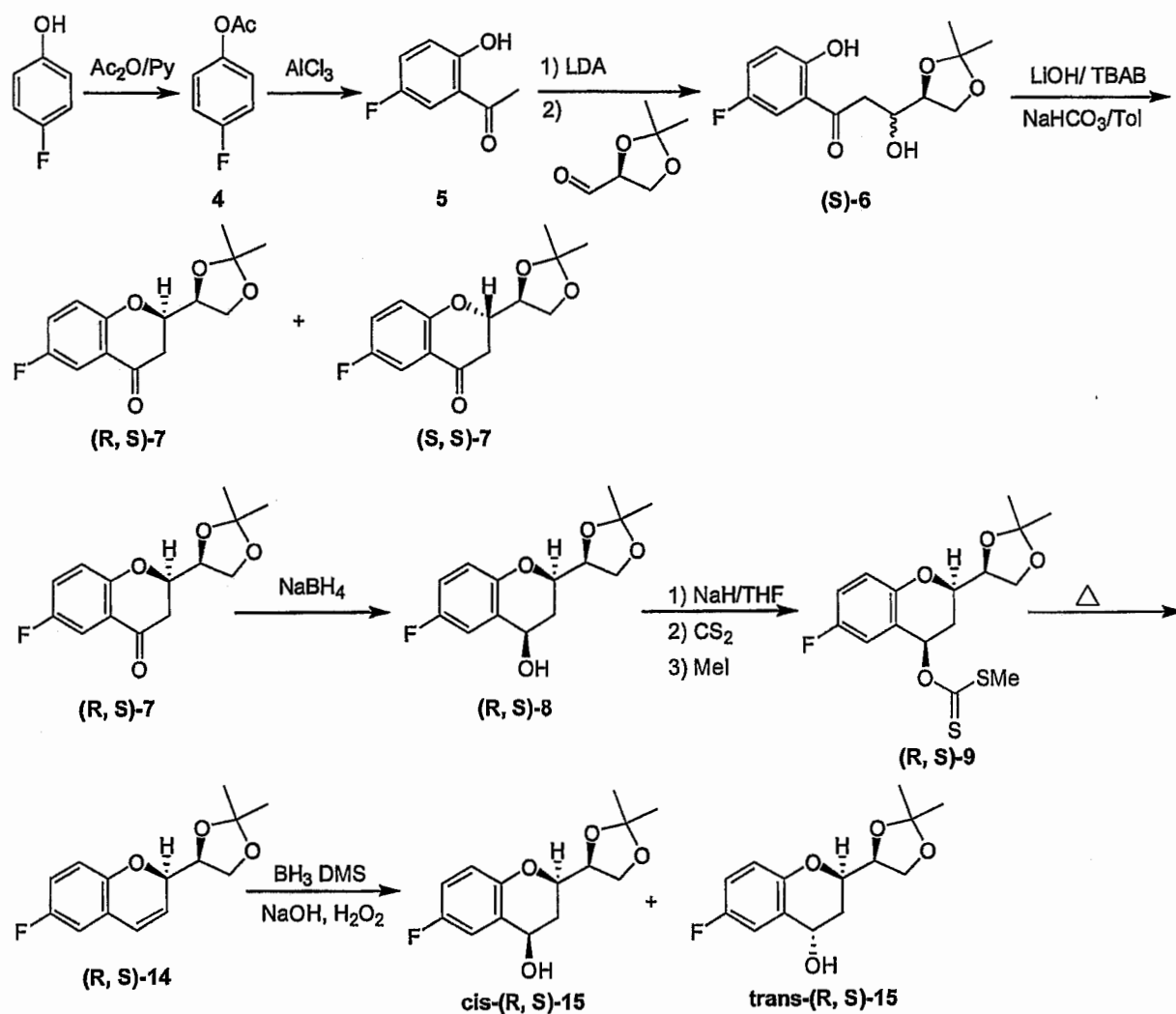


FIGURE 12

The Synthesis of Amine 2, part 2

