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# AN EFFICIENT AND STEREOSELECTIVE SYNTHESIS OF PLATELET-ACTIVATING FACTORS AND THE ENANTIOMERS FROM D- AND L- TARTARIC ACIDS

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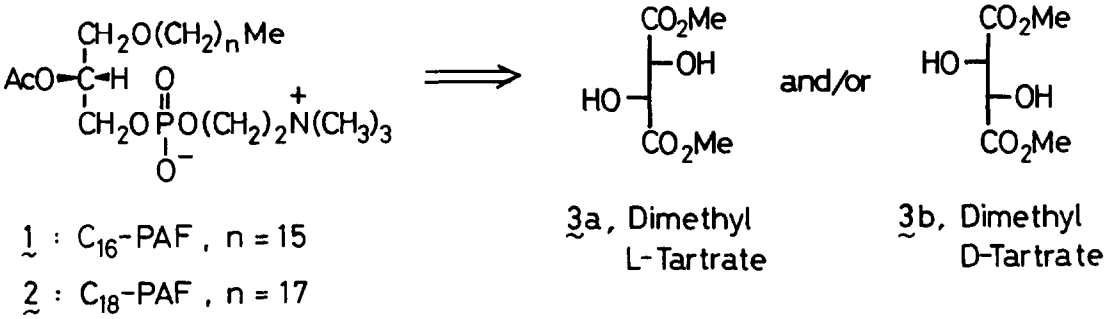
Summary: Acetyl glyceryl ether phosphorylcholines, platelet-activating factors (1 and 2), were efficiently synthesized in a stereochemically unambiguous männer starting from D- and L- tartaric acids as the chiral synthons.

Since its isolation and characterization by Hanahan and his co-workers in 1979[1a], acetyl glyceryl ether phosphorylcholines (1 and 2) as the platelet-activating factors (PAF) have attracted a great deal of synthetic study, because they act as vitally important biological effectors in the physiological processes[1-4]. Specifically, the ether phospholipids act as vasodilators[2], chemotactic agents[3], and selective tumor-cytotoxic agents against a number of different cancer cells[4].

Scheme I




1 : $C_{16}$-PAF , n = 15

2 : $C_{18}$-PAF , n = 17

3a, Dimethyl L-Tartrate

3b, Dimethyl D-Tartrate

However, the scarce and elusive PAF of animal origin[1] and lack of efficient synthetic methods[5] for the preparation of ether phospholipids make difficult to investigate structure-activity relationships of such highly potential phospholipids. Furthermore, there are confusing evidences about the biological activity of natural 1-O-hexadecyl-2-O-acetyl-sn-glycero-3-phosphocholine (1) and the

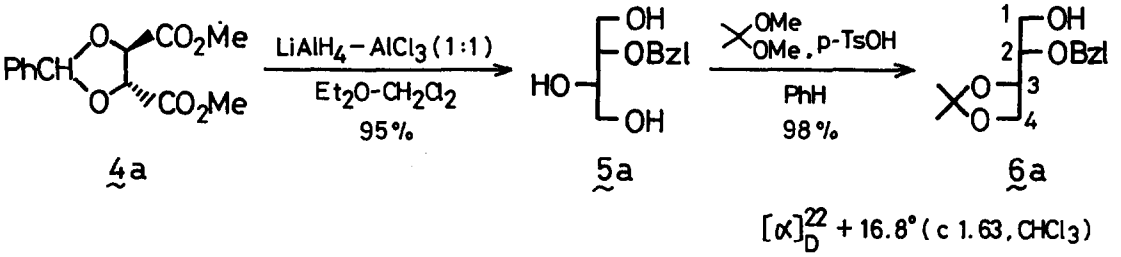
enantiomer, 3-O-hexadecyl-2-O-acetyl-sn-glycero-1-phosphocholine. The enantiomer has been reported to be unexpectedly potent in degranulating rabbit platelets[5], but it has been shown recently that only the natural isomer of PAF is active and the enantiomer is inactive[6,7]. This discrepancy has been attributed in part to racemization of 1,2-isopropylidene glycerol, a key intermediate of PAF obtained from D-mannitol which has been generally used as the starting material[6]. The requirements for a more stereoselective and high-yielding synthesis of ether phospholipids having desired absolute configuration[8] at C-2 are indeed demanding in the exploitation of such highly potential biological effectors[9]. We wish to report here an efficient methodology for the preparation of natural PAF and the enantiomer by highly selective functional transformation of D- and L-tartaric acids.

Synthesis of L- and D-Threitol Derivatives 6a and 6b (Scheme II). The key feature of our approach is based upon the selective transformation of D- and/or L-tartaric acids to the chiral phospholipid skeleton by using one of the two asymmetric carbons of the starting synthons as shown in Scheme I. One of the two hydroxyl groups of 3a and 3b was efficiently protected in the following way. The dimethyl esters 3a and 3b were treated with benzaldehyde to afford O-benzylidene derivatives 4a and 4b [benzene reflux, p-TsOH (catalytic), 1h]. Reductive cleavage[10] with $LiAlH_4$-$AlCl_3$ (ether-$CH_2Cl_2$, 1h at 25°C→1h reflux) afforded triols 5a and 5b quantitatively. The vic-glycols of the triols were protected with isopropylidene[11] (5→6). Thus, L- and D-Threitol derivatives 6a and 6b were obtained as colorless oils in about 68% overall yields.

