40. Synthesis of Unique Ceramides and Cerebrosides Occurring in Human Epidermis

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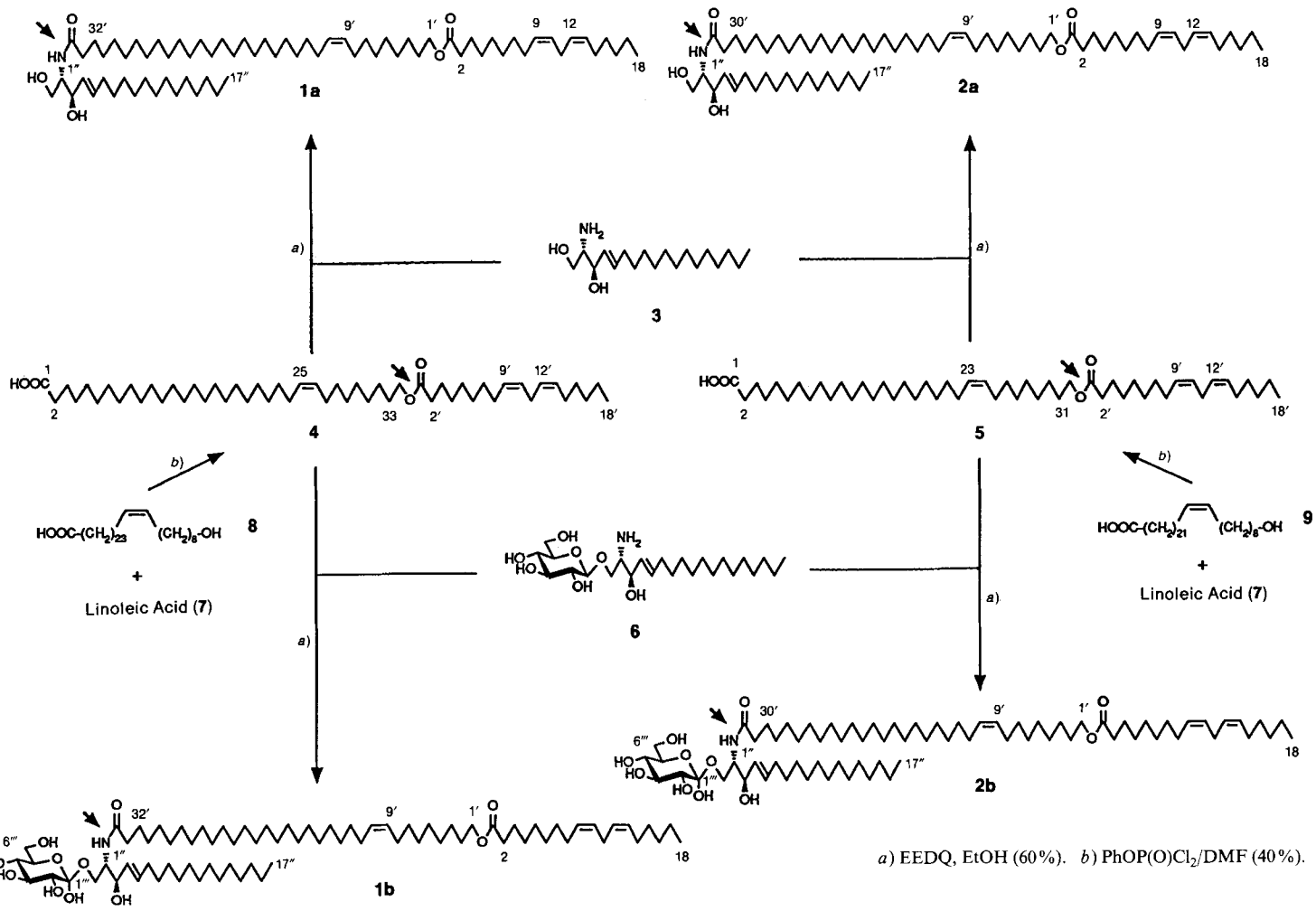
The sphingolipids **1a, b** and **2a, b**, which play important roles in epidermal barrier function, were synthesized by *N*-acylation of C_{18}-sphingosine **3** and 1-*O*-glucosylated C_{18}-sphingosine **6**, respectively, with ω-acyloxy-substituted fatty acids **4** and **5** (*Scheme 1*). These fatty acids were obtained from ω-hydroxy-substituted fatty acids **8** and **9** by esterification with linoleic acid (**7**). The C_{34}-fatty acid **8** was prepared as follows: C_{25}-Compound **18** was obtained by means of a *Wittig* reaction of C_{13}-aldehyde **13** with C_{12}-phosphonium salt **15** or of C_{12}-aldehyde **24** with C_{13}-phosphonium salt **21**, respectively, and subsequent hydrogenation and *O*-deprotection (*Scheme 2*). Alternatively, **8** was prepared *via* **30** by copper-catalyzed coupling of C_{13}-alkyl halide **19** with the *Grignard* reagent derived from C_{12}-alkyl bromide **14** (*Scheme 2*). Oxidation of **18** to aldehyde **39** and *Wittig* reaction with C_9-phosphonium salt **41** furnished the desired ω-hydroxy-substituted fatty acid **8**, after *O*-deprotection (*Scheme 3*). Similarly, *Wittig* reaction of C_{11}-phosphonium salt **22** with C_{12}-aldehyde **24** furnished C_{23}-aldehyde **40**, after hydrogenation, *O*-deprotection, and oxidation; *Wittig* reaction with compound **41** and subsequent deprotection afforded the desired C_{32}-fatty acid **9** (*Scheme 3*). An alternative strategy furnished compound **8** by a coupling reaction of alkyne **53** with ω-bromo-substituted fatty acid **52**, obtained from compounds **24** and **47** by *Wittig* reaction, hydrogenation, and introduction of bromide (*Scheme 4*). Hydrogenation (*Lindlar*'s catalyst) of the resulting C_{34}-alkyne **54** and deprotection furnished **8**.

1. Introduction. – Within the epidermis, some unique sphingolipids are found which play an important role in epidermal barrier function [1]. This barrier prevents transcutaneous H_2O loss. It is localized in the *stratum corneum*, the outermost portion of the epidermis [2]. The lipids occurring in the *stratum corneum* are organized into multiple broad bilayers, localized between the horny cells [3]. Thus, these extracellular membranes appear to constitute the permeability barrier [4].

Cholesterol, free fatty acids, and ceramides are the major components of the *stratum corneum* lipids [5]. The most unusual of the sphingolipids are acylceramides which contain a high portion of esterified linoleic acid and an amide-linked ω-hydroxy-acid with varying chain length [6]. Two examples, ceramides **1a** and **2a**, are shown in *Scheme 1*. The ω-hydroxy-acid moiety is of sufficient length to completely span a typical unit membrane, allowing the linoleate to extend into an adjacent bilayer. It was suggested that this unique structure may function in assembling and organizing the extracellular membranes of the *stratum corneum*, thus providing the intact barrier function [7]. The glucosyl-acylceramides **1b** and **2b** (*Scheme 1*), found within the *lamellar granules*, ovoid organelles of the epidermal *stratum granulosum*, play a similar role [8]. These structures probably serve to flatten and to stack up the liposomes that are observed within *lamellar granules* [1] [7] [9].

Due to their importance [1], the ceramides **1a** and **2a** and the cerebrosides **1b** and **2b** were synthesized in our laboratories for dermatological and cosmetical investigations

Scheme 1



a) EEDQ, EtOH (60%). *b*) $PhOP(O)Cl_2$/DMF (40%).

[10]. In this paper, we present efficient syntheses of these compounds. A similar compound (containing a saturated ω-hydroxy-substituted C_{30}-fatty acid) has been recently described [11].

2. Results and Discussion. – 2.1. *General. Scheme 1* shows our synthetic approach. Bond disconnection in **1a** or **2a** (as indicated by the arrows) leads to C_{18}-sphingosine **3** and to ω-acyloxy-substituted fatty acids **4** and **5**, respectively, as building blocks. Likewise, bond disconnection in **1b** or **2b** leads to glucosylated C_{18}-sphingosine **6** and to fatty acids **4** and **5**. The C_{18}-sphingosine **3** and the glucosylated C_{18}-sphingosine **6** can be prepared as previously described [12]. The ω-acyloxy-substituted fatty acids **4** and **5** consist of two different fatty acids: the ω-hydroxy-substituted fatty acids **8** and **9**, respectively, and linoleic acid **7**.

Unsaturated ω-hydroxy-substituted fatty acids **8** and **9** possess (*Z*)-configuration. Stereospecific (*Z*)-double-bond formation can be achieved by a *Wittig* reaction [13] (*Route A*) or by a stereospecific hydrogenation of triple bonds [14] (*Route B*). In the *Wittig* reaction, salt-free conditions, low temperatures, and polar aprotic solvents lead to increased formation of the (*Z*)-isomer [15]. *E.g., Bestmann et al.* [16] used sodium bis(trimethylsilyl)amide ($NaN(SiMe_3)_2$) to generate (*Z*)/(*E*) ratios of 98:2. The (*Z*)-stereospecific hydrogenation of a triple to a double bond is carried out in the presence of *Lindlar*'s catalyst [17].

