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ORIGINAL ARTICLE

# A Facile and Efficient Method for the Synthesis of Labeled and Unlabeled Very Long Chain Polyunsaturated Fatty Acids

**Mats Hamberg**[1]

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**Abstract** Several methods are available for elongation of fatty acid acyl chains. The present paper describes adaptation to the fatty acid field of a previously published protocol for manganese-based Wurtz type coupling of alkyl bromides. 22-Bromo-3(*Z*),6(*Z*),9(*Z*),12(*Z*),15(*Z*),18(*Z*)-docosahexaene, easily prepared from 4(*Z*),7(*Z*),10(*Z*),13(*Z*),16(*Z*),19(*Z*)-docosahexaenoic acid, was coupled to homologous ω-bromoesters by stirring for 4 hours at 40°C in the presence of manganese powder, a nickel catalyst and terpyridine. This afforded in yields of 70–75% a series of ω3-hexaenoates of chain lengths of 32–40 carbons. The corresponding fatty acids of >98% purity were obtained following saponification and final purification. By using methyl [2,2,3,3,4,4-$^2H_6$] 10-bromodecanoate as coupling partner it was possible to prepare a very long chain fatty acid in isotopically labeled form, i.e., [2,2,3,3,4,4-$^2H_6$]14(*Z*),17(*Z*),20(*Z*),23(*Z*),26(*Z*),29(*Z*)-dotriacontahexaenoic acid. Also prepared were the monounsaturated long chain fatty acids 15(*Z*)-octadecenoic acid and 15(*Z*)-tetracosenoic acid. Very long chain fatty acids have been isolated from retina and other tissues and are of biological relevance. The methodology described will assist in further analytical and biological studies in this field.

✉ Mats Hamberg
mats.hamberg@ki.se

[1] Department of Medical Biochemistry and Biophysics and Larodan Research Laboratory, Karolinska Institutet, Stockholm, S-171 77, Sweden



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## Abbreviations

| | |
|---|---|
| C32 | 14(*Z*),17(*Z*),20(*Z*),23(*Z*),26(*Z*),29(*Z*)-dotriacontahexaenoic acid |
| C34 | 16(*Z*),19(*Z*),22(*Z*),25(*Z*),28(*Z*),31(*Z*)-tetratriacontahexaenoic acid |
| C36 | 18(*Z*),21(*Z*),24(*Z*),27(*Z*),30(*Z*),33(*Z*)-hexatriacontahexaenoic acid |
| C38 | 20(*Z*),23(*Z*),26(*Z*),29(*Z*),32(*Z*),35(*Z*)-octatriacontahexaenoic acid |
| C40 | 22(*Z*),25(*Z*),28(*Z*),31(*Z*),34(*Z*),37(*Z*)-tetracontahexaenoic acid |
| DHA | 4(*Z*),7(*Z*),10(*Z*),13(*Z*),16(*Z*),19(*Z*)-docosahexaenoic acid |
| DHA-Br | 22-bromo-3(*Z*),6(*Z*),9(*Z*),12(*Z*),15(*Z*),18(*Z*)-docosahexaene |
| DMF | *N*,*N*-dimethylformamide |
| $NiCl_2$(glyme) | nickel(II) chloride ethyleneglycol dimethyl ether complex |
| terpyridine | 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine |

## Introduction

Elongation of fatty acid acyl chains is a common task in lipid synthetic chemistry. Apart from producing higher homologues, such procedures can be used for the incorporation of isotopic label into specific positions. For practical

work, several methods are available and include for one-carbon elongation the Arndt-Eistert synthesis, whereby the fatty acid is converted into a diazoketone which is rearranged into the elongated ester (Wotiz and Buco, 1955). An alternative procedure for adding one carbon consists of transforming the fatty acid into its corresponding bromide, which can be further converted into the nitrile and subsequently hydrolyzed to provide the elongated product. Two-carbon elongation is classically performed by malonic ester synthesis (Klenk and Mohrhauer, 1960; Spener and Mangold, 1973). Although this is a widely used procedure it has drawbacks when applied to polyunsaturated fatty acids since it involves exposure to strong base and high temperatures. An improved method for C2-elongation involving formation and fragmentation of a 2,2-dimethyloxazoline intermediate has been published (Kuklev and Smith, 2006). The Kolbe anodic cross-coupling of fatty acids with shorter-chain half-esters offers a versatile method for elongation of acyl chains (Schäfer, 1979). Saturated and monounsaturated fatty acids can be used in this procedure but when applied to polyunsaturated fatty acids yields are generally poor. Coupling of halides to metal derivatives of alkyl halides, such as the $Li_2CuCl_4$-catalyzed coupling of Grignard compounds, offers another flexible method to obtain longer acyl chains (Frisch and Beller, 2005). A drawback is the need of protection and deprotection of reactive functional groups such as alcohol, carboxyl or ester.

