[Chem. Pharm. Bull. 33(3)1055—1061(1985)]

Synthetic Studies on Platelet-Activating Factor (PAF)

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(Received July 10, 1984)

Chemical synthesis of platelet-activating factor (PAF, **1**) and its enantiomer was studied. Several alkoxymethyl alkenyl ketones (**5a**—**c**, $n=14$ or 16) were synthesized from Wittig–Horner reagents (**4**, $n=14$ or 16) with cyclohexanecarboxaldehyde, octylaldehyde, and benzaldehyde, and subjected to asymmetric reduction with BINAL-H[1] which is known to show high enantioselectivity in the reduction of enones. Optical purities of the reduction products (**6**) were determined from the 400 MHz proton nuclear magnetic resonance spectra after conversion of **6** to the esters (**9**) of optically active α-methoxy-α-trifluoromethyl-phenylacetic acid (MTPA). The MTPA ester of (+)-**6b** showed high optical purity (80% ee). Upon oxidative cleavage of the double bond with ozone followed by reduction with $NaBH_4$, the acetate of (+)-**6b** afforded two known compounds (**11** and **12**), which have previously been transformed into natural PAF (**1**).

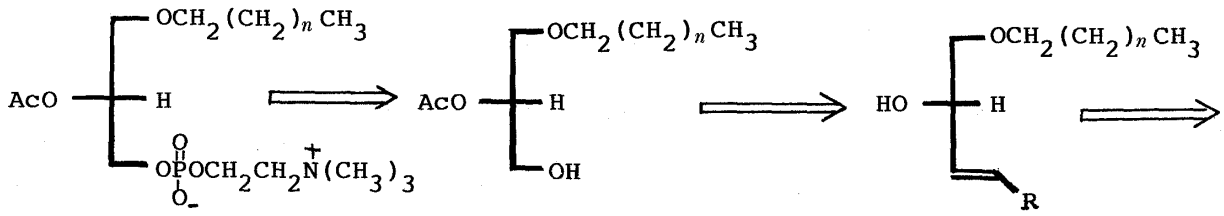
Keywords——phospholipid; platelet activating factor; enantioselective reduction; hypotension; (*R*) or (*S*)-binaphthol; platelet aggregation

Platelet-activating factor (PAF, **1**) is released from leucocytes after immunologic and nonimmunologic stimulation. The structure of this compound has been clarified by Hanahan[2] as 1-*O*-hexadecyl(or octadecyl)-2-acetyl-*sn*-glycero-3-phosphorylcholine. PAF (**1**) is able to provoke platelet and neutrophil activation, hypotension and broncho-constriction at a concentration of 10^{-8} to 10^{-11} M.[3-5] These biological activities are similar in part to those of prostaglandins (PGs). Although this compound has interesting biological activities, the low natural abundance makes further investigation difficult. Furthermore, uncertainty regarding the purity of isolated PAF makes it difficult to evaluate the biological results.

PAF (**1**) has been chemically synthesized by several research groups. These synthetic routes can be divided into three patterns; i) starting from plasmalogen isolated from bovine heart[1,6] or *Hydrologus colliei* (ginzame),[7] ii) starting from isopropylidene glycerol[8,9] derived from D-mannitol,[10,11] L-arabinose,[12] L-ascorbic acid,[13] and L-serine,[14] iii) starting from D- or L-tartaric acid.[15] These syntheses have the common feature that the starting materials are optically active natural products.

Our goal was to find a simple synthetic route to the enantiomers as well as natural PAF (**1**) and its analogues. The designed sequence involves an asymmetric reduction with the complex hydride reagent (BINAL-H) developed by Noyori.[1] The retro synthesis of PAF (**1**) is shown in Chart 1. This sequence starts with the synthesis of alkoxymethyl alkenyl ketones, followed by reduction with (+)- or (−)-BINAL-H and subsequent fission of the double bond, which is required for asymmetric reduction with high enantioselectivity.

