Tetrahedron Letters,Vol.26,No.42,pp 5195-5198,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

AN EFFICIENT AND STEREOCONTROLLED SYNTHESIS OF PLATELET ACTIVATING FACTOR FROM (S)-(-)-MALIC ACID

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Summary: A stereocontrolled synthesis of C_{16}-PAF (11) from (S)-(-)-malic acid (1), employing regioselective hydrogenolytic cleavage of benzylidene acetal derivatives of (S)-1,2,4-butanetriol (2) with borane-tetrahydrofran complex, is described.

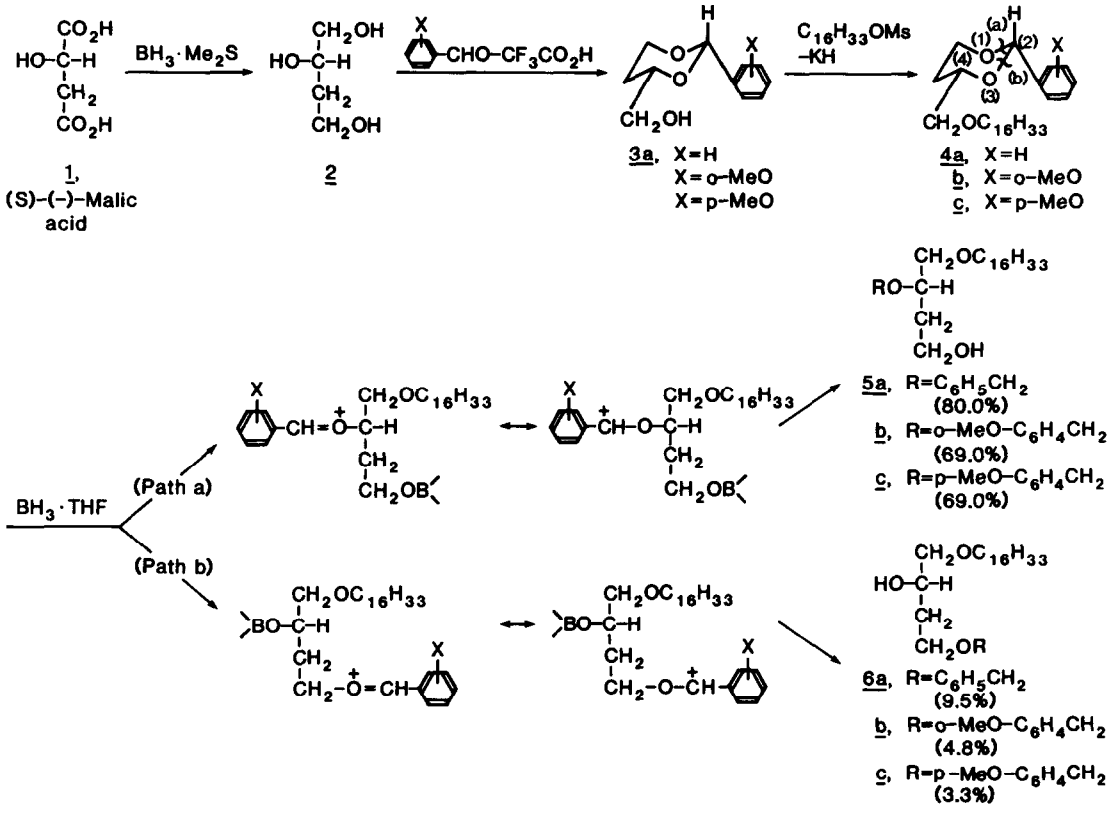
1-O-Alkyl-2-O-acetyl-sn-glyceryl-3-phosphorylcholine, in which the alkyl component is largely comprised of the C_{16} and C_{18} homologues has been identified as platelet activating factor (PAF) by Hanahan et al.[1] and Benveniste et al.[2] in 1979. In the same year, it also was shown to be identical with hypotensive substances designated as the antihypertensive polar renomodullary lipid (APRL) by Muirhead et al.[3] The potent and diverse biological features of PAF[4-6] have stimulated many synthetic studies of them and their analogs and much research on the biological properties of these synthesized substances in recent years.

Since only the natural isomers of PAF have been reported to be biologically active,[7,8] their enantioselective synthesis starting from optically active natural sources such as D-mannitol[9] and D-tartaric acid[10] as the chiral synthons has become of interest. We now wish to report another efficient and stereocontrolled method for synthesizing PAF which uses readily available (S)-(-)-malic acid as the starting material and employs regioselective hydrogenolytic cleavage of benzylidene acetal derivatives of (S)-1,2,4-butanetriol with the borane-tetrahydrofuran complex.

(S)-1,2,4-Butanetriol (2), obtained from (S)-(-)-malic acid (1) by reduction with borane-dimethylsulfide complex,[11] was converted into (S,S)-2-phenyl-, (S,S)-2-(2-methoxyphenyl)- and (S,S)-2-(4-methoxyphenyl)-4-hydroxymethyl-1,3-dioxane (3a, 3b and 3c) by reaction with benzaldehyde, 2-methoxybenzaldehyde and 4-methoxybenzaldehyde respectively in the presence of a catalytic amount of trifluoroacetic acid in CH_2Cl_2.[12] Alkylation of these compounds with n-hexadecylmethanesulfonate and potassium hydride in benzene at 40°C proceeded smoothly to give the corresponding (S,S)-2-phenyl-, (S,S)-2-(2-methoxyphenyl)- and (S,S)-2-(4-methoxyphenyl)-4-hexadecyloxymethyl-1,3-dioxane (4a, 4b and 4c).

