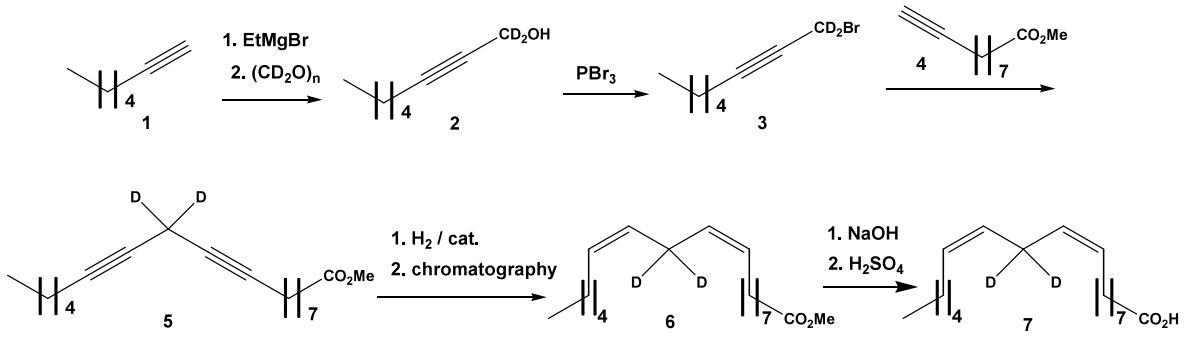
Supplemental Material

Synthesis of 11,11-D2-linoleic acid (7) [29,30]



1,1-Dideutero-oct-2-yn-1-ol (**2**) To a solution of ethylmagnesium bromide prepared from bromoethane (100 ml), 1,2-dibromoethane (1 ml) and magnesium turnings (31.2 g) in dry THF (800 ml), heptyn-1 ((**1**); 170 ml) was added dropwise over 30-60 min under argon. The reaction mixture was stirred for 1 h, and then deuteroparaform (30 g) was carefully added in one portion. The reaction mixture was gently refluxed for 2 h, chilled to -10^{o}C, and then 5-7 ml of water was slowly added. The mixture was poured into 0.5 kg slurry of crushed ice and 40 ml concentrated sulphuric acid and diluted with 0.5 L of hexane. The organic phase was separated, and the remaining aqueous phase was extracted with 5:1 hexane:ethyl acetate (3 x 300 ml). The combined organic fraction was washed with sat. NaCl (1 x 50 ml), sat. $NaHCO_3$, (1 x 50 ml), and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to yield 119.3 g (99%) of colourless oil which was used without further purification. HRMS, *m/z* calculated for $C_8H_{12}D_2O$: 128.1168; found: 128.1173. ^{1}H NMR ($CDCl_3$, δ): 2.18 (t, J = 7.0, 2H), 1.57 (s, 1H), 1.47 (quint, J = 7.0 Hz, 2H), 1.31 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H).

1,1-Dideutero-1-bromo-oct-2-yne (**3**) To a solution of (**2**) (119.2 g; 0.93 mol) and pyridine (19 ml) in dry diethyl ether (300 ml), 36 ml of PBr_3 in 35 ml diethyl ether was added dropwise with stirring over 30 min at -15°C under argon. The reaction mixture was allowed to gradually warm up to r.t. and then refluxed 3 h with stirring and 1 h without stirring. The reaction mixture was then cooled down to -10°C and 500 ml of cold water was added. When the residue dissolved, saturated NaCl (250 ml) and hexane (250 ml) were added, and the organic layer was separated. The aqueous fraction was washed with hexane (2 x 100 ml), and the combined organic fractions were washed with NaCl (2 x 100 ml) and dried over Na_2SO_4 in presence of traces of hydroquinone and triethylamine. The solvent was removed by

distillation at atmospheric pressure followed by rotary evaporation. The residue was fractionated by vacuum distillation (3 mm Hg) to give 147.4 g (82 % counting per deutero-paraform) of pale yellow oil. B.p. 75°C. HRMS, *m/z* calculated for $C_8H_{11}D_2Br$: 190.0324; found: 189.0301, 191.0321. ^{1}H NMR ($CDCl_3$, δ): 2.23 (t, J = 7.0 Hz, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.33 (m, 4H, CH_2), 0.89 (t, J = 6.9 Hz, 3H, CH_3),

