*Tetrahedron: Asymmetry* Vol. 1, No. 8, pp. 537-540, 1990
Printed in Great Britain

0957-4166/90 \$3.00+.00
Pergamon Press plc

# Total Syntheses of Sandalwood Fragrances: (Z)- and (E)-ß-Santalol and Their Enantiomers, ent-ß-Santalene

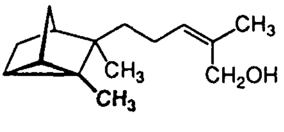
**Achim Krotz and Günter Helmchen***

Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270,
D-6900 Heidelberg, FRG

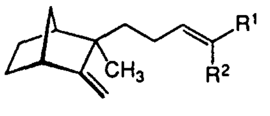
(*Received* 2 *July* 1990)

**Abstract:** Via asymmetric Diels-Alder reactions, large scale preparations of enantiomerically pure norbornane-2-carboxylic acids were carried out. Oxidative degradation furnished 2-norbornanone and 3-methyl-2-norbornanone which gave the title compounds via stereoselective alkylations, subsequent Wittig reactions and reductions.

East Indian sandalwood oil, obtained by steam distillation from the heartwood of Santalum album L., is highly prized in perfumery[1]. Its sweet woody fragrance is due mainly to the two major components (+)-α-santalol (50-60 %) and (-)-(Z)-β-santalol (1) (20-25 %). Numerous minor components, including (-)-(E)-β-santalol (2) and (-)-β-santalene (3), also contribute to the characteristic overall odor character[2].



*(+)-α-Santalol*



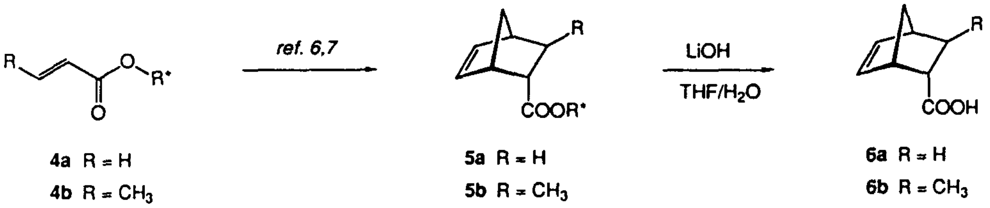
| | $R^1$ | $R^2$ |
|---|---|---|
| **1** | $CH_3$ | $CH_2OH$ |
| **2** | $CH_2OH$ | $CH_3$ |
| **3** | $CH_3$ | $CH_3$ |

For (+)-α-santalol several partial syntheses are known[3]. Concerning total syntheses, work so far was mainly concentrated on the essentially odorless (-)-β-santalene (3)[4]. To our surprise, we found no report on an EPC synthesis of the important fragrance β-santalol (1) in the literature. Accordingly, we concentrated our efforts mainly on this compound. As it is prone to racemization via carbocation rearrangement, we have also prepared its enantiomer **ent-1**, and in addition the double bond isomers **2** and **ent-2**. Our plan for the syntheses of **1** - **3** was based on the well-known preference for exo-attack in alkylations of norbornanones[5].

The requisite enantiomerically pure 3-methyl-2-norbornanones **8b** and **ent-8b** were prepared by oxidative degradation from the norbornene carboxylic acids **6a**, **6b** and their enantiomers. These compounds were obtained by asymmetric Diels-Alder reactions. As was previously described, (R)-pantolactone[6] and (S)-2-hydroxy-N-methyl-succinimide[7] (Scheme 1) are highly efficient chiral auxiliaries that allow the preparation of a variety of 5-norbornene-2-carboxylic acids. Using this technique, the diastereomerically pure esters **5a** and **5b** and corresponding diastereomers of the enantiomeric series were prepared[6,7]. Saponification with LiOH/THF/$H_2O$ gave the enantiomerially pure acids **6a**, **6b**, and their enantiomers[8] which were catalytically reduced to the saturated acids **7a**, **7b**, and their enantiomers, respectively, in quantitative yield (Scheme 2).

