

Fungal Carotenoids

9.* Total Synthesis of Aleuriaxanthin

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The total synthesis of aleuriaxanthin acetate (8, 13 % over-all yield) and aleuriaxanthin (9, 1',2'-dihydro-1',16'-didehydro- β,ψ -carotene-2'-ol) starting with linalool (1) is reported. Photosensitised autoxidation of linalool (1) constituted the key step.

Comparison of the synthetic pigments with those of natural origin proved their identity.

We have recently reported on the structure elucidation of aleuriaxanthin (9, 1',2'-dihydro-1',16'-didehydro- β,ψ -carotene-2'-ol)¹ which is the major xanthophyll of the ascomycete *Aleuria (Peziza) aurantia* of the family Pezizaceae.²

Aleuriaxanthin (9) contains an end group with a terminal methylene and an allylic hydroxyl, which has so far not been encountered in carotenoids, although other natural products with this type of end group have been isolated.^{3,4} Among the carotenoids terminal methylene groups have so far been encountered in bicyclic carotenes isolated from the fungus *Caloscypha fulgens*⁵ and the aphid *Macrosiphium liriodendri*.⁶ The structures of these carotenes have been confirmed by total synthesis.⁷

We now report a total synthesis of aleuriaxanthin (9) hereby confirming the structure assigned to this new fungal carotenoid.

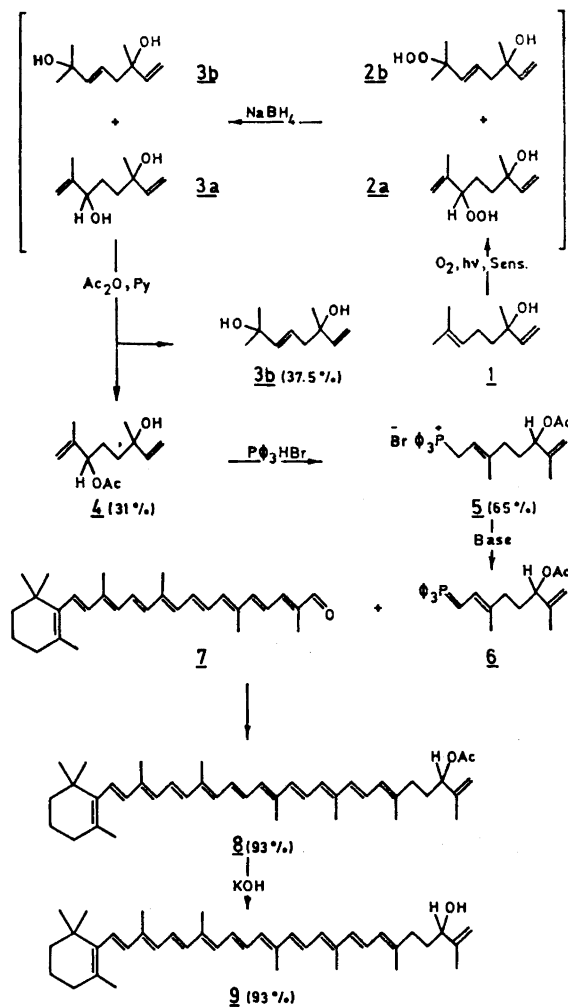
RESULTS AND DISCUSSION

For the synthetic formation of the desired end group photosensitised autoxidation of an isopropylidene structural element seemed to offer advantages over more conventional approaches.⁴ Due to the relative reaction rates of tetra-, tri-, di-, and mono-substituted olefins with singlet oxygen⁸

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specific reaction of the tri-substituted double bond of linalool (*1*) was considered feasible.

The synthesis of aleuriaxanthin (*9*) via the acetate (*8*) is depicted in Scheme 1, including yields.



Scheme 1.

Linalool (*1*) was autoxidised with methylene blue as sensitizer to afford a *ca.* 1:1 mixture of the hydroperoxides *2a* and *2b*. This mixture was reduced with sodium borohydride to give a mixture of the diols *3a* and *3b* which on acetylation provided the acetate *4* and unreacted *3b*. The diol *3b* and

the acetate **4** were separated by column chromatography on silica. The acetate **4** was reacted with triphenylphosphonium bromide to give the phosphonium salt **5**. Condensation of the ylid **6**, generated *in situ* from **5** through the action of an appropriate base, with 8'-apo- β -caroten-8'-al (**7**) afforded a mixture of aleuriaxanthin acetate (**8**) and free aleuriaxanthin (**9**). Judged by the PMR spectrum the phosphonium salt **5** appeared to be homogeneous and it was therefore assumed that the acetoxy function had suffered nucleophilic attack by the base. In order to check this assumption bases of different nucleophilicity were employed. When butyl lithium was used **8** and **9** were obtained in a 20:80 ratio; with trityl lithium the ratio was 63:37 and with sodium hydride in a heterogeneous system the acetate **8** only was obtained. These results confirmed that the presence of free aleuriaxanthin (**9**) in the reaction mixture could be ascribed to nucleophilic attack by the base and was not due to an inhomogeneous phosphonium salt.

