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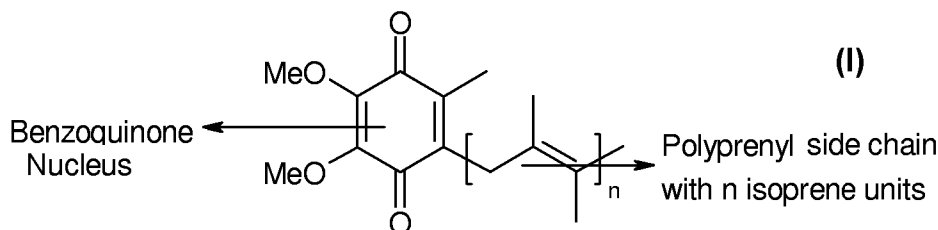
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(54) Title: NOVEL INTERMEDIATES USEFUL FOR THE PREPARATION OF COENZYMES, PROCESS FOR THE PREPARATION OF NOVEL INTERMEDIATES AND AN IMPROVED PROCESS FOR THE PREPARATION OF COENZYMES



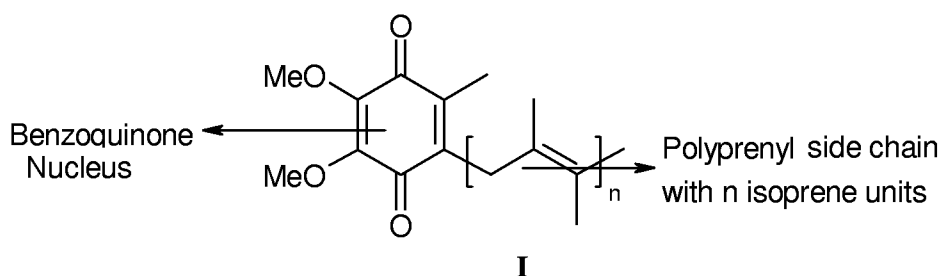
(57) Abstract: The present invention relates to novel intermediates for the preparation of coenzymes, processes for the preparation of the intermediates and an improved process for the preparation of Coenzymes. The present invention particularly relates to an improved process for the preparation of Coenzyme Q, more particularly for Coenzyme Q₉ and Coenzyme Q₁₀. Still more particularly this invention relates to regio and stereo controlled process for the preparation of Coenzyme Q₉ and Coenzyme Q₁₀ of the formula (I), where n = 9 (Coenzyme CoQ₉), and where n = 10. (Coenzyme CoQ₁₀).

**NOVEL INTERMEDIATES USEFUL FOR THE PREPARATION OF
COENZYMES, PROCESS FOR THE PREPARATION OF NOVEL
INTERMEDIATES AND AN IMPROVED PROCESS FOR THE
PREPARATION OF COENZYMES**

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Field of Invention

The present invention relates to an improved process for the preparation of Coenzymes. The invention also relates to novel intermediates for the preparation of coenzymes, and process for the preparation of the intermediates. The present
10 invention particularly relates to an improved process for the preparation of Coenzyme Q, and more particularly Coenzyme Q₉ and Coenzyme Q₁₀. Still more particularly this invention relates to regio and stereo controlled process for the preparation of Coenzyme Q₉ and Coenzyme Q₁₀ of formula **I**.



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where n = 9 (Coenzyme CoQ₉), and where n = 10 (Coenzyme CoQ₁₀).

In the description given below the Coenzyme CoQ₉ is referred to as formula **I₉** and
20 Coenzyme CoQ₁₀ as formula **I₁₀**

Background and Prior art

These coenzymes belong to the class of ubiquinones that occur in all aerobic organisms from bacteria to plants and animals - the name ubiquinone suggests its
25 ubiquitous occurrence. They are involved in mitochondrial processes such as respiration and act as antioxidants.

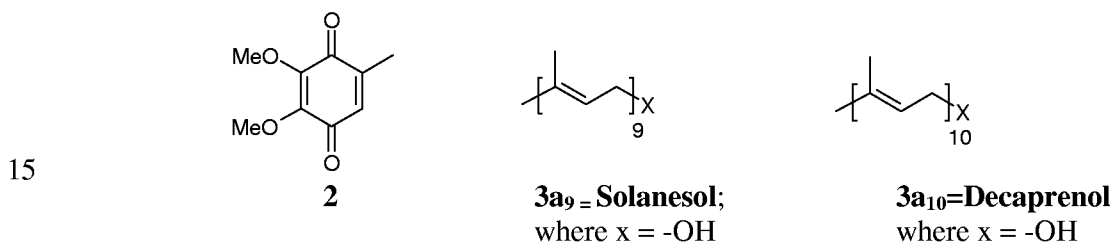
The present invention also provides novel Grignard reagent that is useful for the preparation of above mentioned coenzymes and a process for its preparation.

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The coenzyme Q₁₀ in human has 10 isoprenoid units, and termed as CoQ₁₀. CoQ₁₀ is present in virtually every cell in the human body and is known as the “miracle nutrient”, and plays a vital role in maintaining human health and vigor, maintenance

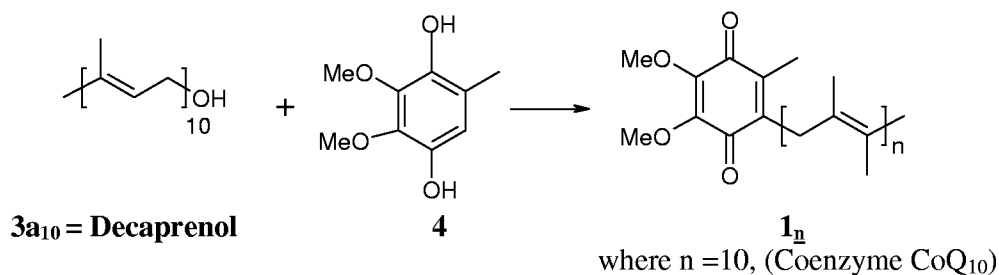
of heart muscle strength, enhancement of the immune system, quenching of free radical in the battle against ageing to name a few (“The miracle nutrient coenzyme” Elsevier/ North – Holland Biomedical Press, New York, 1986; “Coenzyme Q: Biochemistry, Bioenergetics, and clinical Applications of Ubiquinone” Wiley, New York, 1985; “Coenzyme Q, Molecular Mechanism in Health and Disease” CRC press).

As depicted above Coenzyme Q₉ and Coenzyme Q₁₀ of the formula **I** have 2,3-dimethoxy-1,4-benzoquinone nucleus as a head group with a side chain of n isoprene units. The poly prenyl side chain in Coenzyme Q has all - trans configuration. One of the methods of synthesis of these Coenzymes is coupling of the “benzoquinone nucleus” with the “polyprenyl side chain” of solanesol of the formula **3a₉**, where x = -OH and decaprenol of the formula **3a₁₀**, where x = -OH. with retention of its original double bond geometry.



Various methods for introducing polyprenyl side chain into quinone nucleus, to prepare Coenzymes are found in literature. These methods involve functionalisation of the two coupling partners, the “quinone nucleus” and the “polyprenyl chain”.

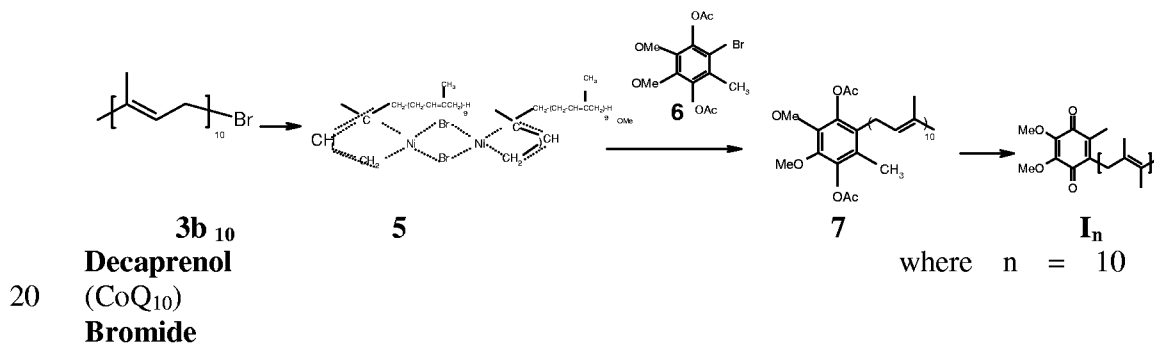
Method 1: Polyprenyl alcohol and hydroquinone using zinc chloride as catalyst; reported in *Huanxue Yu Nianhe*(2002), 6 267(2002) which is shown in the Scheme 1 given below



Decaprenol of the formula **3a₁₀** (1.8 g) dissolved in ether is treated with 2,3-dimethoxy-5-methyl benzohydroquinone of the formula **4**, zinc chloride (anhydrous, 0.28 g), glacial acetic acid (0.02 ml) and stirred for 2 hours under nitrogen atmosphere. Ferric chloride solution is added to the above reaction mixture, stirred for
 5 ten minutes. The ethereal layer is then separated, dried and evaporated to give 2.2 g of crude CoQ₁₀ which is purified by column chromatography to give 0.56 g of the pure CoQ₁₀ of the formula **I₁₀** with an overall yield of 20% (mp 45 - 46 °C, Lit. mp 48 - 50 °C).

10 Low melting point obtained indicates the presence of cis-isomer and thereby making the process not stereoselective. The yield is also too low for commercialization of the process.

Method 2: By making π -Allyl Nickel bromide complex and protected quinone
 15 nucleus; reported in *Bull. Chem. Soc. Jpn* 47,3098(1974), *US* 3,896,153(1975) which is shown in scheme 2



Scheme 2

Nickel tetracarbonyl 4.5g (15% solution in benzene) is treated with decaprenyl
 25 bromide of the formula **3b₁₀** 10.0 g (15% solution in Benzene) at 50°C for 4 - 4.5 hrs. The solution is cooled to below 10°C and the benzene and excess nickel carbonyl is removed under reduced pressure. Decaprenyl nickel bromide of the formula **5** thus formed is then reacted with 6-bromo-2,3-dimethoxy-5-methyl-1,4-hydroquinone diacetate of the formula **6** in 30 ml of hexamethyl phosphoramide at 75°C for 7 hours
 30 yielding 2.2 g of condensed product of the formula **7** with 40% yield. The condensed product of the formula **7** (0.8 g) is added to a suspension of lithium aluminium hydride in 20 ml of dry ether and refluxed for 24 hours. The excess lithium aluminium hydride is decomposed and the product hydroquinone is extracted in ether.

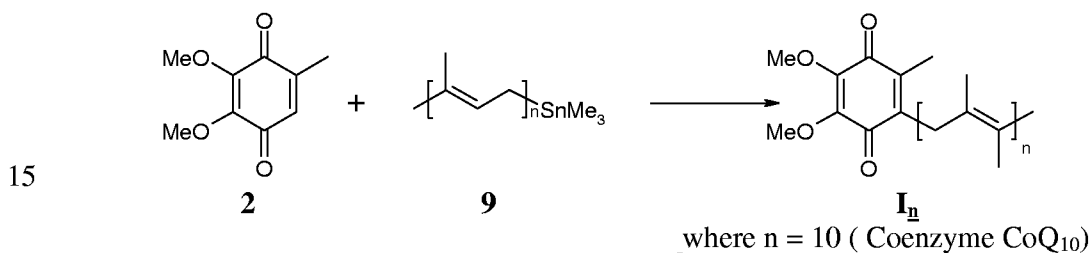
The hydroquinone is oxidized with aqueous ferric chloride at room temperature for 3 hour to give the final product CoQ₁₀ which is further purified by column chromatography to yield the COQ₁₀ of the formula **I**₁₀ with mp 20 - 22 °C (Lit. mp 48 – 50 °C) with 69% yield.

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Author attributes the low melting point to the presence of cis isomer. The process is therefore not stereoselective. Further, the nickel tetracarbonyl used in the process is highly flammable, has the risk of explosion and highly toxic chemical, and cannot be used industrially. The overall yield of the process is only 27.6%. The process is

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Method 3 : From allyl - stannyl and unprotected quinone using borontrifluoride etherate; reported in *J. Org. Chem.* **45**, 4077 (1980), *Chemistry Letters* 885(1979) as shown in scheme 3.



Scheme 3

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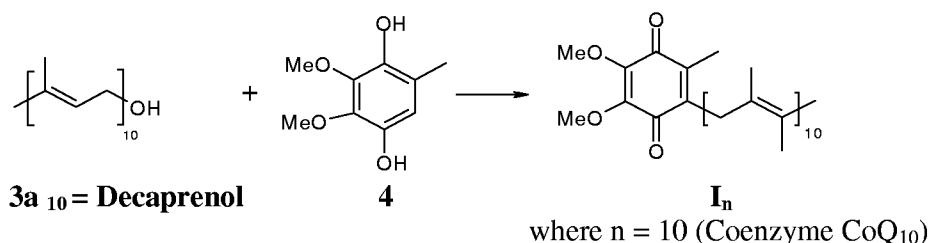
Trimethylstannyl lithium in tetrahydrofuran is slowly added to decaprenyl bromide of the formula **3b**₁₀ at –78° C to – 60° C and the reaction mixture is allowed to warm to room temperature. The reaction mixture is quenched in brine and the organic layer evaporated to form trimethyl decaprenyl stannanes of the formula **9**. The stannyl

25 reagent (0.42 mmol) in a mixture of methylene dichloride (25 ml) and isooctane (1ml) is added to 2,3-dimethoxy-5-methylbenzoquinone (0.111 g, 0.61 mmol) and borontrifluoride etherate (2.6 mmol) in a mixture of methylene chloride (25 ml) and isooctane (1 ml) at – 50 °C and the reaction mixture is maintained at the same temperature for 2 hours. The resulting product is isolated and chromatographed on

30 silica gel to afford the starting quinone (70 mg) and CoQ₁₀ of the formula **I**₁₀ (189 mg) (86% trans).

The method forms 14% cis isomer and therefore far from stereo selective. The reaction does not go to completion and results in poor yield and not suitable for industry.

Method 4: From polyprenyl alcohol and quinone nucleus with silica - alumina as catalyst reported in *US 3,998,858(1976)* as shown in scheme 4



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Scheme 4

2,3-dimethoxy-5-methyl-1,4-benzohydroquinone of the formula **4**, (11 g) is reacted with boric acid (3.6 g) in toluene and water removed azeotropically. The residue is treated with silica-alumina (17 g) and a solution of decaprenol (14 g in 10 ml hexane, 94% purity) and stirred for 1 hour at 30 °C. The adsorbent is removed and the filtrate is washed with water, and concentrated, and extracted in ether. The ethereal extract is treated with silver oxide (6 g) and allowed to stand overnight. The reaction mixture is filtered and concentrated to form 16.3 g of crude CoQ₁₀, which is purified by column chromatography, followed by crystallization with acetone to give 8.5 g of CoQ₁₀ of the formula **I₁₀** (Lit. mp 49 °C).

