A Simple Preparation of Enol Ether Lipids

Hans Rudolf Pfaendler,* Franz Xaver Müller

Institute of Organic Chemistry, University of Munich, Karlstrasse 23, D-8000 Munich, Germany

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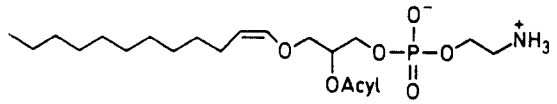
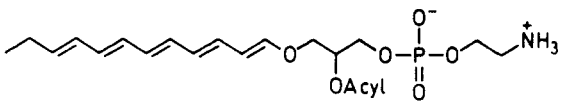
The *cis*- and *trans*-C_{12} enol ether lipids, 3-[(*E* and *Z*)-1-dodecenyloxyl]-1,2-propanediol (**1a**) and (**1b**), were prepared using a novel enol ether synthesis.

Plasmalogens are *cis*-alkenyl ether lipids which occur in plants, in bacteria, as well as in almost all animal organs. From parts of human brain they have been isolated in amounts of up to ten percent of dry weight.[1]



C_{12}-ethanolamine plasmalogen

Recently, an American research group[2] succeeded in isolating and characterizing the precursors of the strongly mutagenic fecapentaenes,[3] the so-called plasmalopentaenes, from feces.



plasmalopentaene-12

The close structural similarity between the two classes of natural products suggests also a common relationship in their biosyntheses. Possibly, the plasmalogens-12 and -14 are the natural precursors of the plasmalopentaenes. Thus, their syntheses have become of interest again.

Like the cephalins with which they are associated in Nature, the plasmalogens occur as mixtures, and lipid extracts contain many glycerides of different acyl and-alkenyl side chains. As such mixtures are separated only with difficulty, it seems obvious, that pure plasmalogens are best prepared by chemical synthesis.

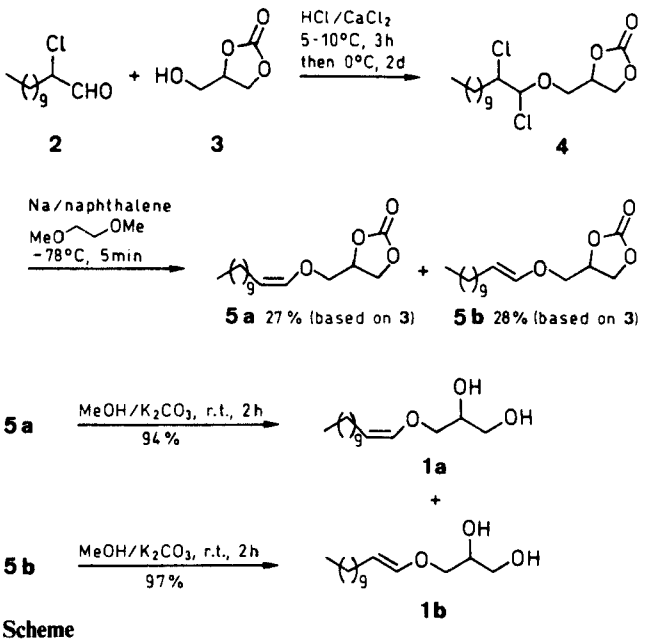
Key intermediates in the synthesis of plasmalogens are 1-alkenyl ether lipids lacking the acyl and phosphate residues. However, known syntheses of these compounds[4] have been reported to be hardly or non-reproducible.[5] For example, catalytic hydrogenation of 1-alkynyl ethers with the Lindlar catalyst[6] is not feasible.[7]

Following another procedure, and in contrast to an earlier report,[8] not only *cis*- and *trans*-1-alkenylglycerols but also their isomeric 2-glycerides were formed.[9] In our hands, experiments[10] failed to prepare the target compounds in a direct approach via 1-chloroalkyl glyceryl ethers by subsequent elimination of hydrogen chloride with several bases,[5] although structurally simple enol ethers such as 1-dodecenyl methyl ether were accessible using this method.[11]

In another approach, elimination of hydrogen iodide from 2-iodoalkyl glyceryl ether was found to be non-specific, affording also 2-alkenyl glyceryl ethers as undesired byproducts.[12]

A seemingly better multistep preparation of *cis*- and *trans*-1-alkenyl glycerols has been reported by Russian chemists. Starting from palmitaldehyde diethyl acetal and glycerol 1,2-carbonate, their synthesis involves an acetate[5] or formate[13] pyrolysis.

