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A study of 1,5-hydrogen shift and cyclization reactions of an alkali isomerized methyl linolenoate

Jorma Matikainen,* Seppo Kaltia, Maija Ala-Peijari, Ninna Petit-Gras, Kirsi Harju, Jaakko Heikkilä, Raija Yksjärvi and Tapio Hase

Laboratory of Organic Chemistry, Department of Chemistry, University of Helsinki, P.O. Box. 55, 00014 University, Finland

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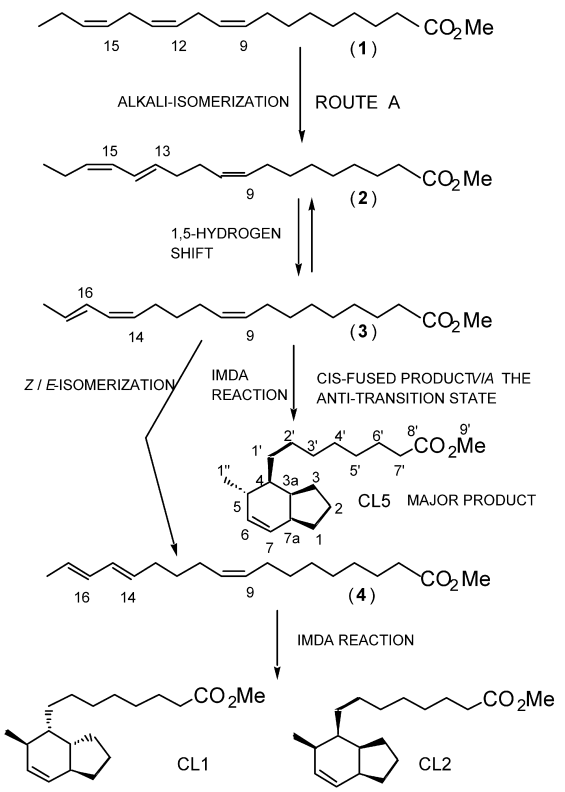
Abstract—Heating a mixture formed by alkali isomerization of methyl linolenoate (**1**) produces a complex mixture with the bicyclic hexahydroindenoic esters 4β-(7-methoxycarbonylheptyl)-5α-methyl-2,3,3aα,4,5,7aαhexahydroindene (CL5) and 4β-ethyl-5α-(6-methoxycarbonylhexyl)-2,3,3aα,4,5,7aα-hexahydroindene (CL6) as main components. Similar isomerization reactions of three synthetic model compounds, methyl 9*Z*,13*E*,15*Z*-octadecatrienoate (**2**), 9*Z*,14*E*,16*E*-octadecatrienoate (**4**) and 9*Z*,11*E*,15*Z*-octadecatrienoate (**5**) corroborated the results obtained with alkali isomerized methyl linolenoate.

We have studied extensively the isomerization and cyclization reactions of various trienoic C18 fatty acids including pinolenic acid (5*Z*,9*Z*,12*Z*-octadecatrienoic acid).[1] Compared to pinolenic acid, linolenic acid leads to a more complex system because isomerizations can now involve all three double bonds. As far as we know there are only a few early reports, lacking rigorous product structure analysis, on such thermal transformations[2–5] of linolenic acid, one of the most important constituents of edible oils.

Part of the original interest in these cyclic and bicyclic fatty acids was due to their possible toxicity which, for instance, prevents the use of tall oil fatty acids as fodder.[6] There are many studies of cyclic fatty acids formed when vegetable oils are heated without prior alkali isomerization.[7–10] A possible mechanism for their formation via allylic radical intermediates has been discussed.[7,10] Such cyclication processes give mainly monocyclic acids and only minor amounts of bicyclic (fused 5 and 6-membered rings) structures have been detected.[9] We find that the main product of heat induced isomerization of alkali pretreated methyl linoleate is a complex mixture of hexahydroindenoic esters.

1. Results and discussion

Under alkaline conditions compounds (**2**) (Scheme 1) and (**5**) (Scheme 2) are favored over the 9*Z*,12*Z*,14*E*-octadecatrienoate and 10*E*,12*Z*,15*Z*-octadecatrienoate esters because the formation of bicyclic products from the former by electrocyclic reactions shifts the equilibrium into their direction. Neither of the primary products (**2**) and (**5**) can cyclize directly via an intramolecular Diels–Alder (IMDA) reaction at 260–270°C but require a prior 1,5-hydrogen shift. However, monocyclic products may result by other



Scheme 1.

Keywords: 1,5-hydrogen shift; intramolecular Diels–Alder; linolenic acid.

* Corresponding author. Tel.: +3-589-1915-0506; fax: +3-589-1915-0366; e-mail: jorma.matikainen@helsinki.fi

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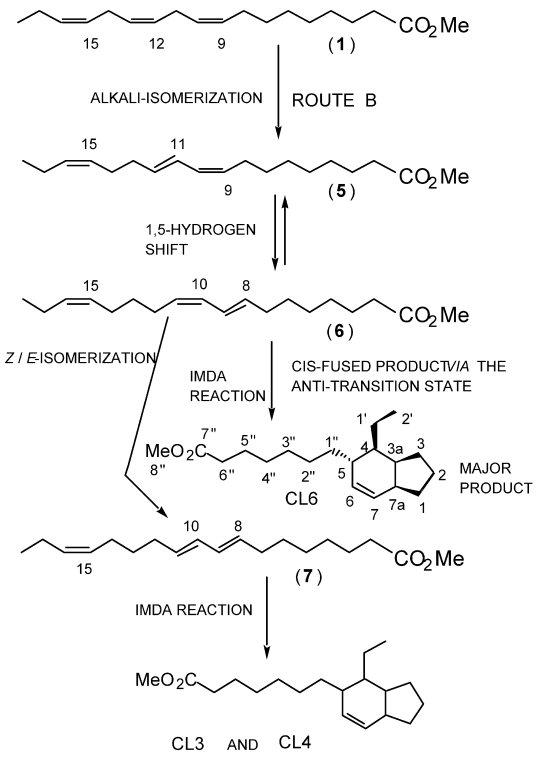
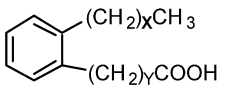