Alkoxyacetic acids (**2**) required for the preparation of Wittig–Horner reagents were easily synthesized, in moderate yields, from 1-hexadecanol or 1-octadecanol and sodium chloroacetate, and converted to the methyl esters (**3**) with CH_2N_2. The reaction of **3** with the lithium salt prepared from dimethyl methylphosphonate and BuLi yielded Wittig–Horner reagents (**4**) in 67% ($n=14$) and 60% ($n=16$) yield. In order to examine the enantioselectivity in reduction with BINAL-H, several alkoxymethyl alkenyl ketones (**5**) were synthesized from



PAF (1)

n=14 or 16

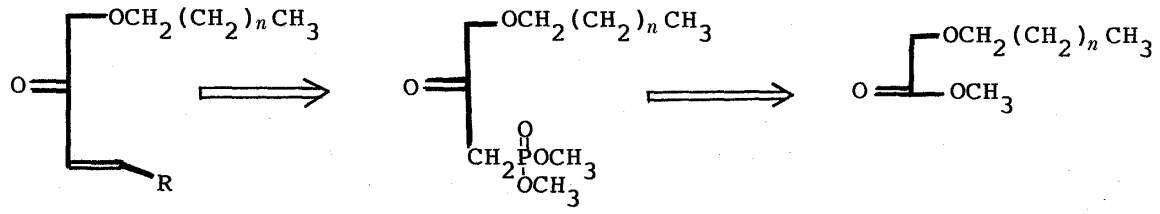
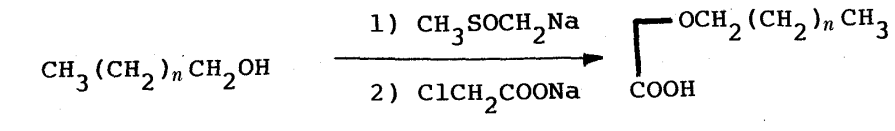


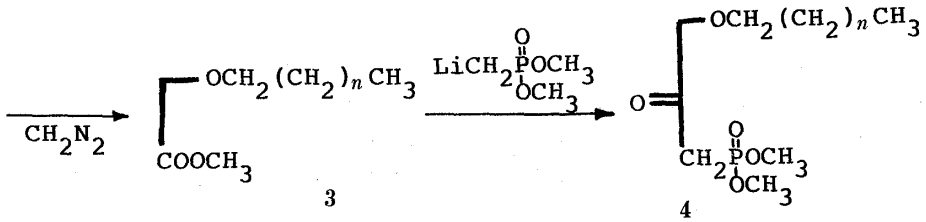
Chart 1



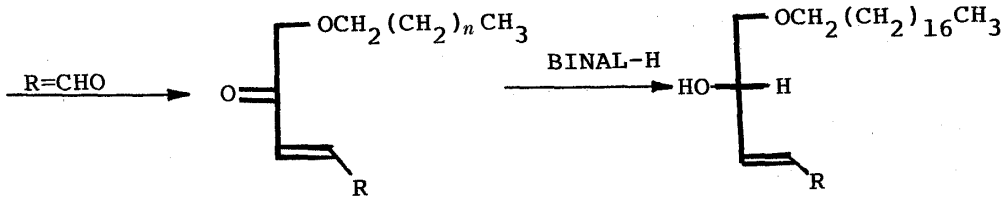
1-hexadecanol (n=14)

1-octadecanol (n=16)

2



3 4



5 6

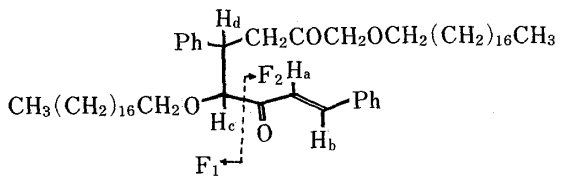
a: R=heptyl
b: R=cyclohexyl
c: R=phenyl

Chart 2

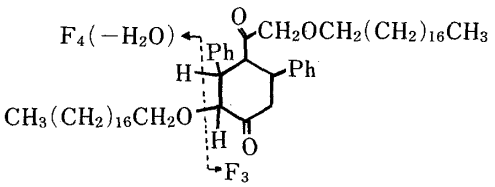
the Wittig–Horner reagents with octylaldehyde, cyclohexanecarboxaldehyde, and benzaldehyde (Chart 2).

The *trans* geometry of the double bond in the enones (**5**) was supported by the large coupling constant (J=16 Hz) in the proton nuclear magnetic resonance (^{1}H-NMR) spectra (see Experimental for the chemical shifts and coupling constants). Wittig–Horner reaction of

benzaldehyde occurred in comparatively low yield, because of the facile formation of the following two dimers (**7** and **8**) as by-products.



