Synthesis of 2-substituted *cis*-8,*cis*-11,*cis*-14-eicosatrienoic acids, precursors for 2-substituted prostaglandins

R. van der Linde, L. van der Wolf, H. J. J. Pabon and D. A. van Dorp

Unilever Research, Vlaardingen, The Netherlands
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Abstract. Various 2-substituted all-*cis*-8,11,14-eicosatrienoic acids have been prepared via coupling of all-*cis*-6,9,12-octadecatrienyl methanesulfonate with diethyl malonate, substituted diethyl malonates, ethyl cyanoacetate or ethyl 2-cyanohexanoate. The substituents are: COOH, $COOCH_3$, $COOC_4H_9$, $COOC_7H_{15}$, CH_2OH, CH_3, C_4H_9, C_6H_5, CH_2OCH_3, $NHCOCH_3$, $NH_2 \cdot HCl$, F, OCH_3, CN and both CN and C_4H_9.

Introduction

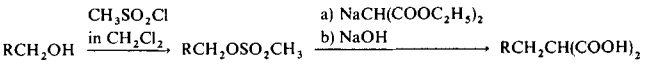
Work on substrate specificity of the prostaglandin synthesizing enzyme complex from sheep vesicular glands has resulted so far in the detection of a number of biologically active prostaglandins, like the ω-nor- and ω-homo-prostaglandins. Moreover, rules could be developed about the relationship between essential fatty acid-activity and the biological activity of the related prostaglandins[1,2]. The influence of substituents in the precursor acids and their bioconversion is the subject of the present investigation. We have therefore prepared a series of all-*cis*-8,11,14-eicosatrienoic acids, having one or two substituents either in the proximal or in the terminal polymethylene part of the molecule. They have been converted enzymatically into the correspondingly substituted prostaglandins. The biosynthetic part of the investigation as well as the biological properties of the prostaglandins thus obtained is published separately[3]. In this publication the synthesis of all-*cis*-8,11,14-eicosatrienoic acids, substituted in the 2-position with a carboxy, alkoxycarbonyl, hydroxymethyl, alkyl, phenyl, methoxymethyl, acetamido, amino hydrochloride, fluoro, methoxy, and cyano group, as well as one with both a cyano and a butyl group in the 2-position is described.

Methods and results

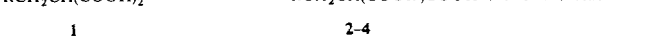
For the synthesis of the various 2-substituted all-*cis*-8,11,14-eicosatrienoic acids "alkatrienylation" of diethyl malonate, substituted diethyl malonates, ethyl cyanoacetate and ethyl 2-cyanohexanoate was used.

Alkatrienylation of diethyl malonate

The starting compound all-*cis*-6,9,12-octadecatrienyl methanesulfonate (**16**) was obtained by reaction of all-*cis*-6,9,12-octadecatrienol with methanesulfonyl chloride in a modification of the existing methods (*cf.* ref. 4), suitable for large-scale preparation. By coupling **16** with diethyl sodiomalonate and subsequent saponification all-*cis*-7,10,13-nonadecatriene-1,1-dicarboxylic acid (**1**) was obtained. Esterification of the latter with 1 eq CH_2N_2 or with 1.5 eq of the appropriate alcohol[5] and separation of the reaction mixture via column chromatography yielded the desired methyl hydrogen (**2**), butyl hydrogen (**3**), and heptyl hydrogen all-*cis*-7,10,13-nonadecatriene-1,1-dicarboxylate (**4**).



$RCH_2OH \rightarrow RCH_2OSO_2CH_3$ (**16**) $\rightarrow RCH_2CH(COOH)_2$ (**1**)

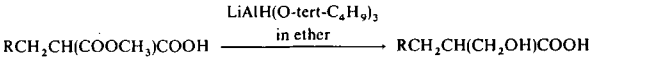


$RCH_2CH(COOH)_2$ (**1**) $\rightarrow RCH_2CH(COOR')COOH$ + diester + diacid (**2-4**)

$R = C_5H_{11}-[CH\overset{cis}{=}CH-CH_2-]_3-(CH_2)_3-$

2 R′ = CH_3 **3** R′ = C_4H_9 **4** R′ = C_7H_{15}

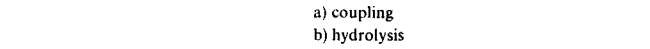
2-Hydroxymethyl-all-*cis*-8,11,14-eicosatrienoic acid (**5**) was obtained by reduction of **2** with $LiAlH(O\text{-}tert\text{-}C_4H_9)_3$ and subsequent purification via column chromatography.



$RCH_2CH(COOCH_3)COOH$ (**2**) $\rightarrow RCH_2CH(CH_2OH)COOH$ (**5**)

Alkatrienylation of substituted diethyl malonates

By coupling of **16** in ethanol, benzene or toluene with the sodio derivative of the appropriate substituted dialkyl malonate[6] until GLC showed no further conversion and subsequent hydrolysis and decarboxylation 2-methyl- (**6**), 2-butyl- (**7**), 2-phenyl- (**8**), 2-methoxymethyl- (**9**), 2-acetamido- (**10**), 2-fluoro- (**12**) and 2-methoxy-all-*cis*-8,11,14-eicosatrienoic acid (**13**) were obtained; 2-amino-all-*cis*-8,11,14-eicosatrienoic acid hydrochloride (**11**) was derived from compound **10**.



