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The synthesis of an isosteric phosphonic acid analogue of platelet activating factor and related materials

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THE SYNTHESIS OF AN ISOSTERIC PHOSPHONIC ACID ANALOGUE OF PLATELET ACTIVATING FACTOR AND RELATED MATERIALS

by

YUE-JIN LIU

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

1993

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6/29/93
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The City University of New York

Abstract

THE SYNTHESIS OF AN ISOSTERIC PHOSPHONIC ACID ANALOGUE OF PLATELET ACTIVATING FACTOR AND RELATED MATERIALS

By

Yue-jin Liu

Advisor: Professor Robert Engel

The main purpose of this thesis was the development of optically active structural analogues of platelet activating factor (PAF) which could be used as probes of biological activity. Of interest in the present work are phosphonate analogues of PAF in which a methylene group has been substituted for the esteric oxygen of a phosphate ester. The carbon-phosphorus bond of the phosphonate is not subject to hydrolysis by enzymes involved in the normal cleavage of phosphate esters.

Syntheses of the analogues of platelet activating factor involved a regioselective epoxide-ring opening procedure. The regioselective ring opening of various epoxy derivatives has been studied in the presence of boron trifluoride etherate, and is reported in this dissertation. In the acid catalyzed epoxide ring opening process, alcohols exhibited a notable regioselectivity, attacking the terminal carbon of the epoxy functional group preferentially.

(*S*)-3-acetyl-4-Octadecanyloxybutane-1-phosphonate choline and (*S*)-(E)-3-acetyl-4-octadecanyloxybut-1-enyl-1-phosphonate choline have been synthesized *via* regioselective epoxy-ring opening of the suitable butanetriol derivatives. Also, some other epoxy-ring opening reactions have been studied using the boron trifluoride etherate catalyst.

Acknowledgments

For my mother, Heng-yuan Xue, who always has given me love, support and encouragement in everything I have done. Thank you for always being there when I need you.

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For all of my family and friends, past and present. Thank you for your friendship, understanding, and encouragement, especially my nieces, Reirei and Leilei.

For Clifford Pratt. Thank your for friendship, which I will always remember.

For my wife. Thank you for your help and understanding in making this thesis possible.

Dedicated to those who made this thesis possible

My mother, my wife, and my family.

1. Yue-jin Liu, Burton E. Tropp, and Robert Engel. *Canadian Journal of Chemistry,* **1993**, *71(2)*, 206-209.

2. Clifford Pratt, Yue-jin Liu, Ting-yi Chu, Karin Melkonian, Burton E. Tropp, and Robert Engel. *Canadian Journal of Chemistry,* **1992**, *70(8)*, 2135-2141.

3. Yue-jin Liu, Ting-yi Chu, and Robert Engel. *Synthetic communications,* **1992**, *22(16)*, 2367-2371.

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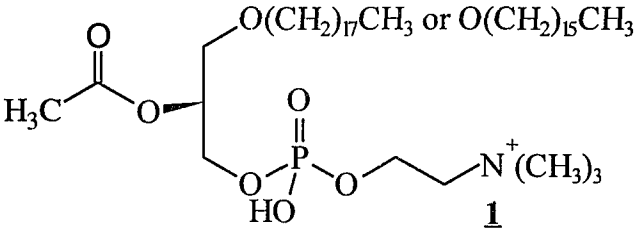
CHAPTER 1 Synthesis of Phosphonic Acid Analogues of PAF

INTRODUCTION

I. Chemical Investigation of Analogues of PAF

A. Synthesis of PAF and its Analogues

Platelet Activating Factor (PAF) is an alkyl ether phospholipid of structure (**1**) bearing primarily C_{18} or C_{16} alkyl ether linkages at the C_3 position. It is a potent activator of various inflammatory cells such as platelets and neutrophils, and is one of the important mediators of anaphylaxis and inflammation. It is a potent hypotensive agent. The presence of PAF has been demonstrated in cells from several species including man, rabbit, mouse and pig. PAF has been shown to induce aggregation of blood platelets from rabbit, man, and rat.[1]

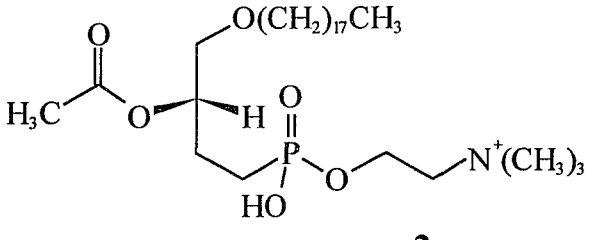


1

Natural PAF: (R) $C_{28}H_{59}NO_7P$ or $C_{26}H_{55}NO_7P$

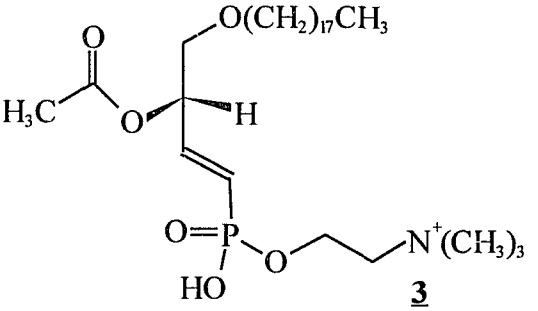
This project is concerned with synthesis of analogues of PAF. Of particular interest were those isosteric with the natural PAFs bearing a methylene group in place of one of the normal esteric phosphate oxygen

atoms (structure **2**), as well as those in which a double bond is present in the backbone (structure **3**). It is intended that the biological properties of the analogues be compared with the natural PAF.



2

(*S*)-$C_{29}H_{61}NO_6P$



3

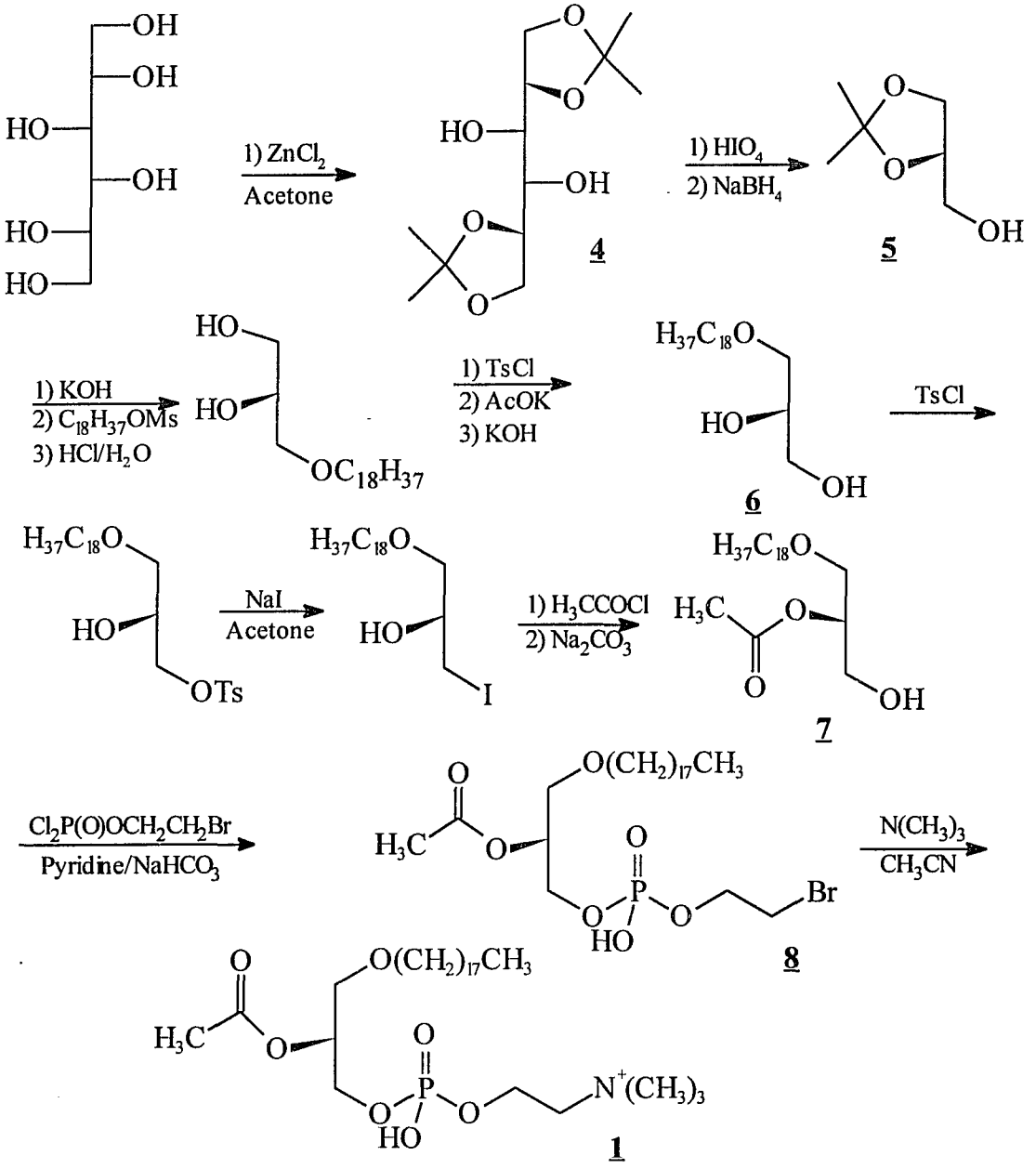
(*S*)-$C_{29}H_{59}NO_6P$

The present syntheses began with (D)-mannitol and (S)-malic acid. The unsaturated phosphonic ester was made through the Wittig reaction. The key step of these syntheses was the epoxide ring opening that gives a stereoselective and regioselective product.[2]

The term platelet activating factor (PAF) was used to describe a fluid phase mediator observed, isolated, and characterized simultaneously by Hanahan, *et al.*[3], and Benveniste, *et al.*[4] Its structure was determined to be an acetyl glyceryl ether phosphorylcholine. Since then, the synthesis of this biologically active phospholipid compound has received great attention.[5-7]

PAF is one of a series of ether phospholipids. Ether phospholipids are important structural constituents of membranes, particularly as they have been shown to possess high levels of activity in a wide range of physiologically vital regulatory events.[8-9] They can act as powerful mediators in such physiological processes as anaphylaxis and inflammation.[10] 1-*O*-

Alkyl-*sn*-glycerophosphocholines have profound properties inducing rabbit platelet aggregation,[11] the release of stored mediators such as serotonin,[12] are found to be potent platelet activators,[13] exhibit strong antihypertensive activity,[14] and function as effective immuno-modulating agents.[15]



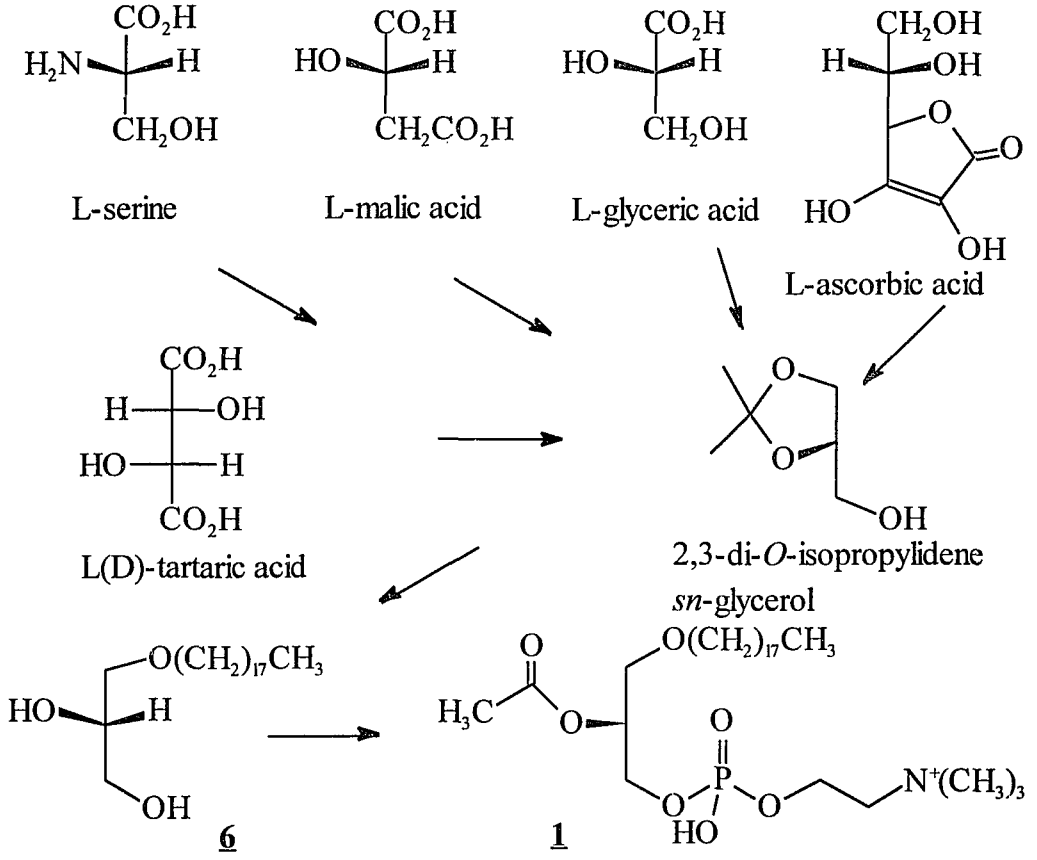
Scheme 1

The first total chemical synthesis of PAF was accomplished by Mangold, *et al.*[16] using D-mannitol as the chiral starting material. This involved generation of the 1,2:5,6-diisopropylidene-D-mannitol from D-mannitol, followed by cleavage of the carbon carbon bond between C_3 and C_4 and reductive work-up to give chiral 1,2-isopropylidene glycerol. The remaining alcohol group of this compound was protected and the adjacent diol group was unmasked. The resultant primary alcohol function was selectively derivatized using an alkyl halide in the presence of base to form the alkyl ether, and the resultant secondary alcohol was acetylated with acetyl chloride. The alcohol on C_3 was then deprotected and esterified with 2-bromoethyl phosphoryl dichloride to give the 1-*O*-alkyl-2-acetyl-*sn*-glycerophospho-2'-bromoethanol. This material was further treated with trimethylamine in the presence of $NaHCO_3$ to afford the final compound, 1-*O*-alkyl-2-acetyl-*sn*-glycerophosphocholine [Scheme 1].

Later, other chiral starting materials were used to prepare the same target compound. Van Dorp, *et al.* started with L-serine,[17] Jung, *et al.* started with L-ascorbic acid,[18] Kamata, *et al.* started with L-malic acid,[19] Ohno, *et al.* used L-tartaric acid,[20] and Hajdu, *et al.* used L-glyceric acid.[21] Although each used different chiral starting materials, isopropylidene glycerol was a common intermediate for all [Scheme 2].

In 1980 Benveniste, *et al.*[22] also accomplished the total chemical synthesis of PAF *via* a chemical method. Benveniste, *et al.* started with the same compound as did Mangold, *et al.*[16] (D-mannitol), but used a different protecting group (trityl was used to protect the alcohol group of

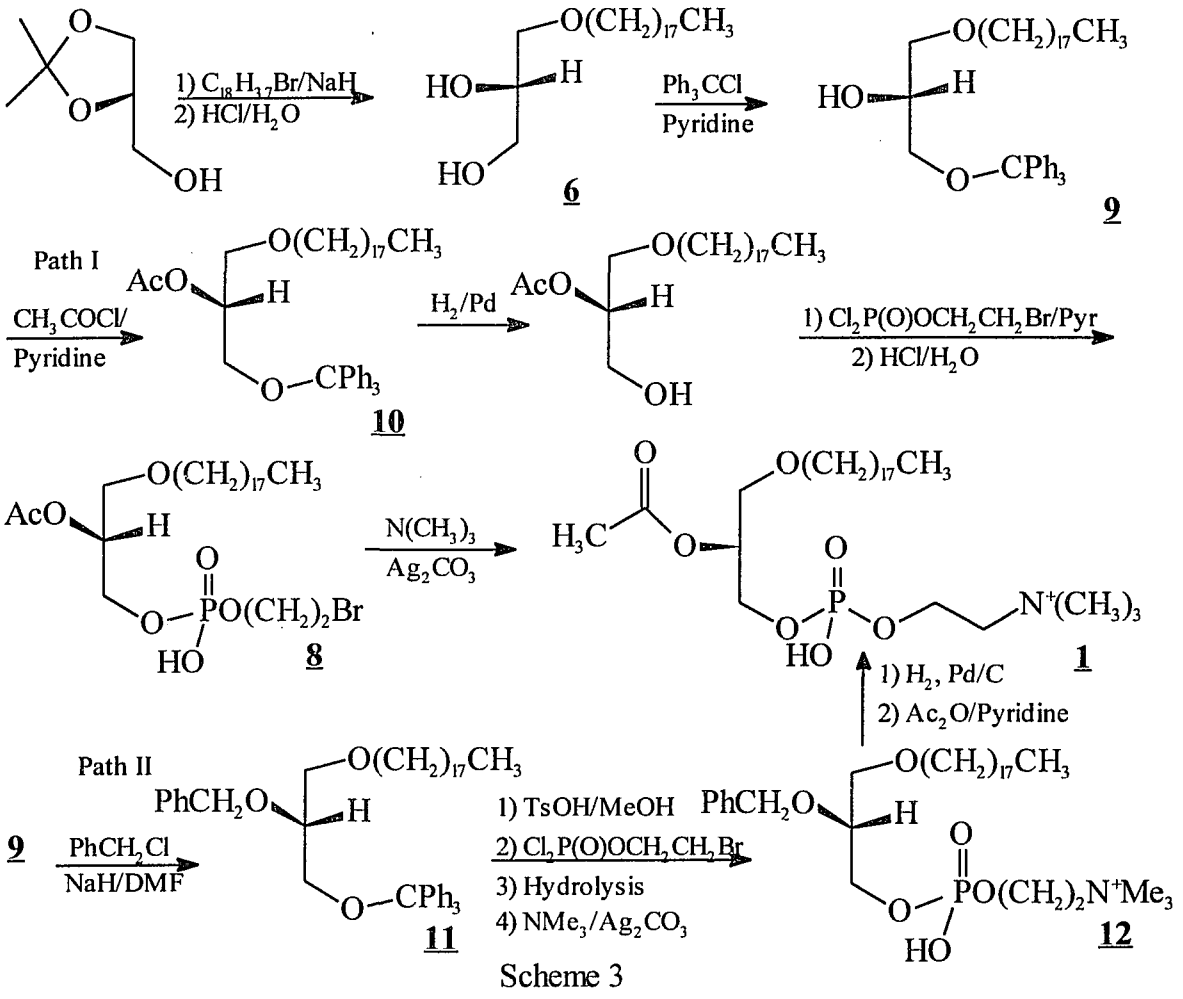
isopropylidene glycerol). After the intermediate was acetylated, the trityl



Scheme 2

group was removed by hydrogenolysis using 5% Pd on charcoal. The deprotected compound was treated with 2-bromoethylphosphoryl dichloride followed by trimethylamine in the presence of silver carbonate to form the 1-*O*-octadecyl-2-acetyl-*sn*-glycerophosphocholine. Later Benveniste, *et al.*[23] improved the reaction yield by changing to a more efficient method. In the new method the acetyl group was added at a later stage. The C_2 position was protected first with a benzyl group and the trityl group was removed by treatment with *p*-toluenesulfonic acid in methanol. After the

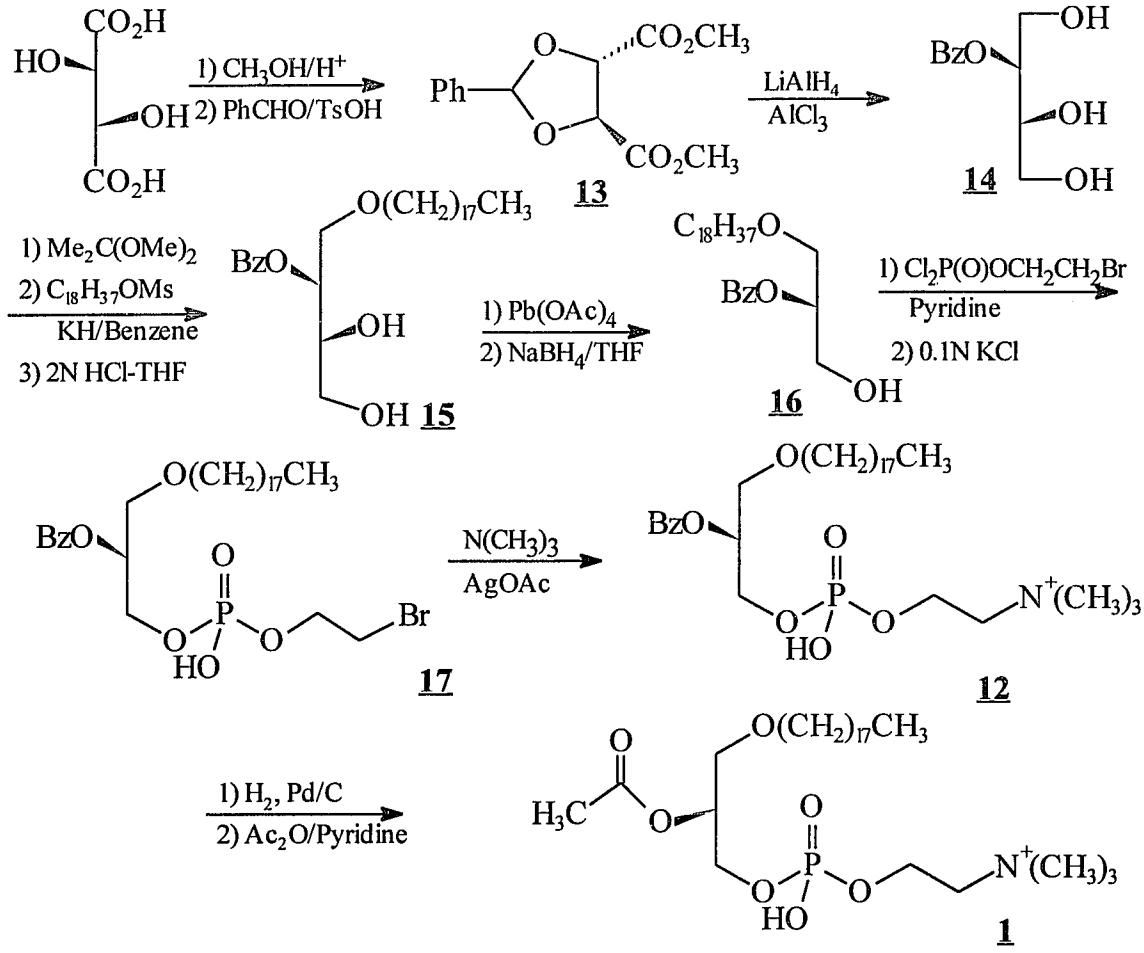
choline group was introduced, the acetyl group was attached in the last step [Scheme 3].



