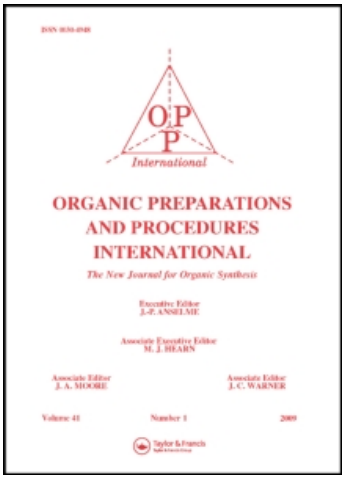

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A HIGHLY STEREOSELECTIVE TRANSFORMATION OF β-SANTALENE TO (*E*)-β-SANTALOL

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A HIGHLY STEREOSELECTIVE TRANSFORMATION OF β-SANTALENE TO (E)-β-SANTALOL

Submitted by (07/06/93)

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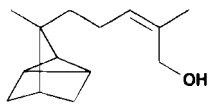
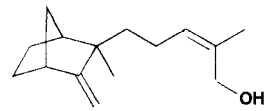
The great fixative properties and woody-sweet odor of East Indian Sandalwood oil are mainly due to α- and β-santalols (**1** and **2**) which constitute more than 90% of the oil.[1,2] Several minor components of the oil such as β-santalene (**3**), *epi*-β-santalene, *epi*-β-santalol also contribute to the perfuming properties to a lesser extent.[3] The synthesis of santalols, santalenes and other fragrance compounds of the sandalwood type has been reported.[4-6] We now describe a highly regio- and stereoselective transformation of β-santalene (**3**) to (E)-β-santalol (**4**) by an N-oxide [2,3]sigmatropic rearrangement.[7]



1



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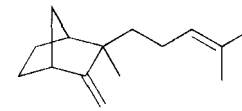
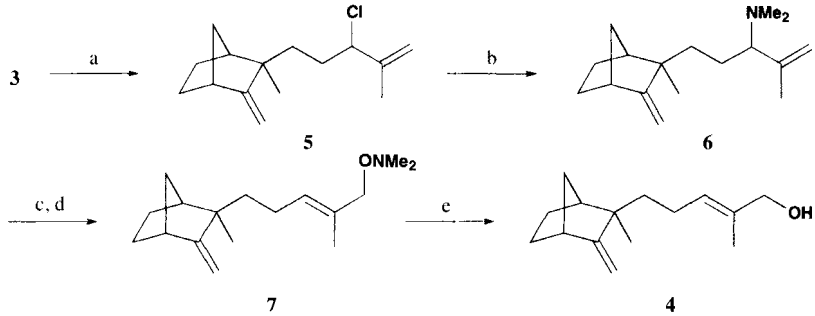


3

Allylic chlorination of β-santalene (**3**)[6] with calcium hypochlorite[7b-e] gave a quantitative yield of **5** which with dimethylamine, gave the tertiary amine **6**. Upon heating at 40-50°, the N-oxide



a) $Ca(OCl)_2$, CO_2 b) Me_2NH (aq.), EtOH c) CH_3CO_3H, Na_2CO_3 d) Δ (40-50°) e) Zn, CH_3CO_2H

obtained by peracid oxidation of the tertiary amine **6**, underwent a [2,3]sigmatropic rearrangement[7] to afford the allyloxyamine **7**. Reductive cleavage of **7** with zinc dust in acetic acid[9] gave (E)-β-santalol (**4**). Its ^1H NMR spectrum exhibited a singlet at δ 3.85 assigned to the -C$\underline{H}_2$OH protons of the E isomer, in good agreement with the reported data.[10] No signal at δ 4.05, diagnostic for the Z isomer was observed, indicating exclusive formation of the E isomer.

EXPERIMENTAL SECTION

GC analysis was performed on a Hewlett-Packard 5730A-3390A instrument. NMR spectra were obtained in $CDCl_3$ on a Hitachi R-600 or Jeol FT-90Q instrument. IR spectra were run on a Shimadzu-8101 FT-IR Spectrometer. Column chromatography was carried out with Silica gel (Sisco, 100-200). Ca $(OCl)_2$ (Fluka, AG) was used as received.

3-*endo*-Methyl-3-*exo*-(3-dimethylamino-4-methyl-4-pentenyl-2-methylenebicyclo[2,2,1]heptane (6).- A solution of β-santalene (**3**) (3.5 g, 17.1 mmol) in CH_2Cl_2 (100 mL) was added to a suspension of 61% $Ca(OCl)_2$ (2.2 g) in 15 mL of aq. saturated Na_2SO_4. Dry ice (25 g) was added in small portions to this mixture under vigorous stirring, over a period of 3 hrs. The mixture was filtered, organic phase was separated, dried ($MgSO_4$) and concentrated on a rotary evaporator to give the allylic chloride **5**. The crude chloride 5 (4.08g, 17.1 mmol) was stirred with 50% aq. dimethylamine (50 mL) and EtOH (15 mL) at room temperature for 3 days. The mixture was concentrated *in vacuo* and extracted with EtOAc (50 mL) and the organic phase was washed (brine), dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (EtOAc:hexane, 1:9 to 1:1) afforded the allylamine **6** (3.2 g, 75%) as a colorless oil, bp. 110-120°/0.4 Torr. IR (neat): 3130, 1645,

1230, 1040, 885 cm^{-1}. ^1H NMR: δ 1.05 (s, 3H), 1.75 (s, 3H), 1.0-2.2 (m, 11H), 2.15 (s, 6H), 2.3-2.7 (m, 2H), 4.45, 4.70 (2s, 2H), 4.95, 5.1 (2s, 2H).

