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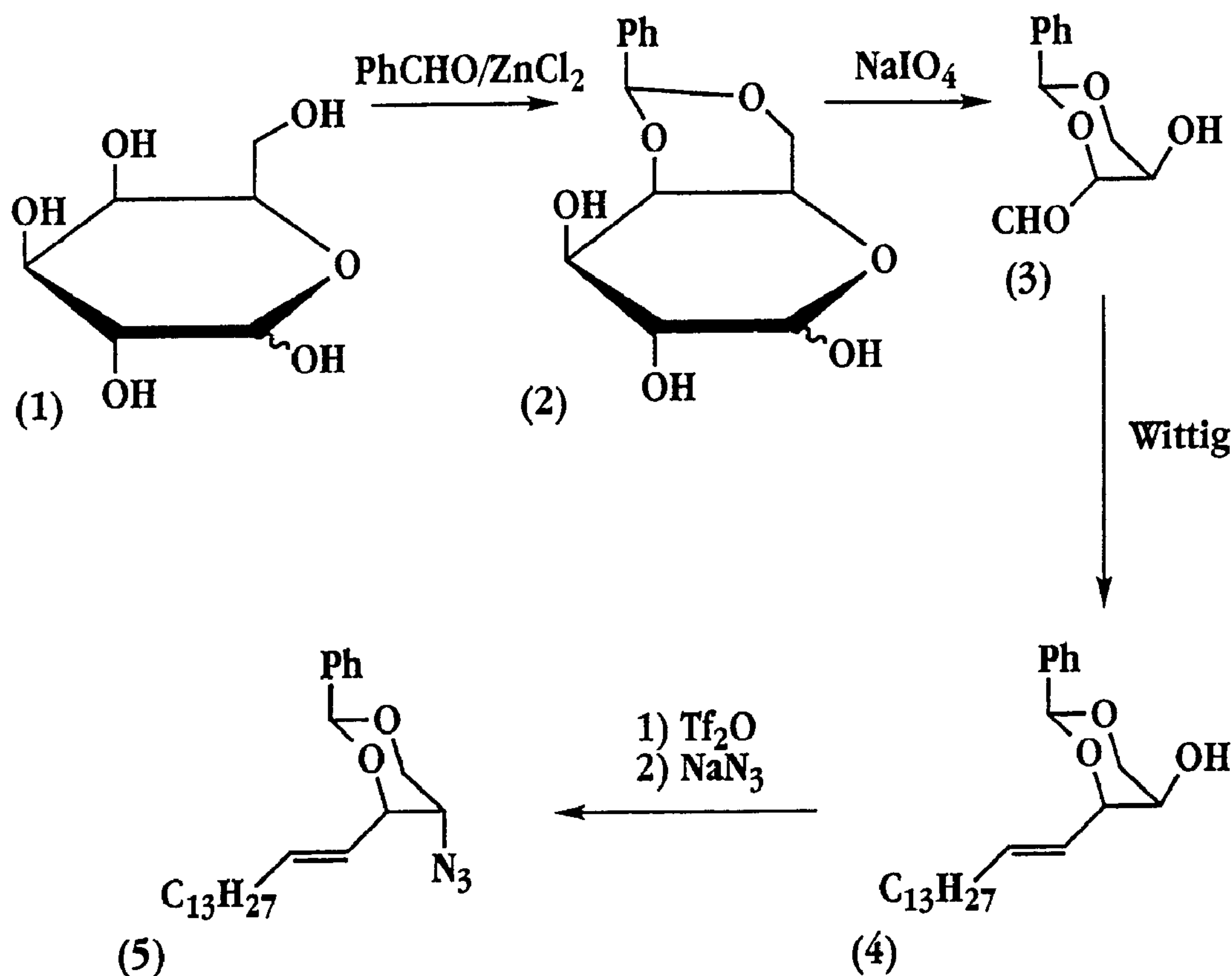
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(54) Titre : PROCÉDE DE PREPARATION A GRANDE ECHELLE DE SPHINGOSINES ET DE CERAMIDES

(54) Title: PROCESS FOR LARGE SCALE PREPARATION OF SPHINGOSINES AND CERAMIDES



(57) Abrégé/Abstract:

Synthetic methods for convenient large scale preparation of D-erythro sphingosines and ceramides of high isomeric purity are described.



