and the residue stirred with 100 mL of pentane to give a green-yellow powder. The product was extracted from the powder with three 50-mL portions of CH_2Cl_2 and the extract filtered through Celite to remove metallic palladium. The green-yellow filtrate was flash chromatographed on an alumina column prepared with pentane. The first, orange, fraction eluted with CH_2Cl_2 contained the product. After removal of the solvent and drying in vacuo the yield of **6** was 0.250 g (96%). Crystals were grown from a CH_2Cl_2/hexane mixture, yellow prisms, mp 151 °C: ^1H NMR δ 8.79 (dd, 1 H, H^o, $^4J_{HH}$ = 1.8, $^3J_{HH}$ = 4.2), 8.08 (dd, 1 H, H^p, $^3J_{HH}$ = 8.3), 7.34 (dd, 1 H, H^m), 7.74-7.17 (m, 13 H, H^{ar}), 4.44 (s, 2 H, CH_2), 3.88 (q, 2 H, CH_2CH_3), 0.79 (t, 3 H, CH_3, $^3J_{HH}$ = 7.1); ^{13}C NMR δ 165.9, 161.8, 157.46, 152.6, 148.9, 156.2, 137.6, 136.3, 135.2, 130.8, 128.5, 128.2, 128.1, 127.9, 127.6, 127.4, 126.3, 123.9, 120.8, 61.6, 29.3, 13.3; IR (cm^{-1}) 1735 (vs) and 1715 (vs). Anal. Calcd for $C_{30}H_{23}NO_4$: C, 78.09; H, 4.99; N, 3.04. Found: C, 78.2; H, 4.9; N, 3.0.

Synthesis of the Fulvenone 7. The crude product was obtained as described for compound **3d**. Crystals were grown by layering hexane on a CH_2Cl_2 solution. The yellow crystals which formed rapidly were separated from the solution and washed with cold hexane: yield 0.065 g (12%); ^1H NMR δ 8.98 (dd, 1 H, H^o), 8.80 (d, 1 H, H^{olef}, $^4J_{HH}$ = 1.4), 8.21-7.44 (m, 5 H, Ar), 4.94 (q, 1 H, H^5), 4.32 (dq (ABX_3), 2 H, CH_2), 3.26 (s, 3 H, OCH_3), 2.30 (d, 3 H, CH_3, $^4J_{HH}$ = 2.0), 1.34 (t, 3 H, CH_2CH_3, $^2J_{HH}$ = 7.1); IR (cm^{-1}) 1747 (vs), 1716 (vs), and 1695 (vs); m/z 365 (M^+), 306 (M - CO_2Me), 292 (M - CO_2Et). Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.5; H, 5.3; N, 3.9.

Acknowledgment. A. Dégremont is gratefully thanked for technical assistance. Financial support of this work by the Commission of European Communities (contract St 2J 0090-1-F(CD)) is acknowledged.

Registry No. 1, 28377-73-3; **2a**, 126205-17-2; **2b**, 71340-03-9; **3a**, 126309-70-4; **3b**, 139243-66-6; **3c**, 126309-72-6; **3d**, 139243-67-7; **3e**, 139243-68-8; **3f,3g**, 126309-73-7; **3g,3f**, 139243-69-9; **3h,3i**, 139243-70-2; **3i,3h**, 126346-80-3; **3l**, 126309-74-8; **3m**, 126309-75-9; **3n**, 139243-71-3; **3o**, 139243-72-4; **3p**, 139243-73-5; **3q**, 139243-74-6; **5b**, 126606-12-0; **5b***, 139243-77-9; **5c**, 139275-99-3; **5d**, 126205-18-3; **6**, 136745-53-4; **7**, 139243-75-7; V, 126460-88-6; DMAD, 762-42-5; HFB, 692-50-2; PhC≡CPh, 501-65-5; PhC≡CCO_2Et, 2216-94-6; MeC≡CCO_2Et, 4341-76-8; PhC≡CCO_2Me, 4891-38-7; PhC≡C-*p*-$C_6H_4NO_2$, 1942-30-9; PhC≡C-*m*-$C_6H_4CF_3$, 126309-76-0; PhC≡C-*p*-$C_6H_4CH_3$, 3287-02-3; PhC≡C-*p*-$C_6H_4OCH_3$, 7380-78-1.

Supplementary Material Available: Figures 1 and 2 showing the X-ray crystal structures of the compounds **3a** and **3c**, respectively, X-ray data, and tables of bond lengths, bond angles, positional parameters, and general temperature factors for **3a** and **3c** (19 pages). Ordering information is given on any current masthead page. This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Notes

Chemoenzymatic Approach to Carbohydrate-Derived Analogoues of Platelet-Activating Factor

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Platelet-activating factor (PAF) (Figure 1), a class of phospholipids with a 1-*O*-alkyl-2-*O*-acetylglycero-3-phosphocholine structure, are highly potent mediators of many biological and physiological activities, among which the ability to aggregate platelets and to lower blood pressure.[1]

In two articles, P. Braquet and J. J. Godfroid[2] reported a study on PAF binding sites and on PAF isosteres which led, after QSAR analysis, to interesting conclusions about the nature and the conformation of the binding site. According to the above authors, many potent antagonists of PAF incorporate a tetrahydrofuran ring in which the oxygen atom is ideally placed for interaction with the binding site; moreover, the antagonistic behavior is often associated to the rigidity imposed by the cycle to the backbone. Finally, the lipidic and the polar arms are placed at the opposite end of the molecules.