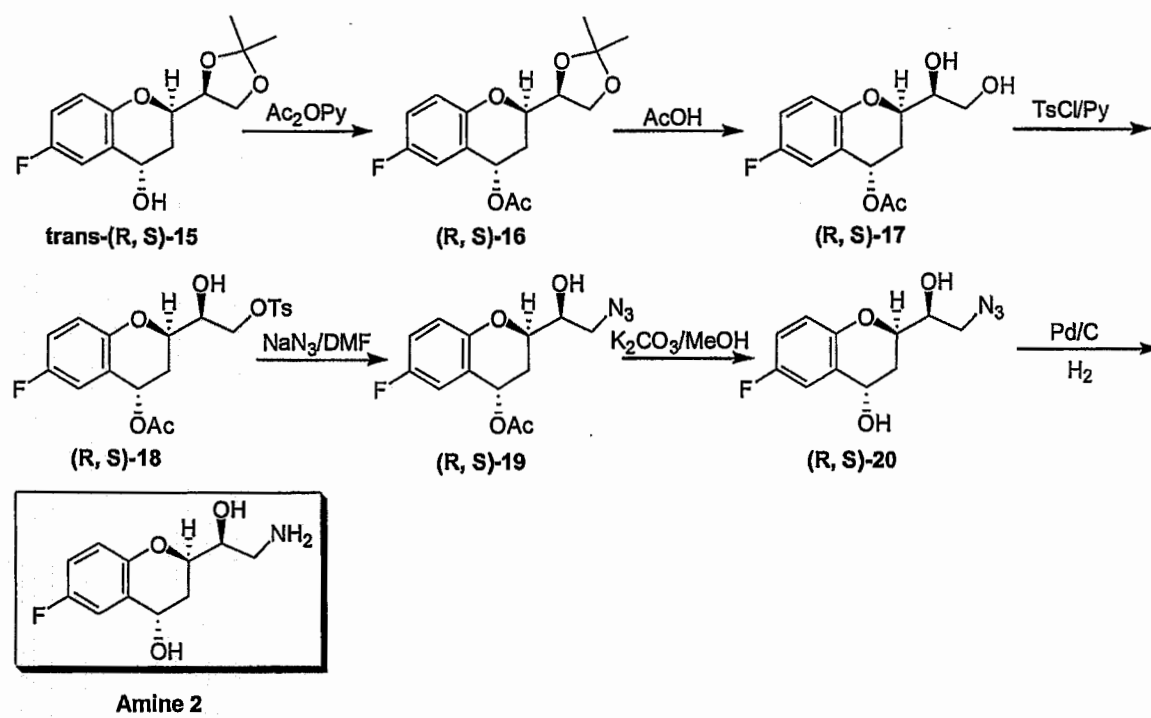


FIGURE 13

The Synthesis of Epoxide 2

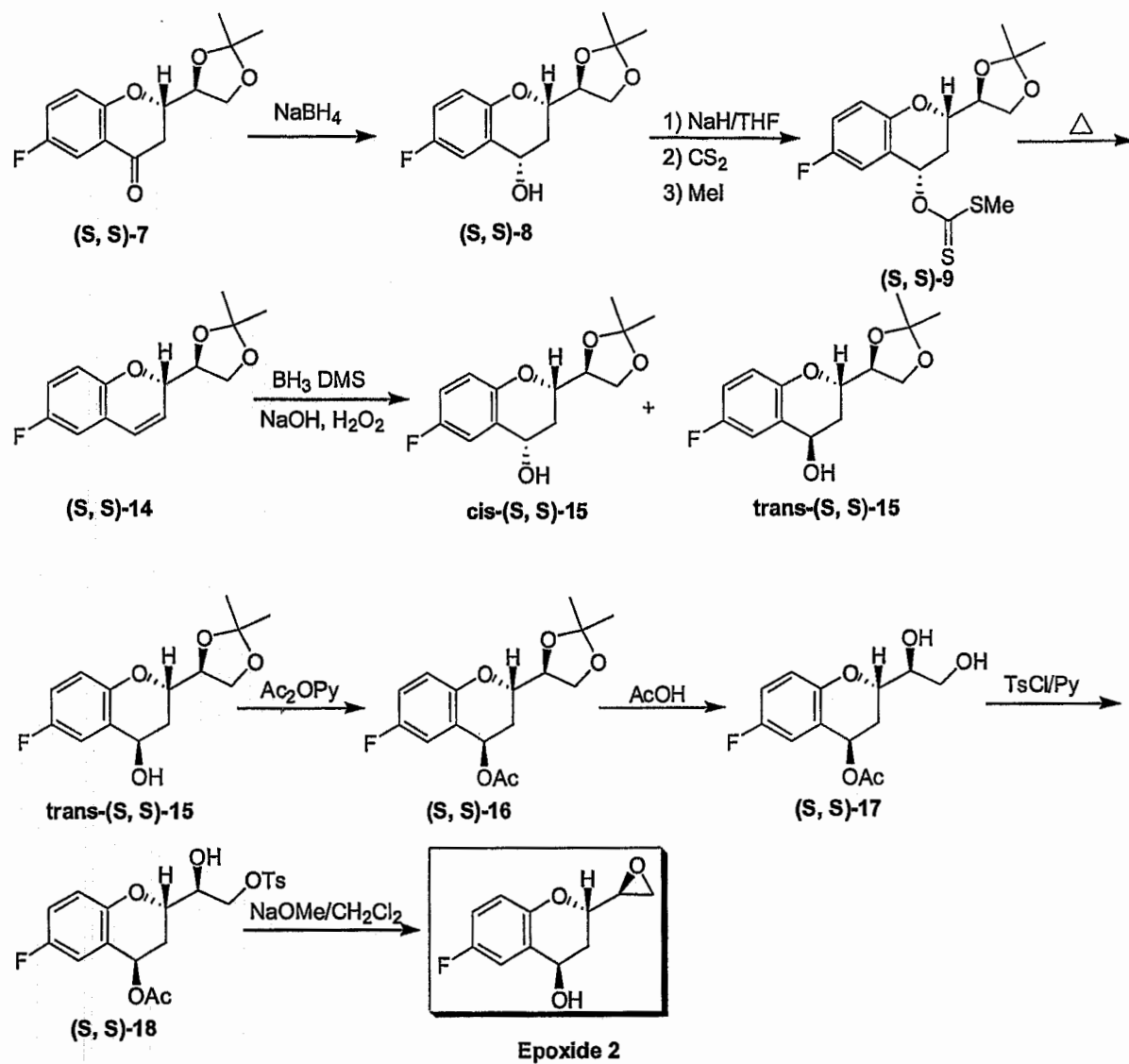


