Convenient Highly Stereoselective Syntheses of (3*R*,7*R*,11*R*)- and (3*S*,7*R*,11*R*)-3,7,11,15-Tetramethylhexadecanoic Acid (Phytanic Acid) and the Corresponding 3,7,11,15-Tetramethylhexadecan-1-ols†

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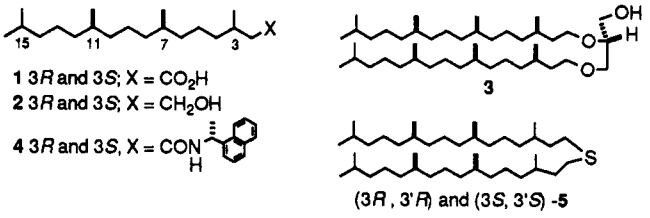
Received April 29, 1993

Phytanic acid (1) and dihydrophytol (2) are naturally-occuring branched isoprenoid compounds of significant biological interest. For instance, patients afflicted with Refsum's disease, a rare inherited disorder involving a metabolic error in fatty acid oxidation, are susceptible to the widespread accumulation of exogenous phytanic acid in organ lipids that may serve as the causative factor in nerve fiber degeneration which eventually leads to death.[1] In addition, it has been determined that the exclusive lipid structural unit of many archaebacterial membranes, such as those of the extremely halophilic organism *Halobacterium cutirubrum*, is (2*R*)-2,3-di-*O*-[(3′*R*,7′*R*,11′*R*)-3′,7′,11′,15′-tetramethylhexadecyl]glycerol (3), a feature which taxonomically separates this unique class of microorganism from eubacteria and eukaryotes.[2] Given these findings and others, there has been considerable activity related to the investigation of (1) the impact of phytanic acid on the stability and dynamics of phospholipid bilayers,[3] (2) the formation and degradation of phytanoyl-containing triacylglycerides via acyltransferases and lipases,[4] (3) the synthesis and physiochemical properties of 1,2-diphytanoyl-*sn*-glycero-3-phosphocholine model membranes,[5] (4) the synthesis of 3,[6] and (5) the physiochemical properties of natural and synthetic archaebacterial membranes.[7] However, due to the extremely limited supply of (3*R*)-2 that can be obtained from natural sources and the impracticalities associated with the stereospecific total

Scheme I



syntheses of 1 and 2,[8] virturally all of the above studies have been conducted with synthetic material derived from using diastereomeric mixtures of (3*R*/*S*)-1 or (3*R*/*S*)-2 since these starting materials can be obtained in a straightforward manner from phytol [(7*R*,11*R*)-3,7,11,15-tetramethylhexadec-2-en-1-ol], which, itself, is commercially available as a 66:33 mixture of *E* and *Z* stereoisomers. Unfortunately, there is strong evidence to suggest that the absolute configuration of the methyl group at the 3-position in 1 and 2 can not only influence, in the case of 1, the kinetics of acyl-activating systems and/or acyltransferases in the formation of lipophilic xenobiotic conjugates,[9,10] but also, it can give rise to distinct differences in the observed physical properties of diastereomeric esters and ethers formed from chiral alcohols and 1 and 2, respectively.[6b,11] Thus, in order to further elucidate the impact on, or the roles served, by 1 and 2 in biological systems, it is essential that a ready supply of (3*R*)- or (3*S*)-1 and (3*R*)- or (3*S*)-2 be made available so that relevant compounds for study can be produced in enantiomerically and diastereomerically pure form. Herein, a simple preparative-scale process is described that meets this objective. In addition, the synthesis and physical properties of (3*S*)-1 and (3*S*)-2 are reported for the first time, as well as a convenient method employing the amide 4 to determine the diastereomeric ratio of 3*R*/*S* mixtures of 1. Finally, as part of a program established to investigate structure/property relationships of self-assembled monolayers,[12] the synthesis and characterization of the dialkyl sulfides, (3*R*,3′*R*)-5 and (3*S*,3′*S*)-5, are documented.[13]

The syntheses of 1, 2, and 5 are based on the highly efficient asymmetric hydrogenation of allylic alcohols using [(*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]diacetatoruthenium(II) (6) as the catalyst.[14] Accordingly, after separation of the *E* and *Z* stereoisomers of phytol by flash

† Contribution no. 8813.