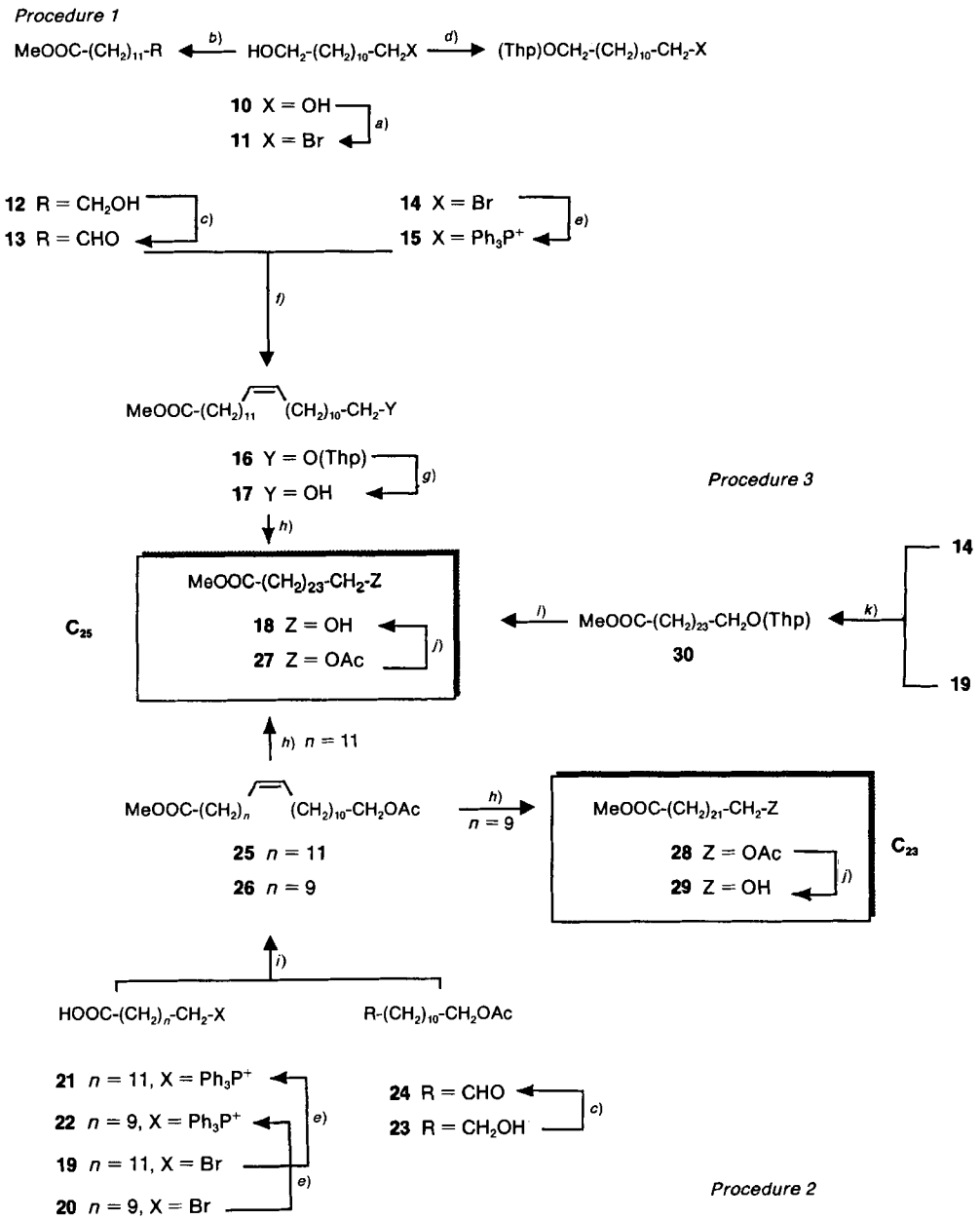
2.2. Route A *to* **8** *and* **9**. For the synthesis of **8** *via Wittig* reaction, a suitable C_{25}-building block is required which has to be prepared from shorter fragments. *Scheme 2* shows three paths (*Procedures 1–3*) which were employed to prepare this C_{25}-building block.

In *Procedure 1*, dodecane-1,12-diol (**10**) was transformed into the monobromide **11**. Substitution of bromide with cyanide and subsequent hydrolysis afforded the free acid [18], which was esterified to **12** (77% yield). Oxidation of **12** with pyridinium chlorochromate (PCC) furnished aldehyde **13**. Phosphonium salt **15**, required for chain extension, was obtained from **11** after protection of the OH group as its tetrahydro-2*H*-pyran-2-yl (Thp) ether **14** and heating with PPh_3. The coupling of **13** and **15** under salt-free conditions afforded the (*Z*)-configurated methyl ester **16**, which was immediately treated with 4-toluenesulfonic acid (TsOH) to give hydroxy-alkenoate **17** in 46% yield (for discussion of the (*Z*)-selectivity, see below). The latter was then hydrogenated over Pd/C affording the desired hydroxy-alkanoate **18** in 95% yield[1]).

In *Procedure 2*, the building blocks change roles in the *Wittig* reaction compared with *Procedure 1*. The crystalline phosphonium salts **21** and **22** were prepared by heating 13-bromotridecanoic acid [20] (**19**) or 11-bromoundecanoic acid (**20**; for the synthesis of **9**), respectively, with PPh_3. The required aldehyde **24** was obtained from alcohol **23** [21] by oxidation with PCC. *Wittig* reaction of **21** or **22** and **24** with $NaN(SiMe_3)_2$ as base and subsequent esterification with diazomethane gave compounds **25** and **26**, respectively, each in 70% yield. In contrast to *Procedure 1*, the solid phosphonium salts, *i.e.* **21** and **22**,

[1]) Following *Procedure 1*, also other starting materials could be used [19]. *E.g.*, the required aldehyde was prepared from 16-hydroxyhexadecanoic acid and treated with a C_9-phosphonium salt, but the resulting C_{25}-compound was formed in a lower yield. Starting from the phosphonium salt derived from 12-bromododecanoic acid and 13-oxotridecyl acetate, it was also possible to prepare a C_{25}-building block according to *Procedure 2*; however, the yield was lower [19].

Scheme 2



a) HBr (76%). *b*) 1. KCN; NaOH, 2. CH_2N_2, Et_2O (77%). *c*) PCC, CH_2Cl_2 (**13**, 81%; **24**, 87%). *d*) Dihydro-2*H*-pyrane, H^+ (93%). *e*) PPh_3, 140° (**15**, 81%; **21**, 100%; **22**, 100%). *f*) $NaN(SiMe_3)_2$, THF, 0°. *g*) TsOH, MeOH (55% from **13**). *h*) Pd/C, H_2, AcOEt (**18**, 95%; **27**, 100%; **28**, 100%). *i*) 1. $NaN(SiMe_3)_2$, THF; 2. CH_2N_2, Et_2O (**25**, 70%; **26**, 70%). *j*) NaOMe, MeOH (**18**, 100%; **29**, 90%). *k*) 1. Li_2CuCl_4, THF, $-20°$; 2. CH_2N_2 (34%). *l*) TsOH, MeOH (80%).

led to better yields in the *Wittig* reactions in all our investigations [10]. Subsequent catalytic hydrogenation led to acetoxy-alkanoates **27** and **28** in very high yields. The latter were deacetylated (NaOMe, dry MeOH) to the desired hydroxy-alkanoates **18** and **29**, respectively[1]).

In *Procedure 3*, the removal of the double bond is not necessary: a saturated C_{25}-compound **30** was obtained in 34% yield by the copper-catalyzed coupling (Li_2CuCl_4, $-20°$) [22] of bromo-acid **19** as its chloromagnesium salt and of the *Grignard* reagent prepared from bromo-ether **14** and Mg, followed by esterification of the crude product with diazomethane. Subsequent treatment with TsOH gave hydroxy-alkanoate **18**. The lower reactivity of compounds with longer chain led to decreasing yields.

Comparison of *Procedures 1–3* with respect to a large-scale preparation of hydroxy-alkanoates **18** and **29** showed that *Procedure 2* furnished the highest overall yields.

The required building blocks for the decisive *Wittig* reaction leading to **8** and **9** were now available (*Scheme 3*). Two alternative strategies were employed, the C_{25}-compound acting either as the phosphonium salt or as the aldehyde in the *Wittig* reaction. The phosphonium salt **34** was obtained in the following manner. Treatment of acetoxy-alkanoate **27** with KOH gave hydroxy-alkanoic acid **31** which was mesylated with methanesulfonyl chloride (→**32**) and then heated with KBr to give bromo-alkanoic acid **33**. The desired phosphonium salt **34** was obtained by heating **33** and PPh_3 at 140° for several h. The required C_9-aldehyde **37** was synthesized from nonane-1,9-diol (**35**) *via* monoacetate **36**. Unfortunately, the ensuing *Wittig* reaction between **34** and **37** in DMSO or DMF as solvents and $NaN(SiMe_3)_2$ as base at room temperature gave only 11% of the desired product **38**. It was assumed that the low solubility of phosphonium salt **34**, which was further decreased by deprotonation after addition of the base, was responsible for the low yield.

Therefore, the strategy was changed (*Scheme 3*). Oxidation of **18** or **29** with PCC gave aldehydes **39** and **40** in 72 and 80% yield, respectively. For high (*Z*)-selectivity in their *Wittig* reaction with phosphonium salt **41** [23], salt-free conditions, an aprotic polar solvent (THF), and low temperatures were chosen. All components **39–41** were soluble in THF and gave, *via* the crude *Wittig* products **42** and **43**, respectively, the hydroxy-alkenoates **44** and **45**, respectively, in 55% yield (based on **39** or **40**). After ester hydrolysis, the desired ω-hydroxy-substituted fatty acids **8** and **9** were obtained in 95 and 93% yield, respectively.

2.3. Route B *to* **8**. For this route, a suitable C_{24}-compound and a C_{10}-compound with a terminal triple bond were required (*Scheme 4*). Thus, phosphonium salt **47** was prepared by heating 12-bromododecanoic acid (**46**) with PPh_3. *Wittig* reaction of **47** with aldehyde **24** and subsequent esterification with diazomethane afforded the acetoxy-alkenoate **48** in 68% yield. Hydrogenation (→**49**), NaOH treatment (→**50**[2])), mesylation (→**51**), and KBr treatment yielded bromo-alkanoic acid **52**. Coupling of **52** with alkyne **53** [25] was carried out in hexamethylphosphoramide (HMPT) in the presence of BuLi as base. Since separation of the starting acid **52** from the produced C_{34}-fatty acid was not possible, the crude product was esterified with diazomethane to provide **54**. Next, the triple bond was hydrogenated in the presence of *Lindlar*'s catalyst and quinoline, furnishing **42** in 97% yield, and finally, the latter was converted to **8** *via* **44** as described above.

