

221. Identification of Twenty-one Novel Constituents of Oriental Tobacco Flavour (*Nicotiana tabacum* L.) Including (*E*)-3-Methyl-non-2-en-4-one, Pentadecan-15-olide, 8 α ,13:9 α ,13-Diepoxy-15,16-dinorlabdane, (*Z*)-Octadec-9-en-18-olide, and (*E*)-2-Ethylidene-6,10,14-trimethyl-pentadecanal

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Summary

Investigation by gas liquid chromatography of a small but organoleptically typical subfraction of *Oriental* tobacco condensate led to the identification of 47 compounds. Of these 21 have hitherto not been reported as *Oriental* tobacco constituents, and 14 appear to be novel to all tobacco types. The latter are (*E*)-3-methyl-non-2-en-4-one (**1**), (*E*)-1-(2,3,6-trimethylphenyl)-but-2-en-1-one (**3**), penta-decan-15-olide (**12**), 8 α ,13:9 α ,13-diepoxy-15,16-dinorlabdane (**17**), (*Z*)-octadec-9-en-18-olide (**18**), (*E*)-2-ethylidene-6,10,14-trimethylpentadecanal (**21**), the norlabdanoids **9**, **10**, **11**, **14**, **15**, **16**, tridecan-2-one, and 2-phenylethyl isovalerate. The macrolides **12** and **18** represent the first musk compounds detected in tobacco. Identifications were made by direct comparison (MS. and/or ¹H-NMR./IR.) with the authentic chemicals synthesized whenever necessary.

Introduction. – In sharp contrast to other major tobacco types such as *Burley* [1] or *Virginia* [2] tobaccos, the so-called *Oriental* or sun-cured tobaccos¹⁾ contain diterpenes of the labdane series accompanied by related ‘nor’ compounds having 14 to 18 carbon atoms [3]. This large variation in the chemical composition of *Nicotiana tabacum* varieties is best accounted for by genetic factors [4] [5]. Notwithstanding the fact that these labdanoids and their presumed metabolites are organoleptically important, the neutral fraction of *Oriental* tobacco condensate contains many other constituents that also contribute to its typical aroma. Two of these are the macrocyclic lactones **12** and **18**²⁾ that represent, to the best of our knowledge, the first musk compounds ever detected in *Nicotiana tabacum*.

Preparation³⁾ and fractionation of oriental tobacco condensate. – The aqueous distillate (about 1800 l) resulting from the steam-distillation of 115 kg of aged,

¹⁾ For instance Greek, Turkish, and Yugoslavian tobaccos.

²⁾ Formulae are numbered consecutively as in the *Table* in order of increasing molecular weight.

³⁾ *Oriental* tobacco condensate was prepared at our pilot laboratory (Dr. H. Strickler), to whom we are grateful.

chopped *Oriental* tobacco⁴) was acidified to pH 3-4 with 50% sulfuric acid and extracted four times with chloroform. There was thus obtained 232 g (0.20% by weight of starting tobacco) of a condensate substantially free of nicotine but presenting excellent flavouring properties. This oil was then separated according to *Scheme 1* and the miscellaneous fractions were organoleptically tested⁵). In this paper we describe the study of subfraction ON3(e) which exhibited a marked woody-type odour with amber and musk notes typical of *Oriental* tobacco.

Investigation of subfraction ON3(e). - Preliminary separation of this subfraction by semi-preparative GC. (gas liquid chromatography) afforded 15 groups of components whose $R_T(sol)$ ⁶) values were in the range 0.47 to 3.53 (5% silicone oil, 5 min at 170°, then 4°/min up to 225°, 2.5 m column). These groups were either directly examined by capillary GC./MS. coupling, or subjected to further semi-preparative separations by GC. combining the use of relatively polar (SP-1000⁷) and non-polar (silicone oil) columns. In certain difficult cases, this process was completed by liquid chromatography on silica gel/AgNO₃ 9:1, carried out with hexane/ether mixtures 19:1 to 0:1. Twenty-one of the 47 compounds thus isolated and identified (see *Table*) have hitherto not been reported as *Oriental* tobacco constituents, although 7 of them occur in other tobacco types (2-furaldehyde [2], *p*-methylacetophenone [2] [9], 2-phenylethyl hexanoate [9], compounds **2** [11], **13** [3] [17], **19** [2] [3], and **20** [20]). The 14 remaining representatives appear to be entirely novel to tobacco and deserve some comments.

(*E*)-3-Methyl-non-2-en-4-one (**1**) ($\geq 0.036\%$ in the tobacco condensate)⁸) is a novel natural ketone containing the relatively uncommon (*E*)-2-methyl-but-2-enoyl moiety. The *E*-configuration of this compound was demonstrated by the appearance of a quartet at $\delta = 6.75$ ppm (C=CH) in its ¹H-NMR. spectrum [23] and confirmed by synthesis from (*E*)-2-methylbut-2-enal (tiglaldehyde). Ketone **1** could possibly be formed in tobacco either by cross-aldol condensation between acetaldehyde and 3-octanone, or *via* hydration of bovolide (**23**) [9] (*Scheme 2*) and decarboxylative elimination of the hypothetical intermediate **24** thus formed. The latter reaction sequence applied to spiroxabovolidine (**25**) [24] would lead to (*E*)-3-methyl-8-hydroxy-non-2-en-4-one (**26**) which was recently found in Greek tobacco [23].