Scheme 3

Ohno, *et al.*[24] used *d* and *l*-tartaric acid as starting materials (Scheme 4) for the synthesis of PAF and its analogues. In this synthetic route, tartaric acid was methylated to form its dimethyl ester, which was then protected by benzaldehyde to afford dimethyl 2,3-*O*-benzylidene-*d*(*l*)-tartrate (**13**). Reductive cleavage of this material with $LiAlH_4$-$AlCl_3$ at room temperature produced 2-*O*-benzyl-*d*(*l*)-threitol (**14**). The vicinal glycol linkage of (**14**)

was protected with 2,2-dimethoxypropane catalyzed by *p*-TsOH to give 2-*O*-benzyl-3,4-*O*-isopropylidene-*d*-threitol. Alkylation of the primary



Scheme 4

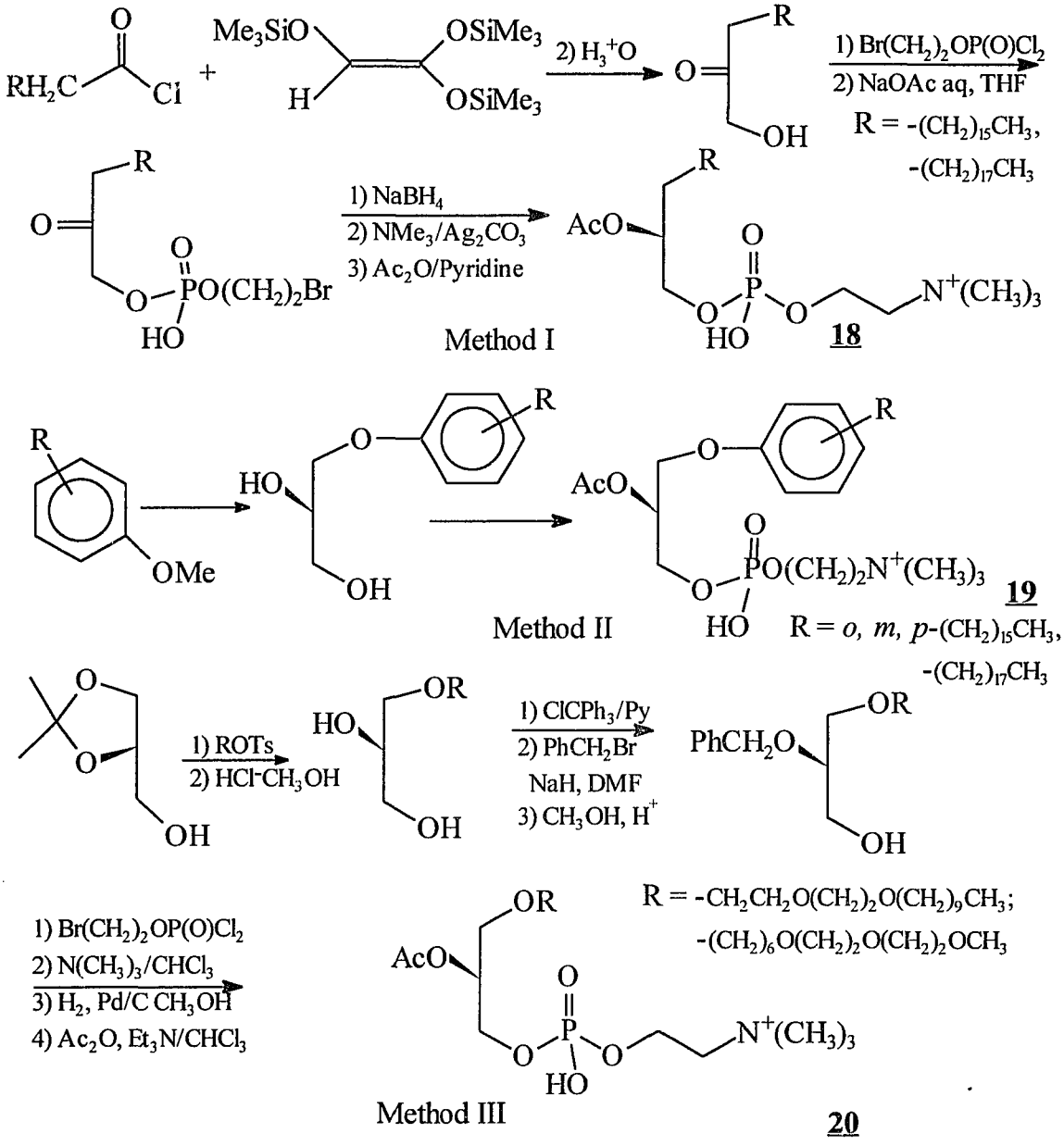
alcohol group with *n*-ROMs facilitated by KH, followed by hydrolysis with aqueous HCl to remove the isopropylidene linkage gave the compound (**15**). The resulting diol was subjected to oxidative cleavage with $Pb(AcO)_4$ followed by reduction with $NaBH_4$ to give 2-*O*-benzyl-1-*O*-alkylglycerol. The compound (**16**) was treated with 2-bromoethyl phosphoryl dichloride followed by hydrolysis and treatment with trimethylamine to afford the

compound (**12**). The compound (**12**) was reduced catalytically by hydrogen in the presence of 5% Pd/C to remove the benzyl groups and then was acetylated to give the final product 1-*O*-hexadenyl-2-*O*-acetyl-*sn*-glycerophosphocholine (PAF) (**1**) [Scheme 4].

In light of the important activities of PAF for platelet aggregation and inducement of hypotension, numerous studies have been made of its structural analogues.

Between 1984-1986 Wissener, *et al.*[25-29] had studied analogues of PAF systematically. The different functional groups on the glycerol backbone and the phosphocholine group were modified in an attempt to determine the structure activity relationship of PAF analogues.

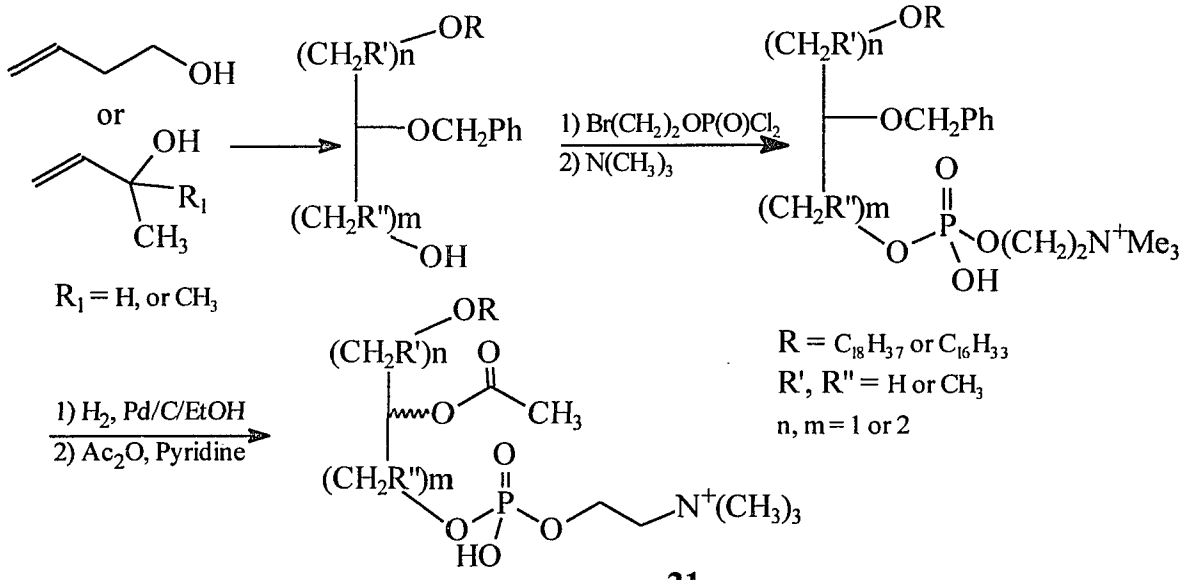
In one series of analogues,[25-26] the alkyl ether group was modified in one of several ways. One involved the removal of the ether oxygen atom from the C_1 position incorporating instead an aliphatic chain (**18**) (Scheme 5). Another analogue involved the placement of an aromatic group between the oxygen atom and the alkyl chain. The position of the alkyl chain attached to the aromatic ring was varied among *ortho*, *meta* and *para* positions of the aromatic ring (**19**) (Scheme 5). Further, the ether alkyl group was replaced with a multi-ether oxygen chain which could affect the lipophilic properties of the chain. In this latter modification, three oxygen atoms were separated by two ethylene units (**20**) (Scheme 5). These modified compounds have been studied for their effect on platelet aggregation and hypotensive activities.



Scheme 5

In a second series,[27] the backbone glycerol group was modified and racemic analogues of platelet activating factor were synthesized. The glycerol backbone was modified by the insertion of a methylene group between carbon atoms C_1 and C_2 or between carbon atoms C_2 and C_3.

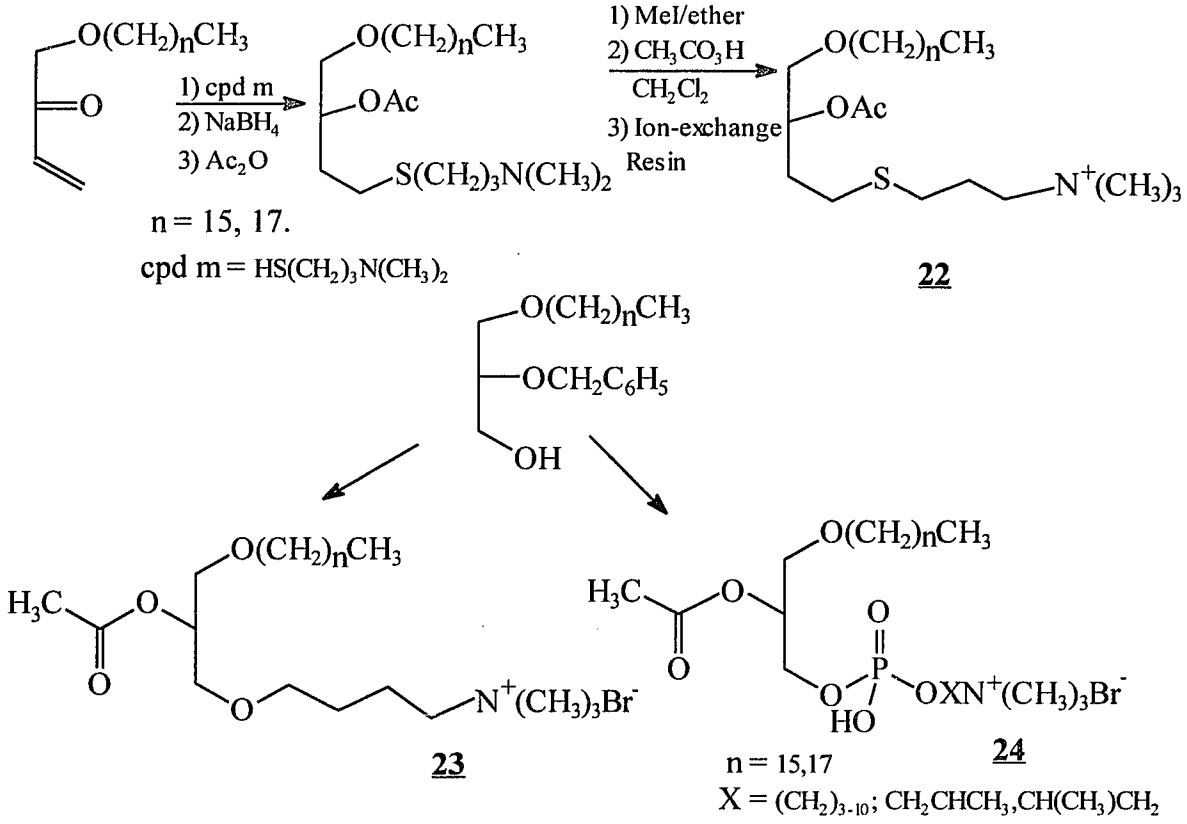
Further, one or both of the hydrogen at the C_1 or C_3 position were replaced with a methyl group(s) to afford the methyl substituted structural analogues of PAF [Scheme 6].



Scheme 6 **21**

In a third series,[28-29] the phosphocholine section was modified in length and nature, including the incorporation of an aromatic ring. In certain of these structural analogues the phosphate group has been removed and an ether or a thio-ether linkage has been placed between the glycerol and choline units to form non-phosphorus lipids. In the synthesis of the thio analogues of PAF, an unsaturated ketone (4-*n*-hexadecyloxy-3-oxo-1-butene) was used which was attacked by an excess of *N*,*N*-dimethyl-3-aminopropanethiol through a Michael addition and followed by reduction using $NaBH_4$ to afford the 4-[3-*N*,*N*-(dimethylamino)propyl]thiol-1-hexadecyloxy-2-butanol. The compound was treated further in several steps to

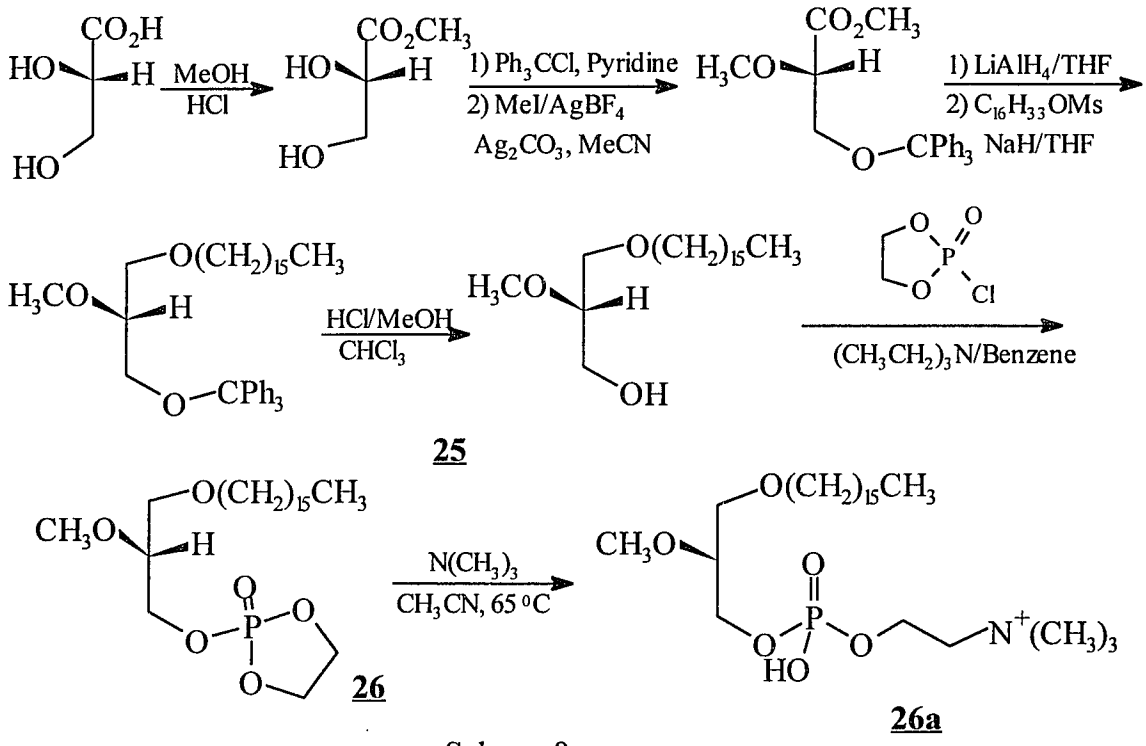
produce the final structural analogue of PAF, 1-*n*-hexadecyloxyl-2-acetyl-4-[3-(*N*,*N*,*N*-trimethylamino)propylthiol]butane [Scheme 7].



Scheme 7

In 1987, Hajdu, *et al.*[21] synthesized several modified structural analogues of PAF. Starting with chiral L-glyceric acid, protected as the methyl ester, the primary alcohol site was protected as the trityl ether and the secondary alcohol site was allowed to react with methyl iodide to form (S)-1-trityloxy-2-methoxy-l-propionate methyl ester. The ester group was reduced to an alcohol which was then alkylated using *n*-octadecyl mesylate to produce compound (**25**). This compound was hydrolyzed using HCl in methanol/chloroform solution to remove the trityl group. After drying over

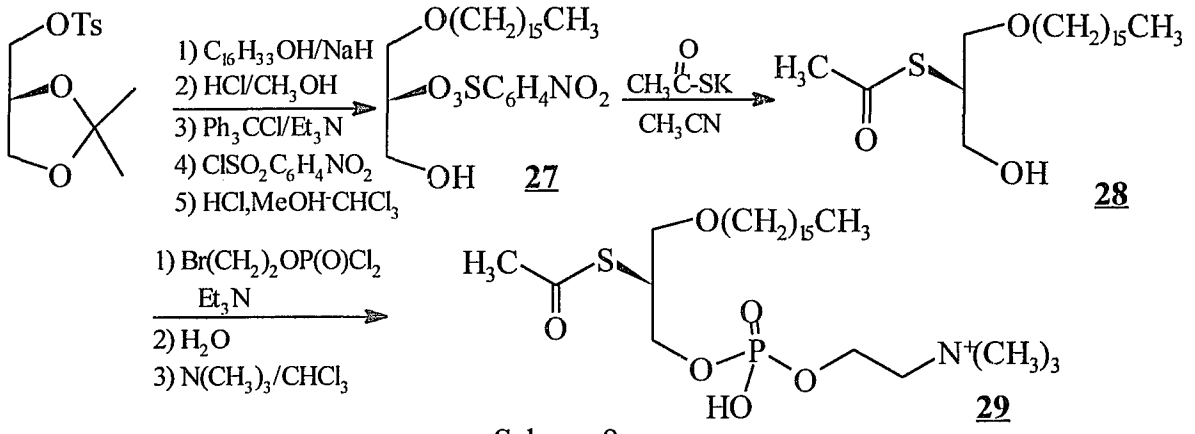
P_2O_5, this material was phosphorylated with 2-chloro-2-oxo-1,3,2-dioxaphospholane in benzene with 1.0 equivalent of triethylamine to give the compound (**26**). This material was then treated with anhydrous trimethylamine under pressure to afford the target analogue of PAF (**26a**). Ohno, *et al.*[24] also made this compound by a different synthetic method [Scheme 8].



Scheme 8

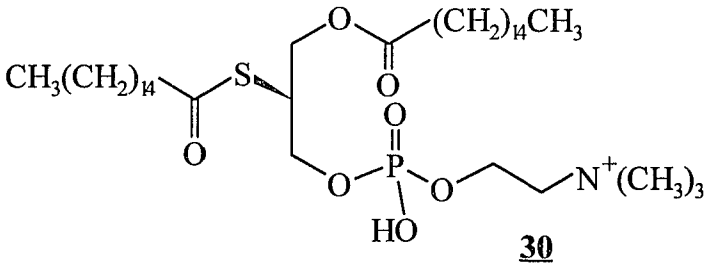
In the same year[30] a 2-thio analogue of PAF was prepared by a stereospecific procedure. In this procedure, the thiol ester group was introduced by the reaction of compound (**27**) with potassium thioacetate in CH_3CN solution. The configuration of the stereogenic center at the C_2 position was inverted in this reaction. The optically active intermediate

compound (**28**) was treated with 2-bromoethyl phosphoryl dichloride to form the thio-PAF target analogue (**29**) [Scheme 9].



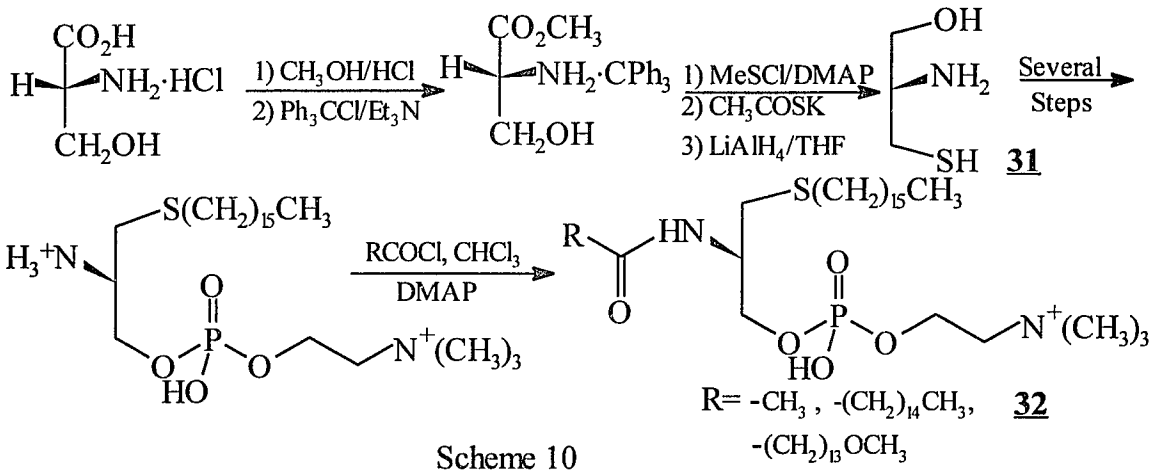
Scheme 9

A similar procedure was used for the preparation of another sulfur containing structural analogue of phosphatidyl choline, compound (**30**).



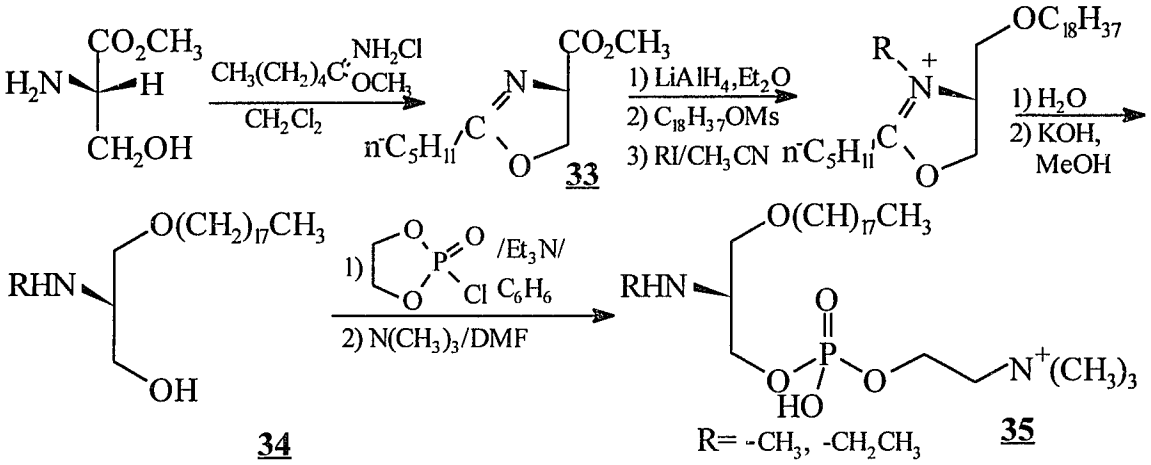
The investigation of PAF analogues was given impetus by the discovery of antitumor activity for several analogues of PAF.[31-33] Of particular note are the thioalkyl ether derivatives of PAF, which exhibited a tumor-cytotoxicity greater than that of the corresponding oxygen compound. The sulfur substitution at the *sn*-1 position appears to lower the platelet aggregating potency of 1,2-dialkylphosphorylglyceride, alleviating an important side effect in antileukemic chemotherapy using PAF analogues.

Hajdu, *et al.*[34-35] synthesized the thioalkyl ether compound in which a sulfur atom was present in place of the oxygen atom at the C_1 position. A chiral amino acid, D-serine, was used as the starting material to provide the optically active center. The alcohol-thiol structure (**31**) is a key intermediate in this synthesis which gives the target material 1-thiohexadecyl-2-*n*-acylamidopropyl-3-phosphocholine (**32**).



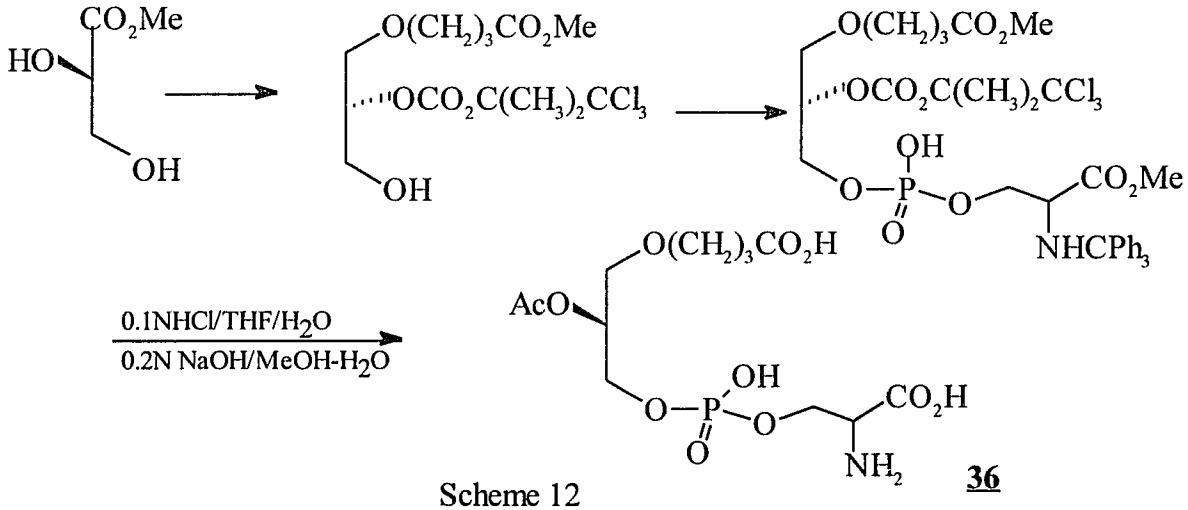
Scheme 10

In 1991 Hajdu, *et al.*[36] synthesized another 2-alkylamino structural analogue of PAF by a different synthetic route. L-Serine was used as a starting stereocenter for construction of the optically active product. The amino alcohol moiety was converted to the corresponding oxazoline derivative (**33**), and then was N-alkylated with methyl or ethyl iodide to give the quaternary oxazolinium derivative which hydrolyzed in aqueous suspension to produce the hexanoyl ester (**34**). This compound was phosphorylated with 2-chloro-2-oxo-1,3,2-dioxaphospholane followed by treatment with trimethylamine to afford the target material 1-*O*-octadecyl-2-alkyl-*sn*-aminodeoxyglycerophosphocholine (**35**).



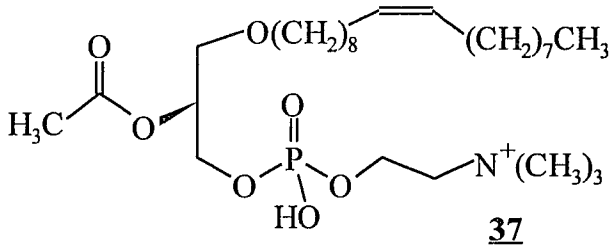
Scheme 11

In the same year[37] a synthesis starting with L-glyceric acid methyl ester was reported. In several steps, a chiral intermediate derivative of glycerol was coupled with *N*-trityl-*O*-phosphoserine methyl ester disodium salt in the presence of triisopropylbenzenesulfonyl chloride in pyridine. Then, the amino group was deprotected by 0.1N HCl (THF-H_2O) followed by sequential base hydrolysis of 1) the serine methyl ester, 2) trichloro-*t*-butyl carbonate and the ω-carboxylic ester together to produce the 1-*O*-(3'-carboxypropyl)-glycero-3-phosphoserine (**36**).



