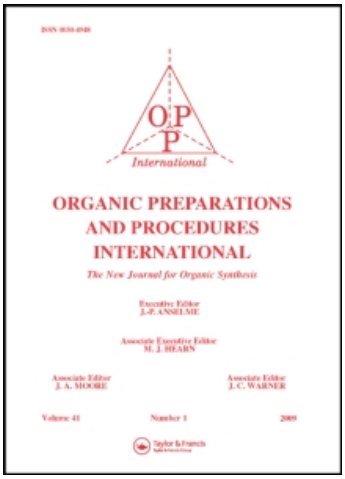

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MULTI-GRAM SYNTHESIS OF DIMYRISTOYL PENTAERYTHRITOL

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MULTI-GRAM SYNTHESIS OF DIMYRISTOYL PENTAERYTHRITOL

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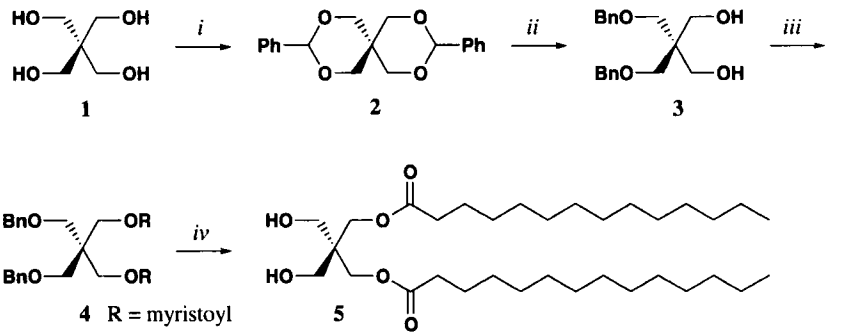
Unnatural lipids have become increasingly important targets because they can sequester and deliver therapeutic reagents.[1] Along these lines, synthetic lipids have been utilized to create polymerized micro-particles and have served as DNA delivery reagents.[2,3] Indeed, our interest in diesters of pentaerythritol first arose during the synthesis of a cationic lipid for use in gene therapy.[3] The difficulties we encountered in producing diester **5** on a large scale and in high yield motivated the present study. The one-step transformation of **1** to **5** (**Scheme**) by direct bis-acylation works moderately well (60% yield) on a mmol scale because column chromatographic separation of unwanted tri-ester is feasible, but this process is unwieldy on multi-gram scale.

Ogasawra and coworkers[4] have shown that diols could be protected as the monobenzyl ether by reductive cleavage of the corresponding benzylidene acetal with diisobutylaluminum hydride (DIBAL-H). We reasoned that this methodology could be extended to the bisprotection of tetrols. We report here the development of a more convenient method for the conversion of **1** to **5** (**Scheme**).



i) C_6H_5CHO (2 eq.), cat. TsOH, C_6H_6, reflux 4h *ii*) DIBAL-H (10 eq.), hexane-CH_2Cl_2, 0°, 12h
iii) $CH_3(CH_2)_{12}C(O)Cl$ (2.2eq.), Et_3N, cat. DMAP, CH_2Cl_2, 0° to rt, 4h *iv*) 10% Pd/C, H_2, EtOAc, 24h

Scheme

Dibenzylidene **2** was prepared from **1** in 99% yield utilizing standard acetalization methodology,[5] and was cleaved by addition of DIBAL-H in CH_2Cl_2 to produce diol diether **3** in 92% yield.[6] Introduction of the fatty acid side chains was accomplished by addition of a stoichiometric amount of the alkanoyl chloride under standard conditions giving diester diether **4** in 96% yield after simple filtration through a bed of silica gel (CH_2Cl_2 eluent). Finally, the benzyl ether protecting groups in **4** were removed by catalytic hydrogenolysis to produce diester diol **5** in 96% yield (9.6 g). The overall four-step yield of **5** from **1** is 83%. We believe this methodology will be generally applicable in the synthesis of *saturated* diesters of pentaerythritol.

EXPERIMENTAL SECTION

All chemicals were purchased from Aldrich. Prior to use, CH_2Cl_2 was immediately distilled from CaH_2. After reaction work-up, solutions were dried using Na_2SO_4 and solvent subsequently removed by rotary evaporation. NMR spectra were recorded with a General Electric QE-300 spectrometer (^1H at 300 MHz, ^{13}C at 75 MHz). Infrared spectra were recorded on a Mattson *Genesis II* FTIR 3000 spectrometer. Melting points are uncorrected. The elemental analysis was performed by Midwest Microlabs (Indianapolis, IN).

2,2-Di(benzyloxymethyl)-1,3-propandiol (3).- To a solution of **2** ([mp 158.4-159.3°; lit.[5] 160°] 10.0 g, 32.0 mmol) in CH_2Cl_2 (100 mL) at 0° was added, dropwise, diisobutylaluminum hydride (300 mL of a 1.0 M solution in hexanes, 300 mmol). Upon complete addition, the reaction solution was warmed to room temperature and stirred for 12 h. The reaction was cooled to 0° and carefully quenched by slow addition of MeOH (ca. 50 mL). Aqueous 10% NaOH (200 mL) was added and the mixture was vigorously stirred for 8 h. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layer was washed with brine and dried. Removal of the solvents and recrystallization of the residue from 1:1 ethanol:water afforded 9.3 g (92%) of **3** as a white solid, mp 70.3-71.7°, lit.[6] 72-74°; IR (neat): 3302, 3033, 2961, 2884, 1602, 1496, 1453, 1119, 1101, 1057 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.61 (m, 2 H), 3.53 (s, 4 H), 3.66 (s, 4 H), 4.46 (s, 4 H), 7.27 (m, 10 H); ^{13}C NMR ($CDCl_3$): δ 44.4, 63.9, 70.9, 73.0, 126.9, 127.1, 127.8, 137.4.

