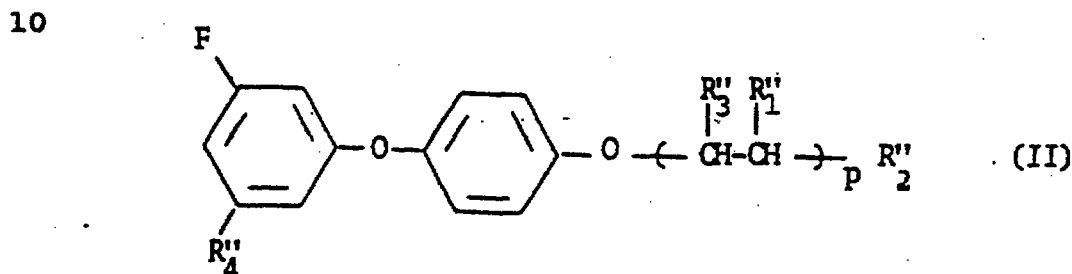


INTERMEDIATES FOR THE PRODUCTION OF NITROGEN-CONTAINING SUBSTITUTED HETEROCYCLIC COMPOUNDS

The present invention relates to intermediates for the production of insect controlling nitrogen-containing substituted heterocyclic compounds.

Accordingly in one aspect the present invention provides compounds of the formula:



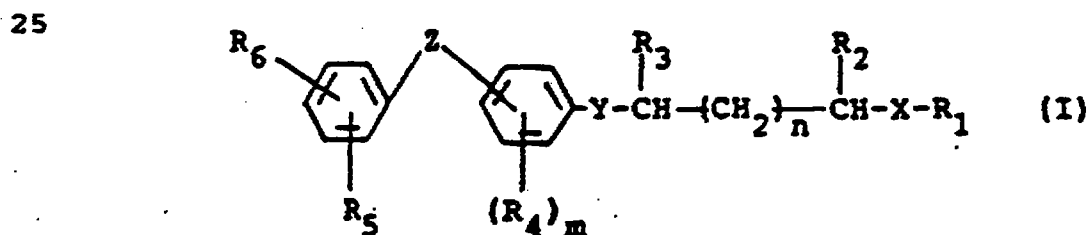
15 where p is 0 or 1,

R''_1 is a halogen atom, a hydroxyl group, a tosyloxy group or a mesyloxy group,

R''_2 and R''_3 are each independently a hydrogen atom or a methyl group, and

20 R''_4 is a hydrogen atom or a fluorine atom when p is 1 or a fluorine atom when p is 0.

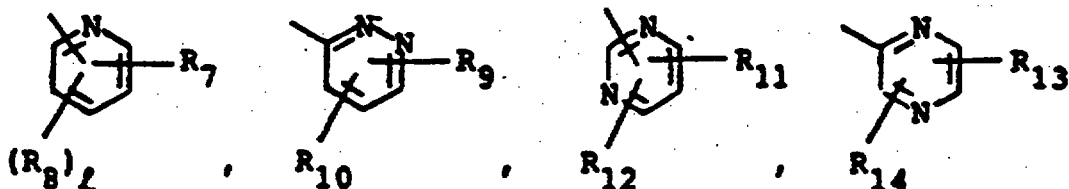
These intermediates derivatives are useful in the preparation of the nitrogen-containing heterocyclic compounds of the formula:



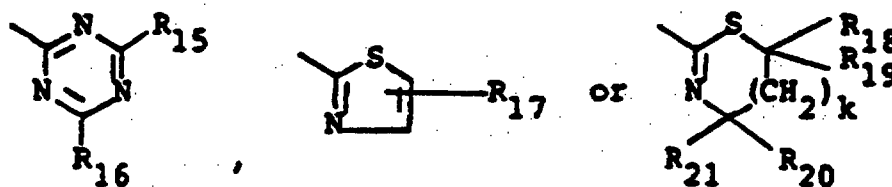
wherein

R_1 is one of the following groups:

5



10



15

(in which R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} ,
 R_{14} , R_{15} , R_{16} , R_{17} are, each independently a
hydrogen atom, a halogen atom, a C_1 - C_4 alkyl group,
a C_1 - C_4 alkoxy group, a C_1 - C_4 alkylthio group,
a trifluoromethyl group or a nitro group, R_{18} , R_{19} ,
 R_{20} and R_{21} are each independently a hydrogen atom
or a methyl group, k is 0 or 1 and l is 0 or an
integer of 1 to 3);

R_2 and R_3 are, each independently a hydrogen
atom, a halogen atom or a methyl group;

25

R_4 is a halogen atom or a methyl group;

R_5 and R_6 are, each independently a hydrogen

atom, a halogen atom, a C_1-C_4 alkyl group, a
 C_1-C_4 alkoxy group, a C_1-C_4 haloalkyl group or
a C_1-C_4 haloalkoxy group;

X, Y and Z are each independently an oxygen
5 atom, a sulfur atom or a methylene group;

m is 0 or an integer of 1 to 4; and

n is 0 or an integer of 1 or 2.

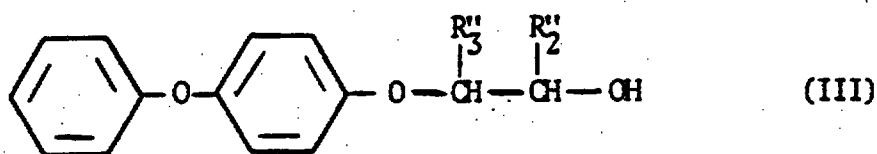
These compounds of Formula (I) are described and
10 claimed in our co-pending Patent Application No.
8210240 (Publication No. 2140010).

By the term "halogen" as used herein is meant
chlorine, bromine, iodine or fluorine.