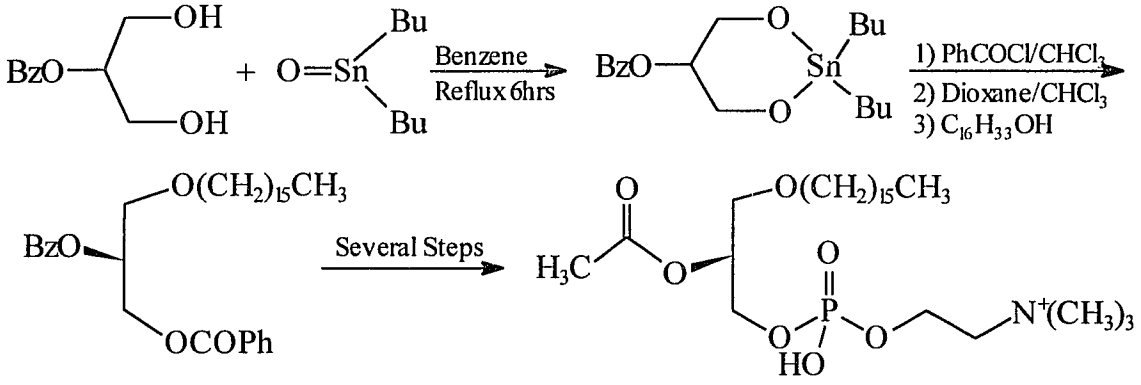
Scheme 12

Hirth, *et al.*[38,39] used D-mannitol as the starting material to synthesize PAF and its enantiomer and unsaturated structural analogues of PAF (**37**). The unsaturated double bond is in the middle of the alkyl chain.



37

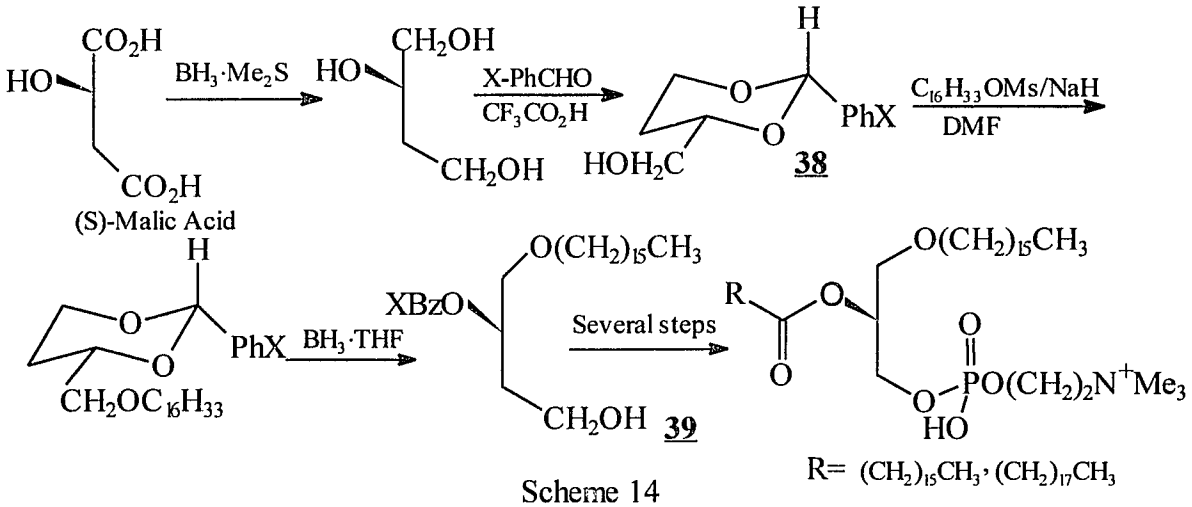
Shanzer, *et al.*[40] demonstrated that a symmetric diol can be converted into monoesters and subsequently to a chiral diester *via* a cyclic tin based intermediate. Max, *et al.*[41] adopted this method and 2-benzyloxy-1,3-propanediol was used as starting material. It was treated with 1.0 equivalent of di-*n*-butyl tin oxide to form in quantitative yield the corresponding stannoxane. The stannoxane was further treated in several steps to produce PAF (**1**).



Scheme 13

Kamata, *et al.*[19] used (S)-malic acid as the starting material which was reduced by borane dimethylsulfide complex to form (S)-1,2,4-butanetriol. The triol was protected by benzaldehyde in the presence of a catalytic

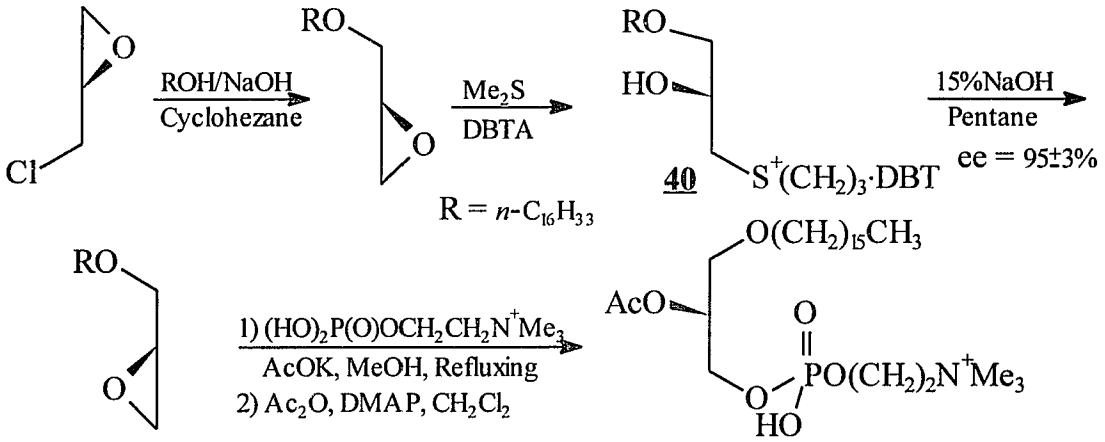
amount of trifluoroacetic acid to form compound (**38**) which was further alkylated by *n*-hexadecyl methanesulfonate in benzene. The important step for this reaction is the reduction the compound by borane tetrahydrofuran complex in which the borane preferentially attacks the less substituted oxygen atom of the dioxane ring and hydrogenolytic cleavage occurs to give the primary alcohol (**39**). This compound was treated in several steps to produce the target PAF.



Scheme 14

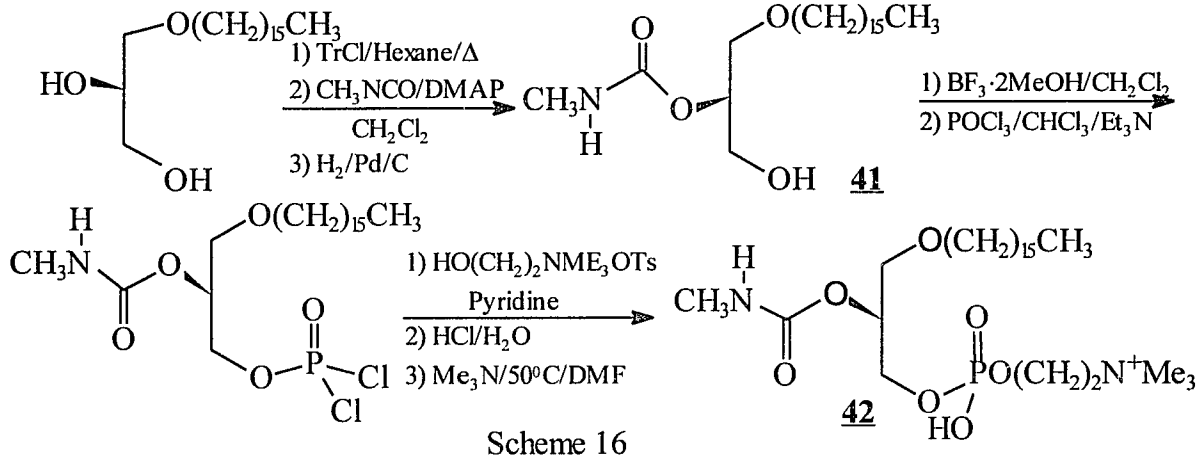
Julia, *et al.*[42] devised a very ingenious method for preparing PAF through an epoxide. An epichlorohydrin was used in reaction with octadecanol under basic conditions and another epoxide formed. This epoxide ring was opened with dimethylsulfide to produce an onium ion (**40**) which can form an optically active oxirane in the presence of D-dibenzoyl tartaric acid. This was a very efficient method to synthesize an optically active compound. The optically active oxirane was treated with

phosphocholine under basic conditions to give the analogue of PAF [Scheme 15].



Scheme 15

Surles, *et al.*[43] made a 2-*O*-methylcarbamyl analogue of PAF in a simple way. In this procedure, the methylcarbamyl group was introduced by

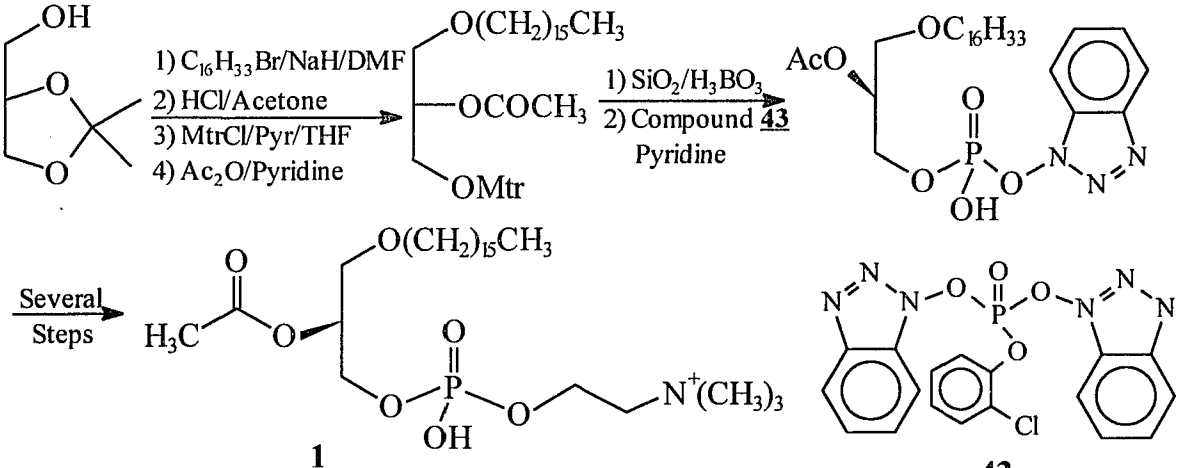


Scheme 16

the reaction of a secondary alcohol with methyl isocyanate. The most important intermediate in this synthesis was the phosphodichloridate monoester which can react further with choline tosylate exclusively in the presence of pyridine. Triethylamine can not catalyze this reaction. This is

strong rationale for the performance of this kind reaction in the presence of pyridine [Scheme 16].

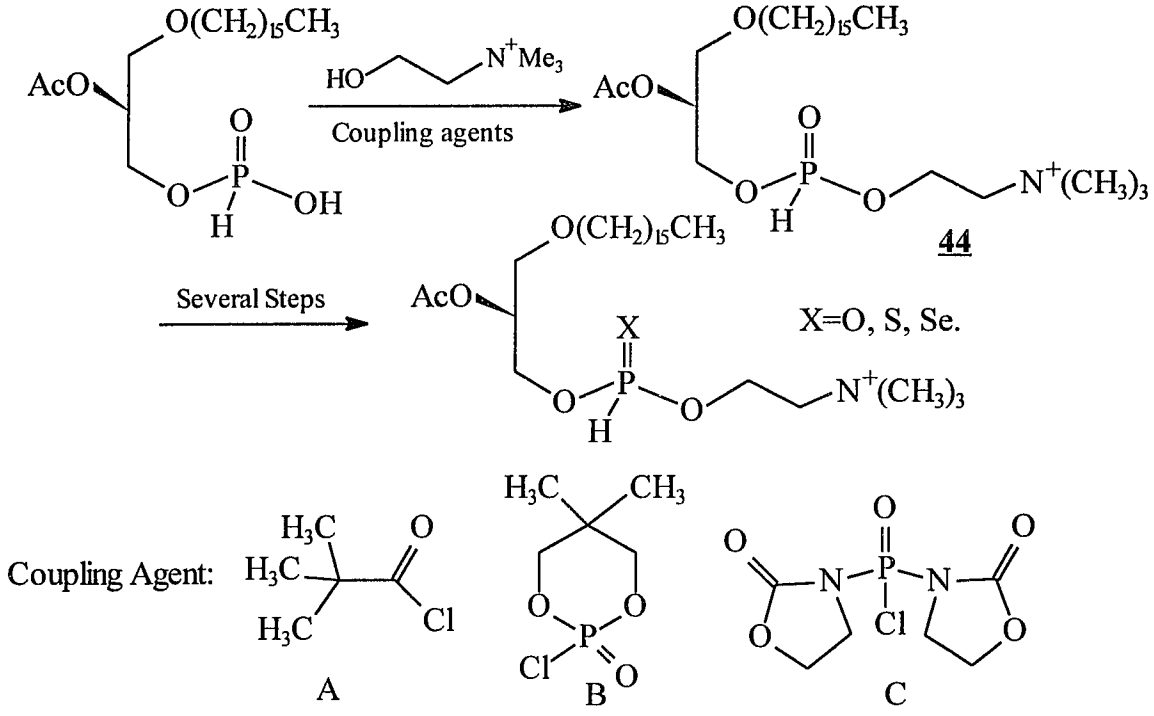
Van Boeckel, *et al.*[44] synthesized the enantiomer of PAF with a different phosphoryl coupling reagent. Starting with 1,2-isopropylidene glycerol, in several steps [Scheme 17], an intermediate of 3-*n*-*O*-hexadecyl-2-acetylglycerol was synthesized and then allowed to react with compound (**43**) to form the final product (**1**) in 75% yield.



1 **43**

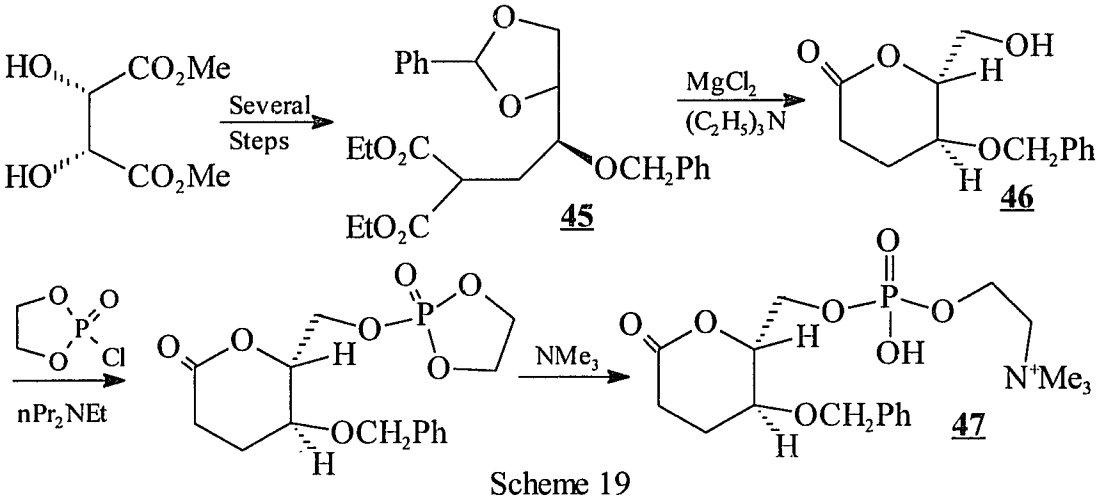
Scheme 17

Stawinski, *et al.*[45] made a glycerophospholipid and some analogues of PAF *via* a H-phosphite intermediate (**44**). In this synthetic route, a very efficient and high yield coupling reagent was applied to the reaction. This coupling reagent allows reactions of phosphite with hydroxylic components to be faster and more efficient. Three coupling reagents were used. Of the three, the reagent B is the best one as it is a stable crystalline material soluble in most organic solvents and ensures clean and reasonably fast coupling without danger of side reaction, even if the reaction mixture is left for a longer time [Scheme 18].



Scheme 18

Nakamura, *et al.*[46,47] made some structural analogues of PAF in which a lactone or cyclic ether group have been introduced. The reaction was

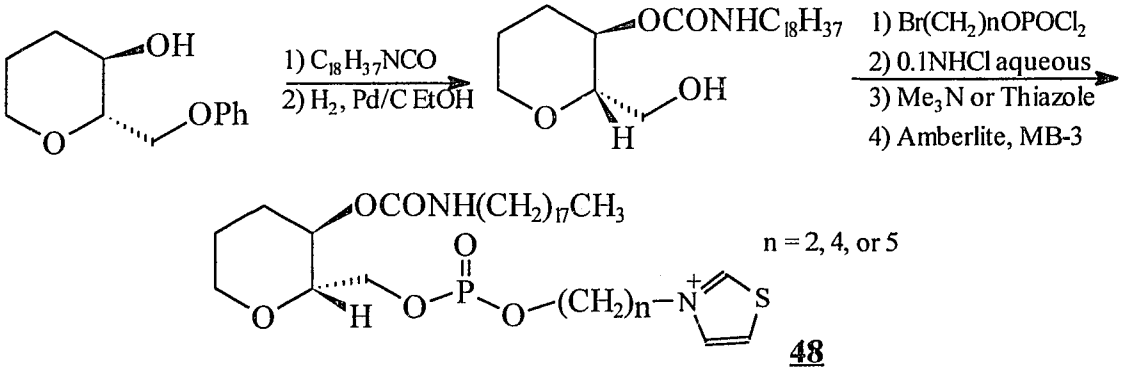


Scheme 19

begun using a dimethyl *meso*-tartrate following the same procedure as used by Ohno, *et al.*[24] to generate the compound (**45**). This compound was

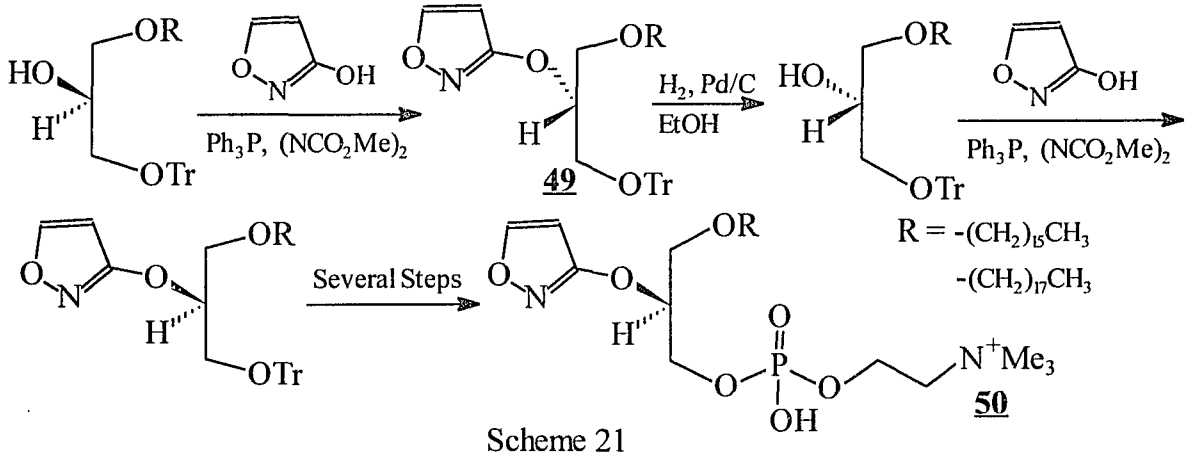
treated with $MgCl_2$ in triethylamine to afford a lactone (**46**) which was further treated with a chlorophosphate to produce a lactone analogue of PAF (**47**) [Scheme 19].

If the cyclic ether intermediates are treated with octadecyl isocyanate,[47] they can be carbamylated and phosphonylated with 2-bromoethyl phosphoryl dichloridate, then treated with thiazole to produce analogues of PAF with antagonistic side chains (**48**) [Scheme 20].



Scheme 20

The analogue of PAF modified with an isoxazolyl group at the C_2 position was synthesized. A 3-isoxazolyloxy group was used as a protected



Scheme 21

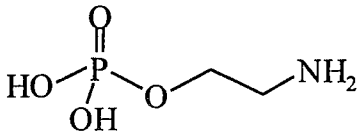
hydroxyl to exert potent agonistic activities (**49**). The glycerol backbone

incorporated a stereogenic center and the reaction procedure involved a Mitsunobu inversion.[48] 3-Hydroxyisoxazole was used as an acidic component to convert a R center to a S stereocenter in (**50**) [Scheme 21].

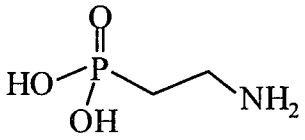
Recently, Schoen, *et al.*[49,50] reported the synthesis of a polymerizable phosphatidyl choline. A conjugated unsaturated long alkyl chain was introduced in place of the alkyl and acyl groups at carbon atoms C_1 and C_2. The resultant compound could form liposomes in aqueous solution below its hydrocarbon chain melting temperature. Under ultraviolet light irradiation, the compound can be polymerized to generate helical or tubular microstructure. The tubule diameters are relatively constant regardless of the nature of the starting material, but the lengths vary widely in the synthesis. The tubular microstructure could be very important in future studies.

B. Synthesis of the Carbon-Phosphorus Analogues of PAF

With regard to phosphonic acid analogues of PAF, much has also been done. The major work in this area was started earlier than the PAF synthesis research itself. In 1959 Horiguchi and Kandatsu[51] isolated 2-aminoethyl phosphonic acid from the acid hydrolysates of the ether-ethanol soluble fraction of ciliate Protozoa of sheep rumen. This special isolation provided the first indication of the possible existence of phosphorus containing lipids in nature in which the normal 2-aminoethyl phosphoric acid **A** is replaced by 2-aminoethyl phosphonic acid **B**.



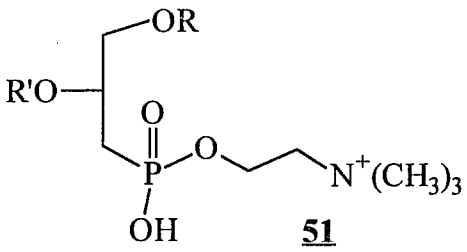
A



B

Later, Kittridge, *et al.* confirmed that 2-aminoethyl phosphonic acid can exist in the sea anemone *anthopleura elegantissima*,[52] *zoanthid zoanthus sociatus*,[53] and in many other species.[54] The presence of a 2-aminoethyl phosphonic acid ester of glycerol in the lipid extracts of the living species would suggest the natural occurrence of phosphonic acid containing lipids resembling structurally the glycerolphospholipids.

Baer *et al.*[55] proposed a generic name for such carbon-phosphorus bond containing lipids as phosphonolipids. They suggested that two general types of phosphonolipids exist in the nature. One has the carbon-phosphorus bond present in the glycerol derived portion (**51**), while the other type has the carbon phosphorus bond in the polar head group, as in (**52**).



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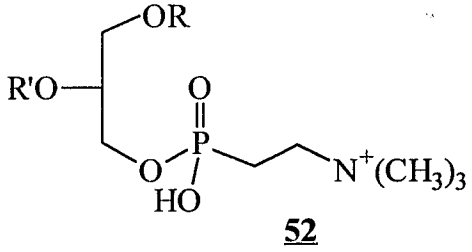
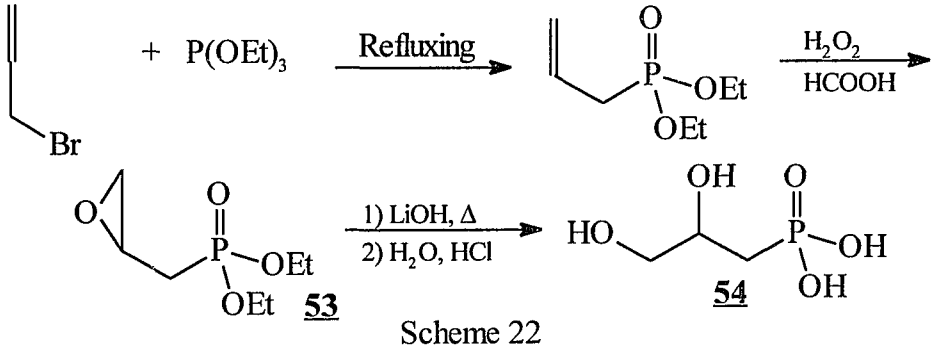


52

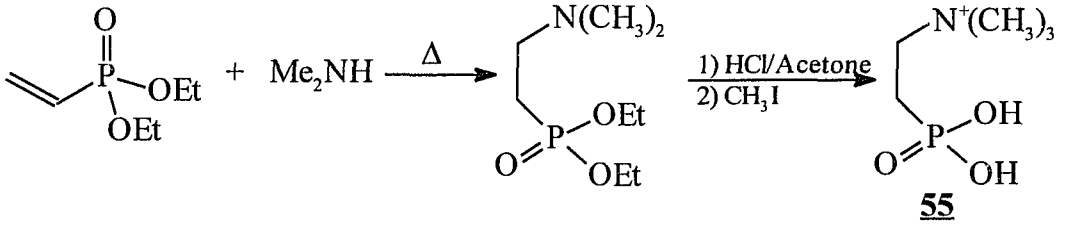
Rosenthal and Geyer[56] were the first to synthesize the glycerol-3-phosphate analogue in racemic form. Allyl bromide was used as a starting material which was first phosphonylated through an Abuzov reaction with trimethyl phosphite. Epoxidation of the double bond and hydrolysis in acid

solution afforded the phosphonic acid (**54**). The procedure was short and efficient [Scheme 22].



