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P. A. Unnikrishnan [a] & P. A. Vatakencherry [a]
[a] Department of Applied Chemistry, Cochin University of Science and Technology, Cochin, 682 022, India

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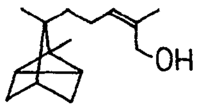
SYNTHESES OF epi-β-SANTALENE, β-SANTALENE AND AN ISOMER OF β-SANTALENE WITH 4-METHYL-4-PENTENYL SIDE CHAIN

P.A. Unnikrishnan and P.A. Vatakencherry*
Department of Applied Chemistry
Cochin University of Science and Technology
Cochin - 682 022, India.

The olfactory characteristics of East Indian Sandalwood oil is mainly due to its major components α-santalol (1) and β-santalol (2), while many of the components like β-santalene (3) and epi-β-santalene (4) also contribute to the perfumery



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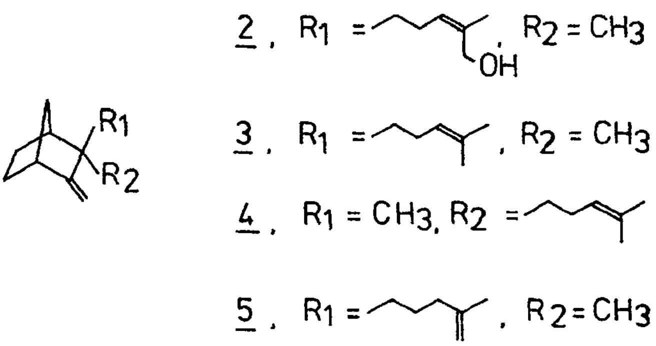
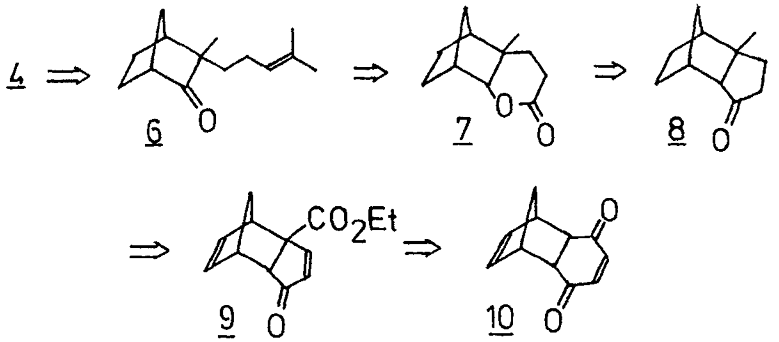


properties[1]. Since the pioneering work of Corey[2], Brieger[3] and Money[4] a number of syntheses of these compounds have appeared[5,6]. Of late there has been great interest in the synthesis of certain minor components of the oil, like the isomer of β-santalene with 4-methyl-4-pentenyl side chain (5).

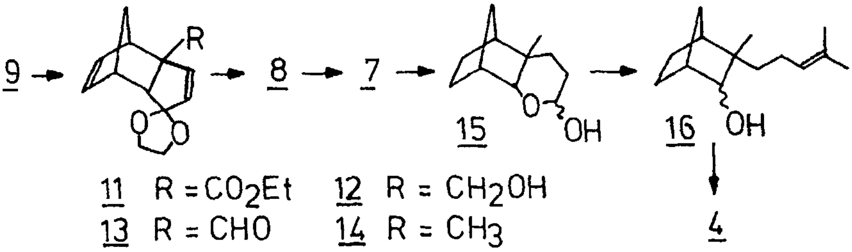
This paper describes a new synthesis of epi-β-santalene (4) using the bicyclic lactone 7 and new syntheses of β-santalene (3) and its isomer 5 using the ketone 21.