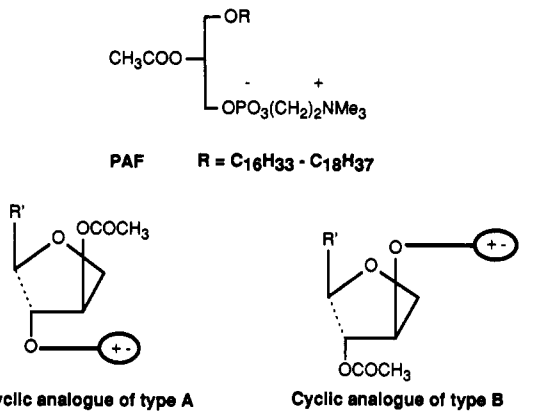

Figure 1.

Following the above conclusions, we planned to synthesize and test carbohydrate-derived analogues of PAF of type A and B in which the above requisites are obeyed.

In this paper we describe the stereospecific synthesis of the cyclic analogues of PAF, **10-17**.

Our synthetic scheme starts from the commercially available 2,3,5-tetra-*O*-benzyl-D-arabinose (**1**), which possesses the appropriate skeleton for the synthesis of derivatives of type A and B, provided that (1) the anomeric center is reduced, (2) the hydroxyl group at C-5 is substituted with a long-chain alkyl group, and (3) the hydroxyl groups at C-2 and/or at C-3 are selectively acetylated and consequently the other hydroxyl group is properly func-

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(2) (a) Goodfroid, J. J.; Braquet, P. *TIPS* **1986**, *September*, 368. (b) Braquet, P.; Goodfroid, J. J. *TIPS* **1986**, *October*, 397.

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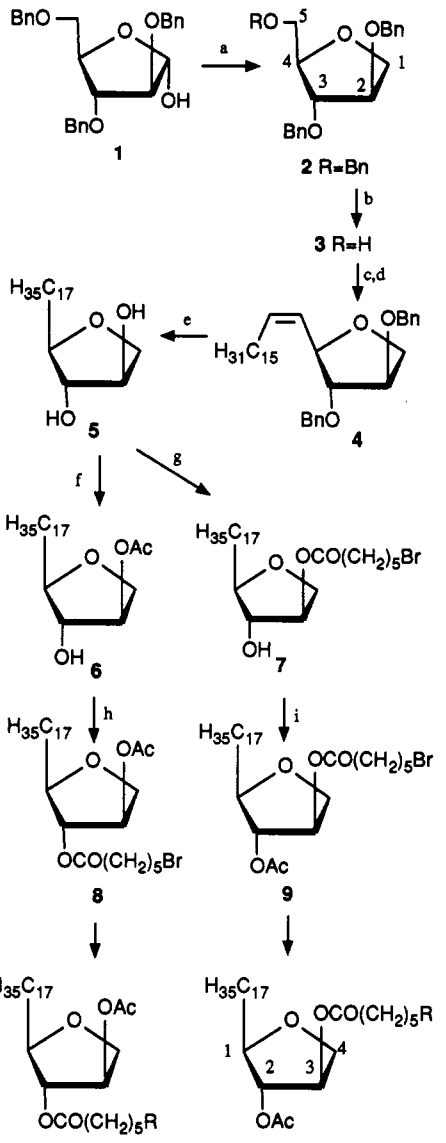
Scheme I[a]



[a] (a) Et_3SiH, BF_3OEt_2, MeCN; (b) CF_3CO_2H, Ac_2O, 0 °C, then NaOH, MeOH; (c) PCC, 3 Å ms, CH_2Cl_2; (d) $Ph_3P{=}CHCO_2Et$, THF, 0 °C; (e) H_2, Pd/C, MeOH; (f) vinyl acetate, PPL, C_6H_6, 40 °C; (g) $Br(CH_2)_5CO_2CH_2CF_3$, PPL, C_6H_6, 40 °C; (h) $Br(CH_2)_5CO$-Cl, Py-CH_2Cl_2; (i) Ac_2O, Py-CH_2Cl_2.

tionalized to introduce the polar arm.

Results and Discussion

Following the proposed scheme, the reduction of the anomeric position of 2,3,5-tri-*O*-benzyl-D-arabinose (**1**) was effected with Et_3SiH in presence of a Lewis acid[3] to afford the 1,4-anhydro-2,3,5-tri-*O*-benzyl-D-arabinitol (**2**). The substitution of the hydroxyl group at C-5 of **2** with a long-chain alkyl group was effected through its selective deprotection by acetolysis[4] and subsequent saponification and oxidation of the obtained 1,4-anhydro-2,3-di-*O*-benzyl-D-arabinitol (**3**) with PCC[5] and reaction of the so

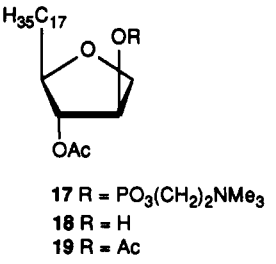


Figure 2.

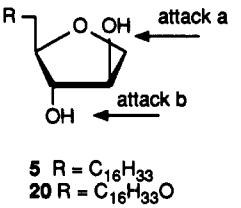


Figure 3.

Table I. Acylation of the Diols 5 and 20 with Lipases from Different Sources: Yields[a] (in Parentheses) and Isomeric Ratios[a] Derived from Attack a and b (Figure 3)

lipase from	attack a/b on **5**	attack a/b on **20**
Humicula lanuginosa	100:0 (94)	96:4 (71)
Pseudomonas fluorescens	97:3 (95)	85:15 (70)
Porcine pancreas	100:0 (95)	91:9 (62)
Chromobacterium viscosum	98:2 (97)	74:26 (54)
Mucor meheii	100:0 (88)	96:4 (73)
Penicillum ciclopium	74:26 (97)	44:56 (91)
Candida cilindracea	97:3 (97)	16:84 (91)

[a] Gas chromatographically determined: Supelco SPB-1, 30 m × 0.75 mm, 1.0-μm capillary column, T = 280 °C.

obtained crude aldehyde with hexadecylidenetriphenylphosphorane. In this way the alkene **4** was obtained in 28% overall yield from **1**. Hydrogenation of **4** with Pd/C gave the diol **5** in quantitative yield.

