Tetrahedron Letters No.1, pp. 41–44, 1970. Pergamon Press. Printed in Great Britain.

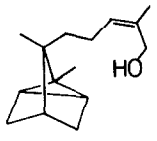
THE TOTAL SYNTHESIS AND GEOMETRIC CONFIGURATION OF dl-β-SANTALOL

Herbert C. Kretschmar and William F. Erman

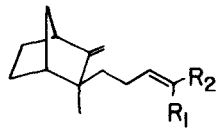
The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

(Received in USA 1 December 1969; received in UK for publication 6 December 1969)

The major constituents of the prized essential oil of East Indian sandalwood (Santalum album Linn) - α-santalol (I) and β-santalol (II) - were isolated and their gross structures characterized over 30 years ago (1). In spite of recorded syntheses of both epimers in subsequent years (2,3), the geometric configuration of the α-isomer was only recently correctly established as the seqcis-structure I (4). We report here the first unambiguous synthesis of dl-seqcis-β-santalol (II) and dl-seqtrans-β-santalol (III). The natural isolate, previously assigned the trans-stereochemistry III (5), is clearly established by this work as the seqcis-isomer II.



I

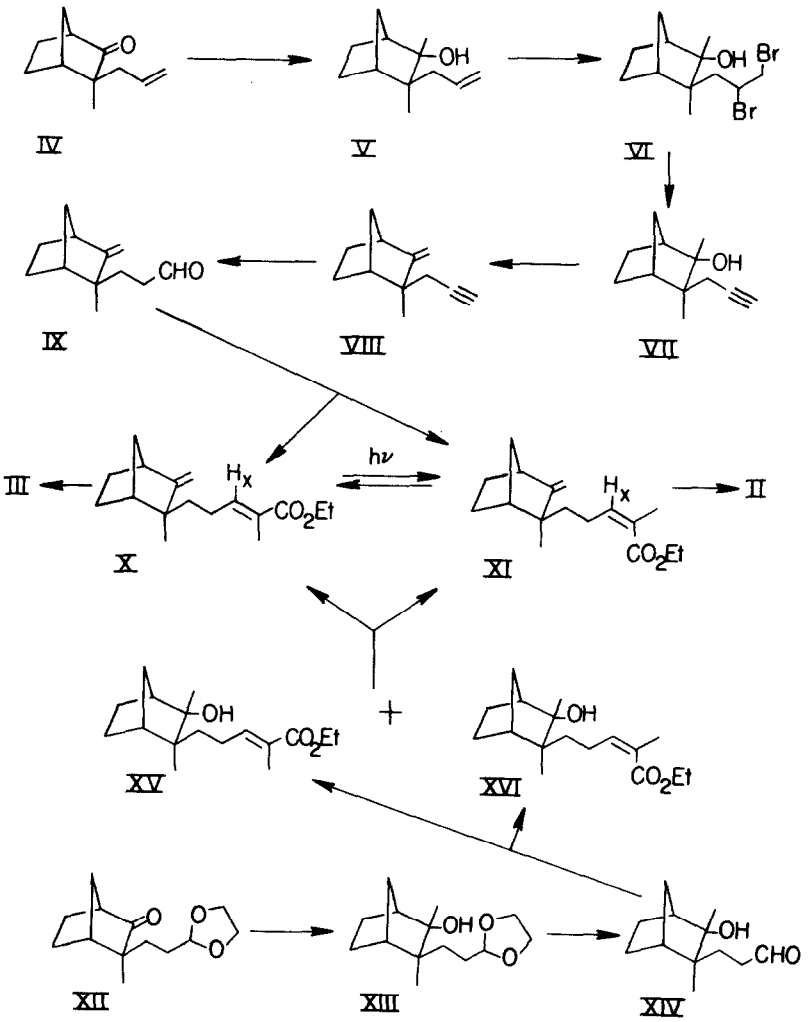


II, $R_1 = CH_2OH$, $R_2 = CH_3$

III, $R_1 = CH_3$, $R_2 = CH_2OH$

The key intermediates in our projected synthesis of II and III were the corresponding esters X and XI which were prepared by two different routes. The first route is depicted in Chart I by the progression IV → X and XI. Treatment of the sodium enolate of 3-methylnorcamphor (6) with allyl bromide in tetrahydrofuran at 66° for 3 hr afforded IV (80%), bp 83-84° (4.0 mm) (7). Addition of excess ethereal methyl lithium to an ethereal solution of IV produced the alcohol V, bp 75-76° (0.7 mm), in 86% yield. Bromination of V in carbon tetrachloride yielded the partially crystalline dibromide VI, which was treated at 27° for a period of 16 hr with excess