Scheme 22

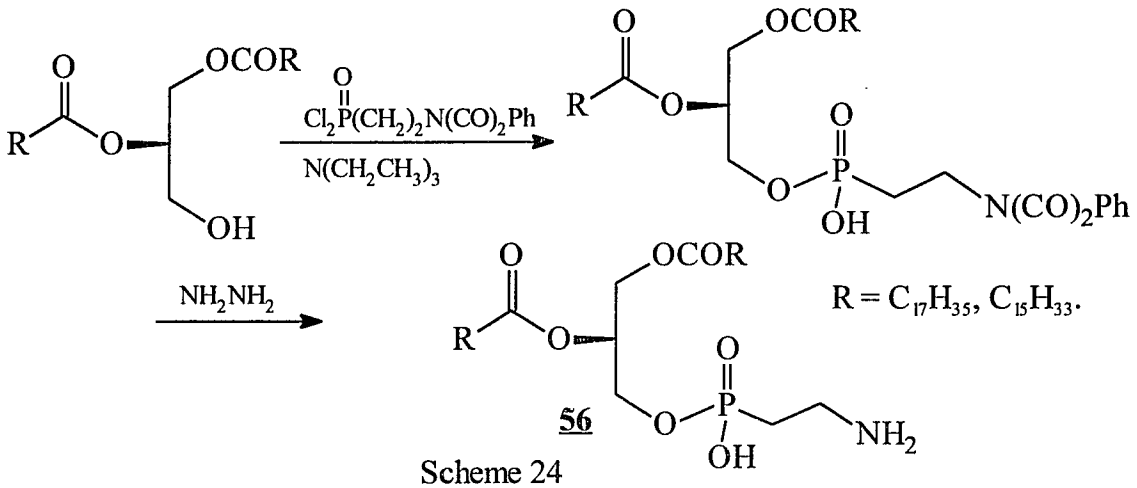
In a similar method,[57] 2-trimethylaminoethyl phosphonic acid (**55**) was synthesized [Scheme 23].



Scheme 23

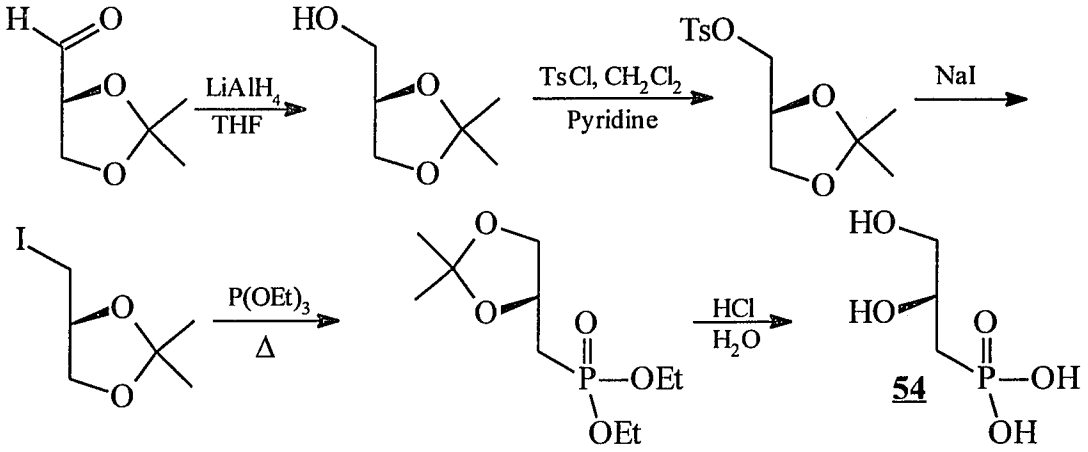
Baer and Stanacev[58] reported the preparation of a dipalmitoyl-l-α-glyceryl-2-aminoethylphosphonate [Scheme 24]. The preparation of the phosphonic acid analogue of cephalin required a reaction of D-α,β-dipalmitin with 2-phthalimido phosphonic acid monochloride catalyzed by triethylamine. The protective phthaloyl group was removed by hydrazinolysis to afford the product (**56**) [Scheme 24].

Baer, *et al.*[59] also prepared analogues with different functional groups. They altered the C_1 and C_2 positions of the glycerol backbone with α,β-distearin and α,β-dimyristin groups. The protecting group was changed



Scheme 24

with diphenylaminoethylphosphonic acid and followed by hydrogenation to produce the amine group.

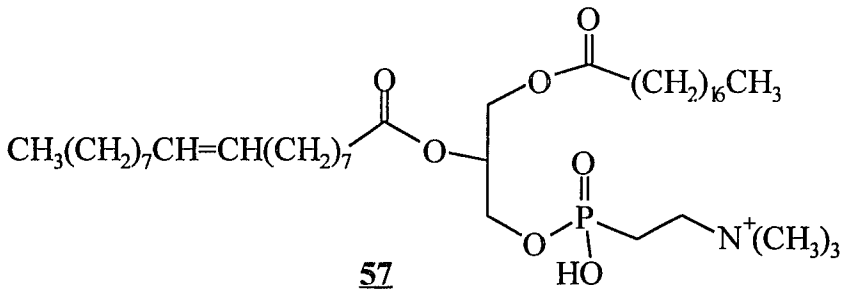


Scheme 25

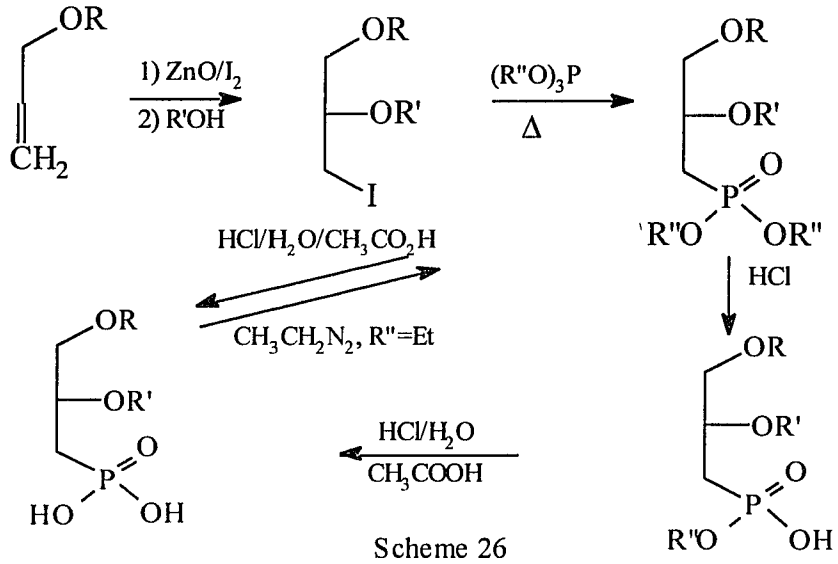
Baer and Basu reported the synthesis of the nonisosteric analogues, L and D-dihydroxypropylphosphonic acid[60] [Scheme 25]. In their procedure, the D-glyceraldehyde acetonide was used as the starting material to produce the D-glycerol acetonide. The alcohol group was converted to a halide and the resultant species was phosphonylated with triethyl phosphite, then

hydrolyzed in dilute aqueous HCl solution to give the target compound, L or D-dihydroxypropylphosphonic acid (**54**).

Baer, *et al.*[61] also proposed the first type of phosphonic acid analogues of lipids, phosphatidic acids, and later reported[62] the synthesis of mixed phosphonocephalins. In this synthesis, the compound was functionalized with an unsaturated ester group at the 2-position and a saturated ester at the 3-position (**57**).



57

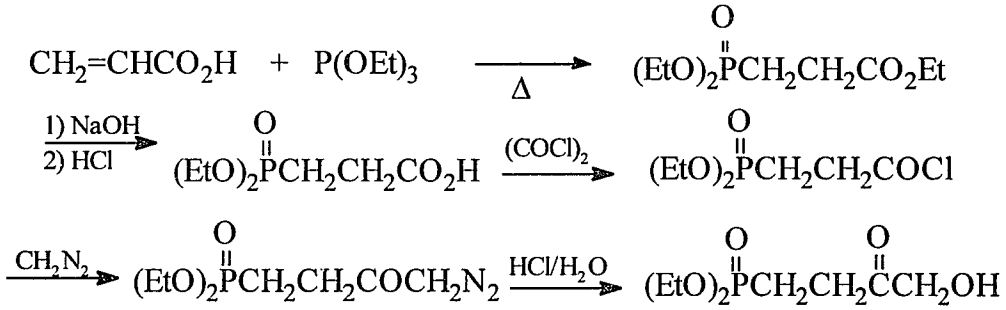


Scheme 26

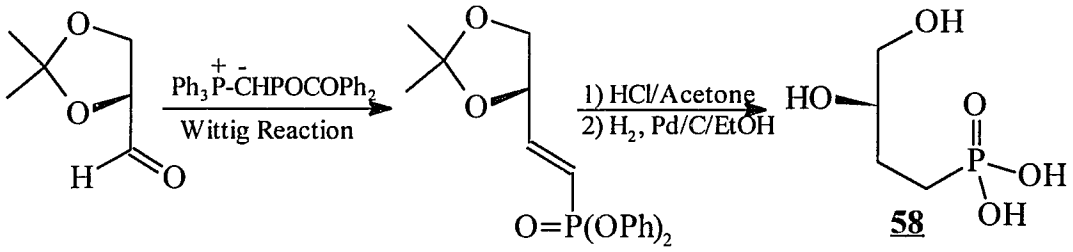
Rosenthal, *et al.*[63] synthesized the dietherphosphonate analogues of phosphatidic acid. They started with vinyl ethyl ether and converted it to a 3-ethoxy-2-methoxyiodopropane. The compound was phosphonylated

through an Abuzov reaction with a trialkyl phosphite and then was hydrolyzed in HCl aqueous solution to afford the final product [Scheme 26].

Dixon and Sparkes[64] synthesized the analogues of dihydroxyacetone phosphate and the 3-phosphoglycerate. In their synthesis acrylic acid was used as the starting material and was treated with triethyl phosphite. A mixture was formed and separated. After hydrolysis, the acid was chlorinated and treated with diazomethane to produce the diazoketone. The diazoketone was further hydrolyzed under acidic conditions to form the final dihydroxyacetone phosphonic analogue [Scheme 27].



Scheme 27

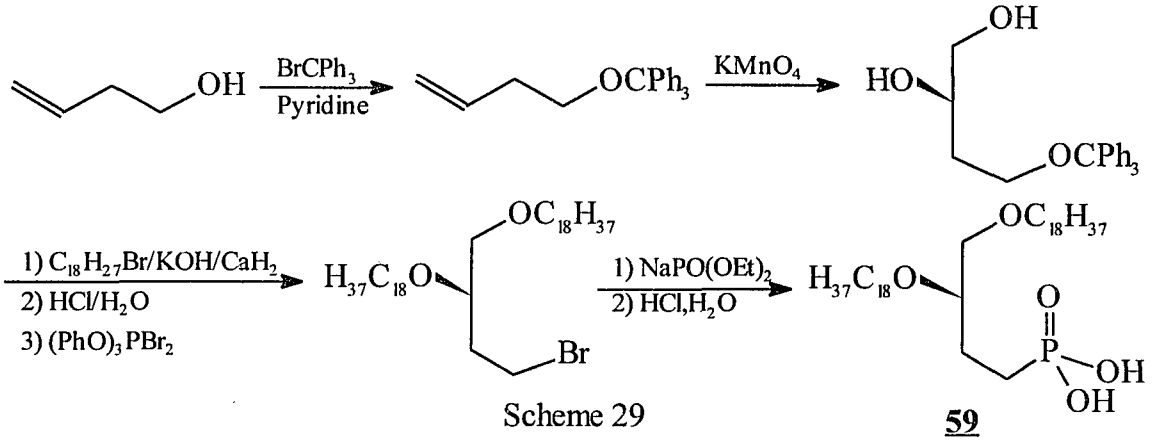


Scheme 28

Adams, *et al.*[65] used a reductive procedure to synthesize an isosteric analogue of *sn*-glycerol-3-phosphate. Starting with isopropylidene glyceraldehyde, an unsaturated isopropylidene diphenyl butylphosphonate was

formed through a Wittig reaction. The compound was reduced catalytically to form the final compound which had two hydroxyl groups in the phosphonic acid (**58**) [Scheme 28].

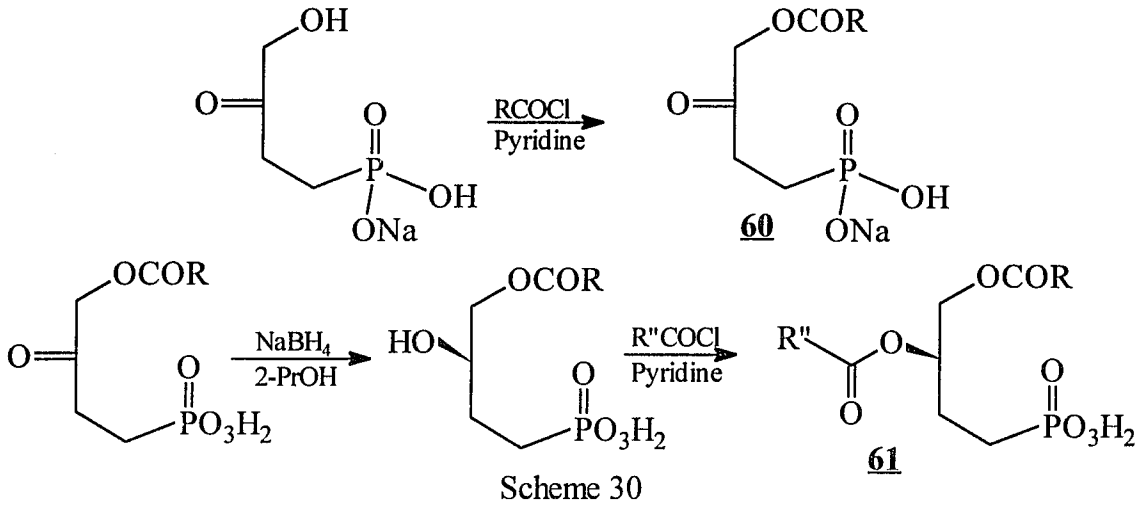
In 1965, Rosenthal, *et al.*[66] reported the synthesis of isosteric analogues of phosphatidic acid. Starting with 3-butene-1-ol, but-3-en-1-yl trityl ether was prepared. Permanganate oxidation then afforded an ether glycol in excellent yield. The dietherification of the compound was carried out in the presence of KH, and it was later hydrolyzed in acid solution to remove the trityl group. After bromination of the alcohol group, the compound was phosphonylated with a sodium phosphite salt to produce the final compound (**59**) [Scheme 29].



Scheme 29 **59**

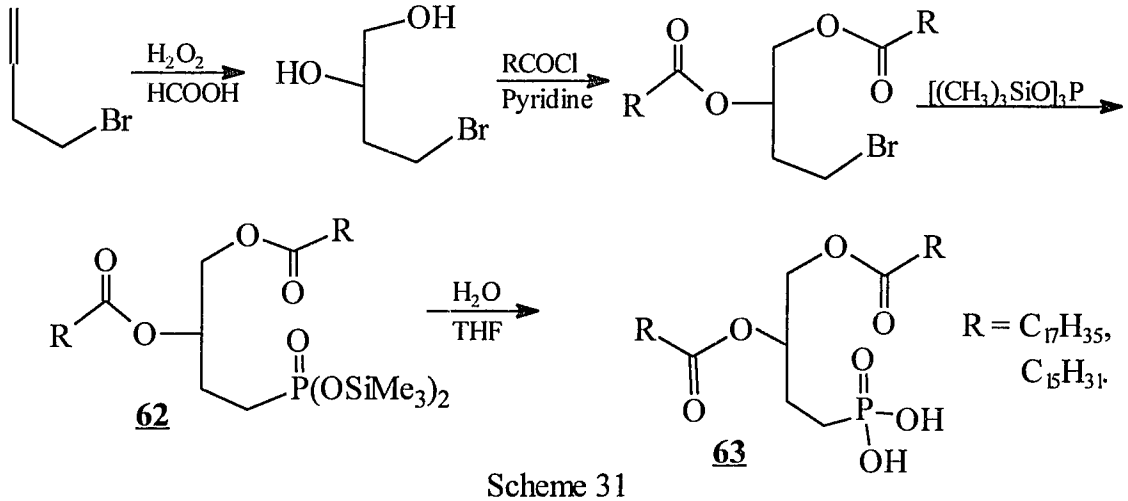
Goldstein, *et al.*[67,68] reported the synthesis of an isosteric analogue of 3,4-dihydroxybutyl-1-phosphonate. Acetoxymethyl vinyl ketone was used as the starting material. Rosenthal *et al.*[69,70] also made two ester-phosphonate analogues of cephalin.

J. C. Tang, *et al.*[71] reported the synthesis of isosteric analogues of phosphonolipids, principally phosphatidic acids (**61**) [Scheme 30].



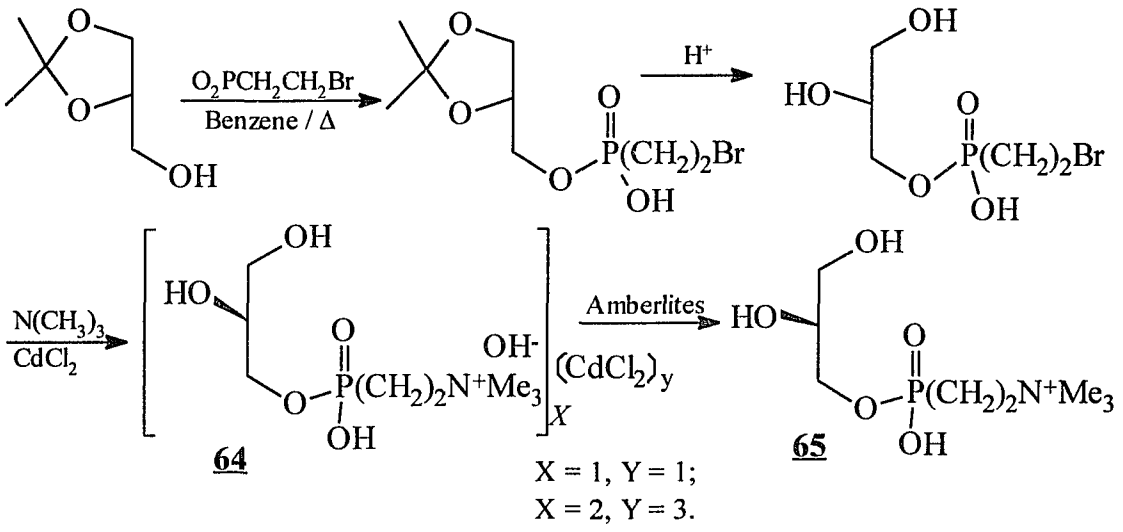
Scheme 30

Tang, *et al.*[72] reported a straightforward Arbuzov method to make phosphonic acids using a silyl phosphite. In the synthesis, tristrimethylsilyl phosphite was used with a halide compound and the resulting product (**62**) was worked-up with water to afford the free acid (**63**) [Scheme 31].



Scheme 31

Baer and Robinson[73] used cadmium chloride as a metal complex to couple the trimethylamine group with the organic halide for the syntheses of choline analogues.



Scheme 32

II. Biological Investigation of the Analogues of the PAF

In biological studies, PAF analogues have been used in order to: a) establish the structural requirements for activity; b) search for new antagonists; c) achieve possible therapeutic effects, such as selective antihypertensive activity, and d) eliminate undesirable actions, such as anaphylaxis. A large number of PAF analogues have been synthesized by varying the substituents of the glyceryl backbone. Natural PAF has an R configuration at the C_2 position. Reversion of the chirality (S isomer) leads to a very significant decrease of the activity of PAF. The 50% effective concentrations (ED_{50}) of isomers are: R = 5.7×10^{-11} M; S = 1.7×10^{-7} M; and racemic = 2.2×10^{-10} M.[23,74]

Much work has also been carried out by changing the substitution of the glyceryl backbone. At the C_1 position, the replacement of the oxygen by an

isosteric group such as sulfur,[75] methylene,[76,77] ester,[76] or various nitrogen groups leads to an almost complete disappearance of agonistic effect.[78] Varying the length of the alkyl chain can also change the effect. The maximum activity for platelet aggregation and hypotension were observed with C_{16}-C_{18} analogues whereas the maximum bronchoconstrictive effect was found with the shorter C_{14} chain.

Also the aromatic functionalized analogues of PAF were synthesized to test their biological properties. Compared to PAF, the *meta* analogue exhibited a similar activity, and the *para* analogue was active, whereas the *ortho* isomer was totally inactive for the hypotensive potency and platelet aggregation.[25] Regarding the degree of saturation, the presence of one or two double bonds in the chain slightly reinforced the agonistic activity of 1-*O*-octadecyl analogues, e.g., (18:2) > (18:1) > (18:0).[79] Multiple oxygen substitution of the alkoxy chain resulted in a significant decrease of biological responses.[25]

At the C_2 position, interest in modifying the ester function in C_2 was promoted by the observation that acetylhydrolase transforms PAF into the inactive metabolite lyso-PAF by removing the acetyl group from the C_2 (R) position.[80] Various modifications of the C_2 ester function, e.g. methyl-carbamate, do not result in an increase in potency, but significantly increase the serum half-life for the PAF isosteres (>1.7 min, half-life of the C_{16} PAF).[81] Although the propionyl homologue is nearly as active as PAF, the activity decreases rapidly as the size of the acyl group is increased.

Surprisingly, the C_2-ethoxy analogue retained ~4% of the PAF activity.[82] The residual PAF-like activity of this isostere demonstrated that no *in situ* transfer of the labile acetyl group is required for the actions of PAF, which was confirmed by the activity of both the nitrate isostere (only 15 times less active than the acetyl ester) and the *n*-Pr analogue (80 times less active).[7] Replacement of the 2-acyl function with fluoride or chloride also reduced proaggregatory activity significantly.[83] Therefore, the requirement for effectiveness seems to be mainly related to the length and the bulk of the C_2 substituent, the maximal activity being observed for substituents with a length 6-7 Angstroms.

At the C_3 position, replacement of the phosphoryl group by a phosphonate function does not modify the activity considerably.[84] However, deletion or replacement by an ethoxide,[85] a carboxyl or a methylene sulfonyl methyl function reduces significantly or abrogates the platelet-stimulatory activity.

Regarding the quaternary polar head group, replacement of the trimethylammonium portion of choline with other nitrogen-containing functions has led to analogues with potent proaggregating activities. In the choline series, the activity decreases significantly in the following order: trimethylammonium > dimethylamino > methylamino > amino group.[86] Among the numerous PAF isosteres reported, it is remarkable that those in which the quaternary ammonium group was replaced by several cyclic derivatives (such as N-methylpiperidinium, N-methylpyrrolidinium, and N-methylmorpholinium) are even more active than PAF itself.[87] The distance

between the phosphoryl group and the positive polar head is also critical: increasing the length of this bridge results in a gradual but progressive decrease in the hypotensive and platelet aggregation responses. Interestingly, the hexyl or the decyl compounds were reported to have no agonistic activity but inhibit PAF-induced platelet aggregation.[88] Similar findings have been demonstrated by substituting the choline chain with various phenyl containing groups. Analogues in which the phosphocholine function has been substituted with a methyl group have been reported. With respect to both the blood pressure and platelet aggregation responses, it is interesting to note that substitution at the alpha position of the nitrogen group significantly enhanced activity in comparison with natural PAF. In contrast, such substitution in the adjacent position to the phosphate moiety only results in little change in the biological responses.[29]

A closer examination of the S and R stereoisomers of C_1 or C_3 methyl homologues of PAF revealed that 1-(S)-methyl-PAF is a selective agonist, possessing stronger antihypertensive activity than PAF by oral dose with lower platelet activation characteristics.[89, 90]

It is also found that the stereochemistry of the 1-alkylglycerophospho-choline at the C-2 position of the glycerol, or the functional group at C-1, 2, 3, position of the backbone glycerol can vary the biological property of the ether phospholipids. Most of these studies have focused on the stereochemistry of analogues of PAF. Recently, much interest has been focused on structural analogues of PAF. It has been established that various structural analogues of the PAF show specific tumor cytotoxicity against a

number of different human cancer cells.[91,92] These observations have initiated vigorous activity in an attempt to explore the use of alkylphospholipids as drugs in antileukemic chemotherapy.