The selective monoacetylation of the diol **5**, which is a crucial step in the synthetic scheme, was first attempted with 1 equiv of acetic anhydride but, also at 0 °C, a mixture of the monoacetylated products **6** and **18** and of the diacetate **19** was obtained, which could be separated only by careful chromatography.

We observed[6] that, employing lipases from different sources, it was possible to acylate complementarily the two hydroxyl groups of 1,4-anhydro-5-*O*-hexadecyl-D-arabinitol (**20**). In particular *Candida cilindracea* lipase was able to catalyze the esterification of the hydroxy group at C-3 (attack b) whereas all the other lipases tested acylated the hydroxyl group at C-2 (attack a) (see Figure 3). **5** differs from **20** only in the absence of an oxygen in the alkyl arm; the enzymatic procedure appeared then promising.

We tested the enzymatic acylation of **5** with different lipases (Table I): all showed good yields and regioselectivity; however the acylation occurred constantly at the hydroxyl group at C-3 (attack a). The best results were obtained with *Porcine pancreatic* lipase which afforded only one monoacylated product in 95% yield.

The regiochemistry of the acylation was deduced from the ^1H NMR spectra of the products, which showed a shift to lower field of the signal of the H-3 which bears the acetoxy group (see the Experimental Section), and the ratio of the isomers was determined gas chromatographically.

(3) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
(4) Eby, R.; Sondheimer, S. J.; Schuerch, C. *Carbohydr. Res.* **1979**, *73*, 273.
(5) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.
(6) Nicotra, F.; Riva, S.; Secundo, F.; Zucchelli, L. *Tetrahedron Lett.* **1989**, *30*, 1703.

Table II. Inhibition of Platelet Aggregation in Rabbit Platelet Rich Plasma in the Presence of PAF and ADP for Compounds 10–17 at 10^{-5} M Concentration[8]

compd	type	% of inhibition PAF	% of inhibition ADP
10	A	29	28
11	B	22	72
12	A	70	11
13	B	34	18
14	A	42	27
15	B	48	31
16	B	78	33
17	B	33	21

Treatment of the diol **5** in benzene at 40 °C with vinyl acetate and *Porcine pancreas* lipase afforded regioselectively the monoacetate **6**, which opened the route to the analogues of type A. To obtain the analogues of type B, we decided to introduce enzymatically on **5** an arm ending with an ammonium group. As the direct enzymatic acylation with an ω-ammonium- or an ω-ammino-activated ester was impracticable,[7] we effected the enzymatic regioselective acylation with 2,2,2-trifluoroethyl 6-bromohexanoate,[7] and then we converted the bromide into the desired ammonium salt. So the diol **5** was enzymatically converted into **7**, which was in turn chemically acetylated to afford **9**. Vice versa, **6**, the product of enzymatic acetylation of the diol **5**, was chemically 6-bromohexanoylated to afford **8**.

The bromides **8** and **9** were converted into the analogues of PAF **10–16** by treatment with the proper amine and, in the case of the analogues of PAF **12** and **13**, also with methyl iodide. The analogue of PAF **17** was obtained by treatment of **18** with $POCl_3$ and then with choline *p*-toluenesulfonate.

The analogues of PAF **10–17** all exhibited inhibition of platelet aggregation (see Table II).[8] However, they do not show increment of activity with respect to the open-chain analogues.[1] No clear differences in the activity of A or B type cyclic analogues could be observed. The inhibition was not specific vs PAF, except for products **13** (type B) and **12** (type A), which, on the other hand, are both cytotoxic.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$; the signals of the side-chain unfunctionalized CH_2 and of the aromatic carbons in the ^{13}C NMR spectra are not reported. $[\alpha]_D$ were measured at 20 °C. Column chromatography was performed utilizing two methods: gravity chromatography, using Merck silica gel 60 (70–230 mesh), and flash chromatography,[9] using Merck silica gel 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed on Merck silica gel-60 F-254 plates, eluted with hexane–ethyl acetate (unless otherwise stated) in the ratio reported in parentheses and visualized with 50% sulfuric acid spry followed by heating at 110 °C for 5 min. All air-sensitive reactions were run under nitrogen in glassware oven-dried overnight at 120 °C and assembled hot. Reagents and dry solvents were added via oven-dried syringes through septa. Usual workup refers to dilution with an organic solvent (CH_2Cl_2), washing with water to neutrality, drying with Na_2SO_4, and evaporating under reduced pressure.

1,4-Anhydro-2,3,5-tri-*O*-benzyl-D-arabinitol (2). To a stirred solution of commercially available (Sigma) **1** (16.8 g, 40 mmol) in dry CH_3CN (200 mL), under N_2, were added triethylsilane (25 mL, 160 mmol) and then freshly distilled $BF_3{\cdot}OEt_2$ (10 mL, 80 mmol). The reaction was monitored by TLC (7:3). After 45 min, addition of water to the reaction mixture and usual workup afforded **2** (15.7 g, 97% yield): oil; $[\alpha]_D$ 0° (*c* 1, $CHCl_3$); ^1H NMR δ 3.58 (1 H, dd, *J* = 6 and 10 Hz, H-5a), 3.65 (1 H, dd, *J* = 6 and 10 Hz, H-5b), 3.94 (1 H, dd, *J* = 4.5 and 10 Hz, H-1a), 3.95–4.11 (3 H, m), 4.40–4.64 (6 H, m, OCH_2Ph), 7.3 (15 H, m, ArH); ^{13}C NMR ppm 70.97 (t), 71.83 (t), 72.16 (t), 72.35 (t), 83.34 (d), 83.85 (d), 85.17 (d). Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.35; H, 7.02.