The present paper describes a Wurtz type coupling protocol for generation of elongated acyl chains. It is based on a nickel-catalyzed manganese-promoted method for bromide coupling described by Prinsell et al. (2010). Application to the bromide derivative prepared from 4(*Z*),7(*Z*),10(*Z*),13(*Z*),16(*Z*),19(*Z*)-docosahexaenoic acid (DHA) and several ω-bromoesters as coupling partners resulted in a series of very long chain fatty acids previously isolated from vertebrate retina (Aveldano, 1987; Aveldano and Sprecher, 1987) and later found to serve as precursors of biologically active oxygenated derivatives, socalled elovanoids (Bazan, 2018).

## Materials and Methods

DHA was purchased from NuChek, Elysian, MN, USA. 15(*Z*)-octadecenoic acid as well as 15(*Z*)- and 15(*E*)-tetracosenoic acids were products of Larodan Co., Stockholm, Sweden. Nickel(II) chloride ethyleneglycol dimethyl ether complex ($NiCl_2$(glyme)), 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (terpyridine), manganese, and anhydrous *N,N*-dimethylformamide (DMF) were purchased from Sigma-Aldrich Sweden AB, Stockholm, Sweden.

### Bromoesters

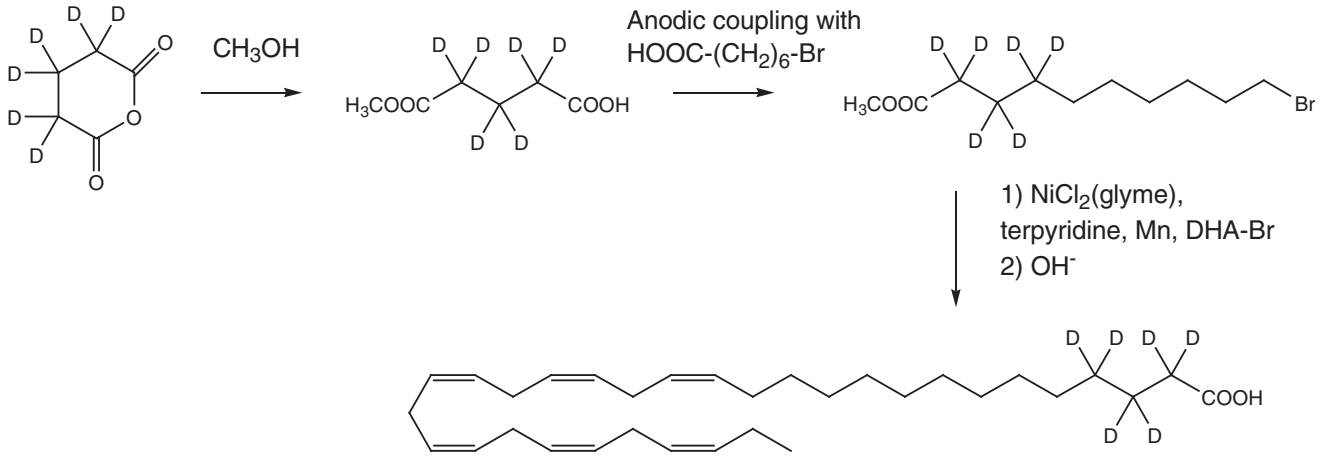
Methyl esters of ω-bromoacids of chain lengths 2–7, 10, 12, and 16 were obtained from Sigma-Aldrich or TCI.