7



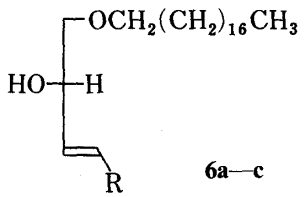
8

The structures of the two by-products were deduced on the basis of spectroscopic analysis. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **7**, the signals of H_c and H_d were observed at δ: 3.93 (1H, d, J=8 Hz) and 3.00 (1H, m), and the olefinic protons (H_a and H_b) of the enone were observed at δ: 6.96 (1H, d, J=16 Hz) and 7.60 (1H, d, J=16 Hz). The ratio of H_a (or H_b) to aromatic protons was 1 to 10. This result suggested the presence of an α,β-unsaturated ketone and two phenyl groups in the molecule. In the mass spectrum (MS), fragment peaks supporting the dimer structure (MW 828) were observed at m/z 697 (F_1) and 131 (F_2). The above data are consistent with the proposed structure (**7**).

In the ^{1}H-NMR spectrum of the other by-product (**8**), ten protons due to two phenyl groups were observed at δ: 7.24, but no olefinic protons were observed. The MS of **8** exhibited fragment peaks at m/z 558 (F_3) and 252 (F_4, 270-18), which strongly supported the dimer structure. On the basis of these data, the dimer structure was tentatively proposed for the by-product (**8**). This facile dimerization[16] was not observed in the cases of cyclohexanecarboxaldehyde and octylaldehyde.

Reduction of the enones (**5**) with BINAL-H was performed at −78 °C in tetrahydrofuran (THF), and the resulting alcohols were purified by preparative thin layer chromatography (TLC). The yield and specific rotation of each alcohol (**6**) are shown in Table I. Poor yield in this reduction may be caused by the low solubility of **5** in THF. The absolute values of pairs of alcohols obtained by reduction with (*R*)- or (*S*)-BINAL-H were not always identical. This might be ascribed to error in measurement. More accurate estimation of the optical purity was made on the basis of the relative intensity of the two methoxy functions in the 400 MHz ^{1}H-NMR spectra after conversion of the alcohols (**6**) to the MTPA esters (**9**) by treatment with

TABLE I. Yields and Specific Rotations of Alcohols (**6**)



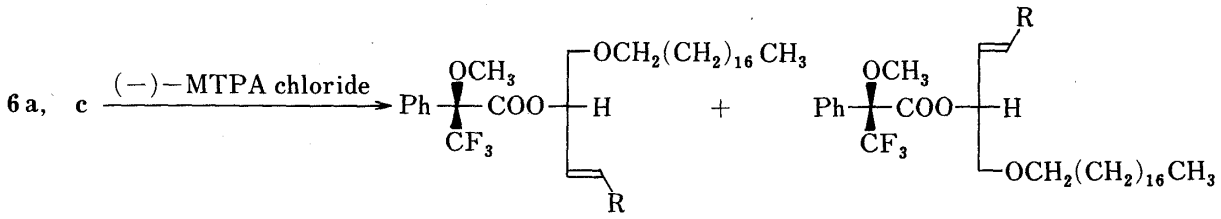
6a—c

a: R=heptyl
b: R=cyclohexyl
c: R=phenyl

Run	R	Binaphthol[a]	Yield (%)	$[\alpha]_D^{31}$ (THF)
1	Heptyl	*R*	16.8	−1.95° (*c*=1.45)
2	Heptyl	*S*	20.5	+2.35° (*c*=2.55)
3	Cyclohexyl	*R*	17.3	−2.10° (*c*=2.20)
4	Cyclohexyl	*S*	13.7	+3.58° (*c*=2.70)
5	Phenyl	*R*	33.1	−3.69° (*c*=3.91)
6	Phenyl	*S*	31.3	+2.85° (*c*=6.63)

a) (+)-(*R*)-Binaphthol $[\alpha]_D^{31}$ +30.0° (*c*=2.11, THF) and (−)-(*S*)-binaphthol $[\alpha]_D^{31}$ −31.5° (*c*=1.95, THF) were used for the preparation of (+)- and (−)-BINAL-H, respectively.