FIGURE 14

The Synthesis of Amine 3

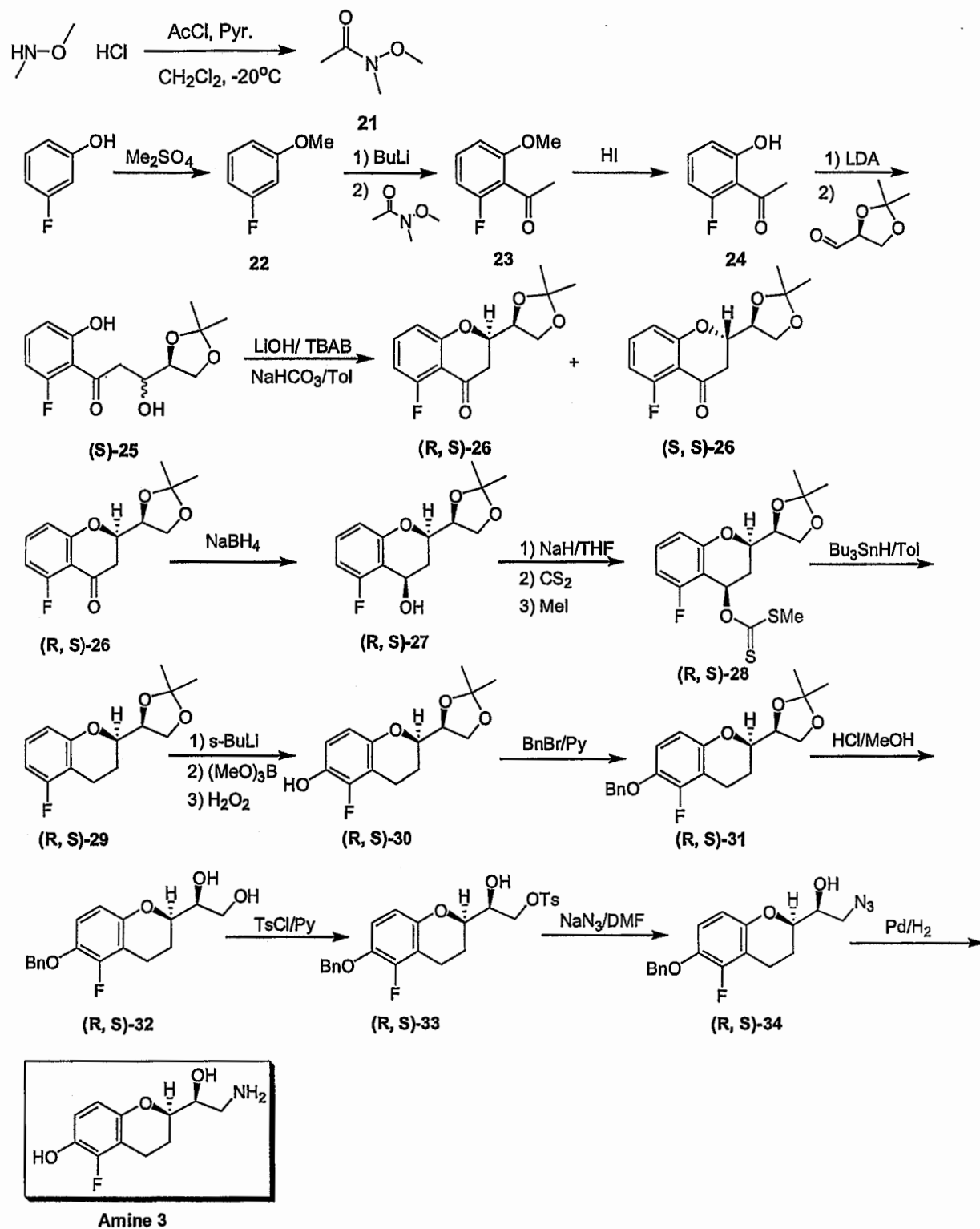