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0022-3263/93/1958-5285$04.00/0

chromatography (FC) on silica gel[15] using a 6:1 hexane/diethyl ether (Et_2O) solvent mixture as the eluant,[16] hydrogenation of the (*E*)-phytol stereoisomer in methanol at 1500 psi using **6** as the catalyst quantitatively provided (3*R*)-**2**. Likewise, (3*S*)-**2** was obtained from the hydrogenation of the (*Z*)-phytol stereoisomer using **6**. Jones oxidation of (3*R*)-**2** and (3*S*)-**2** then respectively provided (3*R*)-**1** and (3*S*)-**1** in a 85% yield. To determine diastereomeric purity, (3*R*)-**1** and (3*S*)-**1** were first converted to their corresponding acyl chlorides with oxalyl chloride and then to the respective amide derivatives, (3*R*)-**4** and (3*S*)-**4**, through treatment of these intermediates with (*R*)-(+)-α-(1-naphthyl)ethylamine (98% overall yield).[17] These latter two compounds display remarkable differences in crystallinity and mobility on solid supports employed in thin layer chromatography (TLC), FC, and high pressure liquid chromatography (HPLC). Using this latter method then, diastereomeric ratios of 3*R*/*S*-**1** mixtures can easily be determined, and in this way, the stereoselectivity of the asymmetric hydrogenation reaction was determined to be ≥100:1.[18] In addition, since it was found that FC (6:1 hexane/ Et_2O) could be used to obtain gram quantities of (3*R*)-**4** and (3*S*)-**4** starting from a 50:50 mixture of (3*R*/*S*)-phytanic acid, reductive removal of the chiral amine auxiliary group[19] would appear to represent another practical, albeit noncatalytic, route to diastereomerically pure (3*R*)-**2** and (3*S*)-**2**. Finally, to obtain the dialkyl sulfides, (3*R*,3′*R*)-**5** and (3*S*,3*S*)-**5**, the respective diastereomers of **2** were first converted to the 3,7,11,7-tetramethyl-hexadecyl bromides **7** (X = CH_2Br in Scheme I) by treatment with aqueous 48% HBr at 100 °C (87% yield) and then to the corresponding sulfides with thiourea (94% yield). These new dialkyl sulfides form well-defined self-assembled monolayers on gold, the complete characterization of which will be reported in due course.

Experimental Section

Manipulations requiring an inert atmosphere of nitrogen or argon were performed using standard Schlenk techniques or a Vacuum Atmospheres glovebox. Dry, oxygen-free solvents were employed throughout. Silica gel (Baker, 400 mesh) was used for flash chromatography and silica gel TLC plates (Merck 60 F-254) were visualized with either a short-wave UV lamp or a 20% solution of phosphomolybdic acid in absolute ethanol (Aldrich), followed by heating the plate on a hot plate. Phytol and (*R*)-(+)-α-(1-naphthyl)ethylamine were used as obtained from Aldrich and [(*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]diacetatoruthenium(II) (**6**) was prepared according to the published procedure.[14b] Elemental analyses were performed by Oneida Research Services, Inc. ^1H and ^{13}C NMR spectra were recorded at 500 and 75 MHz, respectively, using chloroform-*d* as the solvent. Infrared absorption spectra and optical rotations (558 nm, 1-dm pathlength cell) were measured using chloroform as the solvent. Capillary gas chromatography was performed on a 30 m × 0.25 mm column (J & W Scientific, DB-5) and HPLC was performed isocratically on a normal-phase column (5 μm silica, 0.4 × 25 cm) using a 8:1 hexane/ethyl acetate solvent mixture (flow rate: 1 mL/ min).