Aleuriaxanthin acetate (**8**), obtained as thin plates of m.p. 133–134°C from acetone-methanol, had identical physical properties, including mixed melting point and adsorptive properties, with aleuriaxanthin acetate derived from the natural carotenoid. The visible light absorption spectrum is reproduced in Fig. 1. Apart from the common carotenoid CH absorptions the

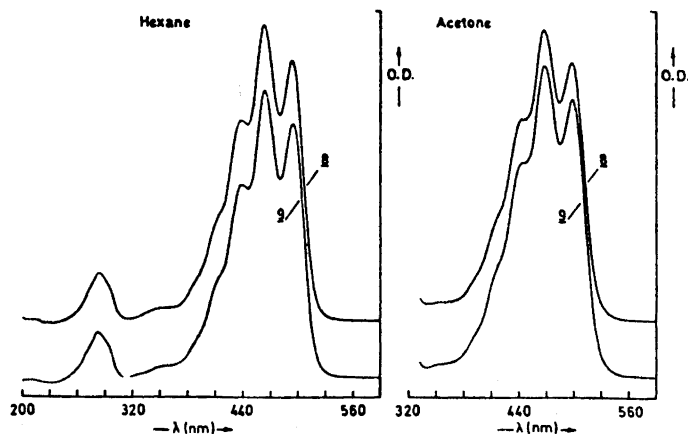


Fig. 1. Absorption spectrum in visible light of synthetic aleuriaxanthin acetate (**8**) and synthetic aleuriaxanthin (**9**) in hexane and acetone solutions.

IR spectrum exhibited acetate carbonyl frequency at 1735 cm^{-1} and an absorption at 900 cm^{-1} caused by the terminal methylene group and was indistinguishable from that of the acetate derived from natural aleuriaxanthin. The PMR spectrum (Fig. 2) exhibited the spectral characteristics which were expected.¹ The methine and terminal methylene signals at τ 4.86 and 5.04, respectively, correspond well with the values obtained for other compounds with this type of end group.³ Addition of $\text{Eu}(\text{dpm})_3$ ⁹ to the PMR sample caused all the signals assigned to the oxygenated end group to move down-

field, thereby confirming the assignments, whereas the signals from the polyene chain and the cyclic end group remained virtually unshifted. The induced shifts relative (in per cent) to the induced shift of the 17'-methyl group were as follows (*cf.* Ref. 10): 16'-H₂ (135 and 61.2), 17'-H₃ (100), 2'-H (491), 18'-H₃ (25.5), 19'-H₃ (0.0), 20'-H₃ (0.0), 20-H₃ (0.0), 19-H₃ (0.0), 18-H₃ (0.0), 16,17-H₆ (0.0), acetate-CH₃ (307).

The mass spectrum (Fig. 3) had the molecular ion at m/e 594.4432 (calc. for C₄₂H₅₈O₂ 594.4436) and fragments at m/e 502, 488, and 436 corresponding to the common losses of toluene, xylene, and dimethylcyclodecapentaene,

