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A Convenient Synthesis of Platelet-Activating Factors and Their Analogues from Chiral Epichlorohydrin

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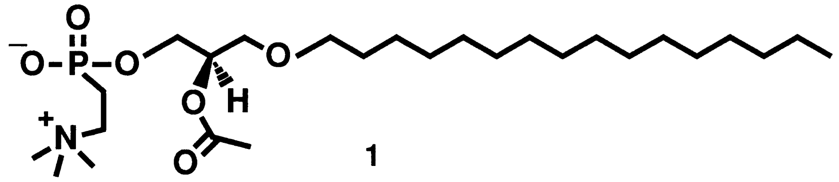
Two platelet activating factors (PAF) were conveniently prepared from optically active epichlorohydrin via 5 steps in 15-16% total yield. Four analogues containing oleoyl, propyl, *p*-trifluoromethylphenoxy, and *N,N*-dimethyldithiocarbamoyl groups were also prepared.

Platelet-activating factor (PAF) is a naturally occuring simple phosphoglyceride with very potent biological activity.[1,2] The structure of natural PAF is 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine (AGEPC), with the alkyl chain varing from C14:0 to C18:1. Two natural PAFs, 1-*O*-hexadecyl-2-acetyl-*sn*-glycero-3-phosphocholine (**1**) and 1-*O*-octadecyl-2-acetyl-*sn*-glycero-3-phosphocholine (**2**) are representative. Since the first synthesis, many synthetic studies of natural PAFs as well as their analogues have been reported from the standpoint of an interest in biological activities as agonists or antagonists.