Separation of (*E*)- and (*Z*)-Phytol Stereoisomers. To a silica gel column (400 × 50 mm), preequilibrated with a 6:1 hexane/Et_2O solvent mixture, a solution of 3 g (10.0 mmol) of phytol (66:33 mixture of *E* and *Z* stereoisomers) in a minimum volume of the same solvent was applied. Elution with the solvent mixture provided fractions which were then subjected to GC analysis to determine isomeric purity. Mixed fractions were combined and subjected to column chromatography once more to provide, in total, 0.86 g of pure (*Z*)-phytol (87% yield) (R_f 0.43 2:1 hexane/Et_2O) and 1.24 g of (*E*)-phytol of 98% isomeric purity (63% yield) (R_f 0.38). Isomeric purity was also assessed by ^1H NMR spectroscopy using the chemical shift difference observed for the vinyl methyl group of the two stereoisomers [δ (ppm) 1.65 for (*E*)-phytol; 1.72 for (*Z*)-phtyol].

(3*R*,7*R*,11*R*)-3,7,11,15-Tetramethylhexadecan-1-ol [(3*R*)-2]. A solution of 0.98 g (3.3 mmol) of (*E*)-phytol and 5 mg (0.006 mmol) of **6** in 3 mL of methanol was placed in a 20-mL glass vial inside a 100-mL Parr bomb and subjected to 1500 psi of hydrogen pressure for 24 h. At this time, GC analysis of a small aliquot showed hydrogenation to be complete, and after removal of the solvent, the crude product was taken up in a minimum volume of hexane, the solution passed through a short column of silica gel to remove the spent catalyst, and the solvent removed to provide 1.05 g of the desired material (100 % yield): TLC R_f 0.49 (2:1 hexane/Et_2O); ^1H NMR δ (ppm) 0.84 (d, 6H, J = 6.6 Hz), 0.86 (d, 6H, J = 6.5 Hz), 0.89 (d, 3H, J = 6.6 Hz), 1.00-1.40 (m, 21 H), 1.52 (sept, 1H, J = 6.5 Hz), 1.58 (m, 2H), 3.67 (m, 2H); ^{13}C NMR δ (ppm) 20.26, 20.32, 23.20, 23.29, 24.95, 25.04, 25.38, 28.55, 30.09, 33.35, 37.91, 37.96, 39.94, 40.53, 40.61, 61.80; IR (cm^{-1}) 3620, 3018, 2956, 2927, 2869, 1522,1463, 1424, 1378, 1366, 1018, 929; $[\alpha]^{27}_D$ = +2.70° (c = 33.3) ($[\alpha]^{22}_D$ = +2.4° for (3*R*)-**2** isolated from *H. cutirubrum*[2c]). Anal. Calcd for $C_{20}H_{42}O$: C, 80.46; H, 14.18. Found: C, 80.54, H, 14.23.

(3*S*,7*R*,11*R*)-3,7,11,15-Tetramethylhexadecan-1-ol [(3*S*-2]. This compound was prepared from (*Z*)-phytol in a fashion identical to that used for (3*R*)-**2**. TLC, ^1H NMR, ^{13}C NMR, and IR spectra identical to those for (3*R*)-**2**, $[\alpha]^{27}_D$ = −2.72° (c = 57.3). Anal. Calcd for $C_{20}H_{42}O$: C, 80.46; H, 14.18. Found: C, 80.25, H, 13.83.

