DAPPALENE

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(54) Title: A PROCESS FOR PREPARATION OF ADAPALENE

(57) Abstract: The present invention discloses a process for preparation of highly pure Adapalene, chemically designated as 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (I) comprising: a) reacting 1-adamantanol with 4-bromophenol (II) in presence of sulphonic acid with or without the use of organic solvent to give 2-(1-adamantyl)-4-bromophenol (III); b) alkylation compound of formula(III) with dimethylsulphate in presence of base in organic solvent to obtain 2-(1-adamantyl)-4-bromoanisole (IV); c) C-C coupling the compound of formula (IV) with methyl-6-bromo-2-naphthoate using magnesium, purified zinc chloride and NiCl2-DPPE in THF at a temperature of 40-60°C to obtain methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (V); d) purifying crude methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (V) using a mixture of organic solvent to obtain pure compound (VI); e) hydrolyzing the compound (V) with a solution of alkali in organic solvent to obtain metal salt of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (VI); f) acidifying metal salt of adapalene (VI) using organic or inorganic acid to obtain crude adapalene (I) and g) recrystallizing the crude adapalene (I) using a mixture of organic solvents to obtain pure adapalene (I).
A process for preparation of Adapalene

Technical Field:
The present invention relates to an improved process for the preparation of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (Adapalene) having formula I.

![Formula I](image)

Background of Invention:
Adapalene is a benzonaphthalene derivative disclosed in US 4,717,720 and used for the treatment of Acne Vulgaris. It is a retinoid and when used in small concentrations is a moderator of cellular differentiation, keratinization, and inflammatory processes.

US4,717,720 / RE34,440 describes a process for the preparation of Adapalene (I), comprising of reacting 1-adamantanol with 4-bromophenol (II) in presence of concentrated sulfuric acid in dichloromethane to give crude 2-(1-adamantyl)-4-bromophenol (III). Recrystallising the crude product in isooctane to provide pure 2-(1-adamantyl)-4-bromophenol (III). Compound of formula (III) is then alkylated with iodomethane in presence of sodium hydride in tetrahydrofuran to obtain crude 2-(1-adamantyl)-4-bromoanisole (IV) which is further purified by column chromatography using mixture of hexane-dichloromethane to yield pure compound (IV). Compound of formula (IV) is then treated with magnesium to form a Grignard reagent, replacing Mg by Zn using zinc chloride and reacting with methyl-6-bromo-2-naphthoate in the presence of [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) or NiCl$_2$-DPPE in THF to provide crude methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (V). Crude product (V) is then purified by column chromatography using mixture of heptane-
dichloromethane and recrystallizing the residue in ethyl acetate to obtain pure compound (V) which is further hydrolyzed with a solution of soda in methanol for 48 hours to obtain crude 6-[3-(l-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (I). On recrystallizing the crude product (I) in a mixture of tetrahydrofuran (THF) and ethyl acetate, pure compound (I) is obtained (Scheme I).

The pure compound of formula I exhibit the following XRPD: (Table 1)

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<thead>
<tr>
<th>Pos. [°2θ]</th>
<th>Rel. Int. [%]</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>6.72</td>
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<tr>
<td>8.75</td>
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</tr>
<tr>
<td>46.81</td>
<td>8.02</td>
</tr>
</tbody>
</table>

A disadvantage of this process is the purification of compound (IV) and (V) using column chromatography, which is expensive, time consuming and impractical at industrial scale.
Another major disadvantage of the process is the time taken by hydrolysis using soda in methanol for 48 hours, which is unproductive, uneconomical and time consuming at industrial scale.

Also use of Zinc chloride does not provide the desired product; the reaction does not go to completion and hence the reaction is not feasible.

*Organic process research & development, 2006, 10, 285-288* describes the process for preparation of 2-(l-adamantyl)-4-bromophenol (III) and 6-[3-(l-adamantyl)-4-methoxyphenyl]-2-naphthoic acid (I) or Adapalene. It describes a process comprising of reacting 1-adamantanol with 4-bromophenol (II) in the presence of concentrated sulfuric acid and acetic acid in dichloromethane stirred for two days to give 2-(l-adamantyl)-4-bromophenol (III).

