

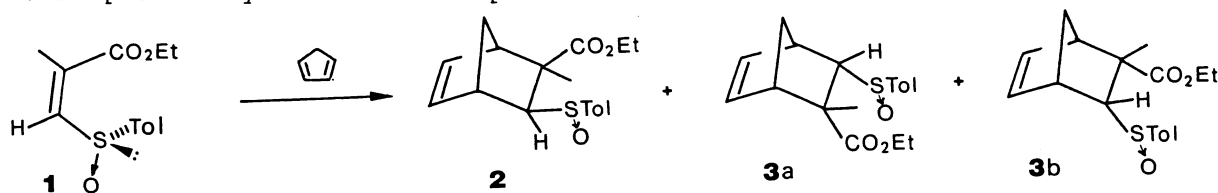
Enantioselective Synthesis of the Functionalized Bicyclo[2.2.1]heptane
Derivatives, Key Intermediates for the Chiral Synthesis of
Santalenes and Santalols

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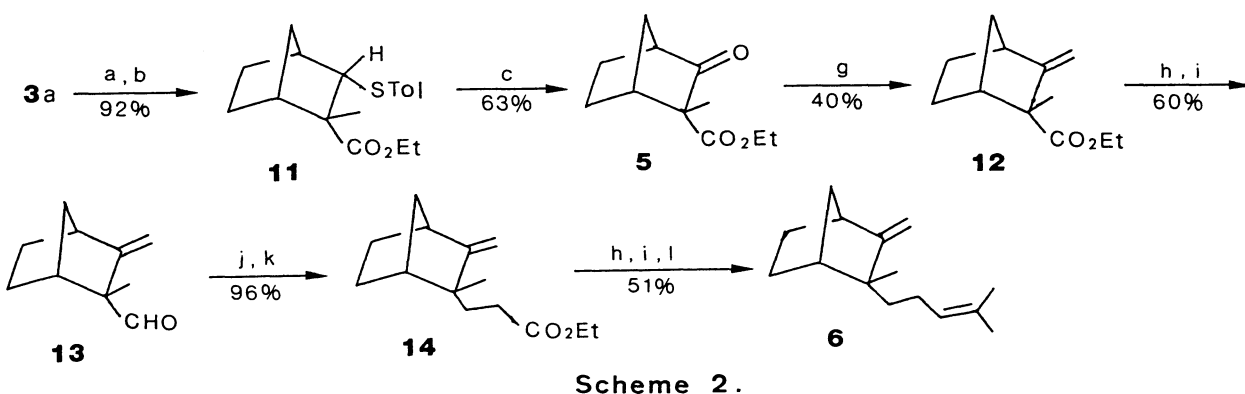
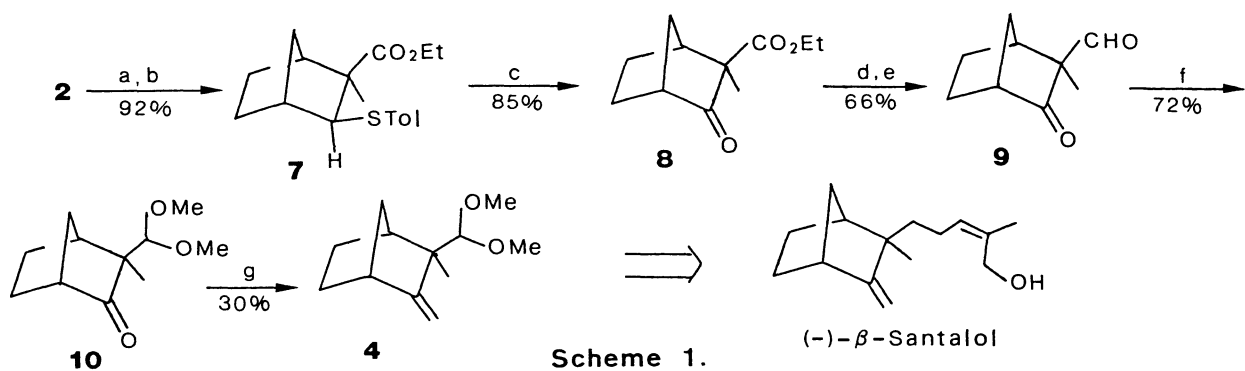
Optically active functionalized bicyclo[2.2.1]heptane derivatives obtained by the asymmetric Diels-Alder cycloaddition of ethyl *p*-tolylsulfinylmethylenepropionate with cyclopentadiene provide the potentially useful intermediates for synthesis of bicyclic sesquiterpenes such as (+)-*epi*- β -santalene.