[3,4] We now wish to report a short and convenient asymmetric synthesis of natural PAFs (**1**,**2**) and their analogues with high optical purity. Synthetic sequence of two natural PAFs via 5 steps in 15-19% total yield is summarized in Scheme 1. The chiral center of PAFs was introduced by using optically active epichlorohydrin.[5] The reaction of (*S*)-epichlorohydrin with *p*-methoxybenzyl alcohol in the presence of phase transfer catalyst (0.05 equiv. benzyltrimethylammonium bromide (BTMAB), aq. NaOH-hexane) gave a substituted product (*S*)-**3**[6] in 76% yield. Nucleophilic addition of hexadecanol to (*S*)-**3** in the presence of NaH (THF, 6 equiv. HMPA, 45 °C, 6.5 h) afforded (2*R*)-alcohol **4a** in 52% yield. Acetylation of **4**with acetyl chloride (pyridine; CH_2Cl_2; O °C (30 min), 25 °C (30 min)) gave (*R*)-acetate **5a**[7] in 97% yield. Oxidative debenzylation of **5a** with dichlorodicyanobenzoquinone (DDQ)[8] (CH_2Cl_2-H_2O, 20 °C, 4 h) gave (*R*)-acetoxy-alcohol **6a** in 97% yield. Phosphocholination[9] of **6a** was carried out in one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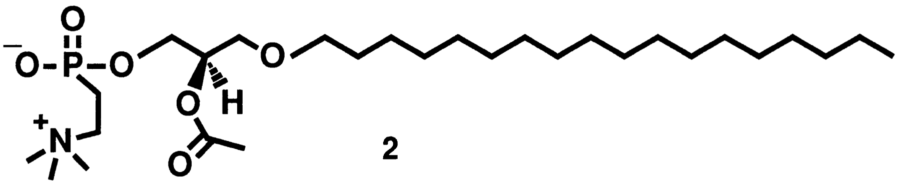
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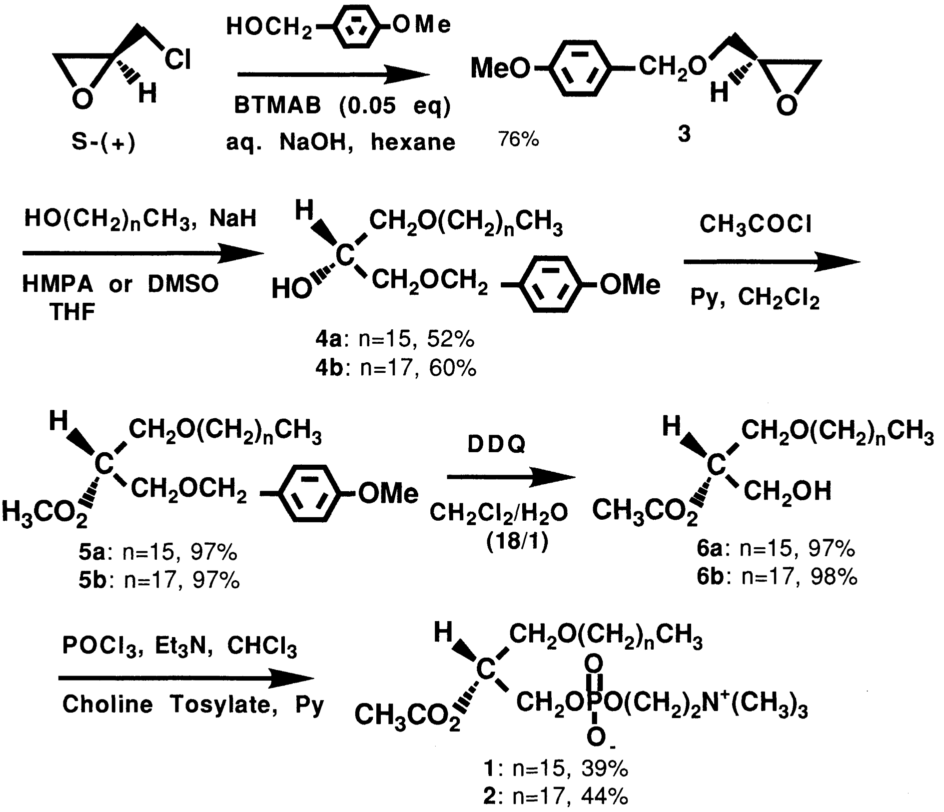
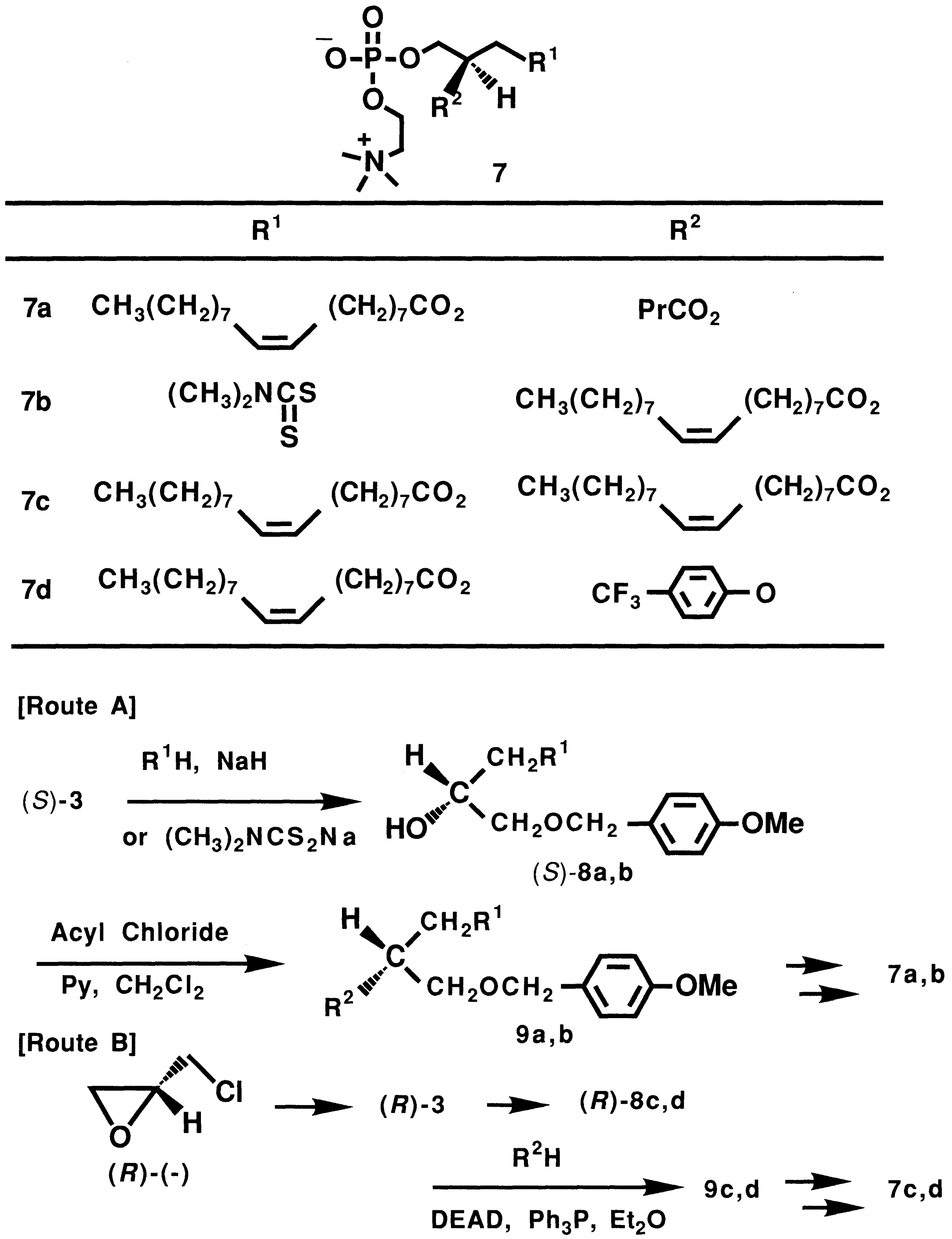


