Lipase-catalyzed enantioselective esterification or hydrolysis of 1-O-alkyl-3-O-tosylglycerol derivatives. Practical synthesis of (S)-(+)-1-O-hexadecyl-2,3-di-O-hexadecanoylglycero...

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Lipase-Catalyzed Enantioselective Esterification or Hydrolysis of 1-*O*-Alkyl-3-*O*-tosylglycerol Derivatives. Practical Synthesis of (*S*)-(+)-1-*O*-Hexadecyl-2,3-di-*O*-hexadecanoylglycerol, a Marine Natural Product

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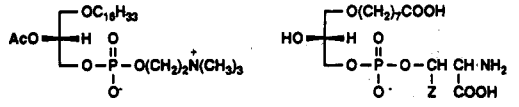
Racemic 1-*O*-alkyl-3-*O*-tosylglycerol derivatives were resolved by acylation with palmitic anhydride in the presence of *Pseudomonas fluorescens* lipase in organic media. The reverse reaction, the enzymatic hydrolysis of 1-*O*-alkyl-2-*O*-palmitoyl-3-*O*-tosylglycerols in isopropyl ether saturated with water was also highly stereoselective. An efficient and simple synthesis of the naturally occurring (*S*)-(+)-1-*O*-hexadecyl-2,3-di-*O*-hexadecanoylglycerol based on this process is reported.

Introduction

Several naturally occurring lipids characterized by the presence of an ether bond at position *sn*-1 of the glycerol backbone play important physiological roles.[1] Platelet activating factor 1, a very potent biological mediator, is the most studied representative of this class.[2] Recently, a structure of ether phosphoglyceride 2 has been proposed for a modulator of the glucocorticoid-receptor complex.[3] Alkyldiacylglycerols 3 are abundant in marine lipids and in the central nervous system.[4] Also, a series of synthetic lipids containing glycerol substituted at position 1 with a thio, oxo, amino or amidoalkyl functionality have been shown to exhibit a broad spectrum of biological activities (antineoplastic,[5] anti-HIV,[6] β-blockers[7]).



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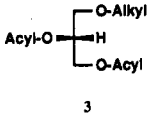

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Chiral glycerol derivatives are versatile C_3 synthons in asymmetric synthesis and accordingly several procedures have been developed for their preparation.[8] We report here the resolution of 1-*O*-alkyl-3-*O*-tosylglycerol derivatives by enzyme-catalyzed hydrolysis or esterification in organic media. Also, we report a short efficient chemoenzymatic synthesis of optically pure (*S*)-(+)-1-*O*-hexadecyl-2,3-di-*O*-hexadecanoylglycerol, a marine natural product.

Results and Discussion

1-*O*-Alkyl-3-*O*-tosylglycerols **4a-c** were readily synthesized from isopropylideneglycerol by standard methods.[9] The resolution of alcohol racemates **4a-c** was accomplished by enzyme-catalyzed acylation as shown in Table I. Racemic alcohols **4a-c** and palmitic anhydride in stoichiometric amount were dissolved in hexane/benzene 4/1. After addition of lipase from *Pseudomonas fluorescens*[10] (PFL) adsorbed on Celite, the reaction progress was monitored by HPLC. The reaction stopped completely at 50% conversion as expected for a highly stereoselective process. In control experiments under the same conditions without enzyme, no acylation was observed. The products resulting from this series of experiments were easily separated by flash chromatography. We have always found that the enzyme preferentially utilizes the *R* enantiomer. Consequently, the ester product has the *R* configuration and the remaining alcohol has the *S* configuration. The assignment of the absolute configuration of **4a** and **5a** products was based on optical rotation measurements and comparison with literature values.[11] The absolute configurations of **4b** and **4c** were determined by comparison with authentic samples prepared by regioselective reaction of the corresponding alcohol (butanol or decanol) with commercially available (*S*)-(+)-glycidyl tosylate according to the method of Guivisdalsky and Bittman.[12] The enantiomeric excess of the remaining substrate was determined by ^{19}F NMR and HPLC analysis of the corresponding (*S*)-MTPA derivatives. The ee values of the ester product were determined by ^1H NMR analysis in the presence of Eu(hfc)$_3$ as a chiral shift reagent.

