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A VERSATILE SYNTHON APPROACH TO THE PREPARATION OF SOME PHOSPHOLIPASE A_2 INHIBITORS

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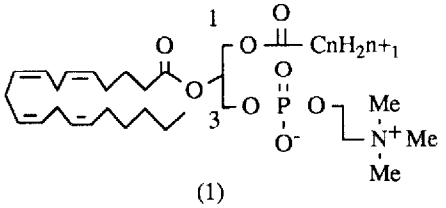
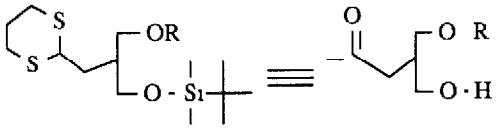
Abstract:- A versatile route for the preparation of 2-ketomethylene phospholipids using dithiane chemistry is described

Cell membranes contain large amounts of arachidonic acid bound at the 2-position of the membrane phospholipids Cleavage of arachidonic acid from the 2-position by phospholipase A_2 is believed to be a major biological source of this versatile reactive acid, which is rapidly transformed into the biologically potent prostaglandins, thromboxanes and leukotrienes[1] We became interested in the inhibition of this class of enzymes for our anti-inflammatory programme by a substrate analogue approach, following the publication of X-ray data for the active site of bovine pancreatic phospholipase A_2[2]

Novel approaches in phospholipid chemistry are of considerable interest in this active area of research New chemical methods in this biologically important domain have only recently received attention from organic chemists We have devised the synthesis of a synthon (2) (Scheme 1) which would permit the preparation of a series of phospholipid analogues in which the labile 2-ester group of (1) has been replaced by a stable ketomethylene function and the substituents at C-1, C-3 and the C-2 ketomethylene function can be readily varied It was surmised that replacement of one oxygen in the molecule by a carbon should not grossly effect incorporation of the analogues into the membrane biolayers

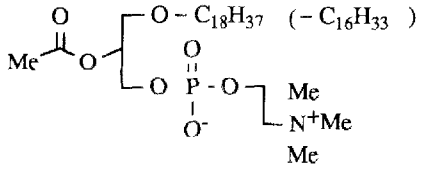


(1)



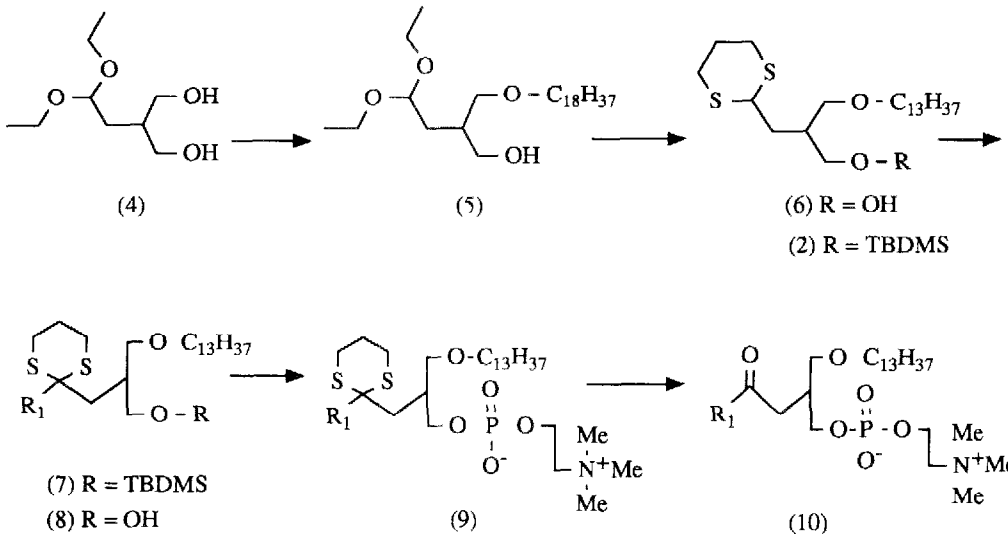
(2)

Initially the C-1 ester group of the phospholipid was replaced by a long chain ether, simplifying the chemistry and at the same time permitting preparation of analogues of the equally interesting platelet aggregating factor (PAF) (3)[3]



(3)

Scheme 1



(4) (5) (6) R = OH; (2) R = TBDMS

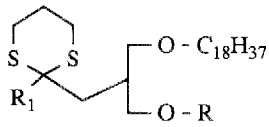
(7) R = TBDMS; (8) R = OH (9) (10)

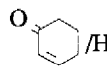
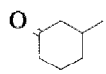
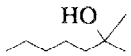
The diethylacetal diol (4) was readily prepared by alkylation of diethylmalonate with bromoacetaldehyde diethylacetal (NaH/EtOH/48 hrs reflux) followed by reduction ($LiAlH_4/Et_2O$) to give (4) as a pale yellow oil (54% overall) Conversion to the octadecylether (5) was accomplished in 84% isolated yield ((i) NaH/THF, (ii) n-octadecylmethanesulphonate /THF/reflux) (The methanesulphonate is more soluble in THF than the tosylate giving better yields)

