

A FORMAL SYNTHESIS OF *l*- α -SANTONIN FROM CHIRAL α,β -EPOXYEUDESMANOLIDE VIA ENZYME-CATALYZED HYDROLYSIS

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(4*S*,5*R*)-Epoxy-(3*S*)-hydroxy-(10*S*)-7 α ,11 β H-eudesman-6 α ,12-olide **4** and (4*R*,5*S*)-epoxy-(3*S*)-hydroxy-(10*R*)-7 β ,11 α H-eudesman-6 β ,12-olide **5** were obtained from (\pm)-**3** using yeast and (3*S*)-acetoxy-(4*S*,5*R*)-epoxy-(10*S*)-7 α ,11 β H-eudesman-6 α ,12-olide **8** was produced from (\pm)-**8** using lipase, respectively. New total syntheses of *l*- α -santonin (**9**) and its $\Delta^{4(14)}$ -isomers (**10** and **11**) were accomplished by a short step synthesis using the optically active key intermediate (10*S*)-**8** (prepared by asymmetric hydrolysis of (\pm)-**8**).

KEYWORDS *l*- α -santonin; lipase; enzyme-catalyzed hydrolysis; enantioselective hydrolysis

Enantioselective synthesis using biological procedures has been proved to be widely useful and is one of the most effective methods to carry out transformation of racemic compounds into chiral ones. Chiral bicyclic compounds are expected to become building blocks for the synthesis of natural products such as sesquiterpenoids and diterpenoids. There are numerous examples¹⁾ of biological transformations of acyclic compounds, but only a few reports²⁾ of bicyclic compounds. We reported asymmetric reduction of bicyclic

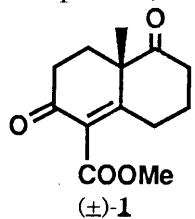
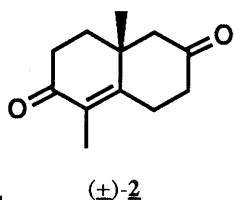


Chart 1



diketones with microorganisms (yeasts) to yield optically active bicyclic compounds which were useful for asymmetric syntheses of natural products.^{3,4)} In those studies, the α,β -unsaturated carbonyl groups of the oxooctalins such as (\pm)-**1** and (\pm)-**2** were shown to be inert, but the saturated carbonyl groups were

reduced regio- and enantioselectively. In general, biological reduction of α,β -unsaturated carbonyl groups seems to be difficult because of the resonance stability. In connection with our series of studies on biological

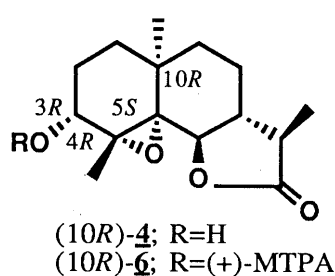
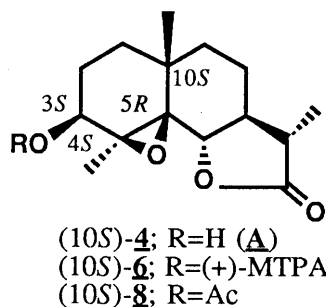
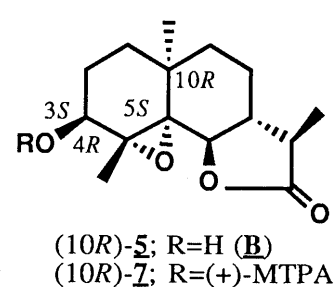
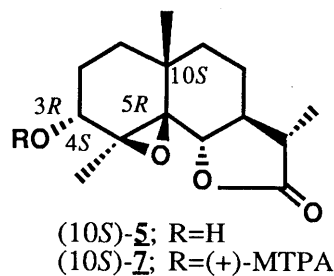


Chart 2



asymmetric induction into bicyclic key intermediates, we now wish to report the enantioselective synthesis of bicyclic epoxy alcohols ((10*S*)-**4** and (10*R*)-**5**) and the utilization to a total synthesis of *l*- α -santonin (**9**), well known as anthelmintics against *Ascaris lumbricoides*.

