Pergamon

Tetrahedron 58 (2002) 8483–8487

TETRAHEDRON

# Total synthesis of (5*Z*,8*Z*,11*Z*,14*Z*)-18- and 19-oxoeicosa-5,8,11,14-tetraenoic acids

Stepan G. Romanov,[a] Igor V. Ivanov,[a,b] Nataliya V. Groza,[a] Hartmut Kuhn[b,*] and Galina I. Myagkova[a]

[a]*M. V. Lomonosov State Academy of Fine Chemical Technology, Pr. Vernadskogo 86, 119571 Moscow, Russian Federation*
[b]*Institute of Biochemistry, University Clinics Charité, Humboldt University, Hessische Str. 3-4, D-10115 Berlin, Germany*

Received 17 June 2002; revised 14 August 2002; accepted 16 August 2002

**Abstract**—18-oxo-ETE was synthesized via the corresponding tetraacetylenic precursor, which was prepared by cross-coupling of three key synthons: methyl 5-hexynoate, the bisfunctional $C_7-C_{13}$ fragment—7-bromo-2,5-heptadiyne-1-ol and *rac*-3-(benzoyloxy)hept-6-yn. The carbonyl function was introduced at the last synthesis step. 19-oxo-ETE was synthesized by coupling of acid anhydride, prepared from monomethyl ester of (5*Z*,8*Z*,11*Z*,14*Z*)-nonadeca-5,8,11,14-tetraen-1,19-dioic acid, either with lithium dimethylcuprate or methylcuprate in a one-step procedure. 

## 1. Introduction

Eicosanoids, such as prostaglandins[1,2] and leukotrienes,[2] are lipid mediators, which have been implicated in a variety of physiological and patho-physiological events in mammals. The biosynthesis of these compounds has been studied for many years but still its mechanism is not completely understood. As reported previously, polyenoic fatty acids oxygenated in hydrophobic part of the carbon backbone constitute valuable tools for mechanistic investigation of eicosanoids biosynthesis.[3,4] As a part of our studies on the metabolic fate of oxygenated fatty acids we worked out a convergent procedure for preparation of (5*Z*,8*Z*,11*Z*,14*Z*)-18- and 19-oxoeicosa-5,8,11,14-tetraenoic acids (18- and 19-oxo-ETEs), which are suitable tools for mechanistic studies on eicosanoid biosynthesis.

## 2. Results and discussion

### 2.1. Preparation of 18-oxo-ETE (13)

Our strategy to synthesize 18-oxo-ETE is based on the preparation of a tetraacetylenic precursor, which could be easily obtained by cross-coupling of three building blocks: commercially available methyl 5-hexynoate (**9**), the bisfunctional $C_7-C_{13}$ fragment—7-bromo-2,5-heptadiyne-1-ol[5] (**6**) and substituted alkynol **5** (Scheme 1). The carbonyl function was introduced at the last synthesis step. *rac*-1-Chloropentan-3-ol (**1**) (bp 73.5–74°C), obtained from commercially available 1-chloro-3-pentanone by reduction with $NaBH_4$, was converted to the corresponding iodide **2** by the reaction with NaI in acetone. Alkylation of acetylene **3** with **2** (*n*-BuLi, THF/HMPA) afforded *rac*-7-(trimethylsilyl)hept-6-yn-3-ol (**4**). Finaly, benzoyl ester formation and acetylene deprotection resulted in *rac*-3-(benzoyloxy)hept-6-yn (**5**) in an overall yield 53%. Cross-coupling of **5** with bromoalcohol **6** under copper(I) catalysis[6] afforded skipped triacetylenic alcohol **7** in 74% yield. Subsequent displacement of hydroxyl group with bromine using $PPh_3/CBr_4$ as reactant followed by final cross-coupling of bromide **8** with methyl 5-hexynoate (**9**) resulted in methyl ester of *rac*-18-(benzoyloxy)eicosa-5,8,11,14-tetraynoate (**10**). Stereospecific hydrogenation of the skipped-triple bonds of **10** with Lindlar's catalyst and quinoline in benzene gave rise to the tetraenoate **11**. Since methanolysis of benzoate **11** did not proceed at high yield we deprotected the functional groups with NaOH in $MeOH-H_2O$ solution to yield **12** in 82%. After the free acid **12** was methylated with diazomethane, the OH-group was oxidized by PCC. Subsequent hydrolysis of the ketoester afforded desirable (5*Z*,8*Z*,11*Z*,14*Z*)-18-oxoeicosa-5,8,11,14-tetraenoic acid (**13**) in 75% yield.