Scheme 2.

isomerization reaction pathways. When the double bonds in the external positions (between C9–C10 or C15–C16) become conjugated with the C12–C13 double bond, the isomerization proceeds via a 1,5-hydrogen shift reaction to a fully conjugated triene system. At 260–270°C the isomerization seems to end up in cyclohexadienoic structures, and in successive aromatization processes, various ω-(*o*-alkylphenyl)alkanoic acids are formed.[11]

ω-(o-alkylphenyl)-alkanoic acids  X + Y = 10

The mixture formed by alkali isomerization of methyl linolenoate (NaOH/glycerol, 210°C/2 h) was re-methylated and cyclized (17 h/270°C/decaline) followed by chromatographic purification to give a mixture that contained, based on GC–MS and NMR, considerable amounts of cyclic fatty acids. The overall yield was 53% based on methyl linolenoate.

The degree of cyclization, estimated from ^{1}H NMR integrals, is 50% in order of magnitude, based on alkali-isomerized methyl trienoates. Most likely the cyclic products have mainly hexahydroindenoic structures. Especially in the ^{13}C-DEPT-spectra the formation of aliphatic methine centers can be deduced from the signals δ ^{13}C=35–45 ppm. In addition, about 12% of the total intensity of protons on sp^2-type carbons is found at δ= 6.5–8.0 ppm thus indicating the formation of aromatic compounds. The aromatic and hexahydroindenoic compounds could be separated by argentation chromatography nearly completely from the other cyclic and straight chain fatty acids.

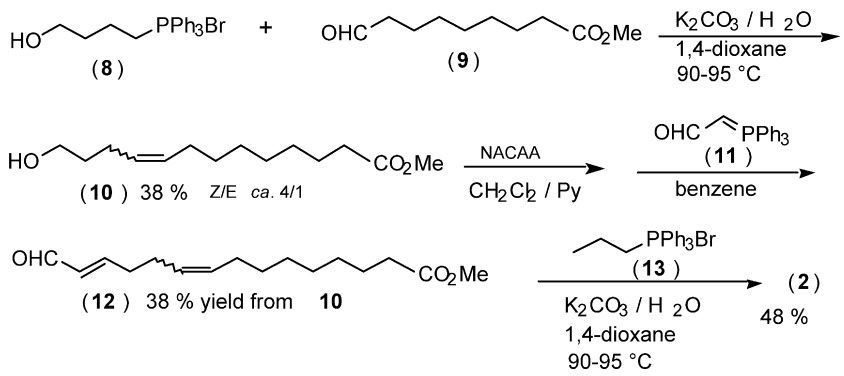
Significantly, none of the main bicyclic isomers have the stereochemistry expected on the basis of similar experiments in the pinolenic series.[12] For instance, the cyclization products CL1 and CL2 from 9*Z*,14*E*,16*E*-octadecatrienoate (**4**) (Scheme 1) are found in minor amounts only among route A reaction products. Probably the cyclization proceeds to a large extent directly via (**3**) (Scheme 1) and 8*E*,10*Z*, 15*Z*-octadecatrienoate (**6**) (Scheme 2) without stereoisomerization of the conjugated diene system from *E*,*Z*- to *E*,*E*-configuration (**4** and **7**). The new *cis*-fused hexahydroindenoic products are formed via the *anti* transition state (TS).[13] In a *cis*-diene where the carbon chain between the diene and dienophile is 1–4 carbon atoms long (and possible longer), an IMDA-reaction proceeds only through the *anti*-TS and forms solely *cis*-fused products.[14] As the *syn*-TS is impossible in IMDA reaction of trienoates (**3**) and (**6**), only two isomers are formed. This fact reduces the possible reaction paths, making the separation of the main compounds easier.

The main cyclization products (CL5 and CL6) of alkali-isomerized methyl linolenoate were isolated in approximately 70–80% purity by standard silica gel chromatography followed by argentation chromatography. As mentioned above, CL5 and CL6 are different from CL1–CL4. Although spectra were measured from these compounds with only 70–80% purity we are nevertheless able to propose structures for CL5 and CL6.

MS fragmentation shows that the main component CL6 of this concentrate has the typical hexahydroindene pattern thus excluding octahydronaphthalenes[11] or cyclohexadienes[10] as possible structures. This compound has M-29 and M-143 ions in its mass spectrum (vide infra) indicating the presence of ethyl and 6-methoxycarbonylhexyl side chains attached to the hexahydroindene ring system.

