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Tobacco Chemistry

18. Absolute Configuration of (9*R*)-9-Hydroxy-4,7*E*-megastigmadien-3-one (3-Oxo-α-ionol)

ARNE J. AASEN, BJARNE KIMLAND and CURT R. ENZELL

Research Department, Swedish Tobacco Co., S-104 62 Stockholm 17, Sweden

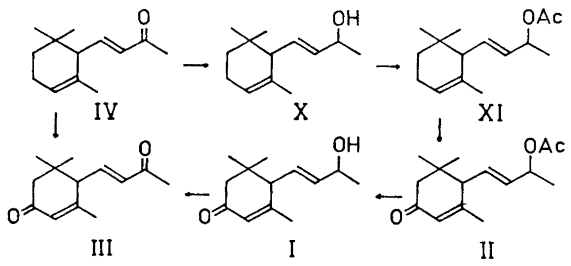
The absolute configuration of (9*R*)-9-hydroxy-4,7-*E*-megastigmadien-3-one has been shown to be R both in position 6 and 9. The MS fragmentation and possible biogenesis of this compound is discussed.

In a recent publication in this series dealing with the volatile constituents of Greek tobacco, *Nicotiana tabacum* L., the structure of one of the major neutral components (3-oxo-α-ionol), now named* (9*R*)-9-hydroxy-4,7*E*-megastigmadien-3-one (I),[1] was reported but without stereochemical assignments.[2] Subsequent studies have revealed the absolute configuration at the two asymmetric centres in this compound and the results are discussed below.

The structure (I) was deduced principally from MS ($C_{13}H_{20}O_2$, accurate mass measurement), UV (235 nm, disubst, conj. ketone), and IR data (3400 cm^{-1}, OH; 1657 cm^{-1}, conj. C=O; 1376 and 1369 cm^{-1}, *gem.* dimethyl; 976 cm^{-1}, *trans* disubst. C=C) and from NMR data of this compound, its acetate (II) and the corresponding diketone (III) as detailed in Table 1 (*cf.* Experimental). The spectral assignments were confirmed by comparison with synthetic (±)-9-hydroxy-4,7*E*-megastigmadien-3-one (I), the corresponding acetate (II) and diketone (III) which were prepared from (±)-*trans*-α-ionone (IV) as indicated in Scheme 1. The diketone (III) has previously been prepared from (±)-*trans*-α-ionone by Prelog and Osgan [3] and later by Roberts [4] who also obtained (±)-9-hydroxy-4,7*E*-megastigmadien-3-one (I), without characterization, as an intermediate in the synthesis of a tobacco additive.

Stereochemistry. (9*R*)-9-Hydroxy-4,7*E*-megastigmadien-3-one (I) isolated from tobacco displayed a fairly high optical rotation ($[\alpha]_D + 177°$) due to the two asymmetric centres, C(6) and C(9). Oxidation of this compound under mild conditions employing a two phase system [5] furnished the optically active diketone III, which exhibited a rotation ($[\alpha]_D + 293°$) very similar to that of the same diketone ($[\alpha]_D + 299°$) prepared from (+)-*trans*-α-ionone (IV). Since

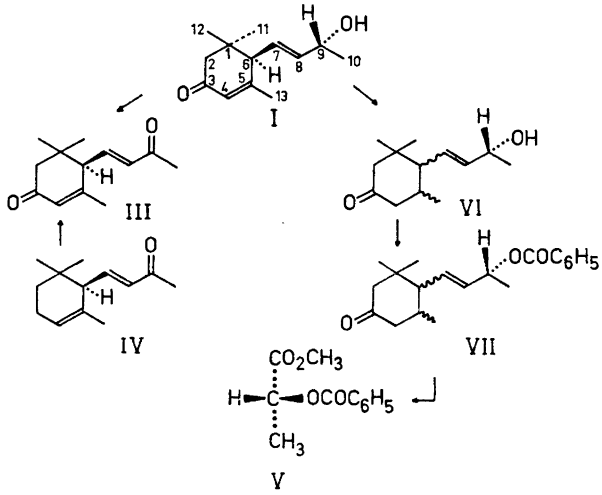
* Nomenclature and stereochemistry as defined in Ref. 1.



