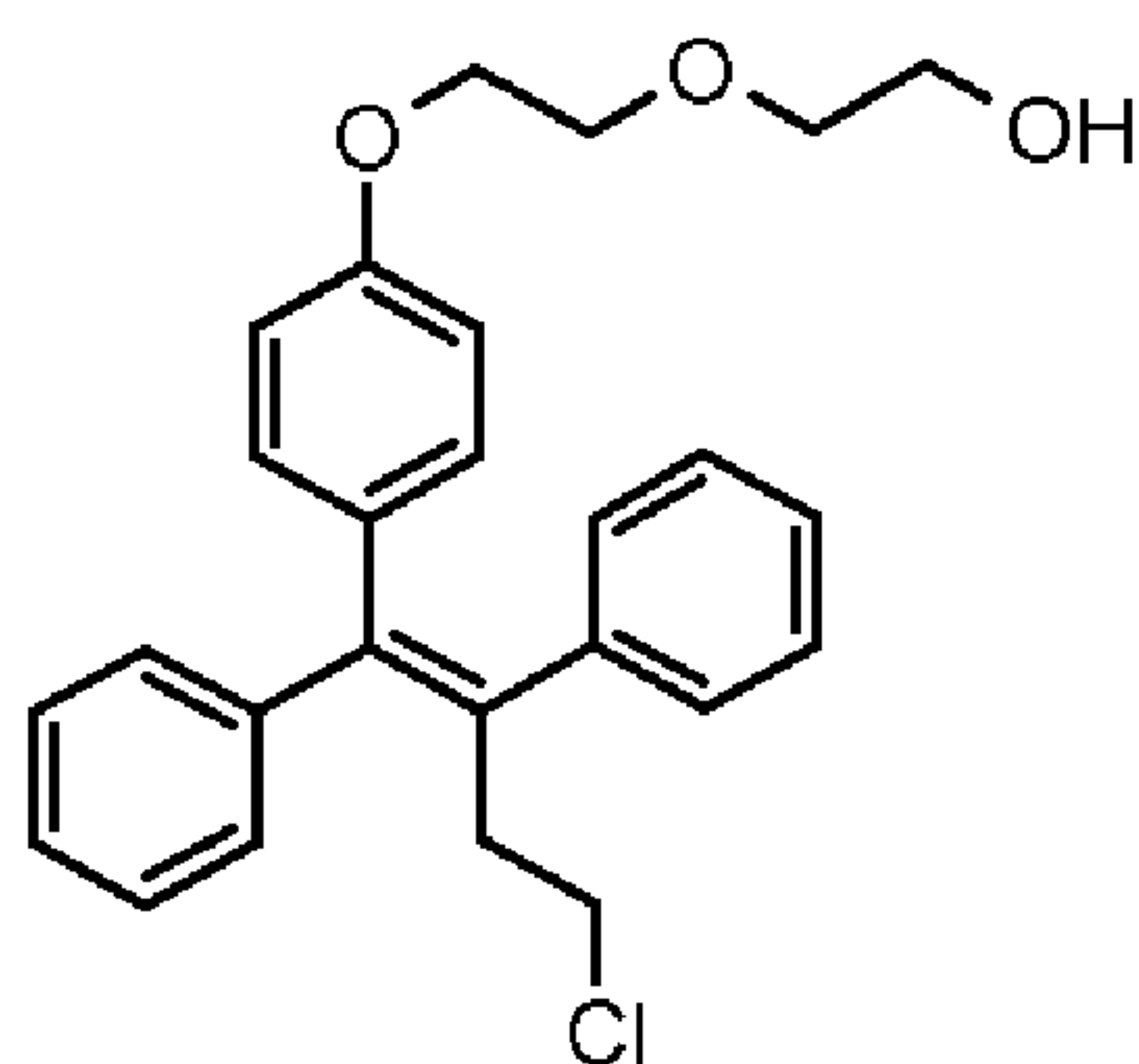




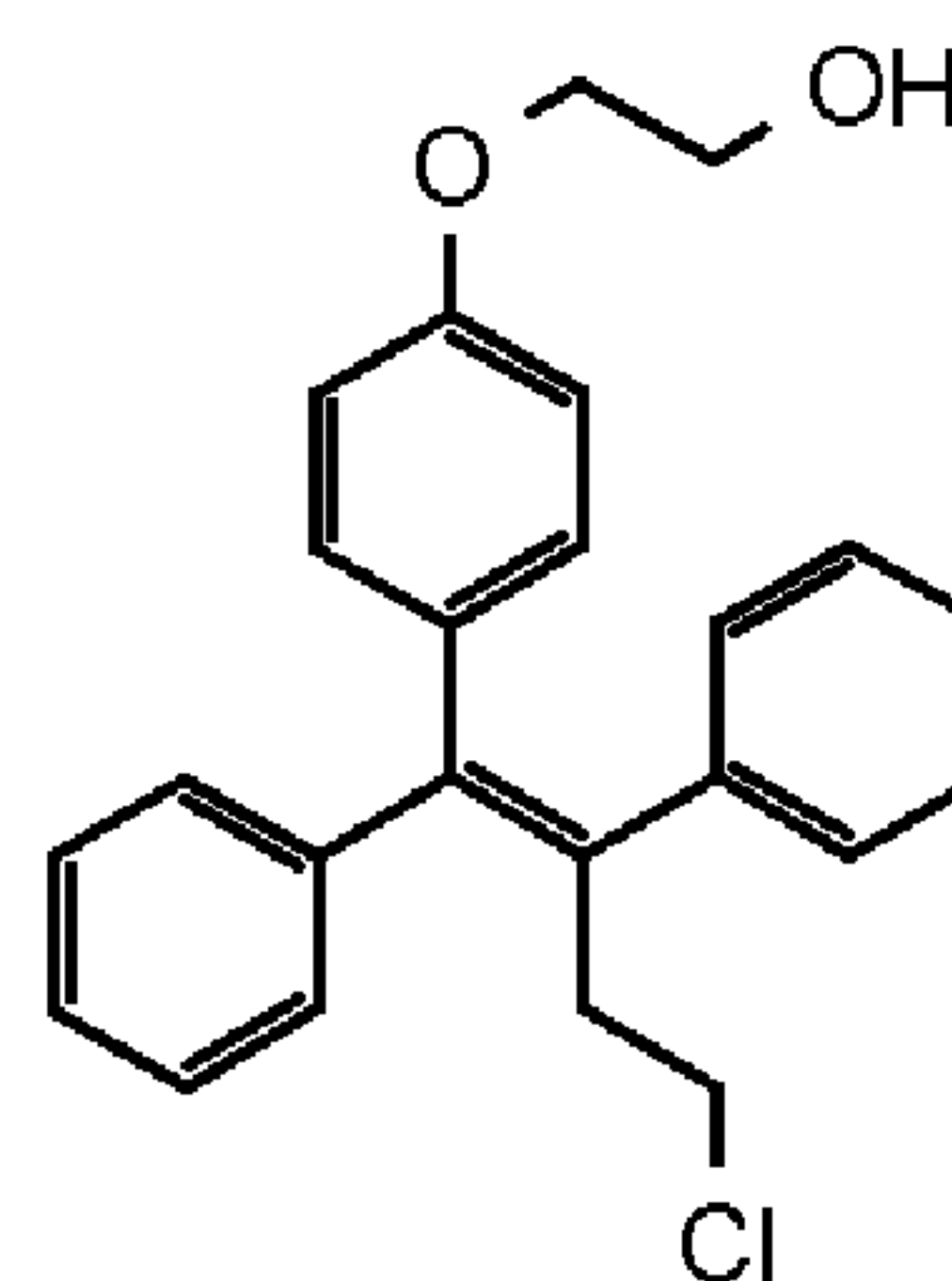
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(54) **Titre : PROCÉDE DE PRÉPARATION DE DÉRIVÉS DE TRIPHENYLBUTÈNE D'UNE VALEUR THÉRAPEUTIQUE**
(54) **Title: METHOD FOR THE PREPARATION OF THERAPEUTICALLY VALUABLE TRIPHENYLBUTENE DERIVATIVES**



(a)



(b)

(57) **Abrégé/Abstract:**

The present invention concerns a method for the preparation of therapeutically valuable triphenylbutene derivatives, especially ospemifene or fispemifene. formula (I).



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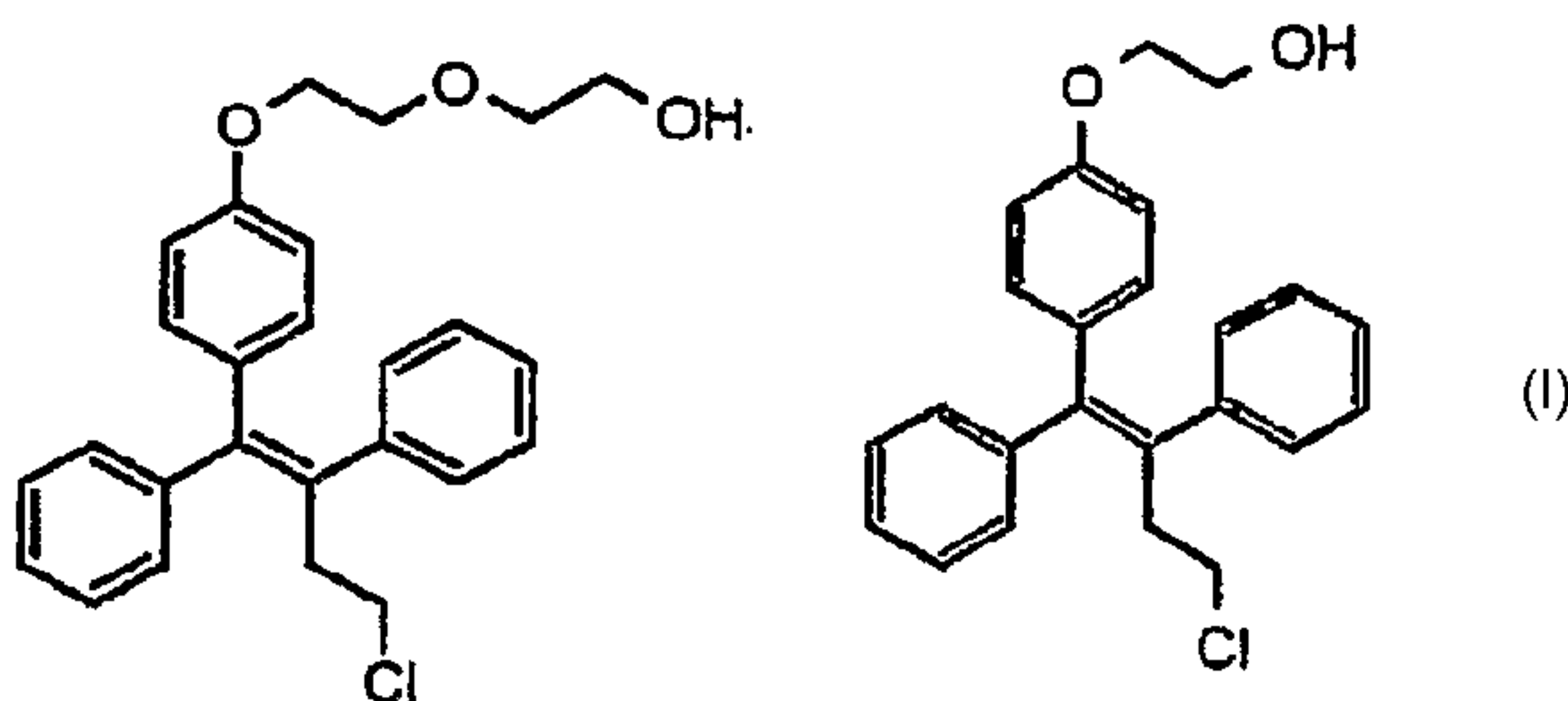
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(54) Title: METHOD FOR THE PREPARATION OF THERAPEUTICALLY VALUABLE TRIPHENYLBUTENE DERIVATIVES



(57) Abstract: The present invention concerns a method for the preparation of therapeutically valuable triphenylbutene derivatives, especially ospemifene or fispemifene. formula (I).



WO 2008/099059 A1

METHOD FOR THE PREPARATION OF THERAPEUTICALLY VALUABLE TRIPHENYLBUTENE DERIVATIVES

BACKGROUND

Field of the Invention

[0001] This invention relates to the preparation of two triphenylbutene derivatives, valuable in therapy as selective estrogen receptor modulators.

Description of Related Art

[0002] Deleted.

10 **[0003]** "SERMs" (selective estrogen receptor modulators) have both estrogen-like and antiestrogenic properties (Kauffman & Bryant, Drug News Perspect. 8:531-539, 1995). The effects may be tissue-specific as in the case of tamoxifen and toremifene which have estrogen-like effects in the bone, partial estrogen-like effect in the uterus and liver, and pure antiestrogenic effect in breast tissue. Based on the published information, many SERMs are more likely to cause menopausal symptoms than to prevent them. They have, however, other important benefits in elderly women: they decrease total and LDL cholesterol, thus minimizing the risk of cardiovascular diseases, and they may prevent osteoporosis and inhibit breast cancer growth in postmenopausal women.

20 **[0004]** Ospemifene, (Z)- 2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethanol, which is one of the main metabolites of toremifene, is known as an estrogen agonist and antagonist (Kangas, Cancer Chemother. Pharmacol. (1990) 27:8-12; WO 96/07402 and WO 97/32574). Ospemifene has relatively weak estrogenic and

antiestrogenic effects in the classical hormonal tests (Kangas, 1990). It has anti-osteoporosis actions and it decreases total and LDL cholesterol levels in both experimental models and in human volunteers. It also has antitumor activity in an early stage of breast cancer development in an animal breast cancer model. Ospemifene is also the first SERM which has been shown to have beneficial effects in climacteric syndromes in healthy women. The use of ospemifene for the treatment of certain climacteric disorders and atrophy-related diseases or disorders in postmenopausal women is disclosed in WO 02/07718 and WO 03/103649.

[0005] WO 01/36360 describes a group of SERMs, which are tissue-specific estrogens and which can be used in women in the treatment of climacteric symptoms, osteoporosis, Alzheimer's disease and/or cardiovascular diseases without the carcinogenic risk. Certain compounds can be given to men to protect them against osteoporosis, cardiovascular diseases and Alzheimer's disease without estrogenic adverse events (gynecomastia, decreased libido etc.). Of the compounds described in said patent publication, the compound (Z)-2-{2-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenoxy]-ethoxy}ethanol (also known under the generic name fispemifene) has shown a very interesting hormonal profile suggesting that it will be especially valuable for treating disorders in men. WO 2004/108645 and WO 2006/024689 suggest the use of fispemifene for treatment or prevention of age-related symptoms in men, such as lower urinary tract symptoms and diseases or disorders related to androgen deficiency in men.

[0006] Known methods for the syntheses of compounds like ospemifene and fispemifene include rather many steps. WO 02/090305 describes a method for the preparation of fispemifene, where in a first step a triphenylbutane compound with a

dihydroxy substituted butane chain is obtained. This compound is in a second step converted to a triphenylbutene where the chain is 4-chlorosubstituted. Then the desired Z-isomer is crystallized. Finally, the protecting group is removed to release the ethanol-ethoxy chain of the molecule.

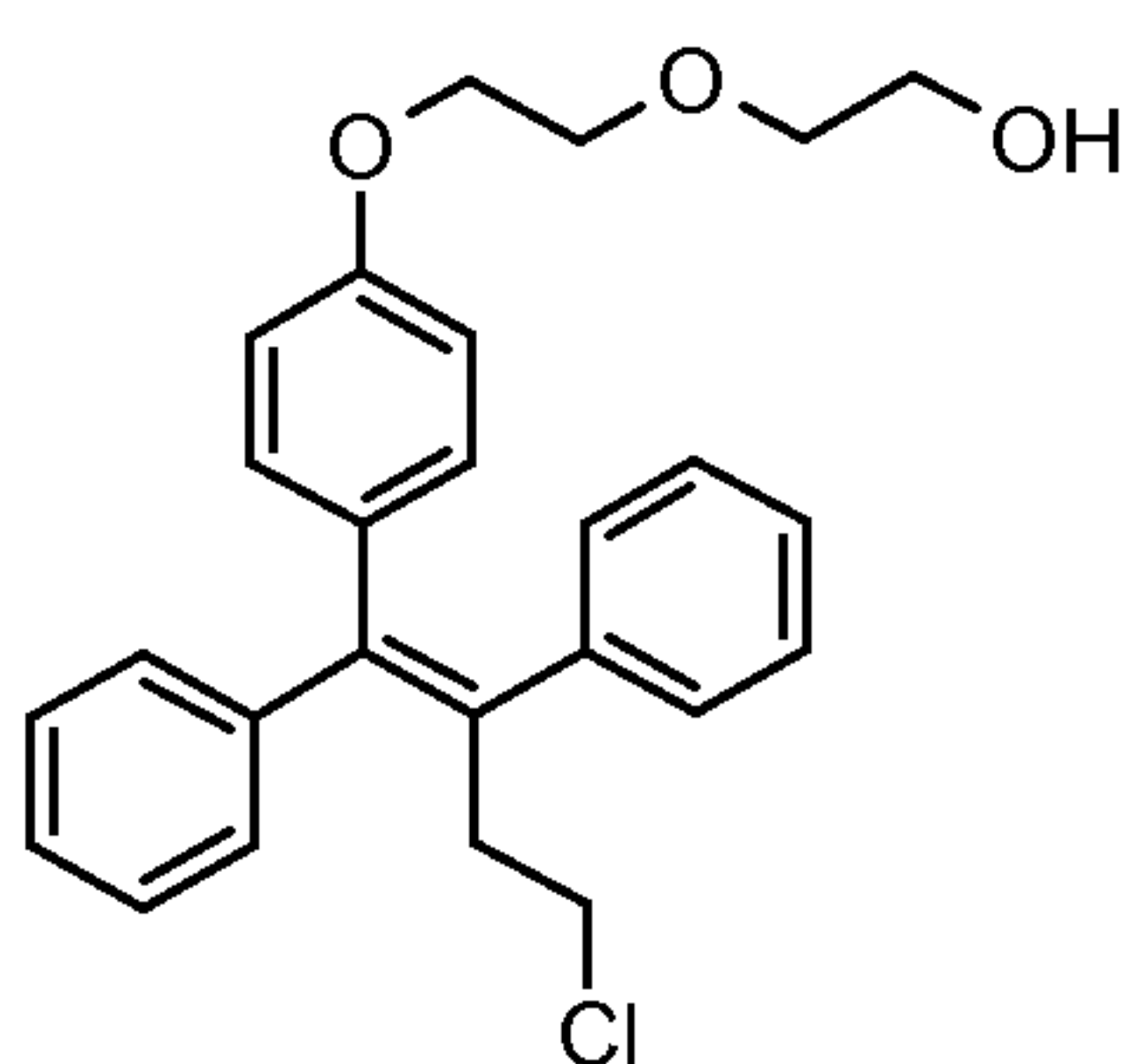
[0007] In the known methods, the separation of the desired Z isomer is tedious. The protection group used to protect the ethanol-ethoxy chain during the reaction steps, benzyl, is rather difficult to remove.

