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AN APPROACH TO THE SYNTHESIS OF β-SANTALENE SESQUITERPENES.
ISOLATION OF *exo*-NORBICYCLOEKASANTALAL FROM EAST INDIAN SANDALWOOD OIL.

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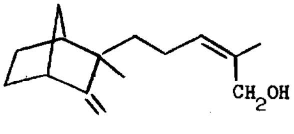
The essential oil of the heartwood of the East Indian Sandalwood tree, *Santalum album Linn*, is a rich source of α- and β-santalene sesquiterpenes.[1] For some time we have been interested in the development of methods for the synthesis of members of the β-series, e.g., β-santalol, **1**.[2] We specifically wished to develop a simple but versatile route which did not suffer from the restriction of dependence upon naturally available bicyclo[2.2.1]heptane precursors. A promising method appeared to exist in the Claisen rearrangement of derivatives of **2**. The expected products of this rearrangement should be easily elaborated into the sesquiterpenes. A secondary question of some interest concerning these rearrangements is the stereochemistry of the products obtained. We wish to report here the successful utilization of this method for the stereoselective synthesis of the aldehyde **3a** and the amide **3b**, and the subsequent identification of **3a** as a minor constituent of East Indian Sandalwood oil.



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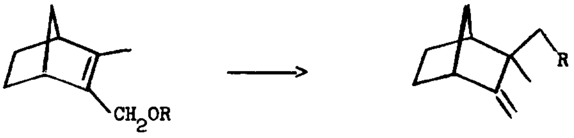
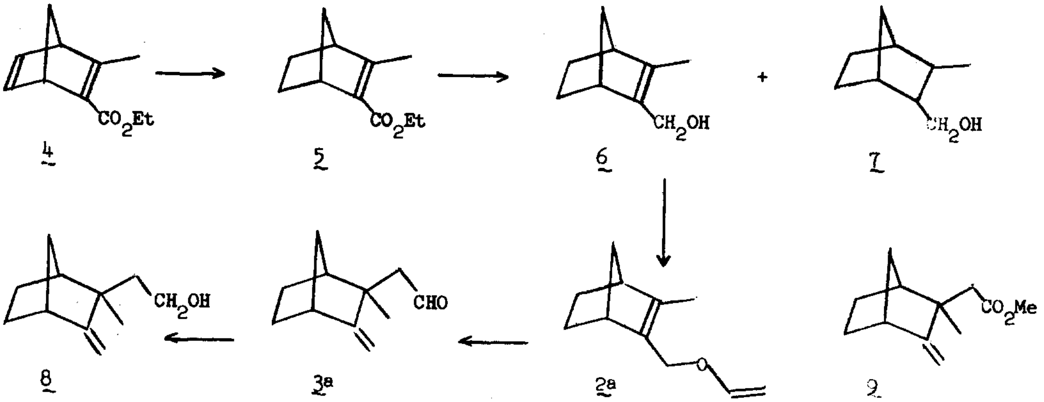


2a, R = $CH{=}CH_2$
2b, R = $C(NMe_2){=}CH_2$

3a, R = CHO
3b, R = $CONMe_2$

The route chosen for the synthesis of the vinyl ether 2a is shown in the scheme. Reaction of ethyl tetrolate with excess dicyclopentadiene at reflux gave the bicyclic ester 4 [bp 51° (8mm); ir (film), 1707 (C=O) and 1636 (C=C) cm^{-1}; ms peaks at m/e 178 (M^{+}) and 91 (base); and nmr signals (CDCl$_3$) at τ 8.72 (3H, t, J = 7 Hz), 8.03 (2H, m), 7.80 (3H, s), 6.64 (1H, bd. s), 6.14 (1H, bd. s), 5.86 (2H, q, J = 7 Hz), 3.30 (1H, m), and 3.14 (1H, m)] in 59% yield.[3,4] Hydrogenation of 4 over platinum oxide at moderate pressures afforded the mono-olefinic ester 5 [ir (film) 1707 and 1636 cm^{-1}, m/e 180 (M^{+}), and nmr signals at τ 8.92 (2H, d, J = 7 Hz), 8.71 (3H, t, J = 7.2 Hz), 8.28 (2H, dt, J = 7 and 2 Hz), 7.90 (3H, s), 7.25 (1H, bd. s), 6.81 (1H, bd.s), and 5.85 (2H, q, J = 7 Hz)] in quantitative yield. Reduction of 5 with lithium aluminum hydride presented difficulties because of over-reduction, leading to an inseparable mixture of the desired allylic alcohol 6 and saturated alcohol 7. The best mixture obtained in this way contained approximately 65% of 6. Reduction of 5 with aluminum hydride[5], however, provided the alcohol 6 [bp 81-2° (12 mm), ir (film) 3340, 1660, and 1000 cm^{-1}, m/e 138 (M^{+}), and nmr signals at τ 8.95 (3H, m), 8.63 (1H, d of quint, J = 8 and 2 Hz), 8.31 (3H, s), 7.40 (1H, bd. s), 7.10 (1H, bd. s), and an AB quartet with doublets at 6.00 and 5.90 (J = 12 Hz)] in 94% yield. Conversion of 6 to the vinyl ether 2a was carried out by reaction with ethyl vinyl ether in the presence of mercuric acetate.[6] Distillation provided nearly pure 2a, [bp 50-55° (2mm), ir (film) 3100, 1635, and 1612 cm^{-1}, and nmr signals at τ 9.02 (1H, d, J = 2 Hz), 8.88 (2H, d, J = 2 Hz), 8.63 (2H, m), 8.43 (1H, m), 8.29 (3H, s), 7.35 (1H bd. s), 7.12 (1H, bd. s), 6.02 (1H, dd, J = 7 and 2 Hz), 5.82 (1H, dd, J = 14 and 2 Hz), 5.75 (2H, s), and 3.50 (1H, dd, J = 14 and 7 Hz)] in 50% yield. Attempts to further purify the ether by



