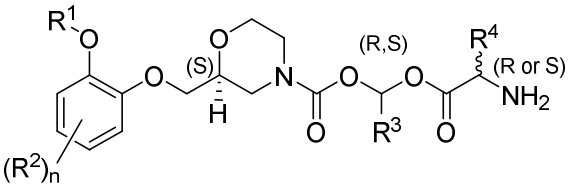
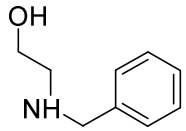
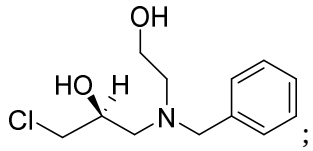
[0013] In another aspect, the invention provides a method of manufacturing a morpholine derivative of formula (IIf):  (IIf); or prodrug or a pharmaceutically acceptable salt thereof, the method comprising:

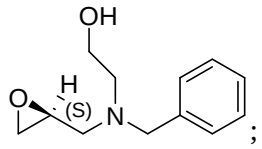
(a) reacting a compound of formula

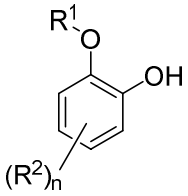


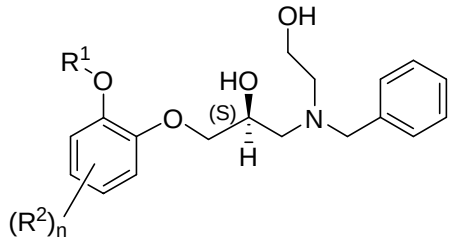
with (S)-(+)-epichlorohydrin to form a chlorohydrin compound of formula

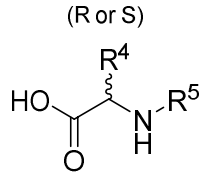
;

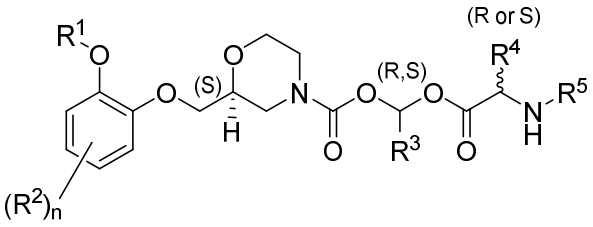
(b) contacting the chlorohydrin compound with a base and a phase transfer catalyst to form an epoxide compound of formula

;

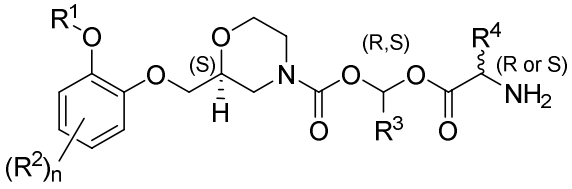
(c) contacting the epoxide compound with base and a compound of formula:  (Ia) to form a diol compound of formula

 (IIa);

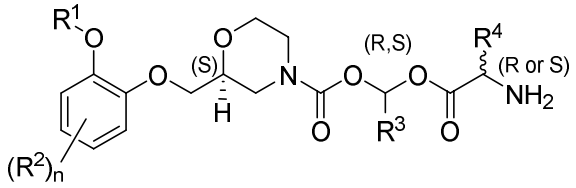
(h) addition of the chlorocarbamate compound to a metal salt of an amino acid derivative of formula  (Id), wherein the amino acid derivative has been pretreated with a metal compound carbonate, to form a protected amine of formula

 (IIe); and,

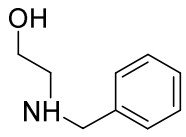
(i) contacting the protected amine with an acid to provide the morpholine derivative having the following formula:

 (IIf);

wherein R^1 is C_1-C_6 alkyl, aryl, heteroaryl, or heterocycloalkyl; 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 C_1-C_6 alkyl, R^5 is an amino protecting group; and *n* is 0, 1, 2, 3, or 4.

