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

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Abstract. The synthesis of the following groups of acids is described: (a) 3-Methyl-*c*-2,*c*-8,*c*-11,*c*-14-, and 3-methyl-*t*-2,*c*-8,*c*-11,*c*-14-eicosatetraenoic acid and 3-methyl-*c*-8,*c*-11,*c*-14-eicosatrienoic acid, (b) *c*-8,*c*-11,*c*-14-eicosatrien-5-ynoic acid, (c) *c*-2,3-methylene-,*t*-2,3-methylene-,3,3-dimethyl- and 4,4-dimethyl-*c*-8,*c*-11,*c*-14-eicosatrienoic acid, (d) 18-methyl-, *(S)*-18-methyl- and 19-methyl-*c*-8,*c*-11,*c*-14-eicosatrienoic acid. They were obtained via coupling of (a) *c*-7,*c*-10,*c*-13-nonadecatrien-2-one with ethoxycarbonylmethylenetriphenylphosphorane and *c*-7,*c*-10,*c*-13-nonadecatrien-2-yl methane sulfonate with diethyl malonate, (b) 1-bromo-*c*-2,*c*-5,*c*-8-tetradecatriene with 5-hexynoic acid, (c) 1-bromo-2,5-undecadiyne with the appropriately substituted 8-nonynoic acids and (d) from the correspondingly substituted 1-bromo pentanes, using standard procedures.

Introduction

Investigations into the substrate specificity of the prostaglandin synthetase enzyme system from sheep vesicular glands have resulted in the formulation of rules governing the pattern of relationship between the structure of unsaturated fatty acids and their essential fatty acid activity, their convertability into prostaglandins and the biological activities of the latter[1,2]. In these investigations, the total chain length and the position of the skipped *cis* tri- and tetraene system in the carbon chain have been varied. We have now prepared a series of *c*-8,*c*-11,*c*-14-eicosatrienoic acids carrying one or two substituents either in the proximal or in the terminal part of the molecule. The synthesis of *c*-8,*c*-11,*c*-14-eicosatrienoic acids with one or two substituents in the 2-position has already been described[3]. This paper gives the synthesis of *c*-8,*c*-11,*c*-14-eicosatrienoic acids having the following substituents and/or functions:

a) a 3-methyl group and an extra *trans* or *cis* double bond in the 2-position,
b) a triple bond in the 5-position,
c) a *trans* or *cis*-2,3-methylene group, or two geminal methyl groups in either the 3*- or the 4-position,
d) a methyl group in either the 18-, *(S)* 18-, or 19-position.

The bioconversion of the acids into the correspondingly substituted prostaglandins as well as the biological properties of the latter have been published separately[4,5].

Methods and results

For the synthesis, two general approaches have been used, namely partial synthesis starting from *c*-6,*c*-9,*c*-12-octadecatrienoic acid (γ-linolenic acid) and total synthesis using intermediates with triple bonds in positions where finally the *cis*-double bonds have to be located.

Partial synthesis starting from c-6,c-9,c-12-octadecatrienoic *acid*

c-6,*c*-9,*c*-12-Octadecatrienoyl chloride, prepared from the corresponding acid according to *Heslinga* et al.[6] using 1,1-dichloromethoxymethane[7] in the presence of some zinc chloride, was coupled with diethyl ethoxymagnesium-malonate. Following acidic hydrolysis of the resulting diester and splitting off both carboxyl groups[8], *c*-7,*c*-10,*c*-13-nonadecatrien-2-one (**1**) was obtained.

$$RCOOH \xrightarrow[ZnCl_2]{Cl_2CHOCH_3} RCOCl$$

$$RCOCl + C_2H_5OMgCH(COOC_2H_5)_2 \longrightarrow$$

$$RCOCH(COOC_2H_5)_2 \xrightarrow{H^+} RCOCH_3$$

1

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

Condensing **1** with ethoxycarbonylmethylenetriphenylphosphorane according to *Rüchardt* et al.[9] afforded a mixture of ethyl 3-methyl-*t*-2,*c*-8,*c*-11,*c*-14-eicosatetraenoate (**2a**) and ethyl 3-methyl-*c*-2,*c*-8,*c*-11,*c*-14-eicosatetraenoate (**2b**) which was separated via column chromatography. Hydrolysis of the esters yielded the corresponding 3-methyl-*t*-2,*c*-8,*c*-11,*c*-14-eicosatetraenoic acid (**3a**) and 3-methyl-*c*-2,*c*-8,*c*-11,*c*-14-eicosatetraenoic acid (**3b**).

$$RCOCH_3 + \left[\bigcirc\right]_3 \overset{+}{P}CH\,COOC_2H_5 \longrightarrow$$

1

$$RC(CH_3)=CHCOOC_2H_5 \xrightarrow[\text{b) hydrolysis}]{\text{a) separation}}$$

2a, 2b

$$\longrightarrow \quad \overset{CH_3}{\underset{R}{}}\!\!>\!C=C<\!\!\overset{COOH}{\underset{H}{}} \quad \text{and} \quad \overset{R}{\underset{CH_3}{}}\!\!>\!C=C<\!\!\overset{COOH}{\underset{H}{}}$$

3a **3b**

* Cf. ref. 4 in which 3,3-dimethyl-*c*-9,*c*-12,*c*-15-heneicosatrienoic acid has been described.

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Reduction of **1** with $NaBH_4$[10], conversion of the resulting *c*-7,*c*-10,*c*-13-nonadecatrien-2-ol (**4**) into its methanesulfonate according to the procedure of *Crossland* and *Servis*[11], and subsequent malonic ester synthesis yielded 3-methyl-*c*-8,*c*-11,*c*-14-eicosatrienoic acid (**5**).

$$\underset{\mathbf{1}}{RCOCH_3} \xrightarrow{NaBH_4} \underset{\mathbf{4}}{RCH(OH)CH_3}$$

$$\xrightarrow[\text{b) Malonic ester synthesis}]{\text{a) } CH_3SO_2Cl} \underset{\mathbf{5}}{RCH(CH_3)CH_2COOH}$$

Total synthesis (cf. ref. 1,2)

i. Starting from 2,5,8-tetradecatriynol[12]

Reduction of 2,5,8-tetradecatriynol in the presence of Lindlar's catalyst[13] and quinoline to *c*-2,*c*-5,*c*-8-tetradecatrienol, conversion of the latter with phosphorus tribromide in the dark[14] into 1-bromo-*c*-2,*c*-5,*c*-8-tetradecatriene (**6**) and coupling of the latter with 5-hexynoic acid yielded *c*-8,*c*-11,*c*-14-eicosatrien-5-ynoic acid (**7**). This product was contaminated with appreciable amounts of products originating from allylic rearrangement of the bromide. The latter could be removed only partially by repeated chromatography.

$$C_5H_{11}[C{\equiv}C{-}CH_2]_3OH \xrightarrow[\text{b) } PBr_3]{\text{a) } H_2/\text{catalyst}} C_5H_{11}[CH\overset{cis}{=}CH{-}CH_2]_3Br$$

6

$$\mathbf{6} + HC{\equiv}C(CH_2)_3COOH \xrightarrow[Cu_2(CN)_2]{C_2H_5MgBr/THF} C_5H_{11}[CH\overset{cis}{=}CH{-}CH_2]_3C{\equiv}C(CH_2)_3COOH$$

7

ii. Starting from 1-bromo-2,5-undecadiyne[12]

Coupling of 1-bromo-2,5-undecadiyne with the appropriately substituted 8-nonynoic acids and subsequent partial hydrogenation in the presence of Lindlar's catalyst and quinoline afforded 4,4-dimethyl- (**14**), 3,3-dimethyl- (**17**), *trans*-2,3-methylene- (**21a**) and *cis*-2,3-methylene-*c*-8,*c*-11,*c*-14-eicosatrienoic acid (**21b**).

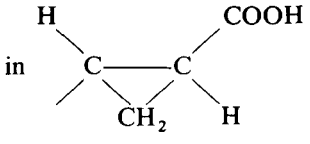
$$HC{\equiv}C(CH_2)_3\underset{\displaystyle R\ R}{\overset{\displaystyle R'\ R'''}{\overset{|\quad|}{\underset{|\quad|}{C{-}C}}}}{-}CH{-}COOH \xrightarrow[\text{(b) } 3H_2/\text{cat.}]{\text{(a) } C_2H_5MgBr/Cu_2(CN)_2} C_5H_{11}[C{\equiv}C{-}CH_2]_2Br$$

12, 16 **19a, 19b**

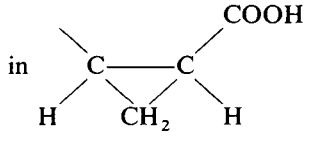
$$C_5H_{11}[CH\overset{cis}{=}CH{-}CH_2]_3(CH_2)_2{-}\underset{\displaystyle R\ R}{\overset{\displaystyle R'\ R'''}{\overset{|\quad|}{\underset{|\quad|}{C{-}C}}}}{-}CH{-}COOH$$

14, 17 **21a, 21b**

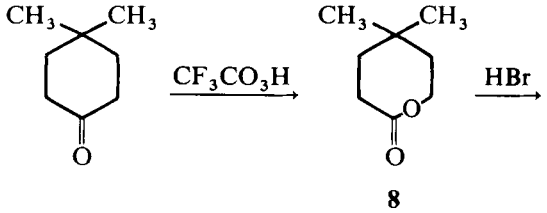
12, 14 $R = CH_3$; $R' = R'' = R''' = H$
16, 17 $R' = R'' = CH_3$; $R = R''' = H$
19a, 21a $R = R' = H$; $R''R''' = CH_2$

in 

19b, 21b $R = R' = H$; $R''R''' = CH_2$

in 

4,4-Dimethyl-8-nonynoic acid (**12**) was prepared starting from 4,4-dimethylcyclohexanone, which was obtained by catalytic hydrogenation of 4,4-dimethyl-2-cyclohexen-1-one[15] in the presence of palladium on carbon. The 4,4-dimethylcyclohexanone was subjected to Bayer-Villiger oxidation with trifluoroperacetic acid[16] according to the procedure of *Smissman* et al.[17] and the resulting lactone (**8**) converted with hydrogen bromide into 6-bromo-4,4-dimethylhexanoic acid (**9**). After esterification and reaction with sodium iodide in acetone, the methyl-6-iodo-4,4-dimethylhexanoate (**10**) thus obtained was extended to methyl 4,4-dimethyl-8-nonenoate (**11**). This was achieved by coupling (**10**) with π-allylnickel bromide[18,19] according to the procedure which *Corey* and *Semmelhack*[20] developed for the coupling of alkyl, aryl and vinyl bromides or iodides with π-allylnickel bromide. Apparently an ester function does not interfere in this reaction. Ester (**11**) was converted into acid (**12**) by hydrolysis, followed by a bromination/dehydrobromination sequence.



