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(54) Title: NOVEL METHOD FOR PREPARING 3-[5'-(3,4-BIS-HYDROXYMETHYL-BENZYLOXY)-2'- ETHYL-2-PROPYL-BIPHENYL-4-YL]-PENTA-3-OL

(54) Titre : NOUVEAU PROCEDE DE PREPARATION DU 3-[5'-(3,4-BIS-HYDROXYMETHYL-BENZYLOXY)-2'-ETHYL-2-PROPYL-BIPHENYL-4-YL]-PENTA-3OL.

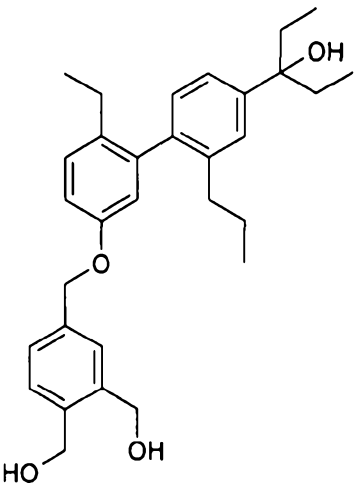
(57) Abstract: The invention concerns a novel method for preparing 3-[5'-(3,4-bis-hydroxymethyl-benzyloxy)-2'- ethyl-2-propyl-biphenyl-4-yl]-penta-3-ol as well as a novel compound, 6-ethyl-4'-(1-ethyl-1-hydroxy-propyl)-2'-propyl-biphenyl- 3-ol, useful as synthesis intermediate in said method.

(57) Abrégé : La présente invention se rapporte à un nouveau procédé de fabrication du 3-[5'-(3,4-bis-hydroxymethyl-benzyloxy)-2'-ethyl-2-propyl-biphenyl-4-yl]-penta-3-ol ainsi qu'à un composé nouveau, le 6-éthyl-4'-(1-éthyl-1-hydroxy-propyl)-2'-propyl-biphenyl- 3-ol, utile comme intermédiaire de synthèse dans ledit procédé.

WO 2006/053985 A1

Novel process for the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol

The present invention relates to a process for the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol of formula:



The compounds of the family of the above 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol and their use in human medicine have been described by the Applicant Company in Patent WO 03/050067.

In this patent application, the synthesis of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol is carried out in 17 stages. The majority of the intermediates generated in this synthesis are purified by chromatography on a silica column, making it difficult to manufacture this product on a large scale.
In addition, due to this large number of stages, the overall yield of this synthesis is very low, less than 0.5%, and the manufacturing times are very long.

In the present invention, the Applicant Company has developed a novel process for the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol in four stages, making it possible to overcome the problems stated above, according to the scheme of **Figure 1**.

The present invention provides a process for the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol with the structure:

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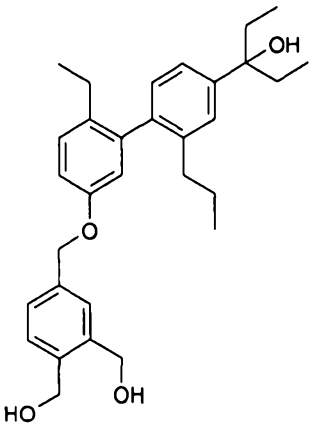


characterized in that it comprises the following 4 stages:

a) conversion of 1-(4-hydroxy-3-propylphenyl)propan-1-one to give trifluoromethanesulphonic acid 4-propionyl-2-(n-propyl)phenyl ester, followed by a reaction with 2-ethyl-5-methoxyphenylboronic acid;

b) demethylation of 1-(2'-ethyl-5'-methoxy-2-propylbiphenyl-4-yl)propan-1-one by heating with an excess of pyridine salts;

c) conversion of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one to give 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol by reaction with ethylmagnesium bromide or with ethyllithium;

d) condensation of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with dimethyl 4-(bromomethyl)phthalate, followed *in situ* by a reduction reaction with lithium borohydride.

