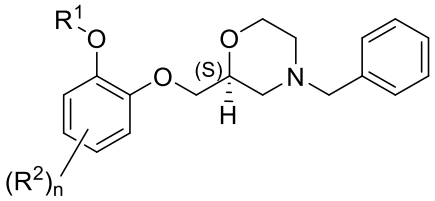
CLAIMS

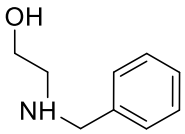
1. A method of manufacturing a morpholine derivative of formula (IIb):



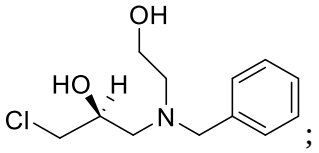
(IIb);

or a pharmaceutically acceptable salt thereof, the method comprising:

(a) reacting a compound of formula

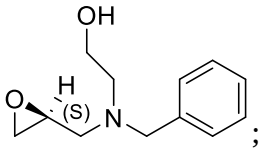



with (S)-(+)-epichlorohydrin to form a chlorohydrin compound of formula



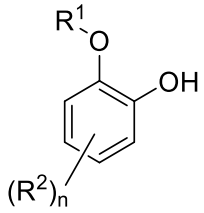
;

(b) contacting the chlorohydrin compound with a base and phase transfer catalyst to form an epoxide compound of formula

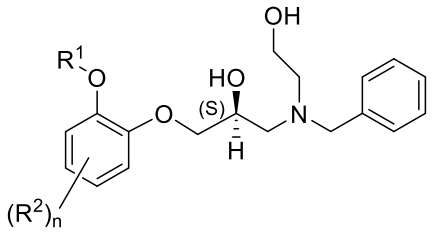


;

(c) contacting the epoxide compound with a base and a compound of formula:

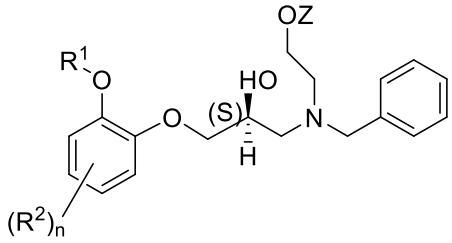


(Ia) to form a diol compound of formula



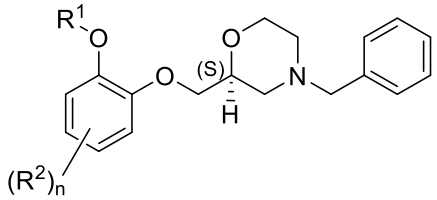
(IIa);

(d) contacting the diol compound with a base followed by addition of a sulfonyl halide compound to form an intermediate sulfonate of formula



(IIa'), wherein Z is a sulfonyl leaving group,

that cyclizes in situ to give an N-benzyl protected morpholine compound of formula



(IIb); and

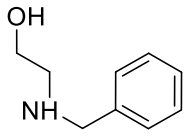
(e) forming the HCl salt of the compound of formula IIb and recrystallizing it to afford the highly pure (S)-enantiomer HCl salt; and

(f) converting the HCl salt of compound (IIb) to the free base;

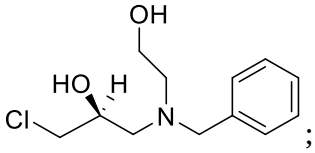
wherein $R^1$ is $C_1$-$C_6$ alkyl, aryl, or heteroaryl; each $R^2$ is independently selected from F, Cl, Br, I, CN, $NO_2$, $C_1$-$C_6$ alkyl, aryl, heteroaryl, or heterocycloalkyl; and *n* is 0, 1, 2, 3, or 4.