Scheme 1.

the absolute configuration of (+)-*trans*-α-ionone has recently been shown to be *R* by Eugster *et al.*[6] by correlating (−)-*trans*-α-ionone with (+)-manool, it follows that the configuration at C(6) is *R* in the tobacco isolate.

It may be noted that although the rotations of our 4,7*E*-megastigmadien-3,9-dione (III) preparations were higher than that reported by Buchecker *et al.*[7] for this compound ($[\alpha]_D + 235°$), the activity of an optically pure specimen might be still higher since the C(6) proton is labile as demonstrated by the fact that almost complete racemization was observed even under mild conditions such as oxidation of the alcohol function of the natural compound under Jones' conditions, which do not normally cause racemization.[8] The lability of this proton might account for the somewhat varying specific rotations reported for (+)-*trans*-α-ionone (IV, see Experimental).[9–11] It cannot be excluded that some racemization might have occurred at C(6) in (9*R*)-9-hydroxy-4,7*E*-megastigmadien-3-one (I) during its isolation from tobacco since alkali was used in the separation of the organic acids from the extracts.



Scheme 2.

The absolute configuration at C(9) was shown to be *R* by comparison of methyl benzoyloxypropanoates (V) derived on the one hand from I, and on the other from (*S*)-lactic acid (L(+)-lactic acid). Selective catalytic hydrogenation of the 4,5-double bond of I under alkaline conditions [12] followed by conversion of the resulting dihydro compound (VI) to the corresponding benzoate (VII) was performed to simplify the isolation of the lactic acid derivative in the subsequent ozonolytic cleavage of the side chain double bond. The ozonolysis of the benzoate (VII) was carried out in methanol at $-70°$ and methyl benzoyloxypropanoate (V), exhibiting a negative rotation ($[\alpha]_D$ $-8.5°$), was obtained after successive treatment with performic acid and diazomethane. The optical activity of the product (V), when compared with that of methyl (2*S*)-2-benzoyloxypropanoate ($[\alpha]_D + 13.9°$) indicated a preponderance of the *R*-isomer to the *S*-isomer of 4:1.

This result is consistent with the fact that the NMR spectrum of the tobacco isolate after the addition of $Eu(DPM)_3$ revealed the presence of two diastereoisomers in the ratio 3:1. It may be concluded therefore that in addition to the main constituent, (9*R*)-9-hydroxy-4,7*E*-megastigmadien-3-one (I), there is some 20 % of the 9*S*-epimer present in this tobacco and eventually, but less likely, minor amounts of the 6*S*-isomer.

Mass spectra. The main feature of the mass spectra of (9*R*)-9-hydroxy-4,7*E*-megastigmadien-3-one (I) and 4,7*E*-megastigmadien-3,9-dione (III) is the dominance of the *m/e* 108 ion for which fragment the genesis shown in Scheme 3 may be invoked. The initial loss of 56 mass units, corresponding to C_4H_8, is readily explained by fissions of the 2,3-bond (α-cleavage) and the doubly allylic 1,6-bond. Subsequent cyclization of the resulting ions, *m/e* 152 and 150, accompanied by expulsion of acetaldehyde and ketene, respectively, yield the stable *m/e* 108 ion corresponding to *m*-cresol. Appropriate metastable peaks were observed for the latter transitions, and the elemental compositions of these ions were confirmed by high resolution mass spectrometry. Replacement of the hydroxyl proton in I by deuterium caused a shift of the base peak and the *m/e* 152 peak by one mass unit supporting the proposed mechanism.

