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Total Synthesis of (±)Variotin and Its Analogs

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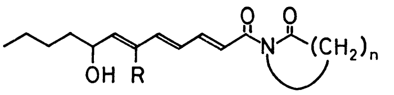
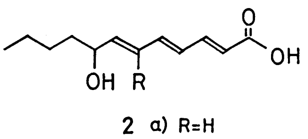
1-Sorboyl-2-pyrrolidone was prepared from sorbic acid and 2-ethoxy-1-pyrroline using 1-methyl-2-chloropyridinium iodide as a coupling reagent. Variotin and its analogs were similarly synthesized from lactim ethers and (2*E*, 4*E*, 6*E*)-8-hydroxy-2,4,6-dodecatrienoic acids without protecting the hydroxyl group at C-8. (2*E*,4*E*,6*E*)-8-Hydroxy-6-methyl-2,4,6-dodecatrienal, a precursor of trienoic acid, was synthesized by the elimination of methanol from (2*E*,6*E*)-8-acetoxy-5-methoxy-6-methyl-2,6-dodecadienal prepared from the reaction of 1-trimethylsiloxy-1,3-butadiene with (2*E*)-4-acetoxy-2-methyl-2-octenal dimethyl acetal.

The structure of variotin (**1b**), an antifungal antibiotic isolated from Pacecilomyces variotin Bainier var. antibioticus,[1] has been established by Yonehara and Takeuchi.[2]

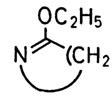
Recently, a method for the preparation of polyenals[3] has been reported and applied to the synthesis of the naturally occurring polyolefinic compounds, vitamin A[4] and *β*-carotene.[5] Also, the synthesis of variotin (**1b**) has been reported briefly in a previous communication.[6b] This paper describes the experimental details employed for the synthesis of (±) **1b** and its analogs (**1a** and **1c**).



1 a) $R=H$ $n=3$
b) $R=CH_3$ $n=3$
c) $R=CH_3$ $n=4$



2 a) $R=H$
b) $R=CH_3$



3 a) $n=3$
b) $n=4$

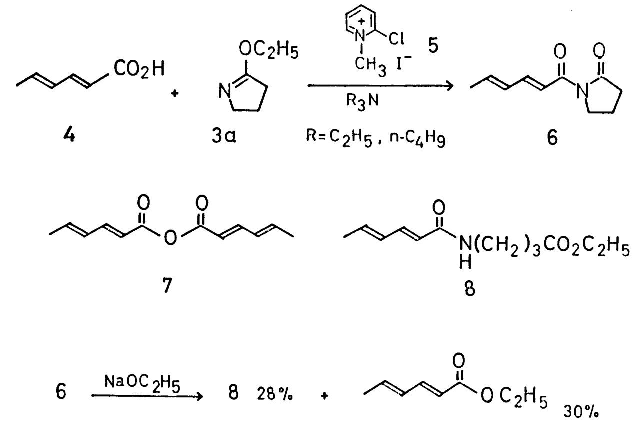
In the synthetic approach towards **1b**, the molecule was regarded as a condensation product of trienoic acid (**2b**) and lactim ether (**3a**). In the preliminary experiment, the reaction between sorbic acid (**4**) and 2-ethoxy-1-pyrroline (**3a**) was studied, employing 1-methyl-2-chloropyridinium iodide (**5**) as a coupling reagent (Scheme 1).

The hydroxytrienoic acids, **2a** and **2b**, may be derived from the corresponding polyenals (**20a** and **20b**).[3]

Results and Discussion

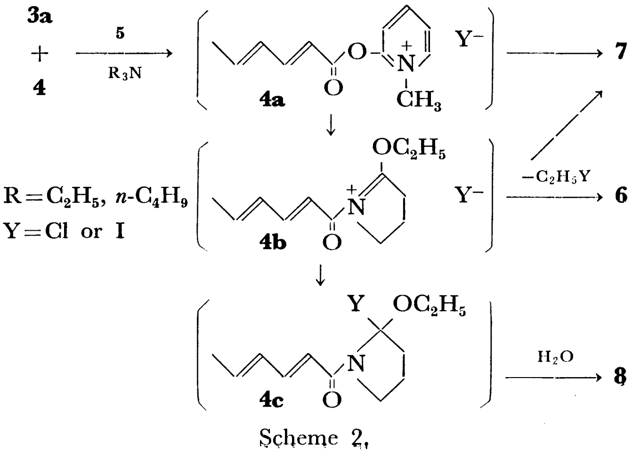
The Reaction of Sorbic Acid (4) and 2-Ethoxy-1-pyrroline (3a).[6a] The preparation of *N*-acyl lactam (**6**) in the presence of **5** and a tertiary amine was investigated under several conditions (Scheme 1).