15

In another aspect the present invention provides
an optically active isomer of a compound of the formula:

20



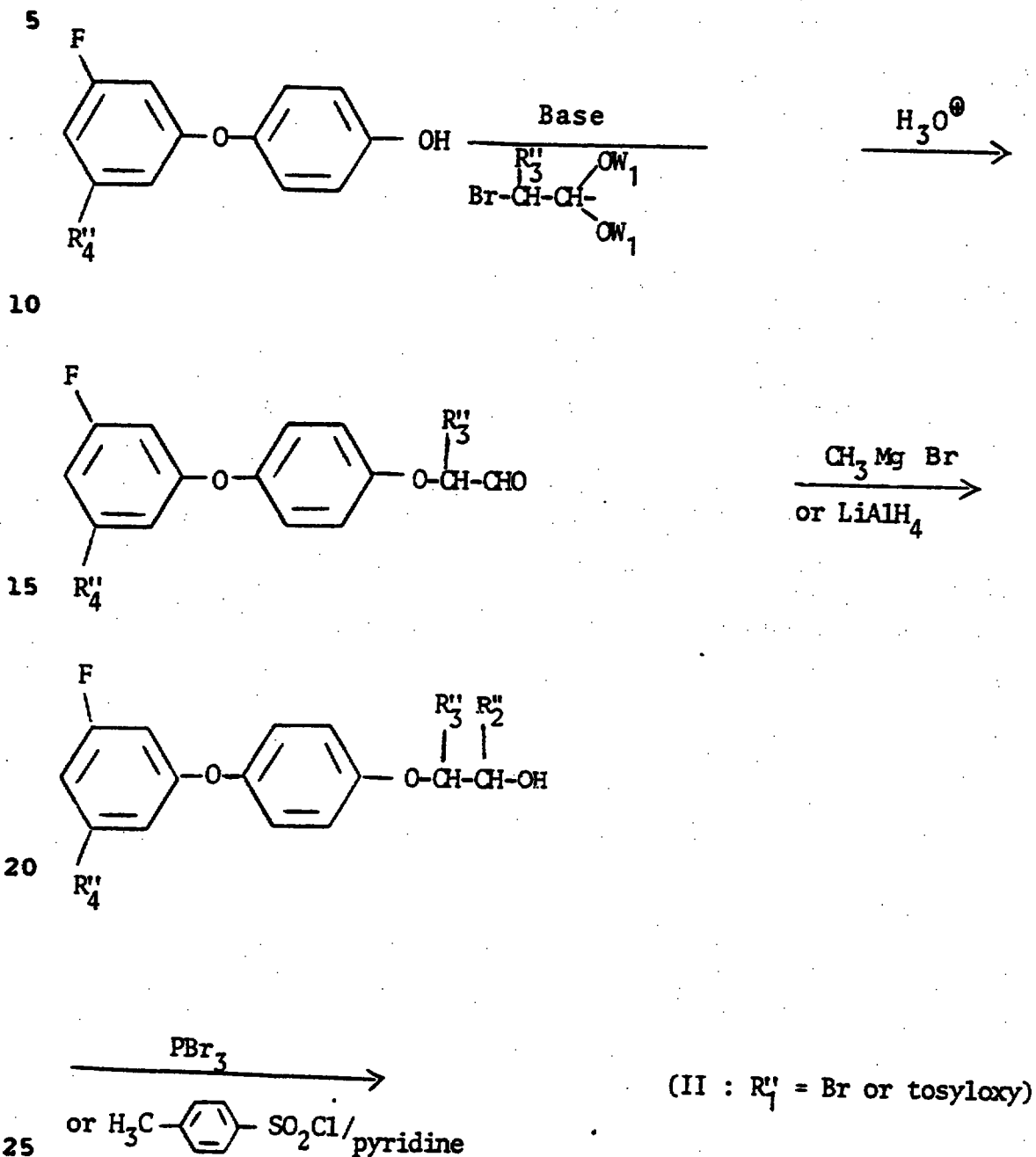
wherein one of R'_2 and R'_3 is a hydrogen atom and the
other is a methyl group.

25

The compounds of Formula (II) of the present
invention may be produced by per se conventional

procedures, of which typical examples are shown in the following reaction schemes.

Procedure 1



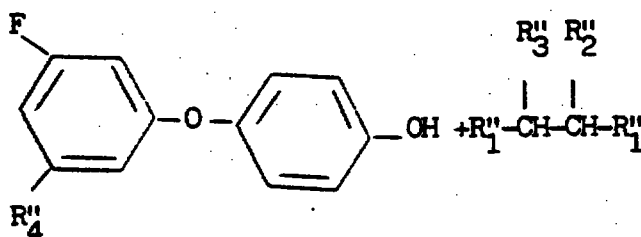
13

- 5 -

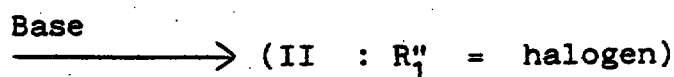
(wherein R_2'' , R_3'' , R_4'' are each as defined above and W, is an alkyl group).

Procedure (2)

5



10

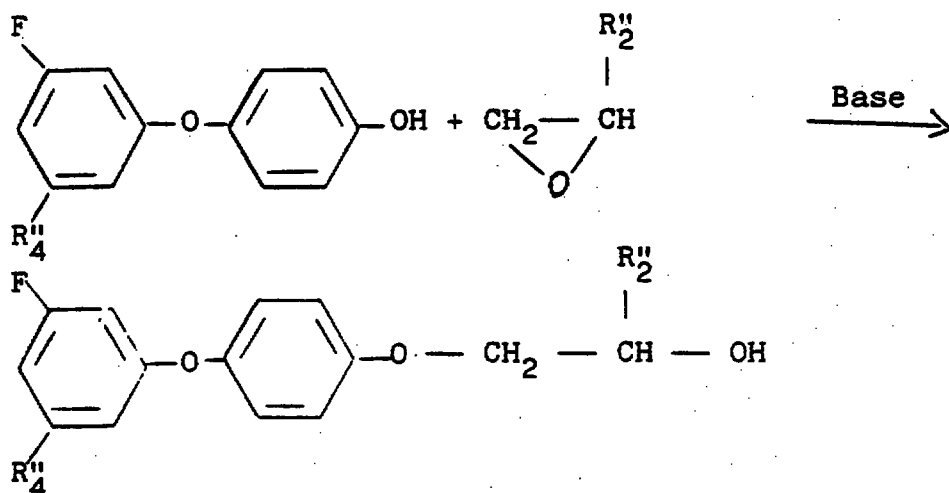


(wherein R_2'' , R_3'' and R_4 are each as defined above).