The invention thus relates to a process for the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol, characterized in that it comprises the following stages:

a) conversion of 1-(4-hydroxy-3-propylphenyl)propan-1-one to give trifluoromethanesulphonic acid 4-propionyl-2-(n-propyl)phenyl ester, followed *in situ* by a reaction of Suzuki type with 2-ethyl-5-methoxyphenylboronic acid;

b) demethylation of 1-(2'-ethyl-5'-methoxy-2-propylbiphenyl-4-yl)propan-1-one by heating with an excess of pyridine salts;

c) conversion of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one to give 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol by reaction with ethylmagnesium bromide or ethyllithium;

d) condensation of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with dimethyl 4-(bromomethyl)phthalate, followed *in situ* by a reduction reaction with lithium borohydride.

More specifically, the process according to the invention comprises the following detailed stages:

- The first stage of this process (stage a) above or I01 in Figure 1) is a one pot reaction for the conversion of 1-(4-hydroxy-3-propylphenyl)propan-1-one (prepared according to Demerseman et al., Bull. Soc. Chim. Fr., 1963, 2559-2562, or Stoughton, Baltzly and Bass, J. Am. Chem. Soc., 56, 1934, 2007) by reaction with trifluoromethanesulphonic anhydride (Tf_2O) in the presence of triethylamine (NEt_3) to give its derivative trifluoromethanesulphonic acid 4-propionyl-2-(n-propyl)phenyl ester, followed by an *in situ* condensation of Suzuki type with 2-ethyl-5-methoxyphenylboronic acid (prepared according to a process described in Patent Application **FR 2 863 613**) in the presence of K_2CO_3 and of a catalytic amount of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$.

This one pot reaction is carried out in solvents such as tetrahydrofuran (THF), dimethylformamide (DMF), aromatic solvents, such as toluene, ethereal solvents, such as diisopropyl ether, halogenated solvents, such as chloroform, or alkanes, such as pentane, hexane or heptane. The solvents preferably used in this reaction are DMF and/or toluene.

The reaction is carried out at temperatures of between 5 and 140°C, preferably at 120°C.

The amounts of catalyst $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ used in this reaction can vary between 0.001 and 0.05 molar equivalent with respect to the amount of 1-(4-hydroxy-3-propylphenyl)propan-1-one. Use will preferably be made of between 0.01 and 0.05 molar equivalent of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$.

- In the second stage (stage b) above or I02 in Figure 1), 1-(2'-ethyl-5'-methoxy-2-propylbiphenyl-4-yl)propan-1-one is subjected to a demethylation reaction with a pyridine salt. The reaction is carried out without solvent at temperatures of between 80 and 200°C, preferably at 170°C.

The pyridine salts used in this reaction can be the hydrochloride, the hydrobromide or the hydriodide and can vary between 1 and 10 molar equivalents. Preferably, 5 molar equivalents will be used.

- The third stage (stage c) above or I03 in Figure 1) is the conversion of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one to give a novel compound, 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol, by reaction with ethylmagnesium bromide or with ethyllithium.

The solvents preferably used in this reaction are ethers, such as ethyl ether, tert-butyl dimethyl ether or tetrahydrofuran.

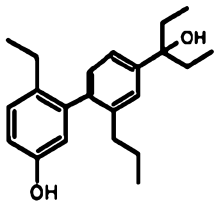
The reaction is carried out at temperatures of between -20°C and 20°C, preferably at 0°C.

The amounts of ethylmagnesium bromide or of ethyllithium used in this reaction can vary between 2 and 5 molar equivalents. Preferably, 2.2 molar equivalents will be used.

- In the following stage (stage d) above or I04 in Figure 1), 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol is condensed with dimethyl 4-(bromomethyl)phthalate (prepared according to a method analogous to that described by E.H. White, D.F. Roswell and O.C. Zafiriou in J. Org. Chem., 34 (8), 2462-2468, 1969, and J.W. Leon, M. Kawa and J.M.J. Frechet in J. Amer. Chem. Soc., 118, 8847-8859, 1996) in the presence of potassium carbonate (K_2CO_3) in tetrahydrofuran at reflux. The two carboxyl functional groups are subsequently reduced *in situ* by the addition of lithium borohydride ($LiBH_4$) and then heating at reflux of the tetrahydrofuran.

