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SYNTHESIS OF PLATELET ACTIVATING FACTOR (PAF) VIA A CYCLIC TIN INTERMEDIATE

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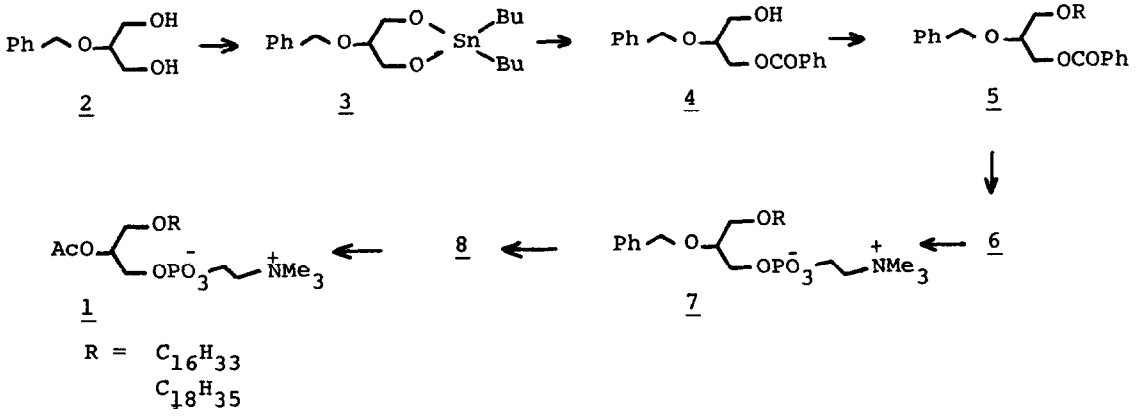
Summary: Condensation of 2-O-benzylglycerol with dibutyl tin oxide gave a cyclic intermediate which was functionalized to give PAF.

The selective protection of primary hydroxyl groups in the presence of secondary hydroxyl groups is an important synthetic skill and has been extensively studied.[1,2] This is frequently encountered in the synthesis of glycerol based compounds and commonly involves the monoderivatization of a multifunctional and often symmetrical substrate. New approaches have recently been developed specifically for the synthesis of glycerophospholipids[3,4] but most involve several protection and deprotection steps. Recently, Shanzer demonstrated that symmetrical diols can be converted to monoesters and subsequently to asymmetric diesters via cyclic, tin-based intermediates.[5] By application of this reaction, a new method for the synthesis of Platelet Activating Factor (1, PAF) is described.



The preferred procedure involved treatment of 1 equivalent of the diol 2[6] with 1 equivalent of di-n-butyl tin oxide in refluxing benzene for 6 hours to generate in quantitative yield the stannoxane 3 which was used without further purification. Compound 3 was then treated with one equivalent of benzoyl chloride in refluxing chloroform for 2 hours followed by the addition of one-third volumes of 4% aqueous dioxane. The homogeneous solution was refluxed for another 2 hours, 1 volume of chloroform was added and the mixture was washed with aqueous bicarbonate, dried over sodium sulfate and evaporated to give 4 as a crude oil. The latter was alkylated by treatment with 1.1 equivalents of sodium hydride in dimethylformamide. After the addition of 1.5 equivalents of alkyl bromide the mixture was allowed to stir at room temperature for 12 hours. Dilution with water followed by extraction into ether, drying over sodium sulfate and evaporation provided the O-alkyl benzoate 5 as an oil. Hydrolysis of the unpurified residue containing 5 with 4 equivalents of potassium carbonate in methanol for 4 hours at room temperature then generated the hydroxy diether 6 which was purified to provide a 30% overall yield of 6 from compound 2.

(R,S)-PAF was then prepared by a modification of the method developed by Benveniste.[7] Alcohol 6 was treated with 1.5 equivalents of 2-bromoethyldichlorophosphate[8] and 6 equivalents triethylamine for 4 hours in trichloroethylene. After hydrolysis of the resulting phosphoro chloridate the product was extracted with ether and washed with water and 1M sodium carbonate to give, after evaporation, the sodium salt of the phosphate bromoethyl ester. Subsequent treatment with 7 ml of 25% aqueous trimethylamine in 13 ml $CHCl_3$:DMF:i-propanol (3:5:5) for 12 hours at 50° C gave the phosphorylcholine 7. This was purified by precipitation from $CHCl_3$/acetone (1:10) to give the product in 38% yield from 6. The benzyl group was removed by hydrogenation over Pd/C in ethanol for 5 hours at 50° C to give the 2-hydroxy derivative 8 in quantitative yield. Acetylation of 8 with an excess of acetic anhydride and triethylamine in chloroform gave (R,S)-PAF (1) in 96% yield.

The simplicity of the steps to generate the hydroxy benzoate 6 makes this an attractive method, and one does not generate any dibenzoate as might be expected via other methods. Hydrolysis of the ether benzoate 5 can be carried out on the crude alkylation product under very mild conditions, thereby avoiding time consuming chromatographic purification.

This procedure demonstrates that diols can be suitably functionalized without having to rely on several protection/deprotection steps. It allows one to reduce the number of steps in what are often long and linear synthetic sequences in lipid chemistry. Using this procedure combined with the recent asymmetric synthesis of glycerol esters[9], the synthesis of chiral PAF should be readily achieved.

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