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# ASYMMETRIC DIELS-ALDER REACTION OF A CHIRAL ALLENIC ESTER : ENANTIOSELECTIVE SYNTHESIS OF (-)-β-SANTALENE [1]

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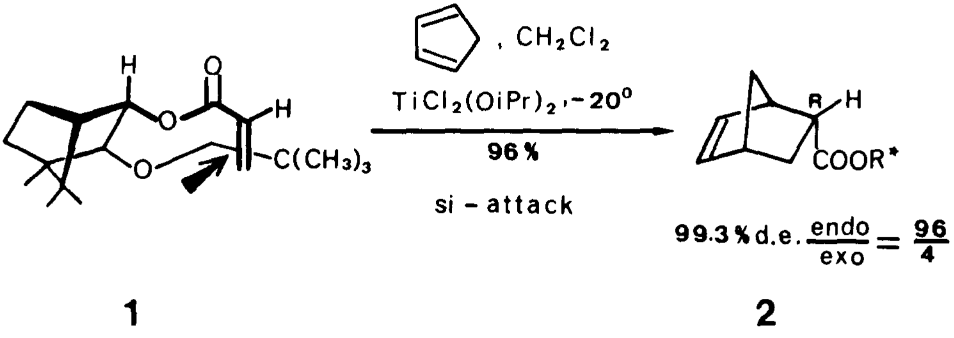
*Abstract.* The Lewis-acid promoted Diels-Alder reaction of the allenic ester 10 provides the adduct 11 with excellent π-facial selection leading to an efficient enantioselective synthesis of (-)-β-santalene and to the recovery of the chiral control element 7.

Asymmetric Diels-Alder reactions using chiral dienophiles or dienes have received a great deal of attention over the last few years [2]. Thus, almost quantitative diastereoface differentiation has been achieved in the acrylate/ cyclopentadiene addition 1 → 2 as recently reported by this laboratory [3] (Scheme 1).

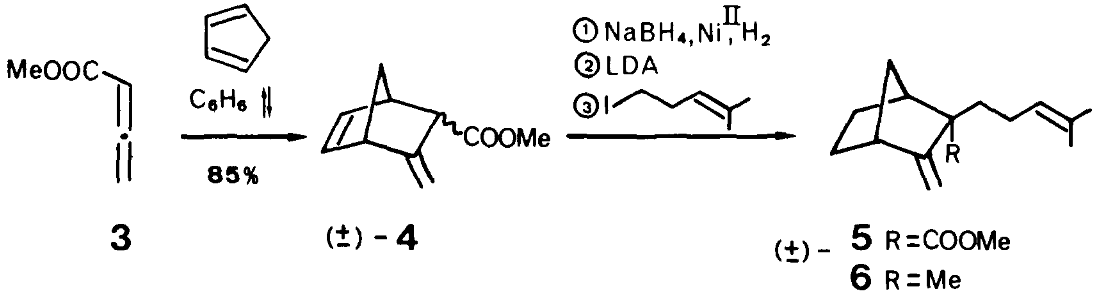
*Scheme 1*



The easy accessibility of the rationally designed, recoverable, camphor-derived control element, together with its predictable and efficient topological bias, offers attractive possibilities for the synthesis of chiral natural products.

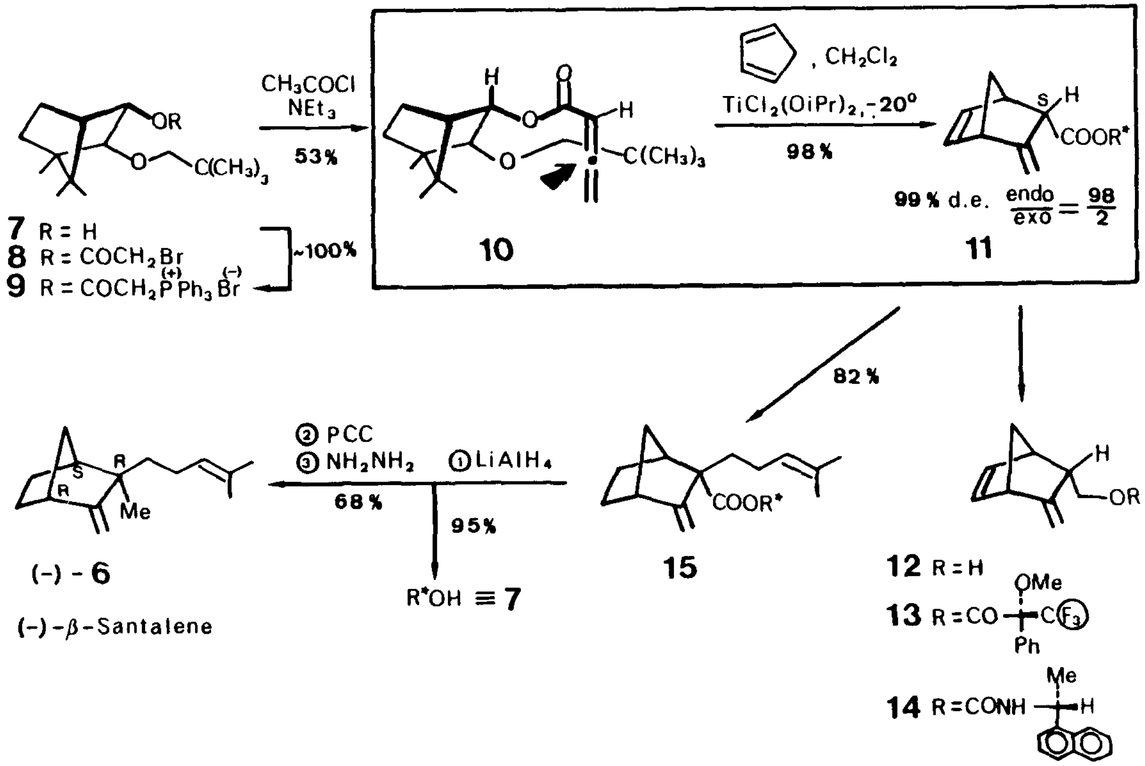
In this context, we present here a highly enantioselective total synthesis of the olfactively interesting sandalwood constituent (-)-β-santalene (6)[4]. Its racemate has been synthesized elegantly by *Bertrand et al.*[5] by means of a thermal allenic ester/cyclopentadiene addition 3 → 4 (Scheme 2)[6].