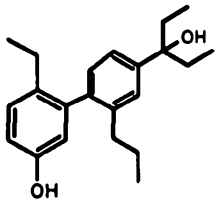
The first reaction can be catalysed by phase transfer agents, such as Aliquat 336 or tetrabutylammonium bromide, in the presence of potassium iodide.

The present invention also relates to the novel compound 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with the structure:

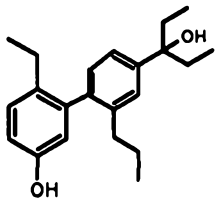


and to its process of manufacture.

The present invention provides a compound 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with the structure:



The present invention also provides a process for the preparation of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with the structure:



characterized in that the compound is obtained from 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one by addition of ethylmagnesium bromide or of ethyllithium in the presence of solvents.

The invention thus also relates to the process for the conversion of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one to give 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol by reaction with ethylmagnesium bromide or with ethyllithium.

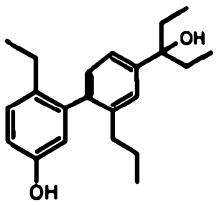
The solvents preferably used in this reaction are ethers, such as ethyl ether, tert-butyl dimethyl ether or tetrahydrofuran.

The reaction is carried out at temperatures of between -20°C and 20°C, preferably at 0°C. The amounts of ethylmagnesium bromide or of ethyllithium used in this reaction can vary between 2 and 5 molar equivalents. Preferably, 2.2 molar equivalents will be used.

After treatment, 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol is crystallized from diisopropyl ether or dichloromethane, making it possible to obtain this product with a purity of greater than 99%.

The invention also relates to the use of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol in the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol.

The present invention further provides the use of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with the structure:



in the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol.

By way of example, without any limiting nature, a description of the process which makes it possible to prepare 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol will be found below.

Example 1: Preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol.

1) 1-(2'-Ethyl-5'-methoxy-2-propylbiphenyl-4-yl)-propan-1-one

203 g of 1-(4-hydroxy-3-propylphenyl)propan-1-one and 1 litre of toluene are charged to a 4 litre reactor under nitrogen. The medium is cooled to approximately -5°C and then the rapid addition is carried out of 176 ml of triethylamine and then of 196 ml of trifluoromethanesulphonic anhydride over 1 hour at between -5°C and +1°C. After stirring for 30 min, 1 litre of a 2M K_2CO_3 solution is introduced, followed by 190 g of 2-ethyl-5-methoxyphenylboronic acid in solution in 610 ml of dimethylformamide. 12 g of tetrakis(triphenylphosphine)palladium(0) are added and the reaction medium is heated at reflux for 2 h. After being brought back to ambient temperature, the reaction medium is washed 3 times with 610 ml of a saturated NH_4Cl solution and then with 610 ml of water. The solvents are evaporated from the organic phase under vacuum. The crude product obtained is taken up in 1 volume of dichloromethane, which is deposited on 3 times its weight of silica. Elution is carried out with 16 volumes of methylene chloride. After evaporating the solvent, 335 g of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one are obtained (beige oil; 100% yield).

2) 1-(2'-Ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one

413 g (1.33 mol) of 1-(2'-ethyl-5'-methoxy-2-propylbiphenyl-4-yl)propan-1-one and 768 g (6.64 mol) of pyridine hydrochloride are placed in a round-bottomed flask. The mixture is heated at 160-170°C for 4 hours with stirring. The reaction medium is allowed to return to 100-110°C and 800 ml of water are added. The mixture is cooled to 30°C and extracted with 1.6 litres of ethyl acetate. After separating by settling, the aqueous phase is extracted with 600 ml of ethyl acetate. The organic phases are combined and washed twice with 800 ml of water. After evaporating under reduced vacuum, 410 g of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one are obtained in the form of an oil.