FIGURE 15

The Synthesis of Epoxide 3

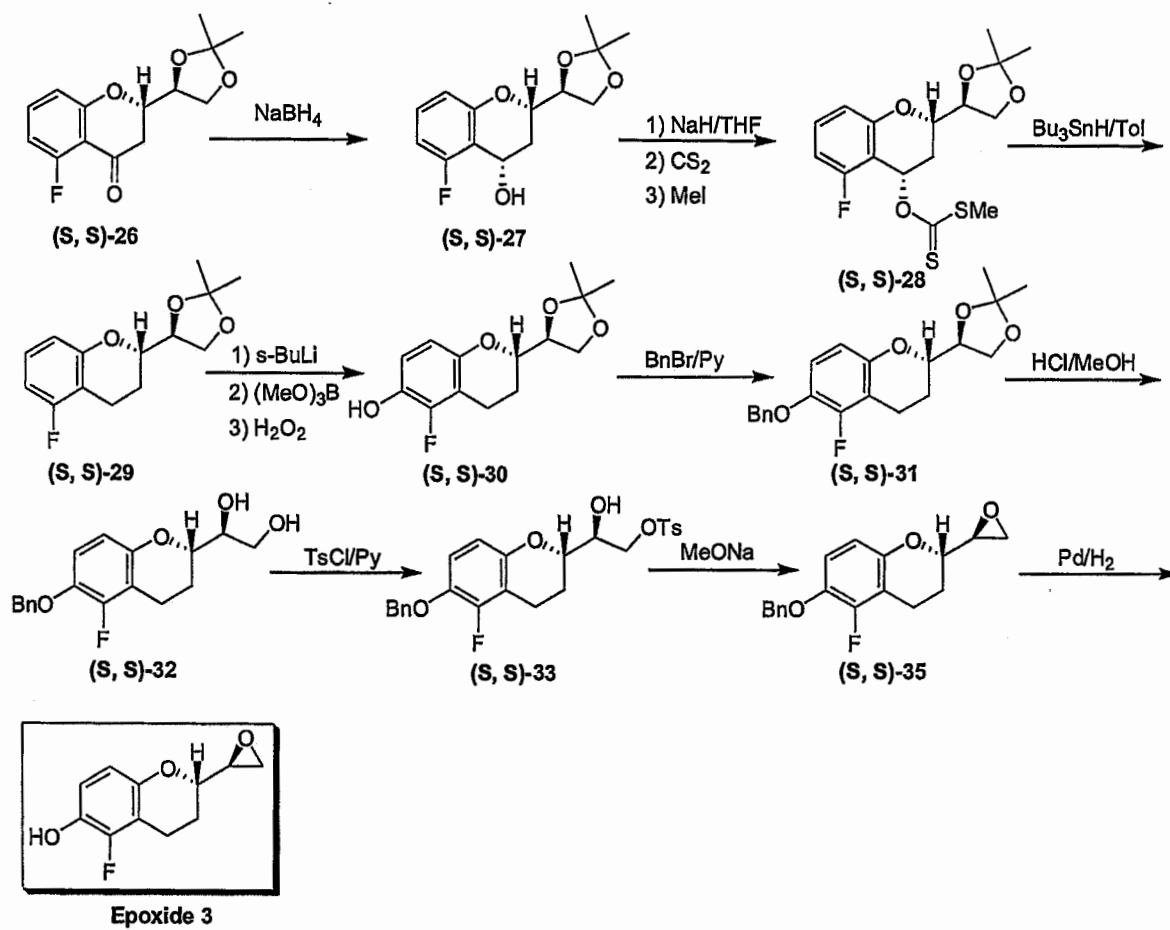


FIGURE 16