(3*R*,7*R*,11*R*)-3,7,11,15-Tetramethylhexadecanoic Acid [(3*R*)-1]. To a solution of 1 g (3.3 mmol) of (3*R*)-**2** in 60 mL of a 2:1 acetone/acetic acid solvent mixture, a solution of 0.80 g (8.0 mmol) of chromium trioxide in 1 mL of water was added dropwise via a pipette at room temperature. Stirring was continued for an additional 1 h whereupon 50 mL of water was first added, followed by enough solid sodium bisulfate to destroy the excess oxidant which is present. The reaction mixture was extracted with Et_2O (3 × 15 mL), the organic layers were combined and dried with anhydrous sodium sulfate, and the solvents were removed *in vacuo* to give a crude material. This was then purified by column chromatography on silica gel using a 2:1 hexane/Et_2O solvent mixture as the eluant to provide 1.01 g of the desired product as a colorless oil (85% yield). TLC R_f 0.51 (2:1 hexane/Et_2O); ^1H NMR δ (ppm) 0.84 (d, 6H, J = 6.6 Hz), 0.86 (d, 6H, J = 6.5 Hz), 0.97 (d, 3H, J = 6.6 Hz), 1.00-1.40 (m, 20 H), 1.52 (sept, 1H, J = 6.5 Hz), 1.96 (oct, 1H, J = 6.5 Hz), 2.14 (ddd, 1H, J_{ab} = 14.97 Hz, J_{ac} = 5.82 Hz, J_{ad} = 2.5 Hz) 2.36 (ddd, 1H, J_{ab} = 14.97 Hz, J_{bc} = 8.23, J_{bd} = 2.50 Hz); ^{13}C NMR δ (ppm) 20.17, 20.23, 23.20, 23.30, 24.91, 25.03, 25.38, 28.55, 30.74, 33.33, 37.55, 37.59, 37.86, 37.96, 38.01, 39.94, 42.20, 42.28, 180.62; IR (cm^{-1}) 3018, 2956, 2927, 2869, 1706, 1522,1463, 1424, 1378, 1366, 1018, 929; $[\alpha]^{27}_D$ = +4.50° (c = 42.2) ($[\alpha]^{22}_D$ = +3.5° for (3*R*)-**1** derived from natural (3*R*)-**2**[2c]). Anal. Calcd for $C_{20}H_{40}O$: C, 76.86; H, 12.90. Found: C, 76.69, H, 13.01.

(3*S*,7*R*,11*R*)-3,7,11,15-Tetramethylhexadecanoic Acid [(3*S*)-1]. This compound was prepared in a fashion identical to that used for 3*R*-**1**. TLC, ^1H NMR, ^{13}C NMR, and IR spectra identical to 3*R*-**1**. $[\alpha]^{27}_D$ = −4.45° (c = 33.1). Anal. Calcd for $C_{20}H_{40}O$: C, 76.86; H, 12.90. Found: C, 76.89, H, 12.94.

(3*R*, 7*R*, 11*R*)-*N*-[(1*R*)-1-Naphthylethyl]-3,7,11,15-tetramethylhexadecanamide [(3*R*)-4]. To a solution of 44 mg (0.14 mmol) of (3*R*)-**1** in 1 mL of Et_2O was added, 5 μL of dimethylformamide followed by 13.6 μL (0.16 mmol) of oxalyl chloride.

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The reaction mixture was stirred at room temperature for 30 min and then the solvent was removed *in vacuo* whereupon 0.5 mL of chloroform was added, followed by a solution of 27 mg (0.16 mmol) in 200 μL of chloroform and 15 μL of triethylamine. After stirring at room temperature for 30 min, TLC showed the reaction to be complete, at which time, the solvent was removed *in vacuo*, the residue taken up in a minimum amount of hexane, and the solution filtered through a short pad of Celite. After removal of the solvent, the crude product was purified by column chromatography on silica gel using a 2:1 hexane/Et_2O solvent mixture as the eluant to provide 65 mg of 3*R*-4 as a viscous colorless oil (98% yield): TLC R_f 0.55 (2:1 hexane/Et_2O); ^1H NMR δ (ppm) 0.82 (d, 3H, J = 6.5 Hz), 0.84 (d, 3H, J = 6.6 Hz), 0.87 (d, 6H, J = 6.4 Hz), 0.88 (d, 3H, J = 5.1 Hz), 1.00-1. 40 (m, 20 H), 1.52 (sept, 1H, J = 6.5 Hz), 1.68 (d, 3H, J = 6.8 Hz), 1.89 (ddd, 1H, J_{ab} = 13.45 Hz, J_{ac} = 8.38 Hz, J_{ad} = 2.4 Hz), 1.97 (oct, 1H, J = 6.0 Hz), 2.16 (ddd, 1H, J_{ab} = 13.45 Hz, J_{bc} = 5.73, J_{bd} = 2.40 Hz), 5.62 (d, 1H, J = 8.13 Hz), 5.96 (dq, 1H, J_{ab} = 7.3 Hz, J_{ac} = 6.89 Hz), 7.40-7.60 (m, 4H), 7.80 (d, 1H, J = 8.14 Hz), 7.86 (d, 1H, J = 8.00 Hz), 8.11 (d, 1H, J = 8.30 Hz); ^{13}C NMR δ (ppm) 20.19, 20.24, 21.21, 23.06, 23.14, 24.91, 24.99, 25.28, 28.48, 31.37, 33.33, 37.75, 37.84, 37.89, 37.99, 39.96, 45.09, 45.15, 45.19, 123.02, 124.16, 125.61, 126.35, 126.97, 128.82, 129.22, 131.77, 134.47, 139.17, 172.09; IR (cm^{-1}) 3436, 3018, 2956, 2927, 2869, 1662, 1516, 1475, 1424, 1018, 929; $[\alpha]^{27}_D$ = +40.75° (c = 12.0) . Anal. Calcd for $C_{32}H_{51}NO$: C, 82.52; H, 11.04, N, 3.01. Found: C, 81.85, H, 10.71, N, 3.02.