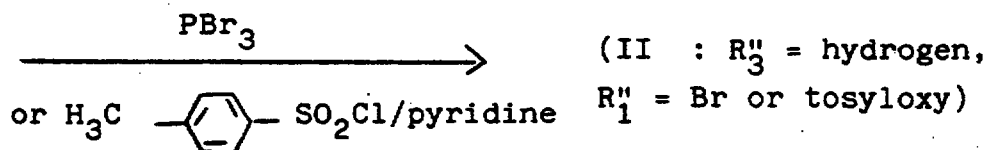
15

Procedure (3)

20

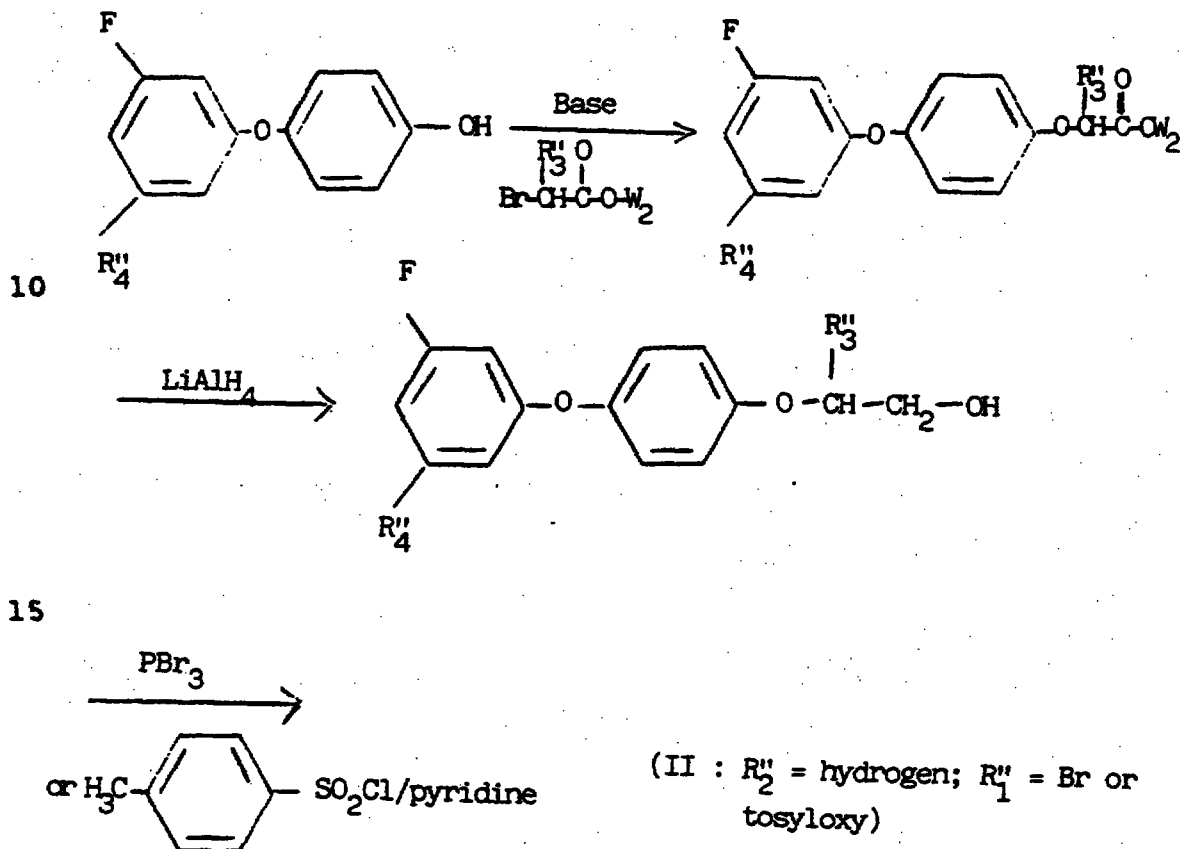


25



(wherein R_2'' and R_4'' are as defined above).

5 Procedure 4

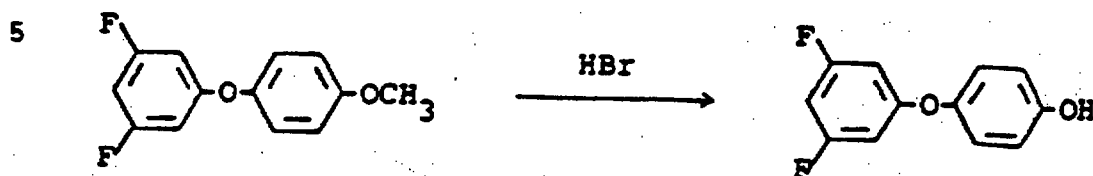
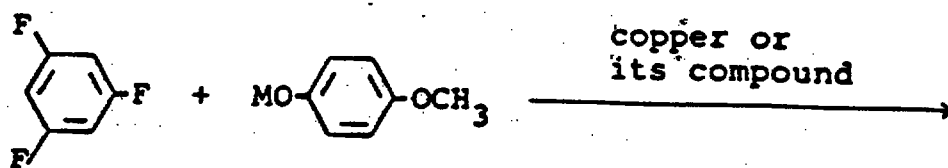


(wherein R_3'' and R_4'' are as defined above and W_2 is an alkyl group).