Chart I



IV V VI VII VIII IX X XI XII XIII XIV XV XVI II III

sodium amide in hexamethylphosphoramide to afford VII (48% overall yield from V), mp 54.5-55.5°. Treatment of VII with thionylchloride in pyridine at 0-5° led to a mixture of olefin VIII and chloro compounds. The mixture was refluxed in pyridine for 3 hr to afford VIII, bp 74° (5.0 mm), in 41% overall yield from VII. Conversion of VIII to IX (61% yield) was effected with one equivalent of disiamylborane in tetrahydrofuran and subsequent oxidation (8). The aldehyde, purified by preparative glc (7), on condensation with excess ethyl 2-(triphenylphosphoranylidene)-propionate afforded the mixture of esters X and XI, bp 110-120° (0.25 mm) (18%), in a ratio of 5:1. In the nmr spectrum of the major product (isolated by preparative glc (7)) the olefinic proton (H_X) beta to the carbethoxy group appeared at ca. 1.0 ppm lower field than the corresponding proton H_X in the minor isomer (τ 3.46 vs τ 4.28). The fact that the chemical shift of the β-proton cis to the carbethoxy group of an α,β-unsaturated ester occurs downfield relative to that of the β-proton trans to the carbethoxy group is well established (9). Consequently, the trans geometry (H_X-cis to the carbethoxy group) can be unequivocally assigned to the major isomer and the cis geometry (H_X-trans to the carbethoxy) can be assigned to the minor isomer.

The same ester mixture was produced in 25% overall yield via the sequence XII → X and XI (Chart I). The acetal XII (6) was converted to XIII, bp 120-125° (0.5 mm), in 75% yield by treatment with an ethereal solution of methyl lithium. Hydrolysis was effected, without concomitant dehydration of the tertiary alcohol function, by heating a solution of XIII, 2.5 ml of 10% sulfuric acid, and 50 ml of tetrahydrofuran at 57° for 16 hr. The resulting hydroxyaldehyde (81% yield) was treated with ethyl 2-(triphenylphosphoranylidene)-propionate to yield the ester mixture XV and XVI in the ratio 5:1. Dehydration with thionyl chloride afforded X and XI in the same ratio.

A solution of X and XI (5:1) in toluene or cyclohexane was irradiated with ultraviolet light (200 w, Hanovia mercury arc lamp) until the ratio of X to XI was approximately 2:1. (The ratio of X to XI reached a minimum of ca. 1:1 on further irradiation; however, further irradiation also led to deconjugation of the double bond.) The two isomers were separated by preparative glc (7), and their spectral properties (nmr, ir, mass) were identical with those of X and XI prepared by the alternate route above.

Reduction of the 5:1 and 2:1 mixtures of esters X and XI with 1.1 equivalent (0.3 mole equivalent) of lithium aluminum hydride in ether at 0° for 1 hr afforded the corresponding

alcohols II and III, bp 100-110° (0.1 mm) (78%), in ratios of 5:1 and 2:1, respectively. The two isomers were separated by preparative glc (7). Although the infrared spectra of the natural isomer (10) and both synthetic isomers were strikingly similar, the glc retention times and nmr spectra were markedly different. The nmr spectra and glc retention times of the synthetic seqcis isomer II and natural β-santalol were identical. In the nmr spectrum (10% in CCl_4) of this isomer the signal for the olefinic methyl hydrogens appears as a singlet at τ 8.28 and the signal for the protons alpha to the hydroxyl group appears as a singlet at τ 6.0. In contrast, in the nmr spectrum of the synthetic trans isomer III,the olefinic methyl signal appears at τ 8.40 and that of the protons alpha to the hydroxyl,at τ 6.20.

Acknowledgments. The authors acknowledge the technical assistant of Mr. Dennis Toepker.

REFERENCES

1. For a review of the isolation, characterization, and general chemistry of the α- and β-santalols, see J. L. Simonsen and D. H. R. Barton, The Terpenes, Vol. III, 2 ed., Cambridge University Press, Cambridge, England (1951), pp. 178-188.
2. S. Y. Kamat, K. K. Chakravarti, and S. C. Bhattacharyya, Tetrahedron, 23, 4487 (1967).
3. J. Colonge, G. Descotes, Y. Bahurel, and A. Menet, Bull. Soc. Chim. France, 374 (1966).
4. R. G. Lewis, D. H. Gustafson, and W. F. Erman, Tetrahedron Letters, 401 (1967).
5. G. Brieger, Tetrahedron Letters, 2123 (1963).
6. H. C. Kretschmar, Z. J. Barneis, and W. F. Erman, preceding paper.
7. The spectral (nmr, ir, mass), analytical (C, H) data, and spectific glc conditions will be reported in the complete paper.
8. H. C. Brown and G. Zweifel, J. Amer. Chem. Soc., 83, 3834 (1961).
9. L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, New York, N.Y., 1959, p. 122.
10. We are grateful to Professor G. Brieger for a sample of natural β-santalol isolated and purified by reported procedures: A. E. Bradfield, A. R. Penfold, and J. L. Simonsen, J. Chem. Soc., 309 (1935); P. C. Guha and S. C. Bhattacharyya, J. Indian Chem. Soc., 21, 261 (1944). Natural β-santalol was also isolated in relatively pure form by preparative glc from a sample of commercial sandalwood oil, Givaudan-Delawanna, Inc.