3) 6-Ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol

370 g (1.248 mol) of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one in solution in 3.7 litres of tetrahydrofuran are placed in a reactor. 915 ml of a 3M solution of ethylmagnesium bromide in ethyl ether are slowly run into this solution cooled to -10°C. At the end of the addition, the reaction mixture is kept stirred for 1 hour and then transferred onto 5 litres of a 2.5 molar solution of ammonium chloride in water. The organic phase is separated by settling and washed twice with 800 ml of water. After evaporating under reduced vacuum, the residue is dissolved with 2.75 litres of methylene chloride at reflux. The medium is allowed to return to ambient temperature

with stirring and is then cooled to 5°C. The crystals are filtered off and then dried under vacuum. 260 g (64%) of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol are obtained.

Melting point: 130°C

^{1}H NMR (d_6-DMSO) (ppm): 0.67-0.74, m, 9H; 0.9, t, 3H; 1.38, m, 2H; 1.71-1.77, m, 4H; 2.13-2.35, m, 4H; 4.48, s, 1H; 6.45, d, 1H; 6.70, dd, 1H; 6.94, d, 1H; 7.07, d, 1H; 7.18, dd, 1H; 7.26, s, 1H; 9.16, s, 1H

4) 3-[5'-(3,4-Bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol

40 g (0.123 mol) of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol, 37 g (0.129 mol) of dimethyl 4-(bromomethyl)phthalate, 17.8 g (0.129 mol) of potassium carbonate, 500 mg of Aliquat 336 and 100 mg of potassium iodide are introduced into 400 ml of tetrahydrofuran in a round-bottomed flask equipped with a mechanical stirrer. The reaction mixture is heated at reflux for 6 hours. After returning to ambient temperature, 4 g (0.184 mol) of lithium borohydride are added portionwise. Heating is again carried out for 4 hours. The medium is allowed to return to ambient temperature and is then slowly transferred onto 600 ml of ice-cold water. After stirring for two hours, the organic phase is extracted with 100 ml of ethyl acetate and washed twice with 200 ml of water. The organic phase is evaporated under reduced vacuum and the residue is dissolved in a diisopropyl ether/ethanol mixture at 50°C.

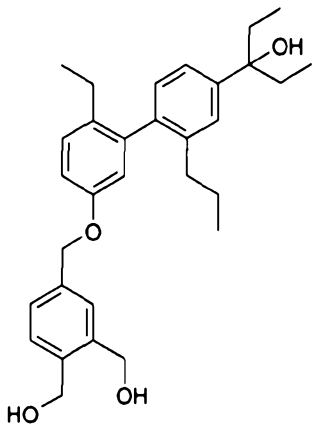
After stirring overnight, the crystals are filtered off and dried under vacuum. 41.6 g (71%) of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol are obtained.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

THE CLAIMS OF THE INVENTION ARE DEFINED AS FOLLOWS:

1. Process for the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol with the structure:



characterized in that it comprises the following 4 stages:

a) conversion of 1-(4-hydroxy-3-propylphenyl)propan-1-one to give trifluoromethanesulphonic acid 4-propionyl-2-(*n*-propyl)phenyl ester, followed by a reaction with 2-ethyl-5-methoxyphenylboronic acid;

b) demethylation of 1-(2'-ethyl-5'-methoxy-2-propylbiphenyl-4-yl)propan-1-one by heating with an excess of pyridine salts;

c) conversion of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one to give 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol by reaction with ethylmagnesium bromide or with ethyllithium;

d) condensation of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with dimethyl 4-(bromomethyl)phthalate, followed *in situ* by a reduction reaction with lithium borohydride.

2. Process according to Claim 1, characterized in that the reaction of stage a) is a reaction for the conversion of 1-(4-hydroxy-3-propylphenyl)propan-1-one by reaction with trifluoromethanesulphonic anhydride (Tf_2O) in the presence of triethylamine (NEt_3) to give its derivative trifluoromethanesulphonic acid 4-propionyl-2-(*n*-propyl)phenyl ester, followed by a condensation of Suzuki type with 2-ethyl-5-methoxyphenylboronic acid, and in that the said reactions of stage a) take place *in situ* in the presence of K_2CO_3 and of a catalytic amount of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$, in solvents such as tetrahydrofuran (THF), dimethylformamide (DMF), aromatic solvents, such as toluene,

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ethereal solvents, such as diisopropyl ether, halogenated solvents, such as chloroform, or alkanes, such as pentane, hexane or heptane.