This is supported by the presence in the ^{1}H NMR spectrum of a typical methyl triplet of an ethyl group at δ 0.92 ppm (J=7.5 Hz) and of a methylene group α to ester carbonyl at δ=2.31 ppm (t, J=7.5 Hz). This last mentioned signal has correlations only to methylene (DEPT) groups in the 2D NMR spectra (GCOSY, TOCSY, GHSQC, GHMBC and NOESY) which shows that it is far from the ring system. Extensive NMR runs made it possible to identify the attachment sites of side chains (4-ethyl and 5-ester side chain) and all stereochemistry defining methine center protons. In the case of CL6, NOESY spectra then gave the stereochemistry: there is correlation between H-3a and H-7a ppm as expected if the ring fusion is *cis*. Furthermore, there is correlation between H-4 and H-5 in the GCOSY spectra but this is missing in the NOESY spectra. This is in keeping with Dreiding models which suggest that H-4 and H-5 protons are in an almost antiperiplanar arrangement if the substituent at C-5 is β (equatorial). A similar analysis of CL5 showed that it is very probably 4α-(7-methoxycarbonylheptyl)-5β-methyl-1,2,3aα,4,5,7aα-hexahydro-indene (CL5).

The isomerization routes A and B (Schemes 1 and 2) consequently produce differently substituted hexahydroindenoic isomers, easily detected by GC–MS. Major fragmentations for hexahydroindenoic isomers of CL3 and



Scheme 3.

CL4 (Scheme 2) include substituent cleavages directly from M^+ (292), giving *m/z* 263 (100%) and 149 (about 95%) by the loss of an ethyl radical and of $MeO_2C-(CH_2)_6$, respectively. Clearly different fragmentations appear for the CL1 and CL2 type compounds (Scheme 1) giving *m/z* 135 (100%) by loss of a $MeO_2C-(CH_2)_7$ radical and *m/z* 277 (5%) by the cleavage of methyl radical. Other similarly substituted hexahydroindenes can be detected by GC–MS in the same manner.[11] Also the ^1H and ^{13}C spectra of CL3 and CL4 were different from CL1, CL2, CL5 and CL6 but consistent with the hexahydroindenoic basic structure. Their stereochemistry remains obscure because in this case an attempted stereochemical NMR analysis was in contradiction to mechanistic predictions for the triene **7**.

The isomerization of synthetic compounds (**2**) and (**5**) confirms the isomerization routes A and B (Schemes 1 and 2). The fragmentation in the mass spectra of the hexahydroindene products of compound (**2**) is similar to that of CL1 and CL2. In contrast, the fragmentation of the cyclization product of compound (**5**) is similar to CL3 and CL4.

The studies on heated fats have shown the possible toxic effects of cyclic fatty acid monomers.[7] It was suggested that cyclic fatty acids from linolenic acid were more toxic than those from linolic acid.[7] It was, however, found that at least cyclopinolenic acids are not significantly toxic, although they are detrimental to the growth of rats.[6]

The results presented in this paper show that hexahydroindenoic structured esters are not minor but main products of heated alkali isomerized methyl linoleate. It is possible that their role in overall health effects—in relation to frying oils for instance—may have been underestimated so far.

The existence of this chemistry in the edible oils calls for a closer study of these reactions. For instance, the oxidative cleavage of a double bond in the six-membered ring of these compounds leads to products where the relation of the polar functions to the cyclopentanoid structure is reminiscent of that found in some prostaglandins.

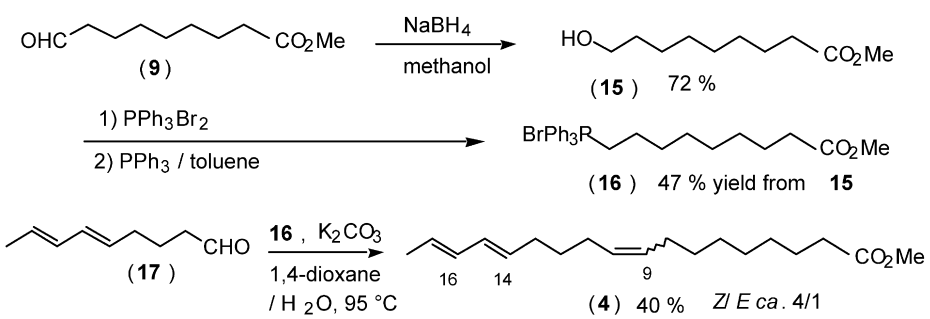
1.1. Synthesis

The stereoselective synthesis of the trienoic carboxylates **2**, **4**, **5** (Schemes 1and 2) relied mainly on the K_2CO_3-mediated phase transfer Wittig reaction.[15]

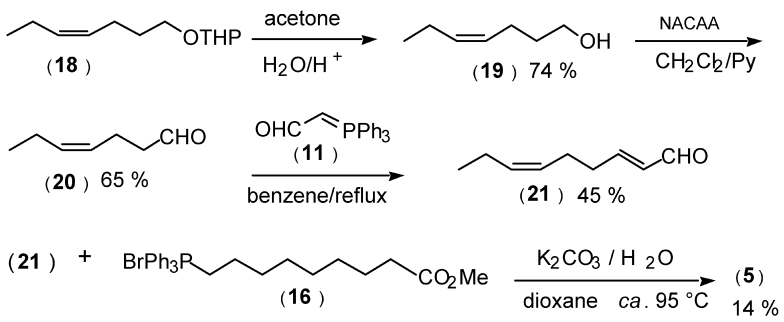
The final products were purified by argentation chromatography, and their structural purity was established by ^1H and ^{13}C NMR spectroscopy.

The reactions of the hydroxyphosphonium salt (**8**) (Scheme 3) with 9-oxononanoic acid methyl ester (**9**), prepared from methyl oleate by ozonolyzis, gave predominantly the 13-hydroxy-9*Z*-methyl ester (**10**). These ω-hydroxyesters were then oxidized to the corresponding aldehydes using the NACAA reagent[16] (nicotinic–chromic mixed anhydride betaine). In the next step Wittig reaction with the ylide (**11**) gave the αβ unsaturated aldehyde (**12**) which in a phase transfer Wittig reaction with propyl triphenylphosphonium salt (**13**), gave (**2**).