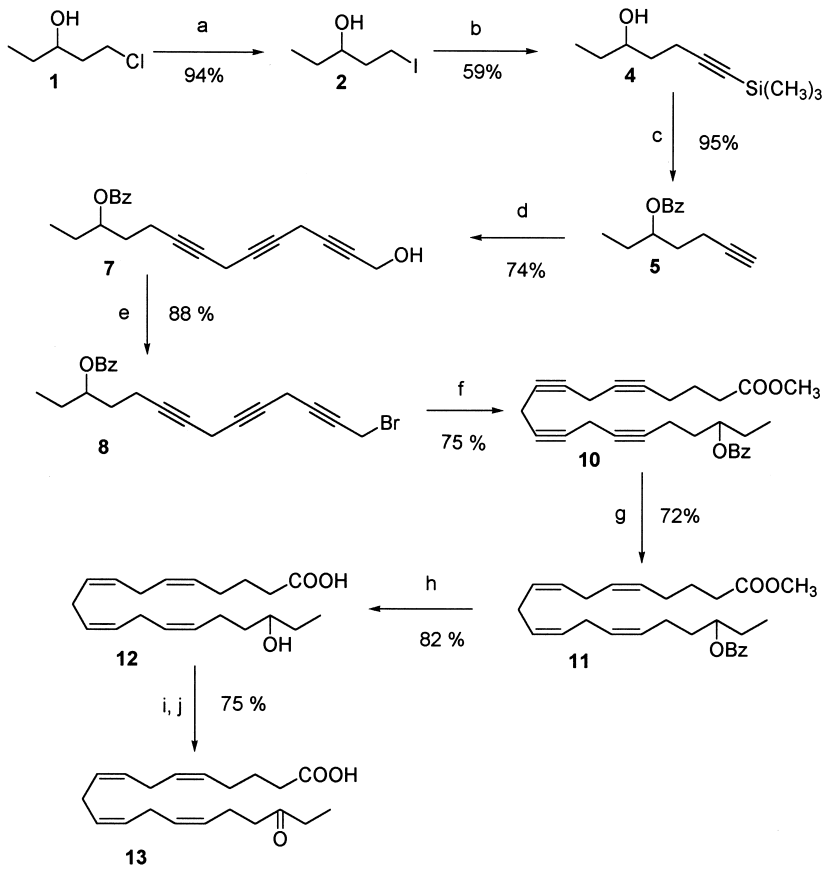
### 2.2. Preparation of 19-oxo-ETE (15)

Total synthesis of 19-oxo-ETE has previously been described,[7] but this procedure required 14,15-epoxy-AA[8,9] which is not commercially available. Monomethyl ester of (5*Z*,8*Z*,11*Z*,14*Z*)-nonadeca-5,8,11,14-tetraen-1,19-dioic acid[10] (**14**) has been reported to be a useful precursor for the

*Keywords*: eicosanoids; keto fatty acids; coupling reactions; copper and compounds.

* Corresponding author. Tel.: +49-30-2093-7539; fax: +49-30-450-528905; e-mail: hartmut.kuehn@charite.de

0040–4020/02/$ - see front matter 
PII: S0040-4020(02)01029-3




**Scheme 1.** (a) NaI, acetone, 75°C, 15 h; (b) TMSC≡CH (**3**), *n*-BuLi, THF, HMPA, −20°C, 5 h; (c) BzCl, Py, benzene, rt, 10 h then *n*-$Bu_4NF$, THF, rt, 2 h; (d) **6**, CuI, NaI, $K_2CO_3$, DMF, rt, 12 h; (e) $CBr_4$, $PPh_3$, $CH_2Cl_2$, rt, 1 h; (f) **9**, CuI, NaI, $K_2CO_3$, DMF, rt; (g) $H_2$/Lindlar's catalyst, quinoline, benzene, 10°C; (h) NaOH, MeOH/$H_2O$, rt; (i) $CH_2N_2$ then PCC, $CH_2Cl_2$, rt; (j) LiOH, MeOH/$H_2O$, rt.

synthesis of arachidonic acid analogues modified in ω-terminal part of the carbon backbone. In this study we used this compound for a one-step preparation of 19-oxo-ETE (**15**) (Scheme 2). Lithium dimethylcuprate is known to react with acid chlorides under mild conditions to afford coupling products in good yields.[11] Following this strategy we observed, that beside the desired 19-oxo-ETE (**15**) substantial amounts (35%) of methyl (5*Z*,8*Z*,11*Z*,14*Z*)-19-hydroxy-19-methyleicosa-5,8,11,14-tetraenoate (**17**) were formed. Even when the molar acid chloride: $Me_2CuLi$-ratio was decreased to 1:1 similar results were obtained and a part of **17** was not reduced. A possible reason for a side product formation may be alkylation of acyl moiety of **15** with a second equivalent of organocuprate (MeCu) formed in the reaction with $Me_2CuLi$. When we used equimolar amount of the less reactive MeCu a single product (**15**) was formed with a satisfactory yield.

