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A SHORT STEREOSELECTIVE SYNTHESIS OF SOME TERPENES FROM THE PHEROMONAL SECRETION OF THE QUEEN AND MONARCH BUTTERFLIES

D. Howard Miles,[1] Peter Loew, and William S. Johnson
Department of Chemistry, Stanford University
Stanford, California 94305

Arthur F. Kluge and J. Meinwald
Department of Chemistry, Cornell University
Ithaca, New York 14850

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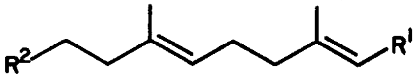
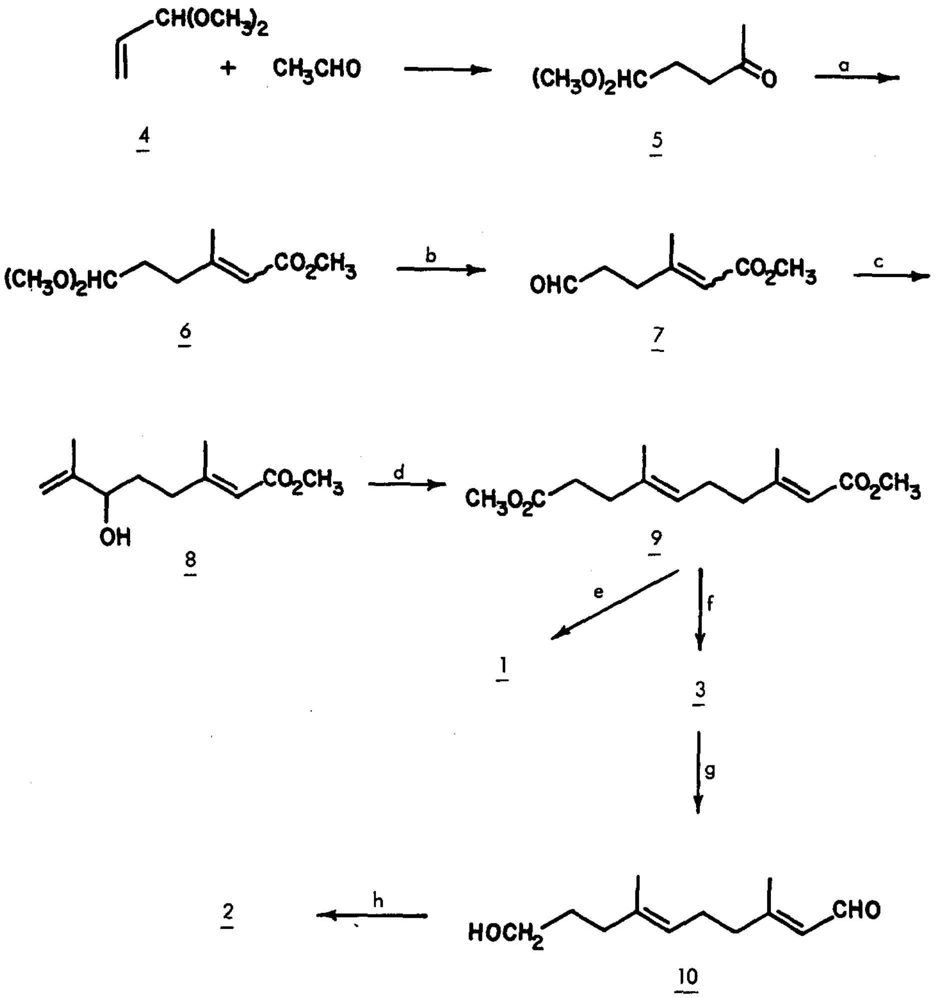
As part of a program to clarify the evolution of a communication system in a group of related animals, Meinwald and co-workers[2,3] have isolated two terpenoid components, 1 and 2, from the "hairpencils" of males of the well-known Monarch butterfly (*Danaus plexippus*) and a closely related diol 3 from the male Queen butterfly (*Danaus gilippus berenice*).[4] Syntheses of these compounds were reported concurrently from derivatives of farnesol. In light of their biological interest, it seemed desirable to design a more efficient route to these substances. Thus,



1, $R^1 = R^2 = CO_2H$
2, $R^1 = CO_2H$, $R^2 = CH_2OH$
3, $R^1 = R^2 = CH_2OH$

we wish to report a short, stereoselective synthesis of 1, 2, and 3 utilizing a modification of the orthoester Claisen rearrangement[5] to form the common intermediate, all *trans* dimethyl 3,7-dimethyl-2,6-decadienoate (9). This synthesis is outlined in the accompanying flow sheet. Although the yields have not been optimized in some of the steps, the method provides a convenient source of these butterfly terpenes.

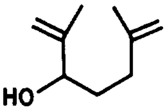
1,1-Dimethoxypentan-4-one (5)[6] was prepared in 70% yield from acrolein dimethyl acetal (4) by reaction with a five fold excess of acetaldehyde and a trace of benzoyl peroxide in an autoclave at 80° for 40 hr.[7] Condensation of the ketoacetal with methyl diethylphosphonoacetate followed by acid hydrolysis of the distilled (55-62°/0.01 mm) product 6 gave aldehyde ester 7 in 76% yield from 5. Analysis by vpc indicated that this product consisted of 73% of the *trans* isomer and 27% of the *cis*. Separation of the isomeric mixture was effected at the next stage of the