25 A typical example for producing the compound 4-(3,5-difluorophenoxy)phenol, is illustrated below.

(15)

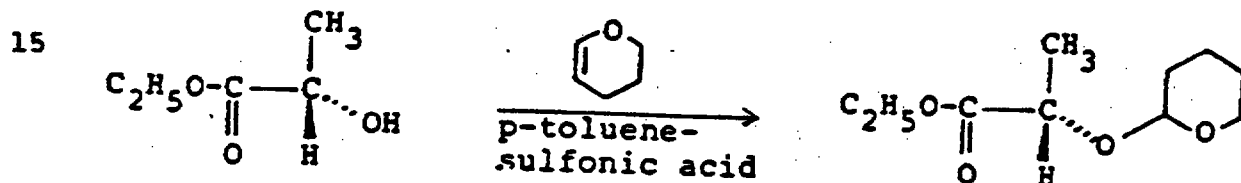
- 7 -



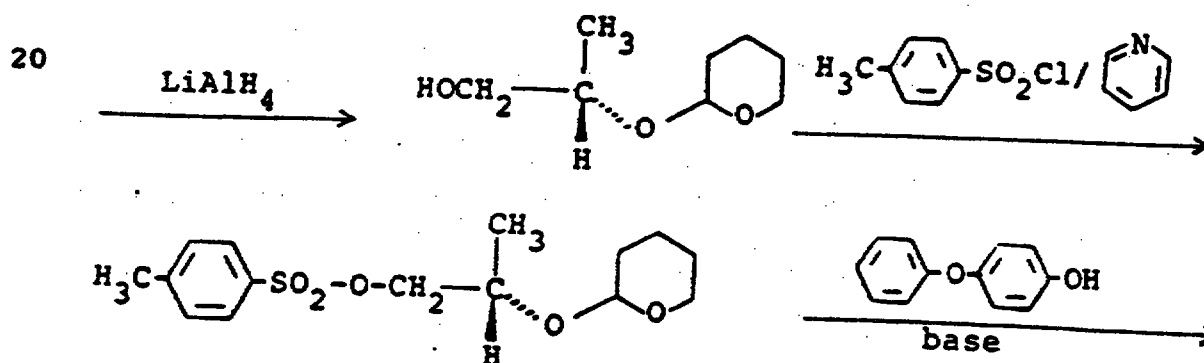
(wherein M is an alkali metal atom).

10

One of the optically active intermediate compounds of the invention, i.e. (S)-(+)-1-methyl-2-(4-phenoxyphenoxy)ethanol, may be obtained in the following manner:

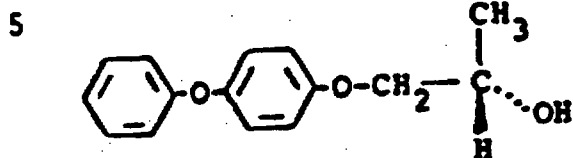
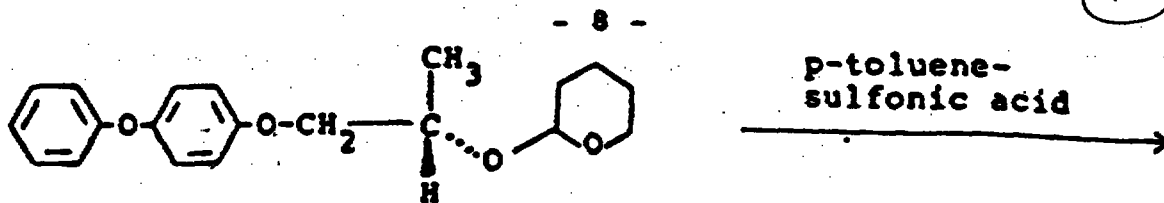


((S)-L-ethyl lactate)



25

(16)



10 Likewise, (R)-(-)-1-methyl-2-(4-phenoxyphenoxy)-
ethanol is prepared from (R)-D-ethyl lactate.

15 The (R)-(-)- or (S)-(+)-isomer of 1-methyl-2-(4-
phenoxyphenoxy)ethanol can be converted into its other
corresponding stereo-isomer according to the following
steps:

20

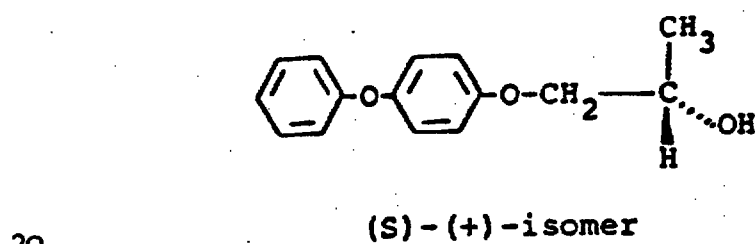
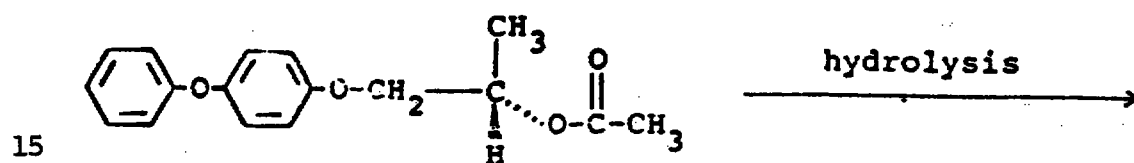
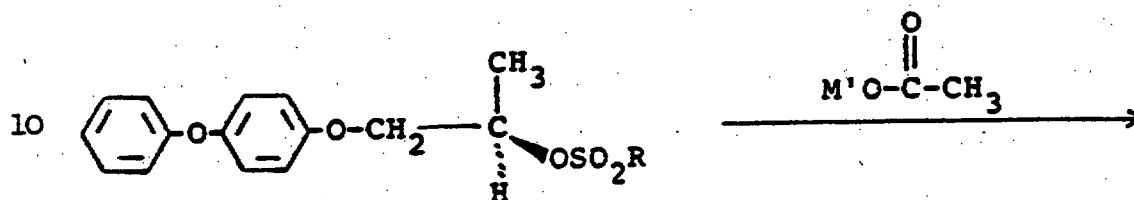
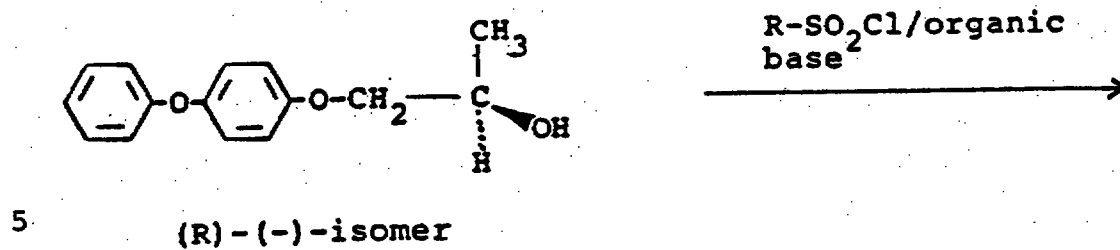
25

30

35

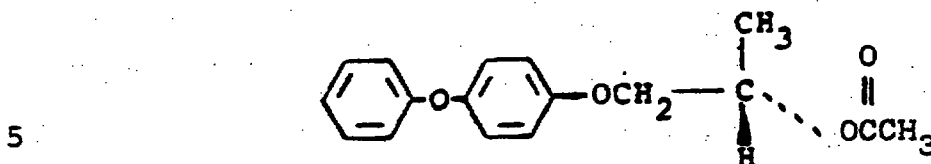
(17)

- 8a -



wherein R is a p-tolyl group or a methyl group and M' is a sodium atom or a potassium atom.

The compound of the formula



is a novel compound and constitutes a preferred aspect of the invention.

10 The following are Examples of the preparation of the compounds of the invention.

Example 1

Preparation of (S)-(+)-1-methyl-2-(4-phenoxyphenoxy)ethanol:-

15 A solution of 4-phenoxyphenol (2.14 g, 11.5 mmol) in toluene (7 ml) was poured into an aqueous solution (3 ml) of sodium hydroxide (0.92 g, 23.0 mmol) and (S)-(-)-propylene oxide (1.0 g, 17.24 mmol; a reagent manufactured by Aldrich; $[\alpha]^{20}_D = 7.2^\circ$ (CHCl₃, c = 1)) was added thereto while stirring. To
20 the resultant mixture, tetra-n-butyl-ammonium bromide (185 mg) was added, and the mixture was stirred at room temperature for 12 hours, followed by addition of (S)-(-)-propylene oxide (1 g). After stirring at room
25 temperature for 6 hours, the reaction mixture was vigorously stirred with addition of water (20 ml) and toluene (20 ml). The toluene layer was separated and

washed with a 20% aqueous sodium hydroxide solution and an aqueous sodium chloride solution in order and dried over magnesium sulfate. Removal of the solvent gave crude (S)-(+)-1-methyl-2-(4-phenoxyphenoxy)ethanol

5 (2.35 g), which was further purified by silica gel column chromatography to give (S)-(+)-1-methyl-2-(4-phenoxyphenoxy)ethanol (1.97 g).

$[\alpha]_D = +14.0^\circ$ (CHCl_3 , $c = 1$) ee.: 72.9 %.

Example 2

10 Preparation of (S)-1-methyl-2-(4-phenoxyphenoxy)-ethyl acetate through
(R)-1-methyl-2-(4-phenoxyphenoxy)ethyl methanesulfonate:

A mixture of anhydrous sodium acetate (82 mg, 1.0 mmol), (R)-1-methyl-2-(4-phenoxyphenoxy)ethyl
15 methanesulfonate (250 mg, 0.78 mmol; ee.: 99.4 %) and dimethylformamide (5 ml) was stirred at an inner temperature of 100 to 110°C for 5 hours. After being allowed to cool, ice-water was added thereto, and the
20 reaction mixture was extracted with toluene three times. The toluene layer was dried over anhydrous magnesium sulfate. The solvent was removed, and the residue was purified by thin layer chromatography using silica gel to give (S)-(-)-methyl-2-(4-phenoxyphenoxy)-
25 ethyl acetate (158 mg). $[\alpha]_D^{23} = -30.6^\circ$ (CHCl_3 , $c = 1$). ee.: 88.8 %.

Example 3

Preparation of 4-(3,5-difluorophenoxy)anisole:-

Sodium hydride (7.56 g, 0.189 mol; 60 % in oil) was washed with n-hexane to eliminate the oil, and N,N-dimethylformamide (100 ml) was added thereto to make a suspension. To the thus prepared suspension, 4-methoxyphenol (25.84 g, 0.208 mol) was gradually added with stirring, and stirring was continued until the generation of hydrogen gas ceased. 1,3,5-Trifluorobenzene (30.00 g, 0.227 mol) and cuprous chloride (0.50 g) were added thereto. The resultant mixture was heated under reflux for 8 hours with stirring. After being allowed to cool, the reaction mixture was poured into ice-water and extracted with toluene. The toluene layer was dried over anhydrous magnesium sulfate. The solvent was removed, and the residual oil was distilled under reduced pressure to give 4-(3,5-difluorophenoxy)anisole (25.42 g). B.P., 98.5°C/0.2 mmHg.