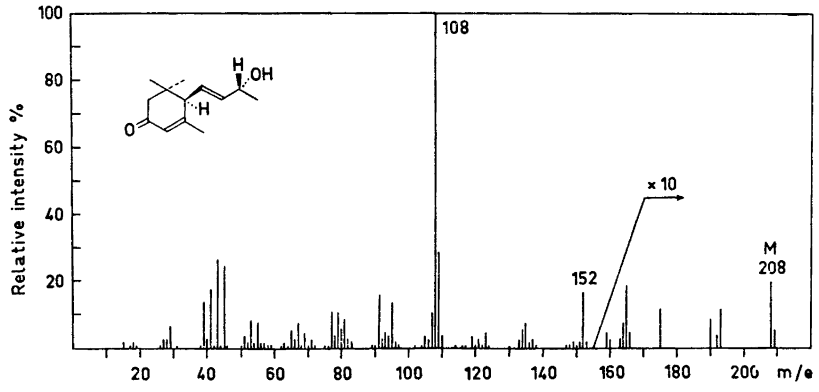
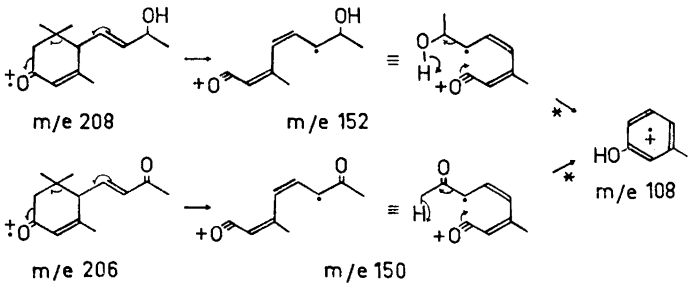


Fig. 1.

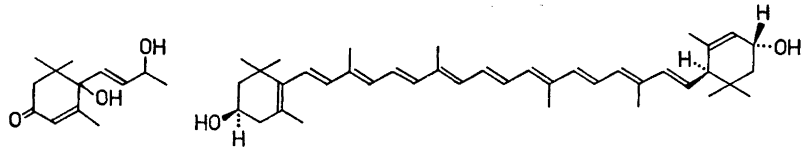


Scheme 3.

Biosynthetic considerations. It has previously been suggested that many isoprenoid cyclic and acyclic tobacco constituents might have higher terpenoids as precursors.[13,14] The constitution of the present compound (I) indicates that it is possibly derived from carotenoids. It is noteworthy that carotenoids like α-carotene [6] and lutein [7,15,16] (VIII) which are both known to be present in tobacco,[17] possess the same absolute configuration in position 6 as the new tobacco compound. (9*R*)-9-Hydroxy-4,7*E*-megastigmadien-3-one (I) might in turn be the precursor of the recently described megastigmatrienones which have been isolated from the same tobacco.[1]

Prelog *et al.*[18,19] studied the fate of α-ionone (IV) when fed to rabbits and they found that an oxygen atom was introduced into position 3. The structure of the product(s) was not determined. Since α-ionone (IV) is not known to be a tobacco constituent,[20] (9*R*)-9-hydroxy-4,7*E*-megastigmadien-3-one (I) might rather originate from hydroxylated carotenoids.

Very recently a structurally related compound, vomifoliol (IX), has been isolated from *Rauwolfia vomitoria*,[21] *Croton sparsiflorus*,[22] and *Podocarpus blumei*.[23] In the last case it was given the name 'blumenol A'.



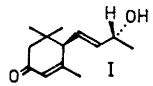
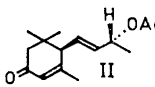
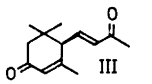
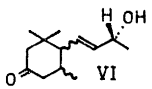
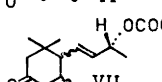
IX VIII

EXPERIMENTAL

NMR spectra were recorded on a Varian A60-A instrument using $CDCl_3$ as solvent, unless otherwise stated, and TMS as internal reference. Mass spectra were obtained on an LKB 9000 instrument operated at 70 eV. IR and UV spectra were recorded on a Perkin-Elmer 257 and a Beckman DK-2A instrument. Optical activities were measured on a Perkin-Elmer 141 polarimeter. Melting points were determined on a Leitz Wetzlar instrument and are uncorrected. Accurate mass determinations were carried out at the Laboratory for Mass Spectrometry, Karolinska Institutet, Stockholm.

