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Article

Design and Synthesis of Novels Alkylglycerols based Acetylenic Derivatives from 1,10-Decanediol and Stearolic Acid Analogues of Bioactive Ether Lipids

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Abstract: Resistance to the existing drugs and increasing numbers of diseases result in identifying new drug candidates with new forms of activity. Marine sources of alkylglycerols such as the liver oil Shark (SLO) mixture of certain species or rat fish (elasmobranch fishes) contain high levels of these compounds as a mixture of few species varying by length and unsaturation or saturation of the alkyl chain. They have multiple biological activities such as hematopoiesis stimulation, lowering radiotherapy-induced injuries, reducing tumor growth and improving vaccination efficiency. The synthesis of two Alkylglycerols (AKGs) containing at least one alkyne moiety in the alkyl chain has been reported. In this work, we describe the synthesis of others unknown AKGs based alkyne 1-*O*-(hexadec-11'-ynyl)-*sn*-glycerol **4** and 1-*O*-(octadec-9'-ynyl)-*sn*-glycerol **5** as analogues of bioactive ether lipids found in the SLO mixture.

Keywords: acetylenic; alkylglycerol; lipid0; solketal; shark liver oil

1. Introduction

Acetylenic natural or synthetic products include all compounds with a carbon-carbon triple bond or alkynyl functional group. They are widely distributed and occurring in plants, moss and lichens, fungi, marine algae, sponges, insects, frogs, and traces quantities in humans [1]. The earliest isolated alkyne-bearing natural product was dehydromatricaria ester, which was isolated but not fully characterized. No compound was characterized as being acetylenic until 1892 (tariric acid), after which only a handful of compounds were isolated before 1952 [2]. It is only within the 30 years that biologically active polyacetylenes having unusual structural features have been reported from plants, cyanobacteria, algae, invertebrates, and other sources. Naturally occurring aquatic acetylenes are of particular interest since many of them display important biological activities and possess antitumor, antibacterial, antimicrobial, antifouling, antifungical, pesticidal, phototoxic, HIV-inhibitory and immunosuppressive properties [3]. Acetylenic enol ethers of glycerol including bioactive of compounds **1-3**, have been isolated from sponge of the *genus Petrosia*. These compounds have exhibed weak cytotoxicity against the human leukemia cell-line K-562 (LC_{50} 9.2, 57, 29 μg / mL) [4] (Figure **1**).

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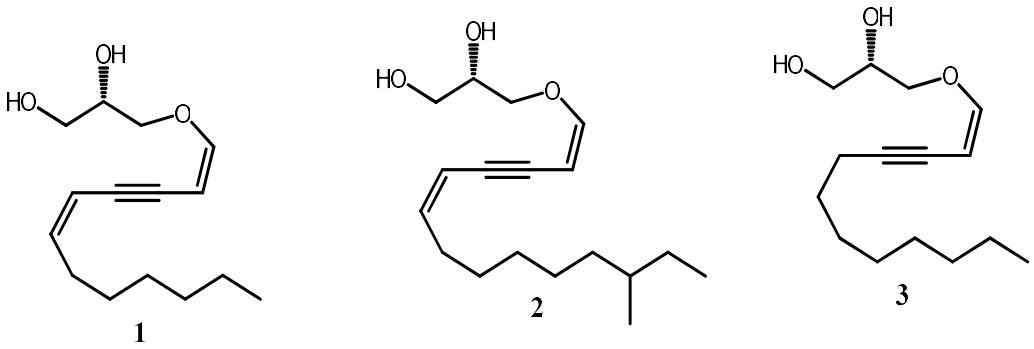

Figure 1. Acetylenic enol ether of glycerol from the Sponge.

Despite all these beneficials effects of alkyne's compounds, most of the papers are restricted to the synthesis of 1-*O*-alkylglycerols (AKGs) with a straight-chain alkane or alkene [5–10] with just one article reporting the synthesis of 1-*O*-alkylglycerols containing at least one alkyne moiety in the alkyl chain [11].

Natural 1-O-alkylglycerols (AKGs) are bioactive ether lipids present in body cells and fluids. They are precursors of ether phospholipids participating in structures and functions of membranes in certain cells such as white blood cells or macrophages. AKGs are also found in bone marrow lipids and in milk [12]. Marine sources of AKGs such as the liver oil of certain shark species or rat fish (elasmobranch fishes) contain high levels of these compounds as a mixture of few species varying by length and unsaturation or saturation of the alkyl chain

They have multiple biological activities such as hematopoiesis stimulation [13], lowering radiotherapy-induced injuries [14], reducing tumor growth [15] and improving vaccination efficiency [16,17]. Currently, resistance to the existing drugs and increasing numbers of diseases result in identifying new drug candidates with new forms of activity. Thus, synthesized non-natural AKGs derivatives could be one new source of drug delivery systems.

Therefore, it was hypothesized that AKGs with one alkyne moiety either at the 9 and 11 position respectively in the alkyl chain could exhibit than their analogues with a straight-chain alkane or alkene more biological activities as it was reported for 8-HETE (hydroxy-(5*Z*,8*Z*,11*Z*,13*E*)-eicosatetraenoic acids) analogues [18]. In the light of positive attributes of AKGs, acetylenics lipids, herein we describe the synthesis of others acetylenic Alkylglycerols namely 1-*O*-(hexadec-11'-ynyl)-*sn*-glycerol **4** from 1,10-decanediol and 1-*O*-(octadec-9'-ynyl)-*sn*-glycerol **5** from stearolic acid as analogues of known bioactive glycerol ether lipids **10** and **11** respectively found in the natural oil liver shark mixture (Figure **2**).