8

$$Br(CH_2)_2{-}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|\quad|}{C}}}{-}(CH_2)_2COOH$$

9

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[18] *B. Bogdanović, M. Kröner* and *G. Wilke*, Justus Liebigs Ann. Chem. **699**, 1 (1966).
[19] Published German Democratic Republic Patent 43533 (Aug. 5th, 1964).
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a) CH_3OH/H^+
b) NaI

$$I(CH_2)_2-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-(CH_2)_2COOCH_3 \xrightarrow{\pi\text{-allylnickel bromide}}$$

10

a) OH^-
b) Br_2
c) $-2\,HBr$

$$H_2C=CH(CH_2)_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-(CH_2)_2COOCH_3 \longrightarrow$$

11

$$HC\equiv C(CH_2)_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-(CH_2)_2COOH$$

12

3,3-dimethyl-8-nonynoic acid (**16**) was prepared via coupling of 1-chloro-5-hexyne with the α-anion of lithium isobutyrate (from isobutyric acid + 2 eq. lithium isopropylcyclohexylamide in tetrahydrofuran (THF) at −78°C), as described by *Creger*[21], followed by chain lengthening of the resulting 2,2-dimethyl-7-octynoic acid (**15**) via a modified Arndt-Eistert technique[22].

$$HC\equiv C(CH_2)_4Cl + LiC(CH_3)_2-COOLi \xrightarrow{THF/-78°C}$$

$$HC\equiv C(CH_2)_4-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-COOH \longrightarrow$$

a) $(COCl)_2$
b) CH_2N_2

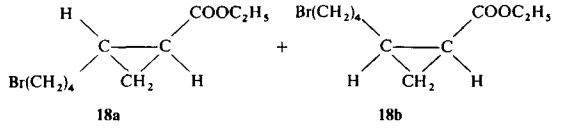
$$\longrightarrow RCOCHN_2 \xrightarrow{\text{2,4,6-trimethylpyridine}} RCH_2COOCH_2-C_6H_5 \xrightarrow{OH^-} RCH_2COOH$$

16

$$R = HC\equiv C(CH_2)_4-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-$$

trans-(**19a**) *and* cis-*2,3-Methylene-8-nonynoic acid* (**19b**) were obtained by reacting 1-bromo-5-hexene (prepared by reduction of 5-hexenoic acid with $LiALH_4$, followed by reaction with PBr_3) with ethyl diazoacetate in the presence of Cu powder[23]. After separation of the mixture of ethyl *trans*-2,3-methylene-(**18a**), and ethyl *cis*-2,3-methylene-7-bromoheptanoate (**18b**) and subsequent hydrolysis, each isomer was coupled separately with lithium acetylide.

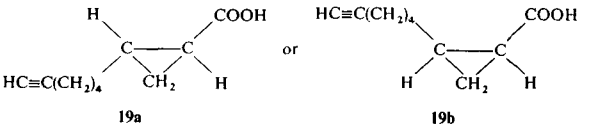
$$Br(CH_2)_4CH=CH_2 + N_2CHCOOC_2H_5 \xrightarrow{Cu}$$



18a **18b**

a) OH^-
b) $LiC\equiv CH$ in liq NH_3

18a or **18b** →



19a **19b**

iii. Starting from substituted pentanols

3-Methylpentanol, (+)-(3*S*)-methylpentanol and 4-methylpentanol were converted into the corresponding substituted 8,11,14-eicosatriynoic acids according to the procedures of *Kunau*[25,26]. 3-Methylpentanol and (+)-(3*S*)-methylpentanol were prepared from 2-methylbutanol and (+)-(2*S*)-methylbutanol respectively, via chain lengthening of the corresponding 2-methylbutyl magnesium bromides with methanal (cf. ref. 24). In a final step, stereospecific partial hydrogenation afforded the substituted *c*-8,*c*-11,*c*-14-eicosatrienoic acids. The syntheses are illustrated by the following scheme:

a) $LiNH_2$/liq NH_3
b) RBr

$$HC\equiv C-CH_2OCH_3 \longrightarrow RC\equiv C-CH_2OCH_3 \xrightarrow{CH_3COBr/ZnBr_2}$$

22a,b,c

$$\longrightarrow RC\equiv C-CH_2Br \xrightarrow{HC\equiv C-CH_2OCH_3/C_2H_5MgBr}$$

23a,b,c

$$\longrightarrow R[C\equiv C-CH_2]_2OCH_3 \xrightarrow{CH_3COBr/ZnBr_2}$$

24a,b,c

$$\longrightarrow R[C\equiv C-CH_2]_2Br \xrightarrow{HC\equiv C(CH_2)_5COOH/C_2H_5MgBr}$$

25a,b,c

$$\longrightarrow R[C\equiv C-CH_2]_3(CH_2)_5COOH \xrightarrow{H_2/catalyst}$$

26a,b,c

$$\longrightarrow R[CH\overset{cis}{=}CH-CH_2]_3(CH_2)_5COOH$$

27a,b,c

22a–27a: R = $CH_3CH(CH_3)CH_2CH_2CH_2-$
22b–27b: R = $CH_3CH_2CH(CH_3)CH_2CH_2-$
22c–27c: R = (18*S*)-$CH_3CH_2CH(CH_3)CH_2CH_2-$

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Experimental

(In co-operation with *J. C. Lindhoudt* and *W. M. M. Möhlmann.*)

All temperatures are uncorrected. Melting points were determined with a Büchi apparatus or a Reichert melting point microscope. Where necessary, the reactions were carried out in an inert gas atmosphere (argon). Reagent-grade solvents were dried on and distilled from $LiAlH_4$ [diethylether, tetrahydrofuran (THF), diglyme (2,5,8-trioxononane)] or from molecular sieve A-4 (dimethylformamide), and distilled under argon prior to use. For the eluents (chloroform, optically pure light petroleum), analytical grade solvents were used. For column chromatography, Kieselgel ex Merck (70–230 mesh) was used. UV spectra were obtained with a Cary 14 spectrophotometer. Mass spectra were obtained with an AEI-MS 9 spectrometer. PMR spectra were obtained from solutions in carbon tetrachloride or hexadeutero acetone (**8**) containing 1% tetramethylsilane as internal zero reference either with a Varian A-60 (**8**, **12** and **22a,b,c**, **25a,b,c**) or with an HR 220 spectrophotometer (**1–5**, **7**, **13**, **15–21a,b**, **26a,b,c** and **27a,b,c**) operating at 30°C.

δ-Values are quoted in ppm downfield and are accurate to within 0.01 ppm while coupling constants are accurate to within 0.2 Hz. The following abbreviations were used in the recording of the PMR spectra: br = broadened, c = complex, d = doublet, d.d = doublet of doublets, dist. = distorted, s = singlet, t = triplet etc.

GLC analyses were performed on a Becker 409 and a Packard-Becker 419 gas chromatograph, both ,equipped with all glass systems; as columns were used a 125 cm 10% SE 30 and a 125 cm 10% OV-101 on Chromosorb W (AW-DMCS-HP) and a 200 cm 5% DEGA on chromosorb W (AW-DMCS). Unless otherwise stated, the "GLC purity" of all compounds prepared was 95% or higher.

Partial synthesis

c-7,c-10,c-13-Nonadecatrien-2-one (**1**)

An amount of 10.6 g (36 mmol) *c*-6,*c*-9,*c*-12-octadecatrienoyl chloride [b.p. 130–140°C/10^{-3} mmHg; purity (GLC) 99%; 1% conjugated dienoic compounds (UV) – prepared by heating *c*-6,*c*-9,*c*-12-octadecatrienoic acid with 1,1-dichloro-methoxymethane and 0.1 mmol/mol $ZnCl_2$ for 1 h at 85°C – (cf. ref. 6, 7)] in 25 ml benzene was added dropwise to 34.1 ml (72 mmol) diethyl ethoxymagnesiummalonate in benzene (2.1 mol/l) and the mixture refluxed for 1.5 h. After cooling, acidification (H_2SO_4; 2 mol/l) and extraction with ether, the combined organic layers were washed acid-free, dried ($MgSO_4$), the solvents evaporated and excess diethyl malonate distilled off at 100°C and 10^{-2} mmHg. The residue was hydrolysed, decarboxylated and worked up as described[8], yielding 11.1 g crude ketone. Purification via column chromatography over silica gel using light petroleum with a gradient of 0–5% ether, afforded 4.9 g (48%) **1**.

UV (hexane): λ_{max}: 230 nm (1% conjugated dienoic compounds); 280 nm (0.3% conjugated trienoic compounds).

IR: CH_3CO 1720, 1360 and 1163 cm^{-1}; $-\overset{H}{\underset{}{C}}=\overset{H}{\underset{}{C}}-$: 3020, 1650 and 720 cm^{-1}; $-CH_2-\underset{}{C}=\underset{}{C}$ 1412 cm^{-1}.

PMR: δ 0.90 (t, *J* 6.8 Hz, 3H, $-CH_3$), 1.1–1.4 (c, 8H, $-CH_2-$), 1.54 (dist. quintet, 2H, $-CH_2-\overset{O}{\overset{\|}{C}}-C-$), 1.9–2.1 (c, 4H, $-CH_2-C=$), 2.03 (s, 3H, $-\overset{O}{\overset{\|}{C}}CH_3$), 2.33 (t, *J* 7.2 Hz, 2H, $-CH_2\overset{O}{\overset{\|}{C}}-$), 2.75 (c, 4H, $=C-CH_2-C=$), 5.27 (*cis* pattern, c, 6H, $-\overset{H}{\underset{}{C}}=$).

