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TOTAL SYNTHESIS OF α-SANTALOL

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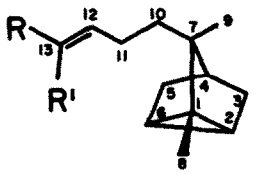
The powerful, sweet, woody fragrance of East Indian sandalwood oil places this isolate of Santalum album Linn among the most prized of the oils essential in the compounding of soap and cosmetic perfumes (1). Although its two major constituents -- α-santalol and β-santalol -- comprise greater than 90% of the commercial oil, total syntheses of these two alcohols have not been recorded (2). Earlier degradations and syntheses established the tricyclic skeleton of α-santalol (3). The more recent synthesis of α-santalene (4) coupled with the conversion of α-santalol to α-santalene and spectroscopic studies on α-santalol (5) indicated that the stereochemistry of natural α-santalol was that represented by the seqtrans structure II (6). We report here the synthesis of the two isomeric α-santalols -- seqcis-α-santalol (I) and seqtrans-α-santalol (II) -- from (+)-π-bromotricyclene (IV). Since a total synthesis of the latter compound has been recorded (4), the present conversion represents a total synthesis and unambiguously establishes the stereochemistry of the natural isomer as that represented by the seqcis structure I rather than the seqtrans structure II (5).

The readily available (+)-α-bromocamphor (III) was converted to (+)-π-bromotricyclene (IV) by known procedures (4). Although displacement of bromide ion from IV was anticipated to be difficult because of the neopentyl nature of the bromo structure, it was found that lithium acetylide-

ethylenediamine complex gave rapid displacement of bromide ion from IV when dimethyl sulfoxide or hexamethylphosphoramide was employed as solvent (7). However, the expected acetylenic product V underwent rapid isomerization to the internal isomer VI under these reaction conditions; consequently VI or a mixture of the two isomers VI and V was isolated in 80-90% yield. The composition of this mixture depends greatly upon the reaction time and temperature as well as the solvent employed. For example: when DMSO was the solvent and the reaction was carried out for 2 hours at 100-110°, IV, V, and VI were found to be present in the product mixture in a ratio of 0:1.0:2.4. However, after 160 hours at 23-25° in DMSO the ratio of IV:V:VI was 0.5:1.6:1. When HMPA was the solvent employed and the reaction was carried out at 25-27° for 22 hours, the ratio of IV, V, and VI in the product mixture was 0:1.0:9.0, but after 160 hours at 25-27° VI was the only product isolated.

Treatment of VI or a mixture of the V and VI for 24 hours with sodium amide in refluxing xylene afforded V (63% yield), b.p. 49-50° (2.5 mm), $[\alpha]_D^{25}$ -23.60° (chloroform), infrared $\lambda_{max}^{CCl_4}$ 3.00, 3.38, 4.72, 6.91 μ, nmr τ_{CDCl_3} 9.12 (2H, singlet), 8.10 (1H, doublet, $J_{10,12}$ = 2.8 cps), 7.98 (2H, doublet, $J_{10,12}$ = 2.8 cps) (8). Anal. Found: C, 89.7; H, 10.0. Alternatively, V was precipitated from an ethanol-water solution of the mixture by silver nitrate addition. The silver salt of V was filtered, washed with ether and suspended in carbon tetrachloride from which pure V was liberated by treatment with hydrochloric acid. The internal isomer VI (8) was recovered from the ethanol-water filtrate by extraction with n-hexane. Monohydroboration of V with one equivalent of a one molar solution of disiamylborane in THF and subsequent alkaline hydrogen peroxide oxidation of the resulting trialkylborane (9) produced tricycloekasantalal (VII) in 60% yield, infrared $\lambda_{max}^{CCl_4}$ 3.40, 3.69, 5.81, 6.88 μ, nmr τ_{CDCl_3}