Entry into the natural santalol series was gained by oxidative degradations. Thus, deprotonation of **7b** with LDA and oxidation of the enolate with oxygen in the presence of triethyl-phosphite gave the corresponding α-hydroxy-acid[9]. The reaction was clean but not complete. Fortunately, the starting material was easily recovered by filtrative chromatography on silica[10]. Reduction, and periodate cleavage of the resultant diol gave 3-exo-methyl-2-norbornanone (**8b**) {$[\alpha]_D$ = -51.5 (19 °C, c = 1.35, chloroform)} in excellent overall yield of 81 % (corr.). The enantiomeric ketone **ent-8b** was prepared by alkylation of (+)-2-norbornanone (**ent-8a**) (88 %). This important intermediate was prepared from the saturated acid **ent-7a** by the same route as described above for **7b** (87 %). An alternative route involved treatment of **ent-7a** with permanganate[11], to give the corresponding α-hydroxy-acid (70 %), reduction to the diol, and periodate cleavage (94 %).

**Scheme 1**



**4a** R = H
**4b** R = $CH_3$

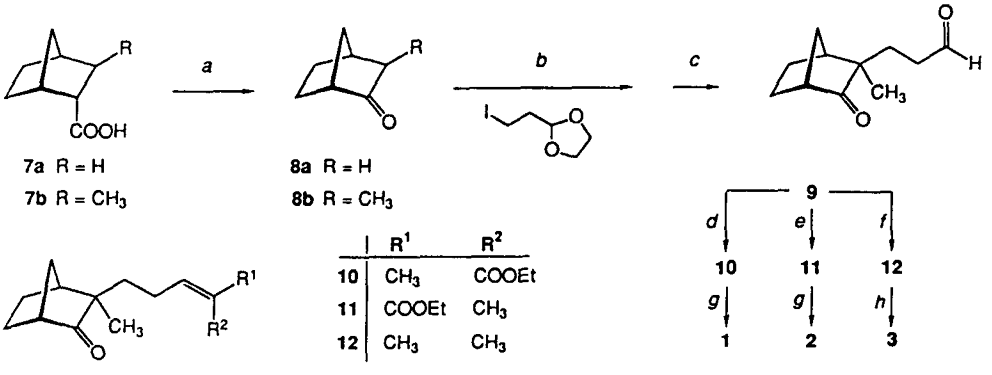
**5a** R = H
**5b** R = $CH_3$

**6a** R = H
**6b** R = $CH_3$

Chiral auxiliary R*OH: for **5a** and **5b**: (R)-pantolactone[6]

for **ent-5a** and **ent-5b**: (S)-2-Hydroxy-N-methylsuccinimide[7]

**Scheme 2**



**7a** R = H
**7b** R = $CH_3$

**8a** R = H
**8b** R = $CH_3$

|  | $R^1$ | $R^2$ |
|---|---|---|
| 10 | $CH_3$ | COOEt |
| 11 | COOEt | $CH_3$ |
| 12 | $CH_3$ | $CH_3$ |

(a) *i*. 2.2 equiv of LDA/1.0 equiv of DMPU/$O_2$/2.0 equiv of $P(OEt)_3$, THF, -90 °C, *ii*. $LiAlH_4$, THF, reflux, 2 h, *iii*. 1.1 equiv of $NaIO_4$, water/EtOH 5:1, rt, 40 min (*i-iii*: 81 %); (b) $NaN(SiMe_3)_2$, Xylol, reflux; (c) $H_2O/H^+$, rt, 4 h (b,c: 69 %); (d) 1.1 equiv of $(EtO)_2OPCH(CH_3)CO_2Et$/1.05 equiv of $KN(SiMe_3)_2$/5.0 equiv of 18-crown-6, THF, -90° to -60 °C, 4 h (75 %); (e) 1.05 equiv of $Ph_3PC(CH_3)CO_2Et$, THF, reflux, 6 h (74 %); (f) 1.03 equiv of $Ph_3PCHMe_2Br/NaNH_2$, THF, rt, 5 min (70 %); (g) *i*. 1.5 equiv of $CH_2Br_2$/4.0 equiv of Zn/1.1 equiv of $TiCl_4$, THF, rt, 12 h, *ii*. 2.2 equiv of DIBAH, $CH_2Cl_2$, -78 ° to 0 °C, 12 h (*i,ii*: 61 %); (h) 1.5 equiv of $CH_2Br_2$/4.5 equiv of Zn/1.1 equiv of $TiCl_4$, THF, rt, 4 d (80 %).