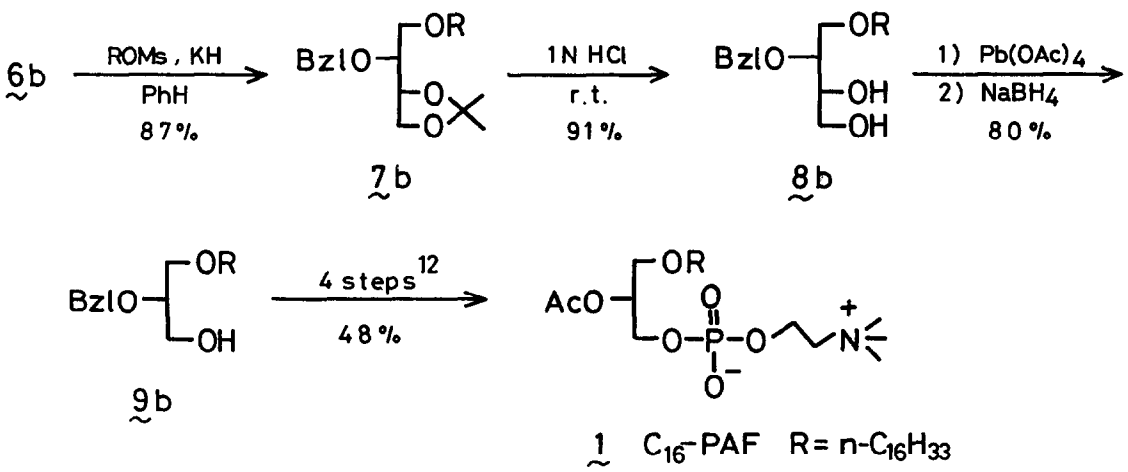
Synthesis of PAF 1 and 2 (Scheme III). The most straightforward synthesis of PAF was achieved starting with 6b. This route was designed to use C-2 chiral carbon of 6b into the chiral phospholipid skeleton. Alkylation of the primary alcohol of 6b proceeded smoothly with $C_{16}H_{33}OMs/KH$ to afford 7b (R=$C_{16}H_{33}$) in an excellent yield. After removal of the isopropylidene group with 1N HCl, resulting glycol 8b was subjected to oxidative cleavage with $Pb(OAc)_4$ and reduction with $NaBH_4$, affording 1-O-hexadecyl-2-O-benzyl-sn-glycerol in a good yield. Then, known 4 step procedures[12] were applied to afford $C_{16}$-PAF 1, $[\alpha]_D^{20}$ -3.3° [c 0.525, $CHCl_3$+MeOH (1:1)], in 48% yield. This approach was also applied for the preparation of $C_{18}$-PAF 2 in the similar manner, and it can be said that this methodology (11 steps, 21% overall yields, 3b to 1) is much superior to that from D-mannitol (15 steps, 6% overall yields). Next, another synthetic route from L-tartaric acid series was investigated, since L-tartaric acid is more easily available from argol. In this case, the absolute configuration at C-2 of 6a can be reasonably used by alkylation at O-3 and introduction of phosphocholine group at O-1, after removal of C-4 carbon. Trityl derivative of 9b was obtained in 4 steps from 6a (TrCl-Py→AcOH→$NaIO_4$→$NaBH_4$). The trityl derivative was already converted to PAF by Heyman et al. This approach is consisted of 13 steps in about 15% overall yields[13]. Significantly, the sequence at outlined here has a great deal of flexibility, providing a convenient general method for the preparation of PAF and a wide range of structurally related ether phospholipids[14].

Synthesis of PAF Enantiomers. $C_{16}$-PAF, $[\alpha]_D^{20}$+3.2° [c 1.0, $CHCl_3$+MeOH (1:1)], and $C_{18}$-PAF enantiomers were prepared from 6a in the same manner as shown in Scheme III. (11 steps from 3a, about 20% overall yields). Preliminary study on the biological activity showed that synthetic PAF 1 aggregates and degranulates rabbit peritoneal neutrophils at $10^{-11}$ to $10^{-10}$M, but the synthetic enantiomer was almost inactive, supporting the recent finding by Wykle et al[7].

Scheme II




Scheme III



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13. All new compounds were purified by column chromatography on silica gel or recrystallization and well characterized by spectroscopic analysis (IR, $^1$H-NMR, and MS) and combustion data. 4a; mp 69-71°C, $[\alpha]_D^{23}$-47.2° (c 1.00 MeOH): 4b; 71-73°C, $[\alpha]_D^{23}$+46.3° (c 1.02 MeOH): 5a; mp 73-76°C, $[\alpha]_D^{22}$+15.7° (c 1.00 MeOH): 5b; 69-72°C, $[\alpha]_D^{23}$-15.2° (c 0.96 MeOH): 6a and 6b; oil, M+ 212: 7b; oil, M+ 476: 8b; mp 40-41°C, $[\alpha]_D^{20}$-6.19° (c 1.0 MeOH), M+ 436: 9b; oil, $[\alpha]_D^{20}$-1.15° (c 3.69 MeOH) M+ 406: 1; 247°C (dec)


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