Initial attempts to resolve **4a-c** involved enzymatic acylation with acetic anhydride[13] but with this acylation

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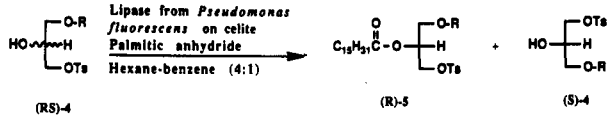
Table I. Lipase-Catalyzed Enantioselective Acylation of 1-*O*-Alkyl-3-*O*-tosylglycerol by Palmitic Anhydride[a]

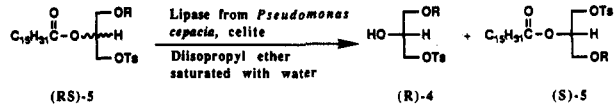


(RS)-4 (R)-5 (S)-4

substrate R	product yield,[b] %	product ee,[c] %	product abs conf	product $[\alpha]^{20}_D$,[e] deg	recovered substrate yield,[b] %	recovered substrate ee,[d] %	recovered substrate abs conf	recovered substrate $[\alpha]^{20}_D$,[e] deg
4a, R = *n*-$C_{16}H_{33}$	45	≥95	*R*	−2.13	43	95	*S*	+6.28
4b, R = *n*-$C_{10}H_{21}$	43	≥95	*R*	−1.79	42	94	*S*	+4.03
4c, R = *n*-C_4H_9	43	≥95	*R*	−2.57	45	96	*S*	+5.41

[a] Conditions: substrate (0.5 mmol), palmitic anhydride (0.5 mmol), lipase from *P. fluorescens* on Celite, hexane–benzene (4/1, 25 mL), 37 °C. [b] Isolated yield (maximum 50%). [c] Determined by ^{1}H NMR in the presence of Eu(hfc)$_3$. [d] Determined by ^{19}F NMR and HPLC (Supelcosil LC-SI) analysis of the corresponding MTPA esters. [e] (*c* 1, $CHCl_3$ except for **4a** in benzene).

Table II. Lipase-Catalyzed Enantioselective Hydrolysis of 1-*O*-Alkyl-2-*O*-palmitoyl-3-*O*-tosylglycerols[a]



(RS)-5 (R)-4 (S)-5

substrate R	product yield,[b] %	product ee,[c] %	product abs conf	product $[\alpha]^{20}_D$,[e] deg	recovered substrate yield,[b] %	recovered substrate ee,[d] %	recovered substrate abs conf	recovered substrate $[\alpha]^{20}_D$,[e] deg
5a, R = *n*-$C_{16}H_{33}$	44	99	*R*	−6.38	46	≥95	*S*	+2.03
5b, R = *n*-$C_{10}H_{21}$	47	99	*R*	−4.21	42	≥95	*S*	+1.68
5c, R = *n*-C_4H_9	45	99	*R*	−5.68	43	≥95	*S*	+2.45

[a] Conditions: substrate (0.2 mmol), lipase Amano PS from *P. cepacia* on Celite, diisopropyl ether saturated with water (20 mL), 37 °C. [b] Isolated yield (maximum 50%). [c] Determined by ^{19}F NMR and HPLC (Supelcosil LC-SI) analysis of the corresponding MTPA esters. [d] Determined by ^{1}H NMR in the presence of Eu(hfc)$_3$. [e] (*c* 1, $CHCl_3$, except for **4a** in benzene).

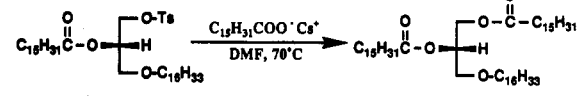
reagent, we observed instability of the product and migration of the acetate group to the adjacent position probably via the formation of a 1,3-dioxolenium ion. Also, the corresponding mesylates gave only moderate ee values (50–60%) at 50% conversion.

The enzymatic hydrolysis of racemic 1-*O*-alkyl-2-*O*-palmitoyl-3-*O*-tosylglycerols **5a–c** in isopropyl ether saturated with water was also highly enantioselective (Table II). Again, PFL or lipase PS (from *P. cepacia*, Amano) reacted preferentially with the *R* enantiomer and at the end of the reaction the alcohol produced was in the *R* form while the ester was in the *S* form. Therefore the two procedures can be considered complementary for the final product composition. This allows one to prepare the enantiomer of choice in either alcohol or ester form by selection of reactions conditions.