$RCH_2OSO_2CH_3$ (**16**) + $NaCR''(COOalkyl)_2 \rightarrow RCH_2CHR''COOH$ (**6-13**)

6 R″ = CH_3 **9** R″ = CH_2OCH_3 **12** R″ = F
7 R″ = C_4H_9 **10** R″ = $NHCOCH_3$ **13** R″ = OCH_3
8 R″ = C_6H_5 **11** R″ = $NH_2 \cdot HCl$

The various disubstituted dialkyl malonates, obtained in the coupling reaction, were hydrolysed by boiling them with NaOH (0.5 mole/l) in 85% methanol until TLC showed hydrolysis to be complete. In one case (R″ = C_4H_9) hydrolysis was incomplete, even after 48 h reflux. Here the mixture of "monoester" and "diacid", was decarboxylated by heating at 150°C for 1 h and the residue hydrolysed again. In two cases (R″ = C_6H_5 and R″ = $NHCOCH_3$) alkaline hydrolysis and decarboxylation occurred simultaneously. In

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[1] *R. K. Beerthuis, D. H. Nugteren, H. J. J. Pabon* and *D. A. van Dorp*, Recl. Trav. Chim. Pays-Bas **87**, 461 (1968).
[2] *R. K. Beerthuis, D. H. Nugteren, H. J. J. Pabon, A. Steenhoek* and *D. A. van Dorp*, Recl. Trav. Chim. Pays-Bas **90**, 943 (1971).
[3] *D. A. van Dorp* and *E. J. Christ*, Recl. Trav. Chim. Pays-Bas **94**, 247 (1975).
[4] *F. Spener*, Chem. Phys. Lipids **11**, 229 (1973).
[5] *F. Fichter* and *S. Lurie*, Helv. Chim. Acta **16**, 885 (1933).
[6] *A. C. Cope, H. L. Holmes* and *R. O. House*, Organic Reactions Vol. IX, p. 107–331, John Wiley & Sons, Inc. New York 1957.

one case (R″ = F) hydrolysis by boiling with HCl (2.3 mole/l) in 1,4-dioxane/water (5:3 v/v) (ref. 7) for 52 h had to be applied; under these conditions decarboxylation occurred simultaneously.

Alkatrienylation of ethyl cyanoacetate and ethyl 2-cyanohexanoate

By coupling **16** with the sodio derivative of ethyl cyanoacetate and ethyl 2-cyanohexanoate respectively, and subsequent hydrolysis 2-cyano-all-*cis*-8,11,14-eicosatrienoic acid (**14**) and 2-butyl-2-cyano-all-*cis*-8,11,14-eicosatrienoic acid (**15**) were obtained.

$$RCH_2OSO_2CH_3 + NaCR''(CN)COOC_2H_5 \xrightarrow[\text{b) hydrolysis}]{\text{a) coupling}} RCH_2CR''(CN)COOH$$

16 **14, 15**

14 R″ = H
15 R″ = C_4H_9

Experimental

(In co-operation with Miss *J. W. Bos* and Messrs. *J. C. Lindhoudt* and *C. Visser*)

All temperatures are uncorrected. Melting points were determined with a Büchi apparatus. Where necessary the reactions were carried out in an inert gas atmosphere (argon or purified nitrogen). Reagent grade solvents were dried on $LiALH_4$ (ether, tetrahydrofuran), $LiAlH_4$ or Na/K alloy (benzene, toluene) or according to standard methods (ethanol) and distilled, prior to use, under argon or purified nitrogen.
For column chromatography Kieselgel (ex Merck; 70–230 mesh ASTM) was used. UV spectra were obtained with a Cary 14 spectrophotometer. IR spectra were obtained with a Hilger and Watts Infrascan H900.2 spectrophotometer (liquid film KBr plates; solids were pressed with KBr to pellets). Mass spectra were obtained with an A.E.I. MS9 mass spectrometer. PMR spectra were obtained from solutions in carbon tetrachloride containing 1% tetramethylsilane as internal zero reference either with a Varian A-60 (**5** and **15**) or an HR 220 spectrophotometer (**1–4** and **6–14**) operating at 40°C and 13°C respectively. δ-Values are quoted in ppm downfield and are accurate to within ±0.01 ppm. Coupling constants are accurate to within ±0.2 Hz. The following abbreviations are used in their recording: abs = absorption; br = broadened; c = complex; d = doublet; d d = doublet of doublets; dist = distorted; s = singlet; t = triplet.
GLC analyses were performed on a Packard-Becker 419 or a Hewlett and Packard 5750 G gas chromatograph equipped with glass columns, packed with either 10% SE 30 or 5% PEGA on Chromosorb W (AW-DMCS; 80–100 mesh).