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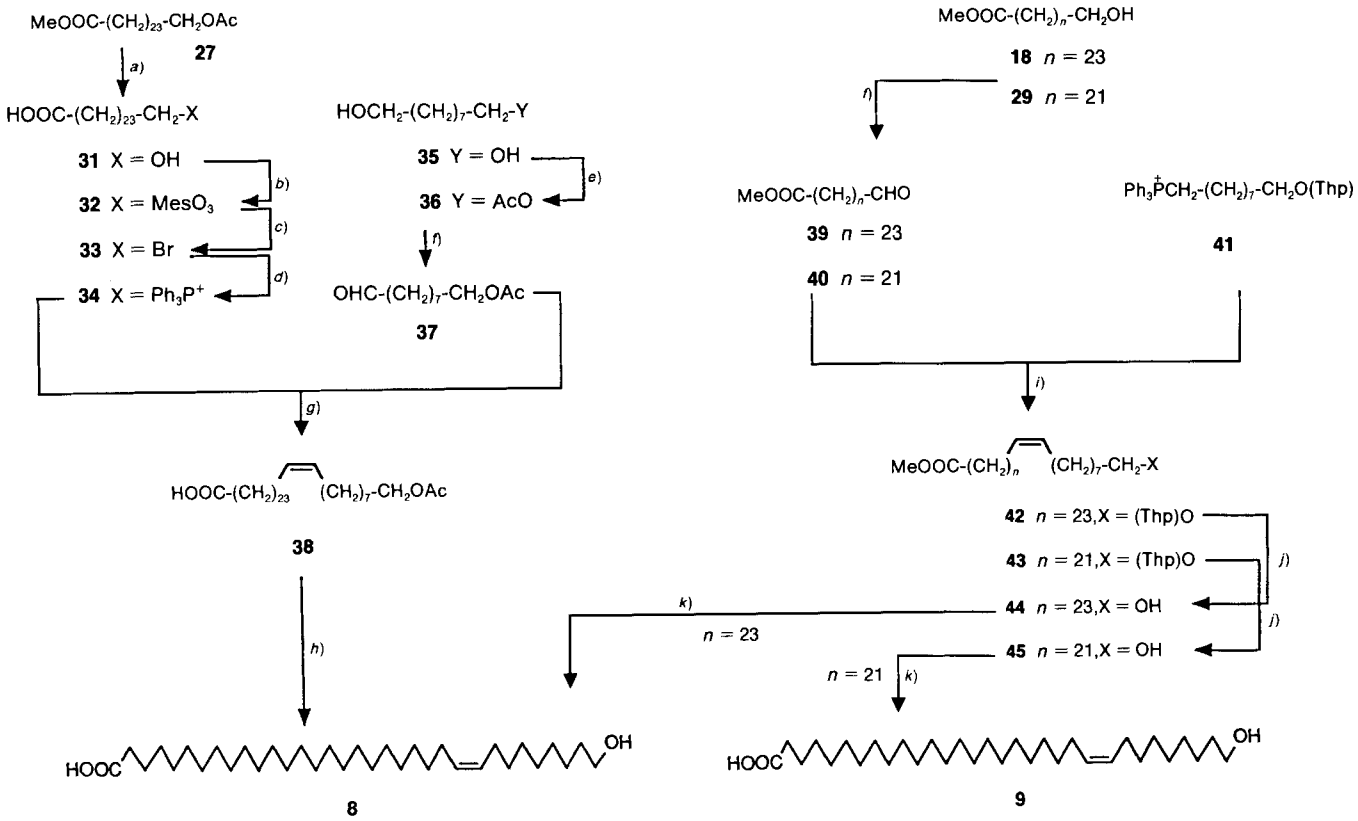
[2]) For a synthesis of **50** *via* a different strategy, see [24].

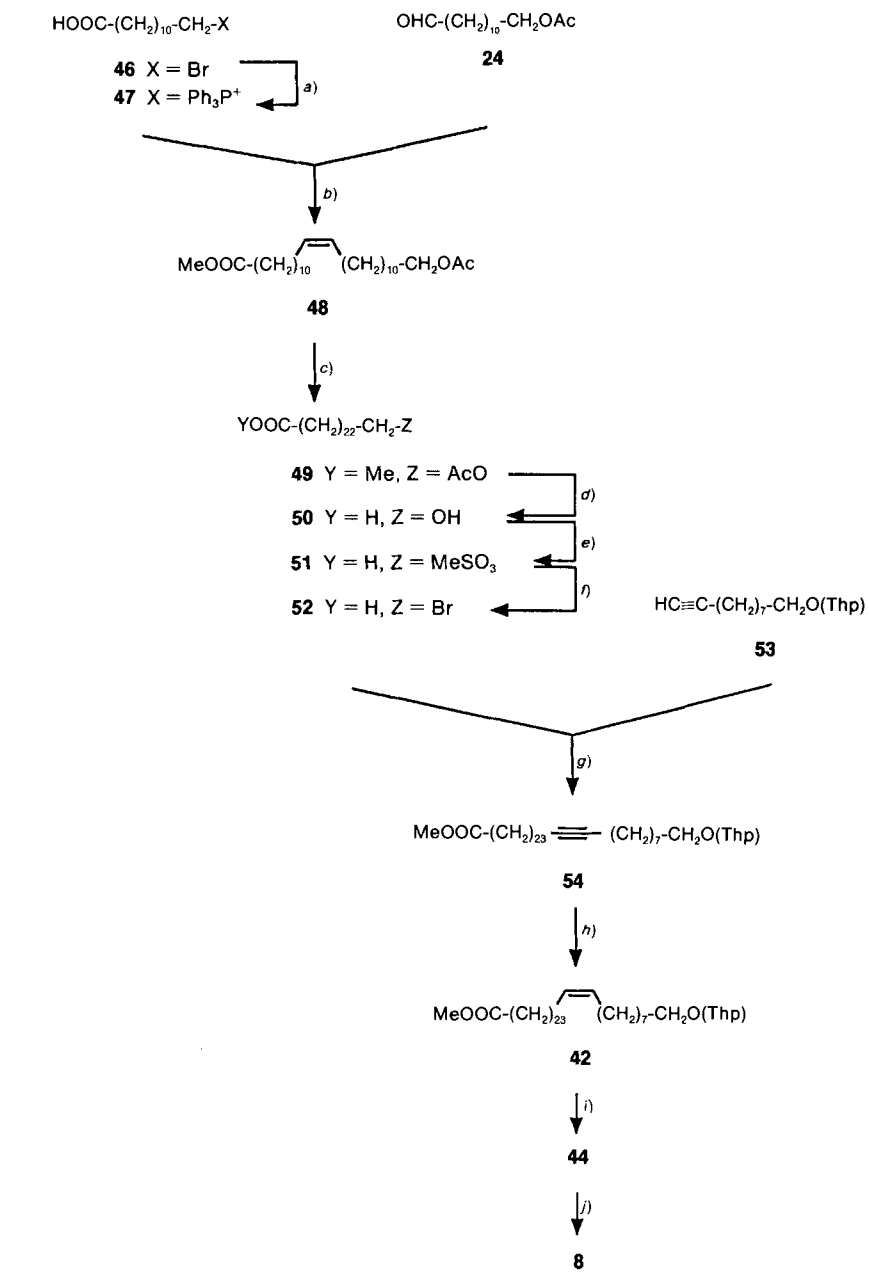
Scheme 3



a) KOH, MeOH (78%). *b*) $MeSO_2Cl$, pyridine (69%). *c*) KBr, toluene, H_2O (81%). *d*) PPh_3, 140° (93%). *e*) AcOH, H_2O (56%). *f*) PCC, CH_2Cl_2 (**37**, 79%; **39**, 72%; **40**, 80%). *g*) $NaN(SiMe_3)_2$, DMSO/DMF (11%). *h*) KOH, MeOH. *i*) $NaN(SiMe_3)_2$, THF, $-20°$. *j*) TsOH, MeOH (**44**, 55% from **39**; **45**, 55% from **40**). *k*) NaOH, MeOH (**8**, 95%; **9**, 93%).

Scheme 4

Route B



a) PPh_3, 140° (100%). *b*) 1. $NaN(SiMe_3)_2$, THF; 2. CH_2N_2, Et_2O (68%). *c*) Pd/C, H_2, AcOEt (97%). *d*) NaOH, MeOH (95%). *e*) $MeSO_2Cl$, pyridine (70%). *f*) KBr (86%). *g*) 1. BuLi, HMPT; 2. CH_2N_2, Et_2O (53%). *h*) *Lindlar*'s catalyst, quinoline, H_2 (97%). *i*) TsOH, MeOH (88%). *j*) NaOH, MeOH (95%).

The overall yield *via Route B* was lower than *via Route A*, but the difference is not significant. *Route B* can also be used for large-scale preparations of **8**.

2.3. *Physical Data of the Fatty-Acid Derivatives.* The physical data of compounds **42** and **44** prepared according to *Route A* were identical to those obtained according to *Route B*. The configuration of the double bonds of ω-hydroxy-substituted fatty acids **8** and **9** was determined by ^{1}H-NMR and IR spectra.

In the ^{1}H-NMR spectra of **8**, **9**, and their precursors, the double-bond signals appeared as symmetrical *t*. Irradiation of the allylic methylene group reduced the signal to a *s*. Only in the case of compound **38**, when prepared at room temperature, a second very small double-bond signal was observed which was assigned to the presence of traces of the (*E*)-isomer. This signal was shifted to lower field (*ca.* 0.03 ppm). Characteristic for a (*E*)-double bond is a strong IR absorption band at *ca.* 965 cm^{-1}. This absorption did not appear in the IR spectra of the fatty acids **8** and **9**.

The fatty acids **8** and **9** prepared according to *Route A* or *B* showed no difference in physical data and ^{1}H-NMR or IR spectra. The physical and spectral data of **9** (prepared involving a *Wittig* reaction) could be matched with published data [26] (synthesized *via* a different strategy involving the hydrogenation of a triple bond).

2.5. *Ceramides* **1a** *and* **2a** *and Cerebrosides* **1b** *and* **2b**. The esterification of linoleic acid (**7**) with the hydroxy-alkenonic acids **8** or **9** proved to be very difficult, because the 1,ω-unprotected fatty acids were almost insoluble in all solvents commonly used for esterification. A second disadvantage was the low reactivity of the OH function. We chose methods which allowed the activation of linoleic acid in a first step followed by the addition of the hydroxy compound. The best results were achieved with phenyl dichlorophosphate/DMF [27] as activating reagent; the desired ω-acyloxy-substituted fatty acids **4** and **5** were, thus, obtained in 40% yield (*Scheme 1*).

Finally, *N*-acylation of C_{18}-sphingosine **3** and of the 1-*O*-glucosylated sphingosine **6** in the presence of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ) with **4** or **5** gave the ceramides **1a** or **2a** and the cerebroside **1b** or **2b**, respectively, in 60% yield (*Scheme 1*). The ^{1}H-NMR data of **1a, b** and **2a, b** were in agreement with the proposed structures and in accord with those of materials isolated from the epidermis [28], if one takes into account that the latter contain 30-(linoleoyloxy)triacontanoic acid as fatty-acid residue, instead of the unsaturated ω-hydroxy-substituted fatty-acid residues contained in the cerebrosides **1b** and **2b**.