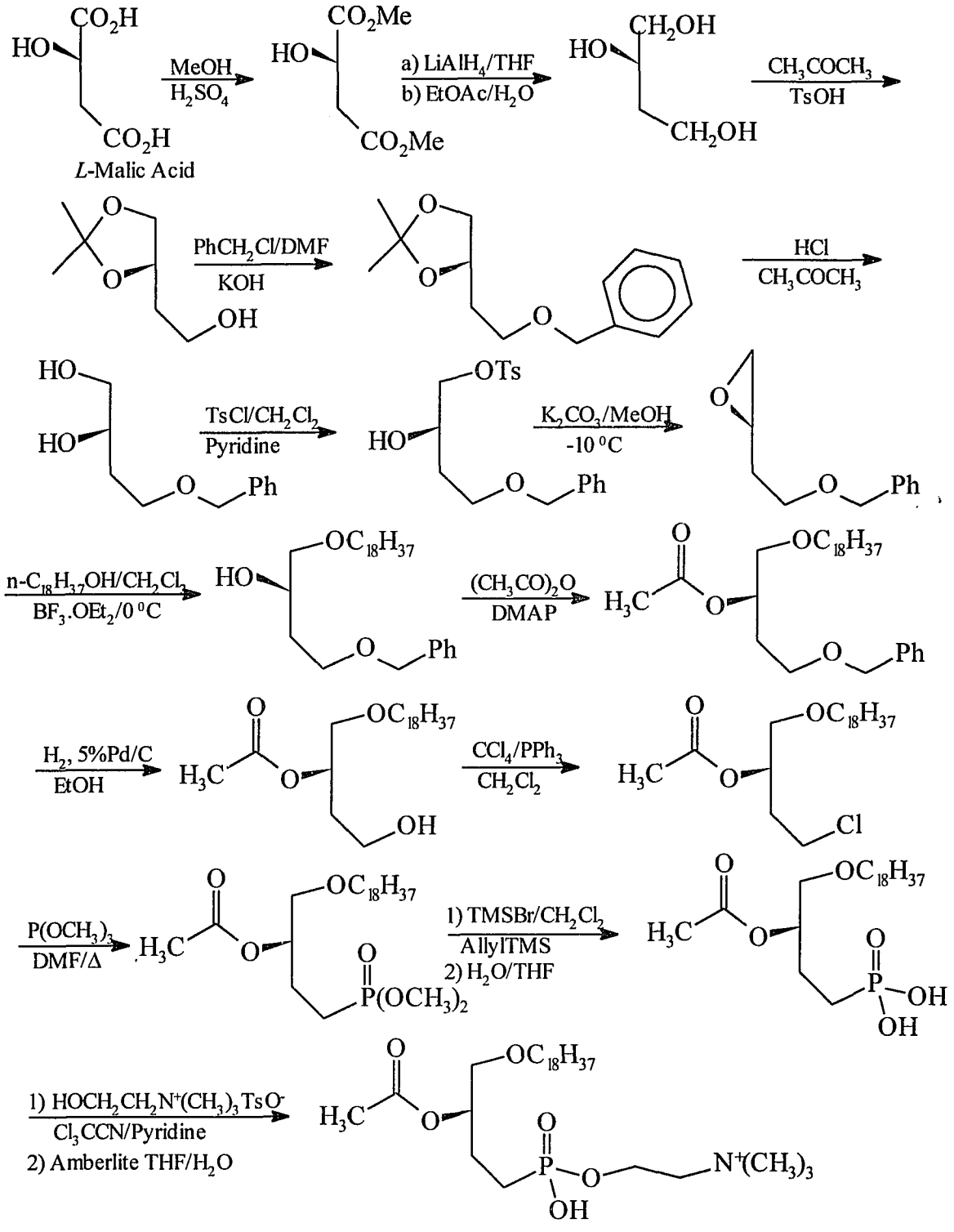
Studies of the structural analogues of PAF have been carried out with structural variation at different positions of the backbone of PAF. Natural PAF has the R configuration at the C_2 position. The S isomer decreases the biological activity in rabbit platelet aggregation, secretion and desensitization. Thus a stereospecific receptor is presumed to be involved in the PAF induced stimulation of cells.

Numerous analogues with modified polar head groups have been reported.[93] These compounds which have been synthesized are phosphoryldimethylethanolamine, phosphonocholine, phosphorylmono-methylethanolamine, phosphorylethanolamine, phosphorylethanol and phosphoryl acid analogues of PAF. Some modifications have been carried out on the methylene group between phosphorus and choline group by increasing the length of the carbon chain in the polar head group. This results in a gradual decrease in the potency with regard to rabbit platelet aggregation and secretion or hypertension.[94]

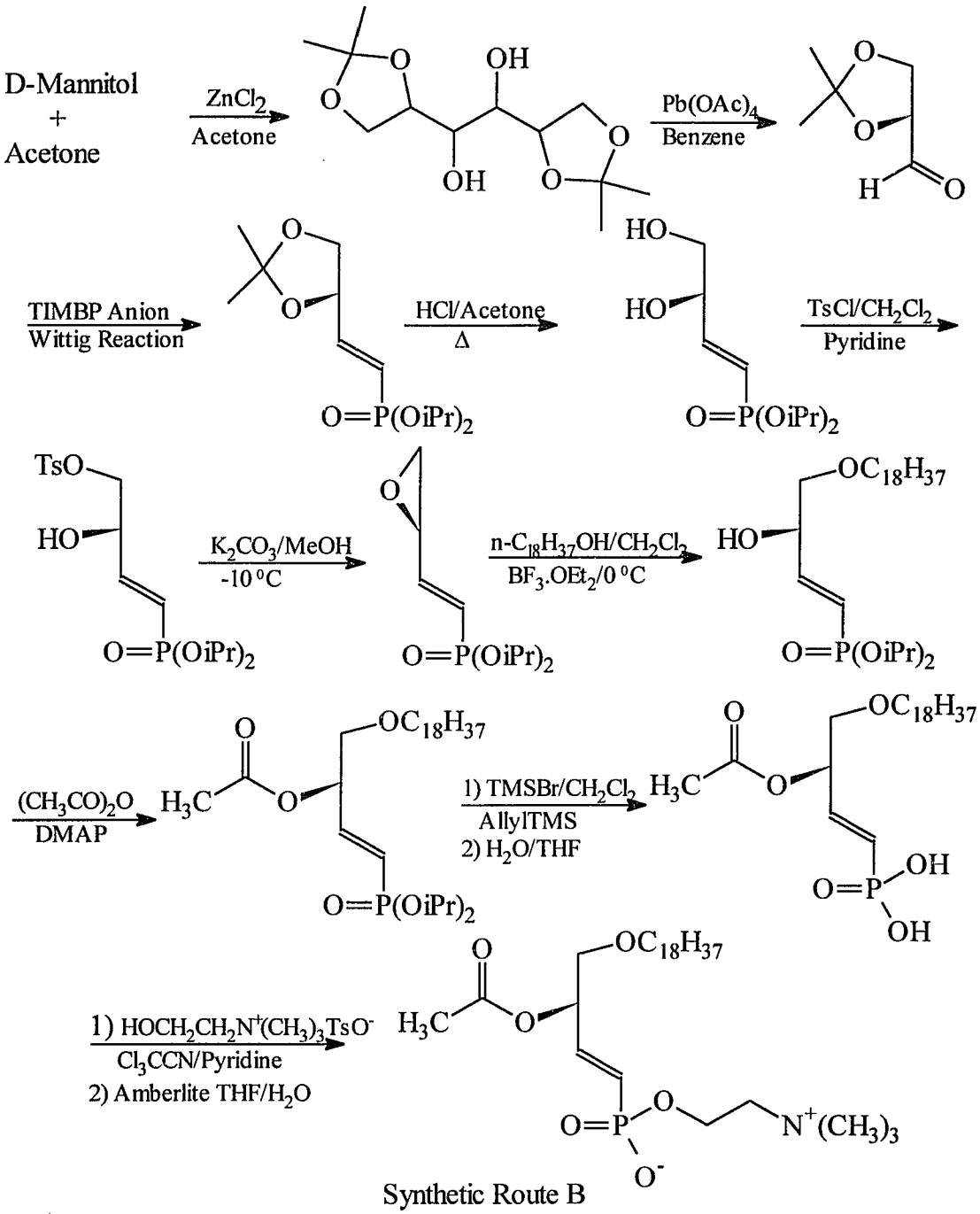
In general, the carbon phosphorus bond is a strong bond which could not be broken under normal biological conditions. This key factor can be very important for other structural analogues of PAF. A methylene group substituted for the oxygen of the backbone presents a phosphonic acid intermediate which may be combined with a choline group to lead to an interesting analogue of PAF. For this analogue, the phosphorus carbon bond

is untouched in the regular metabolism, and can change the biological activity of the material and any membrane of which it is a part.

This project is concerned with the synthesis of phosphonic acid analogues of PAF, isosteric with the natural PAF and bearing a methylene group in place of one of the normal esteric phosphate oxygen atoms.



Synthetic Route A



Synthetic Route B

Results and Discussion

A new synthetic route to an optically pure analogue of PAF was designed and brought to completion through the use of a regioselective and stereoselective procedure. In this approach, (S)-malic acid was used as a chiral starting material to generate a saturated analogue of PAF, and D-mannitol was used as a chiral source to generate an unsaturated analogue of PAF.

A. Synthesis of a Phosphonic Structural Analogue of PAF

In the synthetic route for the preparation of the saturated structural analogue of PAF, malic acid was first esterified with methanol in the presence of concentrated sulfuric acid H_2SO_4 at reflux. After work-up, the reaction mixture was purified by distillation under reduced pressure and pure (S)-dimethyl malate was collected. The ^1H NMR spectrum of (S)-dimethyl malate was in accord with the proposed structure and prior preparations.

The purified dimethyl malate was reduced using lithium aluminum hydride ($LiAlH_4$) in THF solution. After the reaction was completed, the mixture was worked-up in a standard way to afford a pure thick liquid compound, (S)-1,2,4-butanetriol. This material exhibited ^1H and ^{13}C NMR spectra in accord with its proposed structure and prior preparations.

The chiral isopropylidene acetonide type material is a very useful building block and was applied in numbers of synthetic researches.[95] This

compound was introduced as one of synthetic intermediate in this synthesis. The reaction of (S)-1,2,4-butanetriol with acetone was performed in the presence of *p*-toluenesulfonic acid monohydrate, and was worked-up in the standard manner to afford pure (S)-1,2-*O*-isopropylidenebutane-1,2,4-triol. This material also exhibited ^{1}H and ^{13}C NMR spectra in accord with the proposed structure and prior preparations. This material also exhibited a single spot on TLC.

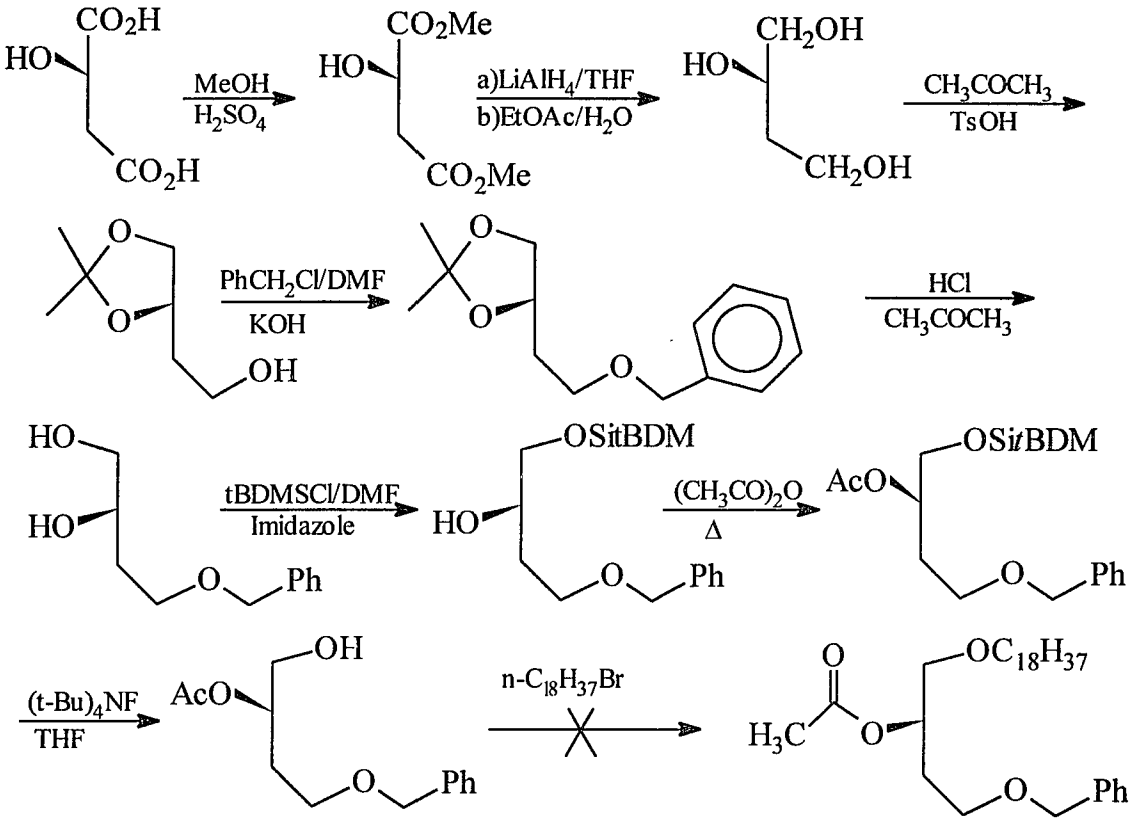
The optically active material was dissolved in dimethylformamide, converted to its potassium alkoxide form and treated with benzyl bromide to produce the (S)-4-benzyloxyl-1,2-butanediol acetonide. After removal of by-products and solvents, the residue was distilled under reduced pressure to give pure (S)-4-benzyloxy-1,2-butanediol acetonide. This compound was again analyzed with ^{1}H NMR and FT-IR, and exhibited spectra in accord with the proposed structure and prior preparations.

This material was hydrolyzed using hydrochloric acid in acetone solution to generate (S)-4-benzyloxy-1,2-butanediol. This reaction mixture was purified by column chromatography, and the resultant material exhibited spectra in accord with the proposed structure and prior preparations.

The pure (S)-4-benzyloxy-1,2-butanediol was dissolved in alcohol free chloroform and was treated with an equivalent amount of *p*-toluenesulfonyl chloride[96] in an excess of pyridine at 0°C. In this reaction, an exact equivalent amount of the *p*-toluenesulfonyl chloride must be added as the substrate. If excess of acid chloride exists in the system, it can react with

both secondary alcohol and primary alcohol group, even though the primary alcohol site reacts with acid chloride faster than does the secondary alcohol site. The resultant ditosylated compound could not produce an epoxide in the next step. The monotosylated compound was analyzed by ^{1}H NMR and exhibited a spectrum in accord with the proposed structure. Tosylation of the primary hydroxyl group produces a downfield shift of the protons attached to the primary carbon. Integration of the shifted signal indicates that monotosylation occurred at the primary position.

The monotosylate was treated with K_2CO_3 in methanol at -10°C.[97] On working-up of the reaction, the product was purified by column chromatography to give pure (S)-1,2-epoxy-4-benzyloxybutane. In this reaction, the use of K_2CO_3 at low temperature and for a short time minimizes side reactions. If the temperature were high, the epoxide could react with methanol and produce a mixture of products. The purified compound was checked by HPLC with a chiral chromatographic column and exhibited only one peak. The ^{1}H NMR spectrum of the material showed signal couplings which could be interpreted only by the presence of an epoxide. The ^{1}H NMR spectrum shows three groups of signals in the region δ = 2.60-3.15. There is a quartet at δ = 2.68-2.72, a triplet at δ = 2.88-2.94, and a multiplet at δ = 3.22-3.28. Each signal represents one proton. The multiplet results from the proton at the chiral center which is coupled to two protons on the epoxide ring and a methylene group next to it. The quartet and triplet signal are an ABX system.



Synthetic Route C

The (S)-1,2-epoxy-4-benzyloxybutane was treated with *n*-1-octadecanol in the presence of boron trifluoride etherate in methylene chloride.[98] This reaction gave regioselective ring opening with preferred addition at primary position. The mechanism of the reaction will be discussed in Chapter 2. Analysis of the crude reaction mixture indicates that the primary substituted product is favored by a factor of 48 over the secondary substituted product. The purified compound was acetylated with acetic anhydride in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) at 0°C.

Before using this regioselective ring opening route to the PAF analogue, use of a silyl ether protecting group to block the primary alcohol was used

while the secondary alcohol was acetylated. In this reaction, DMAP was not used as the catalyst. After acetylation, the silyl ether was removed and formation of a primary ether bond was attempted. This reaction was attempted under several sets of conditions, but all failed. This approach was abandoned (see synthetic route C).

The benzyloxy protecting group was removed by palladium catalyzed hydrogenation[99] in absolute ethanol solution. This procedure is clean with 100% conversion. No acetyl group migration occurred in this step. This migration would form a six member ring which is a slow step. With one carbon less in the system, five member ring formation is faster and the acetyl group migration could occur. The ^{1}H NMR spectra were measured regularly over a period of a month, each time being compared with the previous one; no acetyl group migration was found to occur. The migration could happen on the surface of the silica gel during purification. To prevent this kind migration, the compound was not purified after initial isolation. The compound was chlorinated with carbon tetrachloride catalyzed by triphenyl phosphine. The addition of triphenyl phosphine must be very slow; if addition were too fast, the product was a mixture of several materials. Generally, this addition was done over several hours in 6 mL of dry methylene chloride.

The halogenated compound was phosphonylated with trimethyl phosphite by an Abuzov reaction.[100] After this material was purified, the methyl ester groups were removed by silylation with bromotrimethylsilane in the presence of allyltrimethylsilane,[101] and then was stirred with water to

form the phosphonic acid. Under these conditions the methyl ester groups could be cleaved without breaking any other bond. If no allyltrimethyl-silane was present in the system, the by-product of the reaction, HCl, could affect the reaction and cleave the acetyl bond. The allyl group reacts with any trace of hydrochloric acid that forms during the reaction and prevents any side reaction from occurring.

The choline coupling reaction[102] must be performed under highly controlled conditions. The reaction system must be absolutely dry. All reactants were dried in a hot pistol under vacuum for 48 hours in the presence of P_2O_5 before they were used. All solvents were dried and fresh distilled before they were used. The reaction mixture was kept at a constant 50°C for 72 hours. After removal of the solvents, the residue was purified using an amberlite MB 3 resin eluted with THF-water solvent. A pure phosphonic analogue (2) of PAF was produced.

B. Synthesis of an Unsaturated Phosphonic Structural Analogue of PAF

In the synthesis of an unsaturated phosphonic analogue (3) of PAF, D-mannitol was used as a starting material. D-Mannitol has a C_2 symmetric center between carbon atoms C_3 and C_4. When the carbon-carbon bond between C_3-C_4 is cleaved, the two broken parts are identical. Diacetone D-mannitol was first synthesized by Fischer, *et al.*,[103] and a slightly modified method was followed. Diacetone D-mannitol was precipitated from petroleum ether. After it was dried, diacetone D-mannitol was oxidized by lead (IV) tetraacetate to produce isopropylidene glyceraldehyde. The

optically pure isopropylidene glycerol can undergo a partial racemization at pH<6, but does not undergo racemization at pH>8.[104] The cleavage reaction was pursued at pH = 8-9 to prevent racemization. Next, the aldehyde was treated with a phosphorus carbanion derived from tetraisopropyl methylenebisphosphonate (TIMBP).[105] A double bond was introduced to the backbone of the analogue of phosphonic ester through an Emmons-Horner[106-108] reaction producing a product with a stereogenic center at the C_3 position. The aldehyde used in this reaction must be freshly synthesized without carboxylic acid present.

The isopropylidene protecting group was removed by acid hydrolysis in aqueous acetone. The resultant diol retains the (S)-configuration at the C_3 position. In this hydrolysis, only the acetonide group was removed and the isopropyl groups on the phosphonic ester were not cleaved. Following the same procedure as was used in making compound 2, an epoxide intermediate was generated which could be used to produce an ether bond at the terminal position. The diol was first monotosylated at the primary position. In this reaction, an equivalent amount of *p*-toluenesulfonyl chloride was added to the substrate in chloroform solution. If an excess amount of the *p*-toluenesulfonyl chloride were added to the solution, a lower yield and less pure product would be produced. By TLC and HPLC analyses of the reaction mixture, only materials were found which corresponded to the unreacted substrate and the monotosylated product. After purification, the position of the tosylate group was confirmed by ^1H NMR to be at the primary position. The purified compound was epoxidized

using potassium carbonate at -10°C in methanol. The resultant epoxide was optically active with retention of configuration at C_3. The existence of the double bond next to the chiral center did not affect the epoxy ring formation.

The epoxy compound was treated with *n*-1-octadecanol in the presence of boron trifluoride etherate to effect a regioselective ring opening. On chiral HPLC analysis, the product mixture showed two peaks with an integration ratio of 85:15. After the two fractions were separated, each was analyzed by FT-IR and NMR. The FT-IR spectra for the two compounds were similar, but there was a difference in their proton NMR spectra by which structural differences could be identified. For the major product, the proton on the secondary carbon next to the double bond was farther downfield because of the hybridization of the adjacent carbon. If attack were to occur at the secondary alcohol position, the proton couplings and integral area would have been different. The primary attacked product should be less polar than the secondary product, and the HPLC analysis showed that the major peak had the shorter retention time. This result confirmed that the terminal attacked product was the major compound of the reaction.

This product was acetylated in the presence of a catalytic amount of DMAP. The reaction could be completed at low temperatures in two hours, following the course of the reaction by TLC. The purified compound was analyzed by ^{1}H and ^{13}C NMR. Both ^{1}H and ^{13}C NMR spectra confirmed the proposed structure.

The isopropyl groups on the phosphonic ester were removed by treatment with bromotrimethylsilane in the presence of allyltrimethylsilane. The resultant purified phosphonic acid was a white solid whose spectra and elemental analyses matched the proposed structure. The choline coupling reaction was performed as previously noted for the saturated analogue. After purification using an amberlite MB 3 resin column, the pure unsaturated analogue (3) of PAF was isolated.

EXPERIMENTAL SECTION

General

All chemicals were of reagent quality and used without further purification with the following exceptions: methanol and methylene chloride were dried and distilled over calcium hydride and stored over molecular sieves 3A; THF was dried over sodium metal and distilled under sodium benzophenone ketyl indicator and was used immediately; chloroform was distilled over phosphorus pentoxide and stored over molecular sieves 3A; benzene and toluene was distilled and stored over sodium metal; hexane, ethyl acetate and boron trifluoride etherate were distilled prior to use; pyridine and triethylamine were dried over calcium hydride, distilled, and used immediately; acetone was dried over $MgSO_4$ for several days; dimethylformamide (DMF) was dried over molecular sieves prior to use; boron trifluoride etherate was distilled and mixed with 9 parts of methylene chloride to form a 0.81M solution and stored under a nitrogen atmosphere; choline tosylate was synthesized by a known standard procedure and was dried prior to use; TLC plates were purchased from Eastman Kodak, 0.26 mm thick on plastic film and were predeveloped with ethyl acetate before the application of samples; silica gel was purchased from J. T. Baker Corp. and was of 230-400 mesh; ^{1}H and ^{13}C NMR were recorded using a 60 MHz instrument from Varian E360 and a 200 MHz instrument from IBM Bruker; FT-IR spectra were recorded on a Perkin

Elmer PE1600 instrument; optical rotations were measured using a JASCO DIP-140 spectropolarimeter.

A. Synthesis of an Analogue of PAF

Preparation of (S)-dimethyl malate

51 g (0.38 mol) of (S)-malic acid was added with 100 mL of absolute methanol into a three neck flask which was equipped with a condenser, a drying tube and a thermometer. The mixture was stirred to allow all the malic acid to be dissolved. Then, 6.0 mL of concentrated sulfuric acid was slowly and cautiously added with cooling. Then the reaction mixture was heated at reflux for 18 hr. After it was cooled to room temperature, 10.50 g of anhydrous sodium bicarbonate was added in portions until no further bubbling occurred. The solution was filtered through a sintered glass funnel and the solid was washed with 50 mL of methanol. The filtrates were combined and the solvent was evaporated under reduced pressure. The resultant residue was distilled under vacuum, collecting the fraction boiling between 108-110°C/1.5 Torr.

Yield: 58.7 g (95.1 %).

^{1}H NMR ($CDCl_3$): δ 2.80-2.90, 2H, (t); δ 3.50, 1H, (bs); δ 3.75-3.90, 6H, (d); δ 4.50-4.60, 1H, (t).

Preparation of (S)-1,2,4-butanetriol

Into a three neck 3 L r.b. flask equipped with a Friedrich condenser, a drying tube, a nitrogen tube, and a 125 mL addition funnel, was added 1600 mL of freshly distilled THF, and to it was then added slowly with cautious stirring, 32.00 g of lithium aluminum hydride. Then, 40.5 g (0.25 mole) of (S)-dimethyl malate in 90 mL of dried THF was added dropwise over a period of 2 hr. The reaction mixture was then stirred at room temperature for 18 hr. At that time, the mixture was heated at reflux for 3 hr and stirred at room temperature for another 18 hr.

To the reaction mixture with cooling, 110 mL of ethyl acetate was added slowly in 1 hr and the mixture was stirred at room temperature for another 1 hr. Then, 250 mL of distilled water was added slowly with cooling and stirred for 16 hr at room temperature. The solution was heated at reflux and then cooled to room temperature. The white colloidal suspension was filtered through a course sintered glass funnel and the precipitate was washed with 300 mL ethyl ether and 300 mL ethanol. This procedure took a whole day to finish, because the colloidal aluminum hydroxide was difficult to remove. The filtrates were combined and the solvents were evaporated under reduced pressure. To the residue, 300 mL of chloroform and 280 mL of absolute ethanol were added, and the solution was filtered again and solvents were evaporated. Then, 200 mL of absolute ethanol was added and the solvents were again removed under vacuum. The resultant residue was a thick liquid and could only be dissolved in polar solvents such as ethanol and water. The ^{1}H NMR spectrum was measured in deuterium oxide and the spectrum agreed with the proposed structure.

Yield: 26.00 g (98.1 %).

^{1}H NMR (D_2O): δ 1.80-1.95, 2H, (m); δ 3.50-3.60, 2H, (dd); δ 3.70-3.80, 2H, (t); δ 3.90-4.00, 1H, (q).

Preparation of (S)-1,2-*O*-isopropylidenebutane-1,2,4-triol

In 800 mL of dried acetone 10.1 g (0.095 mol) of (S)-1,2,4-butanetriol was dissolved in a 2 L flask equipped with a drying tube and a condenser. To the well stirred solution 3.0 g of 98% toluenesulfonic acid monohydrate was added and the was stirred at room temperature for 12 hr. At that time, 15.0 g of anhydrous sodium bicarbonate was added to the solution and allowed to stir for another 30 minutes. Then, the solution was filtered and the solid was washed with 100 mL of acetone. The solvent was removed under reduced pressure and the resultant residue was distilled under vacuum, collecting the fraction boiling between 68-70°C/0.45 Torr.

