

Synthesis of the Stereoisomers of 1-*O*-(2'-Methoxyhexadecyl)glycerol and some Phosphocholine Derivatives

Gunnel A. M. Ställberg*

Department of Organic Chemistry, AB Hässle, S-431 83 Mölndal, Sweden

Ställberg, G., 1990. Synthesis of the Stereoisomers of 1-*O*-(2'-Methoxyhexadecyl)glycerol and some Phosphocholine Derivatives. – *Acta Chem. Scand.* 44: 368–376.

All four stereoisomers of 1-*O*-(2'-methoxyhexadecyl)glycerol have been synthesized. The stereoisomer obtained from biological material was shown to have the 2'*R*, 2*S* configuration. The corresponding phospholipid (2'*R*)-1-*O*-(2'-methoxyhexadecyl)-*sn*-glycero-3-phosphocholine and its 2-*O*-acetyl and 2-*O*-methyl derivatives have also been prepared.

Glycerol ethers, which in nature occur as diester ethers and alkyl acyl phosphatides, are constituents of most animal tissues, although in greatly differing amounts. 1-*O*-Alkylglycerols with a methoxy group at the 2-position of the long hydrocarbon chain (MGE) have been found to constitute a small part of the glycerol ether content both in the neutral ether lipids and the phospholipids.¹⁻³ In Greenland shark liver oil, which is very rich in glycerol ethers, MGE constitutes about 3%. Saturated and unsaturated methoxy-substituted glycerol ethers with alkyl chains from 14 to 22 carbon atoms have been identified. The major compounds are those with 16 and 18 carbon atoms in the long alkyl chain.¹⁻³

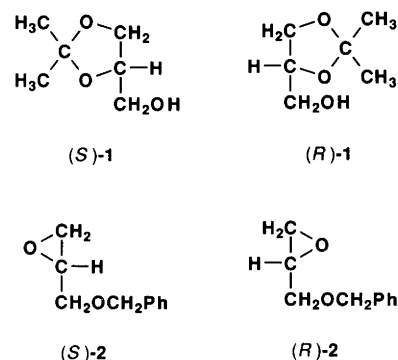
When incorporated in the feed, MGE isolated from Greenland shark liver oil has been shown to inhibit tumour growth and metastasis formation and also to stimulate the immunoreactivity in mice. Retardation of tumour growth in cultured cells has also been demonstrated.^{4,5}

The separation of methoxy-substituted glycerol ethers from unsubstituted ones in the mixture obtained from biological material is however very time-consuming. Synthetic,^{1,6} optically inactive 1-*O*-(2'-methoxyhexadecyl)glycerol was therefore used in some of the tests. This compound also showed the biological effects mentioned above but to a lesser degree. Also it was not as well tolerated as MGE from biological material. It was therefore of interest to synthesize the different stereoisomers of 1-*O*-(2'-methoxyhexadecyl)glycerol, especially that with the same configuration as MGE from biological material.

Naturally occurring alkylglycerols belong to the 1-*O*-alkyl-*sn*-glycerol series (2*S*-configuration).⁷ Rozin *et al.*^{8,9} synthesized 1-*O*-(2'-methoxyhexadecyl)-*sn*-glycerol as a mixture of 2'-epimers and also the corresponding 2-*O*-stearoylglycerophosphocholine. This paper describes the synthesis of all four stereoisomers of 1-*O*-(2'-methoxyhexa-

decyl)glycerol. The phospholipid (2'*R*)-1-*O*-(2'-methoxyhexadecyl)-*sn*-glycero-3-phosphocholine and its 2-*O*-acetyl and 2-*O*-methyl derivatives were also prepared.

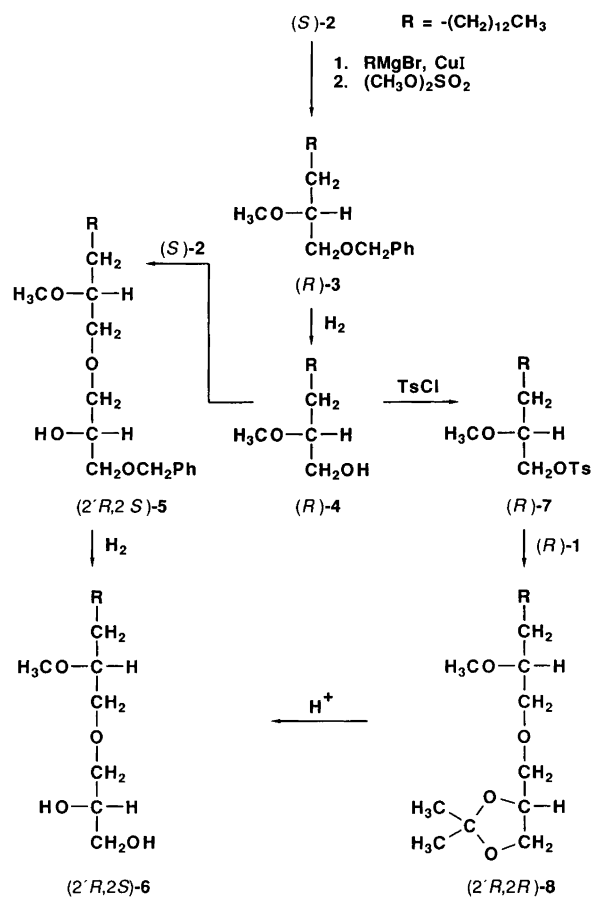
Methods. In the syntheses of the different stereoisomers of 1-*O*-(2'-methoxyhexadecyl)glycerol the isopropylidene glycerols (*S*)-1, (*R*)-1 and the epoxides (*S*)-2, (*R*)-2 were convenient chiral building blocks. (*S*)-1 and (*R*)-1 were avail-



able from D-mannitol^{10,11} and L-ascorbic acid,^{12,13} respectively. (*S*)-2 and (*R*)-2 were both obtained from (*S*)-1 via four-step¹⁴ and seven-step routes, the latter including inversion of configuration.¹⁵

By choosing the appropriate acetone (*S*)-1 or (*R*)-1 and epoxide (*S*)-2 or (*R*)-2 the four stereoisomers of 1-*O*-(2'-methoxyhexadecyl)glycerol were prepared, which is exemplified in Scheme 1 by two routes to (2'*R*)-1-*O*-(2'-methoxyhexadecyl)-*sn*-glycerol [(2'*R*, 2*S*)-6]. The intermediates (*R*)-3 and (*S*)-3 were prepared by the copper-catalysed^{16,17} reaction of tridecylmagnesium bromide with (*S*)-2 or (*R*)-2 and subsequent methylation in the same flask. (*S*)-3 was also synthesized from (*S*)-2. After epoxide opening as above, the configuration was inverted by tosylation and methanolysis.¹⁸

* (Retired). Present address: Östersnäsavägen 18, S-431 36 Mölndal, Sweden.



Scheme 1.

In addition to the routes shown in Scheme 1; (2'*R*, 2*S*)-6, was prepared from (2'*R*, 2*R*)-6 via the Walden inversion^{14,19} of the di-*p*-toluenesulfonate to the diacetate, followed by hydrolysis. The three different routes gave (2'*R*)-1-*O*-(2'-methoxyhexadecyl)-*sn*-glycerol with practically the same optical rotations as shown in Table 1.

(2'*R*)-1-*O*-(2'-Methoxyhexadecyl)-*sn*-glycero-3-phosphocholine and its 2-*O*-acetyl and 2-*O*-methyl derivatives were prepared using routes followed in the synthesis of PAF (platelet-activating factor).^{14,20}

NMR and assignment of the configuration of methoxyalkyl-glycerols isolated from biological material. The ¹H NMR spectra of the diastereomers of (2-methoxyhexadecyl)glycerol showed different patterns in the region of the three OCH₂ groups adjacent to the asymmetric centers (Fig. 1). Proton-proton decoupling and two-dimensional ¹H-¹H correlation spectroscopy (COSY) (Fig. 2) were used in the assignment of the signals.

The ¹H NMR spectrum of the methoxy-substituted hexadecylglycerol, obtained from shark liver oil, agrees with that of synthetic (2'*R*)-1-*O*-(2'-methoxyhexadecyl)-*sn*-glycerol, (2'*R*, 2*S*)-6, but not with that of (2'*S*, 2*S*)-6. The optical rotations for 1-*O*-(2'-methoxyhexadecyl)glycerol from shark liver oil²¹ and for synthetic (2'*R*, 2*S*)-6 are approximately the same (Table 1). Therefore the methoxy-substituted glycerol ethers, isolated from natural material, should be (2'*R*)-1-*O*-(2'-methoxyalkyl)-*sn*-glycerol (alkyl

Table 1. Optical rotations and melting points of methoxy-substituted hexadecylglycerols.

