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Diastereo- and Enantio-Controlled Synthesis of Sandalwood Constituents (−)-β-Santalene and (+)-Epi-β-santalene Starting from the Same (+)-Norcamphor

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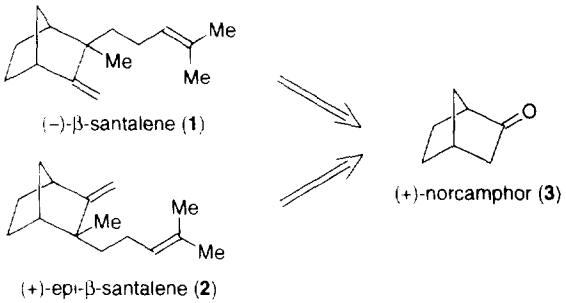
Abstract: (−)-β-Santalene and (+)-epi-β-santalene, both occurring in East Indian sandalwood oil and having an enantiomeric core bicyclo[2.2.1]heptane framework, have been synthesized in diastereo- and enantio-controlled manner starting from the same (+)-norcamphor.

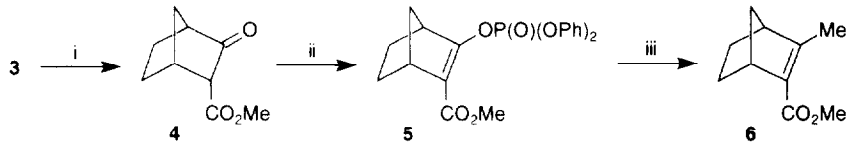
East Indian sandalwood constituents, (−)-β-santalene[1] (**1**) and (+)-epi-β-santalene[2] (**2**), are of interest not only for their fragrant odor character but also for the fact that their absolute structures, except for the diastereomeric quaternary stereogenic center, have been found to be enantiomeric with respect to the core bicyclo[2.2.1]heptane framework. Although the problem in racemic synthesis[3] is merely the matter of diastereoselective control, an additional problem needs to be solved in chiral synthesis when only one particular enantiomer is available as the precursor. Namely, a divergent route making the particular enantiomer utilizable has to be devised.[1d] We wish to report here one such example which allowed use of the same (+)-norcamphor (**3**) as the chiral starting material for the diastereo- and enantio-controlled construction of either (−)-β-santalene (**1**) or (+)-epi-β-santalene (**2**) (**Scheme 1**).



Scheme 1

(+)-Norcamphor (**3**), the only accessible enantiomer in >95% ee at present from commercially available (+)-*endo*-norborneol,[4] was transformed into the keto-ester **4** in satisfactory yield by exactly following the established procedure for the racemic substrate.[5] To introduce the methyl group, **4** was first treated with diphenyl chlorophosphate in the presence of sodium hydride to give the enol phosphate[6] (**5**), $[\alpha]_D^{27}$ −30.4 (*c* 1.0, $CHCl_3$). This compound was next reacted with trimethylaluminum in the presence of a catalytic amount of

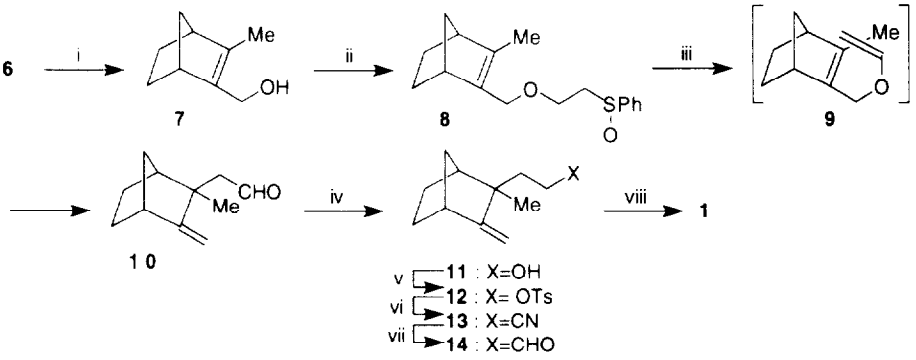
tetrakis(triphenylphosphine)palladium in 1,2-dichloroethane[7] at 80 °C to furnish the cross-coupling product **6**, $[\alpha]_D^{27}$ −111.6 (*c* 0.3, $CHCl_3$), in excellent yield without difficulty. It is noted that the ester function of both the substrate and the product was stable and remained so throughout this transformation (**Scheme 2**).



Scheme 2

Reagents and conditions: i) ref. 7. ii) NaH, $(PhO)_2P(O)Cl$, THF (85%). iii) Me_3Al, $Pd(PPh_3)_4$ (cat.), $ClCH_2CH_2Cl$, 80 °C (85%).