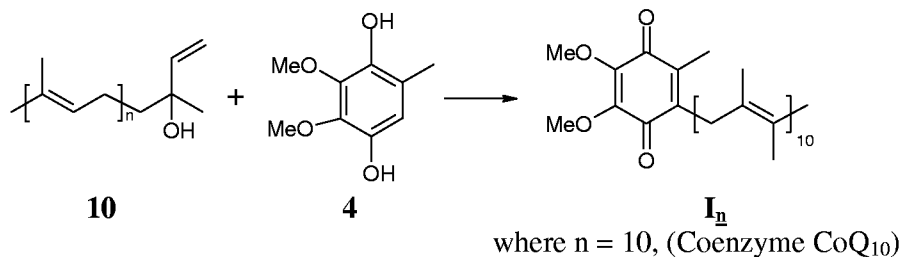
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The melting point value indicates that process may form a stereoselective process using a simple technique of silica-alumina. However the ratio of silica and alumina to be used and also the respective grades would be critical for the reaction and is not mentioned. The inventors of the present invention tried various grades of silica – alumina and found that the reaction does not proceed.

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Method 5 : Polyprenyl alcohol and quinone nucleus *reported in Chemistry Letters 1597(1988)*, as shown in scheme 5

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Scheme 5

Isodecaprenol compound of the formula **10** (38.8 g, 72% purity) is reacted with 2,3 dimethoxy 5 methyl 1,4 benzohydroquinone compound of formula **4** (75.1 g) in the presence of borontrifluoride etherate in hexane and nitromethane at 43 °C. The reaction mixture is quenched in aqueous medium and the nitromethane and the hexane layer is separated. The hexane layer is oxidized with ferric chloride hexahydrate in isopropanol at room temperature. The crude CoQ₁₀ of the formula **I₁₀** is obtained in 51% yield with 8% Z isomer

15 The process forms 8% cis isomer and therefore not stereo selective. Boron trifluoride etherate is a corrosive chemical and not useful for commercialisation.

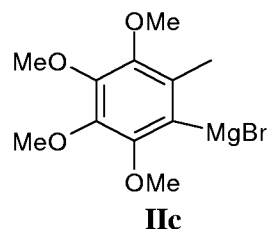
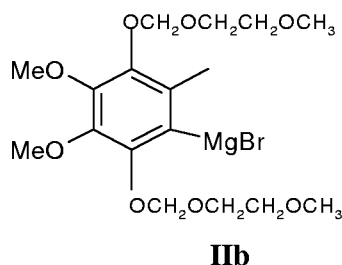
Thus literature does not provide a stereoselective process for coupling of the benzoquinone with the polyprenyl side chain for the preparation of Coenzymes Q, namely CoQ₉ and CoQ₁₀. As shown in the coupling reactions mentioned above, 8% - 20 15% of cis isomer is formed.

It was observed that purification of such a mixture to get the desired all- trans isomer of CoQ₉ and CoQ₁₀ with less than 1% cis, results in 25-30% purification loss. This 25 would decrease the overall yield of production of these coenzymes mainly CoQ₉ and CoQ₁₀, thereby making the commercial process of making the Coenzyme Q₉ or Coenzyme Q₁₀ cost ineffective.

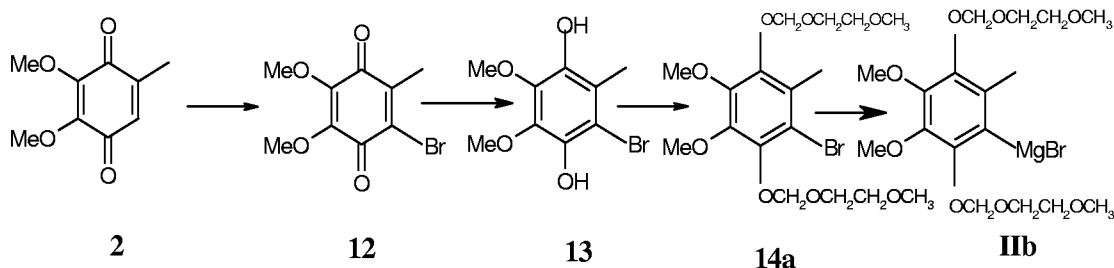
Scope of clinical application of coenzymes specially CoQ₁₀ is becoming wider with 30 its increasing broadband use Therefore if a cost effective process is developed for the preparation of COQ₁₀ it will greatly help in making this coenzyme easily and at affordable prices.

Preparation of coenzymes CoQ_n where n represents the number of isoprenyl units, namely CoQ₉ or CoQ₁₀, by the coupling of the two key units viz the “benzoquinone nucleus” and the “polyprenyl side chain” should be a straightforward route. However as discussed in prior art, the attempts with such coupling, results in isomerisation of the polyprenyl chain and the geometrical configuration of the chain is not retained. Therefore, the focus should be on the “stereoselective” coupling reaction of the “benzoquinone nucleus” with the corresponding “polyprenyl side chain” to obtain CoQ_n where n represents the number of isoprenyl units. Such a condensation would enhance the cost effectiveness of the preparation of these coenzymes mainly Q₉ or Q₁₀.

The inventors have observed that a simple, straightforward, stereo selective process for the preparation of coenzyme CoQ₉ or CoQ₁₀ of the formulae **I₉** and **I₁₀** respectively can be developed, by Grignard coupling of the benzoquinone nucleus and the polyprenyl side chain. For such a coupling the “benzoquinone nucleus” has to be converted to the required Grignard reagent with suitable protecting groups. The protecting groups used in literature for making Grignard reagent of the “benzoquinone nucleus” are methoxyethoxymethyl and methyl of the formula **IIb** & **IIc**.



Literature method for making Grignard reagent compound of formula **IIb** from the compound of the formula **2** as reported in *J. Org. Chem.* 37 1889 (1972), *US* 4,270,003 (1981), *Synthesis* (1981) 469-471 (1982) comprises the methods as depicted in Scheme 6a and Scheme 6b.



Scheme 6a

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In the method described in the **Scheme 6a**, 2,3 dimethoxy -5-methyl 1,4 benzoquinone compound of the formula **2** is brominated to form compound of formula **12**. The bromination is effected using bromine in carbon tetrachloride and the product of the formula **12** is isolated by washing with ethanol and recrystallizing from petroleum ether, in 74% yield. The compound of the formula **12** is reduced employing aqueous sodium hydrosulphite solution in presence of methanol to get the compound of the formula **13**. The compound of the formula **13** is finally converted to compound of the formula **14a** by alkylation. The alkylation is carried out in presence of 50% sodium hydride in mineral oil (106 g) which is added in small portions to a stirred solution of 6-bromo-2,3-dimethoxy -5-methyl hydroquinone compound of formula **12** (262.9 g) in 4 litres of N,N dimethyl formamide at -20°C . Chloromethyl 2-methoxyethyl ether (273 g) is added dropwise over a 2 hours period and the mixture is allowed to warm to room temperature. Excess sodium hydride is destroyed with ethanol and the reaction mixture quenched in water. The ethereal layer containing the extracted product is concentrated and the residue purified by column to obtain the compound of formula **14a** in 91% yield. The compound of the formula **14a** is converted to the compound of the formula **IIb**, by reacting with magnesium in presence of tetrahydrofuran.

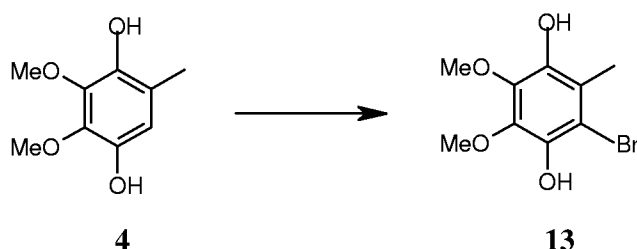
Yield of brominating 3, 4 dimethoxy -5-methyl 1,4 benzoquinone, is only 74% which is low for such a simple reaction. The solvent used is toxic and not suitable for scale up. The inventors observed that reduction using aqueous sodium hydrosulphite solution gives yield of the compound of the formula **13** in not more than 40% and therefore not suitable for the industrial production. Further we observed that bromination followed by reduction of the benzoquinone to obtain compound of formula **13**, results in low purity of not more than 76%.

The alkylation process uses N,N dimethyl formamide as a solvent and in large excess, 15 times the weight of the bromo compound of the formula **13**. N, N dimethyl formamide is a costly solvent and such large excess is not suitable for industry.

5 Sodium hydride used as a base is hazardous and is always present in suspension in oil. The oil also gets extracted in the solvent in which the product compound of formula **14a** gets extracted. Thus the process is not compatible to the industry.

Another method of making 2,3 dimethoxy 5-bromo 6-methyl 1,4 hydroquinone is shown in Scheme 6 b

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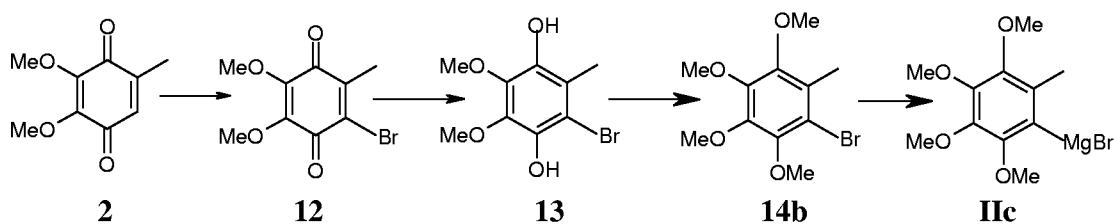
Scheme 6b

In this method, 2,3-dimethoxy-1,4-hydroquinone of formula **4** is brominated in chloroform at 5 °C, and the product isolated from chloroform is in quantitative yield.

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We observed that bromination at 5 °C leads to incompleteness of reaction and isolation of product from chloroform results in yield less than 75%

20 The Grignard reagent of formula **IIc** is prepared as given in scheme 6c



Scheme 6c

In the process depicted in **Scheme 6c**, 2,3 dimethoxy 5 methyl benzoquinone of the formula **2** is brominated in room temperature in carbon tetrachloride in 75% yield, reduced with Zinc and acetic acid with 80% yield and methylated with dimethyl sulphate to get the compound of the formula **14b** in 62% yield. The compound of the

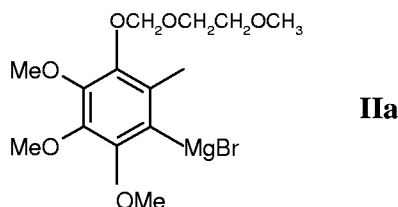
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formula **14b** is converted to compound of the formula **IIc**. Yield at each stage of the process is not substantial for mass scale production.

The inventors observed that the above process of reduction with zinc and acetic acid,
 5 and methylation after bromination results in purity of compound of formula **14b**,
which is not more than 76%.

The inventors have found that to avoid the drawbacks of the hitherto known processes exemplified above, the coenzyme CoQ₉ or CoQ₁₀ may be prepared by a simple,
 10 straightforward, stereoselective process of coupling of the benzoquinone nucleus with
 polyprenyl side chain using Grignard reaction of the formula **IIb** and **IIc** made by an
 improved process as more particularly defined hereinafter.

While developing the improved process for the preparation of the Grignard reagents
 15 of the formulae **IIb** and **IIc**, the inventors developed a new Grignard reagent of the
 formula **IIa**.



Objective of the invention

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The main objective of the present invention is to provide an improved process for the stereoselective preparation of the Coenzymes of formula **I**, namely, CoQ₉ and CoQ₁₀ of the formulae **I₉** and **I₁₀** respectively as given above.

25

Another objective of the present invention is to provide an improved process for the preparation of the coenzymes, namely, CoQ₉ and CoQ₁₀ of the formulae **I₉** and **I₁₀** respectively, which is simple, cost effective and commercially viable.

Still another objective of the present invention is to provide an improved process for the preparation of the coenzymes Q, namely, CoQ₉ and CoQ₁₀ of the formulae **I**₉ and **I**₁₀ respectively with high yield (50 - 56 %) and purity 98%

- 5 Yet another objective of the present invention is to provide an improved process for the preparation of coenzymes **I**₉ and **I**₁₀ by stereospecific coupling of the polyprenyl side chain of formula **3a** or **3b** with the Grignard reagents of the formula **II**.

- 10 Still another objective of the present invention is to provide intermediates of the formula **III**, useful for preparing the coenzymes of formula **I**.

Still another objective of the present invention is to provide a process for the preparation of intermediates of formula **III** useful for preparing the coenzyme of formula **I**.

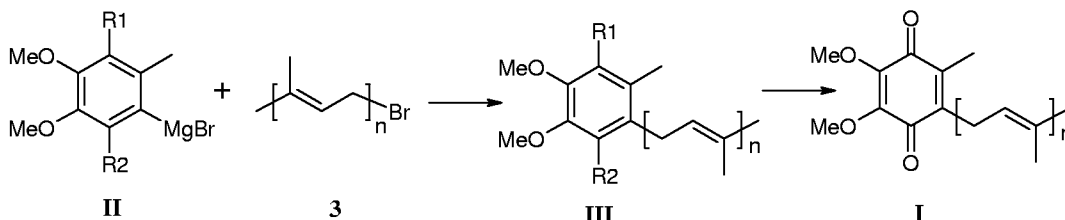
- 15 Still another objective of the present invention is to provide a novel Grignard reagent of the formula **IIa** useful for preparing the coenzyme of formula **I**.

- 20 Yet another objective of the present invention is to provide a process for the preparation of novel Grignard reagent of the formula **IIa** useful for the preparation of the coenzymes of formula **I**.

- 25 Yet another objective of the present invention is to provide an improved process for the preparation of Grignard reagents of the formula **IIb** and **IIc** useful for the preparation of the coenzymes of formula **I**.

Summary of Invention

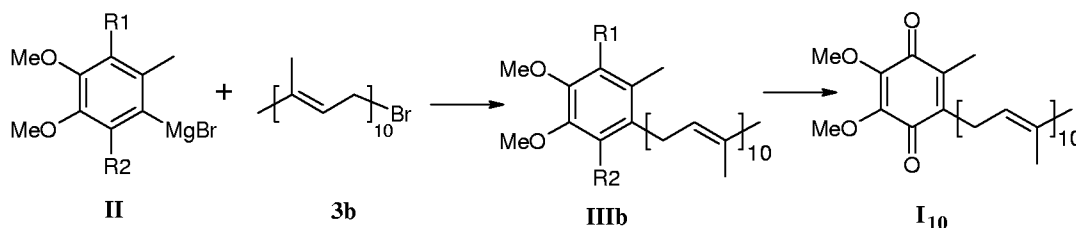
Thus the present invention relates to an improved process for the preparation of coenzyme of formula **I**, as shown in scheme A below:



Scheme - A

where n is an integer selected from 9 or 10; R_1 and R_2 are same or different and are
 5 selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, with the proviso that when R_2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R_1 is not $-\text{OMe}$.