Yield: 12.8 g (92.2 %).

^{1}H NMR ($CDCl_3$): δ 1.35-1.45, 6H, (d); δ 1.80-1.95, 2H, (m); δ 2.90-3.00, 1H, (bs); δ 3.40-3.50, 2H, (m); δ 3.90-4.00, 2H, (m); δ 4.10-4.20, 1H, (m).

Preparation of (S)-4-benzyloxy-1,2-butanediol acetonide

(S)-1,2-*O*-Isopropylidenebutane-1,2,4-triol [14.62 g (0.10 mol)] was added with 60 mL of dry dimethylformamide into a 250 mL three neck flask which was equipped with a condenser, drying tube, addition funnel, and a nitrogen inlet tube. 97% Sodium hydride [3.0 g (0.12 mol)] was slowly

added to the well stirred solution with cooling. After the mixture was stirred at room temperature for 30 min and no further bubbling could be observed, 21.0 g (0.12 mol) of benzylbromide in 20 mL of DMF was added dropwise in one hour, and the mixture was stirred for another 20 min. Then, the mixture was heated with an oil bath at 80°C for 2 hr. At that time the heating was stopped and the reaction mixture was allowed to stir at room temperature for 18 hr. Ethanol (15 mL, 95%) was added along with 75 mL of water. The resultant mixture was extracted with 5 X 75 mL of ethyl ether. The organic layers were combined and were washed with 2 X 50 mL of 10% aqueous sodium bicarbonate solution and 50 mL of water. The organic solution was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was distilled under vacuum, collecting the distillate boiling at 110-112°C/0.8 Torr.

Yield: 18.6 g (78.8 %).

^{1}H NMR ($CDCl_3$): δ 1.35-1.45, 6H, (d); δ 1.80-1.95, 2H, (m); δ 3.50-3.65, 3H, (m); δ 4.00-4.10, 1H, (t); δ 4.12-4.25, 1H, (m); δ 4.55, 2H, (s); δ 7.25-7.35, 5H, (m).

Preparation of (S)-4-benzyloxybutane-1,2-diol

Into a 100 mL r.b. flask, 11.80 g (0.05 mol) of (S)-4-benzyloxy-1,2-butanediol acetonide was added with 35 mL of acetone. After stirring 5 min, 7.0 mL of concentrated hydrochloric acid was added along with 10 mL of water and the mixture was heated at reflux for one hour and at room temperature for a further 16 hr. At that time 25 mL of ethanol was added

and the volatile materials were removed under reduced pressure. Repeated addition of 30 mL portions of ethanol. The residue was purified by column chromatography, packed and eluted with 1:1 hexane/ethyl acetate. The fractions exhibiting R_f = 0.45 (ethyl acetate) were collected. The solvent was removed from these fractions under reduced pressure to give the desired product.

Yield: 9.80 g (100.0 %).

^{1}H NMR ($CDCl_3$): δ 1.65-1.90, 2H, (m); δ 2.85-3.10, 2H, (s); δ 3.45-3.60, 2H, (t); δ 3.65-3.85, 2H, (dd); δ 3.90-4.00, 1H, (m); δ 4.55, 2H, (s); δ 7.25-7.40, 5H, (m). $[\alpha]_{25}$ = -22.04 (c = 1.52 g/100 mL ethanol).

Preparation of (S)-4-benzyloxy-1-tosyloxy-2-hydroxybutane

In a 100 mL r.b. flask, 4.20 g (21.4 mmol) of (S)-4-benzyloxy-1,2-butanediol was added with 50 mL of dry $CHCl_3$ and 3.60 mL (44.5 mmol) of distilled pyridine. After the mixture was stirred at 0°C for 5 min, 4.10 g (21.4 mmol) of 99% *p*-toluenesulfonyl chloride in 5 mL $CHCl_3$ was added dropwise over a period of 2 min. The mixture was stirred at 0°C for 2.5 hr, then was allowed to warm to room temperature, and stirred for another 2 hr. At that time 50 mL of ethyl ether was added and the mixture was stirred for 15 minutes. The solution was transferred to a separatory funnel, and 150 mL of ethyl ether was added into the funnel and the mixture was washed with 2 X 15 mL water. The organic layer was dried over anhydrous $CaCl_2$ and volatile materials were removed under reduced pressure. The residue was a light yellow liquid. TLC eluting with 2:1 C_6H_{14}:EtOAc showed a

major spot with R_f = 0.80 and trace of reactant at origin which was the unreacted substrate.

Yield: 7.00 g (94.1 %).

^{1}H NMR ($CDCl_3$): δ 1.55-1.85, 2H, (m); δ 2.40, 3H, (s); δ 2.90, 1H, (bs); δ 3.50-3.70, 2H, (m); δ 3.90-4.05, 3H, (m); δ 4.55, 2H, (s); δ 7.28-7.48, 5H, (m); δ 7.20-7.85, 4H, (dd).

Preparation of (S)-1,2-epoxy-4-benzyloxylbutane

In a 50 mL r.b. flask, 3.5g (10.0 mmol) of (S)-1-tosyloxy-4-benzyloxy-2-butanol was added with 30 mL of absolute methanol. The mixture was stirred at -10°C for 10 minutes. Then, 1.70 g (12.3 mmol) of finely ground anhydrous K_2CO_3 was added in one portion. The mixture was stirred for 3 hr at -10°C and at room temperature (25°C) for another 2 hr. At that time 50 mL of ethyl ether was added to the solution and stirred for 10 minutes at room temperature. The resultant precipitate was filtered through a pad of Celite (1.0 cm thick) and 100 mL of ethyl ether was used to wash the precipitate. The filtrates were combined and solvents were removed under reduced pressure. The residue was checked with TLC eluted with hexane/chloroform in 2:1. After column chromatography purification, the fractions exhibiting R_f = 0.70 (2:1 C_6H_{14}:$CHCl_3$) were collected. The solvent from the collected fractions was removed under reduced pressure and the residue was the target product, and also 0.15 g of (S)-1-benzyloxy-1,2-butanediol was recovered.

Yield: 1.65 g (98.0 %).

Elemental analysis: Found: C; 74.49%, H; 7.89%. Calculated: C; 74.13%, H; 7.92%.

^{1}H NMR ($CDCl_3$): δ 1.70-1.85, 2H, (m); δ 2.47-2.56, 1H, (dd); δ 2.75-2.85, 1H, (t), δ 3.05-3.15, 1H, (m); δ 3.55-3.70, 2H, (t); δ 4.55, 2H, (s); δ 7.28-7.48, 5H, (s). $[\alpha]_{25}$ = -14.81 (c = 1.452 g/ 100 mL ethanol).

Preparation of (S)-1-octadecyloxy-2-hydroxy-4-benzyloxybutane

In a 50 mL r.b. flask 0.50 mL of 10% boron trifluoride etherate (0.81 M) methylene chloride solution was added to a mixture of 1.60 g (9.0 mmol) of (S)-1,2-epoxy-4-benzyloxybutane and 2.43 g (9.0 mmol) of *n*-1-octadecanol in 25 mL of methylene chloride at 0°C. After stirring for 10 minutes the mixture was allowed to warm to room temperature and was stirred for an additional 24 hr. At that time volatile materials were removed under reduced pressure and the resultant residue was purified by column chromatography, packed with hexane/chloroform and eluted with hexane/ethyl acetate, collecting the fractions exhibiting R_f = 0.60 (3:1 C_6H_{14}:EtOAc). Solvents from the collected fractions were removed under reduced pressure.

Yield: 3.90 g (97.2%, ee: 95%).

Elemental analysis: Found: C; 77.62%, H; 11.68%. Calculated: C; 77.91%, H; 11.83%.

^{1}H NMR ($CDCl_3$): δ 0.80-0.95, 3H, (t); δ 1.15-1.35, 30H, (s); δ 1.65-1.75, 4H, (m); δ 2.80-2.90, 1H, (bs); δ 3.40-3.60, 4H, (m); δ 3.75-3.90, 2H, (m); δ 3.95-4.05, 1H, (m); δ 4.55, 2H, (s); δ 7.25-7.40, 5H, (s).

$[\alpha]_{25}$ = -15.69 (c = 1.02 g/100 mL ethanol).

Preparation of (S)-2-acetyl-1-octadecyloxy-4-benzyloxylbutane

In a 50 mL r.b. flask 3.00 g (6.68 mmol) of (S)-1-octadecyloxy-4-benzyloxy-2-butanol was added with 15 mL of methylene chloride and 15 mL of acetic anhydride. The mixture was stirred at 0°C for 10 minutes after which 20 mg of DMAP (*p*-dimethylaminopyridine) was added. The mixture was allowed to warm up to room temperature and was stirred for 2 hr. At that time volatile materials were removed under reduced pressure and the residue was purified using column chromatography, eluting with chloroform/hexane. Fractions exhibiting R_f = 0.50 (1:1, $CHCl_3$:C_6H_{14}) were collected.

Yield: 3.27 g (100 %).

Elementary analysis: Found: C; 75.61%, H; 11.12%; Calculated: C; 75.87%, H; 11.09%.

^{1}H NMR ($CDCl_3$): δ 0.80-0.95, 3H, (t); δ 1.15-1.35, 30H, (s); δ 1.65-1.75, 4H, (m); δ 2.10, 3H, (s); δ 3.40-3.60, 4H, (m); δ 3.75-3.90, 2H, (m); δ 3.95-4.05, 1H, (m); δ 4.55, 2H, (s); δ 7.25-7.40, 5H, (s).

$[\alpha]_{25}$ = -14.86 (c = 1.40 g/100 mL ethanol)

Preparation of (S)-2-acetyl-1-octadecyloxy-4-butanol

In a 50 mL r.b. flask 2.02 g (4.11 mmol) of (S)-1-octadecyloxy-2-acetyl-4-benzyloxybutane was added with 25 mL of 95% ethanol. The mixture was stirred for 10 minutes under nitrogen. Then, 0.51 g of 5%

palladium on activated carbon was added. A hydrogen balloon was installed on the flask and the solution was stirred at room temperature for 20 hr. At that time the reaction mixture was filtered through a pad of Celite (1.0 cm thick) with a sintered glass funnel to remove the catalyst and the solid was washed with 75 mL of absolute ethanol. Volatile materials were removed from the combined filtrates under reduced pressure. The residue was checked by TLC and exhibited only one spot with R_f = 0.70 (2:1 C_6H_{14}:EtOAc).

Yield: 1.64 g (100%).

Elemental analysis: Found: C; 71.63%, H; 12.00%; Calculated: C; 71.95%, H; 12.08%.

^{1}H NMR ($CDCl_3$): δ 0.80-0.95, 3H, (t); δ 1.28-1.40, 30H, (s); δ 1.45-1.60, 4H, (m); δ 2.10, 3H, (s); δ 2.45-2.55, 1H, (bs); δ 3.30-3.60, 4H; (m); δ 3.85-3.95, 1H, (m), δ 4.20-4.35, 2H, (m).

$[\alpha]_{25}$ = -9.52 (c=1.04 g/100 mL ethanol)

Preparation of (S)-1-chloro-3-acetyl-4-octadecyloxybutane

In a 50 mL r.b. flask 3.90 g (9.73 mmol) of (S)-1-octadecyloxy-2-acetyl-4-butanol was placed with 5 mL of dried CH_2Cl_2 and 3.24 g of dried CCl_4. The mixture was stirred for 10 minutes, and then 3.57 g of triphenyl phosphine (9.73 mmol) in 6 mL of CH_2Cl_2 was added over a period of 5 hr. After the addition was finished, the mixture was stirred at room temperature for another two hours, and then 40 mL of dried pentane was added to the mixture. A white precipitate formed immediately, and the reaction mixture

was stirred for another 30 minutes. The solution was filtered through a sintered glass funnel and the white precipitate was washed with 50 mL of pentane. The filtrates were combined and volatile materials were removed under reduced pressure. The residue was purified by column chromatography eluting with hexane/ethyl acetate. Collecting the fractions exhibiting $R_f = 0.80$ (3:1, C_6H_{14} : EtOAc).

Yield: 3.62 g (88.7%).

Elemental analysis: Found: C; 68.60%, H; 11.20%; Calculated: C; 68.78%, H; 11.30%. GC-MS showed the MW was 419.10.

^{1}H NMR ($CDCl_3$): δ 0.80-0.95, 3H, (t); δ 1.28-1.40, 30H, (s); δ 1.45-1.60, 4H, (m); δ 2.10, 3H, (s); δ 3.40-3.65, 4H; (m); δ 4.20-4.35, 2H, (m); δ 5.10-5.18, 1H, (m). $[\alpha]_{25} = 11.76$ (c = 1.076 g/100 mL ethanol)

Preparation of (S)-3-acetyl-4-octadecyloxybutane-1-phosphonic acid, dimethyl ester

In a 50 mL r.b. flask equipped with a condenser and a nitrogen blanket, 3.62 g (8.63 mmol) of (S)-1-chloro-3-acetyl-4-octadecyloxybutane was added with 10 mL of DMF. After the mixture was stirred for 10 minutes, 15.0 g of freshly distilled trimethyl phosphite was added to the mixture. The reaction mixture was stirred and heated with an oil bath and the temperature was controlled between 135°C and 140°C under a nitrogen atmosphere for 48 hr. At that time the mixture was cooled to room temperature and volatile materials were evaporated under vacuum. The residue was purified by column chromatography, packed and eluted with hexane/chloroform/ethyl

acetate, collecting the fractions exhibiting $R_f = 0.40$ ($CHCl_3$). The solvents from the fractions were removed under reduced pressure and residue was collected.

Yield: 2.5 g (59.0 %).

Elemental analysis: Found: C; 63.44%, H; 10.84%; Calculated: C; 63.39%, H; 10.84%.

^1H NMR ($CDCl_3$): δ 0.80-0.95, 3H, (t); δ 1.28-1.40, 30H, (s); δ 1.45-1.60, 4H, (m); δ 2.10, 3H, (s); δ 3.35-3.70, 4H, (m); δ 3.70-3.90, 6H, (d); δ 4.05-4.35, 2H, (m); δ 5.05-5.18, 1H, (m).

$[\alpha]_{25} = -2.67$ (c = 1.20 g/100 mL ethanol)

Preparation of (S)-3-acetyl-4-octadecyloxybutane-1-phosphonic acid

In a 25 mL r.b. flask flushed with nitrogen, 1.50 g (3.04 mmol) of (S)-3-acetyl-4-octadecyloxybutane-1-phosphonic acid, dimethyl ester was added with 5 mL of dry CH_2Cl_2. After the solution was stirred at -10°C for 10 minutes, 1.50 g of allyltrimethylsilane and 4.0 g of bromotrimethylsilane were added separately. Then the mixture was stirred at -10°C for 15 minutes and at room temperature for 5 minutes. The reaction was stopped by adding 5 mL of 95% ethanol and all volatile materials were removed under reduced pressure immediately. The residue was checked by ^1H NMR spectrum in which the two peaks at δ = 3-4 had disappeared. Then, 5 mL of dry benzene was added to the residue and the mixture was evaporated at 0°C under vacuum for 3 hr to remove all volatile materials.

Yield : 1.28 g (90.5 %).

Elemental analysis: Found: C; 62.01%, H; 10.85%. Calculated: C; 62.04%, H; 10.63%. GC-MS showed the MW was 464.61.

^{1}H NMR ($CDCl_3$): δ 0.80-0.95, 3H, (t); δ 1.28-1.40, 30H, (s); δ 1.45-1.60, 4H, (m); δ 2.10, 3H, (s); δ 3.30-3.55, 4H, (m); δ 4.05-4.20, 2H, (m); δ 5.05-5.18, 1H, (m); δ 7.80-8.30, 2H, (bs).

[α] = -5.05 (c = 0.50 g/100 mL ethanol)

Preparation of (S)-3-acetyl-4-octadecyloxybutane-1-phosphonic acid, choline (analogue of PAF)

In a dry 25 mL r.b. flask 464 mg of dried (S)-3-acetyl-4-octadecyloxy-butane-1-phosphonic acid was added with 7.0 mL of fresh distilled pyridine. After the mixture dissolved under nitrogen protection, 1.60 g of dried choline tosylate was added. After the mixture was stirred at room temperature for 10 min, 2.00 g of trichloroacetonitrile was added. The system was allowed to warm up to 50°C under nitrogen and was stirred for 72 hr at constant temperature. All volatile materials were stripped off under reduced pressure.

Cold acetonitrile (30 mL) was added to the residue. The resultant precipitate was separated by filtration through a sintered glass funnel and the solid was washed with 10 mL of cold acetonitrile. The solid was dissolved in 2.0 mL of THF/H_2O (9:1). An amberlite MB-3 resin (60.0 g) column was packed with water and was rinsed with 300 mL 0.2 N HCl solution and 200 mL deionized water. The material in the 2.0 mL of THF/water was added to the column and was eluted with 500 mL of 9:1

THF/water solvent. The first 300 mL of eluent were collected and solvent was removed under reduced pressure. The residue was dissolved in 10 mL of dry benzene and was evaporated under vacuum at 0°C. 210 mg

Yield: 210 mg (39.2 %).

Elemental analysis: Found: C; 63.36%, H; 11.00%. Calculated: C; 63.36%, H; 11.35%. GC-MS shown the MW was 551.55.

^{1}H NMR ($CDCl_3$): δ 0.80-0.95, 3H, (t); δ 1.28-1.40, 30H, (s); δ 1.45-1.60, 4H, (m); δ 2.10, 3H, (s); δ 3.25, 9H, (s); δ 3.30-3.55, 4H, (m); δ 3.70-3.80, 2H, (m) δ 3.90-4.05, 2H, (m); δ 4.25-4.45, 2H, (m); δ 5.05-5.18, 1H, (m).

$[\alpha] = -4.58$ (c = 0.50 g/100 mL ethanol)

B. Synthesis of Unsaturated of Analogue of PAF

Preparation of diacetone D-mannitol

To 900 mL of acetone in a 1 L Erlenmeyer flask with magnetic stirrer was added 130 g of anhydrous zinc chloride. After the solution was stirred for 4 hr., the solid was filtered with suction and 36.40 g (0.2 mol) of D-mannitol was added to the filtrate.

The reaction mixture was stirred at room temperature for 18 hr. and unreacted D-mannitol was filtered through a fine sintered glass funnel. The filtrate was added to a solution of 220 g of K_2CO_3 and 220 mL of water and 900 mL of ethyl ether was added to the mixture and the mixture shaken vigorously at regular intervals for 2 hr.

The mixture was filtered again and the solid was washed with 4 X 250 mL 1:1 (acetone : ethyl ether). The filtrates were combined and volatile materials were evaporated under reduced pressure. Then, 250 mL of petroleum ether with a boiling point of 30-60°C was added to the residue and the mixture was heated at reflux for 30 min. over a hot plate. After the mixture was cooled, solvents were decanted and the solid was scratched off of the walls of the flask. This procedure was repeated twice. After the solvent was decanted, the solid was dried under vacuum.

Yield: 44.5g (85.1 %).

^{1}H NMR ($CDCl_3$): δ 1.35-1.50, 12H, (dd); δ 2.90-3.10, 2H, (bs); δ 3.45-4.20, 8H, (m).

Preparation of (S)-(E)-3,4-*O*-isopropylidene-3,4-dihydroxybut-1-enylphosphonic acid, diisopropyl ester

To a 1 L three neck flask fitted with a magnetic stirrer, a dropping funnel with a septum, a reflux condenser, and N_2 line was added 36.00 g TIMBP and 550 mL heptane. The system was flushed with N_2 for 1 hr. Then, 48 mL of 2.5 M BuLi in hexane, measured with syringe, was added through a septum cap. The mixture was stirred at room temperature for 3 hr.

Simultaneously, in a 1 L Erlenmeyer fitted with a magnetic stirrer, was placed 18 g of 1,2:5,6-di-*O*-isopropylidene-D-Mannitol in 600 mL of benzene. Then, 28.00 g of anhydrous $Pb(OAc)_4$ was added. The mixture was stirred at room temperature for 3 hr. The precipitate was filtered through with suction and the solvent was evaporated under reduced pressure without

heating. The colorless residue was dissolved in 60 mL of hexane and was added dropwise to the TIMBP anion solution with an ice bath cooling. An additional 60 mL of hexane was added and the mixture was allowed to warm to room temperature.

After the solution was stirred under N_2 at room temperature for 14 hr, the reaction mixture was heated at reflux for another 2 hr. After it was cooled, the mixture was washed with water (2 X 600 mL) and the aqueous layer was extracted with heptane (2 X 300 mL). The organic layers were combined and dried over $CaCl_2$. The solution was filtered and volatile materials were evaporated under reduced pressure.

Yield: 21.03 g (52.4 %).

^{1}H NMR ($CDCl_3$): δ 1.35-1.50, 18H, (m); δ 3.75-3.90, 2H, (m); δ 4.20-4.30, 1H, (m); δ 4.65-4.80, 2H, (m); δ 6.00-6.25, 1H, (dt); δ 6.70-6.95, 1H, (dt).

Preparation of (S)-(E)-3,4-dihydroxybut-1-enylphosphonic acid, diisopropyl ester

In a 250 mL r.b. flask 21.03 g (71.9 mmol) of (S)-(E)-3,4-*O*-isopropylidene-3,4-dihydroxybut-1-enylphosphonic acid, diisopropyl ester was placed with 100 mL of acetone. Then, 35 mL of concentrated hydrochloric acid and 10 mL of water were added into the solution. The mixture was stirred at room temperature for 16 hr. All volatile materials were removed under reduced pressure and 2 X 70 mL of absolute ethanol was added and the mixture was again evaporated. The residue was

decolorized by adding 11.00 g of charcoal and 100 mL of absolute ethanol and the mixture was stirred at room temperature for 3 hr. The mixture was filtered through a pad of Celite and the volatile materials were evaporated under reduced pressure.

The residue was treated with flash chromatography, packed and eluted with chloroform/ethyl acetate. Collecting the fractions exhibiting Rf = 0.65 (1:3 $CH_3COOEt:CHCl_3$) and solvents from the fractions were evaporated under reduced pressure.

Yield: 16.03g (88.3 %).

^1H NMR ($CDCl_3$): δ 1.35-1.50, 12H, (dd); δ 3.75-3.90, 2H, (m); δ 4.00-4.20, 2H, (bs); δ 4.30-4.40, 1H, (m); δ 4.60-4.80, 2H, (m); δ 6.00-6.25, 1H, (dt); δ 6.70-6.90, 1H, (dt).

Preparation of (S)-(E)-4-tosyloxy-3-hydroxybut-1-enylphosphonic acid, diisopropyl ester

In a 150 mL r.b. flask was placed 8.00 g (31.7 mmol) of (S)-(E)-3,4-dihydroxy-but-1-enylphosphonic acid, diisopropyl ester with 50 mL of dried $CHCl_3$ and 5.13 mL (63.4 mmol) of pyridine. After the mixture was cooled to 0°C 6.40 g (31.7 mmol) of 99% *p*-toluenesulfonyl chloride in 10 mL $CHCl_3$ was added dropwise over 15 min. The mixture was stirred at 0°C for 2.5 hr. Then, the ice bath was removed and the mixture was stirred at room temperature for another 2 hr.

At that time 50 mL of chloroform was added to the well stirred solution and stirred for another 15 minutes. Then, it was transferred to a 250 mL

separatory funnel and 100 mL additional chloroform was added and the solution was washed with 2 X 25 mL water. The organic layer was dried over anhydrous $CaCl_2$ and filtered.

Volatile materials were removed under reduced pressure. The residue was a light yellow liquid. The material exhibited showed a major spot on TLC $R_f = 0.75$ (1:3, C_6H_{14}:EtOAc).

Yield: 12.70 g (98.5 %).

The ^1H NMR ($CDCl_3$): δ 1.35-1.50, 12H, (dd); δ 2.45, 3H, (s); δ 3.60-3.90, 2H, (m); δ 4.35-4.45, 1H, (m); δ 4.60-4.80, 2H, (m); δ 6.00-6.25, 1H, (dt); δ 6.70-6.90, 1H, (dt); δ 7.35-8.10, 4H, (dd).

Preparation of (S)-(E)-3,4-epoxybut-1-enylphosphonic acid, diisopropyl ester

In a 100 mL r.b. flask 12.70 g (31.2 mmol) of (S)-(E)-4-tosyloxy-3-hydroxybut-1-enylphosphonic acid, diisopropyl ester was added with 60 mL of dry methanol. Then, 5.18 g (37.5 mmol) of anhydrous K_2CO_3 was added. The mixture was stirred at -10°C for 3 hr and at room temperature (below 25°C) for 2 hr. At that time 50 mL of ethyl ether was added to the solution and a white precipitate was produced. After the mixture was stirred for 10 minutes at room temperature, it was filtered through a pad of Celite (1.0 cm thick) and the precipitate was washed by 100 mL of ethyl ether. The filtrates were combined and volatile materials were evaporated under reduced pressure. There still was some precipitate in the residue and 50 mL of ethyl ether was added and the mixture was filtered. Volatile materials

were again removed under reduced pressure. The residue was purified with flash chromatography packed and eluted with chloroform. Thus, the fraction exhibiting R_f = 0.70 ($CHCl_3$) was collected and solvent was evaporated under reduced pressure and 2.30 g of (S)-(E)-3,4-dihydroxybut-1-enylphosphonic acid, diisopropyl ester was recovered.