A simple preparation of racemic C_{12} enol ether lipids **1a** and **1b** was realized according to the following Scheme:



Scheme

Dry hydrogen chloride gas was introduced into a mixture of 2-chlorododecanal (**2**),[14] cyclic glyceryl 1,2-carbonate **3**[15] and calcium chloride and the reaction mixture left at 0 °C for two days where upon a colorless crystalline mass resulted. The ^{1}H NMR spectrum indicated a mixture of diastereomeric 1,2-dichloroalkyl ethers **4** with resonances at δ = 5.48–5.67.

The crude product **4**, containing **2**, was used without any further purification. When a dilute solution of **4** in 1,2-dimethoxyethane was titrated with a solution of naphthalene/sodium, the stereoisomeric carbonates **5a** and **5b** were formed in 55% yield based on **3**. The isomers **5**, obtained in about equivalent amounts, were separated by simple silica gel column chromatography. On the other hand, the free alkenyl glycerols **1a** and **1b** were not easily separated. They were obtained in 94 and 97% yield,

respectively, by methanolysis of the corresponding isomerically pure carbonates **5a** and **5b** using potassium carbonate as catalyst.

Dehalogenation of readily accessible, suitable 1,2-dichloroalkyl ethers with naphthalene/sodium represents an efficient and simple method for the preparation of enol ether lipids. By the same approach the preparation of *cis,trans*-dodecenyl methyl ether was effected in 78% yield. To our knowledge this synthesis of enol ethers is new,[16] and, because of the very mild reaction conditions (−78 °C, instantaneous reaction in dilute solution), it may be suitable for the preparation of the sensitive enol ether moiety in further syntheses of natural products.

Saturated ether lipids of the PAF (platelet activating factor) type are known to be physiologically potent in many respects,[17] e.g., in producing allergies or gastric ulcers. However, the role of the enol ether lipids in Nature is not yet understood. As synthetic plasmalogens have scarcely been used in biochemical or biophysical studies[18] we trust that the presented simple and reproducible preparation of 1-alkenyl glycerols will promote further research in the wide-spread field of the enol ether lipids.

All reagents and solvents were of commercial quality from freshly opened containers. Glycerol, diethyl carbonate, CH_2Cl_2, toluene, dodecanal, MeOH, naphthalene, 1,2-dimethoxyethane and SO_2Cl_2 were purchased from Fluka Chemical Co. Dimethoxyethane was refluxed under N_2 with $LiAlH_4$ and distilled immediately before use. Analytical silica gel TLC plates and silica gel were purchased from Merck Chemical Co. Melting points were taken on a Büchi 535 apparatus and are uncorrected. Microanalyses were obtained using a Heraeus CHN Standard microanalyser, IR spectra were obtained using a Perkin-Elmer 1420 IR-spectrophotometer and NMR spectra using a Varian VXR 400S (400 MHz) spectrometer.

2-Chlorododecanal (2):
2-Chlorododecanal was prepared according to Ref. 14 in 72% yield. The mobile liquid solidified upon prolonged standing, and was depolymerized by distillation; bp 80–89 °C/0.005 Torr.

