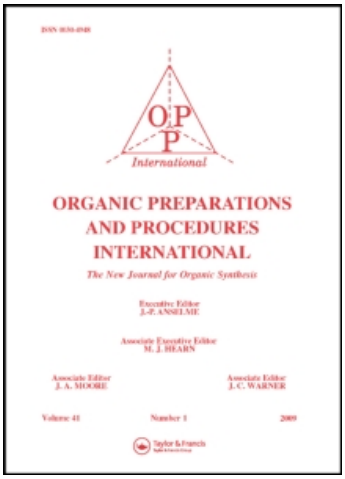

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A CONCISE SYNTHESIS OF 8-PHENYLOCTADECANOIC ACID

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A CONCISE SYNTHESIS OF 8-PHENYLOCTADECANOIC ACID

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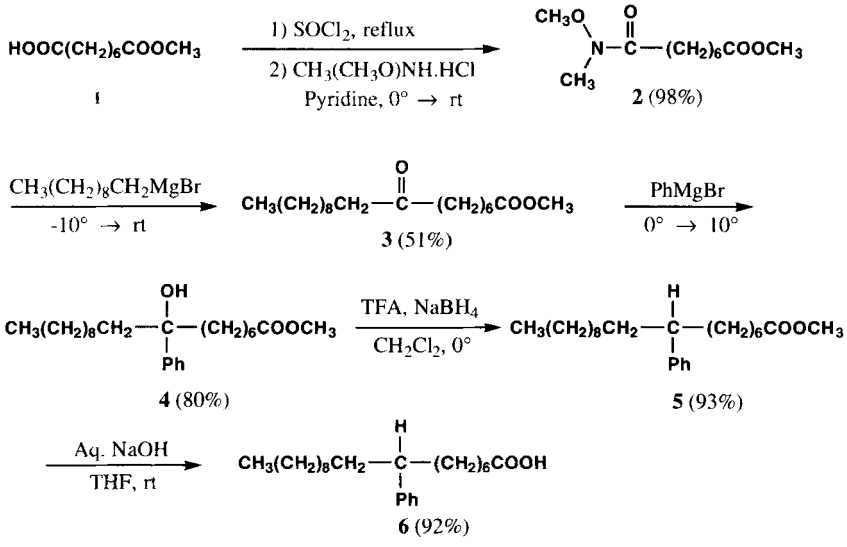
Several branched distearoylglycerols and distearoylphosphatidylcholines containing 8-substituted octadecanoyl side-chains have elevated stimulatory activity of protein kinase C (PK-C), relative to the parent stearoyl analogues.[1,2] Based on this observation, we became interested in exploring whether similarly branched acyl chains would increase the PK-C binding affinity for some L-ribonolactones that function as conformationally constrained forms of diacylglycerol.[3] Several of the 8-substituted fatty acids required for this study have been reported in the literature; however, experimental details for their syntheses are given only for the 8-methyl derivative.[4] Since steric bulk appears to be important for increasing PK-C binding affinity, 8-phenyloctadecanoic acid (**6**) was initially chosen for our study. However, when we attempted to repeat the synthesis of **6** as reported,[4] over-reduction of the phenyl group occurred during the platinum oxide-catalyzed hydrogenation of the double bond. In addition, the reported synthesis employed a cadmium reagent to prepare the key intermediate methyl 8-ketooctadecanoate (**3**), which involved a tedious preparation and purification.[4] Based on these considerations, we decided to pursue an alternative synthetic strategy. Herein, we report an approach which features fewer steps, as well as the ready purification of compound **3** by simple recrystallization. Compound **3** is a valuable intermediate from which other 8-substituted octadecanoic acids can be prepared.[4]

