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(12) **United States Patent**
Pandey et al.(10) **Patent No.:** **US 7,053,210 B2**
(45) **Date of Patent:** **May 30, 2006**(54) **EFFICIENT SYNTHESIS OF
PYROPHEOPHORBIDE A AND ITS
DERIVATIVES**(75) Inventors: **Ravindra K. Pandey**, Williamsville,
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U.S.C. 154(b) by 128 days.(21) Appl. No.: **10/613,474**(22) Filed: **Jul. 2, 2003**(65) **Prior Publication Data**

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2, 2002.(51) **Int. Cl.****A61B 5/055** (2006.01)**A61B 10/00** (2006.01)**C07B 47/00** (2006.01)**C07F 5/10** (2006.01)**A61K 31/555** (2006.01)(52) **U.S. Cl.** **540/145**; 424/9.362; 424/9.61;
534/15; 514/185; 514/410(58) **Field of Classification Search** 540/145;
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See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—James O. Wilson*Assistant Examiner*—Mathew L. Fedowitz(74) *Attorney, Agent, or Firm*—Michael L. Dunn(57) **ABSTRACT**

A process for the preparation of pyropheophorbide a and its
 derivatives, including 3-devinyl-3-(1'-hexyloxy)ethyl-py-
 ropheophorbide-a, otherwise known as HPPH, is provided.
 The process involves treating chlorin e₆, in the form of its
 trimethyl ester, with a base, followed by heating to give
 pyropheophorbide a, which is converted to HPPH by treat-
 ment with acid, followed by hexyl alcohol under basic
 conditions.

11 Claims, No Drawings

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EFFICIENT SYNTHESIS OF PYROPHEOPHORBIDE A AND ITS DERIVATIVES

RELATED APPLICATIONS

Priority is claimed herein under 35 U.S.C. §119(e) to U.S. provisional patent application No. 60/393,617, filed Jul. 2, 2002, to Pandey et al., entitled "EFFICIENT SYNTHESIS OF PYROPHEOPHORBIDE A AND ITS DERIVATIVES." The above-referenced application is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with funding from the National Institute of Health Grant Number NIH CA55792. The United States Government may have certain rights in this invention.

FIELD

Provided herein is a process for the preparation of pyropheophorbide a and its derivatives, including hexyloxy pyropheophorbide a, otherwise known as HPPH. The process involves treating chlorin e₆, in the form of its trimethyl ester, with a base, followed by heating to give pyropheophorbide a, which is converted to HPPH by treatment with hexyl alcohol under acidic conditions.

BACKGROUND

Photodynamic therapy (PDT) is relatively a new treatment method for the destruction of tumors. PDT is based on the accumulation in malignant tissue of a photosensitizer after its administration. Subsequent illumination with light of an appropriate wavelength creates a photochemical reaction, a so-called photodynamic effect (photochemical reaction producing singlet oxygen) that results in tumor destruction.

It is well established that both absorption and scattering of light by tissue increases as the wavelength decreases, and that the most effective sensitizers are those that have strong absorption bands between 660–800 nm. In recent years, a series of photosensitizers have been developed related to pyropheophorbide-a and purpurinimides (obtained from purpurin-18) with a variable lipophilicity exhibiting the longer wavelength absorption at 665 and 705 nm (in vivo absorption) respectively.

Historically, preparation of HPPH has required the isolation of methyl pheophorbide a from *Spirulina Algae* by cryogenic fracturing of the cells followed by extraction, chromatographic purification, and recrystallization. See, e.g., U.S. Pat. No. 5,198,460 and references cited therein. The methyl pheophorbide a obtained in this way was then separately subjected to thermal decarboxylation in collidine at reflux temperature. Following this treatment, the resulting methyl pyropheophorbide a was treated with hexyl alcohol and acid to form the hexyl ether moiety. Finally, the methyl ester was removed by saponification to give HPPH. Thus, four rather laborious steps were required in order to obtain HPPH. This procedure works well in the laboratory scale preparation where the final product is required in small amounts. However, the purification of the intermediates at several stages of the synthesis requires column chromatog-

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raphy. Therefore, there is a need for an alternate synthesis of HPPH suitable for large-scale synthesis.

SUMMARY

Provided herein is a synthetic process for the preparation of hexyloxy pyropheophorbide a and related compounds. The process is suitable for large scale (i.e., multigram to multi-kilogram or more) production of such compounds.

