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NOVEL ENANTIOSELECTIVE SYNTHESIS OF PLATELET ACTIVATING FACTOR AND ITS ENANTIOMER VIA RING OPENING OF GLYCIDYL TOSYLATE WITH 1-HEXADECANOL

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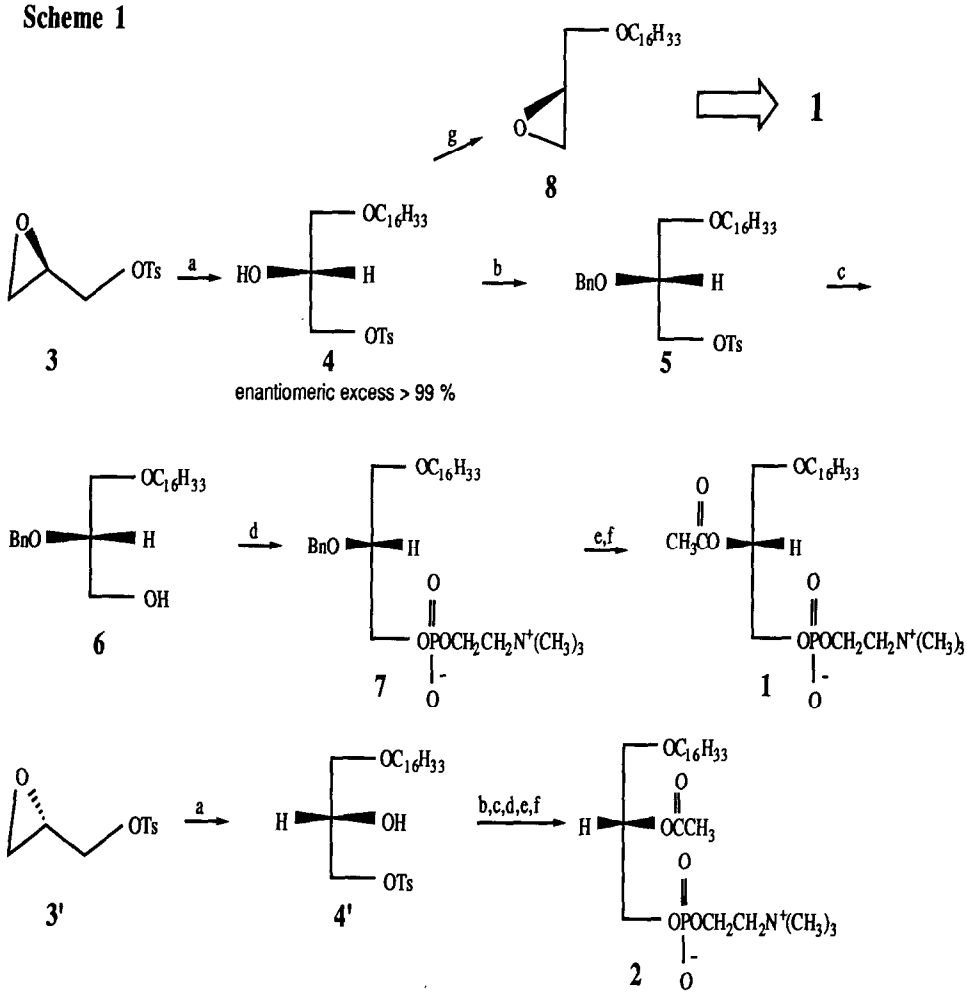
Abstract: (2*R*)- and (2*S*)-Glycidyl tosylates **3** and **3'** were used to synthesize platelet activating factor **1** and its enantiomer **2** in very high optical purity via the ring-opened ether-linked glycerol tosylate **4** and **4'**.

The discovery in 1979 that platelet activating factor (PAF, **1**) is an ether-linked phospholipid has led to the development of efficient chemical methods to prepare biologically active ether phospholipid analogs. The starting materials used in previous synthetic methods to prepare PAF and its analogs include D-mannitol,[1] L-ascorbic acid, [2] L-serine,[3] D-tartaric acid,[4] and *S*-malic acid.[5] Synthesis of the unnatural enantiomer of PAF (**2**) has also attracted considerable interest because **2** is useful in assessing the structural requirements of PAF for biological activity, especially in studies of the involvement of stereospecific receptors.[6] Syntheses of **2** have been achieved from L-tartaric acid, [6] and by inversion of configuration at C-2 of various precursors.[7] Recent advances in the asymmetric epoxidation of low molecular weight allyl alcohols by using catalytic amounts of the required reagents in the presence of molecular sieves, followed by *in situ* trapping of the formed epoxide[8] offer the possibility of a new route to **1** and its enantiomer **2**. We report here the preparation of chiral lipids **1** and **2** in very high optical purity wherein the key step is the stereo- and regioselective opening of epoxides **3** and **3'**.

