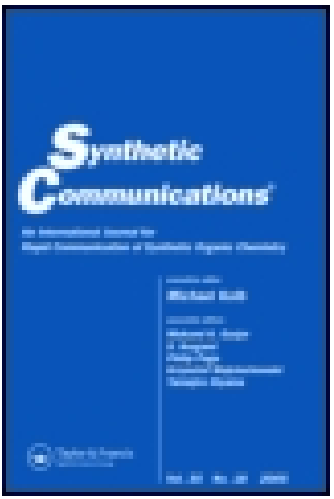

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Synthesis of 1-O-Alkyl-2-O-Acetyl-Sn-3-glyceryl-3-phosphoryl Choline the Enantiomer of Platelet Activating Factor (PAF)

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SYNTHESIS OF 1-O-ALKYL-2-O-ACETYL-Sn-3-GLYCERYL-3-PHOSPHORYL CHOLINE THE ENANTIOMER OF PLATELET ACTIVATING FACTOR (PAF)

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A novel stereospecific synthesis of biologically active ether-phospholipids (PAF) is reported, involving chemoenzymatic approach.

Ether phospholipids are among the most potent biologically active phospholipid derivatives[1-3]. 1-O-Alkyl-2-O-acetyl Sn glyceryl-3-phosphoryl choline in which alkyl component is comprised largely of C-16 and C-18 homologues (1a & b) has been identified as platelet activating factor (PAF).

PAF has been chemically synthesised by several research groups[4-11] but the synthetic stratagies are very long and these procedure employed hydrogenation hence only saturated PAF was obtained.

We wish to report here a novel synthetic methodology for preparation of stereoselective PAF (Scheme I).

The Hexadecanol and Octadecanol (2a & b) on reaction with epichlorhydrine in potassium carbonate gave corresponding epoxy product (3 a & b). Epoxy compound on treatment with

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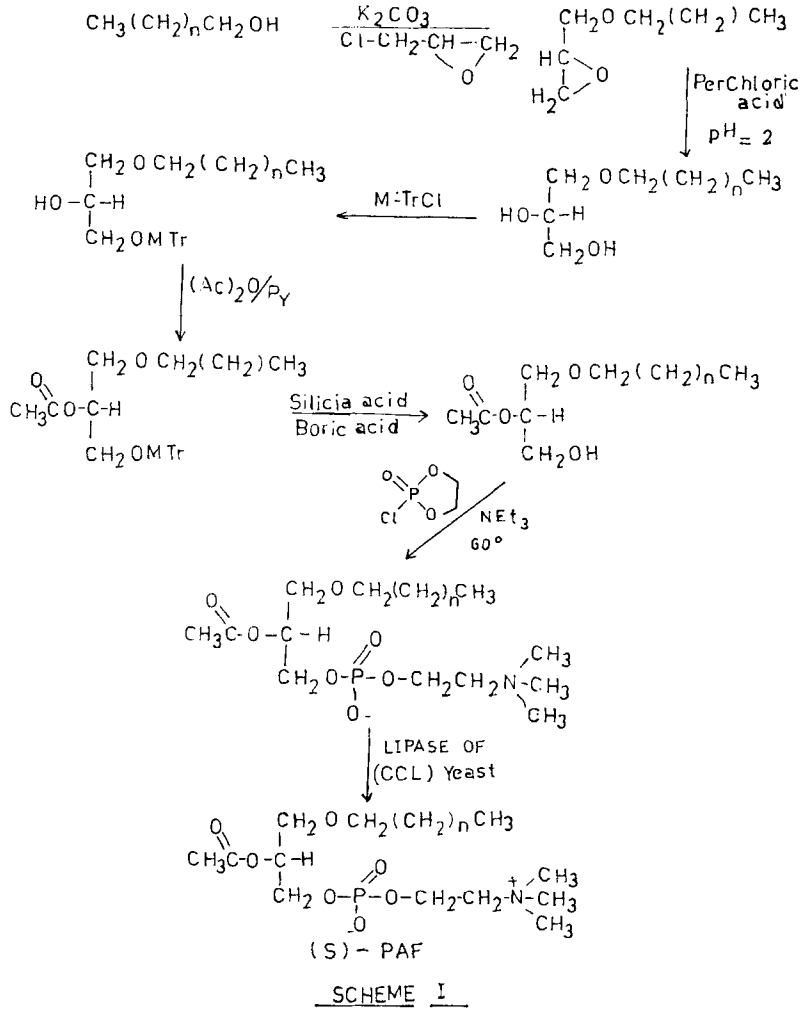