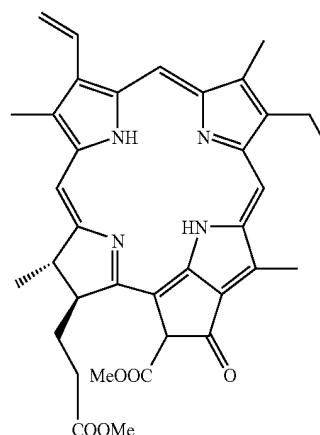
The process provided herein affords the desired product in higher yield and/or purity than known processes. Also, the process provided herein avoids the use of chromatographic purification of intermediates and/or desired product.

DETAILED DESCRIPTION

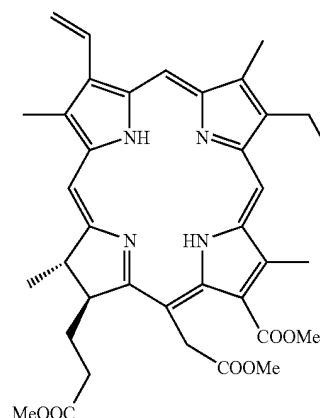
A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, "methyl pheophorbide a" refers to:



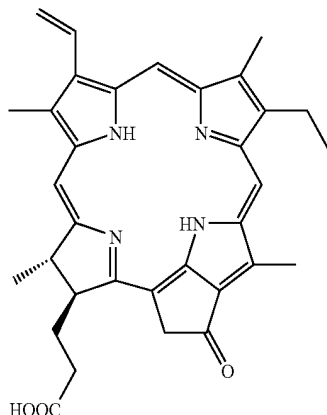
As used herein, "chlorin e6 trimethyl ester" refers to:



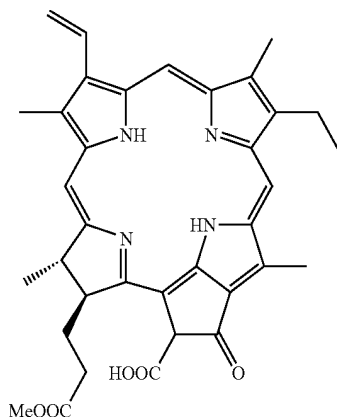
As used herein, an "aromatic solvent" is an organic compound having an aromatic nucleus.

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As used herein, “pyropheophorbide a” refers to:

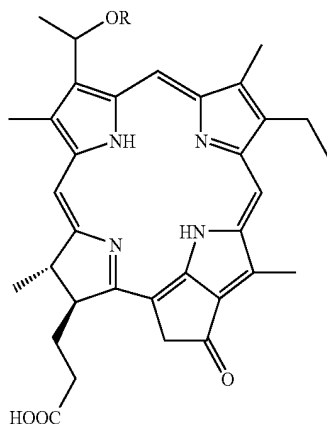


As used herein, a “high boiling aromatic solvent” refers to an aromatic solvent, as defined herein, that has a boiling point high enough to effect decarboxylation of the following compound at reflux:



In certain embodiments herein, the boiling point of a high boiling aromatic solvent is greater than 115° C., 120° C., 125° C., 130° C., 135° C., 140° C., 145° C., 150° C., 155° C., 160° C., 165° C. or 170° C.

As used herein, “ether analogs of pyropheophorbide a” refers to compounds of the general formula:



where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with

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one or more substituents, in one embodiment one to five substituents, in another embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

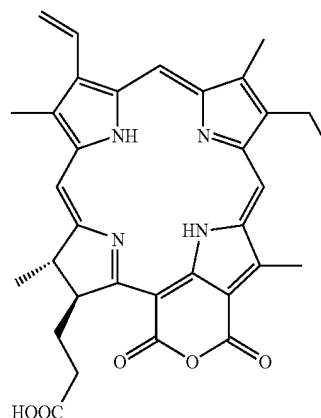
As used herein, “purpurin-18” is:

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As used herein, a “base” is an inorganic or organic compound sufficiently basic to effect a Dieckmann condensation. In certain embodiments, the base is an organic compound. In other embodiments, the base has a pKa of the corresponding protonated form of less than about 15, 10, 8 or 5, relative to water.