(3*S*,7*R*,11*R*)-*N*-[(1*R*)-1-Naphthylethyl]-3,7,11,15-tetramethylhexadecanamide [(3*S*)-4]. This compound was prepared in a fashion identical to that used for (3*R*)-4. An analytically pure sample was obtained by recrystallization from hexane at room temperature. TLC R_f 0.50 (2:1 hexane/Et_2O); mp 68-70 °C; ^1H NMR δ (ppm) 0.80 (dd, 3H, J_{ab} = 6.37 Hz, J_{ac} = 1.89 Hz), 0.84 (d, 3H, J = 6.6 Hz), 0.87 (d, 6H, J = 6.4 Hz), 0.92 (d, 3H, J = 6.6 Hz), 1.00-1.40 (m, 20 H), 1.52 (sept, 1H, J = 6.5 Hz), 1.68 (d, 3H, J = 6.7 Hz), 1.90 (ddd, 1H, J_{ab} = 13.20 Hz, J_{ac} = 8.24 Hz, J_{ad} = 2.8 Hz), 1.97 (oct, 1H, J = 6.0 Hz), 2.14 (ddd, 1H, J_{ab} = 13.20 Hz, J_{bc} = 5.69, J_{bd} = 3.00 Hz), 5.62 (d, 1H, J = 8.13 Hz), 5.96 (dq, 1H, J_{ab} = 7.3 Hz, J_{ac} = 6.89 Hz), 7.40-7.60 (m, 4H), 7.80 (d, 1H, J = 8.14 Hz), 7.86 (d, 1H, J = 8.00 Hz), 8.11 (d, 1H, J = 8.30 Hz); ^{13}C NMR δ (ppm) 20.21, 20.25, 21.29, 23.15, 23.23, 24.91, 25.02, 25.34, 28.52, 31.43, 33.36, 37.77, 37.90, 38.02, 38.05, 39.98, 45.03, 45.12, 45.17, 123.02, 124.16, 125.61, 126.35, 126.97, 128.82, 129.22, 131.77, 134.47, 139.17, 172.09; IR (cm^{-1}) 3436, 3018, 2956, 2927, 2869, 1662, 1516, 1475, 1424, 1018, 929; $[\alpha]^{27}_D$ = +43.39° (c = 11.5). Anal. Calcd for $C_{32}H_{51}NO$: C, 82.52; H, 11.04, N, 3.01. Found: C, 80.16, H, 10.53, N, 2.99.

