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(54) **Title**: IMPROVED PROCESS FOR THE PREPARATION OF D-ALPHA-TOCOTRIENOL FROM NATURAL EXTRACTS

(57) **Abstract**: An improved process for the preparation of d-alpha-tocotrienol from natural extracts comprising mixed tocotrienols, using a solid-phase-supported amino-alkylation step.

IMPROVED PROCESS FOR THE PREPARATION OF D-ALPHA-TOCOTRIENOL FROM NATURAL EXTRACTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims priority benefit of United States Provisional Patent Application No. 61/518,502, filed May 6, 2011. The entire contents of that patent application are hereby incorporated by reference herein.

TECHNICAL FIELD

[0002] This invention relates generally to an improved commercial process for the preparation of d-alpha-tocotrienol of high purity from naturally occurring plant source extracts that comprise mixed tocotrienols, using a solid-phase-supported amino-alkylation step.

BACKGROUND OF THE INVENTION

[0003] The present invention provides a process for the preparation of d-alpha-tocotrienol compositions of high purity from naturally occurring plant source extracts. This process does not include any steps involving chromatography separation and is economically feasible on a commercial scale. This process involves a solid-phase-supported amino-alkylation step comprising a solid-support-bound secondary amine as a base.

[0004] Tocotrienols are present in the oils, seeds, and other parts of many plants used as foods (see pp. 99-165 in L. Machlin, ed., "Vitamin E: A Comprehensive Treatise" for a discussion of the occurrence of tocotrienols in foods). Tocotrienol-containing concentrates can be prepared from certain plant oils and plant oil by-products such as rice bran oil or palm oil distillate. For examples of such isolation processes, see for instance A. G. Top *et al.*, U.S. Pat. No. 5,190,618, or Tanaka, Y. *et al*, Japanese Patent No. JP2003-171376.

[0005] There is a problem inherent in obtaining tocotrienols from natural sources, in that the tocotrienol yield from such processes is a mixture of varying amounts of all of the natural tocotrienols and tocopherols. In order to obtain a pure member of the tocotrienol family, it has been necessary to resort to very expensive procedures such as preparative scale reversed-phase chromatography or simulated moving bed chromatography. For an example of such a purification process, see M. Kitano *et al.*, Japanese Patent No. 2003-02777, or Burger *et al.*, U.S. Pat. No. 4,603,142.

[0006] The synthesis of alpha-tocotrienol in the natural form, having the (2R) chiral configuration and trans double bonding at the proper locations in the side chain, has also been proven to be of considerable difficulty.

[0007] Syntheses of various members of the tocotrienol family in the d,l- or (RS)-form have been published, see for example Schudel *et al.*, *Helv. Chim. Acta* (1963) 46, 2517 2526; H. Mayer *et al.*, *Helv. Chim. Acta* (1967) 50, 1376 11393; H.-J. Kabbe *et al.*, *Synthesis* (1978), 888 889; M. Kajiwara *et al.*, *Heterocycles* (1980) 14, 1995 1998; S. Urano *et al.*, *Chem. Pharm. Bull.* (1983) 31, 4341 4345, Pearce *et al.*, *J. Med Chem.* (1992), 35, 3595 3606 and Pearce *et al.*, *J. Med. Chem.* (1994). 37, 526 541. None of these reported processes lead to the natural form of the tocotrienols, but rather produces racemic mixtures. Syntheses of natural form d-tocotrienols have been published. See for example. J. Scott *et al.*, *Helv. Chim. Acta* (1976) 59, 290-306; Sato *et al.* (Japanese Patent 63063674); Sato *et al.* (Japanese Patent No. JP 01233278) and Couladouros *et al* (US Patent No. 7,038,067).

[0008] Tocotrienols occur largely in palm oil, rice bran oil, barley and annatto. While synthetic and natural tocopherols are readily available in the market, the supply of natural tocotrienols is limited, and generally comprises a mixture of tocotrienols. Crude palm oil which is rich in tocotrienols (800-1500 ppm) offers a potential source of natural tocotrienols. Carotech, Malaysia is one industrial plant that is able to extract and concentrate tocotrienols from crude palm oil. Carotech uses a molecular distillation process (with ultra-high vacuum, super low temperature) in its integrated production plant. This unique process patented in U.S. Pat. No. 5,157,132, allows Carotech to extract valuable phytonutrients, specifically the Tocotrienol Complex (Tocomin®), from the crude palm oil. Tocomin®-50 typically comprises about 25.32% mixed tocotrienols (7.00% alpha-tocotrienol, 14.42% gamma tocotrienol, 3.30% delta tocotrienol and 0.6% beta tocotrienol), 6.90% alpha-tocopherol and other phytonutrients such as plant squalene, phytosterols, co-enzyme Q10 and mixed carotenoids.