[0014] In an embodiment, the invention provides a method of manufacturing a morpholine derivative of formula (IIf):  (IIf); or prodrug or a pharmaceutically acceptable salt thereof, the method comprising:

(a) reacting a compound of formula



[00156] The synthesis of 1-[(*S*)-2-amino-3-methylbutyroxy]ethyl (*S*)-2-[(*o*-ethoxyphenoxy)methyl]-4-morpholinecarboxylate HCl (**12**) via the new route (Scheme VIII) proceeds via the N-benzyl ethanolamine (**1**) opening of (S)-(+)-epichlorohydrin (2, source of chirality) through formation of chlorohydrin **3**, epoxide **4**, diol **6** and cyclization to (S)-4-benzyl-2-((2-ethoxyphenoxy)methyl)morpholine (**7**). The route has been scaled up starting with a total of 1.2 mol of the ethanolamine **1**. Via the new route, crystallization of the crude (S)-4-benzyl-2-((2-ethoxyphenoxy)methyl)morpholine (**7** •HCl) under optimized conditions gives >99% of the (*S*)-isomer.

[00157] **Experimental Details**.

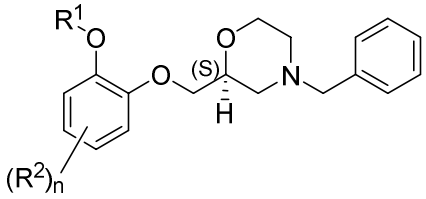
[00158] Step 1: 2-Benzylaminoethanol (**1**, 90.73 g, 600 mmol) and (S)-(+)-epichlorohydrin (**2**, 61.06 g, 660 mmol, 1.1 equivalents) were dissolved in 220 ml of methanol, stirred under nitrogen and warmed to 35 °C for 22 hr. The methanol was evaporated and 100 ml of toluene was added and the toluene evaporated. The toluene addition and evaporation was repeated 3 additional times to remove traces of epichlorohydrin and/or methanol and the oil was dried on a vacuum pump for 4 hr. The product chlorohydrin **3** (155 g) was obtained as a light yellow oil. HPLC (5-50-90% CH_3CN; H_2O/0.075% TFA) showed the main peak at 6.23 min (64% purity).

[00159] Step 2: The crude chlorohydrin **3** (155 g) was dissolved in 300 ml of MTBE. To the solution was added 2.4 g of tetrabutylammonium hydrogen sulfate and a solution of 25.2 g (630 mmol) of sodium hydroxide in 48 ml of water. The mixture was stirred for 1.5 hr at room temperature under nitrogen. The layers were separated and the aqueous layer was extracted with 100 ml of MTBE. The combined extracts were dried over magnesium sulfate and evaporated on a rotary evaporator then dried on high vacuum for 3 hr at room temperature. The epoxide **4** was obtained as a light yellow oil (113 g). HPLC using the same conditions as for **3** showed the product peak for epoxide **4** at 6.74 min (64.3%). LC-MS: $C_{12}H_{17}NO_2$ $[M+H]^+$: 208.17. The ^1H NMR spectrum of **4** is shown in FIGS. 2A-2B.

[00160] Step 3: The epoxide **4** (113 g) and 2-ethoxyphenol (**5**, 90.4 g, 655 mmol) were dissolved in 450 ml of toluene. The mixture was stirred (mechanical stirrer) and cesium carbonate (106.3 g, 327 mmol) was added in portions over ca. 30 min resulting in a temperature rise from room temperature to 34 °C. The mixture was stirred and allowed to cool to 32 °C over

CLAIMS

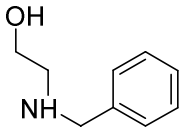
1. A method of manufacturing a morpholine derivative of formula (IIb):