The ozonolyzis product (**9**) proved to be an excellent starting material for the synthesis of phosphonium salt (**16**) (Scheme 4). The aldehyde (**9**) was first reduced to the alcohol (**15**) and then converted to the phosphonium salt (**16**), used in synthesis of the trienes **4** and **5** (Schemes 4 and 5). Non-conjugated alkene synthesis (**10**) (Scheme 3) by Wittig reaction usually gives a *Z*,*E*-isomer ratio of about



Scheme 4.



Scheme 5.

4:1. In contrast, a Wittig reaction with the stable ylide (**11**) (Scheme 5) gives predominantly the *E*-isomer (**21**).

For the remaining Wittig step, the K_2CO_3-mediated phase transfer modification[15]worked very well in the presence of the ω-methoxycarbonyl functional group and gave **4** as expected with an *E*/*Z*-selectivity of about 1:4 (Scheme 4).

2. Experimental

2.1. Chromatography

For argentation chromatography, silica gel (60 g; Kieselgel 60, E. Merck, Darmstadt, no. 9385, 230–400 mesh ASTM; kept overnight in an oven at 120°C) was treated with 100 ml of a 10% solution of $AgNO_3$ in acetonitrile, predried over 3 Å molecular sieves. After the removal of acetonitrile under vacuum in a rotary evaporator at 70°C, the impregnated silica was used to fill a glass chromatography column (23×2.5 cm^2). Flash chromatography was performed on silica gel with CH_2Cl_2 elution unless otherwice indicated.

Ozonolysis was done with apparatus being capable to produce about 3 g ozone/h.

2.2. Spectroscopy

The structure and purity of the products were established by GC/MS and NMR (^1H, ^{13}C, 2D) techniques. Full spectral details are given for new compounds only.

GC/MS analysis was performed with a JEOL JMS-SX102 mass spectrometer equipped with a Hewlett–Packard 5890J chromatograph using a BDS (butanediol succinate) column (silica tubular, 45 m, 0.32 mm, 0.15 μm), He gas as carrier (1.5 bar) and a temperature program (50–200°C, 20°C/min). NMR spectra were obtained on a Varian Gemini 2000, Varian Inova 300 and Bruker Avance DRX spectrometers, running at 200, 300 and 500 MHz respectively; $CDCl_3$ as solvent, and referenced to solvent δ ^1H=7.27 ppm and ^{13}C=77.0 ppm). HRMS were run on a JEOL JMS-SX102 instrument.

Elementary analyses were performed using a EA 1110 CHNS-O elemental analyser (Carlo Erba, Thermo Quest Italia Spa, Milan, Italy). Infrared spectra were recorded on a FTIR Perkin–Elmer Spectrum One.

2.3. 9-Oxononanoic acid methyl ester (9)[17]

An O_3/O_2 mixture was passed through a stirred solution of methyl oleate (16 g, 54 mmol) and methanol (240 ml) in a two necked flask at −30°C. After completion of the reaction (KI assay) argon was passed through the reaction mixture to eliminate excess ozone and oxygen. The ozonide was reduced to the aldehydes by the addition of glacial acetic acid (20 ml), warming up to 20°C and adding zinc powder (9.0 g, 0.14 mol) in small portious (strongly exothermic!) while maintaining the temperature at about 30°C with ice bath cooling. The reaction mixture was filtered, methanol evaporated and the residue was extracted with CH_2Cl_2 and dried on Na_2SO_4. Flash chromatography of the concentrate yielded 4.2 g (41%) of (**9**).

2.3.1. 13-Hydroxy-9*Z*-tridecenoic acid methyl ester (10). The phosphonium salt (**8**) from 4-bromo-butan-1-ol[18] (0.5 g, 1.2 mmol), K_2CO_3 (0.15 g), the aldehyde (**9**) (0.15 g, 0.8 mmol), 1,4-dioxane (2.5 ml) and H_2O (30 ml) were stirred under argon at ca. 95°C. After four days, the product was purified by flash chromatography (elution with ethyl acetate/CH_2Cl_2 1:20), to give 74 mg (38%) of (**10**) as an oil. ^1H NMR δ 1.30 (m, 8H, H-4, H-5, H-6 and H-7), 1.63 (m, 4H, H-3 and H-12), 2.03 (q, *J*=6.5 Hz, 2H, H-8), 2.12 (q, *J*=6.8 Hz, 2H, H-11), 2.30 (t, *J*=7.5 Hz, 2H, H-2), 3.65 (t, *J*=6.5 Hz, 2H, H-13), 3.67 (s, 3H, H-1′), 5.38 (m, 2H, H-9 and H-10). ^{13}C NMR δ 23.6 (C-11), 24.9 (C-3), 27.1 (C-8), 28.98, 29.05, 29.06 (C-4, C-5 and C-6), 29.5 (C-7), 32.6 (C-12), 34.1 (C-2), 51.4 (C-1′), 62.6 (C-13), 128.9, 130.6 (C-9 and C-10), 174.4 (C-1). Anal. Calcd for $C_{14}H_{26}O_3$, C 69.4, H 10.8; found, C 70.6, H 10.00. IR ν 3423,1738, 724.