Pentadecan-15-olide (**12**) ($\geq 0.05\%$ in the tobacco condensate) was identified by its mass and ¹H-NMR. spectra. The powerful fragrance of this naturally occurring musk compound known since 1927 [16] should contribute to the aroma of *Oriental* tobacco.

8 α ,13:9 α ,13-Diepoxy-15,16-dinorlabdane (**17**) ($\geq 0.04\%$ in the tobacco condensate) was synthesized 4 years ago [18] but not found in nature until now. It is practically odourless in spite of the fact that it is isomeric to the well-known pair of amber-like smelling acetals **27** [25] (*Scheme 2*).

⁴) We used a 1:1 blend of 'Yugoslavian Oriental' and 'Northern Turkish Oriental' tobacco brands.

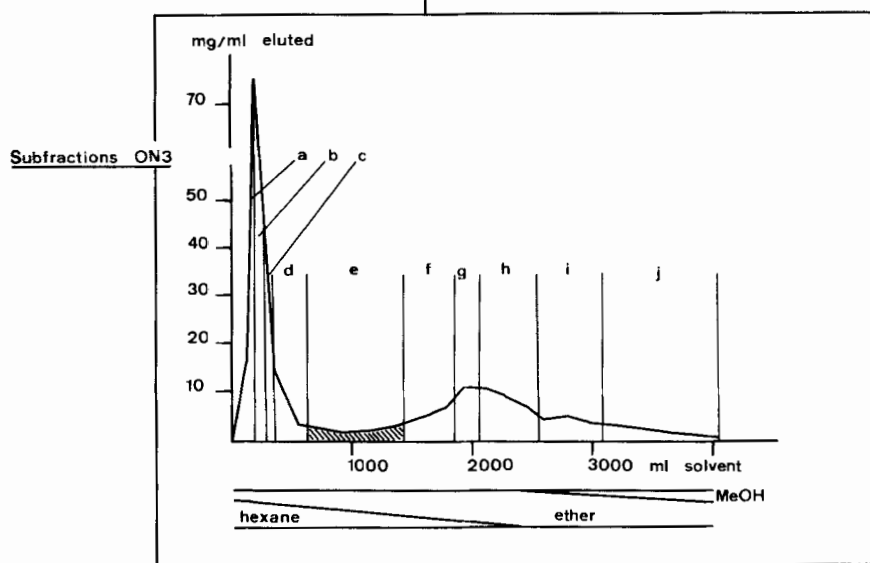
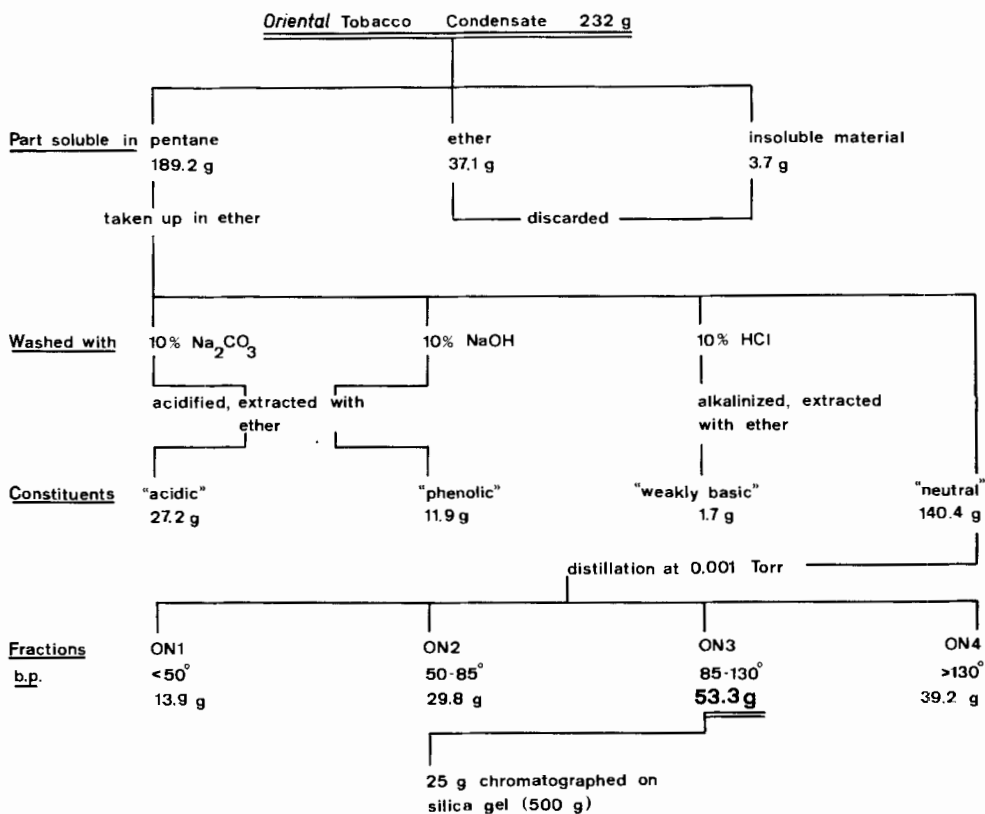
⁵) We are indebted to Dr. P. Dietrich and Mr. A. Y. Smith (Firmenich SA, Geneva) for evaluating the flavouring properties of these fractions.