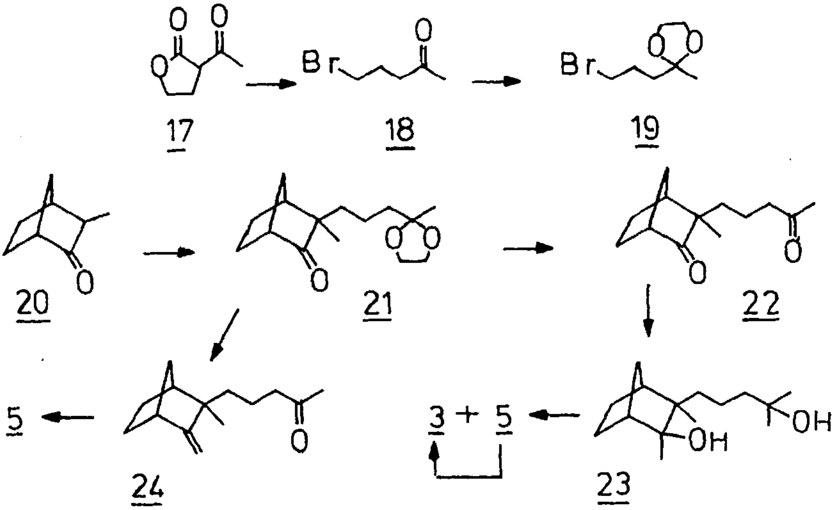
A retro synthesis of epi-β-santalene (4) reveals the importance of the synthon 7 (Scheme 1). The ester 9 easily obtained by a Herz-Favorskii ring contraction[7,8] of the Diels-Alder adduct (10) of cyclopentadiene and p-benzoquinone, after careful ketalisation was reduced with LAH to get the alcohol (12). PCC oxidation of 12 followed by Wolff-Kishner reduction gave 14, which on hydrogenation and deprotection gave the ketone 8. The lactone 7 obtained by Baeyer-Villiger oxidation of 8 was reduced with DIBAL to get the lactol 15 which on Wittig reaction with isopropylidenetriphenylphosphorane gave the alcohol 16 which has already been converted to epi-β-santalene (4)[6].

The ketone 18 obtained from 2-acetylbutyrolactone (17) was converted to the ketal 19 in the presence of catalytic amount of pyridinium-p-toluenesulfonate in 90% yield (conventional methods give only 68% yield[9,10]). Alkylation of


4
6
7
8
9
10
CO2Et

Scheme 1


9
8
7
R
15
OH
16
OH
4
11 R = CO2Et
12 R = CH2OH
13 R = CHO
14 R = CH3


17
Br
18
Br
19
20
21
22
5
24
3 + 5
23
OH
OH

3-exo-methylnorcamphor (20) with the bromide 18 gave 21. Deprotection of 21 followed by reaction with MeLi gave the diol 23 which on dehydration afforded a mixture of β-santalene (3) and its isomer 5 (60:40), which could be isomerised to β-santalene (3) in the presence of p-toluenesulphonic acid. The ketone 24 obtained from 21 was converted to 5 using Wittig reaction. Attempt to synthesise 5 by simultanious Wittig reaction at both carbonyl functions of 22 was not successful.

Experimental

GC analysis was performed on a Hewlett-Packard 5730A-3390A instrument. NMR($CDCl_3$) and IR(CCl_4) spectra were obtained on Hitachi R600 or Jeol FT 90Q and Perkin Elmer 283 instruments.

1. 5-Ethylenedioxy-2-exo-hydroxymethyltricyclo(5.2.1.0^{2,6})deca-3, 8-diene (12)

A mixture of 9 (32.7 g, 0.15 mol) ethylene glycol (14 g, 0.225 mol) and p-TsOH.H_2O (0.100 g) in toluene (300 mL) was heated at reflux with efficient stirring in a Dean-Stark trap for 10 hrs. Addition to 1% aq.Na_2CO_3 and workup gave 11 (37.78 g, 81%)). LAH (13.2 g, 0.35 mol) was added to a solution of 11 (30.0 g, 0.1145 mol) in Et_2O (700 mL) at 0° and stirred at r.t. for 3 hrs. Usual workup and purification by chromatography over silica gel gave 12 (22.3 g, 80%). ^1H NMR: δ 1.4-1.5 (m,2H), 3.3 (b,3H), 3.6 (s,2H), 3.85 (s,4H), 5.5 (d,1H), 6.0 (s,2H), 6.78 (d,1H). IR: 3450, 1260, 1060 cm^{-1}.

2. 5-Ethylenedioxy-2-exo-methyltricyclo(5.2.1.0^{2,6})deca-3,8-diene(14)

A mixture of 12 (15 g, 0.008 mol), PCC (21.8 g, 0.102 mol) and NaOAc (2 g, 0.024 mol) in CH_2Cl_2 (60 mL) was stirred at r.t. for 3 hrs. Dilution with Et_2O, filtration and concentration gave 13 (10.8 g, 72%). The crude 13 (10.8 g, 0.049 mol), hydrazine hydrate (43.3 g, 0.866 mol), powdered KOH (37.6 g, 0.66 mol) and ethylene glycol (60 mL) were mixed and heated for 4 hrs. at 160° and cooled. Addition of water, extraction with pentane, concentration and column chromatography gave 14 (8.2 g, 82%)). ^1H NMR: δ 1.08 (s,3H), 1.35-1.45 (m,2H), 3.3 (b,3H), 3.85 (s,4H), 5.5 (d,1H), 6.0 (s,2H), 6.76 (d,1H). IR: 1060 cm^{-1}.