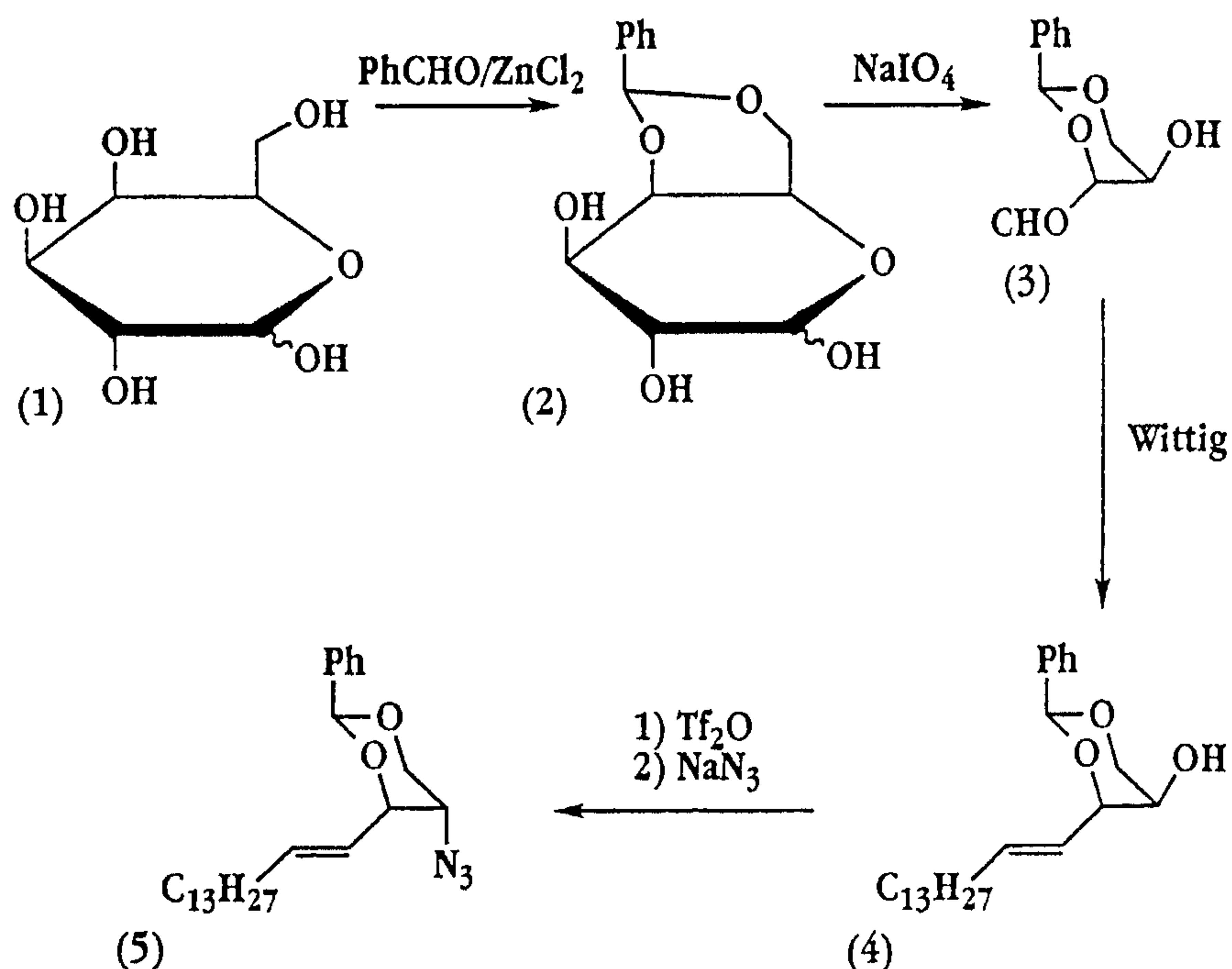
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(21) International Application Number: PCT/IL00/00264 (22) International Filing Date: 9 May 2000 (09.05.00) (30) Priority Data: 60/133,526 10 May 1999 (10.05.99) US (71) Applicant: LIPIDERM LTD. [IL/IL]; Atarot Industrial Zone, P.O. Box 34048, 91340 Jerusalem (IL). (72) Inventor: ROCHLIN, Elimelech; Moshav Zanoach 67, D.N., 99888 Shimshon (IL). (74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL).		(81) Designated States: AU, CA, IL, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>

(54) Title: PROCESS FOR LARGE SCALE PREPARATION OF SPHINGOSINES AND CERAMIDES



(57) Abstract

Synthetic methods for convenient large scale preparation of D-erythro sphingosines and ceramides of high isomeric purity are described.

Process for Large Scale Preparation of Sphingosines and Ceramides**Field of the Invention**

The present invention relates to synthetic methods for the preparation of D-erythro
5 sphingosines and ceramides of high isomeric purity, and in particular to methods suitable for large
scale production.

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20 **Background of the Invention**

Sphingosines constitute a group of related long-chain aliphatic 2-amino-1,3-diols, of which D-
erythro-1,3-dihydroxy-2-amino-4,5-trans-octadecene is the most frequently occurring in animal
tissues. N-acylsphingosines are also referred to as ceramides. Sphingosines, ceramides, and their
glycosides, glycosphingolipids, are of great interest because of their diverse bioactivities and
25 biological roles. These activities include inhibition of protein kinase C activity and transfer of
information between developing vertebrate cells. Sphingosines also serve as chain terminators in
various gangliosides. Galactosyl ceramide has been shown to be a receptor for HIV binding in cells
lacking the CD4 receptor.

Skin ceramides are also believed to play an important role in the water permeability properties
30 of the skin, providing an epidermal water barrier which strengthens the skin structure and reduces
water loss. Ceramides and synthetic analogs have thus been used as components of skin care
compositions, and have been found effective in restoring the water content of dry skin and in
relieving atopic eczema (Kerscher *et al.*; Imokawa *et al.*).

These compounds have proven difficult to extract from natural sources, where they are present
35 in low concentrations. Chemical synthetic methods reported to date have generally been laborious
and expensive. Several reported methods of synthesizing optically pure sphingosines and their

derivatives rely on the use of serine as a chiral building block. See, for example, Polt *et al.*, Herold, and U.S. Patent No. 5,110,987. However, methods utilizing serine as a starting material are quite lengthy and thus are not amenable to potential scale-up. Other synthetic approaches to the preparation of isomerically pure sphingosines and ceramides have employed other chiral starting materials, such as carbohydrates, L-glyceric and D-tartaric acids, and/or asymmetric reactions. Although successful as gram-scale procedures, these strategies generally fail or become prohibitively expensive when applied to kilogram scale processes. Enzymatic methods of synthesis have also been described but are often unpredictable, giving varying results depending on medium or the particular enzyme preparation.