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Experimental Part

General. DMSO was distilled over CaH_2 under vacuum, CH_2Cl_2 over CaH_2, and THF over Na and benzophenon immediately before use. Solvents for chromatography (ratios in *v/v*) were distilled before use; boiling range of petroleum ether, 36–65°. Column chromatography (CC): silica gel *60* (*Merck*; 0.063–0.200 mm). Flash chromatography (FC): silica gel (*J. T. Baker*; particle size 40 μm). Thin-layer chromatography (TLC): 'DC-Plastikfolien' *60* F_{254} (*Merck*; layer thickness 0.2 mm). Optical rotations: *Perkin-Elmer* polarimeter *241 MC*; 1-dm cell. M.p.: uncorrected. ^{1}H-NMR: *Bruker WM 250 Cryospec, Bruker AC 250 Cryospec*; δ in ppm rel. to internal standard tetramethylsilane (TMS), *J* in Hz. MS: *Finnigan MAT 312*; FAB technique; 4-nitrobenzyl alcohol as matrix; *m/z* (% rel. intensity).

(9Z)-*33*-{N-*[(1*S,*2*R,*3*E*)*-2-Hydroxy-1-(hydroxymethyl)heptadec-3-enyl]carbamoyl}tritriacont-9-enyl (9*Z,*12*Z*)*-Octadeca-9,12-dienoate* (**1a**). A suspension of (2*S*,3*R*,4*E*)-2-aminooctadec-4-ene-1,3-diol [12] (**3**; 19 mg, 63.67 μmol), **4** (50 mg, 63.67 μmol), and EEDQ (15.8 mg, 63.89 μmol) in dry EtOH (2 ml) was stirred at 50° for 25

h. After evaporation, the residue was purified by FC ($CHCl_3$/MeOH/dioxane 50:0.5:1 and 15:0.5:1). After another FC ($CHCl_3$/MeOH 95:5), the product was suspended in Et_2O, and after the addition of MeCN, the flocky precipitate was collected and washed with MeCN: **1a** (41 mg, 60%). White solid. M.p. 72–74°. $[\alpha]_D^{20} = -16.8$ ($c = 0.61$, pyridine). TLC (AcOEt/acetone 95:5): R_f 0.60. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.88 (*t*, *J*(17,18) = 6.7, Me); 0.89 (*t*, *J*(16″, 17″) = 6.9, Me); 1.25, 1.30 (2 br. *s*, 43 CH_2); 1.58–1.62 (*m*, 3 CH_2); 1.97–2.06 (*m*, 5 CH_2C=C); 2.23 (*t*, *J*(2,3) = 7.5, CH_2COO); 2.26 (*t*, *J*(32′,33′) = 7.5, CH_2CON); 2.77 (*t*, *J*(10,11) = *J*(11,12) = 5.6, CH_2(11)); 2.85 (*m*, 2 OH); 3.69–3.72 (*m*, H–C(1″)); 3.89–3.97 (*m*, CH_2OH–C(1″)); 4.05 (*t*, *J*(1′,2′) = 6.7, CH_2OCO); 4.32 (*m*, H–C(2″)); 5.32–5.37 (*m*, 3 CH=CH); 5.55 (*dd*, *J*(2″,3″) = 6.3, *J*(3″,4″) = 15.4, H–C(3″)); 5.73–5.82 (*m*, H–C(4″)); 6.29 (*d*, *J*(1″,NH) = 7.1, NH).

(9Z)-*33*-{N-{(*1*S,*2*R,*3*E)-*1*-[(β-D-*Glucopyranosyloxy*)*methyl*]-*2*-*hydroxyheptadec*-*3*-*enyl*}*carbamoyl*}*tritriacont*-*9*-*enyl* (*9Z*,*12Z*)-*Octadeca*-*9*,*12*-*dienoate* (**1b**). A suspension of (*2S*,*3R*,*4E*)-2-amino-1-(β-D-glucopyranosyloxy)octadec-4-en-3-ol [12] (**6**; 260 mg, 0.56 mmol), **4** (440 mg, 0.56 mmol), and EEDQ (170 mg, 0.69 mmol) in dry EtOH (50 ml) was stirred at 50° for 25 h. After evaporation, the residue was chromatographed with $CHCl_3$/MeOH 9:1: **1b** (440 mg, 60%). Colorless solid. M.p. 116–118°. $[\alpha]_D^{20} = -7.3$ ($c = 1$, pyridine). TLC ($CHCl_3$/MeOH 85:15): R_f 0.51. ^{1}H-NMR (250 MHz, $CDCl_3/CD_3OD$ 2:1): 0.89 (*t*, *J*(17,18) = 6.9, Me); 0.9 (*t*, *J*(16′,17′) = 6.9, Me); 1.27, 1.33 (2 br. *s*, 43 CH_2); 1.58–1.63 (*m*, 3 CH_2); 1.99–2.07 (*m*, 5 CH_2C=C); 2.17 (*t*, *J*(2,3) = 7.6, CH_2COO); 2.31 (*t*, *J*(32′,33′) = 7.5, CH_2CON); 2.78 (*t*, *J*(10,11) = *J*(11,12) = 5.6, CH_2(11)); 3.23–3.45 (*m*, H–C(2‴), H–C(3‴), H–C(4‴), H–C(5‴)); 3.57 (*dd*, *J*(*A*,1″) = 2.8, *J*(*A*,*B*) = 10, H_A of CH_2–C(1″)); 3.71 (*dd*, *J*(5‴,6‴*A*) = 5, *J*(6‴*A*,6‴*B*) = 12, H_A–C(6‴)); 3.87 (*dd*, *J*(5‴,6‴*B*) = 2.1, H_B–C(6‴)); 3.98 (*m*, H–C(1″)); 4.07 (*t*, *J*(1′,2′) = 6.6, CH_2OCO); 4.10 (*dd*, *J*(2″,3″) = 7.2, H–C(2″)); 4.18 (*dd*, *J*(2″,3″) = 6.4, *J*(*B*,1″) = 4.3, H_B of CH_2–C(1″)); 4.26 (*d*, *J*(1‴,2‴) = 7.7, H–C(1‴)); 5.27–5.38 (*m*, 3 *CH*=*CH*), 5.45 (*dd*, *J*(3″,4″) = 15.5, H–C(3″)); 5.64–5.73 (*m*, H–C(4″)). FAB-MS (70eV): 1229 (MH^+), 1211 ([MH – H_2O]$^+$), 1050 ([MH – glucose]$^+$). Anal. calc. for $C_{76}H_{141}NO_{10}\cdot H_2O$ (1247.0): C 73.20, H 11.56, N 1.12; found: C 73.13, H 11.19, N 0.99.

(9Z)-*31*-{N-[(*1*S,*2*R,*4*E)-*2*-*Hydroxy*-*1*-(*hydroxymethyl*)*heptadec*-*3*-*enyl*]*carbamoyl*}*hentriacont*-*9*-*enyl* (*9Z*,*12Z*)-*Octadeca*-*9*,*12*-*dienoate* (**2a**). As described for **1a**, from **5** (67 mg, 88.47 μmol), (*2S*,*3R*,*4E*)-2-aminooctadec-4-ene-1,3-diol (**3**; 26 mg, 88.47 μmol), EEDQ (26 mg, 105.1 μmol), and EtOH (5 ml): **2a** (55 mg, 60%). Colorless crystals. M.p. 70–71°. TLC ($CHCl_3$/MeOH/dioxane 15:0.5:1): R_f 0.26. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.88 (*t*, *J*(17,18) = 6.8, Me); 0.89 (*t*, *J*(16″,17″) = 6.9, Me); 1.25, 1.30 (2 br. *s*, 41 CH_2); 1.52–1.68 (*m*, 3 CH_2); 1.97–2.06 (*m*, 5 CH_2C=C); 2.23 (*t*, *J*(2,3) = 7.4, CH_2COO); 2.29 (*t*, *J*(30′,31′) = 7.4, CH_2CON); 2.75 (*m*, 2 OH); 2.77 (*t*, *J*(10,11) = *J*(11,12) = 5.8, CH_2(11)); 3.70 (*m*, H–C(1″)); 3.94 (*m*, CH_2OH–C(1″)); 4.05 (*t*, *J*(1′,2′) = 6.7, CH_2OCO); 4.32 (*m*, H–C(2″)); 5.28–5.41 (*m*, 3 *CH*=*CH*); 5.53 (*dd*, *J*(2″,3″) = 6.4, *J*(3″,4″) = 15.4, H–C(3″)); 5.73–5.82 (*m*, H–C(4″)); 6.24 (*d*, *J*(1″, NH) = 7.2, NH). Anal. calc. for $C_{68}H_{127}NO_5\cdot 0.5\ H_2O$ (1047.8): C 77.95, H 12.31, N 1.34; found: C 78.03, H 12.37, N 1.24.