TABLE II. Optical Yields and Specific Rotations of MTPA Esters (**9**)



9a—c **a**: R=heptyl
b: R=cyclohexyl
c: R=phenyl

Run	R	Binaphthol used for reduction of **5**	Optical yield (%ee)	$[\alpha]_D^{25}$ (THF)
1	Heptyl	*R*	41.4	−16.9° (*c*=1.25)
2	Heptyl	*S*	47.6	−13.4° (*c*=1.87)
3	Cyclohexyl	*R*	71.7	−23.4° (*c*=1.13)
4	Cyclohexyl	*S*	80.6	−25.2° (*c*=1.55)
5	Phenyl	*R*	41.0	−17.5° (*c*=3.40)
6	Phenyl	*S*	49.5	−33.4° (*c*=4.75)

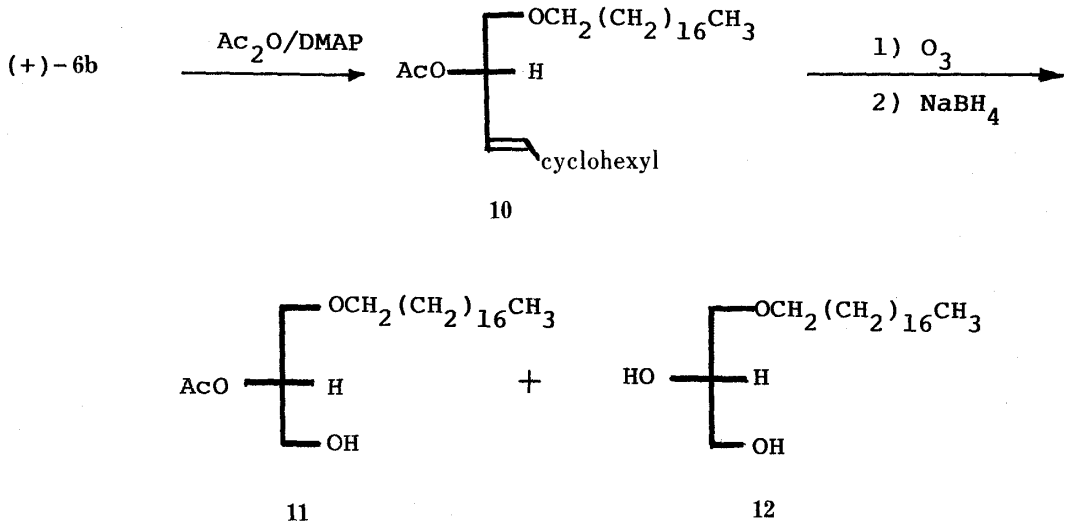


Chart 3

(−)-MTPA chloride. The optical yield and the specific rotation of the MTPA esters (**9**) are shown in Table II. Among the tested esters, **9b** (run 4 in Table II) showed the highest optical purity (80.6%ee) (see Experimental).

In the conversion of the alcohol ((+)-**6b**) (run 4 in Table I) to PAF (**1**), (+)-**6b** was first acetylated with Ac_2O in $CHCl_3$ in the presence of 4-dimethylaminopyridine (DMAP) to afford the acetate (**10**) in good yield (Chart 3). Oxidative cleavage of the double bond in **10** with ozone in a mixture of MeOH and THF, followed by reduction with $NaBH_4$, afforded the hydroxy acetate (**11**) and the deacetylated product (**12**). Compounds **11** and **12** were identical (^{1}H-NMR and the infrared (IR) spectral comparison) with the compounds synthesized and transformed into PAF (**1**) by Hirth.[9] Based on the reported values, the optical purities of **11** and **12** were estimated as 54.6%ee and 51.0%ee, respectively. The decrease of optical purity in the transformation from the alcohol ((+)-**6b**) to **11** and **12** suggests a partial racemization

at the C_2 under the reaction conditions employed.

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on a JEOL LNP-PS-100 spectrometer unless otherwise stated. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-SP polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. All organic solvent extracts were washed with brine and dried on anhydrous sodium sulfate.

Octadecyloxyacetic Acid (2, $n=16$) and Hexadecyloxyacetic Acid (2, $n=14$)——1-Octadecanol (50.0 g) in dimethyl sulfoxide (DMSO) (100 ml) was added dropwise to sodium methylsulfinylmethide [prepared from NaH (50% content, 8.87 g) and DMSO (500 ml) in the usual manner] with stirring at room temperature under a N_2 atmosphere. After 1 h, sodium chloroacetate (21.4 g) in DMSO (100 ml) was added dropwise, and the mixture was stirred for 40 h at 70 °C, then poured into ice-water (3 l), made acidic with 10% HCl and extracted with AcOEt (1 l × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (500 g). The fraction eluted with 5% AcOEt in benzene (v/v) was collected, and removal of the solvent *in vacuo* afforded **2** ($n=16$) (34.5 g, 54.5%) as a semisolid. IR ($CHCl_3$): 3400, 1700, 1245, 1140 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, $J=7$ Hz, $-CH_3$), 3.54 (2H, t, $J=6.5$ Hz, $CH_2C\underline{H}_2O$), 4.09 (2H, s, OCH_2COO). MS *m/z*: 328 (M^+), 283, 252. *Anal.* Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.25; H, 12.21.