2. A method of manufacturing a morpholine derivative or a pharmaceutically acceptable salt thereof, the method comprising:

(a) reacting a compound of formula

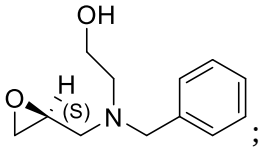


with (S)-(+)-epichlorohydrin to form a chlorohydrin compound of formula



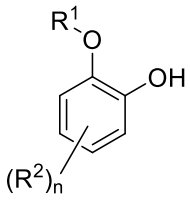
;

(b) contacting the chlorohydrin compound with a base and a phase transfer catalyst to form an epoxide compound of formula

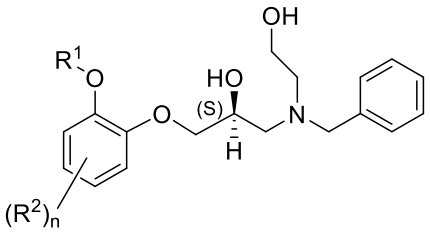


;

(c) contacting the epoxide compound with a base and a compound of formula:

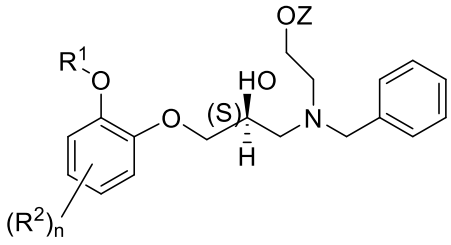


(Ia) to form a diol compound of formula



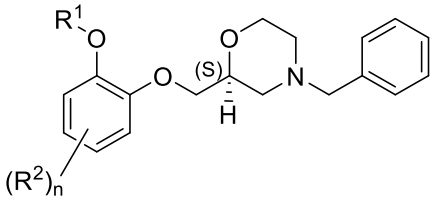
(IIa);

(d) contacting the diol compound with a base followed by addition of a sulfonyl halide compound to form an intermediate sulfonate of formula



(IIa'), wherein Z is a sulfonyl leaving group,

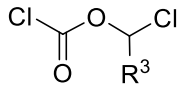
that cyclizes in situ to form an N-benzyl protected morpholine compound of formula

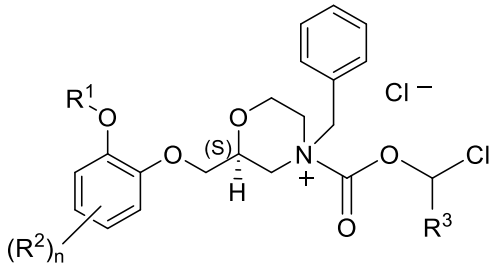


(IIb);

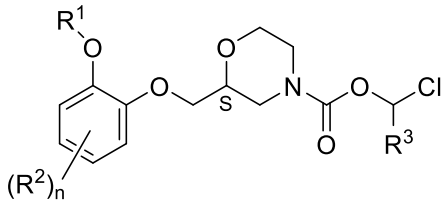
(e) forming the HCl salt of the compound of formula (IIb) and recrystallizing it to afford the highly pure (S)-enantiomer as an HCl salt;

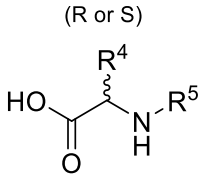
(f) converting the HCl salt of compound (IIb) to the free base;

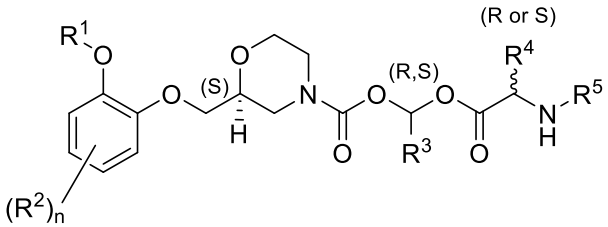
(g) contacting the N-benzyl protected morpholine compound with a chloroformate of formula:  (Ic); to form an intermediate N-benzyl chlorocarbamate salt of formula

 (IIc)

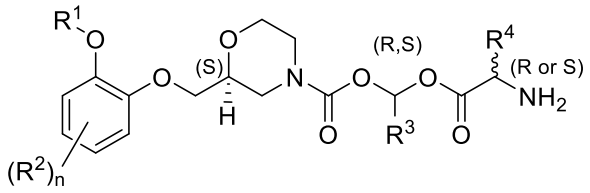
that loses benzyl chloride upon heating to give a compound of formula

 (IId);

(h) addition of the chlorocarbamate compound to a metal salt of an amino acid derivative of formula  (Id), wherein the amino acid derivative has been pretreated with a metal compound, to form a protected amine of formula

 (IIe); and,

(i) contacting the protected amine with an acid to provide the morpholine derivative (IIf) as an acid salt:



(IIf);

wherein $R^1$ is $C_1$-$C_6$ alkyl, aryl, or heteroaryl; each $R^2$ is independently selected from F, Cl, Br, I, CN, $NO_2$, $C_1$-$C_6$ alkyl, aryl, heteroaryl, or heterocycloalkyl; $R^3$ is a $C_1$-$C_6$ alkyl, $R^4$ is a the $C_1$-$C_6$ alkyl, $R^5$ is an amino protecting group; and *n* is 0, 1, 2, 3, or 4.