Isolation. (9*R*)-9-Hydroxy-4,7*E*-megastigmadien-3-one (I) was isolated from an extract of 295 kg sun-cured Greek tobacco, grown in Serres 1968. The fractionation of this extract

Table 1. NMR data of megastigmane derivatives.

Compound	Chemical shifts[a] H-2	H-4	H-5	H-6	H-7	H-8	H-9	H-10	H-11	H-12	H-13
 I	2.06 2.32 AB (16.5)	5.89 q (1.4)	–	2.51 m (7.8)	5.50 m (8[e],15)	5.70 m (5.5[e],15)	4.33 m (5.3)	1.31 d (6.3)	0.99 s	1.04 s	1.91 d (1.4)
 II [b]	2.17 2.25 AB (*ca.* 16)	5.95 q (1.5)	–	2.58 m	*ca.* 5.65 m	*ca.* 5.65 m	*ca.* 5.5 m	1.33 d (6.0)	0.97 s	1.05 s	1.90 d (1.5)
 III	2.32 2.25 AB (16)	(6.04 q (1.5)	–	2.78 d (9.0)	6.72 q (9,15.5)	6.18 d (15.5)	–	2.32 s	1.05 s	1.11 s	1.94 d (1.5)
 VI	2.1–2.5 m		1.2–2.0 m		*ca.* 5.7 m	*ca.* 5.7 m	4.4 m	1.27 d (6.5)	0.85–1.0 m		
 VII [c]	2.2–2.4 m		1.3–2.0 m		*ca.* 5.7 m	*ca.* 5.7 m	*ca.* 5.4 m	1.49 d (6.5)	0.8–1.0 m		

[a] Chemical shifts in ppm. Coupling constants (in Hz) in parenthesis. Multiplicity of signal: AB = AB-pattern, s = singlet, d = doublet, q = quartet, m = multiplet. [b] CH_3CO at δ 2.05 (s) [c] C_6H_5 at δ 7.5 (3H,m) and δ 8.05 (2H,m) [e] Measured after addition of $Eu(DPM)_3$.

into ten main subfractions, B1–B10, has been described in detail elsewhere.[24] 3 g of fraction B9 (6.9 g) was chromatographed on a column containing 210 g silica gel impregnated with silver nitrate[25] using ether-pentane mixtures as eluents. The main fraction (1.32 g), eluted with 60 % ether in pentane, was rechromatographed on 100 g silica gel. Fraction 4 (506 mg) appeared to be homogeneous by thin layer chromatography (TLC) but it could not be induced to crystallize; $[\alpha]_D^{20}$ +177° (*c* 1.5 in $CHCl_3$); λ_{max} (EtOH) 235 nm (ε 9000); ν_{max}(film) 3400 (broad), 2960 (s), 2865 (m), 1657 (s), 1630 (shoulder), 1376 (m), 1369 (m), 1253 (m), 1140 (m), 1065 (m), 976 (m) cm^{-1}; MS: 208 (M^+, 2), 108 (100), 109 (28), 43 (26), 45 (25), 41 (18), 152 (17), 91 (16), 95 (14), 39 (14), 107 (11), 77 (11), 79 (11), 81 (9), 53 (9); accurate mass determinations: *m/e* 208.1457, $C_{13}H_{20}O_2$ requires 208.1463; *m/e* 152.0823, $C_9H_{12}O$ requires 152.0837; *m/e* 108.0563, C_7H_8O requires 108.0575; NMR, see Table 1.

