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# SYNTHESIS OF A NOVEL PLATELET ACTIVATING FACTOR CONGENER FROM DIACETONE GLUCOSE

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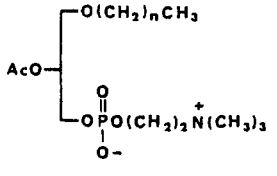
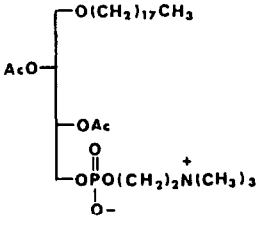
Summary: A synthesis of the novel PAF congener 2 via a monosaccharide template is described.

Since its structure elucidation in 1979 via partial synthesis from bovine heart plasmalogens[1,2], platelet activating factor (1) (PAF) has been increasingly studied for its remarkable biological profile. Its ability to cause platelet aggregation and granule release at concentrations of $10^{-8}$ to $10^{-11}$ M makes it one of the most potent stimulators of human and animal platelets known.[3] It appears that PAF may be a contributing factor in inflammatory and allergic responses[4] and it has recently been discovered that it also possesses anti-hypertensive activities.[5] There are now several reports describing total syntheses of PAF from glycerol derivatives.[6]

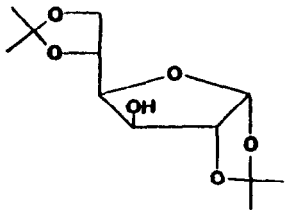



1, n=15,17

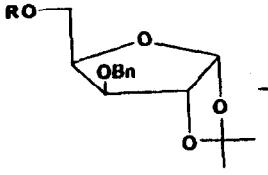



2

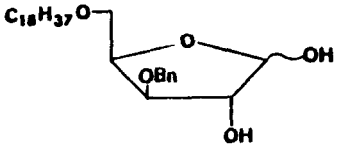
In our program directed towards the discovery of specific PAF-platelet receptor[7] antagonists, we have synthesized the homologous diacetate 2 in an optically pure form via the use of a monosaccharide template.[8] In this note we would like to report our synthesis and the biological efficacy of this novel congener.



3



4 R=H
5 R= $C_{18}H_{37}$



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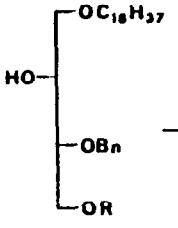
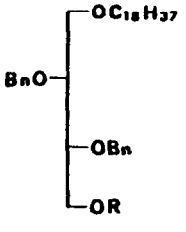
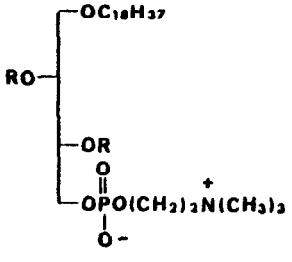


7 R = H
8 R = $Si(CH_3)_2(t\text{-}But)$



9 R = H
10 R = P(O)



11 R= Bn
12 R= H
2 R= Ac

The synthesis was initiated by the preparation of the known alcohol 4[9] from commercially available diacetone glucose (3) in four steps and 65% overall yield [(BnBr,(n-But)$_4$NI,NaH,THF),[10] (0.8% $H_2SO_4$,MeOH,24h), ($NaIO_4$,$H_2O$,dioxane), ($NaBH_4$, EtOH)]. The alcohol 4 was then alkylated using phase transfer conditions[11] to give the octadecyloxy derivative 5 (1.5 eq. $C_{18}H_{37}Br$,0.5 mol% $(nBut)_4NHSO_4$,50% NaOH, 70°C,24h; 86% yield, mp 33-34°C, $[\alpha]_D^{25}$ -25.0° (c 2.9, $CHCl_3$)[12a]) which was then hydrolysed (2% $H_2SO_4$:dioxane, 5:2, 90°C, 3h; 98% yield) to yield the hemiacetal 6. Oxidative cleavage and reduction of the intermediate aldehyde [($NaIO_4$,dioxane, $H_2O$), ($NaBH_4$,EtOH); 65% yield from 6, mp 57.5°-59.0°C, $[\alpha]_D^{25}$ -10.7° (c 5.3,$CHCl_3$)[12a]] afforded the diol 7.

At this juncture the desired fragment, with the correct chirality and oxidation levels, had been excised from the monosaccharide template and it was now necessary to undertake some protective group manipulations to set the stage for the phosphorylation. Thus, the diol 7 was selectively silylated (t-butyldimethyl-chlorosilane, imidazole, DMF; 98% yield, $[\alpha]_D^{25}$ -15.6° (c 1.4, $CHCl_3$)[12a]) to give the alcohol 8 which was then benzylated and then desilylated [(BnBr,NaH,THF), ((n-But)$_4$,NF,THF); 95% from 8, mp 37.0°-38.0°C, $[\alpha]_D^{25}$ -8.8° (c 1.6,$CHCl_3$)[12a]] to give the alcohol 9.

The phosphatidyl choline was introduced by phosphorylation of the alcohol 9 with 2-chloro-2-oxo-1,3,2-dioxaphospholane and ring cleavage of the intermediate 10 with anhydrous trimethylamine[13] to yield the dibenzyl derivative 11 [(ClP(O)$^{\bullet}$], $Et_3N$, DMAP,$CH_2Cl_2$), ($Me_3N$,$CH_3CN$,70°C,24h); 53% from 10]. The benzyl groups were hydrogenolysed (5% Pd/C,$H_2$; 94% yield, $[\alpha]_D^{25}$ +5.19° (c3.85, MeOH)[12b]) and the resultant diol 12 was acylated ($Ac_2O$,DMAP,$CH_2Cl_2$; quantitative, $[\alpha]_D^{25}$ +5.49° (c 2.73,MeOH)[12b]) to give the desired diacetate 2.

The diacetate 2 inhibited the PAF (synthetic, 1, n=15) induced aggregation of human platelets by 18% at 100 μM, thereby proving itself to be a weak antagonist. Interestingly, the diol 12 showed a weak synergistic effect, increasing the platelet response to PAF by 35% at 100 μM.

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