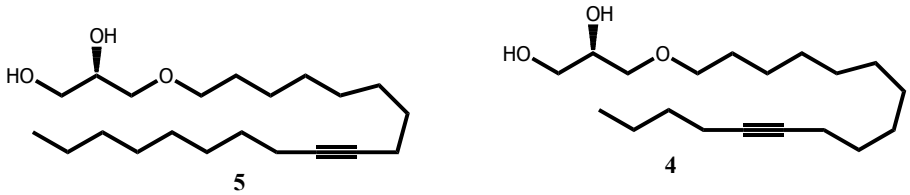

Figure 2. Unknown synthesized alkylglycerol based-acetylenic derivatives **4-5.**

2. Results and Discussion

Alkylglycerols **6-11** are the six prominent constituents found in the SLO mixture from Greenland shark (*Centrophorus squamosus*). The percentage of AKGs in the SLO mixture was determined as follows: 12:0, 1–2% (**6**); 14:0, 1–3% (**7**); 16:0, 9–13% (**8**); 16:1 n-7, 11–13% (**9**); 18:0, 1–5% (**10**); 18:1 n-9, 54–68% (**11**); 18:1 n-7, 4–6%; and minor species (<1%). Beneficial effects of the SLO mixture on health were recognized in traditional medicine of northern countries involved in fishing such as Japan, Norway and Iceland. In these countries, the ancestral use of the SLO mixture was empirically as strengthening or wound healing medication [19]. To assess the biological activity of

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each prominent AKG from the SLO mixture, derivatives **6-11** were individually obtained in pure form by total synthesis and it was observed that the biological activity was heavily dependent upon the unsaturation of the alkyl chain. When this chain was saturated, the corresponding 1-*O*-alkylglycerols **6-9** exhibited little or no activity. However, when it was monounsaturated **10**,**11** a good antitumor activity was observed, thus indicating that the antitumor activity of the SLO mixture was heavily related to its unsaturated components [5]. It was also established that the alkyl chain of a 1-*O*-alkylglycerol was bound to the glycerol backbone at the *sn*-1 position; thus leading to an *S* configuration at the asymmetric carbon [20].

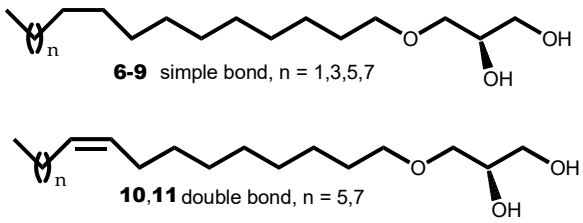
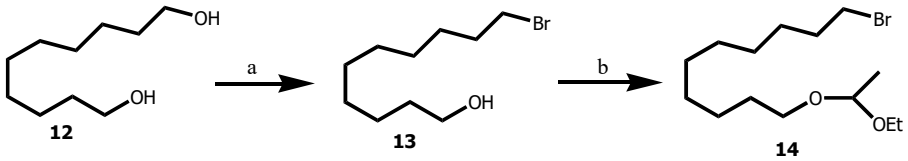


Figure 3. 1-*O*-alkylglycerols **6-11** from the SLO mixture.

To evaluate the effect position of the triple bound on the biological activity, AKG **4-**(16:2) was designed as an analogue of AKG **10-**(16:1) with the same alkyl chain length C_{16} , but with a Δ 11 unsaturation shifted from 3 carbons relative to the usual position Δ 9 unsaturation as found in the SLO. Compound **10** was reported to display antitumor activity [5]. The synthesis of **4** started with the conversion of 1,10-decanediol **12** into 1-bromo-decan-10-ol **13** in 80 % yield by using a two-phase system consisting of 48 % aqueous HBr solution and toluene to assure monobromination [21]. The remaining hydroxyl group was subsequently protected as an acetal **14** (Scheme **1**).



Scheme 1. Synthesis of bromoacetal **14**. Reagents and conditions: (a) 48 % aq. HBr, reflux, 24 h, 80 %; (b) Ethyl vinyl ether, PPTS, CH_2Cl_2, 0 °C, 30 mn, 87 %.

Intermediate **14** was employed in the alkyne alkylation using 1-hexyne **15** in THF and *n*-Buli as a nucleophile resulted in the formation of **16** in 60 % yield. Acetal cleavage under acidic condition using *p*-toluenesulfonic acid in methanol afforded alcohol **17** in 89 yield. Conversion of the alcohol **17** into mesylate **18** in 94 yield was done through mesyl chloride in DCM with trietylamine. **18** was then alkylated with 2,3-isopropylidene-*sn*-glycerol **19** in the presence of NaH in NMP afforded **20** in 81% yield. Acetonide **20** cleavage under acid conditions using catalytic amount of *p*-toluenesulfonic acid monohydrate in MeOH / H_2O afforded the targeted **4** in 87% yield (Scheme **2**).

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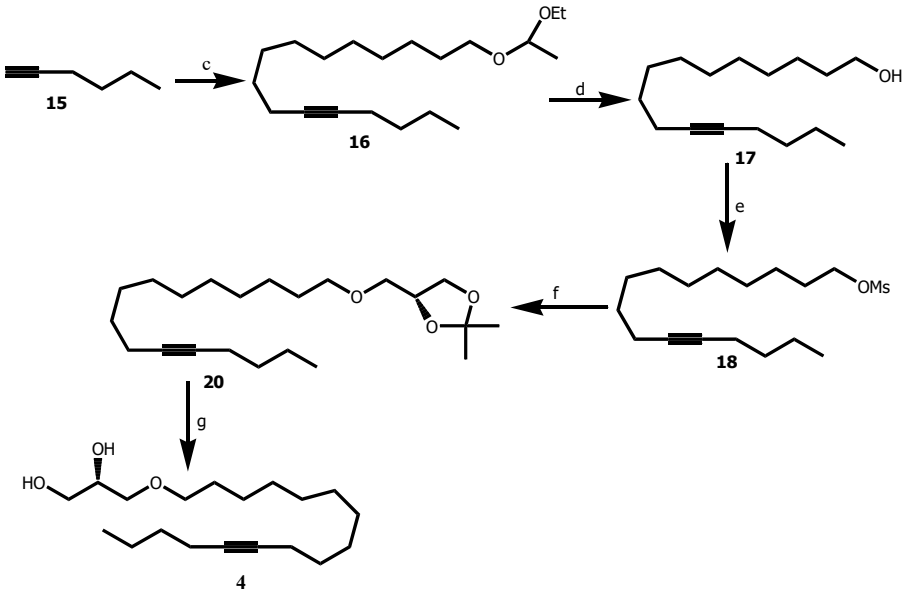

Scheme 2. Synthesis of the AKG based-acetylenic **4**. Reagents and conditions: (c) **14**, *n*-BuLi, THF, 55 min then **15**, rt, 16 h, 60 %; (d) PPTS cat., MeOH, rt, 16 h, 89 %; (e) MsCl, Et_3N, CH_2Cl_2, -40°C, 14 h , 94 %; (f) 2,3-isopropylidene-*sn*-glycerol **19**, NaH, NMP, rt, 18 h, 81 %; (g)) *p*-TsOH.H_2O MeOH / H_2O 10:1, 60 °C, 4 h, 85 %.