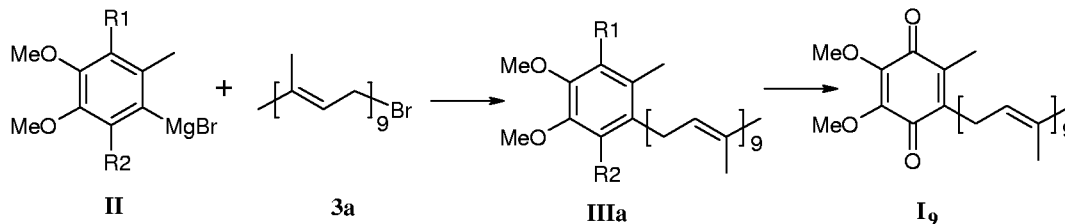
According to a further aspect of the invention, there is provided preparation of
 coenzyme CoQ_{10} ($n = 10$) of the formula I_{10} as shown in scheme 7 below:



Scheme 7

where R_1 and R_2 are same or different and are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$
 or $-\text{OMe}$, with the proviso that when R_2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R_1 is not $-\text{OMe}$

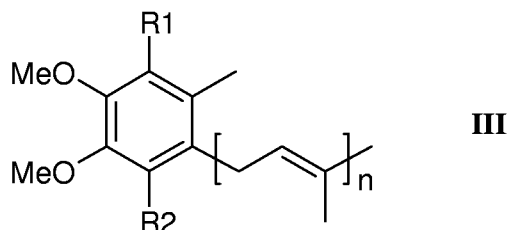
According to still another aspect of the invention, there is provided preparation of
 coenzyme CoQ_9 ($n = 9$) of the formula I_9 as shown in scheme 8 below:



Scheme 8

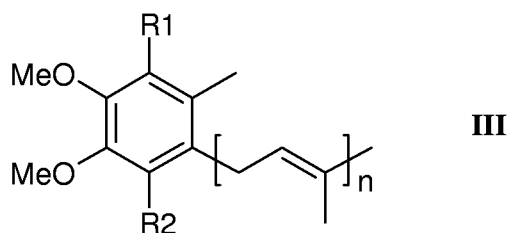
where R_1 and R_2 are same or different and are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$
 or $-\text{OMe}$, with the proviso that when R_2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R_1 is not $-\text{OMe}$

According to yet another aspect of the invention there is provided a novel intermediate of formula **III** useful for the preparation of coenzymes of formula **I**



where R1 and R2 are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, and n is
 5 selected from 9 or 10, with the proviso that when R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R1 is not $-\text{OMe}$.

According to yet further aspect of the invention there is provided an improved process for the preparation of compound of formula **III**, useful for the preparation of
 10 coenzymes of formula **I**

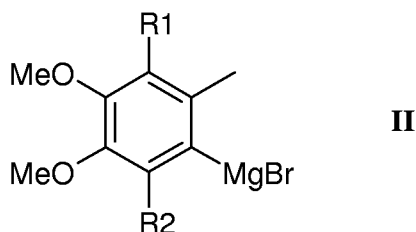


where R1 and R2 are same or different and are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, and n is selected from 9 or 10, with the proviso that
 when R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R1 is not $-\text{OMe}$;

15

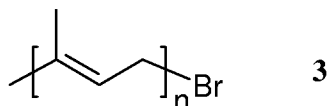
which comprises,

i) reacting Grignard reagents of formula **II**,



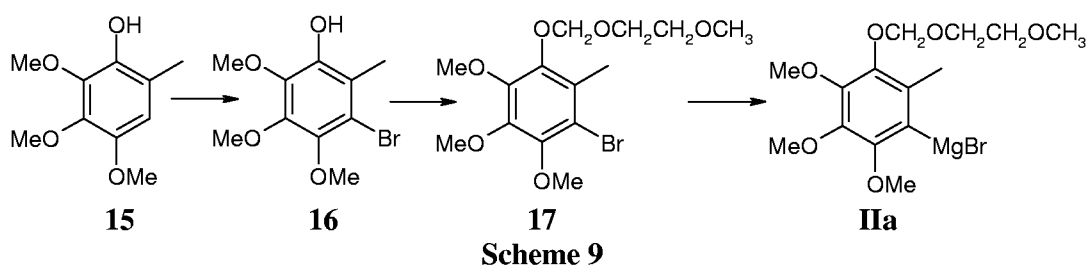
20

with compounds of formula **3**,

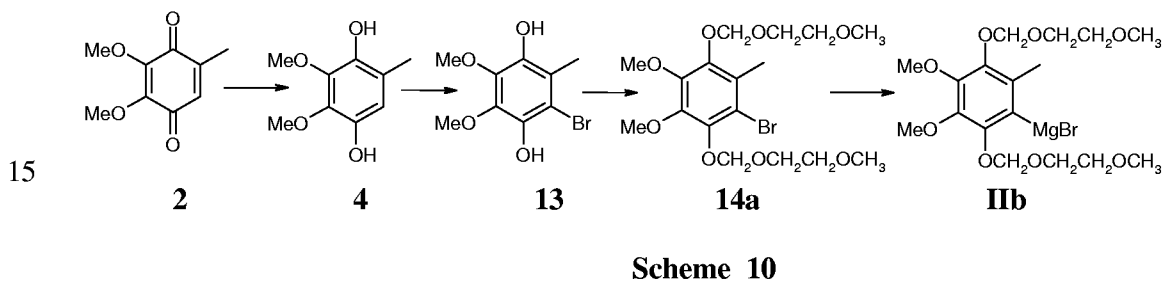


where n is selected from 9 or 10 in presence of cuprous halide in a solvent under inert atmosphere at a temperature in the range of -5°C to 25°C .

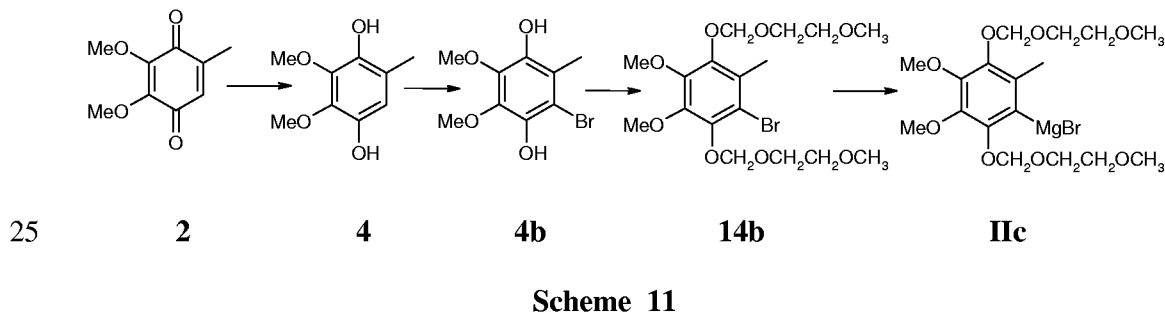
- 5 According to another aspect of the invention there is provided a novel Grignard reagent of formula **IIa**, useful for the preparation of coenzymes of formula **I**, as shown in scheme 9 below:



According to a still further aspect of the invention there is provided an improved process for the preparation of Grignard reagent of the formula **IIb**, useful for the preparation of coenzymes of formula **I** as shown in scheme 10 below:



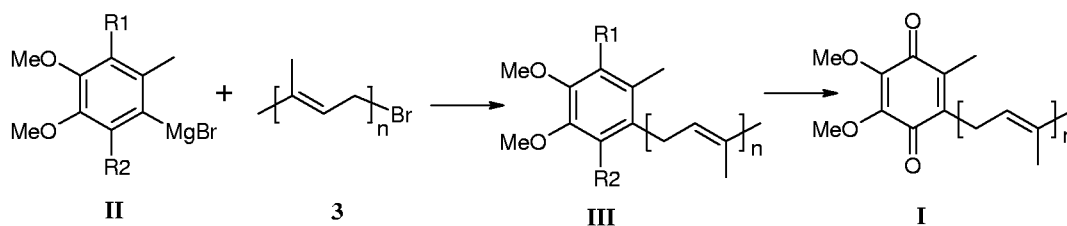
- 20 According to a yet further aspect of the invention there is provided a process for the preparation of Grignard reagent of the formula **IIc**, useful for the preparation of coenzymes of formula **I** as shown in scheme 11 below:



Detailed Description

The present invention provides an improved process for the preparation of the coenzymes of formula I, as shown in the Scheme - A

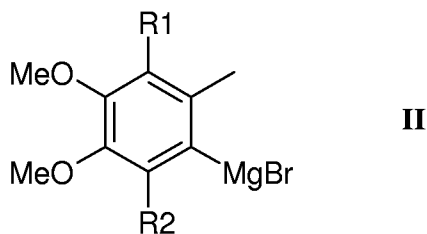
5

**Scheme - A**

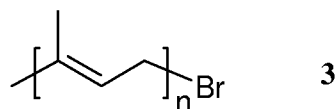
10 where n is an integer selected from 9 or 10; R1 and R2 are same or different and are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, with the proviso that when R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R1 is not $-\text{OMe}$.

which comprises,

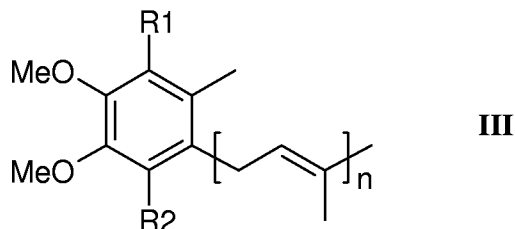
15 i) reacting Grignard reagent of formula II,



where R1 and R2 are same or different and are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, with the proviso that when R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R1 is not $-\text{OMe}$;
 20 with compound of formula 3,



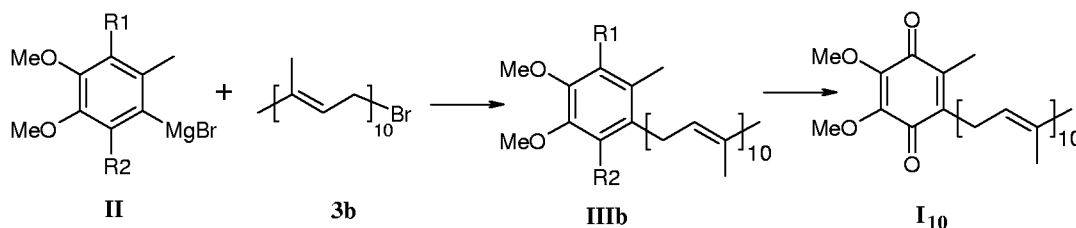
where n is an integer selected from 9 or 10, in presence of cuprous halide in a
 25 solvent under inert atmosphere at a temperature in the range of -5°C to 25°C , to obtain an intermediate of formula III;



- ii) deprotecting the compound of formula **III** (wherein atleast one of R1 and R2 is –OCH₂OCH₂CH₂OCH₃) to obtain the corresponding hydroquinone;
- iii) oxidizing the compound of step (i) or (ii) to obtain the coenzyme of formula **I**;
- 5 iv) isolating the compound of formula **I**; and
- v) purifying and crystallizing the coenzyme of formula **I** by conventional methods.

According to an embodiment of the present invention, there is provided a process for the preparation coenzyme, CoQ₁₀ of the formula I₁₀ as shown in scheme 7:

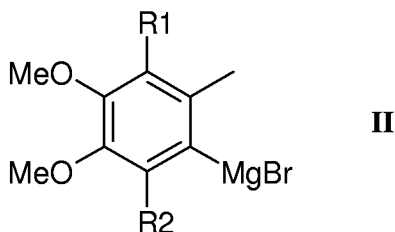
10



where R1 and R2 are same or different and are selected from –OCH₂OCH₂CH₂OCH₃ or –OMe, with the proviso that when R2 is –OCH₂OCH₂CH₂OCH₃, then R1 is not –OMe

15 which comprises,

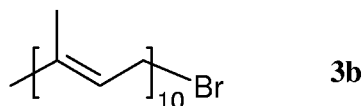
- i) reacting Grignard reagent of formula **II**,



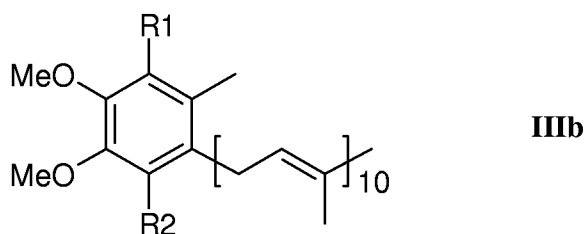
20

where R1 and R2 are same or different and are selected from –OCH₂OCH₂CH₂OCH₃ or –OMe, with the proviso that when R2 is –OCH₂OCH₂CH₂OCH₃, then R1 is not –OMe;

with compound of formula **3b**,



in presence of cuprous halide in a solvent under inert atmosphere at a temperature in the range of -5°C to 25°C , to obtain an intermediate of formula **IIIb**;



5

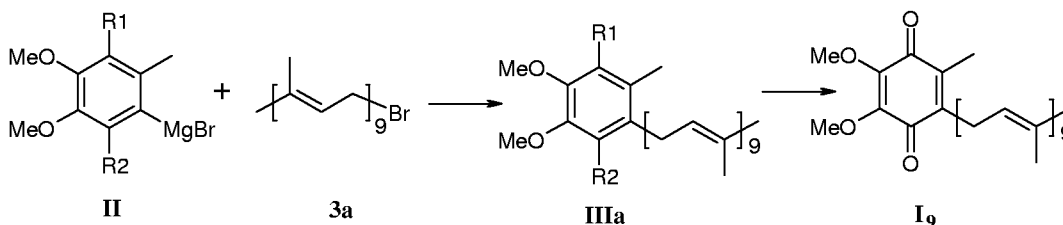
ii) deprotecting the compound of formula **IIIb** (where atleast one of R1 and R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$) to obtain a hydroquinone;

iii) oxidizing the compound of step (i) or (ii) to obtain the coenzyme CoQ_{10} of formula **I₁₀**;

10 iv) isolating the compound of formula **I₁₀**; and

v) purifying the coenzyme CoQ_{10} of formula **I₁₀** and further crystallizing by conventional method to obtain yellow to orange crystals of the coenzyme CoQ_{10} of formula **I₁₀**.