Similarly, **2** ($n=14$) was synthesized from 1-hexadecanol and sodium chloroacetate as a semisolid in 57.8% yield. IR ($CHCl_3$): 3400, 1700, 1250, 1140 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, $J=7$ Hz, $-CH_3$), 3.53 (2H, t, $J=6.5$ Hz, $CH_2C\underline{H}_2O$), 4.09 (2H, s, OCH_2COO). MS *m/z*: 300 (M^+), 256, 224. *Anal.* Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 72.05; H, 12.25.

Methyl Hexadecyloxyacetate (3, $n=14$) and Methyl Octadecyloxyacetate (3, $n=16$)——The acids (**2**) were esterified with CH_2N_2 in ether in the usual manner to afford the esters (**3**), each in quantitative yield as a colorless oil. **3** ($n=16$); IR ($CHCl_3$): 1750, 1280, 1200, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.74 (3H, s, COOMe), 4.07 (2H, s, OCH_2COO). MS *m/z*: 342 (M^+), 250. *Anal.* Calcd for $C_{21}H_{42}O_3$: C, 73.63; H, 12.36. Found: C, 73.55; H, 12.35. **3** ($n=14$); IR ($CHCl_3$): 1745, 1210, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.74 (3H, s, COOMe), 4.06 (2H, s, OCH_2COO). MS *m/z*: 314 (M^+), 256. *Anal.* Calcd for $C_{19}H_{38}O_3$: C, 72.56; H, 12.18. Found: C, 72.72; H, 12.23.

Dimethyl 2-Oxo-4-oxa-docosanylphosphonate (4, $n=16$) and Dimethyl 2-Oxo-4-oxa-eicosanylphosphonate (4, $n=14$)——BuLi (1.5 mmol/1 ml) (15 ml) was added dropwise to a stirred solution of dimethyl methylphosphonate (2.70 g) in THF (2 ml) at −78 °C. The mixture was stirred for 0.5 h, then **3** ($n=16$) (5.00 g) in THF (20 ml) was added dropwise, and the whole was stirred for 0.5 h at −78 °C, then for 2 h at 0 °C. After completion of the reaction, the reaction mixture was diluted with ice-water (100 ml), made acidic with 5% aq. AcOH, and then extracted with CH_2Cl_2 (100 ml × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (45 g). The fraction eluted with AcOEt was collected, and removal of the solvent *in vacuo* afforded **4** ($n=16$) (4.43 g, 60%) as a colorless oil. IR ($CHCl_3$): 1730, 1465, 1260, 1140 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.18 (2H, d, $J=23$ Hz, P–CH_2–), 3.49 (2H, t, $J=7.0$ Hz, $-CH_2C\underline{H}_2O$), 3.78 (6H, d, $J=11.0$ Hz, $POCH_3 \times 2$), 4.12 (2H, s, OCH_2CO). MS *m/z*: 434 (M^+), 166.

In a similar procedure, **4** ($n=14$) was synthesized from **3** ($n=14$) in 66.7% yield. IR ($CHCl_3$): 1730, 1470, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.19 (2H, d, $J=22.0$ Hz, P–CH_2–), 3.49 (2H, t, $J=7.0$ Hz, $-CH_2C\underline{H}_2O$), 3.78 (6H, d, $J=11.0$ Hz, $POCH_3 \times 2$). MS *m/z*: 406 (M^+), 181.