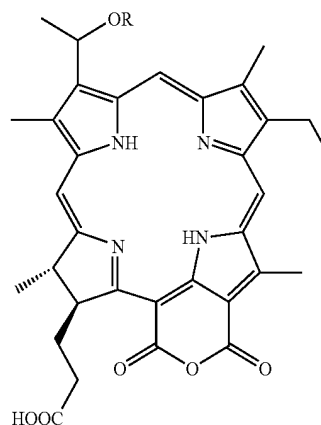
As used herein, “ether analogs of purpurin-18” refers to compounds of the general formula:

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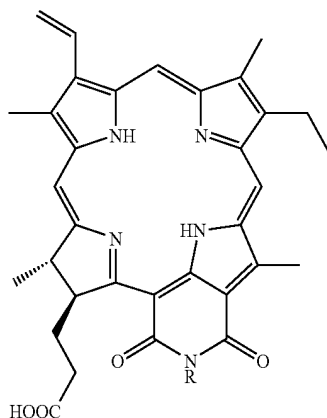
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where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

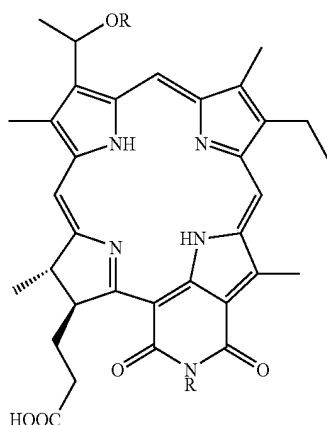
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As used herein, a “purpurinimide” is a compound of the general formula:



where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

As used herein, “ether analogs of purpurinimides” refers to compounds of the general formula:



where R is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

As used herein, an “acid” is an inorganic or organic compound of sufficient acidity to effect addition of an alcohol to a vinyl group. In one embodiment, an acid is an inorganic compound. In another embodiment, an acid has sufficient acidity to effect addition of an alcohol to a vinyl group directly attached to an aromatic porphyrin nucleus.

As used herein, the term “porphyrin” refers to a cyclic structure typically composed of four pyrrole rings, and refers

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to a porphyrin or porphyrin derivative. Such derivatives include porphyrins with extra rings ortho-fused, or ortho-perfused, to the porphyrin nucleus, porphyrins having a replacement of one or more carbon atoms of the porphyrin ring by an atom of another element (skeletal replacement), derivatives having a replacement of a nitrogen atom of the porphyrin ring by an atom of another element (skeletal replacement of nitrogen), derivatives having substituents other than hydrogen located at the peripheral (meso-, β -) or core atoms of the porphyrin, derivatives with saturation of one or more bonds of the porphyrin (hydroporphyrins, e.g., chlorins, bacteriochlorins, isobacteriochlorins, decahydroporphyrins, corphins, pyrrocorphins, etc.), derivatives obtained by coordination of one or more metals to one or more porphyrin atoms (metalloporphyrins), derivatives having one or more atoms, including pyrrolic and pyrromethenyl units, inserted in the porphyrin ring (expanded porphyrins), derivatives having one or more groups removed from the porphyrin ring (contracted porphyrins, e.g., corrin, corrole) and combinations of the foregoing derivatives (e.g. phthalocyanines, porphyrazines, naphthalocyanines, subphthalocyanines, and porphyrin isomers).

As used herein, “chlorin” refers to a class of porphyrin derivatives having a cyclic structure typically composed of four pyrrole rings having one partially saturated pyrrole ring, such as the basic chromophore of chlorophyll.

As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 or 2 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 double bonds and alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, isohexyl, allyl (propenyl) and propargyl (propynyl). As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having from about 1 or about 2 carbons up to about 8 carbons.

As used herein, halogen refers to one of the electronegative elements of group VIIA of the periodic table (fluorine, chlorine, bromine, iodine, astatine).

As used herein, “hydroxy group” generally refers to a hydroxyl group having the formula —OH .

As used herein, “carboxy” generally refers to the radical —C(O)OH .

As used herein, “ester group” generally refers to a substituent of the general formula —C—O—R^1 where R^1 may be either aliphatic or aromatic.

As used herein, “aromatic group” generally refers to a ring structure having cyclic clouds of delocalized π electrons above and below the plane of the molecule, where the π clouds contain $(4n+2)$ π electrons. A further discussion of aromaticity is found in Morrison and Boyd, *Organic Chemistry*, (5th Ed., 1987), Chapter 13, entitled “Aromaticity,” pages 477–497, incorporated herein by reference.

As used herein, “amide group” generally refers to the group —C(O)NRR where each R is independently aliphatic or aromatic.