Furthermore, the AKG **5-**(18:2) was designed as an analogue of the AKG **11-**(18:1) with the same chain length C_{18}, a Δ 9 unsaturation and also as a derivative of stearolic acid **45** which was reported as a novel DNA binding agent [22]. AKG **11** was reported to display antitumor activity [5].

9-octadecynoic acid **21** was reduced into stearolic alcohol **22** in 91 % yield when using Red-Al in THF. **22** was then mesylated using mesyl chloride in DCM with trietylamine afforded **23** in 93 % yield. Alkylation of **23** with 2,3-isopropylidene-sn-glycerol **19** in the presence of potassium hydroxide in DMSO and tetra-*n*-butylammonium bromide gave **24** in 94 % yield, which under acid conditions using catalytic amount of *p*-toluenesulfonic acid monohydrate in MeOH/H_2O afforded the targeted **5** in 85% yield (Scheme **3**).

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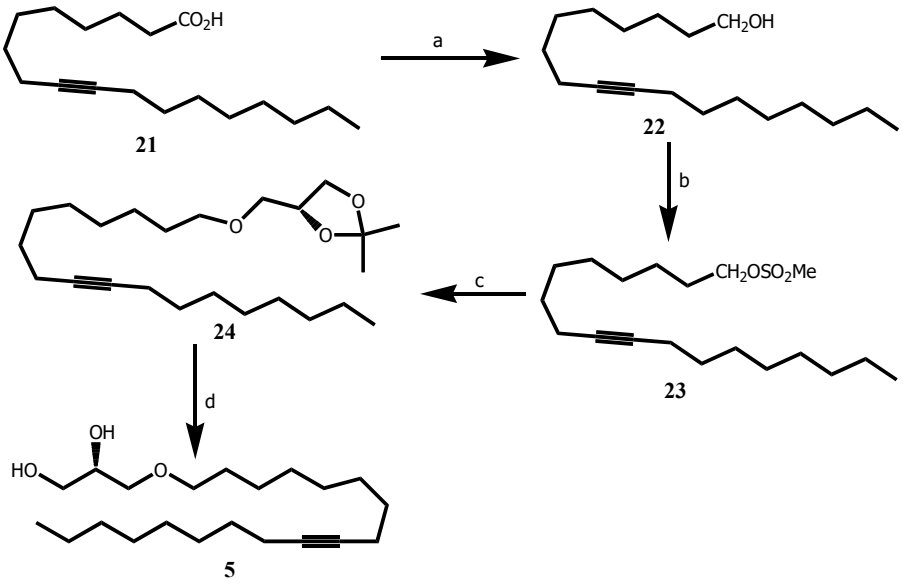

Scheme 3. Synthesis of AKG based-acetylenic **5** an analog of AKG **11**. Reagents and conditions: (a) Red-Al, THF, RT, 15 h, 91 % ; (b) MsCl, Et_3N, CH_2Cl_2, -50°C, 2 h, 93 %; (c) 2,3-isopropylidene-*sn*-glycerol **19**, KOH, *n*-Bu_4NBr, DMSO, 45°C, 24 h, 94 %; (d) *p*-TsOH.H_2O MeOH / H_2O 10:1, 60 °C, 4 h, 85 %.

3. Conclusions

A new series of Alkylglycerols based-acetylenic derivatives analogues of known glycerol ether lipids has been synthesized. Namely 1-*O*-(hexadec-11'-ynyl)-*sn*-glycerol **4** from 1,10-decanediol and 1-*O*-(octadec-9'-ynyl)-*sn*-glycerol **5** from stearolic acid as analogues of known bioactive glycerol ether lipids **10** and **11** respectively found in the natural oil liver shark mixture. The structures of these compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectral studies. We have reported an efficient and flexible strategy for the preparation of these targeted molecules, which will stimulate scientists to further investigate on their biological activities in due course.

4. Experimental

4.1. General Information

Moisture sensitive reactions were performed under nitrogen. Anhydrous THF and diethyl ether were obtained by percolating through a column of a drying resin or by distilling over Na / benzophenone. Anhydrous DMF over molecular sieves was used as commercially supplied (Acros). Room temperature (rt) means a temperature generally in the interval 15-20°C. Basic alumina used for column chromatographies was purchased from Fluka. TLC plates were visualized by UV inspection followed by staining with an acidic ethanolic solution of *p*-anisaldehyde or with a solution of phosphomolybdic acid (5 g in 100 mL 95% ethanol). IR spectra were measured as films between KBr plates for liquids or as KBr disks for solids on a Thermo Nicolet Avatar 250 FTIR spectrometer. ^{1}H NMR spectra (400.13 and 300.13 MHz) and ^{13}C NMR spectra (100.61 and 75.47 MHz) were recorded on Avance 400 and 300 Bruker spectrometers using TMS as an internal standard. Optical rotations were measured using a Perkin Elmer 341 polarimeter (concentration in g/100 mL). High resolution mass spectra were recorded using a MicrO-Tof-Q II spectrometer under electrospray using methanol as solvent. Microanalyses were performed with a CHNS analyzer. 2,3-Isopropylidene-*sn*-glycerol **19** (≥ 95% pure) was purchased from Alfa Aesar.