⁶) $R_T(sol)$ = retention time relative to solanone (**6**) taken as internal standard.

⁷) A modified Carbowax manufactured by Supelco, Inc., Bellefonte, Pennsylvania (U.S.A.).

⁸) Ketone **1** occurs also in *Burley* (0.49%) and *Virginia* ($\geq 0.10\%$) tobacco condensates (*E. Demole & P. Enggist*, unpublished results).

Scheme 1



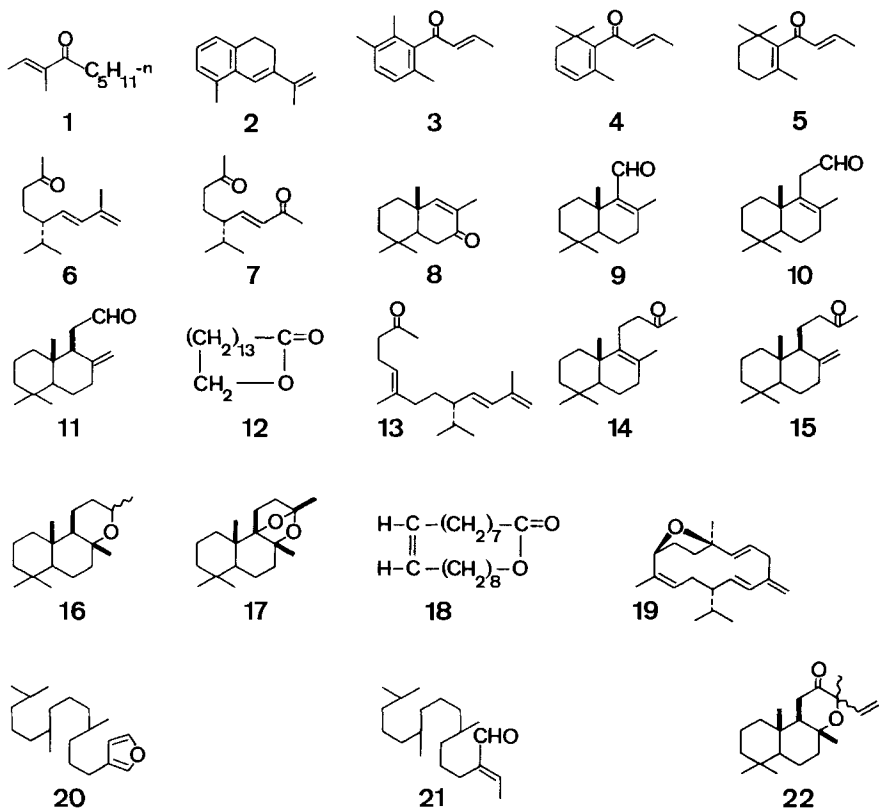
Table^{a)}. Constituents of Oriental Tobacco Flavour

	Formula	M^+	New ^{b)}	Ref.
2-Furaldehyde		96	+	[2]
Benzaldehyde		106		[6]
Benzyl alcohol		108		[6]
5-Methyl-2-furaldehyde		110		[7]
Phenylacetaldehyde		120		[8]
2-Phenylethyl alcohol		122		[6]
<i>p</i> -Methylacetophenone		134	+	[2] [9]
2-Phenylethyl formate		150		[10]
(<i>E</i>)-3-Methylnon-2-en-4-one	1	154	+	
3-Isopropenyl-5-methyl-1,2-dihydronaphthalene	2	184	+	[11]
Tridecane		184		[12]
(<i>E</i>)-1-(2,3,6-Trimethylphenyl)-but-2-en-1-one	3	188	+	[13]
β -Damasconone	4	190		[6]
β -Damascone	5	192		[10]
Solanone	6	194		[3] [6]
6,10-Dimethylundeca-5,9-dien-2-one		194		[6]
Norsolanadione	7	196		[3] [7]
Tetradecane		198		[12]
Tridecan-2-one		198	+	
2-Phenylethyl isovalerate		206	+	
Benzyl hexanoate		206		[10]
11-Nordrim-8-en-7-one	8	206		[14]
2-Phenylethyl hexanoate		220	+	[9]
Drim-8-en-11-al	9	220	+	[15]
Pentadecan-2-one		226		[10]
Pentadecanal		226		[6]
13,14,15,16-Tetranorlabd-8-en-12-al	10	234	+	[16]
13,14,15,16-Tetranorlabd-8(17)-en-12-al	11	234	+	[16]
Pentadecan-15-olide	12	240	+	[16]
Methyl tetradecanoate		242		[6]
Prenylsolanone	13	262	+	[3] [17]
6,10,14-Trimethylpentadeca-5,9,13-trien-2-one		262		[6]
15,16-Dinorlabd-8-en-13-one	14	262	+	[18]
15,16-Dinorlabd-8(17)-en-13-one	15	262	+	[16]
8,13-Epoxy-15,16-dinorlabdane (at least 2 stereoisomers)	16	264	+	[19]
6,10,14-Trimethylpentadecan-2-one		268		[6]
Methyl hexadecanoate		270		[6]
8 α ,13:9 α ,13-Diepoxy-15,16-dinorlabdane	17	278	+	[18]
Di- <i>n</i> -butyl phthalate		278		[6]
(<i>Z</i>)-Octadec-9-en-18-olide	18	280	+	
8,11-Epoxythunberga-2,4(18),6,12-tetraene	19	286	+	[2] [3]
Phytofuran	20	292	+	[20]
Methyl octadeca-9,12,15-trienoate		292		[21]
(<i>E</i>)-2-Ethylidene-6,10,14-trimethylpentadecanal	21	294	+	
Methyl octadeca-9,12-dienoate		294		[21]
Methyl octadec-9-enoate		296		[21]
8,13-Epoxy-14-en-12-one (2 stereoisomers)	22	304		[22]

