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STEREOSPECIFIC TOTAL SYNTHESIS OF dl-SESQUICARENE

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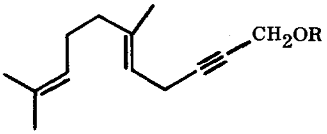
Recently a new sesquiterpene from the essential oil of Schisandra chinensis has been found to possess structure I and has been termed sesquicarene (1). A stereospecific synthesis of this substance as the racemate is described herein.

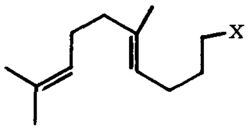
The propargylic alcohol II was prepared in 88% yield from geranyl bromide by alkylation with 2 equiv. of the lithio derivative (2) of propargyl tetrahydropyranyl ether (3) in dry tetrahydrofuran under nitrogen at 25° for 15 hr. followed by treatment with $2\,(10)^{-3}$ M p-toluenesulfonic acid in methanol at 25° for 15 hr. to cleave the intermediate tetrahydropyranyl derivative III (4, 5). Hydrogenation of II using P-1 type nickel boride catalyst (7) and 2 equiv. of hydrogen yielded (90%) the alcohol IV (6, 8), which was oxidized to the corresponding aldehyde V (6) using excess chromium trioxide--pyridine (1 : 2) complex in methylene chloride for 20 min. at 25° (99% yield) and further to the acid VI (6, 9) in 55% yield by means of excess argentic oxide (10) in 9 : 1 tetrahydrofuran--water at 25° for 70 hr. The acid VI was converted to the acid chloride (6) by sequential treatment with 1.1 equiv. of sodium hydride in benzene at 25° and 10 equiv. of oxalyl chloride at 5° for 10 min. and 25° for 20 min., and thence to the diazoketone VII (6) by addition to an excess of dry ethereal diazomethane solution.

The diazoketone VII was heated at reflux for 2 hr. in 10^{-2} M solution in cyclohexane with 2 equiv. of anhydrous cupric sulfate to give the bicyclic ketone VIII (6, 11), which was isolated in 60% yield (overall from the acid VI) and 99% purity by tlc separation (silica gel, hexane--ether 2 : 1, R_f 0.42) and evaporative distillation at 140-150° (bath temp.) and 1 mm. Only one stereoisomeric form of the bicyclic ketone could be detected by infrared, nmr, gc, and tlc analysis of the crude and purified reaction product. The observed stereospecificity of the intramolecular 2 + 1 cycloaddition reaction, the expectation that a cis addition should predominate, and the trans geometry of the double bond undergoing reaction together lead to the assignment of stereoformula VIII. Treatment of the ketone VIII with 2.5 equiv. of sodium hydride in dry dimethoxyethane (under nitrogen) and excess ethyl carbonate at 25° for 9 hr. yielded after chromatographic separation and evaporative distillation (170° bath temp. at 0.4 mm.) the pure ester IX which is partly in the enolic form (6, 12). Exposure of IX to 2 molar equiv. of sodium borohydride in ethanol at -20° for 45 hr. resulted in formation of the β-hydroxy ester X (6) (80% yield after tlc purification) as a mixture of diastereomers. The hydroxy ester X was converted to the benzoate ester XI (6) and thence by reaction with 3 equiv. of potassium