SCHEME I

perchloric acid at pH=2 in dioxane and water (6:4) afforded antidiol (4a & b). Diol 4(a & b) with 4-methoxy trityl chloride yields 5(a & b) followed by acetylation of the free hydroxy group with acetic anhydride and pyridine gave 6 (a & b). The selective removal of the methoxytrityl group (without migration of acetyl group taking place) by passing a solution of 6 in Pet ether through a short silicic acid/Boric acid column yields 7 (a & b).

Phosphorylation of 7 (a & b) with 2-chloro-2-oxo-1,3,2 dioxaphospholone[12] in benzene using triethyl amine at 60°C afforded 8 (a & b). Which on selective enzymatic transesterification by the Lippase from yeast [Candida cyclindracea (CCL)] gave one enantiomers of PAF by deacetylation of (R) PAF. Hence (s) PAF was obtained by chromotography.

EXPERIMENTAL SECTION

1.2. epoxides 3 (a & b)

1-Octadecanol (20.0 mmol) is dissolved in dry benzene (80 ml), then epichlorohydrine (15 ml) and potassium carbonate (10 g, anhydrous) are added. The reaction mixture is heated to reflux for 4-5 hr, and concentrated under vacuum to give 3 (a & b). 3a n=14 yield 72% I.R. (nujol) 915, 840 , 1250 cm^{-1} (C-O-C), ^1H NMR ($CDCl_3$) δ=0.84 (t, 3H, CH_3), 1.24-1.44 m, 28H $(CH_2)_n$], 3.40 (t, 2H, O-CH_2 $(CH_2)_nCH_3$), 3.50 (t, 2H, CH_2-O), 4.21 (m,H,CH)

HC

MS : $[M]^+$ 298

1-O-Octadecyl/Hexaclecyl-2,3,glycerol 4(a & b)

Compound 3 (10. mmol) is taken in dioxane (5 ml) and Perchloric acid (2 ml) in dioxane/water 10 ml (6 : 4) is added. (CH_2)], 2.10 (s, 3H, $COCH_3$), 3.25 (d, 2H, CH_2-O-mTr, J=6.5 Hz). 3.68 (s, 3H, OCH_3), 5.28 (q, 1H), CH-OCOCH_3) J=6.5 Hz), 6.87 (d, 2H, 3H, and 5H of C_6H_4-OCH_3(4) J=8.8 Hz), 7.12-7.67 ppm (m, 12H, mTr).

MS : $[M]^+$ 614

1-O-Hexadecyl/Octadecyl-2-O-acetyl-Sn glycerol 7 (a & b)

A solution of1-O-Hexadecyl/octadecyl-2-O-acetyl-3-O-(4-methoxy trityl)Sn glycerol 6 (15 mmol) in Pet ether was applied to the Boric acid/silicic acid column which was then eluted with Pet ether and concentrated in vacuo to afford 7 (a & b), 1720 (C=O), 1180 (C-O-C) and 3420, 1060 cm^{-1} (OH).

1-O-Hexadecyl/Octadecyl-2-O-acetyl-Sn-3-glyceryl phosphorylcholine 8 (a & b)