20

Example 4

Preparation of 4-(3,5-difluorophenoxy)phenol :-

A mixture of 4-(3,5-difluorophenoxy)anisole (22.0g, 0.093 mol), acetic acid (200 ml) and a 47 % aqueous hydrogen bromide solution (200ml) was heated with stirring under reflux for 8 hours. After allowed to cool, the reaction mixture was poured into ice-water and extracted with a mixture of ether and n-hexane (1 :

25

2). The organic layer was washed with water three times and dried over anhydrous magnesium sulfate. Removal of the solvent gave 4-(3,5-difluorophenoxy)-phenol (20.27 g).

5

Example 5

Preparation of 2-[4-(3,5-difluorophenoxy)-phenoxy]ethanol:-

10 4-(3,5-Difluorophenoxy)phenol (9.0 g, 40.5 mmol) was added to an ethanolic solution of sodium ethoxide prepared from ethanol (40 ml) and sodium (939 mg, 40.9 mmol). To the resultant solution, 2-chloroethanol (3.26 g, 40.5 mmol) was dropwise added with stirring
15 under reflux. After completion of the addition, the resultant mixture was stirred under reflux for 4 hours. After being allowed to cool, ethanol was removed, and the residual oil was dissolved in toluene. The toluene layer was washed with water once, a 20% aqueous
20 potassium hydroxide solution two times and a saturated aqueous sodium chloride solution once in order and dried over anhydrous magnesium sulfate. Removal of the solvent gave 2-[4-(3,5-difluorophenoxy)phenoxy]ethanol (6.50 g).

25

Example 6

Preparation of 1-methyl-2-[4-(3,5-difluoro-

phenoxy)phenoxy]ethanol:-

4-(3,5-Difluorophenoxy)phenol (3.0 g, 13.5 mmol) was added to an ethanolic solution of sodium ethoxide prepared from ethanol (15 ml) and sodium (313 mg, 13.6 mmol). To the resultant solution, 1-chloro-2-propanol (1.60 g, 16.9 mmol) was dropwise added with stirring under reflux. After completion of the addition, the resultant mixture was stirred under reflux for 5 hours. After being allowed to cool, ethanol was removed, and the residual oil was dissolved in toluene. The toluene layer was washed with water once, a 20 % aqueous potassium hydroxide solution two times and a saturated aqueous sodium chloride solution once in order and dried over anhydrous magnesium sulfate. Removal of the solvent gave 1-methyl-2-[4-(3,5-difluorophenoxy)-phenoxy]ethanol (2.24 g).

Example 7

Preparation of 2-methyl-2-[4-(3,5-difluorophenoxy)phenoxy]ethanol:-

A mixture of 4-(3,5-difluorophenoxy)phenol (11.1g, 50.0 mmol), ethyl 2-bromopropionate (9.96 g 55.0 mmol), potassium carbonate (7.25 g, 52.5 mmol) and N,N-dimethylformamide (50 ml) was stirred at an inner temperature of 70 to 80°C for 3 hours. After being

allowed to cool, the reaction mixture was poured into ice-water and extracted with toluene. The toluene layer was dried over anhydrous magnesium sulfate, and the solvent was removed to give ethyl 2-[4-(3,5-difluorophenoxy)-phenoxy]propionate (15.6 g).

The thus obtained ethyl 2-[4-(3,5-difluorophenoxy)phenoxy]propionate (15.6 g) was dissolved in diethyl ether (10 ml). The resulting solution was dropwise added to a suspension of lithium aluminium hydride (1.38 g, 36.3 mmol) in diethyl ether (70 ml) with stirring at an inner temperature of -20 to -10°C. After completion of the addition, stirring was continued for 1 hour while keeping the inner temperature at 0 to 5°C. The reaction mixture was poured into a mixture of ice and hydrochloric acid and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate, and the solvent was removed to give 2-methyl-2-[4-(3,5-difluorophenoxy)-phenoxy]ethanol (12.6 g).

Example 8

Preparation of 2-[4-(3,5-difluorophenoxy)-phenoxy]ethyl bromide:-

To a mixture of 2-[4-(3,5-difluorophenoxy)-phenoxy]ethanol (1.00 g, 3.76 mmol) and n-hexane (50

24

ml), phosphorus tribromide (0.71 g, 2.63 mmol) was gradually added with stirring under ice-cooling. After completion of the addition, the temperature was elevated to room temperature and stirring was continued at the same temperature for 30 minutes, followed by stirring under reflux for 1 hour. After being allowed to cool, the upper n-hexane layer was collected by decantation, and the n-hexane layer was washed with water two times, an aqueous sodium carbonate solution three times and a saturated aqueous sodium chloride solution once in order and dried over anhydrous magnesium sulfate. Removal of the solvent gave 2-[4-(3,5-difluorophenoxy)phenoxy]ethyl bromide (915 mg).

15

Example 9

Preparation of 2-[4-(3,5-difluorophenoxy)-phenoxy]ethyl p-toluenesulfonate:-

20 To a solution of 2-[4-(3,5-difluorophenoxy)-phenoxy]ethanol (2.66 g 10.0 mmol) in pyridine (2.8 g), p-toluenesulfonyl chloride (1.91 g, 10.0 mmol) was gradually added with stirring while cooling at -20°C, and the resultant mixture was allowed to stand in a refrigerator overnight. Diethyl ether was added to the reaction mixture, which was washed with dilute hydrochloric acid until the aqueous layer became

25

acidic, followed by washing with an aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution. The obtained ether layer was dried over anhydrous magnesium sulfate, and the solvent was removed to give 2-[4-(3,5-difluorophenoxy)phenoxy]-ethyl p-toluenesulfonate (3.90 g).

