

A HIGHLY STEREOSELECTIVE SYNTHESIS OF (2Z,6E)-7-METHYL-3-PROPYL-2,6-DECADIEN-1-OL. A PROPOSED REVISION IN THE STEREOCHEMISTRY OF A TETRAHOMOTERPENE ISOLATED FROM THE CODLING MOTH

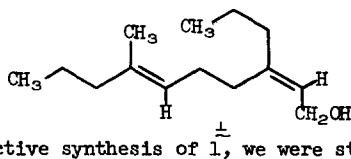
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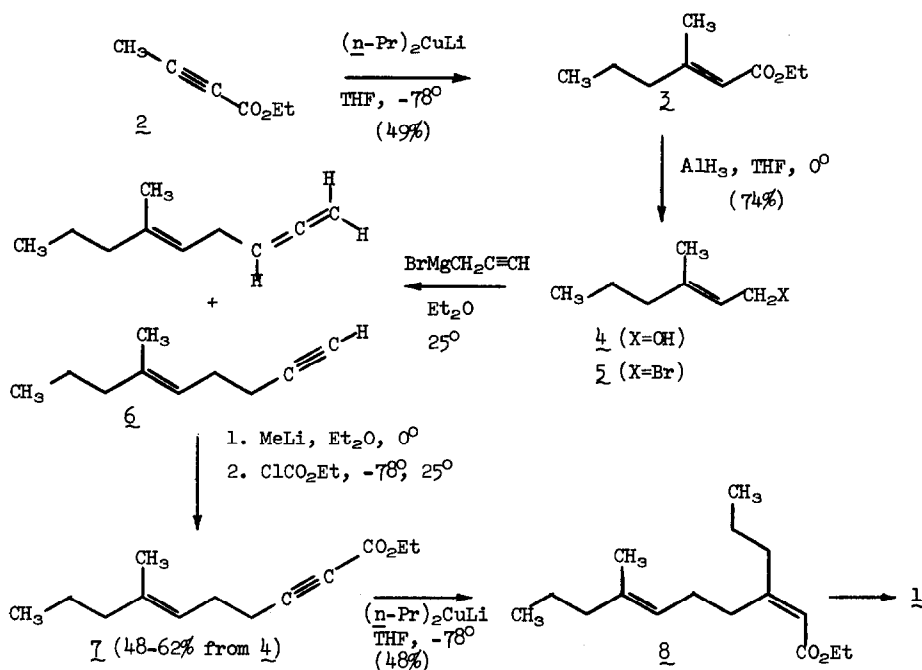
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Recently, McDonough and coworkers have reported the isolation and characterization of a terpenoid alcohol, believed to be a sex pheromone, from the codling moth (Laspeyresia pomonella L.).¹ On the bases of spectroscopic and degradative evidence the novel tetra-homonerol structure, (2Z,6E)-7-methyl-3-propyl-2,6-decadien-1-ol (1), was proposed for this alcohol, the stereochemical assignment of the two olefinic units being based on the chemical shift of the C-7 methyl resonance in the nmr and the relative glpc retention times of all four possible isomers (produced by non-stereoselective synthesis). In this report, we present a highly stereoselective synthesis of 1, and, on the basis of its nmr spectrum and glpc behavior, propose a revision in the stereochemistry of the naturally material.



In considering a stereoselective synthesis of 1, we were struck by the similar disposition of the propyl groups in the two bishomoisoprene units: both are cis to hydrogen. As the conjugate addition of dialkylcopper-lithium reagents to 2-alkynoic esters takes place nearly exclusively in a cis manner,² we felt that this reaction could be profitably applied in the synthesis of this molecule. The synthesis, summarized in the scheme, utilizes as the key reaction in the construction of both olefinic units the conjugate addition of the previously-unreported di-n-propylcopper(I) lithium reagent to acetylenic esters. The route proceeds in

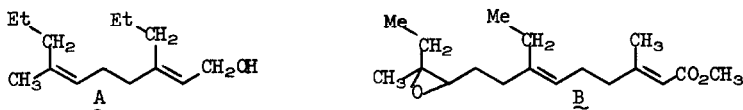
eight steps from commercially available material, with an overall yield of 8-9%.³



Di-*n*-propylcopper(I) lithium was generated by the addition of two equiv propyllithium⁴ to a THF slurry of cuprous iodide at -25° . Treatment of the complex at -78° with 0.5 equiv ethyl 2-butynoate (**2**)⁵ gave ester **3** in 49% yield. Glpc analysis of the crude reaction mixture indicated the presence of ca. 3.5% of (Z)-**3**,⁶ this was reduced to 1.6% by careful thin layer chromatographic purification. Reduction of **3** with excess aluminum hydride in THF⁷ gave in 74% yield the alcohol **4** (bp $81\text{--}83^\circ$, 17 mm). Transformation of **4** to alkynoic ester **7** was accomplished in three steps without isolation of intermediates: the alcohol **4** was treated with 0.34 mol PBr_3 in ether at 0° to give bromide **5**; the crude bromide was reacted with a 1.5 molar excess of propargyl Grignard⁸ to give a mixture of acetylene and allene (**6**) of undetermined ratio. Treatment of an ethereal solution of this mixture with the calculated amount of methyllithium at 0° , followed by an excess of ethyl chloroformate at -78° , gave **7**. The yield of **7** varied in duplicate experiments from 48 to 62% after purification by tlc and bulb-to-bulb distillation (75° , 0.1 mm). The alcohol **1** was obtained by repetition of the propylation-reduction sequence described above (48% and 80% yield, respectively).