Octadecyloxymethyl (*E*)-1-Nonenyl Ketone (5a, $n=16$), Hexadecyloxymethyl (*E*)-1-Nonenyl Ketone (5a, $n=14$), Octadecyloxymethyl (*E*)-2-Cyclohexylvinyl Ketone (5b, $n=16$), and Hexadecyloxymethyl (*E*)-2-Cyclohexylivinyl Ketone (5b, $n=14$)——The phosphonate (**4**, $n=16$) (500 mg) in THF (10 ml) was added dropwise with stirring to a suspension of NaH (50% content, 46 mg) in THF (10 ml) at room temperature. After 1 h, octylaldehyde (134 mg) in THF (5 ml) was added dropwise at 0 °C. The mixture was stirred for 15 h, diluted with H_2O (100 ml), made acidic with 5% aq. AcOH, and then extracted with ether (100 ml × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded a crude oil, which was subjected to column chromatography on silica gel (8 g). The fractions eluted with 20% AcOEt in $CHCl_3$ (v/v) were collected, and the solvent was evaporated off *in vacuo* to afford **5a** ($n=16$) (463 mg, 80.2%) as a semisolid.

In a similar manner, **5a** ($n=14$), **5b** ($n=16$), and **5b** ($n=14$) were synthesized from the corresponding Wittig-Horner reagents and aldehydes. **5a** ($n=16$); IR ($CHCl_3$): 1705, 1635, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (2H, t, $J=6.0$ Hz, $-CH_2C\underline{H}_2O$), 4.15 (2H, s, OCH_2CO), 6.30 (1H, d, $J=16.0$ Hz, $COC\underline{H}=CH$–), 6.99 (1H, dt, $J=16.0$, 7.0 Hz, $COCH=C\underline{H}$–). MS *m/z*: 436 (M^+), 252, 168. *Anal.* Calcd for $C_{29}H_{56}O_2$: C, 79.75; H, 12.92. Found: C, 80.10; H, 12.81. **5a** ($n=14$); 76%, IR ($CHCl_3$): 1710, 1635, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (2H, t, $J=7.0$ Hz, $CH_2C\underline{H}_2O$), 4.14 (2H, s, OCH_2CO), 6.28 (1H, d, $J=16.0$ Hz, $COC\underline{H}=CH$), 6.98 (1H, dt, $J=16.0$, 7.0 Hz, $COCH=C\underline{H}$–). MS *m/z*: 408 (M^+), 224, 168. *Anal.* Calcd for $C_{27}H_{52}O_2$: C, 79.34; H, 12.83. Found: C, 79.38; H, 12.99. **5b** ($n=16$); 90%, IR ($CHCl_3$): 1710, 1695, 1620, 1480, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.45 (2H, t, $J=6.5$ Hz, $CH_2C\underline{H}_2O$),

4.13 (2H, s, OCH_2CO), 6.20 (1H, d, J=16.0 Hz, $COCH$=CH), 6.83 (1H, dd, J=16.0, 6.5 Hz, $COCH$=CH–). MS m/z: 420 (M^+), 252, 152. *Anal.* Calcd for $C_{28}H_{52}O_2$: C, 79.93; H, 12.46. Found: C, 80.10; H, 12.63. **5b** (n=14); 90%, IR ($CHCl_3$): 1705, 1695, 1610, 1480, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.45 (2H, t, CH_2CH_2O), 4.12 (2H, s, OCH_2CO), 6.24 (1H, d, J=16.0 Hz, $COCH$=CH), 6.91 (1H, dd, J=16.0, 6.5 Hz, $COCH$=CH–). MS m/z: 392 (M^+), 309, 152. *Anal.* Calcd for $C_{26}H_{48}O_2$: C, 79.53; H, 12.32. Found: C, 79.70; H, 12.19.

Wittig–Horner Reaction of Benzaldehyde——Wittig–Horner reaction of benzaldehyde with **4** (n=16) was carried out on the same scale as that of octylaldehyde, and the crude product was subjected to careful column chromatography on silica gel (8 g). The fraction eluted with 1% AcOEt in hexane (v/v) afforded a mixture of **7** and **8**, and the fraction eluted with 3% AcOEt in hexane (v/v) afforded **5c** (53%) as a semisolid. The mixture of **7** and **8** was subjected to preparative TLC in 0.5% AcOEt in hexane (v/v). Thus, **7** was obtained as the less polar fraction in 7% yield, and **8** was obtained as the more polar fraction in 15% yield.