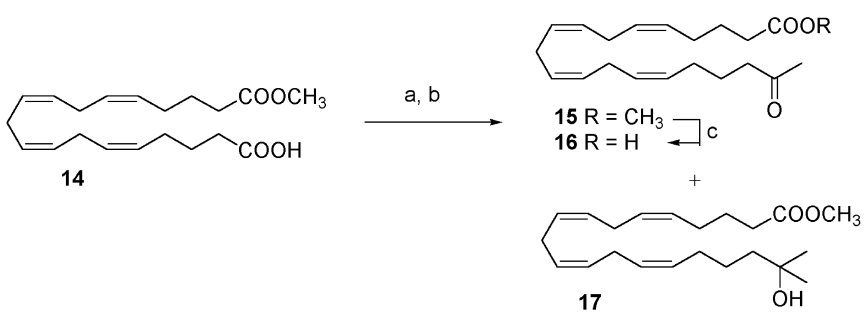
## 3. Conclusions

In conclusion, we have described herein a convergent synthetic approach, which allows the preparation of (ω-*n*)-oxo-ETEs in a fast and economic way. This strategy does further provide the possibility to prepare a variety of novel eicosanoid related compounds.

## 4. Experimental

### 4.1. General

$^1H$ and $^{13}C$ NMR spectra were recorded either on a Brucker MSL 200 or Brucker MSL 300 spectrophotometer in $CDCl_3$ as solvent. Chemical shifts are referenced to tetramethylsilane as an internal standard for $^1H$ NMR or to the




**Scheme 2.** (a) $(COCl)_2$, $CH_2Cl_2$, 10°C; (b) CuI, MeLi, $Et_2O$, −78°C, 20 min; (c) LiOH, MeOH/$H_2O$, rt.

deuterium lock signal of $CDCl_3$ ($\delta$ $^{13}C$=77.19 ppm). IR spectra were recorded on Shimadzu IR-435. HPLC analysis was carried out on a Shimadzu LC-10Avp liquid chromatograph connected to SPD-10Advp UV detector. RP-HPLC analysis was performed on a Nucleosil C18-column; 250×4 mm, 5 μm particle size (Machery–Nagel, Düren, Germany) with different solvent systems: MeOH/$H_2O$ (95:5, by volume) and a flow rate of 1 mL/min were used for analysis of compound **11**. MeOH/$H_2O$/Ac (85:15:0.1, by volume) and a flow rate of 1 mL/min were used for other compounds. Preparative HPLC was carried out on a Lichrospher 100 RP18 column; 250×22.5 mm, 10 μm particle size (Knauer, Berlin, Germany) with MeOH/$H_2O$/AcOH (95:5, by volume) and a flow rate of 10 mL/min. For EIMS analysis a Shimadzu GC–MS QP-2000 system was used with an ion source temperature of 180°C and an electron energy of 70 eV. High resolution mass spectra were recorded either on a MAT 711 mass spectrometer (Finigan MAT) or VG Autospec instrument. Column chromatography was carried out on Silica Gel 60 (Merck, Darmstadt, Germany particle size ranging from 70 to 230 mesh). For thin-layer chromatography we employed precasted Silica Gel 60 F254 sheets (Merck, Darmstadt, Germany). THF was freshly distilled from sodium/benzophenone ketyl, and HMPA was dried over $CaH_2$. All solvents and reagents used were of extra pure grade and purchased from Merck, Aldrich or Across (Germany). MeLi and *n*-butyllithium (Merck) was titrated as described by Watson and Eastman.[12] Prior to use all glassware and syringes were dried at 140°C overnight and all reactions were carried out under atmosphere of dry argon.

**4.1.1. *rac*-1-Iodo-pentan-3-ol (2).** A mixture of chloride **1** (3.81 g, 31.6 mmol) and NaI (14.22 g, 98.4 mmol) in dry acetone (55 mL) was stirred for 15 h at 75°C. After the standard work up procedure final filtration of the raw product over silica gel (hexane/$Et_2O$, 1:1) afforded pure **2** in a yield 94% (6.76 g). TLC: $R_f$=0.39 (hexane/$Et_2O$, 1:1). IR (neat)/$cm^{-1}$: 3470 (OH), 590 (C–I). $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 3.58 (m, 1H, 3-CH), 3.27 (t, 2H, $J$=6.8 Hz, 1-$CH_2$), 1.80–1.95 (m, 2H, 2-$CH_2$), 1.45 (m, 2H, 4-$CH_2$), 0.89 (t, 3H, $J$=6.8 Hz, $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 73.22, 40.66, 30.15, 9.79, 2.84. Anal. calcd for $C_5H_{11}IO$: C, 28.06; H, 5.18. Found: C, 28.01; H, 5.24.

