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THE TOTAL SYNTHESIS OF dl-YOMOGIN[1]

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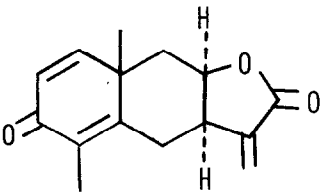
The sesquiterpene lactone yomogin (1), isolated from Artemisia princeps Pamp. by Geismann,[2] contains a cross-conjugated dienone system of the α-santonin type as well as an α-methylene-γ-butyrolactone grouping. Since dienones related to α-santonin readily undergo photochemical rearrangements into hydroazulene derivatives,[3] it appeared that yomogin (or some of its derivatives having the unsaturated lactone function protected) might serve as a useful material for the synthesis of certain cytotoxic guaianolides which also contain an α-methylene-γ-butyrolactone grouping.[4] Therefore, a total synthesis of 1 itself appeared to be of interest and has been carried out.



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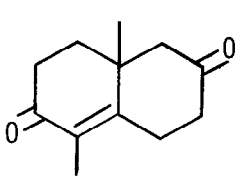
The starting material for the synthesis was 1,10-dimethyl-1-octal-2,6-dione (2).[5] This compound was converted into the enone lactone 4 via a procedure similar to that employed by Marshall, Cohen, and Hochstetler for the synthesis of the corresponding 2-deoxy derivative.[6,7] Treatment of 2 with one equivalent of pyrrolidine in benzene led to selective formation of the enamine 3; and without purification, this material was alkylated with ethyl bromoacetate and the product was hydrolyzed with dilute aqueous acetic acid to give 4 in 56% overall yield. Compound 4 showed: bp 190-196°/0.9 mm, ir ν_{max}^{film} 1730 (ester C=O), 1720 (saturated ketone), 1665 (α,β-unsaturated ketone), and 1615 cm^{-1} (conjugated C=C); nmr $\delta_{TMS}^{CCl_4}$ 1.21 (t, J = 6.5 Hz, 3H, $-CH_2-CH_3$), 1.24 (s, 3H, 10-CH_3), 1.78 (broad s, 3H, 1-CH_3), and 4.08 ppm (q, J = 6.5 Hz, 2H, $-CH_2-CH_3$).[8]



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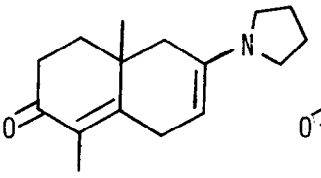

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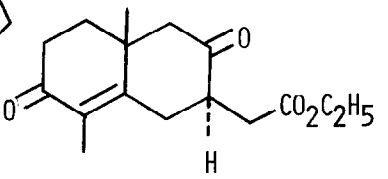

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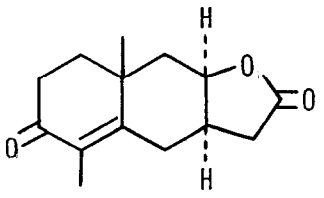
The next step in the synthesis involved the conversion of 4 into the cis-fused γ-lactone 5. Reducing agents such as potassium or sodium borohydride in methanol or tri-isobutylaluminum in benzene could be used for this purpose, but in these cases the desired enone lactone was accompanied by varying amounts of the corresponding 6α-hydroxy enone ester and separation of the mixture was difficult. Best results were obtained using K SELECTRIDE (potassium tri-sec-butylborohydride,[9] 0.5 M solution in tetrahydrofuran (THF), Aldrich Chemical Co.) for the reduction. On treatment of 4 with 1.2 equivalents of this reagent in THF at -78° for 4 hr, reduction of the saturated ketone function occurred exclusively from the α side of the molecule, and after workup and recrystallization of the crude product from diethyl ether 5 was obtained in ca. 60% yield. Spectroscopic examination of the crude product did not reveal the presence of any of the undesired hydroxy ester in this case. The conversion of a keto ester related to 4 into the corresponding cis-γ-lactone in high yield using K SELECTRIDE has recently been reported by Miller and Nash.[7c] Compound 5 showed: mp 115-117°; ir $\nu_{max}^{CHCl_3}$ 1775(γ-lactone), 1663 (α,β-unsaturated ketone), and 1620 cm^{-1} (conjugated C=C); nmr $\delta_{TMS}^{CDCl_3}$ 4.63(mult., 1H, 6 - H), 1.82 (broad s, 3H, 1-CH_3), and 1.30 ppm (s, 3H, 10-CH_3).[8]



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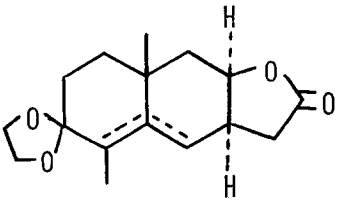

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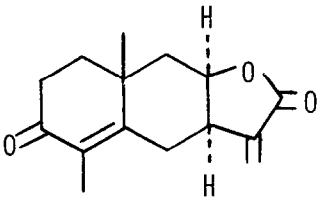

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The procedure of Grieco and Hiroi[10] was employed for the conversion of 5 into the corresponding α-methylene-γ-lactone. The enone function of 5 was first protected by conversion into the ethylene ketal using ethylene glycol and a catalytic amount of p-toluenesulfonic acid in benzene with removal of water by azeotropic distillation. Partial deconjugation of the 1,9-double bond occurred during ketalization and the nmr spectrum of the crude ketal 6 indicated that an approximately 1:1 mixture of the 1,9- and 8,9-double bond isomers was present. Treatment of 6 with 1.2 equivalents of lithium diisopropylamide in THF at -78° gave the corresponding lactone enolate which was converted into the hydroxymethyl derivative by reaction with gaseous formaldehyde (obtained by pyrolysis of paraformaldehyde at 150°) at -20° followed by addition of water. Conversion of this intermediate into the corresponding methanesulfonyl derivative with methanesulfonyl chloride pyridine at 0° and heating of this material in pyridine led to elimination of methanesulfonic acid and formation of the α-methylene derivative of 6. Removal of the ketal grouping by exchange ketalization with acetone using a catalytic amount of p-toluenesulfonic acid afforded the desired lactone 7 in approximately 50% overall yield from 5. Compound 7 showed: mp 168-169; ir $\nu_{max}^{CHCl_3}$ 1764 (α-methylene-γ-lactone), 1660 (α,β-unsaturated ketone), and 1625 cm^{-1} (conjugated C=C); nmr $\delta_{TMS}^{CDCl_3}$ 6.40 (d, J = 2.8 Hz, 1 H, $=CH_2$), 5.78 (d, J = 2.8 Hz, 1 H, $=CH_2$), 4.64 (mult., 1 H, 6-H), 1.83 (broad s, 3H, 1-CH_3), and 1.25 ppm (s, 3H, 10-CH_3).[8]

On oxidation of 7 with 2,3-dichloro-5,6-dichloro-5,6-dicyanobenzoquinone in dry dioxane at reflux for 18 hr, dl-yomogin, mp 170-172°, was obtained in 65% yield. The synthetic material exhibited ir, nmr, and mass spectra identical to those of an authentic sample of the natural product.[11] Its behavior on thin layer chromalography was identical to that of the natural product using several different solvent systems.

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