[0009] Additional commercially available products that may be used in the present invention are for example, Nu Triene Tocotrienol® (30% content, a product of Eastman Chemical Company), various Oryza® tocotrienol products of different tocotrienol concentrations from Oryza Oil & Fat Co. Ltd including Oryza tocotrienol-70 with 70% total tocopherol/tocotrienol content, and a total tocotrienol content of 40% including 14% of alpha-tocotrienol and 24% gamma-tocotrienol, and Oryza tocotrienol-90 with 90% total tocopherol/tocotrienol content and a total tocotrienol content of 60%; Golden Hope Plantations Berhad Tocotrienol oil (70% content), Davos Life Science TRF (63% content), Ginnoway™ a tocotrienol concentrate from palm and rice oil from Beijing Gingko Group, Gold Trie® a product of Sime Darby Biorganic

Sdn Bhd and Palm Nutraceuticals Sdn Bhd (89% content). Delta Tocotrienol-92® (92% pure by HPLC) is a commercially available product from Beijing Gingko Group that may be also used in the present invention.

[0010] Methods for isolation or enrichment of tocotrienol from certain plant oils and plant oil by-products have been described in the literature, but these methods generally produce mixtures of natural tocols in varying amounts and are not economically feasible on a commercial scale. In order to obtain a pure member of the tocotrienol family, it has been necessary to resort to very expensive procedures such as preparative scale reversed-phase chromatography or simulated moving bed chromatography. For some examples of such isolation and purification processes, see for instance Top A. G. *et al.*, U.S. Pat. No. 5,190,618; Lane R *et al.*, U.S. Pat No. 6,239,171; Bellafiore, L. *et al.*, U.S. Pat. No. 6,395,915; May, C.Y *et al.*, U.S. Pat. No. 6,656,358; Jacobs, L. *et al.*, U.S. Pat. No. 6,838,104; Sumner, C. *et al.* Int. Pat. Pub. WO 99/38860, or Jacobs, L. Int. Pat. Pub. WO 02/500054.

[0011] Production of d-alpha tocopherol from natural plant sources has been described in Baldwin *et al.* U.S. Pat No. 4,977,282, where natural plant sources having Vitamin E activity of a concentrate of mixed tocopherols that might include tocotrienols, is transformed into alpha-tocopherol. In this isolation, alpha tocopherol is enriched after amino-alkylating the mixed tocopherols which are then reduced by catalytic hydrogenation to convert the mixture of the non-alpha tocopherols into alpha-tocopherol. In this process, any tocotrienols present would be hydrogenated to tocopherol. See Netscher *et al.*, *Eur J. Org. Chem* (2007) 1176-1183.

[0012] Because of the similar molecular and retention characteristics of the various individual tocopherols and tocotrienols, separation of the individual compounds has been proven difficult and not commercially viable, and although the process for the production of alpha-tocotrienol has been described, it is not available in pure form from major commercial suppliers.

[0013] A process for the isolation, enrichment and/or isolation of alpha-tocotrienol from natural extracts has been described in co-assigned US Patent Publication No. US 2010/105930, but said patent publication does not describe the use of solid-support secondary amines in the amino-alkylation step.

[0014] In light of the above, there still remains a need for efficient and economically feasible manufacturing processes of naturally occurring d-alpha-tocotrienol of high quality, requiring when done on a large commercial scale, a low number of synthesis and purification steps.

[0015] All references disclosed herein are hereby incorporated in their entirety.

DISCLOSURE OF THE INVENTION

[0016] In accordance with the purposes of this invention, in one aspect, this invention relates to an improved process for the preparation of pure d-alpha-tocotrienol from naturally occurring plant source extracts comprising a mixture of tocotrienols that optionally also include alpha tocopherol by using in the amino-alkylation step (Mannich reaction), the base part bound to a solid-support such as a polymer or resin. This simplifies the separation of the Mannich adducts, reduces the amount of solvent used and allows for recovery of the solid-state-bound secondary amine for future use. Under the Mannich reaction conditions, only the β–, γ-, or δ-tocotrienols are reactive and are therefore bound to the solid support as the Mannich adduct. The unreacted materials are separated by a fast and easy filtration without the need of extractions or chromatography. Next the bound materials are removed from the resin by a simple reduction procedure and at the same time converted to α–tocotrienol, and recovered in high purity. This results in a more economical, shorter and easier process.