SUMMARY

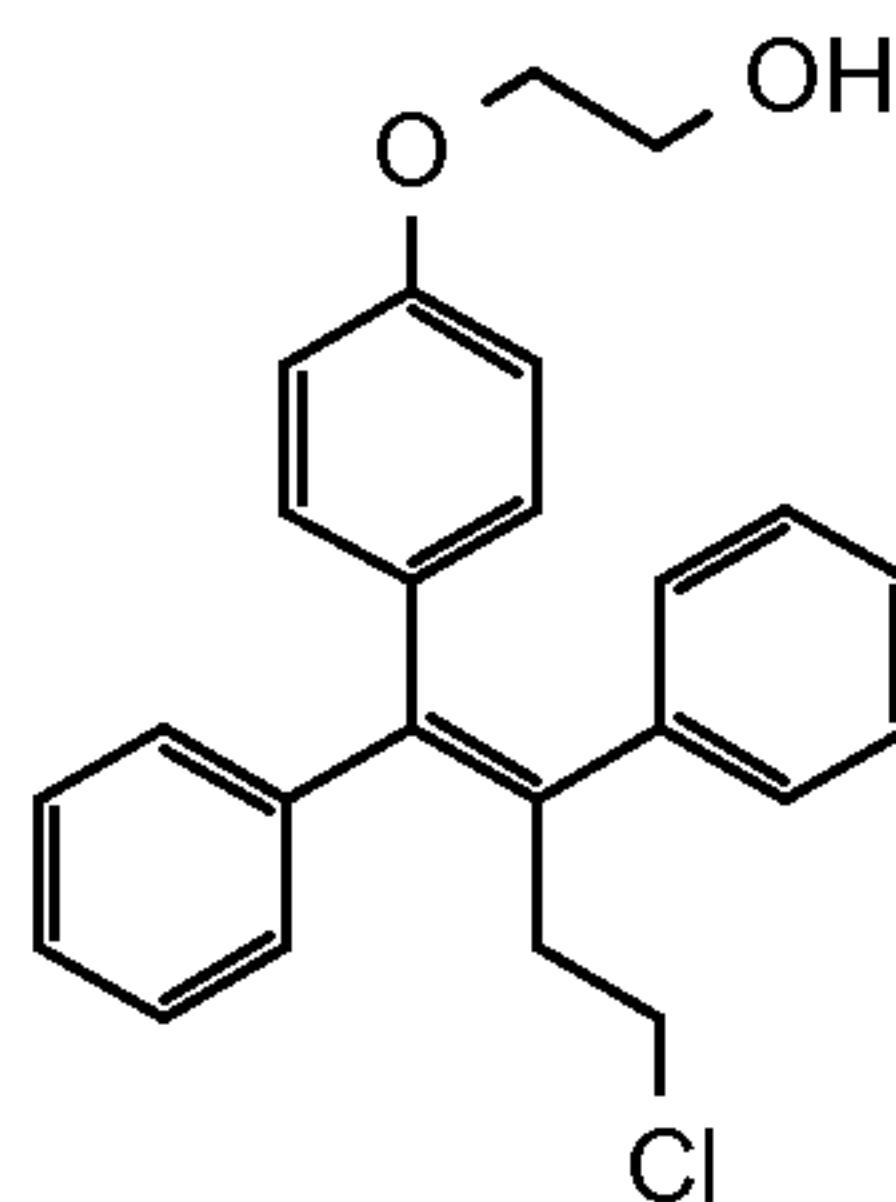
[0008] Both ospemifene and fispemifene are likely to be commercialized in the near future. Thus, there is a great need for powerful methods for the preparation of these compounds in large scale.

[0009] Another object is to provide methods having common features so that the syntheses of the compounds easily can be run by using the same kind of equipment and materials.

[0010] Thus, according to one aspect, this invention concerns a method for the preparation of a compound of formula (Ia) or (Ib):

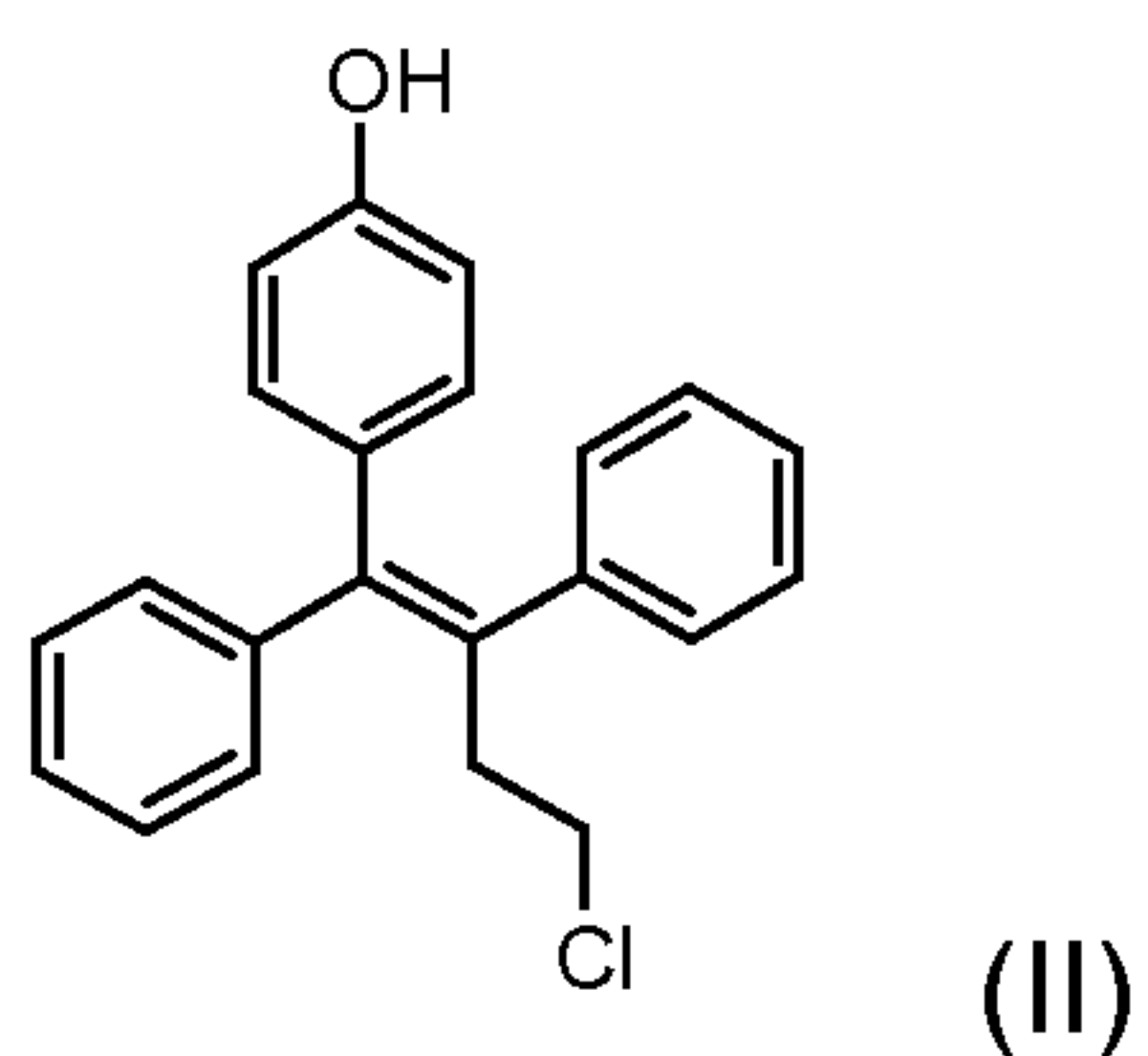


(Ia)



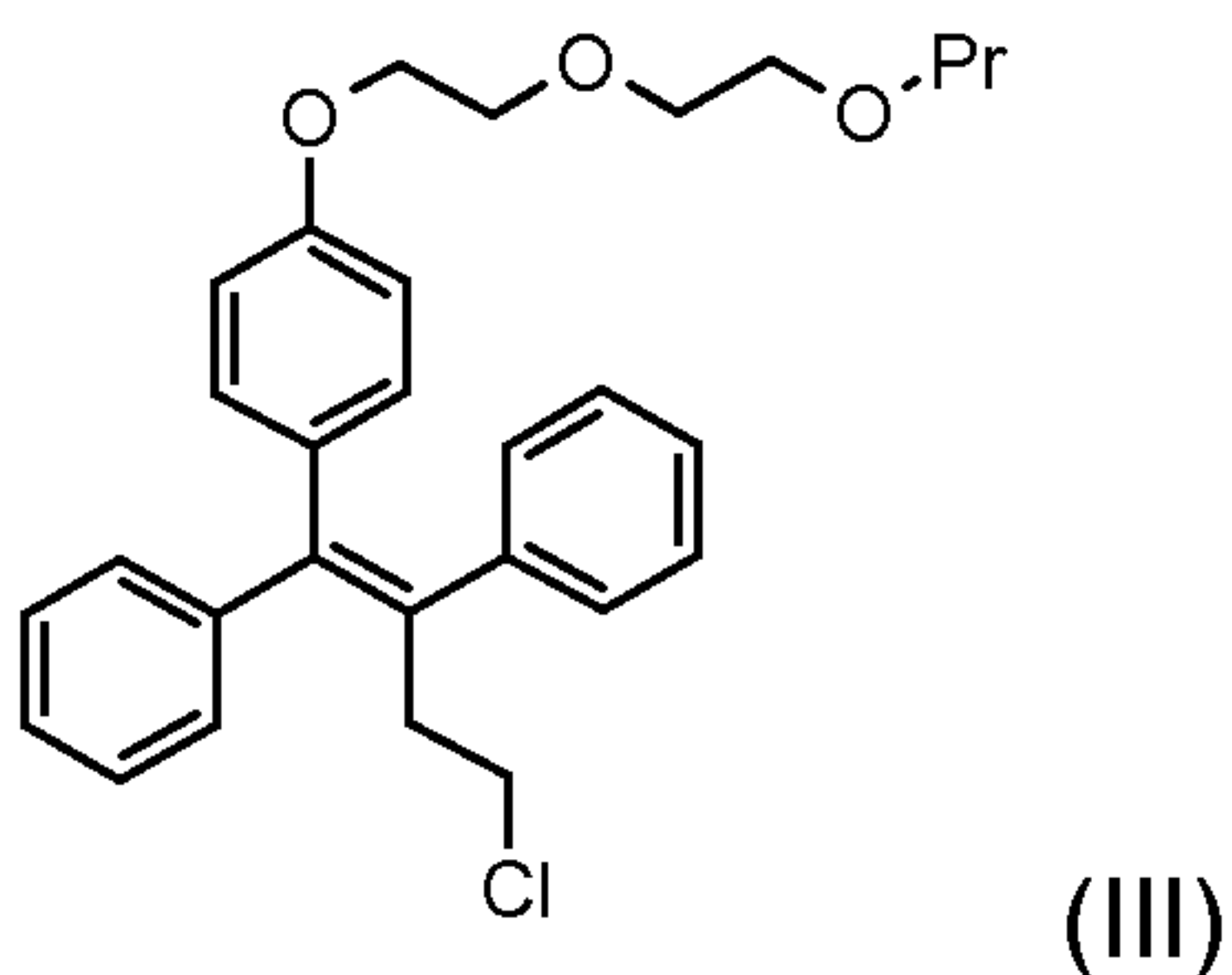
(Ib)

wherein a compound of formula (II)



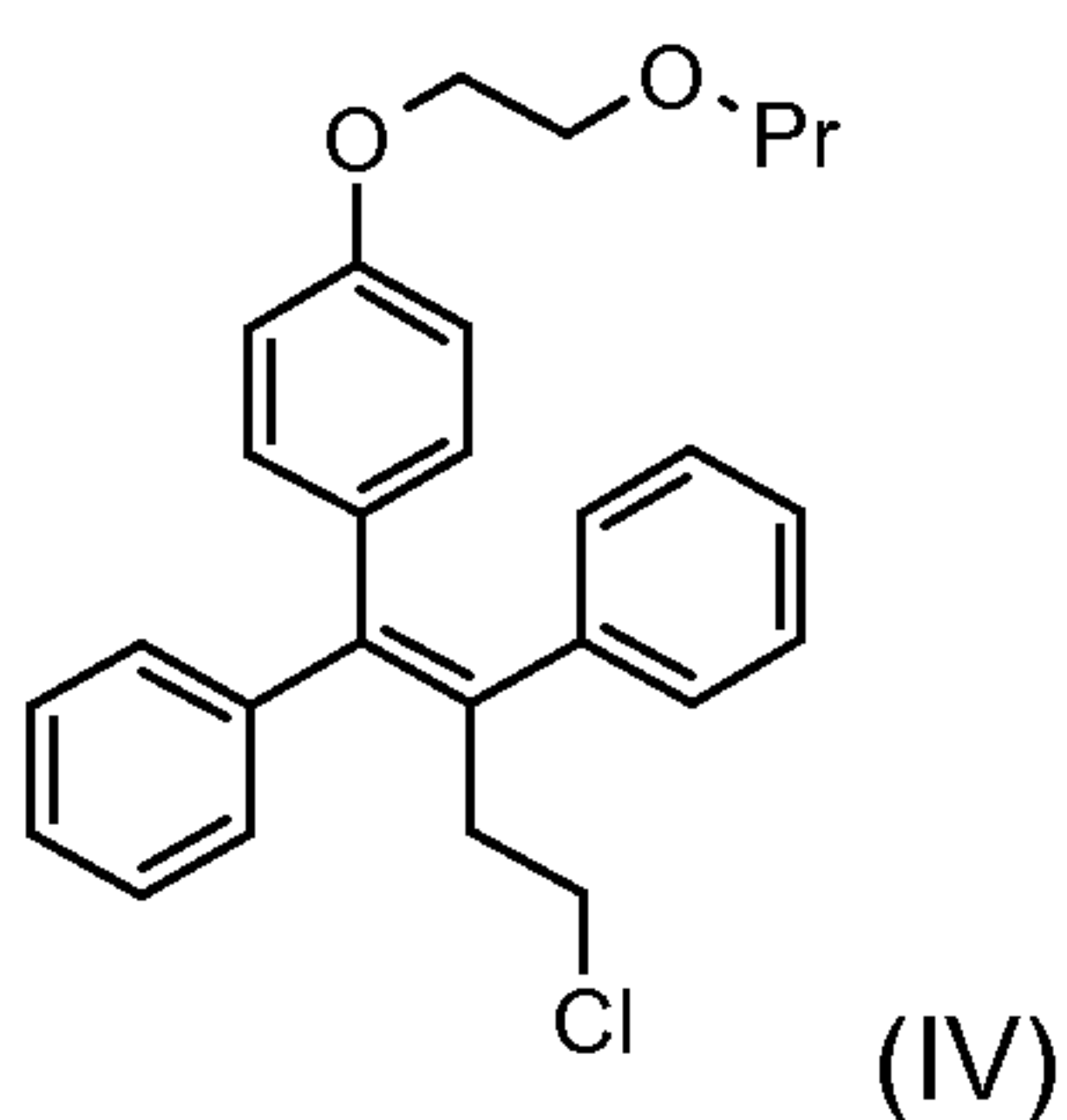
a) is alkylated with an alkylating reagent of the formula $X-(CH_2)_2-O-(CH_2)_2-O-$ Pr ,

where X is Cl, Br, I, mesyloxy or tosyloxy, and Pr is a protecting group, to give a compound of formula (III)



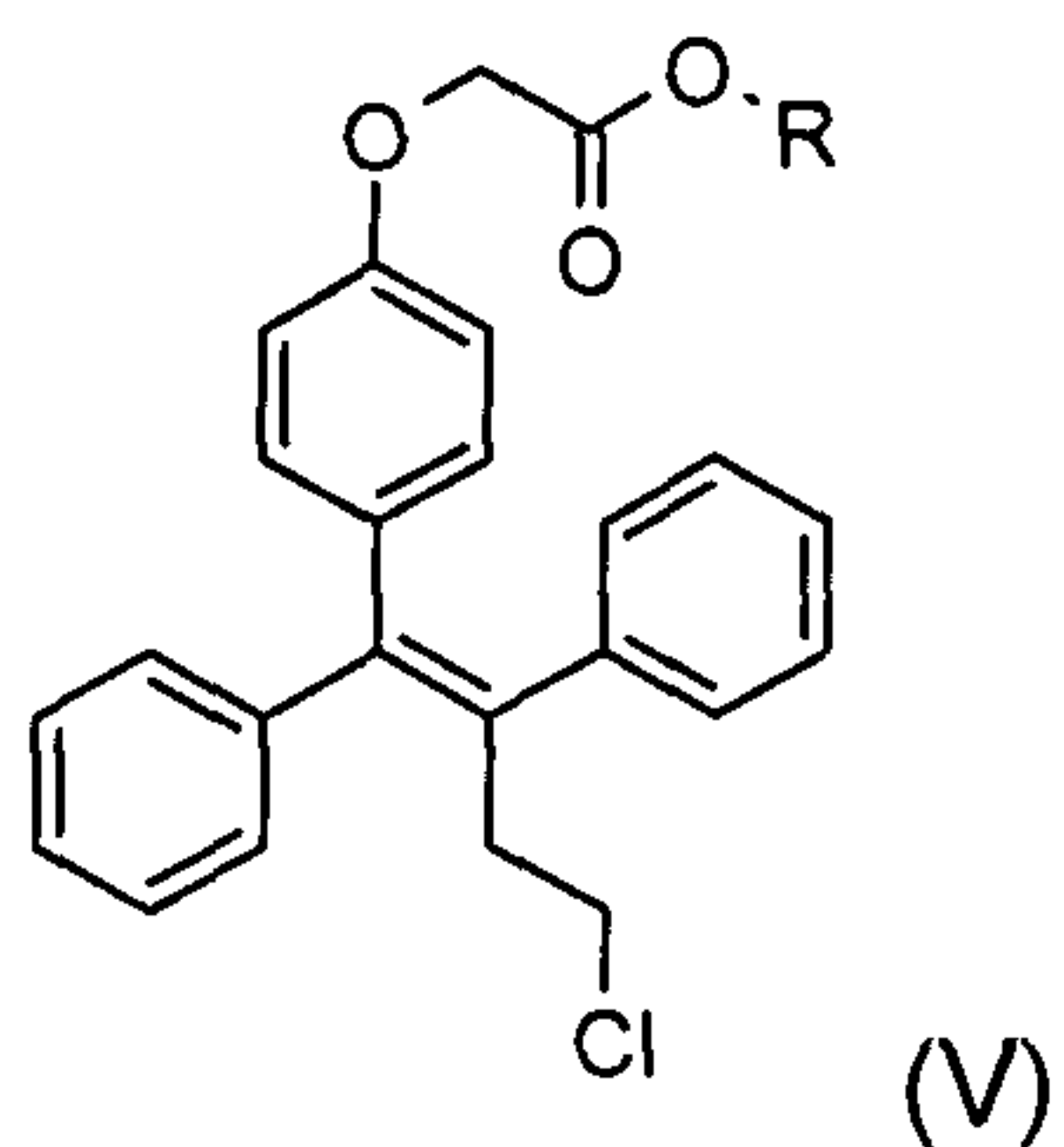
which is subjected to removal of the protecting group Pr to give the compound of formula (Ia), or

b) is alkylated with an alkylating reagent of the formula $X-(CH_2)_2-O-Pr$, where X is Cl, Br, I, mesyloxy or tosyloxy, and Pr is a protecting group, to give a compound of formula (IV)