In order to synthesize (−)-β-santalene (**1**), **6** was reduced with diisobutylaluminum hydride (DIBAH) to give the allylic alcohol **7**, $[\alpha]_D^{31}$ −51.6 (*c* 0.6, $CHCl_3$). Since neither the direct Claisen rearrangement using ethyl vinyl ether in the presence of mercury(II) acetate nor its Johnson modification[8] using triethyl orthoacetate in the presence of acid catalyst was successful in furnishing the corresponding [3,3]-sigmatropic rearrangement products satisfactorily. **7** was first treated with phenyl vinyl sulfoxide[9] in the presence of sodium hydride to give the β-allyloxyethyl phenyl sulfoxide (**8**) which, without purification, was heated at 150 °C in decalin to give the expected aldehyde **10**, $[\alpha]_D^{34}$ −64.3 (*c* 0.4, $CHCl_3$), in 57% overall yield as a single product *via* the vinyl ether (**9**) by concurrent β-elimination and sigmatropic rearrangement. Although the stereochemistry of the product **10** could not be determined at this stage, subsequent transformation revealed that the β-carboethyl group was introduced diastereoselectively from the *exo* face of the intermediate **9** as anticipated.



Scheme 3

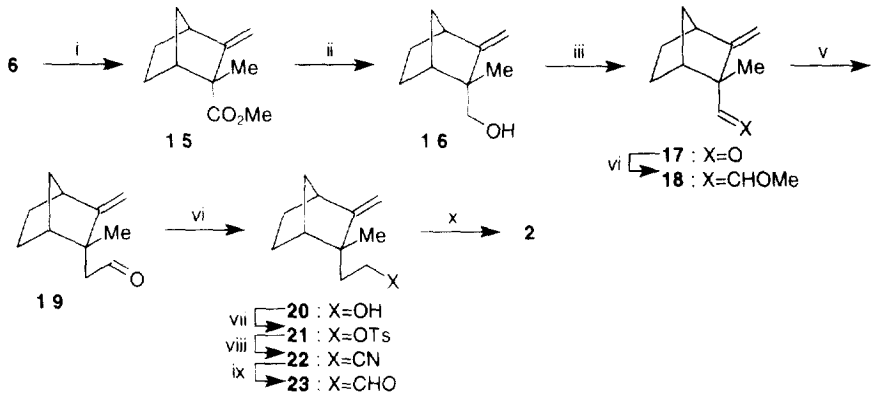
Reagents and conditions: i) DIBAH, CH_2Cl_2, −78 °C (89%). ii) $PhS(O)CH{=}CH_2$, NaH, THF, room temp. iii) decalin, 150 °C (57% from **7**). iv) $NaBH_4$, MeOH. v) *p*-TsCl, Et_3N, 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (cat.), CH_2Cl_2. vi) KCN, DMSO. vii) DIBAH, CH_2Cl_2, −45 °C, then dil. H_2SO_4. viii) *i*-$PrPPh_3I$, *n*-BuLi, THF, −30 °C (23% from **10**).

Thus, **10** was sequentially reduced, tosylated and substituted to furnish the cyanide **13**, $[\alpha]_D^{33}$ −102.8 (*c* 1.3, $CHCl_3$) *via* the alcohol **11**, $[\alpha]_D^{32}$ −110.1 (*c* 0.7, $CHCl_3$), and the tosylate **12**. The cyanide **13** was reduced partially with DIBAH to give the aldehyde **14** after acid workup which, on Wittig condensation,

afforded (−)-β-santalene (**1**), $[\alpha]_D^{29}$ −124.0 (*c* 0.4, $CHCl_3$) [lit.[1b]: $[\alpha]_D^{28}$ −112 (*c* 5.01, $CHCl_3$)], as a single product. Stereochemistry of the intermediate aldehyde **10** was thus determined unambiguously at this point. Overall yield of **1** from **4** was 8.4% (**Scheme 3**).

We next examined, the transformation of the same key compound **6** into (+)-epi-β-santalene (**2**). Treatment of **6** with methyl iodide in the presence of lithium diisopropylamide (LDA) allowed diastereo- and regioselective alkylation[10] to give the *exo*-methyl product **15**, $[\alpha]_D^{26}$ −41.3 (*c* 0.8, $CHCl_3$), exclusively in excellent yield. The stereochemistry of the product was determined unambiguously by subsequent transformation. Thus, reduction of the ester **15** yielded the primary alcohol **16**, $[\alpha]_D^{30}$ +95.1 (*c* 0.6, $CHCl_3$), mp 80.0~81.5 °C. Oxidation of **16** under the Swern conditions yielded the highly volatile aldehyde **17** which, immediately, was transformed into the homologated primary alcohol **20**, $[\alpha]_D^{29}$ +47.3 (*c* 0.5, $CHCl_3$), in sequential Wittig condensation,[11] acid hydrolysis, and reduction *via* the vinyl ether **18** and the aldehyde **19**.