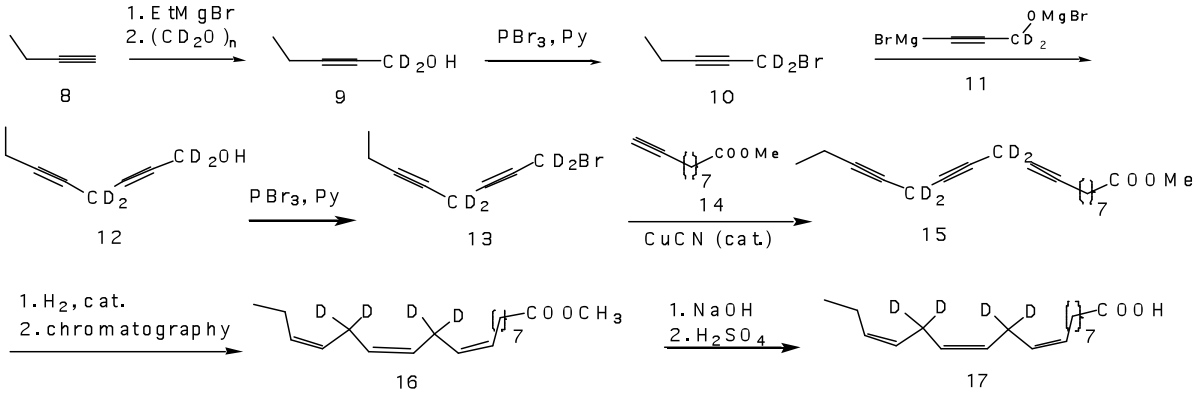
11,11-Dideutero-octadeca-9,12-diynoic acid methyl ester (**5**) CuI (133 g) was quickly added to 400 ml of DMF (freshly distilled over CaH_2), followed by dry NaI (106 g), K_2CO_3 (143 g). Dec-9-ynoic acid methyl ester ((**4**); 65 g) was then added in one portion, followed by bromide (**3**) (67 g). Additional 250 ml of DMF was used to rinse the reagents off the flask walls into the bulk of reaction mixture, which was then stirred for 12 h. 500 ml of saturated aqueous NH_4Cl was then added with stirring, followed in a few minutes by 400 ml of saturated aqueous NaCl and then by a 5:1 mixture of hexane:EtOAc (300 ml). The mixture was further stirred for 15 min and then filtered through a fine mesh Schott glass filter. The residue was washed with hexane:EtOAc mix several times. The organic fraction was separated, and the aqueous phase was additionally extracted (3 x 200 ml). The combined organic fraction was dried (Na_2SO_4), traces of hydroquinone and diphenylamine were added, and the solvent was evaporated *in vacuo*. The residue was immediately distilled at 1 mm Hg, to give 79 g (77%) of a 165-175°C boiling fraction. HRMS, *m/z* calculated for $C_{19}H_{28}D_2O_2$: 292.2369; found: 292.2365. ^{1}H NMR ($CDCl_3$, δ): 3.67 (s, 3H, OCH_3), 2.3 (t, J = 7.5 Hz, 2H, CH_2), 2.14 (t, J = 7.0 Hz, 4H, CH_2), 1.63 (m, 2H, CH_2), 1.47 (m, 4H, CH_2), 1.3 (m, 10H, CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3).

11,11-Dideutero-cis,cis-octadeca-9,12-dienoic acid methyl ester (**6**) A suspension of nickel acetate tetrahydrate (31.5 g) in 96 % EtOH (400 ml) was heated with stirring to approx. 50-60°C until the salt dissolved. The flask was flushed with hydrogen, and then 130 ml of $NaBH_4$ solution, (prepared by a 15 min stirring of $NaBH_4$ suspension (7.2 g) in EtOH (170 ml) followed by filtering) was added dropwise over 20-30 min with stirring. In 15-20 min ethylenediamine (39 ml) was added in one portion, followed in 5 min by an addition of (**5**) (75 g) in EtOH (200 ml). The reaction mixture was very vigorously stirred under hydrogen (1 atm). The absorption of hydrogen stopped in about 2 h. To the reaction mixture, 900 ml of hexane and 55 ml of AcOH were added, followed by water (15 ml). Hexane (400 ml) was added, and the mixture was allowed to separate. Aqueous fractions were extracted by 5:1 mix of hexane:EtOAc. The completion of extraction was monitored by TLC. The combined organic phase was washed with diluted solution of H_2SO_4, followed by saturated $NaHCO_3$

and saturated NaCl, and then dried over Na_2SO_4. The solvent was removed at reduced pressure. Silica gel (Silica gel 60, Merck; 162 g) was added to a solution of silver nitrate (43 g) in anhydrous MeCN (360 ml), and the solvent removed on a rotavap. The obtained impregnated silica gel was dried for 3 h at 50°C (aspiration pump) and then 8 h on an oil pump. 30 g of this silica was used per gram of product. The reaction mixture was dissolved in a small volume of hexane and applied to the silver-modified silica gel, and pre-washed with a 1-3 % gradient of EtOAc. When the non-polar contaminants were washed off (control by TLC), the product was eluted with 10 % EtOAc and the solvent evaporated in vacuo to give 52 g of the title ester (**6**) as a colourless liquid. HRMS, *m/z* calculated for $C_{19}H_{32}D_2O_2$: 296.2682; found: 296.2676. IR (CCl_4): $\tilde{\nu}$ = 1740 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 5.32 (m, 4H), 3.66 (s, 3H, OCH_3), 2.29 (t, J = 7.5 Hz, 2H, CH_2), 2.02 (m, 4H, CH_2), 1.60 (m, 2H, CH_2), 1.30 (m, 14H, CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3).