$C_{12}H_{23}ClO$ (218.8) calc. C 65.88 H 10.60 found 65.94 10.46

IR (CH_2Cl_2): ν = 2940, 2860, 1740 (C=O), 1470 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 0.90 (t, 3H, CH_3), 1.30 [s, 16H, $(CH_2)_8$], 1.90 (m, 2H, CH_2CHCl), 4.10 (td, 1H, J = 6, 2 Hz, $CH_2CHClCHO$), 9.45 (d, 1H, J = 2 Hz, CHO).

TLC: R_f = 0.16 (hexane/Et_2O, 19:1, I_2 staining).

4-Hydroxymethyl-1,3-dioxolan-2-one (Glycerol-1,2-carbonate) (3):[15]
In a dried 250 mL two-necked flask, equipped with magnetic stirrer, reflux condenser and addition funnel containing a two phase mixture of glycerol (46 g, 0.5 mol) and diethyl carbonate (118 g, 1 mol) was added a solution of NaOH (300 mg) in dry EtOH (5 mL), and the mixture heated to 130 °C. After 30 min a clear colorless solution was formed. The reflux condenser was then replaced by a Claisen distillation apparatus and the formed EtOH distilled off at a bath temperature of 120–130 °C (bp 80–82 °C). To the residue five drops of 85% H_3PO_4 were added, which resulted an acidic solution (pH 3) and formation of a white precipitate. Under reduced pressure (80 Torr) the excess diethyl carbonate (60 g) was removed by distillation (bp 40–42 °C). The resulting viscous solution (62.37 g, 106%) was left overnight, where upon a white precipitate was deposited. In order to remove residual glycerol, the crude product was chromatographed on silica gel (63–200 μm, 600 g) with EtOAc. The yield of pure **3** was 54.9 g (93%) after prolonged drying by stirring at r.t. at 0.001 Torr.

IR (CH_2Cl_2): ν = 3600 (OH), 3500 (OH), 2920, 1800 (C=O), 1480, 1400, 1170, 1080 cm^{-1}.

^1H NMR (CD_3CN/TMS): δ = 3.45 (t, 1H, OH), 3.57–3.63 (m, 1H, CH_2OH), 3.76–3.82 (m, 1H, CH_2OH), 4.29–4.33 (m, 1H, dioxolane-CH_2), 4.46–4.51 (m, 1H, dioxolane-CH_2), 4.74–4.80 (m, 1H, dioxolane-CH).

TLC: R_f = 0.36 (EtOAc, I_2 staining).

4-[(1,2-Dichlorododecyl)oxymethyl]-1,3-dioxolan-2-one (4):
In a 10 mL two-necked flask, fitted with a gas inlet capillary tube and a bubbler, freshly depolymerized 2-chlorododecanal **2** (2.33 g, 10.65 mmol) and glycerol 1,2-carbonate **3** (0.69 g, 5.81 mmol) were stirred magnetically at 0 °C for 30 min, and into this mobile and clear liquid dry HCl gas was introduced from a cylinder. The solution was then stirred at a bath temperature of 10 °C for 30 min. The formed H_2O was removed by addition of powdered $CaCl_2$ (600 mg). Introduction of HCl gas was continued for an additional 3 h at 5–10 °C, where upon the mixture became more mobile. Then the HCl flow was stopped, additional $CaCl_2$ (500 mg) added and the mixture left at 0 °C in a refrigerator for 2 d. A glass-like solid was formed. In order to remove excess HCl the flask was evacuated at 13 Torr and then for 15 min at 0.001 Torr. To the residue was added toluene (50 mL) and the solution dried ($MgSO_4$). The mixture was filtered, the solvent removed in vacuo and the resulting clear colorless liquid dried at 0.001 Torr. Upon standing it became crystalline. The yield was 2.73 g (mixture of **2** and product **4**. The ratio **4** to **2** was approximately 1 : 1.3).