As used herein, “amine group” has the general formula —NRR , where each R is independently any alkyl or aryl group.

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As used herein, "cycloalkyl" refers to a saturated mono- or multi-cyclic ring system, in certain embodiments of 3 to 20 carbon atoms, in other embodiments of 3 to 10 carbon atoms. The ring systems of the cycloalkyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion.

As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as unsubstituted or substituted fluorenyl, unsubstituted or substituted phenyl, and unsubstituted or substituted naphthyl.

As used herein, "heteroaryl" and "heteroaromatic group" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 20 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, quinolinyl and isoquinolinyl.

As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 20 members, in another embodiment of 4 to 10 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. In embodiments where the heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, acyl, guanidino, or the nitrogen may be quaternized to form an ammonium group where the substituents are selected as above.

As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

As used herein, "heteroaralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, and azide.

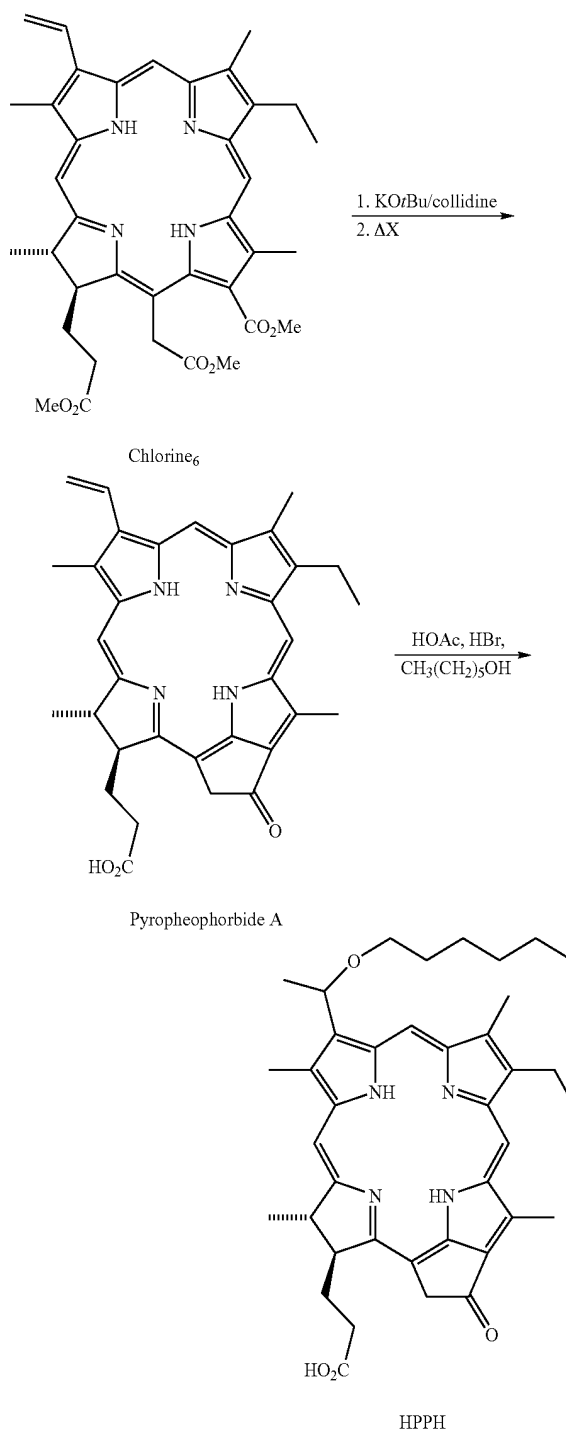
All chemical compounds include both the (+) and (-) stereoisomers, as well as either the (+) or (-) stereoisomer, and also all diastereomers, rotamers and geometric isomers.

B. Process for Preparing Pyropheophorbide a and its Derivatives

The process provided herein, depicted below, avoids a number of shortcomings of the prior art by resorting to another source as the raw material. Chlorin e_6 trimethyl ester undergoes a Dieckmann Condensation to form the additional exocyclic ring, sometimes called an "E-ring", which is present in the pheophorbides, and chlorophyll itself for that matter. See, e.g., Schaefer, J. P.; Bloomfield, J. J. *Org. React.* 1967, 15, 1-203; and Davis, B. R.; Garrett, P. J. *Comp. Org. Syn.* 1991, 2, 806-829. This reaction has traditionally been performed in aromatic solvents, originally benzene, but later

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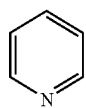
toluene and others for safety reasons. In the case of chlorin e_6 and compounds like it, pyridine has been used for this purpose. See, e.g., Smith, K. M.; Bisset, G. M. F.; Bushell, M. J. *J. Org. Chem.* 1980, 45, 2218-2224. These workers did not use chlorin e_6 itself, but a similar compound in which a methyl group substituent was present at position 5, the δ "meso" position.