All-cis-*6,9,12-octadecatrienyl methanesulfonate* (**16**)

To a solution of 101.4 g (0.384 mole) all-*cis*-6,9,12-octadecatrienol [n_D^{25} 1.4792; purity (GLC) 99%] and 51.2 g (0.423 mole) *s*-collidine (2,4,6-trimethylpyridine) as HCl scavenger (*cf.* ref. 8) in 300 ml dichloromethane 55.1 g (0.48 mole) methanesulfonyl chloride was added at 0°C. After stirring for 2 h at room temperature, care being taken that the reaction temperature did not exceed 30°C, the mixture was poured into 200 ml water, acidified with HCl (4 mole/l) and extracted with dichloromethane. The combined organic layers were washed intensively (10 times) with water (to hydrolyse excess methanesulfonyl chloride), dried over Na_2SO_4 and evaporated, leaving 139.3 g almost pure **16**.

All-cis-*7,10,13-nonadecatriene-1,1-dicarboxylic acid* (**1**)

An amount of 139.3 g almost pure **16** was added to a solution of diethyl sodiomalonate – prepared from 11.8 g (0.512 mole) sodium and 102.4 g (0.64 mole) diethyl malonate in 600 ml ethanol – and the mixture stirred for 2 h at 80°C. Most of the ethanol was then evaporated under reduced pressure, the residue acidified with HCl (4 mole/l) and extracted with ether. The combined ether layers were washed with water, dried over Na_2SO_4 and evaporated. Excess diethyl malonate was for the greater part distilled off at 10^{-2} mmHg (bath temp. 130°C). Non-acidic impurities were removed – after saponification of the crude diester with 2500 ml NaOH (0.6 mole/l) in water/methanol (2:1 v/v) for 2 h at 70°C under N_2 and addition of 800 ml water – by extraction of the hot sodium soap solution with toluene (3 times 500 ml) at 80°C. After cooling and acidification of the soap solution with H_2SO_4 (2 mole/l) and extraction with light petroleum (3 times 500 ml; any emulsion being broken by adding ether) the light petroleum layers were washed acid free, dried over Na_2SO_4 and evaporated, leaving 121.1 g **1** (90% calculated on all-*cis*-6,9,12-octadecatrienol); purity (GLC) 92%. A sample crystallized twice from light petroleum at −25°C showed m.p. 49–51°C and a purity (GLC) of 98%.

IR: −COOH 3500–2500, 1725, 1710, 1417, 1315, 1270 and 935 cm^{-1}; −C(H)=C(H)− 3010 and 725 cm^{-1}; content of "*trans*" double bonds < 2%.

UV (ethanol): λ_{max} 234 nm (2.7% conjugated dienoic compounds), 269 nm (0.2% conjugated trienoic compounds).

PMR: δ 0.89 (t, J = 7 Hz, 3H, $-CH_3$), 1.29 (br s, 4H, $CH_3-(CH_2)_2-$), 1.37 (br s, 8H, $-CH_2-$), 1.91 (c, 2H, $-CH_2C(COO-)_2$), 2.03 (c, 4H, $-CH_2-C(H)=$), 2.74 (t, J = 5 Hz, 4H, $=C(H)-CH_2-C(H)=$), 3.34 (t, J = 7.5 Hz, 1H, $-CH(COO-)_2$), 5.29 (*cis* pattern, 6H, −C(H)=), 12.0 (br s, 2H, $-C(COOH)_2$).

Methyl hydrogen all-cis-*7,10,13-nonadecatriene-1,1-dicarboxylate* (**2**)

An amount of 24.5 g (70 mmole) **1** was esterified with a solution of 70 mmole diazomethane in 180 ml ether. The diester and starting material were separated from the desired compound by passing the mixture through a silica column using light petroleum/ether mixtures as eluents, increasing the amount of ether. Elution with light petroleum/ether 85:15 v/v to 75:25 v/v yielded 10.2 g **2** (40%); n_D^{25} 1.4760.

UV (hexane): λ_{max} 228 nm (1.8% conjugated dienoic compounds), 268 nm (0.3% conjugated dienoic compounds).

IR: −COOH 3500–2500, 1716, 1420, 1290 and 920 cm^{-1}; >C=O ester 1755, 1440, 1270, 1255 and 1170 cm^{-1}; −C(H)=C(H)− 3010, 1650 and 720 cm^{-1}.

MS: parent peak at *m/e* 364 (calcd for $C_{22}H_{36}O_4$ 364).

PMR: δ 0.89 (t, J = 6.8 Hz, 3H, $-CH_3$), 1.2–1.5 (c, 12H, $-CH_2-$), 1.86 (dist quartet, 2H, $-CH_2C(COO-)_2$), 1.9–2.2 (c, 4H, $-CH_2-C(H)=$), 2.75 (dist t, 4H, $=C(H)-CH_2-C(H)=$), 3.27 (t, J = 7.3 Hz, 1H, $-CH(COO-)_2$), 3.70 (s, 3H, $-COOCH_3$), 5.31 (*cis* pattern, 6H, −C(H)=).