2,2-Di(benzyloxymethyl)-1,3-propandiyl Tetradecanoate (4).- To a solution of **3** (7.0 g, 22.1 mmol) in CH_2Cl_2 (100 mL) at 0° was added Et_3N (9.25 mL, 66.4 mmol), 4-(N,N-dimethylamino)pyridine (0.27 g, 2.2 mmol), and myristoyl chloride (13.2 mL, 48.7 mmol). The reaction was gradually warmed to room temperature and stirred 4 h where upon the reaction was quenched by addition of saturated aq. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the organic phase was washed with saturated aq. $NaHCO_3$ and brine, and then dried. The solvent was removed to afford the crude product as a lightly orange-colored oil. Purification was accomplished by passing this material through a short column of silica gel (100 g) eluting with CH_2Cl_2 to give 15.4 g (95%) of **4** as a white solid, mp 49.2-50.2°; IR (neat): 2924, 2849, 1737, 1724, 1467, 1194, 1161, 1108, 1079 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.71 (t, J = 6.6 Hz, 6 H), 1.08 (m, 40 H), 1.38 (m, 4 H), 2.07 (t, J = 7.5 Hz, 4 H), 3.30 (s, 4 H), 3.99 (s, 4 H), 4.29 (s, 4 H), 7.11 (m, 10 H); ^{13}C NMR ($CDCl_3$): δ 14.0, 22.6, 24.8, 29.1-29.6 (5 signals), 31.9, 34.1, 43.5, 62.9, 68.5, 73.2, 127.4, 127.3, 128.2, 138.1, 173.3

Anal. Calcd for $C_{47}H_{76}O_6$: C, 76.58; H, 10.39. Found: C, 76.32; H, 10.30

2,2-Di(hydroxymethyl)-1,3-propandiyl Tetradecanoate (5).- To a solution of **4** (13.2 g, 17.9 mmol) in ethyl acetate (150 mL) at room temperature was added 10% palladium on carbon (6.3 g). The reaction mixture was placed under an atmosphere of hydrogen and stirred 24 h at which time the suspension was diluted with ethyl acetate and filtered through silica. Removal of solvent afforded 9.60 g (96%) of **5** as a white solid, mp 53.3-54.3°; lit.[3] not reported; IR (neat): 3356, 2928, 1740, 1702, 1471, 1174, 1073 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (t, J = 6.6 Hz, 6 H), 1.25 (m, 40 H), 1.60 (m, 4 H), 2.35 (t,

J = 7.5 Hz, 4 H), 3.56 (s, 4 H), 4.14 (s, 4 H); ^{13}C NMR ($CDCl_3$): δ 14.0, 22.6, 24.8, 29.1-29.5 (5 signals), 31.8, 44.6, 62.2, 62.3, 174.3.

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REFERENCES

1. A. D. Miller, *Angew. Chem., Int. Ed.*, **37**, 1768 (1998).

2. T. M. Sisson, W. Srisiri and D. F. O'Brien, *J. Am. Chem. Soc.*, **120**, 2322 (1998).

3. A. M. Aberle, F. Tablin, J. Zhu, N. J. Walker, C. D. Gruenert, and M. H. Nantz, *Biochem.*, **37**, 6533 (1998).

4 S. Takano, M. Akiyama, S. Sato, and K. Ogasawara, *Chemistry Lett.*, 1593 (**1983**).

5. E. Bograchov, *J. Am. Chem. Soc.*, **72**, 2268 (1950).

6. This transformation was accomplished by Issidoridies and coworkers with $LiAlH_4/Al(Me)_3$ in 82% yield. See: A. R. Abdun-Nur, and C. H. Issidoridies, *J. Org. Chem.*, **27**, 67 (1962).

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IMPROVED SYNTHESIS OF *cis*-9,10-DIHYDRO-9,10-PHENANTHRENEDICARBOXIMIDES AND 9,10-PHENANTHRENEDICARBOXIMIDES

Submitted by (02/22/99)

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Aromatic imides play an important role in synthesis (amine group protection,[1] intramolecular cyclization reactions)[2] as well as in pharmaceutical, pigment and materials science applications.[3] 9,10-Phenanthrenedicarboximides (**4**) and their 9,10-dihydro derivatives **3** are less explored group of aromatic imides due to the difficulty in their preparation. Reported condensations of *cis*-9,10-dihydro-9,10-phenanthrenedicarboxylic anhydride (**1**) or 9,10-phenanthrenedicarboxylic anhydride with methylamine led to the corresponding *N*-methylimides **3a**[4] and **4a**[5] in low yields. *N*-Methylimide **4a**