(2*R*)-(-)-Glycidyl tosylate **3** and (2*S*)-(+)-glycidyl tosylate **3'** were synthesized from allyl alcohol by asymmetric epoxidation using (+)-DIPT and (-)-DIPT, respectively, and *in situ* derivatization.[8] Regiospecific opening of epoxide **3** or **3'** with 1-hexadecanol (1.4 equiv) was achieved using catalytic amounts (3 drops) of boron trifluoride etherate in alcohol-free chloroform (25 mL) (Scheme 1). The use of a catalytic amount of boron trifluoride etherate instead of titanium (IV) isopropoxide or chloride avoids ring opening by other nucleophiles such as 2-propanol or chloride generated from the titanium salts. In addition, base-induced opening of epoxide **3** would not be compatible with an enantioselective synthesis of **1** and **2** because of formation of *rac*-**8** by direct tosylate displacement and by ring opening followed by internal tosylate displacement.[9] Tosylates **4** and **4'** were isolated and purified by flash chromatogra-

Scheme 1



(a) 1-$C_{16}H_{33}OH$, $BF_3{\cdot}Et_2O$, $CHCl_3$. (b) BnOTf, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2. (c) CsOAc, DMF / DMSO (4:1); then $LiAlH_4$ / Et_2O. (d) $POCl_3$, Et_3N, $CHCl_3$; then $HO(CH_2)_2N^+Me_3$ OTs^-, pyridine; then H_2O. (e) H_2, $Pd(OH)_2$ / C, MeOH / H_2O (9:1). (f) Ac_2O, DMAP, $CHCl_3$. (g) K_2CO_3, MeOH.

phy in 80% yield, mp 68-69°C; lit. mp 68-69°C;[7] **4**: $[\alpha]_D^{25}$ -6.24 (c 5.0, C_6H_6); lit. $[\alpha]_D^{25}$ -5.55 (c 5.0, C_6H_6);[7] **4'**: $[\alpha]_D^{25}$ +6.37 (c 5.0, C_6H_6); lit. $[\alpha]_D^{25}$ +5.75 (c 5.0, C_6H_6).[7] ^1H NMR analysis (400 MHz) of the Mosher ester of **4** (prepared according to ref. 10) showed > 99% ee; HPLC of the diastereomeric Mosher ester (C18 Carbosphere, CH_3CN-2-PrOH 9:1) indicated > 99% purity. Conversion of **4** into **5** was carried out using mild benzylation conditions[11] with preformed benzyl triflate to avoid base-induced epoxide formation of **4**, affording **5** in 96% yield; $[\alpha]_D^{25}$ -7.32 (c 5.0, $CHCl_3$). Attempted detosylation of **5** with potassium superoxide in the presence of 18-crown-6 [12] gave a complex mixture; however, the reaction sequence of displacement of tosylate **5** with cesium acetate [13] followed by lithium aluminum hydride reduction without isolation of the intermediate acetate afforded alcohol **6** in 92% overall yield; mp 29-31°C; lit. mp 28-30°C; [7] $[\alpha]_D^{25}$ -9.27 (c 5.0, C_6H_6); lit. $[\alpha]_D^{25}$ -8.76 (c 5.0, C_6H_6).[7] Phosphorylation of **6** was achieved using phosphorus oxychloride at -10°C in alcohol-free chloroform in the presence of triethylamine; addition of dry choline tosylate in pyridine at r.t., then water, [14] yielded phosphocholine **7** in 75% overall yield; $[\alpha]_D^{25}$ +3.92 (c 5.0, $CHCl_3$-CH_3OH 1:1); lit. $[\alpha]_D^{25}$ +3.54 (c 5.0, $CHCl_3$-CH_3OH 1:1). [7] Debenzylation of **7** with Pearlman's catalyst for 24 h gave 2-lysophosphocholine (100%), which was filtered, dried, and acetylated to give PAF **1** in 100% yield; mp 247°C (dec); lit. mp 247°C (dec);[6] $[\alpha]_D^{25}$ -3.39 (c 0.53, $CHCl_3$-CH_3OH 1:1); lit. $[\alpha]_D^{25}$ -3.30 (c 0.53, $CHCl_3$-CH_3OH 1:1).[6] Similarly, the same methodology (Scheme 1) was used to convert tosylate **4'** into the enantiomer of PAF (**2**); mp 247°C (dec); lit. mp 247°C (dec); [6] $[\alpha]_D^{25}$ +3.20 (c 0.53, $CHCl_3$-CH_3OH 1:1); lit. $[\alpha]_D^{25}$ +3.18 (c 0.53, $CHCl_3$-CH_3OH 1:1).[6]

Hirth and Barner used 1-*O*-hexadecyl-2,3-epoxypropane (**8**), which was prepared from D-mannitol, as the precursor for the preparation of PAF **1**. [7] We prepared epoxide **8** in quantitative yield from tosylate **4** using potassium carbonate in methanol; mp 42-43°C; lit. 41-42°C; [7] $[\alpha]_D^{25}$ +9.74 (c 5.0, C_6H_6); lit. $[\alpha]_D^{25}$ +9.00 (c 5.0, C_6H_6).[7]

In conclusion, this methodology offers a route for the asymmetric synthesis of other glycerophospholipids from derivatives of glycidol. Our studies of the conversion of other glycidol derivatives, such as its silyl ether, to different PAF analogs and other ether-linked lipids are currently in progress in our laboratory.

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