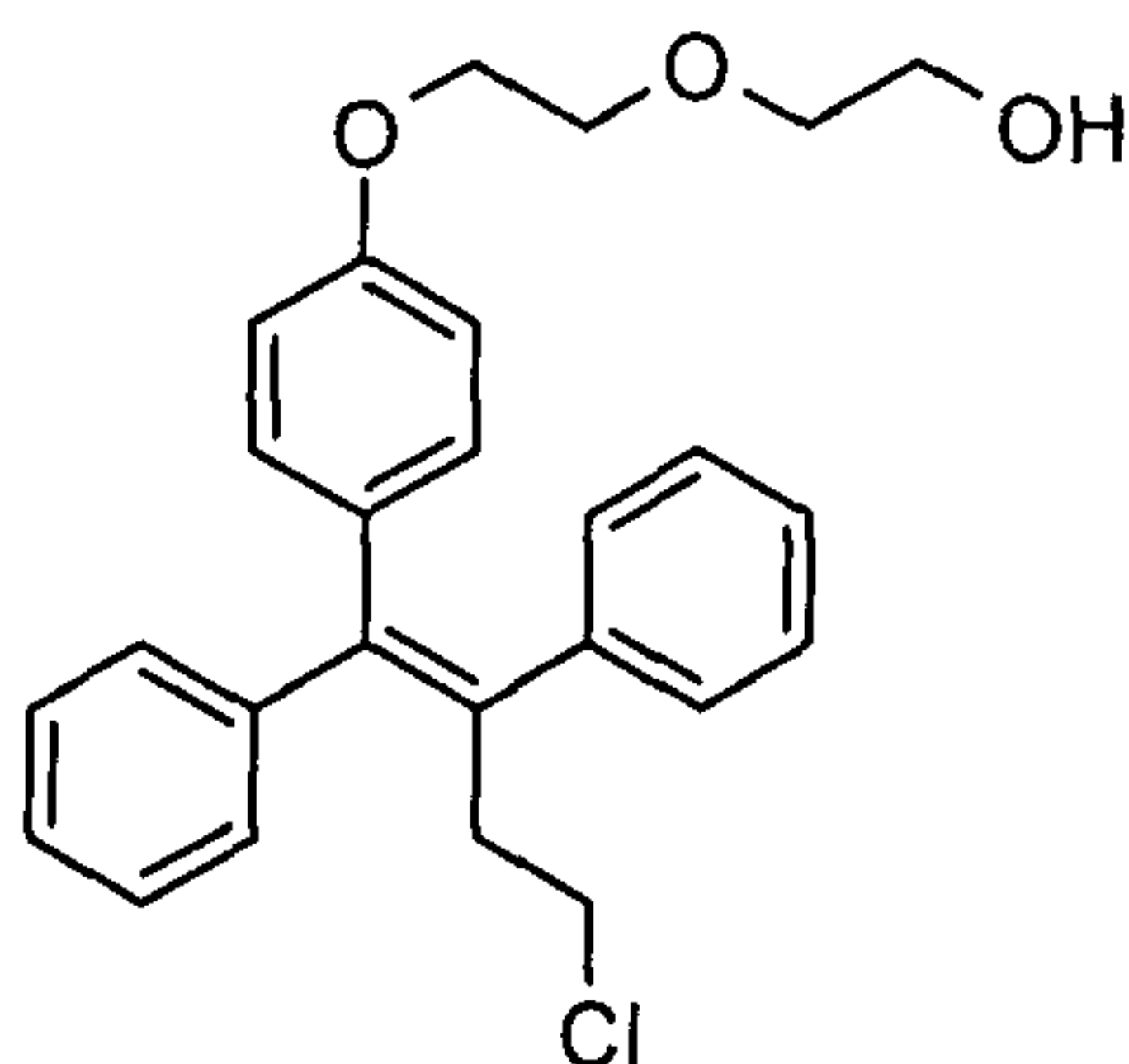
which is subjected to removal of the protecting group Pr to give the compound of formula (Ib), or

c) is alkylated with an alkylating reagent of the formula $X-CH_2-COOR$, wherein X is Cl, Br, I, mesyloxy or tosyloxy, and R is an alkyl, to give a compound of formula (V)



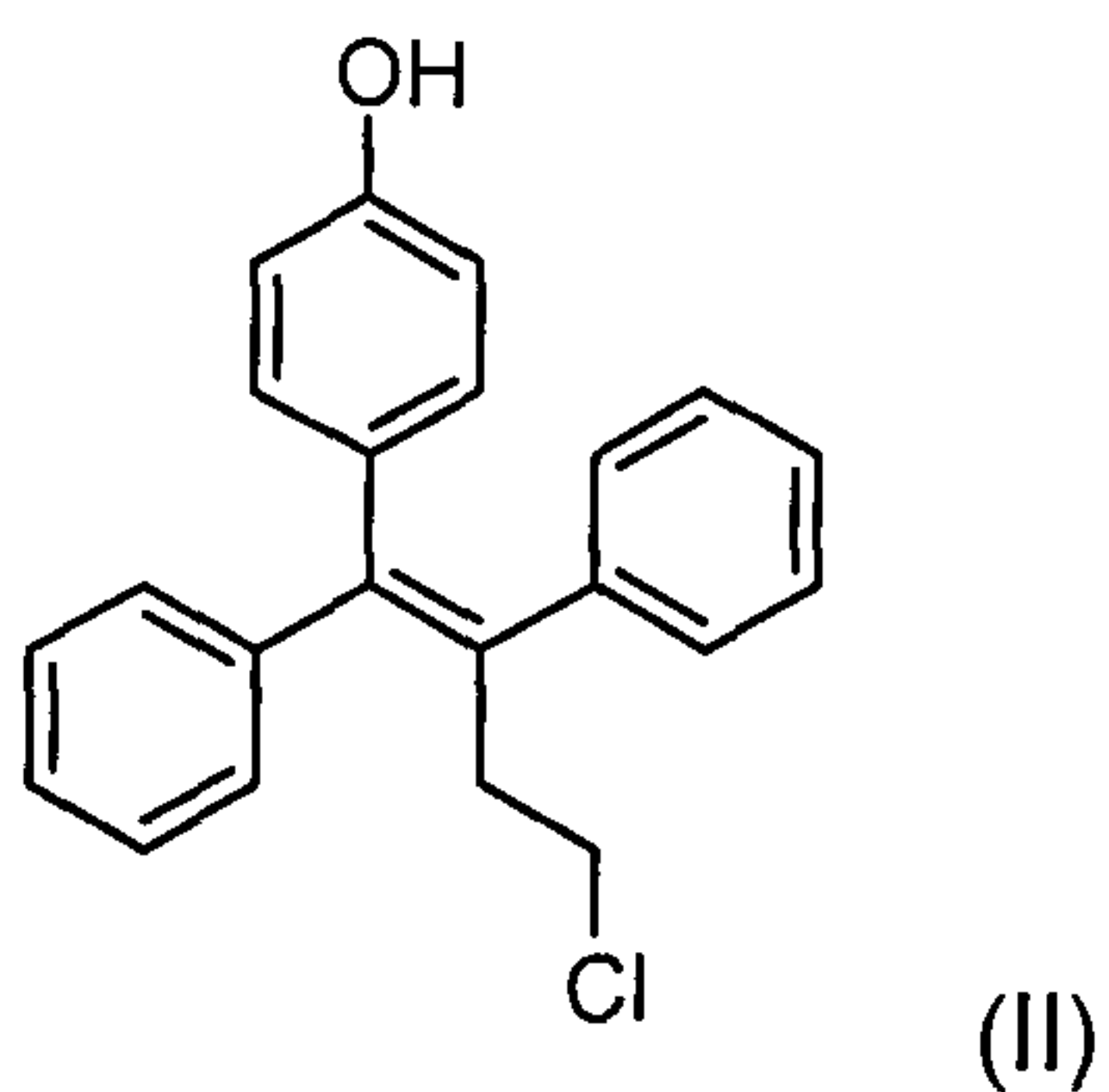
and the ester is reduced to give the compound of formula (Ib).

[0010a] In another aspect, this invention concerns a method for the preparation of a compound of formula (Ia)



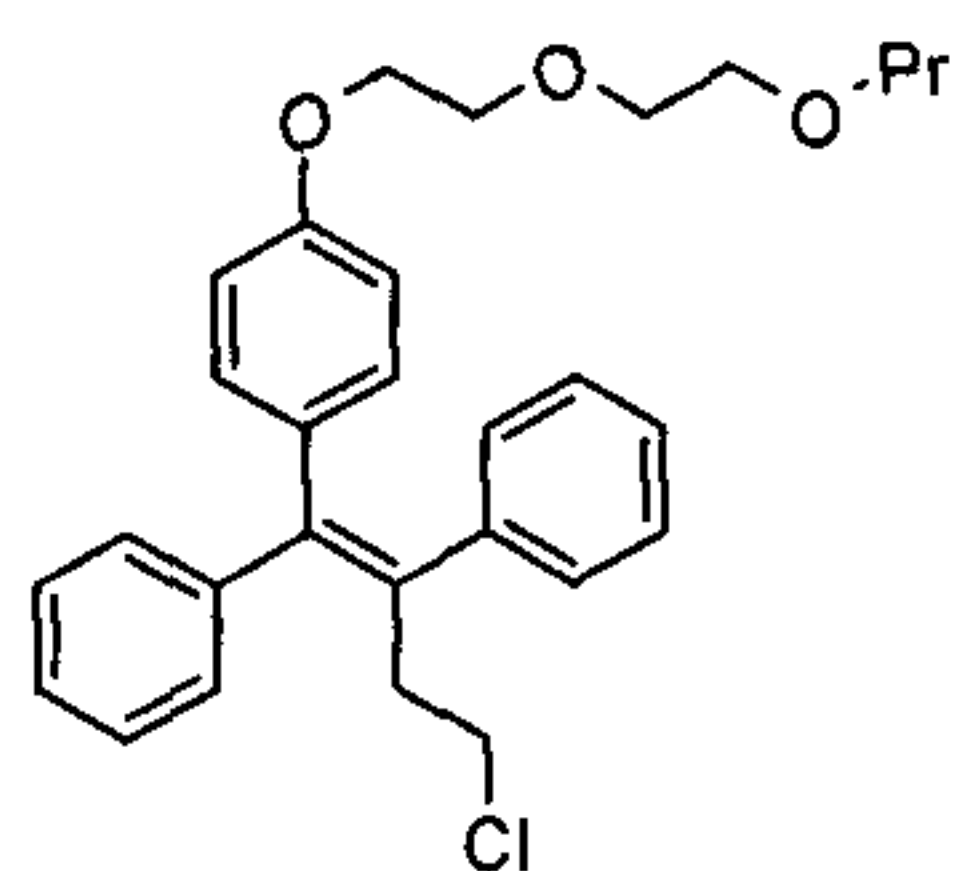
(Ia) comprising:

wherein a compound of formula (II)



is alkylated with an alkylating reagent of the formula $X-(CH_2)_2-O-(CH_2)_2-O-$ Pr,

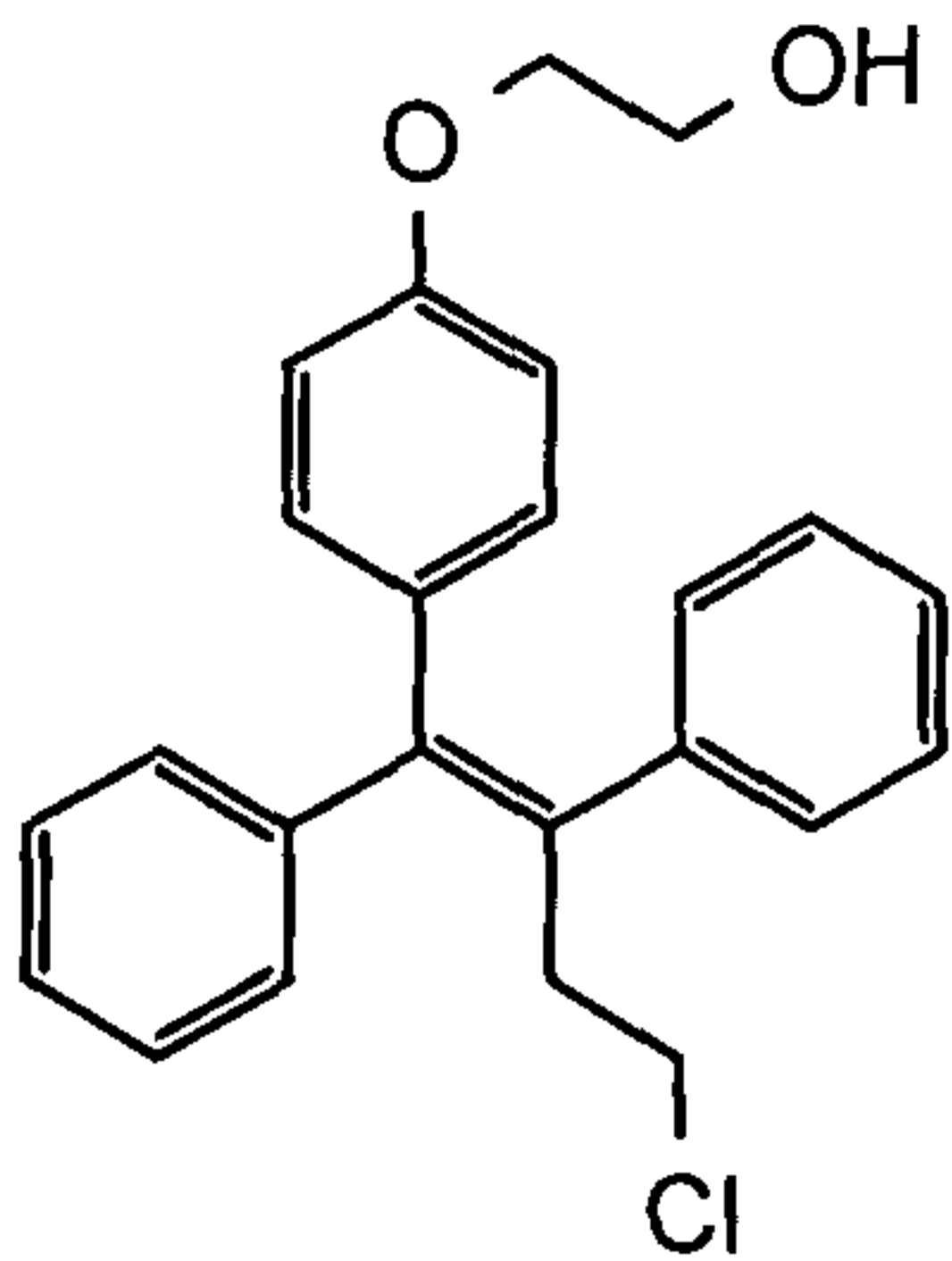
where X is Cl, Br, I, mesyloxy or tosyloxy, and Pr is a protecting group, to give a compound of formula (III)



(III)

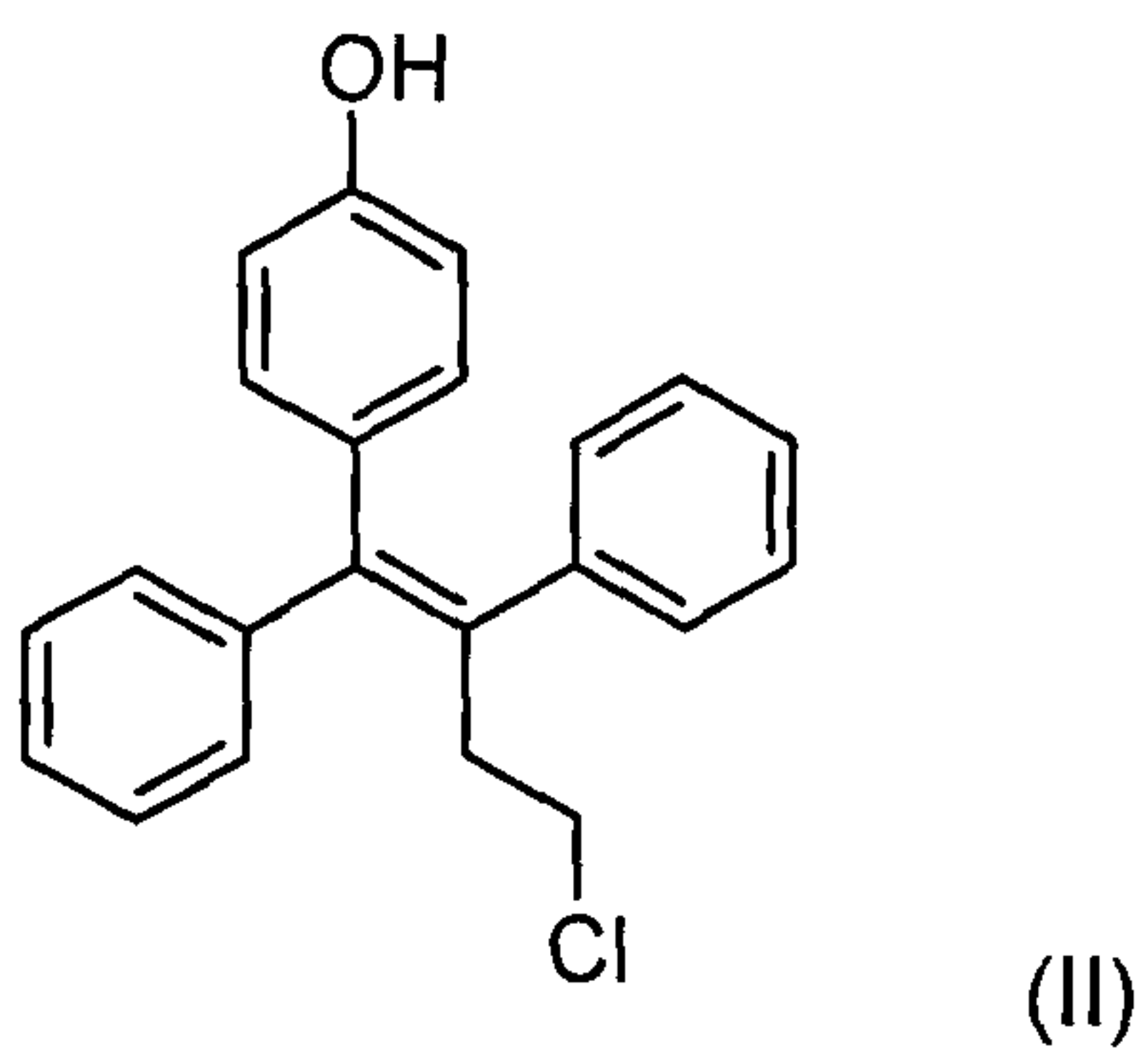
which is subjected to removal of the protecting group Pr to give the compound of formula (Ia), wherein the compound (Ia) is the Z-isomer.