The distribution of products depended on the method of addition (A, or B) as summarized in Table 1. An undesired acyl anhydride (**7**) was obtained as the major product when a solution of triethylamine in 1,2-dichloroethane was added immediately to a mixture of **3a**, **4**, and **5** at 0 or 50 °C (method A). In contrast, 1-sorboyl-2-pyrrolidone (**6**) was formed (63% yield) when a solution of **4** and tributylamine in toluene was added dropwise to a mixture of **3a** and **5** in toluene at 90 °C (method B). In addition to the small amount of **7**, ethyl 4-(sorboylamino)butanoate (**8**) was obtained (18% yield) as a side product identical to that prepared by the reaction of **6** and sodium ethoxide (Scheme 1).



Scheme 1.

The reactions may be explained by assuming the initial formation of an active intermediate **4a**, which in turn reacted with nucleophiles (**3a** or **4**) to afford an intermediate **4b** and acyl anhydride (**7**). Subsequent elimination of ethyl halide from **4b** gave the



Scheme 2.

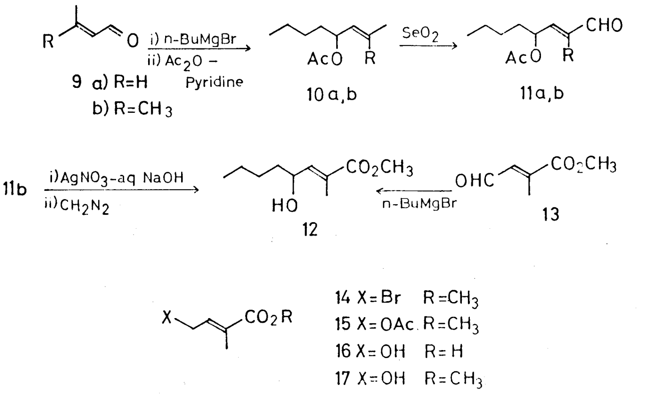
Table 1. The reaction of sorbic acid (**4**) and 2-ethoxy-1-pyrroline (**3a**) in the presence of 1-methyl-2-chloropyridinium iodide (**5**) and a base

Base	Reaction conditions			Addition method	Yield (%)		
	Solvent	Temp	Time (h)		**6**	**7**	**8**
$(C_2H_5)_3N$	$ClCH_2CH_2Cl$	0 °C	1.0	A[a]	—	93	—
$(C_2H_5)_3N$	$ClCH_2CH_2Cl$	50 °C	1.0	A	11	70	—
$(C_2H_5)_3N$	$ClCH_2CH_2Cl$	50 °C	4.0	B[b]	59	8	17
$(C_2H_5)_3N$	CH_3CN	50 °C	4.0	B	61	8	14
$(C_2H_5)_3N$	CH_3CN	refl.	4.0	B	60	6	14
n-Bu_3N	toluene	90 °C	2.0	B	63	7	18

a) The base was added immediately to the mixture of **3a**, **4**, and **5**.
b) The base and **4** were added dropwise to the mixture of **3a** and **5**.

desired acyl lactam (**6**). The amide (**8**) may be formed though an intermediate **4c** produced by the attack of an anion Y$^-$ at the N$^+$=C bond of **4b** (Scheme 2).

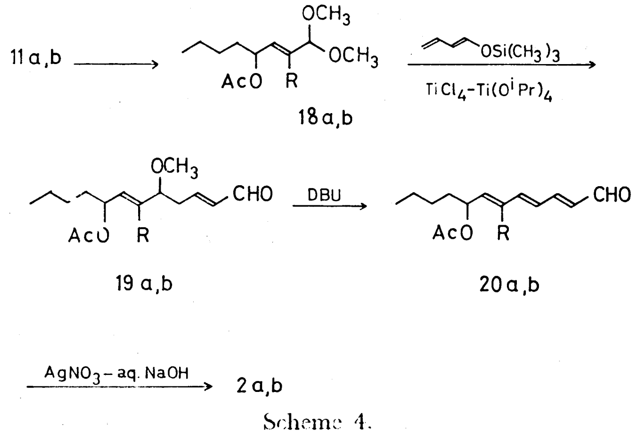
*Synthesis of Hydroxytrienoic Acid (**2a** and **2b**).* (2*E*)-4-Acetoxy-2-methyl-2-octenal (**11b**) was a key intermediate for the synthesis of **2b**. 3-Methyl-2-butenal (**9b**) was chosen as the starting material for the preparation of **11b** (Scheme 3).



Scheme 3.