The synthesis of Amine 4

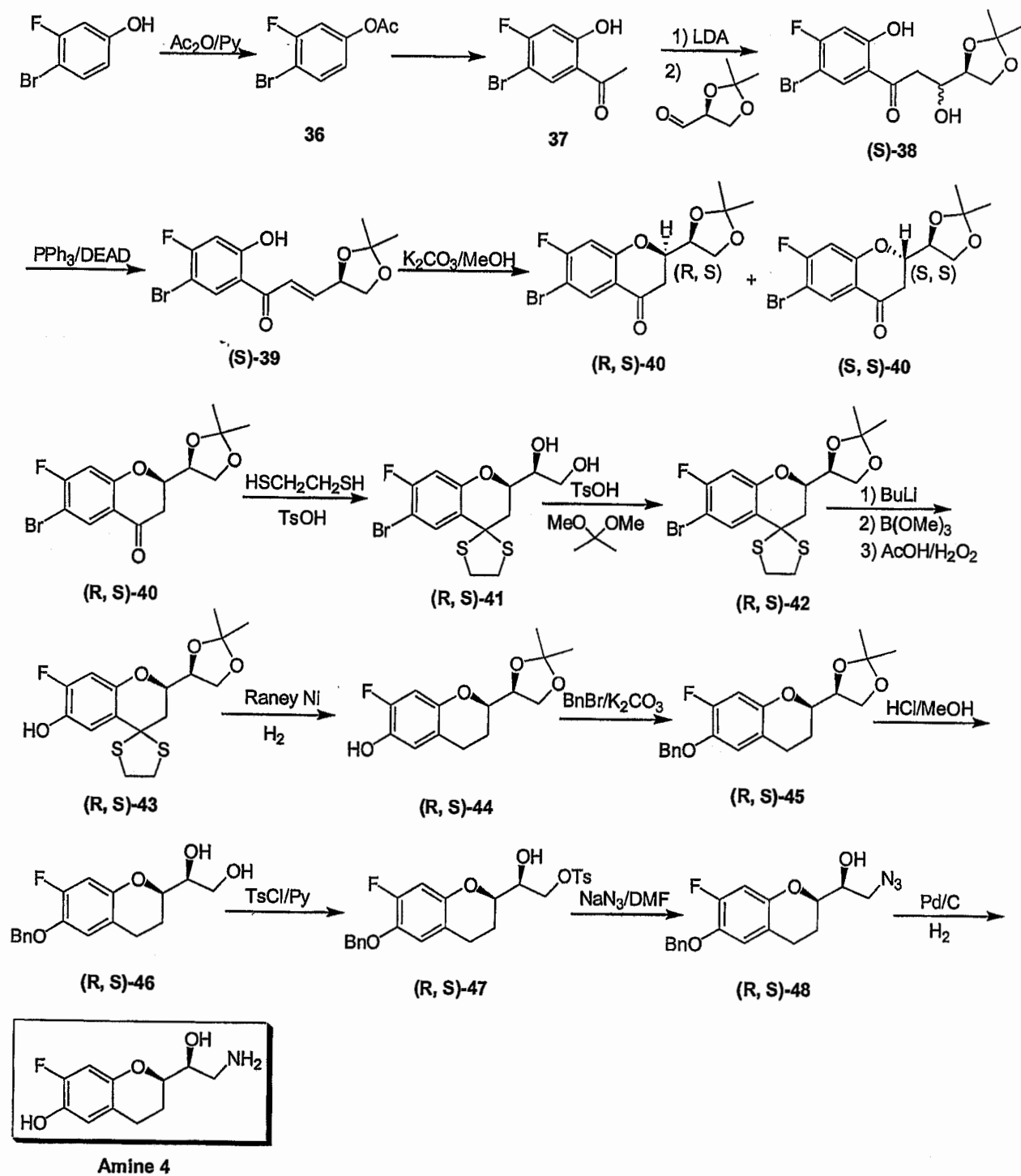


FIGURE 17

The synthesis of Epoxide 4

