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STRUCTURE REVISION AND BIOGENETIC RELATIONSHIP OF AUBERGENONE, A SESQUITERPENOID PHYTOALEXIN OF EGGPLANTS[1)]

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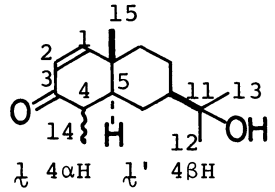
Evidence is presented for structure revision of aubergenone, isolated from diseased eggplants and qualified as a phytoalexin, to 11-hydroxy-4α,5α-eudesm-1-en-3-one (1). A biogenetic pathway to representative stress metabolites of the Solanaceae plants, including aubergenone and rishitinol, is also proposed.

The title compound (1), aubergenone ("enone sesquiterpene"), isolated from diseased eggplants (Solanum melongena, Solanaceae) and qualified as a phytoalexin, was assigned formula 1' on the basis of the extensive spectroscopic studies by Stoessl and coworkers.[2)] However, in continuing synthetic studies on phytoalexins of the Solanaceae plants, we had some doubts about the assigned structure (1'). In this paper we present evidence that the structure (1') should be revised to 11-hydroxy-4α,5α-eudesm-1-en-3-one[3)] (1) and also propose a biogenetic pathway to several representative stress metabolites of the Family,[4)] including aubergenone, because 1 is a sole stress compound with a 5α-eudesmane skeleton among the metabolites and hence stands unique on biogenetic grounds together with rishitinol[5)] (2).

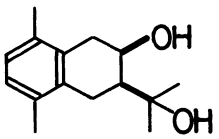
A compound with the assigned structure (1') was first prepared from (+)-α-cyperone[6)] (3) in an unambiguous manner as described below. The compound (3) was converted into "trans-dihydrocarissone"[7)] (4) with the established configuration,[7)] in 76% yield (the Birch reduction, and oxymercuration-demercuration). Treatment of 4 with lithium diisopropylamide (LDA, 2.5 equiv) in THF (-78 °C, 1 h) and then with benzeneselenenyl bromide (PhSeBr, 2.5 equiv) in THF (-78 °C, 10 min)[8)] afforded its 2α-phenylseleno derivative[9)] (5), mp 154-155 °C, $[\alpha]_D$ -132°,[10)] in 75% yield, which on further treatment with sodium periodate ($NaIO_4$, 3 equiv) in 85% aqueous methanol containing sodium hydrogencarbonate (1.5 equiv) (room temp, 3 h)[8)] gave 11-hydroxy-4β,5α-eudesm-1-en-3-one (1'), mp 105-107 °C, $[\alpha]_D$ -53.5°, in 69% yield; m/e 236 (M^+), 221, 218, 203, 178, and 59; λ_{max} 228 nm (ε 5700); ORD (EtOH), [Φ] 0°, -920°, 0°, +1020°, +510°, +2030°, +510°, and +2850° at 500, 365, 346, 328, 282, 255, 240, and 226 nm; ν_{max} (Nujol) 3500, 1670, and 1655 (sh) cm^{-1}; δ 1.06 (3H, s, 15-H), 1.13 (3H, d, J = 7, 14-H), 1.22 (6H, s, 12- and 13-H), and 2.32 (1H, do q, J = 11, 7, 7, and 7, 4-H), 5.84 and 6.71 (each 1H, ABq, J = 10, 2- and 1-H). These spectral data were different from the reported[2)] for aubergenone, indicating the structure (1') to be incorrect. Significant difference in the coupling constant $J_{4,5}$ between the synthetic (11 Hz) and natural samples (6 Hz) suggested that the

C-4 and C-5 protons of the latter would probably be oriented cis (equatorial-axial).