11,11-Dideutero-cis,cis-octadeca-9,12-dienoic acid (**7**) A solution of KOH (46 g) in water (115 ml) was added to a solution of ester (**6**) (46 g) in MeOH (60 ml). The reaction mixture was stirred at 40-50°C for 2 h (control by TLC) and then diluted with 200 ml of water. Two thirds of the solvent were removed (rotavap). Diluted sulphuric acid was added to the residue to pH 2, followed by diethyl ether with a little pentane. The organic layer was separated and the aqueous layer washed with diethyl ether with a little pentane. The combined organic fractions were washed with saturated aqueous NaCl and then dried over Na_2SO_4. The solvent was evaporated to give 43 g of (**7**) (99%). IR (CCl_4): $\tilde{\nu}$ = 1741, 1711 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 10.5 (br s, 1H), 5.32 (m, 4H), 2.33 (t, J = 7.5 Hz, 2H, CH_2), 2.03 (m, 4H, CH_2), 1.60 (m, 2H, CH_2), 1.30 (m, 14H, CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3).

Synthesis of 11,11,14,14-D4-α-linolenic acid (17) [31]



1,1-Dideutero-pent-2-yn-1-ol (**9**) But-1-yne (**8**) was slowly bubbled through a solution of ethylmagnesium bromide prepared from bromoethane (100 ml) and magnesium turnings (31.3 g) in dry THF (800 ml) on a bath (-5°C). Every now and then the bubbling was stopped and the cylinder with but-1-yne was weighed to measure the rate of consumption. The supply of alkyne was stopped shortly after a voluminous precipitate formed (the measured mass of alkyne consumed was 125 g). The reaction mixture was warmed up to r.t. over 30 min, and then stirred for 15 min. The mixture was then heated up to 30°C, at which point the precipitate dissolved, and then stirred at r.t. for another 30 min. Deuteroparaform (28 g) was added in one portion and the mixture was refluxed for 3 h, forming a clear solution. It was cooled down to r.t. and poured into a mixture of crushed ice (800 g) and 50 ml conc. H_2SO_4. Hexane (400 ml) was added and the organic layer was separated. The aqueous phase was saturated with NaCl and extracted with a 4:1 mixture of hexane:EtOAc (1 L). The completion of extraction process was monitored by TLC. The combined organic phases were washed with saturated NaCl, $NaHCO_3$ and again NaCl, and dried over Na_2SO_4. The solvent was removed by distillation at the atmospheric pressure (max vapour temperature 105°C). The residue (70.5 g; 94 %) was used without further purification. HRMS, *m/z* calculated for $C_5H_6D_2O$: 86.0699; found: 86.0751. ^{1}H NMR ($CDCl_3$, δ): 2.21 (q, J = 7.5 Hz, 2H, CH_2), 1.93 (br s, 1H, OH), 1.12 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 87.7, 77.6, 13.7, 12.3 (signal of CD_2 is absent).

1,1-Dideutero-1-bromo-pent-2-yne (**10**) To a solution of (**9**) (70.5 g) and pyridine (16.5 ml) in dry diethyl ether (280 ml), 32.3 ml of PBr_3 in 50 ml diethyl ether was added dropwise with

stirring over 30 min at -10°C under argon. The reaction mixture was allowed to gradually warm up to r.t. over 1 h. A small amount of hydroquinone was added, and the mixture was then refluxed for 4.5 h. The reaction mixture was then cooled down to -10°C and 350 ml of cold water was added. When the residue dissolved, saturated NaCl (350 ml) and hexane (300 ml) were added, and the organic layer was separated. The aqueous fraction was washed with diethyl ether (2 x 150 ml), and the combined organic fractions were washed with NaCl (2 x 50 ml) and dried over Na_2SO_4 in presence of traces of hydroquinone and triethylamine. The solvent was removed at atmospheric pressure, and then the 147-155°C boiling fraction was distilled off. Alternatively, upon reaching 100°C, the distillation at atmospheric pressure was stopped and the product distilled off at 77-84°C (25 mm Hg). Yield: 107 g of clear liquid. HRMS, *m/z* calculated for $C_5H_5D_2Br$: 147.9855; found: 146.9814, 148.9835. IR (CCl_4): $\tilde{\nu} = 2251$ cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.23 (q, J = 7.5 Hz, 2H, CH_2), 1.11 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 89.3, 74.5, 13.4, 12.6 (signal of CD_2 is absent).