2.3.2. 15-Oxo-9*Z*-13*E*-pentadecadienoic acid methyl ester (12). The alcohol (**10**) (0.29 g, 1.2 mmol) was added to a suspension of the NACAA reagent[16](1.1 g, 5.0 mmol) in CH_2Cl_2 (15 ml) and pyridine (1.5 ml). After stirring at ambient temperature for 20 min, the reaction mixture was filtered through a pad of silica gel (70–230 mesh). The eluate was monitored by tlc and the fractions containing the product collected to give 0.30 g of the crude 13-oxo-9*Z*-tridecenoic acid methyl ester as an oil. This aldehyde (0.30 g, 1.2 mmol) and Ph_3P=CHCHO (**11**) (0.45 g, 1.5 mmol) were heated in C_6H_6 (15 ml) under Ar at 60°C. After two days, the product was purified by flash chromatography (elution with ethyl acetate/CH_2Cl_2 1:20), to give (**12**) (122 mg, 38% from **10**) as an oil. ^1H NMR δ 1.30 (m, 8H, H-4, H-5, H-6 and H-7), 1.62 (quintet, *J*=7.5 Hz, 2H, H-3), 2.02 (q, *J*=7.3 Hz, 2H, H-8), 2.25 (q,

J=7.3 Hz, 2H, H-11), 2.30 (t, *J*=7.5 Hz, 2H, H-2), 2.40 (td, *J*=7.3 Hz, 6.7 Hz, 2H, H-12), 3.67 (s, 3 h, H-1′), 5.33 (dtt, *J*=10.8, 7.2, 1.5 Hz, 1H, H10), 5.44 (dtt, *J*=10.8, 7.3, 1.6 Hz, 1H, H-9), 6.13 (ddt, *J*=15.7, 7.9, 1.5 Hz, 1H, H-14), 6.85 (dd, *J*=15.7, 6.7 Hz, 1H, H-13), 9.50 (d, *J*=7.9 Hz, 1H, H-15). ^{13}C NMR δ 24.9 (C-3), 25.5 (C-11), 27.2 (C-8), 29.03, 29.04, 29.09, 29.4 (C-4, C-5, C-6 and C-7), 32.7 (C-12), 34.0 (C-2), 51.4 (C-1′), 127.3 (C-10), 131.6 (C-9), 133.2 (C-14), 158.0 (C-13), 174.3 (C-1), 194.0 (C-15). Anal. calcd for $C_{16}H_{26}O_3$, C 72.1, H 9.8; found, C 71.9, H 9.9. IR ν 1737, 1690, 973.

2.3.3. Methyl 9*Z*,13*E*,15*Z*-octadecatrienoate (2). The phosphonium salt from 1-bromopropane (**13**) (0.35 g, 0.9 mmol), K_2CO_3[15] (0.1 g), the aldehyde (**12**) (0.12 g, 0.45 mmol), 1,4-dioxane (2.0 ml) and H_2O (10 ml) were stirred for 24 h under argon at ca. 90–95°C. The solvent was evaporated under reduced pressure, and the residue extracted several times with hexane. Flash chromatography of the concentrated product yielded 64 mg (48%) of crude (**2**). The product (**2**) was isolated in pure form by argentation chromatography. ^{1}H NMR δ 0.99 (t, *J*=7.5 Hz, 3H, H-18), 1.31 (m, 8H, H-4, H-5, H-6 and H-7),1.61 (br quintet, *J*=7.5 Hz, 2H, H-3), 2.01 (m, 2H, H-8), 2.13 (m, 4H, H-11 and H-12), 2.15 (quintet of doublets, *J*=7.5, 1.5 Hz, 2H, H-17), 2.30 (t, *J*=7.5 Hz, 2H, H-2), 3.65 (s, 3H, H-1′), 5.32 (dt, *J*=11.0, 7.4 Hz, 1H, H-16), 5.37 (m, 2H, H-9 and H-10), 5.87 (dt, *J*=15.1, 6.8 Hz, 1H, H-13), 5.91 (t, *J*=11.0 Hz, 1H, H-15), 6.32 (dd, *J*=15.1, 11.0 Hz, 1H, H-14). ^{13}C NMR δ 14.3 (C-18), 21.3 (C-17), 25.0 (C-3), 27.1 (C-11), 27.2 (C-8), 29.04, 29.1 2C and 29.6 (C-4, C-5, C-6, and C-7), 33.0 (C-12), 34.1 (C-2), 51.4 (C-1′), 125.8 (C-14), 127.9 (C-15), 128.9 and 130.4 (C-9 and C-10), 131.9 (C-16), 133.9 (C-13), 174.3 (C-1). HRMS: $C_{19}H_{32}O_2$ requires 292.2402, found 292.2409.

2.3.4. 5*E*,7*E*-Nonadienal (17). 2*E*,4*E*-Hexadien-1-ol acetate (prepared applying our earlier synthetic process[12] starting from sorbyl alcohol) (3.0 g, 21 mmol) was added to a Grignard reagent prepared from 3-bromopropanal diethyl acetal (7.5 g, 36 mmol) in the presence of dilithium tetrachlorocuprate (5.0 ml of 0.1 M in THF solution) in THF (120 ml) at −30°C. After 3 h, the reaction mixture was quenched with 1.0 ml water and the solvent was removed to give 3.3 g (74%) of the crude product. 2.0 g of this was hydrolyzed by 10% H_2SO_4 (3 ml in 15 ml acetone). Flash chromatography gave the 5*E*,7*E*-nonadienal (**17**) (0.8 g) in 45% overall yield. ^{1}H NMR δ 1.61 (quintet, *J*=7.4 Hz, 2H, H-3), 1.75 (d, *J*=6.3 Hz, 3H, H-9), 2.05 (m, 2H, H-4), 2.45 (m, 2H, H-2), 5.50 (m, 2H, H-5 and H-8), 6.02 (m, 2H, H-6 and H-7), 9.80 (t, *J*=1.6 Hz, 1H, H-1).