15 According to another embodiment of the present invention, there is provided a process for the preparation coenzyme, CoQ_9 of the formula **I₉** as shown in scheme 8:

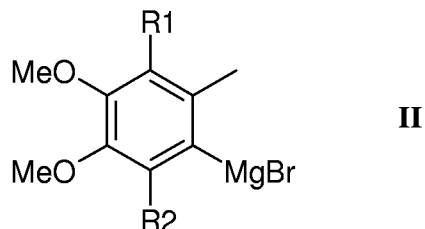


where R1 and R2 are same or different and are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, with the proviso that when R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R1 is not $-\text{OMe}$

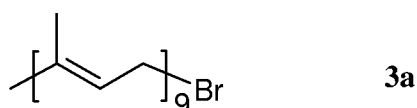
which comprises,

i) reacting Grignard reagents of formula **II**,

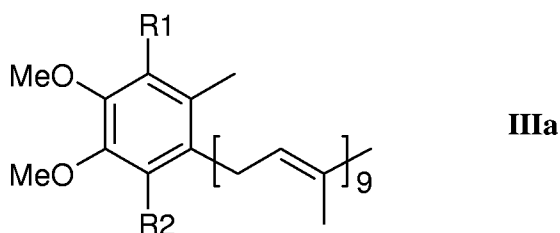
25



where R1 and R2 are same or different and are selected from –
 OCH₂OCH₂CH₂OCH₃ or –OMe, with the proviso that when R2 is –
 5 OCH₂OCH₂CH₂OCH₃, then R1 is not –OMe;
 with compound of formula **3a**,



in presence of cuprous halide in a solvent under inert atmosphere at a temperature in
 the range of –5 °C to 25 °C, to obtain an intermediate of formula **IIIa**;

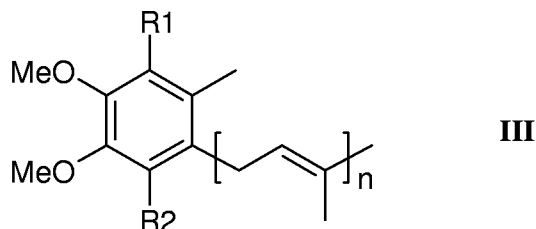


10

- ii) deprotecting the compound of formula **IIIa** (wherein atleast one of R1 and R2 is –
 OCH₂OCH₂CH₂OCH₃) to obtain a hydroquinone;
- iii) oxidizing the compound of step (i) or (ii) to obtain the coenzyme CoQ₉ of formula
 15 **I₉**;
- iv) isolating the compound of formula **I₉**; and
- v) purifying the coenzyme CoQ₉ of formula **I₉** and further crystallizing by
 conventional method to obtain yellow to orange crystals of the coenzyme CoQ₉ of
 formula **I₉**.

20

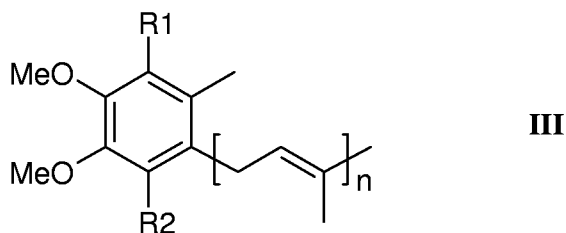
According to still another embodiment of the present invention there is provided
 novel intermediate of formula **III** useful in the preparation of coenzymes of formula **I**



where R1 and R2 are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, and n is selected from 9 or 10, with the proviso that when R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R1 is not $-\text{OMe}$.

5

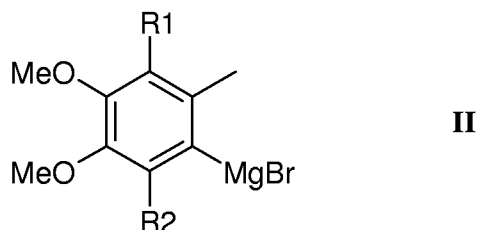
According to yet another embodiment of the present invention, there is provided an improved process for the preparation of intermediates of formula **III** useful in the preparation of coenzymes of formula **I**.



10 where R1 and R2 are same or different and are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, and n is selected from 9 or 10, with the proviso that when R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R1 is not $-\text{OMe}$,

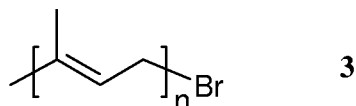
which comprises,

15 i) reacting Grignard reagents of formula **II**,



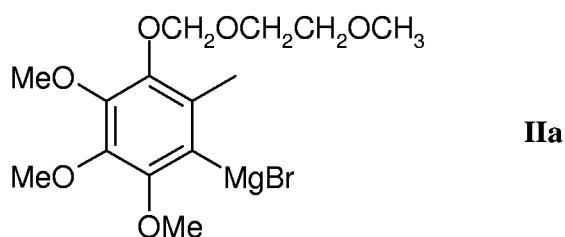
20 where R1 and R2 are same or different and are selected from $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ or $-\text{OMe}$, with the proviso that when R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, then R1 is not $-\text{OMe}$;

with compound of formula **3**,

**3**

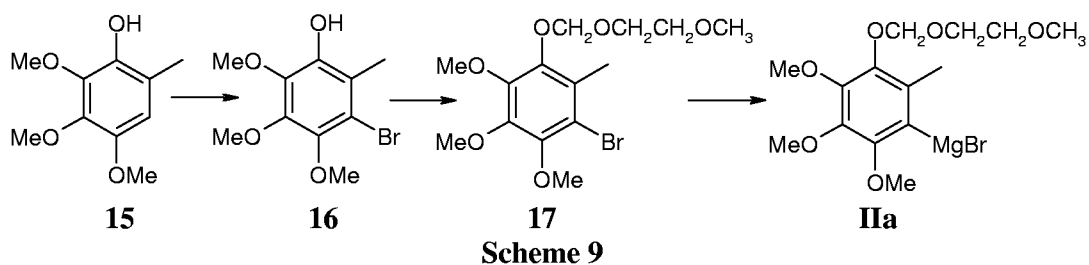
where n is selected from 9 or 10, in presence of cuprous halide in a solvent under inert atmosphere at a temperature in the range of -5°C to 25°C .

- 5 According to still another embodiment of the present invention, there is provided novel Grignard reagent of formula **IIa** useful in the preparation of coenzymes of formula **I**

**IIa**

10

According to yet another embodiment of the present invention, there is provided a process for the preparation of the novel Grignard reagent of the formula **IIa**, as shown in the **Scheme 9**

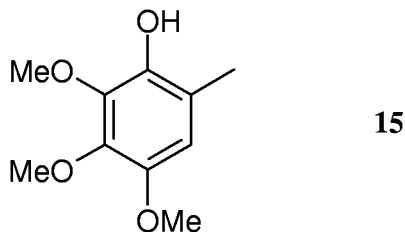


15

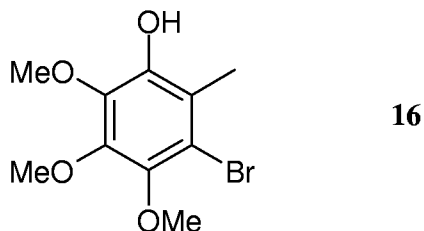
15**16****17****Scheme 9****IIa**

which comprises,

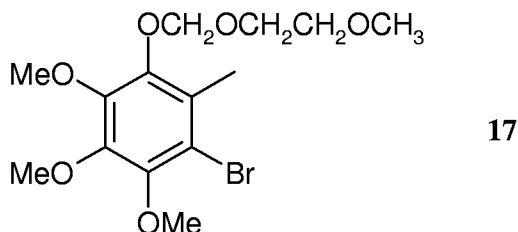
- 20 (i) brominating the compound of the formula **15**

**15**

by known method, to obtain compound of formula **16**;



(ii) Alkylating the compound of the formula **16** obtained in step (i) with methoxyethoxymethyl chloride in the presence of a base, an alkali metal alkoxide or metal hydride, to obtain 2,3-dimethoxy-5-methyl-6-bromohydroquinone-1,4-dimethoxyethoxy methyl ether compound of formula **17**;

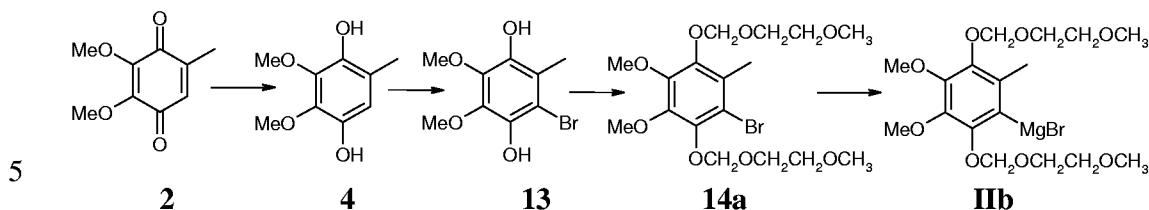


(iii) Reacting the compound of the formula **17** obtained in step (ii) with magnesium in presence of iodine and dibromoethane, using ether as a solvent at a temperature in the range of 0 - 65 °C, to obtain the novel Grignard reagent of the formula **IIa**;

(iv) cooling the resulting reaction mixture to room temperature, filtering to get the novel Grignard reagent in solution.

The compound of formula **15** can be prepared by methods known in the literature. Synthesis of this novel Grignard reagent is most economical as it can be made from the compound of formula **15**, unlike the known Grignard reagents of formula **IIb** and **IIc** that are made from 2,3 dimethoxy-5-methyl 1,4 benzoquinone (CoQ₀), thereby having more number of steps in their preparation. Presence of only one protecting group of methoxyethoxymethyl in compound of formula **IIa**, reduces the requirement of the reagent methoxyethoxyethyl ether as compared to that required in dimethoxyethoxy-methyl ether in **IIb**, thus making it more cost effective. At the same time cleaving of the protecting group of the formula **IIa** employed in the present invention results in the formation of the moiety “2,3,4 trimethoxy 6-methyl phenol” that can be easily oxidised with an inexpensive chemical like ferric chloride unlike ceric ammonium nitrate an expensive oxidising agent required for methyl protection when compound of formula **IIc** is used.

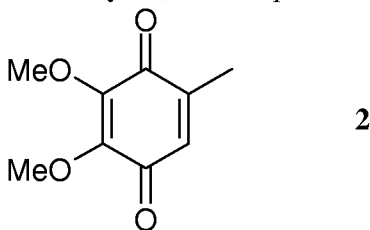
According to still another embodiment of the present invention, there is provided an improved process for the preparation of the Grignard reagent of the formula **IIb** as shown in **Scheme 10**



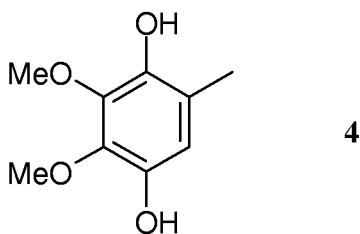
Scheme 10

10 which comprises,

i. Reducing 2,3-dimethoxy -5 -methyl- 1,4 benzoquinone (CoQ₀) of the formula **2**,



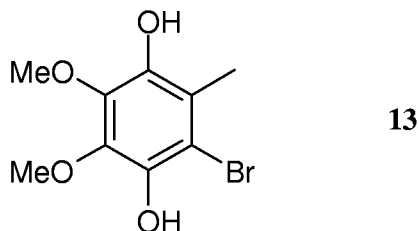
15 with aqueous sodium hydrosulphite, in alkaline medium, in the presence of a water immiscible organic solvent, separating the organic phase, and evaporating the organic phase to obtain a concentrated residue, to which was added a hydrocarbon solvent to precipitate out compound of formula **4**



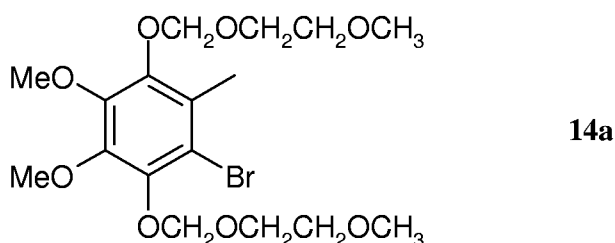
20 ii. Brominating the resulting compound of the formula **4** with bromine in chlorinated hydrocarbon solvent at a temperature in the range of 0 - 25 °C,

iii. Quenching the resultant reaction mixture in step (ii) in aqueous medium to obtain aqueous and organic phase, separating the organic phase and evaporating the organic phase to obtain a concentrated residue, to which was added a hydrocarbon solvent to precipitate out 2,3-dimethoxy -5-methyl-6-bromo 1,4 hydroquinone of the formula

13



iv. Alkylating the 2,3 dimethoxy -5 -methyl -6-bromo 1,4 hydroquinone of the formula **13** obtained in step (iii) with methoxyethoxymethyl chloride in the presence of a base selected from an alkali metal alkoxide or metal hydride, to obtain 2,3-dimethoxy-5-methyl-6-bromo hydroquinone 1,4 dimethoxyethoxymethyl ether compound of formula **14a**,



v. Reacting the compound of the formula **14a** obtained in step (iv) with magnesium in presence of iodine and dibromoethane, using ether as a solvent at a temperature in the range of 0 - 65 °C, to obtain the Grignard reagent of the formula **IIb**; and

vi. Isolating the Grignard reagent of formula **IIb**

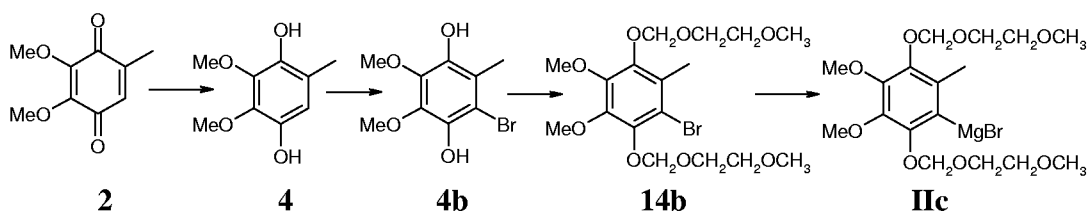
Unlike the prior art where reduction in step (i) to obtain compound of formula **4** is effected in homogeneous phase using water miscible solvent, in the process of the present invention, the reduction is carried out using aqueous hydrosulphite, in alkaline medium in the presence of a water immiscible organic solvent, separating the organic phase, and evaporating to obtain a concentrated residue, to which was added a hydrocarbon solvent to precipitate out compound of formula **4** which thereby increases the yield of the reduced product of the formula **4** substantially (to about 96 % as compared to about 50% as per the prior art process).

According to the improved process of the present invention, the brominated product of formula **13** was isolated by precipitating out the solid in presence of a hydrocarbon solvent. The process described above increases the yield of the brominated compound (to about 96 % as compared to 75 % as per the prior art process).

In the modified process of the present invention the alkylation is carried out in the presence of a base sodium hydride in an inexpensive hydrocarbon solvent, or nonhazardous sodium alkoxide, in an inexpensive solvent like alcohol. Thereby making the process economical as compared to prior art where sodium hydride is used in presence of N,N dimethyl formamide which is an expensive solvent.

The bromo compound of formula **14a** is reacted with magnesium in the presence of ether selected from diethylether, diisopropyl ether, tetrahydrofuran, at a temperature in the range of 0 – 65 °C, to provide Grignard reagent of the formula **IIb** having 92 % purity.