1,1,4,4-Tetradeutero-octa-2,5-diyn-1-ol (**12**) Ethylmagnesium bromide, prepared from ethyl bromide (53 ml) and magnesium turnings (15.8 g) in 400 ml of dry THF, was added in small portions to 350 ml of dry THF, simultaneously with acetylene bubbling through this mixture (at approx. 25 L/h rate) with vigorous stirring. The Grignard reagent solution was fed to the mixture at approx. 10 ml per 2-5 min. When all ethylmagnesium bromide was added (after approx. 2.5 h), acetylene was bubbled through the system for another 15 min. Deuteroparaform (17.3 g) and CuCl (0.2 g) were added under argon, and the reaction mixture was refluxed without stirring for 2.5 h, until deuteroparaform dissolved. Ethylmagnesium bromide solution, prepared from 14.8 g magnesium and 50 ml ethyl bromide in 250 ml of dry THF, was added dropwise to the reaction mixture over 20 min. When the gas emanation ceased, a condenser was attached and 250 ml of solvent were distilled off. The reaction mixture was then cooled to 30°C, and CuCl (1.4 g) was added followed by a dropwise addition, over 15 min, of bromide (**10**) (69 g). The reaction mixture was then refluxed for 5 h, cooled slightly (a precipitate will form if cooling is too fast), and poured into a slurry of crushed ice (1-1.2 kg) and 40 ml concentrated H_2SO_4. The mixture was diluted with hexane (600 ml). The organic fraction was separated, and the aqueous fraction was additionally extracted with 5:1 hexane:EtOAc (2 x 400 ml). The combined organic fraction was washed, with saturated NaCl, followed by saturated $NaHCO_3$ and NaCl. The bulk of the solvent was removed at atmospheric pressure in presence of traces of hydroquinone and triethylamine. The residue was flushed through 100 ml of silica gel (eluent: 7:1 hexane:EtOAc). The bulk of

the solvent was removed at the atmospheric pressure, and the remainder on a rotavap. 49.5 g (85 %) of the title compound obtained was used without further purification. HRMS, *m/z* calculated for $C_8H_6D_4O$: 126.0979; found: 126.0899. IR (CCl_4): $\tilde{\nu} = 3622$ cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.16 (q, J = 7.5 Hz, 2H, CH_2), 1.85 (br s, 1 H, OH), 1.11 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 82.3, 80.4, 78.3, 72.6, 13.7, 12.2

1,1,4,4-Tetradeutero-1-bromo-octa-2,5-diyne (**13**) was synthesised as described for bromide (**3**); 2 ml of pyridine, 14 ml PBr_3 and 250 ml of diethyl ether was used for 54.2 g of alcohol (**12**). The product was purified by distillation at 4 mm Hg. Yield: 53 g (65 %) of (**13**); b.p. 100-110°C. HRMS, *m/z* calculated for $C_8H_5D_4Br$: 188.0135; found: 187.0136, 189.0143. IR (CCl_4): $\tilde{\nu} = 2255$ cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.13 (q, J = 7.5 Hz, 2H, CH_2); 1.07 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 82.5, 81.8, 75.0, 72.0, 13.6, 12.2.