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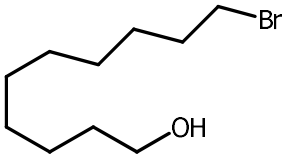
10-bromodecan-1-ol 13

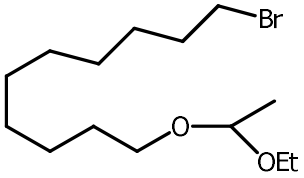


To a solution of 1,10-decandiol **12** (5 g, 28.69 mmol) in toluene (100 mL) under stirring, was added 48% aqueous solution of HBr (4.5 mL, 40.5 mmol, 1.41 eq). The corresponding mixture was refluxed overnight (18 h) and TLC monitoring showed completion of the reaction and cooled at rt. The crude was purified by Kugelrohr distillation (140 °C / 2 Torr) and afforded **13** as colorless oil (5.4 g, 80%). R_f 0.56 (petroleum ether / acetone 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.64 (t, 2H, *J* = 6.6 Hz), 3.40 (t, 2H, *J* = 6.9 Hz), 1.85 (tt, 2H, *J* = 7.4, 6.9, Hz), 1.60 (tt, 2H, *J* = 7.3, 6.7 Hz), 1.37-1.19 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$): δ= 63.15 ($\underline{C}H_2$), 34.06 ($\underline{C}H_2Br$), 32.82 ($\underline{C}H_2$), 32.76 ($\underline{C}H_2$), 29.47 ($\underline{C}H_2$), 29.37 ($\underline{C}H_2$), 29.35 ($\underline{C}H_2$), 28.74 ($\underline{C}H_2$), 28.15 ($\underline{C}H_2$), 25.71 ($\underline{C}H_2$)

1-bromo-10-(1-ethoxyethoxy)decane 14

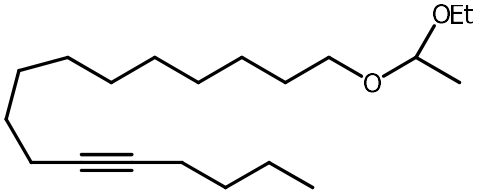


In a flame-dried two necked flask containing a solution of **13** (592 mg, 2.5 mmol) in DCM (5 mL) under stirring and N_2 cooled at 0 °C, was added a solution of ethyl vinyl ether (290 µL, 3.0 mmol, 1.2 eq) and *p*-toluenesulfonic acid (31.2 mg, 0.125 mmol, 0.5 eq). The stirring was maintained 30 min at the same temperature. A saturated solution of $NaHCO_3$ was added to the mixture and the stirring was continued for 10 mn. Extraction was done with DCM (3 x). Organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel (0→1 % acetone in petroleum ether) afforded **14** as a colorless oil (672.1 mg, 87%). R_f 0.59 (petroleum ether / acetone 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.68 (q, 1H, *J* = 5.3 Hz, $C\underline{H}$-CH_3), 3.65 (dq, 1H, *J* = 9.4, 7.1 Hz, $OC\underline{H}_2CH_3$), 3.56 (dt, 1H, *J* = 9.4, 6.7 Hz, $C\underline{H}_2O$), 3.48 (dq, 1H, *J* = 9.4, 7.1 Hz, $OC\underline{H}_2CH_3$), 3.41 (dt, 1H, *J* = 9.4, 6.6 Hz, $C\underline{H}_2O$), 3.40 (t, 2H, *J* = 6.9 Hz, $C\underline{H}_2Br$), 1.85 (tdd, 2H, *J* = 7.7, 6.7, 6.6 Hz, $C\underline{H}_2CH_2Br$), 1.56 (tt, 2H, *J* = 7.0, 6.9 Hz, $CH_2\underline{C}H_2O$), 1.47-1,38 (m, 2H, $C\underline{H}_2$), 1,38-1,24 (m, 10H, 5 $C\underline{H}_2$), 1.30 (d, 3H, *J* = 5.3 Hz, CH-$C\underline{H}_3$), 1.21 (t, 3H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 99.52 ($\underline{C}H$-CH_3), 65.27 ($CH_2\underline{C}H_2O$), 60,65 ($O\underline{C}H_2CH_3$), 34.02 ($\underline{C}H_2Br$), 32.83 ($\underline{C}H_2$), 29.89 ($\underline{C}H_2$), 29.47 ($\underline{C}H_2$), 29.42 ($\underline{C}H_2$), 29.38 ($\underline{C}H_2$), 28.75 ($\underline{C}H_2$), 28.16 ($\underline{C}H_2$), 26.24 ($\underline{C}H_2$), 19.89 (CH-$\underline{C}H_3$), 15.34 ($OCH_2\underline{C}H_3$).

16-(1-ethoxyethoxy)hexadec-5-yne 16



In a flamed-dried flash containing a solution of 1-hexyne **15** (350 µL, 3.0 mmol) in THF (2.5 mL) and HMPA (1 mL) cooled at -80°C , was added a solution of *n*-Buli (3.26 mL) under N_2 and the

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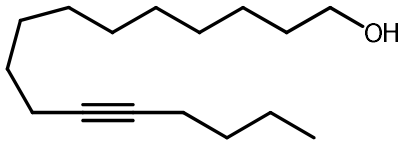
stirring was continued for 1 h at -78°C. Thereafter, a solution of **14** (427 mg, 1.5 mmol) in THF (1 mL) was added and the transfer was completed by THF (2 x 0.2 mL). The corresponding mixture was allowed to stir overnight (16 h) at rt. TLC monitoring showed completion of the reaction. Extraction was done with ethyl acetate and organic layer washed with distilled water and dried over Na_2SO_4. Solvent was removed under reduced pressure to obtain the crude product as yellow light oil. The crude product was purified by silica-gel column chromatography with petroleum ether / Et_3N (99/1) and gave **16** as colorless oil (600 mg, 60%). R_f 0.57 (petroleum ether / acetone 90:10).