Methyl [2,2,3,3,4,4-$^2H_6$]10-bromodecanoate was prepared by anodic coupling (Hamberg, 1971) of deuterated methyl hydrogen glutarate to 7-bromoheptanoic acid (Scheme 1). [2,2,3,3,4,4-$^2H_6$]glutaric anhydride purchased from C/D/N isotopes (Pointe-Claire, Quebec, Canada) (1 g, 8.3 mmol) was added to 0.37 g (11.6 mmol) of dry methanol and the mixture stirred at 23°C for 15 hours and then kept at 50°C for 1 hours. The deuterated methyl hydrogen glutarate thus formed (about 8.3 mmol) together with 3.1 g (14.8 mmol) of 7-bromoheptanoic acid was added to methanol (80 mL) containing sodium methoxide (1.5 mmol). The solution was electrolyzed for 1.5 hours in a thermostatted cell (about 15°C) using Pt electrodes and a current of 1 A (Scheme 1). Extraction with diethyl ether afforded a product from which the title compound was isolated in 39% yield by silica gel chromatography followed by purification by reversed-phase HPLC (column, 250 × 10 mm Nucleosil $C_{18}$, solvent system, acetonitrile-water 8:2 [v/v] at a flow rate of 4 mL $min^{-1}$). The mass spectrum showed prominent ions at *m/z* 270/272 ($M^+$), 239/241 ($M^+$–$OCH_3$), 191 ($M^+$–Br), and 77 ($[CD_2 = C[OD]\text{-}OCH_3]^+$). GC–MS analysis further showed that the sample was >99% deuterated and had the following isotopic composition: 89.5% $d_6$, 8.8% $d_5$, 1.7% $d_4$, and less than 0.2% of $d_3$, $d_2$, $d_1$ and, $d_0$ species. The presence of $d_5$ and $d_4$ species suggested a limited exchange of deuterium in the carboxyl α position, most likely taking place during the anodic coupling step.

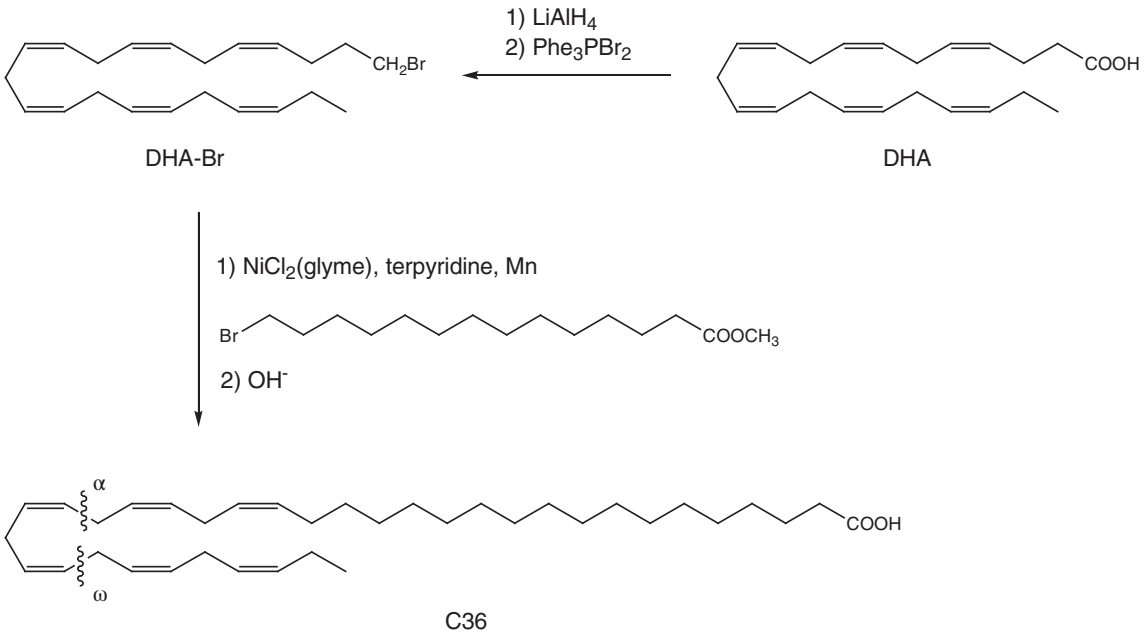
Methyl 14-bromotetradecanoate was synthesized in a yield of 38% by anodic coupling of methyl hydrogen azelate (20 mmol) to 7-bromoheptanoic acid (10 mmol) as described above. The pure bromoester was obtained following purification by silica gel chromatography and reversed-phase high-performance chromatography (solvent system, acetonitrile-water 9:1 [v/v]). Methyl 18-bromooctadecanoate was prepared in an analogous way starting with methyl hydrogen succinate and 16-bromohexadecanoic acid.