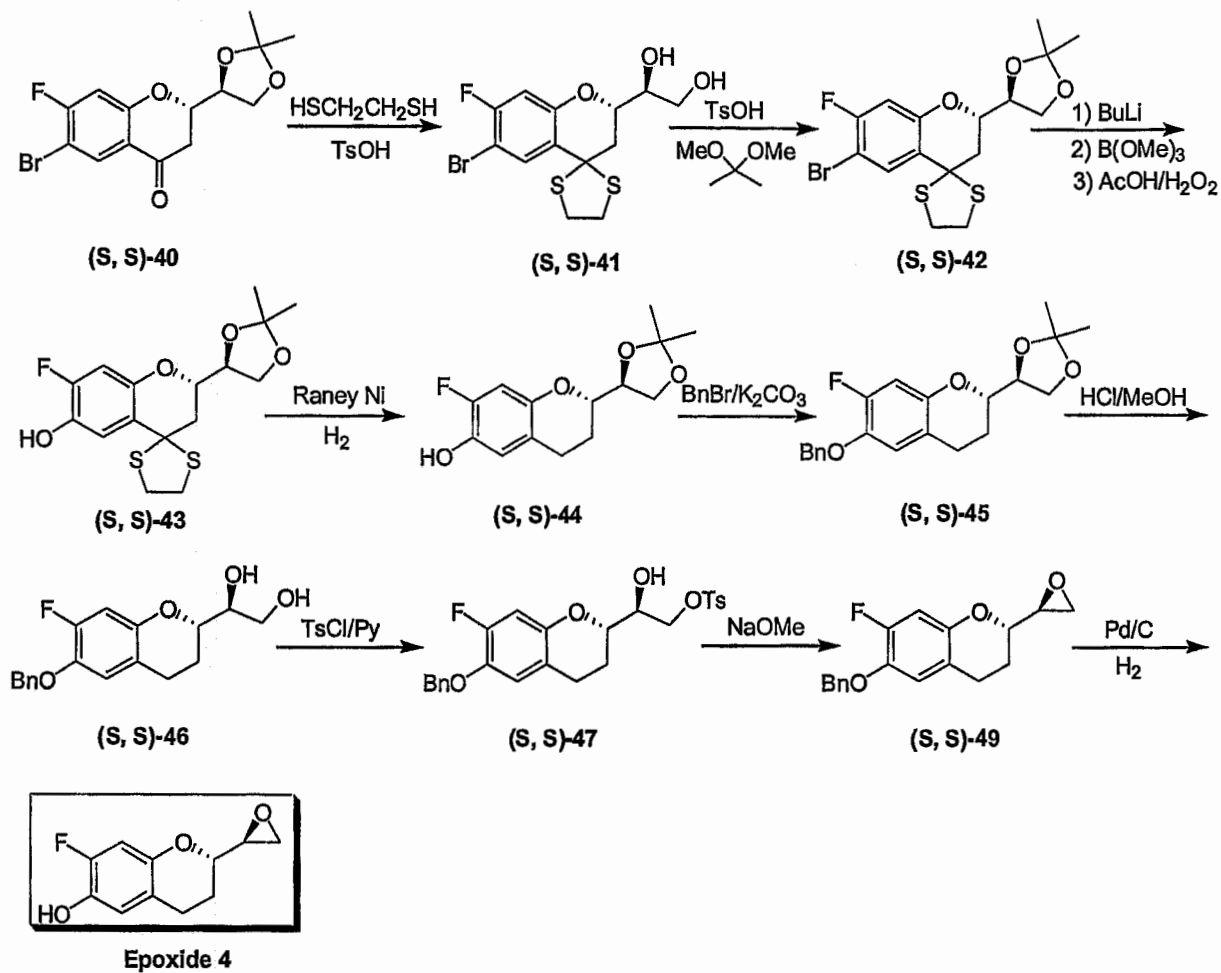
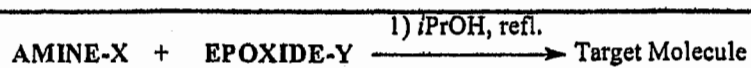