Butyl hydrogen all-cis-*7,10,13-nonadecatriene-1,1-dicarboxylate* (**3**)

Stirring 1.75 g (5 mmole) **1** with 0.56 g (7.5 mmole) butanol in the presence of 0.02 ml conc. H_2SO_4 for 2 h at 60°C, followed by addition of light petroleum, washing with water (until free from SO_4^{--}) and drying over Na_2SO_4, yielded after the separation by column chromatography as described for **2** 0.88 g **3** (43%), n_D^{25} 1.4781.

UV (hexane): λ_{max} 228 nm (1.8% conjugated dienoic compounds), 268 nm (0.7% conjugated trienoic compounds).

IR: −COOH 3500–2500, 1718, 1417, 1285 and 930 cm^{-1}; >C=O ester 1748, 1270, 1178 and 1065 cm^{-1}; −C(H)=C(H)− 3020, 1660 and 725 cm^{-1}.

[7] *F. L. M. Pattison, R. L. Buchanan* and *F. H. Dean*, Can. J. Chem. **43**, 1700 (1965).
[8] *E. W. Collington* and *A. I. Meyers*, J. Org. Chem. **36**, 3044 (1971).

MS: parent peak at *m/e* 406 (calcd for $C_{25}H_{42}O_4$ 406).

PMR: δ 0.89 (t, J = 6.8 Hz, $-CH_3$) and 0.94 (t, J = 7.3 Hz, $-COO-(C)_3-CH_3$), in total 6H, 1.2–1.5 (c, 14H, $-CH_2-$), 1.64 (dist quintet, 2H, $-COO-C-CH_2-$), 1.86 (dist quartet, 2H, $-CH_2C(COO-)_2$), 1.9–2.1 (c, 4H, $-CH_2-C=$), 2.76 (dist t, 4H, $=C-CH_2-C=$), 3.25 (t, J = 7.3 Hz, 1H, $-CH(COO-)_2$), 4.0–4.2 (c, 2H, $-COO-CH_2-$), 5.29 (*cis* pattern, 6H, $-C=$).

*Heptyl hydrogen all-*cis*-7,10,13-nonadecatriene-1,1-dicarboxylate* (**4**)

Compound **4** was prepared in the same way as **3**.
Yield 0.93 g (41%); n_D^{25} 1.4723.

UV (hexane): λ_{max} 225 nm (1.1% conjugated dienoic compounds), 268 nm (0.5% conjugated trienoic compounds).

IR: $-COOH$ 3500–2500, 1718, 1418, 1295 and 920 cm^{-1}; $>C=O$ ester 1750, 1270, 1200, 1175 and 1067 cm^{-1}; $-C=C-$ 3020, 1660 and 720 cm^{-1}.

MS: parent peak at *m/e* 448 (calcd for $C_{28}H_{48}O_4$ 448).

PMR: δ 0.90 (dist t, $-CH_3$) and 0.91 (dist t, $-COO-(C)_6CH_3$), in total 6H, 1.2–1.5 (c, 20H, $-CH_2-$), 1.62 (dist quintet, 2H, $-COO-C-CH_2-$), 1.86 (dist quartet, 2H, $-CH_2-C(COO-)_2$), 1.9–2.2 (c, 4H, $-CH_2-C=$), 2.77 (dist t, 4H, $=C-CH_2-C=$), 3.26 (t, J = 7.3 Hz, 1H, $-CH(COO-)_2$), 4.0–4.2 (c, 2H, $-COOCH_2-$), 5.30 (*cis* pattern, 6H, $-C=$).

*2-Hydroxymethyl-all-*cis*-8,11,14-eicosatrienoic acid* (**5**)

An amount of 3.73 g (50.3 mmole) tert-butanol in 4 ml diglyme (2,5,8-trioxanonane) was added in 10 min to 8.6 ml (16.8 mmole) $LiAlH_4$ solution in ether at 20°C (ref. 9). While stirring 1.46 g (4 mmole) **2**, dissolved in 3 ml diglyme was added at 0°C and stirring was continued for 3 h at 0°C, 2 h at 20°C and 2.5 h at 40°C. After cooling the reaction mixture was acidified, extracted with ether and the combined ether layers washed acid free with water and evaporated. The residue, dissolved in light petroleum was extracted with NH_4OH (4 mole/l) in 75% CH_3OH and the combined ammoniacal layers extracted twice with 20 ml light petroleum. The ammoniacal layers were, after acidification with H_2SO_4 (4 mole/l), extracted with light petroleum and the combined light petroleum layers washed acid free, dried over Na_2SO_4 and evaporated. The residue was brought onto a column of silicagel deactivated with 10% water. Elution with light petroleum/ether 70:30 v/v to 25:75 v/v yielded 0.47 g **5** (35%); n_D^{25} 1.4859.

UV (hexane): λ_{max} 230 nm (1.8% conjugated dienoic compounds), 270 nm (0.3% conjugated trienoic compounds).