IR (CH_2Cl_2): ν = 2920, 2850, 1810 (C=O, carbonate), 1730 (C=O, excess aldehyde), 1460, 1170, 1060 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, ~6H, CH_3 product and aldehyde), 1.24 (s, ~28H, $(CH_2)_8$ product and aldehyde) 1.80–1.90 (m, ~4H, $CH_2CHClCHCl$ product and $CH_2CHClCHO$ aldehyde), 3.60–4.60 (m, ~6H, CH_2CHCl product and aldehyde, OCH_2 product, dioxolane-CH_2 product), 4.88 (m, 1H, dioxolane-CH_2 product), 5.48–5.67 (m, 4d (4 diastereomers), 1H, $CHClCHClOCH_2$ product), 9.45 (d, ~1H, J = 2 Hz, CH=O aldehyde).

4-[(*E* and *Z*)-1-Dodecenyloxymethyl]-1,3-dioxolan-2-one (5):
In a well-dried 500 mL Schlenk-flask, fitted with a rubber septum and a magnetic stirrer, a solution of the crude product **4** (2.73 g, max. 5.81 mmol) in dry 1,2-dimethoxyethane (140 mL) was repeatedly degassed by evacuation using an oil vacuum pump, and the solution was saturated with Ar. A balloon filled with Ar was then attached to the tap and the flask immersed into a dry ice/acetone bath. To this solution at −78 °C under vigorous stirring a freshly prepared solution of naphthalene/sodium[19] in dry 1,2-dimethoxyethane (approx. 35 mL, 20.7 mmol) was added by a syringe within 5 min. The solution was immediately decolorized. Addition was continued until the solution remained dark green for about 1 min before it finally turned pale-yellow. Stirring at −78 °C was continued for 5 min, the dry ice/acetone bath removed and to the mixture *dry* toluene (350 mL) was added. The mixture was then poured into dil. aq HCl (0.1 N, 350 mL) under vigorous stirring. The organic layer was separated, the aqueous layer extracted with toluene (2 × 150 mL), the combined extracts were washed with aq NaCl (15%, 400 mL) and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo affording crude **5** (6.8 g containing naphthalene which partially crystallizes). Chromatography on silica gel 40–63 μm (70 g) with Et_2O/hexane (1:1) (20 fractions, 50 mL each) afforded naphthalene in the first fractions followed by *trans*-**5** (455 mg, 28% based on **3**) mp 16–18 °C (hexane) and then by *cis*-**5** (446 mg, 27%) mp 29–30 °C (hexane).

trans-**5** (**5b**):

$C_{16}H_{28}O_4$ (284.4) calc. C 67.57 H 9.92 found 68.03 10.07

IR (CH_2Cl_2): ν = 1800 (C=O), 1650 and 1670 cm^{-1} (C=C enol ether).

^1H NMR ($CDCl_3$/TMS): δ = 0.88 (t, 3H, CH_3), 1.26 [s, 16H, $(CH_2)_8$], 1.88–1.93 (m, 2H, CH_2CH=), 3.79–3.92 (m, 2H, =$CHOCH_2$), 4.39–4.55 (m, 2H, dioxolane-CH_2), 4.79–4.86 (dt, 1H, $^3J_{2,1}$ = 12.7 Hz, $^3J_{2,3}$ = 7.3 Hz, CH=CHO), 4.86–4.92 (m, 1H, dioxolane-CH), 6.24 (d, 1H, $^3J_{1,2}$ = 12.7 Hz, CH=CHO).

TLC: R_f = 0.46 (toluene/EtOAc, 4:1, I_2 staining).

cis-**5** (**5a**):

$C_{16}H_{28}O_4$ (284.4) calc. C 67.57 H 9.92 found 67.04 9.69

IR (CH_2Cl_2): ν = 1800 (C=O), 1660 cm^{-1} (C=C enol ether).

^1H NMR ($CDCl_3$/TMS): δ = 0.88 (t, 3H, CH_3), 1.26 [s, 16H, $(CH_2)_8$], 2.02–2.07 (m, 2H, $C\underline{H}_2CH$=), 3.87–4.00 (m, 2H, =CHOC$\underline{H}_2$), 4.42–4.55 (m, 3H, C$\underline{H}$=CHO and dioxolane-CH_2), 4.83–4.88 (m, 1H, dioxolane-CH), 5.94 (d, 1H, $^3J_{1,2}$ = 6.3 Hz, HC=C$\underline{H}$O).