II, R = H

III, R = THP

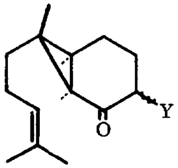


IV, X = CH_2OH

V, X = CHO

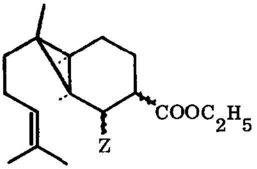
VI, X = COOH

VII, X = $COCHN_2$



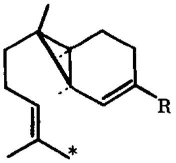
VIII, Y = H

IX, Y = $COOC_2H_5$



X, Z = OH

XI, Z = $OCOC_6H_5$



XII, R = $COOC_2H_5$

XIII, R = CH_2OH

XIV, R = $CH_2OSO_3^-$

I, R = CH_3

t-butoxide in dry t-butyl alcohol under nitrogen to the conjugated ester XII (6, 13) isolated in 66% yield by tlc separation and evaporative distillation at 175° and 0.1 mm. Reduction of XII with lithium aluminum hydride--aluminum chloride (3 : 1) in ether at 0° for 10 min. and 25° for 1 hr. afforded after chromatographic separation using silica gel and evaporative distillation (170°, 1 mm.) the alcohol XIII (6, 14) in 90% yield. The alcohol XIII was transformed into dl-sesquicarene in 86% yield by a new method involving reaction with sulfur trioxide--pyridine complex (2.4 equiv.) in dry tetrahydrofuran at 0° for 10 hr. to form the monosulfate XIV and treatment of the resulting solution with excess lithium aluminum hydride in tetrahydrofuran at 0° for 30 min. and 25° for 5 hr. The infrared and nmr data obtained for synthetic I (15) were identical to those reported for natural sesquicarene (1). Attempts to convert the alcohol XIII to the corresponding chloride or bromide under a variety of conditions with standard reagents for formation of allylic halides (e.g., $SOCl_2$, $(C_6H_5O)_3P^+CH_2C_6H_5$ Br^-) were unsuccessful owing to the great ease with which derivatives of XIII undergo ionization and cyclopropane cleavage.

The stereospecific synthesis of dl-sesquicarene described herein provides additional support for the original (1) assignment of structure and stereochemistry. Further, this synthetic approach clearly should be capable of extension to sirenin, the sperm attractant of the water mold Allomyces (16), which is simply the monooxygenated derivative of XIII with hydroxyl at C*. The synthesis of sirenin will be reported in due course (17).

REFERENCES

1. Y. Ohta and Y. Hirose, Tetrahedron Letters 1251 (1968).
2. Prepared by treatment of propargyl tetrahydropyranyl ether in tetrahydrofuran at -78° with 1 equiv. of n-butyllithium in hexane (Foote Mineral Co.).
3. R. G. Jones and M. J. Mann, J. Am. Chem. Soc. **75**, 4048 (1953).
4. The alcohol II (6) showed a molecular ion at m/e 192.1504 (calcd., 192.1514) and was homogeneous by thin layer chromatography (tlc) on silica gel (R_f 0.17, hexane--ether 4 : 1). Mass spectra were obtained using an AEI-MS-9 double focusing spectrometer.
5. Found for III, molecular ion at m/e 276.2044 (calcd., 276.2089), R_f 0.72 (tlc, silica gel, hexane--ether 4 : 1).
6. The infrared and nmr spectra of this substance were consistent with the assigned structure.
7. H. C. Brown and C. A. Brown, J. Am. Chem. Soc. **85**, 1003 (1963).
8. Found for IV: C, 79.40; H, 12.14. Calcd. for $C_{13}H_{24}O$: C, 79.53; H, 12.32. The following data were also obtained: b.p. 127-128° (2 mm.); n_D^{20} 1.4751; R_f 0.4 (tlc, silica gel, hexane--ether 2 : 1); purity by gc analysis >96% (3 ft. x 0.125 in. column of 5% LAC 446 on silanized support at 145°).
9. Found for VI, molecular ion at m/e 210.1630 (calcd., 210.1620).
10. E. J. Corey, N. W. Gilman, and B. E. Ganem, J. Am. Chem. Soc. **90**, 5616 (1968).
11. Found for VIII: C, 81.03; H, 10.61; infrared max. 5.90 μ (CCl_4). Especially important in the nmr spectrum (CCl_4) was the presence of one 3H singlet due to angular methyl at 1.12 ppm (downfield from internal tetramethylsilane) and two broadened 3H singlets due to two methyls attached to C=C at 1.60 and 1.67 ppm; a single olefinic proton was indicated by a 1H triplet at 5.08 ppm.
12. Found for the ester IX: C, 73.42; H, 9.42; n_D^{20} 1.5051; R_f (silica gel tlc) 0.70 using hexane--methylene chloride--tetrahydrofuran 20 : 4 : 1; infrared max.(CCl_4) at 3.2-3.7 μ (broad, OH) and 5.74, 5.92, 6.07, 6.24 μ (β-keto ester and enol ester C=O and C=C).
13. Found for the conjugated ester XII: C, 77.76; H, 9.92; n_D^{20} 1.5025; $\lambda_{max.}$ (ethanol) 252 nm. (ε 10,400); carbonyl absorption at 5.88 μ (CCl_4).
14. Found for the alcohol XIII: C, 81.72; H, 10.90; molecular ion at m/e 220.1830 (calcd., 220.1827); homogeneous by gc and tlc analysis.
15. Found: C, 88.16; H, 11.68; molecular ion at m/e 204.1874 (calcd., 204.1878); homogeneous by gc analysis; retention time 9.4 min. using a 10 ft. x 0.125 in. column of 10% Carbowax 20 M at 180° with N_2 flow 30 ml./min.
16. L. Machlis, W. H. Nutting, and H. Rapoport, J. Am. Chem. Soc. **90**, 1674, 6434 (1968).
17. This work was supported by the National Science Foundation.