1,4-Anhydro-2,3-di-*O*-benzyl-D-arabinitol (3). To a stirred solution of **2** (10 g, 25 mmol) in Ac_2O (100 mL) was added CF_3COOH (25 mL) at 0 °C. The reaction was monitored by TLC (7:3) and quenched by pouring into ice water (1 L). Usual workup afforded the crude 5-*O*-acetyl-1,4-anhydro-2,3-di-*O*-benzyl-D-arabinitol which was directly submitted to saponification in MeOH (50 mL) with 1 N MeONa (10 mL). The saponification was monitored by TLC (7:3). After 30 min, usual workup and gravity chromatography (1:1) afforded 1,4-anhydro-2,3-di-*O*-benzyl-D-arabinitol (**3**) (5.7 g, 73% yield): oil; $[\alpha]_D$ +24° (*c* 1, $CHCl_3$); ^1H NMR δ 3.68 (1 H, dd, *J* = 12 and 4 Hz, H-5a), 3.79 (1 H, dd, *J* = 12 and 3 Hz, H-5b), 3.92 (1 H, dd, *J* = 10.5 and 4 Hz, H-1a), 3.95–4.09 (4 H, m, H-1b, H-2, H-3, and H-4), 4.51 (2 H, s, OCH_2Ph), 4.55 (2 H, s, OCH_2Ph), 7.3 (10 H, ArH); ^{13}C NMR ppm 62.98 (t), 71.36 (t), 71.67 (t), 72.13 (t), 83.10 (d), 84.00 (d), 84.68 (d). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.31; H, 6.91.

(*Z*,1*R*,2*S*,3*R*)-2,3-Bis(benzyloxy)-1-(heptadec-1-enyl)-oxolane (4). To a solution of **3** (2.2 g, 7 mmol) in dry CH_2Cl_2 (20 mL), under N_2, were added 3 Å molecular sieves (1 g) and PCC (2.2 g, 10 mmol) with stirring. After 2.5 h TLC (1:1) showed the disappearance of the starting material. The reaction mixture was filtered on a short column of silica gel (100 g), eluted with 400 mL of a 1:1 mixture of hexane–ethyl acetate. Evaporation afforded the crude aldehyde (2.1 g), which was dissolved in dry THF (25 mL) and added dropwise, under N_2, to a stirred solution of $Ph_3P{=}CH(CH_2)_{14}CH_3$, obtained by treatment of the hexadecylphosphonium bromide (4.6 g, 8 mmol) in dry THF (50 mL), at 0 °C, with 5 mL of a 1.6 M solution of *n*-butyllithium (8 mmol). After 10 min aqueous NH_4Cl was added to the reaction mixture. Usual workup and gravity chromatography (8:2) afforded **4** (1.45 g, 40% yield): oil; $[\alpha]_D$ −38° (*c* 1, $CHCl_3$); ^1H NMR δ 0.90 (3 H, t, *J* = 7 Hz, CH_3), 1.25 (26 H, m), 2.18 (2 H, m, H-3'a and b), 3.86 (1 H, dd, *J* = 2 and 4.5 Hz, H-2), 3.93 (1 H, dd, *J* = 4.5 and 10 Hz, H-4a), 4.02 (1 H, dd, *J* = 2 and 10 Hz, H-4b), 4.09 (1 H, dt, *J* = 2.2 and 4.5 Hz, H-3), 4.43–4.60 (5 H, m, H-1 and OCH_2Ph), 5.50–5.61 (2 H, m, H-1' and H-2'), 7.3 (10 H, m, ArH). Anal. Calcd for $C_{35}H_{52}O_3$: C, 80.72; H, 10.07. Found: C, 80.54; H, 10.27.

(1*R*,2*S*,3*R*)-2,3-Dihydroxy-1-heptadecyloxolane (5). Catalytic hydrogenation of **4** (6.5 g, 12 mmol) in MeOH (40 mL) with 5% Pd/C (0.6 g), for 72 h, quantitatively afforded **5** (4.3 g): mp 83–85 °C (from Et_2O); $[\alpha]^{40}_D$ +11° (*c* 1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, *J* = 7.5 Hz, CH_3), 1.23–1.35 (30 H, m), 1.63 (2 H, m), 3.60 (1 H, dt, *J* = 6.5, 6.5, and 4.5 Hz, H-1), 3.78 (1 H, d, *J* = 10.5 and 2.5 Hz, H-4a), 3.82 (1 H, dd, *J* = 5 and 2.5 Hz, H-2), 3.95 (1 H, dd, *J* = 10.5 and 4.5 Hz, H-4b), 4.14 (1 H, dt, *J* = 4.5, 2.5, and 2.5 Hz, H-3). Anal. Calcd for $C_{21}H_{42}O_3$: C, 73.63; H, 12.36. Found: C, 73.71; H, 12.28.

Chemical Acetylation of 5. To **5** (800 mg, 2.3 mmol) in dry pyridine (10 mL) was added 1 equiv of Ac_2O (220 μL). The reaction was monitored by TLC (8:2). After 2 h, dilution with water and usual workup afforded an approximately equimolecular mixture of **6**, **18**, **19**, and unreacted **5**, from which **6** and **18** can be only partially separated from each other by careful chromatography (9:1).

