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THE SYNTHESIS OF (±)-GLUTINOSONE[1)]

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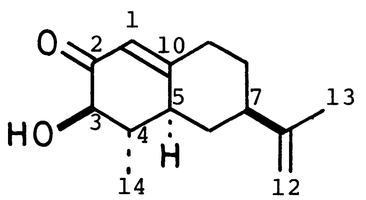
The synthesis of (±)-glutinosone, an antifungal norsesquiterpene from Nicotiana glutinosa infected with tobacco mosaic virus, is described.

Glutinosone (1) is a norsesquiterpene qualified as "phytoalexin" and isolated from leaves of Nicotiana glutinosa infected with tobacco mosaic virus,[2)] and the structure and configuration have been established well and characterized by a nor-eudesmane skeleton with a double bond at an angular position.[2,3)] We describe herein the regio- and stereo-selective synthesis of (±)-glutinosone [(±)-1].

The Robinson annelation[4)] of dimethyl 2-oxocyclohexane-1,4-dicarboxylate[5)] (2) with 1-diethylamino-3-pentanone methiodide[6)] produced a 1:1 mixture of dimethyl 4-methyl-3-oxooctahydronaphthalene-7,10-dicarboxylates[5)] (3), oil, in a 52% yield; m/e 280 (M^+); λ_{max} 246 nm (ε 12,400); ν_{max} (liquid) 1725 and 1664 cm^{-1}; δ 1.88 and 1.91 (total 3H, each s, C$\underline{H}_3$ at C_4), 3.67 and 3.71 (total 3H, each s, COOC$\underline{H}_3$), and 3.75 (3H, s, COOC$\underline{H}_3$). The octalones (3), when hydrogenated over 10% palladium-charcoal (in CH_3COOH, room temp, 15 h), treated with acid ($HClO_4$ in CH_3COOH, room temp, 15 h) and then with base ($NaOCH_3$ in CH_3OH, reflux, 40 min), and esterified with diazomethane,[4,7)] were converted into trans-decalone (4), mp 105-106°C, showing a single peak by GLPC and TLC, in a 66% yield; m/e 282 (M^+); ν_{max} (Nujol) 1735, 1720, and 1169 cm^{-1}; δ 1.08 (3H, d J = 7 Hz, C$\underline{H}_3$ at C_4), 3.06 (1H, do q J = 11, 7, 7, and 7 Hz, $\underline{H}$ at C_4), 3.71 and 3.79 (each 3H, s, 2COOC$\underline{H}_3$). Treatment of the decalone (4) with isopropenyl acetate and acid [p-$CH_3C_6H_4SO_3H$ (PTS), reflux,



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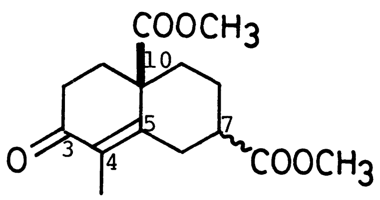

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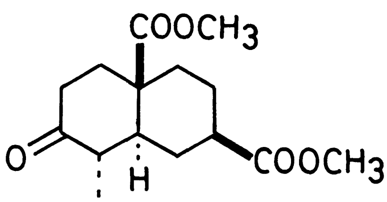