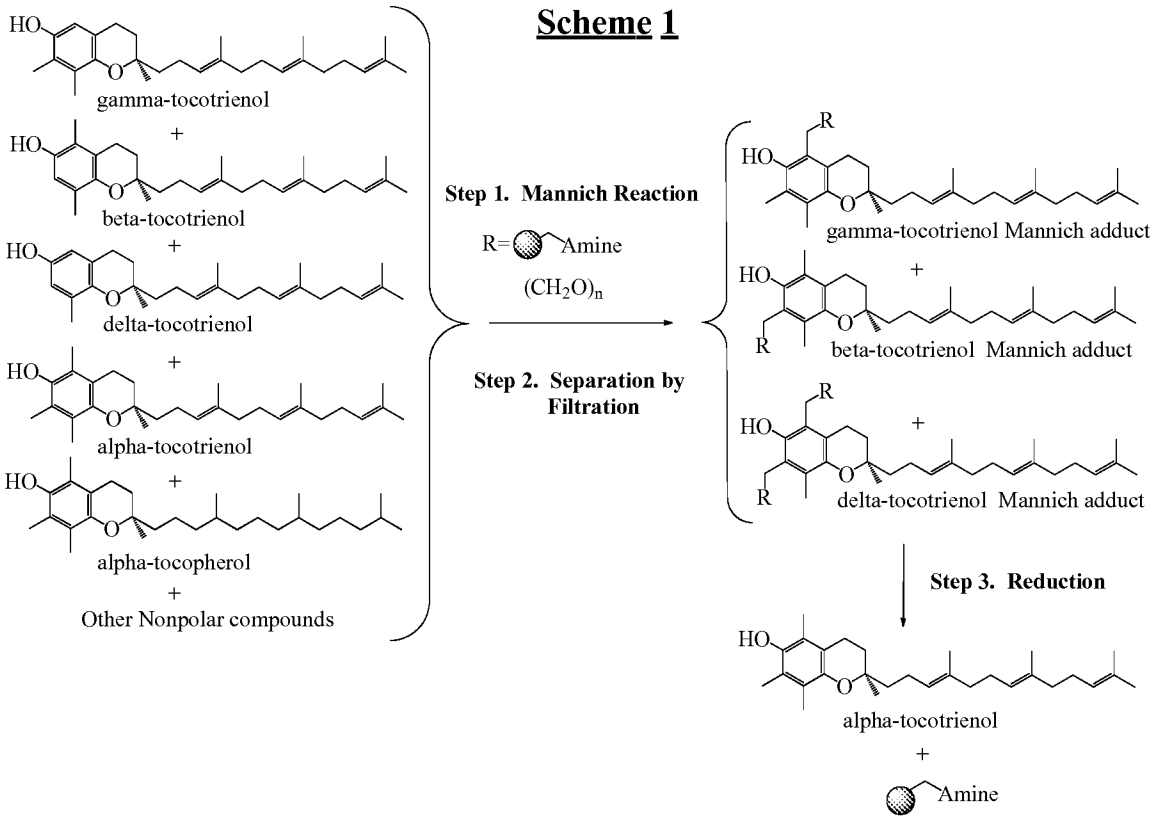
[0017] The invention, as described in Scheme 1 below, comprises the preparation of natural d-alpha-tocotrienol from naturally occurring plant source extracts that comprise tocotrienols and that optionally include alpha-tocopherol or organic impurities, comprising the steps of:

1) heating a mixture of a secondary amine attached to a solid-phase-support and a mixture of tocotrienols and optional alpha-tocopherol from a plant extract in the presence of paraformaldehyde, until the non-alpha tocotrienols disappear from the supernatant, to form solid-support-adducts of beta-, gamma-, and delta-tocotrienols and amine;

2) filtering the solid-support-adduct mixture and washing the solid-support to remove the unreacted materials that may be present; and

3) reducing the solid-support-adduct mixture from step 2 with a reducing agent to cleave the solid-support-amine and yield d-alpha-tocotrienol of high purity.

Scheme 1



[0018] In one embodiment, the functionalization is introduced by amino-alkylation with paraformaldehyde and a solid-phase-bound secondary amine. In another embodiment, the functionalization is introduced by amino-alkylation with paraformaldehyde and a solid-phase-bound cyclic amine such as piperazine, piperidine, or benzotriazole. In some embodiments, the functionalization is introduced by amino-alkylation with paraformaldehyde and solid-phase-bound piperazine. In some embodiments, the functionalization is introduced by amino-alkylation with paraformaldehyde and solid-phase-bound piperidine. In some embodiments, the functionalization is introduced by amino-alkylation with paraformaldehyde and solid-phase-bound benzotriazole.