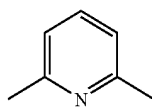
In order to improve the performance of this reaction, the pyridine was replaced with a more substituted analog in order to raise the boiling point of the reaction mixture. Thus, collidine, also called sym-collidine (for symmetrical, see

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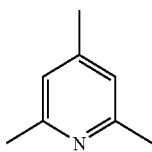
below) or 2,4,6-trimethylpyridine, was used. Other basic aromatic solvents, including but not limited to 2,6-lutidine, could also be used. In this way the temperature of reflux of the reaction mixture is altered—the boiling point of pyridine is 115° C., while that of collidine is 172° C. By raising the temperature of the reaction mixture after completion of the Dieckmann Condensation, it is possible to bring about the subsequent thermal decarboxylation without any intervening purification or unnecessary manipulation of the reaction mixture. As a further benefit, it was found that, under the strongly basic conditions employed to carry out the Dieckmann Condensation, the methyl ester of the pheophorbide system also undergoes cleavage, thus accomplishing three chemical transformations in a single treatment.



Pyridine
Bp 115° C.
pK_a = 5.17



2,6-Lutidine
Bp 144° C.
pK_a = 6.71

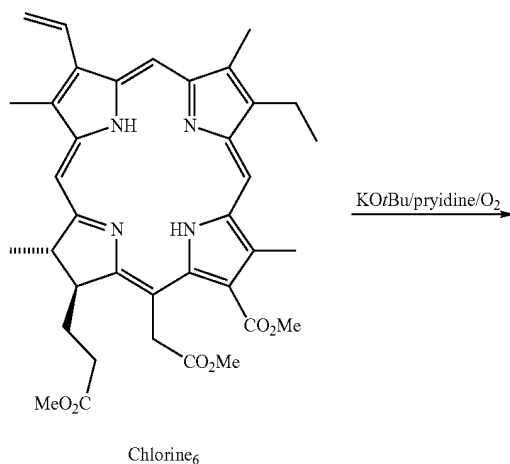


sym-Collidine
Bp 172° C.
pK_a = 7.43

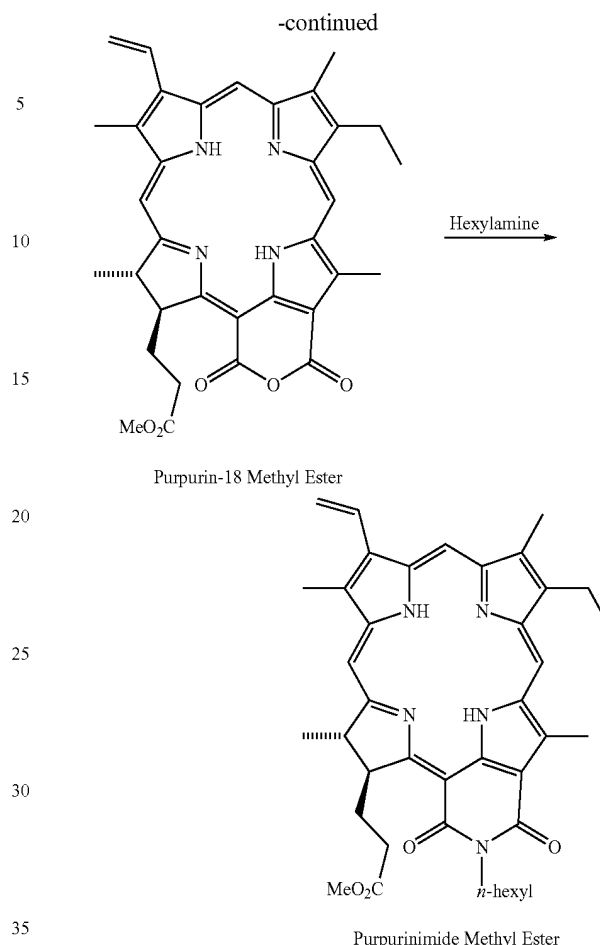
Basic Aromatic Solvents

The pheophorbide a obtained in this way need only be converted to its hexyl ether in order to produce HPPH. This can be done in much the same way as it was done in the older synthesis, giving an overall two-pot preparation of this product.