a) All compounds were identified by MS., and/or by ¹H-NMR./IR. for those having $M^+ \geq 194$.

b) Novel constituents of Oriental tobacco.

(*Z*)-Octadec-9-en-18-olide (**18**) ($\geq 0.05\%$ in the tobacco condensate), the cyclization product of 18-hydroxyoleic acid, is a novel macrolide that exhibits a faint but tenacious musk odour with a peculiar waxywoody note. This compound was identified by direct comparison with the authentic lactone prepared according to Scheme 2, formulae **28-18** (R_T by capillary GC., ¹H-NMR., MS.). The *Z*-configu-

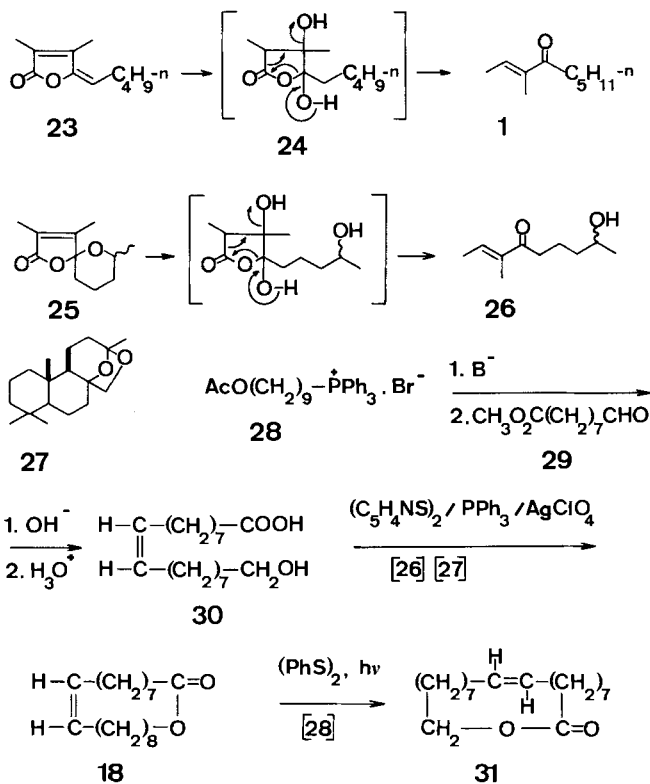


ration of natural **18** was further secured by comparing its R_T with that of the synthetic *E*-isomer **31** [relative R_T : 0.98 (*E*)- and 1.00 (*Z*)-isomer; OV-101, 6 min at 120°, then 2.5°/min up to 180°, 50 m × 0.3 mm column].

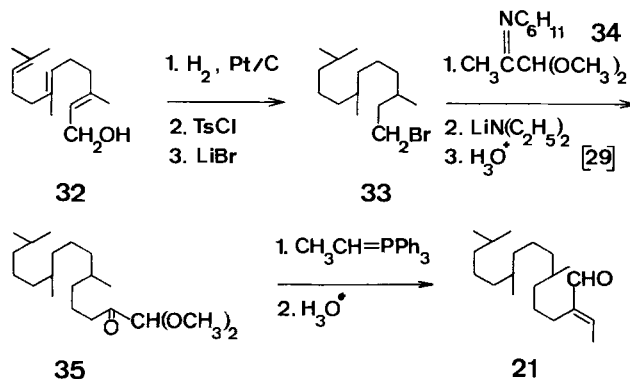
(*E*)-2-Ethylidene-6,10,14-trimethylpentadecanal (**21**) ($\geq 1.06\%$ in the tobacco condensate) is a novel diterpene identified by direct comparison with the authentic material synthesized as shown in *Scheme 3* (IR., $^1\text{H-NMR}$., MS.). The *E*-configuration of natural and synthetic **21** was demonstrated by a CHO singlet appearing at $\delta = 9.37$ ppm in the $^1\text{H-NMR}$. spectrum [$\delta(\text{CHO})$ in (*E*)-2-methylbut-2-enal = 9.34] [30]. However, a second, weak singlet at 10.17 indicated both samples to contain about 3–4% of *Z*-isomer [$\delta(\text{CHO})$ in (*Z*)-2-methylbut-2-enal = 10.14] [30]. The ^{13}C chemical shifts exhibited by the CHO and ethylidene groups also supported the largely prevailing *E*-configuration of **21** [corresponding, respective values recorded [30] for (*E*)- and (*Z*)-2-methylbut-2-enal are given for comparison]: CHO, 194.7 (194.5, 190.9); =CH, 149.3 (149.4, 144); CH_3 , 14.7 (14.8, 12.8). The peculiar location of the aldehydic function in **21** suggests that this compound might have been formed *via* sensitized photooxygenation of the major tobacco constituent neophytadiene [7], in a way similar to that postulated for phytofuran (**20**) [20] but involving an additional, reductive step.