TLC: R_f = 0.40 (toluene/EtOAc, 4:1, I_2 staining).

3-[(*E* or *Z*)-1-Dodecenyloxy]-1,2-propanediol (1a or 1b):

To a magnetically stirred solution of isomerically pure dioxolane, either **5a** or **5b** (284 mg, 1.0 mmol) in MeOH (10 mL) a solution of K_2CO_3 (30 mg) in H_2O (0.5 mL) was added and the mixture stirred at r.t. for 2 h under N_2. TLC indicated a complete reaction. The resulting solution was diluted with Et_2O (70 mL) and washed with aq $NaHCO_3$ (10%, 100 mL). The aqueous layer was extracted with Et_2O (30 mL), and the combined ether solutions were dried ($MgSO_4$). The solution was then filtered, the solvent removed in vacuo and the liquid residue dried at 0.001 Torr. Analytically pure **1a**, mp 20–22 °C (hexane) (242 mg, 94%) or **1b** (from **5b** as starting material), mp 40–41 °C (hexane) (250 mg, 97%) was obtained without further purification. Compounds **1a** and **1b** are sensitive to oxygen and should be stored at low temperature (– 30 °C) under N_2.

cis-**1** (**1a**):

$C_{15}H_{30}O_3$ (258.4) calc. C 69.72 H 11.70 found 70.04 11.71

IR (CH_2Cl_2): ν = 3600 (OH), 3500 (OH), 1660 cm^{-1} (C=C enol ether).

^1H NMR ($CDCl_3$/TMS): δ = 0.88 (t, 3H, CH_3), 1.26 [s, 16H, $(CH_2)_8$], 2.05 (m, 2H, $C\underline{H}_2CH$=), 2.25 (br s, 1H, OH), 2.65 (br s, 1H, OH), 3.62–3.80 (m, 4H, $C\underline{H}_2$(OH)CH(OH)$C\underline{H}_2$O), 3.92 (m, 1H, CH_2(OH)C$\underline{H}$(OH)CH_2O), 4.41 (td, 1H, $^3J_{2,1}$ = 6.3 Hz, $^3J_{2,3}$ = 7 Hz, OCH=C$\underline{H}$$CH_2$), 5.94 (td, 1H, $^3J_{1,2}$ = 6.3 Hz, $^4J_{1,3}$ = 1.5 Hz), OC$\underline{H}$=$CHCH_2$).

TLC: R_f = 0.09 (toluene/EtOAc, 4:1).

trans-**1** (**1b**):

$C_{15}H_{30}O_3$ (258.4) calc. C 69.72 H 11.70 found 69.19 11.43

IR (CH_2Cl_2): ν = 3600 (OH), 3500 (OH), 1670, 1655 cm^{-1} (C=C enol ether).

^1H NMR ($CDCl_3$/TMS): δ = 0.88 (t, 3H, CH_3), 1.26 [s, 16H, $(CH_2)_8$], 1,90 (m, 2H, $C\underline{H}_2CH$=), 2.04 (br s, 1H, OH), 2.52 (br s, 1H, OH), 3.62–3.77 (m, 4H, $C\underline{H}_2$(OH)CH(OH)$C\underline{H}_2$), 3.95 (m, 1H, CH_2(OH)C$\underline{H}$(OH)CH_2), 4.82 (td, 1H, $^3J_{2,1}$ = 12.5 Hz, $^3J_{2,3}$ = 7.4 Hz, OCH=C$\underline{H}$$CH_2$), 6.24 (td, 1H, $^3J_{1,2}$ = 12.5 Hz, $^4J_{1,3}$ = 1.3 Hz, OC$\underline{H}$=$CHCH_2$).

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