Ethyl 3-methyl-t-2,c-8,c-11,c-14- (**2a**), *and ethyl 3-methyl-c-2,c-8,c-11,c-14-eicosatetraenoate* (**2b**)

A solution of 4.71 g (17.1 mmol) **1**, 29.7 g (85.3 mmol) ethoxycarbonylmethylenetriphenylphosphorane – prepared according to *Isler* et al.[27]; m.p. 126–128°C (lit. 116–117°C) – and 0.37 g (3 mmol) benzoic acid in 30 ml benzene was refluxed for 65 h[9]. After distilling off the benzene, the residue was suspended in light petroleum and filtered over 150 g silica gel using light petroleum/ether 9 : 1 v/v as eluent. Evaporation of the eluate left 4.94 of a mixture containing **2a** and **2b**. By three column chromatographic separations over silica gel, using successively eluents with a gradient of 0–5% ether, 0–2.5% ether, and 0–50% chloroform in light petroleum, final evaporation of the solvent left 0.82 g (13%) **2a**, purity (GLC) 91%. By chromatography of the eluates of the previous separations, rich in **2b** using silica gel and an eluent with a gradient of 0–50% chloroform in light petroleum, 0.98 g (15%) **2b**, purity (GLC) 91%, was obtained.

3-Methyl t-*2,c-8,c-11,c-14-* (**3a**), and *3-methyl-c-2,c-8,c-11,c-14-eicosatetraenoic acid* (**3b**)

Hydrolysis of 0.58 g (1.7 mmol) **2a** [13.5 ml NaOH (0.5 mol/l) in ethanol/water 1 : 1 v/v; 19 h reflux], subsequent acidification (HCl; 4 mol/l) and extraction with ether (3 × 30 ml), yielded after washing (saturated NH_4Cl solution), drying ($MgSO_4$) and evaporation of the combined ether layers 0.5 g crude **3a**. Purification via chromatography over silica gel, deactivated with 10% water using a gradient of 0–5% ether in light petroleum afforded 0.27 g **3a** (56%)*.

IR: $-\overset{H}{\underset{}{C}}=\underset{CH_3}{\overset{}{C}}-COOH$ 3600–2400, 1690, 1642, 1420, 1250 and 930 cm^{-1}; $-\overset{H}{\underset{}{C}}=\overset{H}{\underset{}{C}}-$ 3020 and 710 cm^{-1}; $-\overset{H}{\underset{}{C}}=\underset{CH_3}{\overset{}{C}}-$ 870 cm^{-1}.

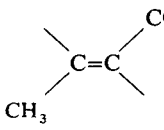
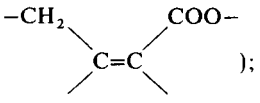
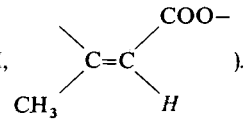
PMR: δ 0.89 (t, *J* 6.7 Hz, 3H, $-CH_3$), 1.2–1.6 (c, 10H, $-CH_2-$); 1.9–2.2 (c, 6H, $-CH_2C=$ + $\begin{matrix} CH_3 & & COO- \\ & \diagdown & \diagup \\ & C=C & \\ & \diagup & \diagdown \\ & CH_2 & \end{matrix}$); 2.15 (br.s, 3H, $\begin{matrix} CH_3 & & COO- \\ & \diagdown & \diagup \\ & C=C & \\ & \diagup & \diagdown \end{matrix}$), 2.75 (dist. t, 4H, $=C-CH_2-C=$), 5.27 (*cis* pattern, 6H, $-\overset{H}{\underset{}{C}}=$), 5.61 (br.s, 1H, $\begin{matrix} CH_3 & & COO- \\ & \diagdown & \diagup \\ & C=C & \\ & & \diagdown \\ & & H \end{matrix}$).

In the same way, hydrolysis of 0.95 g **2b** yielded 0.49 g (62%) **3b***.

IR: $-\underset{CH_3}{\overset{}{C}}=\overset{H}{\underset{}{C}}-COOH$ 3600–2400, 1690, 1640, 1418, 1245 and 930 cm^{-1}; $-\overset{H}{\underset{}{C}}=\overset{H}{\underset{}{C}}-$ 3020 and 710 cm^{-1}; $-\underset{CH_3}{\overset{}{C}}=\overset{H}{\underset{}{C}}-$ 865 cm^{-1}.

* It was impossible to determine the purity by GLC of its methyl ester since re-esterification with CH_2N_2 introduced impurities containing nitrogen and re-esterification with CH_3OH/H_2SO_4 caused substantial isomerization (IR)!

[27] *O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser* and *P. Zeller*, Helv. Chim. Acta **40**, 1242 (1957).

PMR: δ 0.89 (t, *J* 6.5 Hz, 3H, $-CH_3$), 1.2–1.6 (c, 10H, $-CH_2-$), 1.91 (d, *J* 1.3 Hz, 3H, ); 1.9–2.2 (c, 4H, $-CH_2C=$), 2.64 (br.t, *J* 7.5 Hz, 2H, ); 2.76 (dist. t, 4H, $=C-CH_2-C=$), 5.26 (*cis* pattern, 6H, $-C=$), 5.61 (br.s, 1H, ).

c-7,c-*10*,c-*13*-*Nonadecatrien-2-ol* (**4**)

A solution of 3.0 g (11 mmol) **1** in 15 ml ethanol was reduced by stirring with 2.5 g (65 mmol) sodium borohydride in 15 ml ethanol/25 ml water for 2 h at room temperature. After working up, 3.0 g **4** (~100%) was obtained.

UV (hexane): λ_{max} 230 nm (1.6% conjugated dienoic compounds); 270 nm (0.2% conjugated trienoic compounds).

IR: $-CHOH$ 3450 and 1130 cm^{-1}; $-CH=CH-$ 3020, 1650 and 710 cm^{-1}.

PMR: δ 0.90 (t, *J* 6.8 Hz, 3H, CH_3), 1.12 (d, *J* 6.0 Hz, 3H, $-CH(O-)-CH_3$) 1.1–1.5 (c, 12H, $-CH_2-$) 1.9–2.2 (c, 4H, $-CH_2-C=$), 2.76 (c, 4H, $=C-CH_2-C=$), 3.66 (c, 1H, $-CH(O-)-$), 5.27 (*cis* pattern, 6H, $-C=$).

3-Methyl-c-*8*,c-*11*,c-*14*-*eicosatrienoic acid* (**5**) *(cf. ref. 3)*

An amount of 3.7 g (10.4 mmol) *c*-7,*c*-10,*c*-13-nonadecatrien-2-yl methane sulfonate, purity (GLC) 82% – prepared from 3.0 g **4** in 83% yield (cf. ref. 3, 11) – was reacted with diethyl sodiomalonate [from 1.7 g (10.4 mmol) diethyl malonate and 540 mg of a 50% dispersion of sodium in paraffin (11.7 mol) in 50 ml benzene] for 2 h at 23°C and 45 h at reflux. Acidification (HCl; 4 mol/l), extraction with ether and washing with saturated NH_4Cl solution, drying over $MgSO_4$ and evaporation of the combined organic layers left 4.4 g residue. Column chromatography of the latter over silica gel using a gradient of 0–50% chloroform in light petroleum afforded 1.56 g diethyl 2-methyl-*c*-7,*c*-10,*c*-13-nonadecatriene-1,1-dicarboxylate, purity (GLC) 90%. Hydrolysis [30 ml NaOH in methanol/water 1:1 v/v (0.6 mol/l) 4 h, 70°C], decarboxylation (2 h at 170°C at diminished pressure) and a final purification via column chromatography over silica gel, deactivated with 10% water using a gradient of 0–10% ether in light petroleum yielded 520 mg **5** (47%).

UV (hexane): λ_{max} 232 nm (1.1% conjugated dienoic compounds); 270 nm (0.2% conjugated trienoic compounds).

IR: $-COOH$ 3600–2400, 1710, 1410, 1295, 1220 and 935 cm^{-1}; $-CH=CH-$ 3020, 1665 and 710 cm^{-1}; $-CH(CH_3)$ 1380 cm^{-1}.

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

PMR: δ 0.89 (t, *J* 6.8 Hz, 3H, $-CH_3$), 0.97 (d, *J* 6.5 Hz, 3H, $-CH(CH_3)-$), 1.1–1.5 (c, 12H, $-CH_2-$) ~ 1.66 (c, 1H, $-CH(CH_3)-$), 1.8–2.1 (c, 4H, $-CH_2C=$), 2.09 (d.d, *J* 14.8 and 7.8 Hz) and 2.30 (d.d, *J* 14.8 and 5.8 Hz, 2H, $-CH_2COO-$) 2.76 (c, 4H, $=C-CH_2-C=$), 5.27 (*cis* pattern, 6H, $-C=$).

Total synthesis

Starting from 2,5,8-tetradecatrien-1-ol

1-Bromo-c-*2*,c-*5*,c-*8*-*tetradecatriene* (**6**) *(cf. ref. 14)*

In the dark, 7 ml (19.9 g = 73 mmol) PBr_3 was added dropwise to a solution of 42.5 g *c*-2,*c*-5,*c*-8-tetradecatrien-1-ol [purity (GLC) 92% obtained by hydrogenation of 40.4 g 2,5,8-tetradecatriynol in 150 ml light petroleum in the presence of a pre-reduced suspension of 6 g Lindlar's catalyst and 5 ml quinoline; uptake 101.8%] in 500 ml ether at 0°C. After working up as described[14], crude **6** was purified via column chromatography over silica gel affording after elution with light petroleum 47.7 g **6** (83%); purity (GLC) 88%; n_D^{25} 1.4981.

IR: $-CH=CH-$ 3010, 1640 and 720 cm^{-1}; $-C=C-CH_2Br$ 1200 and 600 cm^{-1}.