The epoxy ketone (\pm)-**3**⁶ was selected as the representative substrate. In the screening with various microorganisms, reduction of the epoxy ketone (\pm)-**3** using *Hansenula anomala* produced the two epoxy alcohols **A** {[α]_D -26 ° (c = 1.4, CHCl₃)} and **B** {[α]_D +18 ° (c = 1.7, CHCl₃)} in 9% and 23% yields, respectively. The relative stereochemistry of **A** and **B** was determined by comparison with the ¹H-NMR, IR and MS spectra of the four epoxy alcohol isomers derived from **2**.⁸ The absolute configuration and the optical purity of **A** and **B** were determined by comparison of the ¹H-NMR spectra of (+)-MTPA esters⁹ with those of (10*S*)-**4** and (10*S*)-**5** derived from **2** as well as the racemic epoxy alcohols (\pm)-**4** and (\pm)-**5**. The epoxides **A** and **B** were found to be 80% ee and >99% ee, respectively. Thus the absolute structures of **A** and **B** were determined to be (4*S*,5*R*)-epoxy-(3*S*)-hydroxy-(10*S*)-**4**¹⁰ and (4*R*,5*S*)-epoxy-(3*S*)-hydroxy-(10*R*)-eudesmanolide **5**,¹¹ respectively. But the yield of (10*S*)-**4** having the same configuration as that of the target (**9**) was low. Then we turned our attention to enzyme-catalyzed asymmetric hydrolysis. The epoxy acetate (\pm)-**8**⁷ was subjected to screening by the use of various commercially available lipases. Among them, the lipase from *Rizopus niveus* (Nagase) was found to afford an optically active acetate (10*S*)-**8**¹² (35% yield, 94% ee) and the corresponding alcohol (10*R*)-**4** (52% yield, 57% ee). A typical experimental procedure is as follows: A solution of (\pm)-**8** (10 mg) in 1.0 M phosphate buffer (pH 7.25, 10 ml) was incubated with the lipase (20 mg) for 6 d at 33 °C. After extraction with ethyl acetate, the organic layer was dried over MgSO₄ and evaporated to give a crude product which was purified through a silica cartridge Set-pack using hexane-ethyl acetate (1:1) as eluent. The enantiomeric excess and the chemical yield of products were determined by HPLC analysis using chiral column (column, Chiralcel OD; eluent, hexane: EtOH: *i* PrOH (200:10:5); detection, RI; flow rate, 0.5 ml/min). Assignment of these peaks was confirmed by comparing them with the authentic samples [(10*S*)-**8** and (10*S*)-**4** derived from **2**].¹³ After we obtained the acetate (10*S*)-**8** with high optical purity in moderate yield, it was successfully converted to *l*- α -santonin (**9**)¹⁴ by the sequential reactions of hydrolysis with K₂CO₃, oxidation with Jones reagent, deoxygenation with Fe(CO)₅ in trimethylurea followed by oxidation with DDQ in benzene. In conclusion, asymmetric hydrolysis of the epoxy acetate (\pm)-**8** with the lipase from *Rizopus niveus* (Nagase) was found to afford the desired acetate (10*S*)-**8** with high optical purity. A further transformation from (10*S*)-**8** into *l*- α -santonin has been achieved in four steps in a 15% overall yield. This also means formal syntheses of allosantonin (**10**)¹⁵ and alloisantonin (**11**).¹⁵ Details of the syntheses will be reported elsewhere in the near future.