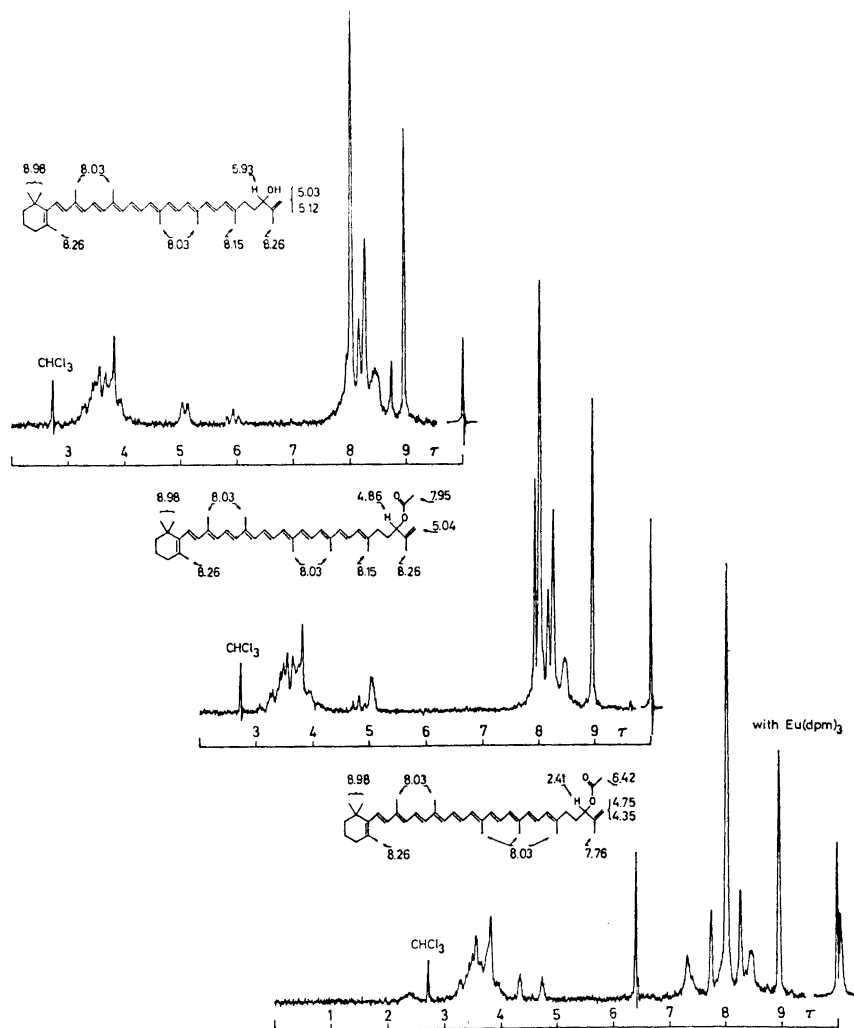
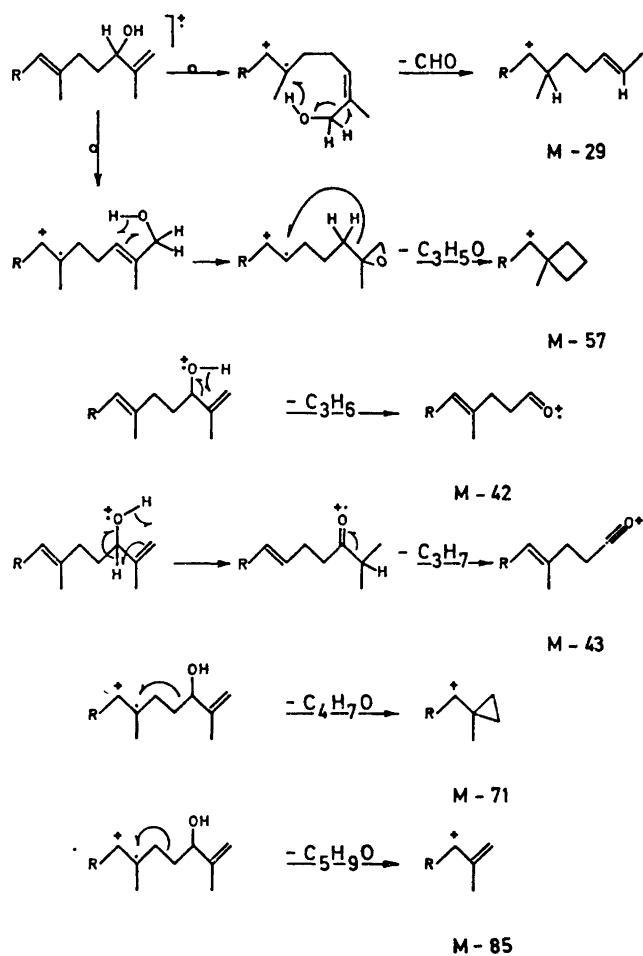


Fig. 2. PMR-spectra (CDCl₃) of synthetic aleuriaxanthin (9) and synthetic aleuriaxanthin acetate (8) alone and in the presence of 0.5 equiv. Eu(dpm)₃.

respectively.¹¹ Other losses of 42, 43, and 60 mass units correspond to the losses of ketene, acetyl, and acetic acid consistent with an acetate.⁹