The disadvantage of the above process is the time taken for condensation of 1-adamantanol with 4-bromophenol for two days, which is unproductive, uneconomical and time consuming at industrial scale.
US5015758 discloses a process specifically intended for the adamantylation of aromatic compounds. US '758 discloses the process for preparation of 2-(1-adamantyl)-4-bromophenol (III) and methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl)naphthoic acid (V) wherein 1-acetoxyadamantane is reacted with 4-bromophenol and methyl 6-(4-methoxyphenyl)-2-naphthoate in the presence of sulphuric acid for 24-48
hours (Scheme II). The patent does not however describe the further process of conversion to Adapalene.

**Scheme II**

Objects of the invention:

An object of the present invention is to provide a process for the preparation of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (Adapalene) having formula I, in high yield and high purity.

A further object of the invention is to provide a simple, economical and industrially feasible process for the preparation of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid of the formula (I) which avoids use of column chromatography.

Summary of the invention:
The present invention provides a process for preparation of highly pure 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (Adapalene) (I) (Scheme III) in high yield comprising:

a) reacting 1-adamantanol with 4-bromophenol (II) in the presence of sulphonic acid with or without organic solvent to give 2-(1-adamantyl)-4-bromophenol (III);

b) alkylation of the compound (III) with dimethylsulphate in presence of base in an organic solvent to obtain 2-(1-adamantyl)-4-bromoanisole (IV);

c) treating the compound (IV) with magnesium to form a Grignard reagent;

d) replacing Mg by Zn using purified zinc chloride and reacting with methyl-6-bromo-2-naphthoate in the presence of [1,2-bis(diphenylphosphino)ethane] dichloronickel (II) or NiCl$_2$-DPPE in THF to provide crude methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (V);

e) hydrolysing the compound (V) with a solution of alkali in a high boiling organic solvent to obtain metal salt of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (VI);

f) acidifying the metal salt of adapalene (VI) with organic or inorganic acid to provide compound (I);

g) optionally converting adapalene to adapalene metal salt and isolating pure adapalene metal salt;

h) optionally recrystallizing adapalene from a mixture of organic solvents to obtain pure compound (I) (scheme III).

The invention further discloses novel metal salts of adapalene and the process for preparation thereof. The invention further describes method of treating acne vulgaris in a subject by administering an effective amount of said metal salts along with pharmaceutical carrier.
Scheme III

(II) → HO-Br

1. 1-Armanthanol
   Acetic acid, H₂SO₄
   OR
   CH₃SO₃H, MDC

(III) → HO-Br

Acetone, K₂CO₃

Dimethyl sulphate.

(IV)

1. Mg, THF
2. Methyl-6-bromo napthoate
3. ZnCl₂, NiCl₂, DPPE

(V)

CH₃O-Br

NaOH
1,4-Dioxane
THF

(VI) (M=Na, K, Mg, Li, Ca)

CH₃O-CH₃

THF

Toluene

Adapalene Pure
Detailed Description of the Invention:
While the invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

According to the invention there is provided a process for the preparation of Adapalene, chemically designated as 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid, having formula (I) comprising:

![Formula (I)](image)

a) reacting 1-adamantanol with 4-bromophenol (II) in presence of sulphonic acid with or without organic solvent at a temperature of 30-100°C to obtain 2-(1-adamantyl)-4-bromophenol (III);

![Formula (III)](image)

b) treating the compound of formula (III) with Dimethyl sulphate in presence of inorganic base in an organic solvent at a temperature of about 10-80°C to yield compound IV.
c) C-C coupling of compound of formula (IV) with methyl-6-bromo-2-naphthoate using magnesium, purified zinc chloride and NiCl₂-DPPE in THF at a temperature of 40-60°C to obtain methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (V);

d) purifying compound of formula (V) using an organic solvents;

e) hydrolysing compound (V) in an ethereal solvent and in presence of an alkali metal hydroxide at reflux temperature of the solvent;

f) Isolating the metal salt of adapalene (VI) from reaction mixture;
g) acidifying metal salt of adapalene with organic or inorganic acids to adapalene.

h) optionally converting adapalene to its metal salt by treating adapalene with alkali metal hydroxide solution in a mixture of solvents and isolating pure adapalene metal salt.

i) purifying Adapalene by recrystallization using THF and Toluene.

According to an embodiment of the present invention, the organic solvent is selected from halogenated solvent, alcohol, ketone, esters, ethers or carboxylic acids, preferably selected from dichloromethane, chloroform, trichloroethane, methanol, ethanol, acetone, ethyl methyl ketone, ethyl acetate, methyl acetate, isopropyl acetate, 1,4-dioxane, tetrahydofuran, 1,2-dimethoxymethane or acetic acid.