Accordingly, a reliable, convenient and versatile method of large scale preparation of these compounds is desirable.

Summary of the Invention

The present invention includes, in one aspect, a convenient process for the large scale preparation of sphingosine, a sphingosine analog, or a ceramide. The process comprises the following series of steps. A stirred slurry of benzaldehyde and a Lewis acid, preferably ZnCl_2 , is formed and contacted with D-galactose, with continued stirring. The resulting mixture is filtered to obtain a solid precipitate and a filtrate. The filtrate is then diluted with a mixture of diethyl ether and a hydrocarbon solvent, preferably a paraffinic solvent such as hexane, ligroin, or, more preferably, petroleum ether, typically in approximately equal proportions. The resulting mixture is extracted with cold water to provide an aqueous extract, which is treated with a base, such as an alkaline or alkaline earth carbonate or bicarbonate, to produce a precipitate of zinc salts. This precipitate is removed to provide an aqueous solution of 4,6-O-benzylidene-D-galactose. Alternatively, the zinc cation may be removed by treatment with an ion exchange resin. The resulting solution is then treated, preferably without isolation, with an oxidizing agent, preferably sodium periodate, which oxidatively cleaves the 4,6-O-benzylidene-D-galactose, to produce the protected hydroxy aldehyde, 2,4-O-benzylidene-D-threose. This compound is then contacted with a Wittig reagent, i.e. $(\text{Ar})_2\text{P}=\text{CHR}$, where Ar is aryl and R is a C_4 - C_{26} branched or unbranched alkyl or alkenyl chain, to produce a hydroxy olefin. Ar is typically phenyl but may also include alkyl substituted phenyl or naphthyl. The resulting compound is then reacted with a triflating agent, such as trifluoromethylsulfonic anhydride, followed by sodium azide, followed by a hydride reducing agent, such as LiAlH_4 or NaBH_4 , to produce an amino olefin. Finally, this compound is deprotected (i.e. the benzylidene group is removed) by contacting it with an acidic ion exchange resin, to produce sphingosine (where R is $\text{n-C}_{13}\text{H}_{27}$, tridecyl) or a sphingosine analog (where R is a longer or shorter alkyl chain, e.g. C_4 - C_{12} or C_{14} - C_{26}).

Alternatively, for the production of ceramides, the amino olefin is acylated, by treating with a

C₂ – C₂₆ acylating agent, such as an acyl halide, anhydride, or carboxylic acid, in the presence of any necessary acylating catalyst, prior to the deprotection step.

The invention also provides convenient large scale processes for the production of two of the intermediates, i.e. 4,6-O-benzylidene-D-galactose and 2,4-O-benzylidene-D-threose, by carrying out
5 the process described above up to the oxidative cleavage step, or through the oxidative cleavage step, respectively. D-threose may also be obtained in large quantities by deprotection of the intermediate, 2,4-O-benzylidene-D-threose.

These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying
10 drawings.

Brief Description of the Drawings

Figure 1 shows a synthetic scheme for the large scale preparation of 1,3-O-benzylidene-2-azido-(D-erythro-sphingosine) (5) from D-galactose (1);

15 Figure 2 shows a synthetic scheme for the large scale preparation of sphingosine (7), dihydrosphingosine (14), and a ceramide (9) from the intermediate (5); and

Figure 3 shows a synthetic scheme for the large scale preparation of N-alkylated sphingosines.

Detailed Description of the Invention

20 The process described herein, suitable for large scale production of sphingosines and ceramides, is based in part on the preparation of 1,3-O-benzylidene-2-azido-(D-erythro-sphingosine) (5) from D-galactose (1) as reported by Schmidt and Zimmerman (1986, 1988, 1990) and the sphingosine and ceramide preparations reported by Kiso *et al.* (1986). However, the present process incorporates significant modifications, resulting in substantial reductions in expenditure of
25 time and labor. As used herein, "large scale" refers to kilogram, preferably multikilogram, quantities. The term "sphingosines" includes sphingosine itself and analogs which have the basic structure of sphingosine but vary in the length of the fatty alkyl chain.

As shown in Figures 1-3, the process may be used for the production of derivatives such as dihydrosphingosines, N,N-dimethyl- and N,N,N-trimethyl sphingosines, and ceramides having fatty
30 acid components of various lengths. The process can also be modified for the preparation of phospho- and glycosphingolipids. The individual steps of the process will now be described.

A. Benzylidenation of D-galactose

The procedure followed by Schmidt and Zimmerman is based on that reported by Gros and
35 Deulofeu (1964). The product, 4,6-O-benzylidene-D-galactose (BG) (2), was isolated from a reaction mixture initially containing benzaldehyde, ZnCl₂, D-galactose, and 1,2,3,4-O-

digenzylidene-D-galactose. The product was isolated by a time- and labor-intensive procedure which included the following steps:

1. Decomposition of the reaction mixture in water,
2. Slow (overnight) separation of organic and aqueous phases at 5°C,
- 5 3. Washing of the organic phase with water,
4. Neutralization and ZnCO_3 precipitation from the combined aqueous solution,
5. Filtration of ZnCO_3 and washing of the filter with additional water,
6. Evaporation of the resulting aqueous solution to dryness *in vacuo* at ~40-45°C,
7. Extraction of the solid residue with boiling ethyl acetate to separate the 4,6-O-benzylidene
10 galactose (BG) from unreacted galactose and salts, and
8. Concentration of resulting ethyl acetate solution and crystallization of BG (2).