Since many other compounds can also be obtained from pyropheophorbide a (see below), this new process affords greatly simplified access to all such compounds. These compounds include purpurin-18 and its derivatives, especially the ethers made from the vinyl group in an analogous manner to the hexyl ether in HPPH, and the purpurinimide series. In these examples, one would omit the high temperature treatment and thermal decarboxylation in order to retain the carboxyl group for the construction of the expanded E-ring used in these systems.



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The following examples are included for illustrative purposes only and are not intended to limit the scope of the subject matter claimed herein.

EXAMPLE 1

Preparation of Pyropheophorbide-a

Chlorin e₆ trimethyl ester (350 mg) was dissolved in dry 2,4,6-collidine (30 mL) and then carefully degassed with nitrogen at 50° C. under vacuum. Potassium tert-butoxide (Aldrich, 5.0 mL, 1 M) was added. The initial bright green color immediately turned orange and the reaction mixture was left stirring at room temperature for 20 min. It was then quenched with degassed glacial acetic acid (10 mL). The flask was then connected to a small distillation assembly (condenser, receiving head and a flask), the acetic acid along with a small amount of collidine (5 mL) were removed under high vacuum. The distillation assembly was dismantled and fresh collidine (15 mL) was added. The reaction flask was then connected to a condenser, and the reaction mixture was heated at reflux under nitrogen for 2 hours. The solvent was removed under high vacuum. The residue so obtained was re-dissolved in dichloromethane (100 mL), washed with water (2×100 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent gave pyropheophorbide-a (as carboxylic acid) in 85% yield after crystallization. ¹H NMR (CDCl₃, δ ppm): 9.35 and 9.15 and 8.50 (each s, 1H, meso H); 7.80 (m, 1H, CH=CH₂); 6.25, 6.10 (each d, 1H, CH—CH₂); 5.22 (dd, 2H, —CH₂, exocyclic ring); 4.41 (q, 1H, 18H); 4.28 (d, 1H, 17-H); 3.75 (q, 2H, CH₂CH₃ merged with one of the ring CH₃); 3.62, 3.35 and 3.10 (each s, 3H,

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ring CH₃); 2.80–2.10 (several m, CH₂CH₂CO₂H); 1.80 (d, 3H, 18-CH₃); 1.60 (t, 3H, CH₂CH₃); -1.78 (each s, 1H, NH).

EXAMPLE 2

3-Devinyl-3-(1'-hexyloxy)ethyl-pyropheophorbide-a (HPPH)

Pyropheophorbide-a (100 mg) was taken in a 50 mL round bottom flask and 30% HBr/HOAc (Aldrich, 2.0 mL) was added. The reaction mixture was stirred at room temperature for 2 hour and the solvent was removed under high vacuum (bath temperature was maintained at 30–40° C.). It was re-dissolved in dry dichloromethane (10 mL). Hexanol (2.00 mL), potassium carbonate (200 mg) were added, and the reaction mixture was stirred at room temperature for 45 min under nitrogen atmosphere. It was poured in water (100 mL), extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue that was crystallized from dichloromethane/hexane in 71% yield; ¹H NMR (CDCl₃, δ ppm): 9.77 and 9.52 (s, 1H, meso-H); 5.90 [q, 1H, CH(o-hexyl)-CH₃]; 5.22 (dd, 2H, 2H, exocyclic ring); 4.41 (q, 1H, 18H); 4.28 (d, 1H, 17-H); 3.75 (q, 2H, CH₂CH₃); 3.62, 3.25 and 3.20 (each s, 3H, ring CH₃); 2.10 (3H, CHCH₃); 1.80 (d, 3H, 18-CH₃); 1.75 (t, 3H, CH₂CH₃); 2.75–2.12 (several m, CH₂CH₂CO₂H); 0.76–1.30 [several m, 10H, (CH₂)₅] 0.43 and -1.78 (each s, 1H, NH). Mass calculated for: C₃₉H₄₈N₄O₄: 636. Found: 637 (M+1).

