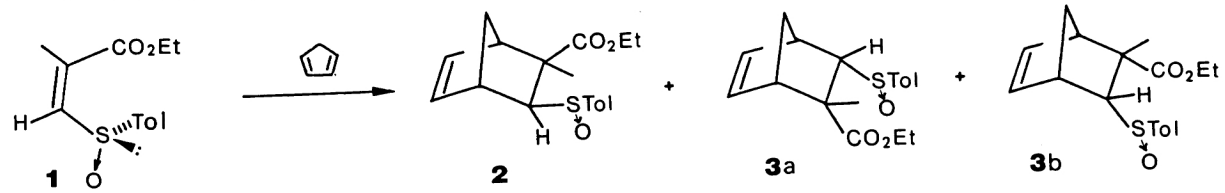
CHEMISTRY LETTERS, pp. 1225-1228, 1986.

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

Yoshitsugu ARAI, Masatoshi YAMAMOTO, and Toru KOIZUMI*
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01

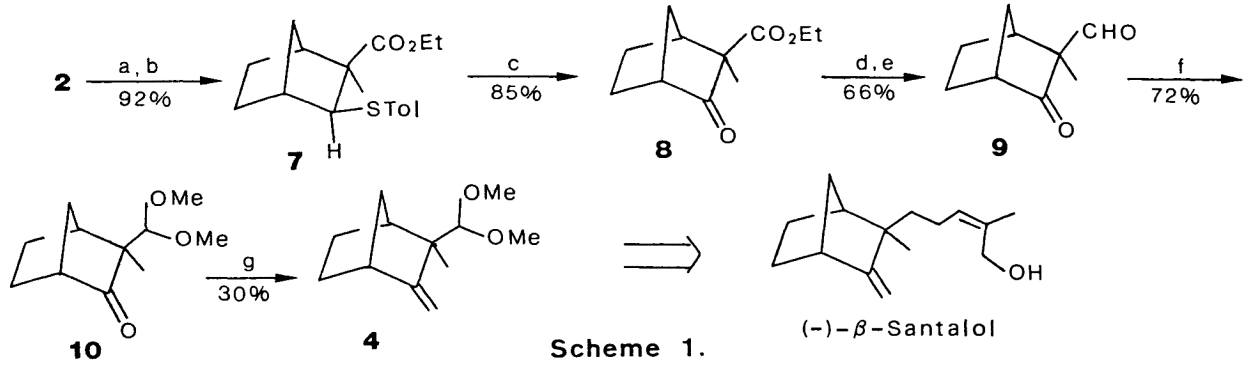
Optically active functionalized bicyclo[2.2.1]heptane derivatives obtained by the asymmetric Diels-Alder cycloaddition of ethyl p-tolylsulfinylmethylenepropionate with cyclopentadiene provide the potentially useful intermediates for synthesis of bicyclic sesquiterpenes such as (+)-epi-β-santalene.

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.

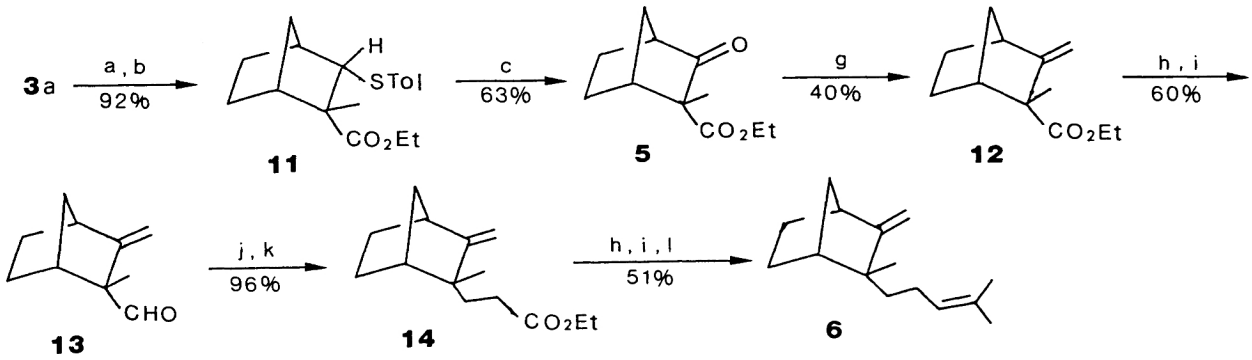


We describe, in this letter, the enantioselective synthesis of the key precursors **4** and **5**, which could be further converted to bicyclic sesquiterpenes. We have also succeeded in the transformation of **5** into (+)-epi-β-santalene (**6**)[4] in enantiomerically pure form.