The 9 further constituents novel to tobacco identified in this investigation comprise (*E*)-1-(2,3,6-trimethylphenyl)-but-2-en-1-one (3) [13] (a plausible metabolite of β -damascenone (4)), 6 norlabdanoids (9 [15], 10 [16], 11 [16], 14 [18], 15 [16], 16 [19]), tridecan-2-one, and 2-phenylethyl isovalerate.

Scheme 2



Scheme 3



Experimental Part

The spectra were obtained with the instruments already described [24] (the mass spectra were determined at 70 eV, inlet temperature 150°; the ¹H- and ¹³C-NMR. spectra were measured in CDCl₃). GC./MS. data were obtained using a gas chromatograph *Carlo Erba*, Model 2101 AC (Ucon 5100, 90–170°, 50 m × 0.3 mm glass column), coupled to a *Varian* MAT 112 mass spectrometer. GC. separations were performed on Models 1820-3 or 2720-3 gas chromatographs (*Varian Aerograph AG*), and *Carlo Erba*, Model 2301 AC. All liquid-solid chromatographic separations were carried out on 0.05–0.2 mm silica gel for column chromatography (*Merck AG*).

1. (*E*)-3-Methyl-non-2-en-4-one (**1**). Tiglaldehyde (21.0 g, 0.25 mol, in 100 ml of anhydrous ether) was added over 30 min at –20° to a stirred solution of pentylmagnesium bromide prepared from magnesium (6.8 g, 0.28 mol), pentyl bromide (38.0 g, 0.25 mol), and anhydrous ether (230 ml). After 2 h further stirring at 20°, the mixture was poured into an ice cold saturated NH₄Cl-solution, extracted twice with ether and washed to neutrality. The crude product was distilled at 10 Torr: fr. 1, b.p. 40–92°, 2.88 g; fr. 2, b.p. 92–95°, 26.99 g. Upon redistillation, fr. 2 gave 24.66 g (63%) of pure 3-methyl-non-2-en-4-ol, b.p. 93–95°/10 Torr; d_4^{20} = 0.858; n_D^{20} = 1.4510. GC. (15% Carbowax, 160°, 2.5 m column) indicated this compound to be a mixture of *E*- and *Z*-stereoisomers (ca. 14:1). – IR. (neat, bands with decreasing intensities): 3400, 1010, 1380, 1460, 830, 1665 cm⁻¹. – ¹H-NMR. (δ, ppm): ~0.7–1.1 (*m*, 3 H, CH₃); ~1.1–1.5 (*m*, 9 H, 4 CH₂, OH); ~1.5–2.1 (*m*, 6 H, 2 C=CCH₃); 4.00 (*t*, *J* = 6 Hz, 1 H, O–CH); 5.47 (*q*, *J* ~ 6 Hz, 1 H, C=CH).

C₁₀H₂₀O (156.26) Calc. C 76.86 H 12.90% Found C 77.15 H 13.03%

3-Methyl-non-2-en-4-ol (10 g, 64 mmol) and activated MnO₂ (100 g) in anhydrous pentane (600 ml) were stirred for 60 h at 20° under N₂. The oil resulting from usual work-up was distilled at 10 Torr, affording 7.16 g (72%) of (*E*)-3-methyl-non-2-en-4-one (**1**), b.p. 89°; d_4^{20} = 0.865; n_D^{20} = 1.4550. GC. (same conditions as above) indicated this compound to contain about 5% of *Z*-stereoisomer. – IR. (neat): 1670, 1380, 1470, 1075, 1250. – ¹H-NMR.: ~0.6–1.1 (*m*, 3 H, CH₃); 1.1–2.0 (*m*, 6 H, 3 CH₂); 1.77 (*s*, 3 H, C=CCH₃); 1.85 (*d*, *J* = 6 Hz, 3 H, C=CCH₃); 2.65 (*t*, *J* = 7 Hz, 2 H, O=CCH₂); 6.75 (*q*, *J* = 6 Hz, 1 H, C=CH). – MS. (*m/e* (% relative abundance)): 154 (*M*⁺, 1), 139 (16), 98 (34), 83 (100), 55 (73).

C₁₀H₁₈O (154.24) Calc. C 77.86 H 11.76% Found C 77.72 H 11.89%

2. Pentadecan-15-olide (**12**) [16]. MS.: 240 (*M*⁺, 7), 222 (13), 180 (11), 152 (7), 138 (11), 124 (13), 110 (21), 97 (41), 83 (55), 69 (72), 55 (100), 41 (91).

3. 8*a*,13:9*a*,13-Diepoxy-15,16-dinorlabdane (**17**) [18]. ¹H-NMR.: 0.84 (*s*, 3 H, CH₃); 0.91 (*s*, 3 H, CH₃); 0.98 (*s*, 3 H, CH₃); 1.37 (*s*, 3 H, O–CCH₃); 1.51 (*s*, 3 H, O–C(CH₃)–O); ~1.1–2.2 (*m*, 15 H, 7 CH₂, CH). – MS.: 278 (*M*⁺, 23), 236 (13), 218 (20), 203 (14), 175 (11), 162 (7), 151 (15), 138 (14), 123 (34), 109 (63), 99 (23), 95 (28), 81 (16), 69 (24), 55 (21), 43 (100).