EXAMPLE 3

Preparation of Purpurin-18 methyl ester

Chlorin e₆ trimethyl ester (175 mg) was dissolved in pyridine (15 mL) and the reaction temperature was maintained at 50° C. A slow stream of air was passed through the solution and potassium tert-butoxide (Aldrich, 2.5 mL, 1.0 M) was added. The reaction mixture was stirred at room temperature for 20 min. It was quenched with glacial acetic acid (5 mL), poured in water, extracted with dichloromethane (2×100 mL). The dichloromethane layer was washed with 2 M HCl (50 mL), then washed with water again. The organic layer was separated and dried over anhydrous sodium sulfate. The residue obtained after evaporating the solvent was re-dissolved in dichloromethane, treated with diazomethane, purified by silica column chromatography, eluting with 2% acetone in dichloromethane and crystallized from dichloromethane/hexane. Yield 80%; ¹H NMR (CDCl₃, δ ppm): 9.60, 9.35 and 8.60 (each s, 1H, meso-H); 7.90 (m, 1H, CH=CH₂); 6.30 and 6.20 (each d, 1H, CH=CH₂); 5.12 (d, 1H, 17-H); 4.40 (q, 1H, 18-H); 3.75 (s, 3H, CO₂CH₃); 3.65 (q, 2H, —CH₂CH₃); 3.60, 3.30 and 3.15 (each s, 3H, ring CH₃); 2.80–1.90 (several m, —CH₂CH₂CO₂CH₃); 1.75 (d, 3H, 18-CH₃); 1.60 (t, 3H, —CH₂CH₃); 0.20 and -0.90 (each br s, 1H, NH).

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

What is claimed is:

1. A process for the preparation of methyl pheophorbide-a, comprising treating chlorin e₆ trimethyl ester with a base in an aromatic solvent having a boiling point at least as high as 144° C., the boiling point of 2,6-lutidine.

2. A process for the preparation of methyl pheophorbide-a, comprising:

(a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent having a boiling point at least as high

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as 144° C., the boiling point of 2,6-lutidine to give methyl pheophorbide-a; and

(b) without isolating the methyl pheophorbide-a from the resulting reaction mixture, heating the methyl pheophorbide-a to a temperature sufficient to effect decarboxylation and saponification of the methyl pheophorbide-a.

3. A process for the preparation of ether analogs of pyropheophorbide-a comprising:

(a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent having a boiling point at least as high as 144° C., the boiling point of 2,6-lutidine to give methyl pheophorbide-a;

(b) without isolating the methyl pheophorbide-a from the resulting reaction mixture, heating the methyl pheophorbide-a to a temperature sufficient to effect decarboxylation and saponification of the methyl pheophorbide-a to give pheophorbide-a; and

(c) treating the pyropheophorbide-a with an acid, followed by an alcohol under basic conditions to effect addition of the alcohol across a vinyl group.

4. The process of claim 3, wherein the alcohol is 1-hexanol (n-hexyl alcohol) to obtain 3-devinyl-3-(hexyloxy)ethyl-pyropheophorbide-a (HPPH).

5. A process for the preparation of purpurin-18, comprising:

(a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent in the presence of air to give purpurin-18 having a —CH₂CH₂COOH group.

6. A process for the preparation of purpurinimides, comprising:

(a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent in the presence of air to give purpurin-18 having a —CH₂CH₂COOH group;

(b) esterifying the —CH₂CH₂COOH group to obtain purpurin-18 ester; and

(c) treating the esterified purpurin-18 with a primary amine.

7. A process for the preparation of ether analogs of purpurinimides, comprising:

(a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent in the presence of air to give purpurin-18 having a —CH₂CH₂COOH group;

(b) esterifying the —CH₂CH₂COOH group to obtain purpurin-18 ester;

(c) treating the esterified purpurin-18 ester with a primary amine; and

(d) treating the resulting purpurinimide with an acid, followed by an alcohol under basic conditions.

8. A process for the preparation of purpurin-18 ester, comprising:

(a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent in the presence of air to give purpurin-18 having a —CH₂CH₂COOH group; and

(b) esterifying the —CH₂CH₂COOH group.

9. A process for the preparation of ether analogs of purpurin-18, comprising:

treating the esterified purpurin-18 obtained by the steps of claim 8 with an acid, followed by treating with an alcohol under basic conditions.

10. The method of claim 8 where the group is esterified using diazomethane to obtain purpurin 18 methyl ester.

11. The method of claim 2 where the aromatic solvent is sym-collidine.