Glycerol ether	Prep. method ^a	[α] _D ²⁰	Melting point/°C (polymorphism)
(2' <i>R</i> ,2 <i>S</i>)-6	1	-2.6 ^b (c 1.3, CHCl ₃) +3.38 (c 5, THF)	Melting began at 40.5, then resolidification, then m.p. 44.8-45.4
(2' <i>R</i> ,2 <i>S</i>)-6	2	+3.42 (c 5, THF)	44.2-44.8, solidified to a semi-transparent mass with m.p. < 28
(2' <i>R</i> ,2 <i>S</i>)-6	3	-3.1 ^b (c 1.3, CHCl ₃) +3.39 (c 5, THF)	Melting began at 39.5, then resolidification, then m.p. 44.2-44.7
From shark liver oil	4	-3.0 ^b (c 1.3, CHCl ₃)	
(2' <i>S</i> ,2 <i>R</i>)-6	1	-3.35 (c 5, THF)	45.0-45.5, solidification at room temp. to a semi-transparent mass with m.p. ca. 27, solidification overnight to a white mass, m.p. 44.5-45.2
(2' <i>S</i> ,2 <i>S</i>)-6	1	-7.18 (c 5, THF)	< 30, 39.5-40.0
(2' <i>S</i> ,2 <i>S</i>)-6	2	-7.30 (c 5, THF)	40.2-40.8
(2' <i>R</i> ,2 <i>R</i>)-6	1	+7.24 (c 7, THF) -7.26 (c 5, CHCl ₃) -2.30 (c 5, C ₆ H ₅ CH ₃)	40.2-40.8

^a 1. via 2-methoxyhexadecyl *p*-toluenesulfonate + isopropylidene-glycerol; 2. via 2-methoxyhexadecanol + 1-benzyloxy-2,3-epoxypropane; 3. via Walden inversion of (2'*R*,2*R*)-6; 4. 2,3-*O*-isopropylidene-1-*O*-(2'-methoxy-4'-hexadecenyl)glycerol was isolated by preparative gas chromatography of the isopropylidene derivatives of a mixture of methoxy-substituted glycerol ethers. Hydrolysis and hydrogenation gave 1-*O*-(2'-methoxyhexadecyl)glycerol.²¹ ^bThe optical rotations of octadecylglycerol in *chloroform* were judged as not reliable.¹⁴

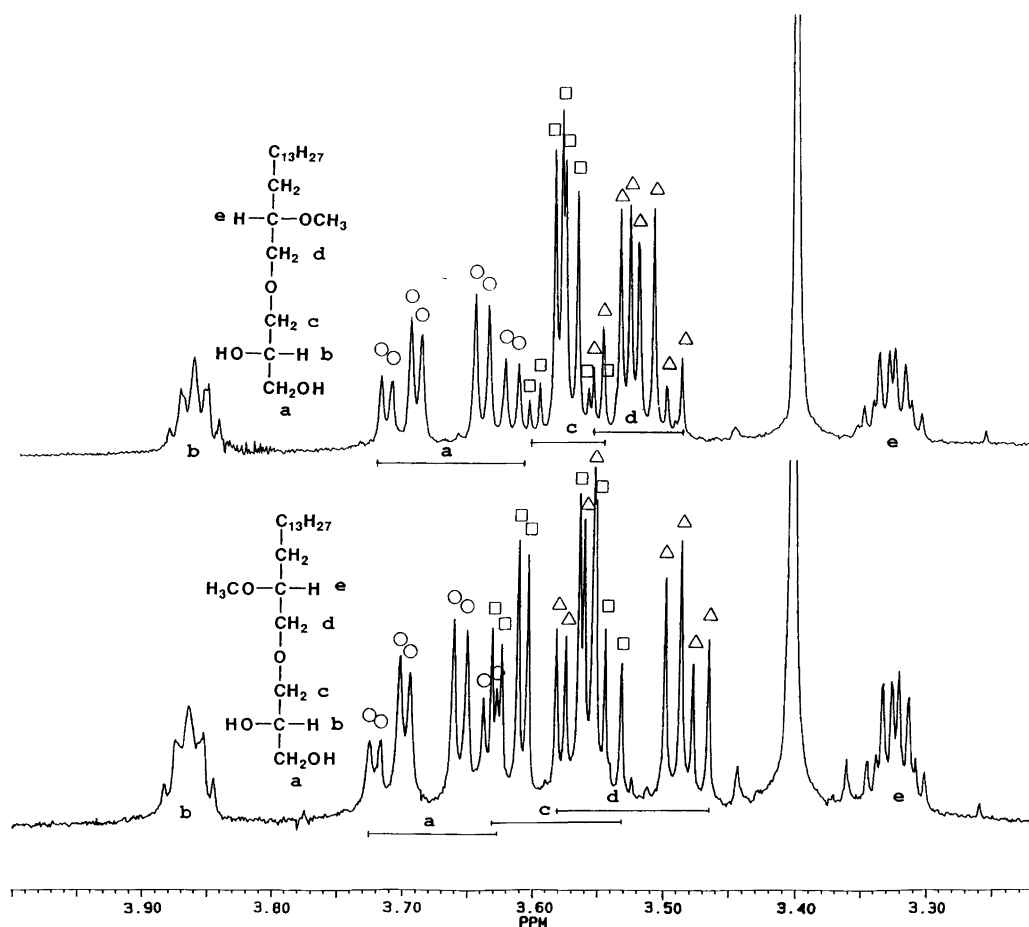


Fig. 1. Parts of the ^1H NMR (500 MHz, $\text{CDCl}_3\text{-D}_2\text{O}$) spectra of diastereomeric 1-*O*-(2'-methoxyhexadecyl)glycerols: (2'*S*,2*S*)-**6** (upper trace) and (2'*R*,2*S*)-**6** (lower trace).

also stands for 4'-alkenyl). The optical rotations for the four stereoisomers of **6** are given in Table 1 together with the melting-point data.

Mass spectra. The four stereoisomers of 1-*O*-(2'-methoxyhexadecyl)glycerol gave similar electron impact (EI) mass spectra with the following characteristic peaks: 347 ($M+1$, 0.1% rel. int.), 315 ($M+1-32$, 1.0), 283 ($M+1-64$, 0.7), 255 [$\text{CH}_2\text{CH}(\text{OCH}_3)\text{C}_{14}\text{H}_{29}$, 0.5] and 241 [$\text{CH}(\text{OCH}_3)\text{C}_{14}\text{H}_{29}$, 70].

Experimental

General methods. Syntheses and separations were monitored by TLC on Merck silica gel plates F₂₅₄, and the spots detected with UV light after the plates had been sprayed with a solution of Rhodamin 6 G in acetone. For column chromatography, silica gel Merck Si-60, 0.063–0.200 mm, or Fluka aluminium oxide type 507 C neutral was used. Gas chromatography was performed on a Hewlett-Packard 5790 chromatograph with FID and an OV-61 fused silica capillary column (25 m × 0.32 mm i.d.). The instrument was

connected to a Hewlett-Packard 3390 A integrator. Melting points were determined on a Büchi capillary melting-point apparatus. Optical rotations were measured at 20°C on a Perkin Elmer 141 or a Perkin Elmer 241 polarimeter. The NMR data were recorded either on a Varian EM-390 instrument or for the final products on a Bruker AM-500 instrument. The mass spectra were recorded on a single focussing magnetic sector instrument. Conditions: electron energy 70 eV, ion source temp. 200°C, accelerating voltage at 5 kV. The samples were introduced to the EI ion source by a liquid chromatography system, which gives reduced or no thermal decomposition.²² Fast atom bombardment (FAB) mass spectrometry²³ was used for estimating the molecular weights of the final products. These were recorded by a ZAB-HF mass spectrometer and an 11-250 data system, VG Analytical. Samples were dissolved in methanol and added to a matrix of 3-nitrobenzyl alcohol on the FAB probe tip. The acceleration voltage was 8 kV and the resolving power was 5000. Scans were acquired by scanning the magnet. The primary beam for bombardment was 7–8 kV (1.4 mA). Mass measurements were performed, adding PEG 400 (polyethylene glycol) solution to the sample/matrix, averaging several scans and then using the data system