(3*R*,7*R*,11*R*)-1-Bromo-3,7,11,15-tetramethylhexadecane [(3*R*)-7]. A mixture of 400 mg (1.34 mmol) of (3*R*)-2, 50 mL of 48% aqueous HBr, and 0.5 mL of concd sulfuric acid was refluxed under a nitrogen atmosphere for 24 h. Upon cooling, the reaction mixture was extracted with hexane (3 × 15 mL), the combined organic extracts were dried with anhydrous sodium sulfate, and the solvent was removed *in vacuo* to give the crude product as a dark brown oil. This material was purified by column chromatography on silica gel using hexane as the eluant to give 421 mg of the desired product as a colorless oil (87% yield): TLC R_f 1.00 (hexane); ^1H NMR δ (ppm) 0.85 (d, 6H, J = 6.6 Hz), 0.87 (d, 6H, J = 6.5 Hz), 0.89 (d, 3H, J = 6.6 Hz), 1.00-1.40 (m, 20 H), 1.52 (sept, 1H, J = 6.5 Hz), 1.66 (m, 2H), 1.88 (m, 1H), 3.40 (m, 1H), 3.46 (m, 1H); ^{13}C NMR δ (ppm) 19.50, 20.30, 23.20, 24.79, 25.03, 25.36, 28.54, 32.26, 32.50, 33.34, 37.37, 37.41, 37.76, 39.96, 40.70; IR (cm^{-1}) 3018, 2956, 2927, 2869, 1522,1463, 1424, 1378, 1366, 1018, 929; $[\alpha]^{27}_D$ = −2.90° (c = 49.3). Anal. Calcd for $C_{20}H_{41}Br$: C, 66.46; H, 11.43. Found: C, 66.59, H, 11.33.

Bis[(3*R*,7*R*,11*R*)-3,7,11,15-tetramethyl-1-hexadecyl] Sulfide [(3*R*,3′*R*)-5]. To a solution of 370 mg (1.02 mmol) of (3*R*)-7 in 10 mL of 95% aqueous ethanol was added 82 mg (1.07 mmol) of thiourea and the mixture refluxed under nitrogen for 3 h. Upon cooling, 0.66 mL of aqueous sodium hydroxide (2.5 M) was added and the reaction mixture refluxed for an additional 2 h. Upon cooling once more, the mixture was diluted with 15 mL of water and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent removed *in vacuo* to give a crude product which was purified by column chromatography using a 6:1 hexane/Et_2O solvent mixture as the eluant to give 286 mg of the desired material as a colorless oil (94% yield): TLC R_f 0.50 (hexane); ^1H NMR δ (ppm) 0.84 (d, 6H, J = 6.6 Hz), 0.87 (d, 6H, J = 6.5 Hz), 0.88 (d, 3H, J = 6.6 Hz), 1.00-1.40 (m, 21 H), 1.52 (sept, 1H, J = 6.5 Hz), 1.58 (m, 2H), 2.48 (m, 1H), 2.54 (m, 1H); ^{13}C NMR δ (ppm) 19.95, 20.01, 20.23, 20.27, 23.21, 23.30, 24.95, 25.06, 25.38, 28.55, 30.44, 32.85, 33.35, 37.41, 37.97, 38.02, 39.95; IR (cm^{-1}) 3018, 2956, 2927, 2869, 1522, 1463, 1424, 1378, 1366, 1018, 929; $[\alpha]^{27}_D$ = −8.21° (c = 43.6), mass spectrum (70 eV), m/e (rel inten) 595 (M^+, 1.00), 313 ($M^+ - C_{20}H_{41}$, 0.63); exact mass calcd for $C_{40}H_{82}S$ 594.6137, found 594.6124. Anal. Calcd for $C_{40}H_{82}S$: C, 80.73; H, 13.89. Found: C, 80.41, H, 13.67.

Bis[(3*S*,7*R*,11*R*)-3,7,11,15-tetramethyl-1-hexadecyl] Sulfide [(3*S*,3′*S*)-5]. This compound was prepared in a fashion identical to that used for (3*R*)-5 without purification of the intermediate alkyl bromide (3*S*)-7 (82% overall yield). TLC, ^1H NMR, ^{13}C NMR, and IR spectra identical to those for 3*R*-7: $[\alpha]^{27}_D$ = +8.73° (c = 40.3), mass spectrum (70 eV), m/e (rel inten) 595 (M^+, 0.82), 313 ($M^+ - C_{20}H_{41}$, 0.52); exact mass calcd for $C_{40}H_{82}S$ 594.6137, found 594.6151. Anal. Calcd for $C_{40}H_{82}S$: C, 80.73; H, 13.89. Found: C, 80.53, H, 13.59.

Acknowledgment is made to the Beckman Institute Research Fund for support of this work.

Supplementary Material Available: HPLC chromatograms showing the analysis of the diastereomeric purity of the amides (3*R*)-4 and (3*S*)-4 (1 page). This material is contained in 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.