(9Z)-*31*-{N-{(*1*S,*2*R,*3*E)-*1*-[(β-D-*Glucopyranosyloxy*)*methyl*]-*2*-*hydroxyheptadec*-*3*-*enyl*}*carbamoyl*}*hentriacont*-*9*-*enyl* (*9Z*, *12Z*)-*Octadeca*-*9*,*12*-*dienoate* (**2b**). As described for **1b**, from **6** (100 mg, 0.217 mmol), **5** (160 mg, 0.217 mmol), EEDQ (54 mg, 0.218 mmol), and EtOH (10 ml): **2b** (156 mg, 60%). Colorless crystals. M.p. 114–115°. $[\alpha]_D^{20} = -9$ ($c = 1.16$, pyridine). TLC ($CHCl_3$/MeOH 85:15): R_f 0.44. ^{1}H-NMR (250 MHz, $CDCl_3$/CD_3OD 2:1): 0.89 (*t*, *J*(17,18) = 6.8, Me); 0.9 (*t*, *J*(16″,17″) = 6.9, Me); 1.27, 1.33 (2 br. *s*, 41 CH_2); 1.49–1.63 (*m*, 3 CH_2); 1.98–2.07 (*m*, 5 CH_2C=C); 2.18 (*t*, *J*(2,3) = 7.5, CH_2COO); 2.32 (*t*, *J*(30′,31′) = 7.5, CH_2CON); 2.78 (*t*, *J*(10,11) = *J*(11,12) = 5.7, CH_2(11)); 3.23–3.46 (*m*, H–C(2‴), H–C(3‴), H–C(4‴), H–C(5‴)); 3.58 (*dd*, *J*(*A*,1″) = 2.9, *J*(*A*,*B*) = 10, H_A of CH_2–C(1″)); 3.71 (*dd*, *J*(5‴,6‴*A*) = 5, *J*(6‴*A*,6‴*B*) = 12, H_A–C(6‴)); 3.87 (*dd*, *J*(5‴,6‴*B*) = 2.4, H_B–C(6‴)); 4.00 (*m*, H–C(1″)); 4.07 (*t*, *J*(1′,2′) = 6.6, CH_2OCO); 4.10 (*dd*, *J*(2″,3″) = 7.3, H–C(2″)); 4.17 (*dd*, *J*(*B*,1″) = 4.3, H_B of CH_2–C(1″)); 4.27 (*d*, *J*(1‴,2‴) = 7.7, H–C(1‴)); 5.28–5.37 (*m*, 3 *CH*=*CH*); 5.45 (*dd*, *J*(2″,3″) = 6.3, *J*(3″,4″) = 15.3, H–C(3″)); 5.64–5.76 (*m*, H–C(4″)); 7.53 (*d*, *J*(1″,NH) = 8.9, NH). FAB-MS (70eV): 1201 (MH^+), 1183 ([MH – H_2O]$^+$), 1021 ([MH – glucose]$^+$), 1003 ([MH – H_2O – glucose]$^+$).

(*25Z*)-*34*-[(*9Z*,*12Z*)-*Octadeca*-*9*,*12*-*dienoyl*]*tetratriacont*-*25*-*enoic Acid* (**4**). Phenyl dichlorophosphate (0.75 ml, 5 mmol) was added to DMF (0.6 ml, 7.75 mmol) at 0° and the mixture stirred for 3–5 min at 0°. Then, dry CH_2Cl_2 (25 ml) and linoleic acid (= (9*Z*,12*Z*)-octadeca-9,12-dienoic acid; **7**; 1.25 ml, 4 mmol) were added. The resulting soln. was stirred for 10 min at r.t. Afterwards, **8** (2.09 g, 4 mmol) was added and stirring continued for 10 min. Then, dry pyridine (1.21 ml, 15 mmol) was added, the mixture stirred for 21 h, the mixture washed 3 times with 0.1N HCl (15 ml) and twice with H_2O (15 ml), the org. layer dried (Na_2SO_4) and evaporated, and the residue chromatographed ($CHCl_3$/MeOH/dioxane 15:0.5:1) several times: pure **4** (1.25 g, 40%). Colorless crystals. M.p. 56–57°. TLC ($CHCl_3$MeOH/dioxane 15:0.5:1): R_f 0.37. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.89 (*t*, *J*(17′,18′) = 6.1, Me); 1.25, 1.30 (2 br. *s*, 32 CH_2); 1.50–1.61 (*m*, 3 CH_2); 2.00–2.06 (*m*, 4 CH_2C=C); 2.29 (*t*, *J*(2′,3′) = 7.6, CH_2COO); 2.35 (*t*, *J*(2,3) = 7.3, CH_2COO); 2.77 (*t*, *J*(10′,11′) = *J*(11′,12′) = 5.8, CH_2(11′)); 4.05 (*t*, *J*(33,34) =

6.7, CH_2OCO); 5.32–5.38 (*m*, 3 C*H*=C*H*). Anal. calc. for $C_{52}H_{96}O_4$ (785.3): C 79.53, H 12.32; found: C 78.94, H 12.08.

(23Z)-32-[(9Z,12Z)-Octadeca-9,12-dienoyl]dotriacont-23-enoic Acid (**5**). As described for **4**, from **7** (1.25 ml, 4 mmol), **9** (1.95 g, 3.94 mmol), DMF (0.6 ml, 7.75 mmol), phenyl dichlorophosphate (0.75 ml, 5 mmol), pyridine (1.21 ml, 15 mmol), and dry CH_2Cl_2 (25 ml). Repeated CC ($CHCl_3$/MeOH/dioxane 15:0.5:1) gave **5** (1.2 g, 40%). Colorless crystals. M.p. 54° ([26]: m.p. 54.4–55.4°). TLC ($CHCl_3$/MeOH/dioxane 15:0.5:1): R_f 0.40. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.89 (*t*, *J*(17′,18′) = 6.8, Me); 1.25, 1.30 (2 br. *s*, 30 CH_2); 1.58–1.63 (*m*, 3 CH_2); 1.97–2.06 (*m*, 4 CH_2C=C); 2.29 (*t*, *J*(2′,3′) = 7.7, CH_2COO); 2.34 (*t*, *J*(2,3) = 7.4, CH_2COO); 2.77 (*t*, *J*(10′,11′) = *J*(11′,12′) = 5.8, CH_2(11)); 4.05 (*t*, *J*(31,32) = 6.7, CH_2OCO); 5.32–5.37 (*m*, 3 CH=CH).

(Z)-34-Hydroxytetratriacont-25-enoic Acid (**8**). A suspension of **44** (3 g, 5.59 mmol) and NaOH (2.2 g, 55 mmol) in MeOH (200 ml) was heated to reflux for *ca.* 20 h. After cooling, the precipitate was collected, suspended in H_2O, and acidified with conc. HCl soln. (pH 1). The product was filtered off and dried *in vacuo*. Recrystallization with Et_2O/$CHCl_3$ gave **8** (2.7 g, 93%). Colorless crystals. M.p. 86°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.50. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.30 (br. *s*, 5 CH_2); 1.43–1.65 (*m*, 2 CH_2, OH); 1.97–2.02 (*m*, C*H*$_2$C=CC*H*$_2$); 2.35 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.64 (*t*, *J*(33,34) = 6.6, C*H*$_2$OH); 5.33–5.37 (*m*, C*H*=C*H*). Anal. calc. for $C_{34}H_{66}O_3 \cdot H_2O$ (540.9): C 75.50, H 12.67; found: C 75.62, H 12.17.

(Z)-32-Hydroxydotriacont-23-enoic Acid (**9**). As described for **8**, from **45** (3.73 g, 7.33 mmol), NaOH (2.9 g, 72.5 mmol), and MeOH (130 ml). After 27 h, recrystallization from Et_2O/$CHCl_3$ gave **9** (3.37 g, 93%). Colorless crystals. M.p. 81–82° ([26]: 81.5–82.5°). TLC ($CHCl_3$/MeOH 9:1): R_f 0.49.

Methyl 13-Hydroxytridecanoate (**12**). From 12-bromododecanol [18] (**11**; 30.4 g, 114.6 mmol) was prepared the free carboxylic acid [18], which was esterified with diazomethane in Et_2O in a usual manner. CC (petroleum ether/AcOEt 1:1) gave **12** (21.6 g, 77%). Colorless, bright crystals. M.p. 42° (petroleum ether/AcOEt; [29]: 40.5–41.5°). TLC (petroleum ether/AcOEt 1:1): R_f 0.60.

Methyl 13-Oxotridecanoate (**13**). To a suspension of PCC (10.6 g, 49.2 mmol) in dry CH_2Cl_2 (15 ml) was added a soln. of **12** (8 g, 32.7 mmol) in dry CH_2Cl_2 (2 ml) under N_2. After 2.5 h at r.t., the mixture was diluted with dry Et_2O (60 ml), the solvent decanted, and the black residue washed twice with dry Et_2O (10 ml). Evaporation and CC (petroleum ether/AcOEt 7:1) gave **13** (6.4 g, 81%). Colorless oil. B.p. 116°/0.04 Torr ([30]: 117–119°).

1-Bromo-12-(tetrahydro-2H-pyran-2-yloxy)dodecane (**14**). A mixture of **11** (29.9 g, 0.11 mol) and 4,5-dihydro-2*H*-pyrane (12.5 ml, 0.14 mol) was stirred at r.t. in the presence of 3 drops of conc. HCl soln. After 3 h, the mixture was diluted with little petroleum ether, washed with sat. $NaHCO_3$ soln., and dried ($MgSO_4$). The solvent was evaporated and the residue submitted to CC (petroleum ether/AcOEt 9:1): **14** (35.7 g, 93%). Colorless oil. TLC (petroleum ether/AcOEt 9:1): R_f 0.55. ^{1}H-NMR: see [31].

Triphenyl[12-(tetrahydro-2H-pyran-2-yloxy)dodecyl]phosphonium Bromide (**15**). A mixture of **14** (5 g, 14.31 mmol) and PPh_3 (3.75 g, 14.31) was heated at 140° for 6 h. After cooling, the clear substance was dissolved in acetone. Addition of Et_2O precipitated the phosphonium salt as an oil. The solvent was decanted and the residue washed twice with Et_2O. For purification, the oil was dissolved and precipitated twice as described above. The oil was dried *in vacuo* at 80° over night: **15** (7.1 g, 81%). Brown-yellow, viscous oil.

Methyl (Z)-25-(Tetrahydro-2H-pyran-2-yloxy)pentacos-13-enoate (**16**). To a soln. of **15** (7.1 g, 11.6 mmol) in freshly distilled, dry THF (80 ml) under N_2 was added 1M $NaN(SiMe_3)_2$/THF (12.8 ml). After 1 h at r.t., the mixture was heated to reflux for 1 h. Cooling with ice to 0° was followed by the addition of a soln. of **13** (3.1 g, 12.8 mmol) in dry THF. Cooling was continued for 1 h. After 15 h at r.t., the mixture was poured into sat. NH_4Cl soln. and extracted with Et_2O several times. The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was used in the next step without further purification. FC (petroleum ether/AcOEt 95:5) gave pure **16**. Colorless, waxy substance. TLC (petroleum ether/AcOEt 9:1): R_f 0.48. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.27 (br. *s*, 16 CH_2); 1.48–1.88 (*m*, 2 H–C(4′), 2 H–C(5′), 2 CH_2, CH_2O); 1.97–2.05 (*m*, C*H*$_2$C=CC*H*$_2$); 2.30 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.38 (*td*, *J*(5′,6′) = 6.6, *J*(6′*A*,6′*B*) = 9.6, 1 H–C(6′)); 3.83–3.87 (*m*, 1 H–C(3′)); 4.58 (*t*, *J*(2′,3′) = 3.5, H–C(2′)); 5.33–5.36 (*m*, C*H*=C*H*). Anal. calc. for $C_{31}H_{58}O_4$ (494.8): C 75.25, H 11.82; found: C 75.14, H 11.64.