Alkylation of **8b** with Stowell's iodide[12] followed by hydrolysis furnished the aldehyde **9** (69 % yield). Using suitable variants of the Wittig reaction, all the target compounds could be obtained from this intermediate. Thus, the reaction with propylidenetriphenylphosphorane gave the ketone **12**[13] in 70 % yield. Reaction of **9** with PPh$_3$C(CH$_3$)COOEt (THF, reflux) furnished a 95:5 mixture of the (E)- and (Z)-enoates **11** and **10**, respectively, from which pure **11** was obtained by LC (70 %). The pure (Z)-isomer **10** was prepared by reacting the aldehyde **9** with (EtO)$_2$OPCH(CH$_3$)COOEt under the conditions worked out by Still[14] (**10**:**11** = 84:16) and subsequent LC separation (62 %). The highly hindered ketones **10-12** were cleanly transformed into the corresponding methylidene derivatives by application of Nozaki's method[15]. Finally, reduction with DIBAH furnished the target compounds.

The enantiomers **ent-1** - **ent-3** were prepared via the same route from **ent-8b** as starting material, except in the case of **ent-12** which was subjected to Nozaki's method and, in addition, a Wittig reaction with Ph$_3$CHLi[17] (47 %). Optical rotations of the various isomers as well as published data are displayed in the Table. Because of the notable discrepancies between our and previous results, we again isolated pure β-santalol and β-santalene of 99 % purity from sandalwood oil[18], essentially following the procedure of Brunke et al.[2c] which, unlike the earlier procedure[2a], cannot cause racemization. The excellent agreement of the optical rotations of the natural and synthetic materials indicates a high degree of enantiomeric purity for the former.

Fragrance properties of the various synthetic compounds are as follows: **1**: Typical sandalwood scent, identical to that of the natural product; **ent-1**: No scent; **2**: Scent similar to **1** but less intense; **ent-2**: No scent; **3**/**ent-3**: Essentially no scent when freshly purified. After several months of storage, the previously odorless compounds developed a week smell.

Table. Optical rotations of sandalwood constituents from various sources.

| | | | | |
|---|---|---|---|---|
| 1: | $[\alpha]_D$ = -109.4 | (20 °C, c = 0.7, methanol), | synthetic, | this w. |
| | $[\alpha]_D$ = -109.5 | (20 °C, c = 0.9, methanol), | isolated, | this w. |
| | $[\alpha]_D$ = -90.5 | (20 °C, neat)[a], | isolated, | ref. 2a |
| ent-1: | $\alpha_D$ = +105.3 | (20 °C, neat)[b], | synthetic, | this w. |
| | $[\alpha]_D$ = +108.4 | (20 °C, c = 1.0, methanol), | synthetic, | this w. |
| 2: | $[\alpha]_D$ = -113.7 | (21 °C, c = 0.33, chloroform), | synthetic, | this w. |
| ent-2: | $[\alpha]_D$ = +113.8 | (21 °C, c = 1.0, chloroform), | synthetic, | this w. |
| 3: | $[\alpha]_D$ = -107.8 | (20 °C, c = 0.8, chloroform), | isolated, | ref. 4a |
| | $[\alpha]_D$ = -108.89 | (20 °C, c = 0.776, chloroform), | synthetic, | ref. 4a |
| | $[\alpha]_D$ = -112 | (28 °C, c = 5.0, chloroform), | synthetic, | ref. 4c |
| | $[\alpha]_D$ = -119 | (20 °C, c = 0.8, chloroform), | isolated, | ref. 18 |
| ent-3: | $[\alpha]_D$ = +108.6 | (25 °C, c = 0.51, chloroform), | synthetic, | ref. 4b |
| | $[\alpha]_D$ = +119.5±1 | (20 °C, c = 0.6, chloroform), | synthetic, | this w. |

(a) Density: 0.975 g/ml (20 °C); (b) Not normalized with respect to density.

## ACKNOWLEDGEMENTS

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Donations of sandalwood oil were obtained from BASF AG, Dragoco, and Givaudan AG. We thank Dr. G. Fráter for the generous gift of β-santalene.