FIGURE 18a

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



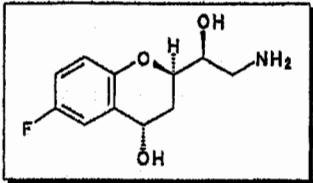
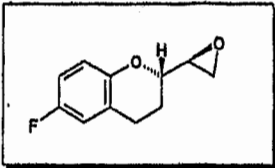
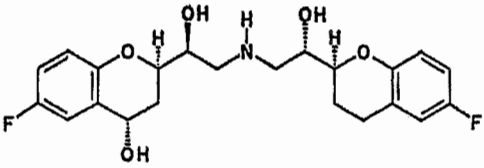
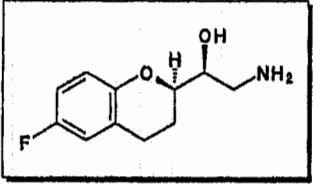
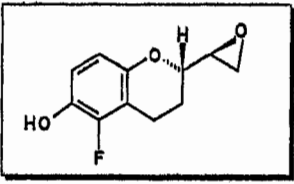
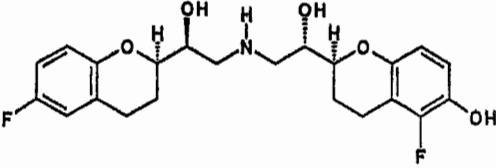
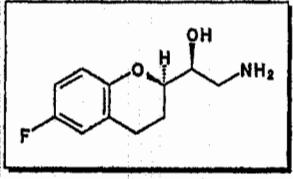
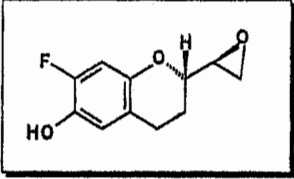
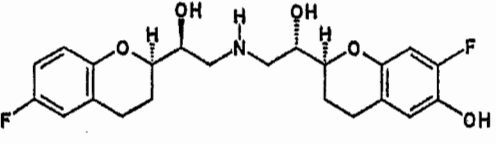
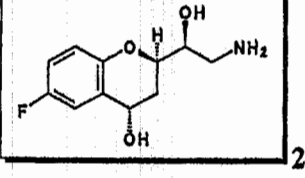
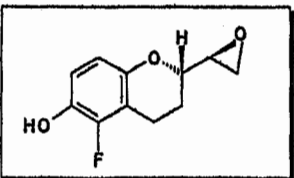
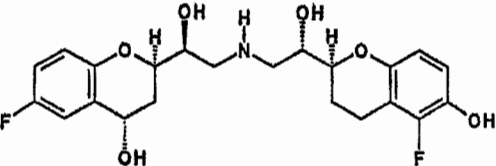
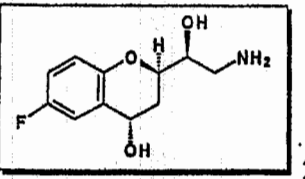
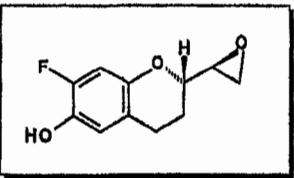
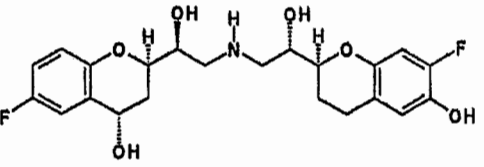
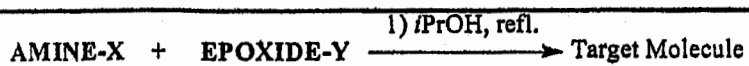
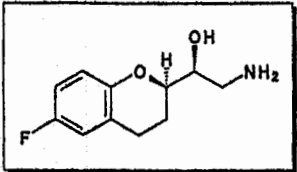
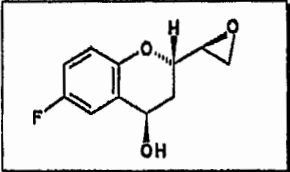
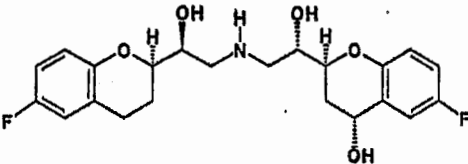