The reaction of **9b** with butylmagnesium bromide in ether, followed by acetylation with acetic anhydride–pyridine, gave 4-acetoxy-2-methyl-2-octene (**10b**). The yield was 81% after purification by distillation. The allylic oxidation of **10b** with 1.5 molar amounts of selenium dioxide[7] in refluxing xylene resulted in (2*E*)-4-acetoxy-2-methyl-2-octenal (**11b**) (43% yield). In order to determine the configuration of the C$_2$-double bond in **11b**, the aldehyde (**11b**) was converted into methyl 4-hydroxy-2-methyl-2-octenoate (**12**) by oxidation with silver oxide under basic conditions and subsequent treatment with ethereal diazomethane in 76% yield based on **11b**. Authentic methyl (2*E*)-4-hydroxy-2-methyl-2-octenoate (**12**) was derived from methyl (2*E*)-4-bromo-2-methyl-2-butenoate (**14**)[8] as follows. Treatment of **14** with potassium acetate in refluxing ethanol[9] afforded acetoxy ester (**15**). Hydrolysis of **15** with 20% KOH solution–methanol afforded (2*E*)-4-hydroxy-2-methyl-2-butenoic acid (**16**) (59% yield based on **14**). Treatment of **16** with diazomethane gave the hydroxy methyl ester (**17**) (85% yield), which on oxidation with pyridinium chlorochromate[10] in dichloromethane afforded methyl (2*E*)-2-methyl-4-oxo-2-butenoate (**13**) (75% yield). The reaction of **13** with butylmagnesium bromide in ether gave authentic (2*E*)-octenoate (**12**) (60% yield). The spectral data, the TLC and the GC behavior of the hydroxy ester (**12**) derived from **11b** were identical with those of the authentic sample obtained by the above route.

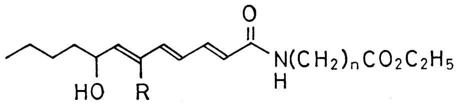
(2*E*,4*E*,6*E*)-8-Hydroxy-6-methyl-2,4,6-dodecatrienoic acid (**2b**) was derived from **11b** as depicted in Scheme 4. (2*E*)-Octenal (**11b**) was readily converted into its dimethyl acetal (**18b**) on treatment with trimethyl orthoformate–methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid (89% yield). The reaction of 1-trimethylsiloxy-1,3-butadiene with the acetal (**18b**) in the presence of titanium tetrachloride and titanium tetraisopropoxide proceeded smoothly at −40 °C to (2*E*,6*E*)-8-acetoxy-5-methoxy-6-methyl-2,6-dodecadienal (**19b**). Preparative TLC gave a yield of 85%. The δ-methoxyl group of **19b** was readily eliminated with 4 molar amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature in the presence of 3A molecular sieves to give (2*E*,4*E*,6*E*)-8-acetoxy-6-methyl-2,4,6-dodecatrienal (**20b**) (75% yield). The acetoxy aldehyde (**20b**) was converted into **2b** on oxidation with silver oxide at room temperature for 24 h (93% yield). (2*E*,4*E*,6*E*)-8-Hydroxy-2,4,6-dodecatrienoic acid (**2a**) was also prepared from crotonaldehyde (**9a**) through a similar synthetic route as described for **2b**.



Scheme 4.

Condensation of Hydroxytrienoic Acid (2) and Lactim Ether (3). For the final step of the synthesis of **1b**, the condensation of **2b** and **3a** in the presence of tributylamine and **5** was conducted under similar conditions used for the preliminary reaction (Scheme 5). The reaction proceeded along a similar path without protecting the hydroxyl group of **2b**, and the yield of (±) variotin (**1b**) was improved (30—37%),[11b] together with ethyl 4-[(2*E*,4*E*,6*E*)-8-hydroxy-6-methyl-2,4,6-dodecatrienamido]butanoate (**21b**) (10—18% yield).

$$\mathbf{2a,b} + \mathbf{3a,b} \xrightarrow[n\text{-Bu}_3\text{N}]{\mathbf{5}} \mathbf{1a,b,c} + \mathbf{21a,b,c}$$



21 a) R=H n=3
b) R=CH$_3$ n=3
c) R=CH$_3$ n=4

Scheme 5.

Similarly, **1a** and **1c** were prepared from **2** and **3** (36 and 27% yields, respectively). The spectral data of synthetic **1b** and **1c** were identical with those reported in the literature.[11,12] The potency of **1b**, thus obtained, against Trichophyton Asteroides was half that of the optically active natural variotin.

Experimental[13]