Hydrolysis of the acetate 8 afforded aleuriaxanthin (9) which was obtained as clusters of prisms of m.p. 125–126°C from ether-petroleum ether. Synthetic aleuriaxanthin (9) was indistinguishable from the natural pigment in all its physical properties, except rotation. The visible light absorption spectrum (Fig. 1) exhibited the same maxima and spectral fine structure as the acetate 8. The IR spectrum was identical with that of natural aleuriaxanthin and showed bonded OH and terminal methylene absorptions at 3300 and 900 cm^{-1} , respectively. The PMR spectrum (Fig. 2, including assignments) had skeletal methyl signals in the same positions as the acetate (and was identical with that of the natural pigment, *cf.* Ref. 1). The terminal



Scheme 2.

methylene protons gave rise to two signals at τ 5.03 and 5.12 due to the magnetic non-equivalence of these protons. Compatible with a secondary, allylic alcohol the methine proton resonated at τ 5.93 (triplet, $J = 6$ Hz). The anisotropic influence of the acetate function on the terminal methylene protons (two signals in **9** and only one in **8**) noted previously¹ was also observed for the synthetic pigments. On electron impact the molecular ion occurred at m/e 552.4334 (calc. 552.4331 for $C_{40}H_{56}O$). The fragmentation pattern of synthetic aleuriaxanthin (Fig. 3) was identical with that of the natural pigment.¹ Losses of 29 (CHO), 57 (C_3H_5O), 42 (C_3H_6), 43 (C_3H_7), 71 (C_4H_7O), and 85 (C_5H_9O) mass units are rationalised in Scheme 2. The losses of CHO and C_3H_5O may be derived by initial allylic rearrangement of the hydroxy group, whereas the losses of C_3H_6 , C_4H_7O , and C_5H_9O involve simple cleavages. The loss of C_3H_7 requires double hydrogen transfer. Of special importance is the loss of C_4H_7O since it reflects the location of the hydroxy group (*cf.* Ref. 1).

EXPERIMENTAL

Materials and methods, summarised elsewhere,¹² were as generally used in our laboratory.

Photosensitized autoxidation of linalool (1). Linalool (**1**, 15.4 g) and methylene blue (30 mg) in methanol (300 ml) were irradiated externally with a tungsten lamp (Philips Argaphoto BM, 500 W) and oxygen was circulated through the solution. The oxygen uptake was monitored with a gas buret. The reaction was stopped after 2.31 l of oxygen had been absorbed (*ca.* 4 h). The crude reaction products, obtained by extraction with chloroform and evaporation, were reduced with sodium borohydride (4 g) in ethanol (150 ml) for 17 h. The reaction products were extracted with chloroform, the solvent evaporated and the crude mixture acetylated with acetic anhydride (7.5 g) in dry pyridine (25 ml) for 40 h at room temperature. Extraction with chloroform and evaporation of the solvent gave 17.4 g crude products which were separated by chromatography on silica (150 g).

6-Acetoxy-3,7-dimethylocta-1,7-diene-3-ol (4) was eluted from the column with benzene. Evaporation of the solvent gave 6.31 g (31 %) crude **4**. A small sample for analysis was distilled, b.p. 55–60°C/0.001 torr; $n_D^{19} = 1.4627$; $\nu_{\max}(\text{liq})$ 3460 (bonded OH), 3100–2820 (CH), 1740 (C=O), 1650 (C=C), 1450 (CH_2 , CH_3), 1372 (CH_3), 1240 (C–O–), 1021 (OH), and 920 ($=CH_2$) cm^{-1} ; τ ($CDCl_3$) 4.07 dd (1 H, $J_{1,2} = 17.5$ Hz, $J_{1',2} = 10.5$ Hz, H-2), 4.81 dd (1 H, $J_{1,2} = 17.5$ Hz, $J_{1',2} = 2$ Hz, H-1 *trans*), 4.83 t (1 H, $J = 6$ Hz, H-6), 4.95 dd (1 H, $J_{1',2} = 10.5$ Hz, $J_{1,1'} = 2$ Hz, H-1' *cis*), 5.09 m (2 H, $J = 1.5$ Hz, H-8), 7.57 s (1 H, OH), 7.97 s (3 H, acetate), 8.29 d (3 H, $J = 1.5$ Hz, CH_3 at C-7), 8.42 m (4 H, H-4, H-5), 8.73 s (3 H, CH_3 at C-3); m/e 212.1408 (M, calc. for $C_{12}H_{20}O_3$ 212.1413).