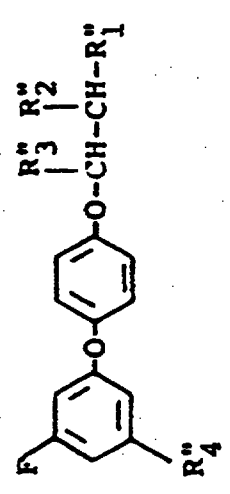
In the same manner as described above, the following compounds as detailed in Tables 1 and 2 were prepared.

15

20

25

TABLE 1



Compound No.	R ₁ ''	R ₂ ''	R ₃ ''	R ₄ ''	Physical constant
1					$n_D^{29.5}$ 1.5364
2					$n_D^{29.5}$ 1.5538
3	OH	H	H	F	$n_D^{29.0}$ 1.5476
4	OH	H	CH ₃	F	$n_D^{28.0}$ 1.5331
5	OH	CH ₃	H	F	$n_D^{29.5}$ 1.5359
6	Br	H	H	F	$n_D^{25.5}$ 1.5589
7	Br	H	CH ₃	F	$n_D^{28.5}$ 1.5459
8	Br	CH ₃	H	F	$n_D^{26.5}$ 1.5473

27

(Continued)

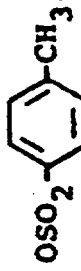
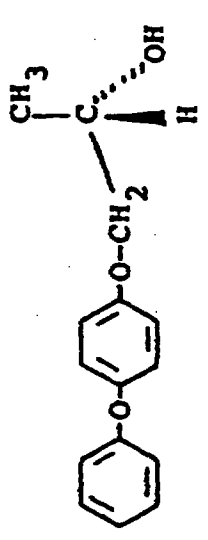
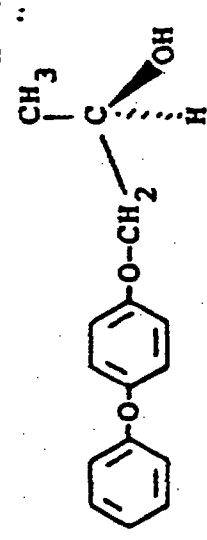
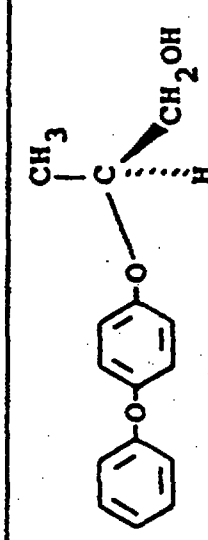
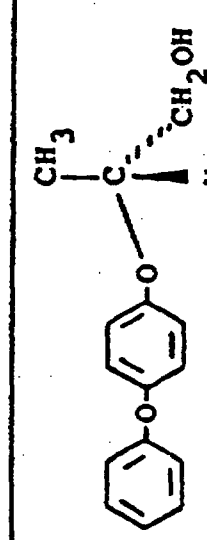
Compound No.	R ₁ ^{''}	R ₂ ^{''}	R ₃ ^{''}	R ₄ ^{''}	Physical constant
9		H	H	F	n _D ^{27.0} 1.5621
10		H	CH ₃	F	n _D ^{27.5} 1.5490
11		CH ₃	H	F	n _D ^{29.0} 1.5508
12	OSO ₂ CH ₃	H	H	F	n _D ^{27.5} 1.4846
13	OSO ₂ CH ₃	H	CH ₃	F	n _D ^{28.0} 1.4715
14	OSO ₂ CH ₃	CH ₃	H	F	n _D ^{26.5} 1.4732
15	OH	H	H	H	n _D ^{21.5} 1.4629
16	OH	H	CH ₃	H	M.P. 40-44°C
17	OH	CH ₃	H	H	M.P. 44.9°C
18	Br	H	H	H	n _D ^{21.5} 1.5757
19	Br	H	CH ₃	H	n _D ^{21.5} 1.5649
20	Br	CH ₃	H	H	n _D ^{21.5} 1.5632

TABLE 2

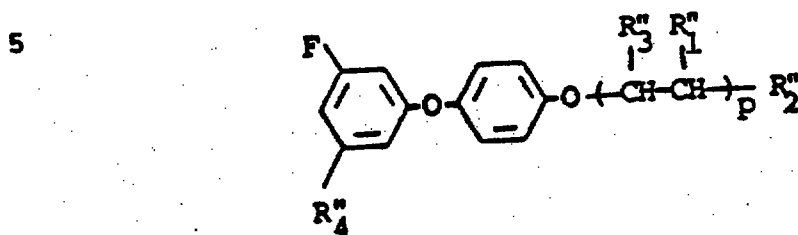
Compound No.	Structure	Physical constant
	 (S)-isomer	$[\alpha]_D^{23} = +18.5^\circ$ $(\text{CHCl}_3, c = 1)$ $ee.: 96.3 \%$
	 (R)-isomer	$[\alpha]_D^{23} = -19.1^\circ$ $(\text{CHCl}_3, c = 1)$ $ee.: 99.4 \%$
	 (S)-isomer	$[\alpha]_D^{23} = +23.1^\circ$ $(\text{CHCl}_3, c = 0.39)$ $ee.: 42.2 \%$
	 (R)-isomer	$[\alpha]_D^{23} = +48.7^\circ$ $(\text{CHCl}_3, c = 0.38)$ $ee.: 89.7 \%$

28



CLAIMS:

1. A compound of the formula:



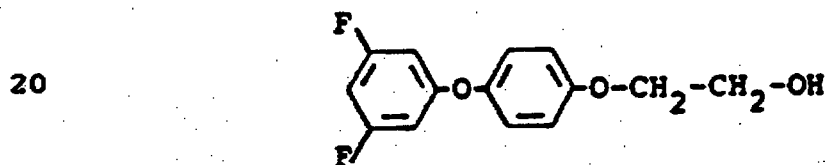
wherein p is 0 or 1.