Octadecyloxymethyl (*E*)-Styryl Ketone (5c), 7 and 8——**5c**; IR ($CHCl_3$): 1700, 1680, 1620, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.52 (2H, t, J=7.0 Hz, CH_2CH_2O), 4.23 (2H, s, OCH_2CO), 6.97 (1H, d, J=16.0 Hz, $COCH$=CH), 7.20—7.60 (5H, m, aromatic-H), 7.70 (1H, d, J=16.0 Hz, $COCH$=CH–). MS m/z: 414 (M^+), 146, 131. *Anal.* Calcd for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.15; H, 11.23. **7**; mp 77 °C (from AcOEt–hexane), IR ($CHCl_3$); 1730, 1680, 1610, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.00 (1H, m, H_d), 3.36 (4H, br t, J=6 Hz), 3.70 (2H, d, J=4 Hz), 3.91 (2H, s), 3.93 (1H, d, J=8.0 Hz, H_c), 6.96 (1H, d, J=16.0 Hz, H_a), 7.18—7.40 (10H, m, aromatic-H), 7.60 (1H, d, J=16.0 Hz, H_b). MS m/z: 697, 414, 344, 261, 131. *Anal.* Calcd for $C_{56}H_{92}O_4$: C, 81.10; H, 11.18. Found: C, 81.27; H, 11.33. **8**; mp 73 °C (from AcOEt–hexane), IR ($CHCl_3$): 1730, 1650, 1380, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.94—3.11 (5H, m), 3.48—4.12 (7H, m), 7.24 (10H, br s, aromatic-H). MS m/z: 558, 414, 252, 218, 170. *Anal.* Calcd for $C_{56}H_{92}O_4$: C, 81.10; H, 11.18. Found: C, 81.13; H, 11.26.

Reduction of the Enones (5, n=16) with (+)- and (−)-BINAL-H——EtOH (194 mg, 4.2 mmol) in THF (2.1 ml) and (−)-(*S*)-binaphthol[17] (1.207 g, 4.2 mmol) in THF (12 ml) were successively added dropwise with stirring to a suspension of $LiAlH_4$ (157 mg, 4.2 mmol) in THF (2.5 ml) at 0 °C under an Ar atomosphere. After 1 h, **5a** (n=16) (546 mg, 1.3 mmol) in THF (1.5 ml) was added dropwise at −78 °C, and the whole was stirred for 10 h. The reaction mixture was decomposed with ether satd. with H_2O. The resulting precipitate was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was subjected to preparative TLC in $CHCl_3$–AcOEt (5:2) to give (+)-**6a** (n=16) (116.9 mg, 20.5%) as a colorless oil. In a similar manner, the enones (**5b** and **5c**) were also subjected to reduction with BINAL-H to afford (+)- and (−)-**6b** and **6c** (see Table I).

(+) and (−)-1-((*E*)-1-Nonenyl)-2-octadecyloxyethanol[(+) and (−)-6a (n=16)]——IR ($CHCl_3$): 3550, 1460, 1110, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (1H, br s, OH), 3.20—3.60 (4H, m, $OCH_2\times2$), 4.22 (1H, m, $CHOH$), 5.40 (1H, dd, J=16.0, 7.0 Hz, $CHOH$–CH=), 5.77 (1H, dt, J=16.0, 7.0 Hz, CH=CH–CH_2). MS m/z: 438 (M^+), 420, 283, 199, 155. *Anal.* Calcd for $C_{29}H_{58}O_2$ ((+)-**6a**, n=16): C, 79.38; H, 13.33. Found: C, 79.54; H, 13.58.

(+) and (−)-1-((*E*)-2-Cyclohexylvinyl)-2-octadecyloxyethanol [(+) and (−)- 6b (n=16)]——IR ($CHCl_3$): 3550, 1460, 1110, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (1H, br s, OH), 3.20—3.60 (4H, m, $OCH_2\times2$), 4.22 (1H, m, $CHOH$), 5.35 (1H, dd, J=16.0, 7.0 Hz, $CHOH$–CH=), 5.73 (1H, dd, J=16.0, 7.0 Hz, CH=CH–). MS m/z: 422 (M^+), 404, 339, 139. *Anal.* Calcd for $C_{28}H_{54}O_2$ ((+)-**6b**, n=16): C, 79.55; H, 12.88. Found: C, 79.59; H, 13.02.