The structure of aubergenone (1) was established by transformation of 3 into 1, which involves preparation of eudesm-4-ene-3β,11-diol[11] (6) by a known procedure (68%)[11] as the first stage. Hydrogenation of 6 over platinum in a 40:1 mixture of ethyl acetate and acetic acid (room temp, 2 h) effected[12] cis-addition of hydrogen from the rear (α) side to the C-4-C-5 double bond to yield 4α,5α-eudesmane-3β,11-diol (7), mp 166-166.5 °C, $[\alpha]_D$ -2.7°; δ 3.75 (1H, do t, J = 10, 5.5, and 5.5, 3-H), which was oxidized with the Jones reagent to give 11-hydroxy-4α,5α-eudesman-3-one (8), mp 41.5-43 °C, $[\alpha]_D$ +2.8°, in 83% yield from 6; ORD (EtOH), a = +23.0°. The configurations of C-4 and C-5 in these compounds (7 and 8) were confirmed by quantitative conversion of 8 into 4 under basic conditions (5% KOH in MeOH, reflux, 6 h). The compound (8), when treated with LDA (2.5 equiv) in THF (-78 °C, 1 h) and then with PhSeBr (2.5 equiv) in THF (-78 °C, 5 min), afforded the 2α-phenylseleno derivative (9), oil, in 82% yield; δ 2.61 (1H, qui, J = 6, 4-H) and 4.49 (1H, do d, J = 12 and 7, 2-H), which underwent oxidative elimination by treatment with $NaIO_4$ (3 equiv) in aqueous methanol (room temp, 2 h) to give α,β-unsaturated ketone, oil, $[\alpha]_D$ -4.0°, in 46% yield; m/e 236 (M^+), 218, 203, 175, and 95 (base); λ_{max} 229 nm (ε 7080); ORD (EtOH), [Φ] 0°, 0°, -130°, -520°, -1670°, 0°, +3830°, +4500°, +2800°, and +4500° at 589, 500, 450, 400, 368, 348, 310, 285, 280, and 275 nm; ν_{max} 3460, 1670, 917, 824, and 752 cm^{-1}; δ 1.13 (3H, d, J = 8, 14-H), 1.16 (3H, s, 15-H), 1.24 (6H, s, 12- and 13-H), and 2.44 (1H, do q, J = 6, 8, 8, and 8, 4-H), 5.87 and 6.78 (each 1H, ABq, J = 10, 2- and 1-H); δ (^{13}C), 13.4, 20.7, 22.4, 26.0, 27.1, 27.5, 36.1, 39.9, 44.3, 45.2, 49.0, 72.5, 125.8, 160.8, and 203.8. These spectral data were completely identical with those (MS,[2b] UV,[2] ORD,[2b] IR,[2] ^1H-[2a] and ^{13}C-NMR[2]) reported for natural aubergenone, indicating that aubergenone is represented correctly by formula 1.



1 4αH 1' 4βH



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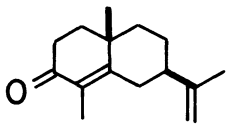

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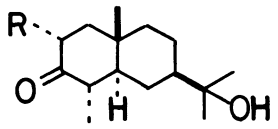
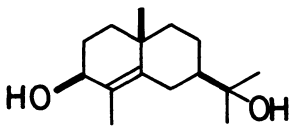


4 R=H 5 R=PhSe



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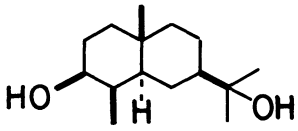

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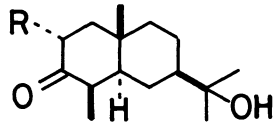
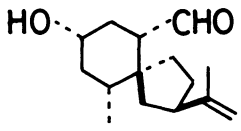