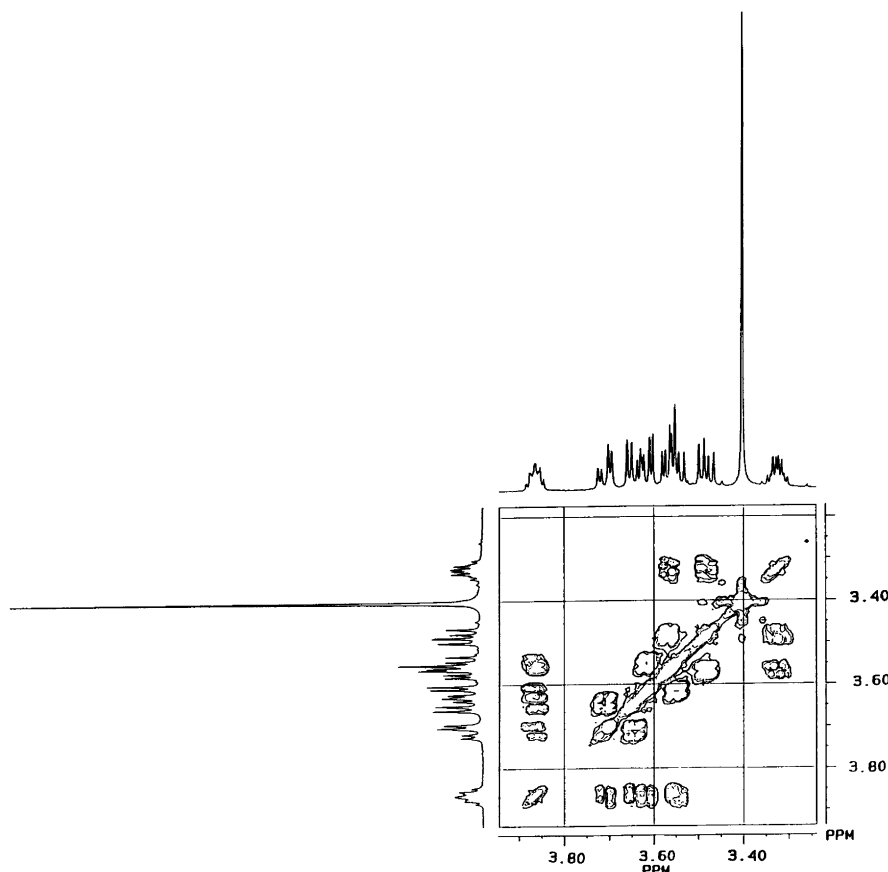


Fig. 2. Part of ^1H - ^1H correlated NMR spectrum of (2'*R*,2*S*)-6 in CDCl_3 , showing the signals from the OCH - and OCH_2 -protons.

to calculate the mass of the sample $M+1$ peak from two adjacent PEG reference peaks. The error in the range covered, using this method, was found by experiment to be within ± 30 ppm.

1,2-Isopropylidene-sn-glycerol [(*S*)-1] was prepared as described by Eibl.¹¹ $[\alpha]_{\text{D}}^{20} +14.3^\circ$ (neat), $[\alpha]_{\text{D}}^{20} +11.8^\circ$ (c 5, methanol). Lit. $[\alpha]_{\text{D}}^{20} +15.2^\circ$ (neat),¹¹ $[\alpha]_{\text{D}} +14.5^\circ$ (neat),²⁴ $[\alpha]_{\text{D}}^{25} +11.3^\circ$ (c 5.2, methanol).²⁵

2,3-Isopropylidene-sn-glycerol [(*R*)-1] was synthesized from L-ascorbic acid acetonide¹² according to the procedure given by Takano *et al.*¹³ $[\alpha]_{\text{D}}^{20} -11.1^\circ$ (c 5, methanol). Lit. $[\alpha]_{\text{D}} -11.17^\circ$ (c 5.148, methanol),¹³ $[\alpha]_{\text{D}}^{24.5} -10.76^\circ$ (c 16.9, methanol).¹²

(*S*)-*1-Benzyloxy-2,3-epoxypropane* [(*S*)-2] was prepared essentially as described by Hirth and Barner¹⁴ by the route (*S*)-1 \rightarrow 3-*O*-benzyl-1,2-isopropylidene-*sn*-glycerol \rightarrow 3-*O*-benzyl-*sn*-glycerol \rightarrow 3-*O*-benzyl-1-*O*-*p*-tolylsulfonyl-*sn*-glycerol \rightarrow (*S*)-2. $[\alpha]_{\text{D}}^{20} -15.5^\circ$ (neat), $[\alpha]_{\text{D}}^{20} -5.56^\circ$ (c 5, toluene). Lit. $[\alpha]_{\text{D}}^{20} -12.06^\circ$ (neat),²⁶ $[\alpha]_{\text{D}} -15.25^\circ$ (neat),²⁷ $[\alpha]_{\text{D}}^{20} -5.35^\circ$ (c 5, benzene).¹⁴

(*R*)-*1-Benzyloxy-2,3-epoxypropane* [(*R*)-2]. Walden inversion of 3-*O*-benzyl-*sn*-glycerol [intermediate in the (*S*)-2 synthesis] gave 1-*O*-benzyl-*sn*-glycerol,¹⁵ which, via the 3-tosyl ester, gave (*R*)-2. $[\alpha]_{\text{D}}^{20} +5.53^\circ$ (c 5, toluene). Lit. $[\alpha]_{\text{D}} +13.9^\circ$ (neat).²⁶

(*R*)-*1-Benzyloxy-2-methoxyhexadecane* [(*R*)-3]. To magnesium turnings, dried at 125°C overnight, (1.7 g, 70 mmol) and a crystal of iodine to start the reaction, was added dropwise a solution of 1-bromotridecane (14.0 g, 53 mmol) in anhydrous tetrahydrofuran (25 ml) at room temperature. The mixture was kept at 60°C for 2 h and then cooled to -25°C . Copper iodide^{16,17} (1.0 g, 5.3 mmol) was added together with a few millilitres of toluene to make the stirring more effective. After 40 min at -25°C (*S*)-2 (5.75 g, 35 mmol) was added over 10 min after which time the cooling bath was removed. After 2 h at room temperature dimethyl sulfate (25 g) was cautiously added and the mixture refluxed for 4 h. The product was taken up in diethyl ether. After evaporation of the solvents on a rotary evaporator under vacuum, 17 g of a brown liquid were left. Chromatography on silica gel, using 4% ether in light petroleum (40 – 60°C) as the eluent, gave 9.6 g (75%) of (*R*)-3 as a colourless oil. $[\alpha]_{\text{D}}^{20} +9.7^\circ$ (c 5, toluene). ^1H NMR (90 MHz, CDCl_3): δ 0.87 (3 H, t, CH_2CH_3), 1.0–1.7 [26 H, br s,

(CH₂)₁₃], 3.3–3.6 (3 H, m, OCH₂CH), 3.36 (3 H, s, OCH₃), 4.60 (2 H, s, OCH₂Ph), 7.42 (5 H, s, Ph).

(*S*)-1-Benzoyloxy-2-methoxyhexadecane [(*S*)-3] was prepared from (*R*)-2 as described above for (*R*)-3. Yield 69% [α]_D²⁰ –9.7° (c 5, toluene).

(*S*)-3 was also synthesized via (*R*)-1-benzoyloxy-2-hydroxyhexadecane, which was prepared from tridecylmagnesium bromide and (*S*)-2 (8.2 g, 50 mmol) as described for the first step in the synthesis of (*R*)-3. The mixture was worked up with aqueous ammonium chloride and diethyl ether. The product (21 g) was fractionated on a silica gel column, using light petroleum/ether (1/1) as the eluent, to give 12.5 g, which after crystallization from hexane gave 10.9 g (60%) of the hydroxy compound as white crystals, m.p. 48.5–49.0°C. [α]_D²⁰ –0.14° (c 5, toluene). ¹H NMR (90 MHz, CDCl₃): δ 0.88 (3 H, t, CH₂CH₃), 1.25 [26 H, br s, (CH₂)₁₃], 2.32 (1 H, s, OH), 3.3–3.5 (2 H, m, OCH₂CHOH), 3.72 (1 H, m, CHOH), 4.55 (2 H, s, OCH₂Ph), 7.42 (5 H, s, Ph).