During the past few years, asymmetric induction reaction by the use of chiral sulfoxides has been recognized as a useful synthetic methodology for the diastereoselective C-C bond formation.¹⁾ As part of our investigations in this area, we have recently reported that the Diels-Alder reaction of the sulfoxide **1** with cyclopentadiene proceeded to give the cycloadducts **2** and **3a,b** with high diastereoselectivity.²⁾ Very recently, De Lucchi *et al.* have designed "the sulfinyl-activated dienophiles" for the asymmetric Diels-Alder reaction and obtained the 2-substituted norbornadienes of high enantiomeric purity.³⁾ However, application of the Diels-Alder cycloaddition using these chiral sulfoxides to natural product synthesis is not precedented.



We describe, in this letter, the enantioselective synthesis of the key precursors **4** and **5**, which could be further converted to bicyclic sesquiterpenes. We have also succeeded in the transformation of **5** into (+)-*epi*- β -santalene (**6**)⁴⁾ in enantiomerically pure form.

The optically active sulfoxide **2** was converted to the sulfide **7** in 92% yield. Chlorination of **7** with *N*-chlorosuccinimide (NCS) followed by oxidative hydrolysis⁵⁾ with copper(II) oxide and copper(II) chloride gave the keto ester **8** in 85% yield.⁶⁾ All attempts to protect the ketone group in **8** were unsuccessful owing to the steric hindrance. Namely, **8** is quite resistant not only to acetalization with a variety of reagents (ethylene glycol/PPTS or trialkyl orthoformate/H⁺) but also to methylenation with methylenetriphenylphosphorane.



a) H_2 (1 atm), 10% Pd-C, rt, 7 h; b) 25% aq. $TiCl_3$ (1.3 equiv.), EtOH, rt, 1 h; c) NCS (5 equiv.), CCl_4 , reflux, 2 h; $CuCl_2 \cdot 2H_2O$ (5 equiv.), CuO (10 equiv.), water-acetone (1:10 v/v), reflux, 15 min; d) $LiAlH_4$ (ex.), Et_2O , $0^\circ C \rightarrow rt$, 3 h; e) $(COCl)_2$, DMSO, $-60^\circ C$, 30 min; Et_3N , $-60^\circ C$, 20 min; f) 0.2 M $CeCl_3 \cdot 6H_2O$ (1 equiv., 1 M = 1 mol dm^{-3}) in MeOH, $HC(OMe)_3$ (3 equiv.), rt, 3 d; g) Activated Zn, CH_2Br_2 , $TiCl_4$, THF, rt, 21 h; h) 1 M DIBAL (2 equiv.) in hexane, $-78^\circ C$, 1 h; i) PCC (3.4 equiv.), molecular sieves 4A, rt, 30 min; j) $(EtO)_2POCH_2CO_2Et$, 1.6 M BuLi (1.7 equiv.) in hexane, THF, $-78^\circ C$, 1.5 h; k) Et_3SiH (1.5 equiv.), $(Ph_3P)_3RhCl$ (cat.), $90^\circ C$, 20 min; EtOH; l) $Ph_3P=CH_2$, THF, rt, 18 h.