3. Process according to Claim 2, characterized in that the reaction of stage a) is carried out at temperatures of between 5 and 140°C and that the catalytic amounts of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ are between 0.01 and 0.05 molar equivalent.

4. Process according to any one of Claims 1 to 3, characterized in that the pyridine salt of stage b) is chosen from a pyridine hydrochloride, hydrobromide or hydriodide at a concentration which can vary between 1 and 10 molar equivalents.

5. Process according to any one of Claims 1 to 4, characterized in that the pyridine salt of stage b) is used at a concentration of 5 molar equivalents.

6. Process according to any one of Claims 1 to 5, characterized in that stage b) is carried out without solvent.

7. Process according to any one of Claims 1 to 6, characterized in that stage b) is carried out at temperatures of between 80 and 200°C.

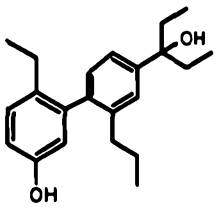
8. Process according to any one of Claims 1 to 7, characterized in that stage b) is carried out at a temperature of 170°C.

9. Process according to any one of Claims 1 to 8, characterized in that stage c) is the conversion of 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one to give 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol by reaction with ethylmagnesium bromide or with ethyllithium in the presence of solvents, such as ethyl ether, tert-butyl dimethyl ether or tetrahydrofuran.

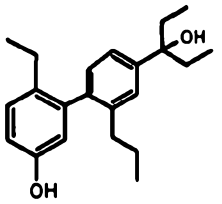
10. Process according to any one of Claims 1 to 9, characterized in that stage d) is the condensation of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with dimethyl 4-(bromomethyl)phthalate in the presence of potassium carbonate (K_2CO_3) in tetrahydrofuran at reflux, and the two carboxyl functional groups are subsequently reduced *in situ* by the addition of lithium borohydride ($LiBH_4$) and then heating at reflux of the tetrahydrofuran.

11. 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol when prepared by the process according to any one of Claims 1 to 10.

12. Compound 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with the structure:



13. Process for the preparation of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with the structure:



characterized in that the compound is obtained from 1-(2'-ethyl-5'-hydroxy-2-propylbiphenyl-4-yl)propan-1-one by addition of ethylmagnesium bromide or of ethyllithium in the presence of solvents.

14. Process according to Claim 13, characterized in that the solvents used are ethers, such as ethyl ether, tert-butyl dimethyl ether or tetrahydrofuran.

15. Process according to the preceding Claim 13 or the preceding Claim 14, characterized in that the reaction is carried out at temperatures of between -20°C and 20°C.

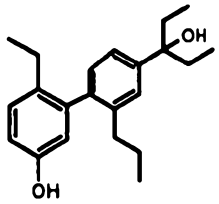
16. Process according to any one of the preceding Claims 13 to 15, characterized in that the reaction is carried out at the temperature 0°C.

17. Process according to any one of the preceding Claims 13 to 16, characterized in that the amounts of ethylmagnesium bromide or of ethyllithium can vary between 2 and 5 molar equivalents.

18. Process according to any one of the preceding Claims 13 to 17, characterized in that the amounts of ethylmagnesium bromide are 2.2 molar equivalents.

19. 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol when prepared by the process according to any one of claims 13 to 18.

20. Use of 6-ethyl-4'-(1-ethyl-1-hydroxypropyl)-2'-propylbiphenyl-3-ol with the structure:



in the preparation of 3-[5'-(3,4-bis(hydroxymethyl)benzyloxy)-2'-ethyl-2-propylbiphenyl-4-yl]pentan-3-ol.