The pure alcohol 1 was isolated from tlc as a liquid, R_f 0.30 (0.5% methanol in benzene, 2 developments); IR (neat film): 3.0μ (OH), $3.3-3.55\mu$ (saturated and olefinic CH), 6.05μ (C=C), 6.9μ (CH_2), 7.3μ (CH_3), 10.0μ (CO), and 12.0μ (trisubstituted olefin); (220 MHz, CCl_4): δ 5.38 (1H, t, $J=6.7$ Hz, $\text{C}=\text{CHCH}_2\text{O}$), 5.07 (1H, unresolved m, $\text{C}=\text{CH}$), 4.02 (2H, d, $J=6.7$ Hz, $\text{C}=\text{CHCH}_2\text{O}$), 2.17 (1H, s, OH), 2.04 (4H, s, $=\text{CCH}_2\text{CH}_2\text{C}=\text{C}$), 1.97 (4H, m, $=\text{CCH}_2\text{CH}_2\text{CH}_3$), 1.57 (3H, s, $\text{C}=\text{CCH}_3$), 1.43 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.89 (6H, d,t, CH_2CH_3); MS^9 (70 eV) m/e (rel. intensity): 210 (5.6, M^+), 192 (2.6), 179 (5.0), 167 (4.1), 149 (10.9), 121 (8.3), 97 (31.2), and 55 (100). At 10 eV the intensity of the parent ion and the noted fragments increased with respect to the base peak at m/e 55. At high resolution (90 eV), the parent ion was found to have mass 210.1979 (calcd for $\text{C}_{14}\text{H}_{26}\text{O}$: 210.1983). Formulas generated from the high resolution spectral data allowed assignment of the above noted fragments in a manner fully consistent with 1 and its anticipated fragmentations.

The spectroscopic properties of our synthetic material are for the most part in agreement with those reported by McDonough for the naturally occurring material. However, a prominent difference appears in the nmr spectrum: the C-7 methyl resonance falls at δ 1.57 in the synthetic material and at δ 1.66 in the natural substance. The E stereochemistry of the synthetic material follows unambiguously both from the known cis selectivity of the conjugate addition reaction² and nmr analysis of both E and Z isomers of the ester 3.⁶ Furthermore, the normal chemical shift of centrally located methyl groups on double bonds of E configuration in polyisoprenoid compounds is 1.57-1.61; those of Z olefins generally resonate at 1.67-1.70.¹⁰ Therefore, it appeared probable that the natural material has the Z configuration about the 6,7-double bond.¹¹ Gpc comparison confirmed that 1 is different from the natural material; when compared with the four possible stereoisomers (prepared by a nonselective route; see ref. 1), the natural material cochromatographs with the component that elutes second and the synthetic material with the component that elutes third; hence, it is most likely that the natural material possesses the 2E,6Z configuration (A), although unambiguous stereochemical assignment must await further synthetic efforts. Nevertheless, it is worthy of note that there is biosynthetic precedent for the sites at which the tetrahomogeranyl structure A bears the extra substituents, in the terminal bishomogeranyl unit in another insect terpenoid, the C-18 cecropia juvenile hormone (B).



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1. L. M. McDonough, D. A. George, B. A. Butt, J. M. Ruth, and K. R. Hill, *Science*, **177**, 177 (1972). Dr. McDonough has informed us (private communication) that more recent studies of field activity have shown that a synthetic mixture of the four possible stereoisomers is inactive, and that the activity originally observed with the natural material may be due to an unidentified impurity.
2. J. F. Normant, *Synthesis*, 63 (1972), E. J. Corey and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969).
3. Satisfactory microanalyses and/or high resolution mass spectra were obtained for all isolated intermediates. Structural assignments not discussed were fully supported by nmr and ir spectra. Yields cited are those of the purified compounds.
4. *n*-Propyllithium was prepared from propyl chloride (Eastman) and lithium wire (1% sodium alloy, Ventron) in heptane.
5. Prepared by esterification of 2-butyric acid (Farchan) by Dowex 50W-8X in ethanol (82% yield).
6. Configurational assignments were confirmed by nmr allylic methyl resonances at δ 2.11 (E) and δ 1.84 (Z). Cf. B. M. Trost, *Acc. Chem. Res.*, **3**, 120 (1970).
7. H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1464 (1966).
8. R. E. Ireland, M. I. Dawson, and C. A. Lipinski, *Tetrahedron Lett.*, 2247 (1970). The use of freshly redistilled propargyl bromide was found to be critical for the success of this reaction.
9. Mass spectra were obtained on Varian-MAT CH-5 (low resolution) and 731 (high resolution) instruments.
10. Numerous references are given in L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Edition, Pergamon Press, 1969, p 225.
11. Dr. McDonough, Agriculture Research Service, Yakima, Washington, kindly performed the gas chromatographic comparison between our synthetic material and the natural alcohol.