Commercially available suberic acid monomethyl ester (**1**) (Scheme) was refluxed with thionyl chloride, and the acid chloride generated *in situ* was treated with N,O-dimethylhydroxylamine



hydrochloride in the presence of pyridine to give the corresponding amide, methyl 7-(N-methoxy-N-methylcarbamoyl)heptanoate (**2**) in quantitative yield. Preferential reaction of **2** at the amide function[5] with decylmagnesium bromide provided methyl 8-ketooctadecanoate (**3**) in 51% yield. Compound **3** reacted selectively at the ketone group with phenylmagnesium bromide to give methyl 8-hydroxy-8-phenyloctadecanoate (**4**) in 80% yield. Deoxygenation of **4** with TFA/$NaBH_4$,[6] produced methyl 8-phenyloctadecanoate **5** in 93% yield. It is noteworthy that compound **4**, a monoarylmethanol derivative underwent deoxygenation in excellent yield, as only diaryl and triarylmethanols are reported to undergo this reaction efficiently.[6] Alkaline hydrolysis of **5** with aqueous NaOH in THF provided 8-phenyloctadecanoic acid (**6**) in 92% yield.

In conclusion, a concise and operationally simple synthesis of 8-phenyloctadecanoic acid (**6**) has been developed.

EXPERIMENTAL SECTION

All chemicals and reagents were obtained commercially and used without further purification. Flash column chromatography was carried out using silica gel 60 (230-400 mesh). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. NMR data were obtained on a Bruker AC250 (250 MHz) and are referenced to the solvent in which they were run.

Methyl 7-(N-Methoxy-N-methylcarbamoyl)heptanoate (2).- A solution of suberic acid monomethyl ester (**1**, 5.00 g, 26.5 mmol) in $SOCl_2$ (40 mL) was refluxed for 2 hrs. Excess $SOCl_2$ was distilled off under vacuum and remaining traces of $SOCl_2$ were co-distilled with anhydrous benzene (25 mL). Anhydrous CH_2Cl_2 (30 mL) was added to the residue and the solution was cooled to 0°; then N,O-dimethylhydroxylamine hydrochloride (3.10 g, 31.80 mmol) was added followed by anhydrous pyridine (6.40 mL, 79.7 mmol). The reaction mixture was stirred at room temperature for 14 hrs. Water (50 mL) was added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 (2 x 25 mL) and the combined organic extract was washed with 1M HCl (2 x 50 mL), water (1 x 50 mL), saturated $NaHCO_3$ solution (1 x 50 mL), and water (1 x 50 mL). The organic extract was dried ($MgSO_4$) and concentrated to give **2** (6.01 g, 98 %) which was used in the next step without further purification. An analytical sample of **2** was obtained by flash column chromatography on silica gel using hexane/EtOAc (3/2) as eluant which provided pure **2** as a clear oil (R_f = 0.33, hexane/EtOAc, 3/2); IR (neat) 1737.7 and 1666.8 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (m, 4 H, >NOCCH$_2$CH$_2$C<u>H$_2$</u>C<u>H$_2$</u>CH$_2$CH$_2$COO), 1.60 (m, 4 H, >NOCCH$_2$C<u>H$_2$</u>CH$_2$CH$_2$C<u>H$_2$</u>CH$_2$COO), 2.25 (distorted triplet, 2 H, C<u>H$_2$</u>COOCH$_3$), 2.36 (distorted triplet, 2 H, C<u>H$_2$</u>CON<), 3.12 (s, 3 H, CON(OCH$_3$)C<u>H$_3$</u>), 3.61 (s, 3 H, CON(OC<u>H$_3$</u>)CH$_3$), 3.63 (s, 3 H, COOC<u>H$_3$</u>).

Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.11; H, 9.16; N, 6.06. Found: C, 57.20; H, 9.21; N, 6.10

Methyl 8-Ketooctadecanoate (3).- A solution of decylmagnesium bromide in diethyl ether (1M, 105 mL) was added over a period of 1 hr to a cold (- 10°C) and stirred solution of **2** (18.1 g, 78.3 mmol) in anhydrous THF (140 mL). The reaction mixture was stirred at -10° for 2 hrs more and then brought to room temperature in 30 min. Quenching of the reaction with 1 M HCl (100 mL)

was performed at 0° and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic extract was washed with 1M HCl (1 x 100 mL), water (100 mL), saturated $NaHCO_3$ solution (100 mL) and water (100 mL). The organic solution was dried (Na_2SO_4) and concentrated to give a yellow solid (ca. 30 g). Recrystallization from hexane provided **3** (R_f =0.36, hexane/EtOAc, 95/5) as a white solid (11.9 g, 51 %); mp 46 - 47° (lit[7]. 46.4 - 46.9°); IR (KBr) 1735.9, 1706.0 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (distorted triplet , 3 H, $C\underline{H}_3(CH_2)_9$), 1.20-1.30 (m, 18 H, $CH_3(C\underline{H}_2)_7(CH_2)_2OC(CH_2)_2(C\underline{H}_2)_2(CH_2)_2COOCH_3$), 1.30-1.60 (m, 6 H, $CH_3(CH_2)_7$-$C\underline{H}_2CH_2OC$-$CH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2COOCH_3$), 2.20-2.40 (m, 6 H, $CH_3(CH_2)_8C\underline{H}_2$-$OCC\underline{H}_2(CH_2)_4C\underline{H}_2COOCH_3$), 3.63 (s, 3 H, $COOC\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.64, 23.58, 23.87, 24.73, 28.84, 28.88, 29.25, 29.28, 29.39, 29.45, 29.53, 29.62, 31.86, 33.96, 42.60, 42.83, 51.42, 174.14, 211.44.

Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.01; H, 11.62. Found: C, 72.92; H, 11.55

Methyl 8-Hydroxy-8-phenyloctadecanoate (4).- A solution of phenylmagnesium bromide in ether (3M, 3.00 mL) was added over a period of 15 min to a solution of ketoester **3** (2.27 g, 7.5 mmol) in a mixture of anhydrous ether (60 mL) and THF (8 mL) at 0°. After stirring at 0° for 2 hrs, the mixture was brought to 10° over 1 hr and then treated with 1M HCl (~25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic extract was washed with water (2 x 50 mL) and dried (Na_2SO_4). Removal of the solvent provided an oil (3.05 g) which was purified by flash chromatography on silica gel using hexane/ EtOAc (95/5) as eluant to yield **4** (R_f = 0.46, hexane/EtOAc, 9/1) as an pale oil (2.25 g, 80 %); IR (neat) 3512.2, 1740.8, 1602.0, 1494.0, 1445.8 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.82 (distorted triplet, 3 H, $C\underline{H}_3(CH_2)_9$), 1.10-1.30 (m, 22 H, $CH_3(C\underline{H}_2)_8CH_2(Ph)C(OH)CH_2(C\underline{H}_2)_3(CH_2)_2COOCH_3$), 1.50 (m, 2 H, $CH_3(CH_2)_9(Ph)C(OH)(CH_2)_4C\underline{H}_2CH_2COOCH_3$), 1.70-1.80 (m, 4 H, $CH_3(CH_2)_8$-$C\underline{H}_2(Ph)C(OH)C\underline{H}_2(CH_2)_5COOCH_3$), 2.22 (t, 2 H, J ≈ 7.5 Hz, $C\underline{H}_2COOCH_3$), 3.62 (s, 3 H, $COOC\underline{H}_3$), 7.15 - 7.40 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$): δ 14.08, 22.64, 23.23, 23.37, 24.83, 28.98, 29.27, 29.49, 29.55, 29.59, 29.99, 31.86, 34.0, 42.91, 42.95, 51.41, 125.18, 126.19, 127.98, 146.39, 174.22.