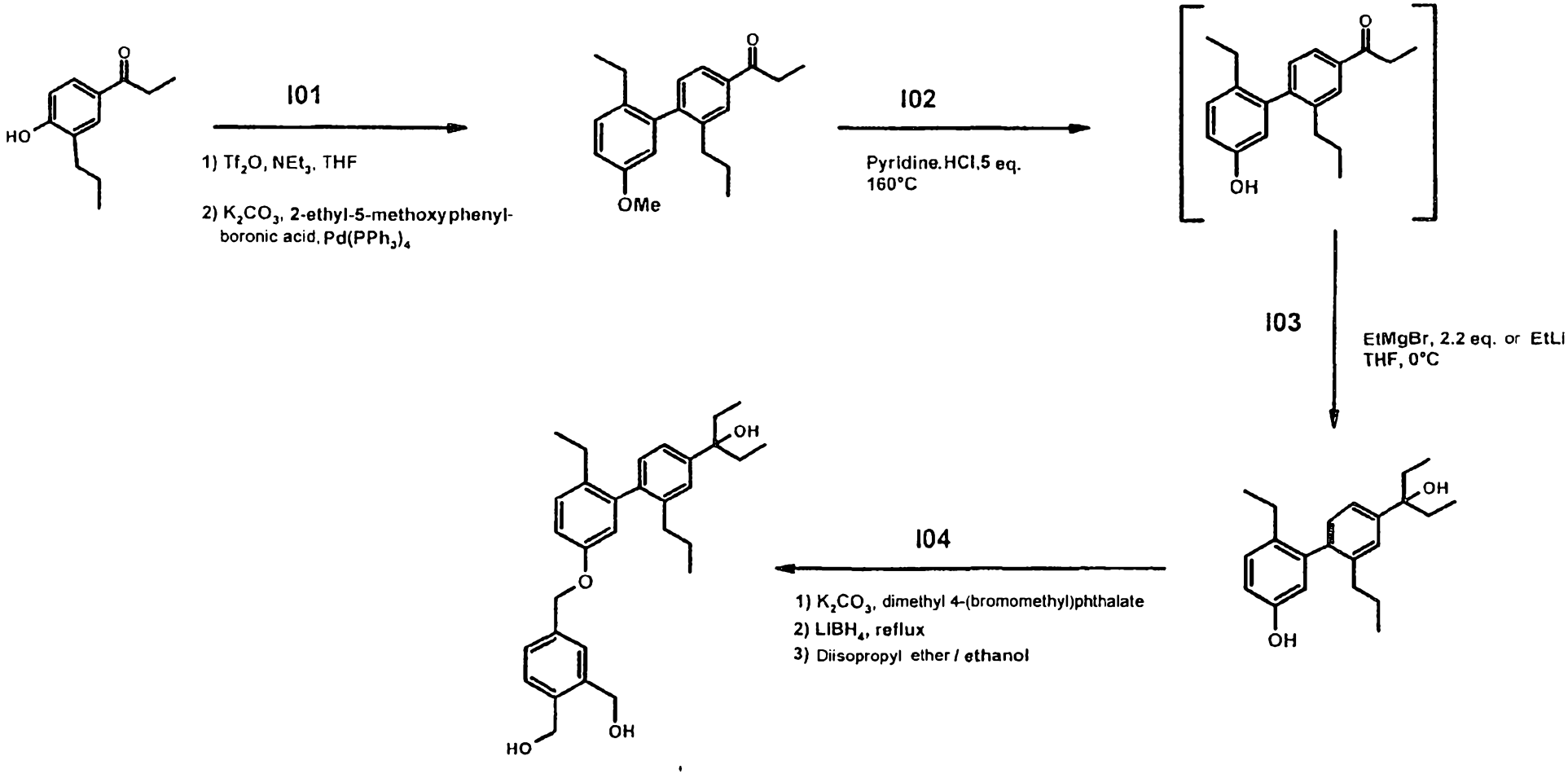

HO
O
101
1) Tf_2O, NEt_3, THF
2) K_2CO_3, 2-ethyl-5-methoxyphenyl-boronic acid, $Pd(PPh_3)_4$
OMe
102
Pyridine.HCl,5 eq.
160°C
OH
103
EtMgBr, 2.2 eq. or EtLi
THF, 0°C
OH
OH
104
1) K_2CO_3, dimethyl 4-(bromomethyl)phthalate
2) $LIBH_4$, reflux
3) Diisopropyl ether / ethanol
HO
OH

Figure 1