**4.1.2. *rac*-7-(Trimethylsilyl)hept-6-yn-3-ol (4).** A 150 mL two-necked round-bottomed flask equipped with a rubber septum and magnetic stirring bar was filled with dry Ar. Then a solution of ethynyltrimethylsilane (**3**) (3.07 g, 30.9 mmol) in THF (50 mL) was placed in it and cooled to −78°C. After *n*-BuLi (16 mL, 1.6 M in hexane) was added the mixture was allowed to warm to −35°C for 35 min. Finally, a solution of **2** (2.21 g, 10.3 mmol) in THF (15 mL) and HMPA (10 mL) was added and the reaction mixture was stirred for 5 h at −20°C and then additionally for 1 h at rt. The reaction was quenched with satd aq. $NH_4Cl$ (100 mL) and acidified with HCl (1 M) to pH 5.0. The organic products were extracted with $Et_2O$ (2×100 mL). The combined extracts were washed with satd aq. NaCl and dried over $Na_2SO_4$. The solvents were evaporated under vacuum and the reaction products were purified by silica gel column chromatography (hexane/$Et_2O$, 3:1) to yield 1.12 g (59%) pure **4**. TLC: $R_f$=0.41 (hexane/$Et_2O$, 1:1). IR (neat)/$cm^{-1}$: 3600–3200 (OH), 2240 (C≡C), 1115 (C–O), 1245, 840 ($Si(CH_3)_3$). $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 3.64 (m, 1H, 3-CH), 2.34 (t, 2H, $J$=6.8 Hz, 5-$CH_2$), 1.50–1.68 (m, 4H, 2- and 4-$CH_2$), 0.92 (t, 3H, $J$=6.8 Hz, CH), 0.12 (s, 9H, $Si(CH_3)_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 107.41, 85.39, 72.74, 35.70, 30.26, 16.70, 9.86, 0.23 (3C). Anal. calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.94. Found: C, 65.25; H, 11.05.

**4.1.3. *rac*-3-(Benzoyloxy)hept-6-yn (5).** A solution of BzCl (0.98 g, 6.99 mmol) in benzene (15 mL) was added to a solution of **4** (0.99 g, 5.38 mmol) in benzene (30 mL) and pyridine (15 mL). The mixture was stirred for 10 h at rt, then acidified with $H_2SO_4$ (1 M, 50 mL). Reaction products were extracted with $Et_2O$ (2×50 mL) and the extracts were concentrated under reduced pressure. The residue was filtrated through a silica gel column (hexane/$Et_2O$, 4:1). The product which showed an $R_f$=0.59 in silica gel thin layer chromatography (hexane/$Et_2O$, 1:1) was dissolved in THF (50 mL) and the silyl group was removed by addition of *n*-$Bu_4NF$ (2.37 g, 7.53 mmol) for 2 h at rt. The mixture was quenched with $H_2O$ (100 mL), organic layer was separated and lipophilic products were extracted from the water phase with $Et_2O$ (2×40 mL). The combined organic layers were washed with satd aq. NaCl (70 mL), dried over $Na_2SO_4$ and concentrated under vacuum. Silica gel chromatography using gradient elution with hexane/$Et_2O$ (from 1 to 10% $Et_2O$) gave pure **5** as a colorless oil in a yield 1.09 g (95%). TLC: $R_f$=0.57 (hexane/$Et_2O$, 1:1). IR (neat)/$cm^{-1}$: 3272 (C≡C), 1725 (C=O), 1273 (C–O), 710 (Ph). $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.05 (m, 2H, *o*-Bz), 7.41 (m, 3H, (*m*+*p*)-Bz), 5.16 (m, 1H, 3-CH), 2.25 (m, 2H, 5-$CH_2$), 1.91 (m, 3H, 4-$CH_2$ and 7-CH), 1.68 (m, 2H, 2-$CH_2$), 0.95 (t, 3H, $J$=6.8 Hz, $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 166.33, 132.88, 131.01, 129.76 (2C), 128.47 (2C), 83.67, 75.18, 68.82, 32.95, 27.18, 15.13, 9.54. Anal. calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.70; H, 7.59.