10 **[0010b]** In yet another aspect, this invention concerns a method for the preparation of a compound of formula (Ib)

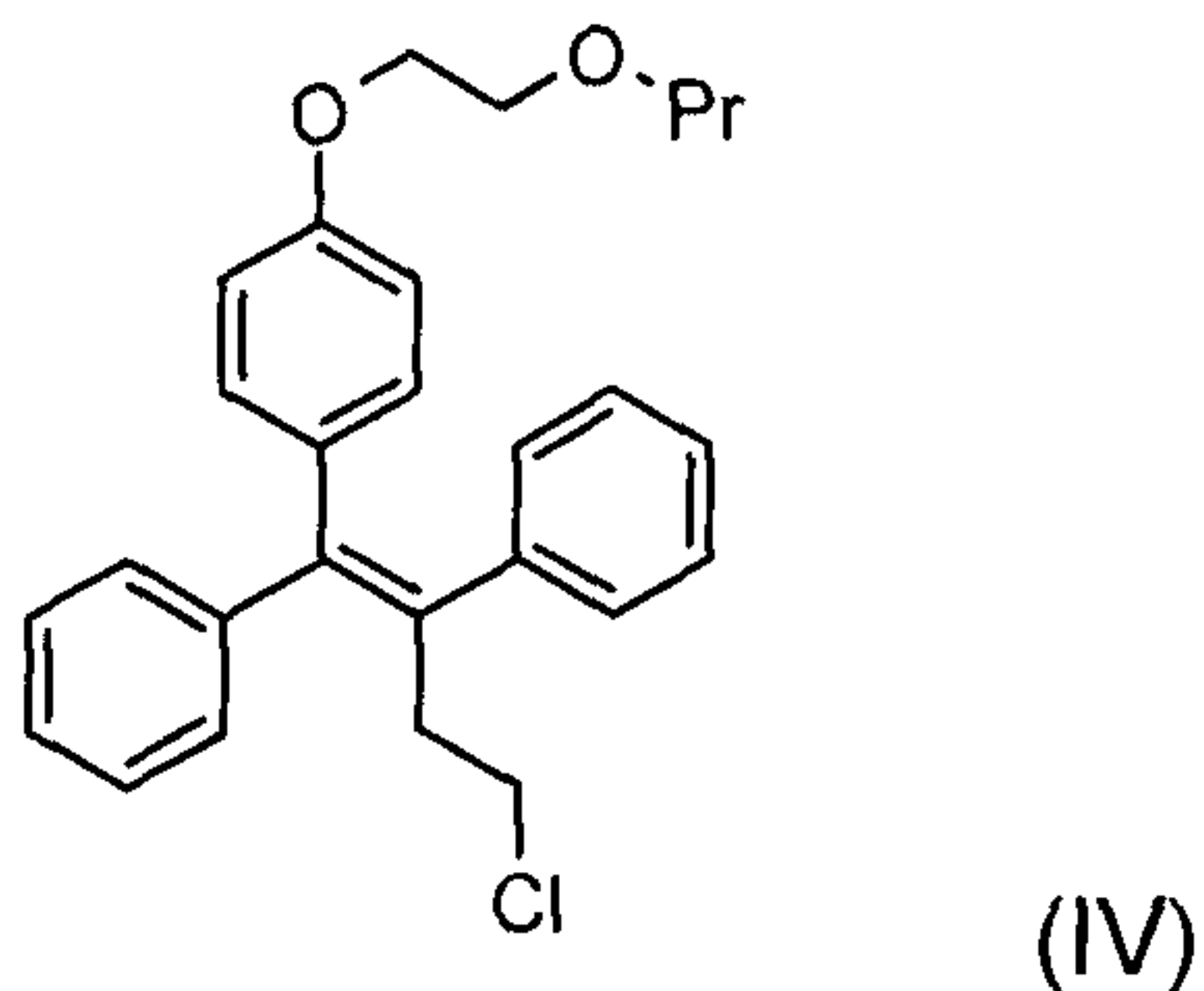


(Ib) comprising:

wherein a compound of formula (II)

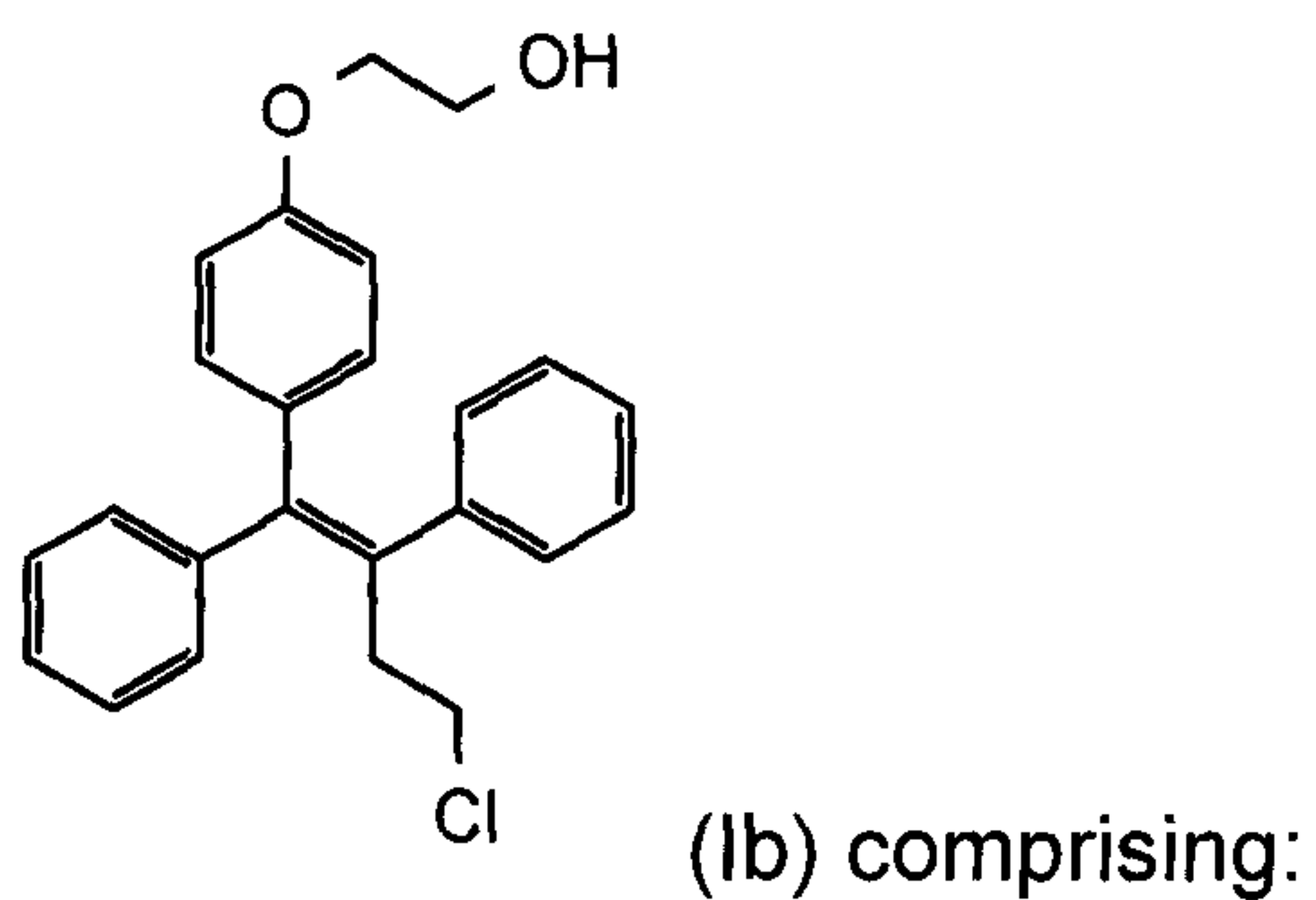


is alkylated with an alkylating reagent of the formula $X-(CH_2)_2-O-Pr$, where X is Cl, Br, I, mesyloxy or tosyloxy, and Pr is a protecting group, to give a compound of formula (IV)

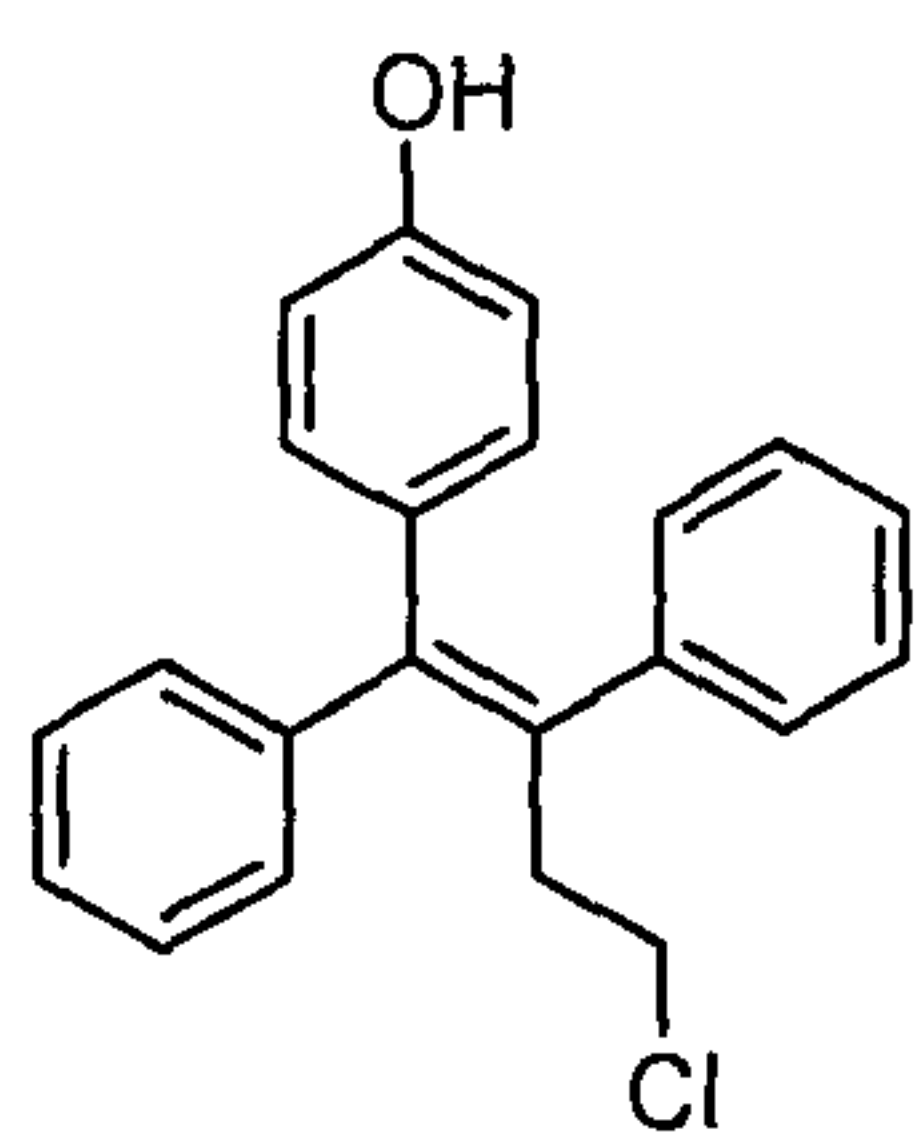


which is subjected to removal of the protecting group Pr to give the compound of formula (Ib), wherein the compound (Ib) is the Z-isomer.

[0010c] In a further aspect, this invention concerns a method for the preparation of a compound of formula (Ib):

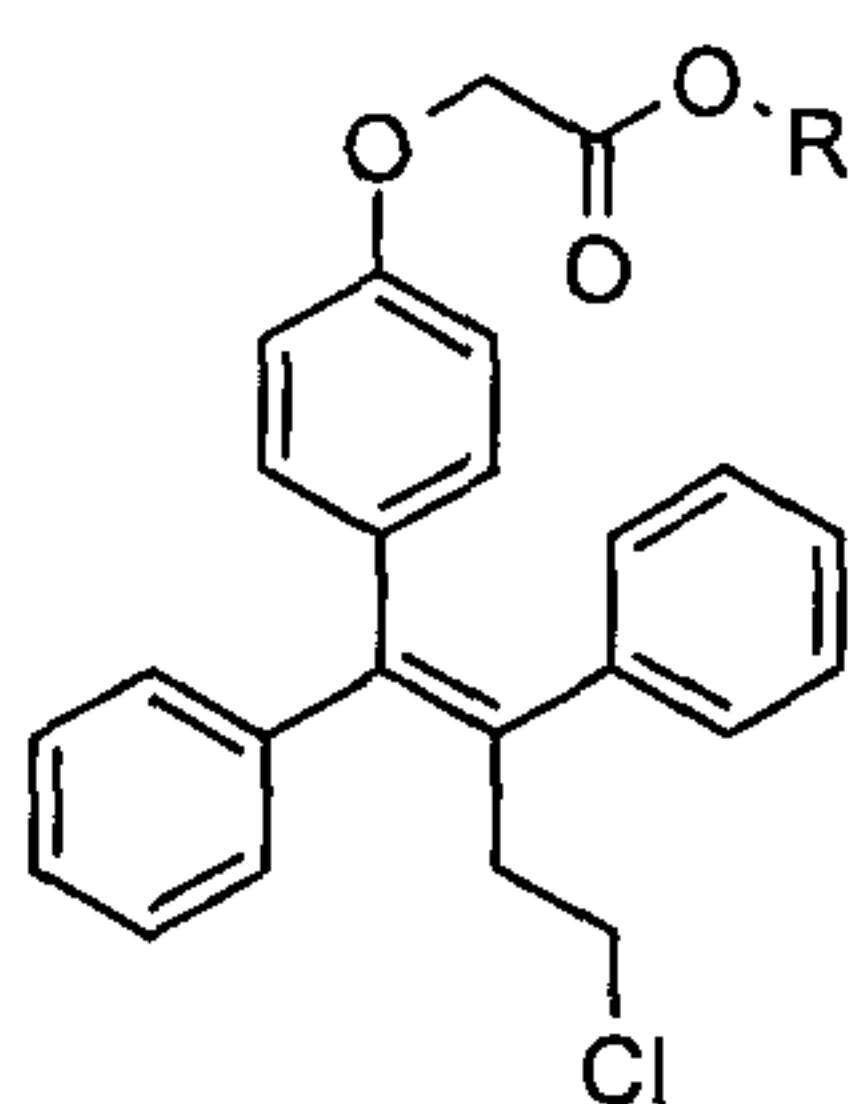


wherein a compound of formula (II)



(II)

is alkylated with an alkylating reagent of the formula $X-CH_2-COOR$, wherein X is Cl, Br, I, mesyloxy or tosyloxy, and R is an alkyl, to give a compound of formula (V)

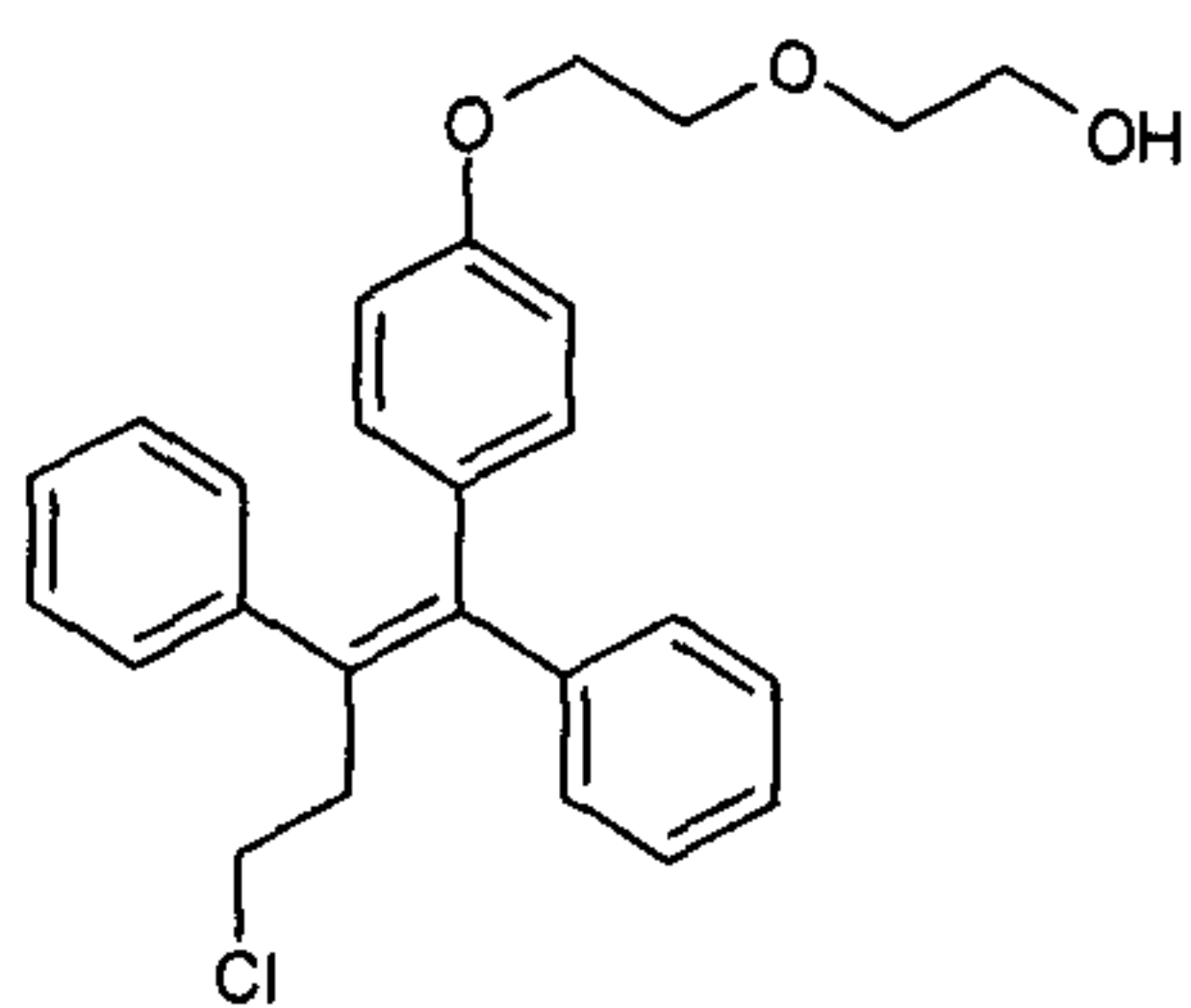


(V)

and the ester group of V is reduced to give the compound of formula (Ib), wherein the compound (Ib) is the Z-isomer.