2.3.5. 9-Hydroxynonanoic acid methyl ester (15). $NaBH_4$[19] (1,3 g, 34 mmol) was added gradually to a solution of 9-oxononanoic acid methyl ester (**9**) (2.5 g, 13 mmol) in methanol (70 ml) at 20–25°C. After stirring overnight water (20 ml) and 2 M HCl (50 ml) were added. A light precipitate was formed. The solvent was evaporated and residue extracted with CH_2Cl_2, washed with water, filtered and evaporated. Yield was 1.8 g (72%). ^{1}H NMR δ 1.30 (m, 8H, H-4, H-5, H-6, H-7), 1.62 (m, 2H, H-3), 1.70 (m, 2H, H-8), 3.60 (t, *J*=7.3 Hz, 2H, H-9), 3.67 (s, 3H, H-1′).

2.3.6. Phosphonium salt from 9-bromononanoic acid methyl ester (16). The alcohol (**15**) (1.27 g, 6.75 mmol) and CBr_4[20] (2.85 g, 6.59 mmol) were stirred in CH_2Cl_2 (15 ml) at −5 to 0°C. PPh_3 (3.05 g, 10.43 mmol) in CH_2Cl_2 (5 ml) was added dropwise to the reaction mixture. After stirring for 1 h the reaction mixture was left to stand overnight at 5°C. The precipitate was filtered and washed with CH_2Cl_2 (3×10 ml). The combined CH_2Cl_2 solvent was evaporated and flash chromatography of the crude product gave 9-bromononanoic acid methyl ester 1.67 g (96%). ^{1}H NMR δ 1.3–1.8 (m, 10 H), 1.90 (quintet, *J*=7.5 Hz, 2H, H-8), 2.30 (t, *J*=7.5 Hz, 2H, H-2), 3.41 (t, *J*=7.4 Hz, 2H, H-9), 3.67 (s, 3H, H-1′). The 9-bromononanoic acid methyl ester (1.05 g, 3.95 mmol), PPh_3 (1.78 g, 6.79 mmol) and a small amount of K_2CO_3 were refluxed in azeotropically dried toluene (25 ml) for two days under Ar. Thereafter the toluene was decanted and the viscous product was washed with toluene and dried under vacum to give 1.0 g (1.95 mmol, 49%) of (**16**).

2.3.7. Methyl 9*Z*,14*E*,16*E*-octadecatrienoate (4). The phosphonium salt from 9-bromononanoic acid methyl ester (**16**) (1.8 g, 3.5 mmol), K_2CO_3[15] (0.5 g), the 5*E*,7*E*-nonadienal (**17**) (0.44 g, 3.2 mmol), 1,4-dioxane (8.0 ml) and H_2O (4 drops) were stirred overnight under argon at ca. 95°C. The solvent was evaporated under reduced pressure, and the residue extracted several times with hexane. Flash chromatography of the concentrate yielded 0.38 g (40%) of crude (**4**) containing 15–20% of the 9*E*,14*E*,16*E*-isomer as a byproduct. The (**4**) was isolated in pure state by argentation chromatography. ^{1}H NMR δ 1.30 (m, 8H, H-4-H-7), 1.44 (quintet, *J*=7.3 Hz, H-12), 1.62 (m, H-3), 1.73 (d, *J*=6.3 Hz, H-18), 2.02 (m, 4H, H-8 and H-11) 2.07 (m, H-13), 2.30 (t, *J*=7.5 Hz, H-2), 3.67(s, H-1′), 5.36 (m, 2H, H-9 and H-10), 5.57 (m, 2H, H-14 and H-17), 6.01 (m, 2H, H-15 and H-16). ^{13}C NMR δ 18.0 (C-18), 24.3 (C-3), 26.7 and 27.2 (C-8 or C-11), 29.06, 29.10, 29.11, 29.4 and 29.6 (C-4, C-5, C-6, C-7, and C-12), 32.1 (C-13), 34.1 (C-2), 51.4 (C-1′), 126.7 (C-17), 129.4 and 130.0 (C-9 and C-10), 130.3 (C-15), 131.5 and 131.7 (C-14 and C-16), 174.2 (C-1). HRMS: $C_{19}H_{32}O_2$ requires 292.2402, found 292.2406.

2.3.8. *Z*-Heptenal (20). Propyltriphenylphosphonium bromide (**13**) (10.0 g, 26 mmol), K_2CO_3[15] (3.5 g), 4-tetrahydropyranyloxybutanal (3.0 g, 17.4 mmol), 1,4-dioxane (25 ml) and H_2O (0.5 ml) were stirred overnight under argon at ca. 95–100°C. The solvent was evaporated under reduced pressure, and the residue extracted several times with ethyl acetate. Flash chromatography of the concentrate yielded 1.33 g (39%) of (**18**). The protecting group was hydrolysed with 30 ml of acetone, 15 ml of H_2O and a few drops of conc. H_2SO_4 at RT overnight. After neutralization with saturated $NaHCO_3$, the acetone was evaporated under reduced pressure, the residue was extracted with ethyl acetate and dried with Na_2SO_4. The removal of the solvent gave 0.56 g (74%) of (**19**). The alcohol (**19**) (0.78 g, 6.8 mmol) was added to a suspension of NACAA (4.7 g, 20 mmol) in CH_2Cl_2 (15 ml) and pyridine (3.0 ml). After stirring at ambient temperature for 20 min, the reaction mixture was filtered through a pad of silica gel (70–230 mesh). The eluate was monitored by tlc and the fractions containing the product collected to give 0.5 g (65%) of (**20**) as an oil.