Anal. Calcd for $C_{25}H_{42}O_3$: C, 76.86; H, 10.84. Found: C, 77.04; H, 10.77

Methyl 8-Phenyloctadecanoate (5).- To a stirred solution of trifluoroacetic acid (3.7 mL, 47.9 mmol) in CH_2Cl_2 (10 mL) at 0° was added solid $NaBH_4$ (0.242 g, 6.4 mmol) in one portion. The mixture was stirred for 10 min at 0° and a solution of **4** (1.20 g, 3.2 mmol) in CH_2Cl_2 (12 mL) was added slowly over 10 min. The resulting mixture was stirred further for 1 hr at 0° and then quenched with saturated $NaHCO_3$ solution (30 mL) at 0°. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with saturated $NaHCO_3$ solution (15 mL), H_2O (20 mL) and dried ($MgSO_4$). Removal of the solvent gave crude **5** as an oil (3.05 g) which was purified by flash chromatography on silica gel with hexane/EtOAc (99/1) as eluant to yield pure **5** (R_f =0.48, hexane/EtOAc, 95/5) as an oil (1.07g, 93 %); IR (neat) 3025.8, 1742.0, 1602.4, 1493.3, 1452.3 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (distorted triplet, 3H, $C\underline{H}_3(CH_2)_9$), 1.10-1.30 (m, 22 H, $CH_3(C\underline{H}_2)_8CH_2(Ph)CHCH_2(C\underline{H}_2)_3(CH_2)_2$-$COOCH_3$), 1.50-1.60 (m, 6 H, $CH_3(CH_2)_8C\underline{H}_2(Ph)CHC\underline{H}_2(CH_2)_3C\underline{H}_2CH_2COOCH_3$), 2.22 (t, 2 H,

J ≈ 7.5 Hz, $C\underline{H}_2COOCH_3$), 2.43 (m, 1 H, PhC$\underline{H}$), 3.62 (s, 3H, $COOC\underline{H}_3$), 7.1 0- 7.30 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$): δ 14.11, 22.67, 24.91, 27.42, 27.61, 29.04, 29.32, 29.35, 29.54, 29.59, 29.63, 29.75, 31.90, 34.05, 36.87, 36.97, 46.03, 51.40, 125.69, 127.63, 128.13, 146.30, 174.27.

Anal. Calcd for $C_{25}H_{42}O_2$: C, 80.15; H, 11.31. Found: C, 79.89; H, 11.21

8-Phenyloctadecanoic Acid (6).- A solution of methyl 8-phenyloctadecanoate **5** (1.184 g, 3.28 mmol) in THF (20 mL) was treated with aqueous NaOH (1M, 13.15 mL) and stirred at room temperature for 20 hrs. The reaction mixture was acidified with 1M HCl to pH ≈ 2, concentrated under reduced pressure, extracted with EtOAc (3 x 20 mL), washed with brine (2 x 20 mL), dried (Na_2SO_4) and evaporated to dryness. The resulting crude oil (1.13 g) was chromatographed on silica gel using EtOAc as eluant to provide pure **6** (R_f =0.13, hexane/EtOAc, 95/5) as a colorless oil (1.053 g, 92%); IR (neat) 1709.1 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (distorted triplet , 3H, $C\underline{H}_3(CH_2)_9$), 1.10-1.30 (m, 22 H, $CH_3(C\underline{H}_2)_8CH_2(Ph)CHCH_2(C\underline{H}_2)_3(CH_2)_2COOH$), 1.50-1.60 (m, 6 H, $CH_3(CH_2)_8C\underline{H}_2$-(Ph)$CHC\underline{H}_2(CH_2)_3C\underline{H}_2CH_2COOH$), 2.28 (t, 2 H, J ≈ 7.5 Hz, $C\underline{H}_2COOH$), 2.43 (m, 1H, PhC$\underline{H}$), 7.10 - 7.30 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$): δ 14.10, 22.67, 24.60, 27.39, 27.61,28.92, 29.31, 29.53, 29.59, 29.63, 29.74, 31.90, 33.99, 36.86, 36.97, 125.69, 127.62, 128.14, 146.27, 180.10.

Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.93; H, 11.19. Found: C, 79.86; H, 11.20

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