*(9*R)-9-*Acetoxy-4,7*E-*megastigmadien-3-one (II).* Acetic anhydride (1.5 ml) was added to a solution of the tobacco compound (I, 59 mg) in dry pyridine (3.5 ml) and kept at room temperature for 2 h. Excess anhydride was destroyed by addition of a few drops of methanol, followed by dilution with water and extraction with ether. The ether solution was washed with dilute acid (HCl), water, and evaporated. Chromatography on silica gel gave TLC pure acetate (II, 37 mg) as a colourless oil. ν_{max}(film) 2960 (s), 2940 (s), 2870 (m), 1735 (s), 1665 (s), 1630 (m), 1440 (m), 1370 (s), 1240 (s), 1145 (m), 1045 (s), 978 (m), 953 (m), 913 (m) cm^{-1}; MS: 250 (M^+, 2), 108 (100), 43 (100), 134 (85), 91 (45), 41 (32), 77 (20), 79 (20), 69 (18), 190 (18), 55 (17), 51 (15); NMR, see Table 1.

*4,7*E-*Megastigmadien-3,9-dione (III).* Treatment of natural (9*R*)-9-hydroxy-4,7*E*-megastigmadien-3-one (I) with Jones' reagent [8] furnished the corresponding, almost completely racemic diketone (III), while the optically active compound was obtained when employing the two-phase system recently communicated by Brown *et al.*[5] To the alcohol (I, 140 mg) in ether (30 ml) was added 0.8 ml of a solution containing sodium dichromate (1 g), water (5 ml) and sulphuric acid (1.36 g). After stirring for 1 h at room temperature water was added and the mixture extracted with ether. The ether solution was washed with water, dried and evaporated. The product (116 mg) was purified on a silica gel column to give TLC pure diketone (III, 73 mg). M.p. 74–75°; $[\alpha]_D^{20}$ +293° (*c* 1.0 in $CHCl_3$), lit.[7] $[\alpha]_D^{20}$ +235 (EtOH); λ_{max}(EtOH) 236 nm (ε 21 400), [lit.[3] *ca.* 236 nm (ε *ca.* 21 000)]; The infrared spectrum was closely similar to that (in nujol) published by Prelog and Osgan [3] and indistinguishable from that obtained for an authentic sample [3] recorded under indentical conditions (KBr); MS: 206 (M^+, 2), 108 (100), 43 (62), 150 (21), 109 (18), 77 (9), 107 (7), 39 (6), 41 (6), 79 (5); NMR, see Table 1. When acetone-d_6 was used as solvent, the four-proton signal at δ 2.32 in the $CDCl_3$-spectrum was resolved into a three-proton singlet at δ 2.28 and a one-proton doublet at δ 2.37 (AB-system).

*Preparation of (±)-9-acetoxy-4,7*E-*megastigmadien-3-one (II).* (±)-*trans*-α-Ionone (IV, 5 g) and sodium borohydride (290 mg) in ethanol (50 ml) were stirred for 3 h at room temperature. The mixture was diluted with water and extracted with ether which was dried and evaporated. The product was purified on a silica gel column to give the corresponding alcohol (X, 3.19 g). This (350 mg) was treated with acetic anhydride (1.5 ml) in pyridine (3 ml) at room temperature for 4 h and excess anhydride subsequently removed by the addition of a few drops of methanol. The acetate XI (366 mg) was isolated and purified as described above for II derived from the natural compound. Both the alcohol (X) and the acetate (XI) exhibited appropriate NMR spectra. Chromium trioxide (170 mg) was added to a solution of the acetate (XI, 200 mg) in acetic acid (5 ml). The mixture was stirred for 2 h at room temperature, diluted with water and extracted with ether. The residue obtained after removal of the solvent was chromatographed on a silica gel column to give homogeneous (±)-9-acetoxy-4,7*E*-megastigmadien-3-one (II, 36 mg). The physical properties of the product (NMR, IR, MS) were identical to those given above for II derived from natural (9*R*)-9-hydroxy-4,7*E*-megastigmadien-3-one (I).