IR (as methyl ester): $>C=O$ ester 1735, 1430, 1260, 1190 and 1165 cm^{-1}; $-C=C-$ 3010, 1645 and 715 cm^{-1}; $-CH_2OH$ 3450 and 1040 cm^{-1}.

MS: parent peak of methyl ester at *m/e* 350 (calcd for $C_{22}H_{38}O_3$ 350).

PMR (as methyl ester): δ 0.89 (t, J = 6.6 Hz, 3H, $-CH_3$), 1.1–1.4 (c, 12H, $-CH_2-$), ~1.53 (c, 2H, $-CH_2-C-COO-$), 2.03 (br quintet, 4H, $-CH_2-C=$), 2.45 (c, 1H, $-CH-COO-$), 2.75 (c, 4H, $=C-CH_2-C=$), 3.60 (c, 2H, $-C(CH_2O-)COO-$), 3.65 (s, 3H, $-COOCH_3$), 5.29 (*cis* pattern, 6H, $-C=$).

*2-Methyl-all-*cis*-8,11,14-eicosatrienoic acid* (**6**)

An amount of 20.9 g (120 mmole) diethyl methylmalonate (ex Fluka), dissolved in 110 ml ethanol was converted into its sodio derivative with 2.2 g (95 mmole) sodium and subsequently reacted with 23.3 g (68 mmole) **16** for 1 h at 75°C. After extraction of the coupling product it was hydrolysed (400 ml NaOH (0.6 mole/l) in 85% methanol; 1.5 h at 70°C) and the non-acidic products separated off according to the procedure described for **5**. Decarboxylation of the crude "diacid" (14.95 g) (2.5 h at 160°C) and molecular distillation (135–140°C; 5×10^{-4} mmHg) yielded 13.45 g **6** (62%), n_D^{25} 1.4758, purity (GLC) 95%.

UV (ethanol): λ_{max} 233 nm (1.4% conjugated dienoic compounds), 269 nm (1.1% conjugated trienoic compounds).

IR: $-COOH$ 3600–2400, 1715, 1420, 1290, 1240 and 940 cm^{-1}; $-C=C-$ 3020, 1650 and 720 cm^{-1}; $-C^{\alpha}-$ 1380 cm^{-1}.

MS: parent peak of methyl ester at *m/e* 334 (calcd for $C_{22}H_{38}O_2$ 334).

PMR: δ 0.89 (t, J = 6.7 Hz, 3H, $-CH_3$), 1.16 (d, J = 7.0 Hz, 3H, $-C(CH_3)-COO-$), 1.2–1.5 (c, 13H, $-CH_2-$ and $-C(H)(CH_3)-C(CH_3)(H)-COO-$), 1.66 (c, 1H, $-C(H)(CH_3)-C(CH_3)(H)-COO-$), 2.03 (br quartet, J ~ 6 Hz, 4H, $-CH_2-C=$), 2.39 (sextet, J = 7 Hz, 1H, $-CHCOO-$), 2.75 (c, 4H, $=C-CH_2-C=$), 5.28 (*cis* pattern, 6H, $-C=$).

*2-Butyl-all-*cis*-8,11,14-eicosatrienoic acid* (**7**)

An amount of 5.2 g (24 mmole) diethyl butylmalonate (ex Merck) in 10 ml benzene was converted into its sodio derivative by addition to 1.3 g (30 mmole) sodium (ex Fluka; as a 50% dispersion in paraffin) in 160 ml benzene, and subsequently reacted with 8 g (24 mmole) **16** for 21 h at 23°C. Extraction and hydrolysis of the coupling products (500 ml NaOH (0.5 mole/l) in 85% methanol; 47 h reflux) yielded after acidification a mixture containing "diacid" and "half-ester" in a ratio of 2:1. Separation from non-acidic products as described for **5** left 5.2 g acid which after decarboxylation (1.5 h at 180°C) and a final hydrolysis (100 ml NaOH (0.5 mole/l) in 85% methanol; 1 h reflux) afforded 2.8 g **7** (32%), purity (GLC) 92%.

UV (hexane): λ_{max} 235 nm (3.6% conjugated dienoic compounds); 270 nm (1.0% conjugated trienoic compounds).

IR: $-COOH$ 3600–2400, 1712, 1295, 1245 and 950 cm^{-1}; $-C=C-$ 3030, 1665 and 728 cm^{-1}.

MS: Parent peak at *m/e* 362 (calcd for $C_{24}H_{42}O_2$ 362).

[9] *H. C. Brown* and *B. C. Subba Rao*, J. Amer. Chem. Soc. **80**, 5377 (1958).

PMR: δ 0.89 (t, J = 6.5 Hz, 3H, $-CH_3$) 0.91 (t, J = 6.3 Hz, 3H, $-\overset{\overset{COO-}{|}}{\underset{|}{C}}-(C)_3-CH_3$), 1.2–1.5 (c, 18H, $-CH_2-$ + $-\overset{\overset{COO-}{|}}{\underset{H}{C}}-\overset{\overset{COO-}{|}}{\underset{H}{C}}-C-$), 1.61 (c, 2H, $-\overset{H}{C}-\overset{H}{C}-C-$), 2.03 (br quartet, 4H, $-CH_2-C=$), 2.27 (c, 1H, $-CHCOO-$), 2.75 (c, 4H, $=C-CH_2-C=$), 5.27 (*cis* pattern, 6H, $-\overset{H}{C}=$), 10.15 (s, 1H, $-COOH$).