[0019] In one embodiment, the separation of the amino-alkylation adducts from the other ingredients is done by filtration.

[0020] In another embodiment, the solid-phase-bound secondary amine is recovered for further future use.

[0021] In some embodiments the completion of the reaction in step 1 is monitored by following the disappearance of the non-alpha tocotrienols from the supernatant.

[0022] Some embodiments include an additional step of purifying the d-alpha-tocotrienol by converting it into a crystalline derivative, followed by recrystallization and cleavage to yield d-

alpha-tocotrienol of high purity. In some embodiments, the d-alpha-tocotrienol is further purified by converting it into a crystalline ester derivative, followed by recrystallization and saponification as described for example in US Patent Applications Nos. 5,670,668 and 6,599,933 hereby incorporated by reference. In some embodiments, the crystalline ester is a stearate, a phenylbenzoate or a palmitate ester. In other embodiments, the crystalline ester is not a stearate, a phenylbenzoate or a palmitate ester. In another embodiment, the d-alpha-tocotrienol is further purified by converting it into a crystalline carbamate derivative.

[0023] In another embodiment, the non-alpha-tocotrienol functionalized homologues (Mannich adducts) are reduced with a hydride reagent such as sodium cyanoborohydride ($NaCNBH_3$). In another embodiment, the non-alpha-tocotrienol functionalized homologues are reduced with a hydride reagent such as sodium borohydride. In yet another embodiment, the non-alpha-tocotrienol functionalized homologues are reduced with a hydride reagent such as lithium aluminum hydride. In yet another embodiment, the non-alpha-tocotrienol functionalized homologues are reduced with a borane complex such as borane-t-butyl amine complex. In another embodiment, the non-alpha-tocotrienol functionalized homologues are reduced electrochemically or with an electron donor such as sodium, lithium, magnesium, or nickel in the presence of a suitable proton source.

[0024] In another embodiment, the reduction is performed with a hydride reagent such as lithium aluminum hydride, lithium borohydride, zinc borohydride, tetraalkylammonium hydride, sodium borohydride or sodium cyanoborohydride.

[0025] In another embodiment, the reduction is performed with a borane, diborane, or a borane complex, such as borane t-butyl amine complex.

[0026] In another embodiment, the reduction is performed electrochemically or with an electron donor such as sodium, lithium, potassium, magnesium, zinc or nickel or amalgams thereof in the presence of a suitable proton source such as ammonium salts or carboxylic acids.

[0027] In another embodiment, the reduction is performed with tributyl tin hydride, or by catalytic hydrogenation that does not hydrogenate the double bonds in the tail (e.g., Raney Nickel).

[0028] In some embodiments, the naturally occurring plant source extract is an enriched tocotrienol extract of palm oil, rice bran oil, barley, annatto or mixtures therof.

[0029] In another embodiment, the naturally occurring plant source extract is a palm oil extract. In another embodiment, the palm oil extract is commercially available Tocomin®. In another embodiment, the palm oil extract is commercially available Tocomin®-50. In another embodiment, the commercial palm oil concentrate Tocomin®, a product of Carotech Bhd.

(Malaysia.), comprises a mixture of tocotrienols and alpha-tocopherol extracted and concentrated from virgin crude palm oil/ palm fruits (*Elaeis guineensis*); and may also include non-tocol phytonutrients such as plant squalene, phytosterols, co-enzyme Q10 and mixed carotenoids that are naturally extracted together with tocotrienols.

[0030] In another embodiment the formulation of the present invention comprises an enriched tocotrienol extract from palm oil, as sold by Carotech, Golden Hope Bioorganic, Carotech, Davos Life Science, Beijing Gingko Group, Eisai, Eastman Corporation, Sime Darby Biorganic Sdn Bhd or Palm Nutraceuticals.

[0031] In another embodiment, the naturally occurring plant source extract is a rice extract. In another embodiment, the plant extract is a rice bran oil extract. In another embodiment, the plant extract is annatto extract. In another embodiment, the plant extract is annatto bean extract.

[0032] In some of the embodiments above, the processes of the invention yield alpha-tocotrienol of high purity. In some embodiments, the purity is in the range of 80% to 99.9%, or in the range of 85% to 99.9%, or in the range of 90% to 99.9%, or in the range of 95% to 99.9%. In some embodiments, the purity is more than 80%, or more than 85%, or more than 90%, or more than 91%, or more than 92%, or more than 93%, or more than 94%, or more than 95%, or more than 96%, or more than 97%, or more than 98%, or more than 99%, or more than 99.5%, or more than 99.9%. In other embodiments, the impurities in the final product are less than 20%, or less than 15%, or less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than 1%, or less than .5%, or less than .1%. In other embodiments, the impurities consisting of tocols or tocol derivatives in the final product are less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than .5% or less than .1%.