- 10 R_1'' is a halogen atom, a hydroxyl group, a tosyloxy group or a mesyloxy group,

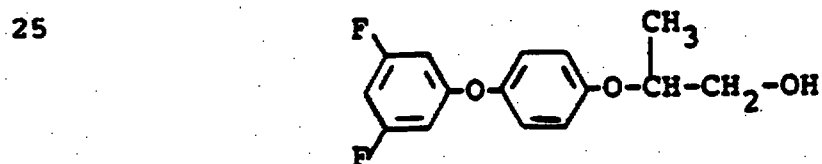
R_2'' and R_3'' are each independently a hydrogen atom or a methyl group, and,

- 15 R_4'' is a hydrogen atom or a fluorine atom when p is 1 or a fluorine atom when p is 0.

2. A compound as claimed in Claim 1, having the formula :



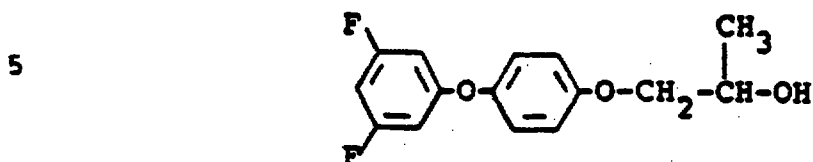
3. A compound as claimed in Claim 1 having the formula:



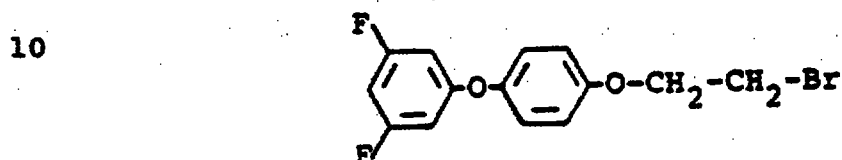


30

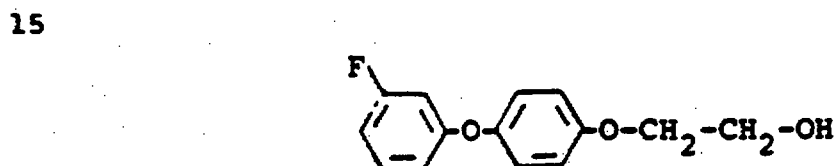
4. A compound as claimed in Claim 1 having the formula:



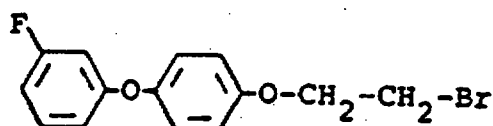
5. A compound as claimed in Claim 1 having the formula:



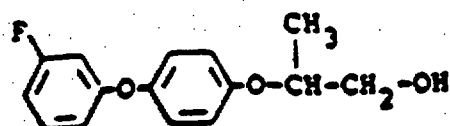
6. A compound as claimed in Claim 1 having the formula:



7. A compound as claimed in Claim 1 having the formula:



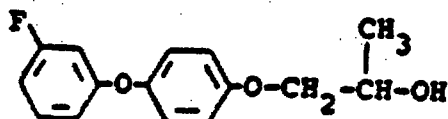
8. A compound as claimed in Claim 1 having the formula:



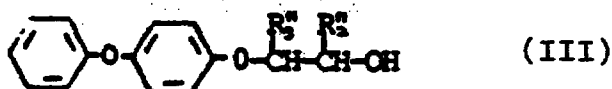
(2)



9. A compound as claimed in Claim 1 having the
5 formula:



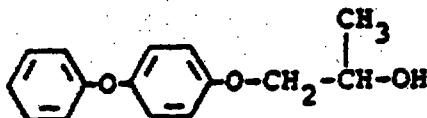
10. An optically active isomer of a compound of
the formula:



15

wherein one of R''_2 and R''_3 is a hydrogen atom and the other is a methyl group.

11. A compound as claimed in Claim 10 which is
an (S)-(+)-isomer of the compound of the formula:



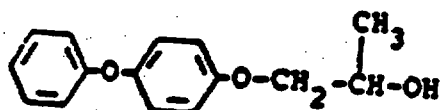
25

12. A compound as claimed in Claim 10 which is
an (R)-(-)-isomer of the compound of the formula:

32

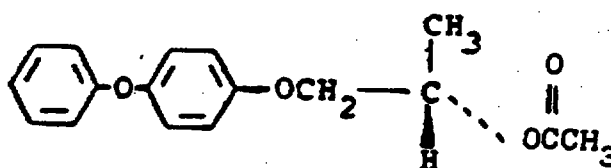


5



10

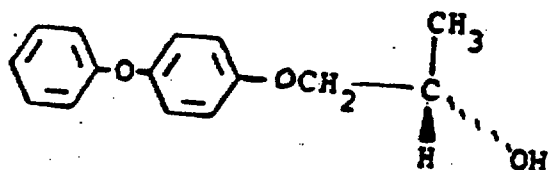
13. A compound of the formula:



15

14. A process for preparing a compound of the formula:

20



25

which comprises the hydrolysis of a compound as claimed in Claim 13.

30

15. A process for preparing a compound as claimed in Claim 1 substantially as hereinbefore described with reference to Procedure 1, 2, 3 or 4 as described herein.

35

16. A process for the preparation of a compound as claimed in Claim 1 substantially as hereinbefore described with reference to any one of Examples 3 to 9.



17. A process for the preparation of a compound
5 as claimed in Claim 10 substantially as hereinbefore
described with reference to Example 1 or Example 2.

18. A compound as claimed in Claim 1 whenever
10 prepared by a process as claimed in Claim 15 or Claim
16.

19. A compound as claimed in Claim 10 whenever
15 prepared by a process as claimed in Claim 17.

20

25

30

35