3,7-Dimethylocta-1,5-diene-3,7-diol (3b) was eluted with chloroform. Evaporation of the solvent gave 6.36 g (37.5 %) crude **3b**. Distillation of a small sample for analysis gave b.p. 58–60°C/0.001 torr; $n_D^{21} = 1.4758$; $\nu_{\max}(\text{liq})$ 3380 (bonded OH), 3100–2820 (CH), 1460 (CH_2 , CH_3), 1410, 1370 (CH_3), 1230, 1155 (OH), 975 (*trans* –CH=CH–), and 920 ($=CH_2$) cm^{-1} ; τ ($CDCl_3$) 4.03 dd (1 H, $J_{1,2} = 17.5$ Hz, $J_{1',2} = 10.5$ Hz, H-2), 4.32 m (2 H, H-5, H-6), 4.81 dd (1 H, $J_{1,2} = 17.5$ Hz, $J_{1,1'} = 2$ Hz, H-1 *trans*), 4.95 dd (1 H, $J_{1',2} = 10.5$ Hz, $J_{1,1'} = 2$ Hz, H-1' *cis*), 7.04 (broad 2 H, OH), 7.75 m (2 H, H-4), 8.70 s (6 H, H-8 and CH_3 at C-7), 8.73 s (3 H, CH_3 at C-3); m/e 170.1303 (M, calc. for $C_{10}H_{18}O_2$ 170.1307).

(6-Acetoxy-3,7-dimethylocta-2,7-dien-1-yl)triphenylphosphonium bromide (5). A solution of **4** (1.96 g) and triphenylphosphonium bromide (3.43 g) in chloroform (10 ml) was stirred at room temperature for 24 h. Addition of water, extraction with chloroform and evaporation of the solvent gave a sirup which was triturated with ether. Crys-

tallisation from chloroform-petroleum ether gave 3.23 g (65 %) **5** of m.p. 169–170°C; ν_{\max} (KBr) 3050–2800 (CH), 1740 (C=O), 1650, 1587 (C=C), 1483, 1438 (CH₂, CH₃), 1370 (CH₃), 1240 (C–O–), 1220, 1112 (C–P–), 1015, 995, 935, 895 (=CH₂), 850, 750, 725 and 692 (arom. CH) cm⁻¹; τ (CDCl₃) ca. 2.20 (15 H, aromatic), 4.87 t (1 H, J = 6 Hz, H-6), 4.97 t (1 H, J = 7 Hz, H-2), 5.17 (2 H, H-8), 5.40 dd (2 H, $J_{\text{H-H}} = 8$ Hz, $J_{\text{H-P}} = 16$ Hz, H-1), 7.97 s (3 H, acetate), ca. 8.1 m (2 H, H-5), 8.43 s (6 H, CH₃ at C-3 and C-7), ca. 8.60 (2 H, H-4).

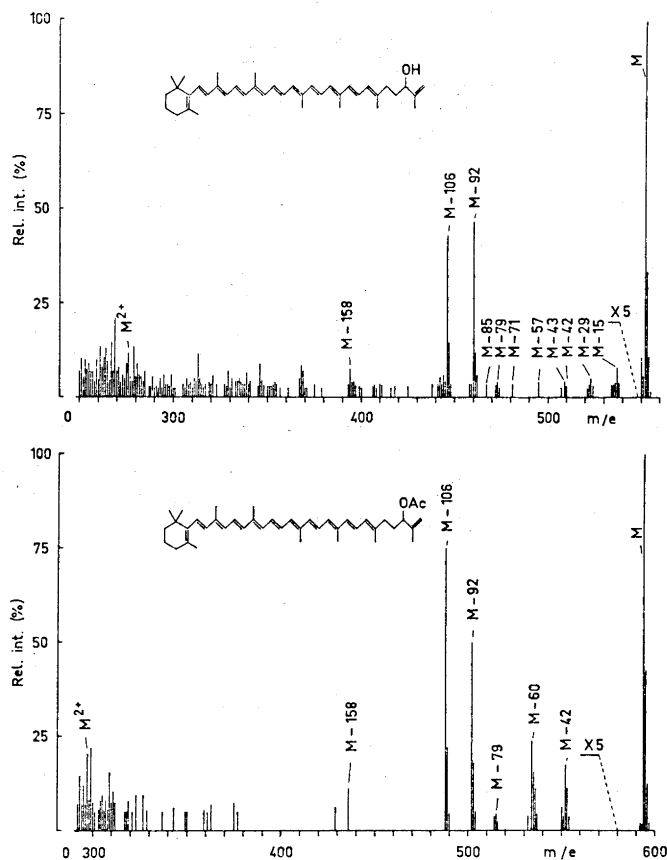


Fig. 3. Mass spectra of synthetic aleuriaxanthin acetate (**8**) and synthetic aleuriaxanthin (**9**).