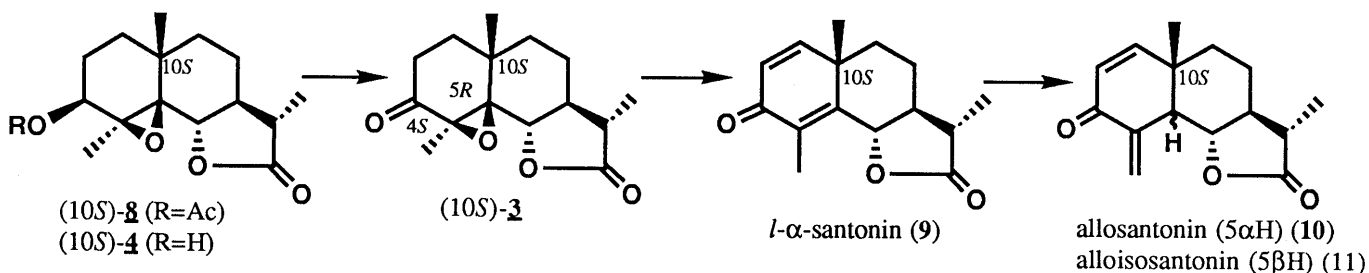


Chart 3

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REFERENCES AND NOTES

- 1) a) K. Mori, *Farumashia*, **17**, 414 (1981); b) K. Nakamura, A. Ohno, *Yuki Gosei Kagaku Kyokai Shi*, **9**, 110 (1991); c) W. -R. Shieh, A. S. Gopalan, C. J. Sih, *J. Am. Chem. Soc.*, **107**, 2993 (1985).
- 2) a) R. F. Newton, S. M. Roberts, *Tetrahedron*, **36**, 2163 (1980); b) C. -T. Hsu, N. -Y. Wang, L. H. Latimer, C. J. Sih, *J. Am. Chem. Soc.*, **105**, 593 (1983); c) W. Zhonggi, Y. Zhihua, L. Haiying, *Org. Chem. (China)*, **5**, 391 (1985).
- 3) a) S. Inayama, N. Shimizu, T. Ohkura, H. Akita, T. Oishi, Y. Iitaka, *Chem. Pharm. Bull.*, **34**, 2660 (1986); b) *idem, ibid.*, **37**, 712 (1989).
- 4) a) S. Inayama, N. Shimizu, T. Ohkura, H. Akita, T. Oishi, Y. Iitaka, *Chem. Pharm. Bull.*, **35**, 429 (1987); b) N. Shimizu, T. Ohkura, H. Akita, T. Oishi, Y. Iitaka, S. Inayama, *ibid.*, **37**, 1023 (1989).
- 5) a) N. Shimizu, T. Ohkura, H. Akita, T. Oishi, Y. Iitaka, S. Inayama, *Chem. Pharm. Bull.*, **37**, 2561 (1989); b) N. Shimizu, T. Ohkura, H. Akita, T. Oishi, Y. Iitaka, S. Inayama, *ibid.*, **39**, 2973 (1991).
- 6) Substrate (\pm)-**3** was obtained by treatment of epoxy acetate (\pm)-**8**⁷⁾ with K₂CO₃ in MeOH, followed by oxidation with Jones reagent.
- 7) Substrate (\pm)-**8** was successfully prepared by applying Abe's procedure.¹⁴⁾
- 8) Y. Fujimoto, T. Shimizu, T. Tatsuno, *Chem. Pharm. Bull.*, **24**, 365 (1976).
- 9) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).
- 10) *Anal.* high-resolution MS Calcd for C₁₅H₂₂O₄ (M⁺, m/z): 266.1518. Found. 266.1508.
IR (CHCl₃): 3475, 1781 cm⁻¹. ¹H-NMR (CDCl₃, 270 MHz): 1.149 (3H, s, 10-CH₃), 1.254 (3H, d, 7 Hz, 11-CH₃), 1.654 (3H, s, 4-CH₃), 3.785 (1H, t, 3 Hz, 3-CH₃), 4.467 (1H, d, 11 Hz, 6-CH₃).
- 11) *Anal.* high-resolution MS Calcd for C₁₅H₂₂O₄ (M⁺, m/z): 266.1518. Found. 266.1501.
IR (CHCl₃): 3523, 1776 cm⁻¹. ¹H-NMR (CDCl₃, 270 MHz): 1.139 (3H, s, 10-CH₃), 1.249 (3H, d, 7 Hz, 11-CH₃), 1.633 (3H, s, 4-CH₃), 3.846 (1H, t, 3 Hz, 3-CH₃), 4.449 (1H, d, 11 Hz, 6-CH₃).
- 12) *Anal.* high-resolution MS Calcd for C₁₅H₂₂O₄ (M⁺-COCH₃, m/z): 266.1518. Found. 266.1505.
IR (CHCl₃): 1780, 1743 cm⁻¹. ¹H-NMR (CDCl₃, 270 MHz): 1.174 (3H, s, 10-CH₃), 1.265 (3H, d, 7 Hz, 11-CH₃), 1.555 (3H, s, 4-CH₃), 2.131 (3H, s, -COCH₃), 3.780 (1H, br, 3-CH₃), 4.467 (1H, d, 11 Hz, 6-CH₃).
- 13) The conversion of *l*- α -santonin to the epoxy acetate (10*S*)-**8** was successfully achieved by the sequential reactions of catalytic reduction with triphenyl phosphine-Rhodium chloride, reduction with NaBH₄ and CeCl₃, epoxidation with MCPBA, and acetylation with Ac₂O in pyridine followed by purification by recrystallization.
- 14) a) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga, *J. Am. Chem. Soc.*, **78**, 1416 (1956); b) *idem, ibid.*, **78**, 1422 (1956).
- 15) S. Inayama, N. Shimizu, T. Shibata, H. Hori, Y. Iitaka, *J. Chem. Soc., Chem. Commun.*, **1980**, 495.

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