*Preparation of (±)-9-hydroxy-4,7*E-*megastigmadien-3-one (I).* The ketoacetate II (25 mg) was saponified by treatment with 2 % KOH in methanol (5 ml) for 30 min. The mixture was diluted with water and extracted with ether. Removal of the solvent followed by purification on a silica gel column yielded the ketoalcohol I (12 mg). The spectral (NMR, IR, MS, UV) and chromatographic properties of the product were indistinguishable from those of the tobacco constituent except for being racemic.

*Preparation of 4,7*E-*megastigmadien-3,9-dione (III).* (±)-*trans*-α-Ionone (IV, 1 g) was added to a solution of chromium trioxide (1 g) in acetic acid (16 ml) and stirred

at ambient temperature for 6 h. Work up as outlined above for (±)-9-acetoxy-4,7*E*-megastigmadien-3-one (II) gave the desired dione III (80 mg). M.p. 73 – 73.5°, undepressed when admixed with authentic [3] material. NMR, IR, UV, and mass spectra were superimposable on those of the diketone derived from the natural ketoalcohol (I). Optically active 4,7*E*-megastigmadien-3,9-dione (III) was prepared from (*R*)-*trans*-α-ionone (IV, 300 mg) and chromium trioxide (400 mg) in acetic acid (10 ml). The product (III, 58 mg) was isolated and purified as detailed above. M.p. 73°; $[\alpha]_D^{20}$ +299° (*c* 0.7 in $CHCl_3$). The (*R*)-*trans*-α-ionone (IV) was obtained from its racemate using the method of Sobotka *et al.*[9] (±)-*trans*-α-Ionone (IV, 57.6 g) was reacted with (−)-menthydrazide[26] (64.2 g) to give the corresponding menthydrazones. (+)-*trans*-α-Ionone (−)-menthydrazone (3.7 g) having constant rotation and melting point was obtained after recrystallization nineteen times from ethanol. M.p. 182 – 183°, [lit. 176°,[9] 178.5°,[10] 183°[11]]; $[\alpha]_D^{20}$ +229° (*c* 1.5 in EtOH), [lit. +230° (EtOH),[9] +232° (C_6H_6),[10] +245° (EtOH)[11]]. In contrast to us Sobotka *et al.*[9] found (−)-*trans*-α-ionone (−)-menthydrazone to be the least soluble of these diastereoisomers. The hydrazone was hydrolyzed by subjecting it to steam distillation in the presence of phthalic anhydride. The distillate was extracted with ether which was dried and evaporated to give (+)-*trans*-α-ionone (IV, 1.6 g). $[\alpha]_D^{20}$ +369° (*c* 3.8 in EtOH), lit. +347° (EtOH),[9] +401° (C_6H_6),[10] +415° (EtOH).[11] The NMR spectrum was superimposable on that of racemic IV.

*(9*R*)-5ξ,6ξ-9-Hydroxy-7*E*-megastigmen-3-one (VI).* (9*R*)-9-Hydroxy-4,7*E*-megastigmadien-3-one (I, 300 mg) in 0.3 N NaOH/EtOH (5 ml) was hydrogenated at ambient temperature and atmospheric pressure in the presence of 10 % Pd/C (75 mg).[12] The theoretical amount of hydrogen was consumed in 2 h, after which the solution was extracted with ether. Removal of the solvent left a colourless oil (305 mg). $[\alpha]_D^{20}$ +4.3° (*c* 1.5 in $CHCl_3$); NMR, see Table 1.

*(9*R*)-5ξ,6ξ-9-Benzoyloxy-7*E*-megastigmen-3-one (VII).* (9*R*)-5ξ,6ξ-9-Hydroxy-7*E*-megastigmen-3-one (VI, 298 mg) and benzoyl chloride (300 mg) in dry pyridine (10 ml) were kept at room temperature overnight. The mixture was diluted with water and extracted with ether. The extract was washed with 5 % H_2SO_4, 5 % $NaHCO_3$, water, and dried over sodium sulphate. Removal of the solvent, followed by chromatography on silica gelfurnished the benzoate VII as a colourless oil (225 mg). $[\alpha]_D^{20}$ −10.4° (*c* 0.8 in $CHCl_3$); NMR, see Table 1.