### Alkyl Bromides

22-Bromo-3(*Z*),6(*Z*),9(*Z*),12(*Z*),15(*Z*),18(*Z*)-docosahexaene (DHA—Br) was prepared in 90% yield by $LiAlH_4$ reduction of DHA (1 g) followed by treatment with triphenylphosphine dibromide in dry dichloromethane and purification by silica gel chromatography (Scheme 2). In the same way, 1-bromo-9(*Z*)-octadecene was prepared from methyl oleate. 8-Bromo-3(*Z*)-octene was obtained by bromination of 5(*Z*)-octen-1-ol purchased from Sigma-Aldrich.




**Scheme 1** Synthesis of methyl [2,2,3,3,4,4-$^{2}H_6$]10-bromodecanoate and [2,2,3,3,4,4-$^{2}H_6$]14(*Z*),17(*Z*),20(*Z*),23(*Z*),26(*Z*),29(*Z*)-dotriacontahexaenoic acid ($d_6$-C32)




**Scheme 2** Synthesis of 18(*Z*),21(*Z*),24(*Z*),27(*Z*),30(*Z*),33(*Z*)-hexatriacontahexaenoic acid (C36) by coupling of 22-bromo-3(*Z*),6(*Z*),9(*Z*),12(*Z*),15(*Z*),18(*Z*)-docosahexaene (DHA—Br) to methyl 14-bromotetradecanoate. The points of cleavage generating the α- and ω-ions in the mass spectrum of the methyl ester of C36 are indicated

## Gas–Liquid Chromatography—Mass Spectrometry (GC–MS)

GC–MS was performed with an Agilent 5977E series GC/MSD equipped with a capillary column of 5% phenylmethylsiloxane (12 m × 0.2 mm, film thickness 0.33 μm) using helium as the carrier gas. For most runs, the oven temperature was programmed from 50°C at a rate of 20°C $min^{-1}$ or from 80°C at a rate of 10°C $min^{-1}$ to a final temperature of 320°C and kept at this temperature for 15 min.

## Thin Layer Chromatography

Thin layer chromatography (TLC) was carried out with DC-Fertigplatten Kieselgel 60 from Merck and a solvent system of hexane-ethyl acetate-acetic acid 90:10:0.5 (v/v/

v). Spots were visualized by spraying with phosphomolybdic acid and heating at 120°C.

### NMR Spectroscopy

$^1$H NMR spectra were recorded using a Bruker 500 MHz instrument. The solvent was deuteriochloroform and tetramethylsilane was used as internal chemical shift standard.

### Procedure for Preparation of Very Long Chain Fatty Acids

For synthesis of very long chain fatty acids having chain lengths of 32–40 carbons (fatty acids C32–C40), DHA-Br (113 mg, 0.3 mmol) and methyl ω-bromoalkanoate (0.9 mmol) were dissolved in 2 mL of dry DMF and $NiCl_2$(glyme) (8 mg, 36 μmol), terpyridine (13 mg, 32 μmol), and manganese powder (73 mg, 1.3 mmol) were added. The suspension was mixed, purged with argon, and stirred at 40°C for 4 hours. The product isolated by extraction with diethyl ether was subjected to silica gel chromatography (elution with diethyl ether-hexane 3:97 [v/v]) to provide the elongated ester (yields, 70–75% based on DHA-Br added, purity >90%). Subsequent treatment with 0.3 M NaOH in 85% ethanol under argon at 60°C for 1 hours afforded the elongated acid, which was further purified on a second silica gel column (elution with diethyl ether-hexane-acetic acid 10:90:0.05 (v/v/v); fractions monitored either by TLC or by GC–MS after methylation). In this way, were obtained C32, C34, C36, C38, C40 as well as [2,2,3,3,4,4-$^2H_6$]C32 having >98% purity as judged by TLC and by GC–MS analysis of their methyl ester derivatives.