Stages of this procedure which are likely to be problematic for scaleup include the extended phase separation (step 2), during which the product is exposed to low pH, the extended evaporation
15 (step 6), and the prolonged extraction of the solid residue with hot ethyl acetate (step 7). The quality of extraction can depend very much on the purity of the ethyl acetate. In some cases, the prolonged hot ethyl acetate exposure causes caramelization of galactose-BG-salt mixture and prevents complete extraction of the product.

In accordance with the present invention, the procedure was modified to overcome these
20 problems, based in part on the following observations made by the inventors:

(1.) The undissolved residue remaining in the reaction mixture following the benzylidenation is not ZnCl_2 as previously reported (Gros and Deulofeu), but unreacted D-galactose. When this residue is filtered off, no D-galactose is detected by TLC in the reaction mixture. Therefore, the unreacted D-galactose can be separated from the product by simple filtration of the reaction mixture
25 prior to its decomposition by water, rather than by later extraction of the product with a hot solvent.

(2.) The phase separation after decomposition of the reaction mixture by water is accelerated by addition of an ether/hydrocarbon (preferably ether/petroleum ether) mixture.

(3.) After the aqueous phase is neutralized by K_2CO_3 or (Na_2CO_3) , and ZnCO_3 is filtered off (or, alternatively, Zn^{2+} cations are removed by ion-exchange resin IRC-50S), an aqueous solution
30 of BG and salts (KCl or NaCl) is obtained. This aqueous solution is suitable for the further oxidation by NaIO_4 ; it is not necessary to isolate the product (4,6-O-benzylidene-D-galactose).

An exemplary embodiment of this procedure is described in detail in Example 1, below. The process has also been carried out successfully using p-methoxybenzaldehyde in place of benzaldehyde.
35

B. Oxidative Cleavage of (2)

In the procedure of Schmidt and Zimmerman, isolated (2) was oxidized in aqueous or aqueous methanolic solution by addition of solid NaIO_4 in the presence of phosphate buffer ($\text{pH} = 7.0-7.6$).

The product, 2,4-O-benzylidene-D-threose (3), was isolated by evaporation of the resulting aqueous solution to dryness and extraction of the solid residue with THF, a very prolonged operation.

5 As stated above, in the present procedure, the aqueous solution of (2) from the previous step is oxidized directly, without isolation of (2). The solution thus obtained is concentrated to about one third of its initial volume and then extracted with dichloromethane (CH_2Cl_2). Other organic solvents such as n-butanol or methyl ethyl ketone may also be used. The organic solution is rapidly dried by filtering through a short silica/ MgSO_4 (or silica/ Na_2SO_4) column. Evaporation of the
10 solvent gave pure (3) as a white fragile foam that was easily broken up to a fine powder.

An alternative and possibly more convenient method of isolating (3) from the reaction mixture employs salting out with Na_2SO_4 (rather than concentrating the solution) and then extracting with an organic solvent. This method would avoid prolonged concentration of the aqueous solution of (3), but larger amounts of solvent would be necessary in this case due to the high solubility of (3) even
15 in concentrated brines.

An exemplary embodiment of the oxidation procedure is described in Example 2, below.

C. Wittig Alkenation of (3); Preparation of Azide (5)

For these steps, conventional procedures, such as described by Schmidt and Zimmerman, were
20 generally suitable for kilogram scale reaction. The Wittig reaction gave a high *trans* selectivity (approx. 97% by NMR) and yielded about 4 kg of olefin (4) from 4 kg of (3). Wittig reagents having alkyl components of different lengths may be used to prepare various sphingosine analogs.

The triflation and azidolysis reactions were carried out according to known methods, giving
25 1,3-O-benzylidene-azidosphingosine (5).

D. Deprotection Reactions

Schmidt *et al.* used azidosphingosine, prepared by HCl- or pTsOH-catalyzed deprotection of (5), as a key intermediate in the synthesis of sphingosine, ceramides, and other sphingolipids. These deprotection conditions, however, present disadvantages which become more pronounced in
30 medium (ca. 50 g) to large scale (1 kg or more) production. The deprotection is incomplete even after extended reaction (12-78 hours) at room temperature, and the reaction mixture contains an appreciable amount of starting material and by-products. Heating the CH_2Cl_2 /MeOH medium or employing THF/HCl leads to degradation of the product. (Although Schmidt *et al.*, 1986, reported that the method was "also successful in larger scale preparations", this observation referred to a
35 20g scale synthesis.)

In addition, use of sphingosine (7) as a starting material in ceramide synthesis generally

requires protection of the OH groups or, alternatively, use of more selective and accordingly more expensive acylating agents. Otherwise, partial acylation of the OH groups occurs, requiring time consuming purification procedures.

For these reasons, 1,3-O-benzylidene sphingosine (6), prepared by reduction of (5) prior to
5 deprotection, was used as the key intermediate in the present process (Figs. 2 and 3). It was synthesized by NaBH₄ reduction of (5) in refluxing isopropanol (Fig. 2), as described in Example 3, below, or alternatively, by LiAlH₄ reduction in ether at room temperature. This product was then used for the synthesis of D-erythro-sphingosine (7), ceramides (9), D-erythro-dihydrosphingosine (14), N,N-dimethylsphingosine (11), and N,N,N-trimethylsphingosine (13) (Figs. 2 and 3).