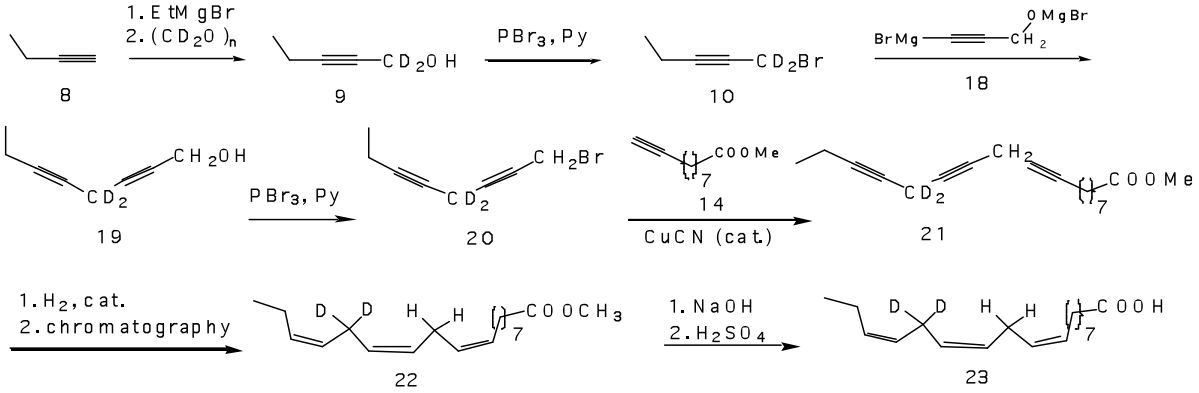
11,11,14,14-Tetradeutero-octadeca-8,12,15-triynoic acid methyl ester (**15**) was synthesised in a way similar to that described for 11,11-dideutero-octadeca-9,12-diynoic acid methyl ester (**5**). CuI (97 g) was quickly added to 400 ml of DMF (freshly distilled over CaH_2), followed by dry NaI (77.5 g), K_2CO_3 (104.5 g). Dec-9-ynoic acid methyl ester ((**14**); 47.5 g) was then added in one portion, followed by bromide (**13**) (48.5 g). Additional 250 ml of DMF was used to rinse the reagents off the flask walls into the bulk of reaction mixture, which was then stirred for 12 h. 500 ml of saturated aqueous NH_4Cl was then added with stirring, followed in a few minutes by saturated aqueous NaCl (300 ml) followed by a 5:1 mixture of hexane:EtOAc (300 ml). The mixture was further stirred for 15 min and then filtered through a fine mesh Schott glass filter. The residue was washed with hexane:EtOAc mix several times. The organic fraction was separated, and the aqueous phase was additionally extracted (3 x 200 ml). The combined organic fraction was dried (Na_2SO_4), traces of hydroquinone and diphenylamine were added, and the solvent was evaporated *in vacuo*. The residue was immediately distilled at 1 mm Hg, to give 45.8 g (62%) of a 173-180°C boiling fraction. An additional crystallisation was carried out as follows. The ester (**15**) was dissolved in hexane (500 ml) and cooled down to -50°C. The crystals formed were washed in cold hexane. The yield of this step is 80 %. HRMS, *m/z* calculated for $C_{19}H_{22}D_4O_2$: 290.2180; found: 290.2200. ^1H NMR ($CDCl_3$, δ): 3.66 (s, 3H, OCH_3), 2.29 (t, J = 7.5 Hz, 2H, CH_2), 2.15 (m, 4H, CH_2), 1.61 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.30 (m, 6H, CH_2), 1.11 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 174.1, 82.0, 80.6, 74.7, 74.6, 73.7, 73.0, 51.3, 33.9, 28.9, 28.6, 28.52, 28.49, 24.8, 18.5, 13.7, 12.2.

11,11,14,14-Tetradeutero-cis,cis,cis-octadeca-8,12,15-trienoic acid methyl ester (**16**) was synthesised in a way similar to that described for 11,11-Dideutero-cis,cis-octadeca-9,12-dienoic acid methyl ester ('**6**'). A suspension of nickel acetate tetrahydrate (42 g) in 96 % EtOH (400 ml) was heated with stirring to approx. 50-60°C until the salt dissolved. The flask was flushed with hydrogen, and then 130 ml of $NaBH_4$ solution, (prepared by a 15 min stirring of $NaBH_4$ suspension (7.2 g) in EtOH (170 ml) followed by filtering) was added dropwise over 20-30 min with stirring. In 15-20 min ethylenediamine (52 ml) was added in one portion, followed in 5 min by an addition of (**15**) (73 g) in EtOH (200 ml). The reaction mixture was very vigorously stirred under hydrogen (1 atm). The absorption of hydrogen stopped in about 2 h. To the reaction mixture, 900 ml of hexane and 55 ml of ice cold AcOH were added, followed by water (15 ml). Hexane (400 ml) was added, and the mixture was allowed to separate. Aqueous fractions were extracted by 5:1 mix of hexane:EtOAc. The completion of extraction was monitored by TLC. The combined organic phase was washed with diluted solution of H_2SO_4, followed by saturated $NaHCO_3$ and saturated NaCl, and then dried over Na_2SO_4. The solvent was removed at reduced pressure. Silica gel for purification was prepared as described for (**6**). 30 g of this silica was used per gram of product. The reaction mixture was dissolved in a small volume of hexane and applied to the silver-modified silica gel, and pre-washed with a 1-5 % gradient of EtOAc. When the non-polar contaminants were washed off (control by TLC), the product was eluted with 10 % EtOAc and the solvent evaporated in vacuo to give 42 g of the title ester (**16**) as a colourless liquid. HRMS, *m/z* calculated for $C_{19}H_{28}D_4O_2$: 296.2649; found: 296.2652. IR (CCl_4): $\tilde{\nu}$ = 1740 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 5.4 (m, 6H, CH-double bond), 3.68 (s, 3H, OCH_3), 2.33 (t, J = 7.5 Hz, 2H, CH_2), 2.09 (m, 4H, CH_2), 1.62 (m, 2H, CH_2), 1.33 (m, 8H, CH_2), 0.97 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 174.1, 131.9, 130.2, 128.2, 128.1, 127.7, 126.9, 51.3, 34.0, 29.5, 29.04, 29.02, 27.1, 25.5, 24.9, 20.5, 14.2.