[0033] In some of the above mentioned embodiments, the process involves an additional optional step, wherein the alpha tocotrienol is oxidized to produce alpha-tocotrienol quinone of high purity.

METHODS FOR CARRYING OUT THE INVENTION

[0034] The invention embraces a method for the preparation of d-alpha-tocotrienol of high purity from natural extracts that comprise mixed tocotrienols by using an amino-alkylation process step comprising secondary amines that are bound to a solid-phase or resin.

[0035] The term "tocols" refers to tocopherols and tocotrienols as described herein.

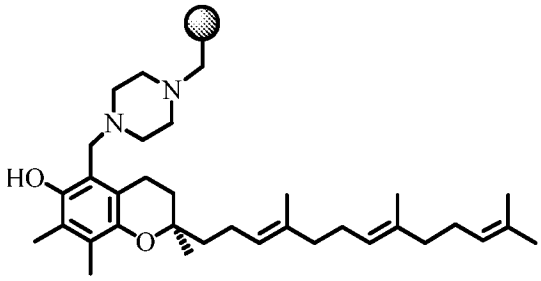
[0036] The term "non-tocols" refers to phytonutrients or organic material that may be present in the extract, but are not tocopherols or tocotrienols.

[0037] The term "amino-alkylation" also known as the Mannich reaction is a reaction accomplished from room temperature up to 140°C for a sufficient length of time to affect amino-alkyl addition. In the embodiments of the present invention the reagents necessary are a source of formaldehyde and a secondary amine that is bound to a solid-phase or resin, not a benzylic amine. The amino-alkylation of the present invention does not include amines that are not attached to a solid-phase. The relative molar concentration of the formaldehyde equivalent and the amine are maintained in equimolar amounts, but the relative concentrations may be varied as long as there is at least one mole of amine and at least one mole of formaldehyde for every mole of free aromatic positions on tocotrienol. Either the amine or formaldehyde component may be present in an amount of from 1 to 20 moles per mole of free aromatic positions on tocotrienol, particularly in a molar amount of at least four times greater than the free aromatic positions on tocotrienol present.

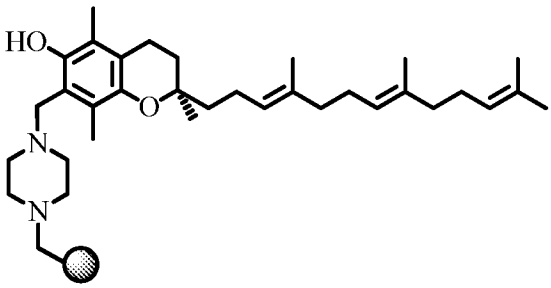
[0038] The starting material is a mixed tocotrienol extract that may also optionally comprise alpha-tocopherol in amounts that may vary depending on the source of the extract. Particularly, the starting material will be amino-alkylated with a solid-support secondary amine to produce an amino-alkylated group attached to a solid-phase that will allow separation by filtration of the non-alpha-tocotrienols solid-support adducts from natural alpha-tocotrienol, alpha tocopherol and other non-tocol phytonutrients or organic impurities that may be present. The separation differs from the one previously disclosed in co-assigned US Application Publication No. 2010/0105930 in that it does not involve any partitioning between different organic solvents or any chromatography. In the spirit of the invention, the alpha-tocotrienol, optional alpha tocopherol and other non polar compounds left in the supernatant will be discarded.

[0039] The terms “solid-support”, “solid-phase-support”, “solid-phase-bound”, “solid-bound”, “resin-bound” and “resin” may be used interchangeably herein. The term “resin” is as used in the art, in particular in the field of solid-phase synthesis. Synthesis on a solid-support or a solid-phase synthesis can be performed in such manner that the synthesis from starting material to intermediates to final product is accomplished by linking at least one of the starting materials to a solid-support such as a resin bead, at the initial step of synthesis. General references for techniques on solid-phase techniques may be found for example in Burgess K., Solid Phase Organic Synthesis (2000) John Wiley & Sons; and Kates, S.A. *et al.*, Solid Phase Synthesis: A Practical Guide. (2000) Marcel Dekker, New York. Methods of isolation, purification and characterization of the intermediates and products of the processes described herein are known to those skilled in the art. Examples of solid-phase-bound Mannich adducts of the non-alpha tocotrienols with solid-phase-bound-piperazine are:

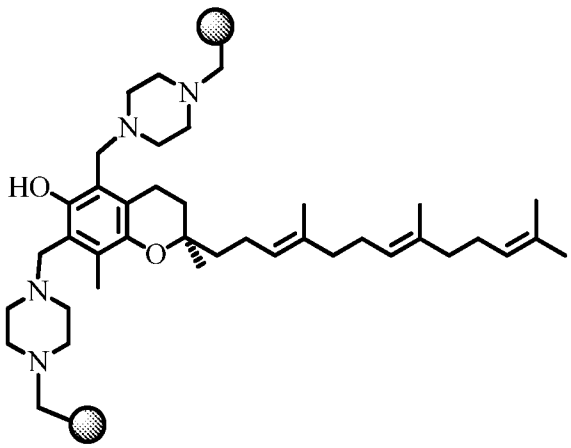
- Gamma-tocotrienol and solid-phase-bound-piperazine Mannich adduct:



- Beta-tocotrienol and solid-phase-bound-piperazine Mannich adduct:



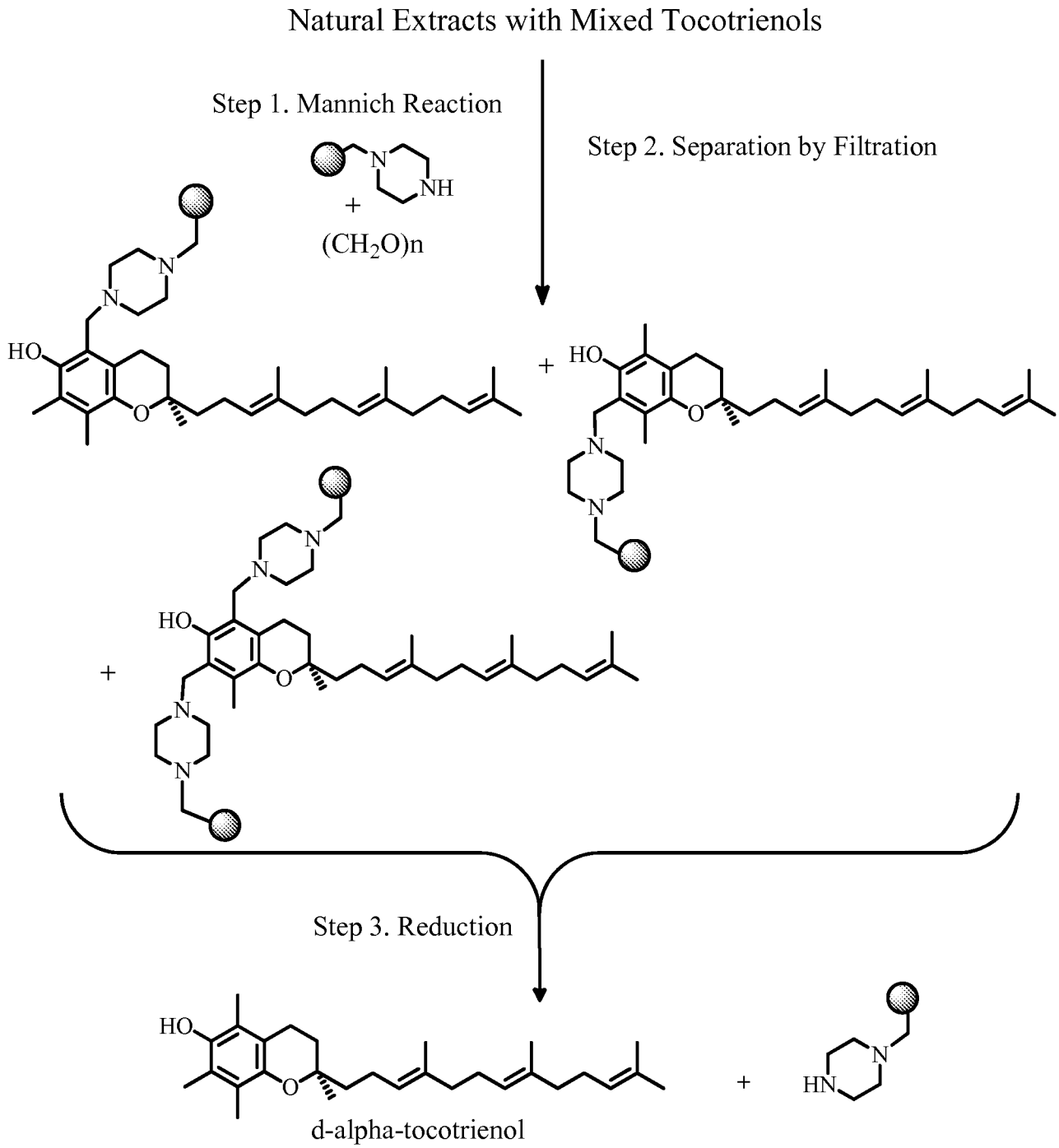
- Delta-tocotrienol and solid-phase-bound-piperazine Mannich adduct:



[0040] By the term "reducing agent" is contemplated a hydride such as lithium aluminum hydride, sodium borohydride, and sodium cyanoborohydride, borane complexes and electron donors such as sodium, lithium, magnesium, or nickel in the presence of a suitable proton source such as ammonium salts or carboxylic acids.