10 The procedure used for deprotection (Figs. 2 and 3) differed from that of Kiso *et al*, who used isopropylidene, rather than benzylidene, derivatives. Benzylidene derivatives give substantially better E/Z selectivity in Wittig alkenation than isopropenylidene derivatives. However, benzylidene deprotection under the conditions used by Kiso (acetic acid with small amounts of water) progresses very slowly at 5-50°C. At higher temperatures (60-80°C), the rate is still unsatisfactory and
15 formation of by-products occurs.

Accordingly, more suitable procedures for deprotection of benzylidene derivatives (6), (8), (10), and (12), using ion exchange resins, were used for the present processes. Exemplary procedures, for conversion of (6) to sphingosine (7), and for deprotection of 1,3-O-benzylidene ceramides (8), are described below in Examples 4 and 5.

20 Figure 3 illustrates the N-alkylation of (6), followed by deprotection, to give N,N-dimethyl sphingosine (11) and the N,N,N-trimethyl ammonium salt (13). The alkylations were carried out using formaldehyde/sodium cyanoborohydride and dimethylsulfate/sodium bicarbonate, respectively. Preferably, alkylation is carried out prior to deprotection. As shown in Figure 2, catalytic hydrogenation of D-erythro sphingosine (7) gave D-erythro dihydrosphingosine (14); this
25 reaction may be carried out before or after deprotection. All of the reactions illustrated in Figures 2-3 have been carried out successfully on a large scale.

The following examples illustrate but are not intended in any way to limit the invention.

EXAMPLES

30 Example 1. Preparation of 4,6-O-benzylidene-D-galactose (2) (BG)

A portion of ZnCl₂ (23 kg, 171 mol) was placed into a reactor, taking measures to exclude moisture. Benzaldehyde (70L, 680 mol) was poured into the reactor, and the mixture was stirred for about 30 minutes using a powerful mechanical stirrer. After initial dissolution of zinc chloride, a thick slurry of a benzaldehyde-ZnCl₂ complex forms. Anhydrous D-galactose (30 kg, 164 mol)
35 and more benzaldehyde (60L, 570 mol) were added to the warm slurry, and the mixture was allowed to react at RT for 24 hours with vigorous stirring. The precipitate was filtered off and

washed portionwise with benzaldehyde (10-15L total) and then with acetone, to give, after air-drying, 6-7 kg of unreacted D-galactose, probably as the monohydrate. The combined filtrate and benzaldehyde washings were diluted with ether and petroleum ether, and the mixture was extracted with ice-cold water. The organic layer was washed 3 times with ice water, and the combined aqueous layers were neutralized by rapid addition of a solution of potassium carbonate. The resulting thick suspension of zinc salts was filtered, and the precipitate was washed thoroughly with water until 500-600 L of filtrate were collected. After extraction with chloroform (70L) and with petroleum ether (70L), the filtrate, containing 4,6-O-benzylidene-D-galactose (2) and a mixture of KCl and KHCO_3 , and having a pH of about 8.7, was used directly for the following oxidation.

Example 2. Preparation of 2,4-O-benzylidene-D-threose (3)

The solution from Example 1 was placed into a reactor and buffered with a mixture of K_2HPO_4 trihydrate (11 kg) and KH_2PO_4 (4.5 kg). Sodium periodate (about 39 kg) was introduced into the solution by portions (approximately 0.5 kg) during 5-6 hours with vigorous stirring, maintaining the pH within 7.0-7.5 by periodic addition of 20% aq. KOH. During the addition, the temperature was kept at 20-25°C by external cooling.

The reaction suspension was concentrated *in vacuo* to approximately 150L. Dichloromethane (160L) was added, and the precipitate of inorganic salts was filtered off and washed thoroughly with CH_2Cl_2 (additional 70L). The two-phase filtrate was allowed to separate, and the lower layer (CH_2Cl_2 solution of (3)) was passed through a column (D = 30 cm) filled with dry MgSO_4 (10 cm column), followed by silica gel (30 cm) and another layer of MgSO_4 (10 cm). The aqueous layer was extracted 3 times with 70L portions of dichloromethane, and the extract was passed through the same column. The column was then eluted with 115 L chloroform to wash residual (3) from the silica gel. The combined eluates were concentrated *in vacuo* to a syrup and diluted with benzene to approximately 90 L. The solution was immediately dried *in vacuo* to give a solid foam. Yields of 2,4-O-benzylidene-D-threose (3) ranged from 12.5 kg to 13.6 kg (about 36-39% from D-galactose).

Example 3. Reduction of 1,3-O-benzylidene azidosphingosine (5)

Azido derivative (5) (100g, 0.25 mol) was reduced using 19 g (0.5 mol) NaBH_4 in 1L of refluxing 2-propanol. The reaction mixture was worked up in the usual manner, filtered, and evaporated to dryness under reduced pressure. The solid residue was extracted with 3×500 ml of boiling petroleum ether (60-80°) or hexane, and the combined extracts were filtered and evaporated. The solid residue was recrystallized from EtOH/ H_2O to give 70 g (75%) of derivative (6): mp 51-52° C; $[\alpha]_D +38.4^\circ$ (c = 0.6, CHCl_3).