The hydroxy compound was converted into the *p*-toluenesulfonate by treatment with *p*-toluenesulfonyl chloride in the presence of pyridine (room temperature, 24 h). The *p*-toluenesulfonate was crystallized twice from hexane and was then dissolved in methanol¹⁸ (5.3 g *p*-toluenesulfonate in 300 ml methanol). After 3 days at 70°C sodium hydrogen carbonate was added. Most of the methanol was distilled off, water was added and the product was extracted with hexane. The crude product was purified on a silica gel column with light petroleum (40–60°C) as the eluent. Yield 2.6 g (60%, calculated on the hydroxy compound). [α]_D²⁰ –9.7° (c 5, toluene). The ¹H NMR spectra of both (*S*)-3 preparations agreed with that of (*R*)-3.

(*R*)-2-Methoxyhexadecan-1-ol [(*R*)-4]. (*R*)-3 (8.50 g, 23.4 mmol) dissolved in tetrahydrofuran (100 ml) was hydrogenated over 10% Pd/C (0.5 g) with stirring for 1 h at room temperature. The product (6.38 g) was recrystallized from methanol. Yield 5.8 g (91%). M.p. 41–42°C, [α]_D²⁰ –7.95° (c 5, toluene). ¹H NMR (90 MHz, CDCl₃): δ 0.88 (3 H, t, CH₂CH₃), 1.3 [26 H, br s, (CH₂)₁₃], 1.95 (1 H, s, OH), 3.35 (1 H, m, CHOCH₃), 3.4 (3 H, s, OCH₃), 3.4–3.8 (2 H, m, CH₂OH).

(*S*)-2-Methoxyhexadecanol-1 [(*S*)-4]. Hydrogenation of (*S*)-3 (8.43 g) and recrystallization of the product from hexane gave 5.57 g (90%). M.p. 41–42°C, [α]_D²⁰ +7.91° (c 5, toluene), [α]_D²⁰ +0.6° (c 5, tetrahydrofuran). The ¹H NMR spectrum agreed with that of (*R*)-4.

(*R*)-2-Methoxyhexadecyl *p*-toluenesulfonate [(*R*)-7]. *p*-Toluenesulfonyl chloride (4.43 g, 23.2 mmol) was added to a stirred solution of (*R*)-4 (5.50 g, 20.2 mmol) in dichloromethane (20 ml) and anhydrous pyridine (8 ml). The mixture was left overnight at room temperature. Work-up gave 8.8 g of a colourless oil. Crystallization from hexane at

–15°C gave 8.0 g (93%) of white, hard crystals, m.p. 36.5–37.2°C. [α]_D²⁰ +3.60° (c 5, toluene). ¹H NMR (90 MHz, CDCl₃): δ 0.87 (3 H, t, CH₂CH₃), 1.3 [26 H, br s, (CH₂)₁₃], 2.48 (3 H, s, PhCH₃), 3.4 (4 H, s+m, OCH₃+OCH), 4.05 (2 H, d, CH₂OTs), 7.45 (2 H, d, Ts), 7.95 (2 H, d, Ts).

(*S*)-2-Methoxyhexadecyl *p*-toluenesulfonate [(*S*)-7] was prepared from (*S*)-4 (5.40 g, 19.8 mmol), to give 8.0 g (95%), m.p. 37–38°C, [α]_D²⁰ –3.58° (c 5, toluene). The ¹H NMR spectrum agreed with that of the (*R*)-compound.

(2'*R*)-1-O-(2'-Methoxyhexadecyl)-2,3-O-isopropylidene-sn-glycerol [(2'*R*, 2*R*)-8]. Powdered potassium hydroxide (1.0 g), *n*-heptane (50 ml) and (*R*)-1 (2.14 g, 16 mmol) were placed in a three-necked flask, fitted with a water separator, reflux condenser, dropping funnel and magnetic stirrer. The mixture was refluxed for 2 h with removal of water by azeotropic distillation. (*R*)-7 (5.53 g, 29.6 mmol), dissolved in *n*-heptane (20 ml), was added dropwise over 5 min. The mixture was refluxed for 8 h. Work-up and purification by chromatography on a silica gel column with light petroleum (40–60°C)/ether (9/1) as the eluent yielded 3.00 g (60%). [α]_D²⁰ –5.60° (c 5, tetrahydrofuran), [α]_D²⁰ –7.11° (c 5, chloroform). ¹H NMR (500 MHz, CDCl₃): δ 0.88 (3 H, t, CH₂CH₃), 1.26 [24 H, br s, (CH₂)₁₂], 1.36+1.42 [3 H+3 H, 2 s, C(CH₃)₂], 1.46 (2 H, m, CH₂CHOCH₃), 3.31 (1 H, quintet, CHOCH₃), 3.40 (3 H, s, OCH₃), 3.46–3.57 (4 H, m, CH₂OCH₂), 3.75+4.05 [2 H, 2 dd, CH₂OC(CH₃)₂], 4.26 [1 H, quintet, CHOC(CH₃)₂].

(2'*R*)-3-O-(2'-Methoxyhexadecyl)-1,2-isopropylidene-sn-glycerol [(2'*R*, 2*S*)-8]. This was prepared as above from (*S*)-1 (7.40 g, 56 mmol) and (*R*)-7 (7.96 g, 186.6 mmol). Yield 4.89 g (68%), [α]_D²⁰ +15.8° (c 5, toluene). ¹H NMR (90 MHz, CDCl₃): δ 0.88 (3 H, t, CH₂CH₃), 1.3 [26 H, br s, (CH₂)₁₃], 1.35+1.41 [3 H+3 H, 2 s, C(CH₃)₂], 3.42 (3 H, s, OCH₃), 3.2–4.45 (8 H, m, 3 OCH₂ + 2 OCH).

(2'*S*)-1-O-(2'-Methoxyhexadecyl)-2,3-isopropylidene-sn-glycerol [(2'*S*, 2*R*)-8]. This was obtained from (*R*)-1 and (*S*)-7. [α]_D²⁰ –15.9° (c 5, tetrahydrofuran), [α]_D²⁰ –9.4° (c 5, chloroform). ¹H NMR (500 MHz, CDCl₃): δ 0.88 (3 H, t, CH₂CH₃), 1.26 [24 H, br s, (CH₂)₁₂], 1.35+1.41 [3 H+3 H, 2 s, C(CH₃)₂], 1.47 (2 H, m, CH₂CH₂CHOCH₃), 3.31 (1 H, m, CHOCH₃), 3.40 (3 H, s, OCH₃), 3.42–3.63 (4 H, m, CH₂OCH₂), 3.75+4.05 [2 H, 2 m, CH₂OC(CH₃)₂], 4.27 [1 H, m, CHOC(CH₃)₂].

(2'*S*)-3-O-(2'-Methoxyhexadecyl)-1,2-isopropylidene-sn-glycerol [(2'*S*, 2*S*)-8], prepared from (*S*)-1 and (*S*)-7, had [α]_D²⁰ +6.11° (c 5, tetrahydrofuran), [α]_D²⁰ +7.65° (c 5, chloroform), [α]_D²⁰ +5.02° (c 5, toluene). ¹H NMR (90 MHz, CDCl₃): δ 0.87 (3 H, t, CH₂CH₃), 1.3 [26 H, br s, (CH₂)₁₃], 1.35+1.40 [3 H+3 H, 2 s, C(CH₃)₂], 3.42 (3 H, s, OCH₃), 3.15–4.40 (8 H, m, 3 OCH₂ + 2 OCH).