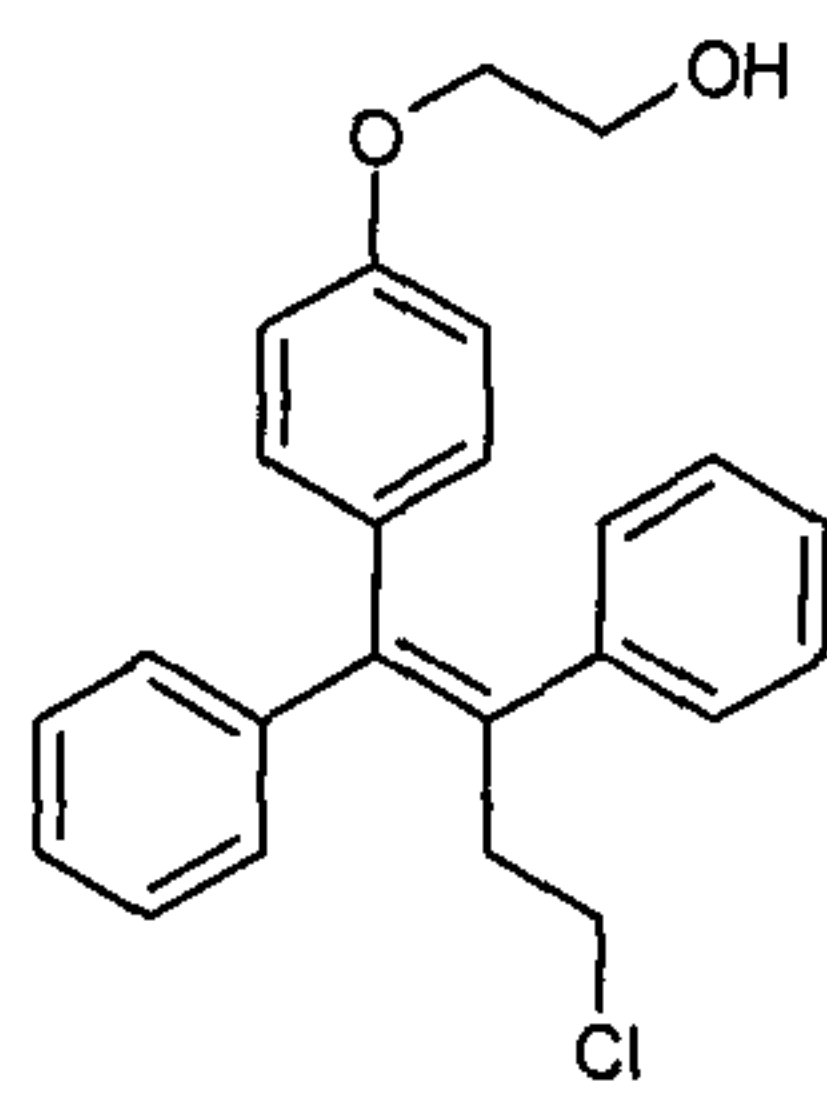
DETAILED DESCRIPTION

[0011] Fispemifene is the Z-isomer of the compound of formula (Ia)

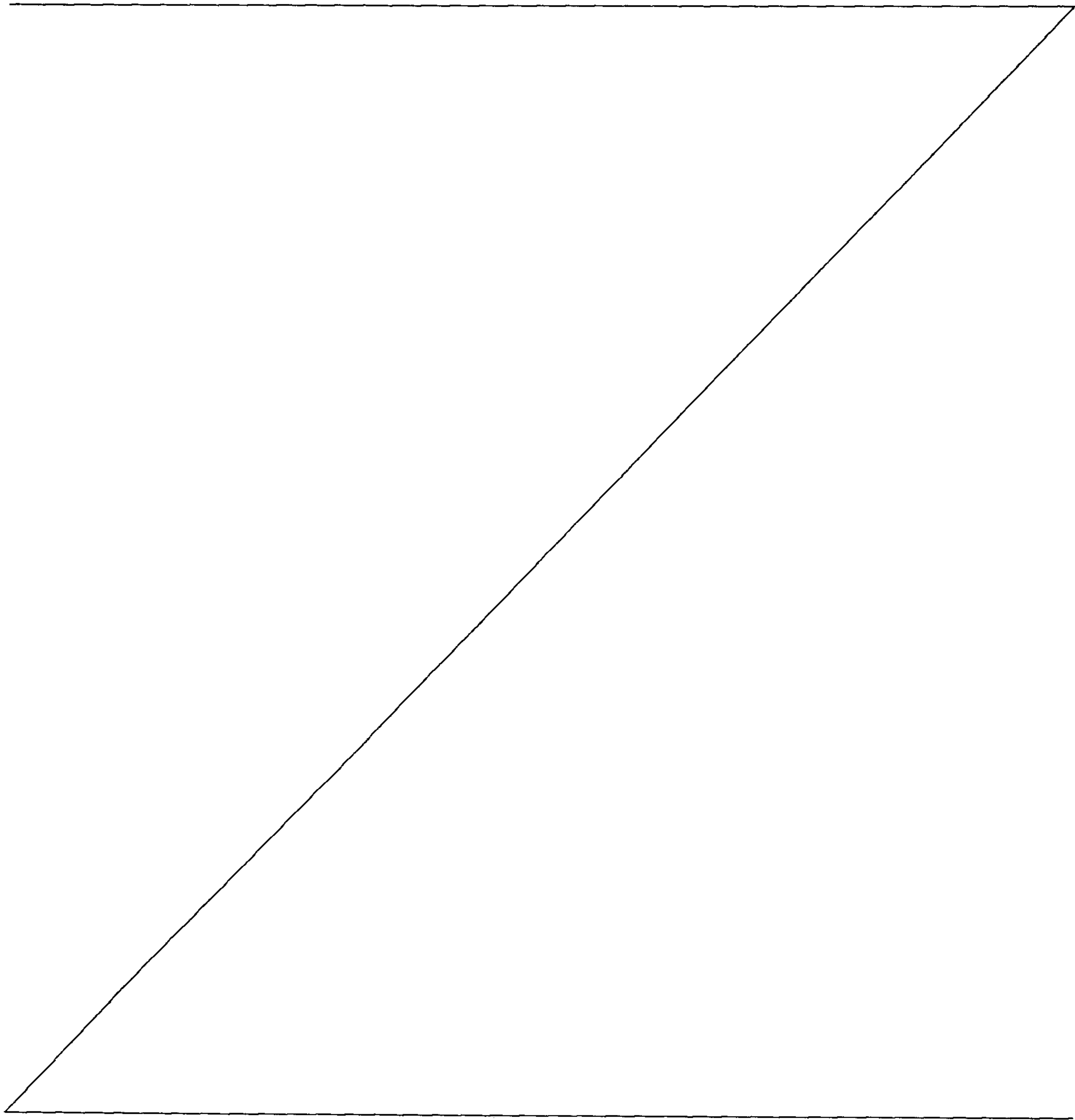


(Ia)

and ospemifene is the Z-isomer of the compound of formula (Ib)



(1b)



5d

[0012] The common starting material in the syntheses of (Ia) or (Ib), namely compound (II), is previously known (Toivola, 1990; EP 0095875). According to a method disclosed in EP 095875, this compound was prepared by dealkylation of a corresponding ether to give (II). The method may be used to produce a mixture of isomers of compounds (Ia) and (Ib), but most preferably is used to prepare the pure E- and Z-isomers of those compounds.

[0013] Particularly in case Z-isomers of the compounds (Ia) or (Ib) are desired, a preferable method for the synthesis of compound (II) is a McMurry reaction of commercially available starting materials, 4-hydroxybenzophenone with 3-chloropropiophenone. The McMurry reaction is a well-known reductive coupling of ketones involving two steps: (1) a single electron transfer to the carbonyl groups from an alkali metal, followed by (2) deoxygenation of the 1,2-diol with low-valent titanium to yield the alkene. This reaction produces mainly the Z-isomer of compound (II).

[0014] The alkylation in steps a) and b) is carried out in an organic solvent, preferably carried out in tetrahydrofuran. It is also preferable to add a base to the solvent, most preferably sodium hydride.

[0015] The step of alkylation is performed at a temperature and a time to achieve substantial alkylation of compound II.

[0016] The protecting group Pr can be any suitable protecting group such as benzyl, substituted benzyl, allyl, tetrahydropyranyl or any other alcohol protecting group obvious to one skilled in the art; see for example Protecting Groups in Organic Synthesis, Third Edition, T.W. Greene and P.G.M. Wuts. Wiley Interscience, 1999 pp 23-200. In a preferable embodiment the protecting group is

tetrahydropyranyl. This protecting group is very easily removable by methods known to those of ordinary skill in the art. For example, acid labile alcohol protecting groups such as a tetrahydropyranyl group (e.g., 2-tetrahydropyranyl) can be removed using acid such as HCl. A benzyl group can be removed using methods such as hydrogenation with Pd on carbon as a catalyst, or reacting with Zn powder and acetyl chloride.

[0017] X is preferably I or Br in the alkylating reagent in steps a) and b).

[0018] In the alkylating reagent in step c) X is preferably I, Br, or Cl, most preferably Br.

[0019] The alkyl substituent R in the alkylating reagent in step c) is preferably a C₁₋₄-alkyl, most preferably ethyl.

[0020] The reduction of compound (V) obtained in step c) is carried out with a reducing agent, preferably lithium aluminum hydride. Other reducing agents are well known to those of ordinary skill in the art.

[0021] The steps of the methods described herein are carried out at temperatures and for times sufficient to achieve the desired compounds (Ia) and (Ib). The selection of the parameters based on the disclosure herein can readily be made by one of ordinary skill without undue experimentation.

[0022] To sum up, the preferred embodiments according to the present invention provides considerable advantages over known methods for producing compounds of formula (Ia) or (Ib):

- The use of tetrahydrofuran as solvent and sodium hydride as a base in the alkylating steps a) and b) gives the desired products in good yields.

- The use of tetrahydropyranyl as protecting group is favorable because this protecting group is easy to remove leading to good yield of the product.
- The McMurry synthesis of compound (II) leads mainly to the Z-isomer. This is of particular importance when Z-isomers of the end products Ia and Ib are desired.

[0023] The invention will be illuminated by the following non-restrictive Examples.

EXAMPLE 1

4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenol (Compound II)

[0024] Zinc (15.0 g, 0.23 mol) and tetrahydrofuran (THF) (180 ml) was added to the reaction vessel and cooled to -10 °C. Titan tetrachloride was added dropwise to the mixture (21.6 g, 0.114 mol) at about -10 °C. After the addition was completed the mixture was refluxed for two hours. Then the mixture was cooled to 40 °C and 4-hydroxybenzophenone (7.68 g, 0.039 mol) and 3-chloropropiophenone (6.48 g, 0.039 mol) dissolved in THF (75 ml) were added to the mixture. Refluxing was continued for additional 3.5 hours. The cooled reaction mixture was poured in aqueous potassium carbonate solution (21 g K₂CO₃ + 210 ml water) and allowed to stand overnight at the ambient temperature. The mixture was filtered and the precipitate was washed with THF. The filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate and washed with water. Ethyl acetate phase was evaporated to dryness and the residue was crystallized first from methanol-water (8:2) and then from methanol-water (9:1). Yield 5.4 g.

[0025] Z-isomer: ^1H NMR (CDCl_3): 2.92 (t, 2H, $=\underline{\text{CH}_2\text{CH}_2\text{Cl}}$), 3.42 (t, 2H, $=\text{CH}_2\underline{\text{CH}_2\text{Cl}}$), 6.48 (d, 2H, aromatic proton ortho to hydroxy), 6.75 (d, 2H, aromatic proton meta to hydroxy), 7.1-7.4 (m, 10H, aromatic protons)

EXAMPLE 2

2-(2-{2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenoxy]ethoxy}-ethoxy)-tetrahydropyran (Compound III, where Pr is tetrahydropyranyl)

[0026] 4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenol (0.33 g, 0.001 mol) was dissolved in tetrahydrofuran (3 ml) under a nitrogen atmosphere. Sodium hydride (0.036 g, 0.0015 mol) was added to the solution and the mixture was stirred at room temperature for an hour. 2-[2-(2-iodo-ethoxy)-ethoxy]-tetrahydropyran (0.6 g, 0.002 mol) was added and the mixture was refluxed for 3 hours. After cooling and adding water the mixture was extracted three times with ethyl acetate. The organic phase was dried with sodium sulphate and evaporated to dryness. The residue was used in the next reaction step without further purification.

EXAMPLE 3

2-{2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenoxy]ethoxy}-ethanol (Compound Ia)

[0027] The residue of the previous reaction step (Example 2) was dissolved in ethanol (10 ml) and the solution was acidified with 2 N aqueous hydrogen chloride. The mixture was stirred over night at ambient temperature. Then the solvent was evaporated, water was added and the mixture was extracted three times with dichloromethane. The organic phase was washed with water, dried with sodium

sulphate and evaporated to dryness. The residue was crystallized from heptane-ethyl acetate (8:2). Yield 0.216 g.

[0028] Z-isomer, ^1H NMR (CDCl_3): 2.92 (t, 2H, $=\underline{\text{CH}_2\text{CH}_2\text{Cl}}$), 3.42 (t, 2H, $=\text{CH}_2\underline{\text{CH}_2\text{Cl}}$), 3.58-3.65 (m, 2H, $\text{OCH}_2\underline{\text{CH}_2\text{OH}}$), 3.7-3.82 (m, 4 H, $-\underline{\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}}$), 3.97-4.04 (m, 2H, $\text{ArO}\underline{\text{CH}_2-}$), 6.56 (d, 2H, aromatic proton ortho to hydroxy), 6.78 (d, 2H, aromatic proton meta to hydroxy), 7.1-7.43 (m, 10H, aromatic protons)

EXAMPLE 4

2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenoxy]-ethanol (Compound Ib)

[0029] 4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenol (0.23 g, 0.689 mmol) was dissolved in tetrahydrofuran (3 ml) under nitrogen atmosphere. Sodium hydride (0.025 g, 1.03 mmol) was added to the solution and the mixture was stirred at room temperature for an hour. 2-(2-iodo-ethoxy)-tetrahydropyran (0.3 g, 1.17 mmol) was added and the mixture was refluxed for 2 hours. Additional portions of 2-(2-iodo-ethoxy)-tetrahydro-pyran (0.5 g, 2 mmol) were added to the mixture during seven hours. After cooling and adding water, THF was evaporated and the mixture was extracted three times with ethyl acetate. The organic phase was washed with 2 N aqueous sodium hydroxide and water, dried with sodium sulphate and evaporated to dryness. The residue (which is Compound (IV) where Pr is tetrahydropyranyl) was dissolved in ethanol and acidified with 2 N aqueous hydrogen chloride solution. The mixture was stirred at room temperature over night, evaporated and extracted with dichloromethane. After washing with water the organic phase was

dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography with dichloromethane/methanol 9.5/0.5 as eluent. Yield 0.17 g, 59 %.

[0030] Z-isomer, ^1H NMR (CDCl_3): 2.92 (t, 2H, $=\underline{\text{C}}\text{H}_2\text{CH}_2\text{Cl}$), 3.42 (t, 2H, $=\text{CH}_2\underline{\text{C}}\text{H}_2\text{Cl}$), 3.85-3.89 (m, 4H, OCH_2CH_2), 6.56 (d, 2H, aromatic proton ortho to hydroxy), 6.80 (d, 2H, aromatic proton meta to hydroxy), 7.1-7.43 (m, 10H, aromatic protons).

EXAMPLE 5

2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenoxy]-ethanol (Compound Ib)

10 **[0031]** The compound was prepared by the same method as described in Example 4 using 2-(2-iodo-ethoxymethyl)-benzene as a reagent and removing the benzylic protecting group using the method described in Example (e) of US Patent No. 6,891,070 B2 . Briefly, the removal is carried out under a nitrogen atmosphere, in the presence of Zn powder and acetyl chloride.

EXAMPLE 6

[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenoxy]-acetic acid ethyl ester

(Compound V where R is ethyl)

20 **[0032]** 4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenol (0.5 g, 0.0015 mol), absolute ethanol (10 ml), potassium carbonate (0.62 g, 0.0045 mol) and ethyl bromoacetate (0.373 g, 0.00224 mol) are mixed under nitrogen atmosphere and refluxed for 2.5 hours. Then the hot mixture was filtered and the precipitate was washed

with absolute ethanol. The filtrate was evaporated, extracted with ethyl acetate and washed with water. Ethyl acetate was dried (Na_2SO_4) and evaporated to dryness. Yield 260 mg, 52 %. The product was used without further purification in the next reaction step.

[0033] ^1H NMR ($\text{CDCl}_3 + \text{MeOH-}d_4$): 1.25 (t, 3H, CH_2CH_3), 2.92 (t, 2H, $=\text{CH}_2\text{CH}_2\text{Cl}$), 3.42 (t, 2H, $=\text{CH}_2\text{CH}_2\text{Cl}$), 4.22 (q, 2H, OCH_2CH_3), 4.49 (s, 2H, ArOCH_2-), 6.56 (d, 2H, aromatic proton ortho to hydroxy), 6.80 (d, 2H, aromatic proton meta to hydroxy), 7.1-7.43 (m, 10H, aromatic protons).

[0034] An alternative way to carry out the alkylation described in Example 6 is to
10 replace absolute ethanol and potassium carbonate by sodium hydride and tetrahydrofuran. Preliminary experiments gave the product in high yield (90 %) after a short reaction time (about 1 hour) at room temperature.

EXAMPLE 7

2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenoxy]-ethanol (Compound I b)

[0035] [4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenoxy]-acetic acid ethyl ester (Example 7) was dissolved in tetrahydrofuran at room temperature under nitrogen atmosphere. Lithium aluminium hydride was added to the solution in small portions until the reaction was complete. The reaction was quenched by adding saturated ammonium chloride solution to the mixture. The product was extracted
20 into toluene, which was dried and evaporated *in vacuo*. The yield 100 mg, 43 %.

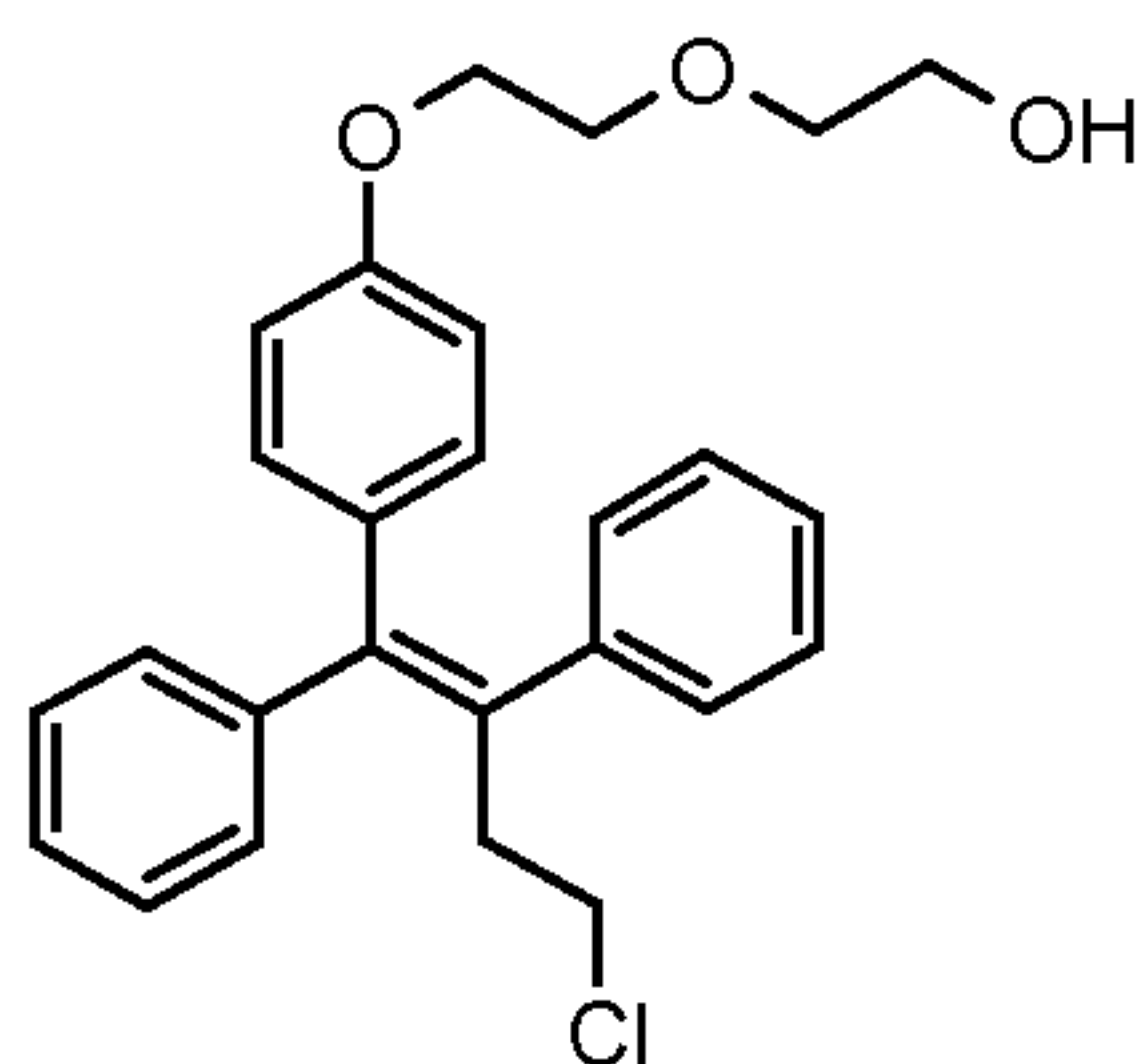
[0036] ^1H NMR (CDCl_3): 2.92 (t, 2H, $=\underline{\text{CH}_2\text{CH}_2\text{Cl}}$), 3.42 (t, 2H, $=\text{CH}_2\underline{\text{CH}_2\text{Cl}}$), 3.85-3.89 (m, 4H, $\text{O}\underline{\text{CH}_2\text{CH}_2}$), 6.56 (d, 2H, aromatic proton ortho to hydroxy), 6.80 (d, 2H, aromatic proton meta to hydroxy), 7.1-7.43 (m, 10H, aromatic protons).