Anal. Calcd for $C_{17}H_{29}N$: C, 82.52; H, 11.82. Found: C, 82.60; H, 11.90

3-*endo*-Methyl-3-*exo*-(5-dimethylaminooxy-4-methyl-3-pentenyl)-2-methylenebicyclo[2,2,1]-heptane (7).- To a mixture of the allylamine **6** (2 g, 8.08 mmol), Na_2CO_2 (0.85 g) and CH_2Cl_2 (75 mL) at -60°, peracetic acid (40%, 1.68 g, 8.88 mmol) was added and the reaction mixture was stirred for 30 min at -60° and then allowed to attain room temperature over a period of 30 min. A saturated aq. solution of $NaHCO_3$ (40 mL) was added to the reaction mixture and stirring was continued for 10 min. The organic phase was separated, the aq. layer was extracted with EtOAc, the combined organic phase was washed (brine), dried ($MgSO_4$) and evaporated *in vacuo* at 40-50° over a period of 1 hr. The residue was purified by column chromatography (hexane:EtOAc, 7:3) to yield the allyloxyamine **7** (1.52 g, 71%) as a pale yellow oil, n_D^{20} 1.478. IR (neat): 3100, 1650, 1240, 1015, 800 cm^{-1}. ^1H NMR: δ 1.04 (s, 3H), 1.65 (s, 3H), 1.0-2.35 (m, 12H), 2.45 (s, 6H), 4.1 (s, 2H), 4.45, 4.75 (2s, 2H) 4.9-5.2 (m, 1H).

Anal. Calcd for $C_{17}H_{22}ON$: C, 77.51; H; 11.09. Found: C, 77.60; H, 11.00

(4)-2-Methyl-5- (2-*endo*-methyl-3-methylene-bicyclo[2,2,1]hept-2-yl)-2-penten-1-ol ((E)-β-Santalol) (4).- A mixture of the allyloxy amine **7** (0.5 g, 1.89 mmol), zinc dust (10 g), acetic acid (10 mL) and water (10 mL) was stirred for 24 hrs at room temperature. Zinc dust was removed by filtration and the mixture was extracted with ether. The ethereal extract was washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Purification by column chromatography (hexane:EtOAc, 1:1) gave **4** (0.38 g, 91%) as a colorless oil, bp. 125-135°/0.3 Torr, homogeneous by gas chromatography. IR (neat): 3330, 2960, 1660 cm^{-1}. ^1H NMR: δ 1.03 (s, 3H), 1.62 (br. s, 3H), 2.55-2.78 (m, 1H), 3.85 (s, 2H), 4.43, 4.70 (2s, 2H), 5.1-5.5 (m, 1H).

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A SUPERIOR METHOD FOR THE SYNTHESIS OF 7a-METHYL-2,3,7,7a-TETRAHYDRINDEN-5(6H)-ONE

Submitted by (11/05/93) H. Surya Prakash Rao* and K. Subba Reddy

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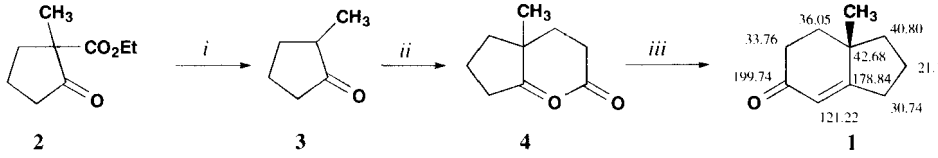
7a-Methyl-2,3,7,7a-tetrahydrinden-5(6H)-one (**1**) is an important synthetic intermediate in the steroid and terpenoid fields.[1] In the course of other work, we required large quantities of this compound. A literature search indicated that the reported Robinson annulations on 2-methylcyclopentanone gave low yields (35%)[2] or used expensive reagents.[3] We report herein a higher yielding method for the synthesis of hydrindenone **1** (Eq. 1).



2 3 4 1 (1)

(*i*) conc. HCl, reflux; (*ii*) MVK, conc. H_2SO_4 (cat) benzene, reflux; (*iii*) 10% ethanolic KOH, reflux

2-Methylcyclopentanone (**3**) is commercially available, but expensive. As this compound was required in large quantities, we had initially tried the reported procedure[4] which involved hydrolysis of ethyl 1-methyl-2-oxocyclopentanecarboxylate (**2**) under basic conditions (aqueous ethanolic