Scheme 1. Synthesis of Natural PAFs (**1**, **2**) from (*S*)-Epichlorohydrin

batch by the reaction of **6a** with phosphoryl chloride (triethylamine, $CHCl_3$, 0 °C, 30 min) and the subsequent treatment with choline tosylate (pyridine, $CHCl_3$, room temp., 14 h). The crude product was purified by column chromatography on ion exchange resin (Amberlite HB-3, THF/H_2O (9/1)) and subsequently with silica gel ($CHCl_3$/MeOH/H_2O, 65/35/6) to give PAF (**1**) in 39% yield. Spectral data and specific optical rotation10) were identical with those of an authentic sample.3)

Furthermore, some analogues were prepared as shown in Scheme 2. Both enantiomers of epichlorohydrin were used as the starting material. Epoxide (*S*)-**3** obtained from (*S*)-(+)-epichlorohydrin was allowed to react with oleic acid in the presence of sodium hydride (0.03 equiv. BTMAB, THF, 90 °C, 22 h), giving oleate **8a** in 71% yield. The reaction of **8a** with butanoyl chloride (pyridine, hexane, 25 °C: 1 h, 50 °C: 17 h) gave diester **9a** in 87% yield. Subsequent debenzylation and phosphocholination of **9a** were carried out as shown in Scheme 1, giving PAF analogue **7a**11) in 8.6% total yield from (*S*)-(+)-epichlorohydrin. Similarly, analogue **7b**12) possessing dithiocarbamoyl group was prepared from (S)-(+)-epichlorohydrin via the reaction of (*S*)-**3** with sodium *N*,*N*-dimethyldithiocarbamate and the esterification with oleoyl chloride.

On the other hand, the synthesis of PAF analogues (**7c** and **7d**) starting from (*R*)-(-)-epichlorohydrin via the inversion of the chirality of C-2 carbon on the esterification of (*R*)-**8** by use of Mitsunobu reaction is described in route B of Scheme 2. Analogue **7c**13) bearing two oleate moieties was prepared in 11.5% total yield via the esterification of (*R*)-**8c** with oleic acid ((*R*)-**8c** (0.829 mmol), diethyl azodicarboxylate (DEAD, 1.23 mmol), Ph_3P (1.25 mmol), Et_2O (5 ml), 25 °C, 24 h; 54.4% yield). Furthermore, analogue **7d**14) was synthesized in 2.1% total yield by using oleic acid and *p*-trifluoromethylphenol.



Scheme 2. Synthesis of PAF analogues 7 from both enantiomers of epichlorohydrin.

The present synthesis is short, experimentally simple and readily provides PAF and its analogues with high optical purity. Especially, the present method involving deprotection of *p*-methoxybenzyl group with DDQ under neutral condition instead of conventional reductive method for removal of a benzyl group is useful for the synthesis of PAF analogues bearing olefinic alkyl chains without any damage of double bonds. The biological test of PAF analogues obtained in this work is in progress.

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5) We thank Nippon Kogyo Co. Ltd. for giving (*R*)- and (*S*)-epichlorohydrins.