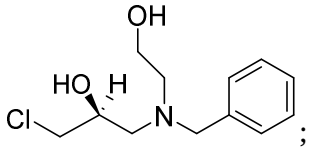
(IIb);

or a pharmaceutically acceptable salt thereof, the method comprising:

(a) reacting a compound of formula

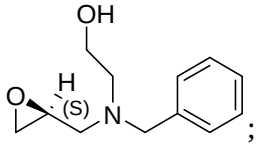


with (S)-(+)-epichlorohydrin to form a chlorohydrin compound of formula



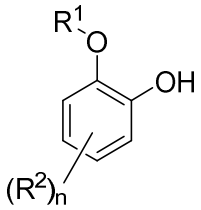
;

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

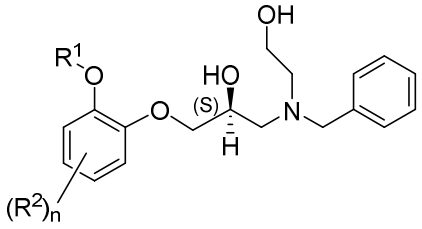


;

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

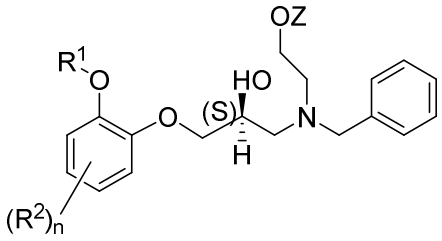


(Ia) to form a diol compound of formula



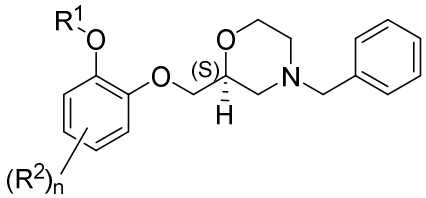
(IIa);

(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

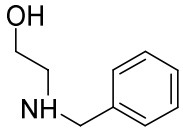
(e) forming the HCl salt of the compound of formula IIb and recrystallizing it to afford the highly pure (S)-enantiomer HCl salt; and

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

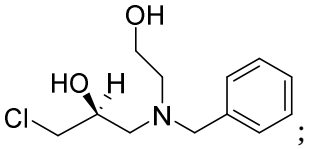
wherein R^1 is C_1-C_6 alkyl, aryl, or heteroaryl; each R^2 is independently selected from F, Cl, Br, I, CN, NO_2, C_1-C_6 alkyl, aryl, heteroaryl, or heterocycloalkyl; and *n* is 0, 1, 2, 3, or 4.

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

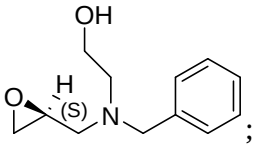
(a) reacting a compound of formula



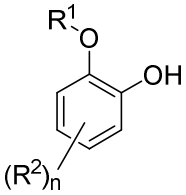
with (S)-(+)-epichlorohydrin to form a chlorohydrin compound of formula



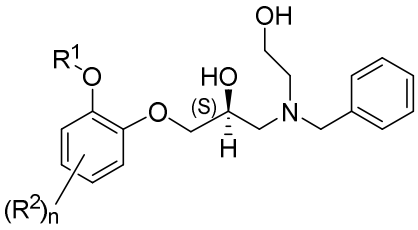
(b) contacting the chlorohydrin compound with a base and a phase transfer catalyst to form an epoxide compound of formula



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

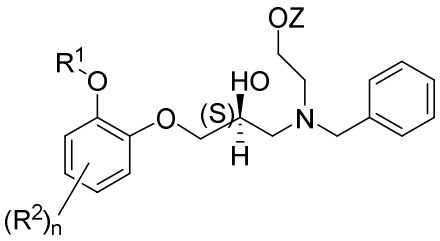


(Ia) to form a diol compound of formula

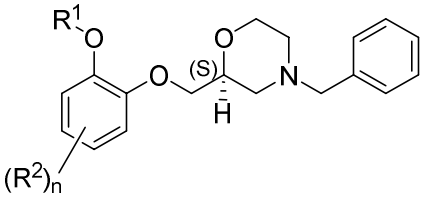


(IIa);