*2-Phenyl-all-*cis*-8,11,14-eicosatrienoic acid* (**8**)

An amount of 3.7 g (16 mmole) diethyl phenylmalonate (ex Merck) was converted into its sodio derivative as described for **7** and reacted with 5.4 g (14 mmole) **16** in 120 ml benzene (24 h reflux; conversion only ~40%). Extraction and hydrolysis of the crude reaction mixture (200 ml NaOH (0.5 mole/l) in 85% methanol; 2.5 h reflux) during which decarboxylation occurred (IR and NMR) simultaneously, left after acidification, isolation and separation from non-acidic material as described for **5** 2.1 g crude **8**. Further purification by column chromatography over SiO_2, deactivated with 10% H_2O, yielded on elution with pentane/ether/acetic acid 99.5 : 0 : 0.5 v/v/v to 79.5 : 20 : 0.5 v/v/v 1.9 g **8** (35%), purity (GLC) 93%.

IR: $-COOH$ 3600–2400, 1714, 1294, 1240 and 940 cm^{-1}; $-C_6H_5$ 3070, 1606, 1502 and 698 cm^{-1}; $-\overset{H}{C}=\overset{H}{C}-$ 3020 and 728 cm^{-1}.

MS: Parent peak at *m/e* 382 (calcd for $C_{26}H_{38}O_2$ 382).

PMR (as methyl ester): δ 0.89 (t, J = 6.8 Hz, 3H, $-CH_3$), 1.1–1.4 (c, 12H, $-CH_2-$), 1.5–1.8 (c, 2H, $-CH_2\overset{|}{C}COO-$), 1.8–2.1 (c, 4H, $-CH_2C=$), 2.6–2.8 (c, 4H, $=C-CH_2-C=$), 3.42 (d d J = 8.3 and 7.3 Hz, 1H, $-CHCOO-$), 3.62 (s, 3H, $-COOCH_3$), 5.30 (*cis* pattern, 6H, $-C=$), 7.1–7.3 (c, 5H, $-C_6H_5$).

*2-Methoxymethyl-all-*cis*-8,11,14-eicosatrienoic acid* (**9**)

An amount of 6.0 g (24 mmole) diethyl (methoxymethyl)malonate – prepared in 44% yield according to *Elks* et al.[10] – was reacted with 1 eq sodium methoxide in methanol and the solution evaporated to dryness in vacuo. The residue suspended in 50 ml benzene was coupled with 7.9 g (21 mmole) **16** in 50 ml benzene (90 h reflux). The reaction mixture, after evaporation of benzene, was chromatographed over SiO_2, deactivated with 10% H_2O, using a gradient of ether in pentane. Fractions containing almost pure "diethyl disubstituted malonate" (as shown by TLC, GLC, IR and NMR analyses) were collected and taken to dryness, leaving 720 mg of an oil. Hydrolysis (100 ml NaOH (0.5 mol/l) in 88% ethanol; 1.25 h reflux), acidification and decarboxylation (35 min at 160°C) finally yielded 566 mg **9** (7%), purity (GLC) 87%.

UV (hexane): λ_{max} 271 nm (1.3% conjugated trienoic compounds).

IR: $-COOH$ 3600–2400, 1715, 1265, 1200 and 950 cm^{-1}; $-\overset{H}{C}=\overset{H}{C}-$ 3020, 1660 and 725 cm^{-1}; $-CH_2OCH_3$ 1125 cm^{-1}.

MS: Parent peak at *m/e* 350 (calcd for $C_{22}H_{38}O_3$ 350).

PMR: δ 0.89 (t, J = 6.8 Hz, 3H, $-CH_3$), 1.1–1.7 (c, 14H, $-CH_2-$), 2.03 (br quartet, 4H, $-CH_2-C=$), 2.56 (dist quintet, 1H, $-CHCOO-$), 2.75 (c, 4H, $=C-CH_2-C=$), 3.27 (s, 3H, $-OCH_3$), 3.37 (d d, J = 9.3 and 6.0 Hz, 1H, $-\overset{H}{C}-O-C-$), 3.50 (d d J = 9.3 and J = 7.2 Hz, 1H, $-\overset{H}{C}-O-C-$), 5.27 (*cis* pattern, 6H, $-C=$).

*2-Acetamido-all-*cis*-8,11,14-eicosatrienoic acid* (**10**)

An amount of 2.6 g (14 mmole) dimethyl acetamidomalonate – prepared in 67% yield according to the procedure of *Hellmann* and *Lingens*[11] – was converted into its sodio derivative as described for **9**. This was suspended in 15 ml toluene and reacted with 5.2 g (15 mmole) **16** in 15 ml toluene (92 h reflux). Filtration and evaporation of the solvent left 7.6 g residue, 5.6 g of which was hydrolysed (250 ml NaOH (0.5 mole/l) in 85% methanol; 1.5 h reflux), acidified and the crude "diacid" isolated. Since GLC showed it to be predominantly "monoacid" heating at 100°C for 45 min could complete the decarboxylation. After separating off non-acidic substances as described for **5** 1.5 g **10** (41%), purity (GLC) 98% was obtained.