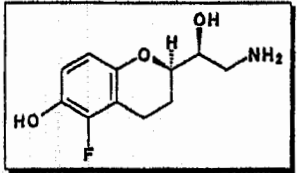
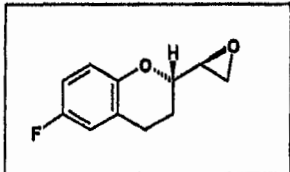
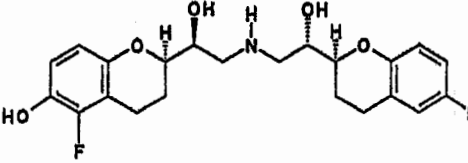
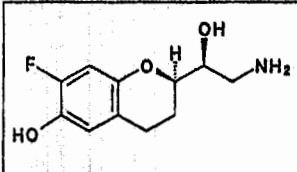
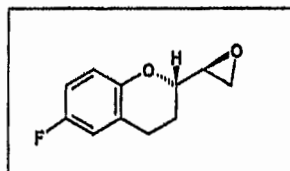
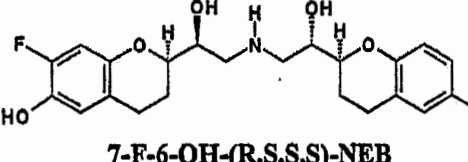
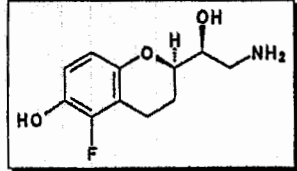
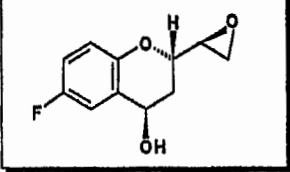
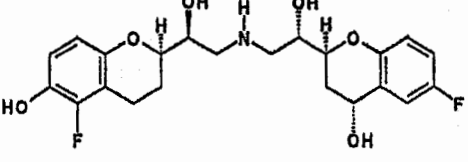
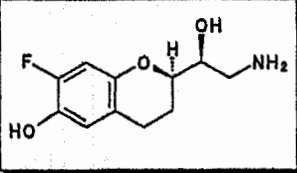
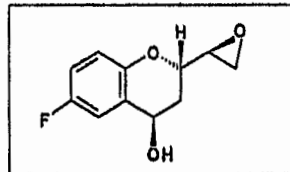
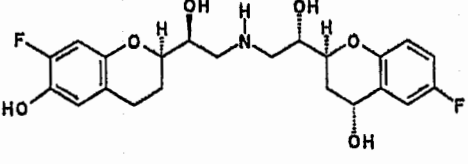
Entry	Amine	Epoxide	Target molecules
1			 4-(S)-OH-(R,S,S,S)-NEB
2			 5'-F-6'-OH-(R,S,S,S)-NEB
3			 7'-F-6'-OH-(R,S,S,S)-NEB
4			 4-(S)-OH-5'-F-6'-OH-(R,S,S,S)-NEB
5			 4-(S)-OH-7'-F-6'-OH-(R,S,S,S)-NEB

FIGURE 18b

Coupling of AMINE-X and EPOXIDE-Y: the synthesis of final nebirolol 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