18: mp 50–51 °C (from Et_2O); ^1H NMR (80 MHz) δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.22–1.40 (30 H, m), 1.65 (2 H, m), 2.07 (3 H, s, CH_3CO), 2.70 (1 H, OH), 3.60–3.90 (2 H, m, H-1 and H-4a), 3.98 (1 H, d, *J* = 10.5 Hz, H-4b), 4.20 (1 H, m, H-3), 4.54 (1 H, dd, *J* = 2 and 5 Hz, H-2). Anal. Calcd for $C_{23}H_{44}O_4$: C, 71.83; H, 11.53. Found: C, 71.59; H, 11.41.

6: mp 64–65 °C (from Et_2O); ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.20–1.40 (30 H, m), 1.64 (2 H, m), 2.05 (3 H, s, CH_3CO), 2.77 (1 H, OH), 3.60 (1 H, dt, *J* = 6.5, 6.5 and 5.5 Hz, H-1), 3.77 (1 H, dd, *J* = 6.5 and 3 Hz, H-2), 3.92 (1 H, dd, *J* = 11 and 3 Hz, H-4a), 4.02 (1 H, dd, *J* = 11 and 5.5 Hz, H-4b), 4.87 (1 H, dt, *J* = 5.5, 3 and 3 Hz, H-3). Anal. Calcd for $C_{23}H_{44}O_4$: C, 71.83; H, 11.53. Found: C, 71.70; H, 11.38.

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(9) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

19: oil; $[\alpha]_D$ +5° (*c* 1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.23–1.44 (30 H, m), 1.65 (2 H, m), 2.08 (6 H, s, CH_3CO), 3.74 (1 H, m, H-1), 3.90 (1 H, dd, *J* = 11 and 2 Hz, H-4a), 4.00 (1 H, dd, *J* = 11 and 4.5 Hz, H-4b), 4.92 (1 H, dd, *J* = 4 and 1 Hz, H-2), 5.09 (1 H, dt, *J* = 4, 1.5, and 1.5 Hz, H-3). Anal. Calcd for $C_{25}H_{46}O_5$: C, 70.38; H, 10.87. Found: C, 70.20; H, 11.01.

Enzymatic Acylation of 5: General Procedure. A solution of **5** (10 mg) in dry C_6H_6 (1 mL) was stirred for 24 h at 40 °C, with the enzyme (100 mg, commercially available) and 2,2,2-trifluoroethyl butanoate (24 μL, 5 equiv). The yield and the ratio of regioisomers (reported in the table) were gas chromatographically determined [Supelco SPB-1, 30 m × 0.75 mm, 1.0-μm capillary column, *T* = 280 °C; retention time: **5**, 7.2 min; 2-$OCOC_3H_7$, 11.4 min; 3-$OCOC_3H_7$, 12.1 min]. In the preparative experiments vinyl acetate or 2,2,2-trifluoroethyl 6-bromohexanoate was employed instead of 2,2,2-trifluoroethyl butanoate, the reaction was gas chromatographically monitored, and the products were recovered by filtration and gravity chromatography (8:2).

(1*R*,2*S*,3*R*)-3-Acetoxy-2-hydroxy-1-heptadecyloxolane (6). Treatment of **5** (300 mg, 0.88 mmol) with vinyl acetate in the presence of *Porcine pancreatic* lipase according to the general procedure afforded **6** (140 mg, 0.37 mmol) and unreacted **5** (155 mg, 0.45 mmol), which was recycled.

(1*R*,2*S*,3*R*)-3-[(6-Bromohexanoyl)oxy]-2-hydroxy-1-heptadecyloxolane (7). Treatment of **5** (500 mg, 1.5 mmol) with 2,2,2-trifluoroethyl 6-bromohexanoate in the presence of *Porcine pancreas* lipase according to the general procedure afforded **7** (580 mg, 76% yield): oil; ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.25–1.74 (36 H, m), 1.87 (2 H, m), 2.37 (2 H, t, *J* = 7 Hz, CH_2CO), 2.88 (1 H, broad s, OH), 3.40 (2 H, t, *J* = 7 Hz, CH_2Br), 3.60 (1 H, dt, *J* = 6, 6, and 5 Hz, H-1), 3.78 (1 H, broad dd, *J* = 6 and 2 Hz, H-2), 3.92 (1 H, dd, *J* = 11 and 2.5 Hz, H-4a), 4.03 (1 H, dd, *J* = 11 and 5.5 Hz, H-4b), 4.87 (1 H, dt, *J* = 5.5, 2.5, and 2.5 Hz, H-3). Anal. Calcd for $C_{27}H_{51}BrO_4$: C, 62.41; H, 9.89. Found: C, 62.53; H, 10.04.

(1*R*,2*S*,3*R*)-2-Acetoxy-3-[(6-bromohexanoyl)oxy]-1-heptadecyloxolane (9). **7** (500 mg, 0.96 mmol) in dry CH_2Cl_2 (10 mL) was treated with Ac_2O (0.4 mL, 4 mmol) and pyridine (0.4 mL, 5 mmol). The reaction was monitored by TLC (4:1). After 48 h, dilution with water, usual workup, and flash chromatography (4:1) afforded **9** (432 mg, 80% yield): oil; $[\alpha]_D$ −9° (*c* 1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.22–1.74 (36 H, m), 1.86 (2 H, m), 2.07 (3 H, s, CH_3CO), 2.35 (2 H, t, *J* = 7 Hz, CH_2CO), 3.39 (2 H, t, *J* = 7 Hz, CH_2Br), 3.74 (1 H, m, H-1), 3.87 (1 H, dd, *J* = 11 and 1.5 Hz, H-4a), 4.00 (1 H, dd, *J* = 11 and 4.5 Hz, H-4b), 4.89 (1 H, dd, *J* = 4.5, and 1.5 Hz, H-2), 5.08 (1 H, m, H-3). Anal. Calcd for $C_{29}H_{53}BrO_5$: C, 62.01; H, 9.51. Found: C, 62.33; H, 9.78.