**4.1.4. *rac*-12-(Benzoyloxy)tetradeca-2,5,8-triyn-1-ol (7).** To a suspension of previously dried salts CuI (1.35 g, 7.10 mmol), NaI (1.06 g, 7.10 mmol) and $K_2CO_3$ (0.74 g, 5.32 mmol) in DMF (25 mL) were added bromide **6** (0.66 g, 3.55 mmol) and acetylene **5** (0.78 g, 3.60 mmol) under argon atmosphere. After stirring for 12 h at rt, the reaction mixture was quenched with satd aq. $NH_4Cl$ (100 mL) and the products were extracted with $Et_2O$ (4×100 mL). The combined organic extracts were washed with satd aq. NaCl (2×50 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/$Et_2O$, 1:2) to afford acetylene alcohol **7**. Overall yield of pure **7** 0.85 g (74%). TLC: $R_f$=0.31 (hexane/$Et_2O$, 1:2). IR (neat)/$cm^{-1}$: 3600–3200 (OH), 2240, 2170 (C≡C), 1725 (C=O), 1115 (C–O), 709 (Ph). $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.98 (m, 2H, *o*-Bz), 7.39 (m, 3H, (*m*+*p*)-Bz), 5.11 (m, 1H, 12-CH), 4.21 (m, 2H, 1-$CH_2$), 3.14 (m, 2H, 4-$CH_2$), 3.03 (m, 2H, 7-$CH_2$), 2.23 (m, 2H, 10-$CH_2$), 1.88 (m, 2H, 11-$CH_2$), 1.70 (m, 2H, 13-$CH_2$), 0.92 (t, 3H, $J$=6.8 Hz, $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 166.47, 132.92, 130.93, 129.76 (2C), 128.47 (2C), 80.18, 80.03, 79.07, 75.40 (2C), 74.45, 74.04, 51.29, 32.95, 27.14, 15.38, 9.98, 9.83, 9.57. Anal. calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.01; H, 6.97.

**4.1.5. *rac*-1-3-(Benzoyloxy)-14-bromotetradeca-6,9,12-triyne (8).** To a solution of alcohol **7** (700 mg, 2.17 mmol) and $CBr_4$ (1025 mg, 3.24 mmol) in $CH_2Cl_2$ (30 mL) was added a solution of $PPh_3$ (849 mg, 3.24 mmol) in $CH_2Cl_2$ (15 mL) at 10°C. The reaction mixture was stirred for 1 h at rt, quenched with MeOH (2 mL) and volatile components were removed under vacuum. Column chromatography on silica gel (hexane/$Et_2O$, 1:1) afforded pure **8**. Yield 735 mg (88%). TLC: $R_f$=0.51 (hexane/$Et_2O$, 1:1). IR (neat)/$cm^{-1}$: 2240 (C≡C), 1740, 1725 (C=O), 1115 (C–O), 710 (Ph). $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.99 (m, 2H, *o*-Bz), 7.40 (m, 3H, (*m*+*p*)-Bz), 5.10 (m, 1H, 3-CH), 3.86 (t, 2H, $J$=2.1 Hz, 14-$CH_2$), 3.18 (m, 2H, 8-$CH_2$), 3.02 (m, 2H, 11-$CH_2$), 2.24 (m, 2H, 5-$CH_2$), 1.85 (m, 2H, 4-$CH_2$), 1.69 (m, 2H, 2-$CH_2$), 0.92 (t, 3H, $J$=6.8 Hz, $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 166.36, 132.88, 131.08, 129.76 (2C), 128.47 (2C), 81.65, 80.10, 75.84, 75.40 (2C), 74.41, 73.49, 39.06, 27.18, 22.77, 15.42, 10.23, 9.87, 9.57. Anal. calcd for $C_{21}H_{21}BrO_2$: C, 65.46; H, 5.49. Found: C, 65.24; H, 5.40.