A mixture of 7 (10 mmol) in dry chloroform (20 ml) and triethyl amine (3 ml) was stirred at room temperature. To this solution 2-chloro-2-oxo-1,3,2-dioxaphospholane (12 mmol) in presence of 4-dimethyl amino pyridine (2 ml) was stirred 5 hr. Reaction mixture was extracted from ethyl acetate and concentrated. To this solution 800 mg CCL (Yeast) (Sigma) in 30 ml of heptane/ n-butyl alcohal (1:2) were added and stirred 20 hr at room temperature. After filtration (S) PAF (8 a & b) were separated by flash chromatography yield 65-68% 8a, n=14 m.p. 248°C $[\ ]_D^{20}$ + 3.50, 8b, n=16 mp 265°C $[\ ]_D^{20}$ + 2.35, 8(a) ^{1}H NMR ($CDCl_3$) : 0.84 (t, 3H, CH_3), 1.20-1.50 (m, 28H $(CH_2)_{14}$), 2.05 (s, 3H, $COCH_3$), 3.32 (s, 9H, $(CH_3)_3N$), 3.45 (t, 2H, $CH_3(CH_2)_n\underline{CH_2}$) J=6.5 Hz), 3.62 (d, $O\underline{CH_2}CH$, J=6.5 Hz), 3.78 (t, $\underline{CH_2}N(Me)_3$, 4.30 (t, 2H, O-P-
The pH of reaction mixture is adjusted to and stirre
4 hr. It is extracted with chloroform (3x200 ml) and co
trated to yield 4 (a & b) yield 70% IR (KBr) 3430 cm^{-1} (OH) 2970 (CH_2), ^{1}H NMR ($CDCl_3$) δ=0.86 (t, 3H, CH_3), 1.24-1.44 (m, 28H $(CH_2)_{14}$) 3.46 (t, 2H, OCH_2), 3.50 (d, 2H, $\underline{CH_2}$-O-$(CH_2)_n$) 4.42 (m, H, CH), 3.56 (d, 2H, $C\underline{H_2}$-OH).

MS : $[M]^+$ 300

1-O-Hexadecyl/octadecyl-3-O-(4-methoxy trityl)-Sn-glycerol 5 (a & b)

A solution of 4-methoxy trityl chloride (12 mmol) in dry tetrahydrofuran (5 ml) is added to a stirred solution of 4(a & b) (10. mmol) in pyridine (10 ml) in an ice-water bath. The reaction mixture was stirred for 2 hr at room temperature and then concentrated in vacuo. The oil was than dissolved in $CHCl_3$ and washed with 10% sodium hydrogen carbonate which was chromatographed on silica gel to yield 5 (a & b) 60%.

1-O-Hexadecyl/Octadecyl-2-O-acetyl-3-O(4-methoxy trityl)Sn-glycerol 6 (a & b)

A mixture of 5 (10 mmol), dry pyridine (10 ml), and acetic anhydride (8 ml) was stirred for 12 hr at room temperature. Then, ice (50 g) was added and then extracted with chloroform (200 ml). The reaction mixture was washed with 10% $NaHCO_3$, water and dried with magnesium sulfate to give 6 (a & b) 80%, IR (Nujol) 1740 (C=O), 1250 cm^{-1} (C-O-C), ^1H NMR ($CDCl_3$) δ=0.84 (t, 3H, CH_3); 3.40 (t, 2H, $CH_3(CH_2)_n\underline{CH_2}$-O, J=6.5 Hz) , 3.65 (d, 2H, O-$\underline{CH_2}$) 1.28-1.50 (m, 2H $O\underline{CH_2}$ J=6.5 Hz) 4.22 (d, 2H, $\underline{CH_2}$ O-P), 5.10 (q, 1H, HCOCOCHS J=6.5 Hz) ^{13}C NMR ($CDCl_3$) δ : 15.4 (s, $\underline{CH_3}(CH_2)_n$), 22.5 (s, $CO\underline{CH_3}$) 24.8 (s, $\underline{CH_2}$, CH_3), 27.5 (s, $\underline{CH_2}$-CH_2-O). 3.01 (s, $CH_3CH_2CH_2(\underline{CH_2})_n$] 3.21 (s, $CH_3CH_2\underline{CH_2}$), 55.4 (s, $N(CH_3)_3$) 66.7 (d, P-OCH_2, JC-P = 6.1 Hz), 60.4 (d, CH_2-OPeh J. C-P=6.1 Hz) 67.6 (br $\underline{CH_2}N(CH_3)_3$) 70.1 (s, CH_3CH_2n-$O\underline{CH_2}$) 73.4 (d, H$\underline{C}$O-Ac), 172.8 (s, $\underline{C}OCH_3$) MS (8a) n=14 $[M]^+$ 532, 8b: n=16 $[M]^+$ 567.

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