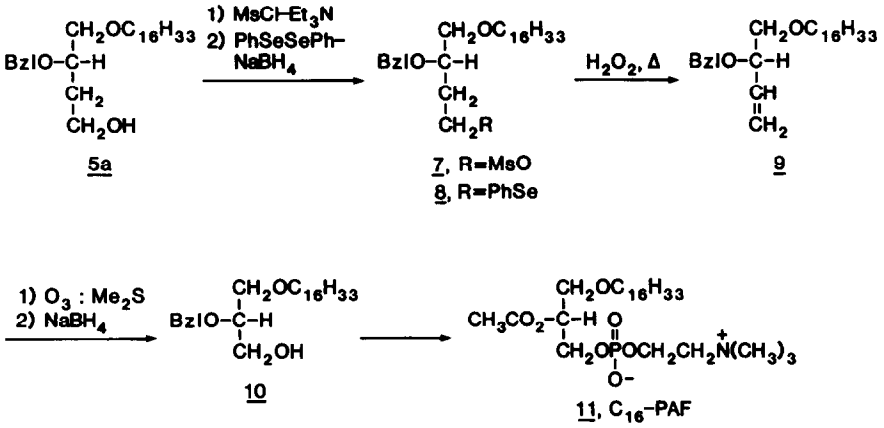
First, we tried to find out the condition to convert these benzylideneacetal derivatives into the corresponding (S)-2-O-benzyl-, (S)-2-O-(3-methoxybenzyl)- or (S)-2-O-(4-methoxybenzyl)-1-O-hexadecyl-1,2,4-butanetriol (5a, 5b and 5c) by selective hydrogenolytic

Scheme I.



cleavage of the benzylidene acetal function. When 4a reacted with diisobutylaluminum hydride (DIBAL) in toluene at 0°C to room temperature, the major product was 6a. The result may be due to initial coordination of the aluminum atom of DIBAL to the O(3) atom of the dioxane ring and the ether oxygen of the side chain and subsequent chelation-directed site-selective cleavage of the dioxane ring at O(3)-C(2) bond (path b in Scheme I). To avoid this six-membered chelation of the aluminum atom with these oxygens and expecting the steric bulkiness of the reagent coordinated with solvent to affect the attack of the reagent at the oxygen atom of the less hindered site of the acetal ring, we next tried the reduction of 4a with DIBAL or a $LiAlH_4$-$AlCl_3$ mixture in a mixture of toluene and an ethereal solvent like ethyl ether, tetrahydrofuran (THF) or dimethoxyethane. This attempt only diminished the reducing ability of the reagents and did not improve the product ratio. When 4b reacted with DIBAL in a 1:1 mixture of toluene and THF under reflux, 5b, 6b and 4b were obtained in 38, 9 and 30% yields, respectively. However, when 4a-b were reacted with borane-tetrahydrofurane complex in THF at reflux temperature, borane preferentially attacked the O(1) atom of the dioxane ring and hydrogenolytic cleavage occurred to give the desired compound, 5a $[\alpha]_D^{25}$ -25.44° (c = 1.00, $CHCl_3$) [lit.[13] $[\alpha]_D^{25}$ -24.52° (c = 1.04, $CHCl_3$)], 5b and 5c. As expected,

Scheme II.



5a

7, R=MsO
8, R=PhSe

9

10

11, C_{16}-PAF

in the case of 4b and 4c, the rate of the cleavage reaction increased but no additional improvement of the product ratio was obtained. The hydrogenolytic cleavage of 1,3-dioxaolanes 4a-c by borane proceeds most probably to the direction as to give the most stable oxocarbonium ion intermediates possible with the electronic factor of the substituent at C(4).[14,15] The predominant cleavage at the O(1)-C(2) bond of the dioxane ring with borane in the case of 4a-c (path a in Scheme I) might rather be affected by the influence of the steric factor of the substituent at C(4).

Next, we tried to convert 5a to 1-O-hexadecyl-2-O-benzyl-sn-glycerol (10), which has already been converted into C_{16}-PAF by Ohno et al.,[10] to accomplish our synthesis of PAF from (S)-(-)-malic acid. Mesylation of 5a proceeded smoothly by reaction with mesyl chloride and triethylamine in CH_2Cl_2 to give 7 quantitatively. Reaction of 7 with potassium tert-butoxide in a solvent like toluene, DMF or DMSO gave the olefine derivative 9 in about 60-65% yield. As the yield of this conversion was not satisfactory, the following procedure was conducted. Compound 7 was converted to phenylselenyl derivative 8 by reaction with phenyl selenol obtained from diphenyl diselenide and sodium borohydride, and then oxidized with hydrogen peroxide, followed by heating in methanol to obtain 9. Overall yield of 9 from 5a was 85%. Ozonization of 9, cleavage of the ozonide with dimethyl sulfide and subsequent reduction of the aldehyde with sodium borohydride afforded 10, $[\alpha]_D^{25}$ -1.21° (c = 3.70, CH_3OH) [lit.[10] $[\alpha]_D^{20}$ -1.15° (c = 3.69, CH_3OH)] in 92% overall yield. Finally, the known four-step procedure[16] was applied to obtain C_{16}-PAF (11). Our nine-step synthesis of the key intermediate of PAF, 9, starting from (S)-(-)-malic acid in 50% overall yield thus proved to be a very efficient and convenient method offering complete stereocontrol.

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(Received in Japan 30 July 1985)