Example 4. Deprotection of 1,3-O-benzylidene-D-erythro-sphingosine (6)

A 50 g portion (0.129 mole) of 1,3-O-benzylidene-D-erythro-sphingosine (6) was dissolved in 1.5 L of 90% MeOH and passed through a column filled with an excess of a strongly acidic ion exchange resin. The column was then slowly eluted with 90% MeOH to elute benzaldehyde. The reaction is usually complete within 20-30 minutes at room temperature. The final product was then
5 eluted with alkalized methanol, and dichloromethane and water were added to the eluate to give a two-phase mixture. The organic (lower) phase was separated, dried over Na_2SO_4 , and evaporated to give ~ 36 g (94%) of 97-98% pure D-erythro-sphingosine, mp 73-76°C; ^1H NMR spectrum in accordance with literature.

This process was also successfully applied to sphingosine analogs, and at a 5 kg scale, without
10 any substantial deviations from the described procedure.

Example 5. Preparation and deprotection of 1,3-O-benzylidene-ceramides (8) with different fatty acid chains

Acylation of 1,3-O-benzylidene-D-erythro-sphingosine (6) was carried out using a variety of
15 carboxylic acids (C_2 - C_{26}), catalyzed by DCC, in CH_2Cl_2 , or acid chlorides in CH_2Cl_2 , according to known procedures. Yields of acyl derivatives (8) were 92-98%.

Protected ceramide (8) (~ 0.1 mol) was dissolved in 1.5-3.0 L (depending on the solubility of the ceramide) acetic acid at 60-70°C. Then ~ 200 g of strongly acidic ion exchange resin were added with stirring, followed by aqueous MeOH. The reaction mixture was stirred at 60-70°C until
20 deprotection was complete by TLC and filtered. The filter was washed with hot acetic acid, and the combined filtrate was allowed to stand overnight at 0-4°C. The precipitate was filtered off, washed with 200 mL cold acetic acid, 1.5-2.0 L water, 500 mL satd. NaHCO_3 , and 1-1.5 L water. After lyophilization, 70-85% yield of ~95% pure material was obtained. For higher purity, the precipitate was dissolved (without lyophilization) in CHCl_3 or CH_2Cl_2 , dried with Na_2SO_4 and
25 purified by column chromatography (1-5% MeOH/ CH_2Cl_2), giving >99% pure ceramide (9).

Example 6. Preparation of D-erythro-dihydrosphingosine

A 0.67 mole portion of sphingosine or a sphingosine analog, prepared by the above methods, was dissolved in 3 L of absolute methanol, and 10 g of 5% Pd/C were added. Hydrogenation was
30 carried out at room temperature under 1 atm pressure of H_2 . The reaction mixture was filtered and concentrated by evaporation, and the residue was recrystallized from n-hexane, giving the product in 80-86% yield with 96-98% purity.

While the invention has been described with reference to specific methods and embodiments, it
35 will be appreciated that various modifications may be made without departing from the invention.

CLAIMS:

1. A process for the large scale preparation of sphingosine, a sphingosine analog, or a ceramide, comprising the steps of:

forming a stirred slurry of benzaldehyde and ZnCl_2 ,
 contacting the stirred slurry with D-galactose,
 filtering the resulting mixture to obtain a solid precipitate and a filtrate,
 diluting the filtrate with diethyl ether and a hydrocarbon solvent,
 extracting the resulting mixture with cold water to provide an aqueous extract,
 removing Zn^{+2} from the aqueous extract by treatment with base or an ion exchange resin, to provide an aqueous solution of 4,6-O-benzylidene-D-galactose,
 treating the solution with an oxidizing agent effective to oxidatively cleave said galactose, to produce a protected hydroxy aldehyde,
 contacting the protected hydroxy aldehyde with a reagent of the form $(\text{Ar})_2\text{P}=\text{CHR}$, where Ar is aryl and R is a $\text{C}_4\text{-C}_{26}$ alkyl chain, to produce a hydroxy olefin,
 reacting the hydroxy olefin with a triflating agent, followed by sodium azide, followed by a hydride reducing agent, to produce an amino olefin,
 acylating the amino olefin, and optionally
 deprotecting the amino olefin by contacting the amino olefin with an acidic ion exchange resin, to produce sphingosine or a sphingosine analog.