2.3.9. *E*,6*Z*-Nonadienal (21). $Ph_3P{=}CHCHO$ (4.0 g, 13.2 mmol) and the aldehyde (**20**) (0.5 g, 4.5 mmol) were refluxed overnight in benzene (30 ml) under Ar. Benzene was evaporated and the residue extracted with CH_2Cl_2/hexane (1:1). Flash chromatography of the concentrate (elution with CH_2Cl_2/hexane 4:3) yielded 0.28 g (45%) of crude (**21**) containing 15–20% of the 2*E*,6*Z*-nonadienal isomer as byproduct. ^{1}H NMR δ 0.96 (3H, t, J=7.6 Hz, H-9), 2.04 (2H, quintet of multiplets J=7.4 Hz, H-8), 2.26 (2H, brq, J=7.0 Hz, H-5), 2.40 (2H, qm, J=7.1 Hz, H-4), 5.31 (1H, dtt, J=10.7, 7.0, 1.5 Hz, H-6), 5.45 (1H, ddm, J=10.7, 7.2 Hz, H-7), 6.13 (1H, ddt, J=15.6, 7.8, 1.5 Hz, H-2), 6.25 (1H, dt, J=15.6, 6.6 Hz, H-3), 9.50 (1H, d, J=7.8 Hz, H-1). ^{13}C NMR δ 14.5 (C-9), 20.8 (C-8), 25.7 (C-5), 33.0 (C-4), 127.0 (C-6), 133.5 (C-2), 133.6 (C-7), 158.4 (C-3), 194.4 (C-1).

2.3.10. Methyl 9*Z*,11*E*,15*Z*-octadecatrienoate (5). The phosphonium salt from 9-bromononanoic acid methyl ester (**16**) (1.8 g, 3.5 mmol), K_2CO_3[15](0.5 g), the 5*E*,7*E*-nonadienal (**17**) (0.44 g, 3.2 mmol), 1,4-dioxane (8.0 ml) and H_2O (4 drops) were stirred overnight under argon at ca. 95°C. Flash chromatography of the concentrate yielded 50 mg (14%) of crude (**5**). The (**5**) was isolated in pure state by argentation chromatography. ^{1}H NMR δ 0.96 (t, J=7.5 Hz, 3H, H-18),1.32 (br s, 6H, H-4, H-5 and H-6), 1.34 (br quintet, J=7.5 Hz, 2H, H-7), 1.62 (br quintet, J=7.5 Hz, 2H, H-3), 2.05 (quintet, J=7.5 Hz, 2H, H-17), 2.15 (m, 6H, H-8, H-13 and H-14), 2.30 (t, J=7.5 Hz, 2H, H-2), 3.65 (s, 3H, H-1′), 5.36 (m, 3H, H-9, H-15 and H-16), 5.66 (dt, J=15.1, 7.2 Hz, 1H, H-12), 5.94 (dd, J=11.2, 10.2 Hz, 1H, H-10), 6.32 (dd, J=15.1, 11.2 Hz, 1H, H-11). ^{13}C NMR δ 14.3 (C-18), 20.6 (C-17), 24.9 (C-3), 27.0, 27.7, 29.0, 29.1(2C), 29.6 C-4), 33.0, 34.1, 51.4 (C-1′), 125.9, 128.3, 128.6, 130.2, 132.1 (C-16), 133.9, 174.3 (C-1). HRMS: $C_{19}H_{32}O_2$ requires 292.2402, found 292.2400.

2.4. Cyclization experiments, general procedure

The methyl octadecatrienoates **2**,**4** or **5** in about 5% solution in decalin under Ar were heated overnight in a sealed ampoule at 260–270°C. The reaction product was then chromatographed over silica (elution with dichloromethane/hexane 1:1). The cyclic compounds were isolated by argentation chromatography (elution with 5% ethyl acetate in dichloromethane or alternatively 5–10% diethyl ether in hexane).

2.4.1. CL1. ^{1}H NMR δ 1.03 (d, J=7.2 Hz, 3H, H-1″), 1.11 (m, 1H, H-1β), 1.20–1.60 (m, 10H, H-3α and H-3β, H-1′, H-2′, H-3′ and H-4′), 1.38 (m, 2H, H-5′), 1.44 (m, 1H, H-4β), 1.52 (m, 1H, H-3aβ), 1.63 (quintet, 2H, J=7.0 Hz, H-6′), 1.71 (m, 2H, H-2a and H-2b), 1.81 (m, 1H, H-1a), 1.82 (m, 1H, H-7α), 2.20 (m, H-5α), 2.33 (t, 2H, J=7.5 Hz, H-7′), 3.67 (s, 3H, H-9′), 5.44 (ddd, 1H, J=9.8, 2.4, 1.0 Hz, H-6), 5.76 (br d, 1H, J=9.8 Hz, H-7). ^{13}C NMR δ 22.2 (C-1″), 22.4 (C-2), 25.0 (C-6′), 25.9 (C-3), 27.3 (C-1′), 28.1, 29.2 (C-1), 29.3 (2C), 29.9, 34.1 (C-7′), 35.7 (C-5) 38.5 (C-7a), 41.0 (C-4), 43.3 (C-3a), 51.4 (C-9′), 129.1 (C-7), 132.3 (C-6), 174.3 (C-8′). HRMS: $C_{19}H_{32}O_2$ requires 292.2402, found 292.2410.