IR (film) ν_{max} 2930, 2855, 2213, 1466, 1456, 1379, 1338, 1134, 1100, 1086, 1061, 951 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ=4.68 (q, 1H, *J* = 5.3 Hz, C<u>H</u>-CH_3), 3.65 (dq, 1H, *J* = 9.4, 7.1 Hz, OC<u>H</u>$_2$$CH_3$), 3.56 (dt, 1H, *J* = 9.3, 6.7 Hz, C<u>H</u>$_2$O), 3.48 (dq, 1H, *J* = 9.4, 7.1 Hz, OC<u>H</u>$_2$$CH_3$), 3.41 (dt, 1H, *J* = 9.3, 6.7 Hz, C<u>H</u>$_2$O), 2.18-2.10 (m, 4H, C<u>H</u>$_2$C□CC<u>H</u>$_2$), 1,56 (ddt, 2H, *J* = 8.3, 6.3, 6.7 Hz, C<u>H</u>$_2$$CH_2$O), 1.51-1.24 (m, 18H, 9 CH_2), 1.31 (d, 3H, *J* = 5.3 Hz, CH-C<u>H</u>$_3$), 1.21 (t, 3H, *J* = 7.1 Hz, OCH_2C<u>H</u>$_3$), 0.90 (t, 3H, *J* = 7.2 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ=99.50 (<u>C</u>H-CH_3), 80.21-80.17 (C□C), 65.27 (CH_2<u>C</u>H_2O), 60.63 (O<u>C</u>$H_2$$CH_3$), 31.27 (<u>C</u>$H_2$), 29.90 (<u>C</u>$H_2$), 29.56 (<u>C</u>$H_2$), 29.50 (<u>C</u>$H_2$), 29.48 (<u>C</u>$H_2$), 29.17 (<u>C</u>$H_2$), 29.16 (<u>C</u>$H_2$), 28.86 (<u>C</u>$H_2$), 26.26 (<u>C</u>$H_2$), 21.94 (<u>C</u>$H_2$, C_{15}), 19.88 (CH-<u>C</u>H_3), 18.76 (<u>C</u>H_2C□C), 18.45 (<u>C</u>H_2C□C), 15.33 (OCH_2<u>C</u>H_3), 13.65 (<u>C</u>H_3).

hexadec-11-yn-1-ol 17

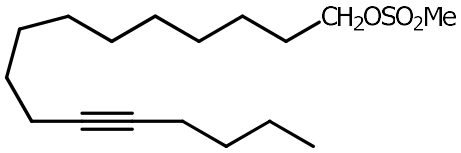


To a solution of **16** (219.1 mg, 0.7 mmol,) in methanol (3.6 mL), was added camphosulfonic acid (9.4 mg, 0.04 mmol, 0.05 eq). The flask was then purged under nitrogen, stoppered and. the stirring was maintained 18 h at rt. TLC monitoring confirmed completion of the reaction and triethylamine (6 drops) was added to neutralise the acid. Methanol was evaporated under reduced pressure and the crude was purified by column chromatography on silica gel (0→2 % acetone in petroleum ether) and afforded **17** as colorless oil (150.5 mg, 89 % yield). R_f 0.16 (petroleum ether / acetone 90:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ=3.64 (t, 2H, *J* = 6.7 Hz, C<u>H</u>$_2$OH), 2.19-2.10 (m, 4H, C<u>H</u>$_2$C□CC<u>H</u>$_2$), 1.56 (tt, 2H, *J* = 7.3, 6.7 Hz, C<u>H</u>$_2$$CH_2$OH), 1.52-1.23 (m, 19H, 9 <u>C</u>H_2 et OH), 0.90 (t, 3H, *J* = 7.2 Hz, C<u>H</u>$_3$)

^{13}C NMR (100 MHz, $CDCl_3$): δ=80.21-80.20 (C□C), 63.07 (<u>C</u>H_2OH), 32.80 (<u>C</u>H_2), 31.27 (<u>C</u>H_2), 29.56 (<u>C</u>H_2), 29.48 (<u>C</u>H_2), 29.43 (<u>C</u>H_2), 29.17 (<u>C</u>H_2), 29.15 (<u>C</u>H_2), 28.85 (<u>C</u>H_2), 25.74 (<u>C</u>H_2), 21.94 (<u>C</u>H_2), 18.76 (<u>C</u>H_2C□C), 18.45 (<u>C</u>H_2C□C) 13.65 (<u>C</u>H_3).

hexadec-11-yn-1-yl methanesulfonate 18



To the stirred solution at -50°C of **17** (121.1 mg, 0.51 mmol), Et_3N (0.21 mL, 1.5 mmol, 2.95 eq) in DCM (2.5 mL) under N_2, mesyl chloride (94 µL, 1.2 mmol, 1.25 eq) in DCM (9 mL) was added drop wise and the reaction mixture was stirred for an additional 5 h at the same temperature. Distilled water (25 mL) was added to quench the reaction and extraction was done with DCM (3 x). Organic phase was washed with brine and dried over Na_2SO_4. Solvent was removed under reduced pressure to obtain the crude product as yellow light oil. The crude product was purified by silica-

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gel column chromatography (0→1 % acetone in petroleum ether) and gave **18** as white solid (114.1 mg, 94%). R_f 0.48 (petroleum ether / acetone 85:15).

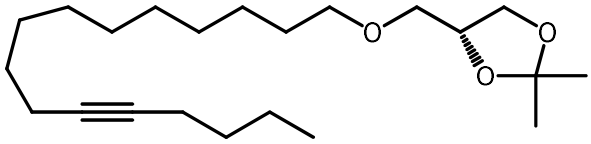
^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.22 (t, 2H, *J* = 6.6 Hz, CH_2OMs), 3.01 (s, 3H, OSO_2CH_3) 2.19-2.10 (m, 4H, $CH_2C{\square}CCH_2$), 1.75 (ddt, 2H, *J* = 8.1, 6.8, 6.6 Hz, CH_2CH_2OMs), 1.52-1.23 (m, 18H, 9 CH_2)

^{13}C NMR (100 MHz, $CDCl_3$): δ=80.20-80.17 (C□C), 70.20 (CH_2OMs), 37.35 (OSO_2CH_3), 31.26 (CH_2), 29.40 (CH_2), 29.37 (CH_2), 29.14 (CH_2), 29.12 (CH_2),

29.10 (CH_2), 29.02 (CH_2), 28.81 (CH_2), 25.42 (CH_2), 21.93 (CH_2), 18.74 ($CH_2C{\square}C$), 18.44 ($CH_2C{\square}C$), 13.65 (CH_3).

