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A SHORT, STEREOSPECIFIC SYNTHESIS OF AN INSECT DEFENCE SECRETION, GYRINIDAL

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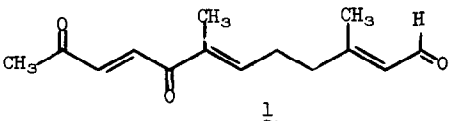
Gyrinidal, a highly-oxygenated nor-sesquiterpene, is a major component in a fish-repelling fluid secreted by abdominal glands of the familiar "whirligig" water beetles (family Gyrinidae). Recently two groups[1,2] have described the isolation and structural characterization of gyrinidal as (E,E,E)-3,7-dimethyl-8,11-dioxo-2,6,9-dodecatrienal (1). In this report we describe a short, efficient, and stereospecific synthesis of gyrinidal in four steps from an easily prepared ester of geraniol The labile diene-dione group in 1 is generated in the last step of our sequence, and a facile rearrangement of an intermediate allylic-propargylic alcohol is described.



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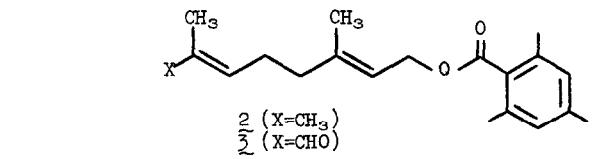
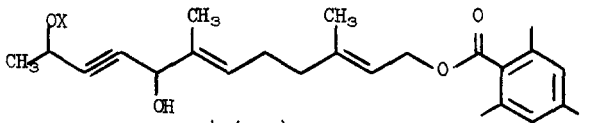
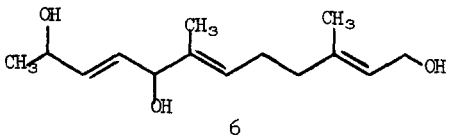
Geranyl mesitoate (2), readily prepared from geraniol and mesitoyl chloride,[3] was oxidized with 2.5 equiv selenium dioxide in refluxing ethanol[4] to give the terminal aldehyde 3 in 43% yield, after chromatography on silica gel. The stereochemical purity of 3 was ascertained by nmr spectroscopy,[5] no trace of the corresponding Z isomer could be detected (detection limit 2%). Addition of 2 equivalents of dilithio 1-butyn-3-ol (prepared by treatment of 1-butyn-3-ol with 2 equivalents of n-butyllithium in THF at 0° for 20 min), afforded the diol 4 in 93% yield after chromatographic purification; NMR ($CDCl_3$) δ 1.40 (d, J=6.5Hz, 3H), 1.75 (broad s, 6H) 2.1 (4H), 2.26 (s, 9H, mesitoate), 4.52 (partially obscured quart, J=6Hz, 1H), 4.70 (s,1H), 4.82 (d, J=7.5 Hz, 2H), 5.5 (broad t, 2H), and 6.82 (s, 2H, mesitoate), IR (film) 3400 (broad), 2270 (weak), and 1725cm^{-1} (strong), MS m/e 384.1 (M^+). The mesitoate ester is completely



2 (X=CH_3)
3 (X=CHO)



4 (X=H)
5 (X=CH(OCH_2CH_3)CH_3)



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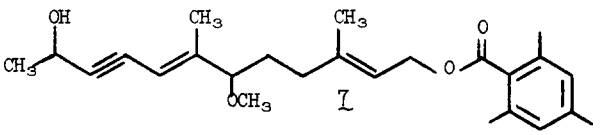
unaffected by the acetylide addition step.[6]

Reduction of the acetylene function to the trans double bond and cleavage of the mesitoate group was accomplished in a single step by reaction with an excess of lithium aluminium hydride, under carefully controlled conditions[7] (5 moles of filtered LAH solution and 10 moles anhydrous sodium methoxide per mole 4, refluxing THF, 20 min, alkaline work up). The triene-triol 6 was obtained in 49% yield, after purification by preparative tlc, NMR ($CDCl_3$) δ 1.25 (d, J=6.5Hz, 3H), 1.57 (d, J=1Hz, 3H), 1.64 (d, J=1Hz, 3H), 2.1 (broad, 4H), 4.08 (d, J=7Hz, 2H), 4.2-4.6 (broad, 2H), 5.2-5.6 (broad, 2H), and 5.6-5.8 (2H); IR (film) 3400 (broad) and 970 cm^{-1} (medium), MS m/e 222 (M-18), 204 (M-36), 177 (M-18-45). The omission of sodium methoxide, or the use of unfiltered LAH solutions or more vigorous reaction conditions, all resulted in reduced yields of 6.[8]