Aleuriaxanthin acetate (**8**). 8'-Apo- β -caroten-8'-al (**7**, 93.2 mg), **5** (250 mg), and sodium hydride (250 mg) in dry methylene chloride (5 ml) was stirred at room temperature under nitrogen for 9.5 h. Excess sodium hydride was decomposed with acetic acid and the products extracted into ether. Chromatography on TLC (silica) afforded 83.5 mg (93 %) aleuriaxanthin acetate (**8**). Crystallisation from acetone-methanol and recrystallisation from acetone gave 16.2 mg **8** of m.p. 133–134°C, undepressed on admixture with aleuriaxanthin acetate (m.p. 134.5–135.5°C) of natural origin;¹ λ_{\max} (acetone) (440), 464 [$E(1\%$, 1 cm) = 2570], and 495 nm; % III/II¹³ = 58; (hexane) 282, 350, 436.5, 461, 492; % III/II = 60.5 (Fig. 1); ν_{\max} (KBr) 3040–2800 (CH), 1740 (C=O),

1650, 1625, 1550 (C=C), 1440 (CH₂, CH₃), 1370 (CH₃), 1230 (C-O-), 1020, 963 and 953 (-CH=CH-), 900 (=CH₂), and 825 (>C=CH-) cm⁻¹; τ (CDCl₃) 3.0-4.2 (15 H, olefinic), 4.86 t (1 H, J = 6 Hz, H-2'), 5.04 m (2 H, W_H = 6 Hz, H-16'), 7.59 s (3 H, acetate CH₃), 8.03 s (4 × 3 H, in-chain CH₃), 8.15 s (3 H, CH₃ at C-5'), 8.26 s (2 × 3 H, CH₃ at C-5 and C-1'), 8.47 (2 × 2 H, non-allylic CH₂), and 8.98 s (2 × 3 H, gem. CH₃ at C-1), for the Eu(dpm)₃ experiment the procedure previously¹⁰ used was followed with additions of 0.5 equiv. (Fig. 3) and 1 equiv. Eu(dpm)₃; m/e 594.4432 (M, calc. for C₄₂H₆₈O₂ 594.4436), 552 (M-42), 551 (M-43), 550 (M-44), 534 (M-60), 502 (M-92), 488 (M-106), and 436 (M-158).

Aleurixanthin (9). Crystalline aleurixanthin acetate (8, 30 mg) was saponified with 5% KOH in methanol-ether (1:1, 100 ml) at room temperature for 5 h. The products were extracted with ether, the extract washed with water until neutral, dried and evaporated. Recovered 28 mg (93%). Purification by TLC (silica) and crystallisation from chloroform-methanol gave 10 mg aleurixanthin (9) of m.p. 125-126°C, undepressed on admixture with natural aleurixanthin of m.p. 122-122.5°C;¹ λ_{max} (acetone) (440), 465 [E(1%, 1 cm) = 2630] and 496 nm; % III/II¹³ = 58; (hexane) 282, (350), 435.5, 460, 490.5; % III/II = 64 (Fig. 1); ν_{max}(KBr) 3300 (bonded OH), 3040-2800 (CH), 1650, 1625, 1550 (C=C), 1440 (CH₂, CH₃), 1370 (CH₃), 1010, 960 (-CH=CH-), 900 (=CH₂), and 825 (>C=CH-) cm⁻¹; τ (CDCl₃) 3.0-4.2 (15 H, olefinic), 5.03 and 5.12 (1 + 1 H, W_H = 4 Hz, H-16'), 5.93 t (1 H, J = 6 Hz, H-2'), 8.03 s (4 × 3 H, in-chain CH₃), 8.15 s (3 H, CH₃ at C-5'), 8.26 s (2 × 3 H, CH₃ at C-5 and C-1'), 8.47 (2 × 2 H, non-allylic CH₂), 8.73 imp. and 8.98 s (2 × 3 H, gem. CH₃ at C-1); m/e 552.4334 (M, calc. for C₄₀H₅₈O 552.4331), 537 (M-15), 534 (M-18), 523 (M-29), 510 (M-42), 495 (M-57), 481 (M-71), 467 (M-85), 460 (M-92), 446 (M-106) and 394 (M-158).

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