Reaction of Sorbic Acid (4) and 2-Ethoxy-1-pyrroline (3a). A solution of **4** (112 mg, 1.0 mmol) and tributylamine (195 mg, 1.05 mmol) in toluene (2 ml) was added dropwise to a mixture of 1-methyl-2-chloropyridinium iodide (614 mg, 2.4 mmol) and **3a** (208 mg, 2.4 mmol) in toluene (1 ml) over a period of 1 h at 85—90 °C under an argon atmosphere. After stirring for 1 h ethyl acetate (30 ml) was added. The resulting mixture was washed with dil HCl, 10% NaHCO$_3$ solution and water, dried and the organic layer concentrated under reduced pressure. The residue, subjected to preparative TLC on silica gel [hexane–ethyl acetate (1:1)] yielded four bands. The first band (highest R_f) consisted of ethyl sorbate (3 mg). IR(neat) 1710, 1640, 1620 cm^{-1}. NMR(CDCl$_3$) δ 7.1—7.6 (1H, m), 6.1—6.25(2H, m), 5.82(1H, d, J=16Hz), 4.24 (2H, q), 1.86(3H, d, J=5Hz), 1.30(3H, t). The second band consisted of sorbic anhydride (**7**) (14 mg, 7%). IR(neat) 1780, 1710, 1640, 1610 cm^{-1}. NMR(CDCl$_3$) δ 7.2—7.7 (2H, m), 6.25—6.45 (4H, m), 5.90(2H, d, J=16Hz), 1.90 (6H, d, J=5Hz). The third band consisted of 1-sorboyl-2-pyrrolidone (**6**) (113 mg, 63%), mp 122—123 °C (recrystallized from ethyl acetate) (lit,[14] mp 124—125 °C). IR (Nujol) 1730, 1660, 1630, 1590 cm^{-1}. NMR(CDCl$_3$) δ 7.15—7.5 (2H, m), 6.1—6.4(2H, m), 3.87(2H, t), 2.60(2H, t), 2.00 (2H, quasi q), 1.87(3H, d, J=5Hz). The fourth band (lowest R_f) consisted of ethyl 4-(sorboylamido)butanoate (**8**) (41 mg, 18%), mp 63—64 °C (recrystallized from ether-petroleum ether). IR (Nujol) 3350, 1730, 1660, 1630, 1610 cm^{-1}. NMR(CDCl$_3$) δ 6.95—7.45 (1H, m), 6.35—6.70(1H, br), 6.0—6.3(2H, m), 5.80(1H, d, J=16Hz), 4.10(2H, q), 3.40(2H, quasi q), 2.40(2H, quasi t), 1.8—2.2 (2H, m), 1.90(3H, d, J=5Hz), 1.22(3H, t). Found: C, 64.26; H, 8.53; N, 6.02%. Calcd for C$_{12}$H$_{19}$NO$_3$: C, 63.97; H, 8.50; N, 6.22%.

Reaction of 1-Sorboyl-2-pyrrolidone (6) with Sodium Ethoxide. To a mixture of sodium ethoxide (1 mmol) and abs C$_6$H$_6$ (5 ml) was added a solution of **6** (180 mg, 1 mmol) in abs C$_6$H$_6$ (4 ml) at room temperature under an argon atmosphere. After stirring for 10 min ethyl acetate (10 ml) and acetic acid (66 mg, 1.1 mmol) were added. The resulting mixture was washed with water and dried over anhydrous Na$_2$SO$_4$. The solvent was removed and the residual oil chromatographed on silica gel. Elution with hexane–ethyl acetate (4:1) afforded 52 mg (30%) of ethyl sorbate. Further elution with hexane–ethyl acetate (1:1) gave 63 mg (28%) of ethyl 4-(sorboylamido) butanoate (**8**).

4-Acetoxy-2-methyl-2-octene (10b). The Grignard reagent was prepared from Mg (1.6 g, 66 mg-atom) and butyl bromide (9.32 g, 68 mmol) in dry ether (25 ml). To this was added a solution of **9b** (5.04 g, 60 mmol) in ether (30 ml) at −30 °C under an argon atmosphere. The mixture was stirred fro 30 min at −30 °C and brought to room temperature. After 2 h, the reaction was quenched by adding sat NH$_4$Cl solution, the mixture extracted with ether and the extract dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residual oil was distilled to afford 7.70 g (90%) of 4-hydroxy-2-methyl-2-octene, bp 100—102 °C /27 mmHg. IR(neat) 3350, 1680 cm^{-1}. NMR(CDCl$_3$) δ 5.20(1H, br d), 4.10—4.60 (1H, br), 1.72(6H, s), 1.1—1.7 (6H), 0.89(3H). A mixture of the above alcohol (7.70 g, 54.2 mmol) and acetic anhydride (10 g, 100 mmol) in pyridine (40 ml) was stirred for 15 h at room temperature. The reaction mixture was poured into ice-cold water, extracted with ether and the extract was washed with dil HCl, 10% NaHCO$_3$ solution, and water, dried over anhydrous MgSO$_4$, and evaporated to give an oil. The oil was distilled to yield 9.02 g (90%) of **10b**, bp 99—102 °C/20 mmHg. IR(neat) 1740, 1680 cm^{-1}. NMR(CDCl$_3$) δ 5.30—5.70(1H, m), 5.10(1H, br d), 2.01(3H, s), 1.71, 1.73(6H, 2s), 1.1—1.7 (6H), 0.9(3H).

In the same manner, 4-acetoxy-2-octene (**10a**) was obtained from **9a** (81% yield), bp 105—107 °C/45 mmHg. IR(neat) 1740, 1670, 1235 cm^{-1}. NMR(CCl$_4$) δ 5.45—5.9(2H, m), 5.0—5.4 (1H, br), 2.04 (3H, s), 1.70(3H, d), 1.1—1.7(6H), 0.9(3H).