4*a*. (*Z*)-Octadec-9-en-18-olide (**18**). BuLi (60 ml of a 7% solution in hexane, 65.5 mmol) was added dropwise at –5°/–10° and under N₂ to 9-acetoxynonyltriphenylphosphonium bromide (**28**) [31] (36.7 g, 69.6 mmol) in anhydrous hexamethylphosphoric acid triamide (HMPA) (105 ml) and tetrahydrofuran (THF) (105 ml) [32]. Stirring was continued for 15 min at –5°, when the mixture was cooled to –60° and methyl 8-formyloctanoate (**29**) [33] (13.1 g, 70.4 mmol) was quickly added. After 15 h further stirring at 20° and 1 h at 50°, the mixture was poured into water (1 l), extracted with ether (3 ×), and washed to neutrality. Usual work-up gave a product (54 g) that was treated (10 ×) with light petroleum (b.p. 30–50°). The resulting soluble fraction (25.6 g) was slowly heated to 100° at 0.001 Torr, kept 5 min at this temperature to remove any volatile material, and refluxed for 3 h with KOH (9 g) in water (45 ml) and methanol (175 ml). Usual separation of neutral and acidic products afforded crude (*Z*)-18-hydroxyoctadec-9-enoic acid (**30**) (13.8 g, 70%). – ¹H-NMR.: 1.3 (narrow *m*, 22 H, 11 CH₂); 1.7–2.1 (*m*, 4 H, 2 C=CCH₂); 2.3 (*t*, *J* = 7 Hz, 2 H, O=CCH₂); 3.6 (*t*, *J* = 5 Hz, 2 H, O–CH₂); 5.3 (*t*, *J* = 5 Hz, 2 H, CH=CH); 8.15 (*s*, 2 H, 2 OH).

Crude **30** (427 mg, 1.43 mmol), 2,2'-dipyridyl disulfide (380 mg, 1.72 mmol), triphenylphosphine (470 mg, 1.79 mmol), in anhydrous benzene (1.5 ml) were kept at 20° for 1.5 h. [26] [27]. The mixture was

then dissolved in anhydrous acetonitrile (35 ml) and added dropwise over 3 h at 65° ($\pm 2^\circ$) to a stirred solution of AgClO_4 (890 mg, 4.3 mmol) in 150 ml of acetonitrile [27]. After 1 h further stirring at 65°, the mixture was cooled and evaporated to dryness *in vacuo*. The residue was taken up in ether (2 \times) and the ethereal solution washed with 5% NaCN (2 \times 20 ml) and water (3 \times). The product (587 mg) resulting from usual work-up was chromatographed on silica gel (10 g) with hexane/toluene mixtures, yielding 196 mg (48%) of (*Z*)-octadec-9-en-18-olide (**18**), b.p. 115°/0.001 Torr; $d_4^{20} = 0.943$; $n_D^{20} = 1.4807$. GC. (OV-101, 6 min at 120°, then 2.5°/min up to 180°, 50 m \times 0.3 mm column) indicated this compound to contain about 5% of *E*-stereoisomer **31**. - IR. (neat): 1735, 1240, 1465. - ¹H-NMR.: 1.33 (narrow *m*, 18 H, 9 CH₂); ~1.5-1.9 (*m*, 4 H, 2 CH₂); 1.9-2.2 (*m*, 4 H, 2 C=CCH₂); 2.35 (*t*, *J* = 6.5 Hz, 2 H, O=CCH₂); 4.14 (*t*, *J* = 5 Hz, 2 H, O-CH₂); 5.35 (sym. *m*, 2 H, CH=CH). - MS. (from GC./MS. coupling): 280 (*M*⁺, 11), 262 (4), 150 (5), 137 (8), 124 (13), 123 (12), 110 (20), 109 (20), 96 (70), 95 (43), 82 (100), 81 (72), 67 (70), 55 (76), 41 (60).

$\text{C}_{18}\text{H}_{32}\text{O}_2$ (280.44) Calc. C 77.09 H 11.50% Found C 77.36 H 11.71%