8 R=H 9 R=PhSe



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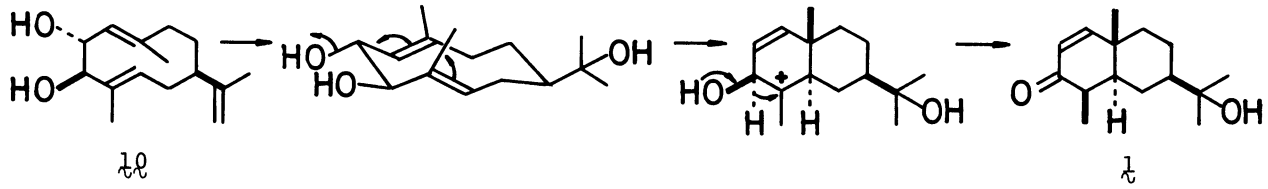
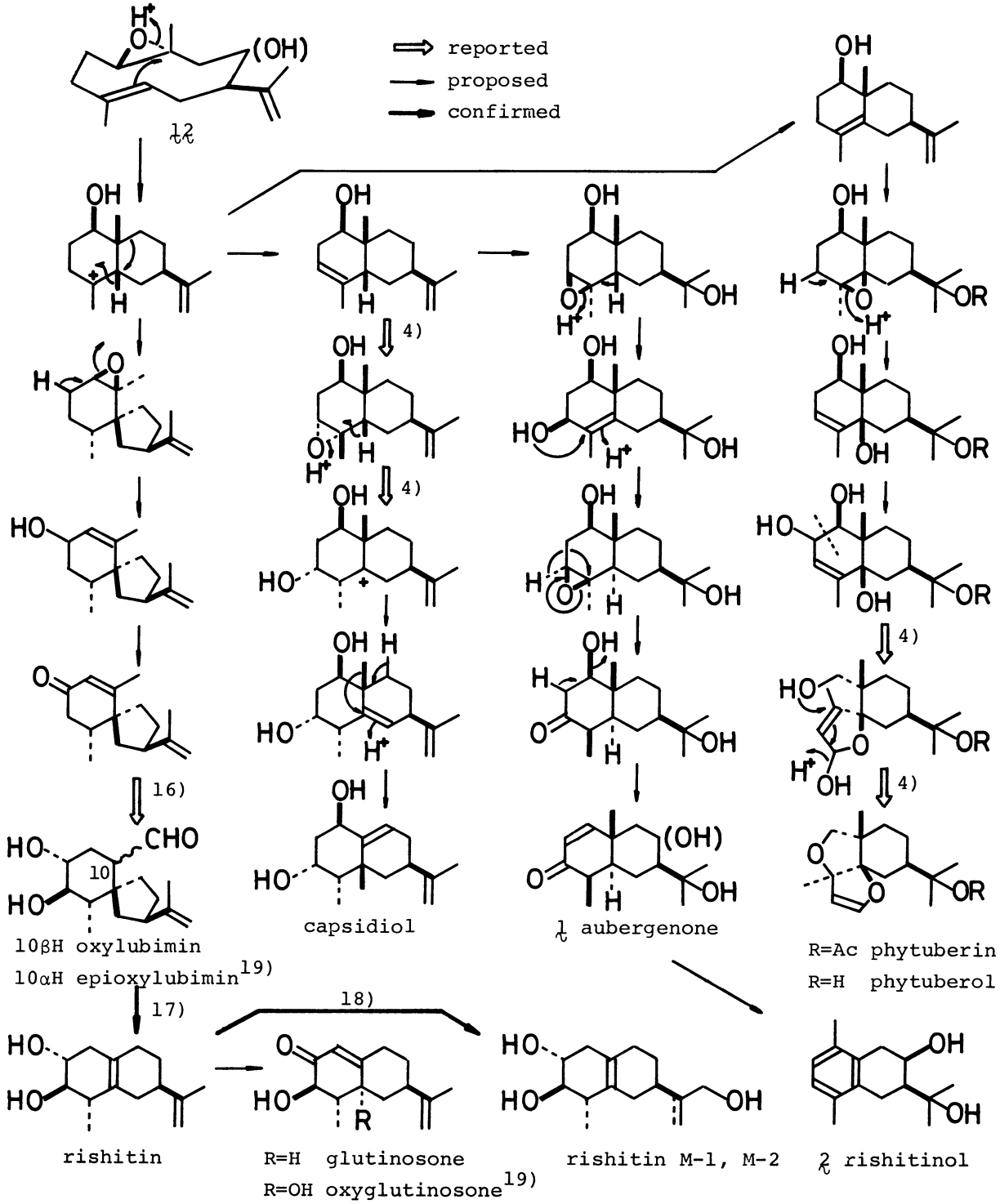
The biogenesis of aubergenone (1) can be described smoothly in a concerted manner on the basis of the revised structure, starting from "2,3-dihydroxy-germacrene"[4,13] (10) with a C-conformation[14] (Scheme 1).[4] However, in view of the coexistence of aubergenone with lubimin (11),[2] we wish to propose a biogenetic pathway to several representative stress metabolites of the Solanaceae plants including 1 and 2 (Scheme 2), which is based on the following assumption: (i) The relevant metabolites are derived from a common starting substance, germacrene oxide (12) with a T-conformation,[14] (ii) hydride and alkanide shifts proceed in a backbone rearrangement manner,[15] and (iii) oxidation stage is not clearly defined.