(1*R*,2*S*,3*R*)-3-Acetoxy-2-[(6-bromohexanoyl)oxy]-1-heptadecyloxolane (8). To a solution of **6** (192 mg, 0.5 mmol) in dry CH_2Cl_2 (15 mL), under N_2, were added 6-bromohexanoyl chloride (160 μL) and pyridine (90 μL), and the reaction was monitored by TLC (4:1). After 18 h, dilution with water, usual workup, and flash chromatography (4:1) afforded **8** (228 mg, 80% yield): oil; $[\alpha]_D$ −10° (*c* 1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.22–1.95 (38 H, m), 2.05 (3 H, s, CH_3CO), 2.35 (2 H, t, *J* = 7 Hz, CH_2CO), 3.40 (2 H, t, *J* = 7 Hz, CH_2Br), 3.72 (1 H, m, H-1), 3.95 (2 H, m, H-4a and H-4b), 4.89 (1 H, dd, *J* = 4.5 and 1.5 Hz, H-2), 5.08 (1 H, ddd, *J* = 4.2 and 1.5 Hz, H-3). Anal. Calcd for $C_{29}H_{53}BrO_5$: C, 62.01; H, 9.51. Found: C, 61.87; H, 9.80.

PAF Analogue 17. To a solution of **18** (115 mg, 0.30 mmol) in dry, ethanol-free $CHCl_3$ (3 mL) were added quinoline (110 μL, 0.90 mmol) and $POCl_3$ (80 μL, 0.9 mmol) under N_2. The mixture was stirred at 50 °C for 45 min; then, at room temperature, choline *p*-toluenesulfonate (440 mg, 1.6 mmol) and pyridine (1.5 mL) were added. After 18 h, dilution with 1 mL of water, stirring for 1 h, and then usual workup afforded the crude product (175 mg), which was dissolved in 1 mL of $CHCl_3$ and crystallized by adding 10 mL of Et_2O to afford pure **17** (150 mg, 83%): $[\alpha]_D$ −6° (*c* 1, $CHCl_3$); ^{13}C NMR ppm 14.03 (CH_3), 54.18 (CH_3N^+), 66.17 (d, $J_{C,P}$ = 4 Hz, CH_2N^+), 66.28 (d, $J_{C,P}$ = 4.4 Hz, CH_2OP), 72.67 (C-4), 79.42 (d, $J_{C,P}$ = 4.4 Hz, C-2), 82.89 (d, $J_{C,P}$ = 7.1 Hz, C-3), 83.26 (C-1), 170.22 (C=O); ^{31}P NMR ppm −1.18. Anal. Calcd for $C_{28}H_{56}NO_7P{\cdot}2H_2O$: C, 57.41; H, 10.32; N, 2.39. Found: C, 57.45; H, 9.96; N, 2.20.

PAF Analogue 16. To a solution of **9** (300 mg, 0.53 mmol) in dry benzene (20 mL) was bubbled Me_3N for 3 h, and the mixture was then stirred overnight. Evaporation and recrystallization from EtOH afforded **16** (210 mg, 64% yield): $[\alpha]_D$ −6° (*c* 1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.20–1.80 (38 H, m), 2.07 (3 H, s, CH_3CO), 2.33 (2 H, broad t, *J* = 7 Hz, CH_2CO), 3.40 (9 H, s, CH_3N^+), 3.56 (2 H, broad t, *J* = 7 Hz, CH_2N^+), 3.71 (1 H, q, *J* = 6 Hz, H-1), 3.84 (1 H, broad d, *J* = 11 Hz, H-4a), 3.97 (1 H, dd, *J* = 11 and 1.5 Hz, H-4b), 4.82 (1 H, broad d, *J* = 6 Hz, H-2), 5.04 (1 H, m, H-3). Anal. Calcd for $C_{32}H_{62}BrNO_5$: C, 61.91; H, 10.07; N, 2.26. Found: C, 61.56; H, 10.17; N, 2.41.

PAF Analogue 11. **9** (280 mg, 0.5 mmol) was treated with morpholine (2.5 mL), and the reaction was monitored by TLC ($CHCl_3$–EtOH, 95:5). After 48 h, the excess of morpholine was evaporated. The residue was dissolved in CH_2Cl_2 (25 mL), washed with 5% HCl and then with aqueous $NaHCO_3$ and finally with water to neutrality. Evaporation and gravity chromatography ($CHCl_3$–EtOH, 95:5) afforded **11** (220 mg, 78% yield): oil; $[\alpha]_D$ −5° (*c* 1, $CHCl_3$); ^1H NMR δ 0.88 (3 H, t, *J* = 7 Hz, CH_3), 1.20–1.80 (38 H, m), 2.10 (3 H, s, CH_3CO), 2.37 (2 H, t, *J* = 7 Hz, CH_2CO), 2.30–2.52 (6 H, m, CH_2N), 3.74 (5 H, m, H-1 and 2-CH_2O), 3.91 (1 H, broad d, *J* = 10.5 Hz, H-4a), 4.03 (1 H, dd, *J* = 10.5 and 4 Hz, H-4b), 4.90 (1 H, dd, *J* = 4 and 1 Hz, H-2), 5.08 (1 H, m, H-3).