Methylenation of **8** by Nozaki's method ($CH_2Br_2/Zn/TiCl_4$)⁷⁾ produced the corresponding terminal olefin in capricious yield (0-15%). On the other hand, reduction ($LiAlH_4$) of **8** and subsequent Swern oxidation⁸⁾ gave the keto aldehyde **9** in 66% yield.⁹⁾ Selective acetalization¹⁰⁾ of **9** with trimethyl orthoformate in the presence of cerium(III) chloride afforded the dimethyl acetal **10** in 72% yield.¹¹⁾ The enantiomeric excess of **10** was proved to be no less than 97% as checked by a chiral shift reagent $Eu(hfc)_3$.¹²⁾ The acetal was methylenated with a combination of dibromomethane, zinc, and titanium(IV) chloride affording **4** in 30% yield (Scheme 1).¹³⁾ The spectroscopic (NMR and IR) data of **4** were consistent with those of the authentic compound reported by the BASF group. The racemic **4** has been successfully employed as an intermediate in the synthesis of (\pm)- β -santalol.¹⁴⁾ The optically active intermediate **4** being available in our hands, the results would permit the synthesis of (-)- β -santalol.

In a similar fashion 3a was converted into the key intermediate 5 (Scheme 2). The major diastereomer 3a was catalytically hydrogenated ($H_2/Pd-C$) and reduced with $TiCl_3$ to afford the sulfide 11.¹⁵⁾ Chlorination of 11 and successive hydrolysis gave the keto ester 5 in enantiomerically pure form.¹⁶⁾ Methylenation of 5 yielded the olefin 12.¹⁷⁾ Reaction of 12 with diisobutylaluminium hydride (DIBAL) and subsequent oxidation (pyridinium chlorochromate (PCC), molecular sieves 4A)¹⁸⁾ of the alcohol gave the unstable aldehyde 13. A Emmons-Horner condensation of 13 with triethyl phosphonoacetate followed by selective reduction¹⁹⁾ with triethylsilane in the presence of Wilkinson catalyst gave 14,²⁰⁾ whose spectroscopic data were consistent with those of an authentic sample.^{4b)} Conversion of 14 into 6 was carried out according to the method previously described.^{4b)} Thus, reduction (DIBAL) of 14 and successive treatment with PCC gave the unstable aldehyde which on Wittig reaction (isopropylidene triphenylphosphorane) afforded enantiomerically pure (+)-epi- β -santalene (6), $[\alpha]_D^{27} +26.4^\circ$ (≤ 0.4 , $CHCl_3$) (lit.^{4c)} $[\alpha]_D^{29} +26.9^\circ$).²¹⁾ Synthetic (+)-6 was identified by comparison (NMR and IR) with an authentic sample.^{4b)}

In conclusion, the successful synthesis of (+)-epi- β -santalene demonstrated that the asymmetric Diels-Alder cycloaddition of acrylates having the p-tolylsulfanyl group should provide a potential methodology for the asymmetric synthesis of the santalene-type sesquiterpenes.²²⁾ The research along this line is now in progress in this laboratory.