3. 2-exo-Methyltricyclo(5.2.1.0^{2,6})decan-5-one (8)

The ketal 14 (4 g, 0.091 mol) was hydrogenated in EtOH (15 mL) in presence of 5% Pd/C (50 mg). Filtered and concentrated. The crude material (2.0 g) was mixed with p-TsOH.H_2O (50 mg) in aq. acetone (6:1, 75 mL),. Addition to aq. Na_2CO_3, usual workup and column chromatography gave the ketone 8 (1.47 g, 93%). ^1H NMR: δ 1.05 (s,3H), 0.95-2.5 (m,3H). IR: 1745 cm^{-1}.

4. 2-exo-Methyl-6-oxatricyclo(6,2,1,0^{2,7})undecan-5-one (7)

A mixture of 8 (0.8 g, 0.0048 mol) and MCPBA (2.06 g, 0.012 mol) in CH_2Cl_2 (10 mL) was stirred for 6 hrs. Addition of water (10 mL), washing off the organic layer with 1% $Na_2S_2O_3$, saturated Na_2CO_3 and concentration followed by distillation (bp 140°, 15 Torr) gave 7 (0.75 g, 85%). ^1H NMR: δ 1.05 (s,3H), 0.9-2.1 (m,10H), 2.1-2.5 (m,2H), 4.2 (d,1H). IR 1740 cm^{-1}.

5. 2-*exo*-Methyl-6-oxatricyclo(6.2.1.0^{2,7})undecan-5-ol (15)

To the lactone 7 (0.9 g, 0.005 mol) in toluene (30 mL) was added DIBAL (5.5 mL, 1 M in hexane) dropwise and stirred for 3 hrs. at -78°. Addition to 10% HOAc (35 mL) and usual workup gave the lactol 15 (0.71 g, 78%). ^1H NMR: δ 1.05 (s,3H), 3.85 (d,1H), 5.15 (m,1H). IR: 2410, 1450, 1200 cm^{-1}.

6. 3-*exo*-Methyl-3-(4-methyl-3-pentenyl)bicyclo(2.2.1)-heptan-2-ol (16)

To a slurry of isopropyltriphenylphosphoniumiodide (1.72 g, 0.004 mol) in toluene (15 mL), *t*-BuOK (1.99 g, 0.012 mol) was added and stirred for 15 hrs. A solution of 15 (0.60 g, 0.0033 mol) in toluene (5 mL) was added dropwise and stirred for 24 hrs. Addition to 1N HCl, neutralisation with $NaHCO_3$, usual workup and column chromatography gave 16 (0.57 g, 82%). ^1H NMR δ 1.0 (s,3H), 1.2-2.5 (m,18H), 5.1 (m,1H). IR: 3390, 1450, 1060cm^{-1}.

7. 1-Bromo-4,4'-ethylenedioxypentane (19)

A mixture of the ketone 18 (41.16 g, 0.245 mol), ethylene glycol (15.50 g, 0.25 mol), pyridinium-*p*-toluenesulfonate[11] and benzene (200 mL) was refluxed with stirring using a Dean-Stark apparatus for 4 hrs. Washing off the mixture with

$NaHCO_3$ solution and workup followed by distillation (104°, 20 Torr) gave the ketal 19 (46.50 g, 90%). ^1H NMR: δ 1.25 (s,3H,$-CH_3$), 1.6-2.2 (m,4H), 3.4 (t,2H,$-CH_2Br$), 3.85 (s,4H,$-OCH_2CH_2O-$).