PAF Analogue 13. **11** (220 mg, 0.39 mmol) was treated with MeI (1 mL), and the reaction was monitored by TLC ($CHCl_3$–EtOH, 8:2). After 2 h, evaporation of MeI afforded **13** (270 mg, 97% yield): mp 50–51 °C (from Et_2O); $[\alpha]_D$ −1° (*c* 1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.20–1.90 (38 H, m), 2.08 (3 H, s, CH_3CO), 2.37 (3 H, t, *J* = 7 Hz, CH_2CO), 3.52 (3 H, s, CH_3N^+), 3.50–4.10 (13 H, m), 4.84 (1 H, broad d, *J* = 4.5 Hz, H-2), 5.08 (1 H, m, H-3). Anal. Calcd for $C_{34}H_{64}INO_6$: C, 57.53; H, 9.09; N, 1.96. Found: C, 57.30; H, 8.66; N, 1.69.

PAF Analogue 10. **8** (600 mg, 1.07 mmol) treated with morpholine as described in the preparation of **11** afforded **10** (380 mg, 62% yield): oil; $[\alpha]_D$ −6° (*c* 1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.20–1.80 (38 H, m), 2.05 (3 H, s, CH_3CO), 2.30–2.52 (8 H, m, CH_2CO and CH_2N), 3.68 (5 H, m, H-1 and 2-CH_2O), 3.86 (1 H, broad d, *J* = 10.5 Hz, H-4a), 4.00 (1 H, dd, *J* = 10.5 and 4 Hz, H-4b), 4.90 (1 H, dd, *J* = 4 and 1 Hz, H-2), 5.07 (1 H, m, H-3).

PAF Analogue 12. **10** (200 mg, 0.35 mmol) treated with MeI as described in the preparation of **13** afforded **12** (250 mg, 97%): mp 48–49 °C (from Et_2O); $[\alpha]_D$ +1° (*c* 1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, *J* = 7 Hz, CH_3), 1.20–1.90 (38 H, m), 2.04 (3 H, s, CH_3CO), 2.37 (3 H, t, *J* = 7 Hz, CH_2CO), 3.52 (3 H, s, CH_3N^+), 3.50–4.15 (13 H, m), 4.84 (1 H, dd, *J* = 4 and 1 Hz, H-2), 5.07 (1 H, m, H-3). Anal. Calcd for $C_{34}H_{64}INO_6$: C, 57.53; H, 9.09; N, 1.96. Found: C, 57.41; H, 8.84; N, 1.73.

PAF Analogue 14. To a solution of **8** (422 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) was added dry pyridine (0.6 mL), and the mixture was refluxed under N_2 for 36 h. The reaction was monitored by TLC ($CHCl_3$–MeOH, 3:1). Evaporation of the solvent (below 40 °C) and gravity chromatography ($CHCl_3$–MeOH, 3:1) afforded 243 mg of starting material and **14** (138 mg, 28% yield): oil; $[\alpha]_D$ +2° (*c* 1, $CHCl_3$); ^1H NMR δ 0.80 (3 H, t, *J* = 7 Hz, CH_3), 1.20–1.70 (38 H, m), 2.00 (3 H, s, CH_3CO), 2.27 (3 H, t, *J* = 7 Hz, CH_2CO), 3.60 (1 H, m, H-1), 3.80 (1 H, broad d, *J* = 11 Hz, H-4a), 3.88 (1 H, dd, *J* = 11 and 4.5 Hz, H-4b), 4.76 (1 H, broad d, *J* = 4 Hz, H-2), 4.87 (2 H, t, *J* = 7 Hz, CH_2N^+), 4.96 (1 H, m, H-3), 8.07 (2 H, t, *J* = 5 Hz, Py-H), 8.48 (1 H, t, *J* = 5 Hz, Py-H), 9.35 (2 H, d, *J* = 5 Hz, Py-H); ^{13}C NMR ppm 14.65 (CH_3), 21.56 (CH_3CO), 62.10 (C-4), 71.93 (CH_2N^+), 79.04, 81.74 and 84.36 (C-1, C-2 and C-3), 170.78 and 172.86 (C=O). Anal. Calcd for $C_{35}H_{58}BrNO_5$: C, 64.40; H, 8.96; N, 2.15. Found: C, 64.73; H, 9.14; N, 2.08.

PAF Analogue 15. **9** (424 mg, 0.75 mmol) treated with pyridine as described in the preparation of **14** afforded **15** (201 mg, 41% yield): oil; $[\alpha]_D$ +6° (*c* 1, $CHCl_3$); ^1H NMR δ 0.83 (3 H, t, *J* = 7 Hz, CH_3), 1.20–1.70 (38 H, m), 2.03 (3 H, s, CH_3CO), 2.30 (3 H, t, *J* = 7 Hz, CH_2CO), 3.67 (1 H, broad d, *J* = 5 Hz, H-1), 3.79 (1 H, broad d, *J* = 11 Hz, H-4a), 3.93 (1 H, dd, *J* = 11 and 4.5 Hz, H-4b), 4.79 (1 H, broad d, *J* = 4 Hz, H-2), 4.94 (2 H, t, *J* = 7 Hz, CH_2N^+), 5.03 (1 H, m, H-3), 8.02 (2 H, t, *J* = 5 Hz, Py-H), 8.50 (1 H, t, *J* = 5 Hz, Py-H), 9.42 (2 H, d, *J* = 5 Hz, Py-H).