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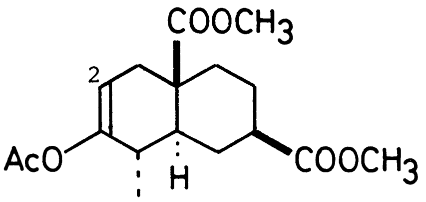
9 h][8] gave the corresponding enol acetate (**5**), oil, in a 91% yield; m/e 324 (M^+); ν_{max} (liquid) 1762, 1742, 1734, and 1683 cm^{-1}; δ 1.04 (3H, d J = 7 Hz, $C\underline{H}_3$ at C_4), 2.10 (3H, s, $OCOC\underline{H}_3$), 3.69 (6H, s, $2COOC\underline{H}_3$), and 5.27 (1H, br d J = 6 Hz, $\underline{H}$ at C_2), which on oxidation with perbenzoic acid formed 2α,3α-epoxy-3β-acetate (**6**), mp 138-139°C; δ 1.18 (3H, d J = 7 Hz, $C\underline{H}_3$ at C_4), 2.05 (3H, s, $OCOC\underline{H}_3$), 3.43 (1H, d J = 6 Hz, $\underline{H}$ at C_2), 3.69 and 3.77 (each 3H, s, $2COOC\underline{H}_3$). Treatment of the epoxy-acetate (**6**) with acid (PTS in CH_3COOH, room temp, 14 h)[9] effected rearrangement to give 3-oxo-2α-acetate (**7**), mp 142-143°C, in an 89% yield from **5**, which, on reflux with tetramethylammonium acetate in acetone (16 h),[10] was transformed into 2-oxo-3β-acetate (8), mp 131-132°C, in a 50% yield, leaving the starting compound (**7**) unchanged (40%). The structure and configuration of two oxo-acetates (**7** and **8**) were deduced from the spectral data: **7**, m/e 340 (M^+); ν_{max} (Nujol) 1762, 1735, and 1730 cm^{-1}; δ 1.09 (3H, d J = 7 Hz, $C\underline{H}_3$ at C_4), 1.68 (1H, t J = 13 Hz, α-$\underline{H}$ at C_1), 2.14 (3H, s, $OCOC\underline{H}_3$), 2.59 (1H, do d J = 13 and 6 Hz, β-$\underline{H}$ at C_1), 3.18 (1H, do q J = 11, 7, 7, and 7 Hz, $\underline{H}$ at C_4), 3.68 and 3.79 (each 3H, s, $2COOC\underline{H}_3$), and 5.05 (1H, do d J = 13 and 6 Hz, $\underline{H}$ at C_2): **8**, m/e 340 (M^+); ν_{max} (Nujol) 1735 cm^{-1}; δ 1.10 (3H, d J = 7 Hz, $C\underline{H}_3$ at C_4), 2.19 (3H, s, $OCOC\underline{H}_3$), 2.35 and 2.76 (each 1H, ABq J = 14 Hz, $2\underline{H}$ at C_1), 3.67 and 3.69 (total 6H, each s, $2COOC\underline{H}_3$), and 4.86 (1H, d J = 10.5 Hz, $\underline{H}$ at C_3). The 2-oxo-3β-acetate (**8**) was converted smoothly [$(CH_2OH)_2$ and PTS in C_6H_6, reflux, 20 h] into the corresponding ethylene acetal (**9**), mp 126-128°C, in an 85% yield; m/e 384 (M^+); ν_{max} (Nujol) 1181 and 1157 cm^{-1}; δ 0.90 (3H, d J = 7 Hz, $C\underline{H}_3$ at C_4), 2.09 and 3.67 (3H and 6H, each s, $OCOC\underline{H}_3$ and $2COOC\underline{H}_3$), 3.85 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), and 4.73 (1H, d J = 11 Hz, $\underline{H}$ at C_3).



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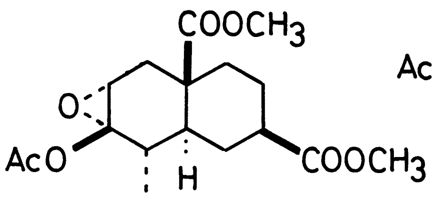

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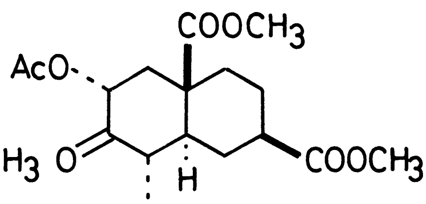

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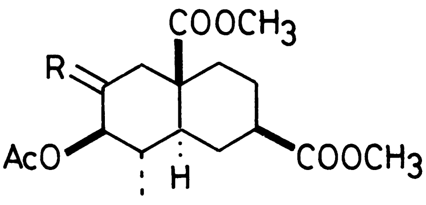
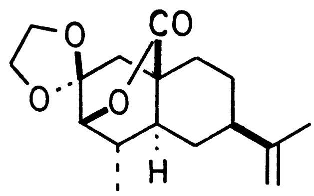


8 R=O
9 $R=OCH_2CH_2O$

Treatment of compound **9** with a large excess of methylenetriphenylphosphorane (in DMSO, 50°C, 3 h)[11] afforded a mixture of δ-lactones, which was separated roughly into two fractions by chromatography. One fraction eluted earlier gave isopropenyl-δ-lactone (**10**), mp 108-110°C, in a 22% yield, while another fraction was hydrolyzed with base (10% KOH in CH_3OH, reflux, 24 h), treated with acetic anhydride and pyridine (room temp, 16 h), and then purified by chromatography to give acetyl-δ-lactone (**11**), mp 146-148°C, in a 50% yield from **9**. The latter (**11**) was again submitted to the Wittig reaction [3 mol equiv $(C_6H_5)_3P=CH_2$ in DMSO, 50°C, 5.5 h] to afford the isopropenyl-δ-lactone (**10**) in an 88% yield: **10**, m/e 292 (M^+); ν_{max} 1757, 1642, and 895 cm^{-1}; δ 1.24 (3H, d J = 7 Hz, 14-CH_3), 1.68 (3H, s, 13-CH_3), 1.85 and 2.08 (each 1H, ABq J = 14 Hz, 2H at C_1), 3.97 (4H, br s W_H = 5 Hz, OCH_2CH_2O), 4.07 (1H, d J = 3 Hz, H at C_3), and 4.68 (2H, br s W_H = 4 Hz, 2H at C_{12}): **11**, m/e 294 (M^+); ν_{max} 1760 and 1710 cm^{-1}; δ 1.29 (3H, d J = 7 Hz, CH_3 at C_4), 1.89 and 2.15 (each 1H, ABq J = 15 Hz, 2H at C_1), 2.18 (3H, s, CH_3CO), 4.01 (4H, br s W_H = 4.5 Hz, OCH_2CH_2O), and 4.12 (1H, d J = 3 Hz, H at C_3).