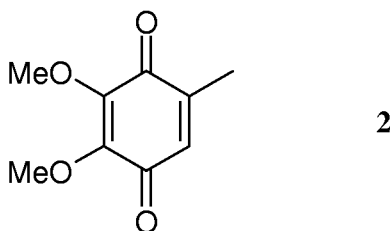
According to yet another embodiment of the present invention, there is provided an improved process for the preparation of the Grignard reagent of the formula **IIc** as shown in **Scheme 11**



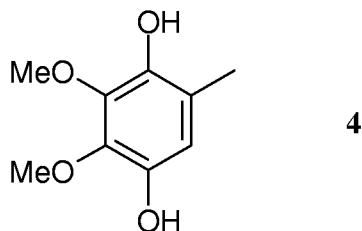
Scheme 11

which comprises,

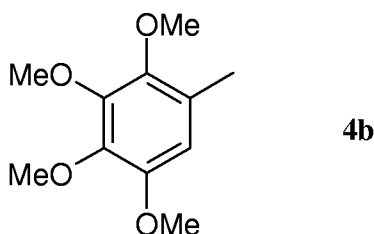
- Reducing 2,3 dimethoxy -5 -methyl 1,4 benzoquinone (CoQ₀) of the formula **2**



with aqueous sodium hydrosulphite, in alkaline medium, in the presence of a water immiscible organic solvent, separating the organic phase and evaporating the organic phase to obtain a concentrated residue, to which was added a hydrocarbon solvent to precipitate compound of formula **4**;



ii. Alkylating the compound of the formula **4**, with alkyl sulphate by known method to obtain 2,3,4,5 tetramethoxy toluene compound of formula **4b**

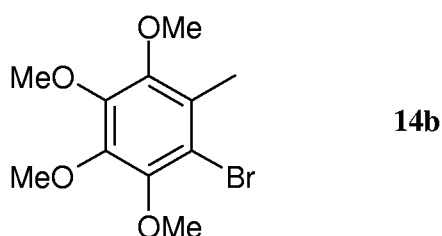


5

iii. Brominating the resulting compound of the formula **4b** with bromine in chlorinated hydrocarbon solvent at a temperature in the range of 0 - 25 °C,

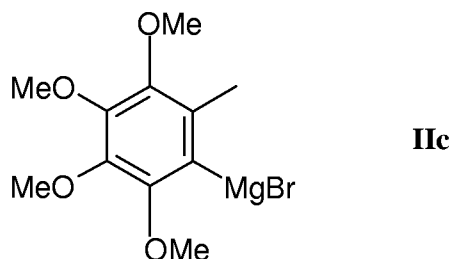
iv Quenching the resultant reaction mixture in step (iii) in aqueous medium to obtain aqueous and organic phase and separating the organic phase, evaporating the organic phase to obtain a concentrated residue to which was added a hydrocarbon solvent to precipitate out 2,3,4,5 tetramethoxy 6-bromo toluene of the formula **14b**

10



v. Reacting the compound of the formula **14b** obtained in step (iv) with magnesium in presence of iodine and dibromoethane, using ether as a solvent at a temperature in the range of 0 - 65 °C, to obtain the Grignard reagent of the formula **IIc**, and

15



20 vi. isolating the Grignard reagent of formula **IIc**.

Unlike the prior art where reduction in step (i) to obtain compound of formula **4** is effected in homogeneous phase using water miscible solvent, in the process of the present invention, the reduction is carried out using aqueous hydrosulphite, in alkaline medium in the presence of a water immiscible organic solvent, separating the organic phase, and evaporating to obtain a concentrated residue, to which was added a hydrocarbon solvent to precipitate out compound of formula **4** which thereby increases the yield of the reduced product of the formula **4** substantially (to about 96 % as compared to about 50% as per the prior art process).

According to the improved process of the present invention, the brominated product compound of formula **14b** was isolated by precipitating out the solid in presence of a hydrocarbon solvent. The process described above increases the yield of the brominated compound (to about 96 % as compared to 75 % as per the prior art process).

In the above mentioned process the purity of 2,3,4,5 tetramethoxy 6 methyl bromo benzene of the formula **14b** is enhanced when formed by first alkylation of 2,3 dimethoxy 5 methyl 1,4 hydroquinone of the formula **2**, to form 2,3,4,5 tetramethoxy toluene compound of formula **4b** which can be purified easily by vacuum distillation.

In a preferred embodiment of the present invention the various steps in the processes described above may be carried out as follows,

Reduction of 2,3-dimethoxy 5 methyl 1,4 benzoquinone, CoQ₀ of the formula **2**, may be carried out by with sodium hydrosulphite in neutral or alkaline medium, preferably alkaline medium more preferably sodium hydroxide by dissolving CoQ₀ in a water immiscible organic solvent like ether, aromatic hydrocarbons, chlorinated hydrocarbons more preferably chlorinated hydrocarbons like methylene chloride, ethylene chloride, preferably methylene chloride. Thus the reaction may be carried out in biphasic, at a temperature in the range of 0^o C to 30^o C preferably, 10 to 20^o C. Isolation of 2,3-dimethoxy-5-methyl-1,4-hydroquinone compound of the formula **4**, thus formed, may be carried out by acidifying the above reaction mixture, separating the organic phase and concentrating the organic phase. The concentrated organic

phase may be added to aliphatic or aromatic hydrocarbon solvent like hexane, heptane, petroleum ether, preferably heptane to precipitate and filter the compound of formula **4**.

5 Bromination of 2,3-dimethoxy-5-methyl-1,4-hydroquinone compound of formula **4**, may be carried out with bromine in the presence of a chlorinated hydrocarbon solvent selected from methylene chloride and ethylenechloride at a tempertaure in the range of 0 to 30⁰ C preferably 10 to 20⁰ C. Isolation of the brominated compound 2,3-dimethoxy-5-methyl-6-bromo-1,4-hydroquinone of formula **13** thus formed, may be
10 carried out by quenching the resulting reaction mixture in aqueous medium, separating and concentrating the organic phase. The concentrated liquid may be added to a hydrocarbon solvent preferably heptane to precipitate and filter 2,3-dimethoxy-5-methyl-6-bromo-1,4-hydroquinone of formula **13**.

15 Alkylation of 2,3-dimethoxy-5-methyl-6-bromo1,4-hydroquinone of the formula **13** may be carried out with methoxy ethoxy methyl chloride in the presence of metal hydride in aromatic hydrocarbons preferably toluene or an alkali metal alkoxide base selected from sodium methoxide, sodium ethoxide preferably sodium methoxide, in alcohol, at a temperature in the range of – 30⁰C to 30⁰C preferably 15 to 25⁰C. 2,3-
20 dimethoxy-5-methyl-6-bromo-1,4-hydroquinone methoxyethoxymethyl ether compound of formula **14a** thus formed, may be isolated by quenching the reaction mixture in alcohol or aqueous medium, extracting in solvent selected from ether, aromatic hydrocarbon, chlorinated hydrocarbons preferably methylene dichloride, and concentrating the solvent.

25

2,3-Dimethoxy-5-methyl-6-bromo-1,4-hydroquinone bismethoxyethoxymathyl ether of formula **14a**, 2,3,4,5-tetramethoxy-6-methyl-bromo benzene compound of formula **14b** or 2,3,4 trimethoxy-5-bromo-6-methyl phenol compound of formula **16** may be converted to the Grignard reagent, as given in literature.

30

2,3-Dimethoxy-5-methyl-1,4-hydroquinone compound of the formula **4** may be alkylated using dimethylsulphate in acetone or in aqueous medium or in presence of alkali, preferably in aqueous medium in presence of alkali. The resulting product 2,3,4,5 tetramethoxy toluene of formula **4b**, may be isolated by extracting in solvent

and distilling out the solvent. The resultant residue may be distilled under vacuum at 0.2 – 10 mm Hg, preferably 0.5 - 0.8 mm Hg, to obtain the distilled 2,3,4,5 tetramethoxy toluene of formula **4b** in more than 96% HPLC purity.

2,3,4,5-tetramethoxy toluene of formula **4b** may be brominated as given above to
5 form 2,3,4,5-tetramethoxy-6-methyl bromo benzene of formula **14b**.

The coupling of the Grignard reagents of the formula **II** with solanesyl bromide or decaprenyl bromide of the formula **3a** or **3b** may be carried out in the presence of cuprous halide selected from cuprous chloride, cuprous bromide or cuprous iodide
10 preferably cuprous bromide. Grignard reagent may be used in equivalent amount or excess of the solanesyl bromide or decaprenyl bromide in molar ratio of 1:1 to 1:4 preferably 1: 1.1 to 1:2. The reaction may be carried out by adding the cuprous salt to the Grignard reagent and allowing to equilibrate for sufficient time. The copper salt is used in 1: 1 to 1:0.1 molar ratio of the Grignard reagent. The solanesyl bromide or
15 decaprenyl bromide of the formula **3a** or **3b** dissolved in a solvent, may be added to the Grignard reagent at temperature range of -25°C to 25°C preferably at room temperature. The solvent used may be the same as used for the Grignard reagent or different like aromatic hydrocarbon, aliphatic hydrocarbon like toluene, hexamethylphosphoric triamide. The solvent for dissolving the solanesyl bromide or
20 decaprenyl bromide may be preferably the same as used in Grignard reaction. The coupling of the Grignard reagent of the formula **II**, with solanesyl bromide or decaprenyl bromide of the formula **3a** or **3b** may also be carried out by adding cuprous salt to the solution of solanesyl bromide or decaprenyl bromide of the formula **3a** or **3b** and the Grignard reagent of the formula **II** may be added to the
25 above reaction mixture. The reaction may be monitored by HPLC and the rate of addition of the polyprenyl bromide solution may be adjusted with the rate of reaction. The reaction may be quenched in an aqueous medium in acidic or ammonium chloride solution preferably ammonium chloride solution, and the respective product of the formula **IIIa** or **IIIb** may be extracted in an water immiscible solvent, solvent
30 evaporated, and the crude compound may be purified by column chromatography to obtain more than 96 % pure compound.

Optional deprotection of **IIIa** (wherein at least one of R1 and R2 is $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$) or **IIIb** (wherein at least one of R1 and R2 is $-$

OCH₂OCH₂CH₂OCH₃) to obtain corresponding hydroquinone may be carried out by method given in literature, followed by oxidation to obtain the final product of compound of formula **I₉** or **I₁₀**.

- 5 The oxidation is carried out with ceric ammonium nitrate in acetonitrile as described in literature to obtain the final product of compound of formula **I₉** or **I₁₀**.

The details of the process are given in the Examples below which are provided for illustration only and therefore they should not be construed to limit the scope of the
10 invention

Example 1

Preparation of Grignard reagent of 2,3 Dimethoxy-5-bromo-6-methyl 1,4 dimethoxyethoxy methyl ether compound of formula IIb.

15

2,3-Dimethoxy 5-methyl-1,4-benzoquinone of formula **2**, (2.5 g) was dissolved in 7.5 ml of methylene dichloride and treated with sodium hydrosulphite (3.56 g) in an alkaline solution at 10 - 20 ° C. After 2 hours the reaction mixture was treated with
20 conc. HCl (3.4 ml) to acidic pH. The reaction mixture was extracted with methylene dichloride and washed with water. The organic solvent was concentrated and poured in hexane. The precipitated solid was filtered to obtain 2.25 g of 2,3-dimethoxy-5-methyl-1,4-hydroquinone compound of formula **4**. The solid was taken in methylene dichloride and treated with bromine (1.96 g) at 10 to 20° C. The reaction was
25 quenched in water after 2 hours and extracted in methylene dichloride. The methylene dichloride was evaporated. The concentrated mass was added to hexane to precipitate out the solid of 2,3-dimethoxy-5-bromo-6-methyl-1,4-hydroquinone (3.06 g). The bromo compound was dissolved in toluene and treated with 1.024 g sodium hydride (60% suspension) in toluene at 0 to -5 ° C. Methoxyethoxy methyl chloride (3.17 g)
30 was added at 5 to 10°C. The temperature was slowly raised to room temperature and the reaction was continued for 2 hrs. The reaction was quenched with methanol, followed by water and the toluene layer separated. The organic layer was distilled under vacuum to obtain 4.65 g of 2,3-dimethoxy-5-bromo-6-methyl-1,4-hydroquinone dimethoxyethoxy methyl ether compound of the formula **14a**. The

compound of formula **14a** (4.65g) was reacted with Magnesium (0.301g) in tetrahydrofuran, in presence of a pinch of iodine at ambient temperature to form the Grignard reagent of 2,3 dimethoxy-5-bromo-6-methyl 1,4 dimethoxyethoxy methyl ether compound of formula **IIb**

5

Example 2

Preparation of Grignard reagent of 2,3 Dimethoxy-5-bromo-6-methyl 1,4 dimethoxyethoxy methyl ether compound of formula **IIb.**

10 2,3 dimethoxy 5-methyl 1,4 benzoquinone compound of formula **2** (2.5 g) was dissolved in 7.5 ml of methylene dichloride and treated with sodium hydrosulphite (3.56 g) in alkaline solution at 10 – 20 °C. After 2 hours the reaction mixture was treated with conc. HCl 3.4 ml to acidic pH. The reaction mixture was extracted with methylene dichloride and washed with water. The organic solvent was concentrated
15 and poured in hexane (10 ml). The precipitated solid was filtered to obtain 2.25 g of 2,3 dimethoxy 5 methyl 1,4 hydroquinone compound of formula **4**. The solid was taken in methylene dichloride 15 ml and treated with bromine (1.96 g) at 10 – 20°C. The reaction was quenched in water after 2 hours and extracted in methylene dichloride. The methylene dichloride was evaporated. The concentrated mass was
20 added to hexane to precipitate out the solid of 2,3 dimethoxy-5 bromo-6-methyl 1,4 hydrquinone (3.06 g). The bromo compound was dissolved in methanol and treated with sodium methoxide (1.5 g) at 5 - 10°C. Methoxyethoxy methyl chloride (3.17 g) was added at 5°C - 10°C, the temperature raised to room temperature and maintained for 8 hrs. The reaction was quenched in water and extracted in diisopropyl ether. The
25 organic layer was distilled under vacuum to obtain 4.75g of 2,3 Dimethoxy-5-bromo-6-methyl 1,4 di methoxyethoxy methyl ether compound of the formula **14a**. The compound was reacted with magnesium (0.34g) in tetrahydrofuran, in presence of a pinch of iodine at ambient temperature to form the Grignard reagent of 2,3 dimethoxy-5-bromo-6-methyl 1,4 dimethoxyethoxy methyl ether of the formula **IIb**.

30

Example 3

Preparation of Grignard reagent of 2, 3, 4, 5 tetramethoxy-6-methyl-bromobenzene compound of formula **IIc**

2,3dimethoxy-5-methyl 1,4 benzoquinone compound of formula **2_a** 2.5 g was dissolved in 7.5 ml of methylene dichloride and treated with sodium hydrosulphite (3.56 g) in alkaline solution at 10 – 20 ° C. After 2 hours the reaction mixture was treated with conc. HCl (3.4 ml) to acidic pH. The reaction mixture was extracted with methylene dichloride and washed with water. The organic solvent was concentrated and poured in hexane. The precipitated solid was filtered to obtain 2.25 g. of 2,3 dimethoxy 5 methyl 1,4 hydroquinone compound of formula **4**. The solid was taken in alkaline solution and dimethyl sulphate (5.75 g) was added at 40 - 50 ° C. The reaction mixture was quenched after 4 hours in water and extracted in methylene dichloride. The solvent was evaporated and the crude obtained was distilled under vacuum at 80 ° C at 0.5 - 1.0 mm Hg to obtain 2.33 g of 2,3,4,5-tetramethoxy toluene. The compound was taken in methylene dichloride (15 ml) and treated with bromine (1.75 g) at 10 – 20 ° C. The reaction was quenched in water after 2 hours and extracted in methylene dichloride. The methylene dichloride was evaporated. The concentrated mass was added to hexane to precipitate out the solid of 2,3,4,5-tetramethoxy-6-methyl bromobenzene (3.03g) of formula **14b**. The compound of formula **14b** was reacted with magnesium (0.30g) in tetrahydrofuran, at ambient temperature, in presence of a pinch of iodine to form the Grignard reagent 2,3,4,5-tetramethoxy-6-methyl bromobenzene of formula **IIc**.