N.B. The product is strongly contaminated with a compound having a *trans* double bond (962 cm^{-1}).

c-*8*,c-*11*,c-*14*-*Eicosatrien-5-ynoic acid* (**7**)

An amount of 4.2 g (37.5 mmol) 5-hexynoic acid in 10 ml diglyme was converted into its di-Grignard derivative by adding 69 ml ethylmagnesium bromide in diglyme (1.1 mol/l; 76 mmol) and stirring for 1 h at 55°C. After addition of 200 mg $Cu_2(CN)_2$ and stirring for another 30 min, the mixture was reacted with 20.3 g (75 mmol – 100% excess) **6** in 40 ml diglyme by keeping for 24 h at 22°C and 24 h at 55°C while stirring. After acidification, the mixture was extracted with ether and the combined organic layers were washed repeatedly with water until free from copper ions, dried on $MgSO_4$ and evaporated. From the residue, dissolved in light petroleum, crude **7** was isolated by extraction with NH_4OH in methanol/water 3:1 v/v (2 mol/l) (cf. ref. 3) giving 6.5 g of an acid fraction. Applying chromatography twice, using a gradient of 0–20% ether in pentane afforded 1.4 g **7** (11%); purity (GLC of methyl ester on OV-101) 85%*; contaminated with 9% of another compound.

IR: $-COOH$ 3400–2600, 1715, 1436, 1245 and 920 cm^{-1}; $-CH_2C\equiv C-$ 1320 cm^{-1}; $-CH=CH-$ 3020, 1650 and 720 cm^{-1}; $-CH=CH-$ 962 cm^{-1}.

* GLC of the methyl ester on DEGA, however, showed the presence of a second contaminant, hardly separable from the main peak and being present in amounts of ~20% of the latter. Its concentration correlates rather well with the intensity of the IR absorption at 962 cm^{-1}, attributed to a compound with an isolated *trans* double bond and estimated to be present in an amount of 20–25% of the main compound.

PMR : δ 0.90 (t, J 6.8 Hz, 3H, $-CH_3$), 1.1–1.4 (c, 6H, $-CH_2-$), 1.78 (quintet, J 7.2 Hz, 2H, $-CH_2-C-COO-$), 2.03 (br.quartet, ~2H, $-CH_2C=$), 2.21 (t.t, J 7.0 Hz and 2.2 Hz, 2H, $\equiv C-CH_2-C-C-COO-$), 2.44 (t, J 7.3 Hz, 2H, $-CH_2COO-$), 2.6–2.8 (c, ~4H, $=C-CH_2-C=$), 2.87 (c, ~2H, $=C-CH_2-C\equiv$), 5.1–5.4 (c, ~6H, $=C(H)-$).

An amount of 294 mg of an acid fraction containing 46% of the unknown compound hydrogenated in 20 ml methanol in the presence of PtO_2 until no more hydrogen was taken up (114 ml; calc. 118 ml) showed, on GLC after esterification, a 49 to 51 ratio of the two main components having "carbon numbers" of methyl eicosanoate and a shorter chain fatty acid ester.
Column chromatography of 625 mg of the same acid fraction, using a gradient of 0–10% ether in light petroleum as eluent, afforded 58 mg of a fraction containing 77% of the unknown compound.

IR : $-COOH$ 3600–2400, 1705, 1410 and 1240 cm^{-1}; $-CH_2C\equiv C-$ 1430 and 1340 cm^{-1}; $-C(H)=C(H)-$ 3005, 1650 and 720 cm^{-1}; $-CH=CH_2$ 3040, 1640, 987 and 918 cm^{-1}.

PMR : δ 0.89 (t, J 6.8 Hz, 3H, $-CH_3$), 1.1–1.5 (c, 6H, $-CH_2-$), 1.81 (quintet, J 7.2 Hz, 2H, $-CH_2-C-COO-$), 2.01 (br.quartet, J ~ 6.5 Hz, $-CH_2C=$), 2.1–2.4 (c, 4H, $-CH_2-C(C=)-C\equiv C-CH_2-$) 2.45 (t, J 7.2 Hz, 2H, $-CH_2COO-$), 2.74 (br.t, J ~ 5.3 Hz, $=C-CH_2-C=$), 3.00 (br.quartet, $-C-C(H)(C=)-C\equiv$), 5.00 (d.t, J 10.0 and 1.3 Hz, $-C-C(CH=C(H)H)-C\equiv$) 5.19 (d.t, J 17.0 and 1.3 Hz, $-C(C=CHH)-C\equiv$) 5.1–5.5 (c, $-C(H)=$), 5.68 (d.d.d, J 17.0, 10.0 and 6.0 Hz, $-C(HC=C)-C\equiv$).

From the GLC analysis and the IR and PMR data it is obvious that the unknown compound is a vinyl branched acid, most probably 7-vinyl-c-9,c-12-octadecadien-5-ynoic acid

$$C_5H_{11}CH=CH-CH_2-CH=CH-CH_2-CH(CH=CH_2)-C\equiv C-(CH_2)_3COOH$$

which may arise from allylic rearrangement during the coupling of **6** with 5-hexynoic acid.

Starting from 1-bromo-2,5-undecadiyne

4,4-Dimethyl-6-hexanolide (**8**)

An amount of 86.5 ml (610 mmol) trifluoroacetic acid anhydride (ex Merck) was added at 0°C to a suspension of 14 ml (510 mmol) 90% hydrogen peroxide in 100 ml dichloromethane and the mixture stirred for 0.5 h (cf. ref. 16). The resulting trifluoroperacetic acid solution was added dropwise in 2 h at 0°C to a cooled solution of 38.7 g (340 mmol) 4,4-dimethylcyclohexanone (b.p. 91–92°C/44 mmHg) in 400 ml CH_2Cl_2 in which 140 g Na_2HPO_4 was suspended (cf. ref. 17). During the addition, the temperature was maintained below 10°C. The precipitate was filtered, washed with CH_2Cl_2 (3 × 100 ml) and the combined CH_2Cl_2 layers were washed with cold $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated, leaving 43 g **8** (89%). Purity (GLC) 90%.

IR : lactone $-C=O$ 1730 cm^{-1}; lactone $-C-O-C=$ 1300, 1200 and 1130 cm^{-1}; "lactone breath" 950 and 898 cm^{-1}; $-C(CH_3)_2$ 1395 and 1366 cm^{-1}.

PMR : δ 1.02 (s, 6H, $-C(CH_3)_2$), 1.3–1.7 (c, 4H, $-CH_2-C(CH_3)_2-CH_2-$), 2.59 (c, 2H, $-CH_2COO-$) 4.19 (c, 2H, $-CH_2OOC-$).

6-Bromo-4,4-dimethylhexanoic acid (**9**)

An amount of 60 g HBr gas was introduced at 0°C into a cold solution of 43 g **8** (303 mmol) in a mixture of 250 ml 48% HBr and 65 ml conc. H_2SO_4. The resulting turbid solution was poured onto 500 g ice, the mixture extracted with ether (5 × 100 ml) and the combined ether layers were washed acid-free with NaCl solution and dried over Na_2SO_4. Evaporation of the solvent left 58.2 g **9** (86%) n_D^{20} 1.4840.

IR : COOH 3600–2400, 1705, 1410, 1288 and 920 cm^{-1}; $-CH_2Br$ 1450 and 640 cm^{-1} $-C(CH_3)_2$ 1385 and 1362 cm^{-1}.

PMR : δ 0.94 (s, 6H, $-C(CH_3)_2$), 1.64 (c, 2H, $-CH_2-C-COO-$), 1.86 (c, 2H, $BrC-CH_2-$), 2.26 (c, 2H, $-CH_2COO-$), 3.32 (c, 2H, $BrCH_2-$).

Methyl 6-iodo-4,4-dimethylhexanoate (**10**)

An amount of 20.1 g (90 mmol) **9** was esterified (200 ml CH_3OH and 6 ml conc. H_2SO_4; 2 h reflux) and the resulting ester (21.3 g; n_D^{20} 1.4700) refluxed overnight with 40 g (267 mmol) NaI in 200 ml acetone, after which GLC showed the conversion to be complete. After filtration and removal of the solvent under reduced pressure, the residue was dissolved in pentane, washed with $NaHSO_3$ solution and water and the pentane layer dried over Na_2SO_4. Evaporation of the solvent left 23.6 g **10** (93%); n_D^{20} 1.4992.

IR : $-COOCH_3$ 1745, 1440, 1265, 1200 and 1175 cm^{-1}; $-CH_2I$ 1208 and 600 cm^{-1}; $-C(CH_3)_2$ 1395 and 1373 cm^{-1}.

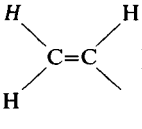
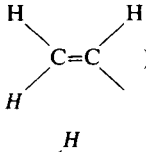
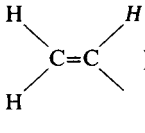
PMR: δ 0.92 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 1.58 (c, 2H, $-CH_2-\overset{|}{C}-COO-$), 1.85 (c, 2H, $I\overset{|}{C}-CH_2-$), 2.20 (c, 2H, $-CH_2COO-$), 3.13 (c, 2H, ICH_2-), 3.62 (s, 3H, $-OCH_3$).

Methyl 4,4-dimethyl-8-nonenoate (**11**) *(cf. ref. 20)*

Warning: Preparation of *bis*(*c*-1,*c*-5-cyclooctadiene)nickel(0), π-allylnickel bromide and **11** should be carried out under rigorous exclusion of air. Use of new glassware and silicon fat for connections and stoppers is highly advisable.

In a 250 ml 3-necked flask equipped with a Wilke stirrer, argon inlet and dropping funnel (50 ml) 14.9 g (83 mmol) π-allylnickel bromide [obtained by reaction of 53.3 g (194 mmol) *bis*(*c*-1,*c*-5-cyclooctadiene)nickel(0)[18] with 23.2 g (191 mmol) allyl bromide in ether at −15°C and two crystallizations at −78°C (cf. ref. 19)] was dissolved in 50 ml dimethylformamide (DMF), while cooling with ice water. After addition of 23.0 g **10** (81 mmol) dissolved in 35 ml DMF at 0°C in 30 min the mixture was stirred overnight at room temperature. The next morning it was poured onto ice (400 g) to which 100 ml HCl (2 mol/l) had been added and the mixture extracted with pentane. The combined organic layers were washed with water, dried on Na_2SO_4 and evaporated leaving 16.6 g residue. Distillation afforded 12.8 g **11** (78%), b.p. 88–89°C/4 mmHg, n_D^{20} 1.4439.