*(2*E*)-4-Acetoxy-2-methyl-2-octenal (11b).* The acetate (**10b**) (7.4 g, 40 mmol) in xylene (30 ml) was refluxed with SeO$_2$ (6.6 g, 60 mmol) for 40 min under an argon atomsphere. The black precipitates were removed by filtration, and the filtrate evaporated to give an oil. The oil was purified by column chromatography on silica gel [hexane–ethyl acetate (4:1) as an eluent] to yield 3.40 g (43%) of **11b**, bp 80 °C/ 0.05 mmHg. IR(neat) 1740, 1690, 1650, 1240 cm^{-1}. NMR (CDCl$_3$) δ 9.45(1H, s), 6.31 (1H, br d), 5.5—5.8(1H, br), 2.07(3H, s), 1.84(3H, s), 1.2—1.8(6H), 0.95(3H).

(2*E*)-4-Acetoxy-2-octenal (**11a**) was obtained in 45% yield by treating **10a** with SeO$_2$ under similar conditions. Bp 104—105 °C/1 mmHg. IR(neat) 1740, 1690, 1640, 1235 cm^{-1}. NMR(CCl$_4$) δ 9.55(1H, d, J=8Hz), 6.75 (1H, dd, J=6,16Hz), 6.10 (1H, dd, J=8,16Hz), 5.30—5.65(1H, br), 2.10(3H, s), 1.10—1.90(6H), 0.95(3H).

*Methyl (2*E*)-4-Acetoxy-2-methyl-2-butenoate (15).* A mixture of methyl (2*E*)-4-bromo-2-methyl-2-butenoate (1.93 g, 10 mmol) and potassium acetate (1.18 g, 12 mmol) in abs ethanol (13 ml) was refluxed for 3 h under a nitrogen atmosphere. The mixture was cooled to 0 °C, the precipitates filtered off and the filtrate evaporated to give an oil. The oil was distilled to yield 1.54 g (90%) of **15**, bp 140 °C/28 mmHg. IR(neat) 1740, 1720, 1660 cm^{-1}. NMR(CDCl$_3$) δ 6.75 (1H, quasi t), 4.75(2H, quasi d), 2.05(3H, s), 1.87(3H, s).

*(2*E*)-4-Hydroxy-2-methyl-2-butenoic Acid (**16**).* To a solution of **15** (372 mg, 2.16 mmol) in methanol (10 ml) was added 20% KOH solution (1.5 ml) at 0 °C. The mixture was stirred for 15 h at room temperature and methanol removed under reduced pressure. The aqueous solution was acidified with dil HCl, extracted with ethyl acetate and the extract dried over anhydrous Na_2SO_4 and evaporated to give an oil. The oil was purified by column chromatography on silica gel [hexane–ethyl acetate (1:2) as an eluent] to yield 163 mg (65%) of **16**, mp 78—80 °C. IR(KBr) 3200, 1670, 1630 cm^{-1}. NMR($CDCl_3$) δ 6.7—7.3(3H, br s), 4.33(2H, d, J=6Hz), 1.82(3H, s).

*Methyl (2*E*)-4-Hydroxy-2-methyl-2-butenoate (**17**).* To a solution of **16** (314 mg, 2.71 mmol) in abs ether (5 ml) was added a solution of diazomethane (excess) in ether at 0 °C. The mixture was kept at 0 °C for 1 h and the solvent removed under reduced pressure. The resulting oil was distilled to afford 298 mg (85%) of **17**, bp 124 °C/7 mmHg. IR(neat) 3400, 1720, 1660, 1260 cm^{-1}. NMR($CDCl_3$) δ 6.85(1H, quasi t), 4.35(2H, quasi d), 3.70(3H, s), 3.01(1H, s), 1.83 (3H, s).

*Methyl (2*E*)-4-Oxo-2-methyl-2-butenoate (**13**).* A solution of **17** (650 mg, 5 mmol) in dichloromethane (5 ml) was added in one portion to the stirred suspension of pyridinium chlorochromate (1.62 g, 7.5 mmol) and sodium acetate (125 mg, 1.52 mmol) in dichloromethane (5 ml). After 2 h, the reaction mixture was conducted according to Corey and Suggs.[10] Distillation of the crude oil gave 480 mg (75%) of **13**, bp 89 °C/15 mmHg (lit,[15] bp 76—78 °C/12 mmHg). IR(neat) 1720, 1680, 1630, 1260 cm^{-1}. NMR($CDCl_3$) δ 10.28(1H, d, J=8Hz), 6.85(1H, quasi d), 3.88(3H, s), 2.35 (3H, d, J=1.5Hz).

2,4-Dinitrophenylhydrazone, mp 206—207 °C (lit,[15] mp 204—205 °C).