## REFERENCES

1 (a) Simonsen, J.L.; Barton, D.H.R. *The Terpenes*; 2nd ed.; Cambridge University Press: Cambridge, 1951, Vol. 3., pp. 178-188.

2 (a) Herout, V.; Jarolim, V.; Pliva, J. *Collect. Czech. Chem. Commun.* **1957**, *22*, 773; (b) Christenson, P.A.; Secord, N.; Willis, B. J. *Phytochemistry,* **1981**, *20*, 1139-1141; (c) Brunke, E.-J.; Böhme, A.; Struwe, H. *Liebigs Ann. Chem.* **1982**, 1105-1110; Brunke, E.-J. *Dragoco Report,* **1981**, *28*, 90.

3 Heathcock, C.H.; Graham, S.L.; Pirrung, M.C.; Plavac, F.; White C.T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York 1983, Vol. 5, p. 249.

4 (a) Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, *68*, 2100; (b) Takano, S.; Inomata, K.; Kurotaki, A.; Ohkawa, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1720; (c) Hodgson, G.L.; MacSweeney, D.F.; Mills, R.W.; Money, T. *J. Chem. Soc., Chem. Comm.* **1973**, 235.

5 Corey, E.J.; Hartmann, R.; Vatakencherry, P.A. *J. Am. Chem. Soc.* **1962**, *84*, 2611 (synthesis of rac-β-santalene via alkylations of 2-norbornanone).

6 Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, 3095.

7 Poll, T.; Abdel Hady, A.F.; Karge, R.; Linz, G.; Weetman, J.; Helmchen, G. *Tetrahedron Lett.* **1989**, 5595.

8 Optical rotations of the carboxylic acids employed here were as follows; **ent-6a**: $[\alpha]_D$ = + 149 (20 °C, c = 2.7, 95 % EtOH); **6b**: $[\alpha]_D$ = -151 (20 °C, c = 3.6, 95 % EtOH); **7b**: $[\alpha]_D$ = -45.9 (22 °C, c = 5.6, 95 % EtOH).

9 Our procedure is a slightly modified version of the method for preparation of 5-norbornene-2-one from **6a** developed by Berson and refined by Paquette and their co-workers: (a) Janusz, J.; Gardiner, L.; Berson, J. *J. Am. Chem. Soc.* **1977**, *99*, 8509; (b) Paquette, L.A.; Doecke, C.W.; Kearney, F.R.; Drake, A.F.; Mason, S.F. *J. Am. Chem. Soc.* **1980**, *102*, 7228.

10 The isolated yield of the α-hydroxy acid was 61 %; recovered starting material: 27.5 %.

11 Kwart, H.; Null, G.D. *J. Am. Chem. Soc.* **1960**, *82*, 2348.

12 Stowell, J.C.; King, B.T.; Hauck, Jr., H.F. *J. Org. Chem.* **1983**, *48*, 5381.

13 The racemic compound was prepared by alkylation of **rac-8b** with 4-methyl-3-pentenyl-iodide; compared to the reaction of Stowell‘s iodide, this reaction was slow and required a large excess of the iodide because of competing elimination.

14 Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, 4405.

15 Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698.

16 Corey, E.J.; Kang, J. *J. Am. Chem. Soc.* **1982**, *104*, 4724.

17 The Wittig reaction was chosen in order to rigorously exclude racemization via a rearrangement process; the samples obtained via the two routes displayed identical optical rotations.

18 The isolation of β-santalene from sandalwood oil was carried out at Givaudan AG, Dübendorf. The isolation procedure started from a previously obtained mixture of β-santalene (**3**) and epi-β-santalene (**epi-3**) of >90 % purity for the two compounds. Further purification involved chromatography (twice) on silica/$AgNO_3$ (n-hexane/ether) which finally furnished a sample of 99.2 % purity with **3**:**epi-3** = 99.6:0.4.
In contrast to the situation of the title compounds, there is satisfactory agreement on the optical rotation of epi-β-santalene: $[\alpha]_D$ = +26.4 ± 1 (27 °C, c = 0.4, chloroform); Cf. ref. 4b; Arai, Y.; Yamamoto, M.; Koizumi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 467; Eck, C.R.; Hodgson, G.L.; MacSweeney, D.F.; Mills, R.W.; Money, T. *J. Chem. Soc., Perkin Trans. I* **1974**, 1938.