11,11,14,14-Tetradeutero-cis,cis,cis-octadeca-8,12,15-trienoic acid (**17**) A solution of KOH (1.5 g, 27 mmol) in water (2.6 ml was added to a solution of ester (**16**) (1.00 g, 3.4 mmol) in MeOH (15 ml). The reaction mixture was stirred at 40-50°C for 2 h (control by TLC) and then diluted with 20 ml of water. Two thirds of the solvent were removed (rotavap). Diluted sulfuric acid was added to the residue to pH 2, followed by diethyl ether with a little pentane (50 ml). The organic layer was separated and the aqueous layer washed with diethyl ether with a little pentane (3 x 30 ml). The combined organic fractions were washed with saturated aqueous NaCl and then dried over Na_2SO_4. The solvent was evaporated to give 0.95 g of (**17**)

(100%). IR (CCl_4): $\tilde{\nu}$ = 1741, 1711 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 11.1 (br s, 1H), 5.37 (m, 6H), 2.35 (t, J = 7.5 Hz, 2H, CH_2), 2.06 (m, 4H, CH_2), 1.63 (m, 2H, CH_2), 1.32 (m, 8H, CH_2), 0.97 (t, J = 7.0 Hz, 3H, CH_3).

Synthesis of 14,14-D2-α-linolenic acid (23) [31]



4,4-Dideutero-octa-2,5-diyn-1-ol (**19**) To a solution of ethylmagnesium bromide, prepared from ethyl bromide (9.2 ml, 123.4 mmol) and magnesium turnings (2.74 g, 112.8 mmol) in 40 ml of dry THF, on an ice bath with stirring, propargyl alcohol (3.16 g, 56.4 mmol) in THF (5 ml) was added dropwise over 10-15 min. The reaction mixture was allowed to warm up to r.t. and stirred for another 2 h, with occasional warming to 40°C. To thus generated dianion, 0.13g of CuCl was added, followed by slow (over 15 min) addition of bromide (**10**) (6.9 g) in THF (20 ml). The reaction mixture was then stirred for 1 h at r.t. and then refluxed for 5 h. The reaction mixture was then refluxed for 5 h, cooled slightly (a precipitate will form if cooling is too fast), and poured into a slurry of crushed ice and 2.5 ml concentrated H_2SO_4. The mixture was washed with hexane (600 ml). The organic fraction was separated, and the aqueous fraction was additionally extracted with 5:1 hexane:EtOAc. The combined organic fraction was washed, with saturated NaCl, followed by saturated $NaHCO_3$ and NaCl, and dried over Na_2SO_4. The bulk of the solvent was removed at atmospheric pressure in presence of traces of hydroquinone and triethylamine. The product was purified by CC (hexane:EtOAc = 15:1) to give 3.45 g (59 %) of the product **19**. HRMS, m/z calculated for $C_8H_8D_2O$: 124.0855; found: 124.0849. IR (CCl_4): $\tilde{\nu} = 3622$ cm^{-1}. ^1H NMR ($CDCl_3$, δ): 4.21 (m, 2H, CH_2), 2.4 (m, 1H, OH), 2.16 (q, J = 7.5 Hz, 2H, CH_2), 1.11 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 82.3, 80.4, 78.3, 72.6, 51.0, 13.7, 12.2.

4,4-Dideutero-1-bromo-octa-2,5-diyne (**20**) was synthesised as described for (**3**), except all solvent was removed on a rotavap. From 3.4 g (27 mmol) of (**19**), 3.9 g (75 %) of the bromide (**20**) was obtained, which was used without further purification. HRMS, m/z

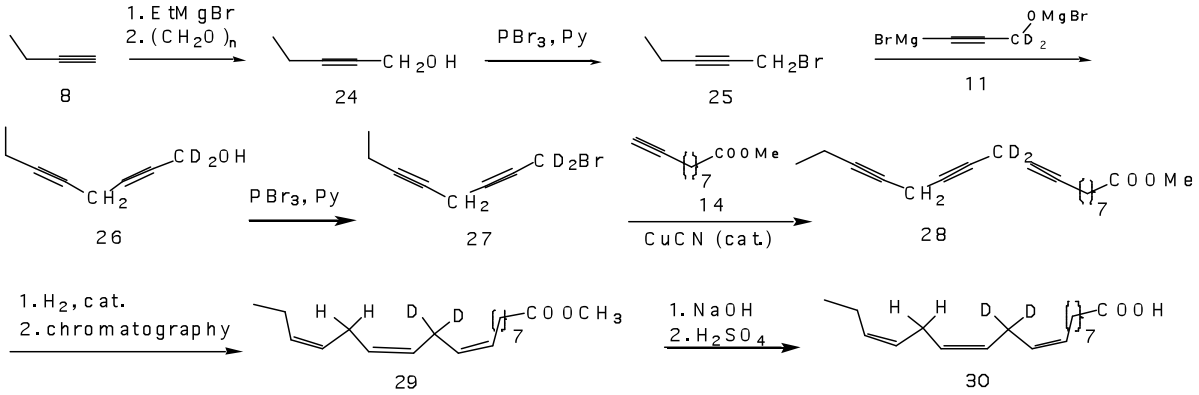
calculated for $C_8H_7D_2Br$: 186.0011; found: 185.0019, 187.0012. IR (CCl_4): $\tilde{\nu}$ = 2255 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 3.88 (br s, 2H, CH_2), 2.13 (q, J = 7.5 Hz, 2H, CH_2), 1.07 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 82.5, 81.8, 75.0, 72.0, 14.8, 13.6, 12.2.