*Methyl (2*E*)-4-Hydroxy-2-methyl-2-octenoate (**12**). From Methyl (2*E*)-4-Oxo-2-methyl-2-butenoate (**13**):* To a solution of the Grignard reagent prepared from Mg (59 mg, 2.4 mg atom) and butyl bromide (357 mg, 2.6 mmol) in ether (1 ml) was added a solution of **13** (256 mg, 2 mmol) in ether (1 ml) at −30 °C under an argon atmosphere. The mixture was stirred for 2 h at room temperature. After the usual work-up a crude oil was obtained. This oil was purified by preparative TLC on silica gel [hexane–ethyl acetate (4:1) as an eluent] to yield 227 mg (60%) of **12**, bp 95 °C/0.04 mmHg. IR(neat) 3400, 1720, 1650 cm^{-1}. NMR ($CDCl_3$) δ 6.68(1H, br d), 4.3—4.8(1H, br). 3.74(3H, s), 2.64 (1H, br s), 1.87(3H, d, J=1.5Hz), 1.1—1.8(6H), 0.90(3H).

*From (2*E*)-4-Acetoxy-2-methyl-2-octenal (**11b**):* To a solution of silver nitrate (408 mg, 2.4 mmol) in water (4 ml) was added a solution of **11b** (396 mg, 2 mmol) in ethanol (8 ml) and aqueous NaOH (368 mg in 5 ml of H_2O). The mixture was stirred for 24 h at room temperature in the dark. The precipitates filtered off and ethanol removed under reduced pressure. The residual aqueous solution was acidified with dil HCl, extracted with ethyl acetate and the extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude acid (324 mg). This was treated with a small excess of ethereal diazomethane at 0 °C for 1 h. After evaporation of ether, the residual oil was purified by column chromatography on silica gel [hexane–ethyl acetate (2:1) as an eluent] to afford 282 mg (76%) of **12**, bp 95 °C/0.04 mmHg. The ester (**12**) was identified by comparison of its GLC retention time,[16] IR and NMR spectrum with those of an authentic sample (**12**) prepared from **13**.

*(2*E*)-4-Acetoxy-2-methyl-2-octenal Dimethyl Acetal (**18b**).* To a solution of **11b** (2.80 g, 14 mmol) and trimethyl orthoformate (4.5 g, 42 mmol) in abs methanol (7 ml) was added a catalytic amount of *p*-toluenesulfonic acid at −10 °C under an argon atmosphere. The mixture was stirred for 10 min at the same temperature and brought to room temperature. After stirring for a further 3 h, the reaction was quenched by adding anhydrous K_2CO_3. The solvent was removed under reduced pressure at 20 °C, the residue dissolved in petroleum ether (bp 30—60 °C), filtered and the filtrate evaporated to give an oil which distilled to give 3.04 g (89%) of **18b**, bp 85 °C/0.04 mmHg. IR(neat) 1740, 1240 cm^{-1}. NMR($CDCl_3$) δ 5.55(1H, br s), 5.45—5.70(1H, br), 4.52(1H, s), 3.30(6H, s), 2.01(3H, s), 1.71(3H, s), 0.9—1.8(9H).

(2*E*)-4-Acetoxy-2-octenal dimethyl acetal (**18a**) was obtained by treating **11a** with trimethyl orthoformate–methanol as described above (85% yield). Bp 98—100 °C/0.5 mmHg. IR(neat) 1740, 1240 cm^{-1}. NMR(CCl_4) δ 5.5—5.8(2H, m), 5.0—5.4(1H, m), 4.70 (1H, br d), 3.20(6H, s), 2.00(3H, s), 1.1—1.7(6H), 0.95(3H).

*(2*E*,6*E*)-8-Acetoxy-5-methoxy-6-methyl-2,6-dodecadienal (**19b**).* To a mixture of $Ti(O^iPr)_4$ (8 mmol) and $TiCl_4$ (8 mmol) in dichloromethane (40 ml) was added a solution of **18b** (976 mg, 4 mmol) and 1-trimethylsiloxy-1,3-butadiene (680 mg, 4.8 mmol) in dichloromethane (10 ml) at −40 °C under an argon atmosphere. After stirring for 30 min at −40 °C, the reaction was quenched by adding K_2CO_3 (7 g in 10 ml of H_2O). The resulting precipitates were removed by filtration and the filtrate extracted with ether and the extract was washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residual oil was purified by preparative TLC on silica gel [hexane–ethyl acetate (4:1) as an eluent] to yield 959 mg (85%) of **19b**. Bp 135 °C/0.04 mmHg. IR (neat) 1740, 1690, 1640, 1240 cm^{-1}. NMR ($CDCl_3$) δ 9.55 (1H, d, J=8Hz), 6.83(1H, ddd, J=16.8, 8Hz), 6.13(1H, dd, J=16,8Hz), 5.2—5.6(2H, br), 3.64(1H, t), 3.22(3H, s), 2.5—2.7(2H, m), 2.01 (3H, s), 1.70(3H, s), 1.1—1.8(6H), 0.9(3H).