**4.1.6. Methyl *rac*-18-(benzoyloxy)eicosa-5,8,11,14-tetraynoate (10).** In an Ar filled previously dried round-bottomed flask equipped with magnetic stirrer anhydrous $K_2CO_3$ (350 mg, 2.53 mmol), NaI (507 mg, 3.38 mmol) and CuI (644 mg, 3.38 mmol) were suspended in DMF (15 mL). Methyl 5-hexynoate (**9**) (213 mg, 1.69 mmol) was added at once to the suspension followed by bromide **8** (650 mg, 1.69 mmol). The reaction mixture was vigorously stirred overnight at rt, then quenched with satd aq. $NH_4Cl$ (200 mL). The lipophilic products were extracted with $Et_2O$ (4×100 mL). The combined organic extracts were washed with satd aq. NaCl (2×150 mL). After drying over $Na_2SO_4$ the ethereal solution was concentrated in vacuum. The crude residue was purified by silica gel flash chromatography (hexane/$Et_2O$, 3:1) under Ar to give pure **10** as yellow oil; yield: 545 mg (75%). TLC: $R_f$=0.39 (hexane/$Et_2O$, 1:1). IR (neat)/$cm^{-1}$ 2240 (C≡C), 1740, 1725 (C=O), 1115 (C–O), 710 (Ph). $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.95 (m, 2H, *o*-Bz), 7.40 (m, 3H, (*m*+*p*)-Bz), 5.05 (m, 1H, 18-CH), 3.56 (s, 3H, $OCH_3$), 3.01 (m, 6H, 7-, 10- and 13-$CH_2$), 2.31 (t, 2H, $J$=7.1 Hz, 2-$CH_2$), 2.12 (m, 4H, 4- and 16-$CH_2$), 1.71–1.90 (m, 6H, 3-, 17- and 19-$CH_2$), 0.85 (t, 3H, $J$=6.8 Hz, $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 173.33, 166.05, 132.61, 130.69, 129.44 (2C), 128.19 (2C), 79.68, 79.39, 77.95, 75.09, 74.90, 74.76, 74.21 (2C), 74.09, 51.27, 32.78, 32.71, 26.86, 23.85, 18.12, 15.11, 9.59 (3C), 9.33. Anal. calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: 77.87; H, 7.15.

**4.1.7. Methyl *rac*-(5*Z*,8*Z*,11*Z*,14*Z*)-18-(benzoyloxy)-eicosa-5,8,11,14-tetraenoate (11).** A suspension of Lindlar's catalyst (500 mg) in dry benzene (15 mL) was saturated with $H_2$ in a 100 mL Erlenmeyer flask at rt and cooled to 10°C. Then a solution of **10** (400 mg, 0.93 mmol) in benzene (35 mL) and quinoline (0.5 mL) were added to the catalyst under a stream of Ar. After the Ar was exchanged with $H_2$ the reaction mixture was stirred for 1 h at 10°C, filtered, washed with HCl (2 M, 2×30 mL). The solvent was evaporated and the residue was filtered over silica gel (hexane/$Et_2O$, 2:1) and purified by preparative RP-HPLC (solvent system MeOH/$H_2O$, 95:5) to yield 293 mg (72%) pure **11**. TLC: $R_f$=0.52 (hexane/$Et_2O$, 1:1). RP-HPLC: $R_t$=6.69 min. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.01 (m, 2H, *o*-Bz), 7.40 (m, 3H, (*m*+*p*)-Bz), 5.25–5.50 (m, 8H, CH=CH), 5.08 (m, 1H, 18-$CH_2$), 3.62 (s, 3H, $OCH_3$), 2.75 (m, 6H, 7-, 10- and 13-$CH_2$), 2.28 (t, 2H, $J$=7.1 Hz, 2-$CH_2$), 2.09 (m, 4H, 4- and 16-$CH_2$), 1.68 (m, 6H, 3-,17- and 19-$CH_2$), 0.93 (t, 3H, $J$=6.8 Hz, $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 173.93, 166.43, 132.76, 131.22, 129.71 (2C), 129.42, 129.09 (2C), 128.68, 128.43 (6C), 75.87, 51.39, 33.86, 33.64, 27.28, 26.79 (3C), 25.81, 25.00, 23.49, 9.64. MS (EI) *m*/*z* 316 (2.74) [$M^+$−BzCOO], 287 (1.25) [$M^+$−BzCOO−$C_2H_5$], 260 (2.66) [$M^+$−BzCOO−$C_4H_9$]. Anal. calcd for $C_{28}H_{38}O_4$: C, 76.68; H, 8.73. Found: C, 76.54; H, 8.67.