Methyl (Z)-25-Hydroxypentacos-13-enoate (**17**). The crude **16** (see above) was dissolved in MeOH and treated with 2 equiv. of TsOH. The mixture was stirred at r.t., until the starting material had disappeared (TLC). After evaporation, the residue was dissolved in Et_2O and washed with sat. $NaHCO_3$ soln. The org. layer was dried ($MgSO_4$) and evaporated. CC (petroleum ether/AcOEt 8:2) gave **17** (2.2 g, 46% from **13**). Colorless crystals. M.p. 43°. TLC (petroleum ether/AcOEt 8:2): R_f 0.21. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.27 (br. *s*, 16 CH_2); 1.51–1.64 (*m*, 2 CH_2, OH); 1.97–2.02 (*m*, C*H*$_2$C=CC*H*$_2$); 2.27 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.64 (*t*, *J*(24,25) = 6.7, C*H*$_2$OH); 3.67 (*s*, MeO); 5.32–5.37 (*m*, C*H*=C*H*). Anal. calc. for $C_{26}H_{50}O_3$ (410.7): C 76.04, H 12.27; found: C 75.93, H 11.96.

Methyl 25-Hydroxypentacosanoate (**18**). a) *From* **17**. A soln. of **17** (2 g, 4.87 mmol) in AcOEt (20 ml) was shaken under H_2 in the presence of 10% Pd/C (100 mg), until the H_2 uptake had stopped. The catalyst was filtered

off and washed several times with $CHCl_3$ to remove precipitated product. Evaporation gave **18** (1.9 g, 95%). Colorless crystals. M.p. 80°. The product was used in the next step without further purification. TLC (petroleum ether/AcOEt 8:2): R_f 0.24. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.51–1.64 (*m*, 2 CH_2, OH); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 3.64 (*t*, $J(24,25) = 6.6$, CH_2OH); 3.67 (*s*, Me).

b) *From* **27**. A suspension of **27** (33.8 g, 74.33 mmol) in dry MeOH (150 ml) was treated with 0.1N NaOMe/MeOH (190 ml). The mixture was stirred at r.t. for complete reaction (TLC). The precipitate was collected and the filtrate evaporated. The residue and the precipitate were suspended in H_2O and acidified with conc. HCl soln. (pH 5). The product was filtered off and used in the next step without further purification, after drying *in vacuo* at 80°: **18** (30.7 g, 100%). Colorless crystals.

c) *From* **30**. A soln. of **30** (500 mg, 1.01 mmol) and TsOH (380 mg, 2 mmol) in MeOH (10 ml) was stirred at r.t. for complete reaction (TLC). After evaporation, the residue was treated with sat. $NaHCO_3$ soln. and extracted several times with $CHCl_3$. The combined extracts were dried ($MgSO_4$) and evaporated: **18** (330 mg, 80%). Colorless crystals.

(12-Carboxydodecyl)triphenylphosphonium Bromide (**21**). A mixture of 13-bromotridecanoic acid [20] (**19**; 46 g, 0.156 mol) and PPh_3 (40.9 g, 0.156 mol) was heated to 140° for 15 h. The clear substance was dissolved in $CHCl_3$, as less as possible. The soln. was added dropwise to Et_2O to precipitate the phosphonium salt. The precipitate was filtered off and dissolved in $CHCl_3$ and precipitated in Et_2O twice. Drying at 80° *in vacuo* over night gave **21** (87.9 g, 100%). Light-yellow crystals.

(10-Carboxydecyl)triphenylphosphonium Bromide (**22**). As described for **21**, from 11-bromoundecanoic acid (**20**; 50 g, 0.19 mol) and PPh_3 (49.4 g, 0.19 mol): **22** (99.4 g, 100%). Light yellow crystals.

12-Oxododecyl Acetate (**24**). As described for **13**, from PCC (53 g, 0.246 mol), CH_2Cl_2 (340 ml), 12-hydroxydodecyl acetate [21] (**23**; 40 g, 0.16 mol), and CH_2Cl_2 (40 ml). CC (petroleum ether/AcOEt 8:2) gave **24** (33.6 g, 87%). Colorless oil. B.p. 143–144°/0.5 Torr ([32]: 143–145°). TLC (petroleum ether/AcOEt 8:2): R_f 0.52. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.27 (br. *s*, 7 CH_2); 1.6–1.62 (*m*, 2 CH_2); 2.05 (*s*, Ac); 2.43 (*dt*, $J(1,2) = 1.8$, $J(2,3) = 7.3$, CH_2CHO); 4.05 (*t*, $J(11,12) = 6.9$, CH_2OCO); 9.77 (*t*, CHO).

Methyl (Z)-25-Acetoxypentacos-13-enoate (**25**). To freshly distilled, dry THF (800 ml) was added under N_2 1M $NaN(SiMe_3)_2$/THF (275 ml). After the addition of **21** (72 g, 0.13 mol) in small portions, the mixture was stirred for 30 min at r.t. and then 1 h at reflux. The mixture was cooled to 0° and a soln. of **24** (31.4 g, 0.13 mol) in dry THF added dropwise. Cooling was continued for 1 h. After 15 h at r.t., the solvent was evaporated and the residue suspended in sat. NH_4Cl soln., acidified with conc. HCl soln. (pH 1), and extracted several times with Et_2O. The combined org. extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was dissolved in Et_2O and esterified with diazomethane in a usual manner. CC (petroleum ether/AcOEt 9:1) gave **25** (41 g, 70%). Colorless oil. TLC (petroleum ether/AcOEt 9:1): R_f 0.46. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.26 (br. *s*, 16 CH_2); 1.58–1.64 (*m*, 2 CH_2); 1.97–2.04 (*m*, $CH_2C{=}CCH_2$); 2.04 (*s*, Ac); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 3.66 (*s*, Me); 4.05 (*t*, $J(24,25) = 6.7$, CHOCO); 5.32–5.36 (*m*, $CH{=}CH$). Anal. calc. for $C_{28}H_{52}O_4$ (452.7): C 74.29, H 11.58; found: C 74.05, H 11.37.

Methyl (Z)-23-Acetoxytricos-11-enoate (**26**). As described for **25**, from **22** (63 g, 0.12 mol), **24** (29.1 g, 0.12 mmol), and $NaN(SiMe_3)_2$ (46 g, 0.25 mol) in dry THF (1000 ml). Esterification with diazomethane gave **26** (35.7 g, 70%). Colorless oil. TLC (petroleum ether/AcOEt 7:1): R_f 0.46. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.27 (br. *s*, 14 CH_2); 1.59–1.64 (*m*, 2 CH_2); 1.97–2.04 (*m*, $CH_2C{=}CCH_2$); 2.04 (*s*, Ac); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 3.66 (*s*, Me); 4.05 (*t*, $J(22,23) = 6.7$, CH_2OCO); 5.33–5.36 (*m*, $CH{=}CH$). Anal. calc. for $C_{26}H_{48}O_4$ (424.7): C 73.54, H 11.39; found: C 73.45, H 11.12.

Methyl 25-Acetoxypentacosanoate (**27**). As described for **18**, from **25** (40 g, 88.35 mmol), AcOEt (400 ml), and 10% Pd/C (2 g): **27** (40.1 g, 100%), which was used in the next step without further purification. Recrystallization (petroleum ether/AcOEt) gave colorless crystals. M.p. 72–73°. TLC (petroleum ether/AcOEt): R_f 0.52. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.58–1.64 (*m*, 2 CH_2); 2.05 (*s*, Ac); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 3.67 (*s*, MeO); 4.05 (*t*, $J(24,25) = 6.7$, CH_2OCO). Anal. calc. for $C_{28}H_{54}O_4$ (454.7): C 73.96, H 11.97; found: 74.10, H 11.88.

Methyl 23-Acetoxytricosanoate (**28**). As described for **18**, from **26** (30 g, 70.64 mmol), AcOEt (250 ml), and 10% Pd/C (1.5 g): **28** (29.1 g, 97%). Colorless, bright little plates. M.p. 69° (petroleum ether/AcOEt). TLC (petroleum ether/AcOEt 7:1): R_f 0.46. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 18 CH_2); 1.59–1.64 (*m*, 2 CH_2); 2.05 (*s*, Ac); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 3.67 (*s*, MeO); 4.05 (*t*, $J(22,23) = 6.7$, CH_2OCO). Anal. calc. for $C_{26}H_{50}O_4$ (426.9): C 73.19, H 11.81; found: C 73.38, H 11.60.

Methyl 23-Hydroxytricosanoate (**29**). As described for **18** (*Method b*), from **28** (28.5 g, 66.79 mmol), MeOH (150 ml), and 0.1N NaOMe/MeOH (170 ml): **29** (23.1 g, 90%) which was used in the next step without further purification. Colorless crystals. M.p. 72°. TLC (petroleum ether/AcOEt 8:2): R_f 0.34. ^{1}H-NMR (250 MHz,

$CDCl_3$): 1.25 (br. *s*, 19 CH_2); 1.54–1.61 (*m*, 2 CH_2); 2.30 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.64 (*t*, *J*(22,23) = 6.6, CH_2OH); 3.67 (*s*, MeO). Anal. calc. for $C_{24}H_{48}O_3$ (384.7): C 74.94, H 12.58; found: C 74.47, H 12.33.