14,14-Dideutero-octadeca-8,12,15-triynoic acid methyl ester (**21**) was synthesised as described for (**5**). The product obtained from 9.7 g CuI, 7.8 g NaI, 10.5 g K_2CO_3, 4.85 g of bromide (**20**), 4.75 g of methyl ester (**14**) and 40 ml of anhydrous DMF, was purified by CC (25:1 hexane:EtOAc) to give 4.5 g (60%) of the title compound. HRMS, *m/z* calculated for $C_{19}H_{24}D_2O_2$: 288.2056; found: 288.2046. ^1H NMR ($CDCl_3$, δ): 3.66 (s, 3H, OCH_3), 3.12 (m, 2H, CH_2), 2.29 (t, J = 7.5 Hz, 2H, CH_2), 2.15 (m, 4H, CH_2), 1.61 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.30 (m, 6H, CH_2), 1.11 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 174.1, 82.0, 80.6, 74.7, 74.6, 73.7, 73.0, 51.3, 33.9, 28.9, 28.6, 28.52, 28.49, 24.8, 18.5, 13.7, 12.2, 9.7.

14,14-Dideutero-cis,cis,cis-octadeca-8,12,15-trienoic acid methyl ester (**22**) was synthesised as described for the linoleic acid derivative (**6**). For a reduction of 4.5 g of (**21**), 2.6 g of nickel acetate tetrahydrate and 3.2 ml ethylenediamine was used. The product was purified on $AgNO_3$-impregnated silica gel as described for (**6**). HRMS, *m/z* calculated for $C_{19}H_{30}D_2O_2$: 294.2526; found: 294.2529. IR (CCl_4): $\tilde{\nu}$ = 1740 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 5.37 (m, 6H, CH-double bond), 3.68 (s, 3H, OCH_3), 2.82 (m, 2H, CH_2), 2.33 (t, J = 7.5 Hz, 2H, CH_2), 2.09 (m, 4H, CH_2), 1.62 (m, 2H, CH_2), 1.33 (m, 8H, CH_2), 0.97 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 174.1, 131.9, 130.2, 128.2, 128.1, 127.7, 126.9, 51.3, 34.0, 29.5, 29.1, 29.04, 29.02, 27.1, 25.5, 24.9, 20.5, 14.2.

14,14-Dideutero-cis,cis,cis-octadeca-8,12,15-trienoic acid (**23**) To a solution of (**22**) (1 g, 3.4 mmol) in MeOH (15 ml), a solution of KOH (1.5 g, 27 mmol) in water (2.6 ml) was added in one portion. The reaction mixture was then processed as described for (**7**) to yield 0.94g (99 %) of the title acid. IR (CCl_4): $\tilde{\nu}$ = 1741, 1711 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 11.1 (br s, 1H), 5.37 (m, 6H), 2.83 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H, CH_2), 2.06 (m, 4H, CH_2), 1.63 (m, 2H, CH_2), 1.32 (m, 8H, CH_2), 0.97 (t, J = 7.0 Hz, 3H, CH_3).

Synthesis of 11,11-D2-α-linolenic acid (30) [31]



Pent-2-yn-1-ol (**24**) Butyn-1 ((**8**); 10.4 g) was bubbled through an ice-cold solution prepared from bromoethane (11.2 ml) and magnesium turnings (3.6 g) in THF (100 ml). The reaction mixture was allowed to warm up to r.t. and then stirred for 15 min. The mixture was then heated up to 30°C, at which point all precipitate dissolved. The heating was removed and the mixture stirred for another 30 min, and then paraform (3 g) was added in one portion. The reaction mixture was refluxed for 3 h (all paraform dissolved), then cooled to r.t., poured into a mixture of crushed ice (80 g) and 8 ml conc. H_2SO_4, and extracted with diethyl ether. The organic phase was washed with saturated $NaHCO_3$ and NaCl, and dried over Na_2SO_4. The solvent was removed on a rotavap, and the residue (7.56 g; 90 %) was used without further purification. HRMS, m/z calculated for C_5H_8O: 84.0575; found: 84.0583.