Scheme 1



Scheme 2



REFERENCES and NOTES

1) a) Part XX of "Studies on the Phytoalexins; Part XIX, T. Masamune, A. Murai, Y. Takahashi, F. Yagihashi, N. Katsui, N. Doke, and K. Tomiyama, (the preceding paper, submitted to Chem. Lett.). b) Part VI of "Synthetic Studies of Rishitin and Related Compounds;" Part V, A. Murai, M. Ono, and T. Masamune, Chem. Lett., 1005 (1978).

2) a) A. Stoessl, J. B. Stothers, and E. W. B. Ward, J. Chem. Soc., Chem. Commun., 709 (1974). b) A. Stoessl, J. B. Stothers, and E. W. B. Ward, Can. J. Chem., 53, 3351 (1975).

3) In this paper we define eudesmane as 4,10β-dimethyl-7β-isopropyldecahydronaphthalene and use the same nomenclature as that for steroids; J. Org. Chem., 34, 1517 (1969).

4) A. Stoessl, J. B. Stothers, and E. W. B. Ward, Phytochemistry, 15, 855 (1976); Can. J. Chem., 56, 645 (1978).

5) N. Katsui, A. Matsunaga, K. Imaizumi, T. Masamune, and K. Tomiyama, Tetrahedron Lett., 83 (1971); Bull. Chem. Soc. Jpn, 45, 2871 (1972).

6) E. Piers and K. F. Cheng, Can. J. Chem., 46, 377 (1968); D. Caine and J. T. Gupton, III, J. Org. Chem., 39, 2654 (1974).

7) D. C. Humber, A. R. Pinder, and R. A. Williams, J. Org. Chem., 32, 2335 (1967).

8) H. J. Reich, J. M. Renga, and I. L. Reich, J. Am. Chem. Soc., 97, 5434 (1975).

9) All new compounds gave satisfactory elementary analyses and spectral data.

10) Optical rotations, UV, IR, and NMR spectra were measured in chloroform, in ethanol, in liquid state, and in chloroform-d, respectively, unless otherwise stated.

11) a) A. R. Pinder and R. A. Williams, J. Chem. Soc., 2773 (1963). b) The yield is not described in ref. 11a, and "68%" is our result.

12) Hydrogenation of "carissone," 11-hydroxyeudesm-4-en-3-one, over palladium in acetic acid and/or in alkaline ethanol gave 4 as a major product.

13) A. Stoessl, J. B. Stothers, and E. W. B. Ward, J. Chem. Soc., Chem. Commun., 431 (1975).

14) Cf., J. K. Sutherland, Tetrahedron, 30, 1651 (1974).

15) a) N. H. Andersen, M. S. Falcone, and D. D. Syrdal, Tetrahedron Lett., 1759 (1970); D. F. MacSweeney, R. Ramage, and A. Sattar, ibid., 557 (1970). b) C. A. Miller and A. R. Pinder, J. Chem. Soc., Chem. Commun., 230 (1977); D. Caine and S. L. Graham, Tetrahedron Lett., 2521 (1976); G. E. Gream, M. H. Laffer, and A. K. Serelis, ibid., 4713 (1975); I. Kitagawa, H. Shibuya, Y. Yamazoe, H. Takeno, and I. Yoshioka, ibid., 111 (1974).

16) E. B. Kalan and S. F. Osman, Phytochemistry, 15, 775 (1976).

17) K. Sato, Y. Ishiguri, N. Doke, K. Tomiyama, F. Yagihashi, A. Murai, N. Katsui, and T. Masamune, Phytochemistry, in press.

18) A. Murai, N. Katsui, F. Yagihashi, T. Masamune, Y. Ishiguri, and K. Tomiyama, J. Chem. Soc., Chem. Commun., 670 (1977); Y. Ishiguri, K. Tomiyama, N. Doke, A. Murai, N. Katsui, F. Yagihashi, and T. Masamune, Phytopathology, 68, 720 (1978).

19) N. Katsui, F. Yagihashi, A. Murai, and T. Masamune, Chem. Lett., (the previous paper, submitted to Chem. Lett.).

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