Synthesis of 15(*Z*)-octadecenoic acid was carried out using the above protocol starting with 8-bromo-3(*Z*)-octene (0.3 mmol) and methyl 10-bromodecanoate (0.9 mmol). GC–MS analysis showed that 96% of the material recovered was due to the coupling products 3,13-hexadecadiene, methyl 15-octadecenoate, and dimethyl eicosane-1,-20-dioate in a ratio of 1:6.5:9. Silica gel chromatography afforded methyl 15(*Z*)-octadecenoate (0.22 mmol; purity >98%). The possible presence of the 15(*E*) isomer in this material was examined by GC–MS using the authentic materials as references. Although <0.3% of the *E* isomer was detectable, this level was also observed for the starting 8-bromo-3(Z)-octene. Saponification of the methyl 15(*Z*)-octadecenoate and crystallization from hexane at -20°C gave pure 15(*Z*)-octadecenoic acid.

Methyl 15(*Z*)-tetracosenoate was prepared using the standard protocol starting with 1-bromo-9(*Z*)-octadecene and methyl 6-bromohexanoate. Following purification by silica gel chromatography, a sample was analyzed by GC–MS using authentic methyl 15(*Z*)- and 15(*E*)-tetracosenoates as references. The methyl tetracosenoate synthesized was >98% of the 15(*Z*) isomer but contained a trace (<1.4%) of the 15(*E*) isomer. 15(*Z*)-Tetracosenoic acid was obtained following saponification and crystallization from hexane.

**Table 1** $^1$H NMR spectral data of 18(Z),21(Z),24(Z),27(Z),30(Z),33(*Z*)-hexatriacontanoic acid (C36)

| Proton | Chemical shift, multiplicity (*J*, Hz) |
|---|---|
| H-2 | 2.32–2.37 t (7.5) |
| H-3 | 1.59–1.67 quint (7.3) |
| H-4 to H-16 | 1.22–1.37 m |
| H-17, H-35 | 2.02–2.12 quint (7.5) |
| H-18, H-19, H-21, H-22, H-24, H-25, H-27, H-28, H-30, H-31, H-33, H-34 | 5.30–5.42 m |
| H-20, H-23, H-26, H-29, H-32 | 2.79–2.87 m |
| H-36 | 0.97 t (7.4) |

### 14(*Z*),17(*Z*),20(*Z*),23(*Z*),26(*Z*),29(*Z*)-Dotriacontahexaenoic Acid (C32)

A colorless oil. The mass spectrum of the methyl ester derivative showed prominent ions at *m/z* 482 ($M^+$), 451 ($M^+$–$OCH_3$), 413 ($M^+$–$CH_2$–CH=CH–$CH_2$–$CH_3$), 306 ($M^+ - [C_{13}H_{19} + H]$, "α-ion"), 133, 108 ($[C_8H_{12}]^+$, "ω-ion"), and 79. The sample was homogeneous on TLC ($R_f = 0.17$).

### 16(*Z*),19(*Z*),22(*Z*),25(*Z*),28(*Z*),31(*Z*)-Tetratriacontahexaenoic Acid (C34)

A colorless viscous oil which solidified at +4°C. The mass spectrum of the methyl ester derivative showed prominent ions at *m/z* 510 ($M^+$), 479 ($M^+$–$OCH_3$), 441 ($M^+$–$CH_2$–CH=CH–$CH_2$–$CH_3$), 334 ($M^+ - [C_{13}H_{19} + H]$, "α-ion"), 133, 131, 108 ($[C_8H_{12}]^+$, "ω-ion"), and 79. The sample was homogeneous on TLC ($R_f = 0.18$).

### 18(*Z*),21(*Z*),24(*Z*),27(*Z*),30(*Z*),33(*Z*)-Hexatriacontahexaenoic Acid (C36)

A semisolid which could be recrystallized from methanol at +4°C; melted to a colorless oil at about 35°C. The mass spectrum of the methyl ester derivative showed prominent ions at *m/z* 538 ($M^+$), 507 ($M^+$–$OCH_3$), 469 ($M^+$–$CH_2$–CH=CH–$CH_2$–$CH_3$), 362 ($M^+ - [C_{13}H_{19} + H]$, "α-ion"), 133, 131, 108 ($[C_8H_{12}]^+$, "ω-ion"), and 79. $^1$H NMR spectral data are given in Table 1. The sample was homogeneous on TLC ($R_f = 0.20$).