(2*E*,6*E*)-8-Acetoxy-5-methoxy-2,6-dodecadienal (**19a**) was obtained by reacting **18a** with dienoxysilane in the presence of $TiCl_4$ and $Ti(O^iPr)_4$ (83% yield). Bp 125 °C/0.08 mmHg. IR(neat) 1735, 1690, 1640, 1240 cm^{-1}. NMR (CCl_4) δ 9.40(1H, d, J=8Hz), 6.70(1H, ddd, J=16,8,8Hz), 6.00(1H, dd, J=8,16Hz), 5.45—5.60 (2H, m), 4.9—5.3 (1H, br), 3.5—3.8(1H, br), 3,20(3H, s), 2.3—2.7 (2H), 1.05—1.70(6H), 0.9(3H).

*(2*E*,4*E*,6*E*)-8-Acetoxy-6-methyl-2,4,6-dodecatrienal (**20b**).* To a mixture of **19b** (282 mg, 1 mmol) and molecular sieves 3A (500 mg) in dichloromethane (8 ml) was added a solution of DBU (304 mg, 2 mmol) in dichloromethane (2 ml) at room temperature under an argon atmosphere. After stirring for 1 h, a solution of DBU (2 mmol) in acetonitrile (3 ml) and molecular sieves 3A (500 mg) were added. The mixture was stirred for 2 h and poured into ice-cold brine containing acetic acid, the organic layer separated, washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residual oil was purified by preparative TLC on silica gel [hexane–ethyl acetate (4:1) as an eluent] to yield 193 mg (77%) of **20b**. IR(neat) 1735, 1680, 1610, 1240 cm^{-1}. NMR($CDCl_3$) δ 9.63(1H, d, J=8Hz), 7.00—7.50(1H, m), 6.5—7.0(2H, m), 6.20(1H, dd, J=16, 8Hz), 5.5—5.8(2H, br), 2.04(3H, s), 1.93(3H, s). 1.1—1.9(6H), 0.9(3H).

(2*E*,4*E*,6*E*)-8-Acetoxy-2,4,6-dodecatrienal (**20a**) was obtained by treating **19a** with DBU under similar conditions (75% yield). IR(neat) 1740, 1680, 1615, 1240 cm^{-1}. NMR ($CDCl_3$) δ 9.50 (1H, d, J=8Hz), 5.7—7.3(6H, m), 5.05—5.40(1H, br), 2.05(3H, s), 1.10—1.75(6H), 0.9(3H).

*(2E,4E,6E)-8-Hydroxy-6-methyl-2,4,6,-dodecatrienoic Acid (**2b**).* To a solution of silver nitrate (646 mg, 3.80 mmol) in water (5 ml) were added a solution of **20b** (791 mg, 3.16 mmol) in ethanol (13 ml) and NaOH (581 mg in 8 ml of H_2O). The mixture was stirred for 24 h at room temperature in the dark. After the usual work-up, **2b** (661 mg) was obtained (93% yield). IR(neat) 3300, 1690, 1620 cm^{-1}. NMR ($CDCl_3$) δ 7.2—7.7(1H, m), 6.3—6.8 (3H, m), 5.90(1H, d, J=16Hz), 5.70(1H, br d), 4.3—4.7(1H, br d), 1.86(3H,), 1.1—1.8(6H), 0.85(3H). UV $\lambda_{\max}^{C_2H_5OH}$ 296 nm (ε 2.6×10^4). MS m/e 225(M^++1), 206, 139, 121. Found: C, 69.88; H, 9.02%. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%.

(2E,4E,6E)-8-Hydroxy-2,4,6,-dodecatrienoic acid (**2a**) was obtained by treating **20a** with silver oxide under similar conditions (90% yield). Mp 85—86 °C (recrystallized from ethyl acetate-hexane). IR(Nujol) 3400—3300, 1700, 1610 cm^{-1}. NMR(CCl_4) δ 7.1—7.4(3H, m), 5.7—6.6 (4H, m), 4.0—4.3(1H, br), 1.1—1,7(6H), 0.9(3H). UV $\lambda_{\max}^{C_2H_5OH}$ 296 nm(ε 2.9×10^4). MS m/e 210(M^+), 192, 125. Found C, 68.41; H, 8.51%. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63%.