The optically active sulfoxide **2** was converted to the sulfide **7** in 92% yield. Chlorination of **7** with N-chlorosuccinimide (NCS) followed by oxidative hydrolysis[5] 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.



Scheme 1.



Scheme 2.

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 °C → rt, 3 h; e) $(COCl)_2$, DMSO, -60 °C, 30 min; Et_3N, -60 °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 °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 °C, 1.5 h; k) Et_3SiH (1.5 equiv.), $(Ph_3P)_3RhCl$ (cat.), 90 °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 oxidation[8] gave the keto aldehyde **9** in 66% yield.[9] Selective acetalization[10] 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 (±)-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 reduction[19] 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°(c 0.4, $CHCl_3$)(lit.[4c] $[\alpha]_D^{29}$ +26.9°).[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-tolylsulfinyl 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.

We thank Dr. W. Gramlich (BASF, Germany) for sending copies of ^{1}H-NMR and IR spectra of **4** and Dr. P. Christenson (Fritzche Dodge & Olcott Inc.) for NMR and IR spectra of epi-β-santalene.

References

1) G.H. Posner, "Addition of Organometallic Reagents to Chiral Vinyl Sulfoxides," ed by J.D. Morrison, Academic Press, New York (1983),Vol. 2, pp. 225-241; G. Solladié, Synthesis, 1981, 185.
2) T. Koizumi, I. Hakamada, and E. Yoshii, Tetrahedron Lett., 25, 87(1984).
3) O. De Lucchi, C. Marchioro, G. Valle, and G. Modena, J. Chem. Soc., Chem. Commun., 1985, 878.
4) For syntheses of **6**, see: a) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, J. Am. Chem. Soc., 84, 2611(1962); G. Brieger, Tetrahedron Lett., 1963, 1949; P. A. Grieco and J. J. Reap, Synthetic Commun., 5, 347(1975); R. L. Snowden, P. Sonnay, and G. Ohloff, Helv. Chim. Acta, 64, 25(1981); b) P. A. Christenson and B. J. Willis, J. Org. Chem., 45, 3068(1980); c) G. L. Hodgson, D. F. MacSweeney, R. W. Mills, and T. Money, J. Chem. Soc., Chem. Commun.,1973, 235.
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°(c 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).
7) K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, Bull. Chem. Soc. Jpn., 53,

1698(1980).
8) K. Omura and D. Swern, Tetrahedron, 34, 1651(1978).
9) **9:** bp 65-75 °C/6 mmHg, $[\alpha]_D^{24}$ -329.1°(c 0.43, $CHCl_3$), 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).
10) A.L. Gemal and J.-L. Luche, J. Org. Chem., 44, 4187(1979).
11) **10:** bp 65-75 °C/3 mmHg, $[\alpha]_D^{24}$ -62.6°(c 0.7, $CHCl_3$), 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, (±)-**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 (±)-norcamphor (MeI, LDA/HMPA) followed by ethoxycarbonylation ($NC-CO_2Et$, LDA/HMPA) produced (±)-**8**. Transformation of (±)-**8** into (±)-**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°(c 0.9, $CHCl_3$).
14) M. Baumann and W. Hoffmann, Liebigs Ann. Chem., 1979, 743.
15) **11:** bp 111-120 °C/0.1 mmHg, $[\alpha]_D^{25}$ -6.5°(c 0.6, $CHCl_3$), 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(A_2B_2, J=8, 4H).
16) **5:** bp 119-123 °C/3 mmHg, $[\alpha]_D^{24}$ -6.3°(c 1.3, $CHCl_3$), 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 ≈100% by the NMR chiral shift reagent method using $Eu(hfc)_3$ as decribed in ref 12). Racemic **5** was prepared starting from (±)-norcamphor in two steps (i)$NC-CO_2Et$, LDA/HMPA, ii)MeI, LDA/HMPA).
17) **12:** bp 85-90 °C/12 mmHg, $[\alpha]_D^{24}$ -44.6°(c 1, $CHCl_3$), 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).
18) J. Herscovici, M.-J. Egron, and K. Antonakis, J. Chem. Soc., Perkin 1, 1982, 1967.
19) E. Yoshii, Y. Kobayashi, T. Koizumi, and T. Oribe, Chem. Pharm. Bull., 22, 2767(1974). Reduction by other reagents (e.g., Li/NH_3) produced low yields of **14** accompanied with over-reduction products of the terminal olefin and ester carbonyl.
20) **14:** bp 140-145 °C/15 mmHg, $[\alpha]_D^{26}$ +25.8 ° (c 2.5, $CHCl_3$), 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.

(Received April 16, 1986)