20

Example 4

Preparation of Grignard reagent of 2, 3, 4, 5 tetramethoxy-6-methyl-bromobenzene compound of formula IIc

25 2,3-dimethoxy 5-methyl-1,4-benzoquinone of formula **2_a** (2.5 g) was dissolved in 7.5 ml of methylene dichloride and treated with sodium hydrosulphite (3.56 g) in alkaline solution at 10 – 20 ° C. After 2 hours the reaction mixture was treated with conc. HCl (3.4 ml) to acidic pH. The reaction mixture was extracted with methylene dichloride and washed with water. The organic solvent was concentrated and poured in hexane. 30 The precipitated solid was filtered to obtain 2.25 g of 2,3-dimethoxy-5-methyl-1,4-hydroquinone of formula **4**. The solid was taken in acetone, potassium carbonate (6.3 g) and dimethyl sulphate (5.75) g were added at 40 - 50 ° C. The reaction mixture was quenched after 4 hours in water and extracted in methylene dichloride. The solvent was evaporated and the crude obtained was distilled under vacuum at 80 ° C at 0.5 -

1.0 mm Hg to obtain 2.33 g of 2,3,4,5-tetramethoxy toluene. The compound was taken in methylene dichloride (15 ml) and treated with bromine (1.75 g) at 10 – 20⁰ C. The reaction was quenched in water after 2 hours and extracted in methylene dichloride. The methylene dichloride was evaporated. The concentrated mass was added to hexane to precipitate out the solid of 2,3,4,5-tetramethoxy-6-methyl-bromobenzene (3.03g), compound of formula **14b**. The compound **14b** was reacted with magnesium (0.30g) in tetrahydrofuran, at ambient temperature, in presence of a pinch of iodine to form the Grignard reagent of 2,3,4,5 tetramethoxy-6-methyl bromobenzene compound of the formula **IIc**.

10

Example – 5

Preparation of novel Grignard reagent of 2,3,4-trimethoxy-5-bromo-6-methyl-hydroquinone-1-methoxyethoxymethyl ether of the formula IIa.

15 2,3,4 trimethoxy-6- methyl-phenol compound of formula **15**, (2.42g) was taken in methylene dichloride 15 ml and treated with bromine 1.96 g at 10 –20⁰ C. The reaction was quenched in water after 2 hours and extracted in methylene dichloride. The methylene chloride layer was evaporated. The concentrated mass was added to hexane to precipitate out the solid of 2,3,4 trimethoxy-5 bromo-6-methyl- phenol (3.22 g) of formula **16**. The bromo phenol of formula **16** was dissolved in toluene and treated with 0.513 g sodium hydride (60% suspension) in toluene at 0 to –5⁰ C. Methoxyethoxy methyl chloride (1.59 g) was added at 5 to 10⁰C. The temperature was slowly raised to room temperature and maintained for 2 hrs. The reaction was quenched in water and the toluene layer separated. The organic layer was distilled under vacuum to obtain 4.03 g of 2,3,4-trimethoxy-5-bromo-6-methyl-hydroquinone-1-methoxyethoxymethyl ether compound of the formula **17**. The compound of formula **17** was reacted with magnesium (0.35 g) in tetrahydrofuran, at ambient temperature, in presence of a pinch of iodine, to form the Grignard reagent of 2,3,4-trimethoxy-5-bromo-6-methyl-hydroquinone-1-methoxyethoxymethyl ether of the formula **IIa**.

25
30

¹ H-NMR (300 MHz, CDCl₃ , 2.33 (3H, -CH₃), 3.38-3.94 (18H, -OCH₂O-, -CH₂CH₂O-, -OCH₃)

Example 6**Preparation of novel Grignard reagent of 2,3,4-trimethoxy-5-bromo-6-methyl-hydroquinone-1-methoxyethoxymethyl ether of the formula IIa.**

- 5 2,3,4 trimethoxy-6- methyl-phenol compound of formula **15**, 2.42 g was taken in methylene dichloride (15 ml) and treated with bromine (1.96 g) at 10 to 20 °C. The reaction was quenched in water after 2 hours and extracted in methylene dichloride. The methylene chloride layer was evaporated. The concentrated mass was added to hexane to precipitate out the solid of 2,3,4 trimethoxy-5 bromo-6-methyl- phenol
- 10 (3.22 g) of formula **16**. The bromo phenol of formula **16** was dissolved in methanol and treated with sodium methoxide (0.75 g) at 5 - 10 °C. Methoxyethoxy methyl chloride (1.59 g) was added at 5 °C to 10 °C and the temperature was raised to room temperature and maintained for 8 hrs. The reaction was quenched in water and extracted in diisopropyl ether. The solvent was distilled under vacuum to obtain 4.0 g
- 15 of 2,3,4-trimethoxy-5-bromo-6-methyl-hydroquinone-1-methoxyethoxymethyl ether compound of the formula **17**. The compound of formula **17** was reacted with magnesium (0.35 g) in tetrahydrofuran, at ambient temperature, in presence of a pinch of iodine, to form the Grignard reagent of 2,3,4-trimethoxy-5-bromo-6-methyl-hydroquinone-1-methoxy-ethoxymethyl ether of the formula **IIa**.
- 20 ¹H-NMR (300 MHz, CDCl₃, 2.33 (3H, -CH₃), 3.38-3.94 (18H, -OCH₂O-, -OCH₂CH₂O-, -OCH₃)

Example 7

- Preparation of compound of the formula **IIIa** (where R1 and R2 = -**
- 25 **OCH₂OCH₂CH₂OCH₃)**

- The Grignard reagent of 2,3 Dimethoxy-5-bromo-6-methyl 1,4 hydroquinone dimethoxyethoxy methyl ether of the formula **IIb** prepared by the process described in Example 1, was cooled to 0 - 5° C. Cuprous bromide (0.65g) was added to the
- 30 Grignard solution of formula **IIb**, stirred at room temperature for 1 hour, followed by dropwise addition of a solution of solanesyl bromide in tetrahydrofuran (4 g in 25 ml tetrahydrofuran). The reaction mixture was stirred for four hours and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.2 g of

crude, which was purified by column chromatography to give 4.4 g of the pure title compound

Example 8

5 Preparation of compound of the formula IIIa (where R1 and R2 = –OCH₂OCH₂CH₂OCH₃)

The Grignard reagent of 2,3 Dimethoxy-5-bromo-6-methyl 1,4 dimethoxyethoxy methyl ether compound of the formula **IIb** prepared by the process described in
10 Example 1, was slowly added to a solution of solanesyl bromide in tetrahydrofuran (4 g in 25 ml tetrahydrofuran) in presence of cuprous bromide (0.65 g). The reaction was continued for four hours at room temperature and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.8 g of crude, which was
15 purified by column chromatography to give 4.0 g of the pure title compound

Example 9

Preparation of compound of the formula IIIa (where R1 and R2 = –OMe)

20 The Grignard reagent of 2,3,4,5 tetramethoxy-6-methyl bromobenzene compound of the formula **IIc**, prepared by the process described in Example 3, was cooled at 0 - 5°C. Cuprous bromide (0.75g) was added to the Grignard solution of formula **IIc**, stirred at room temperature for 1 hour, followed by dropwise addition of a solution of solanesyl bromide in tetrahydrofuran (4g in 25 ml tetrahydrofuran). The reaction
25 mixture was stirred for four hours and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.0 g of crude, which was purified by column chromatography to give 3.78 g of the pure title compound.

30

Example 10

Preparation of compound of the formula IIIa (where R1 and R2 = –OMe)

The Grignard reagent of 2,3,4,5 tetramethoxy-6-methyl bromobenzene compound of the formula **IIc**, prepared by the process described in Example 3, was slowly added to

a solution of solanesyl bromide in tetrahydrofuran (4 g in 25 ml tetrahydrofuran) in presence of cuprous bromide (0.75 g). The reaction was continued for four hours at room temperature and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.0g of crude, which was purified by column chromatography to give 3.36 g of the pure title compound.

Example 11

**Preparation of compound of the formula IIIa (where R1 = -
10 OCH₂OCH₂CH₂OCH₃ and R2 = -OMe)**

The Grignard reagent of 2,3,4-trimethoxy-5-bromo-6-methyl-hydroquinone-1-methoxy-ethoxymethyl ether of the formula **IIa** prepared by the process described in Example 5, was cooled to 0 - 5° C. Cuprous bromide (0.79g) was added to the Grignard solution of formula **IIa**, stirred at room temperature for 1 hour, followed by dropwise addition of a solution of solanesyl bromide in tetrahydrofuran (4 g in 25 ml tetrahydrofuran). The reaction mixture was stirred for four hours and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.2 g of crude, which was purified by column chromatography to give 4 g of the pure title compound.

Example 12

**Preparation of compound of the formula IIIa (where R1 = -
25 OCH₂OCH₂CH₂OCH₃ and R2 = -OMe)**

The Grignard reagent of 2,3,4-trimethoxy-5-bromo-6-methylhydroquinone-1-methoxy-ethoxymethyl ether of the formula **IIa** prepared by the process described in Example 5, was slowly added to a solution of solanesyl bromide in tetrahydrofuran (4g in 25 ml tetrahydrofuran) in presence of cuprous bromide (0.79 g). The reaction was continued for four hours at room temperature and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.8 g of crude, which was purified by column chromatography to give 3.68g of the pure title compound.

Example 13

Preparation of compound of the formula IIIb (where R1 and R2 = –
5 **OCH₂OCH₂CH₂OCH₃)**

The Grignard reagent of 2,3 Dimethoxy-5-bromo-6-methyl 1,4 hydroquinone dimethoxy-ethoxy methyl ether of the formula **IIIb** prepared by the process described in Example 1, was cooled to 0 – 5 °C. Cuprous bromide (0.65g) was added to the
10 Grignard solution of formula **IIIb**, stirred at room temperature for 1 hour, followed by dropwise addition of a solution of decaprenyl bromide in tetrahydrofuran (4.39 g in 25 ml tetrahydrofuran). The reaction mixture was stirred for four hours and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.2 g
15 of crude, which was purified by column chromatography to give 4.39 g of the pure title compound.

Example 14

Preparation of compound of the formula IIIb (where R1 and R2 = –
20 **OCH₂OCH₂CH₂OCH₃)**

The Grignard reagent of 2,3 Dimethoxy-5bromo-6-methyl 1,4 dimethoxyethoxy methyl ether compound of the formula **IIIb** prepared by the process described in Example 1, was slowly added to a solution of decaprenyl bromide in tetrahydrofuran
25 (4.39g in 25ml tetrahydrofuran) in presence of cuprous bromide (0.65 g). The reaction was continued for four hours at room temperature and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.8 g of crude, which was purified by column chromatography to give 3.88 g of the pure title compound.

30

Example 15

Preparation of compound of the formula IIIb (where R1 and R2 = –OMe)

The Grignard reagent of 2,3,4,5 tetramethoxy-6-methyl bromobenzene compound of the formula **IIc**, prepared by the process described in Example 3, was cooled to 0-5⁰ C. Cuprous bromide (0.75g) was added to the Grignard solution of formula **IIc**, stirred at room temperature for 1 hour, followed by dropwise addition of a solution of
5 decaprenyl bromide in tetrahydrofuran (4.39g in 25 ml tetrahydrofuran). The reaction mixture was stirred for four hours and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.0 g of crude, which was purified by column chromatography to give 4.11 g of the pure title compound.

10

Example 16

Preparation of compound of the formula IIIb (where R1 and R2 = -OMe)

The Grignard reagent of 2,3,4,5 tetramethoxy-6-methyl bromobenzene compound of
15 the formula **IIc**, prepared by the process described in Example 3, was slowly added to a solution of decaprenyl bromide in tetrahydrofuran (4.39 g in 25 ml tetrahydrofuran) in presence of cuprous bromide (0.75 g). The reaction was continued for four hours at room temperature and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and
20 evaporated to give 7.0g of crude, which was purified by column chromatography to give 3.65 g of the pure title compound.

Example 17

**Preparation of compound of the formula IIIb (where R1 = -
25 OCH₂OCH₂CH₂OCH₃ and R2 = -OMe)**

The Grignard reagent of 2, 3, 4 - trimethoxy - 5 - bromo - 6 - methyl - hydroquinone-1-methoxyethoxymethyl ether of the formula **IIa** prepared by the process described in Example 5, was cooled to 0 – 5 ⁰ C. Cuprous bromide (0.79g) was added to the
30 Grignard solution of formula **IIa**, stirred at room temperature for 1 hour, followed by dropwise addition of a solution of decaprenyl bromide in tetrahydrofuran (4.39 g in 25 ml tetrahydrofuran). The reaction mixture was stirred for four hours and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether. The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.2 g

of crude, which was purified by column chromatography to give 4.45 g of the pure title compound.

5

Example 18

Preparation of compound of the formula IIIb (where R1 = – OCH₂OCH₂CH₂OCH₃ and R2 = –OMe)

The Grignard reagent of 2, 3, 4 - trimethoxy - 5 - bromo - 6 - methyl - hydroquinone-
10 1-methoxyethoxymethyl ether of the formula IIa prepared by the process described in Example 5, was slowly added to a solution of decaprenyl bromide in tetrahydrofuran (4.39g in 25 ml tetrahydrofuran) in presence of cuprous bromide (0.79 g). The reaction was continued for four hours at room temperature and the mixture quenched in 5% ammonium chloride solution and extracted in diethyl ether.
15 The solvent was dried over anhydrous sodium sulphate and evaporated to give 7.8 g of crude, which was purified by column chromatography to give 3.95 g of the pure title compound.

Example 19

20 **Preparation of CoQ₉ of formula I₉**

The compound of the formula IIIa (4.4 g) prepared by the process described in Example 7 was treated with 48% HBr solution (0.22 ml), in presence of isopropanol for 4 hours. The isopropanol was distilled off and the residue was taken in n-hexane .
25 The hexane solution was washed with water dried over anhydrous sodium sulphate and distilled under vacuum to obtain 3.56 g of the residue of CoQ₉ dihydroquinone. The dihydroquinone was oxidized with ferric chloride (2.56 g) in 1ml water, in presence of isopropanol at room temperature for 3 hours. The reaction was quenched in water and extracted in hexane. The hexane layer was dried over anhydrous sodium
30 sulphate and evaporated to give crude CoQ₉. The crude CoQ₉ was crystallized in ethanol, at 10 - 15⁰ C, to obtain 2.67 g of pure compound, with overall yield from solanesyl bromide as 58%.

Example 20**Preparation of CoQ₉ of formula I₉**

The compound of the formula **IIIa** (3.78 g) prepared by the process described in
5 Example 9 was taken in 48 ml of methylene dichloride and treated with a solution 4 g
of ceric ammonium nitrate in 25 ml of acetonitrile and 25 ml of water at 0 °C. The
reaction mixture was quenched in water and extracted in methylene dichloride
solution. The methylene dichloride was concentrated under vacuum to obtain crude
CoQ₉. The crude CoQ₉ was purified by column chromatography and crystallized in
10 ethanol, at 10 - 15 °C to obtain 2.34 g of pure compound, with overall yield from
solanesyl bromide as 51 %.