2. The process of claim 1, wherein said acylating employs a $\text{C}_2\text{-C}_{26}$ acylating agent.

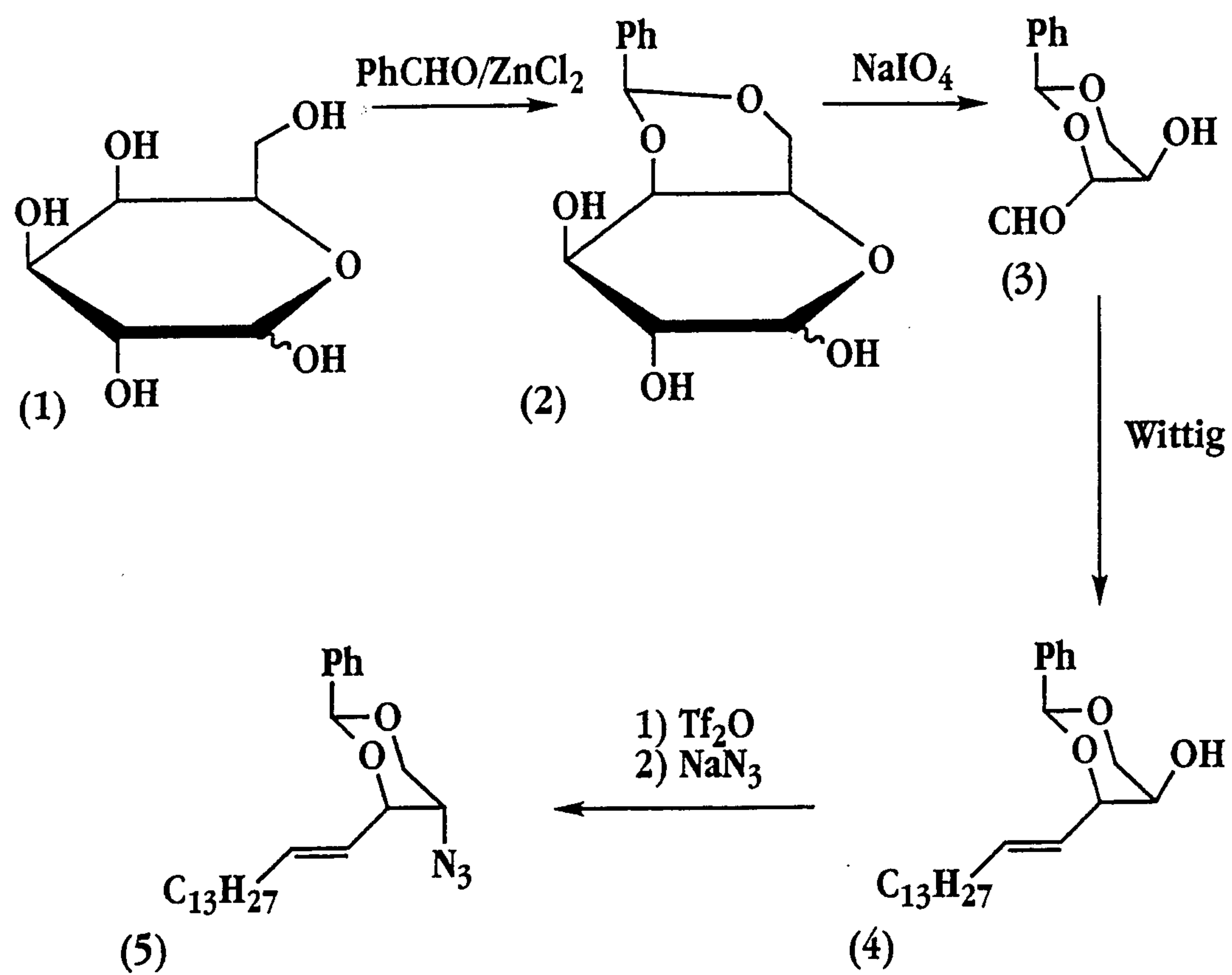
3. A process for the large scale preparation of 4,6-O-benzylidene-D-galactose, comprising the steps of:

forming a stirred slurry of benzaldehyde and ZnCl_2 ,
 contacting the stirred slurry with D-galactose,
 filtering the resulting mixture to obtain a solid precipitate and a filtrate,
 diluting the filtrate with diethyl ether and a hydrocarbon solvent,
 extracting the resulting mixture with cold water to provide an aqueous extract, and removing Zn^{+2} from the aqueous extract by treatment with base or an ion exchange resin, to provide an aqueous solution of 4,6-O-benzylidene-D-galactose.

4. A process for the large scale preparation of 2,4-O-benzylidene-D-threose, comprising the steps of:

- forming a stirred slurry of benzaldehyde and ZnCl_2 ,
- contacting the stirred slurry with D-galactose,
- filtering the resulting mixture to obtain a solid precipitate and a filtrate,
- diluting the filtrate with diethyl ether and a hydrocarbon solvent,
- extracting the resulting mixture with cold water to provide an aqueous extract,
- removing Zn^{+2} from the aqueous extract by treatment with base or an ion exchange resin, to provide an aqueous solution of 4,6-O-benzylidene-D-galactose, and
- treating the solution with an oxidizing agent effective to oxidatively cleave said galactose.