UV (methanol): λ_{max} 233 nm (2.5% conjugated dienoic compounds), 269 nm (1.0% conjugated trienoic compounds).

IR: $-COOH$ 3600–2400, 1720, 1280 and 1220 cm^{-1}; $-\overset{H}{C}=\overset{H}{C}-$ 3020 and 720 cm^{-1}; $-\overset{|}{C}-NHCOCH_3$ 3360, 1600, 1545 and 1350 cm^{-1}.

PMR: δ 0.89 (t, J = 6.5 Hz, 3H, $-CH_3$), 1.1–1.5 (c, 12H, $-CH_2-$), 1.5–1.8 (c, 2H, $-CH_2\overset{|}{C}COO-$), 1.8–2.1 (c, 7H, $-CH_2-\overset{|}{C}=$ + $-\overset{|}{N}-COOCH_3$), 2.75 (c, 4H, $=C-CH_2-C=$), 4.38 (c, 1H, $-\overset{H}{C}HCOO-$), 5.26 (*cis* pattern, 6H, $-C=$), ~7.3 (br abs, 1H, $-NH-$), ~11.5 (br abs 1H, $-COOH$).

*2-Amino-all-*cis*-8,11,14-eicosatrienoic acid hydrochloride* (**11**)

Deacetylation of 4.2 g (12 mmole) **10** [100 ml methanolic HCl (6.5 mole/l); 71 h at 60°C], hydrolysis of the methyl ester thereby obtained (150 ml NaOH (0.5 mole/l) in 85% methanol; 0.5 h reflux) and filtration yielded 0.8 g (16%) of a white powder, identified (IR) as sodium 2-amino-all-*cis*-8,11,14-eicosatrienoate. The filtrate after acidification with HCl (6 mole/l) and addition of ether gave a microcrystalline precipitate, suspended in the ether phase. Collection afforded 0.8 g **11** (15%), purity (GLC of methyl 2-amino-all-*cis*-8,11,14-eicosatrienoate) 84%.

UV (methanol): λ_{max} 235 nm (3.6% conjugated dienoic compounds); 269 nm (2.1% conjugated trienoic compounds).

MS: Parent peak at *m/e* 371–373 (calcd for $C_{21}H_{38}ClNO_2$ 371.5).

IR: $-COOH$ 3200–2400, 1742, 1415, 1210 and 915 cm^{-1}; $-NH_3^+$ 1985, 1600, 1495 and 845 cm^{-1}; $-\overset{H}{C}=\overset{H}{C}-$ 3020, 1660 and 720 cm^{-1}.

PMR (in CD_3OD): δ 0.90 (t, J = 6.8 Hz, 3H, $-CH_3$), 1.2–1.6 (c, 12H, $-CH_2-$), 1.91 (c, 2H, $-CH_2-\overset{|}{C}-COO-$), 1.9–2.1 (c, 4H, $-CH_2-C=$), 2.80 (c, 4H, $=C-CH_2-C=$), 3.91 (t, J = 6.3 Hz, 1H, $-\overset{H}{C}H-COO-$), 5.33 (*cis* pattern, 6H, $-C=$).

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2-Fluoro-all-cis-8,11,14-eicosatrienoic acid (**12**)

An amount of 3.6 g (20 mmole) diethyl fluoromalonate (ex Fluka) in 60 ml toluene was converted into its sodio derivate as described for **7** and subsequently reacted with 6.8 g (20 mmole) **16** (6.5 h reflux). After hydrolysis (HCl (2.3 mol/l) in dioxane/water 5:3 v/v; 52 h reflux) during which decarboxylation occurs simultaneously (*cf.* ref. 7) and separation of non-acidic products as described for **5**, 3.65 g almost pure **12** was obtained. Further purification by column chromatography over SiO_2, deactivated with 10% H_2O, yielded on elution with light petroleum/chloroform 1:1 v/v to 1:3 v/v 1.83 g **12** (28%), m.p. 7–10°C, n_D^{25} 1.4735, purity (GLC) 95%.

UV (hexane): λ_{max} 236 nm (0.8% conjugated dienoic compounds), 268 nm (0.7% conjugated trienolc compounds.

IR: −COOH 3400–2600, 1730, 1400, 1250 and 923 cm^{-1}; −C(H)=C(H)− 3020, 1660 and 720 cm^{-1}; −C(F)− 1160 and 1100 cm^{-1}.

PMR: δ 0.89 (t, J = 6.6 Hz, 3H, $-CH_3$), 1.2–1.6 (c, 12H, $-CH_2-$), 1.7–2.1 (c, 6H, $-CH_2C(COO-)-$ + $-CH_2C=$), 2.75 (c, 4H, $=C-CH_2-C=$), 4.8 (d t, J = 49.0 and 6.0 Hz, 1H, $-CH(H)COO-$), 5.26 (*cis* pattern, 6H, −C=).