4b. (*E*)-Octadec-9-en-18-olide (**31**). *Z*-lactone **18** (1.92 g, 6.85 mmol) and diphenyl disulfide (96 mg) in anhydrous benzene (450 ml) were irradiated at 15° and under N₂ with a UV-lamp (type Philips HPK 125) (quartz vessel) [28]. The isomerization process could be conveniently followed by capillary GC. using the conditions given above for **18**. Two further portions of diphenyl disulfide (96 mg each) were added to the reaction mixture after 25 and 45 h of irradiation. After a total of 88 h of irradiation, a photostationary state was reached consisting approximately of 25% of *Z*-lactone **18** and 75% of the desired *E*-stereoisomer **31**. The reaction solution and that resulting from a preliminary isomerization of 1.12 g of **18** were then combined, and the solvent removed *in vacuo*. Chromatography of the product (3.76 g) on silica gel/AgNO₃ 9:1 (120 g) with hexane/ether (99:1 to 9:1) allowed successive elution of pure (*E*)-octadec-9-en-18-olide (**31**) (650 mg), a mixture of **18** and **31** (2.12 g), and pure **18** (312 mg). After rechromatography of the intermediate fraction there was obtained a total yield of 1.41 g (46%) of (*E*)-octadec-9-en-18-olide (**31**), b.p. 109-110°/0.001 Torr; $d_4^{20} = 0.939$; $n_D^{20} = 1.4792$. - IR. (neat): 1735, 1240, 1460, 970. - ¹H-NMR.: 1.33 (narrow *m*, 18 H, 9 CH₂); ~1.5-1.9 (*m*, 4 H, 2 CH₂); 1.9-2.2 (*m*, 4 H, 2 C=CCH₂); 2.35 (*t*, *J* = 6.5 Hz, 2 H, O=CCH₂); 4.14 (*t*, *J* = 5 Hz, 2 H, O-CH₂); 5.34 (sym. *m*, 2 H, CH=CH). - MS.: 280 (*M*⁺, 18), 262 (4), 137 (9), 123 (20), 109 (35), 96 (78), 82 (100), 67 (90), 55 (100), 41 (92).

$\text{C}_{18}\text{H}_{32}\text{O}_2$ (280.44) Calc. C 77.09 H 11.50% Found C 77.27 H 11.24%

5. (*E*)-2-Ethylidene-6,10,14-trimethylpentadecanal (**21**). Farnesol (**32**) (66.6 g, 0.3 mol) in anhydrous ethanol (300 ml) was hydrogenated for 22 h at 20°/830 Torr in the presence of 10% Pt/C (2.5 g) (H₂ uptake 23.7 l or 3.5 equiv.). The resulting product was distilled at 0.001 Torr: fr. 1, b.p. 55-75°, 28.59 g; fr. 2, b.p. 75-98°, 5.24 g; fr. 3, b.p. 98-100°, 30.49 g. Fr. 3 represented hexahydrofarnesol (yield 44%). - IR. (neat): 1470, 3375, 1380, 1060. - ¹H-NMR.: 0.88 (*d*, *J* = 6 Hz, 12 H, 4 CH₃); ~1.0-1.9 (*m*, 17 H, 7 CH₂, 3 CH); 2.0 (*s*, 1 H, OH); 3.65 (*t*, *J* = 6.5 Hz, 2 H, O-CH₂).

p-Toluenesulfonyl chloride (35 g, 183 mmol) was added in several portions over 15 min at 10° to hexahydrofarnesol (40 g, 175 mmol) in anhydrous pyridine (55 ml). After 16 h further stirring at 20° the mixture was poured into ice water (350 ml) and conc. HCl-solution (52.5 ml), extracted with ether (4 \times), and washed with water (1 \times), 5% NaOH (1 \times), and water (1 \times). Usual work-up afforded 59 g (154 mmol, 88%) of crude hexahydrofarnesyl tosylate. This compound and LiBr (16.7 g, 192 mmol) in anhydrous acetone (580 ml) were stirred for 40 h at 20° and under N₂. After solvent removal at 30° *in vacuo*, the product was taken up in ether (2 \times), washed to neutrality, and distilled at 0.001 Torr: fr. 1, b.p. 48-74°, 1.25 g; fr. 2, b.p. 74-79°, 0.84 g; fr. 3, b.p. 79-93°, 40.40 g. Fr. 3 represented hexahydrofarnesyl bromide (**33**) (yield 79%). - IR. (neat): 1465, 1375. - ¹H-NMR.: 0.88 (*d*, *J* = 5.5 Hz, 12 H, 4 CH₃); ~1.0-2.2 (*m*, 17 H, 7 CH₂, 3 CH); 3.40 (*t*, *J* = 7 Hz, 2 H, Br-CH₂).

Small chips of Li (1.3 g, 187 mmol), freshly distilled diethylamine (12.15 g, 166 mmol), HMPA (34.7 ml), and anhydrous benzene (31 ml) were stirred for 2 h at 18° and under N₂. THF (42 ml) was added to the mixture, followed by imino-acetal **34** [29] (27.62 g, 138 mmol, in 41 ml of THF) over 10 min at -60°. After 1 h further stirring at -50°, hexahydrofarnesyl bromide (**33**) (40.38 g, 138 mmol, in 21 ml of THF) was in turn added over 20 min at -20°. The stirring was continued for 16 h at 20°, when the mixture was poured into ice water, extracted twice with ether, washed to

neutrality, and evaporated to dryness *in vacuo*. The crude product was taken up in THF (350 ml), 2*N* HCl (208 ml) was quickly added, and the mixture was stirred for 2 min. Ethereal extraction (2×, 5% NaHCO₃ and water washings) afforded an oil (54.7 g) that was distilled at 0.001 Torr: fr. 1, b.p. 32–85°, 4.66 g; fr. 2, b.p. 85–134°, 6.16 g; fr. 3, b.p. 134–135°, 31.72 g. Fr. 2 and 3 corresponded to keto-acetal **35** (yield 83%); $d_4^{20} = 0.897$; $n_D^{20} = 1.4454$. - IR. (neat): 1075, 1725, 1465. - ¹H-NMR.: 0.87 (*d*, *J* = 5.5 Hz, 12 H, 4 CH₃); ~1.0–2.0 (*m*, 19 H, 8 CH₂, 3 CH); 2.53 (*t*, *J* = 6.5 Hz, 2 H, O=CCH₂); 3.38 (*s*, 6 H, 2 O-CH₃); 4.42 (*s*, 1 H, O-CH-O).