[0041] This invention is further illustrated by the following example of a preferred embodiment thereof. This example is included merely for purposes of illustration and is not intended to limit the scope of the invention.

EXAMPLE



General Procedures

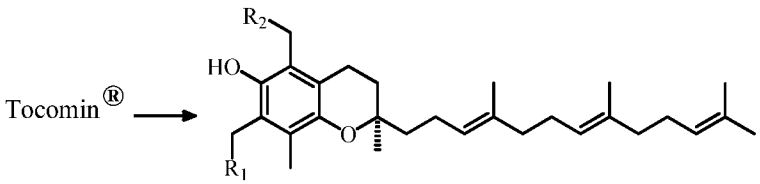
[0042] All solvents and reagents were used as obtained from their respective suppliers except as noted. ^{1}H and ^{13}C NMR were obtained on a Varian Ultrashielded magnet at 400 MHz and 100 MHz respectively in deuterated solvents as noted. All spectra are referenced in ppm to

either their residual solvent peak, as defined in Gottlieb, H. E. et.al; *J. Org. Chem.* (1997), *62*, 7512-7515, or TMS at 0.00 ppm.

[0043] The solid-support secondary amines can be synthesized for example by the methods described in A.R. Katrizky *et al.*, *J.Comb.Chem.* (1999), 1(2) 173-176 and A.R. Katrizky *et al.*, *J.Comb.Chem.* (2003), 3(2) 167-170.

EXPERIMENTALS

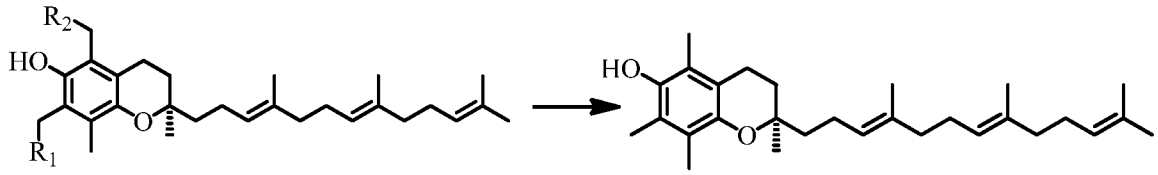
Steps 1 & 2-*Aminomethylation and Filtration.*



R_1, R_2 = H or Resin-bound Piperazine

[0044] To Tocomin®-50 (1.0 wt,) is added paraformaldehyde (0.08 wt, 95%) and resin-bound piperazine (0.3 vol). The suspension is stirred at room temperature for 30 min, and then at 75°C for 2 to 3 h. The solution is heated at 125°C and monitored for conversion of starting material components to product components. The mixture is cooled to at room temperature; filtered from the supernatant, and washed with solvents to remove unreacted materials to yield the solid-phase non-alpha tocotrienol and amine adducts that are used in Step 3.

Step 3- *Reduction.*



R_1, R_2 = H or Resin-bound Piperazine d-Alpha-tocotrienol

[0045] To sodium cyanoborohydride (0.43 wt) is added 3-methylbutanol (2 vol) at room temperature. The suspension is stirred at room temperature for 30 min, and then heated to 125 °C. To this preheated mixture is added over 1.5 h the previously prepared solution of aminomethylated tocols in 3-methylbutanol (3.0 vol) followed by an additional rinse of 3-methylbutanol (0.5 vol). The mixture is heated at 125°C and monitored for conversion of starting material components to product components.