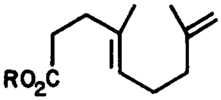
[a]1.3 equiv NaH, 1.5 equiv methyl diethylphosphonoacetate, DMF, 0.5 hr at 20°, 3 hr at 60°; [b]1:1 ether-1N H_2SO_4; [c]2 equiv isopropenylmagnesium bromide, THF, N_2, 0.5 hr at -60°, 0.5 hr at -30°; [d]4 equiv $CH_3C(OCH_3)_3$, 0.1 equiv 2,4-dinitrophenol, toluene, 100°, 17 hr reflux with removal of CH_3OH; [e]6.3 equiv $Ba(OH)_2\cdot(H_2O)_8$, 1:3 MeOH-H_2O, N_2, 0.5 hr reflux; [f]10 equiv $Li(CH_3OCH_2CH_2O)_2AlH_2$, benzene, 10 min, 25°; [g]MnO_2, $CHCl_3$, 1.5 hr, 25°; [h]1 equiv $AgNO_3$, 1:1 EtOH-H_2O, 8.7 equiv NaOH, 3.2 hr, 25°.

synthesis. Reaction of 7 with the Grignard reagent from 2-bromopropene gave crude alcohol 8 which on distillation through a 24-in spinning column gave hydroxyester 8 bp 60-95°/0.01 mm in 60% yield (*cis*:*trans* ratio 2:5 by vpc). Fractional distillation of this product through a 4-in Vigreux column gave, as the higher-boiling fraction, *trans* alcohol 8 (95% pure by vpc) in 39% yield. A sample was further purified by distillation at 95°/0.025 mm (Anal. Found: C,66.70; H, 9.11). The nmr spectrum[6] included doublets (J = 1 Hz) at 1.73 and 2.16 δ for the two vinylic methyl groups, a singlet at 3.14 for the methoxy group, a triplet (J = 6 Hz) at 4.06 (1H) for the proton on the carbon atom carrying the hydroxyl group, a broad "singlet" at 4.90 (2H) for the terminal vinylic protons, and a broad "singlet" at 5.72 (1H) for the proton α to the carbomethoxy group.

The key intermediate diester 9 was prepared by a modification of the Claisen orthoester rearrangement.[5] The reported method involved heating allylic alcohol 11 with ethyl orthoacetate at 138° for 1 hr (with removal of ethanol) in the presence of a trace of propionic acid to give ester 12. Since diester 9 is a known derivative of the natural terpene diacid 1,[2] it seemed desirable to make the methyl ester directly. Accordingly, the reaction of methyl orthoacetate with allylic alcohol 11 was examined under various conditions. It was found that this reaction had to be conducted at a lower temperature (100°), and hence required a much longer time (17 hr) because of the lower boiling point of methyl orthoacetate. When propionic acid was used as the catalyst the reaction could not be driven to completion (maximum 50% yield) presumably because of esterification of the acid by the methanol formed as a byproduct. This difficulty was obviated by selection of an acid which could not undergo esterification. Thus when 2,4-dinitrophenol was used as the acid catalyst[9] the reaction of 11 to give 13 proceeded in 77% yield. Similarly the diester 9 was formed by heating alcohol 8 (203 mg, 1.03 mmoles) methyl orthoacetate (480 mg, 4.0 mmoles), and 2,4-dinitrophenol (20 mg, 0.110 mmoles) in toluene at 100° for 17 hours with stirring (nitrogen atmosphere). The reaction vessel was fitted with a warmed Dean-Stark apparatus to remove methanol formed during the reaction. Purification of the product by evaporative distillation at 100°/0.30 mm[8] gave 189 mg (73% yield, 95% pure by vpc) of diester 9 as a colorless liquid. An analytical sample was obtained by redistillation (Anal. Found:



11



12 (R = C$_2$H$_5$)
13 (R = CH$_3$)

C, 66.10; H, 8.64). The nmr spectrum included doublets (J = 1 Hz) at δ 1.61 and 2.15 for the two vinylic methyl groups, singlets at 3.65 and 3.69 for the two methoxy groups, and broad "singlets" at 5.14 and 5.68 for the two vinylic protons. Synthetic 9 was identical by vpc analysis with the dimethylester of authentic[2] diacid 1.

Saponification of the diester 9 gave the diacid 1, as colorless crystals, mp 100-102°.[6] The specimen of the previously synthesized diacid was probably not as pure since it melted at 93-96°.[2] Reduction of diester 9 with sodium bis-(2-methoxyethoxy) aluminum hydride furnished diol 3[4] as a viscous oil (96% yield, 95% purity by vpc). The natural[4] and synthetic diols were indistinguishable by ir spectroscopy and by tlc.

The synthesis of hydroxy acid 2 was completed by the following two-step sequence. Oxidation of diol 3 with manganese dioxide gave a 96% yield of hydroxy aldehyde 10 as a clear viscous oil, bp 90-110°/0.1 mm[8]; ir (film) 3700-3100, 1670, 1625 cm^{-1}; nmr δ 1.63 (s, 3H), 1.68-2.33 (11H), 2.92 (s, 1H), 3.57 (d, J = 7 Hz, 2H), 5.12 (broad s, 1H), 5.91 (d, J = 8 Hz, 1H), 9.93 (d, J = 8 Hz, 1H); mass spectrum m/e 196 (M+). Oxidation of 10 with silver oxide gave the hydroxy acid 2 in 53% yield (88% pure by vpc) as a very viscous oil. Further purification of 2 by distillation (100°, 0.02 mm)[8] gave an analytical sample[6] the ir of which was superimposable with that of authentic hydroxy acid.[3]

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(6) The nmr spectrum (at 60 M Hz, TMS internal standard, $CDCl_3$ solvent), the ir spectra (film), mass spectra, and combustion analysis were entirely consistent with the assigned structure.

(7) *Cf.* A. Mondon, *Angew. Chem.*, *64*, 224 (1952).

(8) Evaporative bulb-to-bulb distillation using a Buchi Kugelrohrofen.

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