IR: $-COOCH_3$ 1748, 1442, 1265, 1200, 1175 and 1020 cm^{-1}; $CH_2=CH-$ 3090, 1646, 997 and 913 cm^{-1}; $-\overset{|}{C}(CH_3)_2$ 1394 and 1370 cm^{-1}.

PMR: δ 0.86 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 1.1–1.7 (c, 6H, $-CH_2-$), 1.7–2.4 (c, 4H, $-CH_2\overset{|}{C}=$ + $-CH_2COO-$), 3.61 (s, 3H, $-OCH_3$), 4.92 (dist. d, *J* 9.3 Hz, 1H, ), 4.96 (dist. d, *J* 17.3 Hz, 1H, ) 5.87 d.d of t, *J* 17.3, 9.3 and 6.2 Hz, 1H ).

4,4-Dimethyl-8-nonynoic acid (**12**)

An amount of 16 g (81 mmol) **11** was hydrolysed by stirring with NaOH in 70 ml methanol/18 ml water (2.5 mol/l) for 20 h at 23°C. After working up, the 4,4-dimethyl-8-nonenoic acid so obtained (14.5 g; n_D^{20} 1.4538) was dissolved in 100 ml ether and brominated at −20°C by dropwise addition of 4.1 ml (12.6 g = 79 mmol) bromine and continued stirring for 10 min. Washing of the reaction mixture with $NaHCO_3$ solution and drying over Na_2SO_4 left after evaporation of the ether 26.7 g (98%) 8,9-dibromo-4,4-dimethylnonanoic acid (n_D^{20} 1.5080). This was dissolved in 50 ml xylene and dehydrobrominated by adding the solution to a suspension of sodamide (prepared from 9 g (225 mmol) sodium and some $Fe(NO_3)_3$ 9 aq. in 200 ml liq NH_3 to which 100 ml xylene had been added) and stirring overnight. After working up, fractional distillation yielded 8.7 g **12**, b.p. 93°C/3 × 10^{-3} mmHg. Repeating this dehydrobromination procedure with the distillation residue afforded another 3 g **12**. Total yield 11.7 g **12** (85%); n_D^{20} 1.4619.

IR: COOH 3600–2400, 1710, 1415, 1305, 1235 and 935 cm^{-1}; $HC\equiv C-$ 3310, 2130 and 935 cm^{-1}; $-\overset{|}{C}(CH_3)_2$ 1390 and 1370 cm^{-1}.

PMR: δ 0.90 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 1.1–1.7 (c, 6H, $-CH_2-$), 1.82 (t, *J* 2.5 Hz, 1H, $HC\equiv$), 1.9–2.5 (c, 4H, $\equiv C-CH_2-$ + $-CH_2COO-$).

Methyl 4,4-dimethyl-c-8,c-11,c-14-eicosatrienoate (**13**)

An amount of 10.2 g (45 mmol) 1-bromo-2,5-undecadiyne[12] in 40 ml diglyme was reacted for 20 h at 60°C in the presence of 90 mg cuprous cyanide with the di-Grignard derivative of **12** (prepared by adding 71.6 ml (82.3 mmol) ethylmagnesium bromide in diglyme *in vacuo* at −70°C to 7.5 g (41.2 mmol) **12** in 120 ml diglyme) and stirring for 2 h at room temperature (70.4 mmol ethane, 86% of theory developed).

After working up as described for 7, 11.9 g crude acid was obtained which, after esterification (50 ml methanol + 0.5 ml conc. H_2SO_4; 3 h reflux) and molecular distillation, afforded 5.5 g methyl 4,4-dimethyl-8,11,14-eicosatriynoate, b.p. 125–132°C/10^{-3} mmHg; purity (GLC) 87%. On hydrogenating 5.1 g (12.9 mmol) of this ester in 50 ml ethyl acetate in the presence of 2 g Lindlar's catalyst and 4 ml quinoline, hydrogen uptake stopped after 880 ml (102%) had been taken up. Working up left 5.0 g which after column chromatography over a column of $AgNO_3$/silica gel/Celite 1 : 4 : 2 v/v/v (cf. ref. 28) using benzene/pentane 1 : 1 v/v with increasing amounts of ether afforded 1.2 g **13** (9%), n_D^{25} 1.4702.

IR: $-COOCH_3$ 1745, 1440, 1260, 1200, 1170 and 1015 cm^{-1}; $-\overset{H}{\underset{|}{C}}=\overset{H}{\underset{|}{C}}-$ 3010, 1650 and 720 cm^{-1}; $-\overset{|}{C}(CH_3)_2$ 1390 and 1370 cm^{-1}.

PMR: δ 0.85 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 0.89 (t, *J* 6.5 Hz, 3H, $-CH_3$), 1.1–1.4 (c, 10H, $-CH_2-$), 1.50 (A_2 part of A_2B_2 system, 2H, $-CH_2-\overset{|}{C}-COO-$), 1.9–2.0 (c, 4H, $-CH_2\overset{|}{C}=$), 2.15 (B_2 part of A_2B_2 system, 2H, $-CH_2COO-$), 2.75 (c, 4H, $=\overset{|}{C}-CH_2-\overset{|}{C}=$), 3.57 (s, 3H, $-OCH_3$), 5.26 (*cis* pattern, 6H, $-\overset{H}{\underset{|}{C}}=$).

4,4-Dimethyl-c-8,c-11,c-14-eicosatrienoic acid (**14**)

Hydrolysis of 1.1 g (3.2 mmol) **13** [70 ml KOH in methanol/water 9 : 1 v/v (0.1 mol/l); 20 h at 0°C and 45 min at 65°C for completion (TLC)], acidification and isolation by extraction with pentane left, after evaporation of the solvent 1.0 g **14**, purity (GLC) 81%; n_D^{25} 1.4780.

2,2-Dimethyl-7-octynoic acid (**15**) *(cf. ref. 26)*

While stirring 227 ml (550 mmol) butyllithium in hexane (2.42 mol/l) was added at −20°C to 77.5 g (550 mmol) isopropylcyclohexylamine in 375 ml THF. After 30 min at 0°C, 22 g (250 mmol) 2-methylpropionic acid was added, the mixture kept for 2 h at 50°C (and overnight at 23°C) whereafter 14.6 g (118 mmol) 1-chloro-5-hexyne was added at 0°C and the mixture stirred for another 2 h at 0°C. Acidification (HCl; 4 mol/l), extraction with ether (3 × 100 ml), washing of the combined ether layers with water, drying over $NaSO_4$ and evaporation of the ether left 28.6 g which, after distillation, yielded 15.4 g **15** b.p. 86–88°C/0.25 mmHg. Recrystallization from pentane afforded 14.8 g **15** (33%), m.p. 53–54°C.

IR of methyl ester: $-COOCH_3$ 1728, 1430, 1250, 1190, 1170, 1150 and 1125 cm^{-1}; $HC\equiv C-$ 3300, 2110 and 620 cm^{-1}; $-\overset{|}{C}(CH_3)_2$ 1388 and 1362 cm^{-1}.

[28] *E. Stahl*, Dünnschicht Chromatographie, 2. edition, Springer-Verlag, Berlin-Heidelberg-New York, 1967, p. 381.

PMR: δ 1.20 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 1.3–1.6 (c, 6H, $-CH_2-$), 1.76 (t, *J* 2.8 Hz, 1H, HC≡), 2.16 (t.d, *J* 7.0 and 2.8 Hz, 2H, $\equiv C-CH_2-$).

3,3-Dimethyl-8-nonynoic acid (**16**)

Stirring 14.8 g (82 mmol) **15** in 10 ml benzene with 16.8 g (132 mmol) oxalyl chloride for 1.5 h at 23°C and 0.5 h at 80°C, evaporation of solvent and excess oxalyl chloride and distillation of the residue yielded 13.7 g 2,2-dimethyl-7-octynoyl chloride (90%) b.p. 91°C/8 mmHg, n_D^{25} 1.4556. This was added dropwise to 200 mmol diazomethane in 300 ml ether at −20°C and after stirring for 1 h at 23°C, solvent and excess diazomethane were evaporated under reduced pressure leaving 12.8 g crude diazoketone. The latter, dissolved in 60 ml benzyl alcohol and 60 ml 2,4,6-trimethylpyridine was heated quickly to 170°C by immersing the flask in a preheated oil bath and kept at 170°C for 45 min (cf. ref. 22). After addition of pentane and water the layers were separated, the organic layer washed with HCl (4 mol/l) and water, dried over Na_2SO_4 and evaporated, leaving 26.7 g residue. Chromatography over 250 g silica gel, deactivated with 10% water using pentane with increasing amounts of ether as eluents afforded 14.1 g benzyl 3,3-dimethyl-8-nonynoate (78%), purity (GLC) ~ 100%; n_D^{25} 1.4958. Hydrolysis [NaOH in 220 ml dioxane/water 3:2 v/v (0.32 mol/l); 1.5 h at 80°C], acidification, extraction with pentane and isolation of acid as described for **7** afforded 9.5 g crude **16**, giving after distillation 7.0 g **16** (72%), b.p. 87°C/0.75 mmHg; n_D^{25} 1.4567.

IR: −COOH 3600–2400, 1710, 1410, 1310, 1250 and 940 cm^{-1}; HC≡C− 3300, 2120 and 630 cm^{-1}; $-\overset{|}{C}(CH_3)_2$ 1390 and 1370 cm^{-1}.

PMR: δ 1.04 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 1.2–1.6 (c, 6H, $-CH_2-$), 1.77 (t, *J* 2.5 Hz, 1H, HC≡) 2.16 (triplet of doublets, *J* 6.8 and 2.5 Hz, 2H, $\equiv C-CH_2-$), 2.20 (s, 2H, $-CH_2COO-$).

3,3-Dimethyl-c-8,c-11,c-14-eicosatrienoic acid (**17**)

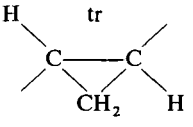
An amount of 15.2 g (67 mmol, 110% excess) 1-bromo-2,5-undecadiyne was coupled in diglyme (20 h at 50°C) with the di-Grignard derivative of 6.1 g (32 mmol) **16** as described for **13**. Isolation of the acids, esterification and distillation afforded 5.1 g (41%) methyl-3,3-dimethyl-8,11,14-eicosatriynoate, b.p. 125–133°C/10^{-3} mmHg, n_D^{25} 1.4842; purity (GLC) 89%.
4.3 g of this ester was hydrogenated [50 ml ethyl acetate, 2.5 g Lindlar's catalyst and 5 ml quinoline; uptake 102%] giving after working up 4.2 g methyl 3,3-dimethyl-*c*-8,*c*-11,*c*-14-eicosatrienoate; purity (GLC) 92%. Final hydrolysis of 1.9 g of this ester [50 ml KOH in methanol/water 9:1 v/v (0.5 mol/l); 3 h at 65°C] and isolation of the acid afforded 1.3 g **17** (27% overall yield), purity (GLC) 92%.