Melting point: 28-30°C.

(*R*)-4-((hexadec-11-yn-1-yloxy) methyl)-2,2-dimethyl-1,3-dioxolane 20



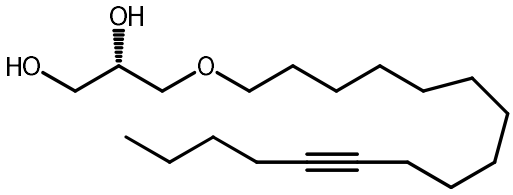
A 60% dispersion of sodium hydride in mineral oil (44 mg, 0.85 mmol, 2.5 eq) was washed three times with petroleum ether under argon. Anhydrous NMP (100 µL) was added and the mixture was cooled at 0°C. A solution of 2,3- isopropylidene-sn-glycerol **19** (56 µL, 0.46 mmol, 1.0 eq) in NMP (50 µL)was added dropwise followed by NMP (2 x 0.2 mL) to complete the transfer of **19**. After stirring 10 min at 0°C, a solution of **18** (133.6 mg, 0.42 mmol) in NMP (0.4 mL) was added to the resulting white suspension. Transfer of **18** was completed by rinsing with NMP (2 x 0.2 mL). This mixture was left under good stirring overnight (18 h) at rt. 10 % solution of ammonium acetate (4 mL) and petroleum ether (5 mL) were added to the mixture and the stirring continued for 10 min. Extraction was done with petroleum ether (3 x). Organic phase was washed with brine and dried over Na_2SO_4. Solvent was removed under reduced and the crude product was purified by silica-gel column chromatography (0→1 % acetone in petroleum ether) afforded **20** as colorless oil (108.1 mg, 81%). R_f 0.56 (petroleum ether / acetone 80:20).

IR (film) ν_{max} 2986, 2928, 2856, 1464, 1456, 1379, 1369, 1255, 1214, 1120, 1056, 847, 514 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ=4.26 (dddd, 1H, *J* = 6.4, 6.4, 5.7, 5.6 Hz, $CHOCMe_2$), 4.06 (dd, 1H, *J* = 8.2, 6.4 Hz, CH_2OCMe_2), 3.72 (dd, 1H, *J* = 8.2, 6.4 Hz, CH_2OCMe_2) 3.52 (dd, 1H, *J* = 9.9, 5.7 Hz, $CH_2O((CH_2)_{10})$, 3.50-3.42 (m, 2H, $OCH_2(CH_2)_9$), 3.42 (dd, 1H, *J* = 9.9, 5.6 Hz, $CH_2O(CH_2)_{10}$), 2.18-2.10 (m, 4H, $CH_2C{\square}CCH_2$), 1.57 (tt, 2H, *J* = 7.3, 6.7 Hz, OCH_2CH_2), 1.52-1.23 (m, 18H, 9 CH_2), 1.42 (s, 3H, C-CH_3), 1.36 (s, 3H, C-CH_3), 0.90 (t, 3H, *J* = 7.2 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ=109.36 ($C(CH_3)_2$), 80.21-80.18 (C□C), 74.77 (CH ◎ de O), 71.89 (CH_2 ◎ de O), 71.83 (CH_2 ◎ de O), 66.95 (CH_2 ◎ de O), 31.28 (CH_2), 29.57 (CH_2), 9.54 (CH_2), 29.49 (CH_2), 29.46 (CH_2), 29.18 (CH_2), 29.15 (CH_2), 28.86 (CH_2), 26.78 (C-CH_3), 26.06 (CH_2), 25.43 (C-CH_3), 21.94 (CH_2), 18.76 ($CH_2C{\square}C$), 18.45 ($CH_2C{\square}C$), 13.64 (CH_3).

(S)-3-(hexadec-11-yn-1-yloxy)propane-1,2-diol 4



To a solution of **20** (60.4 mg, 0.17 mmol,) in THF (1.2 mL), was added *p*-toluenesulfonic acid monohydrate (4.8 mg, 0.03 mmol, 0.15 eq) and distilled water (0.51 mL). The flask was then purged under nitrogen, stoppered and dipped in a preheated bath at 80°C. The stirring was maintained 8 h

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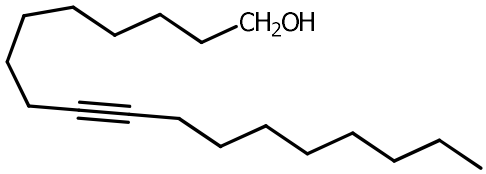
at the same temperature. Sodium carbonate (5.8 mg, 0.07 mmol, 0.04 eq) was added and the stirring was continued for 1 h at 80°C. Extraction was done with EtOAC (3 x). Organic phase was washed with brine and dried over Na_2SO_4. Solvent was removed under reduced and the crude product was purified by silica-gel column chromatography (0→10 % EtOAC in petroleum ether) afforded **4** as white solid (46.3 mg, 87%). R_f 0.06 (petroleum ether / EtOAC 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ=3.85 (ddt, 1H, *J* = 5.6, 5.5, 4.0 Hz, C<u>H</u>OCMe$_2$), 3.71 (dd, 1H, *J* = 11.4, 3.8Hz, C<u>H$_2$</u>OCMe$_2$), 3.63 (dd, 1H, *J* = 11.4, 5.2 Hz, C<u>H$_2$</u>OCMe$_2$), 3.54 (dd, 1H, *J* = 9.9, 4.0 Hz), 3.53-3.46 (m, 3H), 2.20-2.08 (m, 4H), 1.56 (ddt, 2H, *J* = 7.0, 6.8, 6.7 Hz), 1.52-1.18 (m, 21H), 0.89 (t, 3H, *J* = 6.9 Hz, C<u>H$_3$</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ=80.21-80.19 (C□C), 72.52 (<u>C</u>H$_2$), 71.85 (<u>C</u>H$_2$), 70.41 (<u>C</u>H), 64.30 (<u>C</u>H$_2$), 31.27 (<u>C</u>H$_2$), 29.58 (<u>C</u>H$_2$), 29.52 (<u>C</u>H$_2$), 29.48 (<u>C</u>H$_2$), 29.44 (<u>C</u>H$_2$), 29.17 (<u>C</u>H$_2$), 29.14 (<u>C</u>H$_2$), 28.85 (<u>C</u>H$_2$), 26.08 (<u>C</u>H$_2$), 21.93 (<u>C</u>H$_2$), 18.75 (<u>C</u>H$_2$), 18.44 (<u>C</u>H$_2$), 13.65 (<u>C</u>H$_3$)