Example 21**Preparation of CoQ₉ of formula I₉**

15

The compound of the formula **IIIa** (4.0 g) prepared by the process described in
Example 11 was treated with 48% HBr solution (0.22 ml), in presence of isopropanol
for 4 hours. The isopropanol was distilled off and the residue was taken in n-hexane.
The hexane solution was washed with water dried over anhydrous sodium sulphate
20 and distilled under vacuum to obtain 3.24 g of the residue of CoQ₉ hydroquinone. The
hydroquinone was oxidized with ferric chloride (2.56 g) in 1ml water, in presence of
isopropanol at room temperature for 3 hours. The reaction was quenched in water and
extracted in hexane. The hexane layer was dried over anhydrous sodium sulphate and
evaporated to give crude CoQ₉. The crude CoQ₉ was crystallized in ethanol, at 10 -
25 15° C, to obtain 2.30 g of pure compound, with overall yield from solanesyl bromide
as 50 %.

Example 22**Preparation of CoQ₁₀ of formula I₁₀**

30

The compound of the formula **IIIb** (4.39 g) prepared by the process described in
Example 13 was treated with 48% HBr solution (0.22 ml), in presence of isopropanol
for 4 hours. The isopropanol was distilled off and the residue was taken in n-hexane.
The hexane solution was washed with water dried over anhydrous sodium sulphate

and distilled under vacuum to obtain 3.56 g of the residue of CoQ₁₀ dihydroquinone. The dihydroquinone was oxidized with ferric chloride (2.56 g) in 1ml water, in presence of isopropanol at room temperature for 3 hours. The reaction was quenched in water and extracted in hexane. The hexane layer was dried over anhydrous sodium sulphate and evaporated to give crude CoQ₁₀. The crude CoQ₁₀ was crystallized in ethanol, at 10 – 15⁰C, to obtain 2.53 g of pure compound, with overall yield from decaprenyl bromide as 51 %.

Example 23

10 Preparation of CoQ₁₀ of formula I₁₀

The compound of the formula **IIIb** (4.11 g) prepared by the process described in Example 15 was taken in 48 ml of methylene dichloride and treated with a solution 4 g of ceric ammonium nitrate in 25 ml of acetonitrile and 25 ml of water at 0⁰ C. The reaction mixture was quenched in water and extracted in methylene dichloride solution. The methylene dichloride was concentrated under vacuum to obtain crude CoQ₁₀. The crude CoQ₁₀ was purified by column chromatography and crystallized in ethanol, at 10 – 15⁰ C, to obtain 2.54 g of pure compound, with overall yield from decaprenyl bromide as 51.0%.

20

Example 24

Preparation of CoQ₁₀ of formula

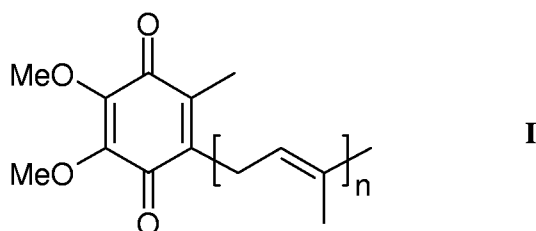
The compound of the formula **IIIb** (4.45 g) prepared by the process described in Example 17 was treated with 48% HBr solution (0.22 ml), in presence of isopropanol for 4 hours. The isopropanol was distilled off and the residue was taken in n-hexane. The hexane solution was washed with water dried over anhydrous sodium sulphate and distilled under vacuum to obtain 3.89 g of the residue of CoQ₁₀ hydroquinone. The hydroquinone residue was oxidized with ferric chloride (2.56 g) in 1ml water, in presence of isopropanol at room temperature for 3 hours. The reaction was quenched in water and extracted in hexane. The hexane layer was dried over anhydrous sodium sulphate and evaporated to give crude CoQ₁₀. The crude CoQ₁₀ was crystallized in ethanol, at 10 - 15⁰ C, to obtain 2.77 g of pure compound, with overall yield from decaprenyl bromide as 55.8 %.

Advantages of the invention

1. Provides Straight forward coupling of the “benzoquinone nucleus” with the
5 “polyprenyl side chain” for the preparation of the coenzymes Q namely, CoQ₉ and CoQ₁₀.
- 2 Provides stereoselective coupling reaction for preparation of coenzymes Q namely, CoQ₉ and CoQ₁₀ by simple Grignard reaction, maintaining the geometrical isomer of
10 the double bond. Controlling cis isomer in the reaction decreases purification loss incurred in removing unwanted cis isomer, thereby making the process cost effective.
3. Provides a novel Grignard reagent compound of formula **IIa** and its preparation, which is useful for the preparation of Coenzymes namely, CoQ₉ and CoQ₁₀.
15
4. Provides novel intermediates compounds of formula **III** useful for the preparation of CoQ₉.
5. Provides novel intermediate compounds of formula **III** useful for the preparation of
20 CoQ₁₀.

We Claim

1. An improved process for the preparation of coenzyme of formula **I**,

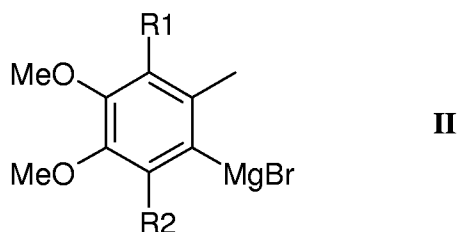


5

where n is an integer selected from 9 or 10, which comprises,

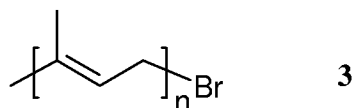
i) reacting Grignard reagent of formula **II**,

10

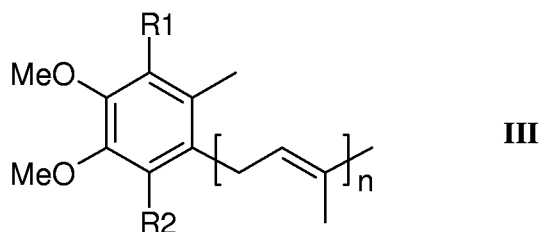


where R1 and R2 are same or different and are selected from –
OCH₂OCH₂CH₂OCH₃ or –OMe, with the proviso that when R2 is –
15 OCH₂OCH₂CH₂OCH₃, then R1 is not –OMe;

with compound of formula **3**,

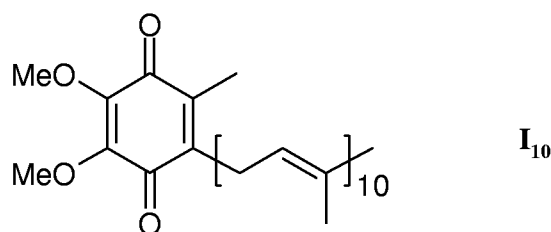


where n is an integer selected from 9 or 10, in presence of cuprous halide in a
20 solvent under inert atmosphere at a temperature in the range of –5 °C to 25 °C, to
obtain an intermediate of formula **III**;



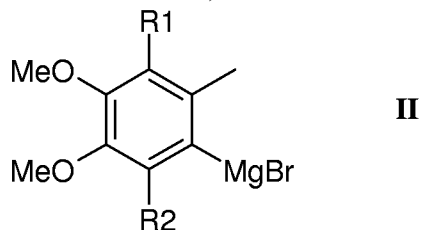
- ii) deprotecting the compound of formula **III** (wherein atleast one of R1 and R2 is – OCH₂OCH₂CH₂OCH₃) to obtain the corresponding hydroquinone;
 iii) oxidizing the compound of step (i) or (ii) to obtain the coenzyme of formula **I**;
 iv) isolating the compound of formula **I**; and
 5 v) purifying and crystallizing the coenzyme of formula **I** by conventional methods.

2. An improved process as claimed in claim 1, wherein n is 10, for the preparation of coenzyme CoQ₁₀ of the formula **I**₁₀



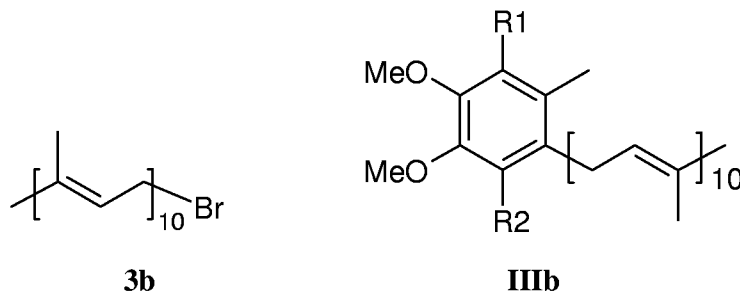
10 which comprises,

- i) reacting Grignard reagents of formula **II**,



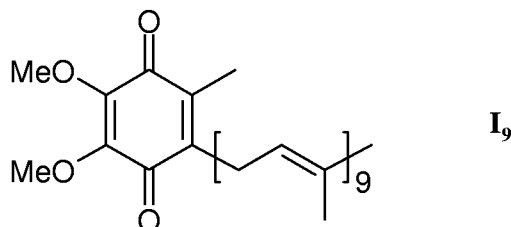
where R1 and R2 are same or different and are selected from –
 15 OCH₂OCH₂CH₂OCH₃ or –OMe, with the proviso that when R2 is – OCH₂OCH₂CH₂OCH₃, then R1 is not –OMe;

with compound of formula **3b**, in presence of cuprous halide in a solvent under inert atmosphere at a temperature in the range of –5 °C to 25 °C, to obtain an intermediate of formula **IIIb**;



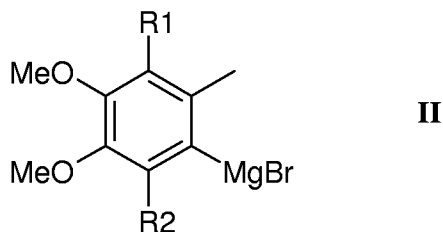
20

- ii) deprotecting the compound of formula **IIIb** (wherein atleast one of R1 and R2 is –OCH₂OCH₂CH₂OCH₃) to obtain the corresponding hydroquinone;
- iii) oxidizing the compound of step (i) or (ii) to obtain the coenzyme CoQ₁₀ of formula **I₁₀**;
- 5 iv) isolating the compound of formula **I₁₀**; and
- v) purifying the coenzyme CoQ₁₀ of formula **I₁₀** and further crystallizing by conventional method to obtain yellow to orange crystals of the coenzyme CoQ₁₀ of formula **I₁₀**.
- 10 **3.** An improved process as claimed in claim 1, wherein n is 9, for the preparation of coenzyme CoQ₉ of the formula **I₉**

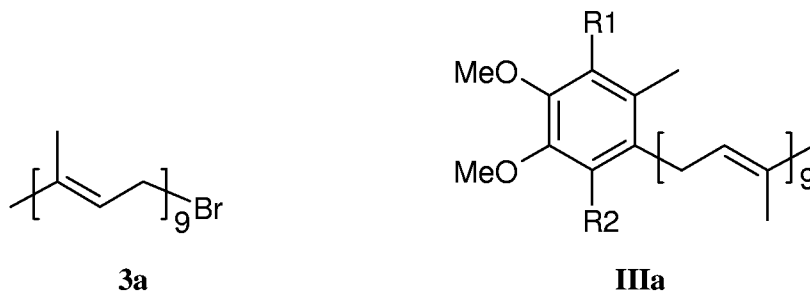


which comprises,

- 15 i) reacting Grignard reagents of formula **II**,

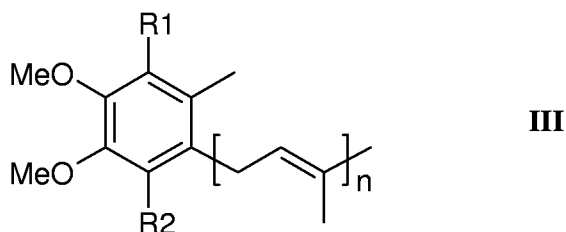


- where R1 and R2 are same or different and are selected from –
- 20 OCH₂OCH₂CH₂OCH₃ or –OMe, with the proviso that when R2 is –OCH₂OCH₂CH₂OCH₃, then R1 is not –OMe;
- with compound of formula **3a**, in presence of cuprous halide in a solvent under inert atmosphere at a temperature in the range of –5 °C to 25 °C, to obtain an intermediate of formula **IIIa**;



- ii) deprotecting the compound of formula **IIIa** (wherein atleast one of R1 and R2 is –
 5 OCH₂OCH₂CH₂OCH₃) to obtain the corresponding hydroquinone;
 iii) oxidizing the compound of step (i) or (ii) to obtain the coenzyme CoQ₉ of formula **I₉**;
 iv) isolating the compound of formula **I₉**; and
 v) purifying the coenzyme CoQ₉ of formula **I₉** and further crystallizing by
 10 conventional method to obtain yellow to orange crystals of the coenzyme CoQ₉ of formula **I₉**.

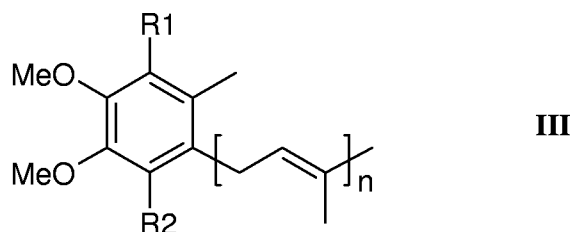
4. Compounds of formula **III** useful for the preparation of coenzymes of formula **I** as claimed in claim 1 are new,



15

where R1 and R2 are selected from –OCH₂OCH₂CH₂OCH₃ or –OMe, and n is selected from 9 or 10, with the proviso that when R2 is –OCH₂OCH₂CH₂OCH₃, then R1 is not –OMe.

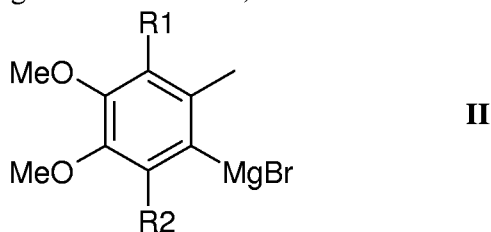
- 20 **5.** An improved process for the preparation of compound of formula **III**, useful for the preparation of coenzymes of formula **I** as claimed in claim 1



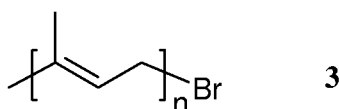
where R1 and R2 are same or different and are selected from –OCH₂OCH₂CH₂OCH₃ or –OMe, and n is selected from 9 or 10, with the proviso that when R2 is –OCH₂OCH₂CH₂OCH₃, then R1 is not –OMe,

5 which comprises,

i) reacting Grignard reagents of formula **II**,



with compounds of formula **3**,



10 where n is selected from 9 or 10, in presence of cuprous halide in a solvent under inert atmosphere at a temperature in the range of –5 °C to 25 °C.