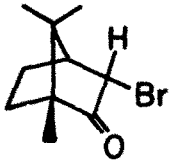


I, R = CH_3, R' = CH_2OH

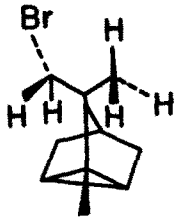
II, R = CH_2OH, R' = CH_3

VIII, R = $CO_2C_2H_5$, R' = CH_3

IX, R = CH_3, R' = $CO_2C_2H_5$



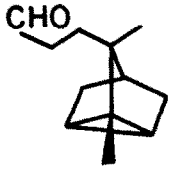
III



IV

V

VI



VII

9.02 (2H, singlet), 7.55 (2H, sextet, $J_{11,12}$ = 2.2 cps, $J_{10,11}$ = 7.6 cps), 0.10 (1H, triplet, $J_{11,12}$ = 2.2 cps).

Treatment of VII with (carbethoxyethylidene)triphenylphosphorane in methanol afforded a mixture (b.p. 128-135°/0.6 mm) of two α,β-unsaturated esters, VIII and IX, in a ratio of 5:1 respectively (86% yield). The use of methylene chloride as the solvent in the above Wittig reaction increased the ratio of VIII to IX to 10:1 (50% yield). The two esters were easily separated by gas chromatography (10). The major component, VIII, had $[\alpha]_D^{25}$ +32.75° (chloroform), infrared $\lambda_{max}^{CCl_4}$ 3.37, 5.86, 6.08 μ, nmr τ_{CDCl_3} 9.07 (5H, singlet), 8.71 (3H, triplet, J = 7.6 cps), 5.86 (2H, quartet, J = 7.6 cps), 3.28 (1H, multiplet, $J_{11,12}$ = 8.0 cps). Anal. Found: C, 77.8; H, 9.7. The minor product, IX, had $[\alpha]_D^{25}$ +8.17° (chloroform), infrared $\lambda_{max}^{CCl_4}$ 3.37, 5.85, 6.09 μ, nmr τ_{CDCl_3} 9.18 (5H, singlet), 8.72 (3H, triplet, J = 7.4 cps), 5.85 (2H, quartet, J = 7.4 cps), 4.16 (1H, multiplet, $J_{11,12}$ = 8.0 cps). Anal. Found: C, 77.9; H, 10.0. The structures of VIII and IX were delineated by nmr spectroscopy. It is well known that the chemical shifts of the signals exhibited by the olefinic protons in α,β-unsaturated esters, such as VIII and IX, depend upon their cis or trans relationship to the β-carbethoxy group (11). The olefinic signal in VIII was centered at τ 3.28 while in IX it was centered at higher field (τ 4.16). Since compound VIII had the lower field olefinic proton signal, it was assigned as the component with the olefinic proton cis to the carbethoxy group, and IX was assigned as the material with the olefinic proton trans to the carbethoxy group.

Reduction of VIII with lithium aluminum hydride in ether at 25-26° afforded the seqtrans allyl alcohol II (60% yield), b.p. 113-119° (0.5 mm), $[\alpha]_D^{25}$ +18.09° (chloroform), infrared $\lambda_{max}^{CCl_4}$ 2.99, 3.48, 5.95 μ, nmr τ_{CDCl_3} 9.17 (5H, singlet), 8.33 (3H, singlet), 6.01 (2H, singlet), 4.59 (1H,

triplet, $J_{11,12}$ = 6.2 cps), τ_{CS_2} 8.42 (3H, singlet). Anal. Found: C, 81.8; H, 11.2. Treatment of IX with lithium aluminum hydride in ether at 25-26° yielded the seqcis allyl alcohol I as a clear oil (55% yield), $[\alpha]_D^{25}$ +18.33° (chloroform), infrared $\lambda_{max}^{CCl_4}$ 2.70, 2.90, 3.35 μ, nmr τ_{CDCl_3} 9.18 (5H, singlet), 8.23 (3H, singlet), 5.90 (2H, singlet), 4.72 (1H, triplet, $J_{11,12}$ = 7.4 cps), τ_{CS_2} 8.32 (3H, singlet). Anal. Found: C, 81.5; H, 11.1. The nmr and infrared spectral data as well as the gas chromatographic retention times for I were identical with those of natural α-santalol.[a]