[0037] The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

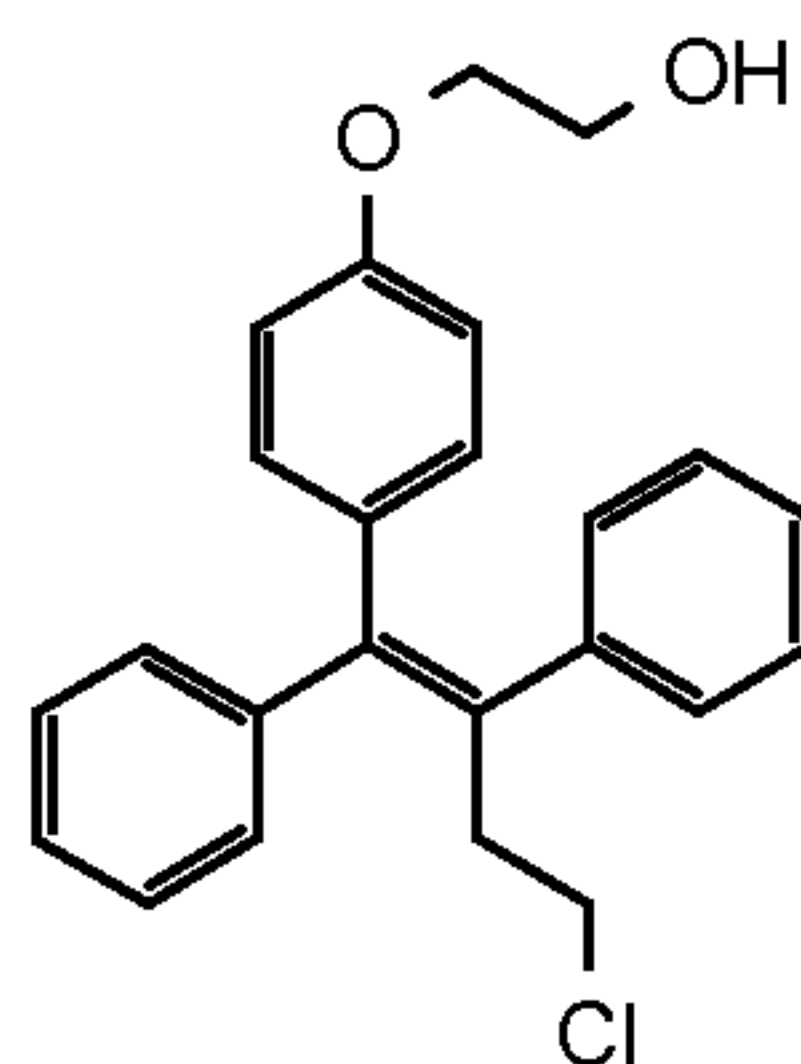
CLAIMS

What is claimed is:

1. A method for the preparation of a compound of formula (Ia) or (Ib)

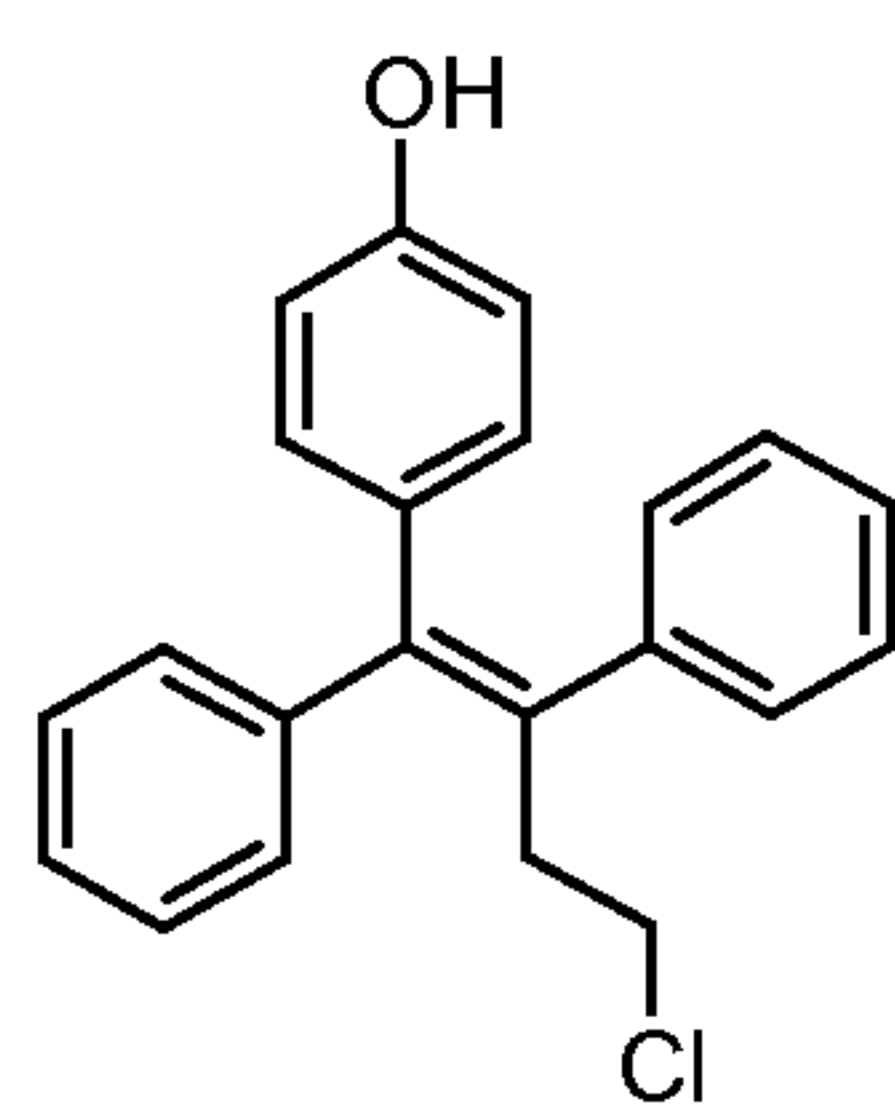


(Ia)



(Ib)

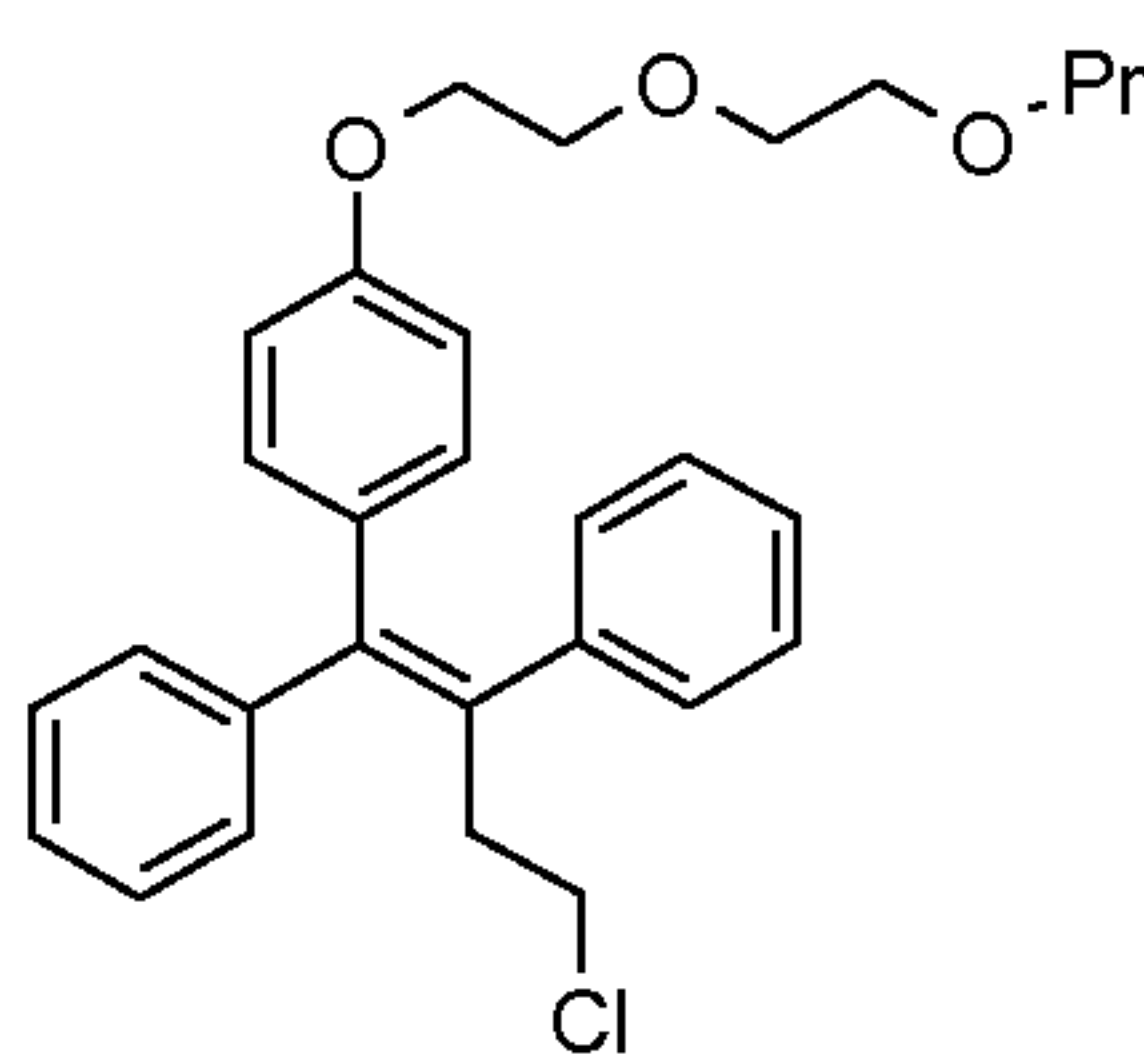
wherein a compound of formula (II)



(II)

a) is alkylated with an alkylating reagent of the formula $X-(CH_2)_2-O-(CH_2)_2-O-Pr$,

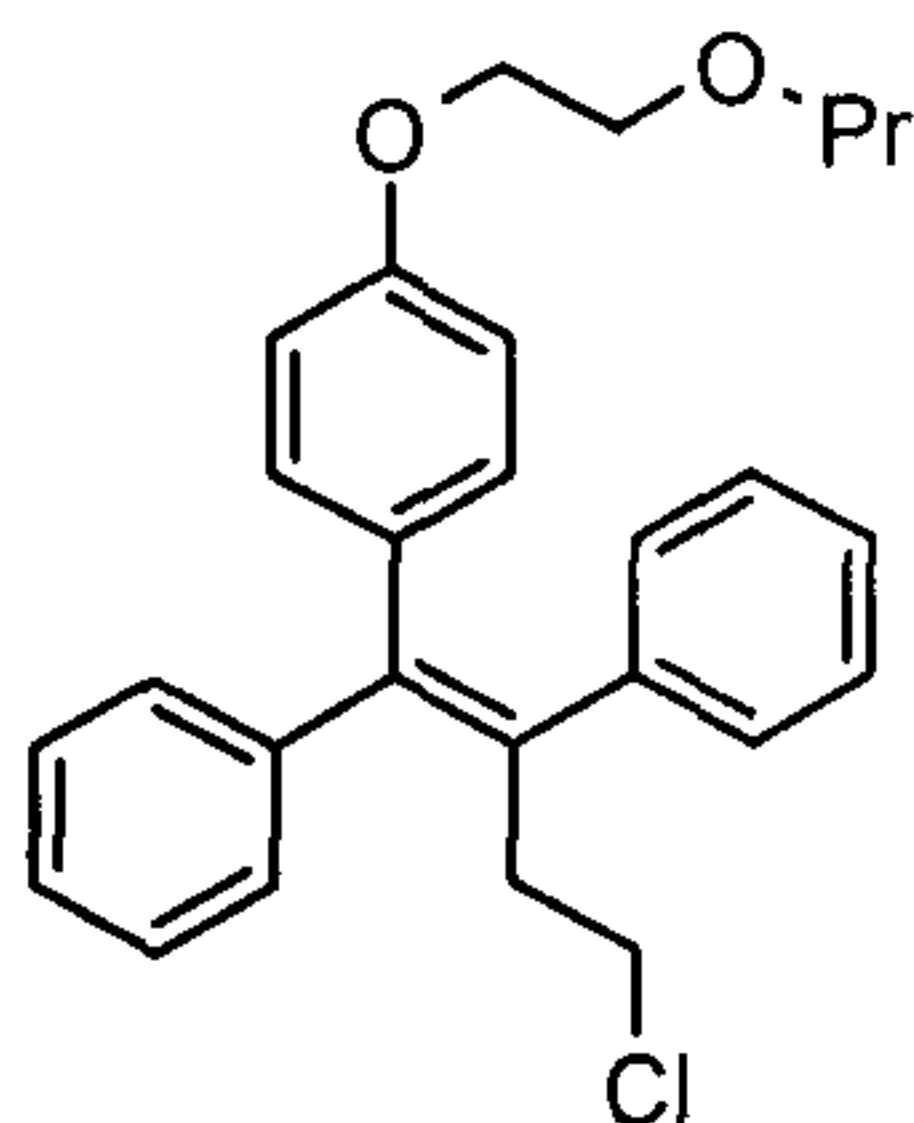
where X is Cl, Br, I, mesyloxy or tosyloxy, and Pr is a protecting group, to give a compound of formula (III)



(III)

which is subjected to removal of the protecting group Pr to give the compound of formula (Ia), or

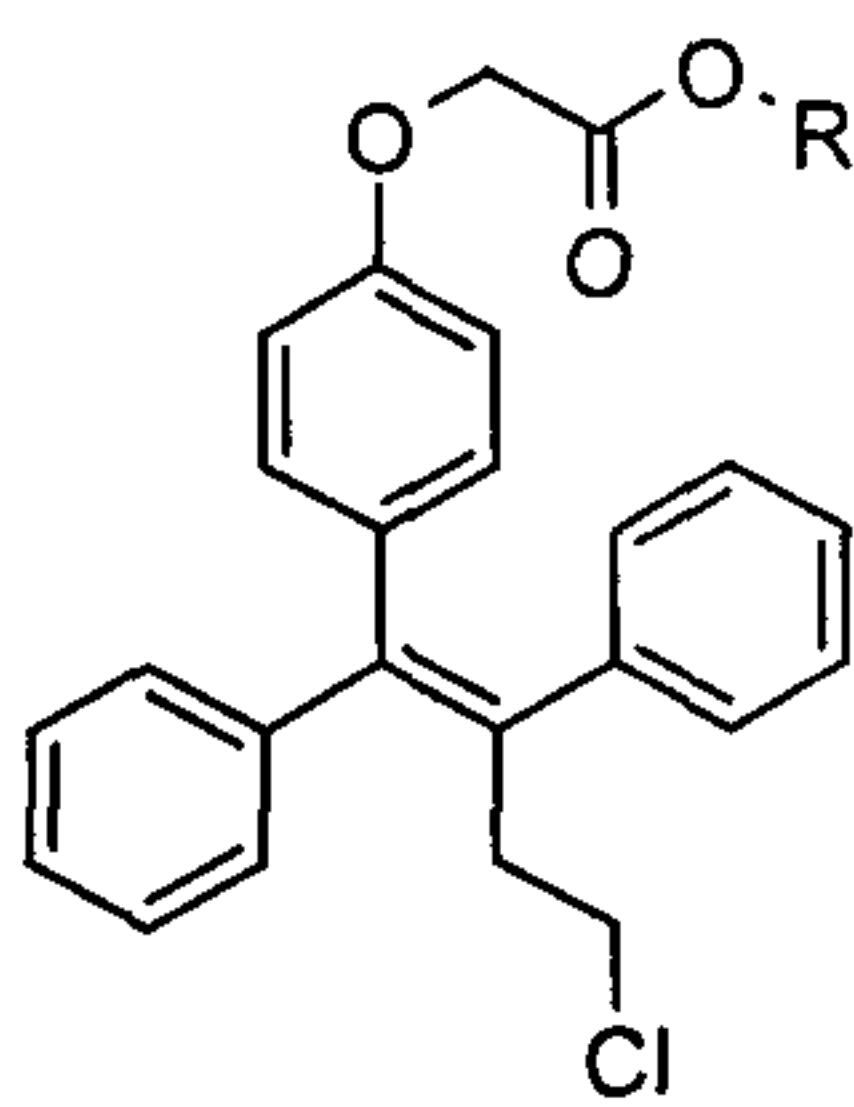
b) is alkylated with an alkylating reagent of the formula $X-(CH_2)_2-O-Pr$, where X is Cl, Br, I, mesyloxy or tosyloxy, and Pr is a protecting group, to give a compound of formula (IV)



(IV)

which is subjected to removal of the protecting group Pr to give the compound of formula (Ib), or

c) is alkylated with an alkylating reagent of the formula $X-CH_2-COOR$, wherein X is Cl, Br, I, mesyloxy or tosyloxy, and R is an alkyl, to give a compound of formula (V)

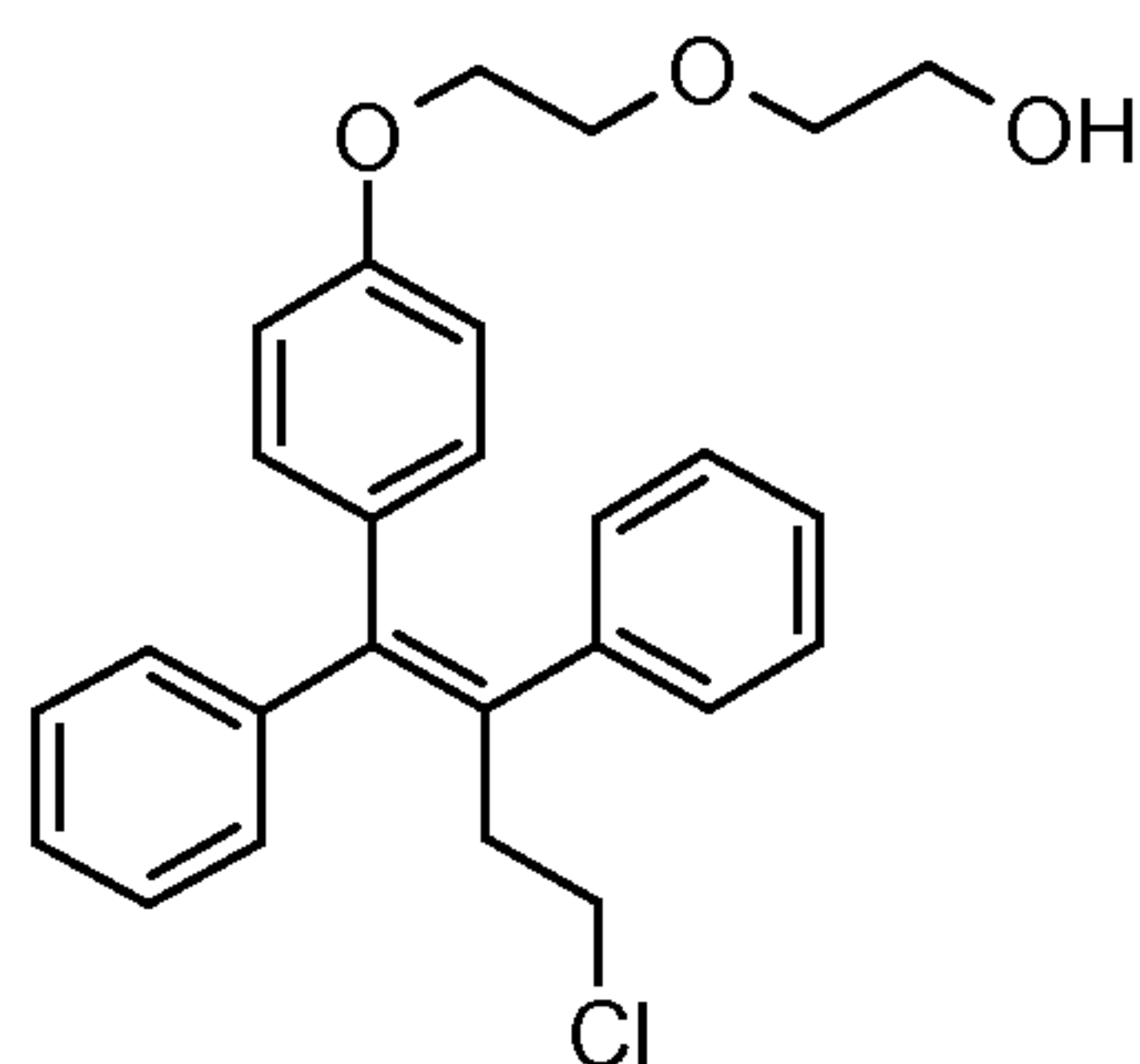


(V)

and the ester is reduced to give the compound of formula (Ib).