6. An improved process as claimed in claims 1 and 5 wherein the reaction mixture obtained in step i) is quenched in ammonium chloride solution, and the compound of
15 formula **III** is extracted in a solvent followed by evaporating the solvent.

7. An improved process as claimed in claim 6 wherein the extracted compound of formula **III** is purified by column chromatography to obtain 95% pure compound of formula **III**

20

8. An improved process as claimed in claim 1 and 5 wherein the compound of formula **3** is selected from solanesyl bromide and decaprenyl bromide

9. An improved process as claimed in claims 1 and 5 wherein the cuprous halide is
25 selected from cuprous chloride, cuprous bromide and cuprous iodide, preferably cuprous bromide in 1:1 to 1:0.1 molar ratio of the Grignard reagent.

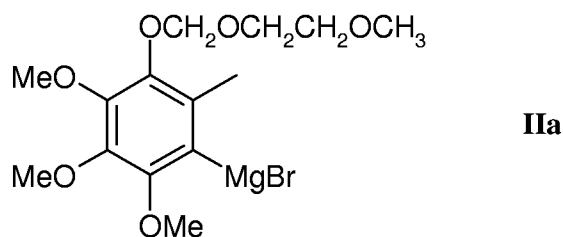
10. An improved process as claimed in claims 1 and 5 wherein the Grignard reagent used is in excess of the compound of formula **3**, in a molar ratio of 1:1 to 1:4 preferably 1:1.1 to 1:2.

11. An improved process as claimed in claim 6 wherein the solvent is selected from water immiscible solvent.

12. An improved process as claimed in claim 1 wherein step iii) is carried out with ceric ammonium nitrate in acetonitrile.

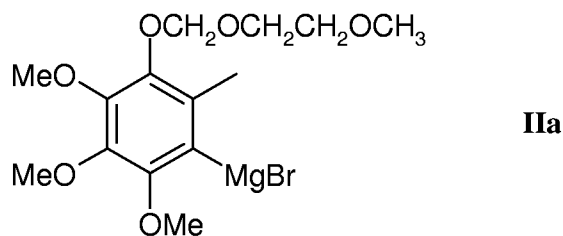
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13. A novel Grignard reagent of formula **IIa**, useful for the preparation of coenzymes of formula **I** as claimed in claim 1,



14. An improved process for the preparation of Grignard reagents of formula **IIa** as claimed in claim 13,

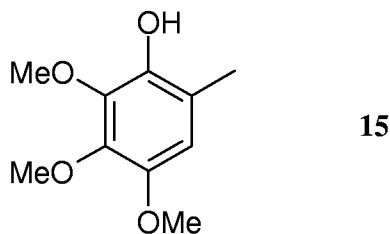
15



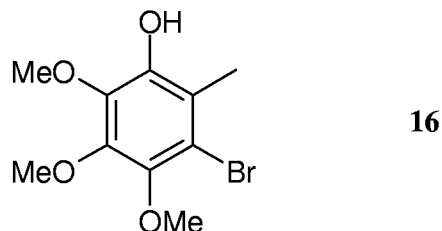
which comprises,

(i) Brominating the compound of the formula **15**

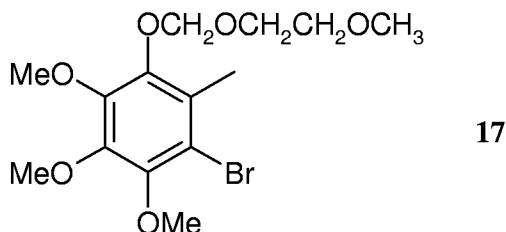
20



by known method, to obtain compound of formula **16**.

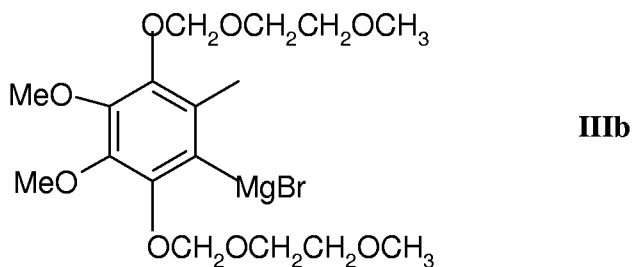


- (ii) Alkylating the compound of the formula **16** obtained in step (i) with methoxyethoxymethyl chloride in the presence of a base, an alkali metal alkoxide or metal hydride, to obtain 2,3-dimethoxy-5-methyl-6-bromohydroquinone-1,4-dimethoxyethoxymethyl ether compound of formula **17**



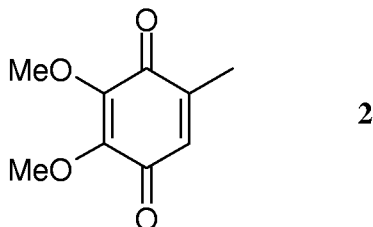
- (iii) Reacting the compound of the formula **17** obtained in step (ii) with magnesium in presence of iodine and dibromoethane, using ether as a solvent at a temperature in the range of 0 - 65 °C, to obtain the Grignard reagent of the formula **IIa**;
- (iv) Cooling the resulting reaction mixture to room temperature, filtering to get the novel Grignard reagent of the formula **IIa**.

- 15.** An improved process for the preparation of Grignard reagent of the formula **IIb**, useful for the preparation of coenzymes of formula **I** as claimed in claim 1,

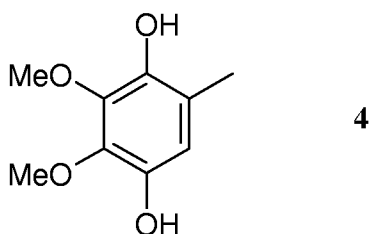


which comprises

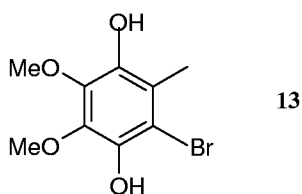
- i Reducing 2,3 dimethoxy -5 -methyl 1,4 benzoquinone (CoQ₀) of the formula **2**



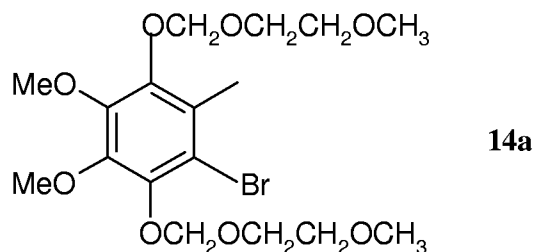
with aqueous sodium hydrosulphite, in alkaline medium, in the presence of a water immiscible organic solvent, separating the organic phase, and evaporating the organic phase to obtain a concentrated residue, to which was added a hydrocarbon solvent to precipitate out compound of formula **4**



- ii. Brominating the resulting compound of the formula **4** with bromine in chlorinated hydrocarbon at 0-25 °C,
- 10 iii. Quenching the resultant reaction mixture in step (ii) in aqueous medium to obtain aqueous and organic phase, separating the organic phase and evaporating the organic phase to obtain a concentrated residue, to which was added a hydrocarbon solvent to precipitate out 2,3-dimethoxy -5-methyl-6-bromo 1,4 hydroquinone of the formula **13**;

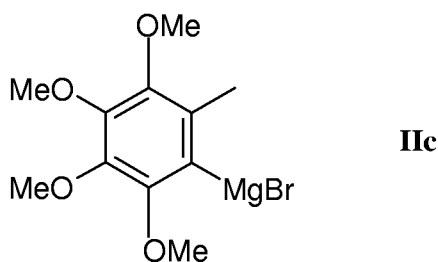


- 15 iv. Alkylating the 2,3 dimethoxy -5 -methyl -6-bromo 1,4 hydroquinone of the formula **13** obtained in step (iii) with methoxyethoxymethyl chloride in the presence of a base selected from an alkali metal alkoxide or metal hydride, to obtain 2,3-dimethoxy-5-methyl-6-bromo hydroquinone1,4 dimethoxyethoxymethyl ether compound of formula **14a**;
- 20



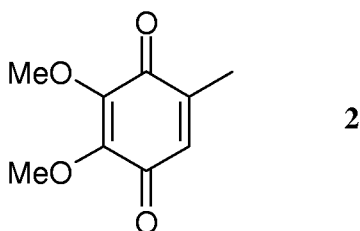
- v. Reacting the compound of the formula **14a** obtained in step (iv) with magnesium in presence of ether, iodine and dibromoethane, at a temperature in the range of 0 - 65 °C, to obtain the Grignard reagent of the formula **IIb**; and
- vi. Isolating the Grignard reagent of formula **IIb**

- 16.** An improved process for the preparation of Grignard reagent of the Formula **IIc**, useful for the preparation of coenzymes of formula (I) as claimed in claim 1,

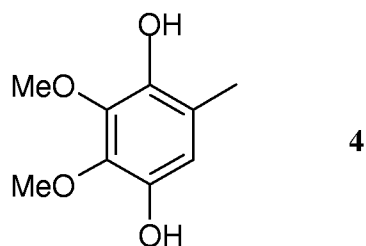


which comprises,

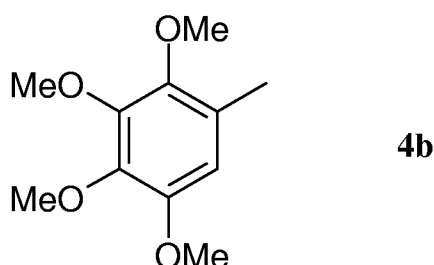
- i. Reducing 2,3 dimethoxy -5 -methyl 1,4 benzoquinone (CoQ₀) of the formula **2**



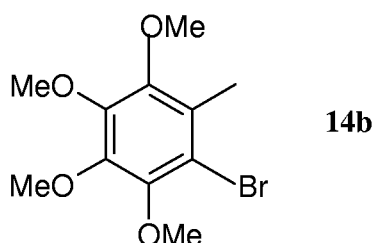
- with aqueous sodium hydrosulphite, in alkaline medium, in the presence of a water immiscible organic solvent, separating the organic phase and evaporating the organic phase to obtain a concentrated residue, to which was added a hydrocarbon solvent to precipitate compound of formula **4**;



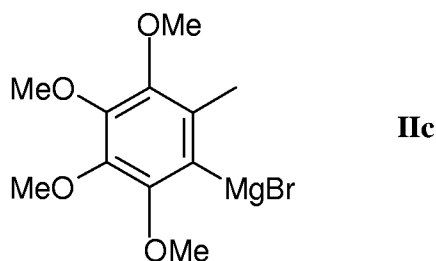
ii. Alkylating the compound of the formula **4**, with alkyl sulphate by known method to obtain 2,3,4,5 tetramethoxy toluene compound of formula **4b**;



- 5 iii. Brominating the resulting compound of the formula **4b** with bromine in chlorinated hydrocarbon at a temperature in the range of 0 - 25 °C;
- iv. Quenching the resultant reaction mixture in step (iii) in aqueous medium to obtain aqueous and organic phase and separating the organic phase, evaporating the organic phase to obtain a concentrated residue to which was added a hydrocarbon solvent to
- 10 precipitate out 2,3,4,5 tetramethoxy 6-bromo toluene of the formula **14b**;



- v. Reacting the compound of the formula **14b** obtained in step (iv) with magnesium in presence of ether, iodine and dibromoethane, at a temperature in the range of 0 -
- 15 65 °C, to obtain the Grignard reagent of the formula **IIc**; and



vi. isolating the Grignard reagent of formula **IIc**.

17. An improved process as claimed in claims 15 and 16 wherein the reduction of 2,3
5 Dimethoxy 5 methyl 1,4 benzoquinone, CoQ₀ of the formula **2**, is carried out using
sodium hydrosulphite in neutral or alkaline medium, preferably alkaline medium
more preferably sodium hydroxide at a temperature in the range of 0⁰ C to 20⁰ C
preferably, 10-20⁰ C.

10 18. An improved process as claimed in claims 15 and 16 wherein the water
immiscible solvent is selected from water immiscible organic solvent like ether,
aromatic hydrocarbons, chlorinated hydrocarbons more preferably chlorinated
hydrocarbons like methylene chloride, ethylene chloride, preferably methylene
chloride.

15 19. An improved process as claimed in claims 15 and 16 wherein the isolation of 2,3
Dimethoxy 5 methyl 1,4 Hydroquinone compound of the formula **4** is effected by
acidifying the above reaction mixture of step iv, separating the organic phase,
concentrating the organic phase, and adding the concentrated residue to aliphatic or
20 aromatic hydrocarbon solvent like hexane, heptane, petroleum ether, preferably
heptane to precipitate and filter the compound of formula **4**.

20 20. An improved process as claimed in claims 15 and 16 wherein the bromination is
carried out using bromine in the presence of a chlorinated hydrocarbon solvent like
25 methylene chloride and ethylenechloride at a tempertaure in the range of 0 - 30⁰ C
preferably at 10 - 20⁰ C.

21. An improved process as claimed in claim 15 wherein the isolation of the
brominated compound 2,3 Dimethoxy-5-methyl-6-bromo1,4 hydroquinone
30 compound of formula **13** formed is carried out by quenching the resulting reaction
mixture in aqueous medium, separating and concentrating the organic phase at a
temperature in the range of 0 to 20⁰ C preferably at 0-5⁰ C and adding the
concentrated residue to aliphatic or aromatic hydrocarbon solvent like hexane,

heptane, petroleum ether, preferably heptane to precipitate and filter the compound of formula **13**

22. An improved process as claimed in claim 15 wherein the alkylation of 2,3
5 dimethoxy 5 methyl 6 bromo hydroquinone compound of the formula **13** is carried out using methoxy ethoxymethyl chloride in the presence of metal hydride in aromatic hydrocarbons preferably toluene or an alkali metal alkoxide base selected from sodium methoxide, sodium ethoxide preferably sodium methoxide, in alcohol, at a temperature in the range of -30°C to 30°C preferably $15 - 25^{\circ}\text{C}$.

10

23. An improved process as claimed in claim 15 wherein the 2,3-dimethoxy-5-methyl-6-bromo 1,4 hydroquinone methoxyethoxymethyl ether compound of formula **14a** formed is isolated by quenching the reaction mixture in aqueous medium, extracting in solvent selected from ether, aromatic hydrocarbon, chlorinated
15 hydrocarbons preferably methylene dichloride, and concentrating the solvent.

24. An improved process as claimed in claim 16 wherein Dimethoxy 5 methyl 1,4 Hydroquinone compound of the formula **4** is alkylated using dimethylsulphate in acetone or in aqueous medium in presence of alkali preferably in aqueous medium in
20 presence of alkali.

25. An improved process as claimed in claim 16 wherein the resulting 2,3,4,5 tetramethoxy toluene compound of formula **4b** is isolated by extracting in solvent and distilling out the solvent, and the resulting residue is distilled under vacuum at $0.2 -$
25 10 mm Hg , preferably $0.5 - 0.8\text{ mm Hg}$,

26. An improved process for the preparation of compounds of formulae **I**, **I₉** and **I₁₀** substantially as described with particular reference to the examples.

30 27. An improved process for the preparation of compounds of formulae **IIa**, **IIb** and **IIc** substantially as described with particular reference to the examples.

28. An improved process for the preparation of compounds of formula **III** substantially as described with particular reference to the examples.