(2'R)-1-O-(2'-Methoxyhexadecyl)-sn-glycerol [(2'R, 2S)-6]. (Method 1). The isopropylidene compound (2'R, 2R)-8 (2.98 g, 7.7 mmol) was hydrolysed by treatment with a mixture of dioxane (20 ml) and 0.2 M hydrochloric acid (1 ml). The mixture was refluxed for 2 h. The solvent was distilled off on a rotary evaporator under vacuum. Water was removed by several evaporations in the presence of hexane. The residue, a yellowish oil (2.65 g) was crystallized twice from a mixture of diisopropyl ether and 2,2,4-trimethylpentane (1/1) at -15°C . Yield 2.14 g (80%), of lustrous plates. M.p. (polymorphism): the crystals began to melt at 40.5°C , solidified again at ca. 41°C ; after solidification m.p. $44.8\text{--}45.4^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} +3.38^{\circ}$ (c 5, tetrahydrofuran), $[\alpha]_{\text{D}}^{20} -2.6^{\circ}$ (c 1.3, chloroform). ^{13}C NMR (125 MHz, CDCl_3): δ 13.99, 22.60, 25.30, 29.27, 29.53, 29.60, 29.72, 30.92, 31.65 (C–C) and 57.20, 63.95, 70.71, 73.12, 73.48, 80.31 (C–O). ^1H NMR (500 MHz, CDCl_3 , COSY): δ 0.88 (3 H, t, CH_2CH_3), 1.26 [24 H, br s, $(\text{CH}_2)_{12}$], 1.47 [2 H, m, $\text{CH}(\text{OCH}_3)\text{CH}_2\text{C}$], 2.46 (1 H, s, OH), 3.11 (1 H, s, OH), 3.33 (1 H, m, CHOCH_3), 3.40 (3 H, s, OCH_3), 3.48 and 3.57 (2 H, 2 dd, $^2J_{\text{AB}}$ 10.5 $^3J_{\text{AX}}$ 6.0, $^3J_{\text{BX}}$ 3.6, $\text{OCH}_2\text{CHOCH}_3$), 3.55 and 3.62 (2 H, 2 dd, $^2J_{\text{AB}}$ 10.1, $^3J_{\text{AX}}$ 6.2, $^3J_{\text{BX}}$ 3.6, OCH_2CHOH), 3.65 and 3.71 (2 H, 2 dd, $^2J_{\text{AB}}$ 11.4, $^3J_{\text{AX}}$ 5.2, $^3J_{\text{BX}}$ 3.9, CHCH_2OH), 3.86 (1 H, m, CHOH). GLC purity 99.83%. MS(FAB) $M+1$ Found: 347.306. Calc. for $\text{C}_{20}\text{H}_{43}\text{O}_4$: 347.316.

(2'S)-1-O-(2'-Methoxyhexadecyl)-sn-glycerol [(2'S, 2S)-6]. (2'S, 2R)-8 (0.91 g, 2.5 mmol) was hydrolysed in a solution of dioxane (8 ml) and 0.02 M hydrochloric acid (1 ml) by being refluxed for 4 h. After recrystallization first from isopropyl ether/2,2,4-trimethylpentane and then from chloroform at -15°C , 0.51 g (63%) needle-shaped crystals with m.p. $40.0\text{--}40.5^{\circ}\text{C}$ were obtained. After solidification, the m.p. was $< 30^{\circ}\text{C}$, then again m.p. $40.0\text{--}40.6^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} -7.18^{\circ}$ (c 5, tetrahydrofuran). ^{13}C NMR (125 MHz, CDCl_3): δ 14.05, 22.66, 25.36, 29.33, 29.58, 29.65, 29.79, 31.02, 31.91 (C–C) and 57.28, 64.08, 70.58, 73.26, 73.57, 80.35 (C–O). ^1H NMR (500 MHz, $\text{CDCl}_3+\text{D}_2\text{O}$): δ 0.88 (3 H, t, CH_2CH_3), 1.26 [24 H, br s, $(\text{CH}_2)_{12}$], 1.46 [2 H, m, $\text{CH}(\text{OCH}_3)\text{CH}_2\text{CH}_2$], 3.33 (1 H, m, CHOCH_3), 3.40 (3 H, s, OCH_3), 3.51 and 3.54 (2 H, 2 dd, $^2J_{\text{AB}}$ 10.6, $^3J_{\text{AX}}$ 6.0, $^3J_{\text{BX}}$ 3.5, $\text{OCH}_2\text{CHOCH}_3$), 3.57 and 3.59 (2 H, 2 dd, $^2J_{\text{AB}}$ 10.0, $^3J_{\text{AX}}$ 6.4, $^3J_{\text{BX}}$ 3.6, OCH_2CHOH), 3.63 and 3.70 (2 H, 2 dd, $^2J_{\text{AB}}$ 11.4, $^3J_{\text{AX}}$ 5.2, $^3J_{\text{BX}}$ 3.9, CHOHCH_2OH), 3.86 (1 H, m, CHOH). GLC purity 99.32%.

(2'S)-3-O-(2'-Methoxyhexadecyl)-sn-glycerol [(2'S, 2R)-6]. Hydrolysis of the isopropylidene compound (2'S, 2S)-8 (2.47 g, 6.39 mmol) and two recrystallizations from isopropyl ether/2,2,4-trimethylpentane (1/1) gave 1.62 g (73%) of lustrous plates m.p. $45.0\text{--}45.5^{\circ}\text{C}$, which solidified at room temp. to a semi-transparent mass of m.p. ca. 27°C , solidified again overnight to a white mass m.p. $44.5\text{--}45.2^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} -3.35^{\circ}$ (c 5, tetrahydrofuran). ^1H NMR (500 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.26 [24 H, br s, $(\text{CH}_2)_{12}$], 1.47 (2 H, m, $\text{CH}_2\text{CHOCH}_3$), 2.20 (1 H, dd,

CH_2OH), 2.88 (1 H, d, CHOH), 3.33 (1 H, m, CHOCH_3), 3.40 (3 H, s, OCH_3), 3.48 and 3.56 (2 H, 2 dd, $\text{OCH}_2\text{CHOCH}_3$), 3.54 and 3.60 (2 H, 2 dd, OCH_2CHOH), 3.64 and 3.70 (2 H, 2 m, CH_2OH), 3.86 (1 H, m, CHOH). GLC purity 99.83%. MS(FAB): $M+1$ Found: 347.309. Calc. for $\text{C}_{20}\text{H}_{43}\text{O}_4$: 347.316.

(2'R)-3-O-(2'-Methoxyhexadecyl)-sn-glycerol [(2'R, 2R)-6]. Hydrolysis of the isopropylidene compound (2'R, 2S)-8 (4.48 g, 11.6 mmol) and crystallization from isopropyl ether and then hexane gave 3.39 g (84%) as lustrous plates. M.p. $40.2\text{--}40.8^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} +7.24^{\circ}$ (c 7, tetrahydrofuran). $[\alpha]_{\text{D}}^{20} -7.26^{\circ}$ (c 5, chloroform), $[\alpha]_{\text{D}}^{20} -2.30^{\circ}$ (c 5, toluene). ^1H NMR (500 MHz, CDCl_3): The same data as for (2'S, 2S)-6. GLC purity 99.83%. MS(FAB): $M+1$ Found: 347.301. Calc. for $\text{C}_{20}\text{H}_{43}\text{O}_4$: 347.316.

(2'R)-1-O-(2'-Methoxyhexadecyl)-3-O-benzyl-sn-glycerol [(2'R, 2S)-5]. This was prepared under conditions similar to those in Ref. 14. In a dry 50 ml, two-necked flask, fitted with a reflux condenser, dropping funnel and magnetic stirrer (R)-4 (2.75 g, 10 mmol), dissolved in anhydrous dimethylformamide (DMF) was added dropwise to a suspension of sodium hydride (55–60% in oil 0.39 g, 9–10 mmol) in DMF (3 ml). The mixture was heated on an oil bath (85°C), until the hydrogen evolution was complete. A solution of (S)-2 (1.3 g, 7.9 mmol) in 1 ml of DMF was added. The mixture was stirred for 3 h at 80°C . Most of the DMF was distilled off under vacuum on a rotary evaporator. The product was taken up in ether. The crude product, 4.1 g of a yellow oil, was fractionated on a silica gel column, using light petroleum/diethyl ether (9/1 \rightarrow 3/1) as the eluent. After unchanged 2-methoxyhexadecanol (1.29 g), the coupling product (1.48 g, 43%) was eluted. $[\alpha]_{\text{D}}^{20} +5.94^{\circ}$ (c 5, toluene). ^1H NMR (90 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.25 [26 H, br s, $(\text{CH}_2)_{13}$], 2.52 (1 H, s, OH), 3.40 (3 H, s, OCH_3), 3.2–3.7 (7 H, m, 3 $\text{OCH}_2 + \text{CHOCH}_3$), 4.00 (1 H, m, CHOH), 4.60 (2 H, s, CH_2Ph), 7.40 (5 H, s, Ph).

(2'R)-1-O-(2'-Methoxyhexadecyl)-sn-glycerol [(2'R, 2S)-6]. (Method 2). The benzyl compound (2'R, 2S)-5 (1.48 g, 3.39 mmol) was dissolved in tetrahydrofuran (35 ml) and exposed with stirring to hydrogen in the presence of 10% Pd/C catalyst (100 mg) at room temperature and atmospheric pressure. After 4 h, the catalyst was filtered off and the solvent evaporated. The product was crystallized from diethyl ether and then from isopropyl ether at -18°C . Yield 0.79 g (68%) as a white powder, m.p. $44.3\text{--}45.0^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} +3.37^{\circ}$ (c 5, tetrahydrofuran). ^1H NMR (500 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.25 [24 H, br s, $(\text{CH}_2)_{12}$], 1.47 [2 H, m, $\text{CH}(\text{OCH}_3)\text{CH}_2\text{C}$], 2.20 (1 H, dd, CH_2OH), 2.87 (1 H, d, CHOH), 3.33 (1 H, m, CHOCH_3), 3.40 (3 H, s, OCH_3), 3.48 and 3.56 (2 H, 2 dd, $\text{OCH}_2\text{CHOCH}_3$), 3.55 and 3.62 (2 H, 2 dd, OCH_2CHOH), 3.65 and 3.71 (2 H, 2 m, CH_2OH), 3.86 (1 H, m, CHOH). GLC purity 99.51%.