8. 3-exo-(4,4'-Ethylenedioxypentyl)3-endo-methylbicyclo(2.2.1)-heptan-2-one (21)

Sodium hydride (3.60 g, 0.075 mol, 50% dispersion in oil) was washed, mixed with the ketone 20[2,12] (9.30 g, 0.075 mol) in DME and stirred at 100° for 4 hrs. The mixture was cooled to 0° and the bromide 19 (32.0 g 0.15 mol) was added. It was stirred at 0° for 2 hrs. and at 30° for 15 hrs. Addition to ice-NH_4Cl slurry, usual workup and chromatography over silicagel gave the ketal 21 (12.0 g, 64%). ^1H NMR: δ 1.03 (s,3H, endo-CH_3), 1.25 (s,3H,$-CH_3$), 1.1-2.5 (m,14H), 3.85 (s,4H, $-OCH_2CH_2O-$). IR: 1745, 1130, 1070 cm^{-1}. MS m/z 252 (M^+).

9. 2,3-Dimethyl-3-exo-(4-hydroxy-4-methylpentyl)bicyclo-(2.2.1)heptan-2-ol (23)

The ketal 21 was treated with p-$TSOH.H_2O$ in aq. acetone to get the diketone 22, which (1.99 g 0.0086 mol) was taken in $Et_2O$and a 1.4 M solution of MeLi (61 mL, 0.086 mol) in Et_2O was added and refluxed for 48 hrs. Addition of ice-water and workup gave the diol 23 (1.82 g, 81%). ^1H NMR: δ 1.04 (s,3H,endo-CH_3), 1.20 (s,3H,CH_3), 1.32 (s,6H,$=C(CH_3)_2$), 1.4-2.5 (m,14H). IR: 3365, 1140 cm^{-1}. MS m/z 240 (M^+).

10. 3-endo-Methyl-3-exo-(4-methyl-3-pentenyl)-2-methylenebicyclo-(2.2.1)heptane. (β-santalene) (3)

A cold solution of $SOCl_2$ (1.66 g, 0.14 mol), in pyridine (5 mL) and the diol 23 (1.5 g 0.0062 mol) in pyridine (3 mL) were mixed and kept at 0°. After 36 hrs., workup was done and the crude material obtained was distilled using microdistillation kit (bp 105-112°, 5 Torr) to get the dehydration products (0.75 g, 59%) β-santalene (3) and its isomer 5 (61%, 37% each by GC). A portion of the mixture (0.50 g) and p-TsOH.H_2O (0.020 g) in benzene (5 mL) was refluxed for 10 hrs. Usual workup and purification by chromatography gave β-santalene (3) (0.450 g, 90%). ^1H NMR: δ 1.04 (s,3H,endo-CH_3), 1.6-1.65 (2s,6H,=$C(CH_3)_2$), 1.0-2.2 (m,14H), 2.5-2.7 (m,1H). IR: 1655, 880, 835, cm^{-1}. MS m/z 204 (M^+), 189, 161, 122, 94.

11. 3-endo-Methyl-3-exo-(4-oxopentyl)-2-methylenebicyclo-(2.2.1)heptane (24)

To a solution of the ketone 21 (5.04 g, 0.02 mol) in ether (40 mL) was added 1.4 M MeLi (143 mL, 0.2 mol) in ether and refluxed for 48 hrs. A portion of the alcohol obtained after workup (2.40 g, 0.0087 mol) was dehydrated using $SOCl_2$ (1.155 g, 0.0096 mol) and pyridine (5 mL) at 0° to get the ketone 24 (1.25 g, 68%). ^1H MNR: δ 1.02 (s,3H,endo-CH_3), 1.2-2.4 (m,13H), 2.03 (s,3H), 2.55-2.75 (m,1H), 4.45-4.7 (2s,2H,=CH_2). IR: 1725, 1655, 885 cm^{-1}. MS m/z 203 (M^+), 188, 160.

12. 3-endo-Methyl-3-exo-(4-methyl-4-pentenyl)-2-methylene-bicyclo(2.2.1)heptane (5)

To a stirred suspension of methyltriphenyl-phosphonium iodide (0.606 g, 0.0015 mol) in THF (2 mL) at 5° was added 1.6 M n-BuLi (1 mL, 0.0016 mol). The mixture was stirred at r.t. for 2 hrs and treated with the ketone 24 (0.21 g, 0.001 mol) in THF (2 mL) and stirred overnight. Addition of NH_4Cl solution, usual workup and purification by chromatography gave 5 (0.135 g, 65%). ^1H NMR: δ 1.04 (s,3H,endo-CH_3), 1.0-2.4 (m,13H), 1.68 (s,3H,-CH_3), 2.5-2.7 (m,1H), 4.4-4.7 (m,4H,2 =CH_2). IR: 1670, 890 cm^{-1}. MS m/z 204 (M^+).

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