^{13}C NMR ppm 14.55 (CH_3), 21.45 (CH_3CO), 61.92 (C-4), 71.80 (CH_2N^+), 78.94, 81.72, and 83.90 (C-1, C-2, and C-3), 170.44 and 172.95 (C=O). Anal. Calcd for $C_{35}H_{58}BrNO_5$: C, 64.40; H, 8.96; N, 2.15. Found: C, 64.55; H, 9.01; N, 2.10.

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Registry No. 1, 73068-66-3; 2, 14233-62-6; 2 (R = Ac), 138858-67-0; 3, 138858-50-1; 4, 138858-51-2; 5, 138858-52-3; 6, 138858-53-4; 7, 138858-54-5; 8, 138858-55-6; 9, 138858-56-7; 10, 138858-57-8; 11, 138858-58-9; 12, 138858-59-0; 13, 138858-60-3; 14, 138858-61-4; 15, 138858-62-5; 16, 138858-63-6; 17, 138858-64-7; 18, 138858-65-8; 19, 138858-66-9; $Ph_3P{=}CH(CH_2)_{14}CH_3$, 103411-90-1; $Br(CH_2)_5COOCH_2CF_3$, 128691-25-8; $Br(CH_2)_5COCl$, 22809-37-6.

Synthesis of (*R*)- and (*S*)-4,5-Diaminovaleric Acids

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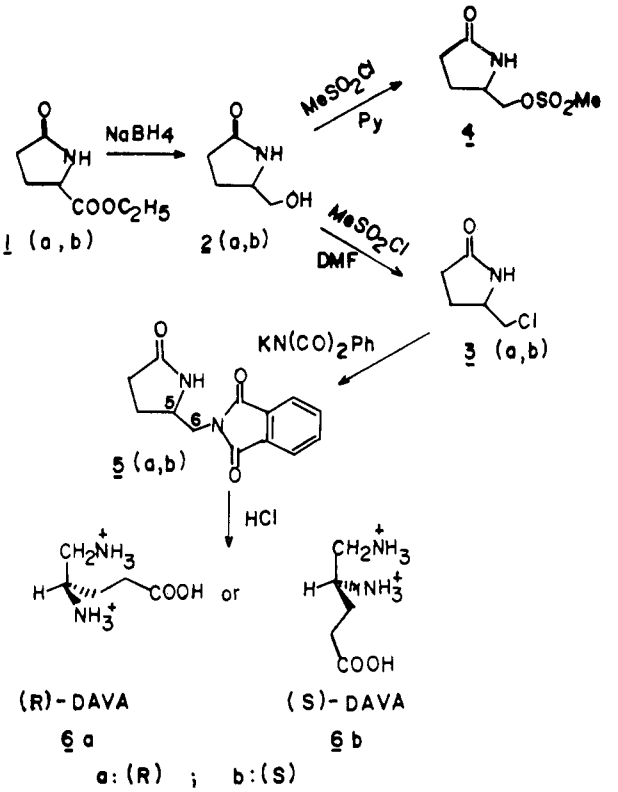
Two completely different pathways exist for the biosynthesis of 5-aminolevulinic acid (ALA), the precursor of all biological tetrapyrroles.[1] In the one pathway the pyridoxal-dependent ALA synthase (EC 2.3.1.37) catalyzes the condensation of glycine and succinyl-CoA; the resulting 2-amino-3-ketoadipic acid is spontaneously decarboxylated to ALA (Shemin pathway).[2] This pathway is found in nonphotosynthetic eukaryotes and in some bacteria. In the other pathway the C_5 chain of L-glutamic acid is converted to that of ALA by a complex reaction sequence involving three enzymes and $tRNA^{Glu}$ (C_5 pathway).[1,3] The C_5 pathway is found in plants and in many very different kinds of bacteria such as cyanobacteria, green sulfur and purple sulfur bacteria,[1c,3c] in the archaebacterium *Methanobacterium thermoautotrophicum*,[4] and even in organisms such as *Escherichia coli*,[5] *Bacillus subtilis*,[6] and *Clostridium thermoaceticum*.[7] In the last step of the C_5 pathway, catalyzed by glutamate-1-semialdehyde (GSA) aminotransferase (EC 5.4.3.8),[8] an intermolecular transamination occurs between two molecules of GSA.[9] This aminotransferase is unusual since no amino donor or acceptor in addition to GSA is required, a circumstance related to the fact that GSA carries an oxo and an amino group on adjacent carbons. It is likely that in the course of the conversion of GSA to ALA an intermolecular amino group transfer occurs, resulting in the formation of 4,5-diaminovaleric acid (DAVA).[10] The role of this putative intermediate has not been investigated. A synthesis of DAVA has been described thus far, via a Bamberger ring cleavage of 3-imidazole-4(5)-ylpropanoate, obtained from urocanic acid by catalytic reduction.[11] This synthesis necessarily yields the DAVA racemate. An attempt of ammonolysis on 4,5-dibromovaleric acid only afforded amorphous material.[12] We report a novel DAVA synthesis that permits the preparation of the required (*R*)-DAVA and (*S*)-DAVA, using commercially available precursors.

Scheme I



The starting materials were the *R* and *S* isomers of 5-carbethoxy-2-pyrrolidone (ethyl pyroglutamate) (1) (Scheme I). The reduction of the carbethoxy residue to give the 5-(hydroxymethyl)-2-pyrrolidone (2) has been achieved in the past using hydrogen at 200–300 atm/220 °C over copper–chromium oxide,[13] hydrogen over Ni Raney at 1000 psi,[14] and lithium borohydride.[15] More recently, the latter reductant was used to reduce the S enantiomer

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