(2'S)-1-O-(2'-Methoxyhexadecyl)-3-O-benzyl-sn-glycerol [(2'S, 2S)-5]. This was prepared from (S)-4 (1.40 g, 5.77 mmol) and (S)-2 (1.42 g, 8.6 mmol) in the same manner as for the isomer. Yield 0.66 g (30%). $[\alpha]_D^{20} +1.93^\circ$ (c 5, toluene). $^1\text{H NMR}$ (90 MHz, CDCl_3): δ 0.87 (3 H, t, CH_2CH_3), 1.25 [26 H, br s, $(\text{CH}_2)_{13}$], 2.70 (1 H, br s, OH), 3.40 (3 H, s, OCH_3), 3.25–3.65 (7 H, m, 3 OCH_2 + CHOCH_3), 3.98 (1 H, m, CHOH), 4.60 (2 H, s, CH_2Ph), 7.45 (5 H, s, Ph).

(2'S)-1-O-(2'-Methoxyhexadecyl)-sn-glycerol [(2'S, 2S)-6]. (2'S, 2S)-5 (0.56 g, 1.28 mmol) was debenzylated in the same way as the diastereomer. After two recrystallizations from isopropyl ether/2,2,4-trimethylpentane (1/1) 0.34 g (76%) of lustrous plates were obtained. M.p. 40.2–40.8°C. $[\alpha]_D^{20} -7.3^\circ$ (c 5, tetrahydrofuran). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.26 [24 H, br s, $(\text{CH}_2)_{12}$], 1.48 (2 H, m, $\text{CHOCH}_3\text{CH}_2$), 2.18 (1 H, dd, CH_2OH), 2.86 (1 H, d, CHOH), 3.32 (1 H, m, CHOCH_3), 3.41 (3 H, s, OCH_3), 3.48–3.60 (4 H, m, CH_2OCH_2), 3.60–3.76 (2 H, m, CH_2OH), 3.87 (1 H, m, CHOH). After addition of D_2O the spectrum was the same as for the previously described (2'S, 2S)-6. GLC purity 99.72%. MS (FAB): $M + 1$. Found: 347.300. Calc. for $\text{C}_{20}\text{H}_{43}\text{O}_4$: 347.316.

(2'R)-1-O-(2'-Methoxyhexadecyl)-sn-glycerol [(2'R, 2S)-6] via Walden inversion.^{14,19} (Method 3). *p*-Toluenesulfonyl chloride (1.43 g, 7.6 mmol) was added to a solution of (2'R, 2R)-6 (1.23 g, 3.35 mmol) in anhydrous dichloromethane (25 ml) and anhydrous pyridine (2.5 ml). The mixture was refluxed for 23 h. Work-up gave 2.13 g of a yellowish oil, which according to $^1\text{H NMR}$ spectroscopy and TLC contained a mixture of di- and mono-*p*-toluenesulfonate. The treatment with *p*-toluenesulfonyl chloride was repeated (reflux for 40 h). The product was purified on a silica gel column, using light petroleum/diethyl ether (7/3) as the eluent. Yield 1.71 g (74%) of the di-*p*-toluenesulfonate. $[\alpha]_D^{20} +2.39^\circ$ (c 5, toluene). $^1\text{H NMR}$ (90 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.25 [26 H, br s, $(\text{CH}_2)_{13}$], 2.45 (6 H, s, 2 PhCH_3), 3.20 (1 H, m, CHOCH_3), 3.33 (3 H, s, OCH_3), 3.45 (2 H, d, $\text{OCH}_2\text{CHOCH}_3$), 3.63 (2 H, d, OCH_2CHOTs), 4.18 (2 H, d, CHCH_2OTs), 4.72 (1 H, quintet, CHOTs), 7.40 (4 H, d, Ts), 7.77 and 7.88 (4 H, 2 d, Ts).

The di-*p*-toluenesulfonate (1.68 g, 2.56 mmol) was treated with molten potassium acetate (1.0 g) in anhydrous dimethyl sulfoxide (6 ml) at 140°C for 30 min. Work-up gave 0.98 g of a brown–yellow oil, which was purified by chromatography on a silica gel column with light petroleum/diethyl ether (9/1 → 6/4) as the eluent, to give 0.77 g (70%) of diacetate as an almost colourless oil. This was hydrolysed in a solution of potassium hydroxide (0.35 g) in methanol/water (8/2, 5 ml). The mixture was refluxed for 30 min. The product (0.68 g) was crystallized twice from isopropyl ether/2,2,4-trimethylpentane (1/1) at –18°C. This gave 0.38 g (58%) as lustrous plates. M.p.: the crystals began to melt at 39.5°C but solidified again at this temperature; then m.p. 44.2–44.7°C. $[\alpha]_D^{20} +3.39^\circ$ (c 5, te-

tetrahydrofuran), $[\alpha]_D^{20} -3.1^\circ$ (c 1.3, chloroform). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.26 [24 H, br s, $(\text{CH}_2)_{12}$], 1.48 (2 H, m, $\text{CHOCH}_3\text{CH}_2$), 2.20 (1 H, dd, CH_2OH), 2.88 (1 H, d, CHOH), 3.32 (1 H, m, CHOCH_3), 3.40 (3 H, s, OCH_3), 3.48 and 3.56 (2 H, 2 dd, $\text{OCH}_2\text{CHOCH}_3$), 3.55 and 3.62 (2 H, 2 dd, OCH_2CHOH), 3.65 and 3.71 (2 H, 2 m, CH_2OH), 3.86 (1 H, m, CHOH). GLC purity 99.78%.

(2'R)-1-O-(2'-Methoxyhexadecyl)-3-O-trityl-sn-glycerol. A mixture of (2'R, 2S)-6 (1.14 g, 3.3 mmol), triphenylchloromethane (1.40 g, 5 mmol), anhydrous pyridine (16 ml), dichloromethane (300 ml) and powdered molecular sieves²⁸ of 4 Å pore size (24 g) was stirred for 24 h at room temperature. The mixture was filtered and the filtrate was washed with water and dried (Na_2SO_4). The solvent was evaporated. Light petroleum was added to the residue and the mixture was refluxed to precipitate triphenylmethanol. After filtration and evaporation of the light petroleum, the residue was purified by chromatography on an aluminium oxide column (type 507 C, neutral, Fluka). The tritylated glycerol ether was eluted with diethyl ether containing 2% methanol. TLC and NMR analysis showed that the product (2.0 g, 104%) contained no unchanged glycerol ether but some triphenylmethanol. The product was used in the next step without further purification.

(2'R)-1-O-(2'-Methoxyhexadecyl)-2-O-benzyl-1-O-trityl-sn-glycerol. To a solution of the tritylated glycerol ether (1.44 g, including some triphenylmethanol) in dry dimethylformamide (15 ml), was added sodium hydride as a 58% dispersion in oil (170 mg, appr. 4 mmol). The mixture was stirred for 1 h at 60°C. Benzyl chloride (2.5 ml, 18 mmol) was added at room temperature and the mixture was stirred for a further 4 h at 60°C. DMF was distilled off *in vacuo* and the residue was taken up in toluene. Chromatography of the crude product (2.07 g) on an aluminium oxide column, using light petroleum/diethyl ether (6/4) as the eluent gave 0.96 g (58%) of a benzylated product. $[\alpha]_D^{20} +6.35^\circ$ (c 5, tetrahydrofuran). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.25 [24 H, br s, $(\text{CH}_2)_{12}$], 1.45 (2 H, m, $\text{CHOCH}_3\text{CH}_2$), 3.12–3.28 (3 H, m, CHOCH_3 + CH_2OCPH_3), 3.33 (3 H, s, OCH_3), 3.4 and 3.6 (2 H + 2 H, 2 m, CH_2OCH_2), 3.76 (1 H, quintet, CHOCH_2Ph), 4.65 and 4.69 (2 H, 2 d, OCH_2Ph), 7.15–7.55 (20 H, m, 4 Ph).