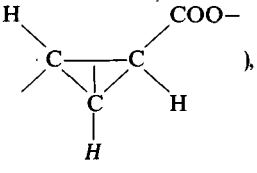
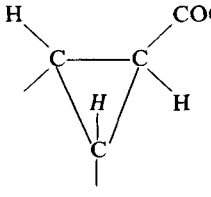
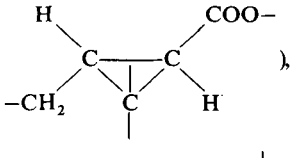
IR: −COOH 3600–2400, 1704, 1405, 1310, 1245, 935 and 915 cm^{-1}; $-\overset{H}{\underset{|}{C}}=\overset{H}{\underset{|}{C}}-$ 3020, 1655 and 712 cm^{-1}; $-\overset{|}{C}(CH_3)_2$ 1388 and 1366 cm^{-1}.

PMR: δ 0.89 (t, *J* 6.8 Hz, 3H, $-CH_3$), 1.02 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 1.2–1.5 (c, 12H, $-CH_2-$), 1.9–2.2 (c, 4H, $=\overset{|}{C}-CH_2-$), 2.18 (s, 2H, $-CH_2COO-$), 2.76 (c, 4H, $=\overset{|}{C}-CH_2-\overset{|}{C}=$), 5.26 (*cis* pattern, 6H, $=\overset{H}{\underset{|}{C}}-$).

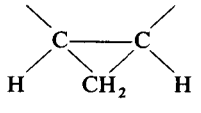
*Ethyl 2,3-*trans*-methylene-* (**18a**)
*and 2,3-*cis*-methylene-7-bromoheptanoate* (**18b**)

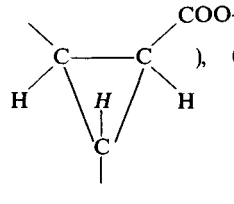
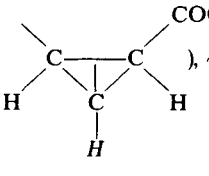
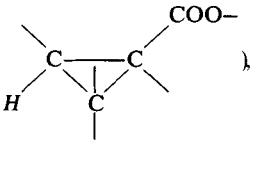
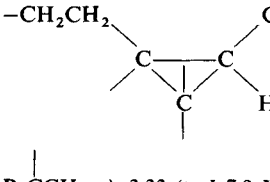
While stirring, 171 g (1.5 mol) ethyl diazoacetate was added over 3 h to a suspension of 5 g (79 mmol) copper powder in 49 g (0.3 mol) 1-bromo-5-hexene (b.p. 60°C/25 mmHg) heated at 100°C[23]. After additional stirring for 1 h at 100°C, the mixture was cooled, diluted with ether, filtered and distilled giving 60 g of a mixture of **18a** and **18b**, b.p. 80–85°C/4 × 10^{-2} mmHg. Column chromatography over silica gel using a gradient of 0–20% ether in light petroleum afforded 24.2 g **18a** (32%).

IR: $-COOC_2H_5$ 2970, 1720, 1448, 1260, 1170 and 1038 cm^{-1}; $-CH_2Br$ 640 and 555 cm^{-1};  3080, 1470, 1405, 1365 and 852 cm^{-1}.

PMR: δ 0.60 (c, 1H, ), 1.09 (c, 1H, ), 1.24 (t, *J* 7.3 Hz, 3H, $-O\overset{|}{C}CH_3$) 1.1–1.4 (c, 4H, ), 1.58 (br.quintet, 2H, $-CH_2-$), 1.89 (br.quintet, 2H, $Br\overset{|}{C}-CH_2-$), 3.35 (t, *J* 7.0 Hz, 2H, $BrCH_2-$) 4.06 (quartet, *J* 7.3 Hz, 2H, $-OCH_2-$).

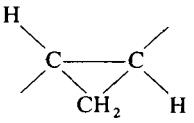
Column chromatography over silica gel of the fractions rich in the *cis* isomer **18b** using a gradient of 0–50% chloroform in light petroleum yielded 16.6 g *cis* isomer **18b** (22%).

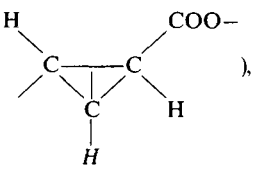
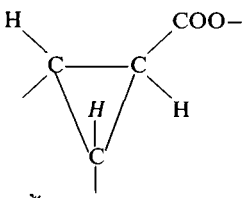
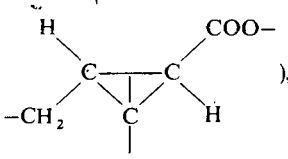
IR: $-COOC_2H_5$ 2980, 1720, 1445, 1260, 1180 and 1040 cm^{-1}; $-CH_2Br$ 640 and 560 cm^{-1};  3080, 1475, 1400, 1380 and 828 cm^{-1}.

PMR: δ 0.86 (c, 1H, ), 0.95 (c, 1H, ), ~1.14 (c, 1H, ), 1.26 (t, *J* 7.3 Hz, 3H, $-O\overset{|}{C}CH_3$), 1.3–1.6 (c, 5H, ), 1.86 (quintet, *J* 7.0 Hz, 2H, $Br\overset{|}{C}CH_2-$), 3.33 (t, *J* 7.0 Hz, 2H, $BrCH_2-$) 4.08 (quartet, *J* 7.3 Hz, 2H, $-OCH_2-$).

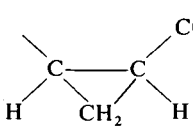
trans- (**19a**) *and* cis-*2,3-Methylene-8-nonynoic acid* (**19b**)

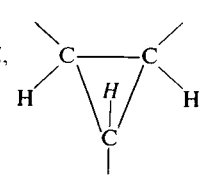
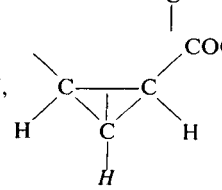
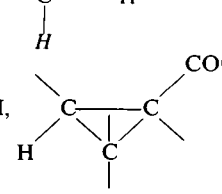
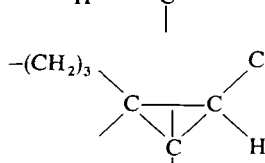
An amount of 18.4 g (83 mmol) *trans*-2,3-methylene-7-bromoheptanoic acid obtained via hydrolysis of **18a** [1.5 eq. NaOH in ethanol/water 1 : 1 v/v (0.2 mol/l); 16 h at 22°C] was dissolved in 200 ml ether and coupled with 23 g (250 mmol) lithium acetylide/ethylenediamine complex in 250 ml liq NH_3 by stirring for 6 h at −33°C and 16 h at −75°C. After evaporation of the ammonia, the mixture was acidified (H_2SO_4; 5 mol/l), extracted with ether and the crude acid isolated by the procedure described for **7**. Column chromatography over silica gel using light petroleum with a gradient of 0–20% ether afforded 13.1 g **19a** (99%).

IR: −COOH 3400–2600, 1690, 1425, 1285, 1225 and 928 cm^{-1}; −C≡CH 3300, 2110 and 630 cm^{-1};  3050, 1075 and 868 cm^{-1}.

PMR: δ 0.72 (c, 1H, ), 1.21 (c, 1H, ), 1.2–1.4 (c, 4H, ), 1.4–1.6 (c, 4H, $-CH_2-$), 1.78 (t, *J* 2.5 Hz, 1H, HC≡), 2.15 (c, 2H, $\equiv C-CH_2-$).

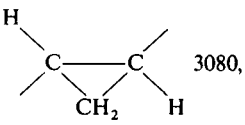
In the same way, *cis*-2,3-methylene-7-bromoheptanoic acid after coupling with lithium acetylide/ethylenediamine complex afforded **19b** in 75% yield; purity (GLC) 89%.

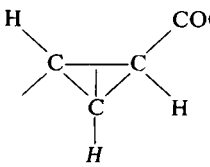
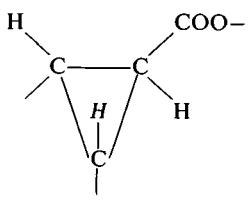
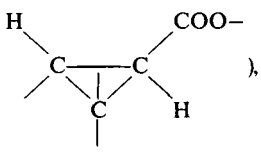
IR: −COOH 3600–2400, 1690, 1230 and 930 cm^{-1}; −C≡CH 3300, 2130 and 635 cm^{-1}  1350 and 820 cm^{-1}.

PMR: δ 0.96 (c, 1H, ), 1.06 (c, 1H, ), ~1.29 (c, 1H, ), 1.3–1.7 (c, 7H, ), 1.75 (t, *J* 2.5 Hz, 1H, HC≡), 2.15 (dist. t of d, 2H, $\equiv C-CH_2-$).

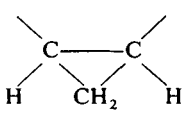
Methyl trans-*2,3-methylene-* (**20a**) *and* cis-*2,3-methylene-8,11,14-eicosatriynoate* (**20b**)

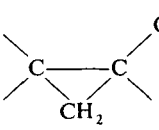
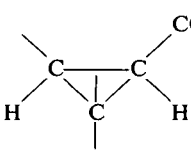
Coupling of 14.5 g (64 mmol, 110% excess) 1-bromo-2,5-undecadiyne with the di-Grignard derivative of 5 g (30 mmol) **19a** in 75 ml diglyme (20 h at 55°C) in the presence of 150 mg $Cu_2(CN)_2$ and isolation of the crude acid yielded 7.4 g crude *trans*-2,3-methylene-8,11,14-eicosatriynoic acid which after esterification and two molecular distillations afforded 4.5 g **20a** (48%); purity (GLC) 94%.