2-Methoxy-all-cis-8,11,14-eicosatrienoic acid (**13**)

An amount of 14.3 g (75 mmole) diethyl methoxymalonate – prepared in 70% yield according to *Grüssner* et al.[12] – was converted into its sodio derivative in 225 ml toluene as described for **7** and then reacted with 21.0 g (61.5 mmole) **16** (2.5 h reflux). After hydrolysis (600 ml NaOH (0.5 mole/l) in 70% methanol; 2 h reflux) non-acidic products were separated off as described for **5** and the acid material decarboxylated (1 h at 130°C at 8 mmHg). Final purification via column chromatography over SiO_2, deactivated with 10% H_2O, yielded on elution with light petroleum/ether/acetic acid 90:10:0.3 v/v/v to 85:15:0.3 v/v/v 12.8 g **13** (62%), n_D^{25} 1.4768 purity (GLC) 99%.

UV (hexane): λ_{max} 235 nm (1.6% conjugated dienoic compounds), 268 nm (2.2% conjugated trienoic compounds).

IR: −COOH 3600–2400, 1720, 1285, 1210 and 925 cm^{-1}; −C(H)=C(H)− 3010, 1658 and 720 cm^{-1}; $-OCH_3$ 2820 and 1130 cm^{-1}.

MS: parent peak at *m/e* 336 (calcd for $C_{21}H_{36}O_3$ 336).

PMR: δ 0.89 (t, J = 6.8 Hz, 3H, $-CH_3$), 1.2–1.6 (c, 12H, $-CH_2-$), 1.70 (c, 2H, $-CH_2C(COO-)-$), 1.9–2.2 (c, 4H, $-CH_2C=$), 2.76 (c, 4H, $=C-CH_2C=$), 3.37 (s, 3H, $-OCH_3$), 3.66 (t, J = 6.0 Hz, 1H, $-CH(H)COO-$), 5.25 (*cis* pattern, 6H, −C=).

2-Cyano-all-cis-8,11,14-eicosatrienoic acid (**14**)

An amount of 2.3 g (20.5 mmole) ethyl cyanoacetate was converted into its sodio derivative with sodium ethoxide in 35 ml ethanol and reacted with 6.9 g (20 mmole) **16** (45 min reflux). Hydrolysis (600 ml NaOH (0.5 mole/l) in 85% methanol; 0.5 h reflux) and separation from non-acidic products as described for **5** afforded after isolation 1.3 g **14** (21%), purity (GLC) 95%.

UV (hexane): λ_{max} 235 nm (1.2% conjugated dienoic compounds), 270 nm (0.8% conjugated trienoic compounds).

IR: −COOH 3600–2400, 1760, 1745, 1275 and 915 cm^{-1}; −C(H)=C(H)− 3020, 1660 and 725 cm^{-1}; −CN 2260 cm^{-1}.

PMR: δ 0.89 (t, J = 6.5 Hz, 3H, $-CH_3$), 1.1–1.6 (c, 12H, $-CH_2-$), 1.95 (br quartet, 2H, $-CH_2C(COO-)-$), 1.9–2.1 (c, 4H, $-CH_2C=$), 2.76 (c, 4H, $=C-CH_2-C=$), 3.51 (t, J = 6.8 Hz, 1H, $-CH(H)COO-$), 5.28 (*cis* pattern, 6H, −C=), 10.67 (s, 1H, −COOH).

2-Butyl-2-cyano-all-cis-8,11,14-eicosatrienoic acid (**15**)

An amount of 3.2 g (19 mmole) ethyl 2-cyanohexanoate – prepared in 88% yield according to an Organic Synthesis procedure[13] – was converted into its sodio derivative as described for **14**, and reacted with 6.8 g (20 mmole) **16**, (55 ml ethanol; 1 h reflux). Hydrolysis (725 ml NaOH (0.5 mole/l) in 85% methanol; 0.5 h reflux) and separation from non-acidic products as described for **5** afforded 2.9 g **15** (40%), purity (GLC) 95%.

UV (hexane): λ_{max} 233 nm (2.8% conjugated dienoic compounds), 270 nm (0.7% conjugated trienoic compounds).

IR: −COOH 3600–2400, 1755, 1720, 1255, 1200 and 915 cm^{-1}; −C(H)=C(H)− 3020, 1660 and 730 cm^{-1}; −CN 2260 cm^{-1}.

MS: Parent peak of ethyl ester at *m/e* 415 (calcd for $C_{27}H_{45}NO_2$ 415).

PMR: δ 0.6–1.1 (c, 6H, $-CH_3$), 1.1–2.3 (c, 24H, $-CH_2-$ + $CH_2C=$), 2.77 (c, 4H, $=C-CH_2-C=$), 5.32 (*cis* pattern, 6H, −C=), 10.73 (s, 1H, −COOH).

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