3. The method according to any preceding claim, wherein the phase transfer catalyst utilized in step (b) is tetrabutylammonium hydrogen sulfate.

4. The method according to any preceding claim, wherein a phase transfer catalyst is utilized in step (d).

5. The method according to claim 4, wherein the phase transfer catalyst is benzyltriethylammonium chloride.

6. The method according to claim 5, wherein the product contains greater than 60% of the (S) enantiomer and the (S)-HCl salt may be crystallized to give the HCl salt with greater than 90% of one enantiomer.

7. The method according to any preceding claim, wherein the sulfonyl halide selected from the group consisting of p-toluenesulfonyl chloride (tosyl chloride), brosyl chloride, nosyl chloride, and mesyl chloride.

8. The method according to claim 7, wherein the sulfonyl halide compound is p-toluenesulfonyl chloride.9. The method according to any preceding claim, wherein cyclization is performed using NaOH.

10. The method according to any one of claims 2 to 9, wherein the crude product chlorocarbamate compound formed step (e) is washed with an alkane solvent, evaporated, or treated with triethylamine to remove the benzyl chloride byproduct before performing the next step.

11. The method according to any one of claims 2-10, wherein the metal salt of step (h) is a cesium salt.

12. The method according to any one of claims 2-11, wherein the metal compound of step (h) is cesium carbonate.

13. The method according to any preceding claim, wherein step (a) further comprises an organic solvent.

14. The method according to claim 13, wherein step (a) further comprises heating to a temperature of at least 30 °C.

15. The method according to any preceding claim, wherein step (b) is performed at room temperature.

16. The method according to any preceding claim, wherein $R^1$ is $-CH_3$ or $-CH_2CH_3$.

17. The method according to any preceding claim, wherein each $R^2$ is independently selected from -F, -Cl, -Br, -I, or $C_1$-$C_6$ alkyl.

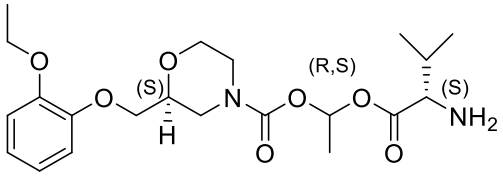
18. The method according to any preceding claim, wherein $R^3$ is $-CH_3$ or isopropyl.

19. The method according to any preceding claim, wherein $R^4$ is isopropyl.

20. The method according to any preceding claim, wherein $R^5$ is *tert*-butoxycarbonyl (Boc).

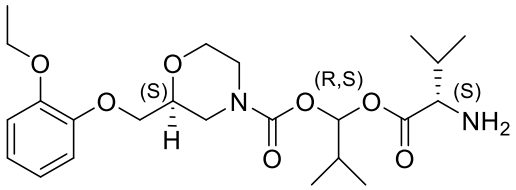
21. The method according to any preceding claim, wherein *n* is 0.

22. The method according to any one of claims 2-21, wherein the morpholine derivative from step (i) has the following formula:



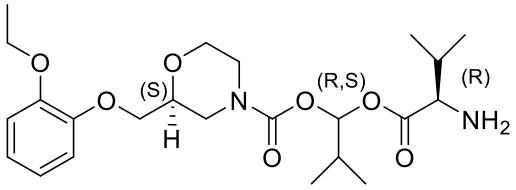

; or a pharmaceutically acceptable salt thereof.

23. The method according to any one of claims 2-21, wherein the morpholine derivative from step (i) has the following formula:




; or a pharmaceutically acceptable salt thereof.

24. The method according to any one of claims 2-21, wherein the morpholine derivative from step (i) has the following formula:




; or a pharmaceutically acceptable salt thereof.