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(a) Natural α-santalol was isolated by gas chromatography at 200° with a column of 20% Reoplex on Chromosorb W, HMDS, helium flow rate of 60 ml/min from a sample of East Indian sandalwood oil obtained from Givaudan-Delawanna, Inc. The gas chromatographic retention times, infrared and nmr spectra of this material were identical to those exhibited by I and differed from the gas chromatographic and spectral data obtained from II. The α-santalol content of seven additional East Indian sandalwood oil samples and one Australian sandalwood oil sample, all obtained from different sources, was investigated by gas chromatography at 175° with a column of 15% EgSSX on gas chrom P, helium flow of 57 ml/min (conditions that separated I and II very well). All of the samples were found to contain only the seqcis-isomer I; none of the seqtrans-isomer II could be detected in any of the oils. The nmr spectrum of our synthetic seqcis-isomer I and that of the natural α-santalol studied by Brieger (and assigned the seqtrans-configuration (5)) were essentially identical and contrasted significantly with the nmr spectrum of the synthetic seqtrans-isomer. We are grateful to Dr. Brieger for sending us the nmr spectrum of his natural α-santalol.

References

1. E. Guenther, The Essential Oils Vol. V, pp. 173-186, D. Van Nostrand Co., Inc., New York (1952).

2. During the preparation of this manuscript, a total synthesis of a mixture of α- and β-santalols appeared; J. Colonge, G. Descotes, Y. Bahurel, and A. Menet, Bull. Soc. Chim. France, 374 (1966). Isolation and identification of the individual components, other than by gas chromatographic retention times on a Reoplex column, were not recorded. Since it has been our experience that the seqcis-seqtrans isomers of α-santalol are not separated by gas chromatography on a Reoplex column, it is impossible to tell whether these authors obtained the seqcis- or seqtrans-isomer or a mixture of both isomers from their synthesis.

3. J. Simonsen and D. H. R. Barton, The Terpenes Vol. III, 2nd Ed., pp. 178-185, University Press, Cambridge (1951) and references therein.

4. E. J. Corey, S. W. Chow, and R. A. Scherrer, J. Am. Chem. Soc. 79, 5773 (1957).

5. G. Brieger, Tetrahedron Letters, 2123 (1963).

6. The seqcis and seqtrans terminology is in accord with the stereochemical rules proposed by R. S. Cahn, C. Ingold and V. Prelog, Angew. Chem. Internat. Ed. Engl. 5, 385 (1966).

7. Displacements on alkyl halides with sodium acetylide in liquid ammonia have been reported previously. See further: (a) M. Picon, Compt. Rend. 158, 1346 (1914); 169, 32 (1919). (b) T. Vaughn, J. Am. Chem. Soc. 55, 3453 (1933). However, we found that neither liquid ammonia/lithium acetylide-ethylenediamine complex nor DMF/lithium acetylide-ethylenediamine complex gave satisfactory displacement of bromide ion from IV.

8. All nmr spectra were obtained at 100 Mc from dilute solutions with tetramethylsilane as internal standard. Complete spectral, physical, and analytical data will be recorded in the full paper to be published.

9. H. C. Brown and G. Zweifel, J. Am. Chem. Soc. 83, 1241 (1961); ibid. 83, 3834 (1961).

10. Gas chromatographic separation of this mixture was accomplished at 200° with a column of 20% S.F.-96 on Chromosorb W, HMDS, helium flow rate of 60 ml/min.

11. L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, p. 122, Pergamon Press, New York, (1959).