octadec-9-yn-1-ol 22

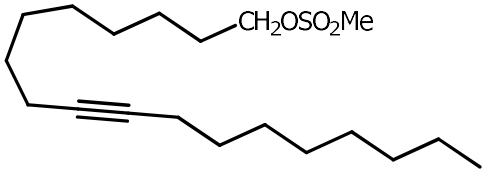


Red-Al (10.2 mL, 33.9 mmol, 1.75 eq) was added dropwise to a solution of **21** (5.43 g, 19.4 mmol) in THF (48 mL) cooled at 0°C under stirring and N_2. The stirring was continued overnight at rt. TLC monitoring confirmed completion of the starting material. Citric acid (5.03 g) was added and distilled water (45 mL) and the stirring was continued for 30 mn. Extraction was done with petroleum ether / EtOAC (80:20). Organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography on alumina gel (0→3 % acetone in petroleum ether) afforded **22** as a colorless oil (4. 69 g, 91 %). R_f 0.48 (petroleum ether / acetone 85:15).

^{1}H NMR (400 MHz, $CDCl_3$): δ=3.64 (t, 2H, *J* = 6.6 Hz), 2.17-2.10 (m, 4H, C<u>H$_2$</u>C□CC<u>H$_2$</u>), 1.56 (tt, 2H, *J* = 7.5, 6.8 Hz), 1.54-1.45 (m, 4H), 1.43-1.25 (m, 18H), 0.89 (pseudo t, 3H, *J* = 6.9 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): □=80.29 and 80.16 (C□C), 63.06 (<u>C</u>H$_2$), 32.77 (<u>C</u>H$_2$), 31.84 (<u>C</u>H$_2$), 29.31 (<u>C</u>H$_2$), 29.21 (<u>C</u>H$_2$), 29.17 (<u>C</u>H$_2$), 29.14(CH$_2$), 29.13 (2<u>C</u>H$_2$), 28.86 (<u>C</u>H$_2$), 28.77(<u>C</u>H$_2$), 25.69 (<u>C</u>H$_2$), 22.66 (<u>C</u>H$_2$), 18.74 (2<u>C</u>H$_2$C□C), 14.09 (<u>C</u>H$_3$).

octadec-9-yn-1-yl methanesulfonate 23



To the stirred solution of **22** (5.14 g, 14.92 mmol), Et_3N (4.03 mL, 28.97 mmol, 1.5 eq) in DCM (58 mL) under N_2 at -40°C, mesyl chloride (1.94 mL, 25.11 mmol, 1.3 eq) in DCM (8.36 mL) was added drop wise. After addition, the reaction mixture was stirred for an additional 2 h at the same temperature. Distilled water (80 mL) was added to quench the reaction and extraction was done with DCM. Organic phase was washed with brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by silica-gel column chromatography (0→1 % acetone in petroleum ether) gave **23** as colorless oil (6.2 g, 93 %). R_f 0.49 (petroleum ether / acetone 85:15).

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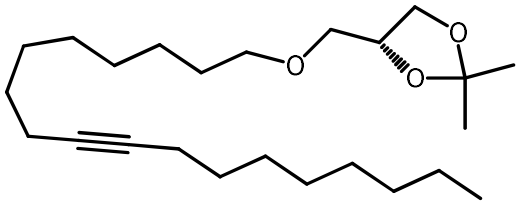
^{1}H NMR (400 MHz, $CDCl_3$): δ=4.23 (t, 2H, *J* = 6.6 Hz, $C\underline{H}_2OMs$), 3.00 (s, 3H, $OSO_2C\underline{H}_3$) 2.17-2.10 (m, 4H, $C\underline{H}_2C\square C\underline{CH}_2$), 1.75 (tt, 2H, *J* = 13.2, 6.6 Hz, $C\underline{H}_2CH_2OMs$), 1.52-1.43 (m, 4H), 1.41-1.22 (m, 18H), 0.89 (pseudo t, 3H, *J* = 6.9 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): □=80.37 and 80.07 (C□C), 70.14 ($\underline{C}H_2OMs$), 37.38 ($OSO_2\underline{C}H_3$), 31.86 ($\underline{C}H_2$), 29.24 ($\underline{C}H_2$), 29.18 ($\underline{C}H_2$), 29.14 ($\underline{C}H_2$), 29.13 ($\underline{C}H_2$), 29.08 ($\underline{C}H_2$), 28.95 (2$\underline{C}H_2$), 28.89 ($\underline{C}H_2$), 28.70 ($\underline{C}H_2$), 25.40 ($\underline{C}H_2$), 22.68 ($\underline{C}H_2$), 18.76 ($\underline{C}H_2C\square C$), 18.73 ($\underline{C}H_2C\square C$), 14.12 ($\underline{C}H_3$).