Yield: 5.10 g (85.1 %).

^{1}H NMR ($CDCl_3$): δ 1.35-1.50, 12H, (dd); δ 2.65-2.80, 1H, (dd); δ 3.05-3.15, 1H, (t); δ 3.35-3.50, 1H, (m); δ 4.60-4.80, 2H, (m); δ 6.00-6.25, 1H, (dt); δ 6.40-6.65, 1H, (dt). [α] = -15.64 (c = 1.10 g/100 mL ethanol).

Preparation of (S)-(E)-4-octadecyloxy-3-hydroxybut-1-enylphosphonic acid, diisopropyl ester

In a 50 mL r.b. flask 1.20 mL of 10% boron trifluoride etherate in methylene chloride was added to a mixture of 4.10 g (17.5 mmol) of (S)-(E)-3,4-epoxybut-1-enylphosphonic acid, diisopropyl ester and 4.73g (17.5 mmol) of *n*-1-octadecanol in 25 mL of methylene chloride at 0°C. After the mixture was stirred at 0°C for 10 minutes, it was allowed to warm up to room temperature and stirred at this temperature for 24 hr, the volatile materials were evaporated.

The residue was purified by flash chromatography, packed and eluted with hexane/chloroform/ethyl acetate. The fractions exhibiting R_f = 0.60 (1:3 EtOAc:$CHCl_3$) compound A were collected.

Yield: 7.50 g (84.9%).

^{1}H NMR ($CDCl_3$): (s); δ 0.80-0.90, 3H, (t); δ 1.15-1.30, 30H, (s); δ 1.35-1.60, 14H, (m); δ 2.90, 1H, (bs); δ 3.45-3.55, 2H, (m); δ 3.60-3.90, 2H, (m); δ 4.35-4.45, 1H, (m); δ 4.60-4.80, 2H, (m); δ 6.00-6.25, 1H, (dt); δ 6.40-6.65, 1H, (dt). $[\alpha]_{25}$ = -7.08 (c = -2.1 g/100 mL ethanol)

Preparation of (S)-(E)-4-octadecyloxy-3-acetylbut-1-enylphosphonic acid, diisopropyl ester

In a 50 mL r.b. flask 2.50 g of (S)-(E)-4-octadecyloxy-3-hydroxybut-1-enylphosphonic acid, diisopropyl ester was placed with 15 mL of acetic anhydride and 10 mL of methylene chloride. After the mixture was cooled to 0°C, 5.0 mg of DMAP was added and the mixture was allowed to warm to room temperature and stirred for another 2 hr. At that time volatile materials were removed under reduced pressure. The residue was purified by flash chromatography and reaction exhibiting R_f = 0.68 (1:6 EtOAc:$CHCl_3$) were collected.

Yield: 2.68 g (100 %).

^{1}H NMR ($CDCl_3$): δ 0.80-0.90, 3H, (t); δ 1.15-1.30, 30H, (s); δ 1.35-1.60, 14H, (m); δ 2.08, 3H, (s); δ 3.45-3.55, 2H, (m); δ 3.60-3.90, 2H, (m); δ 4.35-4.45, 1H, (m); δ 4.60-4.80, 2H, (m); δ 6.00-6.25, 1H, (dt); δ 6.40-6.65, 1H, (dt). $[\alpha]_{25}$ = -4.26 (c = 1.056 g/100 mL ethanol)

Preparation of (S)-(E)-3-acetyl-4-octadecyloxybut-1-enylphosphonic acid

In a 25 mL r.b. flask 500 mg (0.91 mmol) of (S)-(E)-3-acetyl-4-octadecyloxybut-1-enyl phosphonic acid, diisopropyl ester was added under

a nitrogen atmosphere with 5 mL of CH_2Cl_2. The solution was stirred and cooled to -20°C. Then, 1.30 g of allyltrimethylsilane was added. After five minutes, 3.0 g of bromotrimethylsilane was added and the mixture was stirred at -20°C for 15 minutes and at room temperature for 5 minutes. At that time the reaction was stopped by adding 3.0 mL of 95% ethanol and all volatile materials were removed under reduced pressure. Then, 5 mL of dry benzene was added to the residue and the mixture was evaporated at 0°C under vacuum for 3 hr to remove the volatile materials. The white solid was collected of melting point 74-76°C with R_f = 0.50 (15:75:1, CH_3OH:$CHCl_3$:H_2O).

Yield: 350 mg (82.7 %).

Elemental analysis: Found: C; 62.01%, H; 10.85%. Calculated: C; 62.04%, H; 10.63%.

The ^1H NMR ($CDCl_3$): δ 0.80-0.90, 3H, (t); δ 1.15-1.30, 30H, (s); δ 1.45-1.60, 2H, (m); δ 2.08, 3H, (s); δ 3.45-3.55, 2H, (m); δ 3.60-3.90, 2H, (m); δ 4.35-4.45, 1H, (m); δ 6.00-6.25, 1H, (dt); δ 6.40-6.65, 1H, (dt).

$[\alpha]_{25}$ = -9.08 (c = 1.25 g/100 mL ethanol)

Preparation of (S)-(E)-3-acetyl-4-octadecyloxybut-1-enyl-phosphonic acid, choline

In a dry 25 mL r.b. flask 238 mg of dried (S)-(E)-3-acetyl-4-octadecyloxybut-1-enyl phosphonic acid was added with 4.0 mL of freshly distilled pyridine under a nitrogen atmosphere. After the mixture dissolved, 1.48 g of dried choline toxylate was added and 10 minutes later, 1.68 g of

trichloroacetonitrile was added. The system was allowed to warm up to 50°C and was stirred under a nitrogen atmosphere for 72 hr at constant temperature. All volatile materials were evaporated under reduced pressure. Then, 20 mL of cold acetonitrile was added to the residue. The precipitate was separated using a chilled sintered glass funnel and the solid was washed with 10 mL of cold acetonitrile. The solid was dissolved in 2.0 mL of THF/H_2O (9:1). An amberlite MB-3 resin (40.0 g) column was packed with water and was rinsed with 230 mL 0.2 N HCl solution and 160 mL deionized water simultaneously. The compound in the 2.0 mL of THF/water was added to the column and was eluted with 400 mL of 9:1 THF/water. The first 250 mL of eluent was collected and volatile materials were removed under reduced pressure. The residue was dissolved in 10 mL of dry benzene and volatile materials were removed again under vacuum at 0°C.

Yield: 98.8 mg (35.0%).

The ^1H NMR ($CDCl_3$): δ 0.80-0.90, 3H, (t); δ 1.15-1.30, 30H, (s); δ 1.35-1.60, 14H, (m); δ 2.08, 3H, (s); δ 3.25, 9H, (s); δ 3.35-3.55, 4H, (m); δ 3.60-3.70, 2H, (m); δ 4.25-4.45, 2H, (m); δ 5.05-5.18, 1H, (m); δ 6.00-6.25, 1H, (dt); δ 6.50-6.75, 1H, (dt).

Suggestion for Future Research

Our interest in the analogues of PAF has led us to investigate novel methods for their syntheses. Most of the current methods have focused on different routes to make optically active PAF and its analogues. Others have worked on introducing different functional groups at the C_1, C_2 and C_3 position such as ester, ether, amide, thio ether, or thio ester. A few have focused on the polar group. The choline group is an important functional group and key factor in PAF. It has a major effect on platelet aggregation and membrane function. Other studies have shown that when a longer or shorter alkyl group was added, or methyl groups on the tertiary ammonium ion were replaced, the properties of the analogues of PAF could be changed.

Prior results have shown that if the methyl groups are substituted by any multi-functional nitrogen containing group, such as an amino acid or peptide group, the compound could bear an anti-tumor effect. In this type of compound, the amino functional group could combine with protein and change the composition of the tumor cell. It has been suggested that this area might be an important research area for development. Protein analogues of PAF may be very important in changing the property of membranes or the metabolism system.

Some studies have also indicated that thio or amide analogues of PAF can act as anti-tumor drugs. With the introduction of amino or peptide

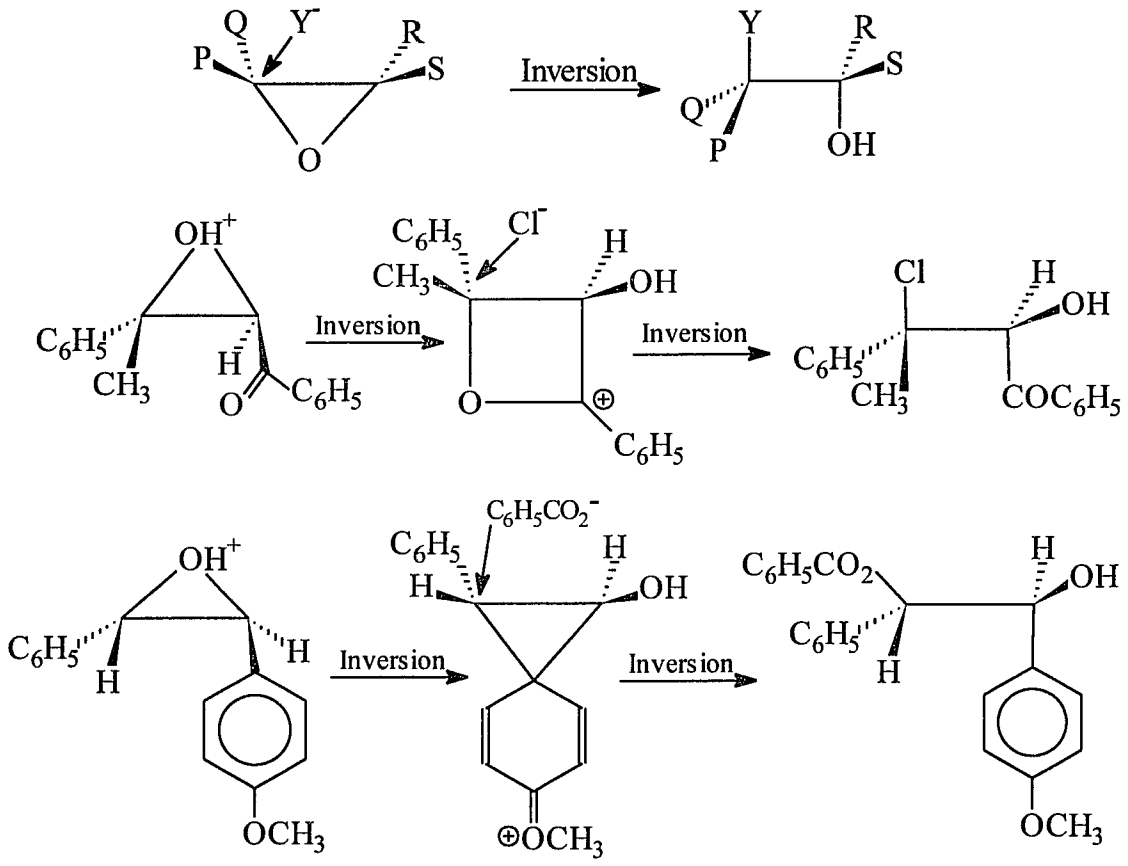
groups at the polar head or hetero atoms, such as sulfur or nitrogen, are placed into the molecule at the C_1 or C_2 positions, analogues of PAF could be generated which would be very useful in anti-tumor studies.

CHAPTER 2: Exploring Epoxy Ring Opening Using Boron Trifluoride Etherate as a Catalyst

INTRODUCTION

As epoxides have a heterocyclic three member ring, they are versatile intermediates in organic synthesis. The inherent polarity and the strain of the ring makes them susceptible to reaction with a number of reagents such as electrophiles, nucleophiles, acids, bases, reducing agents, and some oxidizing agents.[1,2]

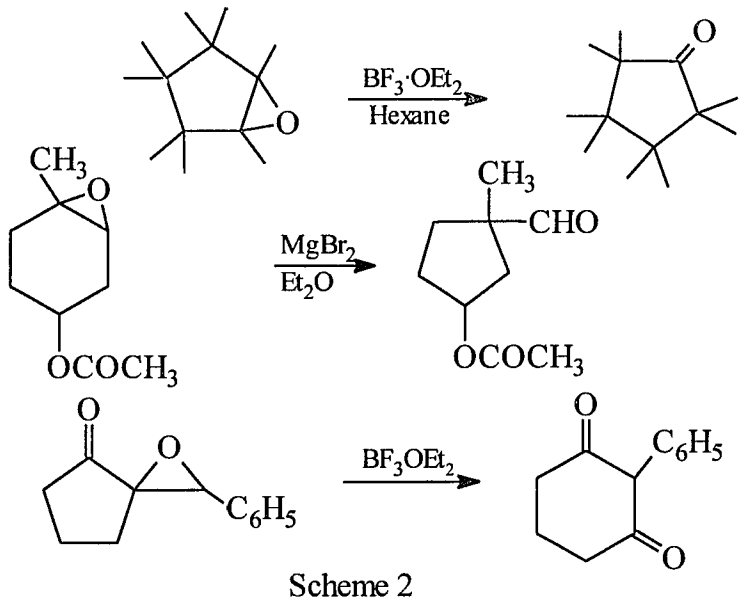
Prochiral epoxide ring opening can provide products with inverted or retained configuration.[3] The inversion product is produced by a *SN*2 reaction mechanism with the approach of the reagent to the remote side of the displaced group. The retention product is produced by two inversion procedures. In this situation, the substituents on the epoxide usually have an unsaturated group (carbonyl or aromatic group) which can form a transition state bond at the backside of the leaving group to prevent the attacking reagents approaching from this side. After the displaced group has departed, the attacking group can approach the carbon on the same side as the leaving group departed, producing the retained configuration product [Scheme 1].



Scheme 1

Rearrangements of epoxides can take place in the presence of a Lewis acid without any external nucleophilic reagent. The rearrangement of the epoxide involves one of the substituents from an adjacent carbon migrating after the leaving group has departed, forming an aldehyde or ketone. Studies[4] have shown that the carbon oxygen bond cleavage can occur when an electron releasing group is present when only a Lewis acid is present. In

this way octamethylcyclopentene oxide is converted to octamethylcyclopentone in a heterogeneous mixture of $BF_3 \cdot OEt_2$ and hexane[5] [Scheme 2].

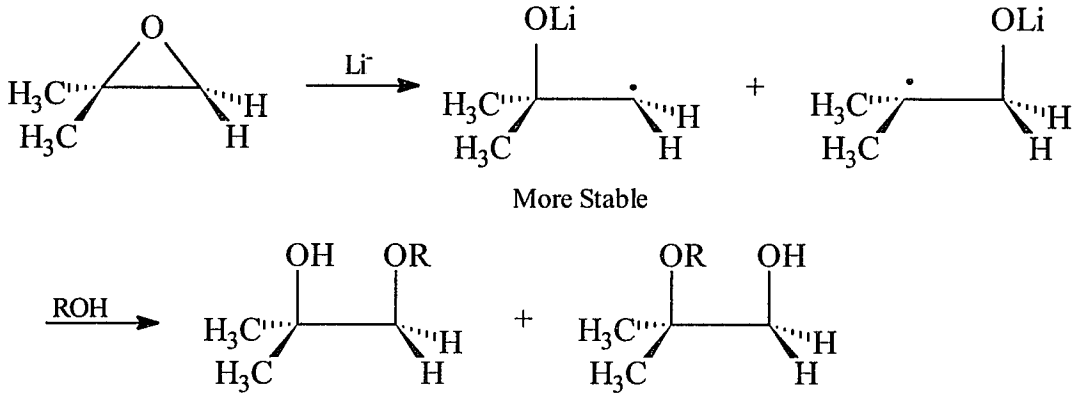


Scheme 2

The current work has focused on the orientation of the ring opening as a function of the reaction conditions.[6] The ring opening can occur in different ways under different condition. Under basic or neutral conditions, the nucleophile usually attaches itself to the carbon atom bearing the greater number of hydrogen atoms and produces a primary attacked product. But under acidic conditions, different products can be formed depending on the substituents of the epoxide and the reaction conditions. The presence of an electron withdrawing group favors the formation of products with ring opening at carbon bearing the substituent.

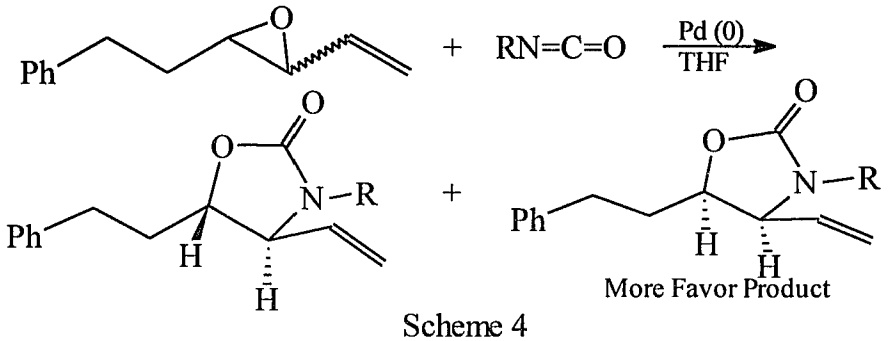
In 1989, Houk, *et al.*[7] reported a reductive cleavage of epoxide with stereoselective formation of product. In this reaction, unsymmetrical alkyl substituted epoxide afforded a more substituted carbinol, which required a

cleavage of the carbon oxygen bond at the less substituted carbon atom. According to 6-31G calculations[8] concerning the two possible radical intermediates, the radical at the primary carbon is more stable than the radical at the tertiary carbon, and most reactions were found to form the primary opened product. With a stronger radical stabilizing substituent, the ring opening could take place at the carbon bearing the substituent [Scheme 3].



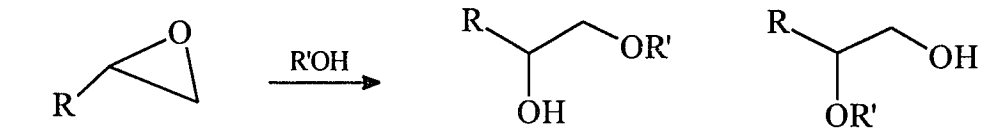
Scheme 3

The reaction of vinyl epoxides with phenyl isocyanate in the presence of a Pd(0) catalyst gives a very effective approach to vinyloxazolidin-2-ones.[9] The vinyl epoxides are stereoselectively converted to the thermodynamically less stable (*Z*)-oxazolidin-2-ones regardless of the stereochemistry of the vinyl epoxides. In this procedure, the *cis* product was the most favored one regardless of the orientation of substrates of the vinyl epoxide [Scheme 4].

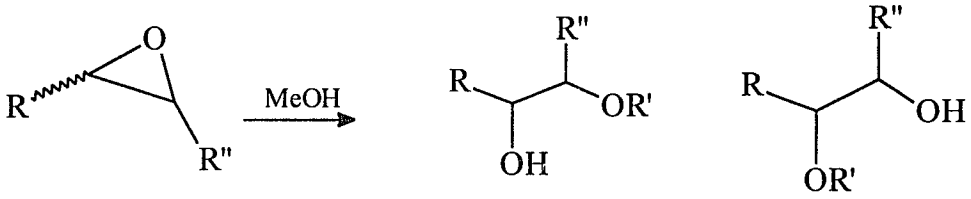


Scheme 4

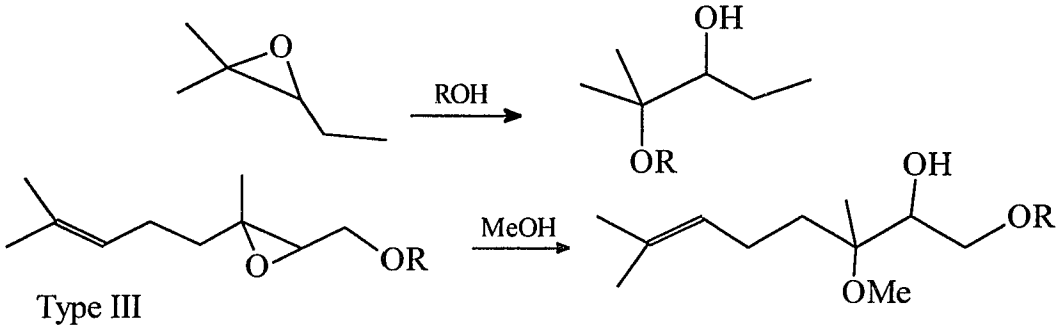
The epoxide ring opening reaction gives a highly regioselective and stereoselective product in the presence of organotin phosphate condensates.[10] In this reaction, the selectivity depends on the structure of the epoxide. Three types of epoxides were investigated. For type I, the epoxide is at the end of an alkyl chain. If an electron withdrawing group is at the β-position of the ring, the nucleophilic attack occurred on the unsubstituted methylene of the α-position. For type II, the epoxide ring is in the middle of the chain. If the substituted group is a typical alkyl group without any heteroatom, it gives a mixture of products. If the substituent group is a long alkyl group, the reaction affords a mixture without any selectivity. But if an electron withdrawing group is substituted at the β-position, the nucleophilic attack occurs at the α-position. For type III, one of the epoxy carbon atoms bears two alkyl groups. When it reacts with an alcohol nucleophile, an exclusive attack of the alcohol group on the tertiary carbon occurs with Sn-P catalyst irrespective of the presence of the functional groups [Scheme 5].



Type I	R	R'OH	1	2
	$ClCH_2$	MeOH	100	0
	$AcOCH_2$	MeOH	100	0
		$PhCH_2OH$	100	0
	$HO(CH_2)_9$	CH_2CHCH_2OH	100	0
		MeOH	53	47



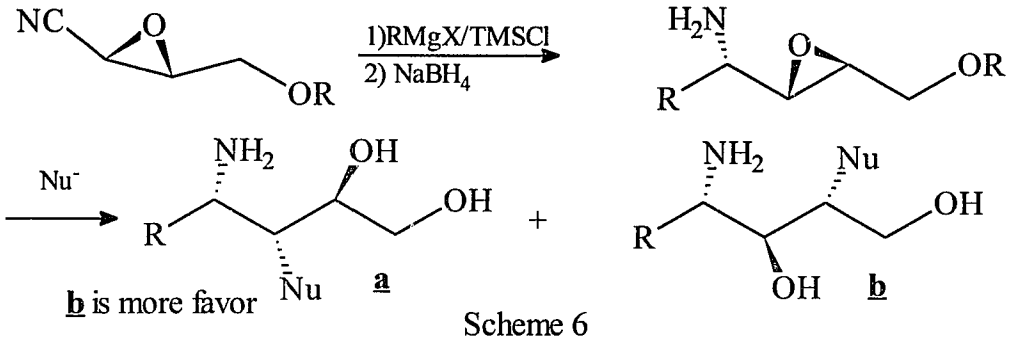
Type II	R	R"		
	$n\text{-}C_5H_{11}$	CH_3	50	50
	$n\text{-}C_3H_7$	CH_2OCH_3	50	50



Type III

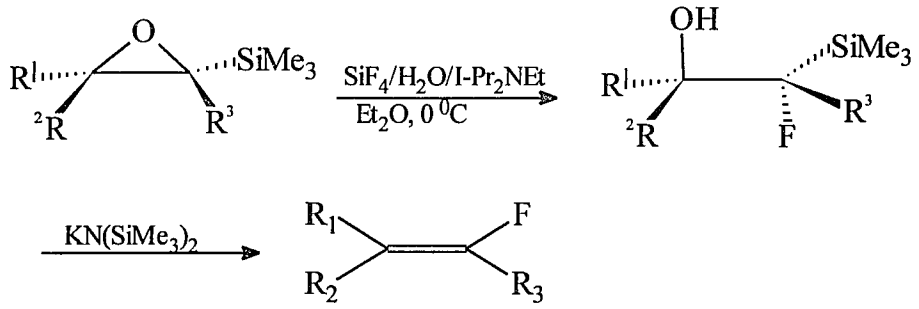
Scheme 5

For *trans* α-amino epoxy alcohol, some work[11] has demonstrated that the compound can be attacked regioselectively and form a product with regioselective ring opening. The reaction affords a preferred 1,3-diol. But if the compound has no α-amino group, the reaction gives only the corresponding 1,2-diol. Also, an alcohol group protected with tBDMS can inhibit the reaction [Scheme 6].