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**Fig. 1**

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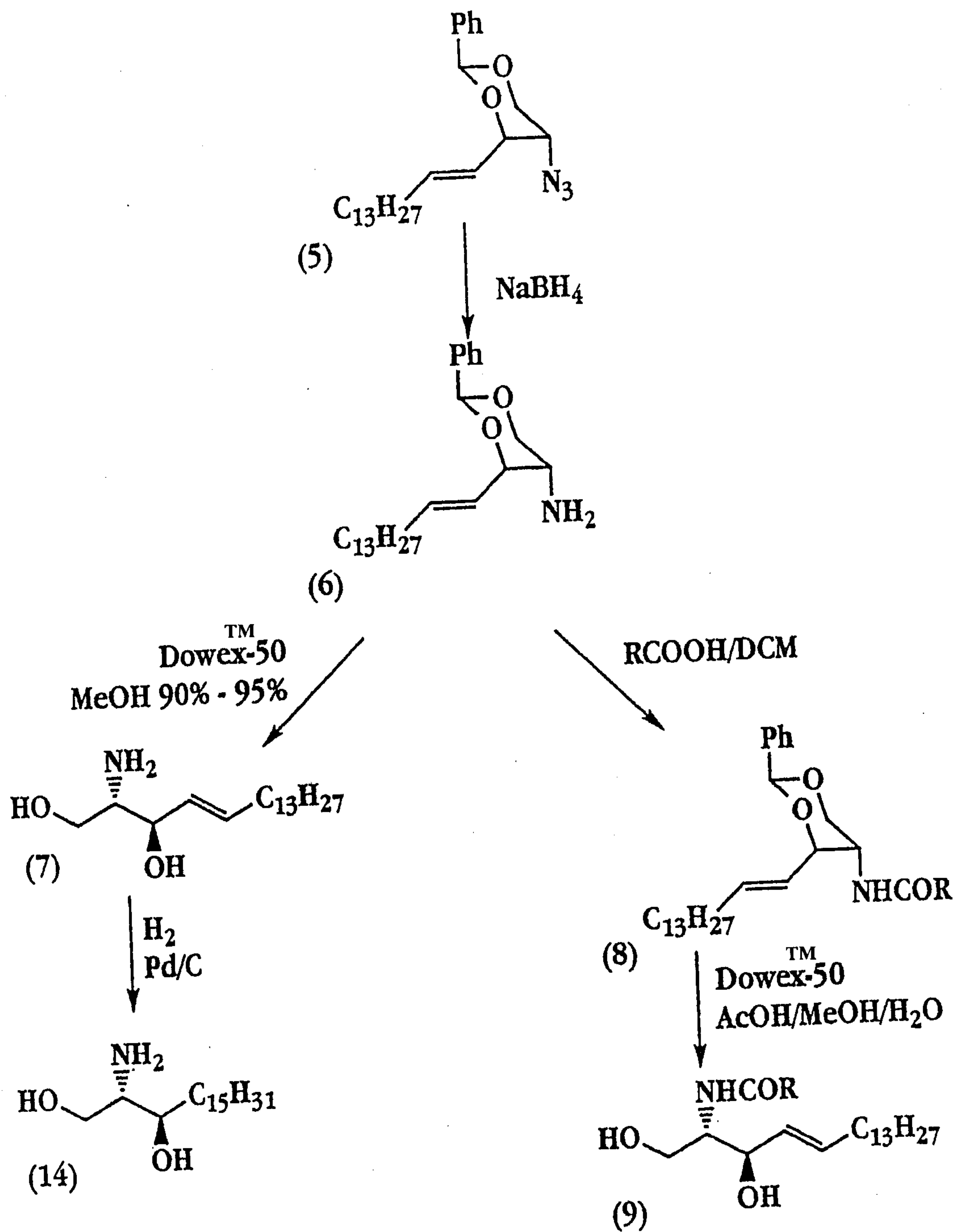


Fig. 2

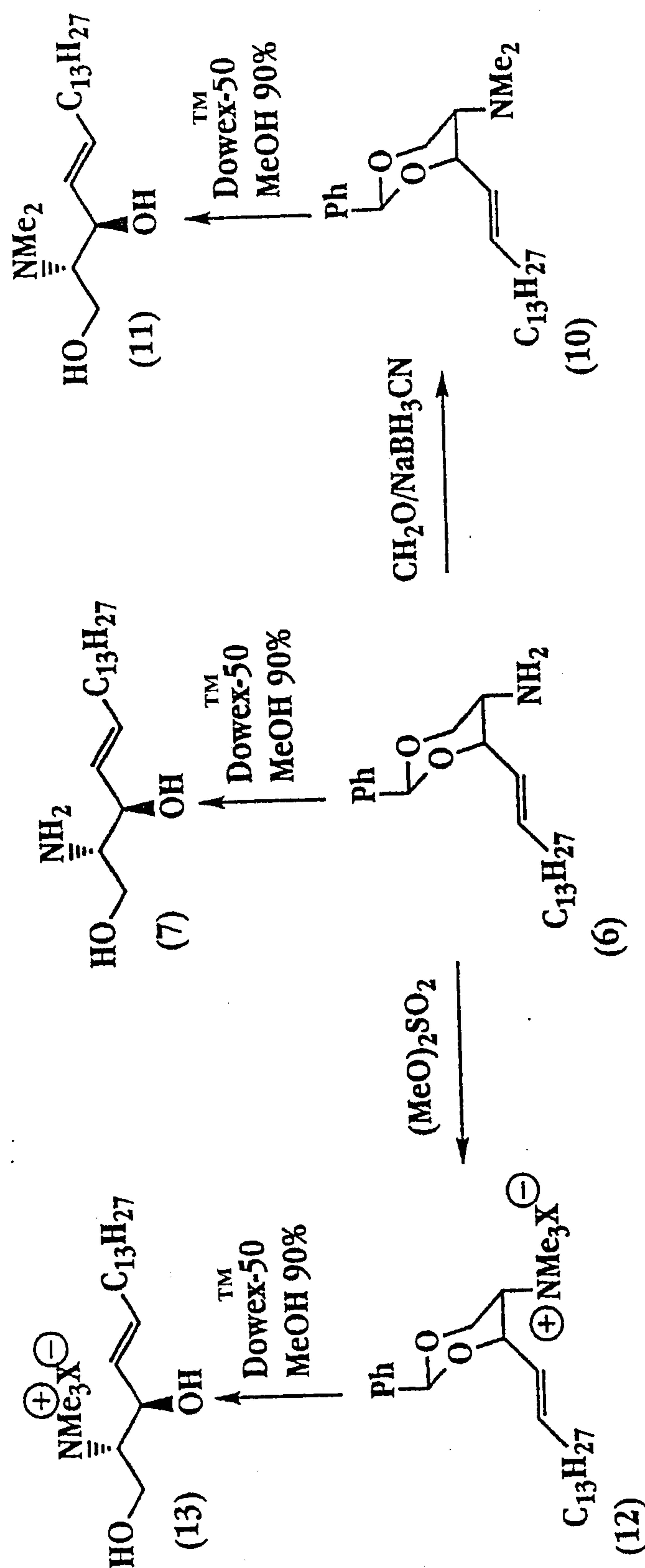


Fig. 3