*Methyl 25-(Tetrahydro-2*H*-pyran-2-yloxy)pentacosanoate* (**30**). To a soln. of **19** (0.3 g, 3 mmol) in dry THF (4 ml) was added under N_2 at $-20°$ 3M MeMgCl/THF (1.1 ml). After the cessation of gas evolution, 0.2M Li_2CuCl_4/THF (0.3 ml) was added, followed by the dropwise addition of the *Grignard* compound prepared from **14** (1.4 g, 4 mmol) and Mg (0.1 g, 4 mmol) in dry THF (2 ml). The mixture was stirred at $-20°$ for 15 h, then poured into dil. H_2SO_4 soln. and extracted with Et_2O several times. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was esterified with diazomethane in Et_2O in a usual manner and submitted to CC (petroleum ether/AcOEt 9:1): **30** (0.5 g, 34%). Colorless crystals. M.p. 59–60°. TLC (petroleum ether/AcOEt 9:1): R_f 0.44. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.41–1.88 (*m*, 2 H–C(4'), 2 H–C(5'), 4 CH_2, CH_2O); 2.30 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.38 (*td*, *J*(5',6') = 6.9, *J*(6'*A*,6'*B*) = 9.5, 1 H–C(6')); 3.48–3.52 (*m*, 1 H–C(3')); 3.67 (*s*, MeO); 3.73 (*td*, 1 H–C(6')); 3.83–3.87 (*m*, 1 H–C(3')); 4.58 (*t*, *J*(2',3') = 3.4, H–C(2')). Anal. calc. for $C_{31}H_{60}O_4$ (496.8): C 74.95, H 12.17; found: 74.71, H 12.41.

25-Hydroxypentacosanoic Acid (**31**). A mixture of **27** (8 g, 17.59 mmol) and KOH (21.1 g, 211.1 mmol) in MeOH (500 ml) was heated to reflux for 24 h. After cooling, the precipitate was collected, suspended in H_2O and acidified carefully with conc. HCl soln. (pH 1). The product was filtered off and used in the next step without further purification: **31** (5.5 g, 78%). Colorless crystals. M.p. 100–101°. TLC ($CHCl_3$/MeOH 8:2): R_f 0.62.

25-(Methylsulfonyloxy)pentacosanoic Acid (**32**). To a suspension of **31** (4.95 g, 12.42 mmol) in dry pyridine (50 ml) and dry THF (75 ml) was added dropwise at 0° a soln. of methanesulfonyl chloride (2.7 ml, 34.83 mmol) in dry pyridine (13.5 ml). Cooling was continued for 30 min, then the mixture was stirred at r.t. for 3–4 h (TLC). After evaporation, the residue was suspended in H_2O, acidified with 3N HCl, and extracted 3 times with $CHCl_3$. The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. For purification, the residue was treated with Et_2O at reflux: **32** (4.1 g, 69%). Colorless crystals. M.p. 103°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.62. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.7 (*m*, 2 CH_2); 2.35 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.01 (*s*, $MeSO_2$); 4.22 (*t*, *J*(24,25) = 6.3, CH_2OSO_2). Anal. calc. for $C_{26}H_{52}O_5S$ (476.8): C 65.50, H 10.99; found: C 65.75, H 10.87.

25-Bromopentacosanoic Acid (**33**). To a suspension of **32** (3.98 g, 8.35 mmol) and KBr (9.94 g, 83.5 mmol) in H_2O (21 ml) and toluene (13 ml) was added $(Bu_4N)HSO_4$ (420 mg, 1.24 mmol). The mixture was stirred at 100° for 4 h. $CHCl_3$ (100 ml) was added while the mixture cooled down. The aq. layer was exctracted 3 times with $CHCl_3$. The precipitate in the org. layer was filtered off. The filtrate and the combined $CHCl_3$ extracts were washed twice with H_2O, dried (Na_2SO_4), and evaporated. The residue was combined with the separated precipitate. Recrystallization from AcOEt gave **33** (3.1 g, 81%). Light yellow crystals. M.p. 88–89°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.57. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.63 (*m*, CH_2); 1.86 (*m*, CH_2CH_2Br); 2.35 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.41 (*t*, *J*(24,25) = 6.9, CH_2Br). Anal. calc. for $C_{25}H_{49}BrO_2$ (461.6): C 65.06, H 10.70; found: C 65.29, H 10.49.

(24-Carboxytetracosyl)triphenylphosphonium Bromide (**34**). As described for **21**, from **33** (2.06 g, 4.46 mmol) and PPh_3 (1.12 g, 4.46 mmol): **34** (3 g, 93%). Light-brown crystals.

9-Hydroxynonyl Acetate (**36**). A mixture of nonane-1,9-diol (**35**; 10 g, 62.4 mmol), AcOH (120 ml), H_2O (90 ml), and conc. H_2SO_4 soln. (0.25 ml) was extracted continuously with cyclohexane/hexane 1:1 for 2 d. The org. extract was evaporated and the product isolated by CC (Et_2O/hexane 1:1): **36** (7 g, 56%). Colorless oil. TLC (Et_2O/hexane 3:1): R_f 0.41.

9-Oxononyl Acetate (**37**). As described for **13**, from **36** (2 g, 10 mmol), CH_2Cl_2 (3 ml), PCC (3.2 g, 15 mmol), and CH_2Cl_2 (20 ml). CC (petroleum ether/AcOEt 8:2 gave **37** (1.6 g, 79%). Colorless oil. B.p. 113–115°/1 Torr ([33]: 112–115°). TLC (petroleum ether/AcOEt 8:2): R_f 0.46. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.32 (br. *s*, 4 CH_2); 1.62 (br. *s*, 2 CH_2); 2.05 (*s*, Ac); 2.43 (*dt*, *J*(1,2) = 1.8, *J*(2,3) = 7.3, CH_2CHO); 4.05 (*t*, *J*(8,9) = 6.7, CH_2OCO); 9.77 (*t*, CHO).

(Z)-34-Acetoxytetratriacont-25-enoic Acid (**38**). To a soln. of $NaN(SiMe_3)_2$ (1.67 g, 9.1 mmol) in dry DMSO (120 ml) under N_2 was added **34** (3 g, 4.14 mmol). After 2 h at r.t., a soln. of **37** (0.83 g, 4.14 mmol) in dry DMSO (2 ml) was added dropwise. Stirring was continued for 15 h. The solvent was evaporated, the residue suspended in sat. NH_4Cl soln., acidified with conc. HCl soln. (pH 1), and extracted several times with $CHCl_3$. The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was chromatographed with petroleum ether/AcOEt 1:3: **38** (0.25 g, 11%), which was used in the next step without further purification. Colorless crystals. TLC (petroleum ether/AcOEt 1:3): R_f 0.44. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.23 (br. *s*, 20 CH_2); 1.28 (br. *s*, 5 CH_2); 1.6 (*m*, 2 CH_2); 2.0 (*m*, $CH_2C{=}CCH_2$); 2.02 (*s*, Ac); 2.33 (*t*, *J*(2,3) = 7.5, CH_2COO); 4.03 (*t*, *J*(33,34) = 6.7, CH_2OCO); 5.33 (*m*, $CH{=}CH$).

For further identification, **38** was esterified with diazomethane in Et_2O. CC (petroleum ether/AcOEt 9:1 gave *methyl (Z)-34-acetoxytetratriacont-25-enoate*. Colorless crystals. M.p. 51°. TLC (petroleum ether/AcOEt 8:2): R_f 0.68. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.3 (br. *s*, 5 CH_2); 1.59 (*m*, 2 CH_2); 2.02 (*m*, $CH_2C{=}CCH_2$); 2.05 (*s*, Ac); 2.3 (*t*, $J(2,3) = 7.5$, CH_2COO); 3.67 (*s*, MeO); 4.04 (*t*, $J(33,34) = 6.7$, CH_2OCO); 5.34 (*m*, $CH{=}CH$). Anal. calc. for $C_{37}H_{70}O_4$ (579.0): C 76.76, H 12.19; found: C 76.74, H 12.19.

Methyl 25-Oxopentacosanoate (**39**). As described for **13**, with **18** (14 g, 33.92 mmol) and PCC (11 g, 51.03 mmol) in dry CH_2Cl_2 (80 ml). Compound **18** was added without dissolving it in CH_2Cl_2 and warming with a H_2O bath accelerated the conversion. At the end of the reaction, no Et_2O was added. Filtration over a short column of silica gel (petroleum ether/AcOEt 8:2) gave **39** (10 g, 72%). Colorless crystals. M.p. 69°. TLC (petroleum ether/AcOEt 9:1): R_f 0.42. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 19 CH_2); 1.38–1.63 (*m*, 2 CH_2); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 2.42 (*dt*, $J(23,24) = 7.3$, $J(24,25) = 1.8$, CH_2CHO); 3.67 (*s*, Me); 9.77 (*t*, CHO). Anal. calc. for $C_{26}H_{50}O_3$ (410.7): C 76.04, H 12.27; found: C 75.77, H 12.09.

Methyl 23-Oxotricosanoate (**40**). As described for **39**, from **29** (4 g, 10.4 mmol) and PCC (3.4 g, 15.77 mmol) in dry CH_2Cl_2 (40 ml). Filtration over *Celite* with $CHCl_3$ and CC (petroleum ether/AcOEt 8:2) gave **40** (3.2 g, 80%). Colorless crystals. M.p. 60–61°. TLC (petroleum ether/AcOEt 9:1): R_f 0.29. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 17 CH_2); 1.59–1.64 (*m*, 2 CH_2); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 2.42 (*dt*, $J(22,23) = 1.9$, $J(21,22) = 7.3$, CH_2CHO); 3.67 (*s*, Me); 9.76 (*t*, CHO). Anal. calc. for $C_{24}H_{46}O_3$ (382.6): C 75.34, H 12.12; found: C 75.59, H 12.02.

Methyl (Z)-34-(Tetrahydro-2H-pyran-2-yloxy)tetratriacont-25-enoate (**42**). a) *From* **39** *and* **41**. To a soln. of [9-(tetrahydro-2*H*-pyran-2-yloxy)nonyl]triphenylphosphonium bromide [23] (**41**; 16.8 g, 29.5 mmol) in freshly distilled dry THF (100 ml) was added, under N_2, 1M $NaN(SiMe_3)_2$/THF (33 ml). After 30 min at r.t. and 1 h at reflux, the mixture was cooled to $-20°$, and a soln. of **39** (5.3 g, 13 mmol) in dry THF was added dropwise. Cooling was continued for 1 h. After stirring at r.t. for 15 h, the mixture was poured into sat. NH_4Cl soln. and extracted several times with Et_2O. The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. For identification, the residue was chromatographed (petroleum ether/AcOEt 9:1): pure **42**. Colorless, waxy compound. M.p. 30–35°. TLC (petroleum ether/AcOEt 9:1): R_f 0.48. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.29 (br. *s*, 5 CH_2); 1.53–1.85 (*m*, 2 H–C(4′), 2 H–C(5′), 2 CH_2, CH_2O); 1.97–2.05 (*m*, $CH_2C{=}CCH_2$); 2.30 *t*, $J(2,3) = 7.5$, CH_2COO); 3.38 (*td*, $J(5',6') = 6.9$, $J(6'A,6'B) = 9.6$, 1 H–C(6′)); 3.48–3.54 (*m*, 1 H–C(3′)); 3.67 (*s*, Me); 3.73 (*td*, 1 H–C(6′)); 3.83–3.91 (*m*, 1 H–C(3′)); 4.58 (*t*, $J(2',3') = 3.5$, H–C(2′)); 5.33–5.36 (*m*, $CH{=}CH$). Anal. calc. for $C_{40}H_{76}O_4$ (621.1): C 77.36, H 12.33; found: C 77.35, H 12.31.

b) *From* **54**. A soln. of **54** (450 mg, 0.73 mmol) in petroleum ether/AcOEt 1:1 (20 ml) was stirred under H_2 with *Lindlar*'s catalyst (200 mg) and freshly distilled quinoline (0.1 ml) until the H_2 uptake had stopped. The catalyst was filtered off. Evaporation followed by CC (petroleum ether/AcOEt 9:1) gave **42** (440 mg, 97%).