**4.1.8. *rac*-(5*Z*,8*Z*,11*Z*,14*Z*)-18-Hydroxyeicosa-5,8,11,14-tetraenoic acid (12).** An aqueous solution (15 mL) of NaOH (129 mg, 3.22 mmol) was added to a solution of **11** (200 mg, 0.46 mmol) in methanol (40 mL) under argon atmosphere. The resulting mixture was stirred overnight at rt. After the reaction was completed, methanol was removed by evaporation under reduced pressure, the residue was carefully acidified to pH 4.5 using dilute HCl (1 M) and the lipophilic products were extracted with $Et_2O$ (3×40 mL). Combined organic extracts were dried over $Na_2SO_4$ and concentrated in vacuum. The crude residue was purified by silical gel column chromatography (hexane/$Et_2O$, 1:3) to give pure **12** (121 mg, 82%). TLC: $R_f$=0.31 (hexane/$Et_2O$, 1:3). RP-HPLC: $R_t$=6.05 min. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.25–5.40 (m, 8H, CH=CH), 3.55 (m, 1H, 18-$CH_2$), 2.65–2.71 (m, 6H, 7-, 10- and 13-$CH_2$), 2.28 (t, 2H, $J$=7.1 Hz, 2-$CH_2$), 2.04 (m, 4H, 4- and 16-$CH_2$), 1.67 (m, 2H, 3-$CH_2$), 1.45 (m, 4H, 17- and 19-$CH_2$), 0.88 (t, 3H, $J$=6.8 Hz, $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 178.44, 129.89, 129.16, 128.97, 128.46, 128.31 (2C), 128.24 (2C), 73.22, 36.78, 33.49, 30.22, 26.65 (3C), 25.80, 24.74, 23.67, 9.85. MS (EI) *m*/*z* 320 (0.55) [$M^+$], 302 (1.02) [$M^+$−$H_2O$], 273 (1.64) [$M^+$−$H_2O$−$C_2H_5$]. HRMS calcd for $C_{20}H_{32}O_3$ [$M^+$]: 320.2351. Found 320.2364.

**4.1.9. (5*Z*,8*Z*,11*Z*,14*Z*)-18-Oxoeicosa-5,8,11,14-tetraenoic acid (13).** The acid **12** (38.2 mg, 0.119 mmol) dissolved in $Et_2O$ (25 mL) was methylated with a diazomethane. $Et_2O$ was removed, and the residue was dissolved in $CH_2Cl_2$ (4 mL). Then a suspension of PCC (102.4 mg, 0.476 mmol) in $CH_2Cl_2$ (8 mL) was added. After the reaction mixture was stirred for 2 h at rt, $Et_2O$ (25 mL) was added and the resulting mixture was filtrated over silica gel. Then solvent was removed and the residue was dissolved in MeOH (30 mL). Finally, a solution of LiOH (65 mg, 1.593 mmol) in $H_2O$ (10 mL) was added and the mixture was left to stir overnight at rt. After the reaction was completed, methanol was removed by evaporation under reduced pressure, the residue was acidified to pH 4 using dilute HCl (1 M) and organic products were extracted with $Et_2O$ (3×40 mL). Combined organic extracts were dried over $Na_2SO_4$, concentrated in vacuum and the crude residue was purified by silica gel column chromatography (hexane/$Et_2O$, 1:2) to give pure **13** (28.4 mg, 75%). TLC: $R_f$=0.36 (hexane/$Et_2O$, 1:3). RP-HPLC: $R_t$=6.20 min. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.25–5.45 (m, 8H, CH=CH), 2.81 (m, 6H, 7-,10- and 13-$CH_2$), 2.25–2.45 (m, 8H, 2-, 16-, 17-, and 19-$CH_2$), 2.07 (m, 2H, 4-$CH_2$), 1.68 (m, 2H, 3-$CH_2$), 1.03 (t, 3H, $J$=6.8 Hz, $CH_3$). $^{13}C$ NMR (50 MHz,

$CDCl_3$) $\delta$ 211.52, 179.51, 129.13, 129.07, 128.92, 128.50, 128.34, 128.32, 128.27, 128.23, 42.17, 36.18, 33.49, 26.58, 25.75 (2C), 25.70, 24.63, 21.86, 7.91. FAB HRMS calcd for $C_{20}H_{30}O_3Na$ $[M+Na]^+$: 341.2087. Found: 341.2080.