preparative gas chromatography were thwarted by partial rearrangement to **3a** in the detector block.

Rearrangement of neat **2a** in a sealed glass tube at 185° was complete in one hour, giving a single volatile product, **3a**, in 77% yield. The structure of the aldehyde, which was homogeneous on two glpc columns, was determined by spectral data [ir (film) 3070, 2730, 1728, 1660, and 885 cm^{-1}, m/e 164 (M^+), and nmr signals at τ 8.80 (3H, s), 7.78 (1H, bd. s), 7.67 (2H, d, J = 3 HZ), 7.32 (1H, bd. s), 5.54 (1H, s), 5.22 (1H, s), and 0.26 (1H, t, J = 3 Hz); 2,4-DNP, m.p. 106-8°] and by lithium aluminum hydride reduction to the known *exo*-alcohol **8**. This alcohol was identified by comparison with an authentic sample.[7]

A similar stereoselectivity was observed in the rearrangement of the acetal **2b** to the liquid amide **3b** [ir (film) 1655 and 881 cm^{-1}, m/e 207 (M^+), and nmr signals at τ 8.78 (3H, s), 7.68 (2H, s), 7.41 (1H, m), 7.33 (1H, m), 7.07 (3H, s), 7.00 (3H, s), 5.48 (1H, s), and 5.22 (1H, s)] in 40% yield. This process[8] is somewhat more convenient than the conventional Claisen rearrangement because it is not necessary to isolate the vinyl ether intermediate, and also because of the formation of a more stable product. The *exo*-nature of this latter rearrangement was proven by hydrolysis (KOH/ethylene glycol) and esterification (diazomethane) to give the single methyl ester **9**, identical with the ester obtained from Ag_2O oxidation/esterification of **3a** [ir (film) 3070, 1745, 1665 and 884 cm^{-1} and nmr signals at τ 8.84 (3H, s), 7.82 (1H, d, J = 14 Hz), 7.64 (1H d, J = 14 Hz), 7.62 (1H, m), 7.34 (1H, m), 7.40 (3H, s), 5.52 (1H, s), and 5.25 (1H, s)]. Numerous processes can be conceived for the convenient conversion of **3** to β-santalene sesquiterpenes, none of which have yet been attempted.

The highly stereoselective nature of the rearrangement step is probably a result of hindrance to *endo* approach of the vinyl group by the *endo* hydrogens of the two-carbon bridge, and has ample precedent in intermolecular additions to the norbornene system (see, for example, ref. **3b**). Dreiding models show that this effect results in more efficient overlap with the π-orbitals on the *exo* face of the norbornene system.

During the time this work was in progress, we succeeded in isolating a C_{11} aldehyde from the volatile fraction of East Indian Sandalwood oil, which showed spectral characteristics identical to synthetic **3a**. A commercial grade of sandalwood oil[10] was fractionally distilled from an 18 inch spinning band column and the portion distilling at 30-55° (0.35 mm) was collected. This fraction was subjected to gas chromatography (10 ft. x 1/4 in. column packed with 20% DC-200 silicone oil on 60/80 mesh chromosorb W-AW-DMCS at 150° and 60 ml/min. He flow) and the components with retention times between 6 and 16 minutes were collected. Gas chromatography of this fraction on a 10 ft. x 1/4 in. column packed with 20% diethyleneglycol succinate on 60/80 mesh Chromosorb W-AW-DMCS under the same conditions of temperature and flow as above showed a complexity of peaks. The component with a retention time of 11 minutes (relative to air) was collected and again subjected to gas chromatography on the DC-200 column at 130°. The component with a retention time of 19.1 minutes (relative to air) was collected as a colorless oil. The ir and nmr spectra of this material were identical with those of synthetic **3a**. To our knowledge, this is the first report of the isolation of **3a** from Sandalwood oil, although the tricyclic isomer, nortricycloekasantalal, has been known for many years.[9]

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