To show the usefulness of the above resolution we have synthesized 1-*O*-hexadecyl-2,3-di-*O*-hexadecanoylglycerol, a marine natural product recently isolated from soft coral.[14] Most natural lipids are complex mixtures and isolation of pure individual compounds is extremely difficult. Pure lipids are therefore frequently obtained by synthetic methods. The optically active (*R*)-**5a** could be readily converted into (*R*)-(−)-1-*O*-hexadecyl-2,3-di-*O*-hexadecanoylglycerol (**6**) in good yield by treatment with cesium palmitate in DMF at 70 °C (Scheme I). The same reaction with (*S*)-**5a** as the starting material gave (*S*)-(+)-**6** which is the naturally occurring enantiomer. The enantiomeric purity of **6** (ee ≥ 95%) was determined by ^{1}H NMR in the presence of Eu(hfc)$_3$.

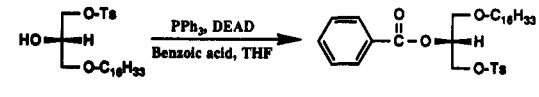
We have also investigated the recycling of the unreactive alcohol (*S*)-**4a** by inversion–esterification under Mitsunobu[15] conditions (Scheme II). The reaction of (*S*)-**4a** with

Scheme I



(S)-5a (S)-6

Scheme II



(S)-4a (R)-7

benzoic acid in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine afforded (*R*)-**7** with virtually complete inversion of configuration and without any group migration.

In summary, this paper describes an efficient enzymatic approach to the preparation of enantiomerically pure 1-*O*-alkyl-3-*O*-tosylglycerols and a practical asymmetric synthesis of a naturally occurring 1-*O*-alkyl-2,3-di-*O*-acylglycerol. The reactions are highly enantioselective and proceed without group migration, which is recognized as a serious problem in glycerol chemistry.[16] Substitution of the good leaving group tosylate by carboxylate or phosphate would give access to a large number of natural ether lipids. Further studies, including the asymmetric synthesis of ether phospholipids, are in progress in our laboratory.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 200 MHz (^{1}H), 50.29 MHz (^{13}C), and 188.15 MHz (^{19}F). Lipase from *P. fluorescens* (31.5 U/mg) was purchased from Fluka and lipase from *P. cepacia* (lipase PS30, 35 500 U/g) was obtained from Amano. HPLC was performed on a silica gel column

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(Supelcosil LC-SI, 25 mm × 4.6 mm, 5 μm particle size) employing a UV monitoring flow system at a flow rate of 1.0 mL min^{-1}. The eluant was hexane–ether (95:5). Adsorption of enzymes on Celite was performed according to the procedure reported by Bianchi et al.[13]

General Method for the Preparation of 1-*O*-Alkyl-3-*O*-tosylglycerols 4a–c. (a) Preparation of 1-*O*-Alkylglycerols. To a mixture of solketal (10.0 g, 75.64 mmol), tetrabutylammonium iodide (280 mg, 0.76 mmol), and NaH (3.63 g, 151.30 mmol) in 250 mL of dry DMF was added 113.50 mmol of the selected bromoalkane. The mixture was stirred for 24 h at room temperature under N_2. The mixture was worked up by successively adding methanol (5 mL) and water (250 mL), followed by extraction with ether. The ether extract was dried with magnesium sulfate and concentrated in vacuo. The crude product was dissolved in 250 mL of methanol/1 N HCl (9/1). The solution was stirred for 3 h at room temperature and concentrated under reduced pressure. CH_2Cl_2 (500 mL) was added and this organic layer was washed with brine, dried (Na_2SO_4), and concentrated, affording the crude 1-alkylglycerol. The product was purified by flash chromatography (CH_2Cl_2–ether, 6:4).

1-*O*-Hexadecylglycerol: 18.2 g, 76%; mp 64.0–65.0 °C; IR (KBr) 3380, 2930, 2860, 1125, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 3 H), 1.26 (m, 26 H), 1.58 (m, 2 H), 2.19 (t, J = 5 Hz, 1 H), 2.63 (d, J = 5 Hz, 1 H), 3.47 (t, J = 7 Hz, 2 H), 3.51 (m, 2 H), 3.64 (dd, J = 11 Hz, J = 5 Hz, 1 H), 3.73 (dd, J = 11 Hz, J = 4 Hz, 1 H), 3.86 (m, 1 H); ^{13}C NMR ($CDCl_3$) 14.21, 22.76, 26.16, 29.74, 31.98, 64.32, 70.40, 71.87, 72.53.