The sulphonic acid is selected from methane sulphonic acid, 4-toluenesulphonic acid and benzene sulphonic acid.

The inorganic base may be selected from sodium carbonate, potassium carbonate, sodium or potassium bicarbonates, sodium hydroxide, potassium hydroxide, or lithium hydroxide.

The ester solvent is selected from ethyl acetate, methyl acetate, isopropyl acetate or mixtures thereof.
The ethereal solvent is selected from 1,4-Dioxane, Tetrahydrofuran (THF), Diethyl ether, diisopropyl ether or mixtures thereof.

The alkali metal hydroxide may be selected from Sodium hydroxide, Potassium hydroxide, Magnesium hydroxide or Calcium hydroxide.

According to the present invention, inorganic acid is selected from mineral acids preferably hydrochloric acid, sulfuric acid or hydrobromic acid.

The organic acid is selected from carboxylic acids preferably formic acid, acetic acid, propionic acid or oxalic acid.

According to preferred embodiment of the present invention the condensation of 4-bromophenol with 1-adamantanol is carried out at a temperature of about 60-80°C for 3 hours in presence of methanesulphonic acid in dichloromethane. Compound of formula III is isolated by diluting the reaction mixture with water, distilling the organic solvent, filtering the white solid and drying. Thus, the process avoids basification and the tedious work up.

The methylation of compound III is achieved using dimethyl sulphate in acetone and in presence of a potassium carbonate.

The C-C coupling of 2-(1-adamantyl)-4-bromoanisole (IV) with methyl 6-bromo-2-naphthoate is carried out by reacting compound (IV) with magnesium turnings in tetrahydrofuran (THF) to form Grignard reagent at a temperature of about 30-70°C, adding purified Zinc chloride at reflux temperature, further adding methyl 6-bromo-2-naphthoate, followed by addition of NiCl₂-DPPE in THF and the reaction mixture is refluxed. The crude methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (V) is isolated by evaporating the solvent.

Commercial zinc chloride when used does not provide the desired product. The process does not go to completion. However it was surprisingly found that using purified Zinc chloride provided the desired product in good yield.

Purification of compound V is carried out by stirring the crude compound in ethyl acetate at a temperature of about 50-80°C and drying the product in conventional manner.
The ester (V) is hydrolysed to a metal salt of adapalene (VI) by refluxing in 1,4-dioxane in presence of aqueous sodium hydroxide solution, adding THF, refluxing and cooling to a temperature of about 25-35°C.

When soda in methanol is used as disclosed in prior art, on concentrating the solution, a sticky mass is obtained and concentrated HCl is necessary to isolate compound of formula (I). However the present invention isolated the metal salt by using 1,4-Dioxane. According to the present invention, the term metal salt of adapalene(VI) encompasses Sodium, Potassium, Calcium or Magnesium salts of adapalene.

Conversion of metal salt of adapalene(VI) to adapalene free base (I) is carried out by treating the salt in water with concentrated HCl till the pH attained about 3 to 4.

Optionally adapalene may be converted to its potassium salt by treating the solution of adapalene in refluxing 1,4-dioxane with aqueous KOH solution, refluxing and cooling.

According to the present invention the crude Adapalene is purified using a mixture of tetrahydofuran and toluene. Crude Adapalene is dissolved in THF at reflux temperature and toluene is added and distilled to yield pure adapalene having purity more than 99.8% and impurity less than 0.1%.

The pure Adapalene thus obtained exhibits XRPD as stated below (Fig 1) Table 2:

<table>
<thead>
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<th>Pos. [°2θ]</th>
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<td>3.88</td>
</tr>
<tr>
<td>22.55</td>
<td>100.00</td>
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</tbody>
</table>
In another embodiment, the commercial zinc chloride is purified, by refluxing the commercial zinc chloride in 1,4-dioxane followed by addition of zinc dust. This mixture is refluxed for 1 hr, filtered through hyflow and filtrate is stirred for 2 hrs at 10-15°C and filtered the solid obtained, followed by washing with 1,4-Dioxane under nitrogen dried under vaccum at 80°C, to obtain pure zinc chloride. The use of purified zinc chloride provides better yield.