*Scheme 2*



Aiming at an efficient π-facial selection in the initial cycloaddition step, we have prepared the allenic ester 10 (Scheme 3).

*Scheme 3*



Acylation of the chiral alcohol 7 [3] with bromoacetyl bromide (2 eq., AgCN (1.4 eq.), benzene, 80°, 20 min) [7], followed by treatment of the resulting bromoester 8 [8] with triphenylphosphine (1.06 eq., benzene, 80°, 15 h) furnished after crystallization ($CCl_4$) the phosphonium salt 9 [8] (m.p. 183-185°, 100% yield from 7). Wittig-type reaction [9] of 9 with acetyl chloride (1 eq., $NEt_3$ (2 eq.), $CH_2Cl_2$, 0° → 40°) gave after distillation the allenic ester 10 [8] (b.p. 145°/0.15 Torr) in 53% yield.

Proceeding to the crucial cycloaddition step, treatment of 10 with cyclopentadiene (3 eq.) in the presence of $TiCl_2(OiPr)_2$ (1.5 eq., $CH_2Cl_2$, -20°, 6 h) [3] afforded the cycloadducts 11 [8] (oil) in 98% yield. To determine the diastereoisomeric purity of 11 it was reduced with $LiAlH_4$ (excess, $Et_2O$, 20°). The resulting *endo*-alcohol 12 [8] contained only 2% of its *exo*-epimer (GC) which was readily removed by preparative GC. Acylation of pure 12 with (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (1.5 eq., DCC (1.5 eq.), DMAP) and $^{19}F$-NMR analysis [10] of the resulting ester 13 in the presence of $Pr(fod)_3$ showed 12 to be enantiomerically pure. Alternatively, 12 was treated with (R)-(-)-1-(1-naphthyl)-ethyl isocyanate[11] in the presence of N-N-dimethyl-2-aminoethanol to give the carbamate 14. HPLC-analysis of 14 confirmed the 99% optical purity of 12. Accordingly, excellent chiral efficiency [12] has been achieved in the Lewis-acid promoted Diels-Alder addition 10 → 11. The absolute sense of induction follows from the conversion of 11 into (-)-β-santalene (6), carried out along the lines of the previously established synthesis of racemic 6 [5].

Selective hydrogenation of crude 11 ($NaBH_4$, $Ni(OAc)_2$, $H_2$), subsequent α-alkylation of the resulting ester [8] (1:LDA, 2:4-methyl-3-pentenyl iodide, THF/HMPA) and simple crystallization (EtOH) furnished the pure ester 15 [8, 13] (m.p. 119-120°) in 82% yield from crude 11. Reduction of 15 with $LiAlH_4$ (excess, $Et_2O$) refurnished the auxiliary element 7 and gave a crystalline alcohol [8] (m.p. 38-40°) which on successive oxidation (PCC, $CH_2Cl_2$) and Wolff-Kishner reduction ($NH_2NH_2$, KOH) afforded optically pure (-)-β-santalene (6). Synthetic (-)-6 was identified by comparison ([α][13], IR, $^1H$-NMR, $^{13}C$-NMR, MS) with (-)-β-santalene of natural origin. We believe that this work demonstrates convincingly that asymmetric C,C-bond-formation by π-facial selection of enoates has reached the stage of practical applicability [14].

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