1-*O*-Decylglycerol: 13.9 g, 79%; mp 36.5–38.0 °C; IR (KBr) 3400, 2920, 2860, 1120, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 3 H), 1.27 (m, 14 H), 1.58 (m, 2 H), 2.55 (m, 1 H), 2.80 (d, J = 5 Hz, 1 H), 3.47 (t, J = 7 Hz, 2 H), 3.51 (m, 2 H), 3.64 (dd, J = 11 Hz, J = 5 Hz, 1 H), 3.73 (dd, J = 11 Hz, J = 4 Hz, 1 H), 3.87 (m, 1 H); ^{13}C NMR ($CDCl_3$) 14.08, 22.65, 26.04, 29.54, 31.86, 64.23, 70.47, 71.82, 72.43.

1-*O*-Butylglycerol: 7.85 g, 70%; IR (neat) 3400, 2960, 2920, 2860, 1110, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.92 (t, J = 7 Hz, 3 H), 1.36 (sex, J = 7 Hz, 2 H), 1.57 (quint, J = 7 Hz, 2 H), 2.21 (m, 1 H), 2.82 (m, 1 H), 3.47 (t, J = 7 Hz, 2 H), 3.51 (m, 2 H), 3.66 (m, 2 H), 3.86 (m, 1 H); ^{13}C NMR ($CDCl_3$) 13.79, 19.18, 31.57, 64.14, 70.61, 71.44, 72.31.

(b) Preparation of Tosylates 4a–c. To a solution of the selected 1-*O*-alkylglycerol (20 mmol) and DMAP (24 mg, 0.196 mmol) in dry pyridine (250 mL) was added tosyl chloride (4.19 g, 22.0 mmol), and the mixture was stirred for 72 h at 0 °C. CH_2Cl_2 (250 mL) was added and the organic layer was washed with 3 N HCl (3 × 250 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography on silica gel (hexane–ether, 4:6) to afford pure 1-*O*-alkyl-3-*O*-tosylglycerol.

1-*O*-Hexadecyl-3-*O*-tosylglycerol (4a): 6.68 g, 71%; mp 57.0–57.5 °C, lit.[11] mp 58–59 °C; IR (KBr) 3550, 2920, 2840, 1595, 1355, 1175, 840, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 3 H), 1.26 (m, 26 H), 1.51 (m, 2 H), 2.39 (d, J = 5 Hz, 1 H), 2.45 (s, 3 H), 3.40 (t, J = 7 Hz, 2 H), 3.43 (m, 2 H), 4.07 (m, 3 H), 7.35 (d, J = 8 Hz, 2 H), 7.81 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 14.21, 21.72, 22.76, 26.09, 29.74, 31.98, 68.31, 70.42, 70.58, 71.78, 127.91, 129.81, 132.64, 144.86.

1-*O*-Decyl-3-*O*-tosylglycerol (4b): 4.87 g, 63%; IR (neat) 3500, 2930, 2860, 1600, 1365, 1190, 1180, 1100, 835, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 3 H), 1.26 (m, 14 H), 1.51 (m, 2 H), 2.45 (s, 3 H), 2.50 (m, 1 H), 3.40 (t, J = 7 Hz, 2 H), 3.44 (m, 2 H), 4.07 (m, 3 H), 7.35 (d, J = 8 Hz, 2 H), 7.80 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 14.05, 21.58, 22.62, 25.95, 29.42, 31.83, 68.22, 70.41, 70.60, 71.70, 127.93, 129.84, 132.63, 144.92. Anal. Calcd for $C_{20}H_{34}O_5S$: C, 62.15; H, 8.87. Found: C, 61.87; H, 8.74.

1-*O*-Butyl-3-*O*-tosylglycerol (4c): 3.45 g, 57%; IR (neat) 3500, 2950, 2920, 2860, 1590, 1355, 1190, 1175, 1095, 825, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.89 (t, J = 7 Hz, 3 H), 1.30 (sex, J = 8 Hz, 2 H), 1.49 (quint, J = 7 Hz, 2 H), 2.44 (s, 3 H), 3.40 (t, J = 7 Hz, 2 H), 3.44 (m, 2 H), 4.06 (m, 3 H), 7.34 (d, J = 8 Hz, 2 H), 7.80 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 13.83, 19.19, 21.62, 31.55, 68.32, 70.45, 70.59, 71.44, 128.00, 129.89, 132.79, 144.97. Anal. Calcd for $C_{14}H_{22}O_5S$: C, 55.61; H, 7.33. Found: C, 55.46; H, 7.17.