IR: $-COOCH_3$ 1730, 1440, 1275, 1210 and 1175 cm^{-1}; $\equiv C-CH_2-C\equiv$ 1420 and 1320 cm^{-1};  3080, 1410, 1090 and 870 cm^{-1}.

PMR: δ 0.63 (c, 1H, ), 0.91 (t, *J* 7.0 Hz, 3H, $-CH_3$), 1.10 (c, 1H, ), 1.1–1.6 (c, 14H $-CH_2-$ + ), 2.0–2.2 (c, 4H, $\equiv C-CH_2$), 3.04 (c, 4H, $\equiv C-CH_2-C\equiv$), 3.61 (s, 3H, $-OCH_3$).

In the same way, **20b** was obtained in 57% yield and purity (GLC) 93%.

IR: $-COOCH_3$ 1730, 1440, 1198 and 1168 cm^{-1}; $\equiv C-CH_2-C\equiv$ 1418 and 1318 cm^{-1}; −C≡C− 2220 cm^{-1};  3080, 1385 and 822 cm^{-1}.

PMR: δ 0.8–1.1 (c, 5H,  + $-CH_3$), 1.1–1.7 (c, 14H, $-CH_2-$ + ), 2.0–2.2 (c, 4H, $\equiv C-CH_2-$), 3.04 (c, 4H, $\equiv C-CH_2-C\equiv$), 3.58 (s, 3H, $-OCH_3$).

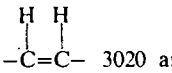
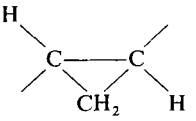
trans- (**21a**) *and* cis-*2,3-Methylene-c-8,c-11,c-14-eicosatrienoic acid* (**21b**)

On hydrogenation of 3.4 g (10.4 mmol) **20a** in 25 ml ethyl acetate (1.5 g Lindlar's catalyst and 3 ml quinoline; H_2 uptake 95% of theory) and purification via chromatography over silica gel using a gradient of 0–10% ether in light petroleum 2.17 g (62%) methyl *trans*-2,3-methylene-*c*-8,*c*-11,*c*-14-eicosatrienoate), purity (GLC) 94% was obtained. A suspension of this ester and 2 g (15 mmol) anhydrous lithium iodide in 20 ml 2,4,6-trimethylpyridine was heated for 3 h at 170°C[29] and after cooling and addition of ether

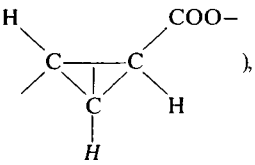
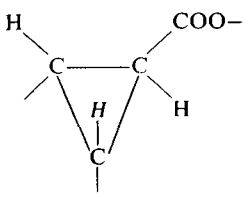
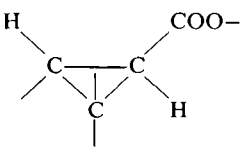
[29] *F. Elsinger, J. Schreiber* and *A. Eschenmoser*, Helv. Chim. Acta **43**, 113 (1960).

extracted with H_2SO_4 (2 mol/l) until free from 2,4,6-trimethylpyridine. The ether layer was washed acid-free, dried over $MgSO_4$ and evaporated leaving 2.09 g **21a** (60%); purity (GLC) 91%.

UV (hexane): λ_{max} 230 nm (2.8% conjugated dienoic compounds); 275 nm (1.4% conjugated trienoic compounds).

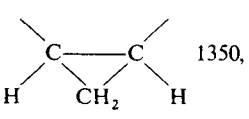
IR: –COOH 3600–2400, 1690, 1435, 1292, 1235 and 940 cm^{-1};  3020 and 720 cm^{-1}  1085 and 880 cm^{-1}.

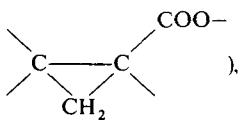
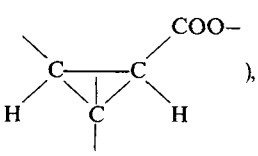
MS of methyl ester: parent peak at *m/e* 332 (calc. for $C_{22}H_{36}O_2$ 332).

PMR: δ 0.70 (c, 1H, ), 0.90 (t, *J* 6.8 Hz, 3H, $-CH_3$), 1.20 (c, 1H, ), 1.1–1.5 (c, 14H, $-CH_2-$ + ), 1.9–2.1 (c, 4H, $=C-CH_2-$), 2.75 (c, 4H, $=C-CH_2-C=$), 5.26 (*cis* pattern, 6H, ).

In a similar way (heating for 1.5 h at 170°C) **20b** was converted into **21b**; chromatography over silica gel deactivated with 10% water using a gradient of 0–10% ether afforded **21b**, in 58% yield.

UV (hexane): λ_{max} 232 nm (1.8% conjugated dienoic compounds); 280 nm (0.2% conjugated trienoic compounds).

IR: –COOH 3400–2400, 1695, 1440, 1230 and 930 cm^{-1}; 3020, 1650 and 710 cm^{-1};  1350, 1045 and 820 cm^{-1}

PMR: δ 0.90 (t, *J* 7.0 Hz, 3H, $-CH_3$), 0.9–1.1 (c, 2H, ), 1.1–1.8 (c, 14H, $-CH_2-$ + ), 1.9–2.1 (c, 4H, $=C-CH_2-$), 2.76 (c, 4H, $=C-CH_2-C=$), 5.26 (*cis* pattern, 6H, ).

Starting from substituted pentanols

1-Methoxy-7-methyl-2-octyne (**22a**)

An amount of 115.3 g (0.7 mol) 1-bromo-4-methylpentane (b.p. 110–115°C/260–330 mmHg; n_D^{25} 1.4452 purity (GLC) > 99.5%) was coupled with 1-lithio-3-methoxy-1-propyne (from 0.74 mol $LiNH_2$ and 51.5 g (0.74 mol) 3-methoxy-1-propyne in 750 ml liq. NH_3/125 ml DMSO) yielding 75.1 g **22a** (69%); b.p. 71°C/7 mmHg; n_D^{25} 1.4435.

IR: $-OCH_3$ 2840 and 1100 cm^{-1}; $HC(CH_3)_2$ 1382 and 1370 cm^{-1}; –C≡C– 2300 and 2230 cm^{-1}; $-CH_2C\equiv C-$ 1325 cm^{-1}.

PMR: δ 0.89 (d, *J* 5.5 Hz, 6H, $-CH_3$), 1.0–1.8 (c, 5H, ), 2.16 (dist. t, 2H, $-CH_2-C\equiv$); 3.26 (s, 3H, $-OCH_3$), 3.98 (t, *J* 2.0 Hz, 2H, $\equiv C-CH_2-O-$).

1-Methoxy-6-methyl-2-octyne (**22b**)

Yield 84.7 g (84%); b.p. 74°C/7 mmHg; n_D^{20} 1.4460.

IR: $-OCH_3$ 2840 and 1100 cm^{-1}; C_2H_5- 2980 cm^{-1}; –C≡C– 2300 and 2230 cm^{-1}; $-CH_2C\equiv C-$ 1325 cm^{-1}.

PMR: δ 0.6–1.0 (c, 6H, $-CH_3$), 1.0–1.8 (c, 5H,), 2.18 (dist. t, 2H, $-CH_2C\equiv$), 3.25 (s, 3H, $-OCH_3$), 3.96 (t, *J* 2.0 Hz, 2H, $\equiv C-CH_2-O-$).

(+)-*(6S)-1-Methoxy-6-methyl-2-octyne* (**22c**)

Yield 12.8 g (78%); b.p. 76–77°C/9 mmHg; n_D^{20} 1.4416. $[\alpha]_D^{25}$ in hexane +10.6°.

1-Bromo-7-methyl-2-octyne (**23a**)

Adding 65.9 g (0.54 mol) acetyl bromide to a solution of 75.1 g (0.48 mol) **22a** and 3.66 g (0.016 mol) $ZnBr_2$ in 150 ml dichloromethane, keeping the mixture for 4 h at 0°C and 1 h at 23°C and working up yielded 101.7 g **23a** (100%); b.p. 83°C/5 mmHg; n_D^{20} 1.4812.

IR: $-CH_2Br$ 1210 and 608 cm^{-1}; $HC(CH_3)_2$ 1390 and 1370 cm^{-1}; –C≡C– 2240 cm^{-1}; $-CH_2C\equiv C-$ 1435 and 1335 cm^{-1}.

PMR: δ 0.89 (d, *J* 5.5 Hz, 6H, $-CH_3$, 1.0–1.8 (c, 5H,), 2.20 (dist. t, 2H, $-CH_2C\equiv$), 3.85 (t, *J* 2.2 Hz, 2H, $\equiv C-CH_2Br$).

1-Bromo-6-methyl-2-octyne (**23b**)

Yield 104.6 g (94.5%); b.p. 84°C/5 mmHg; n_D^{20} 1.4859.

IR: $-CH_2Br$ 1215 and 605 cm^{-1}; C_2H_5- 2980 cm^{-1}; –C≡C– 2250 cm^{-1}; $-CH_2-C\equiv C-$ 1435 and 1340 cm^{-1}.

PMR: δ 0.6–1.0 (c, 6H, $-CH_3$), 1.0–1.8 (c, 5H,), 2.22 (dist. t, 2H, $-CH_2C\equiv$), 3.84 (t, *J* 2.3 Hz, 2H, $\equiv C-CH_2Br$).

(+)-*(6S)-1-Bromo-6-methyl-2-octyne* (**23c**)

Yield 14.2 g (86%); b.p. 81°C/5 mmHg; n_D^{20} 1.4875; $[\alpha]_D^{25}$ in hexane +10.5°.

1-Methoxy-10-methyl-2,5-undecadiyne (**24a**)

Coupling of 100.8 g (0.47 mol) **23a** in 100 ml THF with the Grignard derivative of 3-methoxy-1-propyne, prepared from 39.7 g (0.57 mol) 3-methoxy-1-propyne and 378 ml ethylmagnesium bromide (1.5 mol/l) in THF, in the presence of 0.5 g Cu_2Cl_2, yielded 82.7 g **24a** (88%); b.p. 74°C/10^{-2} mmHg; n_D^{20} 1.4652.