*Reaction of (2E,4E,6E)-8-Hydroxy-6-methyl-2,4,6,-dodecatrienoic Acid (**2b**) with 2-Ethoxy-1-pyrroline (**3a**).* A solution of **2b** (112 mg, 0.5 mmol) and tributylamine (102 mg, 0.55 mmol) in toluene (1 ml) was added dropwise to a mixture of 1-methyl-2-chloropyridinium iodide (307 mg, 1.2 mmol) and **3a** (136 mg, 1.2 mmol) in toluene (1 ml) over a period of 30 min at 85 °C under argon atmosphere. The mixture was stirred for an additional 10 min and the solvent removed under reduced pressure and the residue chromatographed on silica gel. Elution with dichloromethane-ether (4:1) afforded 44 mg (30%) of **1b**. Further elution with dichloromethane-ether (1:1) gave 17 mg (10%) of **21b**. In another experiment under the same conditions, **1b** (54 mg) and **21b** (30 mg) were obtained in 37% and 18% yields, respectively. **1b**: IR(neat) 3400, 1740, 1670, 1600 cm^{-1}. NMR ($CDCl_3$) δ 7.3—7.7(2H, m), 6.4—6.7(2H, m), 5.70(1H, br d), 4.3—4.8 (1H, br), 3.90(2H, t), 2.65(2H, quasi t), 2.50(1H,s), 1.8—2.4 (2H, m), 1.85(3H, s), 1.1—1.8(6H), 0.9(3H). UV $\lambda_{\max}^{C_2H_5OH}$ 320 nm (ε 2.61×10^4). MS m/e 291(M^+), 273, 206. Found: C, 70.03; H, 8.41; N, 4.66%. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65, N, 4.81%. **20b**: IR(neat) 3300, 1740, 1650, 1610 cm^{-1}. NMR($CDCl_3$) δ 7.1—7.6(1H, m), 6.10—6.10(3H, m), 5.95(1H, d, J=16Hz), 5.65(1H, br d), 4.15(2H, q), 4.2—4.7(1H, br), 3.15—3.89(3H, m). 2.2—2.6(2H, m), 1.85(3H, s), 1.25(3H, t), 1.1—2.2(8H), 0.9(3H). UV $\lambda_{\max}^{C_2H_5OH}$ 294 nm (ε 4.0×10^4). MS m/e 337(M^+). Found: C, 67.91; H, 9.45; N, 4.09%. Cacld for $C_{19}H_{31}NO_4$: C, 67.62; H, 9.26; N, 4.15%.

In a similar manner, **1a** was obtained from **2a** and **3a** (36% yield), together with **21a** (16%). Similarly, **1c** (27%) and **21c** (28%) were obtained from **2b** and **3b**. Compound **1a**: IR(neat) 3400, 1730, 1660, 1600 cm^{-1}. NMR($CDCl_3$) δ 7.3—7.6(2H, m), 5.9—6.7(4H, m), 3.9—4.5(1H, br), 3.90 (2H, t), 2.3—2.8(3H, m), 1.8—2.3(2H, br q), 1.1—1.8(6H), 0.9(3(H). UV $\lambda_{\max}^{C_2H_5OH}$ 324 nm (ε 2.68×10^4). MS m/e 278(M^+), 193. Found: C, 69.51; H, 8.38; N, 5.25%. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05%. Compound **21a**: Mp 87—89 °C. IR(KBr) 3400, 3300, 1725, 1615, 1580, 1530 cm^{-1}. NMR($CDCl_3$) δ 7.0—7.5 5.7—6.8(7H, m), 4.0—4.5(1H, br), 4.10 (2H, q), 3.2—3.6(2H, m), 2.35 (1H, s), 2.1—2.7(2H, m), 1.20(3H, t), 1.2—2.2(8H), 0.9(3H). UV $\lambda_{\max}^{C_2H_5OH}$ 295 nm(ε 4.46×10^4). MS m/e 323(M^+), 305, 238. Found: C, 66.59; H, 9.15; N, 4.55%. Cacld for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33%. Compound **1c**: IR(neat) 3400, 1690, 1670, 1600 cm^{-1}. NMR($CDCl_3$) δ 6.4—7.7(4H, m), 5.70(1H, br d), 4.3—4.8(1H, br), 3.6—4.0 (2H, m), 2.53(1H, s), 2.2—2.8 (2H, m), 1.83(3H,s), 1.1—2.2(10H), 0.9(3H). UV $\lambda_{\max}^{C_2H_5OH}$ 317 nm (ε 2.23×10^4). MS m/e 350(M^+), 297, 220. Found: C, 71.05; H, 8.98; N, 4.73%. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59%. Compound **21c**: IR(neat) 3270, 1740, 1650, 1610 cm^{-1}. NMR($CDCl_3$) δ 7.28(1H, dd, J=16, 8Hz), 6.2—6.6(3H, m), 5.95 (1H, d, J=16Hz), 5.63(1H, br d), 4.2—4.7(1H, br), 4.12(2H, q), 3.2—3.6 (2H, m), 2.2—2.7(2H, m), 2.90(1H, s), 1.80(3H, s), 1.23(3H, t), 1.1—1.8(10H), 0.9(3H). UV $\lambda_{\max}^{C_2H_5OH}$ 295 nm (ε 4.1×10^4). MS m/e 351 (M^+) 343, 266. Found: C, 68.54; 9.44; N, 4.11%. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99%.

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