### 20(Z),23(Z),26(Z),29(Z),32(Z),35(Z)-Octatriacontahexaenoic Acid (C38)

A solid, which could be recrystallized from methanol at +4°C affording material having m.p. 40.5–41.0°C. The mass spectrum of the methyl ester derivative showed prominent ions at *m/z* 566 ($M^+$), 535 ($M^+ - OCH_3$), 497 ($M^+ - CH_2$–CH=CH–$CH_2$–$CH_3$), 390 ($M^+ - [C_{13}H_{19} + H]$, "α-ion"), 131, 108 ($[C_8\ H_{12}]^+$, "ω-ion"), and 79. The sample was homogeneous on TLC ($R_f = 0.22$).

### 22(Z),25(Z),28(Z),31(Z),34(Z),37(Z)-Tetracontahexaenoic Acid (C40)

A solid which was recrystallized from methanol at +4°C affording material having m.p. 48.0–48.5°C. The mass spectrum of the methyl ester derivative showed prominent ions at *m/z* 594 ($M^+$), 563 ($M^+ - OCH_3$), 525 ($M^+ - CH_2$–CH=CH–$CH_2$–$CH_3$), 418 ($M^+ - [C_{13}H_{19} + H]$, "α-ion"), 131, 108 ($[C_8\ H_{12}]^+$, "ω-ion"), and 79. The sample was homogeneous on TLC ($R_f = 0.25$).

### [2,2,3,3,4,4-$^2H_6$]14(Z),17(Z),20(Z),23(Z),26(Z),29(Z)-Dotriacontahexaenoic Acid ($d_6$-C32)

A colorless oil. The mass spectrum of the methyl ester derivative showed prominent ions at *m/z* 488 ($M^+$), 457 ($M^+ - OCH_3$), and 419 ($M^+ - CH_2$-CH=CH-$CH_2$-$CH_3$). As expected, the α-ion appearing at *m/z* 306 in the unlabeled molecule was shifted to *m/z* 312 whereas the ω-ion remained at *m/z* 108. The specimen was due to >99% deuterated molecules and had an isotopic composition of 84.0% hexadeuterated ($d_6$) molecules, 14.0% $d_5$, 2.0% $d_4$, and less than 0.2% of $d_3$, $d_2$, $d_1$, and $d_0$ species.

### Methyl 15(Z)-Octadecenoate and 15(Z)-Octadecenoic Acid

The methyl ester was a colorless oil whose mass spectrum showed prominent ions at *m/z* 296 ($M^+$), 264 ($M^+ - CH_3OH$), 222, 180, 152, 74, and 55. The gas chromatogram showed a trace (<0.3%) of the later eluting 15(*E*) isomer. 15(*Z*)-Octadecenoic acid was a crystalline solid, m.p. 41.5–42.0°C (lit. 41–42°C, (Rawling et al., 2010). Its analytical data were identical to those of an authentic sample.

### Methyl 15(Z)-Tetracosenoate and 15(Z)-Tetracosenoic Acid

The methyl ester was a colorless oil whose mass spectrum was identical to that of an authentic sample and showed ions at *m/z* 380 ($M^+$), 348 ($M^+ - CH_3OH$), 306, 264, 83, 69, and 55. The gas chromatogram showed a trace (<1.4%) of the later eluting 15(*E*) isomer. 15(*Z*)-Tetracosenoic acid was a crystalline solid and proved identical to an authentic sample.

## Results and Discussion

Coupling of alkyl bromides in the presence of metallic sodium in diethyl ether was originally described by Adolphe Wurtz (Wurtz, 1855), however, use of this method for reductive dimerization is hampered by variable yields and limited tolerance to functional groups. Modifications using metals such as Cu, Fe, and Pd have been developed but many of them appear to have drawbacks for the present purpose.

Recently Weix and coworkers elaborated a method for nickel-catalyzed dimerization of alkyl halides, alkyl pseudohalides, and allylic acetates (Prinsell et al., 2010). The procedure uses 1 eq. of metallic Mn and catalytic amounts of $NiCl_2$(glyme) and terpyridine and is performed in DMF at moderate temperature. The mildness of the method and the lack of involvement of strong acid or base made it attractive for use in the polyunsaturated fatty acid field. Although described for dimerization of single components (Prinsell et al., 2010), initial experimentation in our laboratory revealed that mixed coupling of two different bromides, i.e., a long-chain alkyl bromide and an ω-bromoester, resulted in good yields of elongated ester provided that an excess of bromoester (3:1) was used. The product consisted of a hydrocarbon, a monoester and a diester. These were readily separated by silica gel chromatography, affording the desired monoester in a purity of >90%. The yields based on alkyl bromide used (0.3 mmol) were 70–75%. Saponification and purification by silica gel chromatography yielded the corresponding free acid in a purity of >98%.