**4.1.10. Methyl (5*Z*,8*Z*,11*Z*,14*Z*)-19-oxoeicosa-5,8,11,14-tetraenoate (15).** *Method A*. To a cooled (−78°C) suspension of CuI (237 mg, 1.24 mmol) in $Et_2O$ (20 mL) MeLi (1.78 mL, 2.49 mmol) was added. The mixture was allowed to warm (−25°C) until grayish solution resulted. After about 5 min at −25°C the temperature was lowered to −78°C. A precooled ethereal solution (5 mL) of acid chloride, prepared from ester **14** (396 mg, 1.18 mmol), was injected. The resulting mixture was stirred for 20 min at -78°C, quenched with satd aq. $NH_4Cl$ (100 mL) and organic products were extracted with $Et_2O$ (2×60 mL). The combined organic extracts were washed with satd aq. NaCl, dried over $Na_2SO_4$ and concentrated under vacuum. TLC analysis of the crude residue revealed two products formed: **15** with $R_f$=0.53 (hexane/$Et_2O$, 1:3) and **17** with $R_f$=0.33 (hexane/$Et_2O$, 1:3) which were separated by column chromatography on silica gel. Yield of **15**: 180 mg (46%); **17**: 146 mg (35%). Analytical data for **15**: RP-HPLC: $R_t$=8.91 min. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.27–5.50 (m, 8H, CH=CH), 3.57 (s, 3H, $OCH_3$), 2.74 (m, 6H, 7-, 10- and 13-$CH_2$), 2.35 (t, 2H, $J$=7.1 Hz, 2-$CH_2$), 2.23 (t, 2H, $J$=7.5 Hz, 18-$CH_2$), 2.04 (m, 7H, 4-,16-$CH_2$ and 20-$CH_3$), 1.59 (m, 4H, 3- and 17-$CH_2$). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 208.14, 173.78, 129.27, 129.01, 128.94, 128.79, 128.35 (2C), 128.20 (2C), 51.28, 43.01, 33.49, 29.70, 26.65 (2C), 25.73 (3C), 24.89, 23.75. FAB HRMS calcd for $C_{21}H_{32}O_3Na$ $[M+Na]^+$: 355.2249. Found: 355.2248. Analytical data for **17**: RP-HPLC: $R_t$=10.82 min. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.25–5.40 (m, 8H, CH=CH), 3.61 (s, 3H, $OCH_3$), 2.77 (m, 6H, 7-, 10- and 13-$CH_2$), 2.27 (t, 2H, $J$=7.1 Hz, 2-$CH_2$), 2.04 (m, 4H, 4- and 16-$CH_2$), 1.65 (m, 2H, 3-$CH_2$), 1.42 (m, 4H, 17- and 18-$CH_2$), 1.15 (s, 6H, $CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 173.99, 130.19, 129.05 (2C), 128.61, 128.35 (2C), 128.13 (2C), 70.87, 51.42, 43.71, 33.60, 29.37 (2C), 27.79, 26.73, 25.81 (3C), 24.96, 24.52. FAB HRMS calcd for $C_{22}H_{36}O_3Na$ $[M+Na]^+$: 371.2557. Found: 371.2561. *Method B*. Compound **15** was prepared by the procedure analogous to Method A using CuI (237 mg, 1.24 mmol), MeLi (0.89 mL, 1.24 mmol) and acid chloride, prepared from ester **14** (410 mg, 1.24 mmol). Yield of **15**: 243 mg (62%).

**4.1.11. (5*Z*,8*Z*,11*Z*,14*Z*)-19-Oxoeicosa-5,8,11,14-tetraenoic acid (16).** An aqueous solution (20 mL) of LiOH (60 mg, 2.52 mmol) was added to a solution of **15** (105 mg, 0.32 mmol) in MeOH (45 mL) under Ar atmosphere. The resulting mixture was stirred overnight at rt. After the reaction was completed, MeOH was removed by evaporation under reduced pressure, the residue was acidified to pH 4 using dilute HCl (1 M) and organic products were extracted with $Et_2O$ (3×40 mL). Combined organic extracts were dried over $Na_2SO_4$, concentrated in vacuum and the crude residue was purified by silica gel column chromatography (hexane/$Et_2O$, 1:2) to give pure **16** (92 mg, 91%). TLC: $R_f$=0.35 (hexane/$Et_2O$, 1:3). RP-HPLC: $R_t$=6.20 min. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.30–5.50 (m, 8H, CH=CH), 5.10 (m, 1H, 18-$CH_2$), 2.72 (m, 6H, 7-, 10- and 13-$CH_2$), 2.35 (t, 2H, $J$=7.1 Hz, 2-$CH_2$), 2.24 (t, 2H, $J$=7.5 Hz, 18-$CH_2$), 2.05 (m, 7H, 4-,16-$CH_2$ and 20-$CH_3$), 1.60 (m, 4H, 3- and 17-$CH_2$). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 208.05, 178.87, 129.27, 128.95 (2C), 128.79, 128.31 (2C), 128.25 (2C), 42.98, 33.50, 29.72, 26.65 (2C), 25.77 (3C), 24.86, 23.79. FAB HRMS calcd for $C_{20}H_{30}O_3Na$ $[M+Na]^+$: 341.2087. Found: 341.2090.

## Acknowledgements

This work was supported in part by the Russian Foundation for Basic Research (02-03-33138), by DAAD (fellowship for I. I.) and by Deutsche Forschungsgemeinschaft (Ku 961/7-1). The authors wish to thank Deutsche Akademische Austauschdienst (DAAD) for providing an HPLC system to I. I. at the Lomonosov State Academy of Fine Chemical Technology. Part of this work was carried out by I. I. during a working stay at the Humboldt University.

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