(*R*)-2,2-dimethyl-4-((octadec-9-yn-1-yloxy)methyl)-1,3-dioxolane 24

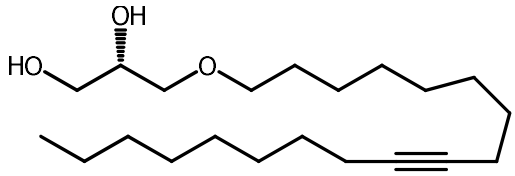


To a stirred solution of **23** (6.19 g, 17.95 mmol), n-Bu_4NBr (2.32 g, 7.18 mmol, 0.5 eq) in DMSO (45 mL), and potassium hydroxide (4.74 g, 71.8 mmol, 4 eq), was added a solution of 2,3-isopropylidene-sn-glycerol **19** (2.7 g, 20.64 mmol, 1.15 eq). The corresponding mixture went under stirring overnight (15h) at 45°C. Distilled water was added and extraction was done with petroleum ether / EtOAC (80:20). Organic phase was washed again with brine, dried over Na_2SO_4. Solvent was removed under reduced pressure. Chromatography of the crude on silica-gel (0→0.2 % acetone in petroleum ether) gave **24** as white solid (6.4 g, 93%). R_f 0.39 (petroleum ether / acetone 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ=4.26 (ddt, 1H, *J* = 6.4, 6.3, 5.7Hz, $C\underline{H}OCMe_2$), 4.06 (dd, 1H, *J* = 8.2, 6.4 Hz, $C\underline{H}_2OCMe_2$), 3.73 (dd, 1H, *J* = 8.2, 6.4 Hz, $C\underline{H}_2OCMe_2$) 3.52 (dd, 1H, *J* = 10.0, 5.7 Hz), 3.48 (dd, 1H, *J* = 6.7, 2.7 Hz), 3.45 (dd, 1H, *J* = 7.0, 6.3 Hz), 3.41(dd, 1H, *J* = 10.0, 5.7 Hz), 2.16-2.10 (m, 4H, $C\underline{H}_2C\square C\underline{CH}_2$), 1.62-1.53 (m, 2H), 1.52-1.41 (m, 4H), 1.47(q, 3H, *J* = 0.6 Hz, C-$C\underline{H}_3$), 1.36 (q, 3H, *J* = 0.6 Hz, C-$C\underline{H}_3$), 1.40-1.20 (m, 20H), 0.90 (t, 3H, *J* = 6.9 Hz, $C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): □=109.37 ($\underline{C}(CH_3)_2$), 80.29 and 80.19 (C□C), 74.76 ($\underline{C}H$ ◎ to O), 71.88 ($\underline{C}H_2$ ◎ to O), 71.84 ($\underline{C}H_2$ ◎ to O), 66.95 ($\underline{C}H_2$ ◎ to O), 31.86 ($\underline{C}H_2$), 29.55 ($\underline{C}H_2$), 29.37 ($\underline{C}H_2$), 29.24 ($\underline{C}H_2$), 29.18 ($\underline{C}H_2$), 29.16 ($\underline{C}H_2$), 29.14 ($\underline{C}H_2$), 29.12 ($\underline{C}H_2$), 28.89 ($\underline{C}H_2$), 28.81 ($\underline{C}H_2$), 26.78 (C-$\underline{C}H_3$), 26.03 ($\underline{C}H_2$), 25.43 (C-$\underline{C}H_3$), 22.68 ($\underline{C}H_2$), 18.77 ($\underline{C}H_2C\square C$), 18.76 ($\underline{C}H_2C\square C$), 14.12 ($\underline{C}H_3$).

(*S*)-3-(octadec-9-yn-1-yloxy)propane-1,2-diol 5



To a solution of **24** (60.4 mg, 0.17 mmol,) in THF (1.2 mL), was added *p*-toluenesulfonic acid monohydrate (4.8 mg, 0.03 mmol, 0.15 eq) and distilled water (0.51 mL). The flask was then purged under nitrogen, stoppered, and dipped in a preheated bath at 80°C. The stirring was maintained 8 h at the same temperature. Sodium carbonate (5.8 mg, 0.07 mmol, 0.04 eq) was added and the stirring was continued for 1 h at 80°C. Extraction was done with EtOAC (3 x). Organic phase was washed with brine and dried over Na_2SO_4. Solvent was removed under reduced and the crude product was purified by silica-gel column chromatography (0→10 % EtOAC in petroleum ether) afforded **5** as white solid (46.2 mg, 85%). R_f 0.05 (petroleum ether / EtOAC 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ=3.85 (ddt, 1H, *J* = 5.9, 5.2, 3.9 Hz), 3.71 (dd, 1H, *J* = 11.4, 3.8 Hz), 3.63 (dd, 1H, *J* = 11.4, 5.2 Hz), 3.54 (dd, 1H, *J* = 10.0, 5.7 Hz), 3.48 (dd, 1H, *J* = 6.7, 2.7 Hz), 3.45 (dd, 1H, *J* = 7.0, 6.3 Hz), 3.41(dd, 1H, *J* = 9.7, 4.0 Hz), 3.49 (dd, 9.7, 6.0 Hz), 3.47 (dd, 1H, *J* = 6.7, 2.5 Hz), 3.44 (dd, 1H, *J* = 9.5, 6.8 Hz),

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2.56-2.52 (enveloppe, 1H, OH), 2.40-2.20 (enveloppe, 1H, OH), 2.17-2.10 (m, 4H, $C\underline{H}_2C{=}CC\underline{H}_2$), 1.62-1.54 (m, 2H), 1.52-1.41 (m, 4H), 1.41-1.22 (m, 18H), 0.89 (t, 3H, J = 6.9 Hz, $C\underline{H}_3$)

^{13}C NMR (100 MHz, $CDCl_3$): □=80.32 and 80.17 (C□C), 72.52 and 71.84 ($\underline{C}H_2O\underline{C}H_2C_{17}H_{31}$), 70.44 ($\underline{C}HOH$), 64.30 ($\underline{C}H_2OH$), 31.86 ($\underline{C}H_2$), 29.57 ($\underline{C}H_2$), 29.35 ($\underline{C}H_2$), 29.24 ($\underline{C}H_2$), 29.18 ($\underline{C}H_2$), 29.14 ($2\underline{C}H_2$), 29.10 ($\underline{C}H_2$), 28.89 ($\underline{C}H_2$), 28.80 ($\underline{C}H_2$), 26.05 ($\underline{C}H_2$), 22.68 ($\underline{C}H_2$), 18.77 ($\underline{C}H_2C{=}C$), 18.76 ($\underline{C}H_2C{=}C$), 14.12 ($\underline{C}H_3$)

Acknowledgments: We also thank CRMPO (Centre Régional de Mesures Physiques de l'Ouest, Rennes, France) for HRMS spectra and microanalyses.

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