The primary alcohol was first transformed into the known cyanide[1d] **22**, $[\alpha]_D^{30}$ +50.8 (*c* 0.31, $CHCl_3$) [lit.[1d]: $[\alpha]_D^{27}$ +27.5 (*c* 0.24, $CHCl_3$)], *via* the tosylate **21** as above. Finally, the cyanide **22** was reduced partially with DIBAH to give the aldehyde **23** after acid workup, which was condensed with the Wittig reagent to yield (+)-epi-β-santalene (**2**), $[\alpha]_D^{31}$ +28.1 (*c* 0.38, $CHCl_3$) [lit.: $[\alpha]_D^{25}$ +25.9 (*c* 0.4, $CHCl_3$),[1d] $[\alpha]_D^{20}$ +26.4 (*c* 1.0, $CHCl_3$),[2d] $[\alpha]_D^{30}$ +27.4 (*c* 1.95, $CHCl_3$)[2e]]. Overall yield of **2** from **4** was 5.5% (**Scheme 4**).



Scheme 4

Reagents and conditions: i) LDA, MeI, THF, −78 °C (87%). ii) $LiAlH_4$, THF (88%). iii) Swern oxid. (75%). iv) $MeOCH_2PPh_3Cl$, NaH-DMSO, THF, 0 °C. v) 10% HCl. vi) $NaBH_4$, MeOH (48% from **17**). vii) *p*-TsCl, Et_3N, DMAP (cat.), CH_2Cl_2. viii) KCN, DMSO (63% from **20**). ix) DIBAH, CH_2Cl_2, −45 °C, then dil. H_2SO_4. x) *i*-$PrPPh_3I$, *n*-BuLi, THF, −30 °C (44% from **22**).

In conclusion, we have devised a diastereo- and enantio-controlled construction of (−)-β-santalene (**1**) and (+)-epi-β-santalene (**2**), both occurring in East Indian sandalwood oil and having an enantiomeric core bicyclo[2.2.1]heptane framework, using the same (+)-norcamphor (**1**) as the chiral starting material.

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12. ^{1}H nmr spectra (300 MHz, $CDCl_3$) of the selected compounds — **6**: δ 3.71 (s, 3H), 3.20 (br s, 1H), 2.78 (br s, 1H), 2.11 (s, 3H), 1.80-1.64 (m, 2H), 1.47-1.37 (m, 1H), 1.27-0.05 (m, 3H). **7**: δ 4.22 (d, 1H, *J*=12.5 Hz), 4.06 (d, 1H, *J*=12.5 Hz), 2.91 (s, 1H), 2.62 (br d, 1H, *J*=0.7 Hz), 1.75-0.85 (m, 7H), 1.69 (s, 3H). **10**: δ 9.83 (t, 1H, *J*=3.0 Hz), 4.86 (s, 1H), 4.54 (s, 1H), 2.73 (br d, 1H, *J*=2.9, 15.3 Hz), 2.34 (dd, 1H, *J*=3.3, 15.1 Hz), 2.26 (br d, 1H, *J*=3.8 Hz), 1.80-1.18 (m, 6H), 1.23 (s, 3H). **11**: δ 4.78 (s, 1H), 4.52 (s, 1H), 3.85-3.63 (m, 2H), 2.68 (br d, 1H, *J*=4.0 Hz), 2.10 (br d, 1H, *J*=2.6 Hz), 1.82-1.15 (m, 9H), 1.07 (s, 3H). **15**: δ 5.02 (s, 1H), 4.80 (s, 1H), 3.69 (s, 1H), 2.74 (br d, 1H, *J*=2.9 Hz), 2.33 (br d, 1H, *J*=1.5 Hz), 1.78-1.19 (m, 8H), 1.33 (s, 3H). **20**: δ 4.75 (s, 1H), 4.51 (s, 1H), 3.86-3.60 (m, 2H), 2.68 (br d, 1H, *J*=4.0 Hz), 1.98 (br d, 1H, *J*=2.9 Hz), 1.80-1.13 (m, 9H), 1.03 (s, 3H). (−)-β-santalene (**1**): δ 5.14-5.04 (m, 1H), 4.72 (s, 1H), 4.46 (s, 1H), 2.66 (br d, 1H, *J*=2.9 Hz), 2.15-1.84 (m, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.57-1.08 (m, 8H), 1.04 (s, 3H). (+)-epi-β-santalene (**2**): δ 5.16-5.06 (m, 1H), 4.71 (s, 1H), 4.47 (s, 1H), 2.67 (br d, 1H, *J*=4.1 Hz), 2.13-1.78 (m, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.58-1.16 (m, 8H), 1.02 (s, 3H).

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