*Ozonolysis of (9*R*)-5ξ,6ξ-9-benzoyloxy-7*E*-megastigmen-3-one (VII).* The benzoate VII (210 mg) dissolved in methanol (10 ml) was treated with excess ozone at −65° for 10 min. The reaction mixture was allowed to reach room temperature and the solvent distilled *in vacuo* to leave a colourless oil to which was added a mixture of formic acid (7 ml) and 30 % H_2O_2 (4 ml).[27] The mixture was refluxed for 30 min, cooled and extracted with ether. The extract was dried with sodium sulphate and concentrated *in vacuo*. Most of the formic acid which had been extracted, was distilled and the residue was treated with excess diazomethane in ether at room temperature for 10 min. Removal of solvent and excess reagent left a colourless oil which was chromatographed on a silica gel column. Elution with 7 % ether in pentane furnished pure methyl 2-benzoyloxypropanoate (V, 34 mg, 25 %). $[\alpha]_D^{20}$ −8.5° (*c* 1.0 in $CHCl_3$); δ 1.61 (3H, d, *J* 7.1 Hz), 3.76 (3H, s), 5.35 (1 H, quartet, *J* 7.1 Hz), 7.52 (3H, m), *ca.* 8.07 (2H, m); ν_{max}(film) 1759 (s), 1725 (s), 1604 (m), 1453 (s), 1360 (m), 1320 (m), 1273 (s), 1218 (s), 1179 (m), 1114 (s), 1072 (m), 1049 (m), 1028 (m), 971 (w), 859 (w), 838 (w), 717 (s), 691 (w) cm^{-1}.

*Methyl (2*S*)-2-benzoyloxypropanoate (V)* (a) Crystalline (*S*)-lactic acid (L(+)-lactic acid, 150 mg, Sigma No. L 1750) was methylated with excess diazomethane in ether solution. After standing for 10 min, the solvent was removed by distillation and the residue chromatographed on a silica gel column. Elution with 15 % ether in pentane gave pure methyl (2*S*)-2-hydroxypropanoate. $[\alpha]_D^{20}$ −13.3° (*c* 2.6 in ether), [lit.[28] −9.5° (neat)]; δ 1.4 (3 H, d, *J* 7 Hz), 3.5 (OH), 3.78 (3H, s), 4.31 (1 H, quartet, *J* 7 Hz). The methyl ester was dissolved in dry pyridine (5 ml) and benzoyl chloride (100 mg) and kept at room temperature overnight. The product was isolated as described above for VII and chromatographed on a silica gel column to give pure methyl (2*S*)-2-benzoyloxypropanoate (V, 135 mg). $[\alpha]_D^{20}$ +13.9° (*c* 4,5 in $CHCl_3$). NMR and IR spectra were identical to those of the corresponding compound derived from (9*R*)-5ξ,6ξ-9-benzoyloxy-7*E*-megastigmen-3-one (VII). (b) 90 % (*S*)-Lactic acid (2 g, Fluka No. 69773) was dissolved in methanol (100 ml) and refluxed for 24 h in the presence of H_2SO_4 (0.2 ml). The solvent was distilled off and the residue extracted with ether. The extract was washed with water, 5 % $NaHCO_3$, and subsequently

distilled. The methyl ester (300 mg, $[\alpha]_D^{20}$ −16.4° (*c* 2.8 in EtOH)) was dissolved in dry pyridine (5 ml) and treated with benzoyl chloride (300 mg) at room temperature overnight followed by isolation and chromatography as described above. $[\alpha]_D^{20}$ +11.2° (*c* 1.3 in $CHCl_3$). NMR and IR spectra were identical to those of the compound derived from VII.

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