Methyl (Z)-32-(Tetrahydro-2H-pyran-2-yloxy)dotriacont-23-enoate (**43**). As described for **42** (*Method a*), with **41** (15.35 g, 26.95 mmol), **40** (5.4 g, 14.11 mmol), THF (100 ml), and $NaN(SiMe_3)_2$ (5.4 g, 29.25 mmol). The crude product was used in the next step. FC (petroleum ether/AcOEt 95:5) gave pure **43**. Colorless crystals. M.p. 37°. TLC (petroleum ether/AcOEt 9:1): R_f 0.46. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 18 CH_2); 1.3 (br. *s*, 5 CH_2); 1.43–1.85 (*m*, 2 H–C(4′), 2 H–C(5′), 2 CH_2, CH_2O); 1.98–2.05 (*m*, $CH_2C{=}CCH_2$); 2.30 (*t*, $J(2,3) = 7.8$, CH_2COO); 3.38 (*td*, $J(5',6') = 6.7$, $J(6'A,6'B) = 9.5$, 1 H–C(6′)); 3.46–3.54 (*m*, 1 H–C(3′)); 3.67 (*s*, MeO); 3.73 (*td*, 1 H–C(6′)); 3.83–3.92 (*m*, 1 H–C(3′)); 4.58 (*t*, $J(2',3') = 3.4$, H–C(2′)); 5.33–5.38 (*m*, $CH{=}CH$). Anal. calc. for $C_{38}H_{72}O_4$ (593.0): C 76.97, H 12.24; found: C 76.83, H 12.17.

Methyl (Z)-34-Hydroxytetratriacont-25-enoate (**44**). a) *From* **42**, *Prepared According to* Method a. As described for **18** (*Method c*), with crude **42**. CC (petroleum ether/AcOEt 8:2) gave **44** (8.7 g, 55% based on **39**). Colorless crystals. M.p. 56°. TLC (petroleum ether/AcOEt 8:2): R_f 0.28. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 20 CH_2); 1.31 (br. *s*, 5 CH_2); 1.54–1.65 (*m*, 2 CH_2, OH); 1.95–2.02 (*m*, $CH_2C{=}CCH_2$); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 3.64 (*t*, $J(33,34) = 6.6$, CH_2OH); 3.67 (*s*, MeO); 5.33–5.37 (*m*, $CH{=}CH$). Anal. calc. for $C_{35}H_{68}O_3$ (536.9): C 78.29, H 12.77; found: C 78.00, H 12.72.

b) *From pure* **42**. As described above, from **42** (420 mg, 0.68 mmol): **44** (320 mg, 88%).

Methyl (Z)-32-Hydroxydotriacont-23-enoate (**45**). As described for **44** (*Method a*), with crude **43** in MeOH and TsOH (2 equiv.): **45** (3.95 g, 55% based on **40**). Colorless crystals. M.p. 60–61°. TLC (petroleum ether/AcOEt 8:2): R_f 0.27. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 18 CH_2); 1.3 (br. *s*, 5 CH_2); 1.54–1.64 (*m*, 2 CH_2, OH); 1.98–2.02 (*m*, $CH_2C{=}CCH_2$); 2.30 (*t*, $J(2,3) = 7.5$, CH_2COO); 3.64 (*t*, $J(31,32) = 6.6$, CH_2OH); 3.67 (*s*, MeO); 5.33–5.37 (*m*, $CH{=}CH$). Anal. calc. for $C_{33}H_{64}O_3$ (508.9): C 77.89, H 12.68; found: C 77.76, H 12.50.

(11-Carboxyundecyl)triphenylphosphonium Bromide (**47**). As described for **21**, with 12-bromododecanoic acid (**46**, 10 g, 35.8 mmol) and PPh_3 (9.4 g, 35.8 mmol): 19.4 g (100%) of **47**. Colorless crystals.

Methyl (Z)-24-Acetoxytetracos-12-enoate (**48**). As described for **25**, with **47** (12.6 g, 23.3 mmol), and **24** (5.6 g, 23.1 mmol). FC (petroleum ether/AcOEt 9:1) gave **48** (6.9 g, 68%). Colorless oil. TLC (petroleum ether/AcOEt 9:1): R_f 0.48. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.27 (br. *s*, 15 CH_2); 1.56–1.65 (*m*, 2 CH_2); 1.97–2.05 (*m*, $CH_2C{=}CCH_2$); 2.05 (*s*, Ac); 2.30 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.67 (*s*, MeO); 4.05 (*t*, *J*(23,24) = 6.8, CH_2OCO); 5.33–5.37 (*m*, $CH{=}CH$). Anal. calc. for $C_{27}H_{50}O_4$ (438.7): C 73.92, H 11.49; found: C 73.71, H 11.28.

Methyl 24-Acetoxytetracosanoate (**49**). As described for **18**, with **48** (6.4 g, 14.6 mmol), AcOEt (50 ml), and 10% Pd/C (0.3 g): **49** (6.3 g, 97%) which was used in the next step without further purification. For identification, the crude product was recrystallized (petroleum ether/AcOEt). Colorless crystals. M.p. 67°. TLC (petroleum ether/AcOEt 9:1): R_f 0.3. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 19 CH_2); 1.56–1.65 (*m*, 2 CH_2); 2.05 (*s*, Ac); 2.30 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.67 (*s*, MeO); 4.05 (*t*, *J*(23,24) = 6.8, CH_2OCO). Anal. calc. for $C_{27}H_{52}O_4$ (440.7): C 73.59, H 11.89; found: C 73.56, H 12.08.

24-Hydroxytetracosanoic Acid (**50**). As described for **8**, with **49** (9.7 g, 22 mmol). The product was filtered off, dried *in vacuo* at 80°, and used in the next step without further purification: **50** (8.3 g, 95%). Colorless crystals. M.p. 100–101° ([24]: m.p. 101–103°).

24-(Methylsulfonyloxy)tetracosanoic Acid (**51**). As described for **32**, with **50** (7.6 g, 19.76 mmol). The mixture was stirred at r.t. for complete reaction (TLC). After evaporation, the residue was suspended in H_2O and acidified with 3N HCl. The precipitate was treated with Et_2O under addition of $CHCl_3$: **51** (6.4 g, 70%). Light yellow crystals. M.p. 103°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.46. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 19 CH_2); 1.63–1.78 (*m*, 2 CH_2); 2.44 (*t*, *J*(2,3) = 7.4, CH_2COO); 3.00 (*s*, $MeSO_2$); 4.22 (*t*, *J*(23,24) = 6.6, CH_2OSO_2). Anal. calc. for $C_{25}H_{50}O_5S$ (462.7): C 64.89, H 10.89; found: C 64.97, H 10.68.

24-Bromotetracosanoic Acid (**52**). As described for **33**, with **51** (7.9 g, 17.07 mmol). Recrystallization from $CHCl_3$/petroleum ether gave **52** (6.6 g, 86%). Light-brown crystals. M.p. 87°. TLC ($CHCl_3$/MeOH 95:5): R_f 0.46. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 19 CH_2); 1.43–1.66 (*m*, CH_2); 1.85 (*q*, *J*(22,23) = *J*(23,24) = 6.9, CH_2CH_2Br); 2.35 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.41 (*t*, CH_2Br).

Methyl 34-(Tetrahydro-2H-pyran-2-yloxy)tetratriacont-25-ynoate (**54**). To a soln. of 8-(tetrahydro-2*H*-pyran-2-yloxy)oct-1-yne [25] (**53**; 2 g, 8.39 mmol) in dry HMPT (10 ml) was added at 0° 1.6M BuLi (5.7 ml) in hexane, while stirring under N_2 (→ deep red soln.). Then, **52** (750 mg, 1.68 mmol) was added, and after 45 min at 0°, stirring was continued at r.t. for 5 h. The mixture was quenched with ice-water and acidified with dil. H_2SO_4 soln, the aq. layer extracted several times with Et_2O, the combined extracts washed with H_2O, dried ($MgSO_4$), and evaporated and the residue dissolved in Et_2O and esterified with diazomethane in a usual manner. FC (petroleum ether/AcOEt 95:5) gave **54** (550 mg, 53%). Colorless crystals. M.p. 47–48°. TLC (petroleum ether/AcOEt 9:1): R_f 0.40. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (br. *s*, 19 CH_2); 1.32 (br. *s*, 4 CH_2); 1.42–1.85 (*m*, 2 H–C(4′), 2 H–C(5′), 4 CH_2); 2.13 (*t*, *J*(23,24) = *J*(27,28) = 6.8, $CH_2C{=}CCH_2$); 2.30 (*t*, *J*(2,3) = 7.5, CH_2COO); 3.38 (*td*, *J*(5′,6′) = 6.9, *J*(6′*A*,6′*B*) = 9.6, 1 H–C(6′)); 3.47–3.54 (*m*, 1 H–C(3′)); 3.66 (*s*, MeO); 3.73 (*td*, 1 H–C(6′)); 3.83–3.91 (*m*, 1 H–C(3′)); 4.58 (*t*, *J*(2′,3′) = 3.5, H–C(2′)). Anal. calc. for $C_{40}H_{74}O_4$ (619.0): C 77.61, H 12.05; found: C 77.68, H 11.90.

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