The Wurtz metal-promoted coupling proceeds by single-electron transfer and an alkyl radical, and it therefore seemed important to check for possible radical-induced *cis-trans* isomerization of double bonds. NMR analysis of the very long chain fatty acids synthesized gave no indication for the presence of *trans* double bond(s), however, the complexity of the signals from the six double bonds at 5.30–5.42 p.p.m. (Table 1) necessitated more precise tests. First, methyl 15-octadecenoate was synthesized by coupling of 8-bromo-3(*Z*)-octene to methyl 10-bromodecanoate. Analysis by GC–MS under conditions where the *Z* and *E* isomers of methyl 15-octadecenoate separate revealed that the product was >99.7% of the 15(*Z*) isomer. Second, 1-bromo-9(Z)-octadecene was coupled to methyl 6-bromohexanoate. The methyl 15-tetracosenoate

thus formed was analyzed by GC–MS using authentic methyl 15(*Z*)- and 15(*E*)-tetracosenoates as references. The tetracosenoate synthesized was >98% of the 15(*Z*) isomer although a small peak (<1.4%) due to the 15(*E*) isomer was also observed. From these experiments it was concluded that no or only insignificant (*Z*) - > (*E*) isomerization of double bonds took place during the coupling reaction. In cases, where a > 99% pure product is needed, further purification by RP-HPLC or crystallization may be required.

As targets for the coupling method were chosen the very long chain fatty acids isolated from bovine retina and other tissues (Aveldano, 1987; Aveldano and Sprecher, 1987; Bazan, 2018). DHA—Br, the bromo derivative of docosahexaenoic acid prepared by reduction of DHA to the alcohol followed by bromination, was coupled to ω-bromoesters having chain lengths of 10–18 carbon atoms. In this way, a set of very long chain (32–40 carbons) fatty acids could be prepared in good yield (Scheme 2). Such compounds have previously been obtained using multistep syntheses involving $Li_2CuCl_4$-catalyzed coupling of Grignard reagents (Raman and Tarwade, 2013). The deuterated very long chain fatty acid prepared, i.e., [2,2,3,3,4,4-$^2H_6$]14(*Z*),17(*Z*),20(*Z*),23(*Z*),26(*Z*),29(*Z*)-dotriacontahexaenoic acid (Scheme 1), appears to be the first example of a very long chain fatty acid obtained in isotopically labeled form.

As expected, the methyl esters of the long chain acids synthesized on GC gave a homologous series of peaks showing considerable broadening (Aveldano, 1987; Aveldano and Sprecher, 1987). Their identities were supported by the mass spectra, which all showed the socalled "ω-ion" at *m/z* 108 ($[C_8H_{12}]^+$) typical of ω3-fatty acid esters (Mjøs, 2004). Another distinctive ion was the socalled "α-ion" ($M^+ - [C_{13}H_{19} + H]$) formed by cleavage at the methylene group subsequent to the two first double bonds counted from the carboxyl end (e.g., cleavage at C-23/C-24 in case of acid C36; Scheme 2) (Brauner et al., 1982; Mjøs, 2004). The $^1$H NMR spectrum recorded on C36 further supported the structure by showing signals typical for DHA (Gunstone, 1990; Sandri and Viala, 1995) as well as a strong signal at 1.22–1.37 p.p.m. due to the hydrogens at carbons C-4 to C-16. DHA has a melting point of -44°C. Although C32 and C34 were also oils at room temperature, C36 was a semisolid and C38 and C40 were crystalline solids having m.p. 40.5–41.0°C and 48.0–48.5°C, respectively.

The scope of the present coupling method is under further study. Of particular interest is its possible use in larger scale syntheses as an alternative to anodic coupling and other coupling procedures currently used in the fatty acid field.

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**Conflict of Interest** The authors declare that they have no conflict of interest.

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