Hydrolysis of the δ-lactone (**10**) with base (10% KOH in CH_3OH, reflux, 3 h) afforded hydroxy acid (**12**), mp 201-203°C, in a 97% yield, which was converted into the corresponding acetate (**12a**), mp 238-241°C, by treatment with acetyl chloride and pyridine (in $CH_3COOC_2H_5$, room temp, 14 h) in an 80% yield, and then esterified with diazomethane to yield the methyl ester (**12b**), mp 139-140°C, quantitatively: **12**, ν_{max} 3325, 1715, 1642, and 890 cm^{-1}; δ 1.08 (3H, d J = 7 Hz, 14-CH_3), 1.72 (3H, s, 13-CH_3), 3.21 (1H, d J = 10.5 Hz, H at C_3), 4.02 (4H, br s W_H = 6 Hz, OCH_2CH_2O), and 4.72 (2H, br s W_H = 4 Hz, 2H at C_{12}): **12a**, ν_{max} 3210 ∿ 2400, 1739, 1711, 1644, 1237, and 893 cm^{-1}; δ 0.88 (3H, d J = 7 Hz, 14-CH_3), 1.71 and 2.11 (each 3H, s, 13-CH_3 and $OCOCH_3$), 2.50 (1H, d J = 14 Hz, H at C_1), 3.96 (4H, br m W_H = 18 Hz, OCH_2CH_2O), and 4.71 (2H, s, 2H at C_{12}), 4.76 (1H, d J = 11 Hz, H at C_3), and 6.60 (1H, br, COOH): **12b**, m/e 366 (M^+). Treatment of the acid (**12a**) with lead tetraacetate and pyridine (in DMF, room temp, 4.5 h)[12] resulted in oxidative decarboxylation to give an olefin mixture (**13**), oil, in a 78% yield; ν_{max} 1737, 1644, 1244, and 895 cm^{-1}; δ 0.95 and 1.13 (total 3H, each d J = 7 Hz, 14-CH_3), 4.93, 4.99 and 5.13 (total 1H, each d J = 11, 10 and 13 Hz, H at C_3), 5.54 and 5.90 (total 2/3H, each br s W_H = 9 and 5 Hz, 2/3H at C_1 and C_9). The olefins (**13**), when treated with base (5% KOH in CH_3OH, room temp, 70 min) and then with acid [$(C_6H_5)_3CBF_4$ in CH_2Cl_2, room temp, 1 h],[13] were transformed into a mixture



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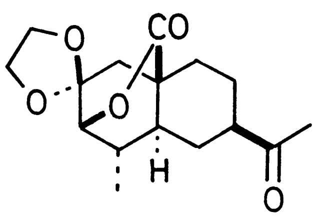

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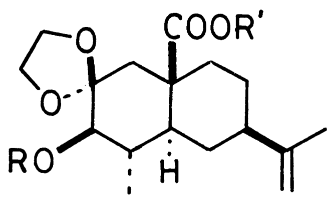
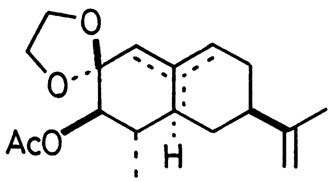


12 R=R'=H
12a R=Ac, R'=H
12b R=Ac, R'=CH_3



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containing phenols, from which α,β-unsaturated ketone, oil, was obtained as a sole isolable product in a 30% yield. The ketone exhibited the following spectra: m/e 220 (M^+), 192, 191, 162, 147, 134, 121, and 94 (base); λ_{max} 234 nm (ε 13,000); ν_{max} 3490, 1676, 1621, and 896 cm^{-1}; δ 1.22 (3H, d J = 6 Hz, 14-$C\underline{H}_3$), 1.73 (3H, s, 13-$C\underline{H}_3$), 3.72 (1H, s, O$\underline{H}$), 3.77 (1H, d J = 12 Hz, $\underline{H}$ at C_3), 4.72 (2H, br s W_H = 5 Hz, 2$\underline{H}$ at C_{12}), and 5.89 (1H, br s W_H = 4.5 Hz, $\underline{H}$ at C_1). All these spectra were identical with those of natural glutinosone (1). The overall yield of (±)-glutinosone [(±)-1] amounted to 2.8% from compounds 3.

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b) All new compounds (3 ∿ 13) gave elementary analyses in good accord with the assigned structures. The UV, IR, and NMR spectra were measured in ethanol, chloroform, and chloroform-d, respectively, unless otherwise stated. Abbreviations "s, d, t, q, m, br, and do" in the NMR spectra denote "singlet, doublet, triplet, quartet, multiplet, broad, and double," respectively.
c) In this paper we regard all new compounds (3 ∿ 13) as eudesmane derivatives and apply the numbering used for eudesmane to the compounds.

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