(2'R)-1-O-(2'-Methoxyhexadecyl)-2-O-benzyl-sn-glycerol. The benzyl–trityl compound (328 mg, 0.48 mmol) was detriylated with hydrochloric acid in dioxane solution under the conditions given in Ref. 14. The mixture was stirred at 90°C for 2 h. Work-up gave 0.27 g of a white mass, which was chromatographed on a silica gel column. Light petroleum/ether (4/1) eluted the triphenylmethanol, and diethyl ether, the detriylated product. Yield 177 mg (84%). $[\alpha]_D^{20} +1.0^\circ$ (c 3, tetrahydrofuran). $^1\text{H NMR}$ (90 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.25 [26 H, br s, $(\text{CH}_2)_{13}$], 2.28 (1 H br s, OH), 3.25–4.00 (11 H, m + s, 3

$\text{CH}_2\text{O} + 2 \text{CHO} + \text{OCH}_3$), 4.70 and 4.80 (2 H, 2 d, CH_2Ph), 7.40 (5 H, s, Ph).

(2'R)-1-O-(2'-Methoxyhexadecyl)-2-O-benzyl-sn-glycero-3-phosphocholine. 2-Bromoethyl dichlorophosphate^{20,29} (b.p. 86–88 °C /0.1 mm Hg, 116 mg, 0.48 mmol) dissolved in dry diethyl ether (1 ml) was added to a solution of (2'R)-1-O-(2'-methoxyhexadecyl)-2-O-benzyl-sn-glycerol (147 mg, 0.337 mmol) in dry diethyl ether (3 ml) containing triethylamine (51 mg, 0.5 mmol). The mixture was stirred at room temp. overnight. Triethylamine (0.2 ml) and water (0.05 ml) was added. Stirring at room temperature was continued for 3 h. The mixture was acidified with 1 M hydrochloric acid and taken up in diethyl ether. The crude product was fractionated on a silica gel column, using chloroform/methanol (85/15) as the eluent. Yield 185 mg (88 %) of β -bromoethyl ester. This was aminated, using the conditions given by Eibl and Nicksch.³⁰ The bromoethyl ester (185 mg, 0.297 mmol) was dissolved in chloroform (1 ml), 2-propanol (1.5 ml) and acetonitrile (1.5 ml). 1 ml of a 40 % solution of trimethylamine in water was added, and the mixture was kept at 45–50 °C for 14 h. Work-up³⁰ gave 163 mg of the crude phosphocholine compound, which was purified by chromatography on a silica gel column, using chloroform/methanol/25 % aqueous ammonia (60/8/0.7 → 65/30/3) as the eluent. Yield 139 mg (78 %). $[\alpha]_D^{20} + 4.7^\circ$ (c 2.7, methanol). Crystallization from chloroform/acetone (1/10) at –15 °C gave 122 mg of lustrous crystals, m.p. 190–195 °C (decomposition). $[\alpha]_D^{20} + 4.6^\circ$ (c 3.3, methanol). ¹H NMR (500 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.25 [24 H, br s, $(\text{CH}_2)_{12}$], 1.45 (2 H, m, $\text{CH}_2\text{CHOCH}_3$), 3.16 [9 H, s, $\text{N}^+(\text{CH}_3)_3$], 3.29 (1 H, quintet, CHOCH_3), 3.38 (3 H, s, OCH_3), 3.4–3.65 (5 H, m, $\text{CH}_2\text{OCH}_2 + \text{CHOCH}_2\text{Ph}$), 3.80 (2 H, quintet, CH_2N^+), 3.91 + 3.96 (2 H, 2 m, CHCH_2OP), 4.18 (2 H, br s, POCH_2), 4.64 + 4.70 (2 H, 2 d, OCH_2Ph), 7.30 (5 H, m, Ph).

(2'R)-1-O-(2'-Methoxyhexadecyl)-sn-glycero-3-phosphocholine. 1-O-Alkyl-2-O-benzylglycerophosphocholine (98 mg, 0.163 mmol), dissolved in methanol (5 ml) was mixed with 50 mg 10 % Pd/C and hydrogenated at room temperature for 4 h. Filtration and evaporation of the solvent from the filtrate gave 77 mg of a white solid, which was purified by chromatography on a silica gel column. The debenzylated product was eluted with chloroform/methanol/25 % ammonia (20/30/1). Yield 75 mg (90 %) of a white powder. M.p. 190–220 °C (decomposition). $[\alpha]_D^{20} - 4.5^\circ$ (c 2.4, chloroform–methanol, 1:1). ¹H NMR (500 MHz, CDCl_3 – CD_3OD , 9:1): δ 0.88 (3 H, t, CH_2CH_3), 1.26 [24 H, br s, $(\text{CH}_2)_{12}$], 1.45 [2 H, m, $\text{CH}(\text{OCH}_3)\text{CH}_2\text{CH}_2$], 3.22 [9 H, s, $\text{N}^+(\text{CH}_3)_3$], 3.33 (1 H, m, CHOCH_3), 3.40 (3 H, s, OCH_3), 3.42–3.55 (5 H, m, $\text{CH}_2\text{OCH}_2 + \text{OH}$), 3.63 (2 H, t, CH_2N^+), 3.8–4.0 [3 H, m, $\text{CH}(\text{OH})\text{CH}_2\text{OP}$], 4.25 (2 H, br s, POCH_2CH_2). MS(FAB) $M + 1$, Found: 512.367. Calc. for $\text{C}_{25}\text{H}_{55}\text{NO}_7\text{P}$: 512.372.

(2'R)-1-O-(2'-Methoxyhexadecyl)-2-O-acetyl-sn-glycero-3-phosphocholine. Acetylation¹⁴ of the phosphocholine compound (51 mg, 0.1 mmol) was performed by treatment overnight at room temperature with a solution of acetic anhydride (300 mg, 2.9 mmol) and 4-dimethylaminopyridine (15 mg, 0.123 mmol) in dichloromethane (2.5 ml). After evaporation at 35 °C under vacuum, the residue was dissolved in tetrahydrofuran/water (95/5) and passed through 2 ml Amberlite MB-3 (Fluka). The solvent was distilled off *in vacuo* (with several additions of ethanol to remove the water). The residue (56 mg) was crystallized from a mixture of dichloromethane and acetone. Yield 40 mg (73 %) of a hygroscopic powder. M.p. ca. 210 °C (decomposition). $[\alpha]_D^{20} + 1.6^\circ$ (c 1.8, methanol). ¹³C NMR (125 MHz, CDCl_3): δ 13.11, 20.28, 21.68, 24.43, 28.35, 28.65, 28.69, 28.83, 30.36, 30.92 (C–C–C) and 53.35, 56.59, 58.23, 62.82, 62.86, 65.35, 69.17, 71.30, 71.36, 72.90, 79.15 (O–C, N–C) and 169.65 (C=O). ¹H NMR (500 MHz, CDCl_3 , COSY): δ 0.88 (3 H, t, CH_2CH_3), 1.25 [24 H, br s, $(\text{CH}_2)_{12}$], 1.41 [2 H, m, $\text{CH}(\text{OCH}_3)\text{CH}_2\text{CH}_2$], 2.05 (3 H, s, COCH_3), 3.26 (1 H, m, CHOCH_3), 3.36 (3 H, s, OCH_3), 3.37 [9 H, s, $\text{N}^+(\text{CH}_3)_3$], 3.39 and 3.47 (2 H, 2 dd, $\text{OCH}_2\text{CHOCH}_3$), 3.57 and 3.63 (2 H, 2 dd, $\text{CH}_2\text{OCH}_2\text{CHOCOCH}_3$), 3.81 (2 H, br m, CH_2N^+), 3.90 and 3.94 (2 H, 2 dd, CHCH_2OP), 4.28 (2 H, br m, POCH_2), 5.13 (1 H, quintet, CHOCOCH_3). MS(FAB): $M + 1$, Found: 554.371. Calc. for $\text{C}_{27}\text{H}_{57}\text{NO}_8\text{P}$: 554.382.