IR: $-OCH_3$ 2840, 1195, 1115, 1100 and 910 cm^{-1}; $HC(CH_3)_2$ 1390 and 1374 cm^{-1}; $\equiv C-CH_2-C\equiv$ 1420 and 1320 cm^{-1}; $-CH_2C\equiv C-$ 1340 cm^{-1}.

PMR: δ 0.89 (d, *J* 5.5 Hz, 6H, $-CH_3$), 1.0–1.8 (c, 5H, $CH-(CH_2)_2-$), 2.11 (dist. t, 2H, $-CH_2C\equiv$), 3.11 (quintet, *J* 2.2 Hz, 2H, $\equiv C-CH_2-C=$), 3.30 (s, 3H, $-OCH_3$), 4.01 (t, *J* 2.2 Hz, 2H, $\equiv C-CH_2-O-$).

1-Methoxy-9-methyl-2,5-undecadiyne (**24b**)

Yield 88.3 g (90%); b.p. 79–80°C/10^{-2} mmHg; n_D^{20} 1.4681.

IR: $-OCH_3$ 2840, 1192, 1115, 1100 and 910 cm^{-1}; C_2H_5- 2980 and 790 cm^{-1}; $\equiv C-CH_2-C\equiv$ 1420 and 1318 cm^{-1}.

PMR: δ 0.6–1.0 (c, 6H, $-CH_3$), 1.0–1.8 (c, 5H, $-CH_2CHCH_2-$), 2.14 (dist. t, 2H, $-CH_2C\equiv$), 3.11 (quintet, *J* 2.2 Hz, 2H, $\equiv C-CH_2-C\equiv$), 3.30 (s, 3H, $-OCH_3$), 4.01 (t, *J* 2.2 Hz, 2H, $\equiv C-CH_2O-$).

(+)-*(9S)-1-Methoxy-9-methyl-2,5-undecadiyne* (**24c**)

Yield 11.1 g (86%); b.p. 67°C/10^{-2} mmHg; n_D^{20} 1.4682; $[\alpha]_D^{25}$ in hexane +9.5°.

1-Bromo-10-methyl-2,5-undecadiyne (**25a**)

Compound **25a** was prepared as described for **23a** except that the reaction mixture was stirred for 25 h at 0°C and 5 h at 10°C. Yield 90.7 g (81%); b.p. 82°C/10^{-3} mmHg; n_D^{20} 1.5022; purity (GLC) 88%.

IR: CH_2Br 1202 and 610 cm^{-1}; $-C(CH_3)_2$ 1380 and 1360 cm^{-1}; $-C\equiv C$ 2260 and 2230 cm^{-1}; $-C\equiv C-CH_2-C\equiv C-$ 1410 and 1310 cm^{-1}.

PMR: δ 0.90 (d, *J* 5.5 Hz, 6H, $-CH_3$), 1.0–1.8 (c, 5H, $CH-(CH_2)_2-$), 2.11 (dist. t, 2H, $CH_2C\equiv$); 3.15 (quintet, *J* 2.3 Hz, 2H, $\equiv C-CH_2-C\equiv$), 3.87 (t, *J* 2.3 Hz, 2H, $\equiv C-CH_2Br$).

1-Bromo-9-methyl-2,5-undecadiyne (**25b**)*

Using the procedure described for **23a** but stirring for 20 h at 10°C yielded 92.2 g **25b** (80%), b.p. 93–94°C/10^{-3} mmHg; n_D^{20} 1.5068.

IR: $-CH_2Br$ 1202 and 608 cm^{-1}; C_2H_5- 2960 cm^{-1}; $-C\equiv C-$ 2260 and 2230 cm^{-1}; $\equiv C-CH_2-C\equiv$ 1410 and 1310 cm^{-1}; "Wotiz" impurity 1710, 1670 and 1590 cm^{-1}.

PMR: δ 0.6–1.0 (c, 6H, $-CH_3$), 1.0–1.8 (c, 5H, $-CH_2CHCH_2-$), 2.13 (dist. t, 2H, $-CH_2C\equiv C-$), 3.14 (quintet, *J* 2.3 Hz, 2H, $\equiv C-CH_2-C\equiv$), 3.87 (t, *J* 2.3 Hz, 2H, $\equiv C-CH_2Br$).

(+)-*(9S)-1-Bromo-9-methyl-2,5-undecadiyne* (**25c**)

Yield 10.6 g (65%); b.p. 80–82°C/10^{-3} mmHg; n_D^{20} 1.5060; purity (GLC) 91%; $[\alpha]_D^{25}$ in hexane +6.6°.

* In compounds **25b** and **26b**, minor impurities occur as shown by extra absorptions in the 1600–1710 cm^{-1} range of their IR spectrum (cf. ref. 30, 31).

30 *J. H. Wotiz, F. A. Miller* and *R. J. Palchak*, J. Amer. Chem. Soc. **72**, 5055 (1950).

31 *B. Hampel*, Z. Phys. Chem., Frankfurt am Main **13**, 123 (1957).

19-Methyl-8,11,14-eicosatriynoic acid (**26a**)

By coupling 8.8 g (32 mmol) **25a** with the di-Grignard derivative of 5.1 g (32 mmol) 8-nonynoic acid in 115 ml diglyme in the presence of 77 mg $Cu_2(CN)_2$ as described for **7**, 2.8 g **26a** (28%), m.p. 34.5°C (ethanol); n_D^{35} 1.4876, was obtained.

IR of methyl ester: $-COOCH_3$ 1745, 1422, 1260, 1205 and 1175 cm^{-1}; $-C(CH_3)_2$ 1390 and 1370 cm^{-1}; $-C\equiv C-CH_2-C\equiv C-$ 1420 and 1324 cm^{-1}; "Wotiz" impurity 1680, 1605 and 1515 cm^{-1}.

PMR: δ 0.90 (d, *J* 5.5 Hz, 6H, $-CH_3$), 1.0–1.8 (c, 13H, $CH-(CH_2)_2-$ + $-CH_2-$), 2.12 (c, 4H, $-CH_2-C\equiv$), 2.32 (dist. t, 2H, $-CH_2COO-$), 3.05 (c, 4H, $\equiv C-CH_2-C\equiv$).

18-Methyl-8,11,14-eicosatriynoic acid (**26b**)*

Yield 2.4 g (24%); m.p. 19–20°C; n_D^{20} 1.4925.

IR of methyl ester: $-COOCH_3$ 1745, 1422, 1260, 1205 and 1175 cm^{-1}; C_2H_5- 2980 cm^{-1}; $\equiv C-CH_2-C\equiv$ 1420 and 1324 cm^{-1}; "Wotiz" impurity: 1680, 1605 and 1515 cm^{-1}.

PMR: δ 0.85 (d, *J* 5.8 Hz, 3H, $-CH(CH_3)-$), 0.88 (t, *J* 6.8 Hz, 3H, CH_3CH_2-), 1.0–1.5 (c, 11H, $-CH_2CHCH_2-$ + $-CH_2-$), 1.64 (dist. quintet, 2H, $-CH_2-C(CH_3)-COO-$), 2.12 (c, 4H, $-CH_2-C\equiv$), 2.32 (t, *J* 7.2 Hz, 2H, $-CH_2COO-$), 3.03 (c, 4H, $\equiv C-CH_2-C\equiv$).

(+)-*(18S)-18-Methyl-8,11,14-eicosatriynoic acid* (**26c**)

Yield 2.3 g (22%); m.p. 29°C; n_D^{20} 1.4960; $[\alpha]_D^{25}$ in methanol +5.3°.

19-Methyl-c-8,c-11,c-14-eicosatrienoic acid (**27a**)

On hydrogenating 2.8 g (9 mmol) **26a** in 25 ml ethyl acetate (room temp., 3 g Lindlar's catalyst, 6 ml quinoline; H_2 uptake 97.2% of theory) and working up, as described before, 2.6 g **27a** (86%), n_D^{20} 1.4783 was obtained.

IR of methyl ester: $-COOCH_3$ 1748, 1440, 1260, 1200, 1175 and 1018 cm^{-1}; $-C(CH_3)_2$ 1390 and 1370 cm^{-1}; $-CH=CH-$ 3025, 1655 and 722 cm^{-1}.

PMR: δ 0.88 (d, *J* 5.6 Hz, 6H, $-CH(CH_3)_2$), 1.0–1.4 (c, 11H, $CH-(CH_2)_2-$ + $-CH_2-$), 1.62 (dist. quintet, 2H, $-CH_2-C(CH_3)-COO-$), 2.01 (c, 4H, $-CH_2-C=$), 2.30 (t, *J* 7.5 Hz, 2H, $-CH_2COO-$), 2.75 (c, 4H, $=CH-CH_2-CH=$), 5.26 (*cis* pattern, 6H, $-CH=$).

18-Methyl-c-8,c-11,c-14-eicosatrienoic acid (**27b**)

Yield 2.0 g (92%); n_D^{20} 1.4776; purity (GLC of methyl ester) 94%.

IR of methyl ester: $-COOCH_3$ 1748, 1440, 1255, 1202, 1175 and 1118 cm^{-1}; C_2H_5- 2980 cm^{-1}; $-\overset{H}{\underset{|}{C}}-\overset{H}{\underset{|}{C}}-$ 3025, 1655 and 735 cm^{-1}.

PMR: δ 0.87 (d, *J* 6.0 Hz, 3H, $-\underset{\underset{CH_3}{|}}{C}-$), 0.87 (t, *J* 7.0 Hz, 3H, $-CH_3$), 1.0–1.5 (c, 11H, $-CH_2\underset{|}{C}HCH_2-$ + $-CH_2-$), 1.62 (dist. quintet, 2H, $-CH_2-\underset{|}{\overset{|}{C}}-COO-$), 2.03 (c, 4H, $-CH_2-\overset{|}{C}=$), 2.30 (t, *J* 7.5 Hz, 2H, $-CH_2COO-$), 2.75 (c, 4H, $=\overset{|}{C}-CH_2-\overset{|}{C}=$), 5.26 (c, 6H, $-\overset{H}{\underset{|}{C}}=$).

(+)-(18S)-18-Methyl-c-8,c-11,c-14-eicosatrienoic acid (**27c**)

Yield 2.0 g (100%); n_D^{20} 1.4822; $[\alpha]_D^{25}$ in hexane +3.67°.

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