Scheme 6

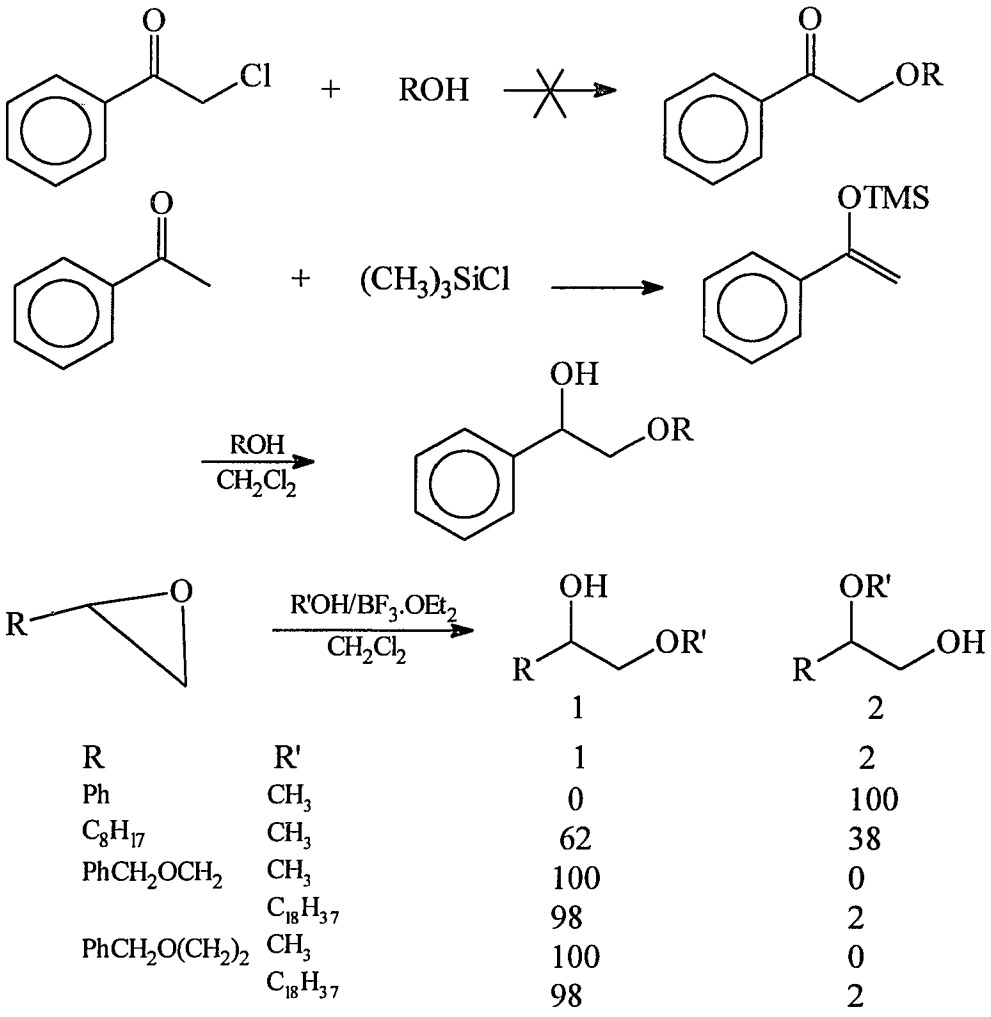
Since there is a strong affinity between silicon and the fluoride anion, desilylation usually occurs in the reaction of fluoride anion with an alkyl silane compound. Recently, Yoshioka[12] reported a new reaction in which α,β-epoxysilanes react with tetrafluorosilane. In this reaction the two substrates mix with water in the presence of diisopropylethylamine and undergo a regioselective fluoridation to afford a β-fluoro-β-silylalcohol without eliminating the silicon functionality. This is a new regioselective synthetic procedure to make fluoroalkenes. [Scheme 7]



Scheme 7

In the synthesis of analogues of PAF, an epoxide was used as the key intermediate to provide a stereochemically preferred product leading to the final compounds **2** and **3**. In this reaction, boron trifluoride etherate ($BF_3.OEt_2$)[13] was used as the catalyst to conduct the reaction and gave the

primary ring opening. These results were contrary to the published literature,[14] since the boron trifluoride etherate is a Lewis acid. To



R	R'	1	2
Ph	CH_3	0	100
C_8H_{17}	CH_3	62	38
$PhCH_2OCH_2$	CH_3	100	0
	$C_{18}H_{37}$	98	2
$PhCH_2O(CH_2)_2$	CH_3	100	0
	$C_{18}H_{37}$	98	2

Scheme 8

confirm our results, several epoxides were selected as substrates to investigate the ring opening reaction.[15] The designed reactions are listed in Scheme 8. Based on the information collected, the reaction could provide a primary nucleophilic attack product if the substituent is an electron

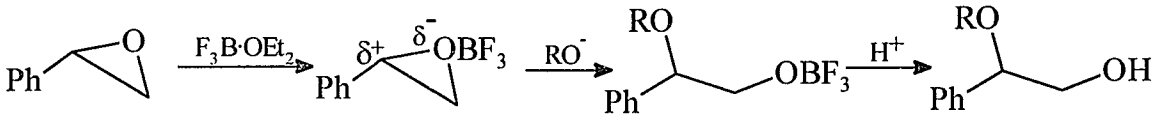
withdrawing group. But when the substituent is changed, the product can be different depending on the character of the functional groups [Scheme 8].

Results and Discussion

In the preparation of the analogues of platelet activating factor, PAF, a regioselective ring opening procedure was used to obtain a product with a stereocenter retained. In the designed procedure, a chiral epoxide was used as an intermediate and through a regioselective epoxy ring opening, a major primary attacked product was produced in the presence of boron trifluoride etherate. In general, epoxy ring opening in which an alcohol attacks usually gives secondary ether bond formation in the presence of a Lewis acid.[14] The contradictory results observed prompted us to investigate this reaction more deeply. Similar types of compounds were selected for the trial reactions (see the attached table). Styrene oxide, benzyl glycidyl ether, 1,2-epoxydecane, and (S)-1,2-epoxy-4-benzyloxybutane were selected as substrates. All reactions were carried out under the same condition. The amount (10~20 mmol) of epoxy compound was dissolved in a pre-dried and pre-distilled methylene chloride and an equivalent amount of alcohol (excess methanol was used) was added to the well stirred solution. The mixture was stirred at 0°C and then a catalytic amount of boron trifluoride etherate (3-5% in mole ratio) in methylene chloride solution was dropped into the reaction mixture. After the reaction mixture was stirred at 0°C for one hour and at ambient temperature for 18 hours, all volatile materials were removed under reduced pressure. The residue was analyzed by high

performance liquid chromatography (HPLC) to determine any regioselectivity.

In the styrene oxide reaction, the resultant product was more like a typical Lewis acid catalyzed mixture,[16] attack occurring at the internal position of the epoxide and forming the secondary ether bond. The reason for the secondary ether bond formation could be explained as following. In the benzyl group, the *p* electrons on the phenyl ring can delocalize to the methylene group and stabilize the cation. After the boron trifluoride etherate complexes with the epoxide structure, the bond to the secondary carbon is weakened and form a secondary cation. The *p* electrons of the benzene ring can delocalize to the adjacent carbon site and make this cation even more stable than the boron trifluoride epoxide complexes. Then, the alcohol attacks the cation and forms the secondary ether bond. The proton from the alcohol substitutes for the boron trifluoride to form the primary alcohol [Scheme 9].



Scheme 9

The structure of the reaction product was confirmed in the following manner. First, the crude mixture of the reaction residue was dissolved in ethyl acetate/hexane solution and was injected to a HPLC column. The peaks were analyzed by their integrated area and the peak with a longer retention time (smaller R_f value) was found to dominate. Then, the mixture

was separated through regular liquid chromatography and one fraction was collected. Second, the separated fraction was oxidized with Sarett's reagent[17] which can oxidize a secondary alcohol to a ketone and a primary alcohol to an aldehyde. The terminal opened product should give a ketone because it is a secondary alcohol, while the internal opened product should give an aldehyde.

For the oxidized compound, proton NMR spectrum was recorded. There was found a new peak in the chemical shift between δ = 8.7-9.0 for the product which is the significant peak for an aldehyde.

Third, the absolute structure of the product was checked. Another synthetic route was carried out to prepare the terminal opened compound. In this method α-methoxyacetophenone was formed which had the same structure as a terminal epoxy ring opening product after reduction to an alcohol. Using acetophenone as the starting material, the compound was treated with chlorotrimethylsilane[18] in a dried methylene chloride solution to form a silylated enol of acetophenone [Scheme 8]. This compound can react with methanol and produce the α-methoxyacetophenone. Then, it was reduced to β-methoxy-1-phenyl ethanol. Comparison of its proton NMR spectrum, the R_f value, and the retention time with methanol attacked epoxy ring opening product, it was found not to be the same as the compound in the ring opening procedure.

In the reaction of 1,2-epoxydecane with alcohol, the product was a mixture of A and B in the ratio 1.62:1. To confirm the absolute structures

of the two compounds, Sarett oxidation reagent was used on both separated fractions. Compound A gave a ketone and B gave an aldehyde. By FT-IR and NMR spectra, both compounds had alcohol functionality. After they were oxidized there were no hydroxyl groups in either of the compounds, but instead there was a doublet peaks at δ = 8.6-8.9 for compound B and there was no such signal for compound A. This information showed that compound A was a secondary alcohol and compound B was a primary alcohol. Also ^{13}C NMR spectra were recorded for both compounds before and after they were oxidized.

Using benzyl glycidyl ether as the substrate to react with the alcohol, under the same conditions a single product was produced. To confirm the structure of the compound, Sarett reagent was used to oxidize the product. In the analysis of both reactant and oxidized product spectra, the reactant had hydroxyl group as shown by both FT-IR and NMR spectra, but in the oxidized product, there was no hydroxyl group and no new peaks between δ = 8.50-9.50 were to be found in ^{1}H NMR spectrum. Also, there was observed a peak at the δ = 170 in the ^{13}C NMR spectrum. This indicates that the methanol nucleophile group attacked the terminal position of the epoxide ring.

In the reaction of (S)-1,2-epoxy-4-benzyloxybutane with methanol, the product gave a mixture of compounds C and D in which the compound C was much more dominant than compound D. When the octadecanol was used as a nucleophile to react with (*S*)-1,2-epoxy-4-benzyloxybutane, the

product was also a mixture of compound E and F with a 98% yield. Compound E was the major product which showing that the reaction had a high degree of regioselectivity. The ratio of the integrated peak areas for compound E and F is 49:1.

Based on these experimental results for the boron trifluoride etherate catalyzed epoxide ring opening with alcohols, It can be concluded that the regioselectivity of the product varies with the nature of the substituent of the oxirane ring. For those compound in which the substituent can stabilize a charge by delocalization from the substituted site (such as a phenyl group), the nucleophile attacks at the internal position exclusively and the reaction could be used for the formation of a single regioisomer. Since the charge of the intermediate can be delocalized, the product could be racemic. For an ordinary alkyl group, however, it does not have the capability to provide a sufficient charge delocalization in the reaction site. The nucleophile can attack the oxirane ring randomly. Because the substituent has some steric effect on the internal position, terminal attack is a slightly more favorable than internal position attack, and this can not be a highly regioselective reaction. If the epoxide is in the middle of an alkyl chain, the product can be a useless mixture. However, when the compound has an electron withdrawing group, one which would disfavor the generation of a positively charge site, the substituent makes the internal C-O bond stronger. The nucleophile attacks at the terminal position with high regioselectivity. Because the internal C-O bond does not cleave, the chirality of the internal

position does not change and give the product with retention. This is of excellent synthetic utility for the production of a single regioisomer and a stereoselective isomer if the reactant is an optically pure compound.

EXPERIMENTAL SECTION

General

All chemicals were of reagent quality and used without further purification with the following exceptions: chloroform was distilled over phosphorus pentoxide and stored over molecular sieves 3A; benzene and toluene were distilled and stored over sodium metal; hexane, ethyl acetate and boron trifluoride etherate were distilled prior to use; pyridine and triethylamine were dried over calcium hydride and distilled, and were used immediately; THF was dried over sodium metal and distilled over sodium benzophenone ketyl indicator, and was used immediately; methylene chloride and methanol were dried and distilled over calcium hydride and stored over molecular sieves 3A; acetone was dried over $MgSO_4$ for several days; dimethylformamide (DMF) was dried over molecular sieves prior to use; boron trifluoride etherate was distilled and mixed with 9 parts of methylene chloride to form a 0.81M solution; acetophenone, styrene oxide and 1-decene were purified by flash chromatography; silica gel was purchased from J. T. Baker Corp. and was of 230-400 mesh; TLC plates were purchased from Eastman Kodak, were 0.26 mm thick on plastic film and were developed with ethyl acetate prior to use; ^{1}H and ^{13}C NMR were recorded using a 60 MHz instrument from Varian E360 and a 200 MHz instrument from IBM Bruker; FT-IR spectra were recorded on a Perkin

Elmer PE1600 instrument; optical rotations were measured using a JASCO DIP-140 spectropolari-meter.

Preparation of α-trimethylsilyloxystyrene

To a well stirred solution of 10.00 g (83 mmol) of acetophenone and 16.80 g of freshly distilled triethylamine in 75 mL of dried *N,N*-dimethyl-formamide (DMF) was added 9.22 g (83 mmol) of chlorotrimethylsilane in one portion at room temperature under a nitrogen atmosphere. After the mixture stirred for 30 minutes, the resultant white precipitate (Et_3NHCl) was removed by filtering through a fine sintered glass funnel with a pad of Celite. The solid was washed with a small amount of DMF and the filtrate was stirred again. More white precipitate separated. Then the reaction mixture was stirred at reflux for 48 hr. After the mixture was cooled to room temperature, it was diluted with 200 mL of pentane. The mixture was washed with 3 X 100 mL of cold 5% Na_2CO_3 aqueous solution. The aqueous solution was extracted with 3 X 100 mL of pentane. Organic layers were combined and washed with 150 mL of cold saturated Na_2CO_3 solution and dried over anhydrous $MgSO_4$. Volatile materials were evaporated under reduced pressure and the residue was distilled under vacuum, collecting the fractions boiling between 85-87°C/2 Torr.

Yield: 14.00 g (87.5%).

^1H NMR($CDCl_3$): δ 0.00, 9H, (s); δ 4.10-4.64, 2H, (dd); δ 6.85-7.22, 5H, (m).

Preparation of α-methoxyacetophenone

Iodosobenzene (5.8 g, 26 mmol) was dissolved in 50 mL of absolute methanol and 6.8 g (48 mmol) of boron trifluoride etherate was added to it in a 100 mL r.b. flask under nitrogen. The mixture was stirred and cooled to -78°C and then 4.6 g (24 mmol) of α-trimethylsilyloxystyrene was added at this temperature and the mixture was stirred two hours. The mixture was warmed up to room temperature over 2.5 hr and stirred continuously for another 45 minutes. Volatile materials were evaporated under reduced pressure, and 50 mL water and 75 mL methylene chloride were added to the residue, and 20 mL of saturated aqueous $NaCO_3$ solution was added slowly while stirring. The organic layer was separated and the aqueous layer was extracted with 3 X 50 mL methylene chloride. The organic layers were combined and dried over anhydrous magnesium sulfate. Volatile materials were evaporated under reduced pressure to give the crude product, which was purified by column chromatography.

Yield: 2.4 g (67.0%).

^{1}H NMR($CDCl_3$): δ 3.40, 3H, (s); δ 4.45, 2H, (s); δ 7.10-7.90, 5H, (m).

Preparation of 2-methoxy-1-phenylethanol

To a 100 mL r.b. flask 1.50 g (10 mmol) of α-methoxyacetophenone was added with 25 mL of absolute methanol. To this solution 0.30 g (1.2

mL) of 25% sodium methoxide solution was added, and 0.80 g of sodium borohydride in 25 mL methanol was added in one portion. The mixture was stirred at room temperature for 5 minutes and the solution was poured into 100 mL of ice water. The resultant mixture was brought to pH = 6.5 by the addition of dilute hydrochloric acid. The solution was extracted with 4 X 50 mL of ethyl ether. The organic layers were combined, washed with 50 mL of water, and dried over anhydrous magnesium sulfate. After filtration and evaporation of all volatile materials under reduced pressure, the residue of pure target materials was obtained without any further purification.

Yield: 1.35 g (89.0%).

^{1}H NMR($CDCl_3$): δ 3.00, 1H, (s); δ 3.40, 3H, (s); δ 3.42-3.60, 2H, (d); δ 4.88-4.95, 1H, (dd); δ 7.20-7.50, 5H, (m).

Preparation of 2-methoxy-2-phenylethanol

In a 50 mL r.b. flask were placed 1.80 g (15 mmol) of styrene oxide with 15 mL of dry methylene chloride and 5.0 mL of absolute methanol. The mixture was stirred in an ice bath under nitrogen for 10 minutes, and then 0.9 mL of 0.81 M boron trifluoride etherate in methylene chloride was added dropwise. The mixture was stirred at 0°C for 35 minutes and at room temperature for 18 hr. At that time the reaction was stopped and volatile materials were removed under vacuum. The residue was purified by column chromatography packed and eluted with hexane/ethyl acetate.

Yield: 2.15 g (94.2%).

^{1}H NMR ($CDCl_3$): δ 2.75, H, (bs); δ 3.30, 3H, (s); δ 3.55-3.75, 2H, (m); δ 4.25-4.35, 1H, (dd); δ 7.20-7.35, 5H, (m).

To confirm the structure of this material, it was oxidized by Sarett's reagent in the next step.

Preparation of methoxyphenylaldehyde

Pyridinium chlorochromate (1.22 g, 6.0 mmol) in 25 mL of methylene chloride (5% solution) was placed into a 50 mL r.b. flask. After all the pyridinium chlorochromate was dissolved, 0.152 g (1.0 mmol) of 2-methoxy-2-phenylethanol in 3.0 mL of methylene chloride was added in one portion to the well stirred solution (1:6 ratio). After 15 minutes, the reaction mixture was filtered through a pad of Celite and washed with ethyl ether (3 X 20 mL). The filtrate was washed with 2 X 10 mL water and the organic solution was dried over anhydrous magnesium sulfate and volatile materials were removed under reduced pressure.

Yield: 0.139 g (92.5%).

^{1}H NMR ($CDCl_3$): δ 3.30, 3H, (s); δ 4.50, 1H, (dd); δ 7.20-7.35, 5H, (m); δ 8.70, 1H, (s).

Preparation of 1,2-epoxydecane

1-Decene (8.5 g, 60 mmol) was placed with 100 mL of methylene chloride and 70 mL of saturated sodium bicarbonate aqueous solution in a

250 mL r.b. flask. The reaction mixture was stirred vigorously at 0°C and 12.2 g (60 mmol) of 85% *m*-chloroperoxybenzoic acid (*m*-CPBA) was added in four portions, each portion being added after 20 minutes. The temperature of the mixture was raised slowly to room temperature in 3 hr and stirred at room temperature for another 15 hr. Potassium iodide starch test paper was used to check that no peroxide was left in the reaction mixture. (If there were any excess of peroxide in the system, sodium thiosulfate solution was added to destroy it.) The solution was separated and aqueous was extracted by 2 X 75 mL methylene chloride. The organic layers were combined and washed with 3 X 60 mL aqueous $NaCO_3$ solution, and then with 100 mL of water. The organic solution was dried over anhydrous magnesium sulfate and volatile materials were evaporated under vacuum. The product was purified by fractional distillation under reduced pressure, collecting the fractions boiling between 80-82 °C/1.00Torr.

Yield: 7.20 g (76.8%).

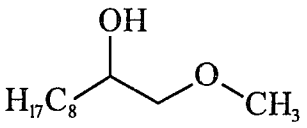
^{1}H NMR ($CDCl_3$): δ 0.80-0.92, 3H, (t); δ 1.15-1.67, 14H, (m); δ 2.45-2.55, 1H, (q); δ 2.70-2.82, 1H, (t); δ 2.84-2.96, 1H, (m).

Opening the ring of 1,2-epoxydecane

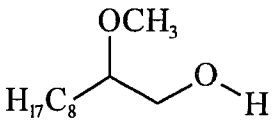
To a well stirred solution of 10 mL of absolute methanol and 20 mL methylene chloride, 2.0 g (12.8 mmol) of 1,2-epoxydecane was added at 0°C under nitrogen. After stirring at 0°C for 10 minutes, 0.65 mL of 0.81 M

boron trifluoride etherate in methylene chloride was added. The mixture was stirred at 0°C for 40 minutes, and then at room temperature for 18 hr. Volatile materials were removed under reduced pressure. The residue was analyzed by HPLC and there were two peaks with a ratio of 1.62 on the graph. Purification was done by column chromatography packed and eluted with hexane/ethyl acetate.

Two fractions were collected which were noted A and B. HPLC was used to test the purity of the fractions. Yield: compound A, 1.46 g; compound B, 0.90 g (95.0%).



A



B

Compound A: ^{1}H NMR ($CDCl_3$): δ 0.80-0.92, 3H, (t); δ 1.15-1.67, 14H, (m); δ 2.40-2.70, 1H, (s); δ 3.16-3.30 and 3.40-3.50, 2H, (dt); δ 3.39, 3H, (s); δ 3.68-3.82, 1H, (m).

Compound B: ^{1}H NMR ($CDCl_3$): δ 0.80-0.92, 3H, (t); δ 1.15-1.67, 14H, (m); δ 2.10-2.30, H, (s); δ 3.19-3.33, 1H, (m); δ 3.40, 3H, (s); δ 3.46-3.55, 1H, (dd); δ 3.62-3.74, 1H, (dd).

Preparation of 2-methoxydecanal

Pyridinium chlorochromate (0.84 g, 3.8 mmol) in 15 mL of methylene chloride (5% solution) was placed into a 50 mL r.b. flask. After all the pyridinium chlorochromate was dissolved, 0.123 g (0.65 mmol) of

compound B in 2.0 mL methylene chloride was added in one portion to the well stirred solution (1:6 ratio). After 15 minutes, the reaction mixture was filtered through a pad of Celite and washed with ethyl ether (3 X 20 mL). The filtrate was washed with 2 X 10 mL water and the organic solution was dried over anhydrous magnesium sulfate and volatile materials were removed under reduced pressure.

Yield: 0.11 g (90.9%).

^{1}H NMR ($CDCl_3$): δ 0.80-0.92, 3H, (t); δ 1.15-1.67, 14H, (m); δ 3.35, 3H, (s); δ 3.45-3.55, 1H, (m); δ 9.40-9.45, 1H, (d).

Preparation of 1-methoxy-2-decanone

Pyridinium chlorochromate (0.66 g, 3.0 mmol) in 15 mL of methylene chloride (5% solution) was placed into a 50 mL r.b. flask. After all the pyridinium chlorochromate was dissolved, 0.095 g (0.50 mmol) of compound A in 2.0 mL methylene chloride was added in one portion to the well stirred solution (1:6 ratio). After 15 minutes, the reaction mixture was filtered through a pad of Celite and washed with ethyl ether (3 X 20 mL). The filtrate was washed with 2 X 10 mL water and the organic solution was dried over anhydrous magnesium sulfate and volatile materials were removed under reduced pressure.

Yield: 0.085 g (91.3%).

^{1}H NMR ($CDCl_3$): δ 0.80-0.92, 3H, (t); δ 1.15-1.67, 14H, (m); δ 3.35, 3H, (s); δ 3.85, 2H, (s).

Preparation of benzyl glycidyl ether

In a 250 mL r.b. flask, 21.60 g (0.2 mol) of benzyl alcohol was added with 150 mL of dried toluene, and to it 4.60 g (0.2 mol) of fresh cut sodium rinsed with hexane was added and the mixture was heated with stirring at reflux until all of the sodium had reacted. The mixture was cooled to room temperature and 14.0 g (0.15 mol) of epichlorohydrin in 10 mL of toluene was added dropwise, and the mixture was stirred and heated at 78°C. Once the exothermic step began, the heating bath was removed and the mixture was maintained at 78°C for 2 hr. Then, the reaction mixture was heated at reflux for another 2 hr. After it was cooled to room temperature and 100 mL of water was added, the aqueous layer was extracted with 2 X 100 mL of ethyl ether. The organic layers were combined and dried over $MgSO_4$. The solution was filtered by gravity and volatile materials were removed under reduced pressure. The residue was distilled under vacuum, collecting the fraction boiling at 85-86°C/0.2 Torr.

Yield: 22.20 g (90.1%).

^1H NMR ($CDCl_3$): δ 2.45-2.60, 1H, (q); δ 2.60-2.75, 1H, (t); δ 3.00-3.20, 1H, (m); δ 3.40-3.65, 2H, (dd); δ 4.55, 2H, (s); δ 7.15, 5H, (m).

Preparation of 1-benzyl-3-methyl-2-glycerol

In a 100 mL r.b. flask 3.30 g (20 mmol) of benzyl glycidyl ether with 25 mL methylene chloride and 15 mL of absolute methanol were added. The

mixture was stirred under nitrogen with ice cooling for 10 minutes, and then 1.0 mL of 0.81 M boron trifluoride etherate was added dropwise. The mixture was stirred at 0°C for one hour, then at room temperature for 18 hr. At that time all volatile materials were evaporated under reduced pressure. The residue was purified by column chromatography, packed and eluted with hexane/ethyl acetate.

Yield: 3.50 g (89.7%).

^{1}H NMR ($CDCl_3$): δ 3.05-3.30, 1H, (bs); δ 3.35, 3H, (s); δ 3.36-3.64, 4H, (dt); δ 3.90-4.10, 1H, (m); δ 4.55, 2H, (s); δ 7.30, 5H, (s).

Preparation of 1-benzyloxy-3-methoxyacetone

Pyridinium chlorochromate (4.0 g, 18 mmol) in 65 mL of methylene chloride was placed into a 100 mL r.b. flask (5% solution). After all the pyridinium chlorochromate had dissolved, 0.59 g (3.0 mmol) of 1-benzyl-3-methylglycerol in 5 mL of methylene chloride was added in one portion to the mixture (1:6 ratio). After 15 minutes, the reaction mixture was filtered through a pad of Celite and washed with ethyl ether, followed be 2 X 10 mL water. The organic solution was dried over anhydrous magnesium sulfate and volatile materials were removed under reduced pressure.

Yield: 0.50 g (85.8%).

^{1}H NMR ($CDCl_3$): δ 3.35, 3H, (s); δ 3.65, 2H, (s); δ 3.70, 2H, (s); δ 4.55, 2H, (s); δ 7.30, 5H, (s).

^{13}C NMR ($CDCl_3$): δ = 164.

FT-IR spectrum was recorded and a singlet peak at 1740 cm^{-1}. This could prove that the compound was a secondary alcohol and it was a primary epoxide ring opened product.

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