(2'R)-1-O-(2'-Methoxyhexadecyl)-2-O-methyl-sn-glycerol. A solution of (2'R)-1-O-(2'-methoxyhexadecyl)-3-O-trityl-sn-glycerol (contaminated with some triphenylmethanol) (0.70 g) in dimethylformamide (2 ml) was added to a suspension of sodium hydride (55–60 % NaH in oil; 83 mg) in dimethylformamide (4 ml). The reaction mixture was stirred at 90 °C for 1 h, until the hydrogen evolution was complete. Methyl iodide (2.8 g) was added and the mixture was stirred overnight at 85–90 °C after which time the solvent was evaporated under vacuum. Toluene was added and the solution washed with water and dried (Na_2SO_4). After evaporation of the solvent, 0.81 g of a brown oil remained. This was fractionated on an aluminium oxide column (Al_2O_3 , type 507 C neutral, Fluka) with light petroleum/diethyl ether (9/1 → 6/4) as the eluent. The methylated product (327 mg) was dissolved in dioxane (4 ml), containing 1 M hydrochloric acid (0.2 ml). The mixture was refluxed for 2 h. The product was taken up in dichloromethane. The crude product (0.33 g) was purified by chromatography on a silica gel column. Light petroleum/diethyl ether (9/1) eluted triphenylmethanol, and diethyl ether the detritylated glycerol ether, 137 mg (70 %, calc. on the intermediate 1-O-alkyl-2-O-methyl-3-O-trityl-sn-glycerol). $[\alpha]_D^{20} + 0.60^\circ$ (c 3, tetrahydrofuran). ¹³C NMR (125 MHz, CDCl_3): δ 14.04, 22.65, 25.34, 29.32, 29.58, 29.65, 29.77, 31.26, 31.90 (C–C–C) and 57.47, 57.76, 62.47, 71.20, 73.93, 79.96, 80.27 (C–O–). ¹H NMR (500 MHz, CDCl_3): δ 0.88 (3 H, t, CH_2CH_3), 1.26 [24 H, br s, $(\text{CH}_2)_{12}$], 1.45 [2 H, m, $\text{CH}(\text{OCH}_3)\text{CH}_2$], 2.41 (1 h, br s, OH), 3.32 (1 H, m,

CHOCH₃), 3.40 (3 H, s, OCH₃), 3.46 (3 H, s, CH₂OH-CHOCH₃), 3.42–3.52 [3 H, m, OCH₂CH(OCH₃)C₁₄H₂₉ + CH(OCH₃)CH₂OH], 3.59 [2 H, m, OCH₂CH(OCH₃)CH₂OH], 3.65+3.76 (2 H, 2 dd, CH₂OH). MS(FAB): *M*+1, Found: 361.325. Calc. for C₂₁H₄₅O₄: 361.332.

(2'*R*)-1-*O*-(2'-Methoxyhexadecyl)-2-*O*-methyl-*sn*-glycero-3-phosphocholine. This was prepared from (2'*R*)-1-*O*-(2'-methoxyhexadecyl)-2-*O*-methyl-*sn*-glycerol (72 mg, 0.20 mmol) as described above for the corresponding 2-*O*-benzyl compound. The product was purified by chromatography on a silica gel column, with chloroform/methanol/25% ammonia (65/30/3) as the eluent, to give 60 mg, which was crystallized from chloroform/acetone (1/9) at -15°C. Yield 55 mg (72%) of the phosphocholine compound as a white powder. M.p. ca. 210°C (decomposition). [α]_D²⁰ +0.8° (*c* 1.8, methanol). ¹H NMR (500 MHz, CDCl₃): δ 0.88 (3 H, t, CH₂CH₃), 1.26 [24 H, br s, (CH₂)₁₂], 1.44 (2 H, m, CH₂CH₂CHOCH₃), 3.29 [1 H, quintet, (CH₂)₁₃CHOCH₃], 3.38 (3 H, s, CHOCH₃), 3.39 [9 H, s, N⁺(CH₃)₃], 3.41 (3 H, s, CHOCH₃), 3.40–3.60 (5 H, m, CH₂OCH₂ + CHOCH₃), 3.83 (2 H, br m, CH₂N⁺), 3.85 + 3.91 [2 H, 2 m, CH(OCH₃)CH₂OP], 4.30 (2 H, br, POCH₂CH₂). MS(FAB): *M*+1, Found: 526.387. Calc. for C₂₆H₅₇NO₇P 526.387.

Acknowledgements. I am greatly indebted to AB Hässle for allowing me to use the laboratory and its facilities after my retirement. I thank my younger colleagues in the Department of Organic Chemistry of Hässle for good fellowship. Particularly I thank Dr. Bo Lamm for his interest in this work and for criticism of the manuscript. For valuable help with the assignment of some of the NMR spectra I am grateful to Dr. Ingemar Nilsson and Dr. Bob Carter. I also thank Mrs. Anita Lundblad for recording most of the 500 MHz ¹H NMR spectra and Mrs. Agneta Sköld for the GLC analyses. For the mass spectra and the estimation of molecular weights from MS(FAB) I am grateful to Dr. Gunnar Stenhagen and Mr. Weston Pimlott, Department of Medical and Physiological Chemistry, University of Göteborg.

References

- Hallgren, B. and Ställberg, G. *Acta Chem. Scand.* 21 (1967) 1519.
- Hallgren, B., Niklasson, A., Ställberg, G. and Thorin, H. *Acta Chem. Scand., Ser. B* 28 (1974) 1029.
- Hallgren, B., Niklasson, A., Ställberg, G. and Thorin, H. *Acta Chem. Scand., Ser. B* 28 (1974) 1035.
- Hallgren, B., Ställberg, G. and Boeryd, B. *Prog. Chem. Fats Other Lipids* 16 (1978) 45.
- Hallgren, B. In: Mangold, H. K. and Paltauf, F., Eds., *Ether Lipids. Biochemical and Biomedical Aspects*, Academic Press, London 1983, Chap. 15.
- Ställberg, G. *Chem. Scr.* 7 (1975) 31.
- Baer, E. and Fischer, H. O. L. *J. Biol. Chem.* 140 (1941) 397.
- Rozin, A. E., Serebrennikova, G. A. and Evstigneeva, R. P. Translated from *Bioorganicheskaya Khimiya* 1 No. 9 (1975) 1312.
- Rozin, A. E., Eremenko, L. E., Serebrennikova, G. A. and Evstigneeva, R. P. Translated from *Bioorganicheskaya Khimiya* 2 No. 11 (1976) 1547.
- Fischer, H. O. L. and Baer, E. *Helv. Chim. Acta* 17 (1934) 622.
- Eibl, H. *Chem. Phys. Lipids* 28 (1981) 1.
- Jung, M. E. and Shaw, T. J. *J. Am. Chem. Soc.* 102 (1980) 6304.
- Takano, S., Numata, H. and Ogasawara, K. *Heterocycles* 19 (1982) 327.
- Hirth, G. and Barner, R. *Helv. Chim. Acta* 65 (1982) 1059.
- Lands, W. E. M. and Zschocke, A. *J. Lipid Res.* 6 (1965) 324.
- Huynh, C., Derguini-Boumechal, F. and Linstrumelle, G. *Tetrahedron Lett.* 17 (1979) 1503.
- Kandil, A. A. and Slessor, K. N. *Can. J. Chem.* 61 (1983) 1166.
- Streitwieser, A., Jr. and Waiss, A. C., Jr. *J. Org. Chem.* 27 (1962) 290.
- Chacko, G. K. and Hanahan, D. J. *Biochim. Biophys. Acta* 164 (1968) 252.
- Heymans, F., Michel, E., Borrel, M.-C., Wichrowski, B., Godfroid, J.-J., Convert, O., Coeffier, E., Tence, M. and Benveniste, J. *Biochim. Biophys. Acta* 666 (1981) 230.
- Ställberg, G. *Thesis*, University of Gothenburg, Gothenburg, Sweden 1974.
- Alborn, H. and Stenhagen, G. *J. Chromatogr.* 323 (1985) 47.
- Barber, M., Bordoli, R. S., Sedgwick, R. D. and Tyler, A. N. *Nature (London)* 293 (1981) 270.
- LeCocq, J. and Ballou, C. E. *Biochemistry* 3 (1964) 976.
- Baldwin, J. J., Raab, A. W., Mensler, K., Arison, B. H. and McClure, D. E. *J. Org. Chem.* 43 (1978) 4876.
- Takano, S., Seya, K., Goto, E., Hiram, M. and Ogasawara, K. *Synthesis* (1983) 116.
- Takano, S., Akiyama, M. and Ogasawara, K. *Synthesis* (1985) 503.
- Kohli, V., Blöcker, H. and Köster, H. *Tetrahedron Lett.* 21 (1980) 2683.
- Hansen, W. J., Murari, R., Wedmid, J. and Baumann, W. J. *Lipids* 17 (1982) 453.
- Eibl, H. and Nicksch, A. *Chem. Phys. Lipids* 22 (1978) 1.

Received September 19, 1989.