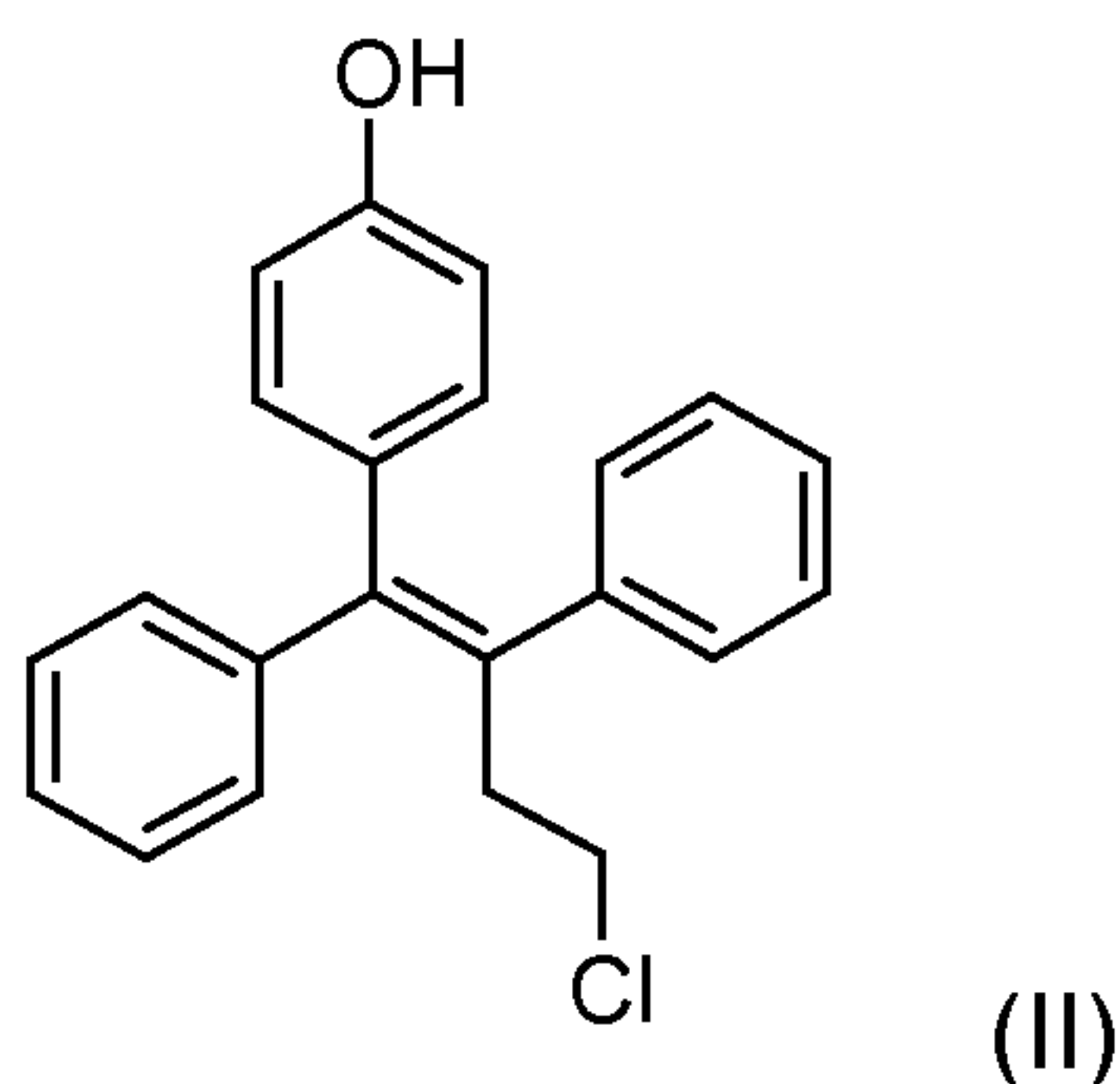
2. The method according to claim 1, wherein the compound of formula (II) is prepared by a McMurry reaction of 4-hydroxybenzophenone with 3-chloropropiophenone.
3. The method according to claim 1 or 2, wherein the alkylation in step a) or b) is carried out in tetrahydrofuran.
4. The method according to claim 1, wherein the protecting group is tetrahydropyranyl.

5. The method according to claim 1 or 2, wherein the protecting group is benzyl.
6. The method according claim 1 or 2, wherein X in the alkylating reagent in step a) or step b) is I or Br.
7. The method according claim 1, wherein X in the alkylating reagent in step c) is I, Br, or Cl.
8. The method according to claim 1 or 2, wherein the alkylation in step c) is carried out in by use of i) potassium carbonate and absolute ethanol, or ii) sodium hydride and tetrahydrofuran.
9. The method according to claim 1 or 2, wherein the reduction of compound (V) obtained in step c) is carried out by lithium aluminum hydride.
10. The method according to any of the foregoing claims where the compound (Ia) or (Ib) is the Z-isomer.
11. A method for the preparation of a compound of formula (Ia)



(Ia) comprising:

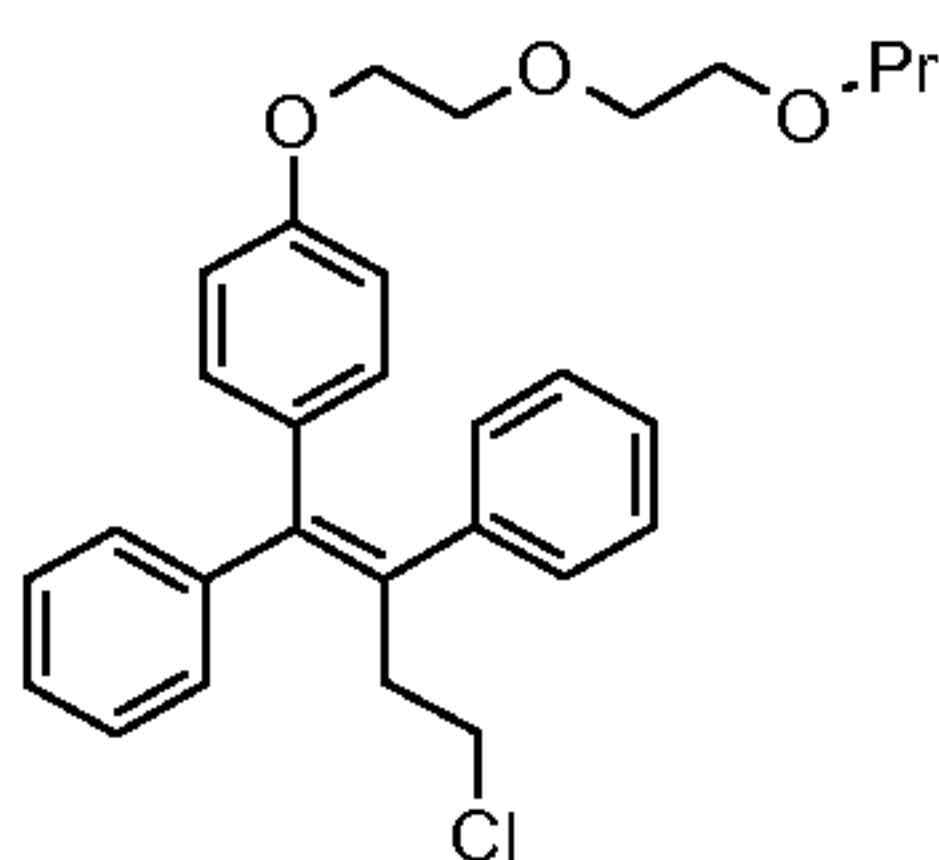
wherein a compound of formula (II)



(II)

is alkylated with an alkylating reagent of the formula $X-(CH_2)_2-O-(CH_2)_2-O-$ Pr,

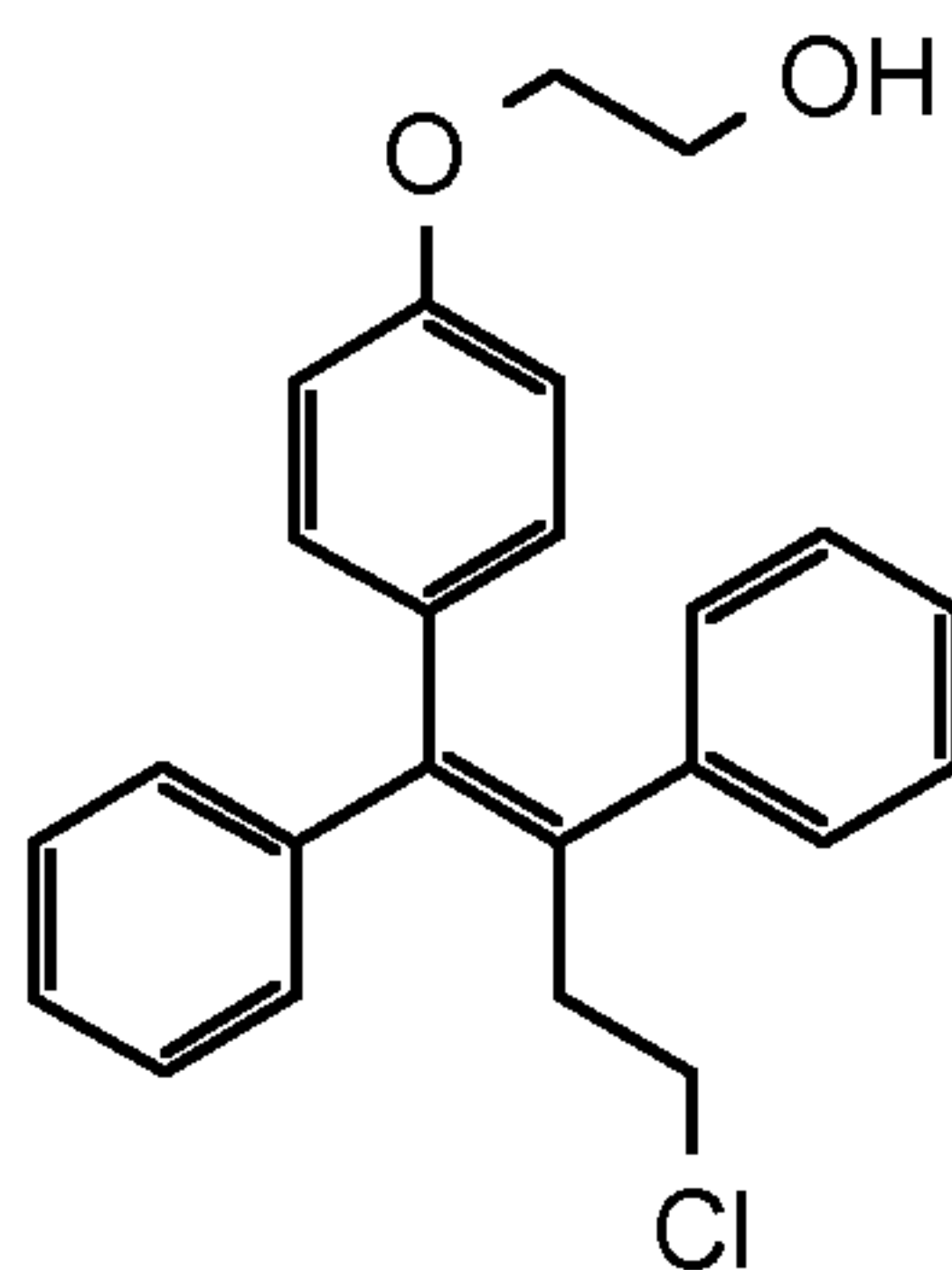
where X is Cl, Br, I, mesyloxy or tosyloxy, and Pr is a protecting group, to give a compound of formula (III)



(III)

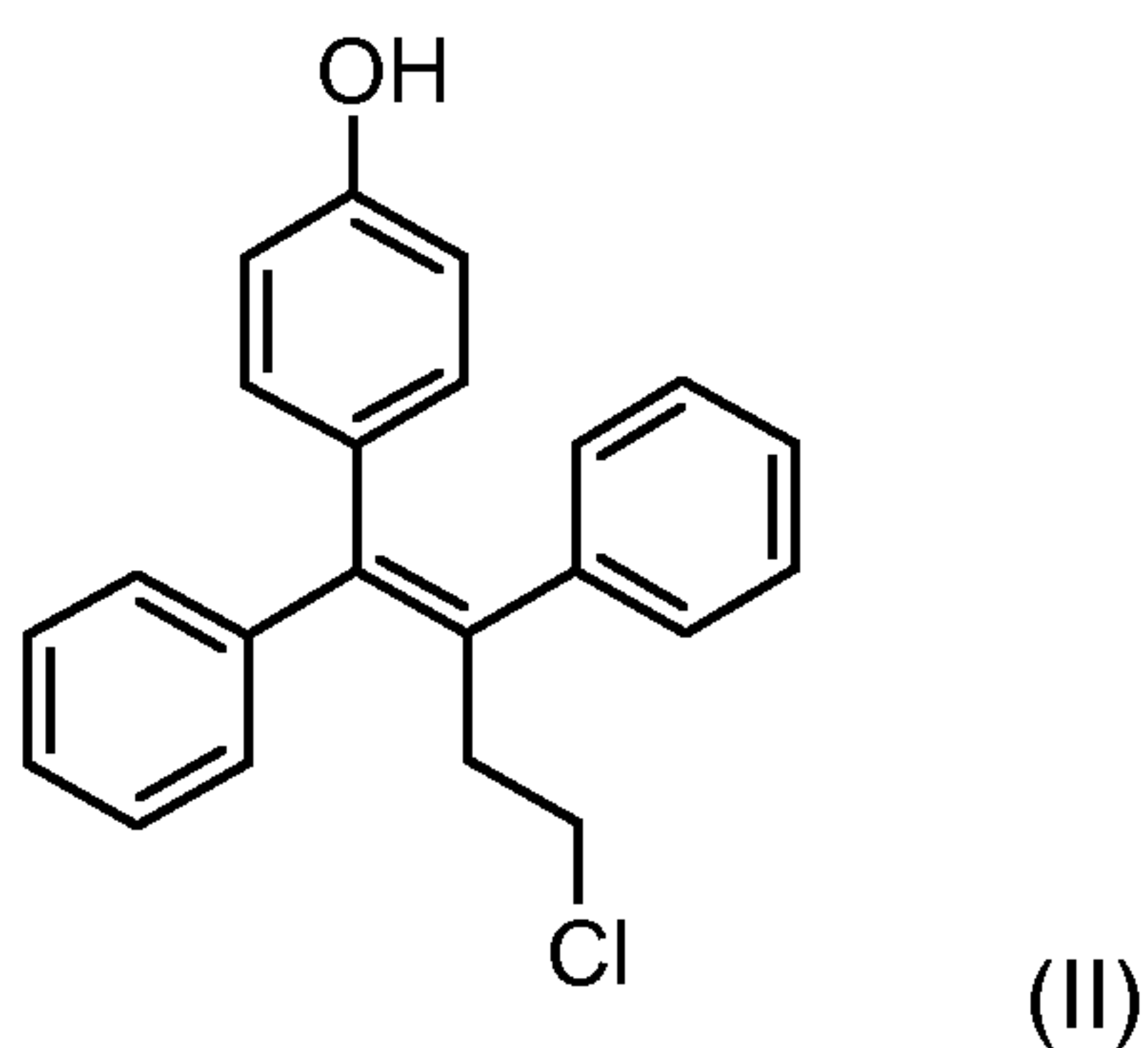
which is subjected to removal of the protecting group Pr to give the compound of formula (Ia), wherein the compound (Ia) is the Z-isomer.

12. The method of claim 11, wherein X is I.
13. The method of claim 11, wherein Pr is tetrahydropyranyl or benzyl.
14. The method of claim 13, wherein Pr is 2-tetrahydropyranyl.
15. The method of claim 11, wherein the protecting group Pr is removed using acid.
16. The method of claim 13, wherein Pr is benzyl and is removed using zinc and acetyl chloride.
17. A method for the preparation of a compound of formula (Ib)

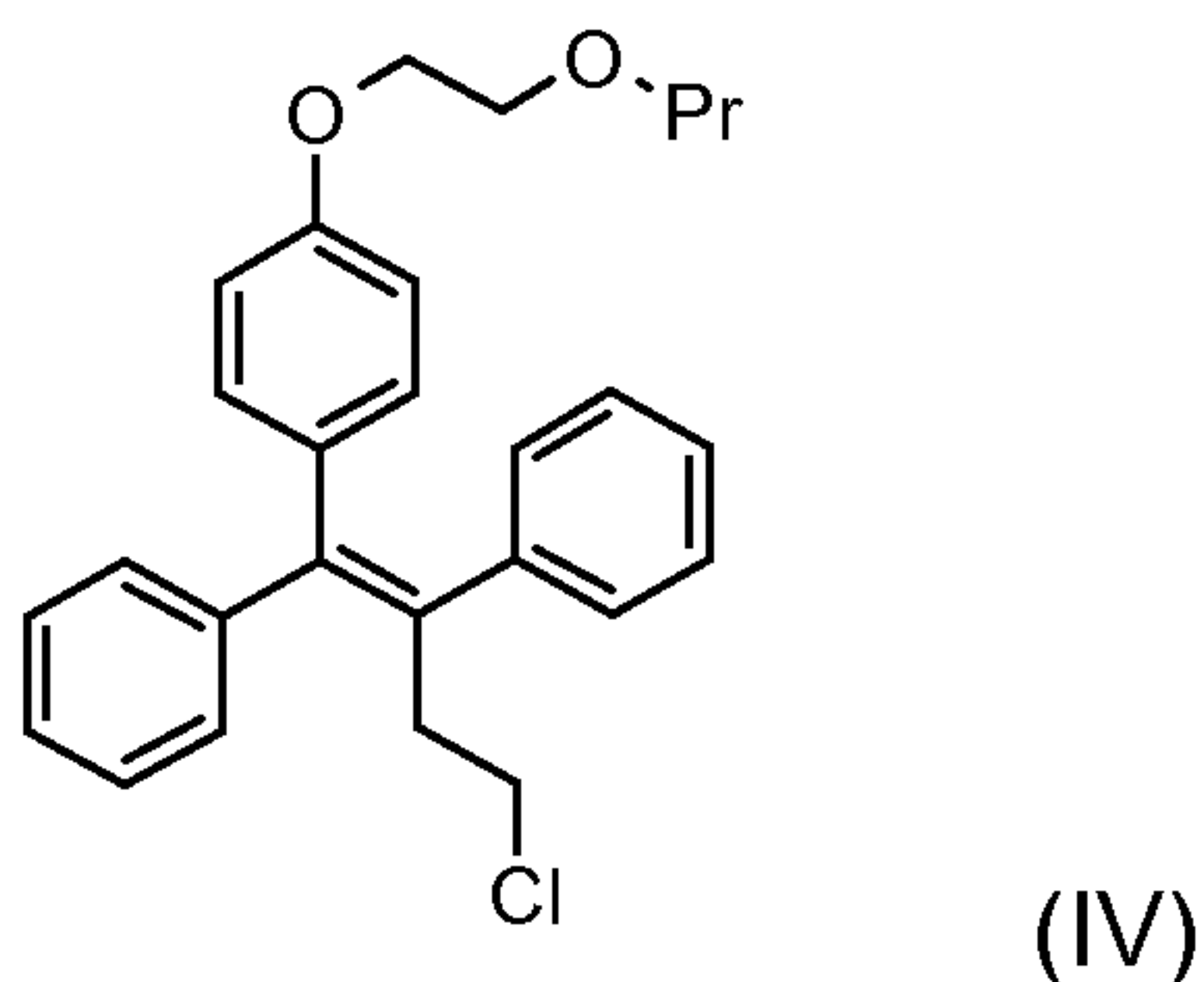


(Ib) comprising:

wherein a compound of formula (II)