In another preferred embodiment, the invention discloses metal salts of adapalene having the formula VI and the process for preparation thereof. The said salts are having a purity of more than 99%. According to this embodiment, the term metal salt of adapalene encompasses Sodium, Potassium, Calcium or Magnesium salts of adapalene.

In a further embodiment, the invention provides method of treating acne vulgaris in a subject by administering the metal salts of adapalene (VI) as provided in the invention.

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

EXAMPLES:
Example 1
Preparation of 2-(1-adamantyl)-4-bromophenol (III):
A mixture of p-bromophenol (10.0 g, 57.8 mmol) and 1-adamantanol (8.78 g, 57.76 mmol) in methane sulphonic acid (15 ml) was stirred for 3 h at 70°C. The reaction mixture was cooled and diluted with water (50 ml). The white solid obtained was filtered, washed with water and dried. [Yield: 17 g, 97%]

Example 2
Preparation of 2-(1-adamantyl)-4-bromophenol (III):
A mixture of p-bromophenol (10.0 g, 57.8 mmol) and 1-adamantanol (8.78 g, 57.76 mmol) in dichloromethane (50 ml) and methane sulphonic acid (3.74 ml, 57.8 mmol) was stirred for 8 h at room temperature. The reaction mixture was diluted with water and dichloromethane was distilled. The white solid obtained was filtered, washed with water and dried. [Yield: 15.5 g, 87.3%]

Example 3
Preparation of 2-(1-adamantyl)-4-bromophenol (III):
A mixture of p-bromophenol (10.0 g, 57.8 mmol) and 1-adamantanol (8.78 g, 57.76 mmol) in acetic acid (20 ml) was stirred at room temperature. Then concentrated sulphuric acid (3.0 ml) was added in dropwise manner for 10 min. The reaction mixture was stirred for 4 h at 70°C. The reaction mixture was cooled and diluted with water (50 ml). The white solid obtained was filtered, washed with water and dried. [Yield: 16 g, 90%]
Example 4
Preparation of 2-(l-adamantyl)-4-bromoanisole (IV):
A mixture of 2-(l-adamantyl)-4-bromophenol (III) (50 g, 162 mmol) and potassium carbonate (33.7 g, 216 mmol) in acetone (250 ml) was stirred at room temperature. Then dimethylsulphate (20.16 ml, 240 mmol) was added dropwise for 15 min at room temperature. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with water, acidified with dilute HCl. The solid separated was filtered and washed with water. The solid was dissolved in dichloromethane (200 ml) and washed with water. The organic layer was dried over sodium sulphate, evaporated and the solid obtain was purified with ethyl acetate (200ml).[Yield: 30 g, 58 %]

Example 5
Preparation of 2-(l-adamantyl)-4-bromoanisole (IV):
To a solution of 2-(l-adamantyl)-4-Bromophenol (III) (50 g, 162 mmol) in acetone 200 ml, Potassium carbonate (33.7 g, 216 mmol) was added and stirred at RT. Dimethyl sulphate (20.53 ml, 244 mmol) was added dropwise for 15 min at RT. The reaction mixture was then refluxed for 4 hrs. The reaction mixture was further cooled to RT, water was added, and the solid separated, was filtered and washed with acetone. The solid was then treated with 3N HCl till pH is about 5 to 6, filtered and washed with water and acetone and then finally dried to obtain compound (IV).
[Yield: 38g, 73%] [44 g, 84%]
Example 6
Preparation of methyl ester of 6-[3-(l-adamantyl)-4-methoxy phenyl]-2 naphthoate (V):
A mixture of magnesium turnings (1.26 g, 51.85 mmol) in THF (10 ml) was stirred at room temperature and 2-(l-adamantyl)-4-bromoanisole (IV) (1.4 g, 4.36 mmol) and 1,2-dibromoethane (0.56 ml) were added under nitrogen atmosphere. The reaction mixture was heated at 40°C for initiation, and then 2-(l-adamantyl)-4-bromoanisole (12.6 g, 39.25 mmol) in tetrahydrofuran (40 ml) was added in a drop wise manner for 30 min at reflux temperature. Purified Zinc chloride (8.4 g, 61 mmol) in tetrahydrofuran (30 ml) was added in a drop wise manner for 15 min at reflux temperature. The reaction mixture was refluxed for 1 hr. Methyl 6-bromo-2-naphthoate (8.0 g, 30mmol) was added, stirred for 10 min, followed by the addition of NiCl₂ZDPPE catalyst (0.21 g). The reaction mixture was stirred at same temperature for 2 hrs and concentrated to obtain a residue, which was treated with dichloromethane (100 ml) and 1 N HCl (100 ml). The dichloromethane layer washed with 10 % EDTA disodium salt, water, dried over anhydrous sodium sulfate and distilled to obtained crude compound. The crude compound was stirred in ethyl acetate (140 ml) for 1 hr at 70°C, cool at 15 0°C for 1h and the solid obtained was filtered and dried. [Yield: 9.45 g, 50%]