[0046] The mixture is cooled to 50°C, diluted with heptane (5 vol), then cooled to 0°C, and treated with 45% w/w aqueous tribasic potassium phosphate solution (5.0 vol) (exothermic, gas evolution) so as to maintain a temperature below 25°C. The two phase mixture is stirred at room temperature for 2 h, the organic layer is separated, washed with 45% w/w aqueous tribasic potassium phosphate solution (3 vol), and concentrated by distillation at up to 50°C under vacuum. To the residue is added toluene (7 vol). The resulting solution is added to a mixture of silica gel (2 wt) and toluene (5.5vol) with an additional rinse of toluene (2 vol). The silica gel suspension is stirred at room temperature for 1 h. The silica gel is removed by filtration and washed with toluene (2 x 5 vol). The combined filtrates are concentrated by distillation at up to 50°C under vacuum. The residue solution is cooled to 30°C and transferred to a rotoevaporator with toluene (2 x 1.4 vol) and further evaporated to dryness by distillation at up to 60°C under vacuum to give alpha-tocotrienol. ^{1}H-NMR (400MHz, $CDCl_3$) =5.17-5.05 (m, 3H), 4.16 (s, 1H), 2.61 (t, J=6.8 Hz,2H), 2.16-2.01 (m, 6H), 2.16 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.01-1.93 (m, 4H),1.87-1.73 (m, 2H), 1.68-1.49 (m, 2H), 1.68 (s, 3H), 1.60 (s, 6H), 1.58 (s, 3H), 1.25 (s, 3H).

[0047] The disclosures of all publications, patents, patent applications and published patent applications referred to herein by an identifying citation are hereby incorporated herein by reference in their entirety.

[0048] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

What is claimed is:

1. A process for the preparation of natural d-alpha-tocotrienol from naturally occurring plant source extracts that comprise tocotrienols and that optionally include alpha-tocopherol or organic impurities, comprising the steps of:

1) heating a mixture of a secondary amine attached to a solid-phase-support and a mixture of tocotrienols and optional alpha-tocopherol from a plant extract in the presence of paraformaldehyde, until the non-alpha tocotrienols disappear from the supernatant, to form solid-support-adducts of beta-, gamma-, and delta-tocotrienols and amine;

2) filtering the solid-support-adduct mixture and washing the solid support to remove the unreacted materials that may be present; and

3) reducing the solid-support-adduct mixture from step 2 with a reducing agent to cleave the solid-support-amine and yield d-alpha-tocotrienol of high purity.

2. The process of Claim 1, wherein the plant source extract is selected from a palm oil extract, a rice extract, a rice bran extract, and an annatto extract, or a mixture therof.

3. The process of Claim 2, wherein the plant source extract is a palm oil extract.

4. The process of Claim 2, wherein the plant source extract is Tocomin®.

5. The process of Claim 2, wherein the plant source extract is annatto extract.

6. The process of Claim 1, where the functionalization in step 1 is introduced by amino-alkylation with paraformaldehyde and a solid-phase-bound cyclic amine selected from solid-phase-bound-piperazine solid-phase-bound-piperidine or solid-phase-bound-benzotriazole.

7. The process of Claim 6, where the amino-alkylation is introduced with paraformaldehyde and solid-phase-bound-piperazine.

8. The process of Claim 1, additionally comprising recovering the solid-phase-bound secondary amine for future use.

9. The process of Claim 1, additionally comprising an additional step of purifying the alpha-tocotrienol from step 3 by converting it into a crystalline derivative, followed by recrystallization and cleavage of said derivative to yield d-alpha-tocotrienol of high purity.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/36669

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/355 (2012.01)
USPC - 514/458
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/458

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/458; 549/408, 549/412

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
*** Databases: WEST (PGPB, USPT, USOC, EPAB, JPAB); Google, Google Scholar *** Search Terms Used: Edison, Giannousis, tocotrienol, formaldehyde, paraformaldehyde, secondary amine, piperazine, piperidine, morpholine, Mannich, alpha, isolated, isolation, isolating, separation, separated, separating, solid support, resin,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0105930 A1 (Wesson et al.) 29 April 2010 (29.04.2010), especially para [0015]-[0016], [0019], [0030]-[0033], [0075], [0108]-[0109], [0119],	1-9
Y	US 2004/0026323 A1 (Kaneko et al.) 12 February 2004 (12.02.2004), especially para [0017],	1-9
Y	US 6,239,171 A (Lane et al.) 29 May 2001 (29.05.2001) col 22-24	1-9
Y	US 6,204,290 A (Lane et al.) 20 March 2001 (20.03.2001) col 23-25	1-9
Y	US 6,143,770 A (Lane et al.) 7 November 2000 (07.11.2000) col 23-25	1-9
Y	US 5,919,818 A (Lane et al.) 6 July 1999 (06.07.1999) col 23-26	1-9
Y	US 5,821,264 A (Lane et al.) 13 October 1998 (13.10.1998) col 23-24	1-9
Y	US 5,591,772 A (Lane et al.) 7 January 1997 (07.01.1997) col 23-26	1-9
Y	WO 2010/051277 A1 (Wesson et al.) 06 May 2010 (06.05.2010) para [0014]-[0040]	1-9

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2012 (23.07.2012)	05 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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