6) (*S*)-**3**: $[\alpha]_D^{22}$ +3.34° (c 3.79, $CHCl_3$); IR (neat) 1615, 1518, 1250, and 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.42-2.91 (m, 2H), 2.91-3.33 (m, 1H), 3.3-3.7 (m, 2H), 3.76 (s, 3H), 4.48 (s, 2H), 6.80 (d, *J*=9 Hz, 2H), 7.23 (d, *J*=9 Hz, 2H).

7) **5a**: Mp 53-54 °C; $[\alpha]_D^{25}$ +1.69 (c 2.95, $CHCl_3$): IR (KBr) 1730, 1615, 1238, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (br t, 3H), 1.25 (br s, 28H), 2.03 (s, 3H), 3.20-3.67 (m, 6H), 3.74 (s, 3H), 4.40 (s, 2H), 5.1 (m, 1H), 6.78 (d, *J*=9 Hz, 2H), 7.15 (d, *J*=9 Hz, 2H).

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10) **1**: $[\alpha]_D^{25}$ -3.7° (c 3.72, $CHCl_3$){lit. (Ref. 3) $[\alpha]_D^{21}$ -3.66° (c 0.71, $CHCl_3$)}. **2**: $[\alpha]_D^{25}$ -3.4° (c 0.7, $CHCl_3$) {lit. (Ref. 3) $[\alpha]_D^{20}$ -4.00° (c 0.71, $CHCl_3$)}.

11) **7a**: $[\alpha]_D^{23}$ +6.10° (c 3.3, $CHCl_3$/MeOH=1/1); IR (neat) 3440, 2960, 1745, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$/CD_3OD=1/1) δ 0.693 (t, *J*=7 Hz, 3H), 0.796 (t, J=7.5 Hz, 3H), 1.10 (m, 20H), 1.37-1.50 (m, 4H), 1.82 (m, 4H), 3,033 (s, 9H), 3.418 (t, *J*=4.29 Hz, 2H), 3.811 (t, *J*=5.92 Hz, 2H), 3.971 (dd, *J*=6.95, 11.99 Hz), 4.095 (br s, 2H), 4.214 (dd, *J*=3.26, 11.59 Hz, 2H), 5.05 (m, 1H), 5.155 (m, 2H).

12) **7b**: $[\alpha]_D^{25}$ +10.6° (c 1.95, $CHCl_3$/MeOH=1/1); IR (neat) 3420, 1740, 1660, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$/CD_3OD=2/1) δ 0.640 (t, *J*=6.46 Hz, 3H), 1.021 (m, 20H), 1.35 (m, 2H), 1.767 (m, 4H), 2.08 (m, 2H), 2.751 (s, 3H), 2.763 (s, 3H), 2.983 (s, 9H), 3.35 (m, 2H), 3.75 (m, 2H), 4.00-4.12 (m, 4H), 4.89 (m, 1H), 5.10 (m, 2H).

13) **7c**: $[\alpha]_D^{23}$ +4.35 (c 5.22, $CHCl_3$/MeOH/H_2O=65/35/6); IR (neat) δ 3450, 1745, 1240, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.696 (t, *J*=7.00 Hz, 3H), 0.96-1.31 (m, 48H), 1.411 (m, 4H), 1.825 (m, 8H), 2.13 (4H, m), 3.038 (s, 9H), 3.424 (m, 2H), 3.804 (m, 2H), 3.962 (dd, *J*=7.11 and 12.10 Hz, 1H), 4.059 (m, 2H), 4.225 (dd, *J*=3.2 and 12.1 Hz), 5.04 (m, 1H), 5.155 (m, 4H).

14) **7d**: $[\alpha]_D^{25}$ + 4.48° (c 2.58, $CHCl_3$/MeOH=1/1): IR (neat) 3400, 1730, 1620, 1245 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$/CD_3OD=2/1) δ 0.638 (m, 3H), 1.030 (m, 24H), 1.31 (m, 2H), 1.765 (m, 4H), 2.046 (6, *J*=7 Hz, 2H), 2.939 (s, 9H), 3.309 (m, 2H), 3.868 (m, 2H), 3.964 (br s, 2H), 4.588 (m, 1H), 5.096 (m, 2H), 6.874 (d, *J*=8.8 Hz, 2H), 7.313 (d, *J*=8.4 Hz).

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