Example 7
Preparation of Sodium salt of 6-[3-(l-adamantyl)-4-methoxy phenyl]-2- naphthoic acid (VI):-
To a solution of Methyl ester of 6-[3-(l-adamantyl)-4-methoxy phenyl]-2 naphthoic acid (25 g, 58 mmol) in 1,4-Dioxane (300ml) was stirred at refluxed temperature. Then sodium hydroxide (7.0 g, 175 mmol) in water (50 ml) was added slowly into the reaction mixture. The reaction mixture was heated at refluxed temperature for 5 h. Then tetrahydrofuran (300 ml) was added slowly and again the reaction mixture was heated at 90°C for 1 hr. The reaction mixture was cooled, solid separated, filtered and dried. [Yield: 24 g, 94 %]
Example 8
Preparation of Potassium salt of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (VI):-
To a solution of Methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2 naphthoic acid (25 g, 58 mmol) in 1,4-Dioxane (300ml) was stirred at refluxed temperature. Then potassium hydroxide (10 g, 175 mmol) in water (50 ml) was added slowly added into the reaction mixture. The reaction mixture was heated at 90°C for 5 h. Then tetrahydrofuran (300 ml) was added slowly and again mixture was heated at 90°C for 1 hr. The reaction mixture was cooled, solid separated, filtered and dried.
[Yield: 24 g, 94%]

Example 9
Preparation of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (I)
A mixture of sodium salt of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2 naphthoic acid (20 g, 58 mmol) in water (200 ml) and concentrated HCl (5 ml) was added slowly till pH becomes 3 to 4. The solid was separated, filtered, washed with water and dried.
[Yield: 15 g, 80%].

Example 10
Purification of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2 naphthoic acid (I)
To a solution of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2 naphthoic acid (25g, 60.6 mmol) in THF (550 ml) was stirred at 65°C. Then toluene (225 ml) was added in dropwise manner for 15 min. The reaction mixture was heated at 65°C for 1 h. The organic solvent was partially distilled from reaction mixture. Then the reaction mixture was cooled at 15-20 °C. The solid obtain was filtered and dried.
[Yield: 15 g, 60%, Purity 99.6%].

Example 11
Preparation of 6-[3-(1-adamantyl)-4methoxy phenyl]-2 naphthoic acid (Adapalene) (I):
The compound (V) (9.45 g, 22mmol) was dissolved in 1,4-Dioxane (95 ml) at reflux temperature and KOH (6.3 g, 11mmol in 30 ml water) was added in a drop wise manner for 15 min. The reaction mixture was refluxed for 2-4 hrs and then cooled when the
potassium salt of adapalene is precipitated, filtered and washed with methanol (25 ml). This salt of adapalene was acidified with 2 N HCl, solid separated, filtered and dried to obtain crude adapalene. The crude was recrystallized from THF-ethyl acetate. [Yield: 5.0 g, 81%; Purity: HPLC > 99%]

Example 12
Purification of Zinc Chloride:
Commercial zinc chloride (1 Kg, 735 mmol containing zinc oxychloride 2-3%) was slowly added in 1,4-Dioxane. The mixture was refluxed and zinc dust (80 g, 122 mmol) was slowly added. The reaction mixture was refluxed for 1 hr. The reaction mixture was filtered through Hyflow and filtrate was stirred for 2 hrs at 10-15°C, solid obtained, filtered washed with 1,4-Dioxane under nitrogen dried under vaccum at 80°C.
Pure zinc chloride yield = 0.55 kg Purity: 99.5%