The dithiane alcohol (6) could be prepared via a protection/deprotection sequence ((i) Ac_2O/pyridine, (ii) 1 2 equiv $HS(CH_2)_3SH$/0 1 equiv BF_3 Et_2O, (iii) K_2CO_3/aq MeOH) or directly (2 2 equiv $HS(CH_2)_3SH$/ 0 6 equiv BF_3 Et_2O) The alcohol was protected as the ^{t}butyldimethylsilyl ether (2) (TBDMSCl/ imidazole/DMF) and purified by flash chromatography Conversion from the octadecyl ether (5) to the protected dithiane (2) can be achieved routinely in better than 90% overall yield on a 50g scale

Formation of the lithium anion of (2) (nBuLi/THF/-20°C/1$^1/_2$ hrs), followed by quenching with various alkyl/arylalkyl halides at -78°C with slow warming to ambient temperature gave the derivatives (entries 1-7) (Table 1)

Table 1



Entry	Electrophile	R_1	(Isolated as R)	(Yield)
1	EtI	Et-	8a	91%
2	nBuBr	nBu-	8b	77%
3	iBuBr	iBu-	7c	69%
4	$C_8H_{17}Br$	C_8H_{17}-	7d	81%
5	$C_{18}H_{37}Br$	$C_{18}H_{37}$-	7e	83%
6	$Ph(CH2)_3Br$	$Ph(CH2)_3$-	8f	54%
7	$Cl(CH_2)_4Br$	$Cl(CH_2)_4$-	7g	87%
8	 /HMPA		7h	34%
9	2-hexanone		7i	46%
10	$(EtO)_2CHCH_2Br$	$(EtO)_2CHCH_2$-	7j	10 4%

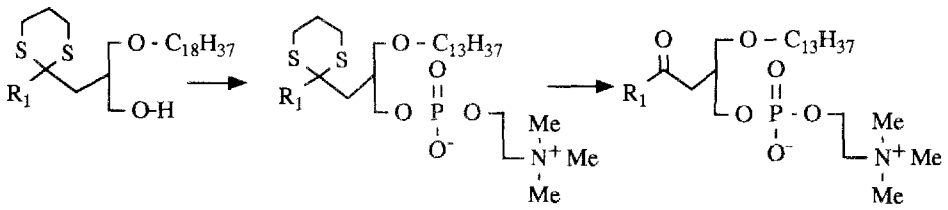
In the presence of HMPA[4] the dithiane anion added to 2-cyclohexen-1-one by a 1,4 addition process exclusively (entry 8) Addition to hexan-2-one gave a moderate yield of the alcohol (7i) whereas addition to the hindered bromoacetaldehyde diethylacetal was very slow giving a very low yield of (7j) The products were purified by flash chromatography either as the TBDMS derivative or after deprotection (1M HCl/acetone)

Since removal of the dithiane moiety at this stage leads to the formation of stable 5-member ring hemiacetals, conversion to the 3-phosphatidyl derivatives (9) by the method of Thuong and Chabrier[5] followed by the removal of the dithiane protecting group was investigated The free alcohol derivatives (8) were treated with 2-chloro-2-oxo-1,3,2,-dioxaphospholane /Et_3N/benzene/DMF/0°C for $1^1/_2$ hrs, filtered, diluted with acetonitrile and heated with excess trimethylamine at 60°C in a bomb for 18 hrs to give the desired derivatives (9) in good yields, (Table 2)

A number of methods were investigated for the removal of the dithiane protecting group Those involving transition metals were found to form tightly bound complexes with the product, making purification

difficult Chloramine T/aq MeOH/THF[6] gave the most consistent results giving acceptable yields of the 2-ketomethylene phopholipids (10) after chromatography ($CHCl_3$/MeOH, (8 2), 1% water)[7]

Table 2



R =	H	6	9k (86%)	10K (80%)
	Et-	8a	9a (87%)	10a (72%)
	nBu-	8b	9b (75%)	10b (70%)
	iBu-	8c	9c (75%)	10c (53%)
	C_8H_{17}-	8d	9d (87%)	10d (74%)
	$C_{18}H_{37}$-	8e	9e (75%)	10e (84%)
	$Ph(CH_2)_3$-	8f	9f (96%)	10f (75%)

This synthetic route provides a versatile and convenient route to these stable analogues which possess interesting biological activity[8] Adaption of this route to a chiral synthesis of these analogues is in progress

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7 Compounds were characterised by 200 MHz ^1H and ^{13}C nmr; mass spectroscopy and C, H, N analysis Yields are not optimized

8 To be reported elsewhere

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