2.4.2. CL2. ^{1}H NMR δ 0.97 (d, J=7.6 Hz, 3H, H-1″), 1.33 (m, 8H, H-2′, H-3′, H-4′, H-5′), 1.36 (m, 2H, H-1′), 1.39 (m, 1H, H-1b), 1.41 (m, 1H H-2b), 1.50 (m, 2H, H-3α and H-3β), 1.62 (m, 1H, H-2a), 1.63 (m, 2H, H-6′), 1.79 (m, 1H, H-1a), 1.90 (m, H-4α), 2.10 (qd, J=9.0, 4.5 Hz, 1H, H-3α), 2.18 (m, 1H, H-5α), 2.32 (t, J=7.5 Hz, 2H, H-7′), 2.57 (m, 1H, H-7α), 3.67 (s, 3H, H-9′), 5.39 (ddd, J=9.9, 2.0, 1.8 Hz, 1H, H-7), 5.65 (ddd, J=9.9, 4.8, 2.4 Hz, 1H, H-6). ^{13}C NMR δ 16.2 (C-1″), 24.6, 25.0 (C-6′), 26.3 (C-3), 27.5, 29.2, 29.3, 29.8, 31.5 (C-5), 32.3, 32.7 (C-1), 34.1 (C-7′), 36.8 (C-4), 39.5 (C-7a), 41.6 (C-3a), 51.4 (C-9′), 130.2 (C-7), 132.3 (C-6), 174.2 (C-8′). HRMS: $C_{19}H_{32}O_2$ requires 292.2402, found 292.2399.

2.4.3. CL3. ^{1}H NMR δ 0.93 (t, J=7.5 Hz, 3H, H-2′), 1.10–1.90 (m, 17 H), 1.81 (m, 1H, H-4), 1.98 (m, 1H, H-5), 2.16 (m, 1H, H-3a) 2.31 (t, J=7.5 Hz, 2H, H-6″), 2.58 (m, 1H, H-7a), 3.67 (s, 3H, H-8″), 5.45 (ddm, 1H, J=10.0, 5.0 Hz, H-7), 5.82 (ddd, J=10.0, 5.0, 2.0 Hz, 1H, H-6). ^{13}C NMR δ 12.4 (C-2′), 24.8, 24.9, 25.0, 26.7, 29.0, 29.2, 29.7, 33.0, 34.1 (C-6″), 37.0, 38.1, 39.8 (C-7a), 40.1 (C-4), 41.1 (C-3a), 51.4 (C-8″), 130.4 (C-6), 130.9 (C-7), 174.3 (C-7″).

2.4.4. CL4. ^{1}H NMR δ 0.88 (t, J=7.0 Hz, 3H, H-2′), 1.10–1.90 (m, 17 H), 1.29 (m, 1H, H-4), 2.02 (m, 1H, H-3a), 2.12 (m, 1H, H-5), 2.31 (t, J=7.5 Hz, 2H, H-6″), 2.37 (qm, J=6 Hz, 1H, H-7a), 3.67 (s, 3H, H-8″), 5.58 (ddd, J=10.0, 5.0, 1.5 Hz, 1H, H-7), 5.65 (ddd, J=10.0, 4.5, 2.5 Hz, 1H, H-6). ^{13}C NMR δ 12.1(C-2′), 21.4, 24.9, 25.0, 27.5, 29.2, 29.7, 30.7, 30.9, 32.8, 34.1 (C-6″), 34.2 (C-5), 38.2 (C-7a), 38.6 (C-3a), 41.5 (C-4), 51.4 (C-8″), 130.4 (C-6), 130.7 (C-7), 174.3 (C-7″).

2.4.5. CL5. ^{1}H NMR δ 0.98 (d, J=7.1 Hz, 3H, H-1″), 1.00–1.77 (m, 17H), 1.31 (m, 1H, H-4α), 1.80 (m, 1H, H-5β), 2.16 (m, 1H, H-3α), 2.31 (t, J=7.5 Hz, 2H, H-7′), 2.51 (m, 1H, H-7α), 3.68 (s, 3H, H-9′), 5.33 (dt, J=10.0, 2.6 Hz, 1H, H-7), 5.38 (dt, J=10.0, 2.1 Hz, 1H, H-6). ^{13}C NMR δ 20.0, 23.0, 23.2, 24.9, 27.1, 29.2, 29.3, 29.8, 31.1, 31.7, 31.8, 34.1, 40.00, 40.04, 41.8, 51.4, 130.5, 133.8, 174.3.

2.4.6. CL6. ^{1}H NMR δ 0.92 (t, J=7.6 Hz, 3H, H-2′), 1.14–1.69 (m, 17H), 1.35 (m, 1H, H-4α), 1.75 (m, 1H, H-5β), 2.20 (m, 1H, H-3α), 2.31 (t, J=7.5 Hz, 2H, H-6″), 2.50 (m, 1H, H-7α), 3.67 (s, 3H, H-9′), 5.37 (dt, J=10.0, 2.2 Hz, 1H, H-7), 5.49 (dt, J=10.0, 2.0 Hz, 1H, H-6). ^{13}C NMR δ 11.9, 22.9, 23.0, 24.3, 25.0, 25.9, 29.2, 29.8, 31.8, 32.8, 34.1, 35.8, 39.4, 39.8, 40.3, 51.4, 130.4, 131.1, 174.3.

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