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.
We Claim,

1. A process for the preparation of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (Adapalene) of formula (I) in purity greater than 99.8% comprising:

   a) reacting 1-adamantanol with 4-bromophenol (II) in the presence of sulphonic acid with or without the use of organic solvent at a temperature of 30-100 °C and isolating 2-(1-adamantyl)-4-bromophenol (III);

   b) treating the compound of formula (III) with Dimethyl sulphate in presence of an inorganic base in organic solvent at a temperature of 10-80 °C to yield compound IV.
c) C-C coupling of the compound of formula (IV) with methyl-6-bromo-2-naphthoate using magnesium, purified zinc chloride and NiCl$_2$-DPPE in THF at a temperature of 40-60 °C to obtain methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (V);

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\text{Formula (IV)}
\]

\[
\text{CH}_3\text{O}-\text{C-C coupling of the compound of formula (IV) with methyl-6-bromo-2-naphthoate using magnesium, purified zinc chloride and NiCl}_2\text{-DPPE in THF at a temperature of 40-60 °C to obtain methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid (V);}
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d) hydrolyzing the compound (V) in ethereal solvent and in presence of an alkali metal hydroxide at reflux temperature of the solvent;

e) isolating the metal salt of adapalene (VI) from reaction mixture;

\[
\text{Formula (V)}
\]

\[
\text{CH}_3\text{O-}
\]

\[
\text{OCH}_3
\]

\[
\text{M} = \text{Na, K, Mg, Li, Ca}
\]

\[
\text{Formula (VI)}
\]

f) acidifying the metal salt of adapalene with organic or inorganic acids to obtain adapalene(I).
g) optionally converting adapalene to its metal salt by treating adapalene with alkali metal hydroxide solution in an ethereal solvent and isolating pure adapalene metal salt(VI).

h) purifying the adapalene by recrystallization using THF and Toluene.

2) The process as claimed in claim 1, wherein the sulphonlic acid is selected from the group of methane sulphonlic acid, 4-toluenesulphonlic acid, benzene sulphonlic acid, benzyl sulphonlic acid preferably methane sulphonlic acid.

3) The process as claimed in claim 1, wherein the organic solvent is selected from halogenated solvents, alcohols, ketones, esters, ethers or carboxylic acids.

4) The process as claimed in claim 3, wherein the halogenated solvent is selected from the group of dichloromethane, chloroform, trichloroethane, preferably dichlorometnane.

5) The process as claimed in claim 3, wherein the alcohol is selected from methanol and ethanol.

6) The process as claimed in claim 3, wherein the ketone solvent is selected from acetone, ethyl methyl ketone or diethyl ketone.

7) The process as claimed in claim 3, wherein the ester solvent is selected from ethyl acetate, methyl acetate or isopropyl acetate.

8) The process as claimed in claim 3, wherein the ether solvent is selected from 1,4-dioxane, tetrahydofuran or 1,2-dimethoxyethane.

9) The process as claimed in claim 3, wherein the carboxylic acid solvent is preferably acetic acid.

10) The process as claimed in claim 1, wherein the inorganic base is selected from sodium carbonate, potassium carbonate, sodium or potassium bicarbonates, sodium hydroxide, potassium hydroxide, or lithium hydroxide preferably potassium carbonate.

11) The process as claimed in claim 1, wherein the alkali metal hydroxide is selected from Sodium hydroxide, Potassium hydroxide, Lithium hydroxide, Magnesium hydroxide, Calcium hydroxide, preferably sodium hydroxide.

12) The process as claimed in claim 1, wherein the metal salts of adapalene encompasses Sodium, Potassium, Lithium, Calcium or Magnesium salts of adapalene preferably sodium salt.
13) The process as claimed in claim 1, wherein the inorganic acid is selected from mineral acids such as hydrochloric acid, sulfuric acid or hydrobromic acid, preferably hydrochloric acid.

14) The process as claimed in claim 1, wherein the organic acid is selected from carboxylic acids such as formic acid, acetic acid, propionic acid or oxalic acid.

15) The process as claimed in claim 1, wherein the recrystallization of adapalene comprises the steps of:
   a) dissolving adapalene in tetrahydrofuran at an elevated temperature;
   b) adding toluene and continuing heating;
   c) partly concentrating the reaction mixture and cooling to and
   d) isolating adapalene.

15) Metal salts of adapalene having formula VI as claimed in claim 1.

16) Metal salts of adapalene having formula VI as claimed in claim 1 having purity more than 99%.

17) Method of treating Acne Vulgaris in a subject, which method comprises administering a composition containing an effective amount of metal salts of adapalene as claimed in claim 15.