(+)- and (−)-1-((*E*)-Styryl)-2-octadecyloxyethanol [(+) and (−)-6c (n=16)]——IR ($CHCl_3$): 3580, 1600, 1110, 965 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (1H, br s, OH), 3.30—3.80 (4H, m, $OCH_2\times2$), 4.48 (1H, m, $CHOH$), 6.17 (1H, dd, J=16.0, 7.0 Hz, $CHOHCH$=), 6.70 (1H, d, J=16.0 Hz, CH=CH–), 7.32 (5H, m, aromatic-H). MS m/z: 416 (M^+), 398, 177, 133. *Anal.* Calcd for $C_{28}H_{48}O_2$ ((+)-**6c**, n=16): C, 80.71; H, 11.61. Found: C, 80.96; H, 11.73.

MTPA Ester of 6——(−)-MTPA chloride (139 mg) was added to a stirred solution of the alcohol (−)-(**6a**) (200 mg) in benzene (3.4 ml) in the presence of pyridine (80 mg) under ice-water cooling. After 7 h, the reaction mixture was diluted with H_2O (20 ml), and then extracted with benzene (50 ml × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded the ester, which was purified by preparative TLC in $CHCl_3$–AcOEt (5:2) to afford the pure ester (**9a**) (290 mg, run 1 in Table II).

By a similar technique, the MTPA esters of (+)-**6a**, (+)- and (−)-**6b** and **6c** were synthesized.

Chemical shifts and relative intensities of 400 MHz ^{1}H-NMR ($CDCl_3$) methoxy signals of MTPA esters

Optically active binaphthol used for reduction of the enones (**5**)		Chemical shifts (Relative intensities)
9a	*R*	3.60 (2.12H), 3.54 (0.88H)
9a	*S*	3.60 (0.79H), 3.54 (2.21H)
9b	*R*	3.60 (2.57H), 3.54 (0.43H)
9b	*S*	3.60 (0.29H), 3.54 (2.71H)
9c	*R*	3.63 (2.11H), 3.55 (0.89H)
9c	*S*	3.63 (0.76H), 3.55 (2.24H)

Acetylation of (+)-6b——A mixture of (+)-**6b** (215 mg), Ac_2O (5 ml), 4-DMAP (50 mg) and Et_3N (2.0 g) in $CHCl_3$ (70 ml) was stirred for 7 h at room temperature. After removal of the solvent *in vacuo*, the residue was diluted with H_2O (50 ml) and extracted with AcOEt (50 ml × 3). The combined extracts were successively washed with brine (50 ml × 2), 3% HCl (50 ml) and brine (50 ml), then dried. Removal of the solvent *in vacuo* afforded the acetate (**10**, 190 mg). IR ($CHCl_3$): 1730, 1250, 1205, 1110, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, COMe), 3.30—3.55 (4H, m, OCH_2 × 2), 5.20—5.84 (3H, m, CHOAcCH=CH). MS *m/z*: 464 (M^+), 422, 404. *Anal.* Calcd for $C_{30}H_{56}O_3$: C, 77.53; H, 12.15. Found: C, 77.40; H, 12.31.

2-*O*-Acetyl-1-*O*-octadecyl-*sn*-glycerin (11) and 1-*O*-Octadecyl-*sn*-glycerin (12)——Ozone gas was bubbled into a solution of **10** (120 mg) in a mixture of MeOH (5 ml) and THF (3 ml) at −78 °C. The reaction was monitored by TLC. After completion of the reaction, $NaBH_4$ (70 mg) was added portionwise under an Ar atmosphere. The mixture was stirred for 15 h at room temperature, diluted with H_2O (30 ml), and then extracted with $CHCl_3$ (50 ml × 2). The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded an oily residue which was subjected to preparative TLC ($CHCl_3$–AcOEt 1 : 2). Thus, **11** [23 mg, mp 45 °C from hexane–AcOEt, mp 47 °C*, $[\alpha]_D^{25}$ −5.30° (*c*=3.8 benzene), −9.70 °*] and **12** [63 mg, mp 69—71 °C from hexane–AcOEt, mp 71 °C*, $[\alpha]_D^{25}$ −1.23° (*c*=5.3 THF), −2.41 °*] were obtained as colorless needles (reported values*).[9]

Acknowledgement The authors are grateful to Dr. H. Akita, Institute of Physical and Chemical Research (Riken Institute), and Dr. C. Tamura, Sankyo Co., Ltd., for measurement of the 400 MHz ^{1}H-NMR spectra. We also thank Dr. N. Nakamura, Sankyo Co., Ltd., for valuable suggestions, and Miss K. Higashi and Miss H. Miyata for their technical assistance.

References and Notes

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