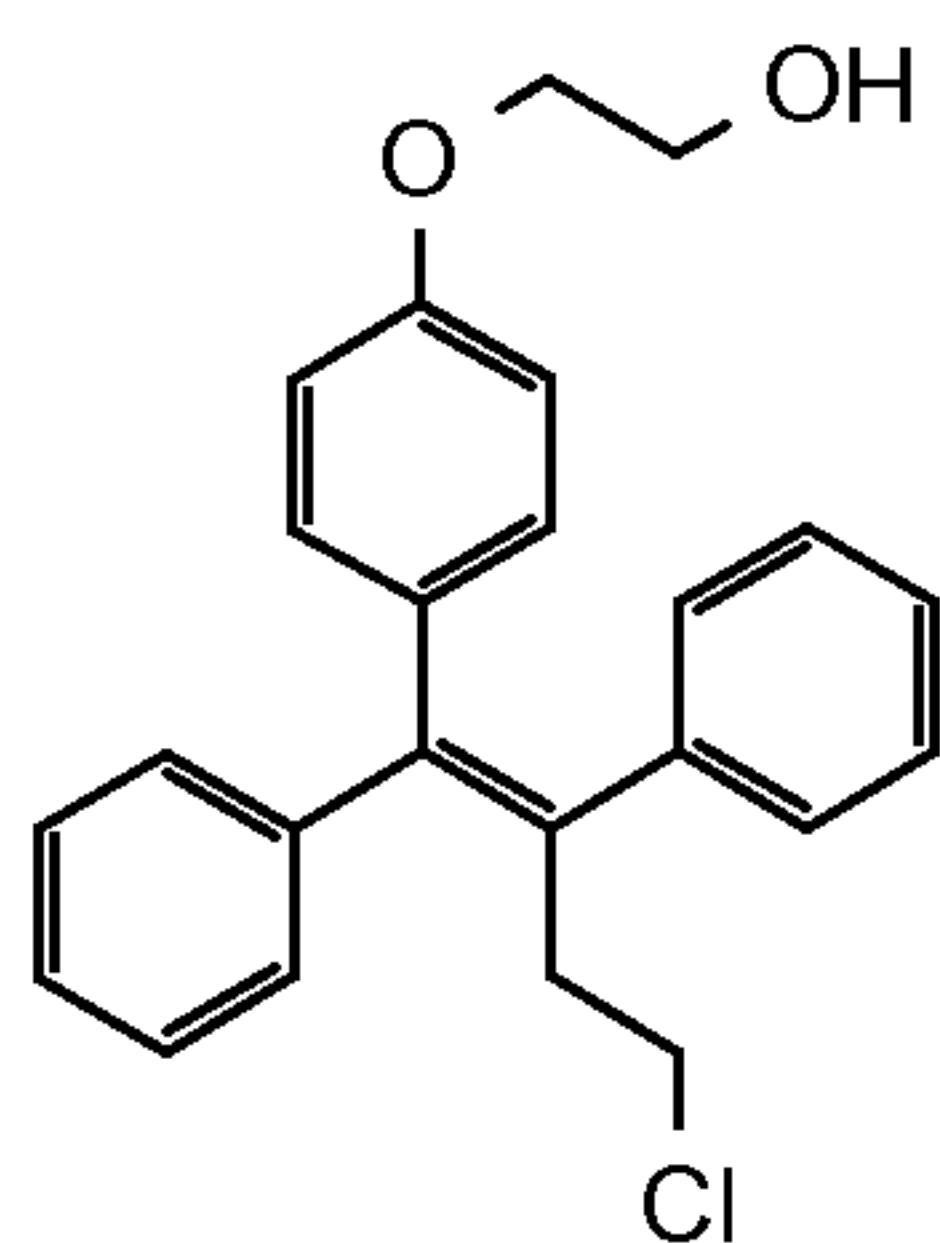


is alkylated with an alkylating reagent of the formula $X-(CH_2)_2-O-Pr$, where X is Cl, Br, I, mesyloxy or tosyloxy, and Pr is a protecting group, to give a compound of formula (IV)



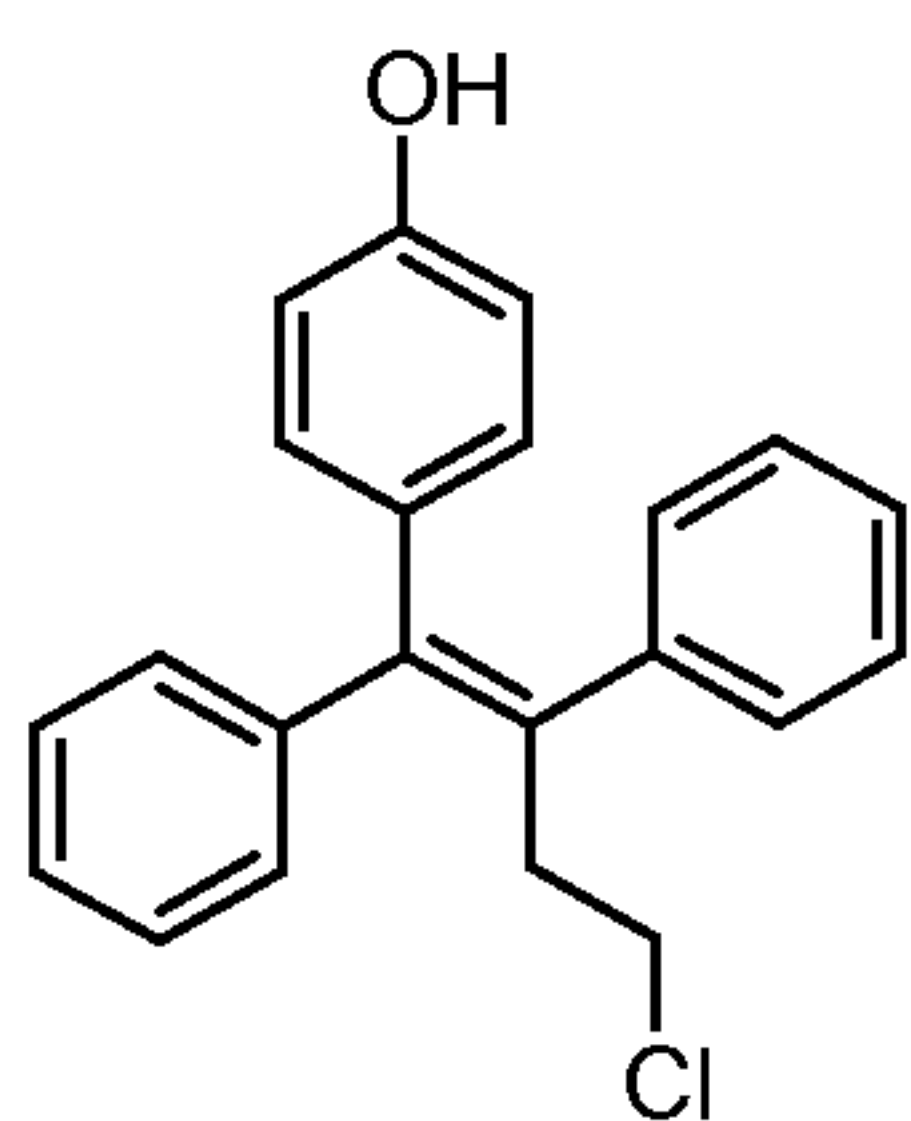
which is subjected to removal of the protecting group Pr to give the compound of formula (Ib), wherein the compound (Ib) is the Z-isomer.

18. The method of claim 17, wherein X is I.
19. The method of claim 17, wherein Pr is tetrahydropyranyl or benzyl.
20. The method of claim 17, wherein Pr is 2-tetrahydropyranyl.
21. The method of claim 20, wherein the protecting group Pr is removed using acid.
22. The method of claim 19, wherein Pr is benzyl and is removed using zinc and acetyl chloride.
23. A method for the preparation of a compound of formula (Ib):



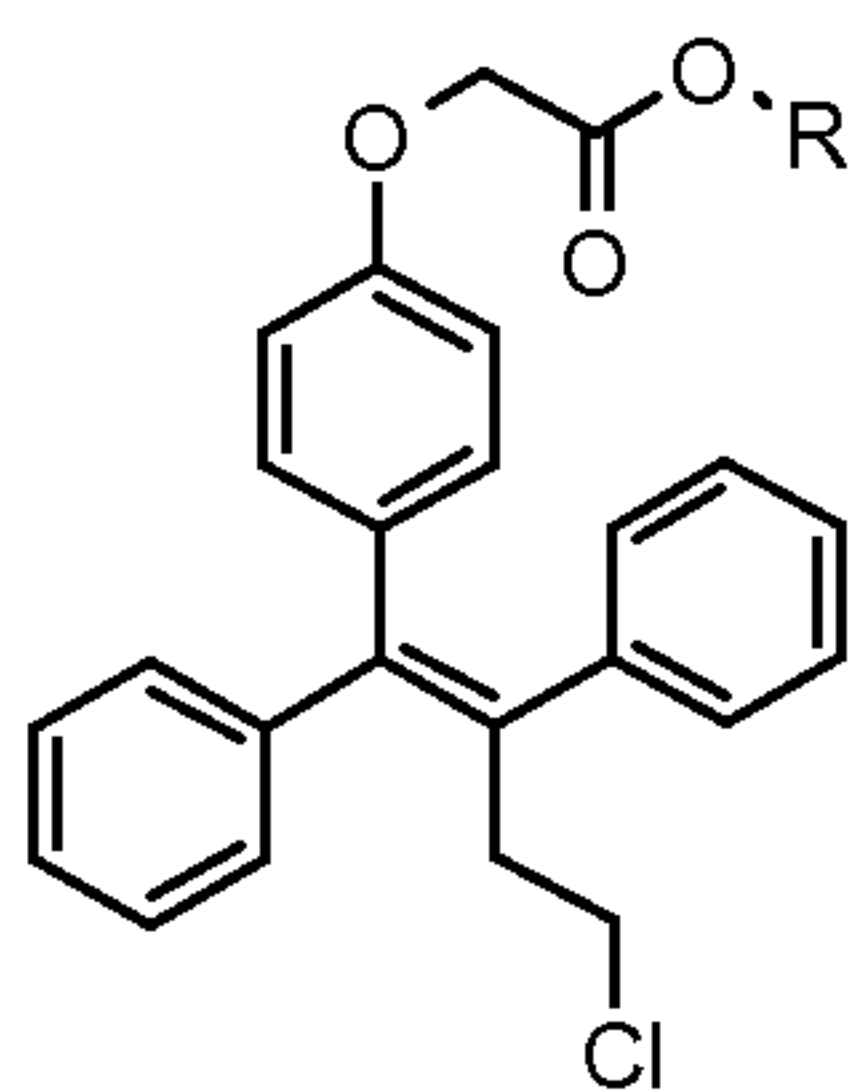
(Ib) comprising:

wherein a compound of formula (II)



(II)

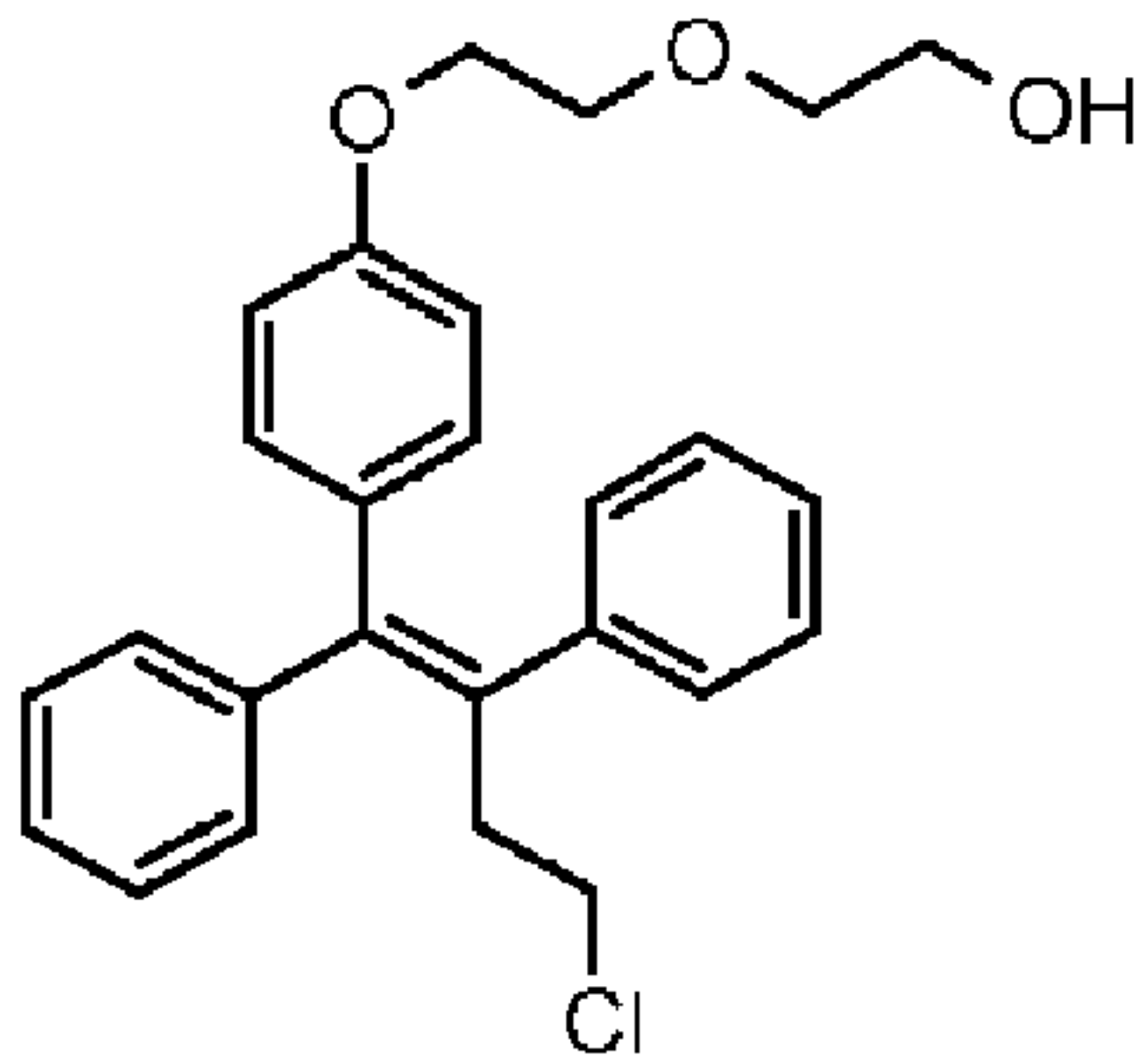
is alkylated with an alkylating reagent of the formula $X-CH_2-COOR$, wherein X is Cl, Br, I, mesyloxy or tosyloxy, and R is an alkyl, to give a compound of formula (V)



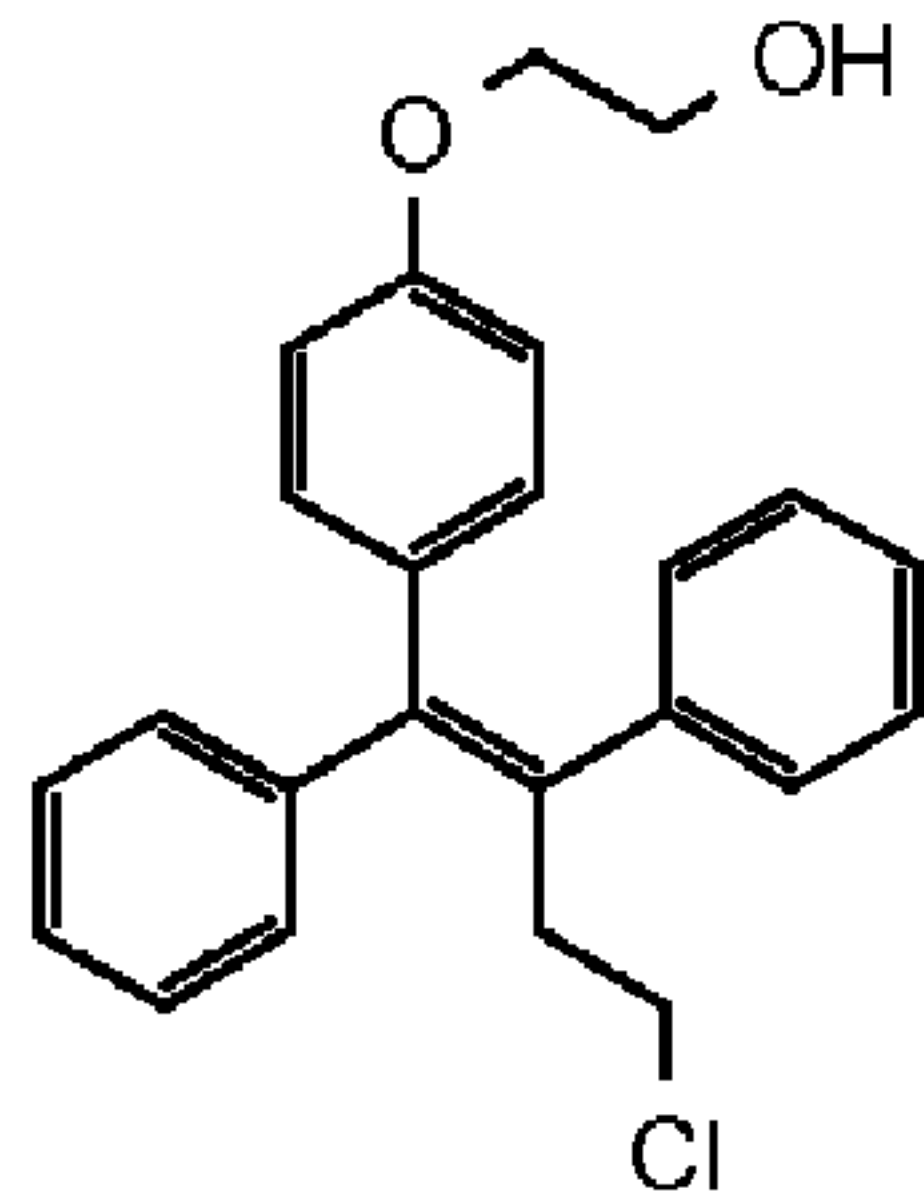
(V)

and the ester group of V is reduced to give the compound of formula (Ib), wherein the compound (Ib) is the Z-isomer.

24. The method of claim 23, wherein X is Br.
25. The method of claim 24, wherein R is a C_{1-4} alkyl.
26. The method of claim 25, wherein R is ethyl.
27. The method of claim 23, wherein said ester is reduced using lithium aluminum hydride.



(a)



(b)