Racemic 1-*O*-Alkyl-2-*O*-hexadecanoyl-3-*O*-*p*-toluenesulfonylglycerols 5a–c (General Procedure). Palmitoyl chloride (1.650 g, 6.0 mmol) was added to a solution of alcohol (±)-**4a** (5.0 mmol) and DMAP (6 mg, 0.05 mmol) in dry pyridine (20 mL). The solution was stirred for 5 h at room temperature under N_2. CH_2Cl_2 (50 mL) was added and the organic layer was washed with 3 N HCl (4 × 75 mL) and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (hexane–ether, 8:2).

1-*O*-Hexadecyl-2-*O*-hexadecanoyl-3-*O*-*p*-toluenesulfonylglycerol (5a): 3.01 g, 85%; mp 61.0–62.5 °C, lit.[11] mp 55–56 °C; IR (KBr) 2910, 2845, 1745, 1600, 1365, 1190, 1180, 840, 830, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 6 H), 1.26 (s, 52 H), 1.50 (m, 2 H), 2.24 (t, J = 7 Hz, 2 H), 2.45 (s, 3 H), 3.36 (t, J = 7 Hz, 2 H), 3.49 (d, J = 5 Hz, 2 H), 4.19 (ddd, J = 4 Hz, 5 Hz, 12 Hz, 2 H), 5.07 (q, J = 5 Hz, 1 H), 7.34 (d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 14.07, 21.60, 22.67, 24.80, 25.98, 29.68, 31.91, 34.14, 68.03, 68.10, 69.54, 71.79, 127.96, 129.82, 132.96, 144.82, 172.93.

1-*O*-Decyl-2-*O*-hexadecanoyl-3-*O*-*p*-toluenesulfonylglycerol (5b): 2.687 g, 86%, mp 36–37 °C; IR (neat) 2930, 2850, 1745, 1600, 1370, 1195, 1185, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 6 H), 1.26 (s, 40 H), 1.45 (m, 2 H), 2.24 (t, J = 7 Hz, 2 H), 2.45 (s, 3 H), 3.36 (t, J = 7 Hz, 2 H), 3.49 (d, J = 6 Hz, 2 H), 4.20 (m, 2 H), 5.08 (q, J = 5 Hz, 1 H), 7.34 (d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 14.10, 21.63, 22.68, 24.80, 25.96, 29.67, 31.90, 34.14, 68.00, 68.10, 69.51, 71.79, 127.96, 129.84, 132.98, 144.87, 172.98. Anal. Calcd for $C_{36}H_{64}O_6S$: C, 69.19; H, 10.32. Found: C, 69.28; H, 10.44.

1-*O*-Butyl-2-*O*-hexadecanoyl-3-*O*-*p*-toluenesulfonylglycerol (5c): 2.271 g, 84%; IR (neat) 2930, 2860, 1745, 1600, 1375, 1195, 1185, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 6 H), 1.26 (s, 28 H), 1.43 (m, 2 H), 2.24 (t, J = 7 Hz, 2 H), 2.45 (s, 3 H), 3.37 (t, J = 6 Hz, 2 H), 3.50 (d, J = 5 Hz, 2 H), 4.19 (m, 2 H), 5.07 (q, J = 5 Hz, 1 H), 7.24 (d, J = 8 Hz, 2 H), 7.78 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 13.81, 14.06, 19.13, 21.59, 22.65, 24.77, 29.64, 31.50, 31.88, 34.11, 67.96, 68.08, 69.47, 71.40, 127.93, 129.80, 132.85, 144.84, 172.86. Anal. Calcd for $C_{30}H_{52}O_6S$: C, 66.63; H, 9.69. Found: C, 66.91; H, 9.80.