C₂₀H₄₀O₃ (328.52) Calc. C 73.12 H 12.27% Found C 73.31 H 12.29%

BuLi in hexane (67.1 ml of a 1.3*M* solution, 87.2 mmol) was added over 10 min at 20° and under N₂ to a slurry of ethyltriphenylphosphonium bromide (33.7 g, 90.8 mmol) in anhydrous ether (300 ml). After 1 h further stirring, keto-acetal **35** (22.9 g, 69.8 mmol, in 300 ml of anhydrous ether) was added over 30 min at 20°. The stirring was continued for 15 h at 20° when the reaction mixture was quenched with anhydrous acetone (10 ml) and evaporated to dryness *in vacuo*. The crude product was taken up in hexane, the insoluble white material removed by filtration, and the clear filtrate concentrated to dryness *in vacuo*. The remaining oil (23.39 g) was stirred for 4 h at 20° in acetone (170 ml) containing 2*N* H₂SO₄ (18.35 ml). After addition of a slight excess of 5% NaHCO₃-solution, the solvent was removed *in vacuo*, and the residue was extracted twice with ether and washed to neutrality. The product was distilled at 0.001 Torr: b.p. 114–118°, 14.36 g. Chromatography of the distillate on silica gel (300 g) with pure toluene followed by toluene/ethyl acetate 98:2 finally afforded (*E*)-2-ethylidene-6,10,14-trimethylpentadecanal (**21**), b.p. 112–118°/0.001 Torr, 9.35 g (45.5%); $d_4^{20} = 0.851$; $n_D^{20} = 1.4620$. - IR. (neat): 1685, 1460, 1375, 1640, 2725, 830. - ¹H-NMR.: 0.86 (*d*, *J* = 6 Hz, probably 3 H, CH₃); 0.90 (*d*, *J* = 6 Hz, probably 9 H, 3 CH₃); ~0.8–1.9 (*m*, 19 H, 8 CH₂, 3 CH); 2.01 (*d*, *J* = 7.5 Hz, 3 H, C=CCH₃); 2.1–2.4 (*m*, 2 H, C=CCH₂); 6.57 (*q*, *J* = 7 Hz, 1 H, C=CH); 9.37 (*s*, 1 H, O=CH). - MS. (from GC/MS. coupling): 294 (*M*⁺, 4), 140 (32), 111 (100), 98 (74), 83 (33), 69 (45), 57 (72), 43 (79).

C₂₀H₃₈O (294.50) Calc. C 81.56 H 13.01% Found C 81.60 H 13.04%

6. (*E*)-1-(2,3,6-Trimethylphenyl)-but-2-en-1-one (**3**). For spectral data see [13].

7. *Drim-8-en-11-al* (**9**) [15]. - MS.: 220 (*M*⁺, 50), 205 (49), 191 (95), 149 (35), 135 (59), 121 (81), 109 (100), 95 (93), 81 (60), 69 (64), 55 (80), 43 (78), 41 (85).

8. *13,14,15,16-Tetranorlabd-8-en-12-al* (**10**) [16]. - ¹H-NMR.: 0.85 (*s*, 3 H, CH₃); 0.92 (*s*, 3 H, CH₃); 0.95 (*s*, 3 H, CH₃); 1.55 (*s*, 3 H, C=CCH₃); ~0.8–2.0 (*m*, 9 H, 4 CH₂, CH); 2.1 (*m*, 2 H, C=CCH₂); 3.10 (broad *s*, 2 H, C=CCH₂C=O); 9.55 (*t*, *J* = 2 Hz, 1 H, O=CH).

9. *13,14,15,16-Tetranorlabd-8(17)-en-12-al* (**11**) [16]. - ¹H-NMR. 0.70 (*s*, 3 H, CH₃); 0.82 (*s*, 3 H, CH₃); 0.89 (*s*, 3 H, CH₃); ~1.0–2.3 (*m*, 10 H, 4 CH₂, 2 CH); 2.45 (*m*, 4 H, O=CCH₂, C=CCH₂); 4.40 and 4.82 (2*s*, 1 H each, C=CH₂); 9.65 (*t*, *J* ~ 1.5 Hz, 1 H, O=CH).

10. *15,16-Dinorlabd-8-en-13-one* (**14**) [18]. - MS.: 262 (*M*⁺, 3), 229 (25), 204 (20), 189 (41), 133 (23), 121 (41), 105 (26), 95 (41), 81 (19), 69 (36), 55 (33), 43 (100), 41 (60).

11. *15,16-Dinorlabd-8(17)-en-13-one* (**15**) [16]. - MS.: 262 (*M*⁺, 16), 247 (16), 229 (18), 204 (28), 177 (25), 137 (85), 107 (39), 95 (58), 81 (62), 69 (49), 55 (40), 43 (100), 41 (60).

12. *8,13-Epoxy-15,16-dinorlabdane* (**16**). For spectral data see [19].

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