Final conversion of the triol 6 into gyrinidal was accomplished by oxidation with manganese dioxide (60 moles per mole 6, CH_2Cl_2, 0°, 5 hr), and the natural product could be isolated in 49% yield after purification by silica gel column chromatography. The synthetic material was homogeneous on tlc (R_f 0.6, 5% MeOH in $CHCl_3$) and had a retention time of 6.6 min on glpc (6 ft. X 0.125 in. glass 3% OV-1 in 80/100 Gas-Chrom Q, 200°, N_2, 30 ml/min),

and 7 min on liquid chromatography (50cm X 6.25 mm 10μ LiChrosorb SI 60 (Merck), 20%-i-PrOH-CH_2Cl_2 in hexane, programmed 5-60% at 5%/min , 1 ml/min). Its spectroscopic properties are the same as those reported for the natural material, NMR (220 MHz, $CDCl_3$) δ 1.89 (d, J=1Hz, 3H) 2.24 (d, J=1.3Hz, 3H), 2.39 (s, 3H), 2.3-2.6 (m, 4H), 5.89 (d, J=8Hz, 1H), 6.5-6.7 (m, 1H), 6.85 (d, J=16Hz, 1H), 7.43 (d, J=16Hz, 1H), and 9.98 (d, J=8Hz, 1H), IR (film) 2780 (weak), 1680, 1660, 1635 (all strong), and 1610 cm^{-1}; UV λ_{max} (MeOH) 238 nm (ε=23,000) and 350 (shoulder, ε ca. 450), MS m/e 219, 216, 205, 191, 125, 109, and 43.

In an earlier route, the protected form of 1-butyn-3-ol, 3-(1-lithio-1-butynyl) 1'-ethoxyethyl ether, was added to 3 to give the protected diol 5. Removal of the ethoxyethyl function with p-toluenesulfonic acid in methanol (18 hr, 25°) resulted in complete isomerization of the allylic alcohol to the conjugated methoxy alcohol 7. Compound 7 underwent a clean reduction with LAH and oxidation with maganese dioxide to give a product with the conjugated methoxy dienone function 8, NMR ($CDCl_3$) δ 1.85 (d, J=1.3Hz, 3H), 2.18 (d, J=1.3 Hz, 3H), 2.28 (s, 3H), 1.5-2.5 (broad, 4H), 3.20 (s, 3H), 3.54 (t, J=6Hz, 1H), 5.87 (d, quart, J=8,1.3Hz,1H), 6.0-6.3 (2 peaks, 2H), 7.42 (d,d,J=11, 16Hz, 1H), and 9.98 (d, J=8Hz, 1H); IR (film) 1675, 1635, 1595 (strong), and 970 cm^{-1}; MS m/e 250 (M^+), UV λ_{max} (EtOH) 239 nm (ε = 24,300) and 283 nm (ε = 34,700).



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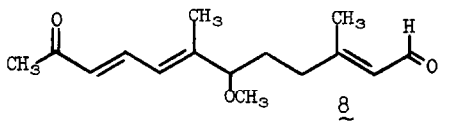

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1. J. Meinwald, K. Opheim, and T. Eisner, Proc. Nat. Acad. Sci. USA, 69, 1208 (1972).

2. H. Schildknecht, H. Neumaier, and B. Tauscher, Justus Liebigs Ann. Chem., 756, 155 (1972).

3. J. A. Katzenellenbogen and R. S. Lenox. J. Org. Chem., In Press, G. M. C. Higgins, B. Saville, and M. B. Evans, J. Chem. Soc., 702 (1965), D. M. Bower, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N. Y., 1955, p 553.

4. U. T. Bhalerao and H. Rapoport, J. Amer. Chem. Soc., 93, 4835 (1971).

5. K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, J. Org. Chem., 33, 3382 (1968).

6. E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, J. Amer. Chem. Soc., 91, 4318 (1969).

7. E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, Ibid., 89, 4245 (1967).

8. For an LAH-induced reduction-elimination of an analogous 1,4-dihydroxy-2-butyne system, see J. Meinwald and L. Hendry, Tetrahedron Lett., 1657 (1969).