Lipase-Catalyzed Acylation of 4a–c (General Procedure). To a stirred solution of the selected racemic alcohol **4** (0.5 mmol) and palmitic anhydride (247 mg, 0.5 mmol) in hexane/benzene (20 mL/5 mL) was added *P. fluorescens* lipase supported on Celite (35 mg, 224 units) and the reaction mixture was stirred at 37 °C. The reaction was monitored by HPLC analysis and stopped at 50% of conversion (48 h). The solid enzyme preparation was filtered off and washed with ether, and the organic layer was concentrated in vacuo. Flash chromatography (hexane–ether, gradient 4:1 to 2:3) afforded (*R*)-**5** and unreacted (*S*)-**4**.

Lipase-Catalyzed Hydrolysis of 5a–c. Racemic ester **5** (0.212 mmol), *P. cepacia* lipase (500 mg, 17750 units) and Celite (300 mg) were added to diisopropyl ether (20 mL) saturated with 0.05 N phosphate buffer (pH 7.0) and the reaction mixture was stirred at 37 °C. The reaction was monitored by HPLC analysis and stopped at 50% of conversion (25 h). The solid enzyme preparation was filtered and washed with ether, and the organic layer was concentrated in vacuo. Flash chromatography (hexane–ether, gradient 4:1 to 2:3) afforded alcohol (*R*)-**4** and unreacted (*S*)-**5**.

(*S*)-(+)-1-*O*-Hexadecyl-2,3-di-*O*-hexadecanoylglycerol (6). Cesium palmitate (165 mg, 0.425 mmol) was added to a solution of ester (*S*)-**5a** (100 mg, 0.141 mmol) in 1 mL of dry DMF and the mixture was stirred for 24 h at 70 °C. The mixture was treated with brine (10 mL) and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by flash chromatography (hexane–ether, 14:1): 68 mg, 61%; mp 56.0–57.0 °C, $[\alpha]^{20}_D$ +7.40° (*c* 1.0, $CHCl_3$), lit.[14] mp 60–61 °C, $[\alpha]^{30}_D$ + 7.50° (*c* 1.0, $CHCl_3$); IR (KBr) 2910, 2850, 1730, 1470, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 9 H), 1.26 (m, 78 H), 1.56 (m, 2 H), 2.30 (t, J = 7 Hz, 2 H), 2.32 (t, J = 7 Hz, 2 H), 3.43 (td, J = 6 Hz, J = 2 Hz, 2 H), 3.54 (d, J = 5 Hz, 2 H), 4.16 (dd, J = 7 Hz, J = 12 Hz, 1 H), 4.33 (dd, J = 4 Hz, J = 12 Hz, 1 H), 5.19 (m, 1 H); ^{13}C NMR ($CDCl_3$) 14.09, 22.68, 24.92, 24.99, 26.05, 29.69, 31.92, 34.17, 34.37, 62.78, 68.97, 70.11, 71.76, 173.11, 173.42.

(*R*)-1-*O*-Hexadecyl-2-*O*-benzoyl-3-*O*-*p*-toluenesulfonylglycerol (7). To a solution of alcohol (*S*)-**4a** (100 mg, 0.212

mmol) in dry THF (2 mL) were added triphenylphosphine (84 mg, 0.320 mmol), DEAD (74 mg, 0.425 mmol), and benzoic acid (40 mg, 0.328 mmol), and the mixture was stirred for 18 h at room temperature under N_2. The mixture was treated with 5% $NaHCO_3$ (10 mL) and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a crude product that was purified by flash chromatography (hexane–ether, 8:2): 67 mg, 55%; mp 53.0–54.0 °C; IR (KBr) 2910, 2840, 1710, 1590, 1360, 1260, 1185, 1120, 1000, 830, 810 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 3 H), 1.26 (m, 26 H), 1.51 (m, 2 H), 2.37 (s, 3 H), 3.41 (t, J = 7 Hz, 2 H), 3.64 (d, J = 6 Hz, 2 H), 4.35 (d, J = 4 Hz, 2 H), 5.30 (m, 1 H), 7.23 (m, 1 H), 7.44 (d, J = 8 Hz, 2 H), 7.50 (m, 2 H), 7.75 (d, J = 8 Hz, 2 H), 7.94 (m, 2 H); ^{13}C NMR ($CDCl_3$) 14.09, 21.59, 22.67, 25.99, 29.68, 31.91, 68.02, 68.25, 70.41, 71.86, 127.90, 128.31, 129.80, 133.23. Anal. Calcd for $C_{33}H_{50}O_6S$: C, 68.95; H, 8.77. Found: C, 69.17; H, 8.95.

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