1-Bromo-pent-2-yne (**25**) To a solution of (**24**) (11.7 g) and pyridine (2.66 ml) in dry diethyl ether (34 ml), 5.2 ml of PBr_3 in 5 ml diethyl ether was added dropwise with stirring over 30 min at -10°C under argon. The reaction mixture was allowed to gradually warm up to r.t. over 1 h. A catalytic amount of hydroquinone was added, and the mixture was then refluxed for 4.5 h. The reaction mixture was then cooled down to -10°C and 35 ml of cold water was added. When the residue dissolved, saturated NaCl (35 ml) and diethyl ether (30 ml) were added, and the organic layer was separated. The aqueous fraction was washed with diethyl ether (2 x 15 ml), and the combined organic fractions were washed with NaCl (2 x 400 ml) and dried over $MgSO_4$. The solvent was removed at atmospheric pressure, and then under reduced pressure (25 mm Hg), the 60-90°C fraction was collected. Yield: 11.1 g (84 %). HRMS, *m/z* calculated for C_5H_7Br: 145.9731; found: 144.9750, 146.9757.

1,1-Dideutero-octa-2,5-diyn-1-ol (**26**) was synthesised as described for (**12**) with 87 % yield. HRMS, m/z calculated for $C_8H_8D_2O$: 124.0855; found: 124.0868. IR (CCl_4): $\tilde{\nu}$ = 3622 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.65 (m, 2H, CH_2), 2.4 (br. s., 1H, OH), 2.16 (q, J = 7.5 Hz, 2H, CH_2), 1.11 (t, J = 7.5 Hz, 3H, CH_3).

1,1-Dideutero-1-bromo-octa-2,5-diyne (**27**) was synthesised as described for (**3**), except all solvent was removed on a rotavap. The product was purified by distillation at reduced pressure. Yield: 86 % (b.p. 100-105°C at 4 mm Hg). (HRMS, m/z calculated for $C_8H_7D_2Br$: 186.0011; found: 184.9948, 187.9999. IR (CCl_4): $\tilde{\nu}$ = 2255 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.66 (m, 2H, CH_2), 2.1 (q, 2H, CH_2), 1.09 (t, 3H, CH_3).

11,11-Dideutero-octadeca-8,12,15-triynoic acid methyl ester (**28**) was synthesised as described for (**5**). The product obtained from 7.1 g CuI, 5.66 g NaI, 7.65 g K_2CO_3, 3.55 g of bromide (**27**), 3.47 g of methyl ester (**14**) and 30 ml of anhydrous DMF, was purified by CC (25:1 hexane:EtOAc) to give 3.7 g of the title compound. HRMS, m/z calculated for $C_{19}H_{24}D_2O_2$: 288.2056; found: 288.2069. ^1H NMR ($CDCl_3$, δ): 3.7 (s, 3H, OCH_3), 3.15 (br. s, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.17 (m, 4H, CH_2), 1.61 (m, 2H, CH_2), 1.48 (m, 2H, CH_2), 1.35 (m, 6H, CH_2), 1.11 (t, 3H, CH_3).

11,11-Dideutero-cis,cis,cis-octadeca-8,12,15-trienoic acid methyl ester (**29**) was synthesised as described for the linoleic acid derivative (**6**). For a reduction of 3.7 g of (**28**), 2.16 g of nickel acetate tetrahydrate and 2.62 ml ethylenediamine was used. The product was purified on $AgNO_3$-impregnated silica gel as described for (**6**) to give 1.5 g. HRMS, m/z calculated for $C_{19}H_{30}D_2O_2$: 294.2526; found: 294.2402. IR (CCl_4): $\tilde{\nu}$ = 1740 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 5.37 (m, 6H, CH-double bond), 3.6 (s, 3H, OCH_3), 2.82 (m, 2H, CH_2), 2.33 (t, J = 7.5 Hz, 2H, CH_2), 2.09 (m 4H, CH_2), 1.62 (m, 2H, CH_2), 1.33 (m, 8H, CH_2), 0.97 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 174.1, 131.9, 130.2, 128.2, 128.1, 127.7, 126.9, 51.3, 34.0, 29.5, 29.1, 29.04, 29.02, 27.1, 25.5, 24.9, 20.5, 14.2.

11,11-Dideutero-cis,cis,cis-octadeca-8,12,15-trienoic acid (**30**) To a solution of (29) (1.5 g, 5.1 mmol) in MeOH (7.5 ml), a solution of KOH (1.5 g, 27 mmol) in water (3 ml) was added in one portion. The reaction mixture was then processed as described for (17) to yield 0,9 g of the title acid. IR (CCl_4): $\tilde{\nu}$ = 1741, 1711 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 11.2 (br s, 1 H, COOH), 5.37 (m, 6H, CH-double bond), 2.83 (m, 2H, CH_2), 2.35 (t, J = 7.5 Hz, 2H, CH_2), 2.06 (m 4H, CH_2), 1.63 (m, 2H, CH_2), 1.32 (m, 8H, CH_2), 0.97 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR

($CDCl_3$, δ): 180.4, 131.9, 130.2, 128.3, 128.1, 127.6, 127.1, 34.1, 29.5, 29.1, 29.03, 28.98, 27.2, 25.5, 24.6, 20.5, 14.2.