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- 5) C. Maignan and R.A. Raphael, *Tetrahedron*, **39**, 3245(1983).
- 6) All new compounds have been characterized by 200 MHz NMR, IR, and elemental analyses and/or high resolution mass spectra. **8**: bp 150-157 °C/5 mmHg (1 mmHg = 133.322 Pa), $[\alpha]_D^{25} -93.7^\circ$ (≤ 0.87 , $CHCl_3$), IR ν 1760, 1725, 1250 cm^{-1} , NMR δ = 1.25(s, 3H), 1.28(t, J=7, 3H), 1.4-2.3(m, 6H), 2.58(br, 1H), 2.77(br, 1H), 4.13(q, J=7, 2H).
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 - 9) **9**: bp 65-75 °C/6 mmHg, $[\alpha]_D^{24} -329.1^\circ$ (c 0.43, CHCl₃), IR ν 1750, 1710 cm⁻¹, NMR δ =1.20(s, 3H), 1.3-2.1(m, 6H), 2.57(br, 1H), 2.83(br, 1H), 9.36(s, 1H).
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 - 11) **10**: bp 65-75 °C/3 mmHg, $[\alpha]_D^{24} -62.6^\circ$ (c 0.7, CHCl₃), IR ν 1740, 1445 cm⁻¹, NMR δ =0.95(s, 3H), 1.12-1.87(m, 6H), 2.37(br, 1H), 2.62(br, 1H), 3.32(s, 3H), 3.38(s, 3H), 4.12(s, 1H).
 - 12) In the NMR spectrum, (\pm)-**10** was resolved to a pair of singlets due to the tert.-Me at 2.97 and 3.10 ppm using a chiral shift reagent Eu(hfc)₃ (1.67 equiv. used). The acetal **10** showed the tert.-Me signal at 2.97 ppm. The peak of the corresponding enantiomer was hardly observed within the limit of detection. Racemic **10** was synthesized as follows. Methylation of (\pm)-norcamphor (MeI, LDA/HMPA) followed by ethoxycarbonylation (NC-CO₂Et, LDA/HMPA) produced (\pm)-**8**. Transformation of (\pm)-**8** into (\pm)-**10** was carried out according to the method as shown in Scheme 1. Ethoxycarbonylation was accomplished by the method of Mander; L. N. Mander and S. P. Sethi, *Tetrahedron Lett.*, **24**, 5425(1983).
 - 13) **4**: bp 120-125 °C/42 mmHg, $[\alpha]_D^{24} -119.3^\circ$ (c 0.9, CHCl₃).
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 - 15) **11**: bp 111-120 °C/0.1 mmHg, $[\alpha]_D^{25} -6.5^\circ$ (c 0.6, CHCl₃), IR ν 1725 cm⁻¹, NMR δ =1.30(t, 3H), 1.1-1.8(m, 6H), 1.40(s, 3H), 2.16(br s, 1H), 2.32(s, 2H), 3.0(br, 1H), 3.15(q, J=7, 2H), 7.10(A₂B₂, J=8, 4H).
 - 16) **5**: bp 119-123 °C/3 mmHg, $[\alpha]_D^{24} -6.3^\circ$ (c 1.3, CHCl₃), IR ν 1750, 1720 cm⁻¹, NMR δ =1.27(s, J=7, 3H), 1.27(t, J=7.5, 3H), 1.2-2.0(m, 6H), 2.53(br s, 2H), 4.13(q, J=7.5, 2H). The enantiomeric excess of **5** was found to be \approx 100% by the NMR chiral shift reagent method using Eu(hfc)₃ as described in ref 12). Racemic **5** was prepared starting from (\pm)-norcamphor in two steps (i)NC-CO₂Et, LDA/HMPA, ii)MeI, LDA/HMPA).
 - 17) **12**: bp 85-90 °C/12 mmHg, $[\alpha]_D^{24} -44.6^\circ$ (c 1, CHCl₃), IR ν 1735, 1720 cm⁻¹, NMR δ =1.27 (t, J=7, 3H), 1.33 (s, 3H), 1.07-1.83 (m, 6H), 2.33 (br, 1H), 2.73 (br, 1H), 4.17 (q, J=7, 2H), 4.83 (s, 1H), 5.03 (s, 1H).
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 - 20) **14**: bp 140-145 °C/15 mmHg, $[\alpha]_D^{26} +25.8^\circ$ (c 2.5, CHCl₃), IR ν 1738 cm⁻¹, NMR δ =1.00 (s, 3H), 1.27 (t, J=7, 3H), 1.0-2.6 (m, 11H), 2.70 (br s, 1H), 4.16 (q, J=7, 2H), 4.53 (s, 1H), 4.78 (s, 1H).
 - 21) The enantiomeric excess of the synthetic **6** should be considered as almost 100% because the possibility of the racemization is hardly conceivable in the reactions utilized from **5** to **6**. Although the optical purity of natural (+)-epi- β -santalene has not been recorded, the identity in the specific rotations indicates that **6** isolated from the natural source is optically pure.
 - 22) For the practical purpose it is not necessary to use the diastereomerically pure **3a**, because (+)-**6**, prepared from a mixture of the cycloadducts **3a**, **b** (ca. 9:1), showed the same degree of the specific rotation.

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