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



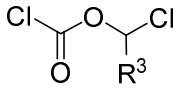
(IIa'), wherein Z is a sulfonyl leaving group, that cyclizes in situ to form an N-benzyl protected morpholine compound of formula

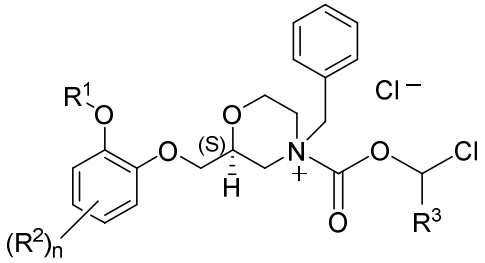


(IIb);

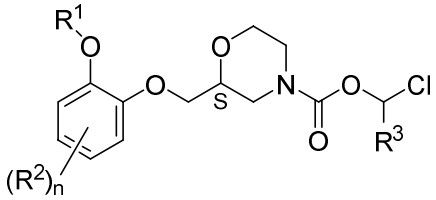
(e) forming the HCl salt of the compound of formula (IIb) and recrystallizing it to afford the highly pure (S)-enantiomer as an HCl salt;

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

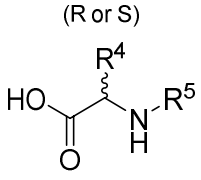
(g) contacting the N-benzyl protected morpholine compound with a chloroformate of formula:  (Ic); to form an intermediate N-benzyl chlorocarbamate salt of formula

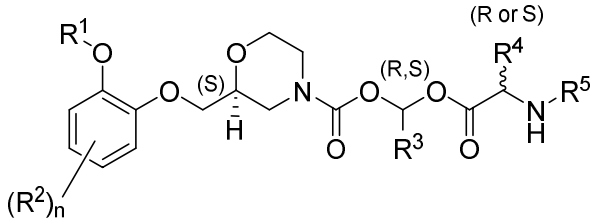
 (IIc)

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

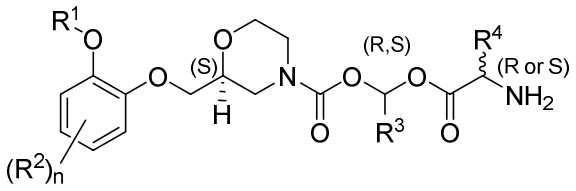
 (IId);

(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 of the forming of the HCI salt of the compound of formula (IIb) used in step (e) contains greater than 60% of the (S) enantiomer and said (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 (g) 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.

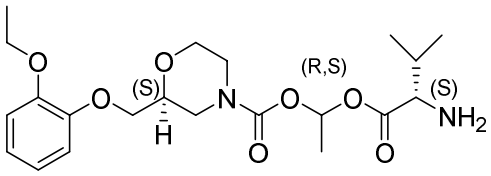
18. The method according to any preceding claim, wherein R^3 is $-CH_3$ or isopropyl.

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).

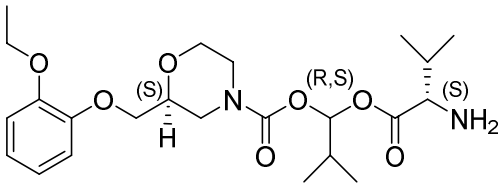
21. The method according to any preceding claim, wherein *n* is 0.

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



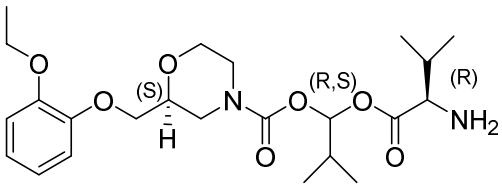
; or a pharmaceutically acceptable salt thereof.

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.